Diverse immune cell profiles and roles found in breast cancer resistance to immunotherapy

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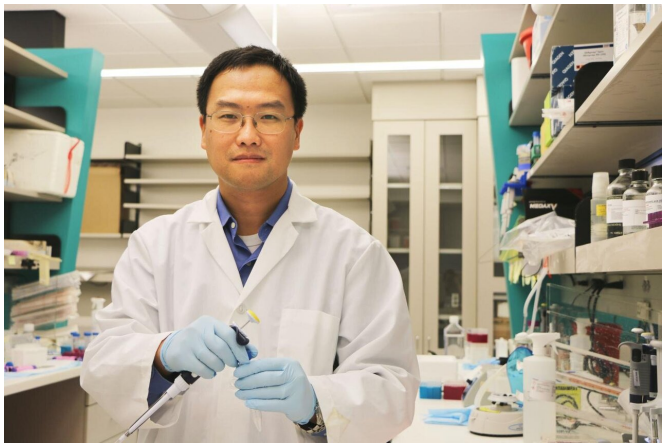

Dr. Xiang 'Shawn' Zhang, the corresponding author of this work. Credit: Baylor College of Medicine

In recent years it has been increasingly appreciated that immune cells within the tumor microenvironment contribute to tumor progression and, importantly, to the tumor's response to therapy. To better understand the specific roles different immune cell types play, a multi-institutional team led by researchers at Baylor College of Medicine profiled the immune cell composition of multiple murine models and clinical datasets of triple negative breast cancers.

Focusing on two types of immune cells, neutrophils and macrophages, they found large diversity in the cells' frequency, including neutrophil-enriched and macrophage-enriched groups whose functionality suggested potential roles in immunotherapy. The work highlights that heterogeneity of both tumor cells themselves and immune composition of the microenvironment are important considerations for therapy. The report appears in the journal *Nature Cell Biology*.

"We know that breast cancer is very heterogeneous. For many years we have recognized different subtypes of breast cancer, for instance, estrogen receptor positive (ER+), ER- and triple negative, and these categories can be further divided into subcategories. To that, we now have to add the diversity of the immune cell component in the tumor microenvironment," said corresponding author Dr. Xiang 'Shawn' Zhang, professor at the Lester and Sue Smith Breast Center and member of the Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine.

With the goal of better understanding the role immune cells within tumors play in tumor growth and in response to therapy, Zhang and his colleagues conducted a series of analyses to characterize the immune cell composition of tumor microenvironments in eight murine models and in clinical datasets of triple negative breast cancers.

"Focusing on neutrophils and macrophages, we investigated whether different tumors had the same immune cell composition and whether seemingly similar immune components played the same role in tumor growth. Importantly, we wanted to find out whether differences in immune cell composition contributed to the tumors' responses to immunotherapy," said Zhang, a McNair Scholar at Baylor.

The researchers found large diversity in the frequency of neutrophils and macrophages among the tumor samples, including some tumors that preferentially attracted macrophages, while others attracted more neutrophils. The predominance of one cell type over the other can be explained in part by the type of molecules produced by the tumor. As Zhang explained, some tumors secrete molecules that attract macrophages, while other tumors produce other molecules that lure

neutrophils to the tumor site.

Interestingly, macrophages and neutrophils seem to work against each other.

"Once one type of cell starts accumulating in the tumor, the other will tend to stay away," Zhang said. "What supports one type of cell, does not seem to support the other."

Exploring the roles macrophages and neutrophils play in tumor growth revealed that in some tumors macrophages favored tumor growth, while in others they helped control it. Neutrophils, on the other hand, tended to promote tumor growth.

"These findings are just the beginning. They highlight the need to investigate these two cellular types deeper. Under the name 'macrophages' there are many different cellular subtypes and the same stands for neutrophils," Zhang said. "We need to identify at single cell level which subtypes favor and which ones disrupt tumor growth taking also into consideration tumor heterogeneity as both are relevant to therapy."

More information: Immuno-subtyping of breast cancer reveals distinct myeloid cell profiles and immunotherapy resistance mechanisms, *Nature Cell Biology* (2019). DOI: 10.1038/s41556-019-0373-7 , https://nature.com/articles/s41556-019-0373-7

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