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Correspondence

Cancer and Epigenetic Reversion—The Fundamental Role of Redox

To the Editor-in-Chief:

It is unfortunate that Maniotis and associates[1] did not refer to our work,[2,3] which predicts and explains their findings and may have stimulated *American Journal of Pathology* readers to design novel experiments. Maniotis et al,[1] like Puck et al,[4] showed that in cancer cells, chromatin is abnormally condensed. Puck et al[4] also showed that the cancer cell surfaces are studded with oscillating knobs and are associated with aggregated actin-containing deposits near the membrane. Both groups showed that cAMP and other agents can reverse the above phenotypic characteristics of malignant cells and concluded that the cytoskeleton carries information from the cell surface and the cellular environment, which determines chromatin organization and gene regulation (mechanogenomics). According to Maniotis et al,[1] "elucidating the mechanism through which extracellular matrix components influence tumor cell and DNA organization may lead to the identification of new potential targets for cancer therapy."

Such a mechanism was proposed by one of us (E.P.-E.) in a redox theory of cellular function and structure.[2] Points relating to neoplasia are described as follows.

1. The cell is a dynamic entity with superimposed oscillations characterized by anisotropic, temporal-spatial fluctuations. The energy sources are protein sulfhydryl groups (SHs) and ATP.
2. Cellular structure, function, and differentiation are determined by the cellular redox (and the associated phosphorylation), its temporal-spatial distribution, and its oscillations. The redox of the actin/myosin system and charge transfer between myosin and actin play a critical role.
3. The main determinants of the cellular redox are the SHs of the acid-soluble proteins.
4. Carcinogens cause oxidation of the extracellular matrix and cells and, thus, changes in the redox oscillations. Cancer cells show similar redox levels and similar anisotropic redox distribution and oscillations; because of these attributes, they have several common characteristics, such as chromatin condensation, oscillating knobs, invasion/metastasis, and aneuploidy.
5. Cancer can be treated by i) oxidizing agents, by which cancer cells are destroyed, but the noncancerous tissue remains oxidized and thus prone to future malignant transformation, and ii) agents that reduce the disulfide bonds of the acid-soluble proteins, which will revert both cells and environment to normal or destroy the cancer cells.

There is evidence that supports the predictions of the redox theory of cancer. All carcinogens oxidize the fast-reacting SH groups. Compared with normal tissue, the tissue of cancer patients—and in particular neoplastic cells—are more oxidized[2] (A. Maniotis, personal communication). Oxidizing agents induce "changes in morphology [loss of actin and microtubular organization and the appearance of blebs (knobs)], cytoskeleton and cell-cell coupling," which are reversed by reducing agents.[5]

Our experimental evidence shows that redox plays a key role in contraction/relaxation (condensation/decondensation) oxidation leading to contraction and reduction to relaxation.[3] Data also exist that "demonstrate a definite periodicity in the initiation of transcription"[6]; "translation is completely coupled with transcription[7]"; "thiol disulphide transformation constitutes one of the mechanisms, which control the functional status of individual proteins important for gene expression."[8]

According to Maniotis et al,[1] cAMP acts through the cAMP-dependent protein kinase A, which in turn is thought to play a critical role in regulating transition through the cell cycle. The protein kinase A activity is redox-dependent.[9] However, as Paul Nurse[10] pointed out, the molecular approaches to cell-cycle control "retreat into an infinite regress of regulators of regulators."

For more than half a century, evidence existed for a cyclic variation of SH groups during the cell cycle. They were thought to be those of glutathione and to be the regulator of the cell cycle. More recently, it has been shown that the SHs are those of the acid-soluble proteins (eg, myosin).[2] In other words, the cell cycle is regulated by the cyclic oscillations of the redox.

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Author's Reply:

We were aware of the redox hypotheses presented by Papadopulos-Eleopulos et al,[1] and as a global hypothesis, it can account for many of the changes in cellular dynamics seen in the contexts of cancer and cell division. It is particularly insightful in that the redox hypothesis, as it is constructed by Papadopulos-Eleopulos et al,[1] explains and predicts the global, coordinated, and integrated events that involve changes in chromatin structure, the cytoskeleton, and the periphery of cells in response to a variety of signals/stimuli.

The role that redox plays in determining the state of chromatin sequestration or exposure among cancer or normal cells was not specifically tested in our work.[2,3] Instead, the work documented how the DNA of different cell types is characteristically sequestered/exposed under defined conditions and within or at the boarders of several human tumors. Experiments with mercaptoethanol and dithiothreitol suggested that the presence of disulfide bond-rich proteins within the nucleus played a key role in sequestration/exposure.[3] We also demonstrated how certain extracellular matrix (ECM) molecules and intracellular actin, microtubules, and intermediate filaments control DNA exposure/sequestration.[3]

However, although we agree that cellular redox, as presented by Papadopulos-Eleopulos et al,[1] may explain and predict a multitude of characteristic subcellular changes observed in cancer and may direct the cAMP-dependent protein kinase A chemistry that coordinates global cell cycle dynamics, our work specifically showed how extracellular matrix, acting through the cytoskeleton, structurally controls cellular and chromatin organization. Thus, we advanced the hypothesis from these observations that the ECM is the upstream constraint that imparts structural information, even when a cell makes partial micro-contacts with laminin, RGD moieties, or vasculogenic mimicry patterns[4] or when sequestered DNA is reversed in breast cancer with cAMP and protein kinase A analogs or ultimately with anti-fibronectin antibody.[3] These observations would suggest a hypothesis that would predict that, regardless of the degree of aneuploidy, the activity of any or all oncogenes or even the intrinsic redox state of a cancer cell versus a normal cell, the epigenetic reversibility of cancer via the manipulation of the ECM, in addition to the phenomena of tumor dormancy, tumor reversion, and vasculogenic mimicry[4] (a state in which highly malignant cancer cells may be metabolically and mitogenically repressed or dampened[5] rather than oxidized), must all be subsumed by how extracellular architectural constraints control downstream events.

The appeal and limitation of redox is that redox is a nonspecific global regulator, and recent evidence suggests that the ECM and, in particular, ECM phenomena, such as vasculogenic mimicry[4] or what we have called tumor biofilms[5], are specific upstream master regulators and thus deserve independent consideration. How would Papadopulos-Eleopulos et al[1] use their theory to explain tumor dormancy? Perhaps, as Papadopulos-Eleopulos et al[1] have postulated, redox may have more to do with the pathogenesis of AIDS than cancer.

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