Endothelial Progenitor Cells in Neurovascular Disorders

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Endothelial progenitor cells (EPCs) are a population of cells that circulate in the blood looking for areas of endothelial or vascular injury in order to repair them. Endothelial dysfunction is an important component of disorders with neurovascular involvement. EPCs have a capacity to repair or replace the damaged endothelium through a differentiation into mature endothelial cells, which are able to embed into the new vessels. Moreover, through a secretion of various growth factors, including stromal cell-derived factor-1α (SDF-1α), vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1), they promote angiogenesis or vasculogenesis and recruit more EPCs. EPCs express various cell markers on their surface, which include both markers characteristic for hematopoietic stem cells (CD34 and CD133) and markers characteristic for endothelial cells, such as VEGFR-2 (vascular endothelial growth factor receptor-2), vWF (von Willebrand factor), VE-cadherin (vascular endothelial cadherin) or CD144, Tie-2, CD62E (e-selectin) and c-kit/CD117.

Keywords: endothelial progenitor cells ; endothelial dysfunction ; Alzheimer disease ; ischemic stroke

1. Alzheimer’s Disease

Studies have demonstrated that previously occurring vascular and endothelial dysfunction lead to the development of Alzheimer’s disease (AD). Comorbid cerebrovascular disease often accompanies AD. It is believed to have an additive effect on cognitive impairment and lower the threshold for dementia [1]. A dysfunction of cerebral vasculature is one of the earliest occurring events in the pathogenesis of AD [2][3]. According to the two-hit hypothesis of AD, first proposed by Zlokovic, vascular pathology appears primary and contributes to Alzheimer’s tau pathology. Vascular risk factors, such as hypertension, diabetes, cardiac disease and/or stroke (hit one) lead to an endothelial dysfunction in the blood–brain barrier (BBB) and a reduction in cerebral blood flow (CBF), which causes oligemia. An endothelial dysfunction of BBB impairs the clearance of amyloid beta (Aβ), whereas oligemia increases production of Aβ, and both processes lead to Aβ accumulation in the brain (hit two). Moreover, endothelial dysfunction within the BBB causes an infiltration of multiple neurotoxic molecules to the brain [4].

2. Cerebral Small Vessel Disease

Endothelial dysfunction has been recognized as the first event that occurs during the pathogenesis of cerebral small vessel disease (CSVD), a primary cause of vascular dementia (VD) [5][6]. Dysfunctional endothelial cells lead to changes in the surrounding cerebral white matter through a secretion of heat shock protein 90α, which hinders oligodendroglial differentiation and, thus, impairs the process of myelination [6]. Moreover, endothelial dysfunction is also related to the impairment of the BBB and a decrease in CBF, and both of these processes are involved in the development of CSVD. An increased permeability of the BBB causes local microhemorrhages and decreases distal blood flow, which leads to an aggravation of the regional ischemia in the brain [7].

Several studies have investigated EPC counts in human individuals with CSVD. Results of the research are conflicting in this regard. Early studies demonstrated that CSVD patients had lower levels of circulating EPCs and decreased EPC cluster counts compared to healthy individuals [8][9]. Later studies differentiated patients according to the burden of CSVD and a very recent study divided EPCs into subpopulations according to their surface markers. Overall, elevated levels of EPCs were related to greater CSVD burden [10][11]. However, circulating CD34+ cells were found to be decreased in the above-mentioned group of patients [11]. These findings suggest that EPC levels may serve as potential biomarkers to track the progression of CSVD.

3. Ischemic Stroke

Endothelial damage, induced by risk factors, such as hypertension, diabetes and hyperlipidemia, is an important event in the pathophysiology of ischemic stroke (IS) [12]. Endothelial dysfunction plays a key role in the onset of stroke through a promotion of atherosclerosis, thrombosis, a disruption of the BBB, oxidative stress, inflammation and increased vascular tone [13]. Patients undergoing an acute ischemic stroke were found to have a severe endothelial dysfunction during the first 24 h of the event [14]. Moreover, endothelial dysfunction also appears as a consequence of IS. Global ischemia, with or without reperfusion, was found to impair endothelium-dependent vascular tone regulation, whereas focal ischemia impairs endothelium-dependent vasodilatation [15].

EPC levels are decreased, overall, in multiple states that elevate the risk of stroke, such as atherosclerosis or hypertension [16][17]. However, the number of early EPCs (CD133+/VEGFR2+) increases during the acute phase of ischemic stroke, together with angiogenic growth factors VEGF and FGF (fibroblast growth factor). However, EPCs and angiogenic growth factor levels were found to be inversely correlated with inflammatory factors, suggesting an unfavorable impact of inflammation on the survival and differentiation of EPCs [18]. One study indicated that the level of circulating EPCs transiently elevates for some time after an acute stroke; first, it gradually increases up to 1 week after stroke onset, then remains elevated at 2 weeks and returns to baseline at day 28 [19]. An increase in SDF-1α was also noted early after the occurrence of IS [20]. A recent study demonstrated that the EPC level in stroke patients is higher in the 3rd and 12th month post-stroke than within 7 days after stroke. The peak in the EPC count was observed at 12 months after an ischemic event and was significantly higher than in healthy controls. However, EPCs from stroke patients showed impaired functionality measured by tube-formation capability compared to EPCs from healthy individuals [21]. A novel in vitro study demonstrated that the secretome of EPCs derived from stroke patients was found to promote angiogenesis and maturation of new vessels together with restoring the function of the BBB in ischemic conditions [22]. It was also found that the EPC level is inversely correlated with severity of ischemic lesion [23]. Moreover, a higher level of CFU-ECs during the first week after IS predicted better functional outcome and was associated with reduced infarct growth [24], whereas a low level of circulating EPCs measured 48 h after IS predicted severe neurological impairment [25]. Migratory and angiogenic capacities of EPCs were also found to be associated with increased collateral flow during the acute phase of the stroke and increased CBF at day 7 post-stroke. On the other hand, no associations were found between EPCs and hemorrhagic transformation or recanalization [13]. Currently, there is one ongoing clinical trial (NCT02980354) that aims to investigate whether the number and functionalities of circulating EPCs could serve as biomarkers of severity and type (cortical/lacunar) of ischemic stroke [26]. In vitro research has demonstrated that OECs migrate to the place of vascular injury and repair it in order to maintain neurovascular homeostasis at a time of or after an ischemic injury in the brain. OECs were observed to establish an equally tight in vitro model of the BBB as brain microvascular endothelial cells (BMECs), which shows their capacity to form tight junctions. Moreover, OECs were found to have a greater proliferative and migratory capacity than BMECs. An exogenous addition of OECs to an in vitro model of the BBB (established with astrocytes, pericytes and BMECs) repaired the wound scratch-induced on a layer of BMECs in serum-free conditions [27]. Additionally, a very recent study demonstrated that an outgrowth endothelial cell-derived conditioned media (OEC-CM) prevents the damaging effects of TNF-α on the BBB since the levels of TNF-α were found to be significantly elevated on days 2, 7, 30 and 90 after ischemic stroke and TNF-α impairs function and integrity of the BBB, which is the main early cause of death after IS [28].

4. Migraine

Endothelial dysfunction is also known to be involved in the pathophysiology of migraine. Oxidative stress and inflammation were identified as two main causes of endothelial damage in migraine. Oxidative stress causes a reduction in the amount of nitric oxide (NO), which leads to vasoconstriction. Moreover, NO insufficiency is associated with perception of pain since NO reduces pain by increasing the cyclic guanosine monophosphate (cGMP) level. Moreover, oxidative stress promotes hypercoagulability. As a consequence, endothelial dysfunction leads to increased vascular tone, inflammation and thrombosis, all of which contribute to migraine [29]. Moreover, studies suggest that migraine, particularly migraine with aura, increases the risk of ischemic stroke [30].

Studies have demonstrated that a lower circulating EPC count is observed in migraineurs. A study by Lee et al. indicated that migraine patients (with or without aura) had a reduced number of EPCs compared to healthy controls and patients with tension type headache (TTH). Moreover, patients with migraine with aura showed lower EPC counts than patients with aura-free migraine. Additionally, EPCs isolated from migraineurs showed reduced migration ability and increased cellular senescence compared to EPCs from normal or TTH subjects [31]. A later study by Rodríguez-Osorio et al. confirmed a lower EPC count in migraine patients and, furthermore, indicated that a number of EPCs decreases with time as migraine progresses [32]. Moreover, one study demonstrated that women suffering from migraine with aura exhibited

decreased (compared to age-matched healthy women) SDF-1α, which promotes mobilization of the EPCs from the bone marrow. These results suggest that the compensatory up-regulation of SDF-1α as a response to an injury in migraineurs is somehow disrupted, which adds to the evidence for endothelial dysfunction in migraine [33]. Furthermore, among participants of this study, an inverse correlation was found between the level of SDF-1α and CD144+ and activated CD62E+ endothelial microparticles (EMPs), which are markers of endothelial dysfunction [33][34]. Another study showed that female migraineurs with aura have an increased level of EMPs [35]. Furthermore, another study by Oterino et al. observed a higher number of CD62E+EPCs, a marker of endothelial activation, in migraine patients, both with and without aura [36]. A reduction in and a dysfunction of EPCs in migraine patients was suggested as a link between migraine and cardiovascular risk [31][36].

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