Biomedicine & Pharmacotherapy 88 (2017) 956–970

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Review

Fundamentals of protein and cell interactions in biomaterials

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ARTICLE INFO

Article history:
Received 30 November 2016
Received in revised form 11 January 2017
Accepted 23 January 2017

Keywords:
Extracellular matrix
Protein-cell interaction

ABSTRACT

The extracellular matrix (ECM) is an active and complex microenvironment with outstanding biomechanical, biophysical, and biochemical characteristics, which can indirectly or directly controls cell adhesion, migration, proliferation, and differentiation, as well as partaking in regeneration and homeostasis of organs and tissues. The ECM has captivated a great deal of attention with the rapid progress of tissue engineering (TE) in the field of regenerative medicine (RM). Approaches to TE, RM and cancer therapy center on the necessity to deliver cell signals to direct cell proliferation and differentiation. These "external signals" are induced from cell-cell, and cell-ECM, interactions, as well as from physico-chemical, mechanical stimuli and growth factors. With the advent of new biomaterials such as casein, we gave a general insight into cell-ECM protein interactions in biomaterials and their applications in TE, RM and cancer therapy. An account of the main ECM molecules and cellular receptors with emphasis on integrins and its ligands was given, their effect on the induction of particular signal transduction pathways is also elucidated.

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http://dx.doi.org/10.1016/j.biopha.2017.01.136
0753-3322/

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1. Introduction

Fabricated nano-and micro devices are becoming an essential part of various scientific discipline and applications. Most of these devices would be beneficial in biotechnology and biomedicals, and would be of great benefit if efficient control over cellular and molecular interactions at the material surfaces could be achieved [1]. This materials must possess the ability of adhering biomolecules, which include DNA and proteins on their surface, and also the control over consequent interfacial interactions between cellular entities like bacteria and mammalian cells, and the materials possessing adherence molecules, such as cell-adhesive proteins [2–5].

Adherence proteins on the surface of synthetic materials are of particular interest, since they are implicated in attachment of cell, cell functions, and various cellular signaling pathways. Cellular responses such as phenotyping, attachment to materials surfaces, proliferation, and changes in morphology, have been shown to be associated with the composition, concentration, and conformation of proteins layer that adhere the synthetic materials [6–10]. The interaction between signaling molecule–protein and protein–protein at biological interfaces, also control countless other biological functions. This shows the normal interactions of cells-environment in vivo, where cells reside in and interact with the extracellular milieu.

In this review, we gave a detail of integrin and its ligands in cell-ECM interactions, taking the advantage of the surface chemistry of natural and synthetic biomaterials, and their application in TE and cancer pathogenesis.

2. Extracellular matrix

The ECM is composed of varieties of molecules which include elastic fibers, families of collagen, proteoglycans, glycosoaminoglycans (GAG), and adhesive glycoproteins. The different combination, immobilization, and spatial arrangement of these secreted substances resulted in the different types of scaffolds formation, making up different organs and tissues in the body [11].

2.1. Transmembrane integrin receptor

The transmembrane (TM) integrin receptors for ECM proteins mediate signal transduction, cell adhesion sites and the actin-containing cytoskeleton organization [12]. They serve as a bridges for cell–cell and cell-ECM interactions. When triggered, integrins initiate chemical pathways (signal transduction), like the mechanical and chemical signal of the ECM, resulting in a response (transcription activation) such as cell shape, cell cycle regulation, and/or movement; or a new receptors being attached to the cell membrane. This permit flexible and fast responses to cell surface events, for instance, signal platelets triggering interaction with coagulation factors. There are various types of integrins, and a single cell may have various types of it residing on its surface. They are found in all multicellular organisms [13]. It works alongside other receptors such as the immunoglobulin superfamily cell adhesion molecules (CAM), cadherins, syndecans and selectins to facilitate cell–cell and cell–matrix interaction. Ligands for integrins include collagen, vitronectin, fibronectin, and laminin.

Integrins are heterodimers comprising of two subunits. Hynes discovered 18 α and 8 β subunits of integrins, summing up to 24 αβ heterodimers through a noncovalent linkage [13]. An electron microscopy outcome indicated that integrins have a globular shaped head and two leg regions (one from α subunits and the other from β subunits) embedded into the plasma membrane (Fig. 1), showing each integrin subunit has a cytoplasmic tail, a TM domain, and an extracellular domain representing the head [14].

The integrin α-subunits usually select the ligands type, and both the α and β subunits are implicated in cell signal transduction mediated by the contribution of CAM. The molecular discovery of integrins in the late 1970s and 1980s, was followed by an additional discoveries of integrin adhesion-related proteins, including signaling molecules and structural protein members [15]. The function of integrin and molecular diversity were primarily discovered in the year 2000 [16]. Based on the distinctive structure of integrins, comprising the α- and β-subunits, integrins can interact with ECM proteins (its ligand), and some other cellular receptors [17]. Among these, a short domains of the integrins in the intracellular milieu may interact directly with several intracellular signaling molecules and cytoskeletal proteins. These associated proteins offer a foundation for modulating important cell processes and several biological outcomes including cell proliferation, cell migration, cell differentiation, and apoptosis [18] by regulating signal transduction pathways.

Integrins transfer bidirectional signaling via the plasma membrane by connecting extracellular conformational changes via the opening and separation of α and β TM and cytoplasmic domains [19]. Two signaling mechanism are involve in this process, the inside-out signals which controls integrin attraction for adhesive ligands (cytoplasmic proteins), and the outside-in signals which depend on ligands that controls cellular responses to adhesion (binds ECM ligands) [20]. Integrins have no fundamental catalytic role, and they are implicated in intracellular signals transduction through adaptor proteins. The integration of these complex signals led to the facilitation of cell biological processes (Fig. 1). Consequently, cell adhesion is the requirement of integrin-mediated biological functions.

2.2. Integrins in cell adhesion

Integrin-mediated cell adhesion to ECM constituents is important for the maintenance, organization, and repair of several tissues [21]. The cell adhesion mechanism is complex and comprises series of steps [22], including binding to the ECM, the recruitment of cytoskeletal elements and receptor clustering. Integrin facilitated cell adhesion take place through a focal adhesions involving the signaling pathway via ILK; representing a multifunctional adaptor protein that connects focal adhesion to the actin cytoskeleton [23], FAK (focal adhesion kinase), phospholipase C (PLC), and the triggering of Pho family proteins (Fig. 2).

FAK controls integrin activity [24] and elevates tyrosine phosphorylation following the activation of integrin depending on an intact integrin β cytoplasmic tail [25]. The Pho family proteins are essential as well. Although the exact association between integrin mediated-signal pathway and GTPase are not fully understood, but, the integrin-dependent control of intracellular pH can occur through Pho GTPase, which has a crucial effects on cell migration and adhesion [26]. The signaling molecules