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Role of NFAT5 in Hypertonic Stress-Induced Atherosclerosis in Endothelium

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Abstract: Globally, consumption of sodium (5.8 g per day) was far above the optimal levels (2.3 g per day). High intake of sodium was the leading dietary risk factor for deaths, which caused by cardiovascular disease [1]. Nevertheless, how high-salt intake leads to the occurrence of many cardiovascular diseases such as atherosclerosis is still not very clear. Dmitrieva has reported that elevated sodium concentration promoted thrombogenesis by activating the signal pathway of NFAT5 (nuclear factor of activated T cells 5), a transcription factor which orchestrates cellular defense against osmotic stress [2]. Inflammatory is accompanied with the entire development process of atherosclerosis. Recently, it has been reported that inhibited inflammation hindered the development of endothelial dysfunction-related atherosclerosis [3]. NLR family pyrin domain containing 3 (NLRP3) inflammasome is a crucial effector involved in inflammatory processes, and its activation contributes to atherosclerosis [4]. Furthermore, PAI-1 (Plasminogen activator inhibitor-1)-induced antifibrinolytic properties reduced the clearance of fibrin in plaques and accelerated the formation of atherosclerosis [5]. Here we unveiled that high-salt-activated NFAT5 controlled the NLRP3 inflammasome activation and PAI-1 expression in vascular endothelium, leading to enlarged atheroprone areas. In our study, NaCl was used to adjust the medium osmolality to a range from 270 mosmol/kg (normal physiological value) to 350 mosmol/kg (severe hypernatremia). We investigated the expression of NFAT5, NLRP3, IL-1β, PAI-1 and other fibrin degradation-related genes in human umbilical vein endothelial cells (HUVECs) under different conditions. Our results showed that the mRNA and protein levels of NFAT5, NLRP3, IL-1β and PAI-1 in HUVECs were significantly up-regulated with increasing sodium concentration. At the same time, Elisa assays also confirmed that high salt obviously promoted the extracellular secretion of IL-1β and PAI-1. Overexpression of NFAT5 enhanced the gene and protein expression of NLRP3, IL-1β and PAI-1, while weakened the expression of PLAT (tissue plasminogen activator), PLAU (urokinase plasminogen activator) and PLG (plasminogen) in HUVECs. On the contrary, the expression of NLRP3, IL-1β and PAI-1 was significantly reduced when inhibited by NFAT5 siRNA, while the expression of PLAT, PLAU and PLG was elevated. Our results suggest NFAT5 as a new target for the therapy of atherosclerosis under hypertonic stress induction.

Keywords: Atherosclerosis; NLRP3 inflammasome; NFAT5; PAI-1; hypertonic stress.

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