Mesoporous bioactive glasses (MBGs) in cancer therapy: Full of hope and promise

Mesoporous Bioactive Glasses (MBGs) in Cancer Therapy: Full of Hope and Promise

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Abstract

Implementing novel approaches for cancer therapy are under continuous progress, and bioactive glasses (BGs) and glass-ceramics show excellent potential in this regard. Although these materials have been mostly used as magnetic substances in hyperthermia approach, some of their subsets, i.e., mesoporous bioactive glasses (MBGs), have been recently proposed not only as magnetic materials but also as drug delivery systems for advanced treatment of bone cancer. Different types of MBGs including granular particles and three-dimensional (3D) scaffolds can be applied for cancer therapy. Based on the results obtained from *in vitro* studies, MBGs seem to have a bright future in the therapeutic strategies to combat cancer; however, their application in this field is still in its beginning, and more research needs to reveal all pros and cons of this newly proposed approach.

Keywords: Biomaterials; Porous materials; Bioactive glasses; Magnetic materials; Cancer therapy; Drug delivery.

1- Introduction

Cancer is among the deadliest diseases of humans, and its prevalence is continuously increasing over the globe. Up to now, a few approaches have been proposed and used for treating cancerous tissues and specifically the metastases, such as chemotherapy, radiotherapy, and hyperthermia [1]. In comparison to the first two approaches, the use of hyperthermia, i.e., increasing the temperature above 40°C in the diseased site to kill the cancer cells, exhibits some merits such as the lack of using chemicals and hazardous radiations [2].

Magnetic bioactive glasses (BGs) belong to the bioceramics superfamily and have been recently proposed for cancer treatment (Figure 1) [3]. BGs were firstly developed for the repair and regeneration of bone defects [4-8] and then, interestingly, were gradually found useful in contact with soft tissues, too (e.g., healing of skin wounds, muscle and nerve repair, cardiac tissue engineering) [9-13]. After being exposed to an external alternating magnetic field, a magnetic BG can act as an anticancer substance via the hyperthermic effect and exhibits a bone regenerative capability, thus eliciting a multifunctional action. Bioactivity is also useful to reduce the risk of material displacement (through bone-bonding) when the glass is implanted in the diseased bone [14]. Stimulation of apoptotic pathways in cancer cells by using some specific formulations of BGs (e.g., vanadium- or lanthanum-doped silicate glasses) has also been reported [15, 16]. It is worth mentioning that some types of non-bioactive glasses are clinically being used for the treatment of specific cancers via a different therapeutic action: for example, ^{90}Y-doped SiO_2-Al_2O_3 radioactive glass insoluble microspheres, commercialized as Theresphere® (Nordion; Ottawa, Ontario, Canada), are systemically administrated for the treatment of unresectable hepatocellular carcinoma and metastatic colorectal cancer (mCRC) [17, 18].

More recently, the use of mesoporous bioactive glasses (MBGs) has also been proposed and applied in hyperthermia and photothermal therapy (PPT) for cancer treatment [19]. These materials, having a porous structure with a highly controllable arrangement and diameters (2 to 50 nm), are recognized as excellent platforms for anti-cancer drug loading and release [20, 21]. Moreover, it is feasible to incorporate some specific elements, for example iron (Fe), into the structure of MBGs to give them magnetic properties and thus improve their anti-tumor effects. As angiogenesis is crucial for the proliferation and metastatic spread of cancer cells, developing novel formulations of MBGs with the ability to suppress new blood vessel formation, regulated via releasing anti-angiogenic ions or delivering anti-angiogenic drugs and chemicals, could be of great importance for designing new therapeutic approaches against cancer.

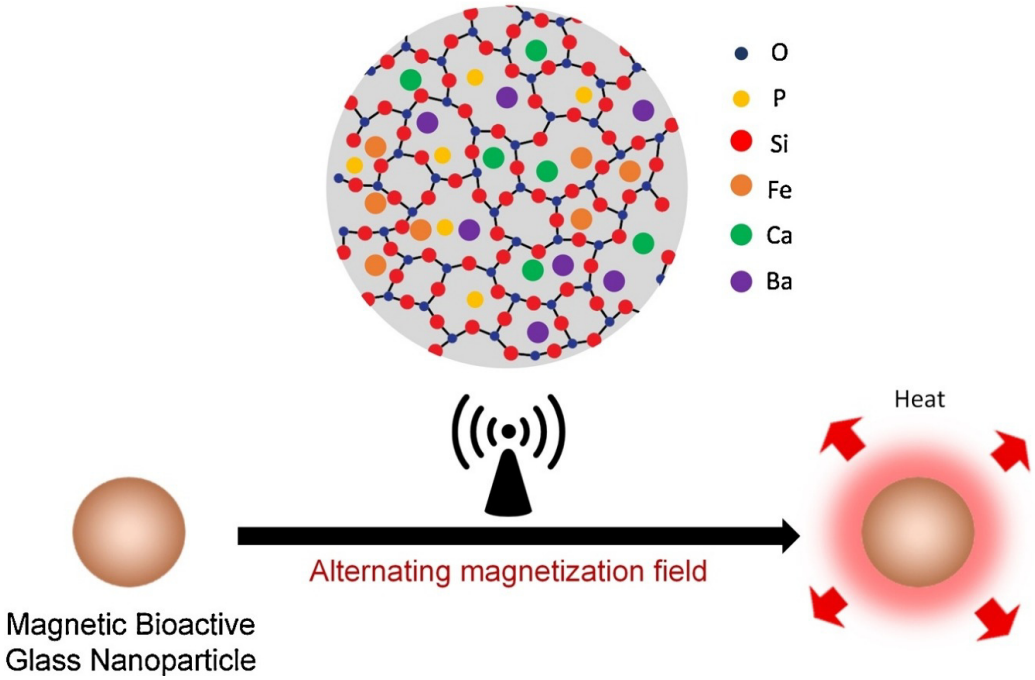

Figure 1. Schematic representation of magnetic BGs developed for hyperthermia therapy of cancer. Reproduced from [14].

The potential of glass-ceramics for cancer therapy has been recently reviewed by Miola et al. [22]; thus, the primary goal of the present study is to evaluate the applicability of MBGs in the treatment of cancer along with the challenges related to their use.

2. MBGs as vehicles for anticancer strategies

The sol-gel process caused a revolution in preparing a new generation of materials, i.e., mesoporous substances with a highly-ordered porous structure at the nanoscale. In 2004 and later in 2006, two scientific groups could take benefit of this technique along with the principles of supramolecular chemistry for developing MBGs for the first time [23, 24]. Since then, the ability of these materials for loading and releasing various drugs (e.g., anti-cancer agents) in a controlled and targeted manner has continuously attracted increasing interest [25]. Based on the current literature, it is apparent that MBGs, in the form of fine powders and scaffolds, are used to fill bone defects and cavities caused by cancers. Furthermore, the incorporation of MBGs into polymeric matrices to prepare composites is an additional strategy to expand the range of their applications [26-28]. The currently-proposed approaches for imparting anti-cancer activities to MBGs include loading of anti-tumor chemicals and drugs (e.g., Imatinib and doxorubicin) [29, 30], incorporation of anti-tumor transition metals (e.g., terbium) [31] into their structure, and the photothermal therapy (PTT) [32].

In regards to drug delivery, MBGs have been widely proved to be valuable release platforms in bone regenerative strategies, where they can elicit a multifunctional action (inherent excellent bioactivity and local therapeutic action of the drug) [33]. The same properties can be exploited in the context of bone cancer treatment to perform local chemotherapy. It has been shown that some

parameters can control the final output of this strategy, including the variation in the pH of the microenvironment, the initial concentration of the loaded drug, and the degradation rate of MBGs [30]. For instance, Shoaib et al. could successfully load an anti-cancer drug, imatinib, into MBGs at a concentration of 1 mg/mL with the efficiency of 77.59%. Their study showed that the release kinetics were indeed controlled by changing the pH (from 4.4 to 10.4) and the initial drug concentration (0.2 –1 mg/mL) so that the maximum cumulative imatinib release of 81% happened during 250 h at the pH of 4.4. In another study, Wang et al. reported doxorubicin-loaded terbium-containing MBGs as promising materials for the treatment of bone tissue lesions [31]. The experimental data clarified that the release of doxorubicin from the MBGs followed a Fickian diffusion mechanism according to the Higuchi model. Similar to the study carried out by Shoaib et al., the authors concluded that the delivery of the doxorubicin from MBGs could be controlled by changing pH and drug concentration.

Targeted therapy is one of the main goals of scientists working on cancer to reduce the side effects of drugs and to improve the efficient killing of tumor cells [34]. This strategy has been proposed for targeted drug delivery from MBGs: for example, Lin and coworkers functionalized the glass particles with folate groups, the receptors of which are highly overexpressed on the surface of the cells of many tumor types [35, 36].

The incorporation of anti-cancer metals into the glass structure is another clever approach to create anti-cancer properties. Some members of lanthanides (e.g., terbium (Tb) and holmium (Ho)) have been recognized as radiopharmaceuticals and are currently used for cancer therapy [37]. For instance, the radionuclide samarium (^{153}Sm) is extensively used as ^{153}Sm-ethylenediaminetetramethylphosphonic acid (^{153}Sm-EDTMP) for stabilizing pain in patients with metastatic bone lesions [38].

Christie et al. also incorporated radioactive yttrium in BGs to prepare radionuclide vectors for cancer treatment [39]. The authors described that a combination of high surface reactivity with a slow release of yttrium is desirable for BGs used in cancer therapy. The release mechanism of yttrium from the glass was reported to be controlled by the coordination environment of yttrium ions and their clustering behavior. As adding yttrium to the BGs leads to a significant decrease in the network connectivity (NC), the glass showed less durability associated with a faster release of ionic species such as yttrium. At present, there is a paucity of reports on MBGs doped with radioactive anti-cancer elements; other options apart from Tb- and Sm-doped MBGs [26, 31] deserve to be considered in future studies.

Photothermal therapy (PTT) is a non-invasive therapeutic technique for the treatment of solid tumors. In this approach, the laser beam (wavelength in the second near-infrared window (NIR-II, 1000-1400 nm)) applied to the target tissue is converted into heat and creates localized thermal damage in the tumor region via surface plasmon resonance of plasmonic materials [40]. In order to utilize this technology for the treatment of bone tumors, Chang et al. recently synthesized copper (Cu)-doped MBGs that possessed both photothermal effects and bone-forming capability [19]. Their results showed that PTT and chemotherapy could be simultaneously achieved using Cu-doped MBGs, and this combination is an excellent approach to enhance the efficacy of tumor therapy.

3. Cancer treatment by using MBG-induced hyperthermia

Treatment of bone cancer by magnetic hyperthermia involves the use of implantable materials to generate heat in the diseased site under the application of an external alternating magnetic field [41]. Malignant cells are selectively killed if exposed to temperatures within 41-47 °C due to their intrinsic microenvironment including low pH, whereas normal cells can

survive at even higher temperatures [42]. Tumors are prone to be more efficiently heated compared to surrounding healthy tissues as their vascular network is poorly structured and cannot dissipate heat efficiently.

While being mostly used as contrast agents for diagnostics, magnetic nanoparticles have been recently applied for the treatment of cancer by hyperthermia. Sadhukha et al. [43] reported that magnetic hyperthermic effect transduced by superparamagnetic iron oxide nanoparticles (SPIONs) could significantly reduce or even eliminate cancer stem cell populations. Aminosilane-coated magnetite nanoparticles (NanoTherm, MagForce, Germany) have been approved by the European Medicines Agency (EMA) for clinical use in selected patients suffering from glioblastoma, a lethal brain tumor with limited therapeutic options [44]. An aqueous dispersion of SPIONs is injected into the tumor site and, once the nanoparticles are safely transferred, an alternating magnetic field is applied to generate heat and delivering a localized treatment.

Unlike SPIONs, BGs typically exhibit a non-magnetic behavior unless magnetic phases, e.g., magnetite (F_3O_4), are somehow embedded in the glass network. Introducing Fe in the sol-gel synthesis is relatively easy, whereas it can be tricky in melt-derived glasses and glass-ceramics. Li et al. [45] first prepared magnetic SiO_2-CaO-P_2O_5 MBGs by introducing iron nitrate in the sol; as a result, MBG powders containing a homogeneous dispersion of F_3O_4 nanoparticles was obtained. The presence of this nanophase did not suppress the textural properties (specific surface area >250 m^2/g, mesopore size within 3.4-3.8 nm), the apatite-forming ability and sustained drug (ibuprofen) release capacity of Fe-doped MBGs, but imparted superparamagnetic properties to the materials, the saturation magnetization of which was found to increase with increasing amounts of Fe species.

Hierarchical Fe-doped MBG scaffolds containing F_3O_4 superparamagnetic nanoparticles were often fabricated by using a co-templating method, in which surfactant molecules (Pluronic P123) act as meso-structure directing agents and a polyurethane open-cell sponge generates the macroporous (200-500 µm) 3D architecture [3, 46] (Figure. 2a). These scaffolds were sintered in air and suffered from high brittleness (compressive strength ~50 kPa); therefore, production of MBG-based composites was thought as a valuable strategy to improve the mechanical properties. Zhu et al. [47] prepared superparamagnetic Fe-doped MBG scaffolds by the co-templating approach described above but performed the thermal treatment of calcination under argon atmosphere, thereby inducing carbonization of the polymeric skeleton. As a result, composite scaffolds with a carbon core coated by a MBG layer were obtained, and the compressive strength was significantly higher than that of the scaffolds calcined in air (>0.3 vs. 0.05 MPa). More recently, the same research group used 3D printing to fabricate Fe-doped MBG/polycaprolactone composite scaffolds showing the potential tri-functionality of enhanced osteogenic activity (due to bioactivity), local anticancer delivery of doxorubicin and magnetic hyperthermia [48].

Magnetic bioactive composites comprising 58S sol-gel glass and different amounts of melt-derived SiO_2-CaO-Fe_2O_3 glass-ceramics were found capable of inducing *in vitro* effective hyperthermia on human osteosarcoma (Saos-2) cells with reduction of cell proliferation and viability [49].

Fe-doped MBGs based on the quaternary SiO_2-CaO-Na_2O-P_2O_5 system were used to prepare multiscale porous scaffolds by using P123 block copolymer as a mesopore former and poly(methyl methacrylate) (PMMA) colloidal crystals to generate the macropores (Figure. 2b) [50]. Interestingly, the transition from paramagnetic to ferromagnetic behavior was observed when the scaffolds are calcined in the argon atmosphere, associated to the formation of

maghemite (γ-F_2O_3) nanoparticles (diameter <100 nm) [51]. Calcination in a non-oxidizing atmosphere was also reported to be the key for inducing the nucleation of magnetic phases (F_3O_4 and/or γ-F_2O_3) in macro-mesoporous bioactive glass-ceramic scaffolds produced by sol-gel foaming [52, 53] (Figures. 2c and d).

Very interestingly, a recent study revealed that other elements apart from Fe can play a role in imparting magnetic properties to MBGs. Koohkan et al. [54] investigated the bioactive and magnetic properties of SiO_2-CaO-P_2O_5 MBGs doped with Fe, Cu or co-doped with both, and showed that the addition of Cu to the MBG composition resulted in better entrance of Fe_2O_3 into the glass structure and, accordingly, better formation of Fe_3O_4 after calcination and higher saturation magnetization (Figure 3). These materials also exhibited other attractive features due to the local release of Cu^{2+} ions, such as antibacterial behavior and stimulation of angiogenesis, along with good biocompatibility with mesenchymal stem cells.

The existing set of studies about the use of MBGs for hyperthermic treatment of bone cancer is limited to *in vitro* assays, but the results are overall promising and motivate further research in animal models. Some key points to be considered will be the optimal material dosage for obtaining a therapeutic effect *in vivo*, the duration and the parameters of the clinical treatment to apply (e.g., frequency and amplitude of the alternating magnetic field).

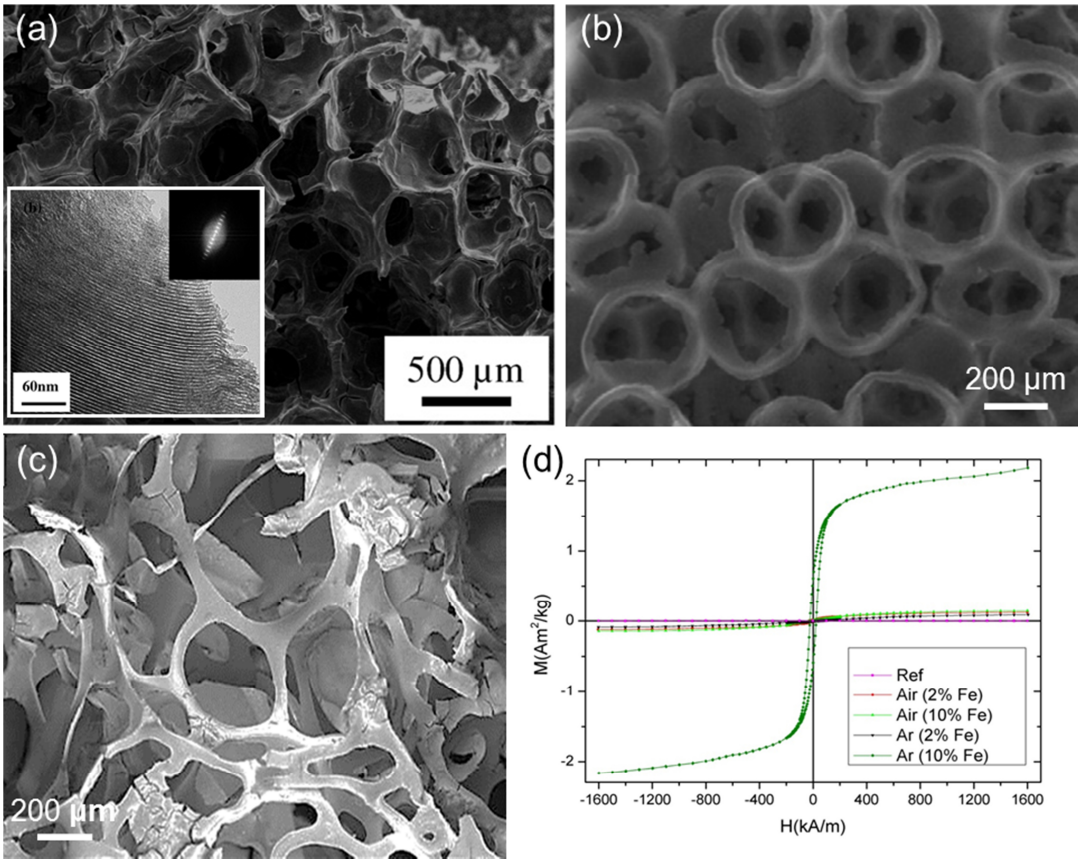

Figure 2. Magnetic hierarchical MBG scaffolds produced by different methods: (a) sponge replication (the TEM inset shows the mesoporous structure) (images reproduced from [3]), (b) use of PMMA crystals as macropore-forming agents (image reproduced from [35]), (c) sol-gel foaming (image reproduced from [38]); (d) influence of the calcination atmosphere (argon vs. air) on the magnetic properties of sol-gel Fe-doped MBG foams (images reproduced from [37]).

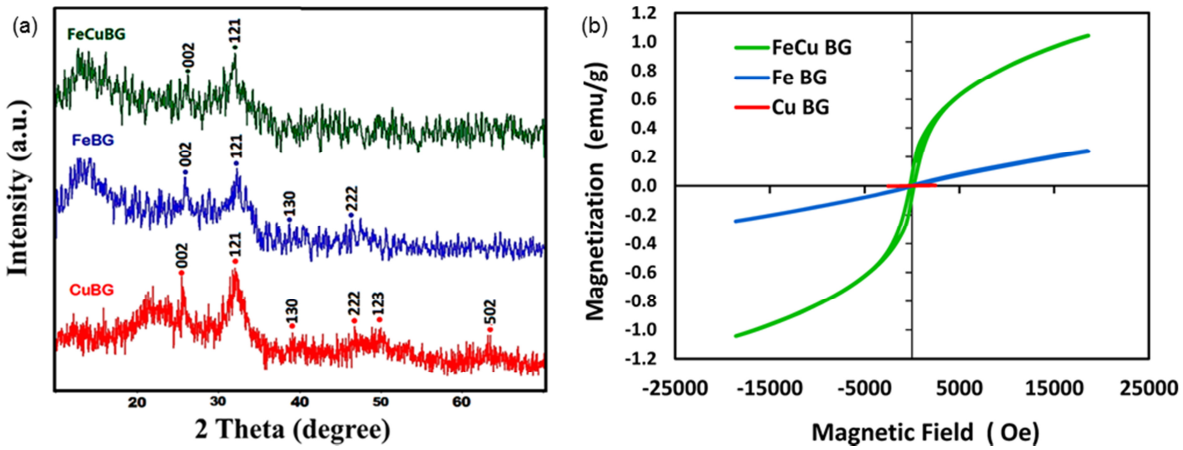

Figure 3. Fe-, Cu- and Fe/Cu-doped MBGs: evidence of (a) *in vitro* bioactive properties (the XRD patterns show the major diffraction peaks of hydroxyapatite after soaking in SBF) and (b) magnetic behavior. Images reproduced from [39].

4. Summary and outlook

Magnetic hyperthermia is a powerful technique for combating against cancerous cells, and its efficacy has generally been well recognized through *in vitro* and *in vivo* experiments.

At present, SPIONs are a promising clinical option to treat cancer via hyperthermia. High interest is also emerging towards the development of multifunctional SPION-based systems formed by a magnetite core functioning as a contrast agent, a biocompatible coating and a therapeutic outer layer targeted with active genes, drug compounds or special biomarkers [55, 56]. However, the toxicity associated with the non-degradable SPION core is still a matter of debate, including problems related to biodistribution, local accumulation and the long-term fate of the nanoparticles *in vivo* [57].

The use of magnetic BGs in the form of thermoseeds [14] could potentially overcome the limitations mentioned above as the solubility of these materials in the biological environment can

be tuned depending on the composition and structure, and the ionic dissolution products from glasses can be metabolized and excreted through physiological paths [58].

Apart from being non-toxic and highly biocompatible, MBGs can allow scientists to move a step forward and develop novel therapeutic strategies that were unthinkable or very difficult to develop with "conventional" melt-derived BGs. In fact, MBGs show great promise for anti-cancer applications due to their unique properties including the easiness of being doped with anti-cancer and magnetic ions (e.g., samarium [26] and iron [59], respectively) as well as of being loaded with anti-tumor chemicals (e.g., Imatinib and doxorubicin) [29, 30] that will be locally released in a controlled way. Moreover, recent studies suggest that some defined formulations of MBGs, e.g., Cu-containing MBGs, can be used in a newly developed strategy for cancer therapy based on PTT, in which not only the thermal ablation of cancer cells upon NIR laser irradiation is achieved, but the release of chemotherapeutic drug can be modulated by the photothermal effect [19].

From the authors' point of view, it should be underlined that the inhibition of angiogenesis via developing specific formulations of MBGs can also be beneficial in cancer therapy as tumor cells need new blood vessels to supply oxygen, nutrients and the removal of waste products as well as to guarantee their growth and proliferation in the body [60, 61]. In this regard, loading and delivery of various anti-angiogenic molecules (e.g., some types of small interfering RNA (siRNAs)) and chemicals (e.g., Sunitinib (anti-VEGFR drug)) by MBGs may be a wise strategy for the inhibition of the growth and progression of cancerous cells. This strategy has already been successfully performed using mesoporous silicate nanoparticles (MSNs) both *in vitro* and *in vivo* [62]; however, there is no report on the use of MBGs for the same purpose in the existing literature.

In brief, this work witnesses that the use of special types of MBGs for cancer therapy is in its beginning and numerous fascinating opportunities deserve further investigation in the future. Although relatively few studies have been focused on this specific application of MBGs, the preliminary results are highly promising and can be attractive for scientists working in this hot research field across materials science and medicine. However, plenty of questions on the usability of these materials for reliable cancer therapy still remain (e.g., optimal dosage of ions and drugs to embed in MBGs, the fate of MBGs *in vivo*, long-term side effects), which should be addressed through performing well-organized *in vitro* and *in vivo* studies. It is expected that interdisciplinary research and effective collaborations between materials scientists, chemists, biologists, and clinicians can potentially overcome all the obstacles on the way of magnetic and multifunctional MBGs and make this novel therapeutic approach as a feasible option in the near future.

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