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Introductory Chapter: Melanoma and Therapeutic Perspectives

Karine Cohen Solal and Ahmed Lasfar

1. Introduction

Malignant melanoma is one of the most aggressive forms of skin cancer, often leading to distal metastasis [1, 2]. Melanoma arises often from transformed melanocytes as a consequence of durable UV radiation. Unprecedented progress in the treatment of advanced melanoma occurred largely through advances in understanding how to target selective genetic mutations in patients with melanoma, and to unleash exiting anti-tumor immune responses [3–5]. While immunotherapy is characterized by induction of durable responses in a limited number of patients, targeted therapy has been characterized by high response rates [4, 5]. The introduction of targeted therapies has considerably improved survival rates in a significant proportion of patients with BRAF-mutant melanomas [6, 7]. However, drug resistance significantly weakens the efficacy of almost all current anticancer therapies [8, 9]. This resistance to therapy is generally driven by intrinsic or acquired tumor mechanisms [10]. Understand underlying mechanisms of resistance is crucial in elaborating novel therapeutic strategies (Figure 1).

Figure 1. Current melanoma therapies. Several therapies are currently used in clinic for the treatment of melanoma patients. Current therapies are based on targeted therapy, immune therapy and combination therapy, consisting on association of both targeted and immune therapies. In addition, alternative therapy. Is used in many cases of drug resistance.

2. Therapeutic resistance to targeted therapy

Emergence of drug resistance, usually within several months considerably limited expected survival benefits [8, 9]. The V600E activating mutation of BRAF (MAPK pathway effector) induces constitutive activation of the kinase in 45–60% of cutaneous melanomas, and inhibitors of BRAF, MEK or both have revolutionized the treatment of patients with BRAF-mutated melanoma [10, 11]. Some mechanisms of drug resistance have been being identified and strategies to circumvent therapy failure are being investigated in preclinical models and clinical studies [12].

Accumulating evidence demonstrated that in the context of acquired resistance, tumor cells will develop mechanisms that not only promote resistance to BRAF V600E targeted therapy but also increase invasiveness favorable to further dissemination and metastasis [10, 13, 14]. The molecular effectors involved in resistance to BRAF V600E targeted therapy are simultaneously playing key roles in melanoma cell motility and invasiveness [8, 10]. Numerous studies documented that resistance is often coupled to the development of an aggressive tumor phenotype, characterized by an active epithelial-to mesenchymal (EMT)-like process, increased motility and invasion [15, 16]. As a well-documented example, transcription factors and coactivators play an active role in resistance to BRAF V600E targeted therapy, through a large variety of mechanisms [17]. In addition to promoting adaptive or acquired resistance, the expression levels of some of these transcription factors promotes a state of intrinsic resistance in the context of melanoma cells harboring BRAF V600E mutations [18–20].

General mechanisms of BRAF inhibitor resistance involve up or down regulation of transcription factors, phosphorylation of transcription factors, as well as modulation of their subcellular localization [17–20]. These alterations are associated with diverse oncogenic mechanisms, such as induced expression of ERK kinases or stabilization of their phosphorylation, an increase and/or activation of specific receptor tyrosine kinases, such as EGFR, IGF-1R, AXL PDGFR β , ERBB3, or the activation of the TGF- β signaling pathway [17, 19]. Moreover, G-protein-coupled receptors are being involved as a new protein class whose dysregulation underlies a cascade of transcriptional events resulting in resistance to BRAF inhibition. These studies altogether strongly suggest that the resistance mechanisms reestablish activation of the MAPK pathway, on which melanoma cells are highly dependent for survival, proliferation, aggressiveness and pro-metastatic behavior [17, 21]. In addition, reactivation of additional pathways, such as the PI3K/AKT pathway or GPCR-mediated cAMP/PKA/CREB pathway further operate for rewiring melanoma cells towards more aggressive characteristics in conjunction with drug resistance [21].

Simultaneous rewiring of oncogenic signaling pathways, phenotypic plasticity favoring pro-invasive behavior, actin remodeling and cytoskeletal tension, and bidirectional interplay between tumor cells and melanoma microenvironment, represent remaining challenges, for overcoming resistance to BRAF V600E inhibitors [22].

Other mechanisms of drug resistance have been identified in both melanoma patients and BRAF-animal models. Recently, it has been reported that BRAF interacts with GRP78 and removes its inhibitory impact on the three major ER stress sensors of UPR, PERK, IRE1 α , and ATF6. Disconnection of GRP78 from these ER stress sensors stimulates UPR that consequently activates cytoprotective autophagy. Thus, inhibition of BRAF-induced ER stress-mediated autophagy can possibly resensitize BRAF mutant melanoma tumors to apoptosis [23].

Melanomas frequently display hyperactivity of nitric oxide synthase (NOS) and NADPH oxidase (NOX), which, respectively, produce nitric oxide (NO $\cdot$) and superoxide (O $_2^{\cdot-}$). The NO $\cdot$ and O $_2^{\cdot-}$ react instantaneously with each other to produce

peroxynitrite (ONOO^-) which is the driver force of melanin chemiexcitation. Melanocytes, the skin cells, specialized in synthesizing melanin, a shield against sunlight's ultraviolet (UV) radiation. However, melanin chemiexcitation paradoxically demonstrates the melanomagenic properties of melanin. In a loop, the NOS activity regulates melanin synthesis, and melanin is utilized by the chemiexcitation pathway to generate carcinogenic melanin-carbonyls in an excited triplet state. These carbonyl compounds induce UV-specific DNA damage without UV [24].

It has been also reported that melanoma cells gain drug resistance to Temozolomide through a complex inflammatory mechanism, involving Inflammasome Sensor NLRP1 [25].

There is emergent indication that altered expression levels of microRNAs (miRNA)s induce drug-resistance in melanoma cells and that restoring adequate expression of miRNAs is critical in the re-establishment of therapeutic sensitivity [26].

3. Immunotherapy resistance

On the other hand, since the first immune checkpoint inhibitor (ICI) approval of an anti-CTLA-4 monoclonal antibody (mAb) in 2011 for unresectable/metastatic melanoma, the class continued to evolve, resulting in an always-changing standard of care for patients. Unfortunately, innate and acquired resistance to ICIs prevent a substantial number of patients with advanced melanoma to benefit from these clinical breakthroughs [27]. As the mechanisms responsible for both innate and acquired resistance to ICIs are further elucidated, therapeutic strategies to overcome these resistances are being clinically evaluated and will undoubtedly provide superior therapeutic efficacy [28].

As an example, clinical trials are currently evaluating inhibitors of myeloid-derived suppressors cells, which have emerged as important components in resistance to cancer immunotherapy [29, 30]. In addition, intra-tumor injection of interleukin-12, GM-CSF, and Toll-like receptors (TLR9) agonists, among other agents are currently evaluated in patients with melanoma refractory to anti-PD1 blockade [31, 32]. Another approach clinically tested in patients with BRAFV600E is the triple combination of an approved anti-PD-L1 monoclonal antibody and an approved combination of BRAF inhibitor/MEK inhibitor; this triplet regimen is based on the rationale that BRAF inhibition increases the penetration of T cells into the tumors, a major factor in the ability to respond to ICIs [33]. Altogether, the different approaches aim at transforming a cold tumor, characterized by a lack or paucity of tumor T cell infiltration, into a hot, inflamed tumor.

4. Alternative therapeutic strategies

Other alternative approaches have been elaborated in the treatment of metastatic melanoma such as Photodynamic therapy (PDT), which relies on a light-activated compound to produce death-inducing amounts of reactive oxygen species (ROS) [34].

Histone Deacetylase Inhibitors have been also developed to overcome resistance to targeted and immunotherapy in Metastatic Melanoma [35].

Nanotechnology, based therapy or neoadjuvant therapy represent an active area of investigation as demonstrated by several clinical trials [36]. These novel strategies may offer a multitude of benefits which could improve the survival outcomes of melanoma patients, with low adverse effects. Their combination with

immunotherapies and vaccines are expected to overcome drug resistance, offering survival benefits to a greater population of patients with advanced melanoma, while maintaining a satisfying quality of life.

5. Conclusion

The future of patients with unresectable and advanced melanoma is looking brighter than a decade ago. Besides immunotherapy revolution, promising approaches are emerging. Currently combination therapy, based on targeted therapy and immune checkpoint inhibitors is commonly recommended for increasing treatment efficacy. However, many challenges remain, regarding the mechanisms of tumorigenesis, the impact of tumor microenvironment on the immunogenicity of melanoma.

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