Scientists unravel tumor neutrophil complexity, discover therapeutic subset

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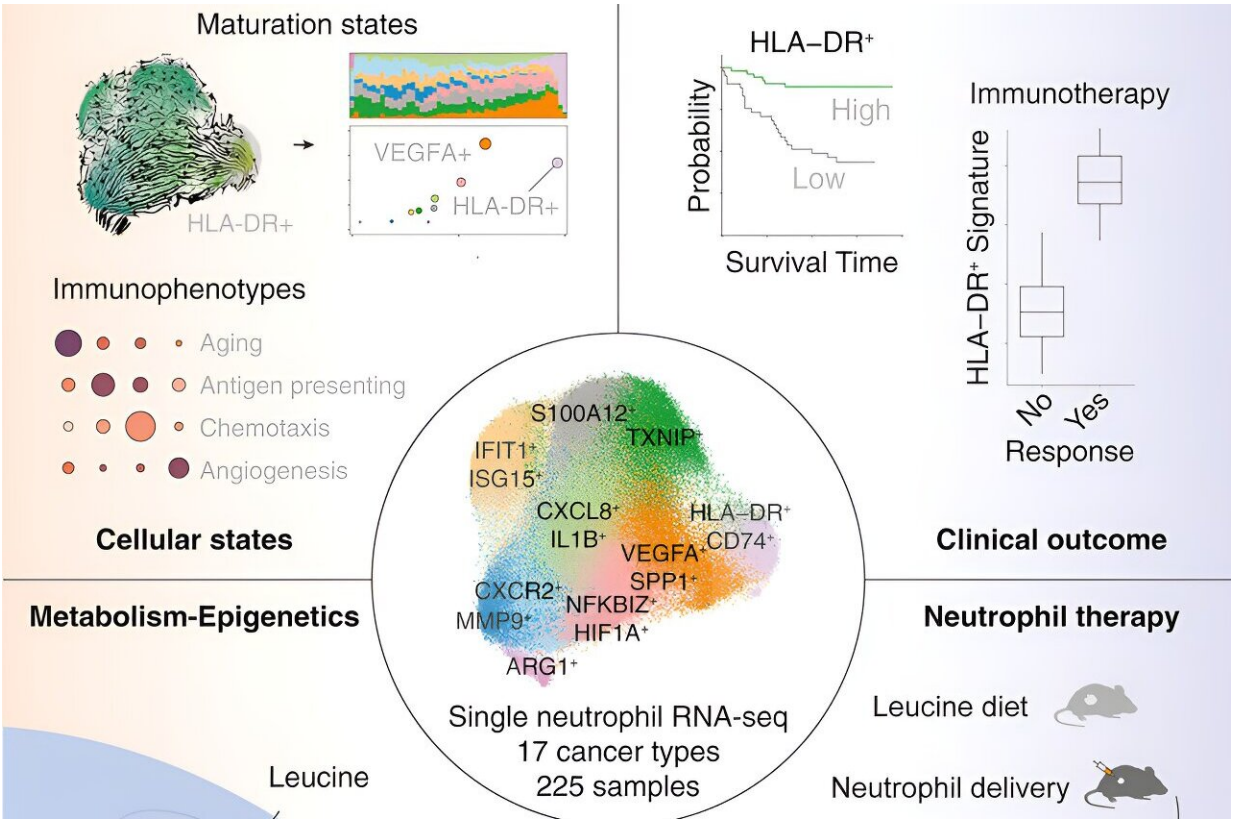

Credit: *Cell* (2024). DOI: 10.1016/j.cell.2024.02.005

In a study published in *Cell* on March 5, Prof. Zhang Xiaoming at the Shanghai Institute of Immunity and Infection (SIII) of the Chinese Academy of Sciences and Profs. Gao Qiang, Fan Jia and Yang Li at

Fudan University have uncovered an unexpected level of complexity hidden within neutrophils, which were previously thought to be a relatively uniform population of short-lived immune cells.

Using cutting-edge single-cell RNA sequencing technology, the researchers analyzed individual neutrophils across a remarkable 17 different cancer types from 143 patients. They revealed that neutrophils can adopt at least 10 highly specialized and distinct functional states related to inflammation, blood vessel formation, and most excitingly, presenting antigens to activate potent cancer-killing T cells.

"We were surprised to find such intricate complexity and divergent roles embedded within neutrophils, which have been overlooked for so long as a simple population," said Prof. Zhang. "What is especially remarkable is their newly discovered capacity to act as antigen-presenting cells, maturing and rallying T cells against cancer. In addition, the abundance of antigen-presenting neutrophils is associated with improved patient prognosis across many tumor types revealed in this study."

Through extensive analysis, the researchers determined that this antigen-presenting state can be switched on through metabolic signaling of the amino acid leucine and ensuing epigenetic changes.

"We've uncovered a way to wake up an untapped army already living within our immune system. Strategically activating these neutrophil states or modulating their behavior through metabolic or dietary means represents an entirely new paradigm to empower cancer immunotherapy," said Prof. Zhang.

The researchers then validated the therapeutic potential of these findings through in vivo models. They found that delivering antigen-presenting neutrophils or simply modulating the leucine diet dramatically boosted the anti-tumor immune response in mice, and the treatments also

markedly improved outcomes of PD-1 checkpoint immunotherapy across a range of cancer types.

"This completely changes how we perceive neutrophils in the context of cancer," said Prof. Gao. "Now we know we could harness the diverse hidden identities of neutrophils to strengthen the effectiveness of immunotherapies. We're thrilled to further explore the potential benefits of these newly uncovered mechanisms in clinics."

This study underscores the value of single-cell sequencing approaches to reveal new functional dimensions even within seemingly well-understood immune cells. Tapping into the hidden potential of neutrophils may provide new insights into cancer diagnosis and treatment.

More information: Yingcheng Wu et al, Neutrophil profiling illuminates anti-tumor antigen-presenting potency, *Cell* (2024). DOI: 10.1016/j.cell.2024.02.005

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