Commentary

The mole theory: primary function of melanocytes and melanin may be antimicrobial defense and immunomodulation (not solar protection)

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Patient: "Doctor, why do we get moles in the first place?"

Physician: "No one has the foggiest notion why God gave us moles on our skin … and that's the honest truth."

Melanocytes are derived from melanoblasts that arise from the neural crest. Melanocyte numbers vary little between human populations, although they differ in size, number, and the structure of melanosomes.[1] In the human epidermis, they have a close association with keratinocytes via dendrites. Although well known for their role in skin pigmentation, this is probably not the only function of these cells. Indeed, melanocytes have numerous enzymes with capabilities in antimicrobial defense, as well as genetic, biochemical, and functional links to the immune system.[2] Melanin, endogenously produced by melanocytes, is able to interact with enzymes and modulate their behavior, is a powerful cation chelator, and can bind and neutralize oxidants, microbicidal peptides, and antimicrobial drugs.[3–6] A better appreciation of the biological effects of melanocytes may assist in all aspects of the evaluation, understanding, and treatment of diseases associated with this cell line, such as vitiligo and melanoma.

There are definite flaws in the media dogma that melanin's main role is in protection against ultraviolet light. To begin with, it fails to explain the increase in the prevalence of melanin and melanocytes in skin not normally exposed to the sun, such as the genitalia,[1] and other body tissues, such as the epithelium of the inner ear, uveal tract of the eye, brain tissue, and the peritoneum.[7] Moreover, many nocturnal animals, such as bats, are highly melanized on their exterior surface. In addition, African albinos, despite the absence of melanin's sun protection, do not have an increased incidence of melanoma.[2]

Melanins are enigmatic pigments which have evolved over 500 million years and are present in all animals, microorganisms, and plants.[8–10] Melanin is important in microbial pathogenesis, as it has been associated with virulence by reducing the susceptibility of melanized microbes to host defense mechanisms.[11,12] Specifically, melanin interferes with protective T-cell responses, antibody-mediated phagocytosis, and antifungal toxic effects of oxidants.[12]

Considerable research has been performed on melanin's immunomodulatory functions in insects. Although much of their immune system is quite similar to ours, antibodies are lacking in insects. Thus, the detection of pathogens by pattern recognition receptors is a critical first step in their immune response.[13] Chemical patterns derived from microorganisms and parasites, such as the lipopolysaccharides on the outer cell envelope of Gram-negative bacteria and the peptidoglycan of bacterial cell walls, initiate the reaction of melanocytes.[14,15] In invertebrates, the enzyme cascade, in which melanin is the end product and tyrosinase is the initial activating enzyme, is called the prophenoloxidase activating system or the Raper–Mason pathway of melanogenesis, and is the central antimicrobial defense system against parasites and pathogens.[14] The prophenoloxidase activation system involves a serine proteinase cascade with similarities to the complement system of vertebrates.[13]

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Indeed, phenoloxidase is vitally significant to insects for the melanization of cuticles for color and camouflage, sclerotization of the insect cuticle, encapsulation and melanization of foreign organisms in the defense reaction, and wound healing.[16–18] Melanotic encapsulation occurs within melanosomes, and is a very effective, well-regulated immune response against parasites and pathogens for insects. The quinine intermediate compounds, cytotoxic free radicals, and other compounds produced during this phagocytosis of microorganisms are toxic to both hosts and pathogens; therefore, activation of prophenoloxidase is tightly regulated and localized.[13]

Grape melanin, in mammalian *in vivo* and *in vitro* studies, interacts with prostaglandins, leukotrienes, and complement, thereby altering immune-mediated inflammation.[9] In addition, fungal melanins interact with human serum to activate the complement system,[19,20] suggesting to Rosas *et al.*[19] that melanin may be a potential mechanism for the pathogenesis of certain degenerative and/or autoimmune processes, as well as for the virulence of melanin-producing microorganisms.

In humans, melanin does not function as the principal form of immune response, although it maintains its capabilities to be involved in the innate immune defense system. Melanocyte activity in human inflammation has been appreciated for years, having been described as "a sensitive barometer of inflammatory conditions of the skin."[10] Moreover, normal human melanocytes have been shown to function as phagocytes against microorganisms as well as foreign material.[21,22] LePoole *et al.*[21] concluded that melanocytes and melanosomes have the phagocytic and enzymatic machinery necessary for antigen processing, and appear to be a component of the skin immune defense system. Indeed, melanosomes are lysosomal structures as they contain numerous lysosomal enzymes, including alpha-mannosidase, acid phosphatase, beta-acetylglucosaminidase, beta-galactosidase, and acid lipase.[23,24] Melanin-concentrating hormone and melanin-concentrating receptor 1 stimulate hormone release and exert immunomodulatory functions.[25,26] Melanosomal matrix protein gp100 also elicits an immune response in which melanosomes undergo a unique maturation process, transforming into fibrillar ellipsoid organelles.[27] Indeed, there is evidence that a major function of melanocytes, melanosomes, and melanin in human skin is to inhibit the proliferation of bacterial, fungal, and parasitic infections in the epidermis and dermis.[2] Mackintosh believes that this function potentially explains the latitudinal gradient in the melanization of human skin, the disparity between melanocyte and melanization patterns in different vertebrate body parts and radiation exposure, and the regulation of the antimicrobial activity of melanocytes by known mediators of inflammation.[2]

There is a link between immunity and melanization, as demonstrated, for example, by recent studies in which attractin potentiated the production of alpha-melanocyte stimulating hormone.[28,29] Of note, attractin is also present on numerous cell types involved in the immune system and accumulates rapidly on the surface of activated T cells. In addition, alpha-melanocyte stimulating hormone also has immunoregulatory effects.[29,30] In response to various stimuli, melanocytes secrete a wide range of signal molecules, including cytokines,[31] melanocortin peptides,[32] catecholamines,[33] serotonin,[34] and nitric oxide. In turn, these secretory products affect keratinocytes, lymphocytes, fibroblasts, mast cells, and endothelial cells, all of which have receptors for these signal molecules.[35] Other mediators of the inflammatory defense system, such as histamine and arachidonic acid, stimulate melanogenesis.[36] Indeed, melanocytes are important local regulators of a range of skin cells and of skin homeostasis. Moreover, these beneficial aspects of melanocytes may be contributing factors in the actions of phototherapy in the treatment of various skin disorders, such as psoriasis, eczema, acne, and vitiligo.

In short, melanocytes are not simply pigment-producing cells, but produce substances with a range of biological functions, including structural strengthening by cross-linking proteins, antimicrobial defense, photon shielding, and chemoprotection. Thus, God gave us melanocytic and moles to provide several physiologically significant functions, including the provision of communicatory links with several different systems, e.g. the skin, central nervous system, and immune/inflammatory responses.

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