

THE 2.7 Å CRYSTAL STRUCTURE OF THE AUTOINHIBITED HUMAN c-FMS KINASE DOMAIN

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c-Fms, a member of the Platelet-Derived Growth Factor (PDGF) receptor family of receptor tyrosine kinases (RTKs), is the receptor for macrophage colony stimulating factor (CSF-1) that regulates proliferation, differentiation and survival of cells of the mononuclear phagocyte lineage. Abnormal expression of *c-fms* proto-oncogene is associated with a significant number of human pathologies, including a variety of cancers and rheumatoid arthritis. Accordingly, c-Fms represents an attractive therapeutic target. To further understand the regulation of c-Fms, we determined the 2.7 Å resolution crystal structure of the cytosolic domain of c-Fms that comprised the kinase domain and the juxtamembrane domain. The structure revealed the crucial inhibitory role of the juxtamembrane domain (JM) that bound to a hydrophobic site immediately adjacent to the ATP binding pocket. This interaction prevented the activation loop from adopting an active conformation thereby locking the c-Fms kinase into an autoinhibited state. As observed for other members of the PDGF receptor family, namely c-Kit and Flt3, three JM-derived tyrosine residues primarily drive the mechanism for autoinhibition in c-Fms, therefore defining a common autoinhibitory mechanism within this family. Moreover the structure provides an understanding of c-Fms inhibition by Gleevec as well as providing a platform for the development of more selective inhibitors that target the inactive conformation of c-Fms kinase.