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## Enzyme Structure Reveals New Targets for Cancer Drugs

By teasing out the three-dimensional structure of an enzyme complex involved in a variety of cell signaling pathways, a team of researchers has exposed how one of the genes most commonly mutated in human cancers helps good cells go bad.

The structure, described in the December 14, 2007, edition of the journal *Science*, should help scientists design new drugs to fight certain cancers, including those of the colon, liver, breast, and ovary.

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Structures always have some intrinsic beauty and interest on their own, but the reason we're particularly interested in this protein is because the gene that encodes it is very commonly mutated in human cancers, said Bert Vogelstein, a Howard Hughes Medical Institute investigator at the Kimmel Cancer Center at Johns Hopkins University School of Medicine. Heretofore, only one structure has been reported in this family of enzymes and it is quite different. The new data show what these differences are and, hopefully, will speed up drug development. Vogelstein is a senior author of the new *Science* paper, along with Sandra B. Gabelli and Mario Amzel, also of Johns Hopkins University.

In the study, Amzel, Gabelli, Vogelstein and their colleagues focused on the enzyme complex called PI3K-alpha, which influences how biochemical signals are interpreted by cells. The enzyme complex is made up of two proteins, known as p110 alpha and p85. The complex, Vogelstein explained, normally responds to events that occur on the surface of the cell, such as growth factor stimulation. It responds to those external events by signaling to other proteins inside the cell. It's kind of the intermediary in the signal transduction pathway, he said.

The p110 alpha protein is produced by the gene *PIK3CA*, one of the two most frequently mutated genes in human tumors. Mutant versions of the complex can amplify growth-stimulating signals too much, or at inappropriate times, contributing to cancer.

Determining the structure of the enzyme complex and mapping the ways in which that structure is commonly mutated will help researchers understand how these growth-stimulating signals work, both in normal and cancer cells, Amzel said. Moreover, he explained, medicinal chemists can use the new understanding of how these mutations alter the enzyme's structure to design drugs with greater potency and specificity.

In the new study, the team has provided the three-dimensional crystal structure of the complex's two proteins, p110 alpha and p85. The three-dimensional structure helps us determine the way these mutations change the structure (of the complex) and activate it, Gabelli said. For example, they found that many of the mutations found in human cancers alter the surface of p110 alpha that interacts with p85. As p85 regulates p110 alpha's enzymatic activity, interfering with this interaction could allow the enzyme complex to promote uncontrolled cell growth.

Understanding common changes to PI3K alpha's structure, Amzel said, will help us determine if we can target the mutations. One goal is to identify specific inhibitors for specific forms of the enzyme, so one of the next steps in this research is to identify how known inhibitors interact with the complex.

That new knowledge, Vogelstein explained, is critical as new classes of cancer-inhibiting drugs are being developed to target mutated forms of the enzyme. The first clinical trial of a broad-spectrum drug that targets all PI3K family members is underway, he said, but the hope is that new trials will soon be initiated to evaluate drugs that zero in on PI3K alpha, the only form that is mutated in cancers.