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# Nuclear Matrix and the Regulation of Gene Expression: Tissue Specificity

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**Abstract** Tissue specific regulation of gene expression by a single transcription factor or group of transcription factors cannot be explained simply by DNA sequence alone. For example, in the same animal a particular transcription factor is capable of interacting with DNA in the nucleus of many different cell types, resulting in unique gene expressions despite the presence of a similar genome in all cells. Historically, these differences in response to a single type of factor within target tissues in the same animal have been suggested to occur through different alterations in chromatin structure. Recent, data has demonstrated that combinations of hormones and transcription factors working together may cooperatively play a role in the regulation of gene expression [Pearce and Yamamoto (1993): Science 259:1161–1165]. However, the molecular mechanisms of this tissue specific regulation of gene expression still remains largely unexplained. Current evidence suggests that in different cell types the interplay between the specific three-dimensional organization of the genome and the structural components of the nucleus, the nuclear matrix, may accomplish the regulation of specific gene expression. 

**Key words:** nuclear skeleton, DNA organization, transcriptional regulation, nuclear structure, gene regulation

The elucidation of the molecular mechanisms involved in the control of gene expression in a tissue specific manner is essential to understanding cell regulation. Considerable work has been carried out to determine the means by which the expression of a particular gene, and in turn its protein product, can be tissue specific. There is evidence that in some systems the 5′ and 3′ flanking DNA sequences can confer tissue specificity and developmental control to certain genes. However, in each tissue, the same flanking sequences exist. These *cis* acting elements are thought to bind nuclear proteins which in turn permit unique DNA looping and allow the specific transcription of certain genes. To accomplish this, chromatin conformation will require a specificity in the non-DNA components. Since the DNA sequences are similar, the DNA methylation pattern of genes has been implicated in their specific expression. However, examination of DNA methylation does not appear to account for the tissue specificity in many systems in which it has been studied.

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Since DNA sequence alone does not appear to fully account for tissue specific control of gene expression, attention has been given to the role of nuclear proteins. Indeed, nuclear proteins have been shown to play an important role in the tissue specific expression of certain genes. Nonhistone chromosomal proteins [Ermekova et al., 1984], nuclear acidic proteins [Davis et al., 1975], nuclear high mobility group (HMG) proteins [Rabbani et al., 1978], and multiple combinations of nuclear DNA binding proteins [Royer and Reinherz, 1987] have all been implicated as determinants in the specific control of gene expression. The above nuclear proteins have not been examined for their role in the three-dimensional organization of the DNA and their role in nuclear matrix structure. The precise positioning of nucleosomes and transcription factors has also been shown to play a role in the tissue specific regulation of gene expression [McPherson et al., 1993]. Histone modification can also regulate chromatin structure [Felsenfeld, 1992], as can topoisomerase activity that has been shown to be associated with the nuclear matrix.

Similarly, in hormone receptor action, many types of cell membrane hormone receptor interactions have been shown to activate a variety of intracellular signalling pathways which often

utilize cascades of enzymes and cellular elements that have different effects in different tissues. The variations in hormone signal pathways are usually explained in terms of differences in receptors and soluble signals but have not often focused on the involvement of three-dimensional cell structure and organization of DNA in the target cells. In addition, it has been demonstrated that steroid hormones interact with their nuclear receptors which in turn interact with hormone responsive elements (HRE) which are DNA sequences. However, it is unknown how the steroid receptor selects a specific HRE over another within the same genome to specifically activate a given gene. Hormones in general have also been shown to be associated with virtually every level of cell structure, including the nucleus, cytoskeleton, and extracellular matrix. How these structures of the tissue matrix interact to finally modulate chromatin structure and regulate cellular function under the influence of hormone is one of the major frontiers of examining the regulation of gene expression.

## NUCLEAR MATRIX

A cell matrix system consists of an integrated three-dimensional skeletal network that organizes cellular structures and functions from the cell periphery through to the DNA. These skeletal networks or matrix systems consist of linkages and interactions of the nuclear matrix, the cytoskeleton, and the cell periphery. The tissue matrix includes the linkage of the cell matrix to the extracellular matrix. The interactive tissue matrix system may be defined as the dynamic structural subcomponent of the cell which interacts to organize and process spatial and temporal information to coordinate cell functions and gene expression [Getzenberg et al., 1990].

The cytoskeleton couples intracellularly with the nuclear matrix that provides the three-dimensional organization of DNA. The nuclear matrix is the residual framework scaffolding of the nucleus and consists of the peripheral lamins and pore complexes, an internal ribonucleic protein network, and residual nucleoli [Berezney and Coffey, 1974]. The nuclear matrix is the salt extracted structure of the nucleus and consists of approximately 10% of the nuclear proteins and is virtually devoid of lipids, DNA, and histones [Fey et al., 1991]. The nuclear matrix resists extraction with detergents, digestion with nucleases, and extractions with moderate or high ionic strength. A majority of the nuclear matrix proteins identified are common to all cell types and physiologic states. There is increasing evidence that some nuclear matrix proteins are tissue specific and others are altered with the state of the cell.

## TISSUE SPECIFICITY OF NUCLEAR MATRIX PROTEIN COMPOSITION

Investigations by a number of laboratories have identified nuclear matrix proteins which are not common to all cell types or conditions. Mitogenic stimulation and the induction of differentiation have been demonstrated to cause alterations in nuclear matrix proteins and structure. Differences in nuclear matrix protein patterns have been noted between different cell lines [Fey and Penman, 1989]. This same study also noted variations in the nuclear matrix proteins between transformed and nontransformed cell lines of similar origin.

The nuclear matrix protein composition is different between normal and transformed cell types. Recent evidence indicates that the nuclear matrix of the rat dorsal prostate is different from the nuclear matrix of Dunning prostate tumors, a set of tumors with different phenotypic properties which are all derived from an original spontaneously arisen rat dorsal prostate adenocarcinoma [Getzenberg et al., 1991b]. The differences in nuclear matrix protein composition between the normal and tumor cells may play a role in the differences in gene expression found in the transformed state. Differences in nuclear matrix proteins have also been found between normal and cancer samples in both human prostate cancer [Partin et al., 1993] and breast cancer [Khanuja et al., 1993].

The nuclear matrix has also been shown to differ in protein composition in a tissue specific fashion in the rat ventral prostate and seminal vesicle [Getzenberg and Coffey, 1990] as well as a number of other rat tissues that were examined. These differences are not only demonstrated between tissues but are also found between individual lobes of the rat prostate [Getzenberg et al., 1991b]. Additionally, the nuclear matrix proteins were demonstrated to vary with the hormonal state of the animal, possibly reflecting changes in gene expression seen in the castrate animal [Getzenberg and Coffey, 1990].

The presence and absence of the nuclear matrix proteins is not the sole mechanism by which

nuclear matrix proteins are regulated. Nuclear matrix proteins have been shown to undergo phosphorylation with growth, during the onset of mitosis and with androgen treatment [Goueli and Ahmed, 1984]. It is of interest to determine how the nuclear matrix proteins are regulated and modified with differences in gene expression. The regulation of the three-dimensional organization of DNA structure and function appears to be essential to specific gene expression, and the role of these tissue specific nuclear matrix proteins in mediating these changes will be important to resolve.

## DNA ORGANIZATION AND THE NUCLEAR MATRIX

In the interphase nucleus, the 30 nm chromatin filaments form 50,000 DNA loop domains each of approximately 60 kbp that are attached at their base to the inner portions of the nuclear matrix [Pardoll et al., 1980]. The nuclear matrix is the nuclear scaffolding which has previously been demonstrated to play a central role in the regulation of important cellular processes such as DNA replication [Gasser, 1991; Cook, 1991] and transcription [Getzenberg and Coffey, 1991].

The nuclear matrix also plays a central role in RNA processing. Newly synthesized heteronuclear RNA and small nuclear RNA are enriched on the nuclear matrix [Huang and Spector, 1991]. The nuclear matrix has also been shown to be the site of attachment for products from RNA cleavage and for RNA processing intermediates [Carter et al., 1993; Xing et al., 1993]. Spliceosome complexes involved in the regulation of RNA splicing have been localized to the nuclear matrix. RNA and ribonucleoprotein particles and fibers may themselves have an important role in the structure of the nuclear matrix [He et al., 1991].

The structural components of the nucleus are known to have a central role in the specific topological organization of DNA. DNA in the nucleus is not randomly organized, and although only approximately 10% of the DNA actually encodes genes, only specific genes are positioned in a manner that permits the expression of both housekeeping and cell type specific genes. The average mammalian somatic cell nucleus contains a linear equivalent of two meters of DNA packed by a 200,000-fold linear condensation into a 10 μm nucleus [reviewed in Pienta et al., 1991]. The DNA has many forms of higher order structure which is organized in a particular pattern that results in the expression only of appropriate tissue specific genes. With the use of in situ hybridization [McNeil et al., 1991], there is now direct evidence for specific three-dimensional organization of the DNA within the nucleus [Carter and Lawrence, 1991; Haaf and Schmid, 1991]. Manuelidis and coworkers demonstrated the specific and reproducible compartmentalization of unique chromosomal domains within the nuclei of human central nervous system cell lines and established that functionally distinct cell types have specific patterns of interphase chromosome three-dimensional organization [Manuelidis and Borden, 1988]. Comparison of the chromosomal topography of human lymphocytes, amniotic fluid cells, fibroblasts, and human cerebral and cerebellar samples have further demonstrated that the topological DNA organization is cell type specific [Emmerich et al., 1989]. In summary, many studies have now demonstrated the specific three-dimensional organization of DNA within the nucleus. Differences in this organization can occur with the same genomic sequence and are dictated in part by DNA interactions with a tissue specific nuclear matrix. Nuclear structure is therefore involved in both this topological organization of DNA and the functional aspects which coincide with this organization.

The nuclear matrix has also been demonstrated to be the site of mRNA transcription. Active genes have been found to be associated with the nuclear matrix only in cell types in which they are expressed. Genes that are not expressed in these cell types are not found to be associated with the nuclear matrix (Table I).

Further investigation into the association of active genes with the nuclear matrix has revealed a DNA loop anchorage site in the enhancer regions or intronic sequences of several genes. These sequences have been termed matrix associated regions (MARs) or scaffold attached regions (SARs) and are usually approximately 200 base pairs in length, are A-T rich, although recent evidence suggests other sequence types exist [Boulikas and Kong, 1993], and contain topoisomerase cleavage sequences along with other sequences such as polyadenylation signals [reviewed in Roberge and Gasser, 1992]. Although these sequences often have a high degree of homology with topoisomerase II cleavage sequences, only one has been found to actually bind topoisomerase II [Sander et al., 1987]. Recently, MARs have been shown to not

**TABLE I. Examples of Actively Expressed Genes Reported to Be Associated With the Nuclear Matrix in Tissues in Which They Are Expressed and Not Associated With the Nuclear Matrix in Nonexpressing Tissues or in States in Which They Are Not Expressed***

| Tissue/cell type | Gene |
|---|---|
| Rat liver | Ribosomal RNA |
| NIH 3T3 cells | SV40 |
| HeLa cells | Newly transcribed sequences |
| Chicken oviduct | Ovalbumin |
| Nine cell types | Polyoma and avian sarcoma viruses |
| Chicken oviduct | Ovalbumin |
| HeLa cells | Newly transcribed sequences |
| Human lymphocytes | Immunoglobulin |
| Mouse lymphocytes | α-globin |
| Chicken liver | Vitellogenin II |
| Chicken erythrocytes | β-globin |
| *Drosophila* | Heat shock |
| Rat ventral prostate | Prostatein C-3 |
| Rat liver | $\alpha_2$-macroglobulin |
| Human skin | Proα2(I) collagen |
| Human erythrocytes | Globin |
| Chicken erythrocytes | α-globin |
| Chicken | Lysozyme |
| Human HL-60 | *c-myc* |
| Human urothelium | Type IV procollagen |

*For references refer to Getzenberg et al. [1991a].

only be A-T rich regions but to comprise other regions, including T-G rich motifs and potential Z-DNA as well as polypurine and polypyrimidine blocks [Boulikas, 1993]. MAR sequences have been shown to play a possible role in relieving superhelical strain of the DNA [Bode et al., 1992]. The MARs have also been shown to functionally confer increased transcriptional activity in genes following transfection. These MAR/SAR sequences have been found to be equally distributed between the internal nuclear matrix and the nuclear lamina [Luderus et al., 1992]. Classic experiments by Stief and colleagues [1989] involved utilizing the matrix associated DNA sequences of the chicken lysozyme gene and inserting this sequence into a transfectable expression vector. When this reporter system is flanked by the 5′ MAR, its expression is markedly elevated and is independent of chromosome position [Stief et al., 1989]. A similar experiment was carried out using the 5′ MAR of the chicken lysozyme gene and a transient transfection system, again demonstrating increased and position independent transcription of the gene construct [Phi-Van et al., 1990]. To further determine the role of these MARs in gene expression, deletion experiments were carried out to remove the MARs from genes which normally contained these sequences and noting this deletion on the transcriptional activity of the gene. In the immunoglobulin kappa gene, deletion of the intronic MAR led to a fourfold decrease in expression. When both the intronic MAR and a MAR in the enhancer region were removed from this gene, the expression dropped elevenfold [Blasquez et al., 1989]. These experiments were then conducted in vivo; when transgenic animals were produced from these constructs, both of the genes with the intact and deleted MARs were expressed in a tissue specific manner, although those genes with a deleted MAR(s) exhibited only two- to threefold lower activity [Xu et al., 1989]. This data demonstrates the importance of precise DNA organization which is necessary to result in appropriate gene expression. The MARs in the β-globin gene are proposed to be mass binding sites for transcription factors, some of which may be developmental state specific and others ubiquitous [Boulikas, 1993].

Recently, nuclear matrix proteins which bind to MAR sequences have been identified by a number of laboratories. These nuclear matrix proteins may serve as the attachment points for the these matrix associated DNA sequences, and it is possible that some of these proteins may be responsible for forming the DNA loop domains. One of these proteins termed SATB1 is primarily a tissue specific MAR binding protein, found typically in the thymus. In in vitro cotransfection studies, this protein appears to act as a transcription suppressor [Dickinson et al., 1992]. Therefore, these proteins and possibly some of the other MAR binding proteins identified may be involved in suppressing the expression of specific genes in a tissue specific manner. Recent investigations have revealed that calmodulin and other nuclear proteins may participate in the association of MARs with the nuclear matrix [Fishel et al., 1993].

Additionally, telomeric DNA sequences have been found to be preferentially associated with the nuclear matrix [de Lange, 1992], indicating that these attachments may be important in DNA organization.

## TRANSCRIPTION FACTORS AND THE NUCLEAR MATRIX

Recent evidence has further demonstrated that transcription factors are localized or seques-

tered on the nuclear matrix and that this localization may play an important role in the regulation of gene expression [Getzenberg and Coffey, 1991; van Wijnen et al., 1993]. Isomura et al. [1992] have identified a protein that they termed RFP, which is a 58 kilodalton (kD) protein with putative zinc finger domains, which associates or is a component of the nuclear matrix, binds preferentially to double stranded and single stranded DNA, and is involved in the activation of the *ret* protooncogene. Recently, a nuclear matrix protein was identified to be the sequence-specific DNA-binding factor F6 which binds upstream of the cluster region of chicken α-globin genes. This protein belongs to a family of GATA proteins which are the chicken equivalents of the transcription factor NFE-1 [Vassetzky et al., 1993]. Stein and his colleagues have examined the regulation of the osteocalcin gene. In the promoter region, they have identified multiple protein-DNA interactions involving two different nuclear matrix proteins. These proteins interact with regions of the gene in proximity to the vitamin D responsive sequences. The first nuclear matrix protein that they characterized is termed NMP-1 and is a ubiquitous cell growth–regulated protein that is related to the transcription factor ATF. The second protein, termed NMP-2, is a cell type specific protein that recognizes binding sites resembling the consensus site for the CCAAT enhancer biding protein C/EBP and is localized exclusively on the nuclear matrix [Bidwell et al., 1993]. Previous work from the Stein laboratory resulted in the identification of two proteins that bound to the nuclear matrix attachment regions upstream of the human H4 histone gene promoter. These proteins were suggested to be from the ATF transcription factor binding family [Dworetzky et al., 1993]. These results together support the concept that transcription factors are localized or sequestered on the nuclear matrix and that the localization of these factors on the nuclear matrix may play an important role in DNA binding and the specific regulation of gene expression.

## NUCLEAR MATRIX AND HORMONE ACTION

The first example of a transcriptional activator found to be associated with the nuclear matrix was that of the steroid receptors. Hormone action is, perhaps, the system in which the role of the nuclear matrix in the regulation of gene expression has been most investigated. The high affinity binding of the steroid receptors to the nuclear matrix in many estrogen and androgen responsive tissues has been demonstrated [Barrack, 1987]. The binding of steroid receptors to the nuclear matrices of individual tissue is both steroid and tissue specific and requires the presence of an activated steroid receptor complex with bound steroid (Table II). For example, androgens were found to bind to the nuclear matrices of androgen responsive tissues and estrogens to the nuclear matrices of estrogen responsive tissues. Tissues that do not demonstrate hormone responsiveness are not found to have hormone receptors on their nuclear matrices. In addition, the level of steroid receptor binding in these nuclear matrices was demonstrated to vary with the hormonal state of the animal. Receptors were not found bound to the nuclear matrix in the hormone withdrawn state, and with subsequent administration of specific hormones the receptor complexes were then again shown to bind the nuclear matrix.

An example of the specificity of the interaction of steroid receptors with the nuclear matrix is the rat ventral prostate, which is under androgen regulation. In the intact adult male, dihydrotestosterone (DHT) receptors are found associated with the nuclear matrix. When these animals are castrated, within 24 h there is a rapid loss of these binding sites from the nuclear matrices. This rapid loss of binding occurs prior to cell death and involution of the gland. Readministration of dihydrotestosterone to these animals restores within 1 h the androgen receptor binding on the nuclear matrix to normal levels [Barrack, 1987]. It is important to note that administration of estrogen to the castrated animal does not restore the DHT receptors to the nuclear matrix.

Thus, using the techniques of labelling in vivo, exchange reactions in vitro, and cell free

**TABLE II. Specific Association of Steroid Receptors With the Nuclear Matrix**

| Tissue | Receptor type |
|---|---|
| Rat uterus | Estrogen |
| Rat ventral prostate | Androgen |
| Rat liver | Thyroid |
| Rat liver | Estrogen |
| Guinea pig seminal vesicle | Androgen |
| Hen liver | Estrogen |
| Human foreskin | Androgen |
| Human prostate cancer | Androgen |
| Human prostate (BPH) | Androgen |
| Rat hippocampus | Corticosteroid |

reconstitutions, steroid receptors have been found to be present in the nuclear matrix of a large number of steroid responsive tissues. Furthermore, this interaction is steroid and tissue specific and only occurs in response to an appropriate hormonal stimulus. It is this positioning of the steroid receptors on the nuclear matrix which may play an important role in the regulation of gene expression.

Steroid receptors interact with the nuclear matrix through acceptors sites which are present on the nuclear matrix and are involved in the saturable, high affinity, specific binding described earlier. One such acceptor protein that has been well characterized is the acceptor protein for the progesterone receptor termed RBF-1 [Schuchard et al., 1991]. This protein is a nuclear matrix protein which has a high affinity for the progesterone receptor. It is proposed that it is through these acceptor proteins that steroid receptors interact with the nuclear matrix and the DNA and therefore may position themselves in the appropriate location for the activation and/or repression of gene expression [Landers and Spelsberg, 1992]. The possible mechanisms by which these androgen receptors located on the nuclear matrix activate genes in a tissue specific manner will now be addressed.

The nuclear matrix is uniquely positioned to regulate chromatin structure and organization and thus be involved in the tissue specificity of steroid hormonal regulation in sex accessory tissues. The model system used in these studies investigates the tissue specific androgen regulation of gene expression comparing the dihydrotestosterone (DHT) response in rat ventral prostate with that of the seminal vesicle from the same animal. Both the ventral prostate and

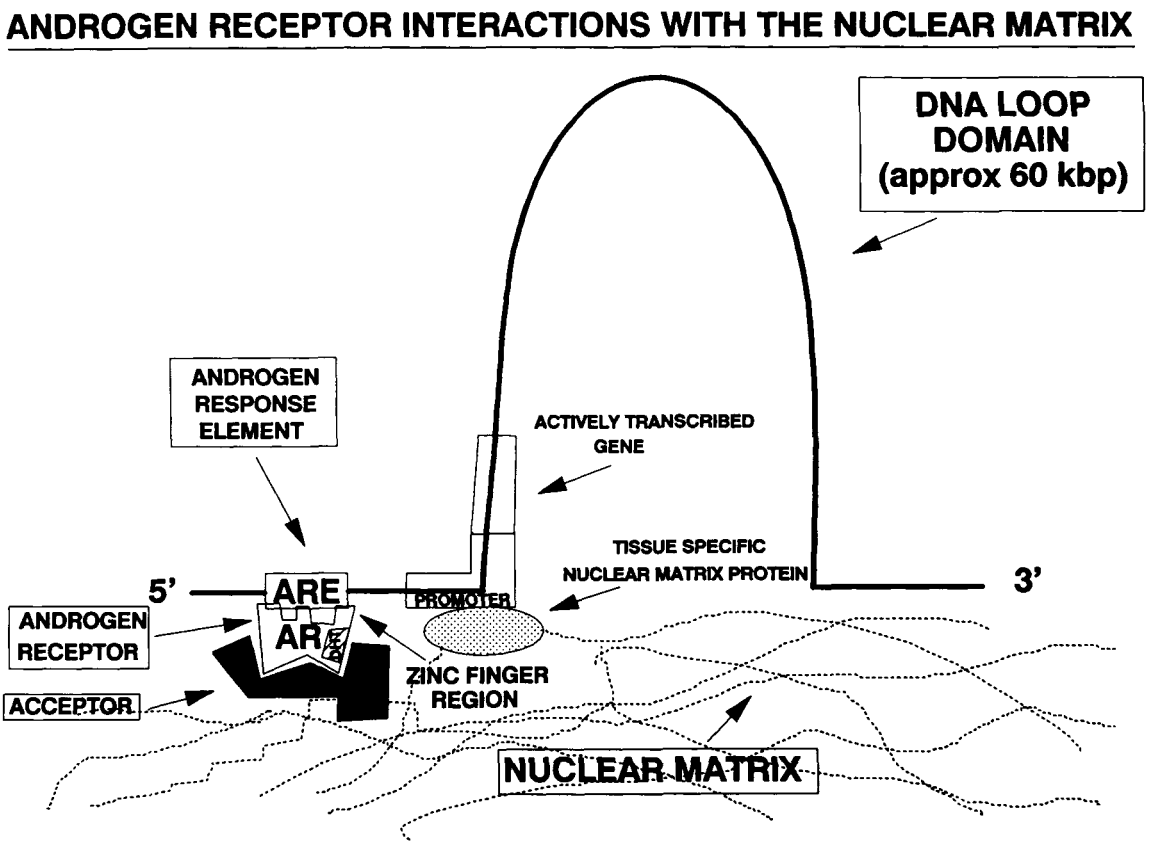


Fig. 1. Schematic of proposed androgen receptor interactions with the nuclear matrix. The activated androgen receptor has previously been demonstrated to interact with the nuclear matrices of both the ventral prostate and seminal vesicle. Additionally, the androgen receptor has been shown to associate with specific DNA sequences which are called androgen response elements (ARE). This schematic demonstrates an interaction of the androgen receptor with the nuclear matrix and the androgen regulated gene. The interaction of the androgen receptor with the nuclear matrix is via a nuclear matrix acceptor protein, possibly similar to the type of protein recently identified by Spelsberg's laboratory [1991] for the progesterone receptor. The nuclear matrix also organizes the DNA three-dimensionally to position the DNA in a proper orientation for the androgen receptor to interact, resulting in the regulation of gene expression.

seminal vesicle possess similar nuclear DHT receptors and contain the same genome but respond to DHT with the production of completely unrelated secretory proteins. The major androgen regulated secretory product of the ventral prostate is a glycoprotein, known as prostatein or prostate binding protein. It has a molecular weight of 40 kilodaltons (kD) and a pI of 4.8 [Lea et al., 1979] and is composed of several subunits that are under androgen regulation. The most abundant subunit of prostatein, C3, which has a molecular weight of 14,000 daltons, serves as an indicator of androgen regulated gene expression in the ventral prostate. Recently, the hormone response elements of this gene were characterized [Tan et al., 1992]. The seminal vesicle produces six major secretory products known as SVS I through SVS VI [Ostrowski et al., 1979]. SVS IV is the most abundant product, has a molecular weight of approximately 17,000 daltons, and is used as a marker of androgen regulated gene expression in the seminal vesicle.

The C-3 and SVS-IV genes are specifically localized on the nuclear matrix in the rat ventral prostate and seminal vesicle. These genes are preferentially localized on the nuclear matrix in the tissues in which they are expressed and are

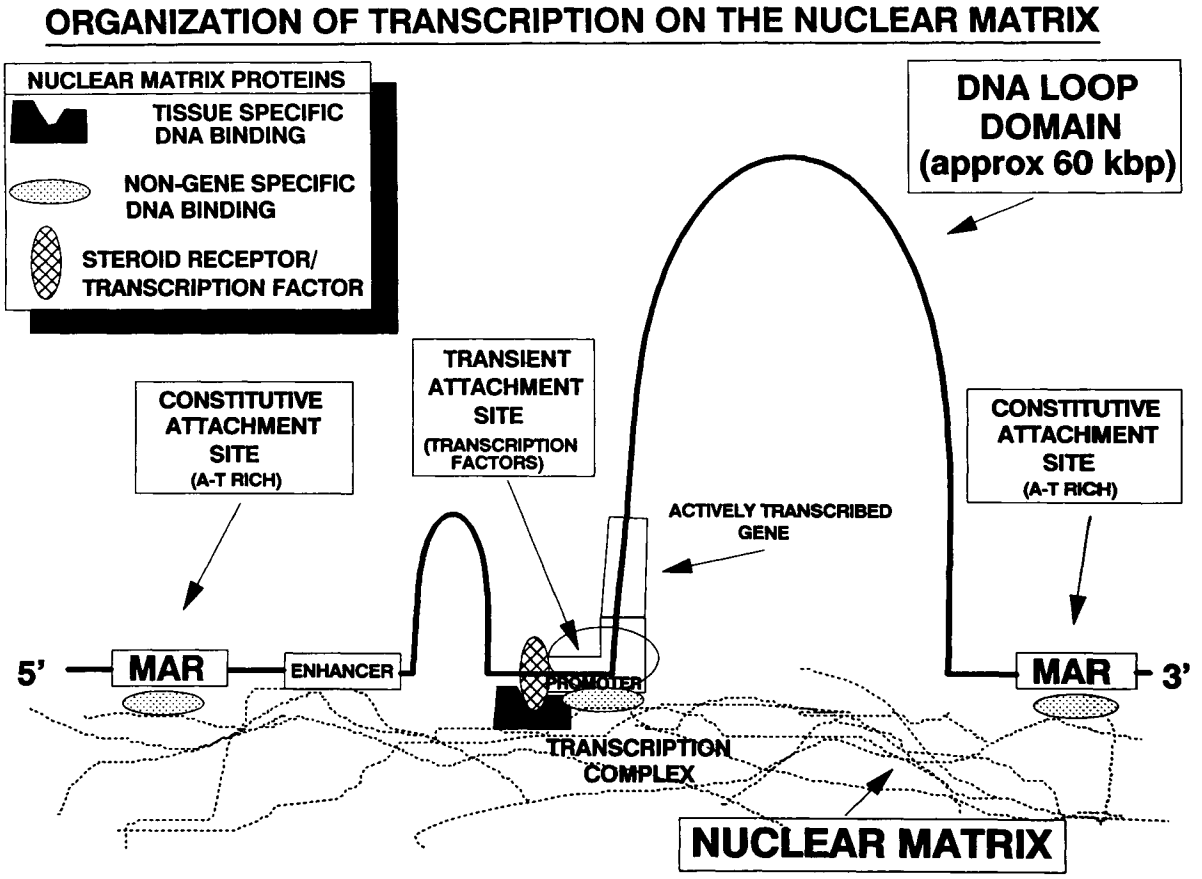


**Fig. 2.** Proposed model for organization of transcription on the nuclear matrix. The nuclear matrix plays a central role in the three-dimensional organization of DNA. The nuclear matrix interacts with the DNA through two different associations. The first is known as a constitutive attachment site which is termed in the literature a matrix associated region (MAR); it is an A-T rich sequence with homology to topoisomerase II cleavage sequences. These association points are constitutive and may represent the sites at which the DNA stably binds to the nuclear matrix to form the 60 kbp loop domains. The DNA is attached at these points by non-gene specific nuclear matrix proteins. The second form of attachment site is a transient attachment site where the DNA is organized with the use of tissue specific nuclear matrix proteins and/or transcription factors which are complexed with the nuclear matrix to form a DNA interaction that would permit the tissue specific activation of genes. This interaction could form a smaller loop of DNA off of the larger 60 kbp loop domains and may include the looping out of regions of DNA between the enhancer and promoter regions to bring these activational sequences in close proximity for specific gene regulation. This binding would position the active gene at the base of the loop in close proximity to the nuclear matrix where the inactive gene would not be associated with the nuclear matrix and would be located peripherally in the loop domain.

located in the peripheral or loop domains in the tissues in which they are not expressed. These genes have also been examined in other tissues, where they are also found in the loop fractions. Southern and gel mobility shift analyses have revealed that there are specific regions of these genes associated with the nuclear matrix and that specific interactions between these genes and the nuclear matrix proteins themselves exist in the tissues in which they are expressed that are not present in the nonexpressing tissues. In addition, as described previously, the nuclear matrix protein components have been shown to be tissue specific not only for these tissues but for others that have been examined [Getzenberg and Coffey, 1990]. Together, the data in this example demonstrate the central role of the nuclear matrix in the regulation of gene expression.

The tissue specific expression of these androgen regulated genes may be explained with the following model. The androgen receptor may interact with the nuclear matrix by association with an acceptor protein(s) which may be similar to the type of protein that has been isolated by Spelsberg's group for the progesterone receptor [Schuchard et al., 1991]. The nuclear matrix not only is involved in the binding of the androgen receptor but also plays a role in the specific organization of DNA by arranging the loop domains in a specific fashion that permits the activated androgen receptor-DHT complex to associate with both the nuclear matrix and the responsive element on the gene of interest. Thus, the nuclear matrix plays a central role in androgen regulated gene expression by providing a site for interaction of the DNA and the transcriptional activator and by organizing the DNA in a tissue specific three-dimensional pattern.

The nuclear matrix has been shown to be the organizing structure of the DNA in the nucleus, and therefore differences in the nuclear matrix components may allow for a different DNA organization in the two tissues. The difference in the three-dimensional organization of the DNA might provide for a tissue specific interaction of the DNA with the DHT receptor or other transcriptional activator. The ability of the DHT receptor to bind to one site on the DNA in the ventral prostate and another site on the DNA in the seminal vesicle could account for the differential gene expression seen between the two tissues (Fig. 1).

## MODEL FOR TISSUE SPECIFICITY

These topological considerations and the precise ordering of gene expression have been difficult to account for without considering the specific spatial organization and higher order structure within the nucleus and cell. The overall coordination of these multiple elements and pathways requires a spatial and temporal precision that would be unobtainable in the absence of a structural order. To permit diversity of function, DNA must be topographically and topologically partitioned into independent functional units or domains. This spatial and temporal control of DNA is accomplished in part by the nuclear matrix. The nuclear matrix provides sites for the specific control of nucleic acids and for intranuclear particulate transport. Furthermore, the nuclear matrix provides a structural connection for DNA to the structural component of the cell, the three-dimensional tissue matrix (Fig. 2). The nuclear matrix may, therefore, play a central role in the regulation of gene expression. By serving as a framework on which to bring together appropriate DNA sequences with activators and/or suppressors of expression, the structure of the nucleus may coordinate gene regulation.

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