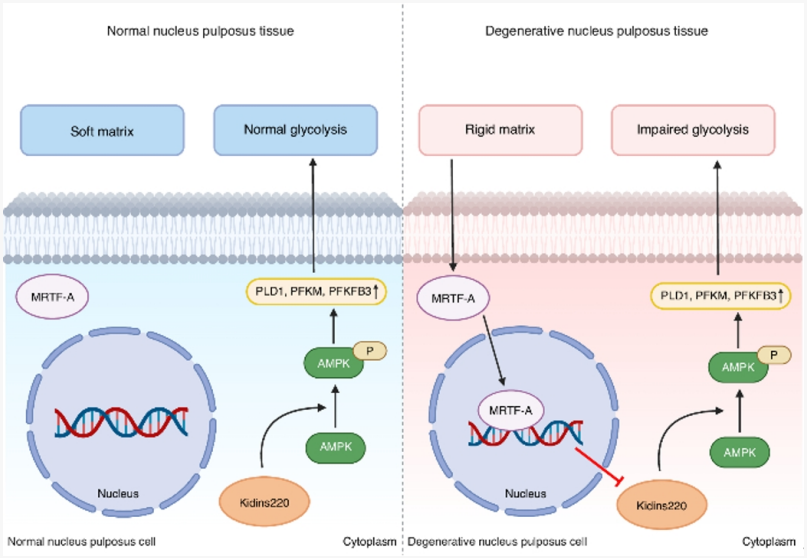
Matrix stiffness and energy crisis in spinal discs: a new pathway to combat degeneration

GA, UNITED STATES, March 3, 2025 /EINPresswire.com/ -- A pioneering study has revealed that increased stiffness in the extracellular matrix (ECM) of spinal discs impairs energy production in nucleus pulposus cells (NPCs), a key factor in intervertebral disc degeneration (IVDD). The research identifies the protein MRTF-A as a critical regulator in this process, showing that its activation under stiff conditions suppresses glycolysis, the primary energy source for NPCs. By targeting MRTF-A, this study proposes a novel therapeutic strategy to mitigate disc degeneration and improve patient outcomes.



Schematic diagram depicting the mechanism of the rigid matrix regulating cell glycolysis in degenerated NPCs.

Intervertebral disc degeneration (IVDD) is a leading cause of chronic back pain and disability, impacting millions of people worldwide. Characterized by the breakdown of the disc's extracellular matrix (ECM), this condition leads to increased stiffness and impaired cellular function. nucleus pulposus cells (NPCs), which depend on glycolysis for energy, are particularly susceptible to these mechanical changes. While previous research has shown that ECM stiffness can alter cellular metabolism, the specific mechanisms linking stiffness to glycolysis in NPCs have remained poorly understood. This gap in knowledge underscores the urgent need to investigate how mechanical changes in the disc environment affect cellular energy production and contribute to the progression of IVDD.

Published (DOI: 10.1038/s41413-025-00402-7) on February 14, 2025, in Bone Research, a study led by researchers from Soochow University and Huazhong University of Science and Technology uncovers the link between matrix stiffness and disrupted cellular energy production in spinal discs. The research demonstrates that increased matrix stiffness activates the protein MRTF-A, which suppresses glycolysis in NPCs. The study employs advanced techniques, including RNA sequencing and gas chromatography-mass spectrometry, to identify a novel pathway involving

MRTF-A and the AMPK signaling pathway, shedding new light on the mechanobiology of IVDD.

The study utilized hydrogels with varying stiffness levels to simulate the mechanical environment of NPCs, revealing that rigid substrates significantly reduce glycolysis and alter the expression of cytoskeletal genes. MRTF-A, a mechanosensitive transcriptional coactivator, was found to be upregulated in degenerated disc tissues and translocated to the nucleus under stiff conditions. This activation of MRTF-A led to the downregulation of Kidins220, a protein crucial for AMPK phosphorylation, which is necessary for glycolysis. Furthermore, inhibiting MRTF-A with the compound CCG-203971 partially restored glycolysis and improved disc health in animal models. These results pinpoint MRTF-A as a key mediator in the mechanotransduction process linking matrix stiffness to impaired cellular energy production, offering a potential therapeutic target for IVDD.

"This study reveals a previously unknown mechanism through which matrix stiffness disrupts cellular energy metabolism in spinal discs," said Dr. Jun Dai, senior author of the study. "By targeting MRTF-A, we could potentially reverse the metabolic dysfunction in NPCs, slow down the progression of disc degeneration, and offer new hope for millions of people suffering from chronic back pain."

The findings have significant implications for IVDD treatment, a condition for which effective therapies are currently limited to symptom management. Identifying MRTF-A as a crucial player in the mechanotransduction process opens the door to developing targeted therapies that could restore cellular energy production and halt disc degeneration. Future research could focus on clinical trials exploring the use of MRTF-A inhibitors like CCG-203971, potentially offering a breakthrough treatment that addresses the root cause of IVDD rather than just alleviating symptoms. This study could also pave the way for further investigations into how mechanical forces influence cellular metabolism in other tissues and diseases.

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