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Abstract: Mesenchymal stromal cells (MSCs) are a subset of heterogeneous non-hematopoietic fibroblast-like cells which play important roles in tissue repair, inflammation, and immune modulation. MSCs residing in the bone marrow microenvironment (BMME) functionally interact with hematopoietic stem progenitor cells regulating hematopoiesis. However, MSCs have also emerged in the last years as key regulator of tumor microenvironment. Indeed, they are now considered as active players in the pathophysiology of hematologic malignancies rather than passive by-standers in hematopoietic microenvironment. Once the malignant event occurs, the BMME acquires cellular, molecular, and epigenetic abnormalities affecting tumor growth and progression. In this context, MSC behavior is affected by signals coming from cancer cells. Furthermore, it has been showed that stromal cells themselves play a major role in several hematological malignancies' pathogenesis. This bidirectional crosstalk creates a functional tumor niche unit wherein tumor cells acquire a selective advantage over their normal counterpart and are protected from drug treatment. It is therefore of critical importance to unveil the underlying mechanisms which activate a protumor phenotype of MSCs for defining unmasked vulnerabilities of hematological cancer cells which could be pharmacologically exploited to disrupt the tumor/MSCs coupling. The present review will focus on the current knowledge about MSC dysfunction mechanisms in the BMME of hematological cancers, sustaining tumor growth, immune escape, and cancer progression.

Keywords: MSCs; tumor transformation; hematological cancers; senescence; inflammation

1. Introduction

Mesenchymal stromal cells (MSCs) are a critical component of bone marrow (BMME) microenvironment whereby they provide newly formed osteoblasts and tightly regulate the homeostasis of hematopoietic stem and progenitor cells (HSPCs) [1]. In this context, MSCs are the major contributor of many key niche factors and maintain the dynamic balance between HSPCs self-renewal, quiescence, proliferation, and differentiation [2, 3]. MSCs are located in the sites of hematopoiesis starting from embryonic developmental stages [4]. Importantly, MSCs and their progeny such as osteoblasts, chondrocytes and adipocytes, are structural components of both

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endosteal and perivascular niches [5]. Within these compartments, MSCs interact with both hematopoietic stem cells and more differentiated hematopoietic progenitors, thus regulating their quiescence, proliferation, and differentiation [6-8] (Figure 1).

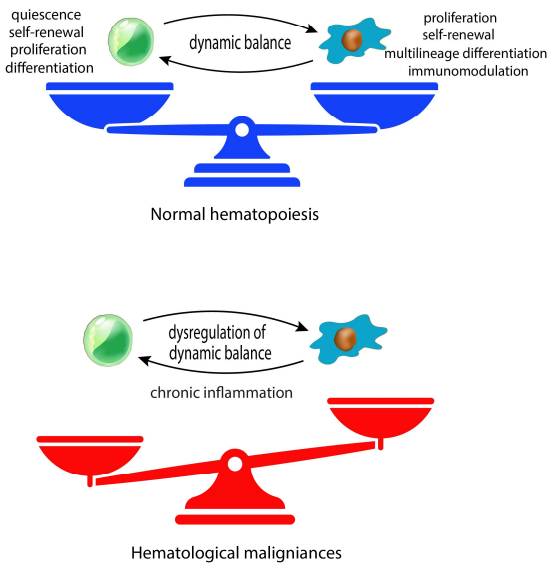

Figure 1. Schematic representation showing dynamic activity of HSPC and MSC when BMME is at homeostasis. The continuous interplay between HSCPs and stromal cells is essential for ensuring normal hematopoiesis. In the hematological cancer scenario, this complex interplay is deeply dysregulated favoring trafficking and infiltration of cancer cells into a protective BM niche.

Different MSC subtypes interact with HSPCs in specific regions of the niche [9]: CD271+ MSCs are bone-lining cells sustaining long-term HSPCs in low oxygen area, whereas CD146+ and CD271+CD146+ MSCs are located in BM sinusoids with activating and fast-proliferating HSPCs [10, 11]. A plethora of supporting factors regulating HSPCs self-renewal and trafficking are provided by MSCs in the BM niche, such as CXCL12 and stem cells factor [12, 13]. Notably, alteration of HSPC and BM-MSC interactions can alter normal hematopoiesis causing hematological malignancies [14-17].

MSC behavior is dynamically regulated both by intrinsic mechanisms and microenvironment factors, highlighting the high plasticity of these cells in adapting to tissue homeostasis and regenerative needs [18]. In this context, the therapeutic use of MSCs in the field of regenerative medicine relies on their ability to migrate to injured tissues and to promote endogenous regeneration sustaining the growth and differentiation of stem resident cells [19, 20]. In details, MSC therapeutic potential for the treatment of immunological diseases result from their ability to suppress or control intensive immune activation by inhibiting immune cell proliferation and inducing immunosuppressive subsets though the secretion of anti-inflammatory factors or direct cell-to-cell contact [20-22]. However, MSCs also take part to tumorigenesis process contributing to BMME malignant transformation and maintenance, finally promoting tumor cell growth, survival, progression, and therapy resistance. Similar to HSPCs, the interactions between cancer cells and BM-MSCs can determinate tumor cell dormancy or proliferation. For example, leukemic stem cells (LSCs) co-localize with CXCL12-secreting MSCs in BM, inducing their quiescence [22]. Furthermore, accumulation of senescent MSCs in BM niche might promote the progression from premalignant to over hematological malignancy [23],[24]. Senescence of MSCs is accompanied by several phenotypic changes, including enlarged cell morphology, decreased proliferative capacity and impaired differentiation ability [25]. Evidence suggests that the presence of increased numbers of senescent MSCs is a characteristic feature of several hematological cancers [26]. When functional and regenerative capacities of aging MSCs are diminished, they enter in a replicative senescence status which promotes BM inflammation and the dysregulation of hematopoiesis [27] (Figure 1). It is well known that senescent cells release pro-inflammatory factors, generally known as Senescence-

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Associated Secretory Phenotype (SASP) which contributes to tumor immunosuppressive microenvironment [28]. Furthermore, it has been shown that SASP factors such as IL-6, CXCL8 and GDF15 can alter HSPC homeostasis in vitro [29]. In detail, IL-6 secreted by aged BM-MSCs induces rapid HSPC expansion, thereby leading to depletion of HSPC pool and increased risk of genomic instability in these cells [23, 30]. MSCs are subject to genetic alterations and chromosomal aberrations contributing to age-and disease-associated MSC dysfunctions [31, 32]. Interestingly, it has been demonstrated that these alterations differ from ones observed in the hematopoietic tumor cells of the same patient, corroborating the idea that unstable MSCs might facilitate the expansion of malignant cells [33]. However, no recurring genetic mutations or cytogenetic aberrations have been found in MSCs from BMME of hematological cancers [33-36], unveiling that epigenetic modifications underlie the activation of their pro-tumor phenotype. In this context, cellular epigenetic architecture is modeled based on the environmental insults and physiological changes to maintain MSC functions, including their self-renewal, differentiation, and niche modulation abilities [37]. Notably, dysfunctions of MSC phenotype persist also after their expansion ex vivo, suggesting a heritable epigenetic dysregulation which persist despite the removal of disease associated BMME. In agreement, the methylome of MSC from hematological cancers was found to be distinct from healthy stromal cells [38-41].

Data from previous studies revealed that a cancer-associated fibroblast (CAF)-like phenotype is activated in MSCs from patients with hematological cancers [42-44]. Indeed, these cells express tumorigenic markers such as alpha smooth muscle actin (αSMA) and fibroblast activation protein (FAP) as consequence of the soluble factors produced by cancer cells [45-47]. In agreement, CAFs might derive from MSCs working as a subset of "specialized" stromal cells [48, 49]. Paunescu and colleagues previously showed that MSCs and CAF have many similarities including their phenotype and the only difference is the secreted cytokines [50]. In their study, CAFs have been demonstrated to derive from a specialization process which converts MSCs inside the tumor structure for better serving tumor cells [50]. A mounting number of studies indicated that growth and survival of leukemic clone is promoted by inflammation-driven changes in the BM-MSCs [51]. In particular, naïve MSCs are able to exert bidirectional effect on tumor cells favoring or inhibiting its growth [52], while tumor "educated" MSCs promote tumor progression, in relation to the inflammatory microenvironment [53]. Compared to the healthy counterpart, MSCs from BM tumor milieu show a distinct transcriptional landscape characterized by cellular stress and upregulation of inflammatory molecules which sustain malignant over healthy clonal hematopoietic cell expansion [34, 54, 55]. The pro-leukemic role of MSCs can also be achieved indirectly by shaping the BMME immune infiltrate [56, 57]. Indeed, the immunomodulatory effect of MSCs on innate and adaptive immunity is a major mechanism by which these cells can affect tumor initiation and progression [58-61]. This feature depends on the type and intensity of inflammatory signals into the BMME. A high inflammatory state causes MSCs to produce T cell suppression, while a low inflammatory state leads to MSC-induced T cell activation [62]. In hematological malignancies, senescent MSCs release more inflammatory signals feeding an inflammatory milieu able to scramble the delicate balance of pathways involved in tissue-specific regeneration and remodeling [63]. Although MSC immunomodulatory activity is primed by cytokines into BMME, it is also dependent on stimulation of toll like receptors (TLRs). In detail, MSCs can be polarized into two distinct phenotypes similar to macrophages, resulting in different immune-modulatory activity and secretome [64]. The TLR4-primed MSCs exhibit a proinflammatory phenotype (MSC1), while the TLR3-primed MSCs activate a more anti-inflammatory profile (MSC2). This concept of MSC polarization could explain the apparently contradictory roles of MSC in inflammation and immunomodulation [20]. Notably, the regulation of the functional profile of MSCs depends not only on the secretion of soluble factors but also on the communication and contact of MSCs with neighboring BM cells. MSCs can communicate with nearby cells through secretion of soluble factors, cell to cell contact, release of extracellular vesicles (EVs) and, as more recently evidenced, through tunneling nanotubes [65-68]. Evidence is arising that altered MSCs help leukemic cell growth and prompt drug resistance by providing nutrients, cytokines, pro-survivals signals and exchanging organelles [44, 69, 70]. Several recent studies have identified stroma-derived metabolites such as lactate, glutamine, and acetate to feed the tricarboxylic acid cycle (TCA) and lipid biosynthesis into hematopoietic cancer cells [71-73]. Of note, metabolism is adjusted during the development of drug resistance [73, 74]. The complexity of this scenario is increased by a

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metabolic heterogeneity and dynamics of BMME which is mainly dependent on different access to oxygen and glucose and on different cell population co-existing in the BM milieu [75, 76]. As result, cancer and stromal cells can compete and/or cooperate for nutrients. In recent years, the role of exosomes as mediators between cancer cells and tumor BMME ha gained increasing attention. For example, leukemia-derived exosomes induced a downregulation of HSPC-supporting factors in MSCs and reduced their capacity to support normal hematopoiesis [77]. Furthermore, while microvesicles (MVs) from healthy MSCs show anticancer action, MM-MSCs release MVs enriched in VLA-4, which facilitated MM cell uptake, enhance tumor cell phenotype and PCs growth [78, 79].

In this review, we will highlight the role of MSCs in tumor microenvironment of hematological cancers, aiming to elucidate the mechanisms involved in the activation of their pro-tumor phenotype contributing to tumor growth and progression.2. Materials and

2.1. Role of MSCs in myelodysplastic syndromes

Myelodysplastic syndromes (MDS) is generally referred as a heterogenous group of clonal hematopoietic diseases characterized by ineffective hematopoiesis resulting in peripheral blood cytopenia potentially shifting to acute myeloid leukemia (AML) [80]. MDS patients display different degrees of cytopenia and dysplasia, therefore constituting the basis for Word health organization MDS classification criteria [81]. To date, no clinically effective treatment is available for preventing progression to AML. Half of patients show cytogenetic alteration, while nearly 90% of them harbor at least one somatic mutation affecting specific genes involved in spliceosome, transcription factors and epigenetics. Despite the clonal dominance, these mutations don't provide a determined advantage for malignant cell growth, as suggested by their coexistence alongside normal HSPCs [82]. Therefore, MDS cells get an extrinsic support from BMME important for malignant cell cloning. Notably, support from BM milieu is essential to maintain MDS cells *ex vivo*. Concerning MSCs, MDS stromal cells are reprogramed to support uniquely MDS clones at the expense of normal HSPCs [35]. MDS-MSCs are characterized by a slower proliferation rate, which is independent by cell cycle distribution and apoptotic events [83]. Therefore, the reason characterizing this phenotype might involve cytogenetic aberrations, which have been difficult to characterize due to the lack of a specific isolation protocol allowing the comparison between different MSCs subpopulations. This goal has been achieved upon Aanei and colleagues published a robust immunoselection-based isolation protocol through two specific mesenchymal-associated markers, STRO-1 and CD73 [84]. Therefore, MDS-MSC cytological characterization highlighted genomic gains involving genes taking part in cell-cell adhesion processes and tumor development. In addition, MSCs isolated from patients harboring 5q- cytogenetic shared common traits including the overexpression of some genomic regions as 7p22.3, 19p13.3, and 19p13.11 [83]. Despite a cytogenetic signature characterizing MDS-MSCs is still missing, it is widely reported how these cells display all the typical marker related to cell senescence [85]. In this context, Fei et al. reported that isolated MDS-MSCs display a profound change in cytoskeletal architecture, in turn showing an increased size, longer podia and a disordered distribution of F-actin [86]. Moreover, MDS-MSCs also display an increased DNA damage level [87]. Coherently with this outcome, an hyperactivation of p53 signaling cascade has been detected in MDS-MSCs, therefore providing a further mechanism leading to MSC senescence [86]. Despite the efforts showing the essential role covered by BMME in MDS, the question asking who the first cell population is to impair the basal crosstalk, therefore triggering MDS pathogenesis, is still standing. A partial answer has been given by the studies describing that, in patients showing a complete hematological remission, the treatment was able to restore a MSC functionality comparable to healthy donors [88]. However, this study has the intrinsic assumption that the treatment has the HSC compartment as only target, excluding a direct effect on MSCs themselves. In this context, it has been recently demonstrated that the antileukemic activity of azacytidine in part depend on its direct effect on the hematopoietic supportive capacity of MDS-MSCs favoring expansion of healthy over malignant hematopoiesis [89]. These data highlighted the crucial role of an epigenetic treatment of dysfunctional MSCs. Other studies corroborate the hypothesis involving the crosstalk between stromal and hematopoietic compartments as driver of MDS pathogenesis, in turn rearranging the surrounding microenvironment to support the expansion of the malignant clone. Indeed, murine models depleted for Dicer or Sbds gene expression exclusively in stromal compartment have shown to develop an MDS-like phenotype characterized by ineffective hematopoiesis, marked dysplasia and

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leukemic progression, despite having no mutation in their HSPCs [90, 91]. Medyouf and colleagues described a scenario in which MSCs are instructed by malignant HSCs to acquire MDS-MSC-like properties, eventually promoting the progression of the malignant clone over the healthy one [35]. This data introduced the "hematopoietic niche unit", sustaining MDS progression also by the establishment of an altered secretome profile, where abundant levels of TNF-α, IFN-γ, IL-1α, IL-6, IL-17 and TGF-β have been detected [92]. These factors account for the establishment of an inflammatory BMME, in turn triggering genetic and epigenetics modifications on BM resident cell populations. Corroborating this, MDS-MSCs show several differentially methylated genes associated to alterations of their phenotype [36]. For instance, HHIP (Hh-interacting protein) gene is hypermethylated in MDS-MSCs [93]. Its downregulation accompanied by activation of the Hedgehog pathway in stromal cells sustain survival of MDS cells. Recently, our group have shown the relevance of an epigenetic-inflammatory interplay in MDS-MSCs supported by macroH2A1/TLR4 axis, prompting a replicative senescent phenotype, hypermethylation and metabolic rewiring which contribute to ineffective hematopoiesis [94]. In agreement, cellular stress and upregulation of inflammatory molecules with inhibitory effects on normal hematopoiesis has been described in MDS-MSCs [95]. In particular, activation of NFkB signaling in MSCs from patients with lower risk MDS (LR-MDS) attenuates normal hematopoiesis in accordance with cytopenia observed in these patients [96]. Moreover, overexpression of the alarmins S100A8/9 in stromal cell compartment has been shown to activate NFkB and a genotoxic stress in HSPCs associated to leukemic evolution in a subset of LR-MDS patients [91]. Supporting the crucial role played by the BM niche in MDS evolution, it has been proposed that the overexpression of CXCL12, in synergy with its receptor CXCR4, keep the myelodysplastic anchored inside the BM niche, in turn providing them with protection and support [97]. In this scenario an in vitro study highlighted the overproduction of IL-6, an interleukin possibly linked to the mechanism promoting MSCs senescence and chronic inflammation [98]. The crosstalk between MDS cells and MSCs is also orchestrated by a plethora of factors, as part of the two populations' secretome. Releasing alarmins such as S100A9 and S100A8, tumor cells activate the inflammasome in stromal cells which results in higher secretion of pro-inflammatory cytokine [99]. Also, EVs secreted by MDS cells have been demonstrated to reduce the hematopoietic supportive capacity of MSCs inhibiting osteolineage differentiation of MSCs [100]. This perturbation of bone metabolism enables MDS clones to outcompete normal HSPCs. In turn, MDS-MSCs have been described to release EVs carrying miRNA, such as miR10a and miR15a, which increase the viability and clonogenicity of MDS cells [101]. Therefore, the multifaced aspects accounting for MSCs significancy need to be further dissected to provide more efficient strategies counteracting MDS progression.

2.2. Role of MSCs in acute leukemia

Acute leukemias are rapidly progressing malignant clonal disorders characterized by uncontrolled proliferation of immature and undifferentiated hematopoietic cells, associated to poor prognosis, and reduced overall survival. They are commonly divided, according to malignant cells lineage in acute myeloid or lymphoid leukemia (AML or ALL). Blast cells have been known to modify the BMME and disrupt non-malignant hematopoiesis [102, 103]. The complex interactions within the tumor BMME significantly influence leukemia survival, disease progression and therapeutic response, with hematopoietic stem cell transplantation often being the only curative option for patients with refractory disease [104]. Several studies showed that the interaction of leukemic cells with MSCs resulted in a functionally disrupted niche specifically supporting tumor cells over healthy HSPCs and therefore establishing a self-reinforcing unit for the repopulation of leukemic cells [105, 106]. In this context, blast cells might exploit physiological mechanisms regulating hematopoiesis as a strategy for gaining competitive advantages [107]. It has been recently described, using mouse models of leukemia, that both ALL and AML blasts express lymphotoxin α1β2 after colonizing the BM. Therefore, blasts trigger lymphotoxin beta receptor (LTβR) signaling in MSCs, turning off IL7 production and preventing non-malignant lymphopoiesis [107]. Among the changes in cytokine profile of AML-MSCs, the overproduction of CCL2 inhibits normal progenitors but not leukemic cells improving cancer survival [108, 109]. Similarly, MSCs from T-ALL patients show reduced ability to support healthy HSCs blocking their differentiation in HPCs, without a direct leukemic MSC-induced

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damage [110]. This finding is consistent with the paradigm that, despite the exhaustion of HPCs in the leukemic milieu, HSCs remain functional upon relocation into non-leukemic BMME [110].

Hematopoietic insufficiency is the hallmark of AML with cytopenia-related complications such as bleeding and infections representing the major causes of death. In AML-MSCs, the downregulation of FOXM1, a member of the fork-head transcription factor family, impairs the hematopoietic MSCs support capacity [111]. Corroborating this, the silencing of this protein in healthy stromal cells affects the growth of CD34+ progenitor cells, mirroring the effects observed when using AML-derived MSCs [111]. Moreover, AML-MSCs displayed alterations in the expression of key hematopoiesis-regulating factors such as JAGGED1 and KITL corroborating that hematopoietic insufficiency in AML patients is at least in part mediated by BMME [112]. More recent studies provided evidence that, when acute leukemia occurs, blast cells remodel the resident MSCs establishing a physical connection and mediating a reprogrammed transcriptome [106, 113]. Of note, healthy MSCs changed their gene expression profile after coculture with AML blasts displaying deregulation of genes matched with AML-MSCs [113]. This transcriptomic behavior, characterized by inflammatory factors and cytokine production pathways, correlate to AML suggesting a dynamic changes in MSCs occurring at leukemia onset as consequence of an instructive role of leukemic cells [112, 113]. As a result, "reprogrammed" MSCs reset the niche crosstalk processes selectively suppressing normal hematopoiesis and favoring the clonal dominance of leukemic cells [106, 114]. The heterogeneity of MSC subpopulation exhibit different BMME for leukemic cells contributing to the heterogeneous kinetics of leukemia relapse. In this context, Kim and colleagues evaluated whether differences in BM stromal cell partners at diagnosis can identify patients with a high risk of relapse [106]. They found that BMME of relapsed patients showed higher numbers of MSCs, osteoblasts and primitive nestin+ MSCs than AML patients who achieved complete remission (CR). Early relapsed patients have a greater primitive MSC content, while late relapsed ones exhibited more MSCs or osteoblasts than CR patients, corroborating a distinct BMME associated with early or late relapse [106]. This evidence suggests that leukemia-induced remodeling of BMME may be responsible for the heterogeneity of the AML clinical course. MSC lineage differentiated cells, including osteoblasts and adipocytes, are essential components of BMME contributing to hematopoiesis [115, 116]. Increasing evidence suggests that the differentiation ability of AML-MSCs is altered [117, 118]; however, the results are controversial. Indeed, some work report that AML cells induce an osteoblast-rich niche in the BM which in turn enhances AML expansion and favors disease relapse [106, 119]. On the contrary, alterations of MSC osteoblastic plasticity resulted in selective promotion of leukemic cells in murine models [14, 120]. Moreover, other researchers reported that leukemia educated MSCs are highly prone to adipocytes differentiation [118]. These conflicting results may be due to the heterogeneity of leukemia. For instance, AML cells of AML-M4 subtype induce MSCs towards adipogenic differentiation propensity [121]. The alterations of osteogenic differentiation capacity of AML-MSCs were also confirmed by specific methylation changes affecting genes regulating cell differentiation and skeletal development [112].

As MDS stromal cells, both AML and ALL-MSCs show accelerated cellular senescence contribute to their impairment in function associated with HSPC support and stemness properties [28, 110]. MSCs exposed to leukemic blasts exhibit common characteristics to MSCs subjected to a physiological aging process, including overexpression of markers related to DNA damage and cell-cycle arrest [122]. Furthermore, leukemia-induced oxidative stress works as driver of pro-tumoral senescence in stromal cells [123]. Targeting senescent MSCs directly inhibits AML cell growth and improves survival of mice with leukemia, revealing the importance of a senescent milieu for the pathophysiology of leukemia [123]. Heterochromatin disorganization is a driver of MSC senescence [124]. AML-MSCs downregulate chromatin remodeling complex CHD1 (modulating chromatin condensation) whose reduction is associated with the decrease of HSPC supportive capacity [125]. Using an integrative approach of a multilevel molecular profiling combining genome-wide expression and DNA methylation high-throughput platforms, AML-MSCs exhibit selective transcriptional alterations associated to epigenetic ones, including adhesions molecules, endocytosis, and metabolic pathways [34]. In this context, accumulating evidence shows a complex metabolic coupling between leukemic cells and MSCs which allows tumors to respond to variations in nutrient availability to maximize cellular proliferation and to acquire survival advantages [126, 127]. In leukemia patients, cancer stem cells or chemoresistant cells rely on mitochondrial oxidative

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phosphorylation (OXPHOS) [128, 129]. MSCs directly provide the increased bioenergetic demand of AML cells, increasing OXPHOS and GSH-related ROS detoxifying tools which contribute to AML growth and chemoresistance [130]. Of note, MSCs supply mitochondria to leukemia cells [44, 131-133], thus providing them with additional energy. In T-ALL, leukemic cells transfer their damaged mitochondria to MSCs through cell adhesion mechanisms, reducing intracellular ROS and promoting chemotherapy-induced apoptosis resistance [134]. Recently, it has been reported that AML-induced MSCs adipogenic differentiation propensity is associated to a switch from glycolysis to OXPHOS [121]. In this context, AML blasts modulate intracellular metabolism of adipocytes into a lipolytic state, resulting in the release of fatty acids (FAs) into the BMME [135]. Ultimately, free FAs are transferred to AML blasts fueling a FA oxidation signature beneficial to the leukemia counterpart [135]. Indeed, blocking lipolysis or inhibiting CPT1A (carnitine palmitoyltransferase 1a), essential for the transfer of FAs to the inner mitochondrial membrane and β-oxidation [136], reduced AML mitochondrial activity and survival [135]. Like AML blasts, ALL cells induce adipocytes to activate lipolysis to support their metabolism [137]. ALL blasts also release EVs which activate a metabolic switch from PXPHOS to aerobic glycolysis in MSCs leading to increased lactate into BMME which can be used by tumor cells [138].

2.3. Role of MSCs in Myeloproliferative Neoplasms

Myeloproliferative Neoplasms (MPNs) are characterized by the clonal proliferation of one or more hematopoietic cell lineages, predominantly in the BMME. MPNs mainly include chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). CML is the BCR-ABL1 oncoprotein-positive MPN characterized by the Philadelphia (Ph) chromosome's presence. Ph- MPNs include PV, ET and PMF, in which clonal proliferation is driven by somatically acquired driver mutations in JAK2, CALR and MPL genes [139]. Nevertheless, Ph- MPNs show a different clinical presentation and outcome [140]. PMF is defined by unique clinical features such as BM fibrosis, osteosclerosis, neo-angiogenesis and extramedullary hematopoiesis which characterize the natural history of PMF patients, significantly affecting quality of life and life expectancy [141]. Similar to MDS-MSCs, stromal cells from CML and higher fibrosis PMF patients display functional alterations, including low proliferative potential and precocious senescence [142, 143]. Changes in MSC behavior are strongly associated with the dysfunction of T cells and the proliferation of Tregs in CML microenvironment [144]. Moreover, CML-MSCs directly orchestrate immunosuppression by also driving activation of myeloid cells in MDSCs [56]. Immune suppression of stromal cells can also be enhanced by CML cell secreted exosomes [145]. For instance, leukemic-derived exosome miR-130a/b has been demonstrated to promote the immunosuppressive properties of stromal cells through inhibition of connexin-43 [146]. In CML patients, CXCL12-expressing MSCs are crucial for maintaining quiescent leukemic stem cells and thus they represent a potential target to overcome drug resistance [147]. Indeed, analysis of gene expression profile reveal that abnormal alterations observed in CML-MSCs compared to normal counterpart persist in patients in deep molecular response after therapy with tyrosine kinase inhibitors [148], corroborating their role in leukemia relapse and drug resistance.

Neoplastic clone development in PMF is deeply influenced by alteration within BBME, highlighted by BM fibrosis, neo-angiogenesis and osteosclerosis [149, 150]. In this context, it may be hypothesized that the progressive stromal cell alterations during myelofibrosis evolution affect the disease course [141]. These cells display an increased expression and deposition of fibronectin correlating with the fibrosis grades [151]. This outcome is further enhanced by megakaryocytes (Mks), aberrantly proliferating, and releasing several growth factors mitogenic for MSCs/fibroblasts and endothelial cells, such as TGF 1 [152, 153]. Corroborating this, in MPN biopsies, MSCs localize with Mks displaying an activated fibronectin-secretory phenotype [154]. This interaction is crucial for the priming of stromal cells in PMF. Compared to healthy or low fibrosis grade MSCs, stromal cells from high fibrosis grade PMF patients show higher capacity to support differentiation of Mks by fibronectin secretion [151], highlighting their key role in supporting Mks hyperproliferation observed in PMF BM biopsies [155]. In agreement with this, MSCs isolated from spleen of MF patients show higher expression of fibronectin to sustain extramedullary hematopoiesis and megakaryocytopoiesis [156]. In addition to this, other inflammatory molecules generated by malignant clones contribute to the microenvironment abnormalities of myelofibrosis niche. For instance, lipocalain-2 (LCN2) primes

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MSCs to differentiate into osteoblasts prompting matrix proteins deposition [157]. Moreover, Mk-derived PDGF activate MSCs and in particular, expression of its receptor strongly correlate with the intensity of MCS reaction and fibrosis grade [158]. We recently demonstrate the involvement of IGFBP6 (Insulin-like growth factor-binding protein 6) in the activation of a CAF-like phenotype of stromal cells controlling the fibrotic process through the activation of sonic hedgehog/TLR4 axis [159]. Using murine MPN models, Schneider and colleagues demonstrated a critical role for Gli1+ MSCs in the pathogenesis of BM fibrosis [160]. After their activation, dependent on Mk-produced Cxcl4, these cells are metabolically reprogrammed, particularly in fatty acid, and differentiate into matrix-producing myofibroblasts. The authors also demonstrated that genetic ablation of Gli1+ MSCs abolished BM fibrosis rescuing BM failure [160]. Of note, increased number of MSCs can be detected in the blood of PMF patients suggesting their involvement in the abnormal HSPC trafficking/homing leading to extramedullary hematopoiesis [161]. Analyzing the whole transcriptomic profile of MPN-MSCs, Martinaud and colleagues revealed a specific pro-fibrotic and inflammatory signature in PMF-MSCs, not observed in TE or PV patients, and characterized by increased osteogenic potential and endogenous production of TGFB1 [162]. Leimkuhler et found that MSCs transcriptionally downregulated niche support and decreased MSC multipotent progenitor status, but upregulated Mk-derived TGFB1 pathway and extracellular matrix proteins, specifically collagens [163]. MSCs from ET patients have also previously reported to decrease hematopoietic supportive capacity and increase ECM remodeling, suggesting an intrinsic defect of stromal cells already in pre-fibrotic MPN [154].

2.4. Role of MSCs in in Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by relentless accumulation of monoclonal mature B-lymphocytes in the peripheral blood, bone marrow and lymphoid tissue [164]. A plethora of molecular prognostic factors have been identified in CLL patients and among them, VLA-4, an exclusive member of the α4 integrin subfamily, represents a CLL negative prognostic marker [165]. VLA-4 plays a prominent role in the homing of high-risk CLL cells within BMME. Notably, MSC-CXCL12 triggers the activation of VLA-4, therefore highlighting a crucial role played by MSCs in CLL cells homing [166]. Furthermore, MSCs might also promote CLL B-cells resting by increasing their CD38 and CD71 expression therefore reflecting an activated phenotype that could be related to disease progression [167].

In agreement with this, CLL cells highly rely on the abundance of supporting stimuli generated by the neighboring cells in the microenvironment, including MSCs. In agreement with this, the resistance of CLL cells to normal apoptotic regulation has been reported to be mediated by direct contact with stromal cells, requiring the simultaneous engagement of β1 and β2 integrins [168, 169]. Therefore, while CLL cells undergo rapid apoptosis when cultured alone, once cocultured with stromal cells they are easily propagated. This outcome is probably a consequence of MSC-EVs which have been recently reported to give to leukemic cells a survival advantage protecting them from spontaneous and drug-induced apoptosis [170]. In this scenario, CLL-derived exosomes establish a feedback loop by activating a CAF-like phenotype in MSCs, therefore improving the secretion of soluble factors promoting CLL cell survival [171]. Corroborating this scenario, CLL cells isolated from blood samples are non-dividing, despite their metabolism is still active [172]. In this context, Jitschin and colleagues reported that CLL cells acquire an increased glucose dependency upon contact with stromal cells [173], in turn promoting glucose uptake in CLL cells by decreasing mitochondrial stress and apoptosis [174]. However, this outcome is still debated. As recently reported, CLL cocultured with MSCs enhance their mitochondrial metabolism, sustaining ATP production along with a nucleotide pool without any change in their proliferation [175]. In agreement with this, it has been reported that CLL cells rely on OXPHOS, and this metabolic process has been associated with poor prognostic outcomes such as IGHV unmutated disease, ZAP70 positivity, increased Rai stage, and higher β2 microglobulin [175, 176]. Therefore, as also described, is possible that leukemic cells modify MSCs metabolism to satisfy their energy demand. Recently, it has been reported that, after contact with CLL cells, MSCs switch their metabolism towards OXPHOS whit consequent lower glucose usage which might be an advantage for CLL survival [174].

As things stand, it might be speculated that MSCs in the CLL context have a crucial role in supporting the malignant clone. In agreement with this, Dig and colleagues demonstrated that

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platelet-derived growth factor (PDGF) secreted by CLL cells activate its receptor PDGFR on MSC membrane [177]. PDGF/PDGFR interaction enhances MSC proliferation, therefore enhancing the production of VEGF and promoting the neovascularization known to be related to disease progression [178, 179].

Moreover, MSCs uptake cystine by overexpressing the cystine transporter [180]. Upon conversion to cysteine, it is released into microenvironment, and it is internalized by leukemic cells for glutathione synthesis and maintenance of the redox balance [180].

2.5. Role of MSCs in in Multiple myeloma

Multiple myeloma (MM) is a hematological disease characterized by uncontrolled proliferation and expansion of monoclonal plasma cells (PCs) in the BMME that leads to the overproduction of abnormal monoclonal protein and immunoglobulin free light chain. MM evolves from an asymptomatic pre-malignant stage termed monoclonal gammopathy of undetermined clinical significance (MGUS), eventually progressing to an intermediate but more advanced pre-malignant stage defined as smoldering myeloma (SMM) and, finally, to overt myeloma [1]. Although the initiation of malignant transformation is based on genetic and epigenetic alterations occurring in MM cells, the BMME plays a key role in mediating survival, proliferation, drug resistance, and progression of the disease [2]. In particular, the interactions of the malignant PCs with other cells in the BM niche, including MSCs, adipocytes, endothelial cells, osteoclasts, osteoblasts and immune cells lead to a host of problems including hypercalcemia, anemia, kidney failure, or bone lesions (i.e., CRAB criteria) [3]. Specifically, mutual modulation of phenotype and functions are observed between PCs and MSCs as a consequence of their bidirectional cross-talking. Bone disease is one of the most prominent clinical symptoms of MM patients, affecting the 80% of MM patients, and seriously impact the quality of life of patients [4]. As MSCs are osteoblasts progenitors, MM-MSCs actively contribute to the pathogenesis of myeloma bone disease. The adhesion of myeloma PCs to the stroma promotes the tumor cell secretion of several proteins, such as DKK1, which prevents the differentiation of MSCs into osteoblasts [5,6]. Importantly, MSCs not only contribute to bone disease because of their reduced osteogenic potential, but also because they ultimately promote activation of osteoclasts. Interacting with tumor cells, MSCs upregulate RANKL and reduce its soluble receptor OPG, thus prompting osteoclastogenesis through activation of RANKL-RANK signaling in osteoclasts [7].

MM-MSCs exhibit a distinct gene expression profile when compared to MSCs from healthy donors [8-11]. Particularly, Fernando and colleagues showed that the main downregulated networks in MM-MSCs are related to cell cycle progression, immune activation and bone metabolism, which might contribute to MM physiopathology [10]. In addition, the expression of specific genes differentiate MGUS-, SMM- and MM-MSCs and, interestingly, gene expression profile of MSCs from patients with PCs dyscrasias have an independent prognostic impact on clinical outcome [9]. In detail, Schinke et al. identified a prognostic MSC three-gene score, including collagen type IV alpha 1 (COL4A1), natriuretic peptide receptor 3 (NPR3) and integrin beta like 1 (ITGBL1), which is able to predict progression-free survival in MM patients and progression of MGUS/SMM to MM [9]. Of note, as MSC from patients which underwent completed treatment show a transcriptome essentially identical to that of patients at diagnosis, a persistent printing could maintain a niche prone to relapse [12]. Single cell sequencing also confirmed that current antitumor therapy fails to counteract MSC inflammation, highlighting their role in disease persistence [13]. MM-MSCs have an early senescent profile characterized by higher cell size, β-galactosidase increased activity, a Senescence-Associated Secretory Phenotype (SASP) and reduced proliferation due to the accumulation of cells in S phase [193, 194]. This phenotypic change is primed by tumor PCs because healthy MSCs showed a phenotype similar with MM-MSCs after exposure to tumor cells [195]. The senescence of MM-MSCs also impairs their differentiation potential and enhances their tumor-supporting capacity [194].

Interestingly, the mechanism behind the establishment of such a phenotype is still unkown. Dicer1, an RNAse III endonuclease essential for miRNA biogenesis, has been demonstrated to be one of the key promoters of cellular senescence in MSCs [17, 194]. Specifically, upregulation of Dicer1 in MM-MSCs reversed cellular senescence and promoted cell differentiation [194]. More recently, Cao et al. provided evidence for a link between MSC senescence and MM progression investigating genes coexpressed by tumor PCs and MM-MSCs [63]. The authors identified a set of signatures of fourteen genes linked to MSC senescence which is essential in predicting MM progression [63].

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Immunosuppression is a common feature of MM associated with disease evolution [196]. Concerning this, our group previously demonstrated that MM-MSCs promote immunosuppressive abilities of surrounding myeloid cells by promoting the expansion of granulocyte-like myeloid derived suppressor cells (G-MDSCs) [197] and immunosuppressive neutrophils [61], leading to cancer cell immune evasion. As the immunological dysfunction of MSCs was observed already in SMM stromal cells but not in MGUS ones, the activation of a MSC-induced immunosuppressive microenvironment might contribute to the transition from MGUS to MM as an evolutionary advantage acquired during the multistep development of MM. Of note, MSC from relapsed patients have an increased immunosuppressive ability compared to those from patients in remission [191]. The support of malignant clone proliferation by MM-MSCs is mediated by stromal activation of PD1/PDL-1 axis disrupting T cell immune response [198, 199]. Similarly, MM-MSCs are able to induce NK cell exhaustion by activation of CD155/TIGT signaling [200]. Furthermore, the tumorigenic behavior of MM-MSCs is directly mediated by tumor PCs through the activation of a TLR4-primed inflammatory phenotype [61]. Using a single-cell transcriptomic approach, De Jong et al. identified specific inflammatory MSCs in MM milieu [192]. As successful antimyeloma therapy is unable to revert MSC inflammatory status, not even in patients whose are undetectable by flow cytometry [192], inflammatory-primed MSCs could be also epigenetically reprogrammed maintaining their dysfunction also in absence of tumor cells. In agreement, epigenetic alterations of stromal cells have been recently associated to the impairment of bone formation in MM patients [39, 201]. Furthermore, members of the Homeobox family, known as key drivers of osteogenic differentiation, result epigenetically and transcriptionally deregulated in MM-MSCs [39]. Of note, epigenetic alterations in stromal compartment already occur in the asymptomatic phases of myeloma and most of these changes are specific to each stage [39]. This phenomenon could be associated to the expansion of MSCs subpopulations which promote tumor progression just as in MM cells [202].

The activation of an immunosuppressive and pro-inflammatory phenotype has been associated to a metabolic rewire of MSCs towards a more glycolytic metabolism, in turn required to sustain the secretion of immunosuppressive factors [203]. In agreement, we recently showed that MM-MSCs are more glycolytic than the normal counterpart [70]. Their relatively independence on mitochondrial metabolism impact MM cell energy making MM-MSCs inclined to transfer more mitochondria to tumor cells [70]. The uptake of functional mitochondria from MM-MSCs occur through several mechanisms, including tunneling nanotubes and CD38 [204], EVs as well as cell-to-cell contact and CXCL12/CXCR4 axis [70]. This mitochondrial trafficking supports the oxidative metabolism of tumor PCs favoring cancer growth and drug resistance [70, 205-208].

3.1. Concluding Remarks and future perspectives

MSCs are key component of the BMME, wherein they exert multiple functions for supporting hematopoietic niche, tissue homeostasis, and immune system modulation. The interest in dissecting the role of MSCs in hematopoietic malignancies has vastly grown over the past years. As we discussed, the BM milieu leukemic transformation causes profound modifications of MSC phenotype, including their morphology and functions with the acquisition of the SASP, which strongly contributes to the development of a proinflammatory microenvironment. Evidence suggests that SASP-related secretome of MSCs might contribute to the progression from benign states to over malignancies [24]. Indeed, the progression of hematological cancers towards a more aggressive phenotype does not solely rely on intrinsic leukemic cell factors but are independently impacted by the biology of the surrounding microenvironment, including MSCs (Figure 2).

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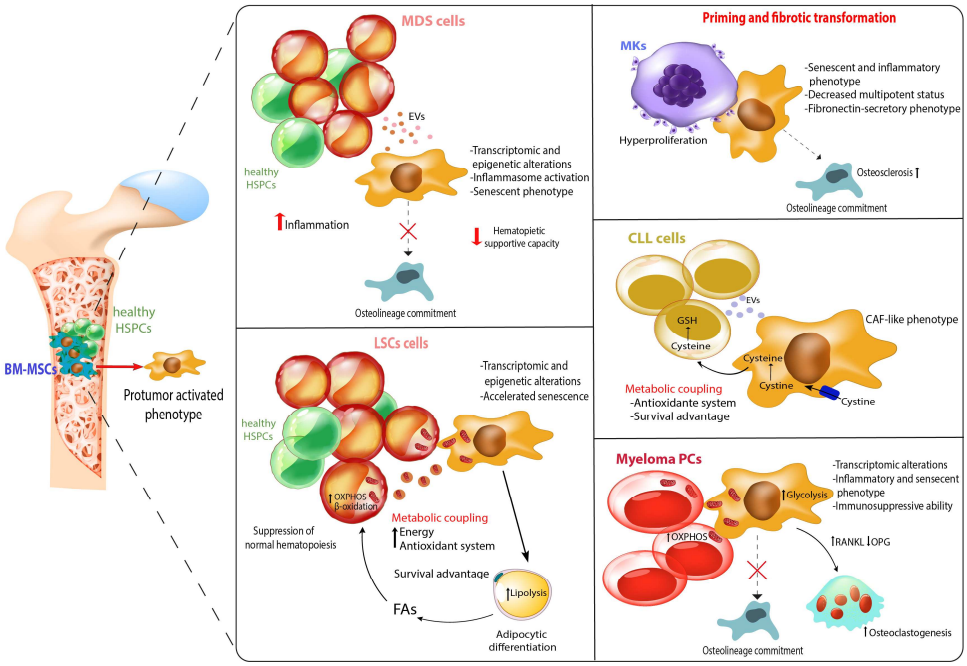

Figure 2. The role of MSCs in different hematological malignancies. The illustration shows how dynamic interactions between malignant cells and MSCs eventually inducing transcriptomic and epigenetic alterations affect stromal secretome and multipotency. A common hallmark of MSCs in hematological cancer is the acquisition of a senescent phenotype associated to a pro-inflammatory profile. Moreover, the interplay between cancer and stromal cells supports a complex metabolic coupling sustaining immune suppressive activity, tumor growth and drug resistance.

Reprogrammed stromal cells provide a nurturing niche that sustain tumor growth, clonal evolution, and drug resistance. Although it has been reported that MSCs from AML patients at time of disease remission recover healthy activities [113], inheritance of epigenetic alterations associated to MSC imprinting could lead to an autonomous status of stromal cells from neoplastic clone. In "absence/decrease" of clonal cells after targeted therapies, the persistence of this pathologic inflamed phenotype of MSCs might be a key component partially explaining disease relapse [209]. Moreover, the importance of BMME is highlighted by the prolonged time to stabilize engraftment after autologous HSPC transplantation. In this case, the prerequisite for transplant success is the rebuilding of the interplay between BMME and HSPCs.

For this reason, targeting the BM niche might represent a valuable novel strategy counteracting blood malignancy. Among the emerging targets the CXCL12/CXCR4 axis disrupts leukemic cell adhesion to MSCs mobilizing tumor cells into circulation and increasing drug-induced apoptosis [210-212]. In our own previous research, the inhibition of this axis also affects tumor/MSC metabolic coupling inhibiting mitochondria trafficking [70]. In this context, it is becoming increasingly clear the importance of the metabolic interplay between stromal and leukemic cells for promoting disease establishment and progression. The mitochondrial transfer support leukemic cell bioenergetics and antioxidant defenses, sparing them from high energetic cost of mitochondrial biogenesis. To understand which metabolic vulnerabilities can be targeted in the leukemic BMME might open new avenues to improve cancer therapy. Recently, niche-calcium homeostasis has been found to be involved in the reprogramming of MSCs into leukemic niche [113]. Compounds blocking the inward movement of calcium modify the transcriptomic and secretome profile of AML-MSCs restoring healthy functions [113]. Furthermore, the current focus has also been on age-related changes of MSCs which characterize the development of hematological cancers. For this reason, pharmacological approaches to eliminate senescent cells have been investigated [213]. Concerning MSCs, targeting senescent MSCs it has been demonstrated a possible strategy to recover hematopoietic supportive capacity of stromal cells improving metabolic fitness of HSPCs [214]. Therefore, the utility of senolytic agents as a potential intervention in the context of hematological cancer might be a promising new strategy to both inhibit pro-tumorigenic effects of inflamed MSCs and improve their hematopoietic supportive capacity.

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In the framework of BMME, the complex interplay between leukemic cells and MSCs include dynamic cell–cell interactions and organization, release of soluble factors and EVs, immunoregulatory properties which hide unrecognized leukemogenic events with innovative treatment opportunities. Therefore, extended investigations of relationship occurring in the leukemic niche may revolutionize treatment strategies to disadvantage cancer cells using niche-directed therapies.

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