Leibniz Institute on Aging –
Fritz Lipmann Institute

Press release
January 10, 2020

Loss of microRNA leads to fibrosis

Fibrosis describes a pathological stiffening of organs or tissues that is caused by the increased synthesis of extracellular proteins. Fibrosis severely impairs organ function and may occur in several organs, like lung, kidney and heart. Fibrosis develops with increasing age and is also found in patients with liver cancer. A research team led by Professor Alfred Nordheim, Interfaculty Institute of Cell Biology of the Eberhard Karls University Tübingen and Scientific Director of the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) in Jena, Germany, identified microRNAs that are responsible for fibrosis development. These findings may suggest potential approaches for the treatment of liver cancer and fibrosis formation in old age. The results are published in the journal *Proceedings of the National Academy of Sciences* (PNAS).

Fibrosis appears during the aging process of an organism, but is also facilitated by an unhealthy lifestyle. Furthermore, tumor formation can be closely linked to fibrosis, as is apparent in liver cancer. In fibrosis, proteins, especially collagens, accumulate in the cells of organ tissue which can lead to hardening of the tissue or even organ failure. This can affect lungs, heart, kidney or liver. In cancer patients, the formation of tumors is often preceded by fibrosis in the affected organ, especially in liver carcinomas such as hepatocellular carcinoma (HCC), a cancer that is often fatal.

Researchers from Heidelberg, Dortmund, Braunschweig and Aachen investigated together with the molecular biologist Professor Alfred Nordheim of the Interfaculty Institute of Cell Biology of the Eberhard Karls University Tübingen and Scientific Director of the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) in Jena, the development and progression of liver cancer in mice and identified the group of anti-fibrotic microRNAs involved in this process.

Inactivation of microRNAs leads to fibrosis

The identified microRNA molecules (miRNA) inhibit the formation of collagens and other proteins associated with fibrosis. In a healthy state, they thus prevent the formation of fibrosis in the liver. During carcinogenesis, however, those miRNAs are switched off (inactivated) so that fibroses occur which promote the progression of liver carcinoma.

The research team analyzed additional data from already existing tumor databases and found these miRNA molecules to be suppressed also in breast and lung cancer in humans. Further research has to show if this inactivation of microRNAs is also relevant in fibrosis of the elderly.

Control through microRNA network

PhD students Ivana Winkler and Catrin Bitter from Tübingen showed that the microRNA molecules cooperate in a network of different microRNAs that is controlled by the regulator protein PPARγ. Only this interaction prevents the formation of fibroses. It is currently investigated in a

mouse model if this central control by PPARγ can serve as therapeutic target; i.e. if the formation of fibrotic tissue in patients can be reduced by a pharmacological activation of PPARγ.

The project has been carried out by the Nordheim research group in cooperation with colleagues from the Department of Computer Science of the University of Tübingen, the German Cancer Research Center (DKFZ) in Heidelberg, the Leibniz Research Centre for Working Environment and Human Factors (IfADO) in Dortmund, the Helmholtz Centre for Infection Research in Braunschweig, and the Institute of Molecular Pathobiochemistry, University Hospital Aachen. The work was funded by the German Cancer Aid (Project 109886) and the German Research Foundation (DFG; SFB/TR 209 (Project ID 314905040), Subproject B02), among others.

Publication

Winkler I, Bitter C, Winkler S, Weichenhan D, Thavamani A, Hengstler JG, Borkham-Kamphorst E, Kohlbacher O, Plass C, Geffers R, Weiskirchen R, Nordheim, A. Identification of Pparγ-modulated miRNA hubs that target the fibrotic tumor microenvironment. *Proceedings of the National Academy of The Sciences of the United States of America* 2019, https://www.pnas.org/cgi/doi/10.1073/pnas.1909145117

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Background information

The **Leibniz Institute on Aging – Fritz Lipmann Institute (FLI)** – upon its inauguration in 2004 – was the first German research organization dedicated to research on the process of aging. More than 350 employees from around 40 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 95 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 20,000 individuals, nearly half of whom are researchers. The entire budget of all the institutes is approximately 1.9 billion EUR. See https://www.leibniz-gemeinschaft.de/en/ for more information.