RAC1 Activation in Metastatic Cutaneous Melanoma

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Metastasis is a complex process by which cancer cells escape from the primary tumor to colonize distant organs. RAC1 is a member of the RHO family of small guanosine triphosphatases that plays an important role in cancer migration, invasion, angiogenesis and metastasis.

RAC1 cutaneous melanoma invasion metastasis therapy resistance

1. Introduction

Melanoma is the most aggressive form of skin cancer representing more than 80% of deaths in cutaneous malignancies [1]. Metastasis is a complex process involving several steps, including migration, invasion, EMT (Epithelial-Mesenchymal Transition), angiogenesis, survival, plasticity and colonization of secondary tissues [2]. Metastatic cutaneous melanoma is a lethal disease with low survival rates, due to rapid acquisition of resistance to most available therapies [3].

Rho GTPases are important molecules that regulate cellular functions such as growth, motility, survival, migration, invasion, and metastasis thereby affecting tumor progression [4][5][6][7]. Rho GTPases are molecular switches that cycle between an active GTP and an inactive GDP bound form. RAC1 is one of the best characterized Rho GTPases that regulate crucial processes for melanoma tumorigenesis and metastasis. RAC1 activation is tightly regulated by activators, including guanine-nucleotide exchange factors (GEFs), and inhibitors, GTPase-activating proteins (GAPs) and guanine-nucleotide disassociation inhibitors (GDIs). In addition, RAC1 is regulated by modifications at its C terminus, including palmitoylation, carboxymethylation, and geranylgeranylation, as well as numerous post-translational modifications that influence its localization, activity, and ability to bind its effectors. RAC1 expression and activity are increased in human malignancies which in some cases correlates with aggressiveness and poor prognosis.

RAC1 signaling pathway is hyperactivated in human cancers and promotes tumor initiation, progression, and metastatic dissemination [8]. RAC1 point mutations and deregulated stability or subcellular localization have been identified as mechanisms that contribute to tumorigenesis and metastasis. Indeed, The Cancer Genome Atlas (TCGA) data shows that RAC1 is upregulated or mutated in over 10% of human cancers, including melanoma, glioblastoma, skin, esophageal, gastric, bladder, head and neck, liver, pancreatic, and prostate carcinomas [9][10]. RAC1P29S is the third most commonly mutated codon in human cutaneous melanoma, after BRAF V600 and

NRAS Q61, and one of the most prominent driver mutations in RAC1 with a frequency of approximately 5% and up to 10% in chronically sun-exposed melanomas [11].

RAC1P29S mutation leads to gain of function and enhances binding to target proteins PAK1 and MAP3K11 (MLK3) activating downstream RAC1 signaling. RAC1P29S has a particular role in early transformation, enhancing cell migration and proliferation [12]. Moreover, this mutation confers resistance to RAF and MEK inhibitors, thus having significance in clinical therapeutic strategies [13]. Interestingly, expression of RAC1P29S in melanoma patients correlates with PD-L1 upregulation contributing to evading antitumor immune response and potentially serving as a predictive biomarker for therapy resistance in melanoma [14].

RAC1 has been implicated in RAS-induced neoplastic transformation. Moreover, malignant melanocytes have elevated RAC1 activity during migration, invasion and metastasis. It has been described that deregulation of GEFs, such as Dbl, Vav, Trio, Ect2, Tiam-1 and P-REX-1 also contribute to aberrant RAC1 signaling in many types of tumors [15][16][17].

In addition, RAC1 signaling can modulate cell motility and invasion through a variety of mechanisms such as promoting membrane protrusions and regulating focal adhesions. RAC1 activation has also been shown to regulate the mode of cell movement to promote colonization of tumor cells. Efficient regulation of RAC1 signaling may be required for cell –cell adhesion, tumor cell migration and invasion during metastasis. Inhibition of RAC1 activity could represent an opportunity to develop novel therapeutic approach to target different stages of tumor cell metastasis [18].

During tumor progression, a significant remodeling of the extracellular matrix (ECM) is evident [19]. RAC1 is involved in invadopodia-mediated ECM degradation [20]. RAC1 activation drives motility by regulating lamellipodia formation, focal adhesions and MMP expression [21].

The best-understood effectors for RAC1 are the p21-activated protein kinases (PAKs). PAKs regulate a multitude of cellular processes including cell motility, survival, proliferation, and organization of the cytoskeleton [22]. PAK1 is overexpressed in a subset of BRAF wildtype melanomas. RAC1 mutant human melanoma cells are resistant to clinical inhibitors of BRAF but are uniquely sensitive to PAK inhibitors [23].

RAC1 can be shuttled from the cytoplasm to the nucleus and abnormal localization, particularly in the nucleus, has been detected in cancer cells. In the nucleus, RAC1 can induce nuclear alterations through nuclear actin promoting nuclear plasticity during invasiveness [24]. Moreover RAC1 localization and activity can be regulated by scaffolding mechanisms. Temporal and spatial localization of RAC1 is tightly regulated by protein-protein interactions [25][26].

RAC1 signaling is also involved in angiogenesis and required for vertical blood vessel sprouting associated with tumor-induced angiogenesis [27]. RAC1 plays an important role in the development of resistance to anti-VEGF therapy, suggesting that the combination of VEGF/VEGFR-targeted therapies with a RAC1 inhibitor may improve the efficacy of the anti-metastasic therapies [28].

2. RAC1 Pathway Activation in Melanoma Formation

There is a growing body of evidence indicating that an enhanced activation of RAC1, either through its overexpression, its hyperactivation by GEFs or the appearance of the P29S mutation, contributes to cutaneous melanoma formation, often associated with activating mutations in *BRAF* or *NRAS*, or inactivating mutation of *NF1* [13][14]. Although the exact downstream pathways by which RAC1 exerts its effects are still being unravelled, there are multiple studies pointing to possible mechanisms.

One of the possible signaling pathways of RAC1 in the promotion of melanoma is through its binding to Bcl-2. It has been shown that Bcl-2 phosphorylated at serine-70 (S70pBcl-2) confers apoptosis resistance to cancer cells [29]. Chong et al. described how RAC1-GTP binds to Bcl-2 leading to the accumulation of S70pBcl-2. Overexpression of RAC1 in melanoma cells increased ROS levels that inhibited PP2A preventing thereby dephosphorylation of Bcl-2. The authors describe a positive feedforward loop between RAC1-GTP and S70pBcl-2 sustaining an anti-apoptotic signaling in these cells [30].

In addition, RAC1P29S has been reported to increase the expression of PD-L1, not only with exogenous expression of RAC1P29S in vitro, but also with endogenous expression in melanoma patients. The exact mechanism by which the oncogene increases the levels of PD-L1 is still unknown, but the authors postulate that this increment helps melanomas to evade the immune system and thereby facilitates its growth [14].

A direct target protein of RAC1 is the lipid kinase phosphatidyl inositol-3 kinase (PI3K)-β [31][32]. Indeed, treatment with selective inhibitors for PI3Kβ in melanoma cell lines harboring the RAC1P29S mutation showed a decrease in proliferation [33]. Other PI3K selective inhibitors, including PI3Kα, δ and γ, appeared to be less effective. Another study relating AKT signaling to survival described how melanocytes with endogenous RAC1P29S had a higher survival rate when cultured in the absence of growth factors or in an anchorage-independent condition. With the use of siRNA and small molecules, the authors were able to associate these events to AKT signaling [34].

RAC1P29S can induce ERK phosphorylation in melanocytes [9]. This capacity of activating MAPK pathway also plays a role in protecting melanoma cells with *RAC1* and *BRAF* mutations from apoptosis when treated with RAF inhibitors. The authors claim that RAC1P29S sustained the levels of pMEK and pERK in the presence of inhibitors and that these levels decreased following RAC1P29S knockdown [13]. In line with the role of RAC1 in this MAPK pathway are the PAKs, one of the best characterized effectors for RAC1 [22]. These proteins promote, among other processes, cell survival and proliferation by phosphorylating different substrates. PAKs have been described as key components of the ERK pathway, not only due to their kinase activity (they are able to phosphorylate c-RAF at S338 and MEK1 at S298), but also to their scaffolding function [35]. Inhibiting PAKs function with Frax-1036 in melanoma cells harboring RAC1P29S mutation, resulted in marked reduction of proliferation and viability. These results were corroborated in in vivo xenograft experiments [23]. Lionarons et al. also described decreased proliferation after genetically inhibiting PAK in their animal model [34]. These results point to a RAC1-PAK- MEK-ERK pathway in the formation of melanoma.

3. RAC1 Signaling in Tumor Cell Migration and Invasion

Cell migration is required for many processes such as embryogenesis or wound healing, but when deregulated it contributes to dissemination of cancer metastases. Melanoma cells can invade not only the dermis, but also other organs such as the lungs, the liver or the brain [36]. RAC1, as a pivotal regulator of the cytoskeleton, plays a main role in this process. It drives motility by promoting among others, lamellipodia formation, focal adhesions and MMP expression [37].

Tumor cells can switch between two different modes of movement. RAC1 is responsible for directing mesenchymal movement, characterized by an elongated cellular morphology and the requirement of extracellular proteolysis. Sanz-Moreno et al. discovered that when activated, RAC1 suppressed RHOA dependent amoeboid movement through decreasing actomyosin contractility. An important RAC1 effector is WAVE2, a member of the WASP-family verprolin-homologous proteins. These proteins regulate the actin cytoskeleton and therefore have an important role in cell migration and invasion. The authors were able to trace decrease in phosphorylation of Myosin Light Chain (MLC) to WAVE2 [38]. Another study pointing to the importance of WAVE2 as a RAC1 effector, described how in mouse melanoma cells with ectopic overexpression of constitutive active RAC1, there was an increase in invasiveness that was reverted by WAVE2 RNAi [39]. Regulation of the cytoskeleton by WAVEs takes place through the activation of the actin nucleation complex ARP2/3 [40] which in turn leads to the activation of SRF/MRTF inducing a transcription program in melanocytes that leads to mesenchymal transition [34].

Another pathway regulated by RAC1 that plays an important role in melanoma is PI3K-AKT, which has also been described to play a role in EMT [41] and migration [42][43]. PI3K -RAC1 activation regulates EMT in melanoma cells and promotes metastasis.

Regarding MMP expression, there is a study that relates MMP-2 to RAC1 in melanoma cells. The authors saw how P-REX1 (PIP3-dependent RAC exchange factor-1), a guanine nucleotide exchange factor that activates RAC1, regulated cell migration and invasion. Cells bearing overexpression of P-REX1 had increased RAC1-GTP, p-PAK1, p-p38 and MMP-2 levels. To further confirm their results, they used RAC1 and p38 inhibitors in control cells and in P-REX1 knockdown cells. Control cells exhibited a pronounced inhibition in migration and invasion, whereas P-REX1 knockdown cells showed no changes. These results highlight the importance of the P-REX1/RAC1/PAK1/p38/MMP-2 pathway in migration and invasion of melanoma cells [43].

RAC1 regulation of invadopodia in melanoma is controversial. Revach et al. observed how expression of wildtype RAC1 in cells led to invadopodia formation, whereas RAC1P29S harbouring cells, with higher migration rate, showed suppressed invadopodia and matrix degradation, but enhanced lamellipodia formation. These confusing results point to different signaling pathways for wildtype and mutant RAC1. Disassembly of invadopodia has been related to a TRIOGEF-RAC1-PAK1-cortactin pathway [44]. Increased number of lamellipodia in melanoma cells expressing mutant RAC1 compared to wildtype has also been described by Mohan et al. [45]. In this study the authors describe how RAC1P29S induced an enhanced lamellipodial branched actin network conferring the cells higher migration and the ability to sequester and phosphoinactivate Merlin, a tumor suppressor known to

downregulate cyclin D1 and prevent cell cycle progression [46]. Interestingly, the authors demonstrate how for the inactivation of Merlin, both PAK activation and the branched actin polymerization driven by mutated RAC1, are necessary. RAC1 through PAK1, Merlin and the cytoskeleton renders the melanoma cells a higher metastatic potential and higher proliferation rate of metastatic cells.

RAC1 not only exerts its pro-metastatic effect through the actin cytoskeleton, but also through its ability to act on the microtubule cytoskeleton. We showed how through PAK1, constitutive active RAC1 acted on the microtubules, and through the Linker of Nucleoskeleton and Cytoskeleton (LINC) complex, connected to the nucleoskleton and induced nuclear plasticity. This allowed the cells to pass through smaller pores and promoted a more invasive phenotype. Disrupting the LINC complex prevented melanoma cells from undergoing invasion [47].

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