IMMUNOTHERAPY

B cells and TLSs facilitate a response to ICI

“Until now, the emphasis has been on T cells”

Tumour-infiltrating B cells have been detected in different solid tumour types, but their role in cancer remains unclear. Now, the findings of three independent studies published simultaneously in *Nature* indicate that B cells and tertiary lymphoid structures (TLSs) are key determinants of a response to immune-checkpoint inhibition (ICI).

In the first study, involving 28 patients with high-risk resectable melanoma, those with a response to neoadjuvant ICI (responders) had higher expression levels of B cell markers and genes involved in B cell function in baseline and early on-treatment tumour biopsy samples than non-responders ($P=0.036$ and $P=0.038$, respectively). Similar observations were made in samples from 18 patients with melanoma and 28 patients with metastatic renal cell carcinoma receiving neoadjuvant or adjuvant ICI. A deeper analysis of samples from the initial melanoma cohort revealed a higher density of CD20⁺ B cells and TLSs and a higher TLS:tumour area ratio in early on-treatment samples from responders versus those from non-responders (all $P<0.002$). In responders, CD20⁺ B cells, CD4⁺, CD8⁺ and FOXP3⁺ T cells often

co-localized in TLSs, the majority of which were characterized as mature secondary follicles.

The expression of a B cell signature was assessed in cutaneous melanoma samples from The Cancer Genome Atlas. Among three distinct melanoma immune classes identified, cluster C was associated with the highest expression of B cell genes and the most favourable overall survival (OS; $P<0.0001$ and $P=0.068$, respectively, both versus cluster A). “Our observations suggest that responses to ICIs require the orchestrated contribution and organization of many cell types in TLSs,” summarizes lead investigator Jennifer Wargo.

In the second study, clusters of CD20⁺ B cells were found in 25% of tumour samples from patients with melanoma before starting ICI ($n=177$). All clusters were surrounded by CD4⁺ T cells in structures identified to be TLSs; CD8⁺ T cells were located outside the TLSs. Furthermore, a higher proportion of CD4⁺ T cells was found in clusters within or adjacent to TLSs enriched in Ki67^{high} (proliferating) B cells. Lead investigator Göran Jönsson hypothesizes: “the presence of TLSs ‘moulds’ the molecular phenotype of tumour-infiltrating T cells”.

In this study, three subgroups of patients were defined according to their clinical outcomes: the presence of both CD8⁺ T cells and TLSs indicated favourable OS; CD8⁺ T cells only were found in an intermediate group; and the absence of CD8⁺ T cells and TLSs was associated with poor OS. Jönsson and collaborators developed a gene signature of TLSs in melanoma, which performed better

than other immune signatures in the prediction of OS of patients with melanoma receiving ICI (across four different cohorts).

In the third study, led by Hussein Tawbi and Wolf Fridman, soft-tissue sarcomas ($n=213$) were stratified according to the composition of their microenvironment. Class E, characterized by a high density of B cells and TLSs, was associated with the highest response rate to ICI. “The presence of B cells is far from being arbitrary since they seem to be organized in TLSs,” notes Tawbi. Tumours with TLSs had significantly higher densities of tumour-infiltrating CD3⁺ and/or CD8⁺ T cells and CD20⁺ B cells (all $P<0.001$).

Among several immune cell-related gene signatures (including one for CD8⁺ T cells), only a B cell signature was significantly associated with extended OS ($P<0.001$). “Until now, the emphasis has been on T cells; B cells and TLSs have largely been neglected”, summarizes Fridman. Wargo adds: “B cells might be performing a supportive role via antigen presentation and other functions — and might also contribute by producing anti-tumour antibodies.”

Further studies are warranted because, as Fridman indicates, “TLSs are a potential new marker for the selection of patients for ICI, which need to be validated in prospective trials.” Tawbi proposes: “A better understanding of the interplay of B cells with T cells and how they might enhance antitumour immunity could open up an entirely novel approach to immunotherapy by targeting B cells and B cell-mediated processes.”

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ORIGINAL ARTICLES Helmink, B. A. et al. B cells and tertiary lymphoid structures promote immunotherapy response. *Nature* **577**, 549–555 (2020) | Cabrita, R. et al. Tertiary lymphoid structures improve immunotherapy and survival in melanoma. *Nature* **577**, 561–565 (2020) | Petitprez, F. et al. B cells are associated with survival and immunotherapy response in sarcoma. *Nature* **577**, 556–560 (2020)

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