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509.BONE MARROW FAILURE AND CANCER PREDISPOSITION SYNDROMES: CONGENITAL

Chromatin Remodeler DEK Is a Sensor to Replication Stress and Contributes to HSC Defects in Fanconi Anemia

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Hematopoietic stem cells (HSCs) have self-renewal capacity and response for life-long hematopoiesis. Any interference with normal DNA replication leads to replication stress, which drives function decline in HSCs. However, the response of HSCs to replication stress remains largely unknown. Here, draw a transcriptional and epigenetic landscape of HSCs under replication stress. We found that HSCs required opened chromatin to counteract replication stress, along with altered H3K27 acetylation and H3K4 trimethylation. The increased chromatin accessibility was mainly attributed to the reduced chromatin remodelers DEK, while DEK overexpressed HSCs confronted with a strong replication challenge, shown by increased γ-H2AX. Excessive DEK protein impeded proliferation and impaired HSC maintenance (>50% reduction), along with reduced oxidative phosphorylation and protein synthesis. Notably, we found that DEK protein was abnormally accumulated in BM CD34 $^{+}$ cells in Fanconi anemia, which arises from mutations in FA genes essential for replication stress tolerance. Inhibition of DEK substantially recovered HSC proliferation capacity in vitro and engraftment in vivo. At the molecular level, we identified that ATF2 directly promoted the transcription of DEK, especially relying on phosphorylated ATF2 (ser69/71) rather than phosphorylated ATF2 (ser490/498). Rad3-related (ATR) induced the phosphorylation of ATF2 at ser490/498 and mediated the reduction of DEK under replication stress. Nonetheless, knock-down of FA genes (FANCD2) in HSCs resulted in increased phosphorylated ATF2 (ser69/71), which might contribute to DEK accumulation in FA. Collectively, our findings uncover the landscape of HSC response to replication stress, reveal a novel ATR-ATF2-DEK axis helping HSCs counteract replication stress, and suggest inhibition of DEK as a therapeutic utility in FA.

Disclosures No relevant conflicts of interest to declare.

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