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DEGENERATIVE DISC DISEASE

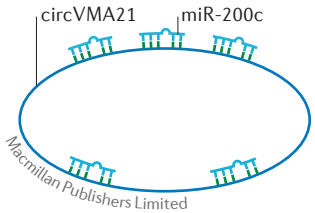
# Circular RNA reduces cell death in IVD disease

Intervertebral disc (IVD) degeneration contributes to low back pain, a leading cause of disability worldwide. Under pro-inflammatory conditions, cells of the nucleus pulposus, which makes up the inner part of the IVD, become apoptotic and produce matrix degrading enzymes. Now, research has revealed a new approach to halting nucleus pulposus cell death by the adenoviral administration of circular RNA (circRNA).

Some endogenous non-coding RNAs, such as circRNAs, are thought to bind to microRNAs (miRNAs) and sequester them from the cytoplasm. By doing so, these non-coding RNAs can influence the transcriptional regulation of mRNAs and thereby affect key cellular processes.

In their new study, Cheng et al. analysed the miRNA content of cells from degenerative nucleus pulposus tissue and found miR-200c to be overexpressed compared with in healthy nucleus pulposus cells. Overexpression of miR-200c in nucleus pulposus cells was linked to a high degree of apoptosis, which could be suppressed using an miR-200c antagonist.

> “Overexpression of miR-200c in nucleus pulposus cells was linked to a high degree of apoptosis”




Bioinformatic prediction identified E3 ubiquitin-protein ligase XIAP, a regulator of apoptosis, as a candidate target for regulation by miR-200c. Cheng et al. found normal levels of XIAP pre-mRNA in cells from degenerative nucleus pulposus tissue, but reduced expression of XIAP protein, which could be rescued by knock down of miR-200c, suggesting that the expression of XIAP is post-transcriptionally suppressed by miR-200c, and that this suppression increases apoptosis in these cells, thereby contributing to disease.

Next, the researchers investigated a circRNA derived from *VMA21* (circVMA21) that was present at high levels in nucleus pulposus cells under normal conditions, but that was greatly reduced in cells from degenerative nucleus pulposus tissue. Upon sequence analysis, Cheng et al. discovered six putative binding sites for miR-200c on circVMA21 and validated five of these sites by luciferase assay and pull-down assay analyses.

To test the ability of circVMA21 to act as an miRNA sponge, the researchers used an adenovirus to administer circVMA21 directly into the intervertebral disc in a rat model of IVD degeneration. At 9 weeks post-administration, rats that had received circVMA21 had reduced IVD degeneration as measured by MRI score and histology, and showed reduced levels of nucleus pulposus cell death compared with vector-treated rats. These results hint at the potential to target post-transcriptional regulation in the future to alleviate disease.

*Joanna Collison*

**ORIGINAL ARTICLE** Cheng, X. et al. Circular RNA VMA21 protects against intervertebral disc degeneration through targeting miR-200c and X linked inhibitor-of-apoptosis protein. *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2017-212056 (2018)