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Homocysteine induces blood vessel global hypomethylation mediated by LOX-1

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ABSTRACT. Homocysteine (Hcy) is an independent risk factor of atherosclerosis through its involvement with the methionine cycle. In this study, we aimed to determine the blood vessel global methylation rate in Hcy-induced atherosclerosis in apolipoprotein-E-deficient ($ApoE^{-/-}$) mice, and to explore the possible mechanism of this change in endothelial cells. $ApoE^{-/-}$ mice were divided into a hyperlipidemia (HLP) group, a hyperhomocysteinemia (HHcy) group, and an HHcy + folate + vitamin B12 (HHcy+FA+VB) group. Wild-type C57BL/6J mice were prepared as controls. Total Hcy, lipids, S-adenosylmethionine (SAM), and S-adenosylhomocysteine (SAH) contents in serum were measured with an automatic biochemistry analyzer and high-performance liquid chromatography. Methylation of B1 repetitive elements in blood vessels was tested using nested methylation-specific-polymerase chain reaction (nMS-PCR). Endothelial cells (ECs) were pretreated with Hcy or by adding FA and VB. Lectin-like oxidized LDL receptor-1 (LOX-1) expressions

were determined by quantitative PCR, Western blot, and nMS-PCR. The HHcy group displayed severe HLP and HHcy. SAM and SAH contents were also elevated in the HHcy group compared with other groups. Methylation of B1 repetitive elements was significantly increased in the HHcy group (0.5050 ± 0.0182) compared to the HLP (0.5158 ± 0.0163) and control (0.5589 ± 0.0236) groups. mRNA and protein expressions of LOX-1 increased (0.2877 ± 0.0341, 0.6090 ± 0.0547), whereas methylation expression decreased (0.5527 ± 0.0148) after 100 μM Hcy stimulation in ECs. In conclusion, Hcy-induced atherosclerosis was closely associated with induced hypomethylation status in the blood vessel, and this process was partially mediated by LOX-1 DNA methylation.

Key words: Homocysteine; Global DNA methylation; Atherosclerosis; Lectin-like oxidized LDL receptor-1