WHOLE-GENOME SEQUENCING DEFINES THE MUTATIONAL LANDSCAPE OF PanNETs

Pancreatic neuroendocrine tumors (PanNET) are classified into three groups: low grade (G1), intermediate grade (G2), and high grade (G3). G3 PanNETs have a universally poor prognosis, whereas G1 and G2 tumors have an unpredictable clinical course. A better understanding of the molecular underpinnings of the disease may enable better risk stratification and the identification of patients who might benefit from early aggressive therapy. Scarpa and colleagues performed comprehensive molecular analyses of 102 clinically sporadic PanNETs. Whole-genome sequencing of 98 PanNETs defined five distinct mutational signatures: MUTYH, APOBEC, BRCA-deficiency, age, and COSMIC signature 5. The MUTYH signature was previously undescribed and was associated with G>C-T>A transversions in tumors with an inactivating germline mutation in the base excision-repair gene MUTYH, suggesting that MUTYH deficiency may contribute to PanNET. Germline mutations were detected in MEN1, CDKN1B, CHEK2, and VHL1, in addition to BRCA1 and MUTYH. Further, 15,751 somatic coding mutations were identified in 2,787 genes, and MEN1 was the most frequently mutated gene. Tumors with ATRX, DAXX, or MEN1 mutations exhibited increased telomere length. There were an average of 29 structural rearrangements per tumor, with rearrangements leading to inactivation of tumor suppressors such as MTAP, ARID2, SMARCA4, MLL3, CDKN2A, and SETD2, or creating oncogenic gene fusions. In total, 66 somatic in-frame gene fusions were identified, including three EWSR1 fusion events leading to EWSR1–BEND2 or EWSR1–FLI1. Although EWSR1–FLI1 is a characteristic Ewing sarcoma fusion gene, the morphologic and pathologic features were consistent with PanNETs. RNA sequencing of 30 PanNET tumors found that common genetic alterations affected DNA damage and repair, chromatin remodeling, telomere maintenance, and mTOR signaling, suggesting possible therapeutic targets. This comprehensive genomic analysis identified mutations, structural rearrangements, and signaling pathways not previously associated with PanNETs, which may aid in risk stratification and the development of targeted therapies.

CKMT1 MAY BE A THERAPEUTIC TARGET IN EVI1-DRIVEN ACUTE MYELOID LEUKEMIA

Chromosomal translocations promote aberrant expression of the proto-oncogenic transcription factor EVI1 (also known as MECOM) to drive a subset of acute myeloid leukemias (AML) that are associated with a poor clinical outcome. EVI1-driven AML is refractory to current therapies, prompting Fenouille, Basil, and colleagues to perform integrated genomic and metabolic screens to identify potential druggable metabolic dependencies. Overexpression of EVI1 resulted in altered levels of many metabolites including those involved in purine and pyrimidine metabolism, amino acid metabolism, the pentose phosphate pathway, and glycolysis. An shRNA screen of genes involved in these metabolic pathways revealed that depletion of the ATP-buffering mitochondrial creatine kinase CKMT1, an enzyme which promotes the metabolism of arginine to creatinine, suppressed the growth of EVI1-expressing AML cell lines, suggesting its potential as a therapeutic target. Further, analysis of 68 primary AML samples showed that the samples with the highest expression of EVI1 also exhibited high CKMT1 expression and enhanced sensitivity to cyclocreatine, a small-molecule inhibitor of CKMT1. Mechanistically, EVI1 reduced expression of the myeloid differentiation regulator RUNX1 by binding directly to its promoter, thereby alleviating RUNX1-mediated repression of the CKMT1 promoter and enhancing CKMT1 expression. Moreover, primary AML samples with high expression of CKMT1 were associated with the subgroup of samples with high EVI1 expression and low RUNX1 expression. Depletion or inhibition of CKMT1 resulted in reduced metabolism of arginine to creatinine and decreased intracellular ATP levels, indicating that CKMT1 is required to promote mitochondrial activity. Cyclocreatine treatment reduced the viability of EVI1-expressing AML cells by inhibiting the cell cycle and inducing apoptosis. In vivo, pharmacologic or genetic inhibition of CKMT1 suppressed the progression of EVI1-positive AML and prolonged survival, and reactivation of the creatine kinase pathway reversed these effects. The identification of the creatine kinase pathway as a metabolic vulnerability in EVI1-positive leukemias suggests that CKMT1 may be a potential therapeutic target in these tumors.

CKMT1 May Be a Therapeutic Target in EVI1-Driven Acute Myeloid Leukemia

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