Leibniz Institute on Aging –
Fritz Lipmann Institute

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Press Release
November 30, 2016

Back to the Start: Re-activation of Embryonic Genes Leads to Muscle Aging

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 re-activation 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. The study is published in the renowned scientific journal *Nature* on November 30, 2016.

Activation of embryonic genes in aging stem cells – a new course of stem cell and tissue aging

The biggest surprise from the current study is that the re-activation 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 re-activation 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 re-activation 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.

Future perspectives: Regenerative medicine

In collaboration with the University Hospital Jena (UKJ), Prof. K. Lenhard Rudolph plans to investigate, "…whether a similar re-activation 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.

Publication

Schwoerer S, Becker F, Feller C, Baig AH, Koeber U, Henze H, Kraus JM, Xin B, Lechel A, Lipka DB, Varghese CS, Schmidt M, Rohs R, Aebersold R, Medina KL, Kestler HA, Neri F, von Maltzahn J*, Tuempel S*, Rudolph KL*. *Co-corresponding authors. Epigenetic stress responses induce muscle stem cell aging by Hoxa9 developmental signals. *Nature* 2016 (in press). Doi: 10.1038/nature20603.

Additional information

Pictures and graphs for download & Video-interviews with the authors can be found here:
http://www.leibniz-fli.de/institute/public-relations/press-campaign-nature-paper/

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Background information

The **Leibniz Institute on Aging – Fritz Lipmann Institute (FLI)** is the first German research organization dedicated to biomedical aging research since 2004. More than 330 members from over 30 nations explore the molecular mechanisms underlying aging processes and age-associated diseases. For more information, please visit www.leibniz-fli.de.

The **Leibniz Association** connects 88 independent research institutions that range in focus from the natural, engineering and environmental sciences via economics, spatial and social sciences to the humanities. Leibniz Institutes address issues of social, economic and ecological relevance. They conduct knowledge-driven and applied basic research, maintain scientific infrastructure and provide research-based services. The Leibniz Association identifies focus areas for knowledge transfer to policy-makers, academia, business and the public. Leibniz Institutes collaborate intensively with universities – in the form of "WissenschaftsCampi" (thematic partnerships between university and non-university research institutes), for example – as well as with industry and other partners at home and abroad. They are subject to an independent evaluation procedure that is unparalleled in its transparency. Due to the institutes' importance for the country as a whole, they are funded jointly by the Federation and the Länder, employing some 18,100 individuals, including 9,200 researchers. The entire budget of all the institutes is approximately 1.64 billion EUR. See www.leibniz-association.eu for more information.

Pictures

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. (Source: FLI/adpic/Fotolia)