Understanding the Biology of Melanoma and Therapeutic Implications

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KEYWORDS

• BRAF • NRAS • Immunotherapy • Targeted therapy • MITF

KEY POINTS

- Melanomagenesis is a complex process that involves carcinogenic exposure (eg, ultraviolet B radiation) and genetic predisposition (MCR1 polymorphisms).
- Microphthalmia-associated transcription factor, the "master regulator of melanocyte development," functions as an oncogene when dysregulated, leading to the upregulation of cell cycle progression and favorable metabolic changes, and the inhibition of apoptosis.
- Mutations of oncogenes (BRAF, NRAS, CKIT, GNAQ, GNA11) and a tumor suppressor gene (NF1) are present in most melanomas, although the rate of each type of mutation varies according to anatomic site subset (eg, mucosal vs cutaneous vs uveal).
- The mitogen-activated protein kinase (MAPK) pathway is upregulated in nearly all melanomas and is susceptible to small molecule inhibition.
- The interplay among the MAPK pathway, tumor antigen expression, and immune infiltration predicts therapeutic synergy with combined molecular and immune targeting.

INTRODUCTION

Over the past 3 decades, several breakthroughs have greatly expanded what is known about melanocyte biology, relevant oncogenic mutations and deletions and amplifications in melanoma, the influence of molecular signaling pathways on melanomagenesis, and the interaction of aberrant signaling pathways with host immune elements. This increased understanding has led to a remarkable number of improvements in the diagnosis, classification, and treatment of this disease. This advancement is an amazing achievement with great relevance, because the number of new cases of and deaths from melanoma continues to increase. A hallmark of this recent success

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is the regulatory approval of 4 therapeutic agents over the past 3 years, with at least another 6 promising agents that have just entered or completed phase III clinical trials.[1–5] Still, most patients diagnosed with metastatic melanoma will die of their disease within a few years of diagnosis.[6,7] To achieve the goal of successfully treating metastatic melanoma for nearly all afflicted, continued breakthroughs will be required to provide clinicians with diagnostic tools to identify subsets of patients most likely to benefit from a specific line of therapy, and improved treatment strategies for these identified subsets. This article reviews the relevant discoveries regarding melanocyte and melanoma biology that have been or are beginning to be translated into transformative therapies.

MELANOMA DEVELOPMENT

Melanocyte Formation in Development

Melanocytes are neural crest–derived cells that develop as a branch of alternative differentiation programs that include the closely related lineages of sympathetic neurons, Schwann cells, or melanocytes. In addition to residing in the basal epidermis and in hair follicles, other melanocyte populations can be found along mucosal surfaces and in the meninges, choroidal layer of the eye, and stria vascularis within the cochlea. The pigments produced by melanocytes are composed of numerous chemical species that have been broadly classified as red/blond pigments (pheomelanin) and brown/black pigments (eumelanin). Although brown/black pigment has a measureable (albeit modest) ultraviolet protective capability, pheomelanin has been associated with increased reactive oxygen species in the skin.[8]

Two forms of skin pigmentation exist: constitutive and adaptive. The constitutive or basal skin pigment level is associated with the type of pigment synthesized and the maturation process of the melanin-containing vesicles (called melanosomes). People of varying constitutive pigmentation are thought to have a constant number of melanocytes but variations in relative pigment production per cell. The adaptive pigmentation response typically reflects melanin synthesis triggered by ultraviolet radiation. This pigment has been shown to be initiated by ultraviolet-induced DNA damage in overlying epidermal melanocytes followed by p53 stabilization and transcriptional activation of the proopiomelanocortin (POMC) gene.[9,10] POMC is posttranslationally cleaved into various small peptides, one of which is the melanocyte-stimulating hormone (MSH) that is secreted and stimulates its receptor (melanocortin receptor 1 [MC1R]) on underlying melanocytes. Activation of MC1R by MSH peptide results in cyclic adenosine monophosphate induction within melanocytes, followed by stimulation of the gene encoding a transcription factor called *microphthalmia-associated transcription factor* (MITF), which activates expression of all known pigment-producing enzymes and nearly all of the machinery required for the packaging, maturation, and secretion of pigment-laden melanosomes. Nonfunctional polymorphic variants of MC1R are frequently responsible for the red hair/fair skin/freckling phenotype in numerous species, including humans.

Role of Ultraviolet Radiation

Ultraviolet radiation is deeply implicated in the formation of common forms of cutaneous melanoma in man. Ultraviolet wavelengths residing within the ultraviolet B portion of the spectrum produce stereotypical nucleotide adducts known as *cyclobutane pyrimidine dimers*, which in turn result in formation of pyrimidine dimer mutations, in which a cytosine located in a dipyrimidine sequence becomes mutated to thymidine. These “ultraviolet signature mutations” are easily recognizable within