【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project : Mechanism for genome instability by activation induced cytidine deaminase induced-reduction of topoisomerase1

Tasuku Honjo
(KyotoUniversity, Graduate School of Medicine, Professor)

Research Area : Medicine, dentistry, pharmacy/Basic medicine/General medical chemistry
Keyword : Somatic hypermutation/Class switch recombination/ RNA editing/ Large scale sequence/Fact complex

【Purpose and Background of the Research】

Since E. Jenner first applied vaccination to small pox, vaccines against wide variety of diseases have been developed. As a result human beings almost completely succeeded in avoiding fatal causality by infectious diseases. Effective vaccination depends on generation of antibodies with memory. For a long time, it was a total mystery how vaccine (or antigen memory) is printed in antibodies. In 2000, we discovered that activation-induced cytidine deaminase (AID) is the enzyme that engraves antibody memory in the genome. AID introduces alterations in the immunoglobulin gene by changing the base sequence in the antibody binding site (somatic hypermutation) as well as replacing the constant region gene to diversify antigen processing mechanisms (class switch recombination). Furthermore, aberrant expression AID causes tumor by introducing genetic alterations in oncogenes. The purpose of this investigation is to understand how AID introduces DNA alterations in the immunoglobulin gene. In addition, we investigate why other oncogenes are also mutated by AID expression.

【Research Methods】

Last year, we found topoisomerase1 (Top1) that regulates the superhelical structure of DNA is reduced by AID, resulting in DNA cleavage of the immunoglobulin gene. Reduction of Top1 induces the structural alteration of the immunoglobulin gene, which causes irreversible cleavage by Top1. We will investigate how AID reduces the Top1 protein amount. Our hypothesis is AID suppresses Top1 mRNA translation. Our hypothesis is that AID edits small molecular RNA to convert C to U. The resultant small molecular RNA will change the translation efficiency of Top1 mRNA. Therefore, we investigate small molecular RNA that was edited by AID by large-scale DNA sequencing. We also isolate RNA and protein that associate with Top1 mRNA. Furthermore, we will investigate DNA sequences cleaved by AID and their DNA structure by whole genome sequencing.

【 Expected Research Achievements and Scientific Significance】

To understand the molecular mechanism of AID and elucidation of the mechanism for antibody memory generation will help not only the development of effective vaccine but also elucidation of the tumorigenesis mechanism by AID. There are reports that AID is involved in gastric cancer, hepatoma, lymphoma, and myloid leukemia. To understand the molecular mechanism for AID to cleave DNA will facilitate the discovery of the method to regulate its function and consequently to prevent tumorigenesis.

【Publications Relevant to the Project】

1) AID-induced decrease in topoisomerase1 induces DNA structural alteration and DNA cleavage for class switch recombination. Kobayashi, M, *Honjo,T. Proc. Natl. Acad. Sci. USA 106 22375-22380 (2009) refereed
2) A memoir of AID, which engraves antibody memory on DNA. *Honjo,T. Nature Immunol. 9 335-337 (2008) not refereed
3) Discovery of activation-induced cytidine deaminase, the engraver of antibody memory. Muramatsu,M., *Honjo,T. Adv. Immunol. 94 1-36 (2007) not refereed
4) *Helicobacter pylori* infection triggers aberrant expression of activation-induced cytidine deaminase in gastric epithelium. Matsumoto,Y., Honjo,T., *Chiba,T. Nature Medicine 13 470-476(2007) refereed
5) Class switch recombination and hypermutation require activation-induced cytidine deaminase(AID), a potential RNA editing enzyme. Muramatsu,M., *Honjo,T. Cell 102 553-563 (2000) refereed

【Term of Project】 FY2010-2014

【Budget Allocation】 343,200 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www2.mfour.med.kyoto-u.ac.jp/
honjo@mfour.med.kyoto-u.ac.jp