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Cathepsin S is up-regulated in psoriatic inflammation and activates the pro-inflammatory cytokine IL-36γ

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The interleukin (IL)-1 family of cytokines are fundamental regulators of the innate immune system, serving to orchestrate inflammation. The recently described IL-1 cytokines IL-36α, IL-36β and IL-36γ have been associated with psoriatic inflammation. IL-36γ is highly expressed in activated keratinocytes and is the main epidermal IL-36 agonist. As with other IL-1 family members, IL-36 cytokines are expressed as inactive precursors and must be truncated by specific proteases to become bioactive. Proteases involved in the cleavage of other IL-1 family members (e.g. caspase 1) do not activate IL-36 molecules. Therefore, our aim was to identify the protease/s responsible for IL-36 activation and explore the potential importance of this activation in psoriasis. Using a keratinocyte based activity assay, we report that IL-36γ-activating proteases reside within the lysosome and in the conditioned media of a number of skin-resident cell types, including fibroblasts and keratinocytes. Importantly, using small-molecule inhibitors we were able to identify the IL-36γ-activating protease as cathepsin S and reproduce this processing using recombinant proteins. In a skin equivalent model, IL-36γ s18, the main product of cathepsin S-dependent IL-36γ cleavage, was shown to induce epidermal changes indicative of psoriatic inflammation. Finally, using lesional psoriasis samples extracted by tape-stripping, it was demonstrated that both IL-36γ and cathepsin S are strongly upregulated in the skin of psoriasis patients, relative to healthy controls or uninvolved skin. Together, these data suggest that the activation of IL-36γ by cathepsin S is an important process in the psoriatic inflammatory response.