Title of Project : Infection/inflammation-assisted acceleration of the carcinogenic spiral and its interception through vector conversion of host response to tumors

Term of Project : FY2010-2014

Masanori Hatakeyama
(The University of Tokyo, Graduate School of Medicine, Professor)

【Purpose of the Research Project】

Cancer is the most common cause of death in developed countries; almost seven million people worldwide die from cancer every year. Our research field focuses on infection-associated cancer that arises from chronic infection with microorganisms (viruses and bacteria), which accounts for 20% of total cancer deaths. Since a single agent (virus/bacterium) causes both inflammation and cell transformation, research on infection-associated cancer provides a great opportunity to elucidate the cellular and molecular nature of the "tumor microenvironment", a cradle that supports survival and expansion of tumor precursor cells, as well as the molecular mechanism underlying the "carcinogenic spiral" that confers genetic instability on precancerous cells. Through analyses of infection-associated cancer, we aim to elucidate the mechanisms underlying the actions of infection and inflammation that cooperatively and robustly promote cancer initiation and progression and to quickly translate the obtained results into the development of innovative methods for cancer prevention and treatment.

【Content of the Research Project】

Representative infection-associated cancers comprise gastric cancer, which is caused by *Helicobacter pylori*, hepatocellular carcinoma, which is associated with hepatitis viruses B and C, cervical carcinoma, which is caused by human papillomavirus, and HTLV-1-associated human T cell leukemia (ATL).

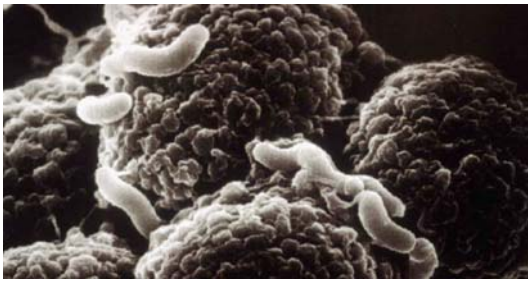

Fig. 1. *H. pylori* and gastric epithelial cells

In this project, the mechanisms underlying the development of infection-associated cancer will be investigated from two major but distinct aspects: 1) the process by which a viral/bacterial oncoprotein that is cognate to the respective microorganism directly confers malignant traits to infected cells and thereby autonomously promotes cell transformation (oncogenic arm) and 2) the role of chronic inflammation caused by host immune response against microorganisms and/or infected host cells (inflammation arm) in promoting multistep carcinogenesis. We will then apply the results obtained through a series of those works to the development of innovative prevention and therapeutics by pursuing 3) development of chemical compounds that specifically neutralize transforming potential of viral/bacterial oncoproteins or interrupt signaling pathways triggered by viral/bacterial oncoproteins, 4) establishment of a maneuver that converts the vector of the pathogenic host-tumor cell interaction in the tumor microenvironment from protection to destruction (conversion of vector of tumor regulation by the host), and 5) a strategy that interrupts the chain-reaction that accelerates accumulation of mutations in the oncogenes and tumor suppressor genes in pre-cancerous cells that constantly arise within the tumor microenvironment (carcinogenic spiral).

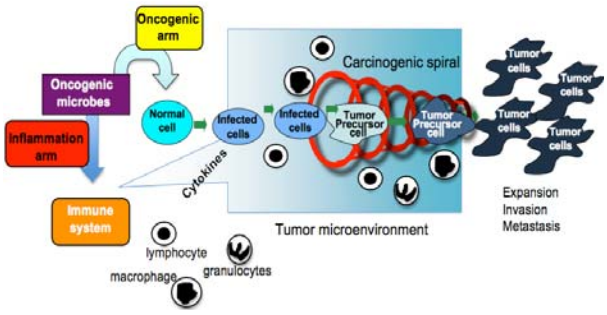

Fig. 2. Tumor microenvironment and carcinogenic spiral

【Expected Research Achievements】

Elucidation of the role of inflammation in the development of malignant neoplasms will not only contribute to the mechanistic understanding of inflammation-associated cancer but also provide important clues to understand more general cancers such as lung cancer, colon cancer and pancreatic cancer, which in most cases require chronic inflammation at the sites of tumor development.

【Key Words】

Carcinogenic spiral: the cellular status that accelerates accumulation of mutations in genes that is required for transformation of cells.

Vector conversion of host reaction to tumors: Reversal of host immune response from protecting to destroying cancer (or precancerous) cells

【Homepage Address】

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