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CELL SIGNALLING

# Dual specificity of SH2 domains

Src homology 2 (SH2) domains bind to phosphotyrosine (pTyr)-containing proteins, thereby linking tyrosine kinase activity to downstream signalling cascades. Earlier studies hinted that lipids can also bind to SH2 domains. Park *et al*. have now characterized these interactions in detail to explain how SH2 domain-containing proteins could be regulated by plasma membrane lipids.

Of 76 human SH2 domains analysed, 74% had high affinity for plasma membrane-mimetic (PM-mimetic) vesicles. Some of these high-affinity SH2 domains bound to phosphatidylinositol-3,4,5-trisphosphate ($PtdInsP_3$) and/or phosphatidylinositol-4,5-bisphosphate ($PtdIns(4,5)P_2$) in preference to isoelectric phosphatidylinositols, which indicates that SH2 domains can recognize lipid headgroups specifically rather than through non-specific electrostatic binding.

In addition to the pTyr-binding pocket, many SH2 domains contain alternative cationic patches (ACPs), mutation of which reduced binding to PM-mimetic vesicles and the plasma membrane localization of SH2 domains in HeLa cells. Thus, ACPs are the primary lipid-binding sites of most SH2 domains. Further studies showed that ACP morphology affects lipid binding; SH2 domains containing an ACP groove — such as the $PtdInsP_3$-selective T cell receptor (TCR) signalling molecule ZAP70-cSH2 — had greater phosphatidylinositol specificity than SH2 domains with a flat ACP. Moreover, ZAP70-cSH2 could bind to a lipid headgroup in the plasma membrane and a pTyr motif in the TCR ζ-chain (TCRζ) simultaneously and independently.

The authors investigated the physiological significance of this pTyr-independent, lipid-binding specificity of SH2 domains using two ZAP70-cSH2 mutants: K176E/K186E, which results in loss of $PtdInsP_3$ selectivity, and K206E/K251E, which reduces non-specific binding to anionic lipids, both of which have similar binding to phosphorylated TCRζ. The K206E/K251E mutant was much less effective than wild-type ZAP70-cSH2 at mediating TCR signalling throughout the whole activation period, whereas the K176E/K186E mutant was almost as active as wild-type ZAP70-cSH2 for the first few minutes but much less active during later stages. Thus, non-specific binding of ZAP70-cSH2 to membrane lipids facilitates the initial interaction with TCRζ, which is later stabilized by binding of ZAP70-cSH2 to $PtdInsP_3$ generated by TCR signalling. The authors propose a general model in which binding of SH2 domains to specific and non-specific lipids can modulate protein binding in a spatiotemporal manner and suggest a new strategy to control dysfunctional pTyr signalling pathways.

> “SH2 domains can recognize lipid headgroups specifically”


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**ORIGINAL ARTICLE** Park, M.-J. *et al.* SH2 domains serve as lipid-binding modules for pTyr-signaling proteins. *Mol. Cell* **62**, 7–20 (2016)
**FURTHER READING** Mayer, B. J. The discovery of modular binding domains: building blocks of cell signalling. *Nat. Rev. Mol. Cell Biol.* **16**, 691–698 (2015)