Identification of potential lysine-specific histone demethylase-dependent mechanisms underlying oxidative stress and inflammation in human and experimental atherosclerosis: a transcriptomics approach

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Complex epigenetic alterations converging to changes in gene function and cell phenotype have been increasingly implicated in atherosclerosis. Within the epigenetic landscape, the role of lysine-specific histone demethylase (KDM)-based pathways in atherosclerosis remains elusive. The aim of this study was to investigate the expression pattern of KDM subtypes in human and experimental atherosclerosis and to determine the potential role of KDM5B in mediating the up-regulation of key genes linked to oxidative stress and inflammation in vitro. Human non-atherosclerotic and advanced atherosclerotic arterial samples and ApoE-/- mice were used. Male ApoE-/- mice were fed a normal or a high-fat, cholesterol-rich diet for 14 weeks. In vitro studies were done on primary mouse monocyte-derived resting (M0), pro-inflammatory (M1) and anti-inflammatory (M2) macrophages (Mac). The occurrence of oxidative stress (NADPH oxidase/Nox) and inflammatory cells/markers (CD45, CD68, NOS2) in the plaques was confirmed by western blot and immunofluorescence microscopy. Microarray-based (SurePrint G3 Human/Mouse gene Expression v2 8x60K) genome-wide expression profiling and bioinformatics analysis predicted the implication of KDM-related signaling pathways in atherogenesis. Real-time PCR and western blot assays revealed the up-regulation of gene and protein expression levels of KDM1A, KDM1B, KDM2A, KDM2B, KDM3A, KDM3B, KDM4A, KDM4B, KDM4C, KDM5A, KDM5B, and KDM5C subtypes in human atherosclerotic tissue samples, atherosclerotic aorta of ApoE-/- mice, and in pro-inflammatory M1-Mac. Pharmacological inhibition of KDM5B by PBIT suppressed the up-regulation of TNFα, MCP-1, Nox1, Nox2, and Nox4 expression levels in M1-Mac. Isoform-specific KDM pharmacological interventions could represent an effective therapeutic strategy to correct the expression of dysregulated genes that are mechanistically linked to atherosclerosis. Work supported by PN-III-P2-2.1-PED-2019-2497, PN-III-P4-ID-PCE-2020-1898.