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501.HEMATOPOIETIC STEM AND PROGENITOR CELLS AND HEMATOPOIESIS: BASIC AND TRANSLATIONAL

TAF1, the Largest Subunit of Tfiid, Is Dispensable for Adult Hematopoiesis

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Temporal and spatial control of gene expression is central to normal hematopoietic stem cell (HSC) biology. Many sequence-specific transcription factors have been identified as key regulators of HSC fate decision, while the function of general transcription factors in HSC behavior is poorly understood. We previously reported that TAF1, the largest subunit of the TFIID complex, plays a critical role in AML1-ETO driven acute myeloid leukemogenesis. To evaluate the function of TAF1 in normal fetal and adult hematopoiesis, we generated TAF1 conditional knockout (CKO) mice and identified an essential role of TAF1 in fetal erythropoiesis. Surprisingly, deletion of TAF1 in adult mice was not lethal to hematopoiesis; rather, we observed a marked expansion of hematopoietic stem and progenitor cell (HSPC) populations, with increased self-renewal and impaired differentiation capacity in these TAF1- null cells. Consistently, we found that TAF1-null HSPCs failed to up-regulate key differentiation-associated genes when induced to differentiate *in vitro*. Using a variety of genome-wide assays and biochemical approaches, we found that TAF1 loss not only disrupted TFIID complex formation and chromatin recruitment, but also reduced promoter accessibility, impaired RNA Polymerase II promoter recruitment and activity, as well as its promoter-proximal pausing mechanism. Thus, the effect of TAF1 loss on normal adult hematopoiesis primarily relates to the inability to upregulate genes involved in differentiation, while HSC self-renewal and the expression of self-renewal genes proceeds relatively normally.

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