

【Grant-in-Aid for Scientific Research(S)】

Biological Sciences (Medicine, dentistry, and pharmacy II)



Title of Project : Role of Wnt signaling in cardiomyocyte differentiation and its implication for the treatment of heart diseases

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Research Area : medicine/dental medicine/pharmacology

Keyword : cardiology/hypertension, regenerative medicine, development/differentiation

【Purpose and Background of the Research】

Patients with heart diseases are increasing in number, and elucidation of the pathophysiology and development of novel therapeutic strategies for heart diseases are mandatory. Wnt signaling pathway plays multiple roles in development and diseases, and recent studies have also implicated Wnt signaling both in heart development during embryogenesis and heart diseases in the adult. Our goal is to elucidate the molecular mechanisms by which Wnt signaling regulates heart development and to develop novel therapeutic strategies for heart diseases by modulating Wnt signaling.

The objectives of the present study are fourfold.

- (1) To elucidate the mechanism of Wnt inhibition by IGFBP-4
- (2) To develop an efficient protocol for cardiomyocyte differentiation from stem cells
- (3) To elucidate the role of Wnt signaling in heart diseases in the adult
- (4) To develop novel therapeutic strategies for heart diseases by modulating Wnt signaling

【Research Methods】

(1) To elucidate the mechanism of Wnt inhibition by IGFBP-4: We have recently shown that IGFBP-4 is an inhibitor of Wnt signaling and that Wnt inhibition by IGFBP-4 is essential for normal heart development. To investigate the mechanism of Wnt inhibition by IGFBP-4, the interaction between two Wnt receptors (Frz and LRP5/6) will be studied using BRET technique.

(2) To develop an efficient protocol for cardiomyocyte differentiation from stem cells: We have previously shown that several growth factors including Wnts, Wnt inhibitors, and BMP inhibitors promote cardiomyocyte differentiation from stem cells. Various combinations of these growth factors will be tested for their cardiomyogenic potential.

(3) To elucidate the role of Wnt signaling in heart diseases in the adult: Recent studies suggest that Wnt signaling is implicated in cardiac stress response such as ischemia/reperfusion injury. To elucidate the mechanism of

Wnt-mediated cardiac damage, Wnts or Wnt-like ligands that are expressed in the heart under stressed condition and the specific cell types that respond to Wnt signaling will be examined.

(4) To develop novel therapeutic strategies for heart diseases by modulating Wnt signaling: Zebrafish hearts regenerate after partial resection. Using zebrafish as a model of heart regeneration, the effects of Wnts and Wnt inhibitors on heart regeneration will be examined. The effects of Wnt inhibitors on heart diseases in the adult will also be examined using mouse model of heart failure.

【Expected Research Achievements and Scientific Significance】

Recent studies suggest that Wnt signaling plays a crucial role both in cardiac development during embryogenesis and heart diseases in the adult. Elucidation of the molecular mechanism of Wnt-dependent regulation of cardiogenesis will lead to the development of novel therapeutic strategies for heart diseases.

【Publications Relevant to the Project】

- Naito AT, Komuro I et al. Developmental stage-specific biphasic roles of Wnt/beta-catenin signaling in cardiomyogenesis and hematopoiesis. Proc Natl Acad Sci USA. 2006;103:19812-7.
- Zhu W, Komuro I et al. IGFBP-4 is an inhibitor of canonical Wnt signalling required for cardiogenesis. Nature. 2008;454:345-9.

【Term of Project】 FY2009-2013

【Budget Allocation】 162,900 Thousand Yen