Subversion of PKCα signalling in B cell progenitors results in an upregulation of PKCβII expression and leukaemogenesis

Anuradha Tarafdar, Milica Vukovic, Rinako Nakagawa, Emilio Cosimo, Karen Dunn and Alison Michie
University of Glasgow, Glasgow, UK

The protein kinase C (PKC) family of serine/threonine protein kinases share structural homology, while exhibiting substantial functional diversity. An increasing number of studies suggest the involvement of PKC family members in regulating leukaemic cell-survival and proliferation. Indeed, our research demonstrates that stable expression of a kinase dead PKCα (PKCα-KR) in lymphoid progenitor cells results in development of a chronic lymphocytic leukaemia (CLL)-like disease both in vitro and in vivo. This model resembles the more aggressive subset of CLL, exhibiting an upregulation of tyrosine kinase ZAP-70 and elevated ERK-MAPK/mTor signalling, resulting in enhanced proliferation and increased tumor load in the lymphoid organs. Interestingly, reduced PKCα function also leads to an upregulation of PKCβII expression, a key pathogenic feature of CLL, leading to elevated phosphorylation of GKS3βSer9. Treatment of these cells with Enzastaurin (PI3K/PKCβ inhibitor) results in a reduction in GKS3β, ERK and S6 phosphorylation levels, accompanied by cell cycle arrest in vitro and reduced tumour load and induction of apoptosis in vivo. As the ERK-MAPK cascade has previously been shown to regulate PKCβII through PKCε/cRaf, we are currently investigating the role of ERK inhibition on PKCβ regulation and cell survival. Overall, this study aims to understand the molecular mechanisms that govern the development of CLL, converging on PKCβII expression and identify novel targets to combat CLL.