ZHANG XU 論文内容の要旨

主　　論　　文

Ex vivo hydrostatic pressure loading of atrial tissues activates profibrotic transcription via TGF-β signal pathway

心房組織の静水圧負荷は TGF-β シグナル経路を介して線維化促進転写を活性化する

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緒　　言

Atrial arrhythmia, especially atrial fibrillation (AF), whose treatment remains thorny, is the most common rhythm disturbance encountered in the clinical setting. The most common pathogenesis of AF is atrial fibrosis. Although excessive mechanical stresses are known to play a critical role in atrial fibrosis development, the molecular mechanism and responsible cells are not clear. We herein tried to investigate the mechanism of atrial fibrogenesis in response to biomechanical stress (hydrostatic pressure) by *ex vivo* approach.

対象と方法

Atrial tissues from C57BL/6 male mice (9-12 weeks) were minced into small fragments and then culturing as “explants” under atmospheric pressure or 50 mmHg hydrostatic pressure loading conditions. At 24 hr after treatment, the expression of fibrosis-related genes in atrial tissues was widely compared using the mouse fibrotic pathway-specific PCR array. We then investigated the time-course dynamics of the transcription on several interested genes by

RT-qPCR. To further understand the responsible cells, the atrial “explants” were daily loaded to 50 mmHg for 3 hr. The cells outgrew from “explants” were monitored, and phenotypical characteristics of outgrowth cells were identified by immunostaining analysis.

結　　果

Ex vivo loading of atrial tissues to 50 mmHg for 24 hr upregulated a series of profibrotic genes, including *Rhoa*, *Rock2*, and *Thbs1*. Interestingly, the expression of *Thbs1* was quickly enhanced within 1 hr, turned to decline at 6-24 hr, and then increased again at 72 hr in the atrial tissues after loading to 50 mmHg. In contrast, enhanced expression of *Tgfb1* in the atrial tissues was only observed at 72 hr after loading to 50 mmHg. About the responsible cells, daily loading to 50 mmHg for 3 hr significantly accelerated the outgrowth of mesenchymal stem-like stromal cells from atrial “explants”; however, we did not observe significant phenotypic changes in these outgrowth cells.

考　　察

Biomechanical forces shape cells and tissues during development and adult homeostasis. As a crucial pumping organ, the heart is constantly subjected to various biomechanical stimuli, such as shear stress, tension stress and hydrostatic pressure. Clinical practices and animal experiments have demonstrated that abnormal mechanical stimuli can cause cardiac remodeling followed by disturbance of cardiac electrical conduction. As a kind of compressive forces, the role of hydrostatic pressure on the cardiovascular system is rarely reported. By *ex vivo* experimental approach, we confirmed that the loading of atrial tissues to 50 mmHg hydrostatic pressure could induce a profibrotic transcription, likely by activating TGF-β signal pathway, and stromal cells in atrial tissues would be the sensitized cells in response to hydrostatic pressure loading. Data from this study provide indirect evidence on the common pathological feature of atrial fibrosis following pressure overload.

（備考）※2000 字以内で記述。Ａ4 版。