Cardiac hypertrophy: comparing models and counting genes

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In the study of cardiac hypertrophy, much has been learned from polygenetic models developed by conventional selective in-breeding techniques (*i.e.* the Spontaneously Hypertensive Rat, SHR). As many cardiovascular disease states comprise a complex multigenic-dependent phenotype, it is particularly valid to use these models for investigation of the natural history of disease development and progression. However a major difficulty with these models has been that hypertrophy and hypertension are frequently coincident and identification of the genetic factors which contribute to cardiac growth independently of blood pressure has been difficult. Furthermore, the failure to co-derive genetically homogenous control strains for some models has further confounded the interpretation of data obtained from these animals.

We have recently reported the development of a novel polygenic rat strain of primary cardiac hypertrophy derived from a cross of Fisher (F344) and SHR (Harrap *et al.*, 2002). Our new Hypertrophic Heart Rat (HHR) strain exhibits cardiac and cardiomyocyte hypertrophy in the absence of hypertension. In parallel we have co-developed a Normal Heart Rat (NHR) strain with small hearts and low blood pressure as a control strain. Exploration of the cardiac growth responses in the HHR and NHR provides an opportunity to characterise the processes underlying the development of load-independent hypertrophy.

A complementary genetic approach which can be of particular value in providing insight into the mechanisms of cardiac hypertrophy is the study of mono-genetically manipulated animal models. We have investigated transgenic and gene-knockout models to explore the role of trophic and metabolic factors in inducing cardiac hypertrophy. Our studies of a transgenic cardiac-specific angiotensinogen over-expressing mouse and a cardiac-specific glucose Glut4 transporter Cre-Lox KO mouse have revealed that similar functional adaptations can be linked with quite different alterations in myocyte calcium handling in hypertrophy.

In both multigenic and unigenic models of cardiac hypertrophy we have applied candidate gene and expression profiling techniques to undertake comparative genotype-phenotype analyses. In our candidate gene investigations we have focussed on expression shifts in transporters important in modulating excitation-contraction coupling. Our genome scale ‘snapshot’ studies have suggested that regardless of the instigating genetic stimulus, the hypertrophic phenotype is associated with a major remodelling of metabolic processes.

Thus, the value of both unigenetic and polygenetic animal models in the study of cardiac hypertrophy is particularly evident when candidate gene analysis and genome-scale expression profiling techniques are used as complementary approaches.

Harrap, S.B., Danes, V.R., Ellis, J.A., Griffiths, C.D., Jones, E.F. & Delbridge, L.M.D. (2002) *Physiological Genomics*, 9, 43-48.