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REVIEW ARTICLE

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Biocompatibility of alumina-based biomaterials–A review

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Abstract

In today's medicine world, alumina-based biomaterials owing to their excellent biomechanical, and biocompatibility properties play a key role in biomedical engineering. However, the literature still suffers from not having a valid database regarding the protein adsorption and subsequently cell responses to these surfaces. Proteins by adsorption on biomaterials surfaces start interpreting the construction and also arranging the biomaterials surfaces into a biological language. Hence, the main concentration of this review is on the protein adsorption and subsequently cell responses to alumina's surface, which has a wide range biomedical applications, especially in dentistry and orthopedic applications. In the presented review article, the general principles of foreign body response mechanisms, and also the role of adsorbed proteins as key players in starting interactions between cells and alumina-based biomaterials will be discussed in detail. In addition, the essential physicochemical, and mechanical properties of alumina surfaces which significantly impact on proteins and cells responses as well as the recent studies that have focused on the biocompatibility of alumina will be given. An in depth understanding of how the immune system interacts with the surface of alumina could prove the pivotal importance of the biocompatibility of alumina on its success in tissue engineering after implantation in body.

KEYWORDS

alumina, biocompatibility, cell responses, protein adsorption

1 | INTRODUCTION

It has been generally accepted that all used biomaterials provoke the immunological responses of body, known as foreign body responses (FBRs), which commonly cause limited in vivo functionality and durability of the used biomaterials (Morais, Papadimitrakopoulos, & Burgess, 2010; Trindade, Albrektsson, Tengvall, & Wennerberg, 2016). However, this phenomenon, in other hand, is an essential response for eradicating cellular debris and preventing the progression of infection (Gethin, 2012). In addition, it has been broadly shown that inhibiting FBRs such as infiltration of macrophages could cause severe tissue destruction (Butterfield, Best, & Merrick, 2006). Therefore, in designing each biomaterial carefully considering the details of immune system responses to the implanted material is essential. During implanting biomaterials in the body, the adsorbed proteins, besides macrophages and dendritic cells (DCs) are the key players in starting communication between cells and the biomaterials (Kou & Babensee, 2011). It has been acknowledged that the rapid adsorption of proteins on the biomaterial's surface starts interpreting the substitute, which their functions are highly dependent on the physical and chemical properties of both the biomaterials surface and proteins properties (Lord, Foss, & Besenbacher, 2010; Walkey, Olsen, Guo, Emili, & Chan, 2012).

In the recent years, ceramics owing to their excellent biomechanical and biocompatibility behaviors have gained a potential attention among orthopedic and dentistry scientists and surgeons (Montazerian & Dutra Zanotto, 2016; Nezafati, Moztarzadeh, Hesaraki, & Mozafari, 2011; Yazdanpanah et al., 2012). Bioceramics can be mainly divided into bioinert, bioactive, and bioresorbable ceramics (Anu & Gayatri, 2016). Bioinert ceramics including alumina

and zirconia have a great chemical stability with high mechanical properties, which after contacting with the bone tissue demonstrate "contact osteogenesis" pattern (Banijamali, Yekta, & Aghaei, 2013; Kurtz et al., 2014; Nazari & Mozafari, 2012; Piconi, Condo, & Kosmač, 2014). Alumina, also called aluminum oxide, has been for a long time used as a favorable candidate in orthopedic joint prostheses due to its great compressive resistance and chemically bioinert properties (Aw & Losic, 2016; Webster, Siegel, & Bizios, 1999). In the 1970s, alumina was presented for the first time; however, its primary clinical trials faced with a fracture rate as high as 13%, which was owing to the fact that this material alone could not be used in density applications (Al-Sanabani, Madfa, & Al-Qudaimi, 2014; Willmann, 2000). The next treated generation of alumina was presented in a decade later, by designing alumina with upper density and lesser grains, which caused in decreasing its fracture rate to fewer than 5% (Armstrong, 2001; Willmann et al., 1998). In these days, a third generation of alumina with greater purity, full density, and improved microstructure is accessible for clinical usage (Qin, Lei, Peng, & Wu, 2015; Takatori, Kadoura, Matsuo, Arakawa, & Tani, 2016). In this generation, the average grain size reduced from 3.2 to 1.8 μm, whereas bending strength in its clinical grade is improved to 650 MPa (Poitout, 2004). As alumina has gained an important place in designing dental and orthopedic biomaterials, deeply studying its biocompatibility has a great importance which is the main concentration of this review. In the presented article, the general principles of FBRs mechanism, and also the role of adsorbed proteins as key players in starting interactions between cells and alumina will be discussed in detail. In addition, the essential physicochemical properties of alumina surface which significantly impact on proteins and cells responses will be given. The discussion will then highlight the recent studies, which deeply investigate the cellular and molecular interactions with alumina surfaces. In addition, a brief review of the current applications of this bioceramic will be discussed.

2 | FOREIGN BODY RESPONSES TO BIOMATERIALS

After implanting a biomaterial into the body some immunological reactions start happening including injury, interactions between blood and material, creation of a provisional matrix, acute and chronic inflammation, granulation tissue formation, FBRs, and ultimately fibrous capsule formation (Scatena, Eaton, Jackson, Lund, & Giachelli, 2017; Trindade, Albrektsson, Tengvall, & Wennerberg, 2016; Vishwakarma et al., 2016). After implanting the biomaterial, it first start interacting with blood through the proteins adsorption and also provisional matrix formation on and around its surface (Silva-Bermudez & Rodil, 2013; Wei et al., 2014). The provisional matrix is mainly considered as the primary thrombus/blood clot at the boundary between tissue and biomaterial, which provokes structural, biochemical, and cellular mechanisms to start wound healing and FBRs processes (Anderson, Rodriguez, & Chang, 2008; Luttikhuizen, Harmsen, & Luyn, 2006). This matrix in the presence of bioactive molecules such as proinflammatory factors starts activating and preventing some mechanisms, which finally consequence in occurring the inflammatory responses. Besides, the damage to vascularized connective tissue more provokes the inflammatory responses and also thrombus development by stimulating the coagulation, complement, fibrinolytic, and kinin-generating systems, as well as platelets (Anderson & Jiang, 2017). These protein-related processes could be related to the protein adsorption mechanisms which will be discussed later in detail. After the primary interactions between blood and biomaterial and development of provisional matrix, acute and chronic inflammation occur in a chronological cascade (Anderson, 2015; Anderson & Jiang, 2017). Stimulated platelets and endothelial cells release chemoattractants, which consequences in activating neutrophils and acute inflammation phase on the implanted site (Selders, Fetz, Radic, & Bowlin, 2017; Ye, Harmsen, van Luyn, & Bank, 2010). Neutrophils through phagocytosis and degranulation mechanisms, challenge to eradicate the biomaterial. In addition to neutrophils, monocytes also reply to the platelet-derived chemoattractants placed on the implantation site and make interactions with fibrinogen, which finally causing in their activation (MacEwan, Brodbeck, Matsuda, & Anderson, 2005; Ward, 2008). These monocytes differentiate into macrophages type 1 at the damage area, which have the talent to release proinflammatory cytokines and chemokines (Scatena, Eaton, Jackson, Lund, & Giachelli et al., 2017; Sheikh, Brooks, Barzilay, Fine, & Glogauer, 2015). The macrophages similar to neutrophils challenge to get rid of the biomaterial, before experiencing "frustrated" phagocytosis, eventually causing further proinflammatory cytokines activation (Scatena et al., 2017). The activated macrophages finally shift to macrophages type 2 which are recognized by decreased degradative capacity, anti-inflammatory cytokines activation, and starting tissue remodeling process (Vasconcelos et al., 2015). Ultimately, in an effort to develop the phagocytic behavior of macrophages, the formation of foreign body giant cells (FBGCs) on the biomaterials surface starts, which is mainly initiated via the stimulation of mast cells, basophils, and T helper (Th) cells (Chung, Maestas, Housseau & Elisseeff, 2017; Galli, Borregaard, & Wynn, 2011; Gordon & Martinez, 2010). These cells ultimately release interleukin (IL)-4 and IL-13 which are the key players in creating macrophage fusion (Brodbeck et al., 2002; McNally & Anderson, 2015). Some studies have shown that mast cells have a great role in activating pro- and anti-inflammatory, angiogenic, and profibrotic factors (Yang, Jao, McNally, & Anderson, 2014). In addition, the presence of T cells at the implanted site and increasing FBGCs through them have been demonstrated; however, their exact mechanism of action in FBRs has not yet precisely detected (Anderson et al., 2008). The determined action of immune cells consequences in passageways guided at separating the biomaterial from the host tissue by fibrotic encapsulation via profibrogenic factors activation such as platelet-derived growth factor, vascular endothelial growth factor, and transforming growth factor beta 1 (Anderson et al., 2008; Norton, Koschwanez, Wisniewski, Klitzman, & Reichert, 2007). In fact, it has been shown that the stimulated

fibroblasts accumulate collagen at the implanted site with the aim of repairing the damaged tissue, nevertheless their unnecessary release consequences in fibrosis (Ward, 2008). If no infection is existent, subsequent to fibrotic encapsulation, the inflammatory reactions eventually will be removed and the implant function leads to tissue regeneration.

3 | PROTEIN ADSORPTION, THE KEY MEDIATOR OF INTERACTION BETWEEN FOREIGN MATERIALS AND CELLS

Before addressing the physicochemical properties of alumina which highly impact on the adsorption of proteins, the basic principles of protein adsorption on the biomaterial's surface should be described in detail here. It has been shown that the bulk concentration of protein in solution highly impacts on the protein adsorption on a biomaterial's surface, which means that upper amounts of a protein in a liquid solution nearby the implanted site causes to further adsorbing protein on the material's surface. Although, this event becomes further intricate when more than one kind of protein is existent in solution (Schmidt, Waldeck, & Kao, 2009). In addition, the movement of proteins in the solution, which is mainly directed by the diffusion rate, is another significant factor that should be taken into consideration. The rate of diffusion also is controlled predominantly through the size of the protein, as smaller and quicker proteins have a tendency to adsorb on the biomaterial's surface before bigger, slower moving ones (Kastantin, Langdon, & Schwartz, 2014; Young, Pitt, & Cooper, 1988). In addition, the affinity of a protein to the substrate's surface, which mentions how probable the protein will adsorb and how powerfully it will stick on the material's surface, is another parameter that plays a key role in this phenomenon (Klapper et al., 2015; Treuel, Docter, Maskos, & Stauber, 2015). It has been demonstrated that proteins with higher affinity capability are further expected to adsorb on the biomaterial's surface. The adsorbed proteins form some intramolecular bonds, such as hydrophobic interactions, ionic bonds, and charge transfers, on biomaterial's surface; so that the proteins with greater affinity present sturdier further connections in comparison with proteins with lesser affinity (Sakata, Inoue, & Ishihara, 2015; Schmidt et al., 2009). In overall, by considering the effects of protein's concentration, rate of diffusion, and affinity on their adsorption to biomaterial's surface, it is not surprising that in a complex solution, proteins are in a high rivalry for adsorbing to the surface. In addition, by passing the time through Vroman effect process, the adsorbed proteins on the biomaterial's surface interchange with other ones (Choi, Yang, & Chae, 2008; Kim, 2016; Young et al., 1988). Some studies have confirmed the fact that the connections between the adsorbed proteins and biomaterial's surface are not totally static and they could be fragmented and renewed erratically. Desorption phenomenon is the opposite of adsorption, which during that molecules formerly connected to the biomaterials surface completely disconnect and reappearance to the bulk phase. When interactions between the proteins and surface are sporadically broken, other proteins could inhabit the binding positions. It has been shown that the former protein could be completely detached from the surface only under the circumstances that all of its links with the surface come to be engaged by the new protein. This phenomenon confirmed the fact that the adsorbed protein layer is a dynamic layer on the biomaterial's surface that its composition varies over time (Roach, Farrar, & Perry, 2005; Schmidt et al., 2009). As it can be seen in Figure 1, the Vroman effect on the hydrophobic and hydrophilic biomaterial's surfaces, which at first the low-molecular weight proteins adsorb and then high-molecular weight proteins come far along on the surface. In addition, the schematic represents that if the high-molecular weight proteins adsorbs earlier than low-molecular ones no angle change happens (Choi et al., 2008). In addition, because amino acids are the main components of proteins, their properties impact on the adsorption properties of proteins. Amino acids might be charged, further polar and hydrophilic which consequently attract to the polar water molecules. These kinds of amino acids tend to be on the external side of a protein and consequently could interact favorably with the polar areas of the biomaterial's surface (Hoefling, Iori, Corni, & Gottschalk, 2010; Schmidt et al., 2009). In addition, proteins have a tendency to adsorb willingly nearby their isoelectric point, which is hypothesized to be owing to decreased electrostatic repulsion with other proteins on the surface of substrate (Lin, Chen, Chen, & Yamamoto, 2001; Rezwan, Meier, & Gauckler, 2005). It has been demonstrated that hydrophilic amino acids have a tendency to bond with hydrophilic surface sites. In addition, when proteins are in solution, hydrophobic residues have a tendency to stay within the three-dimensional (3D) network; nevertheless, they might become uncovered throughout unfolding, whereas the protein makes connections with the surface of substrate (Schmidt et al., 2009; Young et al., 1988). Moreover, the shapes and structures of proteins might also impact on their adsorption. It has been reported that soft proteins with lesser than average thermodynamic stability, fewer interior bonding, and/or crosslinks are more talent to adsorb than hard proteins, which is because of easier unfolding of protein molecules through soft proteins (Ratner, Hoffman, Schoen, & Lemons, 2004). Besides, particular binding positions in the structure of some proteins could only be uncovered when the proteins are in particular conformations (Roach et al., 2005; Schmidt et al., 2009).

4 | THE PHYSICOCHEMICAL SURFACE PROPERTIES OF ALUMINA

It is a well-known fact that physicochemical properties of ceramic materials play key roles in the development of employing them in biomedical applications. It has been acknowledged that alumina has high hardness and abrasion resistance properties (Banijamali, Yekta, & Aghaei, 2012; Liu, Fischer, & Dent, 2003). The surface energy and smoothness of alumina help in having exceptional wear and friction properties (Banijamali & Ebadzadeh, 2016; Portilla & Halik, 2014). It has been shown that there is only one thermodynamically stable

phase, known as alumina, which its mechanical properties and chemical stability make it a promising candidate for skeletal regeneration (Thamaraiselvi & Rajeswari, 2004). It has been shown that in many metastable phases, aluminum oxide could be obtained which conclusively converts into alpha-alumina after heating in the range of 1050–1200°C, depending on the crystal characteristics of the metastable originators (Piconi et al., 2014). In the environment, alumina presents as corundum, or emery if comprises impurities. Alumina presents in the gemstones with a color reliant on the doping components (Railroad; Banijamali, Eftekhari Yekta, Rezaie, & Marghussian, 2008). In addition, for achieving alumina powders with high purity some minerals such as bauxite and native corundum are used (Piconi et al., 2014). The Bayer process is the most common method for refining bauxite to produce alumina (Den Hond, Hiralal, & Rijkeboer, 2016). It has been demonstrated that the exceptional high mechanical properties and also low electric and thermal conductivity

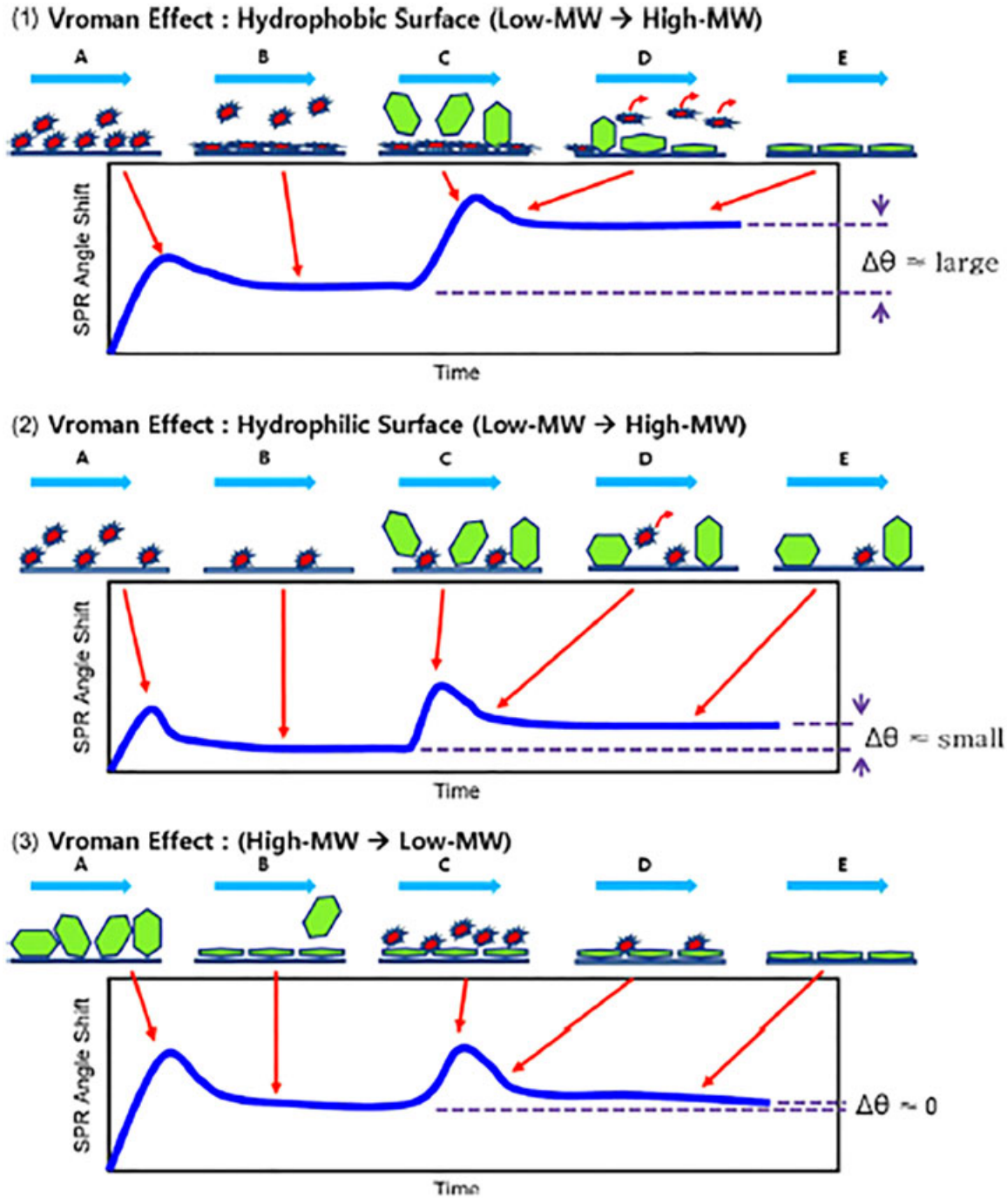

FIGURE 1 A representation of SPR profiles and the Vroman effect (a) on the hydrophobic and (b) hydrophilic biomaterials surfaces when first the low-molecular weight proteins adsorb and then high-molecular weight proteins come far along on the surface. (c) The third schematic represents that if the high-molecular weight proteins adsorbs earlier than low-molecular ones no angle change happens. Reproduced from (Choi, Yang, & Chae, 2008) with the permission from Elsevier. SPR: surface plasmon resonance [Color figure can be viewed at wileyonlinelibrary.com]

of alumina are owing to the robust ionic and covalent chemical bonds between Al^{3+} and O^{2-} (Desai, Wu, Rohlfing, & Wang, 1997). Several of studies have shown that based on the thermodynamic principles, α-alumina is the most stable aluminum oxide in comparison with transient and metastable types (Mahamulkar et al., 2018; Sharma, 2016). Alpha-alumina has a crystal network which its oxygen ions form a close-packed hexagonal arrangement. In its framework, each Al^{3+} is encircled by O^{2-} ions, which cause in shaping two ordered triangles on both sides, deviate by 180 degrees and lying on parallel planes. In other hand, it has been reported that when metal oxides such as Al_2O_3 are uncovered to water or air, their surfaces start making interactions with water to form –OH groups on the surfaces, which further assist them in making more interactions with the adsorbed proteins. However, the high stiffness of alumina leads to high elastic incompatibility between the biological tissue and the implanted alumina (Piconi et al., 2014). In addition, due to the need of biomaterials with high mechanical properties for dentistry and orthopedic applications, in today's medicine world alumina has gained great attention among biomedical scientists and surgeons (Al-Sanabani et al., 2014; Kurtz et al., 2014). Interestingly, an increase in its bending strength is an outstanding property which can be useful in orthopedic applications (Zhang, Yang, Li, & Ren, 2015). The mechanical properties of alumina are mainly governed by its processing criteria such as the kinds of forerunners, powder processing, sintering, and quality control (Kuntz, Masson, & Pandorf, 2009). However, despite the progress that currently presented in its processing, this bioceramic is still a brittle material, and the fracture energy could not be dissipated via yielding at the crack tip so that alumina constituents could be unsuccessful in showing any flexible distortion (Wang, Guo, Fu, & Jia, 2018). Accordingly, its mechanical behaviors are mainly reliant on the existence of flaws which act as stress concentrators (Piconi et al., 2014). It has been shown that bending behavior of alumina has an adverse exponential reliance on porosity. In addition, the quantity and interconnection of pores are two other key factors which have an influence on fatigue behavior of alumina (Piconi et al., 2014). Some studies have demonstrated that open porosity fraction has a particularly sturdy effect on the long-term mechanical behavior of alumina in the body (Sciamanna, Nait-Ali, & Gonon, 2015; Tallon, Chuanuwatanakul, Dunstan, & Franks, 2016). In addition, the development of subcritical physical defects, known as subcritical crack growth by water molecules, is another key factor which leads to reducing the mechanical strength of alumina (Wang et al.,). The difficulty of strength degradation in alumina has been solved after presenting high-purity powders which contain much less amounts of calcia, alkali, and silica impurities. These impurities have a key role in the mechanical stability of alumina (Piconi et al., 2014). It has been reported that CaO interactions with the water molecules are in charge for strength degradation of alumina; however, in other hand, silica improved its fatigue fracture by hampering densification and encouraging grain development in the period of sintering (Krainess & Knapp, 1978; Sinharoy, Levenson, & Day, 1979). In addition, silica and alkalis could at grain frontiers separate, which consequently their dissolution in the body fluids could cause increasing the fatigue fracture (Shirazi et al., 2014). Furthermore, the MgO concentration has to be controlled to decrease the risk of harmful unnecessary development of Al_3MgO_4 spinel. Recently a several of formulations and processing techniques have been presented to enhance the fracture toughness and other mechanical properties of alumina, which are based on two basic approaches including microstructural refinement, and flaw-tolerant approach (Piconi et al., 2014).

5 | PROTEIN ADSORPTION AND CELL RESPONSES TO ALUMINA SURFACE PROPERTIES

A several of investigations have been carried out on the interactions between alumina with cellular and molecular components of body (Akasaka et al., 2012; Ferraz, Hong, Santin, & Karlsson, 2010, 2008). However, in the recent decades, this ceramic has gained an outstanding place in skeletal regeneration, its biocompatibility and biological responses are still being testing. The in vitro biocompatibility tests on alumina have been investigated with various cell lines such fibroblasts and osteoblasts, and immunological cells with various cell environments. In addition, the examined alumina could be in direct or indirect contact with the cultured cells (Piconi et al., 2014). It has been reported that in using the indirect method a significant biological reactivity to alumina could not be detected. However, the outcomes of direct cell contact to alumina powders indicated that its toxicity is highly dependent on its concentration (Piconi et al., 2014). It can also have various physical formations such as powders, granules, and dense or porous bars or pellets structures, which can affect cellular and molecular responses (Ramavath, Papitha, Ramesh, Babu, & Johnson, 2014). It should be noted that if the physical properties of a biomaterial during its in vivo performance change, the biological responses to it will alter, which regarding alumina, this fact has a major importance because of the clinically related wear particles. By considering this fact, it would be not surprising that the alumina nanoparticles are further expected to cause inflammatory responses than monolithic alumina, which consequently cause aseptic loosening (Hatton et al., 2002; Sun et al., 2003). Some studies have revealed that surface contact area plays a key role in cell responses to biomaterial's surface. In addition, it has been reported that the particle size of alumina could have an influence on its biocompatibility, particularly when using nanoparticles owing to the high surface/volume ratio of them (Ferraz et al., 2010; Yagil-Kelmer et al., 2004). However, the association between its particle size and cellular responses has not been totally elucidated. Ferazz et al. (2010) have recently studied the effects of alumina nanotopography on monocyte/macrophage responses. They have cultured the human mononuclear cells on alumina substrates with pore diameters in the range of 20–200 nm and then the cell adhesion, viability, morphology, IL-1β, and tumor necrosis factor-α (TNF- α) release were assessed. Their results indicated a significant dissimilarity in cell responses, and cytokine release reliant on the size of

porosity. Based on the results, by increasing the size of porosity few but extremely initiated cells were detected on the surface of alumina. However, moderately greater number of cells were detected on the alumina surfaces with 20 nm porous structures. In addition, the IL-1β and TNF- α secretions decreased on these surfaces. In overall, the authors demonstrated that nanotopography could regulate the inflammatory reactions to alumina surfaces. Some studies have claimed that two main mechanisms can be involved in determining how macrophages response to biomaterials surface topography. (1) biomaterial nanotopography can have an impact on the adsorption of proteins, regarding their concentration, conformational, orientation, and affinity properties (Sutherland, Broberg, Nygren, & Kasemo, 2001). (2) Surface topography could have an influence on the distribution, proliferation, and differentiation of cells (Curtis & Wilkinson, 1997). Some studies have proved that cells have the ability to recognize structures in nano scale and thus response to these surfaces by altering their cytoskeleton arrangement via membrane receptors, which finally result in changing cell phenotype and functions (Kriparamanan, Aswath, Zhou, Tang, & Nguyen, 2006). In addition, Ferazz and his coworkers in another study revealed that upper degree of plasma proteins including IgM, IgG, C3, and C1q adsorbed on alumina surfaces with 200 nm topography in comparison with the 20 nm pore surfaces (Ferraz et al., 2010, 2008). Furthermore, as few research has been done on assessing the mesenchymal stem cells (MSCs) responses on nanoporous alumina, Song et al. (2013) have currently investigated the responses of these cells on both smooth and nanoporous alumina scaffolds. In this study, alumina scaffolds with 20 and 100 nm pore sizes were prepared and their effects on cell responses evaluated by proliferation, morphology, expression of integrin β1 (the receptor that intermediates the interactions between cells and the nearby environment and is a key factor in cell signaling), and osteogenic differentiation. The MTT test demonstrated reducing cell viability by increasing the porous size of alumina scaffolds. In addition, exceptionally extended cells with noticeable cell membrane protrusions were detected in the cells cultured on alumina with 100 nm pore size. Furthermore, an increase in the integrin β1 expression in MSCs cultured on porous alumina was detected, which indicated that porous structures are further suitable than smooth ones. Among alumina porous structures, upper concentrations of osteoblastic differentiation markers were found in MSCs cultured on alumina with 100 nm pores. The authors concluded that cells reactions to biomaterials are highly dependent on their porous network and also the pore sizes. In addition, in another investigation they have examined the specific MG63 responses to nanoporous alumina surfaces by considering cell viability, expression of integrin β1, ALP activity, and variations of cell morphology. Their outcomes revealed that by increasing the pore size of alumina the cell viability and expression of integrin β1 reduced; however, cell morphology stretched, and the ALP activity and mineralization improved. The authors revealed that surface characteristics of alumina have noticeably effects on MG63 osteoblast-like cells responses (Song et al., 2013). However, it has been exhibited that epithelial cells preferred to growth on alumina surfaces with 30 nm scale size in comparison with greater pore sizes (Chung, Son, & Min, 2010). Mestres et al. (2016) have investigated the biocompatibility of glass slides and silicon nanoparticles with various sizes including 20 and 310 nm that were coated with alumina by using atomic layer deposition. Human dermal fibroblasts and osteoblasts well-proliferate on the alumina surfaces of nanoparticles. In addition, the macrophages released reactive oxygen species (ROS; as a signal of acute inflammation) only when interacted with nanoparticles at 1000 μg/ml concentration, which nanoparticles with 20 nm provoked a greater release of ROS than the 310 nm nanoparticles. The authors concluded that alumina coatings do not negatively provoke immunological cells. Moreover, for more proving the role of nano topography in alumina cell responses, Mussano and his colleages (Mussano et al., 2018) have currently synthetized two alumina surfaces with dissimilar pore diameters in the range of 65–89 nm by the implementation of oxidative anodization. Their results exhibited that both the alumina surfaces encouraged more preosteoblastic MC3T3-E1 cell adhesion and viability. In addition, they demonstrated that the quantity of focal adhesions per surface unit, meaningfully improved on both the alumina surfaces containing nanoporous in comparison with control condition. Therefore, the authors suggested that the greater amount of adherent and viable cells by nano topography approach were related with a substantial increase in focal adhesion concentration. Fohlerova and Mozalev (2017) have more recently designed self-organized arrays of composite oxide nano mounds via anodizing Al/Ta bilayers, which were scattered on surfaces to even cover the tiniest sizes with the aim of fabricating innovative alumina-doped Ta_2O_5 films. The responses of MG-63 cells to the nanostructured surfaces varies in the existence and lack of serum proteins. For the first time, the authors exhibited that the cells have the ability to considerately distinguish the features of surface of biomaterials without preadsorbed proteins. They showed that in the deficiency of serum proteins, the adhesion and growth of MG-63 cells are significantly improved on nanoarrays with 20 and 40 nm sizes, however in complete medium they showed better initial adhesion nanoarrays with 10 nm. In addition, a significant increase in the ALP activity was detected on the 40 nm nanoarray.

Some studies have revealed that adding particular functional groups on the alumina surface could help in improving cellular and molecular responses to it. Bertazzo et al. (Bertazzo, Zambuzzi, Da Silva, Ferreira, & Bertran, 2009) have chemically modified the surface of alumina with low-molecular weight dicarboxylic acid, which formed carboxyl groups on alumina surface and then investigated the MC3T3-E1 cellular responses to it. Their outcomes indicated that the carboxyl groups had the ability to complex with Ca2 þ on the alumina surface, and consequently developing sites of precipitation for calcium phosphates that make alumina biocompatible. In addition, Meder et al. (2012) have examined the effects of functionalization the surface of alumina particles with NH_2, COOH, SO_3H, and PO_3H_2 functional groups on the adsorption of bovine serum albumin (BSA), lysozyme (LSZ), and trypsin (TRY). The authors demonstrated that the functional group types and the predictable electrostatic forces related to investigational conditions had a meaningful effect on

protein responses to alumina surface. These authors in another study (Meder, Brandes, Treccani, & Rezwan, 2013) have more focused on the effects of SO_3H functional group on the protein adsorption to the surface of colloidal alumina particles. As it can be seen in Figure 2, their result indicated that the adsorption of BSA, LSZ, and TRY proteins and inherent protein amino acid composition were highly affected by the amount of SO_3H functional group on the alumina surface. The authors again suggested that by engineering alumina surfaces with some functional groups a better protein–particle interactions could be achieved.

Loosening has been considered as the most commonly detected long-term difficulty of alumina implants in the circumstances of joint replacement, which leads to FBRs of the body contrary to the wear alumina particles (Thamaraiselvi & Rajeswari, 2004). Some studies have proposed that the wear property of bioceramics consequences in releasing nanoparticles in vivo which provide a dissimilar biological behavior from their origin formation. Gibbons and his team (Gibbons et al., 2015) have recently studied the adsorption of human plasma proteins on alumina nanoparticles and monolithic substrates which were the illustrative of both wear particles and bioceramic constituents. The results presented an obvious dissimilarity between the adsorb proteins on nanosurfaces in comparison with macro-surfaces, which some studies have explained some potential reasons for it (Lynch & Dawson, 2008, 2006). In addition, its dissimilar physicochemical properties such as reactive surface, chemical arrangement, and the concentration of impurities could control the biological responses. Akasaka et al. (2012) have examined human serum albumin (HSA) adsorption on the alumina surfaces by using the surface plasmon resonance (SPR) microscopy. The results obtained from SPR revealed that the HSA protein had a quick adsorption behavior which was desorbed after etching its layer. The authors proposed that this protein could not adsorbed for a long time on the surface of alumina. Besides, it has been reported that osseointegration of a titanium implant is a critical issue in skeletal implants over time, which is mainly related with their topography. Smargiassi et al. (2017) have suggested a novel method for improving the bone integration of titanium implants by shooting different alumina particles in contrast to the titanium scaffolds. The authors used two the MLO-Y4 (murine osteocytes) and 293 (human fibroblasts) cell lines to investigate the effects of alumina particles on titanium surfaces. They showed that the surface of treated implants with alumina had a rough morphology, with better cell adhesion and distribution. Based on the achieved outcomes, they suggested that the treated titanium implants with alumina could be promising candidates for dental regeneration.

Few studies have been done with the focus on evaluating its biocompatibility in vivo. Some studies have implanted alumina bioceramic with various physical shapes (such as powders, granules, and dense formations) in different animal models with the aim of studying the protein and cell responses to it (Roualdes et al., 2010; Rousseau, Le, Goutallier, & Van, 2004). It has been demonstrated that in soft tissue, by passing the time, a connective tissue layer is converted into a fibrous membrane nearby the dense alumina implants. However, in hard tissue like bone, a tinny proteoglycan layer is shaped at the bone-biomaterial border which is a representative for bioinert ceramics. In addition, applying stresses during load-bearing conditions increases the bone apposition at the alumina–tissue interface. Some studies have reported fewer granulocytes and lymphocytes after injecting alumina particles in soft tissues in comparison to metals or polyethylene particles (Christel et al., 1988). Because nanoporous alumina biocapsules have been recently presented as successful immune-isolation devices, which could improve the functions of encapsulated β cells, La Flamme et al. (2007) have recently evaluated the biocompatibility of them with the body. The authors examined alumina cytotoxicity, and its ability to stimulate complement and inflammation. In addition, the effects of modifying alumina capsule surfaces with poly(ethylene glycol) (PEG) on the tissue response were also considered. As it can be seen in Figure 3, their outcomes demonstrated that the nanoporous alumina biocapsules are nontoxic and consequently do not meaningfully activate complement activation. Additionally, the in vivo implantation of the alumina capsules in the peritoneal cavity of rats provoked a temporary inflammatory response, which adding PEG in their surfaces helped in lessening these host responses to the capsules.

6 | NOVEL STRATEGIES FOR SURFACE FUNCTIONALIZATION OF ALUMINA

Some studies have shown that the protein and cell responses to alumina surfaces can be highly improved by treating its surface chemistry. Alumina surface functionalization with various functional biomolecules improves its different biological properties, such as its bioactivity, protein adsorption, the adhesion, and proliferation of cells (Xifre-Perez, Ferre-Borull, Pallares, & Marsal, 2015). It has been reported that functionalization of alumina surface with vitronectin and a cellular adhesive peptide could enhance the cellular and molecular responses to it (Swan, Popat, & Desai, 2005). In addition, a phosphorylation modification of alumina surface could highly provoke bone-like apatite formation (Li, Ni, & Webster, 2014). BMP2 has also the ability to provoke osteogenic differentiation and promote bone formation, which could be useful in the functionalization of alumina surface (Benoit, Collins, & Anseth, 2007). Swan et al. (2005) have treated the nanoporous alumina surfaces by physically adsorbing vitronectin and covalently immobilizing arginine–glycine–aspartic acid–cysteine (RGDC) peptide for improving the interactions between osteoblasts and alumina surfaces. The authors reported that RGDC improved the osteoblasts adhesion on the treated substrates after one day of culture and also matrix production after two days, however, the cell secreted matrix was not found on untreated substrates in the same period. In other hands, vitronectin modified surfaces did not demonstrate noteworthy enhancement in cell adhesion in comparison with untreated ones. Kawashita et al. (2016) have modified the surface of α-Al_2O_3 and hydroxyapatite (HAp) with fibronectin (Fn) and then examined the MC3T3-E1 osteoblastic cells adhesion, spreading, proliferation, and differentiation on their surfaces. The outcomes

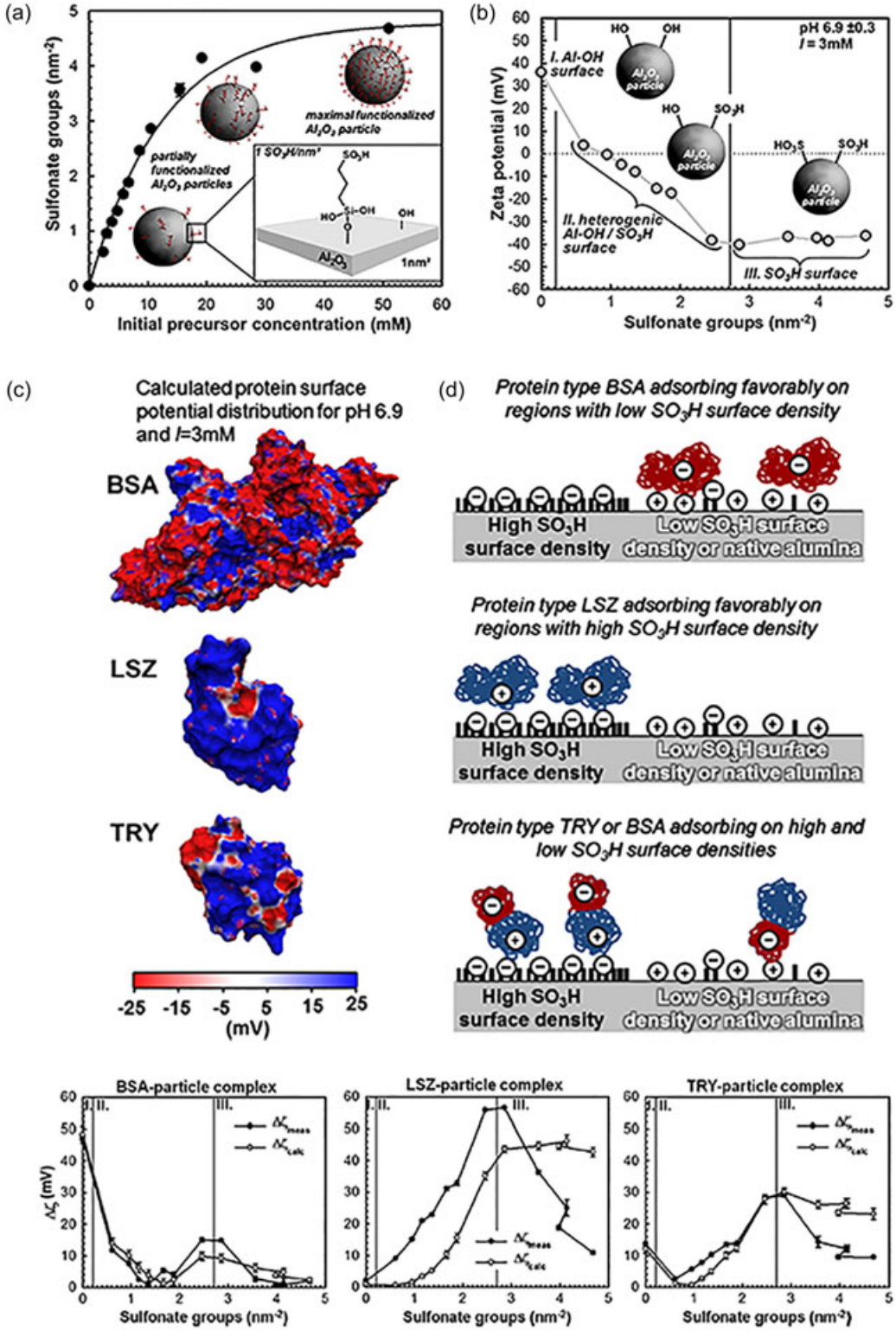

FIGURE 2 (a) The amount of sulfonate group surface on alumina surfaces. (b) Zeta potentials of the alumina particles as a function of concentration of sulfonate group on alumina surfaces at pH 6.9 ± 0.3 and I = 3 mM. 3 surface chemistry groups are demarcated: (I) native alumina particles; (II) particles with simultaneous existing Al–OH and SO_3H surface functions; and (III) SO_3H-dominated particles. (c) Surface possible scattering of BSA, LSZ, and TRY molecules considered from the crystal network by using the protein database file (http://www.rcsb.org), PDB2PQR, APBS, and visualization by VMD (v. 1.8.7) (Baker, Sept, Joseph, Holst, & McCammon, 2001; Dolinsky, Nielsen, McCammon, & Baker, 2004; Humphrey, Dalke, & Schulten, 1996). (d) Schematic of BSA, LSZ, and TRY adsorption on areas with high and low-sulfonate surface masses concurrent on the particle surface. Local accumulations of sulfonate groups and native or area with low-sulfonate surface density may potentially provide local charge optimums for electrostatically driven protein adsorption. (d) The experimentally firmed alteration in the zeta potential after adsorption of proteins as a function of the sulfonate density (Df meas) in comparison with the estimated alteration in the zeta potential (Df calc) using the factors degree of tenancy to protein, and the separate zeta potentials of the particles and of the protein. Reproduced from (Meder, Brandes, Treccani, & Rezwan, 2013) with the permission from Elsevier. BSA: bovine serum albumin; LSZ: lysozyme; TRY: trypsin [Color figure can be viewed at wileyonlinelibrary.com]

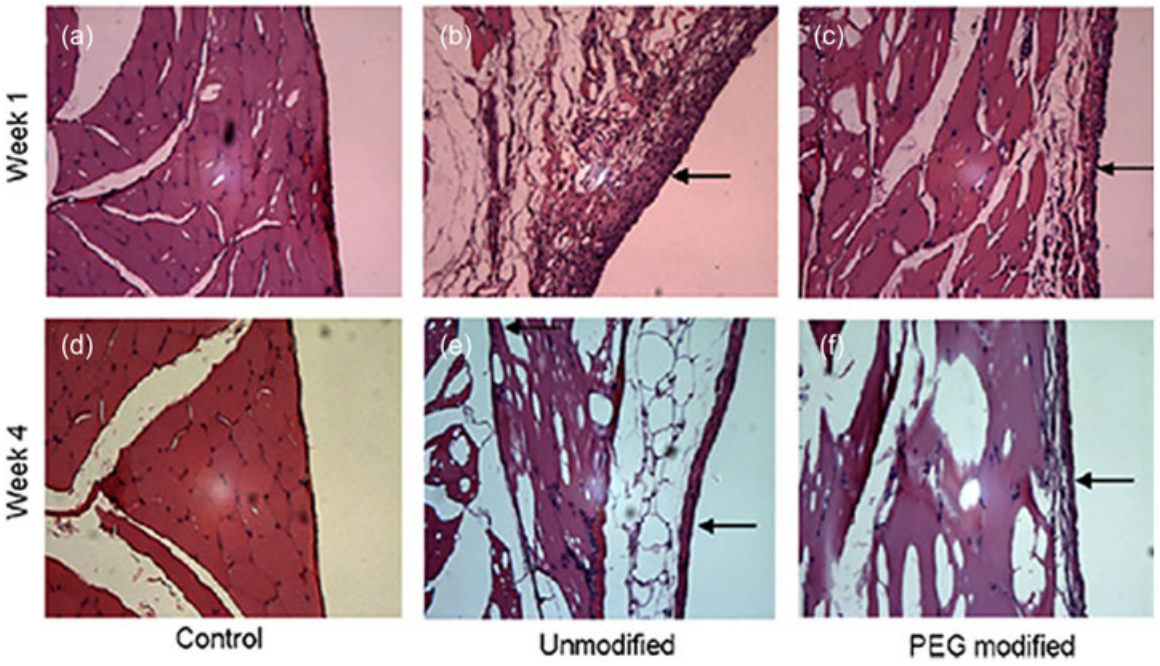

FIGURE 3 Histological analysis of bone tissue exposed to no material (a) and (d), untreated capsules (b) and (e), as well as PEG-treated capsules (c) and (f) after 1 and 4 weeks. As the presence of lymphocytes and macrophages inserted in a granulation layer can be seen, after 1 week, there is some inflammation of the tissue nearby the untreated capsules (b). There is a parallel however more moderate effect in the tissue nearby the PEG-modified capsules (c). The presence of immune cells seems to decrease after 4 weeks (e and f). Arrows show the part of the tissue that was uncovered to the capsule. Reproduced from (La Flamme et al., 2007) with the permission from Elsevier [Color figure can be viewed at wileyonlinelibrary.com]

indicated that Fn coating meaningfully improved MC3T3-E1 cell adhesion and spreading on HAp, but did not have an impact on cellular responses to HAp or α-Al_2O_3. In addition, coating Fn on HAp surface probably does not provoke MC3T3-E1 cells to activate osteoconduction process; however, Fn adsorption might have an influence on the inflammatory cells responses to the implanted material. They suggested that some in vivo studies are required for investigating the influence of serum proteins in cell culture and also the efficiency of coating Fn on HAp and α-Al_2O_3. Surface engineering of alumina is commonly essential to present bioactive molecules that can enhance cellular and molecular responses. Fernandez et al. (2009) have proposed a biocompatible polymer, polyvinylpirrolidone (PVP), to functionalize c-alumina nanoparticles. The outcomes achieved from this study showed that the PVP chains were effectively grafted to the alumina surface, help in calculating the size of the treated particles, and also modifying their biocompatibility. It has been currently reported that alumina particularly, ordered mesoporous alumina (OMA) with great surface areas, ordered porous networks, and large pore size, have a strong affinity to phosphor groups and subsequently to biomacrolecules such as phosphopeptides. Moreover, Wei and his coworkers (2017) have synthesized OMA substrates by using a ligand-assisted solvent evaporation encouraged coassembly route (see Figure 4). The attained OMA owing to its high surface area, large pore volume, and rich Lewis acid sites demonstrated the ability to be an exceptional bioabsorbent in enriching phosphopeptides. Furthermore, Saldana et al. (2007) have modified the surface of alumina blasted Ti6Al4V alloy by using thermal

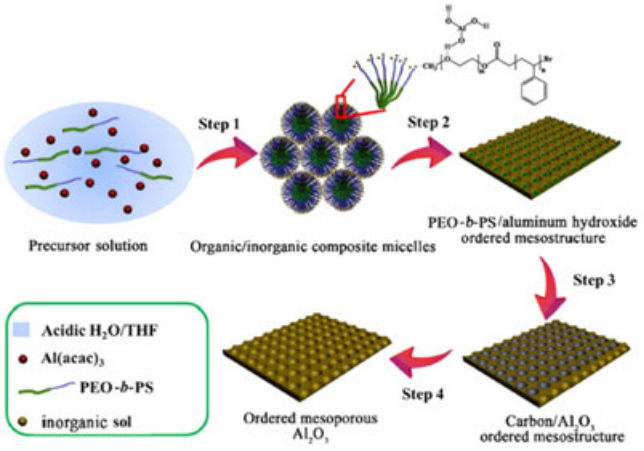

FIGURE 4 Representation of fabrication process of the OMA scaffolds. Step 1: Ligand-assistant solvent evaporation encouraged coassembly process to shape PEO-b-PS/inorganic sol composite micelles with well-arranged mesostructure using PEO-b-PS as a pattern, and Al(acac)3 as a forerunner. Step 2: The well-arranged mesostructure of PEO-b-PS/aluminum hydroxides is stable by more concentration of inorganic sol after aging at 100°C. Step 3: The well-organized mesostructure of carbon/alumina composites obtained after carbonization in N2. Step 4, OMA materials achieved after calcination in air to eradicate the protecting carbon. Reprinted from (Wei et al., 2017) with permission from American Chemical Society (2018). OMA: ordered mesoporous alumina [Color figure can be viewed at wileyonlinelibrary.com]

oxidation approach for improving its biocompatibility. Their findings specified that roughness of the modified substrate did not meaningfully changed; however, chemical surface test showed improving titanium and aluminum oxides stability. In addition, human primary osteoblasts responses, and procollagen I peptide secretion of the cells, were significantly enhanced on the modified substrates. Besides, the treated and untreated implants had no meaningful dissimilarity regarding osteoblastic biomarkers such as ALP, osteocalcin, osteoprotegerin, and mineralized nodule creation.

7 | ALUMINA BIOMEDICAL APPLICATIONS

7.1 | Alumina applications in dentistry

Thanks to the advantages of bioceramic materials an ever increasing progress in dental regeneration has been accomplished in the recent decades. It has been broadly shown that alumina could be a promising candidate in dental and orthopedic applications. High-strength alumina bioceramics are specified in all parts of the mouth for fabricating copings and frameworks of full coverage crowns and fixed prostheses. This bioceramic has been broadly used to improve the mechanical properties of dental porcelains. Zhang et al. (2015) have currently studied the effects of adding 0.25, 2 and 5 wt. % alumina on increasing the mechanical properties and low temperature degradation of yttria-stabilized TZP ceramics for dental application. It was detected that the concentration of alumina, especially in 0.25 wt. %, plays a key role in retarding the degradation of Y-TZP ceramics. In addition, improving the apparent activation energy of Y-TZP degradation was detected in the presence of alumina; however, it was equal for all alumina concentrations. In overall, it could be concluded that alumina can be a promising candidate for improving the mechanical and degradation properties of zirconia surfaces for dental applications. In addition, Zhao et al. (Zhao, Sun, Zhang, & Zhang, 2017) have more currently designed a novel type of submicron grain-sized alumina ceramics with greater optical and mechanical properties for dental applications. Their outcomes demonstrated that regarding polycrystalline alumina ceramics, a typical grain size <1 μm combined with a porosity level <0.7 percent could yield translucency values equal to those of the commercial high-translucency porcelains. In addition, these values were significantly greater than the high-translucency lithium disilicate glass-ceramic and zirconia ceramics. Moreover, the mechanical property of the proposed alumina substrate was meaningfully superior to that of the cubic-containing zirconia and lithia-based glass-ceramics. Some studied have focused their investigations on the in vivo biomechanical and biological responses of alumina surfaces for dental restorations. For instance, some researchers have examined the in vivo functionality of alumina toughened zirconia (ATZ) dental implants which were treated by a hydrothermal process (Schierano et al., 2015). They used a mini-pig animal model for evaluating the bone regeneration by histology and mRNA expression at different times including 8, 14, 28, and 56 days and then compared them with a titanium clinical standard. The authors claimed that the ATZ implants showed a meaningfully greater digital histology index for in comparison with titanium standard at 56 days. They suggested that this class of implant materials could be a favorable candidate for dental regeneration; however, more studies should be done before clinical usage.

7.2 | Alumina applications in orthopedic

Many studies have strongly suggested alumina as a promising candidate for bone regeneration application. For instance, Camilo et al. (2017) have currently proposed an approach for assessing the effects of porous alumina substrates coated with bioglass and HA bioactive materials on bone regeneration. They implanted the coated alumina substrates in rat tibiae and investigated their effects on bone regeneration during 28 days. The findings indicated that alumina implants coated with bioglass and HA could be promising candidates for promoting osseointegration and bone regeneration, especially in implants containing pore sizes in the range of 100–400 μm. Some studies have analyzed the long-term clinical usage of alumina as a substitute for bone regeneration. For instance, some researchers have investigated the clinical effects of using alumina substrates on decreasing aseptic loosening, osteolysis and late dislocations of orthopedic implants (Garcia-Cimbrelo, 2016). The researchers tested 315 Cerafit cups in two dissimilar generations including the first generation of alumina substrates that were clinically used between 1999 and 2005 (124 cups) and second generation (191 cups) of them with a five-year minimum follow-up. Their analysis indicated that Cerafit alumina-on-alumina prostheses demonstrate exceptional outcomes after 15 years. However, loosening was a common difficulty in the first generation alumina cups, it has been currently solved. Although, further follow-up will be essential to define if decreasing in wear between the alumina-on alumina implants in load-bearing bones consequences in fewer osteolysis and loosening. Furthermore, Thornton-Bott et al. (Thornton-Bott, Tai, Walter, & Zicat, 2016) have also followed up the osteolysis and survival rates of Alumina ceramic implants in total hip arthroplasties with a lowest follow-up of 15 years. They considered a sequence of 301 third-generation alumina-on-alumina cementless primary THR in 283 patients. The results of their analysis showed that alumina substitutes in cementless primary total hip arthroplasty had an exceptional persistence rate at 15 years with a satisfactory function, low wear rate and no adverse radiographic variations characteristic of osteolysis. In overall, they highly recommended using this alumina-based ceramics in load-bearing applications in the 21st Century. Interestingly, Lee and his coworkers (Lee & Kim, 2017) have analyzed the occurrence of recent alumina bearing disappointments from a single major ceramic company in approximately 6 million hip implants to recognize the developments in the ways of failure of these implants. They considered the products of CeramTec AG (Plochingen, Germany) during 2000–2013 which over 3.2 million pure alumina (PA) and 2.78 million alumina matrix composite (AMC) ceramic ball heads were used universal. They reported that through this period, there were 672 PA and 28 AMC femoral head fractures, which were examined regarding the time of

failure, head size, and implant parameters. Remarkably, the prevalence of modern PA femoral heads clinical fractures and AMC femoral heads was 1 in 5,000 (0.0201%) and 1 in 100,000 (0.0010%), correspondingly ($p < 0.0001$, which were typically related to particular events including trauma, incompatible components, and dislocations. They concluded that modern PA ceramic heads are potentially promising candidates for using in hip implants with particularly low fracture risk. In addition, in another investigation, Nakamura et al. (2017) have studied the clinical efficiency of using the medial pivot total knee prosthesis with alumina ceramic femoral constituents which was proposed to more precisely biomimic the biological knee kinematics and decrease polyethylene wear. The authors analyzed the long-term use of alumina medial pivot total knee arthroplasties (TKA) for a period of a ten-year follow-up. They found that alumina medial pivot TKAs developed the patients' Knee Society knee scores, function scores, and ranges of motion after the surgery. To sum up, they concluded that alumina medial pivot prosthesis are favorable candidates for long-term usage in load-bearing bone restoration applications.

8 | FUTURE PROSPECTIVE AND CONCLUDING REMARKS

Several of studies have been done on improving the mechanical and biocompatibility properties of alumina; however, still some difficulties in its clinical usage could be seen. Some parameters including powder processing route, sintering temperature, rate and time, and grain boundary chemistry, which control the properties of alumina during its fabrication, should be more deeply investigated. However, in the last few decades, alumina has gained great attention among biomedical scientists due to its excellent biomechanical and biocompatibility behavior, still its practical and clinical perspective remains unclear. In addition, however, some studies have reported good cellular and molecular responses to alumina, still there is a necessity to deeply understanding its biological behavior. Suggesting some novel strategies or even modifying the previous suggested ones with the aim of treating its surface and achieving excellent immunological system response is also essential. However, some studies have analyzed its long-term clinical use, further investigation in this regard is crucial. In other side, more deeply studying the other biological factors that might have an effect on controlling immunological responses to alumina and even other biomaterials surfaces should be taken into account. Many studied have suggested using surface nanotopography strategy for improving alumina biological functions, although further investigations should be done on defining the effects of using this approach on cells fate over elongated period of time. In addition, more deeply studying the effects of pore sizes of alumina, in a wide range, on the molecular and cell responses should be considered (Song et al., 2013). Although in vitro experiments could help in understanding the general cell responses to the biomaterial, in vivo examinations present better understandings of immunological responses to it. Specially regarding alumina nanoparticles, doing some simple in vitro tests like MTT could not strongly predict the biological responses to the wear particle surface. Deeply understanding the effects of in situ protein interactions could cause in enhancing the likelihoods of long-term wear-induced alumina nanoparticles effects. In addition, as only few studies have focused on the effects of adding functional groups on alumina surfaces with the aim of improving their interactions with proteins, there is a crucial need in further studying the effects of different chemical surface modifications strategies on its biological functions. Furthermore, the literature still suffers from not having a valid and strong database regarding precise mechanisms involved in foreign body reactions which should be also taken into considerations by biologists, immunologists. It's a well-known fact that we had the ability to totally understand the principles of cell response to biomaterials, then we could more strongly suggest promising biomaterials for tissue regeneration.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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