II

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Atherosclerosis is a chronic inflammatory disease, where the initiation and progression of lesion formation proceeds with the activation of several pro-inflammatory signals and effector molecules. Subendothelial retention of ApoB100- containing lipoprotein is an early step in atherogenesis. Interaction between atherogenic lipoproteins and proteoglycans involves an ionic interaction between basic amino acids in ApoB100 and negatively charged sulphate groups on the proteoglycans (Skalen K, et al. 2002). Once sequestered in this microenvironment, lipoprotein-proteoglycan complexes are susceptible to modifications including oxidation, enzymatic cleavage and aggregation, which render these particles pro-inflammatory and incite monocyte recruitment into the artery wall. Monocyte recruitment, activation and uptake of modified lipoproteins is beneficial during the initial stages of atherogenesis through their ability to clear these inflammatory lipids from the artery wall. However, pathways for metabolizing lipoprotein-derived cholesterol by macrophages appear to become overwhelmed, leading to promotion of disease-causing foam cells and the establishment of chronic inflammation. (Webb NR et al. 2007 and Woods TC et al. 2004). Later several other immune cells enter the lesion area and release factors that activate smooth muscle cell proliferation and destructive tissue remodelling leading to formation of vulnerable or stable atherosclerotic plaques. This results in blockages in the blood vessels particularly those with a small diameter such as coronary arteries, vessels in limbs and brain. Such a blockade may lead to ischemia in the respective organ and can be fatal.

The disease initiation and progression involves cytokines (IFNs, TNF-α, ILs), chemokines, ROS, enzymes and markers known to be expressed at the site of atherosclerotic lesions. Many of these molecules are under the transcriptional regulation of Interferon regulatory factor (IRF)-1. IRFs are a family of transcription factors originally identified as regulators and mediators of IFN genes and anti-viral IFN-signaling. Accumulating evidence suggests that this family and particularly IRF-1 and its functional antagonist IRF-2, are involved in regulating pleiotropic functions. Published
reports indicate that IRF-1 may be involved in regulating genes that mediate monocyte infiltration and foam cell formation and can also inhibit vascular smooth muscle cell migration and proliferation. However majority of this information is from in vitro studies and injury induced carotid proliferative stenosis in animals. There have been few if any reports on the expression and function of IRFs in atherosclerosis. In the present study we sought to investigate the expression and function of IRF-1 and IRF-2 in a diet-induced model for atherosclerosis. This model closely resembles the disease in human subjects.

Curcumin is a natural plant derived polyphenol, known to have anti-oxidative, anti-inflammatory and atheroprotective properties. It is possible that IRF-1 mediates at least some of the effects of Curcumin. Also if IRF-1 regulates various processes in atherosclerotic disease then physiological agents such as retinoids that induce IRF-1 may influence disease progression. Therapeutic strategies targeted at modulating the activity of enzymes and transcription factors may provide the solution to diseases such as atherosclerosis.