KINASE CONTROL THROUGH A HIGHLY DISORDERED DIMERIZATION AND CALMODULIN-BINDING ELEMENT

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Multi-domain kinases have developed complex mechanisms to integrate and process diverse stimuli. Here, we investigated the mechanism by which the protein tyrosine kinase 2-beta (PYK2) functions as a sensor and effector of cellular calcium influx. PYK2 has important functions in the brain, where it is required for memory consolidation. Accordingly, dysfunctional PYK2 is associated with neurodegenerative disease and brain tumours. Combining NMR, SAXS, bioinformatics, biophysical analyses and cell biology, we show that the linker between the PYK2 kinase and FAT domains (which we call the kinase-FAT linker, KFL) encompasses a novel calmodulin (CaM) binding element. PYK2 KFL is highly disordered and engages CaM through an ensemble of transient binding events. Calcium increases the association by promoting structural changes in CaM that expose supplementary interaction opportunities. KFL also forms fuzzy dimers, and the dimerization strength is enhanced by CaM binding. As a monomer, however, KFL associates with the PYK2 FERM-kinase fragment. Thus, we identify a mechanism whereby calcium influx can promote PYK2 self-association, and hence kinase-activating trans-autophosphorylation. Intriguingly, the KFL also undergoes liquid-liquid phase separation (LLPS), allowing us to study the molecular changes associated with this transition by NMR. Collectively, our findings describe an exceptionally flexible protein module that provides a new paradigm for CaM binding and self-association, and its use for controlling kinase activity.

This presentation would be based on unpublished data, but builds on:

Momin et al. 2019, Passenger sequences can promote interlaced dimers in a common variant of the maltose-binding protein, *Sci. Rep.* DOI: 10.1038/s41598-019-56718-y

Naser et al. 2018, Endogenous Control Mechanisms of FAK and PYK2 and Their Relevance to Cancer Development. *Cancers*, DOI: 10.3390/cancers10060196

Giralt et al., 2018, PTK2B/Pyk2 overexpression improves a mouse model of Alzheimer's disease, *Exp. Neurol.* DOI: 10.1016/j.expneurol.2018.05.020

Molecular basis for calcium sensing by PYK2