Form 3

Report for Joint/usage program for Endocrine/Metabolism

Date: Aril 20, 2017

To:

Director of Institute for Molecular and Cellular Regulation

1. Program No. 15003
2. Research title: Role of Fanconi anemia (FA)/Breast cancer (BRCA) pathway in oncogene-induced replication stress responses

3. Objective of the research: The FA/BRCA pathway plays an important role in maintenance of genomic integrity and tumor suppression. The objective of the present research is to clarify the role of FA/BRCA pathway in oncogene-induced genomic instability.

4. Period April 1, 2016 — March 31, 2017

5. Project organization

Name of Applicant: Toshiyasu Taniguchi
Position: Member
Institution/department: Divisions of Human Biology and Public Health Sciences, Fred Hutchinson Cancer Research Center

Name of Co-applicant:
Position:
Institution/department:

Name of Researcher in IMCR Takayuki Yamashita
Position: Professor

6. Research plans:

   Dr. Yamashita established experimental systems in which inducible expression of cyclin E or c-myc causes aberrant replication and subsequent DNA damage. Taking advantage of these systems, we will first study the behavior of the FA/BRCA pathway by biochemical and immunofluorescence analyses. Second, we will study the effects of deficiency of the FA/BRCA pathway on oncogene-induced replication and DNA damage.

7. Research results:

Dr. Yamashita's group found that c-myc oncogene activation induced stalling of replication forks and that polymerase eta promoted restart of stalled forks. FANCD2 is reported to promote restart of HU-induced stalled forks. Therefore, we asked how polymerase eta and FANCD2 interact in cellular responses to replication stress. To address this question, we performed DNA fiber analysis to evaluate fork restart after HU-induced stalling. We found that depletion of polymerase eta and FANCD2 in combination increased stalled forks in an additive manner. These results suggest that these proteins prevent fork stalling through different pathways.

8. Publications and/or Presentations made through this collaboration

(Please summarize the report in 2 pages)