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Allergic contact dermatitis beyond IL-1 β -role of additional family members

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Abstract:

Contact dermatitis is one of the most frequent pathological manifestations of the skin and plays a central role in clinical and experimental dermatology. The IL-1 family consists a large group of cytokines which currently contains 11 members with different pro- and anti-inflammatory properties. Among the more pro-inflammatory acting cytokines from the IL-1 family IL-1 β , IL-18, IL-33 and IL-36 have been shown to be upregulated in different inflammatory mouse experimental models or skin diseases. The article by Mattii et al. in this issue represents a thorough analysis of the

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expression of IL-1 family members including IL-33 in skin samples from patients with allergic contact dermatitis. Although a lot of research is performed in this area data from human samples are rather scarce. Therefore, Mattii et al. contribute to building the basis for novel therapeutic concepts, which might include the use of antagonistic molecules targeting the IL-1 family network.

Contact dermatitis is one of the most frequent pathological manifestations of the skin and plays a central role in clinical and experimental dermatology. Contact dermatitis can be induced by irritants, which might be chemicals or physical stimuli, or depend on a CD4-T cell dependent type IV immune response. Irritant contact dermatitis is characterised by the onset of a locally limited mainly keratinocyte-driven inflammatory response, which peaks after 24-48h. Allergic contact dermatitis requires a sensitisation phase before the onset of clinical symptoms. The elicitation phase of allergic contact dermatitis is mostly T cell dependent and peaks after 48-72h [1]

Although the pathomechanisms of irritant and allergic contact dermatitis differ in many ways, similarities concerning the early keratinocyte response after contact with the different external stimuli are present. Such early mostly innate immune responses largely depend on the initiation of the IL-1 pathway [2,3].

The IL-1 family consists a large group of cytokines with different pro- and anti-inflammatory properties. It contains currently 11 members and can be categorized into subfamilies according to the length of their precursor and the length of the pro-piece for each precursor (Figure 1). The IL-1 subfamily consists of IL-1 α , IL-1 β , and IL-33, with the longest pro-pieces of the IL-1 family. IL-18 and IL-37 belong to the IL-18 subfamily and contain smaller pro-pieces than IL-1 and IL-33 [2].

Among the more pro-inflammatory acting cytokines from the IL-1 family IL-1 β , IL-18, IL-33 and IL-36 have been shown to be upregulated in different inflammatory mouse experimental models or skin diseases [4,5,6,7,8]. On the other hand no spontaneous disease has been reported in mice deficient in IL-1 β . Upon challenge, however, IL-1 β -deficient mice differ significantly in their responses from wild-type mice. Most dramatic in this regard is the inflammatory response induced by a local irritant [9].

The dominant biological activity of IL-33 is the induction of Th2 cytokines, IL-4, IL-5, and IL-13 as well as other properties anticipated for a Th2 type cytokine. It has recently been shown that interleukin-1 α can control allergic sensitization to inhaled house dust mite (HDM) through epithelial IL-33 [10].

IL-36 α and IL-36 β play potential roles in skin homeostasis, as both are regulated by EGF in the skin [11,12]. This assumption is supported by the observed acanthosis and hyperkeratosis in mice overexpressing the IL-36 α gene in basal keratinocytes [13].

The paper by Mattii et al. in this issue [Exp Dermatol. 2013 Oct 24. Epub ahead of print] represents a thorough analysis of the expression of IL-1 family members including IL-33 in skin samples from patients with allergic contact dermatitis. By using samples from patch test positive patients the authors show increased mRNA but also protein expression of members of the IL-1 family (IL-1 β and IL-1Ra, IL-36a, IL-36b, IL-36g). Despite several limitations (the skin biopsies were derived from eczematous skin induced with different contact allergens and at different time points (72 and 96h), the study provides valuable insights into the onset of IL-1 β cytokine family member expression in allergic contact dermatitis.

Whether these findings depend also on the kind of contact allergen will need to be analysed in future studies. As some cytokines like IL-36 have recently been described to be upregulated in other inflammatory conditions like psoriasis [14] the disease specificity of the findings will need to be addressed in more depth in future studies, e.g. also considering acute atopic dermatitis.

By using an ex vivo human skin model they show for the first time an up regulation of the IL-1 and IL-36 cytokine members at the mRNA level expression after incubation with a contact allergen but not the irritant SDS (except for IL-33). Here it would be an important future step to demonstrate in such a setting a kinetic profile to identify the expression profile of the complete IL-1 family. The experiments showing expression of the IL-36 group after injection of recombinant IL-36Ra would likewise benefit from data with an appropriate control and a time course analysis to pin down the possible cascade of events, which occur during this type of in-vitro setting.

Overall the data from this manuscript provide novel insights into the pathophysiology of IL-1 family members including IL-33 in allergic contact dermatitis in humans. Although a lot of research is performed in this area data from human samples are rather scarce [15]. Therefore, this data can also contribute to build the basis for novel therapeutic concepts, which might include the use of antagonistic molecules targeting the IL-1 family network.

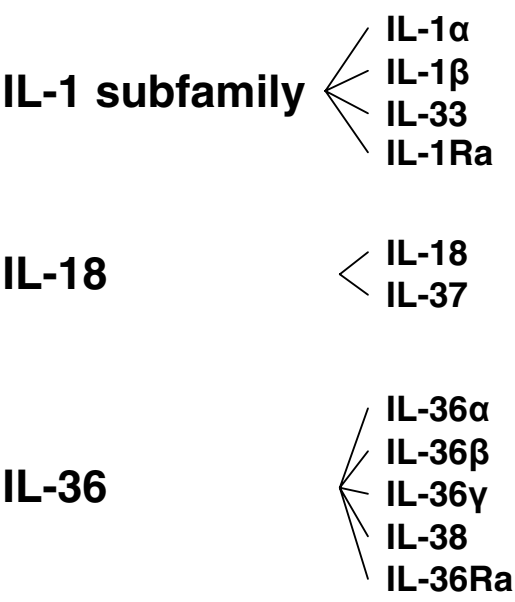
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Conflict of interest: The author declares no conflict of interest.

Figure 1: Subfamilies of IL-1beta*



*modified after van de Veerdong FL, Front Immunol. 2013