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Advances in the pathogenesis and diagnosis of multiple myeloma

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SUMMARY

Multiple myeloma (MM) is a tumor of indolent, bone marrow (BM) localized, isotype-switched plasma cells. Recently, the diagnostic criteria have been amended to include some patients who would previously have been diagnosed with ultra-high-risk smoldering MM and benefit from immediate treatment. Genetically it can be divided into tumors with different recurrent immunoglobulin heavy chain gene translocations (4p16, 11q13, 6p21, 16q23, 20q11) and tumors characterized by hyperdiploidy with multiple trisomies. Recent genomic studies have shown that almost half of untreated patients have a genetic rearrangements of the MYC locus that result in juxtaposition of ectopic super-enhancers adjacent to MYC, as well as somatic mutations that activate the RAS/MAPK pathway (NRAS, KRAS, BRAF, FGFR3). Mutations that result in constitutive activation of the NFkB pathway and that inactivate TP53, CDKN2C, KDM6A, FAM46C, and DIS3 are also recurrent. A major insight from these studies has been the recognition of the high degree of subclonal heterogeneity in MM, which is more frequent in patients with high-risk genetics. The subclones may alternate in dominance under alternating therapeutic pressure, a phenomenon known as 'clonal tides'. The identification of marked subclonal heterogeneity argues in those patients for the use of therapeutic strategies to maximize response, and long-term suppressive therapies to prevent tumor regrowth and development of additional subclones.

INTRODUCTION

Multiple myeloma (MM) is a tumor of antibody secreting plasma cells (PC) in the BM that secrete a monoclonal immunoglobulin and lead to lytic bone lesions, anemia, and renal disease [1]. The incidence of MM is higher in men, than women, and in blacks than whites, accounting in the United States for close to 11 000 deaths a year [2]. With the introduction of thalidomide, its analogs, and of proteasome inhibitors for the treatment of MM, the 5-year survival rate has doubled over the last fifteen years, and now most patients can expect to live more than 5 years [2]. For a subset of patients with cytogenetically defined low-risk MM treated in 1999, 75% were alive 10 years later [3]. We can

expect an even better outcome for similar patients starting treatment today.

A NEW DEFINITION OF MULTIPLE MYELOMA

An asymptomatic, stable monoclonal gammopathy in the absence of end-organ damage precedes almost every case of MM [4] and can be divided into three clinical stages based on tumor burden. Monoclonal gammopathy of undetermined significance (MGUS) is present in about 4% of individuals over the age of 50 [5] and can progress to MM at a rate of approximately 1% per year. MGUS is characterized by having a M-spike of <30 g/L, and less than 10% of clonal bone marrow plasma cells (cBMPC), and no myeloma-defining events [1]. Progression of MGUS to smoldering MM (SMM) and MM occurs as the BM tumor mass expands and is associated with increasingly severe symptoms or organ impairment. Despite an increased understanding of the biology and genetics of MM, we are not able to predict which patients with MGUS will a progress to MM. The definition of MM is the presence of ≥10% cBMPC with one or more myeloma-defining events (Table 1). These include not only evidence of end-organ damage, but also the recently added biomarkers of ≥60% cBMPC, or the involved over uninvolved serum-free light chain ratio ≥100, or the presence of more than one focal bone lesion on MRI [1]. Each of these biomarkers was found to be associated with the development of end-organ damage in 80% of patients within 2 years, with a quarter of those with elevated free light chain ratio eventually presenting with renal failure. In contrast, patients with an IgA or IgG M-spike ≥3 g/dL, or 24 h urine M-spike ≥500 mg or 10–60% cBMPC lacking a myeloma-defining event are diagnosed with SMM. The rate of progression of SMM to MM is biphasic, occurring at 10% per year for the first 5 years and at 3% year thereafter. Several biomarkers have been reported that identify patients with SMM at high risk of progression to MM. The only genetic biomarkers associated with a high risk of progression are t(4;14) and del17p, each associated with a 2-year risk of progression of 50% [1].

RECURRENT IMMUNOGLOBULIN GENE TRANSLOCATIONS ARE PRESENT IN BOTH MGUS AND MM

The immunoglobulin heavy chain (IgH) locus (14q32) or one of the light chain loci (κ, 2p12 or λ, 22q11) is involved in chromosome translocations in about half of MGUS and MM cases. Errors during the physiological process of CSR or SHM are thought to be responsible as the breakpoints are usually located around IgH switch regions, although occasionally near VDJ sequences [6]. Although subclonal heterogeneity is frequently present in MM [7], the primary chromosome translocations are present throughout all stages of tumor progression, compatible with representing

Table 1. Diagnostic criteria for MGUS, SMM and MM

	Non-IgM MGUS	SMM	MM
Bone marrow plasma cells	<10%	≥10–60%	≥10% or biopsy proven plasmacytoma
	AND	OR	
M-spike	<3 g/dL serum or <500 mg/day urine	≥3 g/dL serum or ≥500 mg/day urine	
	AND	AND	AND
Myeloma-defining event	None	None	≥1
Myeloma-defining event	Hypercalcemia (calcium > 11 mg/dL) Renal failure (creatinine clearance < 40 mL/min or creatinine > 2 mg/dL) Anemia (Hemoglobin < 10 g/dL) ≥1 lytic bone lesion on XR, CT, or PET-CT ≥60% bone marrow plasma cells ≥100 involved/uninvolved serum-free light chain ratio >1 MRI focal lesion		

primary oncogenic events in MGUS and MM. IgH translocations are detected in almost half of MGUS or SMM, over half for intramedullary MM, which increase with disease progression, and 85% in PCL [8]. Light chain translocations predominantly involve the lambda chain locus and are present in about 10% of MGUS/SMM, and about 15% of MM [6].

DYSREGULATION OF FGFR3/MMSET, MAF, AND CCND BY PRIMARY IGH TRANSLOCATIONS

Approximately 15% of MM has a t(4:14) translocation with dysregulation of MMSET on der4. In about 80% of these cases, FGFR3 is also dysregulated on der14. About 5% of MM has a t(14;16) translocation with dysregulation of MAF, while dysregulation of MAFB (2%) and MAFA (<1%) is less common. The t(11;14) translocation with dysregulation of CCND1 is present in about 15% of MM, while translocations of CCND2 (<1%) and CCND3 (2%) are less frequent (Figure 1). The CCND2 is indirectly dysregulated by the MAF transcription factor family [9] and is elevated by an unknown mechanisms in t(4;14) MM. In contrast, CCND1 is biallelically dysregulated in patients with trisomy 11 and hyperdiploidy. As a result, a unifying molecular feature is all patients with MGUS/MM is dysregulation of a CCND gene [9]. The role of the two genes dysregulated by t(4;14) is unclear. MMSET is a histone methyltransferase for H3K36me2, and overexpression causes global changes in H3K36 methylation [9, 10]. MMSET has been additionally shown to be recruited to sites of double strand breaks following phosphorylation of Ser102 by ATM. Nearly half of the t(4;14) breakpoints cause a truncation of MMSET that it can no longer be recruited to double strand breaks as it lacks Ser102, causing a loss of the normal DNA damage response pathway [11]. Critically, MMSET may be a good therapeutic target as inhibition of expression suppresses growth of MM [10].

HYPERDIPLOIDY IS AN ALTERNATE GENETIC PATHWAY

There appear to be at least two genetic pathways of pathogenesis in MM. Almost half of MGUS/MM tumors have between 48 and 75 chromosomes (mostly 49–56) and are hyperdiploid (HRD), typically with trisomies of some or all of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21. Nonhyperdiploid (NHRD) tumors have <48 and/or >75 chromosomes). Interestingly, HRD MM usually do not (approximately 10%) have a primary IgH translocation, while nonhyperdiploid (NHRD) MM most often (approximately 70%) have an IgH translocation (Figure 1) [6]. Hyperdiploidy and translocations may represent different path-

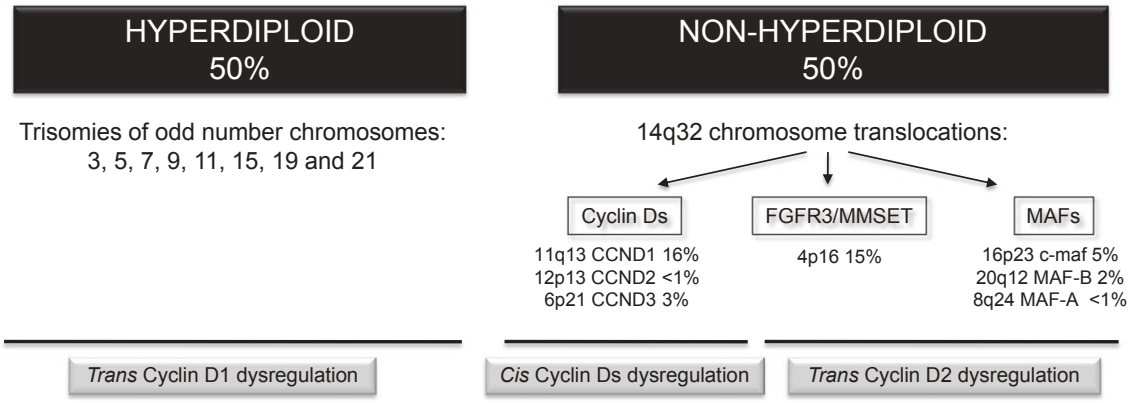

Figure 1. Cyclin Ds dysregulation in MM. MGUS and MM karyotypes can be divided into hyperdiploid and nonhyperdiploid based on chromosomal content. Almost all hyperdiploid tumors have biallelic cyclin D1 trans-dysregulation. Nonhyperdiploid tumors often have t(14q32) translocations affecting the indicated loci (frequency is shown). In about 25% of them, one of the D type cyclin is cis-dysregulated by a 14q32 translocation, and in the other nonhyperdiploid tumors, cyclin D2 expression is trans-dysregulated.

ways of pathogenesis; however, the mechanism and biological consequence of hyperdiploidy is unknown. It is notable that as in acute lymphocytic leukemia, MM patients with hyperdiploidy have a better prognosis than those without.

PROGRESSION OF MGUS TO MM ASSOCIATED WITH SECONDARY GENETIC EVENTS

Many different genetic mutations have been described in MM, which occur with variable frequency in MGUS, SMM, MM, and HMCL, and likely play a role in disease progression (Figure 2).

Myc

The oncogene c-MYC is expressed at a lower level in MGUS compared to MM tumors [12]. Recently, in an MGUS prone mouse strain, the sporadic activation of MYC in germinal center B cells resulted in the MM in the majority of mice [13, 14]. We can conclude therefore that in some cases, dysregulated expression of MYC can cause the progression from MGUS to MM. Complex translocations of *MYC* (mostly c-*MYC*, but sometimes N-*MYC*, and rarely L-*MYC*) frequently do not involve Ig loci and appear to be secondary progression events. Using FISH, they are almost never seen in MGUS, but are found in 15% of untreated

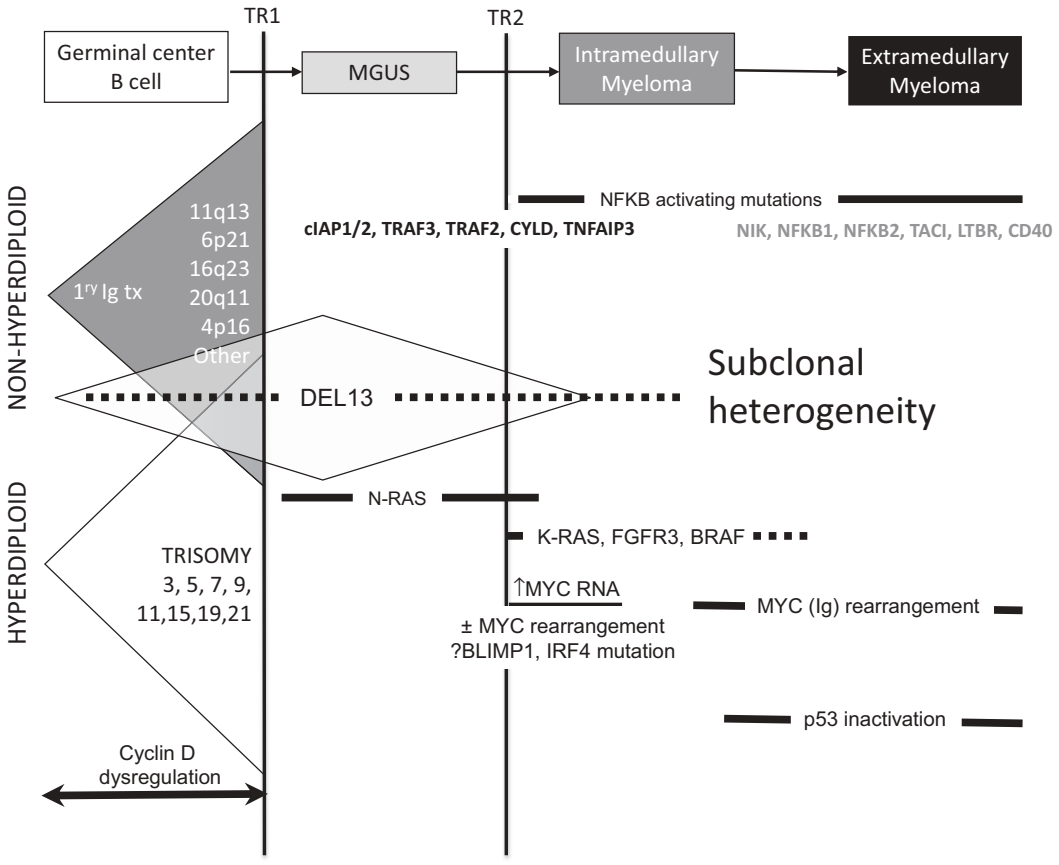

Figure 2. Model for molecular pathogenesis of MGUS and MM. The initial transition (TR1) to a recognizable tumor involves two mostly nonoverlapping pathways (IgH translocations versus multiple trisomies) that include primary events associated with dysregulated CYCLIN D expression in MGUS and MM. The transition (TR2) from MGUS to MM is associated with increased MYC expression, and sometimes with activating mutations of K-RAS or chromosome 13 deletion. Early and late progression events for symptomatic MM tumors are shown. See text for additional details.

MM, 50% of relapsed/refractory MM, and the over 90% of MM cell lines [6]. A recent study using array CGH and next-generation sequencing identified a promiscuous array of rearrangements of the MYC locus in almost half of untreated patients [15]. The rearrangements juxtapose MYC to a wide variety of super-enhancers from elsewhere in the genome and result in cis-dysregulation of MYC. Interestingly, the rearrangements are present in only a quarter of t (11;14), but two-thirds of HRD, and although MYC rearrangements with the Ig loci are equally distributed across genetic subgroups, MYC rearrangements with non-Ig loci are much more common in HRD. Altogether these observations support different genetic mechanisms of progression in the different genetic subgroups of MM. It is possible that MYC dysregulation may be targeted therapeutically using small molecule inhibitors of the bromodomain and end terminal repeat (BET) family of epigenetic readers of acetylated histones [16].

Monosomy 13

Deletion of chromosome 13 can be an early event in MGUS (e.g., t(4;14) or t(14;16) MGUS) or a progression event in MM (e.g., in t(11;14)) [6]. Candidate genes include RB1 that may promote tumorigenesis through haploinsufficiency [8]. Several recent next-generation sequencing studies have identified missense mutations of DIS3, a ribonuclease subunit of the exosome complex, in about 10% of patients.

RAS and *BRAF* activating mutations

Mutations of *NRAS* or *KRAS* are present in about 18–20% of MM [8]. In contrast to MGUS, mutations of *NRAS* are seen in 7%, but mutations of *KRAS* have not been described [6]. This suggests that mutations of KRAS are a genetic mark of the transition from MGUS to MM. In addition, it supports the hypothesis that NRAS and KRAS mutations may play some overlapping, but also some distinct roles in MM biology. Activated but not wild-type *RAS* represents an attractive therapeutic target, as MM tumors depend on its continued expression [17]. Mutations of *BRAF* mutations have been reported in 4–6% of MM tumors, leading to the initiation of clinical studies of BRAF inhibitors in these cases [18].

NFkappaB pathway mutations

Bone marrow stromal cells secrete APRIL and BAFF that stimulate TACI, BCMA, and BAFF receptors on benign and malignant plasma cells, leading to activation of the NF-kappaB pathway. As a result, there is a high-level expression of NFKB target genes in most MM tumors [19], explaining the dependency of MM cells on the BM microenvironment. A promiscuous array of mutations that inactivate negative regulators and activate positive regulators of the NFKB pathway are present in about 20% of newly diagnosed MM, and about half of MM cell lines. It is likely these mutations contribute to extra-medullary growth of MM by decreasing the dependence on BM-localized ligand-dependent NFKB activation [18].

Deletion of chromosome 17p

Deletion of 17p identified using a FISH probe for TP53 is identified in approximately 10% of newly diagnosed MM tumors, and the prevalence increases with disease progression [8]. Mutations of *TP53* were seen in a third of newly diagnosed MM tumors with del17p, but were not identified in patients without del17p [6]. Del17p, even in the absence of TP53 mutations, is an independent poor prognostic factor for overall survival, although it is not clear whether this is due to predisposition to eventual complete inactivation of TP53 by mutation of the single remaining allele, or simply to haploinsufficiency.

Del1p and Add1q

These copy number changes of chromosome 1 are both associated with poor prognosis and frequently occur together in MM [8]. It is not clear which gene(s) is/are responsible for driving the selection for amplication of 1q, although MCL1 has been proposed as a potential candidate. On the other hand, two distinct regions of 1p are associated with a poor outcome: *CDKN2C* at 1p32.3 and *FAM46C* at 1p12 [20]. The bi-allelic deletion of the *CDKN2C* is identified in about a third of MM cell lines and about 5% of newly diagnosed MM and is associated with increased proliferation, whereas the monoallelic deletion is not. FAM46C, a gene of unknown function, has been reported to be mutated in about 10% of patients, often associated with HRD [21, 22].

SUBCLONAL TUMOR HETEROGENEITY IS ASSOCIATED WITH HIGH-RISK MM

As in other tumors, it is clear that subclonal tumor heterogeneity is common in MM. Within the tumor population, there are different subclones with distinct genetic mutations that contribute independently to disease response and tumor progression [7, 23]. Recent reports suggest a high degree of subclonal heterogeneity particularly in patients with high-risk MM [7, 21–23] with alternating clonal 'tides' under therapeutic selective pressure. These observations suggest that the subclones are in competition for limited resources and that suboptimal treatment may preferentially target the more sensitive, less aggressive subclone, making room for the more aggressive drug-resistant subclone to grow. They support a strategy of therapy with multidrug combinations in patients with high-risk disease, that have greater subclonal heterogeneity, and therapy with one or two drugs used in sequence for patients with stable genomes and low-risk disease.

MOLECULAR CLASSIFICATION OF MULTIPLE MYELOMA: CLINICAL IMPLICATIONS

The genetic event most important clinically is the t(4;14) chromosome translocation. It is associated with a poor prognosis for patients treated with IMiDs, proteasome inhibitors, and DNA alkylators [24]. However, in randomized trials, there is a clear survival advantage to the use of bortezomib vs control upfront for t(4;14) MM, and perhaps also to the prolonged use of bortezomib maintenance [24]. The t(14;16), t(14;20), and del17p have each been associated with a decreased overall survival [24]. In addition, patients identified as high risk by GEP-defined risk scores or GEP index of proliferation also do poorly [24]. Unfortunately, in distinction to the t(4:14), no therapy has been shown to be superior to another for these latter subgroups, and alternative approaches should be explored in clinical trials. With the limited clinical data available, the hematologists at the Mayo Clinic have followed a therapeutic strategy based on genetic risk factors for the treatment of patients with MM that are not enrolled on clinical trials [25].

CONCLUSION

We have made significant strides in our understanding of the molecular pathogenesis of MM. Distinct molecular pathways are specifically activated or inactivated both by the tumor microenvironment and also by genetic mutations. As the disease progresses, the genetic mutations accumulate, and the tumor becomes increasingly independent of the BM microenvironment. This information is currently used to improve the diagnosis, prognostication, and risk stratification of patients. This information has also led to development of novel treatment strategies that are increasingly being tailored to the individual genetic composition of a patient's tumor, paving the way for the eventual use of precision medicine in the treatment of MM.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest.

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