Main principles of Ling's physical theory of the living cell

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Purpose of the theory

The purpose of the theory is to establish the physical nature of the living state. The theory explains the physical mechanisms underlying the key phenomenon of life – the distribution of substances between the cell and its environment and among cell compartments. All other mechanisms important for cell physiology and cell biology depend crucially on our understanding of this phenomenon.

Physical mechanisms that the theory uses

The basic physical mechanism is controlled selective adsorption of substances by cell proteins. If some substance accumulates in the cell to a level higher than in the surrounding medium, it means that it is adsorbed by cellular structures. Cell selective permeability, osmotic stability, electrical potentials and active transport are the result of selective adsorption of water and physiologically important cations by cellular proteins. ATP is the main regulator of adsorption through the inductive effect. The theory uses basic physical principles that make it a versatile tool to describe any mechanisms of the functioning of the living cell and its pathology. The long range, dynamic structuring of water molecules is due to what Debye called 'orientation polarization'. The basic physical mechanism includes not just adsorption, which is one form of association, but also electrical polarization, or induction.

Two-state model of cell function

According to the theory, the functioning of the cell is considered as a reversible transition between two states, the resting state and the state of activity. The resting state is a stable state with a favorable negative free energy**.** Constant influx of energy and matter is not necessary to maintain this state. The action of an external stimulus or internal signal is to destabilize the resting state and the cell becomes active. The energy is released and is used to perform biological functions. Metabolic processes start in the activated cell, new ATP molecules are synthesized and the cell re-enters the resting state. A cell in the resting state has a favorable negative free energy owing to the adsorption energy of ATP bound by proteins. Activation of the cell starts with the splitting of ATP. The two-state model can be applied to every structure in the cell down to single protein molecules.

Which proteins determine the sorption properties of the cell?

In the resting state, fully extended proteins adsorb the key components (in the physical sense) of the cell: ATP, water and potassium ions. According to the contemporary literature, 30-40% of all cell proteins are natively unfolded proteins. Perhaps these proteins (or some of them) belong to the set of fully unfolded proteins considered by Ling's theory.

Physical nature of selective adsorption

The following functional groups of proteins have key significance for the theory: the NH- and CO-groups of peptide bonds, and the carboxyl groups of dicarboxylic amino acid residues. The selectivities of peptide groups differ between the two states in respect of: (1) affinity for water molecules, and (2) affinity for the same groups in other peptide bonds in the protein. The selectivity of the carboxylic groups differs in respect of (1) affinity for potassium ions, and (2) affinity for sodium ions or for fixed cationic groups of the protein. The first state of the

groups is inherent in the resting state of the cell (or its parts). The second state indicates the active state of the protein. The affinity depends on electron density in the considered functional groups. Low density is characteristic of the resting state, high density of the activated state. The main regulator of the electron density is ATP, which has electron acceptor properties (Ca^{2+}, signal factors, hormones, and chemical modifications of proteins may also assist). In the resting state, ATP is bound by protein and it displaces the electron density in the protein molecule to a site where it is adsorbed. When ATP is split, the electron density in the functional groups increases and their affinity becomes that of the second state.

Adsorption of water

The polypeptide backbone of any completely unfolded protein exhibits a geometrically regular order of positive (NH) and negative (CO) charges of the dipoles (similar to a one-dimensional crystal grid). This geometry is complementary to a space between the water molecules surrounding the completely unfolded protein. The complementarity creates conditions for multilayer adsorption of water on the protein surface. As a result, much of the cellular water (the most massive component of the cell, about 44 moles/l) is transformed into an dynamically ordered structure (the entropy of the system is decreased). Because of its interaction with the backbone dipoles, the dipole moment of the adsorbed water is greater than that of free water. Water molecules with larger dipole moments form stronger dipole-dipole interactions (hydrogen bonds are not the only way in which water dipoles interact, but they are the major contributors; if you consider all forces involved in the interaction, it is better to talk about strengthening of the dipole-dipole interactions in general). It is more difficult for molecules of a solute to break the stronger interaction between molecules of adsorbed water, so this water is a poor solvent compared to bulk water. Therefore, solutes are displaced from the volume of adsorbed water into the bulk water space. Strongly adsorbed water is a barrier to diffusion of large solutes and solutes with incompatible surface structures. The water on the cell surface (rather than lipids) explains the property of cell selective permeability. When you activate a resting cell or some its structure, water is desorbed from the unfolded proteins and the path for diffusion becomes open. The selectivity of each functional group of the polypeptide backbone changes from water to the other functional group of the backbone, and secondary structures of the protein appear (alpha-helix, for example).

Adsorption of potassium ions

Potassium ions accumulate in the resting cell by selective adsorption by the carboxyl groups of dicarboxylic amino acid residues. When the cell is activated, the carboxyl groups lose their affinity for potassium ions and acquire greater selectivity for sodium ions or to fixed cations of the protein. Potassium ions adsorbed by proteins in the microscopically thin surface layer of a cell produce a resting electrical potential. When the water in the surface layer is desorbed, the water barrier collapses and external sodium ions enter the cell generating a sodium diffusion potential. Sodium ions penetrate into the cell surface and displace potassium ions from the adsorption sites. Potassium ions become free, forming a flow into the environment and generating potassium diffusion potential. These two diffusion potentials shape an action potential.

Structural unit of protoplasm

Protein molecules with bound ATP, water and potassium ions constitute a minimal structure that preserves the basic physical properties of the whole living cell. The vital activity of the cell is reduced to transitions (not a steady-state regime) between the two states:

$$\text{protein}(ATP)_m(H_2O)_n(K^+)_q \leftrightarrow \text{protein} + m\text{ADP} + m\text{Pi} + nH_2O + qK^+$$

The key consequences of the theory

The *resting potential* is the result of the selective adsorption of potassium ions by proteins in the microscopically thin surface layer of the cell.

The *action potential* is a result of desorption of water from the microscopically thin cell surface protein layer and the appearance of (1) a diffusion electrical potential of sodium ions (influx), and then (2) potassium ions (efflux).

The cell is *osmotically* stable, in equilibrium with an isotonic solution, owing to the bound state of water (not because intracellular ions are free). In the resting state intracellular potassium ions (the most massive ions) are not free.

The significance of Ling's theory for cell biology

Ling's theory is a revolutionary approach to solving the fundamental problems of cell physiology and biology. It affords us a fresh look at old and modern problems of biology. It is a new methodology of analysis of normal physiological processes and cellular pathology. The distribution of Ling's theory through the scientific community will give scientists an alternative view of the physical mechanisms that are of principal importance for cell physiology, biology and medicine.

See Ling's papers to follow the development of the theory and its comparison with current views

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Ling's personal web site

Acknowledgments. I thank Gilbert Ling and Paul Agutter for valuable comments on the manuscript.

May 17, 2012
St.Petersburg, Russia