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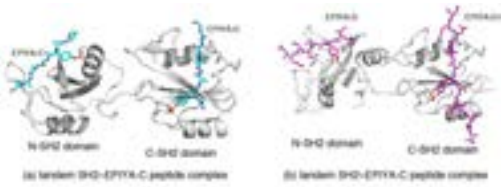
Molecular mechanism of SHP2 activation by CagA from *Helicobacter pylori*

Miki Senda[1], **Takeru Hayashi**[2], **Nobuhiro Suzuki**[1], **Lisa Nagase**[1], **Masanori Hatakeyama**[2] and **Toshiya Senda**[1]
[1]High Energy Accelerator Research Organization, Japan
[2]The University of Tokyo, Japan

Helicobacter pylori which is known as a major risk factor of stomach cancer, delivers an effector protein CagA into gastric epithelial cells. CagA then promiscuously interact with host proteins, SHP2 and PAR1b, to deregulate these proteins, potentiating oncogenic signaling. CagA comprises an N-terminal structured region and a C-terminal intrinsically disordered region which interacts with the host proteins. We already determined the crystal structure of the N-terminal region of CagA (1–3). The crystal structure revealed that the basic amino-acid cluster in the N-terminal region is utilized to localized CagA at the inner face of the plasma membrane. After localization, short segments including Glu-Pro-Ile-Tyr-Ala (EPIYA) motif in the C-terminal disordered region are phosphorylated by Src and interact with SHP2 to deregulate its phosphatase activity. In this study, we have analyzed the structure-function relationship of the EPIYA-segments of CagA. Based on the sequence flanking each of the EPIYA motifs, four types of EPIYA segments, A, B, C, and D, have been identified (4). It is already known that combinations of the EPIYA segments are geographically different (Western and East Asian CagA) and affect CagA's oncogenic activity. While Western CagA with EPIYA-A, B, and C segments has weak oncogenic activity, Western CagA with EPIYA-A, B and multiple EPIYA-C segments shows increased oncogenic activity (5). East Asian CagA, which has much higher oncogenic activity than Western ones, typically possesses EPIYA-A, B, and D in the C-terminal region. Our biochemical data revealed that oncogenic activity of CagA is correlated with binding affinity for SH2 domain of SHP2 (SH2_SHP2). We have analyzed the interaction between SH2_SHP2 and the EPIYA-C/D segment using biochemical, crystallographic, and physicochemical methods and revealed two types of activation mechanisms of SHP2. In our presentation, we will report that East Asian and Western CagA utilize two distinct activation mechanisms of SHP2.



Biography

Miki Senda has completed her PhD at 2008 from Nagaoka University of Technology. She is an Assistant Professor of Structural Biology Research Center in High Energy Accelerator Research Organization (KEK). She has several collaborations, in which she has worked as an expert of protein crystallization and crystal quality improvement. She received Oxford Cryosystems Low Temperature Prize at the 63rd Annual Meeting of the American Crystallographic Association (ACA) in 2013.

miki.senda@kek.jp