Canonical BAF complex regulates the RUNX1-deriven oncogenic program in human T-cell acute lymphoblastic leukemia

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Abstract

Acute leukemia cells require bone marrow microenvironments, known as niches, which provide leukemic cells with niche factors that are essential for leukemic cell survival and/or proliferation. It is well known that CXCR4, which is a physiological receptor for the most important niche factor CXCL12, is expressed on leukemic cells; however, it remains unclear how the responsiveness to CXCL12 is regulated upstream and downstream of CXCR4 in leukemic cells. Using a genome-wide CRISPR screen, we discovered that canonical BAF (cBAF), a variant of the SWI/SNF chromatin remodeling complex, regulates migratory response of human T-cell acute lymphoblastic leukemia (T-ALL) cells to CXCL12. Mechanistically, cBAF maintains chromatin accessibility and allows RUNX1 to bind to CXCR4 enhancer regions. cBAF inhibition evicts RUNX1 from the genome, resulting in CXCR4 downregulation and impaired migration activity. In addition, cBAF maintains chromatin accessibility preferentially at RUNX1 binding sites, ensuring RUNX1 binding at these sites, and is required for expression of RUNX1-regulated genes, such as CDK6; therefore, cBAF inhibition negatively impacts cell proliferation and profoundly induces apoptosis. This anticancer effect was also confirmed using T-ALL xenograft models, suggesting cBAF as a promising therapeutic target. Thus, we provide novel evidence that cBAF regulates the RUNX1-driven leukemic program and governs migration activity toward CXCL12 and cell-autonomous growth in human T-ALL.