Researchers demonstrate green tea is effective in treating genetic disorder and types of tumors

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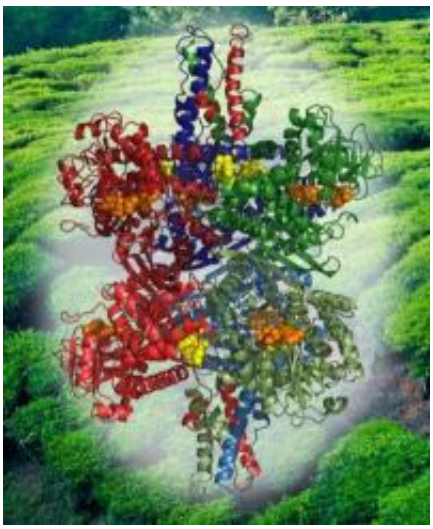


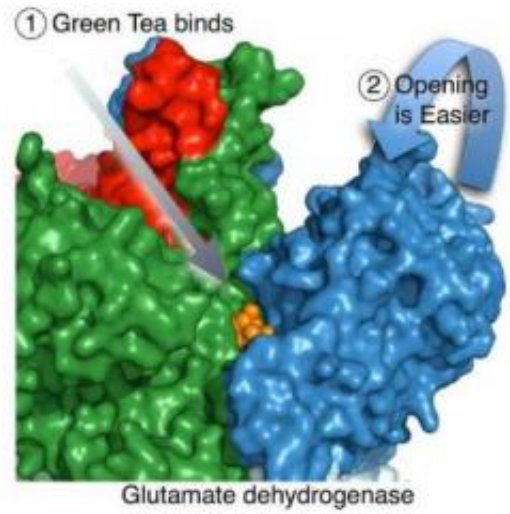
Shown here is a ribbon diagram of glutamate dehydrogenase with each of the identical subunits represented in different colors. The orange spheres represent the substrate and the yellow spheres denote the location of the green tea compounds bound to the enzyme. The background is of a tea plantation in India. Credit: Donald Danforth Plant Science Center

A compound found in green tea shows great promise for the development of drugs to treat two types of tumors and a deadly congenital disease. The discovery is the result of research led by Principal Investigator, Dr. Thomas Smith at The Donald Danforth Plant Science Center and his colleagues at The Children's Hospital of

Philadelphia. Their findings are published in the recent article, "Green Tea Polyphenols Control Dysregulated Glutamate Dehydrogenase In Transgenic Mice By Hijacking The ADP Activation Site" in the *Journal of Biological Chemistry*.

Glutamate dehydrogenase (GDH) is found in all living organisms and is responsible for the digestion of amino acids. In animals, GDH is controlled by a complex network of metabolites. For decades it was not clear why animals required such regulation but other kingdoms did not. This was partially answered by the Stanley group's finding that a deadly congenital disease, hyperinsulinism/hyperammonemia (HHS), is caused by the loss of some of this regulation. In this disorder, patients (typically children) respond to the consumption of protein by over secreting insulin, becoming severely hypoglycemic, often leading to death.

Using atomic structures to understand the differences between animals and plants, Dr. Smith and his colleagues discovered that two compounds found naturally in green tea are able to compensate for this genetic disorder by turning off GDH in isolated and when the green tea compounds were administered orally. The Smith lab also used X-ray crystallography to determine the atomic structure of these green tea compounds bound to the enzyme. With this atomic information, they hope to be able to modify these natural compounds to design and develop better drugs.



Shown here is a surface representation of glutamate dehydrogenase (GDH) with each of the six identical subunits represented by different colors. Also shown is the location of ECG, a major compound found in green tea. From this structure, it appears that ECG inhibits GDH by binding to the back of the active site and forcing it open. This effectively shuts the enzyme down. Our other studies have shown that these green tea compounds are effective at shutting down the enzyme in tissue and in whole animals. This not only treats a deadly congenital disorder but is also useful in treating at least two types of tumors. Credit: Donald Danforth Plant Science Center

Interestingly, two other research groups have validated and extended these findings to demonstrate that blocking GDH with green tea is very effective at killing two different kinds of tumors; glioblastomas, an aggressive type of brain tumor, and tuberous sclerosis complex disorder, a genetic disease that causes non-malignant tumors to grow on a number of organs.

"While these compounds from green tea are extremely safe and consumed by millions every day, they have a number of properties that make them difficult to use as actual drugs. Nevertheless, our ongoing

collaboration with the Stanley lab shows that there are natural compounds from plants that can control this deadly disorder and, with the atomic structure in hand, can be used as a starting point for further drug design."

Provided by Donald Danforth Plant Science Center