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Cytokine-driven crosstalk; the role of IL-6, TNF- α , and NF- κ B signaling in bridging type 2 diabetes mellitus and multiple myeloma pathogenesis

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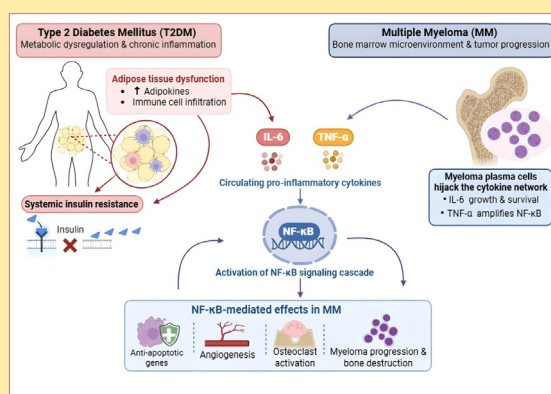
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ABSTRACT

Type 2 diabetes mellitus (T2DM) and multiple myeloma increasingly share a pathophysiological intersection mediated by chronic, low-grade inflammation. Recent epidemiological evidence suggested that patients with T2DM exhibit an elevated risk of developing multiple myeloma, underscoring the clinical relevance of this molecular interplay. This review considers the cytokine-driven crosstalk wherein interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and nuclear factor-kappa B (NF- κ B) signaling bridge the pathogenesis of both diseases. In T2DM, adipose tissue dysfunction and systemic insulin resistance drive the persistent secretion of pro-inflammatory cytokines, notably IL-6 and TNF- α . These circulating mediators systematically activate the NF- κ B transcriptional cascade, establishing a pervasive inflammatory state. In the context of multiple myeloma, this altered systemic milieu profoundly impacts the bone marrow microenvironment. Malignant plasma cells hijack this cytokine network; where, IL-6 acts as a principal autocrine and paracrine growth and survival factor, since TNF- α synergistically amplifies NF- κ B activation. This sustained NF- κ B signaling upregulates anti-apoptotic genes, promotes angiogenesis, and stimulates osteoclast activity, thereby driving myeloma progression and characteristic bone destruction. Consequently, the NF- κ B pathway serves as a critical molecular bridge, translating the metabolic inflammation of T2DM into a permissive, tumor-promoting niche that accelerates multiple myeloma initiation, exacerbates disease course, and fosters therapeutic resistance. The synergistic crosstalk between metabolic dysregulation and hematologic malignancy demonstrates a vicious cycle where diabetic inflammation fuels myeloma pathogenesis, and tumor-derived factors further worsen metabolic homeostasis. Hence, dissecting this IL-6, TNF- α , and NF- κ B axis reveals compelling dual-purpose therapeutic opportunities. Targeting these shared inflammatory pathways may simultaneously mitigate diabetic complications and dismantle the cytokine scaffolding that sustains multiple myeloma, offering a novel paradigm for managing patients with this complex comorbid presentation.



Introduction

The escalating global prevalence of both type 2 diabetes mellitus (T2DM) and multiple myeloma represents an important and growing challenge to modern

healthcare systems, prompting a critical reevaluation of the pathophysiological boundaries between metabolic disorders and hematologic malignancies (1,2). Historically viewed as distinct clinical entities affecting

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Implication for health policy/practice/research/medical education:

The chronic inflammatory milieu of type 2 diabetes mellitus (T2DM) creates a fertile microenvironment that accelerates multiple myeloma pathogenesis through cytokine-driven crosstalk. Central to this synergy are interleukin-6 (IL-6) and TNF- α (TNF- α), which are persistently elevated in T2DM. These cytokines exacerbate systemic insulin resistance while simultaneously hyperactivating the nuclear factor kappa B (NF- κ B) signaling pathway. In multiple myeloma, this hyperactivated NF- κ B cascade acts as a critical molecular bridge, driving malignant plasma cell proliferation, enhancing survival, and conferring apoptosis resistance. Consequently, systemic IL-6 and TNF- α overproduction continuously stimulates the bone marrow microenvironment, fostering a highly pro-tumorigenic niche. This crosstalk implies that the metabolic dysregulation of T2DM directly fuels the oncogenic signaling networks of multiple myeloma. Meanwhile, this shared inflammatory architecture highlights the potential of targeting the IL-6/TNF- α /NF- κ B axis to therapeutically interrupt the pathogenic bridge between these two comorbid conditions.

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different organ systems, emerging epidemiological and molecular evidence strongly suggests that their co-occurrence is not merely a coincidental byproduct of an aging population, but rather, this condition is the result of profound, bidirectional pathophysiological crosstalk (2,3). At the heart of this intersection lies a shared landscape of chronic, low-grade inflammation, often termed metaflammation, which serves as a fertile ground for both metabolic dysregulation and malignant transformation (3). Central to this inflammatory nexus are specific pro-inflammatory cytokines, most notably interleukin-6 and tumor necrosis factor-alpha (TNF- α), along with the ubiquitous transcription factor nuclear factor-kappa B (NF- κ B), which collectively form a molecular bridge linking the pathogenesis of T2DM to the initiation, progression, and therapeutic resistance of multiple myeloma (4,5). Identification of cytokine-driven crosstalk is no longer just an academic exercise; while, it is a clinical imperative for detecting the overlapping toxicities, altered disease characteristics, and potential shared therapeutic vulnerabilities in patients burdened by both conditions (1). This review explores the role of IL-6, TNF- α , and NF- κ B signaling in bridging T2DM and multiple myeloma pathogenesis.

Method of the search

For this narrative review, we performed a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. The search strategy employed a variety of relevant keywords, such as; T2DM, multiple myeloma, metaflammation, adipokines, oxidative stress, renal insufficiency, cast nephropathy, myeloma cells and adipose tissue.

Diabetic bone marrow microenvironment

To find the molecular bridging of T2DM and multiple myeloma, we should first examine the foundational role of adipose tissue dysfunction in T2DM (6). In the state of

caloric excess and obesity, adipose tissue undergoes significant hypertrophy and hyperplasia, eventually outstripping its vascular supply and leading to localized hypoxia and cellular stress (7). This stressed adipose tissue undergoes a phenotypic shift, transitioning from a benign energy-storage depot into a highly active endocrine organ that secretes a plethora of pro-inflammatory mediators, collectively known as adipokines (8,9). Among these, TNF- α and interleukin-6 are released in substantial quantities, primarily by infiltrating M1-polarized macrophages and stressed adipocytes themselves (7). This chronic, systemic release of cytokines establishes a state of metaflammation that directly antagonizes insulin signaling (10). In skeletal muscle, liver, and adipose tissue, TNF- α activates intracellular stress kinases, such as c-Jun N-terminal kinase and inhibitor kappa B kinase β (IKK β) (11). These kinases phosphorylate insulin receptor substrate-1 on specific serine residues, a modification that sterically hinders its interaction with the insulin receptor and targets it for proteasomal degradation (12,13). Consequently, the canonical phosphatidylinositol 3-kinase and Akt signaling cascade is blunted, preventing the translocation of glucose transporter type 4 to the cell membrane and resulting in the hallmark insulin resistance of T2DM (14). Concurrently, interleukin-6 exacerbates this metabolic derailment by binding to its receptor complex, which includes the membrane-bound or soluble interleukin-6 receptor and the ubiquitous signal-transducing component glycoprotein 130 (15). This binding activates the Janus kinase and signal transducer and activator of transcription 3 pathway (16). Persistent activation of this pathway in metabolic tissues induces the expression of suppressor of cytokine signaling 3, a potent negative feedback regulator that binds to the insulin receptor substrate, promoting its ubiquitination and subsequent degradation, thereby further cementing the state of insulin resistance and hyperinsulinemia (17). Although this cytokine milieu is devastating to systemic metabolic homeostasis, its impact does not remain

confined to peripheral metabolic tissues; while, it inevitably spills over into the bone marrow microenvironment, fundamentally altering the niche in which plasma cells reside and function (18,19). In the context of multiple myeloma, interleukin-6 is universally recognized as the paramount survival, proliferation, and drug-resistance factor for malignant plasma cells (20). Under normal physiological conditions, interleukin-6 is produced in the bone marrow by stromal cells, osteoblasts, and immune cells to support the terminal differentiation of B cells into antibody-secreting plasma cells (21). However, in multiple myeloma, this regulatory mechanism is hijacked. Malignant plasma cells not only become exquisitely dependent on exogenous interleukin-6 provided by the bone marrow stroma, but they also frequently acquire the ability to produce interleukin-6 in an autocrine fashion (22). When the systemic hyperinsulinemia and elevated cytokine levels which is characteristic of T2DM penetrate the bone marrow, they act as a potent catalyst for this malignant process (23). The diabetic bone marrow microenvironment is already primed with elevated levels of interleukin-6 due to systemic spillover, effectively lowering the threshold required for malignant plasma cell proliferation (21). Furthermore, the binding of interleukin-6 to its receptor on myeloma cells robustly activates the Janus kinase and signal transducer and activator of transcription 3 pathway, which in turn upregulates the transcription of anti-apoptotic proteins such as B-cell lymphoma 2 and myeloid cell leukemia 1, while simultaneously driving cell cycle progression through the upregulation of cyclin D1 (24,25). This condition creates a vicious, self-perpetuating cycle; since, the diabetic state provides an abundance of interleukin-6 that fuels myeloma growth, and the expanding clone of malignant plasma cells, along with the reactive bone marrow stroma, secretes even more interleukin-6, which spills back into the systemic circulation, further exacerbating peripheral insulin resistance and worsening glycemic control (26). Parallel to the actions of interleukin-6, TNF- α plays an equally critical, albeit distinct, role in bridging the pathogenesis of these two conditions (19). In the diabetic milieu, as previously established, TNF- α is a primary driver of insulin resistance (27). However, its significance in multiple myeloma lies in its unparalleled ability to activate the NF- κ B signaling pathway, which is a cornerstone of myeloma pathogenesis (1,28). It has been detected that, TNF- α binds to its cognate receptors, TNFR1 and TNFR2, on the surface of bone marrow stromal cells and malignant plasma cells (29). This binding triggers the recruitment of adaptor proteins, leading to the activation of the inhibitor of kappa B kinase complex (4). This complex subsequently phosphorylates the inhibitory

protein I κ B α , marking it for ubiquitination and proteasomal degradation (30). The degradation of I κ B α liberates the NF- κ B heterodimer, typically composed of p50 and p65 subunits, allowing it to translocate into the nucleus (31). Once in the nucleus, NF- κ B acts as a master transcriptional regulator, driving the expression of a vast array of genes involved in cell survival, proliferation, angiogenesis, and inflammation (30). In multiple myeloma, constitutive or hyper-inducible NF- κ B activation is a hallmark of the disease, protecting malignant cells from apoptosis induced by physiological stress or chemotherapeutic agents (32). When T2DM is present, the chronic elevation of TNF- α ensures that the NF- κ B pathway in the bone marrow is in a state of persistent, low-grade activation (33). This pre-activation primes the bone marrow stromal cells to be hyper-responsive to additional oncogenic stimuli, facilitating the survival of early clonal plasma cell populations, such as those seen in monoclonal gammopathy of undetermined significance, and accelerating their progression to overt, symptomatic multiple myeloma (26). Importantly, the convergence of interleukin-6, TNF- α , and NF- κ B signaling does not occur in a vacuum; it is profoundly amplified by the unique biochemical abnormalities inherent to poorly controlled T2DM, particularly chronic hyperglycemia and the accumulation of advanced glycation end-products (34). Advanced glycation end-products are formed through the non-enzymatic glycation and oxidation of proteins and lipids in the presence of sustained high glucose levels (35). These modified molecules accumulate in various tissues, including the bone marrow, where they bind to the receptor for advanced glycation end-products, a multi-ligand receptor expressed on macrophages, endothelial cells, and bone marrow stromal cells (36). The binding of advanced glycation end-products to their receptor potently activates the NF- κ B pathway (35). This state creates a synergistic, feed-forward inflammatory loop within the bone marrow microenvironment (1). The hyperglycemic, advanced glycation end-product-rich environment of the diabetic patient continuously stimulates NF- κ B by the receptor for advanced glycation end-products, while simultaneously, the elevated levels of TNF- α and interleukin-6 provide redundant, parallel activation signals for the same transcription factor (1). This compounded NF- κ B activation leads to a massive upregulation of downstream pro-inflammatory cytokines, chemokines, and adhesion molecules within the bone marrow (37, 38). Consequently, the bone marrow stroma becomes highly adhesive and supportive of myeloma cell homing and retention, while simultaneously secreting high levels of vascular endothelial growth factor, which promotes the pathological angiogenesis characteristic of progressive multiple myeloma (1,38). Furthermore, this

intense local inflammation generates significant oxidative stress, leading to DNA damage in resident hematopoietic cells, which may increase the mutational burden and accelerate the genomic instability that drives myeloma evolution (39).

Challenges in the managements of patients with both diseases

This intricate molecular crosstalk inevitably manifests in the clinical setting, presenting unique challenges in the management of patients who suffer from both T2DM and multiple myeloma (6). The overlapping pathophysiological mechanisms translate directly into overlapping clinical toxicities, complicating both diagnosis and treatment (26). Meanwhile, both conditions independently predispose patients to peripheral neuropathy and renal insufficiency (3). In multiple myeloma, renal damage is frequently driven by the filtration of toxic monoclonal free light chains, leading to cast nephropathy, or by the deposition of amyloid fibrils (40). In T2DM, renal damage is driven by advanced glycation end-product accumulation, glomerular hyperfiltration, and diabetic nephropathy (41). When these conditions coexist, the cytokine-driven inflammation, particularly mediated by TNF- α and NF- κ B, exacerbates endothelial dysfunction and podocyte injury in the kidney, accelerating the decline of renal function far more rapidly than either disease would alone (42). Similarly, diabetic peripheral neuropathy, driven by microvascular ischemia and direct glucose toxicity to nerves, is complicated by the neurotoxic effects of myeloma-directed therapies, such as proteasome inhibitors, leading to severe, dose-limiting neuropathic pain that drastically reduces the patient's quality of life (43-46). Furthermore, the cytokine milieu of the diabetic patient may directly alter the pharmacokinetics and pharmacodynamics of myeloma therapies (6). Recent studies found that, immunomodulatory drugs, such as lenalidomide, exert their anti-myeloma effects partly by modulating the bone marrow microenvironment, including the downregulation of pro-inflammatory cytokines like interleukin-6 and TNF- α (47). However, in a patient with profound, systemic metaflammation driven by obesity and type 2 diabetes, the baseline levels of these cytokines may be overwhelmingly high that the modulatory capacity of the drug is blunted, potentially contributing to the primary or acquired resistance to these therapies observed in some diabetic myeloma patients (48).

Therapeutic intervention modalities

Recognizing that T2DM and multiple myeloma are linked by shared cytokine-driven pathways opens up compelling new lines for therapeutic intervention and disease

management (6). The traditional approach to treating these conditions, where an endocrinologist manages the diabetes and a hematologist manages the myeloma, with little cross-communication regarding underlying molecular mechanisms is increasingly recognized as suboptimal (1). Instead, there is a strong rationale for the development of integrated, mechanism-based therapeutic strategies that target the shared inflammatory nodes (1). Similarly, the administration of targeted anti-inflammatory agents could theoretically provide dual benefits (49). While the use of broad TNF- α inhibitors has shown mixed results in hematologic malignancies and carries infection risks, more precise targeting of the interleukin-6 pathway, such as with monoclonal antibodies against the interleukin-6 receptor has shown promise in reducing systemic inflammation and improving insulin sensitivity in metabolic disorders, while simultaneously depriving myeloma cells of a critical survival signal (50, 51). Correspondingly, the development of novel, highly specific inhibitors of the NF- κ B pathway, or downstream effectors like the Janus kinase and signal transducer and activator of transcription 3 pathway, represents a frontier in myeloma therapy that could simultaneously mitigate the metabolic consequences of chronic inflammation (52,53). Beyond pharmacological interventions, lifestyle modifications aimed at reducing adipose tissue mass and improving metabolic control, such as structured dietary interventions and physical activity, should be viewed not merely as supportive care for diabetes, but also should be regarded as an active, disease-modifying anti-myeloma strategies (8). By reducing the volume of inflamed adipose tissue, these interventions directly decrease the systemic production of TNF- α and interleukin-6, thereby starving the bone marrow microenvironment of the cytokine fuel that drives myeloma progression (54). Moreover, the concept of metabolic-oncologic co-management necessitates a shift in clinical trial design and biomarker discovery (18). Future clinical trials evaluating novel myeloma therapies should mandate the stratification of patients based on their metabolic status, including body mass index, hemoglobin A1c levels, and baseline inflammatory markers such as high-sensitivity C-reactive protein or serum interleukin-6 levels (55,56). This modality would allow researchers to determine whether the efficacy of a given myeloma drug is contingent upon the patient's underlying inflammatory and metabolic state (56). Conversely, trials investigating new anti-diabetic agents, particularly those with pleiotropic anti-inflammatory effects, such as sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonists, should carefully monitor hematologic parameters and markers of plasma cell dyscrasia (57,58). There is emerging preclinical evidence that glucagon-like peptide-1 receptor agonists, beyond

their glucose-lowering and weight-loss effects, possess direct anti-inflammatory properties that can suppress NF- κ B activation and reduce the secretion of interleukin-6 and TNF- α from macrophages (59,60). If these effects translate to the bone marrow microenvironment, these widely used diabetic medications could inadvertently provide a protective effect against the progression of monoclonal gammopathy of undetermined significance to multiple myeloma, representing a paradigm-shifting opportunity for chemoprevention (61,62).

Conclusion

This narrative review concluded that, the association between T2DM and multiple myeloma is firmly rooted in a complex, bidirectional, and cytokine-driven crosstalk that fundamentally bridges metabolic dysfunction and hematologic malignancy. The chronic, low-grade inflammation characteristic of type 2 diabetes, driven predominantly by the relentless secretion of interleukin-6 and tumor necrosis-alpha from dysfunctional adipose tissue, which does not remain localized. It systemically permeates the bone marrow microenvironment, where it synergizes with local factors, such as advanced glycation end-products, to hyperactivate the NF- κ B and Janus kinase/signal transducer and activator of transcription 3 signaling pathways. This molecular convergence creates a highly permissive, pro-survival niche that accelerates the proliferation of malignant plasma cells, fosters genomic instability, and promotes resistance to conventional therapies. The clinical manifestations of this crosstalk are evident in the exacerbated overlapping toxicities, particularly nephropathy and neuropathy, and the potential for altered therapeutic responses. Moving forward, dismantling the artificial boundary between metabolic and oncologic care is necessary. By targeting these shared inflammatory pathways through repurposed anti-cytokine therapies, novel signaling inhibitors, and aggressive metabolic optimization, the disruption of this vicious cycle will be hopeful, which finally improve survival outcomes and quality of life for the growing population of patients navigating the dual burden of T2DM and multiple myeloma.

Authors' contribution

Conceptualization: Maryam Aghabozorgi, Ahmadreza Maghsoudi.

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Writing—review & editing: Maryam Aghabozorgi, Seyyed Hamidreza Motafakeran.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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