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Research Advances in Pericyte-Related Functions and Diseases

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Abstract

A pericyte is a wall cell enclosed in the vascular basement membrane, an essential component of blood vessels and the central nervous system. It is closely related to endothelial cells and has the roles of vascular remodeling, maintaining the stability of the blood-brain barrier, controlling cerebral blood flow, and protecting the central nervous system. More and more studies have begun to focus on the mechanism of pericytes in different diseases to provide therapeutic significance to the clinic. In this paper, we summarize the functional roles of pericytes from the origin and identification of pericytes, focusing on the part of pericytes in cancer, diabetic retinopathy, neurodegenerative diseases, and cardiovascular and cerebrovascular diseases.

Keywords: Pericytes • Markers • Pericyte function • Pericyte-related diseases

Introduction

At the end of the nineteenth century, the German scientist Ebert and the French scientist Rouget first described pericytes. It was not until the beginning of the twentieth century that the German scientist Karl Wilhelm Zimmermann dissected blood vessels and discovered new cells in the vascular tissue and around the walls of blood vessels, hence the name pericytes [1]. Pericytes are wall cells wrapped in the basement membrane of blood vessels and are closely related to capillary endothelial cells [2]. The sharing of basement membrane between endothelial cells and peripheral cells means that they play an essential role in the stability of the blood-brain barrier, the formation and remodeling of blood vessels, and the control of capillary blood flow [3]. The quail-chicken mosaic experiment, zebrafish *in vivo* imaging, and pedigree tracking confirmed that the pericytes covered 22-32% of the surface of cerebral capillaries. The pericytes in different parts of the brain come from neural crest cells.

In contrast, mesoderm patients covered the blood vessels of the midbrain, brain stem, and spinal cord, and they proliferated and migrated along endothelial cells [4]. Therefore, it is also considered to be closely related to the neurovascular units of the brain. Recent studies show that peripheral cells play an indispensable role in many central nervous systems, such as Alzheimer's disease, epilepsy diabetic retinopathy, stroke Chen and soon. In these diseases, the loss or damage of peripheral cells will lead to blood-brain barrier dysfunction, capillary damage, neurovascular disintegration, and further disease deterioration [5]. An increasing number of data also suggest that pericytes can resist endothelial cell angiogenesis and stimulate neovascularization. However, our understanding of pericytes in the role of angiogenesis and the promotion of vascular remodeling and neuroprotection in therapy is limited. Therefore, this article reviews the functional characteristics of pericytes and their neuroprotective role in the neurovascular system in different diseases, intending to provide new targets for disease treatment.

Literature Review

Pericyte recognition markers

According to a large number of experimental studies, markers of pericytes help to identify pericyte aggregation as well as the number of pericytes but are not fully specific and have dynamic characteristics and can be expressed by other perivascular and

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mesenchymal cells, so much so that failure to identify pericytes accurately produces conflicting experimental results, thus searching for pericyte-specific markers a challenging task [6]. For example, PDGFR-β, NG2, proteoglycan (CSPG4), Myosin heavy chain 11 (Myh11), aminopeptidase N (CD13), α-Smooth Muscle Actin (α-SMA), a Regulator of G-protein Signaling 5 (RGS5), Desmin, Vimentin, subfamily C (CFTR/MRP), SUR2, alkaline phosphatase, CD146, CD133, endothelin, potassium internal rectifier channel, subfamily J, and interferon-induced transmembrane protein 1 (Ifitm1), etc. [7]. These markers have been widely used at this stage to label pericyte damage and deletion, but pericyte expression is inconsistent across species, tissues, and growth environments. For example, NG2 is a marker of oligodendrocytes and is also expressed by some macrophages. At the same time, it also exists in the angiogenesis of large blood vessels such as the aorta and central nervous system, and peripheral cells also have macrophage-like characteristics, which have the function of clearing A amyloid β- protein and are considered as the most suitable markers for studying mouse peripheral cells [8]. α-SMA is a reliable marker of differentiated my fibroblasts in the adult kidney. Expression of PDGFR-β and α-SMA is reduced in response to renal vascular injury. At the same time, fibrosis and capillary rarefaction are markedly attenuated, and their expression is upregulated only during neovascularization and remodeling but not in adult mice [9]. Of note, α-SMA protein levels may vary according to pericyte location: pericytes close to the side of small arterioles may have higher expression, whereas pericytes in the center of the capillary bed have expression. Also, in transcriptomics, α-SMA mRNA expression levels were deficient, while immunohistochemistry observed high protein levels [10]. It has also been demonstrated that microvascular pericytes derived from mouse embryonic brain and human brain do not express α-SMA, whereas pericytes derived from chicken embryonic brain express α-SMA [11]. The distribution and role of α-SMA in pericytes has been actively discussed. However, in some *in vitro* studies, pericytes are mistaken for macrophages, such as CD163, CD11b, and vimentin, but recent studies have shown that pericytes do not express these markers *in vivo* [12]. Whereas CD13 is specifically associated with pericytes in the blood-brain barrier but not expressed in peripulmonary cells, CD31 is closely associated with endothelial cells [13]. Recently, it was found that fluorescent Nissl dye (NeuroTrace 500/525) can accurately and specifically label intact pericytes and demonstrate the unique morphological and functional characteristics of pericytes and differentially express smooth muscle cells [14].

In summary, due to its potential for multicellular differentiation, the morphology, anatomical location, and specific gene expression during the development of pericytes also need to be taken into account in the identification of pericytes experiments to avoid misidentification of pericytes [15].

Pericyte functions vascular remodeling

Several studies have shown that angiogenesis begins with the pre-existing vascular system, the vascular vasculature that forms during embryonic development and postnatal tissue growth to meet the nutrient requirements of various organs and tissues [16]. Whereas the maintenance, development, and maturation of the vascular system require the interaction of endothelial and mural cells, of which pericytes and endothelial cells are important components of capillaries [17]. Driven by the mutual binding of derived factors in endothelial cells such as PDGF-BB, PDGF-DD, and ET-1 contribute to the stimulation of pericyte proliferation as well as greater motility and invasion, which ultimately control the maintenance and maturation of the capillary system. Recent studies in the literature have confirmed the functional role of VEGF and its receptor VEGFR2 in the tissue angiogenic response *in vivo* in a variety of species and have been shown to play a key role in various vascular abnormalities [18]. VEGF initiates the expression of endothelial cell-inducing factors c-Kit, IL-3Rα, and CXCR4, as well as EC-derived factors that stimulate endothelial cell aggregation, such as PDGF-BB, PDGF-DD, and HB-EGF, which can activate the downstream Notch receptor to enhance the ability of capillaries to rapidly assemble and stimulate morphogenesis and maturation [19]. Similarly, it has been demonstrated using a 3-D *in vitro* microvascular model that pericytes can regulate vascular function, generation, and development through the Notch signaling pathway. Notch3 particularly contributes to the pericyte-induced stabilization of vascular junctions, whereas Notch1 is more inclined to maintain stable pericyte-endothelial cell junctions [20]. Furthermore, it has been proposed that Angiopoietin-1 (Ang-1) is the major physiological ligand for Tie2 and that signaling between pericytes and endothelial cells is regulated by the Angiopoietin 1 (Ang-1)/Tie-2 signaling pathway. Angiopoietin-1 (Ang1) stimulates endothelial cells to recruit pericytes, and Angiopoietin-2 (Ang2) promotes capillary remodeling and maturation by inducing Tie2 receptor autophosphorylation. *In vivo* experimental study of Ang-1/Tie-2-deficient mice, it was found that in the second trimester of pregnancy, the coverage rate of perivascular tissue was reduced and the embryonic angiogenesis defect led to cardiovascular failure and death, that is, the mature primary vascular system could not be formed. This shows that the defects of Ang-1 and Tie-2 will lead to the wrong signal transmission in peripheral cells, endothelial cells, and extracellular matrix. Using a two-photon microscope combined with a complex Cre/loxP tracing technique *in vivo* revealed that normal pericytes can reverse apoptotic pericytes and continue the directional movement of new blood vessels. This longitudinal study further confirmed the remodeling effect of pericytes on blood vessels. In disease management, vascular abnormalities are the main hallmarks of cancer and diabetic retinopathy, where benign tumors have low pericyte coverage compared to malignant tumor vessels, and microvascular pericyte defects are one of the early manifestations of diabetic retinopathy, which is presumably closely related to the conversion of vasculature to vascularity, with poor coverage of pericyte loss in the vasculature system. These data also further suggest that developing pericytes controls capillary germination and vascular remodeling, but it is also possible that endothelial cell survival supports cell regeneration.

Maintaining blood-brain barrier stability

The Blood-Brain Barrier (BBB) is a specialized structure in the cerebral vasculature system that strictly regulates the completion of molecular exchanges between blood and extracellular fluids, and prevents pathogens and foreign bodies from entering the brain. Peripheral cells are the main components of nervous and vascular systems, and they are the key participants in maintaining the blood-brain barrier and vascular stability. The formation of blood-brain barrier microvessels requires the interaction and secretion of Platelet Growth Factor-BB (PDGF-BB) of endothelial cells and Platelet-Derived Growth Factor β (PDGFR-β) of peripheral cells, which can induce the recruitment, differentiation, and maintenance of steady state of peripheral cells. At the same time, astrocytes and pericytes secrete Angiopoietin-1 (Ang-1) through the insulin signaling pathway to promote Tie-2 receptors in the endothelium, thus maintaining the maturation and development of microvessels. According to the postmortem retinal research of 56 clinical human donors, it is found that the loss of peripheral cells and Platelet-Derived Growth Factor β (PDGFR-β) signal lead to retinal vascular abnormalities, brain Aβ deposition and Cerebral Amyloid Angiopathy (CAA), which are the prominent features of blood-brain barrier destruction in Alzheimer's disease. The role of pericytes for vascular stabilization has been similarly demonstrated in a variety of gene-deficient animal experiments, such as in mouse models of AD lacking the PDGFR-β allele showing that progressive loss of pericytes accelerates the development of pathological features of AD, including BBB dysfunction, leakage, and attenuated Aβ clearance from cerebrospinal fluid and neural tangles, as well as hyperphosphorylation of Tau proteins. Likewise, the essential role of endothelial-pericytes in establishing and maintaining the endothelial-pericyte blood-brain barrier was demonstrated in experimental studies of neonatal Intracranial Hemorrhage (ICH) and post-partum hemorrhage treatments using Smad4-deficient mice, which were maintained by the TGF-b signaling pathway and the Notch signaling pathway. In ApoE knockout mice, injection of NMDAR-AB-positive serum resulted in impaired BBB function, which was characterized by neurological abnormalities compared to normal mice. In addition, several studies have found that ApoE4s and PICALM are important genes for late-onset dementia and are not easily cleared once they bind to Aβ and that ApoE2-Aβ and ApoE3-Aβ complexes are more likely to lead to cerebral vascular-like amyloidosis. This suggests that pericytes are a key component of the nervous system, cooperating with endothelial cells to maintain the integrity of the blood-brain barrier, and conversely, the absence of both can lead to blood-brain barrier dysfunction and increased permeability that can manifest in a variety of neurodegenerative diseases.

In summary, many questions continue to be addressed in targeting pericytes in maintaining healthy cerebral vasculature and an intact blood-brain barrier, for example, it is still unclear the structural connectivity and functional linkage between pericytes and neuronal cells as well as the BBB and how it affects BBB permeability; and whether impaired BBB and pericyte disruption is a potential therapeutic target.

Control of changes in capillary blood flow

Pericytes are a major component in the regulation of capillary diameter, and they mostly accumulate between small arteries and veins. It has been found that pericytes are embedded within the basement membrane of the capillary wall, form tight junctions with endothelial cells between the basement membranes, and perform a variety of blood flow control, angiogenesis, and maintenance of the blood-brain barrier by contracting the vessel wall. With the update of scientific instruments, transmission electron microscopy showed that the pericytes and endothelial cells in the brain and retina have filament-staining proteins, which (actin, non-muscle myosin, and tropomyosin) are involved in regulating capillary blood flow and permeability. Michael V anlandewijck used single-cell RNA sequencing research to show that pericyte also expressed some genes involved in SMC actin contraction, such as myosin (myh11, myl9, myh9), regulators of myosin phosphorylation (milk and ppp1r12a, rock1) and L-type voltage-gated calcium channel (CACN1C). In the further experimental study of retina, it was found that the contraction of pericapillary cells was restricted by inhibiting the expression of ι-SMA or promoting the signal transduction of SMC through RhoA-Rho kinase. According to recent statistics, about 40% of AD patients have obvious vascular abnormalities. Microvascular abnormalities were also found to precede cognitive impairment in AD mice in the APPswe/PS1dE9 model. It shows that vascular disorder is the early pathological feature of AD, after which abnormal Aβ deposition, metabolic dysfunction, dysfunction, and gray matter atrophy will occur. Francisco Ferna'ndez-Klett found in patients with ischemic stroke and transgenic mutant rgs5GFP/GFP or RGS5GFP/WT (RGS5GFP) mice that cerebral ischemia can reduce the number of peripheral cells after the cerebral microvascular system is contracted, and at the same time induce the proliferation of a new population of PDGFRβ stromal cells derived from the vascular wall. This shows that pericytes play a key role in functional hyperemia, and in a real-time microscopic analysis of *in vivo* fluorescence angiography, it is proved that pericytes increase the blood flow velocity by regulating the blood flow of capillaries in response to the activity of activated neurons. Also, a 25-30% reduction in pericytes alters microvascular flow. Therefore, pericytes are thought to function physiologically to control flow. However, the exact reason why capillary pericytes contract slower *in vivo* than content α-SMA wall cells is unclear. It can be inferred that the loss of peripheral cells and the decomposition of BBB will cause abnormal blood vessels, insufficient cerebral perfusion will reduce the clearance rate of Interstitial Fluid (ISF) and Cerebrospinal Fluid (CSF), and the deposition of abnormal substances will cause neurodegenerative diseases. These findings further illustrate the molecular mechanism and information transmission pathway that play a role in the development of vascular system-nervous system lesions, the relationship between the three, and whether the treatment of the vascular system can help slow down the pathological changes of the nervous system is a problem worthy of study.

Characterization of mesenchymal stem cells

According to studies, pericytes have the properties of mesenchymal stem cells, and when co-cultured with endothelial cells they can differentiate *in vitro* and *in vivo* into fibroblasts, osteoblasts, chondrocytes smooth muscle cells, and valvular mesenchymal stromal cells, among others. Notably vascular smooth muscle cells and fibroblasts can also be reverse transformed into pericytes. When mesenchymal cells differentiate into pericytes, pericytes, and mesenchymal cells can increase VEGF secretion mediated by Transforming Growth Factor β (TGFβ) and activate PDGFR-β to induce the proliferation and migration of pericytes, thus enhancing the signal transduction between endothelial cells and pericytes and maintaining functional and structural stability. Thomas A. Mendel et al., used specific markers of pericytes to label Adipose-Derived Stem Cells (ASC) and found that injection of ASCs into mice with retinopathy can enhance blood vessel regeneration and reduce capillary shedding. After treatment with Transforming Growth Factor β (TGF-β1), ASC can migrate to and integrate with the retinal vascular system, preventing capillary loss in mice with retinopathy (79% after injection 2 months). Abderahim Gaceb laboratory uses Lipopolysaccharide (LPS) to stimulate human brain pericytes to secrete inflammatory factors and finds that pericytes can secrete growth factors and vesicles, which is helpful to regulate neuroinflammation and promote nerve recovery and regeneration. Similarly, Multiple Scleroderma (MS) is a chronic inflammatory-degenerative neurological disease resulting from the breakdown of the blood-brain barrier with the invasion of leukocytes, especially macrophages, into the nervous system, where pericytes seem to play the role of macrophages responding to the migration of the inflammatory molecules IFN-γ+IL-1β to the damaged site for scar repair. Recent clinical and experimental data have shown that primitive osteogenic progenitor cells can be isolated and identified as pericytes in the connective tissue of human skeletal muscle, suggesting that there is a close link between angiogenesis and muscle tissue, and that pericytes can also differentiate into osteoblasts thereby sustaining proliferation and migration between organisms. Laszlo Hegyi speculated that the cells of progressive ossifying fibrous dysplasia (Fibrodysplasia Ossificans Progressiva (FOP) are characterized by a smooth muscle cell lineage and secrete the specialized osteogenic transcription factor Runx2/Cbfa-1, as well as immunoreactivity for osteocalcin and osteo-sialoprotein, further underscoring that pericytes have the potential to maintain and promote chondrocytes' evolution into osteoblasts.

Although the idea of the pericyte as a pluripotent progenitor cell of pathophysiologic importance is receiving increasing attention, it is important to keep in mind that the overlap of these cellular markers suggests that pericytes can switch from one cell type to another. Caution is therefore needed when interpreting the results and reviewing the existing literature. It has yet to be possible to reliably localize pericytes *in vivo*, and *in vitro*, experiments are often confounded by uncertainty about the origin and identity of so-called pericyte cultures.

Neuroprotective effect

According to research findings, the normal functioning of the brain is ensured by the balance between neural activity and cerebral capillary blood flow, both of which are multifunctional inter-integrated response signals of highly aggregated and dynamic structures, between which evolved a rigorous neuro-vascular system for reciprocal trophic factor delivery and metabolite clearance to support normal physiological activity. Thus, vascular dysfunction is a major cause of injury to the central nervous system or peripheral nervous system, and Central Nervous System (CNS) and peripheral nervous system injuries can lead to vascular system injuries also causing vascular dysfunction. Indeed, pericytes have a high coverage in the vasculature of the central system and are significantly higher than in peripheral tissues, and defects in pericyte development lead to increased endothelial cell trafficking and mis-expression of molecular transporter proteins and leukocyte adhesion molecules, as in the case of Alzheimer's disease, epilepsy, diabetic retinopathy, and stroke, among others. Effective protection of the vascular system during periods of CNS injury stimulates pericyte differentiation and proliferation, contributes to the restoration and inhibition of vascular dysfunction, can prevent and mitigate neuronal injury, and maintains the stability of the neural-vascular system. On the contrary, loss of pericytes leads to constriction and degeneration of cerebral microscopic vessels, especially capillaries, which may cause chronic perfusion stress and hypoxia in the brain, as well as neuronal damage as well as dysfunction due to blood-borne toxin aggregation and ischemia and hypoxia may ultimately cause apoptotic cell death. Of interest, recent experiments using Hypoxyprobe-1 probe as well as electrical stimulation found that in pericyte-deficient mice in the absence of neuronal injury, vascularization could be re-established within one month but in the absence of pericytes from the original vascular injury, the density of positive neuronal cells in the hippocampus and cerebral cortex was significantly reduced. However, clinical acute stroke data found that hypoxia will further lead to pericyte death and reduced CNS microvascular system coverage, neurological impairment, and altered vascular function and brain homeostasis. However, it has also been suggested *in vitro* that under hypoxic conditions, pericytes exhibit cellular differentiation potential and can differentiate vascular and neural spectrum cells, thus attenuating the neuro-vascular system damage associated with hypoxia. These data further demonstrate that pericyte defects lead to more severe neuronal alterations as well as disruption of the blood-brain barrier caused by the coordinated effects of brain perfusion deficits and neurotoxic aggregation. Transforming Growth Factor (TGF)-β is an important signaling molecule performing multiple functions in the CNS, and in CNS disease states, TGF-β rapidly upregulates the expression of microglia and astrocytes and affects the proliferation of neural progenitor cells, which are the main source of pericytes, which may indicate that neurological pathologies such as

Alzheimer's disease and epilepsy are associated with pericyte-loss injury. Similarly, Aβ deposition around the vessel wall resulting in thickening of the basement membrane has been found in animals from AD patients and AD models, and some studies have hypothesized that this is due to the secretion of basement membrane proteins produced by astrocytes and pericytes. Conversely, it has also been suggested that basement membrane thickening and damaged degeneration of pericytes lead to impaired cerebral blood flow and Aβ deposition. In any case, the cause of basement membrane thickening is unclear but it is clear that interactions between astrocytes and pericytes contribute to the development of Alzheimer's disease.

Discussion

Pericyte related diseases

Cancer: Cancer treatment is a very challenging problem that has been plaguing humanity for many years. It has been found that pericytes play an important role in vascular and cancer biological systems. In the microenvironment of tumors, pericytes contribute to tumor vascular proliferation as well as migration due to their mesenchymal stem cell capacity to interact with multiple cell types and extracellular matrix. Pericytes have obvious pro-metastatic features, especially in breast cancer, where pericytes enhance the adhesion of cancer cells while secreting Insulin-like Growth Factor 2 (IGF2) to inhibit intercellular adhesion and the expression of E-calmodulin, which greatly promotes peri-tumor vascular proliferation and the secretion of stromal proteins. Similarly, due to the specific function of pericytes, expression of oncoprotein (GT198) can be stimulated in tumor microvasculature with low pericyte coverage accelerating malignant pericytes to generate tumor cells through angiogenesis, while differentiating into malignant tumor cells through angiogenesis. In a systematic evaluation, pericyte populations were significantly affected during the development and treatment of oral Squamous Cell Carcinoma (SCC) yet there were insufficient data to suggest that targeting pericyte-endothelial cell targets could alter the microenvironment and clinical outcomes. Liu's team, on the other hand, concluded that hypoxia leads to vascular defects and inflammatory responses in the tumor microenvironment, releasing Vascular Endothelial Growth Factor (VEGF) to promote tumor angiogenesis, whereas the reduction of normal pericyte coverage and the absence of basement membranes, which recruits the associated macrophages leading to pericytes, is important for the development and metastasis of squamous cell carcinoma of the oral cavity, ultimately inducing the formation of vasculature lining the tumor cells and further contributing to the entry of cancer cells into the bloodstream for invasion and migration. While VEGF antibody (bevacizumab) as well as sunitinib and related tyrosine kinase inhibitor drugs are applied clinically to inhibit tumor angiogenesis but due to their drug resistance, patients' therapeutic effects are poor, and there is an urgent need to explore new therapeutic targets to resist tumor angiogenesis. One team noted that genetic deletion of IL-33 was found to block PDGF-BB recruitment of tumor-associated macrophages *via* the SOX7 axis in mouse experiments this may be a new therapeutic target for future treatment.

Diabetic Retinopathy (DR)

Diabetic Retinopathy (DR) has been the leading cause of blindness in adults in recent years. Whereas hyperglycemia may induce changes in the microvascular system of the retina, its tendency to lead to visual impairment or even blindness in diabetic patients, which seriously affects the normal life of patients. It has been shown that pericyte loss, as well as dysfunction, are recognized as the earliest pathological features in the early stages of DR. Pericytes and endothelial cells are key players in the pathogenesis of proliferative diabetic retina. Hyperglycemia activates protein kinase C-δ and p38α mitogen-activated protein kinase to induce oxidative stress and inflammatory responses leading to decreased pericyte viability exacerbating capillary blood flow abnormalities, pericyte-endothelial cell crosstalk inducing circulatory deficits in the microvascular system, and insufficient neovascularization to fuel the growth of neovascularization Retinal fibrosis accelerates disease progression. Hanahan D suggested that during the disease process, the cooperative upregulation of Ang-2 and VEGF leads to pericyte loss and angiogenesis, whereas overexpression of Ang-2 in the absence of VEGF leads to vascular regression. In addition, three signaling pathways, PDGFB/PDGFRβ signaling, angiopoietin (Ang) signaling, and Transforming Growth Factor β (TGFβ), have been shown to promote capillary remodeling and maturation in diabetic retinopathy by genetically regulating endothelial cells and smooth muscle cells in capillaries. Loss of all three predisposes to capillary leakage hemorrhage, cell-free capillary proliferation, and eventual microaneurysm aggregation formation. This may be related to impaired growth of capillary remodeling and inhibition of pericytes. Indeed, as diabetic retinopathy worsens, cellular lineage tracing demonstrated that VEGF nourishment of the vascular endothelium through the choroid promotes pericyte proliferation to establish a mature vascular system. Thus, under disease conditions, the activated proliferation of pericytes is thought to promote neovascularization on the one hand, and the other hand, lead to the promotion of pathologic angiogenesis. It is thus clear that it is necessary to block PDGF signaling and VEGF secretion in the early stages of the disease to reduce the formation of acellular chains in the retina and thus more effectively inhibit choroidal neovascularization to prevent vision loss and vascular fibrosis lesions. Imatinib is a cancer therapeutic agent as well as a monoclonal tyrosine kinase inhibitor, Platelet-Derived Growth Factor Receptor (PDGFR), and KIT inhibitor, and as such, it prevents pericyte migration and pathological angiogenesis in oxygen-induced retinopathy *in vitro via* the PDGFs/PDGFRs axis without altering capillary length and inducing BBB damage. This suggests that imatinib alone or in combination with anti-VEGF agents offers a viable therapeutic option for anti-angiogenic therapy and alternative treatment of angiogenic diseases.

Neurodegenerative diseases

It has already been pointed out that pericytes are an important part of the vascular system, especially in the microvasculature, where the pericytes are tightly wrapped around the endothelial cells, form a basement membrane around the vessel, and are wrapped around the ends of astrocytes. Together with neurons, microglia, myocytes, and extracellular matrix, they form the neurovascular unit. These cells keep the blood-brain barrier in a smooth state by delivering oxygen and nutrients through vasodilatation and contraction. It is reasonable to hypothesize that neurodegenerative diseases are closely related to the microvascular system and blood- brain barrier permeability. Alzheimer's disease is a classic neurodegenerative disorder, and Amyloid-β (Aβ) deposition is considered to be its main pathological feature. In a study of C3H/10T1/2 cells and Alzheimer's disease model mice, it was found that implantation of pericytes in model mice directly or indirectly promoted the clearance of Aβ1-40 and Aβ1-42 and increased cerebral blood flow. Clinical studies in AD patients have found a positive correlation between the level of Aβ1-40 deposition and pericyte number/capillary length, which means that both pericytes and vessel length are reduced compared to the non-demented group. Pericyte degeneration and cerebral microvascular basement membrane degeneration have been found in the brain tissue of patients with clinical epilepsy. Similarly, experimental studies have suggested that the primary cause of recurrent epilepsy is associated with loss of pericyte damage with ectopic coverage ultimately leading to neurovascular dysplasia.

In summary, these findings open up the exciting possibility that playing a unique role in the maintenance of the cerebrovascular network and the state of vascular health of pericytes could improve the possibility of preventing further deterioration of neurodegenerative diseases.

Cardiovascular disease

With the improvement of living standards, the prevalence of cardiovascular and cerebrovascular diseases is increasing year by year, while the mortality rate is also increasing year by year. It is worth noting that age affects the microvascular circulation of the heart and brain, with a decrease in pericyte coverage and shrinkage of capillaries, which is one of the main risk factors for cardiovascular and cerebrovascular diseases. It is well known that pericytes are the earliest cell type to respond to cerebral hypoxia-ischemia. Oxidative stress is a mediator of pericyte contraction. Ischemia-reperfusion injury in heart attack, as well as stroke, triggers oxidative/nitrative stress. Excessive pericyte contraction can be prevented by inhibiting oxidative and nitrative mechanisms to restore microcirculatory blood flow to promote tissue reperfusion. Muge Yemisci et al., showed in an ischemic stroke model that pericytes in the cerebral vasculature were in a constant state of contraction, impeding erythrocyte flow. The contractile state of the pericytes persisted even when blood flow was restored after 2 hours. It is suggested that pericyte contraction may hinder thrombolytic therapy for stroke or infarction and lead to poor therapeutic outcomes. RGS5 and T-Box transcription factor 20 (Tbx20) are key players in the maintenance of cardiac pericyte-associated functions and accumulate in senescent pericytes. Using primary human pericytes, the G. Luxan research group found that the maintenance and restoration of pericyte function through RGS5 and Tbx20 and the activation of TbxA2 to control PDGFR-β signaling reduces the pernicious effects of aging in the elderly heart effects. In contrast, GPF transgenic mice were found to have an overall contraction of cerebral capillaries and an increase in luminal pressure under TBxA2 receptor antagonist activation. It is suggested that TbxA2 receptor antagonists can effectively control pericyte contraction and inhibit oxidative-nitrogenic stress injury before reperfusion. Although pericytes play a critical role in the regulation of cardiac and cerebrovascular blood flow, there is a lack of critical evidence for neural coupling of cardiac and cerebral capillary pericytes.

Conclusion

Pericytes are amazing functionally diverse cells that play a key role in pathophysiology. A growing body of evidence suggests a potential role for therapeutic intervention targeting pericytes in the development of cancer, neurodegenerative diseases, diabetic retinopathy, and cardiovascular diseases, among others. In summary, pericytes, as the centerpiece of the neurovascular unit, may also play a crucial role in vascular and neural recovery, but their study must be integrated with other neurovascular cells (endothelial cells, astrocytes, neuronal cells, etc.) to place them in the context of CNS disorders, to understand their cellular biology as well as interactions in the microenvironment, and to tap into the therapeutic potentials for further discovery of more effective pharmacological interventions. To achieve multi-pathway and multi-target therapeutic purposes, thereby delaying and improving the outcome of the clinical process of various diseases.

Ethical Approval

This article does not contain studies involving human participants or animals.

Informed Consent

The authors have consented to the publication of this article.

Conflict of Interest

The authors declare no competing interests.

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