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Keratinocytes express functional CARD18, a negative regulator of inflammasome activation, and its altered expression in psoriasis may contribute to disease pathogenesis

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ABSTRACT

Caspase recruitment domain family member 18 (CARD18, Iceberg) is known as a negative regulatory molecule that inhibits inflammatory events by terminating inflammasome activation due to a direct interaction with pro-caspase-1.

During the investigation of molecular mechanisms in keratinocytes that contribute to the pathogenesis of psoriasis, we found that CARD18 expression differs in healthy and psoriatic skin; moreover, CARD18 demonstrated altered response under inflammatory conditions in healthy and psoriatic skin. In healthy skin, low basal CARD18 expression was detected, which showed significant elevation in response to inflammatory stimuli (lymphokine treatment or mechanical injury). In contrast, higher basal expression was observed in psoriatic non-involved skin, but no further induction could be detected.

We demonstrated that keratinocytes express CARD18 both at mRNA and protein levels and the expression increased in parallel with differentiation. The investigation of cellular inflammatory processes revealed that psoriasis-associated danger signals triggered the expression of inflammasome components (AIM2, Caspase-1) and CARD18 as well as IL-1β production of keratinocytes. Furthermore, gene-specific silencing of CARD18 in cells treated with cytosolic DNA (poly(dA:dT)) resulted in increased IL-1β secretion, suggesting a negative regulatory role for CARD18 in keratinocyte inflammatory signaling.

The differential regulation of CARD18 in healthy and psoriatic uninvolved epidermis may contribute to the susceptibility of psoriasis. Furthermore, our *in vitro* results indicate that CARD18 may contribute to the fine tuning of keratinocyte innate immune processes.

1. Introduction

The innate immune system constitutes the first line of defense that detects pathogen- and damage-associated molecular patterns. Inflammation is a protective physiological response; however, impaired activation and/or down-regulation of inflammatory signaling may result in inflammatory diseases, some of which involve multiple organs. Inflammasomes, located in the cytosol, are part of the innate immune system. These multi-molecular complexes are responsible for the recognition of various cytoplasmic danger signals and provoke inflammatory responses by recruiting and activating pro-caspase-1 through autocatalytic cleavage (Schroder and Tschopp, 2010). The activation of caspase-1 ultimately leads to the processing and, thus, secretion of pro-inflammatory cytokines, most importantly interleukin (IL) 1β and IL-18, and also induces

Abbreviations: AIM2, absence in melanoma 2; CARD18, caspase recruitment domain family member 18; COP, CARD-only protein; DAPI, 4,6-diamidino-2-phenylindole; DNase, deoxyribonucleases; GM-CSF, granulocyte macrophage colony-stimulating factor; IL, interleukin; IFN-γ, interferon-γ; TNF, tumor necrosis factor; IHC, immunohistochemistry; NHEK, normal human epidermal keratinocytes; PBS, phosphate-buffered saline; poly(dA:dT), polydeoxyadenylic acid–polydeoxythymidylic acid double-stranded homopolymer; TS, tape stripping.

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