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Roles of PECAM-1 in cell function and disease progression

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Abstract. – Platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31) belongs to immunoglobulin superfamily, which is key factor for adhesion and accumulation of platelets. It is proved that PECAM-1 is closely correlative with cell migration, proliferation, apoptosis, signal transduction and cellular immunity. Meanwhile, PECAM-1 involves in multiple clinical diseases, such as atherosclerosis, thrombosis and leukemia. This paper reviewed the structure and function of PECAM-1, and its roles in cell function and disease generation and progression.

Key Words:
PECAM-1, Signal transduction, Cell development, Disease progression.

Introduction

Platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31) is transmembrane glycoprotein (relative molecular weight 130 KDa), which belongs to immunoglobulin superfamily. PECAM-1 could be expressed on endothelial cells, circulatory platelets, neutrophilic granulocytes and subgroup of T cells. It also reported that PECAM-1 was expressed during the whole process of hematopoietic stem cell development[1]. PECAM-1 is a kind of cell adhesion molecules (CAM), CAM interact between cell and cell, or cell and extracellular matrix. CAM includes five categories: cadherin, selectin, Ig-superfamily, integrin, and hyaladherin. Both developing and matured vascular endothelial cells expressed PECAM-1, so PECAM-1 was deemed as the marker of vascular endothelial cells. Moreover, PECAM-1 can mediate the cell adhesion and signal transduction, regulate the leukocyte migration and platelet development and inhibit cell apoptosis. PECAM-1 is also closely relative to processes of clinical diseases. This paper reviewed the structure and function of PECAM-1 and its roles in cell function and disease generation and progression.

Gene and Protein Structure of PECAM-1

Gene Structure of PECAM-1

PECAM-1 gene located on terminatio of chromosome 17 long arm (17q23). This kind of transmembrane glycoprotein is composed of extracellular region, cytoplasmic domain and transmembrane domain. The open reading frames include 16 exons. Extracellular region of PECAM-1 includes 574 amino acids encoded by 8 exons, the other 8 exons encoded 19 amino acids to make up the transmembrane domain and also encoded 118 amino acids to make up the cytoplasmic domain. According to alternative splicing of either the transmembrane or cytoplasmic domain exons, there are several alternative spliced variants of PECAM-1 expressed in a cell-type and species-type pattern[2,3].

Protein Structure of PECAM-1

Extracellular region of PECAM-1 includes 6 homologous regions composed by 6 subunits of immunoglobulins, each homologous region is encoded by solitary exon, and each subunit includes respectively 94, 103, 90, 93, 91 and 81 amino acid residues. PECAM-1 of extracellular region directly participated in the cell-cell interactions. Once contacted with endothelial cells, PECAM-1, via its extracellular region amino acids with positive charge, could locate at the cell junction of endotheliocytes[4].

The intracellular region of PECAM-1 contains two consensus sequences (L/I/V/S-x-*Y*-x-x-L/V), which respectively constitutes two immunoreceptor tyrosine-based inhibitory motif (ITIM). The ITIM can specifically bind the SHP-2, a widely expressed cytoplasmic tyrosine phosphatase with two src-homology 2 (SH2) domains. These two tyrosines are Y663 and Y686, Phosphorylated Y663 and Y686 can bind with SHP-2, so as to possess multiple physiological effect. The intracellular region of PECAM-1 contains 12 Ser

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residues, 4 Thr residues, and 5 Tyr residues, which all are phosphorylation sites. To date, only the Ser and Tyr phosphorylation were reported[5]. PECAM-1 homologous binding and non-homologous binding could interconvert. The expressed PECAM-1 of cell surface emerged as two patterns, homologous binding as primary and the other as secondary.

PECAM-1 and Cell Function

PECAM-1 and Cell Migration

In the initial stage of inflammation, PECAM-1 caused leukocyte extravasation, promoted the migration of leukocytes. Both specific anti-PECAM-1 antibody and inhibiter of PECAM-1 expression in endotheliocytes can restrain the leukocytic migration[6] and human umbilical vein endothelial cell migration[7]. PECAM-1 might mediate the cell migration by activating the integrinsβ1, β2 and β3[6,7]. PECAM-1, through combining to its ligands, activated integrins to regulate cell migration. There are reports that PECAM-1, CD99 and JAM participated in leukocyte trans-endothelial cell migration, JAM and its ligand LFA-1 made the leukocyte adhere to endotheliocytes, then PECAM-1 mediated its extravasation, and CD99 completed this process[8,9]. During the transmigration of polymorphonuclear leukocytes, VE-cadherin-containing adherent junctions were relocated aside, not opened or disrupted, whereas PECAM-1-containing junctions were opened during polymorphonuclear leukocytes transendothelial migration[10]. In our study, we found that human umbilical cord blood-derived stromal cells secreted SDF-1 to stimulate PECAM-1 expression in megakaryocytes, and consequently promoted the migration of megakaryocytes. PECAM-1 is relative to SDF-1/CXCR4 axis in MK development[11,12]. It was found that megakaryocytes in PECAM-1$^{-/-}$ mice cannot migrate along with the SDF-1 concentration gradient[13]. Subsequent studies reported that PECAM-1 on the megakaryocytes can chemotactically cause megakaryocytes to migrate by changing the distribution of its own CXCR4[14,15].

PECAM-1 and Cell Apoptosis

PECAM-1 inhibited the cell apoptosis through activating or suppressing the proteins in signal pathways, those proteins contain Akt, Bcl-2, Bcl-X, caspase, p38/JNK and MAPK et al[16]. PECAM-1 might phosphorylate the caspase 8 and P38/JNK to inhibit apoptosis. PECAM-1 binding resulted in viable cells to send out repulsive signals, so macrophagus distinguished between apoptosis cells and viable cells, selectively exerted phagocytosis function. In particular, it has been shown that PECAM-1 binds to different kinases and phosphatases, including the phosphatidylinositide-3-kinase that phosphorylates Akt, which, in turn can up-regulate transcription and function of anti-apoptotic proteins, such as Bcl-2 and Bcl-x or A1, responsible for the rescue from mitochondrial apoptosis. The possible role of PECAM-1 engagement in the prevention of starvation-induced apoptosis of HPC precursors and in the maintainance of their survival is discussed[17]. Homology binding of PECAM-1 and stability of ITIM are very important for inhibiting Bax and promoting cell surviving[18]. On the other hand, PECAM-1 might over-express some protective genes to inhibit apoptosis, such as A20, A1 and HO-1[19]. Some signal pathways related with PECAM-1 anti-apoptosis function include β/g catenin, SHP-2, integrin activation, PI-3 kinase, PLCg1, Stats3 and Stats5 pathways[2].

PECAM-1 and cell Signal Transduction

On the whole, physiological functions of PECAM-1 are closely correlative to signal transduction. Intracellular region of PECAM-1 contains 12 Ser, 4 Thr and 5 Tyr tyrosine residues. Among those, phosphorylation of Tyr663 and Tyr686 is especially important. Phosphorylation of Tyr in PECAM-1 binding to SHP-2, activated SHP-2, then initiated Ras signal pathway, lastly phosphorylated ERK[20]. It has showed that PECAM-1 cleavage under high shear stress is closely related to the activation of calpain and the process of platelet-derived microparticles formation mediated by the GPIb-VWF interaction[21].

PECAM-1 also is the regulatory molecule on the ion channels. There are two ways: the first is direct effect of PECAM-1 intracellular region and ion channels, the second is indirect effect via suppressing the inhibitor of ion channels[22]. Adherence of PECAM-1 is important for cell signal transduction. After cell adhesion, extracellular signals transmit into intracellular amino acid residue Tyr, and then phosphorylation of Tyr triggers cell biochemistry events, on the contrary, the phosphorylation of Tyr also transmits the signals to extracellular region, affecting the cell adhesion[23,24].

PECAM-1 and Angiogenesis

Anti-PECAM-1 antibody inhibited angiogenesis induced by cytokines or tumors in animal models[25,26]; PECAM-1 homology binding promotes the stability of conjunction of endothelium via activating cell catenin[7]. Both PECAM-1 and the integrin beta3 have been implicated in angiogenesis, and in vitro studies, integrin beta3 has been identified as a heterotypic ligand for PECAM-1, anti-beta3 integrin mAbs reduced leukocyte extravasation[27]. In brain gliomas, expression of PECAM-1 on glioma cells mediated the gliomas angiogenesis[28,29].

PECAM-1 and Cellular Immunity

PECAM-1 receptor has been classified as a member of the ITIM-bearing immune co-receptors. Beyond a marker for endothelial cells, PECAM-1 has important regulatory functions on immune cells, which thus far has been neglected. Fornasa et al[30] used PECAM-1 peptide to reduce $CD4^+$-specific immune responses against oxidized low-density lipoprotein, which suggests that PECAM-1 participates in T-cell autoimmunity. PECAM-1 has been shown to inhibit antigen receptor signaling in T- and B-cells through the action of proteintyrosine-phosphatases (SHIP, SHP-1 and SHP-2), which are recruited by its ITIMs. In the thymus, PECAM-1 regulates TCR signaling, affects selection of thymocytes. In mature naive T-cells, PECAM-1 regulates homeostatic expansion, facilitates their access to lymphoid organs. PECAM-1-mediated interactions with DCs regulate T-cell expansion and survival. PECAM-1–PECAM-1 interactions might control the expansion of antigen-specific B-cells and affect NK cell-mediated cell lysis of T-and B-lymphocytes and of dendritic cells. Collectively, the current data point to a unique role of PECAM-1 as a non-redundant co-modulator of T-cell responses[31].

PECAM-1 and Clinical Diseases

PECAM-1 and Atherosis

Lu Fang et al[32] have found the plasma PECAM-1 concentration increased in the coronary artery stenosis patients. During the atherosis, PECAM-1 can influence the stability of atherosclerotic plaque[33]. At the patients of myocardial infarction (MI), the platelets PECAM-1 concentration increased, in addition, at the animal mode of infarction, the anti-PECAM-1 antibody concentration decreased[34]. After the late or frustrated thrombolytic therapy, the level of platelets PECAM-1 in MI patients is higher. It has proved peroxydase can resist oxidization of blood vessels, but the PECAM-1 affects this peroxydase contact with endothelium. Genovariation of PECAM-1 plays key role in progression of coronary artery disease. Diseases like stenocardia, acute myocardial infarction, cardiac shock, and sudden death almost take place from 6 am to 12 am the level of PECAM-1 during this time is closely correlative to those disease occurrence[35]. During the thrombolytic therapy for acute myocardial infarction, the plasma PECAM-1 concentration changed dynamically: at first increased slightly, and then decreased slowly. It is supposed that this change is implicated in ischemia reperfusion of coronary artery.

PECAM-1 and Thrombopoiesis

PECAM-1 is the key factor for platelet adhesion and accumulation, and PECAM-1 inhibits the accumulation of platelets, it plays the negative regulatory role in thrombopoiesis[5]. Each quiescent platelet expressed about 8000 PECAM-1 moleculars, and the activated platelets of thrombus expressed two times PECAM-1 than the former. This mechanism might be that ITIMs phosphorylation of PECAM-1 inhibits the stimulation of collagen, CVX and plasmas to platelet tyrosine phosphorylation and the Ca^+ release. The PECACM-1 interactions between platelets and blood vessel endothelium regulate the thrombotic progression. PECAM-$1^{-/-}$ mice has larger and stable thrombus than wild type mice[36]. At the first 24 hours of acute cerebral infarction, plasma PECAM-1 level of patients increased apparently in Zaremba et al study[37]. The mechanism of high level of PECAM-1 can be regarded as an organism negative feedback. This biological feedback, via PECAM-1, transmits inhibitory signal, restrains platelet adhesion, accumulation and release, curbs the activation of platelets around the thrombus, so as to inhibit the enlargement of thrombus volume, and lessen the brain injury. At the 14^{th} day of acute cerebral infarction, the patients with higher platelet PECAM-1 concentration get less neurologic impairment. It hinted that negative feedback of platelet PECAM-1 level existed in the earlier period of acute cerebral infarction, and to monitor the PECAM-1 level can help to judge the prognosis of acute cerebral infarction.

PECAM-1 and Vessel Reparation

PECAM-1 participates in the lymphatic vessel endotheliocyte proliferation, migration and vessel-like structure formation. In the process of angiopoiesis, endothelial cells contacted each other firstly, then proliferated, and migrated to ground substance, lastly established new cell connection and formed the new vessel. PECAM-1 binds tyrosine phosphorylated β-catenin, modulates β-catenin localization and regulates proliferation of endothelial cells[38,39]. PECAM-1 of ITIM phosphorylation and de-phosphorylation and SHP-2 activation and relocation, regulate the migration of endothelial cells. During the injury reparation, PECAM-1 regulates the migration of endothelial cells, which depends on the small G-protein Rho signaling pathway[40,41].

PECAM-1 Gene Polymorphism and Diseases

The PECAM-1 gene spans about 75 kb and locates on chromosome 17q23[42]. Several polymorphisms have been reported in the PECAM-1 gene including three missense polymorphisms: Val125Leu in exon 3, Asn563Ser in exon 8, and Gly670Arg in exon 12[43]. Val125Leu is in the first Ig-like domain involved in the homophilic interaction[44], whereas Asn563Ser is in the sixth Ig-like domain, which may participate in the heterophilic interaction with integrins[45]. On the other hand, Gly670Arg is in the cytoplasmic domain, playing a key role in signal transduction[46]. Wenzel et al[47] have found that the homozygous combination of Leu125Val and Ser563Asn polymorphisms in the PECAM-1 gene is associated with early severe coronary heart disease. They investigated the genetic variability of the PECAM-1 gene in 103 healthy controls and in 98 patients (median age 42, range 25-50 years) with more than 50% stenosis followed by PTCA or bypass grafting. The allele frequencies of the Leu125Val polymorphism were 0.49/0.51 in controls and 0.35/0.65 in patients ($p < 0.01$). The allele frequencies of the Ser563Asn polymorphism were 0.50/0.50 in controls and 0.37/0.63 in patients ($p < 0.05$). The homozygous genotype combination Val125/Asn563 was significantly increased in patients compared to the controls. Fang et al [48] showed that Leu125Val polymorphism of PECAM-1 gene and elevated soluble PECAM-1 were related to severe coronary artery stenosis in CAD patients of Asian Indian origin in Singapore. They also suggest that PECAM-1 plays an important role in the development of atherosclerosis. Gardemann et al[49] have found Val^{125} elevated mostly in diabetes patients and those with normal blood pressure. Listi et al[50] has detected Leu125Val, Ser563Asn and Gly670Arg, and also get the same outcome with above reports. The homozygous genotype combination Val125/Asn563 in the Ig1/Ig6 domain of the cellular adhesion molecule PECAM-1 may be a genetic risk factor for development of early coronary heart disease. Behar et al[43] believed that Leu125Val mutation changed the PECAM-1 adhesive function, which resulted in coronary artery disease. Another possible explanation for the association of MI with the PECAM-1 polymorphisms is that the responsible disease-related genetic alteration is not in the PECAM-1 gene but is located nearby. It is, therefore, of interest that the ACE gene is mapped on 17q23 near the PECAM-1, implying that the association of MI with the PECAM-1 polymorphisms might be a reflection of linkage disequilibrium between the ACE-D allele and the PECAM-1 563Ser and 670Arg alleles[51].

PECAM-1 and Hematologic Disease

PECAM-1 plays vital roles in development of three line hematopoietic cells. Ballen et al[39] observed the PECAM-1 and CD44 level of bone marrow and peripheral blood of aplastic anemia patients, they have found the concentration of PECAM-1 and CD44 in bone marrow and peripheral blood mononuclear cells are lower in those patients than normal control people. There is a significant positive correlation between the level of PECAM-1 and the number of peripheral blood leukocytes, hemoglobin, platelets and three-line hematopoietic cells in bone marrow. In conclusion, the adhesion molecule expression abnormality might play critical role in aplastic anemia genesis. Besides, multiple myeloma patients secreted and expressed both CD38 and PECAM-1[52]. The expression of PECAM-1 is closely correlative to patient prognosis in chronic B lymphocytic leukemia[53]. In B-cell MALT-type primary gastric lymphoma patients, PECAM-1 was proved to be statistically significant independent unfavorable prognostic factor. In the univariate analysis, PECAM-1(+)/ICAM-3 (-) patients exhibited a significantly decreased overall survival[54]. Wu et al[14] have found megakaryocyte development damage in PECAM-$1^{-/-}$ mice. Gordon et al[55] have reported that cell adhesion molecular make the immature hematopoietic cell stick to bone marrow stromal, and regulate those cell re-

lease and differentiation. When it comes to hematopoietic stem cell transplantation, PECAM-1 gene polymorphisms are implicated in the pathogenesis of graft-versus-host disease (GVHD). More and more proofs suggested PECAM-1 mismatching increased the risk of acute GVHD[56-58].

PECAM-1 and Other Diseases

According to Ruco's report[59], cryostat sections of reactive lymph nodes, obtained from surgical specimens of gastric and breast resections, were immunostained for PECAM-1. The result pointed out that PECAM-1 was constitutively expressed in all types of endothelial cells, sinus macrophages, and in epithelioid granulomas. The PECAM-1 and von Willebrand factor (vWF) positivity observed for all oral hemangioma and pyogenic granuloma cases demonstrated the pivotal role of the angiogenic factors in the etiopathogenesis of these two diseases[60]. Hydrolysis of PECAM-1 by gingipains of *Porphyromonas gingivalis*, increased vascular permeability and neutrophil flux at disease sites, resulted in some periodontal disease[61]. Brain metastasis-selected variant cells, harvested from breast cancer brain metastases in nude mice, contained significantly more PECAM-1-positive blood vessels, which means PECAM-1 participated in pathology of breast cancer brain metastases[62]. Decreased levels of soluble PECAM-1 and P-Selectin in the plasma of patients with autism spectrum disorder (ASD), suggested a role for these molecules in the complex pathophysiology of ASD[63]. In a word, the roles of PECAM-1 in many diseases depend on its multifaceted molecular biological characteristics, as we mentioned before, such as regulation of cell migration, apoptosis, signal transduction, and so on.

Conclusions

PECAM-1 might be the only adhesion molecular on the platelets, but it is not merely expressed on the platelets. At present, more and more researches pay attention to the PECAM-1 construction, function and gene expression. PECAM-1 mediates adhesion between cell and cell, or cell and extracellular matrix, regulates platelet function, inhibits cell apoptosis, and modulates cell signal transduction; PECAM-1 plays pivotal roles in inflammatory reaction, wound healing, and angiogenesis; PECAM-1 also is implicated in multiple diseases, such as artherosclerosis and leukemia[33].

But the mechanism of PECAM-1 needs to be explored. About the mystery of PECAM-1, there are four special questions: (1) PECAM-1 binding. The homology binding and nonhomologous binding directly regulate cell-cell interactions. For example, the confirmation of ligand for PECAM-1 allogenous binding is important for modulating interactions between cells. (2) Phosphorylation of PECAM-1 tyrosine. To find the kinase of Tyr phosphorylation, and explore the mechanism will further the researches on PECAM-1 signal transduction function. (3) To explore the detailed signal transduction pathway of PECAM-1, will help disclose the disease pathological changes related to endotheliocytes[64]. (4) The potential influences of CD31-mediated interactions on the development and function of the immune system have yet to be fully investigated.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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