Table 1. Genes/proteins that modulate the function of cGAS-cGAMP-STINg axis in oncology

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene**  **name**  **Protein name** | **Human uniprot**  **and**  **omim** | **Protein, MW /**  **homo-oligomerization /**  **TM /** | **dominant location** | **natural cofactors,**  **activators, etc.** | **inhibitors, drugs, etc.** | **Cell / issue**  **Expression** | **Activity /**  **modulation of STING** | **General**  **Function** | **Role in oncology** | **other diseases** | **most famous protein interactors** |
| STING1  STING | Q86WV6  615934 | 42/2+/4 | ER→G  with cGAS | cGAS |  | UB (low: brain, retina; high: endothelium, resp. epith, IC (except B cells and eosin) | assembly | dsDNA and dsRNA response | dual |  |  |
| CGAS | Q8N884 | 59/1+2 | N,C | dsDNA |  | UB (low: retina, high: IC) | cGAMP synthase | ds DNA sensing | dual |  |  |
| PARP1 | P09874 | 113 | N |  |  | UB | poly(ADP-ribose) polymerase | DDR | target of PARPi |  |  |
| PARP2 | Q9UGN5 | 66 | N |  |  | UB | = | DDR | = |  |  |
| PARP9 | Q8IXQ6 | 96 | C→N  upon IFNG or IFNB1 |  |  | UB |  | DDR (recruits E3 ligase DTX3L) | ? |  |  |
| TFAM | Q00059 | 29/1 | mito |  |  | UB |  | mito DNA transcription and replication intiation | ? |  |  |
| TBK1 | Q9UHD2 | 38 | C |  |  | UB | phosphorylating innate adapter proteins MAVS, STING1 | IRF3 activator |  |  |  |
| TREX1  DNase III intronless | Q9NSU2 | 33 | ER→N upon ROS, | Mg |  | UB | 3’-exonuclease for with mismatched 3' termini | DDR, degradation of IF-stim DNA | low in cancers |  | SET complex (ANP32A, APEX1, HMGB2, NME1, SET and TREX) |
| HMGB1 | P09429 | 25 | N |  |  | UB |  | binds DNA (transcriptional control), binds TLR4 for inflammation | DAMP |  |  |
| FABP5 | Q01469 | 15 | C |  |  | squamous epithelia, esp esophagus and vagina |  | Binds amantadine and free ARA and RA | promotes cancers through lipid metabolism |  |  |
| PPP6C | O00743 | 35 | C | Mn |  | UB | inactivates CGAS and STING1 | catalytic PP6 (S/T): decelerates mitosis, activates RIG1 | dual |  |  |
| ENPP1 | P22413 |  | C-(PM)-outside | Zn |  |  |  | ECTONUCLEOTIDE PYROPHOSPHATASE/PHOSPHODIESTERASE |  |  |  |
| ATM | Q13315 | 350 | N,C | DNA double-strand breaks (DSBs) |  | UB | activates STING | DNA damage sensor |  | ataxia telangiectasia, an autosomal recessive disorder |  |
| IFI16 | Q16666 | 15 | N | dsDNA |  |  | activates STING | DNA binding |  |  |  |
| ZBP1 | Q9H171 | 20 | C |  |  |  | activates STING | binds Z-RNA;  essential mediator of pyroptosis, necroptosis and apoptosis |  |  |  |
| DDX41 | Q9UJV9 | 69 | N |  |  |  |  | recognize the bacterial second messengers cyclic di-GMP and cyclic di-AMP, resulting in the induction of genes involved in the innate immune response |  |  |  |
| RAD50 | Q92878 | 25 | N | Zn |  |  |  | double-strand break (DSB) repair |  |  |  |
| MRE11 | P49959 |  | N | Mn |  |  |  | double-strand break (DSB) repair |  |  |  |
| MYD88 | Q99836 | 64 | C,N |  |  | UB | can form a complex with STING | Activates IRF1, NF-kB |  |  |  |
| IRF3 | Q14653 | 55 | C,N |  |  | UB |  | Key transcriptional regulator of type I interferon (IFN)-dependent immune responses which plays a critical role in the innate immune response against DNA and RNA viruses |  |  |  |
| IRF7 | Q92985 |  | C,N |  |  | UB |  | Key transcriptional regulator of type I interferon (IFN)-dependent immune responses and plays a critical role in the innate immune response against DNA and RNA viruses |  |  |  |
| RIG-I | O95786 | 30 | C | Zn |  |  |  | Innate immune receptor that senses cytoplasmic viral nucleic acids and activates a downstream signaling cascade leading to the production of type I interferons and pro-inflammatory cytokines |  |  |  |
| MAVS | Q7Z434 | 62 | mitochondrion |  |  |  |  | coordinate pathways leading to the activation of NF-kappa-B, IRF3 and IRF7 |  |  |  |
| RIPK3 | Q9Y572 | 28 | C,N |  |  |  |  | activates necroptosis and apoptosis |  |  |  |
| NLRP3 | Q96P20 | 43 | C, ER, G |  |  |  |  | activation in response to defects in membrane integrity, leading to secretion of inflammatory cytokines IL1B and IL18 and pyroptosis |  |  |  |
| NCOA4 | Q13772 | 35 | N |  |  |  | STING-associated followed by ferropoptosis | Enhances the androgen receptor transcriptional activity in prostate cancer cells |  |  |  |
| SRC | P12931 | 26 | С |  |  |  |  | gene transcription, immune response, cell adhesion, cell cycle progression, apoptosis, migration, and transformation |  |  |  |
| EIF2AK3 (PERK) | Q9NZJ5 | 20 | ER |  |  |  |  | phosphorylates the alpha subunit of eukaryotic translation initiation factor 2 (EIF2S1/eIF-2-alpha) in response to various stress conditions |  |  |  |
| EIF2S1 (eIF2α) | P05198 |  | C |  |  |  |  | Member of the eIF2 complex that functions in the early steps of protein synthesis by forming a ternary complex with GTP and initiator tRNA |  |  |  |
| SLC19A1 | P41440 | - | cell membrane |  |  |  | importer of cyclic GMP-AMP dinucleotides | importer of immunoreactive cyclic dinucleotides, such as cyclic GMP-AMP (2'-3'-cGAMP, thus playing a role in triggering larger immune responses |  |  |  |
| SLC46A2 | Q9BY10 | - | cell membrane  endosome membrane |  |  |  | dominant importer of cyclic GMP-AMP dinucleotides (cGAMPs) in monocyte and macrophage cell lineages | Selectively imports cGAMPs derived from pathogenic bacteria such as 3'3'-cGAMP thus providing for differential immune recognition of pathogenic versus commensal bacteria. During tumorigenesis may transport extracellular tumor-derived 2'3'-cGAMP across the plasma membrane of M1-polarized macrophages to activate the anti-tumoral stimulator of interferon genes (STING) pathway |  |  |  |
| LRC8A  (SWELL1) | Q8IWT6 | - | cell membrane  lysosome membrane |  |  |  | complexes containing LRRC8D inhibit transport of 2'-3'-cGAMP | Essential component of the volume-regulated anion channel (VRAC), an anion channel required to maintain a constant cell volume in response to extracellular or intracellular osmotic changes |  |  |  |
| STAT3 | P40763 | 22 | C, N |  |  |  |  | Signal transducer and transcription activator that mediates cellular responses to interleukins, KITLG/SCF, LEP and other growth factors |  |  |  |
| HELB | Q8NG08 | 65? | C, N |  |  |  |  | 5'-3' DNA helicase involved in DNA damage response by acting as an inhibitor of DNA end resection |  |  |  |
| MAD2L2 | Q9UI95 |  | C, N |  |  |  |  | Adapter protein able to interact with different proteins and involved in different biological processes. During G1 and S phase of the cell cycle, the complex functions downstream of TP53BP1 to promote non-homologous end joining (NHEJ) and suppress DNA end resection. |  |  |  |
| TP53BP1 | Q12888 |  | N |  |  |  |  | Double-strand break (DSB) repair protein involved in response to DNA damage, telomere dynamics and class-switch recombination (CSR) during antibody genesis |  |  |  |
| RIF1 | Q5UIP0 |  | C,N |  |  |  |  | Key regulator of TP53BP1 that plays a key role in the repair of double-strand DNA breaks (DSBs) in response to DNA damage: acts by promoting non-homologous end joining (NHEJ)-mediated repair of DSBs. In the same time, RIF1 and TP53BP1 specifically counteract the function of BRCA1 by blocking DSBs resection via homologous recombination (HR) during G1 phase |  |  |  |
| BRCA1 | P38398 | 220 | C, N |  |  |  |  | The BRCA1 protein is a E3 ubiquitin-protein ligase that specifically mediates the formation of 'Lys-6'-linked polyubiquitin chains and plays a central role in DNA repair by facilitating cellular responses to DNA damage |  |  |  |
| BRCA2 | P51587 | 384? | C, N |  |  |  |  | Involved in double-strand break repair and/or homologous recombination. Binds RAD51 and potentiates recombinational DNA repair by promoting assembly of RAD51 onto single-stranded DNA (ssDNA). |  |  |  |
| TLR3 | O15455 | 20 | ER-membrane  endosome membrane |  |  |  |  | Key component of innate and adaptive immunity. TLRs (Toll-like receptors) control host immune response against pathogens through recognition of molecular patterns specific to microorganisms. TLR3 is a nucleotide-sensing TLR which is activated by double-stranded RNA, a sign of viral infection. Acts via the adapter TRIF/TICAM1, leading to NF-kappa-B activation, IRF3 nuclear translocation, cytokine secretion and the inflammatory response |  |  |  |
| SETX | Q7Z333 |  | C, N |  |  |  |  | Senataxin plays an important cellular role at the interface of transcription and the DNA damage response and that the resolution of R-loop structures is a key event in the maintenance of genome stability. |  |  |  |
| HMMR  (RHAMM) | O75330 | 21 | C |  |  |  |  | Receptor for hyaluronic acid (HA). When hyaluronan binds to HMMR, the phosphorylation of a number of proteins, including PTK2/FAK1 occurs. May also be involved in cellular transformation and metastasis formation, and in regulating extracellular-regulated kinase (ERK) activity. |  |  |  |
| PALB2 | Q86YC2 |  | N |  |  |  |  | Plays a critical role in homologous recombination repair (HRR) through its ability to recruit BRCA2 and RAD51 to DNA breaks. Strongly stimulates the DNA strand-invasion activity of RAD51, stabilizes the nucleoprotein filament against a disruptive BRC3-BRC4 polypeptide and helps RAD51 to overcome the suppressive effect of replication protein A (RPA). |  |  |  |
| FANCD2 | Q9BXW9 |  | N |  |  |  |  | Required for maintenance of chromosomal stability. Promotes accurate and efficient pairing of homologs during meiosis. Involved in the repair of DNA double-strand breaks, both by homologous recombination and single-strand annealing. May participate in S phase and G2 phase checkpoint activation upon DNA damage. |  |  |  |
| MLH1 | P40692 | 27 | N |  |  |  |  | MLH1 is an MMR protein that forms a complex with DNA-repair protein PMS2, and coordinates the other DNA-repair protein effectors to repair mismatches arising during DNA replication. |  |  |  |
| CHK2 | O96017 |  | N | Mg |  |  |  | Checkpoint kinase 2 (Chk2) is a multifunctional enzyme whose functions are central to the induction of cell cycle arrest and apoptosis by DNA damage. |  |  |  |
| CXCL9 | Q07325 | 12 | Secreted |  |  |  |  | Cytokine that affects the growth, movement, or activation state of cells that participate in immune and inflammatory response. |  |  |  |
| CTLA4 | P16410 | 25 | Cell membrane |  |  |  |  | Inhibitory receptor acting as a major negative regulator of T-cell responses. |  |  |  |
| SOCS1 | O15524 |  | N |  |  |  |  | negative regulator of type I and type II interferon (IFN) signaling, as well as that of other cytokines, including IL2, IL4, IL6 and leukemia inhibitory factor (LIF) |  |  |  |
| BLK | P51451 | 33 | Cell membrane |  |  |  | Phosphorylates CGAS, promoting retention of CGAS in the cytosol | Non-receptor tyrosine kinase involved in B-lymphocyte development, differentiation and signaling |  |  |  |
| IDO1 | P14902 |  | C |  |  |  |  | Catalyzes the first and rate limiting step of the catabolism of the essential amino acid tryptophan along the kynurenine pathway.  Involved in the peripheral immune tolerance, contributing to maintain homeostasis by preventing autoimmunity or immunopathology that would result from uncontrolled and overreacting immune responses. Acts as a suppressor of anti-tumor immunity. |  |  |  |
| PDCD1 | Q15116 | 14 | Cell membrane |  |  |  |  | Inhibitory receptor on antigen activated T-cells that plays a critical role in induction and maintenance of immune tolerance to self. The blockage of the PDCD1-mediated pathway results in the reversal of the exhausted T-cell phenotype and the normalization of the anti-tumor response, providing a rationale for cancer immunotherapy |  |  |  |
| ERCC1 | P07992 | 32 | C, N |  |  |  |  | Non-catalytic component of a structure-specific DNA repair endonuclease responsible for the 5'-incision during DNA repair. Responsible, in conjunction with SLX4, for the first step in the repair of interstrand cross-links (ICL). |  |  |  |
| JAK2 | O60674 | 35 | C,N | Mg |  |  |  | Non-receptor tyrosine kinase involved in various processes such as cell growth, development, differentiation or histone modifications. Mediates essential signaling events in both innate and adaptive immunity. In the cytoplasm, plays a pivotal role in signal transduction via its association with type I receptors such as growth hormone (GHR), prolactin (PRLR), leptin (LEPR), erythropoietin (EPOR), thrombopoietin (THPO); or type II receptors including IFN-alpha, IFN-beta, IFN-gamma and multiple interleukins. |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |

N – nuclear, C – cytoplasmic, ER –endoplasmic reticulum, G – Golgi complex, UB – ubiquitous,

BC – breast cancer, EndA – endometrial adenocarcinoma, FTC – fallopian tube cancer, OC – ovarian cancer, PanC – pancreatic cancer, PPC – primary peritoneal cancer, Pt – platinum based chemotherapy, TNBC – triple negative breast cancer, UCC – uterine corpus carcinoma.

Table 2. Representative ongoing clinical trials of STING modulators in oncology

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Drug | Cancer type | Co-Target | Co-treatment | Phase | Register  number |
|  |  |  |  |  |  |

BC – breast cancer, EndA – endometrial adenocarcinoma, FTC – fallopian tube cancer, OC – ovarian cancer, PanC – pancreatic cancer, PPC – primary peritoneal cancer, Pt – platinum based chemotherapy, TNBC – triple negative breast cancer, UCC – uterine corpus carcinoma.

Numerous SYNERGISMS may be exploited