How Cholesterol Influences Intercellular Interaction: Its Possible Role in Metastasis

In a letter (1) on the surface-chemical theory of cancer, it was suggested that cholesterol is responsible both for cell division and cell release and its influence in metastasis would be through decreasing the intercellular adhesional forces, by reducing the interfacial surface tension of the cell membrane. We try in this letter to give another insight into this problem by analyzing the intercellular forces given by the DLVO-theory. Experimental evidence of the validity of this theory (2, 3) on cell adhesion was shown by Gingell and Fornés (4, 5).

We analyze here quantitatively the influence of cholesterol on both components of the force (attractive and repulsive). With respect to the attractive component we have performed calculations following the theory on electrodynamic interactions between cell surfaces described in (6).

The composition and dielectric constants of the various layers of the cell surface are:

Surface coat: 0.2 galactose, 0.2 water, 0.6 albumin, $\epsilon = 5$.

Plasma membrane: $\epsilon = 5$.; we maintain constant the relation between the mole fractions of dipalmitoyllecithin (χ_1) and albumin (χ_2), namely:

$$\frac{\chi_1}{\chi_2} = \frac{0.5}{0.4} = 1.25 = K \qquad [1]$$

The mole fraction of cholesterol (χ_3) is such that

$$\chi_1 + \chi_2 + \chi_3 = 1 \qquad [2]$$

From [1] and [2] we obtain, in function of the variation of cholesterol mole fraction:

$$\chi_1 = K\frac{1 - \chi_3}{1 + K} \qquad [3]$$

$$\chi_2 = \frac{1 - \chi_3}{1 + K} \qquad [4]$$

The composition of the protoplasmic interior and extracellular fluid is considered to be 0.1 albumin and 0.9 water. The value of ϵ is considered to be 80 for these mixtures. The membrane and surface coat thicknesses are considered to be 50 and 75 Å, respectively. The coefficients C_{ik} and the frequencies ω_{ik} of all substances for calculating the intercellular force were taken from (6–8).

The variation of cholesterol concentration was $0.1 \leqslant \chi_3 \leqslant 0.3$. The respective variations in attractive force and energy for 100 Å intercellular distance were 2.60×10^3 dyne/cm$^2 \leqslant F_a \leqslant 2.64 \times 10^3$ dyne/cm^2 and $1.30 \times 10^{-3} \leqslant G_a \leqslant 1.32 \times 10^{-3}$ erg/cm^2. We observe that the electrodynamic attraction hardly changes because the Hamaker function is almost insensible to cholesterol variation. This is valid for any value of the intercellular distance.

We analyze now the repulsive force. A reasonable model is that of Ohshima (9). In his model he obtained for the repulsive component of the force:

$$F_r = \epsilon\kappa^2\psi_0^2/2\pi\left[\exp\left(\frac{1}{2}\kappa h\right) - \left(\frac{1-\alpha}{1+\alpha}\right)\exp\left(-\frac{1}{2}\kappa h\right)\right]^2 \qquad [5]$$

$$\psi_0 = \frac{1}{1+\alpha}\left[\frac{4\pi\sigma}{\epsilon\kappa} + \alpha\left(\frac{4\pi\sigma^*}{\epsilon^*\kappa^*} + \Psi\right)\right] \qquad [6]$$

$$\alpha = \left[\left(\frac{\epsilon\kappa}{\epsilon^*\kappa^*}\right) + \left(\frac{\epsilon\kappa d}{\epsilon'}\right)\right]^{-1} \qquad [7]$$

where ϵ, ϵ^*, and ϵ' are, respectively, the dielectric constants of the extracellular fluid, protoplasmic interior, and membrane, σ and σ^* are, respectively, the charge densities of the outer and inner surfaces of the membrane, d is the membrane thickness, κ and κ^* are, respectively, the Debye–Hückel parameters of the solution outside and inside the cell, Ψ the potential in the protoplasmic interior, and h the intercellular distance.

Putting values to the formulas: $\sigma = \sigma^*$, $\Psi = -50/100$ mV, $d \simeq 100$ Å, $\epsilon \simeq \epsilon^* \simeq 80$ and $\kappa^{-1} \simeq \kappa^{*-1} \simeq 8$ Å in physiological conditions, $3 < \epsilon' < 10$; we observe that ψ_0 is almost insensible to variations in ϵ' but not to the cell surface charge.

So, fundamentally, if cholesterol alters the intercellular repulsive force, it would be altering the surface charge.

Burgheim and Joel (10) stated that the concentration of cholesterol is 0.3 to 0.7% in benign tissue, and from 1 to 3% in neoplastic tissue. Ambrose *et al.* (11) stated: "The average charge density of the tumor cells is almost twice that observed with the normal cells from which they have been derived."

Therefore an interesting experiment to perform would be to put different concentrations of cholesterol in different samples of cells and observe how the surface charge changes.

ACKNOWLEDGMENTS

The author is grateful to Professor Q. I. Pacheco for computational assistance and Professor J. O'M. Bockris for having introduced him to this subject.

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0021-9797/84 $3.00

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Received October 7, 1983