

Abstract

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Pro-atherogenic effect of interleukin-4 in endothelial cells: modulation of oxidative stress, nitric oxide and monocyte chemoattractant protein-1 expression.

Walch L, Massade L, Dufilho M, Brunet A, Rendu F.

UMR7131 CNRS/Université Pierre et Marie Curie (Paris 6), Hôpital Broussais, 102 rue Didot, 75014 Paris, France.

BACKGROUND: Although considered as an anti-inflammatory cytokine, interleukin-4 (IL-4) has been shown to be pro-atherogenic in mice models of atherosclerosis.

OBJECTIVES: In order to elucidate this paradox, we have investigated the effects of IL-4 on characteristic atherogenic parameters in human umbilical vein endothelial cells (HUVECs): production of reactive oxygen species, expression of monocyte chemoattractant protein-1 (MCP-1) and nitric oxide (NO) bioavailability.

RESULTS: Incubation of HUVECs with IL-4 resulted in an increased production of reactive oxygen species and extracellular $O_2^{(-)*}$ measured using fluorogenic probes and Cytochrome c that was inhibited by superoxide dismutase or gp91ds-tat, a selective NADPH oxidase inhibitor. The latter also inhibited IL-4 induced over-expression of MCP-1 mRNA measured by classical and real time RT-PCR. Incubation of HUVECs with IL-4 reduced thrombin-induced NO release, detected by electrochemistry, an effect which was reversed by incubation with superoxide dismutase. Both production of reactive oxygen species and MCP-1 mRNA over-expression induced by IL-4 were fully inhibited by selective inhibitors of phosphatidyl inositol 3-kinase.

CONCLUSION: The data demonstrate that IL-4 up-regulates the expression of MCP-1 and decreases NO bioavailability through activation of NADPH oxidase in endothelial cells. These results are in favor of a pro-inflammatory and pro-atherogenic effect of IL-4 in vascular tissues.

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