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CDH13 and it's signaling partners in the functioning of the endothelium cells

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Motivation and Aim: CDH13 (known as T-cadherin) is an important participant in such cellular processes as the formation of intercellular contacts, the dynamic regulation of morphogenetic processes in embryos and the maintenance of the integrity of adult body tissues. Cadherins function as membrane receptors mediating signals from the outside, activating small GTPases and the beta-catenin/Wnt pathway and leading to dynamic reorganization of the cytoskeleton and phenotype changes. T-cadherin is abundantly expressed on the lumen surface of endothelial cells, but not at the sites of intercellular contact; increased expression is observed in such pathological conditions as atherosclerotic lesions of the human aorta and in endothelial cells of the vascular network of the tumor. However, the exact signaling partners and adapter proteins for CDH13 have yet to be determined.

Methods and Algorithms: This work is based on the existing reference atlas of endothelial cells in the normal lung (Fig. 1), obtained as a result of human RNA sequencing and subsequent iterative clustering with analysis of differential expression of endothelial cells (GSE164829, "Lung and primary pulmonary endothelial single cell RNA seq data" Single Cell RNAseq of Whole Lung Dissociates from control lungs and primary pulmonary endothelial cells) [1]. Using Illumina HiSeq 4000 Six lungs' atlas of scRNAseq datasets were reanalyzed and annotated to identify >15 000 vascular EC cells from 73 individuals. Using the CreateSeuratObject function, an object was created from the source files. Data normalization was carried out using the SCTransform function. After sequentially launching the RunPCA, RunUMAP, FindNeighbors, and FindClusters functions, cluster images were obtained using the DimPlot function. Differential expression analysis of EC revealed signatures corresponding to endothelial lineage, including panendothelial, panvascular, and subpopulation-specific marker gene sets. To find and identify cellular targets and signaling partners of T-cadherin cascades, using FindAllMarkers we analyzed 17 clusters of endothelial cells with different expression of T-cadherin using the STRING.ORG bioinformatics tool by subclustering the protein pool into functional units and tagging biological processes using keywords: "endothelium", "vascular", "vessel" and "blood".

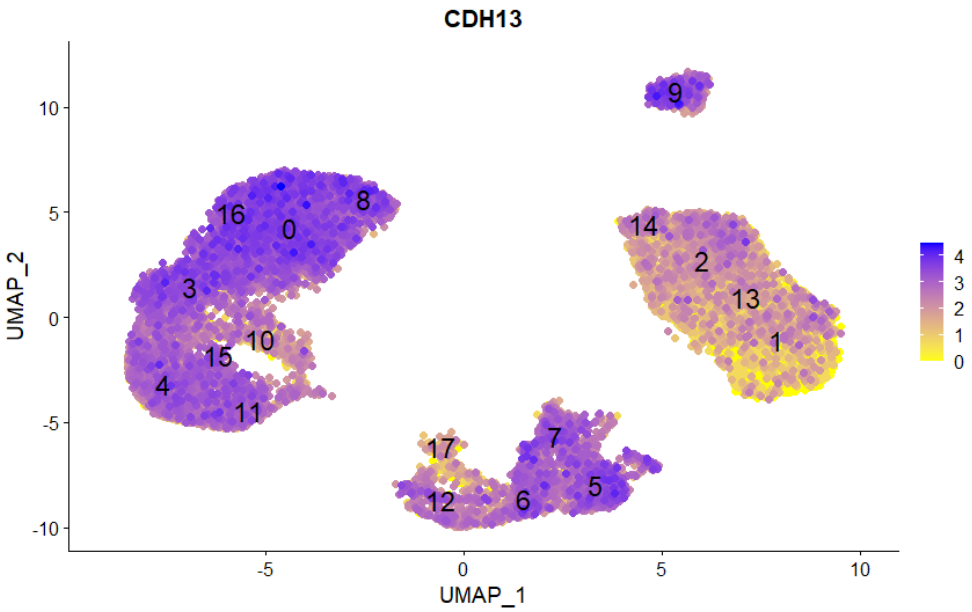

Fig. 1. Atlas of endothelial cells in the normal lung

Results: According to preliminary results, targets common to all endothelial cell clusters involved in the formation and regulation of the lung endothelium in humans and interacting with CDH13 were identified. Among them are nine proteins: CTNNB1 (Catenin beta-1, or beta-catenin β-catenin), CDH5 (Cadherin 5 or VE-cadherin), CDH2 (Cadherin 2 or N-cadherin), CAV1 (caveolin 1), DNMT1 (DNA (cytosine-5)-methyltransferase 1), BRCA1 (BReast CAncer gene 1), SPFR1 (Secreted Frizzled Related protein 1), JUP (Junction Plakoglobin), ADIPOR2 (Adiponectin Receptor 2), which through protein-protein interaction could potentially influence endothelial functions such as positive regulation of endothelial cell differentiation, regulation of vasculature development, blood vessel development and morphogenesis.

Conclusion: Thus, in order to understand the molecular mechanisms and interactions of proteins involved in the physiological and pathological conditions of the human lung endothelium, a bioinformatics analysis was performed to search for new signaling pathways and proteins critical for the functioning of the endothelium that interact with CDH13, as a result of which 9 new targets were found.

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References

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