Journal of Infection (2015) 71, 413–421

BIA
British Infection Association

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REVIEW

The immunology and inflammatory responses of human melanocytes in infectious diseases

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Accepted 10 June 2015
Available online 16 June 2015

KEYWORDS
Melanocyte;
Innate immunity;
Infection;
Inflammation;
Autoimmunity

Summary Melanin is a canonical and major defense molecule in invertebrates but its role in mammalian immunity remains unexplored. In contrast, several recent studies have highlighted the emerging innate immune activities of human melanin-producing cells which can sense and respond to bacterial and viral infections. Indeed, the skin is a major portal of entry for pathogens such as arboviruses (*Chikungunya*, *Dengue*) and bacteria (*mycobacterium leprae*, *Leptospira* spirochetes). Melanocytes of the epidermis could contribute to the phagocytosis of these invading pathogens and to present antigens to competent immune cells. Melanocytes are known to produce key cytokines such as IL-1β, IL6 and TNF-α as well as chemokines. These molecules will subsequently alert macrophages, neutrophils, fibroblasts and keratinocytes through unique crosstalk mechanisms. The infection and the inflammatory responses will control melanocyte's immune and metabolic functions and could contribute to skin manifestations (rash, hyper or de-pigmentation, epidermolysis and psoriasis-like lesions). This review will address the potential role of melanocytes in immunity, inflammation and infection of the skin in health and diseases.

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http://dx.doi.org/10.1016/j.jinf.2015.06.006
0163-4453/

Introduction: melanocytes are immune cells fighting against the odds

Melanocytes are classically known as specialized cells derived from the neural-crest and which can reside within the stratum granulosum.[1,2] They produce melanin, a pigment responsible for the color of the skin and that protects keratinocytes against UV-induced DNA damage.[3,4] Pmel17/gp100, tyrosinase, dopachrome tautomerase, and tyrosinase-relatedprotein-1 (Tyrp1) are the core enzymes involved in melanin synthesis. Microphthalmia-associated transcription factor (MITF) is considered to be the major regulator that governs melanocyte development, melanogenesis, and survival.[5] There are two types of melanin red/yellow pheomelanin and brown/black eumelanin. Melanin containing granules are known as melanosomes and are exported from melanocytes to adjacent keratinocytes. In humans, eumelanin synthesis is regulated primarily via activation of the G-protein-coupled melanocortin 1 receptor (MC1R) by its agonist α-melanocortin (α-melanocyte-stimulating hormone (α-MSH).[6]

Pigmentation differences can arise from variation in the number, size, composition and distribution of melanosomes, whereas melanocyte numbers typically remain relatively constant.[2] However, in the disfiguring and psychologically debilitating disease vitiligo, melanocytes can be targeted by the immune system and eliminated from the lesional skin in association with cytotoxic T-cell (CD8+) infiltrates.[7,8] The initial factor(s) that triggers the autoimmune vitiligo response is still elusive. However, it has been proposed that the appearance of scattered skin/hair depigmentation accompanied with viral infection and the discovery of the causative link between herpes viral infection and vitiligo in a chicken model are plausible links between the onset of vitiligo and viral infection of melanocytes.[9–11] Many viruses have been implicated in the onset and/or the promotion of autoimmune diseases.[12] It could be equally envisaged that viral infection may directly kill the melanocytes and trigger autoimmune responses against melanocytes expressing autoantigens derived from cell debris. If the destruction of melanocytes in vitiligo is mediated by skin-homing autoreactive T cells and involving molecular mimicry mechanisms between pathogens and melanocyte proteins, additional specific and nonspecific immune components, such as antibodies, complement factors, reactive oxygen species (ROS) and nitric oxide (NO) as well toxic ortho-quinones may also contribute to the disease.[7] Of note, melanocytes are particularly susceptible to stress because melanogenesis is an energy-expensive process leading to high levels of mitochondrial ROS, but also with the production of large quantities of proteins. The latter will increase the risk of protein mis-folding in the endoplasmic reticulum which activates the unfolded protein response (UPR) and cell death. Moreover, melanogenesis itself generates hydrogen peroxide, a ROS precursor.

The depigmentation can be also of bacterial origin and with similarities between vitiligo-induced depigmentation and circumscribed hypopigmented lesions caused by *Mycobacterium leprae*[8] or spirochete bacteria such as *treponema carateum* in pinta disease patients.[13]

Many viruses (e.g. varicella-zoster virus, parvovirus, arboviruses) and bacteria (e.g. leptospira spirochetes) are known to directly infect human melanocytes and derived cell lines such as SKMEL-28 or MeWo as illustrated in Fig. 1. These infections may disturb metabolic functions leading to hypopigmentation.[14,15] The mechanisms may be indirect and involving programmed-cell death of the infected melanocytes in an attempt to thwart off the infectious challenge. Arboviruses such as alphaviruses can give rise to maculopapular rash which usually lasts for a few days but is also accompanied by pigmentary changes particularly in infants.[16,17] Harson proposed the paradigm that in congenital varicella syndrome there is a cutaneous zig-zag and hypopigmented scarring presumably as a result of viral disruption of the migrating neural crest cells, which then fail to become melanocytes.[14] Interestingly and in contrast, postinflammatory hyperpigmentation has previously been described in acute HIV- or HCV-infected patients treated or not with interferon (IFN)-type I further arguing that melanocytes may play a role in the reactive epidermal inflammatory system.[18]

Hormones and cytokines such as α-MSH, TGF-β and more recently IFN-γ are known to be involved in the control of skin pigmentation.[19] While α-MSH is secreted by adjacent keratinocytes in response to UV and TGF-β by follicular fibroblasts, the source of IFN-γ would be from the immune cells recruited to the site of skin infection. These factors have also important immunoregulatory activities and could control melanocyte's immunity.[20,21] Hence, keratinocytes as well as fibroblasts together with infiltrating T cells could act in a concerted manner to modulate melanocyte immunobiology and pigmentation.

From another standpoint, melanocytes should not be considered only as a potential sanctuary for pathogens given their increasingly recognized contribution to antimicrobial immunity.[7,22] Melanocytes exhibit similar phagocytic and antigen-presenting functions associated with macrophages. It has been emphasized that melanocytes could actively contribute to local immune responses and particularly as

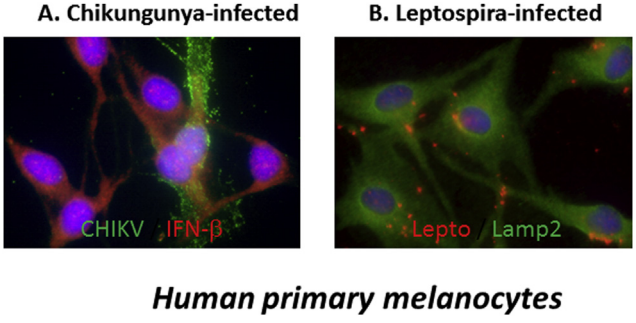

Figure 1 Melanocytes can be targeted by viruses and bacteria. The skin is a major portal of entry for viruses and bacteria. Using primary cultures of human epidermal melanocytes, we found that chikungunya alphavirus (A, green fluorescence) as well as leptospira interrogans (B, red fluorescence) could infect melanocytes. This infection will lead to a canonical innate immune response as illustrated by the staining (Panel A, red fluorescence) for antiviral interferon-β molecule. Lysosome-associated membrane protein 2 (*LAMP2, B green fluorescence*), also known as CD107b, is involved in lysosome biogenesis.