Author's response to reviews

Title: Epigenetic Histone Methylation Modulates TGFBIp and Extracellular Matrix Gene Expression in Corneal Fibroblasts

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Author's response to reviews: see over
Dear Editor:

Please find enclosed our manuscript entitled “Epigenetic Histone Methylation Modulates TGFBIp and Extracellular Matrix Gene Expression in Corneal Fibroblasts” by Maeng, Y.S. et al. We would like to be considered this for publication in BMC Medical Genomics. All authors concur with its submission and it has not been submitted elsewhere for publication.

TGFβ1-induced expression of transforming growth factor β-induced protein (TGFBIp) and extracellular matrix (ECM) genes plays a major role in the development of granular corneal dystrophy type 2 (GCD2: also called Avellino corneal dystrophy). Although some key transcription factors are known, the epigenetic mechanisms modulating TGFBIp and ECM expression remain unclear. We examined the role of chromatin markers such as histone H3 lysine methylation (H3Kme) in TGFβ1-induced TGFBIp and ECM gene expression in normal and GCD2-derived human corneal fibroblasts.

Transcription and extracellular-secretion levels of TGFBIp were high in normal cells compared with those in GCD2-derived cells and were related to H3K4me3 levels but not to DNA methylation over the TGFBI locus. TGFβ1 increased the expression of TGFBIp and the ECM-associated genes connective tissue growth factor, collagen-α2[I], and plasminogen activator inhibitor-1 in normal corneal fibroblasts. Increased levels of gene-activating markers (H3K4me1/3) and decreased levels of repressive markers (H3K27me3) at the promoters of those gene accompanied the changes in expression. TGFβ1 also increased recruitment of the H3K4 methyltransferase MLL1 and of SET7/9 and also the binding of Smad3 to the promoters. Knockdown of both MLL1 and SET7/9 significantly blocked the TGFβ1-induced gene expression and inhibited TGFβ1-induced changes in promoter H3K4me1/3 levels. Those effects were very weak, however, in GCD2-derived corneal fibroblasts. Taken together, the results show the functional role of H3K4me in TGFβ1-mediated TGFBIp and ECM gene expression in corneal fibroblasts. Pharmacologic and other therapies that regulate these modifications could have potential cornea-protective effects for granular corneal dystrophy.

We believe that the findings we report here are significant and will be of great interest not only to investigators who work on corneal dystrophy but will also appeal to a broader audience. We hope the content of this manuscript is suitable for publication in BMC Medical Genomics. Thank you in advance for your time and efforts spent reviewing it.

Best regards,
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