ELECTRONEGATIVE LOW-DENSITY LIPOPROTEIN INDUCES CARDIOMYOCYTE APOPTOSIS THROUGH A CHEMOKINE-CYTOKINE CROSSTALK MECHANISM

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Background: Cardiomyocyte apoptosis plays a critical role in the pathogenesis of heart failure. Human plasma low-density lipoprotein (LDL) can be resolved by charge into five subfractions, L1-L5. L5, the most negatively charged subfraction, induces several atherogenic responses in endothelial cells (ECs), including apoptosis. We studied whether L5 contributes to cardiomyocyte apoptosis indirectly by inducing the secretion of factors from ECs.

Methods: L5 was isolated from human plasma by ultracentrifugation and fast protein liquid chromatography (FPLC). We examined apoptosis of rat H9c2 cardiomyocytes treated with culture-conditioned medium (CCM) of rat ECs that were exposed to L1 or L5. Both early and late stages of apoptosis were examined with Annexin V and Hoechst 33342 fluorescence dye, respectively. Cytokine protein array and ELISA were used to determine the cytokine and chemokine.

Results: Apoptosis at early and late time points was twofold greater in cardiomyocytes treated with L5 CCM than in those treated with L1 CCM. The indirect effect of L5 on cardiomyocyte apoptosis was significantly reduced when ECs were pretreated with inhibitors of phosphatidylinositol 3-kinase (PI3K) or CXC receptor 2 (CXCR2). Cytokine protein arrays revealed that the CCM of L5-treated ECs, but not L1-treated ECs, contained high levels of ELR+ CXC chemokines, including lipopolysaccharide-induced chemokine (LIX) and interleukin (IL)-8. The L5-induced release of these chemokines from ECs was abolished upon inhibition of the lectin-like oxidized LDL receptor (LOX-1). Addition of recombinant LIX or IL-8 to CCM-free cardiomyocyte cultures increased apoptosis and enhanced the production of tumor necrosis factor (TNF)-α and IL-1β by increasing the translocation of NFκB into the nucleus; these effects were attenuated upon inhibition of PI3K and CXCR2.

Conclusions: L5 may indirectly induce cardiomyocyte apoptosis by enhancing the secretion of ELR+ CXC chemokines from ECs, which in turn activate CXCR2/PI3K/NF-κB signaling to increase the release of TNF-α and IL-1β. Our findings provide new mechanistic evidence of how circulating electronegative LDL may contribute to heart failure.