The Bending Elasticity Concept of Biomembrane Function

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Abstract

Cell plasma membranes are composite shells composed of two semiflexible layers: the (smectic liquid crystalline) lipid/protein bilayer and the actin based macromolecular network, which is coupled to the bilayer in a controllable way. The bilayer shell is an open system owing to its coupling to microbuds and vesicles. The important role of these coupled shells for the control of cell adhesion is discussed.

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From a phenomenological point of view biomembranes are two-dimensional smectic liquid crystals which has two important consequences. They exhibit bending elasticity (Evans, 1974) and their lateral organization and local curvature can be sensitively regulated by adsorption of macromolecules. The bending elasticity plays a ubiquitous role for many membrane processes (Sackmann, 1994). Examples are (1) the budding of vesicles by the adsorption of clathrin coats to the lipid bilayer during endocytosis or intracellular trafficking by vesicles (where budding is induced in a controlled way by local bending moments), (2) the control of shapes of cells and intracellular compartments, and (3) the control of adhesion of cells.

A distinct feature of the lipid-protein bilayer is its extremely low bending modulus (κ) which can be reduced to a few k_BT by addition of small amounts of solutes (in particular amphiphiles). Owing to this small bending modulus, membranes exhibit pronounced thermally excited bending undulations which lead to entropy driven repulsion forces between membranes of cells or cell membranes and solids (Helfrich and Harbich, 1984; Lipowsky and Seifert, 1991)). The remarkably strong repulsive potential of the undulation forces of tension free membranes exhibits the same distance (h) dependenc as the van der Waals potential: namely $V_{rep} \approx (k_BT)^2/\kappa h^2$ and can largely compensate the van der Waals attraction between membranes and solids (Rädler et al., 1995). It

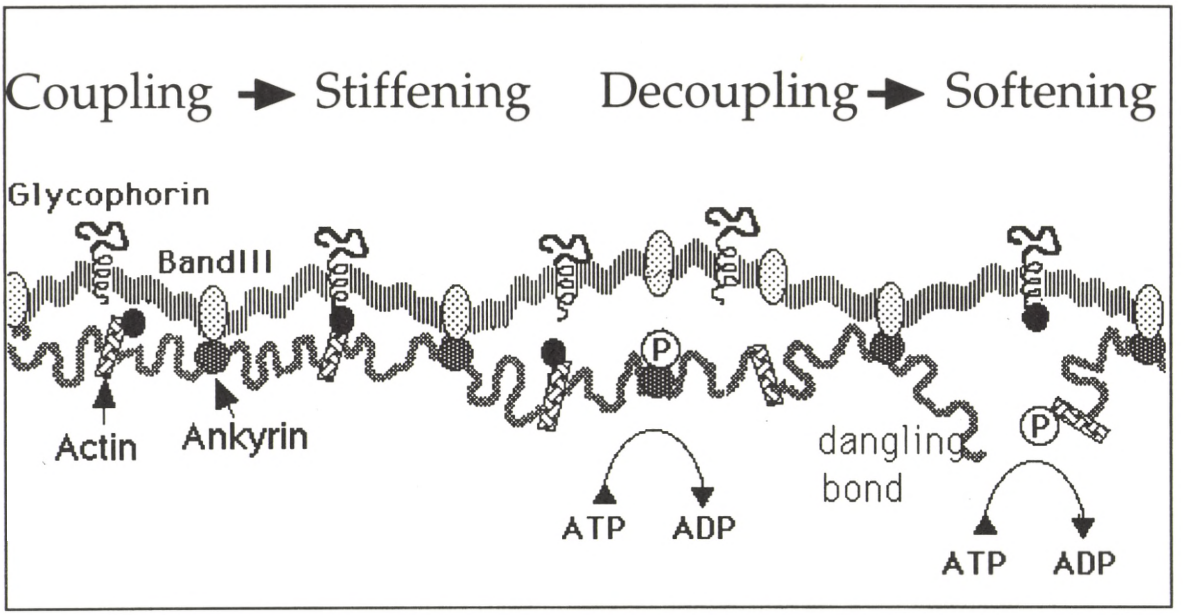

Figure 1. Present view of composite plasma membrane of erythrocytes (viewed parallel to the membrane). The quasi-two-dimensional macromolecular mesh exhibiting roughly a triangular network is composed of flexible spectrin tetramers (end-to-end distances ~80nm) interconnected by actin oligomers. The network is coupled to integral proteins of the bilayer through coupling proteins (ankyrin and band 4.1). However, direct interaction of spectrin with the negatively charged inner leaflet of the bilayer is also possible (as suggested by neutron reflectivity studies of model membrane systems).

may help to prevent the fall of cells into the van der Waals hole.

The development of eukaryotic cells became possible only after Nature found the trick with the composite membrane by combining the hyperelastic bilayers with quasi two dimensional macromolecular networks (Häckl et al., 1998). The red cell membrane is the simplest and most prominent example (Fig. 1).

In most cells the membrane associated macromolecular network consists of a thin shell of the actin based cytoskeleton ($\sim$ 0.2μm thick): the actin cortex. The coupling of the network to the bilayer introduces two new features. The membrane exhibits shear elasticity and the flexural rigidity of the composite membranes can be varied enormously through the degree of coupling of the two shells. Erythrocyte membranes for example are extremely soft (bending $\kappa \sim 10 k_B T$) which is attributed to continuous ATP-driven coupling and decouplings of the coupling protein (ankyrin and band 4.1) to their respective membrane proteins resulting in transient dangling bonds (Sackmann, 1996). The cells exhibit very strong bending fluctuations (so-called flickering) which may be even driven by ATP-dependent chemical fluctuating forces (cf. Sackmann, 1996). The much thicker actin cortex of other cells is coupled to the bilayer through the coupling proteins vinculin plus talin to receptors of the integrin family or through band 4.1-like molecules to receptors for extracellular matrix proteins such as for hyaluronic acid. In this case the composite membrane is much stiffer ($\kappa \sim 1000 k_B T$). Uncoupling the two shells by mutagenic removal of talin, for instance, results in the reduction of the membrane bending modulus from $1000 k_B T$ to $100 k_B T$, the value characteristic for bilayers containing about 50mole% of cholesterol.

The control of the membrane bending elasticity through the bilayer-cytoskeleton coupling plays a key role for the regulation of cell adhesion. This

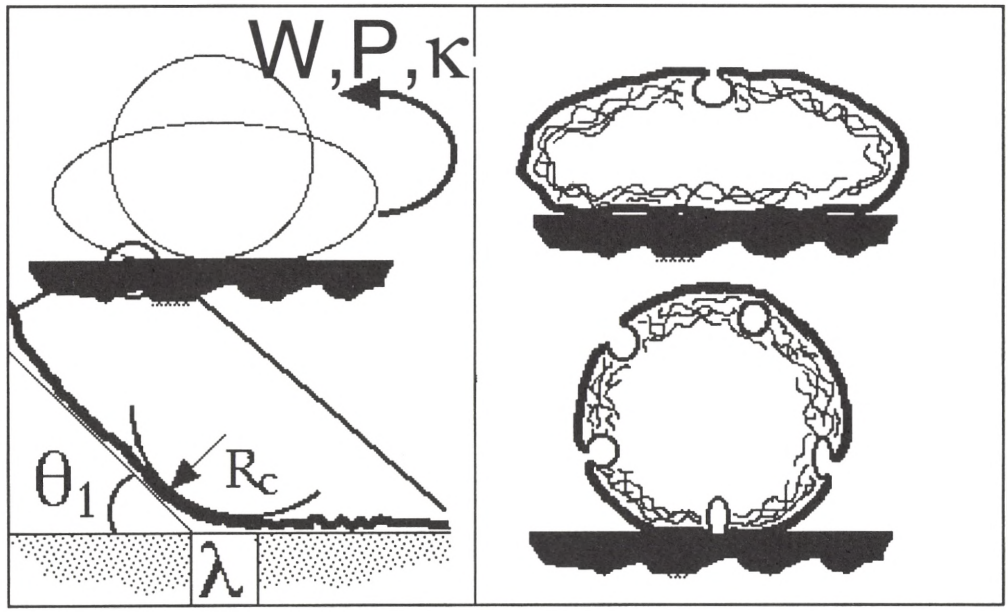

Figure 2. a) Illustration that shell may detach from the substrate by decrease of the adhesion energy (W), by rounding through osmotic swelling (P) and by membrane stiffening (κ). The lower part shows the enlarged contour near the surface. It is determined by the elastic boundary conditions which result in defined values of the contact angle and the contact curvature. b) Demonstration that composite membranes may decrease the effective area-to-volume ratio and unbind by contraction of the cytoskeleton. The excess area of the bilayer can be stored in undulations or in buds or can be released by vesicle fission.

most fascinating phenomenon is controlled by the interplay of specific receptor mediated lock-and-key forces and a manifold of (nonspecific) universal forces (including electrostatic, van der Waals and undulation forces (Sackmann, 1996)); but also by the membrane bending elasticity due to adhesion induced shape changes. The adhesion therefore is described by the general free energy

$$\Delta G = \int pdV - WA_c + \gamma \int dA + \frac{1}{2}\kappa \int \left(\frac{1}{R_1} + \frac{1}{R_2} - C_o\right)^2 dS$$

A_c is the contact area, γ is the membrane tension, R_1 and R_2 are the principal radii of curvature of the soft elastic shell and C_o is the spontaneous curvature. The first three terms correspond to the energy associated with the osmotic pressure, the membrane tension and the adhesion energy, respectively. These contributions describe completely also wetting by fluid droplets. The last term is unique for soft elastic shells and accounts for the bending energy (Evans, 1974) associated with the adhesion induced shape changes.

The adhesion induces tension causing flattening of the membrane near the substrate (which allows the definition of a contact angle θ_1) while the bending elasticity enforces rounding at the contact line (characterized by a contact curvature R_c), cf. Fig. 2. The shape near the surface is essentially determined by the elastic boundary condition which allows quantitative analysis of adhesion solely by considering the shape near the surface by application of microinterferometry (Rädler et al., 1996).

Adhesion induced domain formation is a nucleation process, as illustrated in Fig. 3. The interplay of receptor mediated short range attraction and long range repulsion (e.g. by steric repulsion between macromolecules of glycocalyx and/or undulation forces) leads to the spontaneous forma-

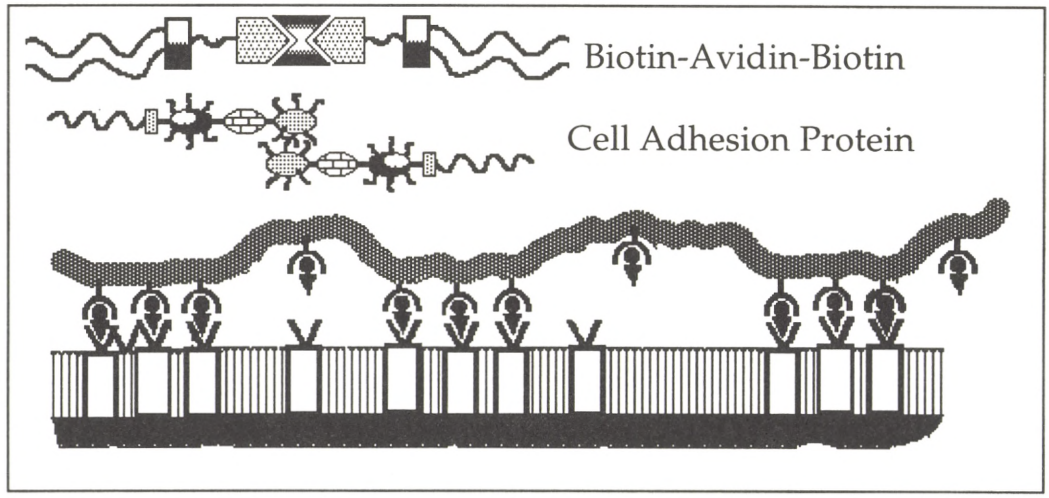

Figure 3. Adhesion induced domain formation. Model system (giant vesicle adhering to supported membrane = phantom cell) showing adhesion plaque formation. The glycocalyx is mimicked by lipopolymers. The specific forces are generated by contact site A cell adhesion molecules or by biotin-streptavidin-biotin linkage. Adhesion plaques are formed as a consequence of interplay of short range receptor mediated forces and long range (polymer-induced electrostactic or undulation-induced) forces favouring different equilibrium distances (after Sackmann (1996)).

tion of tight adhesion domains. The origin of the spontaneous formation of tight adhesion plaques is a consequence of the fact that the attraction and repulsion forces favour different equilibrium distances. In order to form tight bonds, work has to be performed against the repulsive force (e.g. undulation force or any other long range repulsion force). Single bonds are therefore extremely unstable.

The local bending of the bilayer at the transition between the domains is associated with an elastic line tension τ. The line tension must be overcompensated by the gain in adhesion energy, ΔW, which requires a minimum radius of the adhesion cluster $\rho \geq 2\tau/\Delta W$. τ is of the order $\kappa d/R_c^2$ where R_c is the contact curvature (defined in Fig. 2) and d is the height difference between the two types of adhesion domains. Typically $R_c \cong$ 100nm, $d = 100$nm, $W \sim 10^{-6}\mathrm{J/m}^2$ and one finds critical radii of the order of 1μm.

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