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ICAM1 Expression is Enhanced by TNFa through Histone Methylation in Human Brain Microvessel Cells

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Abstract : Intracellular adhesion molecule1 (ICAM1) is a mediator of inflammation and involved in adhesion and transmigration of leukocytes to endothelial cells, resulting in enhancement of brain inflammation. We hypothesized that increase of ICAM1 expression in endothelial cells is an early step in the pathogenesis of brain diseases such as Alzheimer's disease. Here, we report that ICAM1 expression is regulated by pro-inflammatory cytokine TNFa in human microvascular endothelial cell (HBMVEC). TNFa significantly increased ICAM1 mRNA and protein levels at the concentrations showing no cell toxicity. This increase was also shown in micro vessels of mouse brain 24 hours after treatment with TNFa (8 mg/kg, i.v). We then investigated the epigenetic mechanism involved in the induction of ICAM1 expression. Chromatin immunoprecipitation assay revealed that TNFa reduced methylation of histone3K9 (H3K9-2me) and histone3K27 (H3K27-3me), well-known modification as gene suppression, with in the ICAM1 promoter region. However, acetylation of H3K9 and H3K14, well-known modification as gene activation, was not changed by TNFa. Treatment of BIX01294, a specific inhibitor of histone methyltransferase G9a responsible for H3K9-2me, dramatically increased in ICAM1 mRNA and protein levels and overexpression of G9a gene suppressed TNFa-induced ICAM1 expression. In contrast, GSK126, an inhibitor of histone methyltransferase EZH2 responsible for H3K27-3me and valproic acid, an inhibitor of histone deacetylase (HDAC) did not affect ICAM1 expression. These results suggested that histone3 methylation is involved in ICAM1 repression. Moreover, TNFa or BIX01294-induced ICAM induction resulted in both enhancements in adhesion and transmigration of leukocyte on endothelial cell. This study demonstrates that TNFa upregulates ICAM1 expression through H3K9-2me and H3K27-3me within the ICAM1 promoter region, in which G9a is likely to play a pivotal role in ICAM1 transcription. Our study provides a novel mechanism for ICAM1 transcription regulation in HBMVEC.

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