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HYPOCHLOROUS ACID, A MACROPHAGES PRODUCT, INDUCES ENDOTHELIAL APOPTOSIS: THE ROLE OF ENDOPLASMIC RETICULUM STRESS

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Objectives Superficial erosion of coronary plaques due to endothelial loss causes acute coronary syndromes (ACS). Hypochlorous acid (HOCl), a macrophages product can induce

endothelial apoptosis. Disturbing (ER) function results in ER stress and unfolded protein response, which tends to restore ER homeostasis but switches to apoptosis when ER stress is prolonged. Therefore, we aimed to investigate whether prolonged ER stress is induced by exogenous HOCl and its underlying mechanisms.

Methods Apoptosis were determined by Annexin V-PI double staining assay and TUNEL assay. The phosphorylation of Ire1a and PERK, expression of XBP1, GRP78 and CHOP were measured by western-blot. And the nuclear translocation of ATF6 was studied by immunofluorescence.

Results The results showed that HOCl induced endothelial cell apoptosis and ER stress, characterised by the activation of ER stress sensors (phosphorylation of Ire1a and PERK, nuclear translocation of ATF6) and of their subsequent pathways (eukaryotic initiation factor 2a phosphorylation, expression of XBP1 and KDEL chaperones GRP78). Otherwise, exogenous HOCl can also induce apoptosis protein-CHOP and caspase-3 expression. All these effects of HOCl were inhibited by GRP78 gene silencing. The caspase-3 inhibitor DEVD-CHO significantly inhibited HOCl-induced endothelial cell apoptosis, but had no effect on ER stress sensors and CHOP generation.

Conclusions Collectively, these findings suggest for the first time that ER stress plays a critical role in HOCl-induced endothelial cell apoptosis.