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Molecular Classification of Patients with Cutaneous Melanoma: A Reality

Giuseppe Palmieri[1], Carla Rozzo[1], Antonio Cossu[2] and Paolo A Ascierto[3]*

[1]Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, Sassari, Italy
[2]Anatomia Patologica, Azienda Ospedaliero Universitaria, Sassari, Italy
[3]Istituto Nazionale Tumori "Fondazione Pascale", Napoli, Italy

Melanoma is the most aggressive skin cancer and, despite great progresses recently assessed into the biology research and the diagnosis approaches, its incidence and mortality have extremely risen in all developed countries during the last half century [1]. Only in 2010, about 68,130 new melanoma cases were estimated to be diagnosed in USA, with 8,700 patients estimated to die for this disease [1]. Although vast majority of melanoma cases is actually diagnosed when the disease is still localized and surgically resected, the fraction of patients with an advanced melanoma has very poor survival rates [2]. Poor responses to traditional chemotherapies are related to very low levels of spontaneous apoptosis observed in this tumour *in vivo*, compared to other tumour cell types, and its high resistance to drug-induced apoptosis [3]. However, many promising therapeutic approaches are currently under investigation, and, overall, therapies using small-molecule inhibitors directed against oncogenic molecular target are giving new hopes for melanoma management [4]. To this regard, selection of melanoma patients by genetic subgrouping seems to be essential for the success of such targeted therapies in clinical trials.

From the genetic point of view, several gene alterations have been implicated in cutaneous melanoma. Germline mutations in $p16^{CDKN2A}$ gene represent the most recognized cause of inherited melanoma susceptibility. Prevalence of $p16^{CDKN2A}$ mutations seems to be heterogeneously distributed among melanoma patients within different geographical areas [5]. Several low-penetrance candidate genes, such as *breast cancer susceptibility gene 2* (*BRCA2*) and *melanocortin-1-receptor* (*MC1R*), have been also implicated in melanoma predisposition [6]. Inherited mutations of the *BRCA2* gene have been associated to development of both ocular and cutaneous melanomas, in addition to the main predisposition to breast and ovarian cancers [6]. The *MC1R* gene, remarkably polymorphic in Caucasian populations, encodes the melanocyte-stimulating hormone receptor and represents one of the major genes which determine skin pigmentation [7].

From the pathogenetic point of view, the ERK_{1-2} proteins, which represent the downstream components of the MAPK pathway (including the signaling kinase cascade of NRAS, BRAF, and MEK1/2 gene products), have been found to be activated through phosphorylation ($pERK_{1-2}$) in melanoma and implicated in rapid malignant cell growth, mostly as a consequence of mutations in upstream components of the pathway [8,9]. Indeed, the MAPK pathway has been now recognized as the main molecular effector playing a pathogenetic role in both development and progression of cutaneous melanoma [10]. Constitutive activating mutations in *NRAS* occur in about 20% of melanoma cell lines, whereas oncogenic *BRAF* mutations have been described in 30-60% of primary melanomas [11]. Activation of the MAPK cascade and, particularly, activating *BRAF* mutations have been reported to constitutively induce up-regulation of the $p16^{CDKN2A}$ oncosuppressor gene [12]; this phenomenon looks like a sort of protective response to an inappropriate mitogenic signal (as a confirmation, inactivation of $p16^{CDKN2A}$ gene and subsequent loss of the corresponding $p16^{CDKN2A}$ protein expression is strictly associated with malignant tumour invasion) [13].

Finally, widely-confirmed findings support the existence of a dual pathway for the development of melanoma: one related to chronic exposure to the sun and the other related to melanocyte instability [14]. In particular, melanomas developed on skin not chronically exposed to sun usually carry either a mutated *NRAS* or mutated *BRAF* or concurrently mutated *BRAF* and *PTEN* (*BRAF*/*PTEN* and *NRAS* somatic mutations are mutually exclusive). Conversely, melanomas on skin chronically exposed to the sun or on acral skin generally present wild-type *BRAF* or *NRAS* genes and a genomic instability with an increased number of copies of the proliferation-controlling *CyclinD1* or *CDK4* genes (which belong to the signaling cascade downstream $p16^{CDKN2A}$) [10].

All these evidence represent a strong indication that the different molecular pathways associated with the melanomagenesis may correspond to different subsets of melanoma patients, with distinguished biological and clinical behavior of the disease. Identification of such different patients' subsets is now mandatory for its introduction in clinical trials by addressing tissue sections from each melanoma patient to molecular analyses: immuno-histochemistry using antibodies against the main candidate proteins, in order to assess any alteration of their expression levels, fluorescence *in situ* hybridization (FISH) analysis, in order to evaluate the existence of pathogenetic gene amplifications (for *MITF, CyclinD1* or *CDK4* genes), and, mostly, mutation analysis, in order to select patients with gene sequence variations to be appropriately targeted.

Molecular classification at somatic level (on tumor biopsies) is the winning tool for a better management of cancer patients.

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***Corresponding author:** Paolo A Ascierto, Istituto Nazionale Tumori "Fondazione Pascale", Napoli, Italy, Tel: +39-081-5903841; Fax: +39-081-5903841; E-mail: paolo.ascierto@gmail.com

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