Update on Therapeutic Myocardial Angiogenesis

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TSE and LAU: ***Update on Therapeutic Myocardial Angiogenesis.*** *Recent advances in the understanding of the mechanisms of neovascularization and the identification of potent angiogenic growth factors have led to the development of therapeutic angiogenesis for treatment of severe ischemic heart disease. Current clinical studies on therapeutic myocardial angiogenesis generally involved the delivery of recombinant protein or gene of the angiogenic growth factors using various different approaches. Although the initial clinical results are encouraging, the potential side effects of these potent angiogenic growth factors remain a major concern. Large-scale, randomized and placebo control studies will be required to demonstrate the clinical benefit of this novel therapeutic treatment of ischemic heart disease. (J HK Coll Cardiol 2002;10:81-87)*

Ischemic heart disease, therapeutic angiogenesis

摘要
在瞭解新生血管化機制和確認有效的血管生長因數方面的最新進展，促進了治療性血管生成治療嚴重缺血性心臟病的發展。新近有關治療性心肌血管生成的臨床研究通常包括有用各種不同的方法使血管生長因數的重組基因或蛋白的釋放。儘管初步臨床結果令人鼓舞，但有效的血管生長因數的潛在副作用仍是一個憂慮。將需要大規模、隨機和安慰劑對照的研究來證實治療性心肌血管生成治療缺血性心臟病患者的臨床獲益。

關鍵詞：缺血性心臟病　　治療性血管生成

Introduction

Ischemic heart disease (IHD) remains the leading cause of death in the developed countries. In United States, up twelve million American alive today have a history of myocardial infarction, angina pectoris, or both.[1] In Hong Kong, a recent survey has demonstrated that up 14.3% of ambulant elderly with age >65 years suffer from IHD.[2] Current therapeutic approaches aim to relieve symptoms and cardiovascular events by reducing myocardial oxygen demand with medical therapy, to prevent further progression by modifying risk factors, or to restore blood flow by coronary angioplasty (PTCA) or bypass surgery (CABG). However, up to 20-37% of patients with severely symptomatic IHD are unsuitable or received incomplete revascularization with these conventional revascularization procedures.[3] Many of these patients have residual symptoms or myocardial ischemia despite maximal medical therapy. Therefore, such patients require an alternative revascularization strategy to relieve angina and to combat myocardial ischemia.

Collateral vessels develop at the interface between normal and ischemic tissue in response to coronary artery stenosis or occlusion. Blood flow through coronary

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collaterals may be sufficient to preserve wall motion and prevent ischemia at rest and during stress. It is therefore potentially attractive to emulate and enhance neovascularization for treatment of IHD. This article summarizes the current status of therapeutic myocardial angiogenesis.

Processes of Neovascularization

Three different processes contribute to the growth of new blood vessels (Figure 1): vasculogenesis, arteriogenesis, and angiogenesis.[4]

Vasculogenesis

Vasculogenesis refers to formation of new vessels from pluripotent stem cells during the course of embryonic development. Under the influence of multiple factors that include vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), the angiopoietins, and other many factors, these cells undergo differentiation into an endothelial cell network forming a primitive blood vessel plexus. Although preliminary evidence suggests that vasculogenesis may play a role in new-vessel formation in mature tissues, the significance and frequency of this event has not been well defined.

Angiogenesis

Angiogenesis occurs in mature tissues and is responsible for formation of new vessels lacking developed tunica media from post-capillary venules. This is the main postnatal mechanism responsible for new capillary formation. Angiogenesis encompasses sprouting of preexisting capillaries to form a new capillary network, a process tightly regulated by a large number of angiogenic factors, including VEGF, FGF, and placental growth factor. The changes induced by

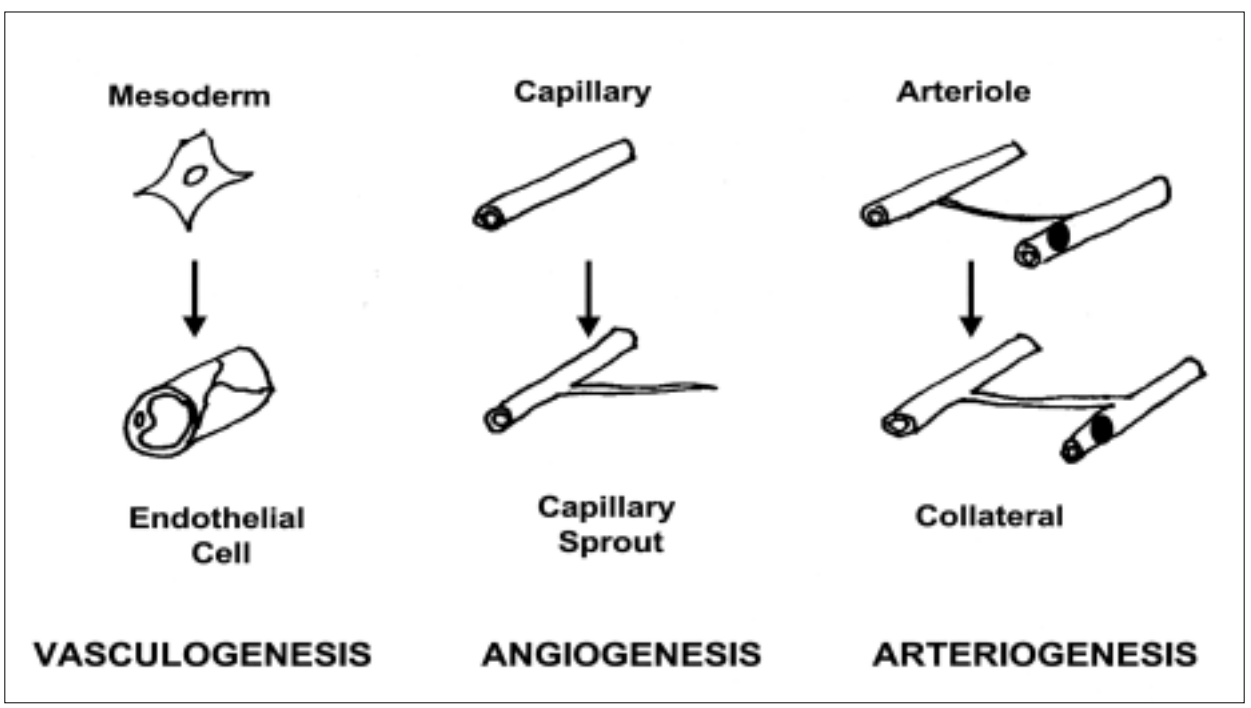

Figure 1. *Mechanisms of neovascularization: Vasculogenesis, Angiogenesis, and Arteriogenesis.*

these growth factors and cytokines include an initial process of degradation of the basement membrane, remodeling of the perivascular matrix, endothelial cell migration and proliferation, and endothelial cell tube formation, resulting ultimately in a new capillary network.

Arteriogenesis

Arteriogenesis is responsible for the formation of arteries possessing fully developed tunica media. This postnatal mechanism of resistance and conductance blood vessel growth involves remodeling of preexisting small arterioles into larger vessels. Following narrowing or occlusion of the main artery, the pressure gradient across the in-parallel arterioles increases, establishing flow and thereby increasing shear stress. Endothelial shear-stress responsive elements mediate increased expression of many genes, including macrophage chemoattractant protein-1 (MCP-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), and intercellular adhesion molecule (ICAM-1). These cytokines recruit monocytes into the subintimal space of the vessel wall and differentiate into macrophages. The macrophages produce abundant angiogenic growth factors that lead to endothelial and smooth-muscle cell proliferation, migration, vessel remodeling, and synthesis of extracellular matrix. Angiographically visible collaterals in patients with advanced obstructive coronary or peripheral vascular disease are examples of arteriogenesis.

Therapeutic Angiogenesis

Protein Versus Gene Therapy

A number of growth factors have been evaluated for their angiogenic potential. These include FGF, VEGFs, hepatocyte growth (HGF), chemokines e.g. MCP-1, growth factors involved in maturation of the vascular tree, e.g. angiopoietins and platelet-derived growth factor (PDGF) and transcription factors, e.g HIF, that stimulate expression of angiogenic cytokines and their receptors. Two approaches have been used to achieve therapeutic angiogenesis: gene transfer and protein therapy. Their advantages and disadvantages are summarized in Table 1. Experience with protein-based (growth factor) therapy has been more extensive than with gene transfer, as it is easier to administrate and avoid the potential severe and long-term side effects of gene therapy. However, the efficacy of the protein-based therapy may be lower due to the short half time of their effects. Furthermore, some angiogenic agents cannot be delivered as proteins and thus may necessitate gene transfer, such as HIF-1α. However, for FGFs and VEGFs, protein therapy may supersede gene transfer, especially given the limitations of current vectors.

Methods of Delivery

The methods available for delivery of growth factors, either using gene therapy or protein, is summarized in Figure 2. Intravenous and intracoronary injections are appealing because of their practicality,

Table 1. Comparisons between gene and protein therapy

	Gene therapy	Protein therapy
Tissue exposure	Sustained	Temporary
Dose response	Unpredictable	Finite tissue half-life
Administration	Single	May need multiple
Slow release	Yes	Need special formulation
Foreign material	Yes	No
Inflammatory reaction	Yes	No
Systemic effect	Unpredictable	Short duration

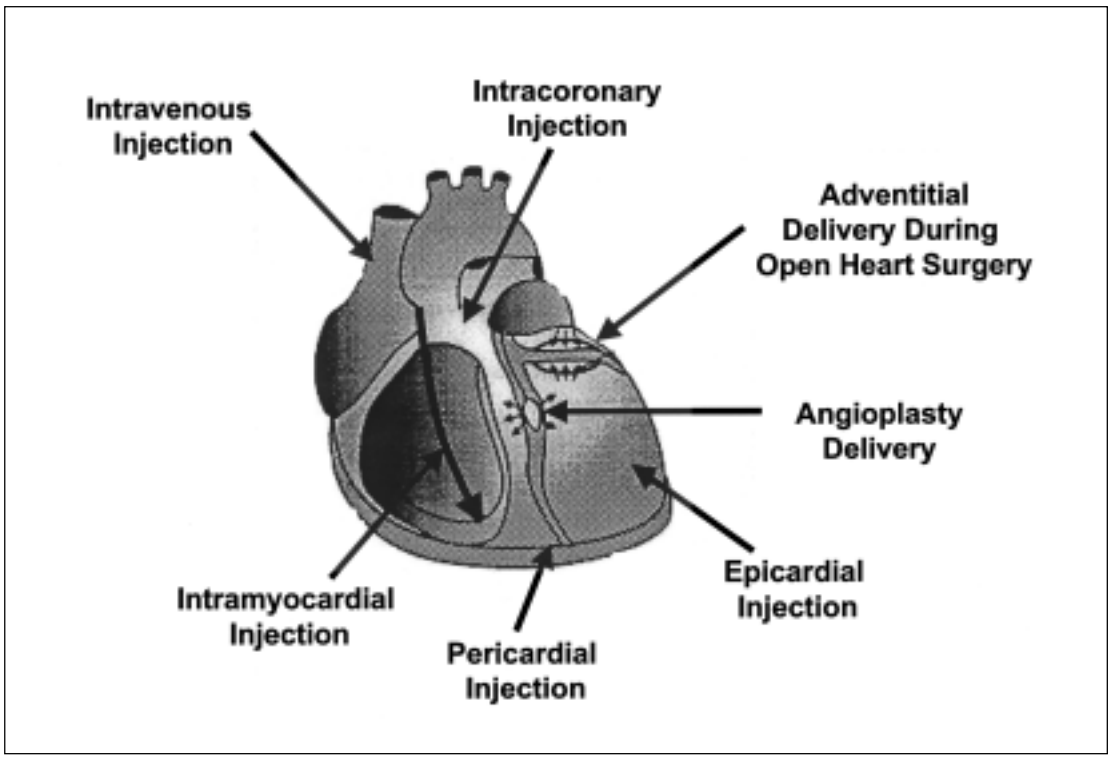

Figure 2. *Methods of delivery of angiogenic growth factors.*

low cost, treatment can be repeated easily, avoidance of open heart surgery and applicability to broad groups of patients. However, the percentage of tissue retention of growth factors is low (<1%), and exposes the patients to the potential systemic side effects of these growth factors. Intrapericardial delivery can achieve up to 5-8% of tissue retention but necessitates entry to the pericardial space and a normal pericardium. It cannot be used in patients with prior open-heart surgery. Perivascular and epicardial delivery during open-heart surgery are effective method for administrating the growth factors. However, they are associated with the mortality and morbidity of open heart surgery. Percutaneous intramyocardial injection may provide a simpler and safer alternative to the surgical methods, and is associated with less systematic exposure of the angiogenic growth factors. The drawbacks are its invasive nature, a requirement for highly specialized equipment, and the need for a high skill level of the operator.

Summary of Clinical Trials

Table 2 summarized the results of clinical trials on therapeutic angiogenesis for IHD in human.[5-17] The majority of this studies are Phase I trial that included a small number of patients and aimed to show the safety and feasibility of the procedure. In general, these Phase I trials using either FGF or VEGF showed improvement if patients symptoms and myocardial perfusion on radionuclide SPECT scan. Although these Phase I studies reported initial encouraging results,[5-9,11-14] these findings were not confirmed by subsequent Phase II studies.[10,15,16] The conflicting results reported in the literature reflecting the uncertainties surrounding the field. The optimal growth factors, forms of growth factor, method of delivery and dosage for therapeutic angiogenesis remain unclear.

Side Effects

The biologic activity of most of the angiogenic agents currently being tested clinically is very potent, and it is likely that the same activities that lead to a therapeutic effect could also cause potential deleterious effects.[17] The potential side effects are summarized in Table 3. If this concept is true, then the critical question

Table 2. Clinical trial on therapeutic angiogensis for IHD

Author	Number of patients	Growth factors	Formulation	Route of administration	Randomized	Results
FGF studies						
Schumacher et al[5]	20	aFGF	Protein	Intramuscular; thorocotomy	Yes	Improved
Sellke et al[6]	8	bFGF	Protein	Perivascular; thorocotomy	No	Improved
Laham et al[7]	24	bFGF	Protein	Intracoronary	Yes	Improved
Unger et al[8]	25	bFGF	Protein	Intracoronary	Yes	Safe
Laham et al[9]	52	bFGF	Protein	Intracoronary	No	Improved
Simons et al[10]	337	bFGF	Protein	Intracoronary	Yes	No effect
Grines et al[11]	79	FGF-4	Gene-Adeno	Intracoronary	Yes	Improved
VEGF studies						
Rosengart et al[12]	21	$VEGF_{121}$	Gene-Adeno	Intramuscular; thorocotomy	No	Improved
Losordo et al[13]	5	$VEGF_{165}$	Gene-plasmid	Intramuscular; thorocotomy	No	Improved
Gibson et al[14]	28	$VEGF_{165}$	Protein	Intravenous	No	Improved
Henry et al[15]	15	$VEGF_{165}$	Protein	Intracoronary	No	Improved
Henry et al[16]	178	$VEGF_{165}$	Protein	Intracoronary+ intravenous	Yes	No effect

we will have to address in large clinical trials is whether the incidence of these risks is sufficiently low so that the risks will be outweighed by the therapeutic benefits.

New Perspective

The mechanisms of atherosclerotic disease in human are extraordinarily complex; enhancing collateral function with therapeutic angiogenesis is more difficult to achieve than in experimental animals. The complexity of the natural process of collateral formation raises the question of what "multiple factor" strategies can be employed. One approach might be to utilize genes that express products that activate or lead to the expression of multiple factors involved in angiogenesis, such as hypoxia-inducible factors. Another multifactor approach is to attract or deliver multipotent progenitor cells to ischemic tissue that can differentiate into endothelial cells and express multiple angiogenic factors for therapeutic vasculogenesis (Figure 3). Recent studies have demonstrated that injection of bone marrow cells

Table 3. Side effects of angiogenesis therapy

Aberrant vascular proliferation in nontarget tissues
Increased vascular permeability
Induction of the development of functionally abnormal blood vessels
Triggering growth of neoplasms
Increase in atherosclerotic plaque mass and instability
Vasodilatation and hypotension
Hazards associated with viral vectors
Hazards associated with direct myocardial delivery

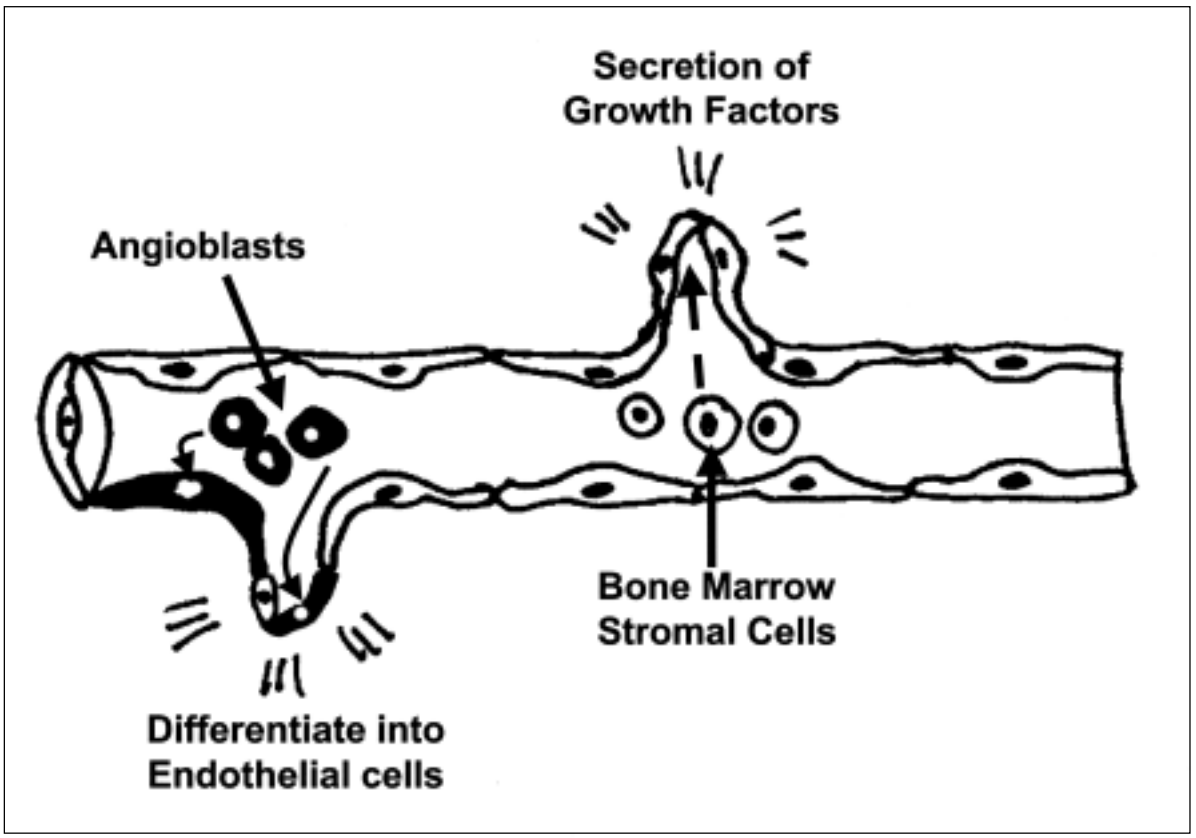

Figure 3. *Potential mechanisms of neovascularization by using bone marrow cells.*

into the ischemic myocardium can induce collateral formation, repair damage myocardium and improve myocardial function.[18-20] Furthermore, the use of a combined strategy of cell transplantation with angiogenic gene therapy may further enhances neovascularization of ischemic myocardium.

Conclusions

The rapid development of therapeutic angiogenesis for patients with advanced IHD over the last 5 years offers hope of a new treatment strategy based on generation of new blood supply in ischemic myocardium. There are still a lot of unresolved issues on the clinical application of therapeutic angiogenesis. Further carefully controlled randomized clinical trial in large number of patients will be required to demonstrate the long term safety, feasibility and efficacy of this new therapy for patients with IHD. Finally, the advent of cell therapy using progenitor cells for angiogenesis promises the beginning of an exciting paradigm for treatment of cardiovascular diseases.

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