Biology and Treatment of Myeloma

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Abstract

In recent years significant progress has been made in the understanding of multiple myeloma (MM) biology and its treatment. Current strategies for the treatment of MM involve the concept of sequential blocks of therapy given as an induction followed by consolidation and maintenance. In an age characterized by emerging and more powerful laboratory techniques, it is of primary importance to understand the biology of MM and how this biology can guide the development of new treatment strategies. This review focuses on the genetic basis of myeloma, including the most common genetic abnormalities and pathways affected and the effects that these have on MM treatment strategies. MM biology is discussed also in the light of more recent theory of intraclonal heterogeneity.

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Introduction

In recent years significant progress has been made in the understanding of multiple myeloma (MM) biology. These advances have translated into the development of new drugs and a different approach to treatment, which has ultimately translated into an unprecedented rate of complete remissions. Current strategies for the treatment of MM involve the concept of sequential blocks of therapy given as an induction followed by consolidation and maintenance. The induction phase aims to debulk the disease, reducing it to the smallest amount possible. Consolidation therapy further reduces tumor bulk, and maintenance is given as a long-term treatment with the objective of keeping residual disease under control and potentially leading to a cure. Immunomodulatory drugs and proteasome inhibitors form the backbone of modern MM treatment, but new and more targeted treatments are under development and are being tested in the context of clinical trials. Therefore, it is of primary importance to understand the biology of MM and how this biology can guide the development of new treatment strategies with the aim of personalizing therapy. The advances made in laboratory techniques have refined the conventional way to classify and prognosticate in myeloma, moving from conventional karyotyping to gene expression profiling (GEP), translocations/cyclins classification, and global gene mapping. The future, with analysis of methylation pathways, analysis of microRNA, and next-generation sequencing techniques, looks even brighter; however, it is important to evaluate how best to use these methods and resources and how the biology of myeloma should drive the development of new and more effective treatment options.

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Genetic Basis of MM

MM can be considered as being initiated via a myeloma-propagating cell (MPC).[1] Such a cell is thought to be the founding unit of the MM clone and harbors the biologic features of both self-renewal and proliferation. In the classical view, MM progression was thought to follow a linear pattern, from the initiating stage of monoclonal gammopathy of undetermined significance (MGUS) to the final stages of extramedullary disease and plasma cell leukemia. In this model, after its initiation, the MPC acquires additional genetic hits that further deregulate its behavior, giving rise to the clinical and biologic features of symptomatic myeloma.

Two of the main pathways that are traditionally thought to initiate the transformation of a normal plasma cell into an MPC are translocations into the *IGH* locus (immunoglobulin heavy locus) and hyperdiploidy.[2] These 2 distinct lesions, both ultimately leading to the deregulation of cyclin D genes,[2] are mutually exclusive in the majority of patients and are not linked to any specific phenotype. Molecular archaeology using *IGH* rearrangements suggests that the germinal center reaction drives the origin of the disease[2-6]; however, recent evidence suggests that, in at least some percentage of patients, the transformation event can be

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attributable at a pro-B-cell stage.[6] In this respect, a recently published genome-wide association study has identified risk loci for MM at chromosomes 3p22.1, 7p15.3, and 2p23.3, accounting for 4% of familial risk in MM, suggesting that alterations of genes mapping in these regions, such as *ULK4* (unc-51 like kinase 4), *DNAH11* (dynein, axonemal, heavy chain 11), *CDCA7L* (cell division cycle associated 7-like), *DNMT3A* (DNA cytosine-5-methyltransferase 3 alpha), and *DTNB* (dystrobrevin beta), might precede *IGH* translocation, leading to an increased risk of developing MM.[7] Furthermore, it has been found that memory B cells of patients with MM show involvement of genes known to be deregulated by *IGH* translocations, such as *FGFR3* (fibroblast growth factor receptor 3), fusion of *IGH* and *MMSET* (Wolf-Hirschhorn syndrome candidate 1 [*WHSC1*]) yielding *IGH-MMSET*, and *CCND1* (cyclin D1), but lack the presence of "later" genetic events such as mutation in the *RAS* genes (rat sarcoma homolog family), once more advocating that the transformation events can occur also at a precursor B-cell stage, despite probably not being sufficient to maintain the MM clone.[8]

Myeloma as a Disease of G1/S Phase, RAS, MYC, and Nuclear Factor–κB

The overexpression of a D-group cyclin is an early molecular abnormality in MM, leading to a deregulation of the G1/S transition. Overexpression of cyclins of the D group can occur via different mechanisms, mainly translocations of the *IGH* gene, leading to the deregulation of genes such as *MAF* (v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog),[9] *FGFR3*, and *MMSET*.[2] It seems, however, that this genetic alteration alone is insufficient to give rise to the clinical hallmarks of MM and that additional events are needed to enable the disease to progress.[10] Mutations in the form of single-nucleotide variants, chromosomal copy number abnormalities, and epigenetic changes are responsible for disease progression.[1,11] Such secondary "hits" drive disease progression, activating key oncogenic pathways that may include the *RAS/MAPK* pathway (*RAS* family/mitogen-activated protein kinase pathway),[12-14] *MYC* (v-myc avian myelocytomatosis viral oncogene homolog),[15] or the NF-κB pathway.[12,16]

The prevalence of activating mutations in one of the *RAS* genes (*NRAS* or *KRAS*) is about 50% in presenting MM[13,14] and is higher in tumors that express *CCND1*.[16] There is increasing evidence that MM depends on the continued expression of activated *RAS*[17]; mutations in the *NRAS* gene have been found also in patients with MGUS, although at a significantly lower frequency (7%).[18] Recently, *BRAF* mutations in approximately 4% of patients with MM have also been described.[12] It is evident, however, that even though mutations in the RAS pathway are a driver event in the progression of MM, they are not present in all MM cells and can be found only in a minor clone. *NRAS* and *KRAS* mutations have similar but nonidentical effects, and this is strengthened by the finding that both mutations can be present in the same patient.[19] Whether the same cell harbors both the mutations or they are present in different clones in a parallel evolution pattern is a question that still needs to be answered, although recent evidence suggests the possibility of parallel evolution being a feature of MM.[19] Recent biotechnologic advances and the possibility of single-cell analysis might further elucidate this important question.

The deregulation of *MYC* is a central feature of MM, as is shown by the fact that MM cell lines depend on *MYC* for their survival.[20] The *MYC* gene is located in the 8p14 locus, and abnormalities involving this genome region are frequent in patients with MM. In presenting myeloma, abnormalities of 8q are generally reported in 15% of cases, and rearrangements at 8q24 have been reported in up to 47% of patients with myeloma.[21-23] *MYC* has also been found to be activated in the transition from MGUS to myeloma, implicating it in disease progression.[24] *MYC* rearrangements result in overexpression of MYC owing to the colocalization of active super-enhancers in the partner loci; frequently the partner chromosome gene, such as *FAM46C* (family with sequence similarity 46, member C), *XBP1* (X-box binding protein 1), or *IGL* (immunoglobulin lambda locus), has a known function in myeloma or B-cell biology.[25]

Nuclear factor–κB (NF-κB) is a transcription factor that was found to be important in the development of MM. Both MGUS and MM highly express genes known to be targets of NF-κB; this could partly explain the dependency of MM cells on the bone marrow microenvironment and suggests a continued role of extrinsic signaling in MM.[26,27] Bone marrow stromal cells produce extrinsic ligands such as APRIL (a proliferation-inducing ligand) and BAFF (B-cell activating factor) that stimulate TACI (transmembrane activator and CAML interactor), BCMA (B-cell maturation), and BAFF receptors, ultimately activating NF-κB pathways and providing critical survival signals to plasma cells.[28] The importance of the NF-κB pathway is further highlighted by the finding that both activating and inactivating mutations in positive and negative regulators of the noncanonical NF-κB pathway, such as *TRAF2* (TNF receptor-associated factor 2), *TRAF3*, *CYLD* (cylindromatosis/turban tumor syndrome), *cIAP1/cIAP2* (baculoviral IAP repeat containing 2/3 [*BIRC2/BIRC3*]), and *NIK* (NF-κB-inducing kinase [*MAP3K14*]), have been identified in 20% of patients and in myeloma cell lines[26,27]; mutations in these genes can activate the NF-κB pathway without the presence of a ligand[12] and might contribute to the spread of extramedullary disease,[16] as well as being related to response to treatment.[26,27]

Other lesions that have a greater predisposition to occur late in the natural history of the disease are gain of chromosome arm 1q, mutation at *TP53* (tumor protein p53), or deletion of chromosome 17p.[14-16,22,29,30]

Importance of Biology in the Prognostic Stratification and Treatment of MM

Many attempts have been made to use biology to stratify risk in MM. Myeloma genetic status was initially assessed with metaphase karyotyping; however, the procedure is long and frequently infeasible in a terminally differentiated cell such as a plasma cell. Fluorescence in situ hybridization (FISH) assessment has progressively taken the place of conventional karyotyping and is now the most-used technique for assessing the biologic risk in patients with MM. Single-nucleotide polymorphism (SNP) analysis can be used as well to perform molecular karyotyping in MM and has been