Molecular Pathogenesis of Multiple Myeloma

Clinical Implications

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KEYWORDS

• Multiple myeloma (MM) • Smoldering multiple myeloma (SMM)
• Monoclonal gammopathy of undetermined significance (MGUS) • Plasma cell (PC)
• Hyperdiploidy • MYC • RAS • NFkB

KEY POINTS

- Primary genetic events divide multiple myeloma into 5 subgroups based on the presence of 1 of 3 types of recurrent immunoglobulin heavy chain gene translocations, hyperdiploidy, or of neither of these.
- The primary and initiating genetic events are present in pre-malignant monoclonal gammopathy and precede overt malignancy by several decades.
- Myeloma-defining secondary genetic events include activation of the MYC, RAS, NFkB, cell cycle pathways, and inactivation of tumor suppressor genes.
- Current therapies target vulnerabilities inherent in the plasma cell phenotype, while therapies targeting genetic mutations have not been yet successful.

INTRODUCTION

Multiple myeloma (MM) is a malignancy of long-lived, bone marrow-localized, plasma cells (PC) that have undergone immunoglobulin gene somatic hypermutation and isotype switch recombination in the germinal center. Its clinical presentation is characterized by hyperCalcemia, Renal failure, Anemia, and lytic Bone disease directly caused by either the tumor PC proliferation or their monoclonal proteins.[1] Errors during the process of isotype switch recombination contribute to the development of immunoglobulin heavy chain gene chromosomal translocations, which together with hyperdiploidy represents the initiating events being present in the earliest stages, including monoclonal gammopathy of undetermined significance (MGUS), and persist throughout all stages of PC neoplasia (**Fig. 1**).[2,3] Multiple secondary genetic events are accumulated and selected over time leading to the development of symptomatic

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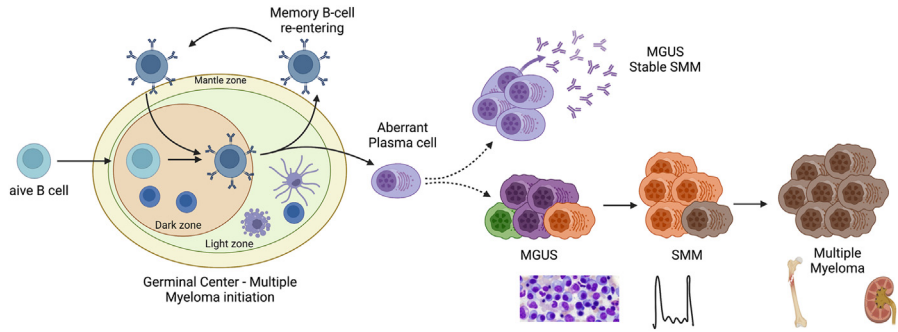

Fig. 1. Initiation of plasma cell (PC) neoplasms in the germinal center. The initial genetics events (chromosome translocations and hyperdiploidy) occur in the germinal center B-cell and are present in all stages of plasma cell neoplasms. Subsequent genetic events cause the progression from monoclonal gammopathy of undetermined significance (to smoldering myeloma and multiple myeloma (MM).Figure was generated using biorender.

MM requiring treatment and contributing to considerable intra-tumor and spatial heterogeneity.[4] Although the various genetic mutations are not the target of current therapies, they provide a framework for disease classification and risk stratification for myeloma precursor conditions progression and early treatment.

MULTIPLE MYELOMA IS PRECEDED BY AN ASYMPTOMATIC MONOCLONAL GAMMOPATHY

MM is consistently preceded by the asymptomatic expansion of clonal PC, termed either "monoclonal gammopathy of undetermined significance (MGUS)" or "smoldering myeloma (SMM)." While, according to the Icelandic iStopp national screening study, these 2 conditions are found in 5% and 0.5% of the adult population over the age of 40, only a small fraction will ultimately progress to MM. In fact, the risk of progression to MM is between 0.2% and 2% per year for MGUS[5] and approximately 10-fold higher for SMM.[6] The incidence of MM per 100,000 (2015–2019) was 7 in the US population, 8.6 in men, 5.7 in women, and 14.3 among African Americans.[7] The increased incidence in Blacks is felt to be due to genetic as opposed to environmental factors as a similarly high incidence of MGUS and MM is seen in Black Africans.[8,9] MM is almost always preceded by MGUS by many years[10–12] and based on sequence analysis the initial genetic lesions occurred decades before symptomatic disease.[13]

IMMUNOGLOBULIN HEAVY CHAIN GENE TRANSLOCATIONS AND HYPERDIPLOIDY ARE PRIMARY GENETIC EVENTS

Every cancer is developed through a clonal and genomic competition of multiple clones originated by a single cell that acquired the initiating event. Since the nineties,[2] we know a catalog of initiating events that occurred as translocations between the immunoglobulin heavy chain gene (IGH) and distinct genomic drivers: CCND1/CCND2/CCND3, MAF/MAFB/MAFA, and NSD2/FGFR3. The initiating role of these translocations in MM pathogenesis is supported by different lines of evidence: 1) they have the strongest impact on gene expression in MM; 2) they are always present in each phase of MM evolution: from MGUS to end stage MM; 3) Based on their structure and mechanisms, they represent very distinct genomic events not observed in any other tumor. Although fluorescence in situ hybridization (FISH) has been the major

technique used, there are now a variety of sequencing approaches that can now be used to detect these abnormalities (Fig. 2). Later, the authors summarize the key clinical and biological features associated to these key events.

Translocations of a Cyclin D Family Gene

Approximately 20% of patients with MM have a 14q32 translocation which dysregulates a cyclin D gene, most commonly cyclin D1 at 11q13,[14] sometimes cyclin D3 at 6p21,[15] and rarely cyclin D2 at 12p13.[1] The translocations result in high-level, "spiked" expression of the cyclin D gene, but do not result in a highly proliferative tumor. MM with cyclin translocations can be divided in 2 main groups: the first is characterized by low genomic complexity compared to other subtypes of MM, more likely to have mutations of CCND1, or a recurrent mutation of *IRF4* and K123 R, and less frequently have rearrangements of MYC (20%).[16] The second group is enriched for complex genomic features including 1q, high APOBEC mutational signatures, chromothripsis, multiple aneuploidies, and biallelic inactivation of tumor suppressor genes. The t(11;14) is more frequent in African Americans, where it is associated with a germline polymorphism CCND1 c.870 G risk allele.[17] It is also more frequent in MGUS (30%)[18] and amyloidosis (40%)[19] then in MM. It has been associated with a more lymphoplasmacytic morphology, and more frequent expression of B cell markers (eg, CD20).[20] Interestingly and in line with its genomic bimodal distribution, by unsupervised gene expression analysis, patients with t(11;14) MM fall into 2 distinct subtypes with a remarkably different clinical course: one-third are labeled CD-1 without, and two-thirds CD-2 with, CD20 expression.[21] The CD-1 is enriched for genomic complexity, while CD-2 has mostly a simple gneomic profile. Of all of the molecular subtypes, CD-1 had the highest (96%), and CD-2 the lowest (45%) rate of complete response following total therapy,[22] and with 10 years median follow-up, CD-1 had the highest PFS-estimated cure fraction (35%) and CD-2 among the lowest (14%).[23] This clinical heterogeneity reflects a distinct pattern of genomic complexity, in which high genomic complexity associates with shorter survival. MM cell lines with t(11;14) show a high dependency on BCL2, and are particularly sensitive to the BCL2 inhibitor venetoclax.[24] In a clinical trial of relapsed refractory MM, the response rate to single agent

Fig. 2. Advantages and disadvantages of different platforms for the detection of genetic abnormalities in MM.

venetoclax was 40% in patients with t(11;14) versus 6% in those without.[25] Although the data are not available at this time, it seems likely that the subset of t(11;14) patients that respond to venetoclax will be enriched in the CD-2 subtype that has a more B-cell phenotype, hopefully improving their relatively poor long-term outcome.

Translocations of a MAF Family Gene

Approximately 6% of patients with MM have a translocation that dysregulates a MAF family gene, most commonly *MAF* on 16q23, sometimes *MAFB* on 20q11, and rarely *MAFA* on 8q24.[1,26] The translocations result in ectopic, high-level expression of the respective MAF family gene. This subgroup is frequently associated with adverse secondary genetic events such as gain1q, del1p, del17p[16] and there is some controversy as to whether the presence of t(14;16) and t(14;20), which are included in the International Myeloma Working Group definition of high-risk myeloma, are independent prognostic factors.[27] Importantly, patients with *MAF*/*MAFB* translocations are often characterized by high APOBEC mutational burden detectable only by whole exome or genome sequencing and known to be one of the worst prognostic markers for outcomes in MM.[28,29] Unlike other molecular subgroups of patients treated in Total Therapy clinical trials at the University of Arkansas, the MAF subgroup did not appear to benefit much from either the addition of thalidomide in Total Therapy 2, or of bortezomib in Total Therapy 3.[30] A possible explanation for the latter observation is that MAF proteins are ubiquitinated and subsequently degraded by the proteasome so that therapy with proteasome inhibitors results in increased levels of MAF proteins.[31] MAF is a transcription factor that directly transactivates a high-level expression of CCND2 and integrin beta-7, enhancing adhesion to bone marrow stroma and stimulating vascular endothelial growth factor (VEGF) production.[32]

Translocations of NSD2/FGFR3

Approximately 15% of patients with MM have a t(4;14) (p16;q32) IgH translocation in the switch regions which associate the JH and Iu exons, and the Eu intronic enhancer on der 4 with coding exons of NSD2, a histone H3 lysine 36 dimethylase.[33–36] The resulting hybrid transcripts encode for either a full length (two-thirds of t(4;14)), or amino-truncated (one-third of t(4;14)) NSD2 protein resulting in a global increase in H3K36 dimethylation and altered gene expression[36] Two independent studies have reported that the presence of an amino-truncating breakpoint is an independent adverse prognostic factor with overall survival of 29 months as compare to 59 to 75 months for non-truncating t(4;14) breakpoints.[37,38] These results suggest that aberrant NSD2 protein contributes to the pathogenesis of MM, and a role for an enzymatic inhibitor of its demethylase activity in the treatment of t(4;14) MM. A phase I clinical trial of KTX-001 (NCT05651932) is testing this hypothesis.

In about 80% of patients with t(4;14), there is also the reciprocal translocation that juxtaposes the powerful 3′ IgH enhancer on der14 to FGFR3, a receptor tyrosine kinase expressed on the cell surface. A quarter of the patients that ectopically express FGFR3 also have an activating mutation indicating a critical role for the tyrosine kinase activity of FGFR3 in MM progression[39] Clinical trials using FGFR3 tyrosine kinase inhibitors dovitinib[40] and erdafitinib (NCT02952573) have not reported clinical responses in patients with t(4;14) MM. Preclinical studies suggest that kinase inhibition will only be effective in the presence of FGFR3 activating mutations, which has not been an eligibility criteria in the clinical trials. An intriguing case has been reported of a patient with a subclone containing an activating mutation of FGFR3 that was completely eliminated by treatment with erdafitinib, suggesting some promise

of this approach if applied to carefully selected patients with clonal activating mutations of FGFR3.[41] In addition, about 10% of patients with t(4;14) have mutations of the serine/threonine kinase PRKD2 which are much less common in other patients with MM. It is unclear if these are activating or inactivating mutations. Patients with t(4;14) have been historically associated with poor outcomes, and this is often driven by a complex combination of additional genomic hits preferentially acquired by tumor cells harboring this translocations such as 1q gain, 13q deletion, and non hotspot DIS3 mutation. Finally, at a level somewhat lower than MAF MM, t(4;14) MM ectopically express CCND2.

Hyperdiploidy

Around half of individuals with MM and myeloma precursor conditions exhibit a distinct cytogenetic profile characterized by multiple large trisomies, frequently involving odd-numbered chromosomes (such as 3, 5, 7, 9, 11, 15, 19, and 21). The tumors are hyperdiploid, most frequently with between 49 and 56 chromosomes, and are enriched in patients lacking IGH translocations.[42] Those hyperdiploid patients with trisomy 11 tend to ectopically express CCND1, while those hyperdiploid patients with disomy 11 express CCND2. The ectopic expression of a cyclin D gene associated with all of the primary genetic subtypes of MM, together with the high frequency of biallelic RB1 deletion in those patients that do not express any cyclin D gene, highlight the nearly uniform dysregulation of the cyclin D/RB pathway as a unifying event in the pathogenesis of MM. Analogous to those with Cyclin D translocations, hyperdiploid MM can be classified into 2 principal groups: one displaying complexity and the other simplicity, with the latter enriched for mutations in the mitogen–activated protein kinase (MAPK) pathway (*BRAF*, *NRAS*, *KRAS*). Furthermore, hyperdiploidy may also encompass other non-odd-numbered chromosomes, like 1q, 6p, and 8q; however, the biological and prognostic implications of these events remain to be fully elucidated.

Additionally, hyperdiploid cases are enriched for translocations of MYC (>50%) of which one-third involve a heavy or light chain immunoglobulin locus, and two-thirds involve other PC super-enhancer loci such as *TENT5C*, *BMP6*/*TXNDC5*, and *FOXO3*.[43] Intriguingly, patients with Ig lambda translocations are associated with poorer outcomes.[44] While hyperdiploidy is often a clonal event maintained throughout various phases, temporal assessments and mathematical modeling suggest that additional trisomies and large gains on odd-numbered chromosomes can be acquired subsequent to the initiating event.[13] Remarkably, these estimates indicate that hyperdiploidy can emerge up to 30 to 40 years before diagnosis, predominantly during the second and third decades of life.

Patients Without Translocations or Hyperdiploidy

Approximately 10% of MM cases lack both hyperdiploidy and IGH translocations. Despite their negative results with routine FISH probes used in clinical practice, these patients exhibit numerous genomic alterations that become apparent through more comprehensive methods like whole exome and genome sequencing. They are characterized by frequent monosomy 13, 14, and 16, and a variety of mutations that activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) pathway including TRAF3 inactivation and translocations of MAP3K14.[16] Moreover, when exploring additional genomic drivers, these patients can be categorized into 2 primary groups: the first group demonstrates a relatively simpler genomic profile with a lower frequency of events, while the second group is enriched for complex genomic alterations.

SECONDARY GENETIC EVENTS CAUSE THE PROGRESSION TO SYMPTOMATIC MULTIPLE MYELOMA

IGH translocations and hyperdiploidy alone are insufficient to drive the complete transformation of a B-cell into MM. Throughout the genomic evolution from a germinal center B-cell to MM, a series of additional secondary events are acquired. The advent of next-generation sequencing has provided an unprecedented glimpse into the intricate complexity of MM at a granular level. Numerous oncogenes and tumor suppressor genes undergo multiple somatic events, including single nucleotide variants, structural variants, and focal/large copy number variants. Despite the remarkable complexity and heterogeneity, a substantial portion of these somatic events, acquired during the progression of MM, contribute to the regulation of 4 key pathways: MYC, RAS, NFkB, and the cell cycle. A concise summary of these events is provided later.

MYC (MYC, MAX)

The most frequent alteration events in MM revolve around somatic events directly or indirectly involving MYC, which are detectable in up to 50% of patients. MYC can undergo upregulation through various mechanisms, including translocations with immunoglobulin genes or non-immunoglobulin superenhancers, as well as through focal structural variants like duplications and chromothripsis events. Moreover, MYC can also be affected by focal amplifications, single nucleotide variants, and deletions and inversions that relocate MYC near the superenhancers of NSMCE2, roughly 2 Mb upstream. While the precise prognostic impact of MYC alterations in newly diagnosed MM (NDMM) remains to be fully clarified, their identification in the context of SMM serves as a potent and accurate prognostic marker for predicting progression to active MM. About 4% of patients have biallelic inactivation of MAX, MYC's obligate heterodimerization partner that is required for MYC's transcriptional and oncogenic activities. As in small cell lung cancer and oligodendroglial tumors, MAX inactivation is mutually exclusive with mutations that activate MYC, and in fact is associated with a very low level of MYC transcription. While the mechanism remains to be elucidated, the data suggest MAX inactivation allows an alternate way of activating the MYC transcriptional pathway.[45]

RAS (NRAS, KRAS, BRAF, FGFR3, PTPN11, NF1)

Mutations affecting the RAS pathway are prevalent in nearly 50% of MM cases, with NRAS, KRAS, and BRAF being the genes most frequently affected. Although KRAS mutations are equally distributed across various key biological subgroups, NRAS mutations are notably enriched in patients exhibiting a simpler genomic profile (eg, hyperdiploid and CCND1 translocated patients).[16] While these genetic events may not currently hold significant prognostic value for NDMM, they have demonstrated a robust predictive capacity for the progression of SMM into active MM.[46] Additionally, they represent a promising potential therapeutic target, with several case reports of responses to targeting BRAF, and a phase 2 clinical trial of dabrafenib plus trametinib in BRAF-mutated MM reporting 2 of 10 patients with a partial response.[47] Disappointingly, it appears that when a single mutated gene in the RAS pathway is targeted, subclonal heterogeneity (see below) allows for the rapid selection of a subclone harboring another mutation in the pathway.[48] Recently, it has been reported that RAS mutations activate MTORC1 in MM, suggesting a possible role for combined inhibition MTOR plus MEK/ERK in the treatment of RAS-mutant MM.[49]

NFkB (TRAF2, TRAF3, BIRC2, BIRC3, CYLD, MAP3K14, NFKB1, NFKB2)

The NFκB pathway plays a crucial role in both normal PC and MM. In the bone marrow, BAFF and APRIL secreted by myeloid and stromal cells are ligands for B cell maturation antigen (BCMA) on the surface of PC, activating the NFkB pathway. The authors postulate that high level gamma-secretase–mediated shedding of soluble BCMA from PC binds these critical survival factors in the surrounding PC niche, preventing their use by encroaching PC clones. This presents a limitation to MM growth and expansion which is overcome by stimulating the environment to increase the supply of these ligands, or by the acquisition of various activating mutations downstream of BCMA (**Fig. 3**). Frequently, genes like TRAF2, TRAF3, BIRC2, BIRC3, and CYLD are implicated through substantial deletions, followed by a second-hit event involving focal structural variants or mutations. Additionally, approximately 1% of MM cases show gain-of-function structural variants affecting MAP3K14. Altogether these mutations are present in about 20% of NDMM, and 50% of cell lines capable of *in vitro* growth.[50]

Glucocorticoids and proteasome inhibitors, mainstays in the treatment of MM, function in part by inhibiting the NFkB pathway. Glucorticoids trans-repress NFkB-induced transcription by tethering to the transcription machinery orchestrated by CBP/EP300 at NFkB DNA binding sites (that partially overlap with glucocorticoid response elements).[51,52] Proteasome inhibitors inhibit the NFkB pathway by blocking the ubiquitin-proteasome–mediated degradation of negative regulators of the NFkB pathway (IkB, cIAP1, cIAP2, TRAF2, TRAF3) as well as processing of NFKB2 p100 to the active p52.[50,53] This has important clinical implications revealed in a randomized controlled trial of lenalidomide and dexamethasone with or without ixazomib in patients with relapsed refractory MM. This trial reported an improvement in progression free survival (PFS) (HR 0.74, $P = .01$), but not overall survival (OS), with the addition of ixazomib.[54] It appears, however, that most of the PFS benefit from the addition of ixazomib was seen in the 15% of patients with mutations of TRAF2, TRAF3, and BIRC2/3 where the hazard ratio was 0.23 ($P = .0005$) versus 0.83 ($P = .39$) in those without mutations.[55] These data suggest a therapeutic role for more specific inhibitors of the NFkB pathway in MM, particularly an inhibitor (eg, TRC694) of the NFkB-Inducing Kinase MAP3K14, which is activated downstream of most mutations.[56] The critical role

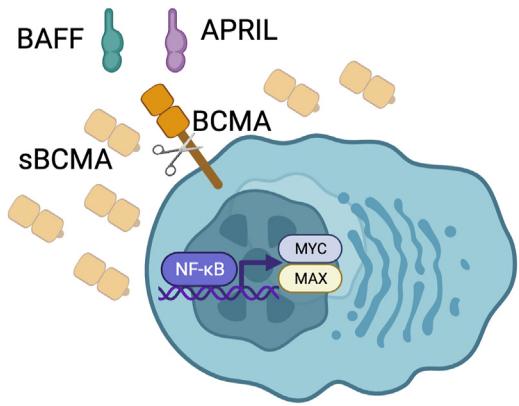

Fig. 3. Soluble B cell maturation antigen (BCMA) protects the PC niche. The BCMA ligands BAFF and APRIL represent limiting growth factors for PC survival. By shedding sBCMA, a PC traps BAFF and APRIL and prevents other PC from encroaching on its niche. For a malignant PC to expand the niche, it needs to increase the supply of BAFF and APRIL, or contitutively activate NFKB and/or MYC.

of NFkB signaling downstream of BCMA likely explains the relatively infrequent mutation of BCMA as a mechanism of resistance to BCMA-chimeric antigen receptor(CAR)-T therapy in MM. Recently, mutations, including those in the CART/T-cell engagers (TCE) BCMA binding site, have been reported as recurrent mechanisms of resistance to immunotherapies. Intriguingly, these mutations do not affect BCMA expression or its signaling, underscoring the critical role of BCMA for MM cells.[57] It also suggests that the presence of NFkB mutations may allow the MM cell to more easily dispense with BCMA as a general mechanism of resistance to BCMA-targeted therapies.[57] This intricate interplay of genetic alterations highlights the significance of NFκB in the context of MM.

Cell cycle (TP53, RB1, CDKN2C)

Biallelelic inactivation of TP53 (4%), RB1 (4%), and CDKN2C (2%) in NDMM significantly perturbs the cell cycle and apoptotic pathways within myeloma cells and has a strong prognostic impact. Biallelic loss of TP53 and RB1 has been associated with particularly unfavorable outcomes. The CDKN2A gene encodes for 2 proteins with unique first exons, but a shared second exon translated in alternate reading frames: p16INK4a binds to CDK4/6 to inhibit cyclin D1 activation of these kinases, while p14ARF forms stable complexes with MDM2 to activate TP53. By reverse transcription-polymerase chain reaction (RT-PCR), Mike Kuehl and colleagues reported no detectable transcription of the first exon of p16INK4a in human MM,[58] and more recently our analysis of RNAseq data from the CoMMpass project found that all of the RNA transcribed from the CDKN2A gene is predicted to encode p14ARF not p16INK4a (Bergsagel, 2023, unpublished). There is minimal transcription (median TPM 0.5), and only rare mutations of CDKN2B and no mutations of CDKN2D. As a result, of the 4 INK4 proteins, only inactivation of p18INK4c encoded by CDKN2C is an important driver of MM pathogenesis.

Copy number abnormalities: 1p loss, 1q gain, monosomy 13, 17p loss

Copy number abnormalities (CNA) involving 1p, 1q, 13, and 17p are prognostically important in SMM and MM, although there remains some uncertainty about the driver genes involved. On 1p, as noted earlier, biallelic inactivation of CDKN2C at 1p32 has the strongest prognostic impact, although RPL5 and EVI5 at 1p22, and TENT5C (FAM46 C) at 1p12 have also been implicated.[59] Gain of 1q in over 30% of NDMM leads to MCL1 overexpression, which can clearly drive MM progression, based on studies in transgenic mice over-expressing related proteins BCL2 and BCL-xL in B cells crossed to MM-prone mice.[60,61] Other candidate genes on 1q (eg, CKS1B)[62] have been shown to be critical dependencies, but not to accelerate disease when-over-expressed. Importantly, most of these genes are involved by focal gains mediated by SV and their expression cumulatively increases with the number of extra copies. Three genes have been implicated on 13: DIS3, RB1, and miR15a/16 to 1. DIS3 on 13q21 is an exosome-associated ribonuclease that is a common essential gene across almost all cell lines examined in the Dependency Map (http://depmap.org) and consistently, the pattern of mutation and deletion suggest that complete loss of function of DIS3 is not tolerated: About half of the mutations involve 1 of 3 hotspot codons, and are never associated with Loss of Heterozygosity.[18] Although the DIS3 homozygous knockout mouse is embryonic lethal, no phenotype was ascribed to heterozygous mice.[63] As noted earlier, biallelic inactivation of RB1 is rare, and there is no evidence for a role of RB1 haploinsufficiency in MM progression.[18] In contrast, one gene that has been shown to accelerate MM progression when haploinsufficient is miR15a/16 to 1.[18] In a cohort of

intensively-treated NDMM, deletion of 17p with p53 mutation was associated with a PFS of 18m, versus 27m with del17p and wildtype p53, and 44m for those without del17p.[64] It is not known if the patients with del17p and wildtype p53 eventually progressed because they eventually inactivated the wildtype copy, suggesting that isolated del17p is high risk because it predisposes to biallelic p53 inactivation. Alternatively, it suggests the presence of another gene on 17p which is haploinsufficient. These genetic events collectively underscore their crucial roles in influencing myeloma pathogenesis and clinical outcomes.

IMPACT OF INTRATUMOR SUBCLONAL HETEROGENEITY ON DISEASE PROGRESSION AND DRUG RESISTANCE

The life history of MM is marked by intricate evolution, where various clones vie competing dominance. Over time, these distinct clones acquire additional somatic alterations that confer advantages in terms of proliferation, anti-apoptosis, and evasion from immune responses. This leads to their expansion and positive selection. Notably, multiple rounds of positive selection occur in each patient, aligning with the punctuated evolution observed in other types of tumors. This spontaneous Darwinian evolution serves as the driving force propelling the progression from MGUS to SMM and eventually to active MM over the course of decades. Conversely, recent genomic insights have demonstrated that within the context of treatment, the evolution and selection of minor subclones can take place within weeks to months. The selective pressure exerted by therapeutic interventions creates a bottleneck where only the most resilient and adept clones survive, thus accelerating the evolutionary process. Understanding this intricate dynamic is paramount for identifying resistance mechanisms and optimizing treatment approaches. Notably, this inherent heterogeneity within MM extends beyond the confines of the bone marrow, as distinct clones populate various anatomic sites. This seeding process can be initiated by a single surviving tumor cell and has been observed to accelerate post-treatment, possibly due to a combination of immunosuppression and heightened disease aggressiveness. Grasping and capturing both the clonal and spatial heterogeneity is imperative for comprehensive profiling of MM's biology, and in turn, enhancing our treatment strategies.

SUMMARY

Although there have been dramatic advances in our ability to molecularly classify and risk-stratify patients with SMM and MM using next-generation sequencing, we are still far from fully understanding the MM genomic history and heterogeneity. The clinical and data complexity we are facing is one of the main reasons why these technologies have not yet entered routine clinical practice. This is likely to change over the next decade as sequencing costs plummet and analytical pipelines improve. From where we stand today, it seems unlikely that therapies will directly target the mutations identified and the goal of the molecular analysis will be to provide a genetic definition of MM that requires treatment, and a risk stratified approach both for the follow-up of those patients that do not require immediate treatment, and a graded treatment approach for those that do.

CLINICS CARE POINTS

- FISH for the identification of t(4;14), t(11;14), t(14;16), t(14;20), 1q21, and 17p13 in bone marrow PC should be a part of the standard work-up for patients with MM.

- FISH for the identification of t(4;14), t(14;16), 1q21, and 13q in bone marrow PC should be a part of the standard work-up for patients with SMM.
- FISH is not required for the work-up of patients with monoclonal gammopathy of undetermined significance.
- Intratumor heterogeneity has limited the impact of molecularly-targeted therapy.
- In the future, RNAseq and whole genome sequencing are likely to provide better disease classification and risk stratification.

DISCLOSURE

None.

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