Heart cell attrition early in life – the beginning of the end?

L.M.D. Delbridge, Department of Physiology, The University of Melbourne, Parkville, VIC 3010, Australia.

There is considerable evidence that perinatal trophic influences have a long-term impact on defining adult growth patterns. An inverse relationship has been demonstrated between birth weight and adult susceptibility to cardiovascular disease. The fetal origins of disease have been most extensively studied with respect to early vascular and renal development, antecedent to the later occurrence of hypertension, kidney disease, diabetes and metabolic syndrome. Cardiac enlargement at maturity is an important and independent predictor of cardiovascular morbidity and mortality. However, relatively little is known about the early developmental origins of the hypertrophic heart. Angiotensin II (AngII) mediates both cardiomyocyte hypertrophy and apoptosis, and appears to be of special importance in regulating neonatal heart growth. The cardiac renin-angiotensin system is particularly active in the fetus and neonate, and is up-regulated in the growth-restricted fetus.

Most of the known physiological functions of AngII are mediated by the AT1 receptor, which is ubiquitously expressed in adult tissues and signals via the classical Gq- pathways. The AT2 receptor is predominantly expressed in fetal and neonatal tissues, and its function is less well delineated. AT2-mediated cardiovascular responses have been characterized as generally opposing AT1-mediated effects, exerting vasodilatory, antigrowth, anti-proliferative, and pro-apoptotic actions. However, some studies of genetically manipulated rodents indicate that the AT2 receptor is also involved in modulating myocyte enlargement and is necessary for left ventricular hypertrophy. Thus, the role of the AT2 receptor remains ambiguous. How the AT1 and AT2 receptor balance regulates cardiac growth and apoptosis in the neonate and predisposes for abnormal adult myocardial growth is not known.

In our experimental studies of genetically determined cardiac hypertrophy in rodents, we have identified a link between cardiac growth restriction in the neonate and the development of cardiac hypertrophy at maturity. Neonatal heart growth suppression occurs in association with a high AT2/AT1 receptor expression ratio, and neonatal cardiomyocytes appear to be predisposed to a significantly increased incidence of AT1A receptor-mediated AngII-induced apoptosis. We have also used adenoviral constructs to manipulate AT1/AT2 receptor expression stoichiometry *in vitro* to characterise growth and apoptotic responses of neonatal cardiomyocytes of normal and hypertrophy pre-destined hearts.

Our studies identify a novel function of the AT2 receptor in modulating cardiac growth and development, and suggest that myocardial cell loss early in life may program for the later development of hypertrophic myocardial pathology.