2012
HIROSAKI UNIVERSITY RESEARCH HIGHLIGHTS

Establishing a Global Identity
Creating with the Community

HIROSAKI UNIVERSITY

Investigation of factors that regulate individual differences in radiosensitivity of hematopoietic stem cells and the application of these factors in regenerative therapy and the determination of radiosensitivity

Purpose and Background of the Research

The present study aims to clarify individual differences in the radiosensitivity of human hematopoietic stem cells (HSCs), which are sensitive to ionizing irradiation. In addition, this study has investigated and is continuing to investigate factors that regulate individual differences in radiosensitivity and the application of these factors in regenerative therapy and the determination of radiosensitivity. This would help in establishing diagnostic methods for the risk assessment of individuals who face a threat of exposure to high-dose radiation at the workplace or patients who have undergone high-dose radiation therapy and chemotherapy.

Research Results

There has been many academic achievements through the support of Hirosaki University Institutional Research between the years of 2009 and 2011. Some of the major research accomplishments are listed below:

1. The potential efficacy of human mesenchymal stem cell-like stroma for hematopoietic regeneration from irradiated hematopoietic stem/progenitor cells was demonstrated. ***Life Sciences***, 84: 598–605 (2009).
2. It was demonstrated that mature megakaryocytes are radiosensitive, but their radiosensitivity decreased in the terminal stages of megakaryocytic maturation, especially for megakaryocytes entering the proplatelet formation. ***Radiat Res***, 172(3): 314-320 (2009).
3. The radiosensitivity of individual HSPC populations is related to the number of progenitor cells in the population; it is particularly dependent on the presence of immature HSPCs such as Tie-2+ cells. ***Radiat Res***, 173(2):184-90 (2010).
4. It was suggested that the antioxidant system associated with Nrf2, which is a key protein in the coordinated transcriptional induction of expression of various antioxidant genes, is involved in the radiosensitivity of HSCs. ***Radiat Res***, 174(2): 177–184 (2010).
5. Ionizing radiation may have the potential to promote both megakaryocytopoiesis and thrombopoiesis. ***Radiat Res***, 176(6):716-724 (2011).

The following list shows the total number of academic achievements each year.

- Original article: 2008, 16 articles; 2009, 21 articles; 2010, 26 articles.
- International conferences: 2008, 10 times; 2009, 11 times; 2010, 20 times.
- Domestic conferences: 2008, 33 times; 2009, 34 times; 2010, 42 times.
- Patent applications: 2008, 3 patents; 2009, 1 patent; 2010, no patents.
- Seminars: 2008, 7 times; 2009, 7 times; 2010, 4 times.

Future Prospects

A member of the Research Center for Biomedical Sciences who performed this study will now contribute in the following ways to Hirosaki University: obtain external grants, corroborate with scientific facilities globally, promote a JST educational program titled "Professionals in Radiation Emergency Medicine" supported by the Japanese government, promote educational and academic activities at Hirosaki University, and develop outreach programs for the community.

Funding

1. Grant for Hirosaki University Institutional Research, FY2008-2011: 24,000 Thousand Yen.
2. JSPS KAKENHI Grant Number 21390336, FY2009-2012: 8,400 Thousand Yen.
3. JST Strategic Funds for the Promotion of Science and Technology, Funds for the Development of Human Resources in Science and Technology, FY2010-2014: 43,890 Thousand Yen.

PROFILE

Ikuo Kashiwakura

Department of Radiological Life Sciences, Graduate School of Health Sciences, Hirosaki University, Professor

E-mail
ikashi@cc.hirosaki-u.ac.jp

The molecular pathology of Parkinson's disease

Purpose and Background of the Research

Synucleinopathy comprises a group of neurodegenerative disorders that share abnormal α-synuclein in selected vulnerable neurons and glial cells. Abnormal α-synuclein is accumulated and fibrillated in the neuronal cytoplasm and processes as Lewy bodies (LBs) and Lewy neurites, respectively, in the brain of patients with Parkinson's disease (PD) and dementia with LBs (DLB), as well as in glial cytoplasmic inclusions in multiple system atrophy (MSA).

LBs consist of a heterogeneous mixture of more than 90 molecules, including PD-linked gene products (α -synuclein, DJ-1, LRRK2, parkin and PINK-1), and molecules implicated in the ubiquitin-proteasome system, autophagy and aggresome formation. LB formation has been considered to be a marker for neuronal degeneration, because neuronal loss is found in the predilection sites for LBs.

Research Results

1. Abnormal α -synuclein in the presynapses in LB disease

Since proteinase K (PK) treatment is known to enhance the immunoreactivity of abnormal α -synuclein, we immunohistochemically examined brains with LB disease (PD and DLB) using this retrieval method. PK-resistant α -synuclein was deposited in LBs and Lewy neurites, as well as in the presynapses in distinct brain regions, including the hippocampus, temporal cortex and substantia nigra. Biochemical analysis revealed that PK-resistant α -synuclein was detected in the presynaptic fraction. Considering that native α -synuclein is a soluble protein localized to the presynaptic terminals, our findings suggest that PK-resistant α -synuclein may disturb the neurotransmission in synucleinopathy. We further demonstrated that NUB1 accumulates in the presynapses in the hippocampus, cerebral neocortex, and substantia nigra in which PK-resistant α -synuclein is deposited (Figure).

2. Autophagy-related proteins in synucleinopathy

Macroautophagy is a dynamic process whereby cytoplasmic components are initially sequestered within autophagosomes. The autophagosome membrane can selectively recognize ubiquitinated proteins and organelles through interaction with adapter proteins such as p62 and NBR1. Although p62 is incorporated into a wide spectrum of pathological inclusions in various neurodegenerative diseases, abnormalities of NBR1 have not been reported in these diseases. Our immunohistochemical examination revealed that the vast majority of LBs in PD and DLB as well as glial cytoplasmic inclusions in MSA were positive for NBR1. Using cultured cells bearing LB-like inclusions, formation of α -synuclein aggregates was repressed in cells with NBR1 knockdown. Immunoblot analysis showed that the level of NBR1 was significantly increased by 2.5-fold in MSA, but not in DLB. These findings suggest that NBR1 is involved in the formation of cytoplasmic inclusions in synucleinopathy.

Double immunofluorescence labeling showing immunoreactivity of synaptophysin (green) and NUB1 (red) in the hippocampal regions of transgenic mice expressing human mutant A53T α-synuclein. Yellow indicates the colocalization of synaptophysin with NUB1.

Future prospects

We believe that activation of autophagy may have a place in PD therapy.

Funding

1. Grant for Hirosaki University Institutional Research, FY2009-2011, 21,500 Thousand Yen
2. JSPS KAKENHI Grant Number 20300123,FY2008-2011, 13,900 Thousand Yen

PROFILE

Koichi Wakabayashi

Department of Neuropathology, Graduate School of Medicine, Hirosaki University,Professor

E-mail
koichi@cc.hirosaki-u.ac.jp

Creative Development of Liquid-Crystalline Materials

Purpose and Background of the Research

This research project was organized along several main themes: discovery of novel LC phases and materials; development of LC materials with a fast response speed for display devices; investigation of environmental- and human-friendly processes in supercritical CO_2, that is, a water-in-CO_2 microemulsion (W/CO_2 μE); and study of biological activity of liquid crystal-related compounds. The purpose is to innovate a research field of liquid crystals.

Research Results

1) We designed mesogenic oligomers exhibiting a liquid-crystalline phase with a hierarchical structure. Especially, chiral liquid crystals possessing a molecular biaxiality were found to stabilize blue phases.
2) We reported a fast electro-optical switching in an amorphous blue phase III (BPIII) stabilized by a chiral T-shaped compound. The present nanotechnology can offer fast switching between a well black state of the BPIII and a homogeneous bright state of the induced nematic phase without surface treatment. An in-plane-switching cell containing a BPIII material exhibited high transmittance, submillisecond response, and hysteresis-free switching at room temperature (Fig.1).
3) This study successfully developed a super-efficient solubilizer 4FG(EO)$_2$, which can solubilize water-to-surfactant molar ratio (W_0) of 80 in spite of industrially-acceptable short fluorocarbon (C4) tails. In addition, one of the iso-stearyl surfactants newly synthesized was able to disperse water in supercritical CO_2 efficiently. The attainable W_0 in W/CO_2 μE was 50, which is the largest efficiency in all hydrocarbon surfactants ever reported.
4) We found that a relationship between anti-tumor activity and liquid-crystallinity of mesogenic compounds, indicating that the supramolecular assembly composed of low-molecular-mass compounds plays an important role in the biological activity. Furthermore, some liquid-crystalline compounds possessing a primary alcohol recognize differences between cancer cells and normal cells (Fig.2). Our findings provide novel insight into the creation of new anticancer drugs.

Future prospects

- Improvement of physical properties of the BPIII material for realizing high-performance liquid crystal displays.
- Development in an efficient, environmentally friendly, and low cost surfactant working at mild pressure (~100 bar) and temperature (~rt) conditions. If it will be possible, the W/CO_2 μE can be used to establish green and sustainable chemical processes for extraction, dry-cleaning, nanomaterial processing, organic synthesis and so on.
- Drug design of anticancer agents using a supramolecular assembly composed of liquid-crystalline molecules.

Funding

1. Grant for Hirosaki University Institutional Research, FY2008-2010, 9,750 Thousand Yen
2. JSPS KAKENHI Grant Number 22350078 FY2010-2012, 9,100 Thousand Yen
3. JST, Project to Develop "Innovative Seeds", Grant Number 02-003, FY2009, 2,000 Thousand Yen
4. JSPS KAKENHI Grant Number 21655045, FY2009-2010, 3,200 Thousand Yen

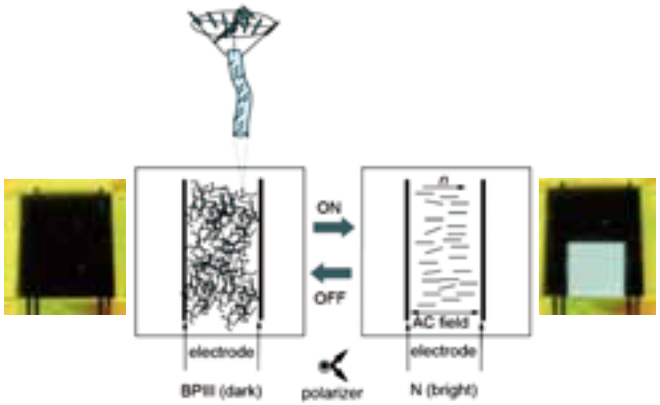


Fig.1 Schematic representation of the electric-field-induced phase transition between BPIII and N.

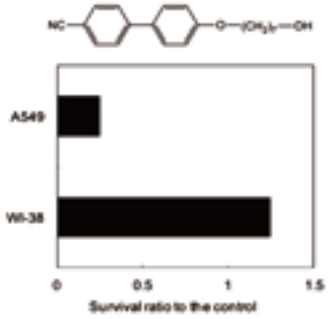


Fig.2 A liquid-crystalline compound possessing a primary alcohol exhibits anticancer activity against A549 human lung carcuinoma cells without toxicity against WI-38 normal fibroblast cells.

PROFILE

Atsushi Yoshizawa

Graduate School of Science and Technology,
Hirosaki University, Professor

Website
http://www.st.hirosaki-u.ac.jp/~lclab/
E-mail
ayoshiza@cc.hirosaki-u.ac.jp

Research and Education by Collaborations between Medicine and Engineering at Hirosaki University

Purpose and Background of the Research

In order to develop medical devices for clinical use, collaborative research activities between medicine and engineering faculties/departments started in 2001 at Hirosaki University. The advanced medical device center, developed in the faculty of science and technology in 2005, has conducted joint activities for research and education on medical engineering. We describe the research results on medical engineering for healthware, conducted at the center[Funding1)].

Research Results

1. Developments of sensors for medical use

1.1 Pressure distribution sensor

In order to examine a contact situation in organs, we developed a pressure distribution sensor constructed with rubber sheets contained fine carbon particles and metal thin film electrodes on the sheet. Fig.1 shows an application result of the sensor, which has a thickness of 270 μm and a space resolution of 90 μm, designed to detect pressure distribution in a knee joint. The data obtained with the sensor were used for medical treatments of the knee joint. In addition, the sensor was applied successfully to measure contact pressure in oral cavity and pharynx for evaluation of swallowing.

1.2 Micro sensor for detecting thrombus formation in a fine blood vessel

In microsurgery of reconstruction of a finger, thrombi tend to form near anastomotic sites in a fine blood vessel of diameter of less than 1 mm. In this case, since tissue failure sometimes occurs, it is necessary to monitor formation of thrombus. For this purpose, we developed a micro sensor detecting diameter changes of the fine blood vessel due to thrombus. The sensor was constructed with a clip actuator to hold the sensor on the outside wall of the blood vessel and a micro thin film strain gage. Using the sensor, diameter changes of 15-150 μm were detect at a high sensitivity. Clinical utilization of the sensor was examined through rat experiments.

2. Wireless data sensing and computer analysis of human movements

Computer data analysis of human movements such as walking and speed during sports is important for healthcare or sports medicine. Portable sensors such as 3-axis accelerometers and angular velocity sensors were installed on a human body and obtained data were analyzed on a host computer. Fig.2 shows analysis results of movements of elbow and shoulder during throwing a ball. From the results, optimum throwing form is proposed to avoid injuries. For this computer analysis, wireless data transmission is a key technology. By customizing software of a commercially available sensor network, data acquisition at a distance of about 100 m at a sampling interval of 10-20 ms became possible.

3. Visualization and computer analysis of blood flow

During extracorporeal circulation in an aortic arch, a sandblast effect by jet blood flow causes crumbling of intimal atheroma or detachment of a cholesterin embolus from the plaque, resulting in atheroembolism. In order to avoid these situations, effects of the shape, position, and direction of an aortic cannula on blood flow direction and flow velocity distribution were investigated with the particle image velocimetry (PIV) and a computer simulation. Fig.3 shows a typical result of blood flow patterns for various type aortic cannula. From these analyses, we attempted to find an optimum condition for cannulation.

Future prospects

More than 15 researchers on engineering joined a teamwork to the advanced medical device center and conducted joint work with medical doctors to develop novel devices for clinical use. Moreover, education for medical engineering is an important mission for the center. To promote a medical device industry in the Aomori area, we are committed to provide sufficient education of medical engineering for engineers in the area[Funding2)]. A new research and education program on healthware science is designed for Master course students at the graduate school of science and technology, Hirosaki University[Funding3)].

Funding

1. Grant for Hirosaki University Institutional Research, FY2008-2010, 21,300 Thousand Yen
2. Strategic Funds for the Promotion of Science and Technology, FY2008-2012, 232,180 Thousand Yen
3. Grant for MEXT Special Expenditures, FY2011-2013, 146,490 Thousand Yen

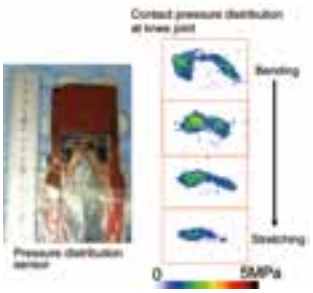


Fig.1 Measurements of contact pressure distribution at knee joint

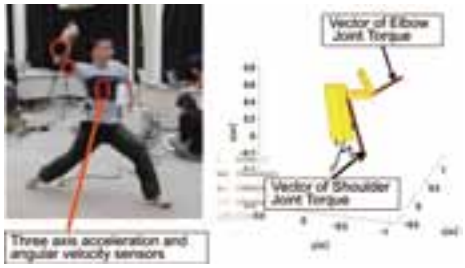


Fig.2 Sensing and computer analysis during Ball-Throwing Movements.

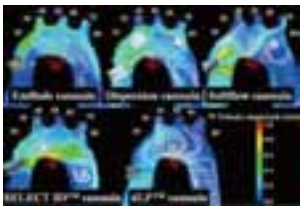
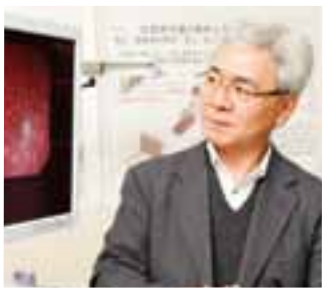


Fig.3 Visualization of blood flow in aortic arch

Eiji Makino



Toshiro Ono

Eiji Makino[1)]
Toshiro Ono[2)]

Graduate School of Science and Technology, Hirosaki University
1)Professor Emeritus
2)Professor, Director of Advanced Medical Device Center

E-mail : tono@cc.hirosaki-u.ac.jp

PROFILE

Jomon Culture: Inheritance from the past opening future doors

Purpose and Background of the Research

Kamegaoka culture flourished during the last stage of the Jomon Era about 2,300 to 3,000 years ago (roughly 1000-300 B.C.) stretching from the southwestern part of Hokkaido to the northern part of the main island, called the Tohoku district. In these areas, this ancient culture has left behind and array of artifects and remains.

The Research Center for Kamegaoka Culture at Hirosaki University was established in 2005. The aim of the center is to research Kamegaoka culture through multidirectional research and contribute to the academic community, as well as, revitalizing the local communities by bringing to life this regional culture.

Research Results

1. Multidirectional Research for the Kamegaoka Culture

Through the excavation of three archeological sites, located in wet sections of land, and applying advanced analytical technology, researchers at the center have been able to reassemble a picture of the Kamegaoka culture in the northern part of the Tohoku region.

2. Storage of Cultural Property and Publication of Scientific Research Results

Our research center stores and maintains a collection of more than 10 thousand items. They are valuable assets for research and education into Japanese history and archaeology. They are indexed and designated Important Cultural Property. These research results and materials are available to the public in exhibition rooms, where nearly one thousand visitors visit every year. The research findings at this center are made available for both the benefit of domestic and international researchers to utilize.

3. Returning the Research Results to Society【Development of a Kamegaoka Design Pattern】

Through the research at this center and references made to the collection, we have been able to revitalize the Kamegaoka culture, especially in our ability to revive the Kamegaoka design pattern. By way of an academic-industrial alliance, traditional handcrafts like the Tsugaru natural indigo dye for textile goods have been produced in the Kamegaoka cultural area of Aomori Prefecture.

Future prospects

-Sharing the fruits of our research into the past for a better future

Recently, there has been a lot of discussion concerning dramatic environmental changes to our planet such as global warming. Future archeological research projects can address such issues by looking at how ancient cultures learned to adapt and survive to environmental changes by developing new and different agricultural crops and resources.

We will not only focus on how cultures adapted to changing environmental patterns through multidirectional and collaborative research with international institutions, but through introducing modern landraces to their corresponding ancient landraces that had acclimated to environmental changes, we can attempt to produce tolerant varieties of crops and undertake the cultivation of them in unstable environments. We believe that this research strategy will not only enhance the future value of local resources, but also promote the revitalization of local area development and an indigenous industry in the future.

Funding

1. Grant for Hirosaki University Institutional Research, FY2009-2011, 21,500 Thousand Yen
2. Grant for MEXT Special Expenditures, FY2011-2015, 384,870 Thousand Yen
3. JSPS KAKENHI Grant Number 22242024, FY2010-2014, 26,400 Thousand Yen
4. JSPS KAKENHI Grant Number 24720349, FY2012-2015, 2,990 Thousand Yen

Fig.1 Excavation of the Jomon site in Aomori

Fig.2 The goggle-eyed figurine

Fig.3 Exhibition Room of Archaeological Cultural Asset

PROFILE

Tatsuhito Sekine

Center for Research of Kamegaoka Culture, Faculty of Humanities, Hirosaki University, Professor

E-mail
sekine@cc.hirosaki-u.ac.jp
Website
http://human.cc.hirosaki-u.ac.jp/kamijo/Kamegaokasennta-top.html

Hirosaki University Special Academic Award are awarded to authors of papers judged to be outstanding contributions to the university's research mission. Papers of recipients must provide a significant advance in the state-of-the-art or understanding of a particular topic.

Electro-optical switching in an amorphous blue phase III stabilized by a liquid crystal oligomer

Blue phases are of particular interest because they have a fluid lattice with a structure stabilized by lattice defects. Blue phases are potentially useful for application as fast light modulators or tunable photonic crystals, but their narrow temperature range presents a critical problem. Generally, a rod-like molecule prefers to show a liquid-crystalline phase. However, we found that U-shaped and T-shaped compounds possessing a molecular biaxiality exhibit marked effects on the blue phase stabilization. Based on the new concept, we designed a chiral T-shaped compound exhibiting an amorphous blue phase III (BPIII). We observed the fast electric-field-induced phase transition from BPIII to nematic (N) of the T-shaped liquid crystal. To obtain a practical BPIII material, we prepared a ternary system consisting of a conventional nematic mixture, a T-shaped BP stabilizer, and a chiral dopant with high twisting power. An in-plane-switching cell containing the BPIII material exhibited high transmittance, submillisecond response, and hysteresis-free switching at room temperature. After the BPIII cell had been preserved for one month at 25 °C, the electro-optical switching was confirmed as identical to that of the virgin state. The present nanotechnology can offer fast switching between a well black state of the BPIII and a homogeneous bright state of the induced N phase without surface treatment, and it can extend liquid crystal science to novel photonics applications.

Atsushi Yoshizawa
Graduate School of Science and Technology,Hirosaki University,Professor

PROFILE

E-mail
ayoshiza@cc.hirosaki-u.ac.jp
Website
http://www.st.hirosaki-u.ac.jp/~lclab/

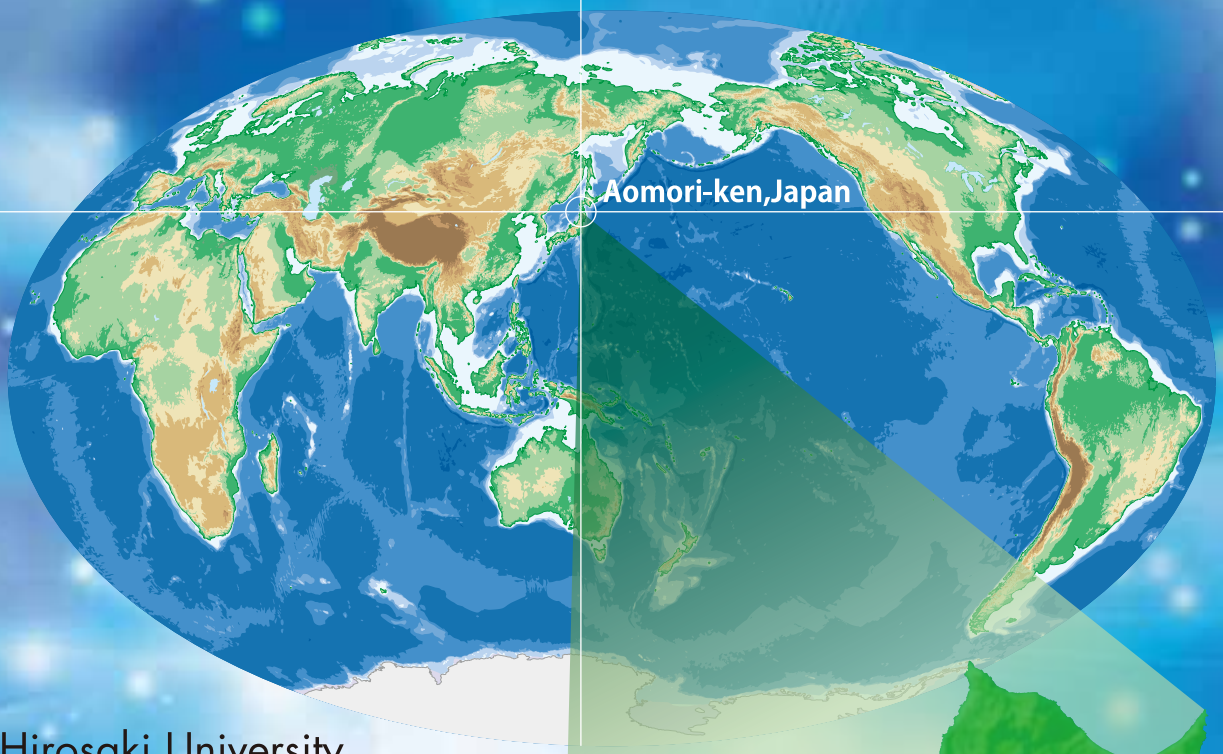
Mechanism of protein aggregation in neurodegenerative diseases

Neurodegenerative diseases (NDs) are debilitating conditions that result in progressive degeneration in the central nervous system. Patients, families and societies have been suffered from NDs. NDs are pathologically characterized by the presence of aberrant aggregates in the central nervous system. Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are representative NDs, which should be conquered. The aggregates in PD are named Lewy bodies and those in ALS are called skein inclusions. Our group has been trying to elucidate the formation processes of those inclusions for more than 10 years. In 2006, we demonstrated that decreased tyrosine hydroxylase immunoreactivity in pigmented neurons is closely associated with Lewy bodies in PD patients. In 2009, we showed that the decreased cystatin C immunoreactivity in the spinal motor neurons is closely associated with the presence of skein inclusions in ALS patients. Our neuropathological findings suggest that perturbations in endogenous levels of functional proteins including tyrosine hydroxylase and cystatin C in neuronal and glial cells may participate in neurodegenerative processes. In 2012, we indicated that several proteins associated with familial ALS may contribute to the formation or degradation of aberrant protein aggregates in NDs including PD and ALS. We believe that the perturbations of functional proteins may contribute to the therapeutic intervention in NDs.

PROFILE

Fumiaki Mori
Department of Neuropathology, Graduate School of Medicine, Hirosaki University, Associate professor

E-mail
neuropal@cc.hirosaki-u.ac.jp



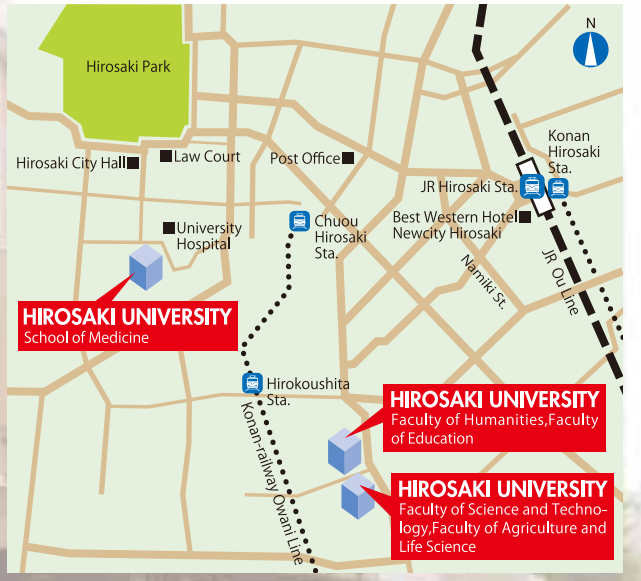
About Hirosaki University

Hirosaki University is a medium-size university with Faculties of Humanities, Educations, Medicine, Science & Technology, and Agriculture & Life Science.The five faculties cover a broad and comprehensive range of undergraduate academic disciplines. The university offers graduate programs, including the independent and interdisciplinary doctoral programs in Regional Studies.

Hirosaki University has a strong commitment to research on topics related to globalisation and global challenges. University staff and student researchers address many of the major challenges that face our society, from global warming to food production, new energy sources to biodiversity. They use innovative research techniques and modern technology, both to examine problems of the modern world and to contribute to local economic growth and development.

In this booklet, we introduce our research findings.

Access Map



HIROSAKI UNIVERSITY

Edited by Research Promotion Department, Academic Information Division,
Hirosaki University, 1 Bunkyo-cho, Hirosaki, Aomori-ken, 036-8560, Japan
URL http://www.hirosaki-u.ac.jp/ E-Mail kenkyu@cc.hirosaki-u.ac.jp
March 2013