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Myeloproliferative disorders

METABOLIC REWIRING FUELS IMMUNOSUPPRESSION AND FIBROSIS IN MYELOFIBROSIS VIA THE LACTATE–GLUTAMATE AXIS

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Introduction: Myelofibrosis (MF) is a severe myeloproliferative neoplasm characterized by clonal hematopoietic stem cell expansion and progressive bone marrow fibrosis, driven by complex tumor–stroma interactions. Emerging evidence suggests that metabolic reprogramming critically contributes to both immune evasion and fibrotic transformation within the tumor microenvironment (TME).
Methods: Serum metabolomics was performed by high-performance liquid chromatography (HPLC). Bone marrow immunohistochemistry and spatial proteomics were conducted using the MACSima platform. RNA sequencing and LC-MS-based proteomics were performed on mesenchymal stromal cells (MSCs). Functional assays employed the MCT1 inhibitor AZD3965 and the mGluR5 antagonist UBP310.
Results: MF sera showed elevated lactate levels that promoted Treg and M-MDSC expansion in healthy PBMCs. Inhibition of MCT1 by AZD3965 significantly reduced these subsets, indicating dependence on MCT1-mediated lactate import. In MSCs, lactate induced a CAF-like phenotype with robust collagen deposition, which was prevented by AZD3965 co-treatment. In vivo, zebrafish hematopoietic niches displayed MCT1 upregulation with MCT4 downregulation, consistent with lactate retention and pro-fibrotic conditioning. Lactate accumulation induced acidosis and glutaminolysis, leading to glutamate release that activated mGluR5 in MSCs. MF sera exhibited elevated glutamate levels. In MSCs, glutamate increased intracellular fumarate, shifted metabolism toward oxidative phosphorylation, enhanced mitochondrial ROS, and triggered a senescence-associated secretory phenotype (SASP) with increased collagen synthesis. Fumarate alone recapitulated the epigenetic remodeling-enhanced chromatin methylation and a stable pro-fibrotic state. Pharmacologic inhibition of mGluR5 with UBP310 reduced intracellular glutamate, SASP activation, and fibrosis. Proteomic profiling revealed coordinated upregulation of lactate-handling and glutaminolysis enzymes, enrichment of extracellular matrix (ECM) organization, and suppression of fatty acid oxidation. Pathways of senescence, oxidative stress, and chromatin modification were activated by glutamate/fumarate and normalized by UBP310. Spatial proteomics revealed a remodeled MSC landscape in PMF, with MCT1-high, CAF-like MSCs enriched in perivascular and peri-megakaryocytic zones and co-localizing with immune aggregates. Neighborhood analyses identified MSC-megakaryocyte-endothelium triads as hotspots of MCT1 expression and ECM remodeling.
Conclusions: MF pathogenesis reflects a dual metabolic insult, as lactate accumulation drives immune suppression and stromal activation, whereas glutamate overload reprograms MSCs through fumarate-dependent metabolic and epigenetic remodeling towards senescence and fibrosis. Targeting MCT1 to block lactate import and mGluR5 to disrupt glutamate signaling attenuates both immune and fibrotic outputs, providing a rational antifibrotic therapeutic strategy in MF.