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SIGNALLING

# SRC and survival

When deregulated, the tyrosine kinase SRC can cause havoc in cells in which it is overexpressed. Recent results from Margaret Frame, Simon Wilkinson, Emma Sandilands and colleagues have shown that, in cancer cells in which the SRC pathway is hyperactive, active SRC is subject to autophagy as a route to enable cancer cell survival.

To examine the consequences of overactive SRC, Frame and colleagues used mouse focal adhesion kinase (*Fak*)-knockout squamous cell carcinoma cells. Loss of FAK means that active SRC is no longer coupled to integrin signalling through FAK or localized to focal adhesions by FAK. In FAK wild-type cells, Tyr416-phosphorylated SRC (active SRC) associates with FAK at focal adhesions; but in FAK-deficient cells, active SRC is present in intracellular puncta (see the image) and the levels of Tyr416-phosphorylated SRC are reduced. Immunogold labelling on electron micrographs suggested that SRC might be present in late autophagosomes in *Fak*-null cells. Staining for markers of autophagy, such as LC3B and ATG7, showed that autophagy proteins colocalize with both FAK and SRC at sites of focal adhesions, and in *Fak*-null cells active SRC colocalizes with autophagy proteins in intracellular puncta. Co-immunoprecipitation experiments showed an association between SRC and LC3B, and inhibition of autophagy by multiple means in *Fak*-null cells resulted in the suppression of this complex and the restoration of active SRC to peripheral adhesions. Additional experiments showed that the targeting of active SRC for autophagy was a consequence of impaired signalling through the integrin–SRC–FAK pathway. Indeed, when loss of adhesion interrupts integrin signalling in FAK wild-type cells, active SRC also becomes associated with LC3B-containing intracellular puncta.

How is SRC targeted for autophagy? SRC associates with a known E3 ubiquitin ligase CBL, and the authors found that the interaction of CBL with SRC was increased in *Fak*-null cells. Moreover, knockdown of CBL using small interfering RNA reduced LC3B binding to SRC. However, experiments using ligase-deficient CBL mutants showed that ubiquitylation of SRC is not the probable mode of association between SRC and LC3B. Instead, CBL binds LC3B through a newly identified conserved motif in CBL, known as the LC3-interacting region (LIR), which is present in multiple autophagy receptors, and mutation of the LIR region results in the loss of SRC targeting to autophagosomes and its relocalization to the cellular periphery in *Fak*-null cells.

What is the biological relevance of this pathway? The inhibition of autophagy in *Fak*-null cancer cells resulted in reduced viability *in vitro* as a result of apoptosis. This indicates that cancer cells need to control the level of active SRC to maintain its oncogenic effect, as opposed to what seems to be a toxic effect in the absence of integrin–SRC–FAK signalling. The authors conclude that the pathway of SRC autophagy, when active in cancer cells, represents a potential vulnerability, and that FAK inhibitors, which are now in clinical trials, might have increased efficacy if combined with an inhibitor of autophagy.

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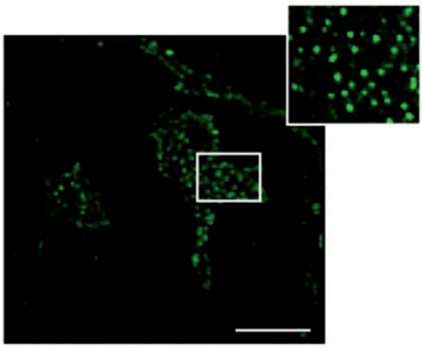
> “active SRC is subject to autophagy as a route to enable cancer cell survival.”

**ORIGINAL RESEARCH PAPER** Sandilands, E. *et al.* Autophagic targeting of SRC promotes cancer cell survival following reduced FAK signalling. *Nature Cell Biol.* 4 Dec 2011 (doi:10.1038/ncb2386)



The image shows that Tyr416-phosphorylated SRC (in green) is present in intracellular puncta in *Fak*-null cells. Image courtesy of M. Frame, University of Edinburgh, UK.