INTERFERON GAMMA SIGNALLING IN ATHEROSCLEROSIS: PROATHEROGENIC ACTIONS AND THERAPEUTIC APPROACHES
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Objectives: To investigate the mechanisms underlying the effects of interferon-gamma on macrophages in atherosclerosis and how therapeutic agents attenuate the actions of this pro-inflammatory cytokine.

Background: Atherosclerosis is an inflammatory disease of medium and large arteries regulated by cytokines. The pro-atherogenic cytokine interferon-gamma (IFN-gamma) plays a pivotal role in all stages of the disease and hence represents a promising therapeutic target. The purpose of this study was to investigate how IFN-gamma modulates macrophage function and properties in this disease along with the mechanisms underlying the inhibition of its actions by therapeutic agents.

Methods: The studies used a combination of macrophage cell lines and primary cultures together with analysis of gene expression and signal transduction pathways, RNA interference assays and biochemical approaches.

Results: IFN-gamma induced macrophage foam cell formation and the expression of several pro-inflammatory genes, such as monocyte chemotactic protein-1 and intercellular adhesion molecule-1, and microRNAs. The extracellular signal-regulated kinase (ERK) pathway played a pivotal role in the action of the cytokine on the promotion of modified lipoprotein uptake by macrophages and the regulation of expression of pro-atherogenic genes. ERK modulated the phosphorylation-mediated activation of signal transducer and activator of transcription-1 (STAT1), a key transcription factor in IFN-gamma signalling. The pro-atherogenic actions of IFN-gamma were attenuated by statins, activators of anti-atherogenic nuclear receptors, and nutraceuticals such as dihomo-gamma-linolenic acid. The mechanisms underlying the inhibitory actions of such agents along with the role of the ERK:STAT1 axis in the promotion of atherosclerotic in vivo are currently being investigated.

Conclusions: The studies provide key mechanistic insights into the pro-atherogenic actions of IFN-gamma and the effects of therapeutic agents on signalling by this cytokine.

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