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博士の専攻分野の名称	博士（医学）
学位記番号	第　２５６５２　号
学位授与年月日	平成24年９月25日
学位授与の要件	学位規則第４条第１項該当 医学系研究科病態制御医学専攻
学位論文名	Hepatocyte Growth Factor Reduces Cardiac Fibrosis by Inhibiting Endothelial-Mesenchymal Transition （肝細胞増殖因子の内皮間葉転換を介した心線維化抑制機序の解析）
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論文内容の要旨

〔目　的(Purpose)〕

Hypertension is one of the most common diseases in middle-aged and older people, and heart failure due to chronic hypertension is a major complication, along with coronary artery disease (CAD) and stroke. To date, with the advent of effective drugs to lower blood pressure, concern is now shifting toward how to manage the causal complications typified by hypertensive heart failure with extremely poor prognosis. Cardiac fibrosis is highly correlated with cardiac dysfunction in patients with a hypertensive heart. Therefore, the reduction or improvement of cardiac fibrosis might be a useful treatment for heart failure. Although cardiac fibrosis is attributed to excess pathological deposition of extracellular matrix components, the mechanism remains unclear. Recent reports revealed alpha smooth muscle actin (α-SMA)-expressing myofibroblasts are primarily responsible for fibrosis. It is believed that myofibroblasts are differentiated from resident fibroblasts, whereas the transformation of vascular endothelial cells into myofibroblasts, known as endothelial-mesenchymal transition (EndMT), has been suggested to be intimately associated with perivascular fibrosis. On the other hand, hepatocyte growth factor (HGF) has been reported to show suppressive actions in various fibropathological conditions like pulmonary fibrosis and renal fibrosis. Thus, we hypothesized HGF prevents cardiac fibrosis by blocking these pathways. The purpose of this study was to investigate the effect of HGF on the pathogenesis of cardiac fibrosis induced by pressure overload in mice.

〔方法ならびに成績(Methods/Results)〕

We analyzed pressure-overloaded HGF-transgenic mouse (HGF-Tg) model made by transverse aortic constriction (TAC). The amount of cardiac fibrosis significantly decreased in pressure-overloaded HGF-Tg mice compared to pressure-overloaded non-transgenic controls, particularly in the perivascular region. This was accompanied by a reduction in the number of α-SMA-positive myofibroblasts as well as expression levels of fibrosis-related genes and by significant preservation of echocardiographic measurements of cardiac function in the HGF-Tg mice ($P<0.05$). The survival rate 2 months after TAC was higher by 45 % ($P<0.05$). Human coronary artery endothelial cells (HCAEC) and human cardiac fibroblasts (HCF) were examined *in vitro* after treated with transforming growth factor beta 1 (TGF-β1) or angiotensin II (Ang II) with or without HGF. TGF-β1 significantly induced the differentiation of HCAEC to the myofibroblast phenotype, as indicated by α-SMA expression, in a dose-dependent manner, while HGF inhibited the differentiation process in HCAEC ($P<0.05$). Similarly, TGF-β1 and Ang II significantly increased the mRNA expression of α-SMA in human cardiac fibroblasts, however, HGF prevented the phenotypic conversion of HCF into myofibroblasts and also gene expression of other ECM-related proteins including collagen I and collagen III ($P<0.05$).

〔総　括(Conclusion)〕

We conclude that HGF reduced cardiac fibrosis by inhibiting EndMT and the transformation of fibroblasts into myofibroblasts. Overall, our present study demonstrates that an increase in HGF resulted in a significant improvement of cardiac performance and mortality in a pressure overload model. The reduction of cardiac fibrosis would be caused by the inhibition of multiple pathways, including EndMT and the transformation of fibroblasts into myofibroblasts. Cardiac fibrosis is one of the adaptive responses or repair reactions to pathological injury caused by pressure overload or disruption of coronary blood flow in hypertension or myocardial infarction. On the other hand, myocardial fibrosis leads not only to heart failure through reduced contractility and compliance, but also to fatal arrhythmia through disordered conductance of the heart. Pathologically cardiac fibrosis could be defined as excess deposition of extracellular matrix components in the heart. The accumulation of ECM causes the increase in myocardial elastance, while the reduction of ECM causes ventricular dilation, both of which are the driving forces for heart failure. So the point is how to manage the imbalanced fibropathological conditions. In this study, the inhibition of fibrosis was necessary and sufficient for the preservation of cardiac performance and the improved survival rate, however, further research is needed to control fibrosis. Since fibrotic change is believed to be irreversible at this time, administration and/or stimulation of HGF might offer potential for the preservation of cardiac performance in the failing heart due to sustained pressure overload.

論文審査の結果の要旨

心疾患は日本のみならず、世界的にも死亡原因における枢要な位置を占め、死亡に至らずともQOLを大きく低下させる要因であり、医療経済的にも極めて大きな負担となっている。心機能の低下には、心筋梗塞後のリモデリングや高血圧症に伴う圧負荷がそうであるように、病理学的に心臓の線維化が深く関わっている。線維化は多くの臓器で観察され、そのメカニズムは一部しか明らかになっていないが、近年、筋線維芽細胞がサイトカインや増殖因子を分泌することが線維化の病態に重要な意味をもつことが明らかになりつつある。本研究では、in vitroの系において冠動脈血管内皮細胞がTGF-βを介した内皮間葉転換によって筋線維芽細胞へと分化する過程、並びに心線維芽細胞が筋線維芽細胞へと形質転換する過程を肝細胞増殖因子(HGF)が抑制し、またin vivoにおいて心臓特異的HGF遺伝子改変マウスが圧負荷に対し心線維化を軽減することで、心機能低下を抑制することを示したものである。これらの内容は学位の授与に値すると考えられる。