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EPIGENETIC DRUG TARGETS TO TREAT OR PREVENT OSTEOARTHRITIS AND CARTILAGE DEGRADATION

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A team of researchers at Washington University in St. Louis has identified an epigenetic pathway and two therapeutic targets that could be used to prevent cartilage loss and counteract the mechanism underlying osteoarthritis. The inventors have seen promising results in a mouse model of arthritis using an FDA-approved small molecule to inhibit one of these targets.

Osteoarthritis (OA) is characterized by progressive degradation and significant loss of articular cartilage. Currently, OA is treated with pain medication and joint surgery but there is no effective treatment that modifies the underlying damage from the condition. While studying the role of epigenetic regulators in OA and inflammation, the inventors elucidated a cellular pathway that could be targeted for this purpose. In particular, they found that DNA Methyltransferase 3B (Dnmt3b) is important in maintaining healthy cartilage - increased levels of Dnmt3b appear to protect against the development and progression of OA. Downstream, methylation by Dnmt3b regulates the levels of aminobutyrate aminotransferase (Abat), a critical regulator of metabolism in cartilage cells. Therefore, harnessing this pathway is a promising strategy to protect cartilage and treat OA. Either increasing the amount of Dnmt3b or inhibiting Abat could potentially slow or stop cartilage degradation or stimulate regeneration. Initial studies in a mouse model of OA have shown that vigabatrin, an FDA-approved Abat inhibitor, protects against cartilage damage.

Validation for Dnmt3b

- Dnmt3b gene is expressed in healthy chondrocytes (human and mouse) and decreased in aging and OA cartilage.
- Mouse models demonstrate that Dnmt3b loss of function results in spontaneous OA-like condition and Dnmt3b gain of function has chondroprotective effects.

Validation for Abat

- In vitro studies indicate that Abat functions downstream of Dnmt3b (Dnmt3b methylates Abat and reduced methylation leads to increased Abat expression).
- Mouse joint studies demonstrate that increased Abat expression accelerates cartilage degradation; conversely, Abat knock down protects against cartilage degradation.
- Vigabatrin (an FDA-approved small-molecule Abat inhibitor) protects against OA in a mouse model.

Applications

- **Osteoarthritis/cartilage degradation drug targets –** epigenetic/protein pathway with validated mechanistic effects on cartilage degradation could be used to identify:
  - compositions to increase Dnmt3b expression (such as Dnmt3b nucleotides)

- compounds to inhibit Abat activity (such as vigabatrin)

Key Advantages

- **Mechanistic targets -** rather than simply treating pain symptoms, compounds that inhibit Abat or increase Dnmt3b expression could directly impact an epigenetic mechanism underlying cartilage degradation
- **FDA-approved compound –** vigabatrin is an FDA-approved Abat inhibitor that could potentially be repurposed for treating osteoarthritis

Publications

- Shen, J., Wang, C., Ying, J., Xu, T., McAlinden, A., & O'Keefe, R. J. (2019). Inhibition of 4-aminobutyrate aminotransferase protects against injury-induced osteoarthritis in mice. *JCI insight*, 4(18).
- Shen, J., Wang, C., Li, D., Xu, T., Myers, J., Ashton, J. M., ... & O'Keefe, R. J. (2017). DNA methyltransferase 3b regulates articular cartilage homeostasis by altering metabolism. *JCI insight*, 2(12).
- Shen, J., Abu-Amer, Y., O'Keefe, R. J., & McAlinden, A. (2017). Inflammation and epigenetic regulation in osteoarthritis. *Connective tissue research*, 58(1), 49-63.

Patents

- DNA methyltransferases for the treatment and prevention of arthritis (U.S. Patent No. 10,123, 983)