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EDITORIAL OPEN ACCESS

The plasma membrane and the cytoskeleton: A gateway to cells for pathogens or new targets with therapeutic potential?

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In the last century, several contributions were made on the organization and structure of the basic components of the cell, such as the plasma membrane. The fluid mosaic model proposed that the lipid bilayer functioned as a two-dimensional solvent, of neutral character and with little influence on the function of membrane proteins [1]. However, we now know that the plasma membrane contains a large variety of lipids that differ in their properties and that the interactions between these lipids originate heterogeneous structures in the plane of the plasma membrane. In this context, cell migration is a process associated with the plasma membrane and the rearrangement of cytoskeletal proteins that is essential for many processes such as embryonic development, healing, immune responses and tissue development; which like the motility are processes that require the reorganization of cytoskeletal and are able by the entry of extracellular calcium allowing cell adhesion [2]. These mechanisms, until some years ago were understood of an individual form, since the knowledge was not available on the way where the proteins that participate in the mechanisms mentioned above are coordinated spatially and temporally to carry out these functions.

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FROM THE OLD SCHOOL: FROM MACROPINOCYTOSIS TO THE LIPID RAFTS

Macropinocytosis is one of the most studied events at the cellular level representing a conserved form of the endocytosis process, this process is practiced by the majority of the cells of our organism for the acquisition of nutrients, this process is quite different from phagocytosis and receptor-mediated endocytosis, where the latter require a ligand-receptor interaction [3, 4]. In this sense, there are some cells that have increased these processes, such is the case of macrophages and dendritic cells, cells that play an important role in the development of the immune response, both in its innate and adaptive form.

Macropinocytosis is characterized by a high-volume internalization pathway, non-selective, actin-dependent and their sizes are of varying diameter (0.2–42 μm). Therefore, this non-selective nature and large volume allows the entry of pathogens in an inevitable manner, since this phenomenon has been observed in macrophages that have been activated by a contact with pathogens. This interaction efficiently regulates a receptor-independent macropinocytosis, in this way, this non-specificity diminishes the cell's ability to eliminate pathogens [5], this process is influenced by molecular factors such as phosphatidic acid among other molecules. From the point of view of the immune response, macropinocytosis is an important event for the processing and presentation of antigens by antigen-presenting cells (APC) such as macrophages and dendritic cells. Activated and mature dendritic cells downregulate macropinocytosis favoring their migration to the lymph nodes for the presentation of these antigens to the T cells [6]. Antigenic peptides derived from internalized material are loaded onto major histocompatibility complex (MHC) molecules; of class I (MHC-I, usually self or endogenous antigens) or class II (MHC-II, foreign or extracellular antigens) for presentation to T cells to induce adaptive immune responses, besides, macropinocytosis can also result

in the cross-presentation of extracellular antigens on MHC-I. On the other hand, phagocytosis is a process used by macrophages and other professional phagocytic cells for the elimination of pathogens, dead cells and/or opsonized molecules of an approximate size of >0.5 μm, this process is based on the recognition of pathogens through a receptor on the surface of the phagocytic cells (pattern recognition receptors, opsonic receptors and apoptotic cell or corpse receptors). Phagocytosis is an important process in organ development, in the maintenance of homeostasis in the tissues and in the immune response, but it also contributes in an indirect and inadvertent way to the development of diseases, to infectious processes and the development of several diseases of bacterial etiology [7, 8].

In 1997, Simons and Ikonen proposed a model for the plasma membrane where cholesterol and sphingolipids can be organized on the exoplasmic side of the cell producing in this way structures called lipid rafts [9]. These structures not only function for the distribution of lipids and proteins on the cell surface, but they are also involved in the transport through the membrane and for intracellular signal functioning as small microdomains. Similarly, lipid rafts have been involved in the development of immune responses and it has been observed that they intervene in the entry of the syncytial virus (SV40) and in the assembly and exit of new virions. Within the lipid rafts exist the caveolae, which are a subtype of lipid rafts initially identified by Palade and Yamada in 1955 based on their morphology. These structures are uniform with a diameter of 50-100 nm and these are characterized by the presence of the protein caveolin. Endocytosis through the caveolae has been analyzed mainly in endothelial cells where it is known as transcytosis, and it is also involved in the phenomenon of potocytosis mainly for the uptake of vitamins. Although, lipid rafts were described in the cells of the immune system in the early 1990s, it has so far been understood to be relevant in signal transduction processes. In a broad sense, lipid rafts, among other things, function as precursors to caveolae, and it has been suggested that lipid rafts may be important in lipid transport and proteins anchored to glycosylphosphatidylinositol (GPI) within an endocytic pathway and could serve as anchoring sites for the entry of some pathogens and toxins. For example, some viruses such as influenza A virus and human immunodeficiency virus (HIV) obtain proteins for their wrapping such as hemagglutinin (HA) and neuraminidase (NA), proteins that are associated with caveolae.

Currently, lipid rafts are defined as small membrane domains (10–200 nm), heterogeneous, highly dynamic and enriched in sterols and sphingolipids, which gives them a certain rigidity, allowing a better interaction between the ligand and the receptor.

THE NEW SCHOOL... FILOPODIA, LAMELLIPODIA AND RUFFLES

In vertebrates, there are four main components that are part of the cytoskeleton: Actin, intermediate filaments, microtubules and septins, and its organization allows some compartmentalization in the cell. The structuring and dynamics of the cytoskeleton depend on the way the cell is related to the extracellular matrix and such a relationship is what determines the biomechanics of the cells. Mechanotransduction is a term that implies that the mechanical forces applied to the cells are transformed into relevant biochemical events and because of them, there are different processes associated with the development, the physiology and the pathology, and this process is composed of three phenomena: mechanosensation, mechanotransmission and mechanorespond. Mechanotransduction, is a process that has been observed in invasion by pathogens such as *Candida albicans*, *Magnaporthe grisea*, and *Entamoeba histolytica*, but could also be relevant for the behavior of pathogens during their interaction with the cells of their hosts.

As is known, cell extensions (protrusions) are essential for chemotaxis, haptotaxis and motile processes and to date are distinguished three types of them, filopodia, lamellipodia and ruffles, and these extensions depend primarily on actin polymerization. Filopodia can be formed anywhere on the cell surface, for instance, emerging from lamellipodia at the cell's leading edge during migration. Macrophages can use filopodia as tentacles to draw particles towards the cell. The actin polymerization in dorsal ruffles or at the leading edges of motile cells provides the platform of branched actin filaments needed to assemble the macropinosomes. Dorsal ruffles and macropinosomes are co-opted or induced by a wide range of human pathogens and infectious agents, from viruses, to bacteria, protozoa and prions, for entry into human cells [10–12]. In macrophages and immature dendritic cells, membrane ruffling occurs constitutively.

CONSIDERATIONS

The selective pressure on hosts has ensured the development of an immune system capable of eradicating most of the parasites, bacteria and viruses, where the plasma membrane and cytoskeleton are involved in these defense mechanisms. However, many pathogens have acquired the ability to decipher the behavior and function of some components of the cell surface and have learned to exploit them for the infection process and its survival. The biology of infection is devoted to understanding the physiological cellular interactions between microbes and their hosts, these interactions during space-time

determine the result of the relationship, that is, determine whether the interactions will be beneficial or detrimental, in this way, the information that emerges from the fields of molecular biology, immunology, biochemistry together with cellular biology have contributed with remarkable advances in the identification, localization, distribution and redistribution of different components of the cytoskeleton, as well as in the generation of knowledge of morphology, and cell surface function as an organelle that allows interaction with extracellular molecules. Finally, the knowledge acquired on the cell surface, the non-selective nature of macropinocytosis, as well as the mechanisms of reorganization of the cytoskeleton, are essential to develop new preventive measures, new vaccines and new drugs to combat common and emerging diseases; as well as to propose new therapeutic strategies for human diseases in which cytoskeletal components are involved.

Keywords: Cytoskeleton, Pathogens, Plasma membrane, Macropinocytosis

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