INTRODUCTION

Structure and biological activity of glasses and ceramics

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Biomaterials for repairing and regenerating parts of the human body play a key role in contemporary medicine, and have an increasing impact in modern society. Given the importance of orthopaedic medicine (bone is the second most replaced organ after blood), bioactive glasses and ceramics represent a key reference to guide technological advances in this field. Their established role in current biomedical applications has already led many research groups worldwide to look into their structural properties, with a view to identifying the molecular basis of their biological activity. As the efforts directed towards this crucial and exciting direction continue to increase, it is now timely to review the situation, in order to guide future investigations on structure–bioactivity relationships. In this introductory article, the field is reviewed, to provide an appropriate context for the contributions to this Theme Issue.

Keywords: bioactivity; structure; interfaces; bioactivity glasses; bioceramics

1. Introduction

During the last decades, the repair of weakened, deteriorated or damaged tissues has increasingly been affected by synthetic substitutes, the use of which will continue to grow. To take the case of bone, which is the second most replaced organ in the body after blood, approximately 2.2 million bone graft procedures are performed worldwide each year (2005 data [1]), and the estimated cost of these procedures approaches $2.5 billion per year [2]. Of these, currently, around 90–95% involve harvesting bone from either the patient or another donor, and thus the grafts require two surgical procedures, even if the replacement tissue is available. Using a synthetic substitute halves the number of invasive procedures, significantly reducing the possibility of infection or other complications, as well as lowering costs. This has been one of the main driving forces for the development of bone substitute materials.

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One contribution of 11 to a Theme Issue ‘Structure and biological activity of glasses and ceramics’.
2. Ceramics for biomedical applications

Approximately 60 per cent of the bone graft substitutes currently available involve ceramics (including glasses), either alone or in combination with another material [3]. Since the primary inorganic component of bone is calcium hydroxyapatite (HAp), ceramic materials, especially calcium phosphates, have been the focus of much of this development. The point of a bone graft is that it promotes new bone growth by acting as a scaffold to which new bone cells migrate, proliferate and differentiate. The cavity into which the graft has been inserted is thus replaced by new bone.

On the other hand, in many cases, the goal is to provide replacement material, as in prostheses such as hip or knee joints, for example. Ceramic materials have been found to be advantageous in these situations because of their good mechanical properties (strength and toughness) and excellent (i.e. low) wear rates. Alumina has been US Food and Drug Administration (FDA) approved for femoral heads and the acetabular cup linings since the 1960s [4], but is being replaced by zirconia-based materials because of their better mechanical properties—higher strength and toughness and lower Young’s modulus [5]. However, zirconia suffers from ageing, even in its stabilized, or partially stabilized, form, a problem associated with low-temperature degradation [6]. A combination of alumina and zirconia, zirconia toughened alumina (ZTA), a composite material, is emerging [7,8] as a possible replacement for both alumina and zirconia.

Originally, materials for such prostheses were chosen on the basis of their inertness (and lack of toxicity, a feature of bioceramics [9,10]), but it was soon realized that improved performance was possible if the materials were bioactive, that is, if they elicited a biological response that led to bonding between the implant and the surrounding tissue. This would promote osseointegration and reduce the need for a further revision procedure to replace the original prosthesis. Presently, the average lifetime of orthopaedic implants is of the order of 15 years [11]. With patients requiring implants getting younger and younger, this is a strong driver to extend the lifetimes of implants, and so reduce the number of revision surgical procedures.

One approach to improve the integration of non-ceramic implants such as the titanium alloys used in femoral stems is to coat the metal with a ceramic [12]. Although alumina has been used, HAp is a preferred contender because it is bioactive and thus will bond to the surrounding bone. In fact, for many years [13,14] it was considered that the precipitation of such an HAp layer on an implant was a key indicator of bioactivity, or bone-bonding ability. This position is now being challenged [15], since some crystalline calcium phosphates (e.g. β-TCP) bond to bone without the formation of an HAp layer.

Inert bioceramics may be considered to be first generation biomaterials; second generation biomaterials include the bioactive glasses pioneered by Hench who has argued that the third generation biomaterials [16] will involve the use of regenerative, instead of replacement, materials. Consequently, a deeper understanding is required of the mechanisms of bioactivity, and the nature of the biological response that leads to bonding between the biomaterial and the surrounding tissue. In particular, one needs to consider the role of the biomaterial in osteogenesis: is it capable of osteoinduction?
This moves us to the realm of tissue engineering [17–19], in general, and back to scaffolds, in particular.

In addition to being bioactive, materials for scaffolds for bone tissue engineering have to provide adequate mechanical strength and exhibit resorption rates equal to that of the new bone growth, since the scaffold is meant to be a transient structure [20]. Such materials should also be osteoconductive, osteointegrative and, perhaps most importantly, osteoinductive. Bioactive glasses are key contenders because they can be engineered to have these properties [21,22].

3. Bioactive glasses

There are several reasons why bioactive glasses continue to attract considerable attention [23]. As is well known, they can bond to both bone and soft tissue, and the extent of the bioactivity can be controlled through adjusting the composition. They have recently been found to show proangiogenic tendencies [24–28], further promoting their use in tissue engineering. They are also resorbable, because the glass structure is fragmented and gradually dissolves during the process of forming an amorphous calcium phosphate layer and afterwards. This process is crucial, since the bioactivity is related to the formation on the glass surface of the layer of HAp which is known to be osteoconductive [29] and osteoinductive [30], and also due to the osteogenic properties of the products of the glass dissolution (see below).

Hench has outlined a multi-stage process to describe the bioactive nature of glasses [31]. The first step involves the exchange of sodium ions in the glass with protons in the biological environment, followed by the destruction of the silica tetrahedral network and the re-precipitation of an amorphous silica gel layer on the surface, onto which the HAp is deposited. Additional steps are related to the bonding of proteins to the glass surface, the adhesion of osteoblasts and the continuing dissolution of the glass [32].

It has recently become appreciated that the glass dissolution products are also of considerable importance: in 2001, Xynos et al. [33] found that ionic dissolution products of the 45S5 Bioglass® were able to regulate gene expression in human osteoblastic cells: this feature contributes to the superior bioactivity of the 45S5 composition (compared with other bioactive materials such as synthetic HAp) and has potential applications in tissue regeneration. Recent reviews of further work on this key property of bioactive glasses are available [34,35].

In addition to their bioactivity and resorbability, glasses are relatively easy to shape and to produce in microporous structures, making them extremely useful in a variety of scaffold applications [36]. For example, a gel casting approach has recently been demonstrated which allows near net shape three-dimensional fabrication [37].

The original Bioglass®, 45S5 [38], was a melt-derived glass, as this is the traditional way of making glasses. However, there is a tendency for some compositions, close to 45S5, to phase separate and crystallize, forming glass ceramics [39]. Crystallization is known to reduce the bioactivity [31]; in the case of 45S5, this results in the dissolution proceeding quite slowly, so there may be some remnant glass in the newly formed bone. There has thus been some work aimed at...
finding compositions that do not crystallize, such as the 13–93 (54.6 mol.% SiO₂, 22.1 mol.% CaO, 6.0 mol.% Na₂O, 7.7 mol.% MgO, 7.9 mol.% K₂O, 1.7 mol.% P₂O₅) [40,41] and the ICIE 16 (49.46 mol.% SiO₂, 36.27 mol.% CaO, 6.6 mol.% Na₂O, 1.07 mol.% P₂O₅ and 6.6 mol.% K₂O) [42] glasses. Alternatively, low-temperature sol–gel routes can be used [43–45]. Because sol–gel-derived glasses are nanoporous, their specific surface areas are larger compared with melt-derived glasses, and so their bioactivity is greater, owing to the higher density of surface silanol groups and accelerated ion release [46]. It should be noted, however, that sol–gel-derived glasses are not suitable for large dense monolithic parts [19].

Although the original bioactive glasses are based on silicate compositions, a number of other glasses based on borate compositions have recently been shown to be bioactive as well [47–50].

4. Need for a more rational approach

Whereas technological progress in the development of new biomaterials has generally been achieved through trial-and-error approaches, it is now clear that further substantial advances require a more fundamental understanding of the processes underlying bioactivity, that is, the integration of the biomaterial with the biological host. Here, we focus on bioceramics and bioactive glasses, because, as we have noted, their chemical properties resemble those of bone. (To be sure, their major drawback is the considerable differences in mechanical properties.) To date, there is no clear explanation for the mechanisms of tissue bonding in ceramics with bone and soft tissue, nor is there a complete understanding of how biomaterials promote osteoblast functions, such as adhesion, proliferation and differentiation [51]. What is clear, however, is that these are associated with the surface structure and chemistry of the biomaterial. It is known, for example, that these features, at the macro- and micro-scales, can have a strong influence on cell behaviour [52], and this point is underlined to a large extent by the observation that nanophase materials seem to offer enhanced bioactivity, at least to the extent of increased osteoblast adhesion [53–56]. The interaction between cells and surfaces has been reviewed recently by Anselme et al. [57]. Although the surfaces in those studies were almost exclusively polymeric, such as the polymethylmethacrylate (PMMA) used by Dalby et al. [58] in their work on the stimulation of human mesenchymal stem cells to produce bone mineral in vitro, it is not unlikely that a similar nanoscale structural disorder on the surfaces of bioceramics and glasses would produce a similar result.

A key issue is thus the characterization of the structure of a biomaterial and, particularly, of its interface with the biological environment. However, the inherent complexity of current (inorganic) biomaterials has somewhat hampered the application of standard experimental (e.g. diffraction) and theoretical (e.g. atomistic simulations) probes to determine key structural features and their correlation with the observed biological activity.

In the past few years, advances in experimental techniques (e.g. high-energy diffraction [59,60], multi-nuclear nuclear magnetic resonance (NMR) [61] and extended X-ray fine structure (EXAFS) [61]), as well as in theoretical approaches [62] (e.g. development of optimized codes to exploit the rapidly growing computer power available) have led to substantial advances in the structural characterization of bioactive glass and ceramics.

Phil. Trans. R. Soc. A (2012)
For instance, the short- and medium-range structure of bulk 45S5 Bioglass® is now relatively well understood, thanks to the high-resolution experimental and theoretical probes available, and recent simulations have provided the first atomistic views of the dry [63] and hydrated Bioglass® surface [64] (figure 1).

Given the central role of these materials in the present and future of biomedical applications, it is vital to use this information to rationalize the way in which biomaterials work. From this perspective, it is now important and timely to identify what has emerged from fundamental investigations on bioceramics and bioglasses so far, in order to guide future work in the field of biomaterials. For instance, understanding in detail the interlink between surface dissolution, ion release and triggering of osteogenic cellular processes in bioglasses is likely to expose features common to other biomedical materials, for which less or no structural information is available.

Thus, in this Theme Issue, we have invited leading practitioners to discuss their recent work. As has been discussed, bioactivity is essentially an interface-mediated property, but our molecular-level understanding of the surface structure of biomaterials and their interface with the physiological environment is somewhat rudimentary. Progress is now being made in this area. The contribution from Cerruti [67] discusses the use of a variety of surface characterization techniques—microscopy, spectroscopy, grazing angle diffraction and nanoscale visualization using scanning electron microscopy (SEM) and atomic force microscopy (AFM)—

*Phil. Trans. R. Soc. A* (2012)
to probe the surface structure of silicate bio-ceramics, as well as suggesting some new approaches which have yet to be adopted by the biomaterials community. The use of \( H_2O \) and \( CO \) as probe molecules to investigate the nature of surface structure and chemistry of HAp is reported by Bolis et al. [68]. Grandfield et al. [69] describe the use of tomographic techniques to achieve nanometre resolution of the interface between biomaterials and bone, as well as of mesoporous titania coatings used in controlled drug delivery.

Some effort has been expended in trying to explain how the structure and bioactivity of glasses depends on chemical composition [34,66,70–72], so that new bioactive compositions may be designed with larger processing windows than 45S5. This has involved both theoretical methods as well as experimental approaches. Here, Kiani et al. [73] discuss the range of techniques that have been used to elucidate the structure of phosphate glasses, focusing on the network connectivity information which can be obtained from two-dimensional magic angle spinning (MAS) NMR correlation experiments. They show how this has led to progress in the processing of these glasses, by describing the structural chemistry of titanium dopants in phosphate glasses.

Above we have noted the versatility of glasses as scaffolds in tissue engineering; Gunawidjaja, et al. [74], who are interested in mesoporous bioactive glasses because of their larger surface areas, also use solid-state NMR to probe both the bulk and surface structures of these biomaterials. They have elucidated details of surface alteration reactions and relate these to the steps in the Hench mechanism of bioactivity [23]. Vallet-Regi et al. [75] discuss in more detail an approach to engineer bioactive glasses (templated glasses) by combining structural and textural concepts of silica mesoporous materials (SMMs) with chemical compositions similar to those of conventional bioactive sol–gel glasses. They also describe the functionalization of the three-dimensional-ordered arrangement of mesopores in SMM, in order to control the rate of release of the drug molecules which are incorporated into the pores.

The nanoporous nature of sol–gel-derived glasses was noted earlier; in this issue, Martin et al. [76] describe a foaming process which produces scaffolds with a hierarchical structure, where the nanoporous walls are organized into a network of interconnected macropores, similar to porous human bone, and suitable for hosting osteogenic cells. They also echo the observation of Cerruti [67] that a range of complementary characterization techniques is required.

The biological response induced by a biomaterial is ultimately determined by its interaction with cells, mediated by proteins adsorbed on the bio-material surface.

Consequently, a fundamental understanding of how proteins adsorb to biomaterial surfaces is essential to prospective biomaterials design for advanced medical devices. This requires an atomic-level description of both protein and biomaterial surface. One approach to obtaining this understanding is the use of computational and simulation tools. Raffaini & Ganazzoli [77] describe a classical combined MM/MD study of protein adsorption on the surface of TiO\(_2\) polymorphs. Giussani et al. [78] also use classical models to elucidate the interactions between an explicitly hydrated pepsin molecule and a silica surface. Although the numbers of atoms in the systems discussed in the previous two contributions preclude a full quantum mechanical (QM) treatment, by limiting attention to specific amino acid groups, it is possible
to investigate with ab initio QM accuracy how side chains interact with biomaterial surfaces, as Rimola et al. [79] discuss for amino acid adsorption at HAp surfaces.

5. Conclusions

Whereas in the past, the tremendous advances in the development of bioactive glasses and ceramics have been largely empirical in nature, it is recognized that there is now a need for a more rational approach, based on a fundamental understanding of the relationship between structure and bioactivity, at the atomic or molecular level. The contributions to this Theme Issue describe the state of the art in this field.

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Phil. Trans. R. Soc. A (2012)
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*Phil. Trans. R. Soc. A* (2012)


