Melanocytes and Skin Immunity

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Melanocytes in skin are melanin-producing cells that are derived from the neural crest. They migrate during embryological development and localize in the epidermis and hair follicles where they pigment skin and hair (Nishimura, 2011). Melanocytes and their production of melanin pigment (a process termed melanogenesis) have important roles in cutaneous physiology (Hearing, 2011). The most obvious and most studied function of melanocytes is to synthesize melanin that confers color on skin and hair, and protects epidermal cells from ultraviolet radiation-induced changes in DNA structure (Plonka *et al.*, 2009). However, accumulating evidence has shown that melanocytes are also active factors in the skin immune system, participate in immune responses, and have immunomodulatory properties.

Possible immunological roles of melanocytes in skin

Histologically, melanocytes, along with keratinocytes and Langerhans cells, being positioned strategically within the epidermis, form a physical barrier that protects the skin from pathogens and other types of injury. The strategic positioning of melanocytes in the epidermis offers opportunities to encounter potentially harmful stimuli from outside, and it raises the possibility that melanocytes respond to potentially hostile environmental insults in addition to ultraviolet radiation. The dendritic nature and large surface area of melanocytes, coupled with their strategic location in the superficial layers of skin, raise the possibility that they are immunologically important cells in the skin immune system (Lu *et al.*, 2002; Plonka *et al.*, 2009). Clinically, it is noteworthy that some infections of skin are more common in individuals with fair skin than in those with dark skin (Mackintosh, 2001). This led us to hypothesize that melanocytes and melanization have an immunological impact on the skin.

Immunity-associated markers and molecules on melanocytes

Toll-like receptors (TLRs) are a class of conserved receptors that recognize pathogen-associated molecular patterns present in microbes, and they are known to have important roles in host defense (Hari *et al.*, 2010; Kumar *et al.*, 2011). Normal human melanocytes express functional TLRs such as TLRs 2–5, 7, 9, and 10 (Ahn *et al.*, 2008b; Yu *et al.*, 2009; Jin and Kang, 2010). Upon ligation of TLRs with lipopolysaccharide, e.g., melanocytes may trigger NF-κB and/or mitogen-activated protein kinase signaling pathways (Ahn *et al.*, 2008a; Ahn *et al.*, 2008b), thereby producing several pro-inflammatory cytokines and chemokines (Ahn *et al.*, 2008b; Yu *et al.*, 2009). These cytokines and chemokines from stimulated melanocytes may modulate the recruitment and activation of different immune cells in the skin. The expression of functional TLRs on melanocytes suggests that they may act as early sensors in immune responsiveness.

Some melanocyte cell lines also express major histocompatibility complex class II molecules (Smit *et al.*, 1993). Intercellular adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and CD40 have also been shown to be expressed by melanocytes (Yohn *et al.*, 1990; Lu *et al.*, 2002). ICAM-1 is the ligand for leukocyte function–associated antigen-1, which mediates nonantigen-specific cell contact. This contact is essential for helper T-cell function, interactions between antigen-presenting cells (APCs) and lymphocytes, cell-mediated cytotoxicity, and antibody-dependent cellular cytotoxicity (Lu *et al.*, 2002). CD40 antigen has a key role in T-cell-dependent activation, proliferation, and differentiation of B cells. Upon CD40 ligation, melanocytes upregulate expression of their co-stimulating and adhesion molecules, indicating that they are likely to be immunocompetent (Lu *et al.*, 2002).

Melanocytes and innate immune responses

Melanization, the production of melanin, involves stepwise oxidation of the amino acid tyrosine and downstream aromatic compounds (Ebanks *et al.*, 2009). Melanization has important protective roles in many species as many toxic intermediates may be produced, including semiquinones, dopaquinone, indolequinones, and many reactive oxygen species (Vavricka *et al.*, 2010). These intermediate compounds are believed to exert strong antimicrobial activities, and melanin, the end-product of melanization, may have the capacity to trap, inhibit, and even kill invading bacteria and other microorganisms (Mackintosh, 2001; Burkhart and Burkhart, 2005; Fuentes

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et al., 2014). Melanin may also have an immunoregulatory role. It has been found to have immunomodulatory activities through inhibition of pro-inflammatory cytokine production by T lymphocytes, monocytes, fibroblasts, and endothelial cells (Wood *et al.*, 1999; Mohagheghpour *et al.*, 2000).

The transfer of acidified melanin-containing organelles (melanosomes) from melanocytes to neighboring keratinocytes in outer portions of the epidermis may have a role in acidifying the statum corneum in darkly pigmented skin. Acidity in the stratum corneum could enhance skin barrier function and the integrity/cohesion of stratum corneum; it might also exert antimicrobial function (Gunathilake *et al.*, 2009).

In response to various stimuli, melanocytes secrete a wide range of immunological molecules, including inducible nitric oxide synthase (iNOS) (Rocha and Guillo, 2001; Fecker *et al.*, 2002), inflammatory cytokines and chemokines (Yu *et al.*, 2009; Tam and Stepien, 2011; Miniati *et al.*, 2014). These cytokines and chemokines from stimulated melanocytes may affect keratinocytes, lymphocytes, fibroblasts, mast cells, and endothelial cells in the skin. Melanocytes could also regulate cutaneous immune response by producing and releasing several immunosuppressive molecules such as alpha-melanocyte stimulating hormone (α-MSH; Tam and Stepien, 2011). α-MSH has a wide array of effects including anti-inflammatory as well as immunomodulatory activities (Luger *et al.*, 2000; Luger *et al.*, 2003).

Melanocytes and adaptive immunity

It has been demonstrated that melanocytes are capable of phagocytosis (Le Poole *et al.*, 1993b). Moreover, melanosomes have functional and structural similarities to lysosomes, and have been considered as indeed specialized lysosomes (Orlow, 1995; Schraermeyer *et al.*, 1999; Ahn *et al.*, 2008b). Because phagocytosis is understood to be a prerequisite for antigen processing and presentation, phagocytosis by melanocytes suggests that melanocytes have antigen presentation potential. Furthermore, it has been demonstrated that cultured human melanocytes are capable of processing and presenting the mycobacterial protein HSP65 and whole-cell sonicate of *Mycobacterium leprae* to $CD4^+$ T cells in an Ag-specific and MHC class II-restricted manner, indicating that melanocytes could function as nonprofessional APCs *in vivo* (Le Poole *et al.*, 1993a).

Melanocytes may be involved in specialized immune cells-mediated skin immunity

Macrophages are key cellular components of the innate immune system. Following tissue injury or infection, macrophages exhibit an inflammatory phenotype and secrete pro-inflammatory mediators such as tumor necrosis factor, NO, and interleukin-1, which participate in the activation of various antimicrobial mechanisms (Murray and Wynn, 2011). Melanocytes are also located in the upper layer of the dermis or in the hair follicle pigmentary unit where melanocytes and their products might communicate with other cells (Plonka *et al.*, 2009). This is in line with our observation that certain soluble factors secreted by murine melanocytes may exert immunologcial influence on macrophage-mediated anti-infection immunity through cross talks with macrophages.

Taken together, accumulating evidence supports the concept that melanocytes are not only professional melanin-producing cells but are also active factors in the cutaneous immune system. However, the immunological potential of melanocytes is far from fully explored. Additional work will be required to develop a comprehensive understanding of the immunologic role played by melanocytes.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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