The epigenetic signature of human tendinopathy

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INTRODUCTION: Tendinopathy encompasses multifactorial tendon disorders characterised by pain and functional limitation that are likely to manifest through a combination of extrinsic and intrinsic factors, including epigenetics modifications. The role of epigenetics in tendinopathy is not well established, therefore, we conducted a comprehensive multi-omic study investigating the epigenetic changes that influence gene expression in tendon disorders.

METHODS: Using control (hamstring tendon from patients undergoing cruciate ligament repair) and diseased tenocytes (supraspinatus tendon from patients undergoing rotator cuff repair), we conducted ATAC-seq to assess differential chromatin accessibility between control and diseased tenocytes. Additionally, we used ChIP-seq to profile histone modifications (H3K4me3, H3K27me3, H4K20Me3) associated with fibrotic disease. Furthermore, we extracted RNA from control and tendinopathic tissue and performed RNA-seq. All procedures and protocols were approved by the local NHS ethics committee.

RESULTS SECTION: ATAC-seq analysis identified 54195 significantly more accessible genomic loci in diseased tenocytes compared to control. Furthermore, comparison between diseased and control cells identified several significantly different peaks in active and repressive histone modifications (H3K4me3 and H3K27me3, respectively). Both ATAC-seq and ChIP-seq analysis indicated that pathways such as cell adhesion and extracellular matrix organisation were dysregulated as a result of epigenetic changes. RNA-seq analysis found 496 genes to be significantly different between control and diseased tendon. Overlay analysis of ChIP-seq/ATAC-seq and RNA-seq data indicated a number of dysregulated genes observed in tendinopathy are epigenetically reprogrammed, including FGFR3, GLIS3 and RIPK4.

DISCUSSION: The current epigenetic study provides insights into the aberrant processes associated with tendon disorder pathogenesis. The greater accessible genome loci indicate disease tenocytes may be more "primed" for gene activation, in particular for those genes and processes associated to tendon disease pathology, i.e collagen and matrix protein turnover.

SIGNIFICANCE/CLINICAL RELEVANCE: The current study indicates, with further investigation, epigenetic-targeted therapies could become a viable treatment option for tendon disorders in future.