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Review

Role of Y Box Protein-1 in cancer: As potential biomarker and novel therapeutic target

Pramod Kumar Maurya[1], Alok Mishra[1], Birendra Singh Yadav[1], Swati Singh[2], Prashant Kumar[1], Amit Chaudhary[1], Shweta Srivastava[1], Suriya Narayan Murugesan[1], Ashutosh Mani[1]✉

1. Department of Biotechnology, MNNIT Allahabad-211004
2. Center of Bioinformatics, University of Allahabad, Allahabad-211002

✉ Corresponding author: E-mail: amani@mnnit.ac.in

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Abstract

The Y-box binding protein (YB-1) is known to be a multifunctional transcription and translation factor during expression of several proteins. It is a vital oncoprotein that regulates cancer cell progression and proliferation. YB-1 is over-expressed in various human cancers such as breast cancer, colon cancer, lung cancer, gastric cancer, oesophageal cancer and glioblastoma. Nuclear expression of YB-1 is found to be associated with multidrug resistance and cancer cell progression. YB-1 is reported to regulate many cellular signalling pathways in different types of cancer proliferation. Knowledge about nuclear localization and nuclear level expression of YB-1 in different cancers has been correlated with prospective prognosis of cancer. This review discusses the prospects of YB-1 as a potential biomarker as well as therapeutic target in lieu of their role during cancer progression and multidrug resistance.

Key words: Y Box Protein-1, cancer, biomarker

Introduction

YB-1 (Y-box binding protein-1) is a cold shock domain protein which is a member of a large family of proteins containing a highly conserved nucleic acid binding motif called cold shock domain (CSD) of about 65 amino acids [1]. YB-1 is primarily localized in cytoplasm but it is localized to nucleus in response to various stresses, including hyperthermia [2], adenoviral infection [3], DNA damage [4] and activation of PI3K, Akt and RSK signalling [5].

Initially, it was identified to bind with the Y-box or inverted CCAAT box of MHC class II promoter and play an important role in inhibition of gene transcription [6]. Later, it was identified that YB-1 binds with the Y-box present in the enhancer and promoter region of a wide variety of genes such as EGFR and HER-2 genes and regulate the transcription [7]. Thereafter, YB-1 was also found to bind with CT-rich elements in the *C-myc* promoter [8]. Several subsequent studies have shown that YB-1 either up-regulate or down-regulate the expression of many important genes such as multidrug resistance 1, cyclin A, cyclin B1, collagen alpha2(I) and matrix metalloproteinase 2 [9, 10, 4].

However, YB-1 is generally present in the cytoplasm and associated with mRNA as mRNP to perform mRNA masking and regulation of translation but studies suggest that concentration of YB-1 also regulates the translation, as low concentration of YB-1 activates translation and high concentration represses it [11, 12]. In nucleus and cytoplasm, YB-1 regulates the mRNA metabolism at various steps such as transcription, translation, splicing and mRNA stability.

Structure of YB-1

The Y-box binding protein-1 is a 324 amino acid-long protein having molecular mass of 35.9 kDa which comprises of three domains: alanine/proline-rich variable N-terminal domain (A/P domain), a highly conserved nucleic-acid

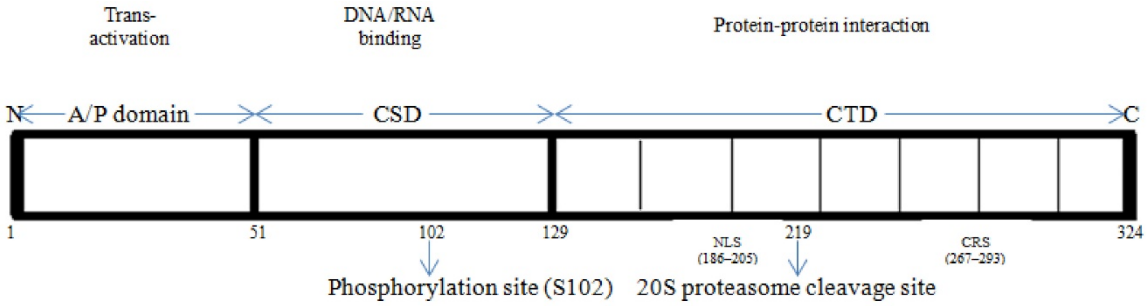

Fig 1: Structural organization of YB-1

binding cold shock domain (CSD) and a large disordered C-terminal domain (CTD) containing alternating clusters of positively and negatively charged amino acids [13]. The CTD also contains nuclear localization signal (NLS), the cytoplasmic retention site (CRS), and the 20S proteasome cleavage site [14, 15]. The studies suggest that the cold shock domain (CSD) has a tertiary structure containing a five-stranded β-barrel with consensus sequences [16] and associated with both specific and unspecific binding with nucleic acid [14]. The CTD has binding sites for both nucleic acid and a number of proteins [17, 18, 19, 20].

The A/P domain has disordered structure and it contains binding sites for splicing factor SRp30c [21], actin [22], cyclin D1 [23] and transcription factor p53 [19]. The CSD domain has binding sites for Akt kinase [5], PDK-1, RSK and E3 ubiquitin ligase FBX33 [24]. The C-terminal domain (CTD) has disordered structure containing alternate regions of basic or acidic amino acids, having about 30 amino acids in length, called a B/A repeat and is involved in protein homo-multimerization [25, 26]. The CTD has binding sites for several important regulatory proteins such as hnRNP D [27], hnRNP K [28], Tata binding protein (TBP) [28], PCNA (Proliferating cell nuclear antigen) [18], EWS (Ewing's sarcoma breakpoint region) and TLS (Translocated in liposarcoma protein) [29], transcription factor p53 [19], E3 ubiquitin ligase RBBP6 [30] and IRP 2 (Iron regulatory protein 2) [31].

Functions of YB-1

YB-1, a multifunctional protein, has multiple roles in regulating transcription and translation of a wide range of important genes and proteins in cancer cell proliferation and progression [32], cell survival [33, 34, 35, 36], DNA replication [37], DNA repair [17], multi-drug resistance [38, 2] and epithelial–mesenchymal transition [39]. As nucleic acid binding protein, YB-1 performs diverse biological functions such as transcriptional and translational regulation, pre-mRNA splicing, chromatin remodelling and environmental stress response [4, 40].

Translation

In order to regulate the transcription, YB-1 either act as a transcription factor by binding to the Y-box sequences present in the promoters and enhancer regions of a wide range of genes and subsequently activate or repress the gene transcription or act as a co-activator/co-repressor to interact with the other transcription factors. The genes activated by YB-1 are EGFR, HER-2, thymidine kinase, multidrug resistance 1 (MDR1), protein tyrosine phosphatase 1B, proliferating cell nuclear antigen (PCNA), cyclin A and cyclin B1, gelatinase A, Smad7 gene, PI3KCA gene, matrix metalloproteinase 2 and DNA topoisomerase II alpha. Genes which are transcriptionally repressed by YB-1 are MHC class II, collagen alpha1, VEGF, Fas, granulocyte-macrophage colony-stimulating factor (GMCSF), LRP/MVP gene, p21 gene and thyrotropin receptor gene [41, 4, 42]. YB-1 play an important role in regulating growth and stress response related genes.

Splicing

YB-1 regulates the selection of splicing site by recognition of splicing specific motifs in pre mRNA containing A/C-rich exon enhancers [43] or by association with splicing factors of SR family [44, 21].

mRNA translation and stability

YB-1 is a major component of mRNPs (messenger ribonucleoprotein particles), as it activates or represses the translation in a dose-dependent manner with mRNA i.e. YB-1/mRNA ratio [11]. YB-1 plays an important role in regulating the translational activity of several growth related mRNA such as HIF1α, LEF-1, Snail 1 and 2, ZEB2 [45, 39]. Due to its chaperone activity, it protects capped mRNA from degradation [46]. YB-1 also regulates the stabilization of transient mRNA by activating several genes including GMCSF [47, 48, 49].

DNA repair and stress response

YB-1 regulates both base-excision repair and mismatch repair pathways by conducting multiple

associations with l DNA repair proteins such as glycosylase NEIL2, DNA ligase III, DNA polymerase beta and delta, MSH2, Ku80, APE1, WRN, endonuclease III [50, 51, 17]. YB-1 also regulates separation of DNA strands in case of mismatch repairs or mutation caused by drugs [18, 52, 51]. The nuclear localization of YB-1 and its proteasomal cleavage [53] is also found to be associated with a number of physiological stresses such as DNA damage, hyperthermia and adenovirus infection [54, 4]. The over-expression of YB-1 protein in nucleus is correlated with the increased multi-drug resistance and cell survival [4, 53]. The YB-1 obtained from fibroblast embryos has shown a reduction in respond to oxidative, oncogene-induced and genotoxic stresses [55]. The studies show that YB-1 is an important protein in stress responses as well as during early and late embryonic development [56].

Tumorigenesis

The overexpression of YB-1 is reported in various types of human cancers [4, 57]. In multiple human cancers, the increased expression level of YB-1 is correlated with multi-drug resistance and poor outcomes [58, 59]. In breast cancer cells, the increased level of YB-1 induces tumour growth and invasiveness [5, 60]. The increased levels of YB-1 has been associated with DNA topoisomerase II activity, proliferating cell nuclear antigen (PCNA) expression in human colorectal cancer [61], lung cancer [62] and cell proliferation in osteosarcoma [63]. YB-1 has a specific role in inhibiting the PI3K or Akt-induced oncogenic transformation [64] and it has been correlated with cytosolic localization and protein synthesis [65, 66]. Thus YB-1 may play crucial role in blocking the translation of growth-related proteins such as kinases, receptors, growth factors and several regulatory proteins of PI3K and Akt pathways [67].

Role of YB-1 in cancer regulation and proliferation

The multifunctional regulatory protein YB-1 is activated by the phosphorylation at serine 102 position [68]. On phosphorylation, YB-1 shuttles from cytoplasm to nucleus where it becomes an oncogenic transcription factor by inducing the expression of growth-promoting genes such as EGFR [69], HER-2 [70], PCNA [18], Cyclin A, Cyclin B [10] as well as also affects the expression of multidrug resistance gene [71].

YB-1 expression level was reported to be highly associated with the cancer cell progression and proliferation [58]. YB-1 was found to be correlated with the expression of many important genes including genes for providing unlimited growth, drug resistance, overriding cell cycle and controlling gene transcription and translation in cancer cells [72, 4]. Such genes which are overexpressed in cancer, have Y -box or CCAAT box sequence in their promoter or enhancer region [73, 74]. YB-1 binds to the Y-box sequence of these genes and trans-activate their expression [75]. For example, YB-1 trans-activates the MDR1 gene, containing Y or CCAAT- box sequence in its promoter region and cause overexpression of MDR1gene. The high MDR1 gene level associated with nucleus YB-1 is reported in case of many types of human cancer such as osteosarcoma, breast, lung, prostate, and synovial sarcoma cancer [76-83].

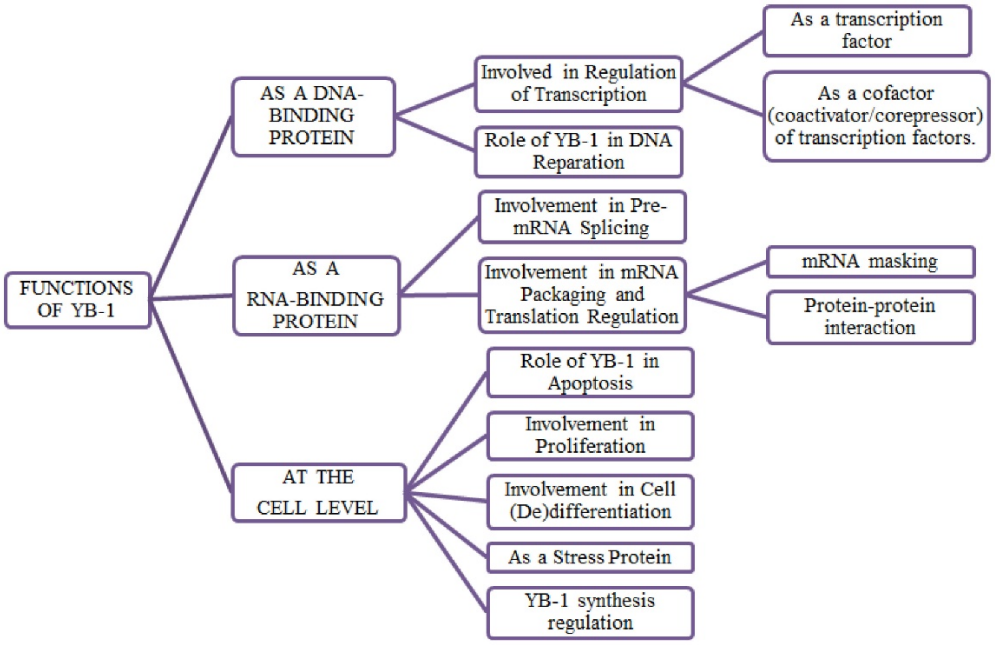

Fig 2: Functions of YB-1

Besides strong correlation with MDR1, the nucleus YB-1 level was reported to co-regulate the growth promoting genes [72]. The multifunctional protein YB-1 has multiple effects on cancer cells by regulating the all the nine "Hallmarks of Cancer" as described by Hanahan and Weinberg [84, 14]. In order to modulate the cell signalling pathways to promote or maintain malignancy in cancer cell, YB-1 plays important role in each hallmark of cancer that are uncontrolled proliferation signalling, evading growth suppressors and cell cycle checkpoints, resisting cell death and evading immune destructions [85, 86, 87].

The YB-1 reduction causes growth repression and apoptosis in a large number of cancer cells such as breast, colon, lung and prostate cancer [87]. The reduction in YB-1 expression was found to be correlated with the inhibition of cancer progression, cell growth and promotion of apoptosis in a wide range of human cancer cells such as- Melanoma, Fibrosarcoma, liver cancer, lung cancer, breast cancer, colon cancer, prostate cancer and paediatric glioblastoma [88, 89]. YB-1 blocks Fas-mediated apoptosis pathway at multiple points to prevent apoptosis [33]. YB-1 promotes uncontrolled cancer cell proliferation by activation of E2F pathways which is a prevalent event in almost all types of cancers [89]. YB-1 inhibits the expression of RB in many ways and also reported to inhibit the expression of p53 gene in cancer cells hence reduce tumour suppression activity [90, 34].

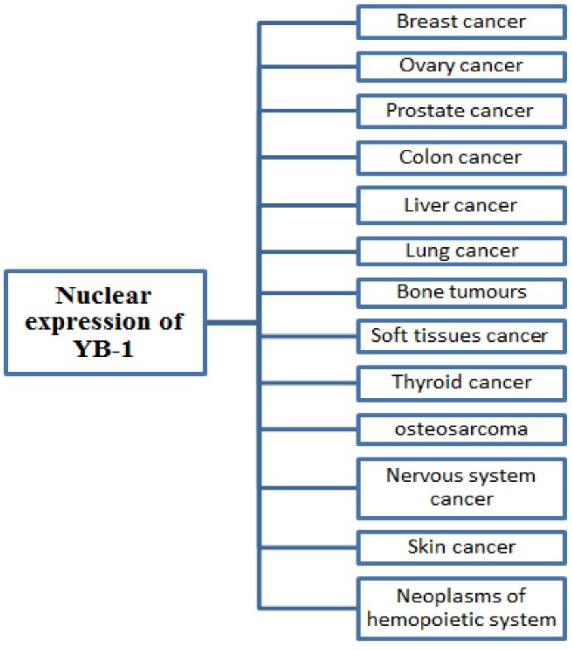

Fig 3: Prognostic association of YB-1 with different types of malignancies

Table 1: The functions of YB-1 in different Cancers

S.No.	Hallmarks of Cancer	Regulated gene/Pathways
1	Uncontrolled Proliferation Signalling	Regulates E2F pathways Regulates PI3K/Akt/mTOR pathway Regulates Ras/Raf/MEK/ERK pathway Regulates MAPK pathway
2	Evading Growth Suppressors and cell cycle checkpoints	Inhibits RB (gatekeeper protein) pathway Inhibits p53 (tumour suppressor protein) pathway
3	Resisting cell death	Inhibits BAX and CASP7-mediated apoptosis Inhibit Fas-mediated apoptosis pathway Proliferation of E2F target genes
4	Enabling replicative immortality	Activation of telomere maintenance mechanism Loss of RB checkpoints Loss of p53 function
5	Inducing angiogenesis	Activate pro-angiogenic genes such as VEGF-A, FDGF-B, IL-8, CXCL-2
6	Activating invasion and metastasis	Regulates SNAI1, LEF1 and TWIST1 to repress CDH1 gene (E-cadherin) Regulate TGF-β, Wnt pathway proteins and Notch 3 receptor
7	Deregulating energy metabolism	Regulating PI3K/Akt/mTOR, Myc, PKM2, RB/E2F1 and p53 pathway
8	Evading immune dystruction	Regulation of gene encoding MHC Class II and Fas Regulation of TGF-β pathway
9	Tumour promoting inflammation	Regulates expression of mTOR, STAT3, MMP-2, CD44, CCL5 AND CCL2

YB-1 as a potential bio-marker

The nucleus expression level of YB-1 is a prognostic biomarker for cancer progression, cell proliferation and multidrug resistance in various human cancers [91]. YB-1 promotes the transcription of proliferation/growth-promoting genes in the nucleus while in cytoplasm, it is found to be associated with mRNA and involved in direct translation.

In different human cancer such as breast, lung, prostate, liver, colon and others, the nuclear expression of YB-1 is associated with poor clinical outcomes. These reports suggest that YB-1 is an important biomarker to predict the patient's prognosis and is feasible for identifying the particular stage treatment protocol [4, 14]. While using YB-1 as a prognostic tool in human cancer, the cellular localization of YB-1 in cell (cytoplasm/nucleus) or the nuclear YB-1 expression level may be used to predict the particular stage of cancer [87, 91].

Many studies have focused on the correlation between overall YB-1 levels and the prognosis of patient. Several studies over time have shown that the overexpression and nuclear localization of YB-1 is also associated with different human cancers such as breast cancer [58], lung cancer [92], liver cancer [93], ovarian cancer [94], colorectal cancer [61], prostate

cancer [95], Synovial sarcoma [96], multiple myeloma [90], osteosarcoma [63], melanoma [97], glioblastoma [98]. Several studies suggested that YB-1 in most of the cancers is nuclear localized and its identification and quantification in cancer cells make YB-1 a powerful prognostic marker. Many studies also shows that overall YB-1 level (cytoplasmic and nuclear) is an efficient predictor for prognosis of cancer [90, 59, 99].

YB-1 as a novel therapeutic target

Many molecular targets have been identified in different human cancers that lead to the establishment of therapeutic approaches [100] as HER-2 in breast cancer [101] and TREK-1 in prostate cancer [102]. YB-1 may be a novel therapeutic target for cancers as it is upstream of the many genes involved in cellular signalling pathways including drug resistance gene (MDRI) as well as other growth related genes such as HER-2, EGFR, proliferating nuclear antigen (pcna), cyclin A, and cyclin B which are responsible for cancer development [100]. Various approaches have been employed to target YB-1 either by directly inhibiting the activation of YB-1 or targeting the activators which activate YB-1 such as PI3K, AKT, PDK and RSK.

The molecular decoy of YB-1 binding site has been successfully used in different cultured cells, showing the inhibition of tumour growth and induction of p53-mediated apoptosis [34, 35]. The development cell permeable peptide (CPP) in cancer has shown to block the YB-1 phosphorylation and down-regulate of growth-promoting genes EGFR and HER-2 which in turn caused 90% cancer inhibition in growth of breast and prostate cancer [103].

The second approach is to directly target the YB-1 by using siRNA and the anti YB-1 siRNAs which has been successfully employed to transfect different cancer cells and shown inhibition of tumour growth, proliferation, differentiation and enhanced apoptosis [90, 89, 104, 105, 106]. This approach involves challenge to deliver siRNA in human including limitation of stability, bioavailability, delivery technologies and understanding molecular chemistry [107].

SiRNAs against YB-1 have been used to block the YB-1 phosphorylation and reduce proliferation in breast cancer [104, 36], lung cancer [108], prostate cancer [109], mesangial cancer [37] and myeloma [90, 110] cell lines. When activated by phosphorylation at serine 102, YB-1 gets nuclear localized, acts as transcription factor and causes overexpression of growth-promoting genes and multidrug resistance genes [5]. Mutation at phosphorylation site by i.e. Ser102 by substituting it to Ala102 shows inhibition of YB-1 nuclear localization and suppression in tumour growth [36].

Another approach to indirectly target the YB-1 is to influence the signal transduction or the activator kinases which phosphorylate the protein to suppress its activity in cancer cells. The blocking of kinases like Akt [45, 5], PDK-1 [111] and RSK [112] has shown reduced YB-1 phosphorylation and transactivation activity. Although Akt play a key role in phosphorylating the YB-1 [5], but when compared to other kinases RSK play a major role in activation of YB-1 [112, 113].

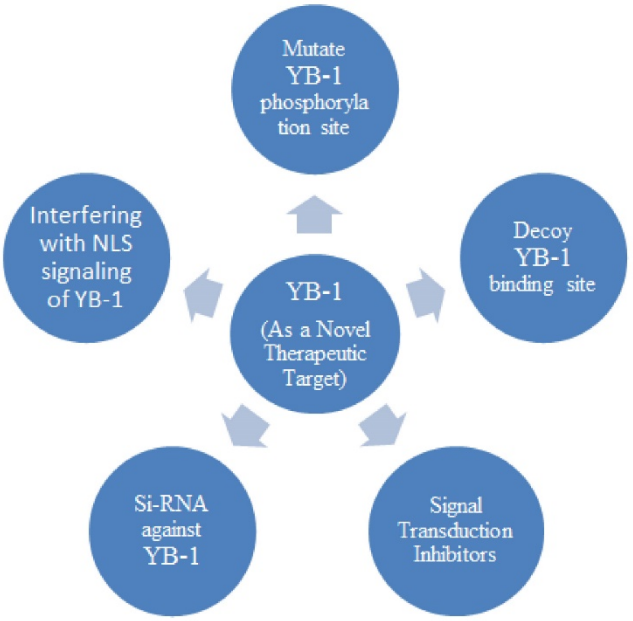

Fig 4: Targeting of YB-1

A hypothetical therapeutic approach to target the YB-1 in cancer cell may be to inhibit the NLS (Nuclear Localization Signal) signalling pathway by simply mutating the NLS site located in the protein. This may prove to be a promising strategy to reduce YB-1 nuclear localization as well as to suppress tumour growth, although there is no significant information available about this signalling pathway and more investigations are needed in this regard. However complete regulatory network information of the protein will certainly be more helpful in identifying a target which directly or indirectly influences variations in the protein expression level or controls the nuclear localization. Direct targeting of YB-1 may not prove to be a promising approach when compared to the indirect targeting, as blocking of kinases PI3K, Akt, PDK-1 and RSK would cause blockage of YB-1 that may cause severely adverse side effects due to their vital role in cellular signalling pathways, making this therapy less feasible.

Conclusion

This review discusses the role of multifunctional YB-1 protein in human cancer biology and mode of regulation of each hallmark of cancer by YB-1. YB-1 is an oncogenic transcription and translation regulator which plays key role in different cellular processes. Further investigations are needed to gain insights of complete function and regulation of YB-1 during proliferation of cancer. In different cancers, the level of YB-1 is correlated with poor clinical outcomes; hence YB-1 may serve as a potential biomarker for cancer progression. The level of YB-1 present in nucleus and cytoplasm of several human cancer cells generally predict the prognosis of cancer.

Despite of rapid technological advances the function and regulation mechanism of YB-1 are not known completely. Being a constitutively expressing protein, targeting the protein as such may be harmful for healthy cells, however targeted drug delivery may be a suitable technique for this purpose.

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Competing Interests

Authors declare no conflicts of interest.

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