

Structure of the N-terminal FERM Domain of the Avian Focal Adhesion Kinase

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Focal adhesion kinase (FAK) is a tyrosine kinase that participates in signal transduction cascades stimulated by adhesion to the extracellular matrix. FAK plays an important role in the regulation of events like cell cycle progression, cell survival, and cell migration. The N-terminal domain of FAK exhibits sequence similarity with the so-called FERM domains, which have been shown to act as mediators of both protein-protein interactions and protein-membrane interactions. The hepatocyte growth factor (HGF) receptor is encoded by the proto-oncogene *c-met*, which can be uncogenically activated through a chromosomal rearrangement that creates a hybrid gene *tpr-met*. It has been demonstrated very recently that FAK is involved in HGF-induced cell motility and its elevated expression renders epithelial cells susceptible to transformation by HGF stimulation. Moreover, it has been found that c-Met directly interacts with FAK and plays a crucial role in the control of integrin-mediated cell behavior. Phosphorylation of c-Met is required for its interaction with the FERM domain of FAK.

To gain structural insights for the N-terminal domain of FAK, we have determined the crystal structure of the FERM domain of FAK using Se-MAD approach by collecting diffraction data at three different wavelengths at Taiwan beamline SP12B2 (Spring 8, Japan). The crystal structure of the N-terminal domain of FAK belongs to space group $P2_1$, with unit-cell parameters $a = 44.8$, $b = 143.5$, $c = 68.3$ Å. Similar to the structures of several other FERM domains, the structure of FAK N-terminal domain reveals a compact structure in which three distinct subdomains come together to form the overall clover-like structure (Fig. 1). In addition, a non-crystallographic dimer was observed. Detailed structural analysis and functional significance of the dimer is currently being investigated.

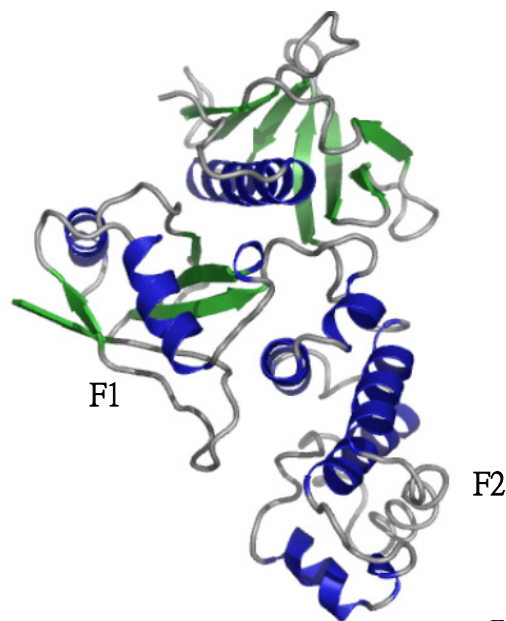


Figure 1. The structure of the FERM domain of FAK reveals a compact structure in which three distinct subdomains (labeled F1, F2 and F3) come together to form the overall clover-like structure.