Inhibition Mechanism of Human Kidney Type Glutaminase to Arrest Cancer Cell Proliferation

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Abstract

A hallmark of cancer cells is the reprogramming of metabolic pathways to meet the bioenergetic and biosynthetic requirements of rapid growth and cell proliferation. The metabolic intermediates from these pathways are gaining increasing attention as cancer targets. Cancer cell metabolism is characterized by a reliance on aerobic glycolysis for ATP production and glutamine-dependent anaplerosis, to maintain high flux of intermediates through the citric acid cycle towards upregulated nucleotide, protein and fatty acid biosynthesis. Glutaminase, the first enzyme of the glutaminolysis pathway which catalyses the conversion of glutamine to glutamate. It has been shown that BCH domain containing protein binds with human kidney type glutaminase (KGA) to reduce the KGA activity and thus leading to lower level of glutamate in neuronal cells. KGA is gaining increasing attention as a potential drug target. Here, we explore the inhibition mechanism of KGA both at its active site and allosteric sites. Small-molecule inhibitors such as BPTES and CB-839, which target the allosteric site of glutaminase with high specificity, demonstrate immense promise as anti-tumor drugs. We revealed that BPTES binds to an allosteric pocket at the dimer interface of KGA, triggering a dramatic conformational change of the key loop (Glu312-Pro329) near the catalytic site and rendering it inactive. The binding mode of BPTES on the hydrophobic pocket explains its specificity to KGA. Further we have studied additional BPTES derived drug lead compounds and compared their inhibitory effect. We show that CB-839 has a 30- and 50-fold lower IC50 than trans-CBTBP and BPTES, respectively. To explore the structural basis for the differences in their inhibitory efficacy, we solved the complex structures of cKGA with 1*S*, 3*S*-CBTBP and CB-839. We found that CB-839 exhibits a greater degree of interaction with cKGA than 1*S*, 3*S*-CBTBP or BPTES[2]. Besides, we have studied the active site inhibition mechanism. Very recently we have identified a new

allosteric site and uncovered the inhibition mechanism with near full length KGA. These findings will lead to develop better inhibitors and strategies for the treatment of cancers addicted with glutamine metabolism.