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Growth signaling at the nexus of stem cell life and death

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Abstract

Stress can activate tumor suppressive mechanisms, causing the loss of adult stem cell function with age. In *Cell Stem Cell* and *Nature*, (Castilho et al., 2009) and (Harrison et al., 2009) highlight the importance of mTOR signaling in stem cell exhaustion and mammalian aging, respectively.

The process of aging is characterized by the reduced capacity to maintain tissue homeostasis and repair damaged tissues following injury. Physiological aging appears to be due, in part, to a decline in the regenerative capacity of adult tissue stem cells. Loss of stem cell function with age can result from cell-intrinsic changes as well as environmental factors. For example, the accumulation of DNA damage in melanocyte stem cells (MSCs) triggers their differentiation, leading to the depletion of the MSC pool and the graying of hair (Inomata et al., 2009). Similarly, the accumulation of DNA damage as well as potential epigenetic changes in hematopoietic stem cells (HSCs) reduce their function with age, a reduction which is related not only to changes in HSC number but also to changes in their mobilization, homing, and differentiation (Rossi et al., 2008). Finally, the aging of satellite cells of muscle can be reversed by exposure to a young blood supply, suggesting that cell-extrinsic, microenvironmental factors may also play a role in the impaired function of certain stem cell populations with age (Conboy et al., 2005).

Recent evidence suggests that stress resulting from DNA damage, oxidative stress, telomerase dysfunction, or persistent growth signaling can lead to the loss of stem cell function by activating tumor suppressive mechanisms that lead to senescence (Rossi et al., 2008). It is known that stem cells from multiple tissues express senescence markers with age. Further, studies addressing the functional role of tumor suppressive mechanisms in aging demonstrated in HSCs, NSCs, and pancreatic islet stem cells that not only do levels of p16^{INK4a} (a known mediator of senescence) increase with age, but that deficiency of this tumor suppressor partially attenuated the age-induced replicative failure of these tissues (Janzen et al., 2006; Krishnamurthy et al., 2006; Molofsky et al., 2006). Addressing the role of oncogenic growth signaling in stem cell function, Yilmaz and colleagues demonstrated that deletion of *Pten*, which negatively regulates proliferation and survival through the phosphatidylinositol-3-OH kinase (PI(3)K) pathway, led to the short-term expansion of HSCs followed by their depletion. Most of these effects were dependent on downstream signaling through the mammalian target of rapamycin (mTOR), as pharmacological

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inhibition of mTOR using rapamycin prevented the phenotypic reduction in HSCs and rescued most of their *in vivo* functions (Yilmaz et al., 2006). While the mechanisms responsible for stem cell depletion observed in the above examples were not conclusively elucidated, and may have involved senescence as well as altered self-renewal or differentiation, these studies nevertheless suggest a general theme wherein tumor suppressive mechanisms play an important role in regulating stem cell function with age.

In this issue of *Cell Stem Cell*, Castilho and colleagues expand on this theme by demonstrating that persistent growth signaling (mediated by Wnt1 overexpression) in hair follicles (HFs) causes aggressive HF growth followed by epithelial cell senescence, loss of the epidermal stem cell compartment, and progressive hair loss (Castilho et al., 2009). Interestingly, while Wnt1 expression led to activation of both β -catenin and the mTOR pathway, hair follicle hyperproliferation and stem cell loss could be largely reversed using rapamycin, suggesting that mTOR plays a dominant role in this process (Figure 1). This work extends the principle that sustained mTOR signaling can lead to the loss of stem cell function to a tissue outside of the hematopoietic system. Further, while the authors cannot conclusively rule out the role of other processes in contributing to the observed loss of hair follicle stem cells, their results suggest that senescence plays a prominent role as a protective mechanism to prevent tumor formation in the face of persistent mTOR activation.

Together, this body of work suggests a delicate balance between the process of aging, which is mediated in part through tumor suppressive mechanisms that lead to the loss of stem cell function, and cancer, which occurs in the absence of such tumor suppressive mechanisms. Moreover, it also suggests a particularly important role for the mTOR pathway in aging and stem cell exhaustion. This begs the question of whether the blockade of senescence-inducing signals such as those produced by persistent mTOR activation can lead not only to the preservation of individual tissue stem cell populations, but even to the slowing of organismal aging. This hypothesis is bolstered by previous observations that TOR inhibition can lead to lifespan extension in invertebrates including yeast, nematodes, and fruit flies (Schieke and Finkel, 2006). Addressing this question for the first time in mammals, a recent study in *Nature* found that rapamycin, when fed to mice beginning at 600 days of age, extends median and maximal lifespan in both males and females (Harrison et al., 2009). On the basis of age at 90% mortality, rapamycin led to a 14% increase in female lifespan and a 9% increase in males. Similarly, when rapamycin treatment began at 270 days, increased survival was also observed in both genders. These highly significant findings reveal a role for mTOR signaling in the regulation of mammalian lifespan as well as demonstrate pharmacological lifespan extension in both genders.

These findings raise many important new questions. For example, was the observed lifespan extension in mice caused by delaying deaths from cancer, delaying the mechanisms of aging, or both? Does mTOR inhibition decrease stem cell senescence or increase the function of various tissue stem cell populations in comparison with age-matched controls? Perhaps most importantly, what are the molecular mechanisms connecting mTOR and aging? Potential clues to this question come from our understanding of mTOR biology. The mTOR kinase nucleates two distinct signaling complexes, mTORC1 and mTORC2, one of which (mTORC1) is allosterically inhibited by rapamycin. The activation of mTORC1 in response to a broad range of pro-growth signals is known to regulate mitochondrial activity, which itself has been shown in several studies to be involved in the regulation of lifespan. Mitochondria may exert this influence through the generation of intracellular reactive oxygen species (ROS) (Schieke and Finkel, 2006), which, in previous work, have been suggested to contribute to HSC exhaustion (Tothova et al., 2007). The connection between mTOR and ROS production is far from understood at the molecular level, but these types of

findings point to a potential direction for future research into the role of mTOR signaling in aging and stem cell function.

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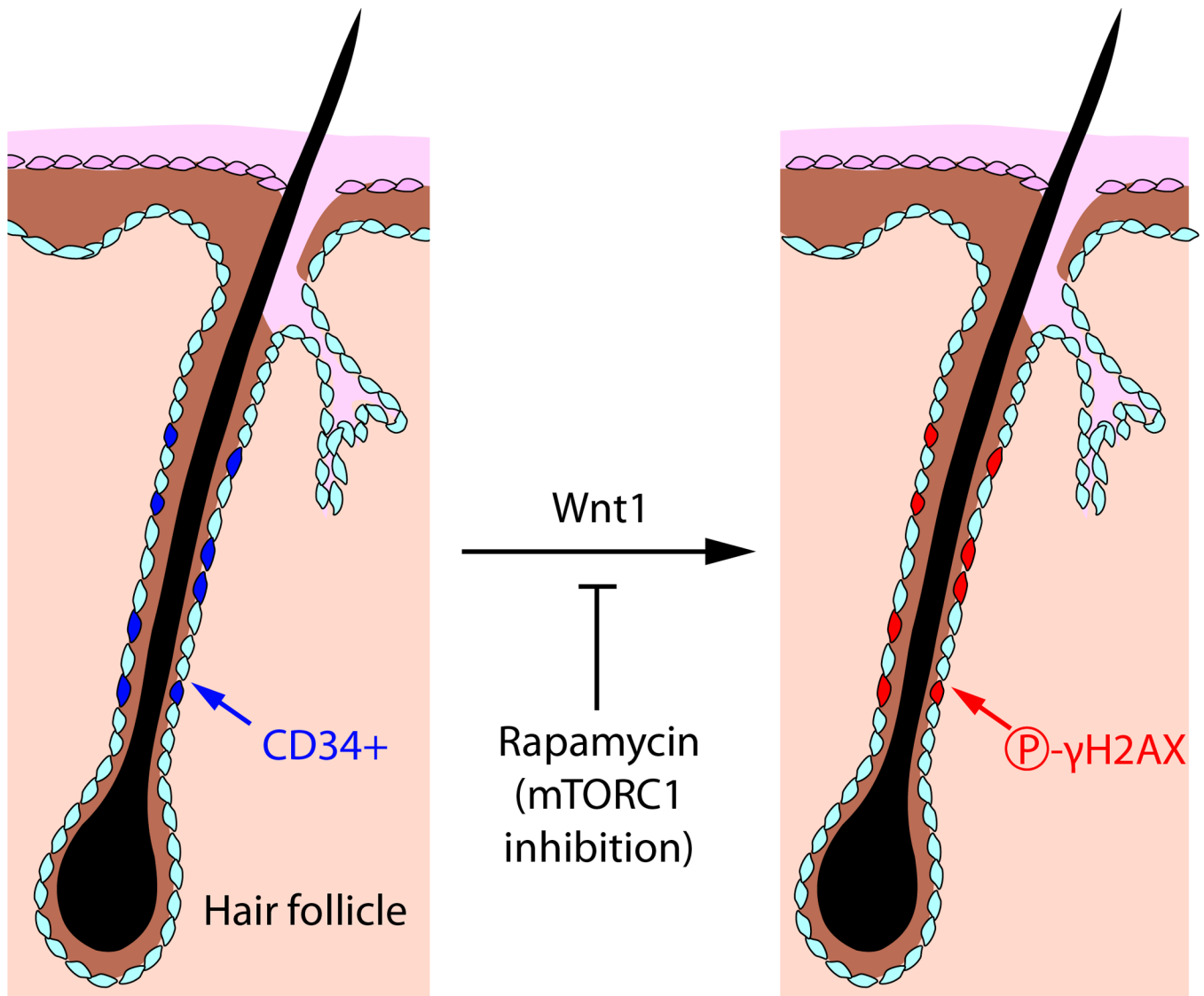


Figure 1. Simplified schematic depicting hair follicle stem cell exhaustion mediated by Wnt1 overexpression

Overexpression of Wnt1 causes rapid hair follicle hyperproliferation (not shown) followed by the loss of CD34+ hair follicle stem cells (blue) and the appearance of nuclear phosphorylated γ H2AX foci (red) indicative of DNA double-strand breaks, a marker of senescence. Wnt1 overexpression also promotes the expression of endogenous β -galactosidase at pH 6, another characteristic of senescent cells, and progressive hair loss. Hair follicle hyperproliferation, the loss of CD34+ hair follicle stem cells, and the appearance of senescence markers can be largely reversed by pharmacological inhibition of mTORC1 with rapamycin.