Glioblastoma is the most prevalent and malignant primary brain tumor in adults, and its response to current therapies is limited. Protein kinase CK2 is overexpressed in glioblastoma and regulates glioblastoma cell survival, proliferation, and migration and brain tumorigenesis. Targeting CK2 for glioblastoma treatment may benefit patients with glioblastoma. Clin Cancer Res; 19(23); 6335–7. ©2013 AACR.

In this issue of Clinical Cancer Research, Zheng and colleagues reveal their finding that CSNK2A1, the gene encoding for CK2α, was amplified in 33.7% of 537 glioblastoma samples via gene copy number variation analyses of The Cancer Genome Atlas (TCGA) database (1). Glioblastoma is a highly malignant and aggressive disease and is the most common primary intrinsic brain tumor in adults. Patients diagnosed with glioblastoma have a mean survival time of only 15 months (2). Glioblastoma can arise either de novo or from lower-grade astrocytomas. According to differing patterns of patients’ gene expression profiles, glioblastoma is classified into four subgroups: proneural, neural, classical, and mesenchymal (2). The report by Zheng and colleagues posits that CSNK2A1 amplification is more common in classical glioblastoma (50.7%) than in nonclassical glioblastoma (21.3%).

Protein kinase CK2, which has more than 300 substrates, is an important and highly pleiotropic protein kinase, and elevated CK2 kinase activity is frequently observed in many types of human tumors. CK2 is a dual-specificity protein kinase and phosphorylates substrates at serine, threonine, and/or CK2α (i.e., αα, αα′, α′α′) — and two regulatory subunits — CKβ. The two catalytic subunits in the holoenzyme make no contacts with each other (3). Although CK2 is traditionally regarded as a constitutively active kinase, studies have shown that ERK phosphorylates CK2α at Thr360/Ser362 and activates CK2α in response to growth factor stimuli, including EGF (4).

CK2 regulates multiple signaling pathways that play instrumental roles in many important cellular activities (Fig. 1). CK2 regulates Wnt/β-catenin signaling cascades via several mechanisms: CK2 phosphorylates α-catenin and disrupts the complex of β-catenin and α-catenin, thereby abrogating the inhibitory effect of α-catenin on β-catenin transactivation induced by EGF (4); CK2 phosphorylates LEF-1 and enhances its binding to nuclear β-catenin in Wnt-signaling cells (5); and CK2 can either increase or decrease cytoplasmic β-catenin stability by phosphorylating β-catenin at different residues or the E2 ubiquitin-conjugating enzyme UBC3B (6, 7). In addition, CK2 can positively regulate PI3K/AKT activity by directly phosphorylating AKT at Ser129 (8). Moreover, CK2 activates the NF-κB pathway by promoting IκB degradation and phosphorylating p65/RelA at Ser529 to enhance the DNA binding ability of p65/RelA (9). CK2 also phosphorylates Janus kinase (JAK) 1 and 2 and promotes JAK-STAT pathway activation (10). Furthermore, CK2 inhibition decreases hypoxia-inducible factor-1 (HIF-1) transcription activity without changes in HIF-1α protein level (11). Given that CK2 regulates multiple signaling pathways involved in tumor cell survival, proliferation, migration, and invasion, downregulation of CK2 by chemical inhibitors or genetic approaches promotes cell apoptosis and inhibits tumor cell migration and tumor growth (12).

Notably, activation of the Wnt/β-catenin, PI3K/AKT, JAK/STAT, and NF-κB pathways has been strongly implicated in glioblastoma development (2). For instance, EGF receptor, the activation of which upregulates CK2 activity by ERK-dependent phosphorylations is overexpressed or mutated in about 50% of glioblastomas, which makes it the most frequent genetic alteration associated with glioblastoma (2, 4). In addition, 36% of glioblastoma samples have mutations or homozygous deletions of PTEN and alterations in genes encoding subunits of PI3K (PIK3R1 and PIK3CA; ref. 2). STAT3, which promotes tumor cell survival, proliferation, and angiogenesis, is overexpressed and constitutively activated in glioblastoma. Furthermore, the NF-κB signaling pathway is also highly activated in glioblastoma (2). Zheng and colleagues reveal that the CK2α gene is amplified in a large percentage of glioblastomas, and inhibition of CK2 with CX-4945, which is a selective, orally bioavailable CK2 inhibitor and currently in a clinical trial for treating multiple myeloma, inhibits glioblastoma growth in mice, indicating that CK2 is an attractive therapeutic target for glioblastoma.
Zheng and colleagues demonstrate that treatment of human glioblastoma cells with CX-4945 reduced JAK2 expression level, inhibited EGF-, interleukin (IL)-6-, or IL-6 family member oncostatin M-induced STAT3 activation, and EGF-induced expression of c-Myc, which is downstream from STAT3 activation. Depletion of CK2α, CK2α0, or CK2β expression by siRNA resulted in reduced IL-6–induced STAT-3 activation, with depletion of CK2α or CK2α0 having the most pronounced effect. In addition, CX-4945 largely blocked EGF-induced STAT5 activation, indicating that CK2 regulates both STAT3 and STAT5 activation in response to EGF stimulation. Besides the effect of the inhibition of CK2 on STAT activation, the inhibition of CK2 by CX-4945 or knockdown of CK2α, CK2α′, or CK2β expression reduced TNF-α– or IL-1β–induced phosphorylation of p65 at Ser529 and the expression of downstream targets, IκBα and IL-8. Furthermore, constitutive phosphorylation of AKT at Ser129 and Ser473 in glioblastoma cells was inhibited by CX-4945 in a dose-dependent manner. These findings indicate that CK2 inhibition reduces the activities of STAT3, NF-κB, and AKT in human glioblastoma cells.

The functional studies revealed that glioblastoma cells became retracted and rounded and had disorganized actin stress fibers after CX-4945 treatment or expression of the siRNA for CK2α and CK2α′ downregulation. In addition, CX-4945 inhibited glioblastoma cell migration. These results indicate that adhesion and migration of glioblastoma cells require CK2 activation. In agreement with these findings, PCR array assay and immunoblotting analyses revealed that integrin α4 (encoded by ITGA4) and integrin β1 (a fibronectin receptor encoded by ITGB1) were downregulated by CX-4945 treatment. Consistent with the role of CK2 in cell survival and proliferation, CK2 inhibition led to cell-cycle arrest, cell senescence, and apoptosis. Using both subcutaneously and intracranially implanted xenograft models, the authors show that administration of CX-4945, which reduced STAT-3, NF-κB, and AKT activities in xenograft tumor cells, reduced tumor growth and prolonged the survival of tumor-bearing mice. Importantly, CX-4945 treatment did not affect the body weights of the mice, the number of white or red blood cells, or the levels of hemoglobin, indicating minor side effects of CX-4945 on mice.

In summary, CK2, the expression of which is amplified in glioblastoma, regulates several important signaling pathways involved in glioblastoma cell survival, proliferation, and migration and brain tumorigenesis. Treating glioblastoma with CX-4945 or other specific CK2 inhibitors could be an attractive targeted approach and may benefit patients with glioblastoma.
Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: H. Ji, Z. Lu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Z. Lu
Writing, review, and/or revision of the manuscript: H. Ji, Z. Lu

Acknowledgments
This work was supported by National Cancer Institute grants 2R01CA109035 (Z. Lu), 1R01CA169603 (Z. Lu), and CA16672 (Cancer Center Support Grant); and research grants RP110252 (Z. Lu) and RP130389 (Z. Lu) from the Cancer Prevention and Research Institute of Texas (CPRIT).

Received October 1, 2013; accepted October 14, 2013; published OnlineFirst October 28, 2013.

References
The Role of Protein Kinase CK2 in Glioblastoma Development
Haitao Ji and Zhimin Lu


Updated version Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-13-2478

Supplementary Material Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2013/12/02/1078-0432.CCR-13-2478.DC1

Cited articles This article cites 12 articles, 3 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/19/23/6335.full.html#ref-list-1

Citing articles This article has been cited by 1 HighWire-hosted articles. Access the articles at:
/content/19/23/6335.full.html#related-urls

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.