

Allergic contact dermatitis (ACD) is caused by topical exposure to chemical allergens. Due to its complexity the skin immune system may have an imperfect ability to distinguish between harmless or self antigens and those that signal invasion. The result is allergy, which results from the cutaneous immune system 'mistaking' encounters at skin surfaces with often innocuous chemicals for incursions that threaten health. Keratinocytes play a key role in innate immunity, as well as in ACD progression. The transmembrane Toll-like receptor 4 (TLR4), strongly implicated in skin inflammation, has the ability to bind Damage Associated Molecular Patterns (DAMPs), like Low Molecular Weight Hyaluronan (LMWHA). We had determined that p-phenylenediamine (PPD) and 2,4-dinitrochlorobenzene (DNCB) modulate keratinocyte HA deposition in a manner correlated to their sensitization. In continuation we investigated putative co-operation of HA and TLR4 in the process of PPD and DNCB-induced keratinocyte activation. Contact sensitizers were shown to significantly increase the expression of Hyaluronan Synthases (HAS) and TLR4 in NCTC2544 human keratinocytes, as demonstrated by western blot and Real-Time PCR. These data, in correlation to earlier shown enhanced HA degradation suggest that the contact sensitizers facilitate HA turnover of keratinocytes and increase the release of pro-inflammatory, LMWHA fragments. Treatment with exogenous LMWHA enhanced TLR4, HAS levels and Nuclear factor-kappa beta (NF- κ B) activation. PPD, DNCB and LMWHA-effects were shown to be partly executed through TLR4 downstream signaling as shown by Real-Time, western blot, siRNA and confocal microscopy approaches. Specifically, PPD and DNCB stimulated the activation of the TLR4 downstream mediator NF- κ B. Therefore, the shown upregulation of TLR4 expression is suggested to further facilitate the release of endogenous, bioactive HA fragments and sustain keratinocyte activation. In conclusion, keratinocyte contact allergen-dependent sensitization is partly mediated through a LMWHA/TLR4/ NF- κ B signaling axis.