Melanoma Treatment and New Alternative Targets for Melanoma Treatment

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Abstract
Melanoma is the most lethal form of skin cancer. Until 2011, the favored therapy was chemotherapy despite their low efficiency. Spectacular progresses were made in melanoma treatment using targeted therapies anti-BRAFV600E / anti-MEK and immunotherapy anti-CTLA-4 / anti PD-1. Unfortunately, more than 50% of patients present intrinsic or acquire resistance and are in treatment failure. So identification of new Druggable pathways is an urgent need and will help to discover more efficient treatments for melanoma.

MELANOMA
Melanoma, which derives to the malignant transformation of the melanocytes, is the most aggressive form of skin cancer. Conversely, melanoma represents only 5% of the skin cancer but causes a large majority of skin cancer deaths [1]. Globally, 132000 new melanomas are diagnosed every year with approximately 48000 deaths associated with melanoma [2,3]. Until 2011, the gold standard for melanoma treatment was non-specific alkylating agents like Dacarbazine [4]. Unfortunately, these compounds failed to demonstrate a real efficiency in melanoma treatment [5].

Approximately 60% of melanomas possess activating BRAF mutations [6] in which the MAPK/ERK pathway is generally upregulated. In 2011, a revolution occurred in melanoma treatment with the development of targeted therapies. Vemurafenib, the first BRAF V600E specific inhibitor acting by blocking the ATP binding site of BRAF V600E was commercialized. This inhibitor decreases the MAPK/ERK pathway activation and dramatically reduces melanoma cells proliferation [7]. In patients, Vemurafenib treatment has clearly demonstrated benefit with 84% overall survival at 6 months in the Vemurafenib treated group against 64% in the chemotherapy group [5]. In 2013, Dabrafenib, a second BRAF V600E specific inhibitor was also used in treatment of BRAF V600E mutated melanoma patients. Globally, the mode of action and efficiency of Dabrafenib is similar to Vemurafenib [8,9]. In parallel of these BRAF inhibitors, MEK inhibitors were also developed. Trametinib was the first MEK1/2 specific inhibitor approved by the FDA in 2013. It binds to MEK1/2 and inhibits the phosphorylation of ERK1/2 but also MEK1/2 by a conformation change of MEK1/2. Curiously, this compound was efficient only on BRAF V600 mutated melanoma [10]. In BRAF mutated patients, the rate of overall survival at 6 months was 81% in the Trametinib group versus 67% in the chemotherapy group [11]. It was also tested in combination to Dabrafenib and the median progression-free survival in the combination group was 9.4 months, as compared with 5.8 months in the Trametinib alone group [12]. In 2015, Cobimetinib, a second MEK inhibitor with the same action mechanism was approved but only in combination with Vemurafenib [13]. The respective overall survival at 9 months in phase III clinical trial was 81% for combination therapy versus 73% for Vemurafenib alone [14]. Despite the efforts which have been made to target different partners in the MAPK pathway, the majority of patients treated with targeted therapies acquire drug resistance after short remission/stabilization period, and recurrence of metastases is observed in almost all cases [15].

In parallel to targeted therapies development, another therapeutic option has emerged. It consisted of boosting the immune system to eliminate cancer cells. In 90s, first attempt was IL-2 treatment to trigger the proliferation of T (CD4+ and CD8+), B and NK cells [16] but efficiency was very low with around 10% of responses and lot of adverse events were observed [17]. 2011 saw the development of Ipilimumab. It is a monoclonal antibody that targets CTLA-4, a protein which mediates immune homeostasis and tends to negatively regulate the T-cell response [18]. The overall survival at 12 months with Ipilimumab is around 40% and the response rate is around 10% [19,20] but important adverse events of grade 3 / 4 were often observed [21]. In 2014, a second generation of immunotherapy was approved for...
melanoma treatment. Nivolumab and Pembrolizumab are two human monoclonal antibodies directed against PD-1. Like CTLA-
4, PD-1 is a T-cell co-inhibitor receptor and is activated through the binding with two known ligands, PD-L1 and PD-L2 [22,23].

Currently, several clinical trials evaluate efficiency of MAPK inhibitor and PI3K inhibitor combination (NCT01902173, NCT01616199 and NCT01512251). Results of these studies should be carefully observed. Concerning immunotherapy, new anti-PD-L1 antibody are currently under clinical evaluation and show early promise results (NCT01375842 and NCT01693562) [26,27]. Another pathway that could be interesting in melanoma treatment is JAK/STAT pathway. STAT3 have been implicated in targeted therapy resistance [28] and therefore is an attractive target. JAK/STAT pathway is also implicated in PD-L1 regulation [29] and could be targeted to enhance Nivolumab/Pembrolizumab efficiency. Other cellular processes could be also targeted like translation and proteins processing. For example, maintenance of the eukaryotic translation initiation factor eIF4F complex have been observed in BRAF V600 or MEK inhibitors resistance melanoma cells suggesting that dual inhibition of BRAF/MEK and eIF4F may overcome drug resistance [30]. Another promising strategy is the targeting of the Unfolded Protein Response pathway which appears as an emerging pathway to selectively target cancer cells. Indeed, neoplastic growth requires synthesis of lot of different proteins and Unfolded Protein Response is activated to deal with the high flux of proteins processed through the Endoplasmic Reticulum to maintained homeostasis [31].

Recently, we have identified a new molecules family, Thiazole Benzensulfonamides, targeting specifically BiP, one of the most activated to deal with the high flux of proteins processed through the Endoplasmic Reticulum to maintained homeostasis [31].

Despite these recent progresses in melanoma treatment, more than 50% of patients will be in treatment failure. Therefore, identification of new potential targets is urgent to improve melanoma treatment. For example, MAPK pathway is not the only pathway deregulated in melanoma. PI3K/AKT pathway is the second most overregulated pathway in this pathology. This specific pathway presents 3 different druggable targets PI3K, AKT and mTOR. Concerning immunotherapy, new anti-PD-L1 antibody are currently under clinical evaluation and show early promise results (NCT01375842 and NCT01693562) [26,27]. Another pathway that could be interesting in melanoma treatment is JAK/STAT pathway. STAT3 have been implicated in targeted therapy resistance [28] and therefore is an attractive target. JAK/STAT pathway is also implicated in PD-L1 regulation [29] and could be targeted to enhance Nivolumab/Pembrolizumab efficiency. Other cellular processes could be also targeted like translation and proteins processing. For example, maintenance of the eukaryotic translation initiation factor eIF4F complex have been observed in BRAF V600 or MEK inhibitors resistance melanoma cells suggesting that dual inhibition of BRAF/MEK and eIF4F may overcome drug resistance [30]. Another promising strategy is the targeting of the Unfolded Protein Response pathway which appears as an emerging pathway to selectively target cancer cells. Indeed, neoplastic growth requires synthesis of lot of different proteins and Unfolded Protein Response is activated to deal with the high flux of proteins processed through the Endoplasmic Reticulum to maintained homeostasis [31].

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To conclude, in spite of the tremendous advances in melanoma treatment with development of targeted therapies and immunotherapies, new barriers appears concerning the handling of resistance. In this context targeting alternative pathways seems essential to bypass melanoma resistance.

ACKNOWLEDGEMENTS

M. Cerezo is a recipient of a postdoctoral fellowship from ARC.
S. Rocchi is supported by the INSERM, University of Nice Sophia-Antipolis, INSERM Transfert (COPOC grant), and ARC.

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