Title of Project : Mechanism for genomic instability during inflammation-associated carcinogenesis

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Research Area : Medicine, dentistry, and pharmacy , Clinical internal medicine

Keyword : Gastroenterology (Upper gastroenterology, Lower gastroenterology, Hepatology)

【Purpose and Background of the Research】

Many cancers develop under the background of inflammation with or without infection. Particularly in the gastroenterology field, it is well established that gastric cancers develop in the presence of chronic gastritis due to *H.pylori* infection, and liver cancers develop from chronic hepatitis due to HCV or HBV infection. Moreover, long lasting ulcerative colitis is often associated with development of colitic cancer.

On the other hand, it is also well known that cancer development is characterized by accumulation of many gene mutations. Indeed, a recent genome wide study revealed that a single cancer cell possesses approximately 60-90 gene mutations, 10 to 15 of which are driver genes. Thus, mutations play important roles in cancer development. However, mechanisms of how inflammation enhances gene mutation with resulting cancer formation is unknown at present.

Gene mutations are suppressed by various mechanisms. However, there is one cell type in which gene mutation is frequently occurred under physiological condition. Those are B lymphocytes which produce various immunoglobulins. Although there is only one immunoglobulin gene existing, we need to produce many different immunoglobulins in order to react with so many different antigens. Accordingly, to produce many different immunoglobulins, immunoglobulin gene has to receive frequent somatic mutations. The molecule that is responsible for the somatic mutation of immunoglobulin gene was discovered in 2000, and was termed as activation-induced cytidine deaminase (AID). AID is, thus, only one molecule that can induce gene mutation in human genome, and its expression is strictly restricted to B cells under normal condition. Surprisingly, however, we found that AID is expressed in not only the gastritis mucosa by *H.pylori* infection but also chronic hepatitis tissues by HCV infection. Moreover, induction of AID enhances gene mutations in gastric mucosal cells and hepatocytes, and plays important roles in the development of cancers.

The purpose of the present study is, therefore, to elucidate mechanisms of AID expression during inflammation, mutation induction by AID, and also eventual cancer development by accumulation of gene mutations by AID.

【Research Methods】

1) Clarification of generalized roles of AID in inflammation-associated carcinogenesis, particularly focusing on esophageal cancer development from reflux esophagitis.
2) Clarification of the mechanisms for specificity of AID for the genes to be mutated.
3) Clarification of the reason why AID induces various mutations in addition to C/G to T/A transition.
4) Elucidation of the relationship between methylated cytosine and mutation induction by AID.
5) Elucidation of roles of AID induction in tissue stem cells in carcinogenesis.

【Expected Research Achievements and Scientific Significance】

Recent cancer research is focusing mainly on epigenetic events in carcinogenesis. But, genetic changes still play a major role in cancer development. However, it has been unclear why mutations occur so frequently during carcinogenesis. Also, it has been unclear whether there are intrinsic factors that accelerate mutations during carcinogenesis. In this regard, AID is the firstly defined intrinsic mutagen in the body. Thus, the research on AID will introduce a novel mechanism for mutation induction in carcinogenesis, and will facilitate our overall understanding on the mechanism of cancer development.

【Publications Relevant to the Project】

・Matsumoto Y, Marusawa H, Kinoshita K, Endo Y, Kou T, Morisawa T, Azuma T, Okazaki IM, Honjo T, Chiba T: Helicobacter pylori infection triggers aberrant expression of activation-induced cytidine deaminase in gastric epithelium. Nat Med 13:470-476: 2007.
・Endo Y, Marusawa H, Kou T, Nakase H, Fujii S, Fujimori T, Kinoshita K, Honjo T, Chiba T: Activation-induced cytidine deaminase links between inflammation to colitis-associated colorectal cancers. Gastroenterology 135: 889-898:2008.

【Term of Project】 FY2009-2012

【Budget Allocation】 120 ,200 Thousand Yen

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