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Activation of IL-36 molecules and their role in psoriatic disease

M. Wittmann, T. Macleod, J.S. Ainscough, A. Alase, D. McGonagle, R. Doble, A. Latzko and M. Stacey

University of Leeds, Faculty of Medicine and Health, LIRMM & Faculty of Biological Sciences, SMCB, Leeds, U.K.

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-36 α, IL-36β and IL-36γ have been associated with psoriatic inflammation as well as antifungal defence. IL-36 is highly upregulated in and also a biomarker for skin psoriasis. Loss of function mutation of the endogenous IL-36 antagonist IL-36RA have been reported to be associated with severe pustular psoriasis phenotypes. As with other IL-1 family members, IL-36 cytokines, including the IL-36RA, are expressed as inactive precursors and must be truncated by specific proteases to become bioactive. Therefore, our aim was to identify the protease/s responsible for IL-36 activation and explore the potential importance of this activation to psoriasis. We identified neutrophil elastase as the most important protease in cleaving the antagonist into its active form. Neutrophil derived serine proteases were also able to cleave IL-36 agonists, however not into full activity as the cleavage product was not the most active one. However, keratinocyte based activity assays, showed that IL-36γ activating proteases reside within the lysosome and 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 differentiation changes indicative of psoriatic inflammation. Finally, using 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. Together, these data suggest that the biologic activity of the IL-36 system is determined by both neutrophil proteases and skin expressed cathepsin S both of which are highly expressed in psoriatic inflammation.