28 August 2006 # This Cancer Cell Will Self-Destruct In 5 Seconds by Kate Melville

A synthetic compound that can initiate suicide in cancer cells could become the future of anti-cancer therapies, say researchers in the journal *Nature Chemical Biology*. The new technique is tipped to be an effective way to introduce personalized cancer treatments, which scientists believe would be a great improvement on the more generalized methods currently available.

The central process involved is apoptosis. When a protein called procaspase-3 - common to most living cells - is activated, it transforms into the executioner enzyme caspase-3, which then triggers programmed cell death (apoptosis). But the signaling pathway to procaspase-3 is switched off in cancer cells, allowing them to multiply and grow into tumors.

Now, scientists have found a synthetic compound - procaspase activating compound 1 (christened PAC-1) - which can restore communications to the cancer cell and trick them into committing suicide. "We have identified a small, synthetic compound that directly activates procaspase-3 and induces apoptosis," said lead author Paul J. Hergenrother, a professor of chemistry at the University of Illinois at Urbana-Champaign. "By bypassing the broken pathway, we can use the cells' own machinery to destroy themselves."

Screening over 20,000 structurally diverse compounds, Hergenrother and colleagues undertook a massive trial and error experiment to identify the compound that could transform procaspase-3 into caspase-3. Once isolated, the team successfully tested the compound's efficacy in cell cultures and a number of mouse models. The team also used PAC-1 to initiate the deaths of cancer cells in 23 tumors sourced from a local hospital. "This is the first in what could be a host of organic compounds with the ability to directly activate executioner enzymes," said Hergenrother.

Perhaps most interesting is the possibility of "customized" cancer treatments for individual patients, an approach that has been garnering increasing interest in recent years. In this case, the amount of PAC-1 used to initiate cell death can be personalized, as cell death is directly correlated to how much procaspase-3 is already present in a cell. "The potential effectiveness of compounds such as PAC-1 could be predicted in advance, and patients could be selected for treatment based on the amount of procaspase-3 found in their tumor cells," explained Hergenrother.

New Telomere Discovery Could Help Explain Why Cancer Cells Never Stop Dividing

A human metaphase stained for telomeric repeats. DAPI stained chromosomes are false-colored in red, telomeres are in green. (Credit: Claus Azzalin, ISREC)
ScienceDaily (Oct. 7, 2007) — A group working at the Swiss Institute for Experimental Cancer Research (ISREC) in collaboration with the University of Pavia has discovered that telomeres, the repeated DNA-protein complexes at the end of chromosomes that progressively shorten every time a cell divides, also contain RNA.

This discovery, published in Science Express, calls into question our understanding of how telomeres function, and may provide a new avenue of attack for stopping telomere renewal in cancer cells.

Inside the cell nucleus, all our genetic information is located on twisted, double stranded molecules of DNA which are packaged into chromosomes. At the end of these chromosomes are telomeres, zones of repeated chains of DNA that are often compared to the plastic tips on shoelaces because they prevent chromosomes from fraying, and thus genetic information from getting scrambled when cells divide.

The telomere is like a cellular clock, because every time a cell divides, the telomere shortens. After a cell has grown and divided a few dozen times, the telomeres turn on an alarm system that prevents further division. If this clock doesn't function right, cells either end up with damaged chromosomes or they become "immortal" and continue dividing endlessly -- either way it's bad news and leads to cancer or disease. Understanding how telomeres function, and how this function can potentially be manipulated, is thus extremely important.

The DNA in the chromosome acts like a sort of instruction manual for the cell. Genetic information is transcribed into segments of RNA that then go out into the cell and carry out a variety of tasks such as making proteins, catalyzing chemical reactions, or fulfilling structural roles. It was thought that telomeres were "silent" -- that their DNA was not transcribed into strands of RNA. The researchers have turned this theory on its head by discovering telomeric RNA and showing that this RNA is transcribed from DNA on the telomere.

Why is this important" In embryonic cells (and some stem cells), an enzyme called telomerase rebuilds the telomere so that the cells can keep dividing. Over time, this telomerase dwindles and eventually the telomere shortens and the cell becomes inactive. In cancer cells, the telomerase enzyme keeps rebuilding telomeres long past the cell's normal lifetime. The cells become "immortal", endlessly dividing, resulting in a tumor. Researchers estimate that telomere maintenance activity occurs in about 90% of human cancers. But the mechanism by which this maintenance takes place is not well understood. The researchers discovered that the RNA in the telomere is regulated by a protein in the telomerase enzyme. Their discovery may thus uncover key elements of telomere function.

"It's too early to give yet a definitive answer," to whether this could lead to new cancer therapies, notes Joachim Lingner, senior author on the paper. "But the experiments published in the paper suggest that telomeric RNA may provide a new target to attack telomere function in cancer cells to stop their growth."