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Nuclear Dreams: The Malignant Alteration of Nuclear Architecture

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Abstract Cancer is diagnosed by examining the architectural alterations to cells and tissues. Changes in nuclear structure are among the most universal of these and include increases in nuclear size, deformities in nuclear shape, and changes in the internal organization of the nucleus. These may all reflect changes in the nuclear matrix, a non-chromatin nuclear scaffolding determining nuclear form, higher order chromatin folding, and the spatial organization of nucleic acid metabolism. Malignancy-induced changes in this structure may have profound effects on chromatin folding, on the fidelity of genome replication, and on gene expression. Elucidating the mechanisms and the biological consequences of nuclear changes will require the identification of the major structural molecules of the internal nuclear matrix and an understanding of their assembly into structural elements. If biochemical correlates to malignant alterations in nuclear structure can be identified then nuclear matrix proteins and, perhaps nuclear matrix-associated structural RNAs, may be an attractive set of diagnostic markers and therapeutic targets. J. Cell. Biochem. 70:172–180, 1998.

Key words: nuclear matrix; nuclear structure; cancer

I do not say that biologists as a general rule try to imagine in any detail the future applications of their science. The central problems of life for them may be the relationship between the echinoderms and the brachiopods, and the attempt to live on their salaries. They do not see themselves as sinister and revolutionary figures. They have no time to dream. But I suspect that more of them dream than would care to confess it.

—J.B.S. Haldane, 1923

Some of the dreamers in the field of nuclear structure have over the years proposed that the study of that structure would elucidate mechanisms of malignancy and spin off applications of value for clinical practice [Berezney, 1979; Pienta et al., 1993; Replogle-Schwab et al., 1996]. In this very brief article we will examine our current prospects of fulfilling this dream and identify barriers to further progress.

There are many ways to approach the study of cancer. Whatever your favorite organelle, molecule, or system, it is undoubtedly affected in some way by malignancy and there is a strong possibility that it has been proposed as a therapeutic target. There are, however, two properties of tumors that are fundamental and that define some tumors as malignant. These are, first, alterations in the architecture of cells and tissues and, second, genetic instability. Both of these hallmarks of cancer may be addressed by an examination of nuclear structure.

The definitive diagnosis of malignant tumors is made by a pathologist examining tissue and cell structure. In this sense, it is clear that architectural changes define the malignant state. Among the most diagnostically important changes observable in all tumors are changes in the structure of the nucleus. These include increases in nuclear size, deformities in nuclear shape, and changes in the internal organization of the nucleus so major that they are observable even in the light microscope. Internal nuclear changes seen at low resolution may include more prominent nucleoli and larger clumps of heterochromatin. There are even tumors (papillary carcinoma of the thyroid), where the optical properties of fixed nuclei have changed so dramatically that they appear translucent. These are sometimes called "ground glass nuclei" or "Little Orphan Annie eyes" [Dominguez-Malagon et al., 1988]. The observation of nuclear changes is especially important with cytologic specimens like pap smears or

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with fine needle biopsies where information about tissue architecture has been lost. As we will discuss below, nuclear changes are progressive with tumor stage and are therefore important predictors of metastasis, tumor progression, and patient outcomes.

The progressive changes in nuclear structure accompanying malignancy are likely to result from changes in the nuclear matrix, the nonchromatin substructure of the nucleus, and from the connections of the nuclear matrix directly to the cytoskeleton and, indirectly through the cytoskeleton, to adjacent cells and the extracellular matrix. Malignancy-specific changes in nuclear matrix proteins have been observed and may be attractive targets for diagnostic assays and therapeutic intervention. The biggest obstacle we face in understanding malignancy-related nuclear changes is that we understand too little about the structural molecules of the nuclear matrix. While ultrastructural studies have imaged structural elements within the internal nuclear matrix, we have yet to identify the molecules that form those elements. It will be very difficult to make further progress toward understanding malignancy-specific changes without a better identification of structural molecules and some understanding of how specific molecules assemble into structural elements.

METHODS AND RESULTS

Nuclear Changes and Malignant Progression

Alterations in nuclear architecture are significant, not only for their diagnostic value, but because they may affect nucleic acid metabolism, thus making nuclear structure a leading actor in the tragedy of malignant progression. This idea is supported by a growing body of work showing that nucleic acid metabolism is architecturally organized in the nucleus. Individual catalytic processes and the biochemical machinery supporting them is structurally constrained to spatial domains [Nickerson et al., 1995]. Most of the spatial organization of the nucleus survives the removal of chromatin, demonstrating that internal nuclear organization is provided by attachments to the nuclear matrix, the nonchromatin nuclear scaffolding that binds most nuclear RNA and organizes chromatin into loops by attachments to specific DNA sequences called matrix attachment regions or MARs. These MARs seem not to have a rigid consensus sequence but rather to share an interesting propensity for duplex destabilization under torsional stress [Benham et al., 1997]. Catalytic processes acting on nucleic acids are also spatially organized. One better characterized example of this is RNA splicing, where spatial organization is accomplished by attachments of both the RNA and of splicing factors to the nuclear matrix [Nickerson et al., 1995].

When we propose that nuclear matrix organizes nucleic acid metabolism we are not only suggesting that matrix attachments keep factors corralled in the right region of the nucleus. We are supporting the more radical idea that catalytic and regulatory factors in cells assemble into complexes on the nuclear matrix and that these complexes act while bound to the matrix. In RNA splicing, for example, the assembly of spliceosomal complexes on the nuclear matrix and splicing in nuclear matrix-associated spliceosomes has been directly demonstrated [Zeitlin et al., 1987, 1989]. RNA splicing involves nuclear matrix proteins that may be both structural and play a role in the mechanism of splicing [Blencowe et al., 1998, 1994].

Another example of a nuclear matrix-associated catalytic process is DNA replication. The nuclear matrix organizes the DNA of the interphase nucleus into loop domains with loop bases formed by MAR interactions with MAR-binding proteins. The elegant and early work of Berezney and Coffey [Berezney and Coffey, 1975] demonstrated a mechanism for DNA replication with DNA reeling through fixed, matrix-associated replication [Berezny et al., 1995] complexes. The elaborate choreography of DNA at mitosis requires a structural support that evolves into the chromosomal scaffold and parts of the spindle [Nickerson and Penman, 1992]. In these and other ways, the nuclear matrix may be seen as the structural guardian of DNA fidelity. Changes in the matrix structure or changes in the matrix association with DNA that affect either DNA replication or chromosomal choreography could have profound effects on the genetic material inherited by daughter cells and thus play a role in the genetic instability, proliferation of mutations, and increasing ploidy that accompany tumor progression. It is interesting to note that the best-characterized malignancy-specific nuclear matrix protein, p114, identified in human breast tumors is a MAR binding protein [Yanagisawa et al., 1996].

Although a large literature shows that increased ploidy and altered nuclear architecture both correlate with tumor progression, it is not clear what the temporal or causative relationship might be. Indeed, despite the compelling nature of the idea, there is little experimental evidence that a relationship exists between aneuploidy and nuclear structure. This is an important deficiency to correct. The information we do have shows that changes in nuclear architecture are observable and diagnostic even in apparently diploid tumors, suggesting that they are not a mere consequence trying to stuff too much DNA or an abnormal hodgepodge of DNA into the same vessel. Changes in nuclei are sometimes observed in early stages of tumor development when most lesions are still apparently diploid. If there is any cause and effect relationship here, increases in ploidy are likely to be the effect of altered nuclear organization. The study of diploid tumor cells with very abnormal nuclei might prove very informative [van Velthoven et al., 1995].

Malignancy-related changes in the structure of the nuclear matrix may affect nucleic acids and their metabolism by changing the positioning of nucleic acids and factors. There are, however, other ways in which malignancy-related changes in nuclear matrix structure and, more generally, in cell architecture might affect gene expression. These are the signal transduction mechanisms by which cell shape and extracellular matrix contact affect gene expression. These mechanisms allow the cell to adapt to its microenvironment and may involve mechanical linkages [Ingber, 1997; Weaver et al., 1996].

What are our current prospects of understanding the progressive changes in nuclear structure with malignancy? The underlying mechanisms responsible for these changes are unknown and are currently difficult to investigate. This is largely because the structural principles and materials that determine nuclear form, even in normal cells, are still unclear. The central obstacle has been the slow progress in identifying and biochemically characterizing the major structural molecules of the internal nuclear matrix and in localizing those molecules within specific structural elements of the matrix. Without this characterization it will be impossible to understand how the design of the nucleus is realized and how this design is altered in tumor cells.

The nuclear matrix is a complicated structure of fibrils and granules connected to the inside of the nuclear lamina (Fig. 1A). When isolated with good ultrastructural preservation, the internal nuclear matrix resembles the ribonucleoprotein (RNP) network, which is observable in intact nuclei [Nickerson et al., 1997]. It is not surprising, therefore, to find many RNP proteins in nuclear matrix protein preparations [Mattern et al., 1996]. The localization of individual RNP proteins in the structure has not been determined. The internal nuclear matrix is built on an underlying network of highly branched 10-nm filaments that connect to the inside of the nuclear lamina and extend throughout the nuclear interior [He et al., 1990; Jackson and Cook, 1988; Nickerson et al., 1997]. These can be seen underlying the fibrils of the internal nuclear matrix (Fig. 1B). The branched 10-nm filaments can be uncovered by the use of a harsher extraction procedure [He et al., 1990]. The core filament network uncovered in this way is attached to the inside of the nuclear lamina and is well distributed through the nuclear interior. Despite some preliminary efforts, the molecular composition of the branched 10-nm core filaments has not been specified. Correcting this deficiency is important since it will be difficult to develop a better understanding of nuclear matrix assembly and function without identifying these major building materials. Without more progress on this front it will be almost impossible to characterize the mechanisms that alter nuclear structure in malignancy, no matter how many nuclear matrix proteins changes we are able to find by two-dimensional gel analysis.

Most of what we know about nuclear structure has been learned using cultured cells that are immortal and malignant. In most studies the closest that we come to a "normal" cell is the cultured fibroblast. Obviously we need to know more about the structure of nonmalignant epithelial cells in order to evaluate malignancy-related changes in tumors of epithelial origin. However, even the study of those "normal" cells in culture may give us a distorted view of the nucleus. The pages of any histology text reveal enormous cell-type-specific differences in nuclear structure, including differences in size, shape, and chromatin organization. We do not observe most of these tissue-specific differences in cultured cells "normal" that seem to have a more "malignant" architecture. Cul-

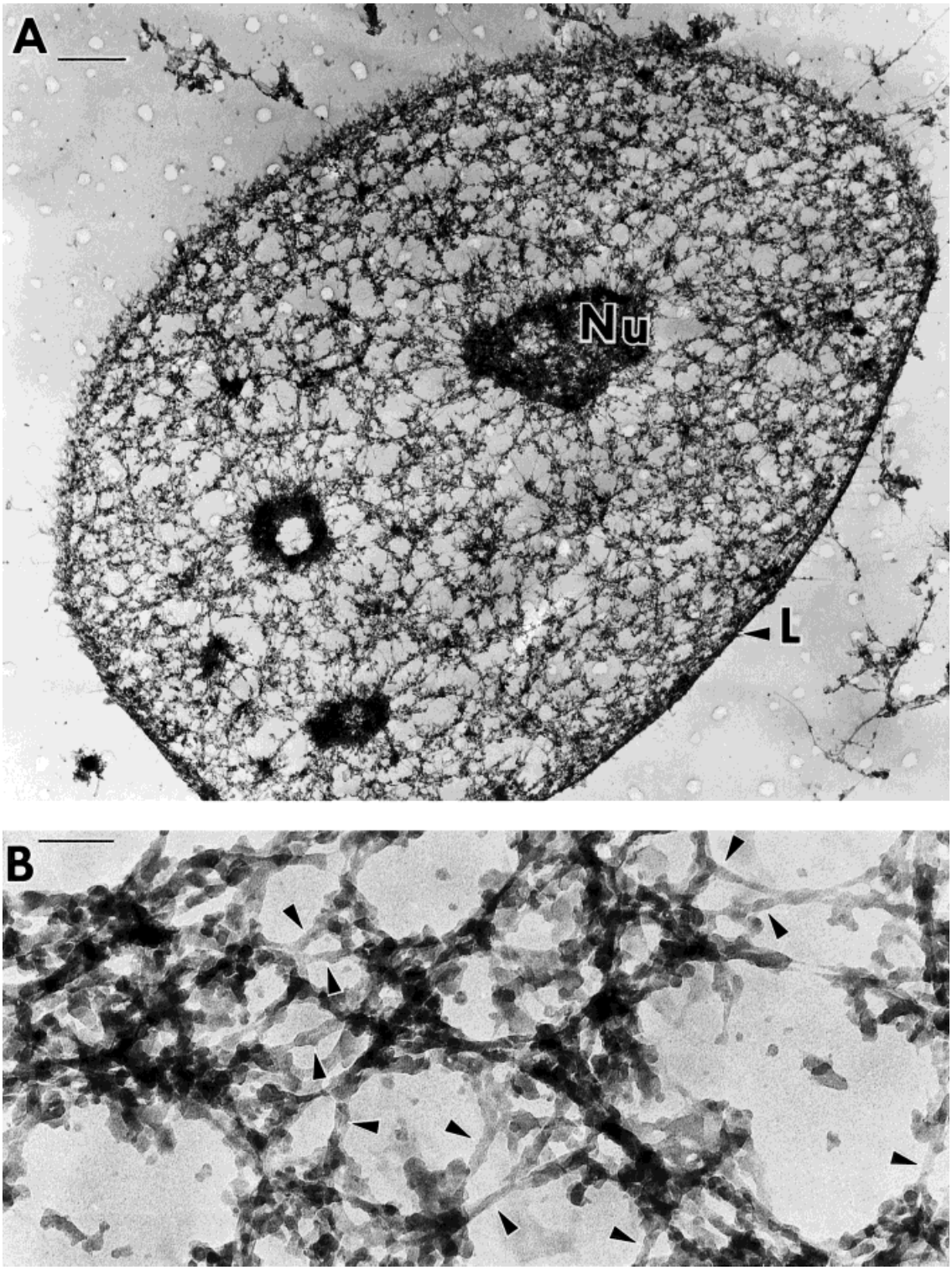

Fig. 1. The architecture of the nuclear matrix revealed by resinless section electron microscopy. The nuclear matrix of a CaSki cell was prepared and visualized by resinless section electron microscopy. The matrix was prepared by permeabilizing the cell to remove soluble proteins and then extensively cross-linking all the structures of the cell with formaldehyde. Chromatin was then removed by a DNase I digestion. This procedure effectively removes chromatin despite the extensive cross-linking. The nuclear matrix remaining after the removal of chromatin closely resembles the fibrogranular RNP network of the intact nucleus [Nickerson et al., 1997]. **A:** The nuclear matrix consists of two parts, the nuclear lamina (L) and a network of intricately structured fibers connected to the lamina and well distributed through the nuclear volume. The matrices of nucleoli (Nu) remain and are connected to the fibers of the internal nuclear matrix. Three remnant nucleoli may be seen in this section. **B:** Viewed at higher magnification, the highly structured fibers of the internal nuclear matrix are seen to be built on an underlying structure of 10-nm filaments which are occasionally branched. These are seen most clearly when, for short stretches, they are free of covering material (arrowheads). The thicker, more complex and irregular fibers with granules well integrated into their structure may be built on this filamentous core structure. The bar shown in panel A represents 1 μM; in panel B it is 100 nm.

tured cells have a more uniform nuclear structure from cell type to cell type than is observed for cells in tissues. This loss of tissue-specific nuclear architecture may result from the loss of appropriate cell shape and extracellular matrix contact that inevitably follow removal of cells from tissue and growth on plastic [Weaver et al., 1996]. The use of tissue-like culture systems in which tissue organization is preserved may be especially useful in future studies of nuclear structure.

Malignancy-Specific Nuclear Matrix Molecules

Changes in the nuclear architecture of tumor cells could reflect changes in nuclear matrix protein composition. Studies on rat and human prostate tumors were the first to reveal changes in nuclear matrix composition with malignancy [Getzenberg and Coffey, 1991]. This work identified a spot on two-dimensional gels, PC-1, which was present in nuclear matrices prepared from human prostate tumors but not present in matrices prepared from normal prostate tissue or from benign prostatic hyperplastic tissue [Partin et al., 1993]. The identity of PC-1 has not been published. If it could be identified it might be of diagnostic value. One attempt at a clinical trial using a PC-1 antibody as a diagnostic tool was foiled when the antibody (PRO:4–216, Matritech, Inc., Newton, MA) was found to recognize the wrong protein [Partin et al., 1997].

Following the discovery of PC-1, additional malignancy-specific two-dimensional gel spots were identified in nuclear matrices prepared from a variety of tumors, including human infiltrating ductal carcinoma [Khanuja et al., 1993], human colon adenocarcinoma [Keesee et al., 1994], rat osteosarcoma [Bidwell et al., 1994], squamous cell carcinoma of the head and neck [McCaffery et al., 1997], and others. Malignancy-specific proteins identified by two-dimensional gel electrophoresis are less abundant proteins and seem unlikely to be the major structural components of the nucleus. It is very difficult to evaluate the role that these proteins may play in altering nuclear structure for two reasons. First, the identification and characterization of malignancy-specific spots detected on two dimensional gels has not been published. Second, as we have discussed above, we understand too little about nuclear matrix structure in terminally differentiated cells and too little about the major structural components of the nucleus or their mechanisms of assembly. Even if we knew the identity of malignancy-specific matrix proteins, it would be difficult to study the role they might play in creating tumor-specific changes in nuclear architecture.

The failure to clearly identify malignancy-specific nuclear matrix spots has been troubling because there are multiple explanations for the existence of such spots. We hope that they represent unique polypeptides that are present in malignant but not in normal tissue. If this is true these proteins may be especially useful diagnostically and may provide unique insights into the process of malignant progression. It is, however, at least equally possible that malignancy-specific gel spots represent posttranslational modifications, proteolysis, or changes in the partitioning of proteins in the malignant cell. Apparent malignancy-specific changes may also be the result of cell-type heterogeneity within tissues or tumors. If any of these alternative explanations is true, then malignancy-specific spots would be much less attractive diagnostic and therapeutic targets.

The malignancy-specific nuclear matrix protein that has been best characterized is p114 [Yanagisawa et al., 1996]. This protein was not identified as a gel spot but by a functional property, namely, the ability to bind an MAR. This suggests that p114 is involved in the higher-order architectural organization of chromatin. p114 is detectable in surgical specimens from a variety of human breast carcinomas (43 out of 43) but not in normal adjacent tissue or in tissue of benign breast conditions, including fibroadenoma, fibrocystic disease, or atypical hyperplasias. Especially exciting is the observation that the MAR-binding activity of p114 in tissue samples correlates strongly and inversely with differentiation status as judged by a histologic grading system. The MAR-binding property of p114 is interesting because it may help to explain chromosomal rearrangements and changes in chromatin organization.

The expression of malignancy-specific proteins such as p114 has generated considerable and justifiable interest. Less attention has been paid to proteins that may be present in matrix preparations from normal tissue but are apparently lost in tumors. These may tell us at least as much about the mechanisms of tumor progression and the disorganization of nuclear structure as the malignancy-specific spots.

In this discussion we have been assuming that important changes in the nuclear matrix will be changes in protein composition. Of course, it is possible to assemble the same protein components in different ways in normal and malignant cells, but there is an equally important and less obvious point to be made. The nuclear matrix has both protein and RNA components. Most RNA in the nucleus is retained in nuclear matrix preparations [He et al., 1990]. This is not surprising for a nuclear matrix that structurally resembles the RNP network of the intact nucleus [Nickerson et al., 1997]. Inhibition of RNA transcription in cultured cells or animals by drug treatment or the ribonuclease digestion of RNA in permeabilized cells causes a collapse of chromatin into progressively larger and fewer clumps (discussed in more detail in Nickerson et al. [1995]). This may be accomplished by altering the attachments of chromatin to the nuclear matrix. The specific RNA molecules involved in this phenomena have not been identified but are likely to be in the hnRNA family. Most hnRNA in the nucleus does not serve as a precursor for cytoplasmic mRNA and has been of unknown function. Among this hnRNA is a growing family of hnRNAs that remain nuclear, have no protein open reading frames, and play important roles in nuclear organization and development. The first and best characterized of these is Xist, a noncoding and nuclear matrix-associated RNA required for X-chromosome inactivation and dosage compensation [Clemson et al., 1996]. More recently, additional noncoding RNAs have been discovered with roles in *Drosophila* development and dosage compensation. Judging by the example of Xist, some of these noncoding hnRNAs may function to remodel the higher-order organization of chromatin. This is entirely consistent with the global observations of chromatin collapse following RNA polymerase II inhibition or ribonuclease digestion. Many of the nuclear changes in malignancy and the changes in chromatin itself might be mediated by RNAs and not by proteins. Molecular techniques are now available to test this idea.

Nuclear Matrix-Based Diagnostics

The observation of cell-type-specific nuclear matrix proteins by Fey and Penman led to the MIT patents covering the use of nuclear matrix proteins for cancer diagnosis (U.S. Patents 4,885,236 and 4,882,268). Of special and obvious interest were malignancy-specific proteins but also cell-type-specific proteins that might be reliable markers of tumor origin. It is the specificity of nuclear matrix protein expression that makes the nuclear matrix such a promising source of diagnostic targets. The discovery of PC-1, the subsequent discovery of other malignancy-specific gel spots, and the hope that these spots represent malignancy-specific polypeptides have intensified interest in the potential of nuclear matrix-based assays in cancer diagnosis.

Cancer diagnostic assays can provide different kinds of information. Screening assays to be used on asymptomatic populations are difficult to develop because they require a very low rate of false positives to be clinically useful. If the rate of false positives were higher than the tumor incidence in the screened population, then the majority of patients receiving expensive and invasive follow-up procedures would, in fact, be tumor-free. The use of malignancy-specific nuclear matrix proteins in screening assays is therefore unlikely, except perhaps as an adjunct to an already-established cytological assay such as pap smear or urine cytology.

Distinguishing malignant from normal tissue is routinely achieved by standard histopathology without the use of special assays. Fine-needle biopsies are more likely to yield ambiguous results since information about tissue architecture is often lost. These samples might benefit most from the additional use of immunocytochemistry to detect malignancy-specific nuclear matrix proteins, if such proteins can be characterized and accurately detected. Determining the cell-type origin of tumors is also a possible application of nuclear matrix-based assays if cell-type-specific nuclear matrix gel spots can be identified, characterized, and targeted.

An important role that nuclear matrix-based diagnostics could ultimately play is in prognosis, predicting tumor aggressiveness and patient outcomes. Tumor-grading systems that predict patient outcomes often use features of nuclear morphology. If there are biochemical correlates to those nuclear changes in the molecular composition of the nuclear matrix, then novel and useful clinical assays may be successfully developed [Samuel et al., 1997]. The increase in p114 levels with breast tumor progression make this protein an attractive target for assay development [Yanagisawa et al., 1996].

One dramatic example of the importance of prognostic indicators is in prostate cancer, where the malignancy-specific nuclear matrix gel spot PC-1 has been found. Prostate cancer may afflict 10 million older American men but only be life-threatening for 7% of them (reviewed in Rinker-Schaeffer et al. [1994]). The decision of how aggressively to treat a patient with histopathologic evidence of prostate cancer is therefore very difficult to make. There is a large literature showing that nuclear size, various measures of nuclear shape, nucleolar features, and chromatin distribution predict metastasis and prostate tumor progression [Chiusa et al., 1997; Partin et al., 1992; Veltri et al., 1996]. If molecular correlates in the nuclear matrix could be found, assays of considerable value for patient management might be developed. It is no coincidence that prominent nuclear matrix researchers have also worked on prostate cancer.

The promise of the nuclear matrix as a diagnostic target was based on the malignancy and cell-type specificity of nuclear matrix protein expression. So far, nuclear matrix-based diagnostics with clear specificity have not come into clinical use. This may be related to the failure so far to identify the polypeptides present in malignancy-specific two-dimensional gel spots and, perhaps, to the relatively low abundance of the corresponding proteins. The one established and FDA-approved clinical assay based on a nuclear matrix protein is the NMP22 test (Matritech, Inc.), which may have value as an adjunct to cytology and endoscopy in the monitoring of patients for disease recurrence after their treatment for transitional cell carcinoma of the urinary bladder [Soloway et al., 1996]. Unfortunately, the target antigen NMP22 is not reported to be specific for either transitional cells or for malignancy. The NMP22 assay instead follows an earlier strategy of measuring the release into urine of a cellular protein or its fragments from dead cells. The amount of protein released is increased in patients with tumor recurrence. This same strategy can be employed with other, nonnuclear proteins, for example cytokeratins, which have a greater cell-type specificity [Basta et al., 1988; Pariente et al., 1997]. The NMP22 kit may be a clinically useful first application of nuclear matrix protein detection in cancer diagnosis but, if matrix-based diagnostics are to fulfill their promise, proteins with tumor- and tissue-type specificity must be identified and targeted. Malignancy-specific bladder cancer nuclear matrix gel spots have been discovered [Getzenberg et al., 1996] and may form the basis for future assays with improved specificity.

The lack of specificity in existing assays is not the only problem facing nuclear matrix-based diagnostics. A second problem is in assay format. Bladder cancer is a special situation where breakdown products of dead cells are readily released into, and rarely cleared from, an accessible fluid. These conditions do not hold for most other tumors. The most obvious assay formats suitable for those more typical tumors are immunocytochemistry and serum-based assays. Immunocytochemistry with antibodies against cell-type or malignancy-specific proteins might have specialized uses in cytology and with fine needle biopsies where tissue geometry has been lost or altered. The feasibility of serum-based clinical assays depends on factors that are difficult to predict, including the level of the target protein in the tumor cell, the rate of nuclear matrix breakdown and solubilization in the dead cell, and the rate of protein fragment clearance from the circulation. Unfortunately, most of the malignancy- and cell-type-specific nuclear matrix proteins so far detected are of lower abundance. Therefore, it seems less likely that serum-based assays with specificity will be sensitive enough to screen patients for early stage disease, though they might have value for detecting very-large-scale recurrence.

Nuclear Matrix as a Therapeutic Target

The nuclear matrix may present a large set of novel targets for drug development (reviewed by Catapano et al. [1996]). Interfering with the architecture supporting and spatially organizing nucleic acid metabolism must have profound effects on function, cell cycle, and viability. Several drugs in current use, including two being tried clinically for prostatic cancer, attack nuclear matrix targets [Catapano et al., 1996; Naik et al., 1996]. Such drugs have generally affected catalytic factors involved in nuclear matrix-associated processes and not structural members of the nucleus. Drug design targeting catalytic functions may be very effective but the structural integration of nuclear metabolism in cells suggests a second design strategy. Drugs that knock catalytic and regulatory factors off of their nuclear matrix docking sites might profoundly affect their biological function with

little effect on their in vitro biochemical activities. Peptide sequences have been identified that attach transcription factors to sites on the nuclear matrix [Zeng et al., 1997; Mancini et al., 1998]). Protein domains such as these may be useful targets for drug design.

The targeting of drugs to structural nuclear matrix molecules is a promising strategy but one that will require a better understanding of matrix structure and molecular composition. The example of successful anticancer drugs that interact with microtubules should inspire us to consider structural elements as targets and especially those involved in mitotic rearrangements. The growing catalog of malignancy-specific gel spots are also an intriguing set of potential targets, if they can be identified and characterized. Antisense knockouts might tell us whether these proteins are necessary for tumor cell growth and survival and for the maintenance of the malignant phenotype.

DISCUSSION

In summary, it may be very difficult to understand the malignant alterations in nuclear architecture until we (1) identify the major structural molecules of the nucleus, (2) understand how those molecules assemble into structures, and (3) understand these features and phenomena in the differentiated cells of tissues. The use of tissue is important since only in tissue do cells have the shape and extracellular matrix contact that may determine normal nuclear form. With a better understanding of normal nuclear form and its determinants, the mechanisms of malignant alteration will be easier to identify. Many malignancy-specific gel spots have been discovered in nuclear matrix protein preparations. The identification and characterization of most of these has not been published and so they remain mysterious. Even with a better characterization it would be difficult to determine the role that these proteins play in malignant alterations of the nucleus without a better understanding of the structural molecules of the nuclear matrix and of their assembly into specific structural elements of the matrix. Though requiring better characterization, nuclear matrix proteins and, perhaps, nuclear matrix-associated RNAs specific to malignancy or cell type remain an attractive set of potential diagnostic markers and therapeutic targets. With further progress Haldane's dreamers, while still worried by the attempt to live on their salaries, may have fewer worries about cancer, and nuclear matrix biologists may yet prove to be revolutionary figures in the fight against a sinister disease.

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