

COMMENTARY

Proteases and itch – a human and animal model of non-histaminergic itch using cysteine protease Ficin

Chronic pruritus is a highly prevalent and burdensome symptom.¹ Antihistamines, which are still recommended first-line antipruritic treatment options are not effective in most pruritic conditions. Surrogate models of pruritus are important tools to study mechanisms of itch and to investigate new antipruritics in preclinical and in proof of concept studies. Cowhage-induced itch is the best-studied non-histaminergic model of itch. The spicules of cowhage (*Mucuna pruriens*) elicit itch due to the release of a cysteine protease mucunain. Cysteine proteases evoke itch by activating the protease-activated receptors (PARs) and Mas-related G protein-coupled receptors (MrgprX1 – in humans and MrgprC11 in mice) on sensory neurons. Arthur and Shelley identified in the fifties Ficin among several further itch-inducing cysteine endopeptidases.²

In this issue of *JEADV*, Malewicz *et al.*³ present results of their investigation of a punctate administration of Ficin and its validation as a human and animal model of non-histaminergic itch. This study brings to our attention that besides mucunain, there are several further itch-inducing cysteine endopeptidases, active in the physiologic pH range, that cause non-histaminergic itch. The authors employed heat-inactivated cowhage spicules, soaked with different concentrations of Ficin to induce itch in human subjects and mice. Additionally, in mice only, ascending doses of Ficin were injected intradermally. Spicules containing Ficin and native mucunain evoked similar sensory responses and dysesthesias, without producing any skin reaction. The concentration of 100 mg/dL of Ficin used for soaking inactivated cowhage spicules was required to evoke comparable magnitudes of nociceptive sensations and reactions as native cowhage spicules. Of note, intradermal injection required larger doses of Ficin to evoke similar behaviours as when applied by spicules. This confirms previous observations, that maximal pruritic response is achieved when pruritogens are deposited more superficially, near the dermo-epidermal junction where free nerve endings are located.

The authors noted, that chronic exposure to fig plants causes sensitization to fig aeroallergens, as prolonged contact with cysteine proteases can lead to the release of alarmins and in

consequence may promote Th2-type response and sensitization. Interestingly, another cysteine protease and a major allergen from the dust house mite Der p1 was shown to activate PAR-2 and human MRGPRX1.⁴ This may explain how atopic dermatitis can exacerbate directly due to exposition to house dust mites. Skin of patients with atopic dermatitis seems to be primed for itch induced by cysteine proteases. Prolonged duration of cowhage-induced itch was reported in patients with atopic dermatitis.⁵ Further studies are needed to investigate these mechanisms and to develop treatment strategies targeting this pathway in AD and pruritus. Well-established preclinical models of protease-induced itch become all the more important tools in this context.

Conflict of interest

I have no conflict of interest to declare regarding this work.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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