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REVIEW

Cell adhesion molecules and their relation to (cancer) cell stemness

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Despite decades of search for anticancer drugs targeting solid tumors, this group of diseases remains largely incurable, especially if in advanced, metastatic stage. In this review, we draw comparison between reprogramming and carcinogenesis, as well as between stem cells (SCs) and cancer stem cells (CSCs), focusing on changing garniture of adhesion molecules. Furthermore, we elaborate on the role of adhesion molecules in the regulation of (cancer) SCs division (symmetric or asymmetric), and in evolving interactions between CSCs and extracellular matrix. Among other aspects, we analyze the role and changes of expression of key adhesion molecules as cancer progresses and metastases develop. Here, the role of cadherins, integrins, as well as selected transcription factors like Twist and Snail is highlighted, not only in the regulation of epithelial-to-mesenchymal transition but also in the avoidance of anoikis. Finally, we briefly discuss recent developments and new strategies targeting CSCs, which focus on adhesion molecules or targeting tumor vasculature.

Introduction

Cancer development and progression are aided by the environmental factors, diet, the individuals' genetic makeup as well as epigenetic alterations (1–4). Accelerated development of our understanding of cancer biology, mainly inspired by the recent genetic and epigenetic studies (5–7), led to the reclassification of common cancers, where sometimes histologically different, yet genetically similar cancers may respond to the similar treatments. Our better understanding of cancer as acquired genetic disease has fuelled research on the development of new classes of drugs (8–12). The knowledge that not all cancer cells within tumors have equal tumor growth-supporting potential [the concept of cancer stem cells (CSCs) and tumor cell heterogeneity] is about to revolutionize the way we develop new anticancer drugs and treat cancer patients (13,14). The focus of this review is on the role of cell adhesion molecules (CAMs) in the interaction between cancer (stem) cell and extracellular matrix (ECM) as well as changes in the expression profile of adhesion molecules as cancer cells leave the primary tumor and travel to form metastases. We highlight parallels between reprogramming and carcinogenesis, as well as between tissue-committed stem cells (SCs) and CSCs.

Unlike higher, multicellular organisms that use tactile cues to survey the surrounding, cells use instead mainly adhesion molecules to sense the surrounding and align themselves appropriately. Interestingly, many of the stemness markers commonly used for narrowing-down the population of CSC are actually CAMs. Thus, below we introduce the main classes of CAM, whereas further details will follow in the corresponding sections in the next pages.

Cadherins, integrins, selectins and members of immunoglobulin family constitute the major groups of CAMs. CAMs play a primary role in cell-to-cell and cell-to-ECM anchoring by maintaining cell and tissue structure, cell signaling, tissue repair and wound healing (15).

Cadherins, whose main function is cell–cell adhesion, are well studied for their role in cell signaling during critical processes such as epithelial-to-mesenchymal transition (EMT), cell migration and gene regulation through catenins, (especially β-catenin/Wnt signaling pathway) (15).

Integrins, on the other hand, are involved both in the cell–cell and cell–ECM interaction, and have cell- and tissue-specific roles. Furthermore, integrins play a crucial role in the cell proliferation, differentiation and migration due to their ability to transfer signals from the ECM to the cell (16).

Selectins and immunoglobulin superfamily (IgSF) members are mainly involved in the wound healing (recruiting platelets and leukocytes) and immune response (communication between immune cells and other constituents of the inflammatory process as well as among components of the immune system). Among other roles, they are 'traffic regulators' in the lymphatic system and attract immunocompetent cells to the site of inflammation (17).

CSCs differentiation, CAMs and cell surface markers

Cancer recurrence is the main cause of high mortality among those affected by the disease. Several hypotheses have been proposed to explain the mechanism of tumor relapse. The CSC concept relies on the formation of CSC following genetic or epigenetic modification of normal SCs or alternatively from more differentiated cancer cells that confer them capability of unlimited growth (18). CSCs have properties similar to those of tissue-committed SCs [or embryonic stem cells (ESCs) in case of teratoma] and are capable of self-renewal and metastasizing in distant organs (19). Several experiments have shown that CSCs are typically more resistant to the majority of chemotherapy and radiotherapy protocols (20–22). As a result, some of them may remain in the patient's body after surgery, radiation and chemotherapy treatments causing tumor relapse. Furthermore, the epigenetic mechanisms are key modifiers of stemness and lineage commitment and are often deregulated during cancer progression. Studies show that epigenetic changes including DNA methylation and histone modifications contribute largely to epigenetic disruption of SCs and occur following the genetic aberrations (23). The canonical Wnt pathway, which is necessary for SC control in the early stages of neoplastic transformation, undergoes very often these epigenetic abnormalities and is well described in colon cancer (24). Recent studies using mouse models demonstrate that upregulation of ESC transcription factors and defects in the appropriate control of gene imprinting can lead to SC expansion and contribute to the early stages of cancer (25,26). Current knowledge suggests that clonal selection of CSCs is driven both by genetic and epigenetic changes, which results in tumor cell heterogeneity. Therefore, epigenetic alterations may also be useful in future

Abbreviations: AJ, adherens junction; APC, adenomatous polyposis coli; BM, basement membrane; BMDCs, bone marrow-derived hematopoietic progenitor cells; CAM, cell adhesion molecule; CSC, cancer stem cells; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-to-mesenchymal transition; ESC, embryonic stem cell; FAK, focal adhesion kinase; GSK-3β, glycogen synthase kinase-3; hESC, human embryonic stem cells; HIF, hypoxia-inducible factor; IgSF, immunoglobulin superfamily; LYX, lysyl oxidase; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; RTK, receptor tyrosine kinase; SC, stem cell; TGF-β, transforming growth factor-β; uPA, urokinase form of the plasminogen activator; VEGF, vascular endothelial growth factor.

clinical applications for the detection of early changes of cancer initiation as well as chemoprevention (27).

As observed in breast and oral squamous cell cancers, SCs in poorly differentiated and highly invasive cancers exhibit loosened attachment and higher motility (28). Thus, characterizing the adhesion molecular signature could help identifying the self-renewing, SC-like subpopulation within the entire cancer cell population. Molecular signatures of cadherins [epithelial cadherin$^-$ (E-cadherin$^-$), N-cadherin$^+$ and cadherin-11$^+$] have been hypothesized to identify EMT, a process that includes alterations in cell–cell and cell–ECM contacts and cytoskeletal rearrangements causing a mesenchymal phenotype with migratory ability (29). EMT occurs prior to and is considered to be a prerequisite quality for cells to become metastatic. Several heteromeric interactions of integrins such as α5β1, α5β3, α5β6 and so on could also act as markers in cell invasiveness, differentiation and proliferation based on their ability to recruit and interact with matrix metalloproteinases (MMPs), transforming growth factor-β (TGF-β) and focal adhesion molecules (28,30). Studies aiming at defining the combination of adhesion molecules typical for given tissue-committed (cancer) SCs are difficult, especially in solid tumors, where the need to disassociate these cells alters their molecular adhesion fingerprint.

Other stemness markers, still under discussion, are the cell surface markers CD44, CD24, CD133 and epithelial CAM. In several cancers including breast, prostate adenocarcinomas, lymphomas and oral squamous carcinomas, CSC could be identified, at least to some degree of probability, as CD44$^+$/CD24$^-$. Similarly, CD133 is a good CSC-predictive marker for gliomas, colon and pancreatic cancers, whereas CD34$^+$/CD38$^-$ along with CD123 identify leukemic SCs (14,31). In breast cancer, the expression of epithelial CAM (when in combination with lin$^-$/CD49f$^+$ phenotype) correlates well with CSC-multipotency. Interestingly, the breast CSCs are characterized by CD44$^+$/CD24$^-$ expression and possess enhanced self-renewal capacity and invasive properties, which is crucial for the early step in metastasis (32). Additionally, CD44$^+$/CD24$^-$ cells are able to give rise to non-tumorigenic cells, which compose the bulk of the tumor (33). There are some evidences that CD44$^+$/CD24$^-$ may favor distant metastases; however, their role in metastasizing has not been revealed and the results are rather inconsistent (32,34). Recently, the CD133$^+$CD44$^+$ stem-like cancer cells were highly enriched in HCT116 colon cancer cells and exhibited metastasis to liver *in vivo* (35).

In glioblastoma, CD133$^+$ subpopulation correlates well with CSC population confirmed by other tests. However, because CD133$^-$ CSCs have been identified in various cancers including gliomas, the value of CD133 as a stemness indicator should be interpreted with caution (36).

Although adhesion molecules and other cell surface markers are useful indicators of stemness properties of given cell populations, they should be used along with other stemness and genomic markers to achieve the best results. The ultimate test for stemness of CSC is the ability to repopulate the tumor upon transplantation into immunocompromised mice.

Cadherins, catenins, cytoskeleton interactions and stemness

Cytoskeletal morphology and cell adhesion are closely linked to cell differentiation and stemness. Arguably, one of the most important factors in cell adhesion is the catenin–cadherin interaction. Cadherins are transmembrane proteins that are components of adherens junctions (AJs) and promote cell adhesion, especially E-cadherin. The catenins family includes cytoskeletal proteins (α-, β-, γ- and δ-catenins) that are important for the formation of AJs between cells, due to their ability to link the actin filaments of the cytoskeleton to cadherins.

Stemness of the cell can be defined as the capability of self-renewal and developing into more differentiated cell types. This distinctive state of the cell is assigned to various cell types, including ESCs, tissue-specific SCs and CSCs. Similarly to ESC, the induced pluripotent stem cells are also capable to differentiate into all three germ layers (pluripotency) (37). Human ESC (hESC) and induced pluripotent SCs display high levels of E-cadherin (38), which is important for self-renewal and maintenance of the undifferentiated state in mouse ESC and hESC (39–42), and its expression is downregulated during differentiation (40).

E-cadherin. Cadherins are calcium-dependent, type 1 transmembrane proteins that are important for cell adhesion (43). E-cadherin belongs to one of the five major subfamilies of cadherins and is expressed in most epithelial cells, including ESC (44,45). The extracellular domain of E-cadherin interacts homophilically with E-cadherin molecules on neighboring cells and promotes cell adhesion (44,46). The cytoplasmic region of E-cadherin binds to β-catenin and can interact with the cytoskeleton via α-catenin and "epithelial protein lost in neoplasm" molecules (47). E-cadherin-mediated intercellular adhesion provides essential signaling for the survival of hESC and induced pluripotent SCs. E-cadherin plays a major role in morphogenesis, tumorigenesis, development and signal transduction (48,49). Recent studies on mouse ESC suggest a broader role for E-cadherin, beyond cellular adhesion, in general cellular homeostasis of ESC (41). The same group also showed that E-cadherin depleted mouse ESC were capable of Wnt-induced β-catenin/T-cell factor signaling, which indicates that E-cadherin is independent of its intracellular mediator β-catenin (41).

Part of this wide role of E-cadherin includes somatic-cell-induced pluripotency by nuclear reprogramming, at least in mice, where E-cadherin is a vital protein for the first step of cell transformation [EMT, mesenchymal-to-epithelial reverting transition (MErT)] (39). E-cadherin is required for reprogramming, as knocking down E-cadherin expression increased N-cadherin levels and a reduced expression of pluripotent genes like left-right determination factor 1 (Lefty1), sex determining region 2 (Sox2) and Krüppel-like factor 4 (Klf4) (39). E-cadherin participates in the regulation of pluripotency, either by ensuring the circulation of autocrine signals in fully compacted cells or cell–cell signal exchange via gap junctions (50). Recent work by Chou *et al.* (51) has also concluded that E-cadherin is a regulator of pluripotency, with downregulation of E-cadherin being closely linked to rapid ES differentiation. The same group showed that E-cadherin expression is a key target of leukemia inhibitory factor/bone morphogenetic protein-4 and that such interaction is responsible for the formation of teratomas (51).

Catenins. The role of α-, β- and p-120 (δ_1-) catenin in regulating hESC pluripotency and adhesion has not yet been fully discerned. Their importance in early development, however, is clearly shown by several groups in *Drosophila*, mouse and other models (52–54). Recent studies have demonstrated the existence of a signaling network that regulates the intercellular adhesion and stabilizes the transcriptional regulatory mechanisms of pluripotency in hESC. Parts of this network include (though probably are not limited to) NMMIIA (non-muscle myosin IIA), E-cadherin and p120-catenin (55). p120-catenin binds to the E-cadherin cytoplasmic domain, stabilizing the cadherin–catenin complex by preventing clathrin-mediated endocytosis (56).

β-Catenin. β-Catenin is a multifunctional protein that plays a major role in embryonic development (axis and mesoderm formation, SC differentiation), organogenesis and cellular homeostasis. This is mediated by β-catenin's function as a transcriptional co-activator in the canonical Wnt pathway and by its structural role in cadherin junctions. Moreover, β-catenin plays a pivotal role in the centrosome separation during mitosis (57).

In the absence of Wnt signaling, β-catenin is bound in a complex with axin, adenomatous polyposis coli (APC) and glycogen synthase kinase-3 (GSK-3β), and is constantly degraded through phosphorylated and ubiquitin-mediated proteasomal degradation. In the presence of Wnt signaling, the binding complex dissociates and β-catenin translocates to the nucleus, where it binds T-cell factor/lymphoid enhancer factor transcription factors, activating target genes involved in cell proliferation and cell adhesion. Some of these genes include MMPs -2, -3, -7, -9 and -13, which degrade the ECM, hence affecting cell adhesion (58,59) (Figure 1). Wnt signaling inhibits the degradation of β-catenin by the transmission of signal from the disheveled protein GSK-3β. The main role of GSK-3β is to phosphorylate the β-catenin within a complex with APC/axin and trigger its ubiquitination and degradation. β-Catenin is also found in a cadherin-bound

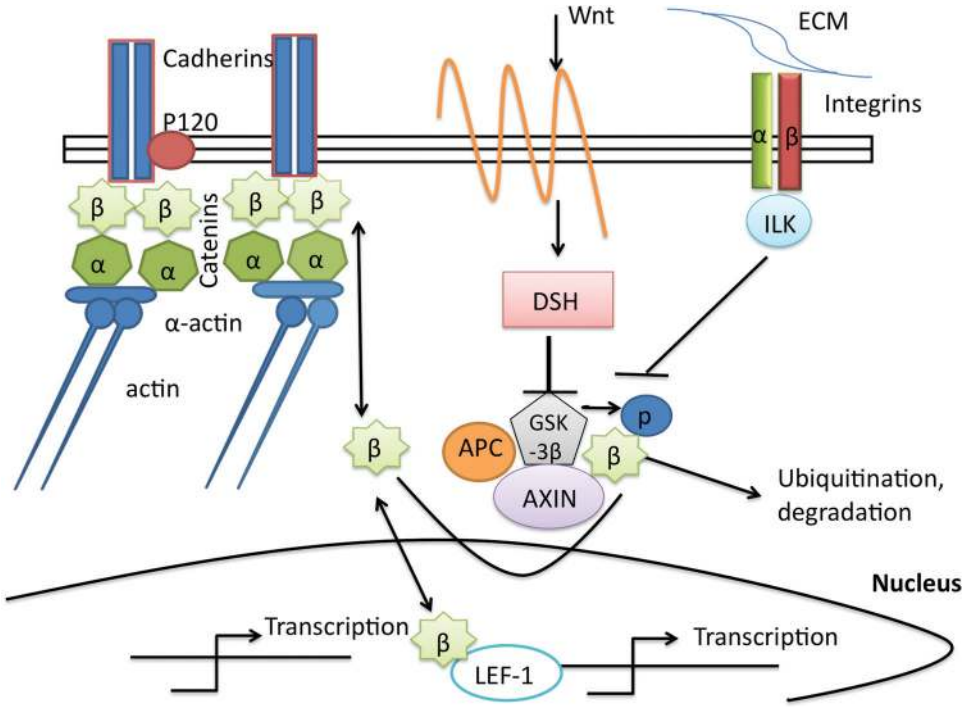

Fig. 1. The role of CAMs in the regulation of Wnt/β-catenin pathway.

form at the plasma membrane, where it is required for the formation and stabilization of AJ in order to support proper tissue architecture and morphogenesis (60,61).

Cell adhesion—EMT and MErT. β-Catenin links the cadherin junctions and the Wnt pathway. Being a phosphorylation target for Akt, which is stimulated by the epidermal growth factor (EGF), β-catenin dissociates from cadherin junctions and shows enhanced nuclear and cytosolic localization (62). In a similar manner, Rac1 activates c-jun N-terminal kinase 2, which in turn phosphorylates β-catenin and controls its nuclear translocation (63). c-Src (a tyrosine kinase) phosphorylates β-catenin at tyrosine residues and thus promotes the dissociation of β-catenin from the cell-to-cell junctions. As a result, cell adhesion is lowered and the expression of T-cell factor/lymphoid enhancer factor target genes is enhanced (64). In some tumor cell lines, β-catenin seems to play a major part in both EMT and MErT through the transcriptional induction of Slug or Twist gene expression that could suppress E-cadherin expression (65). Furthermore, recent studies have shown a connection between Wnt/β-catenin and other EMT/MErT signaling pathways, such as TGF-β and disabled homolog 2-interacting protein (66). β-catenin induced secretion of MMPs contributes to the EMT by degrading the ECM and therefore making tumor cells more invasive (67). Loss of the cell surface E-cadherin also characterizes EMT, particularly in the early embryonic events with the ingression of epiblast cells within the primitive streak (44,49). In addition, studies have shown that E-cadherin represses ligand activation of many receptor tyrosine kinases (RTKs) that are closely linked to the induction of EMT in the epithelial cells (46,68,69). Differentiation of ESC is also linked to the EMT-like event, during which E-cadherin is replaced by N-cadherin and MMPs are produced (70,71).

Integrin-mediated signaling

The mitogen-activated protein kinase pathway. Integrins are α/β heterodimeric transmembrane receptors, which in addition to cell adhesion regulate various cellular responses to promote proliferation, migration and survival. Integrins can directly and indirectly recruit number of signaling components and activate intracellular signaling cascades especially pathways leading to activation of mitogen-activated protein kinase (MAPK) pathway. This pathway elicits many of the responses in cells caused by changes in certain environmental conditions, hormonal exposure and other stimuli (16,72).

There are two major models by which integrins regulate the MAPK pathway, namely direct and indirect signaling. In direct signaling, integrin-β-mediated adhesion leads to activation and autophosphorylation of focal adhesion kinase (FAK). FAK is also capable to bind to other signaling proteins such as SRC tyrosine kinase, phosphoinositide 3-kinase, guanosine triphosphatase regulator associated with focal adhesion kinase, paxillin and talin, which further phosphorylate FAK. This allows the growth factor receptor-bound 2–Son of Sevenless complex to bind FAK and thereby triggering RAS activation and subsequent activation of RAF, Mek and extracellular signal-regulated kinase (73,74) (Figure 2). Integrin engagement has also been reported in direct activation of other arms of MAPK pathway like c-jun N-terminal kinase and p38. This pathway may play a role in cell cycle traverse or cell survival (75). Integrin-mediated MAPK pathway activation can also run in the FAK-independent manner. Subset of integrin-α associates with the Src-family kinase Fyn and the Shc-adaptor protein via the transmembrane protein caveolin-1. The phosphorylation of Shc by Fyn leads to recruitment of growth factor receptor-bound 2–Son of Sevenless and activation of the signaling cascade (76) (Figure 2).

In indirect signaling, integrins and their associated cytoskeletal components regulate signaling cascades initiated by other 'conventional' signaling receptors including RTKs, G-protein-coupled receptors and cytokine receptors. Integrin aggregation is required for triggering tyrosine phosphorylation of different growth factors like EGF, platelet-derived growth factor and fibroblast growth factor receptors. The integrin-dependent cytoskeletal complex can affect signaling downstream of RTKs at three different levels. First, both integrin and presence of growth factor are necessary for the efficient activation of RTKs. There are some insights concerning the formation of the direct or indirect complex between the RTKs and integrins, which enhance the opportunity for RTK dimerization and cross-phosphorylation in order to activate the integrin/RTK/MAPK pathway (77). Second, the activation of downstream kinases Mek and Erk is dependent of RAS and RAF coupling. Loss of integrin-mediated cell anchorage blocks the transmission of the signals from RAS to RAF (78). Third, the integrin-dependent trafficking of the signaling components

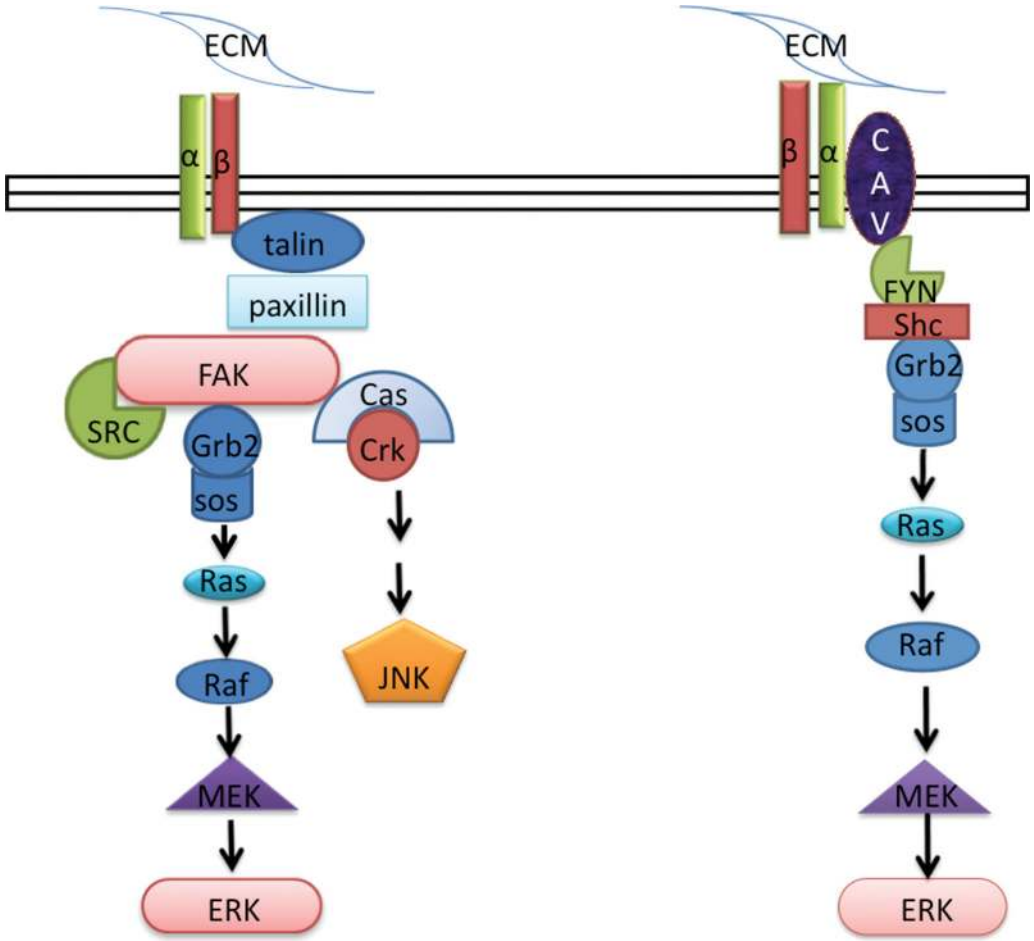

Fig. 2. MAPK pathway activation by direct signaling of integrins.

like extracellular signal-regulated kinase from the cytoplasm to the nucleus is indispensable for the activation of the Jun transcription factor thereby driving cells into the cell cycle (79) (Figure 3).

The ability of integrins to the MAPK pathway via the G-protein-coupled receptors has also been observed. Integrins or their cytoskeletal partners associate with scaffolding proteins such as receptor for activated C kinase 1 and increase the encounters between the active signaling components like protein kinase C and Mek. A very interesting series of studies have also reported the role of integrin-mediated cell anchorage in pathways initiated from multitransmembrane, purigenic G protein-coupled receptors P2Y to phospholipase C β, which finally leads to extracellular signal-regulated kinase activation (76) (Figure 4). Additionally, the MAPK pathway has been suggested to maintain the pluripotency in hESC and is downregulated upon differentiation (80,81).

The TGF-β pathway. The TGF-β is a key molecule that is controlling proliferation and differentiation of cells through activation of SMAD and non-SMAD signaling pathways. TGF-β is secreted as a part of a latent complex in which the TGF-β propeptide functions as the detector (82). Among growth factors that cross talk with integrins, TGF-β stays at the forefront because of the unique ways in which it interacts with the ECM and integrins (83). Various αv integrins interact with the latency-associated peptide/TGF-β_1 fraction and support its activation (84). Upon binding of TGF-β to the extracellular domain of type I and type II TGF-β receptors, the receptor-related SMAD proteins get phosphorylated and translocate to the nucleus to regulate the target genes. There are two main branches of TGF-β signaling involving SMADs. In the first pathway, bone morphogenetic protein and growth differentiating factor bind anaplastic lymphoma kinase 1/2/3/6 receptors and lead to activation of SMAD1, 5 and 8. In the second pathway, activin and nodal protein complexes bind anaplastic lymphoma kinase 4/5/7 receptors and trigger activation of SMAD2 and 3 (72).

TGF-β signaling also plays a key role in cancer as well as stemness. Mutations, missregulation of TGF-β receptors and inactivation of SMAD4 have been observed in variety of human cancers. Moreover, TGF-β signaling is known to promote tumor metastasis via TGF-β-induced EMT (85,86). Various transcription factors, including ZEB1, ZEB2 and Snail/SNAI1, are induced by SMAD/TGF-β signaling and play essential roles in TGF-β-induced EMT (87). Furthermore, bone morphogenetic protein signaling leading to SMAD1, 5 and 8 activation via anaplastic lymphoma kinase 2/3/6 is blocked in undifferentiated cells and becomes activated upon differentiation. SMAD2 and 3 are activated in undifferentiated hESCs and indispensable for the expression of genes controlling Nodal signaling (88). Recent studies have also confirmed involvement of TGF-β signaling in preservation of pluripotency. TGF-β signaling is particularly activated in $CD44^+$ breast cancer cells and maintains their undifferentiated state (89). SMAD2/TGF-β has also been reported to mediate stemness in human glioblastoma in the integrin-dependent manner (90,91).

Cell adhesion, SC niche and control of multipotency

SC is a broad term for cells ranging from rapidly dividing ESC required for tissue growth and formation in the embryo to slowly dividing tissue-committed multipotent cells required for restoring the tissue-specific differentiated cells (92). Unless explicitly stated, the term SC will refer below to the tissue-committed multipotent cells in various tissues. In adult tissue, specialized regions of SCs residency are niches, which possess both anatomical and functional dimensions to regulate SC fate. SC niche protects SCs from damaging stimuli and provides supportive microenvironment for the sustaining their proliferative potential (93,94).

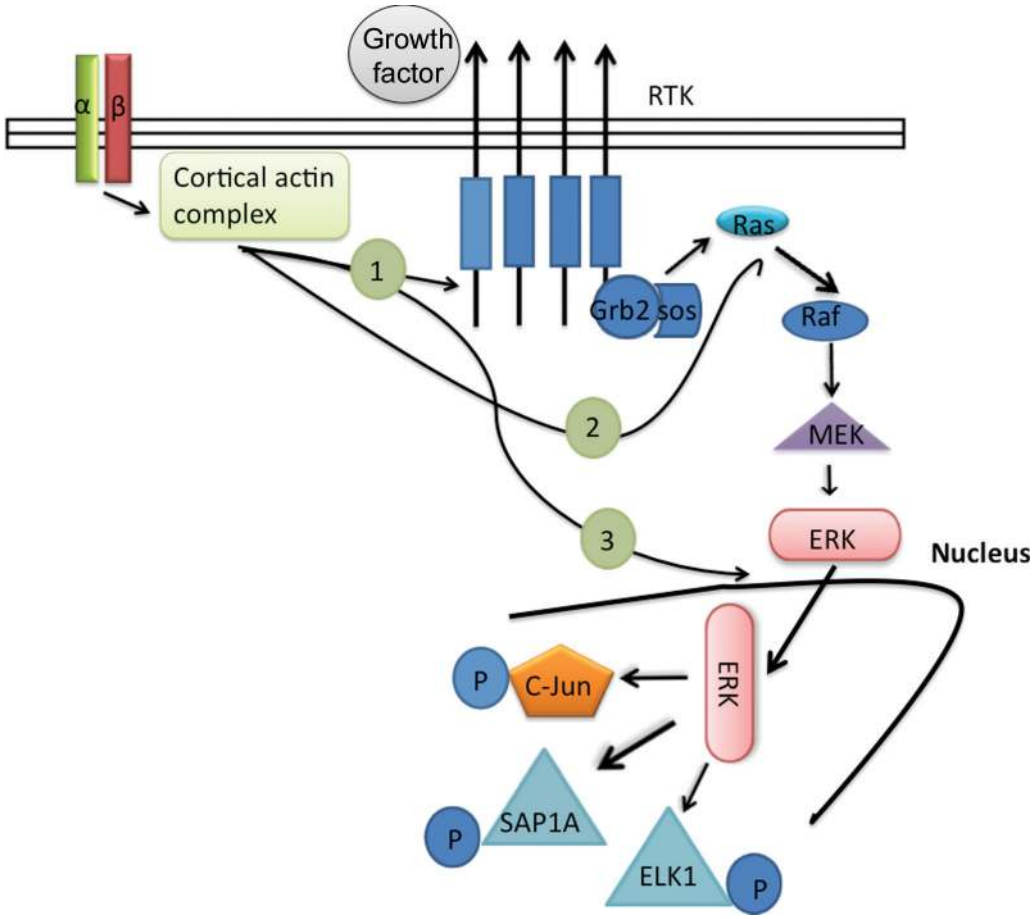

Fig. 3. MAPK pathway activation by indirect signaling of integrins via RTKs.

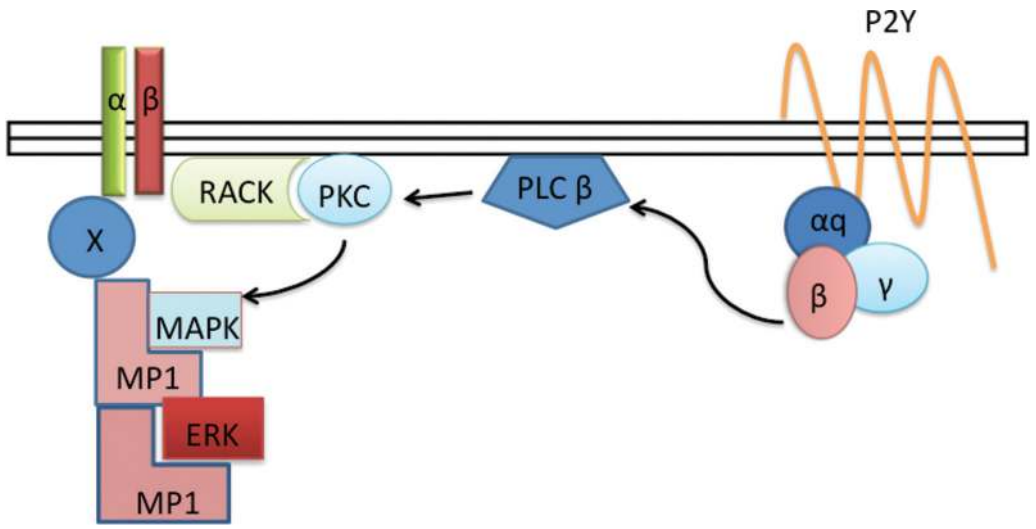

Fig. 4. MAPK pathway activation by indirect signaling of integrins via G-protein-coupled receptors and purinergic receptors P2Y.

Germline SC (GSC) niches were first described in *Caenorhabditis elegans* and *Drosophila*. SC niches are relatively well illustrated in different mammalian tissues including epidermis, intestine, bone marrow, muscle and corneal epithelium, whereas more experimental data are still needed for other tissues such as mammary glands (95,96).

Adhesion molecule constellation in the SC niches. There are two wide classes of niches, namely epithelial and stromal niche. In the epithelial niche, SCs are in direct contact with the basement membrane (BM), whereas in the stromal niche, SCs are in contact with another cell type attached to the BM known as support cell (Supplementary Figure 1, available at *Carcinogenesis* Online). In both types of niches, SCs are in contact with their progeny/daughter cells (97,98). SCs within the niche undergo symmetric and asymmetric divisions, and play an important role in the homeostasis of adult tissues. Symmetric divisions help maintaining and/or increasing the number of multipotent

SCs, and asymmetric divisions produce progenitors that become recruited to generate the differentiated progenies outside the niche (92,99).

SC niche is surrounded by the components of ECM. There are two major sets of adhesion molecules such as cadherins and integrins inside the niche. Various niches encompass similar adhesion molecules, but due to the different anatomical features of each niche, adhesion molecules expressed by SCs and support cells in the niches vary among tissues. For instance, integrin chains such as β_3, β_4, β_6, α_2 and α_7 are expressed in mammary alveolar progenitor, epidermal SCs, prostate SCs and muscle satellite cells, respectively. β-Integrin subunit βPS is expressed by *Drosophila* testis GSC, hub cell and *Drosophila* ovary follicle SC. α-Integrin subunits αPS1 and αPS2 are expressed in *Drosophila* ovary follicle SC. β_1-Integrin expression is found in neural SC, sperm SC and Sertoli cell, epidermal SC, mammary SC, muscle satellite cell and hematopoietic SC (98). Regarding the cadherins, E-cadherin is expressed in *Drosophila* testis germline, somatic SC, *Drosophila* ovary GSC, escorts SC and neural SC. M-cadherin is expressed in muscle satellite cell. N-cadherin expression is seen in the hematopoietic SC, and P-cadherin is expressed in epidermal and mammary SCs (98).

Based on the studies of *Drosophila* gonads, loss of integrin function in the stromal niche leads to the detachment of support cells from the BM, whereas loss of E-cadherin function results in the detachment of SC from the support cell. In contrast, loss of integrin function in the epithelial niche results in SC detachment from the underlying BM (Supplementary Figure 1, available at *Carcinogenesis* Online) (100). Therefore, integrins in the stromal niche are required for the adherence of support cells to the BM (ECM) and cadherins are required for cell-to-cell adhesion. In the epithelial niche, integrins regulate SCs adhesion to the BM (100). Moreover, a recent study conferred evidence that mutant GSC in *Drosophila* ovaries express higher level of E-cadherin and thereby displace the normal GSC with lower cadherin expression in the niche (101). On the other side, E-cadherin expression is declined in the SC niche of *Drosophila* ovaries as well as the somatic niche of *Drosophila* testes during aging. This suggests that E-cadherin might contribute to the reduction of the functional activity of SCs by decreasing the SCs population in the niche (102). Indeed, the level of E-cadherin expression ensures the retention of non-differentiated cells in the niche by rapid displacement of the differentiated cells and mediates the SCs self-renewal potential (98).

Regulation of cell division by cadherins and integrins. Several recent studies have shown that both cadherins and integrins regulate cell division in SCs and other cell types. In the cell division, E-cadherin is linked to the astral microtubules through APC and thereby provides the right positioning of the mitotic spindle by centrosome. Positioning of the mitotic plane in parallel to the support cell and SC adhesion junction leads to asymmetric division in the stromal niche and symmetric division in the epithelial niche (Supplementary Figure 2, available at *Carcinogenesis* Online) (100). Studies have shown that deletion of APC results in the spindle misorientation by changing the direction of mitotic cleavage plane from the normal vertical symmetric division and horizontal asymmetric division (103,104). On the other hand, many studies have surprisingly demonstrated that integrins play a role in the reorientation of the symmetric divisions (in the epithelial niche) to the asymmetric divisions (in the stromal niche). Through the integrin signaling, the axis of division is no longer parallel to the adhesion junction plane and the cleavage plane becomes oblique (Supplementary Figure 2, available at *Carcinogenesis* Online) (105). Decreased abundance of the phosphatidylinositol (3,4,5)-trisphosphate (PI3,4,5-*P3*) and dynactin/dynein (106) or inhibition of GSK-3β can pull the spindle into the oblique direction and reorient the division due to inhibition of APC interaction with microtubules. Blocking of integrins causes the reduction in oblique divisions and these cells are switched back to vertical symmetric divisions. This would explain why loss of integrin has no effect on division angle of SC because these cells may divide in cadherin-mediated fashion (107). Because loss of integrin can lead to detachment of SCs from underlying BM in the epithelial niche, presence of another extracellular cue, which is topologically localized by integrin, and that regulates division angle is hypothetically needed (100). Therefore, E-cadherin-mediated adhesion regulates the cell symmetric and asymmetric division, whereas integrin-mediated adhesion to the ECM regulates the orientation of the cell division axis.

Adhesion molecules also play role in the exit of newborn cells from the niches. The newborn cells usually exit the niches by downregulation of adhesions molecules. In some cases, such as in *Drosophila* and in developing mammalian central nervous system, E-cadherin-mediated adhesion between the SC and daughter cell lasts several hours after division and leads to Notch signaling activation in daughter cell (108). Transient activation of Notch signaling contributes to maintaining the differentiated precursor cell in the SC state and thereby preserves the SC population. Interestingly, the Notch ligand delta-like-1 is attached to cadherins through the scaffolding protein called membrane-associated guanylate kinase 1 (109).

Cell adhesion and cancer metastasis

Most cancer-associated morbidity and mortality (~90%) are caused by tumor cell metastasis, rather than by tumor development at its primary site (110,111). Tumor metastasis can be defined as the development of satellite tumors (typically in distant organs or in lymph nodes) from malignant cells originated from the primary tumor (112). Luckily, the metastatic process represents a cascade of inter-related events that provides targets for pharmacologic modulation and/or other types of interventions. Acquisition of invasiveness and anchorage-independent survival are main events in metastasis (112). The key events that occur in metastasizing tumor are as follows: (i) the increase of tumor mass leading to hypoxia-induced tumor angiogenesis, (ii) pre-metastatic niche formation, (iii) loosening of adherence between tumor cells/EMT (typically, downregulation of E-cadherin), (iv) invasion through the BM supporting the endothelium of local blood vessels, (v) intravasation of the tumor cells into blood or lymphatic vessels (this step is followed by spread of the tumor cells to distant anatomical sites), (vi) adherence of the tumor cells in circulation to the endothelial cell lining the target organ site, (vii) extravasation of the tumor cells and (viii) growth of the tumor (secondary) at the invaded anatomical/organ site (113).

Pre-metastatic niche. Pre-metastatic niche establishment precedes the influx of the tumor cells, wherein the environment for the incoming tumor cells is supportive for survival of the incoming cancer cells. Despite over a decade of research, pre-metastatic niches have not been well defined. The composition of pre-metastatic niches in different organs varies with respect to the adhesion molecules and growth factors, though to some degree, they exhibit a resemblance to the primary tumor microenvironment. It is well known that CAMs play important role in metastasis by helping extravagation of endothelial cells, however, their exact role in the pre-metastatic niche is not clearly understood (Figure 5). Below, we describe the characteristics and interactions within the pre-metastatic niche in the lung while highlighting features described also in other niches.

Bone marrow-derived hematopoietic progenitor cells (BMDCs), which express vascular endothelial growth factor (VEGF-A) receptor-1, are present at the metastasis-destination organ before the influx of the metastatic tumor cell(s) priming the tissue to receive metastatic cells by forming pre-metastatic niches (114). These BMDCs express CD133, CD34 and c-kit thereby retaining the progenitor status and VLA-4 ($\alpha_4\beta_1$-integrin) mediating adhesion to the pre-metastatic niche. It has been found that VLA-4 present on BMDCs helps in formation of the pre-metastatic niche for homing and proliferation of tumor cells in the secondary sites. This concept is actually based on VLA-4-mediated remodeling of circulating progenitor cells ($CD34^+$ BMDCs). Therefore, cancer progression just mimics this normal physiological process (115–117). Additionally, circulating $CD45^+$ $Col1a1^+$ hematopoietic cells called fibrocytes have been found to contribute to pre-metastatic microenvironment by CCL2-dependent recruitment of Ly-$6C^+$ monocytes (118).

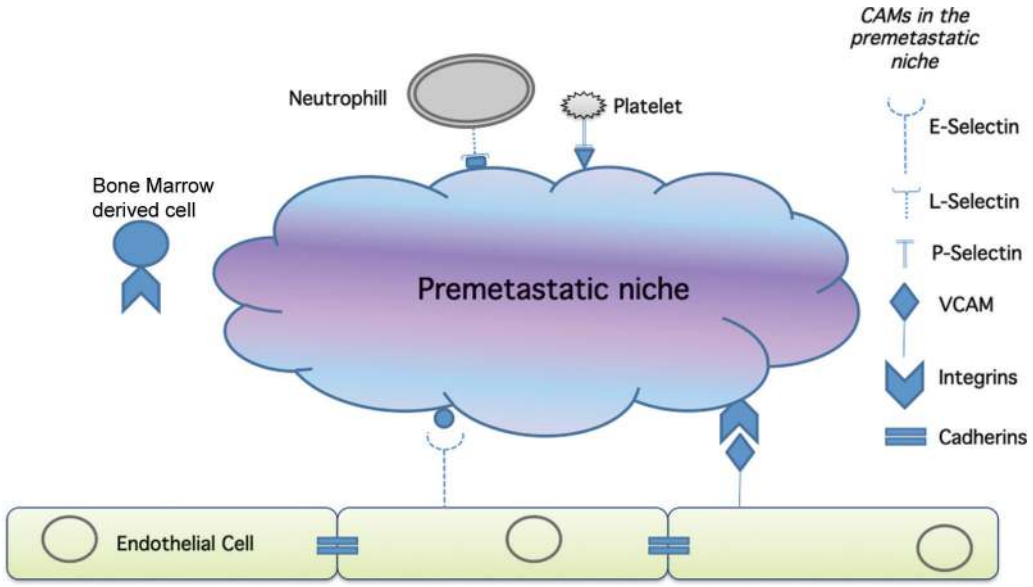

Fig. 5. Schematic representation of the pre-metastatic niche with the indicated role of various adhesion molecules. Formation of the pre-metastatic niche is indispensable for successful establishment of metastatic growth. The composition of pre-metastatic niches in different organs varies with respect to the adhesion molecules and growth factors, however, they exhibit similarities to the primary tumor microenvironment. The establishment of the pre-metastatic niche seems to largely depend on CAMs constitutively synthesized by the endothelium in order to home and accumulate the BMDCs, prior to the influx of the metastatic tumor cells (see main text for details).

Other cells at the metastasis-destination organ express fibronectin that is further upregulated upon tumor cell arrival by the tumor-specific growth factors. Primary tumor secretes pro-angiogenic factors VEGF-A, tumor necrosis factor and TGF-β, which results in the induction of S100A8 and S100A9-inflammatory chemoattractants, which in turn are involved in attracting the $CD11b^+$ ($Mac1^+$) myeloid cells to the pre-metastatic location (114,119). The S100A8 and S100A9 are involved in inducing the release of serum amyloid-A3 in the pre-metastatic lung, which signals nuclear factor-κB via toll-like receptor-4. This leads to accumulation of $CD11b^+$ myeloid cells causing a positive feedback resulting in increased chemoattractant secretion and metastasis in lung (120).

S100A8 and S100A9 also cause the recruitment of other populations of BMDCs, namely myeloid-derived suppressor cells (119) resulting in their maturation and enhanced inflammation (121). These myeloid-derived suppressor cells are also present at the pre-metastatic lesions at the primary tumor site and contribute to the production of multiple matrix MMPs, which are involved in degradation of the matrix (122). Osteopontin is another factor involved in chemoattraction and pre-metastatic niche formation (123).

In the primary breast tumors, lysyl oxidase (LYX) is released in the circulation in the hypoxic surroundings and is involved in the pre-metastatic niche formation. It is a marker for poor survival in breast cancers (124,125). In lung, LYX along with fibronectin localizes at the future location of metastasis, wherein it is involved in crosslinking collagen IV in the BM of the lung. As a result, there is an increased adherence of $CD11b^+$ myeloid cells. $CD11b^+$ myeloid cells produce MMP-2, which cleaves collagen IV, hence helping the invasion of the lung tissue and recruitment of BMDCs and metastasizing tumor cells (124). Fibronectin is also a critical regulator in the pre-metastatic niche formation. The fibronectin fibers are involved in the provision of microenvironments, which regulate LYX catalytic activity (125). Both fibronectin and LYX cooperate in the development of the pre-metastatic niche, which results in the recruitment of BMDCs and other mesenchymal cells.

Furthermore, selectins and IgSF are also involved in the establishment of pre-metastatic niche. The role of P- and L-selectin and its association in formation of the pre-metastatic niche is well known, but the functional contribution in the exact mechanism of metastasis is yet to discover. The upregulation of P- and L-selectin by platelets and leukocytes helps to form the ideal microenvironment for tumor progression (126). In case of IgSF, ICAM-1 (IgSF CAM) is found on the human lymphatic endothelial cells and is responsible for creating the pre-metastatic environment that is followed by micrometastasis of carcinoma cells within lymph node (127,128). The other type of Ig-CAM is METCAM (alternatively CD146 or MUC18) also plays a crucial role in the formation of favorable environment for pre-metastatic niche (129,130).

Tumor angiogenesis. Angiogenesis, or forming of the new blood vessels from the existing ones, is a rare event in adult tissues and takes place mainly during wound healing or female menstrual cycle. Expanding tumors greater than ~1 mm in diameter require blood vessels to support their further growth. Angiogenesis is induced and sustained mainly by hypoxia (113,131). The tumor and tumor stromal cells produce an array of pro-inflammatory and pro-angiogenic cytokines (tumor necrosis factor, VEGF-A, interleukin-8) (Figure 6), with VEGF-A being the most important one which is targeted in the clinic by bevacizumab/avastin (113).

The endothelial cells proliferate and migrate to chemoattractant gradient with the help of (metallo)proteinases, which are involved in degradation of the BM and surrounding stroma. These migrating endothelial cells then form new, often immature vessels that supply the tumor with oxygen and nutrients but can also provide a gateway for metastasis formation (113).

During the development of new vessels, the fine balance between pro-angiogenic VEGF-A, fibroblast growth factors, platelet-derived growth factor, EGF and angio-inhibitory factors (thrombospondin-1, angiostatin, endostatin and tumstatin) shifts to favor pro-angiogenic factors/events, also known as 'angiogenic switch' (132,133). Proteases play an important role in discharge of pro-angiogenic factors from the ECM and stimulating the angiogenic inhibitors (131,134).

Angiogenesis is induced by hypoxic conditions that stabilize hypoxia-inducible factors (HIF-1α and HIF-2α) (113,135). Activation of some oncogenes (e.g. RAS), kinases (e.g. phosphoinositide 3-kinase) or tumor suppressor genes (i.e. VHL, PTEN) also induces HIF-1α accumulation. Surprisingly, recent studies have shown that antiangiogenic therapy by sunitinib and bevacizumab generated intratumoral hypoxia in breast cancer xenografts via HIF-1α activation. Induction of HIF-1α was associated with the increase of the breast CSCs population limiting at the same time the efficacy of the antiangiogenic treatment (136).

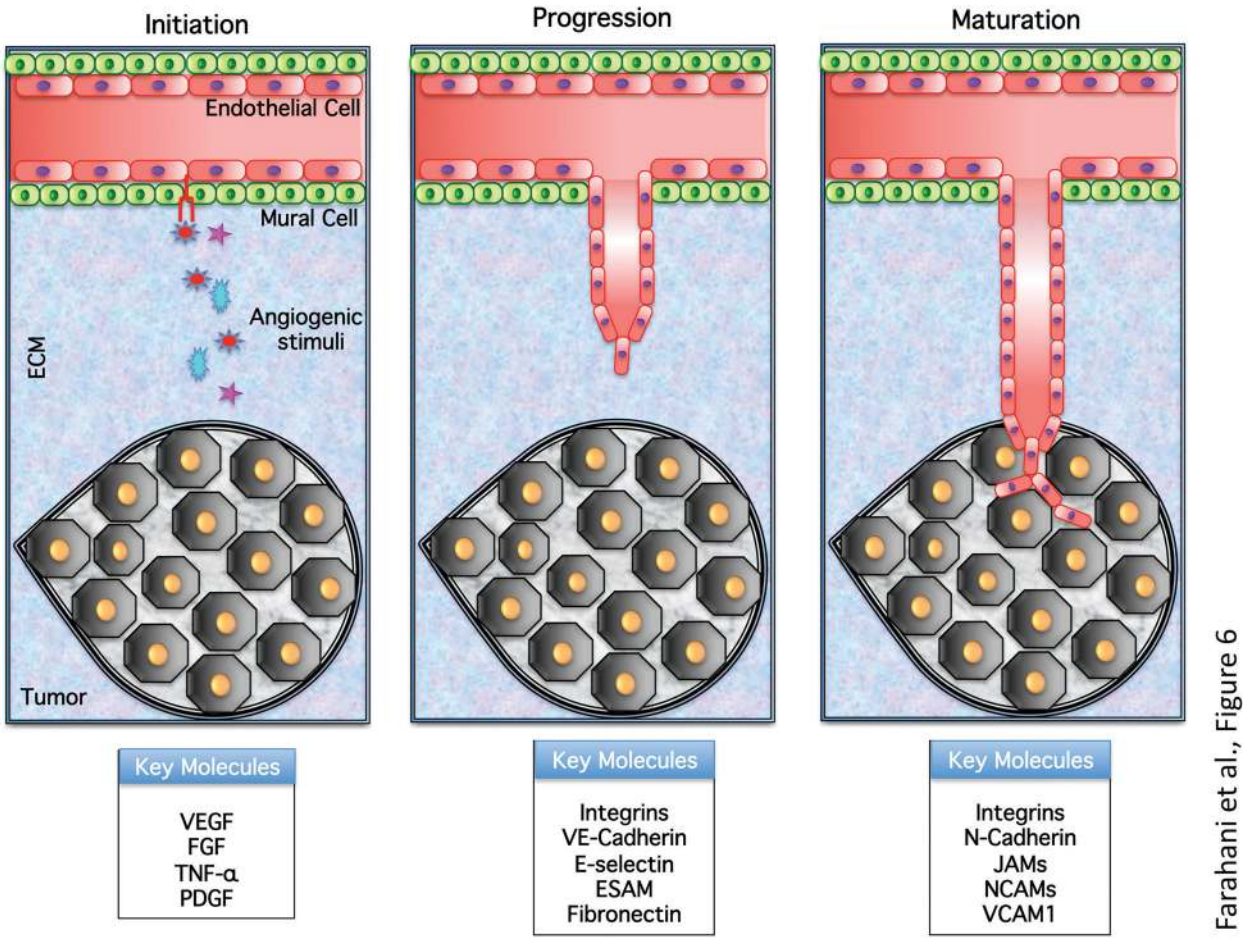

Fig. 6. Processes and molecules governing tumor vascularization. The interaction of tumor and endothelial cells in tumor angiogenesis process is highly dependent on the action of CAMs that mediate the adhesion of cancer cells to endothelial cells. The growth of new vessels plays a critical role in tumor growth and metastasis. Pink stars and light blue explosions concern tumor angiogenic stimuli such as fibroblast growth factor, VEGF and tumor necrosis factor; stars with red filling concern the secondary angiogenic stimuli that are released due to the endothelial cell-mediated degradation of ECM.

The four families of CAMs including integrins, cadherins, selectins and IgSF members are involved in tumor angiogenesis (Figure 6). The different types of integrins are asymmetrically expressed on luminal and abluminal domains of the endothelial cells and play important roles in cell migration. The *in vitro* formation of new capillary-like tubes was supported by *in vivo* observations about their involvement in the angiogenesis and vasculogenesis apart from their implication in cell–cell or cell–ECM interactions (137,138). The critical role of integrins are also evident from the fact that αvβ3 is expressed only in newly growing blood vessels, whereas it is absent in mature ones.

Vascular endothelial cadherin is another CAM expressed during vascularization and localizes at inter cell contact point, namely AJs. Vascular endothelial cadherin serves as regulator of angiogenesis and modulator of blood vessel integrity (139,140).

Endothelial selectin, a membrane glycoprotein, plays the key role for adhesion of leukocytes to cytokine-activated endothelial cells. The *in vitro* report suggests that it might be one of the important factors for tumor angiogenesis as the antibody against enothelial selectin can inhibit the sprouting (capillary-like tube) of the endothelial cells and the *in vivo* data suggest that the external addition of enothelial selectin can induce angiogenesis in organ-like cornea. Similarly, vascular cell adhesion molecule-1 also showed the influence on the angiogenesis (139).

EMT. EMT is an extremely dynamic process where cancer cells undergo reversible transitions between various phenotypic states. Ease of CSC to transit from epithelial-to-mesenchymal state testifies about their plasticity and is crucial for successful completion of the EMT program. The EMT phenotype of CSC is governed mainly by epigenetic regulation, which enables for the EMT-specific gene expression profile in CSC (141). As discussed previously, EMT is a series of changes in expression of adhesion molecules, particularly downregulation of E-cadherin that leads to the conversion of tightly connected epithelial cells into loosely adherent, fibroblastoid phenotype (29). Analysis of the cell lines in the different human carcinomas such as bladder, lung, breast and pancreas revealed that the cell lines, which expressed normal levels of E-cadherins, had epitheloid phenotype and were non-invasive *in vitro*, whereas cell lines with reduced E-cadherin appeared 'fibroblast-like' and were invasive. Transfection of the latter cells with E-cadherin resulted in the loss of invading ability and epitheloid phenotype reversion (142).

Loss or downregulation of E-cadherin is frequently found in primary cancers such as breast, nasopharynx, gastrointestinal tract, pancreas, lung, stomach, kidney, prostate and esophageal cancers (113). Analysis of α-, β- and/or γ-catenin showed downregulation in their expression in some of these tumors (113). Interestingly, the expression of N-cadherin promotes tumor cell metastasis irrespective of E-cadherin status of a given cell (29,143). In addition to angiogenesis, HIF1A activates transcription factors of the Snail family (SNAI1/Snail and SNAI2/Slug) and zinc finger E-box-binding homeobox family (ZEB1 and ZEB2) as well as TWIST1, TWIST2 and E12/E47, which regulate the EMT transcriptome program (144–148). LYX is also upregulated by HIF1A through FAK activation and facilitates EMT (149–151).

Invasion. Upon EMT, tumor cells migrate through the epithelial BM and the ECM. The tumor cells at first attach to BM and other

ECM components while interacting mainly through integrins (113). A common feature of cancer is altered expression of the integrins. High expression of αvβ3-integrin has been shown to be a marker of poor prognosis in melanoma (113). The αvβ3-integrin has also a role in vascular invasion, mediated through binding to L1 on endothelial cells. This induces melanoma cell migration toward the blood vessels, followed by the stromal degradation through binding to vitronectin and increasing MMP-2 expression (113). Other integrins are also involved in the tumor cell migration and invasion of BM and ECM. For example, overexpression of α3β1-integrin resulted in the direct proteolysis around tumor cells expressing the protein. In colon cancer, overexpression of α6β4 is proportional to the invasive capacity of the cells. The α6β4 binds to the laminin and forms a signaling complex with oncogenic RTKs, which includes Met, HER2 and the epidermal growth factor receptor. Furthermore, integrins α4β1 and α5β1 bind to fibronectin because fibronectin–integrin interactions are indispensable for the migration of tumor cells, invasion and metastasis (113).

The BM and other components of ECM are partially proteolysed so that migrating cells can gain some traction. The ECM-degrading proteases are responsible for facilitating the penetration through BM. These include, but not limited to, MMPs, plasmin (see below), cathepsins, elastase and heparanase. Homing receptors and their ligands like selectins, some IgSF receptors, integrins, carbohydrate-rich proteins and chemokine receptors are responsible for the interaction between migrating tumor cells and their surrounding vascular endothelium (112). It has been shown that during the metastatic invasion process, integrins interact with other CAMs like VLA-4 and help docking vascular cell adhesion molecule on endothelial cells, thus the migratory cancer cell can adhere and transmigrate through endothelial cells (152).

The tumors or the surrounding cells also release the urokinase form of the plasminogen activator (uPA) system. This uPA binds to its receptor uPAR and together with MMPs play critical role in tumor cell invasion. The uPA activity is regulated by plasminogen activator inhibitors PAI-1 and PAI-2, which bind to uPAR and prevents its activation. The uPAR is involved in the EGF module-containing mucin-like hormone receptor remodeling, proliferation, cell signaling, migration and survival, and its elevated levels have been reported in many cancers such as breast cancer (113).

In addition to angiogenesis, HIF1A described previously is involved in the regulation of other processes such as cell proliferation, glucose metabolism and VEGF expression (153). Furthermore, it has been described that HIF1A also fosters cell migration and invasion through upregulation of the chemokine receptor CXCR4 in renal cell carcinoma cells *in vitro*. In fact, the high level of CXCR4 in patients with renal cell carcinoma is a poor prognostic marker (149,154).

Intravasation of tumor cells. Intravasation starts with orientation of the tumor cells toward the vessels followed by directional cell migration. Tumor-associated macrophages have a critical role in this process. Macrophages in xenograft and transgenic breast cancer models have been reported to guide the tumor cells to the blood vessels and intravasation sites. This interaction is facilitated by paracrine signaling through CSF1 receptor on macrophages and epidermal growth factor receptor on tumor cells (149).

In N-cam knockout/Rip1-Tag2 mouse models of pancreatic β-cell tumors, the tumor cell clusters passively enter the 'leaky' lymph vessels leading to replacement of endothelial cells by tumor cells and their participation in neovascularization, a process introduced in 1999 and known as vasculogenic mimicry (149,155). Intravasation is often considered as a rate-limiting step in metastasis. This has been shown in the direct correlation between the number of intravasted cells and the number of lung metastases in a rat model with orthotopic breast tumor (149). The tumor cells give rise to metastatic tumors by proliferating intravascularly thereby obviating the need for extravasation (156).

Upon leaving ECM-environment, metastasizing cells lose the supportive, pro-survival signaling mediated mainly via integrins, phosphoinositide 3-kinase and Shc. Lack of such signals may lead to anoikis or detachment-induced apoptosis. Therefore, the metastatic cells have to (re-)activate pro-survival pathways allowing the anchor-independent survival (although some degree of pro-survival signaling could still be delivered via adhesion molecules that are mechanically triggered i.e. by sheer-force in the blood stream). Transcription factors Twist and Snail are involved in anoikis suppression, as shown in various cell systems. The transcriptional co-repressor C-terminal binding protein 1 is involved in suppression of both epithelial and pro-apoptotic genes simultaneously (149). Tyrosine-related kinase B, a neurotrophic receptor involved in the development and function of nervous system, is overexpressed in disease conditions wherein metastatic activity is present. Tyrosine-related kinase B has a role in suppression of anoikis and conferring oncogenic and metastatic potential to the epithelial cells (149). In reality, only ~0.1% of circulating tumor cells survive in their new environment.

Extravasation. The mechanism of extravasation is similar to leukocyte spread and recruitment in immune responses. The main receptors involved are integrins, selectins and IgSF. Selectins are three membrane-bound calcium-dependent lectins, which are involved in adhesion and mediate interaction between endothelial cells, platelets and leukocytes. Selectins are rigorously regulated. Tumor cells use selectins for metastasizing and cytokine release. Sialyl Lewis x and sialyl Lewis a (sLe^a) major binding ligands for selectins are overexpressed on tumor cells (149). Upon exposure to VEGF-A from cancer cells, Src-family kinases are induced in endothelial cells, causing the exit of the cancer cell through disruption of the endothelial cell junctions (113). Very little is known about cancer cells arrest in small capillaries and traversing the vascular wall during extravasation *in vivo*. Recent study has revealed that extravasation of cancer cells is influenced by metastasis-specific gene expression including Twist, VEGF-A and ITGB1 that modifies the cytoskeleton interactions leading to vasculature remodeling. Additionally, these pro-metastatic genes support survival, proliferation and motility of tumor cells. Intravascular movement of tumor cells does not depend on the direction of blood flow but requires β1-integrin-mediated adhesion to the vessel wall (157).

Growth of the tumor at the new site. The tumor cells that reach the new site/tissue are either destroyed, remain dormant for months, even years or may proliferate to form secondary tumors. Adaptive immunity often keeps the tumor in quiescent stage, but tumor-triggered activation of transcription factor Snail causes immunosuppression, thus facilitating tumor growth and metastasis (149). The tumors to grow at the new site eventually induce angiogenesis and local invasion. Pre-metastatic niche formation makes it easier for the tumor cell to survive and grow (113).

Clinical translation

CSC research field is relatively new, with first demonstrations of CSC in leukemia in late 1990s (31). Although the CSC existence is widely accepted in leukemias and lymphomas, in solid tumors it started gaining attraction only recently. The idea of developing drugs that would preferentially target CSC is gaining wide approval, and several screening projects have yielded initial preliminary results (158,159). The development of HER2 targeting agents has revolutionized anticancer therapy and is often considered as a key example of the effectiveness of molecularly targeted therapy. Data suggest that the clinical effectiveness of this therapy may be due to its ability to target the breast CSCs population (160). There is a huge therapeutic promise in the strategies targeting CSC, however, many of them are in the initial phase of experimental validation. Several clinical trials are currently in progress with agents that interfere with signaling pathways in CSC including Wnt, TGF-β, Hedgehog, Notch and PI3-K/Akt signaling pathways (161,162). Targeting adhesion molecules for cancer therapy is currently a very popular concept and many integrin inhibitors for anticancer therapy have entered phase I and phase II clinical trials (163–165). Elimination of CSCs can also be achieved by reversal of their resistance mechanisms. A better knowledge of the mechanisms that govern resistance of CSC to treatment is crucial and may provide a more effective therapy to overcome this limitation. As an example,

reversing chemoresistance in CSC populations can be achieved by specific blockade of multidrug resistance ABC transporters, as shown in human melanoma and pancreatic cancer (166,167).

There was a lot of hope associated with the development of humanized anti-VEGF antibodies that have been used in the clinic under the names bevacizumab or avastin. Unfortunately, despite initial tumor-shrinking effect, this revolutionary antiangiogenic drug failed to achieve conclusive life expectancy improvement in breast cancer, whereas its effect in colorectal and other cancers falls below expectations (168,169). Such treatments will not completely eliminate tumor cells, but rather dissipate them to 1–2 mm microtumors that can exist without the functioning blood vessels. Another relatively new concept in targeting CSC is differentiation therapy. This approach aims at ending the cell cycle of self-renewal by directing cells to differentiate into the specific type of cells. Recent studies have shown that drugs inducing differentiation of CSC are worth studying and differentiation therapy might be an alternative to conventional chemotherapy and radiotherapy (170–173). Majority of anticancer drugs currently in clinical use do not efficiently kill CSC. Thus, several laboratories are working on compounds that preferentially kill CSCs. As an example may serve salinomycin, an antibioticum with K+ ionophore action, that is able to preferentially target breast CSCs (174). Yet, despite initial setbacks, the strategies outlined previously for targeting CSC and/or adhesion molecules will most probably result in effective therapies in clinic, as they target crucial steps in cancer progression.

Supplementary material

Supplementary Figures 1 and 2 can be found at http://carcin.oxfordjournals.org/

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