Editorial

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Angiogenic Gene Therapy: Advances and Perspectives

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The current treatment of peripheral arterial disease (PAD), generally caused by atherosclerosis, or it`s complications as thrombosis, needs interventions in order to save the ischemic limb and life of our patients. Despite new technologies in interventional approaches have produced more successful results, some patients are not suitable for surgical or percutaneous revascularizations, or it does not necessarily conduct to adequate ambulation, sometimes they remain in pain even after procedures or do not have independence life [1,2]. Researches with animals and clinical trials have showed that the use of recombinant angiogenic growth factors may lead to the development of a collateral vascular network, which can be administered as a protein (protein therapy), gene (*in vivo* gene therapy) or via genetically modified cell (*ex vivo* gene therapy) [3-9].

Knowledge of molecular mechanisms in vascular development has shown that therapeutic angiogenesis can occur via two mechanisms: vasculogenesis and angiogenesis [10]. Vasculogenesis is the first process of formulating a vascular network in the body, however, it has been shown that this process also occurs after birth via endothelial progenitor cells from the bone marrow [10]. Usually, vasculogenesis is associated with angiogenesis that occurs by processes of sprouting and splitting of pre-existing vessels. The molecular, cellular, humoral, and mechanical factors result in transformation of vessel wall homeostasis [11,12].

Gene therapy is performed via introduction of exogenous nucleic acids into cells in a process known as transduction (via viral vector) or transfection (via non-viral vector). It may involve the delivery of integral active genes or blocking the expression of an active gene by delivery of an antisense oligonucleotides, microRNA (miRNA) or small interfering RNA (siRNA). These RNAs are small ribonucleic acids that target mRNAs (messenger RNA) to prevent their translation.

Angiogenic gene therapy demonstrated its efficiency in the treatment of ischemic limbs, but some potential risks of controllable adverse events such as edema, proteinuria and hypotension in treated patients, transient increase in C-reactive protein and thrombocytopenia were seen. It is important to note that there was no statistical difference in mortality, retinopathy and evolution to malignant disease in these patients [13,14]. In PAD, there is a proven action of growth factors with angiogenic activity, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and hepatocyte growth factor (HGF) in angiogenic therapy *in vivo*. The efficiency of introduction, gene expression level in the target cells and the time of gene expression determine the efficacy of the final result. The introduction is done through vectors which are known as, the viral and the non-viral vectors [15]. The ideal angiogenic gene therapy would be to transfect the target cells without leakage to avoid the spread of vectors to do not stimulate silent tumors. In practice, this is performed by the intramuscular injection that is a simple and minimally invasive procedure. In addition, some vectors, as the plasmid vectors, can be administered repeatedly and easily even for very debilitated patients [16]. The use of a vector for *in vivo* gene transfer is much easier and less complex than the use of genetically modified cells in the laboratory, which also requires all the controls for cell therapy [17,18].

Clinical studies with gene therapy for PAD may benefit other organs suffering of ischemia like heart and brain. The promotion, formation and remodeling of vessels by gene therapy serve for all ischemic diseases. However, the pathophysiology of each disease must be taken into account in order to better tailor the gene therapy for each case [19].

Neovasculgen is the first gene therapy drug for the treatment of PAD; it is a plasmid vector carrying human VEGF165 under the control of the cytomegalovirus promoter. It was developed by the Human Stem Cells Institute in Russia and approved in Russia in 2011 [20]. These evidences show that the therapeutic angiogenesis is a feasible treatment for patients with advanced PAD [9,12-20]. Angiogenic gene therapy emerges as a prominent therapy for the treatment of critical ischemic disease of the lower limbs, acting as a bypass of the endogenous conduit around occluded peripheral arteries and distal to these, giving the opportunity to change the natural history of this disease.

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