IMMUNOTHERAPY

Sequencing cells of the immune TME

Three studies published in *Nature Medicine* provide new insights on the immune tumour microenvironment (TME) of three cancer types. The findings have important implications for immunotherapy.

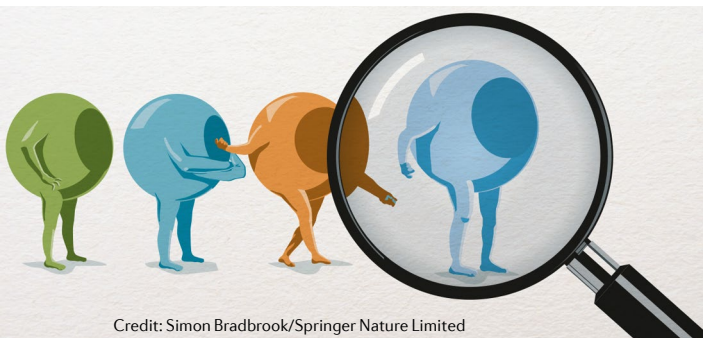
In one study, single-cell RNA sequencing was performed in 12,346 T cells from 14 patients with non-small-cell lung cancer (NSCLC). "By depicting the comprehensive T cell landscape in these patients, our study reveals the heterogeneity of T cells in the TME, including the existence of two previously uncharacterized pre-exhausted $CD8^+$ T cell subsets," explains Zemin Zhang. "We also uncovered lineage transitions between the pre-exhausted T cells and dysfunctional or exhausted T cells." Importantly, a high ratio of pre-exhausted to exhausted T cells was associated with favourable patient outcomes in The Cancer Genome Atlas lung adenocarcinoma cohort, whereas a gene signature of activated regulatory T (T_{reg}) cells portended a poor prognosis. "The discovery of two pre-exhausted T cell subsets might provide not only new avenues for lung cancer subtyping and prognostication but also new cellular and molecular targets for immunotherapies," Zhang opines.

The second study involved profiling of T cells from breast cancers, including multi-parametric flow cytometry analyses of tumour-infiltrating lymphocytes (TILs) for 123 women (129 samples) and single-cell RNA sequencing of 6,311 T cells from 2 women with triple-negative breast cancer (TNBC). High TIL densities have previously been associated with favourable breast cancer outcomes, particularly in the TNBC or $HER2^+$ settings; however, the new data indicate that qualitative differences in TIL populations are also important. "We show that the presence of a specific $CD8^+$ T cell subset, comprising tissue resident memory T (T_{RM}) cells, is associated with a favourable prognosis, suggesting that this T cell subset reflects true tumour-specific immunity," summarizes Sherene Loi. The T_{RM} cells expressed high levels of immune-checkpoint proteins (PD-1, TIM3, LAG3, TIGIT, and CTLA-4) and cytotoxic factors (granzyme B and perforin). Moreover, a small subgroup of T_{RM}-like cells showed signs of proliferation, suggestive of active antitumour responses. Thus, the T_{RM} cell subset might identify not only patients with a favourable prognosis but also good candidates for immune-checkpoint inhibition (ICI), which has generally limited efficacy against breast cancers.

"Interestingly, Zhang and colleagues report, similarly to us, heterogeneity in the T cell population, specifically the $CD8^+$ T cell population. Indeed, they found a number of lung cancer $CD8^+$ T cells subsets that had T_{RM} cell-like features," says Loi. "They describe the transition of T cells through differentiation states reaching a 'pre-exhausted' then 'exhausted' state, with the latter subset expressing high levels of multiple immune-checkpoint proteins," adds Paul Neeson, a co-author of the breast cancer study. "We don't believe that 'exhausted' is the correct term: the cells might not be active in destroying the cancer at the time of tumour sampling owing to the hostility of the TME, particularly the presence of immunosuppressive checkpoint proteins, rather than being exhausted per se," says Neeson. Thus, whether tumour-infiltrating T_{RM} cells and the T cells described as 'exhausted', which seem to be a subset of T_{RM} cells, can be reinvigorated using ICI is an important question.

In the third study, the abundance of $BDCA3^+$ stimulatory dendritic cells (SDCs) in the melanoma TME was positively correlated with peri-tumour TIL densities and responsiveness to ICI. Using bulk tumour RNA sequencing, the authors found that SDC abundance is determined by natural killer (NK) cell-dependent production of FLT3LG in the TME. "A key nuance of our findings is that even though ICI largely targets T cells, other cell types, including NK cells and SDCs acting upstream of T cells, are predictive of patient responsiveness," says Matthew Krummel, who led this study. "Our findings, together with those reported in the other papers, lead to an intriguing hypothesis that SDCs and NK cells in the TME could be important players in reinvigorating T_{RM} cells or exhausted T cells; we propose that targeting novel pathways to increase the number and activation state of NK cells in the TME will prove to have orthogonal benefits to those provided by ICI," he concludes.

David Killock



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ORIGINAL ARTICLES Guo, X. et al. Global characterization of T cells in non-small-cell lung cancer by single-cell sequencing. *Nat. Med.* https://doi.org/10.1038/s41591-018-0045-3 (2018) | Savas, P. et al. Single-cell profiling of breast cancer T cells reveals a tissue-resident memory subset associated with improved prognosis. *Nat. Med.* https://doi.org/10.1038/s41591-018-0078-7 (2018) | Barry, K. C. et al. A natural killer–dendritic cell axis defines checkpoint therapy–responsive tumor microenvironments. *Nat. Med.* https://doi.org/10.1038/s41591-018-0085-8 (2018)