Researchers exploring keys to melanoma progression

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Melanoma is devastating on many fronts: rates are rising dramatically among young people, it is deadly if not caught early, and from a biological standpoint, the disease tends to adapt to even the most modern therapies, known as VEGF inhibitors. University of Rochester researchers, however, made an important discovery about proteins that underlie and stimulate the disease, opening the door for a more targeted treatment in the future.

This month in the journal Cancer Research, Lei Xu, Ph.D., assistant professor of Biomedical Genetics at the University of Rochester Medical Center, proposed that a receptor called GPR56 – which mostly has been studied in the context of brain formation -- has an important role in cancer progression.

Xu and colleagues believe they are the first to show the biological mechanisms of how GPR56 relates to the growth and spread of melanoma, and might even be responsible for triggering one of the lethal processes of cancer progression, known as angiogenesis.

"We are very excited about this work because not only did we find an important new factor in melanoma, but we have also shown the signaling pathways through which these G-protein coupled receptors could impede cancer cell growth," Xu said. "Perturbing these pathways could potentially lead to more effective treatments for malignant melanoma."

Melanoma killed an estimated 8,700 people in the United States in 2010,

and in the last 25 years the incidence has been increasing to the point that it is now the most common form of cancer in young adults 25 to 29, and the second most common cancer among people in their teens and early 20s.

If diagnosed at an early stage the survival rate is 99 percent; however, the survival rate falls to 15 percent for people with advanced melanoma. One of the challenges is relapse. Even when melanoma is successfully controlled for a significant period of time, the disease can recur and act more aggressively than at the initial diagnosis.

The reason for this, according to Xu, is that we do not yet have a single drug therapy or a combination of therapies that reach the source of the problem.

To better understand the source, researchers looked to VEGF, or vascular endothelial growth factor, which plays a key role along the complex chain of interactions that occur as cancer develops and spreads. Most importantly, VEGF provides a potent chemical signal that stimulates new blood vessels. Tumor cells have a distinct need for oxygen and nutrients, and in this environment the nutrients in tumor cells trigger the secretion of the VEGF protein, which then leads to the formation of new blood vessels to fuel the tumor.

The dangerous cycle that feeds cancer cells with nutrients is referred to as angiogenesis. The Food and Drug Administration in recent years has approved several promising cancer drugs, called anti-angiogenesis therapies or VEGF inhibitors, which are designed to block the activity of VEGF protein once it has been secreted and released by the cells. Frequently, though, despite continuous therapy with anti-angiogenesis medications, some of the VEGF escapes, creating an environment for a relapse.

Xu's team wondered if the VEGF could be blocked earlier, before it was produced. Collaborators included post-doctoral fellow Liquan Yang, Ph.D., technical associate Sonali Mohanty, Arshad Rahman, Ph.D., associate professor of Pediatrics, Environmental Medicine, and Pharmacology and Physiology at URMC; and Glynis A. Scott, M.D., professor of Dermatology and Pathology and Laboratory Medicine at URMC.

Knowing that some involvement with cancer cells had been reported in the literature, they began a detailed investigation of G-protein-couple receptors (GPCRs). In the context of other diseases GPCRs constitute 40 percent of drug targets, making it an attractive option to control cancer if a link could be established.

Using a mouse model and four different human melanoma cell lines, researchers explored the mechanics of how GPCRs regulate VEGF and the signaling pathways involved. Xu's team observed an opposing relationship between two key fragments of GPR56 (GPRN and GPRC) that played distinct roles in regulating VEGF in melanoma progression.

As a result, Xu believes that if this relationship between GPR56 fragments is exploited properly, VEGF production in melanoma cells could be shut down at its source.

Although the GPR56 molecule is not a drug target at the moment, Xu said, "we hope our paper creates more interest." The next step is to confirm the laboratory findings with melanoma cells freshly isolated from human patients.

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