Helicobacter pylori CagA, a bacterial protein acting as an oncogenic scaffold/hub in mammalian cells

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Chronic infection with *cagA*-positive *Helicobacter pylori* plays a central role in the development of gastric carcinoma. The *cagA*-encoded 135-KDa CagA protein is delivered into gastric epithelial cells via bacterial type IV secretion and localizes to the inner side of the plasma membrane, where it undergoes tyrosine phosphorylation at the C-terminal EPIYA motifs by Src kinases. Tyrosine-phosphorylated CagA then acts as an abnormal scaffold/hub that displays promiscuous binding capability with a number of host proteins. Most notably, CagA shows versatile interaction with SH2 domain-containing proteins such as SHP2 tyrosine phosphatase and the C-terminal Src kinase (Csk) in an EPIYA phosphorylation-dependent manner. SHP2 is a *bona-fide* oncoprotein, gain-of-function mutation of which is associated with a variety of human malignancies. CagA-SHP2 interaction also deregulates SHP2, causing aberrant activation of Ras signaling in the cytoplasm. In the nucleus, SHP2 dephosphorylates parafibromin/Cdc73, a component of the Polymerase II-associated factor (PAF) complex. Tyrosine-dephosphorylated parafibrmin specifically binds ß-catenin to activate Wnt target genes. Thus, SHP2 is involved in the regulation of the Ras pathway and the Wnt pathway, both of which are closely associated with oncogenesis. CagA-Csk interaction aberrantly stimulates Csk, resulting in the inhibition of Src kinases. By screening human proteome, we isolated a human EPIYA-containing protein, Pragmin/Sgk223, which binds to Csk in an EPIYA phosphorylation-dependent manner. The Pragmin-Csk interaction potentiates Src kinase activity by sequestrating Csk to the cytoplasm. Given that *H. pylori* CagA competitively inhibits Pragmin-Csk interaction while activating Csk through complex formation, reduced Src activity might be important for successful *H. pylori* infection and subsequent pathogenesis in the stomach. CagA also interacts with the polarity regulating kinase PAR1 via the C-terminal CM sequence independently of CagA tyrosine phosphorylation. The CagA-PAR1 interaction inhibits PAR1 kinase activity and thereby causes junctional and polarity defects as well as chromosomal instability. These findings collectively indicate that CagA takes over cancer-related intracellular signaling by creating a versatile signal perturbation complex. We recently succeeded in solving three-dimensional structure of CagA by combining X-ray crystallography and NMR. The tertiary structural information should facilitate our understanding of CagA as a bacterial pathogenic scaffold/hub that underlies transformation of gastric epithelial cells.

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EDUCATIONS/TRAINING

1981	School of medicine, Hokkaido University, Japan (MD)
1986	Graduate School of Medicine, Hokkaido University, Japan (PhD)
1991-1994	Postdoc, Whitehead Institute, MIT, USA

POSITIONS AND HONORS

1986-1991	Assistant Professor, Institute for Molecular and Cellular Biology, Osaka University, Japan
1995-1999	Member and Chief, Department of Viral Oncology, Cancer Institute, Japanese Foundation for Cancer Research (JFCR), Japan
1999-2009	Professor, Institute for Genetic Medicine, Hokkaido University, Japan
2009-Present	Professor, Graduate School of Medicine, The University of Tokyo, Japan

1991:	Incitement Award of the Japanese Cancer Association
1991:	Human Frontier Science Program (HFSP) Long-term Fellowship
1994:	Leukemia Research Foundation Scholarship
2006:	JCA-Mauvernay Award
2011:	Sagawa Special Award

2005-present:	Editorial Board, International Journal of Cancer
2006-present:	Associate Editor, Cancer Science
2009-present:	Director, Japanese cancer Association

RECENT PUBLICATIONS

1. Hayashi T, Senda M, Morohashi H, Higashi H, Horio M, Nagase L, Sasaya D, Shimizu, T, Venugopalan N, Kumeta H, Noda NN, Inagaki F, Senda T, and Hatakeyama M. Tertiary structure-function analysis reveals the pathogenic signaling potentiation mechanism of *Helicobacter pylori* oncogenic effector CagA. ***Cell Host Microbe*** 12, 20-33, 2012.
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3. Takahashi A, Tsutsumi R, Kikuchi I, Obuse C, Saito Y, Seidi A, Karisch R, Fernandez M, Cho T, Ohnishi N, Rozenblatt-Rosen O, Meyerson M, Neel BG, and Hatakeyama M. SHP2 tyrosine phosphatase converts parafibromin/Cdc73 from a tumor suppressor to an oncogenic driver. ***Mol Cell*** 43, 45-56, 2011.
4. Murata-Kamiya N, Kikuchi K, Hayashi T, Higashi H, and Hatakeyama M. *Helicobacter pylori* exploits host membrane phosphatidylserine for delivery, localization and pathophysiological action of the CagA oncoprotein. ***Cell Host Microbe*** 7, 399-411, 2010.
5. Saito Y, Murata-Kamiya N, Hirayama T, Ohba Y, and Hatakeyama M. Conversion of *Helicobacter pylori* CagA from senescence inducer to oncogenic driver through polarity-dependent regulation of p21. ***J Exp Med*** 207, 2157-2174, 2010.
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