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Multifunctional Bone Scaffolds: From Regeneration to Bone Cancer Therapy

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Abstract

Under the umbrella of bone scaffolds, there is a category called multifunctional scaffolds capable of addressing different bone-related issues—bone cancer and regeneration, simultaneously. Up to now, some techniques are being applied in clinics to deal with bone tumors. However, filling up a critical size bone defect caused by a tumor with a biomaterial to not only regenerate the defect, but also preventing recurrence of the tumor is still challenging. The present article is a mini-review introducing multifunctional scaffolds endowed with regeneration ability and more up-to-dated bone cancer therapies—hyperthermia, photothermal, and localized drug delivery.

Keywords: Bone tumor; Multifunctional Scaffolds; Bone Tissue Regeneration

Introduction

A 3D bone scaffold is perceived as a biodegradable porous structure by which the healing process would be significantly accelerated [1]. An ideal bone scaffold is expected to have some basic properties as a porous material, which is

a. Biocompatible with suitable surface functional groups for cell adhesion and proliferation,

b. Biodegradable in a desirable rate close to tissue growth,

c. Highly porous with interconnected structure to support the transport of nutrients and waste removal, and finally,

d. Mechanically strong based on the application [2-4]. There are other scaffolds called multifunctional capable of addressing other issues like osteomyelitis, inflammation, and bone tumors besides possessing the basic requirements [5-8].

Despite of great advancements in recent years, cancer is still regarded as the second general cause of death [9]. Osteosarcoma (bone cancer) is notorious to choose its victims mostly through youth rather than mature [10,11]. Yet applying an effective solution to deal with malignant bone tumors is demanded due to incapability of either surgical intervention or radiotherapy to eradicate multifocal lesions entirely [12]. Moreover, systemic administration of chemotherapeutic drugs in the case of bone cancer has serious side-effects for liver and kidneys [6,13,14]. It is important to take into consideration an issue which is poor diffusion of chemical

drugs molecules through bone tissue compared to a soft tissue and hence, a much higher drug's dosage is required resulting in irreparable effects on different organs of body [15].

Fortunately, newer therapies like hyperthermia, photo-thermal therapy, and localized drug delivery under the umbrella of tissue engineering and regenerative medicine (TERM) have opened alternative therapies to the traditional treatments [16-18]. This question may be brought up that how TERM can push the boundaries of osteosarcoma treatment ahead. The answer is when a bone tumor is removed; it leaves behind a critical size defect, which cannot be healed spontaneously [19]. Therefore, TERM offers a multifunctional bone substitution capable of regenerating the defect beside eradication of remained cancerous cells on the defects wall. Regarding to enormous progress and rapid development in the bone tissue engineering recently, different multifunctional bone scaffolds are designed and developed; these scaffolds can address two critical issues, which are eradication of remained cancerous cells after surgery and restoring the bone defect simultaneously. The present review aims at introducing effective approaches toward bone cancer therapy and regeneration.

Hyperthermia-Based Therapy

Applying magnetism yielded multifunctional magnetic 3D scaffolds which are responsive to an external magnetic field (EMF) to address issues like treatment of bone tumors through hyperthermia-based therapy [20,21]. Hyperthermia-based bone cancer therapy is attracting more attention because of its efficiency to eradicate bone cancerous cells locally and decreasing catastrophic side effects of the other therapies such as radiotherapy (radiation) and non-targeted (systemic) chemotherapy (high dosages of chemotherapeutic drugs) [22]. Nonetheless, multifunctional magnetic 3D scaffolds are reported to have beneficial effects on bone tissue regeneration through stimulating osteoblast cells to be proliferated faster [23]. Shuai, et al. [24] fabricated a superparamagnetic-based scaffold to assess whether EMF has any stimulatory effect on the human umbilical cord-derived mesenchymal stem cells; through both in vitro and in vivo tests, it turned out that bone mineral density and new area bone fraction have been significantly increased in the exposure of EMF. Through hyperthermia therapy and in the exposure of EMF, a magnetic scaffold releases heat in the range of 41-46 ºC based on the intended application [25].

Below the temperature of 41 ºC, there is no effect on the cancerous cells and pointless to be assessed here, but any temperature that falls into the mentioned range (41-46 ºC) is of a great significance from cancer therapy viewpoint. It is noteworthy that there is another category adopting temperatures above 46 ºC (thermo ablation) and this one is reported to affect healthy tissues in a negative way beside cancerous tissues. The range between 42-46 ºC, which has attracted lots of attention, is called moderate hyperthermia and it is able to eradicate bone cancerous cells without adversely affecting healthy tissues [26,27]. It should be mentioned that by synthesis and designing a magnetic-based material in the bone scaffold's structure, hyperthermia therapy can be achieved. It is noteworthy that the magnetization saturation of scaffold, frequency, and magnitude of applied external magnetic field are governing factors by which the internal released heat can be precisely controlled [28]. Figure 1 shows the effects of EMF on osteogenicity and tumor therapy of magnetic scaffolds [29].

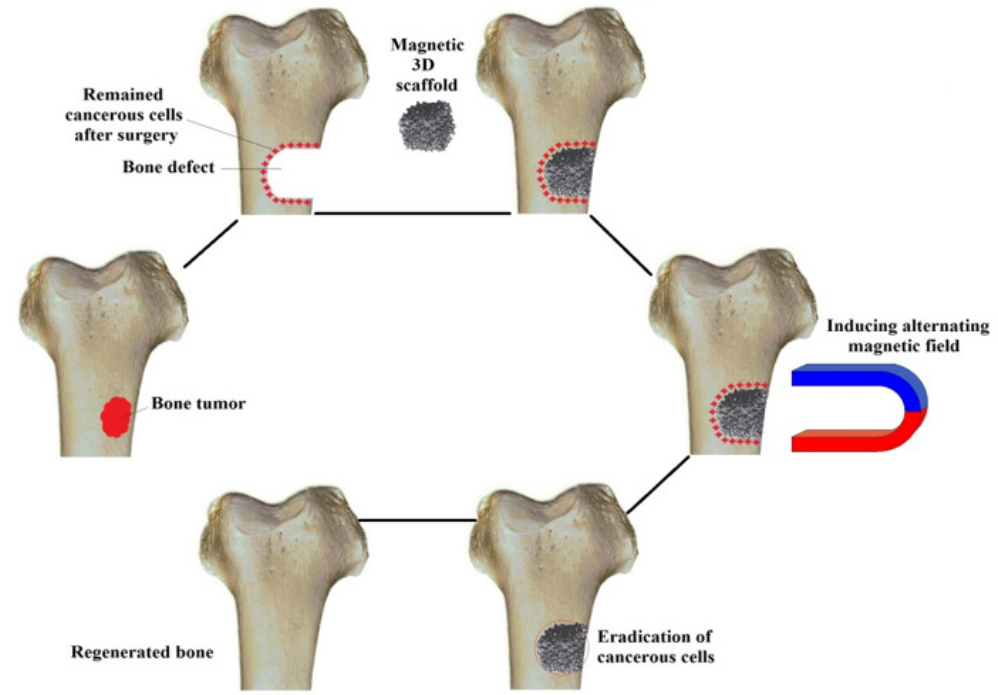

Figure 1: A schematic picture showing the effects of external magnetic field on a bone tumor [29].

Photothermal-Based Therapy

Another approach to kill bone cancerous cells is photothermal therapy which is reputable to be non-invasive and effective [30]. This therapy is based on designing bone scaffolds containing photothermal agents—grapheme oxide, transition metals, MoS_2, carbon, LaB_6, $CuFeSe_2$, etc. [18,30-34]. It is well-known that these photothermal agents have catalytic capability to absorb near Infrared laser (NIR) followed by converting it to heat leading to the death of cancerous cells (Figure 2). Fu, et al. [32] developed a multifunctional bone scaffold composed of Larnite/carbon for simultaneous bone cancer therapy and regeneration; based on the obtained results, the scaffold effectively killed the cancerous cells in vitro and in vivo and the bone regeneration of Larnite/carbon was better than pure Larnite. On the upside, this method requires less high-tech instruments to excite the photo-thermal agents of bone scaffold (easy processing) and also by just addition of a single element through the structure of scaffold this kind of therapy would be available (cost-effective). On the downside, the efficiency of infrared diffusion to excite the photothermal element based on the depth of bone defect is vague and applying more powerful substitutions like ultraviolet is synchronized with other serious problems.

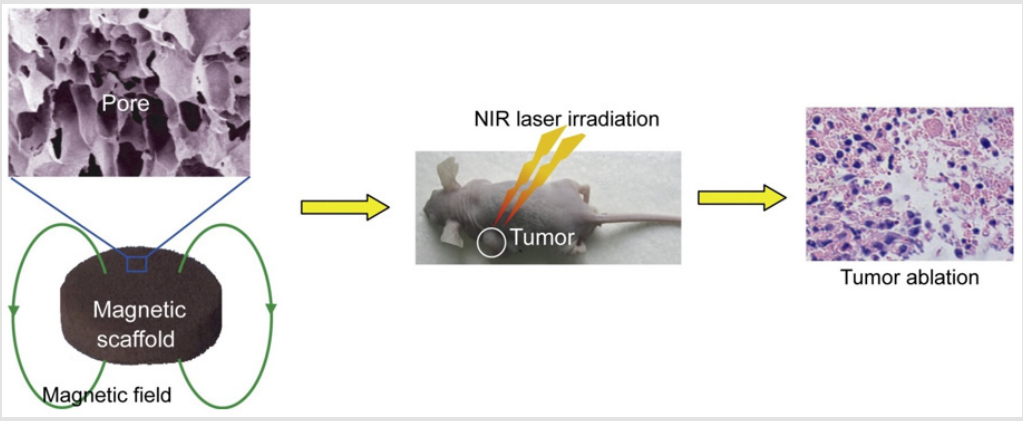

Figure 2: The effect of photothermal therapy on tumor ablation [11].

Localized Drug Delivery

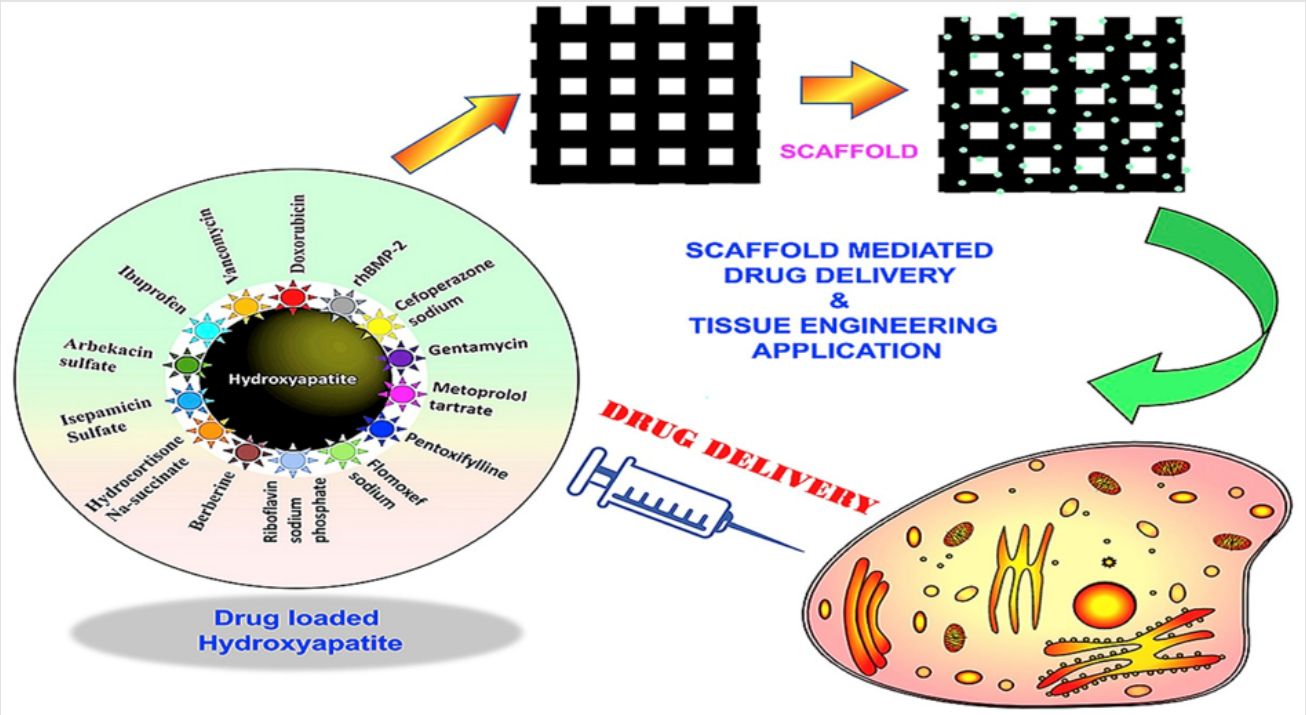

Figure 3: An illustration of different drugs loading on a hydroxyapatite bone scaffold and subsequent localized release of them in the bone defect [42].

Various ways are available for administration of drugs, which generally can be categorized as systemic and localized drug delivery [35,36]. Through the systemic way, a drug is injected through blood stream and then it will be distributed all over the body resulting in poor penetration of drug molecules into targeted tissue and also subsequent disadvantages for renal and liver [13,37]. This way is even more complicated for bone tissue due to poor blood stream through this tissue requiring higher dosages of the drug. Considering that in the case of bone cancer, the chemotherapeutic drugs should be administered and to reach the desired amounts of drug in the targeted tissue how much chemotherapeutic drug is in need. Without a doubt, systemic administration has devastating effects on other organs in the case of bone cancer [38]. On the other hand, localized controlled release can provide desired drug concentration in the targeted tissue and also it is able to enhance drug bioavailability [39,40]. The amounts of drug loading and release rate are completely dependent on the design of scaffold (Figure 3). In recent years, some inorganic scaffolds with effective controlled release capabilities are designed and cisplatin (cis-dichlorodiammineplatinum(II) and doxorubicin as model drugs are used. Although this method showed promising potential to extirpate the remained cancerous cells, these cells can become resistant to this treatment in some cases and consequently fail the whole process [41,42].

Conclusion

To deal with a bone tumor, surgery is the first approach coming into mind followed by radiotherapy and chemotherapy, but none of which is able to eradicate the cancerous cells remained into the defects wall. Newer therapies, which are added to bone scaffolds, have made the scaffolds multifunctional being responsive to the bone cancer-related issues concurrently with regeneration. The multifunctional scaffolds indicated a promising potential to be replaced with the traditional ones. Certainly, shortcomings are still around the multifunctional scaffolds and further investigations are required to afford a safe clinical approach.

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