Cooling skin cancer: menthol inhibits melanoma growth. Focus on “TRPM8 activation suppresses cellular viability in human melanoma”

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YAMAMURA AND COLLEAGUES (17) report that melanoma cells express transient receptor potential melastatin subfamily member 8 (TRPM8) receptors and that their activation suppresses melanoma viability. This effect is mediated by menthol, and the mechanism of action involves the influx of extracellular Ca²⁺. This finding opens new and exciting possibilities in melanoma research, to wit, that natural products such as menthol, which have low toxicity, might be used with benefit in the treatment of this devastating disease.

Malignant Melanoma: Statement of the Problem

Malignant melanoma is a tumor of melanocytic origin that is the most rapidly increasing malignancy in the white population; melanoma is associated with a high mortality rate, second only to lung cancer. The devastating nature of this disease is connected with the fact that it can affect young people and there is no therapy once the metastatic process starts (4). In 2007 an estimated 60,000 Americans developed cutaneous melanoma, with an expected 8,000 deaths from the disease (7, 9). Of note, there has been a 620% increase in the annual incidence of melanoma and a 165% increase in the annual mortality from 1950 to 2000. Melanoma is the fifth leading cancer diagnosed in the United States, and $1.5 billion per year is spent (in the USA) to treat this disease. Although progress has been made in the clinical management of melanoma, including diagnostic staging and surgical therapy for localized disease, metastatic disease is incurable, with a median lifespan of <1 yr for patients with advanced melanoma (4, 7).

Melanocytes

Melanocytes are neural crest-derived cells responsible for the production of a melanin pigment that after transfer to neighboring keratinocytes acts both as an endogenous screen and a buffering system against harmful ultraviolet (UV) wavelengths in sunlight; in addition, melanin plays an important role in social communication or camouflage (see review in Ref. 13). Because of this neuroectodermal origin, melanocytes have conserved significant neuronal capability, including production of neurotransmitters and expression of their functional receptors (13, 15). It has been postulated that melanocytes detect and transduce external and/or internal signals/energy into organized regulatory network(s) for the maintenance of epidermal homeostasis (12). In this context, melanocytes can act as regulatory cells of a skin neuroendocrine system (“neurons” of the skin) (14). Therefore, it is not surprising that they can express ion channels involved in sensory functions including the transient receptor potential melastatin (TRPM) ion channels TRMP1, TRMP7, and TRMP8 (6, 8, 11, 17).

TRPM in Melanocytes

There are eight TRPM channels, which are divided into four groups: TRPM1/3, TRPM4/5, TRPM6/7, and TRPM2/8 (5). TRPM1 (melastatin) is a tumor suppressor protein with high expression in normal melanocytes and decreased expression in melanoma (5, 6). In patients with stage I and II melanoma, preservation of TRPM1 expression predicts prolonged disease-free survival, whereas loss of TRPM1 predicts poor outcome (4). In melanoma patients who experience recurrent disease, diffuse loss of TRPM1 correlates with aggressive disease and shorter survival time (3). The promoter region of this gene contains microphthalmia binding sites, and its gene expression is regulated by microphthalmia transcription factor, a master regulator of the melanocyte differentiation program. TRPM7 is a nonselective cation channel permeable for calcium, magnesium, and trace metals (5, 6) and also plays a role in melanocyte survival through detoxification of the intermediates of melanogenesis (8, 11).

TRPM8 has been identified as a Ca²⁺-permeable cation channel that is stimulated by temperatures below 28°C and is modulated in a voltage channel-dependent fashion (5, 6, 10). Thus, TRPM8 serves as a cold receptor involved in thermosensation with menthol and eucalyptol identified as natural ligands (5, 6, 10). Most recently, Yamamura et al. (17) identified TRPM8 on melanoma cells of which activation inhibited cellular viability, while others reported that activation of TRPM8 inhibits hair growth and pigmentation parameters (1). Interestingly, another TRP channel, TRPML3, is highly expressed in normal melanocytes, and the mutation-induced TRPML3 gain-of-function (Va/Va genotype) stimulates Ca²⁺ overload and melanocyte death (16).

Melanocyte-to-Melanoma Transition

Cutaneous melanoma arises from melanocytes present in normal-appearing skin, from the activated melanocytes of solar lentigo, which can progress to premalignant lesion, lentigo maligna, or, less frequently, from dysplastic melanocytic nevi (Fig. 1). Malignant transformation is the result of complex interactions between genetic, constitutional, and environmental factors of which UV radiation is the most important, being both an initiator and promoter of the neoplastic process (2) (Fig. 1). Thus, melanoma is characterized by the unlimited proliferation of activated or genetically altered epidermal melanocytes that escape host regulatory factors and gain self-regulating capability during the process defined as tumor progression. Moreover, because of the local and environmental influences, the pathology and prognosis of melanoma differs between anatomical sites and their histological characteristics (4).

Routine histopathology supplemented with immunohistochemistry in cases of metastatic or spindle cell melanoma represents the standard of care for the diagnosis and staging of melanoma. However, not all melanocytic tumors can be con-
Identifiedly classified, and the current histological classification does not perfectly predict an individual’s clinical course or therapeutic outcome. Therefore, there is an ongoing effort to define new markers and to use new techniques for the detection, diagnosis, and classification of melanoma to more accurately predict tumor behavior and choose optimal, individualized therapy. Interestingly, expression of melastatin inversely correlates with melanoma prognosis: loss of its expression predicts aggressive behavior and shorter survival time (3, 4). The expression of TRPM7, TRPM8, and TRPML3 during progression of melanocytic lesions remains to be tested.

Menthol and Related Natural Products for Melanoma Therapy

Since knowledge on molecular mechanism of melanoma progression is still limited and the metastatic disease is almost incurable because of lack of effective therapies, there is a need to employ cutting edge technologies or novel rational strategies to design an effective treatment strategy (3, 4, 7). In this context, TRP channels (for example, TRPM1, TRPM7, TRPM8, and TRPML3) represent attractive targets for melanoma and pigment cell researchers, with specific focus on Ca\textsuperscript{2+} loading of normal and malignant melanocytes. This is further emphasized by the findings of Yamamura et al. (17) that activation of TRPM8 channels by its natural ligand menthol significantly decreases melanoma cell viability. Menthol is an organic compound made synthetically or obtained from peppermint or other mint oils, which is used as a nonprescription drug or component of cosmetics or skin care products. Other plant-derived products acting on TRPM8 include, but are not limited to, eucalyptol (10), which is used for flavoring, fragrance, and as a medicinal or cosmetic ingredient. Thus, we may be at the dawn of a new era of systematic investigation of “natural cold” receptor agonists for an economical and rational strategy of managing malignant disorders of pigmentary cells. Although only speculative at this juncture, the clinical implication of these findings can be envisioned as treatment of melanoma with selective TRP agonists that regulate Ca\textsuperscript{2+} load.

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REFERENCES


