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Multi-Functional Composite Scaffolds for Cancer Therapy and Tissue Engineering

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ABSTRACT

Eradication of remaining and metastatic cancer cells to protect cancer recurrence remains a challenge for cancer therapy. Meanwhile regeneration of large defect after surgical resection is desirable for improving the quality of life of the patients. In recent years, multi-functional composite scaffolds with both excellent ablation effect on cancer cells and promotive effect on tissue regeneration have been reported for simultaneous cancer therapy and tissue engineering. Photothermal conversion nanoparticles and reagents have been hybridized with biocompatible polymers or bioceramics to generate the multi-functional photothermal scaffolds. Photothermal ablation, activation of immune cells and promotive tissue regeneration have been demonstrated by *in vitro* cell culture and *in vivo* animal experiments. The review summarizes the latest developments of these multi-functional composite scaffolds.

Introduction

Cancer is the main cause of human death. Many methods have been well established for cancer therapy. The traditional methods include chemotherapy, radiotherapy and surgical resection. Chemotherapy uses anti-tumor drugs to treat the patients. The drugs can kill tumor cells or inhibit the proliferation and migration of tumor cells. A large number of drugs have been used in clinic. However, chemotherapeutic drugs can not only kill tumor cells, but also affect the functions of normal cells because most of chemotherapeutic drugs do not have tumor cell-targeting capacity. Side effects to normal cells and drug resistance after long-term administration are the main problems of chemotherapeutic drugs. Radiotherapy uses high-energy x-ray, γ-ray, electron beams or protons to destroy tumor cells. Exposure of normal cells to radio irradiation can also cause severe side effect. Surgical resection can directly remove the tumor tissues and is widely used in clinic if the tumor tissues are visible and not metastasized. However, sometimes it is difficult to eliminate all the tumor cells by surgical resection. Furthermore, surgical resection is frequently accompanied with large defects, which are difficult to self-heal. Furthermore, in recent years, immunotherapy and hyperthermia therapy have been developed rapidly for cancer therapy. Immunotherapy uses natural immune system for inhibiting primary and metastatic tumor growth. Hyperthermia therapy is based on high temperature-induced damage of proteins and structure to trigger tumor cells apoptosis or necrosis. As one of the hyperthermia therapy methods, photothermal therapy uses the photothermal conversion agents to absorb near infrared (NIR) light and convert it to heat, thereby leading to the destruction of cancer cells.

Although some success of the above-mentioned methods has been achieved, each treatment has its respective limitation. As a new strategy, combination of some of the methods has been proposed by using multi-functional therapeutic scaffolds for cancer therapy [1-14]. Photothermal nanoparticles and reagents have been incorporated in porous scaffolds of biodegradable materials to form multi-functional scaffolds. The composite scaffolds can ablate tumor cells by photothermal heating of the nanoparticles or photothermal reagents. The photothermally ablated tunor cells can be expected to activate immune cells in human body, attacking the remaining tumor cells or metastatic tumor cells. Finally, the scaffolds can serve as a support to initiate the regeneration of resected tissues. In this review, the latest development of such multi-functional scaffolds is summarized and discussed for cancer therapy and tissue engineering.

Preparation of Composite Scaffolds and Application for Photothermal Tumor Ablation

Hyperthermal reagents such as iron oxide nanopartciles, gold nanoperticles, carbon nanotubes, graphene, ceramic nanoparticles and polydopamine have been incorporated in biocompatible and biodegradable polymers and bioceramics to generate multi-functional scaffolds for hyperthermal cancer therapy and tissue engineering [1-12]. Composite porous scaffolds of iron oxide (Fe_3O_4) nanoparticles have been prepared by incorporating them into gelatin porous matrices [1]. The amount of Fe_3O_4 nanoparticles can be adjusted by using different feed ratio of Fe_3O_4 to gelatin solution. The Fe_3O_4/gelatin composite scaffolds have good potothermal conversion efficiency and the heating efficiency increases with the increase of Fe_3O_4 amount. Human cervical carcinoma cell line, HeLa cells, cultured in the Fe_3O_4/gelatin composite scaffolds can be effectively killed by NIR laser irradiation (805nm) and the killing efficiency increases with the amount of Fe_3O_4. To further improve targeting function, a mixture solution of poly-L-lysine (PLL) and gelatin is used for mixing with Fe_3O_4 nanoparticle and folic acid (FA) molecules are conjugated to the amino groups in the scaffolds to prepare FA-functionalized Fe_3O_4/gelatin composite scaffolds [2].

Introduction of cancer cell recognition ligand of FA in the composite scaffolds provides the composite scaffolds with targeting capacity of FA receptor-positive tumor cells. The FA-functionalized Fe_3O_4/gelatin composite scaffolds can efficiently capture tumor cells and kill the captured tumor cells by NIR laser irradiatio. In another report, Fe_3O_4 nanoparticle and carboxyl-functionalized multi-walled carbon nanotubes (MWNTs) have been hybridized with gelatin and akermanite to prepare Fe_3O_4/ MWNTs/ gelatin/akermanite composite scaffolds [3]. The Fe_3O_4/ MWNTs/ gelatin/ akermanite composite scaffolds show good photothermal conversion under NIR irradiation. Composite scaffolds of magnetic $SrFe_{12}O_{19}$ nanoparticles, mesoporous bioglass and chitosan have also been prepared and the composite scaffolds show effective ablation of osteosarcoma by NIR irradiation and promotion on bone tissue regeneration [4].

Gold nanorods (AuNRs) and gold nanostars (AuNSs) with different sizes have been hybridized with gelatin to generate gold nanoparticles/gelatin composite porous scaffolds [5]. The sizes of the three types of AuNRs are 35.0 ×20.4, 65.9 ×13.2 and 117.1 × 27.4 nm in length × width. The sizes of the three types of AuNSs are 37.0, 66.6 and 115.1 nm. All the AuNRs/gelatin and AuNSs/gelatin composite scaffolds show good photothermal conversion efficiency and ablation effect on tumor cells under NIR laser irradiation. When all the six types of gold nanoparticles/gelatin composite scaffolds are compared, the AuNRs/gelatin composite scaffolds prepared with AuNRs having a size of 65.9 ×13.2 nm (defined as AuNRs65/ gelatin composite scaffolds) show the highest photothermal conversion efficiency. The AuNRs65/gelatin composite scaffolds also show excellent ablation of breast tumor cells when breast tumor cells are cultured in the scaffolds and irradiated with NIR laser. Animal experiment by using mouse subcutaneous model, the *in vivo* ablation capacity of the AuNRs65/gelatin composite scaffolds has been confirmed [6]. AuNRs have also been hybridized with bioactive glass nanofibers to prepare composite scaffolds for localized photothermal ablation and tissue regeneration [7].

Polydopamine (PDA) has been hybridized with dopamine-modified alginate to form PDA/alginate composite scaffolds by 3D printing [8]. The PDA/alginate composite scaffolds show effective ablation on breast tumor cells cultured in the composite scaffolds *in vitro* under NIR irradiation. Further *in vivo* subcutaneous implantation in mouse tumor sites demonstrates the photothermal ablation of tumor cells and prevention of local recurrence of the tumor. To prevent bone tumor recurrence and induce bone defect repairing, PDA has been hybridized with $Ca_7Si_2P_2O_{16}$ bioceramics (BC) to prepare PD/BC composite scaffolds by coating a uniformly self-assembled Ca-P/PD nanolayer on the pore surfaces of BC scaffolds [9]. The PD/BC composite scaffolds can kill osteosarcoma cells and breast tumor cells under NIR irradiation. The tumor killing effect of the PD/BC composite scaffolds is also demonstrated by *in vivo* subcutaneous implantation of the composite scaffolds in tumor-carrying nude mouse.

$CaCuSi_4O_{10}$ nanoparticles have been coated on electrospun fibers of poly(ε-caprolactone) and poly (D,L-lactic acid) (PP) to prepare $CaCuSi_4O_{10}$ nanoparticles/PP composite scaffolds [10]. B16F10 skin melanoma cells cultured in the $CaCuSi_4O_{10}$ nanoparticles/ PP composite scaffolds are photothermally ablated by NIR laser irradiation due to their good photothermal performance. The photothermal ablation effect is also confirmed by using B16F10 tumor-bearing mouse. Composite scaffolds of nano-hydroxyapatite and reduced graphene oxide sheets [11], $CuFeSe_2$ nanocrystals and bioactive glass [12] have also been reported for the multi-functional applications. The advantages of these composite scaffolds for photothermal therapy are their holding capacity of a large amount of nanoparticles in the implantation site and repeated heating under NIR irradiation. When tumor cells migrate into the composite porous scaffolds, the tumor cells can be captured by the porous structures or the targeting ligand and then effectively killed by NIR irradiation.

Activation of Immune Cells by Composite Scaffolds

The photothermal composite scaffolds can not only be used to ablate primary tumor cells at the implantation sites but also be expected to activate immune cells to attack metastatic tumor cells. When the primary tumor cells are photothermally abalated by NIR laser irradiation, the ablated cells are remained in the composite scaffolds that can directly or indirectly interact with immune cells and provide various tumor-related antigens to activate immune cells. To demonstrate the capacity of photothermally ablated tumors on activation of immune cells, mouse mammary tumor

cells are photothermally ablated by AuNRs under NIR irradiation and then co-cultured with mouse bone marrow-derived immature dendritic cells (DCs), a typical type of immune cells [13]. Secretion of humoral immunity markers of IL-6, IL-12 and IL-1β and cellular immunity marker of TNF-α is promoted during the co-culture, suggesting activation of immature DCs. Moreover, when DCs are co-cultured with photothermally ablated tumor cells in the AuNRs65/gelatin composite scaffolds, they express high levels of IL-6, IL-10, IL-1β and TNF-α [14]. The photothermally ablated tumor cells in the composite scaffolds can stimulate immature DCs for production of multiple cytokines for triggering of immune responses.

Application Tissue Engineering

Another function of the composite scaffolds for tissue engineering application has been demonstrated by *in vitro* cell culture and *in vivo* animal experiments. Culture of G292 osteoblastic in the Fe_3O_4/MWNTs/gelatin/akermanite composite scaffolds demonstrates the biocompatibility of the composite scaffolds [3]. When human bone marrow-derived mesenchymal stem cells (hMSCs) are cultured in the AuNRs65/gelatin composite scaffolds, the cells adhere and spread well in the scaffolds [6]. The hMSCs cultured in the composite scaffolds proliferate and show adipogenic differentiation. The results indicate that the AuNRs65/gelatin composite scaffolds support adipogenic differentiation of hMSCs and may be useful for adipose tissue engineering [6]. Both gold nanopartciles and gelatin porous scaffolds have shown promotive effects on differentiation of hMSCs for tissue engineering applications [15-19]. Incorporation of calcium phosphate nanoparticles can further promote osteogenic differentiation of hMSCs [20].

The PDA/alginate composite scaffolds have promotive effect on proliferation of human breast epithelial cells when the cells are cultured in composite scaffolds [8]. The PD/BC composite scaffolds support adhesion and proliferation of human osteoblast-like cells and human bone marrow stromal cells during *in vitro* cell culture [9]. *In vivo* implantation of the PD/BC composite scaffolds in critical-sized femoral defects of rabbits shows the promotive effect of the composite scaffolds on bone tissue regeneration [9]. The $CaCuSi_4O_{10}$ nanoparticles/PP composite scaffolds have promotive effect on healing of tumor surgery-related wounds and chronic wounds [10]. Local release of Cu^{2+} and SiO^{4-} ions from the coated $CaCuSi_4O_{10}$ nanoparticles are considered to promote angiogenesis and therefore accelerate would healing [10]. The promotive effects of these composite scaffolds have been confirmed by *in vitro* cell adhesion, proliferation and differentiation and by *in vivo* tissue regenration. The composite scaffolds can interact with somatic cells or stem cells to induce activation of signal transduction pathways through released ions or adhered proteins, resulting in the regeneration of defect tissues.

Conclusion

Composite scaffolds of photothermal reagents and biocompatible materials have been designed and prepared for cancer therapy. The composite scaffolds have multi-functions to photothermally ablate tumor cells, activate immune cells and promote tissue regeneration. The composite scaffolds will provide useful platform for simultaneous cancer therapy and tissue engineering.

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