Team for Advanced Development and Evaluation of Human Disease Models

[2008.4~]

[~2008.3: Shiroishi Research Collaborative Group]

Team Leader

Tetsuo NODA, M.D., Ph.D.

Goal

In augmenting the value of human disease model mutant mice as a resource used for diagnostic, therapeutic, and drug developments, the identification of the causal gene and the nature of mutations of the genes is indispensable. In addition, detailed information on phenotypes based on molecular mechanisms that may correspond to the conditions of human diseases further brings both basic and practical values. Our team is developing advanced mouse phenotype analytical technologies for revealing and augmenting such values of various mutant mice by adding novel phenotype information. Moreover, for human cancer model mice, advanced pathological technologies including in situ histological, genomic, epigenomic, and transcriptomic analysis will be applied to enhance the values of such mice as cancer models.

Activities

1. Development of advanced technologies for phenotypic analysis of mouse models of human diseases.
2. Application of advanced technologies for comprehensive pathological analysis to mouse cancer model.
3. Establishment and analysis of novel mouse model of deafness.

Members

Team Leader

Tetsuo NODA, M.D., Ph.D. (2008.4~)

Research & Development Scientist

Maki INOUE, D.V.M., Ph.D. (2008.4~)
Hiromi MOTEGI, Ph.D. (2008.4~)
Osamu MINOWA, Ph.D. (2008.4~)

Technical Scientist

Hideaki TOKI (2008.4~)

Technical Staff

Ami IKEDA (2008.4~)
Yuko KARASHIMA (2008.4~)
Taeko HIRAYAMA (2008.4~)
Junko MATSUI (2008.4~)
Tomoko KAGAMI (2008.4~)
Ayako SAGA (2008.4~)
Rika HOSHINO (2008.4~)
Aya MURAKAMI (2008.4~2008.6)

Agency Staff

Yuki IINO (2008.4~)
Chieko OOTSUKA (2008.4~)
Nami YAKUSHIJI (2008.4~)
Tadashi OOSHIMA (2008.10~)
Kumiko KUWAHATA (2008.4~2008.10)

Ootsuka, Kagami, Saga, Yakushiji, Matsui
Hirayama, Ikeda(A), Karashima, Iino, Kuwahata, Hoshino
Minowa, Motegi, Noda, Inoue, Toki

Specific Aims

1. Development of advanced technologies for phenotypic analysis of mouse models of human diseases.

To develop technologies for detecting and analyzing latent phenotypes that may emerge before the onset of symptoms (sub-symptomatic phenotypes), we are planning the following three research designs. Using such technologies, novel practical information can be added to mouse disease models.

(1) NMR metabolomic analysis

To analyze sub-symptomatic phenotypes, we are planning to conduct mouse metabolomic analysis using nuclear magnetic resonance spectroscopy (NMR). NMR can detect many hundreds of metabolites containing molecules that are undetectable by the present clinical examination . Moreover, with NMR, by labeling a whole mouse using a stable-isotope-containing molecule, specific metabolic pathways can be detected at high sensitivity. We have already completed a preliminary examination by a mouse labeling method using ^{13}C-glucose in a joint research project with RIKEN Laboratory of Environmental Molecular Biology (Dr. Hirayama), RIKEN PSC Advanced NMR Metabomics Research Unit (Dr. Kikuchi) and RIKEN GSC Population and Quantitative Genomics Team (Dr. Gondo). Study for further development of mouse labeling procedures are being planned to establish other methods of profiling various metabolites and detecting metabolite changes prior to emergence of symptoms.

(2) Global cytokine profiling for environmental response

The failure of an organism's mechanism for responding against various environmental stresses such as pathogen invasion, antigen attack, physicochemical stress, influences and food nutrient deficiency may cause various diseases. If a "dynamic phenotypic response induced by environmental factors" can be detected, it becomes valuable sub-symptomatic phenotypes for mice as disease models. We focused on cytokine level as one of such phenotypes. Our plan is to establish a method of measuring many types of cytokines simultaneously using a small volume of mouse serum. We have already established a system for assessing 11 types of serum adipocytokine using a "Multiplex suspension array" system. An expansion of the system is being planned to analyze the levels of many types of cytokines before and after environmental changes have occurred.

(3) Mutation discovery using nonsense-mediated decay (NMD) inhibition

Nonsense-mediated decay (NMD) is a mechanism that destroys the "immature" mRNA derived from premature

termination codons (PTCs) introduced by base substitutions, or insertion / deletion mutations. Recent investigations have shown that about one-third of genetic alterations that cause human diseases are "PTC-type mutations". Gene Identification by NMD Inhibition (GINI) is a gene identification method by artificial NMD inhibition. Several successful anti-cancer gene identifications have been reported using cultured cells derived from cancer patients. We are planning to apply GINI to in vivo neoplasia using the mouse cancer models that we established.

2. Application of advanced technologies to comprehensive pathological analysis of mouse cancer model.

A number of cancer-prone mouse mutant strains have been developed at RIKEN, which make up one of the significant repertoire of genetically modified mouse cancer models worldwide. Using these mutant mouse strains, the following comprehensive analyses will be performed to develop models consistent with the conditions of human cancer, which will be valuable as targets for clinical application: gene expression analysis at the individual level (whole-mount in situ hybridization), transcriptome analysis, histological gene expression analysis (LMD-microarray analysis), epigenome analysis, and gene product network analyses. To promote these comprehensive analyses effectively, a joint research project with research laboratories (Cancer Institute) that provide advanced human cancer diagnostic technologies based on clinical expertise will be set up. The analyses will greatly facilitate the development of models that will contribute to "hyper-early-stage" cancer diagnostics and anti-cancer drug development.

3. Establishment and analysis of novel mouse model of deafness.

Various deafness mutant mouse lines consisting of those with identified causative genes and mutations and those with still-unknown mutations have been isolated at RIKEN. The latter mutants carry several putative novel gene mutations as determind by mapping and candidate gene examination, indicating the involvement of a novel gene since no roles in the auditory system have been identified thus far. It is very crucial to identify these gene mutations to establish the value of the mouse strains as a deafness model. Furthermore, the establishment of novel deafness mutant models would provide a resource for clinical application research as well as for basic investigation of essential auditory functions that have remained unclear until now. To establish novel deafness mouse models by identifying mutations, we use fine mapping/ positional cloning. Detailed physiological and histological analyses of mutants facilitate the development of better models for understanding the overall mechanism of hearing loss, which can then be used for further practical application.

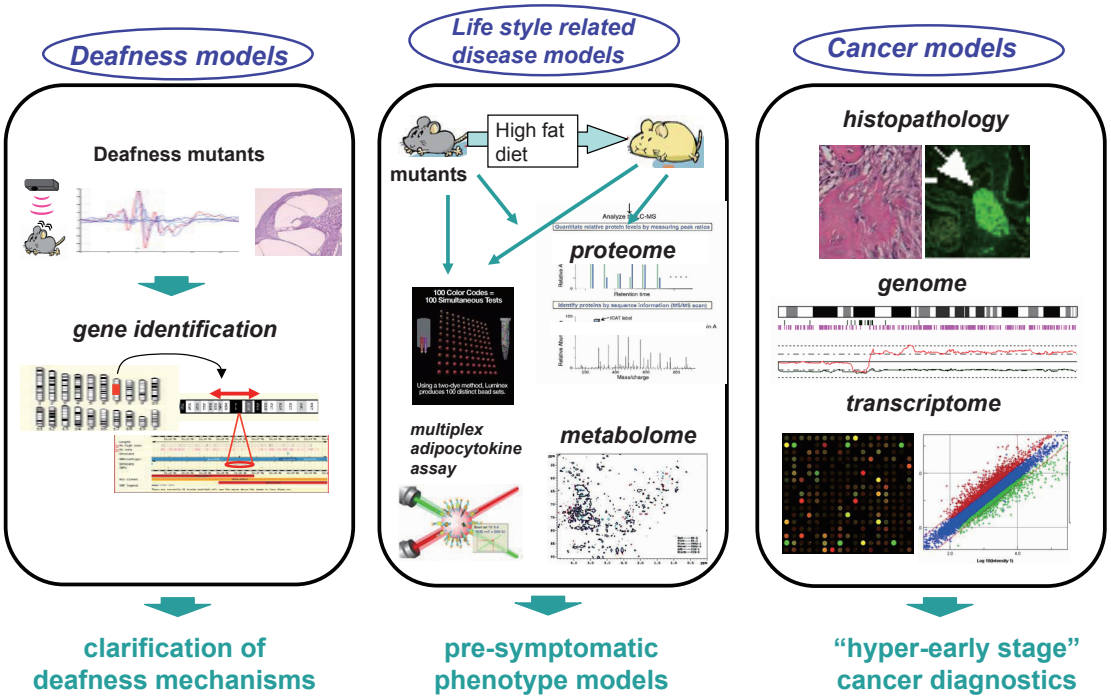

Figure 1. Development of advanced mouse phenotype analysis technologies

Publications

【Original Papers】(*Peer reviewed journals)

1. Ajima R., Akiyama T., Usui M., Yoneda M., Yoshida Y., Nakamura T., Minowa O., Noda M., Tanaka S., Noda T., Yamamoto T.: "Osteoporotic bone formation in mice lacking tob2; involvement of Tob2 in RANK ligand expression and osteoclasts differentiation." FEBS Letters, 582(9):1313-1318 (2008).*

2. Shigeyama Y., Kobayashi T., Kido Y., Hashimoto N., Asahara S., Matsuda T., Takeda A., Inoue T., Shibutani Y., Koyanagi M., Uchida T., Inoue M., Hino O., Kasuga M., Noda T.: "Biphasic response of pancreatic beta-cell mass to ablation of tuberous sclerosis complex 2 in mice." Mol Cell Biol. 28(9):2971-2979 (2008).*

3. Kaminuma E., Masuya H., Miura I., Motegi H., Takahashi K., Nakazawa M., Matsui M., Gondo Y., Noda T., Shiroishi T., Wakana S., Toyoda T.: "Objective evaluation measures of marker selection in large-scale SNP genotyping." Journal of Bioinformatics and Computational Biology, 6:905-917 (2008).*

Oral Presentations

【International Conferences】

1. Wakana S., Suzuki T., Masuya H., Miura I., Kobayashi K., Kaneda H., Furuse T., Yamada I., Motegi H., Toki H., Inoue M., Minowa O., Tanaka N., Noda T., Shiroishi T., Obata Y.: "A plan of Japanese Mouse Clinic in RIKEN BRC." 22nd International Mammalian Genome Conference, Prague, Czech Republic, Nov. (2008).*

2. Suzuki T., Sato H., Ikeda K., Masuya H., Yokoyama H., Nishimura S., Kaneda H., Miura I., Kobayashi K., Toki H., Minowa O., Kurihara Y., Shiroishi T., Wakana S.: "Genetic analyses of inherited retinal degeneration model mouse in ENU mutagenesis." 22nd International Mammalian Genome Conference, Prague, Czech Republic, Nov. (2008).

3. Murata T., Umemura N., Nakayama E., Yamaguchi T., Nakahara A., Karouji K., Ishitsuka Y., Kotaki H., Fukumura R., Makino S., Nakai Y., Toki H., Motegi H., Kaneda H., Noda T., Wakana S., Gondo Y.: "Molecular and mouse level analyses of multiple point mutations of beta-catenin gene obtained by ENU-based Gene-driven mutagenesis." 22nd International Mammalian Genome Conference, Prague, Czech Republic, Nov. (2008).

【Domestic Conferences】 Total 6