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Human acute leukemia utilizes branched-chain amino acid catabolism to maintain stemness through regulating PRC2 function

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Abstract:
Cancer-specific metabolic activities play a crucial role in the pathogenesis of human malignancies. To investigate human acute leukemia-specific metabolic properties, we comprehensively measured the cellular metabolites within the CD34+ fraction of normal hematopoietic stem progenitor cells (HSPCs), and primary human acute myelogenous leukemia (AML) and lymphoblastic leukemia (ALL) cells. Here we show that human leukemia addicts to the branched-chain amino acid (BCAA) metabolism to maintain their stemness, irrespective of myeloid or lymphoid types. Human primary acute leukemias had BCAA transporters for BCAA uptake, cellular BCAA, α-ketoglutarate (α-KG) and cytoplasmic BCAA transaminase-1 (BCAT1) at significantly higher levels than control HSPCs. Isotope-tracing experiments showed that in primary leukemia cells, BCAT1 actively catabolizes BCAA using α-KG into branched-chain α-ketoacids (BCKAs), whose metabolic processes provide leukemia cells with critical substrates for the TCA cycle and the non-essential amino acids synthesis, both of which reproduce α-KG to maintain its cellular level. In xenogeneic transplantation experiments, deprivation of BCAA from daily diet strongly inhibited expansion, engraftment and self-renewal of human acute leukemia cells. Inhibition of BCAA catabolism in primary AML or ALL cells specifically inactivates polycomb repressive complex 2 (PRC2) function, an epigenetic regulator for stem cell signatures, through inhibiting transcription of PRC components, such as zeste homolog 2 (EZH2) and embryonic ectoderm development (EED). Accordingly, BCAA catabolism plays an important role in maintenance of stemness in primary human AML and ALL, and molecules related to the BCAA metabolism pathway should be critical targets for acute leukemia treatment.

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