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aMM asymptomatic Multiple Myeloma	2
BM Bone Marrow	2
BMPC Bone Marrow Plasma Cell	5
MGUS Monoclonal Gammopathy of Undetermined Significance	2
MM Multiple Myeloma	2
MMR Multiple Myeloma Relapse	3
PCL Plasma Cell Leukemia	2
SP Solitary Plasmacytoma	2

Introduction

Multiple Myeloma and Other Monoclonal Gammopathies

Multiple Myeloma (MM) is a hematological malignancy characterized by the clonal expansion of malignant plasma cells primarily within multiple sites of the Bone Marrow (BM). This cancer arises from plasma cells, the antibody-producing cells of the immune system, which undergo malignant transformation resulting in uncontrolled growth and disruption of normal bone marrow function (P. Yang et al., 2022). The prevalence of multiple myeloma has tripled across both Europe and USA from 1980 to 2014 due to an ageing population (Ocias et al., 2016; Turesson et al., 2018). For 2024, 35780 new MM cases and 12540 deaths are estimated for the USA alone (Siegel et al., 2024).

To understand the progression of a healthy plasma cell to MM, one can review other *monoclonal gammopathies*. These are defined by the presence of monoclonal immunoglobulin in the blood serum which is indicative of abnormal plasma cell clones overexpressing the same type of dysfunctional antibody. (Kyle, 1997; Fermand et al., 2018). When no further disease manifestations are present, the condition is termed *Monoclonal Gammopathy of Undetermined Significance* (MGUS), which is the most commonly diagnosed monoclonal gammopathy (Kyle, 1997). MGUS has a 1-5 % annual risk of progression to MM (Rajkumar et al., 2014).

To distinguish MM from other monoclonal gammopathies, diagnosis of MM requires not only identification of a minimum of clonal plasma cells, but also a *myeloma defining event* which is evidence of malignancy or end-organ damage, such as hypercalcemia, renal insufficiency, anemia, or bone lesions (Rajkumar et al., 2014). A localized smaller¹ mass of clonal plasma cells together with a singular primary bone lesion is diagnosed as Solitary Plasmacytoma (SP). SP can progress to MM in 32 % of cases with a median follow-up of 9.7 years (Thumallapally et al., 2017; S. Gao et al., 2024). Studies from Kyle (1997) show that SP cases are rare, constituting only 2.5 % of monoclonal gammopathy diagnoses, whereas MM represent 18 %. Another rare precursor of MM is *smouldering* or *asymptomatic Multiple Myeloma* (aMM), representing 3 % of monoclonal gammopathies (Kyle, 1997). aMM is diagnosed when no myeloma defining event is detected, although the quantities of clonal plasma cells or monoclonal protein align with respective criteria for MM diagnosis. (Rajkumar et al., 2014). Recent reports show that if left untreated, 72 % of aMM patients progress to MM, whereas early treatment can lower the progression rate to 11 % within up to 7.6 years until last follow-up² (Abdallah et al., 2024; Mateos María-Victoria et al., 2013). MM itself can progress to advanced stages, such as *extramedullary involvement/disease* which describes colonization of soft tissues outside the bone marrow (Bladé et al., 2022), but also Plasma Cell Leukemia (PCL) which

¹Rajkumar et al. (2014): “*Solitary plasmacytoma with 10 % or more clonal plasma cells is regarded as multiple myeloma. [...] If bone marrow has less than 10 % clonal plasma cells, more than one bone lesion is required to distinguish [MM] from solitary plasmacytoma with minimal marrow involvement.*”

²For non-high risk aMM patients, treatment lowered MM progression rate to 9 %, compared to 31 % for untreated patients (within up to 6.7 and 7.6 years of follow-up, respectively). For high-risk aMM patients, treatment lowered aMM progression rate to 11 %, compared to 72 % for untreated patients (within up to 5.2 years of follow-up and median time to progression of 2.2 years, respectively) (Abdallah et al., 2024).

is characterized by high levels of circulating plasma cells (Jung & Lee, 2022). However, the most common cause of death is renal failure during the MM stage, caused by excess immunoglobulins or hypercalcemia due to bone degradation (Kundu et al., 2022).

With a 5-year survival rate of 50 % (Turesson et al., 2018), MM can be considered incurable and deadly. MM relapses within the first year in 16 % of patients (Multiple Myeloma Relapse (MMR)), others face relapse at a later time or only continued response to treatment (Majithia et al., 2016). Although treatments have improved, the age-adjusted mortality rate of MM has decreased from 1999 to 2020 by only -1.6% (Doddi & Rashid, 2024). Engelhardt et al. (2024) describes the current standard care for transplant-eligible newly diagnosed MM patients as follows: Induction with a CD38 antibody, proteasome inhibitor, immunomodulatory drug, and dexamethasone, potentially followed by bone marrow transplantation and lenalidomide maintenance (Rajkumar & Kumar, 2020). A major challenge to these treatments is the continued cycle of remission and relapse, with each relapse generally being harder to treat (Podar & Leleu, 2021). Development of such resistance is well described in the literature, often arising from the intraclonal genetic heterogeneity within the myeloma cell population and the protective niche provided by the bone marrow microenvironment (Solimando et al., 2022).

Dissemination of Myeloma Cells

As the name suggests, *multiple* myeloma involves spreading of clonal plasma cells in multiple sites within the body, a process that’s described with the term *dissemination*. Although a single large plasmacytoma is still classified as MM (Rajkumar et al., 2014), the presence of multiple tumor lesions within the BM is very common. More than one or 25 such lesions predict poor prognosis for asymptomatic and symptomatic MM patients, respectively (Kastritis et al., 2014; Mai et al., 2015). Additionally, MM cells can disseminate to extramedullary sites of virtually any tissue, highlighting MM as a systemic disease with potential multi-organ impact (Rajkumar & Kumar, 2020; Bladé et al., 2022). Hence, dissemination is a major contributor to MM progression and poor prognosis, enabling MM cells to colonize new niches that favor survival, quiescent states or are less accessible for therapy, especially with high subclonal heterogeneity (Forster & Radpour, 2022; Keats et al., 2012).

Dissemination of MM is reminiscent of *metastasis*, a term typically associated with solid tumors describing the spread of cancer cells to distant sites. However, it substantially differs from metastasis due to the hematological or “liquid” nature of MM. Long-lived plasma cells originate from migratory B-cells, negating the need for extensive transformative processes such as *epithelial to mesenchymal transition*, which is required for escaping tightly connected solid tissues to enter the bloodstream (Ribatti et al., 2020). Although referred to as “liquid tumor”, MM cells still accumulate as distinct foci within the bone marrow, somewhat mirroring the localized growth of solid tumors. This characteristic has led to MM being proposed as a model for studying solid “micrometastases” (Ghobrial, 2012),

highlighting its unique blend of liquid and solid tumor properties and providing insights into the mechanisms of cancer dissemination and colonization of new niches.

The exact mechanism of MM dissemination is not entirely understood. Nevertheless, attempts to structure this process have been made by Zeissig et al. (2020), describing MM dissemination in five steps: *Retention in the BM*, *release from the BM*, *intravasation*, *extravasation*, and *colonization*. According to Zeissig et al. (2020), MM dissemination begins with MM cells overcoming retention and adhesion within the Bone Marrow environment (BME). Following release, MM cells undergo *intravasation* into the bloodstream, where they can circulate before extravasating into new BM sites. This migration is directed by chemokines and growth factors produced by BM cells. For instance, CXCL12 and IGF-1 are critical in guiding MM cells back to the BM, a process called *homing* (Vande Broek et al., 2008). In the BM they can *colonize* and form new tumor foci.

The review by Zeissig et al. (2020) implies a sequential order of such steps, yet direct proof of this is lacking. Still, the review provides a framework that integrates multiple complex research topics into one coherent context. For instance, Zeissig et al. (2020) states that two adhesive processes are critical for successful dissemination: Lowered adhesion to the BM, but increased adhesion to the endothelium to initiate extravasation (Asosingh et al., 2001; Mrozik et al., 2015). This alone implies stringent separation of different adhesive processes during the dissemination process. Given that cell adhesion molecules (CAMs) have become attractive targets for treating MM (Bou Zerdan et al., 2022; Katz, 2010), such detailed understanding of cell adhesion is crucial for developing successful therapies.

Retention of Myeloma Cells in the Bone Marrow

According to Zeissig et al. (2020), overcoming retention and adhesion to the BME is critical to MM dissemination. Retention of plasma cells to the BME is mediated by multiple mechanisms, which are categorized here into *direct adhesion*, *soluble survival factors* and *chemotaxis*. A fourth notable mechanism is the physical boundary that is bone tissue and extracellular matrix (ECM), which could become important for MM dissemination once degradation of bone tissue has progressed.

Direct adhesion of MM cells to the BM is mediated through ECM components and cell adhesion to other BM resident cells like osteoblasts, osteoclasts and mesenchymal stromal cells (BMSCs) (Bou Zerdan et al., 2022). ECM components include fibronectin, collagens, and proteoglycans such as decorin (Hu et al., 2021; Huang et al., 2015; Katz, 2010; Kibler et al., 1998). Bone Marrow mesenchymal stromal cells (BMSCs) are vital in this niche, supporting cell adhesion through cell adhesion molecules (CAMs) but also by secretion of extracellular matrix (ECM) components (Katz, 2010). Such adhesion acts both as physical anchorage but also provides signaling cues for growth, survival, and drug resistance. A classic example is the binding of MM cell integrins to VCAM-1 on BMSCs, such as $\alpha 4 \beta 1$ (VLA-4) (Bou Zerdan et al., 2022). Since direct adhesion promotes both

retention and tumour growth, it could play an ambiguous role during MM progression.

Soluble survival factors contribute to BM retention, since plasma cells can not survive outside the bone marrow without them. For example, deleting BCMA — a receptor for survival factors — leads to loss of Bone Marrow Plasma Cells (BMPCs) due to unsustained maintenance of cell survival (O'Connor et al., 2004). Soluble survival factors include IL-6, IGF-1, BAFF, APRIL, and VEGF, although IGF-1 has proven to be the primary survival factor (Sprynski et al., 2009). These signals are secreted by the bone marrow MSCs and adipocytes (Kibler et al., 1998; García-Ortiz et al., 2021). *Chemotaxis* is also crucial for BM retention. CXCL12 and CXCL8 are soluble chemotactic signals produced by BMSCs and attract MM cells, but also primes their cytoskeleton and integrins for adhesion (Aggarwal et al., 2006; Alsayed et al., 2007).

Together, BMSCs play a critical role in MM retention, providing direct adhesion, soluble survival factors, and chemotactic signals.

Release of Myeloma Cells from the Bone Marrow

Zeissig et al. (2020) describes the release of myeloma cells from the BME as all steps required for overcoming bone marrow retention, but also putative triggers leading to migration out of the BME. To the author's knowledge, release of MM cells is the least understood within the dissemination process. Still, initial results can be summarized, hinting at mechanisms that could be involved in this process to better understand dissemination.

Loss of adhesion: While the specific microenvironmental stimuli regulating this release are not fully defined, changes in the expression of CAMs play a role. For example, circulating MM cells show lower levels of integrin $\alpha4\beta1$ compared to those residing in the BM, implying a dynamic downregulation of adhesion molecules for release (Paiva et al., 2013, 2011). On the other hand, Terpos et al. (2016) reported increase in adhesion molecule expression of ICAM-1 and VCAM-1 in patients with MM compared to those with MGUS and aMM. This further shows that regulation of CAMs can depend both current microenvironmental factors and on the stage of the disease.

Hence, adhesion molecules can be ambiguous role during in MM dissemination and progression.

A study from Akhmetzyanova et al. (2020) presents CD138 (*aka* Syndecan-1) as a potential *switch* between adhesion and release as treatment with a CD138 blocking antibody has been shown to rapidly induce the mobilization of MM cells from the BM to peripheral blood in a mouse model, suggesting that alterations in adhesion molecule expression facilitate MM cell release. Brandl et al. (2022) builds on that finding, showing that JAM-C inversely correlates with CD138 expression while promoting MM progression in a mouse model.

Notably, active degradation of bone tissue removes both adhesion to ECM components, but also

physical boundaries for MM cells, allowing them to disseminate to other sites. This process is driven by a “vicious cycle” that maximizes bone destruction by extracting growth factors (EGF and TGF-) stored in calcified tissues.

- Survival Factors: MM cells must become partially independent from essential survival factors. This independence is acquired through autocrine survival signaling, as exemplified by the VLA4 –VCAM1 -interface

- Loss of Retention:

- Hypoxia: The hypoxic conditions within the BM during MM growth also influence cell release. Hypoxia induces changes in MM cell adherence to BMSCs and collagen, which may facilitate their release from the BM niche. Hypoxia-induced factors like HIF-2 can decrease MM cell responsiveness to stromal-derived CXCL12, thereby disrupting the CXCR4/CXCL12 retention signal and facilitating MM cell release (Zeissig et al., 2020).

hMSCs: Human Mesenchymal Stromal/Stem Cells

The previous sections mentioned hMSCs several times, being a critical component of the bone marrow microenvironment (BME) in the context of multiple myeloma (Mangolini & Ringshausen, 2020). Before discussing their role in MM specifically, it is important to understand what hMSCs are.

Explaining what a mesenchymal stromal cell (MSC) is, can be challenging. MSCs are derived from multiple different sources, serve a wide array of functions and are always isolated as a heterogeneous group of cells. This makes it particularly challenging to find a consensus on their exact definition, nomenclature, exact function and *in vivo* differentiation potential. Therefore, the following paragraphs provide a brief overview of the biology of MSCs set within a historical context.

hMSCs first gained popularity as a stem cell. Stem cells lay the foundation of multicellular organisms. Embryonic stem cells orchestrate the growth and patterning during embryonic development, while adult stem cells are responsible for regeneration during adulthood. The classical definition of a stem cell is that of a relatively undifferentiated cell that divides asymmetrically, producing another stem cell and a differentiated cell (Cooper, 2000; Shenghui et al., 2009). Because of their significance in biology and regenerative medicine, stem cells have become a prominent subject in modern research. Especially human mesenchymal stromal cells (hMSCs) have proven to be a promising candidate in this context (Ullah et al., 2015).

Mesenchyme first appears in embryonic development during gastrulation. There, cells that are committed to a mesodermal fate, lose their cell junctions and exit the epithelial layer in order to migrate freely. This process is called epithelial-mesenchymal transition (Tam & Beddington, 1987; Nowotschin & Hadjantonakis, 2010). Hence, the term mesenchyme describes non-epithelial embry-

onic tissue differentiating into mesodermal lineages such as bone, muscles and blood. Interestingly, it was shown nearly twenty years earlier that cells within adult bone marrow seemed to have mesenchymal properties as they were able to differentiate into bone tissue (A. J. Friedenstein et al., 1966; A. Friedenstein & Kuralesova, 1971; Bianco, 2014). This was the origin of the “*mesengenic process*”-hypothesis: This concept states that mesenchymal stem cells serve as progenitors for multiple mesodermal tissues (bone, cartilage, muscle, marrow stroma, tendon, fat, dermis and connective tissue) during both adulthood and embryonic development (A. Caplan, 1991; A. I. Caplan, 1994). The mesenchymal nature of these cells (termed bone marrow stromal cells: BMSCs) was confirmed later when they were shown to differentiate into adipocytic (fat) and chondrocytic (cartilage) lineages (Pittenger et al., 1999). Since then, the term “*mesenchymal stem cell*” (MSC) has grown popular as an adult multipotent precursor to a couple of mesodermal tissues. hMSCs derived from bone marrow (BMSCs) were shown to differentiate into osteocytes, chondrocytes, adipocytes and cardiomyocytes (Gronthos et al., 1994; Muruganandan et al., 2009; Xu et al., 2004). Most impressively, these cells also exhibited ectodermal and endodermal differentiation potential, as they produced neuronal cells, pancreatic cells and hepatocytes (Barzilay et al., 2009; Wilkins et al., 2009; Gabr et al., 2013; Stock et al., 2014).

It was later established that cultures with MSC-like properties can be isolated from “virtually every post-natal organs and tissues”, and not just bone marrow (da Silva Meirelles et al., 2006). However, depending on which tissue they originated from, hMSCs can differ greatly in their transcription profile and *in vivo* differentiation potential (Jansen et al., 2010; Sacchetti et al., 2016).

Since hMSCs are a heterogenous group of cells, they were defined by their *in vitro* characteristics. A minimal set of criteria are the following (Dominici et al., 2006): First, hMSCs must be plastic adherent. Second, they must express or lack a set of specific surface antigens (positive for CD73, CD90, CD105; negative for CD45, CD34, CD11b, CD19). Third, hMSCs must differentiate to osteoblasts, adipocytes and chondroblasts *in vitro*. Together, hMSCs exhibit diverse differentiation potentials and can be isolated from multiple sources of the body.

hMSC–Myeloma Interactions

As mentioned in previous sections, MSCs are key drivers of MM pathology through mediating retention and survival of MM cells in the bone marrow (Mangolini & Ringshausen, 2020). Here, we outlay details of such interactions and present further mechanisms how interactions between MM and hMSC contribute to MM progression.

bone marrow microenvironment

it plays a

myeloma bone disease.

Bone is a two-phase system in which the mineral phase provides the stiffness and the collagen fibers provide the ductility and ability to absorb energy (Viguet-Carrin et al., 2006). On a molecular level, bone tissue is composed of extracellular matrix (ECM) proteins that are calcified by hydroxyapatite crystals. This ECM consists mostly of collagen type I, but also components with major regulatory activity, such as fibronectin and proteoglycans that are essential for healthy bone physiology (Alcorta-Sevillano et al., 2020). Bone tissue is actively remodeled by bone-forming osteoblasts and bone-degrading osteoclasts. Osteoblasts are derived from mesenchymal stromal cells (MSCs) that reside in the bone marrow (A. J. Friedenstein et al., 1966; Pittenger et al., 1999). MSCs also give rise to adipocytes (ACs) to form Bone Marrow Adipose Tissue (BMAT), which can account for up to 70% of bone marrow volume (Fazeli et al., 2013).

MM indirectly degrades bone tissue by stimulating osteoclasts and inhibiting osteoblast differentiation, which leads to MM-related bone disease (MBD) (Glavey et al., 2017). MBD is present in 80% of patients at diagnosis and is characterized by osteolytic lesions, osteopenia and pathological fractures (Terpos et al., 2018).

from (Forster & Radpour, 2022):

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- Two new interleukin-6 dependent plasma cell lines carrying a chromosomal abnormality involving the IL-6 gene locus.* Abstract Two plasma cell lines, INA-6 and JK-6, have been initiated and continuously cultured from two patients with malignant plasma cell diseases. Both cell lines are EBNA negative and show morphological and immunophenotypical features of plasma cells. INA-6 expresses the CD39 and CDw75 antigens, JK-6 is strongly positive with CD38 and CD39 antibodies. By flow cytometry they were non-reactive with Ia antibodies and B cell reagents CD19, CD20, CD21, CD22, and CD24. While INA-6 cells are releasing kappa light chains only, JK-6 cells produce IgG kappa. Both cell lines could only be initiated with IL-6 supplemented medium and remained IL-6 responsive throughout continuous culture. INA-6 is strictly dependent on IL-6. No spontaneously secreted IL-6 was found nor could it be induced by IL-1beta /TNFalpha stimulation. Molecular analysis with RT-PCR revealed mRNA for the IL-6 receptor in both lines. No IL-6 mRNA was detectable in INA-6 cells, while in JK-6 minute amounts were observed. Cytogenetic analysis of both lines revealed, among other abnormalities, a deletion (7)(p13). Interestingly, the 7p deletion affects the location of the IL-6 gene. In both cell lines, IL-6 dependent proliferation could be inhibited by IFNalpha. IFNalpha had growth regulatory effects only on JK-6: While high concentrations were inhibitory, low IFNalpha amounts were clearly stimulatory. A wide variety of other cytokines including GM-CSF and IL-11 did not have the capacity to influence proliferation. These plasma cell lines do not only allow to further characterize regulatory events in plasma cell neoplasias but also provide tools to study therapeutic interventions. (n.d.). Retrieved 2023-03-22, from <https://www.cellosaurus.org/cellopub/CLPUB00060>
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Appendices

A Supplementary Data & Methods

A.1 Figures

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A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic