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Short review

The role of supramolecular protein complexes and membrane potential in transmembrane signaling processes of lymphocytes

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Abstract

The formation of protein patterns in lymphocyte plasma membranes is analyzed in the light of past and, also, very recent experiments. The analysis surveys the lateral organization of major histocompatibility complex glycoproteins, intercellular adhesion molecule-1, interlukin-2 and -15 receptors, Kv1.3 K^+ ion channels and the T-cell receptor as well as their behavior under different conditions. These molecules form small- and large-scale clusters in the membrane of human lymphocytes. Many of the association motifs occur in other investigated cell types. The conclusions point toward a possible role for ion channel activities, membrane potential changes and alterations of the lateral organization of proteins in transmembrane signaling and cytotoxic interactions. In our outlook new factors that potentially affect membrane protein cluster formation and interactions are discussed. A role for MHC glycoproteins in concentrating membrane proteins and organizing protein patterns is suggested, and the possibility that the membrane potential may modulate protein conformation and, thereby, affect protein–protein interactions is pointed out. A well-defined role for the presence of ion channels in the immune synapse is offered, which could explain the significance of ion channel accumulation in the immune synapse together with the T-cell receptor.

Keywords: Membrane domains; Organization of membrane proteins; Lipid rafts; MHC glycoproteins; IL-2 and -15 receptors; Kv1.3 potassium channel; Membrane potential

1. Introduction

The plasma membrane is the theater of all kinds of material and information exchange between a cell and its environment, i.e. the "outer world". The plasma membrane is basically a lipid bilayer that accommodates a significant number of proteins with diverse structures and tasks necessary for the proper function of cells.

Our concepts about the architecture of the plasma membrane changed radically during the last decades. The "rigid membrane" concept of Danielli and Davson was replaced by the Singer–Nicolson (S–N) fluid mosaic membrane model in 1972 [1], which postulated the random distribution and free lateral mobility of membrane components. The S–N model was based on the ingenious experiment of Frye and Edidin [2], which demonstrated the intermixing of human and murine MHC I glycoproteins in the plasma membrane of heterokaryons of human and mouse lymphocytes. Despite its indisputable significance, the S–N model had a limited validity. First of all, it was mostly applicable to the quasi-symmetric circulating blood cells. Cells in solid tissues (e.g. epithelia, endothelia) are usually polarized, i.e. their plasma membrane is divided into two discrete regions—the apical and the basolateral domains—displaying distinct lipid and protein compositions required by their biological function. Experimental observations suggesting a locally restricted mobility of proteins in the lipid bilayer [3,4] and the existence of hierarchically built protein complexes even in non-polarized cells also contradicted the S–N model [5,6]. A significant breakthrough was the discovery of lipid rafts

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(i.e. sphingolipid- and cholesterol-enriched lipid microdomains) demonstrating that segregation of lipids detected in model membranes could also occur in the more complex cell membrane [7,8]. These data support the concept of "membrane microdomains", i.e. compartmentalization of membrane components into non-random clusters/structures and explains why the mobility of membrane proteins is not uniform.

Signal transduction processes demand the cooperation of various membrane proteins and are often accompanied by dynamic rearrangement of the two-dimensional macromolecular patterns at the cell surface. The structured, and at the same time dynamic nature of the plasma membrane allows accumulation of relevant molecules in particular membrane areas while excludes others, thus preventing their interaction [9,10].

We have suggested the generic occurrence of functional protein aggregates at the beginning of the 1980s [11], based on the preferential interaction of the genetically determined membrane-spanning α-helices of proteins with each other and with certain types of lipids. This hypothesis is now supported by a substantial amount of observations. Biophysical techniques (e.g. fluorescence resonance energy transfer (FRET), confocal laser scanning microscopy (CLSM), scanning force microscopies and electron microscopy, etc.) revealed non-random homo- and hetero-clustering of membrane proteins at various hierarchical levels [5,6,12]. Protein clusters generated by the physical association/molecular proximity of the molecules (nanometer or small-scale clusters) define the basic organization level of membrane proteins [6]. Accumulation of small-scale clusters in larger islands at the submicrometer/micrometer scale can also be observed in many cases [5,10,13]. The stability of interactions, the dynamic properties of membrane proteins and the boundaries of their regions of mobility can be explored by fluorescence correlation spectroscopy and single particle/dye tracking experiments [12,14–16].

In this minireview, we present selected examples of hierarchically built protein complexes involved in T-cell-mediated immunity. Functional implications of the presented protein patterns and the regulatory role of the lipid domain structure of the plasma membrane will be discussed as well. Other yet neglected factors (e.g. the membrane potential; supercluster formation around MHC glycoproteins) that might influence the organization of membrane proteins and, thus, the efficiency of transmembrane signaling processes will be also discussed.

2. Supramolecular protein complexes in T-cell-mediated immune responses

2.1. Supramolecular complexes of MHC I, MHC II and ICAM-1 molecules in antigen presenting cells

The contact area formed between a T-cell and its target or the antigen presenting cell (APC), i.e. the immunological synapse (IS), is a well characterized example of specialized signaling domains where the dynamic assembly of small- and large-scale protein clusters play a critical role [17,18]. Recognition of the antigen causes the redistribution of numerous molecules in both cells and leads to the formation of well-defined junctional structures at the interface of the two cells [19,20].

Whereas antigen-induced redistribution of the relevant molecules on T-cells (e.g. T-cell receptor (TCR), adhesion and co-stimulatory molecules, co-receptors, cytosolic signaling elements) has been extensively characterized (for reviews see e.g. [21–23]), much less attention has been paid to the behavior of the relevant molecules (e.g. MHC and adhesion molecules) and the mechanisms controlling their accumulation on target cells or APCs. In this section, we concentrate on the organization of these molecular species.

Self-association of class I and class II MHC glycoproteins as well as their hetero-association were detected by FRET at the surface of various human cell types including APCs [24–29]. Electron and scanning force microscopic experiments disclosed the presence of larger scale homo- and hetero-clusters of MHC molecules on the order of several tens of nanometers to microns in size [30,31]. For a detailed review see Gombos et al. in this issue.

Molecular associations also occur between MHC glycoproteins and ICAM-1 adhesion molecules in different human cell lines, including T- and B-lymphoma as well as in uveal melanoma and colon carcinoma cells [24–26,32]. IFN-γ changed the expression levels of MHC and ICAM-1 molecules and induced rearrangement of their membrane topography in colon carcinoma and uveal melanoma cells [24,26]. Similar to MHC glycoproteins, a high degree of ICAM-1 self-association was found on HUT102 B2 human T-lymphoma cells [25]. Constitutive or inducible enrichment of MHC and ICAM-1 molecules in lipid rafts was detected in several cell types [26,32–39]. Disruption of lipid raft integrity by cholesterol depletion dispersed MHC clusters [34,36] and translocated them to the soluble, non-raft membrane fraction [32,33]. These data underline the role of lipid rafts in maintaining MHC clusters.

Physical association of MHC I and ICAM-1 was observed both in detergent-insoluble and -soluble membranes in B-lymphoblasts [32]. Disruption of rafts resulted in a significant loss of MHC I and ICAM-1 from the raft fraction, but their association was still detectable, implying that this interaction does not critically depend on the integrity of rafts. However, enrichment of ICAM-1—MHC I assemblies in lipid rafts allowed their interaction with Src kinases also harbored in lipid rafts, thus facilitating efficient presentation of viral peptides to CTLs [32].

It is conceivable that in vivo formation of the aforementioned complexes of MHC and ICAM-1 molecules may strengthen the APC-T-cell interaction and facilitate IS formation. For a detailed review of data supporting this idea see Gombos et al. in this issue.

2.2. Supramolecular complexes of IL-2/IL-15R and MHC glycoproteins on human T-lymphoma cells

IL-2 and IL-15 are substantially involved in controlling T-cell homeostasis and function [40]. Their receptors comprise three distinct components: whereas the α-chains are cytokine-specific, the β- and γ_c-subunits are utilized by both IL-2 and IL-15. The so-called common γ_c-chain is the component of a series of other cytokine receptors (IL-4, IL-7, IL-9 and IL-21). As a