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Function of Pot1 in the maintenance of hematopoietic stem cell activity under stress

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Hematopoietic stem cells (HSCs) are responsible for blood cell production throughout the lifetime of an individual. However, aging or repeated cell division induces the accumulation of DNA damage, which impairs HSC self-renewal and differentiation capacities. Here, we show that protection of telomeres 1a (Pot1a), a component of shelterin, improves HSC activity under stress. We identified that Pot1a was highly expressed in HSCs, yet this expression declines with age. Knockdown of Pot1a in young HSCs increased DNA damage response (DDR) at telomeric region and induced age-related phenotypes, marked by reduced long-term reconstitution activity and myeloid-biased differentiation. In contrast, overexpression of Pot1a or treatment with exogenous Pot1a protein prevented telomeric DDR and maintained HSC self-renewal activity and rejuvenated the activity of aged HSCs. In addition, we found that the transduction of Pot1a into LT-HSCs reduced production of reactive oxygen species compared with control, indicating the possibility that Pot1a implicates in the energy metabolism of HSCs. Furthermore, human POT1 protein also increased the number of cord blood HSCs. These results indicate that Pot1a/POT1 has an important role in the maintenance of stem cell function under stress condition and can be used to expand functional HSC numbers *ex vivo*.

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