Title	新規心臓線維芽細胞サブセットの機能解析と心筋梗塞後心不全の新たな治療戦略の開発				
Sub Title	Deciphering stromal-inflammatory cell crosstalk identifies a novel mechanism underlying post- infarction cardiac repair				
Author	安西, 淳(Anzai, Atsushi)				
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Abstract	 心筋梗塞(MI)に対する再灌流療法の発達は急性期死亡率を劇的に低下させたが、左室リモデリングによる慢性心不全の有病率をむしろ増加させるというパラドックスを生んだ。MI 後組織修復には免疫応答の賦活化とそれに付随した炎症反応が可欠であるが、これらが一度過剰になるとかえって組織障害を進展させ、心不全を増悪させてしまう。MI 後に免疫応答や炎症反応が通剰となる機序が明らかとなれば新規治療標的となり得ると考えられる。 昨年度の実験結果より、心臓線維芽細胞特異的遺伝子X が重要と考え、心臓線維芽細胞特異的遺伝子XKO(cKO)マウスを作成したところ、MI 後の生存率、心機能がコントロールと比較して有意に改善することを確認した。またcKOマウスでは炎症急性期であるday4でのLy6Chigh単球の浸潤が有意に低く、qPCRで解析した炎症性サイトカインの遺伝子発現も有意に抑制されていた。炎症性サイトカインの産生源となり過剰な炎症に寄与するLy6Chigh単球は、梗塞部局所で産生される炎症性ケモカイン、特にCCL2/CCL7によって誘導され、組織障害を増悪させることが知られている。梗塞部でこれらケモカインの遺伝子発現を検討すると、cKOマウスで有意に減少していた。 心臓から線維芽細胞のみを抽出できる培養条件で細胞を培養し、in vitroでIL-1b、LPS、TGFbなどで24 時間刺激し、遺伝子変化をqPCR 法で検討したところ、X-KOマウスで有意に減少していた。 小臓が分離線維芽細胞では野生型と比較してその上昇が有意に抑制されており、in vivoでの結果が再現された。 Myocardial infarction (MI) is one of the leading causes of death worldwide. Although the mortality rate from MI has steadily declined because of the application of pharmacological and technical innovations, scientific discoveries, and improvements in public health, long-term mortality remains high. MI survivors frequently develop heart failure with maladaptive left ventricular remodeling; while many therapeutics in current use have proven beneficial for this condition, the high mortality indicates an unmet clinical need, requiring a better understanding of the disease's pathophysiology. Based on the experimental results we got last year, we generated cardiac fibroblast-specific gene"XFKO mice (xCO) xCO mice had improved survival and cardiac function and reduced inflammation after MI as seen in X-full KO mice. Gene expression levels of Cc12 and Cc17, which are major monocyte-attracting chemokines, were also decreased in the cKO infarcts. Consistent with the in vivo data, in vitro culture experiments likewise showed that cardiac fibroblasts derived from X-KO mice had reduced expression of those inflammatory chemokines and cytokines, suggesting that gene-X in the cardiac fibroblasts is critical inducer of excessive inflammation and thus a potential therapeu				
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2022 年度 福澤基金研究補助研究成果実績報告書

研究代表者							
1017611424	所属	医学部臨床教室	職名	助教(有期・医学部) Atsushi Anzai	- 補助額	1,500 T P	хm
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