Synopsis of Original Research Paper

Suppressive effect of self-assembling nano-sized heparin on allergic dermatitis

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Allergic contact dermatitis is a delayed hypersensitivity reaction triggered by contact with particular substances or haptens. Molecular mechanisms of the inflammatory disorder are yet to be well established, but in recent years have been suggested to involve activation of natural immunity via Toll-like receptors (TLRs) or Nod-like receptors (NLRs). We have previously developed a glycol-split heparin-sphingosine conjugate and found that it forms self-assembling nano-sized micelles and exhibits an anti-inflammatory effect associated with down-regulation of TLR4 signaling pathway. The present study was initiated to apply self-assembling heparin derivatives to treatment and prevention of contact dermatitis disorders. Firstly, we synthesized the derivatives of glycosaminoglycans (heparins, chondroitin sulfates, and hyaluronic acids), and found that glycol-split low-molecular-weight heparin-stearylamine conjugate (gs-LHST) was the greatest inhibitory effect against lipopolysaccharide-induced TNF-α production in primary cultured murine peritoneal macrophages. Then, we prepared polyethylene glycol ointment containing nano-dispersed gs-LHST, and applied it to a dinitrofluorobenzene (DNFB)-sensitized mouse contact dermatitis model. DNFB-induced ear thickening was significantly suppressed when gs-LHST-containing ointment was applied 2 hours prior to every DNFB sensitization. The anti-inflammatory effect of gs-LHST-containing ointment was comparable to that of prednisolone-containing ointment. However, the effect of gs-LHST-containing ointment was not observed in the genetically TLR4-mutated strain C3H/HeJ, suggesting that blockade of TLR4 signaling pathways by gs-LHST might be attributed to suppression of DNFB-induced ear thickening. Real-time polymerase chain reaction (PCR) analyses indicated that gs-LHST-containing ointment can reduce elevated mRNA expression levels of anti-inflammatory cytokines (TNF-α and IL-1β) and oxidative stress-responsive gene (HO-1). These results suggested that gs-LHST might be effective to inhibit cyclic inflammatory chain reactions involving TLR4 and reactive oxygen species.