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One common genetic variant and bacteria help dictate inflammation, antitumor activity

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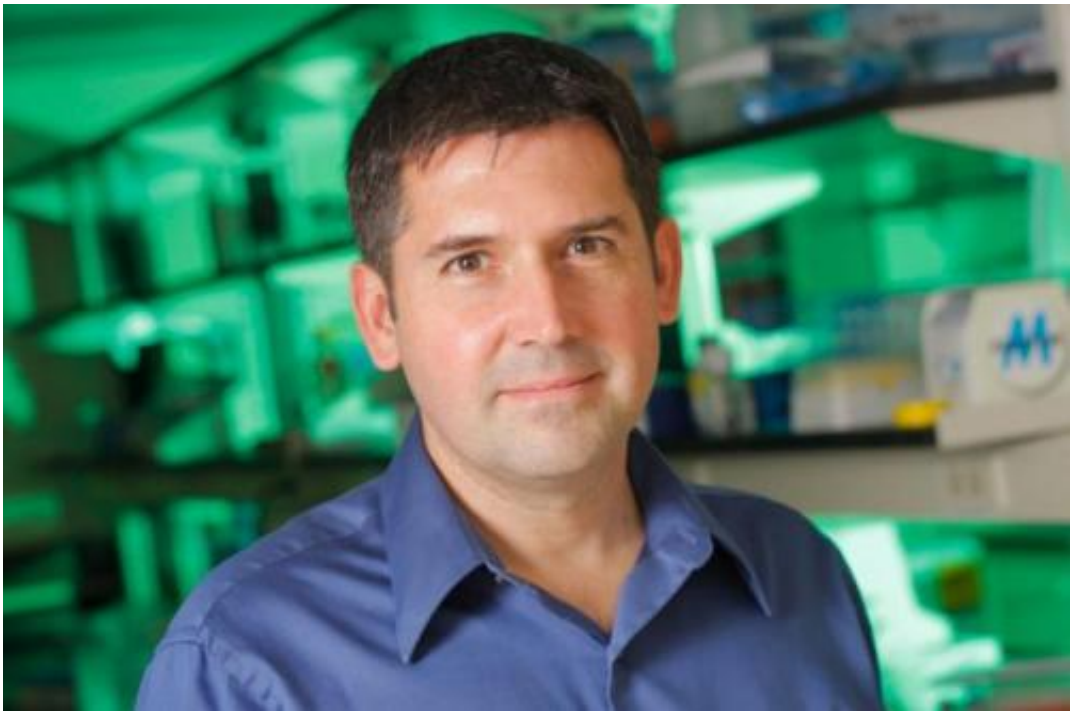

José Conejo-Garcia, M.D., Ph.D. Credit: The Wistar Institute

A common polymorphism - a variation in a person's DNA sequence that is found with regularity in the general population - can lead to a chain of events that dictates how a tumor will progress in certain types of cancer, including a form of breast cancer as well as ovarian cancer, according to new research from The Wistar Institute that was published online by the journal *Cancer Cell*.

The research reveals a more explicit role about the symbiotic relationship humans have with the various bacteria that inhabit our body and their role during tumor progression.

"Our research indicates that interactions between the helpful bacteria in our bodies and immune cells at places situated away from tumors influence systemic responses in the host that alter how these tumors are able to progress," said José Conejo-Garcia, M.D., Ph.D., Associate Professor and Program Leader in the Tumor Microenvironment and Metastasis Program at The Wistar Institute and lead author of the study.

Humans are colonized with trillions of bacteria - known as commensal bacteria because there are benefits to having these bacteria in our bodies - that inhabit the gastrointestinal and respiratory tracts and our skin. These bacteria provide a first line of defense against infection. Recent research has found that interactions between these bacteria and the immune system are critical for providing important defenses against tumors occurring outside of the intestines.

In order for the immune system to recognize commensal as well as microscopic organisms that can cause disease - or pathogens - many of our cells are programmed to recognize pathogen-associated molecular patterns. At least 23% of the general public carries mutations in a group of pathogen recognition receptors called Toll-like receptor (TLR) genes. One of the most abundant polymorphisms, occurring in about 7.5% of the general population, or slightly more than one in fifteen people, which results in loss of function, is in TLR5. Although this polymorphism is found in completely healthy individuals, the people who do carry it are susceptible to illnesses such as Legionnaires disease, urinary tract infections, and bronchopulmonary dysplasia. Knowing that this variant could impact some immune responses, Wistar researchers set out to understand whether TLR5 signaling influences cancer.

The researchers found that TLR5 signaling influences certain types of cancer in different ways and is dependent upon the ability of the tumor to respond to interleukin 6 (IL-6), a small protein that can have both pro-inflammatory and anti-inflammatory properties. In individuals with functional TLR5 expression, commensal bacteria are able to stimulate IL-6 production, greater mobilization of myeloid-derived suppressor cells (MDSCs), which in turn transform gamma delta T cells, a T cell subset that possesses innate-like properties, to produce high amounts of galectin-1, a protein that suppresses antitumor immune activity and hastens tumor progression.

However, the researchers also showed that TLR5 signaling does not always mean that tumors will grow faster. TLR5-deficient mice with tumors that produce low levels of IL-6 have faster tumor progression. In this instance, IL-17, another interleukin closely associated with autoimmune diseases and inflammation, is consistently found in higher levels in TLR5-deficient mice that have tumors, but IL-17 only accelerates cancer when the tumors are unresponsive to IL-6.

Researchers observed these phenomena were dependent upon commensal bacteria. When commensal bacteria were removed with antibiotics, the differences in TLR5-mediated tumor progression were not observed. The researchers noted that the differences in inflammation and progression of tumors are recapitulated in TLR5-responsive and unresponsive patients with ovarian and luminal breast cancer. The researchers performed a survival analysis using data from The Cancer Genome Atlas (TCGA) on patients for whom data on their TLR5 status was known.

"Although independent sets of data and higher numbers of patients are needed, our data suggest that ovarian cancer reflects the evolution of IL-6-dependent tumors, while luminal breast cancer appears to become more aggressive in carriers of the polymorphism that abrogates TLR5

signaling," Conejo-Garcia said.

For ovarian cancer, which is associated with high levels of IL-6, researchers found a significantly higher number of TLR5-deficient patients alive six years after their initial diagnosis compared with patients with TLR5, indicating a correlation between the absence of TLR5 and improved survival. For luminal breast cancer, which is associated with low levels of IL-6, the long-term survival prospects were worse for patients without TLR5.

More information: *Cancer Cell*, www.cell.com/cancer-cell/abstr … 1535-6108(14)00460-7

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