MINI-REVIEW

Significance of the Y-box proteins in human cancers

Ken Matsumoto¹ and Boon-Huat Bay²*

¹Laboratory of Cellular Biochemistry, RIKEN (The Institute of Physical and Chemical Research), 2-1 Hirosawa, Wako, Saitama 351-0198, Japan. ²Department of Anatomy, Faculty of Medicine, National University of Singapore, 4 Medical Drive, Blk MD 10, S 117 597, Singapore

*Correspondence to: Boon-Huat Bay, Email: antbaybh@nus.edu.sg, Tel: +65 6874 6139, Fax: +65 6778 7643

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ABSTRACT

Y-box proteins belong to the cold shock domain family of proteins that are known to be involved in both transcriptional and translational control. Here, we give a brief overview of the structure, regulation and physiological functions of the Y-box proteins. This is followed by examining the role of Y-box protein 1 (YB-1), the most extensively studied of the Y-box protein in tumorigenesis, and its clinicopathological significance. YB-1 has the potential to be a prognostic marker and predictor of chemoresistance in human cancers.

KEYWORDS: YB-1, structure and regulation, tumorigenesis, clinicopathological significance, prognostication, chemoresistance

INTRODUCTION

Deregulation of proper transcriptional and translational control triggers tumorigenesis. Several multifunctional proteins are involved in both transcriptional and translational control (Wilkinson and Shyu, 2001). Here we focus on a family of such multifunctional proteins, the Y-box protein family, in terms of its significance in cell proliferation and cancer. As different aspects of the Y-box proteins have already been reviewed (Matsumoto and Wolff, 1998; Swamynathan et al, 1998; Evdokimova and Ovchinnikov, 1999; Kohno et al, 2003), we briefly appraise the structure and functions of the Y-box proteins with the emphasis on recent findings. We then summarize the role of a Y-box protein YB-1 in cancer and its use in the clinical setting.

Y-box proteins (or Y-box binding proteins) are so named because they were originally identified as DNA binding proteins that are capable of associating with the Y-box (inverted CCAAT-box) sequence of the major histocompatibility complex class II gene. Y-box proteins have thus far been known to regulate positively or negatively a number of genes, such as multidrug resistance 1, cyclin A, cyclin B1, matrix metalloproteinase 2 and collagen alpha2(I) (Higashi et al, 2003a; Jurchott et al, 2003; Kohno et al, 2003). However, members of Y-box protein family are also found in the cytoplasm and associated with mRNAs as major components of messenger ribonucleoprotein particles. Y-box proteins regulate translation in a dose-dependent manner; low concentrations of Y-box proteins activate translation and high concentrations repress it (Evdokimova and Ovchinnikov, 1999). Collectively, Y-box proteins have been implicated in the regulation of mRNA metabolism in multiple steps in both the nucleus and the cytoplasm, including transcription, splicing, mRNA stability and translation.

Structure and cellular localization of Y-box proteins

Y-box proteins consist of three domains: the N-terminal domain, the cold shock domain (CSD) and the C-terminal tail domain (Figure 1). The CSD is a highly conserved nucleic acid binding domain that confers RNA- and single-stranded and double-stranded DNA binding activities to the Y-box proteins. Both the short N-terminal and the C-terminal tail domains are less conserved among the Y-box proteins. The charged C-terminal tail domain of vertebrate Y-box proteins, con-
sisting of alternating clusters of acidic/aromatic and basic amino acids, is likely to account for its RNA-binding activity and ability for associating with various proteins. Y-box proteins have been shown to interact with a number of cellular and viral proteins that are involved in various cellular processes (Figure 2).

**Figure 1.** Schematic diagram depicting the structure of the Y-box protein. ++ and -- indicate clusters of basic and acidic/aromatic amino acids. Functions attributed to each domain are summarized at the bottom.

**Figure 2.** Cellular and viral proteins that interact with the Y-box protein. Numbers in parentheses indicate the references as follows: (1) Shnyreva et al, 2000, (2) Kohno et al, 2003; Swamynathan et al, 1998 and references therein, (3) Higashi et al, 2003b, (4) Safak et al, 1999, (5) Zou et al, 1997, (6) Kojic et al, 2004, (7) Chansky et al, 2001, (8) Moraes et al, 2003, (9) Funke et al, 1996, (10) Raffetseder et al, 2003, (11) Wilhelm et al, 2000, (12) Matsumoto et al, 2005, (13) Balda et al, 2003, (14) Moorthamer et al, 1999, (15) Matsumoto and Wolff, 1998; Evdokimova and Ovchinnikov, 1999 and references therein, (16) Balda and Matter, 2000, (17) Frankel et al, 2005.
In a variety of cell types, Y-box proteins are predominantly found in the cytoplasm. However, given that Y-box proteins regulate transcription, they are expected to localize to the nucleus. Y-box proteins are translocated into the nucleus by a number of conditions and mechanisms, including UV irradiation, hyperthermia, interferon-gamma treatment, adenovirus infection, interaction with p53 and a splicing factor SRp30c and high levels of ectopic YB-1 expression (Higashi et al., 2003a; Kohno 2003; Raffetseder et al., 2003 and references therein; Zhang et al., 2003). Both the CSD and the tail domains are implicated in nuclear localization of YB-1; the tail domain seems to contain a non-canonical nuclear localization signal and the isolated CSD also contributes to nuclear retention (Bader and Vogt, 2005). Y-box proteins are capable of nucleo-cytoplasmic shuttling, which allows them to contribute to the coupling control of transcription and translation. Y-box proteins become associated with nascent transcripts co-transcriptionally and are presumed to accompany mRNA into the cytoplasm (Soop et al., 2003). Interestingly, a mouse Y-box protein MSY2 preferentially associates with mRNAs that are transcribed from genes containing Y-box sequences in their promoter regions and stores those mRNAs in male germ cells (Yang et al., 2005a).

Regulation of the synthesis of Y-box proteins
Experiments with overexpression or down-regulation of the Y-box proteins in cultured cells or animals have shown that the amount of Y-box proteins must be precisely controlled (see below). Therefore, it is important to understand how the synthesis of Y-box proteins is regulated.

Recent data have shown that the synthesis of a Y-box protein, YB-1 (Y-box binding protein-1), is regulated both at transcriptional and post-transcriptional levels. YB-1 mRNA accumulates when cells are treated with cisplatin or UV irradiation (Ohga et al., 1996). Transcription of the YB-1 gene is stimulated by p73 through an enhanced recruitment of the c-Myc-Max complexes to E-box sequences in the YB-1 promoter (Uramoto et al., 2002). Once synthesized, YB-1 mRNA is negatively regulated by its own product. YB-1 protein represses translation of YB-1 mRNA by binding to specific elements in the 5' - and 3' untranslated regions (Fukuda et al., 2004; Skabkina et al., 2005). This self-regulation may contribute towards maintaining the concentration of YB-1 protein optimal in a cell.

Physiological functions of Y-box proteins
In human and mouse, there are three Y-box proteins, two of which are expressed in both somatic cells and germ cells (Table 1). The most extensively studied Y-box protein, YB-1, is ubiquitously expressed in various tissues. Human Contrin and mouse MSY2 are germ cell-specific members of the Y-box protein family. Analyses of the effects of targeting Y-box genes in chicken cells and mice have been widely carried out in the last three years. Chicken B-cell lymphoma DT40 cells are widely used to study functional consequences of disrupting specific genes because of the high frequency of homologous recombination. The YB-1 (or YB-1b) gene in DT40 cells has been disrupted by two independent groups of investigators; one group reported that YB-1(-/-) cells show slow-growth phenotype and increased DNA content (Swamyathan et al., 2002). The other group of researchers found that heterozygous disruption resulted in no growth defects but homozygous gene disruptants exhibited a slow and cold-sensitive growth phenotype (Matsumoto et al., 2005). One research group tried to disrupt YB-1 gene in mice but encountered difficulties in disrupting both alleles of the YB-1 gene (Shibahara et al., 2004). They found hypersensitivity of the YB-1(-/-) cells to genotoxic stresses. However, as was the case in chicken cells, another group recently reported homozygous YB-1 gene disruption, showing the importance of YB-1 in late stages of embryonic development (Lu et al., 2005). They observed developmental defects of YB-1(-/-) embryos after embryonic day 13.5 including craniofacial lesions, hemorrhage and respiratory failure, with YB-1(-/-) MEF cells showing premature senescence and hypersensitivity to different cellular stresses. The reason for the presence or absence of the haplo-insufficient phenotypes is currently unknown. In mice lacking MSY2, both male and female homozygotes are sterile, a consequence of disturbed spermatogenesis due to reduction of postmeiotic germ-cell mRNAs in male and oocyte loss in female (Yang et al., 2005b).

| Table 1. Y-box proteins in human and mouse |
|------------------------------------------|
| **Human** | **Mouse** | **Expression** | **Phenotype in knockout mice** |
| YB-1/DbpB | YB-1/MSY1 | Ubiquitous | Embryonic/perinatal lethality (neuroligical abnormalities, haemorrhage, respiratory failure and growth retardation)* |
| DbpA | MSY4 | Ubiquitous (abundant in heart, muscle and testis) | Unknown |
| Contrin | MSY2 | Germ cells | Male and female infertility** |

*Lu et al., 2005
**Yang et al., 2005b

Role of YB-1 in tumorigenesis
The role of YB-1 in cancer progression has attracted attention in recent years. YB-1 has been found to be upregulated during prostate cancer tumor progression (Gimenez-Bonafe et al., 2004). Increased YB-1 expression has been correlated with DNA topoisomerase IIα and proliferating cell nuclear antigen expression in human lung cancer (Gu et al., 2001) and colorectal cancer (Shibao et al., 1999) and linked to markers of cellular proliferation in osteosarcoma (Oda et al., 1998). YB-1 has been identified as a cell cycle stage-specific transcription factor (Jurchott et al., 2003). Nuclear accumulation of YB-1 in HeLa cells was demonstrated to transcriptionally activate cyclin A and B1 genes, which are crucial for cell cycle progression. Increase in cyclin A has been reported to be associated with poor clinical outcome in breast cancer (Michalides et al., 2002).

In addition, YB-1 is believed to promote metastasis by enhancing the transcription of gelatinase A, a matrix me-
alloproteinase that facilitates cell migration (Cheng et al, 2002). Recently, Berquin et al. (2005) has also shown that YB-1 may induce epidermal growth factor (EGF) independence in mammary epithelial cells via activation of the EGF receptor pathway, thereby contributing to breast tumor aggressiveness. In yet another recent paper, Bergmann and colleagues (2005), using a transgenic mouse model, showed that overexpression of YB-1 may cause breast cancer through the induction of genetic instability.

On the other hand, YB-1 may have anti-oncogenic activity as it is reported to be capable of blocking oncogenic cell transformation (Bader and Vogt, 2005). The phosphoinositide 3-kinase (PI 3-kinase) pathway is known to show gain of function in human cancers (Bader and Vogt 2004). The catalytic subunits of PI 3-Kinase, p110 (of which P3K is a homolog) and Akt are oncoproteins and YB-1 is specifically known to inhibit P3K and Akt-induced transformation involving protein synthesis (Bader et al., 2003). YB-1 may interfere with the synthesis of growth-related proteins including growth factors, receptors, kinases, transcriptional regulators and cell cycle proteins associated with P3K and Akt pathways (Zimmer et al, 2000; Bader and Vogt 2004).

A seminal paper describing YB-1 expression in cancer tissues was first reported by Royer’s group in breast cancer (Bargou et al, 1997). The pathological significance of YB-1 in a variety of cancers is shown in Table 2.

### Table 2. Overexpression of YB-1 and pathological significance in human cancers

| Organ      | Tumors                                                                 | Pathological Significance                                                                 | Reference             |
|------------|------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------|
| Breast     | Invasive ductal breast cancer                                           | Tumor aggressiveness and axillary lymph node positivity                                   | Huang et al, 2005     |
|            |                                                                        | Associated with progesterone receptor positivity but no prognostic value                  | Saji et al, 2003      |
|            | Breast cancer (histologic subtype not specified)                        | Higher risk for relapse without postoperative chemotherapy                               | Janz et al, 2002      |
| Ovary      | Surface epithelial neoplasms (serous, mucinous, endometroid & clear cell) | Co-expression with P-glycoprotein associated with poor survival                          | Huang et al, 2004     |
|            | Surface epithelial neoplasms (mainly serous)                           | Higher nuclear expression in recurrent lesions than in primary tumors                    | Yahata et al, 2002    |
|            | Serous adenocarcinoma                                                  | Poor prognosis                                                                            | Kamura et al, 1999    |
| Lung       | Nonsmall cell lung cancer                                              | Nuclear expression correlated with reduced survival                                        | Gessner et al, 2004   |
|            |                                                                        | Nuclear expression correlated with node metastasis, stage of the disease and poor prognosis | Shibahara et al, 2001 |
|            | Squamous cell carcinoma                                                | Poor prognosis                                                                            | Shibahara et al, 2001 |
|            | Adenocarcinoma                                                         | Associated with T3-4 and Stage II-IV tumors                                               | Gu et al, 2001        |
| Thyroid    | Anaplastic (undifferentiated) carcinomas, papillary carcinomas and follicular carcinomas | High expression in anaplastic carcinoma (known to be rapidly progressive)               | Ito et al, 2003       |
| Soft tissues | Synovial sarcoma                                                        | Poor prognosis                                                                            | Oda et al, 2003       |
| Large intestine | Colorectal adenocarcinoma                                               | Proliferation associated marker                                                           | Shibao et al, 1999    |
YB-1 and chemoresistance in human tumors

Substantial YB-1 expression was demonstrated in multidrug-resistant breast, gastric and pancreatic cell lines (Holm et al, 2004). Altered drug sensitivity to cisplatin, a very potent and widely used anti-cancer agent and mitomycin C has been observed following treatment of cells with antisense YB-1 (Ogga et al, 1996; Torigoe et al, 2005). Expression of YB-1 protein has been reported to reflect the chemosensitivity of ovarian serous adenocarcinoma (Kamura et al, 1999) and breast cancer (Janz et al, 2002; Huang et al, 2005). Increased nuclear localization of YB-1 has been observed in acquired cisplatin-resistant ovarian cancer (Yahata et al, 2002).

YB-1 expression has also been shown to be associated with P-glycoprotein (Pgp) expression in breast cancer cells resulting in drug resistance (Bargou et al, 1997; Saji et al, 2003; Huang et al, 2005). Pgp, encoded by the MDR1 gene, is a member of the ATP-binding cassette transporter superfamily of proteins involved in the protection of cells from xenobiotics and drugs (Kuwano et al, 2003). Pgp has become an important molecular target for limiting chemoresistance as it plays a major role in the development of multidrug-resistant tumor type and is known to mediate resistance to a wide range of anticancer agents (Kuwano et al, 1999). Bay and co-workers have recently demonstrated a direct interaction between YB-1 and Pgp using the computer-based Resonance Recognition Model (Huang et al, 2005). The same investigators observed the occurrence of raised recurrence rates in breast tumor patients with high YB-1 expression who underwent a chemotherapy regime which contained anthracycline (a Pgp substrate). Besides breast cancer, YB-1 has been correlated with Pgp in ovarian cancer (Huang et al, 2004), prostate cancer (Gimenez-Bonafe et al, 2004) and osteosarcoma (Oda et al, 1998).

YB-1 has been shown to bind p53 (Okamoto et al, 2000) and interaction with p53 could be necessary for the self-defense of cells exposed to DNA-damaging agents (Kuwano et al, 2003). As mentioned earlier, p73, a close relative of the p53 family, has also been observed to stimulate transcription of the YB-1 promoter by enhancing the recruitment of the cMyc-Max complex to its target gene (Uramoto et al, 2002). c-Myc, an oncogene with a dual function in cell proliferation and apoptosis can confer resistance to cisplatin. p73 is known to induce apoptosis (Irwin et al, 2000). and p73 overexpressing clones have been observed to be cisplatin resistant (Gong et al, 1999). Hence, c-Myc and p73 may form a complex necessary in YB-1 mediated drug resistance (Uramoto et al, 2002).

CONCLUSIONS

Expression of the YB-1 protein has a prognostic significance in determining disease progression in human cancers. Perhaps more importantly, YB-1 has the potential to be a biological marker which predicts chemotherapy resistance and aid in the selection of appropriate adjuvant chemotherapy. There has been cumulative evidence in the literature to suggest that YB-1 is involved in pleiotropic resistance to different classes of DNA-targeting drugs (Levenson et al, 2000). As clinical drug resistance hampers effective chemotherapy, a recent focus in cancer therapeutic strategy is to develop molecular cancer therapeutics (Kuwano et al, 2003; Holm et al, 2004). In this regard, YB-1 holds promise as target molecule for the development of novel approaches in overcoming multidrug resistance in cancer chemotherapy (Janz et al, 2002).

STATEMENT OF COMPETING INTERESTS

The authors declared no competing interests.

LIST OF ABBREVIATIONS

CSD: Cold shock domain
YB-1: Y-Box binding protein-1
EGF: Epidermal growth factor
PI-3: Phosphoinositide 3-kinase
Pgp: P-glycoprotein

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