# Study shows how certain macrophages dampen anti-tumor immunity

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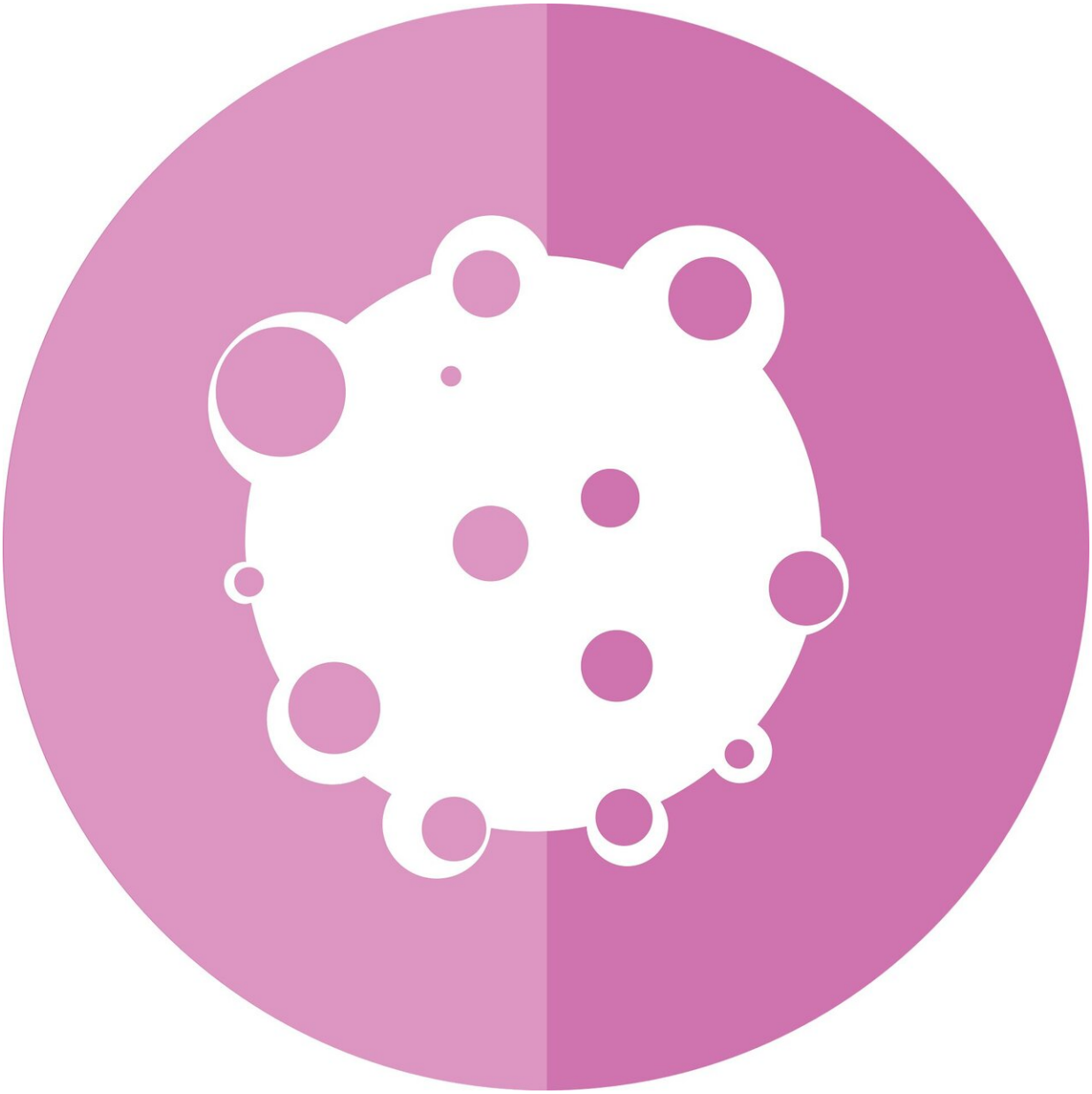

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A Ludwig Cancer Research study adds to growing evidence that immune cells known as macrophages inhabiting the body cavities that house our vital organs can aid tumor growth by distracting the immune system's cancer-killing CD8+ T cells.

Reported in the current issue of *Cancer Cell* and led by Ludwig investigators Taha Merghoub and Jedd Wolchok at Memorial Sloan Kettering (MSK), and Charles Rudin of MSK, the study shows that cavity-resident macrophages express high levels of Tim-4, a receptor for phosphatidylserine (PS), a molecule that they surprisingly found on the surface of highly activated, cytotoxic and proliferative CD8+ T-cells.

"We believe T-cells that infiltrate the peritoneal cavity can be distracted by the interaction with Tim-4-expressing macrophages," explained study first author Andrew Chow, an assistant attending physician at the Ludwig Collaborative Laboratory at MSK.

The researchers also show that blocking Tim-4 in mouse models of cancer can prevent this distractive interaction and enhance the effectiveness of immunotherapies.

"I think in patients who have these serous cavity macrophages expressing high levels of Tim-4, blocking Tim-4 will make immune based therapies more effective," Merghoub, co-director of the Ludwig Collaborative Laboratory at MSK, said.

Just as people living in different cities might have distinct customs or accents, the macrophages in our bodies can adopt specialized functions and respond to disease differently depending on which tissue they

inhabit. Scientists are increasingly interested in such localized responses because macrophage activities can influence recovery from illness or injury and responses to therapy.

Merghoub, Wolchok, Rudin, Chow, and colleagues began exploring the role of macrophages in tumor immunosuppression after noticing that cancer patients with lesions in their pleural and peritoneal cavities—which house the lungs and organs of the gastrointestinal tract, respectively—were substantially less responsive to immune checkpoint blockade therapy, which stimulates a CD8+ T cell attack on tumors.

"That told us there was something immunosuppressive in these cavities, so we went hunting for what that could be," Chow said.

Previous studies have shown that other immunosuppressed sites in the body, such as the liver and bone, harbor macrophages expressing high levels of Tim-4. Others have shown that macrophages living in the pleural and peritoneal cavities of mice also exhibit a strong Tim-4 signal.

The researchers therefore suspected that cavity-resident macrophages might impair the anti-tumor activity of CD8+ T cells through the actions of Tim-4.

These suspicions were partly vindicated when the researchers analyzed the cavity macrophages of human lung cancer patients and found that while Tim-4 levels varied between individuals, those with higher levels of the receptor tended to have a reduced presence of CD8+ T cells that had features of responding to the tumor.

Based on these observations, the researchers explored whether blocking Tim-4 would enhance the efficacy of PD-1 blockade therapies in a pre-clinical mouse model of colon and lung cancer in the peritoneal cavity.

"We showed that you get the best tumor protection when you block both molecules," Chow said.

While blocking Tim-4 alone didn't reduce the number of tumors or improve survival in the mice, it did enhance the tumor protection afforded by PD-1 blockade and boost the numbers of CD8+ T cells in the peritoneal cavity. The researchers also showed that Tim-4 blockade reduces immunosuppression in adoptive T-cell therapy, in which tumor-targeting T-cells are isolated and selectively grown in a lab before they're reinfused into the patient.

"Together, these results suggest that Tim-4 blockade is a strategy to improve immunotherapy, regardless of whether you're trying to boost your immune response through immune checkpoint blockade therapy or via adoptive T-cell therapy," said Chow.

For Merghoub, the new findings demonstrate the need to better understand the diversity of immune landscapes in and around tumors. "In the same way we profile tumor genomes to guide the use of small molecule inhibitors for targeted therapies, we need to profile the immune landscapes of tumors and personalize immune-based therapies on the basis of such studies," he said.

**More information:** Andrew Chow et al, Tim-4+ cavity-resident macrophages impair anti-tumor CD8+ T cell immunity, *Cancer Cell* (2021). DOI: 10.1016/j.ccell.2021.05.006

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