MRTF-A regulates proliferation and survival properties of pro-atherogenic macrophages

Jianbo An[1,2], Taeko Naruse[2], Kunihiko Hinohara[2], Yurie Soejima[3], Motoji Sawabe[3], Yasuaki Nakagawa[4], Koichiro Kuwahara[5], Keiji Kuba[1], Akinori Kimura[2]

[1]Department of Biochemistry and Metabolic Science, Akita University Graduate School of Medicine, [2]Department of Molecular Pathogenesis, Medical Research Institute, Tokyo Medical and Dental University, [3]Department of Molecular Pathology, Graduate School of Health Care Sciences, Tokyo Medical and Dental University, [4]Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, [5]Department of Cardiovascular Medicine, Shinshu University School of Medicine

Atherosclerosis often results in high incidence of vascular occlusion and has been recognized as the major cause of coronary artery disease. We had previously reported that promoter polymorphism of myocardin-related transcription factor A (MRTF-A) is associated with coronary atherosclerosis. However, the contribution of MRTF-A to the development of atherosclerosis remains unclear. Macrophages are known to be important mediators of atherosclerosis. In this study, we found that MRTF-A was highly expressed in lesional macrophages in human carotid atherosclerotic plaque. To investigate the role of macrophagic MRTF-A in the pathogenesis of atherosclerosis, we generated ApoE null MRTF-A transgenic mice ($ApoE^{-/-}$/$MRTF\text{-}A^{tg/+}$), in which human MRTF-A was specifically overexpressed in monocytes/macrophages. We found that $ApoE^{-/-}$/$MRTF\text{-}A^{tg/+}$ aggravated atherosclerosis and accumulated prominent lesional macrophages in the aortic sinus. We also found that MRTF-A promoted proliferation of macrophages and mitigated apoptosis both *in vitro* and *in vivo* due to downregulation of the expression of cyclin-dependent kinase inhibitors. Taken together, our data indicated that MRTF-A contributes to the development of atherosclerosis by modulating functional properties of pro-atherogenic macrophages.