Multiple and integrative approaches to cardiovascular diseases with stem cell technology
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We have been investigating cardiovascular cell differentiation and regeneration using pluripotent stem (ES/iPS) cells. We established a mouse ES/iPS cell differentiation system for cardiovascular cells using Flk1+ cells as common progenitors (Nature, 2000; Circulation, 2008). Based on this system, we are performing broad researches from basic studies for cell differentiation to applied studies for cardiac regeneration. I. Basic studies for cell differentiation: we recently succeeded in demonstrating differentiation stage-specific diverse roles of cyclic AMP (cAMP)/protein kinase A (PKA) signaling during vascular cell differentiation. 1) From pluripotent stage to mesoderm, PKA accelerated differentiation timing with epigenetic silencing of pluripotent genes through methyltransferase G9a (Cell Stem Cell, 2012). 2) During endothelial cell (EC) differentiation from mesoderm, PKA increased vascular endothelial growth factor (VEGF) receptor-2 and neuropilin1 expression in vascular progenitors, which enhanced the progenitor sensitivity to VEGF and EC differentiation (Blood, 2009). 3) That was mediated by direct transcriptional cascade from cAMP-responsive element binding protein, Etv2 transcription factor, to VEGF receptors (Stem Cells, 2012a). 4) Kappa opioid receptor signaling was a novel endogenous inhibitor for PKA and EC differentiation (Blood, 2011). 5) cAMP signal induced dual activation of Notch and beta-catenin and induced arterial specification in ECs (J Cell Biol, 2010). II. Chemical biological approach: We found that an immunosuppressant, cyclosporin-A (CSA), showed a novel effect specifically acting on mesoderm cells to drastically increase cardiac progenitors as well as cardiomyocytes (Biochem Biophys Res Commun, 2009). Applying this system, we screened small molecules and found several novel compounds enhancing cardiomyocyte differentiation and proliferation. These findings would contribute to discovery for cardiac regenerative drugs and efficient induction of cardiac cells from ES/iPS cells. III. Cell therapy: We are also examining cell transplantation methods using the cell sheet technology (Shimizu, Curr Pharm Des, 2009) for cardiac regeneration. Combining our cardiovascular differentiation system and cell sheet technology, we set out to reconstitute cardiac tissue reassembled with defined cardiovascular populations, and examined the effect of the cardiac tissue sheet following transplantation. We observed that cardiac tissue sheet transplantation to rat myocardial infarction model significantly improved systolic function accompanied by neovascularization ( Stem Cells, 2012b). We extended these strategies to human iPS cells. We recently succeeded in developing efficient cardiomyocyte differentiation and purification methods in human iPS cells (PLoS One, 2011a, 2011b). Now we are examining effects of human iPS cell-derived cardiac sheet transplantation in rat and porcine myocardial infarction models. I would like to show and discuss our studies with stem cell, chemical, and vascular biology.