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Mini-review

Targeting drivers of melanoma with synthetic small molecules and phytochemicals

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ABSTRACT

Melanoma is the least common form of skin cancer, but it is responsible for the majority of skin cancer deaths. Traditional therapeutics and immunomodulatory agents have not shown much efficacy against metastatic melanoma. Agents that target the RAS/RAF/MEK/ERK (MAPK) signaling pathway – the BRAF inhibitors vemurafenib and dabrafenib, and the MEK1/2 inhibitor trametinib – have increased survival in patients with metastatic melanoma. Further, the combination of dabrafenib and trametinib has been shown to be superior to single agent therapy for the treatment of metastatic melanoma. However, resistance to these agents develops rapidly. Studies of additional agents and combinations targeting the MAPK, PI3K/AKT/mTOR (PI3K), c-kit, and other signaling pathways are currently underway. Furthermore, studies of phytochemicals have yielded promising results against proliferation, survival, invasion, and metastasis by targeting signaling pathways with established roles in melanomagenesis. The relatively low toxicities of phytochemicals make their adjuvant use an attractive treatment option. The need for improved efficacy of current melanoma treatments calls for further investigation of each of these strategies. In this review, we will discuss synthetic small molecule inhibitors, combined therapies and current progress in the development of phytochemical therapies.

Introduction

Melanoma is a malignant tumor of melanocytes, cells responsible for producing the skin pigment melanin. Of all skin cancers, melanoma is the least common, but because of its metastatic potential, it is responsible for approximately 80% of deaths related to skin cancer [1]. The American Cancer Society estimates that the lifetime probability of Caucasian men being diagnosed with melanoma is 1/35, while for Caucasian women it is 1/54 [2]. Furthermore, it is projected that there will be ~76,710 new cases of melanoma in the United States in 2014, and ~9710 of those cases will result in death [2]. Established risk factors for the development of melanoma include fair features (light skin, hair and eye color) and ultraviolet exposure. In particular, blistering sunburns early in life have been shown to play a causal role [3]. For cutaneous melanomas of low thickness (Breslow depths of up to 1.0 mm) surgery is curative for the majority patients [4]. Rates of survival drop precipitously with increased tumor thickness due to the increased risk of metastasis [4]. This transition from a mostly benign disease to one with a more serious prognosis occurs as melanoma progresses through the radial and vertical growth phases. The prognosis for metastatic melanoma is grim: 5-year survival ranges from 12–28%, depending on the location of the metastasis [4].

Traditional cytotoxic therapy and immunomodulatory agents have failed to demonstrate significant efficacy, with fewer than 5% of patients having complete responses at 5 years [5]. Fortunately, the last decade has been an exciting time for melanoma research, with advances in oncogene related therapies as well as immunotherapies. Immunotherapies that block inhibitory checkpoint molecules, CTLA-4 and PD-1, have been shown to improve survival for patients with metastatic melanoma and have gained FDA approval [6–8]. Likewise, pivotal advances in oncogene directed therapies have led to improvements in patient survival, resulting in FDA approval of agents that target the RAS/RAF/MEK/ERK (MAPK) pathway, such as vemurafenib, dabrafenib and trametinib. Yet, in spite of these

Abbreviations: OS, overall survival; MAPK, mitogen-activated protein kinase; RTKs, receptor tyrosine kinases; PI3K, phosphatidylinositide 3-kinases; GEFs, guanine nucleotide exchange factors; GAPs, GTPase-activating proteins; FTIs, farnesyltransferase inhibitors; mTOR, mammalian targets of rapamycin; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; PFS, progression-free survival; PIP2, phospholipid phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog; eIF4E, eukaryotic translation initiation factor; JAK-STAT, janus kinase–signal transducer and activator of transcription; MITF, β-catenin/microphthalmia-associated transcription factor; NFκB, nuclear factor kappa B; MMP, matrix metalloproteinase; AP-1, activator protein-1; α-MSH, alpha-melanocyte-stimulation hormone; EGCG, epigallocatechin gallate; IL-1β, interleukin-1beta; NLRP1, nuclear localization leucine-rich-repeat protein 1; FAK, focal adhesion kinase; XIAP, X-linked inhibitor of apoptosis protein; Bcl-2, B-cell CLL/lymphoma 2; PCNA, proliferating cell nuclear antigen; Mcl-1, induced myeloid leukemia cell differentiation protein; MST1, macrophage stimulating 1/hepatocyte growth factor-like.

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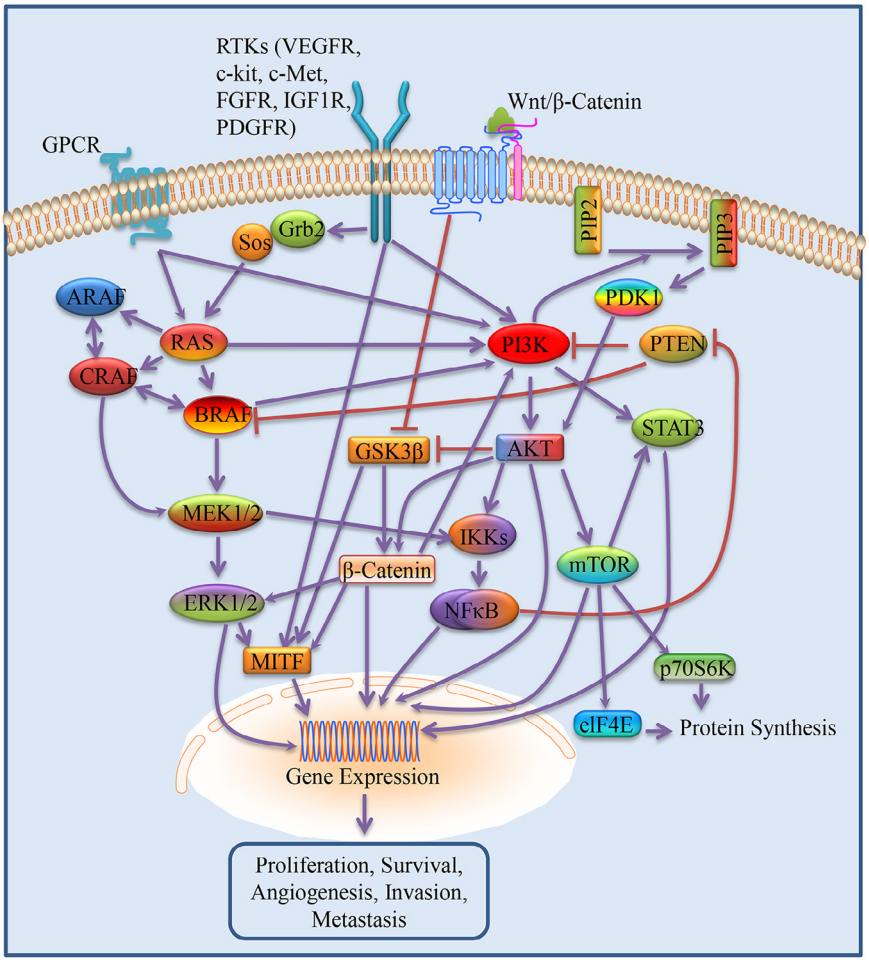

Fig. 1. Signaling pathways activated in melanoma.

advancements, the extension of life offered by these agents is only a matter of months due to the rapid development of resistance. Also, they only target a fraction of the oncogenic signaling that leads to melanoma. Current research in this area is focused on the discovery of additional inhibitors of the MAPK pathway and inhibitors of other pathways that play key roles in melanomagenesis and resistance, such as PI3K/AKT/mTOR (PI3K) and c-kit signaling. The study of combination therapy with existing agents and the further elucidation of mechanisms of resistance are also underway. Furthermore, preclinical studies of phytochemicals, both alone and in combination with traditional cytotoxic and targeted therapies, have recently yielded promising results. The relatively low toxicities of these substances make the adjuvant use of natural agents an attractive treatment option for metastatic melanoma. In summary, the need for improved efficacy of current melanoma treatments calls for innovative strategies, such as the elucidation of combination therapies, continued discovery of novel therapeutic targets, and preclinical investigation of natural agents as adjuvant therapy. In this review, we will discuss progress in targeting MAPK, PI3K, and c-kit signaling pathways, preclinical studies of phytochemicals, and combined oncogene directed therapies (Tables 1–3; Figs 1–3).

RAS/RAF/MEK/ERK (MAPK) signaling in melanoma

Activation of the MAPK has been described in roughly 90% of melanomas [9]. Activation of the MAPK pathway occurs when RAS-GTP causes RAF kinase dimerization [9]. An important target of activated RAF kinases is MEK1/2, which catalyzes the phosphorylation of ERK1/2 [10,11]. ERKs can translocate into the nucleus and regulate numerous cellular processes, including proliferation, differentiation, survival, motility, and angiogenesis [12].

RAS

Some of the first oncogenes described in humans were RAS proteins. Through cellular stimuli, such as receptor tyrosine kinases (RTKs), RAS transmits extracellular signals to intracellular effector pathways, which include the RAS/RAF/MEK/ERK (MAPK) and the PI3K/AKT/mTOR (PI3K) signaling pathways [13]. RAS signaling regulates a multitude of functions, including cell cycle progression, apoptosis, and differentiation [14,15]. The conversion between inactive RAS-GDP and active RAS-GTP is regulated by guanine nucleotide exchange factors (GEFs) and by GTPase-activating proteins (GAPs). GEFs promote the exchange of GDP for GTP leading to RAS activation. GAPs accelerate RAS-mediated GTP hydrolysis and lead to inactivation of RAS [16]. There are three main RAS isotypes: HRAS, KRAS, and NRAS [16]. The most common RAS gene mutation in melanoma is NRAS, which is mutated in 15–20% of all melanomas [17]. In accordance with the importance of NRAS mutations in maintaining melanoma cell growth, inactivation of NRAS in melanoma cell lines by RNA interference leads to induction of apoptosis [18]. The most common NRAS mutation is at codon 61; this prevents RAS GTP hydrolysis, causing the NRAS protein to be constitutively active [19,20]. Less common mutations at codon 12

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