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503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

TET2-Mediated Dysregulation of Heterochromatin in Age-Related Clonal Hematopoiesis

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Aging is one of the major negative factors of normal hematopoiesis, characterized by a decline in the self-renewal capabilities of hematopoietic stem and progenitor cells (HSPCs), alongside a myeloid lineage bias, thereby sabotaging the immune system and increasing the risk of malignant transformation. Epigenetic deregulation is a hallmark feature representative of aging and significantly contributes to age-related dysfunction in multiple systems. DNA methylation drifting is commonly observed during aging, especially within the partially methylated domains (PMDs). PMDs are intriguing heterochromatin regions featured by their late-replicating, lamina-associated, and B-compartment localized properties in HiC analysis. While heterochromatin is generally considered devoid of genes, it nonetheless plays a pivotal role in maintaining genomic stability. However, the link between age-related DNA methylation loss in PMDs and heterochromatin dysfunction remains elusive.
In this study, we juxtapose the influence of aging on both wild-type (WT) and Tet2 knockout (KO) HSPCs. Tet2 depletion was found to counteract the functional deterioration typically associated with aging by preserving robust self-renewal and repopulation capacities in aging HSPCs. This resistance to functional decay may account for the age-related clonal hematopoiesis observed in Tet2KO HSPCs. At a molecular level, we identified distinct epigenetic regulatory mechanisms mediated by Dnmt3a and Tet2 at heterochromatin. These mechanisms are associated with alterations in 3D genome architecture during HSPC aging. Age-related dysregulation of heterochromatin leads to the upregulation of endogenous retroviruses (ERVs), which subsequently activate intracellular innate immune response and contribute to the functional decline of aging HSPCs. The application of reverse transcriptase inhibitors was shown to suppress ERV production and interferon-stimulated genes (ISGs) expression, thereby ameliorating age-related defects in aged HSPCs. Our findings provide compelling evidence supporting the intricate interplay between DNMT and TET in regulating DNA (de)methylation equilibrium in heterochromatin and euchromatin during stem cell aging. Moreover, our study offers critical insights into the mechanisms underlying age-related heterochromatin dysfunction, which contributes to the functional deterioration of HSPCs during aging.

Disclosures No relevant conflicts of interest to declare.

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