Multiple Myeloma: Molecular Pathogenesis and Disease Evolution

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Abstract

Background: Multiple myeloma is the second most common hematologic malignancy, which to date remains incurable despite advances in treatment strategies including the use of novel substances such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies. ***Summary:*** The bone marrow-based disease is preceded by the 2 sequential premalignant conditions: monoclonal gammopathy of undetermined significance and smoldering myeloma. Plasma cell leukemia and extramedullary disease occur, when malignant clones lose their dependency on the bone marrow. Key genetic features of these plasma cell dyscrasias include chromosomal aberrations such as translocations and hyperdiploidy, which occur during error-prone physiologic processes in B-cell development. Next-generation sequencing studies have identified mutations in major oncogenic pathways and tumor suppressors, which contribute to the pathogenesis of multiple myeloma and have revealed insights into the clonal evolution of the disease, particularly along different lines of therapy. More recently, the importance of epigenetic alterations and the role of the bone marrow microenvironment, including immune and osteogenic cells, have become evident. ***Key Messages:*** We herein review the current knowledge of the pathogenesis of multiple myeloma, which is crucial for the development of novel targeted therapeutic strategies. These can contribute to the endeavor to make multiple myeloma a curable disease.

Introduction

Plasma cells are terminally differentiated B cells, which play an integral role in the humoral immune response by secreting antibodies. Errors in the physiologic events leading to plasma cell maturation and antigen specificity can propagate malignant transformation, leading to a variety of diseases termed plasma cell dyscrasias. The clinically most significant plasma cell disorder is multiple myeloma, which is the second most common hematologic malignancy and accounts for 10% thereof [1]. Clinical features of this bone marrow-based disease include bone destruction, hypercalcemia, renal failure, cytopenia, and immune paralysis [1]. Symptomatic multiple myeloma requires systemic treatment and can be preceded by 2 sequential premalignant conditions termed monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM; also known as asymptomatic myeloma), all of which share several genetic features [2]. Precise understanding of the molecular pathogenesis and biology of each state of the disease is necessary to develop prognostic tools and novel therapeutic approaches. Technical advances in the detection of chromosomal aberrations via fluorescence in situ hybridization, mutational analysis using next-generation sequencing, epigenetic profiling, and investigations into the bone marrow microenvironment have added to the understanding of this family of hematologic malignancies. We herein review the current knowledge and provide novel insights into the molecular pathogenesis of plasma cell dyscrasias.

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Table 1. Translocations

IGH translocation	Genes affected	Frequency	Prognostic impact
t(4;14)	*FGFR3, MMSET*	11–15%	High risk
t(6;14)	*CCND3*	Approximately 1–2%	Standard risk
t(11;14)	*CCND1*	Approximately 15%	Intermediate risk
t(14;16)	*MAF*	3–5%	High risk
t(14;20)	*MAFB*	Approximately 1%	High risk

Most common translocations with affected genes, frequencies, and prognostic impact. Data derived from [12, 20, 39].

Physiological B-Cell Development

After undergoing immunoglobulin heavy and light chain rearrangement at the immature B-cell stage, B cells can transition from the bone marrow into the periphery and secondary lymphoid tissues for maturation. T-cell-dependent cytokine stimulation induces a complex B-cell activation in the germinal center that results in selection of B cells with higher-affinity B-cell receptors and longer lasting immunity. This process includes somatic alterations termed somatic hypermutation (SHM) and class-switch recombination (CSR), which are prone to genomic errors [3, 4]. SHM of the heavy and light chains is important to increase the antigen-antibody affinity through mutation of the complementarity determining region [4]. CSR is a process that removes portions of the antibody heavy-chain locus, enabling the production of immunoglobulins of different isotypes with same antigenic specificity [5]. Both processes are mediated by the activation-induced cytidine deaminase, which introduces DNA double strand breaks [6–8].

Translocations and Hyperdiploidy

Translocations can be found in half of MGUS and MM patients [9]. As opposed to other B-cell malignancies, CSR errors are mainly thought to cause translocations in MM [10]. Most translocations involve the IgH locus (14q32), which puts oncogenes under the influence of the powerful IgH enhancer and thus result in upregulation (Table 1) [11, 12]. Translocations involving the immunoglobulin lambda (IgL) locus are present in 10% of patients with newly diagnosed MM and up to 20% in relapsed-refractory MM and are indicative of poor prognosis [13]. IgK translocations are even less frequent, occurring in <5% of newly diagnosed MM [14]. Cyclin D (CCND) dysregulation is the most common result of IgH translocation [15]. It involves t(11;14) (*CCND1*, 15–20%), t(12;14) (*CCND2*, 1%), and t(6;14) (*CCND3*, 1–4%). IgH-NSD2 or t(4;14) is the second most common translocation and results in a dual dysregulation of *NSD2* and *FGFR3* [16, 17]. *NSD2* is thought to be the essential transforming element [18, 19]. It contributes to increased proliferation, a change in cellular adhesion, and high tumorigenicity [20]. IgH-MAF and IgH-MAFB translocations result from t(14;16) and t(14;20), respectively [21, 22]. Both genes belong to the MAF family, which are leucine zipper-containing transcription factors. MAF induces the expression of *CCND2* resulting in accelerated cell division and DNA synthesis as well as integrin B7 leading to increased adhesion to bone marrow stromal cells [23]. Overexpression of MAFB induces proliferation and protects cells from drug-induced apoptosis [4, 24]. Complimentary to translocations, 50–60% of all myelomas are hyperdiploid. Hyperdiploidy is hypothesized to occur during rapid germinal center proliferation that results in chromosome segregation errors [4]. Trisomies commonly affect odd chromosomes [25]. Nonhyperdiploid karyotypes can be further divided into hypodiploid (44/45 chromosomes; approximately 20%), pseudodiploid (44/45 to 46/47; approximately 35%), near-tetraploid (>74; approximately 10%), and hyperhaploid karyotypes (24–34 chromosomes, rare) [26]. Nonhyperdiploid karyotypes are associated with a more aggressive clinical course, especially in the case of hypodiploidy and hyperhaploidy [9, 27–31].

Monoclonal Gammopathy of Undetermined Significance

MGUS is considered a premalignant clonal disorder and is classified based on the involved paraprotein (non-IgM, IgM, and light-chain MGUS) [32]. Diagnostic criteria are listed in Table 2 [33]. MGUS is present in approximately 3% of white individuals aged >70 years, and its incidence increases with age [34]. The most common subtype of heavy-chain MGUS is IgG (70%), followed by IgM (15%), IgA (12%), and biclonal gammopathy (3%). In contrast to IgG, IgA, and biclonal gammopathy, which can precede MM, IgM MGUS is mostly a precursor for lymphoplasmocytic lymphoma [35]. Monoclonal gammopathy of renal significance is an important subgroup, which is characterized by renal impairment and/or proteinuria caused by paraprotein deposition [36] and progresses to end-stage renal disease in one-fifth of all cases [37]. Solitary plasmocytoma is a localized form of MM, confined to a single bone or extramedullary lesion, and is frequently associated with MGUS [38].

Table 2. Diagnostic criteria

Diagnosis	MGUS	Smoldering myeloma	Symptomatic multiple myeloma	
Criteria				
Clonal plasma cells in bone marrow	<10%	10–60%	≥10%	≥60%
	And	*And/or*	*And/or*	*Or*
M-protein (serum)	<30 g/L	≥30 g/L	Detectable	
	And	*And/or*	*And/or*	
Monoclonal light chain excretion (urine)	<500 mg/24 h	≥500 mg/24 h	Detectable	
	And	*And*	*And*	
End organ damage (CRAB-criteria)	No	No	Yes	
	And			
	Abnormal free light chain ratio (only light chain type)			Abnormal free light chain ratio (only light chain type) >100
				Or
				>1 focal lesion on MRI

Diagnostic criteria for each disease stage assessed by bone marrow biopsy, serum and urine markers, and presence of organ damage. MGUS, monoclonal gammopathy of undetermined significance. Derived from [33].
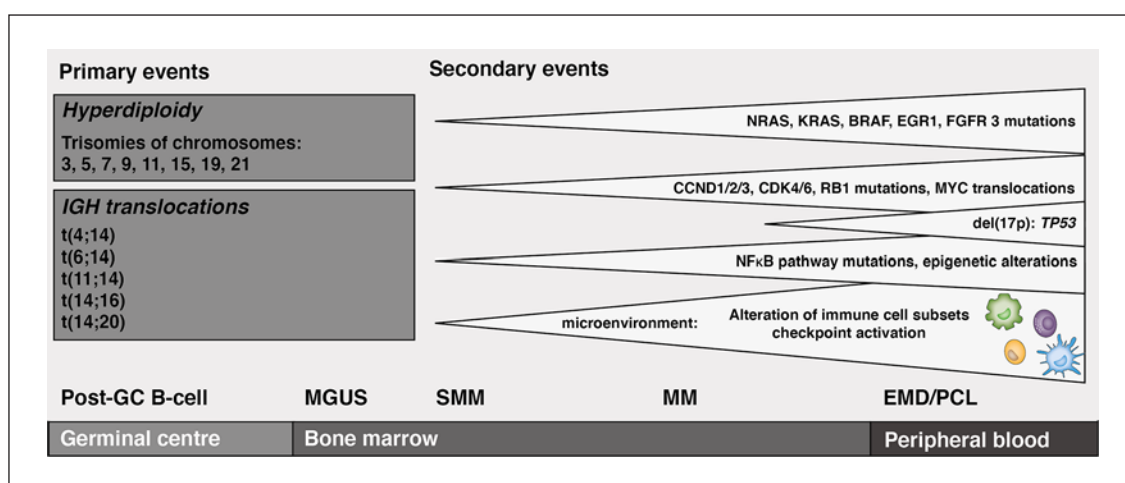

Fig. 1. Key features of multiple myeloma pathogenesis. Errors during physiologic B-cell development can result in primary genetic events such as hyperdiploidy and translocations. Further secondary events, such as mutations in oncogenic pathways, loss of tumor suppressor function through mutation or deletion, epigenetic alterations, and changes in the bone marrow microenvironment, cause the transition to symptomatic myeloma. End-stage disease is characterized by cells circulating in the blood stream/infiltrating other organs. MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; MM, multiple myeloma; EMD, extramedullary disease; PCL, plasma cell leukemia. Illustration adapted from [47].

Mutational Landscape in SMM and MM

The risk of progression to multiple myeloma is around 1% per year [35]. A variety of further genetic aberrations contribute to transformation of MGUS to MM. The crucial pathomechanism lies in the deregulation of oncogenic pathways rather than in single-gene mutations [39]. SMM is an intermediate condition with a higher disease burden than MGUS, which still lacks organ damage (Table 2) [34]. The progression risk of smoldering myeloma to active myeloma is about 10% per year in the first 5 years, 3% for the next 5 years, and 1% 10 years after initial diagnosis [2, 40]. This observation led to the conclusion that there are 2 main mechanisms of myeloma progression. In the "static progression model," the malignant population is already defined at SMM stage, and MM occurs by continuous proliferation of this clone. In the "spontaneous evolution model," disease progression occurs by clonal evolution with acquisition of further translocations, copy number aberrations, and mutations (shown in Fig. 1) [41, 42]. A recent study showed that whole-genome sequencing-based analyses could differentiate MM precursor conditions (MGUS and SMM) with a low or high risk of progression based on the absence or presence of key MM defining genetic events such

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Fig. 2. Branched clonal evolution patterns in plasma cell disorders. Clonal evolution of MM follows a branched pattern from an original propagating cell to symptomatic disease. Several clones may be present at each stage. Treatment can reset the clonal heterogeneity, and different clones can lead to relapse. MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; MM, multiple myeloma; EMD, extramedullary disease; PCL, plasma cell leukemia. Illustration adapted from [20].
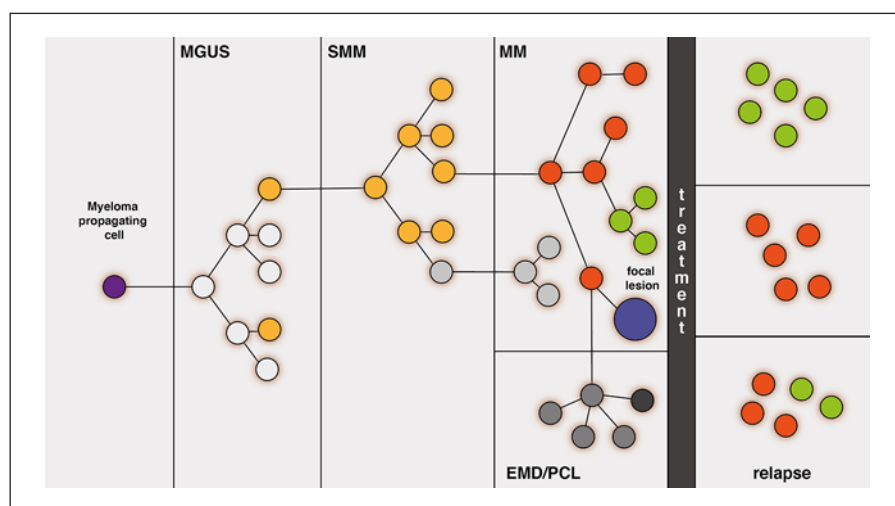
as chromothripsis, templated insertions, mutations in driver genes, and aneuploidy [43]. The frequency of mutations in MM has been determined by next-generation sequencing at about 60 mutations per patient [12] and is thus much higher than in patients with acute leukemias but lower than in solid tumor patients [44]. More than 60 recurrent mutations in driver genes have been identified [45]. Recent studies have shed light on the complex chronological order of MM-driving events using whole-genome sequencing approaches and have determined oncogenic point mutations to occur at rather later disease stages as opposed to disease-driving complex structural events [46]. In about 50% of myeloma patients, mutations induce aberrant signaling in the MAPK/ERK pathway (*NRAS*, *KRAS*, *BRAF* and *EGR1*, and *FGFR3*) [47]. About 15% of MM patients show mutations affecting DNA repair pathways like *TP53*, *ATR*, *ATM*, and *ZFHX4* genes, which are associated with shorter survival [48, 49]. Moreover, mutations involving the NFκB pathway can be detected in about 20% of MM patients, affecting *TRAF3*, *NFKBIA*, *BIRC2/3*, or *CYLD* genes [50]. Alteration of the PI3K pathway occurs in patients with MAF translocations [51]. Mutations in the *CCND1/2/3*, *CDK4/6*, and *RB1* genes deregulate cell cycle control mechanisms and are associated with unfavorable outcomes [48, 49]. To facilitate the export of cellular metabolites such as lactate and sustain the high need for nutrients, MM cells upregulate the expression of metabolically active transmembrane complexes. Their destabilization marks a major means by which IMiDs exert their antimyeloma efficacy [52, 53]. Last, epigenetic changes leading to global DNA hypomethylation and gene-specific DNA hypermethylation play an important role in the progression of MGUS to myeloma [54]. This can be observed in a subgroup of patients with t(4;14) and overexpression of MMSET which encodes a histone methyltransferase transcriptional repressor, leading to DNA hypermethylation [55].

High-Risk, Extramedullary MM and Plasma Cell Leukemia

Despite the recent improvements in therapy for MM patients, a group of high-risk disease patients consistently demonstrates poor outcomes upon standard therapy [56]. High-risk disease, which is present in 20–30% of all cases, cannot be defined by a single pathogenic mechanism, but rather arises from the interplay of several genetic lesions leading to high proliferation rates, evasion of apoptosis, and therapy resistance [20]. This is, in part, achieved by strong dysregulation of the G1/S checkpoint, further proliferation signaling via MYC, RAS-ERK, and NFκB pathways, aberrant signaling within the bone marrow niche, and loss or mutation of the tumor suppressor genes *RB1* and *TP53* [20]. Next to IGH translocations such as t(4;14) and t(14;16), which have been associated with adverse outcomes, gain of chromosome 1q21 has recently evolved as another poor prognostic marker [57, 58]. Biallelic inactivation of *TP53*, either by homozygous deletion (del[17p]) or concurrent mutation, is considered a marker for ultra high-risk disease [49]. In advanced disease stages, some MM clones lose their dependency on the bone marrow microenvironment and can be found circulating in the bloodstream or infiltrating other organs. Plasma cell leukemia is historically defined by the presence of >20% or $>2 \times 10^9$ clonal plasma cells in the peripheral bloodstream [59], whereas extramedullary disease is marked by proliferation and infiltration of MM cells in various extramedullary organs [60].

Clonal Evolution of MM Disease

Traditional cancer progression models proposed a linear process, in which a single malignant cell gives rise to clonal progeny, which acquires further genetic hits [61]. This applies in part to multiple myeloma; however, current studies have revealed a more branched evolutionary pattern according to Darwinian principles of natural se-

lection (shown in Fig. 2) [44, 62]. This is in line with patterns seen in acute myeloid leukemia and other hematologic malignancies [63, 64]. Evolutionary patterns become evident especially in patients at relapse after therapy. A recent study demonstrated that patients at relapse after achieving a complete response had a predominantly branching evolutionary pattern with a greater mutational burden, an altered mutational profile, acquired structural aberrations, and biallelic inactivation of tumor suppressor genes, while patients at relapse after a partial response showed a largely stable mutational and structural profile [65]. Induction therapy reduces the tumor load and can be considered as an evolutionary restriction point, which resets intraclonal dynamics (shown in Fig. 2). Consolidation and maintenance therapy can then control more indolent clones, which persist after induction therapy, leading to a longer survival [66]. Mutations in known MM-driving genes (e.g., *KRAS*), segmental copy number alterations, and inactivation of tumor suppressors, such as *TP53*, drive disease progression by Darwinian clonal evolution, and both mutations in such genes, as well as branched evolution itself, have been associated with an adverse prognosis [67–69]. Another complexity arises from intrapatient spatial heterogeneity, which was shown to be present in 75% of patients analyzed by multiregion sequencing [70]. Biopsies taken from the usual sampling site, the iliac crest, might not provide a representative image of all, possibly high-risk clones, which might be present at other sites or focal lesions. This poses a significant challenge to targeted therapy in multiple myeloma.

Microenvironment

Since patients with MGUS or SMM show IgH translocations and/or hyperdiploidy, other factors seem to be necessary for MM progression. Late oncogenic events are thought to occur in the bone marrow, after the initial clone is completely differentiated into a long-lived plasma cell [39]. This implies an important role of the microenvironment for tumor progression [34, 71]. The microenvironment includes cellular elements like bone marrow stroma cells, mesenchymal stem cells, endothelial cells, immune cells, and soluble factors. The bone marrow microenvironment in MM patients has been shown to differ in its composition compared to that of healthy individuals [72]. Pro-proliferative, antiapoptotic, and chemotactic cytokines such as *IL6*, *CXCL12*, *IGF1*, and *VEGFA* mediate MM cell growth, survival and migration, and following treatment, the development of drug resistance in the bone marrow microenvironment [73]. Moreover, myeloma cells also produce cytokines such as TNF-α, TGF-β, and VEGF, resulting in a positive feedback loop [74].

Osteogenic Niche

Osteoblasts are responsible for apposition of new bone and counterbalance the function of osteoclasts, the bone-resorbing cells. Various hormones, nutrients, drugs, and disease states influence the function of osteoclasts and osteoblasts, normally providing an equilibrium and thus guaranteeing adequate bone mass [75]. In MM patients, the osteoblastic niche is depleted in favor of an overabundance of osteoclasts, which support cancer cell proliferation, resistance to apoptosis, and whose aberrant activity is responsible for lytic lesions and ultimately bone disease [76]. Molecular mechanisms of the antiosteoblastic effects of MM cells include downregulation of Run2 in MSCs and differentiated osteoblast progenitors, increased production of WNT pathway inhibitors including Dickkopf WNT signaling pathway inhibitor 1 (DKK1), secretion of antiosteoblastic factors such as IL-3, TGF-β, hepatocyte growth factor, and constitutive activation of the Notch pathway [77–81]. Increased osteoclastogenesis in MM is largely determined by a loss of the balance between the pro-osteoclastogenic RANKL and the anti-osteoclastogenic RANK decoy receptor osteoprotegerin [82]. A maladaptive prosurvival and bidirectional loop also exists among osteoclasts and MM cells [83]. Osteoclasts contribute to MM pathogenesis, not only via their bone-resorbing properties which results in MM-related bone disease manifesting as osteopenia, lytic lesions, and eventually pathological fractures but also by secreting IL-6 and osteopontin, thus stimulating MM proliferation and angiogenesis, respectively [84]. In return, MM cells promote osteoclast differentiation and activity [85, 86].

Immune Cells

Several studies have demonstrated the capacity of innate and adaptive immune cells to mediate growth control of MGUS/MM [87]. MM cells can escape immunologic surveillance by inducing immune tolerance and T-cell anergy. A loss of effector function of T cells, NK cells, and NKT cells is associated with a progression to MM [88, 89]. The composition of lymphocytes present in the MM microenvironment substantially differs from that in healthy subjects [90, 91]. TH17 cells are a distinct subset of CD4+ T helper cells characterized by a particular pattern of cytokine production and are abundant in the BM of MM patients [92–94]. TH17 cells suppress cancer immune surveillance by secreting *IL-10* and IL-17, which also has a pro-osteoclastogenic effect [94–96]. Cytotoxic CD8+ T cells from MM patients differ from healthy counterparts in their repertoire of T-cell receptor coreceptor molecules and show an increased expression of PD-1. PD-L1 is overexpressed on the surface of MM cells, which conveys further immune tolerance of MM [97, 98]. Although PD-L1 is expressed on MM cells, single-agent PD-1 blockade is not effective in MM, and combination

regimens with checkpoint inhibitors have also rendered disappointing results, especially given an excessive toxicity in combination with IMiDs [99–101].

Conclusion

It has become clear that the pathogenesis of plasma cell disorders is characterized by primary genetic lesions such as translocations and hyperdiploidy, which occur during physiological B-cell development. The transition from a premalignant clone to symptomatic disease is then facilitated by somatic mutations in various oncogenic pathways and tumor suppressors, epigenetic alterations, and a tumor-promoting bone marrow microenvironment. The understanding of these complex processes will support the development of new targeted therapeutic strategies, which should be considered essential if we want to reach the goal of curing MM patients.

Author Contributions

M.He., M.Hö., and K.N. performed literature research and drafted the manuscript. F.B. coordinated the work and wrote the final manuscript. All authors discussed and corrected the final version of the manuscript.

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