Reactivation of embryonic genes leads to muscle aging

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In response to a muscle injury in old age, developmental pathways are re-activated that originally play a major role in embryonic development. Paradoxically, in old age, they heavily decrease the regenerative capacity of the skeletal muscle. Credit: FLI/adpic/Fotolia

Developmental genes and pathways strictly regulate embryogenesis. The

process is strongly driven by so-called Hox-genes. Now, researchers from the Leibniz Institute on Aging (FLI) in Jena, Germany, can show that one of these genes, Hoxa9, is re-activated in old age. This limits the functionality of muscle stem cells and, hence, the regenerative capacity of skeletal muscle. Ironically, these findings show that the same genes that control embryo-developmental processes also impair stem cell functionality and regeneration in the elderly. Nonetheless, it is a process which can be rescued by compounds inhibiting the epigenetic activation of Hoxa9; pointing to novel targets for regenerative therapies in aging. The study is published in the scientific journal *Nature* on November 30, 2016.

The development of the embryo during pregnancy is one of the most complex processes in life. Genes are strongly activated, and developmental pathways must do their job in a highly accurate and precisely timed manner. So-called Hox-genes play an important regulatory role in this process. Although remaining detectable in stem cells of adult tissues throughout life, after birth they are only rarely active. Now, however, researchers from the Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) in Jena, Germany have shown that, in old age, one of these Hox-genes (Hoxa9) is strongly re-activated in murine muscle stem cells after injury; leading to a decline in the regenerative capacity of skeletal muscle. Interestingly, when this faulty gene reactivation was inhibited by chemical compounds, muscle regeneration was improved in aging mice, thus suggesting novel therapeutic approaches aimed at improving muscle regeneration in old age.

Activation of embryonic genes in aging stem cells

The biggest surprise from the current study is that the reactivation of Hoxa9 after muscle injury in old age impairs the functionality of muscle stem cells - instead of improving it. Dr. Stefan Tümpel, co-corresponding author and postdoc at the FLI, explains - "Originally,

Hoxa9-induced developmental pathways are responsible for the proper development of body axes - for example, during development of the fingers of a hand". Dr. Julia von Maltzahn is leading the research group on muscle stem cells at the FLI. She adds that - "A decline in stem cell functionality leads to an unavoidable decrease in the regenerative capacity of the whole skeletal muscle. With age, this may weaken the muscular strength after injury." The courses of stem cell and tissue aging are yet to be completely understood. It has already been recognized that signals which control the development of the embryo become activated in aging stem cells. However, the regulator-genes controlling these signals have not yet been analyzed in aging. "From an evolutionary perspective, Hox-genes are very old. They regulate organ development across almost the entire animal kingdom - from flies up to humans. It is a huge surprise that the faulty reactivation of these genes leads to stem cell aging in muscle. This finding will fundamentally influence our understanding of the courses of aging", expects Prof. K. Lenhard Rudolph, Scientific Director at the FLI.

Altered epigenetic stress response

The activation of developmental genes in an embryo must be timed very precisely, in order to ensure faultless tissue formation and organ development. This fragile process is regulated by alterations of the epigenome - i.e. chemical modifications of the DNA. In collaboration with Dr. Christian Feller and Prof. Dr. Ruedi Aebersold from ETH Zurich, a new methodological approach was applied to identify the epigenetic changes that occur in muscle stem cells after injury, as putative causes for the reactivation of Hox-genes in old age. Simon Schwörer is a PhD Student at the FLI and first author of the paper. He describes how, "Surprisingly, old muscle stem cells did not show a faulty activation of the epigenome in quiescence - the resting stage in non-injured muscle. Only in response to a muscle injury, do the stem cells display an abnormal epigenetic stress response, which leads to the

opening of DNA and, thus, to the activation of developmental pathways." Working alongside scientists from Jena und Zurich were collaborators from Ulm, Heidelberg, Los Angeles and Rochester; all of whom contributed significantly to the astonishing results.

Regenerative medicine

In collaboration with the University Hospital Jena (UKJ), Prof. K. Lenhard Rudolph plans to investigate, "…whether a similar reactivation of embryonic genes is also causative for the loss of muscle maintenance in aging humans." The *Nature* study proves already that medical compounds that limit alterations in the epigenome, may improve the regenerative capacity of muscles in old mice. Thus far, this approach is too unspecific and affects the modification of genes in several cells and tissues. For this reason, a collaborative study with the "Jena Center for Soft Matters" (Dr. Anja Träger) is primed to investigate whether a nanoparticle-induced, target-specific inhibition of Hox-genes in muscle stem cells is feasible and, if so, would it be sufficient to improve muscle regeneration and maintenance.

More information: Simon Schwörer et al. Epigenetic stress responses induce muscle stem-cell ageing by Hoxa9 developmental signals, *Nature* (2016). DOI: 10.1038/nature20603

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