The success of targeted therapies in treating cancer over the last decade has been tempered by acquired drug resistance that follows long-term treatment. There is also emerging evidence for innate mechanisms of cancer cell resistance to targeted therapy that pre-exist as parallel signalling pathways. This aspect is explored by the Alessi group and collaborators from AstraZeneca in this issue of the *Biochemical Journal*, who identify a subset of breast cancer cell lines that are intrinsically resistant to Akt inhibition through constitutive up-regulation of the related AGC serine/threonine kinase SGK1 (serum- and glucocorticoid-regulated kinase 1). The study could help to profile tumours for sensitivity to Akt inhibitors and once more highlights the therapeutic complexity of cancer and the importance of exploring combination therapies in the clinic.

Key words: AGC kinase, Akt, cancer, protein kinase, protein kinase B (PKB), resistance, serum- and glucocorticoid-regulated kinase (SGK), signalling, therapy.

Activation of the PI3K (phosphoinositide 3-kinase) pathway is one of the most common signalling events in cancer. This can occur by multiple mechanisms, the most common being mutation or amplification of RTKs (receptor tyrosine kinases), gain-of-function mutations in *RAS* or *PIK3CA* and/or loss-of-function of *PTEN* (phosphatase and tensin homologue deleted on chromosome 10), leading to increased tumour cell survival, growth, metabolism and motility. Developing drugs that target this pathway is a top priority in the pharmaceutical industry. These efforts have focused on inhibiting RTKs and PI3Ks as well as the downstream effector protein kinase Akt [also known as PKB (protein kinase B)]. As a central node of the RTK/PI3K signalling pathway, Akt is activated in a wide range of cancers, and clinical trials testing the efficacy of Akt inhibitors in various cancers are ongoing.

Akt is an AGC kinase that is activated by binding through its PH (pleckstrin homology) domain to the PtdIns(3,4,5)P₃, membrane lipid second messenger, generated by the class I PI3Ks, and subsequent phosphorylation on Thr³⁰⁸ and Ser⁴⁷³ by two other protein kinases, namely PDK1 (phosphoinositide-dependent kinase 1) and mTORC2 [mTOR (mammalian target of rapamycin) complex 2] respectively (Figure 1). Akt has numerous downstream substrates involved in cell survival (e.g. BAD), proliferation (e.g. forkhead transcription factors), translation and metabolism (e.g. tuberin/TSC2 (tuberous sclerosis complex 2)) and motility (such as Girdin). Crucially, on the basis of studies in *Drosophila, Caenorhabditis elegans* and mammalian systems, Akt has been considered to mediate the majority of PtdIns(3,4,5)P₃-dependent/PI3K signalling, both in normal developmental processes and in cancer [1–3]. Clearly drugs that inhibit Akt activation would be predicted to display low sensitivity, and thus be a potential readout of Akt inhibitor responsiveness. NDRG1 is a SGK1 substrate; however, Sommer et al. [4] demonstrate that, in cells that are sensitive to Akt inhibition (and thus display low SGK1), NDRG1 is likely to be phosphorylated by Akt. Conversely, in Akt-inhibitor-resistant cell lines (which have elevated SGK1), NDRG1 is phosphorylated by SGK1. NDRG1 is a relatively uncharacterized protein, with possible roles in regulation of cancer cell motility (reviewed in [5]). However, further work will be needed to determine whether NDRG1 plays an essential role in PI3K-dependent cancer or is more important as a biomarker for pathway activation. Finally given that mTOR activates SGK1, the authors demonstrate that Akt-resistant/SGK1-dependent cell lines are sensitive to mTORC1/2 inhibition. It will be interesting to see whether these observations can be verified in clinical samples and in other cancer types than breast.

The implications of the study are two-fold. First, the response of NDRG1 phosphorylation to Akt inhibition may be used to stratify tumours into those that are likely to be sensitive to Akt inhibition.

---

**Abbreviations used:** mTOR, mammalian target of rapamycin; mTORC, mTOR complex; NDRG1, N-Myc downstream-regulated gene 1; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homologue deleted on chromosome 10; RTK; receptor tyrosine kinase; SGK, serum- and glucocorticoid-regulated kinase.

1 Correspondence may be addressed to either author (email l.moniz@qmul.ac.uk or bart.vanh@qmul.ac.uk).
Under normal conditions, Akt is activated by phosphorylation by PDK1 and mTORC2 in a PtdIns(3,4,5)P3-dependent manner. SGK1 and SGK3 are also activated by phosphorylation following direct interaction with PDK1 and by phosphorylation by mTORC1/2. Akt and SGK kinases have both distinct and overlapping substrate specificity. In cancer cells, Akt activity is often enhanced and required (I). However, the cell may also utilize SGK1 (II) or SGK3 (III) activity in addition to or instead of Akt to promote cell proliferation, survival and motility. Foxo3, forkhead box O3; GSK3, glycogen synthase kinase 3; MEKK2, mitogen-activated protein kinase/extracellular-signal-regulated kinase kinase kinase 2; PH, pleckstrin homology; PIP3, PtdIns(3,4,5)P3. PX, Phox homology.

Tumours predicted to be resistant to Akt inhibitors may instead be treated with alternative or combination therapies (such as an mTOR or SGK inhibitor). Secondly, and more broadly, the study supports the idea that there are important pathways parallel with or independent of Akt that act downstream of RTK/PI3K/PTEN.

The SGK kinases are taking centre stage in these discussions. As closely related members of the AGC kinase family, SGK1, 2 and 3 share overlapping substrate specificity with Akt as well as similar (but not identical) mechanisms of activation (Figure 1). Unlike Akt, SGK1 and 2 are predominantly cytoplasmic, whereas SGK3 has a PtdIns3P lipid-binding PX (Phox homology) domain and resides in the endosomal compartment. Compared with SGK1 and 3, there are comparatively few studies on SGK2 function.

Early work on SGK1 placed this kinase firmly in the insulin/PI3K pathway playing both overlapping and independent functions to Akt. For instance, in *C. elegans*, both Akt1/2 and SGK1 act downstream of the insulin receptor DAF-2 and phosphorylate the FOXO3a (forkhead box O3a) homologue DAF-16. However, phosphorylation by Akt leads to dauer arrest, whereas phosphorylation by SGK1 is involved in development, stress and longevity [6].

In mammalian cells under normal conditions, SGK family members do not appear to be essential proteins for cell growth or survival, and single or double mouse knockouts of SGK1 and 3 are viable and display mild defects in salt retention and delays in hair growth [7]. However, in the context of cancer, there is mounting evidence that SGK1 and 3 act as alternative effectors downstream of PI3K signalling. Whereas Sommer et al. [4] identified SGK1 as a mechanism of Akt-inhibitor-resistance in breast cancer cell lines, the group of Levi Garraway [8] previously demonstrated that a subset of *PI3KCA*-mutated cell lines display low Akt activation but elevated levels of SGK3, which was required for viability.

Further supporting a more equal role of Akt and SGK in cancer, they were both shown to be overexpressed in 50–60% of a panel of primary human breast cancers [9]. Of interest, SGK2 was previously identified in a synthetic lethal screen and is required for cell survival of human cervical cancer cell lines following loss of p53 [10].

Overall the studies discussed above confirm that the primacy of the PI3K/Akt axis is not absolute. As with most major signalling pathways, normal cells have developed a number of feedback loops in order to rein in high levels and/or constitutive Akt activity. For example, mTORC1 activation leads to feedback inhibition of IGF-1 (insulin-like growth factor 1)/insulin signalling, whereas Akt activity can cause down-regulation of RTK expression and activity [11–14]. In contrast, tumour cells find alternative routes to circumvent these brakes, one of which is through modulation of SGK kinases to compensate for the loss of Akt function.

It is clear that future work will be important to more fully understand the role that the different SGK isoforms play in cancer development and in the response to Akt inhibition. Are they an alternative or a parallel path to Akt? Are SGK-knockout mice less susceptible to cancer? In addition to SGK, other AGC kinases such S6K1 (S6 kinase 1) may also compensate for Akt, suggesting that pan-AGC inhibitors or inhibitors against upstream kinases, PDK1 and mTOR, may find more success in the clinic, although the potential for toxicity may also increase [15]. Taken together these studies demonstrate the complexity of tumours and act as a reminder for exploring combination therapies in the clinic.

**ACKNOWLEDGEMENTS**

We thank Benoit Bilanges for critically reading this paper before submission.
FUNDING
Work in the laboratory of B.V. is supported by Cancer Research UK [grant number C23338/A10200] and Biotechnology and Biological Sciences Research Council [grant number BB/1007806/1].

REFERENCES

Received 2 May 2013; accepted 7 May 2013
Published on the Internet 31 May 2013, doi:10.1042/BJ20130517