B-cell enrichment predictive of immunotherapy response in melanoma, sarcoma and kidney cancer

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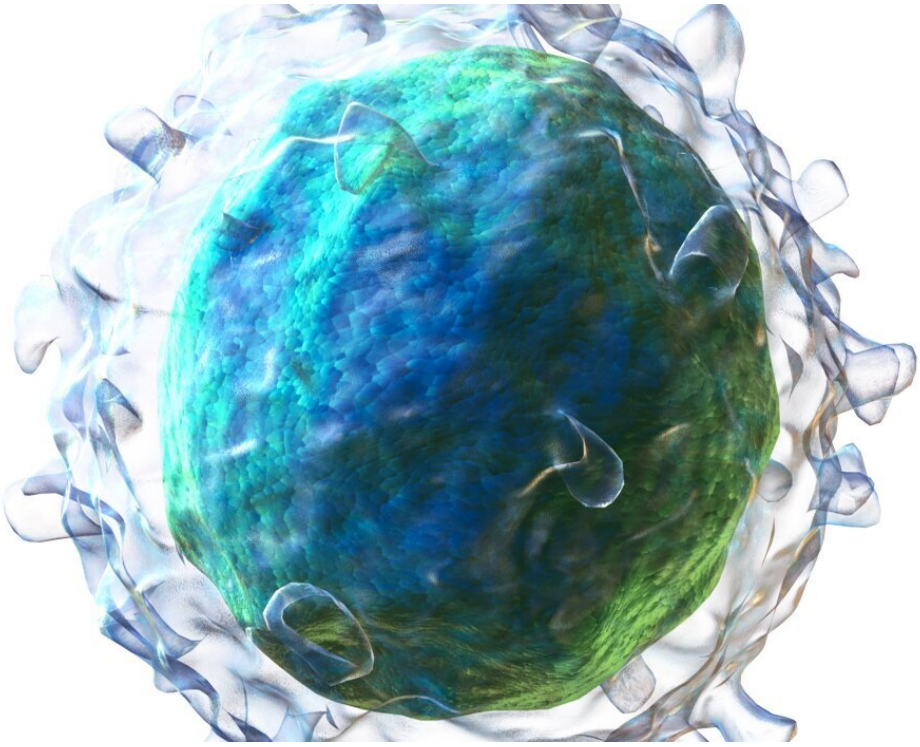

3D rendering of a B cell. Credit: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436. CC BY-SA 4.0

The likelihood of a patient responding to immune checkpoint blockade may depend on B cells in the tumor, located within specialized immune-

cell clusters known as tertiary lymphoid structures (TLS), according to researchers at The University of Texas MD Anderson Cancer Center.

Studies published today in *Nature* conclude that enrichment of B cells, a type of immune cell known for producing antibodies, in TLS was predictive of response to checkpoint blockade in patients with melanoma, soft-tissue sarcomas and renal cell carcinomas (RCC).

Checkpoint inhibitors offer the potential for long-term survival to patients across many cancer types, but not all benefit equally. Researchers previously have identified several useful biomarkers of response, which are helpful in identifying patients that may or may not benefit from checkpoint blockade.

The current studies conclude that the presence of B cells and their location within TLS, which act as a lymph node within the tumor, is critical for response to checkpoint blockade, suggesting a dynamic interaction between several components of the immune system.

Mature B cells in tumors of responders suggest active role in tumor immune response

An MD Anderson-led study found that B-cell markers were the most differentially expressed genes in responders relative to non-responders, and B cells in the tumors of responders appeared to be more mature and specialized. These findings were first presented at the 2019 American Association for Cancer Research Annual Meeting.

"These findings open up a whole new area—that B cells are actually big drivers in cancer immunotherapy, specifically checkpoint blockade," said corresponding author Jennifer Wargo, M.D., professor of Genomic Medicine and Surgical Oncology. "This could lead us to important

biomarkers for therapy response as well as potentially new therapeutic options."

The team analyzed samples from patients with advanced melanoma receiving neoadjuvant, or pre-surgical, checkpoint inhibitors as part of a clinical trial sponsored by MD Anderson's Melanoma Moon Shot, part of the institution's Moon Shots Program, a collaborative effort to accelerate scientific discoveries into clinical advances that save patients' lives.

The researchers also studied a group of patients with metastatic RCC being treated with neoadjuvant checkpoint blockade as part of a clinical trial led by Padmanee Sharma, M.D., Ph.D., professor of Genitourinary Medical Oncology and Immunology, and Jianjun Gao, M.D. Ph.D., associate professor of Genitourinary Medical Oncology.

Tumor samples were collected from patients at baseline and during treatment through the APOLLO platform, and detailed immune profiling was completed in part by the immunotherapy platform, both part of the Moon Shots Program.

In each cohort, the expression of B cell-related genes was significantly higher in responders and was predictive of response to checkpoint blockade. These findings were further corroborated in an analysis of curated melanoma samples from The Cancer Genome Atlas, in which high expression of B-cell markers was associated with significantly improved overall survival.

"These data indicate the importance of cell types other than T cells, such as B cells, in the anti-tumor immune responses generated by immune checkpoint therapies," said Sharma. "There is a great need to identify biomarkers of response to therapy, and these data may allow for future studies focused on developing composite biomarkers that represent both the T- and B-cell responses."

The researchers determined that B cells were localized in the TLS, and the density of B cells and TLS in the tumor was higher in responders. Further analysis of these infiltrating B cells showed that those in responders expressed more markers of mature and differentiated B cells, such as memory B cells and plasma cells.

"Through these studies, we find that B cells are not just innocent bystanders, but are themselves contributing in a meaningful way to the anti-tumor immune response," said first author Beth Helmink, M.D., Ph.D., fellow in Surgical Oncology.

Wargo also collaborated on another study published today, led by Göran Jönsson, Ph.D., and researchers at Lund University in Sweden, which analyzed an additional group of patients with metastatic melanoma and similarly suggests an important role for B cells within these lymphoid structures.

The researchers continue work to clarify the precise role for B cells in driving responses, but suggest they may be producing tumor-specific antibodies that could be leveraged for future therapeutic approaches to enhance checkpoint blockade.

Sarcoma patients with B-cell enrichment have improved survival and response rates

In a cancer type previously thought to be refractory to immunotherapy, profiling of soft-tissue sarcomas established five distinct classes of the disease that predict survival outcomes and response to checkpoint blockade. Those with the best outcomes were marked by enrichment of B cells within TLS in the tumor, according to results published today.

The study was led by Wolf Fridman, M.D., Ph.D., and a team from the

French National Institute of Health and Medical Research together with Hussein Tawbi, M.D., Ph.D., associate professor of Melanoma Medical Oncology at MD Anderson.

"These results suggest there may be new ways of predicting responses to immunotherapy by including B cells as a novel biomarker," says Tawbi. "Perhaps most exciting is this also opens up the possibility for a therapeutic targeting of B cells in ways that could identify new avenues for treating these patients."

Soft-tissue sarcoma is a rare type of cancer that develops in soft tissues of the body, such as muscles and fat. This diverse group of cancers comprises more than 50 subtypes, classified by their appearance under a microscope, which doesn't yield tremendous insight into underlying biological behavior, explained Tawbi.

Thus, the researchers sought to characterize sarcomas by their immune characteristics by profiling expression of immune-related genes in more than 600 patient samples. The resulting classifications grouped sarcomas into five classes, ranging from "immune desert" tumors to "immune high" tumors.

Tumors with highest levels of immune markers had significantly longer overall survival when compared to "immune desert" sarcomas. The expression of B-cell markers was the strongest factor associated with survival in these patients.

A closer look at tumor samples revealed that TLS existed almost exclusively in the "immune high" tumors, and these structures had high densities of many immune cell types, including B cells.

To investigate correlations with response to checkpoint blockade, the researchers analyzed pre-treatment samples from patients enrolled in

SARC028, a multi-center trial performed through the Sarcoma Alliance for Research through Collaboration (SARC) and led by Tawbi. Patients on this trial had metastatic soft-tissue sarcomas and were treated with checkpoint blockade against PD-1.

There were no responders among those with low expression of immune markers, but half of patients in the "immune high" class saw a response to checkpoint blockade. These patients also had a significantly improved progression-free survival compared to those in the "immune desert" classification.

"All of the patients that responded to checkpoint inhibitors did truly have those immune-high signatures, especially with enriched B cells, highlighting the fact that there might be a really important role for these cells in the response to immunotherapy," said Tawbi. "Based on these results, it may now be possible for us to identify more types of sarcomas for which we can use immunotherapy effectively."

The authors are working to validate these findings in a broader cohort of patients and to identify the underlying mechanisms for B cells acting in the tumor, but they suggest these findings can be used to build a novel risk-stratification tool for better utilizing immunotherapies in patients with sarcoma.

More information: B cells are associated with survival and immunotherapy response in sarcoma, *Nature* (2020). DOI: 10.1038/s41586-019-1906-8 , nature.com/articles/s41586-019-1906-8

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