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The Genetic and Molecular Drivers of Multiple Myeloma: Current Insights, Clinical Implications, and the Path Forward

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Background: Multiple myeloma (MM) is a hematological malignancy characterized by the clonal proliferation of malignant plasma cells within the bone marrow. The disease's complexity is underpinned by a variety of genetic and molecular abnormalities that drive its progression.

Methods: This review was conducted through a state-of-The-art literature search, primarily utilizing PubMed to gather peer-reviewed articles. We focused on the most comprehensive and cited studies to ensure a thorough understanding of the genetic and molecular landscapes of MM.

Results: We detail primary and secondary alterations such as translocations, hyperdiploidy, single nucleotide variants (SNVs), copy number alterations (CNAs), gene fusions, epigenetic modifications, non-coding RNAs, germline predisposing variants, and the influence of the tumor microenvironment (TME). Our analysis highlights the heterogeneity of MM and the challenges it poses in treatment and prognosis, emphasizing the distinction between driver mutations, which actively contribute to oncogenesis, and passenger mutations, which arise due to genomic instability and do not contribute to disease progression.

Conclusion & Future Perspectives: We report key controversies and challenges in defining the genetic drivers of MM, and examine their implications for future therapeutic strategies. We discuss the importance of systems biology approaches in understanding the dependencies and interactions among these alterations, particularly highlighting the impact of double and triple-hit scenarios on disease outcomes. By advancing our understanding of the molecular drivers and their interactions, this review sets the stage for novel therapeutic targets and strategies, ultimately aiming to improve clinical outcomes in MM patients.

Keywords: cancer, mutations, translocations, fusions, ncRNA, epigenetics, myeloma

Introduction

Multiple myeloma (MM) is a B-cell malignancy characterized by the clonal proliferation of malignant plasma cells within the bone marrow. While it primarily resides in the bone marrow, its progression can lead to systemic effects impacting various areas of the body.[1]

The pathogenesis of MM is driven by a series of genetic alterations that contribute to the initiation and progression of the disease, from Monoclonal Gammopathy of Unknown Significance (MGUS), then to Smoldering Multiple Myeloma (SMM), and ultimately to symptomatic myeloma, with each stage marked by an increasing mutation load.[2] These abnormal plasma cells produce monoclonal proteins (M-protein), which are abnormal antibodies or parts of antibodies. These proteins are typically composed of heavy chains (types include IgG, IgA, IgD, IgE, or IgM) and light chains (kappa or lambda), which can be detected in the blood or urine and are used as markers for diagnosing and monitoring

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the disease. The presence of these monoclonal proteins can lead to complications such as kidney damage or bone lesions, highlighting the importance of early detection and tailored treatment strategies to manage the disease effectively. Additionally, MM patients may experience hypercalcemia, anemia, and bone pain. An aggressive form of MM, known as extramedullary disease (EMD), occurs approximately in 20% of cases. EMD is characterized by the spread of myeloma cells beyond the bone marrow to other organs, such as the lungs, liver, and soft tissues, significantly complicating treatment and management.[3]

MM is typically categorized into stages 1, 2, and 3, with the stage at diagnosis significantly influencing treatment decisions and prognosis. Historically, the Durie-Salmon staging system classified MM based on tumor cell mass and clinical parameters like hemoglobin, calcium levels, and urine light chain M-component.[2] The International Staging System (ISS) improved on this by using serum beta-2 microglobulin (Sb2M) and serum albumin levels to classify MM into three stages.[3] The Revised International Staging System (R-ISS) refined this approach further by incorporating genetic risks and lactate dehydrogenase (LDH) levels.[4] The second revision of the ISS (R2-ISS) introduced a points-based, four-tier risk stratification system that considers risk factors such as gain(1q), del(17p), and high-risk translocations.[5] This system assigns patients to low, low-intermediate, intermediate-high, and high-risk categories, providing a more nuanced assessment that helps tailor treatment strategies and predict patient outcomes more effectively.

The pathogenesis of MM is driven by a series of genetic events that contribute to the initiation and progression of the disease. The hierarchical layers of drivers in MM, from primary genetic alterations to the complex interactions with the tumor microenvironment (TME), are illustrated in Figure 1.

Driver genes may harbor critical mutations or be disrupted and dysregulated by structural variations or epigenetic aberrations. Driver mutations actively contribute to tumorigenesis and confer a selective advantage to cancer cells. These mutations can exhibit varying degrees of impact, categorized as strong, latent, or weak, and occur at different frequencies within the MM patient population. In contrast, passenger mutations are functionally neutral or even detrimental to cancer cells.[6]

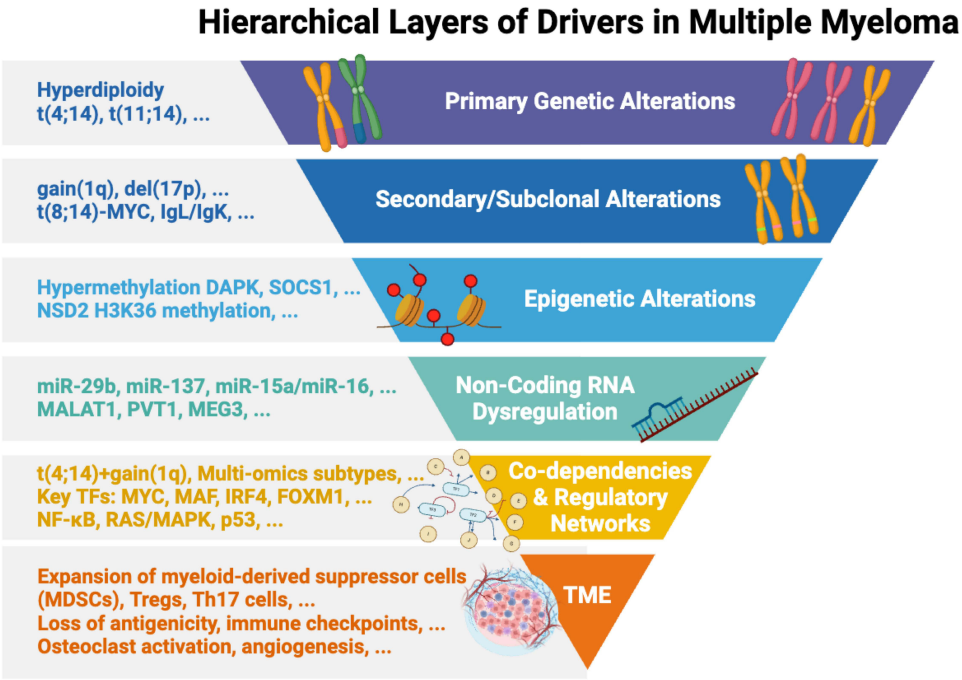

Figure 1 Hierarchical layers of drivers in multiple myeloma. The broadest levels at the top illustrate primary genetic alterations, which include initial chromosomal translocations and hyperdiploidy. As the layers narrow down, secondary genetic alterations, epigenetic alterations, and non-coding RNA dysregulation are shown, reflecting the increasing complexity of interactions. The narrowest levels at the bottom depict co-dependencies and regulatory networks, culminating in the tumor microenvironment (TME), highlighting the intricate network of factors contributing to myeloma pathogenesis and progression.

Remarkably, about 80% of driver mutations in cancer are somatic, originating directly within the cancer cells, while 10% are inherited through the germline, and the remaining 10% occur in both somatic and germline contexts.[7] Although some studies suggest that, on average, around five driver mutational genes are associated with each MM tumor, a recent study found that about 16% of cases in a large cohort of relapsed/refractory (RRMM) patients exhibited no known driver genes, underscoring the genomic complexity and heterogeneity inherent to MM.[8]

MM is highly heterogeneous, and whole-genome characterization studies have been pivotal in identifying and classifying recurrent genetic abnormalities.[9] Computational approaches have been employed to categorize potential drivers of MM, with several studies providing comprehensive insights into its genomic landscape, identifying and classifying key drivers that contribute to MM pathogenesis and progression.[8,10–12]

Recent advances have shed light on the complexity of the clonal architecture of MM, revealing that primary genetic events occur early in the disease course and set the stage for further genetic alterations. High-throughput sequencing technologies have deepened our understanding of clonal evolution in MM, uncovering subclonal heterogeneity and the dynamic nature of the disease.[9–12] This has significant implications for prognosis and treatment, as certain primary events are associated with different clinical outcomes and responses to therapy. The identification of these events can lead to the development of targeted therapies aimed at specific pathways altered by the primary drivers, offering a more personalized approach to MM treatment.

Understanding the roles of drivers can guide the development of precision therapies and enhance our comprehension of the mechanisms behind drug resistance, tumor development, and the identification of cancer biomarkers. Identifying driver aberrations is crucial for preventing disease progression, as even a small number of driver events can initiate disease development.[13] Therefore, pinpointing and validating these mutations is essential to refine risk stratification and improve MM management. While substantial progress has been made in identifying genetic and molecular drivers of MM, the field continues to grapple with distinguishing true drivers from passenger alterations and understanding their precise roles in disease progression. Current tools and datasets often fall short in providing a comprehensive view of MM heterogeneity, leaving important questions unanswered.

This review provides a detailed exploration of the genetic and molecular drivers of MM, presenting both established and emerging factors, including epigenetic modifications, non-coding RNAs, and mutational signatures. We emphasize critical areas where understanding remains incomplete and discuss their implications for developing targeted and precision therapies. We examine how current insights into MM drivers are shaping the development of targeted therapies and precision medicine approaches, bridging the gap between their identification and translational applications. Additionally, we discuss how advanced computational analyses, combined with clinical perspectives, provide a unique view of the oncogenic dependencies that drive MM progression and the therapeutic opportunities that could shape its treatment.

The Genomic Landscape of MM

The genetic makeup and evolutionary history of a tumor constitute its clonal landscape, where drivers contribute to tumorigenesis, clonal expansion, heterogeneity, and response to therapy. Clonal mutations, occurring in the initiating cell of a clonal sweep, are theoretically present in every cell of a tumor, whereas subclonal mutations arise in descendant cell populations.[14] This distinction between primary (clonal) and secondary (subclonal) events is crucial for understanding MM development and tumorigenesis. The genomic alterations that drive MM pathogenesis are non-linear – they are heterogeneous and appear in branched patterns, which adds to disease complexity and can potentially favor the emergence of drug-resistant subclones.[6,7,15] Plasma cells clones can accumulate genomic alterations, gain proliferative advantages, and establish multiple subclonal populations within the bone marrow, further compounding the genetic landscape with primary and secondary translocations among other genomic changes. The interplay between primary clonal developments and the broader genomic landscape highlights how early genetic alterations drive tumor initiation and shape the evolutionary trajectory of MM.

Table 1 summarizes the main cytogenetic alterations in MM, including key translocations, hyperdiploidy, and the most common amplifications and deletions. Figure 2 presents a circos plot illustrating a more comprehensive view of recurrent genetic alterations in MM, encompassing these main cytogenetic changes as well as additional copy number

Table 1 Summary of Main Cytogenetic Alterations in Multiple Myeloma

Alteration Type	Alteration	Affected Genes/Regions	Frequency in MM	Biological/Clinical Significance	References
Translocation	t(11;14)	CCND1	16–24%	Prognostic implications, potential target for therapies involving BCL-2 inhibitors	[12]
Translocation	t(4;14)	NSD2, FGFR3	15%	Poor prognosis, associated with early relapse	[16]
Translocation	t(14;16)	MAF	5%	Poor prognosis	[17]
Translocation	t(14;20)	MAFB	1–2%	**Poor prognosis**	[18]
Translocation	t(8;14)	MAFA	<1%	Poor prognosis	[18]
Translocation	t(4;16)	CCND2	<1%	Associated with increased cell proliferation	[19]
Translocation	t(6;14)	CCND3	<1%	Associated with increased cell proliferation	[20]
Translocation	t(8;14)	MYC	13–25%	Aggressive disease course	[21]
Hyperdiploidy	Gain of odd-numbered chromosomes (eg, 3, 5, 7, 9, 11, 15, 19, 21)	Multiple Regions	50%	Generally associated with a better prognosis compared to non-hyperdiploid myeloma	[22]
Amplification	gain/amp(1q)	CKS1B, ADAR, ILF2, PBX1, …	40%	Poor prognosis, frequently associated with disease progression	[23]
Deletion	del(13q)	RB1, DIS3	45%	Prognostic implications, often seen at diagnosis	[24]
Deletion	del(1p)	FAM46C, CDKN2C	30%	Poor prognosis, associated with high-risk disease	[25]
Deletion	del(17p)	TP53	10%	Poor prognosis, often associated with high-risk disease	[65]

Notes: This table summarizes the main cytogenetic alterations observed in MM, including translocations, deletions, amplifications, and hyperdiploidy. For each alteration, the affected genes or chromosomal regions, frequency in MM, clinical significance, and relevant references are provided.

alterations (CNAs) and single nucleotide variants (SNVs). Together, these figures underscore the genomic complexity and heterogeneity characteristic of the disease.

Primary IgH Translocations

Primary clonal events in MM are mainly characterized by immunoglobulin (Ig) translocations and hyperdiploidy. Ig translocations involve the rearrangement of immunoglobulin genes, located on chromosome 14, that encode antibodies and can affect both heavy and light chains.[8,9] The heavy chain translocations (IgH) are usually classified as primary clonal events, while light chain translocations are secondary. The IgH translocations typically involve seven main recurrent partner loci: CCND1, CCND2, CCND3, MAF, MAFA, MAFB, and NSD2.

The most prevalent is the t(11;14)(q13;q32) translocation involving CCND1, which is found in approximately 16–24% of MM cases.[10–12] Tumors harboring this translocation are characterized by overexpression of cyclin D1, elevated levels of the anti-apoptotic protein BCL-2, and frequent CD20 expression, which are not typically seen in t(11;14)-negative MM.[12] A recent meta-analysis of 13 studies involving 961 patients, suggests that high CCND1 expression correlates with poorer overall survival (OS) in patients receiving chemotherapy.[27] However, those treated with bortezomib tended to have a longer OS. Other studies show that the prognosis of patients with t(11;14) differ subject to co-occurring alterations and respond slowly to proteasome inhibitors.[28] CCND1 is implicated in MM progression by promoting cell survival and proliferation, partly through its interactions with cell adhesion molecules. Other cyclin D genes, such as CCND2 and CCND3, are also implicated in MM pathogenesis, although translocations involving these genes occur less frequently.[21,29] Post-transcriptional mechanisms, alongside Ig translocations, may also upregulate CCND2, contributing to the pathogenesis of the disease.[19]

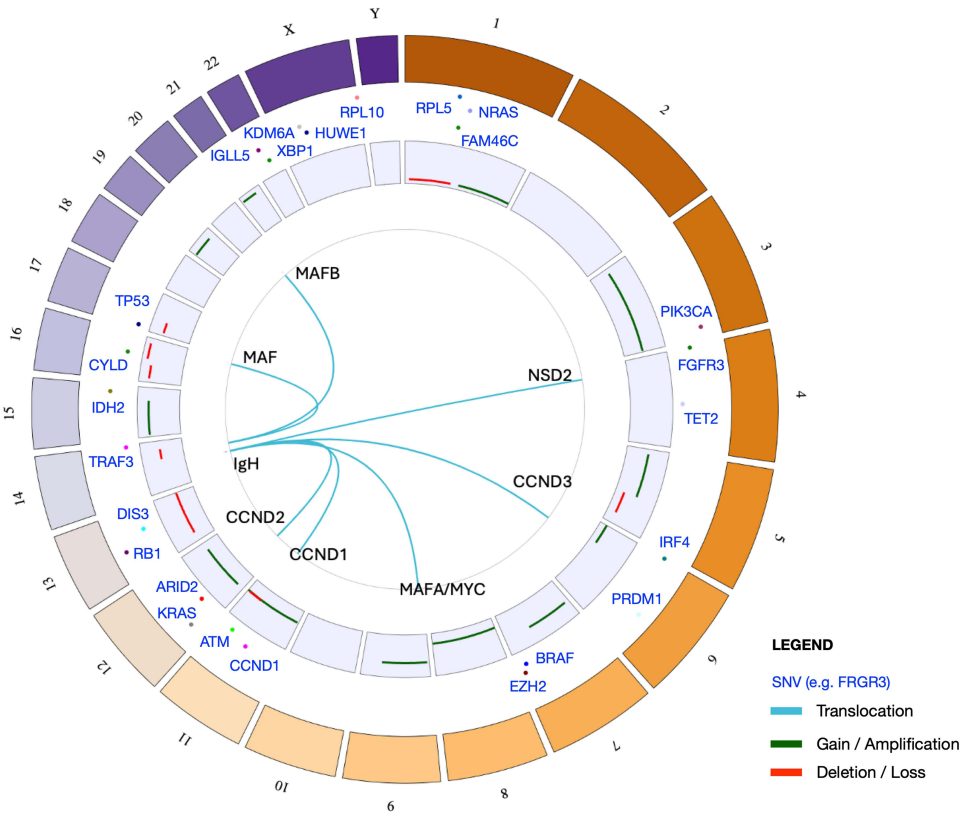

Figure 2 Circos plot summarizing the most recurrent genetic alterations observed in multiple myeloma. This circos plot includes translocations, copy number alterations (CNAs), and single nucleotide variants (SNVs). The outer ring represents the chromosomes, with different colors indicating various types of genetic alterations. Translocations are depicted as lines connecting different chromosomal regions, CNAs are shown as segments along the chromosomes, and SNVs are marked at their respective genomic locations. This visual representation highlights the complexity and heterogeneity of the genomic landscape in multiple myeloma, providing insights into key genetic events that drive the disease.

The translocations t(4;14)(p16.3;q32) and t(14;16)(q32;q23) are found in approximately 15% and 5% of MM cases, respectively. The t(4;14) translocation leads to overexpression of NSD2 (Nuclear Receptor Binding SET Domain Protein 2, also known as MMSET) and FGFR3 (Fibroblast Growth Factor Receptor 3).[30,31] In the revised International Staging System (rISS), this translocation is classified as a high-risk lesion.[4] This is due to its association with a more aggressive disease course and shorter OS. However, our recent Patient Similarity Network (MM-PSN) model based on multi-omics data from NDMM patients, revealed that co-occurrence of t(4;14) and gain of chromosome 1q (gain(1q)) identified patients at significantly higher risk of relapse and shorter survival as compared to t(4;14) as a single lesion.[32]

NSD2 encodes a histone methyltransferase that alters chromatin structure and primarily regulates gene expression through histone methylation, specifically at histone H3 lysine 36 (H3K36).[33] Methylation by NSD2 influences several cellular processes, including gene transcription, proliferation, and cell cycle progression. A recent study on patients affected by t(4;14) identified three distinct breakpoint categories within the NSD2 gene, finding that the location of the translocation breakpoints significantly affected patient outcomes.[34] Concurrently, FGFR3 overexpression, caused by the same t(4;14) translocation, drives cell growth and division, which can contribute to the aggressive nature of certain MM cases.[31,35] However, patients who do not express FGFR3 exhibit poor prognosis, indicating a more critical role of NSD2 in the progression of the disease.[34] NSD2 also interacts with various proteins and manages downstream signaling pathways involved in cell death, cell cycle, DNA repair, and integrin-mediated signaling. The use of proteasome inhibitors, such as bortezomib, has been shown to improve outcomes in patients with this translocation.[36]

The t(14;16) translocation affects the MAF (musculoaponeurotic fibrosarcoma) oncogene, which encodes a transcription factor crucial for various cellular processes.[37] While MAF translocations occur only in 5–10% of cases, c-MAF is overexpressed in 50% of myelomas, enhancing tumor survival.[38] The t(14;16) translocation generally indicates

stable disease in MGUS patients, but in MM patients, it is associated with a higher risk and poorer overall survival.[39] However, like for co-occurrence of gain(1q) and t(4;14), our network analysis found that most patients with t(14;16) also had concurrent gain(1q), which is known to confer poor prognosis, and thus, the prognostic impact of the MAF translocation may be confounded by this.[32]

MAF translocations also contribute to resistance against proteasome inhibitors like bortezomib, often resulting in a poor response in MM patients,[24] with the mechanisms behind the resistance not fully understood. Immunomodulatory drugs have been particularly effective at treating t(14;16 MM).[40]

The t(14; 20) and t(8;14) translocations, involving MAFB and MAFA respectively, occur less frequently, in about 1–2% of cases.[41] Like MAF, MAFB and MAFA are also transcription factors and their overexpression due to translocations can drive oncogenic processes, although their exact roles and impacts on prognosis in MM are less well-studied and need further investigation.

Hyperdiploidy

Hyperdiploidy (HD) in MM is characterized by the trisomy of odd-numbered chromosomes - specifically chromosomes 3, 5, 7, 9, 11, 15, 19, and 21.[6,42] Tumors are classified as either HD or non-HD based on the number of chromosome sets in a cell, with diagnosis typically achieved through flow cytometry, fluorescence in situ hybridization (FISH), or whole genome sequencing.[43] This chromosomal anomaly leads to an increased dosage of genes on these chromosomes, which may affect gene expression and contribute to the disease's development and progression.[44] Interestingly, while HD and non-HD MM differ in gene expression on trisomy chromosomes, a higher proportion of dosage-sensitive genes is found on non-trisomy chromosomes.

The identification of HD often includes the gain of chromosome 11 and increased expression of CCND1. Notably, a subset of patients with the t(11;14) translocation, which involves CCND1, also exhibit this chromosomal gain. This combination can further amplify CCND1 expression, potentially intensifying the aggressiveness of the disease. Such cases may represent a distinct clinical subset of MM with unique characteristics and prognostic outcomes.[32] HD is the most common primary genetic event in MM, affecting 56% of tumors, underscoring its significance in understanding the primary or clonal events in early-stage disease and its progression.[45] Moreover, the presence of HD is typically associated with improved patient survival rates compared to non-HD cases,[46] especially in patients with trisomies of chromosomes 3 and 5. However, this trend does not apply universally. Trisomy of chromosome 21, or co-occurrence of high-risk cytogenetic features such as gain of 1q are exceptions that are linked to poorer survival outcomes.[13,47,48]

Other Ploidy Changes

Beyond the identification of HD, the broader ploidy status of MM cells is a critical factor in disease characterization.[49] Non-hyperdiploid MM, which includes hypodiploid (fewer than the normal diploid number of chromosomes), pseudodiploid (approximately the normal diploid number), and near-tetraploid (close to twice the normal diploid number but not exceeding 75 chromosomes), plays a significant role in the pathogenesis of the disease.

Specifically, hypodiploid MM has been linked to a higher risk of disease progression and shorter overall survival compared to hyperdiploid MM, which tends to have a more favorable prognosis.[50,51] Pseudodiploid MM, which harbors a normal chromosome count but with structural abnormalities, also tends to have an adverse prognosis due to the presence of high-risk cytogenetic abnormalities such as t(4;14), t(14;16), and del(17p).[52] Near-tetraploid MM is less common, and its implications are less clear, but it may be associated with an intermediate profile between hyperdiploid and other non-hyperdiploid subtypes.[53,54]

Overall, the non-hyperdiploid group, particularly with certain cytogenetic abnormalities, is often associated with a more aggressive disease course and resistance to certain therapies, underscoring the importance of ploidy and cytogenetic analysis in understanding primary clonal events and informing treatment planning for MM patients. In addition to primary clonal events, subclonal events, including mutations and MYC rearrangements, further contribute to MM heterogeneity.

Secondary or Subclonal Events

Secondary or subclonal events in MM, which are acquired during tumor progression from the initiating pool of cells, include light chain translocations, copy-number alterations (CNA), non-Ig translocations, somatic mutations in driver genes and other biologically relevant genes, structural variation (SV) events, and alternative splicing events. Co-occurrences of oncogenic markers, as well as influences from the immune system and cellular metabolism pathways like the unfolded protein response (UPR), also contribute to MM progression.[11,55]

Secondary IgH Translocations

Secondary IgH translocations frequently involve the dysregulation of the MYC oncogene. This dysregulation is mediated by the Eα1 and Eα2 enhancers, which are potent regulatory elements within the IgH locus.[56] The progression of MM is driven by several pivotal signaling pathways, notably those involving MYC as well as RAS, and NF-κB. These pathways often exhibit functional redundancy and are typically co-activated, ensuring that at least one is active in the vast majority (95%) of NDMM cases.

MYC, a proto-oncogene, plays a critical role in regulating various cellular processes, including growth, proliferation, apoptosis, differentiation, and transformation.[28] In MM, chromosomal rearrangements or CNAs involving MYC are considered secondary events that can contribute to a more aggressive disease phenotype.[21,29] While chromosomal rearrangements typically lead to increased monoallelic MYC expression, tumors without rearrangements often show high biallelic MYC expression already in the MGUS stage.[57] Translocations involving MYC can disrupt the regulation of other essential driver genes and perturb the expression of downstream genes pivotal to B-cell biology, such as FGF16, ADAMTS1, FBXL7, HRK, PDGFD, and PRKD1. These changes are instrumental in driving the progression of MM.

While the prevailing view supports the occurrence of MYC alterations in the later stages of MM, some evidence suggests that they may also appear in early stages. MYC translocations, which are present in approximately 25%-42% of NDMM cases, are associated with poorer prognosis. These genetic events have been linked to increased mortality and the development of resistance to therapeutic drugs.[30,31]

Immunoglobulin Light Chain Translocations

Secondary Ig translocations in MM can significantly impact disease prognosis and treatment response. Approximately 10% of MM patients exhibit translocations involving the immunoglobulin lambda (IgL) locus, which are associated with a poor prognosis.[32,33] Notably, IgL-MYC translocations, characterized by focal amplifications of enhancers at both the IgL and MYC loci, are linked to a particularly adverse prognosis.[58] These translocations also confer resistance to immunomodulatory drugs (IMiDs), which target the lymphocyte-specific transcription factor Ikaros (IKZF1), known to bind robustly to the IgL enhancer. This resistance highlights the prognostic importance of IgL-MYC translocations, independent of other genetic abnormalities.[35] Despite their significance, IgL translocations do not define a specific gene expression signature, are not associated with any mutations, and occur across all gene subtypes of MM. However, their co-occurrence with HD disease and their status as an independent marker of poor prognosis suggests that some patients diagnosed with HD myeloma may be misclassified due to the presence of an IgL translocation. Patients with HD myeloma and IgL translocations may experience outcomes that are heavily influenced by the broader genomic instability rather than by the translocation itself. Moreover, emerging evidence highlights the heterogeneity within the IgL-MYC translocation subtype, with some patients responding to alternative therapies targeting downstream MYC pathways.[36] This suggests a potential therapeutic avenue for overcoming IMiD resistance in these patients. In addition, recent advances in proteasome inhibitors and bispecific T-cell engagers (BiTEs) have demonstrated efficacy in high-risk MM, including cases with MYC involvement.[36]

Translocations involving the immunoglobulin kappa (IgK) locus are less common than those involving the immunoglobulin lambda (IgL) locus, occurring in approximately 4.5% of cases. Similar to IgL translocations, IgK translocations can also target the MYC gene, leading to the juxtaposition of IgK enhancers to the MYC locus. However, unlike IgL-MYC translocations, those involving IgK do not necessarily result in decreased survival.[35]

Copy Number Alterations

Beyond immunoglobulin translocations, which are critical early drivers of MM, additional genomic alterations arise during disease progression. Among these, copy number alterations (CNAs) represent pivotal secondary events that contribute to tumor evolution by amplifying or deleting segments of the genome, thereby impacting gene expression and cellular function. These abnormalities can manifest as gains, including duplications and amplifications, or losses, such as deletions and loss of heterozygosity (LOH).[8] CNAs are commonly observed in chromosomes 1, 8, 13, 14, and 17, and to a lesser extent in chromosomes 3, 5, 7, 9, 15, 16, 22, and X. While the prognostic relevance of these alterations has been defined and confirmed by multiple studies, the mechanistic underpinning of their presence has not yet been fully characterized, although some of these lesions have been dissected to a greater degree than others.

The most recurrent CNAs include losses of chromosome 13q (del(13q)), observed in 45% of patients, and gains of chromosome 1q, which are seen in about 40% of patients, with high-level gains or amplifications (amp(1q)) in 6.8% of cases.[37–39] The prognostic implication of del(13q) in MM is somewhat variable and may depend on the presence of other cytogenetic abnormalities.[24] It is often considered associated with a worse prognosis, particularly when it occurs alongside other high-risk abnormalities. The aberration primarily encompasses the entire chromosome 13 without a clearly identified specific driver gene. Although RB1 and DIS3 have been posited as candidate loci, only biallelic deletion of RB1 is linked with MM progression, while DIS3, a commonly essential gene, does not exhibit complete inactivation.[41–43] The deletion of the microRNA Mir15a/Mir16-1 locus on chromosome 13, however, has been found to contribute to disease progression in MM mouse models, a phenomenon also noticed in MM patients.[44,45] Further explorations and implications of these findings will be discussed in the miRNA section of this review.

The gain of 1q (gain(1q)) is particularly concerning as it is linked with worse progression-free survival (PFS) and is often observed to increase at the time of relapse.[23,46,59] This aberration has long been considered a high-risk factor and was recently incorporated into the second revision of the International Staging System (R2-ISS).[5] Our recent Patient Similarity Network (MM-PSN) model, based on multi-omics data from NDMM patients, identified six disease subtypes enriched for gain(1q) and revealed that co-occurrence of gain(1q) with other recurrent lesions confers a shorter median time to relapse and death, particularly when co-occurring with the t(4;14) translocation.[48] A minor clone of gain(1q) might represent an earlier stage in the pathogenesis of the abnormality and is prone to evolve into a dominant clone at relapse.[26] The co-occurrence of gain(1q) with other cytogenetic abnormalities besides t(4;14), such as del(1p) or del (17p), also identifies subsets of patients with particularly poor prognoses, and its co-occurrence with del(13q) is considered a driver event in MM progression, defining a distinct subgroup of patients with overexpression of CCND2 and unfavorable clinical outcomes.[47] Our PSN study also showed differential expression of 1q genes across the subtypes enriched with gain(1q), suggesting that different sets of 1q genes may be active in the different subgroups of MM patients. The large size of the genomic region affected has posed a significant challenge in the identification of the drivers of 1q-MM. Most studies so far have focused on genes located in 1q21, a critical focal area of amplification, including MCL1, CKS1B, ADAR1, and ILF2, which have been proposed and validated as drivers of aggressive disease in 1q-MM.[60–63] Their pathogenic roles range from ADAR1's promotion of malignant transformation through RNA editing, ILF2's facilitation of genomic instability tolerance, MCL1's critical involvement in cell survival and resistance to apoptosis, and CKS1B's contribution to cell cycle progression and proliferation. Another recent study has also demonstrated a driver role for a gene outside of 1q21, PBX1, which is located in 1q42, and has been implicated in directly regulating critical oncogenic pathways and a FOXM1-dependent transcriptional program, leading to adverse prognosis and high-risk disease in patients.[64]

Deletion of the short arm of chromosome 17 (del(17p)), specifically at the TP53 locus, 17p13.1, is recognized as a significant adverse cytogenetic marker in MM.[65] Del(17p) is among the most detrimental prognostic factors in MM, and it contributes to the classification of stage 3 disease as per the revised International Staging System (R-ISS).[4] In MM, TP53 abnormalities have a frequency distribution of approximately 8% for deletion, around 6% for mutation, and about 4% for biallelic inactivation. The acquisition of a second detrimental alteration to TP53, often called a "second hit", is suggested to be a significant step towards increased drug resistance and the risk of MM spreading outside the bone marrow.[66] Biallelic inactivation of TP53, which typically results from either a homozygous deletion or a combination of

deletion on one allele and mutation on the other, leads to the complete loss of p53 protein function. Given that TP53 is a crucial tumor suppressor, its impairment, coupled with genetic changes that heighten cell proliferation, likely paves the way for the rapid outgrowth of MM subclones resistant to treatment. This scenario significantly worsens clinical outcomes and elevates the risk of a second relapse.[67]

Deletion of the short arm of chromosome 1 (del(1p)) is another strong predictor of poor outcome in MM patients, particularly those undergoing autotransplant.[25,68] Among patients with NDMM, approximately 11% harbor a focal deletion of 1p32, which is considered the second worst abnormality in MM after del(17p) in terms of prognostic significance.[69,70] Biallelic deletion of 1p32, which involves both copies of a particular region on chromosome 1p, defines an ultra-high-risk group of MM with a median OS of only 25 months.[69] Even monoallelic del(1p32) is a strong prognostic factor, with a median OS of 60 months. Del(1p32) is often found in conjunction with other high-risk cytogenetic abnormalities such as del(17p), t(4;14), or gain(1q). When associated with these abnormalities, the OS of patients with del(1p32) significantly decreases. Chromosome 1p/q abnormalities are also highly associated with chromosome 13/13q deletions.[68] While the specific driver or relevant genes in 1p have not been validated, studies have shown deletions of FAM46C at 1p12 and CDKN2C at 1p32.3 as being associated with poor outcomes.[71] In particular, FAM46C functions as a tumor suppressor and is an active non-canonical poly(A) polymerase that enhances mRNA stability, particularly for genes expressed in B-lymphocytes.[72] Loss of FAM46C function due to mutations or deletions has been shown to promote cell survival and proliferation, while its reintroduction in MM cell lines induced cell death.[73]

The deletion of chromosome 16q (del(16q)) is a CNA observed in approximately 19.5% of NDMM patients and its presence is associated with worse OS.[74] Moreover, the adverse impact on survival is further heightened when del(16q) co-occurs with other poor-risk cytogenetic factors such as t(4;14) and del(17p). LOH on 16q has been identified in three regions: the entirety of 16q, a region focused around 16q12 where the CYLD gene resides, and a region centered on 16q23, the location of the WW domain-containing oxidoreductase gene (WWOX). WWOX, a tumor suppressor gene involved in apoptosis, shows significantly reduced expression in cases with 16q LOH or t(14;16) translocations.[74] The importance of WWOX is underscored by its role as the translocation breakpoint in t(14;16) cases, a recognized high-risk feature in MM. The CYLD gene, located at 16q12, is a negative regulator of the NF-kappaB pathway, a critical pathway in MM pathogenesis.[75] Cases exhibiting low CYLD expression have been employed to define a "low-CYLD signature", indicative of a poor prognosis. Both genes, WWOX and CYLD, and their corresponding pathways offer vital insights into how 16q LOH may confer a poor prognosis in MM patients. Disruption of these genes' functions through deletion can trigger uncontrolled cell growth and resistance to apoptosis, thus intensifying the disease's aggressiveness.

For other recurrent CNAs, the prevalence, driver role, and prognostic impact can vary, and in many instances, remain unclear. In our MM-PSN model, the gain of chromosome 15q emerged as a common alteration in HD patients and was significantly enriched in a subgroup of patients with concurrent t(4;14) and gain(1q).[48] Multivariate cox-regression analysis revealed that gain(15q) confers a protective effect, with its presence resulting in significantly longer PFS and OS. However, the specific mechanism resulting from this alteration has not been described yet, and further investigations are needed to decipher its potential protective effect. The MM-PSN analysis also spotlighted a small subgroup of NDMM patients marked by multiple deletions, including del(16p). While no known driver potential has been ascribed to this lesion beyond its recurring nature, this region encompasses TNFRSF17, the gene encoding BCMA, a significant target of immunotherapies like CAR T cells and bispecific antibodies. Patients with del(16p) are at an elevated risk of biallelic loss of BCMA, which has been demonstrated to trigger resistance to anti-BCMA CAR T and bispecific therapies in MM.[76]

Structural Variants

Beyond CNAs, which primarily involve changes in copy numbers, structural variants (SVs) encompass a broader range of chromosomal rearrangements that disrupt gene function and regulatory networks. These SVs introduce additional layers of complexity to the genomic architecture of MM. While our primary focus so far has been on translocations, it's important to understand that SVs encompass a broader spectrum. This includes various genomic alterations, such as deletions, duplications, inversions, and complex rearrangements, each playing a critical role in the pathogenesis and progression of MM.

A recent comprehensive analysis of SVs in a large patient cohort identified 68 SV hotspots involving 17 new candidate driver genes and potential therapeutic targets such as BCMA (TNFRSF17), SLAMF7, and MCL1.[77] Notably, catastrophic complex rearrangements such as chromothripsis were present in 24% of patients and were independently associated with poor clinical outcomes.

Chromothripsis is a catastrophic event leading to the shattering and random reorganization of chromosomes, resulting in copy number abnormalities. This process contributes to genomic instability, thereby accelerating tumorigenesis.[78,79] Chromothripsis can cause hundreds of rearrangements within a few cell divisions, deregulating multiple drivers and generally leading to an extremely poor prognosis in NDMM.[80] This event is associated with high-risk APOBEC (apolipoprotein B editing complex) mutational activity, potentially due to double-stranded breaks, TP53 inactivation, as well as NSD2 and MAF translocations due to structural alterations, telomere dysfunction, and chromosomal instability. Studies have identified 13 recurrent hotspots involving driver genes such as CDKN2C, MYC, FAM46C, and MAP3L14 where chromothripsis can occur. Notably, oscillations in copy number during these events can activate oncogenes (50%) and inactivate tumor suppressor genes (40%), creating a "double hit" scenario that rapidly propels tumorigenesis.[80] Moreover, 47% of chromothripsis events deregulate at least one MM driver gene, and these events are 1.5 times more likely to occur in polyploid tumors than in diploid ones.

Templated insertions, the second most frequent complex event, involve a similar linking of translocations but are associated with gains in copy number. These events were found to be primarily involved in super-enhancer hijacking and activation of oncogenes like CCND1 and MYC. Interestingly, a recent study revealed that a significant proportion (31%) of patients had two or more putative driver events caused by a single structural event, underscoring the complexity of the genomic landscape in MM and its acquisition through key events during tumor evolution.[77]

The study also highlighted chromoplexy, a distinct complex event characterized by interconnected structural variant breakpoints across more than two chromosomes associated with copy number loss. Found in approximately 11% of NDMM cases, chromoplexy impacts tumor biology and evolution by concurrently causing deletion of key tumor suppressor genes on each involved chromosome. Despite its complexity, chromoplexy has been associated with a neutral prognosis.[81]

Role of Somatic SNVs (Single Nucleotide Variations) in Myeloma Pathogenesis

While SVs and CNAs are major forces driving the pathogenesis and progression of MM, Single Nucleotide Variants (SNVs) and Insertions/Deletions (INDELs) also contribute substantially to its genomic complexity. SNVs involve alterations of a single base pair within the DNA sequence, which, when occurring within coding regions, can induce changes in protein structure and function, potentially impacting cellular processes.

SNVs are possibly the most studied aberration in cancer. A comprehensive analysis, encompassing over 3000 tumor samples from twenty-seven cancer types, indicated that MM exhibits an average mutation rate of approximately 1 mutation per megabase (Mb), positioning it in the intermediate range of the mutation frequency spectrum.[82] In our study of 450 NDMM patients, missense mutations were the most prevalent, constituting 17% of the mutations, while nonsense, splice site, and start codon mutations collectively accounted for less than 3% of the 4,013 potentially pathogenic mutations identified across 3,163 genes.[83] The mutational burden varied widely, with an average of 72.77 mutations per patient. Interestingly, patients with a greater number of subclones exhibited a significantly higher mutational burden. NRAS mutations were notably impactful, influencing gene co-expression patterns, and patients with the t(14;16) MAF translocations exhibited a notably higher mutational burden, possibly due to increase APOBEC activity. While higher mutational burden is typically correlated with poor prognosis, some studies suggest that it may improve response to immunotherapy due to presence of higher load of neoantigens.[84]

The Integrative Onco Genomics (IntOGen) browser hosts pan-cancer mutational driver data, including from MM studies.[85] IntOGen is a framework that automatically extracts comprehensive knowledge based on mutational data from sequenced tumor samples to identify cancer genes and determine their putative mechanism of action across tumor types. It predicts driver genes by using seven different methods that assess mutation count bias, mutation clustering, protein structure and domain, and functional impact for cancer driver gene identification, and then combines the output of these methods to produce a compendium of driver genes. IntOGen lists 55 driver genes in MM, including KRAS, NRAS,

TP53, BRAF, and FAM46C. These findings were derived from an analysis of 1,122 mm patients across three cohorts. However, while some of these genes are known bona fide drivers of MM, others have never been experimentally validated, therefore they remain putative drivers.

Several studies have focused on identifying and characterizing recurrent SNVs in tumor suppressors and proto-oncogenes. Significant driver point mutations in key signaling pathways, including MAPK and NF-κB, were identified.[86–88] These studies have mostly relied on computational analyses employing frequency-based and functional methodologies to categorize mutated genes as drivers, many of which are recognized as significant contributors in various cancer types, indicating a shared oncogenic framework across malignancies. Table 2 lists candidate SNV drivers identified in four different studies, along with information on whether they have been experimentally validated.

Below, we present some functionally validated cancer drivers found to be recurrently mutated through SNVs in MM.

BRAF, KRAS, and NRAS are part of the RAS/MAPK pathway, which is critical in regulating cell division, differentiation, and secretion. Mutations in these genes lead to the activation of downstream signaling that promotes myeloma cell proliferation and survival.[114] BRAF mutations, present in about 4–5% of MM cases, often correlate with a more aggressive disease course and poorer prognosis.[93,115,116] The V600E mutation, the most common, has been targeted successfully by specific inhibitors.[117] KRAS and NRAS mutations, occurring in about 20–25% of patients, are typically activating and have been linked to poor responses to standard treatments.[118,119] Although the prevalence of these mutations suggests potential for therapeutic targeting, results obtained in case studies indicate short-lived responses in patients treated with MAPK inhibitors, including MEK and BRAF inhibitors.[120–122]

CYLD is a tumor suppressor gene that functions as a negative regulator of the NF-κB and Wnt/β-catenin signaling signaling pathways, known to play a critical role in MM pathogenesis. Loss of function of CYLD, due to either mutation or deletion, can lead to dysregulated NF-κB and Wnt activity, promoting cell survival and proliferation.[75] Studies have shown that CYLD mutations are associated with advanced stages of MM and may contribute to therapeutic resistance.[75,123]

DIS3 is an RNA exosome component implicated in RNA processing and degradation. Mutations in DIS3 disrupt its normal function, leading to the accumulation of defective RNA molecules. This disruption can contribute to MM by altering gene expression profiles that favor myeloma cell growth.[43,96] Approximately 10% of MM patients harbor DIS3 mutations, which have been associated with a poor prognosis.[124] Understanding the role of DIS3 in RNA metabolism could provide new avenues for targeted therapy.

The FAM46C gene, considered a tumor suppressor, is frequently mutated in MM. Mutations in FAM46C, leading to a loss of function, are associated with shorter survival in patients, suggesting its potential as a prognostic marker.[7,87,125] A recent study has demonstrated that FAM46C forms a complex with the ER-associated protein FNDC3A, which modulates secretion routes and increases lysosome exocytosis, highlighting its role into the cellular remodeling of trafficking machinery in response to ER stress.[126]

TP53 is a key tumor suppressor gene that plays a crucial role in cell cycle regulation, DNA repair, and apoptosis. In MM, TP53 deletions and mutations are relatively rare but are associated with a highly aggressive form of the disease and a poor prognosis.[111,127] The loss of p53 function allows for the uncontrolled proliferation of myeloma cells, making it a critical target for therapeutic intervention.

FGFR3, a member of the fibroblast growth factor receptor family, is involved in cell growth, differentiation, and angiogenesis. In MM, mutations in FGFR3 are associated with its translocation along with NSD2 (t(4;14)).[48] Activating mutations and the overexpression of FGFR3 due to the translocation contribute to MM pathogenesis.[98] Inhibitors of FGFR3 have been explored as potential treatments for patients with this genetic alteration.[128,129]

TRAF3 is an adaptor protein that negatively regulates NF-κB and non-canonical NF-κB signaling. Mutations or deletions of TRAF3 in MM lead to the activation of NF-κB signaling, which is a key driver of cell survival and proliferation.[112] The loss of TRAF3 function is implicated in MM pathogenesis and may serve as a therapeutic target. Studies have shown that targeting NF-κB signaling can be effective, especially when combined with proteasome inhibitors.[130]

Table 2 Candidate and Validated SNVs in Multiple Myeloma

Gene	Walker et al, 2018[87]	Maura et al, 2019[88]	Vo et al, 2022[89]	Ansari-Pour et al, 2023[90]	Validated
ABCF1	✓	✓	–	–	–
ACTG1	✓	✓	✓	✓	–
ADGRL3	–	–	✓	✓	–
ARID1A	✓	✓	✓	✓	–
ARID2	✓	✓	–	–	–
ATM	✓	✓	✓	✓	[91]
ATRX	✓	✓	–	–	–
BCL7A	–	✓	–	–	[92]
BHLHE41	–	✓	–	–	–
BRAF	✓	✓	✓	✓	[93]
BTG1	–	✓	–	–	–
C8ORF34	✓	–	–	–	–
CCND1	✓	✓	✓	✓	[94]
CDKN1B	✓	✓	–	–	–
CDKN2C	✓	✓	–	–	[95]
CREBBP	✓	✓	✓	✓	–
CYLD	✓	✓	✓	✓	[75]
DIS3	✓	✓	✓	✓	[96]
DNMT3A	✓	✓	✓	✓	–
DTX1	–	✓	–	–	–
DUOX2	–	–	✓	✓	–
DUSP2	✓	✓	✓	✓	–
EGR1	✓	✓	–	–	–
EP300	✓	✓	✓	✓	–
EZH2	–	–	✓	✓	[97]
FAM46C	✓	✓	✓	✓	[72]
FGFR3	✓	✓	✓	✓	[98]
FUBP1	✓	✓	–	–	–
HIST1H1B	–	✓	–	–	–
HIST1H1D	–	✓	–	–	–
HIST1H1E	✓	✓	✓	✓	–
HIST1H2BK	–	✓	–	–	–
HUWE1	✓	✓	–	–	[99]
IDH1	✓	✓	–	–	–
IDH2	✓	✓	–	–	[100]
IGLL5	–	✓	–	–	[32]
IRF1	–	✓	–	–	–
IRF4	✓	✓	✓	✓	[101]
KDM3B	–	–	✓	✓	–
KDM5C	✓	✓	–	–	–
KDM6A	✓	✓	–	–	[102]
KLHL6	✓	✓	–	–	–
KMT2B	✓	✓	✓	✓	–
KMT2C	✓	✓	✓	✓	–
KRAS	✓	✓	✓	✓	[103]
LCE1D	–	✓	–	–	–
LILRA6	–	–	✓	✓	–
LTB	✓	✓	–	–	–
MAF	✓	✓	–	–	[17]
MAFB	✓	✓	–	–	[17]

(*Continued*)

Table 2 (Continued).

Gene	Walker et al, 2018[87]	Maura et al, 2019[88]	Vo et al, 2022[89]	Ansari-Pour et al, 2023[90]	Validated
MAML2	✓	✓	–	–	–
MAML3	–	–	✓	✓	–
MAN2C1	✓	✓	–	–	–
MAX	✓	✓	–	–	[104]
MYH3	–	–	✓	✓	–
NBPF15	–	–	✓	–	–
NCOR1	✓	✓	✓	✓	–
NF1	✓	✓	✓	✓	–
NFKB2	✓	✓	✓	✓	[105]
NFKBIA	✓	✓	–	–	–
NRAS	✓	✓	✓	✓	[103]
PABPC1	–	✓	–	–	–
PIGO	–	–	✓	✓	–
PIK3CA	✓	✓	–	–	[106]
PIM1	–	✓	–	–	[107]
POT1	–	✓	–	–	[108]
PRDM1	✓	✓	✓	✓	[109]
PRKD2	✓	✓	✓	✓	–
PTPN11	✓	✓	–	–	–
RASA2	✓	✓	–	–	–
RB1	✓	✓	✓	✓	–
RFTN1	✓	✓	–	–	–
RPL10	–	✓	–	–	[110]
RPL5	–	✓	–	–	[110]
RPRD1B	–	✓	–	–	–
RPS3A	–	✓	–	–	–
SAMHD1	✓	✓	✓	✓	–
SETD2	✓	✓	✓	✓	–
SF3B1	✓	✓	✓	✓	–
SP140	✓	✓	✓	✓	–
TBC1D29	–	✓	–	–	–
TCL1A	–	✓	–	–	–
TET2	✓	✓	–	–	–
TGD	–	–	✓	✓	–
TGDS	✓	✓	–	–	–
TP53	✓	✓	✓	–	[111]
TRAF2	✓	✓	✓	✓	–
TRAF3	✓	✓	✓	✓	[112]
UBR5	✓	✓	✓	✓	–
XBP1	✓	✓	–	–	[113]
ZFP36L1	✓	✓	–	–	–
ZNF292	✓	✓	✓	✓	–

Notes: This table lists genes with identified SNVs in MM across four studies. Each column represents a distinct study, with a checkmark indicating the presence of SNVs in the specified gene within that study, where the gene was considered a potential driver. The final column indicates whether the gene has been experimentally validated as a driver in MM, based on current evidence, in which case the reference is provided.

Mutational Signatures

Mutational signatures are distinctive patterns of DNA mutations that arise from specific mutagenic processes or DNA repair defects. Each signature reflects the unique activities of mutagenic agents or endogenous enzymatic processes involved in genomic alterations.[131] The analysis of these mutational patterns can provide insights into the underlying

mechanisms of mutagenesis contributing to cancer development. In MM, different mutational signatures have been identified, carrying prognostic value and revealing the contribution of various mutagenic processes.[88]

The APOBEC enzymes, a family of cytidine deaminases, contribute significantly to the mutational burden in MM. APOBEC signatures are particularly enriched in cases with MAF translocations, such as t(14;16) and t(14;20).[48,132] They are also more prevalent in MM cases with MYC rearrangements.[132] The presence of APOBEC signatures is associated with a higher overall mutation load, genomic instability, and poor clinical outcomes. MYC translocations contribute to kataegis, a phenomenon characterized by clusters of localized hypermutations, further compounding genomic instability.

Aging-related mutational signatures, caused by the spontaneous deamination of 5-methylcytosine and other age-associated DNA alterations, are more commonly observed in hyperdiploid MM.[48]

A mutational signature attributable to defective DNA mismatch repair (MMR) is more prevalent in patients with the CCND1 translocation and gain of chromosome 11, but is underrepresented in patients with the MAF translocation.[48] A signature associated with replication by polymerase eta is enriched in patients with the NSD2 translocation, while a signature related to polymerase epsilon exonuclease (POLE-Exo) domain mutations is enriched in patients with either the MAF or the NSD2 translocation associated with gain(1q).[48]

A recent study identified a new mutational signature, MM1, through non-negative matrix factorization. The study found no evidence of BRCA1/BRCA2-mediated homologous recombination deficiency (HD), challenging previous assumptions that a signature associated with BRCA1 and BRCA2 bi-allelic loss and HD in solid cancers was active in MM.[133,134] False positives, such as the tobacco-smoking or the UV light signatures, were ruled out using rigorous validation strategies.

Cytotoxic agents introduce hundreds of unique mutations in surviving cancer cells. Chemotherapy-related signatures are only detectable if a single cancer cell undergoes clonal expansion post-therapy. Another study identified mutational signatures associated with specific chemotherapeutic agents, such as one linked to platinum-based chemotherapy, and a newly characterized SBS-MM1 signature.[135] Chemotherapy-related signatures are responsible for approximately 25.7% of all nonsynonymous mutations at clinical relapse, particularly after high-dose melphalan therapy and autologous stem cell transplant.

These studies underscore the complexity of mutagenesis in MM, revealing the interplay between various mutational processes. In particular, APOBEC-related mutational signatures suggest a DNA repair deficiency even in other translocation groups like t(11;14) and t(4;14), highlighting a broader impact on MM pathogenesis. Conversely, chemotherapy-related signatures emphasize the significant influence of treatment on the mutational landscape of relapsed MM.

Gene Fusions in MM

Most studies in MM have focused on recurrent translocations involving the IgH locus and, to a lesser extent, the IgK and IgL loci. However, recent studies have broadened the scope to investigate the global landscape of gene fusions in MM beyond Ig translocations. One notable study revealed that MM patients exhibit an average of 5.5 expressed fusion genes, highlighting a significant presence of these genetic anomalies in the disease.[136] A considerable portion of these fusion genes involve kappa and lambda light chains along with IgH genes, with kappa light chains participating in more fusions than IgH. This finding suggests that Ig fusions are influenced by the underlying biology of plasma cells and the disease process, reflecting the physiological preference for kappa light chain rearrangement during B-cell maturation. The study also identified novel fusion partners of Ig genes, including B2M, TXNDC5, FOSB, JUND, and JUN.

Patients with high hyperdiploidy, characterized by a significant increase in chromosome number, showed a distinct fusion profile involving genes like UBC and CCNG2, with many intra-chromosomal fusions and an average of four per patient. Chromosome 19, particularly TPM4, was frequently identified as a common fusion partner.

Another recent study reported fusions between Ig loci and MYC or its downstream neighbor PVT1, with MYC or PVT1 usually being the 5′ partner.[137] These fusions have clinical implications; patients with PVT1-IGL fusions experienced worse survival, while those with MYC-IGL fusions showed better outcomes. Additionally, 51 fusions were significantly associated with overexpression of the partner genes, including nine cancer-related genes annotated as a driver, drug target, kinase, oncogene, or tumor suppressor, such as FGFR3, MAPKAPK2, MYC, NTRK1, PAX5, PIM3, RARA, TXNIP, and NSD2.

In the MM-PSN model, TPM4-SIK1 fusions were significantly enriched in hyperdiploid patients, particularly those without trisomies of chromosome 7.[48] Different fusions were also enriched in patients with the t(11;14) translocation of CCND1, including CCND1-KLF2, FOSB-KLF6, and C21orf91-CHODL. Additionally, a significant prevalence of IGK-ITGB7 fusions was identified in patients with the t(14;16) translocation of MAF, concurrent with ITGB7 overexpression. This aligns with prior research indicating that integrin-β7 plays a critical role in MM by promoting cell adhesion, migration, and bone marrow homing, which are crucial for tumor progression and potentially influence therapeutic responses.[138] Recent findings also highlight the significant upregulation of ITGB7 in the t(14;16) and t(14;20) subgroups across all stages of MGUS, SMM, and MM, emphasizing its potential role in disease progression.[139] In one study, patients with highy expressed ITGB7 also exhibited poor response with combination therapy.[138] Furthermore, ITGB7 expression is intricately regulated by a predetermined enhancer state in primary B-cells, transitioning to an active enhancer in the t(4;14) subgroup or a super-enhancer in the t(14;16) subgroup, indicative of complex regulation by chromatin-state alterations and DNA-methylation dynamics.[139]

Double and Triple Hits in MM Progression

MM progression is influenced not only by individual genetic abnormalities but also by their interactions and dependencies. Double and triple hits—co-occurrences of two or three cytogenetic abnormalities—are significantly associated with disease progression and survival outcomes.[140,141] In NDMM, approximately 20% of patients exhibit such multi-hit scenarios, dramatically impacting prognostic expectations.[140,142] For instance, patients with single genetic abnormalities have a predicted overall survival (OS) of about 32 months, while those with double hits face a drastically reduced OS of only 6 months.

Specific combinations of cytogenetic abnormalities are recurrently observed. Common oncogenic pairs include t(11;14) and CCND1 mutations, gain(1q) with t(4;14), co-occurrence of t(4;14) with TRAF3 deletions, and of FAM46C and CDKN2C deletions.[11] Biallelic deletions of tumor suppressors combined with chr(1q) amplifications have been shown to deregulate cell cycle and proliferation pathways.[143] Additionally, monoallelic del(17p)/TP53, an important prognostic marker, appears in 10% of NDMM cases but is more frequent in relapsed/refractory MM (RRMM), affecting 23–45% of cases, pointing towards increasing genomic instability with disease progression.[66,144]

The Role of Germline Mutations in MM Risk, Pathogenesis and Progression

It has long been suggested that MM might have an inherited genetic component, with several families showing multiple cases of MGUS and MM, indicating possible autosomal dominant Mendelian transmission. Systematic epidemiological family studies, particularly in Sweden, have confirmed that first-degree relatives of patients with MM have a 2–4 times higher risk of developing MM and MGUS.[145–147] These relatives also show an increased risk of other lymphoid malignancies and certain solid tumors.[148,149]

Genome-wide association studies (GWAS) have played a pivotal role in identifying genetic risk factors for MM, pinpointing several independent loci associated with the disease.[150,151] Among these, several loci and corresponding genes stand out due to their biological relevance and potential impact on MM development. For instance, the risk allele at 3p22.1 spans ULK4, a gene encoding a serine/threonine-protein kinase involved in autophagy regulation, which is crucial for cellular homeostasis and has been implicated in cancer.[152] Another significant locus is 7p15.3, which includes CDCA7L and DNAH11, with CDCA7L being implicated in cell division and potentially in MYC-mediated transformation events, a known pathway in MM pathogenesis.[152] Additionally, the locus at 2p23.3 involves DNMT3A, a gene that plays a role in DNA methylation, a key epigenetic modification affecting gene expression.[153] These loci, among others identified through GWAS, highlight the genetic complexity of MM and underscore the importance of specific biological pathways in its etiology.

Sequencing studies of familial cases have identified a small number of rare, high-penetrance germline variants in candidate susceptibility genes, including CDKN2A, KDM1A, USP45, ARID1A, DIS3, and EP300.[151] Notably, variants in the KDM1A gene, leading to a frameshift mutation, have been confirmed to confer susceptibility to MM, highlighting the role of histone modification in MM pathogenesis.[154] Similarly, a germline splice donor site variant and a germline stop-loss variant within the DIS3 gene have been associated with familial MM, underscoring the importance of RNA

processing in the disease and suggesting DIS3 as an "intermediate-risk" MM susceptibility gene.[155] The CDKN2A gene, known for its tumor suppressor function, has also been implicated in MM through a duplication variant, suggesting a cross-cancer predisposition mechanism.[156]

A study reported differences in mutation frequency between African American (AA) and Caucasian American (CA) MM patients, highlighting IRF4 as of special interest because it is recurrently mutated in CA patients but not in AA patients.[157] This mutation is linked to the germline risk in the CDCA7L locus. IRF4 is identified as a MM driver in tumors with the IRF4-activating chromosomal translocation t(6;14) and is inversely correlated with clinical outcomes.[158]

Another study identified over a hundred missense variants in germline predisposition genes in familial MM through whole genome and exome sequencing of 21 families with a history of MM or its precursors.[159] The study highlighted genes with tumor suppressor and oncogene functions, such as DAB2IP and ABL2, respectively, and identified strong candidate genes including DAB2IP, ABL2, SAMHD1, KMT2A, USP28, FOXO1, B4GALT1, NKX3-2, and several immune-related genes.

In a recent study, we have investigated the presence of pathogenic germline variants (PGV) in NDMM patients.[160] We found that 8.8% of patients had PGV, particularly those with a family history of hematologic malignancy. Most PGVs involved DNA damage repair (DDR) genes (78%), with homologous recombination (HR) genes being the most commonly mutated (34%). CHEK2 variants emerged as leading drivers of this correlation. The likelihood of being diagnosed with MM before age 40 was significantly higher in PGV carriers. PGVs in CHEK2 were the most common, and two patients carried PGVs in TP53, six patients had germline mismatch repair (MMR) gene defects, and four patients carried PGVs in BRCA2. Our analysis also identified a potential advantage in PFS for carriers of PGV in DNA damage repair genes, suggesting that these may confer sensitivity to MM therapies.

RNA Editing as a Driver of High-Risk MM

As discussed above, the gain of 1q21 is one of the most extensively studied chromosomal abnormalities in MM, chiefly due to its association with poor prognosis. This region of the genome houses ADAR1 (Adenosine Deaminase Acting on RNA 1) among other genes. Additional copies of this chromosomal segment lead to overexpression of ADAR1 and, consequently, elevated and aberrant RNA editing activity.[62,161] ADAR1-dependent RNA editing involves epi-transcriptomic changes, specifically Adenosine-to-Inosine (A-To-I) deamination within double-stranded RNA (dsRNA), where Inosine is interpreted as Guanosine (G) on the mRNA.[162] While thousands of ADAR1-dependent RNA editing events occur in myeloma cells, and RNA editing overall has been suggested as a prognostic factor, only a few have been specifically identified as significantly impacting MM pathogenicity to date. Notable examples include an Alu-dependent editing event of the zinc finger glioma-associated oncogene GLI1 that enhances malignant regeneration through Hedgehog pathway signaling, and a recoding editing event of the DNA repair protein NEIL1 that results in loss-of-function.[62,161]

Although more specific events contributing to MM pathogenicity through key molecular pathways remain to be fully described, global aberrant ADAR1-dependent editing has been identified as a crucial factor in resistance to MM therapies, such as Bortezomib and Lenalidomide.[62,161] Additionally, recent findings suggest that IL6R (interleukin-6 membrane receptor) and ADAR1 may hyperactivate the oncogenic STAT3 pathway, potentially influencing the tumor microenvironment.[163] While this role is yet to be validated, it aligns with the function of ADAR1 as an interferon-inducible gene, specifically the ADAR1-p150 isoform, which is of interest in MM. Notably, patients with wild-type 1q21 can overexpress ADAR1 at levels comparable to those with 1q21 gain, leading to aberrant editing.[164]

The Tumor Microenvironment as a Driver of MM Progression and Immune Evasion

While much attention has been given to the genetic drivers of MM and their therapeutic targeting, it is equally crucial to consider the role of the bone marrow tumor microenvironment (TME). The TME represents a complex and dynamic ecosystem that surrounds myeloma cells and is influenced significantly by their genomic landscape. Comprising stromal cells, immune components, extracellular matrix, and blood vessels, the TME provides a supportive niche that is crucial

for the survival and proliferation of tumor cells.[165,166] Notably, stromal and immune cells within the TME secrete cytokines and growth factors that induce genomic instability in MM cells, leading to the emergence of drug-resistant subclones.[167–169] This bidirectional interaction underscores the complexity of MM pathogenesis, where genomic alterations and the TME mutually reinforce each other. Studies have shown that the progression from early disease stages like MGUS and SMM to MM is influenced by the TME, highlighting alterations such as a decline in cytotoxic memory T cells and an increase in immune-suppressive cell populations, including regulatory T cells and myeloid-derived suppressor cells.[170] Understanding these intricacies is essential for developing targeted therapies that effectively disrupt the complex interactions between the TME and MM cells to improve treatment outcomes.

Among the critical aspects of this interplay is angiogenesis, which is is essential for MM as it enhances tumor growth by improving nutrient and oxygen availability. Key growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF), play significant roles in this process. Levels of these factors are notably higher in the bone marrow than in peripheral blood. VEGF, secreted by MM cells, stimulates both MM cell proliferation and IL-6 expression in endothelial and stromal cells, supporting autocrine and paracrine functions (Iwasaki & Sano, 2003). Additionally, heparin-binding EGF-like growth factor (HB-EGF) contributes to this process through its interaction with the epidermal growth factor receptor (EGFR) (Rao et al, 2020). Elevated levels of EGFR and HB-EGF in bone marrow endothelial cells, particularly in advanced stages like MM compared to precursor conditions like MGUS, promote endothelial cell proliferation and angiogenesis via an autocrine loop. Given its role in promoting angiogenesis and tumor growth, the HB-EGF–EGFR signaling pathway presents a viable target for anti-angiogenic therapy in MM.

Like normal cells, myeloma cells migrate into the bone marrow through sinusoids, primarily adhering to the bone marrow stroma through the chemokine CXCL12 and its receptor CXCR4. This interaction induces α4β1 integrin activity, enhancing the adhesion of cancerous cells to bone marrow components.[171,172] Other adhesion molecules, such as PSGL-1 and CD44, also aid in this process. Once settled, the MM cells alter the surrounding environment to their advantage, notably by activating more osteoclasts (which break down bone) than osteoblasts (which help in bone formation). This imbalance leads to the formation of bone lesions, a hallmark symptom of MM. Additionally, mutations in stromal cells can create a milieu that supports malignant growth and progression.

Several genetic alterations in the tumor, such as del(17p), t(4;14), p53 deletion, loss of CD56 expression, MAFB overexpression, and MYC overexpression, can potentially contribute to tumoral subclone selection and expansion. This may lead to immune escape mechanisms through immunoediting, loss of antigenicity, and inhibition of immune checkpoints, which are further compounded by a pro-inflammatory function of tumoral cells.[173,174] This results in the expansion of immunosuppressive cell types in the TME, such as Foxp3-positive Tregs, pathogenic IL-17 producing Th17 cells, and myeloid-derived suppressor cells.[175] These cell populations mediate suppression of cytotoxic T lymphocytes, impairing anti-tumoral activity by cell-mediated immune mechanisms. Additionally, individual variability of immune response, such as the presence of HLA polymorphisms associated with an increased risk of MM, can lead to disease progression and the development of extramedullary disease (EMD).[176]

Epigenetic Aberrations as Drivers of MM

Epigenetic modifications are reversible changes that do not alter the DNA sequence. Major epigenetic events in MM include DNA methylation, histone modifications, and chromatin remodeling.

DNA methylation is the most studied epigenetic change and involves the addition of a methyl group to DNA. As MM progresses, methylation patterns change, with cancer cells exhibiting global DNA hypomethylation and hypermethylation at transcription start sites, which are typically unmethylated.[177–180] This contributes to genomic instability, disrupts gene expression, and silences cancer-related genes. DNA methylation modifiers include DNA methyltransferases (DNMTs) and tet methylcytosine dioxygenases (TETs).[181] Genes such as p73, p53, p15, p16, E-CAD, SOCS1, DAPK1, BNIP3, RB1, DIS3, CDKN2A, and CDKN2C have been observed to be hypermethylated and silenced in MM. For instance, SOCS1 (Suppressor of Cytokine Signaling 1) acts as a negative regulator of the JAK/STAT pathway, a critical signaling pathway in MM cell survival and proliferation.[182] The hypermethylation and subsequent silencing of SOCS1 can lead to the unchecked activation of the JAK/STAT pathway, promoting MM cell growth and survival. Similarly, DAPK (Death-

Associated Protein Kinase) is involved in apoptosis, and its silencing through hypermethylation can hinder programmed cell death, further contributing to MM progression.[183]

Promoter hypermethylation of specific genes like p16, BNIP3, E-CAD, and DAPK1 has been associated with poor prognosis.[184] In MM patients, hypermethylation is not only restricted to promoter-associated CpG islands but also extends to intronic enhancer regions of B cell-specific genes and transcription factors. This leads to the downregulation of B cell-associated transcription factors such as PAX5, BATF, and STAT5.

Global hypomethylation is linked to chromosomal instability.[185] Specific studies found lower methylation levels of repetitive elements like LINE1 and SAT alpha in non-hyperdiploid compared to hyperdiploid groups.[186] Furthermore, lower levels of methylated Alu and SAT alpha were observed in t(4;14) group, which is associated with a worse prognosis. This pattern of hypomethylation increases heterogeneity in DNA methylation profiles, contributing to the disease's progression and the poor prognosis associated with certain cytogenetic subtypes.[186] The aberrant methylation patterns observed in MM could be in part due to the downregulation of miR-29b, which targets DNMT3A and DNMT3B, resulting in an aberrant methylation profile.[187,188]

Histone modifications, including acetylation and methylation, affect the chromatin's structure and function, thereby influencing gene expression.[187] Histone modifiers can include both histone and non-histone proteins. For instance, NSD2, which is also altered by translocations, catalyzes the dimethylation of H3K36, resulting in active chromatin and conferring chemotherapy resistance.[189,190] Elevated trimethylation of H3K27, when EZH2 is overexpressed, is predominant in advanced stages.[191] EZH2 modifies histones by being recruited to target genes, forming PRC2 complex and catalyzing methylation activity. EZH2 inhibitor drugs can reduce chemotherapy toxicity. Significant histone modifiers in MM include KDMB6, which modulates the MAPK pathway, KDM3A, which catalyzes the removal of methylation in H3K9 affecting heterochromatin architecture, and histone deacetylases (HDAC1/3) that cause bortezomib resistance. IRT6, another HDAC, shows tumor suppressor activity in MM.[192]

Chromatin remodeling refers to the dynamic modifications that affect chromatin structure, thereby influencing gene expression. Aberrations in chromatin structure modifications can influence DNA methylation patterns and contribute to the epigenetic landscape characteristic of MM.[187] Chromatin remodeling is significantly influenced by mutations in MM. For instance, mutations in the noncoding and coding regions of the myeloma genome, including those in BCL7A and ARID family genes, may impact chromatin remodeling as part of the SWI/SNF chromatin remodeling complex, also known as BAF (BRG1/BRM-associated factor) or PBAF (polybromo-associated BAF).[193] When functioning normally, the complex can suppress tumor growth by regulating genes that control the cell cycle and by maintaining a differentiated state of cells. However, mutations or alterations in the expression of BCL7A and other components of the SWI/SNF complex can disrupt this regulatory mechanism, leading to aberrant cell proliferation and contributing to oncogenesis. BCL7A is considered a tumor suppressor gene and its loss and mutation have been specifically linked to the enhancement of the oncogenic activity of IRF4, a transcription factor implicated in the progression of various B-cell malignancies, including MM.[92] Dysregulation of ARID2, another component of the chromatin remodeling complex PBAF, may additionally lead to drug resistance to lenalidomide and impact MYC transcriptional regulation.[194] The MM TME, particularly the bone marrow niche, can also affect MM through chromatin modifications that subtly influence the genomic architecture and disease progression. Factors such as IL6S, CD200, KIT, ITGA4, and CXCR4, along with pathways like NF-kB, p53 signaling, mTOR signaling, cancer stem cell pathway, and NOTCH pathway, maintain crosstalk within the MM microenvironment, activating the chromatin regulatory network in MM.[92]

The Role of Non-Coding RNAs in MM

In addition to epigenetic modifications, which regulate gene expression through changes in chromatin state, non-coding RNAs (ncRNAs) represent another layer of gene regulation in MM. These are a diverse group of RNA molecules that do not code for proteins but play a significant regulatory role in gene expression.[195,196] They are increasingly recognized for their involvement in genomic instability and the acquisition of malignant traits that underlie disease progression. In MM, ncRNAs have emerged as significant contributors to the pathogenesis and progression of the disease.[197]

MicroRNAs

MicroRNAs (miRNA) are short ncRNAs molecules crucial in the regulation of gene expression at the post-transcriptional level. These small RNA sequences, typically 19–22 nucleotides in length, are involved in various biological processes, including cell differentiation, proliferation, apoptosis, autophagy, and stem cell maintenance.[198] A single miRNA can target hundreds of mRNAs and modulate their expression, leading to the complex regulation of multiple pathways implicated in the pathogenesis of various diseases, including MM.[199] One of the well-established dysregulated miRNAs in MM is miR-29b, a known tumor suppressor that may inhibit the formation of mature human osteoclasts, thereby playing a role in MM progression.[200] MiR-29b was also found to be downregulated in tumor-associated dendritic cells (DCs) when compared to normal mature DCs.[201] The enforced expression of miR-29b in DCs co-cultured with MM cells was found to counteract pro-inflammatory pathways, including the signal transducer and activator of transcription 3 (STAT3) and nuclear factor-kappa B (NF-κB), as well as cytokine/chemokine signaling networks. Additionally, miR-29b downregulated interleukin-23 (IL-23) both in vitro and in vivo, leading to the antagonization of a Th17 inflammatory response. In another study, miR-137 and miR-197 have been identified as potential tumor suppressors in MM.[202] They mediate apoptosis in myeloma cells by targeting MCL-1, an anti-apoptotic protein. The reduced expression of miR-137 and miR-197 in MM cell lines and patient samples compared to normal plasma cells suggests their importance in regulating cell viability, apoptosis, colony formation, and migration in MM. miR-22-3p targets DNA ligase 3 (LIG3), whose hyperactivation is crucial for the survival of MM cells.[203] Furthermore, MYC represses transcription of miR-22, which, in turn, targets MYC, establishing a feed-forward loop that can trigger MYC-dependent synthetic lethality. Similarly, miR-15a and miR-16, located on chromosome 13 and often deleted or downregulated in MM, are known to target BCL2, a key anti-apoptotic protein. Their restoration can induce apoptosis in MM cells.[45] The miR-17-92 cluster has been found to be overexpressed in MM. It has oncogenic properties and promotes cell proliferation by targeting pro-apoptotic proteins and regulators of cell cycle checkpoints.[204] Furthermore, certain miRNAs are associated with drug resistance in MM. For instance, downregulation of miR-520g and miR-520h has been observed in bortezomib-resistant MM cell lines. These miRNAs were shown to affect DNA repair and bortezomib resistance through targeting APE1.[205]

Long Non-Coding RNAs

Long non-coding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides that are poorly conserved among species and exhibit high tissue and cell specificity. They are implicated in regulating gene expression at multiple levels, including transcriptional, post-transcriptional, and epigenetic modifications.[199] LncRNAs play roles in cell development, proliferation, differentiation, and apoptosis and can act as oncogenes or tumor suppressors in cancer pathogenesis.[206]

In MM, lncRNAs contribute to disease by regulating cellular processes and signaling pathways commonly deregulated in cancer.[207] They can bind to miRNAs, competing with other RNAs to regulate mRNA expression. A study on RNA-seq data from MM patients identified over 800 differentially expressed lincRNAs in MM compared to normal plasma cells.[208] Fourteen lincRNAs were associated with PFS, and the researchers developed a risk score to categorize patients into high- or low-risk groups, revealing significant differences in median PFS and OS. The lincRNA signature could further stratify patients within established risk categories, suggesting that lincRNAs have an independent effect on MM outcomes.

Several studies have focused on specific lncRNAs in MM, including MALAT1, MEG3, DLEU2, PCAT1, PVT1, UCA1, and the host gene of miR-17.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a lncRNA implicated in gene expression regulation, alternative splicing, and cell cycle control.[209] It is overexpressed in newly diagnosed MM (NDMM) patients and is associated with disease progression and drug resistance.[210] MALAT1 knockdown induces apoptosis in MM cells through the endogenous apoptotic pathway by downregulating BCL2 and upregulating BAX. It also increases HMGB1 expression, mediating autophagy and promoting tumor cell survival. MALAT1 expression levels correlate with HSP90 mRNA levels, which are associated with bortezomib resistance, making MALAT1 a potential predictor of PFS in MM patients.

Maternally expressed gene 3 (MEG3) is a tumor suppressor lncRNA located on chromosome 14q32. In MM, MEG3 expression is often lost due to promoter hypermethylation, particularly in advanced-stage disease.[211,212] MEG3 activates p53 by downregulating MDM2 and promotes osteogenic differentiation of mesenchymal stem cells (MSCs) by targeting BMP4 transcription.[213] It also suppresses angiogenesis by regulating miR-9.[214]

Deleted in leukemia 2 (DLEU2), located at chromosome 13q14.3, hosts miR-15a and miR-16-1. It is frequently deleted in lymphoid malignancies, including MM, and is downregulated in patients with del13.[215] DLEU2 acts as a tumor suppressor by negatively regulating G1 cyclins through miR-15a/miR-16-1, inhibiting cell cycle progression.[216] Its loss contributes to tumor emergence by affecting multiple cyclin proteins.

Prostate cancer-associated transcript 1 (PCAT1), a lncRNA on chromosome 8q24, was initially identified as a prostate-specific regulator of cell proliferation.[217] In MM, PCAT1 levels are significantly higher in patients compared to healthy controls, suggesting its potential as a predictive biomarker.[218] Although the molecular mechanisms of PCAT1 in MM remain unclear, its silencing could inhibit the Wnt/β-catenin pathway, known to promote cancer progression.[219]

Plasmacytoma variant translocation 1 (PVT1), consisting of nine exons and located on chromosome 8q24, is co-implicated with c-Myc in various tumors.[220] PVT1 and c-Myc expression levels are correlated in MM, suggesting a regulatory relationship that impacts cell transformation and tumor progression.[221] PVT1 overexpression is linked to apoptosis suppression, contributing to tumor growth and survival.[222]

Urothelial carcinoma-associated 1 (UCA1), encoded on chromosome 19, was initially identified in bladder carcinoma.[223] It regulates cell proliferation, migration, and invasion while inhibiting apoptosis in bladder cancer cells by modulating CREB expression. In MM, UCA1 expression is downregulated in patients compared to healthy donors, with higher UCA1 levels correlating with advanced disease stages and specific genetic abnormalities.[224]

The miR-17-92 cluster host gene, MIR17HG, hosts the lncRNA lnc-17-92, which functions independently of miRNAs processing pathways.[225] It provides a chromatin scaffold that facilitates the interaction between c-Myc and WDR82, promoting the expression of ACACA, encoding acetyl-CoA carboxylase 1 in de novo lipogenesis, and myeloma growth. Targeting MIR17HG pre-RNA with antisense molecules disrupts lnc-17-92's transcriptional and functional activities, leading to potent antitumor effects both in vitro and in vivo.[226]

Circular RNA

Circular RNAs (CircRNAs) are covalently closed RNAs without 5′ and 3′ ends or poly-A tails. They are involved in various physiological and pathological processes, including cancer.[227,228] CircRNAs are characterized by tissue-specific expression, stability, abundance, and conservation, making them suitable markers for disease diagnosis and prognosis.[229]

A recent study showed that a specific circRNA signature could distinguish MM patients from healthy controls and that hundreds of dysregulated circRNAs were associated with altered signaling pathways like VEGF and MAPK.[230] Certain circRNAs, such as circ-PTK2 and circ-RNF217, are linked to poor therapeutic responses, while circ-AFF2 correlates with positive treatment outcomes. These circRNAs may affect cell sensitivity to chemotherapy and influence chemoresistance by interacting with miRNAs.[231] Circ-PTK2 enhances MM cell vitality and diffusion, inhibits programmed cell death, and influences MM cell activity by stimulating signaling pathways like MEK, ERK, and WNT/β-catenin.[232] Circ-MYBL2, originating from MYBL2, is significantly reduced in MM bone marrow and serum compared to healthy controls and correlates with advanced clinical stages and poor prognosis.[233] It suppresses MM by modifying the phosphorylation of its linear isoform, reducing the transcription of growth-related oncogenes.

CircRNAs are often highly enriched with miRNA binding sites, making them effective miRNA sponges.[234] This phenomenon refers to the capability of circRNAs to bind and sequester miRNAs, preventing them from binding to their target mRNAs. This mechanism regulates gene expression by reducing the inhibitory effect of miRNAs on their target genes. In MM, circRNAs can modulate tumor progression by sponging miRNAs and altering the expression of transcription factors crucial for tumor development. For instance, circ-CDYL is increased in MM tissue and plasma, offering diagnostic and prognostic value. It promotes MM progression by sponging miR-1180 to increase yes-associated protein (YAP), which is often activated in cancers, including MM.[235] Similarly, circ-ATP10A operates as a miRNA sponge, controlling the concentrations of several growth factors by targeting miRNA-6758-3p, miRNA-3977, miRNA-6804-3p, miRNA-1266-3p, and miRNA-3620-3p.[236]

Certain circRNAs can also induce chemoresistance to conventional drugs used in treating hematopoietic cancers. For instance, upregulation of circ-CCT3 (circular RNA chaperonin containing TCP1 subunit 3) corresponds to miRNA-223-3p reduction in bortezomib-resistant MM subjects and cells.[237] The silencing of circ-CCT3 enhances the sensitivity of cells to bortezomib by de-repressing the expression of miRNA-223-3p, which fosters bortezomib sensitivity by suppressing BRD4. Another example is circ_0007841, which enhances doxorubicin resistance in MM cells by increasing ATP-binding cassette transporter G2 (ABCG2) expression.[238] Its expression is higher in doxorubicin-resistant cells compared to parent cells, and silencing circ_0007841 in resistant cells decreases drug resistance.

Additionally, circRNA expression correlates with certain MM complications, such as peripheral neuropathy (PN). Increased levels of circRNA chr2:2744228–2744407+ in the serum exosomes of MM subjects might lead to a decrease in miRNA-6829-3p, an increase in GRIN2B in the serum, and suppressed cell survival.[239] Furthermore, the level of chr2:2744228–2744407+ was positively associated with the occurrence and clinical findings of PN, suggesting that exo-circRNA might represent a possible new therapeutic target for MM-related PN.

Drivers of Relapsed/Refractory MM

Relapsed/refractory multiple myeloma (RRMM) represents a significant clinical challenge, characterized by its high genetic complexity and resistance to standard therapies.[89] Evidence suggests that the genomic landscape of RRMM may be distinct from NDMM, involving specific genetic drivers, mutational signatures, and CNAs that provide insights into disease progression and therapeutic resistance.

A large-scale whole-genome sequencing (WGS) analysis comparing RRMM with NDMM patients identified several key drivers and genomic events enriched at the RRMM stage.[90] Genetic drivers, such as DUOX2, EZH2, and TP53, were significantly enriched in RRMM patients. Notably, biallelic inactivation events involving TP53, along with noncoding mutations in bona fide drivers like TP53BP1 and BLM, were identified. CNAs such as gain(1q) and 17p LOH were more prevalent in RRMM. The study also highlighted double-hit events, such as amp(1q)-ISS3 and gain(1q)-17pLOH, which are significant at the RRMM stage. A defective mismatch repair signature, indicative of therapy-associated expanding subclones, was enriched in RRMM, especially in tumors with a high mutation burden. Moreover, certain genomic aberrations, including TP53, DUOX2, gain(1q), and 17pLOH, increased in prevalence from NDMM to lenalidomide-resistant (LENR) and pomalidomide-resistant (POMR) stages. Additionally, MAML3 enrichment, along with IgL and MYC translocations, distinguished POMR from LENR stages. These genomic drivers in RRMM confer a clonal selective advantage under therapeutic pressure, suggesting their role in therapy evasion. The study also identified novel candidate mutational drivers such as MAML3, TDG, PIGO, and NBPF15. MAML3, TDG, and PIGO showed strong tumor suppressor signals, while NBPF15 exhibited a strong oncogene signal. Network and pathway enrichment analyses suggested that these drivers interact with established MM drivers like RB1, CCND1, and CREBBP, implicating their role in cell cycle regulation, notch signaling, and B-cell receptor signaling.

In a separate study focusing on double-refractory MM (resistant to both PIs and IMiDs), high subclonal heterogeneity and a distinct mutational spectrum were observed.[240] This indicated that the disease evolves genetically during treatment, resulting in a unique combination of mutations, aneuploidies, and mutational signatures. The study emphasized that resistance to chemotherapy in MM may be driven more by complex genomic architecture than by specific mutations or drug-target gene expression. TP53 pathway inactivation was frequent (in 45% of patients), while mutations linked to resistance to IMiDs were rare and subclonal. The RNA sequencing analysis further showed that treatment or mutations did not influence clustering; instead, clustering was affected by karyotypic events, particularly amp(1q) and del(13).

A recent integrative analysis incorporating regulatory networks and gene expression profiles from RRMM patients, leveraging single-cell RNA data, highlighted the clonal evolution of myeloma cells and their interaction with the bone marrow microenvironment in the context of treatment resistance.[241] The study revealed that subclones with a gain(1q) exhibit a specific transcriptomic signature and are prone to expansion during treatment, linking this genetic aberration to treatment resistance. Additionally, RRMM cells were found to contribute to an immunosuppressive bone marrow TME through the upregulation of inflammatory cytokines and interactions with the myeloid compartment. This leads to an accumulation of PD1+ γδ T-cells and tumor-associated macrophages, alongside the depletion of hematopoietic progenitors.

A multi-omics study integrating whole-genome sequencing, single-cell transcriptomics, chromatin accessibility sequencing, and mitochondrial DNA mutations characterized resistance mechanisms at the subclonal level.[242] The high-resolution map of dynamic subclonal architecture revealed that relapse can occur through various resistance mechanisms, including the expansion of subclones with preexisting epigenetic profiles associated with resistance, adaptation of gene expression programs, and changes in interactions between myeloma cells and the bone marrow TME. The study identified a subclone-specific upregulation of heat shock proteins (HSPs) and activation of the NF-κB pathway, linked to resistance to proteasome inhibitors and MEK/BRAF inhibition.

Overall, these findings underscore the complexity of RRMM and highlight the need for a deeper understanding of the disease's evolution and resistance mechanisms to develop more effective treatments. A longitudinal assessment of genomic drivers and the TME will be crucial in identifying actionable targets and improving patient outcomes in this aggressive form of MM.

Oncogenic Dependencies and Systems Biology Approaches

Recent studies provide deeper insights into the genetic landscape and dependencies that characterize MM, revealing that the disease's progression is often dictated by a complex interplay of cytogenetic and molecular abnormalities. One of the major challenges, indeed, lies in this genomic complexity, where multiple driver events often cooperate to drive disease progression. Specific associations between mutations in driver genes and primary cytogenetic abnormalities have shown that primary cytogenetic events predetermine the genomic landscape upon which further mutations build. This leads to a non-random accumulation of genetic hits and influences the disease's evolutionary trajectory. For example, the t(4;14) translocation is frequently associated with mutations in FGFR3, DIS3, and PRKD2. Similarly, t(11;14) commonly co-occurs with mutations in CCND1 and IRF4, t(14;16) is linked to mutations in MAF, BRAF, DIS3, and ATM, and hyperdiploidy is correlated with gains of 11q, mutations in FAM46C, and MYC rearrangements.[87] Cooperative effects between these drivers can result in synthetic lethal interactions, increased genomic instability, and clonal selection. In some cases, drivers are not necessarily mutations or genetic events but rather dysregulated or aberrantly expressed genes as a consequence of complex genetic and epigenetic networks. Systems biology approaches have provided valuable insights into these networks, highlighting their role in driving MM progression.

Sophisticated network analyses have further revealed intricate patterns of co-mutation and mutual exclusivity among genetic events, essential for understanding MM's complexity and heterogeneity.[88] For instance, a synergistic relationship was seen among the co-occurrence of the t(4;14) translocation, TRAF3 deletion, and del(13q14). The study also identified novel patterns of mutual exclusivity, such as between FAM46C and CDKN2C deletions with the t(4;14) translocation. Additionally, TRAF3 deletions were shown to co-occur with NFKBIA mutations but were mutually exclusive with the t(11;14) and t(14;16) translocations, while CYLD deletions were linked with both hyperdiploid cytogenetic status and t(11;14) but were mutually exclusive with t(4;14).

A previous study used logic programming to integrate regulatory networks with gene expression profiles from MM patients and healthy individuals, identifying key regulatory nodes influencing disease progression.[243] The study highlighted the alteration of JUN/FOS and FOXM1 activities in nearly all MM patients, emphasizing their critical role as drivers. The identification of two survival markers and subgroup-specific vulnerabilities suggested that targeting JUN/FOS and FOXM1 could yield new therapeutic avenues.

More recently, a comprehensive transcriptional regulatory network of MM, built based on multi-omics data from a large cohort of patients, revealed how various chromosomal abnormalities and somatic mutations causally perturb transcription regulators, ultimately affecting gene expression.[244] The network model identified genetic programs that stratified patients into distinct transcriptional states, proving more predictive of outcomes than mutations alone. The study demonstrated how dysregulated genetic programs could lead to specific MM phenotypes, including extreme-risk subtypes with distinct vulnerabilities and plausible mechanisms for relapse. The causal-mechanistic approach effectively linked mutations, gene expression, and clinical outcomes, providing a comprehensive framework for understanding the interplay between different levels of MM heterogeneity. Events associated with the risk of disease progression included the activation of FOXM1 via upregulation of E2F1 and the causal relationship between the mutations NRAS, amp(1q), and TP53, which directly activate complementary transcription factor subnetworks. Together, these studies underscore

the importance of transcriptional regulation in MM pathogenesis and progression, revealing potential targets for therapeutic intervention. The alteration of JUN/FOS and FOXM1 activities, in particular, may represent key vulnerabilities for therapeutic exploitation.

In line with these findings, a network biology approach from our team involved analyzing data from a large cohort of NDMM patients to generate a novel network model of myeloma (MMNet), organizing thousands of genes into thirty-seven coexpression modules.[83] The MMNet model identified novel high-risk MM genes and revealed key coexpression modules linked to genomic alterations and clinical traits. Hub genes CDC42BPA and CLEC11A were validated as novel regulators and candidate therapeutic targets in the t(4;14) MM subtype. The integrative analysis showed how CDC42BPA and CLEC11A, as part of an NSD2-related module, drive MM progression despite not being direct genetic drivers. This emphasizes the need to understand the complex interplay between genetic and epigenetic networks in defining disease drivers.

These integrative systems biology models can help dissect inter-patient heterogeneity, an important step toward identifying drivers. According to our MM-PSN model, disease subtypes in MM are strongly defined by patterns of co-occurring structural variations (SVs), copy number alterations (CNAs), gene expression changes and, to a lesser extent, gene fusions.[48] Single nucleotide variants (SNVs), while not significantly contributing to patient stratification, show some interesting patterns. For example, hyperdiploid patients exhibited a higher prevalence of NRAS mutations compared to other subtypes. Confirming previous findings, SNVs affecting FGFR3 were seldom observed in patients without the t(4;14) translocation. Our analysis found a significant presence of DIS3 mutations in patients with co-occurrence of t(4;14) and gain(1q). Mutations in CCND1 were almost exclusively found in patients with the CCND1 translocation t(11;14). Furthermore, biallelic inactivation of TP53, significantly associated with worse prognosis, was primarily observed in a cluster of patients affected by t(11;14) and trisomies of chromosome 11, although this event was relatively rare.

These studies illustrate how integrative network models and systems biology approaches may illuminate the complex interplay of genetic and epigenetic drivers in MM, helping formulate mechanistic hypotheses to connect and harmonize driver lesions in more comprehensive models of the disease.

Therapeutic Implications of MM Drivers

MM treatment has traditionally relied on a combination of therapies that exploit vulnerabilities in myeloma cells without directly targeting specific disease drivers. Table 3 summarizes the main classes of approved MM therapies, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies, and CAR T-cell therapies, along with their mechanisms of action and clinical significance.

Table 3 Summary of Approved Multiple Myeloma Therapies

Therapy Class	Selected Therapies	Mechanism of Action	Clinical Significance
Proteasome Inhibitors	Bortezomib, Carfilzomib, Ixazomib	Inhibition of proteasome	Induces apoptosis in myeloma cells due to high protein turnover
Immunomodulatory drugs (IMiDs)	Thalidomide, Lenalidomide, Pomalidomide	Modulation of immune response	Direct anti-tumor effects, enhances NK cell and T cell activity
Monoclonal Antibodies	Daratumumab, Isatuximab, Elotuzumab	Targeting CD38 (Dara and Isa), SLAMF7 (Elo)	Immune-mediated cell death, direct cytotoxicity
CAR T-cell Therapies	Ide-cel, Cilta-cel	Engineered T cells targeting BCMA	High response rates, durable remissions
Bispecific Antibodies	Teclistamab, Elranatamab, Talquetamab	Targeting BCMA and CD3 (Tecli and Elra), GPRC5D (Talq)	Enhanced T-cell mediated killing of myeloma cells

Notes: This table lists the main classes of approved MM treatments.

Approved MM Therapies

PIs, such as bortezomib, carfilzomib, and ixazomib, work by inhibiting the proteasome, a cellular complex responsible for protein degradation. Inhibition of the proteasome results in the accumulation of misfolded and ubiquitinated proteins, inducing apoptosis in myeloma cells due to their high protein turnover rate.[245]

Immunomodulatory drugs (IMiDs) like thalidomide, lenalidomide, and pomalidomide are integral to MM treatment. They modulate the immune system and exhibit direct anti-tumor effects.[246] IMiDs bind to the cereblon (CRBN) protein, leading to the degradation of transcription factors IKZF1 and IKZF3, which are essential for MM cell survival.[247] They also enhance immune responses by increasing the activity of natural killer (NK) cells and T cells. A new generation of cereblon E3 ligase modulators (CELMoDs), such as iberdomide and mezigdomide, builds on this mechanism.[248,249] CELMoDs have shown enhanced activity in degrading cereblon substrates, leading to more potent anti-tumor effects and improved modulation of immune responses. While still in clinical trials, these drugs represent a promising advancement in MM therapy.

Monoclonal antibodies represent a more recent class of treatments that target surface antigens on myeloma cells, leading to direct cytotoxicity or immune-mediated cell death. Approved monoclonal antibodies include daratumumab, elotuzumab, and isatuximab. Daratumumab targets CD38, a protein highly expressed on MM cells, resulting in antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and phagocytosis;[250] Elotuzumab targets SLAMF7, activating NK cells and inducing ADCC;[251] Isatuximab also targets CD38 with mechanisms similar to daratumumab.[252]

Recent advances have brought new agents with novel mechanisms of action, leading to significant breakthroughs in MM treatment. Selinexor, an exportin-1 (XPO1) inhibitor, blocks the export of tumor suppressor proteins from the nucleus, leading to apoptosis.[253,254] By inhibiting XPO1, selinexor retains MYC inhibitors in the nucleus, indirectly affecting MYC-driven transcriptional programs.

Chimeric antigen receptor (CAR) T-cell therapies and bispecific T-cell engagers (BiTEs) have revolutionized the treatment landscape of MM, providing remarkable clinical outcomes. CAR T-cell therapies like idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) involve engineering a patient's own T cells to recognize and kill myeloma cells expressing BCMA.[255–257] These therapies have demonstrated impressive response rates and durable remissions in heavily pre-treated patients. However, challenges remain regarding manufacturing, accessibility, and potential side effects like cytokine release syndrome (CRS) and neurotoxicity.[258]

Bispecific antibodies, such as teclistamab and elranatamab, are another promising treatment modality.[259,260] Teclistamab targets both BCMA on myeloma cells and CD3 on T cells, bringing T cells into proximity with myeloma cells to enhance cytotoxicity. Elranatamab similarly targets CD3 and BCMA, facilitating T-cell-mediated killing of MM cells. These therapies have shown significant efficacy and represent a breakthrough for patients with relapsed or refractory disease.

Targeting MM Drivers

Despite the wide range of available therapies, most do not directly target specific MM drivers. Instead, they exploit vulnerabilities inherent in myeloma biology, such as high protein turnover or immune evasion mechanisms, or focus on specific antigens expressed on the MM cell surface. Table 4 provides an overview of targeted therapies aimed at inhibiting specific MM drivers, detailing the driver mutations they target, the mechanisms of action, and their clinical relevance. Selinexor (XPO1 inhibitor) is notably the only targeted therapy listed in Table 2 that has been approved for use in MM.

Targeted therapies that aim to inhibit specific MM drivers include repurposed therapeutics originally developed for other indications, such as MEK inhibitors, BRAF inhibitors and BCL2 inhibitors.

BRAF inhibitors like vemurafenib target the MAPK pathway in patients with BRAF mutations, which occur in 4–5% of MM patients. By inhibiting the mutated BRAF protein, these drugs disrupt downstream signaling, reducing cell proliferation. However, their clinical efficacy has been limited, and responses have often been transient.[120,121]

Table 4 Summary of Targeted Therapies for Multiple Myeloma Drivers

Driver/ Target	Selected Targeted Therapies	Mechanism of Action	Clinical Relevance
BRAF	Vemurafenib, Dabrafenib	Inhibition of BRAF protein	Reduces cell proliferation; limited and transient responses
NRAS/ KRAS	Trametinib, Binimetinib	Inhibition of MEK1/2	Reduces activity of downstream signaling molecules, limited responses
FGFR3	Erdafitinib, Dovitinib	Pan-FGFR inhibition	Inhibits MAPK pathway activated by FGFR3 mutations
BCL-2	Venetoclax	BCL-2 inhibition	Induces cell death in MM cells with t(11;14) translocations
MYC	Omomyc, BET inhibitors (JQ1, OTX015), CDK9 inhibitors (Dinaciclib, Atuveciclib)	Disruption of MYC-MAX dimerization, Inhibition of MYC transcription, Inhibition of CDK9	Indirect targeting of MYC; mixed clinical outcomes
IRF4	IMiDs, CELMoDs (Iberdomide, Mezigdomide), STAT3 inhibitors, BET inhibitors	Degradation of IKZF1 and IKZF3, reducing IRF4 expression	Essential for plasma cell development, indirect targeting
MAF/ MAFB	PROTACs, IMiDs, BET inhibitors, MAPK inhibitors	Direct degradation, indirect inhibition	Poor prognosis, overexpressed due to translocations like t(14;16), t(14;20)
NSD2	Proteasome inhibitors (Bortezomib, Carfilzomib), BET inhibitors, HDAC inhibitors (Panobinostat)	Indirect inhibition of NSD2-driven pathways	Co-amplified in t(4;14) MM, potential therapeutic target
XPO1	Selinexor	Inhibition of exportin-1	Blocks nuclear export of tumor suppressor proteins, affecting MYC-driven transcriptional programs (**approved for MM**)
IDH2	Enasidenib	Inhibition of IDH2	Reduces 2-hydroxyglutarate (2-HG) levels, induces myeloid differentiation, and reduces abnormal histone hypermethylation.
IL6/ IL6R	Siltuximab, Tocilizumab	Targeting IL6 (Siltu) and IL6R (Toci)	Reduces proliferation and survival signals from TME.
CD47	Magrolimab	Targeting CD47 "Don't eat me" signal	Promotes macrophage-mediated phagocytosis of MM cells.
KSP	Filanesib	Inhibition of KSP	Mitotic arrest and cell death in myeloma cells
CD200	Samalizumab	Targeting CD200	Modulates immune suppression in the TME, enhancing anti-MM immunity.

Notes: This table provides a summary of targeted therapies aimed at inhibiting specific MM drivers. The table lists drivers or targets, corresponding targeted therapies, mechanisms of action, and clinical relevance. Selinexor, an XPO1 inhibitor, is the only therapy in this table that is currently approved for use in MM.

MEK inhibitors such as trametinib target the MAPK pathway downstream of RAS mutations, which are present in approximately 50% of MM patients. They inhibit MEK1/2, reducing the activity of downstream signaling molecules like ERK1/2. However, their effectiveness in MM has been disappointing, with limited responses in clinical trials.[120,122]

In a recent case study report, we demonstrated that the implementation of a novel triple MAPK inhibition strategy, targeting both BRAF and MEK, may result in a significant, albeit transient, clinical response, which could however bridge a patient relapsing from CAR T therapy to further treatment options, culminating in a stringent complete response.[121]

FGFR3 mutations are often found in patients with the t(4;14) translocation. Erdafitinib, a pan-FGFR inhibitor, targets FGFR1-4 and can inhibit the MAPK pathway activated by FGFR3 mutations.[129] While not specifically approved for MM, erdafitinib is being explored in clinical trials for MM patients with FGFR3 mutations.

Venetoclax is a BCL-2 inhibitor effective in MM patients with t(11;14) translocations, as these cells often rely on BCL-2 for survival.[261] By binding to BCL-2, venetoclax releases pro-apoptotic proteins and induces cell death.[262] Despite promising responses in early trials, subsequent studies showed mixed outcomes, and venetoclax remains unapproved for general MM treatment.

Pevonedistat inhibits the NEDD8-activating enzyme (NAE), disrupting the ubiquitin-proteasome pathway and affecting protein degradation. This leads to the accumulation of cell cycle regulators and apoptosis of MM cells. Though not yet approved for MM, it is being studied in clinical trials.[263]

Dinaciclib is a cyclin-dependent kinase (CDK) inhibitor targeting CDK1, CDK2, CDK5, and CDK9. It inhibits cell cycle progression and induces apoptosis in MM cells. Although not yet approved, it has shown efficacy in clinical trials for relapsed or refractory MM.[264]

Ibrutinib targets Bruton's tyrosine kinase (BTK) in B-cell receptor signaling. While not approved specifically for MM, it has shown activity in patients with MYD88 mutations, which are sometimes observed in MM.[265]

There is growing interest in directly targeting MM drivers, such as MYC, IRF4, MAF, and NSD2. However, targeting these genes presents unique challenges due to their roles as transcription factors and histone modifiers, which have traditionally been considered "undruggable". MYC, a transcription factor regulating genes involved in cell proliferation and growth, is overexpressed in MM due to translocations or amplifications. Directly targeting MYC with small molecules has been difficult, but peptide-based inhibitors like Omomyc, which disrupt MYC-MAX dimerization, have shown promise.[266] Indirect approaches, including BET inhibitors (eg, JQ1 and OTX015) and CDK9 inhibitors (dinaciclib and atuveciclib), inhibit MYC transcription and activity, though clinical outcomes have been mixed.[264,267,268] Selinexor indirectly affects MYC-driven transcriptional programs by retaining MYC inhibitors in the nucleus.[269]

IRF4, a transcription factor essential for plasma cell development, regulates genes crucial for MM cell growth, including MYC. While direct targeting remains challenging, indirect strategies like IMiDs and CELMoDs degrade IKZF1 and IKZF3, essential for IRF4 expression.[270] STAT3 inhibitors and BET inhibitors also reduce IRF4 expression.[267]

MAF family transcription factors, such as MAF and MAFB, are overexpressed in MM due to translocations like t(14;16) and t(14;20). Proteolysis-Targeting Chimeras (PROTACs) offer potential for direct degradation of MAF proteins, while IMiDs, proteasome inhibitors, BET inhibitors, and MAPK inhibitors indirectly inhibit MAF activity.[271]

While NSD2 inhibitors are still in preclinical development, proteasome inhibitors like bortezomib and carfilzomib, BET inhibitors, and HDAC inhibitors like panobinostat indirectly target NSD2-driven pathways.[272] FGFR3 inhibitors like erdafitinib may also indirectly affect NSD2 activity due to frequent FGFR3 co-amplification in t(4;14) MM. Despite these challenges, advances in targeted protein degradation, such as PROTACs and CELMoDs, and indirect inhibition strategies offer promising therapeutic opportunities.

Perspective: Defining and Characterizing Disease Drivers in Multiple Myeloma

The landscape of MM is shaped by a multitude of genetic, epigenetic, and microenvironmental abnormalities that contribute to its pathogenesis and progression. Despite significant advances in understanding these abnormalities, defining disease drivers remains a challenge. It is crucial to clarify that not all frequently aberrant genes are drivers of disease. The term "driver" should be reserved for genetic and molecular alterations that play a causal role in MM development and have been functionally validated to contribute to MM pathogenesis and progression.

Frequent genetic alterations, such as SNVs, translocations, and CNAs, have been catalogued in MM patients. However, many alterations occur as passengers due to genomic instability rather than contributing directly to the disease process. For instance, chromosomal gains and losses in MM can lead to recurrent but non-causal alterations in genes due to proximity or linkage effects. Similarly, many gene fusions, although detectable, might not contribute actively to tumorigenesis. These fusions could merely be by-products of the widespread genomic instability that characterizes many cancers.[273] Consequently, functional validation becomes imperative to identify true drivers. Integrating functional genomics with large-scale sequencing data will be crucial to identify and validate new MM drivers. Techniques such as CRISPR-based gene editing, RNA interference, and proteomics are invaluable tools to assess the biological significance of candidate drivers in MM. Functional studies in preclinical models, including genetically engineered mice, may offer insights into the causal role of specific genes.

Controversies and Challenges in Defining Prognostic Genetic Drivers in Multiple Myeloma

Many abnormalities, such as gain(1q), t(4;14), and t(14;16), are established drivers of MM and have consistently been associated with poor prognosis. However, their prognostic implications remains a subject of debate. While numerous studies have associated gain(1q) with poor prognosis and shorter survival, others have reported conflicting results, particularly when adjustments are made for co-occurring lesions.[274,275] Additionally, although the t(4;14) translocation is included in R-ISS as a high-risk lesion, its significant impact on prognosis often manifests only when it co-occurs with gain(1q).[48] The role of mutations in critical oncogenes such as KRAS and NRAS also continues to spark debate within the MM research community. Different studies present conflicting evidence regarding the impact of these mutations, leading to inconsistencies in patient management strategies.[276]

The effectiveness of targeting specific genetic mutations, such as in BRAF or NRAS, has shown considerable variability, igniting ongoing debates about the role of personalized medicine in MM treatment.[277,278] For instance, while BRAF inhibitors have proven effective in melanoma, their success in MM is hampered by intratumoral heterogeneity and the presence of multiple concurrent mutations.[279] Moreover, targeting alterations in the MAPK pathway, including with MEK inhibitors, has shown benefits, particularly using multiple inhibitors, but are typically short-lived responses.[121,280,281] This variability underscores the need for advanced genomic profiling. Recent advancements have accelerated the discovery of mutations such as those in FAM46C and DIS3. While these discoveries expand our genetic knowledge, the clinical implications of these mutations remain unclear, hindering their integration into targeted treatment protocols.

Additionally, interventions aimed at disrupting the bone marrow TME have shown mixed results, complicating the viability of such approaches as comprehensive treatment strategies.[282,283] These mixed outcomes can be attributed to the complex and redundant nature of interactions within the microenvironment that support MM cell survival in multiple ways.

Leveraging Systems Biology to Unravel the Complex Network of MM Drivers

Systems biology approaches have further advanced our understanding of MM by highlighting the complex networks driving disease progression. These methods can help identify candidate drivers, distinguish them from passenger recurrent alterations, and unveil multiple layers of driver events contributing to MM pathogenesis. For example, transcriptional regulatory networks provide a comprehensive framework linking mutations, gene expression, and clinical outcomes. By revealing distinct genetic programs and transcriptional states, these studies have shown that drivers of MM vary between subtypes, emphasizing the importance of moving from patient subtypes to driver identification.

Moreover, network models like the MMNet and the MM-PSN illuminate intricate patterns of co-mutation and mutual exclusivity among genetic events, providing insights into the interplay between primary cytogenetic events and secondary mutations. These models enable the formulation of mechanistic hypotheses to connect and harmonize driver lesions, offering a roadmap to understanding how different alterations cooperate in the disease process.

Figure 3 illustrates a possible pipeline for a systems biology approach to define MM drivers, starting from patient stratification based on clinical and genomic data. This pipeline involves the identification of candidate drivers using advanced computational approaches, including artificial intelligence (AI) and machine learning (ML). These methods integrate multi-omics data to uncover unique molecular signatures, which are then functionally validated through CRISPR-based gene editing, RNA interference, and preclinical models. This approach provides a comprehensive framework that facilitates the identification of patient-specific drivers and allows for the formulation of mechanistic hypotheses connecting different driver lesions in a more cohesive model of the disease. Such an approach can revolutionize our understanding of MM by distinguishing between recurrent alterations and drivers and unveiling multiple layers of driver events that contribute to MM pathogenesis.

Moving forward, advanced computational approaches, particularly AI and ML, will further dissect MM biology by harmonizing the wealth of available multi-omics data. These tools could identify patient-specific drivers by integrating genetic, epigenetic, transcriptomic, and clinical data to uncover unique molecular signatures. Such personalized

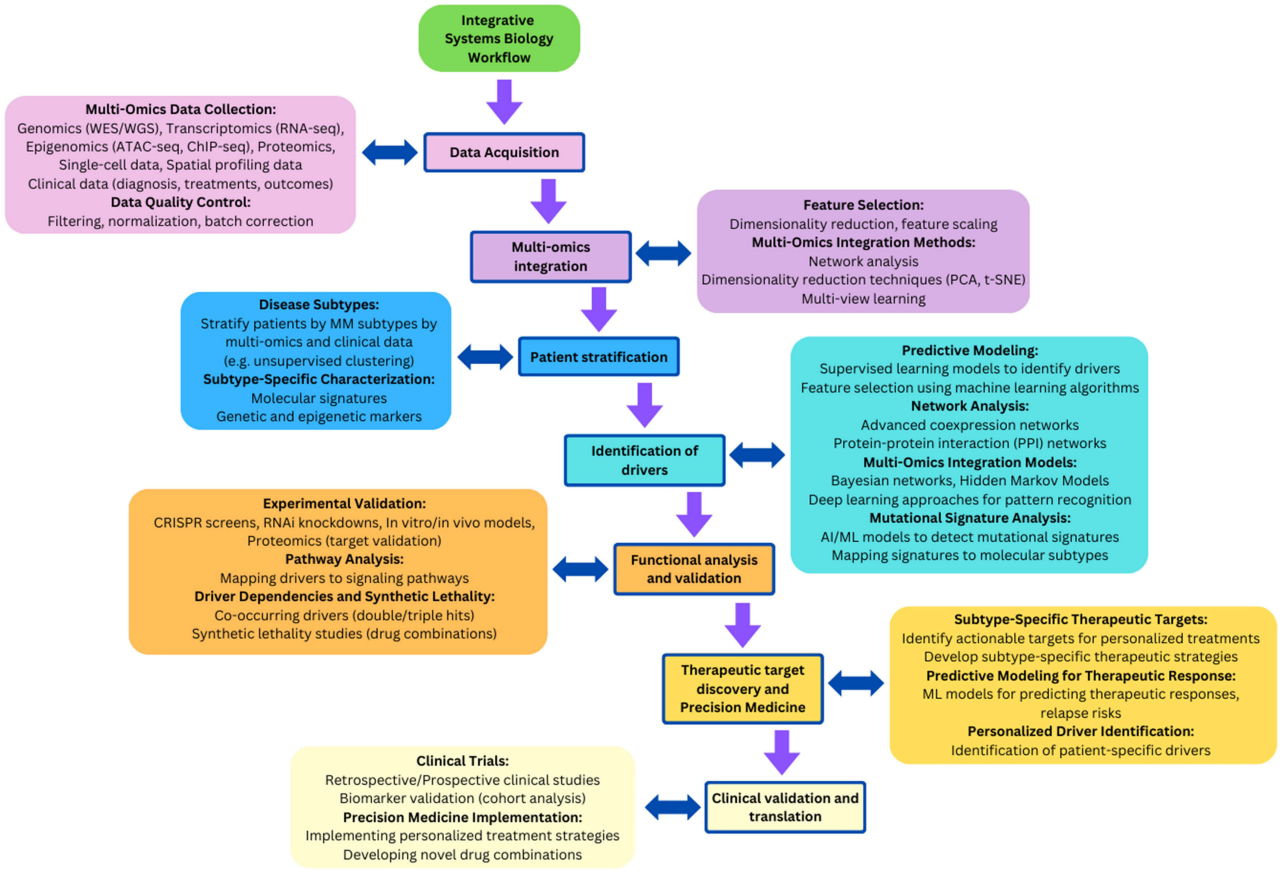

Figure 3 A pipeline for a systems biology approach to define MM drivers based on clinical and genomic data. The schema illustrates a possible workflow for the identification and characterization of drivers in MM, including computational analyses as well as experimental and clinical validation.

identification of MM drivers will significantly enhance precision medicine applications, enabling clinicians to tailor treatments based on individual genetic profiles. Furthermore, ML models could significantly improve the prediction of therapeutic responses, relapse risks, and disease progression, allowing for proactive intervention strategies.

The paradigm shift towards identifying personal drivers in MM has the potential to revolutionize the field by uncovering unique vulnerabilities in individual patients. This enables the development of tailored treatment strategies that integrate specific genetic drivers, the characteristics of the TME, and individual therapeutic responses. Rationally designed drug combinations targeting primary drivers and resistance mechanisms will be essential to overcome resistance and improve long-term disease management.

By incorporating advanced AI/ML techniques and systems biology models, we can refine our understanding of MM heterogeneity and create comprehensive predictive models that account for both primary and secondary driver events. The integration of multi-omics data with AI/ML tools will be instrumental in bridging the gap between recurrent alterations and true drivers, thus helping to harmonize our understanding of MM pathogenesis and progression.

Spatial profiling technologies will further enhance our understanding by providing insights into the spatial organization and interactions of MM cells within the bone marrow TME. This approach will help reveal the spatial distribution of subclonal populations and their interactions with immune and stromal cells, offering new perspectives on disease progression and potential therapeutic targets.

Conclusions

In conclusion, while significant progress has been made in identifying and targeting genetic drivers in MM, the field is characterized by ongoing debates and discrepancies that must be addressed. Significant gaps remain in distinguishing true

drivers from passengers, understanding the functional consequences of low-frequency mutations, and translating these insights into effective therapies. Future research should focus on clarifying the role of controversial genetic alterations and refining therapeutic strategies to better harness genetic insights for patient benefit. The path forward will require a collaborative approach to integrate functional genomics with multi-omics data, leveraging advanced computational tools, and prioritizing experimental validation to refine the landscape of MM drivers and their clinical applications.

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Disclosure

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