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REPRESSOR ACTIVATOR PROTEIN 1 INDUCES PROINFLAMMATORY CYTOKINES PRODUCTION IN MACROPHAGES THROUGH NFKB SIGNALING

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OBJECTIVES: Repressor activator protein 1 (Rap1), an established telomere-associated protein migrates to the cytoplasm and activates nuclear factor kappa B (NFκB) in human carcinoma cell lines. The present study tested the hypothesis that Rap1 induces production of pro-inflammatory cytokines via NFκB signaling in macrophages, a cell type involved in the development and progression of atherosclerotic lesions.

METHODS: Small interfering RNA technology was used to knockdown Rap1 in THP-1 monocytic cells. The expression of lipopolysaccharide-(LPS) induced NFkB dependent genes and proteins in wild type (Rap1WT) and Rap1 knockdown (Rap1KD) cells were measured using real-time PCR and enzyme-linked immunosorbent assays. Co-immunoprecipitation assay was used to identify the protein-protein interaction. Western blotting was applied to determine the expression of Rap1 and proteins involved NFê B signaling pathway (including IKKα, IKKβ, IκBα, p65 and their phosphorylation forms) in Rap1WT and Rap1KD THP-1 cells. The expression of Rap1 and macrophages in human atheromatous lesions was detected by immunohistochemistry.

RESULTS: Rap1 was present in the cytoplasm of differentiated THP-1 cells and associated with IKK. Knockdown of Rap1 suppressed LPS-mediated activation of NFκB, and phosphorylation of IκBα and p65 in THP-1. The reduction of NFκB activity was paralleled by a decreased production NFκBdependent pro-inflammatory cytokines [including interleukin (IL)-8, IL-1α, IL-6 and monocyte chemotactic protein-1], and an increased expression of IL-10, an NFκB-dependent anti-inflammatory cytokine. Immunostaining revealed that Rap1 localized to macrophage-rich areas in human atherosclerotic plaques and that the presence of Rap1 was positively correlated to the advancement of the disease process.

CONCLUSIONS: In macrophages, Rap1 promotes cytokine production via NFκB activation favoring a pro-inflammatory environment which may aggravate the development and progression of atherosclerosis.