Photothermal scaffolds/surfaces for regulation of cell behaviors

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ABSTRACT

Regulation of cell behaviors and even cell fates is of great significance in diverse biomedical applications such as cancer treatment, cell-based therapy, and tissue engineering. During the past decades, diverse methods have been developed to regulate cell behaviors such as applying external stimuli, delivering exogenous molecules into cell interior and changing the physicochemical properties of the substrates where cells adhere. Photothermal scaffolds/surfaces refer to a kind of materials embedded or coated with photothermal agents that can absorb light with proper wavelength (usually in near infrared region) and convert light energy to heat; the generated heat shows great potential for regulation of cell behaviors in different ways. In the current review, we summarize the recent research progress, especially over the past decade, of using photothermal scaffolds/surfaces to regulate cell behaviors, which could be further categorized into three types: (i) killing the tumor cells via hyperthermia or thermal ablation, (ii) engineering cells by intracellular delivery of exogenous molecules via photothermal poration of cell membranes, and (iii) releasing a single cell or an intact cell sheet via modulation of surface physicochemical properties in response to heat. In the end, challenges and perspectives in these areas are commented.

1. Introduction

Regulation of cell behaviors (e. g. adhesion, migration, and proliferation) and even cell fates (e. g. differentiation and apoptosis) is of great significance in diverse biomedical applications such as cancer treatment, cell-based therapy, and tissue engineering [1,2]. During the past decades, various methods have been developed including application of external stimuli (e. g. magnetic field, electricity, and stress/strain), delivering exogenous molecules (e. g. genes and functional proteins) into cell interior and changing the physicochemical properties (e. g. hardness, morphology, and chemical composition) of the substrates where cells adhere to regulate cell behaviors including promotion of cell death to ablate tumors, facilitation of transfection of desired genes for disease diagnosis and cell-based therapy, and stimulation of directional differentiation of stem cells and harvest of cell sheets for tissue engineering [3–6].

Thermal stimulus is a versatile and convenient factor for regulation of cell behaviors because many substances in cells are sensitive to heat and temperature is easily to be controlled on-demand [7]. In general, the heat can affect cell behaviors directly or indirectly. On the one hand, intense heat can cause protein unfolding and aggregation, DNA damage and irreversible protein denaturation, inducing the damage and even death of cells [8,9]. Moreover, proper heat can enhance the permeability of cell membranes without compromising cell viability, facilitating the entry of functional materials or biomacromolecules into cytoplasm for “engineering” cells [10,11]. On the other hand, the heat can change the physicochemical properties of substrates where cells adhere to affect the cell-surface interactions, modulating the cell...
Photothermal scaffolds/surfaces refer to a kind of materials embedded or coated with photothermal agents (PTAs, e.g. noble metal nanomaterials, semiconductor nanomaterials, carbon-based nanomaterials, and conjugated polymers) that can absorb light with proper wavelength (usually in near infrared (NIR) region) and convert light energy to thermal energy, showing great potential for regulation of cell behaviors in different ways as mentioned above. Specifically, in this review the photothermal scaffolds are based on materials with a specific spatial structure that can embed/ wrap PTAs and other functional cargoes (e.g. chemical drugs and photosensitizers) inside the interior of materials. Currently, there are various methods for preparation of scaffolds including conventional methods (e.g. solvent casting, particulate leaching, melting molding, gas foaming, thermally induced phase separation and freeze drying technique) and advanced techniques such as (e.g. electrospinning, rapid prototyping (also known as 3D printing technique) and 4D bioprinting) \cite{17,18}. The photothermal scaffolds/surfaces are generally fabricated by firm immobilization/deposition of PTAs on the surfaces or directly made of materials with photothermal effect. One of the remarkable advantages of the photothermal scaffolds/surfaces is the capability to precise control the heat in space, time, and intensity by changing the conditions of light irradiation because the heat is converted from light. Moreover, NIR light with a wavelength range of 700–1400 nm has the ability to penetrate tissues with low light attenuation and slight damage \cite{19}.

In this review, we summarize the recent progress of research, especially over the past decade, on using photothermal scaffolds/surfaces to regulate cell behaviors, which are further discussed under three headings: (i) photothermal scaffolds for killing tumor cells via hyperthermia or thermal ablation (Section 2); (ii) photothermal scaffolds/surfaces for engineering cells by intracellular delivery of exogenous molecules via photothermal poration of cell membranes (Section 3) and (iii) photothermal surfaces for releasing a single cell or an intact cell sheet via modulation of surface physicochemical properties in response to heat (Section 4) as illustrated in Scheme 1. Additionally, besides photothermal scaffolds/surfaces for regulating mammalian cell behaviors, there are also considerable reports on such scaffolds/surfaces for regulating bacterial behaviors, in particular, killing pathogenic bacteria. These reports are summarized comprehensively in other recent reviews \cite{20-23}. Last, a brief comment on the current challenges and perspectives is provided.

2. Photothermal scaffolds for tumor ablation

Cancer is one of the most serious threats to human health. Currently, there are mainly three strategies for cancer treatment including surgical resection, chemotherapy, and radiotherapy \cite{24-26}, which, however, still have some limitations such as side effects, cancer palindromia, and reduction of the life quality of patient. In recent years, photothermal therapy (PTT) that relies on hyperthermia generated by PTAs from light energy to thermally ablate tumor cells has nowadays attracted considerable attentions. Compare with conventional therapeutic methods, the main advantages of PTT include the ability to penetrate deep tissue and slight side effects of healthy cells that are not selected \cite{27,28}. So far, a variety of nanomaterial-based PTAs (e.g. gold nanoparticles (GNPs), gold nanorods (GNRs), graphene oxide (GO), polydopamine nanoparticles (PDA NPs) and black phosphorus (BP), etc.) have been utilized for tumor ablation \cite{29}. Although these nano-PTAs show good therapeutic effects, they may accumulate in metabolic organs under a long period, leading to tissue toxicity and inflammatory reactions \cite{30,31}. Photothermal scaffolds refer to the scaffolds embedded/loaded with PTAs and thus own the capability to convert the absorbed light energy into heat, which may trigger some hazardous effects such as lysis of cell membrane, aggregation and denaturation of proteins, and evaporation of cytosol, thereby leading to the death of tumor cells. Compared to nano-PTAs, photothermal scaffolds show extra advantages including controlled heat generation, local ablation on tumor sites, and improved biocompatibility. Moreover, together with PTAs, chemical drugs or photodynamic reagents can also be loaded/embedded in the photothermal scaffolds to realize synergistic anti-tumor effects via the combination of PTT/chemotherapy or PTT/photodynamic therapy (PDT). To the best of our knowledge, photothermal scaffolds applied to cancer therapy mainly include hydrogels, electrospun fibers and 3D printing porous scaffolds. Hydrogels are usually prepared through freeze drying method, spraying or mixing method, showing 3D porous structure and being capable of holding large amounts of water. Electrospun fibers are fabricated through electrospinning technique; the high surface area, high porosity and cross-linked porous structure of such fibers are highly

![Scheme 1. Three types of photothermal scaffolds/surfaces for regulating cell behaviors under proper NIR irradiation.](image-url)
similar to tissues and organs. 3D printing porous scaffolds are fabricated through 3D-printing technique that constructs a scaffold by printing layer-by-layer with precise control of macro-nano structures. In Section 2, the development of photothermal scaffolds for tumor ablation are introduced and categorized into three classes: (i) hydrogel-based, (ii) electrosprn fiber-based, and (iii) 3D (three-dimensional) printing porous scaffold-based (Table 1).

### 2.1 Hydrogel-based photothermal scaffolds

Hydrogel is a family of soft matters that has 3D networks of cross-linked hydrophilic polymer chains [67]. Hydrogels are ideal candidates for cancer treatment because they are generally biocompatible and can be loaded/embedded with a series of functional molecules such as drugs and deliver them to targeted sites [68,69]. In recent years, several photothermal hydrogels were fabricated by incorporation of PTAs (e.g. GNPs [33], Fe₃O₄ NPs [34], PDA NPs [38], poly(diketopyrrolopyrrole-alt-3,4-ethylenedioxythiophene) (PDPPEDOT) NPs [39], GO sheets [43]) for eradication of tumor cells and ablation of solid tumors.

In general, the tumor cells can be ablated by the heat directly produced by hydrogel-embedded PTAs under NIR irradiation with proper intensity. For example, Chen and co-workers prepared several gelatin (a natural biopolymer deriving from collagen)-based hydrogels containing different PTAs including GNPs, gold nanostars (GNSTs) and Fe₃O₄ NPs by freeze-drying method, achieving ablation of HeLa cells under 805 nm NIR irradiation [33]. In the following work, in order to achieve the targeted tumor ablation, they introduced folic acid (recognizing folate receptors (FR-α, β, γ) overexpressed in tumor cells [70]) on the surface of composite hydrogels to selectively capture of HeLa cells for further thermal ablation. Compared to the photothermal hydrogel without folic acid modification, the folic acid-modified photothermal hydrogel promoted cell adhesion on surface of hydrogel, improving the killing efficiency correspondingly [34]. They also found that the tumor cells killed by hyperthermia could promote the activation and maturity of dendritic cells, which was expected to activate the immune system to inhibit the metastasis and recurrence of tumors (Fig. 1b) [35].

Common PTT generally requires high temperature (>50 °C) to effectively ablate the tumor cells, however, such high temperature will lead to collateral damage to nearby healthy cells and normal tissues and induce inflammatory diseases by the indiscriminate heating inevitably. Low-temperature (<45 °C) PTT as a clear term has recently emerged to circumvent this problem [71], however, so far, such strategy has not been applied to photothermal scaffolds for tumor therapy. Alternatively, multi-model therapy (e.g. PTT/chemotherapy, PTT/PDT) have been developed to improve the ability of tumor ablation and decrease the laser intensity for PTT. Some anticancer drugs were incorporated into the hydrogels together with PTAs to generate a synergistic anti-tumor effect via the combination of chemotherapy and PTT. For example, Cheng and co-workers immobilized SN38 as anticancer drug on PDA NPs via strong π–π stacking interaction, and incorporated the complexes into a PEG hydrogel [37]. Under NIR irradiation, the generated heat from PDA NPs weaken the π–π stacking interaction to trigger the release of SN38, showing improved ablation efficiency to inhibit the growth of mouse PC-9 tumors in vivo [72]. To better realize the controlled release of drugs in hydrogels, stimulus-responsive hydrogels, in particular, temperature responsive poly (N-isopropylacrylamide) (PNIPAAm)-based hydrogels were chosen as the matrixes. As shown in Fig. 2a, Kim and co-workers developed a dual-responsive composite hydrogel based on a PNIPAAm hydrogel embedded with an anticancer drug DOXO together with PDA NPs loaded with bortezomib (BTZ, another anticancer drug) via the formation of borate bonds between the boronic acid groups of BTZ and catechol groups of PDA [38]. Under NIR irradiation, the produced heat ablated tumor cells and caused the shrinking of hydrogel to release DOXO (Fig. 2b). Moreover, in response to the acidic tumor microenvironment [73], BTZ was released from the surface of PDA NPs due to the dissociation of borate bonds (Fig. 2c). This platform achieved controlled multidrug release and exhibited good thermal ablation ability, showing a super synergistic effect for the tumor treatment. In addition to the combination of PTT and chemotherapy, the combination of PTT and PDT is also an effective method for tumor therapy with improved efficiency. PDT is a non-destructive method that relies on photosensitizer to generate cytotoxic reactive oxygen species (ROS), causing rapid lipid oxidation, protein and DNA damage to kill tumors [74]. The cooperation between PTT and PDT is considered a breakthrough strategy that can overcome their respective shortcomings as PTT can improve the oxygen supply of tumor tissues by increasing blood flow, thereby promoting the PDT effect and reducing the temperature required for PDT [30,75]. For example, Wu and co-workers developed a thermo-responsive chitosan-based hydrogel incorporated with nanosized black titania (B-TiO₂₇) nanoparticles showing a crystalline/amorphous core-shell structure with abundant oxygen vacancies, achieving the antitumor performance by simultaneous PTT/PDT effects [41]. Under a single-wavelength NIR irradiation, the B-TiO₂₇ nanoparticles converted the light energy into heat and generated cytotoxic ROS to kill cutaneous tumor cells in vitro and inhibit tumor growth in vivo.

So far, surgical resection remains the preferred method of treatment of skin cancer, bone cancer and breast cancer [76]. However, after surgical removal of the tumor, there are two possible residual problems: (i) if the tumor tissue is not completely removed, the remaining tumor cells would continue proliferation and metastasis, and (ii) the large area tissue defects caused by surgical resection are hard to recover [77]. It is thus promising to construct a bifunctional material that is able to eliminate tumor and promote tissue regeneration simultaneously. In this regard, a series of bioactive components with capability to promote the regeneration of defective tissues were incorporated into photothermal hydrogels [42–44]. For example, He, Yu and co-workers constructed a stable hydrogel via the self-assemble of two functional materials including reduced graphene oxide (rGO) and nano-hydroxyapatite (nHA) [43]. rGO not only has good photothermal property but also can induce the differentiation of bone marrow stem cells (BMScs) into osteoblasts and promote bone repair in vivo [78]; nHA is widely used as artificial bone to repair bone defects because it can promote the osteogenic differentiation of rBMSC [79]. Under NIR irradiation, this composite hydrogel ablated osteosarcoma cells (MG-63) effectively in vitro and prevented tumor growth in vivo. After the implantation the hydrogel in the bone defect of rabbit, dense new bone tissue was observed on the cross-section of the entire scaffold after eight weeks (Fig. 3a), indicating good osteogenic ability of the hydrogel. In addition to the treatment of breast cancer and bone cancer, hydrogels have more extensive applications in skin cancer and melanoma because the permeable structure is favorable for adsorption of wound exudate and exchange of gas, thus promoting wound regeneration and angiogenesis [80]. To this end, Wu and co-workers developed a smart oligomeric proanthocyanidins (OPC, deriving from grape seed extract)-containing hydrogel to cure melanoma and promote wound healing (Fig. 3) [44]. In this design, OPC was not only used as a natural photothermal agent, but also facilitated wound healing. Under NIR irradiation, the composite hydrogel effectively killed melanoma cells and inhibited tumor growth. Moreover, it also promoted the migration and proliferation of skin fibroblasts and endothelial cells, thereby facilitating the angiogenesis and skin regeneration. Although hydrogels are easy to prepare and have been widely used in PTT, they still have some disadvantages. For example, most of the hydrogels are prepared through freeze drying and simple mixing methods, making it difficult to control the structure, diameter of the pores and the porosity of the scaffolds. Moreover, due to the low mechanical strength and fragile nature of the hydrogels, the feasibility of applying hydrogels is still limited.
### Summary of photothermal scaffolds for tumor ablation

| PTAs | Light wavelength | Functional molecules | Matrix materials | Preparation methods | Performance of scaffolds | Cell Line | Ref. |
|------|------------------|----------------------|------------------|---------------------|--------------------------|-----------|-----|
| Hydrogel-based photothermal scaffolds | 805 nm | N. A. | Gelatin | Ice particulate porogen method | Cancer cell entrapment + PTT | HeLa cells in vitro | [32] |
| Fe3O4 NPs | 805 nm | N. A. | Gelatin | Ice particulate porogen method | Cancer cell entrapment + PTT | HeLa cells in vitro | [33] |
| Fe3O4 NPs | 805 nm | N. A. | Gelatin | Ice particulate porogen method | Cell capture + PTT | HeLa cells in vitro | [34] |
| GNRs | 805 nm | N. A. | Gelatin | Ice particulate porogen method | Cancer cell entrapment + PTT + Immune activation | 4T1-Luc cells in vitro; mDCs | [35] |
| BP | 808 nm | N. A. | PLEL | Spraying method | PTT | MB231-Luc cells tumor-bearing mice in vivo; mouse PC-9 cells | [36] |
| PDA NPs | 808 nm | SN38 | PEG | Mixing method via Michael addition and/or Schiff base reactions | Chemotherapy + PTT | CT26 colon cancer cells in vitro | [37] |
| GNRs | 808 nm | N. A. | Gelatin | Ice particulate porogen method | PTT + Tissue regeneration | MDA-MB-231-Luc cells in vitro; MDA-MB-231-Luc cells tumor-bearing mice in vivo | [38] |
| GO | 808 nm | DOX | CSMA/BPEI/BPEI-GO | Mixing method | Self-healing + Chemotherapy + PTT | HeLa cells | [39] |
| Black titania | 808 nm | Black titania | Chitosan | Mixing method | PTT + PDT + Tissue regeneration | MCF-7 cells in vitro; Mice bearing 4T1 cells in vivo | [40] |
| GNRs | 808 nm | N. A. | Gelatin | Ice particulate porogen method | PTT + Tissue regeneration | HeLa cells | [41] |
| OPC | N. A. | Calcium silicate nanowires and sodium alginate (CS-SA) | Calcium silicate nanowires and sodium alginate (CS-SA) | 3D printing technology | PTT + Would healing | HeLa cells in vitro; Mice bearing B16F10 tumor in vivo; HUVECs/HDFs | [42] |
| Electrospun fiber-based photothermal scaffolds | 808 nm | N. A. | PLA | Electrospinning | PTT | MCF-7 cells in vitro; Mice bearing 4T1 cells in vivo | [43] |
| B3S3 | 810 nm | GO | PCL | Electrospinning | Cell capture + PTT | MDA-MB-231-Luc cells in vitro; MDA-MB-231-Luc cells tumor-bearing mice in vivo | [44] |
| CuS | 980 nm | N. A. | PCL/gelatin | Electrospinning | Biodegradability + Chemotherapy + PTT | MG-63 cells; rBMSCs | [45] |
| PDA NPs | 808 nm | BTZ | Polydioxanone | Electrospinning | Control of drug release + Chemotherapy + PTT | CT26/MCF7 cells in vitro; MCF7 tumor in vivo | [46] |
| PPy | 808 nm | PTX/PolyPy | PCL | Electrospinning | Control of drug release + Chemotherapy + PTT | A549/MCF7 cells in vitro | [47] |
| PDA NPs | 808 nm | DOX for chemotherapy | PCL | Electrospinning | Control of drug release + Chemotherapy + PTT | B16F10 cells in vitro; Mice bearing B16F10 tumor in vivo; HUVECs/HDFs | [48] |
| PDA NPs | 808 nm | DOX for chemotherapy | PCL-Gelatin fiber | Electrospinning | Control of drug release + Chemotherapy + PTT | CCLP1 cells in vitro; PDX model in vivo | [49] |
| CuS | 808 nm | Cu ions for accelerating tissue healing | PLA/PCL | Patterning co-electrospinning | PTT + Tissue regeneration | B16F10/Luc3 cells in vitro; B16F10 tumor-bearing mice in vivo; HUVECs/HDFs | [50] |
| CaCuSi4O10 NPs | N. A. | Cu2+ and SiO4 4- ions for accelerating tissue healing | PCL/PDLLA | N. A. | PTT + Tissue regeneration | B16F10 cells in vitro; B16F10 tumor-bearing mice in vivo | [51] |
| CSO HSMs | 808 nm | Trataminib for chemotherapy; Cu ions and silicate-based biomaterials for accelerating tissue healing | PLA/PCL | Electrospinning | Chemotherapy + PTT + Tissue regeneration | B16F10 cells in vitro; B16F10 tumor-bearing mice in vivo | [52] |
| 3D printing porous scaffold-based photothermal scaffolds | 808 nm | N. A. | β-TCP | 3D-printing and surface modification technology | PTT + Bone regeneration | MG-63 cells in vitro; Saos-2 tumor-bearing mice in vivo; rBMSCs in vitro | [53] |
| PDA | 808 nm | Bioceramic | 3D-printing and surface self-assembly | PTT + Bone regeneration | Saos2/MDA-MB-231 cells in vitro; Saos2 tumor-bearing mice in vivo | [54] |

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### 2.2. Electrospun fiber-based photothermal scaffolds

Electrospun fibers fabricated through electrospinning with polymers have various advantages including high specific surface area, adjustable nano/micro structure, and ability for loading functional molecules such as drugs, growth factors, etc. Therefore, they have attracted wide attention as implantable materials for treatment of solid tumors [81–83]. Photothermal electrospun fibers are constructed by embedding PTAs into interior of fibers or coating PTAs on the surface of fibers. In recent years, various natural polymers and synthetic polymers have been applied to fabricate photothermal electrospun fibers for tumor ablation.

Yu and co-workers prepared poly(l-lactic acid) (PLLA)-based electrospun fibers containing Bi$_2$Se$_3$ through uniaxial electrospraying technology, which achieved efficient ablation of HeLa cells under NIR irradiation. In addition, the tumor surgically incised and covered with Bi$_2$Se$_3$/PLLA fiber was getting smaller, compared to that without fiber coverage or with PLLA fiber coverage [45]. Although these fibers exhibited good efficiency of tumor ablation, the hyperthermia might result in certain harmful effects on normal cells and tissues. In order to decrease the temperature for killing tumor cells, a series of multifunctional electrospun fibers combining PTT and other therapeutic methods were developed [84,85]. For example, Lin, Li and co-workers incorporated core-shell Cu$_3$S$_2$@mesoporous SiO$_2$ nanoparticles embedded with DOX in electrospun fiber membranes composed of polycaprolactone (PCL) and gelatin, achieving efficient ablation of hepatoma H22 tumor (Fig. 4a) [47]. Under NIR irradiation, Cu$_3$S$_2$ nanoparticles produced heat, which not only achieved thermal ablation of tumor cells, but also promoted the release of DOX, enhancing the therapeutic effects. Afterwards, Kim and co-workers developed a series of electrospun fibers

### Table 1 (continued)

| PTAs                   | Light wavelength | Functional molecules                                      | Matrix materials            | Preparation methods                                | Performance of scaffolds                        | Cell Line                          | Ref. |
|------------------------|------------------|----------------------------------------------------------|-----------------------------|---------------------------------------------------|-------------------------------------------------|------------------------------------|------|
|                         |                  |                                                          |                             |                                                   |                                                 |                                    |      |
| MoS$_2$                | 808 nm           | N. A.                                                    | Akermanite (AKT) bioceramic | 3D-printing and hydrothermal method                | PTT + Bone regeneration                        | mice in vivo; rBMSCs in vitro;     | [57] |
|                         |                  |                                                          |                             |                                                   |                                                 | Critical-sized femoral defect model in vivo; |      |
|                         |                  |                                                          |                             |                                                   |                                                 | rBMSCs in vitro;                   |      |
|                         |                  |                                                          |                             |                                                   |                                                 | Critical-sized femoral defect model in vivo;  |      |
|                         |                  |                                                          |                             |                                                   |                                                 | rBMSCs in vitro;                   |      |
| Free carbons           | 808 nm           | Free carbon and larnite for enhancing osteogenic         | Larnite                     | 3D printing and polymer-derived ceramics strategy | PTT + Bone regeneration                        | MNNG/HOS cells in vitro;           | [59] |
|                         |                  | differentia-tion                                        |                             |                                                   |                                                 | HOS tumor-bearing mice in vivo;      |      |
|                         |                  |                                                          |                             |                                                   |                                                 | rBMSCs; critical-sized rat          |      |
|                         |                  |                                                          |                             |                                                   |                                                 | calvarial defects                   |      |
| Fe                     | 808 nm           | N. A.                                                    | AKT bioceramic              | Sol-gel and 3D-printing technology                | PTT + MTT + Osteogenic differentiation          | LM-8 cells, rBMSCs                 | [60] |
|                         |                  |                                                          |                             |                                                   |                                                 |                                    |      |
| Nh$_2$C$_6$ nanosheets  | 1064 nm          | 2D Nh$_2$C$_6$ nanosheets wrapped with S-nitrosothiol   | Bioactive glass             | Solution-soaking approach and 3D-printing technology | PTT + NO therapy + Bone regeneration         | Saso2 cells; Saso2 tumor-          | [61] |
|                         |                  | for providing NO                                         |                             |                                                   |                                                 | bearing mice in vivo; hBMSCs;        |      |
|                         |                  |                                                          |                             |                                                   |                                                 | critical-sized rat calvarial        |      |
|                         |                  |                                                          |                             |                                                   |                                                 | defects                            |      |
| BP                     | 808 nm           | N. A.                                                    | Bioactive glass             | 3D-printing and surface modification method       | PTT + Bone regeneration                        | Saso2 cells in vitro; Saso2 tumor- | [62] |
|                         |                  |                                                          |                             |                                                   |                                                 | bearing mice in vivo; hBMSCs in     |      |
|                         |                  |                                                          |                             |                                                   |                                                 | vitro; critical-sized rat           |      |
|                         |                  |                                                          |                             |                                                   |                                                 | calvarial defects                   |      |
| Ti$_3$C$_2$ nanosheets  | 808 nm           | Ca$^{2+}$, PO$_4^{3-}$ and Ti-based species for         | Bioactive glass             | 3D-printing and soak-coating method                | PTT + Bone regeneration                        | Saso2 cells; Saso2 tumor-          | [63] |
|                         |                  | promoting bone regeneration                             |                             |                                                   |                                                 | bearing mice in vivo; hBMSCs;        |      |
|                         |                  |                                                          |                             |                                                   |                                                 | critical-sized rat calvarial        |      |
|                         |                  |                                                          |                             |                                                   |                                                 | defects                            |      |
| CuFeSe$_2$ nanocrystals| 808 nm           | N. A.                                                    | Bioactive glass             | 3D printing technique with solvothermal method    | PTT + Bone regeneration                        | Saso2 cells in vitro; Saso2 tumor- | [64] |
|                         |                  |                                                          |                             |                                                   |                                                 | bearing mice in vivo;               |      |
|                         |                  |                                                          |                             |                                                   |                                                 | rBMSCs in vitro;                   |      |
|                         |                  |                                                          |                             |                                                   |                                                 | Critical-sized femoral defect       |      |
|                         |                  |                                                          |                             |                                                   |                                                 | model in vivo                       |      |
| Cu, Fe, Mn, Co         | 808 nm           | N. A.                                                    | Bioactive glass–ceramic     | 3D-printing technology                             | PTT + Bone regeneration                        | Saso2 cells in vitro; Saso2 tumor- | [65] |
|                         |                  |                                                          |                             |                                                   |                                                 | bearing mice in vivo;               |      |
|                         |                  |                                                          |                             |                                                   |                                                 | rBMSCs in vitro;                   |      |
|                         |                  |                                                          |                             |                                                   |                                                 | Critical-sized femoral defect       |      |
|                         |                  |                                                          |                             |                                                   |                                                 | model in vivo                       |      |
| La$_5$Ni$_2$ micro-NPs | 808 nm           | N. A.                                                    | β-TCP                       | 3D-printing and soak-coating method                | PTT + Bone regeneration                        | Saso2 cells in vitro; Saso2 tumor- | [66] |
|                         |                  |                                                          |                             |                                                   |                                                 | bearing mice in vivo;               |      |
|                         |                  |                                                          |                             |                                                   |                                                 | rBMSCs in vitro;                   |      |
|                         |                  |                                                          |                             |                                                   |                                                 | Critical-sized femoral defect       |      |
|                         |                  |                                                          |                             |                                                   |                                                 | model in vivo                       |      |

*a Abbreviation: Reduced graphene oxide (rGO); Gold nanostars (GNSTs); Copper silicate hollow microspheres (CSO HMs); Oligomeric proanthocyanidins (OPC); doxorubicin (DOX); Bortezomib (BTZ); Paclitaxel (PTX); Poly-γ-lysine (PLL); Polyvinyl alcohol (PLA); Polyethylene glycol (PEG); Poly(3-lactic acid) (PLLA); Polycaprolactone (PCL); Poly(D, l-lactic acid) (PDLLA); Polypyrrole (PPy); Human umbilical vein endothelial cells (HUVECs); Human skin fibroblast (HSF); Rat bone marrow stem cells (rBMSCs); Human bone marrow stem cells (hBMSCs); Human dermal fibroblasts (HDFs); patient-derived xenograft (PDX); Poly (N-isopropylacrylamide) (PNIPAAm); nano-hydroxyapatite (nHA); Poly(diketopyrrolopyrrole-alt-3,4-ethylenedioxythiophene) (PDPPDOT); Poly(d,l-lactide)-poly (ethylene glycol)-poly(d,l-lactide) (PLEL); Chondroitin sulfate multialdehyde (CSMA), Branched polyethyleneimine (BPEI); BPEI conjugated graphene (BPEI-GO); β-tricalcium phosphate (β-TCP).*
wrapped/loaded with chemical drugs and PTAs, achieving excellent ablation of colon cancer cells and breast cancer cells by synergistic effect of chemotherapy and PTT [48–50]. For example, they prepared a composite fiber composed of polydioxanone (PDO) embedded with PDA NPs as PTAs and BTZ as drugs, which could ablate the colon tumor cells in 3-min NIR irradiation due to the released BTZ and induced hyperthermia (Fig. 4b) [48]. In order to further improve the controlled release of chemical drugs, polypyrrole (PPy) with both excellent photothermal properties and pH-responsiveness was coated in situ on the surface of PCL-based electrospun fiber embedded with a drug of paclitaxel (PTX). In the acidic environment of tumors [73], the swelling of PPy accelerated the release of PTX. Under NIR irradiation, the PPy coating not only realized the efficient thermal ablation of the tumor, but also accelerated the release of PTX, promoting the therapeutic effect and maintaining good biocompatibility.

Similar to hydrogels as mentioned above, it is also of importance to endow electrospin fibers with capability of both tumor ablation and tissue regeneration. To this end, Wu and co-workers developed a series of such dual-functional electrospin fibers [52–54]. For example, they fabricated micropatterned nanocomposite fibers by incorporating Cu_{2}S nanoflowers into poly(D,L-lactic acid) (PDLLA)/PCL fibers (CS-PLA/PCL) via a modified electrospinning method (Fig. 5a) [52]. Because of good photothermal properties of Cu_{2}S nanoflowers, under NIR irradiation the resulted fibers ablated skin tumor cells in vitro and prevented tumor growth in vivo effectively. In addition, the released Cu^{2+} ions from CS-PLA/PCL membranes could promote angiogenesis and enhance the maturity of the extracellular matrix (ECM) via regulation of corresponding gene expression [86], thus promoting the adhesion, migration, and proliferation of normal skin cells in vitro (Fig. 5a), and stimulating angiogenesis and heal full-thickness skin defects in vivo. In another work, inspired by the shape of Chinese sesame sticks, they coated the surface of polyvinyl alcohol (PLA)/PCL electrospun fibers with CaCuSi_{4}O_{10} nanoparticles, showing the similar structure as Chinese sesame sticks (Fig. 5b) [53]. Besides the photothermal tumor ablation property from CaCuSi_{4}O_{10} nanoparticles, the active Cu^{2+} and SiO_{4} ions released from the fibers could stimulate angiogenesis and re-epithelialization [87], thereby promoting chronic wound healing. To further enhance ablation efficiency, they fabricated PLA/PCL composite fibers wrapped with anticancer drug (trametinib)-loaded copper siliate hollow microspheres, achieving synergistic chemo-photothermal killing effects of skin tumor cells and facilitating the healing process in tumor-bearing and diabetic mice [54]. Although the electrosprinning technology can well control the structure of the fibers and prepare a scaffold with a complex structure (such as random or oriented structures), it should be noted that there are many parameters that need to be adjusted carefully during the preparation process. Moreover, the resulted electrospun fibers are generally two-dimensional (2D) membranes with small pores and low thickness.

2.3. 3D printing porous scaffold-based photothermal scaffolds

Compared with 2D membranes, 3D porous scaffolds may have better effects for tissue regeneration of tumor site in situ as the interconnected macro pores of 3D porous scaffolds are necessary to supply adequate space for transportation of nutrients communications of neighboring cells [88]. Various methods to prepare 3D porous scaffolds have been developed, among which the 3D printing technology is the preferred option due to its advantages such as easy and economical fabrication of objects, the end-user customization, and rapid prototyping [89–92]. In addition, it is convenient to incorporate bioactive materials during printing process to endow the printing scaffolds desired functions [93]. In the past few years, the introduction of PTAs into the 3D printing
scaffolds to achieve bone tumor ablation and tissue regeneration has attracted increasing attentions [90]. Some representative examples are introduced as follows.

3D printing bioceramic scaffolds have been demonstrated to be able to stimulate osteoblast differentiation, promote angiogenesis in vitro, and initiate bone regeneration in vivo, because the precise interconnected macropores benefit the nutrient transportation and cell ingrowth, and the released bioactive elements (Si, Ca and P) during the scaffold degradation stimulate bone formation and angiogenesis [94]. Based on these advantages, Wu and co-workers developed a series of 3D printing bioceramic scaffolds with excellent photothermal properties, achieving osteoma ablation and bone regeneration effectively [55–57, 60, 65, 66]. For example, they fabricated a bifunctional GO-modified β-tricalcium phosphate (β-TCP) (GO-TCP) scaffold (Fig. 6a). Under NIR irradiation, the resulted scaffold could ablate >90% of osteosarcoma cells in vitro, and prevent tumor growth in mice effectively. Additionally, the scaffold could stimulate the osteogenic differentiation of BMSCs by up-regulating the expression of bone-related genes, and thus promote bone formation in rabbit bone defects [55]. Afterwards, they introduced PDA coating and MoS2 nanosheets with better biocompatibility as PTAs onto/into the bioceramic scaffold, respectively, which also achieved photothermal ablation of osteoma and promoted bone regeneration [56, 57].

Fig. 2. (a) Scheme of a pH/NIR-dual responsive composite hydrogel for chemo-photothermal cancer therapy. (b) Release profiles of BTZ and DOXO from the composite hydrogel at different pH under cyclic ON/OFF NIR irradiation. (c) Release profile of BTZ from the composite hydrogel at different pH. Reproduced with permission from Ref. 38. Copyright 2016 Springer Nature.
PTT alone, but also reduce the temperature required for PTT, thereby reducing the damage of excessive temperature to surrounding normal tissues. Cao, Chen, Zhang and co-workers incorporated nitric oxide (NO) donors (S-nitrosothiol, SNO) [97] and mesoporous silicon loaded with MXene nanosheets possessing large specific surface and photothermal property into 3D printing bioglass (BG) scaffold to combine gas therapy and PTT together in one scaffold [61]. In the initial stage, the osteoma cells could be ablated effectively by combining PTT and gas therapy under the action of NO with high concentration. In the later stage, NO with low concentration and BG scaffold could enhance vascularization and bone formation (Fig. 7b), so as to achieve excellent tumor ablation and bone formation.

Most of the PTAs used in the above research only have the ability of ablation of osteoma, but have little effect on osteogenesis. To this end, several bifunctional PTAs possessing abilities of osteoma ablation and enhanced osteogenesis were incorporated into 3D printing scaffolds. For example, Shi and co-workers integrated 2D BP nanosheets on the 3D printing BG scaffold (BP-BG) for photothermal ablation of tumors and osteogenesis [62]. Besides the function of photothermal ablation of tumors in the early stage, BP also enhanced biomineralization in situ, thus promoting bone formation under the action of its degradation products. In addition, the oxidation of the BP coating also accelerated the release of phosphate ions (PO$^{4-}$), which could bind the calcium ions from body fluids, thereby promoting the formation of new calcium phosphate.

Fig. 3. Top: a composite hydrogel scaffold containing OPC, calcium silicate nanowires (CS) and sodium alginate (SA) for melanoma therapy and wound healing under NIR irradiation; Down: typical photos of skin wounds at different intervals. (i): blank with no treatment, (ii): CS + SA, and (iii) CS + SA + OPC hydrogel scaffold. Reproduced with permission from Ref. 44. Copyright 2019 American Chemical Society.
nanoparticles (Fig. 8a). Apart from black phosphorus, 2D ultra-thin Ti₃C₂ nanosheets also have such two capabilities of photothermal ability and promoting bone formation [98]. The released Ti-based species in the degradation process by the interaction between water and oxygen could promote the growth of new bones, making Ti₃C₂ nanosheets suitable as dual functional PTAs for fabrication of 3D printing scaffolds to treat bone tumors (Fig. 8b) [63]. The 3D printing technique that can precisely control pore structure of scaffolds has gained strong appeal in the field of tumor treatment. However, the equipment used for 3D printing is expensive and the process takes a relatively long time. Moreover, the types of applicable materials are limited, making it difficult for production in large-scale. In addition to the above three scaffolds including hydrogels, electrospun fibers and 3D printing scaffolds, it is necessary to exploit other photothermal scaffolds integrating simple preparation methods, controllable material structures, and scalable preparation for tumor treatment.

3. Photothermal scaffolds/surfaces for intracellular delivery of exogenous molecules

In addition to generating intensive heat to ablate tumor cells, photothermal scaffolds/surfaces can also produce moderate heat under
suitable light intensity to increase membrane permeability of cells without obvious cell damage, providing the possibility of intracellular delivery of exogenous molecules. Delivery of exogenous functional materials and biomacromolecules into living cells to regulate their behaviors and fates is a crucial step in cell-based therapy as well as tissue repair and regeneration [99], for example, delivering functional genes into immune cells ex vivo to obtain Chimeric Antigen Receptor T (CAR-T) cells for cancer therapy [100] or into adult cells to obtain induce pluripotent stem cells (iPSCs) for tissue regeneration [101]. The plasma membrane of cells, however, is an impermeable barrier for most exogenous molecules [102], and it is still challenging to achieve high delivery efficiency without compromising cell viability. According to the different ways of exogenous molecules passing through the cell membrane, the current intracellular delivery approaches can be categorized into two main classes: carrier-based approaches and membrane disruption-based approaches [103]. Although various carriers such as viral vectors and non-viral vectors including cationic polymers and liposomes have been developed, they still have some limitations including low delivery efficiency, high cell toxicity and limited universality [104]. In contrast, membrane disruption-based approaches transport the exogenous molecules into cells by membrane permeabilization or penetration via membrane disruption agents, mechanical, electrical, optical, acoustical, and thermal means, showing broader applications regardless of targeted cell and delivered molecules [105]. Among these membrane disruption-based methods, photothermal-poration has received great interest due to its various advantages including simple equipment, easy operation, and good spatiotemporal control of delivery [106]. In the photothermal-poration method, under NIR irradiation, the heat generated by the PTAs increases the temperature of surrounding medium or generates shock waves or water vapor nanobubbles.
Fig. 6. (a) Preparation of a 3D printing bifunctional GO-TCP scaffold for ablation of tumor cells and promotion of new bone formation. Reproduced with permission from Ref. 55. Copyright 2016 John Wiley and Sons. (b) Fabrication of 3D printing larnite/C scaffolds for PTT and bone regeneration. Reproduced with permission from Ref. 59. Copyright 2020 Elsevier.
inducing the phase transition of the phospholipid bilayer or the thermal denaturation of the whole glycoprotein to promote the entrance of delivered molecules into target cells [107, 108].

During the recent decade, several photothermal scaffolds/surfaces have been developed as photothermal-poration platforms for effective delivery of various molecules to diverse types of cells, which will be introduced in this section as divided into two categories: (i) photothermal scaffolds/surfaces embedded or deposited with PTAs randomly, and (ii) photothermal surfaces with regular structure (Table 2).

3.1. Photothermal scaffolds/surfaces embedded or deposited with PTAs randomly

Under NIR irradiation, photothermal scaffolds/surfaces embedded or deposited PTAs randomly can produce heat to improve the membrane permeability of the cells cultured on the surfaces, thereby promoting the
entrance of exogenous molecules into cells. So far, the PTAs used mainly included gold nanomaterials, PDA nanoparticles, and magnetic nanoparticles [110–113]. Gold-based nanomaterials (such as GNRs and GNPs) have various characters including excellent photothermal effects, good biocompatibility, easily deposition on substrates [126], therefore, a series of surfaces deposited with gold nanomaterials were developed for intracellullar delivery via photothermal-portation [109–111]. In 2010, Chiou and co-workers developed a cell culture dish immobilized with GNPs by particle bombardment [109]. Under laser irradiation, the modified dish surface generated heat energy to produce water vapor nanobubbles, thus generating the “transient holes” on cell membrane, facilitating the intracellular delivery of molecules. Furthermore, with the assistance of the specific coverage of a photomask, a patterned delivery of fluorescent molecules to human embryonic kidney cells (HEK293) was achieved. However, this method relied on expensive equipment [127]. Additionally, a large-area surface can be obtained by the chemical plating method. More importantly, compared with scattered GNPs in solution, GNPL composited with dense GNPs has a more excellent photothermal effect [128]. Taking advantages of the characteristics of GNPL, we established a universal platform for delivering various molecules into different cell types with high efficiency [110]. The proposed delivery mechanism was illustrated in Fig. 9a, under NIR irradiation, the moderate heat generated by GNPL resulted in the formation of “transient holes” on cell membrane, thus the exogenous molecules could be entered into cell interior through the “transient holes”. The mechanism was confirmed by the results of confocal microscopy, which indicated that the tetra-methylrhodamine isothiocyanate (TRITC)-labeled dextran was delivered into the cell interior, not merely adhered to the outer membrane (Fig. 9b). Although using GNPL outperformed the widely used transfection reagent, Lipofectamine 2000 in gene transfection (i.e. intracellular delivery of plasmid DNA (pDNA)) for c recalcitrant primary cell lines, the efficiency is still not as good as that for easy-to-transfect cell lines. The low efficiency might be resulted from the possible enzymolysis of unprotected pDNA in the extracellular space. In order to enhance the transfection efficiency for hard-to-transfect cells, we further collaborated GNPL with a cationic polymer carrier (polyethylenimine, PEI, 2 kDa) to protect pDNA, realizing high delivery efficiency of plasmid DNA-encoding green fluorescence protein (pGFP) to hard-to-transfect cells (94.0 ± 6.3% for HUVECs, and 88.5 ± 9.2% for mouse embryonic fibroblasts (mEFs)) with high cell viability [111]. Moreover, as a proof-of-concept, a functional pDNA encoding ZNF580 gene (pZNF580) was transfected to HUVECs utilizing this platform, and the “engineered” HUVECs showed enhanced cell attachment in early stage and cell proliferation for long-term culture, showing potentials for endothelialization of blood contacting devices.

Besides gold-based nanomaterials, PDA also has excellent light-to-heat conversion property. Moreover, PDA has been widely used for surface functionalization due to its strong adhesive property regardless of the properties of substrates [129,130]. Therefore, PDA was explored as a photothermal layer for intracellular delivery. For example, Ji, Ren, and co-workers developed a microporous spongy film modified with PDA for gene transfection [112]. In detail, a poly(D, L-lactide-co-glycolide) (PLGA) spongy film with microporous structure was prepared by ultrasonic spray onto polymethyl methacrylate substrate, followed by being coated with PDA and modified by hyaluronic acid with negatively charge for loading pGFP encapsulated with branched PEI (bPEI) (pGFP/bPEI) (Fig. 10a). Under NIR irradiation, the loaded pGFP/bPEI was delivered to the HUVECs attached on the film with high transfection efficiency (85%). Moreover, the spatial control of delivery was realized by controlling the laser irradiation, providing this platform potentials in precision gene therapy. In the following work, they designed another photothermal platform by simply co-depositing PDA and PEI onto the cell culture plate wells, which was easier to prepare and did not need complicated equipment compared to the former PLGA-based photothermal film [113]. Moreover, the PEI pre-immobilized onto surface could increase the loading of pGFP/bPEI complex. The produced heat not only promoted the pDNA release form the surface, but also increased the membrane permeability of cells. The probable delivery mechanism was studied by using Sytox (a red dye that is membrane-impermeable) staining assay. As shown in Fig. 10b, no...
obvious fluorescence was observed for the cells without NIR irradiation, suggesting their intact membranes. In contrast, red fluorescence was observed for the cells without NIR irradiation, and more fluorescent cells after longer irradiation time. In addition, NIR irradiation also led to the obvious fluorescence was observed for the cells after NIR irradiation, and more fluorescent cells outside the cells.

### Table 2: Summary of photothermal scaffolds/surfaces for intracellular delivery of exogenous molecules

| PTAs                  | Laser wavelength | Strategy of loading PTAs onto surfaces | Delivered molecules                                      | Cell types          | Delivery efficiency | Cell viability | Ref  |
|-----------------------|------------------|----------------------------------------|----------------------------------------------------------|---------------------|--------------------|----------------|------|
| Photothermal scaffolds/surfaces embedded or deposited with PTAs randomly
| GNSPs 532 nm          | Bombardment technique | Fluorescent dye | HEK293T cells | N.A. | N.A. | [109] |
| GNPs 808 nm           | Chemical plating method | TRITC-dextran/pGFP | HeLa cells/ mEFs/ HUVECs | HeLa cells with 100%; pGFP delivery to mEFs, HUVECs with 53% and 44%; mEFs/HUVECs with 88.5% and 80% | Near 100% | [110] |
| GNPs 808 nm           | Chemical plating method | pGFP | HeLa cells/ mEFs/ HUVECs | HeLa cells with 100%; pGFP delivery to mEFs, HUVECs with 53% and 44%; mEFs/HUVECs with 88.5% and 80% | Near 100% | [111] |
| PDA 808 nm            | Self-polymerization | pDNA | HUVECs | HUVECs/293T cells | N.A. | N.A. | [112] |
| P-MNPs 808 nm         | Adsorption via magnetic field | Dextran/pDNA | HeLa/mEFs | HeLa/mEFs | 67% for pGFP to HeLa; 30% for pGFP to mEFs | >92.6% | [114] |
| PDA 808 nm            | Self-polymerization | Dextran/BSA/pGFP/2NF580 gene | HeLa/mEFs/ HUVECs/mDCs | HeLa/mEFs/ HUVECs/mDCs | 60% for mDCs | >90% for other cells | [115] |
| GNRs 785 nm           | Microcontact printing | DOX | A498 cells | A498 cells | >90% | N.A. | >90% | [116] |
| GNRs 808 nm           | Embedding GNRs into fibers during electroporocessing | pGFP | NIH3T3 | NIH3T3 | >90% | N.A. | >90% | [117] |
| Photothermal surfaces with regular structure
| TPS Au surface 800 nm/1064 nm | Nanofabrication | FITC-dextran/Calcein | HeLa cells | HeLa cells | 95% for the smallest molecules | Up to 98% | [118,119] |
| TPS TiN MPAs 1064 nm   | Anisotropic etching | Calcein dye | HeLa cells | HeLa cells | >90% | N.A. | >90% | [120] |
| metallic (Ti) tips 532 nm | Sputter deposition | Calcein (0.6 kDa)/FITC-dextran (2000 kDa)/bacterial enzyme β-lactamase (29 kDa)/pGFP | Ramos suspension B cells | Ramos suspension B cells | 84%, 45% and 58% for calcein, FITC-dextran and pGFP delivery | >89% | [121] |
| GNDAs 532 nm          | Chemical lift-off lithography | Calcein (0.6 kDa) | HeLa cells | HeLa cells | >98% | >98% | [122] |
| GNTs 1064 nm          | Focused ion beam milling and secondary electron lithography | PI | NIH3T3 | NIH3T3 | N.A. | N.A. | >90% | [123] |
| SiNWAs 808 nm         | Chemical etching method | RBITC-BSA/pGFP | HeLa/Ramos/T cells | HeLa/Ramos/T cells | 100%, 83% and 80% for pGFP transfection to HeLa, Ramos and T cells, respectively | >95% | [125] |

Abbreviations: gold nanosphere particles (GNSPs); gold nanotubes (GNTs); gold nanodisk arrays (GNDAs); porous magnetic iron oxide nanoparticles (P-MNPs); gold-coated thermoplasmonic substrates (TPS-Au); TiN-coated thermoplasmonic substrates (TPS-TiN); silicon nanowire arrays (SiNWAs); Tetramethylrhodamine isothiocyanate/fluorescein isothiocyanate-labeled dextran (TRITC/FITC-dextran); plasmid DNA-encoding green fluorescence protein (pGFP); pDNA encoding fibroblast factor (pFGF); NIH3T3; human embryonic stem cells (hESCs); human embryonic stem cells (mESCs); human umbilical vein endothelial cells (HUVECs); mouse dendritic cells (mDCs); peripheral blood monocyte-derived macrophages (PB-MDMs); renal proximal tubule epithelial cells (RPTECs).

In addition to high-efficiency delivery of functional molecules, harvesting the “engineered” cells effectively and non-traumatically from the surfaces is also important for the further fundamental research or clinical utilizations such as ex vivo cell-based therapies, e.g., hematopoietic stem cells transplantation to reconstitute dysfunctional cell lineages [131] and T-cell immunotherapy [100], in which the “engineered” cells should be injected to patients. In regard, we developed a nanoplatform based on porous magnetic iron oxide nanoparticles (P-MNPs) with photothermal properties for macromolecular delivery [114]. Before cell seeding, a layer of P-MNPs was deposited on the bottom of the culture plate used a magnetic field, enabling more efficient heat transfer between the cells and P-MNPs, compared with suspended P-MNPs in solution. Under NIR irradiation, successful delivery of pGFP to cells were obtained with negligible cytotoxicity. Most importantly, 97% of the “engineered” cells could be harvested simply by treatment of proteolytic enzymes (e.g. trypsin) while high viability for subculture was maintained, which is crucial for further practical application of the delivery system. Although the “engineered” cells could be recovered from surface of P-MNPs layer by trypsin treatment, the delivery efficiency of pGFP to cells using p-MNPs layers was not very high, especially for the hard-to-transfect cell lines, while trypsin treatment may impair the cell viability. To circumstance this problem, we developed a two-in-one platform for high-efficiency intracellular delivery and cell harvest by gratting thermo-responsive PNIPAaAm chains from a PDA layer to achieve a PDA/PNIPAaAm hybrid film [115]. Because of the excellent photothermal property of PDA, this hybrid film delivered diverse molecules to multiple cell types including hard-to-transfect cells (e.g. HUVECs, mEFs and mouse dendritic cells (mDCs)) under proper NIR irradiation. Moreover, due to the thermo-responsive property of
PNIPAAm, the cells with delivered molecules were released from the film simply by lowering the temperature of cell medium (Fig. 11a), because the surface of PDA/PNIPAAm hybrid film became more hydrophilic state from hydrophobic state [132]. More importantly, the released cells preserved good viability for further subculture, and the delivered biomolecules realized their specific functions. For example, using this platform, recalcitrant HUVECs were transfected with ZNF580 gene, showing improved migration ability compared with untransfected cells (Fig. 11b).

3.2. Photothermal surfaces with regular structure

Although the above-mentioned photothermal scaffolds/surfaces are relatively easy to prepare, they still have some shortcomings. For example, it is difficult to well control the uniformity of the distribution of PTAs on the surface, which may lead to uneven heating of the cells attached to the surface under NIR irradiation, resulting in inconsistent delivery. In addition, a small part of immobilized PTAs or their fragments may be detached from the surface and delivered into cell interior, causing potential cell cytotoxicity [110,133]. To this end, a series of array-type surfaces with photothermal effects were developed including nanopyramid arrays (Scheme 2a), nanodisk arrays (Scheme 2b), nanowire arrays (Scheme 2c) and hollow nanohole arrays (Scheme 2d) to deliver exogenous molecules to the cells [119,122,124,125].

Most of the array-type photothermal surfaces were fabricated by printing or etching to give a uniform surface topography. For example, Mazur, Wolf and co-workers developed plasmonic tipless pyramid arrays using lithographic printing [118]. Under NIR irradiation, the heat produced by the plasmonic arrays resulted in the generation of vapor nanobubbles and pressure waves, improving the membrane permeability of attached cells and promoting the calcein delivery with efficiency of 80%. However, scaling up these arrays using e-beam lithography is relatively difficult and the tipless pyramids need angular gold deposition by a thermal evaporator with rotating stage, affecting precision in reproducibility for large-area samples. To this end, they further developed relatively large gold-coated thermoplasmonic arrays (14 × 14 mm) fabricated by photolithography and template-stripped methods [119]. These arrays presented an upright pyramid array structure and had excellent photothermal effect (Fig. 12a). Under nanosecond laser irradiation, fluorescence-labeled dextrans with different molecular weight were delivered into HeLa cells successfully, in particular, for 150 kDa dextran, delivery efficiency of 73.9% and cell viability reached 82.7%.
viability of 98% were achieved. More importantly, using this platform, high throughput of 50,000 cells/min was offered, and the throughput could be scaled up as necessary. It is noted that the mechanical property of gold is weak and thus the gold film falls off the substrate easily, which may cause residual cell toxicity for long-term clinical applications [134]. In order to overcome this problem, Mazur and co-workers used robust titanium nitride (TiN) instead of gold to coat thermoplasmonic arrays for intracellular delivery, avoiding the potential risks of gold materials in clinic applications. Under 1064 nm NIR irradiation, calcein was delivered to HeLa cells [120]. It is found that template stripping process was relatively complex for sample preparation. To this end, they constructed a gold nanodisk arrays (GNDAs) with large area by a soft lithography and chemical lift-off lithography in a simple and cost-effective way [122]. Here, the substrate (e.g. Si wafer) was coated with gold film functionalized with a self-assembly monolayer (SAM) of hydroxyl-terminated alkanethiol (11-mercapto-1-undecanol). Then a patterned PDMS stamp activated by oxygen plasma was pressed onto the surface and then lifted to selectively remove the contacted SAM. Similarly, the PDMS stamp was rotated 90° and was pressed onto surface again, generating 2D nanosquare SAM region. Finally, GNDAs could be fabricated after removing the exposed metal via wet etching (Fig. 12b). Under nanosecond laser irradiation, delivery of calcein green with high efficiency (>98%) was achieved and the cell viability was well maintained (>98%).

Successful delivery of functional molecules into suspension cells, in particular immune cells, plays an crucial role in immunotherapy such as cancer vaccines and CAR-T therapy [135]. However, different with adherent cells that attach on substrate surfaces naturally, suspension cells typically have insubstantial duration of cell-surface contact, making it more difficult to efficiently deliver exogenous molecules to suspension cells using currently available photothermal surfaces as mentioned above. Aiming at this problem, Chiou and co-workers constructed a uniform microwell array with a 3D nanoscale titanium-coated tips through self-aligned micromachining [121]. Due to the action of gravity, the suspension cells could self-position the microwells and neared sharp tip structures (Fig. 13a). Under NIR irradiation, diverse molecules with different sizes including calcein green, FITC-dextran and pGFP were efficiently delivered into suspended Ramos cells located in microwells with a high throughput of >100,000 cells per minute. In addition, they chose β-lactamase (a bacterial enzyme) as the model exogenous cargo to investigate the biological activity of delivered cargo after entry into cell interior. After the delivery of β-lactamase to cells, the emission wavelength of CCF4 converted from the CCF4-AM as a substrate was changed from 520 nm to 447 nm (Fig. 13b), exhibiting high biological activity.

Although these solid arrays mentioned above show good performance for intracellular delivery, some limitations still exist. One is that the delivered molecules dispersed into cell medium or loaded on substrate surfaces gradually taper off with the extension of delivery process. Another is that it is tedious and difficult to co-deliver or sequential deliver different molecules into the same cell repeatedly. Alternatively, hollow nanohole arrays that are composed of a dense array of hollow nanoholes are promising to solve these problems. The bottom of nanohole arrays can be connected to a microchannel or a fluid storage device where the delivered molecules are stored in, facilitating the delivery of the same or different molecules continuously and repeatedly to the cells attached on the upper surface of the nanohole arrays [123,124]. For example, Chiou and co-workers developed a massively parallel
Fig. 11. (a) Scheme of the performance of intracellular delivery under NIR irradiation and cell harvesting by low-temperature treatment of PDA/PNIPAAm hybrid film. (b) Typical optical microscopic images showing the migration of HUVECs transfected with ZNF580 gene at different times. Reproduced with permission from Ref. 115. Copyright 2019 American Chemical Society.

Scheme 2. Different surface-mediated photothermal-poration methods based on diverse nanoarrays with different structures. (a) Nanopyramid arrays, (b) Nanodisk arrays, (c) Nanowire arrays, and (d) Hollow nanohole arrays.
photothermal biophotonic laser-assisted surgery tool (BLAST) for delivery of diverse cargoes with sizes in micrometer-scale \cite{124}. This BLAST platform consists of an array of hollow trans-film nanohole coated with titanium film on the side walls of these holes. Underneath the hollow nanohole arrays was an array of short and vertical silicon channels that provide fluid passage for cargo delivery and microfluidic storage used to store delivered molecules (Fig. 14a). Under laser irradiation, due to the photothermal property of metallic titanium thin films, the cavitation bubbles caused by heat and vaporization of adjacent water layers grew, aggregated and collapsed, resulting in strong fluid flow, disrupting the cell membrane and facilitating the cargoes stored in the bottom device entering the cells (Fig. 14b). Using this platform,
Various cargoes including antibodies, enzymes, nanoparticles, and living bacteria were efficiently delivered into multiple cell types involving easy-to-transfect cells and hard-to-transfect cells with high throughput, high delivery efficiency, and low cytotoxicity. Importantly, this platform may sequentially deliver multiple exogenous molecules into the same cell through the bottom channel, and thus has potential applications in cell reprogramming [124].

Non-destructive harvesting of “engineered” cells is important for regenerative medicine and ex vivo cell-based therapy [101]. Although such cell harvest was achieved by using a temperature-responsive photothermal surface as mentioned in Section 3.1 [136], however, low temperature treatment may impair cell viability and function and is not suitable for some sensitive cell types. In this regard, we developed a facile platform by combination of silicon nanowire arrays (SiNWAs) and sugar-responsive polymers containing phenyl boronic acid (PHB) that can recognize cells over-expressed sialic acid [125]. As illustrated in Fig. 15, SiNWAs-PHB could capture HeLa cells, Ramos cells and T cells with high efficiency due to the 3D topography structure of SiNWAs and specific recognition of PHB [137, 138], and realize efficient molecular delivery to the captured cells under NIR irradiation due to the excellent photothermal properties of SiNWAs. It is noted that the transfection efficiency of pGFP into recalcitrant suspension T cells was as high as 80%, which was significantly higher than that by using other reported approaches or commercially available transfection agents. Moreover, the “engineered” cells could be recovered non-traumatically from the surface by nontoxic fructose treatment due to the sugar-responsive characteristic of the boronate ester bonds between PHB and cell membrane over-expressed sialic acid. The harvested cells preserved viability and proliferation ability for further use.

4. Photothermal surfaces for cell detachment and cell sheet harvest

Dynamic modulation of cell adhesion-detachment on functional surfaces is of importance in cell biology and tissue engineering and plays a critical role in diverse biomedical applications including isolation of circulating tumor cells (CTCs) from blood for clinical diagnostics [139, 140], and harvest of viable and intact cell sheets for transplantation [3, 141]. Stimuli-responsive biointerfaces with dynamic property and programmable features exhibit unprecedented ability to modulate
cell-surface interactions. In particular, thermo-responsive surfaces based on PNIPAAm have been well investigated to achieve capture and release of target cells and even whole cell sheets [142,143]. Compared to other stimuli (e.g., pH, electricity, enzyme), thermal stimuli for dynamic modulation of cell adhesion-detachment is easier to operate and more biocompatible. However, it is still challenging to realize precise control of regulating cell detachment for these conventional thermo-responsive surfaces. Alternatively, photothermal surfaces change the surface temperature through the produced heat under NIR irradiation, thus achieving the well control of cell detachment in time and spatial compared to the conventional thermo-responsive surfaces, making them good platforms for dynamic modulation of cell adhesion-detachment. The specific modulation mechanisms of these photothermal surfaces rely on the changes of surface properties in response to the surface-generated heat as illustrated in Scheme 3: (i) dissociation of the binding between responsive materials tethered on surfaces or interactions between cells and surfaces (Scheme 3a), (ii) change of properties of thermo-responsive polymers tethered on the surfaces (Scheme 3b), and (iii) dissolution of the “sacrificial layer” coated on the surfaces (Scheme 3c). In this section, we focus on the recent developments of these photothermal surfaces for dynamic modulation of cell adhesion-detachment, which are divided into the two categories including (i) photothermal surfaces for cell detachment and (ii) photothermal surfaces for cell sheet harvest (Table 3).

4.1. Photothermal surfaces for cell detachment

Thermo-responsive DNA that the double strands could dissociate by increasing temperature is a good candidate for fabrication of photothermal surfaces to achieve modulation of cell adhesion-detachment. For example, Qu and co-workers developed a NIR- and pH-dual-controlled surface to catch-and-release cells reversibly [144]. In detail, an indium tin oxide (ITO) surface was modified with PDA-functionalized graphene (PDA-GO) and GNRs as PTAs, sequentially covalently linked with amino-modified duplex DNA (dsDNA, composed by sequences of C-rich DNA1 and G-rich DNA2) through the bonding between the amine group of DNA1 and the catechol group of PDA, and finally arginine-glycine-aspartic acid (RGD) as bioadhesion ligand to promote cell adhesion was coupled on DNA2. Due to the recognition of RGD to cells, the modified photothermal surfaces could capture cells effectively. Under NIR irradiation, the generated heat by PDA-GO and GNRs disassembled the dsDNA, thus the captured cells were non-traumatically detached from the surface. In addition, decrease of pH also led to the dissociation of dsDNA and thus inducing detachment of cells. (Fig. 16a).

In another work, Casares, Marzan and co-workers developed a multifunctional and versatile plasmonic substrate for cell growth, controlled detachment and substrate regeneration under remote NIR irradiation [146]. Firstly, the plasmonic substrate was prepared by depositing small GNPs “seeds” for further chemical growth to form anisotropic GNP. Thiolated cyclic RGD peptides (c-RGD) were then modified on the surface via thiol chemistry for promoting the adhesion of integrin-rich cells. Under NIR irradiation, most cells were detached from surfaces of plasmonic substrate and c-RGD-modified plasmonic substrate without compromising cell viability, while almost no cells adhered on pristine glass were released (Fig. 16b). It is found that the efficiency of cell detachment was related to the average cell area. For example, HUVECs had the largest adhesion area on the surface of the plasmonic substrate and it achieved cell detachment in a short time of 5 min, significantly faster than other cells with a small contact area. The localized photothermal effect was considered to be the primary driving force of cell detachment [148]. As the contact area between cells and surfaces increased, the temperature at the interface of cells and GNP was getting higher and higher, thereby accelerating the detachment of the cells. Moreover, the photothermal surface after detaching the captured cells could be re-used for another cell adhesion-detachment cycle [146]. Compared with graphene and gold-based nanomaterials, organic photothermal polymers have more easily adjustable photophysical properties and better biocompatibility. Kim and co-workers coated the surface of cell culture dishes with a nanofilm of photothermal poly (3, 4-ethylenedioxythiophene) (PEDOT) using solution casting polymerization (SCP) technology and tuned doping level of PEDOT film via electrochemistry for selective collection of mesenchymal stem cells (MSCs) [145]. Under NIR irradiation, the PEDOT film converted absorbed light energy to heat to break down the linkage between the integrin of cells and the ECM proteins, thereby releasing the attached MSCs. The photothermal property of PEDOT film was affected by doping state and...
Scheme 3. Schematic illustration of NIR-triggered release of cells from photothermal surfaces by (a) dissociation of the binding between responsive materials tethered on surfaces (Top) or interactions between cells and surfaces (Down), (b) change of the properties of grafted polymer chains (green lines) on the photothermal surfaces and (c) dissolution of the “sacrificial layer” (purple shapes) coated on the photothermal surfaces.

Table 3
Summary of photothermal surfaces for detachment of cells and harvest of cell sheets.\(^c\)

| PTAs       | Laser wavelength | Responsive materials | Matrix materials | Cell type                          | Applications                                      | Ref.       |
|------------|------------------|----------------------|------------------|------------------------------------|---------------------------------------------------|-----------|
| rGOs/GNRs  | 808 nm           | NIR/pH-responsive dsDNA | ITO              | HUVEC                             | Capture and release of cells                      | [144]     |
| PEDOT      | 808 nm           | PEDOT                | Cell culture surface | MSC                               | Selective harvest of cells                        | [145]     |
| GNPs       | 980 nm           | N. A.                | Glass            | HeLa cell/A549/HUVEC/J774 cell/3T3 fibroblast | Selective detachment of cells                     | [146]     |
| SiNWAs     | 808 nm           | PNIPAAm              | SiNWAs           | MCF-7                             | Selective detachment of cells                      | [147]     |
| GNSTs      | 785 nm           | N. A.                | ITO/glass        | Glioblastoma cell (U87-GFP)       | “Point-and-shoot” selective removal of cells       | [148]     |
| GNRs       | 980 nm           | Gelatin              | Gelatin          | MCF-7                             | Capture and release of cancer cells               | [149]     |
| MoS\(_2\)  | 808 nm           | Gelatin              | ITO              | MCF-7                             | Capture-in situ detection-release of cancer cells | [150]     |
| PEDOT      | 808 nm           | Collagen             | Polystyrene      | human fibroblast                   | Harvest of cell sheets                             | [151]     |
| PEDOT      | 808 nm           | Collagen             | Polystyrene      | hADSC                             | Large-Area and multiple production of cell sheets | [152, 153]|
| Gradient   | 808 nm           | Collagen             | Polystyrene      | Fibroblast/C6 cell/HeLa cell/3T3 cell | Harvest of cell sheets along a predetermined direction | [154]     |

\(^c\) Abbreviations: Reduced graphene oxide (rGO); Indium tin oxide (ITO); Gold nanostars (GNSTs); Duplex DNA (dsDNA, composed by sequences of C-rich DNA1 and G-rich DNA2); Mesenchymal stem cell (MSC); Poly(3,4-ethylenedioxythiophene) (PEDOT); harvested human adipose-derived stem cell (hADSC).
thickness of PEDOT film and could be simply modulated by electrochemical method or SCP process. Thicker PEDOT film exhibited better cell release efficiency. Moreover, it was possible to achieve cell detachment in certain area and certain shape by controlling the NIR laser beam correspondingly, showing potential for single cell separation.

In addition to dissociation of the binding between responsive materials tethered on surfaces or interactions between cells and surfaces, there are other approaches such as change of properties of thermo-responsive polymers tethered on the surfaces and dissolution of the “sacrificial layer” coated on the surfaces for cell detachment. As shown in Fig. 17a, Wang and co-workers developed a NIR-responsive surface based on PNIPAAm modified SiNWAs (SiNWAs-PNIPAAm) for controlled capture and release of cancer cells [147]. Under NIR irradiation, the heat produced by SiNWAs made PNIPAAm chains collapsed and hydrophobic, facilitating the adsorption of biotin-labeled bovine serum albumin (BSA) for incorporation of avidin-labeled epithelial-cell adhesion molecule antibody (anti-EpCAM). In this condition, SiNWAs-PNIPAAm showed higher capture efficiency for EpCAM positive cells (e.g. MCF-7 cells) than EpCAM negative cells (e.g. HeLa cells). Turning off NIR irradiation led to the decrease of temperature to induce the swelling and hydration of PNIPAAm chains, resulting in release of >95% of captured cells. Moreover, SiNWAs-PNIPAAm maintained good cell capture-and-release efficiency over 20 NIR on/off cycles. However, strictly speaking, PNIPAAm is not a bio-inert polymer and its biocompatibility still needs improvement. Therefore, other biocompatible thermo-responsive polymers such as oligo(ethylene glycol)-based (co)polymers [155] and poly(2-oxazoline)s [156] are expected to be used for fabricating photothermal surfaces to regulate cell adhesion and detachment without compromising cell viability. In another work, Huang and co-workers developed a robust platform based on a thermo-responsive gelatin hydrogel embedded with GNRs for separation of cancer cells from blood [149]. The composite hydrogel was prepared by imprinting target cancer cells and incorporating anti-EpCAM on the surface using similar biotin-avidin method, endowing it ability to capture MCF-7 cells efficiently via the synergistic effect between match of cell shape and selective molecular recognition. Under NIR irradiation, the medium temperature increased to 37 °C, leading to the dissolution of gelatin rapidly to release the captured cells. By accurate control of laser area, site-specific release of single MCF-7 cell was achieved. Additionally, efficient capture of cancer cells from lysed or whole blood was realized with 80.7% and 52.0% efficiency, respectively. Using similar method, Xian, Zhang and co-workers fabricated a NIR-switched platform for efficient isolation and downstream analysis of cancer cells [150]. The gelatin mixed with PEG-MoS\textsubscript{2} nanoflakes were firstly modified to ITO surfaces, and then incorporating MUC1 aptamer recognizing MCF-7 cells specifically via coupling reaction to achieve the specific capture for cancer cells (Fig. 17b). Importantly, because the conductivities of MoS\textsubscript{2} of cancer cells are relatively close, it was suitable to detect for a small number of cancer cells in situ using electrochemical method as MoS\textsubscript{2} could amplify electrical signals. After detection, the captured cancer cells were released from the surface on-demand under NIR irradiation for further analysis and diagnosis.

4.2. Photothermal surfaces for cell sheet harvest

Cell sheets refer to cells growing and proliferating into a confluent sheet, showing great potentials for a wide range of applications such as cell therapy and tissue engineering [157,158]. In the past decades, various materials including biodegradable substrates and stimuli-responsive surfaces have been developed to harvest cell sheets with intact extracellular matrix [159–161]. One of the best studied materials is the PNIPAAm-modified surface due to the thermo-responsive wettability, facilitating the formation and detachment of cell sheets simply by changing temperature [160]. However, this kind of surfaces still has its limitations: (i) low-affinity cells need a longer culture time to form a confluent cell sheet layer, while high-affinity cells need a longer time to detach from the surface; (ii) it is hard to achieve spatial control of detachment to harvest cell sheets with certain shape, limiting the practical applications. Recently, combination of a photothermal substrate and a thermo-responsive “sacrificial layer” becomes an effective strategy for harvest of cell sheets [151]. In this method, cells were seeded on the topmost surface of the sacrificial layer for culture until they formed a confluent layer. Under NIR irradiation, the photothermal substrate produced enough heat to dissolve the sacrificial layer to harvest the cell sheet. Compared with PNIPAAm-based harvest technology, this method has following advantages: (i) the time for harvesting cell sheet (about 5 min) is much less than that using PNIPAAm-modified surfaces (about 30 min); (ii) cell sheets with specific shape could be achieved via spatial control of laser; (iii) the viability of detached cell sheet may be better than that treated by PNIPAAm-based substrate due to decreasing temperature would induce certain damage to some sensitive cells.

In recent years, Kim and co-workers developed a series of PEDOT-based photothermal matrixes to achieve non-destructive harvesting of
various types of cell sheets [151–153]. As shown in Fig. 18a, PEDOT was coated on the polystyrene surface by polymer solution casting, followed by drop casting of a collagen layer with thickness of 14–18 μm [151]. Under NIR irradiation with suitable intensity, the heat produced by PEDOT dissolved the collagen layer, facilitating the harvest of human fibroblast cell sheets non-destructively. In addition, the shapes of the harvested cell sheets could be controlled by changing the shapes of the substrates. Although this approach could harvest cell sheets with diverse shapes, it should be noted that the size of cell sheets was relatively small (<1 cm²) and it was difficult to achieve multiple harvest of cell sheets.

To solve these limitations, on the basis of the above collagen coated PEDOT-modified substrate, they added a patterned optical len (POL), diffracting multiple areas with the same shape on the upper PEDOT-modified substrate as the NIR laser passed through the POL, thus achieving multiple harvest of cell sheets with one dose of NIR light without destroying the cell-cell interactions and compromising cell morphology (Fig. 18b) [152]. Additionally, they used this platform to yield cell sheets with a large area of more than 19 cm² and harvested human adipose-derived stem cell (hADSCs) sheets, thereby broadening the applicable types of cell sheets. However, problems still existed that hADSCs were not evenly adhered on the collagens coated PEDOT surfaces and the harvested cell sheets were unstable and showed a broken state after culturing for one day, which might be because the cell-to-cell and cell-to-matrix interactions were relatively poor. In order to harvest a transferrable, free-standing hADSC sheets, they added fibronectin molecules in the cell medium, which are known as cell-adhesion molecules to promote the adhesion and survival of stem cells [153]. A confluent layer of hADSCs formed on the collagen coated PEDOT surface after culturing for one day and their proliferation rate was significantly higher than that without fibronectin molecules. Most noteworthy is that the free-standing hADSCs sheet with an area of 122.6 mm² was transferred and attached onto the chronic wound of genetically diabetic db/db mice. The wound healing effect was significantly better than that using injected cells, exhibiting the potential application in skin reproduction and organ regeneration.

Although intact cell sheets could be produced by using the PEDOT-coated surfaces mentioned above, there are still a lot of problems in clinical trial. For example, in some elaborate clinical trials, obtaining a unified cell sheet operation plays an important role in promoting an ordered, consistent and reproducible production. In order to harvest cell
sheets along a predetermined direction, Lu and co-workers fabricated a PEDOT film with gradient thickness, which could guide cell sheet detachment accurately by thermally-induced collagen
dissociation (Fig. 19a) [154]. Under identical NIR irradiation, the heating rate at the thicker side of the PEDOT film was larger than that at the thinner side, thus the dissociation of coated collage layer as well as
the detachment of fibroblast cell sheet proceeded along the decrease direction of PEDOT film thickness (Fig. 19b). Using this method, it is possible to harvest cell sheet in a controlled manner to obtain cell sheets with predetermined direction.

5. Summary and future perspectives

During the past decade, photothermal scaffolds/surfaces have attracted great interest in regulating cell behaviors by the generated heat under NIR irradiation. In this review, we systematically summarize recent achievements in this promising area and discuss the respective characteristics. As an emerging platform, the interaction between photothermal scaffolds/surfaces and the attached cells can be adjusted by simply adjusting the NIR laser intensity to achieve specific biological phenomenon (e.g. the intensive heat produced under NIR irradiation with high intensity causes tumor ablation, and moderate heat produced under NIR irradiation with relatively low intensity increases membrane permeability of attached cells to promote the delivery of exogenous molecules to cells or changes the surface properties to achieve controlled cell adhesion-detachment), which shows great potential in cancer treatment, tissue engineering, immune therapy, gene editing and other biomedical applications.

Although considerable progress has been made, there are still some remaining challenges that need to be solved in future. (i) Currently, the penetration depth of NIR light is still limited, which restricts the treatment effect to deep tumors. The latest research in optical imaging shows that longer-wavelength NIR light in the NIR-II window (1000–1700 nm) [162–164] has a higher potential for depth imaging than NIR light in NIR-I window (700–900 nm). Therefore, applying PTAs in response to the NIR-II window for fabrication of photothermal scaffolds/surfaces has great potential in many biological applications. Additionally, exploitation of PTAs with higher photothermal effect and absorption coefficient may also be helpful to solve this limitation. (ii) At present, photothermal scaffolds/surfaces prepared by freeze-drying, mixing exploitation of PTAs with higher photothermal effect and absorption coefficient may also be helpful to solve this limitation. (ii) At present, photothermal scaffolds/surfaces prepared by freeze-drying, mixing methods, electropinning or 3D printing technique either have simple preparation method and easy to expand production.

- (iii) Most current photothermal scaffolds/surfaces used for tumor ablation are irradiated by high-intensity NIR laser, which may cause large damage to normal cells and healthy tissues. Therefore, it is still necessary to combine PTT and other therapeutic methods such as chemotherapy and photodynamic therapy to reduce the NIR light intensity for avoiding damage to normal cells, while maintaining effective tumor ablation. (iv) Although considerable progress has been made for intracellular delivery using photothermal scaffolds/surfaces, some important issues need to be addressed. One is the mechanism of membrane disruption should be further explored to provide the theoretical basis for intracellular delivery. Another is that the current intracellular delivery using photothermal scaffolds/surfaces is only carried out in laboratory, however, issues related to scale-up and cost should also be considered for future practical applications. (v) Because biological systems are dynamic, it is of significance for designing dynamic surfaces whose properties such as stiffness can change under NIR irradiation to control cell behaviors beyond adhesion. Moreover, the current platforms are still limited in response to multiple stimuli, combining light stimulus and/or other stimuli together and using different response pairs in turn will have outstanding advantages in regulating cell behaviors.

In summary, this review aims to emphasize the recent developments of regulation of cell behaviors by photothermal scaffolds/surfaces as well as their exploration for tumor therapy, cell engineering, and tissue engineering. With the development of cell biology, biomaterial technology and processing and manufacturing technology, it is foreseen that these materials will gradually solve these current limitations and continue to open up new possibilities for precisely controlling cell behaviors and determining cell fates.

CRediT authorship contribution statement

Yanggui Qu: Writing - original draft. Kunyan Lu: Writing - original draft. Yanjun Zheng: Writing - original draft. Chaobo Huang: Writing - review & editing. Guannan Wang: Writing - review & editing, Funding acquisition. Yanxia Zhang: Writing - review & editing, Funding acquisition. Qian Yu: Conceptualization, Writing - review & editing, Funding acquisition, Project administration.

Declaration of competing interest

The authors declare no conflicts of interest.

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