THERAPY

Combine and conquer

Inhibitors of mammalian target of rapamycin complex 1 (mTORC1) signalling (rapamycin and derivatives thereof) are undergoing clinical testing for numerous types of cancer. However, trials in which patients are not genetically and molecularly stratified have not been as successful as the preclinical data promised. Three papers published in the *Journal of Clinical Investigation* provide evidence for combination therapy that could improve the efficacy of mTORC1 inhibition.

Evidence indicates that non-responsiveness to mTORC1 inhibition results from the release of negative feedback loops whereby pro-survival pathways upstream of mTOR are activated, such as the activation of Akt (termed 'Akt rebound'). To investigate these feedback loops in more detail Carracedo and colleagues analysed tumour biopsy samples from patients with metastatic breast or colon cancer or melanoma enrolled in a phase I trial of the rapamycin derivative RAD001. They found that tumours from all patients treated with a high weekly dose exhibited increased activation of extracellular signal-regulated kinase (Erk; indicative of mitogen-activated protein kinase (MAPK) pathway activation), whereas those treated with a low daily dose did not. They also found that Erk is activated after treatment in a *Pten*-deficient mouse model of prostate cancer and that MAPK pathway activation results from the loss of mTORC1 function. Furthermore, genetic and pharmacological analyses showed that the Ras–RAF1–MEK1–MEK2 arm of MAPK signalling is responsible for Erk–Akt signalling downstream of S6K1–PI3K (phosphoinositide 3-kinase) when mTORC1 activity is lost, indicating that targeting the MAPK pathway might improve the efficacy of mTORC1 inhibition. Indeed, they showed that RAD001 or rapamycin plus MEK inhibitors had an additive effect *in vitro* and *in vivo*.

In a separate paper, Waugh Kinkade and colleagues report the results of a preclinical study of prostate cancer in mice lacking PTEN in prostate tissue treated with the MEK inhibitor PD0325901 plus rapamycin. They showed that the drugs have a combination index of 0.03–0.1, indicating strong synergy. Using both the mice and tissue-recombinant models they assessed the effects of the combination on androgen-dependent and androgen-independent tumours and hormone-refractory tumours. Akt was inhibited upon combined use of rapamycin and PD0325901, and they found that the combination therapy reduced tumour weight and proliferation in androgen-independent and hormone-refractory prostate tumours, but was modestly effective against androgen-dependent prostate tumours. How relevant is this to patients? Using microarrays, the authors independently analysed PTEN–Akt–mTOR and Erk–MAPK signalling pathways in tissue samples from two cohorts of patients with prostate cancer and they showed that the PTEN–Akt–mTOR pathway is frequently altered in prostate cancer progression and at least 20% of patients are likely to benefit from this combination therapy.

The use of combination therapy to overcome Akt rebound after mTORC1 inhibition was also described by Kharas and colleagues, who showed that treatment with a dual mTOR and PI3K inhibitor, PI-103, in combination with imatinib, synergistically reduced cell survival of pre-B-cell acute lymphocytic leukaemia (pre-B-ALL) and Philadelphia chromosome-positive ALL *in vitro* and in mouse models.

Together, these data indicate that understanding signalling feedback loops that lead to the evasion of therapeutic responses can inform combination therapies that can be used to treat patients with progressive or non-responsive disease.

Gemma K. Alderton

ORIGINAL RESEARCH PAPERS Carracedo, A. *et al.* Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. *J. Clin. Invest.* **118**, 3065–3074 (2008) | Waugh Kinkade, C. *et al.* Targeting AKT/mTOR and ERK MAPK signaling inhibits hormone-refractory prostate cancer in a preclinical mouse model. *J. Clin. Invest.* **118**, 3051–3064 (2008) | Kharas, M. G. *et al.* Ablation of PI3K blocks BCR–ABL leukemogenesis in mice, and a dual PI3K/mTOR inhibitor prevents expansion of human BCR–ABL$^+$ leukemia cells. *J. Clin. Invest.* **118**, 3038–3050 (2008)