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Research on PAR-1 in Cancer, Cardiovascular Disease and Nerve-related Diseases

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Abstract: *PAR-1 (protein kinase receptor 1, also known as thrombin receptor) is a member of the G protein-coupled receptor family, and its main ligand is thrombin. PAR-1 is mainly expressed in platelets, endothelial cells, smooth muscle cells and some neural cells, involved in hemostasis and atherosclerosis formation. At present, a great deal of research has also confirmed that PAR-1 is involved in epithelial-to-mesenchymal transition and epithelial-to-endothelial transformation; PAR-1 can regulate the NF-κB pathway, stimulate the formation of tumor angiogenesis, and participate in the development of tumors through a variety of ways. At the same time, the blood state of tumor patients often presents a hypercoagulable state. As one of the thrombin receptors, PAR-1 may participate in the formation of hypercoagulable state in tumor patients. The review focuses on the expression and activation mechanism of PAR-1 and its physiological pathological process; And how to participate in the occurrence and development of tumors and the relationship with cardiovascular diseases. The aim is to point out that PAR-1 may be a potential target for tumor therapy and may be helpful to improve the hypercoagulable state and prolong the survival of patients with advanced cancer.*

Keywords: *PAR-1; EMT; high blood coagulation; atherosclerosis; tumor angiogenesis and metastasis; nervous system*

1. Introduction

According to an article published in the international journal of medicine ' Lancet'[1]: at present, the top two causes of death in China is stroke and ischemic heart disease, and the third cause of death is cancer. With the improvement of people 's living standards and the acceleration of population aging, the incidence of stroke and cancer is also increasing, which will also become the primary threat to the health of people and the primary source of economic burden in our country. Therefore, improving people's awareness of physical examination and developing new drugs have become the primary problems to be solved in China. Stroke is an acute cerebrovascular disease, the main causes are hypertension and atherosclerosis. Atherosclerosis is a chronic inflammatory disease involving the immune system, which mainly leads to a variety of cardiovascular diseases[2]. Numerous studies have shown that PAR-1 plays an extremely important role in the progression of atherosclerosis, and more and more studies have also shown that PAR-1 may participate in the metastasis and infiltration of cancer[3].

2. PAR-1 Activation and Inactivation Mechanism

PAR-1, regard as one of the G protein-coupled receptor family, can be activated by proteases. Its first ligand discovered was thrombin, so it is also known as thrombin receptor. PAR-1 is divided into activated protease and inactivated protease according to the different effects produced by protease cleavage of different sites[4]. Most GPCR are reversible after binding to ligands, but thrombin-activated PARs are irreversible. Thrombin cleaves the N-terminus of PAR-1 and exposes a new N-terminal peptide-------SFLLRN, which bind and activate the PAR-1 transmembrane core[5]. Activated PAR-1 binds to multiple G protein isoforms (Gq/Gi/G12/G13) and participates in different signaling pathways[4]. Subsequently activated signaling pathways are rapidly terminated by G protein-coupled receptor kinase (GRK) - mediated phosphorylation and binding to inhibin[6]. In addition, the rapid release of activated PAR-1 from the cell membrane into the cytoplasm also plays a key role in the termination of PAR-1 signaling[7]. The mechanism may be that the inhibin bound to GPCR binds to the adaptor protein complex 2 (AP-2) and promotes PAR-1 internalization from plasma membrane through the clathrin and dynein-dependent

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pathway of AP-2[8]. Among them, dynamin-like protein is a GTPase, which can regulate the budding of the clathrin-encapsulated inner membrane and promote the detachment of secretory vesicles, and then internalized PAR-1 is transported from the endosome nucleolus to the lysosome and rapidly degraded[9,10].

3. PAR-1 is involved in the formation of atherosclerosis

Atherosclerosis (AS) is a kind of arterial disease characterized by arterial wall thickening, hardening and decreased elasticity. Currently recognized risk factors are: hyperlipidemia, hypertension, smoking, genetic factors, secondary hyperlipidemia and other diseases. Its pathogenesis is currently recognized in the following several theories: (1) Lipid infiltration theory: increased cholesterol in the plasma will be deposited in the arterial intima, causing the proliferation of connective tissue, arterial wall thickening and hardening. (2) Damage-response theory: Under various stimulating factors, the structure and function of endothelial cells are damaged. The damaged endothelial cells can secrete cytokines or growth factors, attract monocytes to gather, adhere to the sub-endothelium, and migrate into the sub-endothelium space. Through the surface receptors, the oxidized lipids that have entered the intima are taken in. (3) The role of arterial smooth muscle cells (SMC): SMC in the arterial media migrated into the intima, took up low density lipoprotein and proliferated. (4) Chronic inflammation theory: Inflammation mechanism runs through the whole process of AS formation.

PAR-1 is expressed in endothelial cells, platelets, and smooth muscle cells and is important for maintaining the stability and integrity of vascular walls[11,12]. PAR-1 activation promotes the transformation of endothelial cells into pro-inflammatory phenotypes, increases vascular permeability, promotes the secretion of cell-related factors, and mediates local aggregation of platelets and white blood cells, thereby participating in hemostasis and anti-infection processes[13]. In normal arteries, expression of PARs in SMC is very small, However, in endothelial dysfunction vessels, the expression of PARs is significantly increased; This suggests that PAR-1 may promote the pathological process of AS by promoting the proliferation and migration of smooth muscle cells and promoting SMC to produce extracellular matrix[14].

PAR-1 may engage in the process of inflammatory response. The body will produce some inflammatory mediators as a result of an inflammatory response. Inflammatory mediators will promote the tissue around the inflammation to produce matrix metalloproteinases (MMPs). MMPs will cleave PAR-1 and activate the signal pathway mediated by PAR-1, increasing intracellular Ca^{2+} [15], promoting the activation of internal and external coagulation pathways, speeding up the development of thrombosis, and promoting the secretion of some cytokines by vascular endothelial cells, which will turn promote the proliferation of vascular smooth muscle cells, accelerating the formation of AS. MMP-1 is prone to rupture and hydrolyzes the fibrous cap of atherosclerotic plaques, which decreases the stability of the plaques. As a result, inhibiting the MMP/PAR1 pathway lowers the prevalence of cardiovascular disease[16]. At present, the thrombin PAR-1 receptor pathway has received more and more attention in the field of cardiovascular research, and related drugs have been developed for the PAR-1 receptor pathway to treat arterial thrombotic diseases[17,18].

4. Role of PAR-1 in neuronal repair

PAR-1 is primarily expressed in astrocytes and neurons in the nervous system, but it is scarcely found in oligodendrocytes and microglia. It is also widely expressed in the nerve sheaths of peripheral nerves and in several significant neural areas of the brain (such as hippocampus, amygdala and substantia nigra). It is a new synaptic response regulator[19]. Relevant studies have demonstrated that thrombin can be made to proliferate astrocytes, activate the MAPKs/NF-B signaling pathway in cells through the PAR-1 receptor, and take part in a variety of physiological and pathological processes in mice with spinal cord injuries[20]. Using a mouse model, Rachel Price also discovered that PAR-1 can suppress synaptic NMDARs in mouse substantia nigra-dopamine neurons[21], and its main mechanism is to participate in the regulation of NMDARs internalization. NMDARs is an ionotropic glutamate receptor, mainly distributed in the postsynaptic membrane of nerve cells. It plays an important role in brain growth, memory-related synaptic plasticity, and central nervous system deterioration[22]. It has been shown that inhibition of NMDARs can enhance the role of dopamine in Parkinson 's disease (PD) mouse model, so PAR-1 as a potential molecular therapeutic target is often used in PD research[23]. In vitro experiments also showed that the expression of PAR-1 enhanced the activity of Schwann cells[24]. Candice E. Junge's linked research, however, revealed the opposite outcomes[25]: After acute focal cerebral ischemia, the infarct volume of animals lacking the PAR-1 receptor dropped by 3.1 times, and the infarct volume was

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decreased by 2.7 times by injecting a PAR-1 antagonist into the lateral ventricle. As a result, PAR-1 blockage protects nerve cells, which is in contrast to the way that PAR-1 protects the nervous system. This appears to be connected to the level of PAR-1 activators and participation in several signaling pathways[26]. The role of PAR-1 in the nervous system remains to be further studied.

5. PAR-1 participates in EMT

Epithelial-mesenchymal transition (EMT) is the fundamental factor for the invasion and migration of epithelial-derived malignant tumors. This process causes the cancer cells to break away from the primary tumors and go to new locations. Epithelial cells into mesenchymal cells gradually lost the phenotype of epithelial cells to obtain the phenotype of mesenchymal cells. The loss of connection between epithelial cells makes it easier for tumor cells to grow invasively to surrounding tissues and form metastases with blood flow to distant sites. Among them, tyrosine kinase receptor signaling pathway, integrin signaling pathway, WNT signaling pathway[27], NF-κB signaling pathway and transforming growth factor-β signaling pathway may be involved in the regulation of EMT.

Through PAR-1, thrombin regulates the NF-B signaling pathway to cause vasculogenic mimicry (VM). Gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, has been demonstrated in related studies to have an effect on VM. EGFR inhibitors may also raise the expression of vascular endothelial growth factor (VEGF) in tumors while being treated, which means that anti-angiogenic therapy may enhance the creation of VM and lead to drug resistance[28]. Thrombin inhibitor r-hirudin or DTIP reduced tumor VM and reduced the expression of N-cadherin, vimentin, and snail[29]. According to research, Twist (an EMT transcription regulator) can regulate the transformation between epithelial and endothelial cells, boosting the creation of VM, and PAR-1 activation in liver cancer can promote Twist expression [30]. By regulating the Hippo pathway, PAR-1, a direct transcriptional target of Twist, can encourage EMT, tumorigenicity, and tumor metastasis [31].

6. PAR-1 promotes proliferation and metastasis of tumor cells through multiple pathways

Oncogene activation, tumor suppressor gene inactivation, metabolic re-editing, apoptosis-regulating gene dysfunction, infinite proliferative capacity/cell immortalization, sustained angiogenesis, acquisition of invasion and metastasis capabilities, evasion of immune surveillance, genomic instability, control of the tumor microenvironment, and epigenetics are all factors in the complex process of tumorigenesis. According to studies, PAR-1 can encourage the development of tumors in the following ways.

6.1. PAR-1 induces tumor angiogenesis and promotes tumor migration

Professor Judah Folkman first proposed that tumor growth and metastasis depend on the surrounding new blood vessels[32]. The absence of blood arteries may induce dormancy in tumor cells[33]. When the body is not stimulated by external environmental factors, blood vessels are usually in a stationary phase. The activation of vascular endothelial cells occurs when static blood vessels are stimulated by outside factors (such as inflammation, hypoxia, and tumor release of VEGF/ANG-2/FEFs). Activated endothelial cells release MMP, which degrades the vascular basement membrane and causes pericytes from the vessel wall to detach. At the same time, activated endothelial cells and tumors release VEGF to increase vascular permeability and plasma protein extravasation, and establish a temporary extracellular matrix scaffold (ECM) around the blood vessels[34]. Then, under the stimulation of VEGF and FGFs, the ECM is remodeled into a vasoactive extracellular matrix network. Endothelial cells then proliferate on the ECM surface while being guided by integrin. They then join together via CD34/E-cadherin to form a lumen structure. In order to sustain neovascularization, mature blood vessels, and finish the growth and metabolism of surrounding tissues, proliferating endothelial cells can induce pericytes to deposit around ECM by NOTCH signal pathway / placental growth factor (PIGF) / fibroblast growth factors (FGFs) [35]. The development of blood vessels is necessary for the growth of tumor tissue, hence stopping angiogenesis in the vicinity of the tumor can slow its growth[36].

Currently, it has been demonstrated in numerous investigations that the expression of PAR-1 is much higher in cancer tissues than in normal tissues [37–39], suggesting that PAR-1 is connected to the development of cancer. Angiogenesis can be promoted by thrombin in vitro through PAR-1, according to a study by Caunt M. This mechanism may be connected to the up-regulation of VEGF and angiopoietin-2 (Ang-2) [40]. Related experiments verified that the activation of PAR-1 will induce VEGF expression [41]. PAFR (platelet activating factor receptor) expression can also be induced by PAR-1[42].

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Endothelial cell proliferation can be induced by PAFR, VEGF, and Ang-2, which also promote angiogenesis. Rafael Perini's mouse model for stomach ulcers demonstrated that thrombin can facilitate platelet release of VEGF via PAR-1 and prevent the release of vascular endothelin, which stimulates vascular development[43].

MMPs play an important role in tumor proliferation, metastasis, apoptosis and angiogenesis[44]. It was demonstrated that MMP-1 can cut and activate PAR-1 and promote the migration of cancer cells in a model using allogeneic transplantation for breast cancer [45]. Cell motility is the basis of tumor migration and metastasis. MMP-1 and thrombin increase the upregulation of myosin IIA and fibrin B, activate PAR-1, cause RhoA and Rac1 phosphorylation, and transfer to the cell membrane. and promote the migration of tumor cells[46]. Eric Yang's research also demonstrated that inhibiting the MMP-1 / PAR-1 signaling pathway can accelerate breast cancer cell death and reduce the risk of lung metastasis[47].

The polarity of diverse cells in various biological conditions was discovered to be regulated by PAR-1 in the study of Drosophila ovarian development. The fact that PAR-1 is required for the separation of border cells from epithelial cells in Drosophila oocytes suggests that PAR-1 may contribute to cell loss of adhesion and encourage tumor spread [48]. The expression of intercellular adhesion molecules can, however, be increased by PAR-1, according to other studies [49]. It is still necessary to confirm the research on PAR-1's role in promoting tumor spread.

6.2. PAR-1 is involved in drug resistance and apoptosis of tumor cells

Tumor heterogeneity, tumor microenvironment, tumor size, tumor growth rate, changes in tumor growth kinetics caused by medication therapy, and other variables have all been linked to tumor resistance, according to some correlation studies [50-51].

Gemcitabine was utilized to treat PAR-1 defective mice and PAR-1 wild-type mice, respectively, in the mouse pancreatic cancer model, according to Karla C.S. Queiroz. As a result of gemcitabine treatment, the tumor growth in wild-type mice was reduced by around two times. Gemcitabine nearly totally prevented the tumor growth in PAR-1-deficient animals after the PAR-1 gene was removed from the microenvironment [52], indicating that PAR-1 might reduce gemcitabine's effectiveness in the treatment of pancreatic cancer. This process might be connected to PAR-1 controlling macrophage recruitment in the tumor microenvironment. The tumor-suppressing M1 and the tumor-promoting M2 are the two primary subtypes of tumor-associated macrophages (ATM), and they can transform into each other in the tumor microenvironment [53]. The number of ATMs was three times lower in PAR-1-deficient animals than in wild-type mice. However, it was discovered that both M2 / M1 were > 95% in PAR-1 wild-type mice and PAR-1-deficient animals, suggesting that PAR-1 is primarily connected to ATM recruitment and is not engaged in regulating ATM polarization [52]. However, the function of PAR-1 in ATM polarization is unclear due to a lack of evidence from recent studies.

Additionally, by preventing tumor cells from dying, PAR-1 can contribute to the resistance of chemotherapeutic medicines. According to Robert D. et al 's research on prostate cancer, thrombin and PAR-1 together will decrease docetaxel's ability to trigger apoptosis by upregulating the BCL-2 family member BCL-XL[54]. The study by Tomoko Suzuki, however, demonstrated the opposing viewpoint [55]. It was discovered that PAR-1 altered the permeability of mitochondria when investigating the mechanism by which elastase-induced apoptosis of human lung epithelial cells was caused by PAR-1. Caspase-9 and Caspase-3 are activated, degrading DNA nuclease, disassembling the cytoskeleton, and promoting apoptosis as a result of the mitochondrial membrane's cytochrome C being detached and dissociated into the cytoplasm. The experiment of Alex C. Chin[56] also confirmed that PAR-1 can promote the apoptosis of gastrointestinal epithelial cells through caspase-3 and destroy the tight junction ZO-1 between epithelial cells, thereby increasing the permeability of intestinal epithelium. However, due of circumstances, PAR-1 concentration, tissue type, and the role of PAR-1 in several signaling pathways, Robert D. et al 's study does not specifically state whether PAR-1 inhibits or promotes apoptosis.

7. PAR-1 is involved in the formation of hypercoagulable state in tumor patients

A growing body of research has demonstrated that cancer patients' blood will become hypercoagulable as a result of both the tumor itself and the anti-tumor therapeutic procedure. Individuals with tumors are approximately 7 times more likely to develop hypercoagulable states than patients without tumors. The risk may even increase by 28 times in some malignant tumors, such as hematological cancers, lung cancer, and gastrointestinal tumors[57]. The development of the patient's own malignancies

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and the hypercoagulable state of their blood promote each other. Certain tumors can release coagulation factors and activate the body's endogenous or exogenous coagulation pathways, which can lead to the development of a hypercoagulable state. The blood's hypercoagulable status will stimulate tumor spread [58,59]. Therefore, effective anticoagulant medication will not only lessen the negative effects of a hypercoagulable state on the body but will also lower the potential for tumor spread in tumor patients [60].

The major way that PAR-1 is involved in blood coagulation is through the activation of the PAR-1 receptor on platelets by thrombin. Thrombosis is a continuous process. First of all, One-stage hemostasis is the temporary stopping of minor hemorrhage after vascular injury, exposure of subcutaneous collagen, activation of platelets, platelet adhesion, and aggregation at the site of vascular injury. Afterwards, prothrombin complex is created by the slow initiation of the endogenous and external coagulation pathways, which activates prothrombin into thrombin. Following this, thrombin activates FXIII to cause fibrin monomers to bind to one another and form water-insoluble fibrin polymers, which are then braided together into networks to form blood clots and finish the coagulation process[61]. Thrombin can activate platelets through PAR-1 and PAR-4 receptors [62-64], promoting the release of ADP, TXA2 and serotonin from platelets. These mediators will react on platelets and promote the aggregation of platelets in the second phase[65], thus initiating the coagulation process. However, it was discovered in a clinical observation trial of lung adenocarcinoma patients that increasing PAR-1 expression was unrelated to the development of thrombosis[66], but the number of cases observed in this study was small, so the results of this study may be biased. At present, there are few studies on the relationship between PAR-1 and hypercoagulable state in tumor patients, and more evidence is needed to confirm and reveal the molecular signaling pathways involved.

8. The prospect and summary of PAR-1

The most researched topic at the moment is PAR-1 as a thrombin receptor involved in the development of atherosclerosis [67-69] and increase tumor metastasis [70,71], and significant progress has been made in this field. For instance, the PAR-1 role in AS was addressed by the development of the PAR-1 antagonist Vorapaxar. Vorapaxar was found to significantly lower the risk of cardiovascular death, infarction, stroke, and emergency coronary revascularization in the medical study TRA20P-TIMI 50, but it also significantly increased the risk of major bleeding and limb swelling [72,73]. Even its bleeding risk was greater than the benefit of its own treatment. Although the FDA authorized Vorapaxar in 2014 [18], the drug also made note of bleeding-related side effects. In cancer research, a large number of research data support that thrombin can promote tumor-associated inflammation, angiogenesis and tumor metastasis through its receptor PAR-1[74-76], and it has been confirmed in non-small cell lung cancer that PAR-1 is the main determinant of thrombin-mediated promotion of lung cancer metastasis[77]. Due to PAR-1's function in the development of malignancies, it may one day be used as a target for anti-tumor therapies, particularly in cases when patients have advanced malignant tumors and a hypercoagulable state.

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