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Coupling of Cell Structure to Cell Metabolism and Function

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Abstract The fact that cells make directed decisions regarding how to use energy, i.e., where to direct intracellular particles or where to move, suggests that energy can be, and is, harnessed in specific ways. It is now well established that the chemical reactions of the cell do not occur in nonorganized soup, but rather in the context of ordered structure. The physical components that make up this ordered structure of the cell are part of the tissue matrix, which consists of the dynamic linkages between the skeletal networks of the nucleus (the nuclear matrix), the cytoplasm (the cytoskeleton), and the extracellular environment (the extracellular matrix). To understand gene function and how the energy of the cell is directed towards accomplishing the tasks directed by DNA (gene expression), a further understanding of how cell structure is tied to cellular energy and function is required. We propose that the structural components of the cell harness cellular energy to direct cell functions by providing a dynamic bridge between thermodynamics and gene expression. © 1994 Wiley-Liss, Inc.

Key words: intracellular particles, tissue matrix, skeletal networks, cytoplasm, extracellular environment

In 1972, Aaron Katchalsky wrote that ". . . all living things are extremely complex and heterogeneous and require a suitable device to *hook-up* the nonsteady thermodynamic flows and forces" [Katchalsky, 1976]. The nature of these devices have remained elusive; the processes by which thermodynamic energy is converted to chemomechanical force are still poorly defined. Life is sustained by biochemical reactions, but a thermodynamic process which occurs in an unstructured environment has no memory of its action. Life must, therefore, have mechanisms to harness the energy of its chemical reactions into functional meaning. We believe that these harnessing mechanisms are to be found in the structural components of the cell, i.e., the tissue matrix.

LAWS OF THERMODYNAMICS AT THE LEVEL OF THE CELL

The first law of thermodynamics states that energy cannot be created or destroyed. Mathematically, this law can be stated as "the sum total of energy within a system is equal to the potential energy or available work plus the total internal or kinetic energy." Examples of the potential energy of life at the cellular level may include the amount of ATP a cell contains or the energy created by a charged and polarized cell membrane. Another example of potential energy lies in the structure of DNA and proteins themselves where the folding and resultant charge of macromolecules imparts to them a potential chemoreactivity. Kinetic energy of the cell can be viewed as the heat production associated with cellular work as well as the physical movement of the cell and its intracellular particles. The conservation of energy that this law implies states that a cell, as it functions, must work to remain in equilibrium with its environment. The fact that cells make directed decisions regarding how to use this energy, i.e., where to direct intracellular particles or where to move, suggests that energy can be, and is, harnessed in specific ways.

The second law of thermodynamics states that it is impossible for any system to undergo a process where it absorbs heat from a reservoir at a single temperature and convert it completely into mechanical work. This second law is also referred to as the law of entropy and is often

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restated as "no process is possible in which the entropy decreases." Simply put, the randomness or disorder of every system is always thought to increase. It appears that life and life processes defy this second law of thermodynamics until death. Upon death, the laws of entropy take over and a once ordered system becomes disordered and random. Life, however, is a system which creates order. Cells structure their biochemical processes in such a way as to stay ahead of entropy. Cells generate mechanical energy (work) through biochemical reactions that release energy in a structured fashion that leads to cellular function. At a nuclear level, DNA, as a biochemical means of holding cellular memory and life pattern, defies entropy. DNA may be considered a chemical script that enables biochemical processes to continue maintenance of the cell, and ultimately, the organism, i.e., within every organism, DNA is the chemical structure which allows a functional jump over the thermodynamic law of entropy or disorder.

The maintenance of the first law, and the defiance of the second, by cells, is accomplished by harnessing the energy of biochemical reactions governed by the laws of thermodynamics into specific functions. The coupling of energy to directed function may be accomplished within the cell by structure. It is well established that the chemical reactions of the cell do not occur in "a soup," but rather in the context of ordered structure. The physical components that make up this ordered structure of the cell are generally referred to as the tissue matrix. The tissue matrix consists of the dynamic linkages between the skeletal networks of the nucleus (the nuclear matrix), the cytoplasm (the cytoskeleton), and the extracellular environment (the extracellular matrix) [Bissell et al., 1981; Isaacs et al., 1981; Pienta et al., 1989]. To understand gene function and how the energy of the cell is directed towards accomplishing the tasks directed by DNA, a further understanding of how cell structure is tied to cellular energy and function is required.

STRUCTURE AND FUNCTION AT THE LEVEL OF THE MOLECULE

Cellular energy can be tied to cellular function at a variety of levels. At the level of the molecules themselves, for example, it is possible to postulate the involvement of electromagnetic force in tieing structure to directed function. Electromagnetism is well described in physics as one of the fundamental forces present in nature. Electromagnetic fields are generated when charged particles or structures are subjected to movement and are represented by the equation $F = q(E + (v \times B))$ where E = electric field density, v = velocity of movement, B = magnetic field density, and q = charge. We speculate that DNA itself within the nucleus can be considered in terms of an electrical component of a circuit. DNA in its solenoidal form may be considered a conductive wire of nucleic acids wrapped around a conductive core of histones. If current (charge) flows through a wire (DNA), a magnetic field is generated in the core (histones), creating an electrical magnet (see Fig. 1). The reverse is also true, a magnetic field will cause current flow in a wire. Potentially, DNA in this form could create and harness electromagnetic force which is significant for the local milieu. As DNA twists and turns, structural currents and magnetic fields could be communicated to surrounding nuclear components. Vice-versa, the mechanical force generated by the movement of DNA and histone cores may create a flux of current in the DNA. If current is generated, then so too is a magnetic field. Within a cell, in addition to the nucleic acids, charges and electric dipoles are found on lipids, proteins, carbohydrates, and in the form of free and bound ions [Tsong, 1990]. It is possible that electromagnetic forces play a role in the transfer of energy into structured, chemomechanical forces. The structure of DNA is bound to the RNA-protein network of the nuclear matrix and is the site of active transcription, involving the function of several enzymes within the local milieu of the nucleus. Tsong [1990] has postulated that enzymes can undergo conformational structural changes by coulombic interactions with oscillating electric fields of small magnitude [Tsong, 1990]. Friedrichs and colleagues have demonstrated the importance of local field effects on tertiary protein structure by describing associative memory Hamiltonians which are not dependent on amino acid sequences but rather on the protein structure within the local charged environment [Friedrichs et al., 1991]. The functional significance of these interactions between molecules and the local environment is unclear, but the vibratory nature of particles such as DNA and proteins within the intracellular milieu necessary to create such fields is well documented [Pienta and Coffey, 1991]. Activity at the site of the matrix may be transduced via electromagnetic force to other nearby sites, set-

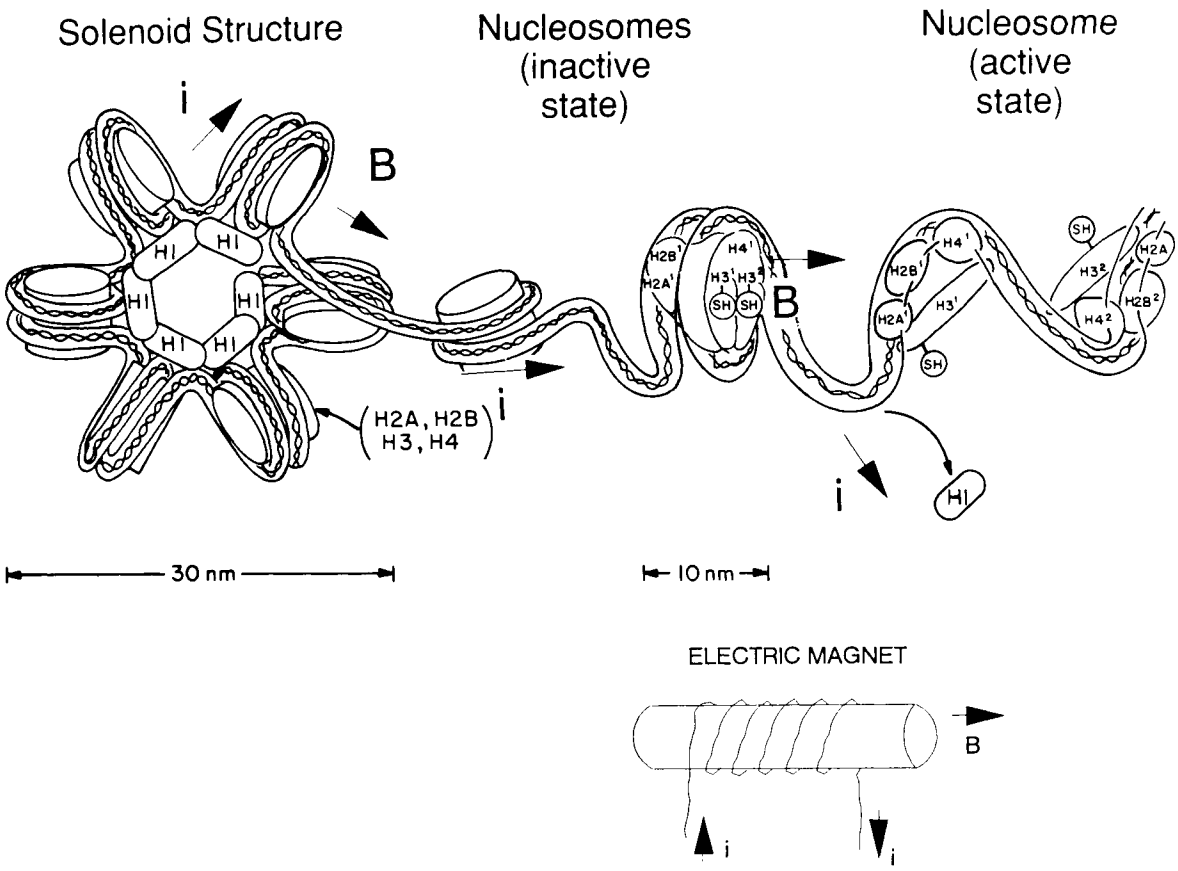

Fig. 1. DNA as a mediator of electromagnetic force. DNA as a charged molecule wraps around charged histones in a solenoidal fashion [Pienta et al., 1989]. In this sloenoidal form, the structure of DNA resembles that of an electric magnet (i = current, B = magnetic field). It is possible to speculate that the forces generated by the torsion and twisting of the DNA molecule could create electromagnetic forces which could affect local molecules and structures.

ting up a chain reaction of response which results in chemomechanical response.

STRUCTURE AND FUNCTION AT THE LEVEL OF THE CELL

We and others have previously suggested that this chemomechanical response may be transmitted over great distances within the cell by a tensegrity tissue matrix structure [Fulton and Isaacs, 1986; Ingber, 1993; Pienta and Coffey, 1991; Wang et al., 1993]. Ingber has pioneered the concept of biologic tensegrity, and has recently demonstrated the existence of operational tensegrity mechanisms at the level of the cell [Ingber, 1993; Wang et al., 1993]. Architecture based on tensegrity was first proposed by Fuller in 1948 as a method of building from the principal of *tens*ional in*tegrity* [Fuller, 1975]. Fuller defined tensegrity as a structural system based on the dynamic interaction of discontinuous compression elements connected by continuous tension cables. In a recent review, Ingber points out that most biologists now accept the principle that actinomyosin interactions within the contractile microfilaments are responsible for generating tension within the cytoskeleton and that all three cytoskeletal networks contribute structural function [Ingber, 1993]. The cytoskeleton is part of a tissue matrix system which forms a structural and functional bridge from the DNA to the cell periphery and beyond to the extracellular matrix as well as other cells. Investigators have demonstrated that cellular metabolism is modulated by cell shape as controlled by this tissue matrix system [Gospodarowitz et al., 1978; Folkman and Moscona, 1978; Pienta and Coffey, 1992]. Zambetti and colleagues demonstrated that disruption of the actin microfilament network by cytochalasin D-induced specific gene expression, suggesting that the nucleus

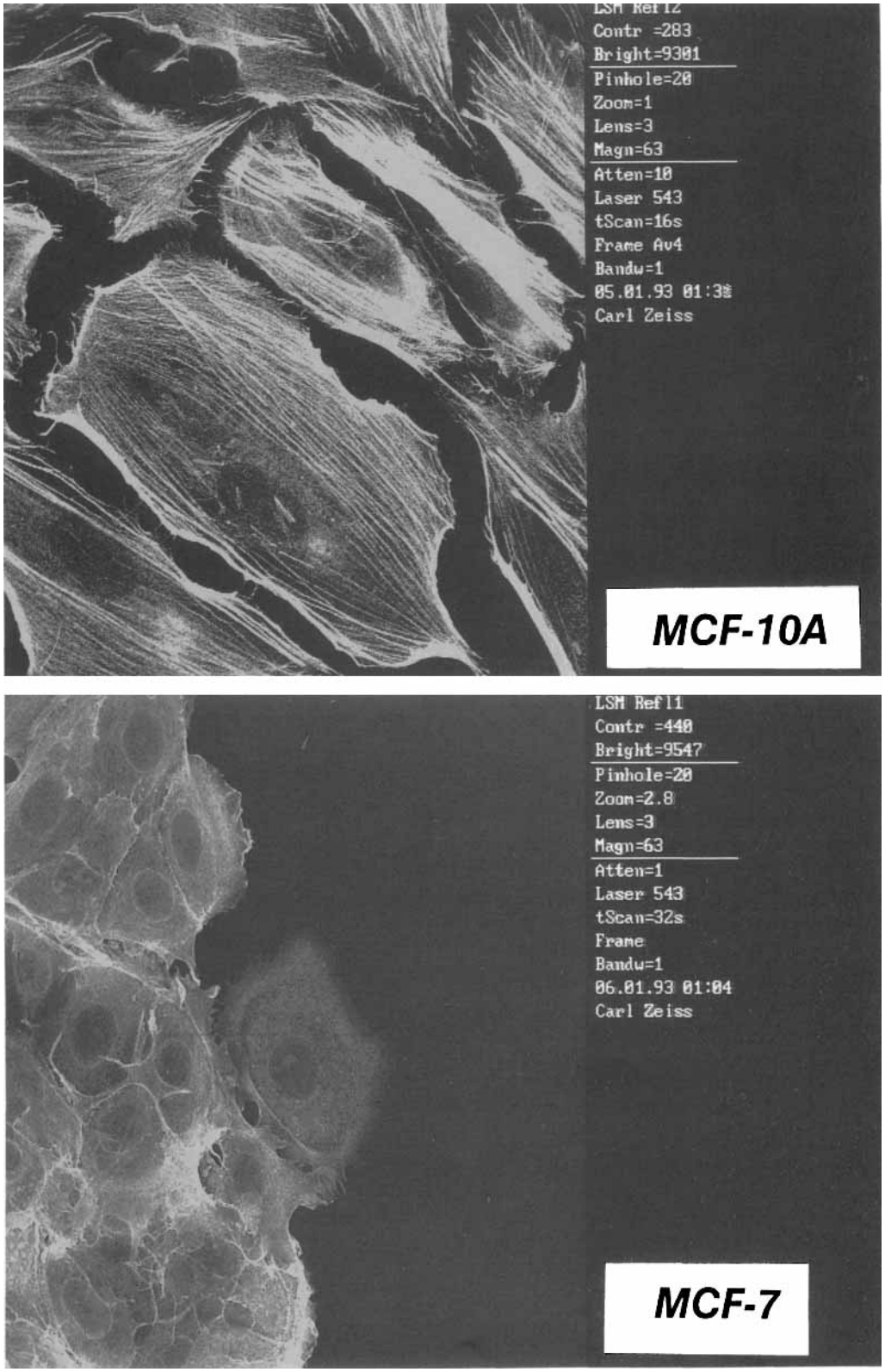

Fig. 2. Confocal images of nontransformed breast epithelial cells (MCF-10A) and transformed breast epithelial cells (MCF-7) stained with phalloidin. The nontransformed cells demonstrate actin stress fibers while the transformed cells do not demonstrate actin stress fibers and have a different morphology (×630).

can respond to signals related to cytoskeletal reorganization [Zambetti et al., 1991].

While these studies demonstrate the connection of structure to cellular function, Epner and colleagues have highlighted the connection of cellular energy and metabolism to cell structure [Epner et al., 1993]. It has been demonstrated that many enzymes associated with cell metabolism, including glyceraldehyde-3-phosphate dehydrogenase (GAPDH), are associated with the cytoskeleton. It has been postulated that this association of cell structure with enzymes that modulate cellular energy leads to the integration of the remodelling of cell architecture with cellular metabolism [Epner et al., 1993; Knull and Walsh, 1992].

Cell structure is poised to provide a bridge that integrates cellular energy to cellular function. The tissue matrix provides the spatial and temporal coordination for successful gene expression by the cell. The study of cancer cells provides information about what deregulation of this tissue matrix system does to the maintenance of cellular energy and function. It is well established that cancer cells have altered cell structure as well as altered cell function and altered energy requirements [Pienta et al., 1989; Epner et al., 1993]. Alterations of cell structure in cancer cells have been observed at all levels of the tissue matrix. Changes in the nuclear matrix between normal and cancer cells have been well documented by several investigators [Fey and Penman, 1984; Getzenberg et al., 1991]. Ben-Ze'ev has pointed out cytoskeletal alterations in cancer cells and hypothesized that cellular functions related to growth are disrupted by these physical alterations [Ben-Ze'ev, 1985]. The extracellular matrix has been demonstrated both to be altered in tumors as well as to exert profound effects on cell structure and function [Bissell et al., 1981; Pienta et al., 1991].

The importance of the relationship of these networks to overall cell structure has been highlighted by the demonstration that nuclear structure (and therefore, nuclear function) of nontransformed normal rat kidney cells in vitro was controlled to a great extent by the actin microfilament system [Pienta and Coffey, 1992]. This actin microfilament-nuclear interaction was altered by K-ras transformation as well as by cytochalasin D. The actin microfilament system has been demonstrated to be altered in many different cancer cell types, including the Dunning rat prostate adenocarcinoma cell line MAT-LyLu and the breast adenocarcinoma cell line MCF-7 (see Fig. 2). Recent work in our laboratory confirms the findings of Zambetti and colleagues that these structural alterations in actin organization cause alterations in cellular function as measured by gene expression [Zambetti et al., 1991] (unpublished data, Pienta).

SUMMARY

Utilizing observations described in the Dunning prostate adenocarcinoma cell line MAT-LyLu by different laboratories, it is interesting to note that alterations in actin organization can be associated with alterations in cell energy metabolism as well as cell function and cell structure [Epner et al., 1993] (unpublished data, Pienta). The actin microfilament skeleton of MAT-LyLu cells is disrupted as compared to normal prostate cells, and this disruption is associated with altered cell structure, altered cell gene expression, and altered energy metabolism. While it is naive to believe that the actin structural alterations cause altered energy use and gene expression, the common thread of structure between all these observations cannot be ignored. Future work in this area will need to concentrate on the "chicken or the egg" phenomenon; since alterations in energy, structure, and function are all observed in cancer cells, which comes first? Are changes in cell structure simply a byproduct of changes in cell function? Do changes in cell structure alter cell metabolism or vice-versa? While the answers to these questions are currently unknown, the data would suggest that cell structure serves as the bridge between cell thermodynamics and cell gene expression as observed in cell functions.

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