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# Molecular mechanisms involved in the antiatherogenic role of beta-carotene in human vascular cells

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Several lines of evidence support a role for oxidative stress and inflammation in atherogenesis. Epidemiological studies suggest that low levels of  $\beta$ -carotene are associated with increased risk for cardiovascular disease and that increased intakes of fruit and vegetable, rich in  $\beta$ -carotene, appear to be protective. However, at the moment, the mechanism(s) of such a protection are still unknown. The aim of this study was to investigate possible interactions between  $\beta$ -carotene and cholesterol and its oxidation product 7-keto-cholesterol, which is known to be present in a large amount in atheromatic plaque, in vascular cells, including macrophages (THP cells), fibroblasts (RAT-1) and endothelial cells (HUVEC). To this purpose, cells were enriched with  $\beta$ -carotene (0.25-2  $\mu$ M) for 24 h, and, then, treated with cholesterol/oxysterols in a wide range of concentrations (0.25-50  $\mu$ M) for different periods of time (12-72 h). The carotenoid was able to counteract the dangerous effects of increased levels of cholesterol and its oxidation product in vascular cells through diverse mechanisms: 1) it decreased the levels of endogenous cholesterol through a decreased expression of the 3-hydroxy-3-methylglutaryl coenzyme A reductase, one of the most important enzyme involved in the synthesis of cholesterol; 2) it reduced the formation of cholesterol oxidation products; 3) it prevented the arrest in cell cycle progression and the increase in apoptosis induction induced by cholesterol and/or 7 keto-cholesterol through modulatory effects on proteins involved in cell cycle progression (cyclin D1), in apoptosis induction (Bcl-2) and in cholesterol metabolism (caveolin-1); 4) it reduced the levels of oxysterol-induced reactive oxygen species through changes in the expression and activity of NADPH-oxidase (NOX-4). This study suggests that  $\beta$ -carotene may act as a potential anti-atherogenic agent in vascular cells by preventing the detrimental effects of cholesterol/oxysterols through different mechanisms.