Colloids and Surfaces B: Biointerfaces 164 (2018) 58–69

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

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

Tuning surface properties of bone biomaterials to manipulate osteoblastic cell adhesion and the signaling pathways for the enhancement of early osseointegration

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ARTICLE INFO

Article history:
Received 1 October 2017
Received in revised form
22 December 2017
Accepted 15 January 2018

Keywords:
Osteoblastic cells
Bone biomaterials
Cell adhesion
Early osseointegration
Signaling pathways

ABSTRACT

Osteoblast cell adhesion is the initial step of early osseointegration responding to bone material implants. Enhancing the osteoblastic cell adhesion has become one of the prime aims when optimizing the surface properties of bone biomaterials. The traditional strategy focuses in improving the physical attachment of osteoblastic cells onto the surfaces of biomaterials. However, instead of a simple cell physical attachment, the osteoblastic cell adhesion has been revealed to be a sophisticated system. Despite the well-documented effect of bone biomaterial surface modifications on adhesion, few studies have focused on the underlying molecular mechanisms. Physicochemical signals from biomaterials can be transduced into intracellular signaling network and further initiate the early response cascade towards the implants, which includes cell survival, migration, proliferation, and differentiation. Adhesion is vital in determining the early osseointegration between host bone tissue and implanted bone biomaterials *via* regulating involving signaling pathways. Therefore, the modulation of early adhesion behavior should not simply target in physical attachment, but emphasize in the manipulation of downstream signaling pathways, to regulate early osseointegration. This review firstly summarized the basic biological principles of osteoblastic cell adhesion process and the activated downstream cell signaling pathways. The effects of different biomaterial physicochemical properties on osteoblastic cell adhesion were then reviewed. This review provided up-to-date research outcomes in the adhesion behavior of osteoblastic cells on bone biomaterials with different physicochemical properties. The strategy is optimised from traditionally focusing in physical cell adhesion to the proposed strategy that manipulating cell adhesion and the downstream signaling network for the enhancement of early osseointegration.

Contents

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https://doi.org/10.1016/j.colsurfb.2018.01.022
0927-7765/

1. Introduction

With the arrival of aging society, bone related diseases have trended steeply upward worldwide [1]. The repair of bone defects remains one of the most challenging topics in clinic as well as in the area of tissue engineering. Applying regenerative bone biomaterials is a promising approach to repair bone defects, thus improving the existing severe skeletal healthcare status [2]. Therefore, it is of great clinical and social significance to develop biomaterials with high osteogenic capacity. Osteoblastic cell adhesion is one of the earliest events in biomaterial and host tissue interaction. Facilitating a favourable cell attachment in the biomaterial surfaces is an important start for the entire bone regeneration process.

Basing on this principle, a number of studies have been carried out to develop biomaterials with beneficial physicochemical properties that can improve cell adhesion [3,4]. It is shown that surface wettability, roughness, electricity properties, pore size of the biomaterials and the use of some bioactive molecules can effectively regulate the osteoblastic cell adhesion. Most of the research efforts have been put in manipulating the physical attachment.

However, osteoblastic cell adhesion is a sophisticated physiological process involving a series of physiochemical changes, ranging from molecular level to cellular level [5]. Increasing evidences have shown that the osteoblastic cell adhesion on biomaterials is a key step in transducting the bio-physicochemical signals from biomaterials into osteoblastic cells, thus initiating the osseointegration cascade and regulating the interaction between osteoblastic cell and biomaterials [6–8]. Favourable osteoblastic adhesion on biomaterials would induce a phenotype beneficial for osteogenesis, thus improving the early integration between bone tissue and implanted biomaterials [9]. Failure of the osteoblastic cell attachment would pose the low proliferation and cell anoikis, impeding the subsequent bone formation, and lead to a failed early osseointegration [10].

These indicate that osteoblastic cell adhesion on biomaterials is not just a simple physical attachment, but an important event in initiating and regulating cell survival, migration, recruitment, osteogenic differentiation, *etc*. These are all vital components of the early osseointegration, which leads to the direct bone apposition onto the surface of biomaterials without the intervention of soft or connective tissues [11]. Manipulating osteoblastic cell adhesion and its downstream signaling pathways may be an effective way to improve early osseointegration and eventual bone regeneration. In addition to optimize physical cell attachment, the adhesion mediated signaling pathways should be emphasized and regulated into one that favors early osseointegration.

Therefore, it is of great significance to deepen the understanding of the osteoblastic cell adhesion process on biomaterials and its activation on the downstream signaling pathways. We offered a comprehensive understanding of the process osteoblasts adhering to biomaterials as well as the subsequent effects on activating intracellular signaling pathways that can regulate cell spreading, proliferation, differentiation and migration. The effects of biomaterial physiochemical properties on modulating the osteoblastic cell adhesion were also discussed. Basing on these principles, the traditional strategy was proposed to be modified into one that tuning the physicochemical properties of bone biomaterials to manipulate cell adhesion and the downstream signaling network for the enhancement of early osseointegration.

2. The process of osteoblastic cells adhere onto biomaterials

It has been well established that osteoblastic cell adhere to biomaterials start in an indirect manner, which is mediated through specific extra-cellular matrix (ECM) proteins especially vitronectin, fibronectin and collagen I [12]. The ECM proteins in the blood can be quickly adsorbed on the surfaces of biomaterials and form an 'extra-material matrix' *via* the weak physiochemical connections (*i.e.*, hydrogen bond, electrostatic force, van der Waal's force) between the substrate's surface molecules and the proteins [13,14]. The protein adsorption helps to form a 'protein layer' which is favourable for the osteoblastic cell adhesion [15,16].

The 'protein layer' is a dynamic structure as the three-dimensional conformation of ECM proteins can be influenced by the surfaces of biomaterials. Osteoblasts are connected to these ECM proteins *via* a specific RGD sequence, an Arg-Gly-Asp tripeptide component shared by collagen I, fibronectin and vitronectin. RGD sequence is the main receptor that interact with osteoblastic cells membrane proteins (mainly Integrins) and initiate subsequent cell spreading, proliferation and differentiation and has long been utilized as an effective surface modification biomolecule for the improvement of cell adhesion [17,18]. The favourable biomaterials should modulate the 'protein layer' into an active formation and help the exposure of RGD motif for the further cell anchorage.

Subsequently, the adhesion cell membrane proteins on osteoblastic cells can recognize and anchor to the matrix *via* specific recognizing the RGD sequence and other ligands [19]. This is a key step of adhesion process, as anchorage is the first step of cell-substrate interaction and is essential for osteoblastic cells to maintain their normal cell phenotype and function [20].

The major ligands-connection between adhesion ECM molecules and osteoblastic cells is Integrin. The primary role of Integrins is to modulate cell anchorage *via* recognition and binding of ECM proteins. Hasebe et al. [21] have shown that osteoblastic cells adhered to secretory osteogenic protein *via* Integrin $\alpha 3\beta 1$. Integrins $\alpha 6\beta 1$ and $\alpha 5\beta 1$ can bind to laminin and fibronectin respectively while $\alpha v\beta 3$ can bind to both vitronectin and fibronectin [22–24].

In addition to influencing the cell anchorage process, β1 Integrins also elicit significant effects on regulating the subsequent osteoblastic cell activities [25]. In vitro studies have shown that the $\alpha 5\beta 1$ Integrin is essential for osteoblastogenesis [26]. The Integrin $\alpha v\beta 1$ was also found to have the ability to promote MSCs