【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy Ⅱ)

Title of Project : Global analysis of genetic and epigenetic alterations during inflammation-associated gastrointestinal cancer development, and elucidation of its mechanism

Tsutomu Chiba
(Kyoto University, Graduate School of Medicine, Professor)

Research Area : Medicine, dentistry, and pharmacy , Clinical internal medicine
Keyword : Gastroenterology (Upper gastroenterology, Lower gastroenterology, Hepatology)

【Purpose and Background of the Research】

Cancers of the digestive organs (GI cancers) are the most significant cause of cancer death. Development of many GI cancers is underlain by inflammation with or without infection, and cancer development is characterized by stepwise accumulation of various gene rearrangements, including gene mutation, deletion and translocation. Interestingly, non-cancerous inflammatory tissues already possess considerable levels of gene mutations. These data suggest that inflammation may accelerate various gene mutations and aberrations.

Recently, we have been focusing on the role of activation-induced cytidine deaminase (AID), in the induction of gene mutation and aberration during inflammation-associated carcinogenesis. We observed that 1) ectopic expression of AID in various cancer development, 2) epithelial cells in the inflammatory tissues are associated with ectopic AID expression together with accumulation of various gene mutations and 3) AID expression is induced in epithelial cells by *H.pylori* or HCV infection, and also by various cytokines. These data suggested that AID plays an important role in the development of inflammation-associated cancers by inducing gene mutations. However, a whole picture of gene mutations and aberrations in inflammation-associated cancers, and precise molecular mechanisms of how those genetic alterations are induced during inflammation are not fully clarified. In this study, therefore, we try to 1) investigate a whole picture of genetic and epigenetic changes induced by inflammation during carcinogenesis, and to 2) elucidate mechanisms of how those genetic and epigenetic changes are induced during inflammation by focusing on the role of AID.

【Research Methods】

By utilizing ultra-deep sequencer, we will perform genome wide analysis of genetic changes induced during inflammation-associated cancer development. For this purpose, we will examine various organs of AID transgenic mice, and various human inflammatory tissues. For genome analysis, we will use whole exome capture system that covers whole exons, and extract all the genetic changes. For epigenetic analysis, DNA will be extracted from all the clinical as well as mouse samples, methylated DNA fragments recovered by binding to methyl DNA binding protein, and applied to ultra-deep sequencer. These genetic and epigenetic changes will be dissected along with expression of AID.

We will establish mouse models in which stem cells are labeled, and by combining with inflammation-associated cancer models, we will observe the relationship between AID expression and genetic changes in tissue stem cells, and elucidate importance of AID expression in stem cells in the development of inflammation-associated cancer.

【Expected Research Achievements and Scientific Significance】

It has been believed for long time that genetic alterations in cancer tissues are introduced mainly by extrinsic mutators. In this study, by focusing on roles of AID, it is expected that the mechanisms for induction of genetic and epigenetic alterations by an intrinsic mutator during inflammation-associated cancer development will be elucidated. In addition, by using second generation genome analyzer, we will be able to clarify the mechanistic relationship between genetic and epigenetic changes in inflammation-associated cancer development.

【Publications Relevant to the Project】

・Takai A, Marusawa H, Watanabe T, Chiba T, et al.: Targeting activation-induced cytidine deaminase prevents colon cancer development despite persistent colonic inflammation. Oncogene 31:1733-1742:2012.
・Matsumoto Y, Marusawa H, Chiba T, et al.: Helicobacter pylori infection triggers aberrant expression of activation-induced cytidine deaminase in gastric epithelium. Nature Medicine 13:470-476:2007.

【Term of Project】 FY2012-2014
【Budget Allocation】 132,100 Thousand Yen
【Homepage Address and Other Contact Information】
http://www.med.kyoto-u.ac.jp/E/grad_school/introduction/1304/