CELL SIGNALLING

Targeting kinases

The spatial regulation of signalling pathways is partly controlled by protein domains that mediate intermolecular interactions. Human MARK (MAP/microtubule affinity-regulating kinases) and PAR1 (partitioning-defective 1) Ser/Thr kinases harbour a kinase-associated 1 (KA1) domain, which has no assigned function. Moravcevic *et al.* now reveal that *Saccharomyces cerevisiae* septin-associated kinases (Kcc4, Gin4 and Hsl1) also contain a KA1 domain, and that KA1 domains bind phospholipids and target kinases to the plasma membrane.

The authors analyzed more than 60 potential membrane-binding proteins identified in a previous study, which all lack a known lipid-interacting domain. They found that a carboxy-terminal domain in Kcc4, and in Gin4 and Hsl1, binds anionic phospholipids and associates with plasma membranes. Using a *S. cerevisiae* strain that cannot produce phosphatidylserine, they showed that this phospholipid is essential for membrane association of this C-terminal domain and plays an important part in the localization of Kcc4 to the bud neck, where it acts.

Next, the authors determined the crystal structure of the C-terminal portion of Kcc4 to 1.7 Å. They found that it is similar to the extended KA1 domain of human MARK3 and confirmed that the phospholipid-binding domain of Kcc4 is a KA1 domain. The KA1 domain of human MARK1 and MARK3 could bind anionic phospholipids and associate with plasma membranes, and basic regions on the KA1 domain surface were shown to drive membrane localization.

So, KA1 is a novel phospholipid-binding domain that is likely to spatially regulate signalling by kinases that harbour it.

Katharine H. Wrighton

ORIGINAL RESEARCH PAPER Moravcevic, K. *et al.* Kinase associated-1 domains drive MARK/PAR1 kinases to membrane targets by binding acidic phospholipids. *Cell* **143**, 966–977 (2010)