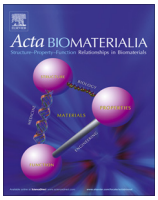
Acta Biomaterialia xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat



Review article

Multifunctional bioactive glass and glass-ceramic biomaterials with antibacterial properties for repair and regeneration of bone tissue

João S. Fernandes [a,c], Piergiorgio Gentile [b], Ricardo A. Pires [a,c,*], Rui L. Reis [a,c], Paul V. Hatton [b,*]

[a] 3B's Research Group – Biomaterials, Biodegradables and Biomimetics, University of Minho, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine, Parque de Ciência e Tecnologia, Zona Industrial da Gandra, 4805-017 Barco, GMR, Portugal
[b] Bioengineering and Health Technologies Research Group, School of Clinical Dentistry, University of Sheffield, Claremont Crescent, Sheffield S10 2TA, United Kingdom
[c] ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães, Portugal

ARTICLE INFO

Article history:
Received 9 February 2017
Received in revised form 26 May 2017
Accepted 30 June 2017
Available online xxxx

Keywords:
Bioglasses
Glass-ceramics
Antibacterial
Bone
Multifunctional biomaterials

ABSTRACT

Bioactive glasses (BGs) and related glass-ceramic biomaterials have been used in bone tissue repair for over 30 years. Previous work in this field was comprehensively reviewed including by their inventor Larry Hench, and the key features and properties of BGs are well understood. More recently, attention has focused on their modification to further enhance the osteogenic behaviour, or further compositional changes that may introduce additional properties, such as antimicrobial activity. Evidence is emerging that BGs and related glass-ceramics may be modified in such a way as to simultaneously introduce more than one desirable property. The aim of this review is therefore to consider the evidence that these more recent inorganic modifications to glass and glass-ceramic biomaterials are effective, and whether or not these new compositions represent sufficiently versatile systems to underpin the development of a new generation of truly multifunctional biomaterials to address pressing clinical needs in orthopaedic and dental surgery. Indeed, a number of classical glass compositions exhibited antimicrobial activity, however the structural design and the addition of specific ions, i.e. Ag^{+}, Cu^{+}, and Sr^{2+}, are able to impart a multifunctional character to these systems, through the combination of, for example, bioactivity with bactericidal activity.

Statement of Significance

In this review we demonstrate the multifunctional potential of bioactive glasses and related glass-ceramics as biomaterials for orthopaedic and craniofacial/dental applications. Therefore, it considers the evidence that the more recent inorganic modifications to glass and glass-ceramic biomaterials are able to impart antimicrobial properties alongside the more classical bone bonding and osteoconduction. These properties are attracting a special attention nowadays that bacterial infections are an increasing challenge in orthopaedics. We also focus the manuscript on the versatility of these systems as a basis to underpin the development of a new generation of truly multifunctional biomaterials to address pressing clinical needs in orthopaedic, craniofacial and dental surgery.

Contents

* Corresponding authors at: 3B's Research Group – Biomaterials, Biodegradables and Biomimetics, University of Minho, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine, Parque de Ciência e Tecnologia, Zona Industrial da Gandra, 4805-017 Barco, GMR, Portugal (R.A. Pires); Bioengineering and Health Technologies Research Group, School of Clinical Dentistry, University of Sheffield, Claremont Crescent, Sheffield S10 2TA, United Kingdom (P.V. Hatton).

E-mail addresses: rpires@dep.uminho.pt (R.A. Pires), paul.hatton@sheffield.ac.uk (P.V. Hatton).

http://dx.doi.org/10.1016/j.actbio.2017.06.046
1742-7061/

1. Introduction

Multiple degenerative and inflammatory joint and bone diseases affect millions of people worldwide. In fact, in 2007 the Bone and Joint Decade's association predicted that the percentage of people over 50 years of age affected by bone diseases will double by 2020 [1,2]. The huge increase in joint and bone implant surgeries parallels that of medical-device associated infections (MDAIs) [3–7]. Bacterial infections associated with contamination of implanted medical devices are a critical complication that often leads to the failure of the implant with significant impact concerning public health in developed countries [8–10]. Moreover, the management of MDAIs often requires the need for surgical intervention or/and prolonged usage of intravenous or oral antibiotic therapies leading to bone loss and significant morbidity resulting in severe limitations to the patients regarding normal life and well-being [7,11,12].

To summarise, there is now a pressing clinical need to develop innovative biomaterials or device surfaces that provide the dual functionality of both: bone tissue regeneration and inhibition of pathogenic microorganisms. Such a technology would contribute significantly to a surgical solution to the problem of increasing infection rates in the most vulnerable patient groups. Extensive research has led to the development of bioactive glasses (BGs) and related glass-ceramics with excellent biocompatibility and bioactivity [2,13–20]. However, clinical applications have so far been limited to what bone bonding and integration concerns. Their range of uses can be extended significantly by a better understanding of the structural role of each component in the glass, allowing intelligent design of the glass and glass-ceramics and thus introducing multifunctionality.

The purpose of this review is to determine whether or not BGs and related glass-ceramic biomaterials have the potential to provide the first generation of multifunctional biomaterials for the manufacture of advanced medical devices for bone surgery in orthopaedic and dental surgery. In addition, the authors will consider how inorganic modifications to glass and glass-ceramics can be used to introduce greater multifunctionality by enhancing antibacterial properties of these systems in order to create a new generation of versatile, multifunctional materials for biomedical applications.

2. Bioactive glass and glass-ceramic biomaterials

Since 1969, Hench [21] and their co-workers were largely responsible for the development of bioactive glasses (BGs) and study their bone bonding properties. Later, the work in this field was comprehensively reviewed by Rees Rawlings [22] in 1993, which included a description of the key features and properties of BGs and their glass-ceramics derivatives. In this framework, remarkable developments in the glass and glass-ceramic biomaterials for bone and joint repair and replacement have been made in the last 5 decades. It began with the development of a "bioinert" material, only aiming to minimise the scar tissue formation at the surface of the host tissue. Then, after extensive research it evolved to a BG concept, such as Bioglass® 45S5 with extraordinary interfacial bond properties between implants and bone [23]. Later, a third generation of biomaterials that aiming functional properties such as enhanced cell proliferation and osteogenic properties or even more recently the antibacterial activity, either by inorganic modifications and/or by intelligent design of the glass and glass-ceramics [1,16,18,21,24–29]. BGs and in particular the mechanisms responsible for their behaviour in the body have been reviewed extensively by some of the leading figures in the field [30–32]. Their sections on BG science were comprehensive and the subject is therefore only covered briefly here. However, relatively little attention has been paid to the development of antimicrobial glasses, and this is therefore reviewed in far more detail in Section 3, as well as their mechanisms of action in Section 4.

Glass biomaterials can predominantly be fabricated either by the traditional melt-quench or sol-gel processes, where a number of simple compounds are able to mix and solidify as a glass [33–36]. The glass structure is composed of network formers (e.g. Si^{4+}, B^{3+} and P^{3+}), usually silica, which contributes to the network formation containing either intermediate oxides (e.g. Al^{3+}, Zn^{2+}, Mg^{2+}) and/or network modifiers (e.g. Sr^{2+}, Ca^{2+}, Na^{+}). Intermediate oxides, depending on the composition of the glass, may play a network or disrupting function, while network modifiers disrupt the network and produce non-bridging oxygen ions.

A second step of controlled heat treatment is necessary to obtain glass crystallisation forming glass-ceramics [37,38]. This second heat treatment that leads to crystallisation involves two stages, first a nucleation and then a crystal growth stage, which promote the re-arrangement of the glass structures generating a well-ordered and crystalline structure. Crystallisation can also be a key factor for the fabrication of multifunctional glass-ceramics, modulating theirs resorbability, cytotoxicity and bioactivity [20,39–42]. However, not all glasses are able to undergo a controlled heat treatment and form glass-ceramics either because they are already too stable or too unstable and difficult to have a controlled heat treatment. Therefore, glasses and glass-ceramics possess the same building units just arranged in many different patterns, which leads to different final properties. The work in this field was comprehensively revised by Hench et al. [21,43], Rawlings et al. [22] and Julian Jones [30].

Silicate glasses, the most used BGs, are well studied to form of a bone-like hydroxyapatite (HA) layer that is fundamental for a strong interfacial bond between the device and bone [21,23]. The mechanism of bioactivity and bone bonding has been extensively studied *in vitro* (immersion in SBF) and *in vivo*, mainly for 45S5 bioglass® and was discussed elsewhere [44,45]. Thus, the bonding ability of glass and glass-ceramics relies in the degradation process of the biomaterials and subsequent formation of a HA layer on their surface, which mimics the mineral bone composition, bonding firmly with living bone tissue. Briefly the process follows the succeeding steps, (1) dissolution of ions from the glass into the medium, (2) reaction of dissolved Ca^{2+} and $(PO_4)^{3-}$ from the media and consequent precipitation of amorphous calcium phosphate (ACP) layer, (3) the pH unbalance and increased dissolution of ions supports the growth of ACP, and (4) ACP layer incorporates $(OH)^{-}$ and $(CO3)^{2-}$ from the media and crystallises as HA layer. Fig. 1 shows a schematic of the steps involved in the formation of HA, as well as SEM micrographs of HA structures formed on the surface of glass particles after immersion of SBF.

Please cite this article in press as: J.S. Fernandes et al., Multifunctional bioactive glass and glass-ceramic biomaterials with antibacterial properties for repair and regeneration of bone tissue, Acta Biomater. (2017), http://dx.doi.org/10.1016/j.actbio.2017.06.046