Geneticists verify cholesterol-cancer link

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University of Rochester Medical Center scientists discovered new genetic evidence linking cholesterol and cancer, raising the possibility that cholesterol medications could be useful in the future for cancer prevention or to augment existing cancer treatment.

The data, published in the online journal *Cell Reports*, support several recent population-based studies that suggest individuals who take cholesterol-lowering drugs may have a reduced risk of cancer, and, conversely that individuals with the highest levels of cholesterol seem to have an elevated risk of cancer.

The cancer-cholesterol question has been debated since the early 20th century, and along with it doctors and scientists have observed various trends and associations. However, until now genetic evidence directly linking cholesterol and malignancy has been lacking, said senior author Hartmut (Hucky) Land, Ph.D., Robert and Dorothy Markin Professor and chair, Department of Biomedical Genetics, and director of research and co-director of the James P. Wilmot Cancer Center at URMC.

"Scientifically it is very satisfying to have data that support longstanding ideas about cholesterol in the context of cancer," Land said. "Our paper provides a rationale for cholesterol targeting as a potentially fruitful approach to cancer intervention or prevention strategies."

Cholesterol is a fat-like substance supplied in foods and made in cells throughout the body. Too much cholesterol is bad for the heart and vascular system. It is typically measured as serum cholesterol by routine

blood tests.

Unlike serum cholesterol that is bound to proteins, however, cholesterol also hides inside cells. While locked inside cell membranes before it is eventually exported, cholesterol has an impact on cell growth and survival. A gene, known as ABCA1, is at the crossroads of the process that shuttles intracellular cholesterol outbound.

Several years ago while conducting unrelated experiments that were published in the journal Nature, Land and colleagues first noticed the importance of ABCA1. At that time, they identified a network of approximately 100 so-called "cooperation response genes" that mediate the action of cancer genes. ABCA1 was found among these genes and is frequently turned off in presence of other mutant cancer genes.

In the latest investigation, Land and co-author Bradley Smith, Ph.D., a post-doctoral fellow in the Land lab, wanted to further understand the role of ABCA1 and cholesterol in cancer. They found that defective cholesterol exportation appears to be a key component in a variety of cancers.

The proper function of ABCA1, in fact, is critical for sensing of cell stress. If ABCA1 function is lost in cancer cells, cholesterol is allowed to build up in the cells' mitochondria, or energy centers, making their membranes more rigid. This in turn inhibits the function of cell-death triggers that normally become activated in response to cell stresses, as for example cancer gene activation. Therefore, when functioning properly ABCA1 has anti-cancer activity – in the sense that by keeping mitochondrial cholesterol low it protects the functioning of cellular stress response systems and acts as a barrier to tumor formation and progression.

Smith and Land also demonstrated that some of the relatively rare

ABCA1 mutations found in human colon cancers by other investigators disabled the gene's ability to export cholesterol. And by re-establishing the cholesterol export function in human colon cancer cells, they inhibited the cells' ability to grow as cancers when grafted onto mice.

The URMC study, therefore, is the first to directly show how ABCA1 loss-of-function and cholesterol may play a role in cancer.

Millions of Americans take cholesterol-lowering drugs or statins, as prescribed by physicians. The drugs work by blocking the action of key enzymes in the liver, which synthesizes cholesterol. Clinical trials also are evaluating statins as a tool against cancer, and some previous studies suggest that when used in combination with chemotherapy, statins might make chemotherapy more effective by sensitizing certain cancer cells to chemotherapy-induced cell death.

Land, however, urges caution and further study. Doctors do not know the appropriate statin dose for cancer prevention or treatment of cancer-related conditions. Side effects cannot be ignored either, and little research has distinguished between the responses among people who take statins.

"The link between cholesterol and cancer is clear," Land said, "but it's premature to say that statins are the answer."

Provided by University of Rochester Medical Center

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