



The regulation of cancer cell glutamine metabolism

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We are grateful to Dorai, Pinto, and Cooper for their insightful Commentary on our manuscript ‘*The oncogenic transcription factor c-Jun regulates glutaminase expression and sensitizes cells to glutaminase-targeted therapy*’ (1,2). As summarized in the Commentary, glutaminase (GLS) catalyzes the first reaction of mitochondrial glutamine catabolism, generating glutamate and ammonia, and is overexpressed in a number of malignancies. Studies using small-molecule inhibitors or genetic approaches to suppress GLS have found that its activity can be important for cancer cell proliferation *in vitro* and for tumor growth *in vivo*. Indeed, the GLS inhibitor CB-839 is currently being evaluated in clinical trials for treatment of hematological cancers and triple-negative breast cancer (TNBC) (3,4). In our study, we found that c-Jun, which is up-regulated in TNBC as well as in a number of other human cancers, drives expression of the *GLS* gene and ultimately causes cancer cells to become dependent on the GLS reaction.

Dorai *et al.* raise a number of intriguing points and propose some attractive hypotheses. They describe the striking differences that have been reported between GLS and the homologous isozyme GLS2. Numerous studies have demonstrated a pro-oncogenic role for GLS, whereas the function of GLS2 in tumorigenesis is less well understood. Notably, *GLS* expression is positively regulated by drivers of cell-cycle progression, including c-Myc and c-Jun, whereas *GLS2* expression is up-regulated by the tumor suppressor p53 in response to redox stress (2,5). Thus we are tempted to speculate that the down-regulation of *GLS2* expression that occurs in some tumors, including those of the liver, might reflect disruption of p53 function rather than direct selection against GLS2 itself. Indeed, in some tumors GLS2 is reported to be pro-oncogenic, such as in neuroblastoma where its

expression is up-regulated downstream of N-Myc (5). Nevertheless, in some contexts ectopic overexpression of *GLS2* has been found to inhibit tumorigenesis (5). We agree with the authors of the Commentary that it is important for the roles of GLS and GLS2 to be better defined, as glutaminase-targeted therapies are developed.

Dorai *et al.* propose a hypothesis that links the metastasis suppressor protein SSeCKS/AKAP12 (encoded by the gene *AKAP12*) with cellular glutamine metabolism. As described in the Commentary, the down-regulation of SSeCKS/AKAP12 is required for v-Jun (and presumably also for c-Jun) mediated cellular transformation. We note a report by Lee *et al.*, who found that SSeCKS/AKAP12 markedly reduced the activating phosphorylation of JNK but not of ERK (6). This led to decreased phosphorylation of c-Jun and c-Fos, and consequently to strongly suppressed activity of AP-1 transcription factors and the down-regulated expression of their target genes (6). We agree with Dorai *et al.* that it would be of great interest to assess whether SSeCKS/AKAP12 suppresses expression of *GLS*. Interestingly, data in The Cancer Genome Atlas (TCGA) indicate that loss/down-regulation of *AKAP12* expression occurs more frequently in TNBCs than in ER+ breast cancers, which is consistent with the findings that both JNK activation and *GLS* expression are elevated in TNBC (2,4,7).

A second hypothesis proposed by Dorai *et al.* is that glutamine regulates its own mitochondrial catabolism in some contexts, based on literature reports that glutamine supplementation stimulates JNK phosphorylation and downstream activation of c-Jun, and also activation of mTORC1. Suppression of *GLS* expression when cellular glutamine is depleted would reserve glutamine for cytosolic amidotransferases, which conserve the amide nitrogen of

glutamine in biosynthetic reactions rather than releasing it as ammonia. We are unaware of any reports of glutamine regulating *GLS* expression, and it will be of interest to test this hypothesis. Notably, a related regulatory mechanism has been described for glutamine synthetase, whose expression is down-regulated following glutamine supplementation (8).

Finally, Dorai *et al.* raise an important point that has been highlighted by recent publications, namely the impact that the microenvironment has on cellular metabolism. The metabolic phenotype of *KRAS*-driven lung tumors differs from tumor-derived cell lines grown in monolayer culture, and highly perfused regions of lung tumors exhibit altered metabolic profiles relative to poorly diffused regions (9,10). As noted in the Commentary, a thorough evaluation of tumor metabolism *in vivo* will be critical for further developing therapeutic strategies that target GLS.

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Footnote

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