Immunology

T cells engineered to target senescence

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Senescence is a hallmark of cellular ageing and contributes to many diseases. A new method enabling immune cells to target senescent cells might offer improved therapeutic options. **See p.127**

Senescence is a form of cellular stress response. In some circumstances it can be harmful, and efforts are under way to develop therapies that target senescent cells. On page 127, Amor *et al.*[1] describe a method that selectively removes senescent cells in mice.

Entry into senescence imposes a stable arrest of the cell cycle, preventing old, damaged or precancerous cells from dividing. Senescent cells secrete a complex cocktail of factors that drive a response called the senescence-associated secretory phenotype (SASP). This recruits T cells and NK cells of the immune system, promoting removal of the senescent cells. Under these conditions, senescence is transient, which benefits the organism[2].

However, when senescent cells linger, they can promote chronic inflammation resulting in age-related diseases such as atherosclerosis, cancer and fibrosis (a type of tissue scarring). The elimination of senescent cells has therefore emerged as a promising therapeutic strategy. It can improve the outcome of many diseases, and increases lifespan in studies in mice[3]. One possible way to target senescent cells is with drugs that kill them selectively, called senolytic drugs. Amor and colleagues take a different approach, inspired by the fact that immune cells are involved in eliminating senescent cells under normal circumstances[4].

The authors adapted a technique that is currently in use for anticancer treatment. In this therapy, T cells are removed from an individual and, before being returned, are manipulated to boost their ability to target cancer cells. Such cells are known as CAR T cells because they are engineered to express what is termed a chimaeric antigen receptor (CAR). The CAR is designed to recognize and bind to a particular fragment of a protein, called an antigen, that is present on the surface of cancer cells. If this interaction occurs, the T cell is activated and kills the tumour cells[5]. Identifying antigens that are expressed exclusively on tumour cells is a key challenge, because the killing of healthy cells by CAR T cells could lead to severe side effects.

To find antigens that are specific to senescent cells, Amor and colleagues analysed the expression of transmembrane proteins found in senescent human and mouse cells. One of the eight most promising candidates identified was the urokinase-type plasminogen activator receptor (uPAR). An examination of previously published data on protein and RNA expression in human tissues revealed that uPAR is either not detected or is present only at low levels in most organs of the human body, including the central nervous system, heart and liver. However, Amor and colleagues found that uPAR is highly expressed in senescent cells both *in vitro* and *in vivo*. Intriguingly, a soluble form of uPAR (suPAR) that lacks a transmembrane region is a component secreted during the SASP response. The presence of suPAR is a hallmark of some chronic disorders, including diabetes[6] and kidney disease[7], in which senescence has a role.

After identifying uPAR as a universal marker of senescent cells, Amor and colleagues engineered CAR T cells to target uPAR (Fig. 1). Given that premalignant cells (those possibly on their way to becoming cancer cells) undergo senescence, and the fact that many anticancer therapies work by causing tumour cells to enter senescence as a way of stopping them dividing, the authors investigated how effective these CAR T cells were in treating cancer. They report that treatment with CAR T cells that target uPAR eliminated senescent premalignant and malignant cells in mouse models of liver and lung cancer. It has already been proposed that anticancer therapies might be improved by following them up with treatments targeting senescent cells[8]. Amor and colleagues' study in mice confirmed that such an approach using their senolytic CAR T cells boosts the effectiveness of anticancer treatment.

Part of the attraction of using senolytic CAR T cells is their potential for treating the many diseases in which senescence is involved. Indeed, Amor and colleagues show that if mice received senolytic CAR T cells, this improved the outcome of liver fibrosis in animal models of non-alcoholic steatohepatitis, a severe form of fatty liver disease.

Navitoclax, a senolytic drug widely used in preclinical studies, can cause toxicity that limits its use. This has led to efforts to identify new senolytic drugs and other ways to target

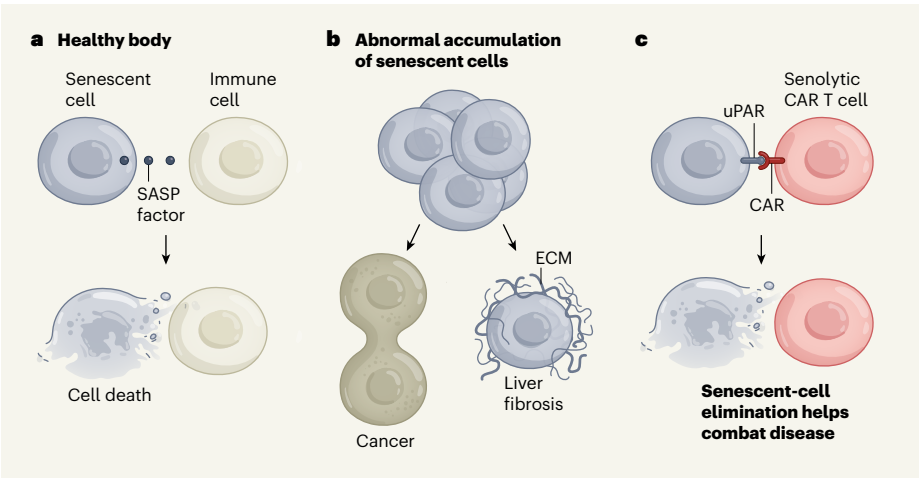

Figure 1 | CAR T cells can be used to remove senescent cells. a, Malfunctioning cells commonly enter a non-dividing state called senescence. These cells exhibit a response called the senescence-associated secretory phenotype (SASP). This is associated with the release of various molecules that attract immune cells, which then kill the senescent cell. **b**, If this process fails and senescent cells linger, they can contribute to diseases such as cancer and liver fibrosis — tissue scarring associated with deposits of extracellular matrix (ECM) material. **c**, Amor *et al.*[1] describe a method that selectively removes senescent cells. The authors identified a protein (uPAR) that is expressed on the surface of senescent cells, and engineered immune cells called T cells to express a receptor that recognizes uPAR. This type of receptor is called a chimaeric antigen receptor (CAR). The recognition process drives the T cells to kill the senescent cells. Amor and colleagues report that such senolytic CAR T cells help to tackle disease in mouse models of cancer and liver fibrosis.

senescent cells[9]. Amor *et al.* suggest that use of senolytic CAR T cells could eliminate some of the side effects and the limited effectiveness associated with senolytic drugs. However, these cells are not necessarily problem-free. A common complication of the therapeutic use of CAR T cells is a condition called cytokine-release syndrome (also known as a cytokine storm), in which an intense T-cell response causes fever and affects blood pressure and breathing[10]. Although the authors observed that high doses of senolytic CAR T cells did cause cytokine-release syndrome, reducing the dosage avoided the problem while retaining the therapeutic potential of the treatment.

The use of CAR T cells for anticancer therapy has other limitations. Long-lasting activity of these cells is required to control tumour growth as cancer cells divide over time. This issue might not be of concern when targeting senescent cells, because they do not proliferate. However, many solid tumours (those that do not arise from blood cells) are associated with an immunosuppressive tissue microenvironment, which can cause CAR T cells to enter a dysfunctional state called exhaustion. Senescent cells can foster an immunosuppressive microenvironment during tumour formation[11]. Although the authors did not observe senescence-mediated immunosuppression in their study, it might be a shortcoming of this approach. A greater understanding is needed of how senescent cells can interfere with immune-system function.

Could senolytic CAR T cells be used to treat patients? The use of such cells in the clinic is expensive, so the criteria for considering such an approach should be chosen carefully. It will also be important to determine whether CAR T cells that target human uPAR are as safe and effective as are the CAR T cells targeting mouse uPAR that Amor and colleagues used. Alternatively, perhaps this method could be improved by using senolytic CAR T cells that target other proteins found on the surface of senescent cells, such as DPP4 and oxidized vimentin[12,13]. The immense advances that are being made in mapping gene expression in humans at the resolution of single cells might reveal further targets for use in the design of senolytic CAR T cells. Merging two promising therapeutic strategies by using CAR T cells to target senescent cells might be a powerful combination for tackling certain diseases.

"When senescent cells linger, they can promote chronic inflammation resulting in age-related diseases."

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