

Review

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Review

ADAM17 as a Central Regulator of the Myeloma Sheddome Linking Immune Evasion, Inflammatory Signaling, and Microenvironmental Remodeling

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Abstract

ADAM17 (a disintegrin and metalloproteinase 17) is increasingly recognized as a central regulator of multiple myeloma (MM) biology beyond its canonical role in TNF- α shedding. Rather than acting as a classical oncogenic driver, ADAM17 functions as a master regulator of ectodomain shedding, controlling the balance between membrane-bound and soluble mediators that shape signaling across the bone marrow microenvironment. Through coordinated processing of cytokines, cytokine receptors, growth factor ligands, and adhesion molecules, ADAM17 amplifies inflammatory signaling, endothelial activation, immune dysfunction, and tumor dissemination. In MM, ADAM17 contributes to key pathogenic processes by modulating the spatial and temporal dynamics of extracellular communication. Shedding of CX3CL1 and adhesion molecules such as JAM-A promotes angiogenesis and vascular niche remodeling, while IL-6R cleavage enables trans-signaling that sustains stromal activation, chronic inflammation, and malignant plasma cell survival. In parallel, ADAM17-dependent processing of immune receptors, including CD62L, alters lymphocyte trafficking and immune surveillance, contributing to an immunologically permissive niche. Proteolytic remodeling of adhesion systems may also facilitate niche escape and extramedullary dissemination. These coordinated shedding events define a dynamic myeloma “sheddom,” in which ADAM17 acts as a systems-level node integrating tumor, stromal, endothelial, and immune signals. This framework helps explain the context-dependent and pleiotropic effects of ADAM17 throughout disease evolution. Clinically, circulating ADAM17 shows promise as a dynamic biomarker reflecting tumor burden, microenvironmental activation, and immune dysfunction. However, therapeutic targeting remains challenging because of substrate redundancy, systemic functions, and the risk of disrupting physiological immune regulation. Future strategies will require selective and context-aware modulation of ADAM17-driven shedding networks to effectively reprogram the myeloma microenvironment.

Keywords: ADAM17; multiple myeloma; tumor microenvironment

Introduction

ADAM17 was initially identified as the protease responsible for the release of soluble TNF- α , but this original definition no longer captures the full biological breadth of the enzyme.^{1,2} Beyond TNF- α processing, ADAM17 regulates ectodomain shedding across multiple substrate classes, including cytokines, cytokine receptors, growth factor ligands, and adhesion molecules, thereby

controlling how signals are generated, spatially distributed, and perceived within tissues.² As proposed by Scheller and colleagues, ADAM17 functions as a molecular switch of inflammation and tissue regeneration because shedding can simultaneously terminate membrane-confined signaling while generating soluble mediators with paracrine activity.³ This systems-level perspective is particularly relevant in cancer, where the biological output of ADAM17 depends less on individual substrates than on the composite extracellular signaling state generated by coordinated shedding events.³

This framework is especially pertinent in multiple myeloma (MM), a disease in which malignant plasma cells are tightly dependent on the bone marrow microenvironment.⁴ Myeloma progression is sustained not only by tumor-intrinsic programs, but also by reciprocal interactions with endothelial cells, stromal cells, osteolineage populations, inflammatory myeloid cells, and dysfunctional lymphoid effectors.⁵ In this context, the pathogenic relevance of ADAM proteases is increasingly linked to extracellular matrix remodeling, cytokine release, and microenvironmental support rather than to classical mutation-driven oncogenic mechanisms.^{6,7}

Within this landscape, ADAM17 is best understood as a regulator of the soluble signaling interface connecting tumor cells to their niche. A paradigmatic MM-specific example is the CX3CL1/fractalkine axis: bone marrow CX3CL1 levels are increased in active MM, correlate with microvessel density, and promote angiogenesis, while its release from endothelial cells depends on ADAM10/17-mediated cleavage in response to tumor-associated inflammatory cues.^{8,9} Similarly, ADAM17-mediated shedding of IL-6R enables IL-6 trans-signaling, expanding inflammatory and trophic signaling beyond IL-6R-expressing cells and reinforcing stromal and endothelial activation.^{10,11}

The immune and adhesive dimensions further strengthen this model. As the main sheddase for CD62L/L-selectin, ADAM17 regulates immune-cell trafficking and activation thresholds, and elevated ADAM17 in MM has been associated with reduced CD62L expression on marrow T-cell subsets and altered immune infiltration patterns.^{12,13} In parallel, ADAM17 substrates include adhesion molecules such as JAM-A/F11R, whose cleavage may shift them from membrane-bound regulators of cell contact to soluble effectors with distinct signaling functions. This is particularly relevant in MM, where JAM-A has already been implicated in endothelial activation, angiogenesis, and disease progression.^{8,9,14-17}

Overall, current evidence supports a model in which ADAM17 does not act as a classical oncogenic driver, but as a network orchestrator of the myeloma microenvironment. By regulating the balance between membrane-bound and soluble mediators, ADAM17 reshapes the spatial range, intensity, and cellular ownership of signaling across tumor, stromal, endothelial, and immune compartments, thereby contributing to disease progression.

Microenvironmental dependency and proteolytic control

The transition from MGUS to overt multiple myeloma (MM) is increasingly recognized as a multicellular evolutionary process driven by progressive reprogramming of the bone marrow ecosystem rather than by plasma cell-intrinsic changes alone.¹⁸ Endothelial and mesenchymal stromal cells are key players in this evolution, acquiring pro-tumorigenic features including enhanced angiogenesis, inflammatory cytokine production, and permissive extracellular matrix remodeling.¹⁹⁻²¹ These changes actively contribute to clonal expansion, immune escape, and dissemination.^{22,23}

This shift toward a tumor-supportive niche highlights the importance of regulatory mechanisms beyond transcriptional control. Among these, proteolytic remodeling of the cell surface and extracellular space has emerged as a critical determinant of disease progression.²⁴⁻²⁶ Several ADAM metalloproteinases, including ADAM8, ADAM9, and ADAM15, have been implicated in MM through effects on proliferation, extracellular matrix interaction, and clinical outcome.⁶ However, their effects are generally linked to localized signaling events such as adhesion turnover or receptor activation.^{27,28}

ADAM17 occupies a distinct position within this network as a master regulator of ectodomain shedding rather than a direct intracellular signaling effector.^{29,30} By controlling the release of cytokines, cytokine receptors, growth factor ligands, and adhesion molecules, ADAM17 regulates the balance between membrane-bound and soluble signaling states.³¹ This is mechanistically important because shedding expands the spatial reach of local signals, allowing endothelial activation or stromal inflammation to propagate across the niche.³² This role becomes particularly relevant during disease progression, when endothelial and stromal compartments adopt inflammatory and pro-angiogenic phenotypes increasingly sustained by soluble mediators.^{33,34} In this setting, ADAM17-dependent shedding links niche reprogramming to functional output by amplifying inflammatory loops and weakening adhesion-dependent retention.^{3,35} This framework helps explain why ADAM17, despite limited evidence as a classical oncogenic driver, remains consistently associated with MM progression).¹⁷ Rather than initiating transformation, ADAM17 acts as a context-dependent amplifier of stromal, endothelial, and immune signals, placing it at the intersection of angiogenesis, chronic inflammation, and loss of niche dependency.^{3,36}

Angiogenesis: a prototypical ADAM17-driven circuit

Angiogenesis is one of the clearest processes linking ADAM17 to multiple myeloma (MM), as bone marrow vascular remodeling is tightly coupled to inflammation and endothelial activation during disease progression. A paradigmatic example is the CX3CL1/fractalkine axis, which illustrates how tumor-derived inflammatory cues are translated into pro-angiogenic endothelial outputs through proteolytic shedding.⁸

CX3CL1 exists as both a membrane-bound adhesion molecule and a soluble chemokine generated through ADAM10/17-mediated cleavage. In MM, bone marrow CX3CL1 levels are increased and correlate with microvessel density, supporting its functional relevance in disease-associated angiogenesis.^{8,9} Importantly, malignant plasma cells are not the main source of CX3CL1; rather, they induce its endothelial expression and release through inflammatory mediators such as TNF- α .³⁷⁻³⁹ This positions ADAM17 as a key amplifier of endothelial inflammatory signaling rather than a direct initiator of angiogenesis.¹³

This model is reinforced by the role of JAM-A in MM.¹⁶ Endothelial JAM-A is upregulated in active disease, correlates with poor outcome, and contributes to angiogenesis, microenvironmental remodeling, and tumor growth.^{40,41} As a dynamic regulator of endothelial permeability and migration, JAM-A can also undergo ADAM17-mediated cleavage, generating soluble fragments with biological activity.^{14,42,43}

Together, these findings support a model in which ADAM17 coordinates endothelial surface remodeling by coupling chemokine release with adhesion reprogramming.^{44,45} The result is a qualitatively altered vascular niche characterized by enhanced permeability, aberrant signaling, and sustained tumor-endothelial cross-talk, thereby contributing to a pro-angiogenic sheddome that supports MM progression.⁴⁶⁻⁵²

Inflammatory amplification and IL-6 trans-signaling

The IL-6 axis is a central signaling dependency in multiple myeloma (MM), sustaining not only malignant plasma cell survival but also the inflammatory architecture of the bone marrow niche.⁵³ Because IL-6 is produced mainly by stromal and accessory cells, its biological impact depends largely on receptor availability and signaling range).⁵⁴

In this context, ADAM17 occupies a pivotal regulatory position through its role in IL-6 receptor (IL-6R) shedding. As one of the principal sheddases of membrane-bound IL-6R, ADAM17 generates soluble IL-6R (sIL-6R), thereby enabling IL-6 trans-signaling.⁵⁵ This mechanism fundamentally expands the spatial reach of IL-6: instead of remaining restricted to IL-6R-expressing cells, IL-6/sIL-6R complexes can activate gp130-positive stromal, endothelial, and immune cells throughout the niche.^{56,57}

In MM, this converts IL-6 signaling from a localized trophic cue into a distributed microenvironmental circuit that reinforces tumor survival, stromal activation, endothelial remodeling, and chronic inflammation.^{58,59} Importantly, IL-6R shedding is dynamic: inflammatory

stimuli and cellular stress enhance ADAM17 activity, increasing sIL-6R release and creating a feed-forward loop in which inflammation amplifies its own signaling network.^{55,60}

From a systems perspective, ADAM17 determines not simply the intensity but the range and persistence of IL-6 signaling within the marrow.⁶¹⁻⁶³ This helps explain why IL-6 remains central to MM despite limited tumor-intrinsic alterations in the pathway: disease dependency may be sustained, at least in part, by proteolytic mechanisms that expand and stabilize inflammatory signaling.⁶⁴⁻⁶⁷ Beyond direct effects on myeloma cells, ADAM17-mediated IL-6 trans-signaling also shapes immune responses and endothelial activation, reinforcing its broader role as an orchestrator of the MM microenvironment.⁶⁸

Immune dysfunction: a context-dependent role

Immune dysfunction is a hallmark of MM, characterized by progressive impairment of both innate and adaptive immunity, including NK-cell exhaustion, T-cell dysfunction, and defective immune surveillance.^{13,65,66} In this context, ADAM17 intersects with immune regulation primarily through ectodomain shedding of key surface receptors.

A paradigmatic substrate is CD62L/L-selectin, which is essential for lymphocyte homing and immune surveillance. ADAM17-mediated cleavage reduces CD62L surface expression and alters trafficking patterns, thereby reshaping T-cell localization and activation dynamics.^{69,70} Clinically, elevated circulating ADAM17 has been associated with reduced CD62L expression on marrow T cells and altered immune infiltration patterns, supporting a role for ADAM17 in remodeling the immune landscape rather than directly suppressing effector cells.^{69,71,72}

However, the role of ADAM17 in MM immunity is not unidirectional. Beyond excessive shedding, physiological ADAM17 activity is also required for receptor turnover and dynamic regulation of immune activation, including NK-cell ligand processing and co-stimulatory pathways.^{66,73} In this sense, both excessive and insufficient shedding may be detrimental: hyperactivation of ADAM17 can promote immune evasion through receptor loss, whereas inadequate shedding may impair receptor turnover, favoring chronic stimulation and functional exhaustion.^{74,75}

Taken together, these observations support a model in which ADAM17 acts as a regulator of immune receptor homeostasis rather than as a simple suppressor of anti-tumor immunity. In MM, perturbations in this balance may contribute to the establishment of an immunologically permissive niche, with important therapeutic implications for strategies aimed at modulating ADAM17 activity.⁷⁴⁻⁷⁶

ADAM17 in adhesion remodeling, dissemination, and biomarker potential

Extramedullary dissemination marks a critical transition in MM, reflecting not only greater aggressiveness and treatment resistance but also a profound reprogramming of tumor-microenvironment interactions.^{62,77} This process depends on disruption of adhesion systems that normally anchor myeloma cells within the bone marrow niche and provide survival and drug-resistance signals.⁷⁸⁻⁸¹

In this context, JAM-A is a particularly relevant substrate. Beyond its structural role at intercellular junctions, JAM-A functions as a signaling scaffold regulating polarity, migration, and tumor-microenvironment interactions, and can undergo proteolytic cleavage into soluble fragments with pro-migratory activity.^{16,82-86} Disruption of JAM-A-integrin-tetraspanin signaling complexes enhances cytoskeletal dynamics and motility, providing a plausible mechanism for niche escape and dissemination.⁸⁷⁻⁸⁹ This is consistent with proteomic data showing that extramedullary MM is associated with circulating signatures enriched for adhesion-related proteins and soluble mediators, supporting a shift from adhesion-dependent retention to circulation-compatible programs.⁶⁷ Together, these findings suggest that ADAM17-dependent adhesion remodeling may facilitate dissemination by weakening niche retention while promoting invasive signaling.⁹⁰

This same systems-level role makes ADAM17 an attractive dynamic biomarker. Recent longitudinal data show that circulating ADAM17 levels increase across disease stages and correlate with clinical burden and organ involvement, including renal dysfunction.^{91,92} Unlike conventional

static biomarkers, ADAM17 may capture the integrated state of tumor burden, microenvironmental activation, and immune dysfunction.^{17,43,93} Given its central role in regulating cytokine, receptor, and adhesion shedding, circulating ADAM17 may provide a real-time readout of extracellular signaling dynamics, with potential value for disease monitoring and early detection of progression, although current evidence remains limited by small cohorts and assay variability.⁹⁴⁻⁹⁸

A unifying model: the myeloma “sheddome”

Current evidence supports a shift from a pathway-centric view of ADAM17 toward a systems-level model in which its pathogenic relevance lies in coordinating extracellular signaling across the myeloma microenvironment.⁹⁹ Ectodomain shedding is not merely degradative: by simultaneously reducing membrane-bound receptor availability and generating soluble ligands or receptor fragments, ADAM17 reshapes the spatial range and duration of signaling within the bone marrow niche.¹⁰⁰

In multiple myeloma, this is reflected in the coordinated release of mediators that regulate angiogenesis, inflammation, immune function, and adhesion. CX3CL1 shedding amplifies vascular remodeling, IL-6R cleavage expands inflammatory trans-signaling, and CD62L processing alters immune-cell trafficking and activation.¹⁰¹ In parallel, proteolytic processing of adhesion molecules such as JAM-A couples niche detachment with migratory and invasive signaling, consistent with the context-dependent role of tight junction proteins in cancer progression.^{93,102}

These processes define a dynamic myeloma “sheddome”: a continuously evolving extracellular signaling state determined by the balance between membrane-bound and soluble cytokines, receptors, and adhesion molecules.^{10,94} In this framework, ADAM17 acts as a central regulatory node that converts localized microenvironmental cues into distributed signaling circuits spanning tumor, stromal, endothelial, and immune compartments, thereby sustaining progression, immune escape, and dissemination (Figure 1).¹⁰³⁻¹⁰⁵

This perspective has important therapeutic implications: the relevance of ADAM17 lies less in individual substrates than in its role as an architect of the extracellular signaling network that sustains disease, suggesting that effective targeting will require modulation of the broader sheddome rather than single pathways.^{106,107}

Therapeutic implications and challenges

Despite its biological relevance, therapeutic targeting of ADAM17 remains challenging because of its broad substrate repertoire, systemic functions, and context-dependent effects across the myeloma niche.^{3,31,104} While ADAM17 promotes tumor-supportive programs in plasma cells, stromal cells, and endothelial compartments, it also contributes to immune receptor turnover and physiological immune regulation, making systemic inhibition potentially detrimental.

This challenge is compounded by substrate overlap within the ADAM family, particularly with ADAM10, which shares multiple cytokine, adhesion, and immune substrates and may compensate for ADAM17 inhibition. This redundancy likely contributes to the limited success of early broad-spectrum metalloproteinase inhibitors and highlights that shedding is regulated by a coordinated proteolytic network rather than a single enzyme.^{29,108}

Future strategies will therefore require more selective and systems-oriented approaches. Rather than global blockade, targeting specific pathogenic shedding events, such as IL-6 trans-signaling or endothelial activation, or modulating ADAM17 activity in stromal and vascular niches while sparing immune compartments may offer a better therapeutic window.¹⁰⁹ ADAM17-directed therapies will likely be most effective in combination settings. By reshaping the extracellular signaling milieu, ADAM17 modulation could enhance both immunotherapeutic and anti-angiogenic strategies, supporting a broader effort to reprogram the microenvironmental circuitry that sustains myeloma progression.^{103,110}

Concluding Perspective

ADAM17 occupies a distinctive position in multiple myeloma biology that is not adequately captured by conventional oncogenic models. Its pathogenic relevance lies less in tumor-intrinsic

genetic alterations than in its ability to regulate the conversion of membrane-bound signals into diffusible mediators, thereby reshaping communication across the tumor microenvironment.^{10,104}

In MM, ADAM17 acts at the interface of malignant plasma cells, stromal cells, endothelial compartments, and immune populations by controlling the shedding of cytokines, receptors, adhesion molecules, and growth factor ligands. Through this function, it regulates not only signal availability but also spatial range, cellular reach, and persistence, thereby influencing angiogenesis, inflammation, immune dysfunction, and dissemination.^{6-8,13} This systems-level role helps explain the context-dependent and often paradoxical effects of ADAM17 in MM.³¹

The key challenge moving forward is not simply to validate ADAM17 as a biomarker or therapeutic target, but to define how its proteolytic activity shapes disease evolution over time, from MGUS progression to drug resistance and extramedullary spread. In this light, ADAM17 should be viewed less as an isolated molecule than as a conceptual framework for understanding MM as a dynamically regulated multicellular ecosystem. Dissecting and ultimately modulating this proteolytic layer may be essential to develop more effective microenvironment-directed therapies.

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