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Abbreviations

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 smaller[1] 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-up[2] (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 is characterized by high

[1] Rajkumar 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."*

[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).

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 [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 (BMME) (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-Mesenchymal Transition (EMT), 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:

1. Retention in the BM
2. Release from the BM
3. Intravasation
4. Extravasation
5. Colonization.

According to Zeissig et al. (2020), MM dissemination begins with MM cells overcoming retention and adhesion within the BMME. 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 succesful 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 Bone Marrow Stromal Cells (BMSCs) (Teoh & Anderson, 1997; 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). BMSCs are vital in this niche, supporting cell adhesion through CAMs but also by secretion of (ECM)

components (Katz, 2010). Such adhesion acts both as physical anchorage but also provides signaling cues for growth, survival, and drug resistance (Chauhan et al., 1996). A classic example is the binding of MM cell integrins to VCAM-1 on BMSCs, such as 4 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 dissemination.

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 BMSCs and adipocytes (Kibler et al., 1998; García-Ortiz et al., 2021). *Chemotaxis* is also crucial for BM retention (T. R. Ullah, 2019). 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). Roccaro et al. (2015) demonstrated that inhibiting CXC4R — the receptor of CXCL12 — with the monoclonal antibody Ulocuplumab decreased MM cell homing to the BM and reduced dissemination via factors associated with EMT. Consequently, CXCL12/CXCR4 signaling has emerged as a promising target of several treatments aiming at preventing myeloma cell migration, as reviewed by Ito et al. (2021) who conclude a need for further studies to develop combined therapies explicitly against tumor cell dissemination.

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 BMME 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 among disseminative processes. Still, in order to gain understanding of how MM dissemination is initiated, one can summarize reports that could be involved.

Studies suggest that CAMs expression indeed plays a role in MM dissemination. For instance, studies demonstrate that circulating MM cells exhibit reduced levels of integrin $\alpha 4\beta 1$, in contrast to those located in the BM (Paiva et al., 2013, 2011). Given that dissemination can be induced in mice by overexpressing the CAM shedding protease heparanase (Y. Yang et al., 2005), it seems reasonable that dynamic loss of adhesive strength is causing release of MM cells from the BM. Another useful comparison is that of CAMs expression at different disease stages, indicative of their role in disease progression, which in turn could serve as a proxy for dissemative potential. For example, Terpos et al.

(2016) reported an increase in adhesion molecule expression of ICAM-1 and VCAM-1 in patients with MM compared to those with MGUS and aMM. However, Pérez-Andrés et al. (2005) reported that CD40 is downregulated in PCL patients, hence, different CAMs could serve ambiguous roles in MM progression. Together, the regulation of CAMs can depend on both momentary microenvironmental factors, but also on the stage of the disease, while the specific stimuli regulating their expression are not fully defined. A study from Akhmetzyanova et al. (2020) presents CD138 (*aka* Syndecan-1) as a potential *switch* between adhesion and release, as mice treated with CD138 blocking antibodies exhibited rapid mobilization of MM cells from the BM to peripheral blood, confirming that alterations in adhesion molecule expression are sufficient to cause 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.

Another often overlooked requirement for MM cell release is the need for independence from essential growth and survival signals provided by BMSC. Autocrine signaling has been proposed as a key mechanism through which myeloma cells gain independence from essential survival factors such as IL-6 (Frassanito et al., 2001; Urashima et al., 1995). Autocrine signaling could also disrupt responsiveness to Mesenchymal Stromal Cell (MSC)-derived chemotactic signals, since MM cells from BM biopsies were shown to express CXCL12 under hypoxic conditions induced by HIF-2α (Martin et al., 2010). Since MM niches turn increasingly hypoxic and circulating myeloma cells upregulate hypoxia associated genes, hypoxia is a promising factor for understanding the release of MM (Garcés et al., 2020).

The degradation of bone tissue could also play a critical role in myeloma cell release by eliminating adhesive anchorage within the ECM, considering that ECM is remodeled even at the MGUS stage Glavey et al. (2017). This degradation is part of a 'vicious cycle' that is well described in osteotropic cancer types and is the key pathway of bone destruction, dissolving bone-resident growth factors like TGF-β that further drive tumor growth (Harada et al., 2021; Siclari et al., 2007; Wang et al., 2019). Notably, it is reasonable to assume that bone destruction drives dissemination by removing physical barriers, yet such concept was not proven yet.

In summary, the release of MM cells from the BM is a complex process that involves dynamic regulation of CAMs, autocrine signaling, and hypoxia, but also the degradation of bone tissue. These processes are not fully understood and require further investigation to formulate strategies that prevent uncontrolled spread of MM cells and support modern therapies.

MSCs: Mesenchymal Stromal (Stem) Cells

The previous sections mentioned MSCs several times as BMSCs, being a crucial component of the BMME in the context of multiple myeloma (Mangolini & Ringshausen, 2020). Before discussing their

role in MM specifically, it is important to understand what an MSC is and what impact this cell type has on biomedical research.

Explaining what an 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.

MSCs 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, generating one daughter cell with maintained stemness, and one differentiated daughter 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. human Mesenchymal Stromal Cells (hMSCs) have been presented as promising candidate in the context of regeneration, given that they feature also intriguing immunomodulatory capabilities, easy isolation and *in vitro* expansion, and safety for both autologous and allogeneic transplantation (I. 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. MSCs 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, MSCs can differ greatly in their transcription profile and *in vivo* differentiation potential (Jansen et al., 2010; Sacchetti et al., 2016).

Since MSCs 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, MSCs 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, MSCs must differentiate to osteoblasts, adipocytes and chondroblasts *in vitro*. Together, MSCs exhibit diverse differentiation potentials and can be isolated from multiple sources of the body.

Today, the potential in MSCs lies not their stemness, but rather in their immunomodulatory capabilities, which could be the reason why conventionally the *'S'* in MSC stands for *Stromal* instead of *Stem*. Althogh, MSCs are not yet established in routine clinical practice —despite thousands of clinical trials covering most of the human body's organs—, they still are among the most studied cell types and are topic of vast research (Abdelrazik, 2023). MSCs are valued for their very high treatment tolerance, but also as an adaptive platform for modifications to improve their therapeutic effects (D'souza et al., 2015). For example, Chen & Zhou (2022) boldly announced the translation of modified MSCs into the clinical practice of treating ischemic strokes, whereas Moñivas Gallego & Zurita Castillo (2024) conclude that *further studies are needed*, a statement that's ubiquitous in publications on MSCs based therapies[3]. Still, many fields of research benefit from this vast general understanding of MSCs biology, including this work and the study of the BMME in the context of cancer pathologies such as MM.

Molecular Interactions between MSCs Myeloma Cells

As mentioned in previous sections, MSCs are key drivers of MM progression through mediating retention and survival of MM cells in the bone marrow through e.g. cell adhesion and chemoattractaction (Zeissig et al., 2020). However, BMSCs play a far more complex role in the overall pathology of MM (Mangolini & Ringshausen, 2020). Since bone tissue represents a sturdy physical barrier that MM cells might have to overcome to disseminate, it is crucial to revisit the impact that myeloma cells leave on the BMME.

In healthy bone tissue, there's an equilibrium between bone formation and degradation to maintain turnover, repair and remodelling. (Väänänen, 1993): Mesenchymal stromal cells (BMSCs) differentiate into bone forming osteoblasts, while bone degrading osteoclasts are derived from hematopoietic stem

[3]Abdelrazik (2023): *"Altogether, the articles published in this Special Issue raise more questions than they answer, given that most of the conclusions carry the statement* ***'further studies are needed'****."*

cells. Myeloma cells shift the equilibrium of bone turnover towards degradation, leading to Multiple Myleoma related Bone Disease (MBD) (Hideshima et al., 2007). MBD is present in 80% of patients at diagnosis and is characterized by osteolytic lesions, osteopenia and pathological fractures (Terpos et al., 2018).

MM cells establish this shift in bone turnover on multiple levels: They directly stimulate osteoclast activity by secreting MIP1α (Oba et al., 2005), but also indirectly through reprogramming BMSCs by having them produce osteoclast stimulating factor RANKL (Tsubaki et al., 2020). This is mediated by NF-κB signaling, a pathway that's crucial for MM pathology which is activated through direct cell-cell contact between myeloma cells and BMSCs via e.g. VCAM1 (Cippitelli et al., 2023; Roy et al., 2018). NF-κB is activated in both myeloma cells and BMSCs, but with different outcomes: In myeloma cells, NF-κB transduces survival signaling (Roy et al., 2017). BMSCs however react with stress-induced senescence and secretion of multiple factors that drive MM pathology, such as RANKL and components of the Senescence-Associated Secretory Phenotype (SASP) (Chauhan et al., 1996; Fairfield et al., 2020).

Another fundamental factor contributing to bone destruction is the suppresion of osteogenic differentiation of BMSCs by myeloma cells: MM cells secrete DKK1, which inhibits Wnt signaling that otherwise induces the key osteogenic transcription factor RUNX2 (Gaur et al., 2005; Qiang et al., 2008; F. Zhou et al., 2013). Instead, BMSCs are driven towards the adipogenic lineage MM by VCAM1 signaling, with MM cells stabilizing the adipogenic transcription factor PPAR-γ (Dotterweich et al., 2016; Liu et al., 2020). Furthermore, MM inhibit osteogenic differentiation of BMSCs on an epigenetic level (Allegra et al., 2022). Key mediator GFI1, a zinc finger protein activated by TNF-α which recruits the chromatin modifier HDAC1 to the promoter of RUNX2 (D'Souza et al., 2011; Adamik et al., 2017). Intriguingly, the same group was able to prevent activation of GFI1 and rescue osteogenic differentiation by inhibition of p62, an adapter protein involved in autophagy that bridges several signaling pathways, including NF-κB (Adamik et al., 2018). Teramachi et al. (2016) previously treated mice with the same inhibitor XRK3F2, which resulted in bone formation restricted to MM containing bones. This approach is intriguing, since NF-κB has remained an untreatable target given its ubiquitous role in cell survival. However, a review by Verzella et al. (2022) clearly disagrees with this notion[4], shifting the focus onto upstream activators and downstream effectors of NF-κB signaling, a principle that was exemplified by the work of Adamik et al. (2018) on the GFI1/p62 interface. This requires a thorough characterization of the transcriptional programs elicited by NF-κB signaling in MM cells and BMSCs, especially during direct cell adhesion.

Overall, MSCs are pivotal within the BMME, serving both structural and responsive roles in MM. NF-κB signaling, essential in MSC-myeloma interactions, plays a crucial role in myeloma survival and MSC function modification (Cippitelli et al., 2023; Roy et al., 2018). Direct contact is necessary to ac-

[4]Verzella et al. (2022): *"Collectively, this bulk of evidence demonstrates that the safe and cancer-selective inhibition of the NF-κB pathway is clinically achievable and promises profound benefit to patients with NF-κB-driven cancers"*

tivate these pathways, exacerbating MM pathology. Targeting components of NF-κB signaling offers therapeutic potential, aiming to disrupt key interactions and inhibit myeloma progression. Deeper molecular understanding of the MSC–Myeloma intreactions could lead to therapies that effectively target a cancer microenvironment that's driving MM progression.

Aims

This PhD thesis is designed to bridge significant gaps in the understanding and analysis of myeloma cell behavior and the handling of complex biomedical datasets. The specific aims are as follows:

- Develop an *in vitro* model to elucidate the mechanisms of myeloma cell dissemination in interaction with mesenchymal stromal cells (hMSCs), focusing particularly on:
  - Observing and quantifying cell proliferation, attachment, and detachment dynamics using time-lapse microscopy.
  - Isolating and characterizing distinct myeloma subpopulations interacting with hMSCs to understand differential gene expression related to cell adhesion and patient survival.
- Design and implement a Python-based software tool, `plotastic`, to facilitate the analysis of multidimensional datasets generated in biomedical research. This tool will aim to:
  - Streamline the data analysis process, making it more efficient and reproducible.
  - Integrate visualization and statistical analysis capabilities to ensure that data analysis protocols are aligned with the ways in which data is visualized.
  - Provide a case study demonstrating the application of `plotastic` in the analysis of *in vitro* dissemination experiments, emphasizing the tool's ability to handle semi-big data and enhance reproducibility.
- Synthesize the findings from the experimental and software development components to advance the understanding of myeloma dissemination and improve research practices in biomedical data analysis.

These aims are crafted to address both the biological and technical challenges in current cancer research methodologies and data science applications in biomedicine, fostering advancements that could lead to novel therapeutic strategies and more robust scientific inquiries.

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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 strongty positive with

CD38 and CD39 antibodies. By flow cytometry they were non-reactive with Ia antibodies and B ceil 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). lnterestingly, the 7p deletion affects the location ot the IL-6 gene. ln 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 turther 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