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Implant surface features as key role on cell behavior

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Abstract: It has been recognized that physical and chemical properties of biomaterial surfaces mediate the quality of extracellular matrix (ECM) that may affect cell behaviors. In nature, ECM is a heterogeneous three-dimensional superstructure formed by three major components, glycosaminoglycan, glycoconjugate, and protein, that anchors cellular compartments in tissues and regulates the function and the behavior of cells. Changes in the biointerface alter the quality of ECM and morphology through cell surface receptors, which, in turn, enable it to trigger specific cell signaling and different cellular responses. In fact, a number of strategies have been used to improve the functionality of surfaces and direct cell behavior through precisely designed environments. Herein, we aimed to discuss, through a science-based viewpoint, the biomaterial surface features on cell behavior and analyze the impact of cell physical modification on dental implant development.

Introduction

Overall surface features are responsible for determining cellular phenotype, behavior and extracellular matrix (ECM) secretion, and therefore can be considered as the ruler of the environment (Diener *et al.*, 2005). In turn, ECM is a heterogeneous three-dimensional superstructure formed by three major components, glycosaminoglycan, glycoconjugate, and protein, that anchors cellular compartments in tissues and regulates the function and the behavior of cells (Kusindarta and Wihadmadyatami, 2018).

Within the dental implant field, biomaterials are developed to restore, maintain or improve damaged tissues. In this sense, it is expected that the dental implanted biomaterials stimulate the ECM production and its replacement by the host tissue (Diener *et al.*, 2005; Dvir *et al.*, 2011). However, for tissue regeneration successfully takes place and contributes to the host cellular and tissue responses, it is necessary to understand the required biomaterial surface properties of implanted medical devices according to the native cell profile (Amani *et al.*, 2019).

Surface features might induce the total number of cells, their morphology, size, cytoskeletal organization and nuclearity, through the quality of proteins immediately adsorbed onto the implanted material (Amani *et al.*, 2019). After a few seconds of biomaterial implantation, the surface becomes rapidly covered by a variety of proteins from blood and interstitial fluids, forming the blood clot (Kikuchi and Okano, 2005; Anselme *et al.*, 2010). Hence, the adsorbed protein layer is responsible for modifying the surface chemistry and energy of the biomaterial implanted substrate and, therefore, to influence the cell layer organization. In other words, properties, such as roughness, wettability and surface free energy (SFE), drive the quality and quantity of proteins adsorbed, as well as protein composition; and the adsorbed protein represents a key mediator of cell's surface receptors.

In fact, the absorbed protein is a key mediator of cell's surface receptors (Anselme *et al.*, 2010). Just after the protein layer formation onto implant material, transmembrane linkers, known as integrins, act facilitating the interactions between the cytoskeleton from cells and the protein layer from the ECM (Siebers *et al.*, 2005; Keselowsky *et al.*, 2007). Remarkably, differences on cell phenotypes might affect and alter gene expression, and consequently, control how cells will respond to the respective environment.

In view of the aforementioned remarks, a crucial point is to control the structure of the adsorbed layer formed on biomaterial through the physical and chemical surface modification. Therefore, understanding how cells interact with each surface profile enables the creation of straightforward strategies and improves the biological performance of biomaterial devices (Feldmann *et al.*, 2013). Herein, we aimed to discuss through a science-based viewpoint the biomaterial surface features on cell behavior and analyze the impact of cell physical modification on dental implant development.

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Main Text

Nowadays, it is already known that biomaterial profile might directly affect cells spreading, migration, proliferation and differentiation, and favor or damage surface-cell interaction. All physicochemical properties inherent to each type of material are initially responsible for the surface-protein interactions (Anselme *et al.*, 2010; Ayala *et al.*, 2011; Rahmati *et al.*, 2020). Therefore, the quality of cell attachment is driven by the structure of the surface exposed to several molecular species during the protein adsorption process, which means that any material construction must consider such physical and chemical material properties (Ayala *et al.*, 2011). Within the dental implant field, this knowledge has affected the development of surfaces to favor and increase the implants' survival.

Surface modification can be conveniently achieved by modification of original material through physical (roughness) (Xu *et al.*, 2004; Zhou *et al.*, 2015) and chemical (wetting and SFE) properties or by coating construction onto original substrate. (Lim *et al.*, 2008; Arima and Iwata, 2007).

Regarding, the first possibility, we can share an important finding regarding the role of specific surface roughness on osteoclast phenotypes. In the past, osteoclast's functions were widely accepted for their ability to resorb bone only. However, studies have revealed that osteoclasts also contribute to bone formation by communicating with osteoblastic cells and osteogenic differentiation through the secretion of coupling factors (Zhang *et al.*, 2018; Sims and Martin, 2014). In this process, surface roughness is responsible for different functional states of osteoclasts and modulates osteogenic differentiation through the induction of different cell morphologies (Fig. 1). Interesting findings have revealed a small number of osteoclast cells with higher number of nuclei per osteoclast on smooth surfaces. By contrast, a high number of osteoclast cells with a low number of nuclei were found on rough surfaces (Zhang *et al.*, 2018). These differences on cell morphology reflect in the catabolic enzyme activity and gene expression of osteoclastogenic markers, which means that the increase in surface roughness, around 1–2 μm, decrease osteoclast-associated features, such as resorption capacity.

In this sense, porosity and pore size in polymeric biomaterials also play critical roles in determining cellular phenotype onto the surface (Oliviero *et al.*, 2012; Perez and Mestres, 2016).

The difference in pore size will determine the quality of cell growth throughout extensive and rapid angiogenesis and the quantity of protein adsorbed. Indeed, the ideal pore size favorable for application depends on the tissue that the biomaterial is intended to replace. For bone regeneration, for example, it was found that pore diameters above 300 μm are advantageous for bone migration (Murphy *et al.*, 2010). By contrast, for soft tissue, it was found that porosity of 60 μm increases the number of cells and tissue infiltration and provides excellent deposition of collagen and elastin, and superior fibrotic tissue distribution (Osorio *et al.*, 2010). From the soft tissue perspective, it was found that smooth surfaces stimulate different kinds of cell responses. Fibroblast and epithelial cells, for example, attach better to flat surfaces in the absence of roughness, lumps, or holes (Xu *et al.*, 2004; Cochran *et al.*, 1994).

Apart from roughness, surface wettability and surface free energy are important chemical factors, which also determine the surface protein adsorption (Guo *et al.*, 2016), the quality of cell–material interaction and subsequent cell attachment (Cai *et al.*, 2020; Alves *et al.*, 2010). Indeed, protein adsorption is the first event after the implantation of a biomaterial into the body and its subsequent contact with biological fluids (Olivares-Navarrete *et al.*, 2008). Each protein is composed of at least 20 amino acids. Each amino acid has a general core network of {–NH–CaHR–CO–}, where R describes a specific functional property. Depending on the R structure, the amino acids can disclose nonpolar, polar, and charged amino acids, and therefore, it determines the biological response through the affinity by specific types of cells (Hirsh *et al.*, 2013). It has been recognized that super hydrophilic surfaces (contact angle between surface and water less than 5°) accelerate and enhance fibronectin and albumin adsorption and, consequently, osteoblast cells attachment. It occurs because both proteins and osteoblastic cells are negatively charged and a super hydrophilic surface exhibits cationic sites, facilitating the interaction (Aita *et al.*, 2009).

Although surface wettability exerts different effects on the adhesion of different types of cells, it is known that overall cells are more likely to adhere to hydrophilic surfaces rather than hydrophobic ones (Wei *et al.*, 2007; Gittens *et al.*, 2014). It can be also explained by the composition of the cell membranes, which are composed by phospholipids from lipid bilayer, embedded proteins, and water. Even though phospholipids are composed by amphipathic molecules (molecules that have both polar and nonpolar parts), polar groups are always prevalent. It means that with the increase of wettability, hydroxyl and carboxyl groups from material surface might attract the cell surface lipids and ions through intermolecular force (hydrogen bonds), and thus improve the adhesion, growth, and cell proliferation.

Hydrophilic surfaces interact closely with blood and biological fluids, allowing normal protein adsorption in a conformation that exposes adhesion motifs and enhances bone cell adhesion (Gittens *et al.*, 2014; Huang *et al.*, 2012). This knowledge has made great contributions to the advancement of new commercial dental implant surfaces. From these discoveries, overall dental implant companies have been racing to fabricate the most hydrophilic surface with superior long-term performance. On the flip side, super-hydrophobic surfaces, with a contact angle of more than 150° are unfavorable to cell growth and adhesion (Cai *et al.*, 2020).

Contact angle between surface and wetting agent reflects the chemical nature of the tested material and consequently how wettable is that surface according to the characteristics of the liquid used for such evaluation. The numerical values corresponding to the contact angle are used to measure the surface free energy (SFE). Surface free energy is defined as the available energy from atoms displaced from the bulk of a material to the surface after intermolecular bonds disruption. The type of dangling bonds exposed at a material's surface determines the SFE categories, i.e., high or low. Materials, which are covalently, ionically, or metallically bonded, disclose high SFE and materials that are bonded by van der Waals bonds disclose low SFE (Gentleman and Gentleman, 2014). Similarly to wetting properties, SFE also affects protein adsorption and controls the early stages of

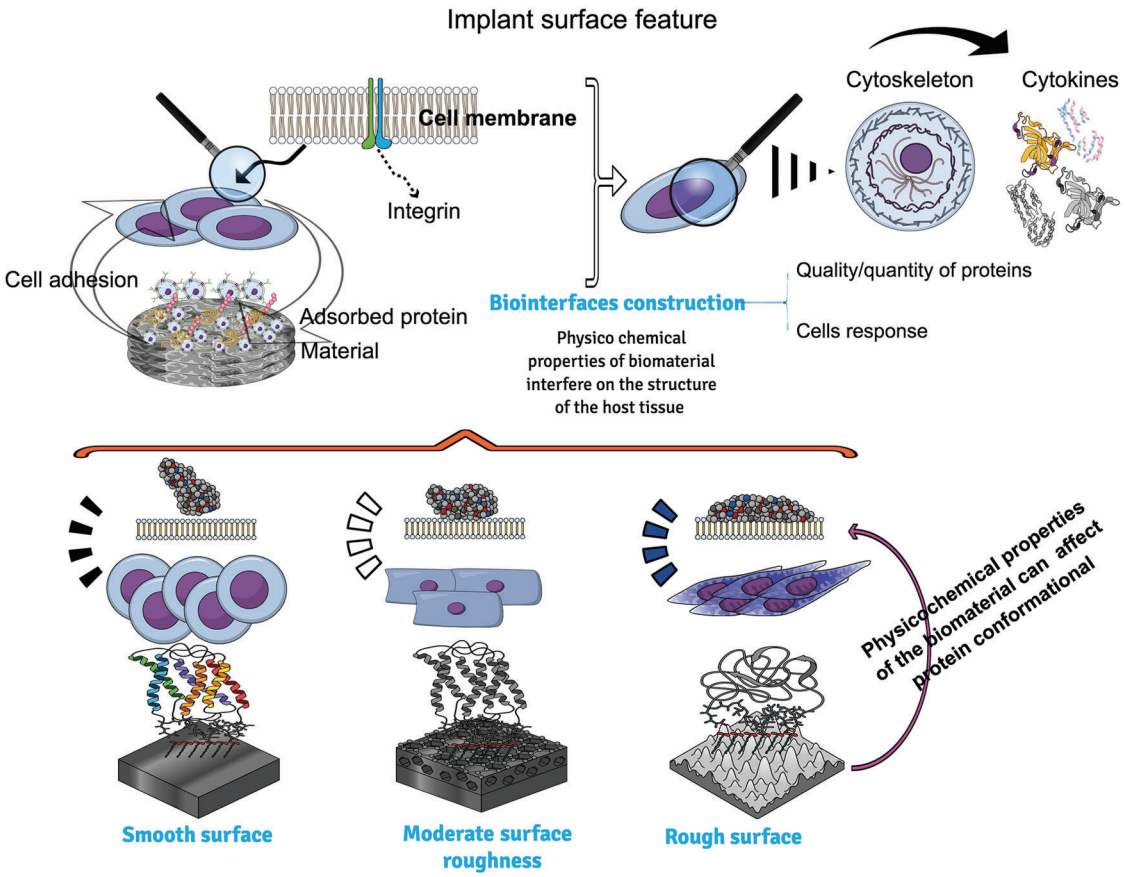

FIGURE 1. An overview of biomaterial surface features and how roughness can affect cell behavior. Different surface topographies may interfere on the quality of protein adhered onto them. The adsorbed protein layer is responsible to modify the surface chemistry and energy of substrate of biomaterial implanted and therefore to influence the cell layer organization. Cells attached on the surface express cytoskeleton proteins and integrin, which interact together to regulate gene expression.

cell adhesion and tissue formation at the material interface; however, the quality of surface-cell interaction will always depend on the chemical nature of local cells analyzed (Gentleman and Gentleman, 2014).

Focusing on chemical substrate, different types of materials have been investigated as implant surface possibilities. Titanium (Ti) and its alloys are still widely used for medical and dental implant field (Rossi *et al.*, 2021; Tendero *et al.*, 2021). The reason for that assumption is due to inherent Ti properties such as excellent corrosion resistance and good biocompatibility (Bosshardt *et al.*, 2017). Zirconia and polyetheretherketone (PEEK) have been also tested in order to improve the esthetic, the performance of implant materials and to create a biomimetic cellular microenvironment (Dong *et al.*, 2020; Rigolin *et al.*, 2017; Guillot *et al.*, 2016). PEEK-based coating has been applied to improve mechanical strength and reduce elastic modulus, in case of zirconia for example, as well as to confer good wear resistance and chemical stability (Qin *et al.*, 2021).

Controlling cell behaviors can be also achieved by polymeric coatings construction (Alves *et al.*, 2010; Tilkin *et al.*, 2020; Chen *et al.*, 2018). Within the tissue regeneration field, polymeric materials have emerged to fabricate artificial biomaterials that can effectively mimic cell–ECM interactions. Among them, poly(hexamethyldisiloxane) (PHMDSO) may exhibit different surface wettability (from hydrophobic to superhydrophilic) by altering the duration of oxygen-plasma treatment, according to the convenience. The greater surface hydrophilicity, the better adhesion and spreading fibroblast cells (Wei *et al.*, 2007). Others important polymers used to film construction are poly-l-lactic acid and polystyrene (PLLA, PS). Both biomaterials were found to stimulate osteoblastic cell adhesion and spreading (Lim *et al.*, 2005). With regards to responsive polymers, thermoresponsive polymers, such as poly [oligo (ethylene glycol) methacrylates] (POEGMA) are frequently used to manipulate cell adhesion (Nagase *et al.*, 2009). In this sense, several methods and strategies to develop polymeric surfaces can be highlight: layer-by-layer (LbL) assembly (de Avila *et al.*, 2019; Verza *et al.*, 2021), lithographic surface modification techniques, electrospun fibers, spin coating, 3D bioprinting, self-assembled monolayers (SAMs) and polymer brush (Cai *et al.*, 2020).

After all, independent of the technology used to construct polymeric thin films, the central idea is to create a non-cytotoxic environment by decorating the polymeric material with suitable chemical, mechanical, and topographical cues for controlling cell adhesion, stem cell differentiation, and cell-cell interactions.

Vision of the future

The development of biomaterials needs to focus on the biointerface construction to match the structure of the host tissue and to meet the biophysical and biochemical requirements of specific cell types. In order to do that, it is

critical to manipulate the surface by physical and chemical parameters to achieve the clinical purpose of the biomaterial. From the clinical standpoint, dental implant survival has advanced from a fairly unpredictable procedure, to a very predictable practice. Two factors, which have been claimed to influence the biological response, are physical and chemical modifications of implant surface properties, which provide an effective and straightforward strategy to improve cell attachment, spreading, and differentiation. (Schneider *et al*., 2003) Focusing on polymeric coating construction, up to date, the knowledge regarding this subject has been limited to *in vitro* and *in vivo* investigations.

However, surface-cell interaction possibilities have encouraged the development of desired surfaces through polymeric surfaces with rational designs in chemical and topographical cues for controlling cell behaviors. Above all, the understanding regarding all factors that generate a response to signal cell events for subsequent control of cell behaviors and functions is essential for materials and life sciences, such as advanced biomedical engineering and tissue engineering.

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