Review Article

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Cell based therapeutic approach in vascular surgery: application and review

Abstract: Multipotent stem cells - such as mesenchymal stem/stromal cells and stem cells derived from different sources like vascular wall are intensely studied to try to rapidly translate their discovered features from bench to bedside. Vascular wall resident stem cells recruitment, differentiation, survival, proliferation, growth factor production, and signaling pathways transduced were analyzed. We studied biological properties of vascular resident stem cells and explored the relationship from several factors as Matrix Metalloproteinases (MMPs) and regulations of biological, translational and clinical features of these cells. In this review we described a translational and clinical approach to Adult Vascular Wall Resident Multipotent Vascular Stem Cells (VW-SCs) and reported their involvement in alternative clinical approach as cells based therapy in vascular disease like arterial aneurysms or peripheral arterial obstructive disease.

1 Introduction

Current and potential therapeutic applications for stem cells are various and complexes. A lot of research fields dealing with stem cells including discovered new sources of highly multipotent stem cells and methods of perpetuating them; creation of induced pluripotent stem cell clones to study genetic disorders or explore pharmacogenomics; utilization in regenerative medicine. Regarding vascular diseased and their treatment by stem cells we provide a brief review of main clinical use of vascular wall resident progenitor cells (VW-PCs). Endothelial cells (ECs), smooth muscle cells (SMCs), and adventitial stromal fibroblasts all derived from mesodermic sheet constitute vascular wall. It is recently demonstrated Recent studies have indicated that resident progenitor cell with angiogenetic properties are located inside arterial wall [1, 2]. These cells arose during embryonic and fetal age, in adult subject remain located in specific niches to guarantee the renewal and repair of vascular tissue and trigger the processes of postnatal angiogenesis [3]. Angiogenesis, characterized by the growth of new blood vessels or capillaries from preexisting vessels, plays a pivotal role in the postnatal tissue remodeling both in physiological and in pathological conditions [4]. Matrix metalloproteinases (MMPs) are enzymes involved in the degradation of the extracellular matrix (ECM) substrates play a regulatory role and participate in key stages of postnatal angiogenesis [5]. Vascularization of several tissues like limbs, retina, and myocardium damaged by ischemia can be restored using hematopoietic progenitors as well as bone marrow-de-

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rived endothelial cells. [6–10]. It is also demonstrated that quiescent multipotent stem cells (SCs) reside in the vascular wall; in sites of vascular pathology like arterial aneurysms they can be activated and differentiate into SMCs [11–13]. Different MMPs expression can regulate wall resident SC biological properties releasing growth factors and activating signaling pathways. [14–16]. The purpose of this review is to examine the role of vascular wall resident stem cells in therapy like restoring vasculature after ischemic events and mainly provide a huge analysis of biomolecular mechanisms that regulate the involvement of vasculature progenitors and the activity of MMPs in natural history of arterial aneurysms.

2 Biology of vascular stem cells

Several studies were made well assess the physiology of stem cells and a lot of factors which maintain stemness [17–23]. Endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) are predominantly descendants of mesodermal cells; nevertheless, some Authors described an ectoderm origin for VSMCs [24, 25]. Many factors regulate the differentiation of mesoderm in vascular cells and this process is really complex and finely regulated. Blood vessels arise from endothelial precursors through a process known as developmental vasculogenesis [26, 27]. Angiogenesis, also called collateral growth, is the transformation of preexistent collateral arterioles into functional collateral arteries could be induced by human bone marrow-derived stromal cells through paracrine mechanisms [28, 29]. The expression of a lot of growth factors and cytokines, such as VEGF and stromal derived factor-1a (SDF-1a) is regulated by hypoxia-inducible factor-1a (HIF-1a) whose activation should be ascribe to the drop in O_2 tension observed in hypoxic tissues or tumors [30]. The release of VEGF and SDF-1a into peripheral circulation lead to recruitment of hematopoietic cells like CFU-ECs and CACs in affected tissues. Afterwards these factors activating angiogenesis process utilizing intracellular Ca^{2+} signals toolkit. [31-39]. Immature VSMCs are still involved in blood vessel morphogenesis. They are able to proliferate, migrate and produce extracellular matrix (ECM) components of the blood vessel wall. The process of VSMV differentiation is triggered by a lot of vascular growth stimuli, such as ischemic injury. Ischemic damage involves matrix proteases, known as matrix metalloproteinases (MMPs). MMPs, thus, are involved in several vascular [40–54] and nonvascular diseases [55].

3 Adult vascular wall resident stem cells and angiogenesis

It is clearly know that several progenitor cells and stem cells are hidden in arterial and venous vessels. Various type of cells are involved like endothelial progenitor cells (EPCs), smooth muscle cell (SMC) progenitors, hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and the mesangial cells, which express either endothelial either myogenic markers [56–59]. Cells expressing CD 34, vascular endothelial growth factor 2 receptor (VEGFR2) and tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (TIE2). Were identified between media and adventitia of human vessels. These cells have the power to switch into ECs, either in physiological pathways either in pathological pathways [14, 59–62]. In human arteries and veins we can find also CD44(+) CD34(−) CD45(−) multipotent MSC-like stem cells, these cells can differentiate into pericytes/SMC. Researchers have demonstrated that these cells are capable to cover the endothelium of new vessels in vivo and in vitro conditions [63]. CD 34+ and sca1+ cells are part of Sonic Hegehog pathway, and they are placed in the inner part of adventitia of arteries in animal models. They seem to build a vasculogenic area [64]. This area plays a central role in the resource of progenitor cells related to the EPCs which circulate and derive from bone marrow. Moreover they are also a reserve for local immune response in the inflammation pathways [65]. In these zones we can find also VW-PCs during their growth from the embryonic phase to adult one. VW-PCs can become SMC and pericytes and have the power to build new capillary sprouts and go towards angiogenic lineage [66]. Vasculogenesis is known as the formation of new vessels from angioblasts, this is the most important pathway involved in blood island vessels formation, dorsal aorta, endocardium, and vitelline vessels in the embryo. On the other hand angiogenesis is known as the formation of new vessels from other vessels in response to pathological or physiological conditions [67]. In this pathway are involved endothelial cell migration, proliferation, and tube formation [68–70]. An important reservoir of non differentiated cells is made by VW-PCs ready to answer to cellular demands modifying their phenotypical characteristics [71]. Neovascularization is linked to endothelial cells, their migration and proliferation ability, and coverage of vessels performed by pericytes. Pericytes allow stabilization and survival of new sprouting vessels; Researchers found either in vivo either in vitro that VW-PCs can differentiate into vascular SMCs and pericytes [72]. During angiogenesis an important reservoir of pericytes and SMCs can be supplied by

MSCs in physiological and pathological conditions. After a vascular injury these cells occur to repair the damaged vascular cells [73-76].

4 Regulatory role of MMPs on vascular wall resident stem cells

MMPs, are a group of zinc dependent proteinases consisting of 28 family members that are able to degrade ECM compounds and other proteins [77] taking a pivotal role in vascular remodeling [78].

Serra et al. have demonstrated MMPs involvement in a lot of vascular diseases [4, 79–84]. Angiogenesis process start with ECM degradation by proteinases leading to release of several factors such as growth factors and their receptors, adhesions molecules, chemokines and apoptosis mediators as well as cell migration [30, 85, 86,]. VW-PCs acquired the ability to differentiate into a smooth muscle cells (SMCs) and pericytes that synthesize some proteins of basement membrane like proteoglycans and various types of collagens [87-89]. Vascular basement membrane (VBM) is a specialized extracellular matrix that surrounds the blood vessels of the body and interacts with paralytic MSCs regulated through an interplay between proteases and protease inhibitors influencing vessel homeostasis and vascular diseases like vessel aneurysms [90–96]. In pericyte–EC interface there are a lot of proteins like fibronectin and a compounds of different type of junctions like tight, gap as well as N-cadherin and b-catenin-based adherens junctions [97]. Fibronectin is degraded by proteolytic enzymes such as MMPs rising biologically active fragments like a 45 kDa fibronectin fragment, involved in vascular remodeling and maturation [98]. MMPs represent the main proteolitic enzyme involved leading to release of angiogenic factors [99–101]. SMCs can express MMP-7 and MMP-3 and express and secrete MMP-2 and MMP-9 under the control of NF-kB. Moreover, MMPs can be released by leucocyte while SMCs are the main source of tissue protease inhibitors [102, 103]. They also constitutively express and secrete several serine proteases [104, 105]; thus, in the vascular wall, SMCs are the main source of TIMPs [106]. As recently reported the expression of Homeobox C11 (HOXC11) results in drastic vessel wall remodeling [107, 108]. MMP-8 and MMP-9 initiate a cascade of events including release and activation of mobilizing factors and cytokines, ECM degradation and remodeling [109–112]. MMPs are also related to mitogenesis and migration of SMCs [113]. In in vivo studies, MMP-3 knockout mice reduced neo-intima formation after carotid ligation and

also attenuated SMCs migration into wound [114]. SMCs are important both to promote arterial remodeling and to modify vessel diameter and/or wall thickness to ensure adequate tissue perfusion [115]. In presence of VEGF, arterial wall resident cells became round-shaped, resembling ECs, and part of the cells acquired CD-31, VE-cadherin, and von Willebrand factor expression, whereas when they are cultured with TGFβ-1 or platelet derived growth factor-BB (PDGF-BB) adopted a rather elongated phenotype, similar to that of SMCs, and part of the cells acquired anti-α-smooth muscle actin (ASMA) and calponin [116]. VEGF also induces the expression of Notch1 through PI3K/AKT pathway in cultured ECs [117]. The roles of Notch include the differentiation in both EPCs and SMC via activation of transcriptional CBF-1/RBP-Jκ-dependent and independent pathways and transduction of downstream Notch target gene expression [118, 119]. These angiogenic factors can induce differentiation from progenitor in media to EPCs and SMCs [14]. Recently it has been shown that pericytes are able to detach from the vascular wall and contribute to fibrosis by becoming scar-forming myofibroblasts in many organs including the kidney. At the same time, the loss of pericytes within the perivascular compartment results in vulnerable capillaries which are prone to instability, pathological angiogenesis, and, ultimately, rarefaction such as aneurysmal disease [120, 121]. Based on these evidences, we could affirm that MMPs may play a central role to regulate the activity of the VWPCs by increasing the biodisponibility of main proangiogenic factors. Another role of MMPs is to promote the differentiation and migration of fibroblast and resident vasculogenic progenitors critically involved in vascular repair by remodeling of ECM [122]. MMPs contribute to VW-PCs during the progression of arterial aneurysms and participate in all crucial stages of this degenerative disease.

5 Vascularwall resident cells and aneurysms

Vascular accidents are very frequent in the western countries, and aneurisms are one of the most important one. Several conditions are linked to aneurism incidence such as alterations of glucose and lipid metabolism, hypertension, trauma, anastomotic disruption, infections, and connective or inflammatory diseases. As already described, arterial aneurysms are divided into central aneurysms, like abdominal aortic aneurysms, and peripheral aneurysms, like aneurysms of the popliteal, femoral, and carotid arteries [123,124]. Two are the pathogenic keys

in the aneurismal formation, medial degenerations and vessel dilatation: low activities of MMPs [125] and Death SMCs causes poor synthesis of elastine [126]. Artery wall is progressively destroyed by ROS damage and chronic inflammation. As already described, in arterial wall are preserved resident stem cells [82, 127-129]. So in the vasculogenic area are hidden VWPCs which are involved in the formation of perycites/SMCs. During endothelial injuries VW-PCs and SMCs evolve to proliferate, migrate and differentiate. This mechanism allow damage repair [130, 131]. SMCs derived from differentiation of VW-PCs occurs at the injury site and migrate into the intima [132]. Adventitia release factors that activate and regulate VW-PCs wall function. Resident stem cells are involved also in structural modifications of artherosclerotic disease acquiring specific structural and morphological features [133, 134]. So is clear that in pathological conditions vasculogenic area plays a central role in the wall injury [135]. Literature underline how other enzyme and cytokynes can influence the mobilization of these cell from their residence zone. These factors are tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), monocyte chemoattractant protein-1 (MCP-1), and stromal cell derived factor 1-alpha (SDF1-α). Reserchers demonstrated that adventitia inflammation allows mobilization of progenitor cells via vasa vasorum [136]. Arterial aneurisms and VW-PCs are probably linked. We have find a description of stem cells role in inflammatory pathway of abdominal arterial aneurism (AAA) by Ryer et al. after analysis of several patients underwent to surgery for infrarenal aneurismal repair. Researchers found a great amount of ckit+ and CD34+ cells. On the other hand they find macrophage marker CD68 expression. But they didn't find SM22 as SMCs marker or FSP1 as fibroblast marker. We know also that CD68+ cells are present at the time with the cellular marker of proliferation Ki67 [131]. So resident stem cells appears to have an important role in pathogenesis of AAA as described and confirmed also by other authors [137,138]. It has been shown that hemodynamic influence stem cells differentiation. Shear stress is linked to endothelial differentiation pathway, on the other side cyclic forces improves smooth muscle cells proliferation. These abnormal differentiation stimuli allow wall disease and lead to aneurism formation [135]. Certain authors like Witte et al. affirm that vacuoles in VW-PCs are the probe of their ability to form capillary lumen. These cells can go or on the side of differentiation or on the side of nescrosis, if RBC goes into the vacuole they go to the necrosis pathway [138]. Afetr tissue injury VW-PCs express CD-34, STRO-1, c-Kit, so they acquire the ability to differentiate into SMCs and fibroblasts, this admit the hypothesis that they have a key role in a repair and remodeling process [120]. To differentiate into ECs and MSCs are required stimuli by angiogenetic citokyne like VRGF, which is stimulate by C-kit cells [139]. The degradation of arterial wall ECM components increased by MMPs activation is the basic moment in aneurismal formation. [140, 141]. MMPs, especially MMP-2 and MMP-9, are released in the aortic wall by SMCs and macrophages. [142, 143]. To occur vascular aneurism is required that medial fibers are impaired, a diminution of SMC and invasion of inflammatory cells in the vascular wall. ECM are strictly linked to its synthesis by SMCs and protease activation. Chronic inflammation due to an aneurismal history cause a diminution of SMCs with vascular impairment and reduction of production of elastine and basement membrane. All of these findings cause the loss of organization of extracellular matrix [70, 144–146]. In neo-intimal lesions and adventitia of atherosclerotic plaques of human corps after autopsies several authors showed the presence of CD34+Sca1+CD133– cells. These cells might be at the origin of endothelial and vascular smooth muscle cells that are at the base o f atherosclerosis [147–150]. Also pericytes are involved in vascular inflammatory response as described by Tigges et al. in restenosis of femoral arteries injuries in mices [82, 151] They contribute to intima hyperplasia due to their mesenchymal stem cell like behavior [152, 153]. VSMs are most representative cells in the media and can perform pro-inflammatory response to several stimuli. Macrophage and t-cells are affected by media cytochines and chemochines, but on contrary VSMCs and EMC can perform also anti-inflammatory pathways. The opposition between the two forces impacts the medial pathology. The medial immune privilege defends the media from injury and inflammation, it provides the typical arteriosclerotic lesions, as the first step of aneurysmal disease. On the contrary when the medial immune privilege is lost. We observe a severe leukocytic infiltrates, loss of VSMCs with alterations of the extracellular matrix architecture. With augmentation of incidence of aneurismal disease and vasculitides [154, 155]. Also CD4+ T cells, CD8+ T cells, and B cells are involved in the immune response in vascular tissues, they are stimulated by factors from apoptotic cells, necrotic cells microvasculature injury, and stroma [156, 157]. Insufficient inflammatory cytokines during chronic inflammatory sites, however, are able to induce MSCs to secrete chemokines and tropic factors without immune inhibitory factors. Son chronic inflammation may lead MSCs to protract the disease recovery or even worsen the disease course such us in aneurysmal disease [158, 159]. From the

bone marrow also osteoblast and osteoclast precursor (also known as osteoprogenitors) could be able to create a process of calcification. According the circulating cell theory from the bone marrow the cell population of osteoprogenitors (OP) could seed the arteries and could be responsible of the damage or, instead, could repair it [160-162]. It is also possible the mechanism of homing: in response to a damage, an injury, an inflammatory phenomena, a stress signal, or in response to an abnormal cytokine signaling or also only to repair the damage, the circulating OP could be recruited in the arteries; they could cross the endothelium, they could invade the target tissue [163, 164]. The homing depends by the endothelial phenotype: every endothelial phenotype has different functions. So, the homing of bone marrow derived stem cells is modulated by endothelial phenotype. In the coronary artery endothelium, for example, is possible a fastest integration of the bone marrow stromal cells. It is essential the interation of vascular cell adhesion molecule molecule-1, very late antigen-4, β1integrins, MMPs secretion, and cytokines [165, 166]. Another important molecule is BMP-2, expressed by pericytic myofibroblasts; it is a powerful bone morphogenic factor. According some studies, in the pathogenesis of atherosclerosis could be involved the MSC because in culture they acquires an osteoblastic phenotype as the WNT pathway is activated [167, 168]. It was noticed in rats with hyperlipidemia and treated with angioplasty that paracrine BMP-2 (one of the most important mediators in the differentiation of MSC along the osteoblastic lineage) mediates the remodeling and it triggers calcification of the vessel walls [169, 170]. It is also known that pericytes represent a reservoir of progenitors cells (including osteoblasts) [171, 172], and they can differentiate themselves into various cell lines, also the chondro and osteogenic ones [173, 174]. This is an interesting example of how the interation among different cells of vessel wall can bring to the calcification. The suppression of MMP by the VW-PCs could be a fundamental element to reduce the aneurismal degeneration. It is also possible that tissue damage could be induced by differentiation of VW-PC into inflammatory cells. The presence of macrophages that are involved into the replenishment of the aneurysm wall probably is due to the VW-PC. It is clear, so, that the vW-PC could be responsible both of the inflammatory state and aneurismal degeneration both of the vascular repair. Different factors are involved, for example cytokines, growth factors, and the activation of specific pathway [175].

6 MSCs application in cardiovascular regenerative therapy

The interest of many studies is concentrated on VW-PC, on circulating EPCs and on umbilical cord blood cells because they can be used for the treatment of many different diseases. The vascular disorders, for example, could be treated using the EPC; the EPC can migrate through the blood, can differentiate into new endothelial cells so that the process of neoangiogenesis can be induced, the endothelium (also of damaged tissues that are distant) can be repaired [176, 177]. The vascular repair, in fact, can be obtained if the EPC can be mobilized from the bone marrow into the peripheral circulation or if the EPC situated into the vascular wall can be activated; EPC form the endothelial cells that are incorporated into the endothelial layer of the injured area to repair the lesion size [186]. It is clearly demonstrated and previously described that VEGF, as well as many other growth factors, utilize are able to activate neoangiogenesis utilizing Ca2+ signaling toolkit which regulates EPCs biological properties like differentiation, proliferative rate, migration and vessel tube formation. Intracellular Ca2+ signals toolkit could be manipulate to repair damaged tissue using genetically transformed cells or represent the target site of cell based therapy through the impairment of EPC-dependent vasculogenesis and adverse tumour neovascularization [178-192]. Also MSC are useful to reduce a lesion because they could be able to stop the process of fibrosis, apoptosis, and could be responsible to induce mitosis in intrinsic cellular progenitors [193]. The reduction of functions of B and T lymphocytes and NK is the cause of these immunomodulating effects [194, 195]. The MSC has not a great immunogenic effect, because of the low levels of HLA–I and the null expression of HLA-II [196, 197]. The MSC could have a reparative effect if administered after an acute event, as demonstrated in porcine with myocardial effect [198-201]; the MSC could also have the ability of differentiate into cells with biologic characteristics of cardiac myocytes and endothelial cells, with the result of an improvement of cardiac function, if compared with untreated controls [202, 203]. Also the postnatal skeletal muscle is able to repair and regenerate itself but in some particular pathological conditions, for example, muscular dystrophy or compartment syndrome, the myogenic progenitors are not be able to do it [204-207]. To prove the structural and functional regeneration of human myofibers, pericytes purified from human myofibers, from fat, pancreas and placenta, were transplanted into mouse with dystrophy and in cardiotoxin treatment; it was noticed that there was a more

efficient regeneration than do myoblasts or endothelial cells. There was also a surprising improvement also with pericytes isolated from patients with Duchenne muscular dystrophy [208-210]. A specific cellular type can be used only in a specific treatment. For example, to obtain the bone regeneration or dental repair or adipose reconstruction can be used the pericytes (studies have demonstrated that osteogenic, odontoblastic and adipogenic progenitors originate from perivascular niches) [211]. MSCs and pericytes derived from cord blood may have a great therapeutic efficacy also in the complete restoration of kidney function, if compared with MSC derived form regular bone marrow; they could seem to secret angiogenic and antiapoptotic factors that could be responsible of renoprotective effects [212, 213]. Furthemore, the umbilical cord is another source of stem cells [214-216]. The pericytes could be useful for many therapies. They can migrate toward the damaged cells, and can produce the vascular endothelial growth factor and keratinocyte growth factor, with antiapoptotic and angiogenic properties, so it is possible to obtain the vascular repair [217-221]. The same MSC are present not only in bone marrow but also around adult vessels; these MSC-like cells seem to be responsible of vasculogenesis, arteriogenesis, angiogenesis. With no doubt, using the MSCs and the MSC-like cells there are no ethical problems, but the only problem is that we don't know their specific mechanisms of action. Different elements have to be considered. Release of vasculogenic-angiogenic factors and/or arteriogenic-stimulating factors, immunomodulation into a different microenviroment, differentiation into vascular tissue, but also cell source, administration route, cell dosage, timing of cell delivery, are important factors to take in consideration. Many different results have been observed and probably are due to other many variables, for example drugs, diseases, inflammatory status, and comorbidities. Studies in vivo demonstrated that MMP activity was inhibited by MSCs and TIMP-1 was influenced by MSCs, instead MMP-2 activity was suppressed ex-vivo. Studies in vitro, instead, showed how MM gene expression in macrophages was suppressed by MSCs. There was, also, a negative correlation between elastin content and MMPs. It was described a reduced expression of inflammatory cytokines, as IL-6, MCP-1, TNF-α, probably implicated in the up-regulation of MMP in the aortic wall. It is probably true that paracrine mechanisms induced by MSCs could be stop the immunopathologic reactions in the aneurismal vascular wall. As regards MSCs coming from bone marrow, they could seem inhibited in vitro the activity of dendritic cells, T cells, NK cells. MMP2 and MMP 9, elastases and chemokines are responsible of induction of mobilization and homing of MSC; MSC is known also

to have particular tropism for inflammation. Important elements of AA are represented by chronic inflammation of the aortic wall induced by chemokines and aortic ECM degradation by MMP-2 and MMP-9, so MSCs that migrate toward MMPs and Chemokines can be useful for therapy of aortic aneurysm [222-225].

7 Discussion

SCs research is both scientifically promising and ethically challenging. In vascular diseases like arterial aneurysm the complexity of pathogenesis involving inflammation, MMPs activation, ECM remodeling, and VSMC dysfunction and apoptosis lead to the weakening of the vessel wall and arterial expansion under the influence of mechanical stimuli [226, 227]. Several complications like rupture, dissection, and distal embolization are frequently observed [228]. The degenerative remodeling seen in arterial aneurysms can result from a combination of excessive destruction and insufficient repair in which SCs play an important role creating a useful microenvironment for vascular regeneration [229]. VW-PCs have been also isolated from the thoracic and abdominal aortas of humans. A specific zone of vascular wall named vasculogenic zone contains specific subpopulation of EPCs [32]. In arterial aneurysms the chronic inflammation lead to MMPs activation inducing the mobilization of local VW-PCs and tissue-resident EPCs involved in an active repair process involving SCs. VW-PCs promote vascular repair by differentiating into vascular SMCs and fibroblasts in vasa vasorum localized in adventitial layer of vascular wall. MMPs activation can induce the secretion of pro-angiogenic cytokines such as VEGF and stimulate host SCs proliferation and differentiation. Share stress is also involved in arterial aneurysms pathophysiology. Arterial ECs proliferation and migration and medial SMC proliferation promotes adaptive enlargement and luminal tortuosity of vascular wall. A lot of papers report that proteolytic activity of ECM degradation by MMPs play a critical role in vascular formation and remodeling promoting the synthesis of pro-angiogenic growth factors and cytokines. Vascular formation and remodeling include recruitment, migration, proliferation, and apoptosis of vascular cells consisting of stem/progenitor cells, ECs, VSMCs, and other cells located in vascular wall. MMP-2, MMP-9, MT1-MMP, MMP-3, MMP-1, and MMP-7 have been recognized in vascular tissue and play pathogenic roles in vascular remodeling via regulating VSMC behaviors [230]. Early outgrowth EPCs induce only transient angiogenesis by secretory activity. Late out-

growth cells probably produce the effect by direct engraftment [231, 232]. VW-PCs exert their functional role in different phases of the natural history of aneurysms. In the early stages, the activity of MMPs lead to growth factors release. Stem cells are quiescent and reside in stem cell niches of the vessel wall but several stimuli can lead their activation. If damage is moderate, the laminar flow will stimulate stem cells to differentiate into ECs to maintain the vessel integrity. When severe damage or atherosclerotic lesion occurs, locally the disturbed flow is induced, resulting in stem cell differentiation towards SMCs, which accumulates within the intima [233, 234]. The existence of VW-PCs provides an exciting prospect to directly manipulate local responses within the vasculature, as it has already happened, in a similar way, in cell therapy for critical limb ischemia [235].

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