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Cyclin E1 regulates hematopoietic stem cell quiescence

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Hematopoietic stem cells (HSCs) give rise to all the different types of blood cells and are the most studied adult stem cells. HSCs proliferate and differentiate to give rise to increasingly lineage-restricted progenitors, which, in turn, give rise to the mature blood cells. To maintain all blood cells throughout the lifetime of an organism, HSCs self-renew to replenish the HSC compartment. Long-lived cells such as HSCs run the risk of accumulating damage during the multiple rounds of DNA replication and cell division, leading to defective hematopoiesis. Hence, alongside self-renewal, quiescence of stem cells plays an important role for the lifelong maintenance of a functional and healthy stem cell compartment by minimizing cellular stress and genomic instability caused by multiple rounds of proliferation. This exquisite balance between proliferation and quiescence is regulated by intracellular regulatory proteins as well as extracellular factors provided by the specialized microenvironments in which stem cells reside (niche). Identification of factors that play important roles in the regulation of stem cell quiescence is critical to understanding stem cell biology, cancer, and aging.

In the December 1, 2013 issue of *Cell Cycle*, Campaner and colleagues report a novel role for cyclin E1 in regulating quiescence and exhaustion of the HSC compartment.[1] Cyclin E1 and E2 constitute the cyclin E subfamily, which bind to and activate Cdk2 at the G_1/S transition of the cell cycle. Deletion of cyclin E1 or cyclin E2 alone in mice does not result in any dramatic phenotypes,[2,3] but double knockouts were embryonic lethal due to placental defects, suggesting that these cyclins act redundantly during development, and the presence of one of them is sufficient for cell division. Cyclin E controls the exit from quiescence in MEFs by loading MCM proteins onto replication origins in a kinase-independent fashion.[4] In this study, the authors uncover an important non-redundant function of cyclin E1 in HSCs in mediating exit from quiescence and rapid entry into the cell cycle during stress hematopoiesis. While young mice lacking cyclin E1 displayed no difference in the fraction of quiescent HSCs under homeostatic conditions, in aged mice lacking cyclin E1, the proportion of quiescent HSCs increased, uncovering a role for cyclin E1 in regulating HSC quiescence during aging. Cyclin E1-null HSCs displayed increased longevity and competitive advantage during serial transplant experiments, most likely due to their reduced exit from quiescence, providing better protection from stem cell exhaustion. It would be interesting to know whether these functions of cyclin E are dependent on kinase activity or not.

This study adds another important cell cycle protein to the complex network of proteins that regulate the balance between proliferation and quiescence in hematopoietic stem cells.[5] The changes in the regulation of quiescence and proliferation in HSCs during aging, and the effects of these changes in normal hematopoiesis and leukemogenesis, remain poorly understood. Recent studies in pluripotent stem cells provide compelling evidence that cell fate decisions are cell cycle-dependent, and that differentiation can be influenced by manipulating the cell cycle.[6,7] These findings warrant careful and lineage-specific investigation of the roles of cell cycle regulators in controlling the balance between quiescence, proliferation, and differentiation of stem cells.

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