Genetic Approach to Cardiovascular Disease

Youngkeun Ahn
Chonnam National University Hospital

The outlook for gene therapy looks promising. However, gene therapy still needs many improvements before it becomes routine treatment for cardiovascular disease in the clinic. Some areas for improvement include selecting appropriate patient populations for clinical trials, evaluating side effects, selecting and ensuring the safety of the genetic material to deliver, and methods for delivering the gene.

We are investigating new vector system and delivering method for increasing efficacy and safety of gene therapy in cardiovascular disease.

First, thermo-responsive hydrogel mediated local gene transfer can be preferentially applied to muscle, since release of DNA into the surrounding tissue can be controlled by 3-dimensional network structure of hydrogel. Indeed, a system for controlled release of therapeutic gene may extend the duration of gene expression, especially in the clinical environment where longer gene expression is desirable after single injection. Here, thermo-responsive and biodegradable polymeric hydrogel has been synthesized and investigated for local gene transfer in heart. Initially, luciferase gene was delivered into mouse heart to test the duration and intensity of gene expression. Gene expression intensity assessed by optical imaging is closely correlated to actual expressed protein concentration measured by luciferase assay with homogenized heart. Polymeric hydrogel-based gene transfer was shown to mediate enhanced gene expression up to 4 fold, compared to naked plasmid, and displayed two expression profiles with peaks at 2 days and around 25 days after local injection. Histological analyses have revealed that high gene expression is initially dominated by myocardium, whereas lower and longer expression is mainly governed by fibrotic and/or inflammatory cells infiltrated into injury site during injection. In an attempt to investigate polymeric hydrogel-assisted therapeutic effect at infarct area, rat myocardial infarction model was made for 1 week and vascular endothelial growth factor (VEGF) plasmid were injected at infarct area with polymeric hydrogel. Enhanced VEGF expression in infarct region mediated by polymeric hydrogel promoted increased capillary density and larger vessel formation, thus enabling efficient angiogenesis.

Second, our previous observation that bacteria mainly locate in hypoxic tumor region gives rise to the idea that bacteria may have a potential to specifically home to hypoxic tissue in the myocardium. Here we present attenuated *Salmonella typhimurium* engineered to express and secrete reporter protein (Rluc8) under the control of inducible promoter. Engineered bacteria emit visible light that is sufficient to be detected and monitored by a cooled charge-coupled device (CCD) detector. After administered intravenously, bacteria specifically home to infarcted myocardium in the anterolateral wall of rat hearts. Reporter gene which is delivered by bacteria is expressed and secreted specifically in the infarcted myocardium with remote-controlled induction of gene expression. The engineered bacteria have further potentials to be designed to carry multiple genes for detection and treatment of myocardial infarction.