

Regulation of arterial remodelling by Wnt proteins as result of hypertension

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Sustained hypertension is a major risk factor in cardiovascular disease, playing a significant role in atherosclerosis and kidney insufficiency. Accumulating evidence suggests that high blood pressure induces impairment of kidney function perhaps affecting the renal vasculature. In the current study, we will investigate whether hypertension induced arterial remodelling in DBA2J mice. Delivery of Angiotensin-II via mini-osmotic pumps for up to 28 days resulted in significantly elevated high blood pressure will induce hypertension and proteinuria. We will assess arterial remodelling in the kidney, heart, aorta and lung at 3, 7 and 28 days using histological techniques including histological staining and immunohistochemistry various phenotype markers such as α -smooth muscle cell actin, smoothelin, myosin heavy chain and extracellular matrix components. These markers of arterial remodelling will be quantified using image analysis. Electron microscopy will be utilised to analyse subcellular composition.

We have recently demonstrated the involvement of Wnt canonical signalling in vascular remodelling (1-4). Using synthetic Wnt antagonists and gene delivery of the endogenous inhibitor of canonical signalling DKK-1 we will determine whether Wnt canonical signalling is essential for arterial remodelling. MMP activity is essential for vascular remodelling and is modulated by Wnt signalling and therefore we will determine whether MMPs including MMP-9 and MMP-7 are involved in Wnt-mediated arterial remodelling in hypertension.

The hypothesis for this PhD is:

Arterial remodelling occurs as a result of hypertension and is regulated by Wnt canonical signalling which results in augmented MMP activity.

For this PhD, the student will undertake in vivo experiments in mice including implantation of mini-osmotic pumps and adenoviral gene transfer. They will gain valuable experience in a number of techniques including Q-PCR, Western blotting, electron microscopy, confocal microscopy immunohistochemistry and histology. In addition the student will gain training in transferable skills and an in depth knowledge of cardiovascular disease via lectures in the MSc in Translational Cardiovascular Medicine programme.

References

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