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The metabolism of cell reprogramming

The Takuya Yamamoto lab shows how two factors, Zic3 and Esrrb, regulate cell metabolism for pluripotency.

During cell reprogramming, a number of molecular and cellular events must occur for the cell to become pluripotent. One example is change in the metabolism, since the pluripotent state brings new energy requirements to the cell. In its most recent work, the Takuya Yamamoto lab reports two transcription factors, Zic3 and Esrrb, have critical roles in regulating the metabolism during cell programming, providing new details about how to convert a cell to the pluripotent state.

Yamamoto explains that metabolism is an essential part of cell reprogramming. "Glycolysis and OXPHOS are partly antagonistic metabolic pathways and their balance should be strictly regulated during reprogramming," he said.

The study shows how Zic3 and Esrrb work together for this regulation. Zic3 activates glycolysis and inhibits OXPHOS. Esrrb, on the other hand, is necessary to activate OXPHOS and at the same time augments the glycolysis activation done by Zic3. This synergy, the study shows, is because Zic3 recruits Esrrb to common binding sites on a gene and may explain why other factors besides Esrrb that activate OXPHOS but do not enhance glyolysis are far less effective at reprogramming.

Other proteins have been found capable of forcing the glycolytic metabolism in cells, but using a different molecular network.

"HIF proteins facilitate reprogramming cells into the primed state by activating glycolysis," said Dr. Masamitsu Sone, who first-authored the study, "but the Zic3-Esrrb synergy works to obtain naïve state independently of HIF."

Naïve and primed pluripotency are thought to describe the state of an embryo before and after implantation into the uterine wall (i.e. before and after pregnancy), respectively. Scientists have had relative ease acquiring both states in mouse cells, but the naïve state has proven more elusive in human cells. Furthermore, both glycolysis and OXPHOS are activated in naïve cells, whereas only glycolysis is activated in primed cells. Consistently, Esrrb is known to bind to factors that promote naïve pluripotency during reprogramming, while Zic3 binds to factors associated with primed pluripotency.

Overall, the study suggests a rigid order of metabolic events that must occur to capture the naïve state, with glycolysis happening early to initiate the process and OXPHOS happening later while glycolysis is retained to complete it.

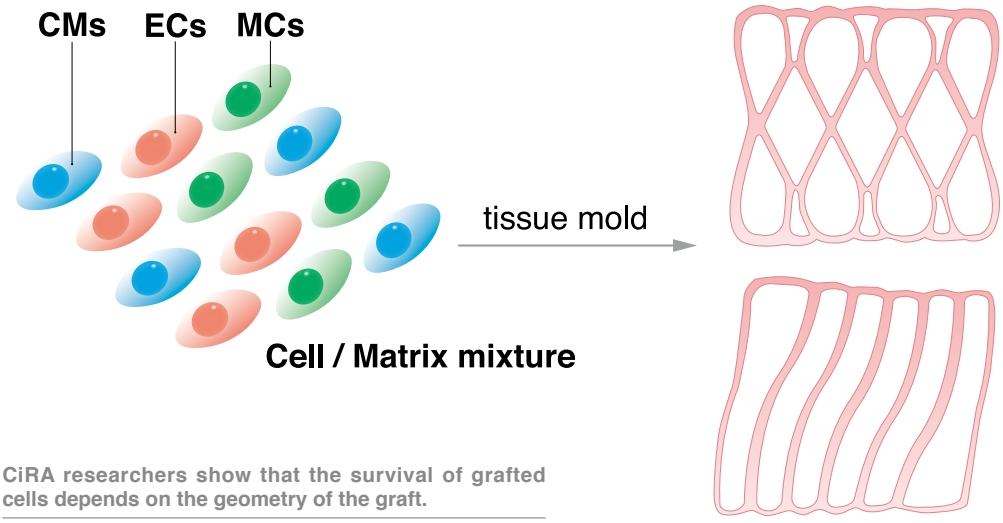
"The transition from naïve to primed pluripotency is fundamental to developmental biology," said Yamamoto. "Our findings show OXPHOS is an important event to establish naïve pluripotency and could provide new molecular pathways for this transition."

Reference

Sone M, Morone N, Nakamura T et al. (2017) Hybrid cellular metabolism coordinated by Zic3 and Esrrb synergistically enhances induction of naive pluripotency. *Cell Metabolism* 25(5): 1103 DOI: 10.1016/j.cmet.2017.04.017

Bioengineering iPSCs for heart therapy

The Jun Yamashita lab has two new reports that push iPSCs toward regerative medicine for the heart.



CiRA researchers show that the survival of grafted cells depends on the geometry of the graft.

The geometry of the graft affects cell survival

To translate iPS cells to new regenerative medicine for the heart, CiRA Professor Jun Yamashita has had a longstanding collaboration with Professor Bradley B. Keller, a pediatric cardiologist at the University of Louisville (United States). In their latest publication, the two labs give evidence that transplantation of their engineered cardiac tissue (ECT) made from human iPS cells could have ameliorative effects on heart failure. Key to the therapeutic benefits is the geometry and cellular components of the custom polymer molds on which the ECT are synthesized.

“ECT transplants work excellently in rats. Generating large enough ECTs that function in humans is the next step,” said Yamashita.

Two major problems lie in the clinical application of ECT. First is the production of enough heart cells and second is shaping the ECT to maximize cell function. The first problem can be solved with iPS cells, of which Yamashita is an expert, and the second can be solved with bioengineering, which is why Professor Bradley B. Keller of Louisville joined the project.

“My lab and Jun’s lab have been working together many years on innovative iPS heart therapies,” said Keller.

To identify the best conditions for ECT fabrication, tissue molds of the same size but of different patterns were loaded with different numbers of cells.

“Asymmetrically shaped ECTs could vary the mechanical stress or nutrition supply to the cells,” said Yamashita.

Unexpectedly, the transplantation into rat hearts of ECT loaded with fewer cells resulted

in better structural and functional heart recovery. Yamashita surmised that loading the mold with more cells could cause competition for oxygen, which would lead to suboptimal performance.

Finally, another factor that has limited their ECT is the maturation of the resulting heart cells.

"Normally, heart cells derived from stem cells are of the fetal type," said Yamashita.

Fetal heart cells and adult heart cells show different beating and force generation, which compromises the quality of the recovery following the transplantation. The study shows that reducing the asymmetry of the polymer mold corresponded with more maturation, but the reasons remain unknown.

"Our ECTs are scalable, so we should be able to make sizes large enough for patients. They also show good structure, function, and maturation. What we do not yet understand are the biological factors responsible for recovery after implantation onto the heart," said Keller.

New protocol to generate endothelial cells

The prospect of growing organs in the lab using iPS cells has the potential to save countless patients who have no option but organ transplantation. One commonality in all organ generation is the need for endothelial cells that form blood vessels. Unfortunately, despite their ubiquity in the body, the generation of endothelial cells from iPSCs has proven challenging. In a new report, the Jun Yamashita lab has made significant gains on this problem by reporting the "stimulation-elimination" method.

To induce the differentiation of iPSCs to endothelial cells, the lab stimulated iPS cells with two factors, VEGF and cAMP. The resulting endothelial cells showed good function, but a major problem remained: Only about 70% of cells were transformed into endothelial cells.

"For regenerative medicine, the purity and viability of the cells must be very high," said Yamashita. "We can purify the cells with antibodies, but many cells are lost, and purified cells may be not so viable."

Interestingly, the Yamashita team found that a certain population did not respond to the stimulation. "We do not know why non-responder cells did not differentiate," said Takeshi Ikuno, who first-authored the study.

Ikuno discovered that removing non-responder cells before the stimulation (stimulation-elimination) secured an endothelial cell population of almost 100%. However, whether the endothelial cells could be used for organ generation was not clear. Endothelial cells can be further divided into arterial, venous, or other tissue-specific endothelial cells based on the direction of blood flow to and from the heart. The group shows that with further manipulation the procured endothelial cells have the potential to specify into any of these endothelial types.

"Our cells are before the stage in which they decide what vascular type they form. Taking the arterial, venous, or other tissue-specific function is an important feature of our endothelial cells," said Yamashita.

Reference

Ikuno T, Masumoto H, Yamamizu K et al. (2017) Efficient and robust differentiation of endothelial cells from human induced pluripotent stem cells via lineage control with VEGF and cyclic AMP. *PLOS ONE* 12(3): e0173271 DOI:10.1371/journal.pone.0173271

Nakane T, Masumoto H, Tinney JP et al. (2017) Impact of cell composition and geometry on human induced pluripotent stem cells-derived engineered cardiac tissue. *Sci Rep* 7:45641. DOI:10.1038/srep45641

Cell therapies for diabetes benefit from anti-allergy drugs

The Kenji Osafune lab finds sodium cromoglicate, a cheap compound used in anti-allergy drugs, could differentiate iPS cells to islets cells.

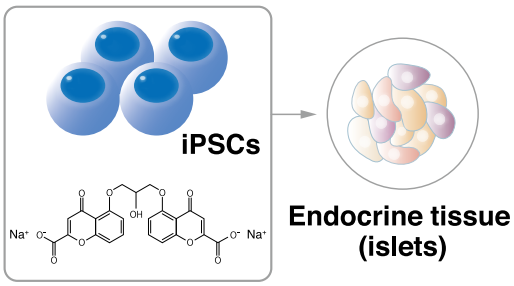
Despite its frequency, type I diabetes can be treated effectively with the transplantation of islet cells or whole organ pancreas. The problem is that there are few donors for these transplants, which has led scientists to seek ways to prepare islet cells in the lab. In its latest study, the Professor Kenji Osafune lab has found that sodium cromoglicate is effective at inducing iPS cells to differentiate into islet cells.

"Transplantation therapy is limited by donor shortage and tissue rejection. Differentiating iPS cells into islet cells could solve this problem," he said.

The ability to prepare human islet cells from iPS cells already exists, but the costs and time make them clinically impractical.

"Small molecule inducers are preferred to differentiate iPS cells because they are cheap," noted Osafune.

Searching for these compounds, his lab found sodium cromoglicate promotes iPS cell differentiation to tissue. Sodium cromoglicate is not unknown in the medical world, as it is commonly used in anti-allergy drugs.



The addition of sodium cromoglicate improves the differentiation of iPSCs to pancreatic cells.

Osafune was not surprised that a substance affecting the immune system could also play a role in islet cell production. "Many compounds affect many systems in the body. It is why as a doctor I always have to consider side effects," he said.

The pancreas can be divided into two sections. The exocrine pancreas is responsible for food digestion, while the endocrine pancreas is responsible for insulin secretion. Mixing the two in cell transplantations could compromise treatment. Osafune found that sodium cromoglicate biased the differentiation of iPS cells to endocrine pancreas, suggesting the protocol minimized the risk of contaminating cells.

"Clinical therapies depend not only on a large cell population, but also a homogeneous population," he said.

At the moment, the number of islet cells produced by sodium cromoglicate is modest compared to methods too expensive for clinical application. However, using sodium cromoglicate, Osafune expects to identify specific molecular pathways that may enhance the differentiation of iPS cells to islet cells. New compounds that target this signaling could produce more islet cells in the lab.

"We found that sodium cromoglicate depresses BMP signaling. Modulating this signaling may increase the number of islet cells," he said.

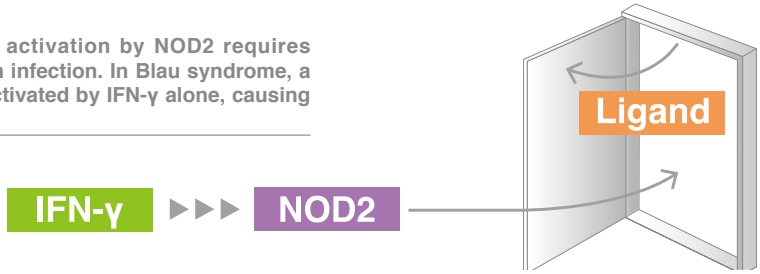
Reference

Kondo Y, Toyoda T, Ito R et al. (2017) Identification of a small molecule that facilitates the differentiation of human iPSCs/ESCs and mouse embryonic pancreatic explants into pancreatic endocrine cells. *Diabetologia* DOI: 10.1007/s00125-017-4302-7

A new drug target for Blau syndrome

The Megumu Saito Lab reveals how a mutation in Blau syndrome patients leads to excessive inflammation.

In healthy subjects, immune activation by NOD2 requires both IFN-γ and the ligand of an infection. In Blau syndrome, a mutation allows NOD2 to be activated by IFN-γ alone, causing autoimmune reactions.



Blau syndrome is a rare inflammatory disorder with little treatment that primarily affects the skin, joints, and eyes, and strikes its victims at preschool age. The cause of Blau syndrome is associated with mutations in the NOD2 gene. The NOD2 protein is a receptor that interacts with ligands found in bacteria to initiate an inflammatory response that kills the bacteria. However, in Blau syndrome patients, NOD2 activates the inflammation absent infection.

"Many studies have suggested IFN-γ contributes to Blau syndrome, but its effects on chronic inflammation and NOD2 is unclear," said Associate Professor Megumu Saito.

In healthy immune systems, IFN-γ primes macrophages to attack an infection by increasing NOD2 production and thus an inflammatory response. Saito shows, however, that in Blau syndrome patients, NOD2 triggers inflammation following IFN-γ stimulation independent of infection.

Using macrophages made from Blau syndrome patient iPS cells, Saito shows that IFN-γ increased NOD2 levels as expected, but that NOD2 went on to automatically produce an inflammatory response regardless if infection had occurred. To validate these findings, his team then forced the NOD2 mutation into iPS cells from healthy donors using CRISPR-Cas9 genome editing technology, finding that macrophages made from these cells showed the same deviant inflammatory properties.

"Our analysis showed that untreated patient macrophages are in a different state from untreated healthy macrophages. Therefore, the inflammation response is different when the macrophages are primed with IFN-γ," explains Saito.

Interestingly, macrophages from patient and healthy donors responded similarly when stimulated with IFN-γ and infection, a result that Saito struggles to explain.

"It is paradoxical. One explanation could be that NOD2 uses multiple pathways to activate inflammation. Blau syndrome patients may be biased toward a ligand-independent mechanism," he said.

Saito added the study implies that preventing IFN-γ activation could benefit patients.

"Blocking IFN-γ signaling could be a potential treatment for managing chronic inflammation."

Reference

Takada S, Kambe N, Kawasaki Y et al. (2017) Pluripotent stem cell models of Blau syndrome reveal an IFN-γ-dependent inflammatory response in macrophages. *J Allergy Clin Immunol* DOI:10.1016/j.jaci.2017.04.013

Synthetic biology towards clinical application

The Hirohide Saito laboratory reports RNA devices and other technology to control cell behavior.

CRISPR-Cas9 gene circuits

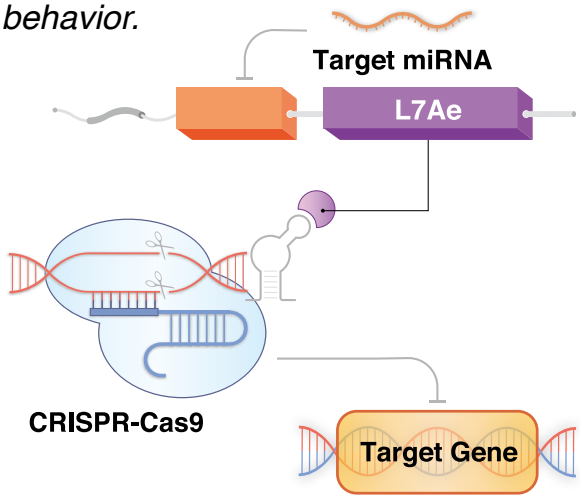
The discovery of the CRISPR-Cas9 system has made gene editing simple and precise. Once inside the cell, the Cas9 protein is guided into the nucleus where it edits the target gene. While powerful, scientists struggle to assure that the system will only edit specific cells of a mixed population. The Hirohide Saito lab now reports new synthetic biotechnology that achieves this goal.

The new biotechnology tool, miR-Cas9 switch, is a variation of the miRNA switch, which Saito first reported two years ago and describes as, "genetic circuits that control gene expression in response to miRNA. We can design a switch that responds to miRNA exclusive to a cell type, so that the gene is expressed or not expressed in only that type."

miRNA switches are composed of a target site that binds to a specific miRNA sequence and RNA that codes for a specific protein, such as Cas9. "We can change the target site and the RNA sequence arbitrarily and independently," he said.

Knowing this, Moe Hirosawa, a graduate student in the Saito lab, investigated whether, "we can control gene editing in different cells by making the expression of Cas9 dependent on our miRNA switch."

Hirosawa prepared a Cas9 protein that edits the green fluorescent protein (GFP) gene and a miRNA switch that controls Cas9 expression. Cells that did not express Cas9 protein fluoresced green, while those that expressed Cas9 did not. To regulate the Cas9 expression, he set the target



New RNA technology regulates the CRISPR-Cas9 system to edit the genome of target cells from a mixed population.

site to one that binds miR-302a, a miRNA that is found at significantly higher levels in human iPS cells than other cell types.

Transfecting this miR-Cas9 switch into a mixture of iPS cells and HeLa cells, he found only the former fluoresced green. By changing the target site to one that binds to miR-21, he could fluoresce HeLa cells only, thus activating the CRISPR-Cas9 system in selected cell types.

However, in this current design, the miR-Cas9 switch only edits a gene if miRNA does not bind to the target site, making it an OFF switch. To create an ON switch, further modifications were needed.

"We added a RNA-binding protein component to the switch. This turned the switch from OFF to ON when miRNA binds to the mRNA," said Saito.

The team believes that though their technology is preliminary, it could provide an effective way to selectively control gene editing and cell fate.

Engineering RNA tools with higher selectivity

A major goal of synthetic biology is the design of gene circuits that control cell behavior, but "many gene circuits depend on adding foreign DNA to the cell, which risks mutating the cell," said Saito.

RNA has a shorter lifetime than DNA and does not enter the cell nucleus, thus avoiding mutations. In another example of his RNA technology, Saito's group has published a device that can respond to the expression of LIN28A, a protein associated with stemness and cellular reprogramming.

"LIN28A has an important role in self-renewal. It is a good protein to choose if you want to target iPS cells," he said.

"Aptamers" describe RNA sequences that bind to target ligands such as proteins and are used by bioengineers to control cellular behavior. Natural aptamers for LIN28A are known, but the protein binding ability is too weak for Saito's aims.

To enhance the binding, first author Shunsuke Kawasaki engineered better aptamers.

"We wanted to stabilize the secondary structure by increasing the number of GC pairs in the stem region, while at the same time not compromising the portion responsible for Lin28A binding," he said.

The modified aptamer was the basis for their device to control gene expressions depending on the amount of LIN28A. In addition, Kawasaki and Saito could deliver the device into living cells, making both device and delivery an all RNA system. Using this technology, they succeeded in distinguishing iPS cells from differentiated cells.

"Because our device is all RNA and because our delivery method is all RNA, it may be safe for use in humans," said Saito.

Apoptosis by aggregation

One challenge delaying the transition of stem cell therapies from the bench to the bedside is the homogeneity of the cell population. While stem cells are used as the cell source for the therapy, they are never directly injected into the patient because of their tumorigenicity. Therefore their removal before cells are transplanted to a patient is imperative. Several technologies exist for separating cells, but they incur high financial cost and damage to the cells.

In several diseases like Alzheimer's, cells die because of protein aggregation due to deviant protein folding. Dr. Yi Kuang, a member of the Saito lab, wondered if it would be possible to induce similar toxic aggregation in stem cells.

"Peptide aggregation can cause cell death. We used alkaline phosphatases (ALP) to trigger peptide aggregation in iPS cells," she said.

ALP are highly expressed in iPS cells, but only at very low levels in somatic cells. Kuang hypothesized that exposing cells to peptides that aggregate after ALP exposure would be toxic only to iPS cells.

Indeed, Kuang found a peptide that can efficiently kill iPS cells within 2 hours but has little effect on somatic cells. She injected a mixture of iPS cells and cardiomyocytes into mice. The recipient mice developed tumors unless the mixture was treated with an ALP-sensitive peptide prior to the transplantation, indicating that the peptide selectively aggregated on undifferentiated cells.

Reference

Hirosawa M, Fujita Y, Parr CJC et al. (2017) Cell-type-specific genome editing with a microRNA-responsive CRISPR-Cas9 switch. *Nucleic Acids Res* DOI: 10.1093/nar/gkx309

Kawasaki S, Fujita Y, Nagaike T et al. (2017) Synthetic mRNA devices that detect endogenous proteins and distinguish mammalian cells. *Nucleic Acids Res* DOI: 10.1093/nar/gkx298

Kuang Y, Miki K, Parr CJC et al. (2017) Efficient, Selective Removal of Human Pluripotent Stem Cells via Ecto-Alkaline Phosphatase-Mediated Aggregation of Synthetic Peptides. *Cell Chem Biol* DOI: 10.1016/j.chembiol.2017.04.010

Cancer drugs for ALS therapy

The Haruhisa Inoue Lab uses iPS cells to show anti-cancer drug repositioning has positive effects against ALS.

Amyotrophic lateral sclerosis (ALS) is a devastating disease that rapidly kills motor neurons. Patients normally live only a couple of years after diagnosis, and even the best drugs extend lifetimes just six months or so.

Moreover, ALS is a heterogeneous disease, meaning its cause is diverse. "Only 10% of ALS cases can be attributed to a genetic mutation," said CiRA Professor and Neurologist Haruhisa Inoue, and even that 10% contains various mutant causes. This heterogeneity makes standard drug screening all the more difficult. Inoue therefore decided to use phenotypic screening to find new candidate drugs. "The one common phenotype in ALS is the death of motor neurons," he said.

His lab prepared iPS cells from the skin or blood cells of patients suffering from different causes of ALS. The researchers then differentiated the iPS cells to motor neurons and conducted drug screenings. Candidate drugs showed a proclivity to target two particular enzymes.

"Srk and c-Abl11 are enzymes that have been associated with various cancers," explained Inoue. "Several anti-cancer drugs inhibit their function."

"ALS motor neurons show an accumulation of protein misfolding. In healthy cells, proper autophagy would prevent the misfolding," he added.

Treating the cells with one candidate drug, bosutinib, promoted autophagy and reduced the amount of protein misfolding. Tests in ALS mouse models showed that bosutinib could extend the lifetime of the mice, again by reducing the amount of protein misfolding. Bosutinib has been approved for patient use in multiple countries, but as an anti-cancer drug. Thus, the bosutinib hit represents not an example of drug discovery using iPS cells but of drug repositioning.

Professor Haruhisa Inoue (left) and first author Assistant Professor Keiko Imamura

Drug repositioning describes the use of a drug already approved to treat one disease for treatment on another. It is estimated that drug repositioning can be one third the cost of drug discovery, because it avoids exhaustive human tests that measure dosage levels and side effects.

CiRA Director Shinya Yamanaka views these findings as another example of the power of iPS cell technology for medical innovation.

"The combination of drug repositioning and patient iPS cells will significantly lower the cost of drug development. This will encourage more companies to invest in difficult diseases and bring new treatments to patients faster."

Reference

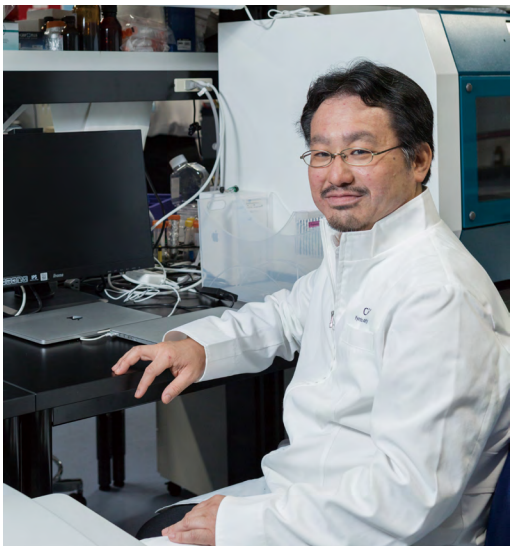
Imamura K, Izumi Y, Watanabe A et al. (2017) The Src/c-Abl pathway is a potential therapeutic target in amyotrophic lateral sclerosis.
Sci Transl Med 9(391) DOI:10.1126/scitranslmed.aaf3962

Greetings from the
Makoto Ikeya Lab

Dept. of Life Science Frontiers

As the main institute of iPS cell research in Japan, many may mistakenly think that the primary focus at CiRA is the reprogramming mechanism that converts somatic cells to pluripotent stem cells. In truth, about half of the CiRA faculty is researching development and using iPS cells to understand how multiple cell lineages derive. Our lab is studying development of ectoderm lineage and how deviations in developmental processes lead to related diseases. One reason we focus on ectoderm is our work on neural crest cells (NCCs). These cells represent an embryonic migratory population that differentiates to a wide range of cell lineages. We propose NCCs are an essential multipotent intermediate from ectoderm to ectoderm lineage. By stabilizing the derivation of NCCs from iPSCs, we propose using this point in the developmental hierarchy to derive key progenitors for specific organs and tissues and using them as a platform for new drug discovery and regenerative medicine. This research is a basis for our participation in the T-CiRA project, which is a massive collaboration between CiRA and Takeda Pharmaceuticals that seeks to translate basic research into drugs in less time and lower cost.

NCCs are also attractive from the perspective of basic development science. Because the final lineage of NCCs is heavily influenced by the final migratory destination, we anticipate they will reveal vital signaling factors for lineage derivation. In addition, because NCCs are mesenchymal cells and because they derive from ectoderm, they make a good model for studying the epithelial-mesenchymal transition (EMT). EMT is a fundamental process for the development of multiple organs, but much about its function is unknown. In addition, the reversal of EMT is considered essential for cell reprogramming.



Makoto Ikeya (Photo: Ko Sasaki)

Another cell type of focus in our laboratory is mesenchymal stem cells (MSCs), which are derived from both NCCs and mesodermal cells. MSC is an interesting cell in that it can give rise to multiple cell types such as bone, cartilage, and adipose. Although MSCs are called stem cells, they go into senescence and stop proliferation after several passages. How to maintain the stemness of MSCs is a pressing problem.

Finally, although we consider ourselves a developmental biology lab, our approach has led to new clinically-related findings. We have identified new signaling pathways that drive fibrodysplasia ossificans progressiva (FOP), a devastating disease in which the immune system triggers the conversion of cartilage to bone to literally ossify the patient, and new candidate drug targets that could prevent the pathology. Our plan is to build on our NCC model by expanding our disease targets.

Who decides what is permissible? Genome editing of human embryos

by Associate Professor Yoshimi Yashiro, Uehiro Research Division for iPS Cell Ethics

In my previous essay, I discussed issues surrounding genome editing. By chance, the topic has since received inordinate media attention, bringing it to the forefront of scientific research to the general public. In some ways, genome editing can be viewed as "hot fashion" in the world of science policy and bioethics. Arguably the biggest debates arise with discussion on how this technology should be applied to the embryo. Current consensus refuses any embryos that have undergone genome editing to be used for impregnation.

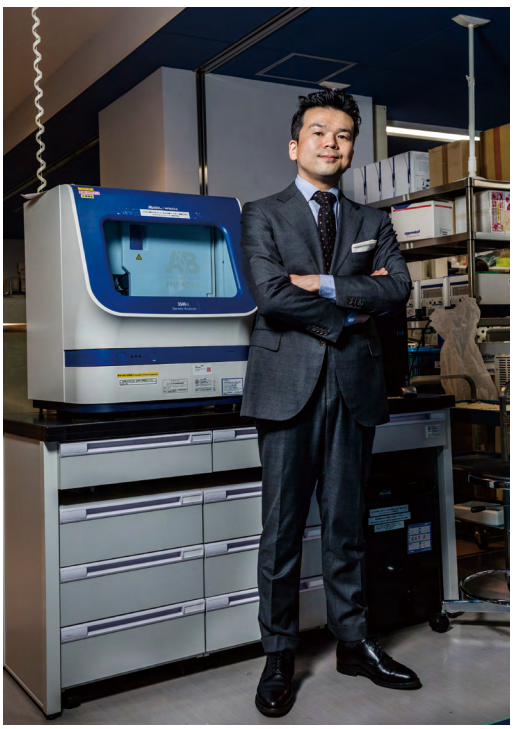
But what about defective embryos available for basic research? How should these be used? On April 19, the Japanese government made an announcement with regards to responsible embryo research. Until then, with regards to other controversial science policy, the government had worked with academic societies to formulate guidelines, and originally this was to be the case for genome editing of the embryo as well. However, in practice, the government was too deferential to academic societies, abnegating responsibility and frustrating scientists who felt they were not receiving sufficient support.

Of course, the government should not completely absolve itself of responsibility for policy on such an important matter. Yet it is the scientists who are using the technology and best informed about its potential benefits and risk. According to the British sociologist Geoffrey Millerson, experts and professionals are capable of self-governing. Too much government influence makes policy vulnerable to political interests and not scientific ones and puts into question the whole purpose of having expert groups.

At the same time, neither would we want scientists to have too much influence on policy making. The current situation is reminiscent of the discussions surrounding human ES cells. Then, it could be argued, researchers in regenerative medicine and embryology were not sufficiently consulted.

The notion of a country taking responsibility gives the sense of security. However, this is not always true, especially when policy could have potentially dangerous impact. In matters like genome editing of the embryo, a proper balance of opinions from experts and the general public is needed.

These are matters that researchers and society should give consideration.



Yoshimi Yashiro (Photo: Ko Sasaki)

CiRA officially opens its 3rd building

The Facility for iPS Cell Therapy (FiT) at CiRA is a cell-processing facility that provides clinical-grade iPS cells to organizations developing novel cell therapies. FiT is arguably CiRA's most important venture, as it is currently recognized as the primary cell-processing facility for the country and provided the iPS cells used for the world's first iPS-cell based therapy along with cells to other projects and organizations that are developing clinical application. In response, a third CiRA research building was completed May 22 that more than doubles the space of FiT and provides three additional floors of lab space for individual CiRA groups and two floors of animal facilities. The official opening was attended by several dignitaries including a senior official of the Ministry of Education, Culture, Sports and Technology (MEXT), Kyoto Deputy Governor Akimasa Yamashita, and Kyoto Mayor Daisaku Kadokawa, who distinguished himself by wearing a Japanese kimono.

Several dignitaries join CiRA Director Shinya Yamanaka at the opening of CiRA's newest research building

CiRA Marathon teams

Many CiRA members partake in annual marathons across Japan such as those in Osaka and Kyoto, in part as means to fundraise. For those intimidated by the distance, CiRA researcher Kenji Ito and administrator Miya Nishida organized two CiRA teams that participated in the 4th Biwako Relay Marathon on May 28. Each team had 9 members and ran a total marathon distance.

Ito has been organizing for years a running club and welcomes anyone regardless of a desire to compete. The group has grown to over 20 members. Weekly runs are every Thursday night along the Kamo River.

"I don't like to call it 'the CiRA Running Club'. I like to run and I like to run with people who like to run," said Ito.

"The average number depends on the season. Now the weather is good, so we see 5-10 people. Maybe as it gets hotter we will see fewer people." Ito had been running well before joining CiRA. Nishida, on the other hand, only discovered this passion a year ago and is slowly building confidence to running an entire marathon on her own.

"Some members who run marathons were telling me I should try," she said.

The two 9-runner teams finished consecutively 18th and 19th among the 80 teams.

CiRA at the Biwako Relay Marathon

Diabetes symposium at Kyoto University

Professor Tim Kieffer of the University of British Columbia (Canada) ended his one-year sabbatical at CiRA in June. In collaboration with a biotechnology company in North America, he is anticipating starting a new clinical trial of a stem cell therapy for diabetes later this year.

"I came to CiRA to be immersed in an environment of stem cell science, to learn new technologies, and to establish new collaborations," he said.

Besides achieving these goals, Kieffer leaves his sabbatical having co-organized the Kyoto Diabetes Mini-Symposium. The June 5 event was initially intended to be an informal get-together of local cell therapy researchers interested in diabetes but grew into one with over 20 speakers from across the country including CiRA faculty Kenji Osafune, Knut Woltjen and Yoshiya Kawaguchi.

"At first I planned for Tim to give a talk at CiRA, but then thought instead to arrange a diabetes workshop with CiRA and hospital colleagues as speakers. We asked Inagaki-sensei to join, and that's when the event got big," said Woltjen.

Inagaki-sensei is Nobuya Inagaki, Director of Kyoto University Hospital. Kieffer says Inagaki was pivotal in facilitating his sabbatical at CiRA, connecting him with Osafune, Woltjen and CiRA Director Shinya Yamanaka.

"He was the catalyst for me coming here. I spoke to him in 2015 at a conference in Vancouver and told him I was interested in coming to CiRA. He made the introduction to Kenji Osafune," said Kieffer, who added that he and Inagaki have co-authored several papers during his one year at CiRA.

With Inagaki behind them and with the cooperation of Associate Professor Daisuke Yabe also from Kyoto University Hospital, the team was able to convince the Japan Society for the Promotion of Science (JSPS) to financially support the attendance of several trainees. Yabe and Osafune reached out to industry for additional funding.

Kieffer remarked that attracting more than 75 participants from across Japan was quite impressive considering the short timeframe between nascent idea and actual event.

"We didn't give a lot of advance notice but nevertheless the symposium was a great success, with a full day of outstanding presentations. We have considered expanding our invitations next time to include scientists in China and Korea."

Kieffer and Woltjen are writing a review in the Journal of Diabetes Investigation on diabetes therapies highlighted at the symposium that is expected out in the next month or two.

Symposium speakers

The Temples and Shrines of Kyoto

Kitano Tenmangū

As with many of the temples and shrines in Kyoto, the history of Kitano Tenmagū Shrine reaches back over a thousand years. It was dedicated to Sugawara no Michizane, a scholar and statesman. Michizane would eventually be ostracized from the court due to political machinations. His death was followed by an assortment of natural disasters that were attributed to his unsettled spirit, leading to a number of posthumous titles that were intend to assuage him. Because of Michizane's scholarship, the shrine is frequented by students, especially during the exam season when they give prey for excellent test results.

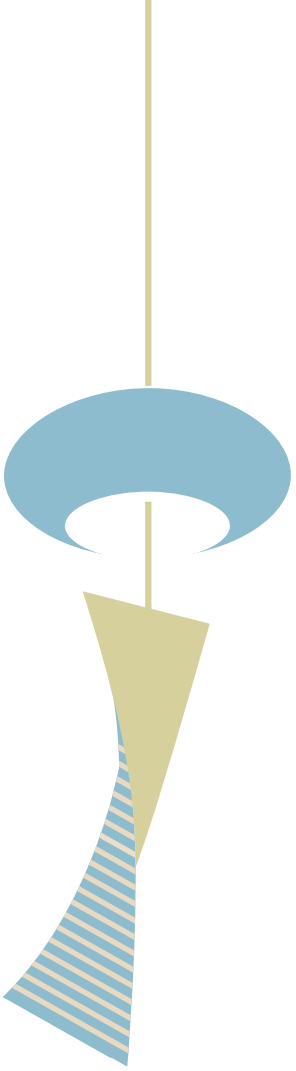
The shrine's most distinguishing marking is arguably at the very edge of the southern property, where a large concrete torii (鳥居) dominates the modern street and welcomes visitors. The following walk along a stone road adorned by lanterns brings anticipation, but leads to a relatively modest brown entrance. Nevertheless, the shrine seems to always be busy in part because it is free, the number of Japanese sweet confectionery shops along the periphery, and the old promenade to the east that is dotted by kimono-wearing residents.

Southern gate

CiRA International Symposium

Mark the date. Nov. 6-8, CiRA will host its next international symposium in Kyoto. Please check the CiRA website regularly for announcements about speakers and abstract deadlines.

http://www.cira.kyoto-u.ac.jp/e/international_symposium



Differentiate

To all cells in the body

What a miracle

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