Ceramics International 42 (2016) 14313–14325

Contents lists available at ScienceDirect

Ceramics International

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

Review article

Bioactivity and osteoinductivity of glasses and glassceramics and their material determinants

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ARTICLE INFO

Article history:
Received 30 March 2016
Received in revised form
9 May 2016
Accepted 11 June 2016
Available online 14 June 2016

Keywords:
A. Sol-gel processes
D. Glass, Glass-ceramics
E. Biomedical applications
Bioactive properties
Osteoinductive materials

ABSTRACT

Bioactive glasses and glassceramics have been used in both bone repair and tissue engineering applications. An important feature of bioactive glasses and glassceramics, which enables them to be used for desired application, is their biological activity. This activity is manifested by the ability of these materials to form a stable bond with bone tissue (bioactivity) and, in some cases, their ability to promote/initiate osteogenesis (osteoinductivity). A stable material-bone bonding (*i.e.* bioactivity) results from specific material surface reactions leading to hydroxyapatite (HAp) formation on the material surface. Bioactivity of materials is often evaluated *in vitro* and the ability of materials to form HAp-like surface layer is usually studied after immersion/incubation of materials in simulated body fluid (SBF). Biological activity of materials can be also defined as their ability to induce specific cell responses leading to faster regeneration of bone tissue. It may be manifested by materials supporting bone cell attachment, proliferation and differentiation (biocompability/osteconductivity), and/or by materials inducing/promoting the expression of multiple bone-related genes that drive osteogenesis (osteoinductivity). Osteoinductivity is often verified *in vivo* by the materials capability to form bone at etopic (*i.e.* extraskeletal) sites. However, a lot of *in vitro* call-based experiments are now offered to determine osteoinductive properties of biomaterials. This review focuses on the silica-based glasses and glass-ceramics, in particular, the sol-gel derived ones, and summarizes their bioactivity and osteoinductivity as major determinants of their biological activity. We highlight the chemistry of bioglasses and glassceramics that affects not only the formation of a stable implant/bone bonding by HAp layer, but also drives the cell response *in vitro* and *in vivo.*

Contents

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http://dx.doi.org/10.1016/j.ceramint.2016.06.077
0272-8842/

1. Introduction

Material's bioactivity and osteoinductivity as determinants of their biological activity are recently the subjects of extensive research because they relate to the modern regenerative medicine. Bioactivity was defined by Larry Hench as the material property that leads to the formation of a very strong bond between the biomaterial and bone tissues [1,2]. This strong biomaterial-bone binding is the result of bone-like hydroxyapatite (HAp) formation on the biomaterial surface. Mechanisms of surface HAp layer formation include both HAp nucleation on R-OH groups forming/present on the material surface (Si-OH, Ti-OH) and HAp particles surface growth due to calcium and phosphate ion supplies from the biomaterial environment. Bioactive materials are represented primarily by bioactive glasses and glass-ceramics of Na_2O-CaO-P_2O_5-SiO_2 system and calcium phosphates (HAp, TCP and BCP). The concept of osteoinductivity has recently attracted attention as an important material feature that drives osteoprogenitor cells to differentiate into osteoblasts, create the bone tissue and deposit mineralized extracellular matrix [3–5]. Such materials are often assumed "intelligent" as they are able to instruct specific cells in the body to form bone [6]. On principle, osteoinductivity is defined as the capability of a substance or a material to form bone at etopic (*i.e.* extraskeletal) sites and this can be evaluated *in vivo* only [3]. However, cell culture-based experiments and the analyses of cell responses may be sufficient to determine osteoinductive properties of biomaterials.

Currently, both bioactivity and osteoinductivity should be assessed for bone-targeting biomaterial since bioactive materials are expected to stimulate bone formation to faster bone regeneration.

Recently, several review papers summarized biomaterials exhibiting the biological activity and they reviewed the bioactive glasses in terms of their structure, properties, fabrication and apatite formation [7–11]. The primary requirements for bioglasses/glass-ceramics to serve as biomaterials are their good biocompatibility, the ability to form hydroxyapatite layer as a result of contact with simulate body fluid (SBF), the lack of cytotoxicity or immunogenicity, and mechanical properties that prevent any structural failure during handling the implant and normal patient's activity. Moreover, for bone engineering and scaffold production, bioglass should display controllable three-dimensional structure and interconnected porosity for cell proliferation and vascularization. Several authors discussed various chemical compositions of bioglasses, *e.g.* silicate, borate/borosilicate and phosphate [7–9]. They indicate that the major challenge is to develop bioglasses that are both mechanically strong and biocompatible. There is though the antagonism between the mechanical properties and bioactivity of a material. Attention has also been given to the development of metallic glasses as well as the modification of glass compositions by addition of specific trace elements to obtain desired properties.

Cormack and Tilocca addressed the relationship between glasses' bioactivity and their structure; in particularly – the identification of the molecular basis of biological activity [8]. The characterization of biomaterial structure and its interface with the biological environment is a key issue. Unfortunately, the standard structural methods (*e.g.* diffraction) can't determine the key structural material features and their correlation with the observed biological activity. Recent advances in experimental techniques (*e.g.* high-energy diffraction) [12,13], multi-nuclear resonance (NMR) and extended X-ray fine structure (EXAFS) [14] have led to substantial advances in the structural characterization of bioactive glass and ceramics. The results of this research allow us to understand better the correlation between structure and bioactivity at the atomic or molecular level.

A significant determinant of materials' biological activity is its osteoinductivity, *e.g.* ability to induce bone formation when implanted at heterotopic sites. Barradas et al. reviewed the osteoinductive biomaterials in terms of their properties, experimental models and biological mechanism of osteoinductivity [10]. The authors emphasize that despite a variety of well characterized osteoinductive biomaterials, there is yet poor understanding of the biological mechanisms of bone formation induced by biomaterials. They further indicate that chemical composition, macro-structural properties, and surface structure of biomaterials have significant impact on their osteoinductivity. The authors indicate that the knowledge of material properties relevant to osteoinduction has tremendously increased in the past decade, despite the limitations of available models to test osteoinductivity. They further emphasize, that all studies performed so far with osteoinductive biomaterials have been performed in preclinical animal models. In their opinion, although these models resemble the clinical situation as closely as possible, only clinical trials can verify the relevance of materials osteoinductivity to human patients.

Currently, a lot of attention is paid to materials useful for scaffold-based tissue engineering. The overall purpose of this strategy is to provide a temporary support structure of the desired shape and dimension for cells forming a new tissue. Rahaman and Day provided the broad overview of recent advances in the development and use of bioactive glasses for tissue engineering [15]. Despite the inherent brittleness, bioglasses display several unique properties and they can be used as materials for scaffold production. Especially new borate-based bioactive glasses have the ability to enhance bone formation when compared to silicate bioactive glass. The former also display controllable degradation rate adapted to the rate of new bone formation. Bioglasses can be modified by special additions of Cu, Zn and/or Sr that benefit healthy bone growth [9]. There is also interest in the gel-derived bioglasses for the production of scaffolds with hierarchical pore structure *i.e.* scaffolds composed of interconnected macropores and nanopores inherent to sol-gel process. This hierarchical pore structure of the scaffold is beneficial for the material-cells interaction as it mimics the hierarchical structure of living tissue [16,17].