Artificial Engineering of Immune Cells for Improved Immunotherapy

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1. Introduction

Immunotherapy has been acknowledged as the most promising therapeutic means for treating many serious diseases. Nowadays, several typical kinds of immunotherapy are being intensively investigated, including the cytokine-based immune modulation (such as interferon-α and interleukin-2 [IL-2]), vaccine, immune checkpoint blockade (ICB), and cellular therapy.[1–5] These therapeutic means are focused on the disease-specific recognition and defense mechanisms of various immune cells. To prime immune response in vivo, systemic administration of cytokines and agonist is usually exploited, which is identified with severe side effects, such as cytokine release syndrome and off-target damages.[6,7] Different from in vivo administration of immune modulation agents, cellular therapy generally includes ex vivo manipulation and adoptive transfer of naturally existing or genetically modified immune cells collected from patients or healthy donors. Ex vivo immune cell manipulation bypasses the need of in vivo targeted activation and associated off-target risks, and it is feasible to realize accurate and specific immune activation, which is, hence, receiving more and more interest for personalized therapy.[4,5] Early trials have demonstrated the therapeutic benefits of tumor-infiltrating lymphocytes (TILs), and subsequently, vast efforts have been devoted to the promotion of TILs’ performances.[8] Considering that the immune cell of different types exerts distinct functions for maintenance of health, development of engineered immune cells, not restricted to T cells, will certainly benefit treatments for various diseases and may update the current therapeutic modality.

Therefore, in addition to lymphocytes, other types of immune cells, such as macrophage and dendritic cell (DC), have also been exploited for adoptive immunotherapy.[9,10] Chimeric antigen receptor (CAR)-T cell therapy is known as one of the most famous examples in the field of cellular therapy.[11,12] With the help of synthetic biology technologies, CAR-T cell is engineered with antigen-specificity and enhanced functions, maintaining robust efficacy and assisting with in situ lymphocytes to attack.[13] CAR-T cells have been approved by the Food and Drug Administration (FDA) for the treatments of leukemia and lymphoma, showing great therapeutic potentials and clinical significance.

However, unsatisfactory clinical and preclinical outcomes are still widely reported, ascribed to various complex factors, including unwanted side effects and in vivo inefficiency.[14,15] For example, tumor microenvironment (TME) is characterized with immunosuppressive features, and thus, both the in situ and reperfused immune cells encounter difficulties in eliciting effective antitumor activities.[16,17] Upon the entry into tumors, the transferred cells readily experience poor response, exhaustion, and re-education toward pro-tumoral phenotypes.[18,19] These in vivo biological barriers represent the major challenges for cellular therapy, indicating that improvement and innovation of cellular therapy are still urgently needed. To address the issue, combination therapy strategy has been raised to improve therapeutic performance of transferred immune cells, such as the combination between radiotherapy and chemotherapy.[20] Combination strategy displays obvious advantages, including improved therapeutic outcomes as compared with monotherapy, synergistic effects, and enlarged therapeutic modalities. However, systemic administration of the introduced combination therapy still faces the problem of off-target side effects, such
as the drug-induced impairment toward immune cells and the systemic toxicity.\[21\]

Nanotechnology and material science have gained impressive developments in many fields, such as drug delivery, biosensor, implanting, and so on.\[22\] Material presents multiple functions that natural immune cells may not possess, which can be organically integrated with immune cells to produce multifunctional biohybrid systems for therapeutic and diagnostic purposes (Figure 1). Material-based carriers and scaffolds enable specific target delivery and high efficacy of therapeutic agents (such as peptide, protein, small molecule drug, and gene products) toward immune cells and immune organs, paving pathways for in vivo and ex vivo immune cell modulation. Materials with imaging contrast capacity provide convenient platforms for in vivo monitoring and help understand more the biological activity of immune cells, thus favoring the development of advanced immunotherapy. Materials capable of responding to external stimuli can render live cells the new functions, such as control over disease targeting, cell-to-cell contact, biosynthetic activities, and cellular phenotypes. Therefore, integration of cellular biology with nanotechnology and material science offers chances for adoptive immunotherapy to achieve high improvement beyond expectation. This review summarizes recent advances in adoptive transfer of artificially engineered immune cells for disease treatment, especially in tumor treatments. The related studies are classified into three sections according to the types of immune cells, including monocyte/macrophage, DCs, and T lymphocytes. In addition, we briefly introduce the studies about the material-induced modulation of in situ immune cells for disease immunotherapy. Finally, we discuss the developing trend in artificial engineering immune cells for immunotherapy and biomedical purposes.

2. Monocyte/Macrophage-Based Therapy

Monocytes are a type of leukocyte that originates from bone marrow-derived progenitors.\[23\] During infection, inflammation, and tumor development, monocytes can follow the gradients of chemokine and growth factors, leave the bloodstream and infiltrate into target tissues, and differentiate into macrophage or DCs in response to the stimuli.\[24\] Monocytes/macrophages have intrinsic therapeutic potential for disease treatment, because they are members of a natural defense system in human body against pathogen invasion and cell mutation. Not only the classically activated inflammatory phenotype (also called M1 macrophages) but also the alternatively activated regulatory phenotype (also called M2 macrophages) of macrophages participate in tissue homeostasis and regeneration.\[25\] Macrophages displayed enhanced proliferation and pro-inflammatory activities in response to inflammation.\[24\] In addition, the special accumulation of macrophages within necrosis tumor tissues featured with hypoxia has been reported and taken as a hot target.\[26\] Monocytes and macrophages have intelligent biological activities for maintaining homeostasis, monitoring disease development, and present intrinsic therapeutic potential for disease diagnosis and therapy, because they are members of the natural defense system in human body against pathogen invasion and cell mutation.\[27\] With the aid of gene technology, advanced macrophage-based biologics have been developed, such as highly sensitive biosensors for early cancer detection and CAR macrophages (CAR-Ms) for antigen-specific phagocytosis and tumor clearance.\[28,29\]

Combined with their natural bio-tropism, researchers have integrated active targeting capacity of man-made materials with live cells to reinforce the targeting effect for better tropism at

![Figure 1. Schematic illustration of artificially engineered immune cells via nanotechnology and material sciences for disease treatment.](www.advancedsciencenews.com)
diseased sites. Muthana et al. engineered macrophages with superparamagnetic iron oxide nanoparticles to obtain magnetic cells for magnetic resonance targeting (MRT).\textsuperscript{[10]} Also, it is feasible to use material to guide cell–cell contact and promote immune recognition. Yuan et al. developed a microparticle-based bispecific linker to simultaneously target the human epidermal growth factor receptor 2 (HER2) on cancer cell surface and the phagocytosis receptors expressed on macrophages.\textsuperscript{[12]} This bispecific linker bind to both cancer cell and macrophage, forcing an artificial contact between them and thus enhancing the recognition and phagocytosis activity of macrophages toward cancer cells in vivo.\textsuperscript{[31]} Our group reported the artificially reprogrammed macrophages for tumor immunotherapy, in which magnetic nanoparticles not only guided macrophages’ tumor tropism but also strengthened macrophages’ therapeutic functions.\textsuperscript{[12]} As overloaded iron ions can induce durable and robust pro-inflammatory activation of macrophages, we engineered macrophages with hyaluronic acid-decorated iron oxide nanoparticles to obtain magnetotactic cell therapeutics named HION@Mac (Figure 2a).\textsuperscript{[32]} The magnetic iron oxide nanoparticles (HION) loaded in macrophages on one hand provide an external guidance for macrophages to actively migrate toward tumor tissues. On the other hand, the overloading of intracellular iron ions due to the sustained degradation of iron oxide within macrophages provided a durable driving force for HION@Mac activation and resistance toward in vivo immunosuppression. Under iron oxide nanoparticles’ regulation, HION@Mac cells produced therapeutic factors including reactive oxygen species (ROS) and pro-inflammatory cytokines to directly suppress cancer cells. Meanwhile, the released pro-inflammatory factors re-educated the in situ pro-tumoral macrophages to transform into antitumor phenotype, which synergized with transferred HION@Mac cells to inhibit tumor growth. This study exploited the intracellular degradation of HION to realize sustained generation and release of cytokine from cells for tumor growth inhibition, displaying superiority in overcoming in vivo immunosuppressive microenvironment than traditional strategies. Unlike our strategy, Shields et al. established a cellular backpack strategy for durably regulating the adoptively transferred macrophages for tumor inhibition.\textsuperscript{[33]} They utilized microcontact printing technology and layer-by-layer (LBL) assembly approach that were used to fabricate a interferon- γ (IFN-γ)-loaded disk-like polymeric backpack o macrophages. This special design is aimed to reduce rapid cellular internalization of IFN-γ and achieve extracellular sustained release of IFN-γ for at least 5 days longer than the spherosoidal particle, thus leading to long-term macrophages regulation.

Macrophages’ therapeutic potency has also been exploited to deal with pathogen infection. Dong and co-workers reported an adoptive macrophage therapy, which was enhanced by nanomaterial, for treating multidrug-resistant bacterial sepsis.\textsuperscript{[34]} An mRNA encoding broad-spectrum antimicrobial peptide IB367 (AMP-IB367) was linked to inactive cathepsin B (CatB) via a CatB-sensitive linker. They loaded this mRNA into the optimized vitamin-derived lipid nanoparticle and equipped macrophages with this nanoparticle for adoptive transfer. Lipid nanoparticle can rupture in lysosomes and release mRNA into cytoplasm for transfection, initiating biosynthesis of AMP-CatB within macrophages. The as-synthesized AMP-CatB conjugate then transferred to lysosome due to the targeting moiety CatB. Within lysosomes, AMP-CatB underwent linker cleavage catalyzed by lysosomal activated CatB, and subsequent AMP liberation. Consequently, the internalized bacteria can be cleared via two pathways: intrinsic microbial lysis reaction in macrophages’ lysosomes and additional AMP bactericidal effect. In this study, the material endowed the macrophages with the capability to synthesize the lysosome-targeted antimicrobial agent in cells.

Figure 2. Monocyte/macrophage-based cell therapy assisted with synthetic materials. a) Schematic illustration showing the composition, preparation, and therapeutic mechanisms of the artificially engineered macrophages HION@Mac. Reproduced with permission.\textsuperscript{[32]} Copyright 2019, Wiley. b) Schematic of in vivo targeting inflammatory monocytes by cucumin-loaded nanoparticles for treating ecephalomyelitis via hindering monocytes’ migration across BBB. Reproduced with permission.\textsuperscript{[14]} Copyright 2020, Elsevier. c) Schematic illustration showing the antibacterial and anti-inflammation therapeutic performances of As@GNC-loaded monocytes. Reproduced with permission.\textsuperscript{[45]} Copyright 2020, Wiley. d) Schematic illustration showing the synthesis of nano-trinity and the molecule mechanism within nano-trinity-regulated macrophages for antifungal therapy. Reproduced with permission.\textsuperscript{[46]} Copyright 2020, ACS Publications.
The synergism between exotic antimicrobial function and macrophages’ bactericidal nature demonstrated potentials for overcoming multidrug-resistant bacteria infection.

As macrophage is a widely distributed cell type and participates in homeostasis, direct in vivo manipulation of in situ macrophages is also explored for disease treatments. Tumor-associated macrophage (TAM) is a hot target for tumor immunotherapy. TAM resides deep into hypoxic area within tumor tissues, presents pro-tumoral M2 phenotype, and releases inhibitory factors that suppress antitumor immunity. In principle, it is favorable for tumor immunotherapy to convert TAM toward antitumor M1 phenotype owing to the plasticity of macrophages. Strategy of reversing TAM for tumor immunotherapy has, been widely explored. For example, anti-CD47 antibody was co-delivered with antigens and regulatory protein alpha (SIRPα) antibody by macrophage-derived exosomes and also with small-molecule toll-like receptor 7 agonist via nanofabrication (such as metal–organic framework and nanoemulsion) to boost macrophages activation. Apart from targeting specific pathways, including CD47–SIRPα signaling using antibody-based therapeutics, researchers excavated multifunctional materials and biomimetic strategies to activate macrophages for antitumor immunotherapy. A core–shell Cu₉O@CaCO₃ nanostructure was designed for targeted and TME-triggered multiple combination therapy, where macrophages were activated in response to hyperthermia and oxidative stress for synergistic antitumor effect. Learning from natural pathogens, a plant virus-like particle assembled from Cowpea chlorotic mottle virus was designed for targeted delivering oligodeoxynucleotides adjuvant for macrophage modulation.

In vivo macrophage modulation is also adaptable for regulating inflammation-associated diseases and treating pathogen infections. Lu et al. targeted peripheral monocytes for treating autoimmune encephalomyelitis using the curcumin-loaded high-density lipoprotein-mimicking peptide-phospholipid nanocarrier (Cur-HPSS) (Figure 2b). Cur-HPSS can specifically target monocytes via scavenger receptor class B type 1 (SR-B1) receptor. Anti-inflammatory curcumin inhibited monocytes’ NF-κB pathway, resulting in downregulation of adhesion molecules such as ICAM-1 and MAC-1. This in vivo monocyte engineering strategy, thus, reduced the migration of monocytes through blood-brain barrier (BBB) and, thus, lowered the morbidity of autoimmune encephalomyelitis in mouse model. Shi et al. injected the aspirin-loaded gold nanocage (As@GNC) into mice and collected the As@GNC-loaded monocytes (AsMon) for adoptive transfer to treat osteomyelitis (Figure 2c). This modified monocytes can actively home to infection sites, transform into macrophages, and elicit bactericidal effect. Under laser irradiation, the loaded As@GNC generated a concentrated thermal effect to synergize with AsMon to eradicate bacteria and simultaneously released aspirin for inflammation inhibition. Gao et al. designed a mannosylated nanotriptych to in vivo manipulate in situ macrophages for treating Candida albicans infection. Decoration of mannose promoted the specific internalization of nanotriptych in macrophages. Imatinib and chitosan oligosaccharides were embedded into polymeric nanotriptych for not only inhibiting M2 polarization but also activating macrophages’ transformation into pro-inflammatory M1 phenotype (Figure 2d). Synergism between inhibiting M2 phenotype and stimulating M1 polarization led to robust macrophage-mediated fungicidal effect.

Studies have demonstrated the feasibility that materials can be exquisitely integrated with monocyte/macrophage for excavating their therapeutic potentials for pathogen eradication, tumor suppression, inflammation recovery, and autoimmune diseases via leveraging different functional phenotypes of macrophages. In most cases, synthetic materials function as stimulus for initiating and strengthening the intrinsic bioactivities of monocyte/macrophage. Some pioneering works attempted to equip monocyte/macrophage with nonnatural abilities, such as magnetotactic migration, bioluminescence imaging, and new types of synthesis capacity, providing opportunities to develop much better cell therapeutics than the parent. In addition, it is expected that macrophage-based biosensor that integrates with synthetic materials such as contrast agents may provide promising methods for early diagnosis of diseases. The topic of cell-based biosensors also arouse many interests and has been developed and reviewed by other researchers.

3. DCs-Based Therapy

DCs play important roles in adjusting both immune tolerance and immunity. Both DCs and macrophages are antigen-presenting cells that uptake, process, and present antigens to T lymphocytes, whereas the former is more powerful in generating antigen-specific T cell immunity. In addition, studies have demonstrated that the DCs are vital for linking innate and adaptive immune responses, making them a hot target and valuable bionic object for developing advanced therapeutics. Taking advantage of DCs’ specific function in coordinating different immune processes, the strategy of DCs-involved vaccination has been developed for disease intervention, especially tumor immunotherapy. For tumor treatment, DCs vaccination is purposed to prime tumor-specific cytotoxic T cells and to induce immunological memory effect for inhibiting tumor growth and relapse. Two methods were usually conducted to acquire mature DCs with therapeutic potentials, including ex vivo pulsing DCs with tumor antigens and in vivo targeting DCs with the delivery system loaded with tumor antigens. Grippin et al. developed an RNA-loaded magnetic liposome for ex vivo transfection of DCs with the mRNA encoding tumor-associated antigens. In the study, the iron oxide nanoparticles complexed with cationic liposomes could increase the transfection efficiency and promote the activation of DCs in comparison with the clinical method of electroporation. After reperfusion of these magnetic liposomes-engineered DCs, the introduced iron oxide nanoparticles provided magnetic resonance imaging (MRI) signals for monitoring DCs transfer toward lymph node and help predict individual response toward DC vaccination in melanoma-bearing mice model. Using biomaterials for in vivo vaccine delivery toward internal DCs is among the most used approach to improve therapeutic outcomes of DCs-based immunotherapy. Another important strategy is to in vivo introduce man-made scaffolds to provide a benign microenvironment for DC recruitment, activation, and transplantation. For example, self-assembled peptide-based hydrogels and mesoporous silica microspheres (MSRs) can not only provide an artificial
niche for DCs, but also form a reservoir for local delivery of therapeutic drugs for combination therapy.

It is noted that the DCs display other types of functional activity. Immature DCs can induce immune tolerance by suppressing the activated T cells or priming the regulatory T cells.\[62\] This special function of DCs can be exploited for treating autoimmune diseases and improving graft transplantation. Considering that DCs are key regulator cells of atherosclerotic inflammation, Yi et al. utilized polymersome to concurrently deliver both 1,25-dihydroxyvitamin D3 (aVD) for maintaining tolerogenic phenotype and antigenic peptide of low-density lipoprotein (LDL) for immunization toward atheroma-resident and splenic DCs.\[63\] The peptide P-D2 with high affinity with the CD11c expressed on DCs was decorated on polymersome to improve its target specificity. The authors demonstrated that in vivo manipulating DCs’ tolerogenic phenotypes could provide atheroprotective effect in a high-fat-diet-fed mice model. Wang’s group utilized cationic lipid-based nanoparticles to deliver CRISPR/Cas9 targeting co-stimulatory molecule of DC. By restricting DCs activation and maturation, the improved transplant tolerance and prolonged graft survival were achieved in a mice model.\[64\]

The development of DCs-based cell therapy includes two major directions: DCs-involved vaccination for prophylactic purpose and regulatory DCs for improving immune tolerances. In this field, materials mainly function as delivery vehicles for successful antigen loading as well as adjuvants for priming DCs’ maturation. The effort of targeting DCs for vaccination has nowadays been focused on optimization over the chemical and physical properties of vaccine formulations.\[65,66\] For inducing immune tolerances, materials that target specific organs where DCs suppress activated T cells (such as thymus) or where DCs prime regulatory T cells (such as peripheral lymphoid organs) may help promote the immune regulation effect.\[62\]

4. T Cell-Based Therapy

Genetically modified T lymphocytes have been applied for adoptive transfer since 1990.\[67\] T cell-based therapy is not a new concept but is recently getting faster development and displays profound potentials in disease treatment especially for tumors, which benefits from both the improved understanding over T cells’ biology and the advanced technologies including genetic method and nanotechnology. Nevertheless, clinical trials show that there is much room for improving T cell-based therapy. The strategy of utilizing materials and nanotechnology to engineer immune cells has been adopted to meet various demands for disease treatment, including priming antigen recognition, improving T cell expansion and survival both ex vivo and in vivo, strengthening cellular function, preventing adverse re-education in vivo, and trafficking T cells migration. This section introduces the major strategies to focus on the artificially engineered T cell-based therapy.

4.1. aAPCs for Priming T Cells

Learning from the minimal T cell activation process, researchers proposed a concept of artificial antigen-presenting cells (aAPCs). In general, nanoscale aAPCs aim at reconstructing dual signals, peptide-loaded major histocompatibility complex (pMHC), and co-stimulatory molecules, by utilizing synthetic nanoparticles, for T cell activation and expansion ex vivo or in vivo. Considering the biochemical components of these two signals, some studies utilize top-down fabrication of live cells to prepare functional cytomembrane-based biomaterials as aAPCs for T cells activation. Our group has reported a fused cell-derived cytomembrane-based nanovaccine for in vivo T cell induction.\[68\] The fused cells originated from cancer cells and DCs, and thus inherited both antigens and co-stimulatory molecules from these cells (Figure 3a).\[68\] Extraction of fused cell-derived cytomembrane contained the multiple cancer antigens and co-stimulatory signal molecules into one system, providing a simplified method for multivalent aAPCs production. Zhang and co-workers utilized cytomembrane from genetically engineered cancer cells that expressed costimulatory molecule CD80, which also presented its natural antigen peptide epitopes, to construct biomimetic nanoparticles for direct T cell stimulation (Figure 3b).\[69\] Xie and co-workers has reported cytomembrane from leucocyte decorated with pMHC and co-stimulatory ligand anti-CD28 (αCD28) for in vitro T cell stimulation and demonstrated the therapeutic potential of this strategy (Figure 3c).\[70\]

With the improved understanding about immune process, researchers also leverage other cues not limited to biochemical compositions involved in immune regulation to optimize material design and improve T cell activation efficiency. Fadel et al. have reported a carbon nanotube-polymer nanoparticles composite (CNP) that can mimic natural APCs for expanding T cells for tumor immunotherapy.\[71\] CNP includes three major components: 1) neutravidin-modified carbon nanotube; 2) biotinylated T-cell stimuli including pMHC and αCD28; and 3) biotinylated poly(lactide-co-glycolide) (PLGA) nanoparticles loaded with IL-2 and magnetite. The authors utilized carbon nanotube to provide a benign substrate with high surface area for signal molecules decoration, similar to the immune synapse. By linking the T cell stimuli and the IL-2-loaded PLGA nanoparticles onto carbon nanotube through neutravidin–biotin interaction, CNP served as aAPCs for efficient T cell initiation and expansion. The loaded magnetite can help separate the activated T cells for subsequent in vivo perfusion. Here, CNP nanoparticles not only serve as a depot for paracrine-like drug/protein release or a tool for cell separation, but also provide a synapse-like interface for T cell interaction. In this study, the topography characteristic of carbon nanotube was elaborately designed, enabling efficient contact between surface cargo and T cells for favorable T cell activation. Similarly, micrometer-scale materials with high aspect ratio for immune cells induction were also studied by Mooney and co-workers.\[72,73\] Liu and co-workers utilized the DNA-assisted self-assembly means to arrange different distribution of signal molecules on red blood cells and evaluated their effect in T cell priming (Figure 3d).\[74\] This idea originates from the process of ligand positioning during T cell activation. The authors took advantage of DNA nanotechnology to simulate this procedure to manipulate immune process.

4.2. Ex Vivo T Cell Engineering for Strengthening In Vivo Performance

The complex environment in vivo is thought as one of the major limiting factors for adoptive T-cell therapy, which may reprogram
therapeutic cells’ phenotype, reduce their functionality, and exhaust their activity.\[^{18}\] For example, immunosuppressive micro-environments in solid tumor usually suppress effector T cells infiltration and impair their antitumor functions.\[^{75}\] To solve this problem, biomaterials have been applied to reinforce the already activated T cells, including CAR-T cells. The strategy of conjugating particles onto cellular surface for strengthening their functional activities is likened to cellular “backpack,” which was proposed for T cell therapy by Irvine and co-workers and has attracted great interest.\[^{76}–81\] In the previous work, Stephan et al. decorated CD8\(^+\) T cells surface with the 300 nm-sized multilamellar lipid nanoparticles loaded with two interleukins through maleimide-thiol coupling.\[^{76}\] The integrated interleukins can cooperatively promote expansion and effector functions of T cells, which requires daily administration at a high dosage. Engineering effector cells with drug-loaded nanoparticles can concentrate drug around their target cell, leading to improved drug-cell interaction and lower systemic side effects. To demonstrate this idea, the authors compared the outcome of this strategy with that of systemic administration of the same interleukins. Sharply different, the latter treatment made little influences on the activation and expansion of T cells in vivo. Evidently, the former provides a simple but versatile strategy for the improved efficacy of cytokine-boosted cell-based immunotherapy.

In the later work, Irvine and co-workers renovated the strategy of nanoparticle-engineered T cells by linking drug release behaviors to cell functions, such as recognition and activation.\[^{79,80}\] Motivated by the abundant thiols expressed on T cells, the authors demonstrated that activated T cells always exhibit a higher reduction state on cell surface, especially when interacted with APCs.\[^{80}\] Thus, a “carrier-free” protein nanogel was prepared by crosslinking adjuvant proteins with disulfide containing bis-N-hydroxy succinimide (NHS) cross-linker to realize antigen-triggered drug release for strengthening T cell. The reduction-responsive nanogel conjugated to the surface of T cells presented advantages in not only the high drug-loading capacity, but also the enhanced regulation effect than nonresponsive nanoparticles that spontaneously leaked drugs.
Targeting metabolic intervention to address the problem of intratumoral T-cell hypofunction caused by cancer metabolite adenosine, Siriwon et al. encapsulated therapeutic inhibitor into the cross-linked multilamellar liposomal vesicles and chemically conjugated these vesicles onto T cells, for blocking surface A2a adenosine receptor to, thus, maintain T cells’ cytotoxic activity in vivo.\[84\]

Xie and co-workers reported a pH-sensitive magnetic nanocluster to improve the abundance and therapeutic functions of adoptive transferred T cell at tumor sites (Figure 4a).\[83\] This nanocluster was constructed by doping 10 nm-sized building units (magnetic nanoparticles) with polyethylenimine. Polyethylenimine provided amino groups for further reaction with benzaldehyde-PEG2000-tetrazine, forming a pH-sensitive benzoic-imine bond that would undergo hydrolysis at the acidic condition in tumors. PD-1 antibody (αPD-1) was modified with trans-cyclooctene to link onto nanocluster via inverse-electron-demand Diels–Alder cycloaddition. The authors decorated cytotoxic T lymphocytes (CTLs) with nanoclusters through interaction between αPD-1 and PD-1 expressed on CTLs’ surface, which can be clearly observed through transmission electron microscopy and confocal laser scanning microscopy.\[83\] The engineered CTLs can be magnetically enriched at tumor, and the tied αPD-1 would be released specifically in acidic TME to synergize with CTLs for tumor suppression.

4.3. Artificial Manipulation and Remote Control of T Cell

Synthetic materials can provide various functions more than simple drug delivery. Researchers excavated this advantage to introduce nonnatural functions, such as ferromagnetism and specific forces generated by synthetic materials, to realize drug-free T cell manipulation. Schneck’s group proposed a reductionist platform for T cell regulation by magnetic fields in vivo. They decorated different signal molecules onto signal-monospecific paramagnetic nanoparticles for binding corresponding T cell receptors, and thus induced the clustering of various receptors on T cell surface in vitro (Figure 4b).\[84\] The authors demonstrated that adoptive transfer of these magnetically controlled T cells possessed therapeutic potentials for melanoma. Distinguished from traditional aAPCs strategy, which can only integrate one or several molecules into one subject, this study flexibly arranged various nanoparticles capable of arming with monospecific signal molecule, displaying potent customizability (Figure 4c).\[84\] In addition, this study provided an external control over the nanoscale organization of the signal molecules on T cell surface. As T cell activation process involves not only biochemical molecules recognition but also organization of various receptors on cellular surface, the authors cleverly exploited this characteristic to boost activation. Schneck and co-workers found that the immune regulation effect of nanoparticles presented size-dependent characteristic, showing the possibility of size-controlled immune regulation.\[85\] Various nongenetic engineering strategies have emerged in attempts of regulating surface receptor clustering in living cells, including but not limited to immune cells. It is expected that these strategies can also be exploited for engineering adoptive cells to reduce the risks of cellular gene modification.\[86,87\]

Majedi et al. examined the influence of oscillatory movement on T cell proliferation and activation, in the presence of superparamagnetic iron oxide nanoparticle-based aAPCs, using an orbital shaker to provide exogenous mechanical forces (Figure 4d).\[88\] The authors found that primary mouse T cells formed a larger cluster in dynamic culture than that in static state, adumbrating that mechanical stimulation may be an external force to control ex vivo T cells expansion. This study provided evidences that immune cell regulation is affected by many factors, including those that may be simply adjusted. The identification of these factors would help find more simple approaches for immune cell regulation.

Figure 4. Artificial strenth control over T cell activity. a) Schematic illustration of using magnetic nanoclusters decorated with PD-1 antibody for magnet guided adoptive T cell therapy and in vivo MRI monitoring. Reproduced with permission.\[89\] Copyright 2019, ACS Publications. b) Schematic illustration of using signal-monospecific paramagnetic nanoparticle-based aAPCs for inducing the receptor clustering on T cell surface under magnetic field control. Reproduced with permission.\[90\] Copyright 2018, ACS Publications. c) Schematic showing and comparing traditional aAPC with separate particle platform with various stimulatory signal-monospecific paramagnetic nanoparticles. Reproduced with permission.\[90\] Copyright 2018, ACS Publications. d) Schematic illustration of co-incubating superparamagnetic iron oxide nanoparticle-based aAPCs and T cells under static and dynamic (mechanical oscillation) conditions (left). Representative bright-field microscopy images of formed clusters by primary mouse T cells with aAPCs (right). Reproduced with permission.\[88\] Copyright 2019, ACS Publications. e) Schematic showing the tumor cell-T cell recognition mediated by the bispecific aptamer (cb-aptamer) for targeted T cell-based immunotherapy. Reproduced with permission.\[88\] Copyright 2020, ACS Publications.
Tan and co-workers proposed a “recognition-then-activation” strategy, which utilized a circular bispecific aptamer, which simultaneously bind cellular surfaces from tumor cells and T cells to facilitate T cell-tumor cell junction and recognition (Figure 4e). The authors injected splenocytes together with the bispecific aptamer intravenously in melanoma bearing mice and subsequently injected commercial stimulating beads for T cell activation. Here, bispecific aptamer functioned like a linker to promote cell–cell interaction and recognition, which may help solve the problem of cancer immune escape. Several studies also adopted the same strategy to improve cell-to-cell contact as well as the targeting efficacy of therapeutic cell, using materials including colloidal nanoparticles decorated with bispecific ligands, dual antibodies-linked magnetic nanomatchmakers, and bioorthogonal supramolecular system equipped with host–guest interaction.

To solve the problem of cancer immune escape. Several studies also adopted the same strategy to improve cell-to-cell contact as well as the targeting efficacy of therapeutic cell, using materials including colloidal nanoparticles decorated with bispecific ligands, dual antibodies-linked magnetic nanomatchmakers, and bioorthogonal supramolecular system equipped with host–guest interaction.

Pan et al. reported on a strategy for remote control and activation of CAR-T cells for tumor immunotherapy. The authors coupled the l-arginyl-glycyl-aspartic acid (Arg-Gly-Asp, RGD) peptide-decorated microparticles to the surface of T cells, where the mechanically sensitive Piezo1 ion channel exists. Under ultrasound stimulation, the conjugated microparticles amplified the mechanical waves and activated Piezo1 channel, leading to calcium influx followed by the initiation of downstream pathways, including the upregulation of downstream anti-CD19 CAR gene. The authors utilized this technology to remotely control the expression of anti-CD19 CAR in peripheral blood mononuclear cells and demonstrated its therapeutic potential in treating B-cell leukemia expressing CD19 antigen.

In situ gene editing in T lymphocytes has been widely explored in recent years. Stephan and co-workers developed a biodegradable poly(β-amino ester)-based nanoparticle to carry leukaemia-targeting CAR genes into T-cell nuclei for programmimg circulating T cells into leukaemia-specific T cells. To promote transfection efficacy, peptides containing microtubule-associated sequences and nuclear localization signals were introduced into the polymer nanocores. Also, anti-CD3e Fab’/F2 fragments were coupled on the nanoparticles for T cell targeting. The authors verified the feasibility of this strategy in tumor treatment, which was comparable to adoptive T-cell therapy.

The unrestricted activity of CAR-T cells can induce neurotoxicity and severe side effect such as cytokine release syndrome, which is difficult to control. Cytokines, nonspecific antiinflammatory drugs, and even cytotoxic drugs such as cyclophosphamide are clinically used to combat the side effects. However, the outcomes are still far from satisfactory. Richman et al. reported a strategy by utilizing small molecule ligands for reversible and tunable inhibition of CAR T cell activity both in vitro and in vivo. The authors utilized genetic technology to fuse CAR with a ligand-induced degradation (LID) domain. Introduction of corresponding ligands can induce the degradation of LID domain followed by the degradation of CAR from the surface of T cells, thus temporarily reducing the activity of CAR-T cells. Also, other efforts were made to restrain T cell activity and reduce the “on-target off-tumor” toxicities, mostly through the genetic technology to improve the design of CAR. This study points out a direction that we can use materials as a controller for not only manipulating T cell activation but also braking T cells’ excessive activation.

In addition to being drug delivery vehicles, materials can directly mediated cell regulation, providing chances for more precise control over T cells. Studies in this field remain to be further explored. With respect to the ease of material design, there are still much room for the improvement in this field before its clinical translation.

4.4. Regulating T Cells for Autoimmune Diseases and Allogenic Transplantation

T lymphocytes represent a large population of different subsets and roughly divided into two types: CTLs and regulatory T lymphocytes, which elicit distinct functions during homeostasis. For suppressing autoimmune diseases, regulatory T lymphocytes display potent efficacy. Exploiting materials to improve the specificity and efficacy of regulatory T cells has also attracted rapidly increasing interest.

Similar to the concept of aAPCs, a strategy of tolerogenic aAPCs has been reported by designing particles containing disease-relevant pMHC to induce the suppressive T cell phenotypes. Singha et al. synthesized a series of stable iron oxide nanoparticles as a ligand multimerization platform for expanding suppressing regulatory T cells to treat inflammatory diseases. By screening the size of nanoparticles as well as the valency and density of pMHC, the authors optimized the constitution of tolerogenic aAPCs via conjugating relatively smaller particles with higher density of pMHC monomers for expanding regulatory T cells in vivo. Higher pMHC density on the surface of nanoparticles would lead to prolonged T cell receptor (TCR)-pMHC interaction and, thus, amplified TCR signaling. Meanwhile, nanoparticles with high pMHC density also facilitated propagation of signaling events from nanoparticles-bound T cells to adjacent unbound T cells. This study provided an important design principle in developing nanoscale systems for manipulating regulatory T cells.

Hess et al. utilized 10 nm-sized uniform CdSe/ZnS core/shell quantum dots (QDs) as a tunable platform to accommodate self-antigens to evaluate the effect of particle dose and antigen density in treating autoimmune encephalomyelitis. By adjusting the ratio of QDs and self-antigen myelin oligodendrocyte glycoprotein peptide (MOG), the authors prepared a series of MOG-QDs with varied sizes and different densities of conjugated peptides. By means of photoluminescence property of QDs, they found that 20 nm-sized MOG-QDs presented optimal lymph node drainage effect. Based on the evaluation of therapeutic efficacy and the monitoring of body weight of mice with encephalomyelitis, a conclusion was drawn that higher dose of modulatory nanoparticles and lower densities of self-antigen is much more effective in inducing immune tolerance. This study fully exploited the merits of QDs, including size for lymph node delivery, photoluminescence for timely in vivo visualization, and tunable surface modification for precise control of self-antigens conjugation. In addition, by utilizing this versatile platform, the authors not only developed a potential nanotherapeutics, but also provided a fundamental discovery in particles design for regulating immune tolerance.

MicroRNA-125a is important for stabilizing regulatory T cell-mediated self-tolerance. Tang and co-workers identified that microRNA-125a was evidently downregulated in patients...
with systemic lupus erythematosus and, thus, exploited it as the potential target for efficient therapy. They developed a nano-delivery system, consisting of monomethoxy (polyethylene glycol)-poly(D,L-lactide-co-glycolide)-poly(L-lysine), to deliver micro-RNA-125a to stabilize self-tolerance in splenic T cells for treating systemic lupus erythematosus.

Another strategy for inhibiting unwanted immune responses is to directly suppress or eradicate T effector cells. Headen et al. constructed Fas ligand-encapsulated microgels using four-arm poly(ethylene) glycol macromers to interact with Fas death receptors, which present along with T cells activation, to induce apoptosis of T effector cells. The microgels work like the chaperone to enhance the availability and function of cotransplanted islets in diabetic mice, confine the immune modulatory effect in situ, and reduce potential infection risks usually occurring in systemic immunosuppression treatments.

In summary, current studies of using materials to modulate regulatory T cells are still in initial stage. Further effort in this field can also facilitate the understanding of T lymphocytes' biological process and provide more information for advanced cellular therapy design.

5. Conclusion and Outlook

Immune cell-based therapy holds great promises for treating diseases including cancer, inflammation, infections, and autoimmune diseases. Immune cells of different types display distinct function and may serve as live therapeutics for many diseases. In brief, monocytes and macrophages are typical inflammatory immune cells with robust tumoroidal and antimicrobial effect. DCs play important roles in linking innate with adaptive immune responses, priming subsequent T cells' activity for prophylactic and therapeutic purposes. Here, T cells are roughly divided into two types: CTLs for diseased cells eradication and regulatory T lymphocytes for autoimmune disease suppression. T lymphocytes-based cellular therapy and DCs-based vaccination were proposed quite early before. However, clinical trials are challenged in many aspects, including the low response rate, impairment of cellular function, and exhaustion of immune cells in complex in vivo environments. Together with the improved understanding over cellular biology, the advances in nanotechnology and material science provide chances to solve these problems. In this review, we have introduced recent progress in the topic of using nanotechnology and material science to artificially engineer immune cells for therapeutic application.

Several representative strategies reported in recent studies are summarized, as shown in Table 1. Herein, immune cells are purposely armed with tailored or even new functions benefit from multifunctional materials. For example, materials can render immune cells with a variety of desired functions, such as active targeting, nonnatural synthetic capability, and on-demand cell–cell contact activity.

Although current studies represent inspiring biomedical benefits, it is a long road for utilizing synthetic materials to tailor and expand the functions of live immune cells for immunotherapy, and there remains many challenges. First, we should notice that nanomaterial can function and serve as a powerful tool more than a monotonous vehicle delivering definite modulation drugs and agents. Researchers have switched efforts in designing artifical actions between synthetic materials and live cells, such as unidirectional action such as using paramagnetic particles to remote control of cellular surface receptor clustering, as well as cross action such as cellular activation-induced drug release and subsequent feedback regulation upon cells. We expect that in the future, designing artificial engineered immune cells will incorporate more intelligent, cascaded, and mutual feedback interactions between the synthetic materials and live cells. Second, the toxicity and influence of nanomaterials upon immune cells should be considered and comprehensively assessed. Currently, little is known about how factors such as size, composition, and surface modification of synthetic materials affect biological processes of immune cells. It is noteworthy that some “adverse” regulation effect and phenomena observed

| Cell type | Nanotechnology and material | Application | Ref. |
|-----------|-----------------------------|-------------|-----|
| Macrophage | Superparamagnetic iron oxide nanoparticles | MRT | [30] |
| Macrophage | Microparticle-based bispecific linker | Direct macrophage's recognition and phagocytosis toward cancer | [31] |
| Macrophage | Hyaluronic acid-decorated iron oxide nanoparticles | Magnetic targeting and macrophage's activation | [32] |
| Macrophage | RNA-loaded lipid nanoparticles | Transfection to strengthen bactericidal capacity | [34] |
| DC | RNA-loaded magnetic liposome | MRI and transfection for vaccination | [55] |
| DC | Man-made scaffolds | Niche for immune activation and combination therapy | [80, 61] |
| DC | Polymersome and lipid nanoparticles | Induction of immune tolerance | [63, 64] |
| T cell | aAPCs | Activation and expansion of T cells | [68–71, 74] |
| T cell | Tolerogenic aAPCs | Induction of immune tolerance | [106–108] |
| T cell | Drug-loaded lipid nanoparticles | Strengthen in vivo performance | [76] |
| T cell | Responsive nanoparticles | On-demand activation | [79, 80, 83] |
| T cell | Signal molecule-modified paramagnetic nanoparticles; peptide-decorated microbubbles | Remote manipulation of cellular surface receptor for activation | [84, 93] |
| T cell | Bispecific aptamer | Direct T cell-cancer cell junction and recognition | [89] |
| T cell | Polymeric particles | In vivo gene editing in T cells | [94–97] |
in inflammation or autoimmune diseases can be taken advantages for treating diseases of other types, which requires highly ingenious ideas and may bring out innovatory strategy. Third, we could observe that current studies mainly revolve round well-developed polymeric particles, liposomes, and superparamagnetic materials for artificial intervention on live cells. Combination with new types of materials may stimulate the development of novel strategies and advanced biohybrid systems, which are highly admired. In addition, in vivo application of advanced materials, in turn, requires in-depth studies about their biocompatibility and underlying mechanisms of action.

Apart from therapeutic purposes, pioneering work in developing immune cell-based biosensors and cell-involved materials for organ/device implantation, tissues recovery, and reconstruction are emerging. Studies that provide material-support platform for organ/device implantation, tissues recovery, and reconstruction of advanced materials, in turn, requires in-depth studies about their biocompatibility and underlying mechanisms of action.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

cell engineering, immune tolerance, immunotherapy, material science, nanotechnology

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