MRes Bioengineering research project

Title of the project:
The role of non-canonical Wnt signalling in endothelial cells exposed to disturbed flow

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Project Description:

Background
Atherosclerotic lesions are found at specific sites within the arterial tree due to the influence of local mechanical forces. Lesions develop at branches, bifurcations and bends where blood flow is disturbed (multidirectional), whereas straight, unbranching vessels where flow is undisturbed (uniaxial) are protected. Endothelial cells that line the blood vessels sense and respond to blood flow and exhibit markedly different phenotypes at sites of disturbed and undisturbed flow e.g. cells exposed to disturbed flow exhibit cobblestone morphology whereas those exposed to undisturbed flow are elongated and aligned. The cellular signalling mechanisms responsible for these effects are poorly understood although we have recently obtained new evidence suggesting a role for the Wnt/β-catenin signalling pathway. Evidence from osteocytes also suggests that non-canonical Wnt signalling via the transcription factor, NFAT (Nuclear factor of activated T-cells) may also be important in mechanotransduction. The role of NFAT in endothelial responses to flow has not been studied to date and may be important in mechanotransduction and the development of atherosclerosis.

Project Aims & Research Plan
This project will investigate the role of the non-canonical Wnt signalling pathway on flow-dependent responses with a particular focus on NFAT. Endothelial cells will be cultured and exposed to disturbed flow using the orbital shaker method developed by Dr Christina Warboys and Professor Peter Weinberg. The student will assess whether disturbed flow promotes nuclear translocation of NFAT by immunostaining and western blot analysis. The potential role of NFAT in mediating typical flow-dependent responses will be assessed by knocking down NFAT expression by siRNA or by specific inhibitors. The student will assess cell morphology and orientation by immunostaining with VE-cadherin and Phalloidin and will assess the expression of flow-dependent genes (KLF2, KLF4, NOS3, E-selectin and MCP-1) by quantitative RT-PCR.

Students will learn the following techniques: cell culture, immunostaining, confocal microscopy, RNA isolation, RT-PCR, western blot

Key techniques: (please include only the names of techniques, not a description)