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Molecular Structure Shows How Tumor Suppressor Restrains Cell Growth

Howard Hughes Medical Institute (HHMI) researchers at the Memorial Sloan-Kettering Cancer Center in New York have determined the three-dimensional structure of a tumor suppressor protein inactivating an enzyme that spurs cell division.

Researchers theorize that nearly one-third of all cancer cases arise when this tumor suppressor fails. The atomic-scale view may tell scientists how tumor suppressors keep cell growth in check. This work appears in the September 17, 1998, issue of the journal *Nature*.

Using x-ray crystallography, Nikola Pavletich, an HHMI investigator at Memorial Sloan-Kettering Cancer Center, and colleagues produced a three-dimensional picture showing how the tumor suppressor p16 locks onto the growth-promoting molecule Cdk6. Using that picture as a guide, they identified regions of the two molecules that are critical for the interaction between p16 and Cdk6. These regions may now serve as targets for drugs that will shut down inappropriate Cdk6 activity, and thus, stop the uncontrolled cell growth that occurs in cancer.

Cdk6 is a member of a family of proteins called cyclin-dependent kinases (Cdks), enzymes that trigger cell growth and division. When Cdks receive the correct signal, they turn on the cell cycle by binding to two molecules: cyclin and ATP, which provides the energy needed to power Cdk6. Tumor suppressors keep this system in check by binding to the Cdks.

"Cells get signals to start growing from a number of different avenues, but if you can inhibit Cdk, you can stop cell growth," says Pavletich.

For reasons that are not clear, the interaction between Cdk and tumor suppressors can fail, as it does in inherited melanoma. This virulent form of skin cancer can occur when a mutation in the p16 tumor suppressor prevents it from binding to Cdk6 and to the related Cdk4, says Pavletich. Similar errors involving interactions between other Cdks and tumor suppressors may be responsible for up to one-third of cancers, he adds.

At a practical level, this study offers several options for drug designers who are interested in creating new cancer therapies. Knowing the shape and chemical composition of the binding site between p16 and Cdk6, it may be possible for researchers to build a molecular mimic that can turn off Cdk6 by outcompeting the damaged molecule for the p16 slot.

Another clever approach involves creating a substitute for the ATP molecule to which Cdk6 must bind in order to promote cell division. "Now that we know what Cdk6 looks like, it may be possible to modify an ATP-like molecule to interfere with Cdks, but not with ATP, which is needed for other cell processes. A molecule that looks like ATP would jam the whole process, stopping Cdk," says Pavletich.

Earlier this year, Pavletich's research team published an article showing how the retinoblastoma tumor suppressor, which works in the same pathway with p16, is inactivated in cancer. Pavletich says he now has his sights set on uncovering how an errant cyclin protein can start a cell down the path toward uncontrolled growth.