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Immune Cells May Pave the Way for Prostate Cancer

A new research study suggests that the very cells that target invading pathogens and mop up dead cells may also permit prostate cancer to flourish under certain conditions.

In an article published in the February 10, 2006, issue of the journal *Cell*, a research team from the University of California at San Diego (UCSD) reports that the interplay between macrophages and prostate cancer cells triggers genetic changes that favor tumor growth. Howard Hughes Medical Institute (HHMI) investigator Michael G. Rosenfeld, and colleagues Ping Zhu, Sung Hee Baek, and David Rose at UCSD, were among the scientists who collaborated on the studies.

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— Michael G. Rosenfeld

Macrophages — which are often called the scavengers of the immune system — have been implicated in atherosclerosis and are suspected in hastening the onset of diabetes mellitus. The new work conducted by Rosenfeld and colleagues now suggests that when macrophages intermingle with prostate cancer cells, the interaction sparks a flurry of chemical chatter. This, in turn, leads to genetic changes that enable the prostate cancer cells to thwart the drugs that would starve them of the hormones that fuel their growth.

There are two faces of the macrophage, said Rosenfeld. It can be a very negative, as well as a positive force. It can start cascades that we're not very keen on having in cancer therapy.

New insights from the study could lead to improvements in treatments designed to deprive the cancer cells of the hormones needed for growth. Existing therapies based on this strategy can become ineffective quickly, Rosenfeld noted. Cancer cells have many ways to defeat any given therapeutic strategy, he added.

The new study indicates that a cancer-cell signaling system goes awry and fuels sex hormone-regulated cancers through genetic change. Rosenfeld speculated that this interaction sets in play a complex series of communication events that were laid down in biology long ago for reasons quite different from promoting the ability of cancer cells to grow. He said this system may very well be an evolutionary artifact, and perhaps closely related to a system that aids development of a newly-implanted embryo.

For this mechanism to be conserved, it must have been important biologically, Rosenfeld explained, describing the cellular interplay as an evolutionarily conserved sensor system.

In the case of prostate cancer, Rosenfeld and his colleagues suspect that when the cancer cells and the macrophages interact, the macrophages are then activated. This activation causes the production of cytokines. Cytokines are chemicals produced by immune cells that can slow or reverse the growth of some cancers. With prostate cancer, however, the macrophages that are exposed to the prostate cancer cells produce cytokines that seem to prompt genetic resistance to the drugs that block the cancer-feeding hormone's action. Thus, the macrophage-produced cytokines are ubiquitous signals that appear to dictate the specific responses of the cancer cell, Rosenfeld said.

After demonstrating in the lab that macrophage-cancer cell interactions occurred in culture, the new HHMI study revealed a consistent release of repression in virtually all tumor samples, which exhibited the same interactions.

The genetic change alters the cancer cell in a way that renders agents known as selective androgen receptor antagonists/modulators (SARMs) ineffective. SARMs are used as standard treatment for prostate cancer, but resistance to the agents, which are designed to block the androgen hormone that fuels the disease, occurs very quickly. The same phenomenon occurs, but at a much lower frequency in the case of breast cancer, a cancer fueled by the sex hormone estrogen.

The main problem is understanding why resistance is so rapid and so universal, said Rosenfeld. The gene expression change that occurs, according to Rosenfeld, enables the cancer cells to call forth the macrophage response program, further favoring proliferation.

The revelation of a macrophage/prostate cancer cell regulatory axis may provide additional strategies to modify therapeutic approaches to specific cancers, Rosenfeld said. There are many attack points suggested by our study.

In addition to Rosenfeld, authors of the *Cell* article from HHMI/UCSD include Ping Zhu, Sung Hee Baek, Eliot M. Bourk, Kenneth A. Ohgi, Ivan Garcia-Bassets, Christopher K. Glass and David W. Rose. Authors Hideki Sanjo, Shizuo Akira and Paul F. Kotel are at Osaka University, and Sung Hee Baek is now at Seoul National University.