ImmunoTools *special* Award 2013

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Immunomodulation of skin inflammatory responses by a glycosidated alkyl-phospholipid

Cutaneous homeostasis and defence is achieved by a cross-talk between epidermal keratinocytes and residual or recruited immune cells (i.e. Langerhans or T-cells), through the production of cytokines. Genomic predisposition and/or environmental influences may cause imbalances in the strictly regulated signal network, leading to a cytokine-based vicious cycle, which results in inflammatory skin disorders. Here the most common are psoriasis and atopic dermatitis.

Up to date, both can only be treated, but not be cured. Psoriasis also represents an emerging risk factor for cardiovascular diseases and the development of the metabolic syndrome. The role of keratinocytes within the pathogenesis of these diseases is mostly underappreciated as keratinocytes take an active part in cytokine synthesis and secretion, such as pro-inflammatory interleukin (IL)-1, -6, -8 and tumor necrosis factor alpha (TNFα) and immunomodulatory IL-10, -12. These cytokines affect the proliferation rate of keratinocytes and with that the usually well-balanced equilibrium between growth and differentiation, that determines the barrier function of the skin.

Synthetic alkyl-phospholipids (ALP) represent a class of drugs with antiproliferative properties in tumour cells. Some ALPs are derivates of the platelet-activating factor (PAF) and are characterized by a glycerol backbone to which a long chain fatty acid and small polar headgroups are linked via ether bonds. In opposite to known cytostatic agents, ALPs do not interfere with the DNA or mitotic spindle apparatus of the cell. Instead, they are incorporated into cell membranes, where they accumulate and interfere with lipid metabolism and lipid-dependent signalling pathways.

Inositol-C2-PAF (Ino-C2-PAF) is a synthetic glycosidated alkyl-phospholipid, which inhibits the proliferation of keratinocytes whilst enhancing the differentiation of these cells. Furthermore the expression of genes that are involved in modulating innate and acquired immune responses is down-regulated by Ino-C2-PAF.

Using microarray technique we could show that target molecules for skin dermatoses, including IL-6, IL-22 and TNFα, are down-regulated after application of Ino-C2-PAF. Thus we suggest that Ino-C2-PAF could be a valuable clinical tool also the field of dermatology. Based on these findings, the anti-inflammatory potential of Ino-C2-PAF shall be characterized in detail using a 2D-cell culture model with primary keratinocytes. Furthermore a 3D-full thickness skin model generated by using primary fibroblasts and primary keratinocytes will be deployed for these experiments.

A combination of cytokines, that are highly expressed in atopic dermatitis such as IL-4, -13, -22 and TNFα or IL-17, -22 and TNFα for psoriasis, respectively, will be used to activate the keratinocytes. Subsequently the amount of cytokine production by keratinocytes, with or without Ino-C2-PAF application shall be evaluated by ELISA technique.

The ability to study not only the changes in mRNA expression but the real amount of cytokines produced by primary keratinocytes and organotypic primary cell culture systems would offer a possibility to further investigate the role of Inositol-C2-PAF under normal and inflammatory conditions. For these experiments I would use cytokines alone or combinations of cytokines for induction of certain diseased states. And consecutively I will measure the amount of cytokines released by keratinocytes using ELISA plates.