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REVIEW

Endothelial cadherins in cancer

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Abstract Cadherins are cell adhesion receptors that play important roles in embryogenesis and tissue homoeostasis. Endothelial cells express various members of the cadherin superfamily, in particular vascular endothelial (VE-) cadherin, which is the main adhesion receptor of endothelial adherens junctions and neural (N-) cadherin, which is normally localized outside the junctions and may mediate adhesion between endothelial cells and non-endothelial cells. Dysregulation of cadherin expression has been implicated in tumor progression, in particular the loss of epithelial (E-) cadherin expression or function and the gain of N-cadherin. Moreover, more recently, aberrant expression of VE-cadherin was observed in certain cancer types. In breast carcinoma, VE-cadherin was shown to promote tumor cell proliferation and invasion through enhancing TGF-β signaling. Thus, in breast cancer, the cadherin switch involves another player, vascular endothelial cadherin, which is part of an intricate interplay of classical cadherins in breast cancer progression.

Keywords Cadherin · Vascular endothelial (VE-) cadherin · Neural (N-) cadherin · Epithelial (E-) cadherin · Breast cancer

Endothelial and epithelial cadherins

Epithelial and endothelial tissue is composed of continuous layers of cells that are interconnected by cell-to-cell junctions, in particular adherens junctions and tight junctions. The main adhesion receptors of adherens junctions are integral membrane proteins called cadherins. These Ca^{2+}-dependent adhesion molecules are typically engaged in homotypic cell-to-cell interactions. Through these interactions, cadherins serve as important mechanical functions (i.e., adhesion of neighboring cells with one another), which is required for tissue formation during development and for the maintenance of the epithelial or endothelial barrier function (Takeichi 2011). Through their association with the intracellular actin cytoskeleton, cadherins not only stabilize junctions and help to maintain cell shape and polarity but also allow for the dynamic regulation of junction opening and closure (Dejana 2004). Cadherins are normally named according to the tissues in which they are primarily expressed. For example, epithelial (E-) cadherin is the main constituent of epithelial cell adherens junctions whereas vascular endothelial (VE-) cadherin is expressed selectively in endothelial adherens junctions; N-cadherin is found in neural tissue and in mesenchymal and endothelial cells. Inside the cell, cadherins can be associated with the actin cytoskeleton via the catenins, α-catenin, β-catenin and p120-catenin (Berx and van Roy 2009; Yilmaz and Christofori 2009; Giannotta et al. 2013). Yet, the classical textbook view of a protein complex composed of these proteins has been challenged (Yamada et al. 2005). In addition to their mechanical functions, cadherins influence signaling pathways involved in cell proliferation, motility, survival and tissue homoeostasis (Dejana 2004; Giannotta et al. 2013). These activities can be accomplished by intracellular junctional proteins (such as β-catenin) that are released from the junctions, translocate into the nucleus and regulate transcription of specific target genes. Moreover, cadherins can interact with growth factor receptors and modulate their activity and downstream signalling. For example, VE-cadherin regulates activity of the high affinity receptors for the vascular endothelial growth factor (VEGF), transforming growth factor

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(TGF)-β and fibroblast growth factor (FGF) (Giannotta et al. 2013).

Endothelial cells form the inner surface of blood vessels and control the passage of substances and cells between the blood stream and adjacent tissues. The presence of VE-cadherin in cell–cell contacts is required for the maintenance of the integrity of the endothelial layer and it contributes to contact inhibition of endothelial cells (Giannotta et al. 2013). During vascular development, VE-cadherin is expressed in an endothelial–cell selective manner (Breier et al. 1996) and its function, in particular for endothelial cell survival, is essential for mouse vascular development (Carmeliet et al. 1999).

Endothelial cells also express N-cadherin but, in most cases, only VE-cadherin is localized at cell–cell contacts, whereas N-cadherin is excluded from these structures (Giampietro et al. 2012). The role of N-cadherin in endothelial cells is only partially understood; it is likely that N-cadherin mediates contact and communication of endothelial cells with other cell types, for example pericytes (Giannotta et al. 2013). VE-cadherin and N-cadherin exert contrasting activities in endothelial cells: while N-cadherin induces cell motility, VE-cadherin limits cell movement. Moreover, VE-cadherin reduces FGF-receptor phosphorylation and signaling whereas N-cadherin maintains high FGF-receptor activity in endothelial cells and induces a set of genes that are crucial for cell migration (Giampietro et al. 2012).

Cadherins and cancer

During tumor development, cancer cells acquire capabilities that allow them to sustain continuous proliferation, evade growth suppression, invade tissues and form distant metastases (reviewed by Hanahan and Weinberg 2000, 2011). A hallmark of cancer progression in carcinomas is the loss of the epithelial phenotype and the gain of mesenchymal characteristics, a process commonly referred to as the epithelial-to-mesenchymal transition (EMT) (Yilmaz and Christofori 2009; Micalizzi et al. 2010). During this process, which also occurs in embryonic development, epithelial adherens junctions are disrupted, leading to disintegration of the epithelial layer and the loss of basal–apical polarity; cells then gain a mesenchymal, invasive phenotype. A key event in EMT noted in various tumors of epithelial origin is the loss of E-cadherin expression (Yilmaz and Christofori 2009). E-cadherin down-regulation can be accomplished by transcriptional repressors such as Snail, Slug, Zeb and Twist, which are induced during EMT (Peinado et al. 2007). Apart from transcriptional repression, inactivating E-cadherin mutations have been reported in certain breast cancer types (Berx and van Roy 2009). Concomitant with the loss of E-cadherin, cancer cells up-regulate N-cadherin, which is normally expressed in neural cells, fibroblasts and endothelial cells (Giannotta et al. 2013). This cadherin is associated with a more invasive and aggressive cancer phenotype (Hazan et al. 2000).

E-cadherin is considered as a tumor suppressor protein (Yilmaz and Christofori 2009). This activity is, at least in part, due to the fact that E-cadherin can bind with its cytoplasmic domain to β-catenin, sequester it and prevent its nuclear translocation (Yilmaz and Christofori 2009). When released from cadherins, β-catenin can translocate to the nucleus and stimulate transcription of various genes involved in EMT. For example, β-catenin induces expression of the intermediate filament vimentin in breast cancer cells, leading to the acquisition of a mesenchymal phenotype (Gilles et al. 2003). In consequence, epithelial cytokeratins are down-regulated (Micalizzi et al. 2010).

VE-cadherin and cancer

Expression of VE-cadherin in blood vessel endothelium is normally associated with a resting, anti-proliferative state, which is partially a consequence of reduced VEGF receptor-2 activity (Giannotta et al. 2013). However, VE-cadherin is also present in tumor endothelium and application of VE-cadherin-specific antibodies in experimental tumors was able to block angiogenesis and tumor growth (Liao et al. 2000; Corada et al. 2002). Thus, VE-cadherin is involved in tumor angiogenesis (Cavallaro et al. 2006).

VE-cadherin deficiency is likely to play a role in the development of vascular tumors such as angiosarcomas because down-regulation of VE-cadherin expression in such tumors is associated with an increase in endothelial tumor growth and hemorrhagic complications (Zanetta et al. 2005); this effect was probably mediated by β-catenin and increased localization of N-cadherin at junctions.

However, VE-cadherin can also be expressed in cancer cells of non-endothelial origin. This was not entirely unexpected because aberrant expression of endothelial receptors has been observed in various tumor types before, for example expression of the endothelial-selective VEGF receptor-2. This receptor is expressed abundantly by the tumor vasculature and is stimulated by VEGF, leading to paracrine stimulation of tumor angiogenesis (Breier and Risau 1996). However, in certain malignancies, such as pancreatic cancer, VEGF receptor-2 can be expressed also by cancer cells and stimulate VEGF-driven autocrine tumor cell proliferation (von Marschall et al. 2000).

Aberrant expression of VE-cadherin in cancer cells was first detected in malignant eye tumors called uveal melanoma (Hendrix et al. 2001). The authors of this study have previously reported that intratumoral vascular channels of aggressive and metastatic intraocular melanoma can be lined by tumor cells instead of endothelial cells and had termed this phenomenon "vasculogenic mimicry" (Maniotis et al. 1999). Such vascular channels contained erythrocytes and had a basement membrane, suggesting that they function as blood vessels that contribute to the perfusion of the tumor tissue (Maniotis et al. 1999). Aggressive melanoma cells (but not less aggressive melanoma cells) expressed Tie-1 and VE-cadherin but lacked endothelial cell markers such as CD31 (PECAM) and VEGF receptor-2 (Hendrix et al. 2001). Vasculogenic mimicry was hypothesized to serve as a selective advantage for tumor cells (Seftor et al. 2012). The biological significance of this phenomenon has been debated (McDonald et al. 2000). However, several studies have suggested that patients with vasculogenic mimicry in their tumors have a poorer prognosis than patients without vasculogenic mimicry. Thus, the adoption of vascular cell characteristics by cancer cells may have implications for diagnosis and therapy. Vasculogenic mimicry was also observed in other tumor types, including carcinomas, sarcomas and brain tumors (reviewed by Paulis et al. 2010). Altogether, these observations show that tumor cells have remarkable plasticity.

More recently, evidence for a signaling function of VE-cadherin in tumor cells was reported by Labelle et al. (2008), who observed aberrant expression of VE-cadherin in aggressive breast carcinoma cells. In a mouse model of mammary carcinogenesis, VE-cadherin expression was observed at the cell surface of cancer cells that had undergone EMT and had down-regulated E-cadherin. In experimental tumors and human breast cancer specimens, VE-cadherin-expressing cells occurred as clusters in a pattern different from the "patterned vascular channels" described for malignant melanoma by Maniotis et al. (1999), suggesting that vasculogenic mimicry is not or not the primary function of VE-cadherin expression in breast cancer cells. Rather, VE-cadherin stimulated tumor cell proliferation and invasion by enhancing the protumorigenic TGF-β signaling. This activity of VE-cadherin was unexpected because VE-cadherin expression in endothelial cells is normally associated with a resting state of cells (Dejana 2004). Interestingly, VE-cadherin also enhances TGF-β signaling in endothelial cells, by interacting directly with TGF-β receptors (Rudini et al. 2008). TGF-β inhibits the proliferation of normal cells and even of cancer cells in early stages of tumor progression; however, in advanced tumors, TGF-β promotes cell proliferation and EMT, leading to a more aggressive and invasive cell phenotype (Yilmaz and Christofori 2009). This phenomenon is known as the TGF-β paradox. Thus, VE-cadherin can either inhibit or stimulate cell proliferation, depending on the effect that TGF-β signaling has: in endothelial cells, VE-cadherin enhances the growth inhibitory activity of TGF-β, whereas in cancer cells, it stimulates its protumorigenic activity.

Interplay of VE-cadherin, N-cadherin and E-cadherin in breast cancer cells

In endothelial cells, both overlapping and divergent signaling pathways have been reported for VE-cadherin and N-cadherin (Giampietro et al. 2012). Moreover, VE-cadherin inhibits N-cadherin localization at the adherens junctions and N-cadherin expression, by reducing p120-catenin availability and the transcriptional activity of β-catenin (Giampietro et al. 2012). Thus, these cadherins may act in concert and influence each other.

Members of the cadherin superfamily are expressed in the normal mammary gland: E-cadherin is expressed exclusively in mammary epithelium, whereas N-cadherin is found in mesenchymal cells of the stroma (Andrews et al. 2012). As described above, N-cadherin is upregulated in mammary carcinoma cells and is associated with a more aggressive behavior, as indicated by a migratory, invasive and metastatic phenotype (Hazan et al. 2000). N-cadherin and E-cadherin can be co-expressed in malignant epithelial mouse breast cancer cells that have not undergone EMT; however, E-cadherin expression is lost after the cells have undergone EMT and adopted mesenchymal characteristics (Labelle et al. 2008). Silencing of N-cadherin in mesenchymal breast cancer cells greatly reduced tumor growth and restored the epithelial phenotype to a large extent, as indicated by re-expression of E-cadherin at cell contacts (Rezaei et al. 2012; Fig. 1a). This process, termed mesenchymal-to-epithelial transition (MET), is known to occur during metastasis, as well as during embryogenesis (Yilmaz and Christofori 2009). MET was accompanied by redistribution of β-catenin from the nucleus to the periphery of mouse mammary carcinoma cells and by reduced expression of EMT regulators, Snail and SIP1 (Rezaei et al. 2012; Fig. 1a). VE-cadherin silencing had a less pronounced effect on tumor growth and on the mesenchymal phenotype but led to the localization of N-cadherin to the cell junctions (Fig. 1b). Taken together, these observations show an intricate interplay between the classical cadherins, E-cadherin, N-cadherin and VE-cadherin in breast cancer cells that influences their expression and localization and hence most likely specific signaling pathways associated with these receptors: whereas E-cadherin acts as a tumor suppressor, the

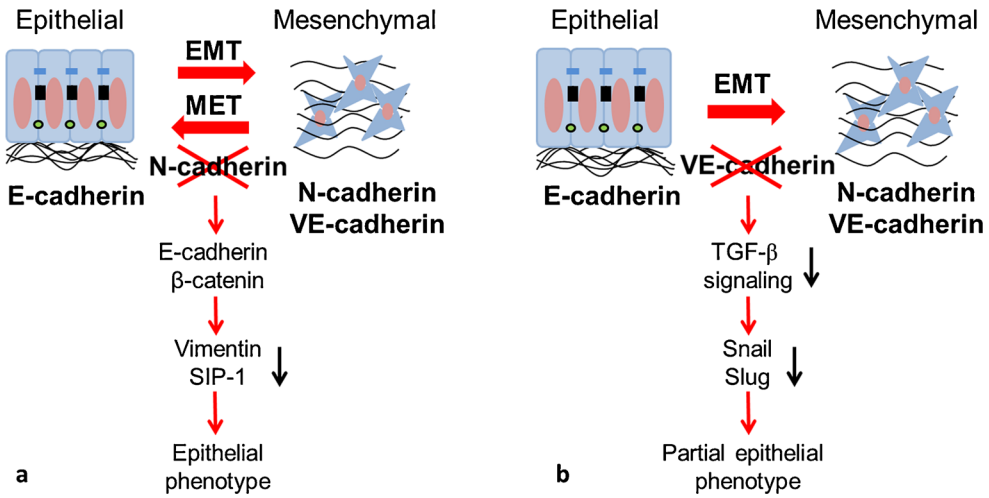

Fig. 1 VE-cadherin and N-cadherin have overlapping and divergent functions in breast cancer cells, as revealed by the effects of gene silencing (Rezaei et al. 2012). **a** N-cadherin silencing reverses TGF-β-induced EMT, leading to the gain of the epithelial phenotpye. In this scenario, E-cadherin is re-expressed at cell contacts and recruits β-catenin. Moreover, the EMT regulators, vimentin and SIP-1 are down-regulated. **b** VE-cadherin silencing only partially restores the epithelial phenotype, though reducing TGF-β signaling and EMT regulator expression. *EMT* epithelial to mesenchymal transition, *MET* mesenchymal to epithelial transition

endothelial cadherins, N-cadherin and VE-cadherin promote cancer growth through distinct mechanisms (Rezaei et al. 2012).

The tumor suppressor function of E-cadherin in breast cancer cells may, however, not be unconditional. Nieman et al. (1999) observed that N-cadherin is able to promote motility regardless of E-cadherin expression. Moreover, certain human basal-type breast cancer cell lines have undergone EMT but have not lost E-cadherin expression, showing that E-cadherin deficiency is not an absolute necessity for EMT of carcinoma cells (Hollestelle et al. 2013). E-cadherin silencing might, therefore, be a consequence, rather than the cause, of EMT induction (Dumont et al. 2008).

Conclusions

Numerous studies suggest that the loss of E-cadherin and concomitant gain of N-cadherin represents a key event during the conversion of epithelial cancer cells into mesenchymal cells that gain the capability to invade tissues and metastasize to distant organs. According to this model, E-cadherin functions as a tumor suppressor, whereas N-cadherin promotes motility, invasiveness and metastatic spread of cancer cells. More recent evidence shows that the cadherin switch in breast cancer is not restricted to these two classical cadherins but involves another player, VE-cadherin, which is normally expressed selectively by endothelial cells and stimulates protumorigenic TGF-β signaling in cancer cells. Thus, N-cadherin and VE-cadherin act in concert to promote breast cancer progression.

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