LEKTI domain 6 displays anti-inflammatory action in vitro and in a murine atopic dermatitis model

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Abstract

Background: Lympho-epithelial Kazal-type-related inhibitor (LEKTI) is a serine protease inhibitor consisting of multiple domains. A loss of function mutation is described in Netherton patients that show severe symptoms of atopic lesions and itch. Objectives: LEKTI domain 6 (LD6) has shown strong serine protease-inhibitory action in *in vitro* assays and thus it was tested *in vitro* and *in vivo* for potential anti-inflammatory action in models of atopic skin disease. Methods: Human skin equivalents were treated with LD6 and an inflammatory reaction was challenged by kallikrein-related endopeptidase 5 (KLK5). Furthermore, LD6 was tested on dorsal root ganglia cells stimulated with KLK5, SLIGRL and histamine by calcium imaging. The effect of topically administered LD6 (0.4–0.8 %) in lipoderm was compared to a topical formulation of betamethasone-diproprionate (0.5 %) in a therapeutic setting on atopic dermatitis-like lesions in NC/Nga mice sensitized to house dust mite antigen. Endpoints were clinical scoring of the mice as well as determination of scratching behaviour. Results: KLK5 induced an upregulation of CXCL-8, CCL20 and IL-6 in skin equivalents. This upregulation was reduced by pre-incubation with LD6. KLK5 as well as histamine induced calcium influx in a population of neurons. LD6 significantly reduced the calcium response to both stimuli. When administered onto lesional skin of NC/Nga mice, both LD6 and betamethasone-dipropionate significantly reduced the inflammatory reaction. The effect on itch behaviour was less pronounced. Conclusions: Topical administration of LD6 might be new therapeutic option for treatment of lesional atopic skin.

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Fig 1

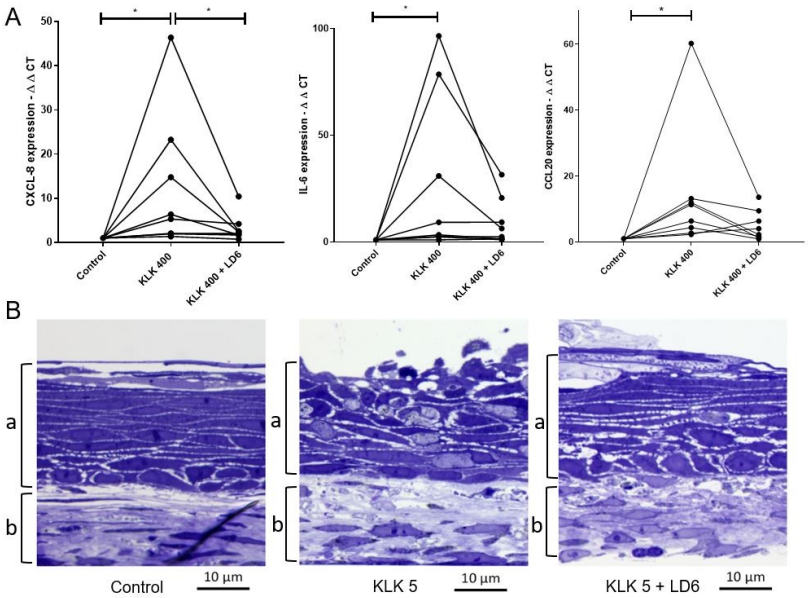
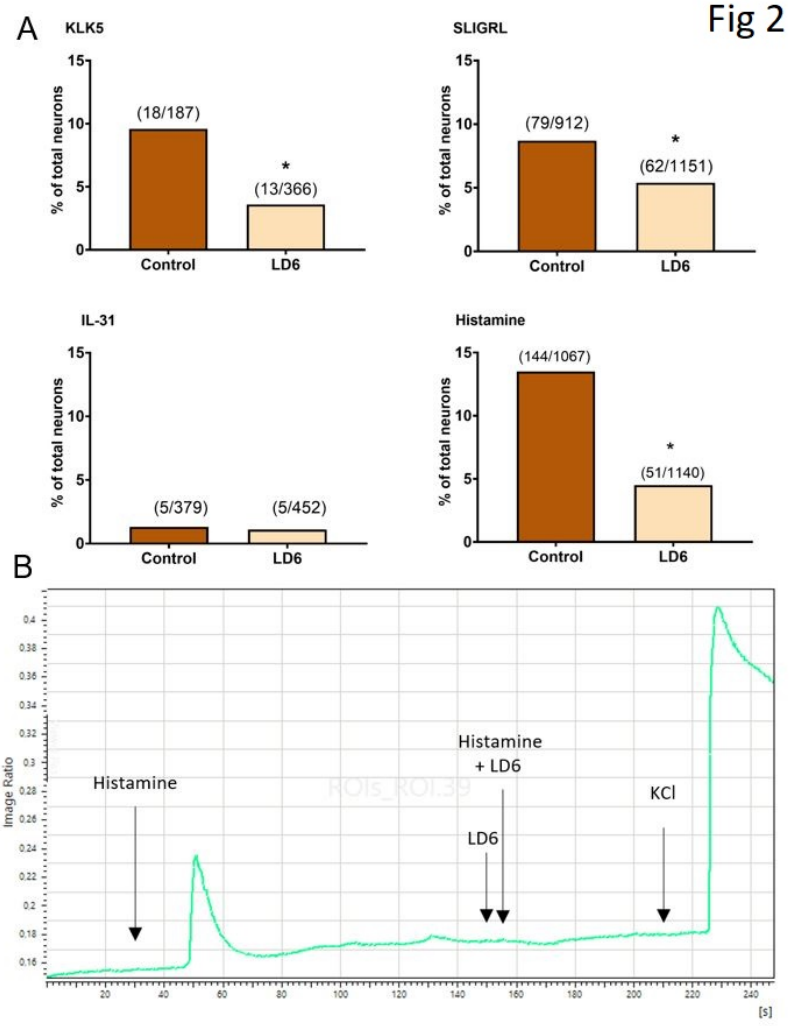


Fig 2



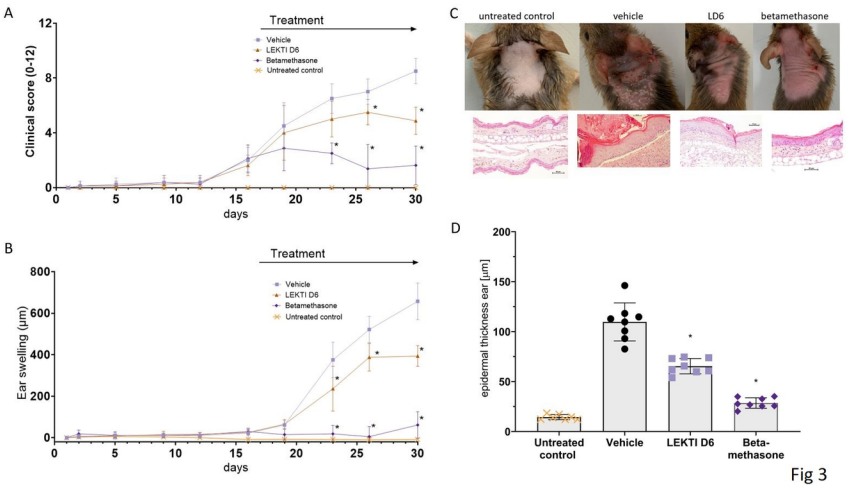


Fig 3