Title: Lycopene regulation of cholesterol synthesis and efflux in human macrophages.

Article Type: Research Article

Keywords: lycopene; cholesterol; HMG-CoA reductase; ABCA1; caveolin-1; THP-1 cells.

Abstract: Hypercholesterolemia is one of the most important risk factors for atherosclerosis and tomato lycopene has been suggested to have beneficial effects against such a disease, although the exact molecular mechanism(s) is unknown. We tested the hypothesis that lycopene may exert its anti-atherogenic role through changes in cholesterol metabolism. Incubation of THP-1 cells with lycopene (0.5-2 μM) dose-dependently reduced intracellular total cholesterol. Such an effect was associated with a decrease in cholesterol synthesis through a reduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase expression and with an increase in cholesterol efflux through enhanced ABCA1 and caveolin-1 (cav-1) expressions. In addition, lycopene enhanced RhoA levels in the cytosolic fraction, activating peroxisome proliferator activated receptor gamma (PPARγ) and liver-X receptor α (LXRα) expression. Concomitant addition of lycopene and the PPARγ inhibitor GW9662 or lycopene and mevalonate blocked the carotenoid-induced increase in ABCA1 and in cav-1 expression. These results imply a potential role of lycopene in attenuating foam cell formation and, therefore, in preventing atherosclerosis by a cascade mechanism involving inhibition of HMG-CoA reductase, RhoA inactivation and subsequent increase in PPARγ and LXRα activity, and enhancement of ABCA1 and cav-1 expression.