A Vaccine against FAP (fibroblast activation protein) improves murine cardiac fibrosis by preventing the accumulation of myofibroblasts

Department of Health Development and Medicine, Graduate School of Medicine

Endowed Chair Professor Hironori Nakagami Researchmap https://researchmap.jp/hironorinakagami?lang=en

Endowed Chair Associate Professor Hiroki Hayashi Researchmap https://researchmap.jp/hayashi-hiro?lang=en

Abstract

Myofibroblasts are primary cells involved in chronic response-induced cardiac fibrosis. Fibroblast activation protein (FAP) is a relatively specific marker of activated myofibroblasts and a potential target molecule. We demonstrated that a vaccine targeting FAP could eliminate myofibroblasts and reduces cardiac fibrosis in chronic cardiac stress model mice. No systemic or organ-specific inflammation due to the FAP vaccine was observed. Our study demonstrates the FAP vaccine can be a therapeutic tool for cardiac fibrosis.

Background & Results

We coadministered a FAP peptide vaccine with a cytosine-phosphate-guanine (CpG) K3 oligonucleotide adjuvant to male C57/BL6J mice and confirmed an elevation in the anti-FAP antibody titer. After continuous angiotensin II and phenylephrine administration for 28 days, we evaluated the degree of cardiac fibrosis and the number of myofibroblasts in cardiac tissues.

We found that cardiac fibrosis was significantly decreased in the FAP-vaccinated mice compared with the angiotensin II and phenylephrine control mice (3.45±1.11% versus 8.62±4.79%; $P=4.59\times10^{-3}$) and that the accumulation of FAP-positive cells was also significantly decreased, as indicated by FAP immunohistochemical staining (4077±1746 versus 7327±1741 cells/mm^2; FAP vaccine versus angiotensin II and phenylephrine control; $P=6.67\times10^{-3}$). No systemic or organ-specific inflammation due to antibody-dependent cell cytotoxicity induced by the FAP vaccine was observed. Although the transient activation of myofibroblasts has an important role in maintaining the structural robustness in the process of tissue repair, the FAP vaccine showed no adverse effects in myocardial infarction and skin injury models.

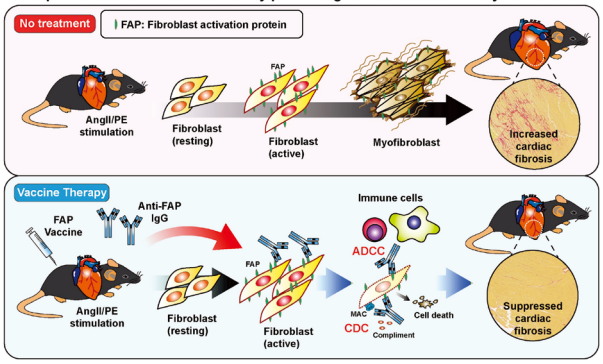
Significance of the research and Future perspective

Chronic stress, such as hypertension, causes cardiac fibrosis, which eventually progresses to heart failure with ventricular dilation and cardiac hypertrophy.

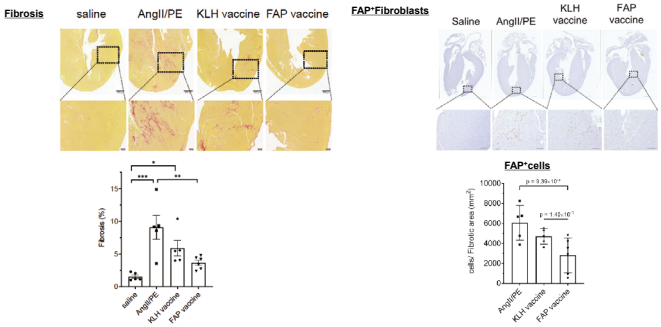
Myofibroblasts are involved in cardiac fibrosis, and treatments may target myofibroblasts.

Although myofibroblasts play an important role in maintaining structural robustness in the process of tissue repair, the FAP vaccine showed no adverse effects in myocardial infarction and skin injury models. Our study provides the first evidence of the efficacy of FAP vaccines in the treatment of cardiac fibrosis. This study also demonstrates that FAP vaccination or FAP antibodies have fewer adverse events and may be applicable in a wider range of patients.

Graphical abstract, Yoshida et al, A vaccine against fibroblast activation protein improves murine cardiac fibrosis by preventing the accumulation of myofibroblast.



Improvement of cardiac fibrosis by elimination of activated Fibroblast with FAP cell elimination vaccine



Patent

Treatise Yoshida, Shota; Hayashi, Hiroki; Kawahara, Takuro et al. A Vaccine against fibroblast activation protein improves murine cardiac fibrosis by preventing the accumulation of myofibroblasts. Circ Res. 2025, 136(1), 26-40. doi: 10.1161/CIRCRESAHA.124.325017

URL

Keyword cardiac fibrosis, myofibroblast, vaccine