MESOGLYCAN INDUCES KERATINOCYTE ACTIVATION BY TRIGGERING SYNDECAN-4 PATHWAY AND THE FORMATION OF THE ANNEXIN A1/S100A11 COMPLEX

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Introduction: Wound healing is a dynamic process comprising multiple events, such as inflammation, re-epithelialization, and tissue remodeling. 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. Troubles can arise during the re-epithelialization phase of skin wound healing particularly in keratinocyte migration, resulting in chronic non-healing lesions, which represent a serious clinical problem. 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.

Materials and methods: Here, 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. The effect of treatment on HaCaT cell motility was investigated by Wound-Healing and invasion assays. Protein modulation following treatments has been verified through Western Blot, and protein localization through microscopic analysis. Ca^{2+} mobilization in HaCaT keratinocytes was analyzed with or without mesoglycan treatment with a fluorescent reading. To evaluate the mesoglycan effects on keratinocyte activation process, we next performed haemocytometric cell counting analysis of cell growth and flow cytometry analysis.

Results: Our in vitro data suggest that mesoglycan induces keratinocyte migration and differentiation, two important processes for the correct repair of skin lesions and some of these effects carried out through the activation of the SDC4 / PKCα pathway. Furthermore, our results show that the mesoglycan was able to induce the formation of the ANXA1 / S100A11 complex on the inner surface of the plasma membrane and that this event was mediated by activation of the SDC4 pathway.

Discussion and conclusions: 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/S100A11 complex. Our data suggest that mesoglycan may be useful as a new pro-healing drug for skin wound care.