

Acute Stroke and Attenuation in Endothelial Progenitor Cells: Cause or Effect?

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Endothelial damage represents the balance between the magnitude of vascular injury and the capacity for repair. Evidence suggests that cardiovascular risk factors induce endothelial injury and that impaired endothelial function reflects ongoing vascular injury. Endothelial progenitor cells (EPCs) are bone marrow-derived cells that are mobilized to the circulation in response to tissue or vessel injury and are incorporated into the sites of injury [1-5].

Circulating EPCs co-express CD133, CD34, and vascular endothelial growth factor receptor 2 (VEGFR-2) antigens on their surface. These cells have self-renewal capacity and capability of differentiation into mature endothelial cells [2-4]. Thus, EPCs have a pivotal role in the process of vascular (arterial) repair by promoting re-endothelization following injury [3,6,7]. EPCs have been shown to mobilize and be incorporated into denuded parts of the vessel wall after balloon injury – a process associated with accelerated endothelial regeneration [6].

In humans, a rapid increase in the levels of circulating EPCs was observed following acute vascular insults [8] or coronary artery stenting [7-9], implying that focal endothelial injury may trigger mobilization of EPCs into the peripheral circulation [10]. EPCs also have the potential to secrete a variety of cytokines and growth factors, which provide nutritional and anti-

apoptotic support for the circulating and resident EPCs and other cells (endothelial cells, cardiomyocytes, neurons, neural stem cells, among others). Circulating human EPCs injected into nude mice after transient middle cerebral artery occlusion demonstrated a neurovascular protective effect and contributed considerably to the recovery of neurological function [11].

In this issue of *IMAJ*, Blum and co-authors [12] depict an abnormal profile of circulating EPCs in the first 24 hours after an acute cerebrovascular ischemic event. These patients were characterized by a low number of EPCs in the circulation and reduced function of the EPCs as reflected in decreased numbers of colony-forming units compared to a healthy control group. The study group was unique in that it did not include subjects with the traditional risk factors of atherosclerotic cardiovascular disease, although the nature of the cerebrovascular event was lacunar infarct which is typical of local atherosclerotic disease.

Is this observation valid to determine association or causation between an abnormal EPC profile and the ischemic event? Causation would mandate determination of the EPC profile before and after the acute event. Otherwise, one cannot exclude the fact that the observed abnormality in the number and function of circulating EPCs was a negative acute-phase response to the cerebral ischemia. Moreover, the pathogenesis of the lacunar infarction might involve a transient abnormality in platelet reactivity. Notably, platelets have been shown to play an essential role in the process of recruitment and homing of EPCs to the site of arterial injury in the acute phase fol-

lowing the injury [13,14]. Hence, a primary change in reactivity of platelets may precede the alteration in EPC profile, which may further augment the tissue injury.

The observation of Blum et al. [12] suggests a role for statin treatment in patients with acute lacunar stroke. Statins have a central role in the treatment of atherosclerosis cardiovascular diseases. In addition to their cholesterol-lowering properties, statins exert a number of pleiotropic vasculo-protective effects including mobilization and proliferation of EPCs [15-18]. Furthermore, statin withdrawal during the acute phase of stroke increases brain damage and worsens functional outcome [19]. Statin treatment during the acute phase of stroke has been independently associated with a greater EPC increment during the first week after stroke onset [20]. This effect was complemented by a reduction in infarct growth and neurological and functional improvement at 3 months [20]. The accumulating data regarding the abnormal EPC profile in the early stage of acute ischemic stroke call for further research regarding the role of EPCs in acute stroke and possible pharmacological modulation of EPCs in this setting.

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Capsule

Sending tumors a message

T cells need to overcome an immunosuppressive environment for successful cancer immunotherapy. **Hewitt** et al. leveraged a platform for messenger RNA (mRNA) delivery to devise a combination of factors that would ramp up antitumor immunity. Intratumoral injection of three specific mRNAs led to tumor regression in several cancer models. The triplet

therapy also rendered normally resistant tumors susceptible to immunotherapeutic checkpoint blockade, activity which could one day be translated to human patients.

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Capsule

Tumor-educated B cells selectively promote breast cancer lymph node metastasis by HSPA4-targeting IgG

Primary tumors may create the premetastatic niche in secondary organs for subsequent metastasis. Humoral immunity contributes to the progression of certain cancers, but the roles of B cells and their derived antibodies in premetastatic niche formation are poorly defined. Using a mouse model of spontaneous lymph node metastasis of breast cancer, **Gu** et al. show that primary tumors induced B cell accumulation in draining lymph nodes. These B cells selectively promoted lymph node metastasis by producing pathogenic IgG that targeted glycosylated membrane protein HSPA4, and activated

the HSPA4-binding protein ITGB5 and the downstream Src/NF-κB pathway in tumor cells for CXCR4/SDF1α-axis-mediated metastasis. High serum anti-HSPA4 IgG was correlated with high tumor HSPA4 expression and poor prognosis of breast cancer subjects. These findings identify a key role for tumor-educated B cells and their derived antibodies in lymph node premetastatic niche formation, providing potential targets for cancer intervention.

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“Love is never lost. If not reciprocated, it will flow back and soften and purify the heart”

Washington Irving (1783–1859), American short story writer, essayist, biographer, historian, and diplomat in the early 19th century

“Millions saw the apple fall, but Newton was the one who asked why”

Bernard Baruch (1870–1965), American financier, stock investor, philanthropist, statesman, and political consultant