Press Release

One hormone, two roles: Sugars differentiate seasonality and metabolism

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Scientists at ITbM, Nagoya University and the University of Chicago have discovered the mechanism on how a single hormone manages to trigger two different functions, i.e. seasonal sensing and metabolism, without any cross activity.

Figure 1. Mouse measuring the seasonal time. (Mice on the ancient Japanese clock 'Wadokei')
In the ancient Japanese timekeeping system, the length of one hour varied with the seasons (i.e. 24 hours was divided into 6 hours of daylight and 6 hours of night-time. Daylight hours were longer in the summertime and shorter in the winter). Laboratory mice were believed to be non-seasonal animals for a long time. Ono et al. reported that mice transmit seasonal information from the pituitary gland to the hypothalamus by using thyrotropin. Image by Takashi Yoshimura.

Nagoya, Japan – Through an extensive national and international collaboration, Professor Takashi Yoshimura and Dr. Keisuke Ikegami (currently at Kinki University) at the Institute of Transformative Bio-Molecules (ITbM) of Nagoya University, Prof. Samuel Refetoff of the University of Chicago and co-workers have uncovered the mechanism of how thyrotropin, the **t**hyroid **s**timulating **h**ormone (TSH), which triggers two different functions, manages to avoid functional crosstalk when released into the bloodstream. TSH is a glycoprotein (a protein that contains carbohydrate) secreted from two parts of the pituitary gland in the brain. Previous studies have shown that TSHs secreted from both regions of the pituitary gland have the same protein structure. TSH has been known for a long time to be a hormone secreted from the front of the pituitary gland (pars distalis) that stimulates the thyroid gland to synthesize and secrete thyroid hormones, which in turn regulates metabolism and growth. On the other hand, Yoshimura's group has uncovered the novel function of TSH secreted from the stalk of the pituitary gland (pars tuberalis) that acts on the hypothalamus as a spring calling hormone, which sends information on seasonal changes. Up till now, it has been a mystery on how these two TSHs manage to distinctively trigger biologically significant processes without interfering with one another. The study, published online on October 30, 2014 in the journal, *Cell Reports*, reports a new finding where the same molecule imparts different functions without cross activity through tissue-specific glycosylation (attachment of sugars) and subsequent recognition by the immune system. This new paradigm is expected to be of high significance in the fields of both glycobiology and immunology as well as contribute towards the understanding of diseases related to the synthesis and secretion of TSHs.

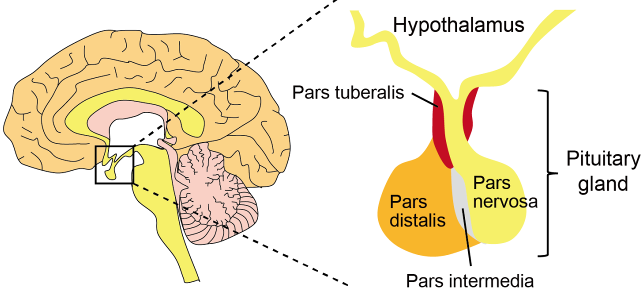

Figure 2. Structures of the hypothalamus and the pituitary gland in the human brain.

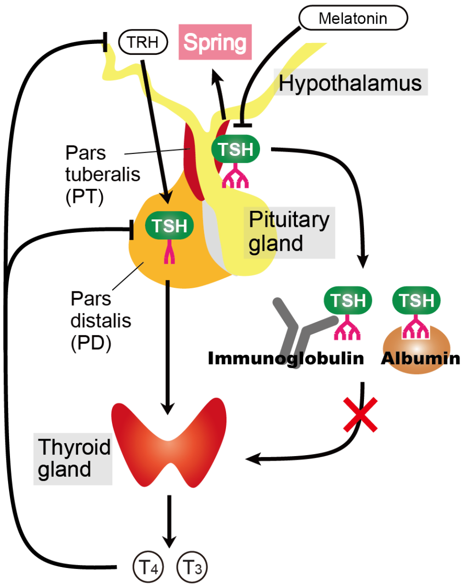

Figure 3. Mechanism showing how TSH undertakes two roles. TSH in **p**ars **d**istalis (PD-TSH) is controlled by the **h**ypothalamus - **p**ituitary gland - **t**hyroid gland (HPT) axis. The hypothalamus secretes the **t**hyrotropsin-**r**eleasing **h**ormone (TRH), which stimulates the synthesis and secretion of PD-TSH. PD-TSH, then acts on the thyroid gland, which secretes thyroid hormones, T_4 (precursor thyroxine) and T_3 (bioactive triiodothyronine), and the expression of PD-TSH is controlled by negative feedback. On the other hand, TSH in **p**ars **t**uberalis (PT-TSH) is not controlled by the HPT-axis but is regulated by melatonin, which is secreted by the pineal gland during the evening, and sends the message of spring to the hypothalamus. Both PT-TSH and PD-TSH are secreted into the bloodstream, but PT-TSH is trapped by immunoglobulin and albumin through its distinct carbohydrate chains leading to loss of bioactivity and thus, has no effect on the thyroid gland.

Many organisms adapt to seasonal changes by detecting changes in day length. Examples of physiological activities regulated by changes in day length, include seasonal breeding, bird migration, hibernation of bears and wool shedding of sheep. The mechanism on how organisms sense spring has been a long-term mystery. Fortunately in 2008, Yoshimura and co-workers have finally elucidated the mechanism on how mammals sense seasonal changes. They identified that upon the arrival of spring (i.e. longer day length), TSH secreted from the **p**ars **t**uberalis (PT-TSH) in the pituitary gland acts as a spring calling hormone and sends information on seasonal changes to the hypothalamus in the brain. On the other hand, it has been known for a long time that TSH is a hormone secreted by the **p**ars **d**istalis (PD-TSH) that stimulates the thyroid gland to synthesize and secrete thyroid hormones, which regulate growth and metabolism in the body. Hormones affect the target organ through circulation in the bloodstream. “It has been a great mystery on how the activities of TSHs were being differentiated. Initially, it has been suggested that TSHs arising from the pars tuberalis and pars distalis were being regulated differently at each source,” says Prof. Takashi Yoshimura who led the research. “From our investigations on knock-out mice, we found that PD-TSH was being regulated by the **t**hyrotropin-**r**eleasing **h**ormone (TRH) secreted by the hypothalamus, whereas PT-TSH was not controlled by TRH but was being controlled by a hormone called melatonin, which is a hormone secreted by the pineal gland during the night.”

Upon studying the structures of PT-TSH and PD-TSH by MALDI mass spectrometry analysis, it was discovered that they both shared the same protein structure but had different types of carbohydrate chains attached to them. PD-TSH had sulfated bi-antennary carbohydrate chains, which could be easily metabolized. On the other hand, PT-TSH had sialylated multi-branched carbohydrate chains, which could form stable macro-TSH complexes with immunoglobulin and albumin present in the blood. "Since starting this research in 2008, we had to revisit our hypotheses many times, and finally found that tissue-specific glycosylation occurred in the pars tuberalis and pars distalis of the pituitary gland, which differentiates each of their TSH to prevent cross activity," explains Prof. Yoshimura. "Interestingly, the bioactivities of PT-TSH and PD-TSH themselves showed no difference. Meanwhile, PT-TSH loses its bioactivity in the bloodstream by forming stable macro-TSH complexes, and thus, does not act upon the thyroid gland."

Glycosylation, the covalent addition of oligosaccharides to proteins, is a post-translational modification that increases the diversity of the proteome. Although the fundamental importance of glycosylation has been recognized in recent years, its physiological role has remained unclear. This study illustrates the first example of the involvement of tissue-specific glycosylation in preventing functional crosstalk between signaling molecules. Prof. Yoshimura says, "As the genome is finite, organisms use the same protein to serve multiple functions. Through our studies, we were able to uncover the elegant strategy of the organism, where tissue-specific glycosylation and subsequent immune recognition is used to impart two distinctive functions on a single hormone. We envisage that this new paradigm will be of great significance to researchers in a variety of fields including glycobiology, immunology, endocrinology, physiology, and neuroscience, along with contribution towards agriculture (animal reproduction) and human health."

This article "Tissue-specific post-translational modification allows functional targeting of thyrotropin" by Keisuke Ikegami, Xiao-Hui Liao, Yuta Hoshino, Hiroko Ono, Wataru Ota, Yuka Ito, Taeko Nishiwaki-Ohkawa, Chihiro Sato, Ken Kitajima, Masayuki Iigo, Yasufumi Shigeyoshi, Masanobu Yamada, Yoshiharu Murata, Samuel Refetoff, Takashi Yoshimura is published online on October 30, 2014 in *Cell Reports*.
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About WPI-ITbM (http://www.itbm.nagoya-u.ac.jp/)

The World Premier International Research Center Initiative (WPI) for the Institute of Transformative Bio-Molecules (ITbM) at Nagoya University in Japan is committed to advance the integration of synthetic chemistry, plant/animal biology and theoretical science, all of which are traditionally strong fields in the university. As part of the Japanese science ministry's MEXT program, ITbM aims to develop transformative bio-molecules, innovative functional molecules capable of bringing about fundamental change to biological science and technology. Research at ITbM is carried out in a "Mix-Lab" style, where international young researchers from multidisciplinary fields work together side-by-side in the same lab. Through these endeavors, ITbM will create "transformative bio-molecules" that will dramatically change the way of research in chemistry, biology and other related fields to solve urgent problems, such as environmental issues, food production and medical technology that have a significant impact on the society.

Professor Takashi Yoshimura

Author Contact
Professor Takashi Yoshimura
Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University
Furo-Cho, Chikusa-ku, Nagoya 464-8601, Japan
TEL/FAX: +81-52-788-4056
E-mail: takashiy@agr.nagoya-u.ac.jp

Media Contact
Dr. Ayako Miyazaki
Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University
Furo-Cho, Chikusa-ku, Nagoya 464-8601, Japan
TEL: +81-52-789-4999 FAX: +81-52-789-3240
E-mail: press@itbm.nagoya-u.ac.jp

Nagoya University Public Relations Office
TEL: +81-52-789-2016 FAX: +81-52-788-6272
E-mail: kouho@adm.nagoya-u.ac.jp