【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Biological Sciences)

Title of Project : Mechanism and regulation of "Hit-and-Run" carcinogenesis by *Helicobacter pylori* CagA

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Research Area : Cancer Biology
Keyword : Carcinogenesis, Inflammation and cancer, Tumor microenvironment, Oncogene

【Purpose and Background of the Research】

Gastric cancer is the third-leading cause of cancer-related deaths, accounting for approximately 10% of total cancer deaths worldwide. Most if not all gastric cancer cases are etiologically associated with chronic *Helicobacter pylori* infection. In particular, the CagA oncoprotein of *H. pylori*, which is delivered into gastric epithelial cells, plays a key role in the development of gastric cancer by perturbing multiple intracellular signaling pathways. Once established, however, gastric cancer cells no longer require *H. pylori* or CagA for maintaining their malignant phenotypes, indicating that the neoplastic transformation of gastric epithelial cells follows a process of "Hit-and-Run" carcinogenesis. In this study, the process of gastric carcinogenesis will be investigated by dividing it into CagA-dependent and CagA-independent stages. Elucidation of the molecular mechanisms underlying each of these oncogenic stages will shed light on the mechanism of the "Hit-and-Run" carcinogenesis, which will pave the way for gastric cancer prevention.

【Research Methods】

Investigation of the CagA-dependent stage will focus on the role of CagA-SHP2 complex formation in determining gastric cancer risk through quantitative analysis, the physiological role and the oncogenic contribution of the newly identified SHP2 substrate parafibromin, the mechanism by which the level of CagA tyrosine phosphorylation is determined, and the pathophysiological collaboration of *H. pylori* CagA and EBV in the neoplastic transformation of gastric epithelial cells. The tyrosine-phosphorylated recombinant CagA protein will become a powerful tool that enables quantitative analysis for the study of gastric carcinogenesis. Investigation of the CagA-independent stage will be performed by establishing genetically engineered mice that conditionally switch on/switch off the expression of CagA. Genetic and epigenetic analyses of pre-neoplastic/neoplastic lesions induced by conditional CagA expression will uncover molecular mechanisms that confer CagA independence to epithelial cells.

【Expected Research Achievements and Scientific Significance】

This study will allow for a deeper understanding of the mechanism that mediates *H. pylori*-induced gastric cancer through comprehensive studies on "Hit-and-Run" carcinogenesis of the stomach by integrating multiple layers of investigation. Unique animal models to be established in this study should act as powerful experimental tools not only for the study of *H. pylori*-associated gastric cancer but also for searching for principles common to a variety of infection/inflammation-associated cancers. A molecular understanding of the mechanism underpinning the "Hit-and-Run" carcinogenesis of the stomach would enable prognosis prediction of individual *H. pylori* eradication in cancer prevention, thereby having important clinical significance in terms of precision medicine.

【Publications Relevant to the Project】

・Saju P, Murata-Kamiya N, Hayashi T, Senda Y, Nagase L, Noda S, Matsusaka K, Funata S, Kunita A, Urabe M, Seto Y, Fukayama M, Kaneda A, *Hatakeyama M. Host SHP1 phosphatase antagonizes *Helicobacter pylori* CagA and can be downregulated by Epstein-Barr Virus. **Nat Microbiol.** 1: 16026 (2016)

・Hatakeyama M. *Helicobacter pylori* CagA and gastric cancer: a paradigm for Hit-and-Run carcinogenesis. **Cell Host Microbe** 15: 306-316 (2014)

【Term of Project】 FY2016-2020

【Budget Allocation】 141,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.microbiol.m.u-tokyo.ac.jp