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Secreted immunoregulatory proteins in the skin

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ABSTRACT

The skin, thought initially to protect the body passively from pathogenic organisms and other environmental insults, is now recognised additionally as a sophisticated immune organ that actively regulates local immunity. Studies linking local innate and adaptive immunity to skin health and disease have revealed a complex network of cell communication and cytokine signalling. Here, we review the last 10 years of literature on this topic, and its relevance to skin immunity.

1. The skin as immune organ

The skin, as a passive barrier, protects the body from environmental insults and pathogenic microorganisms. However, it also functions as an immune organ, and supports a flora of commensal bacteria and fungi. Therefore, skin cells have to distinguish commensal, symbiotic microorganisms from potentially harmful pathogens and mount appropriate immune responses.

The skin comprises keratinocytes, fibroblasts, endothelial cells and various residing and infiltrating immune cells, which together form a complex host-protective immunoregulatory network. Genetic error or environmental perturbation of the network can lead to pathology including psoriasis, eczema and cancer. Better understanding of the network should assist with management of skin pathology. This review overviews recent studies on intracellular signalling to and from epidermal keratinocytes.

1.1. Skin-located cells contributing to innate and adaptive immunity

Some immune cells are skin-resident. These include bone marrow-derived epidermal Langerhans cells (LCs), which function as professional antigen-presenting dendritic cells (DCs); mast cells, which are a first line of defence, recruiting and activating natural killer (NK) and NKT cells; resident skin macrophages, which survey tissue for antigen and can have either pro-inflammatory or regulatory function; and resident T cells, including regulatory T cells [1] and resident memory T cells [2]. T cells, and various myeloid cells, also home to skin, mostly to the dermis, when inflammation is present. Additionally, keratinocytes themselves contribute to immune signalling in the skin by releasing cytokines and chemokines, either actively or by lytic release, and by expressing surface receptors for secreted mediators of immune function (reviewed in [3]). Furthermore, other cell types that are not classically considered as immune cells nevertheless play a role in skin immunity. Endothelial cells express Toll-like receptors (TLR) and respond to pathogen-associated molecular patterns (PAMPs) [4] and other inflammatory triggers, and thereby modulate immune reactions [5]. Fibroblasts, which were considered as contributing to tissue homeostasis only by secreting extracellular matrix components, are now known to play a more active role in skin immunity by inhibiting mast cells [6] and cross-talking with immune cells, thus modulating the immune environment within the dermis [7,8].

1.2. Antigen presentation

Self antigens and non-self antigens in skin, after uptake by professional antigen-presenting cells (APCs) including epidermal LCs, macrophages and dermal DCs, can be presented as peptides in the context of MHC to cells of the adaptive immune system, predominantly in draining lymph nodes. Antigen uptake, transport and APC activation is facilitated by C-type lectin receptors, as well as TLRs and pro-inflammatory cytokines. LCs, a subset of APCs, comprise about 2% of all epidermal cells [9]. Although LCs were thought originally to promote inflammation, the consensus now leans rather towards immune surveillance and regulation [10]. Similarly, DCs of the dermis have been shown to fulfil opposing functions, either activating functional immune response or inducing peripheral tolerance in $CD8^+$ T cells, depending on the activation status of the antigen presenting DCs [11–13]. Under

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some circumstances keratinocytes themselves, although lacking conventional costimulatory molecules such as CD80 and CD86, can present antigen to primed T cells [14]. A keratinocyte-derived cell line (A431) can present antigen and induce T cell activation and recruitment in a MHCII-dependent fashion [15]. Presentation of antigen to $CD4^+$ and $CD8^+$ T cells by HaCaT cells and HPV-immortalised keratinocytes is restricted by HLA type II and requires ICAM [16]. In normal epidermal keratinocytes, CD80 expression is increased upon stimulation, arguing a role for keratinocytes as antigen-presenting and co-stimulatory cells [17]. In the presence of staphylococcal superantigen, keratinocytes serve as accessory APCs in activating T cell response [18]. However, it remains unclear to date whether keratinocytes can effectively process and present antigen to activate naïve T cells.

2. Cytokines and chemokines in the epidermis

In addition to their function as APCs, keratinocytes produce and secrete a wide array of immunoregulatory proteins such as cytokines, chemokines and defensins, which contribute to efficient immune responses. These molecules can serve both as activators and attractors for infiltrating cells as well as inhibit self-directed immune response. Keratinocytes not only secrete cytokines but express several cytokine receptors themselves, thereby enabling autoregulatory loops of immunity within the epidermis.

Classical pro-inflammatory cytokines are IL-1α, IL-1β, IL-6, IL-17, IL-18, IL-23 and TNFα [16–20]. Anti-inflammatory or regulatory cytokines are – among others – IL-4, IL-5, IL-7, IL-10, IL-33 and IFN-γ [21–27]. However, it should be noted that the either pro-or anti-inflammatory action of any particular cytokine is restricted to a defined context (tissue, target/secreting cell, competing/cooperating cytokines, amount and sequence of cytokines etc.) [28].

Chemokines can induce chemotactic effects in tissues in which these molecules are bound by G-protein-coupled receptor superfamilies. 47 chemokines and 18 chemokine receptors have been identified to date, with many of the receptors binding several ligands, allowing for a complex signalling network with extensive overlap [19,20].

Generally, cells do not store cytokines but rather synthesise them upon stimulation. An exception to this are IL-1 and IL-18 which are constitutively expressed as inactive precursors which are cleaved into their active forms upon activation of Caspase-1 via the NLRP-3 inflammasome, for example after UV-damage [21,22]. Cytokine action occurs via specific receptors, some of which are expressed on all somatic cells, or through direct contact of membrane-bound cytokines with their counterparts. Many cytokine receptors are multicomponent, with part-sharing between different receptors. Cytokines can work together to enhance an immune response or, conversely, can act antagonistically. In addition, different cytokines can have similar effects on different cell types (redundancy) [19]. Together, cytokines and chemokines and their respective receptors form a complex, tissue-specific network that needs to be tightly regulated.

3. Cytokines secreted by keratinocytes

The first defined cytokines were discovered as products of leukocytes. Tissue cells including keratinocytes were initially regarded as “passive” recipients of immune signalling. However, keratinocytes were observed to produce pro-inflammatory signals, subsequently associated with production of IL-1 and −18, activated by cleavage through Caspase-1 upon stimulation of the inflammasome (reviewed in [23]). It is now clear that keratinocytes constitutively shape the skin immune environment, regulating skin homeostasis and differentiation, wound healing, response to bacterial infection, inflammation and tumour development. Further, keratinocyte-derived IL-34 has a non-redundant role in lymphocyte development during embryogenesis and homeostasis [24]. Injury and other external stimuli have recently been shown to induce keratinocyte production of some novel cytokines and chemokines. Dermokine, a peptide resembling the carboxyl terminus of some chemokines, is produced by granular layer keratinocytes and enhances epidermal barrier function [25] during contact hypersensitivity, UV-induced skin injury and wound healing [26]. Interleukin-19 upregulates keratinocyte growth factor (KGF) and increases epidermal cell migration [27] and, together with the other IL-10 family cytokines IL-20 and IL-24, is differentially regulated in inflammatory skin conditions [28].

3.1. Cytokine signalling in injury and wound healing

After skin injury, immune cells are recruited to control infection and inflammation. IL-8 expression is upregulated in subcutaneous wounds, and attracts and activates CD11b neutrophils [29]. Somewhat surprisingly, activation of Toll-like receptor 4 (TLR4) on keratinocytes promotes wound healing, enhancing production of IL-1β and IL-6 [30]. Cytokine production by keratinocytes accelerates leukocyte migration to wounds, and was recently shown to be facilitated by antimicrobial host defence peptides (HDPs) such as AG-30. This has led to development of a more stable synthetic peptide called AG-30/5C as a therapy to enhance wound healing [31]. Keratinocytes also assist the fibroblast contribution to wound healing through cytokine production [32].

Keratinocytes can fine-tune the expression and release of cytokines not only to the type of injury but also to the extent of the insult. Keratinocyte-mediated production of several chemokines of the CXC family, as well as the cytokine IL-1β and the chemokine IL-8, are more upregulated in keratinocytes adjacent to large burn wounds than to small burns, where chemokines of the C, CC and CX3C families, along with IL-13RA1, IL-13 and IL-5RA are reduced [33,34]. Fine-tuning the interleukin response becomes particularly apparent in studies that screen for several cytokines, and reveal synergistic networks. For example, IL-1α, together with IL-17 and TNFα, is important for activating innate immunity in skin, by inducing antimicrobial peptide expression [35] or 100A7-psoriasin and β-defensin2 [36]. In collaboration with IL-6, IL-8, TGFα, MCF and VEGF on the other hand, IL-1α is involved in allergic reaction to house dust mites [37]. In gingival keratinocytes, IL-1α, as well as IL-8, is increased in response to nicotine or LPS [38]. Similarly, IL-1β can exert a variety of functions depending on the context: Together with IL-6, IL-1β is induced by TLR4/p38 and JNK MAPK signalling in early wound healing [30], while in psoriasis, it drives insulin-independent proliferation of keratinocytes by inducing insulin resistance through p38MAPK signalling [39]. Together with TNFαR, it plays a role in hypertrophic post-burn scars [40], and is induced in acute and chronically UV-induced epidermis where it contributes to photo-ageing [41]. These studies demonstrate the versatility of skin cell cytokine responses. Recent studies with skin equivalents show that keratinocytes even respond to pressure. Several cytokines were shown to be released by keratinocytes in response to sustained mechanical loading, in particular IL-1α, IL-1β, IL-8 and TNFα [42,43], thereby significantly contributing to the inflammatory environment in pressure ulcers.

Cytokines secreted by skin cells are not only important in wound healing but also influence scar formation. IL-10 promotes scarless wound healing in the foetus, and the same effect can be achieved by overexpressing IL-10 in postnatal skin [44,45]. On the other hand, IL-6 promotes fibrosis in auto-inflammatory conditions, and can increase scarring after wounding [46], and the type I helical cytokine Leptin can promote keloid and hypertrophic scars [47]. These findings imply that manipulating the skin

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