Molecular aging and rejuvenation of human muscle stem cells.

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Public Summary:
This work establishes that experimental changes in specific molecules can boost the regenerative performance of muscle stem cells, which have been isolated from old people.

Scientific Abstract:
Very little remains known about the regulation of human organ stem cells (in general, and during the aging process), and most previous data were collected in short-lived rodents. We examined whether stem cell aging in rodents could be extrapolated to genetically and environmentally variable humans. Our findings establish key evolutionarily conserved mechanisms of human stem cell aging. We find that satellite cells are maintained in aged human skeletal muscle, but fail to activate in response to muscle attrition, due to diminished activation of Notch compounded by elevated transforming growth factor beta (TGF-beta)/phospho Smad3 (pSmad3). Furthermore, this work reveals that mitogen-activated protein kinase (MAPK)/phosphate extracellular signal-regulated kinase (pERK) signalling declines in human muscle with age, and is important for activating Notch in human muscle stem cells. This molecular understanding, combined with data that human satellite cells remain intrinsically young, introduced novel therapeutic targets. Indeed, activation of MAPK/Notch restored 'youthful' myogenic responses to satellite cells from 70-year-old humans, rendering them similar to cells from 20-year-old humans. These findings strongly suggest that aging of human muscle maintenance and repair can be reversed by 'youthful' calibration of specific molecular pathways.