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ZMAT3 prevents hematopoietic stem cells exhaustion and contributes to the transformation of cells in Fanconi anemia disease.

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Fanconi anemia (FA) is a rare genetic disease characterized by the appearance of an early bone marrow aplasia early in life, frequently followed by the development of acute myeloid leukemia and/or solid tumors. For several years, we have been taking advantage of cellular and murine model we developed, to understand the natural molecular mechanisms that arise in FA cells and limit stem cells exhaustion, promote cell survival, drive them towards a preleukemic state and finally leukemia.

Recently, we identified several genes whose expression is altered in murine FA-deficient hematopoietic cells, pointing the exacerbation of the p53 pathway and overexpression of ZMAT3, an RNA-binding protein. In the pathogenesis of FA, direct alteration of p53 is uncommon. The most frequent and early event of bone marrow transformation is associated with a gain of chromosome 1q driving enforced *MDM4* oncogene, a natural inhibitor of p53. A pre-cancerous state in FA requires additional events to facilitate cellular transformation. Recurrent 3q amplification has been associated with leukemic progression in FA patient. This 3q amplification includes the *ZMAT3* gene.

To decode the function of ZMAT3 along FA disease we first isolated hematopoietic stem cells (HSC) from FA-KO mice in which we downregulated the expression of *Zmat3*. Performing CFU-assay, *Zmat3* depletion leads to reduces number and capacity of KO hematopoietic cells to form CFU. Given the challenge of isolating FA-KO HSC due to high cell mortality we next used a human fibroblast cell line derived from FA patient depleted for *ZMAT3* to highlight

cellular and molecular mechanisms. From this cell line, we demonstrated that depletion of *ZMAT3* reduces proliferation and enhanced cell death. Additionally, using RNAseq, we identified 805 differentially expressed genes. The GSEA analysis revealed an enrichment of genes associated with proliferation, cell cycle, and apoptosis pathways, along with dysregulation of several metabolism pathways. Through metabolic and lipidomic approaches, we were able to discern a significant involvement of ZMAT3 in sphingolipid metabolism. More precisely, depletion of *ZMAT3* leads to decrease of the ceramidase ASAH1, an enzyme crucial for the hydrolysis of ceramide into sphingosine, leading to accumulation of ceramide. Thus, our study revealed an essential role of ZMAT3 in FA-deficient cells survival, by promoting proliferation, limiting cell death, and preventing ceramide accumulation.