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REVIEW ARTICLE

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The nuclear matrix in pathology

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Abstract For a long time the molecular basis of nuclear structure has been a matter of debate rather than an established fact. In the last decade the concept of the nuclear matrix has emerged, and the molecular basis of this nuclear infrastructure, although still incomplete, is gradually being unravelled. In early studies concerning the nuclear structure, autoantibodies derived from patients with collagen disease had a significant role. This matrix, the structure remaining after extraction of membranes, nucleic acids and histones, consists of the nuclear lamina, the nucleolus and a fibrillogranular network. The nuclear lamina is composed of the lamins. The nucleolar matrix contains the proteins involved in rRNA processing. The fibrillogranular network is composed of nuclear matrix proteins, a wide variety of which has been discovered. It has become clear that the nuclear matrix not only provides a structural basis for nuclear architecture but also plays a part in regulating nuclear function. Lamins provide mechanical continuity between cytoskeleton and nuclear interior. Aberrant patterns of lamin expression have been described in cancer; these are not sufficiently specific to be used in histopathological diagnosis, however. Nucleolar size and expression levels of nucleolar proteins have been shown to correlate well with proliferative activity, which may revitalize interest in nucleolar organizing regions as a tool in histological diagnosis of cancer. The fibrillogranular network is involved in functional compartmentalization of replication and transcription. A variety of nuclear matrix proteins has been described, which appear to be specifically expressed in cancer cells. Analysis of expression of these proteins might play a significant role in cancer diagnosis.

Key words Nucleus · Nuclear matrix · Lamin · Nucleolus · Fibrillogranular network

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Introduction

Cell nuclei are important in the everyday life of every practising pathologist. In a variety of diseases nuclear morphology, as reflected in haematoxylin-stained images, provides important clues to the diagnosis. The characteristic nuclear alterations in cancer cells constitute the clearest example of this notion. Nuclear pleomorphism, hyperchromasia, chromatin clustering and prominence of nucleoli are more or less constant features of the malignant cell. For a long time it was assumed that these morphological changes reflect abnormalities in the nuclear DNA content. Although genomic instability, which leads to these alterations in nuclear DNA content, is very much a feature of cancer cells, it is not present to the same extent in all cancer cells. It is also true that in some cancers the abnormalities of nuclear morphology are not accompanied by an abnormal DNA content, reinforcing the notion that there is more to a nucleus than just DNA.

The structure of the chromatin fibre, with its characteristic nucleosomes formed in a particular association of DNA with the histone proteins and its packaging in chromosomes, has been long resolved. To what extent the nonchromatin compartment of the nucleus has a defined infrastructure, however, is much debated. Some of the early tools used in the elucidation of nuclear structure came from antinuclear autoantibodies in patients with collagen disease, most notably lupus erythematosus, rheumatoid arthritis and scleroderma. This category of disease is therefore, after neoplasia, the second domain of pathology with direct links to the nuclear structure. What exactly is responsible for the generation of these antinuclear autoantibodies remains a mystery, but the antibodies as such have proved to be important, in allowing the identification of specific proteins that have a dominant role in the nuclear structure.

It is the purpose of this review to discuss what is known about the structure of the nucleus in the context of pathology. We will discuss the morphologically identifiable compartments of the nucleus and their chemical composition. We will review the role of these compart-

ments in the functions of the nucleus and along the line we will discuss to what extent nuclear structure might be involved in pathological processes.

Nuclear morphology

A classic electron micrograph of a nucleus shows limited details of the nuclear structure. Easily recognizable (Fig. 1) are the nuclear envelope with its pores, the heterochromatin, the euchromatin and the nucleolus. Treatment with calcium-chelating agents such as EDTA (ethenediamine tetraacetic acid) results in inverse staining of the nucleus. The heterochromatin is now bleached, allowing the euchromatin to show its structural details: the fibrillogranular compartment, the perichromatin and interchromatin granules and the perichromatin fibrils (Fig. 2). In the nucleolus the fibrillar and granular domains can be clearly distinguished. The functional role of these structures has been only partly resolved. We will come back to this point later on.

Electron microscopy of chromosomes (Fig. 3) reveals a fibrillar chromatin structure. The fibrils seem to bear beads, because the chromatin fibre is coiled much like the coils in a telephone wire. The chromatin fibre itself has the characteristic beads-on-a-string morphology because of the presence of nucleosomes, beads formed of aggregated histone proteins around which the nucleosomal DNA is wound, linked by internucleosomal stretches of DNA.

The nucleus is composed mainly of three categories of macromolecules: nucleic acids, the (basic) histone proteins and the (acidic) nonhistone proteins. Nucleic acids fall outside the scope of this review, as do histones. Histones do, however, contribute importantly to chromatin structure and also function prominently in the regulation of gene transcription [56]. It has also been shown that histone deacetylation alters chromatin structure and in this way blocks transcriptional activity [6, 23]. Mad-Max heterodimers repress transcription by recruiting proteins involved in histone deacetylation [29].

Structure of the nuclear matrix

A striking nuclear morphology is obtained when salt extraction procedures are used to remove the nuclear proteins. A protein scaffold remains, around which a halo of DNA loops can now clearly be visualized. Such images have strongly contributed to the notion that chromatin and chromosome structure is held together by a stable proteinaceous backbone, which seems to connect the cytoskeleton with the interior of the nucleus and which also encompasses components of the nucleolus. It is this basic nuclear infrastructure that is called the “nuclear matrix”.

As defined by Berezney and Coffey [4], the nuclear matrix is “the residual proteinaceous structure that remains after the nuclei are depleted of the nuclear membranes, histones, soluble nuclear proteins and nucleic acids.” This is achieved by treating isolated nuclei with DNA-se and subsequently eluting nuclear proteins by ammonium sulphate and high salt concentrations. What remain are probably relatively insoluble proteins and stretches of DNA attached to this protein backbone, presumably because this attachment makes them DNA-se insensitive. As a consequence, matrix preparations have been shown to contain 85–95% proteins and 5–15% nucleic acids. Given that nuclear matrix preparations are obtained under highly unphysiological conditions, the question has been asked whether or not it is a real physiological structure or rather a preparation artefact. The retention of a more or less similar structure after fairly different treatment protocols is an important argument in favour of the biological validity of the concept of the nuclear matrix. The structures that remain in these matrix preparations are the *nuclear lamina*, the *nucleolus* and the *fibrillogranular network*, which we will briefly discuss in terms of structure, function and involvement in pathological processes.

The nuclear lamina

The nuclear lamina constitutes a network of intermediate-sized filaments at the nucleoplasmic site inside the nuclear membrane. The main proteins in the nuclear lamina are the lamins. The lamins form part of the family of intermediate filament proteins because they share the same basic structure: an aminoterminal globular head, a central rod of α-helices and a globular carboxy-terminal domain. Two types of lamins, the A-type and the B-type, are distinguished. A-type lamins (A and C) are derived from the same genes by alternate splicing, and their expression, although widespread, appears to be differentiation related. The B-type lamins, B1 and B2, arise from two different genes and so far seem to be constitutively expressed in most cells. Lamins probably play an important part in maintaining nuclear structure (for a review, see [14]). During mitosis the lamins are phosphorylated, which inhibits their aggregation.

Dephosphorylation allows them to be reassembled in their habitual configuration. Lamins bind directly to DNA but also support the nuclear membrane. In this way lamins are probably important for the maintenance of the architecture of the nucleus. Recent studies have shown that nuclear lamins can also be detected inside the nucleolus [36]. The lamins, therefore, might not only form the external rim of the nucleus but also be involved in the internal nuclear structure. Lamin B is directly involved in the formation of the nuclear envelope. Lamins are also directly associated with the cytoskeleton and might thus play a part in signal transduction between nucleus and cytoplasm.

Lamin expression has been investigated in a variety of normal tissues [9] and pathological conditions. In normal tissues expression of type A lamins seems to be mostly limited to differentiated cells, whereas the expression of type B lamins is fairly widespread.

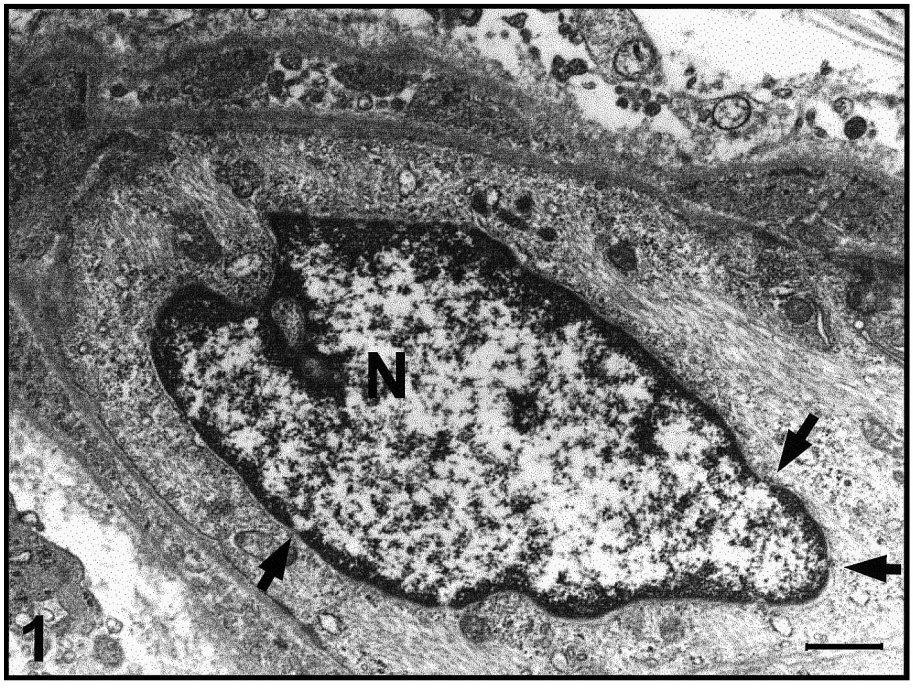

Fig. 1 Electron micrograph of a conventionally processed connective tissue containing a (myo)fibroblast. Note the nucleolus (*N*), the clusters of dense heterochromatin, the nuclear membrane with its pores (*arrows*). *Bar* 500 nm

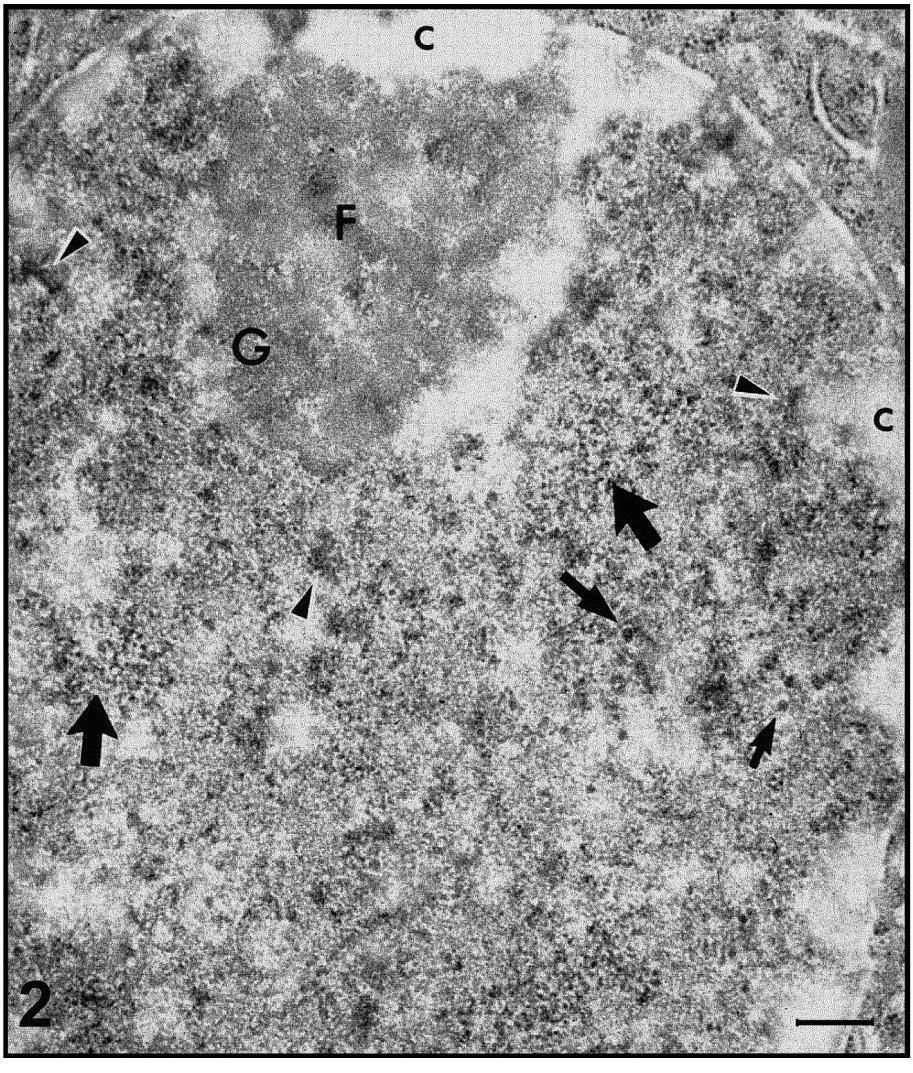

Fig. 2 Electron micrograph of inversely stained nucleus. The nuclear membrane and the condensed chromatin (*C*) are (almost) unstained. The nucleolus with its fibrillar (*F*) and granular (*G*) components is seen excentrically situated in the nucleus. The nucleus now shows interchromatin granules (*large arrows*) and perichromatin granules (*small arrows*) as well as perichromatin fibrils (*arrowhead*). (Electron micrograph courtesy of Dr. S. Fakan, Centre for electron microscopy, Lausanne.) *Bar* indicates 100 nm

Hytiroglu et al. [20] studied lamin expression in liver cell regeneration and hepatocellular carcinogenesis. Lamin A and B types were constantly expressed under these conditions, which contrasts with the differentiation-related expression of A-type lamins in normal cells. Broers et al. [8] found constitutive B-type lamin expression in all of a large series of lung cancer cell lines. A-type lamins were expressed in all non-small-cell lung cancer (SCLC) cell lines but absent in most SCLC cell lines. Lamin expression has also been studied in leukaemia, where Muller et al. [38] found B-type lamin expression was strongly related to proliferation. Jansen et al. [22] studied lamin expression in Hodgkin's disease. Expression of A-type lamins in Hodgkin and Reed-Sternberg cells was taken as an indication of the relative maturity of these cell types. Strikingly, lamin B2 was not found in follicular centre cells, indicating that this lamin subtype is not always expressed in nucleated cells. The same group studied lamin expression in testicular germ cell tumours [34]. In choriocarcinomas, teratomas and endodermal sinus tumours both A- and B-type lamins were expressed. Seminomas showed expression of B-type lamins only, which corresponds to what was found in spermatogonia. Carcinoma in situ of the testis showed exactly the same pattern. A rather unusual pattern of lamin expression was found in embryonal carcinomas, as these expressed only lamin C.

Lamin expression has been studied in a few non-neoplastic conditions. A reduction of the expression of A-type lamins in hibernating myocardiocytes has been explained as dedifferentiation of cardiomyocytes [2]. An interesting finding has been the existence of specific interleukin-1 converting enzyme (ICE)-related proteases that cleave lamins during apoptosis, suggesting that not only endonuclease DNA fragmentation but also dissolution of the nuclear matrix is involved in programmed cell death [31, 46, 58].

Among the nuclear autoantibodies in patients with systemic lupus erythematosus anti-lamin antibodies (mostly anti-lamin B2) have been reported [7]. Similarly, anti-lamin B1 antibodies have been found in the chronic fatigue syndrome [26]. In primary biliary cirrhosis autoantibodies occur that recognize the lamin B receptor in the inner nuclear membrane [33, 40].

Altogether, the data on lamin expression in neoplasia seem to confirm the fairly constitutive widespread type-B lamin expression, with type-A lamin expression mostly restricted to the differentiated cellular phenotype. In rare cases fairly specific lamin expression patterns are found, for example, the occurrence of only lamin C in embryonal carcinomas. These data have little impact on histopathological classification of tumours or on prognosis. Lamin expression may, however, clarify some aspects of disturbed nuclear structure and function in neoplasia. Lamins appear to be specific caspase targets during apoptosis. Nuclear autoantibodies in autoimmune disease may be directed against lamins or their nuclear membrane receptors.

The nucleolus

The second component remaining in nuclear matrix preparations is the nucleolus. The nucleolus is the most distinct structure within the nucleus, except during mitosis when it is briefly disassembled (for extensive review, see [17]). The nucleolus is responsible for rRNA packaging into ribosomes, and in actively synthesizing cells it therefore tends to be rather voluminous, occupying up to 25% of the nuclear volume [12].The nucleolus is not bound by a membrane. It has a characteristic ultrastructure with several fibrillar centres surrounded by a dense fibrillar component, which is in turn surrounded by a granular component (Fig. 4). Ribosomal RNA synthesis from large loops of the DNA from several chromosomes is confined to the fibrillar component. Attached to the nucleolar skeleton, the fibrils contain the polymerases, topoisomerases and other proteins necessary for transcription. Each of these DNA loops is called a nucleolar organizer region (NOR). Maturing rRNA transcripts are passed on to the granular component and are further assembled into the ribosome [51].

Recently [12], it was reported that there is a clear correlation between nucleolar size and cell proliferation rate in cancer cell lines. In addition, a close correlation has been found between the quantity and functional activity of the nucleolar proteins topoisomerase I, fibrillarin, RNA polymerase I and upstream binding factor (UBF), with cell-doubling time. Cancer cell rRNA transcriptional activity and nucleolar size were, as a consequence, inversely related to cell-doubling time.

Silver-staining nucleolar organizer regions (AgNOR) have raised considerable interest in tumour pathology in recent years because of their proposed use as a prognostic indicator in neoplasia. The silver-staining capacity of nucleolar organizing regions has been known for quite some time, and NORs were initially identified by this methodology. It was mainly Crocker's group who introduced AgNOR staining into diagnostic pathology, basing this on the notion that size and/or number of AgNORs, being strongly correlated with cellular proliferative activity, might be correlated with tumour behaviour [13]. Effectively, for a variety of tumours AgNOR parameters have shown a remarkable correlation with prognosis. In spite of early enthusiasm, AgNOR staining has not become as widely used as a prognostic marker as was initially expected. One of the important reasons is that the silver impregnation technique is rather troublesome, with important reproducibility problems. To what extent quantitation of NOR-associated nucleolar proteins might be used as immunostaining targets to replace silver staining remains to be seen.

Given the difficulties with silver staining of NOR, several investigators have indeed attempted to identify the proteins responsible for NOR silver staining or to immunostain them. Along these lines, Derenzini et al. [11] used silver staining of sodium dodecyclsulfate polyacrylamide gel electrophoresis (SDS-PAGE)-separated protein blots to study the nature of the reactive

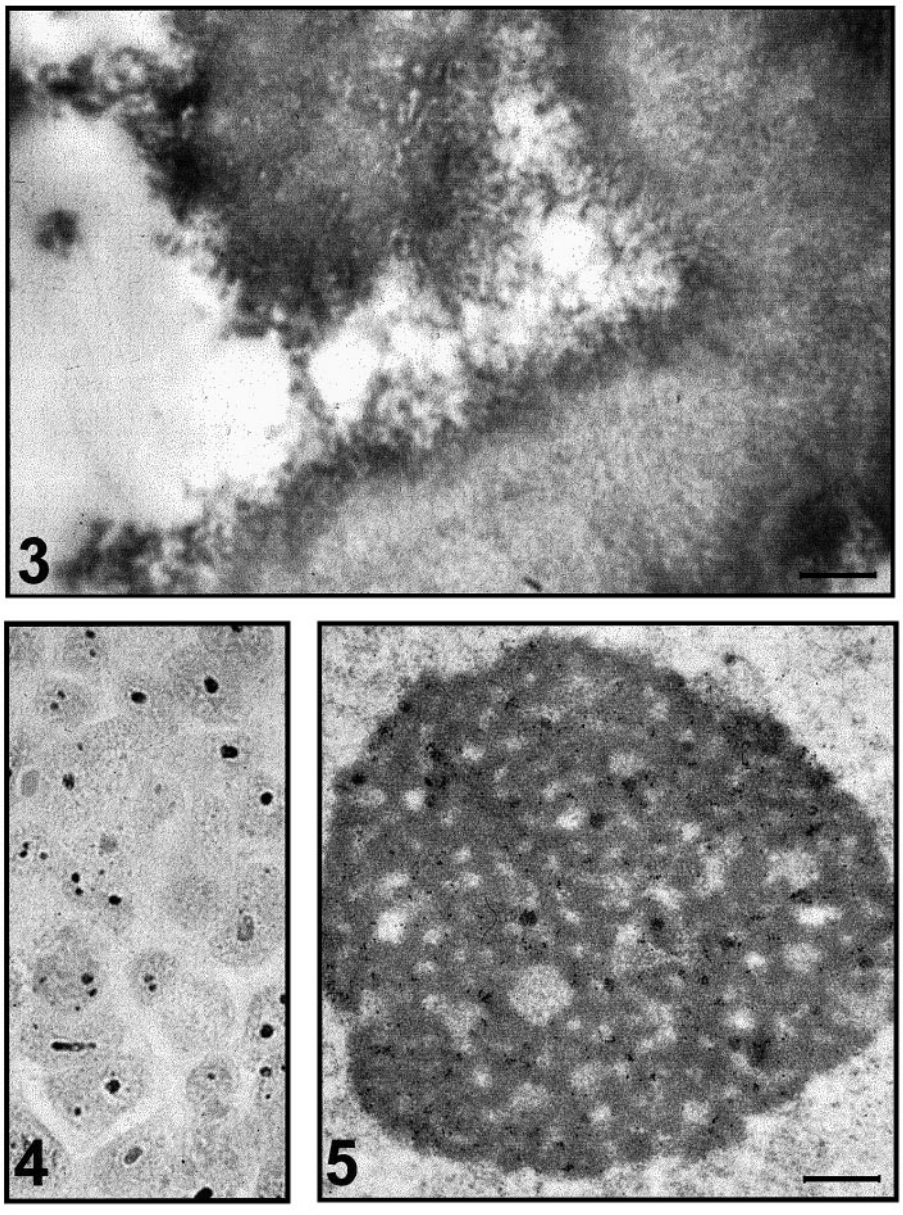

Fig. 3 Human chromosome immunostained with an anti-ds DNA antibody. Note the beaded chromatin fibres protruding from the chromosomal surface. *Bar* 100 nm

Fig. 4 Human colorectal carcinoma cell line ($CaCO_2$) stained with a human antinucleolar autoantibody. ×800

Fig. 5 Immunoelectronmicrograph of a $CaCO_2$ cell nucleolus stained with a monoclonal anti pre rRNA antibody (1E10). Note homogeneous staining (immunogold labelling) of the fibrillar component of the nucleus. *Bar* 50 nm

proteins and found C23/nucleolin and B23/nucleophosmin to be largely responsible for AgNOR staining. Roussel et al. [48] reported that in interphase nucleoli C23 nucleolin and B23 nucleophosmin were the most important proteins, whereas in mitosis mainly the RNA–polymerase I protein complex is NOR associated. In agreement with this finding, Chou and Yung [10] reported a shift of B23/nucleophosmin from a predominantly nucleolar localization in exponential growth to a predominantly nucleoplasmic localization in a stationary phase of growth. We [41] found B23/nucleophosmin to be abundantly present in colorectal adenomas and carcinomas, in adenomas in a predominantly nucleolar localization but in carcinomas also with a more diffuse nuclear distribution, in addition to the nucleolar localization. Nucleophosmin mRNA expression levels did not correlate with proliferative activity. In this context, the use of monoclonal antibodies that recognize preribosomal rRNA species is also promising (Fig. 4) [54]. Of late, AgNORs have regained some interest, following improvements in the silver-staining techniques and the introduction of computerized quantitation techniques [42].

Particular interest attaches to the involvement of the nucleophosmin gene in the t(2; 5) (p23; q35) translocation associated with Ki-1-positive anaplastic large cell lymphoma. This translocation leads to a fusion protein which includes a domain of ALK, a novel tyrosine kinase gene at 2p2.3 and a domain of nucleophosmin at 5q3.5 [27, 28]. The role of the fusion protein – if any – in the pathogenesis of this type of lymphoma remains unknown.

Anti-nucleolar autoantibodies have been known for quite some time in human connective tissue disease [18]

Table 1 Nuclear target antigens of some autoantibodies in collagen diseases (*ds* double stranded, *snRNP* small nuclear ribonucleoprotein, *ss* single stranded)

Target antigen[a]	Disease specificity[b]	Staining pattern
ds DNA	SLE, correlates with glomerulonephritis	Nuclear, rim or homogeneous
ss DNA	Rheumatoid arthritis	Only after denaturation, diffuse
DNA–histone complex	SLE, drug-induced LE	Nuclear, rim or homogeneous
Histone	SLE, drug-induced LE	Nuclear, rim or homogeneous
RNA-splicing enzymes		
U1 snRNP (mo)	Mixed connective tissue disease	Speckled
U3 snRNP (fibrillarin)	Scleroderma	Nucleolar
U1, U2, U4–6 snRNP (sm)	SLE	Speckled
Topoisomerase I	Scleroderma	Speckled
Transcription termination factor for RNA polymerase II (SS-B)	Sjögren's disease	Speckled
RNA-polymerase I, II, III	Scleroderma	Nucleolar

[a] Antibody nomenclature is noted in round brackets
[b] More frequently occurring in conditions named

as well as in murine silver-induced autoimmunity [1]. Interestingly, anti-nucleolar autoantibodies occur predominantly in scleroderma, with a small overlap with polymyositis (Table 1). Some of the antigens recognized by these autoantibodies have been identified and include several RNA polymerase complex components as well as fibrillarin and enzymes involved in the splicing process, which occurs during ribosomal maturation. There appears to be a remarkable degree of specificity in the occurrence of these autoantibodies. Anti-topoisomerase I and anti-RNA polymerase each occur in about 25% of scleroderma patients and are mutually exclusive. Other antibodies, including antifibrillarin, are not specific for scleroderma. Autoantibodies against nucleolar antigens (Fig. 5) have been taken as epiphenomena in the pathogenesis of these diseases, but given their striking specificity their involvement in the pathogenesis of the disease manifestations, although unresolved, remains an attractive possibility [52].

The fibrillogranular network

Electron-microscopical studies on nuclear matrix preparations have shown that the matrix consists of fibres and granules surrounded by empty regions, which in the intact nucleus are probably occupied by condensed chromatin domains. The fibrogranular network seems to be associated with a variety of nuclear functions. Knowledge of the proteins involved in the maintenance of this nuclear infrastructure is, however, lagging behind (for a review, see [5]). A major component of the nuclear matrix core filaments seems to be the nuclear mitotic apparatus protein (NuMA), a large (>200 kDa) coiled coil-forming protein that might function in nuclear matrix organization [19]. The nuclear pore complex proteins or nucleoporins constitute a further component of the matrix. It also contains protein kinases, diacylglycerol kinase, phospholipase C and protein kinase C, which suggests the existence of an intranuclear regulatory signalling pathway.

Attempts to identify nuclear matrix proteins have been based on two-dimensional electrophoresis. This approach has disclosed several classes of proteins that occur in a variety of cells and therefore seem to be universal. Others appear to be dependent on cell type or hormonal or differentiation state [5]. Two-dimensional electrophoresis has been instrumental in the detection of the matrin family of proteins, which consists of at least 12 members with molecular weights exceeding 40 kDa [39]. Detailed analysis of these proteins is not yet available, except for a high-molecular-weight matrin (Matrin p250) that appears to be identical to a form of RNA polymerase II. Immunohistochemical studies have shown matrin p250 localization in a fibrogranular structure with 30–50 brightly staining foci and hundreds of less intensely staining granules [37]. Immunoprecipitation experiments have shown matrin p250 to be associated with splicing complexes in vitro.

Interesting data concerning the spatial organization of nuclear functions have been published by Van Driel et al. [51]. Fluorescent metabolic labelling of nascent RNA by BrdU in their experiments resulted in hundreds of irregularly shaped and heterogeneously sized nuclear domains. The number of domains was smaller than the number of genes transcriptionally active at any time in a cell, suggesting that each domain probably represents several transcriptionally active genes. Subsequent immunofluorescence studies showed that RNA polymerase II, which is responsible for the synthesis of pre-mRNA, colocalizes with these sites, and detailed ultrastructural studies of the sites suggest that they coincide with perichromatin

fibrils. Components of the splicing machinery, including snRNPs, splicing factor SC35 and hnRNP proteins, appear to localize in speckles, whose size coincides with interchromatin granules but not with perichromatin fibrils. This suggests that these speckles are interchromatin granules and that they constitute a reservoir of splicing tools, splicing itself taking place in parallel with transcription alongside the perichromatin fibrils. NuMA has been shown to associate specifically with splicing complexes in vitro and to colocalize with interchromatin granules. The function of NuMa might therefore be to bind the splicing apparatus with the nuclear matrix.

Wansink et al. [57] studied the spatial distribution within the nucleus of DNA replication activity. This appears to be organized in hundreds of small domains scattered throughout the nucleus. Apart from replicating DNA, these domains also contain cyclin-dependent kinase (cdk)2, cyclins, PCNA and DNA methyltransferase, components of the replicating machinery. Briefly labelled nascent DNA appears to be associated with the nuclear matrix, which suggests that the replication machinery is bound to the nuclear matrix. The currently favoured model is that during replication DNA is reeled through immobilized replication 'factories'. Detailed analysis of double-labelling experiments has shown a lack of overlap of transcription and replication domains, which indicates that transcription is temporarily halted when replication takes place.

What are the consequences of these observations for our understanding of the organization of the nucleus? Although the picture is far from complete, the most likely model is that of well-defined nuclear domains immobilized on the nuclear matrix, in which replication and transcription take place. Replication and transcription are spatially dissociated. Replication takes place in clusters of replicons or replication factories (the clustersome model). Transcription is organized in like manner in clusters from which nascent RNA emanates in the form of perichromatin fibrils. The transcription-cluster-associated interchromatin granules contain the components of the splicing machinery.

A variety of studies addressing the question as to specific differences between the nuclear matrix of normal and of cancer cells [47] have been published. This approach was pioneered by Coffey's group [16, 43]. Generally speaking, these studies have shown consistent differences in nuclear matrix proteins of cancer cells [24]. Getzenberg et al. [15] reported specific nuclear matrix protein composition in bladder cancer. In their study, 6 nuclear matrix proteins occurred exclusively in bladder cancer tissue samples and not in parallel biopsies of the normal mucosa. Antibodies to nuclear matrix protein 22 have been used to detect its urinary level, as a measure for tumour recurrence [50]. Several groups [25, 49] detected nuclear matrix proteins specific for renal cell carcinoma. Izzo and Pellecchia [21] studied epithelial dysplasia and carcinoma in colonic inflammatory bowel disease and demonstrated nuclear matrix proteins that occurred in cancer only, in dysplasia only, or in both. Several groups [16, 43] have detected nuclear matrix proteins that appear exclusively in prostate cancer. Such studies have recently been taken further, showing that some of these proteins occur specifically in aggressive forms of prostate cancer [30]. In addition, immunohistochemistry using monoclonal antibodies to the nuclear matrix protein PC-1 could distinguish normal prostate and benign hyperplasia from prostate cancer [44]. Barboro et al. [3] described nuclear matrix protein alterations during hepatic carcinogenesis. The function of the proteins identified by this approach is as yet unknown. They bear no resemblance to the proteins known to be involved in the transcriptional process or replication.

Taken together, these findings indicate that the search for specific matrix protein differences between cancer cells and normal cells is a promising area and merits intensive exploration [53]. The clear indications of consistent differences hold promise for applications in cancer diagnosis and prognosis. The biological significance of the observed differences is little understood, however. Somewhat unexpectedly, most cancer-associated nuclear matrix proteins seem to be tissue specific. Questions as to whether and how these proteins figure in the development of cancer require additional investigations. Such studies will most probably also contribute to our knowledge of the regulation of nuclear functions by matrix proteins.

The occurrence of antinuclear autoantibodies specifically recognizing some of these nuclear components [35] has contributed to our knowledge of the chemical basis of nuclear structure. Especially interesting in this context are the autoantibodies against some of the enzymes involved in transcription and in RNA splicing. These antibodies and their (relative) specificities are listed in Table 1. The most important antibodies in studies of the structural basis of RNA splicing have been those of the sm type, which show a speckled pattern of nuclear staining. Some antibodies recognize small nuclear ribonucleoprotein particles (snRNPs), 6 types (U1–U6) of which have been identified. U1, 2 and 4–6 snRNPs are all involved in RNA splicing, which is why the speckles that they show on immunofluorescence coincide with the interchromatin granules. U3 snRNP (fibrillarin) is associated with rRNA processing and therefore localizes in the nucleolus. Early studies on snRNP function used blockade of human autoantibodies as one of the main tools. With the identification of the nature of the macromolecular complexes involved this has become less important. In a clinical context the immunofluorescence patterns are useful, because they provide an initial indication as to the nature of the antigen, which correlates to an important degree with specific diagnoses [55]. With immunoblotting, the antigens can be identified with more certainty, which has led to the recognition that relatively specific antibodies occur in different collagen disease categories. To what extent these autoantibodies are involved in the pathogenesis of the diseases is unknown [32]. The anti-DNA–histone complex antibody is responsible for the LE-phenomenon, which is diagnostic

but not necessarily responsible for (any part of) the pathogenesis of SLE [45]. The possibility that the autoantibodies are an epiphenomenon, and not related to the pathogenesis of the clinical manifestations of these diseases, has certainly not been excluded.

Conclusion

A number of points crystallize out from this brief excursion through nuclear structure and its emerging role in pathology. In general terms, even though the concept of the nuclear matrix has become relatively well established, it is clear that much remains to be discovered. Application of the existing knowledge to problems in (tumour) pathology will lead to interesting new diagnostic tools. Conversely, studies concerning the involvement of the nuclear matrix in pathologic processes will undoubtedly contribute to our understanding of how the nucleus functions.

More specifically, several exciting findings deserve to be summarized here.

1. Histones function in the regulation of gene transcription as modulators of the accessibility of the DNA template. A new link in this context is DNA methylation – histone deacetylation.
2. Relatively specific patterns of nuclear lamin expression have been observed in human cancer. Although practical use of this knowledge in the future can be envisioned, these patterns are not sufficiently enlightening to justify their use in diagnostic pathology.
3. More detailed knowledge of nucleolar and nucleolar organizer structure might revitalize the potential use of nucleolar and AgNOR staining patterns as indices for tumour grading.
4. The matrix proteins associated with the fibrillogranular network of the nuclear matrix have shown striking tumour-specific expression patterns, which may have important diagnostic applications.
5. Detailed analysis of immunoreactivity patterns of nuclear auto-antibodies remains unsurpassed as a tool in the laboratory diagnosis of collagen-diseases.

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