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Review Article

The role of keratinocytes in inflammation

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ABSTRACT

The epidermis is the external layer of the skin and is composed mainly of keratinocytes. Therefore, keratinocytes play an indispensable role as inherent constituents of the skin barrier in physical defenses against environmental threats. Keratinocytes also exert an active protective role against invasion by pathogens. This competency is of particular importance when physical defenses fail as a consequence of skin injury. During the inflammatory phase of healing, keratinocytes act as immuno-modulators, managing inflammation via a rigorously coordinated network of inflammatory cascades, triggered by keratinocyte-receptor communication with the surroundings in a paracrine and autocrine manner. This review summarizes current understandings of the coordinated inflammatory network and focuses on recent progress regarding the role of keratinocytes in early phases of skin wound healing.

Contents

Abbreviations: NF-κB, nuclear factor kappa-light chain enhancement of activated B cell; NLR, (Nod)-like receptor; NLRP 3, (Nod)-like receptor pyrin domain containing 3 inflammasome; IL-1α, interleukin-1-alpha; IL-1β, interleukin-1-beta; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; IL-17A, interleukin-17A; IL-18, interleukin-18; IL-22, interleukin-22; IL-24, interleukin-24; IL-33, interleukin-33; IL-1R, interleukin-1 receptor; IL-8R, interleukin-8 receptor; IL-18R, interleukin-18 receptor; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor-α; HMGB1, high-mobility group box protein 1; HSP, heat shock protein; DAMPs, damage-associated molecular patterns; TLRs, Toll-like receptors; TIR, Toll/IL-1 receptor; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; K1, keratin 1; K5, keratin 5; K6, keratin 6; K10, keratin 10; K14, keratin 14; K15, keratin 15; K16, keratin 16; K17, keratin 17; JNK, c-Jun N-terminal kinase; p38 MAPK, p38 mitogen-activated protein kinase; ICAM, intercellular adhesion molecule; TACE, TNF-α converting enzyme; TNFR1, TNF-α receptor 1; TNFR2, TNF-α receptor 2; MMP-1, matrix metalloproteinase-1; MMP-9, matrix metalloproteinase-9; C/EBPβ, CCAAT/enhancer binding protein beta; PGE_2, prostaglandin E2; PGD_2, prostaglandin D2; NSAIDs, non-selective anti-inflammatory drugs; ROS, reactive oxygen species; LPS, lipopolysaccharide; MyD88, myeloid differentiation factor-88; EGF, epidermal growth factor; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; IκB, inhibitor of kappa B; IKK, IκB kinase; TRAF-2, TNF receptor-associated factor 2; TRAF-6, TNF receptor-associated factor 6; TRADD, TNFR1-associated death domain protein; RIP, receptor-interacting protein.

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Introduction

A key objective of skin, as the largest peripheral organ, is to create a protective barrier against the external environment. Injury to skin tissue constitutes a crucial deterioration of this protective ability and leaves the body vulnerable to infection. Therefore, concerns about skin wound healing to restore skin integrity for human health have been expressed since ancient times (Reinke and Sorg, 2012). In the 5th century BC, Hippocrates already emphasized the pivotal role of inflammation, when he pointed out the importance of draining pus from the wound (*'Ubi pus, ibi evacua'*) (Eming et al., 2007). It is generally accepted that the role of inflammation lies in elimination of infection caused by invading pathogens and necrotic tissue in the wound bed. However, scarless healing of wounds to fetal skin that lacks the common inflammatory response, provides clear evidence that inflammation is an underlying prerequisite for scarring. Therefore, the question of whether inflammation is mandatory for successful healing remains a subject of controversy (Redd et al., 2004).

The epidermis is the upper layer of the skin, consisting almost entirely of keratinocytes. Thus, keratinocytes are in direct contact with the environment and form the first line of defense against environmental threats. For many years, the one and only assignment of keratinocytes was considered to be a physical barrier of the skin. Currently however, keratinocytes are regarded as active cells contributing to preservation of the immune barrier (Suter et al., 2009). In the intact epidermis, resting keratinocytes exert basal anti-inflammatory actions by the production of antimicrobial peptides (Soong et al., 2015). As a result of injury-induced imbalance, keratinocytes release pre-stored and newly formed acute phase proteins that challenge other skin cell types, as well as keratinocytes. Newly arriving neutrophils destroy bacteria and eliminate inflammation in the wound area, thus enabling successful healing (Soong et al., 2015; Weinheimer-Haus et al., 2015).

This review summarizes current views on keratinocytes as sensors of infection and powerful producers of key inflammatory mediators that alert skin cells to danger. It also provides new insights into interconnected pathways that regulate the inflammatory response, helping to identify potential targets for anti-inflammatory therapies.

Acute inflammation in response to injury

Acute skin inflammation may arise in response to physical wounding, UV irradiation, chemical irritants or exposure to allergens. Normally, this biological response is resolved within two weeks with no adverse effects on the tissue. Inflammation is a first stage of the wound healing process and is artificially divided into three overlapping phases: inflammatory phase (hemostasis and inflammation), proliferative phase (tissue formation) and maturation (tissue remodeling). Successful skin repair requires healing to be precisely timed and molecularly regulated (Eming et al., 2007; Singer and Clark, 1999).

In direct response to injury, platelets and extravasated leukocytes captured in a nascent hemostatic plug release growth factors and cytokines such as interleukins IL-6, IL-1α, IL-1β, interferon gamma (IFN-γ) and tumor necrosis factor-α (TNF-α) to initiate the inflammatory process (Reinke and Sorg, 2012).

Activation and active role of keratinocytes during inflammation

Exposure to pro-inflammatory cytokines, as well as a wound-generated electric field and loss of contact inhibition, results in activation of keratinocytes (Behm et al., 2012; Freedberg et al., 2001; Koivisto et al., 2011). Activated keratinocytes switch from their inactive status to a migratory, proliferative and pro-inflammatory phenotype. This shift is associated with alterations in cytoskeletal proteins (keratins) and expression of transmembrane receptors (integrins), as well as production and deposition of extracellular matrix components, including laminin-332 (Komine et al., 2000). Thus, the keratinocytes in the immediate neighborhood of the wound area lose their adhesive properties and begin to migrate over a provisional matrix; the keratinocytes behind the actively migrating cells start to proliferate (Hopkinson et al., 2014; Santoro and Gaudino, 2005).

Injured keratinocytes release the first signals, known as alarmins, consisting of high-mobility group box protein 1 (HMGB1), heat shock protein (HSP), antimicrobial peptides (defensins, cathelicidin, calgranulin A/B), cytokines (IL-1α, IL-33) and chemokines (IL-8) (Eckhart et al., 2013). These endogenous molecules are considered to be a subgroup of host-derived damage-associated molecular patterns (DAMPs) that signal tissue and cell injury via Toll-like receptors (TLRs), which, in turn, initiate immune responses (Bianchi, 2007; Lessard et al., 2013; Oppenheim and Yang, 2005). Activation of the TLR signaling pathway leads particularly to nuclear factor kappa-light chain enhancement of activated B cell (NF-κB) nuclear translocation and transcription of downstream target genes such as pro-inflammatory cytokines IL-1 family, IL-6, TNF-α, chemokine IL-8 or the enzyme cyclooxygenase-2 (COX-2) (Freedberg et al., 2001; Suter et al., 2009). The secretion of these pro-inflammatory molecules attracts neutrophils into the wound area, enabling the elimination of infectious agents. This is necessary to reestablish the epidermal barrier during wound healing (Takazawa et al., 2015). In addition, TNF-α and IL-1 can provide positive feedback to NF-κB and amplify the inflammatory response (Feldmeyer et al., 2010).

Following injury, the intracellular sensing of infection or stress by the nucleotide-binding oligomerization domain (Nod)-like receptor (NLR) promotes assembly and activation of an inflammasome. This multiprotein complex is involved in maturation of pro-inflammatory cytokines and thus mediates inflammation (Lee et al., 2015a). In the early stages of wound healing, keratinocytes express components of the NLR pyrin domain containing 3 (NLPR3) inflammasomes (Feldmeyer et al., 2010). This leads to activation of the protease procaspase-1, the key constituent of the inflammasome that contributes to inflammation via proteolytic processing of IL-1β or IL-18 (Weinheimer-Haus et al., 2015) and most likely IL-33 (Keller et al., 2008; Ogura et al., 2006) or IL-1-α (Gross et al.,

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