

The potential factors regulating endogenous regeneration.

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The regeneration of injured tissues/organs is known to be highly depended on not only the “seed = stem/progenitor cells” but also the “soil = tissue microenvironment”. By monitoring the kinetic changes of cytokines/chemokines and extracellular matrix/adhesion molecules in liver and heart of mice after experimental injuries, we have tried to find the potential factors regulating endogenous regeneration of liver and heart. Although our preliminary data suggests that some factors likely involve in the regenerative process of liver and heart after injury, serious experiments *in vitro* and *in vivo* are asked for further identification.

Biography:

1991 *M.D.*, Jiangxi Medical College, China.

2000 *Ph.D.*, Yamaguchi University, Japan.

2004 *Assistant Professor*, Yamaguchi University Graduate School of Medicine, Japan.

2008 *Research Scientist*, Cedars-Sinai Medical Center, USA.

2011 *Professor*, Nagasaki University Graduate School of Biomedical Sciences, Japan.

Cell-based therapy with modified mononuclear cells for radiation-damaged salivary glands.

Yoshinori Sumita

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Xerostomia is one of the important complications following the radiotherapy for head and neck cancer. However, unfortunately, there are no adequate treatments for patients with such irreversible glandular damages at present. Therefore, our group has recently investigated the cell-based therapies using the modified bone marrow or peripheral blood mononuclear cells. In this presentation, I will show the current progress of our approaches regarding the cell-based therapy for the radiogenic xerostomia.

Biography:

1995 *D.D.S.*, Aichi University, Japan.

2007 *Ph.D.*, Nagoya University, Japan.

2007 *Postdoctoral Fellow*, Faculty of Dentistry, McGill University, Montreal, Canada.

2009 *Assistant Professor*, Nagasaki University Graduate School of Biomedical Sciences, Japan.

2012 *Associate Professor*, Nagasaki University Graduate School of Biomedical Sciences, Japan.

2015 *Adjunct Professor*, Faculty of Dentistry, McGill University, Montreal, Canada.

Remodeling the vasculature niche in the decellularized lung scaffold.

Tomoshi Tsuchiya

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Bioengineered lungs consisting of a decellularized lung scaffold that is repopulated with a patient's own cells could provide desperately needed donor organs in the future. However, existing bioengineered lungs are fragile, in part because of their immature vascular structure. The application of adipose-derived stem/stromal cells (ASCs) improved the quality of engineered pulmonary vasculature via differentiation ability and cytokines secretion; which remodels the vasculature niche in the regenerated lung.

Biography:

1993 *M.D.*, Nagasaki University School of Medicine, Japan.

2002 *Ph.D.*, Nagasaki University Graduate School of Biomedical Sciences, Japan.

2002 *Postdoctoral Fellow*, University of California, Riverside, USA.

2008 *Assistant Professor*, Nagasaki University Graduate School of Biomedical Sciences, Japan.

2011 *Visiting Scientist*, Yale University, USA.

2010 *Associate Professor*, Nagasaki University Graduate School of Biomedical Sciences, Japan.

Regenerative medicine in digestive organ.

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Here, we introduce our inventions of regenerative medicine, mainly utilizing the cell sheet technology in digestive organ, including esophagus, liver, and islet cells of pancreas.

In clinical esophageal surgery, we have developed to apply the fibroblast cell sheet to prevent the stricture of the esophagus after endoscopic submucosal dissection. In liver and islet cell, we have demonstrated to achieve functioning cell sheet in animal model, and further trying to develop cell sheet which sufficiently function even under the skin.

Biography:

1994 *M.D.*, Nagasaki University School of Medicine, Japan.

2000 *Clinical Fellow*, Chang-Gung Memorial Hospital, Kaohsiung, Taiwan.

2002 *Ph.D.*, Nagasaki University Graduate School of Biomedical Sciences, Japan.

2005 *Assistant Professor*, Nagasaki University Graduate School of Biomedical Sciences, Japan.

2009 *Lecturer*, Nagasaki University Graduate School of Biomedical Sciences, Japan.

2016 *Associate Professor*, Nagasaki University Graduate School of Biomedical Sciences, Japan.

Harnessing micro- and nano-technologies for better cell therapies.

Ke Cheng

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No therapy currently available can reduce the size of an established scar on the heart. Cell therapy aims to alter this fixed trajectory for MI survivors: to intervene adverse heart remodeling, to reduce scar size, and to actually regenerate viable myocardial tissue. The last one and half decades witnessed the booming of stem cell therapies for multiple diseases. Our lab has been studying heart-derived cardiac stem cells (CSCs) in the past 7 years. Efficacy in cell transplantation is hampered by low rates of cell retention and engraftment in the tissue parenchyma. We have developed multiple bioengineering strategies to enhance the delivery of stem cells. Also, Stem cells must be carefully preserved to keep them alive and functioning until the time of transplant, and there are some risks involved in cell transplantation as well. We have engineered synthetic stem cells to overcome these barriers.

Biography:

2004 *B.S.*, Zhejiang University, China.

2008 *Ph.D.*, University of Georgia, USA.

2008 *Research Scientist Faculty*, Cedars-Sinai Medical Center, USA.

2010 *Assistant Professor*, Cedars-Sinai Medical Center, USA.

2013 *Associate Professor*, North Carolina State University, USA.

2016 *Adjunct Associate Professor*, UNC Eshelman School of Pharmacy, USA.

Exosomes generated from stem cells prevent cardiomyocyte apoptosis in the ischemic myocardium.

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Induced pluripotent stem cells (iPS) exhibit enhanced survival and proliferation in ischemic tissues. However, the therapeutic application of iPS cells is limited by their tumorigenic potential. We hypothesized that iPS cells can transmit cytoprotective signals to cardiomyocytes via exosomes/microvesicles. Exosomes/microvesicles secreted from mouse cardiac fibroblast (CF)-derived iPS cells (iPS-exo) were purified from conditioned medium and confirmed by electron micrograph, size distribution and zeta potential by particle tracking analyzer and protein expression of the exosome markers CD63 and Tsg101. We observed that exosomes are at low zeta potential, and easily aggregate. Temperature affects zeta potential (-14 to -15 mV at 23 °C vs -24 mV at 37 °C). The uptake of iPS-exo protects H9C2 cells against H₂O₂-induced oxidative stress by inhibiting caspase 3/7 activation (P < 0.05, n = 6). Importantly, iPS-exo treatment can protect against myocardial ischemia/reperfusion (MIR) injury via intramyocardial injection into mouse ischemic myocardium before reperfusion. Furthermore, iPS-exo deliver cardioprotective miRNAs, including nanog-regulated miR-21 and HIF-1 α -regulated miR-210, to H9C2 cardiomyocytes in vitro. In summary, Exosomes/microvesicles secreted by iPS cells are very effective at transmitting cytoprotective signals to cardiomyocytes in the setting of MIR. iPS-exo thus represents novel biological nanoparticles that offer the benefits of iPS cell therapy without the risk of tumorigenicity and can potentially serve as an "off-the-shelf" therapy to rescue ischemic cardiomyocytes in conditions such as MIR.

Biography:

1993 *M.D.*, Shanghai Jiao Tong University, China.

2002 *Ph.D.*, Fudan University, China.

2003 *Postdoctoral Fellow*, University of South Florida, USA.

2004 *Assistant Professor*, University of South Florida, USA.

2008 *Associate Professor*, Keck Graduate Institute, Claremont University Consortium, USA.

2013 *Associate Professor*, Medical College of Georgia, USA.

2017 *Professor (Tenured)*, Medical College of Georgia, USA.

E2F1 in EPC oxidative metabolism and endothelial differentiation.

Gangjian Qin

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The majority of current cardiovascular cell-therapy trials use bone marrow progenitor cells (BM PCs) and achieve only modest efficacy; the limited potential of these cells to differentiate into endothelial-lineage cells is one of the major barriers to the success of this promising therapy. We have previously reported that the E2F transcription factor 1 (E2F1) is a repressor of neovascularization following ischemic injury, but whether E2F1 regulates BM PC function is unknown. In this study, we found that ablation of E2F1 (E2F1^{-/-}) in mouse BM PCs increases oxidative metabolism and reduces lactate production, resulting in enhanced endothelial differentiation. The metabolic switch in E2F1^{-/-} BM PCs is mediated by a reduction in the expression of pyruvate dehydrogenase kinase 4 (PDK4) and PDK2; overexpression of PDK4 reverses the enhancement of oxidative metabolism and endothelial differentiation. Deletion of E2F1 in the BM increases the amount of PC-derived endothelial cells in the ischemic myocardium, enhances vascular growth, reduces infarct size, and improves cardiac function after myocardial infarction. Our results suggest a novel mechanism by which E2F1 mediates the metabolic control of BM PC differentiation, and strategies that inhibit E2F1 and/or enhance oxidative metabolism in BM PCs may improve the effectiveness of cell therapy.

Biography:

1989 *M.D./M.S.*, Tongji Medical University, China.

1992 *Lecturer*, Tongji Medical University, China.

2001 *Instructor in Medicine*, Tufts University School of Medicine, USA.

2004 *Assistant Professor*, Tufts University School of Medicine, USA.

2007 *Assistant Professor*, Northwestern University Feinberg School of Medicine, USA.

2012 *Associate Professor*, Northwestern University Feinberg School of Medicine, USA.

2016 *Professor (Tenured)*, Director of Molecular Cardiology Program, Vice Chair of Research, School of Medicine/School of Engineering, The University of Alabama at Birmingham, USA.

Bmi-1 high-expressing cells enrich cardiac stem cells and respond to heart injury.

Yucai Xie

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Bmi-1 gene is well recognized as an oncogene, but has been recently demonstrated to play a role in the self-renewal of tissue-specific stem cells. By using Bmi-1^{GFP/+} mice, we investigated the probable role of Bmi-1 in cardiac stem cells and myocardial repair after myocardial infarction. RT-PCR and flow cytometry analysis indicated that the expression of Bmi-1 was significantly higher in cardiac side population than the main population from CD45⁻Ter119⁻CD31⁻ heart cells. More Sca-1⁺ cardiac stem cells were found in Bmi-1 GFP^{hi} subpopulation, and these Bmi-1 GFP^{hi} heart cells showed the potential of differentiation into SMM⁺ smooth muscle-like cells and TnT⁺ cardiomyocyte-like cells *in vitro*. Otherwise, myocardial infarction induced a significantly increase (2.7-folds) of Bmi-1 GFP^{hi} population at one week after infarction. These preliminary data suggests that Bmi-1^{hi} heart cells are enriched in cardiac stem cells and may play a role in myocardial repair.

Biography:

1986 *M.D.*, Bengbu Medical University, China.

2002 *Associate Professor*, Ruijin Hospital, Shanghai Jiao Tong University, China.

2005 *Professor*, Ruijin Hospital, Shanghai Jiao Tong University, China.

2010 *Ph.D.*, Joint Program of Stowers Institute for Medical Research, USA and Shanghai Jiao Tong University School of Medicine, China.

2011 *Project Scientist*, Cedars-Sinai Medical Center, USA.

Stem cell therapy to prevent heart failure: Repair, Regeneration, Rejuvenation.

Ren-Ke Li

Department of Surgery, Division of Cardiac Surgery at the University of Toronto, Canada.

Heart failure results from cardiomyocyte necrosis after myocardial infarction (MI). The heart achieves limited repair through tissue resident and circulating stem cells post MI. Resident cardiac stem cells are believed to be a legacy of cardiac development, residing in the myocardium but retaining the capacity for regeneration in times of injury. We recently found inceptive resident cardiac stem cells of hematopoietic origin that can independently direct endogenous repair. Age negatively influences the cardiac environment in transplantation recipients and reduces the cardiac tissue's functional capacity for effective stem cell transplantation. Whereas the cardiac environment in a young recipient can recuperate aged stem cells, young stem cells perform inadequately in aged recipients. This paradox suggests that successful stem cell implantation for cardiac repair depends not only on the regenerative capacity of the stem cells, but also on the proper myocardial milieu. We demonstrated recently that resident cardiac stem cells of hematopoietic origin govern cardiac repair. Rejuvenation of aged bone marrow increases regenerative capacity by restoring this resident cardiac stem cell niche. Cardiac resident stem cells play an important role in restoration of cardiac function and repair.

Biography:

1978 *M.D.*, Harbin Medical University, China.

1988 *M.S.*, University of Toronto, Canada.

1992 *Ph.D.*, University of Toronto, Canada.

1993 *Assistant Professor*, University of Toronto, Canada.

2002 *Professor (Tenured)*, University of Toronto, Canada.

2011 *Fellow* of the Canadian Academy of Health Sciences.

What determines differences in regenerative abilities between mice and newts?

Takashi Takeuchi

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Mammals can not regenerate almost all major organs other than the liver, but newts can. What determines the difference? To answer the question, we have focused on cardiac regeneration and cell cycle regulation of cardiomyocytes. We found that silencing of several genes is necessary for inhibition of cardiac regeneration in mice. The mechanism is currently investigated.

Biography:

1983 *B.S.*, Kyoto University, Japan.

1991 *Ph.D.*, Nagoya University, Japan.

1991 *Research Scientist*, Mitsubishi Kagaku Institute of Life Sciences, Japan.

2001 *Principal Investigator*, Mitsubishi Kagaku Institute of Life Sciences, Japan.

2009 *Professor*, Faculty of Medicine, Tottori University, Japan.

2015 *Director*, Life Science Speciality, Graduate School of Medical Sciences, Tottori University, Japan.