Structural Basis for Distinct Oncogenic Activities of Helicobacter pylori CagA Variants

Helicobacter pylori CagA undergoes tyrosine-phosphorylation to interact with the pro-oncogenic phosphatase SHP2 and thereby triggers gastric carcinogenesis. Here we determined the crystal structure of the CagA-SHP2 binding interface. Structure-function analysis revealed that East Asian-specific CagA exploits a characteristic Phe residue present at the phosphotyrosine+5 position to achieve binding to SHP2 with more than 100-fold greater affinity compared to the world-standard CagA, which contains Asp residue at the equivalent position. Small-angle X-ray scattering also demonstrated the conformational change of activated SHP2 upon CagA-binding in solution. The present study clarified the structural mechanism underlying the highest incidence of gastric cancer in East Asia.

CagA undergoes tyrosine-phosphorylation to interact with the pro-oncogenic phosphatase SHP2 (complexed with EPIpYA-D (left, PDB ID: 5X94) or EPIpYA-C (right, PDB ID: 5X7B). The views focus on the N-SH2/peptide interface.

Figure 1: Structures and biochemical properties of CagA-SHP2 interaction. (A) Crystal structures of tandem SH2 domains of SHP2 complexed with EIPY-A-D (left, PDB ID: 5X6B) or EIPY-A-C (right, PDB ID: 5X7B). The views focus on the N-SH2/peptide interface. (B) Possible conformational changes in the SH2 domain on binding of EIPY-A-D and the SH2-D domain on binding to Gly-68 in N-SH2. (C) Dissociation constants for the interaction of a series of CagA peptides with SHP2 were measured by surface plasmon resonance analysis. The data show that peptides VSPEPIpYATIDDL and VSPEPIpYATIDDL, in which a Phe residue at the pY+5 position in EPIYA-D was sticking inwards, revealed that the aromatic side chain of the Phe located at the pY+5 position in EPIYA-D resulted in drastic reduction in the SHP2 interaction. Reciprocally, Asp-to-Phe and Asp-to-Trp substitutions at the pY+5 position in EPIpYA-C significantly promoted the binding capacity. These data consolidate the functional relevance of the pY+5 position in EPIYA-D to achieve binding to SHP2.

Figure 2: SAXS analysis of SHP2-C459A complexed with EIPY-A-D. (A) Summary of structural parameters. (B) SAXS data of peptide-free SHP2 was evaluated by the CRYSOL program (left), and the calculated surface and envelope models were obtained (top right). Schematic for the closed inactive form of SHP2 is shown (bottom right). (C) SAXS data of SHP2 complexed with EIPy-A-D was refined by the CORAL program (left), and the calculated surface and envelope models were obtained (top right). Schematic for the open active form of SHP2 upon EIPY-A-D binding is shown (bottom right). The exposed catalytic center in the phosphatase (PTP) domain is indicated in red.

Figure 3: Structural basis of SHP2 binding to CagA. The present study demonstrates the structural basis for the functional impact of the single amino-acid polymorphism in CagA and clarifies the cancer-predisposing mechanisms of SHP2 activation that are differentially achieved by two major oncogenic CagA isoforms.

REFERENCES


BEAMLINES

BL-10C, BL-17A and BL-5A

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