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ROLE OF METABOLIC ALTERATIONS IN THE MARROW MICROENVIRONMENT IN THE RESPONSE TO IMMUNOTHERAPY IN MULTIPLE MYELOMA

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Multiple myeloma (MM) relies on a profound metabolic dependency on the bone marrow niche, which supplies bioenergetic and redox support to malignant plasma cells while shaping immune surveillance and therapeutic responsiveness. Within this environment, myeloma cells progressively impose nutrient competition, altered metabolite availability, and chronic metabolic stress. These adaptations promote disease persistence but undermine immune cell metabolic fitness, providing a mechanistic explanation for the heterogeneous depth and durability of immunotherapeutic responses in MM. A key driver of this remodeling is dysregulated nicotinamide adenine dinucleotide (NAD^+) metabolism. Myeloma cells reprogram NAD^+ homeostasis by increasing consumption and preferentially exploiting extracellular precursors. Among the enzymes involved, CD38 functions as a dominant metabolic regulator. Its aberrant expression establishes CD38 as a major NAD^+ sink, depleting intracellular NAD^+ pools and degrading extracellular precursors. This tumor-centered NAD^+ consumption supports plasma cell survival and stress adaptation, while imposing metabolic constraints on surrounding non-malignant cells. Disruption of NAD^+ precursor availability further exacerbates this asymmetry. Nicotinamide (NAM), nicotinic acid (NA), nicotinamide riboside (NR), and nicotinamide mononucleotide (NMN) represent a shared and limited resource within the niche. Their dysregulated utilization and extracellular degradation contribute to a compartmentalized NAD^+-depleted state, disproportionately affecting immune effector cells that require sustained metabolic support to maintain function, persistence, and cytotoxic capacity. In line with this model, our previous work demonstrated that pharmacological modulation of NAD^+ biosynthesis directly alters the activity and efficacy of anti-MM therapies, establishing a causal link between NAD^+ metabolic state and therapeutic response. As a consequence of tumor-driven NAD^+ depletion, immune cells operate under chronic metabolic stress, compromising mitochondrial function, redox balance, and the metabolic programs required for sustained activation. Immune dysfunction therefore arises not solely from impaired antigen recognition or inhibitory signaling, but from a tumor-imposed metabolic limitation that constrains immune fitness at a fundamental level. In parallel, altered NAD^+ metabolism reshapes stromal and myeloid compartments, fostering immunosuppressive niches that further restrict effective immune surveillance. Collectively, these tumor-intrinsic and tumor-extrinsic mechanisms converge on a unified model in which NAD^+ dependency within the bone marrow niche acts as an upstream determinant of microenvironmental dysfunction and immunotherapy resistance in MM. Targeting this metabolic axis thus represents a rational, mechanism-based strategy to restore immune fitness and enhance the depth and durability of immunotherapeutic responses in MM.

References

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