

P004 Focal adhesion kinase inhibits anoikis by influencing Bax subcellular localisation

James A. Keeble, Nadia K. Zouq and

Andrew P. Gilmore.

Wellcome Trust Centre for Cell Matrix Research, Faculty of Life Sciences, The University of Manchester, United Kingdom.

Adhesion to the extracellular matrix (ECM) is essential for the survival of mammary epithelial cells. Absence of the correct ECM commits normal cells to a form of apoptosis termed anoikis. Adhesion dependant signals suppress anoikis and are propagated intracellularly by numerous signalling enzymes and scaffold proteins. Focal adhesion kinase (FAK) plays a central role in adhesion-mediated survival signalling and is up-regulated in ~90% of breast cancers. To establish the role of FAK in mammary epithelial cell survival we utilised a constitutively-active, myristoylated form of FAK (mFAK). Here we show that mFAK blocks anoikis by influencing the subcellular localisation of the pro-apoptotic Bcl-2 family protein, Bax. Loss of cell/ECM adhesion results in the rapid redistribution of Bax from the cytoplasm to the outer mitochondrial membrane. Expression of mFAK inhibits redistribution of Bax and suppresses anoikis. Mutation of Paxillin, Grb2 or Src binding sites within mFAK abolishes the survival signal, yielding mutant constructs that can no longer influence the activity of Bax. Reattachment of cells to ECM prior to their becoming committed to apoptosis results in Bax accumulating back in the cytoplasm. By using a tamoxifen-regulated form of mFAK, we found that activation of FAK following detachment is sufficient to drive this redistribution. Our data show that FAK suppresses apoptosis by regulating the trafficking of Bax between subcellular compartments.