Editorial

Review of the complexities of the PI3K/mTOR pathway presages similar handling of other critical topics

Since the cloning of the PTEN gene in 1997, the phosphatase and tensin homolog/phosphatidylinositol-3-kinase (PTEN/PI3K) pathway has been shown to play a central role in the origin and progression of malignant glioma, as evidenced by the high prevalence of loss of heterozygosity, deletions, and mutations of the gene in primary and secondary glioblastomas and advanced breast, prostate, and lung cancers.1,2 The PTEN/PI3K pathway controls physiological signals crucial to proliferation, apoptosis, survival, migration, and angiogenesis via its PI3K/AKT (serine/threonine kinase)/mTOR (mammalian target of rapamycin) signal axis.3,4 Thus, PI3K, AKT, and mTOR have become major targets for the development of small-molecule inhibitors. Several mTOR inhibitors have led the way in this regard, being applied clinically to recurrent glioblastoma; however, these inhibitors have shown disappointingly little activity when used as single agents. This lack of activity suggests that alteration of the PTEN/PI3K pathway is not the only driver in gliomagenesis and progression; alterations of other parallel and interacting pathways, including those involving multiple receptor tyrosine kinases, the RB (retinoblastoma) and p53 proteins, and others yet undiscovered must be taken into consideration for therapeutic intervention.

In this issue, an article from Paul Mischel’s group at the University of California-Los Angeles (Akhavan et al.5) presents a detailed and concise overview of the PI3K/mTOR pathway and its many cross-talk and feedback loops that provide the means for cells to escape the effects of mTOR inhibitors and thereby survive mTOR-based treatments. The relationship between epidermal growth factor receptor (EGFR), the EGFRvIII mutation, and PI3K activation is discussed in detail, as this relationship demonstrates potential mechanisms by which single-agent therapy with an EGFR inhibitor or mTOR inhibitor may fail. Mischel and colleagues also describe the link they found between the PI3K pathway and lipid metabolism in their own work, which uncovered another escape mechanism that cancer cells frequently use to survive when put under metabolic stress from hypoxia or oxidation. This concise review thus provides a comprehensive and highly informative synopsis of one of the most important and most complicated signaling pathways central to cellular survival.

Additional reviews to follow

This paper also illustrates the beginning of a more concerted effort to bring to our readers timely reviews of current and important topics in neuro-oncology and brain tumor research. The journal has published many reviews that were initiated by authors. The Akhavan et al. review, however, is the first of several invited reviews initiated by the journal editors. Our goal is to bring our readers critical and thorough analyses of current and even controversial topics, written by experienced investigators in those fields who can provide balanced, concise, and up-to-date overviews with in-depth perspective and a clear vision of future developments related to the topics at hand. We do not want to monopolize the choice of topics, nor should we presume we know all the needs of our diverse readers. Thus, we encourage you to suggest topics and potential reviewers by simply sending an e-mail to the editorial office or one of the journal editors. We will consider your suggestions carefully and initiate the invitation process as needed.

W. K. Alfred Yung, Editor-in-Chief
References


