AB021. Discovery of a new role for the WNK1 kinase in corneal wound healing

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Background: Damage to the corneal epithelium triggers important changes in the composition of the extracellular matrix (ECM) to which the basal human corneal epithelial cells (hCECs) attach. These changes are perceived by integrins, a family of trans-membrane receptors that activate different intracellular signalling pathways, ultimately leading to re-epithelialization of the injured epithelium. Our goal is to study the impact of the pharmacological inhibition/activation of specific signal transduction mediators on corneal wound healing using both monolayers of hCECs and tissue-engineered human corneas (hTECs) as *in vitro* models.

Methods: hTECs were produced by the self-assembly approach and wounded with a 8-mm biopsy punch. Total RNA and proteins were isolated from the wounded and unwounded hTECs to conduct gene profiling analyses and protein kinase arrays. The wounded tissues were then incubated either with the lysine deficient protein kinase 1 (WNK1) inhibitor WNK463, the WNK1 indirect agonist AM1241, or with the vehicle alone (DMSO; negative control) and wound healing was monitored for 6 days. The impact of WNK1 inhibition/activation on hCECs monolayers was determined using scratch wound assays.

Results: Gene profiling analyses and protein kinases arrays revealed that expression and activity of several mediators from the integrin-dependent signalling pathways were altered in response to the ECM changes taking place during corneal wound healing. Phosphorylation of the WNK1 kinase turned out to be the most striking activation event occurring during wound healing. Since the pharmacological inhibition of WNK1 by WNK463 significantly reduced the rate of corneal wound closure in our hTECs and hCECs monolayers compared to their respective negative controls, we believe that the pharmacological activation of WNK1 could turn out to be an interesting avenue to accelerate corneal wound closure.

Conclusions: These results will contribute to a better understanding of the cellular and molecular mechanisms involved in corneal wound healing. Furthermore, they identified a new function for the WNK1 kinase in corneal wound healing and might lead to the identification of a new therapeutic target in the field of corneal wounds.

Keywords: Cornea; wound healing; lysine deficient protein kinase 1 (WNK1)

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