ASHBi Key Investigators' Profiles
講演者研究内容のご紹介

Kyoto University
Institute for the Advanced Study of Human Biology

京都大学高等研究院
ヒト生物学高等研究拠点

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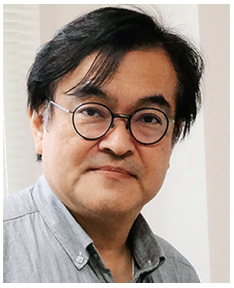
Key Investigators

SESSION 1

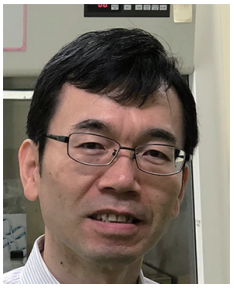


Tadashi Isa
伊佐　正

Motoko Yanagita
柳田　素子

SESSION 2

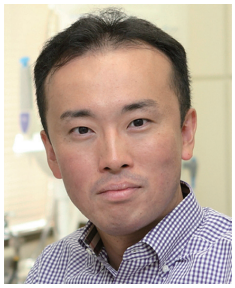
Anne
Ferguson-Smith



Masatsugu Ema
依馬　正次

Takuya Yamamoto
山本　拓也

SESSION 3



Mitinori Saitou
斎藤　通紀

Guillaume Bourque

Takashi Hiiragi
柊　卓志

Mototsugu Eiraku
永樂　元次

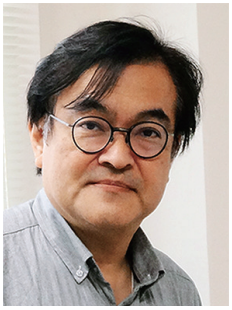
SESSION 4

Yasuaki Hiraoka
平岡　裕章

Seishi Ogawa
小川　誠司

Hideki Ueno
上野　英樹

Misao Fujita
藤田　みさお



Tadashi Isa

Professor

Graduate School of Medicine,
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Evaluation Systems Neuroscience

Resarch Overview

Motor systems are developed for individual animal species to best fit their living environment. We are studying the neural circuits controlling the fine motor skills, which are especially developed in higher primates, that is, dexterous hand movements and saccadic eye movements using non-human primate model. We also study the cognitive functions related to the control of these movements, such as attention and motivation, and also the mechanism of functional recovery after injury of the neural systems. First, dexterous hand movements, the ability to independently control individual fingers, are specially developed in higher primates and considered to be based on the interplay between the evolutionally novel pathway, that is the direct connection from the motor cortex to spinal motor neurons, and other old descending motor pathways, originating from the brain stem and spinal cord. We are studying how these parallel systems are coordinated with each other. We are also studying how the evolutionally old systems can compensate for the impaired function of the new systems in case of brain and spinal cord injury. Second, saccadic eye movements are normally controlled by visual inputs through the visual cortex. However, it is known that after damage to the visual cortex, saccadic eye movements can recover, however, without conscious perception of the objects, the phenomenon called “blindsight”. We have clarified that blindsight is supported by phylogenetically old visual systems centered on the superior colliculus in the midbrain. We are studying the large-scaled network underlying blindsight and how kind of functions are preserved and impaired and state of consciousness in blindsight. In ASHBi, on top of these preceding studies, we will try to elucidate the genetic basis of the evolution of these motor systems using single cell RNA-seq of homologous neurons in rodents and primates, and generating and analyzing the knock-down macaque monkeys by genome editing of the key genes for the evolution.

研究概要

運動を制御する神経系はそれぞれの動物種が自ら生活する環境に最もよく適合するように発達しています。私たちは高等霊長類において特に発達している精緻な運動系、つまり手の巧緻運動と急速眼球運動を制御する神経回路、さらにこれらの運動の制御に関わる注意や動機付けなどの認知機能、そして関連する神経回路の損傷後の機能回復のメカニズムを、主として非ヒト科霊長類モデルを用いて研究してきました。まず、手の巧緻運動について、個々の手指を独立して制御する能力は特に高等霊長類で発達していますが、それはこれらの種において固有に発達した、大脳皮質運動野と脊髄運動ニューロンを直接つなぐ進化的に新しい経路と、進化的に古い、脳幹や脊髄に由来する経路の相互作用によって制御されているとされています。私たちこれら並列する回路がどのように協調して作動しているか、また脳や脊髄の損傷によって「新しい経路」が損傷された場合に「古い経路」がどのように機能代償するかを研究しています。次に急速眼球運動は、通常は大脳皮質視覚野を介する視覚入力によって制御されていますが、視覚野が損傷された後は、系統発生的に古い視覚システムである中脳の上丘によって代償されることで、視覚的意識を伴わないかたちで機能回復することが知られており、その能力は「盲視」と呼ばれています。私たちは盲視に関わる大規模な神経ネットワークと、そこにどのような認知行動機能が残されているのか、また視覚的意識がどのような状態になっているのかを研究してきました。そして私たちは今回、ASHBi において、これまでの研究を基盤として、げっ歯類と霊長類の相同神経細胞の単一細胞の遺伝子発現解析と、そこで明らかになる「進化の鍵となる遺伝子」を操作したゲノム編集マカクザルモデルの作製とその解析を通じて、これらの運動制御系の進化の基盤となる遺伝子機構を明らかにすることを目指しています。

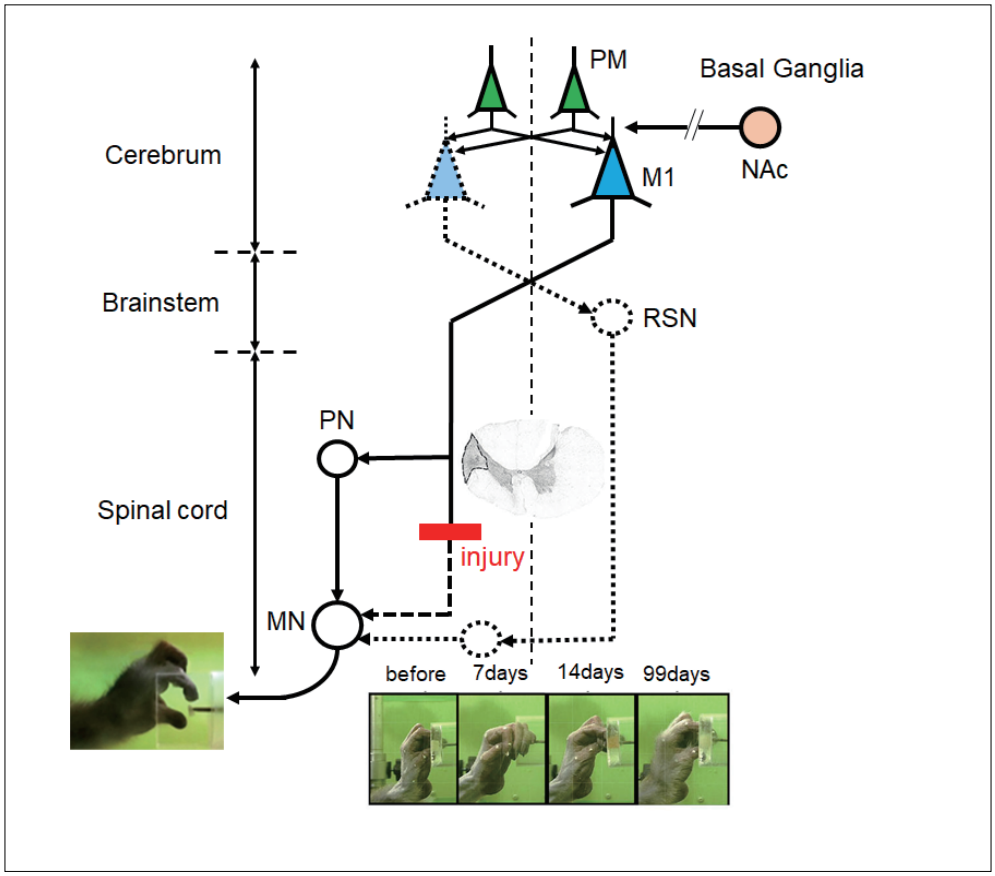


Figure 1

Recovery of dexterous hand movements after lesion of the direct connection from the primary motor cortex (M1) to hand motoneurons (MNs)（red line）. Hand movements are once impaired, but recover in 1-3 months. Abbreviations; NAc = nucleus accumbens, PN = propriospinal neurons, PM = premotor cortex, RSN = reticulospinal neurons

図 1

一次運動野 (M1) から手の筋肉の運動ニューロン (MNs) への直接結合の切断（赤線）からの手の巧緻運動の機能回復。略語 ;NAc= 側坐核、PM= 運動前野、PN= 脊髄固有ニューロン、RSN= 網様体関図路ニューロン

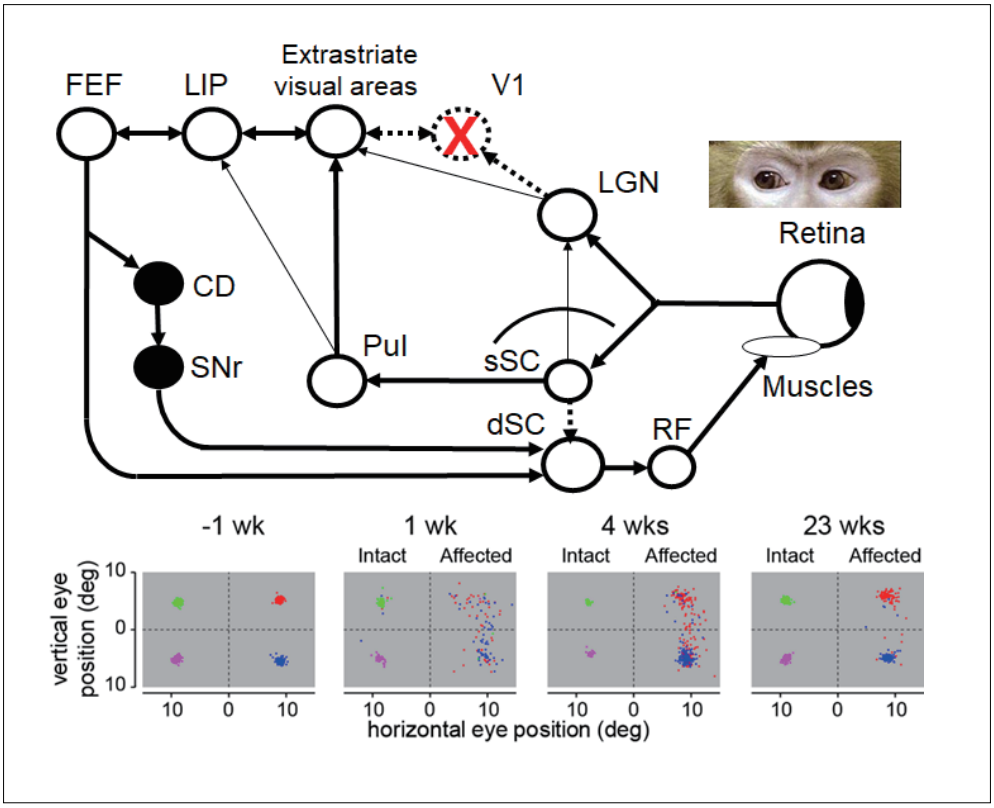


Figure 2

Recovery of saccadic eye movements after unilateral lesion of the primary visual cortex (red cross), the time course of which is shown below. After V1 lesion, the lateral geniculate nucleus（= LGN）-extrastriate cortical pathway, and superficial layer of the superior colliculus (sSC)-pulvinar (Pul)- extrastriate cortical pathway are involved in the recovery. Abbreviations; CD=caudate nucleus, dSC = deeper layer of the superior colliculus, FEF=frontal eye field, LIP=lateral intraparietal area, RF=reticular formation, SNr=substantia nigra pars reticulalta are once impaired, but recover in 1-3 months. Abbreviations; NAc = nucleus accumbens, PN = propriospinal neurons, PM = premotor cortex, RSN = reticulospinal neurons

図 2

一次視覚野の片側損傷（赤×印）後の眼球サッケード運動の機能回復。回復のタイムコースは下記参照。一次視覚野の損傷後、外側から高次視覚野ないしは上丘浅層（sSC）―視床枕から高次視覚野に至る経路が関与している。略語 ; CD= 尾状核、dSC= 上丘深層、FEF= 前頭眼野、LIP= 外側頭頂間溝、RF= 脳幹網様体、SNr ＝黒質網様部

Selected Publications / 主要な論文

Isa, T. (2019) Dexterous hand movements and their recovery after central nervous system injury. *Annual Review of Neuroscience*, in press.

Kinoshita, M., Kato, R., Isa, K., Kobayashi, K., Kobayashi, K., Onoe, H. and Isa, T. (2019) Dissecting the circuit for blindsight to reveal the critical role of pulvinar and superior colliculus. *Nature Communications*, 10(1):135. doi: 10.1038/s41467-018-08058-0.

Tohyama, T., Kinoshita, M., Kobayashi, K., Isa, K., Watanabe, D., Kobayashi, K., Liu, M. and Isa, T. (2017) Contribution of propriospinal neurons to recovery of hand dexterity after corticospinal tract lesions in monkeys. *Proceedings of National Academy of Science USA*, 114:604-609.

Sawada, M., Kato, K., Kunieda, T., Mikuni, N., Miyamoto, S., Onoe, H., Isa, T. and Nishimura, Y. (2015) Function of nucleus accumbens in motor control during recovery after spinal cord injury. *Science*, 350: 98-101.

Kinoshita, M., Matsui, R., Kato, S., Hasegawa, T., Kasahara, H., Isa, K., Watakabe, A., Yamamori, T., Nishimura, Y., Alstermark, B., Watanabe, D., Kobayashi, K. and Isa, T. (2012) Genetic dissection of the circuit for hand dexterity in primates. *Nature*, 487: 235-238.

Motoko Yanagita

Professor

Graduate School of Medicine,
Kyoto University

Nephrology

Resarch Overview

More than 320,000 patients with renal failure are undergoing hemodialysis in Japan. We are studying the regenerative ability of the kidney, which can be linked to the treatment of kidney disease. We have identified the cell populations responsible for kidney injury and repair, and have revealed the intercellular crosstalk which controls the development and progression of kidney disease.

Fibrosis and renal anemia are the hallmarks of advanced kidney diseases. Previously we have found that these two features are caused by the fibroblasts-to-myofibroblasts transdifferentiation in the kidney. In addition, we have shown that the transdifferentiation of fibroblasts is induced by renal tubular damage, and that fibroblasts acquire the ability to produce retinoic acids during the transdifferentiation, which promotes tubular repair. Furthermore, we have shown that renal tubule has self-repairing ability, although the ability is not sufficient if the damage is severe. Elderly people have incomplete renal repair capacity, but the reason of incomplete repair was not clarified. We have shown that tertiary lymphoid tissues (TLTs) are formed in aged injured kidneys, and sustained inflammation due to TLT formation delays kidney regeneration. Interestingly, fibroblasts in the kidney acquire distinct phenotypes which promotes TLT formation in aged kidneys.

In this project, we will extend our current understanding of the mechanisms of kidney injury with monkey models and human tissues.

研究概要

日本では 32 万人以上が血液透析を受けています。腎臓はいったん障害されると「治らない」臓器のように考えられてきましたが、私達は腎臓には「修復力」があると考えており、それを増強することで腎臓病の治療に結びつけることができる可能性があると期待しています。

私達の研究室では、腎臓の障害と修復を担う細胞集団を特定し、腎臓病の進展を制御する細胞間クロストークを明らかにしてきました。

腎臓病が進展すると、線維化と腎性貧血が起こりますが、それが腎臓内の線維芽細胞の形質転換によること、その形質転換は尿細管上皮細胞障害が誘導することを明らかにしました。一方、形質転換した線維芽細胞はレチノイン酸産生能を獲得することで尿細管修復を促進することも見出しました。さらに、尿細管には自己修復力があるものの、障害が強いと完全に修復できないことも見出しました。高齢者は特に腎修復が不完全ですが、その一因として、高齢者の腎障害後には三次リンパ組織が形成され、そこを起点とした炎症が遷延することで修復が遅延すること、三次リンパ組織形成には腎臓内の線維芽細胞が重要な役割を果たすことを見出しました。私達はサルの腎臓病モデルとヒト組織を用いた検討で、これらの知見をさらに発展させることで、ヒト腎臓病の修復メカニズムに迫りたいと考えています。

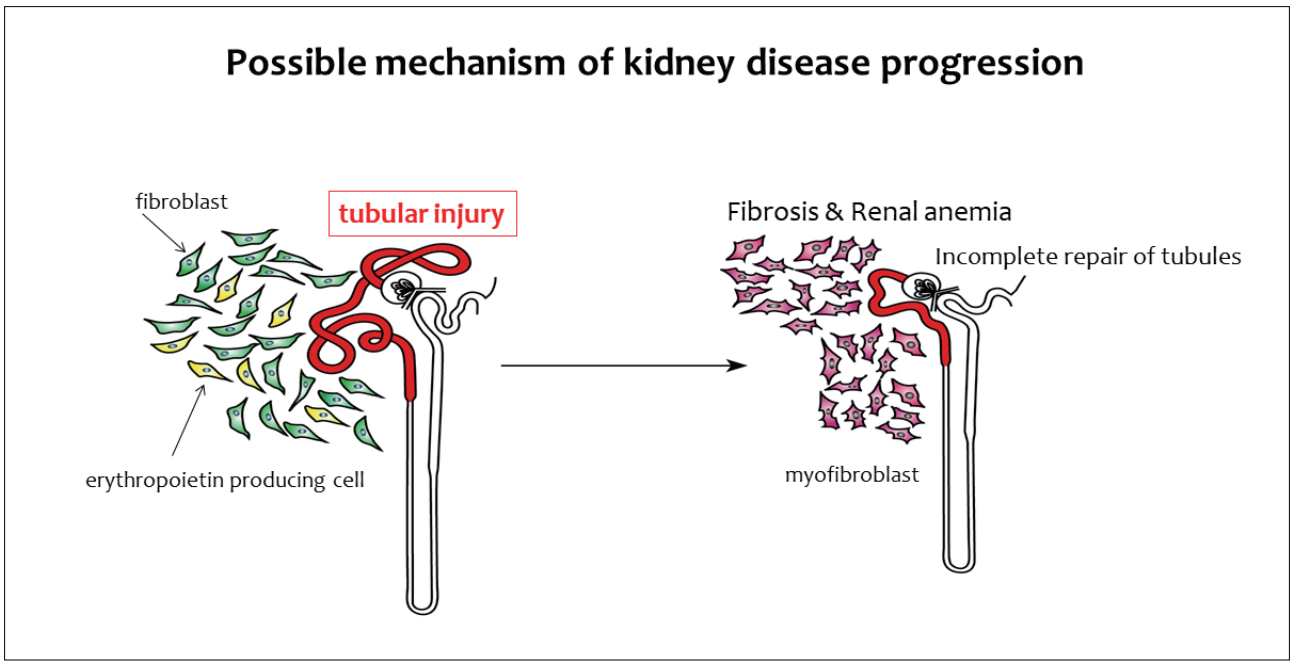


Figure 1

Possible mechanism of kidney disease progression

図 1

腎臓病の進展機構

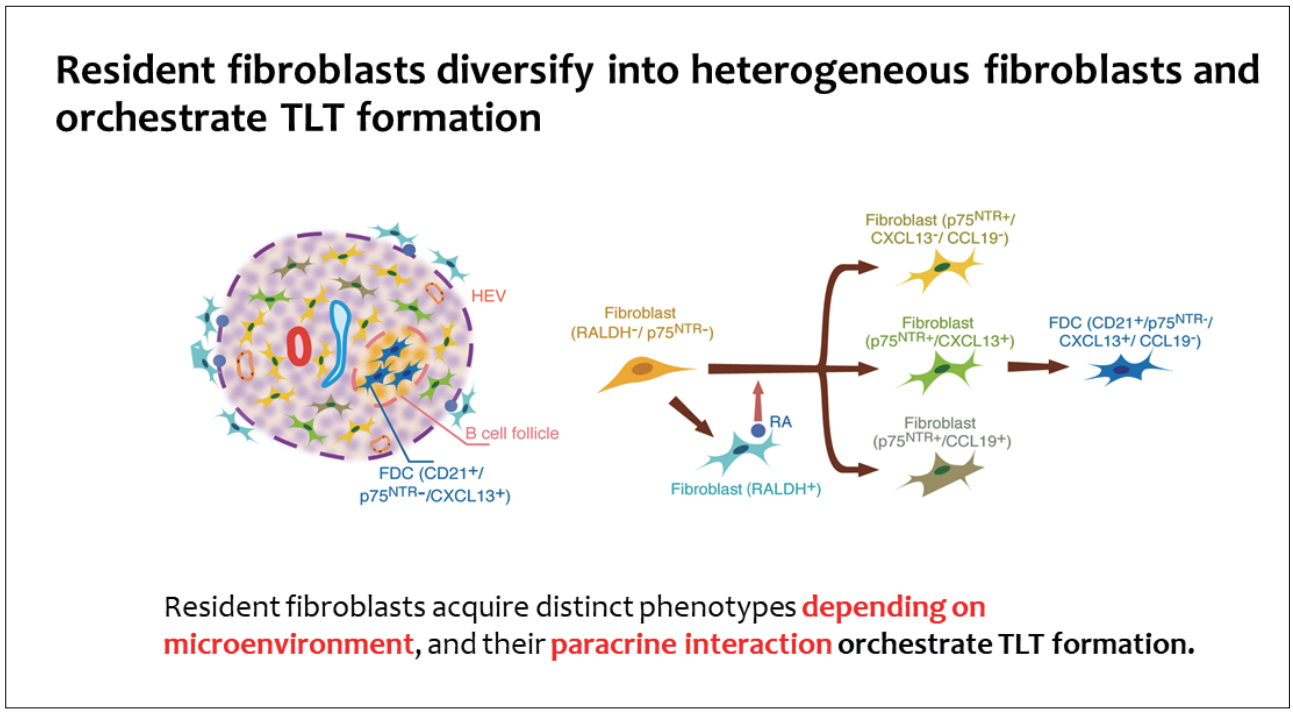


Figure 2

Resident fibroblasts diversify into heterogeneous fibroblasts and orchestrate TLT formation

図 2

腎臓内の線維芽細胞が多彩な機能を獲得することで三次リンパ組織形成が進展する。

微小環境に応じて多彩な形質を獲得した線維芽細胞のパラクライン作用を介して三次リンパ組織形成が進展する。

Selected Publications / 主要な論文

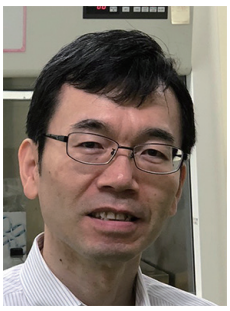
Nakamura, J., Sato, Y., Kitai, Y., Wajima, S., Yamamoto, S., Oguchi, A., Yamada, R., Kaneko, K., Kondo, M., Uchino, E., Tsuchida, J., Hirano, K., Sharma, K., Kohno, K., Yanagita, M. (2019) Myofibroblasts acquire retinoic acid-producing ability during fibroblast-to-myofibroblast transition following kidney injury. *Kidney Int*. in press.

Sato, Y., Mii, A., Hamazaki, Y., Fujita, H., Nakata, H., Masuda, K., Nishiyama, S., Shibuya, S., Haga, H., Ogawa, O., Shimizu, A., Narumiya, S., Kaisho, T., Arita, M., Yanagisawa, M., Miyasaka, M., Sharma, K., Minato, N., Kawamoto, H., Yanagita, M. (2016) Heterogeneous fibroblasts underlie age-dependent tertiary lymphoid tissues in the kidney. *JCI Insight*. 1, e87680.

Takaori, K., Nakamura, J., Yamamoto, S., Nakata, H., Sato, Y., Takase, M., Nameta, M., Yamamoto, T., Economides, AN., Kohno, K., Haga, H., Sharma, K., Yanagita, M. (2016) Severity and Frequency of Proximal Tubule Injury Determines Renal Prognosis. *J Am Soc Nephrol*. 27(8), 2393-406

Asada, N., Takase, M., Nakamura, J., Oguchi, A., Asada, M., Suzuki, N., Yamamura, K., Nagoshi, N., Shibata, S., Rao, TN., Fehling, HJ., Fukatsu, A., Minegishi, N., Kita, T., Kimura, T., Okano, H., Yamamoto, M., Yanagita, M. (2011) Dysfunction of fibroblasts of extrarenal origin underlies renal fibrosis and renal anemia in mice. *J Clin Invest*. 121(10), 3981-90.

Tanaka, M., Asada, M., Higashi, AY., Nakamura, J., Oguchi, A., Tomita, M., Yamada, S., Asada, N., Takase, M., Okuda, T., Kawachi, H., Economides, AN., Robertson, E., Takahashi, S., Sakurai, T., Goldschmeding, R., Muso, E., Fukatsu, A., Kita, T., Yanagita, M. (2010) Loss of the BMP antagonist USAG-1 ameliorates disease in a mouse model of the progressive hereditary kidney disease Alport syndrome. *J Clin Invest*. 120(3), 768-77.



Masatsugu Ema

Professor

Research Center for Animal Life Science,
Shiga University of Medical Science

Developmental Biology,
Developmental Engineering

Resarch Overview

Mice are valuable for human disease modeling; thus many genetically modified mice have been created over 40 years. However, mice poorly recapitulate some human diseases such as Parkinson's disease, and others. Accordingly, it is required to establish animal models to recapitulate human diseases more faithfully. In this regard, nonhuman primates (NHPs) are considered one of the most valuable animal models, because NHPs are closer to humans in organ size and anatomical structure, and therefore have higher potential to recapitulate human diseases, while difficult genetic manipulation is a major issue for creation of the disease models. So far, we have established techniques to create transgenic and genome editing cynomolgus monkeys. By using these techniques, we have explored an intractable human disease, Autosomal dominant polycystic kidney disease (ADPKD) with CRISPR/Cas9 technique, and demonstrated that targeted disruption of PKD1, a causative gene for ADPKD can recapitulate the human ADPKD pathology. We believe that disease modeling with genetically modified-cynomolgus monkey will open the way for the elucidation of molecular mechanism of human diseases and new therapeutic approaches. This approach also may lead to the understanding how a species difference arises among mice, monkeys and humans during the evolution.

We are also interested in primate-specific cellular and genetic program during embryonic development, especially epiblast versus primitive endoderm specification, and cardiovascular development.

研究概要

遺伝子改変マウスはヒト疾患モデルとして長い間使用されてきましたが、ある種のヒト疾患の病態を再現するのが困難であったため、よりヒト病態を忠実に再現する動物モデルが待望されていました。一方、非ヒト霊長類は解剖学的にヒトに近いため、ヒト疾患を再現することが分かっていましたが、遺伝子改変の困難さが課題でした。これまでに我々は、非ヒト霊長類の 1 種であるカニクイザルに対して、レンチウイルスを用いたトランスジェニックおよび CRISPR/Cas9 法を用いたゲノム編集技術を確立し、ヒト疾患モデルカニクイザルを効率的に作出する基盤を築いてきました。一例として、ヒト指定難病の一つである多発性嚢胞腎（ADPKD）は、げっ歯類では病態の再現が困難であることが知られていましたが、ADPKD の原因遺伝子である PKD1 を標的に遺伝子改変を行ったところ、両側の腎に嚢胞の発生を認めています。今後、各種尿細管マーカーの発現解析やトランスクリプトーム解析から、嚢胞発生機序に関わる全く新しい知見が得られ、治療法の開発に繋がっていくものと期待しています。遺伝子改変カニクイザルを用いた疾患モデリング研究から、げっ歯類、サル、ヒトの間に、細胞レベルおよび遺伝子発現レベルでどのように種差が生じたのかの理解に繋がるかもしれません。また、それと関連して、我々の研究室は霊長類特異的な遺伝的な制御プログラムに関心があり、特に初期胚発生および心血管系の発生プログラムに興味を持って取り組んでいく予定です。

Figure 1

GFP transgenic cynomolgus monkey (Seita et al., Sci. Rep., 2016). Left: transgenic (Tg), right: wild-type (WT).

図 1

GFP トランスジェニックカニクイザル。左:GFP トランスジェニックカニクイザル(Tg)、右:野生型(WT)。GFP 蛍光フィルター越しに撮影。

Figure 2

PKD1-edited cynomogus monkey.

図 2

PKD1 ゲノム編集カニクイザル

Selected Publications / 主要な論文

Azami T, Matsumoto K, Jeon H, Waku T, Muratani M, Niwa H, Takahashi S, Ema M. (2018) Klf5 suppresses ERK signaling in mouse pluripotent stem cells. *PLoS One*. 13(11): e0207321.

Azami T, Waku T, Matsumoto K, Jeon H, Muratani M, Kawashima A, Yanagisawa J, Manabe I, Nagai R, Kunath T, Nakamura T, Kurimoto K, Saitou M, Takahashi S, Ema M. Klf5 maintains the balance of primitive endoderm to epiblast specification during mouse embryonic development by suppression of Fgf4. (2017) *Development*. 144, 3706-3718

Seita Y, Tsukiyama T, Iwatani C, Tsuchiya H, Matsushita J, Azami T, Okahara J, Nakamura S, Hayashi Y, Hitoshi S, Itoh Y, Imamura T, Nishimura M, Tooyama I, Miyoshi H, Saitou M, Ogasawara K, Sasaki E, Ema M. (2016) Generation of transgenic cynomolgus monkeys that express green fluorescent protein throughout the whole body. *Sci Rep*. 6:24868.

Ishitobi H, Wakamatsu A, Liu F, Azami T, Hamada M, Matsumoto K, Kataoka H, Kobayashi M, Choi K, Nishikawa S, -I, Takahashi S, Ema M. (2011) Molecular basis for Flk1 expression in hemato-cardiovascular progenitors in the mouse. *Development* 138, 5357-5368

*Ema M., Mori D., Niwa H., Hasegawa Y., Yamanaka Y., Hitoshi S., Mimura J., Kawabe Y., Hosoya T., Morita M., Shimosato D., Uchida K., Suzuki N., Yanagisawa J., Sogawa K., Rossant J., Yamamoto M., Takahashi S., * Fujii-Kuriyama Y. (2008) Krüppel-like factor 5 is essential for blastocyst development and the normal self-renewal of mouse ES cells. *Cell Stem Cell* 3: 555-567 * Co-correspondence

Takuya Yamamoto

Associate Professor

Center for iPS Cell Research and Application,
Kyoto University

Molecular Biology, Bioinformatics

Resarch Overview

In order to achieve a comprehensive understanding of the regulatory mechanisms underlying gene expressions, it is necessary to investigate multiple regulatory hierarchies including higher-order genomic structures, epigenetic regulation, transcriptional regulation, post-transcriptional regulation and translational regulation (Figure 1). Comprehensive understanding further involves elucidating the intracellular DNA-RNA networks in gene expressions by unveiling relationships between the regulatory hierarchies through the integrative analysis of multiple omics data sets. For this purpose, by taking advantage of molecular biology, biochemistry, cell biology, genetics, genome-wide analyses and bioinformatics techniques, this research group aims to develop an advanced system to investigate a series of regulatory mechanisms that process genomic information into protein synthesis. Ultimately, this system will be used to understand how different phenotypes emerge among different species despite similarities in DNA, RNA, proteins and other cellular infrastructure. Especially, by focusing on the processes responsible for somatic cell reprogramming, cellular differentiation, and organism aging, we have studied the molecular regulatory mechanisms underlying cell fate conversion processes. This PI is also responsible for the single-cell genome analysis core, which supports all research at this institute, by providing and developing various genome-wide analytical approaches at the single-cell level.

研究概要

遺伝子発現制御機構を包括的に理解するためには、染色体高次構造制御、エピジェネティック制御、転写制御、転写後修飾制御、翻訳制御といった多階層にわたる制御レベルでの解析が必要です (図 1)。さらに、統合的な解析を通してさまざまな制御レベル間の関連性を明らかにし、細胞内での DNA-RNA 制御ネットワークを解明することも重要です。私たちの研究室では、分子生物学、生化学、細胞生物学、遺伝学、網羅的解析技術、バイオインフォマティクス、等を駆使しながら、DNA 配列から遺伝情報を読み出し、タンパク質合成に至る一連の制御機構の全体像を捉えるシステムを構築し、種差表出機構に繋がる DNA-RNA 制御機構の解明を目指しています。特に、体細胞初期化過程、細胞分化過程、個体老化過程等を対象実験系として用い、細胞が自身の運命を変換させる過程おける分子制御機構に関する研究を行なっています。また、本主任研究者は、「単一細胞ゲノム情報解析コア」も担当し、世界最先端のゲノムワイドな網羅的計測手法、解析技術を導入することによって、単一細胞レベルでの解析を可能にする多くの新技術の開発に取り組みながら、拠点の研究推進をサポートします。

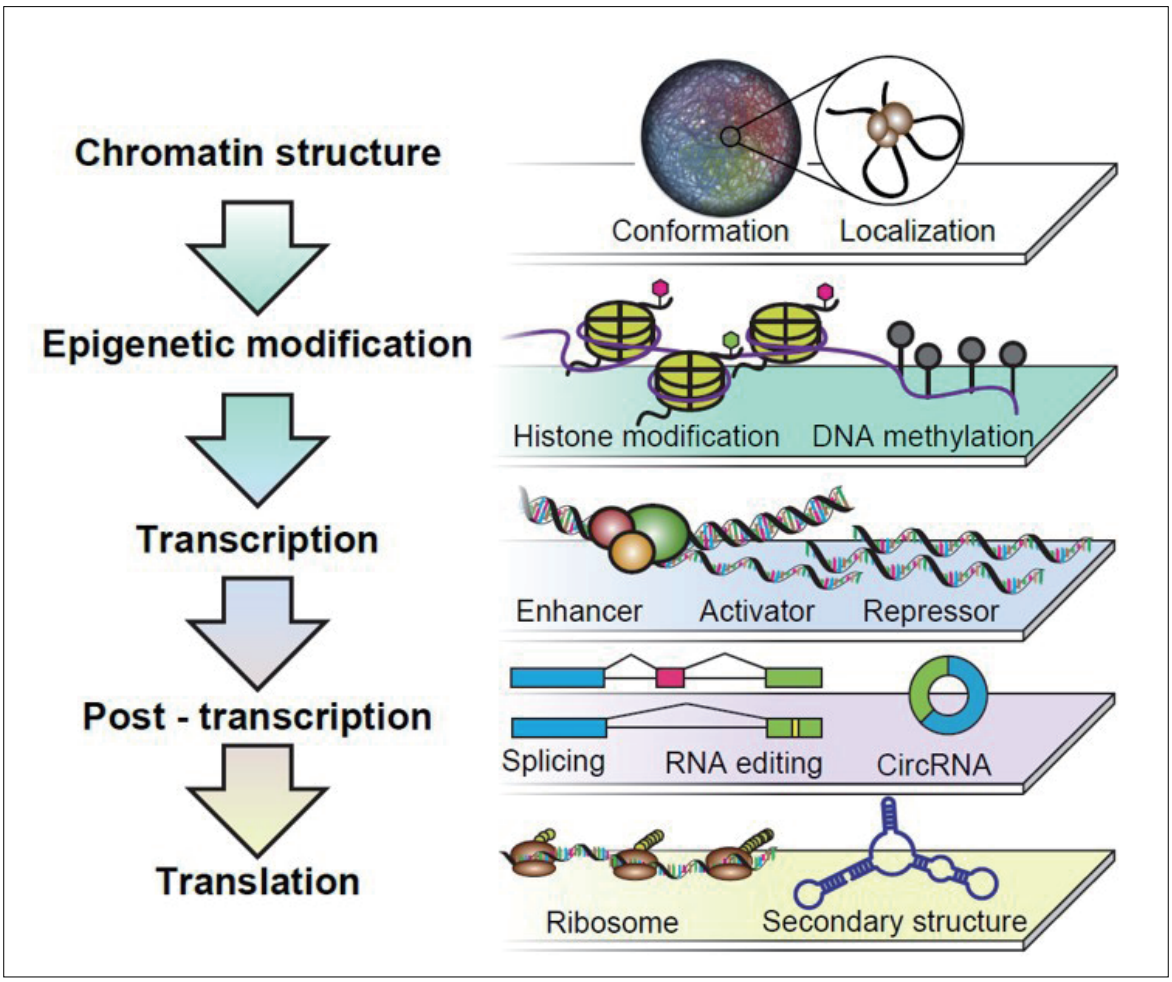


Figure 1

Deciphering genetic information by multi-hierarchical omics data.

図 1

多階層網羅的解析による統合的遺伝子発現制御機構の解明

Selected Publications / 主要な論文

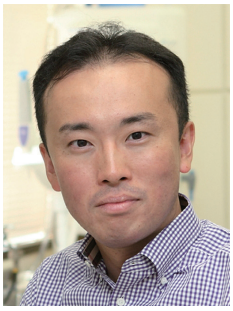
Shibata, H., Komura, S., Yamada, Y., Sankoda, N., Tanaka, A., Ukai, T., Kabata, M., Sakurai, S., Kuze, B., Woltjen, K., Haga, H., Ito, Y., Kawaguchi, Y., Yamamoto, T. and Yamada, Y. In vivo reprogramming drives Kras-induced cancer development. *Nature Communications* 9, 2081 (2018)

Ikeda, H., Sone, M., Yamanaka, S. and Yamamoto T. Structural and spatial chromatin features at developmental gene loci in human pluripotent stem cells. *Nature Communications* 8, 1616 (2017)

Yagi, M., Kishigami, S., Tanaka, A., Semi, K., Mizutani, E., Wakayama, S., Wakayama, T., *Yamamoto, T. and *Yamada, Y. Derivation of ground-state female ES cells maintaining gamete-derived DNA methylation. *Nature* 548, 224-227 (2017)
* Co-correspondence

Sone, M., Morone, N., Nakamura, T., Tanaka, A., Okita, K., Woltjen, K., Nakagawa, M., Heuser, JE., Yamada, Y., Yamanaka, S. and Yamamoto, T. Hybrid Cellular Metabolism Coordinated by Zic3 and Esrrb Synergistically Enhances Induction of Naive Pluripotency. *Cell Metabolism* 25, 1103-1117 (2017)

Nakamura, T., Okamoto, I., Sasaki, K., Yabuta, Y., Iwatani, C., Tsuchiya, H., Seita, Y., Nakamura, S., Yamamoto, T. and Saitou, M. A developmental coordinate of pluripotency among mice, monkeys, and humans. *Nature* 537, 57-62 (2016)



Mitinori Saitou

Professor

Institute for the Advanced Study of Human Biology,
Kyoto University

Germ Cell Biology, Stem Cell Biology

Resarch Overview

The germ cell lineage ensures the creation of new individuals, perpetuating/diversifying the genetic and epigenetic information across the generations. We have been investigating the mechanism for germ cell development, and have shown that mouse embryonic stem cells (mESCs)/induced pluripotent stem cells (miPSCs) are induced into primordial germ cell-like cells (mPGCLCs) with a robust capacity both for spermatogenesis and oogenesis, and for contributing to healthy offspring. We have also shown that human induced pluripotent stem cells (hiPSCs) robustly generate human primordial germ cell-like cells (hPGCLCs). Furthermore, by investigating the development of a non-human primate model, cynomolgus monkeys, we have defined a developmental coordinate of pluripotency among mice, monkeys, and humans, and shown that the germ cell lineage in primates is specified in the nascent amnion, providing a pivotal insight into the biological relevance of the hPGCLC induction pathway. More recently, we have succeeded in differentiating hPGCLCs into human oogonia that undergo a proper epigenetic reprogramming and acquire an immediately precursory state for meiotic entry. We hope that these lines of research will lead to a better understanding of the mechanism for the transmission/diversification of genetic information, for the regulation of epigenetic information, and for the acquisition of totipotency, among mice, monkeys, and humans.

研究概要

生殖細胞は、始原生殖細胞を起源とし、精子・卵子に分化し、その融合により新しい個体を形成する細胞です。すなわち、生殖細胞は、我々の遺伝情報やエピゲノム情報を次世代に継承、さらにはその多様性（進化）を生成します。生殖細胞の発生機構の解明は、遺伝情報継承機構・エピゲノム制御機構の解明や幹細胞の増殖・分化制御技術の開発、不妊や遺伝病発症機序の解明につながると期待されます。

私たちの研究室は、培養ディッシュ上で、マウス胚性幹細胞（embryonic stem cells: ES 細胞）や人工多能性幹細胞（induced pluripotent stem cells: iPS 細胞）から、精子・卵子・さらには健常な産仔に貢献する能力を有する始原生殖細胞様細胞を誘導する技術を開発しました。また本培養系を用いて、始原生殖細胞を誘導する転写・シグナル機構の解明、エピゲノムリプログラミングの本態の解明、始原生殖細胞の増殖法の開発、始原生殖細胞から精子幹細胞の試験管内誘導、生殖細胞の雌性化機構と減数分裂開始機構の解明、などに成功しました。これら成果を基盤に、ヒト iPS 細胞からヒト始原生殖細胞様細胞を誘導する技術を開発しました。さらに、ヒトに近縁のカニクイザルを用いた研究を推進し、マウス・サル・ヒトにおける多能性スペクトラムの発生座標を解明し、霊長類生殖細胞系譜が初期羊膜を起源とすることを見出しました。さらに最近、ヒト始原生殖細胞用細胞をヒト卵原細胞に分化することに成功しました。私たちは、これらの研究を発展させることで、マウス・サル・ヒトにおける遺伝情報継承・エピゲノム制御・全能性獲得機構とその進化機構を解明したいと考えています。

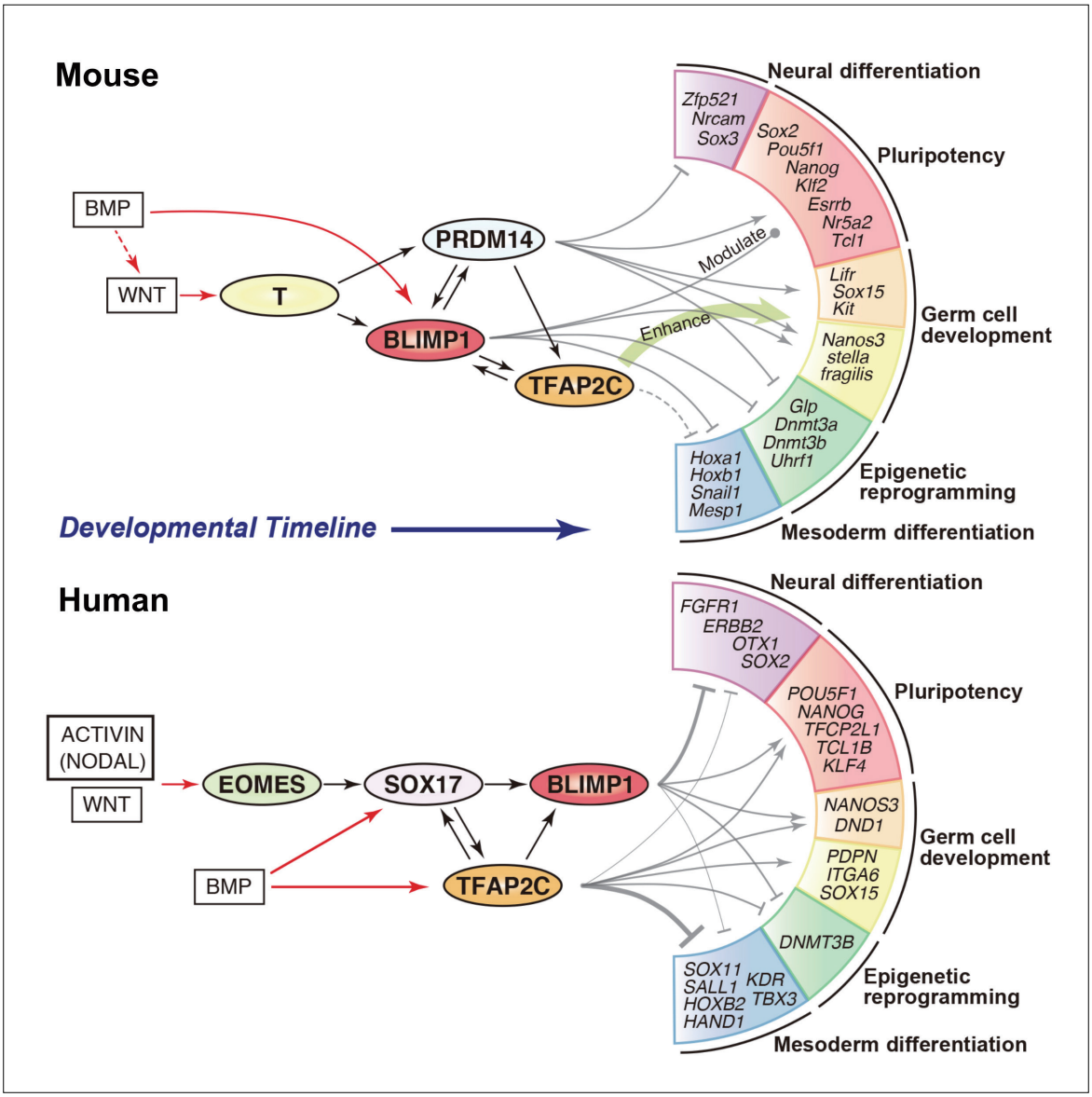


Figure 1

A model for the signaling and transcription architectures for mouse (top) and human (bottom) germ cell specification (Kojima et al., Cell Stem Cell, 2017).

図 1

マウス（上）及びヒト（下）生殖細胞形成に関与するシグナル・転写機構 .

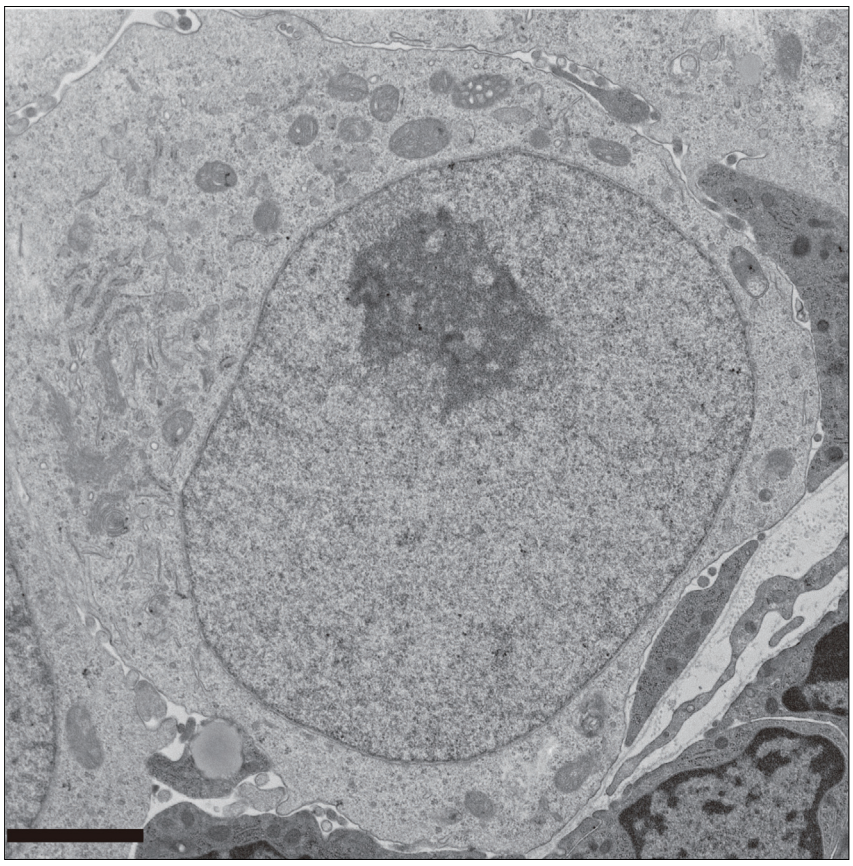


Figure 2

Ultrastructure of hPGCLC-derived oogonium in xenogeneic reconstitute ovaries (xrOvaries) (Yamashiro et al., Science, 2018). The cell bears a clear cytoplasm with sparsely distributed mitochondria with villiform cristae and an ovoid nucleus with loosely packed chromatin and a prominent granular nucleolus. These properties are highly similar to those of human oogonia/gonocytes. Bar, 2mm

図 2

異種間再構成卵巣内でヒト始原生殖細胞様細胞から分化したヒト卵原細胞の超微構造。本細胞は、明調な細胞質、絨毛様クリステを有する疎に配列するミトコンドリア、円形の核、疎にパックされた染色体、顆粒状の顕著な核小体を有し、ヒト卵原細胞に酷似する。スケールバー : 2 mm.

Selected Publications / 主要な論文

Yamashiro, C., Sasaki, K., Yabuta, Y., Kojima, Y., Nakamura, T., Okamoto, I., Yokobayashi, S., Murase, Y., Ishikura, Y., Shirane, K., Sasaki, H., Yamamoto, T., and Saitou, M. (2018). Generation of human oogonia from induced pluripotent stem cells in vitro, *Science*, in press.

Kojima, Y., Sasaki, K., Yokobayashi, S., Sakai, Y., Nakamura, T., Yabuta, Y., Nakaki, F., Nagaoka, S., Woltjen, K., Hotta, A., Yamamoto, T., and Saitou, M. (2017). Evolutionarily Distinctive Transcriptional and Signaling Programs Drive Human Germ Cell Lineage Specification from Pluripotent Stem Cells, *Cell Stem Cell*, 21, 517-532.

Miyauchi, H., Ohta, H., Nagaoka, S., Nakaki, F., Sasaki, K., Hayashi, K., Yabuta, Y., Nakamura, T., Yamamoto, T., and Saitou, M. (2017). Bone morphogenetic protein and retinoic acid synergistically specify female germ cell fate in mice, *The EMBO Journal*, 36, 3100-3119.

Hirota, T., Ohta, H., Powell, B. E., Mahadevaiah, S., K., Ojarikre, O. A., *Saitou, M., and *Turner, J. M. A. (2017). Fertile offspring from sterile sex chromosome trisomic mice, *Science*, 357, 932-935.
* Co-correspondence

Ohta, H., Kurimoto, K., Okamoto, I., Nakamura, T., Yabuta, Y., Miyauchi, H., Yamamoto, T., Okuno, Y., Hagiwara, H., Shirane, K., Sasaki, H., and Saitou, M. (2017). In vitro expansion of mouse primordial germ cell-like cells recapitulates an epigenetic blank slate, *The EMBO Journal*, 36, 1888-1907

Guillaume Bourque

Asoociate Professor

McGill University

Bioinformatics, Comparative epigenomics

Resarch Overview

We seek to understand transcription regulation in mammals and characterize the contribution of non-coding DNA variants to human disease. With consortiums such as ENCODE and the NIH Roadmap, the number of datasets characterizing the epigenomic state of different cell types and conditions has been steadily growing. Nonetheless, studies trying to infer the impact of non-coding DNA variants have had to rely on limited functional datasets to train their model and make predictions, which has proven difficult. We have shown that by using an evolutionary perspective to interpret functional genomic datasets, we can better decrypt the role of non-coding human DNA. To improve on this even further, we now propose to build comprehensive epigenomic profiles of specific cell-types in multiple human individuals and in various non-human primate species (including chimpanzee, bonobo, gorilla, rhesus and marmoset). We will then use these datasets profiling intra and inter-species epigenomic variation, to develop and train algorithms to predict the impact of non-coding DNA variants in unprecedented ways (Figure 1). Areas of interest include: the evolution of regulatory sequences, the role of transposable elements in gene regulation and the impact of genome rearrangements in evolution and cancer. One objective is to develop computational methods and resources for the functional annotation of genomes with a special emphasis on sequencing-based assays (e.g. ChIP-seq, RNA-Seq, exome- and whole-genome sequencing, single-cell analysis). We are also involved in the Global Alliance for Genomics and Health (GA4GH) and develop tools which facilitates data sharing (Figure 2).

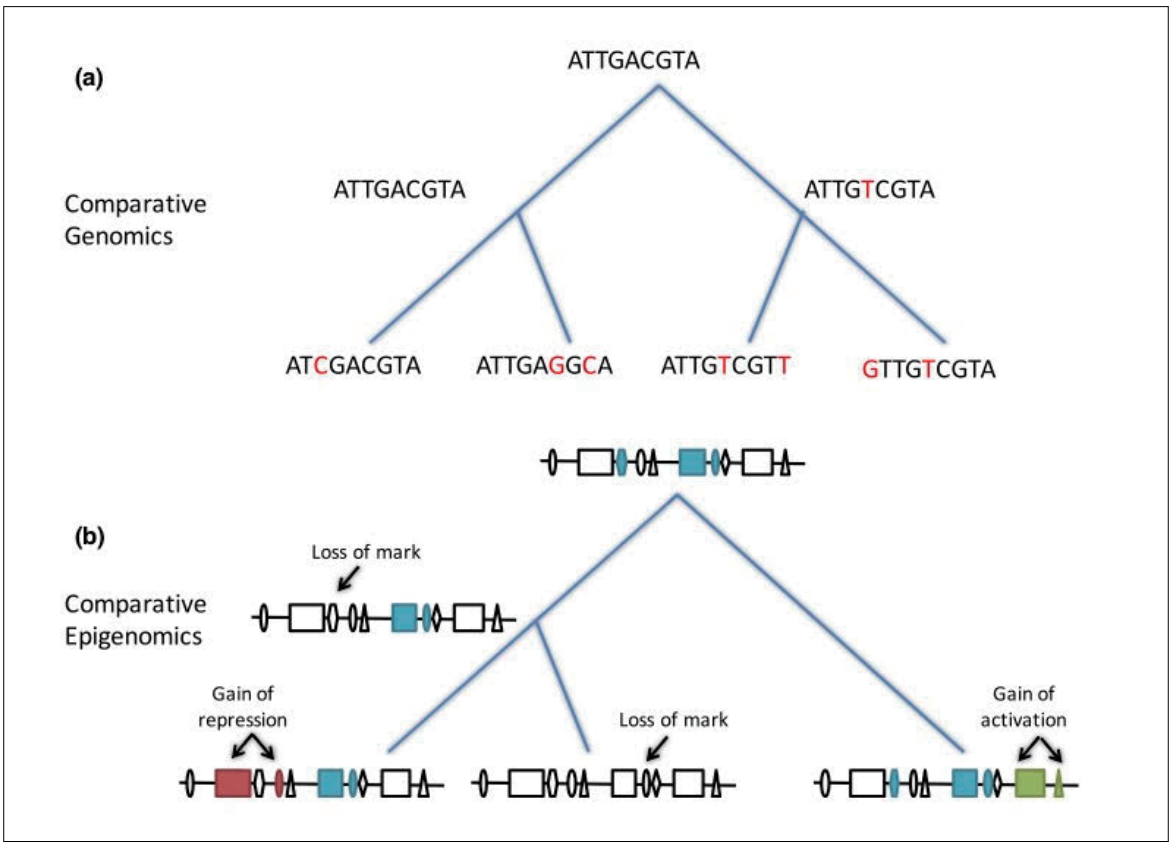


Figure 1

(a) Comparative genomics ancestral genome reconstruction using phylogenetic tree (maximum parsimony method).
(b) Ancestral epigenome reconstruction using parsimony method and counting loss, change in state, and adding of epigenomic marks as mutations (from Venuto and Bourque 2018).

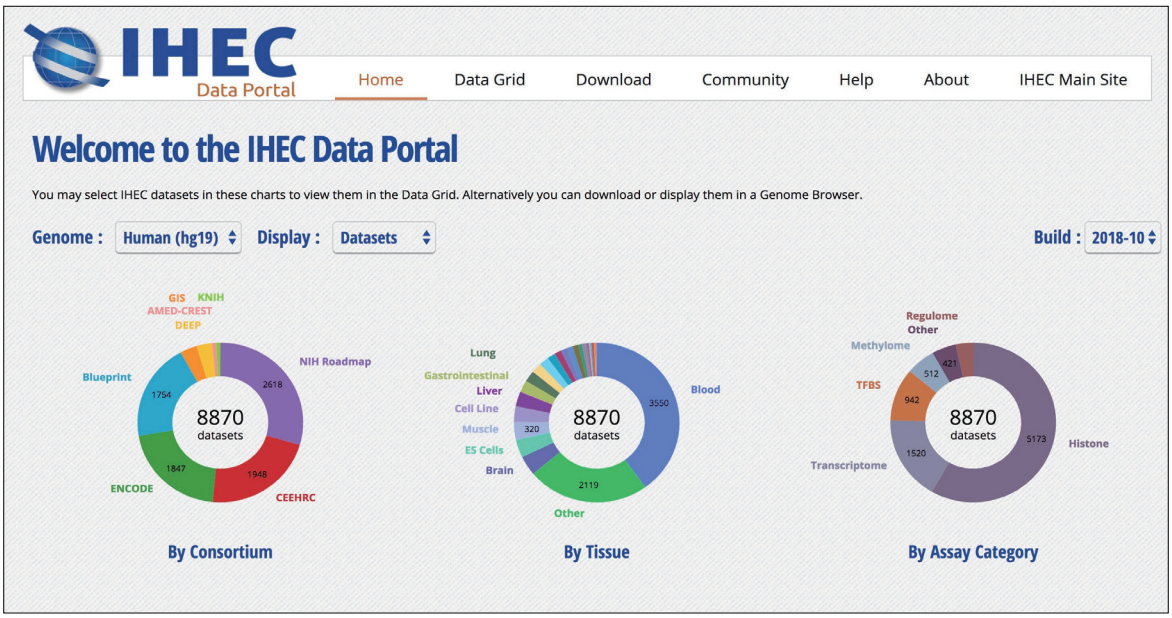


Figure 2

Screenshot of the International Human Epigenome Consortium (IHEC) Data Portal (Bujold et al. 2016) a tool we developed to facilitate analysis and sharing of epigenomic datasets.

Selected Publications / 主要な論文

Bourque G, Burns KH, Gehring M, Gorbunova V, Seluanov A, Hammell M, Imbeault M, Izsvak Z, Levin HL, Macfarlan TS, Mager DL & Feschotte C. Ten things you should know about transposable elements. *Genome Biol* 2018. 19(1):199.

Goerner-Potvin P. and Bourque G. Computational tools to unmask transposable elements. *Nat Rev Genet* 2018. 19, 688-704.

Venuto D, Bourque G. Identifying co-opted transposable elements using comparative epigenomics. *Dev Growth Differ*. 2018. 60(1):53-62.

Monlong J, Cossette P, Meloche C, Rouleau G, Girard SL, Bourque G. Human copy number variants are enriched in regions of low-mappability. *NAR* 2018. 46(14):7236-7249.

Bujold D, Morais D, Gauthier C, Côté C, Caron M, Kwan T, Chen KC, Laperle J, Markovits AN, Pastinen T, Caron B, Veilleux A, Jacques PE, Bourque G. IHEC Data Portal: a resource for discovering, analysing and sharing epigenomics data. *Cell Syst*. 2016 3(5):496-499.e2.

Takashi Hiiragi

Group Leader

The European Molecular Biology Laboratory

Developmental Biology

Resarch Overview

A defining feature of living systems is the capacity to break symmetry and generate well-defined forms and patterns through self-organisation. Our group aims to understand the design principle of multi-cellular self-organisation using early mammalian embryos. Our studies revealed that morphogenesis and gene expression in the early development are highly dynamic and stochastically variable in space and time (Figure 1). Determining how embryos robustly establish a size, shape and pattern at the right time despite the preceding variability remains a fundamental open question. We have recently developed an experimental framework that integrates biology, physics and mathematics (Figure 2). We aim to understand how molecular, cellular and physical signals are dynamically coupled across the scales for tissue self-organisation. Furthermore, we will identify developmental mechanisms shared and distinct among mammalian species. To this end, we will first establish the early primate developmental atlas at single-cell resolution by integrating single-cell omics data into 4D morphogenetic and lineage map derived from advanced microscopy. We adopt a wide variety of experimental strategies including embryology, genetics, advanced microscopy, biophysics and theoretical modelling in order to address fundamental questions in development and cell biology at molecular, cellular and systems levels.

研究概要

生命システムの特徴の一つは、対称性を破り、高度に秩序立った形態やパターンを創り出すことで、自己組織化と呼ばれています。私たちの研究室では、哺乳類の初期胚を用いて、多細胞生物の自己組織化の設計原理を理解することを目指しています。

これまでに私たちは、哺乳類の初期発生における形態形成や遺伝子発現は、予め決められているのではなく、時空間で確率論的に変動することを明らかにしてきました（図１）。しかし、こうしたゆらぎを乗り越えて、胚が適切なタイミングで適切な大きさや形、パターンを確実に獲得する仕組みは未だ明らかになっていません。私たちの研究室では、分子や細胞レベルのシグナルと物理的なシグナルがどのようにして動的にスケールを超えて結びつき、生体の自己組織化を導くかを明らかにするために、生物学と物理学、数学を融合した研究基盤を築いてきました（図２）。これを基に、哺乳類の発生において、種間で保存されている原理と異なる機構を明らかにします。まず、霊長類の初期胚の一細胞オミックスデータと最先端顕微鏡により得られる形態変化や細胞系譜の４次元データを統合し、発生アトラスを一細胞解像度で描きます。私たちは、発生学や遺伝学に加えて顕微鏡技術や生物物理学的手法、数理モデルを含めた幅広い実験技法を取り入れ、発生生物学や細胞生物学における根本的課題に分子、細胞、システムレベルで取り組みます。

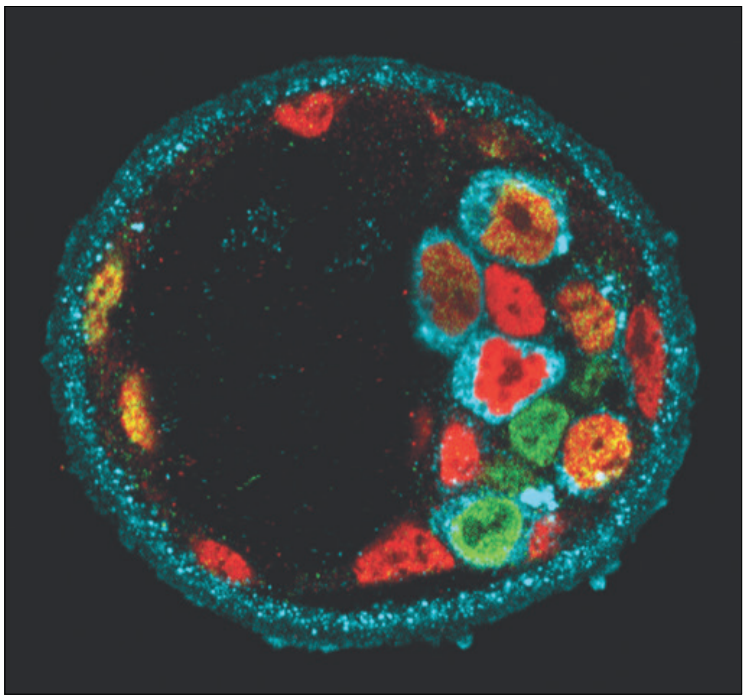


Figure 1

Molecular heterogeneity during mouse blastocyst patterning. Cells expressing Nanog (green), Gata6 (red) or Serpinh1 (blue).

図 1

マウス胚盤胞のパターン形成時には細胞間でゆらぎのある遺伝子発現が見られる。ここでは細胞内の Nanog (緑)、Gata6 (赤)、Serpinh1 (青) が標識されている。

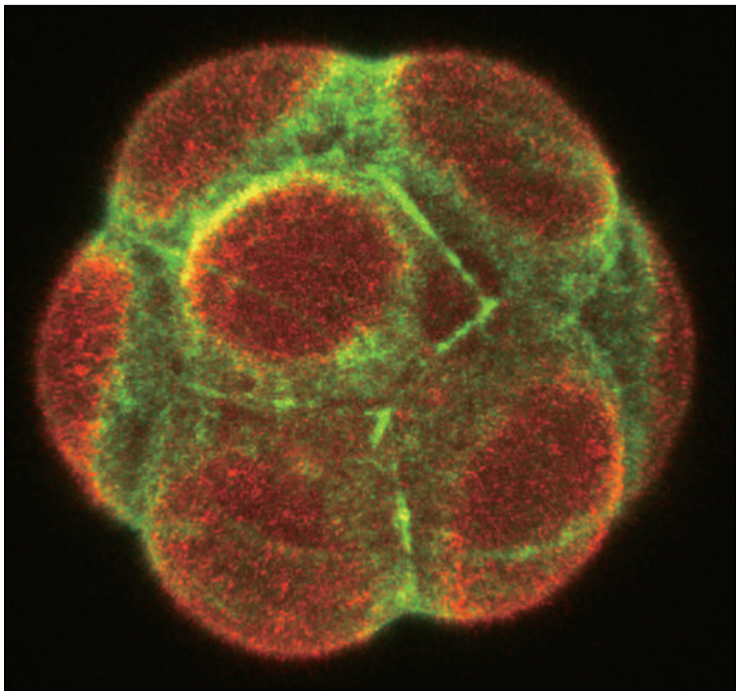


Figure 2

Symmetry breaking in the mouse embryo at the 8-cell stage (the emerging apical domain marked with Ezrin, red; Actin, green).

図 2

8 細胞期のマウス胚における対称性の破れ。細胞膜上に Ezrin (赤) で標識されるアピカル膜ドメインが出現している。緑はアクチン。

Selected Publications / 主要な論文

Korotkevich, E., Niwayama, R., Courtois, A., Friese, S., Berger, N., Buchholz, F. and Hiiragi, T. (2018). The Apical Domain Is Required and Sufficient for the First Lineage Segregation in the Mouse Embryo, *Developmental Cell*, 40, 235–247.

Maître, J.-L., Turlier, H., Illukkumbura, R., Eismann, B., Niwayama, R., Nedelec, F. and Hiiragi, T. (2016). Asymmetric division of contractile domains couples cell positioning and fate specification, *Nature* 536, 344–348.

Dietrich, J.-E., Panavaite, L., Gunther, S., Wennekamp, S., Groner, A.C., Pigge, A., Salvenmoser, S., Trono, D., Hufnagel, L. and Hiiragi, T. (2015) Venus trap in the mouse embryo reveals distinct molecular dynamics underlying specification of first embryonic lineages, *EMBO reports*, 16, 1005-1021.

Maître, J.-L., Niwayama, R., Turlier, H., Nédélec, F. and Hiiragi, T. (2015). Pulsatile cell-autonomous contractility drives compaction in the mouse embryo, *Nat Cell Biol*, 17, 849–855.

Ohnishi, Y., Huber, W., Tsumura, A., Kang, M., Xenopoulos, P., Kurimoto, K., Oleś, A.K., Araúzo-Bravo, M.J., Saitou, M., Hadjantonakis, A.-K. and Hiiragi, T. (2014). Cell-to-cell expression variability followed by signal reinforcement progressively segregates early mouse lineages, *Nat Cell Biol*, 16, 27–37.

Mototsugu Eiraku

Professor

Institute for Frontier Life and Medical Science,
Kyoto University

Developmental Biology, Stem Cell Biology

Resarch Overview

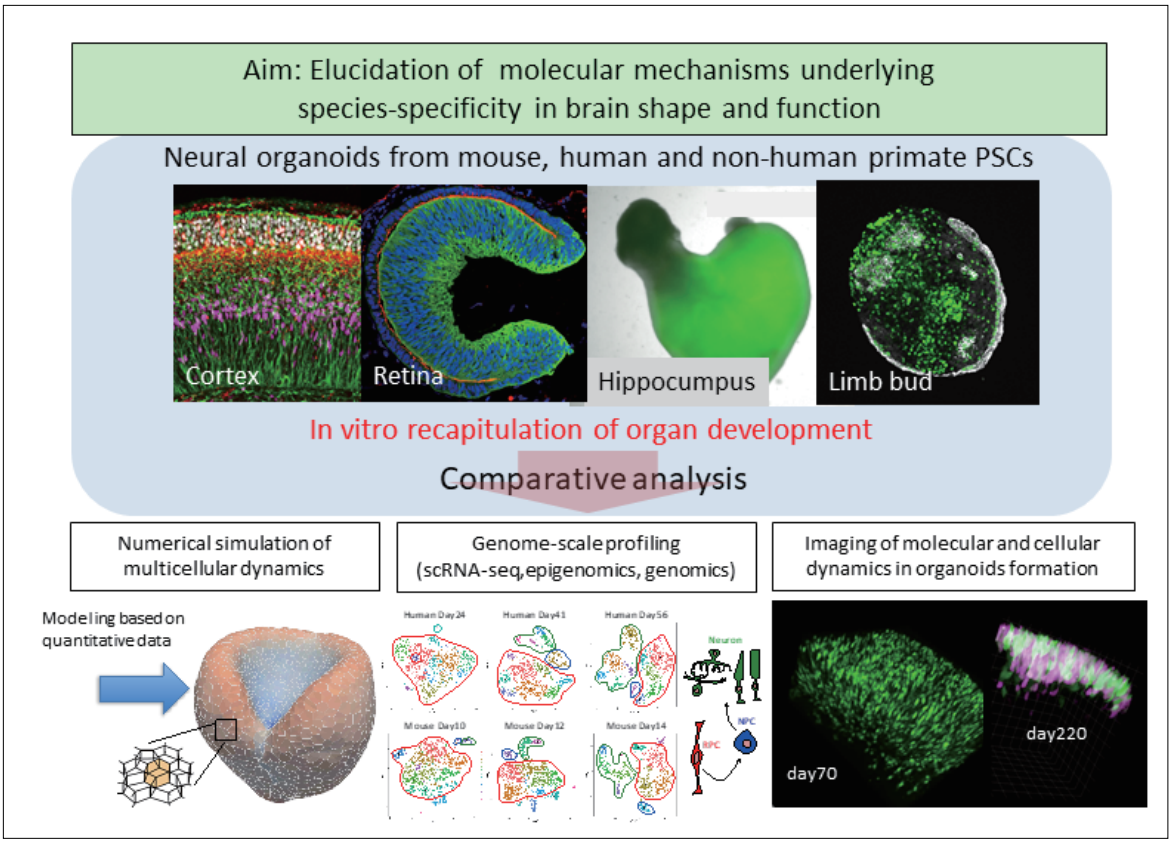
Human brain consists of nearly 1000 times neurons compared with mouse, and the time it takes to complete the human brain is 20 times longer than mouse. Although it is widely accepted that species-specific brain shapes and functions exist in vertebrates, the molecular basis that gives rise to such species specificity is still unknown.

We have developed means to self-organize the brain and retinal tissue (neural organoids) in a cultured dish from mouse and human pluripotent stem cells (ES/iPS cells). By analyzing the formation process of neural organoids, we have clarified the molecular and cellular mechanisms of self-organization in tissue patterning and morphogenesis. Furthermore, previous studies have revealed that differences in species-specific brain development can be recapitulated in organoids culture. Therefore, we aim to clarify the underlying mechanisms that give rise to species specificity in brain shape and function through comparative studies of neural organoid as a model. We also hope to contribute to future regenerative medicine and drug discovery through the development of stem cell technology to form more complex organoids with tissue functions.

研究概要

ヒトの脳はマウスに比べて 1000 倍近い数の神経細胞から構成され、胎生期において 20 倍もの時間をかけて作られます。また、脳はその形状および機能において種特異性が高いため、その発生過程の多様性も大きいことが知られています。しかし、脳の種特異性を生む分子基盤や細胞動体はほとんど明らかにされていません。

私たちの研究室ではこれまでに、マウスおよびヒトの多能性幹細胞（ES/iPS 細胞）から、層構造を持つ大脳組織や網膜組織（神経オルガノイド ）を培養ディッシュ内で自己組織化的に形成する技術を開発してきました。また、神経オルガノイド の形成過程を細胞生物学的手法および数値シミュレーションを用いて解析・予測することで、自己組織的なパターン形成や形態形成の分子・細胞メカニズムを明らかにしてきました。さらに、これまでの研究により in vitro のオルガノイド 誘導培養系においてもマウスおよびヒトの種特異的な発生様式の違いは再現されることを明らかにしています。そこで、本研究グループでは様々な種由来の多能性幹細胞を用いて神経組織の発生素過程を再現し、 1 細胞遺伝子発現解析、エピゲノム解析、イメージング解析および数値シミュレーションなどの技術を用いて比較解析することで、不明な点の多い種特異性を生むメカニズムの細胞・分子レベルでの理解を目指します。また同時に、より多様な機能をもつ複雑なオルガノイドを形成するための幹細胞制御技術や人為的に発生時間スケールを制御する技術の開発にも取り組み、将来の再生医療や創薬に寄与したいと考えています。



Selected Publications / 主要な論文

Okuda S, Takata N, Hasegawa Y, Kawada M, Inoue Y, Adachi T, Sasai Y, Eiraku M. (2018) Strain-triggered mechanical feedback in self-organizing optic-cup morphogenesis. *Sci Adv*. 4, eaau1354.

Sakaguchi H, Kadoshima T, Soen M, Narii N, Ishida Y, Ohgushi M, Takahashi J, Eiraku M, Sasai Y. (2015) Generation of functional hippocampal neurons from self-organizing human embryonic stem cell-derived dorsomedial telencephalic tissue. *Nat Commun*. 6, 8896.

Kadoshima T, Sakaguchi H, Nakano T, Soen M, Ando S, Eiraku M, Sasai Y. (2013) Self-organization of axial polarity, inside-out layer pattern, and species-specific progenitor dynamics in human ES cell-derived neocortex. *Proc Natl Acad Sci USA*. 110, 20284-20289.

Eiraku M, Takata N, Ishibashi H, Kawada M, Sakakura E, Okuda S, Sekiguchi K, Adachi T, Sasai Y. (2011) Self-organizing optic-cup morphogenesis in three-dimensional culture. *Nature*. 472, 51-56.

Eiraku M, Watanabe K, Matsuo-Takasaki M, Kawada M, Yonemura S, Matsumura M, Wataya T, Nishiyama A, Muguruma K, Sasai Y. (2008) Self-organized formation of polarized cortical tissues from ESCs and its active manipulation by extrinsic signals. *Cell Stem Cell*. 3, 519-532.

Yasuaki Hiraoka

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Topological data analysis, applied mathematics

Resarch Overview

Topological data analysis is an emerging concept in applied mathematics in which we characterize “shape of massive and complex data” using topological methods. In particular, persistent homology and mapper are nowadays applied to a wide variety of scientific and engineering problems including materials science, life science and social networks etc. By combining various mathematics such as topology, representation, statistics and probability theory, our group has succeeded in making topological data analysis powerful and general methods for practical problems. For example, we have applied these methods to structural analysis in materials science so far, and the developed techniques by our group are expected to be a key technology for materials informatics. In ASHBi, we aim to understand the principle of species differences among humans, non-human primates, and rodents by applying topological data analysis, dynamical system, and machine learning to multi-species, multi-cell types, multi-hierarchical omics information. This analysis will also be extended into the identification of the principles for the species differences on the scales of time and physical dimensions in development and growth. We hope that interdisciplinary researches between biology and mathematics in ASHBi will develop powerful advanced mathematical methodology for massive and complex biological data, and contribute to the progress of life science.

研究概要

今世紀に開発された新たなデータ解析手法であるトポロジカルデータ解析は，膨大かつ複雑なデータの「形」の特徴づけを可能にします．トポロジカルデータ解析の代表的な手法であるパーシステントホモロジーや Mapper は，現在，材料科学，生命科学，ソーシャルネットワーク解析といった諸科学産業の問題へ実際に応用が進められています．我々のグループでは，これまでトポロジー，表現論，確率論，統計理論などを融合させることで，トポロジカルデータ解析をより強力かつ汎用的な手法へ拡張することに成功しました．また応用方面では材料科学の構造解析へ適用しており，我々の手法は今後の材料インフォマティックスの重要な手法になることが期待されています．ヒト生物学高等研究拠点（ASHBi）では，トポロジカルデータ解析，力学系，機械学習といった数学手法を用いて多階層・多スケールにわたる多生物種・多細胞種データを解析することで，ヒト，非ヒト科霊長類，齧歯類において種差が表出するメカニズムの解明を目指します．本拠点における生物学と数理科学の学際研究を通じて，生物学に現れる膨大かつ複雑なデータ解析に対する強力な解析手法を開発することで，生命科学の発展に貢献することを目指します．

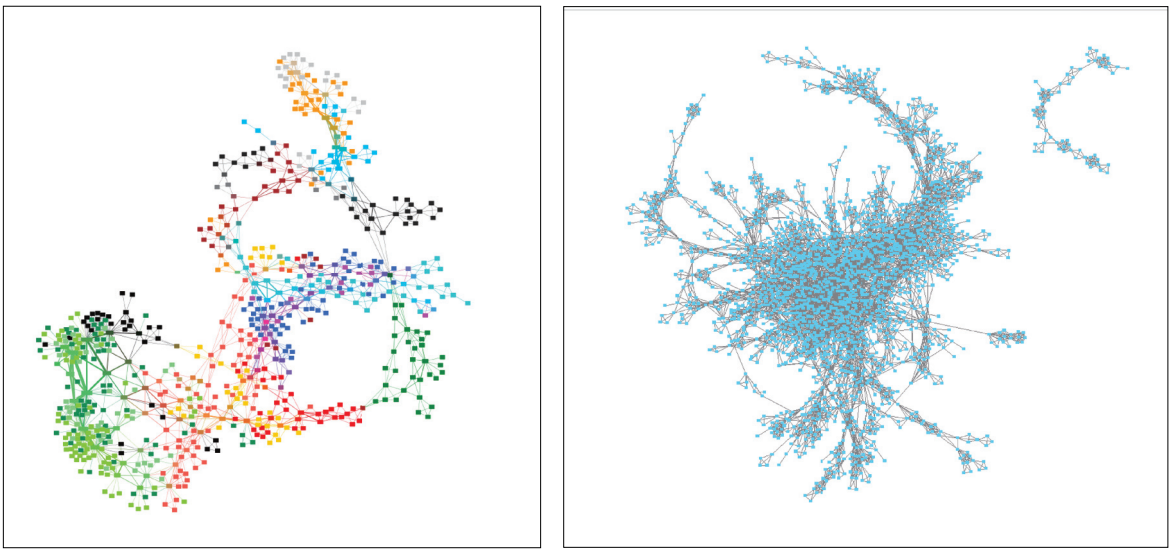

Figure 1

Topological clustering on single cell analysis data of monkeys by mapper (Left: cell clusters. Right: Gene clusters)

図 1

Mapper を用いたサルの単一細胞解析データに対するトポロジカルクラスタリング
（左：細胞クラスタリング．右：遺伝子クラスタリング）

Selected Publications / 主要な論文

I. Obayashi, Y. Hiraoka, M. Kimura. Persistence Diagrams with Linear Machine Learning Models. J. Appl. and Comput. *Topology* (2018), 1, 421–449.

G. Kusano, K. Fukumizu, and Y. Hiraoka. Kernel method for persistence diagrams via kernel embedding and weight factor. *Journal of Machine Learning Research* 18 (2018) 1-41.

M. Kimura, I. Obayashi, Y. Takeichi, R. Murao and Y. Hiraoka. Non-empirical identification of trigger sites in heterogeneous processes using persistent homology. *Scientific Reports* 8, Article number: 3553 (2018).

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Ogawa Seishi

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Molecular Genetics

Resarch Overview

Clonal expansion in aged normal tissues has been implicated in the development of cancer. However, the chronology and risk dependence of the expansion are poorly understood. Here we intensively sequence 682 micro-scale esophageal samples and show, in physiologically normal esophageal epithelia, the progressive age-related expansion of clones that carry mutations in driver genes (predominantly NOTCH1), which is substantially accelerated by alcohol consumption and by smoking. Driver-mutated clones emerge multifocally from early childhood and increase their number and size with ageing, and ultimately replace almost the entire esophageal epithelium in the extremely elderly. Compared with mutations in esophageal cancer, there is a marked overrepresentation of NOTCH1 and PPM1D mutations in physiologically normal esophageal epithelia; these mutations can be acquired before late adolescence (as early as early infancy) and significantly increase in number with heavy smoking and drinking. The remodeling of the esophageal epithelium by driver-mutated clones is an inevitable consequence of normal ageing, which - depending on lifestyle risks - may affect cancer development.

研究概要

がんの発生には、加齢に伴って正常組織でみとめられるクローン性増殖が関与している可能性が示唆されています。しかし、こうしたクローン性増殖の経時的な変化やリスク依存性については、ほとんど分かっていません。我々は、食道から採取した 682 個の微小試料について詳細な塩基配列解読を行うことにより、生理学的には正常と考えられる食道上皮においても、ドライバー遺伝子に変異を獲得したクローンが加齢に伴って進行性に増殖を来していること、また、この過程は喫煙や飲酒により大幅に促進されることを明らかにしました。ドライバー変異を有するクローンは、幼少期から多発性に生じ、加齢に伴ってその数とサイズの増加をみとめ、著しい高齢者においては、食道上皮のほぼ全面がこれらのクローンで置換されます。食道がんで認められる変異と比較して、生理学的に正常な食道上皮では、NOTCH1 や PPM1D 遺伝子の変異頻度の顕著な増加が認められました。これらの変異は、思春期後期までに (早くは乳児期早期において) 獲得される場合があり、多量の喫煙や飲酒により有意に増加することがわかりました。これらの研究結果は、ドライバー変異を有するクローンによる食道上皮の再構成は、通常の加齢に伴う不可避の結果であり、生活習慣のリスクに依存してがんの発生に影響を与えうること考えられます。

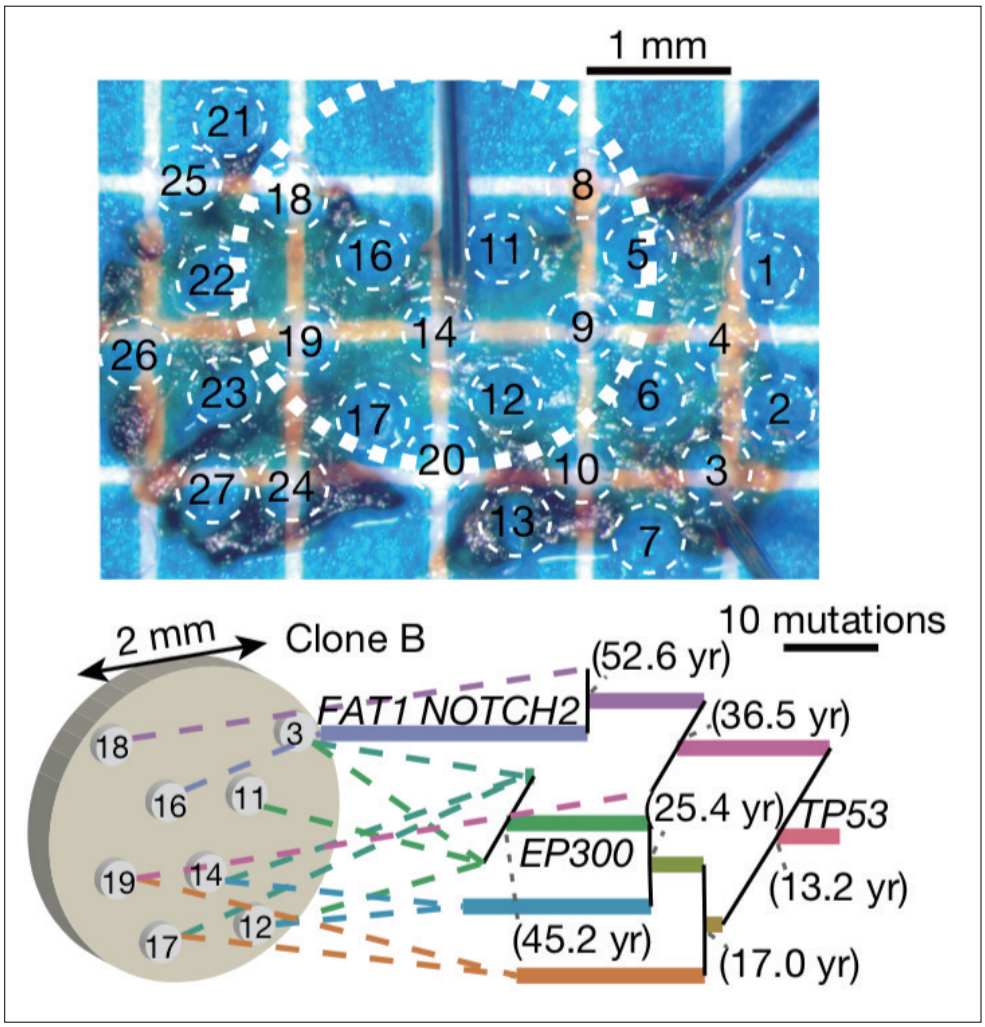

Figure 1

Evolution of a representative clones observed in physiologically normal samples from a 70-year-old man. Phylogenetic trees of clones (middle) are projected onto the positions of samples, as indicated by images of biopsy specimens (top). The estimated age of branching is also shown.

図 1

70 歳男性の健常食道上皮で認められたクローンの進化。系統樹 (下段) と採取したサンプルの位置 (上段) を併せて示した。進化に過程における分岐の年代と遺伝子変異を系統樹中にしめした。

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Yokoyama A, Kakiuchi N, Yoshizato T, Nannya Y, Suzuki H, Takeuchi Y, Shiozawa Y, Sato Y, Aoki K, Kim SK, Fujii Y, Yoshida K, Kataoka K, Nakagawa MM, Inoue Y, Hirano T, Shiraishi Y, Chiba K, Tanaka H, Sanada M, Nishikawa Y, Amanuma Y, Ohashi S, Aoyama I, Horimatsu T, Miyamoto S, Tsunoda S, Sakai Y, Narahara M, Brown JB, Sato Y, Sawada G, Mimori K, Minamiguchi S, Haga H, Seno H, Miyano S, Makishima H, Muto M, Ogawa S. Age-related remodelling of oesophageal epithelia by mutated cancer drivers. *Nature*. 2019;565(7739):312-317.

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Suzuki H, Aoki K, Chiba K, Sato Y, Shiozawa Y, Shiraishi Y, Shimamura T, Niida A, Motomura K, Ohka F, Yamamoto T, Tanahashi K, Ranjit M, Wakabayashi T, Yoshizato T, Kataoka K, Yoshida K, Nagata Y, Sato-Otsubo A, Tanaka H, Sanada M, Kondo Y, Nakamura H, Mizoguchi M, Abe T, Muragaki Y, Watanabe R, Ito I, Miyano S, Natsume A, Ogawa S. Mutational landscape and clonal architecture in grade II and III gliomas. *Nat Genet*. 2015;47(5):458-468.

Kataoka K, Nagata Y, Kitanaka A, Shiraishi Y, Shimamura T, Yasunaga J, Totoki Y, Chiba K, Sato-Otsubo A, Nagae G, Ishii R, Muto S, Kotani S, Watatani Y, Takeda J, Sanada M, Tanaka H, Suzuki H, Sato Y, Shiozawa Y, Yoshizato T, Yoshida K, Makishima H, Iwanaga M, Ma G, Nosaka K, Hishizawa M, Itonaga H, Imaizumi Y, Munakata W, Ogasawara H, Sato T, Sasai K, Muramoto K, Penova M, Kawaguchi T, Nakamura H, Hama N, Shide K, Kubuki Y, Hidaka T, Kameda T, Nakamaki T, Ishiyama K, Miyawaki S, Yoon SS, Tobinai K, Miyazaki Y, Takaori-Kondo A, Matsuda F, Takeuchi K, Nureki O, Aburatani H, Watanabe T, Shibata T, Matsuoka M, Miyano S, Shimoda K, Ogawa S. Integrated molecular analysis of adult T cell leukemia/lymphoma. *Nat Genet*. 2015;47(11):1304-1315.

Hideki Ueno

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Icahn School of Medicine at Mount Sinai

Immunology

Resarch Overview

CD4+ T cells represent a major cell component of the adaptive immune system. Naive CD4+ T cells differentiate into different types of effectors in periphery upon encounter with antigen-presenting dendritic cells. Effectors are composed of fairly diverse cell populations called subsets. During the initial differentiation process, signals via various receptors on T cells, e.g., T cell receptor, co-stimulatory molecules, and cytokine receptors, affect the differentiation fate. While the function of CD4+ T cell subsets is relatively conserved among mammals, the major pathways involved in the differentiation process are different in many instances. Furthermore, even within human-derived naïve CD4+ T cells, cells isolated from different human organs, e.g., cord blood, adult peripheral blood, tonsils, and spleen; and isolated from subjects with different ages, e.g., infants, young adults, and elderly, display different features and differentiation trajectory. The molecular and epigenetic mechanisms underlying the differences in the CD4+ T cell differentiation among species, anatomical sites, and ages remain ill defined. In this project, we aim to define the genetic, transcriptomic, and epigenetic factors that regulate the differentiation of naïve CD4+ T cells that differ in origins. In parallel, we will analyze monocytes as a representative cell type within the innate immune system. We anticipate to reveal the molecular mechanism by which immune cells respond differently among species; mouse, macaques, and humans (Aim1); among anatomical sites in human organs; peripheral blood, tonsils, spleen, and gut (Aim 2); among different ages (Aim 3).

研究概要

CD4 陽性 T リンパ球は獲得免疫系細胞の一つです。ナイーブ細胞と呼ばれる胸腺由来の細胞は体内で樹状細胞などの抗原提示細胞と会合しエフェクター細胞といわれる様々な機能を持った細胞へと分化します。機能の異なるエフェクター細胞をサブセットと呼び、ナイーブ細胞は非常に多くのサブセットへと分化します。このサブセットへの分化は、ナイーブ細胞が樹状細胞と会合する際に受ける様々な受容体、例えば T 細胞受容体、副刺激分子、サイトカイン受容体など、からの刺激の質や量がサブセットの分化に大きく関与します。興味深いことに、分化したサブセットの機能は哺乳類種間で類似していますが、サブセットへの分化制御機構は種間で異なることが多いことが判明しています。さらに、ヒト由来のナイーブ T 細胞であっても異なる臓器や年齢の異なる血液サンプルから得た場合、異なるサブセットへと分化しやすいことが分かっています。その一方で CD4 陽性 T 細胞の分化制御機構がどのような分子機構、エピゲノム制御の違いによるかはほとんど分かっていません。このプロジェクトでは、ナイーブ CD4+ T 細胞を獲得免疫系のモデルとして、また単球を自然免疫系のモデルとして、遺伝子、トランスクリプトーム、エピゲノム由来の因子がどのように免疫応答反応制御機構の違いに関与するかを解明します。私たちは、免疫応答反応が異なる種、異なる臓器、異なる年齢によってなぜ違うのか、その分子機構を解明したいと考えています。

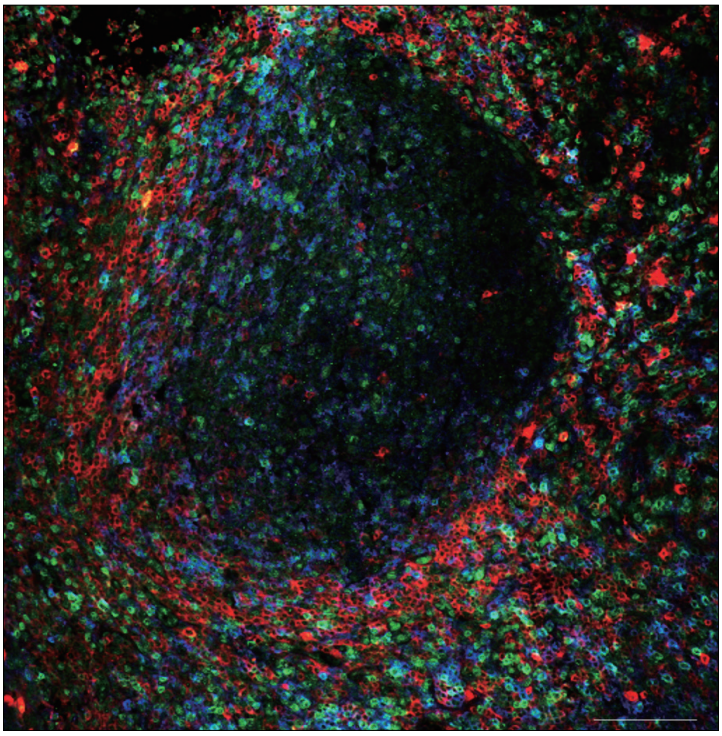

Figure 1

CD4+ T cell subsets within germinal centers in human tonsils.

図 1

ヒト扁桃の胚中心に存在する CD4+ T 細胞サブセット。

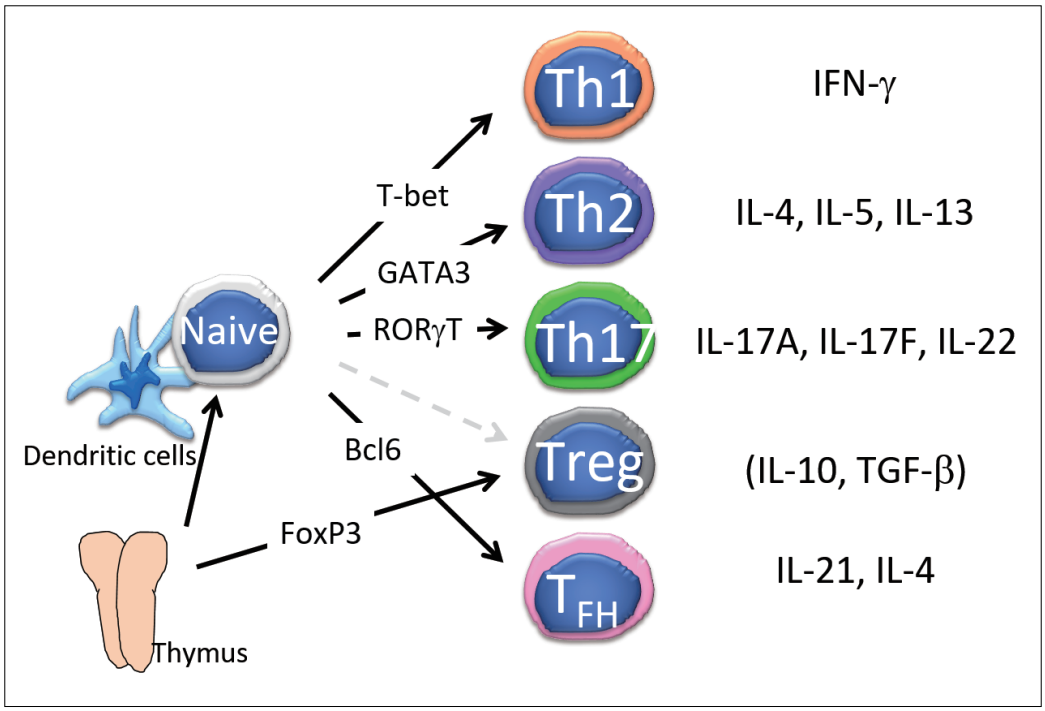

Figure 2

CD4+ T cell subsets. The differentiation of naïve CD4+ T cells into effector subsets depends on a specific transcription factor. The major pathways that induces the specific transcription factors differ among species.

図 2

CD4 陽性 T 細胞サブセット。ナイーブ CD4+ T 細胞のエフェクターサブセットへの分化は特異的な転写因子に依存している。その転写因子を誘導する主な経路は種間で異なることが多い。

Selected Publications / 主要な論文

Morita R, Schmitt N, Bentebibel SE, Ranganathan R, Bourdery L, Zurawski G, Foucat E, Dullaers M, Oh S, Sabzghabaei N, Lavecchio EM, Punaro M, Pascual V, Banchereau J, Ueno H. Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. *Immunity*. 2011;34(1):108-21.

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Schmitt N, Liu Y, Bentebibel SE, Munagala I, Bourdery L, Venuprasad K, Banchereau J, Ueno H. The cytokine TGF-beta co-opts signaling via STAT3-STAT4 to promote the differentiation of human TFH cells. *Nat Immunol*. 2014;15(9):856-65.

Jacquemin C, Schmitt N, Contin-Bordes C, Liu Y, Narayanan P, Seneschal J, Maurouard T, Dougall D, Davizon ES, Dumortier H, Douchet I, Raffray L, Richez C, Lazaro E, Duffau P, Truchetet ME, Khoryati L, Mercie P, Couzi L, Merville P, Schaeverbeke T, Viallard JF, Pellegrin JL, Moreau JF, Muller S, Zurawski S, Coffman RL, Pascual V, Ueno H*, Blanco P*. OX40 Ligand Contributes to Human Lupus Pathogenesis by Promoting T Follicular Helper Response. *Immunity*. 2015;42(6):1159-70. * Equal contributors.

Schmitt N, Liu Y, Bentebibel SE, Ueno H. Molecular Mechanisms Regulating T Helper 1 versus T Follicular Helper Cell Differentiation in Humans. *Cell Rep*. 2016;16(4):1082-95.

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Bioethics, Psychology

Resarch Overview

Bioethics is an interdisciplinary field of research dealing with "ethical issues" that cannot be judged by traditional values, which arise as the advancement of science and technology. Ethical issues, such as whether human embryos may be created from human stem cell-derived artificial gametes, conditions in which we need moral considerations for human brain organoids, etc., which the society would face in the future have to be discussed in advance. Furthermore, bioethics considers how rules and procedures should be implemented to conduct research appropriately. For the advancement of science and technology and to be trusted by society, it is essential to study these ethical issues and hold open discussions in society.

Therefore, in our laboratory we are engaging in the following activities:

1) Theoretical research: We will extract and organize issues to be considered from an ethical point of view, such as literature research on the moral status of human embryo organoids and human brain organoids, and deepen philosophical discussions.

2) Empirical research: Based on the findings of the theoretical research, we are conducting surveys on the attitudes of the general public and scientists toward human stem cell-derived artificial gametes, genome editing of human embryos, and so forth.

3) Policy proposals: We will provide points of discussion and issues extracted from the theoretical research as well as the results of empirical research to the Cabinet Office and the Ministry of Education, Culture, Sports, Science, and Technology to implement regulations, and aim to reflect the opinion of the people and researchers in further discussion.

4) Outreach activities: We will try to initiate social discussions by disseminating the research results widely across society. We will deploy these research works by collaborating with other scientists at our institution, and aim to build a new research model that combines humanities and science.

研究概要

生命倫理学とは、先端科学技術の発展に伴い、従来の価値観ではその是非が判断できないような「倫理的課題」を扱う学際的な研究領域です。例えば、ヒト幹細胞由来の人工生殖細胞からヒト胚を作製してもよいのか、神経活動を有するヒト脳オルガノイドに道徳的配慮が必要となる要件とは何か等、将来社会が直面し得る課題に事前に取り組み、対応できるように備えます。また、適切に研究が行われるための規制や手続きのあり方についても検討します。新しい科学技術が社会で信頼されながら発展していくためには、こうした倫理的課題についても研究し、社会の中で開かれた議論を行うことが不可欠です。

そこで、私たちの研究室では次のような取り組みを行っています。1) 理論研究：ヒト胚オルガノイドやヒト脳オルガノイドの道徳的地位に関する文献研究等、倫理的観点から検討すべき課題の抽出と整理を行い、哲学的な議論を深めます。2) 調査研究：理論研究で得られた知見を踏まえて、人工生殖細胞作製やヒト胚へのゲノム編集等に関する一般市民や自然科学研究者を対象とした意識調査等を実施しています。3) 政策提言：理論研究から抽出した論点や課題、調査研究の結果等を内閣府や文部科学省等の規制策定の場に提供し、そこでの議論に民意や研究者の意向を反映させることを目指します。4) アウトリーチ活動：研究成果を社会に広く発信することで、社会的議論の創生を試みます。本拠点の他の自然科学研究者らと協働しながらこれらの研究を発展させ、文理融合の新たな研究モデルの構築を目指します。

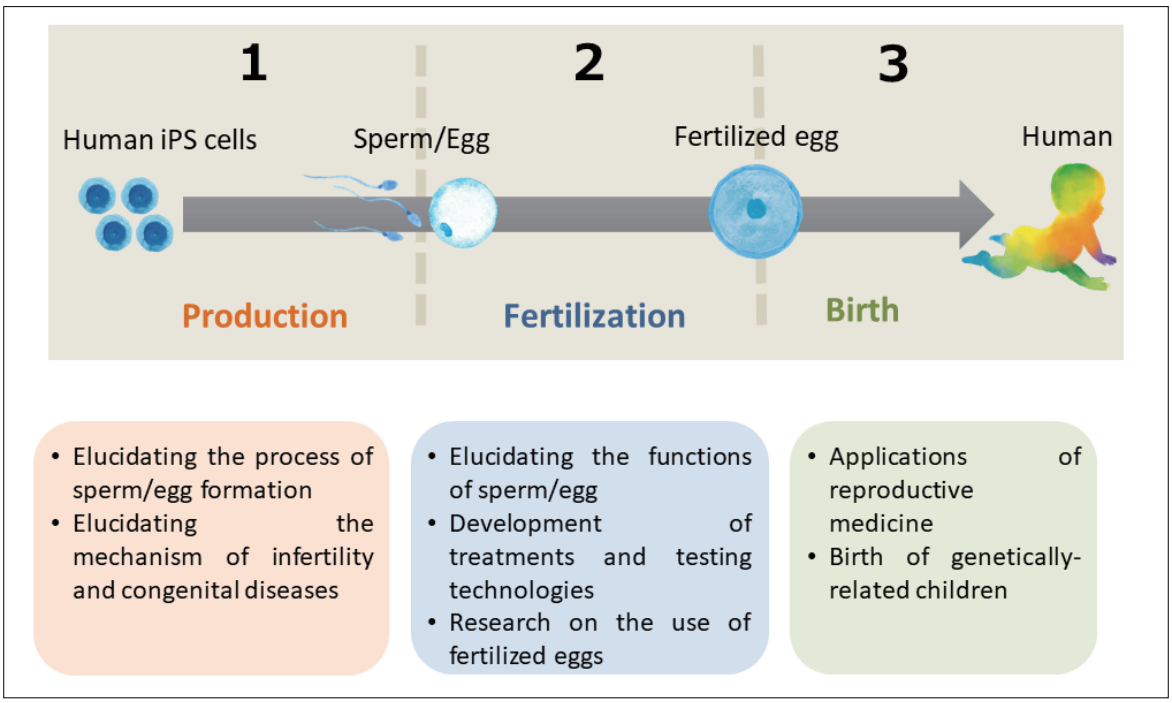

Figure 1

Illustration of the artificial gametes production research used in the attitude survey.

図 1

意識調査で用いた人工生殖細胞作製研究の説明図

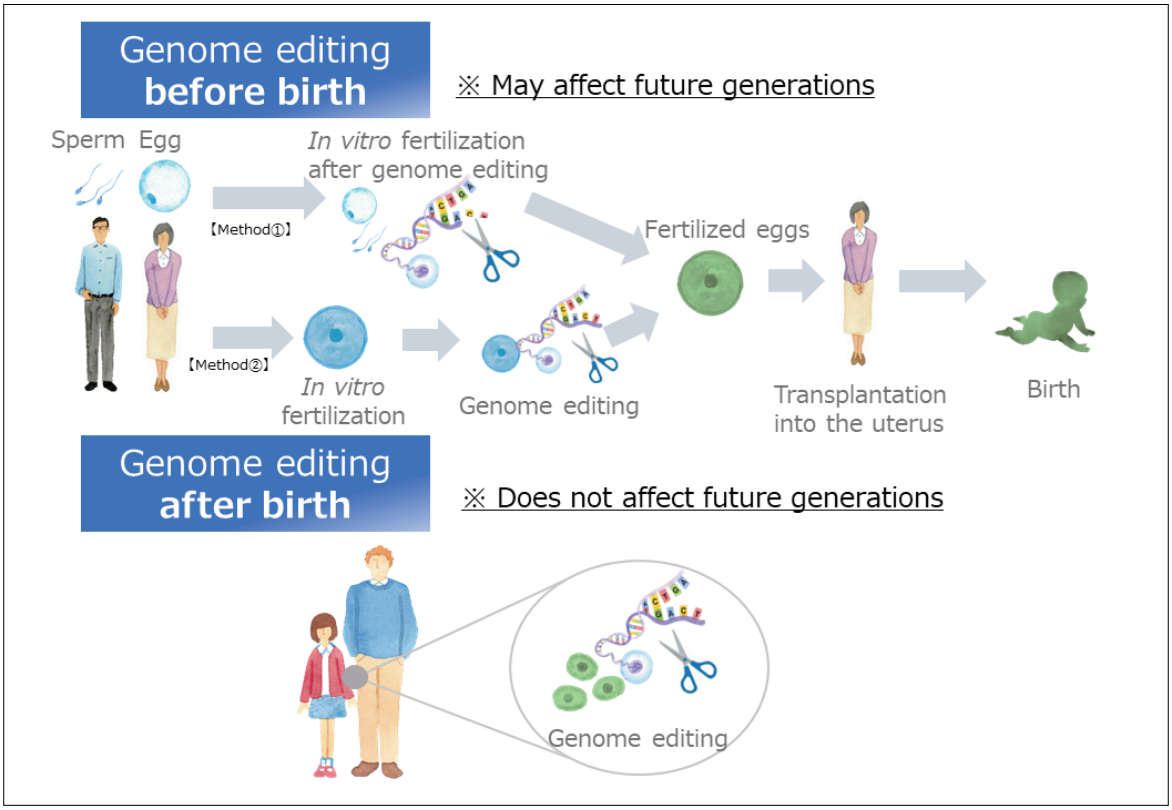

Figure 2

Illustration of research on genome editing in human cells used in the attitude survey.

図 2

意識調査で用いたヒトの細胞にゲノム編集を行う研究の説明図

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