Review

# Skin inflammation can be triggered by caspase-8 deficiency

UHN Microarray Centre

*Summary of: Kovalenko A, Kim J-C, Kang T-B, Rajput A, Bogdanov K, Dittrich-Breiholz O, Kracht M, Brenner O, Wallach D. Caspase-8 deficiency in epidural keratinocytes triggers an inflammatory skin disease. JEM 2009, 206(10):2161*

A healthy epidermis is maintained by equilibrium between proliferating keratinocytes in the basal layer and the differentiation of cells into the suprabasal layer, and the fine balance that occurs at the epidermal surface between cell survival and cell death (1). Caspases, a family of cysteine-protease enzymes, play a key role in the induction of apoptosis in animal cells (2). Epidermal keratinocytes express all known caspases which can be induced by ligands of the tumour necrosis factor (TNF) family to initiate cell death (3). Caspase-mediated cell death of epidermal keratinocytes contributes to the pathological damage of the skin in conditions such as sunburn (4), eczematous dermatitis (5), and toxic epidermal necrolysis (6). However, caspases may also be involved in other non-apoptotic cellular functions including adhesion and migration (7), and immune defence (8). Kovalenko and colleagues have also found that a caspase-8-deficiency in keratinocytes can trigger severe skin inflammation associated with aberrant epidermal growth and differentiation (3).

In order to identify the molecular changes involved in this inflammatory skin disease and its trigger, the gene expression in the skin of *Casp-8*$^{F/-}$K5-Cre and wild-type mice were compared at the UHN Microarray Centre using the Agilent platform. This expression analysis found that many genes were up-regulated in the *Casp-8*$^{F/-}$K5-Cre epidermis, including several groups that code for proteins involved in inflammation, in addition to proteins known to participate in the IFN response and to depend on the activation of the transcription factor IRF3 (9). Evidence that an IRF3 activation pathway is constitutively activated in suprabasal caspase-8-deficient epidermis is presented, suggesting that the cornification process could be a possible trigger for its activation (3). Mouse Whole Genome 4x44K (Agilent) arrays were used to study cultured keratinocytes and to determine whether the up-regulation of inflammatory genes occurs autonomously in caspase-8-deficient keratinocytes or depends on extracellular stimuli. This experiment found that the increased expression of some inflammatory genes gradually abated during the course of passaging the cells. This finding suggests that some other molecular determinant in the skin contributes to the activation of inflammatory genes in caspase-8-deficient keratinocytes (3).

This study found that the chronic skin inflammation in mice triggered by inactive caspase-8 (or the deletion of *caspase-8*) in basal keratinocytes was independent of TNF, IL-1α, IL-1β, dermal macrophage function, or the expression of the toll-like receptor adapter proteins MyD88 and TRIF (3). The finding that IL-1α and IL-1β do not contribute to the inflammatory skin disease refutes the recent observation that the induced generation of IL-1α mediates the inflammatory skin disease inflicted by caspase-8 deficiency in the epidermis (1). In addition, this study found that caspase-8-deficient keratinocytes transfected with DNA triggered a greater response of genes in the IRF3 pathway than caspase-8-expressing cells (3).

Kovalenko *et al*. also discuss the debate surrounding the involvement of caspases in the nonpathological cell death process that causes cornification. Earlier studies have suggested that activated caspases were required for the programmed cell death of cells associated with cornification (10,11), however, this study found that caspase-8-deficient keratinocytes did not interfere with the effectiveness of the cornification process. This finding is consistent with other studies that cast doubt on the belief that caspases play a role in cornification (12-14).



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