

Downregulating Rho Kinase (ROCK) in the developing ventricle wall causes early sarcomeric defects which contribute to the development of adult cardiovascular disease.

Bailey KE, Blain A, Tual-Chalot S, Mohun T, Bamforth SD, Henderson DJ, Phillips HM.

Congenital heart disease is extremely common and accounts for a third of all congenital malformations. In addition, adult heart disease is the main cause of death in the UK. Defects acquired during development may predispose to disease later in life and have a detrimental lasting effect on heart function. Therefore understanding the underlying mechanisms involved in cardiac development and disease progression is extremely important.

The serine threonine kinase, Rho Kinase (ROCK) is the main effector of the small GTPase RhoA and it is involved in a number of diverse cellular functions including regulation of cell morphology, migration, proliferation, apoptosis and polarity as well as being a key regulator in actin-myosin contraction. ROCK is required for normal heart development; however the exact function of ROCK in the cardiomyocytes is unknown.

Conditional downregulation of ROCK specifically in the heart using Cre-LoxP technology has allowed for the investigation of ROCK specifically in the developing cardiomyocytes. ROCK downregulation in the epicardium and myocardium during development results in heart defects, which include an abnormally thin myocardium and persisting trabeculae. Analysis at the cellular level indicates abnormalities in sarcomere assembly in mutant hearts which are present from early in development. Interestingly these mice survive into adulthood where they develop characteristics associated with cardiomyopathy including hypertrophy, fibrosis and a reduction in heart function. This model highlights the importance of understanding developmental defects and how they contribute to adult disease. This model will help in identifying cellular mechanisms underpinning the development of adult cardiovascular disease.