Cancer-inflammation 'vicious cycle' detailed in new study

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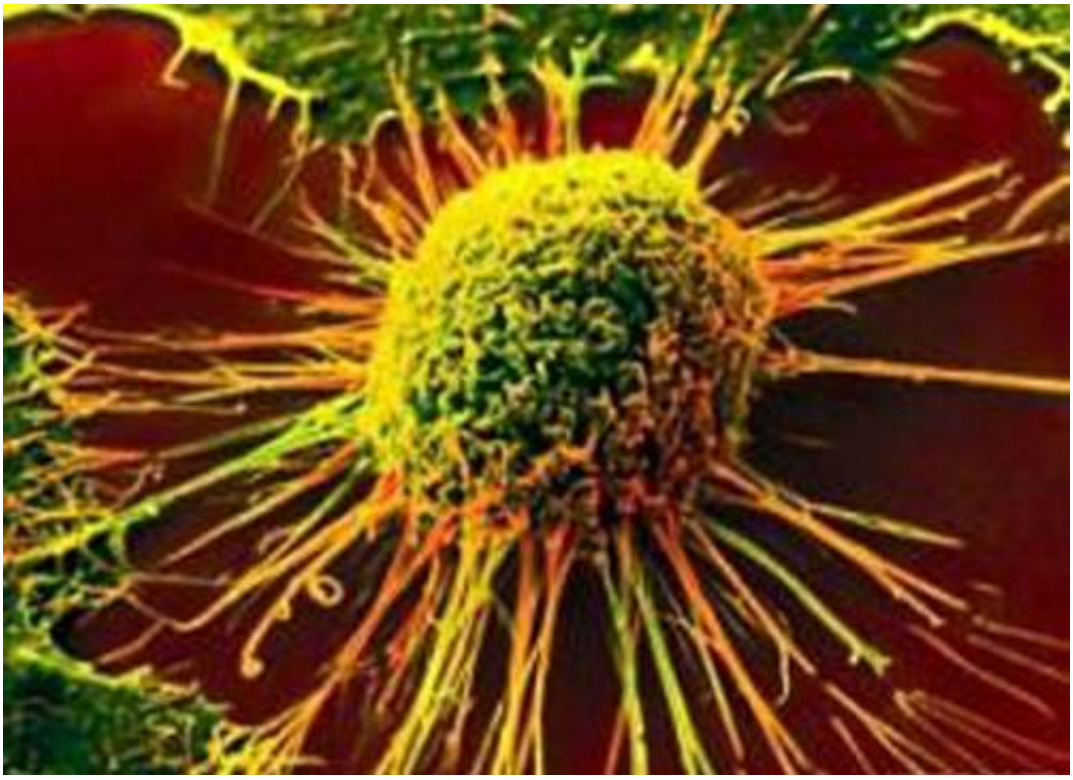

New findings hidden within the complex machinery behind the vicious cycle of chronic inflammation and cancer are presented today by researchers from the University of Pittsburgh Cancer Institute, partner with UPMC Cancer Center, at the American Association for Cancer Research (AACR) Annual Meeting in Philadelphia.

The research is funded by the National Institutes of Health (NIH) and Fondazione RiMED, of Palermo, Italy.

Inflammation is an important immune system tool that helps the body rid itself of foreign invaders, such as bacteria. However, chronic inflammation can fuel tumor growth by facilitating formation of cancer blood vessels, supplying nutrients and setting cancerous cells free to colonize other parts of the body.

The basic research into the specific mechanisms promoting cancer inflammation is a critical step in the development of drugs that could interrupt this process.

"In the last 20 years we've recognized that chronic inflammation and cancer are connected - long-term inflammation leads to the development of dysplasia and tumor progression," said lead author Sandra Cascio, Ph.D., a research associate in Pitt's Department of Immunology. "Recently, scientists have provided detailed insights into molecules and cellular pathways linking inflammation and cancer. In our study, we found a new mechanism that had previously escaped us."

The mechanism is driven by a complex of MUC1, a molecule long studied in the laboratory of senior author and Pitt immunologist Olivera Finn, Ph.D., and p65, a molecule belonging to a protein complex family known to be activated in inflammation.

Dr. Cascio, in collaboration with Dr. Finn, looked for MUC1/p65-mediated epigenetic modifications affecting inflammatory genes. Epigenetics refers to outside factors that modify the activity of a gene, but do not cause a more obvious genetic mutation. Sure enough, the researchers discovered that this complex, which they found specifically in cancer cells, was causing DNA to be transcribed differently than expected.

"Normally MUC1 is covered in sugar molecules, like leaves cover a tree in spring," said Dr. Cascio. "When it is made by a tumor, it lacks sugar and is more like a tree in fall. Our research shows that this form of MUC1 associates with p65 and regulates transcription of pro-inflammatory cytokine genes in tumor cells. This leads to the recruitment of inflammatory cells into the tumor site. Inflammatory cells, including macrophages, produce additional cytokines that enhance the activity of MUC1 and p65, establishing a continuous positive feedback loop, or a vicious circle, resulting in tumor progression."

In order to pinpoint this altered pro-inflammatory mechanism in cancer cells, Dr. Cascio and her team combed through more than 20 types of epigenetic modifications and 300 factors that allow for the remodeling of chromatin, which are macromolecules in cells that control gene expression and DNA replication.

Specifically, the researchers found that MUC1 and p65 involve an enzyme called the Enhancer of Zeste homolog 2, or EzH2, known to induce epigenetic modifications, in order to prompt chromatin remodeling on cytokine gene promoters.

"Developing drugs that could keep these genes from being improperly turned on and off could interrupt this cancer-inflammation process and stop the tumor growth and spread," said Dr. Cascio. "It's a promising avenue for future exploration."

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