

## ***Young at heart***

Mammals, humans included, are capable of regenerating the tips of their digits, provided the organism is young enough. As in a regenerating salamander limb, a blastema composed of progenitor cells forms at the tip of the digit, and new epidermis is regenerated from ectoderm-restricted progenitor cells while new bone comes from osteoblast progenitor cells (Fernando et al. 2011; Lehoczky et al. 2011; Rinkevich et al. 2011). This regenerative capacity seen in the young is not restricted to just the digits, however. Heart tissue can regenerate in mice, but only within the first week of life. After that, the ability is lost. This age-related loss of regeneration is suggested to be associated with the generally widespread temporal withdrawal of cells from the cell cycle, as seen in differentiating cardiomyocytes (Porrello et al. 2011). It is known, though, that cardiomyocytes in adult mammals (as in adult zebrafish) will respond to a heart attack by re-entering the cell cycle, presumably contributing to injury repair (Senyo et al. 2013).

Perhaps regeneration in mammals is not much different from that in a fish or salamander. It has recently been shown that the neonatal regenerative ability of the heart in mice is dependent on cardiac neural inputs. Does this sound similar to the requirement for innervation during salamander limb regeneration? (See Figure 24.31 and Figure 2 in Further Development 24.8, online.) Similarly, in the neonatal mouse, mechanical denervation or chemical inhibition of cholinergic nerve function prevented both myocardial cell proliferation and regeneration of heart tissue. Moreover, Neuregulin-1 (as in salamander limb regeneration) is upregulated in the epicardium of injured neonatal mouse hearts, and this expression is lost if the heart is denervated. Misexpression of Neuregulin-1 (along with Nerve Growth Factor) in the injured denervated neonatal mouse heart can rescue its regenerative ability (Mahmoud et al. 2015). This dependence on innervation as well as the role of Neuregulin-1 signaling is also conserved during zebrafish heart regeneration (see Figures 1 and 2 in Further Development 24.13, online). Furthermore, it appears that neuregulin signaling can also function as a mitogenic signal in the uninjured heart, causing myocardial hyperplasia (increase in cell number) and leading to abnormally large hearts (Gemberling et al. 2015). These results identify neuregulin signaling as a conserved mechanism for neural-controlled regeneration; however, its mitogenic powers suggest that significant regulatory controls over this system must be in place to “switch” it on during injury and off upon completion of regeneration.

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