

Interleukin-1 Receptor-Associated Kinases (IRAKs) and Multiple Myeloma (MM) development

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Abstract

Multiple myeloma (MM) develops within an inflammatory, TLR-responsive bone-marrow niche where innate-immune signaling shapes plasma-cell behavior and microenvironmental interactions. This review examines the Interleukin-1 receptor-associated kinase (IRAK) family, which are serine/threonine kinases and pseudokinases that regulate MyD88-dependent TLR/IL-1R pathways, and outlines their emerging relevance to MM biology. We summarize the structural and functional features of IRAK1, IRAK2, IRAK3, and IRAK4; their roles in NF- κ B activation, cytokine production, immune tolerance, and stromal–myeloid communication; and how these pathways differ between mutation-driven signaling in other B-cell malignancies and microenvironment-driven activation in MM. The review highlights how IRAK-dependent signaling integrates intrinsic plasma-cell stress responses with extrinsic cues from macrophages, dendritic cells, and stromal cytokine networks. We also evaluate current and emerging therapeutic strategies—including IRAK4 inhibitors, dual IRAK1/4 blockade, IRAK1 degraders, and IRAK3-modulating approaches—and discuss how targeting IRAK family members may enhance immunotherapy responsiveness and reshape precision-medicine strategies in MM. Together, these topics provide a framework for understanding IRAK signaling as a central regulator of MM progression, immune evasion, and therapeutic resistance.

Keywords: bone marrow microenvironment, multiple myeloma, Interleukin-1 receptor-associated kinases, therapeutics

1. Introduction

Multiple myeloma (MM) is a malignant disorder of plasma cells that typically expands within osteolytic bone lesions and remains incurable despite major therapeutic advances. A main challenge for curing multiple myeloma is the rapid mutation of the cancer cells, which split into many subtypes. These subtypes have different drug sensitivities and take shelter in the bone marrow, where the surrounding environment helps them resist treatment. Chronic inflammation in the bone marrow, together with signaling driven by Interleukin-1 Receptor-Associated Kinases (IRAKs), fuels multiple myeloma progression, promotes drug resistance, and reshapes immune cell behavior within the marrow microenvironment (2,3). MM continues to be a disease marked by near-certain relapse, reinforcing the need for a deeper understanding of the bone marrow tumour microenvironment. The complex signalling and interactions among myeloma cells, stromal cells, and immune cells shape this niche, and mapping these relationships is essential for identifying new therapeutic targets that improve patient outcomes (2,3). Notably, multiple myeloma cells express high levels of Toll-like receptors (TLRs) and demonstrate active IRAK signaling in both patient samples and cell-line models, where TLR4 stimulation enhances proliferation and expansion of cancer cells (2,4–6).

Interleukin-1 Receptor-Associated Kinases (IRAKs) are a family of serine-threonine kinases that function as central regulators of innate immune and inflammatory signalling. Within this

family, IRAK1 and IRAK4 act as positive activators of MyD88-dependent pathways (4), which promote inflammatory responses downstream of TLRs. During normal immune homeostasis, these pathways are activated when pattern-recognition receptors detect microbial components, such as bacterial lipopolysaccharide or viral nucleic acids, triggering transient IRAK-mediated signalling that supports pathogen clearance and restores tissue equilibrium. Conversely, IRAK3 serves as a myeloid-restricted negative regulator that modulates TLR/Interleukin-1 receptor (IL-1R) responses and shapes inflammatory homeostasis (3,7). Dysregulation of IRAK activity has been implicated in diverse malignancies, particularly in hematological malignancies, where altered expression can promote proliferation, survival, and microenvironmental remodeling (3,5,8).

Recently, increasing attention has focused on the role of IRAK3 in multiple myeloma, where its context-dependent behavior in other cancers raises important questions about its function in plasma cell biology (3,9). This review comprehensively examines current findings linking IRAK family function to MM initiation, progression, and microenvironmental interactions, and outlines how these insights may inform future therapeutic strategies targeting IRAK pathways.

2. MM and Normal Plasma Cell Biology

Plasma cells are part of the adaptive immune system and are terminally differentiated. They arise from germinal-center B cells that have undergone somatic hypermutation and affinity maturation. Plasma cells mainly secrete high volumes of antibodies, which is supposed by expansion of the endoplasmic reticulum, elevated protein-folding capacity, and transcription factors responsible for transforming germinal-center B cells into plasma cells. Long-lived plasma cells migrate to and persist within specialized bone marrow niches, where stromal cells, osteoblasts, and myeloid populations provide essential survival cues, including IL-6, BAFF, APRIL, and CXCL12. These signals maintain plasma-cell longevity, metabolic stability, and controlled immunoglobulin production (4,6).

This normal biology creates the foundation for multiple myeloma pathogenesis. Healthy plasma cells depend on cytokine-rich, TLR-responsive marrow microenvironments; this is also what sustains malignant plasma cells. The bone marrow niche that normally sustains long-lived immunity becomes a protective reservoir for transformed plasma cells, enabling them to resist apoptosis, remodel stromal interactions, and co-opt inflammatory signaling pathways. MM cells retain and amplify many features of normal plasma-cell physiology, like high secretory load, reliance on IL-6, and sensitivity to innate immune cues, but they redirect these programs toward uncontrolled proliferation, genomic instability, and microenvironmental manipulation (2,5).

Plasma cells naturally express Toll-like receptors, and many of their survival signals run through MyD88-dependent pathways, which makes them inherently sensitive to IRAK-mediated signaling. In healthy immunity, TLR and IL-1R inputs help fine-tune antibody production and manage cellular stress. In multiple myeloma, these same pathways become chronically activated by stromal cytokines, bone-derived danger signals, and myeloid-cell interactions, leading to persistent nuclear factor kappa-light-chain-enhancer of activated B cell (NF- κ B) activity and supporting malignant growth. This is why MM cells, though lacking

MyD88 mutations, show continuous IRAK1/IRAK4 signaling and strong responses to TLR4 and TLR9 stimulation within the inflammatory marrow niche (2,4).

3. IRAK Family Genomic Structure

The IRAK family is distributed across distinct genomic loci, reflecting their functional divergence within innate immune signaling. IRAK3, located on chromosome 12q14, encodes a protein of around 596 amino acids and contains approximately 12 exons spanning the N-terminal death domain (DD) and the C-terminal pseudokinase domain, consistent with its inhibitory structural configuration. Notable mutations include promoter variants associated with altered myeloid responsiveness and cancer-linked SNPs reported in specific cohorts [cite]. IRAK1 resides on chromosome Xq28 and encodes approximately 712 amino acids, while IRAK4, located on chromosome 12q24, encodes around 460 amino acids. The IRAK2 gene is located at position 3p25.3. Comparative genomic studies identify conserved homologues across vertebrates, including zebrafish IRAK3 and IRAK4 orthologs that retain DD and kinase-domain architecture (10), supporting the evolutionary stability of IRAK domain structure and highlighting the essential role of these proteins in innate immune signaling across species.

4. IRAK Family Protein Structure

IRAKs are a conserved family of serine–threonine kinases defined by a shared N-terminal death domain (DD) and a C-terminal kinase or pseudokinase domain, enabling assembly of receptor-proximal complexes downstream of Toll-like receptors (TLRs) and IL-1 receptors (IL-1Rs) (4). Across vertebrates, IRAK1, IRAK2, IRAK3, and IRAK4 maintain this core architecture, but their distinct catalytic and scaffolding capacities shape how each contributes to innate immune signaling (4).

4.1 Domain Architecture

All IRAKs contain an N-terminal death domain (DD) that mediates interactions with MyD88 and other DD-containing adaptors, forming the core of the Myddosome signaling complex (4). Structural analyses show that conserved DD residues are essential for receptor docking and signal initiation (11).

The C-terminal domain determines catalytic potential. IRAK4 and IRAK1 possess active kinase domains, with IRAK4 functioning as the initiating kinase that phosphorylates IRAK1 during early Myddosome assembly (4,5). Conversely, IRAK2 and IRAK3 contain pseudokinase-like domains lacking key catalytic residues, enabling scaffold or inhibitory functions rather than enzymatic activity (4,5). IRAK3's pseudokinase domain is structurally adapted for negative regulation, stabilizing inactive Myddosome conformations and suppressing downstream NF- κ B signaling (7).

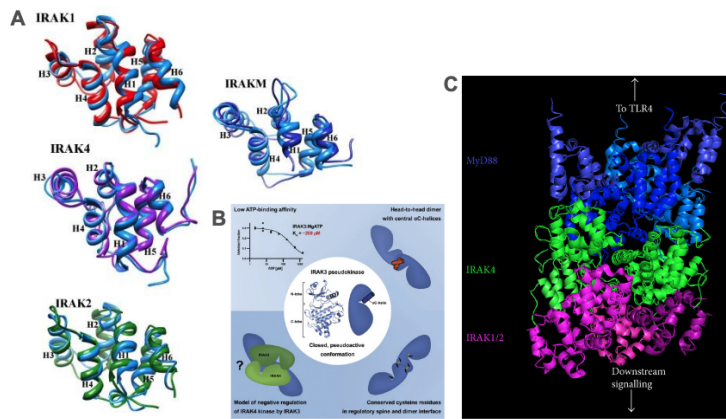
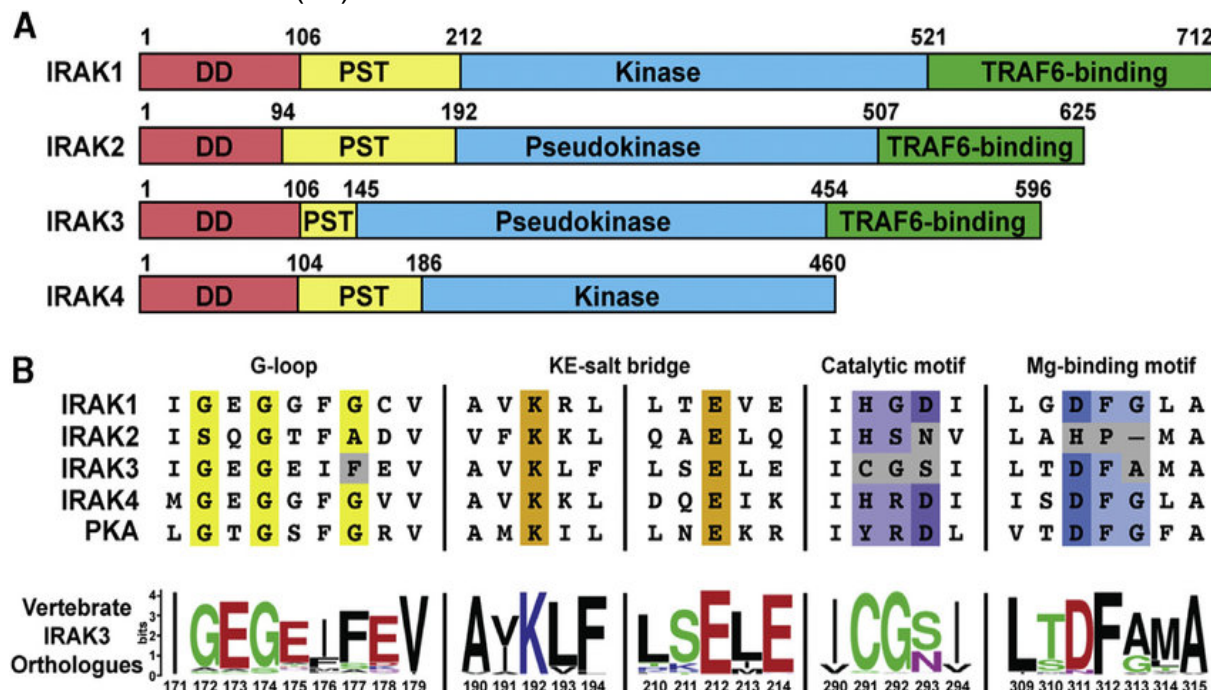


Figure 2. A) Domain architecture of the IRAK family. All IRAKs contain an N-terminal death domain for MyD88 binding, followed by either a catalytic kinase domain (IRAK1, IRAK4) or a pseudokinase scaffold domain (IRAK2, IRAK-M), and a C-terminal regulatory region. Functional differences arise from kinase activity, scaffold roles, and inhibitory functions in macrophages. Images taken from Gosu 2012 (10). B) IRAK3 pseudokinase structure and function. Its head-to-head dimer structure enables it to clamp on IRAK4 despite lacking catalytic activity, enforcing suppression of downstream signaling. By blocking TRAF6 activation, IRAK3 suppresses TLR signaling and drives macrophages toward M2/TAM-like states. These states promote anti-inflammatory programs and support tumor-associated remodeling. Image taken from Lange 2021 (12). C) Myddosome assembly. Image taken from Vallance 2017 (13).



4.2 Evolutionary Structural Conservation

Comparative analyses show strong evolutionary conservation of DD and kinase-domain residues across vertebrates, reflecting the essential role of IRAKs in innate immune signaling(11). IRAK4-like kinases appear to represent the ancestral form, with IRAK3 diverging later to acquire inhibitory pseudokinase features. Phylogenetic studies support this

model, demonstrating early branching of IRAK4 orthologs and later emergence of IRAK3-like inhibitory modules in mammals (10).

4.3 Structural Determinants of Activation

The catalytic IRAKs (1 and 4) initiate early Myddosome activation, and their active kinase domains directly shape signal propagation. IRAK4's kinase domain contains the conserved catalytic residues required to phosphorylate IRAK1 and stabilize early Myddosome assembly (5). Structural studies of selective IRAK4 inhibitors highlight the accessibility of its ATP-binding pocket and activation loop, enabling rational drug design (14). IRAK1 likewise contains a phosphorylation-dependent activation loop essential for downstream signaling, and once activated, IRAK1 is ubiquitinated and degraded—a process dependent on structural motifs within its kinase domain (15).

In contrast, the pseudokinase IRAKs (2 and 3) rely on non-catalytic structural features to modulate signal duration, scaffold complex formation, and maintain immune balance. Although IRAK2 lacks catalytic residues, its pseudokinase domain supports TRAF6 recruitment and polyubiquitin chain formation, functioning primarily as a scaffold during sustained signalling (4). Through this scaffolding role, IRAK2 facilitates the assembly of TRAF6–TAK1 complexes, enabling K63-linked ubiquitination events that propagate downstream signaling and ultimately activate the IKK complex, thereby promoting NF- κ B transcriptional responses during prolonged TLR stimulation. IRAK3's structure is optimized for inhibitory function; early work showed that it maintains Myddosome complexes in an inactive state, preventing NF- κ B activation and promoting tumor-induced immune tolerance (7). More recent structural studies reveal a guanylate cyclase-like motif within IRAK3, enabling noncanonical regulation of NF- κ B through cGMP production (9). Together, these domain-level distinctions illustrate how catalytic versus pseudokinase architectures fundamentally determine each IRAK family member's role in shaping innate immune responses.

5. IRAK Signaling Functions

IRAKs are central regulators of innate immune signaling downstream of TLRs and IL-1Rs. Their functions span catalytic activation, scaffolding, negative regulation, and cross-talk with other inflammatory pathways. Although structurally related, IRAK1, IRAK2, IRAK3, and IRAK4 exhibit distinct biochemical behaviors that determine the amplitude, duration, and cellular context of inflammatory responses (4). IRAK4 initiates rapid signaling, IRAK1 amplifies and propagates it, and IRAK2 maintains late-phase responses. IRAK3 terminates signaling, creating a tightly regulated temporal sequence (4,11).

5.1 Canonical TLR/IL-1R Signaling

Upon ligand binding, IL-1Rs and TLRs recruit MyD88, which nucleates formation of the Myddosome, a multimeric complex containing MyD88, IRAK4, IRAK1, and IRAK2 (4,11). IRAK4 is the initiating kinase: it phosphorylates IRAK1, enabling IRAK1 activation and subsequent propagation of downstream signaling(5). Activated IRAK1 dissociates from the

receptor complex and interacts with TRAF6, promoting lysine-63 (K63)-linked polyubiquitin chain formation. These ubiquitin scaffolds recruit TAK1 and the IKK complex, culminating in NF- κ B, MAPK, and AP-1 activation (4,11). IRAK2 functions primarily as a scaffold that stabilizes TRAF6-dependent ubiquitin signaling, particularly in sustained TLR responses (4). Under homeostatic conditions, activation of NF- κ B, MAPK, and AP-1 induces transient transcriptional programs that support cytokine production, antimicrobial defense, and controlled cell proliferation. NF- κ B promotes survival signals needed for immune cell activation, while MAPK and AP-1 regulate genes involved in differentiation, stress responses, and limited proliferative expansion.

In contrast, inappropriate or chronic activation of these pathways—such as through persistent TLR stimulation in the bone marrow niche—drives pathological inflammation, enhances MM cell proliferation, and reinforces resistance to apoptosis. Constitutive NF- κ B signaling supports survival of malignant plasma cells, MAPK hyperactivation accelerates growth and metabolic adaptation, and AP-1 contributes to cytokine loops that remodel the tumor microenvironment and promote disease progression.

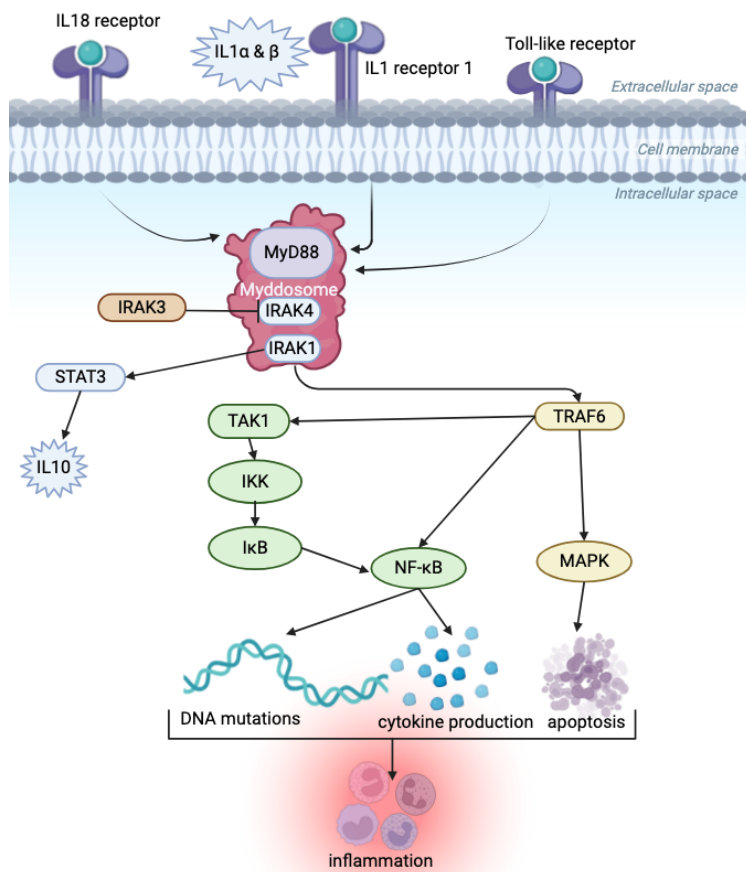


Figure 3. IL-1R/TLR–Myddosome signaling cascade and downstream inflammatory outputs. Schematic overview of IL-1R and TLR activation leading to Myeloid differentiation primary response 88 (MyD88)-dependent Myddosome assembly, IRAK1/IRAK4 signaling, and downstream NF- κ B and MAPK activation. IRAK3 acts as a negative regulator, promoting IL-10 production and limiting inflammatory output. These pathways coordinate cytokine production, apoptosis regulation, and inflammatory responses.

5.2 Negative Regulation of Signaling

IRAK3 (IRAK-M) is a myeloid-restricted negative regulator that prevents dissociation of inactive Myddosome complexes, thereby blocking IRAK1/IRAK4-dependent NF- κ B activation(7). Its inhibitory function is essential for maintaining immune homeostasis and preventing excessive inflammation. Early work demonstrated that IRAK3 is required for tumor-induced immune tolerance, suppressing macrophage activation and antigen presentation(7).

Recent studies reveal that IRAK3 possesses guanylate cyclase-like activity, generating cGMP that further suppresses NF- κ B signaling through noncanonical mechanisms (9). This expands IRAK3's functional repertoire beyond pseudokinase-mediated inhibition.

5.3 Context-Dependent Signaling Roles

IRAK functions vary across immune and stromal compartments. In myeloid cells, IRAK3 dominates, enforcing tolerance and limiting TLR responsiveness (7) and is expressed at particularly high levels in macrophages, monocytes, and granulocytes, where it shapes the magnitude and duration of innate immune activation {cite}. Lymphoid cells contain high expression of IRAK1 and IRAK4, driving activation, proliferation, and cytokine production (4). In the tumor microenvironment, IRAK3-mediated suppression contributes to immune evasion, while IRAK1/IRAK4 activation promotes inflammatory remodeling (3).

IRAK-dependent signaling intersects with multiple oncogenic and inflammatory pathways {and in healthy cells, this activation supports pathogen clearance by inducing pro-inflammatory cytokines, enhancing antigen presentation, and coordinating adaptive immune priming (5), functions that become dysregulated and co-opted in cancer}. IRAK1/IRAK4 activation is a major upstream driver of canonical NF- κ B signaling in hematologic malignancies (2). IRAK-mediated NF- κ B activation also synergizes with B-cell receptor (BCR) signaling, particularly through SYK and BTK activation, which enhances NF- κ B and MAPK pathway output, thereby reinforcing anti-apoptotic signaling and promoting malignant B-cell survival-driven pathways (16), reinforcing survival signals in malignant B cells (6). IRAK-dependent cytokine production (e.g., IL-6) activates JAK/STAT and PI3K/AKT pathways, contributing to proliferation and therapeutic resistance (3).

IRAK dysregulation contributes to tumorigenesis through several mechanisms. IRAK1 promotes NF- κ B activation, metastasis, and resistance to therapy across multiple cancers (8) by enhancing epithelial-mesenchymal transition, increasing motility and invasion, and supporting survival of disseminated tumor cells in distant tissues (8); IRAK1-driven NF- κ B signaling also reduces sensitivity to apoptosis-inducing therapies, including chemotherapeutics and targeted agents that rely on mitochondrial stress or death-receptor pathways (17). IRAK4 sustains inflammatory signaling in hematologic malignancies and supports survival of malignant clones (5). IRAK3 enforces immune suppression, dampens antigen presentation, and shapes tumor-associated macrophage phenotypes (7,18). These functions position IRAKs as central nodes linking inflammation, immunity, and cancer biology.

5.4 MyD88 Mutations in IRAK signal activation and Hematologic Malignancy development

Myeloid differentiation primary response 88 (MyD88) is the central adaptor protein for nearly all TLR and IL-1R signaling pathways. Its role in assembling the Myddosome, via death-domain interactions with IRAK4 and IRAK1, makes MyD88 a critical upstream determinant of IRAK-dependent NF- κ B activation. Although multiple myeloma rarely harbors MyD88 mutations, understanding MyD88-driven oncogenic signaling in other hematologic cancers provides essential context for why IRAK pathways remain highly active in MM despite the absence of genetic lesions in MyD88 itself.

5.5 The L265P Mutation in IRAK1/4 activation and signalling

Mutations in the MyD88–IRAK signaling axis play a central role in shaping inflammatory signaling, NF- κ B activation, and therapeutic vulnerabilities across multiple cancers {and are clinically important because they create constitutive signaling states, alter dependency on upstream kinases, and define molecular subtypes with distinct prognoses and treatment responses (19). Although MyD88 mutations are common in several B-cell malignancies, they are comparatively rare in multiple myeloma (MM), making it important to distinguish mutation-driven signaling from the microenvironment-driven IRAK activation that predominates in MM (20). The most well-characterized MyD88 mutation is L265P, a leucine-to-proline substitution in the Toll/interleukin-1 receptor (TIR) domain. This single amino-acid change induces constitutive Myddosome assembly, enabling ligand-independent recruitment of IRAK4 and IRAK1. As a result, cells exhibit chronic NF- κ B activation, elevated cytokine production, and enhanced survival signaling.

This mutation is a defining feature of several malignancies through IRAK1/4-driven NF- κ B signaling. The MYD88 L265P mutation is a defining genetic driver across several B-cell malignancies, with its impact varying by disease context. In Waldenström macroglobulinemia (WM), L265P is present in approximately 90% of cases and functions as a founding mutation that constitutively activates MyD88-IRAK signaling, establishing the NF- κ B-dependent transcriptional program characteristic of the disease. In activated B-cell–type diffuse large B-cell lymphoma (ABC-DLBCL), L265P occurs in approximately 30–40% of cases, where it contributes to the hallmark NF- κ B-high phenotype and supports the survival of malignant clones. Marginal zone lymphoma exhibits lower but meaningful frequencies (around 10–15%), indicating a broader role for aberrant MyD88 signaling in indolent B-cell neoplasms. Together, these patterns highlight L265P as a recurrent oncogenic lesion that reinforces chronic innate immune signaling across diverse lymphoma subtypes.

In these cancers, MyD88 L265P creates a dependency on IRAK4 kinase activity, making IRAK4 inhibition a rational therapeutic strategy. Indeed, IRAK4 inhibitors demonstrate potent suppression of NF- κ B signaling in MyD88-mutant lymphoma models, validating the MyD88–IRAK axis as a druggable pathway.

Although multiple myeloma does not typically carry MyD88 mutations, MM cells exhibit increased expression (though rare, their clinical significance remains under investigation

(21). When present, these mutations may be associated with more aggressive disease behavior or altered responsiveness to immunomodulatory therapies, but definitive correlations are still emerging (21). of TLRs (especially TLR4 and TLR9), constitutive NF- κ B activation, and dependency on IL-1R/TLR-driven cytokine loops, as well as active IRAK1/IRAK4 signaling. In MM, increased IRAK pathway activation is thought to arise from microenvironmental cytokines (e.g., IL-6, BAFF, APRIL), epigenetic upregulation of TLRs, and chronic inflammatory signaling within the bone marrow niche rather than from recurrent MyD88 mutations (21).

6. IRAKs in Multiple Myeloma: Intrinsic and Extrinsic Roles

MM is characterized by chronic activation of innate immune signaling pathways, including TLR- and IL-1R-dependent cascades that converge on NF- κ B. IRAK family members play central roles in shaping both intrinsic plasma cell biology and the extrinsic tumor microenvironment (TME). Dysregulated IRAK activity contributes to proliferation, survival, immune evasion, and therapeutic resistance in MM through coordinated effects on malignant plasma cells, stromal elements, and myeloid populations (4).

6.1 IRAKs Intrinsic Roles Within MM Cells

MM cells frequently overexpress TLRs, particularly TLR4 and TLR9, leading to heightened responsiveness to microenvironmental ligands. Engagement of these receptors activates MyD88-dependent signaling, recruiting IRAK4 and IRAK1 to assemble the Myddosome and initiate NF- κ B activation (4,11). IRAK4 phosphorylates IRAK1, enabling IRAK1 dissociation and TRAF6-mediated ubiquitin signaling. TRAF6-activated IKK complex phosphorylates I κ B α , marking it for proteasomal degradation. This releases NF- κ B (such as p50/RelA), allowing it to translocate into the nucleus, initiate transcription of immune and inflammatory genes, and promote cell survival.

IRAK1 enhances NF- κ B activation, promotes metabolic adaptation, and contributes to resistance to apoptosis. In other hematologic malignancies, IRAK1 drives metastatic behavior and therapeutic resistance (8), and similar mechanisms are increasingly recognized in MM, where NF- κ B activation is a hallmark of disease biology.

Although IRAK3 is classically a negative regulator in myeloid cells, MM plasma cells can express IRAK3 at variable levels. Emerging evidence suggests that IRAK3 may exert context-dependent effects, potentially modulating stress responses or dampening excessive inflammatory signaling within malignant plasma cells (3). Its recently described guanylate cyclase-like activity adds a noncanonical layer of regulation, influencing NF- κ B activity through cGMP-dependent mechanisms (9).

6.2 Extrinsic Roles Within the MM Tumor Microenvironment

IRAK3 is highly expressed in tumor-associated macrophages and myeloid-derived suppressor cells, where it enforces immune tolerance by preventing Myddosome activation

and suppressing NF- κ B signaling (7). The foundational demonstration of IRAK3-mediated tumor immune tolerance showed that IRAK3 inhibits macrophage activation and antigen presentation, enabling tumors to evade immune detection by blocking TLR/IL-1R-driven costimulatory molecule upregulation and reducing pro-inflammatory cytokine release, thereby limiting effective antigen processing and presentation to T cells (7). In MM, this contributes to a TME characterized by dysfunctional macrophages, impaired dendritic cell activation, and reduced T-cell priming resulting in weakened antigen presentation, diminished recruitment of effector T cells, and a shift toward an immunosuppressive cytokine milieu that favors malignant plasma-cell persistence.

In addition to immune interactions, bone marrow stromal cells produce IL-6, BAFF, APRIL, and other cytokines that activate IRAK-dependent pathways in MM cells. IRAK1/IRAK4 signaling amplifies these cytokine loops including IL-6–STAT3, BAFF/APRIL–NF- κ B, and IL-1 β –MyD88 pathways}, reinforcing NF- κ B activation and promoting plasma-cell survival {by enhancing anti-apoptotic gene expression, supporting metabolic fitness, and sustaining high immunoglobulin-production capacity (4). Stromal IRAK signaling also contributes to osteoclast activation and bone destruction through induction of RANKL, inflammatory cytokines, and chemokines that stimulate osteoclast differentiation and resorptive activity, a hallmark of MM progression. IRAK-dependent NF- κ B activation in stromal and myeloid cells drives production of pro-angiogenic and pro-inflammatory mediators, contributing to vascular remodeling by increasing VEGF, IL-8, and matrix-remodeling enzymes that promote neovascularization and alter marrow architecture and supporting MM growth (2).

7. IRAKs as Therapeutic targets

7.1 Targeting IRAK1: Amplifier of NF- κ B and Stress Responses

Broad IRAK-pathway inhibitors are advancing through clinical development, including emavusertib, a multi-kinase agent with potent IRAK4 activity now being evaluated in hematologic malignancies and solid tumors (22). Small-molecule inhibitors, such as Pacritinib, inhibit IRAK1 activity and slow tumor growth. PROTAC-based strategies eliminate IRAK1 protein entirely, disrupting both catalytic and scaffolding functions. Combination therapy through co-targeting IRAK1 alongside BCL2 inhibitors enhances elimination of malignant clones. Rhyasen et al. demonstrated that dual IRAK1 and BCL2 inhibition more effectively eradicates myelodysplastic syndrome clones, establishing IRAK1 as a druggable vulnerability in MDS. Emerging agents such as Pacritinib, Rosoxacin, and the covalent IRAK1 inhibitor JH-X-119-01 show activity across inflammatory diseases and B-cell lymphomas. Selective IRAK1 degraders such as JNJ-101 offer an additional strategy by targeting IRAK1's scaffolding role (17). Given MM's dependence on NF- κ B, IRAK1 inhibition may synergize with proteasome inhibitors or IMiDs.

7.2 Targeting IRAK2

Targeting IRAK2 is gaining traction as a strategy to restrain pathological inflammation, slow tumor progression, and modulate metabolic disease. IRAK2-NF- κ B signaling promotes glycolysis-dependent tumor growth in pancreatic cancer, as shown by Yang et al (23).

Topical siRNA approaches have been used to selectively reduce epidermal IRAK2 expression in models of skin inflammation, achieving local immune modulation without systemic toxicity. In settings where IRAK2-driven interferon signatures dominate, downstream modulation using FDA-approved JAK inhibitors such as baricitinib has been explored to mitigate inflammatory consequences (23).

7.3 IRAK3 and Therapeutic Resistance

IRAK3 (IRAK-M) is a pseudokinase that enforces immune tolerance by preventing Myddosome activation and suppressing NF- κ B signaling in macrophages and dendritic cells (7). Its role in tumor-induced immune suppression is well established: IRAK3 inhibits antigen presentation, reduces macrophage activation, and promotes a tolerogenic TME (7). Recent studies show that IRAK3 expression correlates with reduced immunotherapy response in lung adenocarcinoma (18) and that IRAK3 possesses guanylate cyclase-like activity, generating cGMP that further suppresses NF- κ B signaling (8,9). IRAK3 also shapes myeloid phenotypes that blunt anti-tumor immunity (3). These findings position IRAK3 as a negative regulator of immunotherapy efficacy, making it a high-value target for strategies aiming to reprogram the TME. IRAK-dependent signaling forms a bidirectional axis between MM cells and the TME. MM cells activate IRAK1/IRAK4 and NF- κ B, driving cytokine production that recruits and polarizes myeloid cells. Myeloid IRAK3 then suppresses anti-tumor immunity and reinforces stromal support. Stromal IRAK signaling amplifies IL-6 and BAFF loops that feed back to MM cells, creating a self-reinforcing inflammatory circuit that promotes MM progression, immune evasion, and resistance to therapy.

7.4 Targeting IRAK4

IRAK4 is the proximal kinase that phosphorylates IRAK1 and stabilizes Myddosome assembly. Its well-defined ATP-binding pocket has enabled development of selective small-molecule inhibitors (14). These agents block early TLR/IL-1R signaling, suppress NF- κ B activation, and reduce inflammatory cytokine production. In hematologic malignancies, IRAK4 inhibition disrupts survival pathways driven by MyD88-dependent signaling(5). Several IRAK4 inhibitors have advanced into preclinical and early clinical evaluation, demonstrating reduced NF- κ B activation, impaired cytokine loops, and sensitization of malignant cells to apoptosis. Given MM's reliance on inflammatory signaling, IRAK4 inhibition represents a rational therapeutic strategy.

The most clinically advanced IRAK4 inhibitor is emavusertib (CA-4948), which has shown meaningful activity in MyD88-mutant lymphomas and AML. In phase I/II studies, emavusertib reduced NF- κ B-driven cytokine production, induced apoptosis in malignant clones, and demonstrated objective responses in patients with MyD88 L265P-mutant Waldenström macroglobulinemia and ABC-DLBCL (22). Preclinical work also shows that emavusertib sensitizes AML cells to azacitidine and venetoclax by lowering inflammatory survival thresholds. Challenges include on-target cytopenias, dose-limiting fatigue, and the need to identify biomarkers that predict durable response. Additional IRAK4 inhibitors—such as PF-06650833 and ND-2158—have shown potent suppression of IL-1R/TLR signaling in

preclinical models, though clinical development has been slower due to pharmacokinetic limitations and toxicity concerns (17).

7.6 Synergistic Therapeutic Strategies

IRAK inhibition may enhance the efficacy of multiple therapeutic classes and thus may synergize with existing therapies to promote better patient outcomes. One promising area involves proteasome inhibitors: reducing IRAK1/IRAK4-driven NF- κ B activation may lower the threshold for bortezomib-induced apoptosis. Proteasome inhibitors such as bortezomib work by blocking degradation of misfolded proteins and preventing turnover of key NF- κ B pathway components, including I κ B α . In MM cells, high NF- κ B activity raises the apoptotic threshold and reduces bortezomib sensitivity. By inhibiting IRAK1/IRAK4 upstream, NF- κ B signaling is dampened, restoring I κ B α stability and making malignant plasma cells more susceptible to proteasome-induced ER stress and apoptosis. This mechanistic complementarity provides a strong rationale for combining IRAK inhibitors with proteasome-based regimens.

IMiDs modulate cereblon-dependent pathways that intersect with IRAK-driven cytokine networks, and IRAK inhibition may dampen IL-6 and BAFF loops that blunt IMiD activity. In parallel, cross-talk between IRAK-dependent NF- κ B signaling and B-cell receptor pathways (6) suggests that dual targeting may suppress redundant survival signals. Taken together, IRAK3 inhibition may reverse myeloid suppression, improving antigen presentation and T-cell priming, thereby enhancing checkpoint blockade responses (18).

7.7 Precision Medicine and Biomarker Development

IRAK expression patterns, MyD88 mutation status, and TLR profiles may serve as biomarkers for selecting patients likely to benefit from IRAK-targeted therapies. For example, high IRAK1/IRAK4 activity may predict responsiveness to kinase inhibitors. Or, elevated IRAK3 expression may identify patients with myeloid-driven immunosuppression who could benefit from IRAK3-modulating strategies (18). Integration of IRAK-based biomarkers into clinical decision-making could refine therapeutic selection and improve outcomes.

7.8 Future Directions: Advancing IRAK-Targeted Strategies in Multiple Myeloma

A major future direction is identifying biomarkers that predict responsiveness to IRAK inhibition. Candidates include TLR expression patterns, Myddosome composition, IRAK1/IRAK4 phosphorylation states, cytokine-driven loops such as IL-6, BAFF, and APRIL, and myeloid IRAK3 levels. Incorporating these biomarkers into clinical decision-making could guide precise use of IRAK inhibitors and inform combination strategies with proteasome inhibitors, IMiDs, or checkpoint blockade therapies.

Single-cell RNA sequencing, spatial transcriptomics, and proteomic imaging now allow precise mapping of IRAK expression and activation states across diverse marrow compartments. These approaches can identify which stromal, myeloid, and plasma-cell

subsets rely most heavily on IRAK-dependent signaling. They may also reveal micro-niches where IRAK3-mediated immune suppression is strongest, guiding targeted disruption of tolerogenic myeloid populations.

Recent evidence that IRAK3 possesses guanylate cyclase-like activity suggests previously unrecognized layers of regulation. Determining how cGMP production influences NF- κ B dynamics, metabolic adaptation, and macrophage polarization in MM could uncover new therapeutic angles. Structural studies may also clarify whether IRAK3's pseudokinase domain can be modulated indirectly through protein-protein interaction inhibitors or allosteric regulators.

8. Conclusion and final remarks

MM arises within an inflammatory, TLR-responsive bone-marrow niche, where chronic innate-immune signaling fuels malignant plasma-cell survival, therapeutic resistance, and microenvironmental remodeling. Interleukin-1 receptor-associated kinases (IRAKs), which are a family of serine-threonine kinases and pseudokinases, serve as central regulators of MyD88-dependent TLR/IL-1R pathways, positioning them as key determinants of MM biology. IRAK1 and IRAK4 function as catalytic activators of NF- κ B and cytokine production, while IRAK2 and IRAK3 modulate signal duration, immune tolerance, and stromal-myeloid interactions. Dysregulation of these kinases contributes to oncogenic signaling across cancers, but their roles in hematologic malignancies, particularly MM, remain underexplored compared with solid tumors. Emerging evidence highlights a research gap: whereas MyD88 mutations drive constitutive IRAK signaling in lymphomas, MM relies on microenvironment-driven activation despite lacking recurrent MyD88 lesions. This distinction underscores the need to understand how IRAK-dependent pathways integrate intrinsic plasma-cell stress responses with extrinsic cues from stromal cells, macrophages, and cytokine networks. Therapeutically, IRAKs have become compelling targets, with IRAK4 inhibitors, dual IRAK1/4 blockade, IRAK1 degraders, and IRAK3-modulating strategies showing promise in overcoming NF- κ B-driven survival and myeloid-mediated immune suppression.

Given IRAK3's central role in enforcing immune tolerance, strategies that modulate IRAK3 activity in tumor-associated macrophages and dendritic cells may enhance immunotherapy efficacy. Approaches under exploration include epigenetic suppression, which typically involves DNA methylation of the IRAK3 promoter, reduced H3K27 acetylation, or increased H3K27 trimethylation at regulatory regions. All of these decrease IRAK3 transcription. HDAC inhibitors and DNMT inhibitors have been shown to downregulate IRAK3 in macrophages, shifting them toward pro-inflammatory phenotypes of IRAK3, inhibition of its guanylate cyclase-like domain, and reprogramming of IRAK3-high myeloid cells toward pro-inflammatory phenotypes. Combining IRAK3 modulation with immune checkpoint inhibitors most relevant to MM, which include anti-PD-1 (pembrolizumab, nivolumab), anti-PD-L1 (atezolizumab), and anti-CTLA-4 (ipilimumab). These agents aim to restore exhausted T-cell function, but their efficacy in MM is limited by suppressive myeloid cells—

precisely the population regulated by IRAK3 or CAR-T therapy may overcome myeloid-driven resistance mechanisms. MM-directed CAR-T cells are typically engineered to target BCMA, although newer constructs target GPRC5D or FcRH5. Enhancing CAR-T efficacy in IRAK3-high environments may involve adding cytokine-supportive signaling domains (e.g., IL-7/CCL19 secretion), incorporating dominant-negative TGF- β receptors to resist suppression, or engineering CAR-T cells with intrinsic NF- κ B boosters to withstand inhibitory myeloid signals.

Structural insights into IRAK4's ATP-binding pocket and activation loop continue to inform small-molecule design, but future inhibitors may incorporate improved selectivity, dual-targeting of IRAK1/IRAK4, or context-specific modulation of pseudokinase domains. Parallel efforts to target upstream adaptors (MyD88) or downstream ubiquitin scaffolds (TRAF6) may broaden the therapeutic landscape. Longitudinal studies tracking IRAK signaling across disease stages may clarify how inflammatory signaling evolves under therapeutic pressure(1). Understanding whether IRAK-dependent pathways contribute to clonal selection, metabolic rewiring, or resistance to proteasome inhibitors could inform adaptive treatment strategies.

Together, these future directions highlight the growing recognition that IRAK signaling is not merely a downstream inflammatory pathway but a central regulator of MM progression, immune evasion, and therapeutic resistance. Continued integration of structural biology, immunology, and translational research will be essential for realizing the full potential of IRAK-targeted interventions in multiple myeloma.

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