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Novel therapy for idiopathic pulmonary arterial hypertension: Can hepatocyte growth factor be beneficial?

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1 Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a progressive, nearly fatal condition that until recently has had very few treatment options. Median survival time for untreated IPAH was 2.8 years without effective drug intervention. IPAH is characterized by deregulated proliferation of pulmonary arterial endothelial and intimal smooth muscle cells resulting in progressive pulmonary vascular remodeling and an increase in pulmonary arterial pressure. In order to alleviate their symptoms, anticoagulants, diuretics, calcium channel blockers and inotropic agents have been used to treat patients with PAH. Moreover, specific targeted therapies using prostacyclins, endothelin-receptor antagonists and phosphodiesterase type-5 inhibitors have been developed recently. However, because of the insufficient proof of efficacy and poor tolerability of these agents, new therapeutic modalities continue to be explored.

Hepatocyte growth factor (HGF), which was first purified as a mitogen for hepatocytes from the plasma of patients with fulminant hepatic failure, has mitogenic, motogenic, morphogenic, and antiapoptotic activities in various cell types. The pluripotent activities of HGF are mediated by a membrane-spanning tyrosine kinase receptor encoded by the c-Met proto-oncogene. HGF acts as a safe and effective organotrophic factor for protection from injury and ischemia of various organs. Phase-II and Phase-III clinical trials of HGF gene therapy for the treatment of peripheral arterial disease have been completed in both the USA and Japan. In the lung, biological and pulmotrophic roles for HGF have been well documented. In response to acute lung injury, HGF plays a role in lung regeneration and protection. Furthermore, research elucidating the pulmotrophic role of HGF has led to the development of therapeutic approaches for the treatment of chronic lung diseases.

2 The mechanism of HGF treatment of idiopathic pulmonary arterial hypertension

2.1 Effects on endothelial cells

On the one hand, HGF may prevent endothelial dysfunction and disease progression in PAH through participation in postnatal neovascularization and re-endothelialization by mobilizing endothelial progenitor cells. Evidence from animals and human lung specimens suggested endothelial dysfunction may play a central role in the development of IPAH. It is believed that endothelial progenitor cells (EPCs) constitute one aspect of the endothelium repair process. Some studies reveal that HGF mobilizes and recruits Lin-c-kit$^+$Sca-1$^+$CD34$^+$ progenitor cells from bone marrow into the injured organ through SCF-mediated mechanism, and our previous study proves that HGF creates an adhesive microenvironment in the target organ after stem cells are recruited.[1]

On the other hand, HGF is mitogenic, motogenic, and induces survival and prevents apoptosis in pulmonary endothelial cells. The three predominant pathways implicated in survival by HGF are ERK/MAPK, PI3K/Akt, and signal transducer and activator of transcription-3 (STAT3).[2] In addition, it is confirmed that activation of HGF/c-met system has great significance for the prevention of injury to the pulmonary vascular endothelial and the maintenance of the stability of pulmonary vascular structure. Down-regulated HGF and *c-met* expression is likely to play a role in promoting the development of IPAH.

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2.2 Inhibition of interstitial remodeling

Pathophysiologically, the proliferation of pulmonary artery smooth muscle cells and matrix accumulation contribute to pulmonary arterial stenosis and remodeling in IPAH. Many investigations have reported that HGF gene transfer attenuates medial hyperplasia and matrix accumulation in IPAH of rats. Additionally, a deficiency in HGF secretion by fibroblasts in the lungs of patients with idiopathic pulmonary fibrosis suggests that it would have therapeutic value to increase HGF expression in lung tissue for the prevention of fibrosis. HGF up-regulates the expression of urokinase-type plasminogen activator and matrix metalloproteinases (MMPs) such as membrane-type MMP and MMP-9, and exogenous HGF reduced lung expression levels of endothelin-1 and transforming growth factor, which are critically involved in pulmonary hypertension linked fibrogenic events, and thus decreased the total collagen deposition in the lung.[3]

2.3 Angiogenesis

In advanced IPAH, decreased pulmonary blood flow becomes evident and leads to lung hypoxia. Under ischemic states, parenchymal destruction is further aggravated and associated with the expansion of interstitial fibrotic spaces. Therefore, a strategy to increase pulmonary blood beds should be considered for stopping these pathological cycles. Accumulated studies proved that HGF had a potent ability to induce angiogenesis. It is proved that HGF supplementation improves the number of lung vessels concomitant with the enhanced proliferation of endothelial cells.[3] Thus, HGF-mediated angiogenesis in PAH could be responsible for a decline in pulmonary arterial pressure.

2.4 Activation of nitric oxide synthase

HGF can also affect endogenous nitric oxide synthase (eNOS) expression of vascular endothelial cell. Cartwright *et al*.[4] found HGF can be a strong stimulus iNOS expression of HGSVEC cells (saphenous vein endothelial cells). In addition, it has been shown that HGF can lead to rapid microvascular relaxation, and can be inhibited by NO blockers. The reason for this short-term effect is due to HGF-induced eNOS increased expression.

2.5 The influence on other cytokines

It is shown that, either *in vitro* or *in vivo*, HGF can significantly promote the expression of VEGF mRNA; and they are both in a synergistic effect and angiogenesis role. Yang *et al*.[5] found that hepatocyte growth factor plays a critical role in the regulation of cytokine production. These cytokines played an extremely important role in the PAH development and formation.

3 HGF acts as a safe and effective factor for pulmonary hypertension

HGF has less side effects. It does not cause edema like VEGF. In addition, HGF specifically supports growth in epithelial and endothelial cells, but not in myofibroblasts, which may be required for antifibrotic tissue repair and endothelium protection in IPAH. These beneficial effects of HGF reverse the key pathogenetic cascades for the development of IPAH. Recently, we have performed a animal study to investigate whether expression of HGF through the transplantation of genetically modified MSCs could offer therapeutic benefit. Compared with PAH and MSCs groups, hemodynamic parameters, vascular smooth muscle cell proliferation, extracellular matrix, and vascular density were significantly improved in HGF group.

In summary, although the effectiveness and safety of HGF for IPHA is preliminary, further evaluations in clinical trials are needed. We believe HGF therapy sheds light on the development of new therapeutic modalities aimed at treating patients with IPAH.

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