学位論文抄録

An emerging pathogen *Helicobacter cinaedi* as a potential etiological factor for cardiovascular diseases
(心血管病における新興感染症菌ヘリコバクター・シネディの病因論に関する研究)

シャザダ　カーン
Shahzada　Khan

熊本大学大学院医学教育部博士課程医学専攻微生物学

指導教員

赤池 孝章 教授
熊本大学大学院医学教育部博士課程医学専攻微生物学

Abstract of the Thesis

Background and purpose: Previous investigations have indicated that one of the potential etiological factors involved in cardiovascular diseases (CVD) could be chronic infection. Until now, many pathogens including *Chlamydophila pneumoniae* and *Helicobacter pylori* have been suggested to be associated with CVD. *Helicobacter cinaedi* is recognized as an emerging pathogen, which can cause recurrent bacteremia in immunocompetent hosts. It is yet unknown, however, whether *H. cinaedi* can contribute to CVD. The aim of this study was to explore the association of *H. cinaedi* with atrial arrhythmia and atherosclerosis, two of the most prevalent CVD.

Methods: To assess the association of *H. cinaedi* with atrial arrhythmia, a retrospective case-control study was performed at Kumamoto University Hospital. Seropositivity for *H. cinaedi* was determined using our previously developed ELISA system. Multiple logistic regression analysis was used to identify independent risk factors. To explore the association of *H. cinaedi* with atherosclerosis, human aortic atherosclerotic tissues collected post mortem from nine patients were used for immunohistochemical detection of *H. cinaedi*. Three different mouse models were orally challenged with *H. cinaedi* for evaluation of in vivo atherosclerosis development. Cell culture studies were performed for analysis of differentiation of monocytes into macrophages as well as foam cell formation.

Results: Patients with atrial arrhythmia (n =132) had significantly higher anti-*H. cinaedi* IgG levels than control subjects (n=137) ($p < 0.001$). Logistic regression analysis showed that *H. cinaedi* seropositivity was an independent risk factor for atrial arrhythmia (odds ratio 4.9, $p < 0.001$). In immunohistochemical analysis of human atherosclerotic tissues, *H. cinaedi* antigens were detected inside $CD68^+$ macrophages in all nine patients tested. Oral challenge with *H. cinaedi* markedly enhanced atheroma formation in apolipoprotein E-deficient mice, with increased accumulation of $F4/80^+$ foamy macrophages in atherosclerotic lesions. Infection with *H. cinaedi* also induced lipid accumulation and foam cell formation in cultured primary macrophages, which seemed to be due to reduced level of ATP-binding cassette transporter G1 protein in infected cells. This infection also morphologically differentiated THP-1 monocytes into macrophages, mainly via toll-like receptor 2-dependent pathway.

Conclusions: These findings provide the first evidence for the association of *H. cinaedi* with atrial arrhythmia and atherosclerosis and may open a new era for development of effective prophylactic and therapeutic approaches to these diseases.