Toll-like receptor 3 mediates expression of clusterin/apolipoprotein J in vascular smooth muscle cells stimulated with RNA released from necrotic cells.

Clusterin/Apolipoprotein J is a protein that is upregulated in a broad spectrum of diverse pathological processes. The predominant form is a secreted glycoprotein (sCLU) with cytoprotective and anti-inflammatory properties which shows enhanced expression in vascular smooth muscle cells (VSMC) following aortic injury and in atherosclerotic disease. Recent evidence indicates that during atherosclerosis, Toll-like receptors (TLRs) are activated in vascular cells by endogenous ligands. Here, we analyzed whether CLU expression in VSMC is controlled by TLRs, and stimulated by factors associated with or released by necrotic cells. Activation of TLR3 by the synthetic RNA analogue polyinosinic-polycytidylic acid (poly(I:C)) in CRL2018 VSMC and in mice led to induction of CLU mRNA and protein synthesis, respectively. In TLR3-deficient 10A yolk sac cells, induction of CLU by poly(I:C) challenge depended on the ectopic expression of human TLR3. In mice lacking the TLR3-signaling adaptor protein TRIF (TIR-domain-containing adaptor protein inducing IFN-?) CLU induction by poly(I:C) was abrogated. In addition to poly(I:C) CLU gene expression in CRL2018 cells was induced by purified cellular RNA and RNA present in necrotic cell lysate. Our data indicate that cellular RNA
following its release from necrotic cells in atherosclerotic lesions can act as an endogenous TLR3 ligand to induce CLU expression in VSMC and in vivo. Thus, they expand the view on TLR2 and TLR4 as known pro-atherosclerotic effectors toward TLR3. Conclusively, TLR3 activation induces expression of cytoprotective and anti-inflammatory CLU by VSMC and mice, to potentially counteract atherosclerotic pathology.