海外特別研究員最終報告書

採用年度 平成29年
受付番号 394
氏名 例

海外特別研究員としての派遣期間を終了しましたので、下記のとおり報告いたします。
なお、下記及び別紙記載の内容については相違ありません。

記
1. 用務地（派遣先国名） 用務地：ニューヨーク （国名：アメリカ）
2. 研究課題名（和文）※研究課題名は申請時のものと違わないように記載すること。

ヒト遺伝性脳疾患に関連する遺伝子変異・機能の解析

3. 派遣期間：平成29年4月1日～平成30年3月31日

4. 受入機関名及び部局名
The Rockefeller University Strang Laboratory of Apoptosis and Cancer Biology

5. 所期の目的の遂行状況及び成果…書式任意（書式任意 A4判相当3ページ以上、英語で記入も可）

（研究・調査実施状況及びその成果の発表・関係学会への参加状況等）
（注）「6.研究発表」以降については様式10-別紙1〜4に記入の上、併せて提出すること。

The Rockefeller University is one of the top biomedical research institutes in the world
and produces a number of well-known scientists with prestigious awards including the
Nobel prize. Particularly, I chose to conduct postdoctoral research in the Rockefeller
University under the guidance of Dr. Hermann Steller for his pioneering works in
physiological regulation of a major cellular protein breakdown machinery using genetic
approaches.

Selective intracellular protein degradation is essential for quality control of
proteins as well as protein turnover that are involved in most of intercellular
mechanisms. The major protein degradation system in eukaryote cells is the ATP-dependent Ubiquitin Proteasome System (UPS). UPS is characterized by degradation of polyubiquitin-tagged substrates by the 26S proteasomes\(^1\). In addition to its role in the degradation of unwanted proteins, proteasomal degradations play important role in cellular signaling, gene expression, apoptosis, cell cycle, and DNA repair\(^2\). Defects in this process is associated with human diseases such as cancer and neurogenerative disorders. Despite the essential role of proteasomes, the proteasome field is largely focused on biochemistry and structural biology, with minor emphasis on their physiological roles. Thus, how the proteasome itself is regulated to meet the high demand for the protein breakdown during development and postnatally are largely unknown. To date, majority of studies investigating the physiological effects of proteasome inhibition \textit{in vivo} have relied on pharmacological inhibitors or focused on E3 ligases, which determine substrate specificity. Thus, there are limitations in understanding the physiological regulation of proteasome activity during development and postnatally. One of such limitations is the systematic toxicity of pharmacological inhibitors. It is possible that subtoxic concentration of inhibitors or mild inhibition of the proteasome may mask the actual effects of the proteasome inhibition\(^3\).

The 26S proteasome is composed of two subcomplexes: a catalytic 20S core particle and 19S regulatory particle(s). Classically, it was assumed that the rate-limiting step of proteasomal degradation is recognition of unwanted proteins. However, it is now known that the assembly and activity of the 26S proteasome are tightly regulated\(^1\). One such regulator is PI31, identified first as a 20S proteasome inhibitor \textit{in vitro}\(^4,5\). Dr.
Steller’s laboratory showed in *Drosophila* that the physiological function of PI31 is to activate 26S proteasomes upon ADP ribosylation by Tankyrase, a poly(ADP-ribose) polymerase. These observations shed light on the physiological importance on the regulation of proteasome itself.

To overcome the current limitations in understanding physiological importance of the proteasome regulation, my investigation in Dr. Steller’s laboratory aimed to identify proteasome regulator(s) using mouse as a model and to further investigate the mechanism of proteasome regulation during development and aging. During my fellowship period, by identifying proteasome regulator(s), my study provided a powerful strategy to genetically modulate the proteasome activity in spatio-temporal manner *in vivo*. Taking advantage of the strength of the lab in studying proteasomes, I was able to dissect the mechanisms of action of the regulator(s) in physiological context. Furthermore, through collaborating with researchers in other institutions, I was able to conduct experiments which were not possible at the Rockefeller University. With collaborative work, my research provided the deeper understanding of physiological importance of the regulation of proteasome. I anticipate finishing the final manuscript by 2020. I am confident that my research will expand our knowledge of the complex regulation of proteasome activity during development and aging and will provide new insights into causes of human diseases associated with the failure of UPS.

Not only achieving the scientific goal, JSPS fellowship helped me to achieve my personal goal during my postdoctoral training to be involved in the community to break the old but persisting image of scientists - male scientist in his laboratory white coat. The Rockefeller University is well-known for its unique diverse scientific
environment that serves as a hub for talented young as well as senior scientists. There are a number of influential female professors at the Rockefeller University and the university offer various opportunities to mentor female students as outreach projects. During my JSPS fellowship period, I was able to be a part of this stimulating academic environment to learn from influential figures, develop to be a better scientist and to mentor underrepresented young students. Particularly, to mentor underrepresented young students, I learned how to behave as a mentee to be well prepared. It was mind provoking to learn how to mentor especially underrepresented students and there are many tips that can be applied to female students/scientists back in Japan.

Thanks to JSPS fellowship, I had an amazing experience that led to new exciting biological findings, but also gave me an opportunity to realize my passion to become a PI to help students to visualize barriers and logically fight to create their unique careers ahead of them.

References


