

2013

HIROSAKI UNIVERSITY RESEARCH HIGHLIGHTS

Medicine

Humanities

Education

**Establishing a Global Identity
Creating with the Community**

*Agriculture
and Life Science*

*Science and
Technology*



Hirosaki University Institutional Research Grant (2011–2013) “The Great East Japan Earthquake-capable Radiological Research Program”

Purpose and Background of the Research

The aim of this program has three main points. Firstly, it aims to contribute to the restoration and reconstruction efforts of the Great East Japan Earthquake of 2011. Secondly, it aims to contribute to Hirosaki University's Second Mid-term goals and medium-term plan. Thirdly, it aims to contribute to the safety and security of Aomori Prefecture, as well as, to the whole nation. This program is a cooperative project with The Institute of Radiation Emergency Medicine and Research Center for Biomedical Sciences at Hirosaki University. The program is composed of the following three major research subjects: 1) Radiation evaluation and environmental radioactivity; 2) Dose-contamination assessment of individuals exposed to radiation; 3) Treatment of individuals exposed to radiation.

Research Results

There has been many academic achievements through the support of Hirosaki University Institutional Research between the years of 2011 and 2013. Some of the major research accomplishments are listed below:

*Scientific Reports*¹⁾, 1:8 (2011); *PLoS One*²⁾, 6(11): e27761 (2011); *Scientific Reports*³⁾, 2: 507 (2012); *PLoS One*⁴⁾, 8 (7): e70503 (2013); *Scientific Reports*⁵⁾, 3:2283 (2013); *Environmental International*⁶⁾, 61:73-76 (2013).

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

- Original article: 2011, 48 articles; 2012, 59 articles.
- International conferences: 2011, 17 times; 2012, 19 times.
- Domestic conferences: 2011, 80 times; 2012, 40 times.
- Patent application: 2012, 1 matter*.
- Seminars: 2011, 5 times; 2012, 5 times; 2013, 5 times (as of December, 2013).

Future Prospects

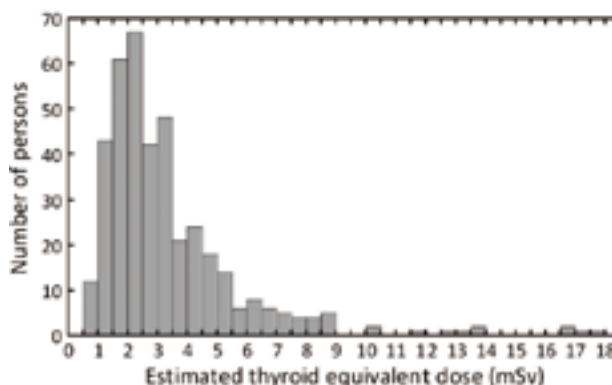
A member of the project will contribute in the following ways to Hirosaki University: obtain external grants, corroborate with scientific facilities globally, promote a JST educational program titled “Professionals in Radiation Emergency Medicine” supported by the Japanese government, promoting educational and academic activities at Hirosaki University, and develop outreach programs for the community.

Funding

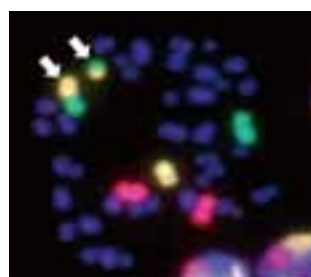
1. Grant for Hirosaki University Institutional Research Grant, FY2011-2013: 19,950 Thousand Yen.
2. JSPS KAKENHI #21390336, FY2009-2011: 8,400 Thousand Yen; #22659216, FY2010-2011: 2,800 Thousand Yen; #25293256, FY2013-2016: 13,900 Thousand Yen (I. Kashiwakura); #24310002, FY2012-2014: 13,600 Thousand Yen;

#24110004–A02, FY2012-2016: 60,100 Thousand Yen (M. Yamada) *et al.*

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.

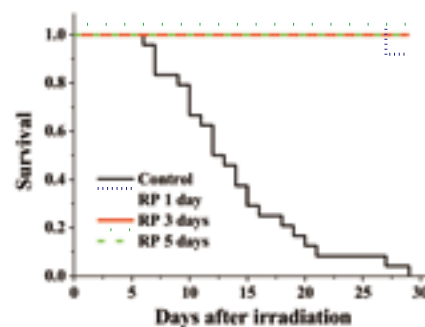


Frequency distribution of estimated thyroid equivalent dose excluding the value under the minimum detectable amount (Research subject #1⁶⁾).



A typical morphology of abnormal human chromosome (Research subject #2).

The radioprotective effects of romiplostim (RP) alone on the survival of mice exposed to lethal 7 Gy γ -irradiation (Research subject #3*).



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Using Economic Theory and Research for the Reconstruction Plan that considers QOL from the Great East Japan Earthquake: A Case Study of "Team All Hirosaki"

Purpose and Background of the Research

The purpose of this research is to look at the role that external volunteers have on building relationships between the local residents and to examine the main factors that may contribute to the recovery of the local residents' sense of identity in the disaster hit areas.

The Great East Japan Earthquake of 2011 has been classified as a wide area disaster. Survivors in the stricken areas not only needed support from the more populous and affluent areas of the South, but also from areas in the North. Our university is located in Hirosaki City, which is about 3 hours north by bus from one of the affected villages of this earthquake, Noda Village. The university's close proximity to these stricken areas allows researchers and students to do volunteer activities in the area in an affordable way. Universities naturally have a strong body of students who are young, strong, and eager to help people affected by this disaster and also have background knowledge in various academic fields. Due to this, universities are in a special situation to play in a active role in supporting areas hit by the earthquake. During our volunteer work in these areas, we have listened closely to the voices of the local survivors. They wanted to record the old memories they had of Noda Village and were also willing to know more about other areas also affected by the disaster. They feared listening directly to other people's stories of suffering and hardship. They passionately wanted their stories to be delivered to the local government. From these experiences interacting with local community, we developed a research program to support volunteer activity. This research aims to record the life histories of local residents through interviews, survey the residents' current feelings and attitudes, analyze the current situation in the area, and discover the resources and advantages of the region.

Research Results

This study looks at the factors that influence whether the local residents of Noda in Iwate Prefecture will remain in their village or relocate to a different village following the 2011 Great East Japan Earthquake. Using data gathered from our original questionnaire, younger villagers, women, and unmarried individuals showed a greater likelihood of relocating. Though respondents from higher-income households indicated that they had a stronger intention to remain in their hometown, which seems to correspond with the compensating wage hypothesis. Damage to homes, loss of jobs, or reduction of household income did not significantly affect intentions to relocate. However on the other hand, villagers who suffered the loss of a family member and/or family network stated having a stronger intention to relocate after the disaster.

We analyzed not only how the earthquake affected one's intention to relocate, but also how the disaster altered villagers' perception of what is valuable in life. Loss of human life and the human networks between people proved to be a greater indicator for motivation to relocate among the residents than loss of material capital. This study points out the importance for Japan's disaster recovery programs to consider ways to reestablish human networks between the residents in these disaster hit areas simultaneously with the rebuilding effort of the villages.

Future prospects

Action research is a deeper form of research, utilizing collaborative practices that can build a broader and far reaching relationship between the survivors of a disaster and the researchers. Collaborative practices are an essential part of action research and the better the collaborative practices the more meaningful research the researcher can do and in the end more deeply understand the survivors' situation. Therefore collaborative practices and action research are survivor-centered and will obviously take more effort and time to accomplish compared to a simple questionnaire. We will try to continue improving, modifying, and updating our approaches and methods to doing action research.

Funding

Hirosaki University Institutional Research Grant FY 2013
300 Thousand Yen
JSPS KAKENHI Grant Number 24243056 FY2012-2014
43,810 Thousand Yen

Table 1 Extent of Damage Suffered and Its Effect on Intentions to Relocate

Variable	Damaged		Non Damaged	
	Coeff.	SE	Coeff.	SE
Male	-0.4173	0.4412	-0.8140**	0.3897
Age	-0.0637***	0.0194	-0.0513***	0.0154
Married	-0.9444	0.6405	-0.9247*	0.4936
Child	0.7524	0.6447	-0.2522	0.5323
Household Income	-0.0008	0.0010	-0.0007	0.0009
Hometown	-1.0752**	0.4902	-0.9258**	0.3910
House ownership	0.2789	0.4817	-1.0979***	0.4152
Families and Relatives Network	-0.1329**	0.0548	0.0187	0.0166
Local Human Network	-0.0323	0.0465	-0.0091	0.0158
Agriculture	-14.9616	1809.7230	-0.6558	1.0596
Fishery	-16.1852	1626.6970	0.6470	0.6240
Obs.	266		440	
Pseude R ²	0.2528		0.2152	
Log L	-78.786974		-120.63415	

Note: Coeff., coefficient; Obs., observed.

*** Significant at, or below, 1 percent.

** Significant at, or below, 5 percent.

* Significant at, or below, 10 percent.



Volunteer Bus (University students and Citizens)



Removing debris



Recovering Lifeline(infrastructure)



Classifying assistance materials



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Biological systems from the point of view of RNA

Purpose and Background of the Research

With recent progress in genome sequencing, we have come to know that a much larger-than-expected number of RNA species function in a cell. The purpose of our research project is to revisit the biological systems based on RNA from new viewpoints and to approach new RNA systems through investigations of various kinds of RNA molecules of unknown functions.

1. Translation often stalls in various situations in cells. In bacterial cells, *trans*-translation mediated by tmRNA (transfer and messenger RNA) rescues the stalled ribosome by changing the truncated mRNA to the coding region of tmRNA, which has both features of mRNA acting as a messenger of the genetic information encoded by the genome and tRNA acting as a tool for decoding, to continue translation. We have extensively studied the molecular mechanism of *trans*-translation as well as its cellular functions.
2. Ribosome is an RNA-based macromolecule having multiple functional sites to facilitate protein synthesis, and it is synthesized through highly complicated processes including stepwise cleavages of the RNA precursors, modifications of ribosomal proteins and RNAs, and assemblies of ribosomal proteins with rRNAs with the aid of dozens of *trans*-acting factors. We have extensively studied this highly complicated ribosome maturation process.

Research Results

1. The molecular mechanism of the *trans*-translation system has been revealed: The globular domain of SmpB, a tmRNA binding protein, mimics the lower half of the translating tRNA at every step of *trans*-translation, while the C-terminal tail of SmpB is located along the mRNA path of the ribosome. During these processes, SmpB structurally and functionally mimics both tRNA and mRNA. Our recent model explains how tmRNA preferentially recognizes the stalled ribosome, and what substitutes for a codon-anticodon interaction.
2. The function of RsgA, a novel ribosome small subunit-dependent GTPase, has been found: It dissociates RbfA from the ribosomal small subunit at nearly the last stage of maturation. This is the first example of the action of a GTPase on the bacterial ribosome assembly described at the molecular level.

Future prospects

1. We are now investigating other ribosome rescue systems to understand the whole picture of ribosome rescue systems in a bacterial cell.
2. At present, we only understand a fraction of the process of the bacterial ribosome biogenesis. The roles of other maturation factors and the order of their actions are currently under investigation.

Funding

1. Hirosaki University Institutional Research Grant FY2010-2012 20,000 Thousand Yen
2. JSPS, Grant-in-Aids for Scientific Research, Grant Number 20380045, FY2011-2014 15,100 Thousand Yen
3. JSPS, Grant-in-Aids for Scientific Research, Grant Number 23380054, FY2011-2013 14,500 Thousand Yen
4. Ministry of Education, Culture, Sports, Science and Technology, Grant-in-aid for Scientific Research, Grant Number 22020001, FY2010-2011 3,200 Thousand Yen

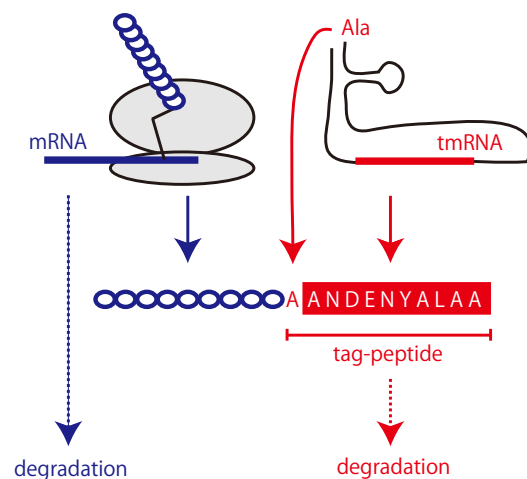
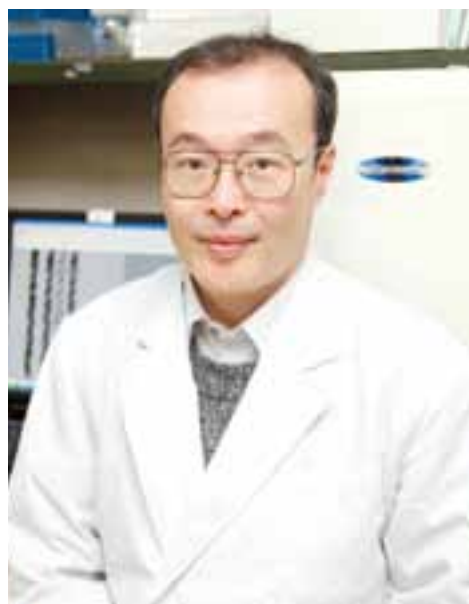


Figure legend

Trans-translation mediated by tmRNA

Both terminal regions of tmRNA can form a secondary structure resembling the upper-half of the cloverleaf-like structure of tRNA of which the 3' end accepts alanine, while tmRNA has a short coding sequence for tag-peptide that serves as a target of cellular proteases. This hybrid RNA molecule facilitates an extraordinary translation termed *trans*-translation: a single polypeptide is synthesized from two mRNAs. It allows resumption of translation stalled on a truncated mRNA, producing a chimeric polypeptide comprising the C-terminally truncated polypeptide derived from truncated mRNA and the C-terminal tag-peptide encoded by tmRNA with an alanine residue derived from alanine aminoacylated to tmRNA in between them.



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Molecular mechanisms for coronary artery spasm

Purpose and Background of the Research

Coronary artery spasm plays an important role in the pathogenesis of variant angina and other acute coronary syndromes. We showed that the basal and stimulated coronary artery vasomotor tone of patients with coronary spastic angina (CSA) is enhanced. Phospholipase C (PLC) produces IP₃ and diacylglycerol, both of which are related to vascular smooth muscle cell (VSMC) contraction. We previously demonstrated that PLC activity in cultured skin fibroblasts obtained from CSA patients was enhanced, and a major PLC isozyme detected was the $\delta 1$ isoform. We further demonstrated PLC- $\delta 1$ 864 G to A mutation and consequently amino acid replacement of arginine 257 to histidine (R257H) in about 10% of the male CSA patients. This variant PLC- $\delta 1$ showed enhanced PLC activity compared with the wild type (WT). On the other hand, we recently reported up-regulation of p122 protein, a positive regulator of PLC- $\delta 1$, in CSA patients. Thus, the increased PLC- $\delta 1$ activity caused by structural mutation or increased positive regulators plays an important role in the pathogenesis of coronary spasm. Here, we generated transgenic (TG) mice with the increased PLC- $\delta 1$ activity specific to the VSMCs by inducing human R257H variant PLC- $\delta 1$. We compared the coronary vasoconstrictor responses among homozygous TG, heterozygous TG and WT mice with differential enzymatic activities (homozygous TG > heterozygous TG > WT mice).

Research Results

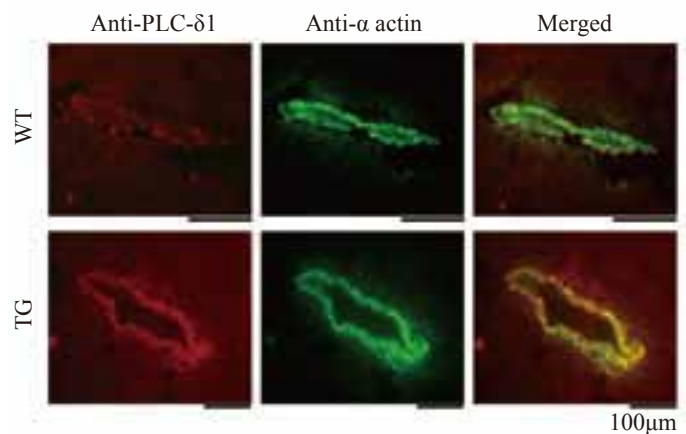
In the current TG mice, variant PLC- $\delta 1$ was overall expressed, especially in the aorta, coronary artery (Figure 1), and skin. PLC enzymatic activities in the coronary artery and aorta were significantly increased in the following order: homozygous TG > heterozygous TG > WT mice (all $p < 0.05$). Intravenous ergometrine promptly induced ST segment elevation on an electrocardiogram in 17 of 18 homozygous TG (94%), 6 of 20 heterozygous TG (30%), and 3 of 22 WT (14%) (Figure 2). ST elevation was often followed by advanced atrioventricular block, leading to cardiac arrest. Microvascular filling study demonstrated ergometrine-induced focal narrowing of the coronary artery in 3 of 5 TG, but none in 7 WT. In isolated Langendorff-perfused hearts, coronary perfusion pressure was significantly increased in homozygous TG after ergometrine but not in heterozygous TG or WT. Intracellular calcium concentration in the cells transfected with the variant or WT PLC- $\delta 1$ was significantly elevated compared with those without transfection. The peak increase in intracellular calcium concentration after acetylcholine was significantly greater in the cells transfected with the variant PLC- $\delta 1$ than in those with WT PLC- $\delta 1$ or those without transfection.

Future prospects

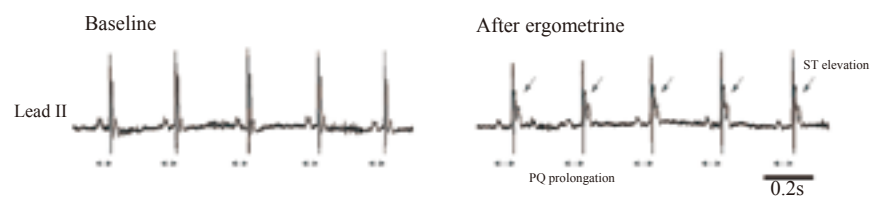
Increased PLC- $\delta 1$ activity found in the current TG mice causes enhanced coronary vasomotility such as seen in patients with CSA. The role of p122 protein in CSA remains to be determined in future studies.

Funding

1. JSPS KAKENHI (2006-2007), Grant Number 18590758 (3,400 Thousand Yen)
2. JSPS KAKENHI (2008-2010), Grant Number 20590856 (3,600 Thousand Yen)
3. JSPS KAKENHI (2011-2013), Grant Number 23591077 (4,000 Thousand Yen)



Immunofluorescence microscopy of the heart sections containing the coronary arteries.



ECG tracings before and after ergometrine in PLC- $\delta 1$ -overexpressing homozygous transgenic mouse.



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2013 Pick Up



Newly Adopted Projects For COI STREAM (Center of Innovation Science and Technology based Radical Innovation and Entrepreneurship Program) “Development of an innovative strategy for disease prediction and prevention by combining neuroscience research and analysis of “big health” data”

Project Leader: Toshihiko Kudo(Executive Director, MCS Corporation)

Research Leader: Shigeyuki Nakaji(Dean, Hirosaki University Graduate School of Medicine)

Website:

http://www.mext.go.jp/a_menu/kagaku/coi/index.htm (MEXT)

<http://www.jst.go.jp/coi/index.html> (JST)

(These sites are only available in Japanese.)

Hirosaki University was adopted to COI STREAM(Center of Innovation Science and Technology based Radical Innovation and Entrepreneurship Program) in October 2013. With increasing numbers of elderly in Japan, we are facing a serious social problem of expanding health care costs. Under a strong industry-government-academia partnership, we will establish an integrated strategy for predicting brain diseases using “big health” data collected from a cohort established in Aomori prefecture coupled with the development of innovative computer software. Based on the resultant prediction, we will conduct and test preventive strategies including general health care guidance and a new anti-aging method. Thus, this project will realize the transformation of medical care in Japan from “expensive advanced medicine for the patient” to “preventive risk-managing medicine” to expand the healthy life expectancy of people.

About Hirosaki University

Hirosaki University is a medium-size university with Faculties of Humanities, Education, Medicine, Science & Technology, and Agriculture & Life Science. These five Faculties cover a broad and comprehensive range of undergraduate academic disciplines. The university is also home to seven graduate programs, including the independent and interdisciplinary doctoral course in Regional Studies. Hirosaki University has taken full advantage of its location in Aomori Prefecture to advance its educational and research goals. First of all, within Aomori Prefecture there is great potential for energy production and development, including the nuclear energy and nuclear fusion-related facilities located within its borders. The Shirakami Wilderness World Heritage Site, located along the border of Aomori and Akita prefectures, offers many possibilities for the study of global warming and other environmental issues. Finally, in this era of reoccurring food crises and concern over food security, Aomori Prefecture serves as a national food production base. Hirosaki University has tailored its educational, research, and community outreach programs to focus on these areas of study, to develop the needed human resources to meet the challenges they pose, and to project its research findings globally, regionally and locally.

In this booklet, we introduce our research findings that it was involved in correspondence when the earthquake(Great East Japan Earthquake) broke out in 2011.



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