MUSCLE STEM CELL ACTIVATION IN AGING: NOTCH SIGNALING AND THE ENHANCEMENT OF MUSCLE REGENERATIVE POTENTIAL

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In the setting of aging muscle, the ability of resident progenitor cells to maintain, repair, or replace injured tissue is a critical compensatory mechanism to avoid muscle loss. It is known that in aged muscle, there is a loss of regenerative potential compared with normal, young muscle. The focus of our recent work has been to understand the regulation of that regenerative potential by studying both the muscle stem cells themselves as well as the environment in which they reside and function. Under normal conditions, the Notch signaling pathway plays an important role in different phases of the activation, proliferation, commitment, and differentiation of the primary muscle stem cell, the satellite cell, and its progeny. Inhibition of Notch signaling profoundly impairs muscle regenerative potential. Intriguingly, with age, there is a failure of activation of this pathway in satellite cells in response to injury, and this accounts for much of the impaired regenerative potential of aged muscle. Among the key aspects of impaired Notch signaling in aged tissue is the failure to upregulate the expression of the Notch ligand, Delta. When Delta is not induced, the Notch signaling pathway is not activated and satellite cells fail to generate sufficient progeny for effective muscle repair. However, when Notch signaling is directly stimulated, bypassing the need for ligand-induced activation, aged satellite cells are as effective in mediating effective regeneration as are young satellite cells. Therefore, the older satellite cells retain the intrinsic regenerative potential, and it is really the environment that limits effective regeneration Furthermore, when muscles of aged mice are exposed for 6-8 weeks to the systemic milieu of younger animals by parabiotic pairings, the regeneration of the aged muscle is indistinguishable from that in the younger partners. This enhanced regenerative potential is paralleled by an upregulation of Delta in response to injury in the aged muscle. Clearly, factors in young serum are capable of modifying the aged progenitor cells or their niche such that, in response to injury, aged muscle displays a youthful phenotype both at a molecular level and at a histological level. These studies suggest that the age-related impairment of muscle regeneration may not be due to an irreversible loss of progenitor cells, or an irreversible loss of their potential, but may in fact be amenable to systemic treatment to promote more effective tissue repair and maintenance.