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Review

YBX1 at the crossroads of non-coding transcriptome, exosomal, and cytoplasmic granular signaling

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ABSTRACT

YBX1 (Y box binding protein 1) is an RNA-/DNA-binding multifunctional protein harboring the classical cold shock protein (CSD) domain, an A/P domain, and a long C-terminal domain with alternating positively and negatively charged amino acids. It is a well-established oncogenic transcriptional factor, and regulates apoptosis, translation, cell proliferation, mRNA splicing, repair, differentiation, and stress response. The non-coding transcriptome has added yet another layer of complexity to the YBX1-mediated master regulation of cellular functions. Interestingly, YBX1 has been shown to localize to cytoplasmic granules such as P granules and stress granules. These granules regulate the non-coding transcriptome profile as well as mRNA translation and degradation. In this review, we discuss the recent findings on YBX1 signaling as mediated by various classes of non-coding RNAs, and on the functions of YBX1 at P granules, stress granules, exosomes, and mitochondria. YBX1 is a well-established target for cancer therapy and understanding its functions at organelles and ncRNA transcriptomes will shed new insights for devising organelle based anti-cancer therapies.

1. Introduction

Bacteria express cold induced proteins (Cips) containing an evolutionarily conserved cold shock domain (CSD) upon rapid decreases in temperature. This helps the cells to adapt to harmful effects of temperature shifts (Phadtare et al., 1999; Keto-Timonen et al., 2016). CSDs are nucleic acid-binding modules and are present in several prokaryotic and eukaryotic stress-induced proteins. One such eukaryotic stress protein that harbors a CSD belongs to the YBX family. Proteins in this family bind to the Y box sequence (5′-CTGATTGG-3′) on DNA (Prabhu et al., 2015). This family consists of three members, namely *YBX1 (Y-box binding protein 1)*, *YBX2 (Y-box binding protein 2)*, and *YBX3 (Y-box binding protein 3)*, whose genes are located on 1p34.2, 17p13.1, and 12p13.1, respectively (Prabhu et al., 2015). All three family members, which are involved in DNA- and RNA-binding functions, have an A/P rich domain (alanine/proline rich domain), a cold shock domain (CSD), and a long C-terminal domain with alternating positively and negatively charged amino acids (Eliseeva et al., 2011; Prabhu et al., 2015). Although they share structural similarities, their functions are diverse. YBX1 (Y box binding protein 1), also known as YB-1, is a multifunctional protein that regulates apoptosis, cell proliferation, differentiation, and stress response. YBX2, which is expressed in germ cells, regulates the stability of germ cell mRNAs, whereas YBX3, which is expressed during embryonic development, regulates several growth promoters (Prabhu et al., 2015). YBX3 is expressed in testis and Ybx3 null mice show reduced fertility and spermatid differentiation defects (Snyder et al., 2015).

YBX1 was discovered as a protein that binds to the Y box motif (5'-CTGATTGGCCAA-3') in the promoter of the major histocompatibility complex II gene *HLA-DRα* (Lyabin et al., 2014). Human *YBX1* codes for a 324-amino acid protein with a CSD that shares 44% homology with the cold shock protein A of *E. coli* (Goldstein et al., 1990). In addition to the Y box, YBX1 binds to the single-stranded motif GGGG and either single- or double-stranded forms of the motifs CACC and CATC and regulates transcription (Zasedateleva et al., 2002).YBX1 mediated gene regulation need not be only through transcriptional repression or activation, but through pre-mRNA processing since there are reports that YBX1 has affinity for RNA in addition to the Y box or GC rich elements on DNA (Dolfini and Mantovani 2013; Lyabin et al., 2014).It can regulate mRNA levels by influencing co-transcriptional events. This is seen in case of ABCB1 (ATP binding cassette binding subfamily B member 1) regulation where YBX1 has more affinity for APE1 and histoneacetyltransferase p300 associated with MDR1 than the Y box element on ABCB1 (Kaszubiak et al., 2007). The protein-protein interactome of

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