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Substrate recruitment and inhibition of the PAR polarity complex

N. McDonald[1]

[1]*London Research Institute, Structural Biology Laboratory, London, UK*

The aPKC [atypical PKC (protein kinase C)] isoforms ι and ζ play crucial roles in the formation and maintenance of cell polarity and represent attractive anti-oncogenic drug targets in Ras-dependent tumours. Deregulation of PKCι signalling has multiple effects including aberrant cell polarity, which is a hallmark of aggressive cancers. PKCι associates with two discrete polarity complexes; one containing the polarity proteins Par3 and Par6 (the PAR complex) and the other contains Crumbs, Stardust and PatJ (the Crbs complex). Both complexes are found in vertebrates and invertebrates where they are crucial for maintaining apical-basal polarity. We are interested in how these two complexes recruit Par6-aPKC to the cell membrane and how aPKC activity is stimulated once within the PAR complex. Several substrates of the PAR complex are also able to inhibit its catalytic activity suggesting a complex regulatory mechanism. Our structural, biochemical and in vivo results from studying the PAR complex will be presented. Our data indicate a hierarchy among PAR complex substrates. In parallel, we have characterised somatic mutations found in PKCι in human cancer, indicating that perturbing a substrate-specific recruitment site selectively disrupts the polarizing activity of PKCι. Finally, a series of ATP-competitive thieno[3,2-d]pyrimidine- based PKCι inhibitors that show potent and selective inhibition of PKCι in biochemical, cellular and in vivo models will be presented.

Keywords: protein kinase complex, cell polarity, chemical inhibitors