Cell Adhesion Molecules in Plasticity and Metastasis

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ABSTRACT

Prior to metastasis, modern therapeutics and surgical intervention can provide a favorable long-term survival for patients diagnosed with many types of cancers. However, prognosis is poor for patients with metastasized disease. Melanoma is the deadliest form of skin cancer, yet i*n situ* and localized, thin melanomas can be biopsied with little to no postsurgical follow-up. However, patients with metastatic melanoma require significant clinical involvement and have a 5-year survival of only 34% to 52%, largely dependent on the site of colonization. Melanoma metastasis is a multi-step process requiring dynamic changes in cell surface proteins regulating adhesiveness to the extracellular matrix (ECM), stroma, and other cancer cells in varied tumor microenvironments. Here we will highlight recent literature to underscore how cell adhesion molecules (CAM) contribute to melanoma disease progression and metastasis.

Introduction

Despite recent therapeutic advancements, metastatic melanoma remains the deadliest form of skin cancer with an estimated 6,850 deaths from 100,350 diagnoses in 2020 (www.cancer.org). Mortality is largely attributed to metastases of the central nervous system, lungs, and liver. Metastatic dissemination requires dynamic plasticity of cell adhesion molecule (CAM) expression to regulate the adhesiveness and intercellular communication within the tumor microenvironment. CAMs are a large family of cell surface proteins that mediate attractive or repulsive forces to the extracellular matrix (ECM), stroma, and other cancer cells, playing a significant role in modulating the invasive and proliferative phenotypes of melanoma. This review offers an update to prior articles (1–7), providing a broad overview of recent literature illustrating how CAMs contribute to melanoma disease progression. We limit our review to select CAMs of the integrin, cadherin, IgSF, connexin, and mucin families, focusing on the varied roles CAMs play in the metastatic process and the implications of CAM expression as both prognostic determinants and therapeutic targets in melanoma (**Table 1**).

Phenotype Switch

Metastatic dissemination is a complex stepwise alteration of gene programming that enables colonization of distant organs. To facilitate this, cancers of epithelial origin undergo epithelial–mesenchymal transition (EMT), where primary malignancies gain invasive properties and lose features maintaining cellular polarity and context-specific adhesions (8, 9). Melanoma disease progression differs from this as melanocytes are more mesenchymal in nature (10). Melanocytes arise from the neural crest: a multipotent lineage in development that manifests from the neuroepithelium, a component of the neural ectoderm (11). Here a combination of ligand-directed signaling and dynamic changes in contact-mediated cues induce a subset of cells to delaminate and migrate away from the neural tube (11, 12). These highly motile, melanin-producing cells termed melanoblasts employ complex spatial sensing to ultimately position themselves among keratinocytes at the dermal–epidermal junction (13–15). Through paracrine and adhesion signals, keratinocytes instruct melanoblasts to further differentiate into nonmotile, highly dendritic melanocytes where each melanocyte interacts with approximately 30 keratinocytes (3, 16). During melanocyte development, aspects of both EMT and mesenchymal-to-epithelial transition (MET) are dynamically utilized, a trait that may underlie the plastic nature of melanoma progression.

While melanoma are not epithelial cells and thus cannot undergo true EMT, EMT-like changes occur and are necessary for melanoma to metastasize. The gene-programming alterations in melanoma are collectively referred to as the "phenotype switch" (17, 18), a plastic and dynamic modulation between proliferative and invasive states (17, 19–21). Phenotype switching can be regulated by several factors including: Wnt signaling (22), endothelins (20), BRN2 (23), CD271 (24), among others; however, the prominent regulator is microphthalmia-associated transcription factor (MITF) (25, 26). High MITF expression is associated with enhanced proliferation and increased sensitivity to BRAF and MEK inhibitors (7, 27, 28). Conversely, low MITF expression is associated with a more drug resistant and invasive state (**Fig. 1**; refs. 7, 27, 28). Of note, both gene-programming states were identified by single-cell RNA-sequencing within individual tumor lesions (29), suggesting intralesional heterogeneity, and thus may represent a "moving target" for therapeutic approaches. Indeed, recent work highlights increased growth and invasiveness of heterogeneous melanoma populations compared with tumors with little variation in the phenotype switch gene-programming spectrum (**Fig. 2**; refs. 27, 30). The phenotype switch underlies the dynamic changes in CAM expression outlined below.

Integrins

Integrins are a family of heterodimeric cell surface proteins which adhere to the ECM and serve as a signaling nexus (31). With at least 18 alpha and 8 beta subunits, 24 heterodimers are known to exist (32). Integrins can receive and transduce signals from a variety of extracellular ligands (32); a process that plays a profound role in normal melanocyte development and function, cancer progression, and metastatic tropism (33–37).

Integrin-based signal transduction is often mediated by association with intermediaries recruited to activated integrin heterodimers (38).

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Table 1. Select cell adhesion molecules, role in melanoma, and therapeutic progress.

CAM	Role in melanoma	Therapy	Progress	References
Cadherin-11 (CDH11)	Metastatic suppressor, inactivation promotes cancer dissemination (114)	Anti-CDH11 miR-335 mediated mAb treatment	Preclinical *in vivo* studies against breast cancer	212
CEACAM1	Implicated with enhanced melanoma motility and invasiveness. Indicator of melanoma disease progression (137–139)	Novel mAb (MRG1) targeting CEACAM specific N-domain	Preclinical *in vivo* studies against melanoma	147
Connexin 43 (Cx43) Connexin 26 (Cx26)	Form gap junctions, facilitate pro-tumor processes, associated with CNS tropism (171)	Combination dioscin with HSV-tk/GSV gene therapy treatment	Preclinical *in vivo* studies against melanoma	213
		Oleamide and oleamide derivatives	Preclinical *in vivo* studies against melanoma	214, 215
Integrin αv	Consists of all integrins with the αv subunit. Promotes cancer progression and therapy resistance (37)	Abituzumab	Preclinical *in vitro* studies against prostate cancer, completed Phase II clinical trial in metastatic castration resistant prostate cancer (NCT01360840) and Phase I/II trial in metastatic colorectal cancer (NCT01008475).	66–68
Integrin αvβ3/αvβ5	Role in melanoma progression and therapy resistance. Widely considered tumor markers and can increase tumor survival and invasiveness (37, 42, 54)	αvβ3-specific CAR T-cells (lower affinity hLM609v11, higher affinity hLM609v7)	Preclinical *in vivo* studies against melanoma	55
		ROS generating drug (bioengineered $DLDH^{RGD}$)	Preclinical *in vivo* studies against melanoma	53
		RGDechi-hCit (αvβ3 selective peptide antagonist)	Preclinical *in vitro* studies against melanoma	58
		Tetrastatin (230 amino acid sequence from collagen IV)	Preclinical *in vivo* studies against melanoma	85
		Cell-targeted c(AmpRGD)-sunitinib molecular conjugate	Preclinical *in vivo* studies against melanoma	56
		Fully human anti-αv (β3 and β5) integrin monoclonal antibody intetumumab (CNTO 95)	Completed several clinical trials, including Phase I/II trial in melanoma (NCT00246012) and Phase II trial in metastatic hormone refractory prostate cancer (NCT00537381)	70, 216
		Cilengitide (EMD 121974)	Completed a Phase II clinical trial (NCT00082875) against metastatic melanoma. Completed multiple clinical trials against other cancers, including non-small cell lung cancer (NCT01118676), prostate (NCT00121238) and gliomas (NCT00679354), among others.	63, 217
		MK-0429 (selective ITGαvβ3 inhibitor)	Preclinical *in vivo* studies against melanoma	218
		Abergrin (etaracizumab, MEDI-522) humanized mAb	Completed Phase I/II clinical trials (NCT00111696, NCT00066196) against melanoma.	37
Integrin α5β1	Proangiogenic factor (37)	Volociximab (M200, chimeric mAb)	Completed Phase II clinical trial (NCT00099970) against melanoma. Completed clinical trials against non-small cell lung cancer (NCT00654758, NCT00666692), ovarian and primary peritoneal cancer (NCT00635193) and metastatic pancreatic cancer (NCT004015700	210, 219, 220
		ATN-161 (peptide antagonist)	Phase II clinical trial against renal cancer (NCT00131651) and Phase I/II clinical trial against recurrent malignant glioma (NCT00352313)	37

(Continued on the following page)

Table 1. Select cell adhesion molecules, role in melanoma, and therapeutic progress. (Cont'd)

CAM	Role in melanoma	Therapy	Progress	References
L1CAM	Transmembrane glycoprotein with increased expression in metastatic melanoma (131, 132)	L1–14.10 (IgG1 isotype) and L1–9.3/2a (IgG2a isotype) antibodies	Preclinical *in vivo* studies against ovarian and pancreatic carcinoma	161
MCAM (CD146)	Indicator of poor prognosis and implicated in the S100A8/A9 axis. Considered a melanoma biomarker (155–157)	Utility in circulating tumor cell (CTC) analysis	Preclinical *in vitro* studies against melanoma	152
		Anti-CD146 mAb	Preclinical *in vivo* studies against bone metastasis in prostate cancer.	221
Muc1	Highly glycosylated protein promoting cell-cell interactions, can lead to loss of adhesion when dysregulated (174, 186)	mAb 3D1-MMAE antibody-drug conjugate	Preclinical *in vivo* studies against breast cancer	187
N-cadherin (CDH2)	Mediates homophilic interactions between melanoma cells and stromal components. Expression associated with metastasis and poor prognosis (92, 110, 113)	N-cadherin interfering peptide ADH-1	Completed Phase II trial against melanoma (NCT00421811), among others.	18, 126, 127
		MiRNA-145	Preclinical *in vivo* studies against lung adenocarcinoma	222
		Metformin	Preclinical *in vitro* studies against prostate cancer	223
		mAb against conserved HAV sequence in N-cadherin	Preclinical *in vivo* studies against prostate cancer	224
NCAM (CD56)	Increases melanoma invasiveness and metastasis through Wnt and Akt/mTOR signaling (150, 151)	Promiximab	Preclinical *in vivo* against small cell lung cancer	225
		Lorvotuzumab Mertansine (IMGN901, Anti-CD56 antibody conjugated to a linker drug for cytotoxic effects)	Preclinical *in vivo* against small cell lung cancer. Completed Phase I/II clinical trial in leukemias (NCT02420873)	226, 227

For instance, integrin-linked kinase (ILK) is known to regulate dendricity and motility of melanoblast colonization in normal development (35). Paralleling this, ILK activity correlates with increased metastasis and poor prognosis in with melanoma (39, 40). Other integrin associated factors, such as ADAR-1, matrix metalloproteinase-16 (MMP16), and HACE1 are known to be direct effectors of integrin activity in melanoma (41–43).

Integrin interaction with ECM-associated molecules like biglycan can enhance invasiveness and regulate melanoma cell and tumor microenvironment stiffness (44, 45). Melanoma cells can also secrete their own ECM, a process that influences integrin binding and thus signaling. Interestingly, BRAF inhibitor treatment is known to enhance ECM deposition (46, 47) and induce integrin surface reorganization (48). These phenomena contribute to reactivation of ERK1/2 signaling and cell survival providing an ECM-related mechanism for resistance to targeted inhibitors (48).

Recent data indicate that alignment, concentration, and stiffness of matrix fibers has a significant impact on metastatic proclivity across many cancer types, including melanoma (49–51). For instance, a bell-shaped curve can be fit to melanoma invasiveness; a behavior dependent on collagen concentration (**Fig. 2**; ref. 50). Given that melanoma incidence rises with age (49), understanding how age-related changes impact the ECM and tumor microenvironment is paramount. As recently reviewed, the interplay between the ECM/stroma and melanoma can dictate plasticity, gene expression, and may represent novel therapeutic avenues (52).

Drugs targeting integrins can include antibody, peptide, or small-molecule–based agents designed to interfere with integrin–substrate binding or used as a delivery vector for cytotoxic moieties (33, 37, 53). As an example, αvβ3 integrin is known to play a predominant role in melanoma progression and therapy resistance (37, 54). Because of its overrepresentation, this heterodimer has been the focus of therapeutic strategies ranging from a CAR T-cell target (55) to designer drug fusions (53, 56, 57) to direct peptide-based antagonism (58). Cilengitide (EMD121974), a prominent RGD-based αvβ3, αvβ5 targeting agent, held significant preclinical promise in multiple cancer models including melanoma (59–62); however, this agent has been disappointing in solid tumor clinical trials (63, 64). Integrin αv is also the target of abituzumab (EMD 525797), a mAb (65). Abituzumab has preclinical efficacy in prostate cancer model systems (66), but demonstrated modest effects in the clinic (67, 68). Common themes of poor efficacy with anti-integrin–targeting agents center around inappropriate preclinical model systems for proper evaluation and the inherent redundancy/overlap of integrin function, among other considerations (69). Clinical trials of integrin-targeting agents have issues with specificity, efficacy and toxicity, yet remain promising targets due to well established connections between aberrant integrin expression and cancer (37, 63, 69–72).

Surface expression of integrins can influence the metastatic tropism of melanoma (37, 73–75). Metastatic tropism is the inherent tendency of a primary cancer to metastasize to a specific organ (76). This varies significantly between different cancer types and can have unique temporal kinetics. For instance, prostate cancer is highly tropic to the skeletal system with a long latency, whereas melanoma can quickly metastasize to multiple organs including the brain, lungs, and liver (76, 77). Recently, melanoma derived integrin containing exosomes have been shown to prepare distant sites for eventual metastatic colonization (37, 78); a phenomenon that may be underpinned by the RAB GTPase, RAB27A (**Fig. 2**; ref. 79). Peptide-based integrin blocking agents prevented tumor exosome adhesion in metastatic locations, highlighting a potential therapeutic avenue (78). Integrin interaction with TGFβ1

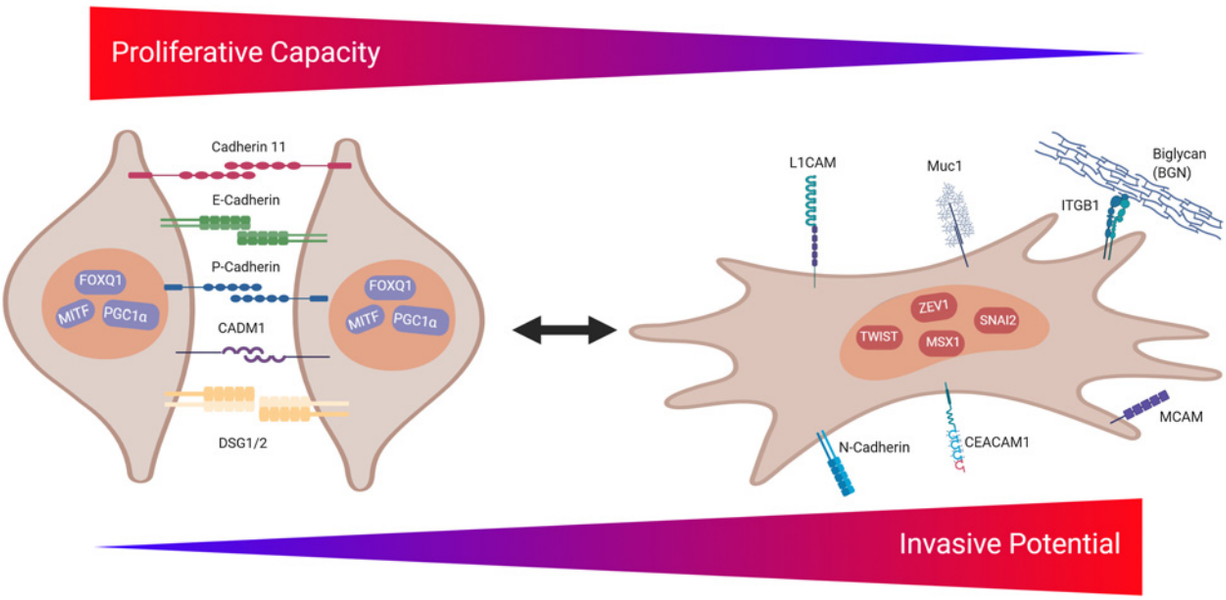

Figure 1.

Phenotypic characterization of select CAMs in melanoma plasticity. Schematic representation of the dynamic spectrum and heterogeneity that underlies melanoma progression and metastatic potential. The left side of the figure depicts two melanoma cells with a high proliferative capacity and low invasive potential. Select CAMs known to contribute to this state are highlighted as well as transcription factors associated with high proliferation/low invasiveness. The melanoma cell on the right is portrayed with select CAMs and transcription factors associated with a highly invasive, slow cycling phenotype.

can enhance tumorigenesis (80, 81) and inhibiting this interaction may have therapeutic benefit. Recent structural data suggest that the integrin αvβ8 heterodimer uniquely binds to latent TGFβ and targeting this interaction may represent a more efficacious avenue compared with systemic TGFβ inhibition (82). Furthermore, preclinical models demonstrate that integrin targeting combined with immune checkpoint inhibitors confers improved survival compared with each agent alone (83, 84). In addition to cytotoxic approaches, integrin-based therapies can inhibit metastatic traits. Examples include Tetrastatin, the NC1 domain of collagen IV, and antibodies targeting tetraspanins–a family of transmembrane proteins involved in integrin heterodimer scaffolding known to contribute to cell adhesion properties (85, 86). Tangentially, the BRAFi vemurafenib was found to suppress metastasis, at least in part, by acting through the PGC1α–ID2–TCF4–integrin axis (87) and targeting ILK has shown preclinical efficacy (35).

Cadherins

Cadherins are calcium-dependent cell-adhesion proteins involved in tissue integrity, organization, development, and cellular rigidity (50, 88, 89). In cancers, including melanoma, shifts in cadherin expression are implicated in metastasis and prognosis (89, 90). To gain invasive properties, melanoma cells overcome strong cell:cell adhesions by downregulating E-cadherin and upregulating the weaker N-cadherin; a process commonly termed the "cadherin switch" (**Fig. 1**; ref. 90). The cadherin switch, which is a prominent feature of EMT and EMT-like transitions (91, 92) has been associated with resistance to immune checkpoint blockades (93) and is considered a prognostic factor (94). This process is regulated through many transcription factors (95), including members from the SNAI (91, 96, 97), FOX (98), TWIST (96, 97), and ZEB (96, 99) families (**Fig. 1**).

E-cadherin is typically expressed by both keratinocytes and melanocytes, mediating an adhesive, stationary phenotype (89). This is associated with nucleation of a β-catenin–based complex that creates a rigid cytoskeletal anchor (100). Recently, E-cadherin was found to bind CD103 expressed on lymphocytes (88, 93), an interaction associated with improved immune checkpoint inhibitor function (93). In addition to transcriptional regulators that affect cadherin expression, there are other methods of regulation, including through IL32 (101), DNA methylation (102), SIRT1 (103), FGFR3 (104), and UBE2N (105), among others. As an example, SIRT1 was found to be upregulated in metastatic melanoma and promoted EMT through decreasing expression of E-cadherin. Because levels of E-cadherin mRNA were unchanged, it was found that SIRT1 was promoting autophagic degradation of E-cadherin through Beclin-1 (103). While the canonical role of E-cadherin is antimetastatic due to its proclivity to cause strong adhesions, in breast cancer model systems, E-cadherin expression was recently found to promote resistance to oxidative stress and "collective invasion" (106). These data are relevant to melanoma as E-cadherin was found to be an indicator of more aggressive uveal melanomas (107). The rationale for this is not fully understood; however, it is speculated that E-cadherin expression in uveal melanoma cells is associated with a more undifferentiated, precursor stem cell–like state, amenable to invasion and metastasis (108). This observation has since been validated, and E-cadherin expression is routinely assayed in standard uveal melanoma molecular profiling (109).

N-cadherin mediates homophilic interactions between melanoma cells and stromal components (89, 110). Generally, N-cadherin expression is associated with metastasis, invasion, and poor prognosis (**Fig. 1**; refs. 89, 92, 94). Melanocytes express E-cadherin and not N-cadherin; however, during melanoma progression, the cadherin profile shifts, reducing E-cadherin and enhancing N-cadherin levels (111). This shift coincides with augmented interactions with dermal fibroblasts and

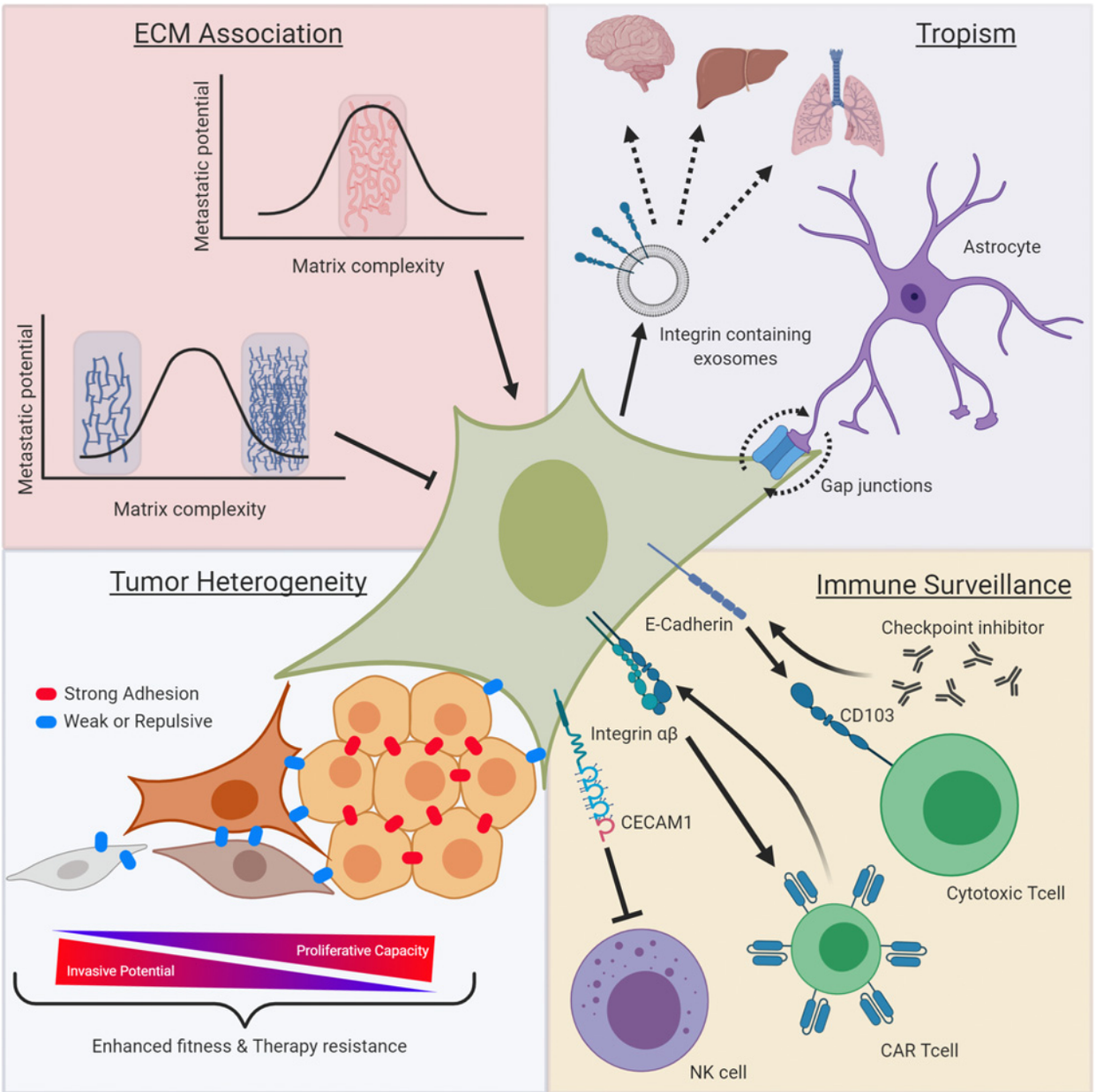

Figure 2.

Differential CAM function in melanoma progression. Graphical representation of select CAM-associated functions in melanoma progression. From top left, clockwise: ECM association: The metastatic potential of melanoma can be dictated by ECM concentration and complexity. Both less dense, low complexity and dense, high complexity ECM can inhibit melanoma invasiveness. Whereas an optimal ECM complexity and density can serve to facilitate invasiveness. Tropism: CAMs contribute to the metastatic tropism of melanoma. Melanoma-derived, integrin-containing exosomes can prepare the metastatic niche for subsequent colonization. In addition, CAMs directly interact with organ-specific cell types; the gap junction–mediated protumor signaling loop between melanoma and astrocytes highlights the role of connexins in CNS tropism. Immune surveillance: CAMs can stimulate and inhibit cytotoxic response and can be prognostic determinants for immunotherapy efficacy. For instance, immune checkpoint inhibitor treatment is more efficacious when melanoma-derived E-cadherin associates with CTCs. CAR T cells have been engineered to target melanoma with over-represented integrin αβ expression. Expression of certain CAMs can inhibit innate immune surveillance/response. As an example, the IgSF CEACAM1 has been shown to inhibit the cytotoxic function of NK cells. Tumor heterogeneity: heterogeneous CAM expression is associated with increased fitness and therapy resistance. A spectrum depicting highly proliferative/poorly invasive melanoma cells (cluster on right) to highly invasive/slow cycling cells (left) are depicted.

vascular endothelial cells, while reducing association with epidermal keratinocytes (111, 112). N-cadherin expression also facilitates homotypic aggregation of melanoma cells, a phenotype linked to Akt signaling and reduced anchorage-independent cell death (110). Together, these data support a protumor role for N-cadherin in melanoma.

Transcriptional control of N-cadherin intriguingly includes the carcinoma oncogene FOXQ1, which represses N-cadherin levels in

melanoma (98). In addition, recent data demonstrate that keratinocytes regulate N-cadherin levels through cell:cell contact (113). Although the interactions between E- and N-cadherin are often thought to be solely homophilic, recent data suggest the possibility of heterophilic cadherin binding, implying a more dynamic landscape of cadherin-defined phenotypes (88).

While N- and E-cadherin garner significant attention, prominent roles of other cadherin members have been uncovered. Both cadherin 11 (CDH11; ref. 114) and P-cadherin (115–117) have been implicated as metastatic suppressors (**Fig. 1**). In addition, in a series of recent studies, the ECM crosslinker hyaluronan and proteoglycan link protein 1 (HAPLN1), was found to modulate ECM complexity and have a direct role in metastatic proclivity to the lymphatics through VE-cadherin (49, 118). Interestingly, HAPLN1 secretion is lost with age, and is associated with reduced VE-cadherin junctions, a setting that is permissive to both in-transit and visceral metastasis (49, 118). These data underscore the relationship between age and metastatic prevalence in patients with melanoma and highlights a role for VE-cadherin as a prognostic determinant. Desmogleins are a subfamily of cadherins most often found in structural desmosomes (119). In normal skin, desmoglein 1 (DSG1) is involved with maintenance of melanocyte: keratinocyte adhesions, regulating melanocyte dendricity and keratinocyte pigmentation (**Fig. 1**; ref. 120). Interestingly, UV light downregulates DSG1 in keratinocytes (121), and this response may be linked to atypical melanocyte localization to the upper epidermal layer; a hallmark of melanocytic nevi and early melanomagenesis (120, 122). Paralleling this, downregulation of both DSG1 and DSG2 exhibits increased migration and invasiveness (123–125).

As cadherins are widely involved in metastasis, their potential as a therapeutic target in melanoma is under investigation (92). Most prominently featured are N-cadherin antagonists, including the mAb GC-4 and the N-cadherin–interfering peptide ADH-1 (18, 126). While ADH-1 showed promising preclinical data in combination with chemotherapy (18, 126), it has yet to demonstrate efficacy in clinical trials (127).

Immunoglobulin-containing CAMs

The large immunoglobulin-containing super family (IgSF) are surface receptors containing at least one 60–100 amino acid immunoglobulin-like domain (128). While this family consists of growth factor and antigen receptors, among others, for the purposes of this review, we will highlight select studies focusing on IgSF members involved with cell adhesion.

IgSF CAMs are often glycosylated; regulating the metastatic potential of melanoma by affecting interactions between tumor cells and the ECM (129, 130). For instance, N-glycosylation of L1CAM is considered a biomarker for aggressiveness and staging (**Fig. 1**; ref. 131). Recently, L1CAM fucosylation status was linked to melanoma invasiveness (130, 132). Here, highly aggressive melanoma had upregulated fucosyltransferase, FUT8, which modifies L1CAM, providing a shield from proteolytic cleavage (130). In addition, L1CAM is a novel substrate for membrane type matrix metalloproteinase MMP16 and expression of L1CAM appears to have a context-specific role in metastasis (43).

Recently, our group identified cell adhesion molecule 1 (CADM1) as a metastatic suppressor of melanoma. CADM1 is negatively regulated by the canonical EMT-associated transcription factor TWIST1 (**Fig. 1**; ref. 133). CADM1 is inversely correlated with disease progression and positively associates with overall and progression-free survival (**Fig. 1**; ref. 133). Expression of CADM1 decreased invasiveness and was correlated with caspase-independent cell death of melanoma cells cultured in nonadherent conditions. Together, these data suggest suppression of CADM1 may be an important step in metastatic progression and the viability of circulating melanoma tumor cells (133). In parallel, CADM1 was found to be epigenetically regulated via the histone methyltransferase EZH2. Here, in melanoma with increased long noncoding RNA lymph node metastasis–associated transcript (LNMAT1), facilitates recruitment EZH2 to the CADM1 promoter, reducing expression, and thus promoting metastatic traits (134).

The four Ig domain containing CEACAM1 has long been considered an indicator of melanoma disease progression (135–137). Most CEACAM1 isoforms enhance motility and invasiveness (138) and have been considered a predictor for poor prognostic outcomes in cutaneous melanoma (139) and potentially uveal melanoma (**Fig. 1**; ref. 140). Reduction in CEACAM1 correlates with downregulation of the ERK1/2 effectors Fra-1 and TWIST1 (141), a response that may be associated with its ability to modulate melanoma proliferation independent of its binding status (142). Paradoxically, CEACAM1 may be directly regulated by MITF (143). Perhaps this observation indicates a more intricate, multifaceted role for MITF in melanoma disease progression and the phenotype switch. CEACAM1 is also known to play a role in immune response (144). CEACAM1 expression interferes with NK and T-cell function via intercellular homophilic interactions (145, 146), and inhibiting this association may improve immunotherapy approaches (**Fig. 2**; ref. 147).

Other IgSF cell adhesion members have been implicated in melanoma progression, including TMIGD2, NCAM, and MCAM. The single Ig domain containing TMIGD2 is known to regulate endothelial cell:cell adhesions and permeability (148). Interestingly, TMIGD2 expression in a B16F model system enhanced tumor-directed angiogenesis resulting in increased tumor growth (149). Neural cell adhesion molecule (NCAM) increases melanoma invasiveness and metastasis through Wnt signaling (150), and more recently is associated with Akt/mTOR signaling (151). Melanoma cell adhesion molecule (MCAM, CD146) is an indicator of poor prognosis (**Fig. 1**) and used as a determinant for circulating melanoma cells (152–155). MCAM was recently implicated in the S100A8/A9 signaling axis, which is upregulated in many cancers, contributing to tumor development and metastasis (156, 157).

Historically, circulating tumor cell (CTC) analysis was limited to cancers of epithelial origin, as isolation techniques relied on Ep-CAM, an epithelial specific CAM (158). Consequently, this diagnostic tool typically ignores nonepithelial cancers like melanoma. However, newer technology utilizes multiple biomarkers including MCAM, expanding CTC detection capabilities and facilitating melanoma CTC profiling and noninvasive real-time assessment of therapy response (152, 158). In addition to its utility in CTC isolation, therapeutic targeting of MCAM has yielded promising results in mouse models of pancreatic cancer and melanoma (159). NCAM and L1CAM have also been thought of as druggable targets in melanoma (130, 150), and have shown efficacy in other cancer types. NCAM inhibitors have shown efficacy *in vivo* against small-cell lung cancer (160) and L1CAM inhibitors have been effective against ovarian and pancreatic carcinomas (161), suggesting that these other IgSF molecules in melanoma may well be a therapeutic avenue.

Connexins

While not adhesion proteins in the traditional sense, connexins are a family of surface proteins which oligomerize and form gap junctions

joining adjacent cells (162). These interactions can be both tumor–tumor or connect the tumor to surrounding stroma, facilitating the transfer of ions, small molecules, and metabolites between cells via gap junctional intracellular communication (GJIC; ref. 162). Connexin expression and GJIC contribute to neural crest cell development (163, 164) and have a complex role in melanomagenesis and metastatic progression. For example, gap junctions between melanocytes and keratinocytes are thought to maintain skin homeostasis (112). However, connexin expression is also implicated in various steps in the metastatic cascade including invasiveness, diapedesis, therapy resistance, and metastatic tropism (162, 165–167). Given this dichotomy, connexins have been referred to as conditional tumor suppressors (1, 168).

Recent work supports the conditional tumor suppressor role for Connexin 43 (Cx43, GJA1) during melanomagenesis. Cx43 is reduced in dysplastic nevi and *in situ* melanoma compared with normal melanocytes; however, expression is increased in melanoma adjacent to vasculature (165). Interestingly, Cx43 was found to be increased in melanoma cells from distant metastases; however, these cells lacked Cx43 containing gap junctions (169). The elevated levels of Cx43 were found in intracellular compartments (169), suggesting a potential role in cell signaling (1, 169). In addition, Cx43 was recently found to contribute to gene expression by direct interaction with promoter regions in the nucleus (170). Collectively these data demonstrate a complex, versatile function for Cx43 in melanomagenesis.

A significant line of evidence suggests that melanoma tropism to the CNS is, at least in part, associated with connexin expression and the beneficial effects of gap junctions formed with the brain stroma. Cx43 is a TWIST1-regulated determinant of CNS tropism in several model systems (171). Additional work mechanistically highlights how Cx43-based gap junctions between melanoma and astrocytes provide the foundation of a protumor signaling loop. Melanoma-derived cGAMP is transferred via gap junction to astrocytes, inducing the secretion of IFNα and TNFα, which then drive mitogenic and therapy-resistant phenotypes in melanoma (**Fig. 2**; ref. 172).

Mucins

Mucins are a family of highly glycosylated transmembrane proteins predominantly found in mucosal layers contributing to epithelial lubrication and pathogenic protection (173). In addition, mucins have important functions in development, cell attachment, tissue hydration, and carcinogenesis (174). A hallmark feature of mucin proteins are tandem repeat domains: serine-, threonine-, and proline-rich repeats that facilitate extensive O-linked glycosylation that modulates hygroscopic and adhesive tendencies (175). A small intracellular signaling domain is known to stimulate pathways for inflammation, differentiation, and apoptosis (176). Similar to other CAM families described above, mucins are thought to contribute to cancer metastasis by propagating cues detected from extracellular stimuli, in addition to the physical adhesive and repulsive associations with adjacent stromal and other cancer cells (173, 175). While this family is known to contribute to cutaneous disease progression (174), the role of mucins in melanoma is poorly understood.

Muc1 has been labeled an "oncomucin" for its association with EMT-like changes, immune evasion, apoptotic resistance and enhancement of mitogenic signaling pathways like ERK1/2 and PI3K/Akt (177–179). Many of these findings hold true in melanoma model systems. Muc1 expression regulates activity of canonical EMT transcription factors like TWIST1 (180), ZEB1 (181), and others known to contribute to melanoma disease progression (133, 182, 183). Muc1-expressing melanoma cells displayed increased motility and invasiveness, elevated Akt activity, and enhanced lung colonization (**Fig. 1**; ref. 184). Conversely, knockdown was associated with reduced Akt activity, fewer lung colonies, and slower syngeneic tumor growth (184). These results coincide with similar studies demonstrating Muc1 is associated with anoikis resistance; potentially underscoring a role for Muc1 expression in melanoma CTC viability and representing an intriguing target to block metastatic spread (185). Indeed, studies of Muc1-targeting therapeutics have had promising results in breast and lung preclinical model systems (186, 187), and a recently developed Muc1-based cancer vaccine demonstrates an approximately 50% reduction in B16 lung colonization model (188).

Muc4 is a very large mucin that is correlated with poor prognosis in many cancers (189). While Muc1 and Muc4 consist of both an extracellular α and transmembrane β subunit, the α subunit of Muc4 can be significantly larger than Muc1; potentially having up to 20 times more tandem repeat domains (176, 190, 191). This trait facilitates Muc4 to have more O-linked glycosylation and a stronger negative net charge compared with Muc1. Because of its size, it is theorized that Muc4 expression impedes cell:cell interactions by exerting its homophilic repulsive forces and outreaching the adhesive tendencies of smaller CAMs, thus facilitating increased motility (192). Muc4 is upregulated in a number of skin pathologies including squamous cell carcinoma (193). In addition to its anti-adhesive role, Muc4 stabilizes ERBB2 through multiple EGF-like domains (194, 195) stimulating PI3K/Akt signaling and suppressing apoptosis (196–198). In line with this, a recent study of a melanoma patient cohort found expression of certain Muc4 isoforms can be considered an independent prognostic predictor of poor overall and progression-free survival (199).

CAMs and Immune Checkpoint Inhibitors

As previously mentioned, CAM expression is known to modulate immunotherapy efficacy, and given that immunotherapy is first line treatment for many patients with metastatic melanoma, a more complete understanding of this interplay is critical. CAMs direct interactions between tumor cells and immune cell types, modulating immune cell trafficking, activation, and proliferation, and defining the immunologic synapse (200–202). Cadherins (93), IgSF molecules (144–147, 203), connexins (204), and integrins (83, 203) have all been demonstrated to contribute to the immunologic response. For instance, intercellular adhesion molecule 1 (ICAM-1) and integrin interaction is a common form of receptor-ligand binding within the immunologic synapse (203), and connexin-based gap junctions aid cytotoxic T-lymphocyte (CTL)-mediated killing of melanoma cells (204).

Because immune checkpoint inhibitors function by modulating interactions in the immunologic synapse (200), targeting CAMs alone or in combination with FDA-approved immunotherapy agents is currently being explored. mAbs targeting CEACAM1 were found to be efficacious and more specific than existing immunotherapies (147). As another example, treatment with established immune checkpoint inhibitors is improved when VLA-4, an αβ integrin, is cotargeted with radionucleotide therapy (**Fig. 2**; ref. 83). In addition to serving as therapeutic targets, differential CAM expression may be indicators of immunotherapy response (205, 206), although this approach may be controversial (207).

Conclusion

In melanoma progression, CAMs are critical effector proteins, which dictate signaling, motility, invasiveness, and ultimately metastatic proclivity. CAMs provide a variety of adhesive or repulsive forces via interaction with ECM, stroma, and other cancer cells to navigate the microenvironment. These interactions are dynamic; with individual cells adapting to environmental cues and metastatic needs, as well as heterogeneous–evidenced by intralesional diversity (29). These features likely contribute to melanoma's penchant for quickly acquiring resistance to various treatment modalities (208, 209). However, the plastic nature of CAM expression may represent a therapeutic opportunity. To this end, a wide array of CAM-targeting agents is currently under development (**Table 1**). While these treatments are unlikely to provide significant benefit as monotherapies, they may act to stave off further metastatic dissemination (78), and work in concert with immunotherapies (83, 84, 147), or targeted inhibitors (47, 48).

Recent work suggests improved fitness when melanoma lesions consist of cells from each end of the phenotype switch spectrum (30), and by extension populations with varied CAM expression. Moreover, this study demonstrated reduced heterogeneity and overall tumorigenicity when melanoma-derived fibronectin was depleted (30); an effect that could potentially be mimicked by integrin-targeting agents such as volociximab (210, 211). Thus, in a broader sense, anti-CAM targeting factors could be used to skew the heterogeneous tumor population to a more homogenous state, thereby increasing the susceptibility to other therapeutics, an approach that may forestall drug resistance. Taken together, a better understanding of CAM function and temporal regulation in melanoma disease progression will improve drug design, prognostic accuracy, and give insights for efficacious combinatory treatment regimes.

Authors' Disclosures

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