Missing Puma reveals cancer conundrum

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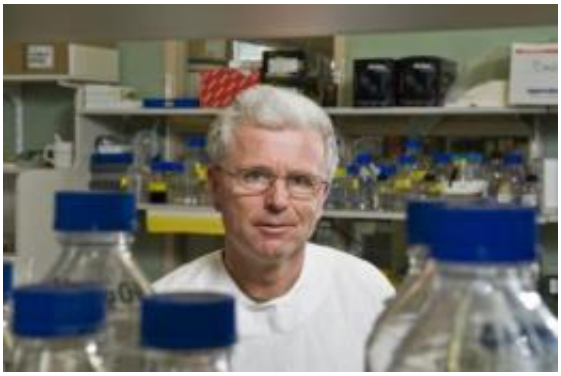

Professor Andreas Strasser from the Walter and Eliza Hall Institute in Melbourne, Australia, has made a discovery that has upended scientists' understanding of programmed cell death and its role in tumor formation. Credit: Walter and Eliza Hall Institute of Medical Research

Walter and Eliza Hall Institute researchers in Melbourne, Australia, have made a discovery that has upended scientists' understanding of programmed cell death and its role in tumour formation.

Programmed cell death, also called apoptosis, is an important process in human biology as it removes unwanted and damaged cells from our bodies. This process protects us against cancer development and autoimmune disease.

The research team's discovery, led by Professor Andreas Strasser from the institute's Molecular Genetics of Cancer Division, has implications for the understanding of how cancers develop and will inform the

ongoing development of a new class of anti-cancer drugs called BH3 mimetics.

"Until now everybody believed that a failure of damaged cells to undergo suicide allowed mutated cells to proliferate, which contributes to tumour development," Professor Strasser said. "That's certainly still true but we discovered that, in certain settings, the opposite holds: the body's natural cell-suicide program can fuel tumour development."

The research team's experiments revealed that repeated cycles of cellular depletion and tissue regeneration, by activating stem cells, could promote tumour development.

In situations where the DNA in many cells is damaged, such as when the body is repeatedly exposed to low doses of radiation, there are repeated cycles of cell death in the body's tissues. "Attempts by the body's stem cells to repopulate the depleted tissue can then actually drive the tumour development," Professor Strasser said. "That's because the radiation, while killing many cells within a tissue, will create mutations in some of the surviving stem cells. When such abnormal (mutated) stem cells repopulate the tissue, they will divide many times and this can promote the development of tumours."

The research, done in collaboration with Dr Ewa Michalak, Dr Cassandra Vandenberg, Mr Alex Delbridge, Dr Li Wu, Dr Clare Scott and Professor Jerry Adams, is published in today's issue of the international journal *Genes and Development*.

Crucial to the team's research was an understanding of what happens to mice exposed to radiation when a gene called Puma is missing. "If normal mice (which have the Puma gene) are given a low dose of radiation it destroys around 80 per cent of the white blood cells," Professor Strasser said. "That does not kill the mouse but it does mean

the stem cells in the bone marrow have to work extra hard to replenish the blood system. This can lead to the formation of tumours of white blood cells, called leukaemias, if the stem cells doing the repopulating have cancer-causing mutations.

"The surprise was that mice that don't carry the Puma gene are protected from this type of tumour development. Puma is essential for the death of cells that have damaged DNA. If mice don't have the Puma gene when they receive low doses of radiation the white blood cells are not destroyed, so you don't force mutated stem cells to become activated (and divide) to replenish the blood system."

Professor Strasser said the research suggested that the risk of cancer was increased in people who experienced cycles of tissue destruction followed by tissue re-population by stem cells. "Such cycles may account for the liver cancers frequently associated with viral (hepatitis C) infection or alcohol-related liver damage." The research also helps explain the so-called secondary cancers that sometimes arise in patients who were cured of their primary cancer by chemotherapeutic drugs that cause DNA damage."

The findings will also inform the ongoing development of a new class of anti-cancer drugs called BH3 mimetics. These drugs are designed to kill cancer cells. "Chronic exposure to such drugs could lead to the death of large numbers of normal cells that would then need to be replaced," Professor Strasser said. "In certain circumstances this could promote the development of secondary cancers, particularly if patients are receiving treatments such as chemotherapy or gamma-radiation that can lead to cancer-causing mutations in stem cells."

Provided by Walter and Eliza Hall Institute