Bioactive glass: antibacterial efficacy and dose dependent in vitro modulation of dendritic cells

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Introduction
Among emerging biomaterials, bioactive glasses (BGs) are widely explored for various applications in tissue engineering. Key advantages of bioactive glasses include their ability to dissolve and release ions when immersed in an aqueous environment, as well as the formation of an apatite surface layer on the glass during dissolution. Due to the lower chemical durability of borate glasses and their ability to transform rapidly to hydroxyapatite, an increasing amount of research has started to focus on the use of borate bioactive glasses. To further improve the performance of bioactive glasses, it is possible to introduce therapeutic ions with specific effects, e.g. copper and zinc to avoid infections. However, the effects of BG on immune cells and specifically on DCs, which are the most potent antigen presenting cells of the immune system, have to be assessed as a novel biocompatibility criteria for biomaterials, since with the increased application possibilities of BGs, modulation of the immune system may induce potential complications and undesired side effects. However, the effects of BG exposure on specific immune cells are not well understood.
Methods
Based on the well-known 13-93 silicate glass, borate glasses, where all the SiO2 was replaced by B2O3, and Cu/Zn-doped borate bioactive glasses were produced by melt-quenching and characterized using FTIR, SEM/EDX as well as XRD. Then, to study the dissolution behavior, bioactive glass particles (300-500 µm) were immersed in different relevant solutions and ICP measurements were conducted to confirm the release of the different ions. We investigated the antibacterial properties of these borate BGs by an agar diffusion test. Cell culture media, conditioned with release products of bioactive glasses, was then used to incubate murine dendritic cells. After incubation of DC with different concentrations of BGs the effect of the different ions on the immune cells was examined regarding their cell viability, their phenotype (by FACS) and their T cell stimulatory properties (by MLR) measurements.
Results and Discussion
Four different borate glasses doped with Copper or/and Zinc were successfully produced. Depending on the composition and the release conditions (static/dynamic, dissolution media), the glasses dissolve and release therapeutic active ions in relevant amounts. However, the release of zinc from Zn-doped borate glasses could not be measured; instead the zinc was incorporated in the formation of an apatite layer. During the release, a similar increase of pH was observed for all tested glasses. By an agar diffusion tests, the antibacterial effect depending on the compositions of the borate BGs could be proven. A concentration dependent effect on the viability of dendritic cells, by the released ions, was observed, whereby the magnitude of viability was different between the used ion-doped glasses. Furthermore, surface expression of DC-specific activation markers, such as major histocompatibility complex (MHC)-II, CD86, CD80 and CD25 were modulated. In addition also DC mediated T-cell proliferation was remarkably diminished by high dose B3-Cu and B3-Cu-Zn treatment. Interestingly, the release of inflammatory cytokines was increased after incubation with B3 and B3-Zn compared to mock-treated DCs. Considering the essential role of DCs in the modulation and regulation of immune responses, these findings provide first evidence on phenotypic and functional consequences regarding the exposure of BGs in vitro.
Conclusion
From this study, we concluded that BGs, especially doped with copper and/or zinc, represent a powerful tool to avoid bacterial growth. Furthermore, BGs possess interesting immune-modulatory properties on DCs, which should be further explored to specifically modulate the immune system, (i) in case of autoimmunity and transplantation as well as (ii) in case of infections and neoplastic disorders.

Keywords : Bioactive glass, antibacterial efficacy, dendritic cells, surface molecules, mixed lymphocyte reaction, cytokines
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