# Annexin A1 contained in extracellular vesicles promotes the activation of keratinocytes by mesoglycan effects: An autocrine loop through syndecan-4 pathway and formyl peptide receptors

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Wound healing is a dynamic process comprising multiple events, such as inflammation, re-epithelialization and tissue remodelling. Re-epithelialization phase is characterized by the engagement of several cell populations, mainly of keratinocytes that sequentially go through cycles of migration, proliferation and differentiation to restore skin functions. Over the last decades, the efforts aimed to find new pharmacological approaches for wound care were made; yet almost all current therapeutic strategies used remain inadequate or even ineffective. As such, it is crucial to identify new drugs that can enable a proper regeneration of the epithelium in wounded skin.

We have investigated the effects of the fibrinolytic drug mesoglycan, a glycosaminoglycans mixture derived from porcine intestinal mucosa, on HaCaT human keratinocytes that were used as *in vitro* experimental model of skin re-epithelialization. We found that mesoglycan induces keratinocyte migration and early differentiation by triggering the syndecan-4/PKCα pathway and that these effects were, at least in part, because of the formation of the annexin A1 (ANXA1)/S100A11 complex. Moreover, syndecan-4 participates to the formation and secretion of microvesicles (EVs), which may contribute to wound healing. We found that the mesoglycan increases the release of EVs which amplify its same effects. ANXA1 contained in the microvesicles is able to promote keratinocytes motility and differentiation by acting on Formyl Peptide Receptors (FPRs). Thus, the extracellular form of ANXA1 may be considered as a link to intensify the effects of mesoglycan.

Our work, for the first time, identified an interesting autocrine loop ANXA1/EVs/FPRs in human keratinocytes, induced by mesoglycan. Taken together, these data suggest that mesoglycan may represent a useful pro-healing drug for skin wound care. Its effects are triggered by the syndecan-4 activation, which leads to the ANXA1 secretion and the formation of a positive loop through FPRs.

## Speaker Biography

Antonello Petrella is currently working as a professor of pharmacology at University of Salerno-Department of Pharmacology, Italy. He has over 60 publications that have been cited over 1300 times, and his publication H-index is 23 and has been serving as an editorial board member of reputed Journals.

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