Beating the STATs: targeting the metabolome in acute myeloid leukemia

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In the current issue of *Haematologica*, Gil *et al*. provide new insights into the role of signal transducer and activator of transcription (STAT)-3 in regulating mitochondrial function in acute myeloid leukemia (AML).[1] Beyond its transcriptional activity, STAT3 translocates to the mitochondria where it interacts with voltage-dependant anion channel-1 (VDAC1), a regulator of mitochondrial calcium, oxidative phosphorylation (OXPHOS) and apoptosis. Disrupting this axis impairs mitochondrial metabolism, reduces leukemic cell viability, and leukemic stem cell (LSC) engraftment, supporting a role for STAT3 and its downstream effectors as potential therapeutic targets in AML.

AML is an aggressive disease with a high rate of relapse contributing to the poor overall survival of affected patients. Increasing evidence suggests that, similar to the hierarchical structure of normal hematopoiesis, a subset of LSC gives rise to the bulk leukemia and often mediates relapse. The seminal work by Craig Jordan, as well as others, has uncovered the unique metabolic dependencies of LSC, demonstrating their reliance on OXPHOS as a source for energy rather than glycolysis as in normal hematopoietic stem cells. It was further demonstrated that LSC OXPHOS relies on influx of amino acids and fatty acids, highlighting metabolic vulnerabilities and pathways of resistance.[2]

Key signal transduction pathways and common mutations were shown to modulate and support the reprogrammed metabolic needs of the leukemia cells. IDH1/2 mutations were linked to mitochondrial dysregulation with enhanced OXPHOS metabolism. RAS pathway mutations were shown to upregulate MCL-1, with higher rates of fatty acid oxidation and amino acid metabolism, as alternative OXPHOS fuel,[3] thus linking aberrant signaling with metabolic rewiring.

Aberrant activation of the Janus kinase (JAK)/STAT pathway, and specifically STAT3 and STAT5, has been increasingly recognized as a key driver in the pathogenesis of both myelodysplastic syndromes and AML. Mutations in upstream tyrosine kinases such as FLT3, BCR-ABL, KIT, and components of the RAS pathway commonly enhance STAT3/5 signaling, and functional studies have demonstrated that STAT activation is essential for the leukemogenic potential of these mutations.[4,5]

STAT3 signaling as a metabolic regulator

While STAT proteins are best known for their function as transcription factors, emerging data highlight their non-canonical roles in regulating key metabolic pathways that support LSC and proliferation. Early works have shown that STAT3 can localize to the mitochondria rather than the nucleus, supporting electron transfer and OXPHOS metabolism in the context of RAS-dependent transformation.[5] It was suggested that STAT3 resides in the inner mitochondrial membrane and integrates into electron transport complex I.[6] Mitochondrial STAT3 requires phosphorylation at serine 727 (Ser-727), in contrast to the nuclear STAT3 which is phosphorylated on tyrosine 705 (Y705). Interestingly, while both nuclear and mitochondrial STAT3 can modulate cell metabolism, they result in divergent metabolic effects (Figure 1). In breast cancer cells, substitution of Ser-727 for an alanine reduced tumor growth and complex I activity, and resulted in accumulation of reactive oxygen species, suggesting that mitochondrial STAT3 supports OXPHOS potential.[7] In contrast, the transcriptional effect of nuclear STAT3 was shown to upregulate hypoxia inducible factor (HIF)-1α in epithelial tumor cells, supporting glycolysis.[8] Work done in primary AML LSC demonstrated that STAT3 supports OXPHOS via upregulation of its target genes including Bcl-2[9] and MYC, which in turn upregulates the mitochondrial transporter SCL1A5 and influx of glutamine and OXPHOS metabolism. STAT3 silencing in primary AML cells resulted in cell death and reduced engraftment, which was less evident in normal hematopoietic progenitors.[10] Finally, STAT3 transcriptional activity was shown to promote several key regulators of lipid metabolism supporting fatty acid oxidation, including peroxisome proliferator-activated

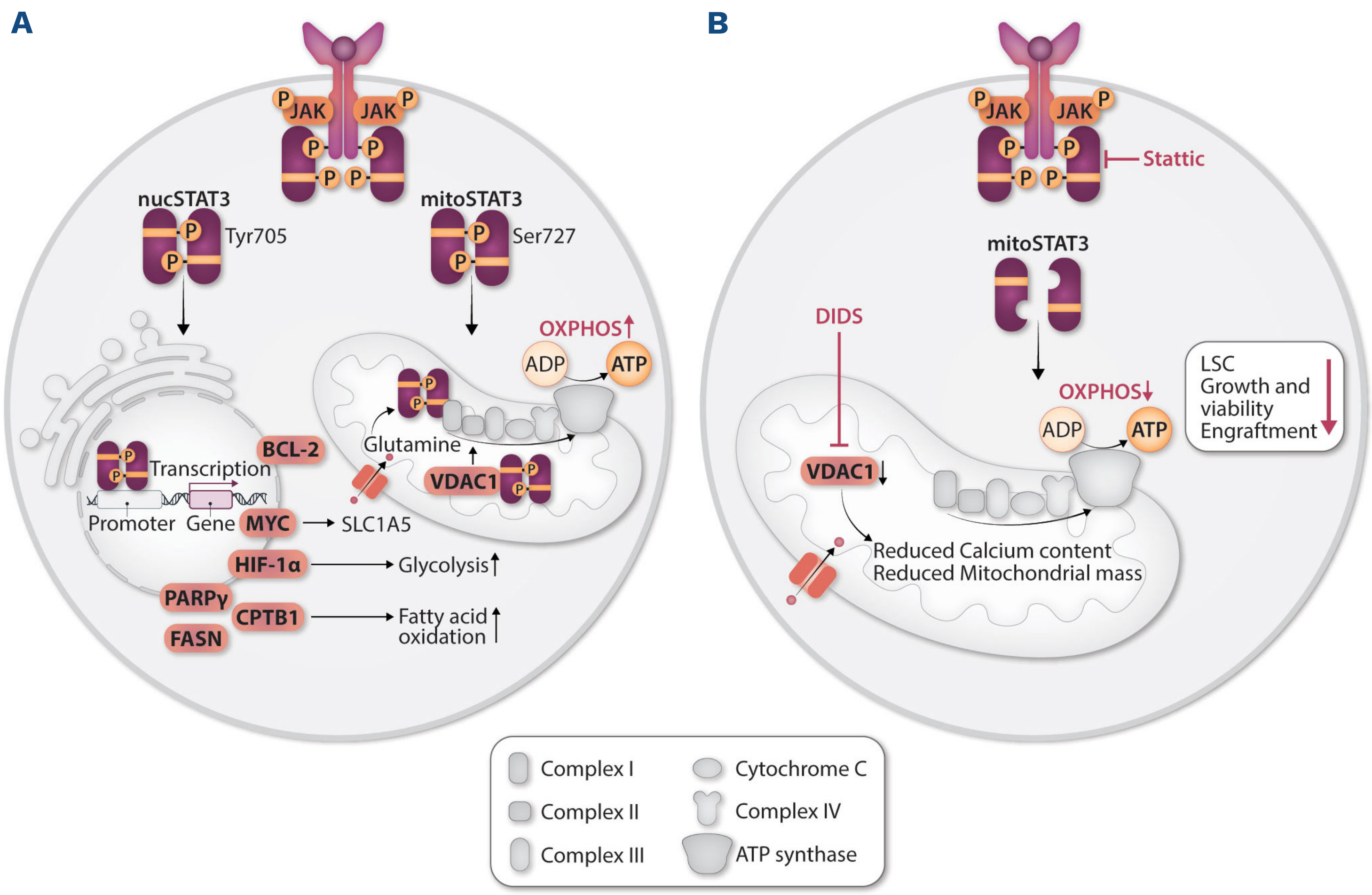

Figure 1. STAT3 regulates mitochondrial and nuclear metabolic pathways in acute myeloid leukemia. (A) Schematic representation of STAT3 activity in the nucleus and mitochondria. Nuclear STAT3 promotes transcription of key metabolic genes. In the mitochondria, phosphorylated (S727) STAT3 interacts with VDAC1, supporting OXPHOS metabolism. (B) Targeted inhibition of STAT3 or VDAC1 disrupts mitochondrial function, leading to impaired OXPHOS and reduced leukemic cell viability and stemness. STAT3: signal transducer and activator of transcription 3; HIF1α: hypoxia-inducible factor 1 alpha; OXPHOS: oxidative phosphorylation; BCL-2: B-cell lymphoma 2; PARP: poly (ADP-ribose) polymerase; FASN: fatty acid synthase; DIDS: 4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid (VDAC1 inhibitor); LSC: leukemia stem cells.

receptor gamma (PPARγ)[11] and carnitine palmitoyltransferase 1B (CPT1B). Fatty acid oxidation was shown to support LSC as an alternative fuel, especially under therapeutic pressure of drugs that target OXPHOS, such as the Bcl-2 inhibitor venetoclax, mediating resistance and relapse.[2,3] Based on these data, co-targeting STAT3 signaling and OXPHOS metabolism (e.g., with azacytidine and venetoclax) may prove synergistic in AML.

In the current issue of *Haematologica*, Gil *et al*. provide further evidence for the pivotal role of STAT3 in mitochondrial function and survival of AML cells. The investigators utilized AML cell lines and primary patients' samples to demonstrate that STAT3 is preferentially expressed and phosphorylated in the mitochondria of leukemic cells. They next recognized candidate proteins that interact with STAT3 in the mitochondria by immunoprecipitation assays followed by mass spectrometry analysis and identified VDAC1 for further investigation. Co-immunoprecipitation assays confirmed the intimate interaction between STAT3 and VDAC1.

From a functional standpoint, pharmacological and transcriptomic inhibition of STAT3 (with Stattic and siSTAT3, respectively) both resulted in reduced mitochondrial calcium and mitochondrial membrane potential, an effect also replicated by selective VDAC1 inhibition. VDAC1 overexpression in the context of STAT3 inhibition partially salvaged mitochondrial calcium content suggesting that the effect of VDAC1 is downstream of STAT3 activation. Additionally, STAT3 and VDAC1 inhibition reduced OXPHOS measures, such as oxygen consumption rates and production of reactive oxygen species, with a net reduction in oxidative stress. The deleterious effects of STAT3 and VDAC1 inhibition on OXPHOS and mitochondrial calcium metabolism were also reflected by reduced mitochondrial mass in treated leukemic cells.

Finally, Gil *et al*. demonstrate that inhibition of STAT3 with Stattic reduced the growth and viability of LSC, including engraftment of primary AML cells in a mouse xenograft model. These data complement other preclinical studies demonstrating that Stattic can induce apoptosis and decrease LSC activity, particularly in FLT3-mutant AML cells.[12] Other STAT3 inhibitors, either alone or in combination with other therapies such as venetoclax, have shown efficacy *in vitro* and in mouse xenograft models, while clinical data are still limited.[13]

One important aspect of the work by Gil *et al.* is that the STAT3-VDAC1 pathway remained relevant to mitochondrial function and LSC survival in the context of venetoclax resistance, a yet unmet challenge with few therapeutic options.

In conclusion, the study by Gil *et al*. as well as previous works highlight the role of STAT3 in the metabolic adaptation of leukemic cells. As evidence accumulates, targeting metabolic pathways regulated by STAT, either alone or in combination with existing therapies, offers a complementary approach to current treatment strategies.

Disclosures

OW reports research support, speaker honoraria, and an advisory role with AbbVie. BN reports speaker honoraria, and an advisory role with AbbVie.

Contributions

BN and OW co-wrote the Editorial.

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