Cancer as a Disease of DNA Organization and Dynamic Cell Structure

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Cancer cells develop resistance to all known natural and synthetic drugs; normal cells do not. This resistance is a reflection in part of the wide diversity of functions expressed by cancer cells within a tumor. This variation in function (pleiotropism) is accompanied by variation in structure (pleomorphism), and together they form the basis for tumor cell heterogeneity. This tumor cell heterogeneity provides malignant tumors with a tremendous biological diversity, which enables them to succeed in a competitive environment that includes therapeutic manipulations. The driving force in the development of tumor cell heterogeneity is thought to be genetic instability (1–4). However, it is unknown whether cell structure determines this instability or whether the instability of the DNA itself produces the instability in structure (5, 6). It is well recognized that chromatin structure can regulate DNA function within the cell (7–11). The purpose of this “Perspectives” article is to provide an overview of the importance of nuclear and cell structure in DNA organization and suggest how these may be altered in the cancer cell.

The Nuclear Matrix

How the vast array of DNA is arranged within the nucleus in an organized fashion is difficult to comprehend. For example, if the nucleus were magnified in size to a sphere 3 feet in diameter, the DNA molecule would extend as a filament for 100 miles. Following replication and before mitosis, this filament length would double to 200 miles. This vast amount of DNA must be spatially organized in order to avoid any entanglement during replication and subsequent mitosis. This could not be accomplished by free-floating or soluble DNA but must require a precise 3-dimensional organization and topological considerations. The organization of interphase DNA is believed to be accomplished by the interaction of the DNA at specific sites to a nuclear matrix system.

The nuclear matrix is defined as the dynamic structural subcomponent of the nucleus that directs the 3-dimensional organization of DNA into loop domains and provides sites for the specific control of nucleic acid intranuclear and particulate transport (12). Conceptually, the nuclear matrix can be viewed as the nuclear equivalent to the cytomatrix. These matrix structures had also been termed “skeletal” or “scaffolding” components, until it became apparent that they exhibited dynamic properties and were not simply rigid framework structures. The nuclear matrix is not a single structural entity but a complex that contains specific subcomponents such as the core-complex laminas, residual nucleoli, and internal ribonucleoprotein particles attached to a dynamic fibrous network of proteins, RNA, and polysaccharides (13–20). The nuclear matrix structure is essentially devoid of histones and lipids and represents less than 15% of the mass of the intact nucleus (Fig. 1).

The nuclear matrix is an important structural component in a variety of nuclear functions reviewed in Table 1. Primarily, the nuclear matrix serves an important role in DNA organization and nuclear structure. DNA loop domains are attached at their bases to the nuclear matrix (21, 22), and this organization is maintained throughout both interphase and metaphase (23–27). These loops are 50–150 kbp2 long and are equivalent in size to the replicon, i.e., the amount of DNA replicated as a unit during DNA synthesis that resides between adjacent replicating forks (21). There are approximately 50,000 to 100,000 of these DNA loops per nucleus. Constrained at their bases to the matrix, the DNA loops are often supercoiled (22), which may control in part the chromatin structure through changed DNA topology. Topoisomerase II, one of the enzymes that modulates DNA topology, is associated with the interphase nuclear matrix (28, 29) and with the mitotic chromosome scaffold (30).

The nuclear matrix also plays an important role in DNA replication (31). The matrix contains fixed sites for DNA synthesis (21, 32–34) located at the base of the loops. During DNA synthesis the loop domains are rewound down through the attached replicating complexes. When the total DNA attached to the nuclear matrix is treated with EcoRI restriction enzyme, a minute fraction of the DNA still remains on the matrix that is enriched in replicative forks (35). Vogelstein et al. (22) have been able to visualize and follow the rate of movement of labeled DNA into these loop domains as they are replicated. Furthermore, Tubo et al. (36) have reported that matrix-bound DNA synthesis in vitro continued from replication sites being used for DNA synthesis in intact nuclei in vivo at the time of isolation. The DNA-replicating complex located at the base of the loop has been isolated and termed the replisome (37). The replisome is a 24–30-nm-diameter particle with a molecular weight of approximately 5 million and contains at least eight enzymes which include ribonucleoside diphosphate reductase, thymidylate synthetase, dihydrofolate reductase, DNA methylase, topoisomerase, and DNA polymerase (37). This large multienzyme complex appears to be under allosteric control (38). The DNA replication fork, DNA polymerase α, and newly replicated DNA have all been closely associated with the nuclear matrix during DNA synthesis (32–36, 39). Earnshaw and Heck (30) have shown that the scaffold or matrix of the metaphase chromosome contains topoisomerase II, which is also a component of the interphase nuclear matrix during the time of DNA synthesis (28, 29). Nelson et al. (40) have reported that newly synthesized DNA can be covalently attached to topoisomerase II of the interphase nucleus. With time the newly labeled DNA moves away from the topoisomerase, which indicates that the topoisomerase II is located at the base of the DNA loops in close proximity to, but in the wake of, the replicating fork. This is consistent with the observations of Noguchi et al. (41) that topoisomerase is part of the replicase particle that forms the replisome complex for a fixed site for DNA synthesis. Recently, Dijkwel and Hamlin (42) have identified specific matrix DNA attachment regions that are positioned near replication initiation sites and interamplicon junctions in the am-
Table 1 Nuclear matrix is the dynamic structural subcomponent of the nucleus that directs the functional organization of DNA into loop domains and provides organizational sites for many of the functions involving DNA

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<td>Nuclear regulation: The nuclear matrix has specific sites for steroid hormone receptor binding. DNA viruses are synthesized in association with the matrix. The nuclear matrix is a cellular target for transformation proteins, some retrovirus products like the large T antigen, and E1A protein. Many of the nuclear matrix proteins are phosphorylated at specific times in the cell cycle.</td>
<td>43–46, 66–72, 74, 75, 81</td>
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Cell Dynamics and DNA Organization

Fig. 1. Isolation of the nuclear matrix. The nuclear matrix of a normal rat liver nuclei is isolated by sequential extractions using nonionic detergent, brief DNase I digestion, and a hypertonic salt buffer. These extractions remove over 98% of the DNA, 70% of the RNA, and 90% of the nuclear proteins resulting in a residual structure that is essentially devoid of histones and lipids (12–20).

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The nuclear matrix is a major site of steroid hormone receptor binding (66–72). Barrack et al. (66–68) have shown that in the presence of specific steroids, 40–60% of all nuclear steroid receptors (estrogens or androgens) are associated with this matrix. In addition, the nuclear acceptor for the steroid-bound receptor appears to be part of the nuclear matrix in steroid target tissues (69, 70). New properties of the nuclear matrix have recently been identified. Fey and Penman (73) have reported that nuclear matrix proteins, localized to the interior of the nucleus, vary in a cell type-specific manner, suggesting that the nuclear matrix may play an important role in development and tissue organization.

In cancer cells transformation products appear to be associated with the nucleus, and many of these appear to be involved with the matrix. For example, the nuclear matrix is reported to be one of the targets for retrovirus myc oncogene protein (74, 75), adenovirus E1A-transforming protein (76), and polyoma large T antigen (77–79). Numatrix, a nuclear matrix protein, has been associated with the induction of mitogenesis (80). Nuclear matrices from various cells contain binding sites for myb proteins (81), and the nuclear matrix has been shown to be altered during transformation (82–85). Since steroid receptors and transforming proteins such as the nuclear oncogene products affect DNA function in target cells, more insight is required into how they alter the functions of the nuclear matrix.

DNA Organization

The packaging and 3-dimensional organization of DNA within chromatin, metaphase chromosomes, and the interphase nucleus remain largely unsolved. Dynamic reorganization of chromatin is visually apparent in the cell cycle from interphase to metaphase. How the DNA loop domains are maintained throughout these transitions of the cell cycle is still unclear. The actual structure of these loop domains has only recently begun to be understood. Three higher order levels of DNA organization have been identified: nucleosomes, 30 nm chromatin fibers, and DNA loop domains. Although controversy still exists about the exact nature of each of these structures, they are well accepted as basic units of DNA organization. The DNA loop domain was first proposed by Cook et al. (86) in 1976 when they suggested that loop structures are involved in the superhelical organization of eukaryotic DNA. In 1980, Vogelstein et al. (22) reported that DNA loop domains were attached
at their base to the nuclear matrix and that these loops were
topologically constrained by that attachment. Furthermore, the
nuclear matrix contained fixed sites for replication of DNA
loops that Pardoll et al. (21) showed were the structural equiva-
cents of replicons, the basic lengths of DNA synthesized as
continuous units (87). The DNA loop domain defines a basic
unit of higher order DNA structure which is present throughout
the cell cycle in eukaryotic cells (88, 89). These loops have been
estimated to be between 10 and 180 kbp pairs with an average
of 63 ± 14 kbp (90). An average loop would be large enough to
contain 300 nucleosomes wound with 6 nucleosomes per sole-
noid turn into a 30-nm fiber utilizing the model proposed by
Finch and Klug (91) and supported by the observations of others
(92–94). Williams et al. (95) have demonstrated that the 30-
nm fiber could also be constructed with crossed-linker nucleo-
somal organization; however, the DNA packing ratio of both
30-nm fibers is similar. The 30-nm fiber forms the filament of
a loop, a basic structure of both interphase and metaphase
DNA. If a human diploid nucleus contains 6 × 10^9 base pairs,
there would be approximately 100,000 of these DNA loop
domains within a single nucleus. The full organization of these
loop domains within the interphase nucleus and metaphase
chromatid has still not been elucidated. In interphase, several
lines of evidence support a model that has the DNA loops
attached to the inner portions of the nuclear matrix. Many
investigators have demonstrated that newly synthesized DNA
occurs throughout the interior of the nucleus and not just at
the periphery or lamina areas as was once believed (21, 96–99).

In metaphase, DNA loop domains are preserved in chromo-
somes (100), structures devoid of nuclear envelope and lamina
proteins. The higher order structure of metaphase chromo-
somes remains controversial. Several different models have
been described which include radial loop (100–102), folded
fiber (103), unit-fiber (104), spiral coil (105), and coiled-coil
(106) models. We compared the amounts of DNA in a chro-
matid of the No. 4 human chromosome with the measured
chromatid dimensions at maximum condensation. DNA loops
can be packed into actual chromatid dimensions only when a
radial loop model and current concepts of higher order DNA
structure are used (See Fig. 2 and Table 2) (90). This model
features loops wrapped radically around the central axis of the
chromatid as they stack to achieve overall chromosome length.
Our analysis revealed that there would be 18 DNA loops per
radial turn of the chromatid. This 18-loop unit forms an as yet
theoretical higher order structure of DNA organization that we
have termed the “miniband” because it represents the smallest
achievable band of a chromatid (90). The miniband is equiva-
elent to one full radial turn of 18 loops, each of 60 kbp, around
the central axis of the chromatid to form minibands of approx-
imately 1 million base pairs of DNA (18 × 60 kbp).

The nuclear matrix provides a dynamic framework for DNA
organization. Insight into the dynamic process of the matrix
has been provided by fluorescent antibody studies of changes in
the distribution of nuclear matrix antigens at different times
during the mitotic cell cycle (107–109) (see Fig. 3). The DNA
loop domains present in the metaphase chromosome maintain
their association with the nuclear matrix in the interphase
nucleus. The telomere regions on the end of the chromosome
are attached to the peripheral lamina. As the nucleus ap-
proaches metaphase, the nuclear lamina proteins are phospho-
rylated and have been shown to diffuse as small vesicles into
the cytoplasmic area as the nuclear envelope disintegrates (110,
111). The chromosomes, now free of the lamina, collapse into
condensed mitotic structures. At the end of telophase, the ends
of the chromosome serve as an organizing center for the con-
densation of lamina proteins to reform the lamina of the nucleus
(111–113). In this model some nuclear matrix structures at the
base of the DNA loops will be maintained as the core scaffold-
ing of the minibands (90). In this model some nuclear matrix structures at the base of the DNA loops will be maintained as the core scaffold
in the interphase or metaphase matrix within the chromosome. In support of this theory, the nuclear matrix has been shown to share many common
proteins, including topoisomerase II, with the chromosome
scaffold (23–30, 114). In the future much work will be needed
to determine how DNA loops interact with the nuclear matrix,
how the replicating complex is formed during S phase, and how
the matrix-organizing centers control and reestablish nuclear
structure. Additionally, it remains to be seen how the nuclear
matrix-DNA complex is organized and altered with the devel-
opment of cancer that is associated with distorted nuclear
structures.

DNA and Chromosomal Rearrangements in Cancer

Chromosome translocations have been proposed to be a
common factor in many types of human neoplasias (115, 116).
When large translocations occur, there is also a transfer of
chromosomal banding patterns. In the model in Fig. 2, struc-
tural elements of the core of the chromosome and the nuclear
matrix that anchor the DNA loops must be transferred in the
translocation process. Since sister chromatid exchanges occur
at the site of DNA replication that is on the matrix, the nuclear
matrix components may be involved in these rearrangements
(117). These types of DNA reorganization in cancer that include

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**Fig. 2.** Schematic of the levels of organization within a chromatid of a chromosome. Approximately 160 base pairs (b.p.) of 2-nm DNA helix is wound
twice around the histone octamers to form the 10-nm nucleosomes. These
nucleosomes form a “beads on a string” fiber which winds in a solenoid fashion
with 6 nucleosomes per turn to form the 30-nm chromatin filament. The 30-nm
filament forms the 60-kbp DNA loops that are attached at their bases to the nuclear matrix structure. The loops are then wound into the 18 radial loops that
form a miniband unit. The minibands are continuously wound and stacked along
a central axis to form each chromatid. Variations in interchromosomal length are
achieved by altering the number of minibands in each chromatid. Variations in
intrachromosomal length are achieved by the winding, unwinding, and compact-
ing of the minibands (90).
organizing a single chromatid in the interphase nucleus. During S phase the DNA have all been demonstrated in both animal and human gene amplification (118), sister chromatid exchange, and a in small vesicles. The matrix attached to the DNA loops condenses during loops replicate. During prophase the matrix separates and disengages the telomere or increase progression. Any of these rearrangements which gene amplification (118), sister chromatid exchange, and a series of different subtypes of rearrangements and deletions (119) have all been demonstrated in both animal and human tumors. Each of these processes involves a change in the order of arrangement of the DNA sequence and as such has been proposed to be involved in the initiation of carcinogenesis and/ or increase progression. Any of these rearrangements which bestows a growth advantage on the cells could cause a hyperplasia or tumor formation. If a DNA rearrangement places an error within the genomic apparatus such that further genetic instability ensues, a wide variety of cells would result. This type of genetic instability may be the basis of progression and the formation of tumor cell heterogeneity (1-5, 120). Elucidation of the molecular events which produce this genetic instability is critical to the understanding of cancer. It will be necessary to define the relationship between genetic instability and the alterations of cell structure, which is the morphological hallmark of cancer diagnosis, in order to further our understanding of the cancer process. The concept of a dynamic tissue matrix system may form a basis for this understanding.

The Tissue Matrix System

The nuclear matrix forms an interlocking network with the cytomatrix that extends throughout the cell and makes external contact with the ECM (Fig. 4). The cytomatrix is composed in part of networks of actin microfilaments, intermediate filaments, and microtubules. The ECM includes the basement membrane and ground substance of the stroma and is composed in part of collagens, laminins, fibronectin, and proteoglycans. Several investigators have proposed that these structural ele-
induce some of the cytoskeleton changes that occur with transformation. Observations on the importance of external surface contact and anchorage-independent growth of tumor cells have focused much attention on the importance of the cytoskeleton and its relationship to the ECM in tumor progression. In classic studies, Folkman and Moscona (131) controlled the shape of normal cells in vitro by varying the substratum adhesiveness of the culture plates to which the cells were attached. Gospodarowicz et al. (132) observed that cell shape determines the mitogenic response of a given cell. Additionally, the ECM has been implicated in the control of genetic expression (133), and Reid (134) has demonstrated that the ECM components glycosaminoglycans and proteoglycans can induce morphological changes, induce gap junction synthesis, and regulate tissue-specific gene expression. It is well recognized that the ECM clearly plays an important inductive function in embryonic development and may also modulate adult cells. For example, Cunha et al. (135) demonstrated that the ECM can be responsible for functional differentiation in development when they showed that urogenital sinus mesenchyme induces urinary bladder epithelial cells to form prostatic epithelial cells and acini. Reddi and Anderson (136) observed that mature fibroblasts underwent redifferentiation to form new chondroblasts and chondrocytes when they were exposed to demineralized bone collagen matrix. All of these and many other experiments demonstrate that what a cell touches is important in determining what it becomes and how it functions (121). We still know very little about the integration and control of these cytoskeleton and extracellular matrix processes and how the information is transmitted to the nucleus. In summary, the cell may transmit signals by direct mechanical linkages via the tissue matrix system that can regulate DNA function (119–121, 137). We do know that in the cancer cell the cell matrix can be highly dynamic. This is exemplified by cell motility.

Cancer Cell Motility

In 1940, George Gey (138) was the first to use time lapse cinemicroscopy to study the activity of cancer cells derived from spontaneous transformation of normal cells in tissue culture. In 1966, Sumner Wood wondered whether cell motility was important in the pathogenesis of cancer or simply a cell culture artifact. He used a transparent rabbit ear chamber to study the in vivo motility of V2 carcinoma cells (139–141). V2 carcinoma cells migrated at velocities comparable to those of leukocytes and 200 times faster than macrophages. Coman (142) demonstrated heterogeneity in the motility of tumor cells and suggested that the degree of motility correlated with histological differentiation and invasive potential.

This relationship between cell motility and metastatic potential is starting to be explored. Platelet-derived growth factor (143), transforming growth factors (144), insulin (145), and epidermal growth factor (146) have all induced motility in normally quiescent cells. Normal cells demonstrated transient enhanced motility after treatment with phorbol ester (147) and ruffling, which was observed with time lapse cinematography (148, 149, 150). Injection of the p21ras protein product directly into the cell induced a transient motility (151). Recently Liotta and Schiffman (152) have identified an autocrine motility factor secreted by tumor cells which increases tumor cell motility. Hosaka (153, 154) used time lapse videomicroscopy to show differences in cell motility between various rat hepatoma cell lines that exhibited different propensities for metastasis. Haemmerli and Strauli (155) extended this technique to the study of human neoplastic cells and suggested that their in vitro motility reflected their invasive behavior in vivo.

Recently, time lapse videomicroscopy and a visual grading system have been utilized to evaluate cell membrane ruffling, undulation, pseudopodal extension, vectorial translation, and irregularity of the pathway of translation in normal and malignant cells (156, 157). The Dunning R3327 rat prostatic adenocarcinoma model provides many histologically indistinguishable sublines of varying metastatic potential which originated from a single animal (158). No biological, biochemical, or morphological discriminator has previously been capable of identifying the individual sublines or predicting their metastatic potential (158). Mohler et al. (156, 157) demonstrated that five sublines and normal rat prostate cells could be identified by a visual grading system of cell motility. More recently, Partin et al. (159) have developed a new system for quantitatively assessing all aspects of cell motility. This new quantitative method was able to correlate cell motility changes with an increase in metastatic ability in the Dunning tumors (159). Furthermore, Partin et al. (160) demonstrated that motility and metastatic potential can be induced in the Dunning tumors by transfection and expression of the V-Harvey-ras oncogene. Thus motility of individual cancer cells in vitro has been shown to be sufficiently characteristic to allow accurate assessment of their metastatic potential in vivo. Current pathological grading systems depend upon the appreciation of cytological and architectural features of dead, fixed histological sections of malignant tissues. A grading system of motility of live cancer cells may better predict the behavior of a live tumor system.

Tensegrity

The types of mechanical systems that can transfer information within a cell are just beginning to be resolved. Ingber and Jameson (161) have suggested a tensegrity model to explain how cells composed of structural elements may be capable of such information transfer. Tensegrity was defined by Buckminster Fuller in 1948 as a structural system composed of discontinuous compression elements connected by continuous tension cables, which continually interacted in a dynamic fashion. This structure allows great motility as each part is in coupled equilibrium so that mechanical forces can be transferred throughout the entire system. Recently, Dennerl et al. (162) have observed and measured a tension and compression system in neurites. They suggest a complimentary force interaction between an actin network under tension and the microtubule network under compression. A tension-derived tensegrity structure may be a more appropriate way to view cell structure than a rigid scaffold framework system. These changes progress to a cell with increased motility and an ability to metastasize.

Conclusion

The pioneering biophysicist Aaron Kachalsky stated in 1962 that “life may be defined as a chemomechanical engine.” The highly motile yet structured cancer cell may also be viewed as a chemomechanical engine in which structure and function are intimately interrelated. Disruptions or changes in the matrix system may help explain genetic instability and tumor cell heterogeneity. Our present view of this process is depicted in Fig. 5. It is now obvious that cell transformation is a multistep process involving genomic changes that can involve oncogenes acting at different sites within the cell. These changes progress
Fig. 5. The transformation process. Transformation from a normal cell to a malignant one appears to involve multiple steps. These steps are usually considered in terms of "initiation" and "progression." This process may be viewed at the mechanism/site of action of the different oncoproteins involved in tumor progression. One class of the oncoproteins, those acting on the nucleus, e.g., myc, alter the structural stability of cells. This leads to immortalization and concomitant DNA and structural instability. A second class of oncoproteins, those acting on the periphery of the cell, e.g., ras, induce motility into the cell and may impart the ability to metastasize.

to a cell with increased motility and an ability to metastasize. Understanding this carcinogenic process will require a more complete knowledge of the interlocking matrix systems that extend from the extracellular matrix to the DNA and that govern cell shape and function.

REFERENCES


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