

**P008** PLC $\gamma$ 1 mediates the PI3K-dependent Akt activation in FGF-2 signalling

**Tania Maffucci, Ian Zachary and Marco Falasca**

*Department of Medicine, University College London, UK*

Phosphoinositide 3-kinase (PI3K)/Akt pathway plays a key role in both vascular endothelial growth factor (VEGF)- and fibroblast growth factor (FGF)-mediated angiogenesis. Similarly, phospholipase C $\gamma$ 1 (PLC $\gamma$ 1) regulates crucial events at least in VEGF-dependent angiogenesis. Activation of PLC $\gamma$ 1 generally occurs through phosphorylation of the enzyme. Interestingly, we have demonstrated that PLC $\gamma$ 1 can be activated in a mechanism involving the PI3K product phosphatidylinositol-3,4,5-trisphosphate (PtdIns-3,4,5-P $_3$ ) and that this PI3K/PLC $\gamma$ 1 pathway is crucial for cell migration. Here we show that in HUVEC, FGF-2 activates PLC $\gamma$ 1 in a mechanism completely dependent upon PI3K activation. Interestingly, blockade of PLC $\gamma$ 1 completely inhibits the FGF-2-mediated activation of Akt. Data indicate that the PLC $\gamma$ 1-dependent Akt activation is mediated by protein kinase C (PKC) $\alpha$ . Inhibition of either PI3K, or PLC $\gamma$ 1 or PKC $\alpha$  or Akt completely blocks the FGF-2-induced endothelial cells migration, which is one of the crucial step in angiogenesis. Indeed, blockade of PLC $\gamma$ 1 inhibits the FGF-2-dependent angiogenesis suggesting a critical, central role for PLC $\gamma$ 1 in this process. These data define a novel PI3K/PLC $\gamma$ 1/PKC $\alpha$ /Akt pathway and identify for the first time PLC $\gamma$ 1 as a key mediator for the PI3K-dependent activation of Akt in endothelial cells. More importantly, the PI3K/PLC $\gamma$ 1-dependent activation of Akt is necessary for the FGF-2-mediated angiogenesis.