Starve Cancer Cells by Cutting the Food Supply

This report features the work of Jayaraman Sivaraman, Boon Chuan Low, and their co-workers published in Proc. Natl. Acad. Sci. USA ***109****, 7705 (2012).*

Cancers comprise normal cells that grow out of control. The mutations of oncogenes in a cancer cell allow it to escape its original destiny, wander in the body and cause serious damage. Evidence indicates that, during carcinogenesis, the metabolic regulation in cancer cells is also altered to support the abnormal proliferation and metastasis of cancer cells.[1, 2, 3]

An enhanced uptake of glucose is a common feature of cancers of many types. Normal cells utilize glucose as a main energy source. Glucose is converted into pyruvate, an intermediate compound, in a sequence of steps and proceeds through a Kreb's cycle in mitochondria, a metabolic mechanism in eukaryotic cells to generate most energy in the form of ATP to sustain cell life. Cancer cells can adapt alternative glucose metabolic paths, albeit less efficient, to generate energy so as to bypass the generation of pyruvate, which in turn inhibits the growth of cancer cells. Besides glucose, glutamine and other amino acids and fatty acids proceed into Kreb's cycle to generate energy.

Glutamine plays a role more important than other amino acids in the proliferation of cells. Like glucose, cancer cells increase the uptake of glutamine. Besides, glutamine serves as a main source of carbon and nitrogen in cells. Glutaminolysis, a process in which glutamine is converted into glutamate by enzyme glutaminase, allows cells to generate energy via Kreb's cycle using glutamate. Two isoforms of glutaminase exist in human beings of kidney type and of liver type. Small inhibitors that target glutaminase, such as BPTES [bis-2-(5-phenyl-acetamido-1,2, 4-thiadiazol-2-yl) ethyl sulde], have been developed to ease or to cure diseases caused by glutaminase. Towards understanding the structure and functional mechanism of glutaminase, researchers target cancer cells through this alternative metabolic path.

Dr. Sivaraman from National University of Singapore leads a group of scientists to study human kidney-type glutaminase (KGA) and to solve the structure of the catalytic domain of KGA (cKGA).[4] This group used beamlines I911-3 at MAX-lab (Lund, Sweden), X12B and X25 at Brookhaven National Laboratory, and **13B1** at NSRRC (Taiwan) (Fig. 1). By determining the structures of cKGA with various chemical compounds, including L-glutamine as substrate, L-glutamate as product, BPTES and its derivatives as inhibitors, they drew the following conclusions. cKGA consists of two domains, I and II. The active site is located at domain II, and forms several hydrogen bonding contacts with the bound ligand. BPTES binds at a previously unknown location at the dimer interface of cKGA, approximately 18 Å away from the active site. The intrinsic symmetry of BPTES interacting with the hydrophobic clusters of both cKGA in dimer forms an allosteric pocket (Fig. 2). The binding of BPTES induces a movement of a

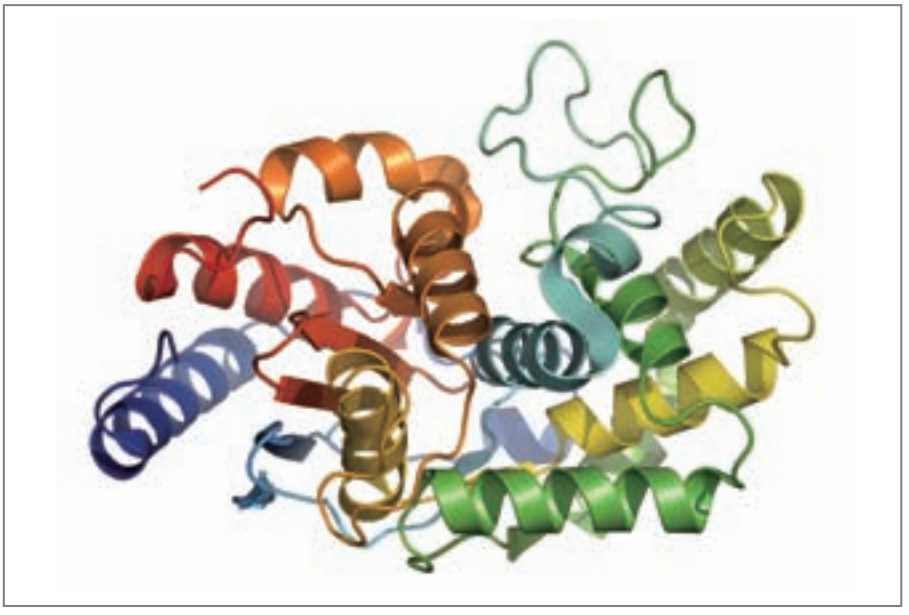

Fig. 1: Overall structure of the catalytic domain of human kidney-type glutaminase. It consists of two domains: domain I on the left has an anti-parallel β-sheet surrounded by six α-helices; domain II on the right has seven α-helices. The active site sits on the interface of the two domains.

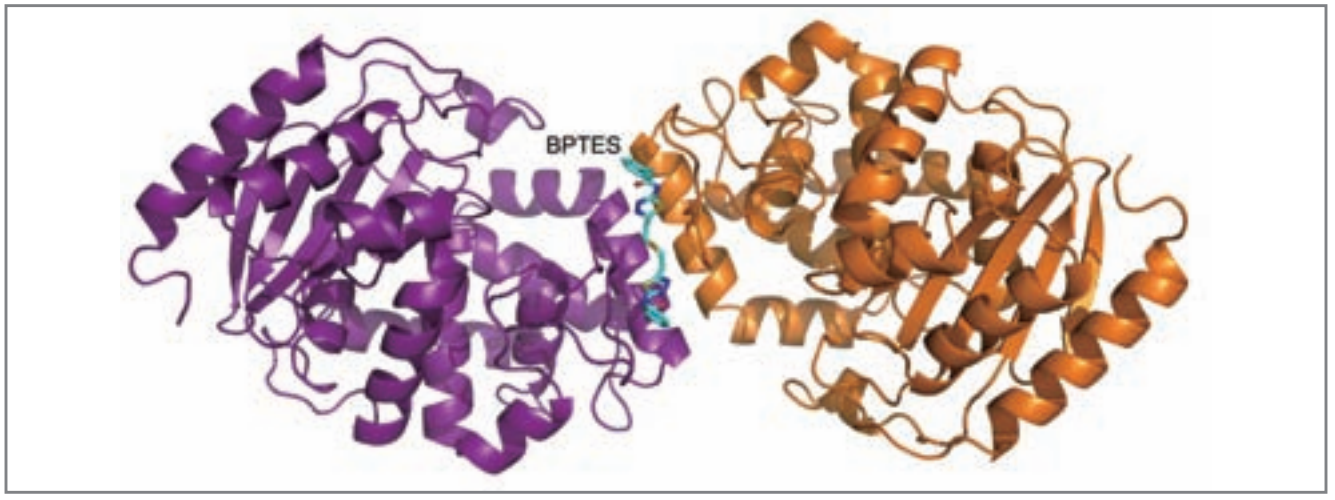

Fig. 2: Binding of BPTES (cyan) in-between dimer of cKGA. (courtesy of Dr. Jayaraman Sivaraman)

key loop (Glu312-Pro329) of cKGA away from the active site, thus rendering cKGA inactive (Fig. 3). A similar structure is found in the structures of cKGA-glutamate and cKGA-glutamine, indicating BPTES to be an uncompetitive inhibitor of cKGA. Moreover, these researchers showed that binding of BPTES stabilizes the inactive tetramer of cKGA. Understanding these mechanisms will help to design a better inhibitor of KGA in medical applications.

References

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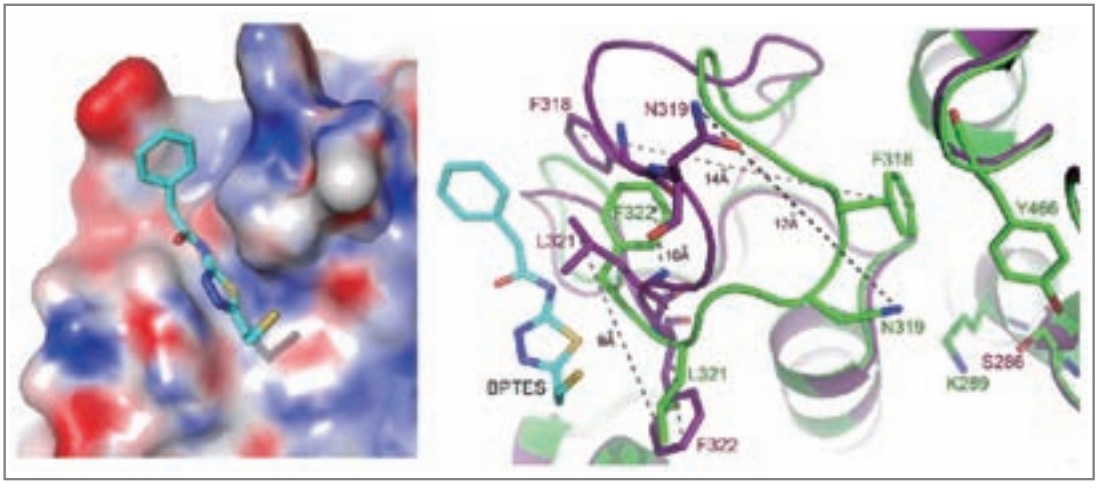

Fig. 3: Detailed view of BPTES (cyan) binding. BPTES binds on the surface of cKGA (left). Conformation changes caused by BPTES binding moves an important loop (312-329, purple) ~18 Å away from active site (right). This explains how BPTES inhibits the function of cKGA. (courtesy of Dr. Jayaraman Sivaraman)