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POT1 maintains hematopoietic stem cell activity by protecting against DNA damage and metabolic alterations

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Repeated cell divisions and aging impair stem cell function. However, the mechanisms by which this occurs are not fully understood. Here, we show that POT1a, a component of shelterin complex, improves hematopoietic stem cell (HSC) activity under stress and during aging. We found that POT1a was highly expressed in HSCs, yet this expression declined with age. POT1a knockdown in HSCs increased DNA damage response (DDR) and inhibited self-renewal. Conversely, POT1a overexpression or treatment with exogenous POT1a protein prevented DDR, maintained HSC self-renewal and rejuvenated the activity of aged HSCs. Notably; we found that POT1a negatively regulated mTOR and Raptor expression and POT1a transduction prevented the expression of oxidative phosphorylation-associated genes and reduced the production of reactive oxygen species, indicating a novel non-telomeric function of POT1a in HSC maintenance. Furthermore, exogenous POT1 protein treatment also maintained human HSC activity. Collectively, these results show that POT1a/POT1 can be used to expand HSC numbers ex vivo.

Biography

Fumio Arai is a Professor of Department of Stem Cell Biology and Medicine, Graduate School of Medical Sciences, Kyushu University. In 2002, he moved to School of Medicine, Keio University, Tokyo and investigated the molecular mechanism of the regulation of hematopoietic stem cells (HSCs) in their niche. His research interest is in studying the mechanisms of the cell fate regulation of HSCs at the single cell level for the establishment of the system that is able to expand HSCs.

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