EDITORIAL

Metabolic epigenome targeting hits *KMT2A*-rearranged acute lymphoblastic leukemia

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Targeted and individualized therapy is the upcoming promise towards safer and more efficient treatment of acute leukemias and cancer in general. Attacking aberrant metabolic dependencies and the deregulation of epigenetic mechanisms are two of the most promising approaches for developing leukemia-specific therapies, particularly in high-risk disease. Tee and colleagues now elegantly combine these two promising fields of interest to develop a novel therapeutic approach, sparking new hope for patients with *KMT2A*-rearranged (KMT2Ar) acute lymphoblastic leukemia (ALL): disrupting KMT2Ar-driven histone methylation through methionine (Met) restriction and enhancing the effect with histone deacetylase (HDAC) inhibition.[1]

S-adenosyl-methionine (SAM) serves as a universal (methyl) donor for cellular methyltransferases and is thus essential for the epigenetic machinery to maintain or reshape the epigenome. The main source for SAM is the Met-folate cycle, which converts Met to SAM and replenishes the Met pool through conversion of S-adenosyl-homocysteine (SAH) to homocysteine (Hcy) and back to Met. Overall, Met dependence is not a new phenomenon in cancer, and efforts have been made to exploit its depletion via methioninase - analogous to the well-known asparagine-depleting asparaginase - or via Met restriction.[2,3] However, Met is an essential amino acid, and its depletion is not without side effects. Therefore, it is crucial to identify cancer subtypes that are particularly dependent on the Met cycle and to implement these new findings into synergistic treatment regimens. While it may seem intuitive that cancers driven by chromosomal translocations involving histone methyltransferases (HMT) could be particularly vulnerable to Met/SAM-depleting therapies, this potential vulnerability has so far been insufficiently investigated.

In this study, Tee and colleagues close this gap of knowledge by systemically testing the dependence on methionine/SAM in B-cell precursor (BCP)-ALL. Starting from Met restriction coupled with a global metabolomics approach, the team identified a particularly high dependence of KMT2Ar ALL on increased levels of Met, both *in vitro* and *in vivo*. Notably, it is not a general restriction of metabolic activity that kills leukemia cells upon Met/SAM restriction but rather the opposite: when non-KMT2Ar ALL cells enter a quiescence-like state under Met/SAM restriction, KMT2Ar ALL cells fail to adapt. As a result, they are deprived of the pyrimidines uracil and cytosine while accumulating SAH, which further acts as a suppressor of methyltransferase activity, exacerbating the effects of the SAM restriction. Consistent with this, a global reduction in histone methylation was observed, most severely affecting the KMT2Ar-driven H3K4, H3K36 and H3K79 marks. This resulted in the downregulation of key target genes of KMT2Ar, indicating that Met/SAM restriction directly targets the oncogenic lesion driving the leukemia.

While these findings mark an important step toward developing a potential tailored, diet-based therapy for KMT2Ar ALL, the study next addresses a broader issue of clinical relevance: Met restriction alone - like many other targeted therapies - is insufficient as a monotherapy. Rather than simply integrating or implementing Met restriction into existing treatment regimens, Tee and colleagues chose a more sophisticated approach by conducting a combinatorial drug screen using the MAT2A inhibitor FIDAS-5, which blocks the conversion of Met to SAM. This revealed a highly synergistic effect with HDAC inhibition. Importantly, the combined Met/SAM restriction strategy was highly efficient in primary ALL cells, both *in vitro* and *in vivo* in patient-derived xenografts.

Targeting ALL at the metabolic level is a story of success, but so far, it has been restricted to asparagine depletion. The challenge lies in identifying cancer subtypes with specific metabolic dependencies and discovering drug combinations that selectively exploit these vulnerabilities while

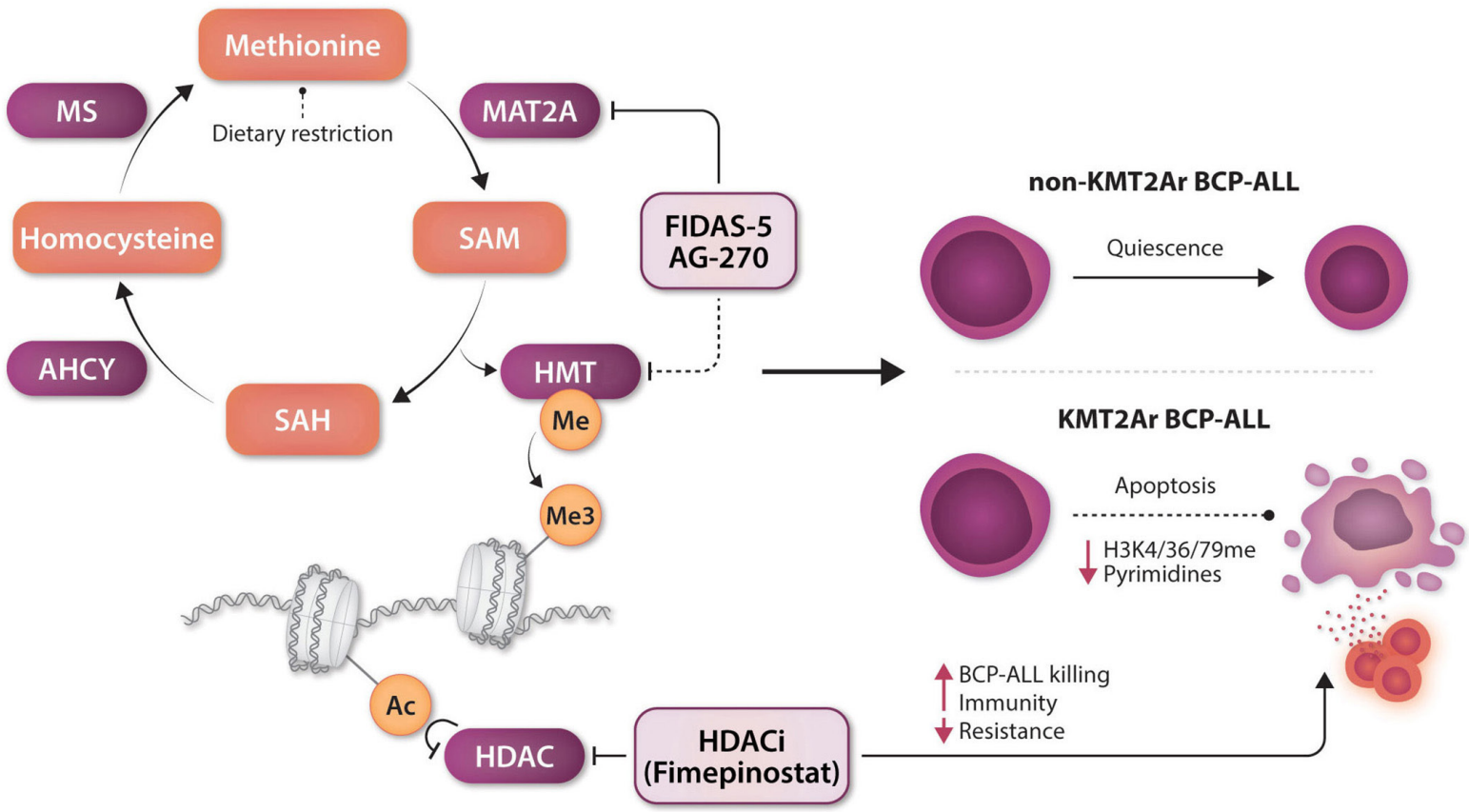

Figure 1. SAM depletion cooperates with histone deacetylase inhibition to eliminate *KTM2A*-rearranged B-cell precursor acute lymphoblastic leukemia. Inhibition of the methionine cycle by restricting methionine intake or by methionine adenosyltransferase 2A (MAT2A) inhibition (FIDAS-5, AG270) depletes the methyl donor S-adenosyl-methionine (SAM) and reduces histone methyltransferase (HMT) activity, predominantly affecting methylation of histone 3 and lysines 4, 36 and 76. SAM depletion results in apoptotic cell death in *KMT2A*-rearranged (KMT2Ar) B-cell precursor acute lymphoblastic leukemia (BCP-ALL) due to lack of adaptation, *KMT2A* target gene deregulation, and depletion of pyrimidines. Non-KMT2Ar BCP-ALL enters a quiescent cell state instead. Histone deacetylase (HDAC) inhibition (Fimepinostat) synergistically boosts the effect of SAM depletion in KMT2Ar BCP-ALL and potentially boosts therapeutic efficacy through block of chemotherapy resistance and increased immunologic activity. MS: methionine synthetase; SAH: S-adenosyl-homocysteine; AHCY: adenosylhomocysteinase; Ac: acetyl; Me: methyl.

minimizing side effects. With routine testing for KMT2Ar at diagnosis, the availability of Met-reduced diets, and clinically approved HDAC inhibitors (HDACi), the study by Tee and colleagues now provides a promising, easy, efficient, and directly applicable way that addresses these gaps. Notably, recent clinical trial results on the MAT2A inhibitor (AG-270),[4] together with emerging evidence that HDACi may have broader activity in ALL and their ability to sensitize leukemic cells to chemotherapy - even in the absence of P53 - further highlights the potential of this strategy.[5,6] This makes it an especially attractive option, even in light of growing interest in the new class of Menin inhibitors.[7]

Taken together, this current work - alongside complementing studies in acute myeloid leukemia[8] and other malignancies[2] - paves the way for implementing Met reduction strategies in acute leukemias, particularly in BCP-ALL. Current treatment regimens are highly effective and increasingly incorporate immunotherapeutic approaches such as Blinatumomab or chimeric antigen receptor T cells, which may themselves be positively affected by addition of HDACi,[9] but due to their complexity the translation of the findings by Tee and colleagues into clinical practice will be challenging. Nonetheless, the proposed regimen of a Met-reduced diet with HDACi is readily applicable and represents a valuable and promising approach, especially for patients with relapsed or refractory disease. Its multimodal action on both KMT2Ar BCP-ALL cells directly, the interaction with other therapeutic agents, and the immune system highlights its high potential by affecting the tumor, microenvironment and resistance prevention, where salvage therapies often fail.

Studies like the one by Tee and colleagues are a great representation of the vibrant and highly active ALL research community, which is increasingly focused on offering more patient-tailored treatment options and exciting years of clinical research lie ahead to implement all these findings, with the goal of enhancing treatment efficacy while minimizing toxicity.

Disclosures

No conflicts of interest to disclose.

Contributions

DH and ER drafted the Editorial.

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