スポーツにおける心臓の代償性肥大と非代償性肥大を分類する線維化バイオマーカーの検索

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Bio-Marker for Cardiac Fibrosis in Exercise Induced Cardiac Hypertrophy

by

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ABSTRACT

Continuous pressure overload induces myocardial hypertrophy as an adaptive response. Cardiac fibrosis often follows hypertrophy to prevent myocytes from over-extension. However, massive fibrosis makes cardiac function impaired, which is a maladaptive response. Although a considerable number of studies have demonstrated a series of transcriptional pathways, it still remains equivocal which molecule（s）plays

an important role in initiation of cardiac fibrosis. Therefore, it is important to identify a molecular inducer of fibrosis as a therapeutic target for heart failure. A rat model of cardiac hypertrophy and fibrosis were generated by pulmonary artery banding（PAB）.

Four to six weeks after operation, histological analyses with Masson Trichrome stain on short axis section of right ventricular papillary muscles identified that they could be clearly divided into the interstitial fibrosis group（Fibrosis; 17.1±1.5% of fibrosis area）and the non-fibrotic, but hypertrophic group（Hypertrophy; 3.0±0.3%）, in comparison with the sham-operated control（Sham; 2.5±0.2%）. We comprehensively analyzed the mRNA expression of 29215 known rat genes in the right ventricle by using GeneChip® Rat Gene 1.0 ST Array（Affymetrix®）to compare a gene expression profile among Sham, Hypertrophy, and Fibrosis（n=3 each）. We found that the expression levels of some genes that have not been recognized as a fibrosis-related molecule were significantly higher in Fibrosis than those in Sham and Hypertrophy. Among them, we selected FGF23 and Ncam1, and confirmed expression levels of these genes by RT-PCR（n=6 each）. Using OLETF rats under exercise, we found that adult exercise group rapidly gained body weight when they stopped exercise, and showed significantly higher expression levels of FGF23, Ncam1 and TGF-beta than those in OLET-F young exercise and OLET-F non-exercise group. These data suggest that 1）FGF23 and NCAM1 can be used for cardiac fibrosis-related biomarker and 2）stopping exercise followed by rapid weight gain would be one of the risk factors for cardiac fibrosis.

要　旨

心臓の病態末期には線維化が認められ，収縮不全や不整脈発症の原因因子と考えられている．しかしながら，その発症には未だに不明な点が多い．我々はラット圧負荷モデルを用いて，線維化特異的に増加する因子を網羅的解析にて検索した．圧負荷モデルにおいて線維化特異的に増加した因子はFGF23とNcam1であった．この線維化特異的増加因子が，運動を行った動物モデルにおいても心筋線維化バイオマーカーとして有用かどうか確認するため，OLET-Fラットの自発運動群を用いた検討を行った．OLET-Fラットの壮年期運動群は運動解除によって急速に体重が増加した．一方で，FGF23とNcam1は壮年期運動群で若年期運動群や非運動群と比較して有意に増加していた．これらのことから，FGF23とNcam1は新規心臓線維化バイオマーカーとして有用であるとともに，壮年期開始運動の途中離脱による急激な体重増加は心臓線維化のリスクが上昇する可能性が示唆された．