AN ATYPICAL CENTRAL MEMORY LIKE PHENOTYPE CAN BE INDUCED IN HUMAN T CELLS BY INNATE TCRαβ ENGAGEMENT

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Background The αβ T cell receptor (TCR) has immense diversity, primarily for peptide-MHC (pMHC) complexes that clonally interact with complementarity-determining region (CDR) 3 motifs assembled by quasi-random somatic gene rearrangement of TCRα and TCRβ gene segments. This adaptive biology is shown to an even greater extent by TCRγδ with its ligands being qualitatively more diverse than pMHC. However, TCRγδ can also function as an innate receptor whereby germline-encoded variable γ residues are sufficient to engage butyrophilin (BTN) or BTN-like (BTNL) that drive a variety of phenotypic outcomes distinct from clonal CDR3-mediated interactions. This broadened perspective on TCR biology has not hitherto been systematically extended to αβ T cells.

Methods A panel of human TCR variable β (TCRVβ) chain targeting antibodies was assembled, and their binding motifs determined. Using multi-colour flow cytometry and single-cell RNA sequencing, the impact of these antibodies on peripheral blood T cells was assessed by comparison with the impacts of anti-CD3ε reagents, including OKT3.

Results Antibodies engaging germline-encoded regions of human TCRVβ chains consistently activated primary human T cells towards an atypical central memory (TCM)-like phenotype distinct from those induced by anti-CD3ε stimulation. Although the cells show myriad surface markers associated with chronic stimulation, they are not exhausted but are highly proliferative with strong cytolytic/Tc1 effector profiles, including expression of T-bet and IRF4. Strikingly, this phenotype can be induced in cells previously driven toward effector memory (TEM) and effector memory T cells re-expressing CD45RA (TEMRA) states.

Conclusions In sum, the use of TCRαβ as an innate receptor offers new insight into T cell biology and an approach in which antibody mediated TCR agonism may be relevant to distinct clinical settings.

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Ethics Approval Anonymized leukocyte cones were sourced from healthy adult donors attending blood donation clinics at the National Blood Service (London, UK). Use of human samples was approved by local ethical committees, in accordance with the Declaration of Helsinki.