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Review

Receptor-ligand interactions: Advanced biomedical applications

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ABSTRACT

Receptor-ligand interactions (RLIs) are at the base of all biological events occurring in living cells. The understanding of interactions between complementary macromolecules in biological systems represents a high-priority research area in bionanotechnology to design the artificial systems mimicking natural processes. This review summarizes and analyzes RLIs in some cutting-edge biomedical fields, in particular, for the preparation of novel stationary phases to separate complex biological mixtures in medical diagnostics, for the design of ultrasensitive biosensors for identification of biomarkers of various diseases at early stages, as well as in the development of innovative biomaterials and approaches for regenerative medicine. All these biotechnological fields are closely related, because their success depends on a proper choice, combination and spatial disposition of the single components of ligand-receptor pairs on the surface of appropriately designed support.

Contents

1. Introduction

Highly specific molecular recognition is one of the fundamental principles of functioning of living systems being involved in all the most important biological processes, such as hormone-receptor and antigen-antibody interactions, enzymatic reactions, transmembrane transport of various substances, among others. From a general point of view, molecular recognition is a key concept of supramolecular chemistry. It can be described as a process of high affinity interaction and selective binding of a ligand by a receptor [1]. Usually the ligands are relatively simple substances of various nature, for example, peptides, proteins, short DNA or RNA, steroids, parts of virus or bacteria or artificial compounds and drugs. On the contrary, receptors are water-soluble, membrane-anchored or membrane-embedded macromolecules with a

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complex 3D structure [2–5]. Ligand-stimulated alterations of cell receptors' state result in physiological responses, which constitute the biological activity of various biomolecules, as well as the action of pharmaceutical drugs [6,7].

Receptor and ligand form a complementary pair with relatively strong non-covalent bonds formed by Van der Waals forces, hydrophobic, π-, ionic or electrostatic interactions. The type of this interaction depends on the structural and energetic compatibility of the biopartners [8]. Receptor-ligand pair formation is a complex process and may include different stages. For protein-protein interaction, that is one of the most complicated cases of receptor-ligand pair formation, it consists of (1) *primary recognition* of receptor by corresponding ligand at the large distance by means of electrostatic forces, (2) *orientation* and change of structural conformation in order to achieve the proper interface contact, and (3) *physical binding* of two molecules [9] (Fig. 1).

Sometimes the ligands contain multiple recognition sites and thus might bind to clustered receptors. This multivalent binding can drastically enhance the affinity of receptor-ligand interaction [10,11].

Upon receiving the signal generated by binding of a ligand to its complementary receptor, a cascade of chemical reactions occurs. The high affinity receptor-ligand pairs form in the cell an extremely complex network of interacting molecules [12]. One signaling molecule can activate multiple downstream signaling pathways through different receptors, while one receptor might propagate various signals depending on ligand partners.

Ligand-receptor interactions are fundamental for the communication of a cell with its neighbours and the whole organism and initiate not only dynamic processes, such as proliferation, apoptosis, movement, but also maintain cell homeostasis and equilibrated functioning of all cell systems.

The research carried out during the last decades allowed noticeable improvement of our knowledge concerning the mechanisms of interaction between biomolecules, that was caused by huge progress in genetic engineering, X-ray crystallography, computational and various physicochemical techniques [13–15]. The information, which can be gathered by identification and characterization of RLIs, is of paramount importance for discovering new receptors and ligands, understanding pathogenesis and molecular mechanisms of endogenic ligands' and pharmaceutical drugs' action, as well as for the development of novel approaches to the treatment of a wide spectrum of various diseases. Various ligand-receptor pairs and RLIs of living cells can be used to create so-called smart biomaterials for a plenty of physicochemical and biomedical applications in the fields of life sciences, industrial biotechnology and pharmacology, tissue engineering, design of highly sensitive diagnostic tools, etc. In particular, three nanotechnological areas have been influenced to the major extent by the advancing of our knowledge on peculiarities of RLIs and discovery of new cell signaling pathways: 1) high affinity separations; 2) construction of ultrasensitive biosensors; 3) design of biomaterials for tissue engineering and regenerative medicine. Though being very far at a first glance, all these nanotechnological fields, are closely related. Indeed, all of them are based on the receptor-ligand interactions, where one of the components of ligand-receptor pair is immobilized on a solid support, as for stationary phase in affinity chromatography and sensing surface of biosensors, or it can be located on bioactive surfaces or live cell membranes in tissue engineering. In all three cases the choice, combination and disposition of the components of receptor-ligand pairs on the interfaces are of crucial importance for the desired outcome. In the case of biomaterial design, the target is not only to form a high affinity ligand-receptor complex, but also to create a bioactive surface or bulk material in order to induce a controllable response in biological environment, which can result in regulation of cell adhesion, migration, proliferation, etc. Thus, the creation of biomaterials aimed to be used in living systems is the highest and the most complicated level of bionanotechnology, where a number of various parameters have to be taken into account, including the interaction with neighbouring cells and tissues, as well as the cross-talk with other ligand-receptor signaling queues.

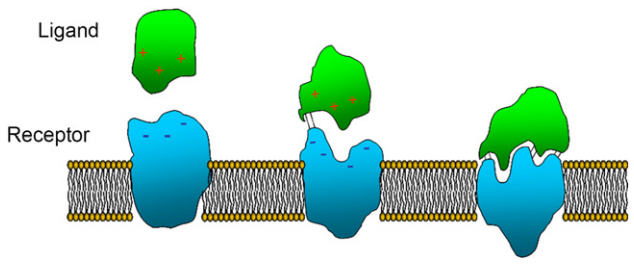

Fig. 1. Ligand-receptor complex formation (from left to right): primary recognition, orientation and physical binding.

This review represents an attempt to summarize and classify the huge amount of more and more sophisticated approaches of bionanotechnology from the point of view of ligand-receptor interactions lying on their base. We moved from the simplest (affinity chromatography) to the most complicated (advanced biomaterials) field to show how to govern *in vitro* and *in vivo* behaviour and functionality of modern artificial media using the unique principle of biocomplementarity. This knowledge is fundamental for the creation of the artificial constructs aimed to be incorporated into the living systems without affection of the metabolic processes. Here, we tried to summarize and analyze various types of ligand-receptor pairs used in different fields of bionanotechnology and biomedicine and to highlight the importance of RLIs for their future development.

2. RLIs in bioseparation

2.1. Monolithic stationary phases

The discovery of the principle of highly specific molecular recognition and the understanding of the fundamentals of interaction between biomacromolecules stimulated the development of a number of highly efficient and fast methods for separation of complex biological mixtures, as well as for purification of low-abundant biomolecules. Affinity chromatography is one of the most powerful tools applied for analysis and purification of biological products of different classes, such as enzymes, hormones, receptors, recombinant proteins, DNA, etc., where one of the components of the affinity pair, i.e. ligand or receptor, is immobilized on a stationary phase, whereas another one is dissolved in a flowing liquid. Among three above mentioned bionanotechnological fields it represents the easiest case, since the modification of solid support with the components of ligand-receptor pairs is aimed to achieve only a selective adsorption followed by a desorption of targeted molecules (Fig. 2).

A plenty of various bioseparation approaches have been developed in the last decades due to the improvement in our knowledge about the peculiarities of ligand-receptor complex formation, the strength of non-covalent bonds inside the complex and how to arrange in space the components of receptor-ligand pairs in order to achieve the highest affinity for target molecules [16–18].

The efficiency of affinity chromatography depends not only on the proper selection and spatial disposition of the components of the ligand-receptor pair, but it is also closely related to the characteristics of solid support and the mechanism of mass transfer between liquid and solid phases. Therefore, a big attention has been paid to the development of new generations of stationary phases, where the influence of solid support on kinetics and thermodynamics of ligand-receptor interaction was minimized [19]. At present, a variety of sorbents have been proposed for the immobilization of biospecific ligands, for example, natural polymers (cross-linked highly swelling agarose and dextran), synthetic polymers (polyacrilamide), inorganic porous supports (silica gels, macroporous glasses), as well as different composites. Among these conventional materials monolithic stationary phases, both organic and inorganic (mostly silica-based), are of particular interest because of