INTERFERON GAMMA SIGNALLING IN ATHEROSCLEROSIS: PRO-ATHEROGENIC ACTIONS AND THERAPEUTIC APPROACHES

T.S. Davies[1], H. Gallagher[1], F. Jaafar[1], J.W. Moss[1], T.R. Hughes[2], **D.P. Ramji[1]**
1. School of Biosciences, Cardiff University, Cardiff, UK
2. School of Medicine, Cardiff University, Cardiff, UK

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.
Funding: British Heart Foundation