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ALK5, A Novel Binding Partner of Lumican in Corneal Wound Healing

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Commentary

Recently, Yamanaka et al. published a paper in PLOSone [1], which revealed that recombinant mouse lumican (Lum) protein purified from *E. coli* was capable of interacting with transforming growth factor beta receptor 1 (TGFβR1, ALK5) and further demonstrated that the interaction between these two is critical for the wound healing activity of Lum *in vitro* and *in vivo*. This paper was important because it addressed a central issue about Lum; namely its cell surface receptor mediating the multiple biological functions as a matrikine in physiological and pathophysiological conditions. The results convincingly demonstrate that ALK5 is the Lum receptor, which has remained elusive for the past two decades since the suggestion of a putative Lum receptor by Funderburgh et al., in 1997[2].

Some background about Lum may be needed to understand the significance of this novel discovery. Lum belongs to the small leucine rich proteoglycan (SLRPs) family. It is ubiquitously expressed in connective tissues as a non-sulfated glycoprotein, except in the corneal stroma where it exists as one of the major keratan sulfate proteoglycans forming the extracellular matrix (ECM). Lum has multiple functions in the establishment and maintenance of transparent cornea and identity of other connective tissue, e.g. sclera, skin. Lum-null mice display skin laxity, connective tissue defects and corneal opacity with thinner corneal stroma. Like other SLRPs, more recent studies have suggested that Lum may also have essential roles as a matrikine during corneal wound healing and inflammation. In normal cornea, keratan sulfated Lum is exclusively expressed in corneal stroma, while the non-glycan form of Lum is transiently expressed in migrating corneal epithelial cells to modulate cell adhesion, migration and proliferation, thus contributing to corneal epithelial wound healing [3].

Wu et al. [4] have reported that Lum interacts with TLR4 to mediate its function in inflammation albeit the potential Lum receptor underlying corneal wound healing was missing until ALK5 was identified as the cell surface receptor of Lum in Yamanaka's paper. The discovery of ALK5 as the binding partner of Lum was initially performed by screening a mouse cDNA library using the bacterial two hybrid system (our unpublished data) and was further confirmed by GST pull-down, IP-western and molecular docking. Furthermore, ALK5 loss-of-function studies provided convincing and prevailing data showing that specific shRNA or pharmacological inhibitor against ALK5 efficiently abolished Lum function on corneal wound healing. In Yamanaka's paper, the author also discovered that the GS domain of ALK5 interacts with the conserved C-terminal domain of Lum which is the region functioning in corneal wound healing. These data support the notion that ALK5 is the receptor that mediates Lum function as a matrikine in wound healing. In addition, this paper reported that eukaryote-specific posttranslational modifications are not required for Lum binding ALK5 and the wound healing activity of Lum as the fusion protein GST-lum used in this study was purified from *E. coli*. This finding is consistent with previous reports that it is the Lum core protein that is essential for wound healing. Together, Lum plays essential roles in corneal wound healing via interaction with its receptor of ALK5.

The molecular mechanism by which Lum-ALK5 interaction stimulates corneal wound healing was not explored in this paper; however, a hint was given suggesting that the interaction between Lum and ALK5 caused the phosphorylation of ERK1/2 in the wound edge indicating that the Lum-ALK5 interaction might directly trigger an unknown signaling cascade leading to activation of the ERK1/2 pathway thereby regulating corneal wound healing. This signaling cascade generated by Lum-ALK5 binding may be independent of the TGFβ canonical signaling pathway which can be tested by examining changes in the key mediators (TGFβR2, Smads) of TGFβ canonical signaling pathway with/without exogenous Lum/ALK5 treatment during the initial phase of wound healing process in cultured human telomerase-immortalized corneal epithelial cells (HTCE). Genetically and biochemically knock-down/knock-out technology can be used to identify downstream mediators upon Lum-ALK5 interaction if the signaling transduction triggered by Lum-ALK5 interaction is independent of TGFβ canonical signaling.

On the other hand, Lum-ALK5 interaction may have some influence on TGFβ canonical signaling pathway during corneal wound healing. This cannot be excluded as ALK5 is one of the key components of TGFβ signaling and it has been shown that the TGFβ canonical pathway plays an irreplaceable role in regulating cell cycle arrest and cell migration in the initial phase and cell proliferation and differentiation in the late phase of corneal wound healing. Collectively, corneal wound healing is the integrated consequence of a coordinated interplay, in part, between canonical TGFβ signaling and the effect caused by Lum-ALK5 interaction. More studies are needed to investigate the exact molecular mechanism underlying Lum-ALK5 interaction during corneal wound healing.

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