論　文　概　要

○ 論 文 題 目　**The role of tenascin-C during the development of left ventricular remodeling after myocardial infarction in mice model**
（心筋梗塞後左室リモデリングにおける テネイシン-C の役割の解明）

○ 指 導 教 員　　人間総合科学研究科　　疾患制御医学専攻

青沼　和隆 教授

（所　　属）　筑波大学大学院人間総合科学研究科　　疾患制御医学専攻

（氏　　名）　王　政

目　　的： Tenascin-C (TN-C), an extracellular matrix glycoprotein, transiently appeared in myocardial tissue after acute myocardial infarction (AMI) and is suspected to play important roles during repair process. It was reported that the AMI patients with higher serum TN-C levels had worse long-term prognosis. However, the biological function of TN-C in ventricular remodeling after myocardial infarction was not fully understood. Therefore, our research was planned to investigate the effects of TN-C on LV remodeling during the later phase after MI in mice.

対象と方法： The 10 to 12 weeks old male wild type (WT) and TN-C knock-out (KO) mice were divided into 4 groups of WT+Sham, KO+Sham, WT+MI and KO+MI. Mice were performed by myocardial infarction surgery, and sham group mice were done the same procedure without LAD ligation. For acute MI research, hearts samples of survived mice were taken at day 1, 3, 5 and 7 after MI for biochemical analysis. For chronic MI research, mice and the survived mice of 4wks, 8wks and 12 wks post-MI were taken examination of echocardiography. Finally survived mice of 12wks post-MI were sacrificed, some hearts were conserved by 10% formalin for histopathology, and the others were frozen in liquid nitrogen, stored at −80 °C for biochemical analysis.

結　　果： Mice 12 weeks post-MI, the survival rate of both WT+MI (48.3%,14 of 29 mice) and KO+MI (55.6%,15 of 27 mice) groups had no

significant difference. TN-C KO group had the better cardiac function (LVEF, 10.63±4.43% vs. 19.02±6.31%; $p<0.001$). WT group had the higher degree of cardiomyocyte hypertrophy at remote area than TN-C KO group. And the size of fibrosis in the remote myocardium had no significant difference between WT and TN-C KO group, whereas interstitial fibrosis of border area was significantly enlarged in the WT group. By the RT-PCR analysis, during chronic MI phase, WT+MI group showed significantly higher expressions of the heart failure marker (ANP) than that of KO+MI at the border+infarct areas. During the acute MI phase, anti-inflammatory cytokine (IL-10) had a significantly higher expression in KO+MI group than WT+MI group at MI+border areas. Further, from the analysis of FACS, we found no significant changes of the population of each type of measured immune cells between WT and KO 3 days after MI. 7 days after MI, the M2 macrophages significantly inceased in the KO group compared to the WT group.

考　　察： It was reported that deletion of TN-C improved ventricular remodeling in association with the reduction in interstitial fibrosis in the border area 4 weeks after MI. My data confirmed the previous reports, and moreover we indicated that deletion of TN-C suppressed the worsening of LV remodeling over the longer-term period. During acute MI phase, the significant increasing of M2 macrophages at day7 indicated TN-C protein may play an important role in the activation of immune responses after the MI. Additionally, TN-C increased during acute phase of MI in the border area, and could prevent the

shift from pro-inflammatory to anti-inflammatory phase. As a result, it kept pro-inflammatory state longer, encouraged the fibrosis in the border area, and consequently, worsened LV remodeling during chronic phase.

結　　論：TN-C aggravates the deterioration of LV function due to MI during chronic phase partly through the promotion of inflammation via suppression of anti-inflammatory M2 macrophages during acute phase.