**IN THE SPOTLIGHT**

**mTORC 2:1 for Chemotherapy Sensitization in Glioblastoma**

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**Summary:** mTOR signaling is frequently deregulated in cancer, including brain tumors. Although the signaling of mTOR complex 1 (mTORC1) has been subject to intensive investigations and mTORC1 itself has been a well-established cancer drug target for years, the role of the second complex, mTORC2, remains elusive. Tanaka et al. reveal an EGFRvIII-mTORC2-NF-κB signaling cascade and demonstrate that mTORC2 mediates cisplatin resistance through NF-κB in an Akt-independent manner in glioblastoma. Uncovering the role of mTORC2 in chemotherapy resistance in glioblastoma highlights the need for further investigations of mTORC2 inhibition. *Cancer Discovery*. 1(6); 475-76. ©2011 AACR.

Commentary on Tanaka et al., p. 524 (4).

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**INTRODUCTION**

Serving as a central signaling hub that integrates multiple intra- and extracellular cues, the serine/threonine kinase mTOR is an attractive anticancer target. mTOR is involved in the formation of at least two multiprotein complexes, mTORC1 and mTORC2, that direct cell metabolism, growth, proliferation, survival, and angiogenesis.

Whereas signaling via the rapamycin-sensitive mTORC1 through its direct phosphorylation of the ribosomal protein S6 kinase 1 (S6K1) and the eukaryotic translation initiation factor 4E (eIF4E) binding protein 1 (4E-BP1) is well understood and involved in the promotion of anabolic processes, including biosynthesis of proteins, lipids, and organelles, and limitation of catabolic processes such as autophagy (1), the biology of mTORC2 is far less clear. Although the authors of previous work showed that mTORC2, contrary to mTORC1, acts upstream of AKT and is necessary for the maximum activation of Akt via S473 phosphorylation (2), the precise function and especially the regulation of mTORC2 has not yet been fully clarified. Aberrant signaling of the epidermal growth factor receptor (EGFR) through amplification (40%) or overexpression (>60%) accounts for the most common mutational changes in primary glioblastoma, and EGFRvIII, a constitutively active genomic deletion variant of the EGFR, is the most frequent mutational variant found in glioblastoma, causing a persistent activation of the phosphoinositide 3-kinase (PI3K) signaling pathway (3).

By using this oncogenic EGFR variant, Tanaka et al. (4) show in this issue of *Cancer Discovery* that EGFRvIII stimulates mTORC2 activity, which promotes glioblastoma proliferation (Fig. 1). Most importantly, they propose an EGFRvIII/mTORC2/NF-κB signaling cascade and point out that mTORC2 mediates cisplatin resistance through NF-κB in an Akt-independent manner in glioblastoma.

They highlight that EGFRvIII-dependent mTORC2 activity was suppressed by reconstitution of PTEN, suggesting a role for mTORC2 downstream of PI3K/Akt and allowing for speculation that other cancers may also demonstrate mTORC2 activity-related chemotherapy resistance. The relevance for glioblastoma is stressed by the finding that mTORC2 signaling was hyperactivated and associated with NF-κB and phospho-EGFR in the majority of the examined clinical samples. The observed NF-κB-driven chemoresistance towards cisplatin certainly raises questions about the modulation of the response towards radiation therapy and alkylating agents, especially temozolomide, the most important drug in the treatment of glioblastoma. Further exploration of the mechanism of NF-κB induction and a possible mTORC2/NF-κB resistance network, including additional mediators, should be truly promising, especially because NF-κB is known to drive O6-methylguaninyl-methyltransferase, a key resistance factor for temozolomide action (5).

Other investigators have shown that growth factors stimulate mTORC2 activity. The novelty in the present study stems from the fact that oncogenic EGFR (EGFRvIII) stimulates this kinase activity and that PTEN suppresses it. EGFR itself is an attractive target for glioblastoma therapy. However, caution is needed with EGFR inhibitors because hypoxia and low glucose levels might convert the cytotoxic effects of EGFR inhibition into a cyto-protective effect (6).

In addition to its contribution to the understanding of EGFR/mTOR signaling, this work by Tanaka et al. (4) helps us understand why efforts to target one of the most logical targets in brain tumors, mTOR, have been largely unsuccessful, at least in all published studies. A number of single- or multi-targeted therapies, including the mTOR inhibitor rapamycin or its derivatives, the “rapalogs” everolimus (RAD001), deforolimus (AP23573), and temsirolimus (CCI-779) (7), targeting the EGFR/PI3K/Akt/mTOR signaling pathway, have failed to demonstrate convincing clinical activity in relapsed glioblastoma, either alone or in combination with EGFR inhibition (8, 9).

In line with this finding, Tanaka et al. (4) found mTORC2 activation in glioblastoma during the course of rapamycin treatment *in vitro* and *in vivo*. Hence these data suggest the possibility that failure to suppress mTORC2 signaling,
including NF-κB signaling, may underlie the resistance to rapamycin and the associated poor clinical outcome in some patients with glioblastoma. Dual inhibition of mTORC1 and mTORC2, which inhibits tumor growth and leads to tumor cell death in the presented preclinical paradigm, or mTORC2/chemotherapy combinations, may be worth investigating in the clinic. Another approach that aims for additive or even synergistic activity that is currently being attempted by the Brain Tumor Group of the European Organization for Research and Treatment of Cancer (EORTC 26082/22081) is the combination of mTOR inhibition not with chemotherapeutic agents but rather with radiotherapy (http://www.eortc.be). In this non-comparative actively controlled phase II study, CCI-779 at 25 mg or temozolomide is combined with radiotherapy in patients with newly diagnosed glioblastoma.

Studies to identify markers predicting response to EGFR inhibitors in patients with recurrent glioblastoma have shown significant correlation of response to therapy with coexpression of the PTEN tumor suppressor and the EGFR deletion mutant variant III (EGFRvIII) (10). However, this has been suggested to be a prognostic phenomenon (11). It may be worth testing these parameters with new therapies, such as mTORC2 inhibition plus chemotherapy, or other molecular parameters, like NDRG1 or NF-κB, for predictive properties in future trials.

The results presented here suggest mTORC2 as a target for combination cancer therapy and provide new insights into its role in mediating chemotherapy resistance, suggesting new treatment strategies. Preclinical data, including more glioblastoma-specific therapies, such as radiotherapy and temozolomide, will be important to delineate the next steps and possibly revitalize the EGFR/mTOR axis as a therapeutic target in glioblastoma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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REFERENCES

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