European Journal of Cell Biology 89 (2010) 638–644

Contents lists available at ScienceDirect

European Journal of Cell Biology

journal homepage: www.elsevier.de/ejcb

Short review

Interleukin-1, inflammasomes and the skin

Laurence Feldmeyer[a], Sabine Werner[b], Lars E. French[a], Hans-Dietmar Beer[a,b,*]

[a] Department of Dermatology, University Hospital Zurich, CH-8091 Zurich, Switzerland
[b] Institute of Cell Biology, Department of Biology, ETH Zurich, CH-8093 Zurich, Switzerland

ARTICLE INFO

Article history:
Received 29 March 2010
Received in revised form 26 April 2010
Accepted 26 April 2010

Keywords:
IL-1
Skin
Inflammasome
Caspase-1
Inflammation

ABSTRACT

Interleukin (IL)-1 is a highly active and pleiotropic pro-inflammatory cytokine. Recent data impressively demonstrate that activating mutations in a human gene involved in proIL-1β maturation or loss-of-function mutations in the gene encoding IL-1 receptor antagonist (IL-1Ra) cause excessive activity of this cytokine. This can result in life-threatening systemic and local inflammation, particularly in the skin. Interestingly, experiments in mice revealed that epidermal keratinocytes can secrete large amounts of IL-1α, which induces an inflammatory response in the skin. Secretion of IL-1 requires caspase-1 activity, and activation of the protease takes place in innate immune complexes, called inflammasomes. As keratinocytes express and activate caspase-1 in an inflammasome-dependent manner, these epithelial cells might be critically involved in the innate immunity of the skin. In this review we summarize the current knowledge on IL-1 and inflammasomes in the skin, particularly their involvement in skin homeostasis and disease. In addition, we discuss the hypothesis that keratinocytes are not only static bricks of the epidermal wall, but immunologically active cells critically involved in different (auto)-inflammatory (skin) diseases.

Introduction

Inflammation represents a protective attempt by an organism to restore a new homeostatic state after its disturbance by a harmful stimulus. Depending on these stimuli the term inflammation is used for a broad range of conditions. For example, infections rapidly activate the innate immune system and induce an inflammatory response, which initiates the defence of the host against the invading pathogen. Tissue damage also results in local and acute inflammation, thereby allowing an efficient tissue repair response (Medzhitov, 2008). IL-1 plays an important role in these fundamental and beneficial processes (Dinarello, 2009a). However, inflammation can also be "undesired", chronic and destructive. It can contribute to major human diseases such as type 2 diabetes, atherosclerosis, asthma, Alzheimer's disease and cancer (Martinon et al., 2009). An involvement of IL-1 in the pathogenesis of these diseases has also been demonstrated. In particular, it is a leading actor in the recently defined auto-inflammatory diseases (Goldbach-Mansky and Kastner, 2009). These diseases are characterized by "sterile" inflammation without infection and the presence of autoantibodies or auto-reactive T cells. Reducing the activity of IL-1 results in rapid remission of symptoms (Aksentijevich et al., 2009; Goldbach-Mansky et al., 2006; Reddy et al., 2009). Interestingly, several auto-inflammatory diseases also affect the skin, and IL-1 activity plays an important role in inflammatory and allergic skin diseases such as psoriasis or contact dermatitis, demonstrating the importance of IL-1 in the skin (Goldbach-Mansky and Kastner, 2009; Numerof and Asadullah, 2006). Several lines of evidence suggest that keratinocytes are a major source of IL-1 in the skin (Feldmeyer et al., 2007; Lee et al., 2009; Szabowski et al., 2000). These non-professional immune cells represent the major cell type of the epidermis.

In this review we highlight the recent advances in the understanding of the role of IL-1 and inflammasomes in skin homeostasis and disease. In addition, we discuss a possible role of keratinocytes as sensors of danger and producers of IL-1.

The skin

In mammals, the skin consists of two layers, which are separated by the basement membrane (Fig. 1). The epidermis is the surface layer, a keratinized, stratified and squamous epithelium

Abbreviations: AIM, absent in melanoma; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CAPS, cryopyrin-associated periodic syndrome; CH, contact hypersensitivity; DAMPs, damage-associated molecular patterns; DC, dendritic cells; DIRA, deficiency in IL-1Ra; IL-1, interleukin-1; IL-1RI, IL-1 receptor type I; IL-1Ra, IL-1 receptor antagonist; LPS, lipopolysaccharide; LRR, leucine-rich repeat; MDP, muramyl dipeptide; NF-κB, nuclear factor κB; NLRP1, nucleotide-binding domain, leucine-rich repeat-containing receptor protein 1, also known as NALP1; PAMPs, pattern-associated molecular patterns; PRRs, pattern recognition receptors; ROS, reactive oxygen species; TNF, tumour necrosis factor; TLRs, Toll-like receptors; TNP, trinitrophenylchloride.

* Corresponding author at: Department of Dermatology, University Hospital Zurich, Gloriastrasse 30, J10, CH-8006 Zurich, Switzerland. Tel.: +41 44 6345390, fax: +41 44 6345345.
E-mail address: Hans-Dietmar.Beer@usz.ch (H.-D. Beer).

0171-9335/$ – see front matter © 2010 Elsevier GmbH. All rights reserved.
doi:10.1016/j.ejcb.2010.04.008

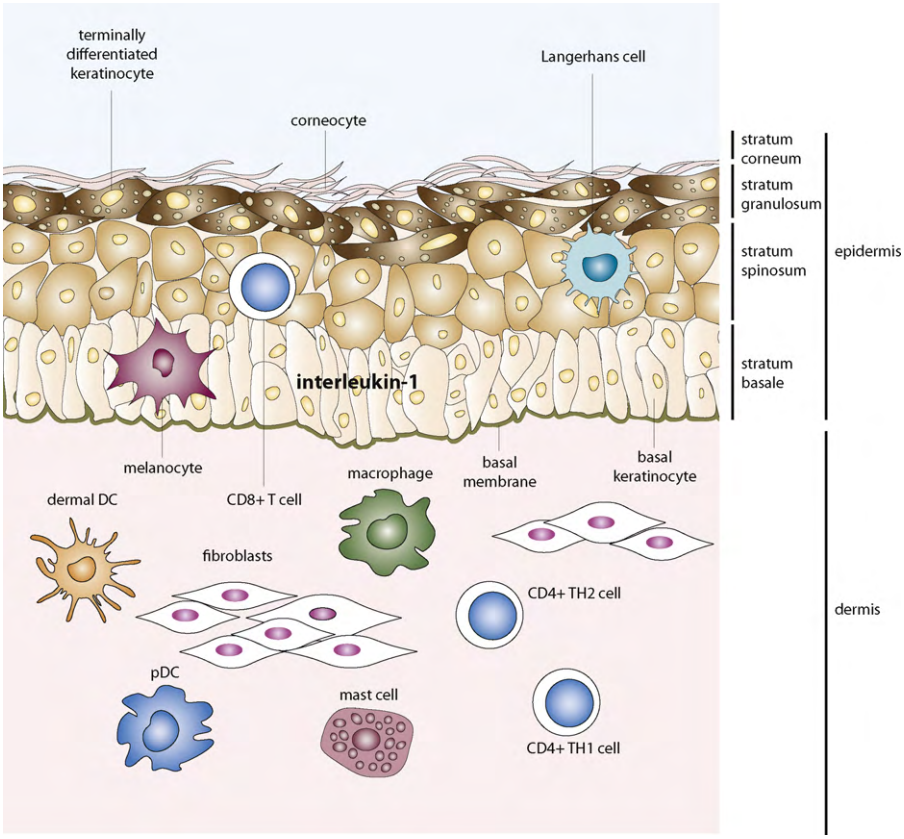

Fig. 1. The cellular composition of the skin. Keratinocytes are a major source of IL-1. When activated and secreted, the cytokine induces an inflammatory response through activation and recruitment of immune cells (inspired from Nestle et al., 2009a).

that is in permanent contact with the environment. The underlying dermis is a connective tissue composed of collagen, elastic fibres and a mixture of other extracellular matrix protein. It contains nerve endings, blood and lymphatic vessels, extracellular matrix-producing fibroblasts and several different types of immune cells such as macrophages, dendritic cells (DC), mast cells, and T cells (Nestle et al., 2009a). In contrast, the epidermis is made up almost exclusively of densely packed keratinocytes at different stages of differentiation. In addition, a few Langerhans cells, a type of DCs, and pigment-producing melanocytes can be found. The epidermis is in a constant equilibrium between proliferation of stem cells and transit-amplifying cells in the basal layer, and a terminal differentiation program of suprabasal keratinocytes (Fuchs and Raghavan, 2002). Keratinocyte terminal differentiation is an apoptosis-like process that generates dead, anucleated, flat and keratin-filled corneocytes in the *stratum corneum* at the surface of the epidermis, which are continuously replaced by new cells. The entire epidermis and in particular this layer of dead cells has an essential function as the first barrier against the environment.

The skin as an immune organ

Through its architecture and cellular composition the skin provides protection from injury and infection. The challenge for the largest organ of our body is to ensure efficient defence against pathogens and reliable immunosurveillance, but to avoid excessive immune responses, which might result in auto-immunity and chronic inflammation. The epidermis is in constant contact with multiple microbes (1 million/cm^2). The interaction between these microorganisms, which produce bacteriolytic enzymes, antibiotics and antifungal substances, and their competition for the colonization of the surface helps maintaining the skin's homeostasis. In addition, an antimicrobial lipid layer produced by sebocytes covers the skin surface. Keratinocytes are an important source of antimicrobial peptides. They are produced constitutively (e.g. lysozyme and psoriasin), or after infection/inflammation (e.g. human β-defensins and cathelicidin LL-37) (Glaser et al., 2005). Besides their antimicrobial activity, antimicrobial peptides such as LL-37 have a chemotactic role and modulate the immunological properties of DC and T cells (Nestle et al., 2009b). Lymphocytes, mainly T cells and B cells, and their receptors are responsible for the acquired immunity. The adaptive immune response allows to specifically recognize and remember "non-self" antigens of pathogens, and to mount a strong attack on these pathogens each time they are encountered. However, at the first time when the acquired immune system gets into contact with a new antigen, this mounting requires some days. In contrast, the innate immunity is less specific, but much faster. It relies on the recognition of highly conserved non-self pathogen-associated molecular patterns (PAMPs), and this recognition results for example in the expression of pro-inflammatory cytokines. These cytokines are able to activate and attract immune cells, which in turn attack the pathogens. PAMPs are recognized by Toll-like receptors (TLRs), also called pattern recognition receptors (PRRs), which are expressed by immune cells such as monocytes, macrophages, DCs and granulocytes, but also by keratinocytes. This indicates that they initiate a first line response to various pathogen-derived components (Creagh and O'Neill, 2006; Kollisch et al., 2005; Ting et al., 2006). Agonists of TLRs include bacterial lipopeptides, peptidoglycan and lipoteichoic acid (TLR2), double-stranded RNA (TLR3), lipopolysaccharides (LPS) (TLR4), flagellin (TLR5), imidazoquinoline and single-stranded RNA (TLR7 and TLR8), as well as CpG-containing DNA (TLR9) (McInturff et al., 2005).

Besides professional immune cells such as macrophages, neutrophils, dendritic cells and lymphocytes, keratinocytes have been

demonstrated to play an important regulatory role in cutaneous inflammatory and immune responses by producing various types of cytokines (Nestle et al., 2009a). Keratinocytes are responsive to DCs and T cell-derived cytokines, including interferons, tumour necrosis factor (TNF)α, IL-17 and the IL-20 family of cytokines. These stimuli induce expression of pro-inflammatory cytokines (e.g. IL-1, IL-6 and TNFα) as well as of chemokines, small heparin-binding proteins with chemotactic activity such as IL-8 (CXCL8), CXCL10, and CCL29 (Nestle et al., 2009b).

In pathological situations with an accumulation of T cells such as psoriasis, allergic contact dermatitis, and lichen planus, keratinocytes serve as non-professional antigen presenting cells and express MHC II, intercellular adhesion molecules (ICAM-1) and CD-36 antigen, demonstrating that they can interact with mononuclear cells via adhesion molecules or via the release of cytokines (Barker et al., 1991).

Interleukin-1 (IL-1)

IL-1 is a pleiotropic pro-inflammatory cytokine, which induces systemic and local responses to infection. It induces expression of adhesion molecules on endothelial cells. Together with the induction of chemokines, this stimulates the infiltration of inflammatory and immunocompetent cells (Dinarello, 2009a). In addition, IL-1 causes fever, vasodilatation, hypotension and enhances pain sensitivity. Based on these activities, it functions as a central mediator in various acute and chronic inflammatory diseases, thus representing a potential target for therapeutic intervention (Dinarello, 1998, 2004). Expression of IL-1 is regulated at the transcriptional level by nuclear factor κB (NF-κB) that is also responsible for expression of TNFα. Vice versa, IL-1 and TNFα can both activate NF-κB. TNFα is considered to act upstream of IL-1 in several conditions, which lead to the paradigm 'TNF-induced, IL-1-mediated disease'. However, there are several IL-1-specific diseases (see below) (Dinarello, 2004). Biological responses of IL-1 are mediated by the IL-1 receptor type I (IL-1RI), which is ubiquitously expressed (Dinarello, 2009a). Interestingly, IL-1RI and TLRs share the same cytoplasmic signalling domain, the Toll/interleukin-1 receptor (TIR) domain, demonstrating the prominent role of IL-1 signalling for inflammation (Dinarello, 2009a). Agonists of IL-1RI are IL-1α and -β, which are both initially expressed with an amino-terminal propeptide. ProIL-1β cannot bind and activate IL-1RI, whereas proIL-1α has the same biological activity as mature IL-1α. In most cases proIL-1β is activated by the protease caspase-1 (Dinarello, 2009a; Kuida et al., 1995; Li et al., 1995). However, other proteases were identified that are able to process proIL-1β, e.g. neutrophil elastase or mast cell protease (Guma et al., 2009; Mizutani et al., 1991). ProIL-1α and -β lack a signal peptide for protein secretion and they leave the cell through one or several poorly understood mechanisms, which do not depend on the classical endoplasmic reticulum (ER)/Golgi pathway and are collectively called unconventional protein secretion (Nickel, 2003). IL-1 activity is also regulated by the expression of the conventionally secreted IL-1 receptor antagonist (IL-1Ra) (Dinarello, 2009a). IL-1Ra binds to IL-1RI, however, this binding prevents binding of IL-1α and -β, cannot induce signal transduction, and, therefore, blocks the receptor.

Inflammasomes

Caspase-1 activity is required for the activation of proIL-1β, but also for the unconventional secretion of proIL-1α and of many other proteins involved in inflammation, repair and cytoprotection (Keller et al., 2008; Nickel and Rabouille, 2009). Caspase-1 is initially expressed as an inactive precursor, which is activated in large complexes called inflammasomes (Martinon et al., 2009). In a cell-free system from a macrophage cell line, the NLRP1 (nucleotide-binding domain, leucine-rich repeat-containing receptor protein, also known as NALP1) inflammasome was identified as a caspase-1-activating platform (Martinon et al., 2002). The complex consists of the large backbone protein NLRP1, the small ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) adaptor protein, procaspase-1 and -5. The NLRP1 inflammasome assembles via homotypic interactions of death domain folds. Thereby, procaspase-1 and -5 are brought into close proximity, which leads to their activation. Active caspase-1 in turn activates proIL-1β and -18, resulting in secretion of the active cytokines and therefore in inflammation *in vivo*. Meanwhile, other inflammasome complexes have been identified, including the NLRP3, NLRC4 (also known as IPAF) and the (absent in melanoma) AIM2 inflammasome. They bind and activate caspase-1 via ASC, although binding of ASC to NLRC4 is under debate (Schroder et al., 2009; Stutz et al., 2009).

Activation of inflammasomes

What are the signals that induce assembly and activation of inflammasomes? TLRs possess a leucine-rich repeat (LRR) domain for agonist binding, and this domain can also be found on NLRs, suggesting that the latter can be considered as intracellular PRRs and as sensors for inflammasome assembly. Indeed, a lot of agonists have been identified that activate the different inflammasomes (see Table 1). Whereas the stimulus for assembly and activation of the NLRP1 inflammasome in humans is unknown, anthrax lethal toxin activates caspase-1 in an NLRP1-dependent manner in mice (Martinon et al., 2009). The NLRC4 inflammasome assembles upon incubation of macrophages with flagellin from different species (flagellin is also a TLR5 agonist). The NLRP3 complex is activated by pore-forming toxins, but interestingly also by different molecules released from stressed and damaged cells, now collectively called damage-associated molecular patterns (DAMPs), such as ATP and gout-causing uric acid crystals (Martinon et al., 2009). In addition, exposure to other exogenous crystals, asbestos and silica particles, and aluminium adjuvants, results in NLRP3-dependent caspase-1 activation, demonstrating that this complex represents an important link between innate and acquired immunity. AIM2 directly binds dsDNA, and this binding results in inflammasome assembly, in caspase-1 activation and in proIL-1β processing. In contrast, a direct binding of the above mentioned structurally very different inflammasome agonists to NLRPs could not be demonstrated and more indirect mechanisms for caspase-1 activation have been proposed (Martinon et al., 2009).

IL-1 in murine skin

Whereas mice lacking caspase-1, IL-1α, IL-1β, or both cytokines develop normally and do not exhibit spontaneous disease symptoms (Dinarello, 2009a), IL-1Ra knockout mice suffer from arteritis, arthritis and skin inflammation (Horai et al., 2000; Nicklin et al., 2000; Shepherd et al., 2004). This demonstrates that the expression of IL-1Ra is essential for the regulation of the activity of IL-1 in murine skin. Transgenic mice overexpressing IL-1α in keratinocytes suffer from spontaneous inflammation in the skin (Groves et al., 1995), and additional overexpression of IL-1RI in keratinocytes aggravates this phenotype (Groves et al., 1996), demonstrating that keratinocyte-derived IL-1 activity and IL-1 signalling in these cells are able to induce an inflammatory phenotype. Transgenic mice overexpressing caspase-1 in the epidermis show a spontaneous recalcitrant dermatitis and skin ulcers (Yamanaka et al., 2000). Surprisingly, mice lacking caspase-8 in

Table 1
Inflammasome agonists. Agonists of the different inflammasomes and the cell types, in which activation was identified, are listed (Dostert et al., 2009; Fritz et al., 2006; Martinon and Tschopp, 2007; Mishra et al., 2010; Petrilli et al., 2007; Schroder et al., 2009).

Inflammasome	Agonists	Cell type
NLRP1b	Microbial toxins	
	Lethal factor from *Bacillus anthracis*	Macrophages (mouse BMDM)
NLRP3	PAMPs	
	Peptidoglycan/MDP	Macrophages
	Bacterial RNA	Macrophages
	Poly I:C	Macrophages
	Microbial toxins	
	Nigericin (*Streptomyces hygroscopicus*), aerolysin (*Aeromonas hydrophila*), maiotoxin (marine dinoflagellates), listeriolysin O (*Listeria monocytogenes*), gramicidin (*Bacillus brevis*), alpha-toxin (*Staphylococcus aureus*)	Macrophages
	Live bacteria	
	Staphylococcus aureus, *Listeria monocytogenes*, *Escherichia coli*, *Mycobacterium tuberculosis*	Macrophages
	Viruses	
	Sendai virus, influenza virus, adenovirus	Macrophages
	Fungi	
	Candida albicans, *Saccharomyces cerevisiae*	Macrophages
	Parasites	
	Malarial hemozoin	Macrophages
	DAMPs	
	Extracellular ATP (via P2X7 receptor)	Macrophages
	Hyaluronan	Macrophages (mouse alveolar)
	Glucose	Macrophages (THP1)
	Amyloid-beta	Microglial cells (murine)
	K^+ efflux inducing agents (ATP, NAD+)	Macrophages
	Calcium influx	Keratinocytes
	Reactive oxygen species (ROS)	Macrophages (THP1)
	Imidazoquinoline compounds (R837 and R848)	Macrophages
	TNP (trinitrophenylchloride), TNCB	Keratinocytes
	Gout (MSU) and pseudogout crystals (CPPD)	Macrophages
	Exogenous crystals (asbestos, silica)	Macrophages
	Aluminium adjuvants	Macrophages
	Genetic activating mutations in NLRP3	
	UV irradiation	Keratinocytes
	SDS	Keratinocytes
NLRC4/IPAF	PAMPs	
	Intracellular flagellin	Macrophages (mouse BMDM)
	Live bacteria	
	Gram-negative bacteria (*Legionella pneumophila*, *Salmonella typhimurium*, *Shigella flexneri*, or *Pseudomonas aeruginosa*)	Macrophages
NAIP	Live bacteria	
	Legionella pneumophila	Macrophages (peritoneal)
AIM2	Intracellular dsDNA	Macrophages
Unknown	*Listeria*	
	Francisella	

keratinocytes suffer from strong cutaneous inflammation because of enhanced production and inflammasome-dependent secretion of proIL-1α (Lee et al., 2009; Sollberger and Beer, 2009). This is partially due to IL-1α signalling to dermal fibroblasts, which in turn induces expression of growth factors required for proliferation of keratinocytes. Such a double-paracrine mechanism has also been demonstrated in a two-dimensional culture model of keratinocytes and fibroblasts (Szabowski et al., 2000). However, a recent paper doubts an involvement of IL-1α in the inflammatory phenotype of keratinocyte-specific caspase-8 knockout mice (Kovalenko et al., 2009). The discrepancy may be explained by the involvement of recently discovered IL-1 family members such as IL-1F6, because overexpression of this cytokine also leads to an inflammatory skin phenotype (Blumberg et al., 2007). In summary, these mouse models demonstrate the importance of IL-1 signalling and particularly the impact of keratinocyte-derived IL-1 activity for skin homeostasis and inflammation. However, it should be kept in mind that mice represent a model system, whose skin is anatomically quite different from human skin.

The inflammasome in human keratinocytes

Human and murine macrophages express IL-1 only upon stimulation, e.g. with TLR agonists. In contrast, human keratinocytes constitutively synthesize proIL-1α, -β, and IL-1Ra. However, they do not activate and secrete these pro-inflammatory cytokines under normal conditions (Feldmeyer et al., 2007). Whereas inflammatory skin diseases are successfully treated with low doses of UVB, high doses can cause sunburn (Maverakis et al., 2010), which represents an inflammatory reaction. It has been known for a long time that human keratinocytes secrete IL-1β upon UVB irradiation, however, the pathway leading to its maturation was unknown (Kondo et al., 1994). Even the question whether keratinocytes are able to activate caspase-1 has been a matter of controversy (Mizutani et al., 1991; Zepter et al., 1997). Human keratinocytes express all inflammasome proteins *in vitro* and most likely also *in vivo* (Faustin and Reed, 2008; Feldmeyer et al., 2007; Watanabe et al., 2007). Irradiation of these cells with a physiological dose of UVB induces secretion of large amounts of mature IL-1β and of proIL-1α, comparable to the amount secreted by activated

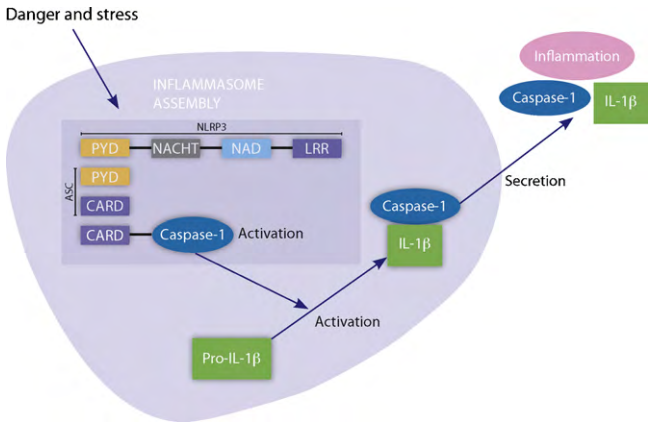

Fig. 2. The NLRP3 inflammasome. The NLRP3 inflammasome is the prototype of a caspase-1-activating complex, which assembles upon sensing of several danger and stress signals (see Table 1). This results in activation of caspase-1, which in turn processes proIL-1β, and in secretion of the active pro-inflammatory cytokine. *In vivo*, secretion of IL-1β induces inflammation. Human keratinocytes express all components of the NLRP3 inflammasome, and these proteins are required for UVB-induced secretion of IL-1β and of proIL-1α (Feldmeyer et al., 2007; Martinon et al., 2009).

macrophages. This secretion is completely blocked by treatment with caspase-1 inhibitors (Feldmeyer et al., 2007). IL-1β activation is dependent on the release of Ca^{2+} from intracellular stores, but does not require *de novo* protein synthesis. In contrast to macrophages, neither an efflux of intracellular K^+ nor stimulation with ATP induces IL-1β secretion in keratinocytes. Using an siRNA approach it was shown that the NLRP3 inflammasome is mainly responsible for UVB-induced maturation and secretion of IL-1β, although NLRP1 also plays a role (Feldmeyer et al., 2007). Most importantly, studies with caspase-1 knockout mice and wild-type littermates revealed that UVB-induced inflammation in the skin of these animals requires caspase-1, suggesting that UVB induces IL-1 release by keratinocytes also *in vivo* (Feldmeyer et al., 2007). As murine keratinocytes express proIL-1α but very little proIL-1β, UVB-induced inflammation in mice is most likely dependent on proIL-1α. Recently, it was shown that unconventional secretion of proIL-1α requires caspase-1 activity, demonstrating that caspase-1 not only regulates IL-1β activation, but also proIL-1α activity (Keller et al., 2008). These results demonstrate that also non-professional immune cells such as human keratinocytes express inflammasome proteins, which are required for the activation of proIL-1β as well as for the secretion of mature IL-1β and of proIL-1α (Fig. 2).

The inflammasome in contact-mediated hypersensitivity

Contact hypersensitivity (CH) to haptens is a clinically relevant syndrome known as allergic contact dermatitis. An established mouse model for CH is also available. CH represents an adaptive immune response, which consists of two phases. Haptens are applied to the skin, which primes T cells (sensitization phase). Subsequent skin exposure to the hapten leads to a localized inflammatory response that manifests within about 24 h (elicitation phase). This reaction is thought to depend on DC (Langerhans cell) migration to the lymph node, antigen presentation and recruitment of T cells after expansion to the exposed skin. The involvement of Langerhans cells as activators or inhibitors in CH is under debate (Nestle et al., 2009a), and CH is also found in mice without T cells (O'Leary et al., 2006), suggesting a considerable amount of redundancy in this model. Interestingly, mice lacking IL-1β or wild-type mice treated with IL-1Ra showed impaired CH reactions, demonstrating a requirement of IL-1 signalling in this adaptive immune response (Kondo et al., 1995; Shornick et al., 1996). Consequently, CH reactions are strongly diminished in mice lacking NLRP3 or ASC. Depending on the model, the inflammasome is required for the sensitization or elicitation phase (Sutterwala et al., 2006; Watanabe et al., 2007). This links IL-1 and the inflammasome to the development of adaptive immunity in the skin.

IL-1 and the inflammasome in (skin) diseases

Due to the important role of IL-1 in the induction of inflammatory responses, aberrant activity of the cytokine and of the inflammasomes is involved in the pathogenesis of many diseases, including skin diseases (Dinarello, 2009a). Inhibition of the activity of IL-1β through IL-1Ra (Anakinra, originally approved for the treatment of rheumatoid arthritis) or other IL-1 blockers allows the successful treatment of these diseases (Dinarello, 2009a).

The cryopyrin-associated periodic syndrome (CAPS) comprises a spectrum of rare inherited inflammatory disorders, which are associated with mutations in the *NLRP3* gene. These mutations result in constitutive activation of the NLRP3 inflammasome and, therefore, in uncontrolled activity of IL-1β, demonstrating the importance of NLRP3 and of IL-1β in humans. CAPS is characterized by a broad spectrum of clinical manifestations, including fever, fatigue, inflammation of the skin, bones, joints (arthritis) and of the central nervous system. This sterile inflammation can result in sensorineural hearing loss, intellectual impairment and meningitis (Goldbach-Mansky et al., 2006; Leslie et al., 2006; Ross et al., 2008). IL-1 blockade in patients suffering from CAPS results in a complete remission of symptoms as long as the treatment is given. Experiments with a CAPS model using an *NLRP3* mutant knock-in mouse carrying the mutation found in human CAPS patients showed that the disease required an intact inflammasome, was only partially dependent on IL-1β, and was independent of T cells (Brydges et al., 2009).

Deficiency in IL-1Ra (DIRA) due to homozygous mutations in this gene causes life-threatening auto-inflammation, affecting mainly the skin (severe pustulosis and ichthyosiform lesions) and the bones, similar to symptoms of patients suffering from CAPS (Aksentijevich et al., 2009; Reddy et al., 2009). This demonstrates that the expression of IL-1Ra is essential for the regulation of the activity of IL-1 in human skin. DIRA belongs to the recently defined auto-inflammatory diseases (see above), which all respond to IL-1 blockade, and many of these disorders affect the skin (Dinarello, 2009b). Also in patients suffering from type 2 diabetes mellitus, Anakinra is beneficial, improving the glycemic control (Dinarello, 2009b; Larsen et al., 2007).

IL-1 plays a role in the development of cancer, and its neutralization inhibited tumour angiogenesis, development and invasiveness in experimental tumour models (Apte et al., 2006a,b; Bar et al., 2004). In line with this finding is the constitutive secretion of IL-1β by human melanoma cells, resulting in auto-inflammation and thereby contributing to the development and progression of melanomas (Okamoto et al., 2010). Interestingly, highly invasive melanoma cells induce the expression of matrix metalloproteinase-1 in an IL-1α and FGF2 dependent manner, and this is required for tumor invasion and metastasis (Loffek et al., 2005). As IL-1α and FGF2 secretions are both regulated by caspase-1 activity (Keller et al., 2008), this also points to a role of the inflammasome in melanoma. However, recently it has also been shown that the NLRP3 inflammasome is required for efficient anti-cancer immunity (Aymeric et al., 2010; Ghiringhelli et al., 2009). These contradictory observations may reflect the paradoxical role of inflammation in cancer development (de Visser et al., 2006).

Vitiligo is an autoimmune skin disease, in which melanocytes in the skin are destroyed, and this causes depigmentation in patches of the skin. Patients affected by vitiligo also suffer with a higher frequency from other autoimmune disorders like autoimmune thyroid disease, rheumatoid arthritis, diabetes and lupus erythematosus. DNA sequence variants in the *NLRP1* region confer susceptibility to autoimmune and auto-inflammatory diseases that are associated with vitiligo (Jin et al., 2007). Because NLRP1 is a part of the NLRP1 inflammasome, which is expressed by keratinocytes (see above), and because serum IL-1β levels are elevated in patients with generalized vitiligo, this suggests the involvement of NLRP1 and of IL-1 in the pathogenesis of this disease (Jin et al., 2007).

Many anti-inflammatory and immunomodulatory drugs are on the market, and the molecular mechanisms by which these drugs exert their pharmacological activities are often only partially characterized. Interestingly, thalidomide, which is used for the treatment of inflammatory diseases and cancer, has recently been shown to inhibit caspase-1 and, therefore, liberation of IL-1 activity (Keller et al., 2009). In addition, the herbal anti-inflammatory compound parthenolide and other IKKβ inhibitors are also able to inhibit caspase-1 (Juliana et al., 2010). Therefore, it can be expected that more anti-inflammatory drugs inhibit the immune system through a blockade of IL-1 and of inflammasomes.

Conclusions and perspectives

During the last years a lot of evidence has accumulated that IL-1 signalling is essential for the homeostasis of the skin and critically involved in several (auto)-inflammatory (skin) diseases. IL-1 activity is determined through the balance of IL-1 to IL-1Ra (Dinarello, 2009a). Ablation of IL-1Ra in humans and mice results in strong cutaneous inflammation (Aksentijevich et al., 2009; Horai et al., 2000; Nicklin et al., 2000; Reddy et al., 2009; Shepherd et al., 2004). Overexpression of IL-1α in epidermal keratinocytes of mice induces a chronic inflammatory skin phenotype, demonstrating that these non-professional immune cells can secrete large amounts of IL-1 (Groves et al., 1995, 1996). Caspase-1 is required for the generation of IL-1 activity through activation of proIL-1β and regulation of unconventional secretion of IL-1β and of proIL-1α (Keller et al., 2008). Overexpression of the protease in keratinocytes in mice also results in skin inflammation (Yamanaka et al., 2000). Human primary keratinocytes express high levels of proIL-1α and -β and of inflammasome proteins (Feldmeyer et al., 2007; Watanabe et al., 2007). The latter are required for UVB-induced activation of caspase-1, and subsequent (pro)IL-1 secretion and/or activation. In addition, activating mutations in the human *NLRP3* gene cause a similar inflammatory phenotype in the skin as inactivation of the *IL-1Ra* gene (Aksentijevich et al., 2009).

These data also suggest a function of keratinocytes in the immunity of the skin through the sensing of danger and the generation of IL-1 activity. Such a role is surprising, since the skin contains a variety of different professional immune cells. For an estimation of the contribution of keratinocytes to a cutaneous inflammatory response, mouse models are necessary, which allow the conditional ablation of IL-1 or of inflammasome proteins in these cells. A second challenge is to examine a possible crosstalk between keratinocytes and other cells in the skin, which may be required for the induction of an inflammatory response and for its maintenance. Although IL-1 blockers are increasingly used for the treatment of (auto)-inflammatory diseases, which affect the skin, a better understanding of inflammation at the cellular and molecular level might allow the development of new and more specific drugs for therapeutic intervention. Due to its accessibility the skin offers unique possibilities in this respect. Finally, only a few stimuli are known, which activate the NLRP3 inflammasome. In the future it can be expected that more inflammasome activators and inflammasome complexes will be identified, which activate caspase-1 in keratinocytes but also in other cells of the skin.

Acknowledgements

The funding by the Swiss National Science Foundation (grant 3100A0-104170 to D.B. and grant 3235B0-102873 to L.F.) and by the European Science Foundation (grant 31EM30-126141 to D.B.) is acknowledged. We thank Hannes Bärtschi for the illustrations. We apologize to those authors whose work could not be cited due to space limitations.

References

Aksentijevich, I., Masters, S.L., Ferguson, P.J., Dancey, P., Frenkel, J., van Royen-Kerkhoff, A., Laxer, R., Tedgard, U., Cowen, E.W., Pham, T.H., Booty, M., Estes, J.D., Sandler, N.G., Plass, N., Stone, D.L., Turner, M.L., Hill, S., Butman, J.A., Schneider, R., Babyn, P., El-Shanti, H.I., Pope, E., Barron, K., Bing, X., Laurence, A., Lee, C.C., Chapelle, D., Clarke, G.I., Ohson, K., Nicholson, M., Gadina, M., Yang, B., Korman, B.D., Gregersen, P.K., van Hagen, P.M., Hak, A.E., Huizing, M., Rahman, P., Douek, D.C., Remmers, E.F., Kastner, D.L., Goldbach-Mansky, R., 2009. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N. Engl. J. Med. 360, 2426–2437.

Apte, R.N., Dotan, S., Elkabets, M., White, M.R., Reich, E., Carmi, Y., Song, X., Dvozkin, T., Krelin, Y., Voronov, E., 2006a. The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor–host interactions. Cancer Metastasis Rev. 25, 387–408.

Apte, R.N., Krelin, Y., Song, X., Dotan, S., Recih, E., Elkabets, M., Carmi, Y., Dvorkin, T., White, R.M., Gayvoronsky, L., Segal, S., Voronov, E., 2006b. Effects of micro-environment- and malignant cell-derived interleukin-1 in carcinogenesis, tumour invasiveness and tumour–host interactions. Eur. J. Cancer 42, 751–759.

Aymeric, L., Apetoh, L., Ghiringhelli, F., Tesniere, A., Martins, I., Kroemer, G., Smyth, M.J., Zitvogel, L., 2010. Tumor cell death and ATP release prime dendritic cells and efficient anticancer immunity. Cancer Res. 70, 855–858.

Bar, D., Apte, R.N., Voronov, E., Dinarello, C.A., Cohen, S., 2004. A continuous delivery system of IL-1 receptor antagonist reduces angiogenesis and inhibits tumor development. FASEB. J. 18, 161–163.

Barker, J.N., Mitra, R.S., Griffiths, C.E., Dixit, V.M., Nickoloff, B.J., 1991. Keratinocytes as initiators of inflammation. Lancet 337, 211–214.

Blumberg, H., Dinh, H., Trueblood, E.S., Pretorius, J., Kugler, D., Weng, N., Kanaly, S.T., Towne, J.E., Willis, C.R., Kuechle, M.K., Sims, J.E., Peschon, J.J., 2007. Opposing activities of two novel members of the IL-1 ligand family regulate skin inflammation. J. Exp. Med. 204, 2603–2614.

Brydges, S.D., Mueller, J.L., McGeough, M.D., Pena, C.A., Misaghi, A., Gandhi, C., Putnam, C.D., Boyle, D.L., Firestein, G.S., Horner, A.A., Soroosh, P., Watford, W.T., O'Shea, J.J., Kastner, D.L., Hoffman, H.M., 2009. Inflammasome-mediated disease animal models reveal roles for innate but not adaptive immunity. Immunity 30, 875–887.

Creagh, E.M., O'Neill, L.A., 2006. TLRs, NLRs and RLRs: a trinity of pathogen sensors that co-operate in innate immunity. Trends Immunol. 27, 352–357.

de Visser, K.E., Eichten, A., Coussens, L.M., 2006. Paradoxical roles of the immune system during cancer development. Nat. Rev. Cancer 6, 24–37.

Dinarello, C.A., 1998. Interleukin-1 beta, interleukin-18, and the interleukin-1 beta converting enzyme. Ann. N. Y. Acad. Sci. 856, 1–11.

Dinarello, C.A., 2004. Therapeutic strategies to reduce IL-1 activity in treating local and systemic inflammation. Curr. Opin. Pharmacol. 4, 378–385.

Dinarello, C.A., 2009a. Immunological and inflammatory functions of the interleukin-1 family. Annu. Rev. Immunol. 27, 519–550.

Dinarello, C.A., 2009b. Interleukin-1beta and the autoinflammatory diseases. N. Engl. J. Med. 360, 2467–2470.

Dostert, C., Guarda, G., Romero, J.F., Menu, P., Gross, O., Tardivel, A., Suva, M.L., Stehle, J.C., Kopf, M., Stamenkovic, I., Corradin, G., Tschopp, J., 2009. Malarial hemozoin is a Nalp3 inflammasome activating danger signal. PLoS One 4, e6510.

Faustin, B., Reed, J.C., 2008. Sunburned skin activates inflammasomes. Trends Cell Biol. 18, 4–8.

Feldmeyer, L., Keller, M., Niklaus, G., Hohl, D., Werner, S., Beer, H.D., 2007. The inflammasome mediates UVB-induced activation and secretion of interleukin-1beta by keratinocytes. Curr. Biol. 17, 1140–1145.

Fritz, J.H., Ferrero, R.L., Philpott, D.J., Girardin, S.E., 2006. Nod-like proteins in immunity, inflammation and disease. Nat. Immunol. 7, 1250–1257.

Fuchs, E., Raghavan, S., 2002. Getting under the skin of epidermal morphogenesis. Nat. Rev. Genet. 3, 199–209.

Ghiringhelli, F., Apetoh, L., Tesniere, A., Aymeric, L., Ma, Y., Ortiz, C., Vermaelen, K., Panaretakis, T., Mignot, G., Ullrich, E., Perfettini, J.L., Schlemmer, F., Tasdemir, E., Uhl, M., Genin, P., Civas, A., Ryffel, B., Kanellopoulos, J., Tschopp, J., Andre, F., Lidereau, R., McLaughlin, N.M., Haynes, N.M., Smyth, M.J., Kroemer, G., Zitvogel, L., 2009. Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. Nat. Med. 15, 1170–1178.

Glaser, R., Harder, J., Lange, H., Bartels, J., Christophers, E., Schroder, J.M., 2005. Antimicrobial psoriasin (S100A7) protects human skin from *Escherichia coli* infection. Nat. Immunol. 6, 57–64.

Goldbach-Mansky, R., Dailey, N.J., Canna, S.W., Gelabert, A., Jones, J., Rubin, B.I., Kim, H.J., Brewer, C., Zalewski, C., Wiggs, E., Hill, S., Turner, M.L., Karp, B.I., Aksentijevich, I., Pucino, F., Penzak, S.R., Haverkamp, M.H., Stein, L., Adams, B.S., Moore, T.L., Fuhlbrigge, R.C., Shaham, B., Jarvis, J.N., O'Neil, K., Vehe, R.K., Beitz, L.O., Gardner, G., Hannan, W.P., Warren, R.W., Horn, W., Cole, J.L., Paul, S.M., Hawkins, P.N., Pham, T.H., Snyder, C., Wesley, R.A., Hoffmann, S.C., Holland, S.M., Butman, J.A., Kastner, D.L., 2006. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. N. Engl. J. Med. 355, 581–592.

Goldbach-Mansky, R., Kastner, D.L., 2009. Autoinflammation: the prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. J. Allergy Clin. Immunol. 124, 1141–1149, quiz 1150-1141.

Groves, R.W., Mizutani, H., Kieffer, J.D., Kupper, T.S., 1995. Inflammatory skin disease in transgenic mice that express high levels of interleukin 1 alpha in basal epidermis. Proc. Natl. Acad. Sci. U.S.A. 92, 11874–11878.

Groves, R.W., Rauschmayr, T., Nakamura, K., Sarkar, S., Williams, I.R., Kupper, T.S., 1996. Inflammatory and hyperproliferative skin disease in mice that express elevated levels of the IL-1 receptor (type I) on epidermal keratinocytes. Evidence that IL-1-inducible secondary cytokines produced by keratinocytes in vivo can cause skin disease. J. Clin. Invest. 98, 336–344.

Guma, M., Ronacher, L., Liu-Bryan, R., Takai, S., Karin, M., Corr, M., 2009. Caspase 1-independent activation of interleukin-1beta in neutrophil-predominant inflammation. Arthritis Rheum. 60, 3642–3650.

Horai, R., Saijo, S., Tanioka, H., Nakae, S., Sudo, K., Okahara, A., Ikuse, T., Asano, M., Iwakura, Y., 2000. Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin 1 receptor antagonist-deficient mice. J. Exp. Med. 191, 313–320.

Jin, Y., Mailloux, C.M., Gowan, K., Riccardi, S.L., LaBerge, G., Bennett, D.C., Fain, P.R., Spritz, R.A., 2007. NALP1 in vitiligo-associated multiple autoimmune disease. N. Engl. J. Med. 356, 1216–1225.

Juliana, C., Fernandes-Alnemri, T., Wu, J., Datta, P., Solorzano, L., Yu, J.W., Meng, R., Quong, A.A., Latz, E., Scott, C.P., Alnemri, E.S., 2010. The anti-inflammatory compounds parthenolide and Bay 11-7082 are direct inhibitors of the inflammasome. J. Biol. Chem. 285, 9792–9802.

Keller, M., Ruegg, A., Werner, S., Beer, H.D., 2008. Active caspase-1 is a regulator of unconventional protein secretion. Cell 132, 818–831.

Keller, M., Sollberger, G., Beer, H.D., 2009. Thalidomide inhibits activation of caspase-1. J. Immunol. 183, 5593–5599.

Kollisch, G., Kalali, B.N., Voelcker, V., Wallich, R., Behrendt, H., Ring, J., Bauer, S., Jakob, T., Mempel, M., Ollert, M., 2005. Various members of the Toll-like receptor family contribute to the innate immune response of human epidermal keratinocytes. Immunology 114, 531–541.

Kondo, S., Pastore, S., Fujisawa, H., Shivji, G.M., McKenzie, R.C., Dinarello, C.A., Sauder, D.N., 1995. Interleukin-1 receptor antagonist suppresses contact hypersensitivity. J. Invest. Dermatol. 105, 334–338.

Kondo, S., Sauder, D.N., Kono, T., Galley, K.A., McKenzie, R.C., 1994. Differential modulation of interleukin-1 alpha (IL-1 alpha) and interleukin-1 beta (IL-1 beta) in human epidermal keratinocytes by UVB. Exp. Dermatol. 3, 29–39.

Kovalenko, A., Kim, J.C., Kang, T.B., Rajput, A., Bogdanov, K., Dittrich-Breiholz, O., Kracht, M., Brenner, O., Wallach, D., 2009. Caspase-8 deficiency in epidermal keratinocytes triggers an inflammatory skin disease. J. Exp. Med. 206, 2161–2177.

Kuida, K., Lippke, J.A., Ku, G., Harding, M.W., Livingston, D.J., Su, M.S., Flavell, R.A., 1995. Altered cytokine export and apoptosis in mice deficient in interleukin-1 beta converting enzyme. Science 267, 2000–2003.

Larsen, C.M., Faulenbach, M., Vaag, A., Volund, A., Ehses, J.A., Seifert, B., Mandrup-Poulsen, T., Donath, M.Y., 2007. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N. Engl. J. Med. 356, 1517–1526.

Lee, P., Lee, D.J., Chan, C., Chen, S.W., Ch'en, I., Jamora, C., 2009. Dynamic expression of epidermal caspase 8 simulates a wound healing response. Nature 458, 519–523.

Leslie, K.S., Lachmann, H.J., Bruning, E., McGrath, J.A., Bybee, A., Gallimore, J.R., Roberts, P.F., Woo, P., Grattan, C.E., Hawkins, P.N., 2006. Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations. Arch. Dermatol. 142, 1591–1597.

Li, P., Allen, H., Banerjee, S., Franklin, S., Herzog, L., Johnston, C., McDowell, J., Paskind, M., Rodman, L., Salfeld, J., et al., 1995. Mice deficient in IL-1 beta-converting enzyme are defective in production of mature IL-1 beta and resistant to endotoxic shock. Cell 80, 401–411.

Loffek, S., Zigrino, P., Angel, P., Anwald, B., Krieg, T., Mauch, C., 2005. High invasive melanoma cells induce matrix metalloproteinase-1 synthesis in fibroblasts by interleukin-1alpha and basic fibroblast growth factor-mediated mechanisms. J. Invest. Dermatol. 124, 638–643.

Martinon, F., Burns, K., Tschopp, J., 2002. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol. Cell. 10, 417–426.

Martinon, F., Mayor, A., Tschopp, J., 2009. The inflammasomes: guardians of the body. Annu. Rev. Immunol. 27, 229–265.

Martinon, F., Tschopp, J., 2007. Inflammatory caspases and inflammasomes: master switches of inflammation. Cell Death Differ. 14, 10–22.

Maverakis, E., Miyamura, Y., Bowen, M.P., Correa, G., Ono, Y., Goodarzi, H., 2010. Light, including ultraviolet. J. Autoimmun. 34, J247–257.

McInturff, J.E., Modlin, R.L., Kim, J., 2005. The role of toll-like receptors in the pathogenesis and treatment of dermatological disease. J. Invest. Dermatol. 125, 1–8.

Medzhitov, R., 2008. Origin and physiological roles of inflammation. Nature 454, 428–435.

Mishra, B.B., Moura-Alves, P., Sonawane, A., Hacohen, N., Griffiths, G., Moita, L.F., Anes, E., 2010. Mycobacterium tuberculosis protein ESAT-6 is a potent activator of the NLRP3/ASC inflammasome. *Cell Microbiol*. doi:10.1111/j.1462-5822.2010.01450.x. (E-pub ahead of print).

Mizutani, H., Black, R., Kupper, T.S., 1991. Human keratinocytes produce but do not process pro-interleukin-1 (IL-1) beta. Different strategies of IL-1 production and processing in monocytes and keratinocytes. J. Clin. Invest. 87, 1066–1071.

Nestle, F.O., Di Meglio, P., Qin, J.Z., Nickoloff, B.J., 2009a. Skin immune sentinels in health and disease. Nat. Rev. Immunol. 9, 679–691.

Nestle, F.O., Kaplan, D.H., Barker, J., 2009b. Psoriasis. N. Engl. J. Med. 361, 496–509.

Nickel, W., 2003. The mystery of nonclassical protein secretion. A current view on cargo proteins and potential export routes. Eur. J. Biochem. 270, 2109–2119.

Nickel, W., Rabouille, C., 2009. Mechanisms of regulated unconventional protein secretion. Nat. Rev. Mol. Cell Biol. 10, 148–155.

Nicklin, M.J., Hughes, D.E., Barton, J.L., Ure, J.M., Duff, G.W., 2000. Arterial inflammation in mice lacking the interleukin 1 receptor antagonist gene. J. Exp. Med. 191, 303–312.

Numerof, R.P., Asadullah, K., 2006. Cytokine and anti-cytokine therapies for psoriasis and atopic dermatitis. BioDrugs 20, 93–103.

O'Leary, J.G., Goodarzi, M., Drayton, D.L., von Andrian, U.H., 2006. T cell- and B cell-independent adaptive immunity mediated by natural killer cells. Nat. Immunol. 7, 507–516.

Okamoto, M., Liu, W., Luo, Y., Tanaka, A., Cai, X., Norris, D.A., Dinarello, C.A., Fujita, M., 2010. Constitutively active inflammasome in human melanoma cells mediating autoinflammation via caspase-1 processing and secretion of interleukin-1{beta}. J. Biol. Chem. 285, 6477–6488.

Petrilli, V., Dostert, C., Muruve, D.A., Tschopp, J., 2007. The inflammasome: a danger sensing complex triggering innate immunity. Curr. Opin. Immunol. 19, 615–622.

Reddy, S., Jia, S., Geoffrey, R., Lorier, R., Suchi, M., Broeckel, U., Hessner, M.J., Verbsky, J., 2009. An autoinflammatory disease due to homozygous deletion of the IL1RN locus. N. Engl. J. Med. 360, 2438–2444.

Ross, J.B., Finlayson, L.A., Klotz, P.J., Langley, R.G., Gaudet, R., Thompson, K., Churchman, S.M., McDermott, M.F., Hawkins, P.N., 2008. Use of anakinra (Kineret) in the treatment of familial cold autoinflammatory syndrome with a 16-month follow-up. J. Cutan. Med. Surg. 12, 8–16.

Schroder, K., Muruve, D.A., Tschopp, J., 2009. Innate immunity: cytoplasmic DNA sensing by the AIM2 inflammasome. Curr. Biol. 19, R262–R265.

Shepherd, J., Little, M.C., Nicklin, M.J., 2004. Psoriasis-like cutaneous inflammation in mice lacking interleukin-1 receptor antagonist. J. Invest. Dermatol. 122, 665–669.

Shornick, L.P., De Togni, P., Mariathasan, S., Goellner, J., Strauss-Schoenberger, J., Karr, R.W., Ferguson, T.A., Chaplin, D.D., 1996. Mice deficient in IL-1beta manifest impaired contact hypersensitivity to trinitrochlorobenzone. J. Exp. Med. 183, 1427–1436.

Sollberger, G., Beer, H.D., 2009. Caspase-8 for outer harmony. Sci. Signal. 2, pe40.

Stutz, A., Golenbock, D.T., Latz, E., 2009. Inflammasomes: too big to miss. J. Clin. Invest. 119, 3502–3511.

Sutterwala, F.S., Ogura, Y., Szczepanik, M., Lara-Tejero, M., Lichtenberger, G.S., Grant, E.P., Bertin, J., Coyle, A.J., Galan, J.E., Askenase, P.W., Flavell, R.A., 2006. Critical role for NALP3/CIAS1/Cryopyrin in innate and adaptive immunity through its regulation of caspase-1. Immunity 24, 317–327.

Szabowski, A., Maas-Szabowski, N., Andrecht, S., Kolbus, A., Schorpp-Kistner, M., Fusenig, N.E., Angel, P., 2000. c-Jun and JunB antagonistically control cytokine-regulated mesenchymal-epidermal interaction in skin. Cell 103, 745–755.

Ting, J.P., Kastner, D.L., Hoffman, H.M., 2006. CATERPILLERs, pyrin and hereditary immunological disorders. Nat. Rev. Immunol. 6, 183–195.

Watanabe, H., Gaide, O., Petrilli, V., Martinon, F., Contassot, E., Roques, S., Kummer, J.A., Tschopp, J., French, L.E., 2007. Activation of the IL-1beta-processing inflammasome is involved in contact hypersensitivity. J. Invest. Dermatol. 127, 1956–1963.

Yamanaka, K., Tanaka, M., Tsutsui, H., Kupper, T.S., Asahi, K., Okamura, H., Nakanishi, K., Suzuki, M., Kayagaki, N., Black, R.A., Miller, D.K., Nakashima, K., Shimizu, M., Mizutani, H., 2000. Skin-specific caspase-1-transgenic mice show cutaneous apoptosis and pre-endotoxin shock condition with a high serum level of IL-18. J. Immunol. 165, 997–1003.

Zepter, K., Haffner, A., Soohoo, L.F., De Luca, D., Tang, H.P., Fisher, P., Chavinson, J., Elmets, C.A., 1997. Induction of biologically active IL-1 beta-converting enzyme and mature IL-1 beta in human keratinocytes by inflammatory and immunologic stimuli. J. Immunol. 159, 6203–6208.