

Laboratory Opossum (*Monodelphis domestica*) Model for Melanoma Chemoprevention

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Abstract

Melanoma is the most aggressive form of skin cancer. Developments in melanoma basic research and therapeutic interventions have advanced tremendously with help of animal models of this disease. Transgenic and knockout mice have provided a wide array of melanoma models, which are primarily used for studying molecular pathways and developing treatment strategies. To the best of our knowledge, there has been no natural animal model for research on chemoprevention of melanoma induced by UV light alone. In this editorial, we discuss the potential of the laboratory opossum (*Monodelphis domestica*) as a natural model for research on chemoprevention of melanoma.

Keywords: *Monodelphis domestica*; Opossum; Melanoma; Chemoprevention; Animal models

Introduction

Melanoma is the most aggressive form of skin cancer, with approximately 76,250 new cases of melanoma and 9,180 deaths estimated to occur in the United States in 2012 [1]. A steady rise in the incidence of cutaneous melanoma is being reported every year. It is widely established that the major event which leads to melanoma initiation is the malignant transformation of melanocytes. The foremost factors that contribute to this malignant transformation are ultraviolet-B (UV-B) radiation and growth factors; however the interactions between these factors are poorly understood. Melanomas are classified histologically based upon location, radial or vertical growth phase of transformed melanocytes, and stages of progression to lymph nodes or visceral organs. Even though genetic predisposition and environmental factors are known to be important in disease progression, understanding the mechanisms by which the disease is initiated is crucial to developing new preventive strategies.

In addition to genetically engineered mouse models (transgenic and knockout models), Syrian hamsters, guinea-pigs, *Xiphophorus* fish and opossums have all been used as melanoma models based on sunlight dependent etiology [2].

Cancer chemoprevention is the use of natural or synthetic substances to reverse, suppress, or prevent premalignant molecular or histologic lesions from progressing to invasive cancer [3,4]. An ideal animal model for chemoprevention of melanoma would precisely reiterate human melanoma, mainly the UV-based etiology including initiation and progression of the nevus to metastatic melanoma, and also would resemble human cutaneous melanoma both genetically and histopathologically. *Xiphophorus* fish develop spontaneous melanomas in response to UV radiation, but the histology of the induced tumors differs substantially from human melanomas, limiting their use as chemopreventive models. On the other hand, Syrian hamsters and guinea pig models require an initial carcinogenic insult to promote the disease, also limiting their use as ideal models for melanoma [2,5].

The laboratory opossum (*Monodelphis domestica*) is a natural model which responds to UV-B radiation and recapitulates the initiation and progression stages of the human disease, making it an attractive model for melanoma chemoprevention research. We have reported previously

that some suckling young opossums developed melanocytic nevi after receiving a dose of 0.87-5.0 kJ/m² divided equally among up to 14 exposures during the 19 days after birth [6]. Further exposure of the affected animals, 3 times/week at 125 J/m² of UV-B for up to 45 weeks resulted transformation of the nevus to malignancy in some animals. Nevi of 8 of 20 chronically-exposed animals progressed to malignant melanoma with metastases to lymph node(s). Lymph node metastasis is a primary outcome of treatment failure for advanced melanoma in humans. Our results from *Monodelphis* have established that UV-B radiation alone can act as a complete carcinogen for the initiation of melanoma to its distant metastasis, and that exposure of sucklings can lead to metastatic melanoma by middle age [7]. This species has great potential for identifying genes that affect mechanisms leading to UV-induced skin lesions and for investigating environmental factors that may contribute to the increasing incidence of skin cancer in human populations [8]. These results indicate that laboratory opossums are a unique model for recapitulating the risk of malignant melanoma in humans' consequent to early exposure to sunlight, which acts as an initiating factor for this disease in later life.

Determination of the molecular mechanisms of UV-induced melanomagenesis, use of an animal model to test candidate prevention agents, and use of molecular and histologic markers as surrogate end point markers are prerequisites for melanoma chemoprevention [9]. As an initial consequence of UV mutagenesis, pyrimidine dimers are generated in *Monodelphis* skin cells [10]. Any agents that could reverse or repair UV-induced DNA damage or are capable of promoting apoptosis in melanoma cells can be investigated for their chemopreventive potential in laboratory opossums.

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Mutations in the tumor suppressor gene family are commonly detected in melanoma. CDKN2A/p16^{INK4} of the 9p21 chromosome region is commonly altered in melanoma; it exists as a recessive germ-line mutation in 30-50% of members of human melanoma kindreds [11]. UV-exposed human melanocytes do not induce mechanisms mediated by the human p53 tumor suppressor system. Failure of this tumor suppressor system is important in the initiation of melanoma [9]. In addition anti-apoptotic protein Bcl2 has been reported to be over expressed in human melanoma and thus could be a relevant prevention target [12]. As in humans, the p53 gene is not altered and CDKN2A/p16^{INK4} is mutated in the melanocytic nevi of *Monodelphis*, further emphasizing the potential of this animal model for prevention studies [13,14].

Several target genes of the CDKN2A pathway including E2F1, cyclin dependent kinase 4 (CDK4), activator proteins (AP-1, AP-2, Cyclin D1), and retinoblastoma protein (Rb) represent potential targets for chemoprevention. Another important molecular pathway as an initial event in photocarcinogenesis is associated with alterations in Ras [15,16], which affect its anchorage to the plasma membrane and farnesylation [9]. Therefore, membrane disposition of Ras and farnesylation could be attractive molecular targets for prevention. We believe that the unique characteristics of *Monodelphis domestica* as a model for chemoprevention of melanoma should be exploited aggressively to move this field forward. Using this model to investigate chemopreventive agents that might prevent UV-induced melanocytic nevi from forming or that might block their progression to melanoma could have a tremendous impact on broadening our knowledge about the molecular mechanisms of UV-induced melanomagenesis, as well as facilitate the identification, development and validation of early biomarkers of melanoma.

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