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Researchers use genetics to probe immune system's role in fighting cancer

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To better understand the immune system's role in the fight against cancer, University of North Carolina Lineberger Comprehensive Cancer Center researchers have searched thousands of tumors for genetic signatures that might serve as clues for whether immune cells had invaded tumors to stage a defense.

They found that for many cancers, higher levels of immune cell gene expression signatures inside tumors – which they believe is a sign of higher numbers of invading immune cells – was most often linked to better survival. However, for a few cancer types, higher immune signature levels were linked to a poor prognosis.

The researchers say their findings, published in the *Journal of the National Cancer Institute*, could lay the foundation for future studies to assess whether their approach can be used as a tool to guide cancer treatment. They showed that the signatures typically predict a better prognosis, and believe it may prove to be also possible to use a patient's immune system's gene expression characteristics to identify patients who will respond to certain immunotherapy drugs.

"Our hypothesis is that genomics interrogation of the immune system will help us develop clinically viable biomarkers for immunotherapy," said Benjamin Vincent, MD, a UNC Lineberger researcher and assistant professor in the UNC School of Medicine Division of Hematology/Oncology. "We wanted to see if we could use our genomics approach to gauge differences in the immune system's response to

tumors. We believe this study can lay the foundation for biomarker development in the future."

For the study, UNC researchers analyzed data for more than 3,400 of tumors across 11 types of cancer. Vincent said the novelty of the study was their ability to look at such a large number of tumors. They used data from The Cancer Genome Atlas project, a federally-funded, multi-institution effort to map genetic changes in multiple cancer types.

"There were a number of important findings from this analysis of thousands of tumors, including that we cannot assume immune cells are functioning the same across all tumor types," said study co-author Charles M. Perou, PhD, a UNC Lineberger member and the May Goldman Show Distinguished Professor of Molecular Oncology, whose lab collaborated on the study. "In addition, this work is laying the foundation for future biomarker development, with these immune signatures having the logical potential to predict response to immune checkpoint inhibitors."

Vincent and his colleagues found that higher levels of expression of immune cell genes was linked to higher survival for many cancers, such as breast cancer, head and neck cancer, lung adenocarcinoma, uterine cancer, and melanoma, but not all cancer types.

Some cancer types, including glioblastoma, kidney cancer, and colorectal adenocarcinoma, were exceptions. Immune infiltration predicted worse outcomes in glioblastoma. In kidney cancer, they found that high levels of B-cell expression signatures and lower numbers of B-cell antigen diversity predicted poor survival in patients. Previous studies found there are larger numbers of B-cells that regulate the immune system in kidney cancer, which may help explain the finding. But they are still investigating.

"Our findings in kidney cancer suggest that somehow, those B-cells are supporting tumor growth either directly or indirectly," Vincent said. "We don't fully understand that, but we're actively investigating it now."

Vincent said plans for future studies include using their approach to analyze the immune system characteristics of cancer while patients are undergoing treatment with immunotherapy.

"We will be working to develop biomarkers for responsiveness to immunotherapy drugs in the context of ongoing UNC Lineberger clinical trials," Vincent said.

More information: Michael D. Iglesia et al. Genomic Analysis of Immune Cell Infiltrates Across 11 Tumor Types, *Journal of the National Cancer Institute* (2016). DOI: 10.1093/jnci/djw144

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