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MEMBRANE CHANGES IN MALIGNANT CELLS - MODULATION OF RECEPTORS AND ANTIGENS BY LIPIDS

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Abstract

The dynamic characteristics of lipid regions in biological membranes can be expressed in terms of microviscosity parameters. These parameters not only determine the lateral and rotational movements of specific membrane sites but also their degree of exposure to the outer surrounding. Changes in microviscosity can thus reversibly displace the vertical position of antigens or receptor sites and modulate their active expression. The lipid mediated modulation of antigens and receptors may play an active role in the various physiological manifestations of malignant cells.

Zusammenfassung

Die dynamische Charakteristik lipider Regionen in biologischen Membranen kann ausgedrückt werden als Funktion von Mikroviskositätsparameter. Diese Parameter bestimmen nicht nur die lateralen und rotatorischen Bewegungen spezifischer aktiver Membranorte, sondern auch ihren Grad der äusseren Exposition ihrer Umgebung gegenüber. Aenderungen in der Mikroviskosität können so reversibel die vertikale Position von Antigenen und Rezeptoren verschieben und ihre Aktivität verändern. Die lipoidbedingte Aktivitätänderung von Antigenen und Rezeptoren kann eine aktive Rolle in den verschiedenen physiologischen Manifestationen maligner Zellen spielen.

In the last decade the main field of interest among biophysicists has abruptly turned from macromolecules to supramolecular structures like biological membranes. With the ever unfailing improvement of highly specialized physico-chemical techniques we have witnessed how the molecular architecture of biological membrane is being steadily unwound, and we

are now slowly approaching the stage where complex membrane functions could be expressed in terms of structural-dynamic processes of its molecular constituents.

Up until recently it was generally accepted that the two integral components of biological membranes - proteins and lipids - share distinctive tasks. The proteins were confined to specific membrane functions like receptor sites, transport mediators and regulatory enzymes, whereas the lipids were believed to merely provide the proper fluid matrix which regulates the activity of the proteins. However, it has been now realised that such a distinction is in fact blurred, and the determination and maintenance of the various fluidity and functional properties of the membrane is achieved by full cooperation between proteins and lipids.

The current notion on structure of biological membranes is of a protein network, among which fluid lipid domaines are spread, and which is underlined with a texture of actin-myosin type filaments. Some of the membrane proteins are believed to be attached, chemically or physically, to these filaments and thus to conduct exogeneous signals into the cell interior.

Except for the lipids which are in direct contact with the proteins, the lipids which form the fluid domains of the membrane are in a constant thermal motion and reshuffling. The fluidity characteristics of these domains are obviously complex and change markedly at different sections of the lipid bilayer. However, in the hydrocarbon core of the lipid layer the fluidity can be described in terms analogous to viscous flow in hydrocarbon liquids (e.g. paraffin oil), which are well characterized and understood. Thus, the analogous term for viscosity in hydrocarbon liquids is microviscosity, which was introduced by us some six years ago, and which applies to the hydrocarbon core of the membrane.

The lipid microviscosity which surrounds a specific functional protein in the membrane determines its dynamic properties as manifested by the various modes of its lateral and rotational motions. These types of motion, in turn, determine the turnover rate of the protein function be it enzymic activity, transport or signal transduction. However, superimposable on this important collaboration between lipids and proteins lies a less predictable collaborative mode between the two, which has been recently discovered, and still being investigated in our laboratory. Changes in lipid microviscosity apparently displace vertically membrane proteins to an equilibrium position which will maintain the structural-function integrity of the membrane. An increase in microviscosity will squeeze out proteins, and probably even functional glycolipids, which will then become more exposed to the aqueous surrounding. Conversely, decrease in lipid microviscosity will conceal the proteins and may even turn off their specific function. Needless to say, the degree of exposure of functional sites in the cell plasma membrane may play an important role in determination and regulation of cellular functions. Moreover, changes in membrane microviscosity may be involved in the

mechanisms by which specific antigens or receptors are modulated during developmental and differentiation processes, and in the various steps of malignant transformation. This modulation mechanism can be of functional importance when the antigenic recognition of cancer cells is altered during the various stages of tumour development.

Since the above proposed modulation is mediated by changes in lipid microviscosity, the physical and the biochemical mechanisms underlying membrane microviscosity will be discussed in the following.

Generally and qualitatively speaking, the following processes can lead to an increase in membrane microviscosity: a) increase in cholesterol level, b) decrease in degree of unsaturation or length of the phospholipid acyl chains, c) increase in mole ratio of sphingomyelin to lecithin and d) increase in protein to lipid ratio. Obviously, there are subtle differences between the effects induced by each of these changes, and in some cases they may collaborate in order to induce the proper dynamic change. Moreover, when a specific membrane site is monitored, its local lipid surrounding, which will strongly affect its function, can be of different composition than the bulk lipid pool. Unfortunately, in most cases the currently available methods for following lipid dynamics give us overall type answers concerning the whole lipid population of the membrane. In principle, however, long range effects could be of substantial importance in controlling the dynamics of specific sites, and therefore an overall picture of membrane dynamics is still valid for drawing information relating to modulation of a specific receptor or antigen.

About half of the cholesterol molecules in cell outer membranes are readily exchangeable with exogenous lipid pools like the blood serum. Such an exchange can lead to a net translocation of cholesterol towards an equilibrium state where the mole ratio of free cholesterol to phospholipids in the membrane and in its surrounding is about equal. This process is especially pertinent to blood cells - erythrocytes, leukocytes and platelets - which are in full contact with the serum. In these cells the cholesterol level was shown to modify reversibly morphological and functional characteristics. In solid tissue cells the contact with the serum cholesterol is indirect, and presumably involves receptors for the β-lipoprotein, which is the main source of free cholesterol in the serum. Through the complex with the receptor cholesterol translocation in cells of solid tissues can be effective though it occurs less readily than in blood cells.

The cholesterol translocation processes are presumably confined to the outer half of the cell plasma membrane. There are two other biosynthetic mechanisms which at least initially affect the cholesterol level of the membrane inner half. These are intracellular cholesterol

biosynthesis, and the synthesis and hydrolysis of cholesterol esters. Since cholesterol esters are not integral components of biological membranes the latter mechanisms will affect the membrane cholesterol level indirectly. When the cholesterol biosynthesis is considered it should be correlated with the rate of phospholipid synthesis, as the cholesterol to phospholipid mole ratio is in fact the parameter which determines the lipid microviscosity of the membrane. In addition, thermal displacement of cholesterol between the outer and inner halves of biological membranes is a slow process which nevertheless should be considered. The physiological effects which follow the above described changes in cholesterol level could therefore be of different magnitudes at different time scales. In any event, exposure of cells to constant physiological conditions for long periods of time, days or weeks, will equally affect the cholesterol level in both sides of the membrane.

The mechanisms described above, which control the cholesterol level and the related effects on membrane dynamics, were extensively studied in the last decade. However, other processes which may be equally important are now only partially elucidated. One of these concerns the degree of unsaturation of the phospholipid acyl chains. Free fatty acids are incorporated relatively rapidly into cell membranes where they can change the membrane fluidity according to their degree of unsaturation, the cis or trans configuration of the double bonds and the number of carbon atoms. The incorporated fatty acid can rapidly migrate to inner cell membranes and to sites where they are being utilized for biosynthesis of phospholipids. Part of the phospholipids which contain the incorporated fatty acids as acyl chains will eventually settle in the cell surface membrane where their effect on fluidity properties will be expressed.

Unlike cholesterol and fatty acid, the rate of phospholipid translocation between cell membranes and the outer surrounding is negligible compared to the biosynthetic rates. Changes in the phospholipid composition of the cell membrane which result from changes in intracellular metabolic pathways were observed upon aging, differentiation and malignant transformation. The most prominent of these is the change in the relative level of the most prevalent phospholipids - lecithin and sphingomyelin. Lecithin has several common structural features with sphingomyelin and in some membranes it can be converted enzymatically to the latter. However, the effect on microviscosity paramters of these two phospholipids is markedly different. Generally, maturation or differentiation of cells, as from brain or nerve tissues, is associated with a net conversion of lecithin to sphingomyelin which will qualitatively contribute to an increase in membrane microviscosity.

In a series of studies with model membrane systems which are still in progress, we could de-

monstrate the proposed vertical movement and the change in degree of exposure of membrane proteins, upon changing the lipid microviscosity. Currently, the amount of data available for intact viable cells which can support the modulation mechanism presented here is still very limited, and the prevalence of the proposed mechanism in vivo should be tentatively regarded as a working hypothesis.

Lymphocytes are among the cells in which correlations between function and membrane microviscosity were extensively studied. We have shown that maturation of lymphocytes is accompanied by an increase in membrane microviscosity partially due to passive acquisition of serum cholesterol by the immature cells after they are extruded into the blood stream. It is plausible that this increase in microviscosity contributes to the emergence of antigens and immunoglobulins in the cell surface of the various lymphocyte sub-populations. Moreover, the microviscosity of a mature lymphocyte may pass a level where the exposure of immunoglobulins will be so great that it will eventually lead to a complete detachment of the protein, a process which may take place in antibody excretion.

In solid tissue tumours the transformation of primary tumour cells to metastatic cells can be the result of modulation or loss of antigenic determinants. It is not yet known whether this transformation is indeed accompanied by the appropriate changes in cell membrane microviscosity. If this will turn out to be the case, it may open new approaches to treatment and control of the yet undefeated process of metastasis of malignant cells.

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