

## Cell metastasis in Melanoma

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### ABSTRACT

*Cutaneous melanoma stands out as a model disease on which to study tumor progression and metastasis for several reasons. If undetected or diagnosed late, melanoma is a highly invasive tumor and almost invariably leads to metastatic spread. It tends to metastasize at a time when the tumor burden is low compared to other cancers, which is evident by the size (thickness) of the primary tumor being measured in millimeters. The fact that the majority of the almost 70,000 new melanomas diagnosed in the United States every year are detected when they are still curable, is presumably largely owed to its prominent site of origin, the skin. As a consequence, tissue from early stages of tumor development is relatively easily available for analysis, allowing for the investigation of the whole spectrum of tumor progression and the metastatic process in humans.*

*It is somewhat surprising that comparative genomic approaches to date have not yet consistently identified gene signatures reflecting genes or gene sets that are associated with metastasis or prognosis of melanoma. Nevertheless, tremendous progress has been made in recent years identifying mechanisms leading to metastasis in melanoma. In this review, we highlight some of the key molecules and pathways that have been discovered as drivers of metastatic progression in this disease.*

### INTRODUCTION

The incidence of melanoma continues to rise and it is expected that in 2011 almost 9,000 patients will die from this disease in the United States [1]. Despite recent exciting progress in the treatment of patients with advanced melanoma,

such as the use of agents targeting oncogenic driver mutations and antibodies blocking immune-checkpoints such as CTLA-4 [2-4], the prognosis of most patients remains poor once the tumor has metastasized to distant organs. Most melanomas initially progress from an *in situ* to a radial growth phase (horizontal spread of small cell clusters

within the epidermis and papillary dermis), subsequently to a vertical growth phase (vertical spread of nodules of tumor cells into the papillary dermis, reticular dermis, or subcutaneous tissue), which is associated with a higher tendency for metastatic spread. While many melanoma patients with metastases to the regional lymph node basin are still curable by surgical resection, lymph node metastasis is associated with increased risk for distant metastases and significantly decreased overall survival [5]. Metastasis is therefore the key prognostic factor limiting outcome in melanoma patients. As a result, it is critical to understand the molecular mechanisms that are responsible for the metastatic behavior of melanoma cells.

Organ-specific metastasis is guided by many different molecular mechanisms. The long-held view that only a small fraction of a primary melanoma has the potential for metastasis, has been called into question in recent years based on molecular profiling of tumors that identified gene signatures in primary tumors that are correlated with the probability of metastatic spread [6]. Several characteristics are required for the capacity of tumor cells to metastasize: motility, the ability to invade the adjacent tissue and enter into the circulation, to survive the transit, re-entry into tissue at a distant site, and colonize a distant organ while evading tumor surveillance [7]. In this mini-review we discuss recently described key pathways and molecules operational in the metastatic behavior of melanoma cells.

## GENE EXPRESSION PROFILING

Different comparative genomic approaches such as microarray analysis, real-time PCR, and next generation sequencing have been employed to define transcriptional signatures of melanoma progression and metastasis. A large-scale gene expression analysis in melanoma was performed on melanoma cell lines with low versus high metastatic potential and identified differences in genes playing a role in extracellular matrix assembly and regulation of the actin-based cytoskeleton [8]. Gene expression profiling of primary melanomas and metastases from different sites using biostatistical and functional analyses revealed different gene clusters linked to melanoma aggressiveness, many genes also involved in the regulation of the cytoskeleton and the extracellular matrix [9]. More recently, gene

expression profiling of more than one hundred primary melanomas revealed a set of 254 genes that were linked to the development of metastases. Many of the genes identified are coding for molecules that are members of functional groups such as cell cycle regulation, mitosis, and DNA replication [10]. Distinct gene expression signatures for different stages of melanoma progression have also been identified by comparative gene expression analysis of primary melanoma versus metastatic tissue, benign melanocytic nevi, and different subtypes of melanomas [11-12]. Of note, gene expression signatures observed in metastatic melanoma tissue were found in melanoma primaries of different origin, suggesting that metastatic signatures can be imprinted in the primary tumor, a notion that is different from the concept that only a small number of clones within a primary tumor have the ability to metastasize [11]. Nevertheless, the identification of a consistent, reproducible prognostic or metastatic gene signature has so far been elusive in melanoma. With rare exceptions, no overlapping genes have been reported in microarray studies published to date. Potential reasons for this include the heterogeneity of analyzed tissue (poorly characterized or mixed histology of primary tumors), variable sites of metastases, differing array platforms and biostatistical approaches, insufficient clinical annotation of samples, small patient cohorts, and lack of validation on independent data sets [13].

## CHEMOKINES

Human chemokines are a superfamily of secreted receptor ligands with many functions, most prominently the ability to induce cell migration. Chemokines or their receptors have been implicated in the control of metastatic spread, directing tumor cells towards specific tissues [14-17]. CXCR4 is widely expressed on many different cancers and the CXCL12–CXCR4 axis has been found to be of particular relevance for tumor cell migration to the lung, liver, and bone marrow [18]. CXCL12, the unique ligand for CXCR4, is highly expressed at sites of melanoma metastasis [19]. CXCR4 expression of primary melanomas was found to be associated with decreased time to progression and survival [20]; CXCR4 was also expressed in more than 50% of human melanoma metastases [21]. Even early in melanoma

metastases from sentinel lymph nodes, CXCR4 expression was correlated with an increased risk for progression [22]. Transfection of the murine B16 melanoma line with CCR4 leads to increased metastases to the lung [23]. The adhesion of CXCR4 expressing B16 melanoma cells to endothelial cells was shown to be mediated *in vitro* and *in vivo* via beta 1 integrin through CXCL12 [24].

In addition to the CXCL12-CXCR4 axis, other chemokines contribute to site-specific melanoma metastasis. CCR7 has been demonstrated to directly control melanoma cell migration to the lymph nodes. A non-metastatic mouse melanoma line that did not express chemokine receptors metastasized to the lymph node upon transfection with CCR7 [25]. In B16 murine melanoma, there is evidence that CCR10 promotes lymph node metastasis, possibly by enhanced survival of melanoma cells in the lymph node because of immune evasion [26].

In humans, the CCR9/CCL25 axis was recently found to be critical in the migration of melanoma cells to the small intestine, potentially explaining the relatively high incidence of this somewhat unusual metastatic site for solid tumors that occurs more commonly in melanoma patients [27]. In this study, 88 of 102 (86.3%) patients with small bowel metastases expressed CCR9 as measured by qRT-PCR, whereas no CCR9 expression was detected in any of the 96 distant metastases from other sites. In a separate study, 64% of patients with expression of CCR9 in their primary melanomas and 45% of patients with expression of CCR9 in locoregional lymph node metastases ultimately developed small bowel metastases, suggesting that small bowel metastasis could be predicted by RT-PCR or immunohistochemistry (IHC) for CCR9 at an early stage in these patients [28].

## MICRORNAS

The alteration of microRNA (miRNA) profiles is an attractive concept to account for metastatic potential of tumor cells, because miRNAs can control multiple target genes simultaneously. As a consequence, different cellular processes can be affected by one miRNA [29]. miRNA signatures have been identified by expression profiling of different tumors and associated with tumor stage and prognosis [30]. Relatively high expression levels of miR-30b and -30d were recently found in

metastatic melanoma tissue from 59 patients by miRNA array analysis and RT-PCR validation [31]. Of note, in a subset of 17 paired samples from the same patient, both miRNAs were significantly overexpressed in the metastatic tissue compared to the primary tumor. Furthermore, miR-30b and -30d expression in melanoma primaries was correlated with tumor thickness, nodular (more invasive) tumor type, and the rate of metastasis. Importantly, overexpression of miR-30d/30b increased melanoma invasiveness *in vitro* and metastatic potential *in vivo* in a B16 melanoma mouse model, whereas miR-30d/30b silencing produced the opposite effects. The effect was mediated predominantly by the GalNAc transferase GALNT7. Importantly, miR-30b/30d-mediated repression of GALNT7 resulted in increased production of the immunosuppressive cytokine IL-10 with accumulation of T-regulatory cells and decreased recruitment of CD3+ T cells, suggesting that miR-30b/30d-GALNT7 might be mechanistically involved in the immunosuppressive milieu of melanoma metastases.

Conversely, another miRNA, miR-211, whose expression is restricted to the melanocyte lineage, was recently linked to decreased invasiveness and reduced migration of melanoma cells. IGF2R, TGFBR2, and NFAT5, whose role in melanomagenesis had been previously established, demonstrated inversely correlated expression with miR-211 and were identified as miR-211 biological target genes [32].

## METALLOPROTEINASES

Tumor cells have the ability to disrupt the physiologically tight control of extracellular matrix proteases, allowing for proteolytic activity on basement membranes and extracellular matrices. The activity of matrix metalloproteinases (MMP) has been associated with cancer metastasis and results not only in increased tissue invasion, but also in the generation of bioactive peptides. One of these peptides, cryptic collagen epitope HU177, has been related to angiogenesis and tumor growth *in vivo* [33]. Increased serum titers against HU177 in patients with primary melanomas have been associated with increased tumor thickness, increased recurrence rates, and poor survival, suggesting its likely relevance in the metastatic process [34-35].

Both MMP-8 and MMP-27 are frequently mutated in melanoma; wild-type MMP-8 is associated with decreased melanoma progression suggesting that it is a tumor suppressor gene [36]. MMP-19 expression correlates with increased invasion, migratory behavior and early metastasis of melanoma cells, whereas MMP-9 expression was decreased with increasing thickness of melanomas [37-38]. MMP-1 and MMP-2 have also been linked to melanoma progression [39-40]. Interestingly, MMP-2 specific CD4+ T cells, exhibiting a detrimental inflammatory Th2 profile (secreting mainly TNF- $\alpha$ , IL-4, and IL-13) were recently found in tumor infiltrating lymphocytes of melanoma patients [41]. Comprehensive mutational analysis of another metalloproteinase family, ADAMTS, found that ADAMTS-18 is highly mutated in melanoma patients and linked to increased proliferation, cell migration, and metastasis [42].

## TGF-BETA

TGF-beta is secreted by tumor cells and different cell types within the tumor microenvironment and promotes invasion and metastasis through various auto- and paracrine loops (in contrast to its anti-proliferative, tumor suppressive role in early carcinogenesis) [43]. It induces epithelial mesenchymal transition, leading to tumor invasion and ultimately metastasis through changes in the expression of cell-cell adhesion molecules and the activity of metalloproteinases [44]. Increased TGF-beta 1 and 2 plasma levels have been found in patients with metastatic melanoma. TGF-beta signaling through the Smad pathway has been linked to increased extracellular matrix invasiveness, increased anchorage independent growth, and the production of pro-metastatic molecules such as osteopontin, IL-11, and CXCR-4. The transcription factor GLI2, whose activation to a great extent depends on autocrine TGF-beta signaling, was recently found to mediate critical steps in melanoma progression, such as loss of E-cadherin and transition to N-cadherin expression, mesenchymal transition, and increased invasiveness of melanoma cells [45]. Since GLI2 is a critical substrate that is necessary for response of the hedgehog (HH) pathway, cross-talk between the TGF-beta and HH pathways may induce a positive feedback loop, promoting tumor progression and metastasis [46]. TGF-beta leads to

MMP-2 upregulation in several cancers and expression of the two proteins has been found to be correlated in plasma from advanced melanoma patients [47]. Intravital imaging and microarray analysis of B16 melanoma tumors demonstrated that TGF-beta signaling can reverse features that are characteristics of differentiated melanocytes and increase cell motility [48].

## MELANOMA METASTASIS AND EMBRYONIC DEVELOPMENT

Increasing evidence for a link between embryonic development and metastasis has recently emerged in melanoma. Several melanocyte developmental transcription factors, such as TWIST, YANG, SLUG, and MITF, have been found to be critically important for metastatic progression in this disease. MITF is a member of the microphthalmia-related transcription factors which are important for growth, differentiation, expression of melanogenic enzymes, and survival of melanocytes. It is considered a lineage-specific master regulator of melanocytic differentiation. In melanoma, it was identified as a "lineage addiction" oncogene and found to be amplified in 10-20% of melanomas [49-50]. MITF amplification correlated with BRAF mutation, p16 inactivation, and was found to be more common in metastatic melanoma. It was also linked to decreased overall survival of melanoma patients. The contrasting roles of MITF in melanocytes versus tumor cells remain largely unexplained. The "phenotype switching" model attempts to reconcile the contrasting MITF activities by linking two distinct transcriptional melanoma cell signatures with either high MITF expression (proliferative) versus low MITF expression (invasive) [51].

Nodal, a member of the TGF-beta superfamily, was recently identified as a signaling pathway in melanoma that is linked to an aggressive phenotype. Inhibiting Nodal signaling reduced invasiveness of melanoma cells as well as their ability to form vascular networks on a three-dimensional collagen matrix. Furthermore, Nodal was expressed in 60% of human melanoma skin metastases, whereas it was absent in the primary tumors as measured by IHC [52]. The prominence of this pathway at the interface of embryonic and tumorigenic pathways also underscores the importance of the TGF-beta superfamily in the metastatic process of melanoma [52].

A comparative oncogenomics approach was used to identify NEDD9 (Neural precursor cell expressed, developmentally downregulated), a member of the family of adapter molecules, as an important melanoma metastasis gene [53-54]. The Nedd9 protein is a component of the focal adhesion complex, which is critical for cell invasion and was shown to play an important role in cell invasion and the development of metastases in melanoma. Using quantitative RT-PCR and IHC on tissue microarrays, overexpression of NEDD9 at the transcript and protein levels was confirmed in 35%–52% of human metastatic melanomas.

Most recently, in a conditional melanoma mouse model based on melanocyte-specific PTEN loss and the BRAF<sup>V600E</sup> activating mutation, the  $\beta$ -catenin/wnt signaling pathway was identified as a critical mediator of metastasis [55]. Importantly, the genetic alterations and cellular phenotypes studied in this mouse model were very similar to human melanoma.

## CONCLUSION

In conclusion, the spectrum of biological processes and molecules implicated in melanoma cell metastasis is extensive. Gene expression profiling studies of primary and metastatic

melanomas including a recent meta-analysis have not produced a uniform signature that would be suitable as a predictive or prognostic marker. Future approaches in this arena need to control more stringently for homogeneous clinicopathological staging of the patient cohorts under investigation, consistently include independent validation cohorts, and provide sufficient clinical outcome data. Rapidly evolving new technologies such as comparative genomic approaches and the identification of new classes of molecules such as miRNAs have led to the discovery of novel molecules, many of whom are potential drug targets or candidates for biomarkers. Unexpected associations such as the role of matrix metalloproteinases in the immune response to melanoma open up potential new avenues for therapeutic intervention. Further advancement in our understanding of melanoma genomic alterations interactions with host factors in the tumor microenvironment such as immune responses will provide additional opportunities for therapeutic intervention.

## CONFLICT OF INTEREST

The authors have no conflict of interest.

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