# 6 Summary

Heart failure describes the inability of the heart to pump enough blood to fulfill the needs of the body. In order to investigate the etiology and molecular events underlying the disease, the expression profiling of the spontaneously hypertensive heart failure rat (SHHF) compared with nonfailure controls were investigated. SHHF is a genetically inbred strain that have many similarities to the human disease for it slowly develops hypertension, hyperinsulinemia, diabetes mellitus, and heart failure. The spontaneously hypertensive rat stroke prone (SHRSP) serve as the control strain for its hypertension background, and the Wistar Kyoto rat (WKY) as the normotensive control. The candidate genes selected from Affymetrix chips analysis could be clustered into 9 groups according their functions. The genes of collagen type I and III, thrombospondin 4, heat shock 70, cyclin D, and cysteine rich protein showed consistent changes in the SHHF with previous studies of heart failure. In particular, the genes involved in fatty acid metabolism e.g. *Cd36*, and pyruvate dehydrogenate kinase 4 were downregulated, and genes related to glucose metabolism such as fructose bisphosphatase 2, uncoupling protein 1, and retinoid X receptor were upregulated in the SHHF compared with the two controls. Protein tyrosine phosphatase and PS20 were also found increase in SHHF strain. These changes were further confirmed with the quantitative Real Time PCR.

Cd36, a heavily glycosylated integral membrane protein, is implicated in the binding to long-chain fatty acids and oxidized low-density lipoprotein, its deficiency leads to severe decrease in fatty acid uptake in the tissues active in fatty acid metabolism. *Cd36* deficiency has also been linked to insulin resistance, cardiac hypertrophy, and tolerance to ischaemia in rodent models with a diversity of heart disease. *Cd36* was found downregulation in the SHHF compared with WKY and SHRSP by expression profiling and Real Time PCR in this study. The normal transcript of CD36 was not observed in SHHF animals, whereas two novel extended transcripts of *Cd36* were found. The full lengths of the cDNA sequences were acquired. The gene *Cd36* has three and a half homologues in the normal rat chromosome 4. While on the SHHF rat genome, about 164.68 kb fragments were deleted between the intron 4 of the first copy and the last homologues of *Cd36* gene. From these results, it is suggested that the abnormal transcription of *Cd36* in SHHF may result in the nonfunctional product, or obviously lower translation of Cd36.

To further investigate the link between *Cd36* and heart failure in SHHF model a linkage analysis of *Cd36* to heart failure was performed using *Hin*fI RFLP along with three markers

on either side of *Cd36* in (SHHF×WKY) F2 crosses (n=191). The calculated hemodynamic parameters were used as the indicators in response to heart failure. The locus on chromosome $4q^{11\text{-}12}$ showing suggestive linkage to heart failure that was determined from the cardiac output parameter in F2 male rats.