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Circulating Angiogenic Cells and Alzheimer's Disease: Contribution of the Bone Marrow to Pathogenesis of the Disease

Martin J. Sadowski

Departments of Neurology, Psychiatry, and Pharmacology, New York University School of Medicine, New York, New York, USA

The most prevailing view on the pathogenesis of sporadic Alzheimer's disease (AD) assumes that chronic imbalance between production and clearance of amyloid- β (A β) leads to accumulation of this hydrophobic and aggregation prone peptide in the brain and induces a neurodegenerative cascade [1]. Removal of A β through the blood-brain-barrier (BBB) to the bloodstream constitutes one of the critical pathways of A β clearance from the brain. Connected by tight junctions, endothelial cells line the cerebral vasculature and constitute the luminal layer of the BBB. Such endothelial cells are directly responsible for the active transport of numerous blood-borne elements to the brain and express the low density lipoprotein receptor-related protein 1 (LRP-1) which serves as a major A β clearance receptor. Numerous data indicate damage and dysfunction of the endothelial cell layer in AD patients and in AD transgenic animals, which undoubtedly contributes to the dysfunction of the BBB and impairment of its protective A β clearance capacity [2]. This dysfunction is exacerbated by A β itself, which shows pronounced vasculotropism and vasculotoxicity. Virtually all AD cases have some extent of cerebral amyloid angiopathy. A β peptide was shown to inhibit angiogenesis [3] and to be directly toxic to brain endothelial cells [4]. In this issue of the *Journal of Alzheimer's Disease*, Dr. Soon-Tae Lee and colleagues described dysfunction of circulating angiogenic cells (CACs) in patients with sporadic AD [5]. Recently, the same group also reported a reduced number of CACs in AD patients [6], which inversely correlated with severity of the disease on cross-sectional study. These original observations contribute to our understanding of the etiopathogenesis of the vasculopathy and BBB dysfunction associated with AD.

CACs, including the endothelial progenitor cells, are produced by the bone marrow and released into the bloodstream under stimulatory effect of a number of cytokines and nitric oxide [7]. CACs are capable of proliferating and differentiating into endothelial cells, and, thus, they are essential for supporting angiogenesis and vascular repair. Because of their potential to regenerate and rejuvenate endothelium, several studies have investigated potential CACs dysfunction in patients with cardiovascular disease. In fact, the number and function of CACs correlates inversely with combined Framingham risk factor score for cardiovascular diseases and reactivity of the vasculature [8]. Furthermore, the number of CACs appears to be a prognostic factor in the clinical outcome of coronary artery disease. Increased number of CACs was associated with a reduced risk of death from cardiovascular causes, a first major cardiovascular event, revascularization rate and a number of further hospitalizations [9].

Correspondence to: Martin J. Sadowski, MD, PhD, Departments of Neurology, Psychiatry, and Pharmacology, New York University School of Medicine, 550 First Avenue, PRR, Rm. RR 311, New York, New York 10016, USA; Tel: 212-263-2152, Fax: 212-263-7721, sadowm01@med.nyu.edu.

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In their experimental work, Dr. Soon-Tae Lee and colleagues isolated CACs from the blood samples of patients with early to moderate AD and cognitively normal controls. Both groups were well matched for age, gender, medical history, Framingham score of cardiovascular risk, and concomitant use of medications. Isolated cells were then cloned *in vitro* and subjected to a number of assays. CACs derived from AD patients appeared to show dysfunctional chemotaxis, paracrine function, ability to form capillary tubes *in vitro*, and altered gene expression profile. The authors rationally concluded that dysfunctional CACs in AD patients may have negative impact on their potential to regenerate the cerebral vasculature and the BBB and, thus, they indirectly contribute to A β brain accumulation. In light of the observation made by the authors showing impaired quality of CACs circulating in the blood stream and a parallel published study demonstrating reduced number in AD patients [6], it appears that the cerebral vasculature endothelium in AD is not only severely affected but also deprived a critical repair mechanism. These studies raise a critical question as to why AD patients show both reduced number and quality of CACs. This problem remains only partially explored in the manuscript. The reduced number of CACs may arise either from their limited mobilization from the bone marrow or consumptive loss in the periphery. Altered quality may result from an originating defect in the bone marrow or loss of their qualities while circulating blood-borne. Since the differentiation and release of CACs from bone marrow is clearly dependant on the stimulatory effect of nitric oxide and various cytokines, one may consider lack of proper stimulation as being explanatory of the observed phenomena. It has been shown that toxicity of A β limits release of nitric oxide by the endothelium of the cerebral vasculature [10]. On the other hand, it is not clear that the differentiation and release of CACs from bone marrow is particularly dependent on the integrity of the cerebral portion of the vasculature, or rather is a function of the entire body vasculature endothelium. To elucidate possible reasons for the dysfunction of CACs isolated from AD patients, the authors applied mRNA arrays to the protein expression profile. 1112 genes were detected to be up- or down- regulated (>2.5 fold) in AD patients compared to controls. The majority of these genes were related to cell metabolism, signal transduction, transcription, and cell cycle. While this emphasizes that CACs in AD patients are different from controls, the dilemma as to whether this represents an inherent or acquired feature remains. If the former is true, one may put forward a hypothesis that a primary bone marrow dysfunction is contributory to AD pathogenesis. If the latter notion is true, what then makes CACs to lose their qualities while blood-borne? The authors demonstrated increased susceptibility of CACs isolated from AD patients to synthetic A β ₄₂ at the concentration of about 500 times above serum level of A β found in AD patients. However, at a lower and physiological concentration, A β ₄₂ had no effect on the viability of CACs.

The elegant work of Wu and colleagues [2] demonstrated reduced expression of the homeobox gene MEOX2, which is a regulator of vascular differentiation, in the primary brain endothelial cells from AD patients. This in turn resulted in lower LRP1 expression and was contributory to defective BBB A β clearance. Using their gene arrays the authors also looked into MEOX2 and LRP1 expression in CACs to investigate whether this aspect of endothelial dysfunction originates in the precursor cells. In this regard, while no MEOX2 expression was detected, the LRP1 expression was actually increased by 2.9 fold in CACs of AD patients, suggesting that the downregulation of LRP1 is an acquired feature of the cerebral endothelium in AD.

Since CACs are capable of proliferating and differentiating into endothelial cells, they appear to be a promising target for vascular regeneration approaches [11]. Increases in the number of circulating CACs and increases in their incorporation in the endothelial layer may provide an opportunity for therapeutic interventions. Offering such promise, experimental animal studies involving either chemokine mobilization or transfusion of CACs support neovascularization and rejuvenation of the injured endothelial monolayer [7,12]. Additionally,

repeated injections of endothelial progenitor cells derived from the bone marrow also appears to reduce the rate of plaque formation without altering serum lipid level in a mouse model of atherosclerosis [13]. Also, a short-term functional benefit of intracoronary infusion of bone marrow cells after acute myocardial infarction was demonstrated in a small scale clinical trial [14]. Building upon the observations made by Soon-Tae Lee and colleagues, one can speculate that the enhanced mobilization of CACs from the bone marrow through stimulation or increasing their number through a transplantation may benefit AD patients. However, it remains to be seen whether there are any downsides to enhancing the number and function of CACs. Possible concerns include exacerbating abnormal angiogenesis in conditions such as diabetic retinopathy or tumor angiogenesis. Increases in the number of circulating CACs can also be achieved by lifestyle modifications including physical exercise [15], statin therapy [16], or estrogen therapy [17] which, perhaps not coincidentally, are all relevant to the risk of sporadic AD. Given that conventional cardiovascular risk factors constitute risk factors for sporadic AD, further studies on the origin of functional abnormalities of CACs in both AD and cardiovascular disorders might provide a pathogenic link between the pathogenesis of vascular disorders and AD and, in turn, lead to the development of novel therapeutic approaches benefitting patients with both AD and vascular disorders.

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