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Connective tissue growth factor regulates the developing retinal transcriptome in a cell type-dependent manner

Like all tissues, the retina contains a specifically configured extracellular matrix (ECM). Dynamic regulation of the ECM leads to changes in cellular proliferation, differentiation, adhesion, migration, and axonal growth and guidance, all of which shape retinal development. As a constituent of the retinal ECM, connective tissue growth factor (CTGF/CCN2) is essential for postnatal angiogenesis and blood-retinal barrier maintenance. However, its role in the developing neural retina is less clear. To investigate CTGF/CCN2 in this context, we performed bulk RNA sequencing (RNA-seq) and gene set enrichment analysis (GSEA) on embryonic day (E)18 CTGF/CCN2+/+ and CTGF/CCN2-/- retinas. CTGF/CCN2 deletion downregulated multiple ECM-associated gene sets, including the core matrisome, a set representing all known ECM glycoproteins, collagens, and proteoglycans. While this gene set as a whole was repressed following CTGF/CCN2 deletion, ECM genes associated with structure, adhesion, and angiogenesis were disparately affected. To understand cell type-specific effects of CTGF/CCN2, we performed single-cell (sc)RNA-seq on E18 CTGF/CCN2+/+ and CTGF/CCN2-/- retinas. Notably, each cell type was characterized not only by expression of canonical cell markers, but also by a unique ECM expression signature. The vast majority of Ctgf+ cells clustered with retinal progenitor cells (RPCs), which specifically expressed Cyr61 (CCN1), Col2a1, and Col5a1. Furthermore, CTGF/CCN2 deletion downregulated fibrillar collagen genes Col1a2 and Col5a2 in RPCs, but not in other cell types. Surprisingly, GSEA of retinal cell types revealed that in CTGF/CCN2-deleted retinas, the core matrisome was downregulated in RPCs, but upregulated in retinal ganglion cells and horizontal interneurons. These results suggest cell type-specific effects of CTGF/CCN2 in the developing retina and agree with other reports that CTGF/CCN2 regulates myriad developmental and pathologic processes in a context-dependent manner.