Rev-erb agonist improves adverse cardiac remodeling and survival in myocardial infarction through an anti-inflammatory mechanism

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論文の内容の要旨
Abstract of thesis

（目的　Purpose）

Myocardial infarction (MI) is one of the leading cause of death worldwide. The purpose of this study is to clarify the roles of rev-erb, a member of the nuclear receptor superfamily, in cardiac remodeling after MI and examine the effects of rev-erb agonist SR9009 on cardiac function and survival.

（対象と方法　Materials and Methods）

Wild-type C57BL6 male mice (n=165) were used to perform sham operation or permanent ligation of the left anterior descending coronary artery to induce MI. The applicant examined the expression of rev-erb (rev-erb α and β) during the early phase of post-MI (up to 7 days) and the survival was evaluated at 14-day post-MI. SR9009 or vehicle was administered by intraperitoneal injection (100 mg/kg/day) 1 day before the surgery and four experimental groups (Sham + vehicle, Sham + SR9009, MI + vehicle, MI + SR9009) were prepared for the analyses. The effect of SR9009 on post-MI cardiac functions was evaluated by echocardiography, gene expression analyses by real-time PCR, protein expression analyses by Western blotting and immunofluorescence staining. Immune cell infiltration into the left ventricle (LV) was evaluated by flow cytometry.

（結果　Results）

The applicant first established the time course of rev-erb expression during MI and showed that it decreased at post-MI day 7. She then showed that survival after MI was significantly improved by pre-treatment with SR9009. Specifically, LV ejection fraction was improved, and mRNA expression and plasma concentration of brain natriuretic peptide were significantly decreased. Moreover, the expression levels of inflammatory-related genes such as *Il6*, *Mcp1*, *Ly6g*, *Cd11b* and matrix metalloproteinase-9 (MMP-9) protein and gene expression, as well as signaling molecules, including phosphorylated (p-)NF-kB p65, p-Erk, and p-p38 were significantly lower in SR9009-treated MI group than vehicle-treated MI group. Finally, the applicant showed that infiltrations of neutrophils and proinflammatory M1 macrophages into the infarct and border zone during the acute phase were significantly suppressed by SR9009.

（考察　Discussion）

1) The applicant suggested that SR9009 improved LV function and survival by suppressing the production of inflammatory cytokines and MMP-9, as well as infiltration of inflammatory cells into the infarcted and border zone during the acute phase of MI. There was no apparent toxicity of SR9009 in the current study which was consistent with the precious report.
2) The applicant suggested that the mechanism of rev-erb was not only through the direct binding to the rev-erb α binding motif on the inflammatory cytokine genes but also through suppression of the NF-kB activity, ERK, and p38 signaling pathways.
3) Although SR9009 showed a significant improvement of LV functions, collagen deposition appeared unaffected by SR9009 at 7-day post-MI. Further analysis is required for the evaluation of SR9009 on collagen deposition in chronic phase of post-MI.
4) Pharmacological activation of rev-erb during acute phase of post-MI may offer an effective strategy to mitigate vicious cycle of inflammatory amplification, adverse LV remodeling and cardiac rupture.

審査の結果の要旨
Abstract of assessment result

（批評　General Comments）

The applicant presented the novel finding on the temporal expression pattern of rev-erb α and β during early phase of MI. Based on these findings, the applicant demonstrated that pre-treatment of SR9009 prior to induction of MI improved survival of animals and suppressed inflammatory cell infiltration into infarcted and border zone of LV. She provided the evidence that SR9009, an agonist of rev-erb, was beneficial to suppress acute phase of events after MI, such as inflammatory cytokine production, inflammatory cell infiltration and adverse remodeling caused by MMP-9. These findings are novel and provide a basis for the new therapeutic strategy for MI.

（最終試験の結果　Assessment）

The final examination committee conducted a meeting as a final examination on January 16, 2018. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

（結論　Conclusion）

Therefore, the final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Medical Sciences.