Researchers identify fish protein that may inhibit cancer metastasis

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Researchers at the University of Maryland School of Medicine have identified a peptide, or protein, derived from Pacific cod that may inhibit prostate cancer and possibly other cancers from spreading, according to preclinical research published online in the *Proceedings of the National Academy of Sciences* (*PNAS*).

"The use of natural dietary products with anti-tumor activity is an important and emerging field of research," says senior author Hafiz Ahmed, Ph.D., assistant professor of biochemistry and molecular biology at the University of Maryland School of Medicine and scientist at the Institute for Marine and Environmental Technology (IMET). "Understanding how these products work could allow us to develop foods that also act as cancer therapeutics and agents for immunotherapy."

Most people who succumb to cancer die because tumor cells invade the surrounding tissue and migrate into the nearby blood and lymph vessels, a process known as metastasis. For example, prostate cancer typically spreads to the bones, lungs and liver. Cancer cells that metastasize to other parts of the body grow new blood supplies and eventually overcome the person's organ systems.

"This study is among the first to explore the therapeutic utility of a bioactive cod TFD-containing glycopeptide to inhibit prostate cancer from progressing," says Dr. Ahmed, who also is affiliated with the University of Maryland Marlene and Stewart Greenebaum Cancer

Center. The TFD (Thomsen-Friedenreich disaccharide) antigen in the fish protein is hidden in normal human cells but is exposed on the surface of cancer cells and is believed to play a key role in how cancer spreads.

Polar fish, such as northern cod, express glycoproteins that are rich in the TFD antigen, which protect them from freezing. The research team developed a special form of TFD, called TFD100, purified from Pacific cod.

Using animal models, the researchers found that TFD100 binds to galectin-3, a protein that is overexpressed in prostate cancer cells, and blocks its interaction with the TFD antigen found on the surface of the cells. Galectin-3 (gal3) enables cancer cells to adhere to the walls of blood vessels and also kills activated T-cells, a type of white blood cell, which helps the cancer cells to spread throughout the body and evade the immune system. The researchers observed that TFD100 prevents cancer cells from attaching to the vessel walls, suppresses T-cell death and boosts the immune response.

"Because the gal3-TFD interaction is a key factor driving metastasis in most epithelial cancers, this high-affinity TFD100 should be a promising anti-metastatic agent for the treatment of various cancers, including prostate adenocarcinoma," the researchers conclude in the study, which was published online March 11 in PNAS' Early Edition.

"This research breaks new ground in our ongoing quest to discover new ways to prevent cancers from metastasizing to distant parts of the body," says E. Albert Reece, M.D., Ph.D., M.B.A., Vice President for Medical Affairs at the University of Maryland and the John Z. and Akiko K. Bowers Distinguished Professor and dean of the University of Maryland School of Medicine. "If we could one day offer patients a natural dietary supplement, derived from fish proteins, which could help to block that

process, we could have a significant impact on improving patients' outcomes and survival."

Co-investigator Dhan V. Kalvakolanu, Ph.D., a professor of microbiology and immunology at the School of Medicine, notes that additional research is needed to develop a dietary supplement from the cod peptide that could complement chemotherapy and other standard treatments. "No single drug on its own is going to offer protection against advanced cancers. We need a multi-pronged approach to successfully treat this disease," he adds.

The study was conducted by researchers from Dr. Ahmed's laboratory, in collaboration with Dr. Kalvakolanu and other investigators at the University of Maryland Greenebaum Cancer Center and the IMET. Prasun Guha, Ph.D., a postdoctoral fellow in Dr. Ahmed's laboratory, was the study's lead author.

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