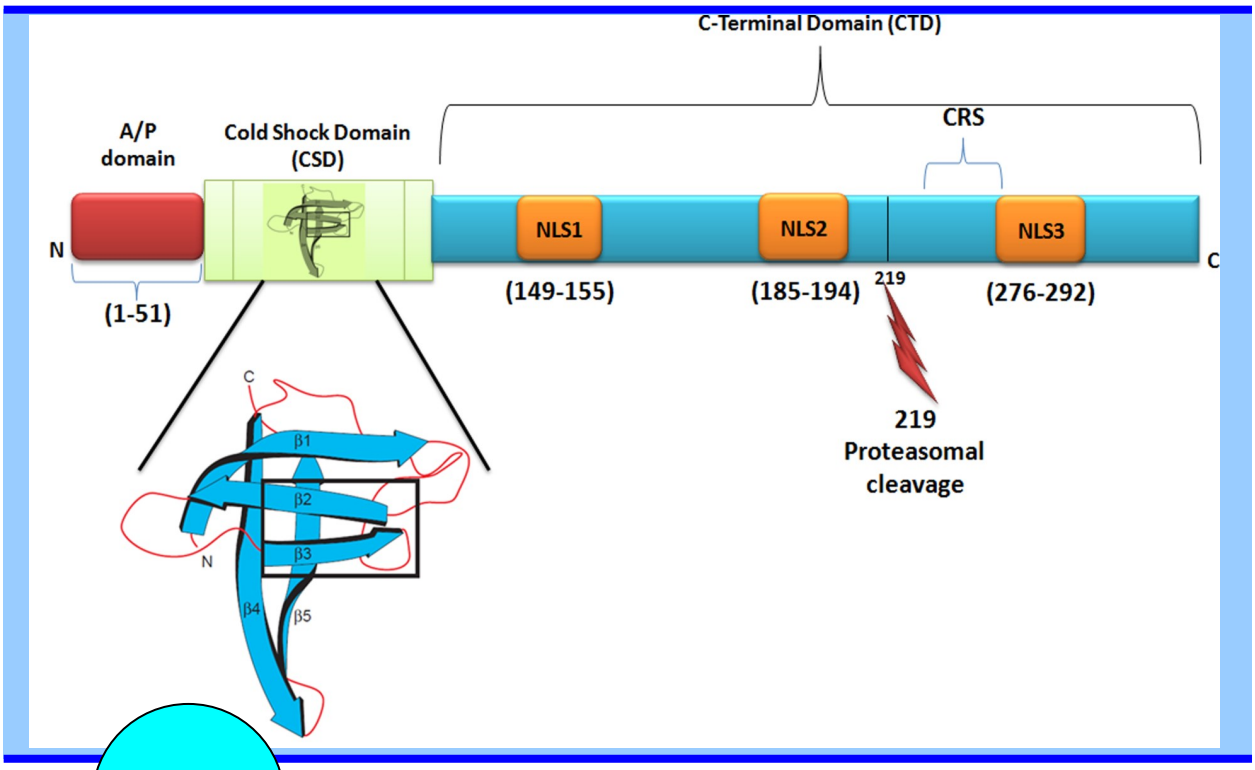

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Mini-review

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Mini-review

Nuclear shuttling of Y-box binding protein 1, its clinical relevance to cancer and as a therapeutic target

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Abstract

Y-box binding protein 1 (YB-1) is an imperative biomarker for the clinical outcome of cancer patients. An overexpression of YB-1 in cancerous and adjoining tissues is an indication of aggressiveness and advanced stages. In normal resting cells, YB-1 is localized in cytoplasm while in stress conditions like cancer, nuclear shuttling of YB-1 takes place. In this review, the clinical importance of YB-1 in different cancers and the mechanism behind YB-1 nuclear shuttling have been discussed in detail. Targeted chemotherapies or molecularly targeted drugs of great importance can target and block specific molecules implicated in tumor growth and progression. YB-1 has been considered as a bonafide oncogene and accumulating evidences show the therapeutic importance of YB-1. Therapeutic strategies targeting YB-1 may improve the survival rate in cancer patients. This review extensively discusses the therapeutic importance of YB-1.

Introduction

Y-box binding proteins are the members of cold shock proteins large family conserved from prokaryotes to human (Hunt and Morimoto, 1985; Horwitz et al., 1994). These proteins were first discovered in birds (duck) and mammals (rabbit recticulocytes) as major components of cytoplasmic mRNP (Morel et al., 1971). In human, there are three members of this protein family i.e. a) DNA binding protein A (DbpA), b) DbpB (YB-1), c) DbpC (contrin) (Shinichi et al., 1995; Kohno et al., 2003). In 1988, DbpB was sequenced and identified as a DNA binding protein interacting with Y-box motif present in the major histocompatibility complex class II gene (latter Y- box motif identified in various gene promoters) so named Y-box binding protein (YB-1) (Didier et al., 1988).

Screening of human placental cDNA library constructs led to the identification of dbpA and dbpB genes and the sequence analysis showed that dbpB is completely and dbpA is 46% identical to YB-1. The location of YB-1 and dbpA was confirmed on chromosome 12p13 and 1p34 along with the location of many pseudogenes on other chromosomes (Ozer et al., 1993). A characteristic large first exon of 497 bp is present in the promoter region of YB-1 (Makino et al., 1996). There are, at present, multiple E-boxes in between -1855 and -555 of the promoter region with a significant promoter activity in the first exon up-stream region. +24 to +127 region constitutes the promoter region for transcription initiation point (Makino et al., 1996).

Human YB-1 contains 324 amino acids (Minich et al., 1993). The structure of it might be subdivided into three domains namely N-terminal domain, cold shock domain and C-terminal domain. A/P domain, the short N-terminal domain contains 1-51 residues and is rich in alanine and proline. The central part of the YB-1 is CSD (52-129 residues) comprises of ~70 amino acids conserved from bacteria to human. The diagrammatic representation of YB-1 is given in Figure 1.

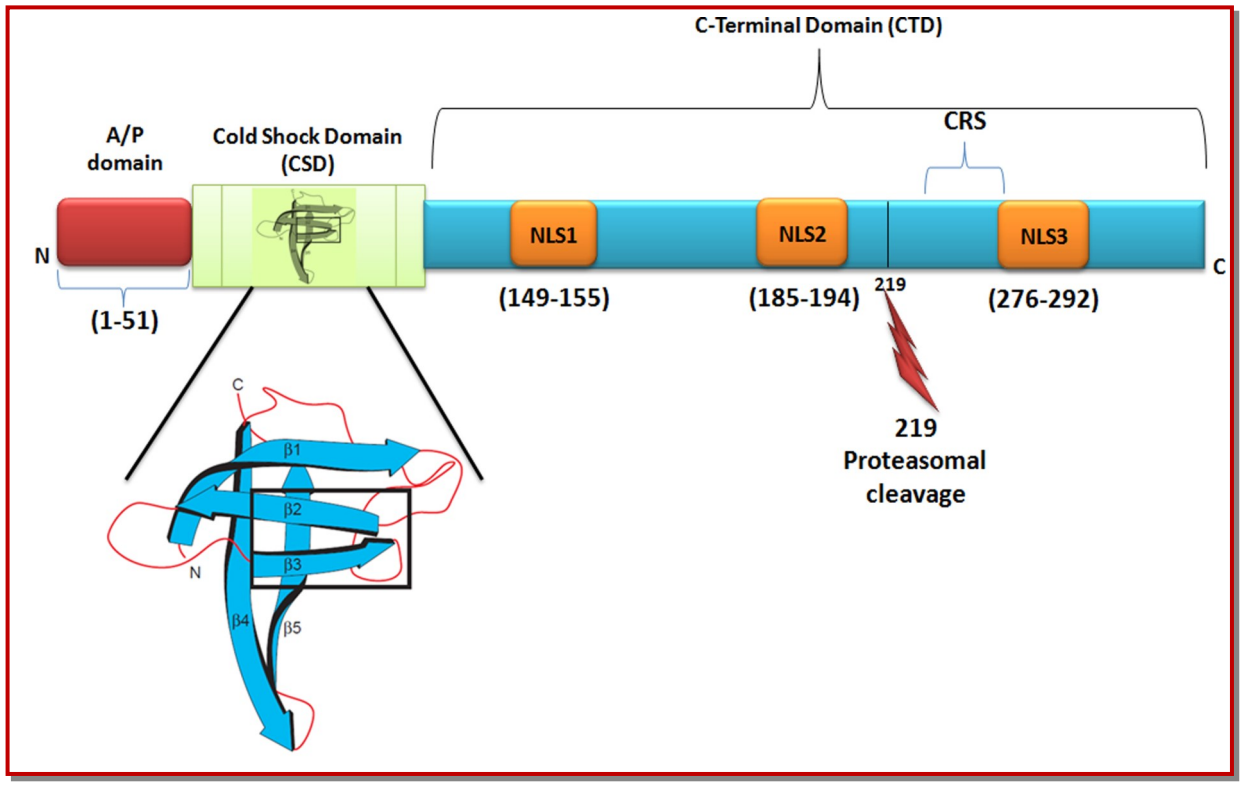

Figure: 1 Structure of YB-1

The structure of YB-1 might be subdivided in to three domains such as N-terminal domain, cold shock domain and C-terminal domain. The central part of the YB-1 is cold shock domain (52-129 residues) comprises of ~70 amino acids. As is evident by NMR structural studies of cold shock domain, the cold shock domain forms backbone of the protein and consists of five β- strands 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). β2-β3 has a fixed orientation while β1-β2 and β4-β5 can adopt different orientations. 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 (Kloks et al., 2002)

In normal resting cells, full length YB-1 is mainly present in the cytoplasm of cells under stress during pathological conditions including inflammation, oxidative stress and cancer conditions. Particular segment of the YB-1 flips to the nucleus (Koike et al., 1997; Higashi et al., 2011).

In this review, with the nuclear shuttling, clinical significance of YB-1 in cancer and as a therapeutic target have been evaluated from the existing literature. The present literature analysis shows the prospective role of YB-1 in cancer progression and drug resistance which could be harnessed to make it a promising therapeutic target.

Nuclear shuttling of YB-1

Since a number of functions have been assigned to YB-1, therefore, the sub-cellular protein shuttling needs to be highly stringent. In general, specific nuclear export signals and nuclear localization signals (NLS) contribute and direct the multifunctional shuttling and tasking (Bader and Vogt, 2005). Literature suggests three nuclear localization signals in YB-1 i.e. NLS1 (aa149-55), NLS2 (aa185-94) and NLS3 (276-92) (van Roeyen et al., 2013). The NLS3 is bipartite in composition and both the parts are essential for functionality. Irrespective of this, the changes of the spatial organization of 2 parts doesn't affect nuclear shuttling. Both NLS2 and NLS3 are essential for functionality and contain tyrosine residues which are required for phosphorylation. The full length YB-1 phosphorylated at tyrosine 281 in NLS3 has been found to be localized in the nucleus while the unphosphorylated YB-1 localized in the cytoplasm. This indicates that the phosphorylation at T-281 renders complete YB-1 to be localized in nucleus under normal conditions (van Roeyen et al., 2013). At the time of stress or cell stimulation, nuclear flipping of shortened YB-1 having N-terminal portion of the proteins takes place through a highly regulated process (Bader and Vogt, 2005; van Roeyen et al., 2013). Jürchott et al. (2003) suggested that the both C-terminal and cold shock domain of YB-1 are involved in nuclear translocation. Phosphorylation of S102 in cold shock domain may induce conformational changes which mask the cytoplasmic retention sequence and/or exposes the NLS. Certain molecular mechanisms are known to date that explain the nuclear flipping of YB-1 (Lorsch, 2002; van Roeyen et al., 2013). However, S102 phosphorylation via proteins or kinases control nuclear translocation of YB-1 in cancer growth and survival

signaling such as P13K/AKT, RSK, Ras/MAPK (Dalby et al., 1998; Lorsch, 2002; Sinnberg et al., 2012; Shen et al., 2011; Astanehe et al., 2012) and PKC signaling (Fujii et al., 2009) cascades. Another mechanism involves the proteasome-mediated cleavage of YB-1 between NLS and cytoplasmic retention sequence which further triggers the gathering of trimmed YB-1 deficient in cytoplasmic retention sequence in DNA damaged cell nuclei *in vitro* as well as *in vivo* in response to genotoxic stress (Kim et al., 2013). Inhibition of YB-1 (S102 to A102) phosphorylation by site directed mutagenesis leads to reduction of nuclear translocation but still 50% YB-1 (A102) exists in nucleus (Wu et al., 2006). Additionally, phosphorylation reduces transcriptional activity of YB-1 by affecting its binding to DNA. For example, YB-1 phosphorylated at S102 binds with the EGFR promoter and regulates EGFR expression but mutated YB-1 (A102) is not competent to bind with EGFR promoter (Stratford et al., 2007). Moreover, S102 phosphorylation disables YB-1 interaction with cap 5′ terminus of mRNA, thereby promotes the translation of various oncogenes such as IGF-1, VEGF and FOS (Evdokimova et al., 2006; Coles et al., 2005).

YB-1 has been assigned many regulatory functions along with the regulation of YB-1 transcription such as DNA repair as it unwinds DNA helices and binds to the repair proteins (Lenz et al., 1990). A difference in the survival rate of the doxorubicin-treated fibroblast NIH3T3 cells having truncated YB-1 (HA-YB-1; 1-219) has been observed. The utmost expression of complete and trimmed YB-1 remained unchanged 24 hours after doxycycline treatment and even while further cell passaging over a 7-day period. The complete wild type YB-1 (HA-YB-1) was maximally localized in the cytoplasm while the trimmed YB-1 was nuclear localized. YB-1 has a cell specific effect on the cell growth and proliferation. Both the complete and trimmed YB-1 showed a similar effect on drug resistance at low doses of drug while at higher doses the truncated YB-1 was found to be more effective in imparting resistance to the cells. Even MG132 (proteasome inhibitor) pre-treatment eliminated the influence of complete YB-1 but did not affect the role of trimmed YB-1 suggesting that the trimmed YB -1 and not the complete YB-1 is required for the increased survival of the fibroblast cells during doxorubicin treatment. The trimmed YB-1 (1-219) was found to be involved in the DNA repair pathways as it enhances the resistance to DNA damaging agents (Kim et al., 2013).

Evdokimova et al. (2006) suggested that P13K inhibitor wortmannin blocked IGF-1 stimulation-induced phosphorylation of YB-1, thus completely prevent the nuclear translocation, whereas S102 mutation to alanine was not completely blocked. Hence, it supports the involvement of other phosphorylation sites in YB-1 translocation. Accumulating evidences suggest that phosphorylation of Ser21 and Ser36 in the N-terminal domain enhance the transcriptional activity of YB-1. It should be pointed out that Ser21 and Ser36 present in the transactivation domain of YB-1 which are targets for many kinase proteins like GSK3β, AKT, RSK1 and ERK2 of different signalling cascades involved in tumor angiogenesis and cell cycle (Wu et al., 2007). It is also predicted that the p85 subunit of P13K may phosphorylate at Tyr197 of YB-1 CTD, probably alter the interaction of YB-1 and other proteins that facilitate the translocation (Bader and Vogt, 2005).

Here, we are going to discuss about two major proteins influencing YB-1 shuttling i.e. SRp30c and p53. First, SRp30c, a SR family member, involves in the constitutive and alternative splicing processes. It is present in most of the tissues and exhibits similarities with the more intensively studied alternative splicing factor ASF/SF2. This protein family has been named as SR-proteins due to arginine/serine dipeptides within C terminus. SRp30c and RNA interact directly through 2 independent RNA recognition motifs which are connected by a glycine-hinge (Raffetseder et al., 2003).

There are many reports indicating the role of SRp30c in interaction with the proteins involved in the nuclear architecture maintenance like nuclear and nucleolar protein (Nop 30) (Stoss et al., 1999), heterogenous nuclear ribonucleoprotein A1-interacting protein (HAP) (Denegri et al., 2001), and *src* activated during mitosis (Sam68) like mammalian protein (SLM2) (Stoss et al., 2001). HAP and SLM2 function in the organization of the nuclear architecture and RNA-trafficking, and both of these proteins are localized in the Sam68 nuclear bodies (Chen et al., 1999). Splicing patterns are regulated by changing the local concentrations of SRp30c or by employing SRp30C to other compartments in nucleus (Denegri et al., 2001).

Moreover, a direct YB-1/SRp30c interaction results in a shift in YB-1 localization from cytoplasm to nucleus on changing the concentration of splicing factors and increased cellular SRp30c concentration. First, the same nuclear domain of YB-1 that interacts with the SRp30c is required for the nuclear YB-1 localization and secondly, heat shock treatment which leads SRp30c to stress-induced Sam68 (Denegri et al., 2001) nuclear bodies results in the reversal of nuclear YB-1 shift within 1 hour (Raffetseder et al., 2003).

YB-1 expression in central portions of nucleolus precursor bodies or large Cajal bodies in 2 celled embryos (deficient in trancriptionally active nucleoli) of mouse has been observed. However, there was no expression in the small Cajal bodies (Bogolyubova et al., 2014). It is well-known that a portion of the embryo has RNA polymerase I transcription modules (Zatsepina et al., 2003). Immunostaining methods indicated colocalization of YB-1 with RNA polymerase I which was remarkably characterized in hepatocytes nuclei which showed high transcriptional activity. YB-1 and RNA

polymerase I were found to be colocalized in the large Cajal bodies and in hepatocyte nucleoli which suggests YB-1 involvement in the biological progressions in nuclear organelles (Bogolyubova et al., 2014).

Other than transcription of various genes, the nuclear localization of YB-1 also activates SOS pathway to repair DNA damage from genotoxic factors, drugs and UV irradiation (Ohga et al., 1996).

YB-1 dependence on p53 for nuclear translocation

Zhang et al. (2003) showed that the nuclear flipping of YB-1 is dependent on p53 functional activity and not the YB-1/p53 complex formation. Experiments based on p53 mutants show the attenuation of proline rich deleted mutants for nuclear YB-1 flipping which indicates p53 response due to DNA damage towards YB-1 nuclear translocation (Baptiste et al., 2002). Furthermore, co-transfection of YB-1 with p53 inhibits p53 function to transactivate APAF1 and Noxa promoters and hence reverses p53 mediated cell death, suggesting that the inhibition of p53 transactivation may be dependent on nuclear flipping of YB-1 which results in the inhibition of p53 ability to mediate death in a discerning mode (Zhang et al., 2003).

Functional activation of inducible p53 cell lines with 4-OHT resulted in the substantial amount of YB-1 in the nucleus and in un-induced cell lines YB-1 was present in the cytoplasm. This suggests that the transactivation of one of p53 down-stream target genes results in the product which is an 'effector' of YB-1 translocation into nucleus. Furthermore, stimulation of p53 results in the cell cycle arrest without any increased cell mortality. Eventually the p53 mediated cell death occurred in the cells in which YB-1 expression was inhibited using antisense oligonucleotides. There was no increment in the proteins responsible for p53 mediated cell death after p53 activation rather increase was there after antisense YB-1 oligonucleotide treatment in a p53-dependent manner (Zhang et al., 2003). The study suggested that the YB-1 selectively controls p53 transactivation by binding to p53 and reduces its availability for promoter binding resulting in affinity dependent inhibition of promoter binding.

Clinical relevance of YB-1 in cancer

Prognostic biomarkers may be helpful for identifying patients who are likely to undergo recurrence or be insensitive to the standard chemotherapy. YB-1 could be a prognostic biomarker of high importance and various advancements in therapeutic strategies may provide a great deal of survival improvement in cancer patients. There are many reports indicating amplified YB-1 expression in different types of cancers (Table I).

Any defect in transcriptional and translational processes may lead to tumorigenesis. Owing to this the multifunctional Y-box proteins might perform a significant part in the cell proliferation and cancer. The overexpression of YB-1 in cancer cells is an important biomarker for clinical outcome of the cancer patients and to an extrapolation it is assumed that the appearance of YB-1 in cell nuclei or its increased content in adjoining tissues of tumor is an indication of the aggressiveness and advanced stages as suggested by many cancer studies (Ha et al., 2015). A number of genetic links between YB-1 and other genes have been discovered indicating the part of YB-1 during tumor initiation and advancement. A connection between YB-1 and breast tumor-initiating cells has been found suggesting YB-1 induced CD44 and CD49f expression results in the growth and resistance in breast tumor-initiating cells (To et al., 2010). But still, it is not possible to find a link between YB-1 expression with the clinical pathological symptoms. Initially it was considered that YB-1 overexpression in different malignancies or during YB-1 nuclear localization and expression is related to various proliferation markers. Later it was suggested that the transient and stable suppression of YB-1 results in an increased cell population in the G1 phase (Wang et al., 2015). At the same time, an increased YB-1 expression was also found to be associated with hyperplasia (To et al., 2010). Many mechanisms suggest the ways through which YB-1 can influence the cell proliferation. Such as, it can regulate the synthesis of the proteins directly involved in the DNA replication and/or it can regulate the amount of proteins which promote the cell cycle progression (Uchiumi et al., 2006). Other than cell proliferation YB-1 can protect the cancer cells from apoptosis (Schittek et al., 2007) by inhibiting p53 ability.

The role of YB-1 in cancer is gaining importance now-a-days. There are studies in different types of cancers on the role of YB-1 for its involvement in tumor differentiation (Fotovati et al., 2011), tumor invasion (Schittek et al., 2007), lymph node metastasis (Guo et al., 2015), initiation and progression of cancer (Schittek et al., 2007). Many research groups are working in YB-1 as a therapeutic target for different types of cancers. The present body of knowledge shows that YB-1 imparts a major part in tumorigenesis and progression. Table I depicts functions of YB-1 in different phases of cancer progression. The prognostic value of YB-1 in different phases of tumor development has been discussed below:

YB-1 and colorectal cancer

Colorectal cancer is amongst the most frequent malignancies across the world and third foremost cause of deaths. For colorectal cancer patients with regional invasion, the 5-year survival rate is 70.4% and for distant metastasis 12.5% (De Santis et al., 2014). The overexpression of YB-1 has been enforced to be more frequent in the malignant tissues than normal tissues among most of the colorectal cancers (Yan et al., 2014). In a recent qRT-PCR study on 32 paired primary

Table I

Role of YB-1 in cancer initiation and progression pathways

Stage of cancer progression	Type of cancer	*In vivo/in vitro*	Expression Nuclear/ cytoplasmic	Interactive gene	Remarks	Reference
Initiation	Breast cancer	*In vivo, in vitro*	Nuclear	CD44, CD49f	Enhanced self-renewal, mammosphere growth	(To et al., 2010)
	Glioblastoma	*In vivo, in vitro*	Nuclear, cytoplasmic	CD44, CD49f	Association of YB-1 with undifferentiated state of neural stem cells and brain tumor initiating cells	(Fotovati et al., 2011; Faury et al., 2007)
Proliferation	Multiple myeloma	*In vivo, in vitro*	Nuclear	Ki67	Expressed in anaplastic MM cells, disease progression, drug resistance	(Chatterjee et al., 2008)
	Prostate	*In vivo, in vitro*	Nuclear	RSK, AR, MTA1	Knockdown of YB-1 sensitizes cancer cells for chemotherapy	(Shiota et al., 2013; Shiota et al., 2014; Adhami et al., 2013; Sheridan et al., 2015)
	Malignant non-Hodgkin lymphomas	*In vivo*	Cytoplasmic	Overexpressed YB-1	Shorter progression free survival and low survival rate	(Szczuraszek et al., 2011)
	Breast cancer	*In vivo, in vitro*	Nuclear	Overexpressed YB-1	Transgenic mice model, mitotic failure and centrosome amplification	(Bergmann et al., 2005)
	Ovarian cancer	*In vivo, in vitro*	Nuclear, Cytoplasmic	CyclinA, CXCL12-CXCR4	-	(Oda et al., 2007)
Angiogenesis	Brain tumors (tumor vessels), glioblastoma	*In vivo*	Nuclear, Cytoplasmic	CD34, Ki67	High expression of YB-1 in glomeruloid microvascular endothelial cells solid tumors	(Kim et al., 2013) Lenz et al., 1990)
	Epithelial derived ovarian cancer cells (hypoxic conditions)	*In vitro*	Nuclear	Proangiogenic genes, VEGF-A, CXCL12	Overexpression of YB-1 is linked to poor survival rate	(Basaki et al., 2007; Kryczek et al., 2005)
	Stomach and colon cancer	*In vivo*	Nuclear and cytoplasmic	CD34, Ki-67	Overexpresses YB-1 results in resistance to oxaliplatin	(Tsofack et al., 2011)
Invasion, metastasis and epithelial mesenchymal transition	Renal cell carcinoma	*In vivo, in vitro*	Nuclear	EZH2	Overexpression of YB-1 and EZH2 has been found to be significantly related to RCC stage and metastasis	(Wang et al., 2015)

Table I

Role of YB-1 in cancer initiation and progression pathways (Cont.)

Stage of cancer progression	Type of cancer	*In vivo/in vitro*	Expression Nuclear/ cytoplasmic	Interactive gene	Remarks	Reference
	Sarcoma	*In vivo, in vitro*	Nuclear	HIF1α, G3BP1	Reduced YB-1 expression in sarcoma is related to reduced Stress Granule formation	(Somasekharan et al., 2015)
	Bladder cancer	*In vivo*	Nuclear	Twist1	Promotes bladder cancer growth invasiveness and metastasis	(Shiota et al., 2011)
	Non-small cell lung cancer	*In vivo, in vitro*	Nuclear, cytoplasmic	p53, CyclinD1	Irregular cell cycle and tumor progression	(Sacco et al., 2012; Petrakis et al., 2012)
	Breast cancer	*In vitro*	Nuclear, cytoplasmic	MT1, MMP, vimentin, E-cadherin, HoxC6, Mnt, PRICKLE1, Snail1, Twist, Zeb2	Cellular proliferation and epithelial phenotype, activation of mesenchymal gene expression program	(Evdokimova et al., 2009; Lovett et al., 2010)
	Colorectal cancer	*In vivo, in vitro*	Nuclear	E-cadherin, N-cadherin, Snail, Slug, Twist, Zeb2	Cellular proliferation and epithelial phenotype	(Yan et al., 2014)
	Gastric cancer	*In vivo, in vitro*	Nuclear	Akt-LOH of PTEN	Activation and overexpression of YB-1	(Oki et al., 2007)
Stem cell like properties	Breast cancer	*In vitro*	Nuclear	Her2, Sox2, P63, *CD44, CD10, CD24, CD49f*	Basal like breast cancer phenotype	(Stratford et al., 2007; Lovett et al., 2010)
	Glioblastoma	*In vivo, in vitro*	Nuclear, cytoplasmic	Nestin, Musashi, Bmi1	Stem cell like phenotype	(Fotovati et al., 2011; Tania et al., 2014)

colorectal cancer and matched normal tissues, a significantly higher YB-1 mRNA expression was detected in cancerous tissues as compared to control as confirmed by immunohistochemical studies showing high YB-1 staining in colorectal cancer tissues. The YB-1 mRNA expression was increased in 26 (81.3%) of colorectal cancer patients and the patients with overexpressed YB-1 had lower overall survival ($p = 0.002$), and disease free survival ($p = 0.001$) as compared to their matched normal counterparts (Yan and Yan, 2014).

Chromatin immunoprecipitation assays have revealed that YB-1 preferentially regulates 62 genes involved in cell cycle control including transcription of CCNB1 in HCT116 colorectal cancer cells (Jürchott et al., 2010). Dual-specificity phosphatase (DUSP6) has feedback regulatory effect on MAPK cascade which is essential to outline its biological action irrespective of primary mode of activation. The YB-1 has been found to regulate DUSP6 indicating its role in MAPK cascade (Blüthgen et al., 2009). Moreover, the relationship between YB-1 and RTK/RAS (Jürchott et al., 2010) pathway including the down-stream effectors of RAS, ERK and AKT has been worked upon by many researchers. For breast cancer, such studies have anticipated the association of YB-1 in epithelial cell transformation by AKT pathway (Sutherland et al., 2005) and role of YB-1 as a target for ERK down-stream kinases RSK1 and RSK2 (Astanehe et al., 2012). These findings may be extrapolated to the colorectal cancer cells where YB-1 inhibition studies have specified mediation of YB-1 functions by ERK and/or RSK1/2.

Moreover, YB-1 overexpression in SW480 colon cancer cells results in resistance to oxaliplatin. In YB-1cDNA clone with Tandem Affinity Purification (TAP) construct the resistance was elevated due to 1.7-fold higher YB-1 expression than SW480 cells. Thus, indicating the role of YB-1 in cancer resistance. The cells which expressed TAP-YB-1 were accumulated in G2/M phase thus affecting mitosis. Further, knockdown studies revealed that siRNA against non-POU domain containing actamer binding (NONO) and RALY hnRNP -associated with lethal yellow homolog (mouse) steadily increase the responsiveness of oxaliplatin in SW480 and HT29 colon cancer cells (Tsofack et al., 2011). NONO codes for an RNA binding protein which is involved in a number of nuclear processes like transcriptional regulation and RNA processing along with dsDNA break repair (Dong et al., 2009). RALY, a heterogeneous nuclear ribonucleoprotein gene family member is linked to the spliceosome complex (Jurica et al., 2002).

YB-1, NONO and RALY proteins share a common biological process of mRNA processing (Jurica et al., 2002; Tsofack et al., 2011). In YB-1 overexpressing oxaliplatin resistant colon cancer cell lines, RALY and NONO gene knockdown resulted in decreased YB-1 and drug resistance. Moreover, knockdown of NONO and RALY have resulted in increased sensitization to oxaliplatin in resistant cells (Tsofack et al., 2011).

A comparative YB-1 overexpression in 80 colorectal cancer to matched normal tissue samples has been observed to be associated with EMT. YB-1 was directly associated to N-cadherin and vimentin while a negative correlation with E-cadherin indicates its role in EMT in colorectal cancer. Moreover, in a study by Yan et al. (2014) in HT29 colorectal cancer cell lines YB-1 knock-down had negative result which confirms the association between YB-1 and epithelial to mesenchymal.

YB-1 and breast cancer

YB-1 is a strong forecaster of all breast cancer types and patient survival as compared to hormonal receptors (Habibi et al., 2008). 80% of primary breast tumors show a high copy number of chromosome 1 (Bergmann et al., 2005). HER2, luminal A, luminal B and basal like breast cancer (BLBC) are 4 categories of primary breast tumors (Sørlie et al., 2003). The basal like tumors are clinically known as 'triple negative' as they do not express estrogen receptor or progesterone receptor or amplified HER2 (Stratford et al., 2007). High nuclear expression of YB-1 is correlated with HER2 in cancer cells. HER2 overexpression is predictive for disease-free survival in breast cancer patients with lymph node positivity. HER2 overexpression is also predictive of poor prognosis in patients with gastric cancer (Bergmann et al., 2005).

YB-1 stimulates metastasis in MCF-7 breast cancer cells during slight changes in the cellular level and localization of MT1-matrix metalloproteinase protein (Lovett et al., 2010). Nuclear YB-1, complexed with activating protein (AP)-2 and p53, binds to the promoter of the metalloproteinase 2 gene and increases its expression (Mertens et al., 1998).

YB-1 induces breast cancer development in an animal model suggesting its oncogenic role and up-regulation of YB-1 mammary epithelial cells activates epithelial growth factor receptor pathway and induces epidermal growth factor-independent growth. During G1-S phase transition, nuclear localization of YB-1 takes place along with up-regulation of cyclin-A and cyclin-B linking YB-1 and breast cancer cell growth, which might contribute to poor prognosis (Mertens et al., 1998; Bergmann et al., 2005).

Moreover, a p-Akt-insensitive mutation into YB-1 reduces EGFR and HER2 expression which shows the possible interaction of YB-1 and EGFR/HER2 in human breast epithelial cells. No up-regulation of HER2 was observed in YB-1 overexpressed human breast epithetlial cells while EGFR was up-regulated suggesting that HER2 and YB-1 are not directly linked (Berquin et al., 2005).

A recent study shows an association between elevated cytoplasmic expression of YB-1 with tumor aggressiveness and poorer patient survival in early stage breast cancer. However, a direct relationship between nuclear YB-1 and aggressiveness of cancer was observed.

EGFR is considered as one of the hallmarks of the cancer as it is highly expressed in BLBC. YB-1 up-regulates EGFR mRNA and protein by binding to the enhancer sites of EGFR-gene in ER-positive MCF-7 cells (Mertens et al., 1998). S102 phosphorylation of YB-1 in DNA binding domain leads to its direct attachment to EGFR promoter in 1kb of transcription start site specifically to YRE located at -968 and -940. A penetrance rate of 100 % in mammary tumors has been observed with targeted YB-1 expression. Up-regulated YB-1 in breast cancer facilitates monolayer and anchorage independent growth. Thus, it shows a relationship between YB-1 and EGFR in BLBC (Mertens et al., 1998) as EGFR signals through MAPK pathway (Sinnberg et al., 2012) and p90 ribosomal S6 kinase also phosphorylates YB-1 (Stratford et al., 2008). Till date many growth promoting genes form YB-1 target (Jensen et al., 1999). The phosphorylation of YB-1 at S102 site is carried out by PI3K pathway as well as MAPK pathway (Sinnberg et al., 2012). As compared to AKT1 dependent phosphorylation, RSK1 and RSK2 are more specific in phosphorylating YB-1 at S102 (Startford et al., 2008). Researchers have also questioned the ability of PKC to phosphorylate YB-1.

In BLBC cell lines P-YB-1^{S102} was present along with RSK even in the absence of AKT indicating that MAPK pathway components and EFGR are associated more closely with the basal like subtypes and not to AKT1. The RSK is activated by ERK2 which subsequently activates YB-1 in basal like tumors. Further, direct phosphorylation of YB-1 by ERK2 at N-terminal transactivates VEGF (Coles et al., 2005).

Recent studies provide links that show relationship between CTCF (CCCTC-binding factor; Zinc finger protein) and YB-1 in tumorigenesis (Docquier et al., 2005; Ramli et al., 2012). CTCF a constituent of BORIS-CTCF family codes for a transcriptional regulator protein which negatively regulates *c-myc* oncogene without any genomic amendments in various cancers. CTCF is considered as a cancer-linked hot spot with a rearranged zinc finger domain in breast cancer (Filippova et al, 1998). YB-1 has been isolated as a potential CTCF-interacting partner from cell extracts which interacts with CTCF to form specific complexes (Chernukhin et al., 2000).

A comparative *in vitro* study on Tet-repressed YB-1 (HTRY) human mammary epithelial cells (HMECs) expressing YB-1 and Tet-repressed Lac-Z (HTRZ) LacZ-expressing control cell line showed an up-regulated YB-1 in HTRY cell lines as compared to HTRZ cell lines (Davies et al 2014). The study was conducted to study the transformation of human mammary epithelial cells into BLBC. YB-1 overexpressed cells were seen to have phenotypic changes such as formation of acini with lumen along with the expression of tumor initiation cell markers i.e. CD44, CD49f and BMI1 were expressed in earlier YB-1 overexpressed luminal cells (Davies et al., 2014).

Interestingly, YB-1 overexpressed cells showed features akin to invasive ductal carcinoma indicating invasive cell type transformation. Additionally mature HMEC cells with up-regulated YB-1 get transformed into TICs via activation of CD44, BMI1 and CD49f through p300-mediated chromatin remodeling. These cells were characterized as tumorigenic and basal like breast cancer cells. p300-mediated acetylation of 9th lysine residue (H3K9) on histone protein triggering effects resulted in BMI1, CD44 and CD49f overexpression in HMECs (Figure 2) (Davies et al., 2014). CDKN2A/p16INK4a is a CDK4 kinase inhibitor (Ichimura et al., 1996).

Furthermore, a study comprising 4,049 patient samples showed an immunopositivity in 41% samples and the patients were followed-up to 20 years. About 80% of the patients with negligible YB-1 showed survival for five years without any cancer recurrence while 60% of the patients having high YB-1 expression showed early cancer recurrence. Moreover, a survival of 90% in patients with low YB-1 and 75% in patients with high YB-1 also indicated predictive potential of YB-1. The prognostic potential and predictive value of YB-1 for relapse free survival was found to be higher as compared to HER2 or ER and had a greater risk for reduced breast cancer specific survival than HER2/ER. Moreover, a high expression of YB-1 and mammary gland tumor grade shows a relation in cancer specific survival and as in a low-risk group of 1,292 patients i.e. Grade I to II without any proof of lymph node association about 437 patients were found to be YB-1 positive and had more chances of death due to cancer (Habibi et al., 2008). Thus, the prediction of survival/disease even in the low-risk tumors is also possible by considering the prognostic potential of YB-1. Thus, YB-1 demonstrates a high prognostic and predictive significance in breast cancer as compared to other tumor biological factors (Grøndahl Hansen et al., 1993).

YB-1 and ovarian cancer

YB-1 makes a prognostic marker for ovarian carcinoma. In a study involving 40 primary ovarian tumors 30% samples show a positive nuclear YB-1 expression with a low survival rate (Kamura et al., 1999). In contrast, some studies indicate no significant overall survival difference in patients with epithelial ovarian cancers having high YB-1 nuclear expression and those having no YB-1 expression (Yahata et al., 2002). The clinico-

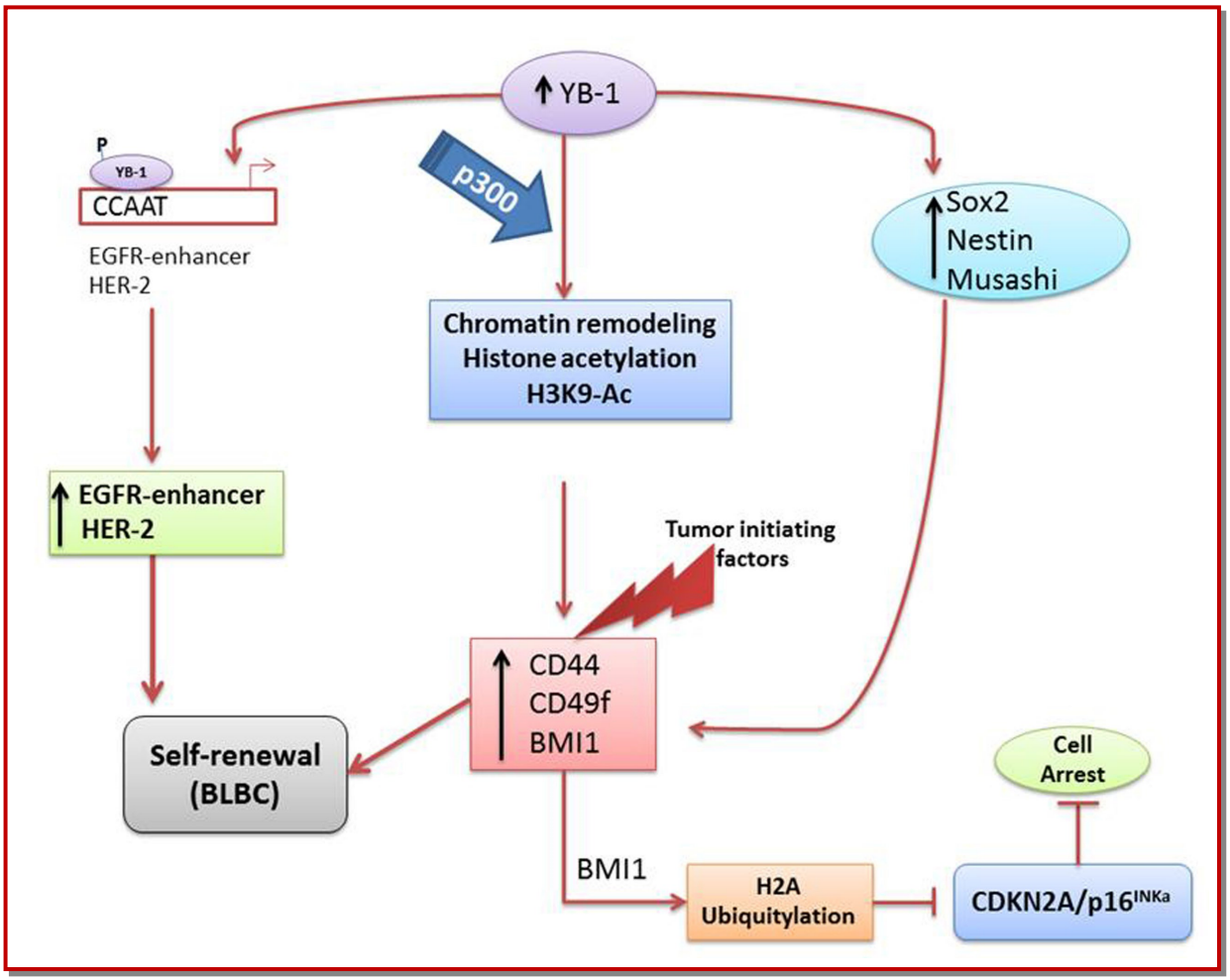

Figure: 2 Role of YB-1 in breast cancer tumor initiation and self-renewal

The p300-facilitated chromatin remodeling leads YB-1 binding to TIC-associated gene promoters. BMI1 induction results in histone H2A ubiquitylation and repression of CDKN2A (cyclin-dependent kinase inhibitor 2A) locus which is responsible for CDK4 kinase inhibition hence, $p16^{INK4a}$ mediated cell arrest inhibition. This consequently results in self-renewal and development of BLBC (Davies et al., 2014)

pathological studies support nuclear YB-1 association and malignant characteristics acquirement (Cybulski et al., 2015). Immunohistological studies show the association of YB-1 and p-Akt, P-gp and lung resistance-related vault protein/major vault protein in ovarian cancers (Basaki et al., 2007; Oda et al., 2007).

Another study shows the positive expression of YB-1 in 40% of the specimens out of 35 pairs of primary and matched recurrent cisplatin resistant ovarian lesions. The pre-therapeutic surgical specimens expressed cytoplasmic YB-1 while there was a nuclear YB-1 expression in post therapeutic specimens. Moreover, in cisplatin resistant ovarian KFr cell lines YB-1 expression was drastically increased in nucleus. YB1 nuclear translocation might be responsible for this cisplatin resistance. In human poorly differentiated epithelial ovarian cancers of advanced III and IV stage cyclin A expression has been found to be positively correlated to YB-1. Cyclin A has been reported to be overexpressed in aggressive tumor types (Yahata et al., 2002). Chemokine motif receptor 4 gene (CXCR4) has been observed to be up-regulated in human ovarian cancer cell lines by YB-1. A TATA box lies in the functional promoter region of CXCR4 gene along with transcription start site in 2.6kb 5'-up-stream region (Caruz et al., 1998). Moreover, a consensus Y-box-binding site (CCAT) is also present from -685 to -81 (Basaki et al., 2007). It is speculated that Akt mediated phosphorylation of YB-1 might be related to CXCR4 up-regulation for which chemokine motif ligand 12 (CXCL12) or chemokine stromal cell derived factor (SDF-1α) is a single natural ligand. CXCL12-CXCR4 interactions have been found to result in ovarian cancer cell proliferation (Oda et al., 2007).

In CXCR4 expressing cancers, CXCL12 is involved in outgrowth, metastasis and angiogenesis. CXCR4 expression is up-regulated by many factors including VEGF. Regulation of VEGF by Akt or Akt mediated over-

expression of VEGF is associated with CXCR4 expression. CXCR4 has been shown to up-regulate the phosphorylation of Akt and increased VEGF expression. Moreover, a high VEGF/VEGF receptor and EGF/EGF receptor expression has been observed in ovarian cancers and CXCR4/CXCL12-VEGF axis has been found to be involved in angiogenesis *in vivo* (Basaki et al., 2007; Kryczek et al., 2005). Thus, VEGF/VEGF receptor, EGF/EGF receptor and CXCL12-CXCR4 receptor crosstalk may also result in triggering of angiogenesis and cell proliferation in ovarian cancers.

YB-1 and hepatocellular carcinoma

Hepatocellular carcinoma stands at the fifth position in most regular malignancy and forms third cause of neoplastic mortalities all over the world (Andrade et al., 2009; Parkin et al., 2005). Major etiological factors include Hepatitis B virus, alcoholism and aflatoxicosis (Bosch et al., 1999). Lakhtakia et al, (2003) developed the *X15-myc* transgenic mice for HCC which has bicistronic expression of truncated HBX (viral x protein) and c-*myc 1* (Lakhtakia et al., 2003). The higher expression of these proteins develops the liver cancer between 20 and 28 weeks in mice through modulating various signaling pathways. Transcriptomic profile of *X15-myc* transgenic mice were analyzed which clearly indicates that the transcriptomic level of YB-1 was increased and coupled with various proteins involved in cell cycle progression, apoptosis and other growth related genes (Lakhtakia et al., 2003; Fatima et al., 2012). A number of studies are available to cite akin relation between hepatocellular carcinoma and chronic inflammation (Parkin et al., 2005; Yan et al., 2014). Chronic inflammation due to viral infections induces liver cirrhosis subsequently progressed to hepatocellular carcinoma (Yan et al., 2014). Our tissue microarray studies with hepatitis and hepatocellular carcinoma human tissue samples clearly suggest overexpression of YB-1 in both hepatitis and hepatocellular carcinoma samples. Moreover, YB-1 expression was high in HCC tissues when compared with hepatitis hence it is suggested that the YB-1 level is increasing while hepatocellular carcinoma tumor progression (Gunasekaran and Ganeshan, 2014).

Furthermore, a study on 82 hepatocellular carcinoma patients with surgical resection of hepatocellular carcinoma shows an affirmative connection between YB-1 and HCC progression. Both nuclear and cytoplasmic YB-1 expression has been found in metastatic liver cancer. About 65 out of 82 samples were positive for only cytoplasmic and 8 out of 82 for both nuclear and cytoplasmic expression of YB-1. Also YB-1 positive cell number was high in hepatocellular carcinoma as compared to the cirrhotic hepatocytes of non-tumorous regions from the same liver. Moreover, nuclear YB-1 expression is seen to be associated with portal vein invasion stage advancement (III and IV) of hepatocellular carcinoma. Follow-up study of 34 YB-1 positive (cytoplasmic and nuclear) patients showed major disproportion in the death rate between nuclear YB-1 positive and negative cases. Poor survival observed in nuclear positive cases was correlated with invasion and metastasis (Yasen et al., 2005).

Interestingly, siRNA mediated inhibition of YB-1 reduced the prostaglandin (PGE_2)-induced invasion in HCC cell lines (Huh7 and Hep3B). Moreover, PGE2 pretreatment to Huh7 and Hep3B cells resulted in increased YB-1 expression. Furthermore, EP1 receptor agonist 17-P-T-of PGE_2 pretreatment of HCC cells significantly increased YB-1 level *via* EP1 receptor. The EP1 receptor agonist activates p44/42 MAPK in a time dependent manner and the activation of EGFR and Src by PGE_2 also resulted in the phosphorylation and activation of p44/42 MAPK which further increased YB-1 expression. Another fact revealed by this study was the involvement of mTOR pathway (with mTOR complex 1) which is responsible for YB-1 overexpression by 17-P-T-PGE_2 agonist. Further, YB-1 was also associated with the overexpression of EMT associated genes namely vimentin, snail, t-Erk, and reduced level of E-cadherin (Zhang et al., 2014).

Recently, in a cohort of 140 hepatocellular carcinoma patients about 41.4% samples were found to smad 7 expression associated with YB-1 overexpression showing a positive correlation ($p<0.0001$). A nuclear localization of both smad 7 and YB-1 indicated them as independent predictors associated with poor patient outcome. Their expression was found to interfere with the tumor suppressive activities of TGFβ in hepatocellular carcinoma cell lines (Feng et al., 2015).

In another well defined cohort study, fragment of YB-1i.e. YB-1/p18 was isolated from the plasma of the patients with different cancers and leukemia (Tacke et al., 2014). The fragment of 18kDa was the CSD with peptides corresponding to aa81-137 of YB-1 protein. There was almost undetectable p18 in the plasma of normal human, patients with inflammatory diseases, renal or hepatic failure. In another heterogenous group of patients with different malignancies an increased positive rate of p18 occurrence in plasma of cancer patients was detected as compared to other tissue markers. YB-1 deregulation is a frequent attribute seen in tumor tissues as is explained by seropositivity of YB-1/p18 in various cancer patient samples. Such finding suggest that de-regulated YB-1 might be freed in the circulation as fragments, though the release of theses fragments is not specific for the cancer type and/or stage (Tacke et al., 2011; Tacke et al., 2014).

Earlier reports indicated the presence of p18 fragments in the patients with chronic liver diseases including hepatocellular carcinoma and advanced liver carcinoma (Tacke et al., 2011). Such studies put YB-1/p18 forward

to be considered as a potential preliminary prognostic marker, may be for the high risk population.

YB-1 and multiple myeloma

Till date no much information is available regarding the task which YB-1 plays in multiple myeloma. YB-1 expression in normal premalignant, malignant and precursor plasma cell *in situ* was studied by Chatterjee, et al. (2008). Immunohistochemical studies exposed that YB-1 is strongly expressed in bone marrow cells and in subset of multiple myeloma samples *in vivo*. No expression was seen in normal, premalignant and plasma cells from patients with monoclonal gammopathy of unknown significance (MGUS). YB-1 was localized in the cytoplasm as well as nucleus of the YB-1$^+$ MM cells and expression of YB-1 in multiple myeloma cells was correlated with a proliferative phenotype as an enhanced proliferation rate was observed. Expression of YB-1 was positively interrelated with Ki-67 expression which is an excellent marker for determination of growth fraction in multiple myeloma cells *in situ*. Moreover, knockdown of YB-1 induced apoptosis and reduced proliferation rate in INA-6MM and MM1s cells on treatment with pSUPER-derived siRNA indicating YB-1 functioning in cellular proliferation and its prognostic values in MM (Chatterjee et al., 2008).

Moreover, multiple myeloma patients have been shown to express an MYC activation signature. MYC mRNA translation involving YB-1 in multiple myeloma is associated with MYC-IRES mutation. YB-1/MYC co-expression in malignant plasma cells shows a clinical relevance of YB-1 in disease progression. Moreover, the expression of MYC mRNA is independent of IRES mutation and depends on YB-1 expression. This forms a feed-forward loop in which MYC is responsible for YB-1 expression and YB-1 regulates MYC translation (Bommert et al., 2013).

YB-1 and prostate cancer

Prostate cancer is the most universal non-cutaneous cancer and the second foremost cause of cancer-related death in the male population (Bhardwaj et al., 2012). Although most prostate cancers are initially androgen dependent and respond well to androgen-deprivation therapy, but the relapse rate to such therapies is high which leads to castration resistance due to aberrant activation of androgen receptor signaling. This may happen due to AR overexpression, mutation, AR-co-regulators, activators or activation of AR-signal transduction pathway. *De novo* androgen synthesis may also result in resistance (Karantanos et al., 2013). YB-1 has been found to be overexpressed in human prostate cancer tissues during tumor progression, and even after androgen ablation in a mouse xenograft model (Shiota et al., 2013).

Ribosomal S6 kinase family (RSK1, RSK2, RSK3 and RSK4) proteins hinder apoptosis by defending mitochondrial veracity and regulate proliferation as well as patient survival in many human cancers at elevated levels (Stratford et al., 2008; Sulzmaier and Ramos, 2013).

RSK1 and RSK2 are up-regulated in prostate cancer and RSK2 regulate the phosphorylation of YB-1 and its activity (Stratford et al., 2008). Indirect YB-1 inhibition by inhibiting its upstream kinase RSK2 suppresses androgen receptor up-regulation and abolishes AR induction (Suzuki et al., 2003; Shiota et al., 2014a; Shiota et al., 2014b).

The signaling cascade of RSK/YB-1 upregulates androgen receptor, targeting which can inhibit receptor elevation and androgen-deprivation therapy could yield better results (Shiota et al., 2014a; Shiota et al., 2014b). This may provide a promising therapeutic target to overcome castration resistance. Moreover, targeting YB-1 or YB-1 upstream kinases also increases sensitivity of prostate cancer cells towards chemotherapeutic drugs.

Many translationally regulated mRNAs direct vital cellular functions necessary for cancer progression. PI3K-Akt-mTOR translational targets including YB-1 and chromatin remodeling protein metastasis associated-1 (MTA-1) protein can endow prostate epithelial cells with invasive potential and are essential to preserve the invasive qualities of prostate adenomcarcinoma. Specific alterations in the activities of the translational machinery driven by oncogenic signaling pathway direct tumor initiation and progression in prostate cancer via aberrant translation of distinct mRNA networks, which includes YB-1 and MTA1 (Adhami et al., 2013; Sheridan et al., 2015). A recent study shows a very early YB-1 requirement in prostate tumorigenesis as YB-1 expression was found to be increased in PC in a step-wise manner from normal epithelium to pre-invasive prostatic intraepithelial neoplasia and cancer. On the other hand MTA1 expression was up-regulated in cancer tissues only. The elevated levels of YB-1 and MTA1 have been observed early in disease pathogenesis within prostatic intraepithelial neoplasia lesions prior to the development of invasion and metastasis. Thus, identification of MTA1 and YB-1 as prognostic biomarkers may help clinicians to prognosticate the aggressive nature of a prostate adenocarcinoma. High levels of YB-1 and MTA1 within prostatic intraepithelial neoplasia lesions are significantly associated with a shorter time to cancer relapse as well as a 3-fold increase for the requirement of future androgen deprivation therapy or radiation therapy (Sheridan et al., 2015). This may help for the prediction and sorting out of the patients who require future androgen deprivation or radiation therapy.

Recently, small non-coding RNAs of class miRNA have

been studied for their role in prostate cancer due to their tumor suppressive activity. MiR-190a is a member of miRNA family which is present at tail intron site of 2 genes at 15q22.2. In LNCaP and LNCaP/DHT prostate cancer cells a down-regulated expression of MiR-190a by androgen receptor protein upon androgen treatment was seen. miRNA expression is inversely related to androgen receptor protein expression and miRNA down-regulates androgen receptor in prostate cancer as the level of MiR-190a in androgen receptor positive prostate cancer cell lines was amplified. Thus, MiR-190a inhibits AR transactivation while YB-1 works as an androgen receptor activator in PC. Luciferase studies show that YB-1 is a possible target for miR-190a which specifically interacts with YB-1 through 3′-UTR direct binding. Overexpressed miR-190a hampers YB-1 expression in prostate cancer cells and consequently AR-expression is also down-regulated *in vitro*. Similar types of results were observed in prostate tumor growth *in vivo*. Direct binding of androgen/AR to the androgen receptor element in miR-190a promoter inhibits miR-190a expression. Thus, AR/miR-190/YB-1 cascade constitutes an auto-regulatory negative feedback loop in PC (Xu et al., 2015).

YB-1 and renal cell carcinoma

Renal cell carcinoma is one of a major health problem owing to the poor survival rate of about 9% for 5 years in case of metastatic conditions. About 33% of renal cell carcinoma patients develop metastasis at diagnosis which is a reason for poor prognosis (Singer et al., 2013).

Histone modification is a crucial phenomenon happening in a multiplicity of human cancers. YB-1 has been found to elevate the level of enhancer of zeste homolog 2 (EZH2), a histone methyl transferase (HMT) (Jenuwein and Allis, 2001; Müller et al., 2002).

Augmentation of EZH2 gene locus and its overexpression has been correlated with several malignancies (Cai et al., 2011; Yu et al., 2014). Overexpression of YB-1 and EZH2 has been found to be considerably interconnected with renal cell carcinoma stage as well as metastasis. Overexpression of YB-1 is concomitant with renal cell carcinoma incidence and aggressiveness. Immunological and inhibition studies confirmed the correlation of YB-1 and EZH2 in renal cell carcinoma (Wang et al., 2015). Moreover, YB-1 has been found to promote the bladder cancer growth invasiveness and metastasis, and is positively correlated to Twist1 (Shiota et al., 2011). Twist1 can enhance the life span of mesenchymal cells of bone marrow origin and induces EZH2 recruitment to regulate histone methylation (H3K27me3) through the *Ink4A/Arf* gene locus (Cakouros et al., 2012). Expression of EZH2 is directly correlated to the expression of Twist1. Twist1 is considered as an oncogene which can interfere with p53 and related pathways. Twist1 silencing by siRNA induces G1 arrest and apoptosis while the YB-1 expression by YB-1 plasmid co-transfection can rescue Twist1 siRNA-induced cell arrest. This proposes YB-1 as a down-stream target for Twist1. Twist1 has been found to be overexpressed in metastatic cancers as shown in Figure 3 (Shiota et al., 2011).

Moreover, YB-1 legalizes cancer cell invasion and its knockdown reduces renal cell carcinoma proliferation while YB-1 suppression induces G1 phase arrest. A down-regulated YB-1 is correlated with reduced STAT3 level in renal cell carcinoma on treatment with cycloheximide (CHX; a translational inhibitor) suggesting a proteasomal degradation dependent reduction of STAT3 in renal cell carcinoma *in vivo* and *in vitro* (Takeuchi et al., 2013). STAT3 has been found to be phosphorylated at S727 in variety of cancers through a process transcriptionally regulated by YB-1 (Yeh et al., 2006). Furthermore, PI3K/AKT mediated phosphorylation at S21 of EZH2 results in an increased STAT3 activity. The phosphorylation of EZH2 results in STAT3 methylation and thus its activation by phosphorylating tyrosine residue (Kim et al., 2013). It has been reported that the immune modulatory properties of STAT3 obstruction can improve the therapeutic effectiveness of IFN-α immunotherapy in murine melanoma model (Takeuchi et al., 2013).

YB-1 and lung cancer

An amplified expression of YB-1 positively controls cyclin D1 expression in non-small-cell lung cancers. Intrinsic YB-1 binds to the cyclin D1 promoter and may regulate the transcription of cyclin D1 gene (Harada et al., 2014). Moreover, YB-1 expression was also correlated with CDC6 which binds to ORC-origin complex and forms pre-replication complex (Sacco et al., 2012). Overexpression of CDC6 increases genomic instability (Petrakis et al., 2012). Cyclins and associated cyclin-dependent kinases form basic cell-cycle control apparatus. Cyclin D1 is an important factor to promote G1 to S transition (Harada et al., 2014; Kanie et al., 2012). Cyclin D1 activation in G1 phase is dependent on growth factors like EGF and IGF, estrogens and angiotensin II. Thus, an increased YB-1 level may increase the level of cyclin D1 leading to irregular cell cycle and tumor progression (Harada et al., 2014; Kanie et al., 2012). In another report high nuclear expression of YB-1 was correlated with the non-small-lung cancer where the survival rate was very low. Patients with nuclear YB-1 and p53 mutations were found to have worst prognosis with a median survival of 3 months while the non-nuclear but high YB-1 expression patients showed a better survival of 15 months (Gessner et al., 2004). This indicates that nuclear expression of YB-1 and more aggressive stages of non-small-lung cancers are interrelated. Correlation of nuclear YB-1 expression and clinicopathological markers exposed a connection of nuclear YB-1 expression with metastasis and tumor

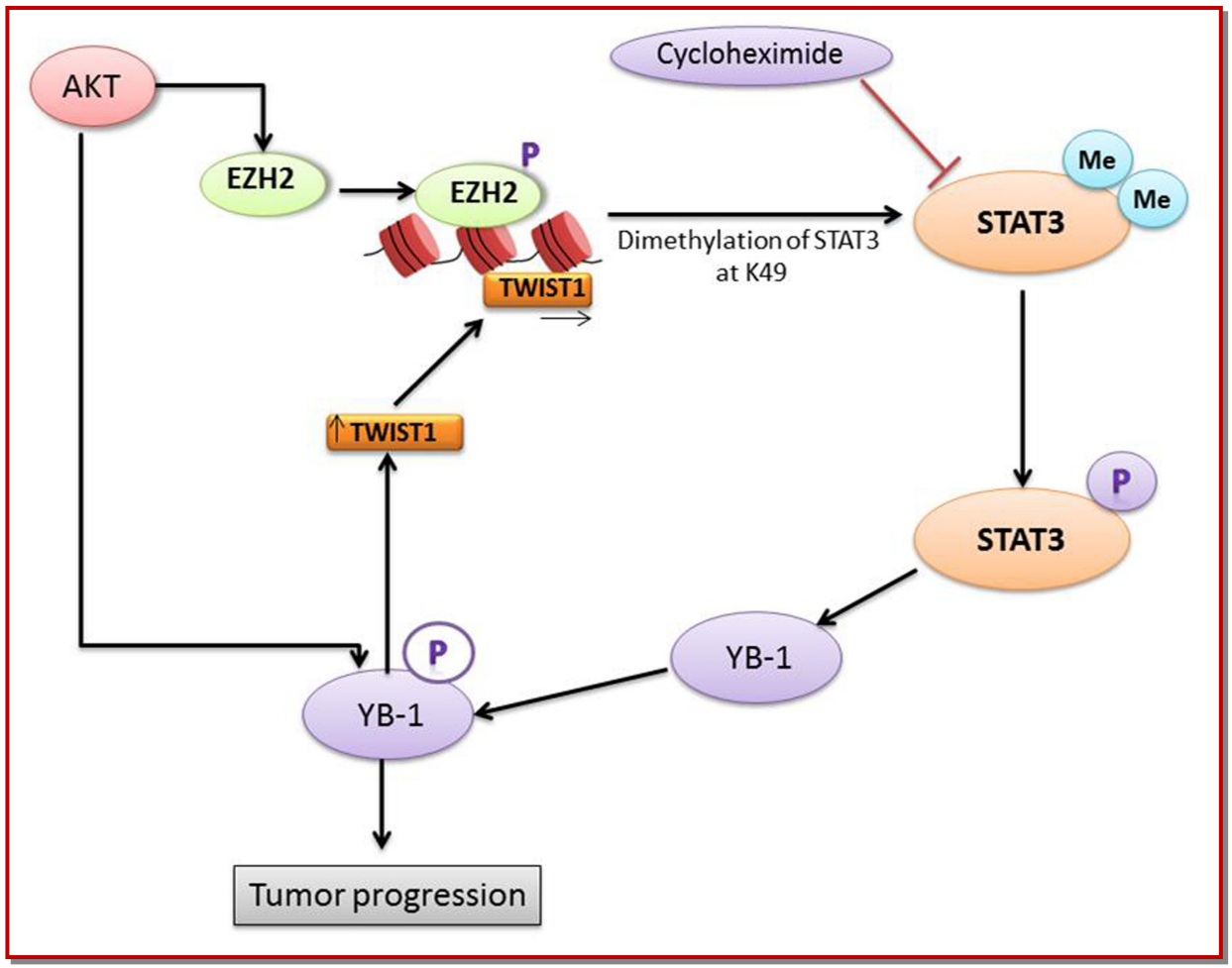

Figure: 3 Role of YB-1 in metastasis

Twist1 regulates AKT2 gene expression and might be involved in AKT1 regulation which is involved in YB-1 phosphorylation and metastasis (Shiota et al., 2011)

stratification.

YB-1 and brain cancer

About one third of YB-1$^{-/-}$ homozygous mice embryos were found to display abnormal brain development while no abnormalities were observed in the heterozygote littermates. To study YB-1 expression in the brain Unkrüer et al, (2009) transcardially perfused the brain tissue from a six year old adult male macaque (*Macaca fascicularis*) in 0.1 M phosphate buffer and processed. Other than this, 3 µm thin tissue sections of hippocampus from a former neuropathological study were used to evaluate the YB-1 expression in human brain. Neurons show a predomi-nant YB-1 expression adult rat, macaque and human brains. YB-1 has been found to be imperative for the maintenance of mouse neuronal stem cells (Unkrüer et al., 2009). Fotovati et al., (2011) found a high expression of YB-1 in sub-ventricular zone of normal E14 mouse tissues. In the adult brain, neuronal stem cells were found to be mostly limited to the sub-ventricular and sub-granular zone of the dentate gyrus. In rat brain, the YB-1 is found to be highly expressed in the dentate gyrus, cornua-mmonis pyramidal cell layer and layer III of the piriformcortex. Neuronal YB-1 expression in explicit brain areas ranges to the adult brain and amounts relevant altitudes in the adult rat, macaque and human brain (Unkrüer et al., 2009). However, a decline in the YB-1 brain expression in the postnatal phase has been described (Funakoshi et al., 2003). Main localization of YB-1 in the cytoplasm indicated existence of a large sub -fraction of YB-1 in an efficient reserve state which can be activated by various stress signals. *In vitro* hippocampal and mouse brain studies also showed a primary cytoplasmic localization of YB-1 (Funakoshi et al., 2003; Spitkovsky et al., 1992).

There are different types of brain cancers depending on their origin in the brain. Amongst all brain cancers glioblastoma is the deadliest. Though there are many chemotherapy and surgical treatments available, still the survival rate of glioblastoma patients is very less

(Mrugala, 2103). To find an answer to reduced survival and cancer recurrence a great deal of research on the cancer stem cells is needed. For brain cancer stem cells many signaling pathways have been identified at transcriptional and protein level. The brain cancer stem cells have been observed to activate various YB-1 targeted signaling pathways in cancer stem cell, such as STAT3, NFκB, PKB/AKT and MAPK/ERK (Wu et al., 2007; Jürchott et al., 2010). In addition to function as a transcription factor YB-1 also activates gene expression of the EGFR, MMP-2 and of the receptor tyrosine kinase c-MET associated with tumor cell adhesion, invasion and metastasis (Davies and Dunn, 2011). Moreover, the YB-1 expression is also controlled by Twist1 and Twist1 is transcriptionally regulated by STAT3 and plays a major role in EMT, maintenance of cancer initiating cells and MDR (Cheng et al., 2008; Tania et al 2014).

In a study on thirty two pediatric glioblastoma a poor survival of patients was found to be associated with increased YB-1 expression as the patients with comparatively high nuclear YB-1 survived for a small period of time (minimum 1 month and maximum 36 months) post surgery as compared to those with relatively less YB-1 expression. The YB-1 expression was correlated with Akt, Ras pathways, EGFR and poor patient outcome (Faury et al., 2007). A new study reveals the relation between YB-1 in glioblastoma where the association of Golgi phosphoprotein 3 (GOLPH3) and YB-1/mTOR pathway has been studied. GOLPH3 is involved in cell invasion and positive correlation with YB-1 expression and mTOR activity (Zhang et al., 2015). Moreover, down-regulation of YB-1 increases the chemosensitivity of glioblastoma to temozolomide (Zhang et al., 2014).

As far as, the part which YB-1 plays in brain tumor initiation is concerned, no much data is available on this front. There is a report available which shows that hindering YB-1 protein expression delays onset of cancer in mice. The same study also states that YB-1 takes part in tumor initiation, with CD44 expression in breast TICs (To et al., 2010).

YB-1 and gastric cancer

Throughout the world gastric cancer stands at fifth position and still the number of cancer patients is increasing. AKT mediated phosphorylation of YB-1 has been found to induce resistance in gastric cancer patients to various chemotherapy drugs. High expression of phosphorylated AKT has been found to be associated with the nuclear expression of YB-1. Loss of heterozygosity (LOH) of tumor suppressor phosphatase and tensin homolog deleted on chromosome 10 (PTEN) has also been found to mediate YB-1 activation along with AKT (Oki et al., 2007). Moreover, YB-1 overexpression is related to N (lymph node) stage ($p<0.001$), M (metastatic) stage ($p = 0.013$), TNM (tumor node metastasis) stage ($p<0.001$) and microvessel density ($p<0.001$) in vascular endothelial cells in 163 surgically resected primary gastric cancer patients as compared to matched controls (Wu et al., 2014). A role of YB-1 in metastasis has also been studied in gastric cancer. A strong immunoreactivity and staining to YB-1 in 29.6% gastric cancer samples out of 98 cases was observed which was more common in intestinal/non-scirrhous cancer along with significant vascular invasion, metastasis and reduced disease free survival (Wu et al., 2012).

An association between angiogenesis and YB-1 overexpression in gastric cancer cells has been observed. For extensive tumor growth vascular supply is required. Vascular endothelial growth factor (VEGF) imparts a significant role in angiogenesis (Byrne et al., 2005), and a targeted inhibition of VEGF pathway in angiogenesis may provide a room for cancer therapeutics (Niu and Chen, 2010). Another study shows inhibition of cell migration on YB-1 silencing by ~60% at 48h post transfection ($p = 0.048$) in NUGC3 GCC. Moreover, the overexpression of YB-1 has been linked to the aggressiveness of gastric cancers which links the prognostic importance of YB-1 with its overexpression (Guo et al., 2013).

YB-1 and malignant non-Hodgkin's lymphomas

Malignant non-Hodgkin's lymphomas is ranked sixth amongst all the malignant tumors (Skarin and Dorfman, 1997; Szczuraszek et al., 2011). Prognostic protocols involve histopathological, mitotic, immunophenotypic and karyotypic studies. YB-1 was found to be only localized in the cytoplasm of the 56 untreated non-Hodgkin's lymphomas patients. Though no relation between YB-1 and clinicophatological variables have been found for non-Hodgkin's lymphomas but the survival analyses showed a smaller progression free survival in the patients with elevated YB-1 expression (Szczuraszek et al., 2011). This makes YB-1 a strong cytoplasmic and novel unfavorable prognostic marker to explore the importance of YB-1 in non-Hodgkin's lymphomas .

YB-1 and melanoma

Malignant melanoma incidence has been rapidly increased in the last few decades. Up-regulated YB-1 expression and protein tanslocation in nucleus of metastatic melanoma cells has been found in SKMEL28 melanoma cells. A reduced YB-1 expression resulted in the diminished expression of many genes of proliferation pathways e.g. MMP-2, bcl-2, cyclin D1, p53 and p16INK4A, AKT. Moreover, p21CIP1 (CDK inhibitor) protein was up-regulated. Furthermore, in SKMEL 28 melanoma cells YB-1 down-regulation caused significantly ($p<0.01$) increased sensitivity (~2-

fold) to chemotherapeutic drugs like cisplatin and etoposide and apoptosis (~6-fold). In a human tissue microarray with 100 melanocytic lesions, PI3K/AKT mediated YB-1S102 phosphorylation and activation were observed while NF-κB signaling inhibited YB-1 phosphorylation. Further, it has been shown that, in early senescence the cells accumulate G1-specific CDK inhibitors p16InK4a and p21Cip1 as a result of YB-1 paucity (Schittek et al., 2007).

YB-1 is important in the melanoma inhibitory activity/ cartilage derived retinoic acid-sensitivity protein (MIA/ CD-RAP) dependent regulatory region of the $p54^{nrb}$ promoter which plays a role in chondrocyte differentiation and cartilage development. A small, secreted protein MIA/CD-RAP is involved in cartilage differentiation and melanoma progression which is secreted by melanoma cells and chondrocytes. p54nrb acts as a mediator of MIA/CD-RAP action to promote the progression of malignant melanoma (Schmid et al., 2013).

YB-1 in other cancers

In skin cancer studies, *in vitro* immortalized HaCaT keratinocytes irradiated with UVB-20 mJ/cm^2 once in a week for 10 weeks, YB-1 overexpression has been observed along with reduced apoptosis. An increased Ser102 phosphrylation is observed in transformed cells which show reduced cdk6 and increased MMP and PCNA expression (Syed et al., 2014). Furthermore, YB-1 has been found to be overexpressed in cisplatin resistant-KB-cells and oral squamous cell carcinomas. In anaplastic thyroid carcinoma a strong YB-1 expression in cytoplasm and nucleus with high immunoreactivity in cytoplasm also suggests a prognostic role of YB-1 in tumor stratification as comparatively less YB-1 overexpression was detected in follicular and papillary thyroid carcinoma (Ito et al., 2003).

In synovial carcinoma also nuclear YB-1 has been suggested as an independent prognostic factor because of a positive correlation with poor survival, high TOPO II α labeling and association with P-glycoprotein expression in relation to multidrug resistance (Oda et al., 2003).

YB-1 is a potential therapeutic target for cancer

Currently there are many ways of cancer treatment available such as radiation therapy, surgery and chemotherapy but all the treatments have significant drawbacks. For decades, chemotherapy is the first choice of cancer treatment by delivering cytotoxic agents into the cancer cells. However, severe side effects, multidrug resistance and cancer stem cells are the major obstacles for chemotherapy towards successful cure (Kuo, 2009). Targeted cancer drugs or "molecularly targeted drugs" block growth and cancer spread by prying with specific molecules involved in tumor growth and progression (Mubeen and Kini, 2012). To develop such targeted therapies identification of potential targets which play an important role in cancer progression and survival is must. This review extensively discusses the various strategies being investigated to assess the promising role of YB-1 as a therapeutic target.

Inhibition of YB-1-HER2/EGFR axis

YB-1 has been considered as a bonafide oncogene due to its ability to cause mammary tumor development with high penetrance rate in the transgenic mice (Bergmann et al., 2005). Accumulating evidences clearly show that YB-1 could be a prognostic biomarker of high importance and various advancements in therapeutic strategies targeting YB-1 may provide a great deal of survival improvement in cancer patients. YB-1 has been identified to be overexpressed in aggressive type of breast cancers which induces growth promoting genes such as HER-2 (Shibao et al., 1999), EGFR (Stratford et al., 2007), PCNA (Syed et al., 2014), cyclin A and cyclin B (Jürchott et al., 2003).Inhibition studies show that the YB-1 inhibition suppresses growth of cancer cell lines even in the triple negative breast cancer (Stratford et al., 2007). YB-1 silencing by siRNA in seven breast cancer cell lines including HER2 positive and triple negative cell lines shows ~50% growth inhibition in two HER positive cell lines such as BT474-m1 and Au565 and also ~40 to 80% growth suppression was observed in cell line with triple negative characteristics. In HER2 positive cell lines, the growth inhibition was due to the down-regulation of EGFR, HER2 and ERK1/2 signaling by YB-1. Inhibition of YB-1 in HER2 positive cell lines BT474 mL and Au565 showed that the decrease in the phosphorylation of STAT3 at S727 site and its downstream gene MCL-1. But YB-1 silencing did not affect the actual concentration of STAT3 and also its downstream target survivin (Lee et al., 2008). It was previously reported that YB-1 transcriptionally activates HER2 and ERK which facilitate phosphorylation of STAT3 but is not involved in transcriptional activation of STAT3. Moreover, the reduced $P\text{-}STAT3^{S727}$ correlated with the decreased signaling through $P\text{-}ERK1/2^{T204/Y204}$, $mTOR^{S2448}$ and total mTOR even in the triple negative SUM149 breast cancer cells. Phosphorylation of STAT3 results in cancer cell protection from apoptosis and increase in proliferation. Thus, inhibition of YB-1 and subsequent STAT3 phosphorylation perturbs the cancer cell growth in cell lines and also in establishment of tumors in mice (Lee et al., 2008). Increased expression of cell cycle inhibitors like p21, p16 and p53 on reduced cyclin D1due to YB-1 inhibition also shows the role of YB-1 in targeted therapy (Yu et al., 2010). RNAi-mediated down-regulation of YB-1 has been observed to result in decreased IL-6 expression and increased epithelial like

cell characteristics (Castellana et al., 2014). IL-6 has been found to be implicated in tumor cell metastasis and is known as an EMT inducer (Sullivan et al., 2009). Reduction in IL-6 by YB-1 knockdown may help in improving therapeutic approach.

Inhibition of YB-1 – RSK axis

The p90 ribosomal S6 kinases, RSK1 and RSK2 take part in activating a broad range of substrates related to cell proliferation, motility and survival in breast cancer. RSK signaling deregulation may play a role in pre-neoplastic to neoplastic progression. Recently RSK2 has been reported to be a leading molecular target for triple negative breast cancer. RSK2 is a predominant kinase which carries out phosphorylation of YB-1 at S102 (Stratford et al., 2007). After phosphorylation P-YB-1 translocates to nucleus and promotes the induction of growth factors like EGFR, HER2 (Lee et al., 2008; Wu et al., 2015) and MET receptor (Finkbeiner et al., 2009) as well as tumor initiating cell associated genes CD44 and CD49f (To et al., 2010). Tumor initiating cells are resistant to chemotherapies and radiation therapy and have a high capacity to initiate tumor formation and hypothesized as the root cause of cancer recurrence. YB-1 binding to the promoters of tumor initiating cells induces the expression of specific genes in tumor initiation. Moreover, YB-1 silencing resulted in decreased CD44 expression and increased sensitivity to chemotherapeutics (To et al., 2010). Further, Notch signaling pathways play important roles in development and cell fate determination in mammary gland. Notch4 isoform mRNA levels were found to be highest in undifferentiated bipotent human mammary progenitor cells and decrease upon differentiation (Raouf et al., 2008). Aberrant expression of the active intracellular domain of Notch4 (N4ICD) has been observed to prevent differentiation and induce mammary carcinomas in mice. Nuclear YB-1 binding to the promoters of various stem-cell-associated genes including Notch4 has been observed. This makes YB-1as a promising molecular target for the treatment of aggressive forms of breast cancer (Reipas et al., 2013).

Inhibition of YB-1 – FAK axis

Focal adhesion kinase is a non-receptor tyrosine kinase having a vivacious role to play in many oncogenic trails (Owens et al., 1995; Golubovskaya, 2010). Augmented focal adhesion kinase expression has been stated in many tumors like colon, ovary and breast cancers and its inhibition sensitizes cancer cells to chemotherapy (Owens et al., 1995). Higher tumor expression of YB-1 and FAK has been found to be associated with higher cancer mortality. Moreover, tumors with high focal adhesion kinase were found to have high YB-1 nuclear expression. Focal adhesion kinase inhibitor VS-6063 results in focal adhesion kinase inhibition which subsequently leads to AKT and YB-1 inhibition (Kang et al., 2013). Thus, indirect inhibition of YB-1 through focal adhesion kinase inhibition may provide alternative therapeutic strategy to overcome resistance.

Inhibition of YB-1–topoisomerase 1 axis

Certain topoisomerase targeted drugs have been found to obstruct the breakage and rejoining function of topoisomerase enzymes via enzyme/drug/DNA complex formation. Such drugs can be used as anticancer agents. The accumulation of drug-induced cleavable complexes in cancer cells may be cytotoxic and of therapeutic importance. Recent reports have assessed the control mechanisms for cellular sensitivity to topoisomerase targeted drugs. YB-1 and topoisomerase 1 are imperative for stress responses in cells and maintenance of genomic stability. Consequently, the interaction between YB-1 and topoisomerase 1 has important inferences in cancer chemotherapy response (Wu et al., 2014). Currently, camptothecin has been observed to increase YB-1-topoisomerase 1 complex generation in prostate cancer cells. The increased complex formation is almost equal between 4 and 24 hours incubation post camptothecin exposure even at minimal concentration. Moreover, an inhibition in camptothecin induced YB-1-topoisomerase 1 complex formation was observed after treating cells with antioxidant N-acetylcysteine. However, no significant changes were observed in the expression levels of YB-1 and topoisomerase 1 after 4 hours drug treatment. Thus, interaction of YB-1 and topoisomerase 1 is influenced by drug-induced oxidative stress. YB-1-topoisomerase 1 association shows no significant difference in prostate cancer cells treated by adriamycin. Adriamycin acts differently to camptothecin which acts by targeting topoisomerase 1, increases reactive oxygen species formation which induces DNA damage in cancer cells. While adriamycin targets topoisomerase 2 without resulting in oxidative stress as evidenced by unchanged apoptotic potential of adriamycin even after anti-oxidant treatment in cancer cells (Wu et al., 2014).

Small molecules targeting YB-1

So far, very few molecules are reported to interact directly with YB-1 and reduce the activity of YB-1. Various surface plasma resonance spectroscopy studies exposed that interaction between YB-1 protein and some small molecules from natural resources exists and inhibits the YB-1 oncogenic activities some of such active compounds are luteolin (Reipas et al., 2013), fisetin (Adhami et al., 2013; Khan et al., 2014), grape seed procyanindin (Zhao et al., 2013) and *Morus alba* (white mulberry) root extract (REM) (Choi et al., 2013) which are having potential anticancer activity against various cancers both *in vitro* and *in vivo.*

Luteolin

Luteolin, a flavonoid analogue (Lin et al., 2008) has been found to successfully knockdown (~80%) the P-YB

-1 protein by interacting with critical ATP binding residues in RSK1 and suppress the growth of both triple negative breast cancer cell lines in monolayer, soft agar and mammosphere culture conditions. It also inhibits the growth of CD44+/CD24- cells in monolayer and mammospheres. Inhibition of RSK2 also has a potent inhibitory effect on the triple negative breast cancer growth. RSK2 inhibitors like eriodictyol have been identified so far to suppress RSK2 activity. Several studies are available that show inhibitory effects of luteolin on NF-κB signaling in breast cancer. Thus, luteolin has its effects on tumor suppression through many pathways which can prevent the development of the *de novo* resistance in cancer cells. Such inhibitors in combination with chemotherapy drugs could be used for the treatment of multidrug resistant tumor types (Reipas et al., 2013).

Fisetin

Another biochemical flavonoid compound fisetin (Adhami et al., 2013) has been tested for its YB-1 inhibitory effect. This molecule interacts with cold shock domain of YB-1 and inhibits its phosphorylation at Ser102 both *in vitro* and *in vivo*. Fisetin has been found to reduce the YB-1 overexpression induced EMT like characteristics in non-tumorigenic prostate cells. Forced overexpression of YB-1 resulted in EMT in non-tumorigenic prostate cancer cells. Fisetin is a dual inhibitor of both PI3K/Akt pathways which is one of the major kinase for YB-1 phosphorylation. Molecular docking experiments showed direct interaction of fisetin with CSD of YB-1 which is important for binding of kinases and phosphorylation to activate YB-1. Binding of fisetin to YB-1 results in topology changes in YB-1 and inhibition of Akt mediated YB-1 phosphorylation. Akt weakens the cap binding properties of YB-1 by phosphorylating YB-1 and facilitates translational activation of silenced mRNA which includes EMT related mRNA. TGFβ induced EMT is also inhibited by fisetin through mTOR pathway (Khan et al., 2014). This shows that fisetin results in inhibition of YB-1 and TGFβ induced EMT which makes it a potential candidate for combinational chemotherapeutics.

Grape seed procyanindin

Grape seed procyanindin is a polyphenol flavonoid compound having wide range of biological activity including antiviral, anti-inflamatory and anti-allergic action. Grape seed procyanindin blocks the function of p-gp and reverse the MDR in blood brain barrier; likewise it reverses the drug resistance in paclitaxel resistant overian cancer cell. Grape seed procyanindin has been found to inhibit the expression and function of MDR1 in A2780/T paclitaxel resistant ovarian cancer cells. The down-regulation of MDR1 was mediated by the inhibition of NF-κB and MAPK/ERK mediated cascade in grape seed procyanindin treated cells. Grape seed procyanindin inhibited activation of NF-κB and MAPK/ERK inhibition resulted in the suppression of cytoplasm to nuclear shuttling of YB-1 thereby decreased the MDR1 expression. Also, grape seed procyanindin has led to the inhibition of IκB-α activity which is related to the NF-κB activation (Zhao et al., 2013).

Morus alba root extract

White mulberry or *Morus alba* root extract, has also been studied for its anti-MDR properties in doxorubicin resistant MCF7 cell line. It has been shown to inhibit YB -1 dependent MDR1 expression by JNK1/2 activation. Chromatin immunoprecipitation and luciferase assays confirm that root extract inhibits YB-1 binding to the MDR1 gene promoter. REM induced JNK1/2 activation has been found to inhibit MDR1 at a concentration of 100 µg/mL when treated with root extract for 15 min as compared to untreated cells. Combination of doxorubicin and REM gives better response than the doxorubicin alone through reduced multidrug resistance and cell viability. Moreover, it modulates the drug efflux in doxorubicin resistant cell line and reduces cell viability through the activation of JNK-cJun/c-Fos pathway. Interestingly, root extract protects the doxorubicin induced cell death in H9c2 cardiac myoblast cells, however, kills the drug resistant cancer cells with no or less side effect of doxorubicin *in vivo* (Choi et al., 2013). Hence, targeting YB-1 is gathering great importance in the development of combination drug strategies with less toxicity.

Overexpression of YB-1 aids viral therapy

Among all the targeted cancer therapeutics replication-selective oncolytic adenoviruses are novel and very popular. The adenoviruses proliferate selectively in tumors and break them without any significant damage to other adjacent normal tissues (Parato et al., 2005). YB-1 facilitates E-1 free adenoviral duplication by directing the adenoviral E2-late promoter. In MDR cancer cells with nuclear YB-1 the replication of E1A-mutated adenovirus was found to be regulated by YB-1 (Holm et al., 2002). Deletion of the adenoviral E1B19K protein (Bcl-2 homolog) which blocks apoptosis induction has been found to increase the cancer cell death (Alemany, 2007). Many adenoviruses/modified adenoviruses have been developed like d1520, Ad-Delo3-RGD (modification of d1520) to treat cancer cells. Ad-Delo3-RGD replication was found to be dependent on nuclear YB-1 as knockdown of YB-1 by shRNA reduced the replication rate. For combinational therapy adenoviruses are not potential enough though some chemotherapy drugs have been found to upsurge the replication efficiency of adenoviruses. Moreover, in nuclear YB-1 overexpressed brain cancer stem cells which show high CAR expression effectual viral duplication and cell killing was observed on treatment with Ad-Delo3-RGD under normoxic and hypoxic conditions. Ad-Delo3-RGD kills differentiated cancer cells along with CD44 high/CD24

low breast cancer and CS133 high glioma cancer stem cells. Moreover, in mouse model of TMZ resistant R28 CSC intracranial glioblastoma showed a prolonged survival when treated with Ad-Delo3-RGD. Thus, YB-1 can facilitate viral replication and can form a potential target for viro therapy even for cancer stem cells (Mantwill et al., 2013).

Conclusion

The survey of the existing knowledge about YB-1 overexpression suggests its role and prognostic importance in different types of human cancers. Moreover, it gets more significance in late cancer stages and aggressive tumor types. YB-1 expression studies will not only help in prognosis but also in cancer stratification and thus treatment. The YB-1 nuclear expression and occurrence of resistance can help in overcoming the problem of poor prognosis. Association of YB-1 expression with epithelial mesenchymal transition and CSCs/TICs can be extrapolated to anticipate tumor recurrence. Improvement in clinical cancer diagnosis criterion by considering YB-1 can enhance the therapeutic approach and survival rate. Further researches based on large samples are needed to assign significant clinical importance to YB-1. As far as YB-1 mediated therapy is concerned many small inhibitor based therapies have evolved besiding the conventional molecular targeted therapies and immunotherapies. Virotherapy is another upcoming area which sought great attention. To get YB-1 accepted as a clinical prognostic marker in practice lot of evidences are there but a lot more of research is needed towards YB-1 based therapeutics.

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Conflict of Interest

Authors declare no conflict of interest

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