CHAPTER 10
MARs AND MARBPs
Key modulators of gene regulation and disease manifestation

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Abstract: The DNA in eukaryotic genome is compartmentalized into various domains by a series of loops tethered onto the base of nuclear matrix. Scaffold/ Matrix attachment regions (S/MAR) punctuate these attachment sites and govern the nuclear architecture by establishing chromatin boundaries. In this context, specific proteins that interact with and bind to MAR sequences called MAR binding proteins (MARBPs), are of paramount importance, as these sequences spool the proteins that regulate transcription, replication, repair and recombination. Recent evidences also suggest a role for these cis-acting elements in viral integration, replication and transcription, thereby affecting host immune system. Owing to the complex nature of these nucleotide sequences, less is known about the MARBPs that bind to and bring about diverse effects on chromatin architecture and gene function. Several MARBPs have been identified and characterized so far and the list is growing. The fact that most the MARBPs exist in a co-repressor/ co-activator complex and bring about gene regulation makes them quintessential for cellular processes. This participation in gene regulation means that any perturbation in the regulation and levels of MARBPs could lead to disease conditions, particularly those caused by abnormal cell proliferation, like cancer. In the present chapter, we discuss the role of MARs and MARBPs in eukaryotic gene regulation, recombination, transcription and viral integration by altering the local chromatin structure and their dysregulation in disease manifestation.

1. INTRODUCTION
The eukaryotic nuclei once referred to as “merely a bag of chromatin” has now been recognized to be a highly ordered structure or a ‘hub’ of cellular activities. The nucleus is seen as a three dimensional mosaic of nucleolus, inter-chromatin regions and condensed chromatin, dispersed in a nuclear ground substance.

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traditionally called the “Nuclear Matrix” (NM). The NM is a dynamic fibro-granular structure postulated to contain chromatin and ribonucleoprotein domains (Berezney and Coffey, 1977; Smith et al., 1984), serving as the structural milieu for gene function. The multitude of genomic functions occurring in nuclear matrix include gene replication (Smith and Berezney, 1980; Berezney and Buchholtz, 1981), transcription (Jackson and Cook, 1985) and RNA splicing and processing (Mariman et al., 1982; Zeitlin et al., 1987). All the cellular processes are highly coordinated and programmed and this demands that the genome be organized as a set of genes and gene clusters. Such an orderly arrangement of nuclear domains is brought about by anchorage of specific sequences to the matrix at interphase (Berezney and Coffey, 1974) and chromosomal scaffolds during mitosis (Mirkovitch et al., 1984). These signature sequences known as S/MARs (Scaffold/Matrix Attachment Regions) serve as boundary elements that punctuate chromosomal DNA into topologically restricted functional units, defining borders between chromatin domains (Breyne et al., 1992; Chung et al., 1993). Several studies also indicate the insulator nature of these elements, that together control single or multiple gene expression, by serving as Locus Control Regions (LCRs) (Grosveld et al., 1987).

MARs are also known to aid cell specific expression by their co-habitation with enhancers (Forrester et al., 1994) and reduce the position effect variegation from local chromatin structures (Blasquez et al., 1989). This is done by recruiting topoisomerase II (Razin et al., 1991; Berrios et al., 1985) and absorbing torsional stress by their base unwinding ability (Bode et al., 1992). Thus they orchestrate topological organization of functional chromatin domains. Since MARs organize and govern the accessibility to local chromatin structures, they are also targets for viral integration and replication. Recent reports indicate the effect of MARs juxtaposed to retroviral integration sites on human genome. Several studies report that integration is favored near DNaseI hypersensitive sites or active genes (Mooslehner et al., 1990). Small nuclear genome containing tumor viruses like HPV16, HBV, SV40, and HTLV-1 have also been shown to integrate near MARs (Shera et al., 2001). Recent observations regarding the retroviral integrations reveal that HIV-1 and MoMuLV favor active genes for their integration (Schroder et al., 2002; Mitchell et al., 2004). Most of these integration sites (95%) have been shown to be flanked by S/MARs, around 1 Kb region of integration that could serve as promoters (Kulkarni et al., 2004; Johnson and Levy, 2005). In this context, specific proteins that bind to S/MARs, called MARBPs become significant, as they govern the chromatin accessibility of the region. For example the ratio of SATB1 and Cux/CDP, two well known MARBPs in various tissues for Mouse Mammary Tumor Virus region (MMTV) defines the transcriptional status of the virus (Zhu et al., 2000; Liu et al., 1999). Similarly, a study by Stunkel et al., showed that Cux recruits HDAC1 to the LCR MAR of E6 promoter of Human Papilloma Virus (HPV) and represses this oncoprotein (2000).

MARBPs have been routinely isolated using high salt extraction of the matrix and their ability to have base unpairing potential (Galande and Kohwi-Shigematsu, 1999). Several studies report the ability of these MARBPs to control
MARs and MARBPs

gene expression by binding to MAR sequences within the regulator regions of the gene and activate or repress the gene expression. They are often found in a complex with co-activators or co-repressors, modulating gene function by remodeling or covalently modifying the chromatin structure. Most of these MARBPs have been shown to be drastically affected upon malignant transformations. Since aberrant gene expression gives rise to malignancies and abnormal cell cycle progression, understanding the nature and order of these proteins assumes great importance in the current scenario of chromatin biology and disease manifestation.

2. DEFINING MAR

The available literature on MARs reveals that they can enhance the expression of reporter genes by forming a domain and insulating them from position variegation effect at the integration site \( \text{Breyne et al., 1992; Allen et al., 1993} \). Their main function is to bring together control elements like promoters and enhancers loaded with their transcriptional factors, creating a transcription factor and enzyme rich nuclear microenvironment.

While there is no steady and fast rule for identifying MARs, certain traits make the AT rich DNA elements function as MARs. The AT richness confers DNA unwinding potential, so that in their single stranded form specific DNA unwinding proteins bind to MARs, relieve the torsional stress and the energy is used to relax positive supercoiling generated ahead of transcription elongation point \( \text{Bode et al., 1992} \). Studies by \( \text{Amati et al., 1990} \) and \( \text{von Kries et al., 1991} \) although suggest that this property of MARs might not be essential for matrix binding. A number of studies show that MARs can allow the induction of DNase I hypersensitive sites in chromatin. This has been substantiated with several experimental observations that MAR sites overlap with DNase I hypersensitive sites. The proposed mechanism is that MARs become DNase I hypersensitive at the time of their activation as a result of binding of single strand binding proteins (SSBPs) specifically during transcription and replication due to removal of nucleosomes that preludes ORI activation \( \text{Hsieh et al., 1993} \).

Several triple helical or Z form, cruciform structure of MARs has also been proposed. The cruciform loop part is susceptible to DNaseI and hence characteristic nicking occurs. The role of MARs in chromatin dynamics has also been tested using an artificial MARBP called MATH 20 \( \text{Strick and Laemmli, 1995} \). This protein has numerous linked DNA binding domains called AT hooks, which preferentially bind to AT tracts. Since this protein could then bind MARs and associated chromatin specifically, this was used to study chromatin condensation in Xenopus oocytes. It was found that titration of MARs with MATH 20 specifically inhibited chromatid conversion without inhibiting condensation resulting in abortive mitotic structures. When MATH 20 was added to chromatids, it leads to a structural collapse and formation of chromatid balls. Thus, it is speculated that S/MARs could be target of binding proteins that mediate or facilitate formation and juxtapositioning of
metaphase chromatin loops \cite{Hart1998}. Similarly, MAR sites have been found to be sites of illegitimate recombination, since these elements are found at the site of DNA insertion, deletion and translocation \cite{Sperry1989, Shapiro1987}.

### List of well known MARBPs and functions

| Name          | Species          | Tissue specificity                          | Function                                      | Interactome                  |
|---------------|------------------|---------------------------------------------|-----------------------------------------------|------------------------------|
| SATB1/L2a-P1/ | Homo sapiens, Mus musculus | Predominantly thymus, minute amounts in brain | Repressor                                     | CDP, HDAC1, ACF1, ISWI       |
| Nucleolin     | Homo sapiens     | erythroleukemia cell line K562              | Glycosaminoglycan stabilisation              | Glycosaminoglycans          |
| SAF-B         | Homo sapiens     | Ubiquitous                                  | Repressor                                     | RNA Pol II                  |
| SAF-A         | Homo sapiens     | HeLa, Embryonic kidney cell line 293, K562  | Activator                                     | p300, DNA PK                |
| NFκB, Cux/CDP | Mus musculus     | Breast, Ubiquitous                          | Important in organ development               | SATB1, HDAC1, SMAR1         |
| p114          | Homo sapiens     | Infiltrating ductal carcinoma tissues, normal breast tissue, benign breast diseases | Combined property of PARP and SAF-A (hnRNP-U) | PARP, Ku                    |
| Bright        | Mus musculus     | Ubiquitous                                  | B cell regulator of immuno-globulin heavy-chain transcription | Sp100, LYSp100/p140          |
| SP100         | Homo sapiens     | Ubiquitous                                  | Repressor of Bright chromosome condensation, subunit of DNA-dependent protein kinase downregulated during cellular senescence | Bright, PARP               |
| Ku (subunit of PARP) | Homo sapiens | SKBR3 cell line | Bright chromosome condensation, subunit of DNA-dependent protein kinase downregulated during cellular senescence | PARP, SAF-A |
| DNA-PK        | Homo sapiens     | Breast cancer                               |                                              |                             |
| MARBP | Species | Function | Effect |
|-------|---------|----------|--------|
| LYSp100/p140 | Homo sapiens | B cells | Co-activates Bright |
| SMAR1 | Homo sapiens, Mus musculus | Ubiquitous but predominant in thymus | Represses transcription, downregulated in breast cancer cells |
| MeCP2/ARBP | Homo sapiens | Ubiquitous, particular high levels in neuron of the post natal brain | Mutations in the MECP2 gene cause Rett syndrome |
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3. **ROLE OF MARBP S IN MODULATING MAR S AS FUNCTIONAL ELEMENT**

Gene expression status involves changing of attachment points of chromatin loops and hence implies the dynamicity of MARs and its association with nuclear matrix, regulated and governed by cell type (Liebich et al., 2002). The intrinsic activity of MAR is not sufficient to bring about position effects or transcriptional regulation but may depend on the contribution of protein factors that specifically bind to these motifs. These are classified based on their recognition sites as: abundant multifunctional matrix proteins like High Mobility Group proteins (HMGs), transcription factors like H box, Y box and CAAT binding proteins. Some class of proteins like ARBP, MeCP2, SATB1, CDP and SMAR1 also interfere with the MAR- matrix productive effects on transcription, unlike Bright that activate transcription. The varied effects of MARBPs could involve changes in the chromatin structure and activity by the recruitment or interaction with chromatin remodeling complexes. For example MAR binding repressors like ARBP, MeCP2, SATB1, SMAR1, CDP and CRBP mediate transcriptional repression by recruitment of components of histone deacetylating pathways. This is in contrast with activator MARBPs like SAF-A and Bright that recruits SWI or p300 and affect the acetylation and remodeling of chromosomes. Apart from affecting chromatin remodeling, gene regulation is also achieved by the direct interaction of MARBPs like SAF-B with RNA polymerase II and/ or with RNA processing factor. Hence, MARBPs serve as molecular base to assemble transcriptome and chromatin remodeling network. (Fig. 1)

4. **MARBP S WORK IN CONSORT**

Proteins that mediate MAR function (MARBPs) appear to control numerous genes expressed in differentiated cells. SMAR1, one such MARBP, has been shown to be ubiquitously expressed in all tissues, predominantly in thymus and governs the transition of T cells from DN to DP stage. SATB1 is expressed predominantly in thymus but also in brain and several other organs, while CDP expression occurs
Figure 1. MARs serve to enrich the nuclear milieu by bringing in transcription factors and enzymes to regulate transcription

in all but terminally differentiated cells. Binding of SATB1 and CDP to regulatory elements has been associated with transcriptional repression of numerous genes expressed in differentiated cells. For instance, SATB1 regulates gene expression both spatially and temporally during T-cell development. Recently, SATB1 null-mice were generated, and genome-wide expression profiling analysis indicated that about 2% of all genes become significantly derepressed in thymocytes (Alvarez et al., 2000). In contrast, the activator Bright is present in differentiated cells, where it may compete with repressors for MAR-binding sites. Thus, there would be a dynamic process of activation/ repression forming temporary sites of DNA attachment. Bright overexpression was found to enhance transgene expression, indicating that the normal activator protein level is limiting. In contrast, cotransfection of CDP abrogated Bright transactivation and reduced the basal expression level, indicating that CDP is able to override the DNA binding and/or transactivation capacity of Bright (Herrschler et al., 1995). Some MARBPs, depending on the context, either function as transcriptional repressors or activators. MARBPs such as Cux/CDP and SATB1 can function as transcriptional repressors in non-B cells by interacting with their target MAR sequences flanking the IgH intronic enhancer (Alvarez et al., 2000). On the other hand, the MARBP Bright acts as a transcriptional activator in B cells (Schubeler et al., 1996) and this activation is context-dependent as it requires an intact IgH enhancer core (Zahn-Zabal et al., 2001).
Different degrees of repression could be mediated by competition between repressors and activators for MAR binding. For example, MARβ, which resides 400 bp upstream of TCRβ enhancer (Eβ), is the docking site for three MARBPs: SMAR1, Cux and SATB1 (Chattopadhyay et al., 2000). MARβ (HS1) is the major DNase I hypersensitive site induced during the TCR co-receptor CD4−CD8− double negative (DN) to CD8+CD4+ double positive (DP) stage of thymocyte development. This induction is concomitant with halt of TCRβ V(D)J recombination in DP thymocytes. Studies by Chattopadhyay et al. (1998) identified that SMAR1 binds to this region along with Cux and SATB1 (Fig. 2).

The 114 Kd protein PARP, exclusively found as a mixture with DNA-PK has been implicated in repair after DNA damage. Evidences show that PARP and Ku 70/86 interact together and synergistically enhance their binding to DNA (IgH MARs)

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Figure 2. TCRβ locus showing eleven DNase1 hypersensitive sites. (a) HS1 and HS2 represent Eβ enhancer and MARβ sites respectively that are located upstream of Vβ14 segment. (b) DNase1 hypersensitivity assay showing four sites within a 6.6 kb BamH1-BglII genomic fragment. Panel 1: P4890 representing Rag mutant double negative (DN) lymphoma T cell line. Panel 2: DP cells of Rag mutant TCRβ transgenic mice. Panel 3: Mature single positive T cells from lymph node stimulated with ConA. Panel 4: Mature B cell line. No DNase hypersensitive sites were observed in B cells indicating that all four hypersensitive sites are specific for T cell and (c) A current model of possible role of MAR sites in maintaining cross-talk between Eβ enhancer, MARs and MARBPs that together control V(D)J recombination and transcription at TCRβ locus.
Similarly, PARP and SAF-A contribute to the MAR binding ability of p114. Together, these observations suggest that the different MAR-binding proteins associate with diverse sets of proteins involved in transcriptional regulation and also cross-talk amongst each other, constituting a functional nuclear matrix.

5. MARBPs AND DISEASE MANIFESTATION

Since most cases of malignant transformations occur by means of deregulation of genes or viral integrations, the role of MARs and MARBPs become crucial. The composition of nuclear matrix has been reported to be altered during the course of transformation and the MARBPs that associate with transcriptional units might be involved in the progression/cessation of disease. The uncontrolled cell proliferation and invasion of the cancer cells would naturally require an altered organization of the chromatin, to assure the differential expression of a subset of proteins compared to their normal counterparts. These genes have to be expressed or repressed ectopically. For example, the expression pattern of nuclear matrix proteins is considerably different between normal breast epithelial cells and malignant cells (Khanuja et al., 1993).

The abnormal levels of MARBPs, apart from their altered cellular distribution, seems to govern the progression of proliferative diseases. Studies to identify the nuclear matrix binding proteins associated with aggressive cancer phenotype have lead to the identification of PARP, Ku, High mobility group proteins (I/Y), NMP, SAF-A/B that have binding affinity to double stranded BURs. The expression of these proteins is dramatically increased upon malignant transformation and marks the advanced cancer phenotype leading to metastasis. Unlike other MARBPs that are highly expressed at the onset of malignant transformation, SMAR1 level is downregulated in breast cancer derived lines, which may be explained in part to its regulation of Cyclin D1 gene, a hallmark of breast and prostate cancer (Rampalli et al., 2005). In most cases of cancer, there is gene duplication or loss of transcriptional control of this gene that leads to uncontrolled cell proliferation, leading to cancer. We have shown that SMAR1 forms a co-repressor complex with HDAC1 and mSin3a, recruits this complex to the Cyclin D1 promoter on a segment that is rich in ATCs (putative MAR sequence as evaluated by MAR finder program MAR-WIZ). The recruited complex then deacetylates histones (H3K9 and H4K10) at the loci, leading to chromatin condensation and eventually shuts down transcription. (Fig. 3)

Several reports have highlighted the ability of such MARBPs to recruit chromatin modifying enzyme complexes to control gene transcription, showing that differential expression of these proteins is critical too. For example in breast cancer derived cell lines, SMAR1 levels are downregulated that correlates to an induced Cyclin D1 levels. Another example is HMG-I, an architectural chromatin protein that binds to minor groove of double stranded DNA. Recent reports suggest the role of HMG-I, C and Y proteins in cellular proliferation and neoplastic transformation
Figure 3. (a) Western blot analysis of breast cancer derived cell lines showing an induced Cyclin D1 levels that correlates to a decreased SMAR1 expression. (b) A schematic representation of SMAR1 recruitment of HDAC1 on CyclinD1 promoter, that switches off the transcription.

HMG-I has been identified as a target gene for c-myc and is involved in c-myc mediated neoplastic transformation. Distant metastasis is reported in animals injected with HMG-I or -C (Wood et al., 2000a, b). The mechanism of transformation has been attributed to the identification of HMG-C AT hooks in chimeric proteins associated with lipomas and mesenchymal tumors (Schoenmakers et al., 1995; Rogalla et al., 1997). These chimeras are thought to function by binding to DNA via the AT hooks and alter the gene regulation by transcriptional regulatory domains they acquire by rearrangement (Ashar et al., 1995; Wunderlich and Botter, 1997; Bustin, 1999). Apart from this, HMG-C, truncated transgenic mice display gigantism and lipomatosis while the null mice develop pygmy phenotype. (Battista et al., 1995; Zhou et al., 1995). This reveals that the levels of the MARBPs must be kept under a tight leash to avoid abnormal cellular proliferation and transformation.

Protein modifications of MARBPs also assume great importance as their binding properties can be altered. MARBPs like SATB1 and SAF-A get modified with special reference to a particular cellular process. For example, the cleavage of SATB1 by Caspase 6 disrupts the PDZ domain mediated dimerization, resulting in the formation of SATB1 monomers that do not have DNA binding ability. This causes detachment of the protein from chromatin that eventually leads to rapid and efficient disassembly of higher order chromatin structure and facilitates apoptosis in T cells, an important event in T cell receptor rearrangement (Galande et al., 2001).
Likewise, the SAR binding domain of SAF-A loses its DNA binding potential upon proteolytic cleavage during apoptosis (Gohring and Fackelmayer, 1997). There are reports that nuclear matrix proteins associate with granular nuclear bodies and undergo modifications in cells that undergo apoptosis (Zweyer et al., 1997). In most of the cases, the loss of DNA binding ability of MARBPs becomes central to the altered function. For example, Ku deficiency leads to extreme radiation sensitivity and high levels of chromosom al aberrations (Gu et al., 1997). This is due to the fact that the Ku heterodimer (Ku 70/80) binds to DNA double strand breaks and facilitate repair by non-homologous end joining pathway (Walker et al., 2001). In case of invasive breast cancer, a specific nuclear matrix binding protein called NMP has been identified, that recognizes a unconventional MAR in the promoter, stimulates the levels of NFκB, that in turn increases the DNA binding activity of NFκB observed in c-erb2 and BRCA1 positive human breast tumors, suggesting a role in breast cancer progression (Raziuddin et al., 1997). HET/SAF-B was originally cloned as a nuclear matrix protein that binds to the MAR of hsp27 promoter and represses it in breast cancer cells (Oesterreich, 1997). In addition, it has been shown to bind to ER and function as its co-repressor (Townson et al., 2000). There are also reports suggesting that the overexpression of HET causes growth inhibition in M phase of cell cycle and causes multicellularity. Consistent with this, it is also known to cause aneuploidy in breast tumor specimens and causes lower proliferation (Townson et al., 2000). This suggests that these factors might have important and distinct roles in tumorigenesis independent of their transcriptional functions. The MARBPs have also been identified to play major role in normal tissue differentiation and organogenesis. For example, Cux has been shown to play role in specifying the identity of external sensory organs during peripheral nervous system development. It has also been implicated in controlling proliferation and differentiation (Nepveu, 2001). Cux knock out mice show retarded growth, curly whiskers, late development of lung epithelia, defective hair follicle development, infertile male progeny and less number of T and B cells and more myeloid cells (Sinclair et al., 2001, Tufarelli et al., 1998). On the other hand, Cux-1 transgenic mice show organomegaly and hyperplasia of different organs (Ledford et al., 2002).

Certain novel isoforms of MARBPs have been suggested to play key role in disease manifestation. Two isoforms of Cux/CDP were previously known till Goulet et al., showed that a novel isoform of Cux (p75) showed a higher binding affinity to DNA and represses the transcription of CDK inhibitor p21 and activated DNA polymerase a gene promoter. They also identified that a novel intronic transcription initiation was responsible for the expression of this isoform. Although this isoform is predominant in CD4+ /CD8+ and CD4+ T cells, expression was also activated in breast tumor cell lines and in primary human breast tumors. The stable lines expressing p75 isoform could not form tubule structures in collagen but developed as solid undifferentiated aggregates of cells. Some studies also indicate that Cux is a downstream target of Notch, activated in T cell leukemia. Cux could thus serve as a downstream target marker for Notch activation (Goulet et al., 2002). Activation of CDP/Cux at the G1/S transition involved the proteolytic processing of the protein...
to generate a shorter isoform in uterine leiomyomas (Moon et al., 2002). Similarly, CUTL1 activity is associated with increased migration and invasiveness in numerous tumor cell lines, both in vitro and in vivo transcriptional target of transforming growth factor beta (TGFβ) and a mediator of its promigratory effects CUTL1 expression is significantly increased in high-grade carcinomas and is inversely correlated with survival in breast cancer. This suggests that CUTL1 plays a central role in coordinating a gene expression program associated with cell motility and tumor progression (Michl and Downward, 2006).

SMAR1 is shown to exist in two isoforms, the shorter form having a deletion of 117 bp at the N terminus (Chattopadhyay et al., 2000). The 39 aa deleted shorter form has been shown to be more effective in regressing B16F-10 induced melanoma (Kaul et al., 2003). SMAR1 transgenic mice showed abnormal V(D)J recombination and organomegaly of lymphoid organs with cellular infiltrations, suggesting a necessity for fine tuning of protein expression to continue cellular process (Kaul-Ghanekar et al., 2005) (Fig. 4). This reveals that various isoforms of MARBPs may have different roles in the context of cellular functions.

Apart from serving as modulators of transcription, MARBPs alter cellular functions by their protein interactions. Nucleolin first described by Orrick et al., (1973) is a major nucleolar protein involved in ribosome biogenesis. Recent reports also suggest that nucleolin binds to cell surface adhesion molecules like L-selectin expressed on leucocytes and hemopoietic stem cell progenitors (Harms et al., 2001). Modulation of hepatitis delta viral replication is also well documented (Lee et al., 1998). This protein is also linked to actin cytoskeleton and inhibits HIV infection by cytokine midkine. Reports by Christian et al., (2003) show that nucleolin on cell surface is a marker for endothelial cells and its interaction with Acharan sulfate (AS) may be a key in solving the mechanism of AS mediated inhibition of tumor growth. The identification of cancer cell specific markers led to the identification of a subset of nuclear matrix proteins (NMPs) that exist in prostate, bladder, colon and renal cancer (Konety et al., 1998). These NMPs can be detected in the serum samples of the patients because of these factors as tumor cells undergo degeneration and lysis. NMP 22 has been now routinely used to assess bladder cancer and similarly L4 is a candidate for identification of colon cancer (Brunagel et al., 2002).

Several ubiquitous transcription factors like Lys 100/ p140, SP100 are also known to bind to MARs. While p140 is known to co-activate transcription by Bright, SP1 represses transcription. AP-1 family transcription factor is also known to associate with nuclear matrix (van Wijnen et al., 1993) and allow the expression of Igk gene in response to LPS stimulation (Schanke et al., 1994). p53 another well known transcription factor, the function of which depends on its DNA binding ability to different promoters. Wild type p53 is known to be a tumor suppressor while mutant form exerts oncogenic functions of its own (Dittmer et al., 1993; Levine et al., 1995). The “gain of function” of mutant p53 has been demonstrated partly due to its high affinity to bind to MARs (Will et al., 1998). These MARs have a typical AATATATT unwinding motif, promoting structural alterations in
chromatin, thereby affecting cellular replication. Since mutations in p53 constitute the most frequent alteration in a single gene in human cancer [Hainaut et al. 1997], the MAR binding potential of the mutant form could form the molecular basis of oncogenic potential documented for mutant p53.

6. MARBPs AS PROGNOSTIC MARKERS AND FUTURE PERSPECTIVES

The aberrant expression of MARBPs upon malignant transformation makes them a reliable marker for diagnosis of advanced diseased conditions. For instance, the NMP 22 levels in urine have now been routinely used to identify bladder and ductal cancer. Similarly, p114 MAR-binding activity has been detected in aggressive tumors, while significantly weaker p114 activity has been observed in
less aggressive tumors. Hence, PARP, an interactor of p114 could be used as a marker for identifying invasive breast cancer. The novel isoform of Cux (p75) is a reliable marker for identifying breast cancer. MAR binding protein, p230, is detectable in rat hepatoma cells but not in normal liver and suggests that this protein is a diagnostic and prognostic marker for liver cancer. It is clear that nuclear matrix proteins hold a considerable promise as diagnostic tools for pathologists.

MARBP s with their newly discovered role as linkers between chromatin remodeling, signal transduction and cell cycle regulation form an important part of chromatin biology. Most importantly, direct correlation of disease manifestation and the MARBP s will make them an important tool in understanding disease progression. Present evidence, suggests that nuclear matrix proteins may be useful biomarkers of neoplastic diseases in the serum, body fluids, and tissues. Nuclear matrix proteins are also potential candidates for the use as tumor prognostic factors and targets of anticancer drugs through apoptosis.

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GLOSSARY

SAR/MARs  
Scaffold Attachment Region
SAF-A: Scaffold Attachment factor A
Nuclear matrix binding proteins
Matrix Associated Region Binding lproteins(MARBP s)
Tumor suppressor p53
Nucleases
DNase I hypersensitivity assay
Locus control Region (LCR)
SMAR1
Human immunodeficiency Virus 1
HTLV
MMTV
TCRβ locus
Cyclin D1
mSin3A complex
V(D)J recombination
SATB1: Special AT-rich sequence binding protein I
Cux/CDP
CUTL1
Eβ enhancer

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