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# Photoaging and skin cancer: Is the inflammasome the missing link?

Fawaz Awad[1], Eman Assrawi[1], Camille Louvrier, Claire Jumeau, Irina Giurgea[*], Serge Amselem[*,2], Sonia-Athina Karabina[*,2]

*Sorbonne Université, INSERM, UMR_S 933, Assistance Publique Hôpitaux de Paris, Hôpital Trousseau, Département de Génétique médicale, Paris, F-75012, France*

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ABSTRACT

Photoaging and epithelial skin tumorigenesis are complex processes triggered mainly by UV radiation from chronic sun exposure. This leads to DNA damage and reactive oxygen species (ROS) production, which initiate an inflammatory response that alters cell structure and function.

Changes in cell homeostasis and ROS production activate intracellular multiprotein platforms called inflammasomes. Inflammasomes nucleate around cytoplasmic receptors mainly of the NLR (nucleotide-binding domain and leucine-rich repeat) family and regulate caspase-1-dependant secretion of pro-inflammatory interleukin (IL)1β and IL18 cytokines, and an inflammatory form of death named pyroptosis.

NLRP1 inflammasomes have taken centre stage in skin biology, as mutations in NLRP1 underlie the genetic etiology of dermatological diseases and increase the susceptibility to skin cancer. Targeting inflammasome(s) might be an important approach to improve skin inflammation, photoaging and reduce the risk of epithelial skin tumorigenesis. In this context, we discuss the potential implication of NLRP1 and NLRP3 inflammasomes.

## 1. Introduction

Human skin which is the largest organ in the body, it interacts with the environment, protects from mechanical pressure and radiation and plays an important role in defense against invading pathogens. Like other organs, human skin undergoes intrinsic (chronological) aging as well as extrinsic aging (photoaging) mainly due to the effect of ultraviolet (UV) radiation (UVR), from chronic sun exposure (Fisher et al., 2002). UV radiation (which comprises UVA and UVB) leads to DNA damage and production of reactive oxygen species (ROS), both of which promote inflammation and tumorigenesis (Calleja-Agius et al., 2013; Pillai et al., 2005; Yaar and Gilchrest, 2007; Bachelor and Bowden, 2004; Hussain et al., 2003). Interestingly, ROS, damaged DNA and altered cell homeostasis are also activators of intracellular protein platforms known as inflammasomes (Martinon, 2012). Following stimulation, keratinocytes the major cell type present in the skin, and to a lesser extent melanocytes and Langerhans cells, secrete pro-inflammatory cytokines (Feldmeyer et al., 2007; Sollberger et al., 2015; Mantovani et al., 2008), which regulate innate and adaptive immune responses (Nasti and Timares, 2012; Ortiz et al., 2015). Cytokines and growth factors through paracrine and autocrine actions define a local microenvironment capable of either supporting or limiting inflammation and tumor growth (de Visser et al., 2006; Lin and Karin, 2007; Smyth et al., 2006). Persistent chronic inflammation and altered inflammasome activity have been recently implicated in inflammatory skin disorders including cancer (Feldmeyer et al., 2007; Sollberger et al., 2015; Zhong et al., 2016; Grandemange et al., 2017; Elinav et al., 2013; Grivennikov et al., 2010; Tang and Wang, 2016). This mini review aims to discuss the role of inflammasome in skin inflammation linked with photoaging and skin cancer, in humans.

## 2. NLRs and inflammasomes

Immune cells express a number of membrane-bound and intracellular pattern recognition receptors in order to detect homeostatic changes that can lead to disease. Intracellular proteins which can nucleate inflammasomes belong to the family of Nucleotide-binding domain and Leucine-rich Repeat containing receptors, (NLRs), the PYHIN family (PYD and HIN domain containing proteins) or the tripartite motif family (TRIM) (Fig. 1). In this review we will focus on the NLRs due to their recent implication in skin pathologies. NLRs are multidomain proteins (Ting et al., 2008), subdivided into subgroups based on their N-terminal effector domain. Among the N-terminal domains important for downstream interactions can be a pyrin (PYD), or a caspase activation and recruitment domain (CARD) (Fig. 1). All NLRs also contain a central NACHT nucleotide-binding domain, (also known as

* Corresponding authors at: INSERM UMR_S933, Batiment Ketty Schwartz, Hôpital Armand Trousseau, 26 avenue du Dr. Arnold Netter 75012 Paris, France.
*E-mail addresses:* irina.giurgea@inserm.fr, serge.amselem@inserm.fr (I. Giurgea), sonia.karabina@upmc.fr (S.-A. Karabina).
[1] Equally contributing first authors.
[2] Equally contributing.

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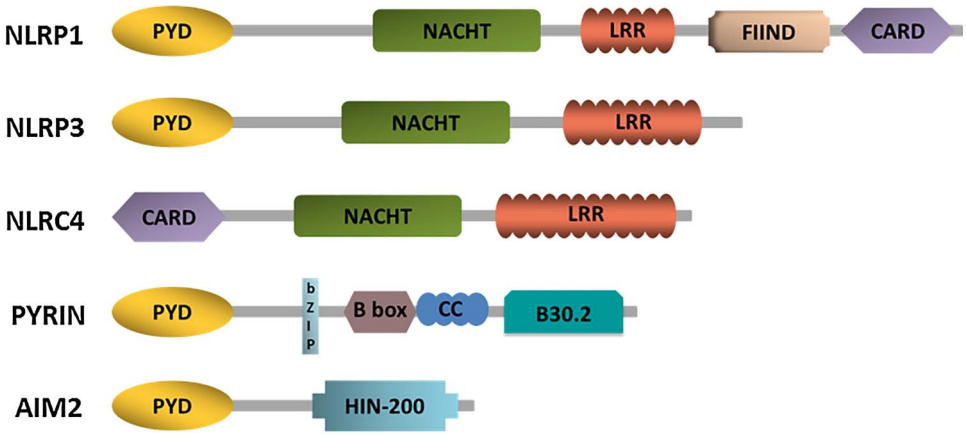


**Fig. 1.** Schematic representation of the human inflammasome-forming proteins. The (so far) known cytoplasmic receptors forming inflammasomes are: NLRP1, NLRP3, NLRC4, Pyrin and AIM2. NLRP1, NLRP3, NLRC4 belong to Nucleotide-binding domain and Leucine-rich Repeat receptors (NLR). NLRs contain a central NACHT domain which mediates ATP-dependent self-oligomerization, common to all NLRs, in addition to a C-terminal leucine-rich repeat (LRR) and variable N-terminal interaction domain. The N-terminal domain is responsible for homotypic protein–protein interactions and it can be a pyrin domain (PYD) as in NLRP3, or a caspase recruitment domain (CARD) as in NLRC4. NLRP1 is unique among the NLR family as it is characterized by a N-terminal PYD domain and a C-terminal CARD domain in addition to a FIIND ("function to find domain"). Pyrin is part of the protein family termed TRIpartite Motif (TRIM), which contains, a B-box, a coiled-coil (CC), and a B30.2 domain. TRIM proteins are antiviral proteins involved in innate immunity. AIM2 (which belongs to the PYHIN family) contains a PYD domain and a DNA-binding HIN domain.

NOD), required for ATP-dependent self-oligomerization and a C-terminal leucine-rich repeat (LRR) domain. NLRs sense infection and/or stress through the recognition of cytoplasmic pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs) (Martinon, 2008) or, as the more recently defined, homeostasis-altering molecular processes (HAMPs) (Liston and Masters, 2017). Detection of a DAMP or a PAMP by the LRR domain activates the NLR, leading to the formation of the inflammasome, a multiprotein signaling platform. Inflammasomes are generally assembled through homotypic interactions between the N-terminal PYD domain of the NLR and the PYD domain of the adaptor protein ASC (Apoptosis-associated Speck-like protein containing a CARD), which then recruits pro-caspase-1 through CARD–CARD domain interactions. This leads to formation of an active caspase-1 heterodimer (Martinon and Tschopp, 2004), which then proteolytically processes the pro-forms of (interleukin 1β) IL1β and (interleukin 18) IL18 pro-inflammatory cytokines, leading to their maturation and secretion.

The presence of caspase-1 is central to what is known as "canonical inflammasome"; however, today pro-inflammatory caspases −4 and −5 have also been demonstrated in non-canonical (caspase-1–independent) inflammasomes, which do not require a cytoplasmic receptor like NLR for the pathogen detection. Both caspase −4 and 5 can directly bind LPS *in vitro* (Shi et al., 2014) and, in human macrophages, caspase-4 is critical for non-canonical inflammasome responses against virulent gram-negative bacteria (Casson et al., 2015). The different tissue expression profile between caspase-4 and caspase-5 (Lin et al., 2000), suggests that they may have cell/tissue-specific roles. The fact that LPS can be directly detected by caspase −4/-5 in the cytoplasm of non-myeloid cells (Shi et al., 2014) and the broad expression of these caspases in non-immune cells suggested that this might be a protective mechanism of pathogen detection from non-immune cells. Apart from cytokine secretion, activation of inflammasomes results in pyroptosis, an inflammatory cell death due to the formation of pores in the plasma membrane and consequent release of the cytosolic content into the extracellular space (Aachoui et al., 2013). The mechanism of pyroptosis was recently clarified by the identification of gasdermin D which can be cleaved by caspases-1, −4 or −5 (Shi et al., 2015). Following cleavage, the N-terminal domain of gasdermin D associates with cell membrane and oligomerizes creating pores. Pyroptosis is specific to caspase-1, caspase-4 and caspase-5 activation, and is considered a way of cell death, which promotes clearance of intracellular microbes and infected cells, exposing pathogens to extracellular defenses (Miao et al., 2011).

More than 22 NLRs are known in humans and although the major attributed roles are linked to immunity (Harton et al., 2002), several NLRs also play important roles during embryonic development and reproduction (Kufer and Sansonetti, 2011; Lupfer and Kanneganti, 2013; Murdoch et al., 2006). Under physiological conditions, inflammasomes mainly regulate host defense and pathogen clearance through pro-inflammatory signaling. However, a dysregulated inflammasome activity leads to disease (Strowig et al., 2012). The best illustration of this, are the hereditary auto-inflammatory syndromes caused by mutations in *NLRP3,* encoding for the protein NLRP3/cryopyrin, which lead to a constitutively active inflammasome, and increased levels of IL1β in patients' cells are the hallmark of the disease. Interestingly, in these auto-inflammatory syndromes named CAPS (cryopyrin associated periodic syndromes), the majority of the patients, in addition to fever and serosal inflammation, also present with inflammatory skin lesions (Hoffman et al., 2001; Aksentijevich et al., 2002). Inflammasome activity has been implicated in the pathophysiology of a number of inflammatory and metabolic diseases (Strowig et al., 2012). In addition, sequence variants in several NLRs are associated with multifactorial polygenic human diseases, such as polymorphisms in *NOD2* predispose to the development of Crohn's disease (Abraham and Cho, 2006; Rehaume et al., 2010; Paramel et al., 2015). Genome-wide association studies (GWAS) have identified risk alleles in NLR genes in a number of diseases including multiple sclerosis, multibacillary leprosy and vitiligo (reviewed in (Zhong et al., 2013).

## 3. Biology of NLRP1 and NLRP3 inflammasomes

NLRP1 inflammasome was the first to be described in "immunoprecipitated" THP1 cell extracts. The complex contained NLRP1, caspase-1, caspase-5 and the adaptor protein ASC (Martinon et al., 2002). Unlike other NLRs, NLRP1 contains a N-terminal PYD domain whereas at the C-terminal it contains a FIIND ("function to find domain") and a CARD domain (Chu et al., 2001). Experiments using baculovirus-expressed recombinant proteins, to reconstitute the NALP1 inflammasome showed that the CARD domain of NLRP1 directly interacts with the CARD domain of pro-caspase-1 without a requirement for the presence of the adaptor protein ASC (Faustin et al., 2007). The presence of ASC intensified pro-caspase activation (Faustin et al., 2007). However, in a cell-based system Finger et al. (2012), demonstrated that human NLRP1 activity is ASC-dependent. The authors proposed that NLRP1 inflammasome formation requires ASC dimers. The dimers are formed through interactions of the ASC-PYD domains. Through their CARD domains ASC dimers interact with the C-terminal CARD domain of NLRP1 and the CARD domain of pro-caspase-1, forming the inflammasome (Fig. 2). These results were later confirmed by Zhong et al. (2016). Furthermore the authors showed that human NLRP1 activity depends on autolytic proteolysis between amino acids Phe1212 and Ser1213 within the (FIIND) domain (Finger et al., 2012). Single nucleotide polymorphisms or alternative mRNA splicing near the cleavage site, impact profoundly NLRP1 processing and inflammasome activity (Finger et al., 2012; D'Osualdo et al., 2011). Importantly, this

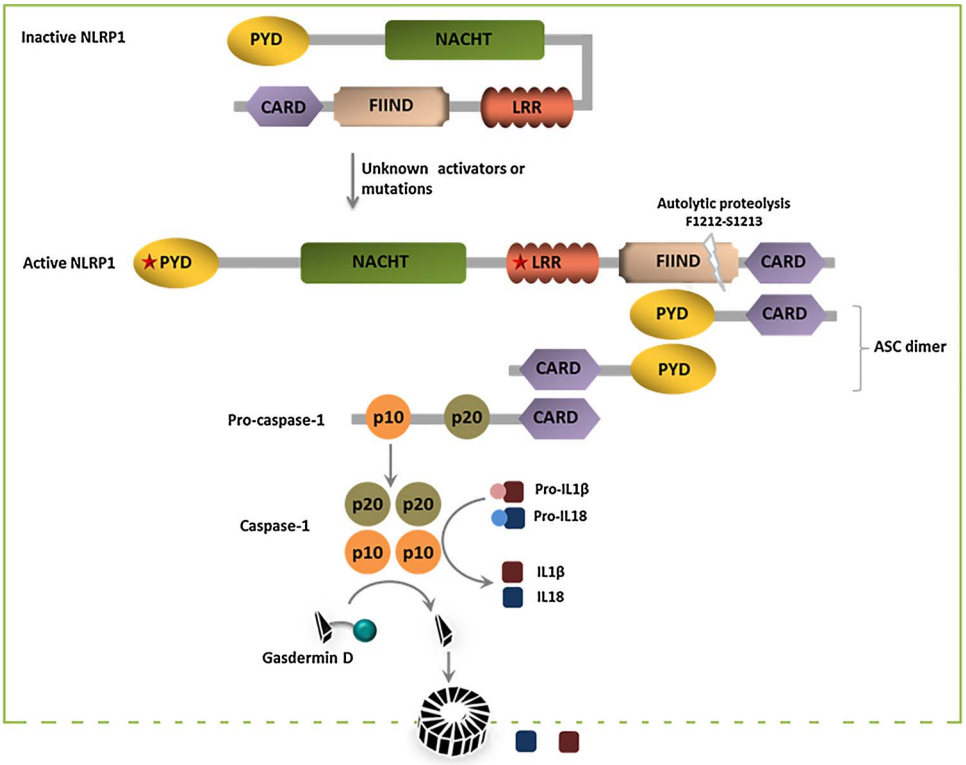


**Fig. 2.** NLRP1 inflammasome activation. Under resting conditions, the PYD domain of NLRP1 keeps the protein in an auto-inhibited state through interactions which are not yet well characterized. Activation of human NLRP1 occurs by unknown –so far- activators or through recently identified mutations in PYD or LRR domains (indicated with a star symbol). Active NLRP1 undergoes autolytic proteolysis between Phe1212 and Ser1213 (F1212-S1213) in the FIIND domain. The cleavage product remains associated through non-covalent binding and interacts with ASC through CARD–CARD domain interactions. A second ASC molecule is recruited through its PYD domain, which then recruits pro-caspase-1 to the complex through CARD–CARD domain interactions between ASC and pro-caspase 1. This leads to caspase-1 activation followed by IL1β and IL18 proteolytic maturation and release of proinflammatory cytokines by an unknown mechanism. Caspase-1 activation induces also pyroptosis (an inflammatory cell death) through the cleavage of Gasdermin D, a membrane-pore-forming protein also leading to release of proinflammatory cytokines and other alarmins in the extracellular space.

post-translational event depends on the highly conserved His1186. Following autoproteolysis the cleavage product remains associated with the rest of the molecule through non-covalent binding (Finger et al., 2012; Chavarría-Smith et al., 2016). The contribution of the PYD domain in NLRP1 inflammasome activation was recently clarified as it was shown that it keeps NLRP1 in an inhibitory state (Zhong et al., 2016). Mutations in the PYD-NLRP1 domain were associated with a constitutive NLRP1 self-oligomerization and inflammasome activation (Zhong et al., 2016) (Fig. 2). Furthermore, proteolysis within a specific N-terminal linker region removing the PYD domain was sufficient to activate human NLRP1 (Chavarría-Smith et al., 2016). Zhong et al. suggested that the different function of NLRP1-PYD as compared to the other PYD-containing proteins may be linked to structural differences. Indeed the NLRP1-PYD forms a bundle of five α helices (Hiller et al., 1993), as compared to the six helices formed by the canonical death domain fold superfamily. Sequence comparison of all PYDs encoded in the human genome revealed that NLRP1 PYD defines its own group (Zhong et al., 2016). Mutations in the LRR domain showed similar results to those of the PYD domain (both leading to NLRP1 autoactivation) (Fig. 2) also suggesting a potential inhibitory role of LRR on NLRP1 (Zhong et al., 2016; Grandemange et al., 2017).

Interestingly, NLRP1 is not conserved across species. In mice, Nlrp1 exist in three paralogs; Nlrp1a, Nlrp1b and Nlrp1c all of which are devoid of the N-terminal PYD domain present in the human protein (Boyden and Dietrich, 2006). The presence of *Bacillus anthracis* lethal toxin in the cytoplasm of mouse cells specifically activates Nlrp1 (Boyden and Dietrich, 2006; Hsu et al., 2008) as does muramyl dipeptide, a bacterial cell wall fragment (Faustin et al., 2007), which is also an activator of NOD2. Recent studies showed that neither lethal toxin nor muramyl dipeptide can activate human NLRP1 (Yu et al., 2018). *Toxoplasma gondii* was shown to activate human NLRP1 inflammasome in monocytic cells (Witola et al., 2011). The molecular basis of the interaction between the ligand and NLRP1 remains inconclusive.

NLRP3 is the best characterized inflammasome. NLRP3 has an N-terminal PYD domain necessary for the interaction with ASC (Yu et al., 2006), a central NACHT domain required for auto-oligomerization and a C-terminal LRR region probably involved in the recognition of different pathogen and danger signals (Figs. 1 and 3). NLRP3 is primarily expressed in cells of the myelomonocytic lineage (Manji et al., 2002; Feldmann et al., 2002) and is induced upon exposure to inflammatory stimuli (O'Connor et al., 2003; Awad et al., 2017). NLRP3 is also expressed in keratinized epithelial cells although weakly (Kummer et al., 2007), a finding that could explain the urticaria-like rash in CAPS patients.

NLRP3 inflammasome formation is regulated both at the transcriptional and posttranslational level. A priming step usually involves LPS signaling through Tolllike Receptor resulting in the activation of NF-κB and transcription of *NLRP3* and *IL1B*. Posttranslational modifications of NLRP3 have also been described as priming step (Juliana et al., 2012). The second step triggers assembly of the NLRP3 inflammasome complex and can be of a variable nature, a DAMP, a PAMP, or a HAMP (Tschopp and Schroder, 2010; Kingsbury et al., 2011; Guo et al., 2015; Liston and Masters, 2017) (Fig. 3). NLRP3 inflammasome is activated by several microbial patterns like the bacterial toxin nigericin and LPS, by environmental irritants and nanoparticles and by cellular damage molecules like ATP, glucose (Schroder and Tschopp, 2010), cholesterol crystals (Duewell et al., 2010), or even virus and parasites (Ichinohe et al., 2010; Thomas et al., 2009; Zamboni and Lima-Junior, 2015; Franchi et al., 2012). Many of these activators are involved in the pathogenesis of common metabolic inflammatory and infectious diseases making NLRP3 inflammasome one of the most studied in human pathophysiology (Guo et al., 2015). Due to the highly variable structures of all these molecular patterns, a unifying molecular mechanism, linking them to NLRP3 inflammasome activation is still missing. The prevailing model suggests that NLRP3 senses molecular patterns indirectly and cellular stress signals are proposed as potential intermediate steps in NLRP3 inflammasome activation (Latz, 2010). Alterations in ion homeostasis, mainly in cytosolic $K^+$ efflux (Pétrilli et al., 2007) or $Ca^{2+}$ mobilisation (Murakami et al., 2012) appear among the plausible bridging mechanisms. Another mechanism applying to DAMPs which are phagocytized, is through lysosomal damage

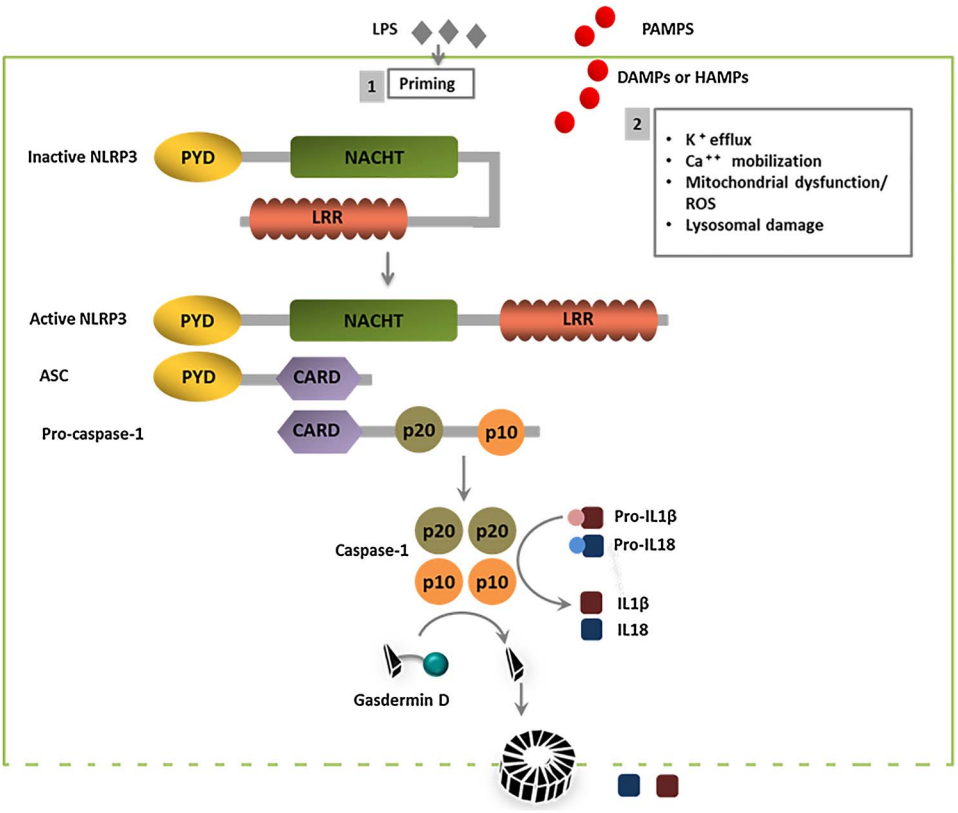


**Fig. 3.** NLRP3 inflammasome activation. NLRP3 inflammasome activation requires two signals: A first signal (most commonly LPS) induces transcriptional activation of *NLRP3* and *IL1B* through TLR4 signaling. Deubiquitination of NLRP3 is also possible during this step. A second signal, a DAMP or a PAMP or a HAMP leads to NLRP3 oligomerization (not shown). ASC associates with NLRP3 through PYD domain interactions which bring pro-caspase-1 in the complex through CARD domain interactions. Activation of pro-caspase-1 leads to active caspase-1 (p20-p10 dimers which in solution associate in tetramers) which maturates IL1β and IL18 leading to their release by a yet unknown mechnism. Caspase-1 activation induces also pyroptosis (an inflammatory cell death) through the cleavage of Gasdermin D, a membrane-pore-forming protein also leading to the release of proinflammatory cytokines and alarmins in the extracellular space. Due to the variety of the patterns which can activate NLRP3, it is suggested that NLRP3 does not recognize them directly and cellular stress signals are proposed as potential intermediate steps in NLRP3 activation. Among the most prevailing are: increase in potassium efflux, calcium mobilisation, ROS production, mitochondrial dysfunction, lysosomal damage and cathepsin release.

(Hornung and Latz, 2010) and release of lysosomal proteases such as cathepsin-B, which then activate the NLRP3 inflammasome. An important role for mitochondria and reactive oxygen species has also been reported in NLRP3 inflammasome activation (Tschopp and Schroder, 2010; Nakahira et al., 2011; Zhou et al., 2011; Shimada et al., 2012; Subramanian et al., 2013).

Canonical inflammasome activation is characterized by caspase-1 cleavage, the maturation and release of IL1β and IL18 and the induction of pyroptosis. The methods commonly used to study inflammasome activation in response to a DAMP/PAMP in stimulated cells or tissue homogenates include gene expression of inflammasome components, protein expression of the inflammasome/NLR receptor, release of cleaved caspase-1 by western blot, secretion of mature IL1β and IL18 by western blot and ELISA and release of Lactate Dehydrogenase (LDH) to identify pyroptosis. ASC specks which are oligomers of ASC, are visible under the microscope, and are used to study inflammasome activation for the inflammasomes requiring ASC (Beilharz et al., 2016; Fernandes-Alnemri et al., 2007; Stutz et al., 2013). ASC specks can also be detected extracellularly (Baroja-Mazo et al., 2014; Franklin et al., 2014).

## 4. NLRP1, NLRP3 inflammasomes in photoaging and skin disorders including cancer

UVR leads to decomposition of sebaceous lipids and initiation of an inflammatory process. Physiological doses of UVA oxidize squalene, one of the major lipid components of sebum. When oxidized squalene derivatives from human sebum were applied to cultured skin, they induced inflammatory cytokine expression, that promoted downstream inflammation (Kostyuk et al., 2012). As oxidized skin surface lipids have a diagnostic value in the inflammatory skin disorders and photoaging, their potential action as inflammasome activating danger signals merits further consideration (Oyewole and Birch-Machin, 2015; De Luca and Valacchi, 2010).

Keratinocytes express several inflammasome related-genes supporting the hypothesis that inflammasomes may have a role in skin inflammation (Feldmeyer et al., 2007; Sollberger et al., 2015). UVB exposure induces NLRP3 inflammasome activation and IL1β secretion in HaCaT cells, an immortal keratinocyte cell line, through disturbances in $Ca^{2+}$ homeostasis (Ahmad et al., 2017). NLRP3 expression was higher in human basal cell carcinoma tumor samples and this was accompanied by higher IL1β levels and caspase-1 activation as compared to healthy skin (Ahmad et al., 2017). Caspase-4 is important for efficient UVB-induced activation of caspase-1 and in turn for IL1β and IL18 secretion in human keratinocytes (Sollberger et al., 2012). Pannexin-1 channels shown to be implicated in keratinocyte differentiation (Celetti et al., 2010) and in ATP release from pyrinergic receptors which induce inflammasome activation (Latz et al., 2013), are present in skin melanocytes and are up-regulated during melanoma progression in mouse melanoma cell lines (Penuela et al., 2012).

*NLRP1* is strongly expressed in human skin as compared to other NLRs (Zhong et al., 2016; Uhlén et al., 2015). Polymorphisms in coding and non-coding regions of *NLRP1* have also been associated with vitiligo, an autoimmune disease affecting skin melanocytes, where patients are reported to have elevated serum IL1β levels (Jin et al., 2007; Levandowski et al., 2013). *NLRP1* genetic variations have been shown to induce susceptibility to psoriasis (Ekman et al., 2014) and corneal intraepithelial dyskeratosis (Soler et al., 2013). In a recent work, Grandemange et al. showed that mutations in *NLRP1* are causal for a new auto-inflammatory disease in which patients present with arthritis and dyskeratosis, accompanied by high levels of serum caspase-1 and IL18 (Grandemange et al., 2017).

As shown in a Swedish case–control study (Verma et al., 2012) polymorphisms in *NLRP1* and *NLRP3* are associated with sporadic malignant melanoma, one of the most severe skin cancers. Furthermore, in a Brazilian case/control cohort of sporadic malignant melanoma, selected polymorphisms in the inflammasome-related genes *CARD8*, *IL1B* and *IL18* have been shown to associate with melanoma susceptibility and progression (Da Silva et al., 2016). In the same study, *IL1 B* and *CARD8* expression was increased in melanoma as compared to benign nevus. Interestingly, *IL18* was decreased, potentially suggesting

a protective role of this inflammasome-dependent cytokine in melanoma development and progression (Da Silva et al., 2016).

Using human melanoma cell lines established from different disease stages as well as human melanoma specimens, Okatomo et al. showed that cells from late stage human melanoma secrete active IL1β spontaneously without a requirement of exogenous stimulation. Intermediate stage melanoma cells require activation for active IL1β secretion similar to cells from early stage melanoma (Okamoto et al., 2010). The latter provided evidence that late stage human melanoma cells show similar characteristics as cells from patients with auto-inflammatory diseases (caused by gain-of-function mutations in *NLRP3*), suggesting that the constitutive secretion of active IL1β and its downstream effectors may be causal in the aggressiveness of this type of skin cancer. These results also suggested a role for the inflammasome component ASC in human melanoma. Several studies have shown an implication of ASC in cancers, through *ASC* methylation and silencing, although the mechanism remains unclear (Stimson and Vertino, 2002). In human melanoma cells, ASC may play a dual role through differential regulation of NF-κB. In metastatic melanoma, ASC promotes tumorigenesis, whereas in primary melanoma, ASC inhibits tumor growth (Liu et al., 2013). Interestingly, this dual role of ASC is supported by results in a mouse model of epithelial skin carcinogenesis where the function of Asc is tissue-specific. In keratinocytes, Asc acted as a tumor-suppressor, whereas in myeloid cells, it promoted tumorigenesis (Drexler et al., 2012). Furthermore, ASC is down-regulated in human primary epithelial skin cancers, but not in inflammatory proliferative skin diseases. However, at the genetic level Da Silva et al. did not confirm an implication of *NLRP3* in melanoma (Da Silva et al., 2016).

Recent work suggests that NLRP1 is the most important inflammasome sensor in human skin (Zhong et al., 2016; Uhlén et al., 2015), and pathogenic germline *NLRP1* mutations in two Mendelian monogenic skin disorders, namely multiple self-healing palmoplantar carcinoma and familial keratosis lichenoides chronica, are gain-of-function mutations, leading to inflammasome activation (Zhong et al., 2016). The authors showed that the mutations, which disrupt the PYD and LRR folding domains, lead to constitutive NLRP1 self-oligomerization and inflammasome activation. Surprisingly, the PYD domain of NLRP1, unlike the PYDs from other NLRs, functions as an auto-inhibitory domain. Keratinocytes from those patients show spontaneous inflammasome activation and cytokine secretion, with IL1β being the most prevalent. Furthermore, using *ex-vivo* organotypic skin models, it was shown that treatment with IL1α, IL1β and IL18 leads to epidermal hyperplasias (Zhong et al., 2016).

## 5. Potential therapeutic approaches

Thymoquinone, a bioactive phytochemical constituent of Nigella sativa seeds oil, has been shown to inhibit migration of human and mouse melanoma cells in a mouse model of melanoma by targeting NLRP3 inflammasome (Ahmad et al., 2013). Similarly, green tea polyphenol epigallocatechin-3-gallate was shown to suppress melanoma growth by inhibiting NLRP1 inflammasome and IL1β-mediated secretion (Ellis et al., 2011). Several biological agents are used successfully today to block IL1 signaling in auto-inflammatory disorders (Dinarello et al., 2012), which may also represent a potential therapeutic option for targeting skin inflammation and preventing skin tumorigenesis.

## 6. Conclusion

Skin is a dynamic organ maintaining homeostasis and providing protection against environmental stimuli and pathogens. However, these mechanisms can become overwhelmed over the time (aging) or through constant stimulation (photoaging), resulting in irreversible structural damage, chronic inflammation and carcinogenesis. Inflammasomes play central roles in human pathophysiology, regulating pro-inflammatory signals and host defense. Regulation of their expression, assembly and activation has important implications in the inflammatory process of skin diseases including cancer where cytokines modulate cancer progression and invasiveness. Inflammasomes may provide early biomarkers indicating photo-damage and beginning of an inflammatory process in skin that require observation and supervision. Thus targeting inflammasome(s) might be important to improve skin inflammation, photoaging and the risk of tumorigenesis.

## Author contribution

FA, EA, CL CJ, IG, SA, SAK Conception, writing and revision of the manuscript.

## Disclosure of potential conflicts of interest

No potential conflict of interest.

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