RESEARCH HIGHLIGHTS

IMMUNOTHERAPY

Excessive cardiac fibrosis plays an

important role in the progression

and heart failure, but there are

currently no therapies available

of various forms of cardiac disease

CAR-T cells combat cardiac fibrosis

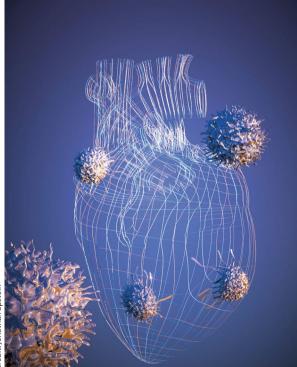
by engineered T cells.

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that directly target this pathological process. Writing in Nature, Epstein and colleagues now demonstrate that engineered chimeric antigen receptor (CAR) T cells can be applied to reduce cardiac fibrosis and restore function in a mouse model of hypertensive heart failure. The use of a CAR to redirect

cytotoxic T cells to recognize specific antigens on cancer cells has produced dramatic results in cancer therapy. Epstein and colleagues reasoned that engineered T cells could be used to target non-cancer cells, and set out to investigate whether the activated cardiac fibroblasts that contribute to fibrosis following heart



injury could be effectively targeted

First, the authors generated mice in which a xenogeneic antigen that is not normally found in mice ovalbumin peptide (OVA) — could be conditionally presented on the surface of activated cardiac fibroblasts, using a tamoxifeninducible Cre recombinase targeted to the periostin locus (periostin has previously been shown to be expressed by activated cardiac fibroblasts induced by injury, but not by quiescent cardiac fibroblasts). To model hypertensive cardiac injury and fibrosis, mice were infused with angiotensin II (AngII) and phenylephrine (PE). During the AngII/PE infusion, mice received regular intraperitoneal injections of tamoxifen to ensure OVA expression. One week later, engineered CD8+ T cells expressing a cognate T cell receptor against the OVA peptide were adoptively transferred into the mice. At 4 weeks, there was significantly less fibrosis in the treated mice compared with control mice, accompanied by a partial rescue of the heart to body weight ratio.

Next, the authors set out to identify an endogenous protein expressed by activated fibroblasts that could be specifically targeted by engineering T cells. To do this, they analysed gene-expression data from an RNA-sequencing database consisting of 238 left ventricular tissue samples of human heart transplant donors and recipients. The cell surface glycoprotein fibroblast activation protein (FAP) was identified as the most upregulated fibroblast-specific gene in the myocardium of patients with either hypertrophic cardiomyopathy or dilated cardiomyopathy compared with control, non-failing donor hearts. Immunohistochemistry

of human heart samples confirmed this differential expression pattern. To test the feasibility of using

FAP as the target for their CAR-T cell approach, the authors again studied the AngII/PE mouse model of hypertensive cardiac injury and fibrosis. FAP was undetectable in control mouse hearts, but was apparent in activated fibroblasts after 1 and 2 weeks of AngII/PE exposure. With the aim of depleting these FAP-expressing fibroblasts, engineered FAP CAR-T cells were adoptively transferred into mice. By week 4, cardiac fibrosis was significantly reduced in injured mice that had been administered FAP CAR-T cells compared with controls, and fibrosis remained limited at 8 weeks. In addition, diastolic and systolic function was partially rescued.

Importantly, extensive analysis revealed no signs of toxicity in this model system, which is in agreement with previous mouse studies in which CAR-T cells against FAP have been used for cancer treatment. Notably, CAR-T cells against FAP have also been administered to humans as part of a clinical trial for the treatment of mesothelioma.

Although further work is required to determine whether FAP is the optimal target for treatment and to ensure that safety risks are minimized, these results provide proof-of-concept for the possibility of treating cardiac fibrosis with engineered T cells. The authors plan to extend their work to large animal models of heart failure and to investigate other conditions including ischaemic heart disease and muscular dystrophy.

Sarah Crunkhorn

ORIGINAL ARTICLE Aghajanian, H. et al. Targeting cardiac fibrosis with engineered T cells. Nature https://doi.org/10.1038/s41586-019-1546-z (2019)

