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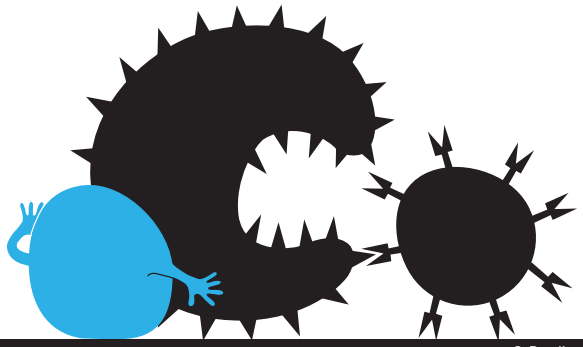

S. Bradbrook/NPG

IMMUNOTHERAPY

CAR T cells pursue CLL cells and avoid innocent bystanders

Despite considerable therapeutic advances, refractory chronic lymphocytic leukaemia (CLL) remains extremely difficult to treat. Adoptive cell therapy using chimeric antigen receptor (CAR) T cells holds promise in this setting, but current CARs targeting CD19 or CD20 lack selectivity for malignant B cells. Researchers have now developed a potentially more-selective approach.

Hinrich Abken, who led the study, explains: "early phase trials with anti-CD19 CAR T cells showed particular success in the treatment of refractory CLL, with the induction of long-term remissions in 27% of patients; however, anti-CD19 CAR T cells produce substantial 'on-target, off-tumour' toxicities owing to the elimination of healthy B cells. Thus, patients require lifelong immunoglobulin substitution and are at risk of recurrent infections."

The researchers sought alternative CAR targets that might enable 'bystander' nonmalignant B cells to be spared, and identified the IgM Fc receptor (FcμR) as a promising candidate. They found that FcμR is highly and consistently overexpressed on $CD19^+CD5^+$ cells from patients with CLL, with considerably lower levels detectable on nonmalignant $CD19^+$ B cells and $CD5^+$ T cells from healthy donors. By contrast, levels of CD19 expression are higher on nonmalignant B cells than on CLL cells.

Abken and colleagues engineered a CAR comprising a single-chain variable fragment of an anti-FcμR antibody as the targeting moiety, and confirmed that this construct enabled specific targeting of primary CLL cells and CLL cell lines, but not nonmalignant $CD19^+$ B cells or $CD3^+$ T cells. Upon co-incubation with CLL cells, anti-FcμR CAR T cells generated comparable levels of inflammatory cytokines and cytolytic proteins, and had similar cytolytic efficiency to that of T cells expressing anti-CD19 CARs with the same intracellular signalling domains. Of note, neither allogeneic nor autologous anti-FcμR CAR T cells significantly depleted the levels of nonmalignant B cells, whereas their anti-CD19 equivalents resulted in near complete elimination of these cells. Interestingly, *in vivo* experiments in a mouse xenograft model revealed that anti-CD19 or anti-FcμR CAR T cells delayed the onset of CLL to a similar extent when co-injected with CLL cells.

Abken summarizes: "FcμR-specific CARs redirect and activate patients' T cells with a high level of specificity and selectivity towards CLL cells while sparing healthy B cells; the persistence of a fully functional antibody response represents an important improvement on currently explored anti-CD19 CAR T-cell therapies." He concludes, "our data therefore suggest that anti-FcμR CAR T-cell therapy might be a more-selective treatment, with a superior therapeutic index."

David Killock

ORIGINAL ARTICLE Faitschuk, E. *et al.* Chimeric antigen receptor T cells targeting Fc μ receptor selectively eliminate CLL cells while sparing healthy B cells. *Blood* http://dx.doi.org/10.1182/blood-2016-01-692046 (2016)
FURTHER READING Jackson, H. J., Rafiq, S. & Brentjens, R. J. Driving CAR T-cells forward. *Nat. Rev. Clin. Oncol.* **13**, 370–383 (2016)