Research reveals how cancer hijacks immune cells to promote tumor growth

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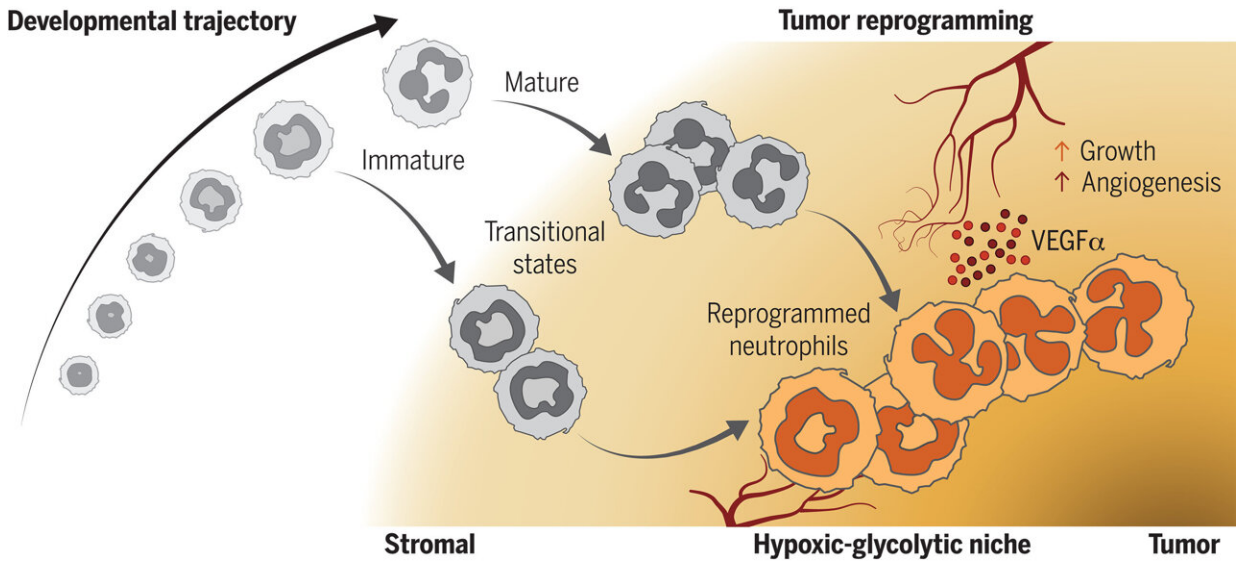

Tumor-infiltrating neutrophils undergo convergent reprogramming into pro-angiogenic neutrophils that support tumor growth. Credit: *Science* (2024). DOI: 10.1126/science.adf6493

A new research study led by A*STAR.Singapore Immunology Network (A*STAR.SIgN) has found that neutrophils—one of the most abundant white blood cells in our body—change drastically in certain cancers, adopting a new function whereby they promote tumor growth.

By carefully studying neutrophils as soon as they enter the tumor,

scientists from A*STAR.SIgN also uncovered ways to accurately differentiate tumor-promoting neutrophils from normal neutrophils present in the rest of the body. Neutrophils play important and irreplaceable roles in fighting infections, hence, depletion of neutrophils due to chemotherapy usually leave cancer patients susceptible to potentially fatal infections.

With the ability to specifically single out tumor-promoting neutrophils, this represents a novel way in which tumors can be targeted while preserving the normal neutrophil response. The study, "Deterministic reprogramming of neutrophils in tumors," was published in *Science* on 12 January 2024.

Neutrophils are characterized as the first responders of the immune system, as they migrate rapidly from the blood into tissues to fight off disease-causing pathogens.

In cancer, scientists have previously shown that various types of neutrophils present within the tumor play a crucial role in supporting tumor growth, which in turn lead to poorer clinical outcomes in cancer patients. Yet, it was unclear how these different types of neutrophils were generated, and whether they worked in a co-operative fashion to drive tumor progression. Thus, specific targeting of tumor-promoting neutrophils could not be achieved.

To address this, a team of A*STAR.SIgN scientists utilized an experimental pre-clinical model of pancreatic cancer, demonstrating that diverse types of neutrophils acquired new characteristics and functions once they migrated into the tumor, a process that was termed "reprogramming."

Neutrophils that had undergone this reprogramming process would then be unified as a singular population regardless of their initial starting

point. Thus, by tracking the reprogramming process, the team could now study how reprogrammed neutrophils ensured the continued growth of the tumor.

Reprogrammed neutrophils promoted the growth of new blood vessels within the center of the tumor, which likely allowed the tumor to overcome the limited access to oxygen and nutrients.

When the researchers specifically blocked this vessel-promoting function of reprogrammed neutrophils, or removed them from interacting with the tumor, they were able to reduce the growth of pancreatic tumors in pre-clinical models.

The team also found similar instances of reprogramming when they re-analyzed other published data sets in humans, indicating a common pathway where neutrophils can be similarly modified to promote tumor growth in certain solid cancers. As such, this study holds promise for future therapeutic approaches in cancer that target neutrophil reprogramming and their eventual function, synergizing with current treatment and immunotherapies that activate the immune system to destroy tumors.

Dr. Melissa Ng, SIgN fellow at A*STAR.SIgN and co-corresponding author on the study, said, "This study leverages the team's previous work, which identified how diverse neutrophils can be."

"In this study, we expand on our previous knowledge by uncovering the mechanisms through which tumors induce neutrophils to adopt a tumor-promoting response. This allows us to selectively target reprogrammed neutrophils, which will improve and diversify treatment options for human cancers, while lessening the impact from just targeting neutrophils in a non-specific manner."

Prof Lam Kong Peng, Executive Director at A*STAR.SIgN, said, "Breakthrough science, such as this study led by A*STAR.SIgN, is integral as it allows us to build the next generation of cancer immunotherapeutics to improve clinical outcomes for Singapore and Singaporeans."

The team plans to further investigate the factors that drive neutrophil reprogramming in human cancers. This is crucial for developing more effective ways to target and treat cancer through strategies focused on neutrophils.

More information: Melissa S. F. Ng et al, Deterministic reprogramming of neutrophils within tumors, *Science* (2024). DOI: 10.1126/science.adf6493

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