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Molecular pathology of malignant melanoma: changing the clinical practice paradigm toward a personalized approach

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Summary Melanocytic proliferations are notoriously difficult lesions to evaluate histologically, even among experts, as there is a lack of objective, highly reproducible criteria, which can be broadly applied to the wide range of melanocytic lesions encountered in daily practice. These difficult diagnoses are undeniably further compounded by the substantial medicolegal risks of an "erroneous" diagnosis. Molecular information and classification of melanocytic lesions is already vast and constantly expanding. The application of molecular techniques for the diagnosis of benignity or malignancy is, at times, confusing and limits its utility if not used properly. In addition, current and future therapies will necessitate molecular classification of melanoma into one of several distinct subtypes for appropriate patient-specific therapy. An understanding of what different molecular markers can and cannot predict is of the utmost importance. We discuss both mutational analysis and chromosomal gains/losses to help clarify this continually developing and confusing facet of pathology.

1. Introduction

Molecular diagnostics have played an increasing role in the diagnosis and management of patients with melanocytic lesions. Melanocytic proliferations are notoriously difficult lesions to evaluate histologically, even among experts, as there is a lack of objective, highly reproducible criteria, which can be broadly applied to the wide range of melanocytic lesions encountered in daily practice [1-4]. This underscores the notion that current histologic evaluations may not be the optimal method to classify nevi [5]. The proper application of ancillary molecular studies can assist in the proper diagnosis in difficult lesions. In addition, with the advent of therapies tailored to specific molecular mutations, it is imperative that the lesions are properly categorized as they can directly impact which therapies are chosen for proper management of the patient's disease. Molecular subtyping has become prominent in other cancer subtyping [3,6-9]. For example, classification of lung carcinoma has evolved from simply classifying tumors as small cell or non–small cell to subclassifying adenocarcinoma and squamous cell carcinoma into a specific molecular subtype for the purpose of guiding proper therapeutic choices now available [10].

The molecular profile of melanocytic lesions is already vast and constantly expanding. The application of molecular diagnostics for the diagnosis of benignity or malignancy is, at times, confusing and undoubtedly limits its utility if it is not understood and used properly.

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2. Key molecular pathways

2.1. Melanoma growth and survival pathways

Melanocytic proliferations use the MAPK (mitogen-activated protein kinase) and AKT (protein kinase B) pathways to facilitate their growth and survival (Fig. 1) [6]. Several genes in these pathways have been shown to be important in both benign and malignant melanocytic lesions (Table 1). In addition, many of the mutations described in Table 1 have a predominant type of melanocytic lesion with which they are associated.

Table 1 Melanoma genes and incidence

Gene	Incidence
BRAF	~50% cutaneous melanomas
KIT	~25% acral, mucosal, CSD melanomas
NRAS	~50% congenital nevi
HRAS	~15% Spitz nevi, but absent in acquired, congenital, and dysplastic nevi
GNAQ	~85% blue nevi, ~50% uveal melanoma
PTEN	~10% of melanoma
TERT	~30% primary, ~85% metastatic melanoma
NF1	~15% cutaneous melanoma
ARID2	~10% cutaneous melanoma
CDKN2A	~25% cutaneous melanoma

NOTE. Many mutations have specific melanocytic lesions with which they are associated. Several gene mutations have been implicated in specific types of melanoma. These gene products are targets for current and future inhibitors.
Abbreviation: CSD, chronically sun damaged.

2.2. BRAF

BRAF (protooncogene B-raf/v-Raf murine sarcoma viral gene homologue B1) has been extensively studied with regard to melanocytic proliferations. Mutations in *BRAF* can be identified in approximately 50% of melanomas [11]. *BRAF*-mutated melanomas are most often found on nonchronically sun-damaged skin and rarely found in melanomas arising in sun-damaged skin and acral or mucosal sites. More than 80% of the mutations are V600E mutations, which constitutively activate the BRAF enzyme [12]. The second most common mutation is V600K (10%-20%) [12-14]. Other *BRAF* mutations have been identified but are relatively rare (Table 2).

Not surprisingly, *BRAF* mutations are also identified within benign melanocytic nevi. *BRAF* mutations are often

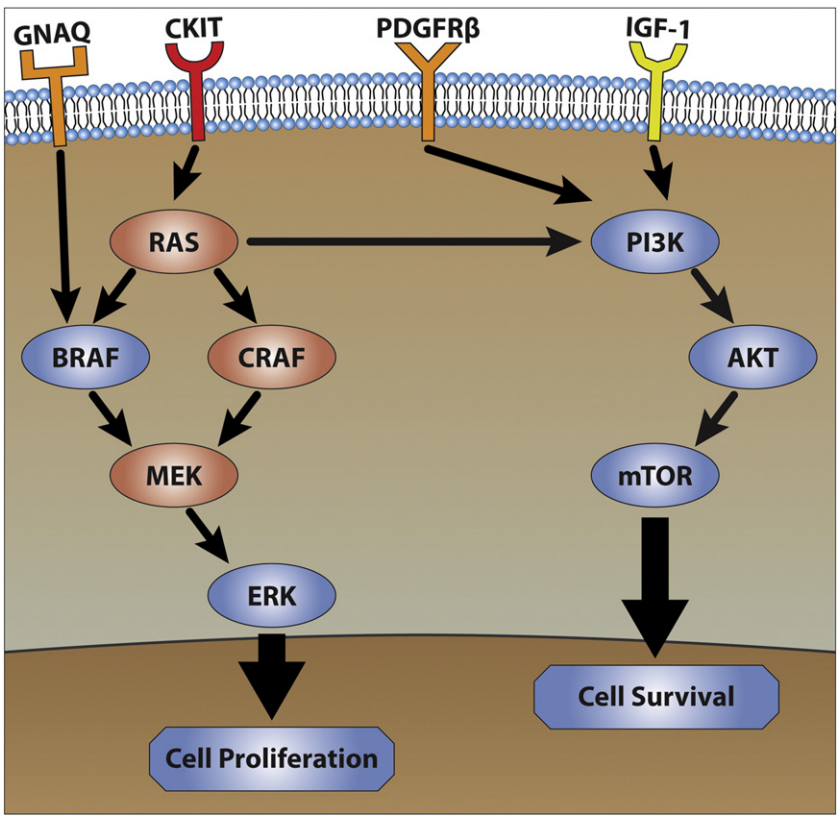

Fig. 1 MAPK and AKT pathways are the 2 predominant pathways involved in malignant melanoma and regulate cell proliferation and survival. The MAPK pathway leads to an increase in cell proliferation, whereas the AKT pathway leads to inhibition of apoptosis and increased cell survival. BRAF dimerization and activation are facilitated by RAS. ERK normally produces negative feedback. The *BRAF* V600E mutation causes the kinase to be constitutively activated, which leads to increased proliferation.