The hVps34-SGK3 pathway alleviates sustained PI3K/Akt inhibition by stimulating mTORC1 and tumour growth

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We would like to apologise for the oversight in not referring to another recently published study that some of us co-authored (Castel *et al*, 2016), which demonstrates a role for SGK1 in mediating resistance to PI3K α (BYL719) inhibitor therapy. We also wish to clarify which of the structurally similar SGK inhibitors were used in the Castel's study (SGK1) and our investigations (SGK3) to avoid confusion.

The centre of attention of both studies is model breast cancer cell lines possessing mutations that elevate signalling through the PI3K/Akt pathway. The Castel *et al*'s (2016) study focuses on ER-negative cell lines that are intrinsically resistant to PI3K α (BYL719) inhibitor therapy and demonstrates that this is caused by a high basal level of SGK1 expression. The Bago *et al*'s (2016) study focused on ER-positive cell lines that display low basal expression of SGK1 and, consistently, are initially sensitive to PI3K/Akt inhibitor treatment. Prolonged treatment of these cells with Akt (MK-2206 and AZD5363) or pan-PI3K class I (GDC0941 and BKM120) inhibitors upregulated SGK3 mRNA and protein as well as SGK3 catalytic activity, under conditions where SGK1 mRNA and protein level remained low and essentially unchanged. Despite the similarity of these isoforms, the mechanism of regulation of these kinases is substantially different. For instance, SGK3 activation was shown to be dependent on the human class III PI3K, hVps34, which generates the lipid messenger PtdIns(3)P.

The studies also reveal that both SGK1 (Castel *et al*) and SGK3 (Bago *et al*) stimulated mTORC1 by phosphorylating TSC2 and that

SGK1 and the hVps34-SGK3 pathway represent two mechanisms influencing sensitivity to PI3K/Akt pathway inhibitors. Together, these studies provide strong evidence that inhibiting SGK isoforms is a promising novel strategy to restore the sensitivity of breast cancers tumours to PI3K/Akt pathway therapy. The Castel *et al*'s study also suggested the feasibility of targeting PDK1, an upstream regulator of SGK1, in suppressing cancer.

Both studies exploit recently described structurally similar SGK inhibitors termed 14g (used in the Castel *et al*'s study) and 14h (used in the Bago *et al*'s study) that were originally developed by Sanofi. The Castel's study employed the compound initially termed 14g, which was renamed SGK-IN in their paper. The potency and selectivity of the 14g/SGK-IN and 14h, as well as other structurally similar compounds, was compared side by side in Bago *et al*. This paper also reports that 14h prevents the activation of SGK3 by PDK1 and mTORC2. It is not known whether 14g/SGK-IN would additionally interfere with the activation of SGK3, or whether either 14g/SGK-IN or 14h would also affect activation of SGK1.

Reference

Castel P, Ellis H, Bago R, Toska E, Razavi P, Carmona FJ, Kannan S, Verma CS, Dickler M, Chandarlapaty S, Brogi E, Alessi DR, Baselga J, Scaltriti M (2016) PDK1-SGK1 signaling sustains AKT-independent mTORC1 activation and confers resistance to PI3K α inhibition. *Cancer Cell* 30: 229–242