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The reduced APE1/Ref-1 inhibits inflammatory responses in vascular endothelial cells.

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Objectives:

Apurinic apyrimidinic endonuclease 1/Redox factor-1 (APE1/Ref-1, also known as Ref-1) is a multifunctional protein; its N-terminal region is involved in redox activity and regulates multiple transcription factors, and its C-terminus is involved in base excision DNA repair activity levels of APE1/Ref-1 were also observed in the blood of endotoxemic rats and in bladder cancer, implying that APE1/Ref-1 functions as a secreted protein. we hypothesized that secreted APE1/Ref-1 could be an effective regulator in inflammatory reactions via its reduction. We tested this hypothesis using TNF-α-treated human umbilical vein endothelial cells (HUVECs) as a vascular inflammation model.

Methods:

Reduction activity of recombinant human APE1/Ref-1 (rh APE1/Ref-1) was analyzed using biochemical reducing activity and a modified biotin-switch assay. To examine the effect of APE1/Ref-1 we were pre-treated rhAPE1/Ref-1 for 1h before stimulation of human umbilical vein endothelialcells (HUVECs) with TNF-alpha and interleukin-1β (IL-1β). HUVECs lysates were obtained and immunoblotting forVCAM-1 was performed.

Results:

To evaluate the function of the reducing APE1/Ref-1, the effect of rh APE1/Ref-1 on TNF-α -induced VCAM-1 expression was determined. Pre-treatment with the reducing APE1/Ref-1 (0.5–2 μg/ml) suppressed TNF-α -induced VCAM-1 expression in a concentration-dependent manner, suggesting that extracellular secreted APE1/Ref-1 has an anti-inflammatory function. Based on our studies, inflammatory reactions stimulated by cytokines through the IL-1 receptor or the Toll-like receptor (each has 5 disulfide bonds in the extracellular domain) were effectively attenuated by exposure to APE1/Ref-1. In accordance with TNF-α /TNFR regulation, the IL-1 or LPS-stimulated inflammatory signal was also inhibited by reduction of disulfide bonds, implying a broad-spectrum reducing effect of APE1/Ref-1.

Conclusions:

These results strongly indicate that anti-inflammatory effects in TNF-α-stimulated endothelial cells by the reducing APE1/Ref-1, which inhibits TNF-α binding to TNFR1 by reductive conformational change, with suggestion as an endogenous inhibitor of vascular inflammation.