Editorial

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An Update on Cellular Treatments for Angiogenesis in Ischemic Limbs

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In addition to clinical treatments, regular exercise, or smoking cessation among patients who have symptomatic peripheral arterial disease (PAD) or critical limb ischemia (CLI), the conventional or endovascular surgical revascularization can improve the state and the evolution of PAD or CLI, and obtain positive results for relief of critical symptoms or for limb salvage [1]. Despite the fact that surgical revascularization for ischemia of lower limbs can avoid amputation, this treatment does not necessarily lead to an efficient limb blood supply or mobility without pain, nor to independence of the patient [1-4]. When progression of atherosclerosis is not interrupted by the used treatments, graft failure or thrombosis may require additional interventional procedures [1-5]. Some patients can reach the disease stage in which the local circulatory system contains arteries of small caliber, with circulation maintained by an extensive network of collateral vessels that cannot provide an adequate supply of blood to tissues. The local anatomy, limited percutaneous access, reduction of autologous vein graft options for revascularization, as well as serious disease of the distal vascular bed, minimize the potential benefits of revascularization procedures or their feasibility. In this context, there is a class of patients in a pre-amputation stage with advanced CLI of the lower limbs that are not candidates for surgery. Besides poor survival rates, prognosis with respect to limb preservation in CLI patients remains also poor, particularly in no-option CLI patients, where 6-month major amputation rates have been reported to range from 10% to 40% [1-5].

The vascular system is very dynamic and responsive to local tissue functional demands consequent to hypoxia. The hypoxia-inducible factor-1 alpha (HIF-1α) induces local production of angiogenic and vasculogenic growth factors as well as mobilization of distant progenitor cells, mainly from the bone marrow. They can normally promote angiogenesis and vasculogenesis, i.e. local increase of blood vessels by sprouting as well as formation of new vessels by incorporation of circulating progenitors, respectively. It is not surprising that the regenerative therapies using either progenitor cells, or different cell products have been proposed and extensively studied [6].

The human bone marrow represents a reservoir of multiple stem cell populations, among which endothelial progenitor cells (EPC) and mesenchymal stem cells (MSC) are relevant for vascular regeneration. They are a part of the bone-marrow mononuclear cell population (BM-MNC), which has been used in the majority of preclinical and clinical studies. The EPCs are derived from the common hematopoietic progenitors hemangioblasts, with which they share the surface markers CD34 and CD133, and represent close to 1% of the total BM-MNC. Similar to other hematopoietic progenitors, they can be mobilized to the peripheral blood circulation and collected in the peripheral MNC fraction [7].

In vitro studies have shown that EPC proliferation is stimulated by other BM-MNCs, while *in vivo* studies have clearly indicated that MSC-derived perivascular cells or pericytes are required for stabilization of newly formed endothelial sprouts. In this context, the bone marrow-derived MSC can be relevant for regenerative angiogenesis, although they are also common in the muscle and can be mobilized to the growing blood vessels from the resident tissue population. Cell therapy of ischemic tissues has been done through intramuscular or intravascular delivery. Direct comparison of the clinical outcome in the two approaches was not yet convincing, in part due to dose-dependent differences [6].

Preclinical studies on cell therapy for critical limb ischemia have given promising results. Clinical studies have been less convincing, although are still promising. A recent meta-analysis has been done using data on 774 patients [8]. Compared with no therapy, cell therapy significantly reduced major amputation and improved ulcer healing and ankle-brachial index. All-cause mortality was similar in both groups, indicating the safety of the therapy. However, all estimates were nonsignificant following reanalysis using placebo-controlled clinical studies only.

This information raises the question of a need for development of new preclinical models for cell therapy in limb ischemia. Human leg is unique in its anatomy and function. Rodent models, mostly used in preclinical studies, are quite different from the human body. They display a broad spontaneous capacity to heal ischemic lesions, and the time course of their reaction to cell infusion is rapid. Larger animals including primates were only rarely used.

On the other hand, most of clinical studies were done with heterogeneous cell populations, such as bone marrow or peripheral mononuclear cells. The cells expected to be the major players in regenerative processes such as EPC or MSC are only a minor fraction usually under 1% of the total collected cells. Enrichment of such a population by selection using the surface markers is stressful for cells, and requires large starting population in order to reach a threshold compatible with cell injection into large targets such as limbs. Mesenchymal cells can be expanded *in vitro* maintaining their capacity to differentiate into other cells of the similar origin, including into the blood vessel wall cells. Only a few clinical studies were done using these cells. They can be used alone or in combination with freshly collected mononuclear cells of the same donor, since they are known to display potent paracrine stimulation on cell proliferation and differentiation.

Improvements of cell therapies may benefit of better characterization of the used cells in the context of their interaction with other components of the putative therapeutic agent and the receptor tissues. These studies can be done in the 3D *in vitro* models, which can be nowadays representative of human tissues.

References

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, et al. (2007) Inter- society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 45: S5–S67.
2. Reis PEO (2005) Bone marrow stem cells and their role in angiogenesis. J Vasc Bras 4: 366-370.
3. Reis PEO, Reis IFO, Neves D, Matsumoto PK, Han SW, et al. (2012) Lower limb ischemia: current outlook for cell therapy and gene therapy. Rev Bras Cardiol 25: 330-339.
4. Abu Dabrh AM, Steffen MW, Undavalli C, Asi N, Wang Z, et al. (2015) The natural history of untreated severe or critical limb ischemia. J Vasc Surg 62: 1642-1651.
5. Reis PE, de Carvalho LP, Yasumura E, da Silva FH, Garcia BC, et al. (2014) Impact of angiogenic therapy in the treatment of critical lower limb ischemia in an animal model. Vasc Endovascular Surg 48: 207-216.
6. Cooke JP, Losordo DW (2015) Modulating the vascular response to limb ischemia Angiogenic and cell therapies. Circ Res 116: 1561-1578.
7. Raval Z, Losordo DW (2013) Cell therapy of peripheral arterial disease: from experimental findings to clinical trials. Circ Res 1121: 1288-1302.
8. Liew A, Bhattacharya V, Shaw J, Stansby G (2016) Cell therapy for critical limb ischemia: a meta-analysis of randomized controlled trials. Angiology 67: 444-455.