Take new look at cellular suicide

July 6 2006

Like a bodyguard turned traitor, a protein whose regular job is to help repair severed DNA molecules will, in some cases, join forces with another protein to do the opposite and chop the DNA to bits, according to new research at the University of Minnesota.

The chopping up of a cell's DNA occurs in response to damage, for example, from ultraviolet light, and appears to be a means of killing the cell before it can become dysfunctional or cancerous. The proteins are produced by two cellular processes, both of which must be set in motion before the proteins can gang up on the DNA molecule and seal the cell's fate. The researchers describe their discovery in the July 7 issue of *Archives of Internal Medicine*.

The self-killing of cells is termed apoptosis, and its purposes include not only culling damaged cells but shaping an embryo by getting rid of webbing tissue between fingers and toes. By contributing to the understanding of how apoptosis works, the researchers, led by Zigang Dong of the university's Hormel Institute in Austin, Minn., hope someday to see the process used to kill cancer cells or other unwanted tissue.

The "bodyguard" protein belongs to a class of proteins called histones, which act like spools for the "thread" of DNA molecules. Rather than float in the cell nucleus like an overlong piece of spaghetti, the DNA molecule loops around regularly spaced histones, which not only support the DNA but play various roles in managing its functions.

"In the past, people thought histones were just for packaging DNA," said Dong, who studied a histone named H2AX. "People believe H2AX plays a role in DNA repair. But we find that if DNA can't be repaired, the cell undergoes apoptosis. The histone H2AX is probably important for both apoptosis and DNA repair."

Dong and his colleagues were led to the discovery by their previous work on the biochemistry of skin cancer. They had previously found that various forms of an enzyme known as JNK played a role in the development of the cancer. Working with cells from the skin of mice, they have now discovered that after they expose cells to damaging amounts of ultraviolet light, a form of JNK initiates both of the cellular processes that culminate in DNA destruction.

In one process, JNK starts a chain reaction that leads to the activation of an enzyme that chops up DNA. In the other process, JNK activates the histone H2AX. The activated enzyme and the activated histone work together to make mincemeat of the DNA. Dong and his colleagues are the first to show that activation of H2AX is necessary for apoptosis to occur by means of the DNA-chopping enzyme. The work was supported by the Hormel Foundation and the National Institutes of Health.

Source: University of Minnesota