Worth a thousand words: Hopkins researchers paint picture of cancer-promoting culprit

January 4 2008

They say that a picture can be worth a thousand words. This especially is true for describing the structures of molecules that function to promote cancer. Researchers at Johns Hopkins have built a three-dimensional picture of an enzyme often mutated in many types of cancers. The results, published Dec. 14 in Science, suggest how the most common mutations in this enzyme might lead to cancer progression.

“Now that we have a better picture of the protein and how it is altered in cancer, we can envision development of mutation-specific inhibitors for cancer therapy,” says Victor Velculescu, M.D., Ph.D., associate professor at the Johns Hopkins Kimmel Cancer Center.

The enzyme known as PIK3CA is mutated frequently in many cancers, including colon, brain, stomach, breast and lung. Moreover, most of the reported mutations occur in a few so-called hotspots in the protein. All known mutations make PIK3CA more active than normal, which causes cells to divide more frequently or faster than normal to give rise to cancer.

“We tried to guess how the enzyme’s activity was affected by the mutations based on their locations along the length of the protein,” says L. Mario Amzel, Ph.D., professor and director of biophysics and biophysical chemistry at Hopkins. “But without a 3-D structure, it’s hard to do. It’s like having a puzzle but missing critical pieces.”

The research team isolated purified PIK3CA and part of another protein it normally binds to, grew crystals of the purified enzyme bound to its partner and figured out its 3-D structure using techniques that shoot X-rays through the protein crystals. Using computers, they analyzed the X-ray pattern and assembled a 3-D model of the enzyme. Onto this model the researchers then mapped all the cancer-associated mutations.

According to Sandra Gabelli, Ph.D., an instructor of biophysics and biophysical chemistry at Hopkins, the researchers originally suspected that the mutations somehow interfered with the way PIK3CA interacted with other proteins and parts of the cell and therefore must be on the outside surface of the enzyme. However, their results show that nearly all the mutations map to regions within the enzyme. “Somehow, these internal mutations must cause the protein to subtly change how it works and interacts with itself,” says Amzel. “It’s an interesting problem to solve, trying to figure out what slight shape and structural changes can make an enzyme work better-usually we’re trying to figure out why things stop working.”

The team currently is unraveling the structure of mutated PIK3CA so that they can compare mutated to unmutated to better understand how the mutations lead to cancer. Another goal is to find drugs that can specifically interfere with PIK3CA and turn it down, to develop cancer-fighting therapies.

Source: Johns Hopkins Medical Institutions