COST Action TD 1206 "StanDerm"
Seminar on
"Etiology and prevention of occupational contact dermatitis: New challenges"

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ABSTRACT

Topic: Skin barrier and susceptibility

Title: Mechanisms of chemical induced skin inflammation – new approaches for causative treatment of allergic contact dermatitis

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Background: Allergic contact dermatitis (ACD) is a T cell mediated inflammatory skin disease. Up to now, the mechanisms driving DC activation in response to contact sensitizers was not clear.

We show now that there are two ways to activate DCs via TLR triggering by sensitizers. First metal ions like nickel and cobalt can directly bind to histidine residues in the human TLR4; second organic sensitizers activate TLR4 via an indirect mechanism involving the release of endogenous danger signals in the skin.

We show that sensitizers induce the production of reactive oxygen species (ROS) mediating the breakdown of high MW hyaluronan (HA) and upregulion of p38MAPK-dependent hyaluronidase activity. Low MW HA fragments are known as endogenous TLR2/4 activators. Interestingly, topical antioxidant treatment, interference with hyaluronidase activity or with p38MAPK signaling was able to block both sensitization as well as elicitation in the murine contact hypersensitivity (CHS) model. In addition, we addressed the role of neutrophils as innate immune cells rapidly infiltrating the inflamed skin and capable of releasing high amounts of ROS. Interestingly, our results show that depletion of neutrophils leads both to a reduction in the second, myeloperoxidase (MPO) dependent ROS peak in the skin and prevents sensitization and elicitation of CHS.

This underlines our hypothesis that the induction of a pro-inflammatory milieu within the skin is a crucial pre-requisite for the sensitization and thus provides new starting points for the development of causative treatments.