(PS1957) METABOLIC REWIRING BY ONCOGENIC JAK2V617F CREATES A GLUCOSE TRANSPORT VULNERABILITY IN MYELOPROLIFERATIVE NEOPLASMS

Topic: 15. Myeloproliferative neoplasms - Biology & translational research

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Background

Myeloproliferative neoplasms (MPN) are clonal hematologic malignancies driven by mutations in *JAK2*, *CALR*, or *MPL*. Although these mutations result in persistent JAK-STAT activation and dysregulated hematopoiesis, current therapies fail to eliminate the malignant clone. We previously identified hypoxia–inducible factor 1 (HIF-1) as a selective vulnerability in JAK2V617F–mutant cells. However, the downstream metabolic dependencies sustaining this oncogenic state remain poorly defined.

Aims

To characterize the metabolic landscape governed by the JAK2–HIF-1 axis and evaluate glucose transport as a therapeutically exploitable vulnerability in MPN.

Methods

Slc2a1 (GLUT1), *Slc2a3* (GLUT3), or both glucose transporters were knocked out using CRISPR–Cas9 in *Jak2*V617F and *Jak2*WT 32D MPL cells, and the resulting phenotypes were assessed by RNA sequencing, glucose uptake assays, Seahorse extracellular flux analysis, and proliferation and apoptosis assays.
Metabolic dependencies were further investigated in vivo using a murine *Jak2*V617F knock-in model to evaluate the effects of HIF-1 inhibition with acriflavine (ACF) and GLUT inhibition with Glutor and KL-11743 on disease burden and hematopoiesis. The translational relevance of GLUT1/3 targeting was validated ex vivo using primary peripheral blood mononuclear cells from a clinically diverse cohort of MPN patients harboring *JAK2*, *CALR*, or *MPL* mutations and healthy donors.

Results

Metabolic profiling revealed that JAK2V617F forces a hypermetabolic state with increased glycolytic and oxidative flux, heavily dependent on a functional redundancy between GLUT1 and GLUT3. While single–transporter loss was well–tolerated, dual genetic pharmacological ablation collapsed glucose uptake and glycolytic capacity. This metabolic crisis selectively induced apoptosis in *Jak2*V617F cells, whereas *Jak2*WT cells demonstrated superior metabolic resilience and maintained higher viability (57.8 ± 10.8% (*Jak2*WT) vs 10.6 ± 6.4% (*Jak2*V617F) viable cells, mean ± SD, $p < 0.0001$, Fig. A).
Transcriptomic analysis demonstrated that *Jak2*V617F cells lack the metabolic plasticity required to adapt to glucose deprivation. In contrast to *Jak2*WT controls, *Jak2*V617F cells failed to engage compensatory pathways, instead activating DNA repair and cell cycle stress programs.
In vivo, HIF-1/GLUT inhibition modulated erythroid niche distribution but was insufficient to reverse the MPN phenotype. Importantly, primary MPN patient samples across all three mutation subtypes exhibited significantly greater sensitivity to these single-agent treatments than healthy donor cells yielding highly selective suppression of proliferation (ACF/Glutor: $p < 0.0001$; KL-11743: $p = 0.0002$, Fig. B), viability (ACF/Glutor: $p = 0.0002$; KL-11743: $p = 0.0045$, Fig. C), and clonogenicity (Glutor/KL-11743: $p = 0.0238$, Fig. D). Interestingly, co-treatment with the glutaminase inhibitor CB-839 provided no further benefit.

Summary/Conclusion

Our results define the HIF-1–GLUT1/3 axis as a central, targetable metabolic bottleneck in MPN. The selective exhaustion of patient–derived clones, regardless of the specific driver mutation, establishes glucose transport as a shared therapeutic vulnerability. These data provide a mechanistic rationale for further investigation of HIF-1 or GLUT inhibitors. By targeting this fundamental metabolic requirement, such agents may help overcome clinical limitations to achieve disease modification and eradicate the malignant MPN clone.