RIOT
Research Information Outreach Team

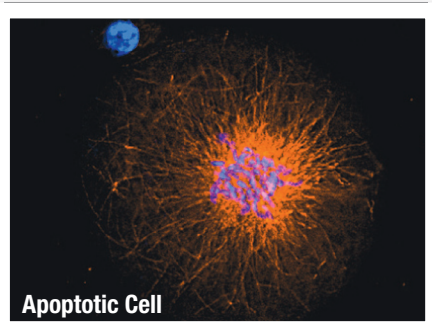
Ten Hallmarks of Cancer Series

Resisting Cell Death: Hallmark #5

The human body is made up of trillions of cells, which are its basic building blocks. Cells contain all our hereditary material. They can grow, divide to make copies of themselves, and die. Cell death is a normal process that takes place at specific times both before and after birth, and is necessary for normal development and maintenance of the body. For this reason, cell death is often a well-organized event that follows a step-by-step program. An important kind of programmed cell death is called apoptosis.

Apoptosis is an efficient way for the body to eliminate cells it does not need. For example, before birth, apoptosis takes place in cells found between fingers and toes, allowing them to separate. After birth, apoptosis protects the body by eliminating damaged cells. If a cell has grown old or has an error in its DNA (its genetic material) that cannot be repaired, it will normally undergo apoptosis. This is a very important process, because if a cell with damaged DNA divides (creating two new cells), each new cell will receive a full set of abnormal genes. Altered cells with abnormal genes can then become cancerous. In fact, an important hallmark of cancer is the breakdown of the orderly program of cell death that occurs with damaged cells.

With the realization that cancer cells do not turn on their apoptotic steps properly, the search for effective treatments that will restore the cell's ability to undergo programmed cell death has intensified. Over the last two decades, scientists' efforts to understand why cancer cells resist death have revealed the existence of two sets of reactions in normal cells: one that causes apoptosis (pro-apoptotic) and another that interferes with this process (pro-survival). In some cancer cells, pro-survival processes are amplified, whereas in others the pro-apoptotic mechanisms are silenced. One of the research areas in my laboratory is the identification of proteins that promote survival in normal skin cells, and how these proteins may be amplified in squamous cell carcinomas and in melanomas.


Apoptotic Cell

Worldwide, over 14 million new cancer cases are diagnosed yearly (http://globocan.iarc.fr/). Every person with cancer has a unique combination of genetic changes in their tumour. This means that every cancer is as unique as the person who suffers from it. So, although there are over 100 types of cancer, based on location or tissue type, in reality there are hundreds of varieties of each. Therefore, there can be many alterations in the pro-apoptotic and pro-survival processes, and these changes differ in each unique cancer. This makes targeting of these processes especially difficult.

Not surprisingly, overcoming resistance to cell death is one of the top goals in cancer treatment. One strategy is to copy the action of apoptosis-inducing factors in cancer cells. A second approach is to use drugs that block the abnormally high activity of pro-survival factors in these cells. Several drugs isolated from plants and marine organisms are currently under development. These substances can effectively inhibit pro-survival cell factors that are present in abnormally high amounts in several human tumour cells used in research laboratories, ultimately killing the cancer cells. The problem is that most human cancers are a mixture of cells with abnormal death programs. Some of these cells are susceptible to treatments that cause apoptosis, but many others are not, causing resistance to treatment. Overcoming therapy resistance is, therefore, a major goal in cancer research.

The largest stumbling block to-date in the development of drugs that promote cell death is the finding that these drugs also cause substantial death of normal cells in patients. Consequently, many of the earliest pro-apoptotic drugs were never approved for human therapy. Several newer drugs with fewer side effects and lower toxicity to normal, non-cancerous cells are currently under investigation. These drugs hold much promise, but it will take several years before they can be fully studied and potentially become clinical treatment options.

Targeting the apoptosis machinery has proven to be a tricky business, but it may become the therapy with greatest potential for many aggressive tumours. There are many cancers with very high resistance to cell death, which either have no effective treatment at present, or quickly become resistant to therapy. These cancers include melanoma, pancreatic cancer and brain cancer, as well as many colon, breast and prostate cancers. The use of drugs or drug combinations that cause apoptosis is thus a promising approach for their effective treatment.

Article written by Lina Dagnino, PhD