RESVERATROL COUNTERS ATHEROGENIC EFFECTS OF INTERFERON-GAMMA ON CHOLESTEROL EFFLUX IN THP-1 HUMAN MONOCYTES/MACROPHAGES

ACC Poster Contributions
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Background: We report here that resveratrol, a plant polyphenol with cardioprotective properties, can inhibit atherosclerosis by enhancing expression of reverse cholesterol transport (RCT) proteins critical for preventing lipid overload and macrophage foam cell formation (FCF). These RCT proteins include the cholesterol-metabolizing enzyme 27-hydroxylase (27-OHase) and ATP binding cassette transporters (ABC) A1 and G1. In THP-1 human monocytes and monocyte-derived macrophages (MDM), resveratrol upregulates these proteins and prevents their diminution by the inflammatory cytokine interferon-γ (IFN-γ).

Methods: THP-1 monocytes/MDM, a pertinent model of atherosclerosis, were incubated for 24h ± resveratrol (50 μM) and ± IFN-γ (500 U/ml). RCT protein mRNA was evaluated by real-time PCR. THP-1 monocytes (106/ml) were differentiated into adherent MDM (phorbol dibutyrate), then lipid-loaded (acetylated LDL, 50μg/ml, 48h) ± resveratrol and ± IFN-γ. FCF by MDM was quantified as percent oil red O stained cells. Studies were done in triplicate.

Results: Resveratrol significantly increased 27-OHase message (mean ± SEM, 246.2 ± 20.4% of control, P= 0.0011) in monocytes. Resveratrol negated downregulation of 27-OHase by IFN-γ (132.4 ± 12.1% of control for resveratrol + IFN-γ vs. 49.3 ± 2.9% for IFN-γ alone, P= 0.0014). Reseratrol increased ABCA1 and ABCG1 mRNA (194.2 ± 14.8% and 736.5 ± 61.4% of control, respectively). Reseratrol abolished IFN-γ-induced suppression of each RCT protein. For ABCA1: 149.6 ± 14.6% for resveratrol + IFN-γ vs. 67.0 ± 3.9% for IFN-γ alone, P= 0.0035. For ABCG1: 413.8 ± 45.0% for resveratrol + IFN-γ vs. 64.1 ± 3.5% for IFN-γ alone, P= 0.001. FCF by THP-1 MDM was significantly reduced with resveratrol compared to control (22.2±5 vs. 35±5 p=0.03).

Conclusion: We reported that IFN-γ promotes FCF and diminishes 27-OHase and ABCA1 in cells relevant to atherogenesis. This supports the hypothesis that excess IFN-γ promotes atherosclerosis in autoimmune disorders such as lupus by disrupting cholesterol homeostasis. Resveratrol nullifies pro-atherogenic effects of IFN-γ. RCT upregulation by resveratrol restores a critical defense mechanism against atherosclerosis.