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Communication between bone marrow mesenchymal stem cells and multiple myeloma cells: Impact on disease progression

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Abstract

Multiple myeloma (MM) is a hematological malignancy characterized by the accumulation of immunoglobulin-secreting clonal plasma cells at the bone marrow (BM). The interaction between MM cells and the BM microenvironment, and specifically BM mesenchymal stem cells (BM-MSCs), has a key role in the pathophysiology of this disease. Multiple data support the idea that BM-MSCs not only enhance the proliferation and survival of MM cells but are also involved in the resistance of MM cells to certain drugs, aiding the progression of this hematological tumor. The relation of MM cells with the resident BM-MSCs is a two-way interaction. MM modulate the behavior of BM-MSCs altering their expression profile, proliferation rate, osteogenic potential, and expression of senescence markers. In turn, modified BM-MSCs can produce a set of cytokines that would modulate the BM microenvironment to favor disease progression. The interaction between MM cells and BM-MSCs can be mediated by the secretion of a variety of soluble factors and extracellular vesicles carrying microRNAs, long non-coding RNAs or other molecules. However, the communication between these two types of cells could also involve a direct physical interaction through adhesion molecules or tunneling nanotubes. Thus, understanding the way this communication works and developing strategies to interfere in the process, would preclude the expansion of the MM cells and might offer alternative treatments for this incurable disease.

Key Words: Multiple myeloma; Mesenchymal stem cells; Bone marrow microenvironment; Soluble factors; Extra-cellular vesicles; Cells adhesion molecules; Tunnelling-

nanotubes

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Core Tip: Mesenchymal stem cells (MSCs), the main cell population of the bone marrow (BM) stroma, can influence BM microenvironment through their paracrine activity, involving both soluble factors and extracellular vesicles, but also through direct communication. Being the BM the predominant localization of multiple myeloma cells (MM), finding the appropriate conditions at this niche, is key for the survival and expansion of tumour cells and thus, for the progression of the disease. Since the activity of BM-MSCs could determine the fate of MM cells at BM, these cells could be interesting targets for the design of new antitumor drugs.

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INTRODUCTION

Multiple myeloma (MM) is one of the most common hematological diseases, only second to non-Hodgkin lymphoma[1]. MM affects mainly older adults, with the median age of diagnosis being around 69 years. Only in 2020, 32270 new cases and 12830 deaths in the United States were estimated by the American Cancer Society Statistics Centre. In global terms, the cases would reach 160000, accounting for 0.9% of all cancer diagnosis. Importantly, incidence of MM has risen 126% globally, and hence, there is an increasing need to find new effective treatments for this incurable disease[2,3].

Besides the initial treatments for MM, consisting in alkylating agents often combined with corticosteroids, the last couple of decades have seen an important advance in the available treatments for this disease. We first saw the introduction of proteasome inhibitors (Bortezomib), histone deacetylase inhibitors (Panobinostat) and drugs such as Selinexor, with a nuclear export inhibition activity. In recent years monoclonal antibodies such as Daratumumab (anti-CD38) or Elotuzumab (anti-SLAMF7), and more recently the use of chimeric antibody receptor (CAR) T-cell products, has introduced immunotherapy as a viable approach to MM treatment[4]. According to data from the National Cancer Institute (Bethesda, MD, United States), all these treatments have had a deep impact on patients' survival, substantially raising the survival rate to 55% in the period between 2011 and 2017. More recently, the use of small molecules, with a molecular weight smaller than 1kDa, has also improved treatments, since it offers important advantages compared to the former therapies, as the easy cell entry, the simplicity of the molecules, and a much lower production cost than other drugs[5]. However, despite these advancements, there are still limitations to existing treatment options. Some patients may not respond to or may develop resistance to certain medications, many patients can become refractory to treatment and thus, there is a high risk of relapse. This promotes the search for new treatments to handle relapsed or refractory MM.

MM is caused by aberrant plasma cells (PC) proliferation in the bone marrow (BM). The premalignant states, known as monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM, transition under specific conditions to the malignant state of PC leukemia or extramedullary myeloma [6]. A key characteristic of MM is the infiltration into and the colonization of the BM, one of the two primary lymphoid organs[7]. This colonization produces typical lytic bone lesions that would be present in approximately 80% of patients with newly diagnosed MM and are the major source of morbidity[8]. The bone lesions, resulting from the stimulation of bone resorption by B-cell plasmacytomas, are associated with hypercalcemia and often, severe bone pain and bone fractures[8,9].

While the initiation of a tumor mainly depends on the accumulation of genetic defects, the transition from a premalignant to a malignant state highly relies on the interaction of the tumor cell with a permissive microenvironment that would support the malignant transformation and the proliferation of the tumor cells, aiding them to evade apoptosis. The relevance of tumor microenvironment in disease progression was first discussed in the "seed and soil hypothesis" formulated by Stephen Paget in 1889, where the establishment of tumor metastatic sites is influenced by the cross-interaction between the seeds (cancer cells) and the soil (a particular microenvironment)[10]. This is not different in MM[11,12]. The progression to MM, which would occur in approximately 50% of patients diagnosed with MGUS [6], requires multiple genomic events, but also a permissive BM microenvironment[13]. MM cells proliferate almost exclusively within the BM niche, highlighting the role of this microenvironment in

supporting cancer growth. In fact, there is also mounting evidence indicating this BM microenvironment is not only key for PCs survival, but also has a crucial role in resistance to treatment and disease recurrence[14,15].

The MM cells infiltrating the BM will encounter a complex microenvironment formed by cellular and non-cellular components. Amongst the non-cellular components influencing the BM microenvironment, it is important to consider the extracellular matrix (ECM) proteins as well as a milieu of cytokines, chemokines, and growth factors. Many of these factors can have a positive effect on MM cells, boosting their proliferation and survival and the resistance to different types of drugs. A good example of these cytokines supporting MM progression are interleukin (IL)-6 and ligands of the B-cell maturation antigen, such as a proliferation-inducing ligand and B-cell activating factor (BAFF)[16,17]. Regarding the cellular components of the BM niche, many different types of bone cells (osteoblasts, or bone forming cells, and osteoclasts, or bone resorbing cells, and osteocytes) and cells from the immune system (macrophages, natural killer cells and regulatory T-cells) share this niche. Other cells present here are fat cells (adipocytes), fibroblasts, endothelial cells and two multipotent stem cells, BM mesenchymal stem cells (BM-MSCs), which differentiate into different mesodermal cell lineages, and hematopoietic stem cells (HSCs), that would differentiate into hematological lineages, including the myeloid lineage that would give rise to osteoclasts. MM cells are likely to interact with all the cells in the BM niche and elicit mutual influence[18]. In fact, it is known that communication between MM cells and BM-MSCs is essential in the progression of MM[19]. Once MM cells infiltrate the BM, their presence in the BM niche alters the activity of many of the cells found there, including those involved in bone homeostasis such as osteoclasts[20,21] and osteoblasts[22-24]. While in normal bone homeostasis, the activities of osteoblast and osteoclasts are carefully balanced to ensure a correct bone regeneration, the influence of MM cells disrupts this balance increasing both the resorptive activity of osteoclast and their numbers, and decreasing osteoblasts numbers as well as their osteogenic capacity[25], overall leading to an increase in bone destruction and the appearance of the aforementioned osteolytic lesions typical of this disease. Other cells at the BM niche which activity is highly influenced by MM cells are BM-MSCs. The presence of MM cells at the BM niche alters the MSCs behavior in different ways. In fact, changes in the expression of certain microRNAs (miRNAs) in BM-MSCs leading to important alterations of their secretory profile and osteogenic differentiation potential have been observed after co-cultivation of BM-MSCs and MM cells[26,27]. These changes at the BM niche upon MM invasion produce a microenvironment that would support disease progression. Indeed, there is strong evidence indicating that is precisely this interaction what leads to the formation of the lytic bone lesions[28]. One of the characteristics of this permissive microenvironment is the high presence of pro-inflammatory cytokines that would favor the progression of neoplasia[29]. The crosstalk between MM cells and the BM-MSCs at the BM niche is key to sustain this pro-inflammatory microenvironment and thus, to allow MM cell persistence and growth[30]. It is important to clarify, that this pro-inflammatory microenvironment would be the result of the action not only of the infiltrated MM cells but also of other cells residing at the BM niche, including BM-MSCs.

MSCs, have a key role in regulating the BM microenvironment through their paracrine activity, but also through direct cell-to-cell interaction. Regarding their paracrine activity, these cells produce a plethora of soluble biomolecules and vesicular components, known altogether as “secretome”, that exert multiple actions on other cells at the BM microenvironment[31]. BM-MSCs role in MM disease development and progression has been reported as having both inhibitory[32] and supportive roles[33, 34]. Sadly, the latter is the most frequent. Once at the BM niche, MM will exert their influence on resident MSCs, altering their signaling and gene expression pattern and thus, also their secretion pattern. After interaction with MM cells, MSCs will produce a secretome rich in pro-inflammatory cytokines. In fact, it has been previously described how MSCs react to IL-1 produced by the myeloma PCs by producing large quantities of IL-6, a cytokine that would in turn stimulate the survival of the MM cells[35,36]. Therefore, the soluble part of this secretome has a key role in the progression of tumor. Moreover, in the last few years, several molecules (miRNAs) that are present in the cargo in the extracellular vesicles (EVs) produced by BM-MSCs upon MM cells stimulation also seem to have a key role in the disease promotion. Although the soluble proteins and EVs produced by the BM-MSCs are the main actors in the communication between BM-MSCs and MM cells, other ways of communication have also been implicated. This will be discussed in the following sections.

Current available treatments for MM patients mainly target MM cells but have none or limited effect on other cells in the BM or de BM microenvironment. Knowledge of the different interactions between BM-MSCs and MM cells is key to understand how MM cells behave and grow within the BM and how osteolytic lesions are formed. In this work, we will address key aspects of the different ways of communication between MSCs and MM cells as well as the outcome of this crosstalk.

SOLUBLE FACTORS IN THE COMMUNICATION BETWEEN BM-MSCs AND MM CELLS

The multiple cellular interactions taking place in the BM, make this microenvironment a dynamic compartment with a myriad of soluble factors that would affect the behavior of the various cell types

concurring at that microenvironment. Although many of those cells have paracrine activity, BM-MSCs are the ones that have a stronger impact in the BM microenvironment due to the wide variety of soluble and non-soluble factors secreted by these cells. Various constituents of the, so called, BM-MSC secretome orchestrate the fate of the MM cells, from the first step encompassing the homing of those cells to the BM, onwards.

Role of soluble factors in the homing of MM cells to the BM

A key factor in the communication between BM cells and MM cells during the first stages of BM colonization, is the cytokine stromal cell derived factor 1 α (SDF1 α), also known as CXCL12. This factor, produced by BM-MSCs, works as a chemoattractant, being responsible of the homing of HSCs to the BM once they abandon the fetal liver during development[37]. SDF1 α activity is mediated by the binding to a specific G-protein 7-span transmembrane receptor (CXCR4) at the target cells. CXCR4 is expressed at the surface of different cells in the BM microenvironment[38], and also at the surface of MM cells and other tumor cells[39]. Thus, SDF1 α /CXCR4 interaction might have a relevant role in directing de metastasis of hematopoietic malignancies. Similar to its effect on HSCs, the interaction of SDF1 α with its receptor at the MM cells, increases their migration, homing and adhesion towards the BM, in fact, knock down of CXCR4 in BM-MSCs or the use of the CXCR4 inhibitor AMD3100 (AnorMED), that blocks the binding of SDF1 α to its receptor[40], seems to inhibit the migration of MM towards the BM[41]. The binding of SDF1 α to its receptor at the MM cells, also triggers the activation of the phosphatidylinositol 3-kinase (PI3K) and the MAPK kinase (MEK)-extracellular signal regulated kinase (ERK, MEK/ERK) pathways, inducing a rearrangement in the cytoskeleton of MM cells that facilitates BM colonization [41]. SDF1 α has also been described to act in a more indirect way, not mediated by the binding to CXCR4. SDF1 α interacts with other molecules including matrix metalloproteinases (MMPs), integrins or growth factors such as hepatocyte growth factor (HGF), insulin like growth factor-1 (IGF-1) or molecules of the GTPases family. All of these effects elicited by SDF1 α , in one way or another, lead to a promotion in MM cells migration, homing or adhesion into the BM[38].

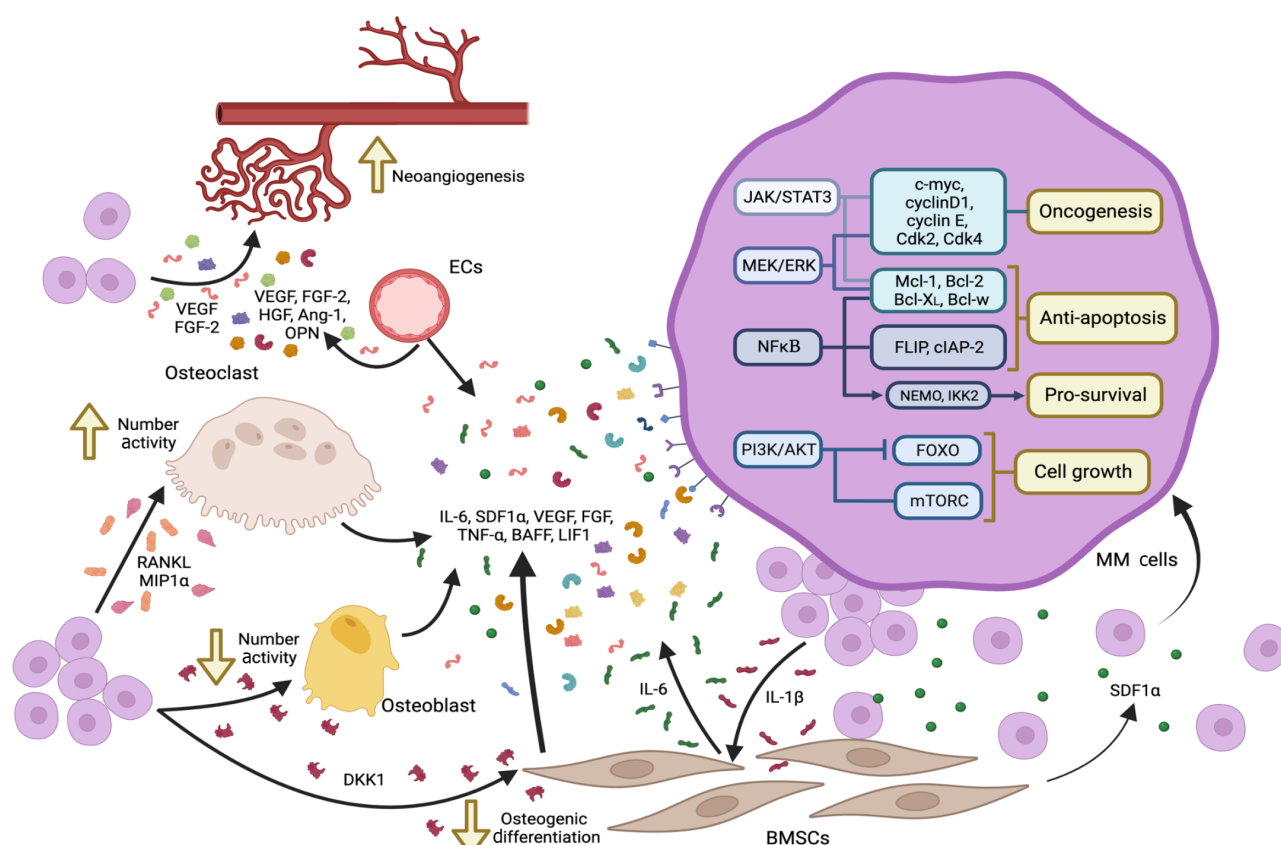
Role of soluble factors in the promotion of proliferation and MM cell survival

Many of the factors secreted by BM-MSCs and by other cells of the BM microenvironment, activate key signaling pathways in the MM cells that would increase their chances to survive and proliferate in the BM microenvironment. A summary of these factors as well as the signaling pathways involved in this communication are shown in [Figure 1](#). In fact, some mutations activating those pathways have also been found in patients with MM. We will address some of those key pathways in this section.

Once in the BM, for the tumor to progress further, MM cells would need a permissive microenvironment. This microenvironment would be created by multiple soluble factors secreted by the different cell types present at the BM. The soluble factors produced by the BM-MSCs seem to be the main, but not the only, effectors of the changes elicited in the MM cells. Besides SDF1 α , BM-MSCs seem to secrete other important soluble factors such as IL-6, IL-17, vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), tumor necrosis factor- α (TNF- α), BAFF or leukemia inhibitory factor-1; osteoclasts mainly secrete IL-6 and VEGF; and vascular endothelial cells secrete cyclophilin-A[42,43]. These factors will activate specific signaling pathways in the MM cells such as PI3K/Akt, MEK/ERK, Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3, JAK2/STAT3) pathways, related to cell survival, proliferation and drug resistance[43]. It is important to highlight that this communication is bi-directional, since MM cells would also produce cytokines such as IL-1 β , VEGF, and transforming growth factor-beta (TGF- β) that would exert their effect on BM-MSCs, activating the nuclear factor kappa-B (NF κ B) pathway and thus, inducing further secretion of cytokines by the BM-MSCs into the BM microenvironment, particularly IL-6[44,45].

IL-6 is the main activator of the JAK2/STAT3 pathway, known to be implicated in the pathogenicity of cancer. JAK2/STAT3 pathway activation promoted by IL-6 leads in MM cells to the expression not only of potent proto-oncogenes such as c-myc and cyclin D1, but also of anti-apoptotic genes like Mcl-1, Bcl-XL and Bcl-2. Moreover, STAT3 activation has also an immunosuppressive effect since it regulates T-cell mediated cytotoxic immune response[46], contributing to the establishment of an immunosuppressed microenvironment that would contribute to the survival and proliferation of the MM cells in the BM. On the other hand, IL-6 activation of JAK2/STAT3 pathways, also has an important role in bone destruction, a hallmark of MM. IL-6/JAK2/STAT3 axis induces the expression of the receptor activator of NF κ B ligand (RANKL)[36,47] whose binding to its receptor at the surface of pre-osteoclasts, promotes their differentiation towards mature osteoclasts, activating bone resorption and thus, promoting the formation of osteolytic lesions.

It is important to highlight that the NF κ B signaling pathway also has an important role in the survival of MM cells and in the maintenance of the tumorigenic microenvironment at the BM. Both canonical and non-canonical NF- κ B pathways are activated by different factors present in the BM microenvironment, including IL-6, IGF-1, TNF- α or BAFF[48]. While IGF-1 is able to activate NF κ B pathway, inducing the expression of anti-apoptotic, caspase-8 inhibitors FLIP and cIAP-2[49], TNF- α has a pro-survival effect through NF κ B pathway mediators such as NF κ B (NEMO) and I κ B kinase subunit 2[44]. On the other hand, BAFF activates NF κ B non-canonical pathway upregulating the expression of antiapoptotic proteins including Mcl-1, Bcl-XL, Bcl-w and Bcl-2[50]. There is also evidence indicating that IL-6 is



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Figure 1 Schematic representation of the main factors involved in the bidirectional communication between multiple myeloma cells and cells in the bone marrow microenvironment (bone marrow mesenchymal stem cells, osteoclasts, osteoblast, etc.). The main signaling pathways activated by these factors are also depicted (Created with Biorender.com). VEGF: Vascular endothelial growth factor; FGF: Fibroblast growth factors; HGF: Hepatocyte growth factor; OPN: Osteopontin; ECs: Endothelial cells; IL: Interleukin; SDF1 α : Stromal cell derived factor 1 α ; TNF- α : Tumor necrosis factor- α ; BAFF: B-cell activating factor; DKK-1: Dickkopf-1; MM: Multiple myeloma; BM-MSC: Bone marrow mesenchymal stem cells; JAK: Janus kinase; STAT3: Signal transducer and activator of transcription 3; NF κ B: Nuclear factor kappa-B; PI3K: Phosphatidylinositol 3-kinase; RANKL: Receptor activator of NF κ B ligand; Ang-1: angiopoietin-1; MEK: MAPK kinase; ERK: Extracellular signal regulated kinase; LIF1: Leukemia inhibitory factor-1. Created with BioRender.com.

linked to the expression of VEGF in MM cells, being some of the VEGF isoform expression driven by the NF κ B pathway[51,52].

The MEK/ERK pathway is the signaling pathway most found activated in MM patients, with a prevalence in between 43% and 53% of the patients[53]. Changes in MEK/ERK pathway have important effects in cell cycle, due to the alteration in the expression of molecules such as cyclin D1, cyclin E, Cdk2 and Cdk4 and in apoptosis prevention by the induction of the phosphorylation of the pro-apoptotic protein Bim. This phosphorylation results in the release of anti-apoptotic molecules such as Mcl-1, Bcl-XL and Bcl-2, also related to Akt pathway[54]. In the absence of mutations that activate this pathway, the stimulation of the MEK/ERK pathway in the MM cells might also occur by the action of different soluble factors present in the BM microenvironment such as BAFF, IL-6, SDF1 α , VEGF or TNF- α among others[42]. As with other relevant signaling pathways that become activated in MM, the MEK/ERK is also studied as a potential therapeutic target.

PI3K/Akt signaling pathway also has a relevant role in cell proliferation, cell cycle and apoptosis. Alteration of the PI3K/Akt/mTOR pathway due to genetic modifications or its hyper-activation contributes to carcinogenesis, metastasis, invasion, proliferation and drug resistance of tumor cells. However, no activating mutations have been described in MM cells yet. Despite this fact, PI3K/Akt/mTOR pathway is important for MM cells survival[55,56].

Role of soluble factors in angiogenesis and bone homeostasis

Up to this point, we have mentioned some of the effects of the pro-tumorigenic microenvironment in the BM on the MM cell survival and growth. However, once modified by the BM microenvironment, MM cells will start to release different soluble factors that will not only perpetuate that tumorigenic microenvironment, but also will have a deep impact in angiogenesis and bone homeostasis.

Neovascularization in the bone is an essential feature for MM progression and the presence of high density of micro-vessels in the BM microenvironment is characteristic in MM. Cells residing at BM, such as BM-MSCs, osteoblasts, HSCs, or endothelial precursor cells, commonly express various angiogenic

factors, such as VEGF, FGF-2, TNF- α , HGF, IL-6, BAFF, SDF-1 α , angiopoietin-1 or osteopontin (OPN). Also, MM cells are able to directly produce VEGF establishing a VEGF autocrine loop where the produced VEGF would stimulate MM cells proliferation through the MEK-1/ERK pathway[57,58]. FGF-2 is another key pro-angiogenic molecule that would be produced by both MM cells and BM-MSCs[59]. However, contrary to VEGF, which is produced by all MM cells, FGF-2 production by MM does not seem to be a general feature in all MM cases[59]. Other molecules with pro-angiogenic activity such as MMPs[60,61] or OPN, also produced by MM cells, have also a relevant role in promoting micro-vessels formation in the BM microenvironment. The overall increase in the production of such angiogenic factors is elicited by the MM cells. The activation of angiogenesis linked to tumor progression is known as “angiogenic switch”[62].

Bone homeostasis is a dynamic process driven by osteoclasts, osteoblast and osteocytes. Alterations in the balance between these cell types will lead to the remodeling of the bone. The characteristic bone lesions found in MM derive from the disruption of bone homeostasis initiated by the activation of JAK2/STAT3 pathway by IL-6 and the subsequent induction of RANKL expression by MM cells. Not only this but, as will be discussed later, cell-to-cell interaction of MM cells with BMSCs also induce the expression of the macrophage inflammatory protein (MIP)-1 α [63]. Both RANKL and MIP-1 α are mediators in the bone destruction driven by MM as they have an both in the number of osteoclasts and in their activity. MIP-1 α is a chemoattractant for osteoclasts and stimulates osteoclast formation[64], while RANKL after being recognized by its receptor RANK, will induce the commitment of the macrophage/monocyte precursor cells to the osteoclast lineage[65].

Secreted by MM cell in response to the activation of the JNK pathway, Dickkopf-1 (DKK-1) is also a disruptor in bone homeostasis[66]. DKK-1 is an extracellular inhibitor of the Wnt pathway. DKK-1 interacts with membrane receptors as transmembrane proteins Kremen 1/2 and the human low-density lipoprotein receptor-related protein 5/6, thus competing with Wnt[67]. As one of the main regulatory pathways for osteogenic differentiation of BM-MSCs into osteoblasts[68], the inhibition of the Wnt/ β -catenin pathway by DKK-1 will result in a reduced number of osteoblasts. By the action of these factors, RANKL, MIP-1 α and DKK-1, the balance between bone formation and bone resorption driven by osteoblasts and osteoclasts is disrupted, resulting in the characteristic bone lesions present in MM patients.

A table summarizing the latest scientific evidence regarding key factors involved in MM/BM-MSCs communication and their effect is shown (Table 1).

EVs-MEDIATED COMMUNICATION BETWEEN BM-MSCs AND MM CELLS

Under non-pathological conditions, BM homeostasis is maintained by cell-to-cell contact, soluble molecules, and EVs. Whereas, over the years solid evidence has accumulated about the relevance of the first two, the involvement of EVs-mediated communication in the maintenance of BM homeostasis has started to be contemplated only in the last few decades[69]. Despite being a fairly new field, important advances have been made in the knowledge of EVs, such as their classification, in terms of their size and biogenesis, into three major categories (exosomes, micro-vesicles, and apoptotic bodies) and the fact that its content varies according to the state of their parental cells[31].

As we have previously discussed, MM cells have the capacity to alter the environment in which they reside[70] as well as the characteristics of cells present in that microenvironment. Thus, it is not surprising that the EVs produced by MM cells also play a key role in disease progression. In fact, it has recently been shown that, exosomes (a particular class of EVs) produced by both BM-MSCs and MM cells are largely responsible for MM pathogenesis[71]. This recent demonstration of the relevance of EVs in MM progression has resulted in several studies in the last few years, however, the multitude of agents and interactions involved in the development and progression of this disease has made it difficult to fully understand the molecular mechanisms involved. In this section we aim to gather the available information so far.

Effect of MM-EVs on the BM-MSCs and bone homeostasis

As previously mentioned, osteolysis, one of the main hallmarks of MM disease, is linked to the negative effect of MM cells on cells responsible for bone homeostasis, such as MSCs, osteoblasts and osteoclasts [72]. In particular, myeloma bone disease (MBD) has a unique feature compared to other diseases that encompass bone destruction, since in MBD osteoblast activity is also severely impaired[24]. Several authors have suggested that an essential part of this bone damage is related to EVs directly produced by MM cells (MM-EVs). Zhang *et al*[73] demonstrated that the cargo of MM-EVs was enriched in various molecules which negatively regulate osteogenesis. They confirmed that MM-EVs induced high expression of miR-103a-3p in BM-MSCs, which led to impaired osteogenesis *in vitro*. Moreover, they showed that injection of MM-EVs in mouse tibia resulted in defective bone formation. Interestingly, *in vitro* assays also revealed that MM-EVs were also able to influence MM cells increasing viability and IL-6 production, known to regulate MM cell proliferation thus, establishing an autocrine feedback. MM-EVs also increased miR103a-3p expression in MM cells however, in those cells the increased prolifer-

Table 1 Summary for the key soluble factors involved in multiple myeloma/bone marrow mesenchymal stem cells communication

Soluble factors	Origin	Function	Ref.
SDF1 α	BMSCs	Chemoattractant of MM cell towards the BM microenvironment	[38]
IL-1 β	MM cells	Act over BMSCs inducing the secretion of soluble factors, mainly IL-6	[45]
IL-6	BMSCs	Closely related with cancer pathogenicity due to its proto-oncogenic and anti-apoptotic effect over MM cells Immunosuppressive effect over T cells Also related with bone destruction by inducing the expression of RANKL by the MM cells	[46,47]
VEGF	BM cells, MM cells	Promotes bone neovascularization, essential for tumour progression	[58]
RANKL	MM cells	Induce the commitment of the macrophage/monocyte precursor cells to the osteoclast lineage. Promoting indirectly bone destruction	[63]
DKK-1	MM cells	Disruptor of bone homeostasis by inhibiting BMSCs differentiation into osteoblasts	[66,67]

SDF1 α : Stromal cell derived factor 1 α ; BM-MSC: Bone marrow mesenchymal stem cells; MM: Multiple myeloma; IL: Interleukin; RANKL: Receptor activator of NF κ B ligand; VEGF: Vascular endothelial growth factor; DKK-1: Dickkopf-1.

eration of MM cells after exposures to MM-EVs does not seem to be related to miR103a-3p but to other miRNAs also present in the MM-EVs cargo, such as miR107 and miR181a-3p[24].

Among the different biomolecules found as part of the exosome cargo, long non-coding RNAs (lncRNAs) and miRNAs have been the focus of attention due to their key regulatory roles. Various miRNAs found in MM-EVs have been studied for their involvement in the disruption of osteogenesis. miR-129-5p was identified as a player in vesicle-mediated bone disease[74]. In particular, miR-129-5p seemed to inhibit the transcription factor specificity protein 1, leading to a reduction of ALPL, both at the mRNA and protein levels, during the early osteogenic differentiation of MSCs. On the other hand, the long non coding RNA Long Intergenic Non-Protein Coding RNA 461, found as part of the MM-exosomes cargo, has also been found to inhibit osteoblast differentiation by reducing the activity of Wnt/ β -Catenin pathways, responsible for osteoblast proliferation, differentiation and activity[75]. Other molecules, such as soluble proteins present in the MM-EVs cargo also showed anti-osteogenic activity. Faict *et al*[72] revealed that Wnt/ β -Catenin inhibitor DKK-1 is present in MM-EVs and observed a lower expression of Osterix (OSX), Collagen 1A1 and alkaline phosphatase in differentiated MC3T3-E1 cells after MM-EVs treatment.

Runx2 is the master regulator of early osteogenic differentiation, and therefore a possible target for the anti-osteogenic effect of MM-EVs. In fact, lncRNA RUNX2-AS1 present in the MM-EVs cargo was identified as a bioactive molecule able to reach MSCs and form a transcriptionally repressed RNA duplex with RUNX2 premRNA, reducing the osteogenic activity[76]. In addition, a MM-EVs impact in osteoblastic differentiation through reduction of Runx2, together with OSX and OCN, has been described by Liu *et al*[77]. These authors also record increased levels of IL-6 secretion *via* APE1/NF- κ B which, as aforementioned, is an important survival factor of MM cells.

Once the EVs produced by MM cells reach the BM-MSCs, their cargo modifies the BM-MSCs behaviour in the benefit of MM cells. A clear example of this is miR-146a which acts in a positive loop to favor disease progression[19]. Once this miRNA targets BM-MSCs, it produces an increase in the secretion of several cytokines and chemokines from those cells, including CXCL1, IL-6, IL-8, inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), and CCL-5, which, in turn, once released into the BM microenvironment, would favor MM cell viability and migration. In addition, MM-EVs cargo miR-146a and miR-21, participate in proliferation and transformation of MSCs into cancer associated fibroblasts (CAFs). This is a type of cell which could contribute to a tumour-supportive microenvironment through secretion of cytokines, including IL-6 and TGF- β [78].

Interestingly, it has been shown that conventional chemotherapeutic agents including melphalan, and anti-proteases such as bortezomib and carfilzomib can stimulate a considerable MM-EVs release. The EVs produced under these circumstances are called “chemoexosomes”. These chemoexosomes are characterized by the high presence of the heparanase enzyme in their surface. This heparanase is implied in several cellular changes leading to chemoresistance and the subsequent relapse of the patient. Heparanase EVs content is delivered in MM cells and activate ERK pathway as well as TNF- α production by macrophages, matrix degradation and migration promotion[71].

Effect of EVs produced by BM-MSCs on MM cells and MM progression

So far, we have analyzed the influence of MM-EVs on BM-MSCs, however, this communication, as previously mentioned, is bidirectional. In 2016, Wang *et al*[69] showed that BM-MSC-EVs from MM patients contained a lower level of the tumor suppressor miR-15a, and higher levels of oncogenic

proteins, cytokines, and adhesion molecules, when compared to EVs from healthy BM-MSCs. Cytokines such as IL-1 α , interferon-IP-10, MCP-1, MIP-1 α , MIP-1 β , and SDF1 α were detected in murine BM-MSC-EVs. They confirmed that BM-MSC-EVs from MM patients act on MM cells activating proliferation, survival, and migration, as well as drug resistance to bortezomib, a widely used clinical drug for MM treatment.

In a similar study, a reduction of mir-15a levels in the cargo of BM-MSCs-EVs from MM patients was also detected. This change was shown to promote cell proliferation and dissemination or metastasis to other niches, which is a hallmark of MM. The same authors also revealed the importance of some of the proteins present in BM-MSCs-EVs cargo, as they detected higher content levels of IL-6, CCL2, γ -catenin and fibronectin, which are key to MM pathogenesis[70]. Other miRNAs cargo were also implicated in these processes. miR-483-5p was found packed in BM-MSCs-EVs and was responsible for promoting MM cell proliferation and reduced apoptosis *via* the miR-483-5p/TIMP2 axis[79]. Umezue *et al*[80] highlighted the role of miR-10a in MM disease since its transference *via* BM-MSC-EVs promoted cell proliferation in several MM cell lines (RPMI 8226, KMS-11, and U266) compared to BM-MSC-EVs with miR-10a blocked. Moreover, Gao *et al*[81] studied miR-155 present in BM-MSC-EVs cargo, which turned out to be involved in viability, stemness and drug resistance in MM cells. The role of miR-155 was underscored by the fact that incubation of the MM cells line mitochondrial pyruvate carrier 11 (MPC-11) with miR-155-mimics for 24 h resulted in a significantly reduced cell apoptosis *in vitro* and augmented expression of stemness maintenance markers OCT-4 and Nanog and drug resistance-associated proteins MRP1, ABCG2 and P-g.

As in the previous section, a table summarizing the main works referred to the relevance of communication between MM cells and BM-MSCs through EVs and the role of their cargo is shown (Table 2).

The resistance to treatment is precisely one of the major problems in MM at the clinical level, as this is directly responsible for the relapses. Some studies investigating the mechanisms behind this resistance have highlighted the implication of the activation of several signaling pathways, including p38, p53, c-Jun N-terminal kinases and Akt through the assessment of bortezomib treatment. The role of BM-MSC-EVs in interfering with the antitumor effect developed by bortezomib in MM was confirmed through different experiments. BM-MSC-EVs were able to alter apoptosis-related proteins Bcl-2, Bax, caspase-8, caspase-9, and caspase-3 promoting an antiapoptotic profile in both murine and human cells. These EVs blocked the significant reduction of Bcl-2 expression caused by bortezomib and reduced cleaved caspase-9, caspase-3, and PARP either in the absence or presence of bortezomib. Moreover, the use of GW4869, a neutral sphingomyelinase inhibitor of the formation of exosomes by the ceramide pathway, in combination with bortezomib treatment led to a significant effect on tumor load reduction[71,82].

In conclusion, the two-way communication between MM cells and BM-MSCs mediated by EVs is extremely intricate and plays a pivotal role in the progression of the disease. Since BM-MSCs-EVs have a key role in supporting MM development, this could become a key target to develop new therapies for the treatment of this hematological disease.

COMMUNICATION THROUGH CONTACT DEPENDENT MECHANISMS

As well as the already described interactions through paracrine secretion of different cytokines and EVs, MM cells also interact with BM-MSCs by direct cell-to-cell contact. These cell-to-cell interactions are not restricted to MM and BM-MSCs since MM cells also interact with other cells of the BM microenvironment such as osteoclasts and osteoblasts, endothelial cells, and lymphocytes. It is known that these contacts are also key to protect MM cells against chemotherapy, helping them to accumulate inside the BM[83], to adhere to endothelium, and to spread into the bloodstream[84], although the detailed mechanisms involved in those processes have not been completely elucidated[85].

Cell adhesion molecules in MM/BM-MSCs communication

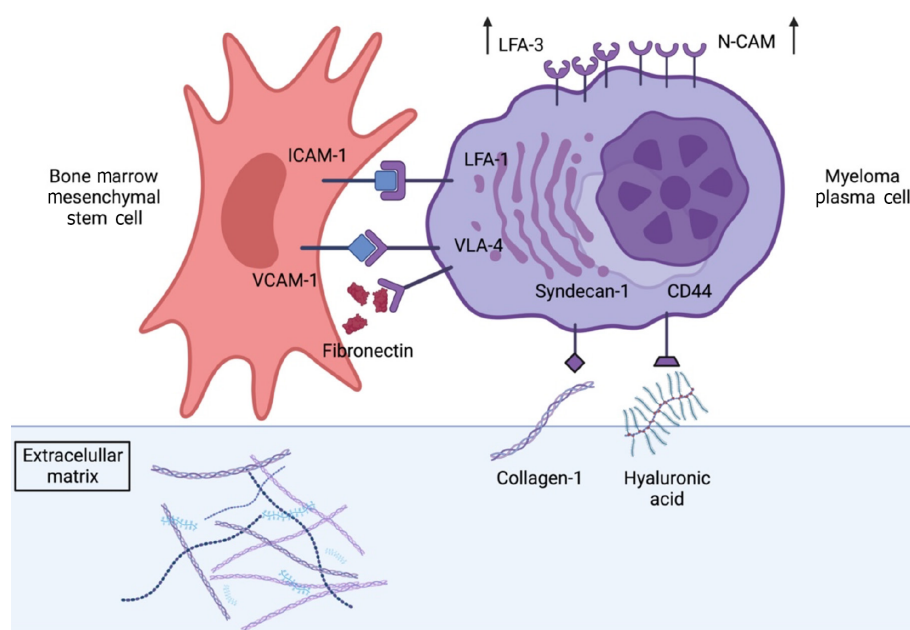
Direct cell-to-cell adhesion and communication mechanisms have been known for more than 40 years [86,87]. These cell-to-cell communication is mediated by Cell Adhesion Molecules (CAMs), a subcategory of adhesion proteins located at the cell surface, involved in binding either to other cells, or in attaching cells to proteins of the ECM[88], such as fibronectin, laminin or collagen (Figure 2). While it has been well documented that the ECM promotes the survival of different types of tumors, much less is known about the influence of the direct contact of BM-MSCs in their progression.

CAMs play a central role in cell communication and the maintenance of tissue homeostasis[89]. There are different superfamilies or groups of CAMs with different specificities and distributions. These families would include the Immunoglobulin superfamily CAMs (IgCAMs), integrins, cadherins and one superfamily of proteins that contain a C-type lectin-like domain (C-type lectin domain proteins or CTLDs)[89]. Following other criteria, CAMs can be classified into calcium-independent or calcium-dependent molecules[90], meaning that these molecules would need Ca²⁺ ions binding to different domains of the protein in order to rigidify their extracellular domains and enable interaction[91]. Integrins and IgCAMs belong to the calcium independent group whereas CLTDs and selectins belong to

Table 2 Summary of evidence about the relevance of different cargo molecules in the extracellular vesicles of multiple myeloma cells and bone marrow mesenchymal stem cells to the progression of multiple myeloma

	Function	Ref.
MM-EVs cargo		
lncRNA RUNX2-AS1	Form a RNA duplex with RUNX2 premRNA, reducing the osteogenic activity in MSCs	[76]
miR-146a	Increase the secretion of several cytokines in BM-MSCs that favor MM cell viability and migration and induce CAF transformation	[78]
DKK-1	Lower expression of OSX, COL1A1 and ALP in osteoblast precursor cell line (MC3T3-E1)	[72]
MSC-EVs cargo		
mir-15a	Promote MM cell proliferation and dissemination to other niches	[70]
miR-483-5p	Induce MM cell proliferation and reduced apoptosis	[79]
miR-155	Reduce MM cell apoptosis and augment expression of stemness maintenance and drug resistance markers	[81]

EVs: Extracellular vesicles; MM: Multiple myeloma; BM-MSC: Bone marrow mesenchymal stem cells; CAF: Cancer associated fibroblast; DKK-1: Dickkopf-1; OSX: Osterix; COL1A1: Collagen 1A1; ALP: Alkaline phosphatase.



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Figure 2 Schematic representation of the main cell adhesion molecules in multiple myeloma cells and bone marrow mesenchymal stem cells. The main interactions between cell adhesion molecules (CAMs) of these two types of cells as well as the interactions of these CAMs with proteins of the extracellular matrix are displayed (Created with Biorender.com). ICAM-1: Inter cellular adhesion molecule 1; VCAM-1: Vascular cell adhesion molecule-1; LFA-1: Leukocyte function-associated antigen 1; N-CAM: Neural cell adhesion molecule; VLA: Very late antigen. Created with BioRender.com.

calcium dependent group[92]. Cell adhesion molecules bind to different ligands. Cadherins, selectins and IgCAMs are associated with the cell-to-cell contact, while integrins are involved in the attachment of MM cells to the ECM[93]. All these molecules are integral in modeling cellular mechanisms such as growth, contact inhibition and apoptosis. In fact, changes in cell adhesion, involving these molecules, can be the defining event in a wide range of diseases, including cancer development[94], as lower intercellular adhesiveness allows malignant cells to scape from their site, thus, destroying the architecture of the original tissue, commonly the first step leading to cancer[94].

As well as the already described interactions through paracrine secretion of different cytokines and EVs, MM cells also interact with BM-MSCs by direct cell-to-cell contact. In fact, recent studies revealed that many of the changes undergone by BM-MSCs supporting the progression of MM, are acquirable by physical contact with MM cells[95]. In MM, this cell-to-cell interactions are not restricted to MM and BM-MSCs since MM cells also interact with other cells of the BM microenvironment such as osteoclasts and osteoblasts, endothelial cells, and lymphocytes. All these interactions are regulated by CAMs. It is

known that these contacts are key to protect MM cells against chemotherapy, helping them to accumulate inside the BM[83], to adhere to endothelium, and to spread into the bloodstream[84], although the detailed mechanisms involved in those processes have not been completely elucidated[85].

The most relevant role of CAMs in MM pathophysiology is related to the homing of malignant PCs to the BM. To complete the process of homing, mediated by CXCL12, MM cells need to adhere to either ECM proteins or BM-MSCs. This is mediated by CAMs such as very late antigen (VLA)4, VLA5, CD44, leukocyte function-associated antigen 1 (LFA-1), intercellular adhesion molecule 1 (ICAM-1), MPC-1 and syndecan (Figure 2).

One way of ensuring adhesion of MM to the ECM is the binding of its integrin VLA-4 to fibronectin, a common component of the ECM. VLA-4, which is in fact a heterodimer of two integrins CD49d(a4) and CD29(b1), also mediates the interaction of MM cells with BM-MSCs, through the vascular cell adhesion molecule-1 (VCAM-1), located at the BM-MSCs[96]. This interaction activates the secretion of MIP-1 α and MIP-1 β in MM cells, leading to an increase of osteoclastogenic activity[97]. Moreover, the direct contact of these two types of cells through VLA-4 also induces the production of DKK-1 by MM cells, which inhibits osteoblastic differentiation of BM-MSCs. Thus, these two actions, promotion of osteoclastogenesis and inhibition of osteogenesis, would have a detrimental effect on bone structure, contributing to the typical osteolytic lesions in MM. In addition, BM-MSCs unable to undergo osteoblastic differentiation would produce higher levels of IL-6, a cytokine that would stimulate the proliferation of DKK-1-secreting MM cells[25]. Moreover, it has been observed that VLA-4–fibronectin binding is an essential step that supports the IL-6-mediated induction of PCs in normal BM, since antibodies against VLA-4 were found to inhibit the secretion of IL-6 in co-cultures of MM cells and BM-MSCs cells[96,98,99].

The interaction between MM cells and BM-MSCs is also mediated by ICAM-1 (CD54) and LFA-1 (CD11 α /CD18) expressed in BM-MSCs and MM respectively. The glycoprotein ICAM-1 is the main ligand for b2 integrins and its expression is induced in response to an inflammatory microenvironment [100], such as the one resulting in the BM following the colonization by MM cells. The ICAM-1/LFA-1 interaction seems to have a key role in the progression of MM since the blocking of LFA-1 through the use of monoclonal antibodies, inhibits the production of IL-6 by BM-MSCs. Thus, this interaction is focus of various studies aimed to the development of treatments for MM[101].

Syndecan (CD138) is the principal transmembrane proteoglycan expressed in the surface of MM cells and has in fact been used as a marker for the detection of this pathology. Syndecan has multiple functions in MM. This molecule mediates de adhesion of MM cells to the collagen in the ECM through direct interaction with collagen molecules but can also mediate myeloma cell-cell adhesion[102]. Syndecan-1 also plays a broad role in cells signaling since heparan sulfate chains on syndecan-1 can bind to and sequester growth factors and cytokines, regulating their availability to cells. Also, a recent study has shown that syndecan contributes to the survival of mature MM cells by enhancing IL-6 signaling[103]. Finally, the binding of syndecan to VEGF and other angiogenic factors, has been shown to promote angiogenesis in MM[104].

Finally, CD44, a transmembrane glycoprotein, interacts mainly although not exclusively with hyaluronic acid in the ECM[105]. CD44 signaling has been shown to activate various signaling pathways in different types of cancer including PI3k/AKT, MAPK/ERK and NF- κ B[106], which, as we have seen, promote MM cell survival.

Although normal PC and MM cells express basically the same set of CAMS, some of these molecules were found to be more significantly overexpressed in MM cells when compared to healthy patients. In this group we can include, leukocyte adhesion molecule LFA-3 (CD58)[107] and neural cell adhesion molecule (CD56)[108]. MM cells can also express the lymphocyte function-associated antigen LFA-1 (CD11 α /CD18) which was associated with tumor growth and homotypic tumor cell adhesion or aggregation[109]. It is also worth mentioning that some homing molecules could not be detected on MPCs: Selectin molecule L-selectin and collagen receptor VLA-2[89]. Although this study provides relevant information, for this information to be biologically relevant, ligands of these receptors had to be available within the tumor environment.

Overall, given the importance of some of these CAMs in the process of MM cells homing, these molecules could be important targets for designing antitumoral treatments. Several approaches have been explored, including antibodies specifically targeting these molecules on the cell surface, as well as small molecule inhibitors that interfere with the binding of the CAMs to their ligands. Moreover, receptor-blocking antibodies against most of these CAMs (VLA-4, CD56, MPC-1, CD21) were found to partially block MM cells adhesion to the BM stroma. This partial effect could be attributed to an additional adhesion mechanism yet to be discovered[110,111].

In MM a specific type of drug resistance seems to be mediated by CAMs, the so called, CAMs mediated drug resistance[112]. CAMs can activate intracellular pathways that promote cell survival, promote cancer cell adhesion to the ECM and regulate the expression of drug transporters that could pump chemotherapy drug out of cancer cells and reduce their efficacy. It is also important to highlight that MM spreading in the last stages of the diseases also involve important changes in cell adhesion. MM can abandon de BM microenvironment and become stroma independent because of different processes involving changes in the expression levels of CAM and certain cytokines. Once this happens, cells can be found to spread extramedullary at different sites such as lungs, liver, or pleural fluid[113, 114].

Role of tunneling nanotubes in MM/BM-MSCs communication

As we have seen, communication between MM and BM-MSCs cells can take place through mechanisms that can be classified as contact-dependent and/or contact-independent mechanisms[115]. While the previous section has been dedicated to direct communication mediated by cell adhesion molecules, in this last section we will briefly discuss transport *via* tunneling nanotubes (TNTs), another form of contact-dependent interaction.

TNTs are transient intercellular structures formed by the polymerization of F-actin which provide an important and general mechanism of cell-to-cell communication[116,117] and constitute a reliable infrastructure for vesicle and protein trafficking[118]. Numerous examples of communication between MSCs and malignant hematological cells such as B cells, MM and chronic lymphocytic leukemia, are already known, as well as the effects of this communication, such as increased drug resistance. This has already been demonstrated in acute myeloid leukemia (AML), B-cell precursor acute lymphocytic leukemia (ALL) or CML[119,120]. Therefore, TNTs are considered one of the key pharmacological targets in current research.

The role of TNTs is to deliver autophagosomes, mitochondria and other lipophiles to MSCs. This induces the secretion of specific cytokines, including interferon- γ -IP-10, CXCL10, IL-8, MCP-1 and CCL2 and other growth factors which, in turn, induce tumor cell survival, enhanced growth and even drug resistance[121]. This has been checked in AML, where increased survival of cells against chemotherapy treatments is observed by means of mitochondrial transfer from MSCs routed by TNT. In this case, the mitochondrial transfer translates into an increase of up to 14% in mitochondrial mass in co-cultures of tumor cells with MSCs and a 1.5-fold increase in mitochondrial adenosine triphosphate production (ATP), making them less prone to mitochondrial depolarization and thus resulting in increased survival against chemotherapy treatments[122].

Numerous lines of treatment are currently under development for various hematological diseases that reduce the formation of TNT by blocking actin polymerization. This inhibits the cellular communication that promotes disease progression. Those treatments include cytochalasin D, cytarabine, latrunculin A and B, daunorubicin, everolimus, metformin, nocodazole CK-666, ML-141 or 6-thio-GTP [123]. In addition, vinca alkaloids or taxanes are also being targeted because of their role in the polymerization of microtubules[124].

Although the fate of mitochondria transferred into tumor cells remains unclear, there is evidence indicating that MSCs play a key role in the progression of AML, ALL, MM and mitochondrial transfer chemoresistance. It is well known that the initiation of cancer requires metabolic adjustments, since rapid proliferation cancer cells have high metabolic requirements. This mitochondrial and/or mitochondrial DNA transfer to cancer cells increases mitochondrial content and enhances the mitochondrial process of oxidative phosphorylation (Oxphos), which generates a larger quantity of ATP than glycolysis, thus, promoting cell proliferation and invasion[125]. Therefore, targeting mitochondrial respiration and Oxphos is also a treatment option, FOXM1 is known to regulate myeloma cell metabolism by increasing glycolysis and Oxphos. NB73 is a FOXM1 inhibitor that promotes FOXM1 degradation and thus growth of MM cells, making it a potential drug targeting Oxphos[126].

Studies to date have elucidated that mitochondrial transfer dynamically induced resistance occurs between MM cells and other cells in the BM microenvironment *via* TNT, providing a starting point for the development of new targeted therapies[127]. An example of this line of treatment for MM is the use of anti-CD38 monoclonal antibodies[128]. These antibodies have different mechanisms of action, including cell apoptosis[129]. Moreover, their administration in mice has shown inhibition of mitochondrial transfer, a reduction in tumor volume and, in general, increased survival[1]. However, it should be noted that, although patients who have received this treatment show increased survival, it has been observed that resistance to these treatments can be acquired in the long term.

CONCLUSION

Conditions at the BM microenvironment are essential for the establishment and progression of MM. The complex BM microenvironment encompasses hematopoietic cells, immune cells, and cells involved in bone homeostasis such as osteoclasts, osteoblasts and BM-MSCs. Thus, it is understandable that the disruption of microenvironment homeostasis by MM cells results in angiogenesis, osteolysis, immune suppression and anemia[69].

As key regulators of this microenvironment, BM-MSCs play an important role in the progression of the disease. The crosstalk between MM cells and BM-MSCs takes place at different levels, through soluble cytokines, EVs, and direct cell-to-cell contact.

The interaction between these two cell types can have both positive and negative effects on the proliferation and survival of MM cells. The communication between MM cells and BM-MSCs can promote tumor growth. The survival and proliferation of MM cells once they reach the BM is associated with immune suppression, eliminating the possibility of an effective antitumor response. Although it is the interaction between all cells in the BM what produces this immunosuppressive microenvironment, BM-MSCs have a relevant role in the construction of this particular microenvironment due not only to their

important paracrine activity, but also to their ability to establish direct communication with other cells in that microenvironment. All these direct or indirect interactions activate a pleiotropic proliferative and antiapoptotic cascades favoring disease progression.

On the other hand, the communication between MM cells and BM-MSCs can also have a negative impact on cancer cell growth and survival. BM-MSCs can secrete factors that inhibit the growth and survival of MM cells.

Currently, therapeutic advances in the treatment of this disease are based on targeted therapies using monoclonal antibodies or CAR-T. These treatments have improved patient prognosis, although long-term resistance is still observed, and further research is needed into the specific mechanisms by which cells acquire this resistance. In the quest for new effective treatments for MM, the importance of communication between MM cells and BM-MSCs cannot be overstated. Understanding the molecular mechanisms involved in this two-way communication can provide valuable insights into MM pathogenesis and help identify key targets involved in the survival and proliferation of MM cells in the BM microenvironment and thus, opening new opportunities for the design of targeted therapies to avoid disease progression.

FOOTNOTES

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