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Therapeutic inorganic ions in bioactive glasses to enhance bone formation and beyond

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Bioactive glasses (BG) are being widely used for bone tissue engineering applications due to their bioactivity (ability to form strong bonds to bone) and their stimulating effects on bone formation. Recently, progress has been made to enhance the biological impact of BGs by incorporating specific metallic ions in silicate (or phosphate) glasses, including boron, copper, cobalt, silver, zinc and strontium. This review summarizes the newest developments on novel compositions of bioactive glasses in the field of bone tissue engineering related to osteogenesis and angiogenesis. Furthermore, new applications areas for bioactive glasses, including nerve regeneration and cancer treatment, are highlighted.

Bioinorganics and metallic ions

During the last few decades specific "bioinorganics", *e.g.* metallic ions such as copper, strontium, zinc, cobalt, silicon and boron, have emerged as potential therapeutic agents with the potential to enhance bone formation due to their stimulating effects on osteogenesis, as well as on angiogenesis.[1–3] Furthermore, some of them (*e.g.* copper, zinc, silver) have additional therapeutic effects, like anti-inflammatory and antibiotic capabilities.[4,5] In the context of bone tissue engineering involving biomaterial engineered scaffolds, therapeutic inorganic ions (TII) exhibit various advantages compared to organic biomolecules (*e.g.* growth factors), such as the lack of risk of decomposition, their ability to interact with other ions to alter biological functions and the possibility to be processed at the typical manufacturing conditions required for production of inorganic biomaterial scaffolds.[2,6] Thus loading inorganic matrices (scaffolds) with TII could offer a great opportunity to develop robust carrier systems to be used for releasing specific ions in bone engineering strategies. Certainly, the potential toxicity of metallic ions when delivered locally has to be taken into account.[3,7] Even though metallic ions present in the body are in a concentration range of trace quantities,[2] *in vitro* studies with TII released from bioactive glasses cover a larger range of ionic concentrations and show stimulating effects on cells also at higher concentrations, in many cases without any toxic effects. In literature reports, ionic concentrations of TII released from inorganic scaffolds are in the range of several ppm, as summarized in previous studies.[6,8,9] In most cases the effects of the ionic dissolution products are dose-dependent and are specifically related to cell type, culturing conditions and materials morphology.[8]

Bioactive glasses

Bone tissue engineering applications

Bioactive glasses and their corresponding multifunctional glass-derived scaffolds have the potential dual capability to serve as matrices for bone tissue engineering (BTE) and as *in situ* drug delivery systems, particularly for TII.

Research done on bioactive glasses in recent years has produced several new compositions, which are leading to attractive biomaterials with high bioactivity exhibiting new functionalities induced by the intentional release of loaded TII.[8,10] Novel bioactive glasses have been produced by introducing controlled amounts of specific therapeutic ions during the production of the bioactive glass by melting,[11] sol–gel[12] or molten salt ion exchange[13] methods. The incorporation of selected metal ions into silicate matrices has resulted in enhanced bone formation and angiogenesis,[8] whereby phosphate-based glasses can also be used as effective carriers for TII.[10] These effects have been shown for various silicate systems incorporating B, Sr or Cu, Zn.[8] Other ions recently suggested for use as TII include Ce and Ga. Even though it has received little attention as a TII in tissue engineering so far, Ce, for example, was shown to support differentiation and proliferation of osteoblast cells in a dose-dependent manner.[14] Only recently Shruti and colleagues reported on sol–gel derived mesoporous glasses doped with Ce along with Zn and Ga.[15,16] Beside their antibacterial potential,[14,17] Zn and Ga are

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also well-known for their stimulating effects on bone formation[2,18] and beneficial effects on the mechanical strength of the skeleton system,[19] respectively. Also, Ga-loaded 45S5 bioactive glass scaffolds[20] and Ga-containing phosphate glasses,[21] both showing antibacterial effects, have been reported in the literature.

Boron (known for stimulating effects on bone formation[22]) incorporated into a mesoporous silicate glass-based scaffold significantly enhanced proliferation and expression of osteogenesis-related genes in osteoblasts.[23] Also, boron-containing silicate glasses were shown to convert rapidly to biomimetic hydroxyapatite materials, leading to enhanced formation of new bone tissue *in vivo*.[24] Boron-based glasses (B_2O_3 content > 50%) show higher degradation rates compared to silicate glasses, while the dissolution rate can be tailored by controlling the glass composition.[24] Furthermore, borate glasses might be promising for wound healing applications, since it was recently shown that nanoscaled borate-glass fibres mimicking the structure of a fibrin clot have a beneficial effect on the wound healing process.[25]

Recent investigations have shown that silicate glasses containing Sr^{2+} enhance osteoblast differentiation, indicated through upregulation of several osteogenic genes.[26,27] In addition, and since a highly vascularised structure is essential for successful clinical application of engineered bone constructs, the use of TIIs as angiogenic agents is being proposed to directly stimulate angiogenesis and vascularisation.[8] For example, copper ions have been known for decades to be able to stimulate angiogenesis and to promote formation (and maturation) of blood vessels.[28] These cases of Cu, B and Sr are just representative of a wide range of possible applications of therapeutic metallic ions in the context of bone tissue engineering.

Beyond bone tissue engineering

Beside BTE, various other potential fields for use of bioactive glasses combined with metallic ions are starting to emerge, including nerve guidance conducts[29,30] and materials for cancer treatment.[31–36] For example, bioactive silicate glasses containing ZnO_2 and CeO_2 were proposed to be used as a component in bioactive glass/polymer composites for nerve guidance conducts (NGCs), while exhibiting required ion release rates of Ca^{2+} and Zn^{2+} (both known to be involved in peripheral nerve regeneration[37,38]). Ce also is known as a neuroprotective agent,[39] aside from the beneficial effects on osteogenesis mentioned above.

In the field of cancer treatment recent efforts suggest the application of ferromagnetic (bioactive) glasses for use in hyperthermia treatment.[33–36] In one exemplary study, magnetic Fe-containing sol–gel-derived mesoporous glass scaffolds were proposed to be used for treatment of malignant bone disease using hyperthermia by inducing heat in the area of diseased bone and killing tumor cells.[36] While also providing osteoconductive properties, these scaffolds can be used as templates for bone tissue regeneration in an additional step, thus combining treatment of malignant bone and tissue regeneration.[36]

On the other hand, in radionuclide therapy, bioactive glasses doped with yttrium are considered as promising materials providing desired radioisotope properties.[31,40] In this application, the biodegradability of the bioactive glass matrix is advantageous in order to remove the radionuclide particles after the radioactive treatment.[31]

Conclusions

Looking into the future, we can anticipate that smart combinations of novel synthesis techniques, template systems and suitable additives will lead to the development of new types of multifunctional bioactive glasses that merge their intrinsic (well-known) bioactive behaviour with TII carrier ability. Future challenges are related to developing novel materials with controlled degradability, exhibiting well-defined and predictable ion release kinetics that can be tailored through adjusting the microstructure, specific surface area and porosity of the scaffolds.[41,42] The research efforts should also address the testing conditions for degradation studies, which define the ion release kinetics from BG scaffolds. It has been recently shown that amorphous BG scaffolds degrade faster under quasi-dynamic conditions where the ion concentration gradient is sustained compared to static conditions.[41]

The work in this area is just beginning, but it is possible to envisage the enormous potential of TII-delivering bioactive glasses for designing multifunctional scaffolds for BTE. One significant challenge in developing such biomaterial platforms with ion delivery capability is to ensure local release of critical concentrations of the relevant metal ions, to control the relative release kinetics of different ions being released simultaneously and to avoid toxic levels being released into the physiological environment.[4,6] Thus, future research efforts will include systematic approaches and a combination of *in vitro* and *in vivo* studies also considering the use of bioreactors to assess the impact of metallic ions under dynamic physiological conditions, aiming at unveiling the mechanism of interaction between TII released from bioactive glasses and human cells. The field is in its infancy and the future is promising: research efforts are bound to increase in this field.

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