**Cross reactive T cells hold up against Omicron**

After a flurry of articles describing antibody evasion by Omicron, several reports now detail cellular immune responses against the highly mutated SARS-CoV-2 variant. Investigating CD4+ and CD8+ T cells in vaccinated and convalescent individuals, these studies show a high degree of preservation of T cell epitopes between the ancestral strain and Omicron. However, the degree of cross-reactivity varies among individuals, likely as a consequence of genetic aspects of antigen presentation. Gao et al. report a significantly lower magnitude of responses to the Omicron spike protein in T cells from convalescent compared to BNT162b2 vaccinated individuals, indicating that ‘boosting’ may benefit those with ‘natural immunity’. Keeton et al. also investigated patients hospitalized with Omicron and found a similar magnitude of T cell responses as previously observed in patients infected with other variants. A comprehensive analysis of T cell responses against variants from Alpha to Omicron, at different time points after vaccination (with BNT162b2, mRNA-1273, Ad26.CoV2.S or NVX-CoV2373), was presented by Tarke et al. It shows that 84% of CD4+ and 85% of CD8+ memory T cell responses to the Omicron spike protein are preserved, compared to an average of 90% and 87% respectively for the other variants. This contrasts sharply with a marked reduction of memory B cell recognition of Omicron spike. Overall, these observations could explain why vaccines or previous infection still provide robust protection against severe disease with Omicron, even when levels of neutralizing antibodies are insufficient to prevent infection, and indicate that viral evolution is not driven by T cell escape.

**Cytotoxic CD4+ CAR T cells implicated in long-term leukaemia remission**

Durable clinical responses after treatment with chimeric antigen receptor (CAR) T cells require the functional persistence of these cells. However, little is known about the fate of these cells once transferred to the patient. Now, a report by Melenhorst et al. in Nature presents a functional and molecular characterization of CAR T cells from two patients who have remained in remission for more than a decade after treatment for chronic lymphocytic leukaemia (CLL).

The patients had received CD19-targeted CAR T cells (CTL019) as part of a phase I clinical trial in 2010. The leukemic clone had been undetectable in both patients since 6 months after the infusion, whereas the CTL019 cells remained readily detectable for more than 10 years of follow-up. This provided a unique opportunity to study CAR T cell characteristics that are associated with long-term remission. A longitudinal study using bulk and single-cell multi-omic approaches mapped the clonal evolution of the CAR T cells, with clones identified on the basis of their T cell receptor (TCR) β-chain rearrangement or the integration site of the CAR construct. The authors detected two phases of CAR T cell therapy response. The initial phase was dominated by cytotoxic CD8+ CAR T cells, and in one patient also by CD4 CD8+ γδCAR T cells that had upregulated the transcription factor Helios, which distinguished these cells from otherwise similar cytotoxic CD8+ T cells. Unexpectedly, the long-term remission phase in both patients was dominated by a small number of highly activated CD4+ CAR T cell clones, which constituted over 97% of CAR T cells at later timepoints.

These cells expressed the proliferation marker Ki67, the activation markers CD38, HLA-DR and CD95, the transcription factors EOMES and TOX, the checkpoint markers CTLA4, LAG3 and TIGIT, as well as the memory markers CD27 and CCR7.

Transcriptomic analysis further showed an enrichment in T cell activation, TCR signalling, oxidative phosphorylation, vesicle component and mitochondrial protein complex pathways, as well as an upregulation of GZMK and GZMA, which encode cytotoxic enzymes. When stimulated with CD19-expressing cells ex vivo, they upregulated the expression of CD107a, a marker of degranulation, as well as CCL4, perforin and granzyme A, indicative of direct cytotoxic function. These features suggest that long-persisting CAR T cells are cytotoxic, proliferating, and remain functionally active rather than exhausted.

Overall, these results reveal the surprising finding that long-term cytotoxicity against leukemic cells after CAR T cell treatment appears to be mediated by a limited number of metabolically active but checkpoint inhibitor-restrained cytotoxic CD4+ CAR T cell clones.

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