Introduction

- Small leucine rich proteoglycans (SLRPs) regulate the formation and maintenance of cartilage matrix through altering collagen fibrillogenesis and modulating growth factor presentation.
- Chondroadherin-like (CHADL) is an SLRP that is expressed in chondrocytes during periods of high matrix synthesis. CHADL is relatively uncharacterized but may function to slow chondrogenic differentiation and promote matrix (Tillgren, 2015).
- A genome-wide association study (GWAS) has uncovered a rare genetic variant in CHADL associated with high risk of hip osteoarthritis (Styrkarsdottir, 2017).
- The efficient use of the CRISPR/Cas9 ribonucleoprotein (RNP) system has been established in primary human chondrocytes as a method to generate engineered cartilage with the complete knockout of target genes (D’Costa, 2019).

8 bp insertion mutation in CHADL (rs523464664)

Characterization of Chadl knockout mice

- Chadl knockout mice show normal development, allowing for investigation of protein function during cartilage matrix production.
- Chadl knockout mice allow for investigation of age-related OA without confounding factors.
- Inserting the 8 bp in murine neuro2A cells paves the way for making a novel genetically-engineered mouse.
- Overexpression of plasmid DNA with the 8 bp insertion allows for overexpression in HEK-293 and human chondrocytes.

Discussion

- The high risk of OA with a genetic variant in CHADL suggests that this protein may regulate optimal cartilage function.
- The complete knockout of CHADL in primary human chondrocytes allows for investigation of protein function during cartilage matrix production.
- The rs523464664 mutation is an 8 bp insertion in the open reading frame of CHADL exon 3, causing both a frameshift and premature stop. While the transcript may be susceptible to nonsense mediated decay before translation, if made the truncated protein would contain 106 novel amino acids at the C-terminus (Styrkarsdottir, 2017).
- The efficient use of the CRISPR/Cas9 ribonucleoprotein (RNP) system has been established in primary human chondrocytes as a method to generate engineered cartilage with the complete knockout of target genes (D’Costa, 2019).

References