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Neutrophil mediated proteolysis of IL-36 members has both regulatory and inflammatory consequences

T. Macleod, R. Doble, M. Wittmann, M. Stacey, D. McGonagle

University of Leeds, Leeds, United Kingdom

The IL-36 cytokines, IL-36 α , β , γ and the receptor antagonist, are members of the IL-1 superfamily that have a strong link to psoriatic inflammation. High levels of IL-36 α and IL-36 γ are a prominent characteristic in psoriatic plaques, whilst mutations in the receptor antagonist are highly linked to pustular psoriasis subtypes. As observed with other IL-1 superfamily proteins, the IL-36 members require precise N-terminal cleavage for full biological activity. Using different blood leukocyte and skin resident preparations, and recombinant proteins, we have identified several neutrophil proteases that cleave all members of the IL-36 family generating both active and inactive truncations. Incubation of IL-36 agonists with neutrophil proteases generated biologically inactive truncations (IL-36 α I7, IL-36 γ Y16 and Q17) when tested on primary fibroblasts and keratinocytes, whilst incubation of IL-36Ra generated a biologically active antagonist IL-36Ra V2. However, prolonged incubation of IL-36Ra resulted in further truncation producing IL-36Ra S4, deactivating the antagonist. IL-8, CCL20 and hBD2 were used as outcome measures for biological activity. These findings suggest neutrophils are an important element when considering the dynamics of IL-36 mediated inflammation. Whilst traditionally thought to act in an inflammatory capacity, these findings indicate a regulatory role by generating inactive agonist truncations and activating IL-36Ra. Clearly, neutrophils are capable of influencing IL-36 mediated inflammation to produce both pro- and anti-inflammatory outcomes, yet whether one outcome is favoured over the other and what factors might sway the balance is yet to be clarified. Given their abundance in psoriatic lesions, and the importance of IL-36 in psoriatic inflammation, a clear understanding of how neutrophils influence IL-36 mediated inflammation is of great importance.