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Reprogramming the tumor microenvironment by genome editing for precision cancer therapy

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Abstract

The tumor microenvironment (TME) is essential for immune escape by tumor cells. It plays essential roles in tumor development and metastasis. The clinical outcomes of tumors are often closely related to individual differences in the patient TME. Therefore, reprogramming TME cells and their intercellular communication is an attractive and promising strategy for cancer therapy. TME cells consist of immune and nonimmune cells. These cells need to be manipulated precisely and safely to improve cancer therapy. Furthermore, it is encouraging that this field has rapidly developed in recent years with the advent and development of gene editing technologies. In this review, we briefly introduce gene editing technologies and systematically summarize their applications in the TME for precision cancer therapy, including the reprogramming of TME cells and their intercellular communication. TME cell reprogramming can regulate cell differentiation, proliferation, and function. Moreover, reprogramming the intercellular communication of TME cells can optimize immune infiltration and the specific recognition of tumor cells by immune cells. Thus, gene editing will pave the way for further breakthroughs in precision cancer therapy.

Keywords: Gene editing, TME, Precision cancer therapy, Reprogramming TME cells, Reprogramming cell-cell communication

Introduction

The cellular environment in which tumor cells reside is called the tumor microenvironment (TME). It consists of immune cells, fibroblasts, endothelial cells and mesenchymal cells [1]. The TME allows tumor cells to escape host immunity and is involved in cancer development and metastasis. Recent studies have shown that the TME varies among individuals and is strongly associated with clinical prognosis [2, 3]. Therefore, TME reprogramming is becoming an essential strategy for cancer treatment (Fig. 1).

The understanding of TME reprogramming was previously restricted due to technological limitations. Researches in this field have rapidly increased with recent advances in gene editing technologies. Currently, it is possible to individualize cancer therapy by reprogramming different cells in the TME, and some of these strategies have already been used in the clinic. This personalized approach represents one of the most attractive and promising strategies for cancer therapy in the future. However, systematic reviews on the role of gene editing in TME reprogramming are scarce. Herein, we summarize the recent advances in TME reprogramming based

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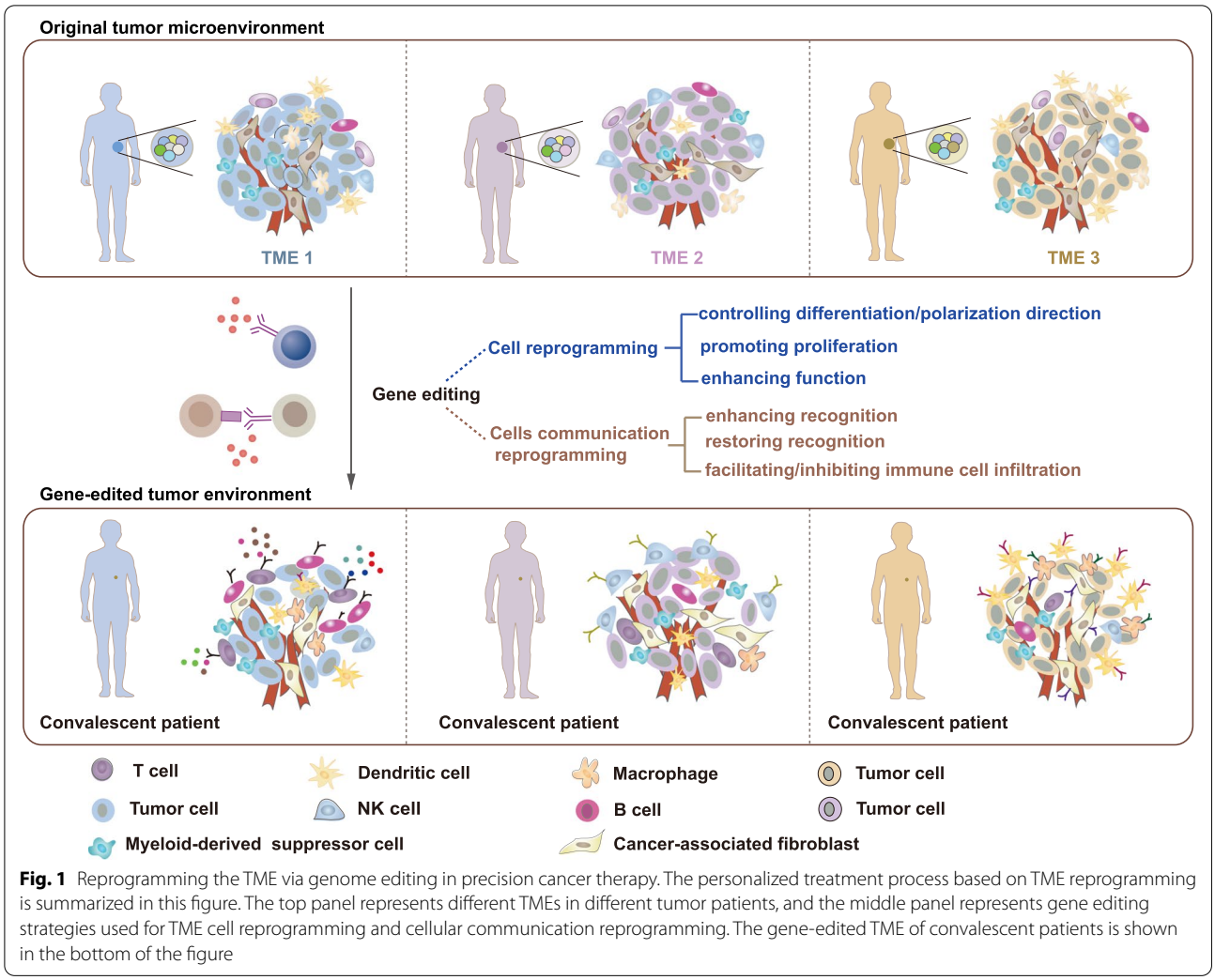

Fig. 1 Reprogramming the TME via genome editing in precision cancer therapy. The personalized treatment process based on TME reprogramming is summarized in this figure. The top panel represents different TMEs in different tumor patients, and the middle panel represents gene editing strategies used for TME cell reprogramming and cellular communication reprogramming. The gene-edited TME of convalescent patients is shown in the bottom of the figure

on the application of gene editing to affect TME cells and their communication.

Gene editing technologies

In 1952, Salvador Luria discovered the DNA restriction-modification system of bacteria. Based on this discovery, researchers have created a series of technologies to modify genes, including gene targeting and RNA interference. After more than half a century of perfecting and improving these approaches, gene editing technologies have become increasingly mature. Currently, there are four main types of gene editing technologies: Meganucleases (MegaNs), Zinc finger nucleases (ZFNs), Transcription activator-like effector nucleases (TALENs), and Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated proteins (Cas) systems (Fig. 2, Table 1).

MegaNs splice DNA at specific recognition sites that naturally and occasionally occur in any genome. MegaNs have often been used to edit genes in crop or animal cells but rarely those in human cells [4]. ZFNs are artificially engineered endonucleases that consist of a DNA recognition domain and the nonspecific endonuclease FokI [5]. The former is responsible for identifying the base sequence of DNA-specific sites, and the latter performs the splicing function. ZFNs have been used to edit tumor and immune cells to optimize precision cancer therapy [6]. Similar to ZFNs, TALENs contain a recognition domain that is composed of highly conserved repeats derived from transcription activator-like effectors (TALEs) [7]. This customizable DNA-binding domain guides the FokI enzyme to trim sequences in the specified site. A repeat can recognize only one nucleotide, which makes the editing performed by TALENs more flexible and specific [8]. T cells engineered with TALENs enhance the antitumor efficacy of adoptive immunotherapy [9]. TALENs have also been applied to edit the genome of human

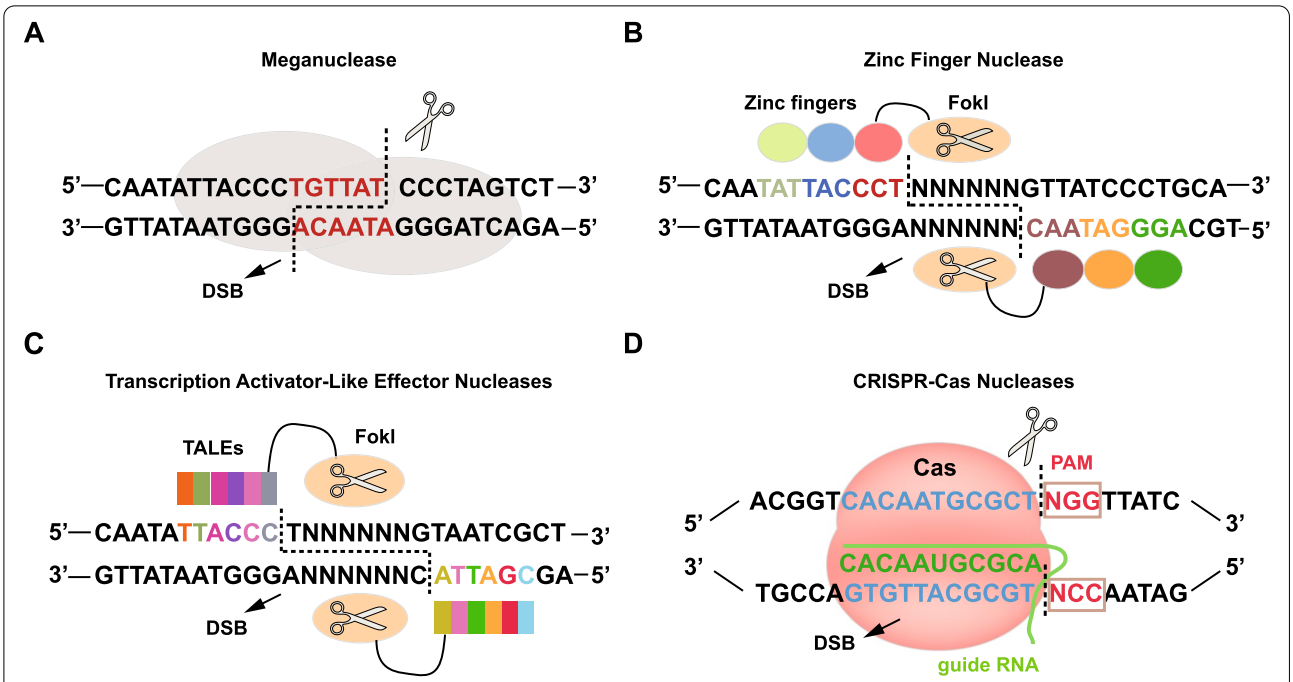

Fig. 2 Gene editing technologies. Editing principles of the four technologies. **A** Meganucleases, **B** Zinc Finger Nucleases, **C** Transcription Activator-Like Effector Nucleases, **D** CRISPR-Cas Nucleases. DSB: DNA double-strand break; PAM: protospacer adjacent motif

Table 1 Comparison of MegaNs, ZFNs, TALENs and CRISPR-Cas systems

	MegaNs	ZFNs	TALENs	CRISPR-Cas systems
DNA recognition domain	Homing endonucleases (binding domain)	Zinc finger protein	a series of repeats of transcription activator-like effector proteins	Single-strand guide RNA
DNA cleavage domain	Homing endonucleases (cleaving domain)	*FokI* endonuclease	*FokI* endonuclease	Cas protein
Target sequence size	14–40 bp	18–36 bp	28–40 bp	20 bp gRNA sequence and PAM sequence
Mechanism of target specificity	Naturally occurring	One zinc finger protein recognizes three nucleotides	One repeat of transcription activator-like effector proteins recognizes one nucleotide	sgRNA imparts targeting specificity through DNA-RNA complementarity
Advantages	High specificity Easy to deliver in vivo	Moderately specificity Easy to deliver in vivo	High specificity Relatively easy to engineer	High specificity Easy to engineer
Disadvantages	Hard to engineer	Hard to engineer	Relatively hard to deliver	Limited in vivo delivery

induced pluripotent stem cells (iPSCs), making these cells differentiate into immune cells with potential antitumor activity [10]. The emergence of the CRISPR/Cas system produced a revolution in gene editing technology. CRISPR/Cas is an acquired immune system in bacteria that is used to fight invading DNA, plasmids, and phages [11]. The CRISPR/Cas system consists of CRISPR-derived RNA (crRNA) and Cas proteins. crRNA directs the Cas proteins to a specific location, while the Cas proteins are responsible for splicing DNA [12, 13]. The CRISPR/Cas system, the fastest growing editing technology in recent years, can also be used to eliminate tumors by editing target genes in TME cells. Currently, the leading gene editing technologies used to reprogram the TME are TALENs and the CRISPR/Cas system. The effectiveness and safety of gene editing technologies in cancer treatment have been established in several clinical trials [14, 15].

Cell reprogramming

Cells in the TME can be categorized into immune and nonimmune cells. Both are important for the development of tumors and can be reprogrammed. Different gene editing strategies should be selected based on cell function and characteristics. In general, gene editing can be performed to eliminate tumors based on three aspects: controlling the direction of naive cell differentiation/polarization, promoting proliferation, and enhancing the function of effector cells (Fig. 3, Table 2).

Immune cells

Immune cells are the primary effectors involved in eliminating tumor cells. The primary target cells for gene editing in the TME are T cells, natural killer (NK) cells, and macrophages.

$CD8^+$ T cells

T cells coordinate multiple aspects of adaptive immunity throughout life, including responses to pathogens, allergens, and tumors. They are classified as $CD8^+$ and $CD4^+$ T cells based on their expression of CD8 or CD4 molecules, respectively. $CD8^+$ T cells are the main subset that directly kill tumor cells in the TME. Their infiltration is correlated with prognosis in several solid tumors [161, 162]. However, long-term antigenic stimulation in the TME causes $CD8^+$ T cells to be unable to proliferate effectively and function persistently, preventing them from killing tumor cells [163]. Therefore, gene editing strategies aim to restore or enhance these two aspects of $CD8^+$ T cells in the TME.

$CD8^+$ T-cell proliferation is mainly stimulated by cytokines. Therefore, cytokine receptors on the cell surface are primary targets for gene editing. Cytokine receptors can be divided into two categories: those expressed in a variety of cells and those expressed in specific cells. Interleukin (IL)-2 was the first essential cytokine identified to maintain the survival and growth of T cells in vitro [164]. It has been used as a clinical cancer therapy. However, the pleiotropic properties of IL-2 cause severe toxicity due to the low specificity of IL-2 receptor (IL-2R) [164–168]. IL-2Rα on $CD8^+$ T cells can be edited to bind to mutant IL-2 precisely [169]. Thus, intraperitoneal injection of mutant IL-2 was shown to specifically promote the proliferation of gene-edited $CD8^+$ T cells in mice. This approach reprograms $CD8^+$ T cells to be specifically stimulated to proliferate. Increasing IL-2 accumulation in the TME via fusion of IL-2 with tumor-targeting molecules is another way to explicitly promote $CD8^+$ T-cell proliferation and reduce toxic side effects [170]. The second category of receptors can be artificially expressed in effector $CD8^+$ T cells to promote cell proliferation specifically. For example, effector $CD8^+$ T cells can be artificially engineered to express IL-7Rα. These reprogrammed cells can proliferate effectively in response to IL-7 stimulation both in vivo and in vitro, even in the presence of regulatory T cells (Tregs) [171]. Compared with IL-2-based approaches, these strategies can precisely promote the proliferation of effector $CD8^+$ T cells and reduce cytokine-induced side effects by taking advantage of receptor specificity. In addition to IL-7, IL-15 and IL-21 specifically promote memory cell proliferation and are also candidates for gene editing [172, 173].

The ability of $CD8^+$ T cells to persistently function is mainly limited by T-cell exhaustion due to prolonged antigenic stimulation. Exhausted $CD8^+$ T cells are characterized by the loss of effector functions resulting from the upregulation of inhibitory receptors, such as programmed cell death 1 (PD-1), hepatitis A virus cellular receptor 2 (TIM-3), lymphocyte activating 3 (LAG-3), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and other immune checkpoints [171, 174]. Gene editing can reprogram $CD8^+$ T cells to maintain function in two ways: inhibiting exhaustion development and restoring or enhancing exhausted cell function. The development of exhaustion in $CD8^+$ T cells is regulated by several transcription factors, including T-bet, Eomes, Blimp1, NFAT, BATF, VHL, FOXO1, FOXP1, TCF1, nuclear receptor subfamily 4 group A (NR4A), IRF4, and thymocyte selection-associated high mobility group box (TOX) [47, 48, 175–177]. Altering the expression of these factors can reduce $CD8^+$ T-cell exhaustion [178, 179]. For example, TOX is a recently identified vital transcription factor that promotes $CD8^+$ T-cell exhaustion. It functions in cooperation with NR4A [176]. $CD8^+$ T cells from mice with TOX or NR4A knocked out were transplanted into tumor-bearing mice and showed reduced exhaustion [49, 180]. Controlling the expression of transcription factors via gene editing allows $CD8^+$ T cells to remain functional and effectively destroy tumor cells. On the other hand, gene editing can be used to restore exhausted $CD8^+$ T-cell functions by eliminating inhibitory receptors or reversing inhibitory receptor signaling. The most widely studied inhibitory receptor is PD-1. Knocking out PD-1 in $CD8^+$ T cells with the CRISPR/Cas9 system was demonstrated to have antitumor effects in several preclinical and clinical studies, including studies on cancers including melanoma, glioblastoma, ovarian cancer, prostate cancer, B-cell lymphoma, gastric cancer, and breast cancer [181–189]. In addition, gene editing can be used to reverse inhibitory signaling. CD28 is a founding member of the costimulatory molecule subfamily and plays a role in amplifying TCR signaling [190]. Fusing PD-1 expressed by $CD8^+$ T cells to CD28 via CRISPR/Cas9

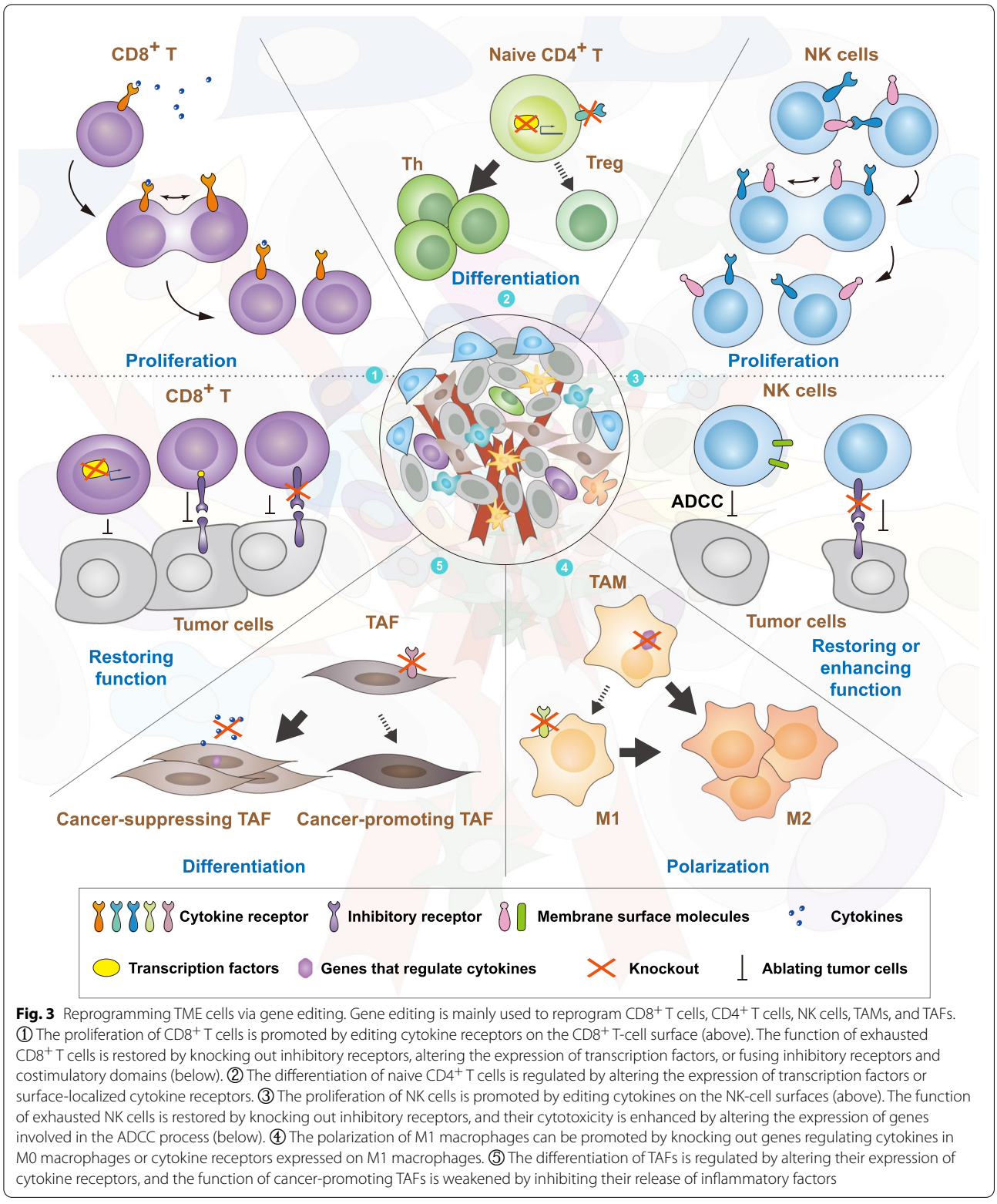

Fig. 3 Reprogramming TME cells via gene editing. Gene editing is mainly used to reprogram $CD8^+$ T cells, $CD4^+$ T cells, NK cells, TAMs, and TAFs. ① The proliferation of $CD8^+$ T cells is promoted by editing cytokine receptors on the $CD8^+$ T-cell surface (above). The function of exhausted $CD8^+$ T cells is restored by knocking out inhibitory receptors, altering the expression of transcription factors, or fusing inhibitory receptors and costimulatory domains (below). ② The differentiation of naive $CD4^+$ T cells is regulated by altering the expression of transcription factors or surface-localized cytokine receptors. ③ The proliferation of NK cells is promoted by editing cytokines on the NK-cell surfaces (above). The function of exhausted NK cells is restored by knocking out inhibitory receptors, and their cytotoxicity is enhanced by altering the expression of genes involved in the ADCC process (below). ④ The polarization of M1 macrophages can be promoted by knocking out genes regulating cytokines in M0 macrophages or cytokine receptors expressed on M1 macrophages. ⑤ The differentiation of TAFs is regulated by altering their expression of cytokine receptors, and the function of cancer-promoting TAFs is weakened by inhibiting their release of inflammatory factors

Table 2 Potential edited genes that regulate cells proliferation, differentiation or function in TME

Cell type	Function	Gene	Reference
CD8$^+$T cell	Promote proliferation	IL-2Rα, IL-2Rβ, IL-4Rα, IL-7Rα, IL-10Rα, IL-10Rβ, IL-12R, IL-15Rα, GITR, HDAC1, NFAT1, NR4A1, SLAT, SUMO2, TL1A, DOCK8, TIS21, STAT6, TNFRSF4, TNFRSF8, TNFRSF9, TNFRSF25, CD25, CD4, CD62L, CD27, CD70	[16–37]
	Inhibit proliferation	FOXP1, FOXO3, JNK2, VDR, IL-10R2, PD-1, TIM-3, CD38, CD160	[38–46]
	Inhibit function	PD-1, TIM-3, LAG-3, CTLA-4, TIGIT, T-bet, BLIMP1, NFAT, BATF, VHL, FOXO1, FOXP1, SLAMF6, TCF1, NR4A1, TOX, FGL1, B7H3, CD73, CD39, CD244, CD160	[47–65]
CD4$^+$T cell	Control differentiation	IL2Rα, IL-4R, IL-6R, IL-10R, IL-12R, IL-13R, IL-21R, IL-23R, IL-25R, STAT1, STAT4, STAT6, GATA3, PPARG, IKZF2, CXCR5, FOXO1, FOXP3, CD8α, CD103, USP22, BRD9, RNF20, IRF4, CIC, PRDM1, TBX21, SATB1, HIVEP2, HDAC6, BCL6	[66–86]
NK cell	Promote proliferation	IL-2, IL-4, IL-12, IL-10, IL-15, IL-18, IL-21, IL-15Rα, CD16A, KLF2, TNFRSF4	[87–97]
	Inhibit proliferation	CD2	[98]
	Enhance toxicity effect	NKG2D, TNFRSF9, GRAIL, CD16, CD244, NTB-A, CS1, SCF	[99–104]
	Inhibit function	LAG-3, PD-1, TIM-3, TIGIT, KLRG1, KIR, NKG2A, CD96	[105–109]
TAF	Activate	IL-1R1, FGFR, GPER, TGFR, TNFR, GFs, VDR, NF-κB, JAK, STAT3, NLRP3, YAP, TAZ	[110–118]
	Regulate immune microenvironment	TGFβ, CCL2, CCL5, CCL7, CCL16, CXCL1, CXCL2, CXCL8, CXCL12, G-CSF, LIF, IL-6, IL-11, IL-33, NOX4, M-CSF, PGE2	[110, 119–127]
	Promote tumor growth, migration, invasion and epithelial-mesenchymal transformation	HGF, FGF1, PDGF, POSTN, OPN, CTGF, FOXF1, IL-17A, Cav1, FAP, α-SMA, FN1, VEGF, MMPs, MFAP5, ET-1	[122, 128–142]
	Inhibit tumor growth	ISLR, WFDC1	[143, 144]
TAM	Polarize to M1	TLR, DNMT3b, JMJD1A, HDAC3, HDAC9, STAT1, NF-κB, IRF5, Notch signaling, ERK5, MGLL, IRF1, IRF5, IRF8	[145–151]
	Polarize to M2	CSF-1R, CCR2, IL-1R, IL-4R, IL-10, IL-12R, IL-13R, IL-18R, GPR132, PRMT1, SMYD3, JMJD3, SIRT, BET, STAT3, STAT6, MYC, IRF3, IRF4, KLF4, PPARγ, COX-2, PI3Kγ	[146, 148, 152–160]

gene editing reverses the original inhibitory signaling to achieve stimulatory cell signaling. This reprogramming strategy ultimately restores the effector function of exhausted CD8$^+$ T cells [187–189].

CD4$^+$ T cells

Although CD8$^+$ T cells are currently the most studied T cells, a large number of studies have shown that CD4$^+$ T cells also have essential functions in the TME [191]. CD4$^+$ T cells can differentiate into different subtypes. Their roles in the TME are different or even opposite in terms of immunity. CD4$^+$ T helper cells and Tregs are two major subtypes. CD4$^+$ T helper cells help regulate the gene expression profiles of CD8$^+$ T cells to enhance tumor-eliminating effects [192]. In contrast, Tregs act as immune suppressors [193].

Two strategies can be employed to reprogram CD4$^+$ T cells using gene editing: controlling their differentiation into helper cells and inhibiting Treg function. Currently, the genes known to influence the differentiation fate of CD4$^+$ T cells mainly include IL2Rα, PPARG, and IKAROS family zinc finger 2 (IKZF2) [66, 194, 195]. Based on function, different strategies should be used. For example, knocking out the IL2Rα enhancer with CRISPR/Cas9 reprograms CD4$^+$ T cells to differentiate from naive cells into Th17 cells [195]. In contrast, knocking out IKZF2 via CRISPR/Cas9 reprograms human fetal naive CD4$^+$ T cells to differentiate into Tregs [194]. Gene editing could be designed to induce CD4$^+$ T cells to differentiate into cells that promote immune responses.

Furthermore, gene editing has been utilized to reverse the immunosuppressive effects of Tregs [196]. This type of cell is characterized by high expression of forkhead box P3 (FOXP3), which plays a vital role in immunosuppressive functions [197]. Loss of FOXP3 function is associated with autoimmunity in both humans and mice [198]. Knocking out FOXP3 in Tregs via gene editing is beneficial for promoting an immune response in the TME. Therefore, identifying genes upstream of FOXP3 via gene editing technology can help reverse the immunosuppressive phenotype. Several studies have used CRISPR screening to identify upstream regulators of FOXP3, including ubiquitin specific peptidase 22 (Usp22), bromodomain containing 9 (Brd9), and Rnf20 [67, 68]. Knocking out Usp22 and Brd9 was shown to reduce FOXP3 expression and impair the immunosuppressive

function of Tregs in mice. The CRISPR/Cas9 system can be employed in this strategy to reprogram the immunosuppressive effect of Tregs and ultimately inhibit tumor growth. Other FOXP3 regulators identified using the CRISPR library include FOXO1, IRF4, GATA3, CIC, PRDM1, TBX21, SATB1, and HIVEP2 [199]. They provide several targets for Treg reprogramming.

NK cells

NK cells can kill tumor cells directly, showing better safety than $CD8^+$ T cells with minor cytokine release syndrome (CRS) and neurotoxicity [200–202]. The limitations related to the clinical use of NK cells are weak proliferation and cytotoxicity. Given these two points, gene editing can reprogram NK cells to promote their effective proliferation and persistent functionality.

The proliferation of NK cells is mainly regulated by the cytokines IL-2, IL-12, IL-15, IL-21, and IL-18 [203]. Among these cytokines, IL-15 is recognized to have essential roles in cell survival and proliferation. Gene editing can be used to edit IL-15 in NK cells to promote NK-cell proliferation in vivo. NK cells overexpressing IL-15 exhibit both a stronger proliferative ability and potential side effects [204]. Therefore, membrane-bound IL-15 (mbIL-15) was developed. This protein is a fusion protein of IL-15 and the NK-cell CD8α transmembrane structural domains located on the cell membrane [205]. This engineering allowed mbIL-15 to stimulate adjacent NK cells without inducing the side effects caused by free cytokines. This strategy has the potential to maintain NK-cell proliferation.

The toxic effect of NK cells can be enhanced by promoting their toxic effects or restoring the toxic effects of inhibitory cells. NK92 cells are an NK cell line with an indefinite proliferative ability that are widely used in clinical trials [206, 207]. However, they exhibit lower toxicity to tumor cells than primary NK cells, which has limited their development. Gene editing can be used to overcome this challenge. Antibody-dependent cell-mediated cytotoxicity (ADCC) is one of the most critical mechanisms by which NK cells kill tumor cells. CD16 expressed on NK cells recognizes the Fc portion of IgG bound to the tumor cell surface and eliminates tumor cells through ADCC [207]. Therefore, CRISPR/Cas9 can be used to reprogram NK cells to improve the ADCC effect by overexpressing CD16 [208]. On the other hand, the function of NK cells is limited by the activation of inhibitory receptors. Knocking out these receptors via gene editing can restore cell function. The primary identified inhibitory receptors of NK cells are LAG-3, PD-1, TIM3, and TIGIT [209]. TIGIT is a newly identified shared inhibitory receptor in exhausted $CD8^+$ T and NK cells. Moreover, TIGIT but not CTLA-4 or PD-1 is associated with NK-cell exhaustion in tumor-bearing mice and colon cancer patients [105]. CRISPR/Cas9 has been used to specifically knock out TIGIT in mouse NK cells. The results showed that these cells exhibited restored cytotoxicity and killing ability specific for tumor cells [105]. Similar to TIGIT, other inhibitory receptors on NK cells can be knocked out to restore the tumor-killing function of these cells.

Tumor-associated macrophages (TAMs)

TAMs are macrophages in the TME. They are a double-edged sword for tumor cells. Cytokines can polarize TAMs into M1 or M2 macrophages that exhibit anticancer or procancer functions, respectively. There are two strategies to reprogram TAMs via gene editing: polarizing them into M1 macrophages and promoting M2 macrophage death. TAM polarization into M1 macrophages is mainly regulated by the cytokines IL-9, IL-27, and IL-12 [210–212]. Upregulation of these cytokines by gene editing promotes M1 macrophage polarization. It was reported that high expression of IL-12 in TAMs results in a more than four-fold increase in the M1/M2 macrophage ratio [212]. In addition, regulating upstream signaling pathways of IL-2, including the signal transducer and activator of transcription 3 (STAT3)/NF-Kappab/C-REL and inhibitor of nuclear factor-kappa B kinase subunit beta (IKKβ)/NF-Kappab signaling pathways, can also affect the TAM polarization direction. Knocking out STAT3 or IKKβ in TAMs via gene editing was shown to induce M1 macrophage polarization and effectively inhibit tumor growth in mice [213, 214]. TAM polarization into M2 macrophages is mainly related to the activation of colony-stimulating receptor (CSF1R) and C-C motif chemokine receptor 2 (CCR2) on the cell surface. Knocking out CSF1R repolarizes M2 macrophages into M1 macrophages and enhances phagocytic activity [215]. Current phase I and II clinical trials of drug therapies targeting CSF1R in giant cell tumors have yielded promising results [216]. However, serious side effects were observed in patients. Blocking the CCL2/CCR2 signaling pathway via gene editing results in TAM polarization into M1 macrophages and promotes antitumor immune responses in various mouse models, including lung, esophageal, and liver cancer models [217–219].

Nonimmune cells

Nonimmune cells in the TME are culprits in tumorigenesis, providing nutrition and energy for tumor cells. There are many nonimmune cells in the TME, including tumor-associated fibroblasts (TAFs), endothelial cells, mesenchymal stem cells, and adipocytes. Currently, gene editing is mainly used to reprogram TAFs, which are the main focus of our discussion.

TAFs

TAFs are significant components of the TME cell population in solid tumors [220, 221]. They are heterogeneous and act as either the foundation or walls of tumors. Depending on their roles in tumors, they can be classified into cancer-promoting TAFs and cancer-suppressing TAFs [222, 223]. The former promotes tumor progression dependent on IL-1R activation and the subsequent release of inflammatory factors, including TSLP, IL-6, and CXCL12 [223]. The latter may inhibit tumor progression by remodeling the collagen structure [143]. Therefore, gene editing can reprogram TAFs to inhibit tumor progression by inhibiting the function of cancer-promoting TAFs or enhancing the function of cancer-suppressing TAFs.

For cancer-promoting TAFs, gene editing aims to inhibit their activation. IL1/IL-1R is essential for activating cancer-promoting TAFs and promotes the release of proinflammatory factors via the activation of the JAK/STAT3, PI3KCA/AKT, and NF-κB signaling pathways [224–226]. Therefore, gene editing can reprogram TAFs by blocking IL-1R activation and reducing the secretion of inflammatory factors. In a study, fibroblasts with or without IL-1R1 knocked out and breast cancer cells were coimplanted into the lateral abdomen of BALB/c mice. Compared with the WT fibroblast group, the $Il1r1^{-/-}$ fibroblast group showed inhibition of tumor cell growth following coimplantation [225]. In addition, TAFs have been shown to have a reduced proinflammatory phenotype when the downstream IL1/IL-1R pathway (JAK/STAT3 and PI3KCA/AKT) is inhibited.

For cancer-suppressing TAFs, gene editing can alter the expression of genes to increase their tumor-suppressive ability. Cancer-suppressing TAFs have been poorly studied. To date, it has been found that TAFs expressing immunoglobulin superfamily containing leucine rich repeat (ISLR) or Caveolin-1 (CAV-1) can inhibit tumor progression [143, 227]. ISLR was the first identified marker of cancer-suppressing TAFs in human and mouse pancreatic ductal carcinoma (PDAC). High expression of ISLR in TAFs correlates with a good patient prognosis [143]. Ablation of TAFs expressing ISLR in mouse models leads to malignant progression, while exogenous expression of ISLR inhibits tumor progression. ISLR is a potential therapeutic target for reprogramming TAFs for cancer therapy. The mechanism of tumor growth inhibition mediated by CAV-1-expressing fibroblasts is unclear. The functional mechanism of tumor-suppressive TAFs needs to be further studied.

Other cells

In addition, gene editing can also reprogram other cells, such as B cells and dendritic cells (DCs). B cells produce membrane-bound or secretory immunoglobulins in lymphoid tissues or plasma. At present, researchers mainly use gene editing to induce B cells to express antibodies [228, 229]. Since tumor cells often evade host immunity by expressing inhibitory receptors, gene editing can reprogram B cells to express monoclonal antibodies. This is a potential approach for cancer treatment, as these antibodies can competitively bind to inhibitory receptors. DCs are special antigen-presenting cells, and their costimulatory signaling molecule CD40 is critical in regulating T-cell activation and promoting graft rejection. Knocking out CD40 in DCs via CRISPR/Cas9 prevents transplant rejection, which is one of the barriers to adoptive therapy for cancers [230]. Many other cell types have not been thoroughly studied. They are also potential target cells for gene editing.

Reprogramming cell–cell communication

Complex intercellular communication among TME cells provides inhibitory or stimulatory signals that influence tumor cell fate [231]. Therefore, the effectiveness of tumor cell killing by immune cells is determined by the intrinsic properties of both cell types and is intimately associated with intercellular communication. Gene editing provides a flexible and safe tool to reprogram TME intercellular communication for cancer therapy (Fig. 4). It is becoming a focus in tumor immunotherapy.

Immune cell–tumor cell communication

T cells and tumor cells

Intercellular communication between T cells and tumor cells is the most studied type of intercellular communication. It includes adjacent cell–cell communication through recognition between receptors and ligands on the cell surface and distant communication through secreted mediators (cytokines, chemokines, adhesion molecules, and exosomes). At present, gene editing is more widely used to modulate the former. The Food and Drug Administration (FDA) has approved genetically modified T cells as drugs for the treatment of tumors, including tisagenlecleucel (Tisa-cel), axicabtagene ciloleucel (Axi-cel), lisocabtagene maraleucel (Liso-cel), and brexucabtagene autoleucel (Brexu-cel) [232–234]. This section will introduce how gene editing is used to reprogram cell–cell communication to eliminate tumors.

Adjacent communication Adjacent cell–cell communication is dependent on physically adjacent structures or ligand–receptor interactions. The latter can

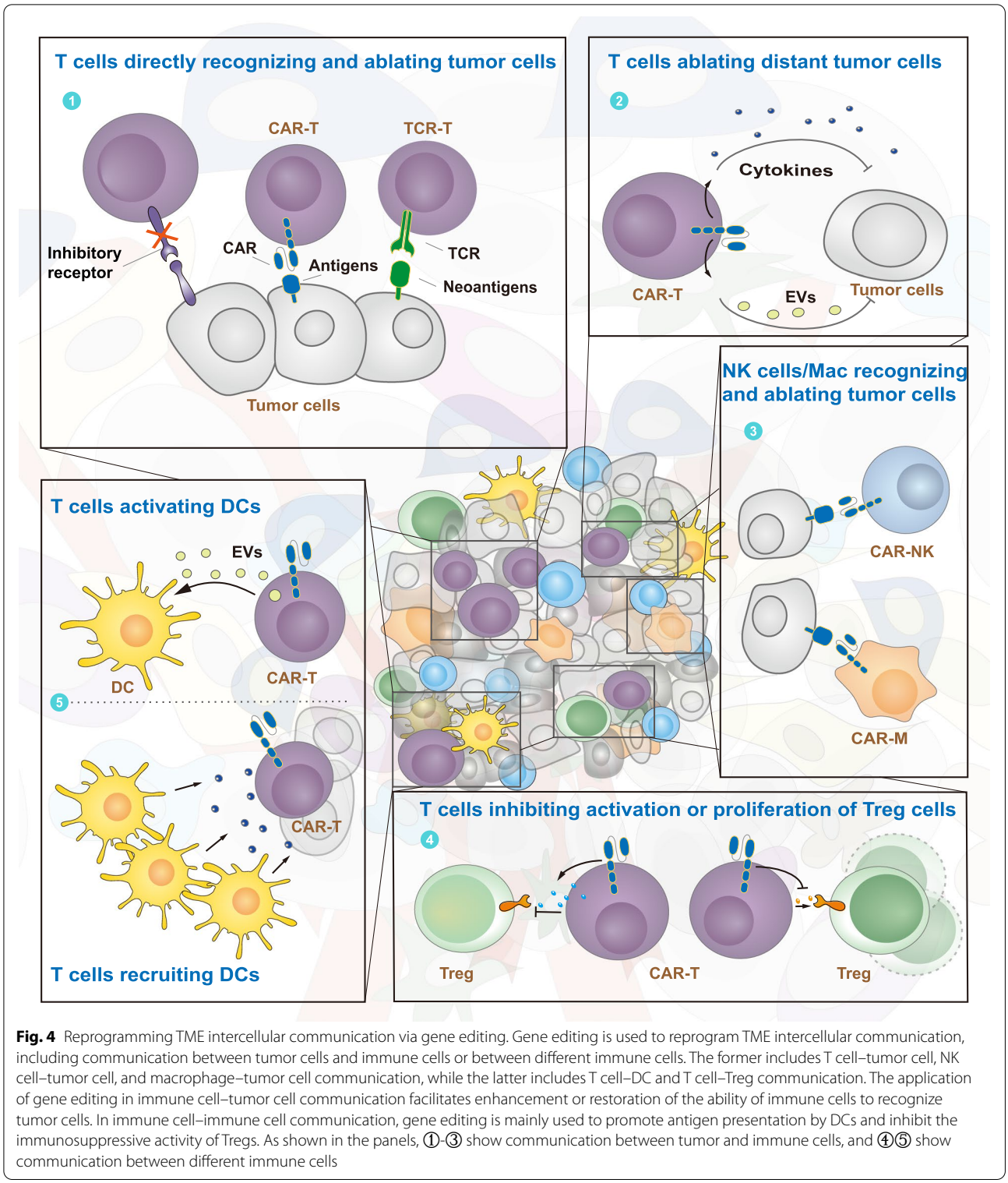

Fig. 4 Reprogramming TME intercellular communication via gene editing. Gene editing is used to reprogram TME intercellular communication, including communication between tumor cells and immune cells or between different immune cells. The former includes T cell–tumor cell, NK cell–tumor cell, and macrophage–tumor cell communication, while the latter includes T cell–DC and T cell–Treg communication. The application of gene editing in immune cell–tumor cell communication facilitates enhancement or restoration of the ability of immune cells to recognize tumor cells. In immune cell–immune cell communication, gene editing is mainly used to promote antigen presentation by DCs and inhibit the immunosuppressive activity of Tregs. As shown in the panels, ①-③ show communication between tumor and immune cells, and ④⑤ show communication between different immune cells

be reprogrammed by gene editing. Currently, the most effective and promising application in this area is adoptive T-cell therapy (ACT) [232, 235]. ACT refers to isolating T cells from a patient, equipping the T cells with modified antigen recognition receptors via gene editing, and reinfusing them into the patient's body after expansion. According to the autologous or allogenic modified antigen recognition receptor introduced, T cells utilized

for ACT can be divided into chimeric antigen receptor T (CAR-T) cells and recombinant T-cell receptor T (TCR-T) cells [236].

CAR-T cells are designed to recognize cancer cells that escape surveillance by unmodified T cells. They bind to specific antigens on the tumor cell surface; secrete the cytokines IL-12, IL-15, and IL-18; and then recognize and eliminate tumor cells [237]. The CAR consists of extracellular recognition, transmembrane, and intracellular signaling domains. Modifying the CAR extracellular domain via gene editing enables T cells to recognize antigens on tumor cells. Cancer cells in tissues are highly heterogeneous. The antigens on the cell surface may differ, or several antigens may be expressed simultaneously. The elasticity of gene editing makes the antigen recognition mode of CAR-T cells flexible, thus promoting clinical application. The main target antigens and applied tumor types for CAR-T cells are shown in Table 3. Among these antigens, CD19 is the most important and studied. It is evenly distributed in malignant B cells and considered a prime target for T-cell recognition [238]. Gene-edited CAR-T cells targeting CD19 can identify and eliminate tumor cells [239]. Compared with single antigen-recognition, multiple-antigen recognition increases the affinity of CAR-T cells for tumor cells. These CAR-T cells can recognize tumor cells expressing various antigens individually or simultaneously. Gene editing has supported the generation of second-, third-, and fourth-generation CAR-T cells. In addition to CD19, CD22 is widely distributed on the B-cell surface in most cases of B-cell acute lymphoblastic leukemia (B-ALL) [240]. These antigens can exist on the same or different tumor cell surfaces. A tandem CAR was developed and introduced to T cells to target these two antigens. CD19-CD22 CAR-T cells exhibited better tumor elimination than CD19 CAR-T cells in patient-derived xenograft (PDX) models [241]. Compared with previous approaches, CAR recognition of three antigens has further improved the recognition ability and affinity. A typical example is as follows. Human epidermal growth factor receptor 2 (HER2), interleukin-13 receptor subunit alpha-2 (IL13Rα2), and ephrin-A2 (EphA2) are specifically expressed on the surface of glioblastoma, recurrent medulloblastoma, and ependymoma cells [242]. CAR-T cells targeting these three antigens can recognize and eliminate tumor cells in PDX mouse models [242, 243].

TCR-T cells are cells with a modified endogenous TCR antigen recognition domain designed to enhance the recognition of tumor cells by T cells [15]. They have been mainly used to recognize the mutation-derived neoantigens of cancer cells. TCR-T cells recognize specific antigens presented in linear 8–11 amino acid peptides presented by MHC class I. Thus, TCR-T cells can recognize peptides derived from an entire cell, including the cell surface, cytoplasm, and nucleus. Gene editing can be used to modify the endogenous TCR antigen recognition domain to recognize a mutant peptide derived from a neoantigen. Currently, nearly 200 clinical trials are evaluating the safety or effectiveness of TCR-T cell therapy. The most commonly targeted and promising cancer cell antigen is NY-ESO-1. NY-ESO-1^{c259}-specific TCR-T cells were produced with the goals of recognizing and eliminating antigen-positive tumor cells [15, 336]. TCR-T cell treatment has shown a relatively good clinical effect. Twelve recurrent or metastatic synovial sarcoma patients received NY-ESO-1^{c259} TCR-T cell treatment, tumors shrank significantly in half of the patients, and no fatal severe adverse events occurred [337]. Similarly, TCR-T cells recognizing the $MyD88^{L265P}$ mutation can target tumor cells carrying this mutation in B-cell malignancies [338]. In addition to cytoplasmic antigens, membrane antigens can be recognized by TCR-T cells. The most studied antigen is mesothelin (MSLN). Compared with TCR-T cells targeting other epitopes, TCR-T cells specifically targeting $Msln^{406–414}$ epitopes show relatively high affinity for tumor cells in pancreatic ductal adenocarcinomas (PDAs).

During ACT treatment, a considerable amount of tumor tolerance is observed. Immune escape mediated by immune checkpoints is recognized as one of the main reasons. To promote immune escape, immune checkpoint molecules expressed on the tumor cell membrane bind to paired receptors on the surface of immune cells. Knocking out immune checkpoint molecules in CAR-T and TCR-T cells with CRISPR/Cas9 technology allows these cells to recognize escaped tumor cells and restores intrinsic recognition. Compared with immune checkpoint inhibitors, gene editing targets specific immune cells and does not require systemic immune blockade or induce immune-related side effects [339]. In addition, according to the individual differences among patients, gene editing can knock out one or multiple immune checkpoint genes to achieve personalized immunotherapy. PD-1 and CTLA4 are the most studied checkpoint molecules. In a refractory pan-cancer dataset, knocking out PD-1 improved the recognition of tumor cells by NY-ESO-1^{c259} TCR-T cells [15]. Similarly, in CD19 CAR-T cells, PD-1 knockout significantly improved the recognition of tumor cells in refractory non-small cell lung cancer, lymphoma, and chronic myelogenous leukemia [14]. In acute lymphoblastic leukemia (ALL) and bladder cancer, knocking out CTLA-4 augmented recognition by T

Table 3 Targeted antigens of CAR-T cells, CAR-NK cells and CAR-Ms in cancers

Cell Type	Target antigen	Application	Reference
CD8+ T cell	CD19	Acute Lymphoblastic Leukaemia, Multiple Myeloma, B-Cell Lymphoma	[244–247]
	CD20	Melanoma, Diffuse Large B-Cell Lymphoma, Non-Hodgkin Lymphoma, Burkitt Lymphoma	[247–251]
	CD22	B Acute Lymphoblastic Leukemia, Burkitt Lymphoma	[251, 252]
	CD30	Hodgkin's Lymphoma	[253]
	CD33	Acute Myeloid Leukemia	[254]
	CD56	Rhabdomyosarcoma	[255]
	CD70	Renal Carcinoma, B-Cell Lymphoma	[256–258]
	CD133	Cholangiocarcinoma, Hepatocellular Carcinoma, Pancreatic Carcinomas, Colorectal Carcinomas	[259, 260]
	CD138	Multiple Myeloma	[261]
	CD171	Neuroblastoma	[262]
	HER2	Biliary Tract Cancer, Pancreatic Cancers	[263]
	EGFR	Non-Small Cell Lung Cancer, Cholangiocarcinoma, Biliary Tract Cancers, Pancreatic Carcinoma	[259, 264–266]
	MSLN	Gastric Cancer, Pancreatic Cancer, Pleural Mesothelioma, Ovarian Carcinoma, Biliary Tract Cancer, Tubal Cancer, Esophageal Cancer, Cervical Cancer, Triple-Negative Breast Cancer	[189, 267–270]
	LMP1	Lymphoma, Nasopharyngeal Carcinoma	[271, 272]
	FR-α	Ovarian Carcinoma, Colorectal Carcinomas, Pancreatic Cancer, Lung Cancer	[273]
	EGFRIII	Glioblastoma	[274, 275]
	GPC3	Hepatocellular Carcinoma, Pancreatic Carcinoma, Ovarian Carcinoma	[276, 277]
	PSCA	Chronic Myelogenous Leukemia, Gastric Cancer	[278, 279]
	MUC1	Lung Cancer, Seminal Vesicle Cancer,	[280, 281]
	MAGE-A1/3/4	Lung Adenocarcinoma	[282]
	EPCAM	Chronic Myelogenous Leukemia, Breast Cancer, Lung Cancer, Acute Myeloid Leukemia, Colorectal Cancer	[283–286]
	PSMA	Prostate Cancer	[287]
	AXL	Breast Cancer	[288]
	MUC16	Ovarian Cancer	[289]
	DR5	B-Cell Malignancies	[290]
	c-MET	Hepatocellular Carcinoma, Gastric Cancer, Renal Cell Carcinoma	[291–293]
	BCMA	Multiple Myeloma	[294–296]
	GPC3	Hepatocellular Carcinoma	[297]
	CS1/SLAMF7	Multiple Myeloma,	[298]
	NKG2D	Hepatocellular Carcinoma, Glioblastoma	[299, 300]
	CLL-1	Acute Myeloid Leukemia	[301, 302]
	CEA	Colorectal Cancers, Pancreatic Malignancy, Hepatocellular Carcinoma	[270, 303, 304]

Table 3 (continued)

Cell Type	Target antigen	Application	Reference
NK cell	CD5	T Cell Malignancies	[305]
	CD7	Lymphoma, Leukemia	[306]
	CD19	Acute Lymphoblastic Leukaemia, Chronic Lymphocytic Leukemia, B Lymphoblastoid, Monocytic Leukemia, Ovarian Cancer, Chronic Myelocytic Leukemia, Breast Cancer, Lung Cancer, Gastric Cancer, Epidermoid Carcinoma, Bladder Cancer	[201, 307, 308] [309–311]
	CD20	B-Cell Malignancies, Burkitt Lymphoma	[312, 313]
	CD33	Acute Myeloid Leukemia.	[314]
	CD38	Acute Myeloid Leukemia.	[315]
	CD123	Acute Myeloid Leukemia, Blastic Plasmacytoid Dendritic Cell Neoplasm	[316–318]
	CD138	Multiple Myeloma	[319]
	CS1	Ovarian Cancer, Multiple Myeloma	[320, 321]
	EBNA3C	Leukemia	[322]
	EGFRvIII	Glioblastoma	[323]
	EPCAM	Breast Carcinoma	[324]
	GD2	Neuroblastoma, Ewing Sarcomas,	[325, 326]
	GPA7	Melanoma	[327]
	GPC3	Ovarian Cancer	[328]
	HER-2	Glioblastoma, Breast Cancer, Renal Cell Carcinoma	[329–331]
	HLA-A2	Melanoma	[327]
	HLA-DR	Glioblastoma	[332]
	HLA-G	Leukemia	[333]
	MSLN	Ovarian Cancer	[334]
	PSCA	Ladder Carcinoma	[335]
Macrophage	HER2	Chronic Myelocytic Leukemia	[309]
	MSLN	Chronic Myelocytic Leukemia	[309]

cells. In addition, gene editing can simultaneously inhibit the expression of multiple immune checkpoint molecules via knock out of mutual regulators. For example, nuclear factor of activated T cells (NFAT) is a key transcription factor regulating T-cell activation [340]. It increases the expression of multiple inhibitory receptors, including PD1, LAG3, TIM-3, and GITR, on the cell surface. Knocking out NFAT using gene editing was shown to significantly inhibit the expression of these inhibitory receptors in vivo [50].

Distant communication Distant T cells and tumor cells can communicate through mediators, including cytokines, chemokines, adhesion molecules, and extracellular vesicles (EVs). These factors can also be reprogrammed. However, gene editing strategies targeting these factors are still in the preclinical phase. Among them, the most studied target is EVs. EVs are nanoscale vesicles secreted by almost all cells and contain bioactive molecules. They transmit information from donor to recipient cells and participate in physiological and pathological processes. In recent years, they have been found to regulate the TME and affect immune cell functions [341, 342].

Gene editing can be used to edit cells to produce attractive substrates that can be delivered by EVs and enhance EV targeting. Gene editing can be used to add genes encoding CAR-targeting antigens to traditional CAR molecules, allowing CAR-T cells to express such antigens. These antigens are then packaged into EVs and delivered to tumor cells. Specifically, the EVs localize at the tumor cell membrane and deliver antigens to the tumor cells. Then, the target tumor cells develop increased antigen expression on the cell surface. In this way, CAR-T cells can recognize tumor cells without expression or

with low expression of antigens [343]. Gene editing can directly modify EVs derived from T cells so that cargo can be more accurately packaged into the EVs. The tetraspanin CD9 is a marker molecule located on the EV membrane [344]. In T cells, genetic fusion of CD9 with other proteins can better enrich the target molecules in EVs. Then, these molecules can play a role in suppressing tumors after the EVs reach the target cells. For example, fusing CD9 with HuR by gene editing can enrich HuR-binding RNAs in EVs. These RNAs reach target cells in the EVs and kill tumor cells [345]. Similarly, fusing CD9 with PhoCl can achieve light-controlled release of cargo proteins after arrival. Fusion of CD9 with CD70 can successfully localize CD70 on the surface of target cells and thus provide costimulation to T cells [346]. In addition to EVs, other factors secreted by CAR-T cells, such as IL-12, IL-15, and IL-18, play roles in killing tumor cells [347].

NK cells and tumor cells

In the clinic, CAR-T cell treatment is limited by graft-versus-host disease (GVHD) and the long production cycle. Thus, CARs can be introduced into other immune cells as well. Among these cells, NK cells are most commonly used. Compared with T cells, NK cells have a more comprehensive tumor recognition range and more robust antitumor function. The lack of TCR expression by NK cells prevents them from causing GVHD. The assembly of antigen recognition receptors on the surface of NK cells can enable CAR-engineered NK (CAR-NK) cells to recognize tumors more accurately and exert a powerful tumor-killing effect. The development of CAR-NK cells is attracting significant attention.

Gene editing can reprogram NK cells to increase specific recognition and remove inhibitory immune checkpoint molecules on the surface. Most of the CARs that have been introduced into NK cells were designed for CAR-T cells. Working from traditional CAR structures, using gene editing to replace 4-1BB/CD28 with 2B4 (an NK cell-specific costimulatory domain), CARs specifically designed for NK cells can be obtained. The main target antigens and applied tumor types for CAR-NK cells are shown in Table 3. For these antigens, the most studied CARs are those recognizing CD19 and CD5. NK cells equipped with CD19 showed powerful recognition and a strong killing effect against $CD19^+$ relapsed or refractory tumors. Eight patients showed remission among the 11 lymphoid patients who received treatment [201]. Moreover, due to the lack of TCR expression and IL-6 release, patients who received CAR-NK allografts did not develop CAR-T cell-related serious toxic effects, including neurotoxicity, cytokine release syndrome, and GVHD [201]. CD5 is highly expressed in malignant T cells and considered one of the characteristic antigens of malignant T cells [348]. In this case, due to the similarity between normal and malignant T cells, CD5 CAR-T cells may produce fratricide and cause normal T-cell hypoplasia. CD5 CAR-NK cells can be used to accurately recognize $CD5^+$ tumor cells and prolong T-cell acute lymphoblastic leukemia (T-ALL) xenograft mouse survival [305]. Other similar targets include CD20, CD123, GPC3, MSLN, CD38, CD147 and EGFR [312, 315, 349]. Gene editing can modify them to produce the corresponding CAR-NK cells to eliminate tumors. However, CAR-NK cells are still in the preclinical research stage. Inhibitory immune checkpoint molecules, such as PD-1 and TIGIT, are also expressed on the surface of NK cells and inhibit their recognition activity. In colon cancer, by knocking out these inhibitory immune checkpoint molecules, CRISPR/Cas9 technology restores the recognition ability of NK cells and promotes NK cell-dependent antitumor immunity [105].

Macrophages and tumor cells

In most cancers, macrophages are widely distributed in the TME. Compared with other immune cells, macrophages can penetrate tumor tissues more readily. The lack of TCR expression prevents macrophages from causing GVHD. In addition, macrophages perform phagocytosis and antigen presentation and exhibit cytotoxic activity [350]. While the recognition function of macrophages is nonspecific, equipping macrophages with CARs via gene editing can increase their recognition of tumor cells. The main target antigens and applied tumor types for CAR macrophages (CAR-Ms) are shown in Table 3. In addition, gene editing can be used to enhance phagocytosis by macrophages.

Primarily, gene editing can be used to increase the recognition of tumor cells. Similarly, the most important and studied CAR introduced into macrophages is the CD19 CAR. For instance, CD19 CAR-Ms were shown to decrease the tumor burden and prolong overall survival in solid tumor xenograft mouse models [309]. In addition, MSLN is another common molecule exploited in gene editing. MSLN is highly expressed in mesothelioma, pancreatic adenocarcinoma, ovarian cancer, and lung adenocarcinoma [349]. CAR-Ms targeting MSLN show increased phagocytic activity against ovarian/pancreatic cancer cells expressing MSLN [310].

CARs for phagocytosis (CAR-Ps) can be introduced into macrophages to enhance phagocytosis. For example, multiple EGF-like domains (Megf10) and an Fc receptor (FcRɣ) robustly trigger phagocytosis in macrophages. Inclusion of Megf10 and FcRɣ in CD19 CAR-Ms vastly enhances their phagocytic ability [311]. An additional

tandem PI3K recruitment domain further promotes the phagocytosis of tumor cells.

Immune cell–immune cell communication

Interactions among different immune cells in the TME exert immunostimulatory or immunosuppressive effects. Gene editing can be used to reprogram immune cell–immune cell communication to eliminate tumors. However, there are only a few investigations in this area.

T cells and Tregs

Immunosuppression mediated by Tregs is an important cause of CAR-T-cell failure in clinical practice. Gene editing can be used to suppress the communication between effector T cells and Tregs to inhibit the immunosuppressive effect of Tregs. Conventional CAR-T cells secrete IL-2 upon antigen encounter, which leads to the generation of Tregs. CD28 induces the production of IL-2, while mutant CD28 can inhibit the production of IL-2. Utilizing gene editing to substitute two amino acids in the PYAP Lck binding motif in the CD28 domain (ΔCD28) of CARs can inhibit the production of IL-2 and generation of Tregs [351]. In this way, decreasing Treg levels weakens their immunosuppressive effect. In addition, gene editing can be used to suppress Treg function. IL-12 is critical in suppressing the function of Tregs. When IL-12 is included in CAR molecules, CAR-T cells can secrete IL-12 to inhibit the suppressive function of Tregs. Significant Treg inhibition and tumor clearance have been observed in animal models of thymoma and glioblastoma [347, 352].

T cells and DCs

DCs are essential antigen-presenting cells. Most antigens are processed by DCs and then presented to T cells. Gene editing can be used to improve communication between T cells and DCs. For example, the highly structured noncoding RNA RN7SL1 can be introduced into CAR-T cells via gene editing. Then, RN7SL1 can be carried by exosomes to act on DCs and promote their activation and antigen-presenting functions [343]. In addition, factors released by gene-edited T cells can increase the infiltration of DCs. CCL19 and CD40L are important DC chemoattractants. Engineered T cells with inserted CCL19 or CD40L can release these molecules, increasing the infiltration of DCs into tumors [353, 354].

Conclusion and perspective

In this review article, we summarize the application of gene editing for reprogramming TME cells and intercellular communication. In this way, gene editing promotes the killing effect of immune cells on tumor cells. Tumor tissues are highly heterogeneous, and the features of tumor cells and immune cells in the TME are very different even within a single tumor. In response to this heterogeneity, gene editing can accurately change the features of immune cells or tumor cells in a flexible and changeable way. The entire microenvironment is reprogrammed to become unsuitable for tumor survival. With the application of gene editing technology in epigenetics, epitranscriptomics, and proteomics, the methods for reprogramming the TME have expanded from traditional gene knock in and out strategies to making various modifications to genes, transcripts, and proteins. This means that cell reprogramming can be more diversified and accurate according to cell features. In addition, the number of cell types that can undergo gene editing has increased and now includes pluripotent stem cells and hematopoietic stem cells. To date, FDA-approved gene editing treatments are based on T cells. In short, with further improvements in the safety and effectiveness of gene editing, an increasing number of edited cell types will be used in the clinical treatment of tumors. Overall, gene editing can be used to reprogram the TME and promote precision treatment of tumors.

Abbreviations

TME: Tumor microenvironment; MegaNs: Meganucleases; ZFNs: Zinc finger nucleases; TALENs: Transcription activator-like effector nucleases; CRISPR/Cas: Clustered regularly interspaced short palindromic repeats/ CRISPR-associated proteins; TALEs: Transcription activator-like effectors; iPSCs: Human induced pluripotent stem cells; CrRNA: CRISPR-derived RNA; NK cells: Natural killer cells; TCR: T cell receptor; IL-2: Interleukin 2; IL-2R: IL-2 receptor; IL-7: Interleukin 7; Tregs: Regulatory cells; IL-15: Interleukin 15; IL-21: Interleukin 15; PD-1: Programmed cell death 1; TIM-3: Hepatitis A virus cellular receptor 2; LAG-3: Lymphocyte activating 3; CTLA-4: Cytotoxic T-lymphocyte associated protein 4; TIGIT: T cell immunoreceptor with Ig and ITIM domains; NR4A: Nuclear receptor subfamily 4 group A; TOX: Thymocyte selection associated high mobility group box; IKZF2: IKAROS family zinc finger 2; FOXP3: Forkhead box P3; Usp22: Ubiquitin specific peptidase 22; Brd9: Bromodomain containing 9; CRS: Cytokine release syndrome; mbIL-15: Membrane-bound IL-15; ADCC: Antibody-dependent cell-mediated cytotoxicity; TAM: Tumor-associated macrophages; IL-12: Interleukin 12; STAT3: Transducer and activator of transcription 3; IKKβ: Inhibitor of nuclear factor kappa B kinase subunit beta; CSF1R: Colony-stimulating receptor; CCR2: C-C motif chemokine receptor 2; Axi-cel: Axicabtagene ciloleucel; TAF: Tumor-associated fibroblast; ISLR: Leucine rich repeat; CAV-1: Caveolin-1; PDAC: Pancreatic ductal carcinoma; DC: Dendritic cells; Tisa-cel: Tisagenlecleucel; Liso-cel: Lisocabtagene maraleucel; Brexu-cel: Brexucabtagene autoleucel; ACT: Adoptive T-cell therapy; CAR-T: Chimeric antigen receptor T cells; TCR-T: T-cell receptor T cells; B-ALL: B cell acute lymphoblastic leukemia; HER2: Human epidermal growth factor receptor 2; IL13Rα2: Interleukin-13 receptor subunit alpha-2; EphA2: Ephrin-A2; PDXs: Patient derived xenografts; MSLN: Mesothelin; PDAs: Pancreatic ductal adenocarcinomas; NFAT: Nuclear factor of activated T cells; EVs: Extracellular vesicles; GVHD: Graft-versus-host disease; CAR-iMac: Pluripotent stem cell-derived CAR-macrophage cells; CAR-Ps: CARs for phagocytosis; Megf10: Multiple EGF like domains; FcR: Fc receptor.

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Authors' contributions

Conceptualization: JYY and XPL. Compilation of literature: KL, JJC, YZ, QYOY and QSL. Article writing and editing: KL, JJC, YZ and DHY. Figure organization:

YZ and QYOY. Supervision: JYY and XPL. All authors read and approved the final manuscript.

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