Protein Tyrosine Phosphatase-1B (PTP1B) Regulates EGF-induced Stimulation of Corneal Endothelial Cell Proliferation

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Human corneal endothelial cells (HCECs) do not normally proliferate in vivo. However, they divide in response to wounding ex vivo and proliferate in culture media when stimulated by appropriate growth promoting agents. Elucidating the mechanisms of HCEC proliferation opens a window to novel therapeutic strategies for corneal disease caused by abnormal endothelial cells.

Epidermal growth factor (EGF) stimulates HCEC proliferation, but the level of DNA synthesis and number of cells that divide in response to this agent are relatively low, particularly in older donors. EGF, in addition to several other growth factors, signals via membrane-bound receptors with intrinsic protein-tyrosine kinase activity. Receptors of this type are termed receptor tyrosine kinases (RTKs). In the case of the EGF receptor (EGFR), RTK activity is stimulated by ligand binding, resulting in autophosphorylation of specific tyrosine residues located within the COOH-terminal of the intracellular domain of the receptor. This tyrosine phosphorylation is reversible and plays an important role in regulating downstream cellular pathways. After ligand binding and tyrosine autophosphorylation, EGFR is rapidly internalized into endosomes and remains active for several minutes before being either engulfed by lysosomes for degradation or recycled back to the plasma membrane. The fate of the receptor and output of the signaling process depend on continued ligand binding and kinase activity.

Protein tyrosine phosphatases (PTPs) comprise a large family of receptor-like and non-receptor enzymes that share a highly conserved catalytic domain specific for phosphotyrosine hydrolysis. PTPs act as "on" and "off" switches for numerous signaling events, thus acting as regulators of the signaling process. Protein tyrosine phosphatase-1B (PTP1B) is a widely expressed non-receptor PTP originally identified in the placenta and consists of 435 amino acids with a molecular weight of approximately 50 kDa. PTP1B contains a phosphatase catalytic domain at its NH_2-terminus, a region containing proline-rich motifs that promotes interaction with proteins containing SH_2-domains. PTP1B also contains a COOH-terminal hydrophobic region necessary for localization of PTP1B to the cytoplasmic face of the endoplasmic reticulum and nuclear envelope. PTP1B dephosphorylates several RTKs, including EGFR, the platelet-derived growth factor BB receptor, and the fibroblast growth factor receptor, thereby attenuating ligand-induced signaling. Besides its role in regulating growth factor-based signaling, PTP1B is also involved in regulating insulin and leptin-induced signaling.

Several laboratories are developing PTP1B inhibitors to block the down-regulation of important signaling processes. On a theoretical basis, these agents may enhance the proliferative potential of HCECs. Intracameral use of such agents can decelerate HCEC attrition, hence increasing the longevity of these cells in transplanted or diseased corneas. However, several obstacles must be overcome before the clinical use of PTP1B inhibitors. Firstly, it remains to be determined to what extent PTP1B inhibitors augment HCEC proliferation in vivo and whether other agents play any role. Secondly, intracameral use of these agents awaits conclusive evidence of their safety for delicate

intraocular structures such as the trabecular meshwork and crystalline lens.

Suggested Readings:

1. Zhu C, Rawe I, Joyce NC. Differential protein expression in human corneal endothelial cells cultured from young and older donors. *Mol Vis* 2008;14:1805-1814.
2. Jukunas UV, Rawe I, Bitar MS, Zhu C, Harris DL, Colby K, et al. Decreased expression of peroxiredoxins in Fuchs' endothelial dystrophy. *Invest Ophthalmol Vis Sci* 2008;49:2956-2963.