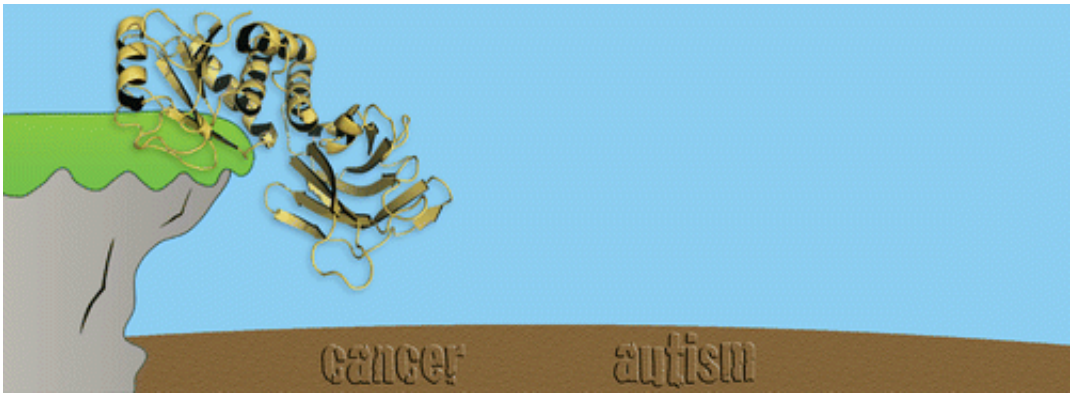
# New insight into a fragile protein linked to cancer and autism

February 18 2015




In recent years, scientists have found a surprising a connection between some people with autism and certain cancer patients: They have mutations in the same gene, one that codes for a protein critical for normal cellular health. Now scientists have reported in the ACS journal *Biochemistry* that the defects reduce the activity and stability of the protein. Their findings could someday help lead to new treatments for both sets of patients.

Ronald T. Raines and Sean B. Johnston explain that a small subgroup of people with autism and many patients with uninherited cancers have abnormalities in the genetic blueprint for a protein called PTEN. This protein helps promote genetic stability, repair DNA and regulate cell

growth. Glitches in these processes can lead to uncontrolled cell proliferation and disease. But researchers have yet to fully understand how defective versions of the protein contribute to the development of autism and cancer. Raines and Johnston wanted to flesh out a piece of that puzzle.

In the lab, the researchers tested PTEN proteins from patients with three different kinds of cancer and from patients with PTEN-related autism spectrum disorders. They found that the compromised proteins, particularly from the cancer patients, easily lost their shape and couldn't function well at body temperature. They conclude that drugs designed to stabilize these fragile proteins could represent a promising direction for new therapies.

**More information:** Conformational Stability and Catalytic Activity of PTEN Variants Linked to Cancers and Autism Spectrum Disorders, *Biochemistry*, Article ASAP. DOI: 10.1021/acs.biochem.5b00028

**Abstract**
Phosphoinositides are membrane components that play critical regulatory roles in mammalian cells. The enzyme PTEN, which catalyzes the dephosphorylation of the phosphoinositide PIP3, is damaged in most sporadic tumors. Mutations in the PTEN gene have also been linked to autism spectrum disorders and other forms of delayed development. Here, human PTEN is shown to be on the cusp of unfolding under physiological conditions. Variants of human PTEN linked to somatic cancers and disorders on the autism spectrum are shown to be impaired in their conformational stability, catalytic activity, or both. Those variants linked only to autism have activity higher than the activity of those linked to cancers. PTEN-L, which is a secreted trans-active isoform, has conformational stability greater than that of the wild-type enzyme. These data indicate that PTEN is a fragile enzyme cast in a crucial role in cellular metabolism and suggest that PTEN-L is a

repository for a critical catalytic activity.

Provided by American Chemical Society