The epigenetic landscape in Dupuytren’s fibrosis

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INTRODUCTION: Dupuytren’s disease (DD) is a fibroproliferative soft tissue disease affecting the palmar fascia of the hand causing permanent and irreversible flexion contracture. Aberrant fibrosis is likely to manifest through a combination of extrinsic, intrinsic, and environmental factors, including genetics and epigenetics. However, the role of epigenetics in soft tissue fibrosis in diseases such as DD is not well established. Therefore, we conducted a comprehensive multi-omic study investigating the epigenetic profiles that influence gene expression in DD pathology.

METHODS: Using control (patients undergoing carpal tunnel release) and diseased fibroblasts (patients undergoing Dupuytren’s fasciectomy), we conducted ATAC-seq to assess differential chromatin accessibility between control and diseased fibroblasts. Additionally, ChIP-seq mapped common histone modifications (histone H4; H3K4me3, H3K9me3, H3K27me3, H4K16Ac, H4K20Me3) associated with fibrosis. Furthermore, we extracted RNA from control and DD tissue and performed bulk RNA-seq. All procedures and protocols were approved by the local NHS ethics committee.

RESULTS SECTION: ATAC-seq analysis identified 2470 accessible genomic loci significantly more accessible in diseased fibroblasts compared to control. Comparison between diseased and control cells identified numerous significantly different peaks in histone modifications (H4K20me3, H3K27me3, H3K9me3) associated with gene repression in control cells but not in diseased cells. Pathway analysis demonstrated a substantial overlap in genes being derepressed across these histone modifications (Figure 1). Both, ATAC-seq and ChIP-seq analysis indicated pathways such as cell adhesion, differentiation, and extracellular matrix organisation were dysregulated as a result of epigenetic changes. Moreover, de novo motif enrichment analysis identified transcription factors that possibly contributed to the differential gene expression between control and diseased tissue, including HIC1, NFATC1 and TEAD2. RNA-seq analysis found that these transcription factors were upregulated in DD tissue compared to control tissue.

DISCUSSION: The current epigenetic study provides insights into the aberrant fibrotic processes associated with soft tissue diseases such as DD. The data indicate diseased fibroblast to be more “primed” for cell activation by decreased gene repression. Further analysis shows, de-repression of key transcription factors may result in increased expression of genes associated with fibrotic pathology.

SIGNIFICANCE/CLINICAL RELEVANCE: The preliminary data from this study indicate that epigenetic-targeted therapies may be an interesting viable treatment option in future for fibrotic disease pathologies.

Figure 1. Venn diagram showing the number of overlapping gene associate peaks with significantly different peak intensities of histone modifications associated with gene repression.