"*Molecular Regulation of ADAMTS-5 by IL-17 and its signal transduction pathway in human monocytes THP-1 Cells*"

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Atherosclerosis is usually initiated when lipoproteins are trapped by proteoglycans in the arterial intima. Macrophages play vital roles in this disease which includes formation of foam cells and regulation of inflammatory response. It also participates in plaque stabilisation through the secretion of matrix metalloproteinases. A study has reported that ADAMTS-5 proteolytic activity on versican and biglycan (major LDL-binding proteoglycans) had caused the release of LDL from human aortic lesion. However, the putative signalling pathways which mediate the effects of IL-17A on ADAMTS-5 expression in macrophages are poorly understood. Hence, the aim of this research is to study the dose and time response of IL-17A on ADAMTS-5 expression in human monocytes THP-1 cells and to determine the putative signal transduction pathways undertaken by IL-17A to exert its effects on ADAMTS-5 expression. The mRNA and protein expression levels of ADAMTS-5 were significantly up-regulated when differentiated THP-1 cells were treated with 100 ng/ml of IL-17A for 24 hours. ADAMTS-5 expression decreased as the concentration of IL-17A increased to 150 and 200 ng/mL. We also determined that the expression of ADAMTS-5 mRNA was highest after 8 hours of incubation with 100 ng/ml of IL-17A in time course study. Subsequent inhibition study was conducted by using a panel of inhibitors targeting the NF-κB (150 nM of NF-κB activation inhibitor IV and 10 μM of IKK-2 inhibitor), ERK (25 μM of PD98059 and 5 μM of ERK inhibitor), JNK (20 nM of CEP 1347 and 40 nM of SP600125) and p38 MAPK (35 nM of p38 MAP kinase inhibitor) pathways. IL-17A up-regulation of ADAMTS-5 was shown to be attenuated by PD98059, ERK inhibitor, CEP 1347 and SP600125. The results indicated that both ERK and JNK pathways might be involved in mediating the expression of ADAMTS-5 in THP-1 macrophages. Phosphorylation studies were then performed to map out the detailed pathway undertaken by IL-17A. This study focused on elucidating the ERK pathway because treatment with PD98059 exhibited most significant reduction in ADAMTS-5 mRNA expression level. ADAMTS-5 was shown to be up-regulated through the activation of p-c-Raf (S338), p-MEK1/2 (Ser217/221), p-p44/42 MAPK (Thr202/Tyr204), and p-Elk1 (Ser383). ERK1/2 siRNA transfection further proved that ERK pathway is involved in the expression of ADAMTS-5 in IL-17A-stimulated THP-1 cells. In conclusion, this present study successfully elucidated the detailed ERK pathway mediated by IL-17A on the expression of ADAMTS-5 in THP-1 differentiated macrophages.

Funded by Toray Science Foundation, Japan

Presented at the MTSF Grant Research Symposium held on 26 November 2019.