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Dysfunction in the mitochondrial respiration leads to cartilage degenerative diseases

A disturbed energy metabolism in the cells causes cartilage tissue to be built up incorrectly / research group of the UoC's Faculty of Medicine publishes study in the 'Journal of Biological Chemistry'

A team led by Professor Dr Bent Brachvogel, Head of Experimental Neonatology at the Faculty of Medicine and University Hospital Cologne, has discovered previously unknown regulatory mechanisms of tissue organization. Together with other researchers in Brachvogel's team, first author of the new study and licensed pharmacist Kristina Bubb investigated changes in the so-called extracellular matrix (ECM) and established a connection between the mitochondrial respiratory chain (a series of reactions in cells) and the balance of the ECM. The study 'Mitochondrial respiratory chain function promotes extracellular matrix integrity in cartilage' has now appeared in the *Journal of Biological Chemistry*.

Musculoskeletal diseases are the leading cause of chronic pain and loss of mobility worldwide. Both significantly limit people's quality of life. Often, early childhood disorders or age-related changes in the extracellular matrix lead to long-term chronic diseases and dysfunctions of the musculoskeletal system. A change in the ECM can, for example, lead to arthrosis and osteoporosis.

The ECM is the tissue between cells in the so-called intercellular space, mainly in connective tissue. It is produced by the cells, embeds them and forms the stabilising framework of the tissue. However, since little is known about the connections between disturbances in the ECM and musculoskeletal diseases, specific treatment options are currently not available. The research team discovered that the mitochondrial respiratory chain in cartilage tissue plays a key role in maintaining the balance (homeostasis) of the ECM. The respiratory chain is part of the energy metabolism of

cells: a series of biochemical reactions take place in the mitochondria, the ‘power houses of the cells,’ which are responsible for energy production in organisms. This can influence the integrity and mechanical stability of the ECM in cartilage, and presumably also in many other tissues.

In a model organism, the researchers demonstrated that dysfunction of the mitochondrial respiratory chain in cartilage is associated with a postnatal delay in skeletal growth. To further investigate the molecular relationships, the scientists used the latest sequencing and measurement techniques: they applied a combined approach of high-resolution scRNA sequencing, mass spectrometry, and electron microscopy to investigate cartilage-specific inactivation of respiratory chain function. They discovered that loss of mitochondrial respiration leads to tissue disorganisation and expansion, as well as stiffening of the cartilage matrix. This is caused by impaired metabolic signalling, which secondarily altered the composition and mechanical properties of the cartilage.

According to the researchers, these results are a significant milestone towards a better understanding of musculoskeletal diseases. In the medium and long term, they could advance the development of new diagnostic and therapeutic approaches. Professor Brachvogel is also spokesperson of the research group FOR2722 ‘New molecular factors of musculoskeletal extracellular matrix homeostasis’ funded by the German Research Foundation (DFG). He said, ‘The energy metabolism of the cell is very important for the production of the extracellular matrix, but the interactions between these components have not been sufficiently understood so far. We have demonstrated for the first time the importance of the mitochondrial respiratory chain as an essential energy supplier for extracellular matrix homeostasis in cartilage.’

Kristina Bubb added, ‘Our research has identified the mitochondrial respiratory chain as a new therapeutic target for treating a defective extracellular matrix in degenerative cartilage disease.’

Based on these findings, the exact molecular connections between cellular energy metabolism, EZM homeostasis and the development of musculoskeletal diseases will be clarified. In the future, the results will be incorporated into the development of new treatment strategies for degenerative diseases of the musculoskeletal system.

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