Single Cell Analysis of Failing Heart

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There are about 1.2 million heart failure (HF) patients in Japan and although general population is decreasing, the number of HF patients is expected to be increased until 2035. Thus, HF is a big problem in Japan and novel treatments based on the mechanisms have been awaited.

To discriminate between disease trajectory and health trajectory, we have started single cell analysis for HF. tSNE analysis revealed that pressure overload (PO) changed transcripts so different from normal state first and then transcripts returned to near normal but they were not homogenous. There were two pathways from hypertrophied cardiomyocytes (CMs) after PO, failing and adaptive pathways. To elucidate how failing CMs are induced, we determined transcripts of the fork and found that there was a network of genes consisting of many targets of p53. CM specific p53 KO mice did not show HF after PO. Failing CMs were recognized in wild type mice but not in p53KO mice. Transcription pattern is conserved in human HF. There were two trajectories also in human, adaptive and failing. DNA damage response genes were expressed in failing CMs. The levels of DNA damage response genes were high in failing heart and were even higher in non-responder to treatments than responder. Transcripts of normal CMs are homogeneous and those of failing CMs are inhomogeneous. Many inflammatory cytokines were upregulated in failing CMs. IGFBP7, which is known to be secreted from DNA damage-induced senenscent cells, was upregulated in failing CMs. Random forest analysis revealed that there were many proteins in serum which are corelated to the progression of HF and IGFBP7 was the protein most corelated to that. IGFBP7 is mildly upregulated in non-advanced HF patients and robustly upregulated in advanced HT patients. We established the system to determine the responsible genes for cardiomyopathy. Using this panel, we determined the responsible genes of 120 patients with dilated cardiomyopathy and I will also talk about our recent results on cardiomyopathy.