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Bifunctional scaffolds for tumor therapy and bone regeneration: Synergistic effect and interplay between therapeutic agents and scaffold materials

Jiongpeng Yuan [a], Zhaoyi Ye [a], Yaoxun Zeng [a], Zhenxing Pan [a], ZhenZhen Feng [a], Ying Bao [a], Yushan Li [a], Xujie Liu [a,*], Yan He [a,**], Qingling Feng [b,***]

[a] School of Biomedical and Pharmaceutical Sciences, Guangdong University of Technology, Guangzhou, 510006, China
[b] School of Materials Science and Engineering, Tsinghua University, Beijing, 100084, China

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ABSTRACT

Bone tumor patients often face the problems with cancer cell residues and bone defects after the operation. Therefore, researchers have developed many bifunctional scaffolds with both tumor treatment and bone repair functions. Therapeutic agents are usually combined with bioactive scaffolds to achieve the "bifunctional". However, the synergistic effect of bifunctional scaffolds on tumor therapy and bone repair, as well as the interplay between therapeutic agents and scaffold materials in bifunctional scaffolds, have not been emphasized and discussed. This review proposes a promising design scheme for bifunctional scaffolds: the synergistic effect and interplay between the therapeutic agents and scaffold materials. This review summarizes the latest research progress in bifunctional scaffolds for therapeutic applications and regeneration. In particular, it summarizes the role of tumor therapeutic agents in bone regeneration and the role of scaffold materials in tumor treatment. Finally, a perspective on the future development of bifunctional scaffolds for tumor therapy and bone regeneration is discussed.

1. Introduction

Cancer is a life-threatening disease with high rates of morbidity and mortality [1]. As a type of cancer, malignant bone tumors are mainly divided into primary bone tumors and metastatic bone tumors [2,3]. Osteosarcoma often occurs in children and adolescents as a primary malignant bone tumor [4]. However, most tumors tend to metastasize to the bone, among which prostate cancer [5] and breast cancer [6] all have a high chance of bone metastasis. The clinical treatment of bone tumors is generally based on surgery supplemented by radiotherapy and/or chemotherapy [7,8]. However, bone tumors are not sensitive to radiotherapy [9,10] and are prone to drug resistance [8,11]. Surgical resection often causes bone defects. The erosion of bone tumors in patients' bones, bone defects caused after surgery, and tumor recurrence are the most important reasons for low survival rates and low quality of life in patients with bone tumors [8]. Along with the developing bionanotechnology, several innovative therapies have been designed for tumor therapy. Unlike traditional treatments, most innovative therapies are less toxic and non-invasive, such as photothermal therapy (PTT), photodynamic therapy (PDT) [12–15], chemodynamic therapy (CDT) [16], drug delivery systems (DDS) [13,17], and immunotherapy [18–20]. These therapies are promising in improving the efficiency of treating tumors in the clinic [13,21].

Although these emerging therapies have produced impressive results, clinical treatment of patients with bone tumors requires consideration of both the complete removal of all tumor cells and the bone defects caused by the surgery [8]. Researchers have provided several routes to solve the problem of bone defects [22–25], one of which is the use of bioactive scaffolds [26–28]. The clinical standards for bone grafting are autografts, which are considered the "gold standard" for bone repair and allografts. However, both grafts suffer from limited quantity and potential donor-site morbidities. Bioactive scaffolds are emerging as a new category of ideal implantable materials for bone regeneration as an alternative to bone grafts. These bioactive scaffolds are characterized by good mechanical properties, biocompatibility, high porosity, large pore size, and biodegradability [29–31]. Even though these types of biological

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: liuxujie@gdut.edu.cn (X. Liu), heyan129@gdut.edu.cn (Y. He), biomater@tsinghua.edu.cn (Q. Feng).

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scaffolds are making a splash for bone repair, scaffolds with bioactivity alone lack the efficiency to treat tumors. Combining therapeutic nanomaterials and bioactive scaffolds to produce bifunctional scaffolds with both therapeutic and reparative functions may be a future direction for bone tumor treatment [32]. In the past 10 years, the number of publications and citations on the application of bioactive scaffolds in bone tumors has increased annually (Fig. 1) (Web of Science database, topic: "bone tumors & bone defects & scaffolds," search date: February 28, 2022). This reflects the vital interest of many researchers in the postoperative treatment of bone tumors and the repair of bone defects.

Researchers have summarized the progress in the application of bioactive scaffolds for tumor therapy and bone regeneration [33]. Huang et al. summarized bifunctional scaffolds for tumor therapy and bone regeneration in recent years [34] and Chen et al. summarized regenerative materials related to thermal stimulation [35]. Yang et al. summarized the scaffold materials for the delivery of immunotherapeutic agents [36], Liao et al. summarized bifunctional materials for bone tumor therapy [37] and Wei et al. summarized the smart stimuli-responsive biomaterials for bone therapeutics and regeneration [38]. However, the synergistic effect of bifunctional scaffolds on tumor therapy and bone repair, as well as the interplay between therapeutic agents and scaffold materials in bifunctional scaffolds, have not been emphasized and discussed. Therefore, in this review, we summarize bifunctional scaffolds for tumor therapy and bone regeneration and emphasize the interplay between therapeutic agents and scaffold materials. Specifically, the interaction refers to the fact that the therapeutic agent can be used to enhance bone regeneration and the scaffold materials can be used to inhibit tumor activity (Fig. 2). Section 2 briefly summarizes the recent developments in bifunctional scaffolds for tumor therapy and bone regeneration. The role of therapeutic agents in bone regeneration and the role of scaffold

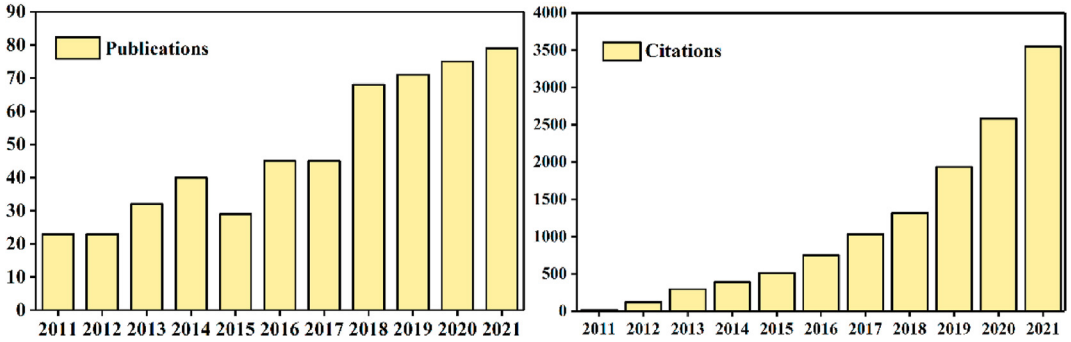

Fig. 1. Number of publications and citations in the last 10 years (Web of Science database, topic: "bone tumors & bone defects & scaffolds," search date: February 28, 2022).

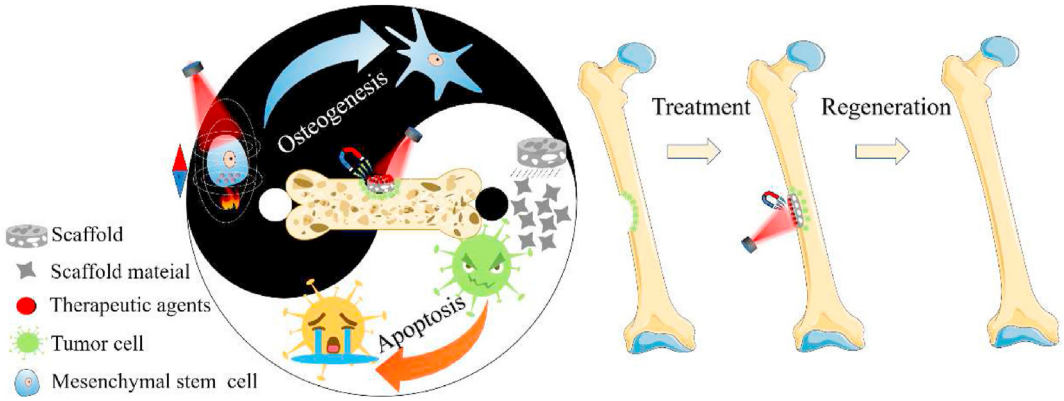

Fig. 2. Schematic strategy of synergistic effect and interplay between therapeutic agents and scaffold materials. The therapeutic agents and scaffold materials share a similar function: treating tumors with accelerated bone regeneration.

Table 1
Partial bifunctional scaffolds based on DDS and the role of the therapeutic agents in bone regeneration.

Bifunctional scaffold	Therapeutic agents	Scaffold material	Tumor therapy method	Effect of therapeutic agents on osteogenesis	Ref.
PHM Scaffolds	DOX	HEMA and MMA	Chemotherapy	N.A.	[44]
DESCLAYMR DOX scaffold	DOX	PCL, CS, nanoclay and β-TCP	Chemotherapy	N.A.	[39]
CS/nHA/Zol scaffolds	Zol	CS and nHA	Chemotherapy	N.A.	[40]
CDDP and DOX @CaP/HA scaffold	CDDP and DOX	TCP and HA	Chemotherapy	N.A.	[45]
PLLA/nHA/MET scaffold	MET	PLLA and nHA	Chemotherapy	MET loaded scaffold promoted osteogenic differentiation of hBMSCs.	[41]
DOX/PLGA/nHA/collagen scaffold	DOX	nHA and collagen	Chemotherapy	N.A.	[46]

AbbreviationsPoly (HEMA-co-MMA) (PHM), doxorubicin (DOX), hydroxyethyl methacrylate (HEMA), methyl methacrylate (MMA), not applicable (N.A.), poly (ε-caprolactone (PCL), chitosan (CS), tricalcium phosphate (TCP), zoledronic acid (Zol), nanohydroxyapatite (nHA), *cis*-diamminedichloroplatinum (CDDP), calcium phosphates (CaP), poly (L-lactic acid) (PLLA), metformin (MET), human bone marrow mesenchymal stem cells (hBMSCs), poly (lactic-co-glycolic acid) (PLGA).

materials in tumor therapy are discussed in Sections 3 and 4, respectively.

2. Bifunctional scaffold for tumor therapy and bone regeneration

Patients with bone tumors still face both tumor cell remnants and bone defects after surgery. The researchers have developed several bifunctional scaffolds for tumor therapy and bone regeneration in response to the issue mentioned above. To achieve the "bifunctional," investigators usually combine therapeutic agents with bioactive scaffolds [39]. Different therapeutic agents have been introduced into bifunctional scaffolds, including two emerging therapeutic agents, photothermal agents and magnetic nanoparticles. Both photothermally and magnetic fluid hyperthermia functionalized scaffolds can ablate tumor cells by hyperthermia induced by laser or magnetic fields. In addition to hyperthermia, chemokinetic therapies, immunotherapies, etc., can be combined with tissue engineering scaffolds. Moreover, researchers have developed bifunctional scaffolds by using synergistic treatment methods. This section classifies and summarizes bifunctional scaffolds for tumor therapy and bone regeneration and discusses their advantages and disadvantages. We have listed them in Tables 1–3, along with some examples of the effect of therapeutic agents on bone regeneration.

2.1. Bifunctional scaffold with drug delivery systems (DDS)

Chemotherapy is one of the mainstays of the clinical treatment for bone tumors. Based on this, the localized DDS based on bioactive scaffolds has been noticed. The bifunctional scaffolds based on DDS have been listed in Table 1. Sun et al. developed a doxorubicin-loaded bioactive scaff1old [39]. Specifically, doxorubicin-loaded bioactive

Table 2
Partial bifunctional scaffolds based on PTT or MFH and the role of the therapeutic agents in bone regeneration.

Bifunctional scaffold	Therapeutic agents	Scaffold material	Tumor therapy method	Effect of therapeutic agents on osteogenesis	Ref.
GO-β-TCP scaffold	GO	β-TCP	PTT	The upregulation of osteogenesis-related genes laterally indicated that GO modification was beneficial for osteogenic differentiation.	[47]
DTC@BG scaffold	DTC	BG	PTT	The BMD of the DTC@BG group was determined to be greater than that of the BG group by quantitative analysis of micro-CT images.	[59]
CS/nHA/CDs scaffolds	CDs	CS and nHA	PTT	CDs-doped scaffolds promoted the adhesion and osteogenic differentiation of hBMSCs.	[60]
CaPCu scaffold	$CaCuSi_4O_{10}$ nanosheets	$CaCO_3$ and PCL	PTT	H&E, Masson and Goldner trichrome stained photographs showed that CaPCu scaffolds acquired more new mineralized bone components.	[61]
Cu-TCPP-TCP scaffolds	Cu-TCPP	β-TCP	PTT	An infusion of Cu-TCPP-TCP scaffold upregulated the osteogenic differentiation-related genes.	[48]

Bifunctional scaffold	Therapeutic agents	Scaffold material	Tumor therapy method	Effect of therapeutic agents on osteogenesis	Ref.
BGM scaffolds	MoS_2	BG and PCL	PTT	Mo elements in the scaffold were involved in the synthesis and metabolism of rBMSCs, and the expression of osteogenic genes and calcium deposition were higher in the BGM group than in BG alone.	[62]
MBCS	$SrFe_{12}O_{19}$	$CaSiO_3$ and CS	PTT	With more $SrFe_{12}O_{19}$ doping on the scaffold, more osteogenesis-related genes were expressed.	[63]
Larnite/C scaffold	Larnite/C	Larnite/C	PTT	After free carbon embedding of the larnite scaffold, the scaffold upregulated the expression of osteogenic genes in rBMSCs.	[64]
β-TCP-CA scaffold	CA	β-TCP	PTT	The addition of carbon aerogel coating stimulated the osteogenic differentiation of BMSCs by modulating the FAK/ERK1/2 signaling pathway.	[65]
$GdPO_4/CS/Fe_3O_4$ scaffolds	Fe_3O_4	$CePO_4$ and CS	PTT	N.A.	[66]

Bifunctional scaffold	Therapeutic agents	Scaffold material	Tumor therapy method	Effect of therapeutic agents on osteogenesis	Ref.
$CePO_4$/CS/GO scaffolds	GO	$CePO_4$ and CS	PTT	N.A.	[67]
BG-CFS scaffold	$CuFeSe_2$	BG	PTT	The Cu, Se, and Fe ions released by the BG-CFS scaffold together with the Ca, Si, and P ions in the BG promoted bone regeneration.	[68]
nHA/GO/CS scaffold	GO	CS and nHA	PTT	GO in the scaffold and the thermal stimulation combined to increase the osteogenic differentiation of hBMSCs.	[69]
Ti_3C_2-BG scaffold	Ti_3C_2	BG	PTT	The data of BV/TV, BMD, and porosity indicate that the doping of Ti_3C_2 powder provided the better osteogenic activity of the BG scaffold.	[70]
TCP-PDLLA-LB scaffolds	LaB_6	PDLLA and β-TCP	PTT	The TCP-PDLLA-LB scaffold promoted the expression of osteogenesis-related genes.	[71]
Cu-MSN-TCP scaffold	Cu-MSN	β-TCP	PTT	Cu-MSN could upregulate the expression of osteogenic-related genes.	[72]

Bifunctional scaffold	Therapeutic agents	Scaffold material	Tumor therapy method	Effect of therapeutic agents on osteogenesis	Ref.
α-TCP/CS/Fe_3O_4/GO scaffolds	Fe_3O_4 and GO	α-TCP and calcium sulfate	MFH	Alizarin red staining demonstrated that the α-TCP/CS/Fe_3O_4/GO group produced more calcified nodules than the other groups.	[73]
MGO@Fe_3O_4/PVA/SA/HA scaffold	MGO and Fe_3O_4	PVA/SA/HA	MFH	With Fe_3O_4 doping on the scaffold, the highest ALP expression and calcium deposition were observed.	[74]

Abbreviations: graphene oxide (GO), tricalcium phosphate (TCP), photothermal therapy (PTT), rabbit bone mesenchymal stem cells (rBMSCs), NIR-absorbing cocrystal (DTC), bioactive glass (BG), bone mineral density (BMD), carbon dots (CDs), human bone marrow mesenchymal stem cells (hBMSCs), CaCO3/PCL/CaCuSi4O10 nanosheets (CaPCu), poly (ε-caprolactone) (PCL), hematoxylin and eosin (H&E), a class of metal-organic frames (Cu-TCPP), MoS_2-integrated composite bioactive glass (BGM), magnetic nanoparticles modified-mesoporous bioglass/chitosan porous scaffold (MBCS), free carbon-embedding larnite (Larnite/C), carbon aerogel (CA), bone mesenchymal stem cells (BMSCs) focal adhesion kinase/extracellular signal-regulated kinase signaling pathway (FAK/ERK1/2 signaling pathway), not applicable (N.A.) $CuFeSe_2$ (CFS), bone volume/tissue volume (BV/TV), poly(d,L-lactide) (PDLLA), LaB_6 (LB), Mesoporous silica nanospheres (MSN), magnetic fluid hyperthermia (MFH), magnetic graphene oxide@Fe_3O_4polyvinyl alcohol/sodium alginate/hydroxyapatite (MGO@Fe_3O_4/PVA/SA/HA).

Table 3
Partial bifunctional scaffolds based on synergistic therapy and the role of the therapeutic agents in bone regeneration.

Bifunctional scaffold	Therapeutic agents	Scaffold material	Tumor therapy method	Effect of therapeutic agents on osteogenesis	Ref.
Fe-AKT scaffold	Fe ions	AKT	PTT and MFH	AKT scaffolds doped with Fe promoted osteogenesis better than AKT scaffolds alone.	[49]
BG@NbSiR scaffold	R837 and Nb_2C	BG	PTT and Immunotherapy	Nb_2C@SiR nanosheets in the scaffold accelerated osteogenesis.	[79]
AKT-Fe_3O_4–CaO_2 scaffold	CaO_2 and Fe_3O_4	AKT	MFH and CDT	Ca^{2+} release from the degradation of therapeutic agents may promote bone regeneration.	[81]
DOX/P24/BP/TCP/PLGA scaffold	BP and DOX	β-TCP	PTT and Chemotherapy	Degradation of BP nanosheets in the scaffold, delivery of P24 peptide facilitated the osteogenic differentiation of rBMSCs.	[82]
MBS scaffold	Nb_2C nanosheets	BG	PTT and gas therapy	Release of NO accelerated angiogenesis and bone regeneration.	[80]
Fe doped HT scaffold	Cisplatin and Fe ions	HT	MFH and Chemotherapy	N.A.	[83]
Bifunctional scaffold	Therapeutic agents	Scaffold material	Tumor therapy method	Effect of therapeutic agents on osteogenesis	Ref.
FeMg-SC	FeMg-NPs and PDA	β-TCP and PLGA	PTT and CDT	FeMg-SC released osteoinductive Mg^{2+} continuously to enhance bone regeneration	[84]

Abbreviations: akermanite (AKT), photothermal therapy (PTT), magnetic fluid hyperthermia (MFH), immune adjuvant-loaded and niobium carbide MXene-modified 3D-printing biodegradable scaffold (BG@NbSiR), a class of immune adjuvant (R837), black phosphorus (BG), chemodynamic therapy (CDT), black phosphorus (BP), P24 peptide (P24), rabbit bone mesenchymal stem cells (rBMSCs), hardystonite (HT), scaffold 3D-printed from the FeMg nanoparticles-containing nanoink (FeMg-SC), FeMg nanoparticles (FeMg-NPs), polydopamine (PDA), poly (lactic-co-glycolic acid) (PLGA).

scaffolds continuously released doxorubicin (DOX) at the tumor site and maintained DOX at a higher concentration. Moreover, high and low DOX contents on the scaffolds did not significantly affect the formation of unmineralized collagen fibers. In a similar study, Lu et al. reported a bifunctional scaffold for simultaneous tumor inhibition, bone repair and infection eradication. The chitosan (CS)/nanohydroxyapatite (nHA) scaffolds were loaded with zoledronic acid (Zol) [40]. The CS/nHA/Zol scaffolds exhibited negligible toxicity toward human bone marrow mesenchymal stem cells (hBMSCs) but could kill tumor cells by inducing cell apoptosis. Moreover, the CS/nHA/Zol scaffolds showed the same osteoinductivity as the CS/nHA scaffolds. In addition to DOX and Zol, metformin (MET) has also been added into the bioactive scaffolds. Tan et al. fabricated bifunctional scaffolds of poly (L-lactic acid) (PLLA)/nanohydroxyapatite (nHA) encapsulated with MET (PLLA/nHA/MET) [41]. Surprisingly, MET could both kill tumor cells and accelerate bone regeneration. The PLLA/nHA/MET scaffolds induce osteosarcoma cell death *in vitro*. In addition, after 7 days, the high ALP expression was observed in osteogenic medium with PLLA/nHA/MET scaffold. It has been proved that the addition of MET enhanced the osteogenic differentiation of hBMSCs.

Chemotherapy is the typical postoperative treatment of bone tumors. These chemotherapeutic drugs have serious side effects under systemic administration, such as alopecia, bone marrow suppression, mucositis, nausea, and vomiting [42]. Moreover, the bone defect caused by tumor resection cannot be healed spontaneously. Unlike the systemic administration route, drug-loaded scaffolds can locally release chemotherapeutic drugs and alleviate the side effects of drugs. Meanwhile, the bifunctional scaffolds could also repair the bone defects caused by surgical resection. However, there are still relevant issues with drug-loaded scaffolds; most drug-loaded scaffolds cannot meet the zero-order release, and it causes local drug concentrations to be unstable during treatment [43]. In addition, the toxicity of chemotherapeutic drugs may be unbeneficial for bone regeneration.

2.2. Bifunctional scaffold with photothermal therapy (PTT) or magnetic fluid hyperthermia (MFH)

Apart from drug-loaded scaffolds, photothermally/magnetic fluid hyperthermia functionalized scaffold is one method for addressing tumor cell residues and repairing bone defects. Unlike drug-loaded scaffolds, photothermally/magnetic fluid hyperthermia functionalized scaffolds utilize the high temperature provided by photothermal agents/magnetic nanoparticles to kill tumor cells. The bifunctional scaffolds based on photothermal/magnetic fluid hyperthermia have been listed in Table 2. Exceptionally, Wu et al. performed relevant and outstanding studies in this field [47–51]. For example, back in 2016, Wu et al. prepared a β-tricalcium phosphate (TCP) photothermally functionalized scaffold modified by graphene oxide (GO) (GO-TCP) [47]. The scaffold complex GO possesses near-infrared (NIR) photothermal conversion properties. At a low-density power of 0.36 W/cm^2, this scaffold can be heated up to 52 °C in 10 min. Therefore, bone tumors were suppressed by PTT. Moreover, in *vitro* study showed that after a week of culture, the expression of runt-related transcription factor 2 (Runx2), osteocalcin (OCN), and bone sialoprotein (BSP) in rabbit bone mesenchymal stem cells (rBMSCs) cultured on GO-TCP scaffolds were significantly higher than those cultured on β-TCP-scaffolds. In a recent study, their group reported a 3D-printed bioceramic scaffold with Fe_3S_4 microflowers (Fe_3S_4-AKT scaffolds) [51] (Fig. 3). Magnetic Fe_3S_4 microflowers provide magnetic fluid hyperthermia (MFH) and promote H_2O_2 decomposition to generate reactive oxygen species (ROS). Thus, synergistic magnetothermal and chemodynamic therapies can kill LM-8 tumors in nude mice. Moreover, the Fe_3S_4-AKT scaffolds significantly improved new bone formation and enhanced bone repair and integration compared to Akermanite (AKT) scaffolds in a rabbit model.

As emerging therapy methods, PTT and MFH both have the advantages of being non-invasive, reducing systemic damage and controllable. However, they both have their respective disadvantages. Most photothermally functionalized scaffolds rely on the first NIR window (NIR-I, 650–950 nm) laser wavelength. Compared to the second NIR window (NIR-II, 1000–1700 nm), NIR-I has the disadvantages of low tissue penetration and higher scattering [52,53]. Therefore, NIR-I responsive photothermally functionalized scaffolds may be challenging to clear the deep layer of bone tumor cells. In addition, the NIR-I laser at high power (> 0.33 W/cm^2) caused superficial tissue damage [54,55]. For MFH, the transformation of magnetic energy into heat correlates with magnetic nanoparticle size. For most studies, magnetic nanoparticles are far superior to micrometric particles [56]. Therefore, it increases the difficulty of preparing magnetic fluid hyperthermia functionalized scaffold. Moreover, the effects of alternating magnetic field lead (AMF) on normal tissues also need to be studied in details [57,58].

2.3. Bifunctional scaffold with synergistic therapy

Along with bionanotechnology development, new innovative treatment options have been designed for tumor therapy. However, a single therapy modality often suffers from limited therapeutic efficacy. Recent

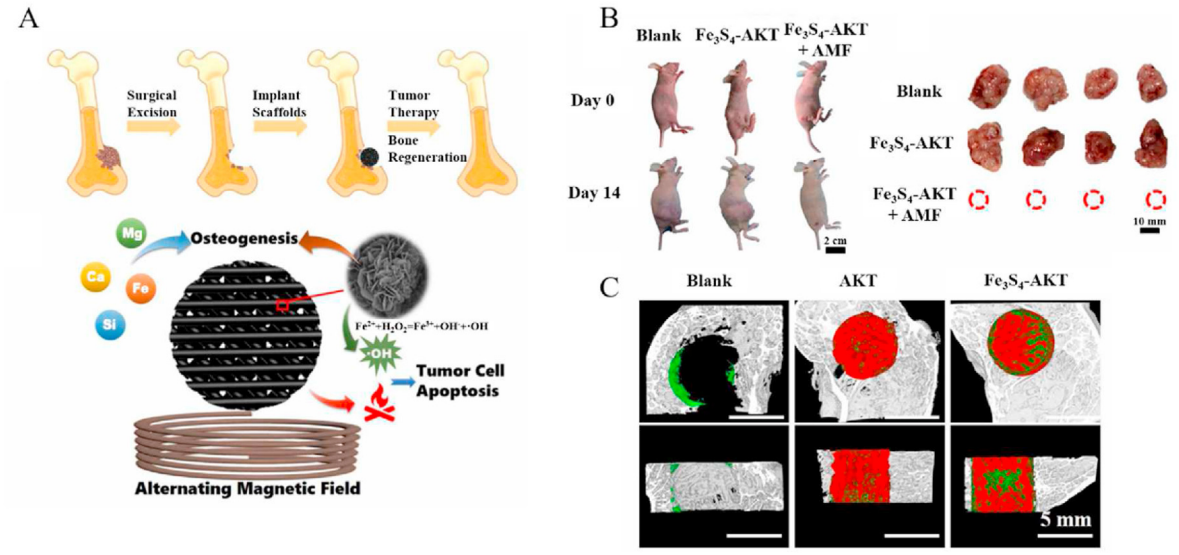

Fig. 3. Fe_3S_4- Akermanite scaffold (FS-AKT) for the therapy of bone tumors and repair of bone defects. (A) Schematic illustration of FS-AKT scaffold with synergistic therapy to treat bone tumors while enhancing bone repair. (B) Photographs of mice and tumors in different groups at day 0 and day 14. (C) Micro-CT analysis of bone defect region (red: scaffolds; green: new-formed bone). Reprinted with permission from ref. [51] © 2021 IOP Publishing Ltd. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

advances in cancer therapy have gradually shifted from a focus on single therapy to synergistic therapy [75–77]. Based on the synergistic enhancement interactions between two or more therapy, which may result in ostentatious superadditive (namely "1 + 1>2") therapeutic effects [78]. A series of bifunctional scaffolds had been designed based on the synergistic therapy. Some bifunctional scaffolds with synergistic therapy were summarized and listed in Table 3. He et al. reported a bifunctional scaffold combining immunotherapy with PTT for tumor therapy and bone regeneration [79]. The bifunctional scaffold (BG@NbSiR scaffolds) was modified with niobium carbide (Nb_2C) MXene and loaded with an immune adjuvant (R837). Combined with the PD-L1 checkpoint blockade, the scaffold could eliminate primary and metastases tumors in BALB/c mice. In addition, the biodegradable products of BG@NbSiR scaffolds could enhance bone repair. Similarly, Yang et al. fabricated a bifunctional scaffold combining gas therapy with PTT using 3D printing [80] (Fig. 4). This scaffold released NO in a laser-controlled manner. Under laser irradiation, synergistic gas therapy and PTT positively affected subcutaneous Saos-2 osteosarcoma tumors in nude mice. Moreover, the scaffold released NO, which accelerated vascular and bone regeneration. By contrast, AKT-Fe_3O_4–CaO_2 scaffolds prepared by Dong et al. have been reported [81]. The AKT-Fe_3O_4–CaO_2 scaffolds were effective in treating bone tumors and repairing bone defects. The CaO_2 in the scaffold provided H_2O_2 in an acidic environment to enhance the Fenton reaction rate of the Fe_3O_4 nanoparticles. The photothermal effect and chemokinetic reaction brought about by the Fe_3O_4 nanoparticles enabled good ablation of osteosarcoma cells. In addition to providing H_2O_2, the Ca ions released after CaO_2 can effectively promote osteogenic differentiation. Similarly, Zhao et al. prepared a bifunctional scaffold by doping Fe_3O_4 nanoparticles and hydrated $GdPO_4$ nanorods into a bioactive CS matrix ($GdPO_4$/CS/Fe_3O_4 scaffolds) [66]. Surprisingly, incorporating $GdPO_4$ nanorods could be beneficial for M2 macrophage polarization, thus promoting angiogenesis and accelerating bone regeneration by activating the BMP-2/Smad/RUNX2 signaling pathway.

Synergistic therapy is the cooperation among different therapy methods with integration into a single nanoplatform, which yields much stronger therapeutic effects than the theoretical combination of the corresponding individual therapy [78]. For bone tumor therapy, repairing bone defects still needs attention. Most bifunctional scaffolds are simply a combination of therapeutic modalities while ignoring the synergistic effect between therapeutic agents and scaffold materials.

3. Role of therapeutic agents in bone regeneration

In recent decades, researchers have developed bifunctional scaffolds for treating bone tumors and regenerating bone defects. However, improving the tumor treatment and bone defect repair efficiency of these bifunctional scaffolds still remains a major concern. Generally, bifunctional scaffolds comprise therapeutic agents and scaffold materials. Bioactive scaffolds with osteoinductivity and biocompatibility play indispensable roles in bone repair. In terms of bone tumor therapy, therapeutic agents have always been used only as killers for tumor cells. However, among the recently reported bifunctional scaffolds, therapeutic agents can play an important role in promoting osteogenesis. This section summarizes the roles of therapeutic agents in bone regeneration. These therapeutic agents can affect osteogenic differentiation by modulating cellular signaling pathways after endocytosis [85]. Therapeutic agents include metal nanomaterials [61,62,68,73,81], carbon nanomaterials [47,64,65,73,86], BP [86], etc. In addition, the effect of thermal and magnetic stimulation on inducing osteogenic differentiation has also been included and discussed [69,87–89].

In previous studies, the physicochemical properties of scaffolds, such as stiffness, pore size, composition, and surface properties, have been considered to correlate with the osteogenic differentiation of cells [90]. The degradation product of the scaffold is another critical parameter for regulating cell behavior. Some biologically active ions are released by the degradation of bioactive scaffolds when they are implanted at bone defect sites. The effect of magnesium (Mg)-incorporated scaffolds (PLGA/Mg) on bone tumors and defects was investigated [91]. Mg particles can provide PTT for tumor therapy and accelerate bone regeneration. These results suggest that the PLGA/Mg scaffold with higher Mg content effectively kills bone tumor cells (Saos-2) *in vitro* with NIR laser irradiation. Both Mg ions and the slightly alkaline pH resulting from scaffold degradation contributed to the higher osteoblastic MC3T3-E1 cell viability on the PLGA/Mg scaffold. These cells on the scaffold also expressed higher levels of osteogenic markers (Runx2, Osterix, and BMP2). In a similar study [92], a novel porous PLGA/TCP/Mg (PTM) scaffold was fabricated to treat steroid-associated osteonecrosis (SAON).

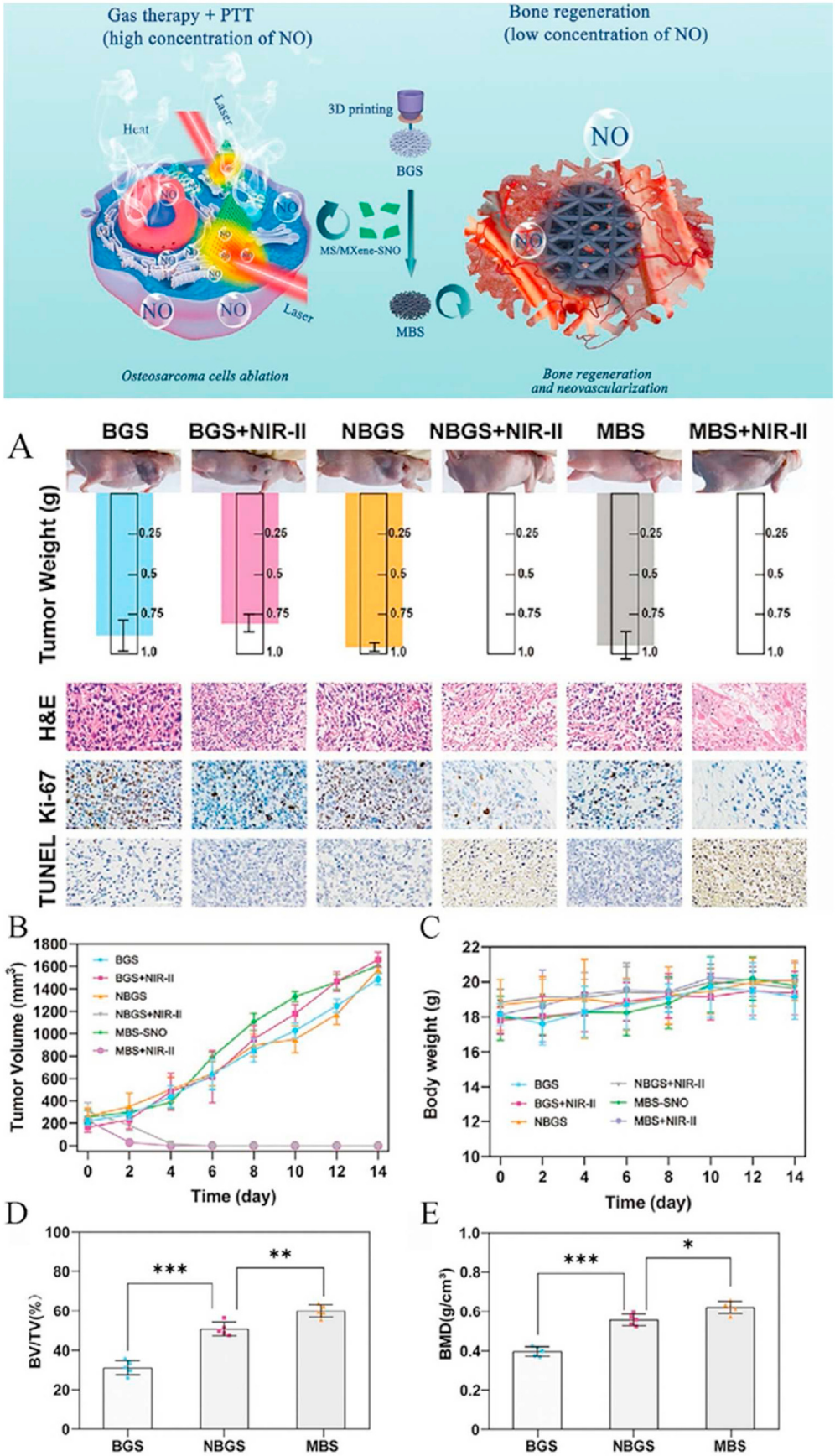

Fig. 4. Bifunctional scaffold combining photothermal therapy and gas therapy. Top: Schematic illustration of the multifunctional therapeutic platform. (A) Digital photographs of osteosarcoma-bearing mice following different treatments on the 14th day, and H&E, TUNEL (apoptosis) and Ki-67 (proliferation) staining of the tumor tissues. Scale bar represents 10 μm. Inset: tumor weights on the 14th day after varied treatments (n = 5). (B) Time-dependent tumor-growth curves after different treatments (n = 5, mean ± standard deviation (s.d.)). (C) Time-dependent body-weight curves after different treatments. (D), (E) Quantitative fundamental parameters of bone volume/tissue volume (BV/TV) and bone mineral density (BMD) in newborn osseous tissue based on the histomorphometric micro-CT analysis. *p < 0.05, **p < 0.01, and ***p < 0.001. Reprinted with permission from ref. [80] © 52,020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

These scaffolds were tested *in vivo* using a bone defect model and SAON model in rabbits. *In vivo* data indicated a high bone volume and bone mineral density (BMD) after implantation of the PTM scaffold after 4, 8, and 12 weeks. Moreover, the Mg ions released from the PTM scaffold into the blood circulation did not trigger immune responses or liver and kidney malfunction.

Graphene oxide (GO), as a representative class of carbon nanomaterials, is also an excellent photothermal agent. In previous studies, GO has been proved to be biocompatible [93]. Recently, the effect of GO doped in mesoporous bioactive glass (MBG) scaffolds (MBG-GO) for bone tissue engineering was investigated [94]. The porous MBG-GO scaffolds containing different amounts of GO were fabricated using the high temperature calcination technique. The MBG-GO scaffold extracts resulted in a high percentage of the proliferation of rBMSCs in a week. *In vitro* study showed that after a week of culturing, the expression of alkaline phosphatase (ALP) and type I collagen (COL-1) for scaffolds extracts containing high content of GO was significantly higher than other groups. In particular, the new bone and vessel formation repair efficiency of MBG-GO scaffolds in a Sprague–Dawley (SD) rat model were investigated. Results suggest that the MBG scaffold containing GO, significantly promoted the bone repair and vascularization of mass bone defect 12 weeks after implantation. Other carbon nanomaterials have also been incorporated to promote bone regeneration. In one study, the osteopromotive carbon dots (CDs) were fabricated using ascorbic acid [85]. The results showed that the osteogenic differentiation of pre-osteoblasts was more favored when cultured in osteogenic medium with CDs. After 14 and 21 days, the highest ALP expression and calcium deposition were observed in osteogenic medium with CDs. Further, it was proved that CDs activated the protein kinase RNA-like ER kinase (PERK)-eukaryotic translation initiation factor 2α (eIF2α)-activated transcription factor 4 (ATF4) pathway to mediate osteogenic differentiation.

Besides the metal nanomaterials and carbon nanomaterials, black phosphorus (BP) has also been demonstrated to accelerate bone regeneration for the reason that BP can be degraded into phosphorus ions and thus capture calcium ions [86,95,96]. Huang et al. introduced BP nanosheets into a hydrogel (BP/PEA/GelMA) [95]. The effect of the BP nanosheet in hydrogel scaffolds on osteogenic differentiation of human dental pulp stem cells (hDPSCs) was investigated. The maximum mineralization was observed on the BP/PEA/GelMA scaffold. Moreover, the expression of osteogenic genes and synthesis of osteogenic proteins Col I, BMP-4, and Runx2, were the highest on the BP/PEA/GelMA scaffold. These results suggest that osteogenic differentiation was enhanced upon doping with BP nanosheets in the PEA/GelMA scaffold (Fig. 5). In previous studies, GO and BP nanosheets were incorporated into the poly (propylene fumarate) scaffold to promote cell adhesion, proliferation, and osteogenic differentiation [86].

PTT has opened a promising avenue for precise cancer treatment owing to its intrinsic advantages of low toxicity, minimal invasiveness, and convenient operation. It employs photothermal agents that accumulate at the tumor site to generate heat from NIR laser irradiation, causing the ablation of tumor cells by rapidly increasing the local temperature [97]. In addition to ablating tumor cells, the heat generated by PTT also accelerates bone regeneration. As early as 2013, thermal stimulation to accelerate osteogenesis was investigated [98]. These results suggested that mild thermal stimulation facilitates early osteogenic differentiation. Furthermore, the effects of thermal stimulation on osteogenic genes are highly dynamic. Under thermal stimulation, osteogenic gene expression of BMP2, Runx2, and osteopontin (OP) was downregulated in the early stage but upregulated in the late stage. This study also demonstrated that the promotion of osteogenic differentiation by thermal stimulation was related to heat shock proteins (HSP) expression. PTT is a new treatment method for tumors. The principle of PTT is to ablate tumor cells via thermal stimulation produced by photothermal agents. The photothermal effect on bone regeneration has been investigated recently [69,99,100]. Zhang et al. reported porous AuPdalloy nanoparticles (pAuPds) to accelerate the cell proliferation and bone regeneration via photothermal stimulation [100]. At 48 h after photothermal stimulation, the cell proliferation rate of the experimental group (PBS + pAuPds + laser irradiation group) was higher than that of the control group. Evaluation of osteogenic ability *in vivo* was performed using a rat cranial defect model. The results showed the highest bone volume after six weeks of PTT. This demonstrated the osteoinductive ability of PTT. In a similar study, Ma et al. reported electrospun PCL/MoS_2 nanofiber membranes combined with PTT for bone regeneration [99]. The PCL nanofiber membranes containing MoS_2 did not affect the cell viability. Under laser irradiation, the highest cell proliferation and osteogenic expression (RUNX2, ALP, BMP2, COL1a1, OCN, and OPN) were observed on PCL/1 %MoS_2 nanofiber membranes. Tong et al. prepared a degradable biocomposite (BPs@PLGA) made of BP nanosheets and PLGA for photothermal control of bone regeneration [101]. Due to the photothermal effect and the PO_3^{2+} generated from BPs@PLGA degradation, the BPs@PLGA specimen mediated by low-intensity and periodic NIR irradiation could effectively upregulate the expression of HSP and promote osteogenesis *in vitro* and *in vivo*. Unlike other reports, Ma et al. reported a photothermal functionalized CS scaffold for tumor therapy and bone regeneration [69]. (Fig. 6). The photothermally functionalized CS scaffold (nHA/GO/CS) was coated with nano hydroxyapatite (nHA) and GO. The effects of NIR irradiation on osteosarcoma cells and the promotion of osteogenesis were investigated. Under different intensities of NIR irradiation, it was found that the nHA/GO/CS scaffolds could reach a temperature of 48 °C to kill osteosarcoma cells and reach a temperature of 42 ± 0.5 °C to promote osteogenesis of hBMSC. For the evaluation of *in vivo* tissue regeneration, tissue staining and micro-CT images indicated that the nHA/GO/CS scaffold showed the highest significant new bone formation in the SD rat model.

PTT functions via photothermal effects induced by converting light energy into heat upon NIR laser irradiation. Similarity, hysteresis, and relaxational losses of magnetic nanoparticles in an AMF can also result in the production of thermal energy [102]. Therefore, magnetic fluid hyperthermia (MFH) generated from magnetic nanoparticles is used to treat tumors. In contrast to AMF, magnetic nanoparticles exhibit good osteoinductivity in a static magnetic field (SMF) [103–105]. Magnetic stimulation can promote osteogenesis by accelerating extracellular calcium ions to pass through the cell membrane [103]. Xia et al. reported an iron oxide nanoparticle (γIONP) -incorporated calcium phosphate cement (CPC) scaffold for accelerated bone regeneration [106]. The doped γIONP in the CPC scaffold provided support for magnetism. The results from the CCK8 quantitative analysis indicated that the cell proliferation in γIONP media and γIONP-CPC scaffolds increased when applying SMF. After 7 and 14 days, the highest ALP expression and calcium deposition were observed in the γIONP medium with SMF. Moreover, the γIONP-CPC scaffolds significantly improved the new bone formation and enhanced bone repair and integration compared to the other groups in the SD rat model. Similarly, Hao et al. fabricated PLGA nanocomposites containing oleic acid-modified iron oxide (IO-OA) nanoparticles for accelerated bone regeneration [87]. *In vitro* study showed that after two weeks of culturing on IO-OA/PLGA nanocomposites with 5% IO-OA NPs, the expression of ALP, OCN, BMP2, and piezo-type mechanosensitive ion channel component 1 (Piezo1) with SMF were significantly higher than other groups. It was recently reported that Piezo1 expression and activity were upregulated after mechanical stress loading, subsequently promoting BMP2 expression and osteoblast differentiation [107]. They speculated that IO-OA/PLGA composite-induced accelerated osteogenesis may be related to the mechanical stress stimulation. Moreover, the combined effects of external SMF with a magnetic nanocomposite scaffold on osteoblastic function and bone formation have been investigated [107]. In both *in vitro* and *in vivo* studies, the results showed that the magnetic nanocomposite scaffold

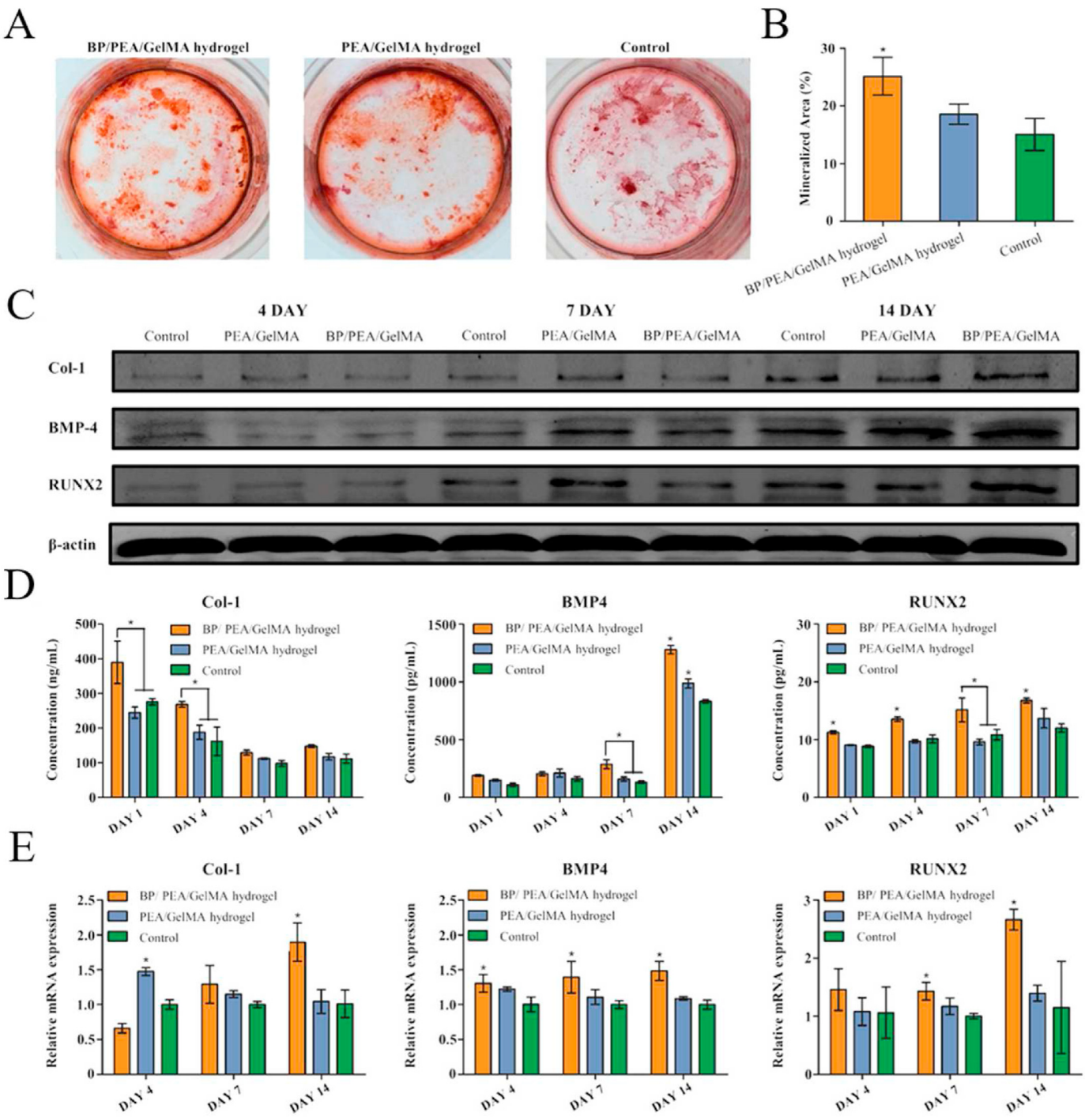

Fig. 5. *In vitro* osteogenic differentiation of human dental pulp stem cells (hDPSCs) cocultured with a BP/PEA/GelMA hydrogel or PEA/GelMA hydrogel: (A) Alizarin Red S staining images of hDPSCs cultured for 15 days. (B) ImageJ analysis of the mineralized area of a culture dish. (C) Western blot assay for evaluating the amounts of Col-1, BMP4, RUNX2, and β-actin in hDPSCs. (D) Effects on Col-1, BMP4, and RUNX2 synthesis in hDPSCs after incubation with or without a hydrogel for 1, 4, 7, or 14 days. Concentrations of Col-1, BMP4, and RUNX2 in the culture medium were measured by ELISAs. (E) Osteogenic gene expression in hDPSCs was evaluated with RT-qPCR. The data were normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) expression (*$P < 0.05$ as compared with the control group). Reprinted with permission from ref. [95] © 2019, American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

could accelerate bone regeneration with SMF. Synergism was demonstrated to activate integrin signaling pathways, such as focal adhesion kinase, paxillin, Rho A, mitogen-activated protein kinase, and nuclear factor-kappa B (NF-kB), as well as in the up-regulation of BMP2 and phosphorylation of Smad1/5/8 (Fig. 7).

Overall, the osteoinductivity of several therapeutic agents, including metal nanomaterials, carbon nanomaterials, and BP, has been summarized. Moreover, thermal and magnetic stimulation generated by therapeutic agents can accelerate bone regeneration. Therefore, researchers can select photothermal agents or magnetic nanoparticles as therapeutic agents incorporated into bifunctional scaffolds. The interplay between therapeutic agents and scaffold materials in bifunctional scaffolds can accelerate bone regeneration.

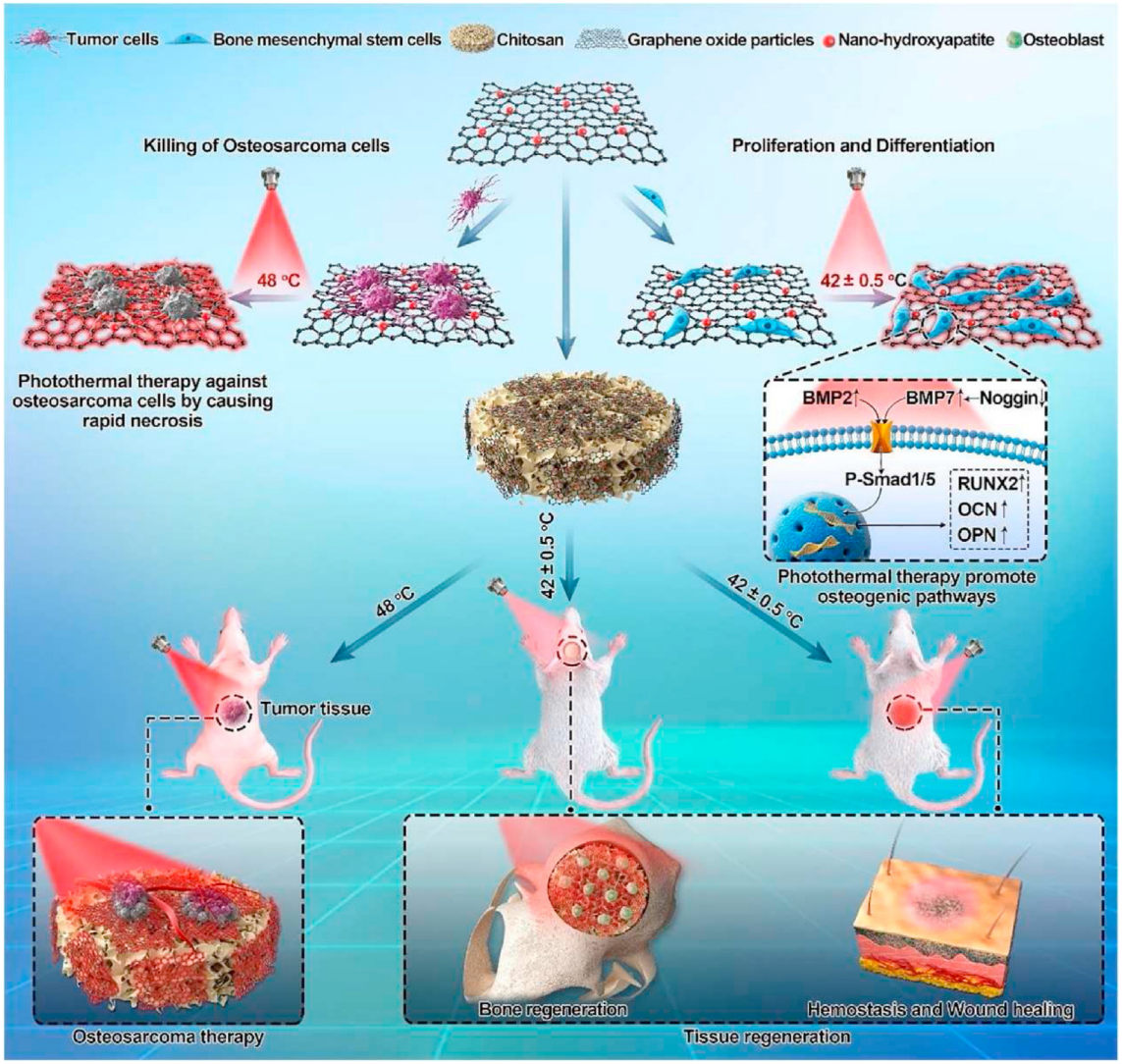

Fig. 6. Schematic illustration of nanohydroxyapatite/graphene oxide/chitosan (nHA/GO/CS) scaffold for photothermal treatment of tumors combined with photothermal osteogenesis. Reprinted with permission from ref. [69] © 2019 Elsevier Ltd.

4. Role of scaffold materials in tumor therapy

Bone tissue engineering is a highly interdisciplinary field that seeks to address bone-related clinical issues [108]. The major components of bone tissue engineering are the cells, growth factors, and scaffolds. The biocompatibility and osteogenic activity of the scaffold materials have been widely investigated and summarized. As for the bone defect caused by bone tumor, the biofunctional scaffolds are highly needed. Among the reported bifunctional scaffolds, there have been several examples that use therapeutic agents combined with scaffold materials to accelerate bone regeneration synergistically. However, there are few reports on the interplay between therapeutic agents and scaffold materials in bifunctional scaffolds to improve tumor treatment effects. As a bifunctional scaffold for the treatment of bone tumors and repair of bone defects, we prefer to have more efficient effects in both aspects. Therefore, it is necessary to fully exploit the anti-tumor potential of scaffold materials. In this section, as examples, we list two common scaffold materials, hydroxyapatite (HA) and chitosan (CS), and discuss their role in tumor treatment [109–122].

HA is a natural mineral constituent of human bones and teeth. Owing to its excellent bioactivity, compositional similarities with bone minerals, versatility, and tailorable biodegradability, it has been extensively studied in tissue engineering and drug delivery [123]. Recently, the antitumor effect of HA nanoparticles (HANPs) has been reported [119,121,124,125]. Li et al. reported bone-like selenium-doped HANPs nanoparticles (B-SeHANs) for bone tumor inhibition [119]. After 48 h of B-SeHANs incubation, the MNNG/HOS cell viability was reduced to approximately 50%. B-SeHANs induced apoptosis and autophagy via the ROS-mediated Akt/mTOR and JNK signaling pathways. Moreover, B-SeHANs controlled osteosarcoma growth and bone destruction in nude mice. In addition to selenium, Zn-doped HA can enhance the effect of chemotherapy on tumors [124]. Zhao et al. reported the application of spherical HANPs in anti-tumor applications [121] (Fig. 8). Members of this group have demonstrated antitumor activity and have explored the underlying mechanisms. The results showed that the HANPs inhibited the viability of malignant cells. Particularly, the inhibition rate was 70% in the 4T1 cells. The proliferation inhibition of 4T1 cells by HANPs was chiefly embodied in suppressing cell activity, arresting the cell cycle, eliciting DNA damage, and ultimately expediting cells. In one study, HAPNs combined with DOX were investigated to overcome tumor multidrug resistance [109]. The results showed that DOX-loaded HANPs (DHANPs) exhibited a 150-fold reduction in the half-maximal inhibitory concentration (IC50) compared with free DOX for human MDR breast cancer (MCF-7/ADR) cells. HAPNs overcome multidrug tumor resistance

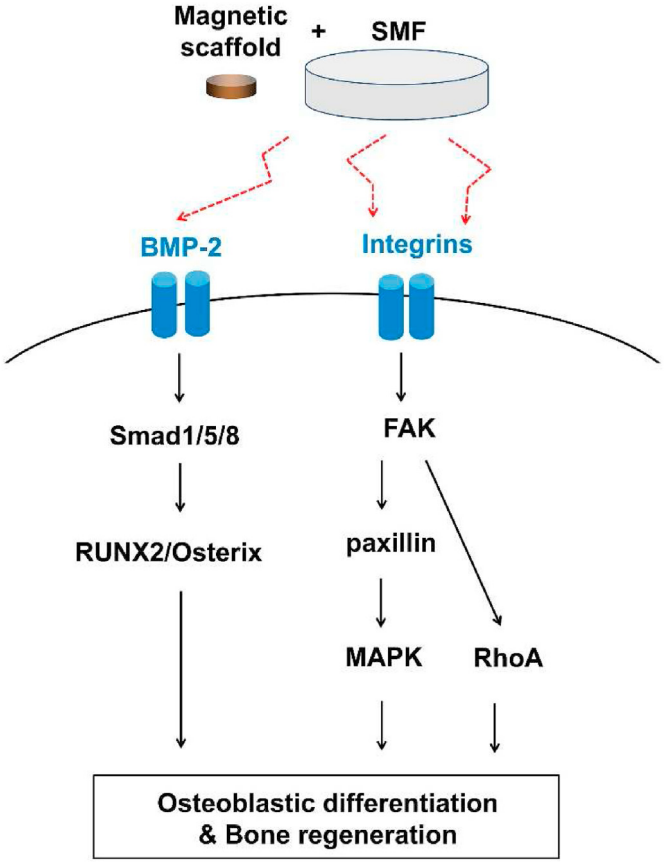

Fig. 7. Schematic illustrating the integrin, BMP, MAPK, and NF-kB signaling pathways in osteoblasts synergized by the culture with SMF and magnetic scaffolds, which ultimately stimulate osteoblastic differentiation and bone regeneration. Reprinted with permission from ref. [88] © 2016 Elsevier Ltd.

by damaging mitochondria and reducing ATP production in MCF-7/ADR cells. Moreover, the HAPNs were cytotoxic to MCF-7/ADR cells. Cytotoxicity of HANPs was derived from induced apoptosis in MCF-7/ADR cells. In addition, Wang et al. reported that HANPs downregulated the FAK/PI3K/AKT signaling pathway to ablate osteosarcoma in osteosarcoma cells [125]. Similarly, the effect of HANPs on tumor and bone regeneration has been investigated [126]. HANPs inhibits tumor growth and metastasis in rabbits. Moreover, the 3D-printed porous titanium scaffold with an HANPs coating inhibited tumor growth while accelerating bone regeneration in the bone defect model in the tumor environment.

CS, derived from chitin, is a natural cationic polysaccharide. The antimicrobial properties, biodegradability, and biocompatibility of CS make it a popular choice for bone tissue engineering and drug delivery [127–129]. Similar to HA, the role of CS in tumor therapy has been investigated [110,112,115–117,122]. As early as 2001, CS has been reported to induce apoptosis in bladder tumor cells [111]. Moreover, the *in vivo* antitumor effects of CS nanoparticles have been reported [130]. CS nanoparticles exhibited impressive antitumor activity in S-180 and H22 bearing mice. For H22 bearing mouse model, tumor-weight inhibition of CS nanoparticles by three administration routes achieved were 52%, 51%, and 54% respectively. In one study, carboxymethyl chitosan (CMCS) was investigated for antitumor metastasis [115]. The results showed that CMCS inhibited the expression of matrix metalloproteinase-9 (MMP-9) in tumor cells. Tumor growth and lung metastases in CMCS-treated mice were reduced compared to those in control mice after 14 days. Pan et al. reported that chitooligosaccharides (COS) induce apoptosis and autophagy via the p53/mTOR pathway in osteosarcoma cells [117]. Moreover, COS increased the sensitivity to cisplatin *in vitro*. The PI3K-AKT pathway is an essential kinase-signaling network involved in cancer development and treatment. Amirani et al. summarized the antitumor effects of CS/COS via the PI3K-AKT pathway [131] (Fig. 9). Inhibition of AKT signaling by CS and COS is considered to be an anticancer mechanism that contributes to apoptosis improvement and anti-proliferative effects. In one study, HA delivered CS as an

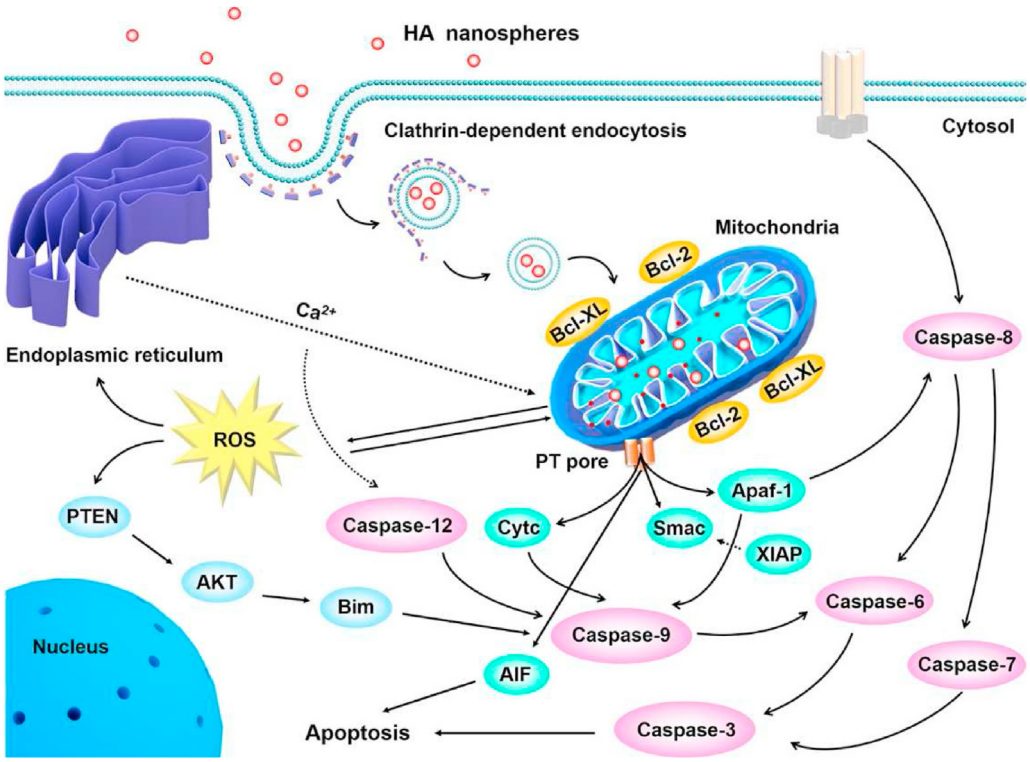

Fig. 8. Schematic illustration of possible molecular mechanism of HA nanosphere-induced inhibitory effect in 4T1 cells. Reprinted with permission from ref. [121] © 2018, American Chemical Society.

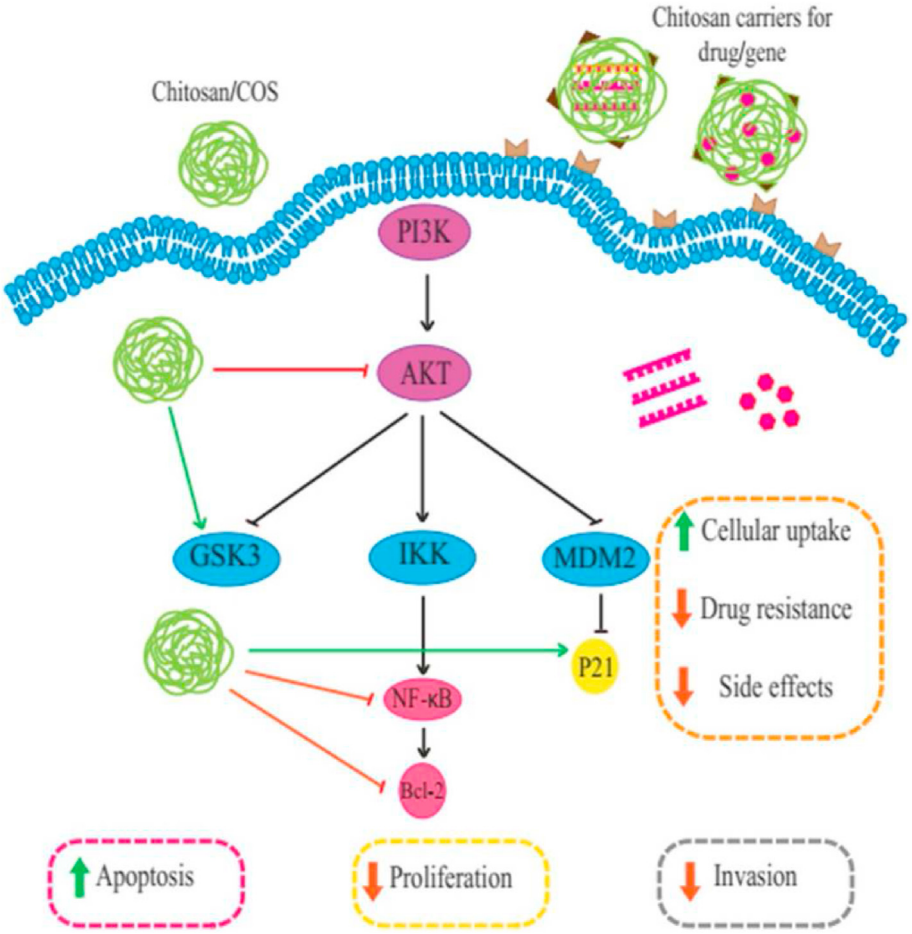

Fig. 9. Schematic illustration of the role of chitosan in regulating the AKT pathway in cancer. Reprinted with permission from ref. [131] © 2020 Elsevier B·V.

antitumor agent [132]. The results showed that CS had a significant inhibitory effect on the viability of osteosarcoma cells MG-63, while it showed no toxic effect on osteoblasts.

5. Conclusion and outlook

Bifunctional scaffolds usually comprise therapeutic agents and scaffold materials, and must meet two key requirements. First, bifunctional scaffolds must exhibit excellent antitumor effects to eliminate residual tumor cells in the lesion location. Second, bifunctional scaffolds must be biocompatible and osteoinductive to promote bone regeneration. While solving this problem is essential, it is equally important to increase the effects of tumor therapy and bone regeneration. Herein, we proposed a promising design scheme for bifunctional scaffolds: the synergistic effect and interplay between the therapeutic agents and scaffold materials. We summarized the role of tumor therapeutic agents in bone regeneration and the role of scaffold materials in tumor treatment. Generally, the antitumor effect of therapeutic agents and the accelerated bone regeneration effect of scaffold materials have been confirmed. Various signals from therapeutic agents (therapeutic agents and their degradation products, thermal stimulation, and magnetic stimulation) to accelerate bone regeneration and scaffold materials (nHA and CS) for tumor therapy have been investigated. This class of therapeutic agents and scaffold materials share a similar function, treating tumors with accelerated bone regeneration. Although their tumor therapy and bone regeneration mechanisms are different, their outcomes in tumor therapy and bone regeneration are similar. Some possible directions for bifunctional scaffolds for tumor therapy and bone repair may arise for further development, such as breast tumors, oral tumors and melanoma. For breast cancer with bone metastasis, the tumor of the breast tissue still needs to be addressed, in addition to the problem of the lesion bone site. Similarly, mastectomy can cause tissue defects. Similarly, oral tumors are often accompanied by facial bone damage and melanoma treatment is accompanied by skin damage. Based on the above issues, The synergistic effects and interplay between therapeutic agents and scaffold materials proposed for similar issues in this review are promising for the solution of the above issues.

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.

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