All Roads Lead to the Ribosome

Steven Whittaker,[1,2] Matthew Martin,[3] and Richard Marais[3,*]
[1]Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA
[2]The Broad Institute, 7 Cambridge Center, Cambridge, MA 02142, USA
[3]Institute of Cancer Research, 237 Fulham Road, London, SW3 6JB, UK
*Correspondence: richard.marais@icr.ac.uk
DOI 10.1016/j.ccr.2010.06.008

In this issue of *Cancer Cell*, She et al. show that in cancer cells a protein called 4E-BP1 is a key integrator of protein synthesis downstream of the ERK and AKT signaling pathways, providing an intriguing rationale for why their simultaneous targeting could enhance therapeutic efficacy.

Intracellular signaling pathways mediate cell responses to extracellular signals. In cancer, acquired somatic mutations in components of these pathways create activated oncogenes that drive constitutive mitogen-independent signaling, upon which the cancer cells come to depend for proliferation and survival. This phenomenon of "oncogene addiction" (Weinstein and Joe, 2008) is believed to underlie the selective activity of targeted therapies against cancer cells over normal cells. However, despite the implications of its name, oncogene addiction is rarely absolute because aberrant signaling from several pathways drives cancer cell proliferation and survival in vivo. Thus, effective therapy requires simultaneous targeting of more than one oncogene-driven pathway. To this end, the possible benefits of concurrent inhibition of the RAF/ERK and PI3K/AKT pathways appears attractive because they are downstream of oncogenic RAS or are often jointly activated by somatic mutations in genes such as *BRAF* and *PIK3CA* (Figure 1).

These pathways can be inhibited separately, but in this issue of *Cancer Cell*, She et al. elegantly reveal that it may be possible to target both simultaneously through a common downstream effector (She et al., 2010). Their starting point was to identify cancers cells that require both pathways for survival. Critically, they then demonstrated that the pathways converge on a repressor of protein synthesis called 4E-BP1. Obviously, new protein synthesis is essential for tumor growth and for many of the essential proteins—such as the cell cycle regulator cyclin D1, the antiapoptotic protein bcl2, and the proangiogenic growth factor VEGF—the rate-limiting step in synthesis is binding of the eIF4F initiation complex to the 5′ cap of their messenger RNAs, which initiates ribosome assembly and protein translation (Graff and Zimmer, 2003). 4E-BP1 inhibits protein synthesis by binding to the eIF4E initiation complex and preventing it from binding to the 5′ cap, but this inhibition is overcome by 4E-BP1 phosphorylation, which releases the eIF4E complex (Richter and Sonenberg, 2005). By using small molecule inhibitors, RNA interference, and genetic knockout cells, She et al. show that RAF/ERK and PI3K/AKT signaling must both be inhibited to stimulate 4E-BP1 dephosphorylation, demonstrating that they independently contribute to protein synthesis in cancer cells.

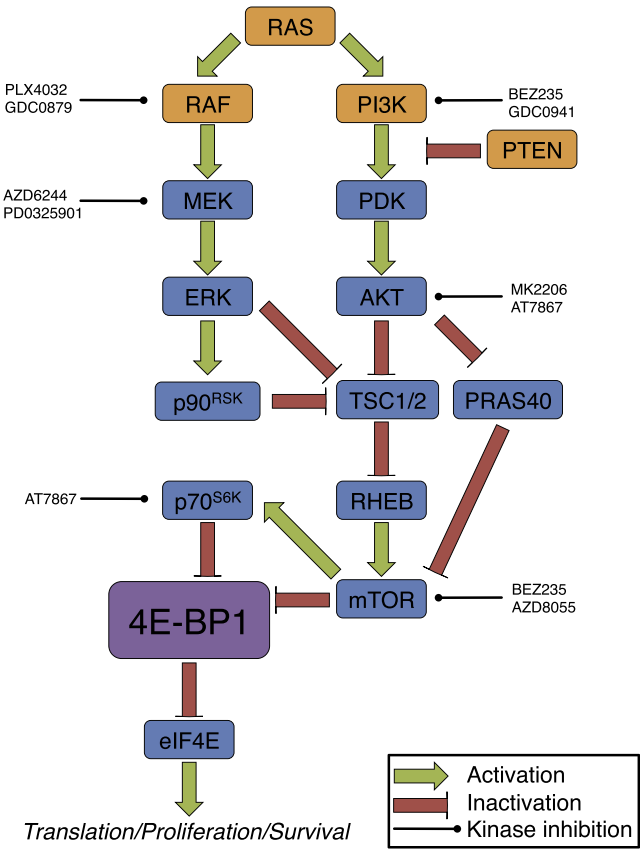

Figure 1. The RAF/ERK and PI3K/AKP Pathways Interact to Regulate Protein Synthesis
The RAF/ERK and PI3K/AKT pathways can be activated by mutations in key oncogenes or tumor suppressors (orange). These pathways both stimulate 4E-BP1 phosphorylation, which initiates protein synthesis by releasing eIF4E. Thus, inhibition of both pathways may be needed to block protein synthesis and induce cancer cell death.

The regulation of protein synthesis is immensely complex, but a key integrator of this process is a protein kinase called mammalian target of rapamycin (mTOR), which directly phosphorylates 4E-BP1 (Figure 1). Notably, ERK and an ERK downstream kinase called p90^{RSK} phosphorylate and inhibit the TSC1/2 complex, allowing the small

G protein RHEB to activate mTOR (Tee and Blenis, 2005). AKT also phosphorylates and inhibits TSC1/2 and additionally inhibits the action of the mTOR inhibitor PRAS40 (Vander Haar et al., 2007). Thus, She et al. conclude that both pathways stimulate protein synthesis through mTOR and go on to demonstrate that MEK and AKT inhibitors synergize to suppress the growth of colon cancer tumors that carry *RAS* and *PIK3CA* mutations, that these inhibitors cooperate to block in vivo phosphorylation of 4E-BP1, and that constitutively active 4E-BP1 slows tumor growth. These results reinforce the importance of protein synthesis for tumor growth and robustly support the identification of 4E-BP1 as a critical integrator of RAF/ERK and PI3K/AKT signaling.

A key implication of these data is that 4E-BP1 is a potential therapeutic target in both pathways. Although 4E-BP1 itself may not be a tractable target, the mTOR inhibitor AZD8055 is relatively effective at blocking 4E-BP1 phosphorylation (Chresta et al., 2010), suggesting that mTOR drugs could suppress protein synthesis downstream of ERK and AKT pathway oncogenes. This important node could thus be used to inhibit both pathways simultaneously or to enhance the effects of upstream drugs. Dual PI3K/mTOR inhibitors such as BEZ235, which already achieve some degree of combined blockade, may be the most effective to combine with ERK pathway drugs in the class of tumor studied by She et al. Note, however, that this combination may not be effective in all tumors, because the antiproliferative activity of BEZ235 is independent of *BRAF*/*PTEN* mutation in some cells (Brachmann et al., 2009).

The findings of She et al. highlight the importance of understanding the biology of signaling, the underlying genetics of a specific tumor, and the mechanisms of action of targeted therapies, in order to best deploy combinations of inhibitors or dual kinase inhibitors in patients. Our naive view of cancer signaling is maturing into an understanding that the pathways are not linear, but embedded in highly versatile networks that can adapt to inhibition at single points. Thus, to achieve effective therapy, the networks must be targeted at several critical nodes and here we note that genome-wide sequencing shows that cancer cells acquire 20,000–30,000 somatic mutations (McCarthy, 2010), warning us that our understanding of signaling complexity, although quite advanced, may still be in its infancy. Studies such as the one presented by She et al. could change treatment paradigms in cancer, but they will surely need to be underpinned by a comprehensive snapshot of the genetic aberrations of an individual tumor to allow appropriate clinical decisions to be made. As advances in technologies to provide this information move ahead at breathtaking pace, the need for improved understanding of the underlying biology as provided by She et al. becomes all the more important. Their data show that some cancer cells can tolerate loss of signaling from either pathway, a process of "oncogene addiction switching" that could represent a major hurdle in cancer treatment. However, this study also provides hope that we may be able to overcome this problem. In identifying an important integrator of the RAF/ERK and PI3K/AKT, they provide a potentially new target, a possible biomarker for measuring responses to treatment, and a firm rationale for why it is important to inhibit both pathways in this class of tumor.

REFERENCES

Brachmann, S.M., Hofmann, I., Schnell, C., Fritsch, C., Wee, S., Lane, H., Wang, S., Garcia-Echeverria, C., and Maira, S.M. (2009). Proc. Natl. Acad. Sci. USA *106*, 22299–22304.

Chresta, C.M., Davies, B.R., Hickson, I., Harding, T., Cosulich, S., Critchlow, S.E., Vincent, J.P., Ellston, R., Jones, D., Sini, P., et al. (2010). Cancer Res. *70*, 288–298.

Graff, J.R., and Zimmer, S.G. (2003). Clin. Exp. Metastasis *20*, 265–273.

McCarthy, N. (2010). Nat. Rev. Cancer *10*, 161.

Richter, J.D., and Sonenberg, N. (2005). Nature *433*, 477–480.

She, Q.-B., Halilovic, E., Ye, Q., Zhen, W., Shirasawa, S., Sasazuki, T., Solit, D.B., and Rosen, N. (2010). Cancer Cell *18*, this issue, 39–51.

Tee, A.R., and Blenis, J. (2005). Semin. Cell Dev. Biol. *16*, 29–37.

Vander Haar, E., Lee, S.I., Bandhakavi, S., Griffin, T.J., and Kim, D.H. (2007). Nat. Cell Biol. *9*, 316–323.

Weinstein, I.B., and Joe, A. (2008). Cancer Res. *68*, 3077–3080.