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Mild photothermal therapy assist in promoting bone repair: Related mechanism and materials

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ABSTRACT

Achieving precision treatment in bone tissue engineering (BTE) remains a challenge. Photothermal therapy (PTT), as a form of precision therapy, has been extensively investigated for its safety and efficacy. It has demonstrated significant potential in the treatment of orthopedic diseases such as bone tumors, postoperative infections and osteoarthritis. However, the high temperatures associated with PTT can lead to certain limitations and drawbacks. In recent years, researchers have explored the use of biomaterials for mild photothermal therapy (MPT), which offers a promising approach for addressing these limitations. This review provides a comprehensive overview of the mechanisms underlying MPT and presents a compilation of photothermal agents and their utilization strategies for bone tissue repair. Additionally, the paper discusses the future prospects of MPT-assisted bone tissue regeneration, aiming to provide insights and recommendations for optimizing material design in this field.

1. Introduction

Recently, multiple strategies have been explored and developed for directional and precise modulation of target tissues, particularly for applications in the field of BTE. It has led to the emergence of various materials that respond to stimuli and achieve the desired functionality to match the healing and regeneration of bone and surrounding tissues [1–4]. Among these triggered conditions, light stimulation has emerged as a safe and effective external stimulus, for its potential unique spatiotemporal selectivity and minimal side effects [5–9]. Light stimulation, which encompasses ultraviolet light, visible light, infrared light, and near-infrared (NIR) light, has developed many types of therapy, such as photodynamic therapy (PDT), photothermal therapy (PTT), and shown great potential in various combined therapies with chemotherapy and immunotherapy [10]. Among these therapies, PTT has demonstrated promising therapeutic effects on various orthopedic diseases, including clinical tumors, rheumatoid arthritis, and wound infections, via the photothermal effect [11–14]. With the rapid development of nanotechnology, a series of materials that could produce efficient thermal stimulation to achieve good thermotherapy effectiveness emerged. What attracts us is the photothermal nanomaterials that respond to NIR light with efficient light absorption and conversion efficiency. These materials, known as photothermal agents (PTAs), include carbon-based nanomaterials, metal nanostructures, metal compounds, and other nanostructures [15].

Based on the interaction between NIR light and PTAs, the photothermal conversion effect of the materials can be initiated. PTAs exhibit high photothermal conversion efficiency, which ensures that NIR light can penetrate the skin to reach deep tissue layers at low power. It enables PTAs to accurately target tissues and achieve safe and efficient PTT [16]. The existing research on photothermal treatment for orthopedic diseases has primarily focused on its applications in antitumor [15,17–20] and antibacterial therapy [18,21–23], especially at elevated temperatures.

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Generally, PTT (>45 °C) might have better effectiveness for the treatment of tumor or infection. However, it also faces security issues that affect bone repair. For example, the heat resistance of bacteria and the destruction of tissue could lead to changes in cytoskeleton and cell membrane structure [24,25], which resulting in loss of corresponding functions such as cell motility and signal transduction [26]. As a result, the mild photothermal therapy (MPT) (37–42 °C) has attracted attention for the treatment of associated disorders [27].

Recent studies have shown that after implanting nanophotothermal materials with high photothermal efficiency *in vivo* and applying long-term cycle, gentle NIR irradiation can promote bone cell proliferation, tissue regeneration, and mineralization. It reflects the huge potential of MPT in the field of bone repair [28–31]. Unlike PTT in hyperthermic phase, MPT provides a safe and effective treatment option that not only offers a better choice for treating clinical tumors and infections but also inspires the treatment of clinical bone defects. MPT can create a win-win situation by assisting bone tissue repair between the defect site and the normal parts of the bone.

Hence, this review aims to provide a comprehensive summary of recent developments in MPT for promoting bone mineralization and repair, with a focus on the underlying mechanisms involved, for elucidating the potential relationship between MPT and bone repair. Subsequently, a systematic overview of materials that achieve mild thermotherapy through photothermal effects is followed, covering the mode of action and applications. Furthermore, bionic design strategies for promoting bone repair and suggestions for future directions in material and scaffold design are offered. Guided by the MPT design ideas, the different ways to apply multiple PTAs, which is based on the stages of bone tissue repair, is shown in Fig. 1.

2. Matching the process of bone regeneration

It has traditionally been assumed that warming promotes the dilation of blood vessels, which provides more nutrients and oxygen [32]. Recently, hyperthermia has been found to be effective in enhancing bone regeneration by upregulating the expression of osteogenesis-related proteins. Increasingly, MPT has gained significant interest and has been utilized to aid in bone repair and matching the bone regeneration process in recent years [33,34]. It has been found that the MPT is beneficial to osteogenesis, particularly the mineralization process of bone tissue. However, most of these studies only reported the upregulation of the expression of alkaline phosphatase (ALP) and heat shock proteins (HSPs) as possible mechanisms.

HSPs protect cells under various physiological and environmental conditions, such as chemical and heat stress. When induced, it can reactively regulate the stability and function of signaling proteins to improve cell tolerance, and it have been thought to have the chaperone function [35,36]. In the current study, it was found that both HSP47/HSP70 were up-regulated after MPT treatment [33,34,37]. HSP70 is a molecule that has been extensively studied for its relationship with bone tissue formation. Previous studies have shown that HSP70 plays a crucial role in regulating protein structure, controlling activity, and protecting protein integrity. It is able to suspend the protein folding process and maintain the protein in an immature structural form or bind to mature proteins to inhibit their activity, achieving different functions [38]. The related information is shown in Fig. 2. Additionally, studies have shown that heat shock proteins such as HSP60/HSP90 and some small HSPs (such as HSP22, HSP27) are also involved in bone metabolism stages such as bone resorption and bone regeneration [35,36,38]. As kinds of highly conserved protein in the body, HSPs play crucial roles in protecting cells from harsh environmental stresses and adapting to various "dangerous conditions" such as ionizing radiation, oxidative stress, and excessive heat. They can regulate protein expression and conformation in response to various chemical or physical stimuli, such as heat shock or oxidative stress, thus participating in various biochemical processes [35].

Nevertheless, recent research advances on MPT promoting bone repair are still insufficient and lack unified standards, particularly regarding the mechanism by which MPT assists in bone repair [39,40]. Existing related researches suggest that it may increase cell permeability, drive HSPs to resist thermal damage. In addition, HSPs are also involved in immune processes including antigen uptake, antigen processing, and modulation of inflammatory responses, and can even play a role in regulating bone-related protein expression pathways [41–44].

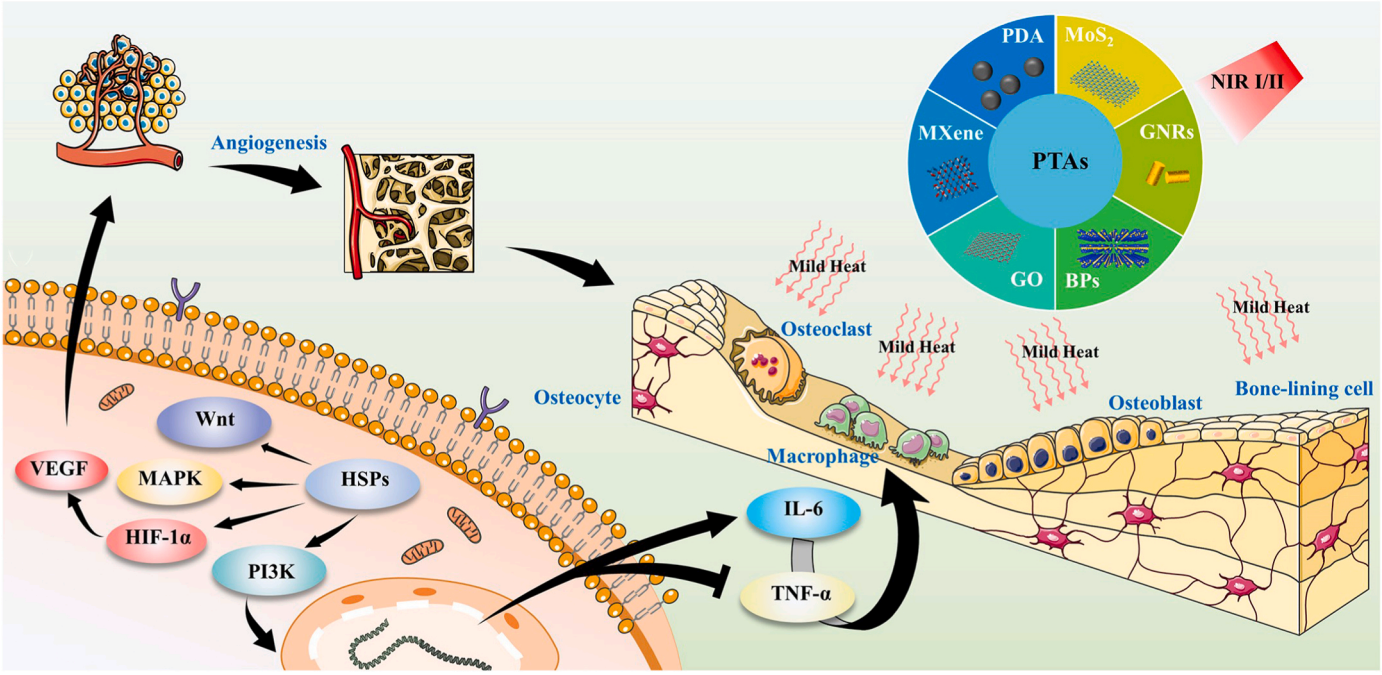

Fig. 1. NIR initiates MPT-assisted bone tissue regeneration. MPT elicits the activation of HSPs via heat stress, subsequently influencing bone metabolic pathways and angiogenesis pathways. This molecular response plays a crucial role in regulating the proliferation and differentiation of macrophages, osteoclasts, and osteoblasts within bone tissue.

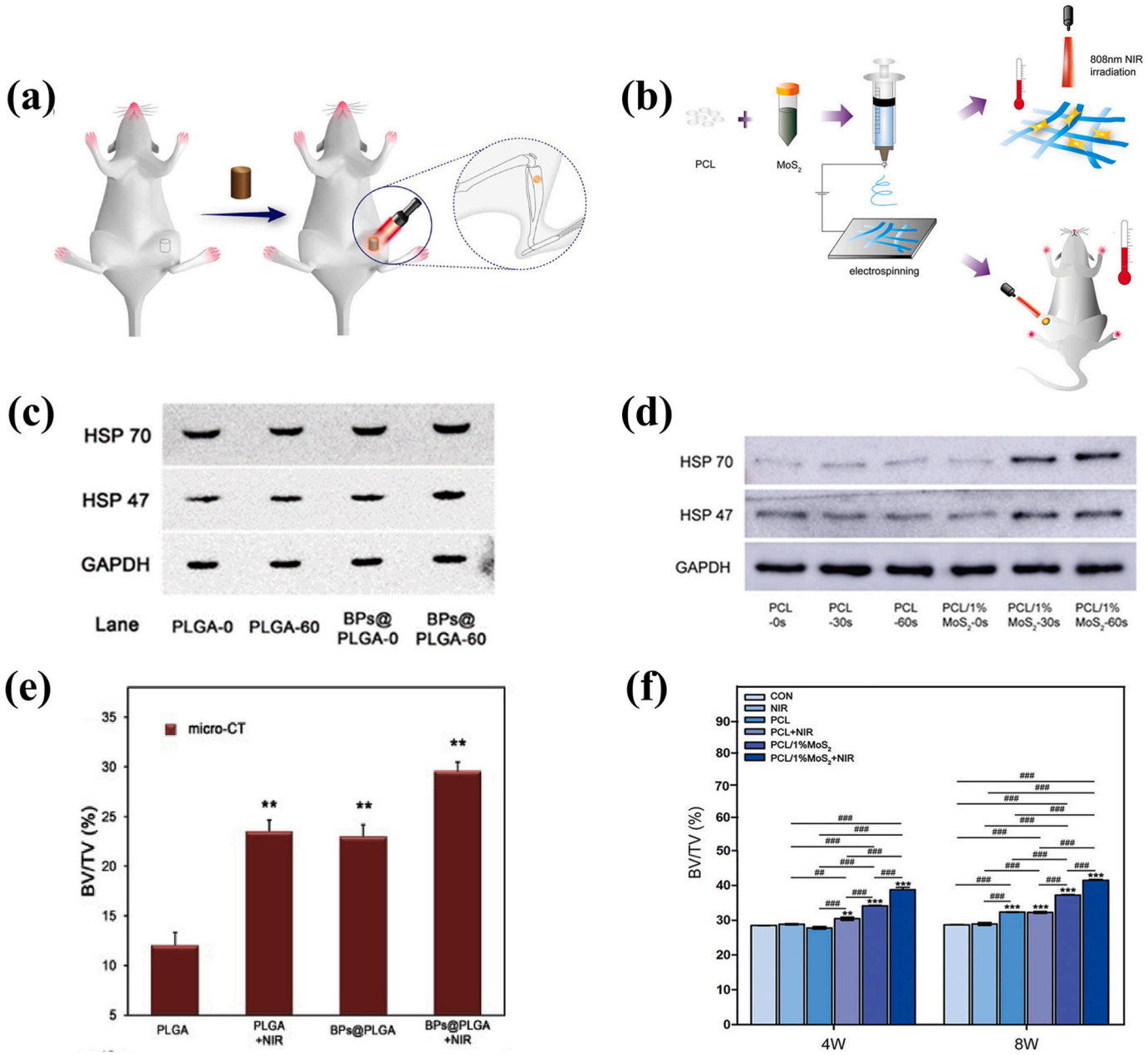

Fig. 2. Schematic illustration and experimental results showing the effect of NIR radiation on enhancing osteogenesis. (a) Photothermal stimulation is induced by NIR irradiation after implantation. (b) Schematic illustration of the function of the implants *in vitro* and *in vivo*. (c–d) The expression levels of HSP70 and HSP47 proteins in cells or tissues after photothermal treatment. (e–f) Micro-CT analysis showing the bone volume/total volume (BV/TV) ratio after NIR irradiation [33,34].

The exact mechanism of how MPT drives bone repair has not be well explored, but it is reported that it may involve the regulation of HSPs expression and metabolic processes in cells. However, few reports have discussed the exact mechanism and there are still lots of issues about the use of PTT for osteogenesis that need to be addressed [45–47]. According to current literature reports, HSP60 in many HSPs can promote osteoclast formation (via p38 MAPK and NF-κB pathways), while affecting the state of osteoblasts to regulate their proliferative ability; HSP70 and HSP90 balance bone resorption and bone regeneration, while regulating other HSPs, and so on [35]. Relevant information is presented in Fig. 3.

Therefore, in this section, it has been summarized that the biological process of bone repair and briefly described the unique role played by different HSPs with mild photothermal effects in assisting the repair of the musculoskeletal system. It might provide a theoretical basis for elucidating the role of MPT in promoting osteogenesis.

2.1. *Inflammatory stage*

The initial step in the bone regeneration process is the formation of a hematoma caused by immune cells. It induces the recruitment of stem cells and immune cells such as monocytes or T cells, creating a bone immune microenvironment that facilitates subsequent bone regeneration processes. At this stage, the immune system, which includes macrophages, neutrophils, and related inflammatory factors such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and chemokines monocyte chemotactic protein (MCP-1/CCL2), stimulates osteoprogenitor cells to differentiate into osteoblast lineages for bone healing. However,

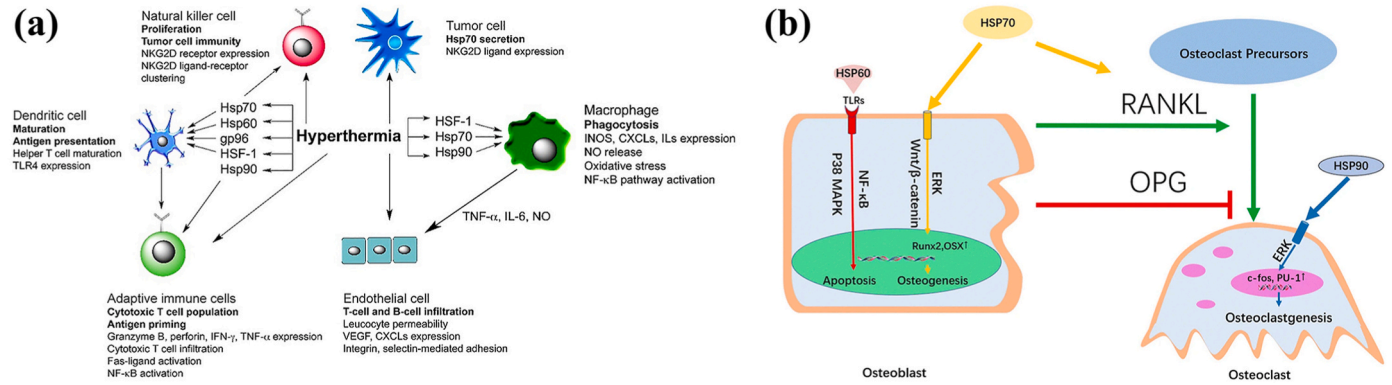

Fig. 3. (a) Hyperthermia induces inflammatory effects on various types of cells [41]. ©2020 Wiley Periodicals, Inc. (b) HSP60/70/90 regulates the balance between osteoblasts and osteoclasts [35]. Copyright 2018, Cell Stress Society International.

prolonged exposure to factors causing inflammatory changes can lead to an excessive immune response and cause harm to the body [48], as is also seen when promptly clearing a hematoma.

Neutrophils are pivotal in the initial phases of hematoma formation following an injury, as they enter the site of the hematoma during the inflammatory stage, and can be seen as an early marker of osteogenic activity. Another noteworthy point is that existing studies have shown that the interaction between neutrophils and T cells is bidirectional, further confirming that the interaction between these two cell types is worthy of further in-depth investigation [49]. Particularly, M1 and M2 macrophages importantly affect the microenvironment of bone regeneration through the secretion of cytokines, thereby affecting bone immunity. Mesenchymal stem cells (MSCs) are stimulated to migrate and proliferate, and the microenvironment provides abundant resources for subsequent osteogenesis. Macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-kappa B ligand (RANKL) are known to promote macrophage differentiation into osteoclasts. For instance, Wang et al. investigated the effects of three types of dense hydroxyapatite (HA) disks with different size grains on macrophage polarization and function status. Nanotopography of HA ceramics can enhance the transition of macrophages from pro-inflammatory M1 type to anti-inflammatory M2 type, consequently, increasing the proportion of M2 macrophages and decreasing tissue inflammation through the up-regulation of related genes. This effect may be attributed to the differential expression of integrins that regulate the activation of intracellular signal cascades [50]. Interferon-γ (IFN-γ) and reactive oxygen species (ROS) promote M1 macrophage production, inducing TNF-α and IL-6 to affect osteoclast formation, whereas M2 macrophages can inhibit osteoclasts by releasing vascular endothelial growth factor (VEGF), thus supporting bone matrix deposition and mineralization, as well as vascular maturation.

PTT induces hyperthermia in target tissues via light irradiation. On the one hand, it enhances the induction of inflammatory cytokines such as IL-6 and NO through the nuclear factor kappa-B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways. On the other hand, it has been reported that PTT higher than 45 °C can generate a large amount of ROS, inducing macrophages to express TNF-α. Studies have shown that HSP70, provided by PDT treatment of damaged cells, can stimulate macrophages to accelerate phagocytosis and induce further maturation and activation, which may explain the promotion effect of mild photothermal heat on macrophages [51].

Moreover, PTT induces the binding of heat shock transcription factor-1 (HSF-1) directly to heat shock response elements in cytokine promoter regions, resulting in transcriptional suppression. This suggests that HSPs, especially HSP27 or HSP70, produced during PTT can exert potent immune regulatory effects in the inflammatory microenvironment. Under laser control, HSP27 is capable of regulating the formation of osteoclasts from mouse bone marrow-derived macrophages induced by RANKL, demonstrating its potential for the clinical treatment of osteoporosis [52]. Furthermore, HSPs may act as danger signals to stimulate the immune response *in vitro* and as negative regulators to control inflammation *in vivo* [53].

Wang et al. investigated the effect of periodic heat shock at different thermal dosing and frequencies and found that mild periodic hyperthermia improved proliferation and osteogenesis of MSCs. Particularly, it may also mitigated the inhibition of pro-inflammatory cytokine effects on MSC growth in the early stage of differentiation [31]. The tissue anti-inflammatory activity could be regulated via the expression of inflammatory factors altered by HSPs [54,55]. As mentioned above, mild hyperthermia can initiate autoimmune regulation through the upregulation of heat shock proteins, and at the same time block the pro-inflammatory cascade through the PI3K/AKT signaling pathway and cell adhesion molecules [56]. The RANK/RANKL/OPG signaling pathway is well known to control osteoclast differentiation and activation. Bone resorption regulated by HSP60 may involve the RANKL/-RANK system. During estrogen deficiency, HSP60 induces osteoclastic bone resorption through Toll-like receptor 2 (TLR-2), suggesting that HSP60 and TLR-2 may be novel mediators of estrogen deficiency-induced bone loss [57]. Blockade of HSP90 by SNX-2112 (a selective HSP90 inhibitor) acts in the bone marrow microenvironment to significantly inhibit osteoclastogenesis by downregulating ERK/c-fos and PU.1 [58].

Additionally, some animal models have shown that muscle in animals mass rose within 7 days following a single whole-body heating (60 min, 41–42 °C) and even a single heat shock for 30–60 min can stimulate muscle growth at 39–41 °C [59]. Similar to the body's response to systemic fever, local MPT can also stimulate the immune system and associated inflammatory processes to achieve resistance to diseases [60]. Besides, MPT has been demonstrated to be more effective than thermal ablation in activating the immune system in the context of oncology and infection treatment [41]. MPT, unlike systemic fever, usually works only locally and its potential effects on systemic pathways remain to be investigated. While earlier literature suggested that heat stress could stimulate macrophages to secrete pro-inflammatory cytokines and regulate the immune response by inducing the release of HSP70, recent studies have shown that periodic mild photothermal (41 ± 1 °C) can actually drive macrophages towards the anti-inflammatory M2 phenotype and increase the expression of anti-inflammatory cytokines [56].

Moreover, HSP70 has been found to possess a distinctive immunomodulatory effect in the course of bone tissue remodeling. This effect is noticeable in the inflammatory microenvironment when exposed to heat stimulation. At mild temperatures ranging from 38.5 °C to 41 °C, DNA binding of HSF1 can be observed, inducing HSPs synthesis, which increases with prolonged exposure [61]. When the temperature reaches 42 °C, the induced HSP70 mRNA and protein levels dramatically

increase. TLR agonists, such as lipopolysaccharide or the inflammatory cytokine IL-1β, can further enhance high-temperature-induced HSP70 expression [54,55]. Additionally, Expression of HSP70 can also be induced in monocytes by lipopolysaccharides alone, inactivated streptococcus, and tumor necrosis factor [50,62]. HSP70 is capable of forming non-covalent bonds with certain ubiquitin-like proteins, which can prevent aggregation into folded peptide chains for enabling organization and controlling activity, thereby reducing the production of osteoclasts induced by macrophages. For instance, HSPA8 is a constitutively expressed member of the HSP70 family, regulates RANKL-induced osteoclastogenesis in RAW264.7 cells [63].

Recently, skeletal stem cells (SSCs) with a unique immunophenotypic have been discovered, and they have the potential to differentiate into bone, cartilage, and so on. However, the mechanism of osteogenesis of SSCs still needs further investigated [64,65]. One of the interactions between macrophages and SSCs has been observed. Macrophages regulate the regeneration of SSCs, while SSCs inhibit the function of M1 macrophages and enhance M2 production of anti-inflammatory cytokines [66]. When there is an imbalance in bone immunity, it can lead to failed fracture self-healing. Surprisingly, HSP70 may also play an important role in myogenic differentiation and neointima formation [67]. This may also suggest that in addition to its potential benefits for oxidative stress and chronic inflammation [68], upregulation of HSPs may also have positive effects on muscle growth and fiber type switching. Calcium and calcineurin, known as regulators of muscle remodeling and fiber type switching in response to exercise stimulation, may play a role in the production of HSPs *in vitro*, and related HSP signaling molecules can synergistically stimulate the Akt-mTOR signaling cascade.

2.2. Vascularization stage

Traditional studies have believed that hyperthermia can increase the formation of new blood vessels by inducing ringing of endothelial cells [69,70]. When supplemented with biological ions, biological agents, etc., the “hot spring effect” can be simulated to speed up repair [71]. Vascularization also plays critical role in the bone regeneration process, bridging the gap between inflammation and mineralization. The ideal microenvironment created by vascularization provides nutrients, oxygen, growth factors, and minerals for tissue repair, while also removing waste products from tissue metabolism [72]. Particularly, VEGF is a key angiogenic cytokine that can upregulate osteogenic growth factors to promote endothelial cell migration, proliferation, and osteogenesis [73]. Recent researches have shown that endothelial cells associated with osteogenesis can be classified based on the expression of CD31 (platelet and endothelial cell adhesion molecule 1) and endomucin (EMCN). Kusumbe et al. defined H-type endothelial cells, which promotes tissue angiogenesis, as having high expression of CD31 and EMCN [73]. The primary motivation for coupling angiogenesis with osteogenesis is to provide oxygen to the tissue. When oxygen concentration falls below 1 %, the hypoxia-inducible factor-1α (HIF-1α) signaling pathway is activated to up-regulate VEGF expression. There is an intricate interplay among various factors, such as fibroblast growth factor (FGF), TNF-β, IL-1, platelet derived growth factor (PDGF), and others, that contribute to angiogenesis. Additionally, Osteoblasts produce bone morphogenetic protein-2 (BMP-2) to facilitate mineralization, which is facilitated by self-stimulation and activation of BMP-2 expression through associated MSCs that secrete VEGF [74]. Li et al. investigated the effects of mild hyperthermia (41 °C) on the co-culture system of human outgrowth endothelial cells (OECs) and primary osteoblasts (POBS) and found that HSPs play a vital role in up-regulating angiogenesis and osteogenesis [75]. They studied the effects of MPT in the pre-osteogenesis period, which showed that it could enhance cell proliferation in the inflammatory and vascular phases by modulating HSPs.

MPT has the potential to impact VEGF through the upregulation of HSPs at 41 °C for a duration of 1 h to promote proliferation and enhance the migration and invasion of endothelial cells. Additionally, MPT may activate biological factors including BMP and IL-6, which can trigger the release and recruitment of angiogenic cells. However, the specific mechanism by which this occurs has yet to be determined [75]. Recent research has revealed that heat treatment at temperatures between 40 °C and 41 °C can induce the formation of endothelial cells and enhance neovascularization at the site of ischemia [71].

Local hyperthermia-induced heat stress has been found to promote the development of micro-vessel networks in rats by activating HIF-1 and TLRs, leading to the regulation of bone resorption and new bone formation. Previous studies suggested that HSF1 could be triggered by hypoxia and ischemia to regulate the mobilization and recruitment of bone marrow cells for angiogenesis [76].

In addition, heat shock can also activate the PI3K/Akt signaling pathway, which is involved in the regulation of cell survival and proliferation. This pathway can promote the expression of HSPs and VEGF, as well as enhance the migration and tube formation of endothelial cells. Moreover, heat shock can induce the expression of matrix metalloproteinases (MMPs), which are involved in the degradation of ECM and the remodeling of tissues. MMPs can promote angiogenesis by releasing growth factors and cytokines from the ECM. Therefore, heat shock may have a potential therapeutic effect on angiogenesis-related diseases, such as ischemic heart disease and peripheral arterial disease. However, further studies are needed to elucidate the underlying mechanisms and optimize the treatment protocols. However, the results of related studies among HSPs are contradictory.

HSP27 is a highly conserved molecular chaperone and a member of the small HSPs family. Its functions include inhibiting protein aggregation, protecting cell-related proteins from external stimulation, and preventing irreversible denaturation and loss of function, which can lead to apoptosis [77]. According to literature reports, HSP27 can activate the NF-κB signaling pathway of vascular endothelial cells by acting on TLR3, thereby activating the secretion of IL-8 and VEGF, thereby inducing their migration and angiogenesis [78–80]. It suggests that HSP27 may play a role in regulating vascularization and angiogenesis under heat stimulation conditions. HSP27 also helps to stabilize the newly formed blood vessels by preventing their regression and promoting their maturation. In addition, HSP27 has been shown to have anti-inflammatory properties, which can help to reduce inflammation at the site of injury and promote healing. It also protects cells from oxidative stress, which can occur during the bone repair process. Overall, the function of HSP27 in the bone repair process of vascularization is to promote the formation and stabilization of new blood vessels, reduce inflammation, and protect cells from oxidative stress. These functions are essential for the successful healing of bone tissue. Typically, systemic warming facilitates blood flow to the wound, which in turn promotes angiogenesis through the use of vascularization-promoting elements.

While HSP27 induction is critical for transforming growth factor-β(TGF-β) induced VEGF release in osteoblasts [81], whereas HSP70 acts as a negative regulator in the TGF-β-stimulated synthesis of VEGF via p44/p42 mitogen-activated protein (MAP) kinase and p38 MAP kinase [82]. At the same time, HSP22 plays a positive regulatory role in the synthesis of IL-6 and VEGF induced by PGF2α [83]. Previous studies have also demonstrated that hyperthermia can upregulate HSP90, contribute to the activation of the Akt/eNOS/NO pathway, and induce angiogenesis in hindlimb ischemic mice [84]. Moreover, several recent studies revealed that autophagy and heat shock may complement each other under cellular stress conditions. HSP70 can be regulated by the level of HSF-1 to inhibit human exercise-induced autophagy [85,86]. Current studies have shown that the molecular signals provided by endothelia cells can alter the osteogenesis niche and promote the bone progenitor cells differentiate into osteoblasts via the Notch signaling pathway [87,88]. The regulation of endothelial cell signaling pathways through MPT remains to be studied in the future.

2.3. Osteogenesis stage

In the present day, the widely accepted perspective on osteogenesis is that communication between different cells and biological factors during bone regeneration is crucial. The stimulation in the osteoblast microenvironment plays a significant role in regulating the expression of related genes and molecules in osteoblast lineage through various signaling pathways, ultimately leading to successful bone regeneration [89]. As mentioned above, macrophages differentiate into osteoclasts, which are primarily responsible for bone resorption through the activation of M-CSF and RANKL. The interactions between osteoblasts and osteoclasts coordinate bone maintenance [90].

The process of bone repair also depends on the involvement of sensory and sympathetic nerves, and there have been many studies on the involvement of regulatory nerves in regulating the relative balance between osteoblasts, osteoclasts, and MSCs to accelerate bone tissue repair [91,92]. In particular, Recent studies have found that the differentiation of bone progenitor cells is closely associated with the activity of nerve cells and Schwann cells in the niche, which is regulated by neurotrophic proteins. Sensory nerves regulate bone homeostasis by monitoring bone metabolism through the secretion of prostaglandin E2 (PGE2) by osteoblasts. Besides, PEG2 activate its receptor 4 in the sensory nerve in this process, which inhibits central nervous system-mediated sympathetic activity, ultimately regulating osteogenesis [93]. HSPs may act as inflammatory regulation in the nervous system initiating a new pathway of osteogenesis dominated by MPT [94].

It is compared that the related behavior of human MSCs and normal human dermal fibroblasts (NHDFs) at 40/42/44 °C in certain studies. It was discovered that even at 42 °C, hyperthermia caused MSCs to delay adhesion, decrease protein expression level and suspend at the G2/M phase of the cell cycle, resulting in increased apoptosis and senescence levels. However, there were no significant side effects on the proliferative activity and viability of MSCs, which may contribute to enhancing the osteogenic differentiation potential of MSCs [95]. Some studies have exposed human bone marrow-derived stromal cells and MG-63 cells to varying degrees of heat shock, which have shown that mild hyperthermia may enhance the expression of HSP70, thereby promoting the proliferation and mineralization of MSCs [96].

HSP70 has been found to promote osteogenesis by activating signaling pathways such as PI3K/AKT, NF-kB and ERK [38,97]. Chen et al. observed that osteogenesis could be enhanced by the periodic hyperthermia treatment of MSCs at 41 °C, which upregulates the expression of HSP70 [98]. Moreover, they found that hyperthermia drives HSP70 and increases the expression of genes related to osteogenesis, such as RUNX-2, OSX, and ALP *in vitro* cell experiments, which clarifies the mechanism of osteogenic differentiation through the ERK pathway [99]. Additionally, the ERK signal pathway have also been reported by other studies [100] (Fig. 5c).

Bone marrow mesenchymal stem cells (BMSCs) or MC3T3-E1 cells through realizing the periodical MPT at 39–44 °C by NIR exposure [34,44,101,102]. More importantly, it is usually explained as up-regulating the expression of HSPs (like HSP70 and HSP47). Kajiya H et al. found that it can increase the osteogenesis of MC3T3-E1 cells by MPT at 42 °C and activate HSP47 to improve the expression of osteogenic-related molecules such as ALP, RUNX-2, and Osterix (OSX) [103]. Tan et al. achieve MPT to regulate HSPs and MMPs, and stimulate the Wnt/β-catenin-RUNX2 axis for the recruitment of osteoblasts [104]. Similarly, some studies mentioned that it promotes bone regeneration through HSP47 and BMP-2 expression [43], which might activate the Wnt/β-catenin signaling pathway by MPT [105] (Fig. 5b). Additionally, it is found that SOX-9 interacts with RUNX-2 to induce differentiation of osteoblasts and also stimulates osteoblast maturation via the same signaling pathway [106,107].

Studies have shown that HSP22 present in MC3T3-E1 cells can negatively regulate TGF-β-stimulated cell migration [108]. Besides , it have found that HSP60 is upregulated when mitochondria are damaged, and when HSP60 is overexpressed, it can also cause mitochondrial dysfunction. It may indicate a role for HSP60 in bone healing under different conditions such as oxidative stress [109,110]. Furthermore, HSP60 might also regulate the proliferation by inducing TLR-dependent apoptosis in the osteoblast lineage affecting the status of osteoblasts [35].

Sayed S et al. seeded MC3T3-E1 cells on biphasic calcium phosphate scaffolds with periodic heat treatment at 41 °C. As shown in Fig. 4, the study revealed that this treatment increased cellular proliferation and osteogenic differentiation by raising the ROS levels and enhancing the expression of HSP27 and HSP70 [62]. According to relevant literature, HSP27 is not expressed in the calcified bone matrix under heat stress conditions, but is expressed at higher levels in osteoblasts around the uncalcified bone matrix and in primary cavernous bone [53,111]. Moreover, previous studies have reported that decreased HSP27 levels can impact the expression of osteocalcin [112]. This observation suggests the involvement of HSP27 in the bone regeneration stage.

Additionally, it has been observed that the expression levels of HSP70 and HSP90 reach their peak after 48 h of exposure to 42 °C for 1 h [117]. Furthermore, HSP90 exerts a critical function in regulating the expression of HSP70, as its inhibition results in an upregulation of HSP70 synthesis [118]. Given its involvement in various cellular processes, HSP90 is involved in diverse cellular processes and is capable of sensing heat stress directly, thereby modulating MAPK and PI3K/Akt signaling pathways [119,120]. Equivalently, the strategy proposed by Shan et al. suggests that MPT might enhance the MAPK and PI3K/Akt signal transduction and promote osteogenic factor expression [115] (Fig. 5e). Notably, HSP90 inhibitors have been shown to enhance subchondral bone thickness and suppress macrophage activation [35]. Similarly, other forms of thermal effects (e.g., electromagnetic, microwave, etc.) have been reported to promote bone tissue regeneration, which can provide insights into the research on MPT for assisting bone tissue repair through the same pathway. Wang et al. developed a system to achieve mild magnetic hyperthermia therapy at 41–42 °C. This system promotes vascularization by enhancing the expression of HIF-1α and osteogenesis through HSP90, which activates the PI3K/Akt signal pathway [121].

However, Lei et al. findings revealed that there was no significant difference between the NIR group and the blank control group during the osteogenesis process at 42–45 °C [18]. It might indicate that the balance between cell proliferation and death might be disrupted when temperature exceed 42 °C. Exceptionally, it was found that this system can promote osteogenesis at 45 °C, which is a higher temperature than what is typically used [116] (Fig. 5f). Moreover, osteoblasts can differentiate earlier by utilizing the BMP-2 modification in this system, while the addition of curcumin effectively alleviates inflammation. The key role played by the materials used in the process of bone regeneration may be the reason why osteogenesis is promoted at a higher temperature than 42 °C, particularly in the use of BMP-2 on the BMPs/Smad pathway. Additionally, Zhang et al. found that low intensity pulsed ultrasound (LIPUS) and the temperature rise caused by LIPUS facilitate bone defect repair via the up-regulation of HSPs and the BMPs signaling pathway [122]. According to the researchers, Ma et al. used NIR irradiation to realize MPT in order to target antineoplastic therapy and bone repair. This system achieves varying functions through different temperatures, particularly utilizing NIR irradiation to achieve MPT, which promotes osteogenesis via the BMP-2/Smad pathway at 42 ± 0.5 °C [113](Fig. 5a). These findings suggest that mild hyperthermia may have a similar potential mechanism. HSPs play a crucial role in these pathways, particularly in regulating the progress of bone tissue repair via materials that respond to temperature changes. Surprisingly, some studies have also found that periodic MPT can achieve better results, Shi et al. conducted experiments where ectomesenchyme stem cells (EMSCs) were exposed to mild hyperthermia at 41 °C for 1 h per 7 days, and the results showed that periodic heat stimulation increases the activity of ALP and promotes mineralization through the YZP signal

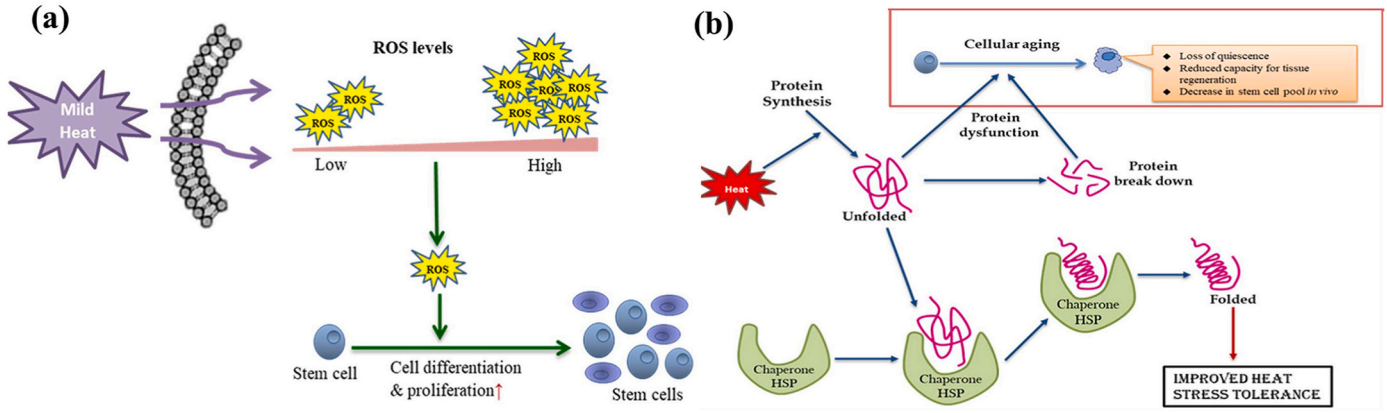

Fig. 4. (a) Heat stress mechanism inside the cell. (b) Role of HSP during protein synthesis under heat stress [62]. © 2019 Elsevier B.V. All rights reserved.

pathway [123].

At present, studies on MPT for anti-tumor and antibacterial are extensive. By combining HSP inhibitors, enzymes, and specific drugs, to achieve combined gene therapy, immunotherapy, etc., which can not only overcome the resistance of cancer cells and bacteria caused by HSPs , but also reduce the damage caused by high temperature [114,124–127] (Fig. 5d). But relatively speaking, mild photothermal antibacterial requires a higher temperature, which may be related to the biological structure of the bacteria itself [128].

Similar to HSPs, the hedgehog (Hh) signaling pathway and the Notch signaling pathway are also highly conserved. The current study found that there is a cascade reaction between Hh signal transduction and signal axes such as Wnt/BMP. In addition, oxidative stress has also been shown to inhibit MSC osteogenic differentiation by modulating Hh signaling. The role of Notch depends on the cellular environment, it can affect OSX, RUNX2, etc., influencing bone formation.Additionally, Notch can induce osteoclast differentiation by activating T cells through the activation of NF-κB.It is not difficult to find that some parts of MPT-induced HSP involved in bone tissue metabolism coincide with Hh and Notching signaling pathways [129,130]. It may be possible to discover unreported crosstalk between the Hh signaling pathway and the Notch signaling pathway via HSPs in the future.

3. Materials of MPT

Compared to other hyperthermia techniques such as ultrasound, microwaves, and magnetic and electric hyperthermia, PTT incorporates the use of PTAs to achieve hyperthermia through NIR irradiation, making it a promising strategy for treating diseases like cancer, infection, and so on [28,131]. NIR as a light source for PTT usually has two forms: NIR-I and NIR-II. NIR-I biological window (700–1000 nm) can achieve photothermal effect in a milder form and reduce additional damage; NIR-II (1000–1500 nm) has higher tissue penetration ability and higher photothermal conversion efficiency [27]. Currently, there is a growing focus on the research of combining MPT with immunotherapy, gene therapy, and other methods in the fields of anti-tumor and antibacterial treatments. Particularly, there is an increasing emphasis on utilizing NIR-II in these studies [132,133]. Consequently, the properties of PTAs must be taken into consideration. In addition to high photothermal conversion efficiency, ideal PTAs should exhibit excellent biocompatibility, low or non-toxicity, biosafety, optimal surface modification, and more [134,135]. Particularly for promoting bone repair, PTAs can act as "raw materials" for bone regeneration and mineralization through external regulation [13], it can even serve as carriers for adsorbing drugs or therapeutic factors to provide multiple functions [136]. Moreover, PTT can be combined with various other approaches utilizing PTAs, such as chemotherapy (CT) [137], PDT [138], immunotherapy, and gene therapy [139], which have the potential to enhance treatment outcomes through various approaches.

Currently, a wide range of nanomaterials has been extensively developed. This includes organic materials such as porphyrins and polypyrroles, as well as inorganic materials such as metal nanoparticles (e.g., gold, silver, and copper) and their compounds, oxides, and other vulcanization compounds. These materials have been the subject of extensive investigation. Additionally, carbon-based nanomaterials such as graphene and graphyne, as well as semiconductors represented by MXene and black phosphorus (BPs), have also emerged as promising PTAs. These materials have shown great potential in achieving efficient hyperthermia on target tissues and enhancing therapeutic outcomes. Through further exploration, PTAs have the potential to significantly advance the field of hyperthermia therapy [14,140]. This part of the review aims to discuss the classification of PTAs (Table 1).

3.1. Metal-based PTAs

3.1.1. Metallic materials

Noble metal nanomaterials, such as gold and silver, are extensively employed as PTAs due to their exceptional NIR absorption capabilities. Gold nanoparticles have gained extensive use in biomedical research for their unique characteristics and exceptional biocompatibility [146]. Various forms of gold nanoparticles have been developed to achieve optimal light-thermal conversion efficiency, including gold nanorods and gold nanocages. By combining bioactive glass(BG) on the surface of gold nanoparticles, doping with hydrogel, or modifying with endogenous proteins, the immune rejection can be reduced and the material can be multifunctional to achieve ideal performance [115,147,148]. At present, there are some studies combining Au and Pb through wet chemical strategies to form a core-shell structure to achieve periodic MPT [43]. In addition, there are also hybridization of lanthanides and Au through up-conversion technology to improve its therapeutic effect [149]. It has been discovered that Au nanoparticles used in MPT might be advantageous in accelerating the proliferation of osteoblasts and promoting bone regeneration. Furthermore, gold nanomaterials used in MPT have displayed little toxicity to cells and tissues and may positively affect bone regeneration processes.

There are also studies that use Ag nanoparticles (AgNPs) as a photothermal agent to eliminate infection at high temperature to accelerate bone tissue healing [150]. Cu can also be used as PTAs, which can achieve good photothermal performance by combining with bioactive glass, and copper ions can also exert certain angiogenesis activity [151,152]. In addition, some studies have found that Bi-doped BG has high photothermal conversion efficiency, and can also produce suitable high temperature and maintain good biological activity [153]. By adding iron element, it can not only endow the material with good photothermal performance, but also produce a certain magnetocaloric effect at the same time, and the dual-mode hyperthermia has a higher heating effect

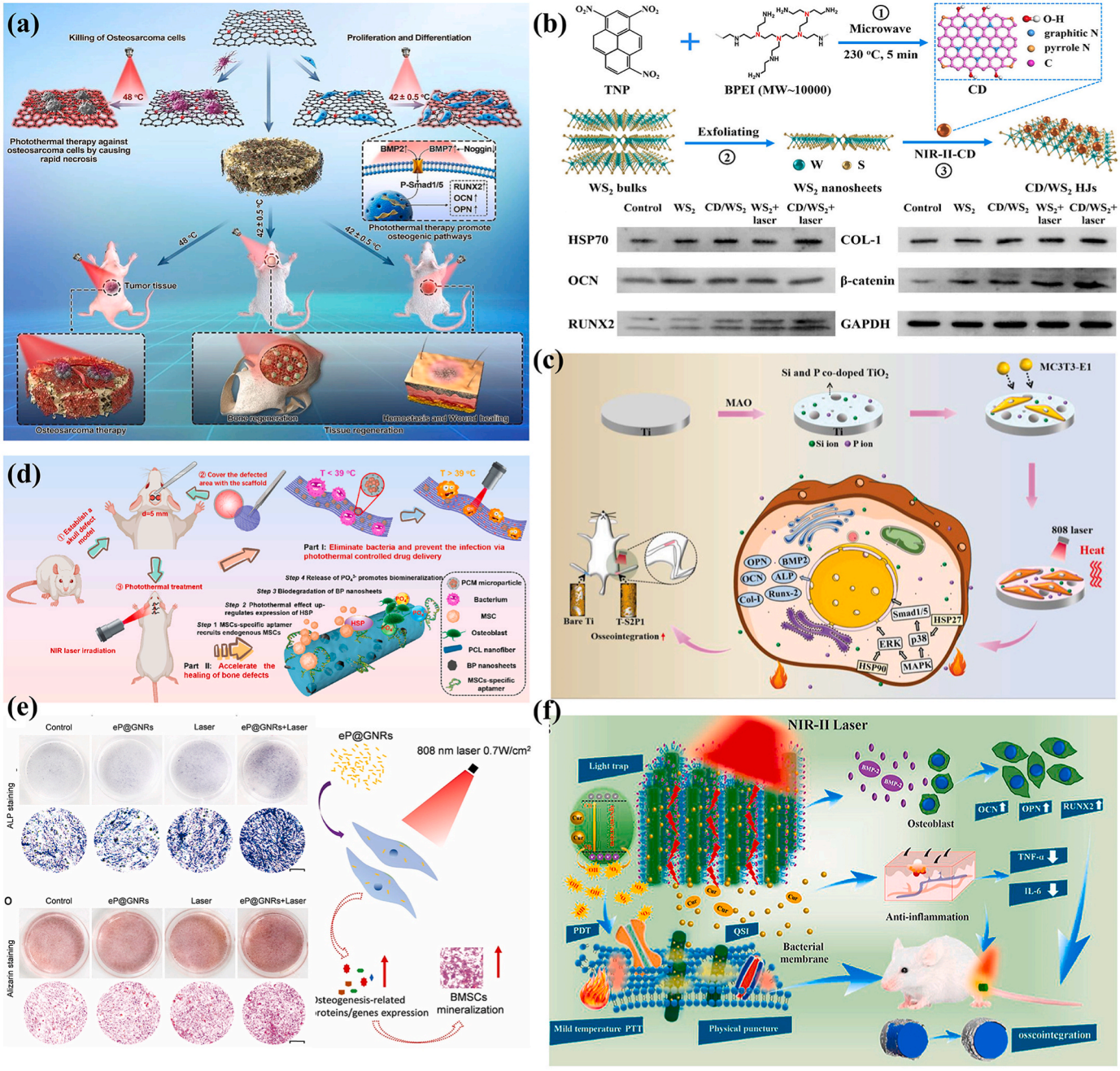

Fig. 5. Using MPT as an aid to bone regeneration involves the utilization of heat shock proteins. (a) Employing PTT for tumor treatment followed by MPT to assist in bone regeneration [113].© 2019 Elsevier Ltd. All rights reserved.; (b) Using NIR-II to modulate HSP70 [105]. © 2019 Elsevier B.V. All rights reserved.; (c) Utilizing MPT to modulate HSP27/HSP90 for bone repair [100]. © 2022 Wiley-VCH GmbH; (d) Combining MPT for antibacterial and auxiliary bone regeneration [114]. Copyright ©2023, American Chemical Society; (e) Conducting *in vitro* osteogenesis experiments under NIR irradiation [115]. ©2022 Elsevier Ltd. All rights reserved.; (f) Exploring antibacterial and assisted bone regeneration under NIR-II [116]. ©2020 Elsevier Ltd. All rights reserved.

[154].

3.1.2. Metal compounds

In recent years, there has been extensive research on the utilization of CuS nanoparticles in PTT. These nanoparticles have shown demonstrated remarkable attributes in terms of their size, morphology, surface characteristics, as well as their photothermal and biological properties. The comprehensive investigation of CuS nanoparticles in PTT has yielded significant advancements, highlighting their potential for diverse applications in this field [155,156]. Zhang et al. combined CuS nanoparticles and reduced graphene oxide (rGO) nanosheets to synergistically integrate PTT and PDT for accelerating osseointegration and promoting vascularized bone regeneration with the aid of Cu ions [157].

Similarly, Noor Al-Jawuschi et al. showcased the use of Bi_2S_3 nanoparticles with strong photothermal effects for anti-tumor applications, which also showed the potential for drug release regulation. However, certain studies have reported poor dispersion of Bi_2S_3 nanoparticles in water, necessitating modifications at this stage. To address this issue, Zhou et al. successfully incorporated Bi_2S_3 nanoparticles into a hydrogel matrix for antibacterial applications, resulting in improved functionality and performance [158]. Furthermore, Ma et al. demonstrated the acceleration of osteogenesis and bone healing through MPT using a system composed of poly(ε-caprolactone) (PCL) nano membranes, with exfoliated MoS_2 nanosheets acting as PTAs [34]. Similarly,

Table 1
Typical PTAs employed for MPT.

Classification	PTAs	Temperature (°C)	Light irradiation parameters	The stage of function	HSPs	References
Metal compounds	MoS_2	46.1	808 nm 1.0 W cm^{-2} 10min	bone regeneration		[37]
Metallic materials	pAuPds	40.0–43.0	808 nm 2.0 W cm^{-2} 3min	bone regeneration	Hsp47	[43]
	GNR	40.0–43.0	808 nm 0.4 W cm^{-2} 15 min	M2 polarization increase blood flow osteogenic differentiation	Hsp47	[115]
Metallic oxide	TiNTs	42.0	808 nm 0.3 W cm^{-2} 10 min	decrease the EPC secretion enhance osteoblasts differentiation	HSP70	[141]
	T-S2P1	37.0–42.0	808 nm 0.25 W cm^{-2} 5 min	Osteoblast adhesion, differentiation	HSP27/HSP90	[100]
Carbon-based PTAs	GNP	40.0–43.0	808 nm 1.0 W cm^{-2} 5 min	the proliferation of cells		[102]
	CD	40.0–41.0	1064 nm 0.6 W cm^{-2} 5 min	osteogenesis	HSP70	[105]
	CNT	42.0	808 nm 4.0 W cm^{-2} 10 min	mineral deposition	HSP27	[103]
	GO	41.5–42.5	808 nm 1.0 W cm^{-2} 1 min	osteogenic differentiation	Hsp47/Hsp70	[113]
Other molecules	PDA	40.0–42.0	808 nm 0.75 W cm^{-2} 15min	enhance metabolic activity M2 polarization osteogenesis	Hsp70	[56]
	BPs	39–40.2	808 nm 0.8W·cm^{-2} 6 min	drug release; osteogenesis	HSP47/HSP70A	[114]
	BPs	40.0–41.0	808 nm 1.0 W cm^{-2} 1 min	osteogenesis		[142]
	BPs	42.0	808 nm 1.0 W cm^{-2} 5 min	improve osteoblastic migration osteogenesis	Hsp27/Hsp70/Hsp90	[104]
	PDA	42.0	808 nm 1.0 W cm^{-2} 30 min	osteogenesis		[143]
	PDA	39.5–40.5	808 nm 0.99 W cm^{-2} 1 min	osteogenesis		[144]
	BC	40.0–43.0	808 nm 0.4 W cm^{-2} 10 min	regulate the osteoimmunology	Hsp47	[145]

Zhang et al. created a biomimetic cellular environment by seeding rat BMSCs onto a novel photothermal tissue-engineered bone (PTEB), which effectively induced osteogenesis, primarily utilizing MoS_2 for PTT [37].

Moreover, there are some other types of metal compounds that can also achieve PTT [159]. In addition to the aforementioned metal sulfides, other types of metal compounds have also garnered attention. For instance, Dang et al. utilized BG scaffolds functionalized with $CuFeSe_2$ nanocrystals (BG-CFS) to make them effective in bone tumor treatment and bone regeneration. The BG-CFS scaffolds exhibit remarkable photothermal performance upon exposure to NIR [160]. Feng et al. synthesized CuSi nanowires and used MPT to achieve anti-infection while promoting the proliferation and migration of vascular endothelial cells, showing a good ability to promote vascularization [161].

3.1.3. Metallic oxide

In addition to the aforementioned metal compounds, metal oxides such as TiO_2 [141], CuO [162] and Fe_3O_4 [163] are commonly utilized as PTAs. For instance, Xu et al. introduced a new hydrogel system by combining the Cu_2O nanoparticles with TiO_2. It has the potential to accelerate the release of Cu ions and achieve MPT when exposed to NIR radiation, which can aid in tissue regeneration [143]. Another research has developed the titania nanotubes array (TiNTs) for the treatment of peri-implantitis through the use of MPT. Moreover, associated cells such as macrophages, endothelial progenitor cells, and osteoblasts displayed positive changes in their phenotype through MPT. Notably, macrophage polarization occurred in the M2 direction, promoting anti-inflammation and pro-healing, while endothelial progenitor cell function was inhibited for abnormal angiogenesis inhibition and the differentiation of osteoblast increased. Additionally, TiNTs-transmitted MPT has the potential to regulate inflammation and promote bone repair, as evidenced by the results of the study [141]. Yang et al. demonstrated the use of Si and P-doped TiO_2 for MPT, which resulted in favorable bone regeneration effects. The photothermal ion microenvironment created by these PTAs played a regulatory role in osteoblast behavior through the activation of p38/Smad and ERK signaling pathways [100].

Besides, Lu et al. used novel magnetic $SrFe_{12}O_{19}$ nanoparticles to modify mesoporous scaffolds, which can not only be used as PTA to effectively kill residual tumors through PTT, but also activate BMP-2/Smad/Runx-2 pathway promotes osteogenic differentiation and new bone regeneration [164]. Zhang et al. utilized the FeOOH to successfully eliminate bacterial infections both pre- and post-implantation underNIR light. Simultaneously, the released Fe ions enhanced the microenvironment and provided a favorable substrate for cell proliferation and bone tissue regeneration [165].

Furthermore, studies conducted by $SrCuSi_4O_{10}$ have explored the use of NIR-II in PTT [166,167]. The main factor contributing to the promotion of bone regeneration in these studies is the release of copper ions triggered by two types of phototherapies, which might suggest that the phototherapy effect produced by NIR may have a synergistic effect when combined with treatment methods such as metal ions. These studies have shown that photothermal anti-tumor treatment can also stimulate the continuous release of bioactive ions, thereby enhancing vascularized bone regeneration.

3.2. Carbon-based PTAs

Various carbon-based PTAs, like CDs, graphene, graphene oxide (GO) and so on, have been employed in MPT for bone regeneration. Geng et al. utilized an ultrafast microwave-assisted hydrothermal method to synthesize CDs, which were then electrostatically assembled onto both sides of negatively charged WS_2 nanosheets for anti-tumor and bone regeneration. Importantly, this hybrid junction(HJ) was found to significantly up-regulate bone-related gene expressions, particularly HSP expression under NIR-II light irradiation, suggesting its great potential for bone repair applications [105].

Yanagi et al. developed a novel device consisting of an agarose gel (AG) infused with carbon nanotubes (CNTs), which accelerated mineral deposition in rat critical-sized calvarial defects when stimulated by NIR at 42 °C compared to nonthermal stress controls. Moreover, the device was found to upregulate the expression of osteogenic-related genes (ALP, OSX, and osteocalcin) in DNA/protamine scaffold cells and MG63 preosteoblasts, demonstrating its potential for bone repair applications [168]. Similarly, Kajiya et al. created a unique photothermal device composed of an AG infused with CNTs. This research highlights the promising potential of photothermal-assisted bone regeneration for treating osteoporosis and other bone disorders [103].

Zhang et al. designed a porous scaffold made of graphene nanoplatelets, which demonstrated that the scaffold could enhance the proliferation of MC3T3-E1 cells by adjusting the cycle and duration of MPT to achieve a temperature range of 40–43 °C [102]. These findings emphasize the potential of this method as a versatile tool for both cancer therapy and bone tissue regeneration. Additionally, Ma et al. developed a multifunctional scaffold that consisted of nHA, GO and chitosan (CS). They explored the effect of composite particles in various proportions on human osteosarcoma cells, MC3T3-E1 cells, and BMSCs with or without NIR irradiation. The results showed that bone regeneration was enhanced when BMSCs were exposed to MPT at 42 ± 0.5 °C in

conjunction with nHA, demonstrating the potential of this scaffold for bone repair [113].

Furthermore, Li et al. innovatively created composite nanofibers composed of MXene nanosheets and HA nanoparticles. It demonstrated that the composite nanofibers exhibited excellent biocompatibility and successfully induced the growth and adhesion of BMSCs under NIR illumination [101]. Wu et al. employed Ti_3C_2 MXene as PTAs, along with an injectable photocurable hydrogel, to investigate the synergistic effects of MPT in immune regulation, anti-infection, and tissue regeneration. Similarly, some studies have demonstrated the use of Nb_2C MXene for achieving photothermal anti-tumor effects and subsequent angiogenesis/osteogenesis under NIR-II conditions at a wavelength of 1064 nm [169,170]. Furthermore, the study revealed that periodic MPT could enhance the material's capacity to scavenge free radicals [171].

3.3. Other molecules

There are various other widely usedPTAs, including PDAs and BPs, among others. Wu et al. demonstrated this by developing a novel hydrogel platform, composed of PDA. Notably, this MPT hydrogel platform exhibits exceptional osteogenic effects in the treatment of bone defects by the accession of PDA [144]. Analogously, Li et al. creating a core-shell nanorod-like coating on the surface of titanium with PDA. Periodic MPT (41 ± 1 °C) enhances the migration of adherent macrophages, on the other hand, the coating was found to suppress inflammation to some extent, attributed to its ROS scavenging capacity [56].

Moreover, Fan et al. have established a delivery gel platform that enhance bone regeneration through blood clotting. It is worth noting that this biomaterial can be prepared from autologous blood. When exposed to NIR, MPT enhances osseointegration due to the deep-red hue of the blood clot gel. Furthermore, implanting blood clots and utilizing laser therapy modulates osteoimmunology by recruiting a large number of macrophages and controlling their polarization at different stages to modify the immune niche within the microenvironment of the bone defect [145].

Tong et al. utilized BPs to achieve MPT in order to encourage bone defect repair at 40.5 ± 0.5 °C [33,104]. Zhang et al. harnessed the photothermal properties of BPs to facilitate drug release and modulate HSPs, thereby regulating material degradation and achieving multiple effects including anti-infection, recruitment of MSCs, and promotion of bone tissue regeneration [114]. There are also studies that investigate the combination of BPs with other compounds to achieve additional functionalities. Wu et al. enhance the bone repair process by multifunctional bone implants with the addition of BPs and zinc sulfonate ligands (ZnL_2). While BPs primarily induce photothermal effects, the scaffold's effectiveness in promoting osteogenesis during the later stages of bone repair is attributed to two factors: the MPT range of 40–42 °C and the extended release of Zn^{2+} and PO_4^{3-} from the scaffold [142]. By integrating $SrCl_2$ and BPs into PLGA, Wang et al. revealed that local Sr^{2+} release at alternate time intervals regulated by NIR irradiation promotes bone regeneration [172]. Additionally, Red phosphorus (RPs), as an allotrope of phosphorus, has also attracted extensive attention for its efficient photothermal performance [21,173].

4. Fabrication of MPT materials system

Generally, bone regeneration is a dynamic and complex process due to its unique structure. It means that any system used for the regeneration of bone must match the process of osteogenesis. The system should possess characteristics such as biocompatibility, vascular inducibility, bone induction, and positively impact cellular metabolism and differentiation. In case of fractures combined with clinical diseases like tumors, infections, or diabetes, adverse conditions like delayed union of fractures may occur. Among these biomaterials, PTAs-based platforms have garnered more attention, particularly those systems that are constructed with photothermal functions and therapeutic effects for MPT. At present, as depicted in Fig. 6, the experimental investigations focusing on treatment research utilizing MPT are primarily conducted in rat models. For instance, Tong et al. prepared a film-like structure by blending BPs with PLGA powder in varied proportions. Upon short periodic NIR radiation, the structure could maintain a temperature of approximately 40.5 ± 0.5 °C. It was observed that the mild thermal stimulation of BPs@PLGA triggered induced by NIR irradiation can foster bone regeneration by regulating the expression of HSPs [33]. Accordingly, it is necessary to design a BTE system that matches the process of osteogenesis and to understand the function of each stage in order to comprehend how bone defects should be repaired under varying pathological conditions [174]. The system is usually constructed by electrospinning, phase inversion, 3D printing scaffold, hydrogel, high temperature sintering, gas foaming, etc. When PTA is included in the system to achieve PTT, even the temperature can be adjusted to make it play the role of MPT. This will ensure that the MPT system has excellent photothermal functions and therapeutic effects (Table 2).

4.1. Electrospinning

Thanks to its versatility and customization, electrospinning enables the fabrication of materials with diverse shapes, ranging from membranes to scaffolds. In recent years, advancements in techniques such as coaxial electrospinning and multiaxial electrospinning have further expanded the capabilities of this technology. Electrospinning also offers the potential for incorporating stimuli-responsive and drug-carrying functionalities into the produced materials [175].

Ma et al. fabricated a membrane by adding different scales of MoS_2 and PCL into hexafluoroisopropanol using an electrospinning machine. When exposed to NIR irradiation, the temperature reached 40.5 ± 0.5 °C which resulted in the up-regulated the expression of HSPs. This membrane showed osteogenic effects due to the enhanced HSPs expression [34]. Surprisingly, Yu et al. used the photothermal effect of mild temperature for material preparation, and used photothermal welding technology to form a gradient structure of the fibrous membrane prepared by electrospinning, so as to achieve a gradient mineralized structure simulating the tendon-bone interface. Natural variation [176]. Unlike the structure of the material fabricated in this study, Wang et al. utilized a seed-mediated method to design an electrospinning scaffold with GNRs that was modified by polyetherimide and loaded onto BG fibers. However, the study solely suggested that the scaffold exhibited the ability to induce cancer cell death at a temperature of 42.5 °C and markedly enhance cell proliferation under 37 °C [147]. Chen et al., in the process of constructing scaffolds by electrospinning, also achieved temperature-controlled drug release through phase change materials (PCM), and achieved tumor elimination under mild temperature conditions in a compound way [124].

In summary, electrospinning technology holds great promise for optimizing photothermal systems by capitalizing on its advantages of high surface area and favorable preparation conditions. It serves as an effective approach for fabricating nanofiber materials with enhanced photothermal performance. However, it should be noted that the specific outcomes may vary depending on the choice of materials and the specific parameters employed in the electrospinning process. Further research and optimization are necessary to achieve desired results.

4.2. 3D printing

3D printing technology includes laser sintering, melt extrusion, stereolithography and other technologies, which can be selected according to different materials and applicable fields, and are gradually widely used in disease modeling and BTE. Under the premise of ensuring that the physical properties such as mechanical strength and elastic modulus meet expectations, the scaffolds prepared by 3D printing are combined with PTAs to achieve better biocompatibility and responsiveness, thereby regulating bone tissue regeneration [177].

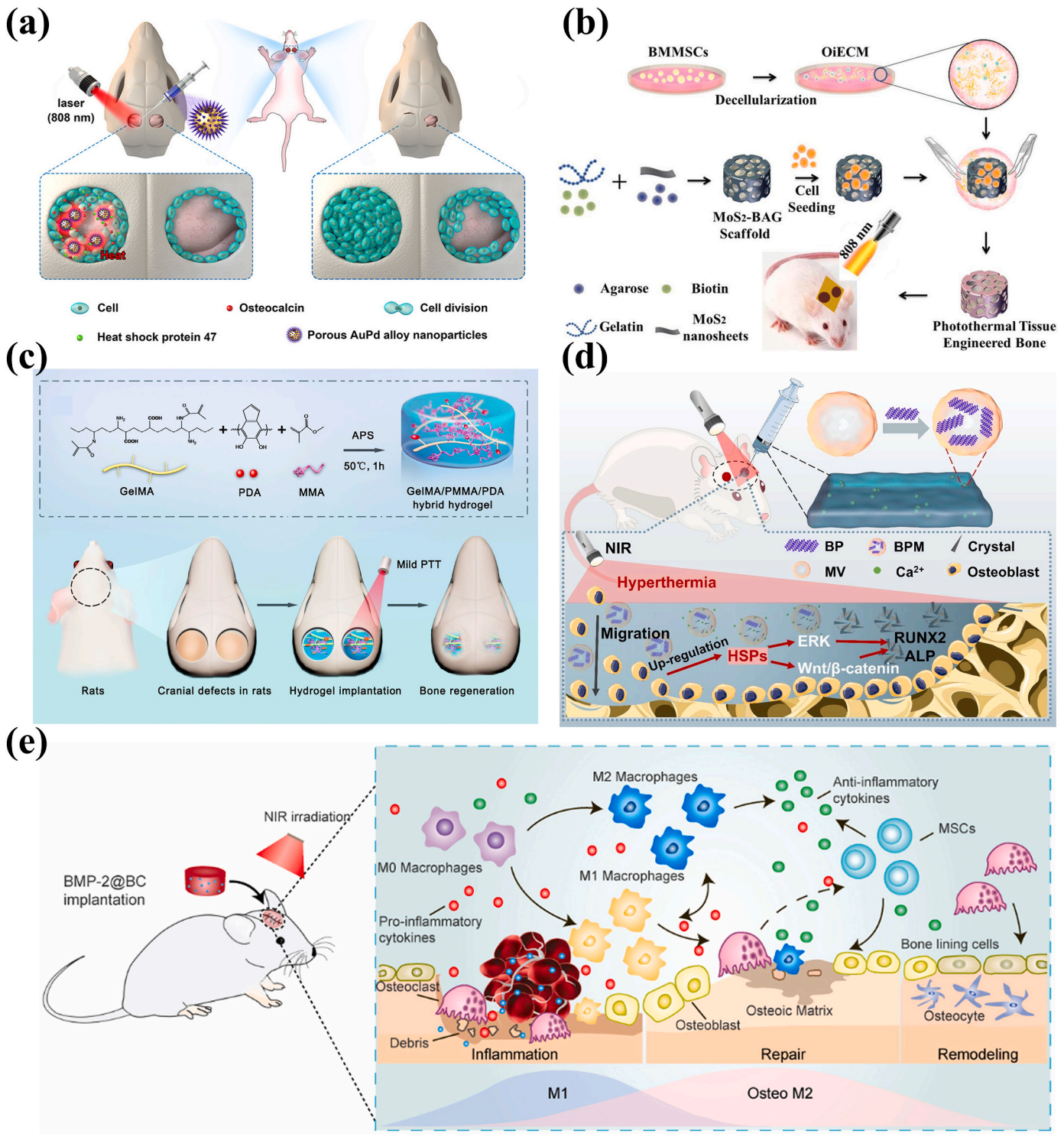

Fig. 6. Schematic illustration of the preparation of MPT-assisted tissue engineering scaffolds and their model for critical-size bone defects in rats [37,43,104,144,145]. © 2021 Wiley-VCH GmbH; Copyright © 2019, American Chemical Society; © 2021 Elsevier B.V. All rights reserved.

As mentioned earlier, Zhang et al. used 3D printing technology to build scaffolds with graphene nanosheets and apatite-gelatin composites, achieving periodic stimulation of osteoblastoma for cell proliferation at 43 °C under MPT [102]. In addition, BPs as a highly efficient PTA was used in the exploration of Wu et al. to bind to HA scaffolds, based on zinc sulfonate ligands to improve the thermal sensitivity of bacteria around the implant, to achieve mild thermal stimulation through photothermal action, and to promote bone tissue healing and regeneration based on antibacterial [142].

Currently, numerous studies have leveraged the customization capabilities of 3D printing to fabricate multifunctional scaffolds using composite materials. Dang et al. developed a kind of BG scaffolds containing $CuFeSe_2$ nanocrystals for treating bone tumors and reconstruction under NIR control [160]. Similarly, Zhu et al. achieved successful photothermal regulation of drug delivery for the treatment of bone tumors and osteomyelitis by utilizing a 3D printed polyetheretherketone scaffold loaded with graphene [178]. Zhao et al. used 3D printing technology to prepare akermanite ($Ca_2MgSi_2O_7$, AKT) scaffolds,

Table 2
Summary of strategies to construct materials system of MPT.

Strategies	Materials system	Temperature (°C)	Advantages of the system	Disadvantages of the system	References
Electrospinning	BG@GNR	42.5	The material has a high surface area to incorporate a large number of GNRs.	Electrospinning technology encounters challenges such as slow fabrication speed and multiple factors that influence the final product , and it will also face uneven distribution of the matrix.	[147]
	PCL/MoS_2	40.0–41.0	Enhancing the mechanical properties of the fiber membrane, it will also cause uneven distribution of the matrix.		[34]
3D printing	HA/Gr	40.0–43.0	Make the slurry more uniform through composite materials.	3D printing is constrained by material limitations, and achieving a balance between accuracy and printing efficiency has always posed a challenge to be addressed.	[102]
	ZnL_2-BPs@HAP	40.0–42.0	It is capable of integrating multiple materials to fulfill diverse functionalities.		[142]
Physical/chemical crosslinking	PTEB	41.0	The system could use the seeded cells to mimic microenvironments.	There are various methods for hydrogel synthesis. Generally, physical cross-linking methods tend to result in hydrogels with poor mechanical properties and stability. On the other hand, chemical cross-linking methods often leave behind residual substances, which can compromise the biocompatibility of the hydrogels.	[37]
	CNT-AGs	42.0	Combining CNT and hydrogel to achieve photothermal response.		[103]
	nHA/GO/CS	41.5–42.5	On the basis of ensuring mild light and heat effects, multi-elements ensure the dual functions of the material.		[113]
	GelMA/ PMMA/PDA	41.5–42.6	The hydrogel system is conducive to the dispersion of PDA, and the addition of PDA ensures the mechanical properties and at the same time endows the material with photothermal properties.		[144]
	Chitosan/ collagen/BPM hydrogel	42.0	The hydrogel uses its own network to retain MSC-coated BP, slow down the degradation of BP, and realize photothermal and osteogenesis.		[104]
	BMP-2@BC	40.0–43.0	Use autologous blood to exert photothermal potential, regulate bone immunity, and promote osteogenesis.		[145]
Wet-chemical synthesis method	PDA@HA	40.0–42.0	Using hydrothermal growth combined with micro-arc oxidation and PDA deposition to realize the regulation of immune regulation and osteogenesis under photothermal conditions.	Controlling the reaction process and observing phenomena can be challenging when using the hydrothermal method. Besides, it has higher requirements on equipment.	[56]
	pAuPds	40.0–43.0	The synthesized pAuPd has a larger LSPR absorption band and enhanced light absorption in the NIR region.	This method of wet chemical combination still has some aspects such as unknown growth mechanism and complicated heterostructure design.	[43]
	GNR	45.0	Endogenous protein modification of GNR reduces immune responses while enabling mild photothermal effects.	The seed-induced growth method still has limitations in terms of controlling the dispersion of materials and ensuring size consistency. It can be challenging to precisely control the growth rate of the materials using this method.	[115]
	BP-$SrCl_2$/PLGA	45.0	The material system uses the photothermal effect of BP to realize the release of NIR controllable Sr^{2+}, and the thermal effect can effectively improve the osteogenesis.	The oil-in-water emulsion solvent evaporation method still faces challenges in terms of emulsification efficiency for film formation and stability. It is more suitable for materials with relatively small sizes and simple shapes.	[172]
	BPs@PLGA	40.0–41.0	By using PLGA to effectively alleviate the degradation of BPs and ensure a long period of mild light and heat, the use of BPs can also provide the elements needed for osteogenesis.	The phase transition method for film preparation is associated with certain limitations, including difficulties in controlling the thickness and shape of the film, as well as limitations in material compatibility.	[33]

combined with boron carbonitride nanosheets produced after freeze-drying, to achieve photothermal therapy for bone tumors, and also studied the effect of the scaffold on bone tissue regeneration mechanism [179]. Similarly, Wang et al. applied MoS_2 nanosheets to the surface of 3D printed bioceramic AKT scaffolds, which also realized the dual functions of anti-tumor and bone repair [180].

It is evident that 3D printing, combined with photothermal materials, offers expanded possibilities for MPT due to its inherent customization capabilities. While 3D printing technology shows potential in enhancing the photothermal effect, successful implementation requires careful consideration of various factors, including material selection, printing parameters, and structural design. Therefore, continued research and optimization are necessary to fully harness the potential of 3D printing technology in the field of MPT.

4.3. Physical/chemical crosslinking

Hydrogels can be cross-linked physically or chemically, and adding PTAs during the preparation process can also achieve photothermal response. As a class of materials with a 3D network structure formed by cross-linking polymer molecules, hydrogels have good biocompatibility and are widely used in wound repair, drug delivery and other fields [4, 181].

As mention before, Kajiya H et al. use the system of AG, which showed increased expression of HSF-2 by MPT at 42 °C [103]. Similarly, Yanagi T et al. utilized CNT-AG to improve the biomineralization of mouse osteoblast precursor cells by regulating HSPs under MPT [168]. Wu et al. used methacrylic acid alginate (Alg-MA) and PDA to prepare injectable photocurable hydrogels, and coated Ti_3C_2 MXene nanosheets to realize the regulation of macrophage polarization under mild temperature conditions by using photothermal effect, and at the same time endow the implant with certain anti-infection and bone regeneration capabilities [171].

There are also numerous studies aiming to utilize hydrogel systems to mimic the tissue environment and achieve improved compatibility. Zhang et al. synthesize a scaffold by biotin-agarose-gelatin and MoS_2 nanosheets, in conjunction with osteo-inductive OiECM to accelerate bone regeneration. This approach demonstrated improved bone regeneration through NIR irradiation at 41 °C. Additionally, the authors highlight that the application of a thermal cycle could potentially

enhance the efficacy of NIR irradiation [37](Fig. 6b). Tan et al. developed an injectable hydrogel that effectively fills skull defects by combining BMPs and BPs with the CS/collagen hydrogel that mimics the ECM. They also activated HSPs through mild thermal stimulation induced by NIR radiation [104] (Fig. 6d). Fan et al. have developed a delivery gel platform that incorporates BMP-2 to enhance bone regeneration through blood clotting while also modulating macrophage phenotype changes. The blood clots, as a novel photoacoustic tissue agent is particularly noteworthy. This approach allows for the exploitation of the immune response elicited by blood clots in the early stages of regeneration, while also enabling a gentle photothermal effect underNIR irradiation in the later stages. Additionally, the controlled release of BMP-2 can be achieved through temperature modulation, further enhancing the efficacy of this platform for bone regeneration [145] (Fig. 6e).

Additionally, Ma et al. prepared scaffolds using CS incorporating composite particles of nHA and GO, which promoted cell proliferation and had hemostatic and soft tissue repair effects under NIR exposure [113]. Wu et al. modified GelMA by incorporating PMMA to enhance its mechanical properties and added spherical PDA to achieve MPT, on the one hand, it can promote bone remodeling through the MPT, on the other hand, PDA microspheres, released by the hydrogel, play a synergistic role in the enhancement of cell vitality [144](Fig. 6c).

4.4. Wet-chemical synthesis method

In the preparation process of photothermal system materials, there are many studies on the direct use of nanomaterials, and most of them use wet chemical synthesis to prepare materials. This includes hydrothermal synthesis, electro/chemical deposition, emulsion polymerization, sol-gel, etc [182,183]. Wet chemistry synthesis also offers excellent controllability, allowing for precise control of the structure, morphology, and properties of photothermal materials through adjustment of reaction conditions and proportions. This method typically exhibits high reaction efficiency and product purity, enabling the preparation of high-quality photothermal materials within a short timeframe. These advantages provide strong support for the application of wet chemistry synthesis in the field of MPT.

Zhang et al. developed a wet-chemical synthesis method to produce pAuPds for MPT. The addition of Pd to Au allowed for the regulation of localized surface plasmon resonance (LSPR), enabling the strong absorption to shift from wavelength range, which is at the MPT temperature of 40–43 °C. The results showed that the function of pAuPd system in promoting osteogenesis [43] (Fig. 6a). Interestingly, Chen et al. conducted an investigation on microspheres that are responsive to NIR through the use of GNR and gelatin/HA, utilizing emulsion techniques to create a microstructure with diameters ranging from 10 to 50 μm. The microspheres were capable of achieving a temperature of 42 °C in order to facilitate MPT. However, no experiments related to biology were conducted during the study [148]. Shan et al. designed a nanorods system using GNRs to address clinical bone defects. Besides, the GNRs were modified with endogenous proteins to prevent an excessive immune response. This platform has the potential to promote bone repair via intravenous infusion, which can increase the tissue temperature up to 45 °C under NIR irradiation without causing tissue injury [115].

Geng et al. successfully combined hydrothermally synthesized CD with negatively charged WS_2 to achieve a mild photothermal effect guided by CT during intravenous injection. Their study revealed that this HJ significantly accelerated biomineralization at 40.5 ± 0.5 °C under 1064 nm NIR irradiation (5 min). Additionally, the researchers attempted to elucidate the mechanism of action of photothermal stimulation on osteogenesis differentiation by detecting the expression of genetic markers or HSPs [105].

In contrast, Wang et al. utilized an oil-in-water emulsion technique to pack BPs and strontium dichloride into PLGA, thereby creating biodegradable microspheres with NIR-controlled ion release. Although the study mainly attributed the acceleration of bone regeneration to the promotion of Sr^{2+} release by light heat, it should be noted that this process also supplies a gentler temperature stimulation to tissues [172].

Xu et al. utilized anodic oxidation technology to create TiO_2 nanoarrays on Ti plates. This allowed for gentle photothermal regulation of macrophage phenotype differentiation to M2 type, resulting in the regulation of bone regeneration. The study is particularly noteworthy for demonstrating the reversible modulation of inflammation through the prolonged use of MPT [141]. Li et al. modified the titanium-based surface through a nanorod array composed of PDA and HA, achieving the photothermal effect achieved by periodic NIR irradiation, with strong ROS clearance ability. This can inhibit inflammation and drive adherent macrophages to M2 phenotype under MPT conditions of about 41 °C, stimulating MSC osteogenesis through paracrine [56].

5. Summary and perspectives

In conclusion, this review is attempted to systematically summarize recent advances in the regulation of osteoblast proliferation, differentiation, and bone repair by mild photothermal effects, as well as the related mechanism.

Recently, more and more research has focused on photothermal scaffolds or surfaces as a way to regulate the behavior of osteoblasts using mild heat generated by NIR irradiation. But there are still some problems associated with mild photothermal-assisted bone regeneration that need to discuss:(1) Whether the mild photothermal effect is only the thermal effect that promotes bone regeneration, and whether NIR has the effect? Although it is mentioned that simple NIR exposure does not seem to have much effect on bone regeneration in the articles [18,34], Wu et al. considered that the photoelectric microenvironment also has the potential to affect inflammation and vascularization processes during bone remodeling through gene expression photon uptake in the mitochondria [73]. Besides, it might need to consider the positive effect of NIR irradiation frequency. It has also been reported that NIR stimulation not only activates neurorehabilitation and angiogenesis, but also induces ubiquitination of biological clock proteins in the cell nucleus, which in turn activates associated sodium voltage-gated channels to promote bone tissue regeneration [184]. (2) Under what temperature conditions, the effect of mild photothermal-assisted bone regeneration is more durable? Most articles believe that the temperature of 39–42 °C is suitable for promoting bone regeneration through hyperthermia [44, 121], but some articles can still maintain good protection for the surrounding tissues and a good bone regeneration effect because of the advantages of their material system when the temperature reaches 42 °C or even 45 °C [101,115]. Furtherly, whether the material system based on mild temperature can carry drugs to achieve synergistic effects with other treatments? Though as mentioned before, many types of research had studied the function and mechanism of MPT for bone regeneration, there have been many other papers reported that use NIR to realize the control delivery or release of drugs or others particles [185]. Cell therapy, gas therapy, and other treatment methods have initially already obtained some brilliant results at this stage, and it may be possible to achieve a joint effect with those therapies under mild photothermal conditions in the future. (3) Some articles believe that to achieve a mild photothermal effect, materials with low photothermal conversion efficiency should be selected to effectively protect the surrounding tissues; However, most articles believe that it is possible to control the platform to achieve a mild temperature by adjusting the intensity of the NIR laser, the irradiation time and the irradiation frequency as a system to up-regulate the bone regeneration. Interestingly, some PTAs with high photothermal conversion efficiency have the potential to promote bone tissue regeneration. (4) As mentioned before, the mechanism of MPT-assisted bone repair is not only to promote vasodilation but also to regulate the phenotype of macrophages and the regulation of multiple pathways of bone regeneration through the expression of HSPs [56]. Additionally, other thermotherapies, such as magnetothermal therapy

and ultrasonic therapy, have garnered attention for their advantages of deep tissue penetration, non-invasiveness, and controllability [27]. Research has demonstrated the effectiveness of magnetic thermal therapy [121,186] and ultrasonic hyperthermia [122,187] in bone repair and regeneration. The consistent outcomes observed across different thermal modalities further highlight the promising potential of utilizing mild temperature for clinical treatments.

In the early years, research focused on the effect of increasing temperature on blood flow, through local vasodilation and vasoactive factor stimulation, during the warming process, the "dormant" capillaries open, which can increase muscle blood flow to a certain extent. Recent studies have shown that mild warming caused by NIR radiation can trigger myotube contraction to a certain extent and promote the remodeling of muscle tissue. The behavior of mild warming on myoblasts was explored and it was found that although mild heat stimulation had little effect on cell migration, it could significantly promote their proliferation, especially local mild warming could effectively promote satellite cell activity in myofibers. Meanwhile, going a step further, studies have shown that mild heat-induced myoserotic differentiation is controlled by modulating the peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) and myosin axes.

In addition, studies have shown that the release of drugs carried by the high-temperature photothermal acceleration material system can not only promote drug penetration, but also effectively promote the recovery of mouse muscle tissue, but in the article mentioned that drug release is temperature-related and high temperature causes skin tissue inflammation [188]. But more precisely, it has also been shown that the ideal temperature (39 °C) favoring satellite cell activity, which promotes muscle genesis, differs from the ideal temperature (41 °C) for bone tissue regeneration. Although some studies have shown that excessive inhibition of the inflammatory response will inhibit the regeneration process of skeletal muscles to a certain extent, it may be possible to promote bone tissue regeneration at the same time under the condition of promoting osteogenesis by combining immunity or related biological proteins and factors [189]. In the future, it may be possible to protect normal tissues under mild photothermal conditions, avoid surgical infection, and accelerate the repair of diseased tissues.

Despite using MPT to assist bone regeneration having made significant progress, there are still some challenges to be addressed in the future. Especially, the effect of a simple mild photothermal effect in a short period to promote bone tissue regeneration is not obvious, and long-term periodic irradiation is required to have better results. Besides, the complex mechanism of the MPT in promoting bone repair still needs to be further studied. Moreover, since HSPs are ATP-dependent when considering the regulation of osteogenesis-related expression pathways by stimulating HSPs through mild photothermal effects, materials or drugs that damage energy supply (such as mitochondria, enzymes, etc.) should be avoided in the system. In the future, with the design and development of more materials systems, MPT may be able to achieve selective regeneration by combining with other treatments (immunotherapy, acoustic therapy, etc.) to realize more functions, but whether materials that achieve MPT could be optimized and achieve synergy with other things (gas, drugs, etc.) is another problem need to face.

With the development of cell biology, biomaterial technology, and processing and manufacturing technology, it is foreseeable that these materials will gradually solve these current limitations and continue to open up new possibilities for precise control of osteoblast behavior and determination of bone repair fate. Developments in cell biology, biomaterials, and processing and manufacturing technology have made it possible to create a new system for precise control of osteoblast behavior and repair of bone defects at a faster rate to solve the current limitations. Overall, MPT-assisted bone tissue repair is an effective strategy proposed in BTE in recent years. It is hoped that this review can inspire more researchers in this field.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mtbio.2023.100834.

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