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Editorial Open Access

Multifunctional Bioceramic Scaffolds for Tumor Therapy and Bone Tissue Engineering

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Editorial

Three-dimensional scaffolds with interconnected pores and proper pore size are promising for treating bone defects in tissue engineering [1]. Nowadays, bioceramic scaffolds, such as hydroxyapatite (HA) [2], calcium phosphate [3] bioactive glasses (BG) [4], and silicate-based bioceramics [5], have been successfully fabricated and widely used for clinical applications due to their excellent bone regeneration ability. However, these bioceramic scaffolds could not satisfy the treatments of bone defects caused by bone tumors completely owing to the postoperative proliferation of residual tumor cells, which results in the tumor recurrence after bone regeneration. Therefore, successful bone regeneration combined with the control of residual cancer cells presents a challenge for bone tissue engineering.

To date, much effort has been made to design and fabricate bioceramic scaffolds with the abilities for killing tumor cells and simultaneously promoting bone regeneration. Owing to the easy functionalization for bioceramics, one of the most efficient strategies is proposed to fabricate multifunctional bioceramic scaffolds with anti-tumor functions, including chemotherapy, photothermal therapy, magnetic hyperthermia therapy, etc.

Chemotherapy is a common therapeutic modality relying on the use of toxic anti-tumor drugs, and the systemic administration of anti-tumor drugs would result in serious side effect and low utilization. Thus, design and fabrication of bioceramic scaffolds with local anti-tumor drug delivery would be promising [6-9]. For example, Chai et al. [6] proposed a method based on cyclodextrin polymer functionalized hydroxyapatite scaffold for achieving a high local drug concentration with a sustained release profile and a better control of residual tumor cells *via* local drug delivery and promotion of the reconstruction of bone defects. Hess et al. [7] reported calcium phosphate beads and matrix scaffolds with a long-term co-delivery of cis-diamminedichloroplatinum (cisplatin, CDDP) and doxorubicin hydrochloride (DOX) to fill bone defects caused by the resection of tumors. The results showed that the CDDP and DOX coloaded beads/matrix scaffolds enhanced activity towards MG-63 cells up to ~75% toxicity while reducing the released drug quantity, and calcium phosphate matrix endowed with excellent bone regeneration ability. Bischoff et al. [8] fabricated hydroxyapatite scaffolds coated with DOX-loaded cyclodextrin for implantation at the original tumor site, and the findings indicated that such strategy enhanced the drug-targeting effect on tumor cells while protecting the more sensitive healthy cells for a period of time after implantation.

Photothermal therapy employs the photothermal agents to generate heat under near-infrared irradiation to ablate tumor cells, which is a targeted and local therapy with minimal invasiveness and high efficiency [10]. In recent years, photothermal therapy has been rapidly developed, and many photothermal agents have been used, such as organic particles [11], gold nanoparticles [12], molybdenum sulfide (MoS_2) [13], graphene oxide (GO) [14], etc. Therefore, it is possible to functionalize bioceramic scaffolds with photothermal agents for achieving the combined functions of bone regeneration and tumor therapy. For example, Liu et al. [15] prepared the elements (Cu, Fe, Mn, Co)-doped bioactive glass-ceramic scaffolds *via* 3D-printing. The results showed that the elements-doped scaffolds had excellent photothermal effect to kill tumor cells *in vitro* and inhibit tumor growth *in vivo*, and at the same time significantly stimulated the osteogenic proliferation and differentiation of bone-forming cells. Lu et al. [16] reported magnetic $SrFe_{12}O_{19}$ nanoparticles modified-mesoporous bioglass/chitosan porous scaffolds, which showed good bone regeneration due to the bioglass matrix and excellent anti-tumor efficacy against osteosarcoma *via* the photothermal ablation. Ma et al. [17] fabricated the 3D-printed bioceramic scaffolds with Ca-P/polydopamine nanolayer surface. The functionalized scaffolds significantly inhibited tumor growth in mice due to the excellent photothermal effect of polydopamine, and could significantly promoted the formation of new bone tissues in rabbit bone defects even under photothermal treatment. Yang et al. [18] reported black-phosphorus modified BG scaffolds, which showed that black phosphorus acted as photothermal agents for cancer therapy and initiators for guiding bone generation. In addition, Wang et al. [13] fabricated $Ca_2MgSi_2O_7$ scaffolds by 3D printing of $Ca_2MgSi_2O_7$/F127 inks and sintering at 1350°C, and then the $Ca_2MgSi_2O_7$ scaffolds were modified with MoS_2 layer by hydrothermal method. Dang et al. [19] fabricated bioactive glass (BG) scaffolds by 3D printing, and then functionalized them with $CuFeSe_2$ *via* solvothermal method. These studies also demonstrated that the functionalized bioceramic scaffolds have the ability to kill tumor cells and stimulate new bone formation.

Magnetic hyperthermia is considered as an effective treatment modality for tumors without adverse side effects. This approach aims to deactivate cancer cells through raising the temperature to 43°C-48°C, whereas the temperature increase (or heat generation) is caused by magnetic nanoparticles (MNPs) due to the hysteresis loss and/or Néel and Brownian relaxations of MNPs under an alternating magnetic field [20]. Currently, some researchers have attempted to fabricate magnetic bioceramic scaffolds with magnetic hyperthermia ability for repairing bone defects caused by tumors [21-25]. Zhang et al. [21] reported the 3D–printed magnetic Fe_3O_4 nanoparticles containing mesoporous bioactive glass/polycaprolactone (Fe_3O_4/MBG/PCL) composite scaffolds, and the scaffolds showed excellent magnetic heating ability and significantly stimulated proliferation, differentiation of human bone marrow-derived mesenchymal stem cells (h-BMSCs) due to the contributions by magnetic Fe_3O_4 and bioactive MBG. Singh et al. [22] proposed to prepare the cobalt and iron substituted β-$Ca_3(PO_4)_2$ as a

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potent scaffold for application in magnetic hyperthermia and as a bone substitute. Koohkan et al. [23] synthesized Cu-containing magnetic bioactive glass (FeCu BG) scaffolds for potential treatment of bone defects caused by malignant tumors, and the results indicated that the FeCu BG scaffolds had suitable biological behavior and good magnetic heating ability. Zhang et al. [24] successfully prepared a multifunctional β-tricalcium phosphate bioceramic scaffold by modifying the surface with Fe_3O_4 nanoparticles/graphene oxide layers. Interestingly, the scaffolds can generate heat to achieve the temperature range 50°C-80°C under an alternating magnetic field by controlling magnetic intensity and Fe_3O_4 content, which can induce more than 75% cell death for osteosarcoma cells (MG-63) *in vitro*. Furthermore, the scaffolds have good bone-forming activity.

It is obvious that bioceramic scaffolds with a chemotherapy, photothermal therapy and/or magnetic hyperthermia therapy function could facilitate the treatment of bone defects caused by tumors due to the synergistic effect. Bioceramic scaffolds are easy to modify with functional components, which makes more possibilities to design the multifunctionality for bioceramic scaffolds. However, the functional components should satisfy the biological requirements. In conclusion, the development of bioceramic scaffolds with tumor therapy function show great potential application in bone defects caused by tumors.

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