

W0625

Structural Basis for PYK2 Adhesion Targeting in Osteoclast Activation. Wang Yimin, Senthil Ranganathan, Zhican Qu, Xu Feng, Wen-Cheng Xiong, Rongbao Li, Southern Research Inst., Birmingham, AL 35205; Dept. of Pathology, Univ. of Alabama, Birmingham, AL 35294.

Proline-rich tyrosine kinase 2 (PYK2) is a major kinase in the integrin-mediated cell adhesion and is related to focal adhesion kinase (FAK). While FAK is widely expressed in various tissues, PYK2 is primarily expressed in the central nervous system and in cells derived from hematopoietic lineages, such as osteoclasts. PYK2 localizes to adhesion structures through interactions between its C-terminal region and cytoskeletal proteins and plays an important role in cell adhesion and migration. The PYK2 C-terminal region is highly homologous to the focal adhesion targeting (FAT) domain of FAK. However, PYK2, not FAK interacts with gelsolin, an actin-binding protein found in osteoclastic adhesion structures. This specific interaction regulates the osteoclastic actin ring formation and osteoclast activation and is a potential target for bone resorption and metastasis of common cancers. The PYK2 FAT domain containing 138 residues crystallizes in space group P21 with cell dimensions of $a = 49.8 \text{ \AA}$, $b = 130.8 \text{ \AA}$ and $c = 49.9 \text{ \AA}$. The crystal structure of the PYK2 FAT domain has been determined at 2.5 \AA resolution by molecular replacement. The current model contains four molecules in the asymmetric unit and has been refined to $R_{\text{cryst}} = 0.20$ and $R_{\text{free}} = 0.26$. The crystal structure reveals a four-helix bundle with surface features required for binding to the LD motifs of paxillin and gelsolin. Comparison between PYK2 and FAK reveals the structural basis for specific interactions of PYK2 with gelsolin and a target site for specific inhibitor design to the integrin-mediated osteoclast activation.

We thank NE-CAT at APS for access to beamline 8-BM. This research is supported by NCI/NIH grant CA102998.