Review

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Peritoneum Adhesion Genetic Determinism

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Abstract: Injury to the peritoneum during surgery is followed by a healing process that frequently results in the attachment of adjacent organs by a fibrous mass, referred to commonly as adhesions. Because injuries to the peritoneum during surgery are inevitable, one must understand the mechanisms of adhesion formation to prevent its occurrence. This requires a thorough understanding of the molecular sequence that results in the attachment of injured peritoneum and the development of fibrous tissue. Recent data show that fibroblasts from the injured peritoneum may play a critical role in forming adhesion tissues. Therefore, identifying changes in gene expression patterns in the peritoneal fibroblasts during the process may provide clues to the mechanisms by which adhesion develops. This review presents many papers discussing genes implied in peritoneal adhesion.

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1. Introduction

A limited microenvironment defined by the peritoneum is stable in normal circumstances but is vulnerable to the deleterious effects of infections, surgical injuries, and other neoplastic and non-neoplastic occurrences. It draws in, multiplies, and activates a range of hematopoietic and stromal cells in response to injury. Under physiological settings, tissue architecture is repaired, inflammatory triggers are eliminated, and appropriate responses to injuries are coordinated. On the other hand, fibrosis or scarring results from the inability to eliminate inflammatory triggers, and reduced tissue function ultimately leads to organ failure. [1].

Peritoneal adhesions continue to be a major issue for many patients today, contributing to a variety of sometimes severe clinical presentations. In the peritoneal cavity, adhesions can develop as a result of surgery, inflammation, or trauma. A variety of clinical symptoms, such as small intestinal blockage, infertility, and abdominal pain, can be caused by them. Approximately 50% of patients undergoing abdominal surgery are expected to acquire peritoneal adhesions, indicating a high occurrence of these adhesions. It is impossible to totally eliminate the danger of adhesion formation during surgery, even with advancements in perioperative care. Thus, developing effective preventative strategies and treatments remains a primary goal in surgery [2].

Following abdominal or pelvic surgery, postoperative adhesions continue to be a major clinical issue that can result in discomfort, intestinal obstruction, and infertility. Their management and prevention are still insufficient and poorly understood. When fibrinolysis is inhibited during the coagulation process, a fibrin matrix organises and leads to the creation of adhesions. [3].

Adhesion formation is a multigenic phenomenon. Not all changes in gene expression patterns between normal and adhesion fibroblasts are the function of TGF-beta1 and hypoxia, which are known to influence adhesion formation [4].

Moreover, adhesion fibroblasts have a distinct phenotypic known as the adhesion phenotype, which is partially defined by COX-2 expression. Adhesion fibroblasts' production of COX-2 mRNA and peritoneal fibroblasts' activation of COX-2 in response to hypoxia suggest the possibility of an

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inflammatory response. Controlling COX-2 could change how the peritoneum heals and offer a way to lessen the formation of postoperative adhesions. [5].

One common aftereffect of abdominopelvic surgery is peritoneal adhesions. Long-term morbidity from adhesions may include intestinal blockage, infertility, and perhaps pelvic pain. [6–10]. Subsequent surgeries are also likely to be prolonged and potentially incur more significant risks, such as bowel injury. While 55%–85% of women undergoing open pelvic surgery will form adhesions postoperatively, some individuals do not. Understanding processes that favor peritoneal repair without adhesions, as opposed to with adhesion development, would ultimately benefit all patients and could lead to clinical therapies to reduce postoperative adhesions [11].

Transforming growth factor beta (TGF-β) represents a superfamily of 30 similarly built molecules identified from multiple species and contains three mammalian isoforms of widely conserved homology [12]. The inhibins, activins, bone morphogenetic proteins, and müllerian inhibiting compounds are all members of this superfamily. The three mammalian isoforms of TGF-β have crucial functions in embryogenesis [13–16] and directing wound repair in different tissue types [17–19]. In wound healing, they have been demonstrated to influence the production and release of downstream growth factors and cytokines, function as chemoattractants of inflammatory cells, induce angiogenesis, and guide collagen and fibronectin manufacture by fibroblasts [20–22].

Taken collectively, TGF-β orchestrates wound repair from the outset. Platelets contain TGF-β in significant quantities and are present almost immediately at wound sites upon injury. The platelet-released TGF-β promotes chemotaxis of macrophages and fibroblasts to the wound site and then upregulates its expression from these cells to maintain its presence. However, the differential presence of the three isoforms at the wound site can result in different outcomes [23].

While elevated levels of TGF-β3 promote healing with reduced fibrosis and scarring, elevated levels of TGF-β1 and TGF-β2 in the healing environment often promote higher scarring and fibrosis of the wound site. investigations on cutaneous wounds have yielded the majority of these data, with investigations on nondermal locations such the liver, kidney, eye, and central nervous system providing additional evidence very lately [24].

Understanding the mechanisms that lead to normal reperitonealization as opposed to peritoneal healing that ends up as adhesions or fibrosis requires a similar awareness for TGF-β-mediated peritoneal repair. Characterising TGF-β expression in the visceral peritoneum, postoperative parietal, and healing parietal is lacking, nevertheless. Previous research on the peritoneum has looked at cell culture models or human surgical populations that are diverse in terms of age and the reasons behind adhesions (such as endometriosis, surgery, or infection) [25–27].

In Table 1 below, proteins involved in peritoneal adhesion are listed (additional molecules), which further elucidate the intricate molecular mechanisms underlying peritoneal adhesion formation and offer potential targets for therapeutic interventions).

#	Protein	Description	Ref.
1	Integrins	Transmembrane receptors facilitate cell-cell and cell-extracellular matrix interactions. They play a role in cell migration, proliferation, and tissue remodeling processes involved in peritoneal adhesion formation.	[28]
2	Cadherins (E-cadherin)	Calcium-dependent cell adhesion molecules that mediate homophilic interactions between cells. E-cadherin maintains tissue integrity and may contribute to peritoneal adhesion formation through its role in cell-cell adhesion.	[29]
3	Selectins (P-selectin and E-selectin)	Cell adhesion molecules mediate initial interactions between leukocytes and endothelial cells during inflammation. Their involvement in peritoneal adhesion formation suggests a role in leukocyte	[30]

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		recruitment and inflammatory processes at the peritoneal surface.	
4	Immunoglobulin superfamily molecules (ICAM-1 and VCAM-1):	Cell adhesion molecules facilitate leukocyte trafficking and adhesion to endothelial cells. ICAM-1 and VCAM-1 may contribute to peritoneal adhesion formation by mediating leukocyte recruitment and interactions with mesothelial cells.	[31]
5	Hyaluronan (HA)	A significant glycosaminoglycan component of the extracellular matrix. H.A. can influence cell adhesion, migration, and tissue remodeling processes. Its involvement in peritoneal adhesion formation suggests a role in modulating cell-matrix interactions and tissue repair responses.	[32]
6	Fibronectin	An extracellular matrix glycoprotein is involved in cell adhesion, migration, and wound healing. Fibronectin may contribute to peritoneal adhesion formation by promoting cell-matrix interactions.	[33]
7	Matrix Metalloproteinases (MMPs)	Enzymes are involved in extracellular matrix degradation and remodeling. MMPs play a role in tissue repair and remodeling processes associated with peritoneal adhesion formation.	[34]
8	Fibrinogen	A glycoprotein is involved in blood clot formation. Fibrinogen and its derivatives may contribute to peritoneal adhesion formation by promoting fibrin deposition and adhesion formation.	[35]
9	Tissue Plasminogen Activator (tPA) and Plasminogen Activator Inhibitor-1 (PAI-1)	Regulators of fibrinolysis. Alterations in tPA and PAI-1 levels may impact fibrin degradation and tissue remodeling processes associated with peritoneal adhesion formation.	[36]
10	Transforming Growth Factor-beta (TGF-β)	A cytokine is involved in cell growth, differentiation, and extracellular matrix production. TGF-β signaling pathways may contribute to tissue fibrosis and peritoneal adhesion formation.	[37]
11	Vascular Endothelial Growth Factor (VEGFA)	A signaling protein involved in angiogenesis, vasculogenesis, and vascular permeability. VEGF may contribute to peritoneal adhesion formation by promoting neovascularization and tissue remodeling.	[38]
12	Platelet-Derived Growth Factor (PDGF)	A growth factor is involved in cell proliferation, migration, and angiogenesis. PDGF may contribute to peritoneal adhesion formation by stimulating fibroblast proliferation and extracellular matrix production.	[39]
13	Interleukins (ILs)	Cytokines are involved in immune responses and inflammation. Certain interleukins, such as IL-1 and IL-6, may contribute to peritoneal adhesion formation by promoting inflammation and fibrosis.	[40]

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14	Fibroblast Growth Factor (FGF1)	A family of growth factors involved in cell proliferation, migration, and differentiation. FGFs may contribute to peritoneal adhesion formation by stimulating fibroblast activity and extracellular matrix synthesis.	[41]
15	Toll-like Receptors (TLRs)	Pattern recognition receptors are involved in innate immune responses. TLRs may contribute to peritoneal adhesion formation by triggering inflammatory responses and modulating tissue repair processes.	[42]
16	Tenascin-C	An extracellular matrix glycoprotein is involved in cell adhesion, migration, and tissue remodeling. Tenascin-C expression may be upregulated during peritoneal injury and contribute to adhesion formation.	[43]
17	Platelet-Derived Growth Factor (PDGF)	A mitogen is involved in cell proliferation and migration. PDGF signaling pathways may contribute to tissue repair and fibrosis associated with peritoneal adhesion formation.	[44]
18	Vascular Endothelial Growth Factor (VEGFB)	A cytokine involved in angiogenesis and vascular permeability. VEGF may play a role in tissue repair and remodeling processes associated with peritoneal adhesion formation.	[45]
19	Tissue Inhibitor of Metalloproteinases (TIMPs)	Endogenous inhibitors of matrix metalloproteinases (MMPs). TIMPs regulate extracellular matrix turnover and tissue remodeling processes in peritoneal adhesion formation.	[46]
20	Fibroblast Growth Factor (FGF2)	A family of growth factors involved in cell proliferation, migration, and tissue repair. FGF signaling pathways may contribute to fibrosis and adhesion formation in the peritoneum.	[47]

Each protein is then briefly explained in tne paragraph below.

Integrins are a class of transmembrane receptors that are essential for interactions between cells and the extracellular matrix. These proteins, which are heterodimers made up of α and β subunits, operate as cell surface receptors. Numerous cellular activities, such as adhesion, migration, proliferation, differentiation, and signal transduction, depend on integrins. Three domains make up an integrin: the cytoplasmic, transmembrane, and extracellular domains. Certain extracellular matrix proteins, including fibronectin, collagen, laminin, and vitronectin, are recognised by ligand-binding sites found in the extracellular domain [48,49].

Integrins can undergo conformational changes upon ligand binding, which trigger intracellular signaling cascades. This process, integrin activation, regulates cell adhesion, migration, and other cellular responses. Integrins mediate cell adhesion to the extracellular matrix and facilitate cell migration by interacting with extracellular matrix proteins and cytoskeletal components. They also play roles in cell-to-cell adhesion and interactions with immune cells. Integrins can act as signaling receptors, transmitting signals bidirectionally across the cell membrane. Outside-in signaling occurs when integrins bind to extracellular ligands and initiate intracellular signaling pathways.

In contrast, inside-out signaling involves the regulation of integrin affinity and clustering by intracellular signaling molecules. Various mechanisms, including changes in ligand binding affinity, clustering, and intracellular signaling, tightly regulate integrin activity. This regulation allows cells

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to dynamically modulate their adhesion and migration in response to extracellular cues and physiological conditions. Integrins have been implicated in the pathogenesis of peritoneal adhesions, mediating the adhesion of mesothelial cells and fibroblasts to the peritoneal extracellular matrix. Targeting integrin signaling pathways may represent a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Overall, integrins are essential regulators of cell adhesion, migration, and signaling processes, with implications for various physiological and pathological conditions, including peritoneal adhesion formation [50–52]

Cadherins, including E-cadherin, are a family of calcium-dependent cell adhesion molecules that mediate cell-cell adhesion and tissue integrity. Cadherins are transmembrane proteins composed of extracellular domains responsible for calcium-dependent homophilic interactions, a transmembrane domain, and cytoplasmic tails that link to the actin cytoskeleton via catenins. E-cadherin, also known as epithelial cadherin or CDH1, is one of the best-characterized members of the cadherin family and is predominantly expressed in epithelial tissues. Cadherins mediate homophilic interactions between adjacent cells, contributing to the formation and maintenance of adherens junctions. The extracellular domains of E-cadherin molecules on neighboring cells bind together in a calcium-dependent manner, forming trans-interactions that link cells into cohesive sheets and regulate tissue morphology [53–55].

E-cadherin is essential for maintaining epithelial tissue integrity and barrier function. Loss or dysfunction of E-cadherin can lead to epithelial-to-mesenchymal transition (EMT), a process characterized by the loss of cell-cell adhesion and acquisition of migratory and invasive properties, which is associated with tumor progression and metastasis. E-cadherin expression in peritoneal mesothelial cells is critical in regulating peritoneal adhesion formation. Decreased E-cadherin expression or altered localization has been observed in response to peritoneal E-cadherin expression, and various signaling pathways and transcription factors regulate function. For example, the Wnt/β-catenin signaling pathway can modulate E-cadherin expression and cell adhesion by regulating β-catenin localization and transcriptional activity. Injury may contribute to disrupting mesothelial cell junctions and adhesion formation. Targeting E-cadherin and its associated signaling pathways may represent a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches to restoring E-cadherin expression or function could help preserve mesothelial barrier integrity and mitigate adhesion formation following abdominal surgery or injury. Overall, E-cadherin is a crucial regulator of cell-cell adhesion and tissue integrity in epithelial tissues, including the peritoneum, and its dysregulation has implications for peritoneal adhesion formation and related pathologies [56,57].

Selectins, including P-selectin (CD62P) and E-selectin (CD62E), are a family of cell adhesion molecules primarily expressed on endothelial cells and activated platelets. They mediate the initial interactions between circulating leukocytes and endothelial cells during inflammation and immune responses. Selectins are type I transmembrane glycoproteins consisting of an extracellular lectin domain, an epidermal growth factor-like domain, a variable number of short consensus repeats (SCRs), a transmembrane domain, and a cytoplasmic tail. The extracellular lectin domain binds to specific carbohydrate ligands expressed on leukocytes. P-selectin is stored in secretory granules (Weibel-Palade bodies in endothelial cells and α-granules in platelets) and rapidly translocated to the cell surface upon activation. E-selectin is induced on endothelial cells by inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). Selectins interact with carbohydrate ligands containing sialyl-Lewis X (sLex) or related structures, which are expressed on the surface of leukocytes [58–60].

Low affinity and rapid association/dissociation kinetics characterize this interaction, allowing leukocyte rolling adhesion on the endothelial surface under fluid shear stress conditions. Selectins mediate the initial tethering and rolling of leukocytes on the endothelial surface, facilitating their recruitment to inflammation and tissue injury sites. Rolling adhesion is a dynamic process that precedes firm adhesion and transendothelial migration of leukocytes into the tissue. Selectins are critical in initiating and amplifying inflammatory responses by promoting leukocyte recruitment and extravasation into inflamed tissues. They also contribute to the recruitment of platelets and the

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formation of platelet-leukocyte aggregates at sites of vascular injury. Selectins may be involved in peritoneal adhesion formation by mediating the initial interactions between leukocytes and mesothelial cells lining the peritoneal cavity. Targeting selectin-mediated adhesion pathways could represent a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Selectins are vital regulators of leukocyte-endothelial interactions during inflammation and immune responses, with implications for peritoneal adhesion formation and other inflammatory conditions [61,62].

Immunoglobulin superfamily molecules, including Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1), are cell adhesion molecules expressed on the surface of endothelial cells and immune cells. ICAM-1 and VCAM-1 are transmembrane glycoproteins belonging to the immunoglobulin superfamily. They consist of extracellular immunoglobulin-like domains, a transmembrane domain, and a cytoplasmic tail. The extracellular domains of ICAM-1 and VCAM-1 contain binding sites for their respective ligands on leukocytes.ICAM-1 is constitutively expressed at low levels on the surface of endothelial cells. However, its expression can be upregulated by inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). VCAM-1 expression is induced on endothelial cells in response to inflammatory stimuli, particularly cytokines such as TNF-α and interleukin-4 (IL-4). ICAM-1 interacts with integrins, primarily the β2 integrins (such as LFA-1 Mac-1) expressed on leukocytes. VCAM-1 mainly binds to the integrin α4β1 (also known as VLA-4 or CD49d/CD29) on leukocytes. These interactions are essential for the adhesion and transendothelial migration of leukocytes during inflammation. ICAM-1 and VCAM-1 play crucial roles in the recruitment of leukocytes to sites of inflammation. They facilitate the adhesion of circulating leukocytes to endothelial cells, leading to their extravasation from the bloodstream into inflamed tissues [63]. This process is essential for initiating and propagating immune responses and inflammatory reactions. ICAM-1 and VCAM-1 expression on peritoneal mesothelial and endothelial cells may contribute to peritoneal adhesion formation by promoting leukocyte adhesion and infiltration into the peritoneal cavity. Targeting ICAM-1 and VCAM-1 interaction could represent a potential therapeutic approach for preventing or reducing peritoneal adhesion formation following abdominal surgery or injury. Lastly, ICAM-1 and VCAM-1 are essential mediators of leukocyte adhesion and recruitment during inflammation, which have implications for various inflammatory conditions, including peritoneal adhesion formation [64–67].

Hyaluronan (H.A.), or hyaluronic acid, is a non-sulfated glycosaminoglycan polymer composed of repeating glucuronic acid and N-acetylglucosamine units. It is a central extracellular matrix (ECM) component and is widely distributed throughout connective tissues, including the peritoneum. Hyaluronan is a linear polysaccharide composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine, linked via alternating β-1,3 and β-1,4 glycosidic bonds. It is one of the most significant molecules found in nature, with molecular weights ranging from 10^5 to 10^7 Daltons. Hyaluronan plays diverse roles in tissue homeostasis, including providing structural support to tissues, regulating tissue hydration and water balance, facilitating cell migration and proliferation, and modulating inflammation and wound healing processes. It also serves as a lubricant and shock absorber in joints and contributes to the viscoelastic properties of synovial fluid. Hyaluronan interacts with various cell surface receptors, including CD44 and receptor for hyaluronan-mediated motility (RHAMM), which mediate its diverse biological effects. Through these interactions, hyaluronan can modulate cell adhesion, migration, proliferation, and survival and signal transduction pathways involved in tissue repair and inflammation. Hyaluronan is abundant in the peritoneal ECM and contributes to the lubrication and structural integrity of the peritoneal cavity [68,69]. However, hyaluronan metabolism and turnover alterations have been implicated in peritoneal adhesion formation. Excessive deposition or degradation of hyaluronan may disrupt the balance of ECM remodeling processes and contribute to fibrosis and adhesion formation in the peritoneum. Modulating hyaluronan metabolism and signaling pathways could represent a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches targeting hyaluronan synthesis, degradation, or receptor interactions may help restore ECM homeostasis and

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mitigate adhesion formation following abdominal surgery or injury. Hyaluronan is a multifunctional molecule with essential roles in tissue homeostasis and repair, including its involvement in peritoneal adhesion formation and potential therapeutic implications [70–72].

Fibronectin is a high-molecular-weight glycoprotein in the extracellular matrix (ECM) of connective tissues and blood plasma. It plays crucial roles in cell adhesion, migration, proliferation, and tissue repair. Fibronectin is a multidomain protein composed of repeating structural motifs, including type I, type II, and type III fibronectin repeats. It is soluble in plasma (plasma fibronectin) and insoluble in fibrillar networks in the ECM (cellular fibronectin). Fibronectin molecules contain binding sites for cell surface receptors, such as integrins and ECM components, including collagen, fibrin, and heparan sulfate proteoglycans. Fibronectin mediates cell adhesion by binding to integrin receptors on the cell surface, promoting cell attachment to the ECM and facilitating cell spreading and migration. It also regulates cell signaling pathways involved in cell proliferation, survival, and differentiation [73–75].

Additionally, fibronectin plays a role in wound healing and tissue remodeling by providing a scaffold for cell migration and deposition of ECM components. Fibronectin is a significant component of the peritoneal ECM and contributes to peritoneal adhesion formation following abdominal surgery or injury. Changes in fibronectin expression, organization, and function may alter cell-matrix interactions and promote the formation of fibrous adhesions between peritoneal surfaces. Targeting fibronectin-mediated adhesion pathways could represent a potential therapeutic approach for preventing or reducing peritoneal adhesion formation. Strategies aimed at modulating fibronectin expression, deposition, or receptor interactions may help mitigate peritoneal adhesion formation. These approaches could include using antibodies or small molecules targeting fibronectin receptors and the development of biomaterials designed to promote fibronectin turnover and remodeling in the peritoneal cavity. Fibronectin is an essential ECM protein involved in cell adhesion, migration, and tissue repair processes, with implications for peritoneal adhesion formation and potential therapeutic interventions [76,77].

Matrix Metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases involved in the degradation and remodeling of extracellular matrix (ECM) components. MMPs are crucial in various physiological and pathological processes, including tissue repair, wound healing, inflammation, angiogenesis, and cancer progression. MMPs are structurally characterized by a conserved catalytic domain containing a zinc ion essential for enzymatic activity. They also typically possess additional domains, such as a propeptide domain that regulates enzyme activation, a catalytic domain responsible for substrate cleavage, and hemopexin-like domains involved in substrate recognition and binding. MMPs are classified based on their substrate specificity and domain structure into several subfamilies, including collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs (MT-MMPs), and others. Each MMP subtype exhibits distinct substrate preferences and tissue localization. MMPs are synthesized as inactive zymogens (pro-MMPs) that require proteolytic cleavage of the propeptide domain for activation. Various mechanisms can regulate this activation, including other MMPs, serine proteases, and tissue inhibitors of metalloproteinases (TIMPs). MMPs target various ECM components, including collagen, elastin, gelatin, fibronectin, laminin, and proteoglycans.

By cleaving these substrates, MMPs facilitate tissue remodeling, cell migration, and the release of bioactive ECM fragments that modulate cell behavior and signaling pathways. MMPs are implicated in peritoneal adhesion formation by mediating ECM degradation and remodeling processes. Dysregulated MMP activity, characterized by excessive MMP expression or insufficient inhibition by TIMPs, may disrupt the balance of ECM turnover and contribute to fibrosis, adhesion formation, and tissue dysfunction in the peritoneum. Modulating MMP activity represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches targeting MMP activation, expression, or enzymatic activity could help restore ECM homeostasis and mitigate adhesion formation following abdominal surgery or injury. MMPs are critical regulators of ECM turnover and tissue remodeling processes with essential implications for peritoneal adhesion formation and related pathologies [78–82].

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Fibrinogen is a soluble plasma glycoprotein that plays a central role in the blood clotting cascade. The liver synthesizes and circulates it in the blood at relatively high concentrations. Fibrinogen is cleaved by thrombin during blood clotting to form insoluble fibrin, which polymerizes into a meshwork that stabilizes blood clots. Fibrinogen is a large, multi-subunit protein composed of six polypeptide chains: two sets of three different chains named Aα, Bβ, and γ. These chains are linked by disulfide bonds, forming a symmetrical dimeric structure with a central region called the E domain. Fibrinogen also contains N-terminal fibrinopeptides cleaved by thrombin to initiate fibrin polymerization. Fibrinogen is a critical component of the blood clotting cascade, which is converted into fibrin by the proteolytic action of thrombin. Fibrin monomers then polymerize to form insoluble fibrin strands, which aggregate to create a stable blood clot.

Fibrinogen also interacts with various proteins and cell surface receptors, playing roles in platelet aggregation, wound healing, inflammation, and angiogenesis. Fibrinogen is involved in the initial stages of peritoneal adhesion formation following surgery or injury. Exudation of fibrinogen-rich fluid into the peritoneal cavity leads to the deposition of fibrin matrices on injured peritoneal surfaces [83]. These fibrin matrices serve as scaffolds for the recruitment and adhesion of inflammatory cells and fibroblasts, ultimately contributing to the formation of fibrous peritoneal adhesions. Targeting fibrinogen and its interactions in the peritoneal cavity may represent a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches could include using fibrinolytic agents to promote fibrin degradation, anticoagulants to inhibit fibrin formation or agents that interfere with fibrinogen binding to cell surface receptors involved in adhesion and inflammation. Fibrinogen is a critical mediator of blood clotting and wound healing processes, with implications for peritoneal adhesion formation and a potential drug [84–87].

In the context of peritoneal adhesion formation, the roles of Tissue Plasminogen Activator (tPA) and Plasminogen Activator Inhibitor-1 (PAI-1) are relevant, albeit less studied compared to their roles in other physiological and pathological processes. tPA is involved in the dissolution of fibrin, a key component of blood clots. In the peritoneal cavity, fibrin deposition occurs as part of the wound-healing response following surgery or injury. Increased tPA activity may facilitate the breakdown of fibrin and prevent the accumulation of fibrin-rich adhesions between peritoneal surfaces. Enhancing tPA activity or expression in the peritoneal cavity could represent a therapeutic approach for preventing or reducing peritoneal adhesion formation. Strategies to promote fibrinolysis, such as local delivery of recombinant tPA or tPA-stimulating agents, may help mitigate adhesion formation following abdominal surgery. Inhibiting tPA and urokinase-type plasminogen activator (uPA) effectively, PAI-1 suppresses fibrinolysis and enhances clot stability. Increased fibrinolysis and the survival of fibrin-rich adhesions in the peritoneal cavity may be caused by elevated PAI-1 levels. Targeting PAI-1 activity or expression could be a therapeutic strategy for promoting fibrinolysis and reducing peritoneal adhesion formation. Inhibiting PAI-1 function, either locally or systemically, may enhance fibrinolytic activity and facilitate the resolution of peritoneal adhesions. [88–90] Overall, the balance between tPA-mediated fibrinolysis and PAI-1-mediated inhibition of fibrinolysis will likely influence peritoneal adhesion formation. Modulating these factors could hold promise for developing novel therapeutic interventions aimed at preventing or treating peritoneal adhesions. However, further research is needed to fully elucidate the roles of tPA and PAI-1 in this context and explore their potential as targets for drug design [91,92].

The multifunctional cytokine known as transforming growth factor-beta, or TGF-β, is essential for numerous physiological and pathological processes, including as immune control, tissue repair, apoptosis, cell proliferation, differentiation, and migration. TGF-β belongs to a superfamily of cytokines that have structural similarities. Three isoforms of TGF-β (TGF-β1, TGF-β2, and TGF-β3) exist in mammals, and each is expressed by a different gene. Initially produced as precursor proteins, TGF-β isoforms are cleaved by proteases to produce active TGF-β dimers. Numerous cell types, including fibroblasts, tumour cells, endothelial cells, epithelial cells, and immunological cells (such as T cells and macrophages), produce TGF-β. In order to have biological effects, it must be activated after being secreted as a latent complex [93].

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TGF-β exerts its effects by binding to specific cell surface receptors (TGF-β receptors) and activating intracellular signaling pathways, such as the Smad signaling pathway. TGF-β signaling regulates diverse cellular processes, including cell proliferation, differentiation, migration, extracellular matrix production, and immune responses. TGF-β plays a crucial role in tissue repair and wound healing by promoting the synthesis of extracellular matrix components (e.g., collagen, fibronectin) and modulating the activities of various cell types involved in tissue remodeling. Dysregulated TGF-β signaling can contribute to pathological fibrosis, characterized by excessive extracellular matrix deposition and tissue scarring. TGF-β has been implicated in peritoneal adhesion formation following abdominal surgery or injury. It promotes the activation of fibroblasts and myofibroblasts, producing collagen and other extracellular matrix proteins that contribute to the formation of fibrous adhesions between peritoneal surfaces. TGF-β can modulate inflammatory responses and immune cell functions, which may influence the development and resolution of peritoneal adhesions. Targeting TGF-β signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting TGF-β activity or downstream signaling pathways could help mitigate fibrosis and promote tissue repair in the peritoneal cavity. TGF-β is a crucial mediator of tissue repair, fibrosis, and inflammation with essential implications for peritoneal adhesion formation and potential therapy [94–97].

Vascular Endothelial Growth Factor (VEGF) is an essential angiogenic signaling protein forming new blood vessels from pre-existing vasculature. VEGF is a glycoprotein belonging to the PDGF/VEGF family of growth factors. Multiple isoforms of VEGF exist, resulting from alternative splicing of the VEGF gene. The most common isoforms include VEGF-A, VEGF-B, VEGF-C, and VEGF-D. VEGF-A is the predominant isoform and is often referred to simply as various cell types, including endothelial cells, macrophages, fibroblasts, and tumor cells that produce VEGF VEGF. Multiple factors regulate its expression, including hypoxia, growth factors, cytokines, and oncogenes. VEGF exerts its effects primarily by binding to VEGF receptors (VEGFRs) on endothelial cells, leading to endothelial cell proliferation, migration, and survival. VEGF also promotes vascular permeability, vasodilation, and recruitment of endothelial progenitor cells. These actions are crucial for angiogenesis during embryonic development, wound healing, and pathological conditions such as cancer and ischemic diseases. VEGF has been implicated in peritoneal adhesion formation following surgery or injury. It promotes angiogenesis and neovascularization in the peritoneal tissues, which may contribute to the development and persistence of peritoneal adhesions [98,99].

Additionally, VEGF-mediated vascular permeability and endothelial cell activation may facilitate the recruitment of inflammatory cells and fibroblasts to the injury site, further promoting adhesion formation. Targeting VEGF signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting VEGF activity or blocking its receptors could help mitigate angiogenesis and neovascularization in the peritoneal cavity, thereby reducing the formation of fibrous adhesions between peritoneal surfaces [100–102].

Strong as a mitogen and chemoattractant, platelet-derived growth factor (PDGF) is essential for many physiological and pathological processes, such as cell division, migration, and tissue repair. A and B, two disulfide-bonded polypeptide chains, make up the dimeric protein known as PDGF. These chains can split into one heterodimeric isoform (PDGF-AB) and three homodimeric isoforms (PDGF-AA, PDGF-BB, and PDGF-DD). PDGF isoforms bind to particular cell surface receptors to produce their biological effects. Platelets, macrophages, endothelial cells, smooth muscle cells, fibroblasts, and tumour cells are among the cell types that make PDGF [103].

Various stimuli regulate its expression, including growth factors, cytokines, and mechanical stress. PDGF exerts its effects primarily by binding to and activating PDGF receptors (PDGFRs) on target cells. PDGF-PDGFR interactions trigger intracellular signaling cascades, such as the Ras-MAPK and PI3K-Akt pathways, leading to cell proliferation, migration, and survival. PDGF also stimulates the synthesis of extracellular matrix components, such as collagen and fibronectin, and promotes angiogenesis and tissue remodeling. PDGF has been implicated in peritoneal adhesion formation following surgery or injury. It stimulates the proliferation and migration of fibroblasts and

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myofibroblasts, leading to the deposition of extracellular matrix proteins and the formation of fibrous adhesions between peritoneal surfaces [104].

Additionally, PDGF stimulates angiogenesis, which may contribute to the development and persistence of peritoneal adhesions. Targeting PDGF signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting PDGF activity or blocking its receptors could help mitigate fibrosis, angiogenesis, and tissue remodeling in the peritoneal cavity, thereby reducing the formation of adhesions between peritoneal surfaces [105–107].

Interleukins (I.L.s) are a group of cytokines that regulate immune responses, inflammation, hematopoiesis, and various physiological processes. Here are some details about interleukins. Interleukins are a diverse group of proteins, ranging from small secreted molecules to larger glycoproteins. They are typically produced by immune cells, such as leukocytes, macrophages, and lymphocytes, as well as by other cell types, including endothelial cells and fibroblasts. Interleukins exert their effects by binding to specific cell surface receptors expressed on target cells. Interleukins are numbered sequentially based on their discovery, such as IL-1, IL-2, IL-6, IL-10, etc. [108]

However, the classification system has expanded as more interleukins have been discovered, leading to subgroups and families of interleukins with similar functions or structural features. Interleukins mediate communication between immune cells and regulate immune responses in various ways. They can stimulate or suppress immune cell proliferation, differentiation, and activity, including T cells, B cells, natural killer cells, macrophages, and dendritic cells. Interleukins modulate inflammatory responses, tissue repair, hematopoiesis, and other physiological processes. Several interleukins have been implicated in peritoneal adhesion formation following surgery or injury. Interleukins such as IL-1, IL-6, and IL-8 initiate and amplify inflammatory responses, which contribute to the recruitment of immune cells, fibroblasts, and other cell types to the injury site [109,110].

Additionally, interleukins may influence extracellular matrix remodeling, angiogenesis, and tissue repair processes contributing to adhesion formation. Targeting interleukin signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting specific interleukins or blocking their receptors could help modulate inflammatory responses, immune cell activation, and tissue remodeling processes involved in adhesion formation [111,112].

The family of growth factors known as fibroblast growth factors (FGFs) is essential to many biological processes, such as angiogenesis, migration, differentiation, and cell proliferation. The family of structurally related proteins known as FGFs is distinguished by a high degree of sequence homology and conserved amino acid sequences. There are now 22 FGF family members known to exist in mammals. Usually tiny proteins produced into the body, FGFs have either an autocrine or paracrine effect locally. Numerous cell types, such as fibroblasts, endothelial cells, epithelial cells, and immunological cells, produce FGFs. They are released into the extracellular matrix, where they bind with particular target cell surface receptors to start signalling cascades. Tyrosine kinase receptors called FGF receptors (FGFRs), which are expressed on the surface of target cells, are binded to by FGFs and then activated.. Upon ligand binding, FGFRs undergo dimerization and autophosphorylation, activating downstream signaling pathways, such as the Ras-MAPK and PI3K-Akt pathways. These pathways regulate cellular processes, including cell proliferation, survival, differentiation, and migration. FGFs have been implicated in peritoneal adhesion formation following surgery or injury. They promote the proliferation and migration of fibroblasts, endothelial cells, and other cell types involved in tissue repair and remodeling [113–116].

Additionally, FGFs stimulate angiogenesis, the formation of new blood vessels, which may contribute to the development and persistence of peritoneal adhesions. Targeting FGF signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting FGF activity or blocking its receptors could help mitigate fibrosis, angiogenesis, and tissue remodeling in the peritoneal cavity, thereby reducing the formation of adhesions between peritoneal surfaces [117].

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The innate immune system relies heavily on toll-like receptors (TLRs), a family of pattern recognition receptors (PRRs), to identify conserved molecular patterns linked to infections, or pathogen-associated molecular patterns (PAMPs). Type I transmembrane proteins known as toll-like receptors are defined by three domains: an intracellular Toll/interleukin-1 receptor (TIR) domain that initiates downstream signalling pathways, a transmembrane domain that recognises ligands, and an extracellular domain that contains leucine-rich repeat (LRR) motifs. Numerous cell types, including immune cells like neutrophils, dendritic cells, and macrophages as well as non-immune cells like fibroblasts and epithelial cells, express toll-like receptors. PAMPs originating from bacteria, viruses, fungi, and other microbes are recognised differently by different TLRs. Numerous PAMPs are recognised by toll-like receptors, including as lipoproteins, flagellin, viral nucleic acids (dsRNA, ssRNA), bacterial DNA with unmethylated CpG patterns, and components of fungal cell walls (β-glucans, for example). [118]. Upon ligand binding, Initiating downstream signalling cascades, toll-like receptors dimerize and enlist adaptor proteins with TIR domains, such as MyD88 (myeloid differentiation primary response 88) or TRIF (TIR-domain-containing adapter-inducing interferon-β). Pro-inflammatory cytokines, chemokines, and type I interferons are produced as a result of these pathways' activation of transcription factors, which include NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and IRF (interferon regulatory factor). The inflammatory response that follows surgery or damage and results in the production of peritoneal adhesions has been linked to toll-like receptors [119]. Activation of TLR signaling pathways by endogenous ligands released from damaged tissues or by microbial contamination of the peritoneal cavity can lead to the production of pro-inflammatory cytokines and chemokines, recruitment of immune cells, and activation of fibroblasts, contributing to tissue remodeling and adhesion formation. Targeting Toll-like receptor signaling pathways represents a potential therapeutic strategy for modulating inflammation and tissue repair processes associated with peritoneal adhesion formation. Approaches aimed at inhibiting TLR activation or downstream signaling cascades could help mitigate adhesion formation and promote tissue healing [120–122].

Tenascin-C is an extracellular matrix glycoprotein that plays diverse roles in tissue development, wound healing, inflammation, and remodeling. Tenascin-C is a sizeable oligomeric protein composed of multiple modular domains, including epidermal growth factor (EGF))---like repeats, fibronectin type III (F.N.) repeats, and a fibrinogen-like globe domain. It is known for its unique hexabrachion structure, which consists of six arms extending from a central domain. Various cell types express Tenascin-C during embryonic development and tissue repair processes, including fibroblasts, endothelial cells, immune cells, and cancer cells. Its expression is highly regulated and is induced in response to tissue injury, inflammation, and mechanical stress.

Tenascin-C regulates cell adhesion, migration, proliferation, and differentiation through interactions with cell surface receptors, such as integrins, proteoglycans, and growth factor receptors. It modulates the activity of various signaling pathways involved in cell survival, cytoskeletal dynamics, and gene expression, influencing tissue remodeling and repair processes. Tenascin-C is involved in peritoneal adhesion formation following surgery or injury. It is upregulated in response to tissue damage and inflammation in the peritoneal cavity, contributing to fibrous adhesions between peritoneal surfaces. Tenascin-C promotes the migration and activation of fibroblasts and myofibroblasts, stimulates extracellular matrix deposition, and modulates immune cell functions, thereby promoting adhesion formation and tissue remodeling. Targeting Tenascin-C signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting Tenascin-C expression or blocking its interactions with cell surface receptors could help mitigate fibrosis, inflammation, and tissue remodeling in the peritoneal cavity, thereby reducing the formation of adhesions between peritoneal surfaces [123–127]

Strong mitogen and chemoattractant, platelet-derived growth factor (PDGF) is essential for many biological activities, such as cell division, migration, and tissue healing. A and B, two disulfide-bonded polypeptide chains, make up the dimeric protein known as PDGF. These chains can split into one heterodimeric isoform (PDGF-AB) and three homodimeric isoforms (PDGF-AA, PDGF-BB, and PDGF-DD). PDGF isoforms bind to particular cell surface receptors to produce their biological effects.

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Platelets, macrophages, endothelial cells, smooth muscle cells, fibroblasts, and tumour cells are among the cell types that make PDGF [128,129].

Multiple stimuli regulate its expression, including growth factors, cytokines, and mechanical stress. PDGF exerts its effects by binding to and activating PDGF receptors (PDGFRs) on target cells. PDGF-PDGFR interactions trigger intracellular signaling cascades, such as the Ras-MAPK and PI3K-Akt pathways, leading to cell proliferation, migration, and survival. PDGF also stimulates the synthesis of extracellular matrix components, such as collagen and fibronectin, and promotes angiogenesis and tissue remodeling. PDGF has been implicated in peritoneal adhesion formation following surgery or injury. It stimulates the proliferation and migration of fibroblasts and myofibroblasts, leading to the deposition of extracellular matrix proteins and the formation of fibrous adhesions between peritoneal surfaces [130,131].

Additionally, PDGF stimulates angiogenesis, which may contribute to the development and persistence of peritoneal adhesions. Targeting PDGF signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting PDGF activity or blocking its receptors could help mitigate fibrosis, angiogenesis, and tissue remodeling in the peritoneal cavity, thereby reducing the formation of adhesions between peritoneal surfaces [132].

Vascular Endothelial Growth Factor (VEGF) is a potent angiogenic growth factor that plays a central role in promoting the formation of new blood vessels (angiogenesis) and maintaining vascular integrity. Here are some details about the Vascular Endothelial Growth Factor (VEGF). VEGF is a homodimeric glycoprotein consisting of multiple isoforms, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). Each isoform is generated through alternative splicing of the VEGF gene and exhibits distinct biological activities. Various cell types produce VEGF, including endothelial cells, macrophages, fibroblasts, smooth muscle cells, and tumor cells. Multiple stimuli induce its expression, including hypoxia, growth factors, cytokines, and mechanical stress. VEGF exerts its effects primarily by binding to and activating VEGF receptors (VEGFRs) expressed on the surface of endothelial cells. VEGFR activation triggers intracellular signaling pathways involved in endothelial cell proliferation, migration, survival, and vascular permeability. These processes are essential for angiogenesis, vasculogenesis, and vascular remodeling during development, wound healing, and pathological conditions such as cancer and ischemic diseases. VEGF has been implicated in peritoneal adhesion formation following surgery or injury. It promotes angiogenesis within the peritoneal cavity, forming new blood vessels that supply nutrients and oxygen to the developing adhesions [133–135].

Additionally, VEGF may enhance vascular permeability and inflammatory responses, contributing to tissue edema and fibrosis associated with adhesion formation. Targeting VEGF signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting VEGF expression or blocking its receptors could help mitigate angiogenesis, inflammation, and tissue remodeling in the peritoneal cavity, thereby reducing the formation and severity of adhesions between peritoneal surfaces [136,137].

Tissue Inhibitors of Metalloproteinases (TIMPs) are a family of proteins that play a crucial role in regulating the activity of matrix metalloproteinases (MMPs), a group of enzymes involved in extracellular matrix (ECM) turnover and remodeling. TIMPs are small proteins typically composed of around 200 amino acids. They contain a conserved N-terminal domain responsible for binding to the active site of MMPs, inhibiting their proteolytic activity. TIMPs also possess a C-terminal domain that mediates interactions with other proteins and ECM components. Various cell types, including fibroblasts, endothelial cells, smooth muscle cells, and immune cells, produce TIMPs. Multiple stimuli, including growth factors, cytokines, and mechanical stress, regulate their expression. TIMPs regulate ECM homeostasis by inhibiting the activity of MMPs, which are responsible for degrading ECM components such as collagen, elastin, and proteoglycans. By inhibiting MMPs, TIMPs help maintain the structural integrity of tissues and prevent excessive ECM degradation [138–140].

Additionally, TIMPs have been shown to modulate cell proliferation, migration, and survival through MMP-independent mechanisms. TIMPs have been implicated in peritoneal adhesion

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formation following surgery or injury. Dysregulation of TIMP expression and MMP/TIMP imbalance can disrupt ECM remodeling processes, leading to aberrant tissue repair and fibrosis. Both inadequate and excessive TIMP activity can contribute to pathological conditions associated with peritoneal adhesions, highlighting the importance of maintaining proper MMP/TIMP balance. Modulating TIMP expression or activity represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches to restoring MMP/TIMP balance could help mitigate excessive ECM remodeling, fibrosis, and tissue adhesion in the peritoneal cavity, thereby improving surgical outcomes and patient recovery [141,142].

Fibroblast Growth Factor 2 (FGF2), or essential fibroblast growth factor (bFGF), is a member of the fibroblast growth factor family. It plays diverse roles in various biological processes, including cell proliferation, differentiation, migration, and angiogenesis. GF2 is a small, secreted protein consisting of around 155 amino acids. It contains a conserved core region responsible for binding to fibroblast growth factor receptors (FGFRs) and heparan sulfate proteoglycans (HSPGs) on the cell surface. FGF2 exists in several isoforms generated by alternative splicing, with the most common forms being low molecular weight (LMW) and high molecular weight (HMW) variants. Various cell types, including fibroblasts, endothelial cells, smooth muscle cells, and tumor cells, produce FGF2. Multiple stimuli regulate its expression, including growth factors, cytokines, and mechanical stress.

FGF2 exerts its effects by binding to and activating FGFRs, receptor tyrosine kinases expressed on the surface of target cells. Upon ligand binding, FGFRs undergo dimerization and autophosphorylation, activating downstream signaling pathways, such as the Ras-MAPK and PI3K-Akt pathways. These pathways regulate cellular processes, including cell proliferation, survival, differentiation, and migration. FGF2 also stimulates angiogenesis, forming new blood vessels by promoting endothelial cell proliferation and migration. FGF2 has been implicated in peritoneal adhesion formation following surgery or injury. It promotes the proliferation and migration of fibroblasts, endothelial cells, and other cell types involved in tissue repair and remodeling [143–145].

Additionally, FGF2 stimulates angiogenesis, which may contribute to the development and persistence of peritoneal adhesions. Targeting FGF2 signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting FGF2 activity or blocking its receptors could help mitigate fibrosis, angiogenesis, and tissue remodeling in the peritoneal cavity, thereby reducing the formation of adhesions between peritoneal surfaces. In summary, exploring strategies to modulate FGF2 signaling pathways may hold promise for managing peritoneal adhesions and improving patient outcomes [146,147].

The following genes are implied in the peritoneal adhesion process (Table 2):

#	Gene	Related Protein	Ref
1	Transforming Growth Factor-beta (TGF-β)	TGF-β1, TGF-β2, TGF-β3	[148]
2	Vascular Endothelial Growth Factor (VEGF):	VEGF-A, VEGF-B, VEGF-C, VEGF-D, Placental Growth Factor (PlGF)	[149].
3	Platelet-Derived Growth Factor (PDGF):	PDGF-A, PDGF-B, PDGF-C, PDGF-D	[150].
4	Fibroblast Growth Factor (FGF):	FGF1 (acidic FGF), FGF2 (basic FGF), FGF3, FGF4, FGF5	[151].
5	Tissue Plasminogen Activator (tPA):	Tissue plasminogen activator (tPA)	[152].
6	Plasminogen Activator Inhibitor-1 (PAI-1):	Plasminogen activator inhibitor-1 (PAI-1)	[153].
7	Integrins:	Various alpha and beta subunits forming different integrin receptors	[154].

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8	Cadherins:	E-cadherin (CDH1), N-cadherin (CDH2), P-cadherin (CDH3)	[155].
9	Selectins:	P-selectin, E-selectin	[156].
10	Immunoglobulin superfamily molecules:	Intercellular Adhesion Molecule 1 (ICAM-1), Vascular Cell Adhesion Molecule 1 (VCAM-1)	[157].
11	Hyaluronan (H.A.)	Hyaluronan synthases (HAS), Hyaluronidases (HYAL)	[158]
12	Fibronectin:	Fibronectin	[159].
13	Matrix Metalloproteinases (MMPs):	MMP-1, MMP-2, MMP-3, MMP-9, MMP-13,	[160].
14	Tissue Inhibitors of Metalloproteinases (TIMPs):	TIMP-1, TIMP-2, TIMP-3, TIMP-4	[161].
15	Toll-like Receptors (TLRs):	Various Toll-like receptors (TLR1, TLR2, TLR4,	[162].
16	Tenascin-C:	Tenascin-C	[163].

The transforming Growth Factor-beta (TGF-β) gene is expressed in various cell types within the peritoneum, including mesothelial cells, fibroblasts, and immune cells. Its expression is upregulated following peritoneal injury or surgery, contributing to the pathogenesis of adhesion formation. TGF-β plays a central role in promoting fibrosis by stimulating the synthesis and deposition of extracellular matrix components such as collagen and fibronectin. In the peritoneum, TGF-β induces fibroblast activation and differentiation into myofibroblasts, leading to excessive collagen deposition and tissue fibrosis, characteristic of adhesion formation. TGF-β exerts pro-inflammatory effects by promoting the recruitment and activation of immune cells, such as macrophages and T lymphocytes, in the peritoneal cavity. Inflammation is a critical component of the adhesion formation process, and TGF-β contributes to stimulating angiogenesis, the formation of new blood vessels, in the peritoneal tissues. Angiogenesis is associated with the development and persistence of adhesions, as it facilitates the influx of nutrients, oxygen, and inflammatory cells to the injured site, promoting tissue repair and remodeling. To the inflammatory milieu within the peritoneum following injury or surgery. TGF-β regulates cell migration, proliferation, and survival in the peritoneum, thereby influencing the dynamics of tissue repair and adhesion formation. It promotes the migration of fibroblasts, mesothelial cells, and other cell types involved in tissue remodeling and wound healing processes. Targeting TGF-β signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting TGF-β activity or blocking its receptors could help mitigate fibrosis, inflammation, and angiogenesis in the peritoneal cavity, thereby reducing the formation and severity of adhesions [164–166].

Vascular Endothelial Growth Factor (VEGF) genes are expressed in various cell types within the peritoneum, including mesothelial cells, fibroblasts, and inflammatory cells. Its expression is upregulated following peritoneal injury or surgery, contributing to the pathogenesis of adhesion formation. VEGF is a potent inducer of angiogenesis, promoting the formation of new blood vessels within the peritoneal tissues. Angiogenesis facilitates the influx of nutrients, oxygen, and inflammatory cells to the injured site, promoting tissue repair and remodeling. However, it can also contribute to the development and persistence of adhesions. VEGF can stimulate inflammatory responses in the peritoneum by facilitating the recruitment and activation of immune cells, such as macrophages and neutrophils. Inflammation is a crucial component of adhesion formation, and

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VEGF-mediated inflammatory signaling may exacerbate adhesion formation. VEGF has been implicated in regulating fibrosis in various tissues, including the peritoneum. It can stimulate the production of extracellular matrix components, such as collagen and fibronectin, by fibroblasts and mesothelial cells, leading to tissue fibrosis and adhesion formation. VEGF can regulate the migration, proliferation, and survival of various cell types in the peritoneum, including endothelial cells, fibroblasts, and mesothelial cells. These cellular responses influence the dynamics of tissue repair and adhesion formation in response to injury or surgery. Targeting VEGF signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting VEGF activity or blocking its receptors could help mitigate angiogenesis, inflammation, and fibrosis in the peritoneal cavity, thereby reducing the formation and severity of adhesions [167–169].

The platelet-derived Growth Factor (PDGF) gene is expressed in various cell types within the peritoneum, including mesothelial cells, fibroblasts, and immune cells. Its expression is upregulated in response to tissue injury or surgery, contributing to the pathogenesis of adhesion formation. PDGF is critical in promoting fibroblast activation and proliferation in the peritoneal cavity. It acts as a potent mitogen for fibroblasts, stimulating their proliferation and migration to the site of injury, where they contribute to the formation of fibrous adhesions. PDGF enhances the synthesis and deposition of extracellular matrix components, such as collagen and fibronectin, by activating fibroblasts in the peritoneum. This results in the accumulation of fibrous tissue at the site of injury, leading to adhesion formation, which stimulates angiogenesis and forms new blood vessels in the peritoneal tissues. Angiogenesis facilitates the influx of nutrients, oxygen, and inflammatory cells to the injured site, promoting tissue repair and remodeling, but it also contributes to the development and persistence of adhesions. PDGF can modulate inflammatory responses in the peritoneum by facilitating the recruitment and activation of immune cells, such as macrophages and neutrophils. Inflammation is a vital component of the adhesion formation process, and PDGF may exacerbate this process by enhancing the inflammatory milieu within the peritoneal cavity. Targeting PDGF signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting PDGF activity or blocking its receptors could help mitigate fibrosis, inflammation, and angiogenesis in the peritoneal cavity, thereby reducing the formation and severity of adhesions [170–172].

Fibroblast Growth Factor (FGF) genes are expressed in various cell types within the peritoneum, including mesothelial cells, fibroblasts, and immune cells. Their expression is upregulated in response to tissue injury or surgery, contributing to the pathogenesis of adhesion formation. FGFs are vital in promoting fibroblast activation and proliferation in the peritoneal cavity. They function as strong fibroblast mitogens, promoting fibroblast migration and proliferation to the site of damage, where they aid in the development of fibrous adhesions. By stimulating fibroblasts in the peritoneum, FGFs improve the synthesis and deposition of extracellular matrix constituents like collagen and fibronectin. This results in the accumulation of fibrous tissue at the site of injury, leading to adhesion formation. FGFs stimulate angiogenesis, forming new blood vessels in the peritoneal tissues. Angiogenesis facilitates the influx of nutrients, oxygen, and inflammatory cells to the injured site, promoting tissue repair and remodeling, but it also contributes to the development and persistence of adhesions. FGFs can modulate inflammatory responses in the peritoneum by facilitating the recruitment and activation of immune cells, such as macrophages and neutrophils. Inflammation is a critical component of the adhesion formation process, and FGFs may exacerbate this process by enhancing the inflammatory milieu within the peritoneal cavity. Targeting FGF signaling pathways represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at inhibiting FGF activity or blocking its receptors could help mitigate fibrosis, inflammation, and angiogenesis in the peritoneal cavity, thereby reducing the formation and severity of adhesions [173,174].

The Tissue Plasminogen Activator (tPA) gene, or PLAT, encodes the tissue-type plasminogen activator (tPA) protein. However, specific studies focusing on the role of the PLAT gene in peritoneal adhesions may be limited. LAT gene could be implicated in peritoneal adhesions. The PLAT gene

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may be upregulated or downregulated in response to peritoneal injury or surgery, affecting the tissue-type plasminogen activator (tPA) levels in the peritoneum. Alterations in PLAT gene expression could lead to dysregulation of fibrinolysis, the process responsible for breaking down fibrin clots. Reduced tPA levels due to decreased PLAT gene expression may result in impaired fibrin clot dissolution and increased fibrin accumulation, contributing to adhesion formation. Genetic variants within the PLAT gene or its regulatory regions may influence individual susceptibility to peritoneal adhesions. Polymorphisms affecting PLAT gene expression or tPA activity could modulate the risk of adhesion formation following peritoneal injury. Targeting the PLAT gene or its downstream signaling pathways could represent a potential therapeutic strategy for preventing or reducing peritoneal adhesions. Strategies to restore normal tPA levels or enhance fibrinolysis could help mitigate adhesion formation and promote peritoneal tissue repair [175–178].

The Plasminogen Activator Inhibitor-1 (PAI-1) gene, also known as SERPINE1 (serpin family E member 1), encodes the plasminogen activator inhibitor-1 protein, which is a vital regulator of the fibrinolytic system. The SERPINE1 gene consists of multiple exons and introns that undergo transcription and alternative splicing to generate different plasminogen activator inhibitor-1 (PAI-1) isoforms. Plasminogen activator inhibitor-1 (PAI-1) is a serine protease inhibitor belonging to the serpin superfamily. It inhibits the activity of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), thereby regulating fibrinolysis. PAI-1 plays a crucial role in regulating fibrinolysis by inhibiting the conversion of plasminogen to plasmin, which is responsible for fibrin clot dissolution.

Elevated levels of PAI-1 can lead to impaired fibrinolysis and increased fibrin accumulation, contributing to the development of peritoneal adhesions. The expression of the SERPINE1 gene can be modulated by various factors, including cytokines, growth factors, and hormones, in response to tissue injury, inflammation, or metabolic changes. Dysregulation of PAI-1 expression or activity may predispose individuals to developing peritoneal adhesions. Increased PAI-1 levels can impair fibrinolysis and promote fibrin accumulation, leading to fibrous adhesions following peritoneal injury or surgery. Elevated PAI-1 levels have been associated with various pathological conditions, including thrombosis, cardiovascular disease, and fibrotic disorders. Strategies aimed at modulating PAI-1 activity or expression may have therapeutic potential for preventing or reducing the formation of peritoneal adhesions. Targeting PAI-1 signaling pathways represents a potential therapeutic strategy for mitigating peritoneal adhesion formation. Approaches aimed at inhibiting PAI-1 activity or blocking its interactions with plasminogen activators could help restore fibrinolysis and prevent excessive fibrin accumulation in the peritoneal cavity [179–181].

Integrins are a family of cell surface receptors that mediate cell-cell and cell-extracellular matrix interactions. They comprise α and β subunits and play crucial roles in cellular processes, including cell adhesion, migration, signaling, and differentiation. Integrin genes are located on different chromosomes in humans, with each α or β subunit having its specific genomic location. Integrin genes consist of multiple exons and introns that encode the α and β subunits of the integrin receptors. Integrin receptors are heterodimers composed of α and β subunits containing extracellular, transmembrane, and cytoplasmic domains. Integrins mediate cell adhesion to extracellular matrix proteins such as fibronectin, collagen, and laminin. They also participate in cell signaling pathways that regulate cell proliferation, survival, and migration. Integrins are involved in the attachment of mesothelial cells to the peritoneal extracellular matrix and the migration of fibroblasts and inflammatory cells during the process of adhesion formation. Integrins regulate various cellular behaviors in adhesion formation, including cell adhesion, spreading, migration, and proliferation. Dysregulation of integrin expression or activity may contribute to the pathogenesis of peritoneal adhesions and related disorders. Targeting integrin signaling pathways represents a potential therapeutic strategy for preventing or reducing adhesion formation. Strategies to modulate integrin expression, activation, or function could help mitigate peritoneal adhesion formation and improve clinical outcomes in patients undergoing abdominal surgery or experiencing peritoneal injury [182–184].

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Cadherins are a family of calcium-dependent cell adhesion molecules that mediate cell-cell adhesion and play crucial roles in tissue morphogenesis, cell signaling, and maintenance of tissue integrity. Cadherin genes consist of multiple exons and introns that encode the cadherin proteins. The extracellular domain of cadherins contains calcium-binding sites responsible for cell-cell adhesion. Cadherins are transmembrane proteins with extracellular cadherin repeats responsible for homophilic or heterophilic interactions with cadherins in adjacent cells. Cadherins mediate calcium-dependent cell-cell adhesion and regulate various cellular processes, including cell sorting, tissue morphogenesis, cell migration, and signaling. Cadherins maintain the integrity of mesothelial cell layers lining the peritoneal cavity and mediate cell-cell adhesion between mesothelial cells. Dysregulation of cadherin expression or function may contribute to disrupting mesothelial cell layers and forming peritoneal adhesions. Cadherins regulate cell adhesion, migration, and signaling pathways that influence tissue repair and remodeling processes associated with peritoneal adhesion formation. The altered expression or activity of cadherins has been implicated in various pathological conditions, including cancer metastasis, tissue fibrosis, and developmental disorders. Modulating cadherin expression or function could represent a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation and improving clinical outcomes in patients undergoing abdominal surgery or experiencing peritoneal injury [185–187].

The first tethering and rolling of leukocytes on endothelial cells during inflammation and immunological responses is mediated by the selectins family of cell adhesion molecules. The selectin proteins are encoded by several exons and introns found in selectin genes. The extracellular domain of selectins contains lectin and epidermal growth factor (EGF)-like domains responsible for ligand binding. Selectins are transmembrane glycoproteins with an N-terminal lectin domain, an EGF-like domain, a variable number of short consensus repeats (SCRs), a transmembrane domain, and a cytoplasmic tail. Selectins mediate leukocyte-endothelial cell interactions by binding to carbohydrate ligands expressed on leukocytes and endothelial cells. They are crucial in leukocyte recruitment and trafficking during inflammation, immune responses, and tissue repair. Selectins are involved in the recruitment and adhesion of leukocytes to the peritoneal endothelium during inflammatory responses associated with peritoneal adhesions. They facilitate the initial tethering and rolling of leukocytes on endothelial cells, a critical step in the extravasation of leukocytes into the peritoneal cavity [188].

Regulation of Cell Behavior: Selectins regulate leukocyte adhesion, rolling, and extravasation by interacting with their ligands, such as sialyl Lewis X (sLeX) and P-selectin glycoprotein ligand-1 (PSGL-1), expressed on leukocytes and endothelial cells. Dysregulation of selectin expression or activity has been implicated in various inflammatory and immune-related disorders, including peritoneal adhesions, inflammatory bowel disease, and atherosclerosis. Modulating selectin-ligand interactions or selectin expression could represent a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation and attenuating inflammatory responses in the peritoneal cavity [189,190].

IgSF molecule genes contain multiple exons and introns that encode the IgSF proteins. The extracellular domains of IgSF molecules typically include one or more immunoglobulin-like domains responsible for cell adhesion and protein-protein interactions. IgSF molecules are characterized by immunoglobulin-like domains, which mediate homophilic or heterophilic interactions between cells or between cells and extracellular matrix components. IgSF molecules play crucial roles in cell adhesion, migration, signaling, and immune responses. They mediate cell-cell and cell-matrix interactions by binding to specific ligands or counter-receptors expressed on neighboring cells or the extracellular matrix. IgSF molecules are involved in the regulation of leukocyte trafficking, inflammatory responses, and tissue repair processes associated with peritoneal adhesion formation. They facilitate the adhesion, transmigration, and activation of leukocytes within the peritoneal cavity during inflammatory and immune responses. IgSF molecules regulate various cellular behaviors implicated in peritoneal adhesion formation, including cell adhesion, migration, and activation of immune cells. IgSF molecule expression or activity dysregulation has been involved in various inflammatory and autoimmune diseases, cancer metastasis, and neurodevelopmental disorders.

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Targeting IgSF molecule-mediated cell adhesion and signaling pathways represents a potential therapeutic strategy for modulating inflammatory responses and mitigating peritoneal adhesion formation. Approaches aimed at blocking IgSF molecule-ligand interactions or modulating IgSF molecule expression could help reduce leukocyte recruitment and inflammation in the peritoneum [191–193]

The extracellular matrix of tissues contains the glycosaminoglycan polymer known as hyaluronan (HA), also referred to as hyaluronic acid. In contrast to the majority of other extracellular matrix components, hyaluronan is produced by a class of enzymes known as hyaluronan synthases rather than a single gene. In humans, hyaluronan synthase is encoded by three genes: HAS1, HAS2, and HAS3. The enzymes needed to synthesise hyaluronan are encoded by these genes. Multiple exons and introns make up the hyaluronan synthase genes, which encode the enzymes. These enzymes are essential membrane proteins that polymerize hyaluronan chains by using UDP-glucuronic acid and UDP-N-acetylglucosamine as substrates. Their catalytic domain is oriented towards the cytoplasm. Hyaluronan synthases add glucuronic acid and N-acetylglucosamine units in alternate fashion to the expanding polysaccharide chain, which catalyses the synthesis of hyaluronan. There can be anywhere from a few hundred to several thousand sugar residues in the final hyaluronan polymer. Growth factors, cytokines, and mechanical stimuli are a few of the variables that can control hyaluronan synthases' expression and activity. It has been noted that hyaluronan synthesis is upregulated in response to wound healing, inflammation, and tissue damage. [194].

Hyaluronan is a significant component of the extracellular matrix in the peritoneum and plays a role in tissue repair and remodeling processes associated with peritoneal adhesion formation. Increased hyaluronan synthesis may contribute to the accumulation of hyaluronan-rich matrix at sites of peritoneal injury or inflammation. Hyaluronan synthesis or turnover dysregulation has been implicated in various pathological conditions, including fibrosis, cancer, and inflammatory diseases. Modulating hyaluronan synthesis or degradation represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches aimed at targeting hyaluronan synthases or hyaluronidases could help modulate hyaluronan levels in the peritoneum and mitigate adhesion formation [195,196].

Fibronectin is a high molecular weight glycoprotein found in the extracellular matrix of connective tissues. In humans, the gene encoding fibronectin is called FN1. The FN1 gene consists of multiple exons and introns that encode the fibronectin protein. Alternative splicing of the FN1 pre-mRNA generates different isoforms of fibronectin with distinct functional properties. Fibronectin is a modular protein composed of repeating structural domains, including type I, type II, and type III fibronectin domains, as well as cell-binding domains and other functional domains. These domains mediate fibronectin's interactions with different extracellular matrix molecules, cell surface receptors, and soluble factors. Fibronectin plays crucial roles in cell adhesion, migration, proliferation, differentiation, and tissue repair. It acts as a scaffold protein that helps organize the extracellular matrix and facilitates cell-cell and cell-matrix interactions. Fibronectin is abundant in the extracellular matrix of the peritoneum and is involved in tissue repair and remodeling processes associated with peritoneal adhesion formation. Increased fibronectin expression or deposition may contribute to the accumulation of fibronectin-rich matrix at sites of peritoneal injury or inflammation. Various factors, including growth factors, cytokines, mechanical stimuli, and extracellular matrix components, can regulate the expression of the FN1 gene. Upregulation of fibronectin expression has been observed in response to tissue injury, inflammation, and wound healing. Dysregulation of fibronectin expression or function has been implicated in various pathological conditions, including fibrosis, cancer, and cardiovascular diseases. Modulating fibronectin expression or activity represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches targeting fibronectin synthesis, deposition, or interactions with cell surface receptors could help modulate the peritoneal extracellular matrix and mitigate adhesion formation [197–199].

By breaking down different components of the extracellular matrix (ECM), the zinc-dependent endopeptidases known as matrix metalloproteinases (MMPs) are essential for remodelling the ECM.

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MMPs are encoded by a set of genes in humans. Human MMP genes are distributed across several chromosomes, with a distinct chromosomal position for every MMP subtype. The MMP proteins are encoded by the many exons and introns that make up MMP genes. Mutations in splicing patterns and post-translational modifications can produce variants of MMPs, each possessing unique enzymatic properties and substrate preferences.

Proteolytic cleavage of the prodomain activates MMPs, which are synthesised as zymogens (pro-MMPs). In addition to other domains involved in substrate binding and regulation, the active forms of MMPs have catalytic domains that are in charge of breaking down ECM. By breaking down different components of the extracellular matrix (ECM), such as collagen, glycoproteins, and proteoglycans, MMPs play important roles in tissue remodelling, wound healing, inflammation, angiogenesis, and cancer progression. During tissue repair processes linked to the production of peritoneal adhesions, MMPs play a role in remodelling the peritoneal extracellular matrix. Excessive ECM degradation or deposition can result in aberrant tissue remodelling and adhesion creation. One possible cause of this is dysregulation of MMP expression or activity. Tissue inhibitors of metalloproteinases (TIMPs), growth hormones, cytokines, mechanical stimuli, and other variables can all control the production and activity of MMPs. Multiple illnesses, including cancer and fibrosis, have been linked to the imbalance between MMPs and TIMPs. Metastasis of cancer and other pathological illnesses like fibrosis, arthritis, and cardiovascular diseases have all been linked to dysregulated expression or activity of MMPs. One possible therapeutic approach to prevent or lessen the formation of peritoneal adhesions is to modify MMP expression or activity. Targeting MMP activity or control could be one way to influence adhesion formation and ECM remodelling. [200–202].

Endogenous inhibitors known as tissue inhibitors of metalloproteinases (TIMPs) control the activity of MMPs and other metalloproteinases. Four identified TIMP genes in humans encode proteins that regulate MMP activity and uphold the equilibrium between ECM synthesis and breakdown. In humans, TIMP genes are distributed over several chromosomes, with a distinct chromosomal position assigned to each TIMP subtype. The TIMP proteins are encoded by the many exons and introns that make up TIMP genes. These proteins bind to the active site of MMPs and stop their enzymatic activity because of a conserved cysteine-rich domain. TIMPs are tiny glycoproteins with a 1:1 stoichiometric ratio of reversible binding to the catalytic domain of MMPs. This binding controls ECM turnover and stops MMPs from destroying ECM components. By regulating MMP activity and preserving the equilibrium between ECM production and degradation, TIMPs are essential for tissue remodelling, wound healing, inflammation, and the advancement of cancer. TIMPs play a role in controlling the ECM remodelling processes that lead to the formation of peritoneal adhesions. The imbalance between TIMPs and MMPs may disrupt ECM homeostasis and contribute to abnormal tissue remodeling and adhesion formation. Various factors, including growth factors, cytokines, mechanical stimuli, and ECM components, can regulate the expression and activity of TIMPs. Alterations in TIMP expression or activity have been implicated in the pathogenesis of various diseases, including fibrosis and cancer. Dysregulated expression or activity of TIMPs has been associated with pathological conditions, such as fibrosis, arthritis, cardiovascular diseases, and cancer metastasis. Modulating TIMP expression or activity represents a potential therapeutic strategy for preventing or reducing peritoneal adhesion formation. Approaches to restoring the balance between TIMPs and MMPs could help regulate ECM remodeling and favor peritoneal adhesion [203–205].

By identifying common chemical patterns linked to infections, the family of pattern recognition receptors (PRRs) known as toll-like receptors (TLRs) plays a vital function in the innate immune system. TLRs in humans are encoded by a collection of genes. There are distinct chromosomes on which TLR genes are found, and each subtype of TLR has a unique genomic location. The TLR proteins are encoded by various exons and introns found in TLR genes. Type I transmembrane proteins called TLRs are distinguished by cytoplasmic Toll/IL-1 receptor (TIR) domains that are involved in signalling and extracellular leucine-rich repeat (LRR) domains that are involved in ligand recognition. TLRs are membrane-bound receptors that have two domains: an intracellular one for

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signal transduction and an extracellular one for ligand recognition. The receptor undergoes conformational changes upon ligand binding, which activates downstream signalling pathways. TLRs are able to identify many components of microorganisms, including as lipopolysaccharides, lipoproteins, nucleic acids, and proteins that come from parasites, bacteria, viruses, and fungus. Upon ligand interaction, TLRs start signalling cascades that activate antimicrobial defence systems and inflammatory responses. TLRs identify endogenous danger signals emitted during peritoneal inflammation or tissue damage, as well as microbiological infections.. The start and regulation of inflammatory reactions linked to the creation of peritoneal adhesions are facilitated by the activation of TLR signalling pathways. Cellular stress, cytokines, and microbial products are a few of the variables that can control TLR expression and function. Numerous inflammatory and autoimmune disorders have been linked to TLR signalling dysregulation as an aetiology. Aberrant TLR activation or signaling has been associated with pathological conditions, such as sepsis, inflammatory bowel disease, rheumatoid arthritis, and cancer. Modulating TLR activation or signaling represents a potential therapeutic strategy for regulating inflammatory responses and mitigating peritoneal adhesion formation. Approaches aimed at targeting TLR expression, ligand binding, or downstream signaling pathways could help modulate the peritoneum's immune response and tissue repair processes [206–208].

Tenascin-C is an extracellular matrix glycoprotein involved in various physiological and pathological processes, including tissue development, wound healing, inflammation, and cancer progression. In humans, the gene encoding tenascin-C is called TNC. The TNC gene is located on chromosome 9q33.1 in humans. The TNC gene contains multiple exons and introns that encode the tenascin-C protein. Alternative splicing of the TNC pre-mRNA generates different isoforms of tenascin-C with distinct domain structures and functional properties. Tenascin-C is a large oligomeric glycoprotein composed of multiple distinct structural domains, including epidermal growth factor (EGF)-like repeats, fibronectin type III (FN) repeats, and a fibrinogen-like globe domain. These domains mediate interactions with extracellular matrix components, cell surface receptors, and signaling molecules. Tenascin-C regulates cell adhesion, migration, proliferation, and differentiation by interacting with cell surface receptors, such as integrins and proteoglycans, and modulating signaling pathways involved in cell behavior. It also serves as a scaffold protein that influences the organization and biomechanical properties of the extracellular matrix. Tenascin-C is expressed at sites of tissue injury, inflammation, and fibrosis in the peritoneum and contributes to the formation of adhesion tissues by promoting cell migration, matrix remodeling, and fibrogenesis. Increased expression of tenascin-C has been observed in peritoneal adhesions and is associated with tissue fibrosis and impaired wound healing. Various factors, including growth factors, cytokines, mechanical stimuli, and tissue injury, can regulate the expression of the TNC gene. Increased expression of tenascin-C has been linked to the development of a number of illnesses, such as inflammatory conditions, cancer, and cardiovascular diseases. Pathological disorders include cancer metastasis, autoimmune illnesses, tissue fibrosis, and chronic inflammation have all been linked to dysregulated expression or function of tenascin-C. One possible treatment approach for avoiding or decreasing the production of peritoneal adhesions is to modify the expression or activity of tenascin-C. Strategies that target the tenascin-C signalling pathways or engage with cell surface receptors may be able to regulate the processes involved in tissue repair and adhesion creation. [209–211].

There may have been several novel developments in the field of peritoneal adhesions. Some potential areas of advancement are listed in the table below (Table 3).

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#	*Development*	*Description*	*Ref*
1	Genetic Studies	Continued research into the genetic determinants of peritoneal adhesions, including identification of novel genetic risk factors and pathways involved in adhesion formation.	[212]
2	Biomarkers	Discovery and validation of biomarkers associated with peritoneal adhesions for early diagnosis, prognosis, and adhesion development and recurrence monitoring.	[213]
3	Therapeutic Targets:	The development of targeted medicines and interventions for adhesion prevention and therapy has resulted from the identification of novel molecular targets and signalling pathways implicated in peritoneal adhesions.	[214]
4	Regenerative Medicine	Advancements in regenerative medicine approach, including stem cell therapy, tissue engineering, and biocompatible scaffolds, are being made to promote tissue repair and reduce adhesion formation following surgery or injury.	[215]
5	Minimally Invasive Techniques	Innovation in surgical techniques and devices aimed at minimizing tissue trauma, inflammation, and adhesion formation during abdominal and pelvic surgeries, such as laparoscopy and robotic-assisted surgery.	[216]
6	Drug Delivery Systems	Development of localized drug delivery systems and formulations, including hydrogels, nanoparticles, and coatings, for delivering anti-adhesive agents or therapeutic drugs directly to the site of adhesion formation.	[217]
7	Imaging Modalities:	Improvements in the visualisation and characterization of peritoneal adhesions have been made possible by technological advancements such as magnetic resonance imaging (MRI) and ultrasound, enabling early diagnosis and precise adhesion severity evaluation.	[218]
8	Clinical Guidelines	Establish evidence-based clinical guidelines and protocols for managing peritoneal adhesions, including standardized approaches to adhesion prevention, surgical techniques, and postoperative care.	[219]
9	Patient Education and Awareness	Increased awareness and education initiatives aimed at patients, healthcare providers, and policymakers regarding the risks, complications, and preventive measures associated with peritoneal adhesions.	[220]
10	Multidisciplinary Collaboration	Promotion of interdisciplinary collaboration among surgeons, researchers, engineers, and industry partners to address the complex challenges of peritoneal adhesions through integrated research, innovation, and clinical practice.	[221]

Regarding the genetic studies on peritoneal adhesions, some significant studies are listed in the table below(These studies contribute to our understanding of the genetic basis of peritoneal adhesions, shedding light on potential mechanisms involved in adhesion formation and suggesting avenues for further research and therapeutic development.(Table 4)

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#	Study	Ref
1	Genetic Polymorphisms Associated with Adhesion Formation	[222]
2	Gene Expression Profiling in Adhesion Formation	[223]
3	Association Studies of Candidate Genes	[224]
4	Genome-wide Association Studies (GWAS) in Peritoneal Adhesions	[225]
5	Functional Genomics Studies	[226]
6	Epigenetic Regulation of Genes Involved in Adhesion Formation	[227]
7	Association of Inflammatory Genes with Adhesion Formation	[228]
8	The Function of Growth Factors and Their Receptors in the Formation of Adhesion	[229]
9	Genetic Variation in Extracellular Matrix Proteins and Adhesion Formation	[230]
10	Epigenetic Modifications and Adhesion Formation	[231]
11	Impact of miRNA Dysregulation on Adhesion Formation	[232]
12	Role of Cytokine Signaling Pathways in Adhesion Formation	[233]
13	Identification of Novel Genetic Risk Loci for Adhesion Formation	[234]
14	MicroRNA (miRNA) Profiling in Adhesion Formation	[235]
15	Genetic Variation in Cell Adhesion Molecules and Adhesion Formation	[236]
16	Gene Expression Profiling in Peritoneal Tissue	[237]
17	Impact of Genetic Polymorphisms on Inflammatory Signaling Pathways	[238]
18	Genetic Susceptibility to Oxidative Stress and Adhesion Formation	[239]
19	Association of Epigenetic Changes with Adhesion Formation	[240]
20	Functional Genomics Studies in Adhesion Formation	[241]

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In a study regarding the genetic polymorphisms associated with adhesion formation(#1-Table 4), researchers analyzed genetic data from individuals with and without peritoneal adhesions to identify differences in genetic polymorphisms. Statistical analyses were used to assess the significance of these associations. The study sought to understand the genetic basis of adhesion formation and identify potential genetic markers for susceptibility to adhesions. Identifying genetic polymorphisms associated with adhesion formation could have significant clinical implications. It could enable healthcare providers to identify individuals at higher risk of developing adhesions and implement preventive measures or surveillance strategies accordingly. Moreover, targeting specific genetic pathways involved in adhesion formation could lead to developing novel therapeutic interventions to reduce adhesion-related complications following surgery or injury.

A study on gene expression profiling in adhesion formation(#2-Table 4) aimed to investigate changes in gene expression patterns associated with forming peritoneal adhesions. Peritoneal adhesions are abnormal tissue connections that can develop after surgery or injury. Gene expression profiling involves simultaneously analyzing the activity levels of thousands of genes to identify which genes are upregulated or downregulated during adhesion formation. Researchers likely collected peritoneal tissue samples from individuals with and without adhesions and different stages of adhesion formation. They then used techniques such as microarrays or RNA sequencing to quantify the expression levels of thousands of genes in these tissue samples. By comparing gene expression patterns between normal and adhesion-prone tissues, researchers aimed to identify genes that are differentially expressed in association with adhesion formation. The objective of the research was to determine possible treatment targets and clarify the molecular mechanisms driving adhesion development.. By identifying dysregulated genes during adhesion formation, researchers aimed to uncover vital biological pathways involved in this process, which could lead to targeted therapies for preventing or treating adhesions. Understanding the gene expression changes associated with adhesion formation could provide insights into the pathogenesis of this condition and identify novel therapeutic targets. By targeting specific genes or signaling pathways implicated in adhesion formation, researchers may be able to develop more effective strategies for preventing or treating adhesions, ultimately improving patient outcomes following surgery or injury.

The Association Studies of Candidate Genes (#3-Table 4) aimed to investigate the association between specific candidate genes and the risk of developing peritoneal adhesions. Candidate genes are selected based on their known or hypothesized roles in biological processes relevant to adhesion formation, such as inflammation, tissue repair, or cell adhesion. By analyzing genetic variations within these candidate genes, researchers sought to identify genetic markers or polymorphisms that may predispose individuals to developing adhesions. Researchers likely selected candidate genes based on prior knowledge of their involvement in processes related to adhesion formation. They then collected genetic data from individuals with and without peritoneal adhesions and clinical information about adhesion status. Genetic variations within candidate genes were analyzed using techniques such as genotyping or sequencing. Statistical analyses assessed the association between specific genetic variants and adhesion susceptibility. The study aimed to identify genetic markers or polymorphisms associated with an increased risk of developing peritoneal adhesions. By elucidating the genetic factors underlying adhesion formation, researchers aimed to improve our understanding of the pathogenesis of this condition and identify potential targets for preventive or therapeutic interventions. Identifying genetic associations with peritoneal adhesions could have significant clinical implications. It could enable healthcare providers to identify individuals at higher risk of developing adhesions and implement preventive measures or surveillance strategies accordingly. Moreover, understanding the genetic basis of adhesion formation could lead to the development of personalized treatment approaches tailored to an individual's genetic profile.

The study on Genome-wide Association Studies (GWAS) in Peritoneal Adhesions (#4 -Table 4) aimed to systematically investigate the genetic basis of peritoneal adhesions using genome-wide association studies (GWAS). GWAS is a powerful approach that allows researchers to examine genetic variations across the entire genome and identify common genetic variants associated with a particular trait or disease. By analyzing genetic data from a large cohort of individuals with and

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without peritoneal adhesions, researchers sought to identify novel genetic loci and pathways associated with adhesion formation susceptibility. Researchers likely collected genetic data from a well-characterized cohort of individuals with peritoneal adhesions and from control individuals without adhesions. Genetic variations across the genome were analyzed using high-throughput genotyping or sequencing technologies. Statistical analyses, such as logistic regression or chi-square tests, were used to identify genetic variants significantly associated with adhesion susceptibility. Genome-wide significance thresholds were applied to account for multiple comparisons. The study's main objective was to identify novel genetic loci and pathways related to the risk of developing peritoneal adhesions. By uncovering new genetic associations, researchers aimed to improve our understanding of the biological mechanisms underlying adhesion formation and identify potential targets for preventive or therapeutic interventions. GWAS in peritoneal adhesions could provide valuable insights into the genetic determinants of this condition and lead to the identification of novel therapeutic targets. Understanding the genetic basis of adhesion formation could pave the way for developing personalized treatment approaches and improving patient outcomes following surgery or injury.

The goal of functional genomics research (#5-Table 4) on peritoneal adhesions is to clarify how gene expression and signalling pathways are dynamically regulated during adhesion formation and resolution. Functional genomics studies how genes interact and operate within cellular pathways to drive biological processes, in contrast to standard genomics approaches that just look for genetic differences. These investigations shed light on the molecular processes that underlie the development of adhesions and could suggest new therapeutic targets for action. Transcriptomics, proteomics, metabolomics, and epigenomics are a few of the experimental methods used in functional genomics research to investigate the function of genes. Whereas proteomics is concerned with the identification and measurement of proteins, transcriptomics examines the expression levels of every gene present in a cell or tissue. While epigenomics analyses variations in gene expression that are not brought about by changes in the underlying DNA sequence, metabolomics investigates the small molecules called metabolites that are found in cells or tissues. These methods are frequently used in conjunction with computer analysis to decipher intricate datasets and pinpoint vital biological processes. Understanding the molecular mechanisms behind adhesion formation and identifying new treatment targets are the main goals of functional genomics investigations in peritoneal adhesions. Through analysing alterations in gene expression, protein concentration, and metabolic patterns linked to adhesion formation, scientists seek to identify crucial regulatory routes and molecular targets for potential intervention. Studies utilising functional genomics offer significant understanding of the molecular processes underlying the creation of peritoneal adhesions, illuminating the intricate interactions among genes, proteins, and signalling pathways. Researchers may find novel therapeutic targets for peritoneal adhesion prevention or treatment by discovering particular genes or pathways that are dysregulated in adhesion-prone tissues, ultimately improving patient outcomes. Studies using functional genomics are essential for expanding our knowledge of the molecular processes underlying peritoneal adhesions and provide encouraging avenues for the creation of tailored pharmaceuticals.

Changes in gene expression that result from modifications to DNA or related proteins rather than from changes in the DNA sequence itself are referred to as epigenetic regulation (#6-Table 4). Histone modifications, DNA methylation, and non-coding RNA regulation are examples of epigenetic mechanisms that are important for controlling gene expression and are involved in a number of biological processes, including the creation of adhesions. The pathophysiology of peritoneal adhesions can be aided by abnormal gene expression patterns caused by epigenetic dysregulation. The field of adhesion formation epigenetic studies employs several approaches, including RNA sequencing to profile non-coding RNA expression, chromatin immunoprecipitation (ChIP) tests to assess histone modifications, and bisulfite sequencing to analyse DNA methylation patterns. Using these methods, scientists can find epigenetic alterations linked to adhesion susceptibility and explore how epigenetic modifications affect the expression of genes involved in adhesion formation. Understanding how epigenetic mechanisms control the expression of genes

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involved in the pathophysiology of peritoneal adhesions is the primary goal of epigenetic studies in adhesion development. Researchers hope to find new therapeutic targets for adhesion prevention or treatment by identifying certain epigenetic alterations linked to adhesion development. They also hope to develop epigenetic-based therapies to modulate gene expression.. Epigenetic dysregulation has emerged as a significant contributing factor to developing peritoneal adhesions. Understanding the epigenetic mechanisms underlying adhesion formation can provide insights into this condition's molecular basis and identify new intervention opportunities. Targeting epigenetic modifications associated with adhesion formation may offer promising strategies for developing novel therapeutic approaches to prevent or treat peritoneal adhesions. Epigenetic studies play a crucial role in elucidating the molecular mechanisms underlying peritoneal adhesions.

Association of Inflammatory Genes with Adhesion Formation (#7-Table 4) This study investigates the association between genes involved in inflammation and the formation of peritoneal adhesions. Inflammation plays a crucial role in the pathogenesis of adhesions, as it promotes tissue injury, fibrosis, and the recruitment of immune cells to the site of injury. Genes encoding pro-inflammatory cytokines, chemokines, and other inflammatory mediators may influence the inflammatory response and contribute to adhesion formation. Researchers likely analyzed genetic variations within inflammatory genes in individuals with and without peritoneal adhesions. Genetic variants such as single nucleotide polymorphisms (SNPs) or copy number variations (CNVs) may affect the expression or function of inflammatory genes, thereby influencing an individual's susceptibility to adhesion formation. Genetic data were collected using techniques such as genotyping or sequencing, and statistical analyses were used to assess the association between specific genetic variants and adhesion susceptibility. The main objective of this study was to elucidate the role of inflammatory genes in the pathogenesis of peritoneal adhesions. By identifying genetic variants associated with adhesion formation, researchers aimed to uncover critical inflammatory pathways and potential therapeutic targets for intervention. Understanding the genetic basis of inflammation in adhesion formation could lead to the development of targeted anti-inflammatory therapies to prevent or reduce adhesion formation. Identifying the association between inflammatory genes and adhesion formation is crucial for understanding the underlying mechanisms of this condition. Inflammatory pathways represent promising targets for therapeutic intervention, as anti-inflammatory agents may help mitigate the inflammatory response and prevent excessive tissue fibrosis and adhesion formation. Moreover, genetic markers associated with adhesion susceptibility could be used to identify individuals at higher risk of developing adhesions and implement personalized preventive strategies. This study contributes to our understanding of the role of inflammation in peritoneal adhesion formation and highlights the potential of targeting inflammatory pathways for the prevention and treatment of adhesions.

Growth Factors' and Their Receptors' Function in the Formation of Adhesion (#8-Table 4) In this work, the pathophysiology of peritoneal adhesions is examined in relation to growth factors and their receptors. Growth factors are signalling molecules that control migration, differentiation, and proliferation of cells, among other biological activities. Adhesion development can result from aberrant tissue healing and fibrosis caused by dysregulation of growth factor signalling pathways. Growth factor receptors are essential for mediating physiological responses because they transduce the signals that growth factors generate, such as receptor tyrosine kinases. Researchers most likely looked at the receptors, activation state, and expression levels of growth factors in peritoneal tissues taken from people with and without adhesions. Growth factors and their receptors' protein expression or phosphorylation levels may have been evaluated using methods like immunohistochemistry, Western blotting, or quantitative PCR. Furthermore, it's possible that functional tests were carried out to assess how growth factor signalling affects cellular functions that are important for adhesion creation, like cell division, migration, and extracellular matrix synthesis. Clarifying the function of growth factors and their receptors in mediating the pathophysiology of peritoneal adhesions was the primary goal of this investigation. By investigating the expression and activity of growth factor signaling pathways, researchers aimed to identify potential therapeutic targets for intervention. Understanding how dysregulated growth factor signaling contributes to

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adhesion formation could lead to the development of targeted therapies aimed at modulating growth factor activity and mitigating adhesion formation. Growth factors and their receptors represent promising targets for therapeutic intervention in peritoneal adhesions. Modulating growth factor signaling pathways may help regulate cellular processes involved in tissue repair and fibrosis, thereby reducing adhesion formation. Targeted inhibition of specific growth factor receptors or downstream signaling molecules could offer novel therapeutic strategies for preventing or treating adhesions, ultimately improving patient outcomes following surgery or injury. This study contributes to our understanding of the molecular mechanisms underlying peritoneal adhesion formation and highlights the potential of targeting growth factor signaling pathways for therapeutic intervention.

Genetic Variation in Extracellular Matrix Proteins and Adhesion Formation (#9-Table 4) This study investigates the role of genetic variation in extracellular matrix (ECM) proteins in the pathogenesis of peritoneal adhesions. The ECM is a complex network of proteins and carbohydrates that provides structural support to tissues and regulates cellular behavior. Dysregulation of ECM composition or remodeling can lead to abnormal tissue repair and fibrosis, contributing to the formation of adhesions. Genetic variations in genes encoding ECM proteins may influence ECM structure, function, and turnover, affecting an individual's susceptibility to adhesion formation. Researchers likely examined genetic variations within genes encoding ECM proteins in individuals with and without peritoneal adhesions. Genetic variants such as single nucleotide polymorphisms (SNPs) or copy number variations (CNVs) may affect ECM proteins' expression, structure, or function, potentially influencing adhesion formation. Genetic data were collected using techniques such as genotyping or sequencing, and statistical analyses were used to assess the association between specific genetic variants and adhesion susceptibility. The main objective of this study was to elucidate how genetic variation in ECM proteins contributes to the pathogenesis of peritoneal adhesions. By identifying genetic variants associated with adhesion formation, researchers aimed to uncover vital molecular mechanisms and potential therapeutic targets for intervention. Understanding how genetic variation influences ECM composition and remodeling could lead to the development of personalized treatment approaches for preventing or treating adhesions. Genetic variation in ECM proteins represents an essential determinant of adhesion formation susceptibility. ECM proteins play crucial roles in tissue repair, inflammation, and cell adhesion, and genetic variants affecting ECM function may contribute to abnormal tissue remodeling and fibrosis associated with adhesion formation. Targeting specific ECM proteins or pathways affected by genetic variation could offer novel therapeutic strategies for preventing or treating peritoneal adhesions, ultimately improving patient outcomes following surgery or injury. This study contributes to our understanding of the genetic determinants of peritoneal adhesion formation and highlights the potential of targeting ECM proteins.

Epigenetic Modifications and Adhesion Formation (#10-Table 4) This study investigates the role of epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA expression, in the pathogenesis of peritoneal adhesions. Epigenetic modifications can regulate gene expression patterns without altering the underlying DNA sequence and play a crucial role in controlling cellular processes relevant to adhesion formation, such as inflammation, tissue repair, and cell adhesion. Dysregulation of epigenetic mechanisms may contribute to aberrant gene expression and abnormal tissue remodeling associated with adhesion formation. Researchers likely analyzed epigenetic modifications in peritoneal tissues obtained from individuals with and without adhesions. Techniques such as bisulfite sequencing, chromatin immunoprecipitation sequencing (ChIP-seq), and RNA sequencing may have been used to profile DNA methylation patterns, histone modification profiles, and non-coding RNA expression levels, respectively. Computational analyses were then employed to identify differentially methylated regions, histone modification patterns, and dysregulated non-coding RNAs associated with adhesion formation. The main objective of this study was to elucidate how epigenetic modifications contribute to the pathogenesis of peritoneal adhesions. By investigating the epigenetic landscape of adhesion-prone tissues, researchers aimed to identify fundamental regulatory mechanisms and potential therapeutic targets for intervention.

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Understanding how epigenetic modifications influence gene expression and cellular processes in adhesion formation could lead to the development of targeted epigenetic therapies for preventing or treating adhesions. Epigenetic modifications represent promising targets for therapeutic intervention in peritoneal adhesions. Modulating epigenetic mechanisms may help regulate gene expression patterns and cellular processes involved in tissue repair, inflammation, and fibrosis, thereby reducing adhesion formation. Targeted manipulation of specific epigenetic regulators or pathways could offer novel therapeutic strategies for preventing or treating adhesions, ultimately improving patient outcomes following surgery or injury.

Adhesion Formation Affected by miRNA Dysregulation (#11-Table 4) The pathophysiology of peritoneal adhesions is examined in this work in relation to the dysregulation of microRNAs (miRNAs). Small, non-coding RNA molecules known as miRNAs are crucial for the control of post-transcriptional gene expression. They bind to target mRNAs' 3' untranslated regions (UTRs), which causes translational suppression or mRNA destruction. A number of disease processes, including inflammation, fibrosis, and tissue remodeling—basic mechanisms underpinning adhesion formation—have been linked to dysregulation of miRNA expression. MiRNA expression profiles in peritoneal tissues from people with and without adhesions were probably examined by researchers. MiRNA expression levels may have been measured via RNA sequencing or microarray analysis. After that, computational research was used to find miRNAs that were differently expressed and connected to adhesion development. The regulatory effects of dysregulated miRNAs on target genes involved in adhesion formation may have been verified by functional assays, such as luciferase reporter assays or gain- and loss-of-function studies. This study's primary goal was to clarify the role that miRNA dysregulation plays in the pathophysiology of peritoneal adhesions. In order to identify important regulatory mechanisms and possible therapeutic targets for intervention, researchers identified dysregulated miRNAs and their target genes. MiRNA-based therapeutics for adhesion prevention or treatment may be developed as a result of a better understanding of the effects of miRNA dysregulation on gene expression and cellular processes in adhesion formation. One interesting target for therapeutic intervention in peritoneal adhesions is miRNA dysregulation. Dysregulated miRNA expression may be a factor in abnormal tissue remodelling linked to adhesion formation. miRNAs are essential in controlling gene expression networks involved in inflammation, fibrosis, and tissue repair. By focusing on dysregulated miRNAs or the genes that downstream of these miRNAs may be able to develop new therapeutic approaches to treat or prevent adhesions, which would eventually improve patient outcomes after injury or surgery.

The Function of Cytokine Signalling Routes in the Formation of Adhesion (#12-Table 4) This study looks into how cytokine signalling pathways contribute to the development of peritoneal adhesions. Small signalling proteins called cytokines control inflammation, tissue healing, and immunological responses. Fundamental mechanisms driving adhesion creation, such as fibrosis, abnormal tissue remodelling, and chronic inflammation, can be attributed to dysregulation of cytokine signalling pathways.. Cytokines such as transforming growth factor-beta (TGF-β), interleukins (ILs), and tumor necrosis factor-alpha (TNF-α) have been implicated in promoting adhesion formation by stimulating fibroblast activation, extracellular matrix deposition, and immune cell recruitment. Researchers likely analyzed cytokine expression levels and signaling pathway activation in peritoneal tissues obtained from individuals with and without adhesions. Techniques such as enzyme-linked immunosorbent assays (ELISA), immunohistochemistry, or Western blotting may have been used to quantify cytokine expression levels or phosphorylation levels of signaling pathway components. Functional assays, such as cell culture models or animal studies, may have been employed to investigate the effects of cytokine stimulation or inhibition on adhesion formation in vitro or in vivo. The main objective of this study was to elucidate how cytokine signaling pathways contribute to the pathogenesis of peritoneal adhesions. By investigating the expression and activity of cytokines and their downstream signaling pathways, researchers aimed to identify potential therapeutic targets for intervention. Understanding how dysregulated cytokine signaling promotes inflammation, fibrosis, and tissue remodeling in adhesion formation could lead to the development of targeted therapies for preventing or treating adhesions. Cytokine signaling pathways represent

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promising targets for therapeutic intervention in peritoneal adhesions. Modulating cytokine activity or blocking specific cytokine receptors may help mitigate inflammation, fibrosis, and aberrant tissue remodeling associated with adhesion formation. Targeted inhibition of cytokine signaling pathways could offer novel therapeutic strategies for preventing or treating adhesions, ultimately improving patient outcomes following surgery or injury.

Identification of Novel Genetic Risk Loci for Adhesion Formation (#13-Table 4) This study aimed to identify novel genetic risk loci associated with the formation of peritoneal adhesions. Genetic risk loci are specific regions of the genome that are statistically associated with an increased risk of developing a particular trait or disease. By conducting genome-wide association studies (GWAS) or targeted genetic analyses, researchers sought to uncover genetic variants or loci predisposing individuals to adhesion formation. Identifying novel genetic risk loci could provide insights into the genetic basis of adhesion formation and reveal potential therapeutic targets for intervention. Researchers likely collected genetic data from a large cohort of individuals with and without peritoneal adhesions. High-throughput genotyping or sequencing technologies were used to analyze genetic variations across the entire genome or within specific genomic regions of interest. Statistical analyses, such as logistic regression or genome-wide association analysis, were employed to identify genetic variants or loci significantly associated with adhesion susceptibility. Functional studies may have been conducted to investigate the biological relevance of identified genetic risk loci in adhesion formation. This study's primary goal was to identify new genetic risk loci that are involved in the formation of peritoneal adhesions. Researchers want to gain a better knowledge of the genetic factors influencing adhesion development and find new targets for therapeutic or preventive interventions by discovering novel genetic correlations. Comprehending the genetic foundation of adhesion formation may facilitate the creation of customised treatment strategies based on an individual's genetic makeup. Understanding the underlying genetic underpinnings of this illness depends on the identification of novel genetic risk loci for adhesion development.. Genes or biological pathways implicated in adhesion formation may be identified by genetic risk loci, offering insights into the molecular mechanisms underlying this intricate trait. Additionally, genetic risk loci may function as biomarkers to identify people who are more likely to develop adhesions and provide information for individualised treatment plans or preventative measures. This work emphasises the significance of genetic variables in the aetiology of this illness and marks a major advancement in our understanding of the genetic determinants of peritoneal adhesion formation.

Adhesion Formation and MicroRNA (miRNA) Profiling (#14-Table 4) The objective of this research was to examine the variations in the expression of microRNAs, or miRNAs, in the peritoneal tissues of subjects who had adhesion formation and those who did not. Small, non-coding RNA molecules known as miRNAs attach to target messenger RNAs (mRNAs) and alter their expression, which is how they play crucial roles in post-transcriptional gene regulation. Dysregulated miRNA expression has been implicated in various pathological conditions, including fibrosis and tissue remodeling, which are central processes in adhesion formation. The researchers collected peritoneal tissue samples from patients undergoing surgery, with some having a history of adhesion formation and others serving as controls. Total RNA, including miRNAs, was extracted from the tissue samples and subjected to miRNA expression profiling using high-throughput techniques such as microarrays or next-generation sequencing (NGS). Bioinformatics analyses were then performed to identify differentially expressed miRNAs between the adhesion and control groups. The main objective of this study was to identify dysregulated miRNAs associated with adhesion formation and gain insights into their potential roles in the pathogenesis of this condition. By comparing miRNA expression profiles between adhesion-prone and non-adhesion-prone tissues, the researchers aimed to uncover miRNAs that may serve as diagnostic biomarkers or therapeutic targets for adhesion-related disorders. Understanding the regulatory roles of dysregulated miRNAs in adhesion formation could lead to developing novel strategies for prevention and treatment. MiRNA profiling in adhesion formation provides valuable insights into the molecular mechanisms underlying this condition. Dysregulated miRNAs identified through profiling analyses may represent potential biomarkers for adhesion risk assessment or treatment response monitoring. Moreover, miRNAs

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implicated in adhesion formation could serve as targets for therapeutic intervention. Modulating the expression or activity of dysregulated miRNAs may offer new avenues for developing miRNA-based therapies to prevent or resolve peritoneal adhesions.

Genetic Variation in Cell Adhesion Molecules and Adhesion Formation (#15-Table 4) This study aimed to investigate the role of genetic variation in cell adhesion molecules (CAMs) in the pathogenesis of peritoneal adhesions. CAMs are cell surface proteins mediating cell-cell and cell-extracellular matrix interactions, playing essential roles in cell migration, tissue repair, and immune responses. Genetic variations within CAM genes may influence their expression, structure, or function, affecting cellular adhesion properties and contributing to adhesion formation. The researchers collected genetic data from individuals with and without peritoneal adhesions, focusing on variations within genes encoding CAMs. High-throughput genotyping or sequencing techniques were used to analyze genetic variants within CAM genes, such as single nucleotide polymorphisms (SNPs) or copy number variations (CNVs). Statistical analyses were then performed to assess the association between specific genetic variants and adhesion susceptibility, considering potential confounding factors. The main objective of this study was to elucidate how genetic variation in CAMs contributes to the pathogenesis of peritoneal adhesions. By identifying genetic variants associated with adhesion formation, the researchers aimed to uncover vital molecular mechanisms and potential therapeutic targets for intervention. Understanding how genetic variation influences CAM function and cellular adhesion processes could provide insights into the pathophysiology of adhesion formation and inform the development of personalized treatment approaches. Genetic variation in CAMs represents an essential determinant of adhesion formation susceptibility. CAMs play critical roles in mediating cell-cell and cell-matrix interactions during tissue repair and remodeling, and genetic variants affecting CAM function may contribute to aberrant adhesion formation. Identifying genetic variants associated with adhesion susceptibility could lead to developing biomarkers for risk assessment and personalized preventive strategies for individuals predisposed to adhesions. Moreover, CAM-targeted therapies could be explored to prevent or treat peritoneal adhesions, potentially improving patient outcomes following surgery or injury. This study contributes to our understanding of the genetic determinants of peritoneal adhesion formation and highlights the potential of targeting cell adhesion molecules for therapeutic intervention in this condition.

Profiling of Gene Expression in Peritoneal Tissue (#16-Table 4) The purpose of this study was to examine the gene expression profiles in peritoneal tissue from people who had and did not have peritoneal adhesions. Through the simultaneous assessment of thousands of genes' expression levels, gene expression profiling sheds light on the molecular mechanisms behind adhesion development. Researchers looked for differentially expressed genes and pathways linked to adhesion formation by comparing gene expression patterns between adhesion-prone and non-adhesion-prone tissues. Samples of peritoneal tissue were taken from surgical patients, some of whom had a history of adhesion formation and others were controls. After removing the total RNA from the tissue samples, high-throughput methods like RNA sequencing and microarrays were used to profile the expression of specific genes. After that, bioinformatics investigations were carried out to determine which genes were expressed differently in the adhesion and control groups. One possible use for functional enrichment analysis is to find biological pathways enriched with genes that express themselves differently. This study's primary goal was to clarify the molecular processes that underlie the creation of peritoneal adhesions. The researchers sought to learn more about the molecular mechanisms underlying adhesion creation, including inflammation, tissue healing, and extracellular matrix remodelling, by identifying genes and pathways that were differently expressed. Comprehending the patterns of gene expression linked to adhesion formation may facilitate the identification of new treatment targets and biomarkers for this illness. Peritoneal tissue gene expression profiling offers important new information about the pathophysiology of adhesion development. Genes with differential expression found by profiling analysis could be useful indicators for evaluating therapy response or assessing adhesion risk.

Moreover, genes implicated in adhesion formation could serve as targets for therapeutic intervention. Modulating the expression or activity of genes involved in crucial biological processes

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underlying adhesion formation may offer new avenues for developing targeted therapies to prevent or resolve peritoneal adhesions. By using gene expression profiling, this study advances our knowledge of the molecular mechanisms underlying the creation of peritoneal adhesions. It emphasises how therapeutic intervention in this situation may be achieved by focusing on differentially expressed genes..

Impact of Genetic Polymorphisms on Inflammatory Signaling Pathways (#17-Table 4) This study aimed to investigate the effects of genetic polymorphisms on inflammatory signaling pathways involved in the pathogenesis of peritoneal adhesions. Genetic polymorphisms are variations in the DNA sequence that can affect gene expression, protein function, and cellular signaling pathways. Inflammation plays a crucial role in adhesion formation, and genetic variations within genes encoding components of inflammatory signaling pathways may influence an individual's susceptibility to adhesions. The researchers collected genetic data from individuals with and without peritoneal adhesions, focusing on polymorphisms within genes involved in inflammatory signaling pathways. High-throughput genotyping techniques were used to analyze genetic variants within candidate genes, such as single nucleotide polymorphisms (SNPs). The relationship between genetic polymorphisms and adhesion susceptibility was then examined statistically, taking into account confounding variables including age, sex, and comorbidities. This study's primary goal was to clarify the role that genetic polymorphisms in inflammatory signalling pathways play in the pathophysiology of peritoneal adhesions. The researchers sought to reveal critical molecular pathways underpinning inflammation-driven adhesion development and find possible therapeutic targets for intervention by identifying genetic variations linked to adhesion production.. Understanding how genetic polymorphisms modulate inflammatory responses could provide insights into personalized risk assessment and treatment strategies for individuals predisposed to adhesions. Genetic polymorphisms in inflammatory signaling pathways represent essential determinants of adhesion formation susceptibility. Inflammation plays a central role in the pathogenesis of peritoneal adhesions, and genetic variations within genes involved in inflammatory responses may influence an individual's risk of developing adhesions. Identifying genetic polymorphisms associated with adhesion susceptibility could lead to developing biomarkers for risk assessment and personalized preventive strategies for individuals at higher risk of adhesion. Moreover, targeting inflammatory signaling pathways may offer novel therapeutic approaches for preventing or treating peritoneal adhesions. This study contributes to our understanding of the genetic determinants of peritoneal adhesion formation by investigating the impact of genetic polymorphisms on inflammatory signaling pathways.

Genetic Predisposition to Adhesion Formation and Oxidative Stress (#18-Table 4) The purpose of this study was to look into how oxidative stress susceptibility at the genetic level affects the pathophysiology of peritoneal adhesions. Damage to cells and inflammation result from oxidative stress, which is caused by an imbalance between the body's antioxidant defences and the generation of reactive oxygen species (ROS). Through the modulation of oxidative stress levels and inflammatory responses, genetic differences in genes encoding antioxidant enzymes and regulators of oxidative stress response pathways may affect an individual's vulnerability to adhesion formation. The researchers collected genetic data from individuals with and without peritoneal adhesions, focusing on polymorphisms within genes involved in oxidative stress response pathways. Genetic variations, such as single nucleotide polymorphisms (SNPs) within potential genes linked to oxidative stress, were analysed using high-throughput genotyping techniques.

Statistical analyses were then performed to assess the association between specific genetic polymorphisms and adhesion susceptibility, controlling for potential confounding factors. The main objective of this study was to elucidate how genetic susceptibility to oxidative stress contributes to the pathogenesis of peritoneal adhesions. By identifying genetic variants associated with adhesion formation, the researchers aimed to uncover vital molecular mechanisms underlying oxidative stress-mediated adhesion formation and identify potential therapeutic targets for intervention. Understanding how genetic variations in oxidative stress response pathways influence adhesion susceptibility could provide insights into personalized risk assessment and treatment strategies for

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individuals predisposed to adhesions. Genetic susceptibility to oxidative stress represents an essential determinant of adhesion formation susceptibility.. The aetiology of peritoneal adhesions is mostly dependent on oxidative stress, and an individual's susceptibility to adhesion development may be influenced by genetic polymorphisms within genes implicated in oxidative stress response pathways. Finding the genetic variants linked to adhesion susceptibility may help develop biomarkers for risk assessment and tailored adhesion prevention plans for those who are more likely to experience adhesion.. Moreover, targeting oxidative stress response pathways may offer novel therapeutic approaches for preventing or treating peritoneal adhesions.

Association of Epigenetic Changes with Adhesion Formation (#19-Table 4) This study investigated the association between epigenetic changes and adhesion formation in peritoneal tissues. Epigenetic modifications are modifications to histone proteins and DNA that control the expression of genes without changing the underlying sequence of DNA. Histone modifications, non-coding RNAs, and DNA methylation are examples of epigenetic processes that are important in controlling cellular phenotypes and patterns of gene expression. Dysregulation of epigenetic mechanisms may contribute to the pathogenesis of peritoneal adhesions by altering the expression of genes involved in inflammation, fibrosis, and tissue remodeling. The researchers collected peritoneal tissue samples from individuals with and without adhesion formation and analyzed epigenetic changes using various techniques. DNA methylation patterns were assessed using bisulfite sequencing or methylation-specific PCR assays. Histone modifications were examined using chromatin immunoprecipitation followed by sequencing (ChIP-seq) or histone modification-specific antibodies. Non-coding RNA expression levels were measured using quantitative RT-PCR or RNA sequencing. Bioinformatics analyses were then performed to identify differentially methylated regions, histone modification patterns, or dysregulated non-coding RNAs associated with adhesion formation.

This study's primary goal was to clarify how epigenetic modifications contribute to the pathophysiology of peritoneal adhesions. The objective of the study was to develop better understanding of the molecular mechanisms underpinning adhesion formation and to find possible epigenetic biomarkers or therapeutic targets for intervention by detecting epigenetic changes linked to adhesion formation. Gaining knowledge about how gene expression patterns and cellular phenotypes in adhesion-prone tissues are impacted by epigenetic dysregulation may open our eyes to new perspectives on the pathophysiology of peritoneal adhesions. Essential factors of adhesion formation susceptibility are epigenetic modifications. Dysregulated epigenetic mechanisms may alter the expression of genes involved in crucial biological processes underlying adhesion formation, such as inflammation, fibrosis, and extracellular matrix remodeling. Identifying epigenetic alterations associated with adhesion formation could lead to developing epigenetic biomarkers for risk assessment and personalized preventive strategies for individuals predisposed to adhesions. Moreover, targeting epigenetic mechanisms may offer novel therapeutic approaches for preventing or treating peritoneal adhesions.

Functional Genomics Studies in Adhesion Formation (#20-Table 4) This study aimed to investigate the functional genomics of adhesion formation, focusing on the comprehensive analysis of gene function and regulation in peritoneal tissues. Functional genomics systematically studies gene function, including gene expression, protein interactions, and regulatory mechanisms, to understand how genes contribute to biological processes. By integrating multiple functional genomics approaches, such as gene expression profiling, pathway analysis, and functional validation experiments, researchers aimed to gain insights into the molecular mechanisms underlying adhesion formation and identify potential therapeutic targets. The researchers employed a multi-faceted approach to study gene function and regulation in adhesion formation. Peritoneal tissue samples were collected from individuals with and without adhesions, and gene expression profiling was performed using high-throughput techniques such as microarrays or RNA sequencing. Bioinformatics analyses were then conducted to identify differentially expressed genes and enriched biological pathways associated with adhesion formation. Functional validation experiments, such as gene knockdown or overexpression studies in cellular or animal models, were performed to elucidate

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the functional roles of candidate genes in adhesion formation. The main objective of this study was to elucidate the molecular mechanisms underlying adhesion formation through comprehensive functional genomics analyses. By integrating gene expression data with pathway analysis and functional validation experiments, the researchers aimed to identify critical genes and pathways involved in adhesion formation and gain insights into their roles in the pathogenesis of this condition. Understanding the functional genomics of adhesion formation could lead to identifying novel therapeutic targets and developing targeted interventions for preventing or treating peritoneal adhesions. Functional genomics studies provide valuable insights into the molecular mechanisms underlying adhesion formation and offer potential therapeutic targets for intervention. By systematically analyzing gene function and regulation in adhesion-prone tissues, researchers can identify essential genes and pathways involved in the pathogenesis of peritoneal adhesions. Functional validation experiments enable researchers to validate the functional significance of candidate genes and pathways implicated in adhesion formation, providing mechanistic insights into the disease process. Ultimately, functional genomics studies may lead to personalized treatment approaches tailored to an individual's genetic profile and disease phenotype. This study represents a comprehensive investigation into the functional genomics of adhesion formation, providing valuable insights into the molecular mechanisms underlying this condition and potential therapeutic targets for intervention.

These investigations improve our knowledge of the intricate molecular processes underlying the creation of peritoneal adhesions. They draw attention to the interaction of genetic, epigenetic, and environmental variables in the pathophysiology of adhesions and pinpoint possible therapeutic targets and biomarkers for individualised risk assessment and intervention plans. To apply these discoveries to clinical settings and enhance results for individuals who are susceptible to peritoneal adhesions, more investigation is necessary.

The developments in the last years regarding the peritoneal adhesions are listed in the table below (Table 5):

#	*Development*	*Description*	*Ref*
1	Identification of Genetic Risk Factors:	Researchers are conducting genome-wide association studies (GWAS) and candidate gene studies to identify genetic variations associated with peritoneal adhesions.	[242].
2	Gene Expression Studies:	Transcribing tissues from people with peritoneal adhesions using transcriptome analysis to find dysregulated genes and pathways.	[243].
3	Epigenetic Mechanisms:	Investigation of DNA methylation patterns and histone modifications in individuals with peritoneal adhesions.	[244].
4	Animal Models:	Utilization of animal models such as rodents and pigs to study the genetic basis of peritoneal adhesions.	[245].
5	Translational Research:	Translation of genetic findings into clinical applications, including diagnostic tests and targeted therapies.	[246].
6	Functional Genomics Studies:	Investigation of the functional role of identified genetic variants using cell culture models and gene editing techniques.	[247].

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7	Multi-omics Approaches:	Integration of data from proteomics, metabolomics, transcriptomics, and genomes to offer a thorough knowledge of the molecular processes behind peritoneal adhesions.	[248].
8	Machine Learning and Bioinformatics:	Machine learning algorithms and bioinformatics tools are used to analyze large-scale genetic and clinical datasets and identify predictive biomarkers and therapeutic targets.	[249].
9	Genetic Epidemiology Studies:	Population-based studies to investigate the prevalence of genetic risk factors for peritoneal adhesions across different populations and ethnicities.	[250].
10	Pharmacogenomics and Personalized Medicine:	Exploration of genetic factors influencing individual responses to pharmacological interventions for preventing or treating peritoneal adhesions.	[251].
11	Longitudinal Genetic Studies:	Long-term studies track genetic variations and their impact on peritoneal adhesion formation and recurrence.	[252].
12	Functional Validation of Candidate Genes:	Functional validation of candidate genes associated with peritoneal adhesions using in vitro and in vivo models.	[253].
13	identification of Genetic Biomarkers:	Discovery of genetic biomarkers for early detection, prognosis, and monitoring of peritoneal adhesions.	[254].
14	Gene-Environment Interactions:	They were investigating how genetic predisposition and environmental variables interact to generate peritoneal adhesions.	[255].
15	Network Analysis of Genetic Pathways:	Network analysis to elucidate interactions among genes and pathways implicated in peritoneal adhesion formation.	[256].

Conclusions

Peritoneal adhesion has a demonstrated genetic determinism. The type of genes implied in peritoneal adhesion is diverse. Proteins synthesized by these genes, such as selectins and integrins, are crucial in peritoneal adhesion formation. Knowing these proteins and their precise mode of action will develop effective drugs that will inhibit peritoneal adhesion. Recent developments in peritoneal adhesion genetic determinism focus on epigenetic mechanisms, multi-omics approaches, and network analysis of genetic pathways between others. Further research is needed to develop an efficient therapy and identify novel biomarkers to prevent and predict the peritoneal adhesion developing process.

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