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STRUCTURAL AND FUNCTIONAL ASPECTS OF Y BOX BINDING PROTEIN IN RELATION TO ITS INTERACTIONS WITH DNA/RNA/ EXTRACELLULAR RECEPTORS

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ABSTRACT
Y Box binding protein-1 (YB-1) is evolutionary conserved human member of Cold shock protein family involved in various cellular processes. YB-1 was first identified as a DNA binding protein which specifically binds to inverted CCAAT box (Y-box) of the MHC-II promoter and regulates its transcription. But, latter it was evidenced that YB-1 can bind with wide range of sequences in DNA and RNA. YB-1 regulates transcription as well as translation of various cellular proteins via its ability to binds with DNA and RNA. Recent studies clearly emphasize that extracellular YB-1 fragments appear while cancer or inflammation condition and interacts with extracellular NOTCH-1 receptors thereby activates carcinogenesis and tumor progression. In this review, we discussed about the structure of YB-1 and the function of YB-1 in transcriptional and translational regulatory mechanisms.

KEYWORDS: Y Box binding protein-1; Cold shock protein; transcription; translation.

INTRODUCTION

Cold shock proteins (CSP) are evolutionarily conserved protein family sharing a cold shock domain from prokaryotes to eukaryotes.[1-4] Cold Shock Proteins are up-regulated in bacteria to rescue the growth during the cold shock (decrease in temperature).[1,5] In eukaryotes, CSPs are involved in various cellular processes including embryonic development[6], proliferation[7,8], differentiation[9] and various stress responses.[10-13] Y box binding protein-1 (YB-1) belongs to the family of cold shock proteins and interacts with DNA and RNA to control the transcription and translation of specific genes. In this review the structural and functional aspects of YB-1 in relation to transcription and translation have been discussed.

Structure of YB1

The majority of Cold Shock Domain containing proteins in vertebrates have high degree of structural homology.[14] Human Y box binding protein-1 (YB-1) is a member of the Y box protein family, containing 324 amino acids.[15] It is the first structure solved for eukaryotic member of the cold-shock protein family. Structurally YB-1 consists of three domains i.e. N-terminal domain, Cold-shock domain and C-terminal domain. The short N-terminal domain or A/P domain(1-51residues) is rich in alanine and proline. The central part or CSD (52-129 residues) comprises of ~70 amino acids. The CSD is the backbone of the protein and consists of five β- strands which are arranged as anti-parallel β barrel connected with three tight type-I turn (β1-β2, β2-β3 and β4-β5) and flexible loop (β3-β4).[16]

Like other CSD containing protein, YB-1 CSD contains consensus sequences RNP-1 and RNP-2 respectively K/N-G-F/Y-G-F-I/V and V-F-V-H-F which participate in specific and nonspecific DNA and RNA interaction.[17-19] Unlike bacterial CSD, human YB-1 CSD has large flexible loop which is absent in prokaryotic proteins is associated with its stability. At the end, long C- terminal domain (130-324) contains positive and negative charged clusters. Each cluster is nearly 25-30 amino acids long and present alternatively.[16-20] Moreover, intermolecular interaction between the positively and negatively charged clusters leads to YB-1 oligomerization. Hence, YB-1 easily forms large oligomeric complexes of 150 – 800 KDa in *in vitro I*.[21,22] By the way, it produces unexpected electrophoretic mobility pattern corresponding to the molecular mass of about 50 KDa but it's real molecular mass is near to 36 KDa. Moreover, electron and atomic force microscopy studies found that oligomers adsorbed on a substrate is rounded shape with the diameter of 35-40 nm and 9-10 nm height.[23] The x-ray scattering studies show that at low ionic strength YB-1 molecule has a globular structure while at high ionic strength it has a more extended

(unfolded) conformation. The spectrum analysis of YB-1 shows the presence of poly-L-Proline II (PPII) helices which are converted to β-structure. PPII helices presence in YB-1 confirms the observations on the so-called "natively unfolded" proteins and polypeptides.[24,25]

Interaction of YB-1 with DNA

YB-1 was first identified as a DNA binding protein which specifically binds to inverted CCAAT box (Y-box) of the MHC-II promoter and regulates its transcription.[26] But, latter it is evidenced that YB-1 can bind with wide range of sequence in DNA. It has higher affinity with ssDNA than dsDNA and binds specifically to the pyramidine-rich strand in the dsDNA and single-stranded DNA sequences. Moreover it acts as a nucleic acid chaperon and melts double helices, including those in the promoter region.[27,28] One NMR based YB-1 and DNA interaction study clearly shows that DNA binding sites comprises residues Trp15, Phe24, Phe35 and His37. Lys14 and Tyr22 are also likely to be part of the binding site having surface exposed side chains and being close to many residues that show changes upon DNA binding.[16] The structural characteristics of CSD of YB-1 are very similar to the (oligonucleotide binding) OB-fold family with 5 strands and a shear number of 8.[28,29] Unlike in many other OB-fold proteins it does not contain α-helix.[16,30] Although CSD is sufficient to bind to ssDNA, the C-terminal domain facilitates ssDNA binding and is needed for strong interaction. Possibly these domains are involved in additional interactions with ssDNA and accounts for extra stability of the CSD domain, resulting in a tighter binding. Isolated CSD has also been found to bind DNA less tightly and with lower specificity than intact YB-1 which shows participation of other YB-1 fragments in DNA binding.[16,30]

YB-1 associates with other proteins and interacts with DNA in almost all DNA related processes by regulating the activity of its binding proteins.[31,32] For instance, YB-1 binds DNA as a complex with Topoisomerase1 (TOPO1) and carries out all DNA dependent processes by providing an appropriate environment for TOPO1 to relax the DNA duplex.[33] TOPO1 is known to relax the supercoiled DNA, which separates the DNA duplex into single strands during replication, transcription, and repair mechanisms.[34] TOPO1 activity is affected by many cellular proteins through direct interactions.[35,36] Furthermore, particular oxidative DNA damage promotes TOPO1-DNA binding and cleavable complexes formation, or triggers multiple communications between YB-1 and various DNA repair proteins. Therefore, YB-1-TOPO1 interaction might respond to drug-specific oxidative cytotoxicity in tumor cells, which warrants further in-depth researches.YB-1induces TOPO1 inhibitor camptothecin cellular sensitivity and promotes the DNA relaxation potential of TOPO1 via a direct interaction between them.[33] The interaction also results in a cellular response to chemotherapy-induced oxidative-stress. As a result, YB-1 functions as avital biological response modifier of intranuclear TOPO1 and can regulate drug efficacy on cancer cells.

Moreover, YB-1 affinity chromatography experiments have shown the presence of specific DNA repair proteins from elute after UV treatment which includes DNA polymerase δ, MSH2, Ku80 and Werner syndrome gene product (WRN).[37] The WRN is involved in the repair of cross-linked DNA lesions base excision repair (BER).[38] The YB-1 interacts with WRN during DNA repair through p53 tumor suppressor which may stabilize the YB-1/WRN complex or acts as a bridging molecule.[38] p53 has also been found to translocate GFP-YB-1 in the nucleus in MCF7 cells. WRN protein also accelerates p53 dependent GFP-YB-1 nuclear translocation.Upon UV treatment nucleolar WRN leaves the nucleoli and relocates to nucleoplasmic foci of DNA repair which contributes to p53 activation. Enough activated p53 accumulation in the cells results in YB-1 translocation in the nucleus. A fraction of YB-1 gets in touch with both p53 and WRN at precise nuclear foci in the nucleus. The UV light produces oxidative damage resulting in DNA base modifications, which is repaired by BER. YB-1 has been found to increase the activity of hNth1 (an exonuclease implicated in BER)[39], on the other hand WRN is believed to participate in BER.[38] Thus, YB-1, p53 and WRN may complex together to repair the damage caused by UV light.

In mammals CSP regulates a wide range of genes at the transcriptional level. Genes involved in cell proliferation i.e. DNA polymerase α and cyclins A and B1, in cell death e.g. FAS receptor etc. are the targets for CSP. Further plethora of target genes includeshuman leukocyte antigen (HLA) expression[26], inflammatory responses[40], granulocyte macrophage colony-stimulating factor (GM-CSF)[41], and coordinate matrix synthesis.[42] There is a far long list of the genes enlisted as CSP targets. Transcriptional regulatory events occur in cooperation with partnering proteins such as RelA[43], YY1[44], AP2 and p53.[45] Many functions are attributed to YB-1 in cell differentiation, proliferation, stress response and gene expression as a cell cycle stage specific transcription factor.[46] Activity of YB-1 as a transcription factor was first demonstrated by regulatory binding to the MHC class II promoter.[26] When in the nucleus, YB-1 regulates the transcription of many genes, including the multidrug resistance gene-1 (MDR-1)[47-49], epidermal growth factor receptor (EGFR)[50], DNA polymerase-α[51] and matrix metalloproteinase-2 (MMP-2)[52] and genes involved in the apoptosis.[53,54] It is notable that YB-1 may regulate gene expression in a cell-type specific manner, e.g. trans-repression of MMP-2 gene promoter in podocytes[55] and trans-activates the same promoter in mesangial cells.[52] Trans-repression of the GMCSF gene by YB-1 has been reported in human embryonic lung (HEL) fibroblasts and transcription activation in Jurkat T cells.[41] YB-1 as mRNPs permits storage and release of mRNA[56], rennin[57] and also regulates translational activities.[58-60] Thus, YB-1 fulfils

functions that may be described as RNA "chaperone".[61] Some studies have evidenced a regulatory role of YB-1 for mRNA processing, like splicing in collaboration with splicing factors like SRp30c.[62]

An increase in the amount of YB-1 in the cell or nuclear translocation of YB-1 from cytoplasm is accompanied by the rising or declining quantity of mRNAs/proteins encoded by many genes responsible for cell division, differentiation, multiple drug resistance.[45] It can be suggested that YB-1 involvement in transcription is realized solely through growing mRNAs for which YB-1 shows a higher affinity than that for DNA. Although this may be in agreement with transcription activation but it disagrees with transcription inhibition because no RNA is synthesized in this case, and YB-1 has nothing to bind.[63] YB-1 can change the expression of genes with or without their promoters.[64] Further, studies have shown non availability of any bioinformatics method to reveal YB-1 specificity either to the Y-box or any other DNA sequence.[63] Transcription factor NF-Y has been found to be a Y-box binding protein.[64] YB-1 binds specifically to the pyramidine-rich strand in the dsDNA and single-stranded DNA sequences. Moreover,as a nucleic acid chaperone it melts double helices, including those in the promoter region.[63] YB-1 direct interaction with p53 modulates p53 expression which subsequently can activate cell cycle checkpoint proteins and pro-apoptotic proteins. Overexpressed YB-1 hinders p53-dependent transcription activation of pro-apoptotic genes e.g. APAF1, NOXA and BAX and of cell cycle inhibitor genes.[64] In another mechanism YB-1 represses Fas-receptor transcription leading to activation of pro-apoptotic signaling pathway of the gene CASP7 coding for caspase.[65] Moreover, YB-1 is an actin-bundling protein and plays a structural functional role in membrane endocytosis and recycling.[66]

Interaction of YB-1 with mRNAs and its role in translation

The interaction of YB-1 with mRNAs starts in the nucleus itself. YB-1 binds with pre-mRNAs while transcription on chromosomes and accompanies with mRNAs throughout their lifespan. YB-1 interacts with mRNAs by means of specific as well as non-specific manner hence almost involved in all mRNA biogenesis and functions.[67] YB-1 was isolated as a protein that associates with mRNA and has been denoted as p50 in this context which takes part in the formation of mRNPs.It also selectively regulates the synthesis of various proteins including its own mRNA.[60] YB-1 has high affinity with wide variety of nucleotide sequences but the reduction in affinity takes place when the size of the RNA is below ~50 nucleotides.[60] Also, YB-1 interacts with different homopolyribonucleotides with different affinity and its affinity decreases in the order of poly (G)> poly (U)> globin mRNA ≈16s rRNA> poly (A) > poly (C). YB-1 binds with mRNAs by two RNA binding domains (RNP-1 & RNP2) of CSD and CTD.[68] Positively charged and aromatic aminoacids present in YB-1 CSD interacts with mRNA and form monomers whereas, CTDs interacts with each other to form large multimeric complexes. A large YB-1 multimeric complex composed of 15-18 molecules is about 20nm in diameter, 7nm in height. At the peak of the YB-1 complex an mRNA fragment of about 600-700 nucleotides is present on their surface. Long mRNA can be lodged at several multimers so mRNA packaging by YB-1 is similar to DNA packaging on nucleosomes.[69]

In general, YB-1 inhibits or activates the translation of various mRNA depending on the YB-1/mRNA ratio. In complexes with a high YB-1/mRNA ratio, mRNA termini are thought to be buried inside, thus being inaccessible to translation machinery and to exoribonuclease degradation complexes. At a comparatively low YB-1/mRNA ratio, monomeric YB-1 interacts with RNA through both its CSD as well as CTD and causes mRNP unwinding. Inside these complexes, mRNA termini are exposed to both translation initiation factors and ribosomes hence activate the translation.[69] The above model is consistent with experiments on the effect of YB-1 on *in vitro* mRNA translation.[60] YB-1 removal from the cell free system results in the inhibition of mRNA translation at the initiation stage. It is believed that deficient YB-1 makes the whole mRNA exposed to RNA-binding initiation factors. Then these factors are scattered over entire mRNA instead of being accumulated at its 5' untranslated region (UTR), which strongly reduces efficiency of translation initiation. And also YB-1 specifically binds with some mRNAs at 3' UTR and selectively inhibits the translation of these mRNAs even at relatively low YB-1/mRNA ratio i.e. auto regulation of YB-1 mRNA.[63]

In the cytoplasm of somatic cells YB-1 is known as a core component of both translationally active and inactive mRNPs.[42,102] mRNPs are inactive at a high ratio of YB-1 to mRNA (~20 molecules of YB-1 per mRNA molecule).[69] The overexpression of Y-box proteins in somatic cells results in a substantial repression of translation. Thus, in addition to function as a structural component of cytoplasmic mRNPs Y-box proteins have strong impact on the fate of mRNAs in the cytoplasm. The C-terminal domain of Y-box proteins also has RNA binding activity.[4] The tail domain in vertebrate Y-box proteins consists of alternative clusters of acidic and basic amino acids, and its amino acid sequence is less well conserved among organisms. The tail domain is required for homomultimerization and association with various proteins.[28] CTD presence is sufficient for YB-1 to be incorporated into mRNPs and repress translation. YB-1 has been found to work as an RNA chaperone.[63] As per a review by Lorsch (2002) RNA chaperone melt the secondary structure of mRNA and thereby make the mRNA accessible to the translational machinery. At low YB-1/mRNA ratio YB-1 stimulates single stranded DNAs or RNAs annealing, whereas at high YB-1/mRNA ratio it causes RNA to melt.[23] Therefore, Yb-1 may

contribute to the appropriate packaging of mRNA to facilitate translation at low temperatures.

Y-box protein-associated acidic protein (YBAP1) has been shown to restore protein synthesis during YB-1 mediated translation inhibition.[70] YBAP1 is a 35-k-Da protein identical to chicken 38K protein which assembles skeletal muscle myosin . The human homologue of YBAP1 was originally isolated by copurification with splicing factor ASF/SF2. YBAP1 is an acidic protein with pI of 4.4, while YB-1 has clusters of basic amino acid residues in its C-terminal tail domain. YB-1 binding inhibited the β-actin mRNAtranslationbut addition of YBAP1 resulted in increased complex formation that migrated faster than those complexes which were formed in the absence of YBAP1 which suggests that YBAP1 relieves the translation repression. YBAP1 restored protein synthesis when YB-1 inhibited translation by 80%. Thus, YBAP1 interacts with YB-1 in an RNA-independent manner. It displaces YB-1 from YB-1-mRNPs and helps in remodeling of mRNPs which brings structural changes in mRNPs, and thus affects the stability and translational activity of mRNAs.[70]

YB-1 inhibits the translation process only at initiation stage by displacing the eIF4F subunit from mRNA complex before the binding of mRNA with small ribosomal subunit. The CSD of YB-1 is involved in inhibition as it displaces translation initiation factor eIF4C from complex with mRNA. CSD of YB-1 interact with the cap-structure or with the adjacent region and displace almost all the subunits of eIF4G, eIF4E, eIF4A and eIF4B from the mRNA complex[58] thereby inhibit the translation at initiation stage.[71] YB-1interacts with free non-translated mRNPs as only major core protein but the translated polysomal mRNPs contains other major components involved in RNA biogenesis.[69] While translation almost half of the YB-1 dissociate from mRNPs and replaced by PABP to its poly (A) tail. At high concentration PABP, it interacts with eIF4G and enhances the affinity of eIF4F with mRNA and comparatively displaces the YB-1 from the mRNA complex even at high YB-1 concentration. This results in translation activation under the action of PABP. At low YB-1 concentration, even a low PABP can prevent YB-1 interaction with mRNA.[71]

On other hand, YB-1 selectively regulates the translation of certain mRNA enriched with internal ribosome entry site (IRES). It is reported that YB-1 activates the translation of IRES containing – mRNAs of *myc* family proto-oncogenes.[72] In addition, YB-1 activates the translation of ferritin mRNA based on the iron ion concentration. At low iron concentration, Iron regulatory protein-2 (IRP-2) binds to the hairpin structure IRE (iron responsive element) in the 5' UTR and inhibit the translation of ferritin mRNA. If iron concentration increases, YB-1 interacts with oxidized IRP-2 and abrogates its interaction the 5' UTR of ferritin mRNA. At translational level Cyclin A and B1 activation by YB-1 in the nucleus depicts the importance of YB-1 in cell cycle progression. At translational level unphosphorylated YB-1 selectively interacts with mRNAs coding for cyclins, growth factors, and translation factors and suppresses their translation. Phosphorylation of YB-1 by PI3K/Akt kinase pathway results in decreased ability of YB-1 to suppress the translation of these mRNAs and promotes cell growth and proliferation. YB-1 can regulate cell cycle by preventing apoptosis.[73] The synthesis of YB-1 is proliferation dependent and takes place by different signaling pathways like mTOR, MAPK, and inhibition of YB-1 synthesis in HER2 breast cancer cells results in PTEN/mTOR/STAT3 signaling pathway which prevents apoptosis.[74] These described functions are fulfilled by one single protein requires highly regulated shuttling between the nucleus and the cytoplasm.

Extracellular YB-1 as a mitogen

Recent studies on rat model for mesangioproliferative diseases show that YB-1 is secreted by mesangial cells and monocytes acts as an extracellular mitogen which binds to the Notch-3 receptors involved in carcinogenesis and tumor progression. The extracellular YB-1 has been found to increase the DNA synthesis rate by 40-90% in control and mesangial nephritis model. A similar type of result has been reported in mammary tumor cell lines which show an increased number of cells by 10-40% after adding recombinant extracellular YB-1 in culture media.[75]

YB-1 can be secreted by the cells under inflammatory stress after chemokine challenge by a mechanism other than the classical mechanism (via golgi apparatus and endoplasmic reticulum) of protein secretion as it lacks the N-terminal signal sequence required for classical mechanism and thus, retains molecular mass. Under inflammatory response YB-1 co-localizes with protein RAB7 (vesicle transport marker) and is secreted by non-classical endolysosomal pathway.[75]

Extracellular YB-1 links with outer cell membrane apparatus and interacts with extracellular Notch-3 receptor domains. Rauen et al., 2009 have suggested extracellular YB-1 co-localization with Notch-3 at cellular membranes.[76]

Though extracellular domain s of both Notch-1 and Notch-3 have 45% resemblance, and both are composed of a series of EGF repeats and Notch/Lin-12 repeat regions still the interaction of YB-1 is specific for Notch-3 but not to Notch-1.[76] Furthermore, Notch-1 and Notch-3 have almost same mechanism of interaction with the conventional Notch DSL ligands, *i.e.* Jagged1 and Delta-like-1. The EGF-like repeats 13–33 in Notch-3 interact with YB-1. The Notch receptor signaling triggered by extracellular YB-1 is secretase-dependent and includes HES2 promoter induction. Notch receptor-mediated induction of HES2 by Dll4 (a membrane-bound ligand) has been reported. Many reports signify a

dynamic role of HES2 in proliferative processes, such as spontaneous malignant transformation of stem cells and various tumors like thatof the gastrointestinal tract and Ras-transformed astrocytes. YB-1 knock-out mice exhibit neural tube defects with abnormal patterns of cell proliferation within the neuroepithelium.[77] The increase in HES2 transcript numbers in embryonic neural progenitor cells might be responsible for YB-1 signaling via Notch-3 through a direct link that is operative in nervous system development. Recently it has been found that YB-1 expression and subcellular localization are highly regulated in the course of mesangioproliferative disease and tumorigenesis.[45] In healthy tissue YB-1 protein localizes strictly to the nuclear compartment of glomerular and tubular as well as vascular cells.[76]

YB-1 in stress granules

Formation of stress granules (SG) and up-regulation of stress proteins are essential for cellular defense against acute stress may it be physical or chemical. The stress granules assemble through aggregation of TIA protein, leading to accumulation of translation-silenced mRNAs during stress response.[77]

Stress granules have been documented to be formed in various pathological tumors and brain diseases.[78] The aggregation of stress granules requires specific RNA binding proteins including TIA-1 and G3BP1. G3BP1 contains low complexity or intrinsic disordered regions necessary for dimerization which enables this protein to be a nucleating factor for stress granule assembly.[78,79] YB-1 has been found to form stress granules in cultured sarcoma cells where it co-localizes with G3BP1. Tissue microarray studies of human sarcoma cases validate the correlation of G3BP1 and YB-1 in SGs. Furthermore, G3BP1 has been found to be involved in *in vivo* SG formation, invasion and metastasis. Expression of G3BP1 is associated with lymph node metastasis and survival in esophageal squamous cell carcinoma suggesting its prooncogenic functions. A reducing YB-1 expression in sarcoma cancer shows a reduced SG formation and the translation of G3BP1 have been observed to be regulated by YB-1.[79]

YB-1 interacts with many proteins involved in cellular phenomena. It has been observed that under stress conditions YB-1 is also incorporated into the stress granules[79], and can sometimes be used as a marker of these granules indicating that YB-1 plays role in the translational regulation of stress responses. YB-1 contributes to translation initiation inhibition through assoaciation with t-RNA- derived fragment, which is cleaved by stress activated ribonucleaseangiogenin.[80] Under arsenite-induced stress the mRNA of a molecular chaperone, HSP70, has been found to be excluded from stress granules even under stress situations in which many mRNAs are taken up by the granules and their translation suppressed. Under stress conditions YB-1 binds to HSP-70 mRNA and increases the expression of HSP-70 suggesting an induction of mRNA translation. Under stress conditions GluR2 level in non-polysomal fractions was increased on the other hand in contrast, the amount of HSP70 mRNA was decreased in the non-polysomal fractions. Here YB-1 has been found to be necessary for the stress-induced translation of HSP70 mRNA, but not for the translational induction of GluR2 mRNA, even though YB-1 is a component of stress granules. In the YB-1 depleted cells an increased HSP70 mRNA was detected. There was observed the formation of stress granules even in the YB-1 depleted cells suggesting that YB-1 is not necessary for the stress granule formation rather a negative effect on the granule formation was observed as large number of granules were formed in the YB-1 depleted cells. The GluR2 mRNA was incorporated in the stress granules even in the YB-1 depleted cells and its translation was still repressed. The level of HSP70, a molecular chaperone, increases in response to cellular stress and protects proteins from misfolding or abnormal aggregation.[81]

Proteasomal degradation of YB-1

Degradation of YB-1 mainly regulated by Retinoblastoma binding Q protein 1 (RBQ-1) and Retinoblastoma binding protein 6 (RBBP6) also known as p-53-associated cellular protein testes derived protein is a 250-kDa multidomain protein that has been strongly implicated in tumorigenesis.[82] YB-1 has been observed as a novel binding partner of RBBP6 and RBBP6 ubiquitinates YB-1, leading to its degradation in the proteosome. RBBP6 is one of the few proteins known to interact directly with both tumour suppressor proteins p53 and pRb.[83] RBBP6 plays a role in facilitating the interaction between p53 and its primary regulator Hdm2, leading to ubiquitination of p53 and its degradation in the proteasome.[84] RBBP6 is an E3 ubiquitin ligase due to the presence of the RING finger domain.[84] YB-1 incubation with RING finger and ubiquitin indicates that the RING finger is capable of facilitating ubiquitin attachment to YB-1 for ubiquitination. Moreover, RBBP6 leads to a decrease in the intracellular levels and transactivational activity of YB-1 by interacting directly with YB-1.[83,84] YB-1 has previously been shown to be ubiquitinated as result of an interaction with F-box domain of F-box protein 33 (FBX33). FBX33 is a member of the SCF (skp-1/Cul1/F-box) family of E3 ubiquitin ligases, whereas RBBP6 is a member of the RING finger-containing E3 ligase family. In addition, the interaction between YB-1 and FBX33 involves cold-shock domain of YB-1 rather than C-terminal B/A domain as in the case of RBBP6.[85] RBBP6 is a nuclear associated protein and has a high basic charge. Therefore, YB-1 and RBBP6 may affect localization of each other.[83]

CONCLUSION

Interaction of YB-1 with DNA and RNA is a key to many processes involved in DNA replication and damage repair. Moreover, the involvement of YB-1 in stress and inflammatory responses predicts its impact on cell cycle and apoptosis. Additionally, as a component of

cytoplasmic mRNPs Y-box proteins affect the fate of mRNA in the cytoplasm. All these active functions of YB-1 make it a vital molecule of various cellular regulatory processes.

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