BL-17A/2016G513

Crystal structure of the SH2 domain of Fer tyrosine kinase bound to a phosphotyrosine peptide

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1 Introduction

Fer is a ubiquitously expressed nonreceptor tyrosine kinase composed of an N-terminal F-BAR domain, a central Src homology 2 (SH2) domain, and a C-terminal kinase domain. Fer is highly homologous to Fes kinase, and the tyrosine kinase activity of Fes has been shown to be positively regulated by the binding of phosphotyrosine-containing peptide to the SH2 domain. Upregulation of Fer has been implicated in many human cancers, and Fer is an attractive target for drug development. Here, I report a crystal structure of Fer SH2 domain bound to a phosphopeptide [1].

2 Experiment

Crystals of human Fer SH2 domain bound to a synthetic phosphopeptide (D-E-pY-E-N-V-D) were grown by hanging drop vapor diffusion method. X-ray diffraction datasets were collected at Photon Factory beamline BL-17A using an EIGER X 16M detector at a wavelength of 0.98 Å. The structure was solved by molecular replacement using NMR structure of human Fer SH2 domain (PDB code, 2KK6) as a search model.

3 Results and Discussion

I determined the crystal structure of Fer SH2 domain bound to the DEpYENVD peptide by molecular replacement at 1.37 Å resolution. The structure was refined to free and working R-factor values of 18.55% and 16.46%, respectively. There were six Fer-peptide complexes in the asymmetric unit (ASU).

Interestingly, the structure revealed three distinct binding modes for the same phosphopeptide, indicating that all three residues C-terminal to pY can contribute to specific recognition in diverse ways (Fig. 1). In the binding mode 1, the peptide binds to Fer in a type I β-turn conformation (Fig. 1a). This binding mode was observed at four out of the six binding sites in the ASU, and this may be the most energetically favorable binding mode for this peptide. In the binding mode 2, the backbone of the peptide is twisted at pY+2, but the peptide is not in a β-turn conformation (Fig. 1b). In the binding mode 3, the peptide adopts an extended conformation (Fig. 1c). The binding modes 2 and 3 are likely suboptimal binding modes, which are induced because of spatial proximity of neighboring SH2 domains in the crystal.

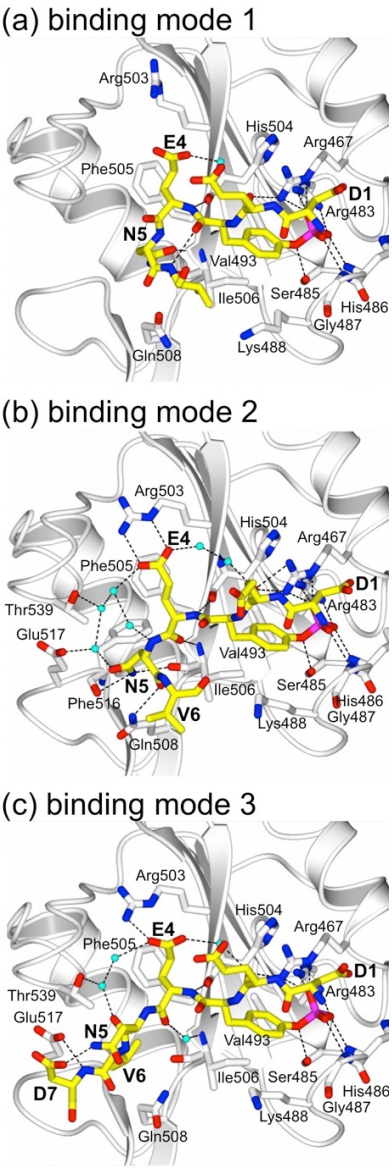

Fig. 1: Details of the interactions between human Fer SH2 domain and the DEpYENVD peptide in three distinct binding modes (PDB code, 6KC4).

References

[1] Y. Matsuura, *Protein Science* **28**, 2011 (2019).

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