Contents

Introduction

Human Mesenchymal Stem/Stromal Cells

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 heterogenous 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 embryonic 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. This offers great opportunity for regenerative medicine, if the particular hMSC-subtype is properly characterized.

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 smaller[1] mass of clonal plasma

[1]Rajkumar et al. (2014): *"Solitary plasmacytoma with 10 % or more clonal plasma cells is regarded as multiple*

cells together with a singular primary bone lesion is diagnosed as *solitary plasmacytoma* (SP). SP can progress to MM in 32 % of cases (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 MM* (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-up[2] (Abdallah et al., 2024; Mateos María-Victoria et al., 2013). MM itself can progress to advanced stages, such as *extramedullary involvement/disease* (EMD) which describes colonization of soft tissues outside the bone marrow (Bladé et al., 2022), but also *plasma cell leukemia* (PCL) which 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 surival rate of 50 % (Turesson et al., 2018), MM can be considered incurable and deadly. MM relapses within the first year in 16 % of patients, 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).

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."

[2]For 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 patiens, 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).

Dissemination of Myeloma Cells

As the name suggests, multiple myeloma (MM) 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 bone marrow (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.

Dissemination in multiple myeloma (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 mechanisms of MM dissemination are still not entirely understood. Nevertheless, attempts to structure the process have been made by Zeissig et al. (2020), describing MM dissemination in five-steps: retention in the BM environment (BME), release from the BME, intravasation, extravasation, and colonization (Zeissig et al., 2020). Critical to these processes is the ability of MM cells to overcome retention and adhesion within the BME, despite their dependency on the BM for survival factors.

BME plays a role in dissemination (Forster & Radpour, 2022): "Preventing the infiltration and spread of myeloma cells to sites where they are capable to turn into quiescent states or colonize niches that are less accessible for standard therapies might play a significant role in overcoming EMM."

Loss of adhesion factors such as CD138 could be significant in this context (Akhmetzyanova et al., 2020; Brandl et al., 2022).

The BME plays a crucial role in the regulation of dissemination, where strategies to prevent the infiltration and spread of MM cells into less accessible niches for standard therapies could

be pivotal in overcoming extramedullary myeloma (EMM) (Forster & Radpour, 2022).

According to Zeissig et al., the retention of MM cells within the BM stromal niche is mediated by various mechanisms. BM mesenchymal stromal cells (BMSCs) are vital in this niche, supporting MM cell growth through direct adhesion and secreted extracellular matrix (ECM) components. The binding of MM cell integrins, such as 4 1 to vascular cell-adhesion molecule 1 (VCAM-1) and fibronectin on BMSCs, is particularly crucial. This binding decreases MM cell response to chemotactic factors *in vitro* (Shibayama et al., 1995), thus playing a significant role in their retention within the BM (Zeissig et al., 2020).

Release from the BM niche involves MM cells overcoming strong adhesive interactions, which act as retention signals. While the specific microenvironmental stimuli regulating this release are not fully defined, changes in the expression of adhesion molecules play a role. For example, circulating MM cells show lower levels of integrin 4 1 compared to those residing in the BM. Furthermore, treatment with a syndecan-1 blocking antibody has been shown to rapidly induce the mobilization of MM cells from the BM to peripheral blood in mouse models, suggesting that alterations in adhesion molecule expression facilitate MM cell release (Zeissig et al., 2020).

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).

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, where they can colonize and form new tumor foci. This complex interplay of cell signaling, adhesion, and the microenvironmental conditions not only dictates the dissemination paths of MM cells but also influences their survival and proliferation in new niches (Zeissig et al., 2020)

paragraphs from (Zeissig et al., 2020):

Further processes are intravasation, circulation, extravasation and colonization

Myeloma-hMSC Interactions

bone marrow microenvironment

Since plasma cells can not survive outside the bone marrow, MM cells also require survival

signals for growth and disease progression. These signals are produced by the bone marrow microenvironment, including ECM, MSCs and ACs (Kibler et al., 1998; García-Ortiz et al., 2021).

it plays a

from (Forster & Radpour, 2022):

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).

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Appendices

A Supplementary Data & Methods

A.1 Figures

A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic