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Review

Functional relevance of SATB1 in immune regulation and tumorigenesis

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ABSTRACT

The Special AT-rich Sequence Binding Protein 1 (SATB1) is a chromatin organiser and transcription factor which regulates numerous cellular processes such as differentiation, proliferation and apoptosis through effects on gene expression. SATB1 undergoes various post-translational modifications, which determine its interaction with co-activators and co-repressors to induce regulation of gene transcription. SATB1 is an identified oncogene, its increased expression is associated with poor prognosis in many cancers. This paper provides a review on SATB1-mediated immune responses and on its target genes in the context of tumorigenesis and tumour progression. Specifically, we discuss the role of SATB1 in tumour immunity, Epithelial to Mesenchymal Transition (EMT), metastasis and multidrug resistance. Therapeutic targeting of aberrant SATB1 may be an important strategy in the treatment of cancer.

1. Introduction

The identification of key oncogenic regulators is critical in both defining mechanisms for carcinogenesis as well as for the development of strategies for the diagnosis and treatment of cancer clinically. The special AT-rich sequence-binding protein1 (SATB1) is a nuclear protein and an oncogene, which induces tissue-specific effects on gene regulation and is dysregulated in many cancers [1–3].

SATB1 is a known chromatin organiser and a global regulator of gene expression across various cell types. The genome is anchored to the nuclear matrix through the matrix attachment regions (MARS) [4]. SATB1 specifically binds to the AT-rich motifs of the MAR regions of double stranded DNA [5] and in doing so, it forms a “cage-like” network around heterochromatin, organising it into distinct loops [6–8]. These AT-enriched sites have base unpairing affinity and are known as base unpairing regions (BUR). SATB1 anchored to the BURs provides a docking site for chromatin remodelling proteins and transcription factors for the regulation of many genes [6–9] (Fig. 1). Thus, the nuclear organisation of SATB1 tightly controls long-range regulation of genes located distal to the SATB1 bound loci. Post-translational modification of SATB1 such as phosphorylation and acetylation are also important in regulating gene expression. These modifications serve as molecular switches, conferring onto SATB1 the ability to act as activator or repressor of gene expression [10,11].

The structure of SATB1 consists of six functional domains including; the nuclear localization signal (NLS) domain, the PDZ domain which facilitates protein interactions, the BUR-binding domain which contains the CUT1 domain and a part of CUT 2 domain, and the homeodomain (HD) which is a DNA binding motif (Fig. 2). The BUR and HD domains confer specific and high binding affinity to the core unwinding elements of BURs. Thus through these six domains, SATB1 exerts its function of global gene regulation.

SATB1 functions as gene activator or repressor through its interaction with the chromatin modifying enzymes at the PDZ domain. These interactions are context specific as they are determined by its post-translational modification [10–12]. The phosphorylation of SATB1 by protein kinase C (PKC) at serine186, regulates interaction of SATB1 interactionwith histone deacetylase 1 (HDAC1), increasing its DNA binding affinity and facilitating its function as a repressor of gene expression [10,13]. However, when SATB1 is dephosphorylated, it is acetylated by histone acetyltransferase P300/CBP-associated factor (PCAF), at lysine136. This results in unbinding of SATB1 from DNA, the dissociation of HDAC1 and the de-repression or activation of gene expression [11] (Fig. 3).

SATB1 is also regulated by small non-coding RNAs called microRNAs (miRs), which are post-transcriptional regulators of gene expression [14]. The increased expression of miR-191 in epidermal keratinocytes induces senescence through the downregulation of SATB1 and Cyclin Dependent Kinase 6 [15]. miR-191 also down regulates SATB1 to promote tumorigenesis in breast cancer [16]. Contrary to this,

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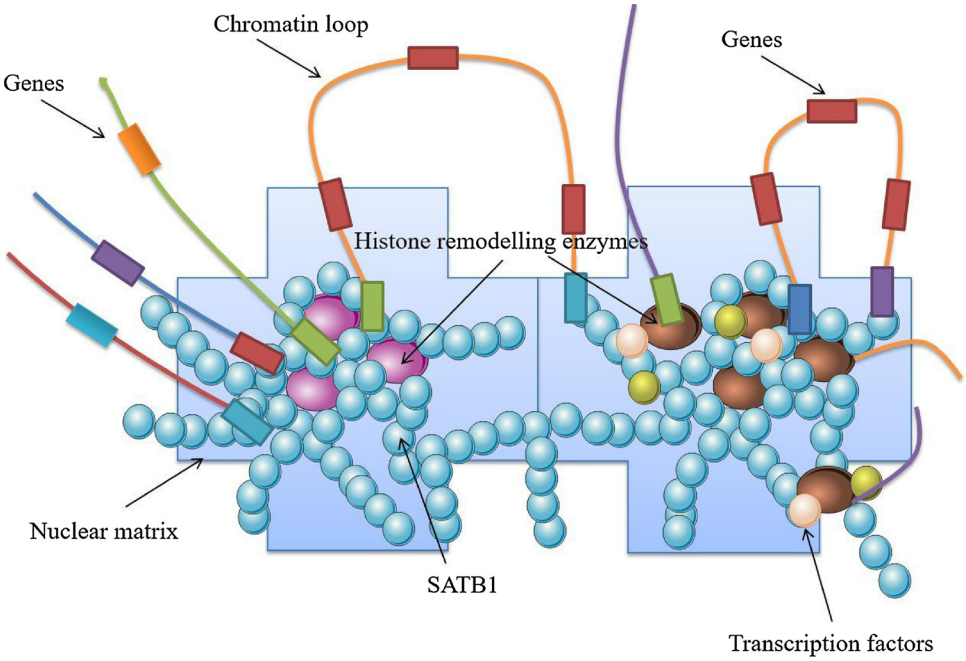

Fig. 1. SATB1 mediated chromatin loop formation. SATB1 forms chromatin loops through the anchoring of chromatin to the nuclear matrix and mediates long distance gene regulation providing docking sites for histone remodelling enzymes and transcription factors.
Figure adapted from [106].

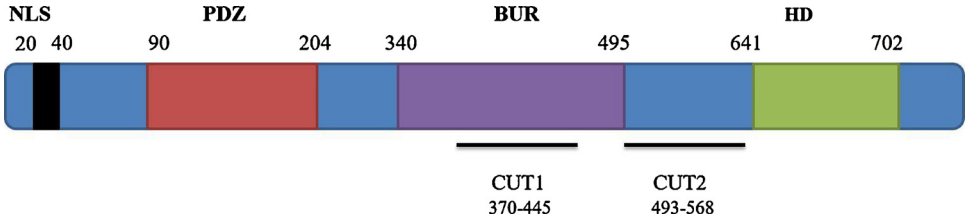

Fig. 2. Primary protein structure of SATB1 with its functional domains.
The nuclear localization signal domain (NLS), the protein binding domain PDZ, the Base Unpairing Region (BURs) and the DNA binding region, the homeodomain (HD). [Figure adapted from http://atlasgeneticsoncology.org/Genes/SATB1ID44225ch3p24.html].

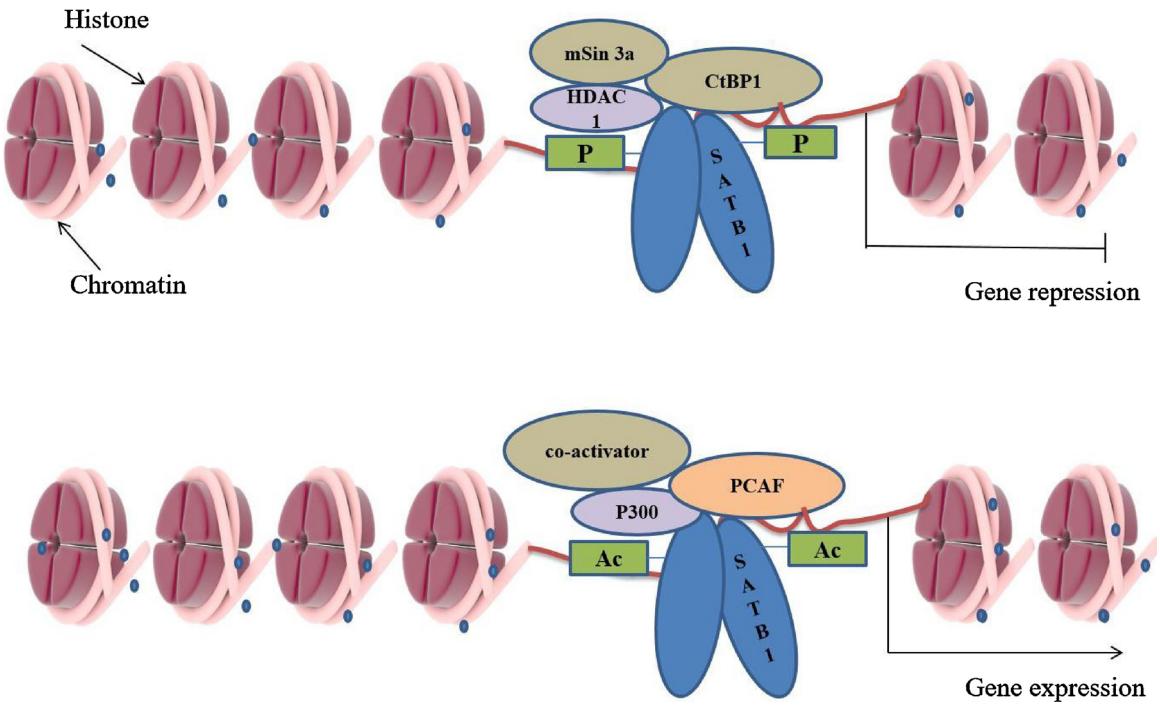

Fig. 3. Depicts post-translational modifications of SATB1-induced gene regulation. Phosphorylation of SATB1 leads to its interaction with histone deacetylase 1 (HDAC1) and CtBP1 resulting in repression of gene expression [10]. On de-phosphorylation, SATB1 is acetylated as it interacts with acetyltransferase PCAF, leading to the disassociation of HDAC1 and CtBP1 and activation of gene expression [11].

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