Introduction

Cell adhesion molecules are substances of a protein character that are necessary for normal embryogenesis, morphogenesis, tissue formation and repairation, but they are also involved in many pathophysiological processes such as inflammation, angiogenesis, thrombosis, tumour invasion and metastasis. In general, cadherin adhesion molecules are a large group of adhesion molecules located at intercellular junctions called adherent junctions. They play an important role in embryogenesis and morphogenesis in animals and humans due to their adhesive and cell-signalling functions. Disturbances of the expression or function of cadherins and their associated proteins called catenins are crucial for the initiation and development of many pathological states. E-cadherin is an epithelium-specific cadherin required for the development and maintenance of the normal function of all epithelial cells in tissues. The loss or down-regulation of E-cadherin is a key event in the process of tumour invasion and metastasis. The assessment of E-cadherin immunoreactivity may be a useful prognostic marker in some cancers, complementary to the established prognostic factors. VE-cadherin is an endothelium-specific cadherin, which plays a relevant role in vascular homeostasis. It has been demonstrated that VE-cadherin is required for normal vasculogenesis, angiogenesis, and for the maintenance of vascular integrity. Disruption of VE-cadherin-catenin complexes by some inflammatory agents such as thrombin, by inflammatory cells, or shear stress is accompanied by an increase in vascular permeability in vivo and in vitro.

Key words: Cadherin family, E-cadherin, VE-cadherin, Cancerogenesis, Endothelial permeability
Function of the cadherins

Catenins interact with membrane proteins including transmembrane receptors. They are responsible for cell-to-cell adhesion and they have a very important cell signaling function. Cadherins mediate homotypic interactions by binding to their homologues on an adjacent cell. However, it has been found that some members of this family can provide heterotypic interactions, but this is not the predominant adhesion mechanism (27). There are several ways of how cadherin could be involved in cell signalling events. First, through their homotypic binding they can approach the opposing membranes of neighbouring cells in close proximity and enable interactions of ligands and receptors of these opposing cells and stimulate juxtacrine signalling. Second, because cadherins are able to control the polarity of cells they can affect signaling via their influence on the distribution of membrane proteins, including transmembrane receptors. Finally, cadherins may behave as ligands or receptors and hence they have been found to directly signal cell-cell contact activity (18). All these signaling functions of cadherins are associated with the activation of some regulatory cascade comprising the action of tyrosine kinases and tyrosine phosphatases. Cell signaling domains of cadherin, beta-catenin and plakoglobin are common targets of these regulatory proteins (38). Adhesive and signaling properties of cadherins can not be separated. Any changes in the expression or function of cadherins might lead to initiation or progression of pathological processes. Within many members of the cadherin superfamily, the present authors have focused on two extensively studied ones, E-cadherin and VE-cadherin.

Epithelial cadherin (E-cadherin, LCAM, ovomorulin)

E-cadherin is an epithelium-specific cadherin. This cadherin is a member of the classical cadherin subfamily. Normal expression and function of E-cadherin is required for proper embryogenesis and morphogenesis of various tissues. Variations in E-cadherin expression have been noted during specific events in embryonic morphogenesis (30). Mutation of the E-cadherin gene leads to early embryonic lethality which is proceeded by a loss of cell-cell adhesion at the morula stage (5). E-cadherin is necessary during normal neural development (5). It has been demonstrated to occur locally and persistently in the murine central and peripheral nervous system during normal development (36). Expression of E-cadherin (together with P- and N-cadherin) has been observed in murine primordial germ cells. E-cadherin is concentrated at the sites of cell-cell contacts of primordial germ cells (PGCs), suggesting an active role in PGCs-PGCs interaction and recognition (6). In the last years, the alteration in expression and function of E-cadherin has been correlated with cancer development (5). Loss or reduction of E-cadherin expression is in relation with enhanced aggressiveness and dedifferentiation of many carcinomas which has been reviewed by Beavon (4). Ageron et al. have shown that decreased E-cadherin expression is frequent in breast cancer and that a loss of E-cadherin expression is associated with a loss of heterozygosity in the infiltrating lobular breast carcinomas but not in the infiltrating ductal carcinomas. Furthermore, the loss of expression of E-cadherin is an important prognostic marker, especially for disease recurrence in node-negative breast cancer patients and may even be more informative than tumour size or oestrogen receptor expression (3). Ghadimi et al. have shown that reduced expression of E-cadherin and even oestrogen is observed in primary colorectal carcinoma. Moreover, they were able to demonstrate a significant correlation between the histological grading of the tumours and an increased loss of E-cadherin and oestrogen expression. Defective expression was significantly more frequent in less differentiated carcinomas (G3-4) with a pronounced loss of epithelial morphology than in better differentiated tumours (G1/G2) (17). Garcia del Muro et al. have suggested that E-cadherin and beta-catenin as confirmed by immunohistochemistry are important prognostic markers in patients with bladder carcinoma. This leakage of E-cadherin expression was associated with high grade and invasive stage of bladder carcinoma. Further, a loss of E-cadherin expression was a significant prognostic indicator of decreased survival, independent of known prognostic factors such as stage, grade, or p53 status (23). There are many other studies which have described a relation between decreased E-cadherin and/or catenin expression and its correlation with dedifferentiation, infiltrative tumour growth, distant metastasis, and poor survival for patients with gastric carcinoma (37), pancreatic carcinoma (40,16), prostate cancer (41).

Despite the fact that E-cadherin is extensively studied in relation to cancerogenesis, Bobryshev et al. have elucidated expression of E-cadherin in human atherosclerotic lesions (42). It has been described that E-cadherin is expressed by macrophage origin intimal cells transforming themselves into foam cells, but there were no expression of E-cadherin in non-atherosclerotic intima. They suggested that E-cadherin might be important for foam cell aggregation. If E-cadherin is involved in foam cell aggregation, it might also be involved in the development of the lipid core which is an important step of progression of atherosclerosis (9).

Vascular endothelial cadherin (VE-cadherin, catenin 5 or 7B4)

VE-cadherin is endothelium-specific cadherin and it is located strictly at intercellular junctions (zonula adherens) of essentially all types of vessels both in vivo and in vitro (14,15). VE-cadherin has been first identified by Lam-pugnani et al. by adopting an indirect approach of developing mouse mAbs to human endothelial cells (20). In term of the structure, VE-cadherin is composed of an extracellular domain, a transmembrane segment, and a cytoplasmic domain that form complexes with catenins and mediate the association of VE-cadherin with the actin cytoskeleton. However, compared with classical cadherins, the VE-cadherin amino acid sequence shows considerable differences (only 23% identity when compared with classical cadherins such as E-, N- and placentals (P)-cadherins) (11,24).

VE-cadherin is required for normal vasculogenesis and angiogenesis and for the maintenance of vascular integrity and permeability in adults (13). VE-cadherin is expressed in the embryos at very early stages of vascular development in mesodermal cells of the yolk sac mesenchyme. At later embryonic stages, VE-cadherin expression is restricted to the peripheral layer of mesodermal cells which rise into the endothelial cells (10). The role of VE cadherin permeability control is consistent with the observation that the VE-cadherin-catenin complex is the target of the action of permeability-increasing agents. Rabiet et al. have shown that thrombin, which is known to induce profound alterations of endothelial cell monolayer permeability in vivo and in vitro, caused endothelial cell retraction accompanied by a redistribution of VE-cadherin and catenin from adherence junctions. This disassembly of adherence junctions was accompanied by an increase in vascular permeability (28). The proinflammatory cytokines tumour necrosis factor- alpha (TNF-alpha) and interferon-gamma (INF-gamma) act synergistically in vitro and in vivo to activate the endothelium, resulting in cellular responses such as altered morphology, loss of barrier function, and adhesion molecule upregulation and/or redistribution (31,32). Wond et al. have described that tumour necrosis factor- (TNF-alpha) and interferon-gamma (INF-gamma), in combination, affect the barrier function of the vascular endothelial lining by direct stimulation of the endothelium that results in the disruption of VE-cadherin mediated cell-cell adhesion, which is succeeded by an increase in the permeability of mesenteric venules (44). Andriopoulos et al. have studied the effect of histamine, another mediator of inflammatory reaction, on adherens junction organization in cultured endothelial cells. They have reported that histamine induces tyrosine phosphorylation of VE-cadherin and catenins, which results in an increase in endothelial permeability. The effect of histamine was specific for VE-cadherin, another
actin cytoskeleton. Other catenins can also be associated with the cytoplasmic domain of cadherins, including different isoforms of the so-called p120
catenin. It has been found that this catenin interacts with a membrane-proximal region of cadherin that has been shown to be responsible for lateral clustering. This suggest that p120
catenin can regulate the strength of cadherin-mediated adhesion (43). In general, the interaction of cytoplasmic domain with the actin cytoskeleton via catenins significantly increases the strength of the intercellular junctions (45).

**Function of the cadherins**

There are two main functional features of cadherins. They are responsible for cell-to-cell adhesion and they have a very important cell signalling function. Cadherins mediate homotypic interactions by binding to their homologues on an adjacent cell. However, it has been found that some members of this family can provide heterotypic interactions, but this is not the predominant adhesion mechanism (27). There are several ways of how cadherin could be involved in cell-signalling events. First, through their homotypic binding they can approach the opposing membranes of neighbouring cells in close proximity and enable interactions of ligands and receptors of these opposing cells and stimulate juxtacrine signalling. Second, because cadherins are able to control the polarity of cells they can affect signalling via their interaction with the activation of membrane receptors. Finally, cadherins can help to maintain the integrity of the muscle cytoskeleton and transmembrane receptors.

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herin is concentrated at the sites of cell-cell contacts of prirmordial germ cells (PGCs), suggesting an active role in PGCs-PGCs interaction and recognition (6).

In recent years, the alteration in expression and function of E-cadherin has been correlated with cancer development (43). In general, the interaction of cytoplasmic domain with the actin cytoskeleton via catenins significantly increases the strength of the intercellular junctions (45).

\[ \text{Fig. 1: Structure of cadherin-catenin complex.} \]

Representation of cadherin-catenin complex depicting cadherin ectodomain, transmembrane region (TM) and carbo-
xy-terminal cytodomain (CTYO) and catenins that link cadherin to the cytoskeleton. Ectodomain of classical cad-
herin consists of five repeated domains (C1-C5) with ad-
hesive interface located at C1 domain. Carboxy-terminal cytodomain has binding sites for β-catenin and γ-catenin (plakoglobin) and membrane proximal binding site for p120
catenin. α-catenin and γ-catenin are associated with ecatenin which provide linkage to actin cytoskeleton.

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major endothelial cadherin (2). In addition to agonists described above, endothelial permeability is affected by a group of inflammatory cells, namely polymorphonuclear leukocytes (PMNs) (33). Several groups have shown that activated polymorphonuclear leukocytes (PMNs) dramatically alter molecular composition and organization of VE-cadherin-catenin complexes in endothelial cells. This disruption of VE-cadherin-catenin complexes leads to disassembly of adherens junctions which is followed by an increase in endothelial permeability (42.1). These inflammatory agents and cells are not the only ones that might exert effects on VE-cadherin-catenin complexes. The structure and physiology of endothelial cells are influenced by shear stress of blood flow. The most obvious structural responses of endothelium to shear stress are changes in the cell shape and orientation; in areas of low or inconsistent shear stress, in vivo or in vitro endothelial cells form a cuboidal, cobblestone shape, whereas they elongate and align in the direction of flow when shear stress is moderate or high (21). Noria et al. have examined transient and steady-state effects of shear stress on the cadherin-catenin complex at endothelial adherens junctions. They have reported that increase of shear stress on endothelium causes partial disassembly of adherens junctions followed by a reassembly that reflected shear-induced reorganization of actin distribution. After adaptation to shear stress, adherens junction proteins were localized in adhesion plaques (adherens plaques) that were distinct from the linear belt-like distribution that predominates in static cultures. Thus, adherens junctions in the endothelium exposed to physiological levels of shear stress are structurally distinct from such junctions in static endothelial cell cultures or in epithelial mono-layers (26). As mentioned above, the normal expression and function of VE-cadherin is necessary for the maintenance of normal endothelial permeability; however, it is important in vasculogenesis in the embryo as well as in adults. Bobryshev et al. have examined the expression of VE-cadherin in atherosclerotic lesions. They have demonstrated that VE-cadherin is expressed in early sprouts of neocapillaries and it suggests that VE-cadherin is involved in the ingrowth of medial capillaries into the intima (8). This neo-vascularization is important for local immune-inflammato- ry reactions in atherosclerotic plaques (7).

Conclusion

In this review the authors have described structure and function of cell adhesion molecules from cadherin family. We have focused on two extensively studied E-cadherin (1), which is involved in various aspects of human physiology, and cadherin-5 (7B4), an endothelial-specific cadherin which is expressed by endothelial cells and plays important role in vascular homeostasis. It is required for vasculogenesis and maintenance of vascular permeability. Its expression and function is disturbed during inflammation.

In our prospective study we would like to described behaviour of these two cadherins during development and progression of atherosclerosis (on rabbit model of ather- osclerosis) because changes in vascular permeability, neo-vascularization and formation of lipid core are crucial for formation of atherosclerotic plaques.

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Conclusion

In this review the authors have described structure and function of cell adhesion molecules from cadherin family. We have focused on two extensively studied E-cadherin (43,1). Both VE-cadherin and E-cadherin are crucial for proper embryogenesis, morphogenesis but they are involved in many pathological states. Changes in expression and function of E-cadherins seem to be important for development of carcinoma in various tissues. VE-cadherin is developed cadherin which is expressed by endothelial cells and plays important role in vasculogenesis. It is required for vasculogenesis and maintenance of vascular permeability. Its expression and function is disturbed during inflammation.

In our prospective study we would like to describe behaviour of these two cadherins during development and progression of atherosclerosis (on rabbit model of atherosclerosis) because changes in vascular permeability, neo-vascularization and formation of lipid core are crucial for formation of atherosclerotic plaques. Acknowledgment

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