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Myeloproliferative disorders

THE UNCOUPLED NRF2-HMOX1 AXIS AND PERSISTENT OXIDATIVE STRESS IN MYELOFIBROSIS NEUTROPHILS, BEYOND JAK BLOCKADE

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Introduction: Myelofibrosis (MF) is a chronic myeloproliferative neoplasm characterized by the excessive proliferation of myeloid cells, leading to bone marrow (BM) fibrosis, extramedullary hematopoiesis, and significant constitutional symptoms. The disease is often driven by mutations in JAK2, CALR, or MPL, which contribute to chronic inflammation, oxidative stress, and a disrupted BM microenvironment. Pathologically activated polymorphonuclear neutrophils (PMNs) play a critical role in disease progression by exacerbating oxidative stress and mitochondrial dysfunction. This comprehensive study investigate transcriptional and metabolic states of circulating PMNs and their contribution to disease pathology and the impact of ruxolitinib (Ruxo) therapy.

Methods: To dissect the transcriptional and metabolic states of circulating PMNs, we combined in vitro assays, FACS, metabolomic and single-cell RNA-seq analysis comparing healthy donors (HD), naïve MF patients, and MF patients following ruxolitinib therapy (Post-Ruxo).

Results: At disease onset, PMNs exhibited significantly increased mtROS production, elevated mitochondrial mass, and depolarized mitochondrial membranes, confirming profound metabolic alterations. Single-cell RNA-seq analysis revealed strong enrichment of pro-inflammatory and stress-related pathways, together with an activated unfolded protein response (UPR) and oxidative phosphorylation. Notably, in naïve MF patients, the antioxidant transcription factor NRF2 (NFE2L2) was transcriptionally induced, while its canonical downstream effector HMOX1 was repressed, indicating a state of "NRF2 uncoupling" due to chronic oxidative pressure. Following Ruxo treatment, it was observed residual oxidative stress and persistent NRF2 (NFE2L2) activation without full restoration of HMOX1 expression, compared to naïve MF patients.

Conclusions: These findings support the concept that oxidative and proteostatic rewiring are central features of PMNs dysfunction in MF and may represent therapeutic targets beyond JAK blockade.