Role of ATM on self-renewal capacity of hematopoietic stem cells.

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The hematopoietic stem cells (HSC) are maintained in an undifferentiated quiescent state in a niche. Quiescent stem cells show resistance to various stresses, suggesting that mechanisms for protection of HSC from stress contribute to maintenance of self-renew through a whole life in animals. In this study, we demonstrate that cell-cycle checkpoint molecule, ATM (ataxia telangiectasia mutated), is essential for maintenance of capacity of regeneration in HSC.

Ataxia telangiectasia (A-T) is an autosomal recessive disorder caused by mutational inactivation of the ATM. ATM and its homologue have a central role in maintenance of genomic stability via regulating cell cycle checkpoint in response to DNA damage, stability of telomere and oxidative stress. A-T patients display variety of symptoms including premature aging. We hypothesized that a signaling pathway for regulating aging and longevity may be involved in stem cell functions. Hence we analyzed a role of ATM in self-renewal and repopulating capacity of HSCs.

In this study, we demonstrate that ATM has an essential role in the reconstitutive capacity of the haematopoietic stem cells (HSC), but is less required for the differentiation or proliferation into progenitors. $ATM^{-/-}$ mice over the age of 24 weeks showed progressive bone marrow failure due to a defect in HSC function that was associated with up-regulation of $p16^{INK4A}$ and $p19^{ARF}$ in response to elevated reactive oxygen species (ROS). Treatment of anti-oxidative agents restored the reconstitutive capacity of $ATM^{-/-}$ HSCs. These data demonstrate that the self-renewal capacity of HSC depends on ATM-mediated inhibition of oxidative stress.