AB040. Single-cell transcriptomics identifies cell-specific signatures of pathological angiogenesis

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Background: To treat vascular proliferative diseases, anti-VEGF therapies have shown systemic adverse effects attributable to the lack of selectivity between pathological and physiological angiogenesis. Thus, identifying the molecular mechanisms that are only specific to pathological cell types is crucial to develop better precision medicine.

Methods: Here, we used different cell type enrichment approaches combined with single-cell RNA sequencing to define the transcriptomic changes within each retinal cell types in a mouse model of ischemic retinopathy. This retinal model develops pathological neovascularization (NV) in response to local hypoxia following oxygen-induced vessel obliteration (P7 to P12). The NV phenotype is characterized by the progressive appearance of vascular tufts resulting from misguided, abnormal proliferation of endothelial cells that we monitored at 3 consecutive time points—P12, P14 and P17 (peak of NV).

Results: By following the dynamic response to hypoxia, our experimental design reveals how pathological angiogenesis is specifically associated with significant metabolic adaptations in different subtypes of endothelial cells (i.e., Tips vs Stalk cells). We also identify a pathological subtype of glial cells over-expressing VEGFA and pro-inflammatory IL-1 receptor subunits. This subtype of activated glial cells was targeted using selective IL1R antagonist treatment which reduced glial activation, inflammation, NV and promotes physiological angiogenesis, therefore improving tissue regeneration.

Conclusions: Our results illustrate how analyzing cell type heterogeneity in tissues developing pathological angiogenesis allows establishing better targeting therapies to restore vascular integrity.

Keywords: Single-cell RNAseq; angiogenesis; pathological vascularization; metabolism; inflammation