

College PhD studentship in Cardiovascular Science Research

Studentship number: MBSP/10/05

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Project description :

MS1-a two faced general regulator of proliferation and differentiation

MS1, also known as STARS or ABRA is a cardiac stress response protein that is overexpressed as an early response to pressure overload in animal models of hypertension. It is involved in the regulation of gene expression through a mechanism that releases MRTFs from the cytosol for transfer to the nucleus in an indirect mechanism involving actin polymerisation. In the nucleus MRTFs stimulate gene expression via the central regulator SRF. In sustained pressure overload such a mechanism is believed to be involved in cardiac remodelling ultimately leading to hypertrophy and subsequent heart failure.

MS1 possesses an actin binding portion that is reasonably well characterised. Based on a combination of biophysics and structural biology studies an unexpected binding ability for a new ligand was identified that opens up alternative mechanisms in which MS1 could influence the regulation of gene expression in cardiomyocytes.

The project will focus on an initial characterisation of the interaction using a range of molecular biology, protein chemistry, biophysical and cellular techniques. Once optimal conditions for establishing the complex are identified its structure will be determined by NMR spectroscopy or X-ray crystallography.

The structure will be analysed to identify the precise mechanism of interaction, especially regarding its specificity. Conclusions will be validated by point mutants probed by a range of biophysical methods. Mutants that show a specific response will be investigated in cellular and *in vivo* assays to evaluate the importance of specific interactions in living organisms.