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Disease-Model Animals-Based Screening for Genes Involved in Molecular Pathogenesis of Cardiac Hypertrophy and Heart Failure

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Summary

Sustained pressure overload onto heart leads to hypertrophy of cardiac muscle, which is eventually followed by heart failure. Although pumping failure of heart is still one of the leading causes of human death, little is still understood for the underlying mechanism how ability of cardiac muscle becomes impaired. Studies on this issue have been seriously hampered by the difficulty in sampling human ventricle specimens at various stages in the development of hypertrophy-to-heart failure course. Dahl salt-sensitive rats are genetically hypersensitive to sodium intake. When fed a high sodium diet, they develop systemic hypertension, followed by cardiac hypertrophy and finally heart failure within a few months. Therefore, Dahl rats represent a good model with which to study how heart failure is developed *in vivo*. With the use of “GeneChip” DNA microarray technology, we have obtained gene expression profiling in cardiac myocytes during the course of heart failure in Dahl rats. In addition, we have developed a novel epigenetics technology, "ChIP-to-seq" method, by coupling chromatin immunoprecipitation (ChIP) to a high-throughput sequencing system. Our ChIP-to-seq enables to annotate ~200,000 ChIP products simultaneously, and clarifies the changes in epigenetic profile among failed hearts at a very high resolution and fidelity. Application of the ChIP-to-seq method to the Dahl rat as well as human clinical specimens has, for the first time, revealed a disease-dependent epigenetic profile in heart.