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REVIEW ARTICLE

SATB family chromatin organizers as master regulators of tumor progression

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Abstract

SATB (Special AT-rich binding protein) family proteins have emerged as key regulators that integrate higher-order chromatin organization with the regulation of gene expression. Studies over the past decade have elucidated the specific roles of SATB1 and SATB2, two closely related members of this family, in cancer progression. SATB family chromatin organizers play diverse and important roles in regulating the dynamic equilibrium of apoptosis, cell invasion, metastasis, proliferation, angiogenesis, and immune modulation. This review highlights cellular and molecular events governed by SATB1 influencing the structural organization of chromatin and interacting with several co-activators and co-repressors of transcription towards tumor progression. SATB1 expression across tumor cell types generates cellular and molecular heterogeneity culminating in tumor relapse and metastasis. SATB1 exhibits dynamic expression within intratumoral cell types regulated by the tumor microenvironment, which culminates towards tumor progression. Recent studies suggested that cell-specific expression of SATB1 across tumor recruited dendritic cells (DC), cytotoxic T lymphocytes (CTL), T regulatory cells (Tregs) and tumor epithelial cells along with tumor microenvironment act as primary determinants of tumor progression and tumor inflammation. In contrast, SATB2 is differentially expressed in an array of cancer types and is involved in tumorigenesis. Survival analysis for patients across an array of cancer types correlated with expression of SATB family chromatin organizers suggested tissue-specific expression of SATB1 and SATB2 contributing to disease prognosis. In this context, it is pertinent to understand molecular players, cellular pathways, genetic and epigenetic mechanisms governed by cell types within tumors regulated by SATB proteins. We propose that patient survival analysis based on the expression profile of SATB chromatin organizers would facilitate their unequivocal establishment as prognostic markers and therapeutic targets for cancer therapy.

Introduction

A plethora of studies involving molecular and genomic studies from the last decade revealed that tumors exhibit complex and tissue-specific gene regulatory mechanisms controlled by a multitude of transcription factors binding to enhancers or promoters, thereby orchestrating expression of a specific set of genes. Regulation of gene expression occurs through alteration in chromatin accessibility via recruitment of nucleosome-remodeling complexes, histone-modifying enzymes [1–4] and chromatin organizers that coordinately regulate multiple genes via modulation of higher-order chromatin architecture [5–14].

SATB (Special AT-rich binding protein) family proteins have emerged as key regulators that integrate higher-order chromatin organization with the regulation of gene expression [15–21]. Recent studies have demonstrated that both SATB1 and SATB2 are instrumental in cancer progression [17, 19, 22–26]. Both members of the SATB family chromatin organizers are involved in long-range enhancer function [27–29] extension of chromatin modifications [29, 30] and dynamic tethering of chromatin loops [15, 31, 32].

Post-translational modifications of SATB1 act as dynamic molecular switches regulating the expression of a large number of genes during T cell activation [33]. SATB2 was identified as a protein belonging to the SATB chromatin organizer family and implicated in transcriptional

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control and chromatin remodeling [34]. Last decade has witnessed elucidation of roles of SATB1 in an array of biological phenomena including X chromosome inactivation [35], T cell development [36, 37] and differentiation [38–40], anti-tumor immunity [41], autoimmune diseases [42–44], Wnt signaling [38], hematopoiesis [45, 46] and neuronal development [47–49]. SATB2, a relatively less characterized homolog of SATB1, is known as a versatile regulator functioning in the differentiation of multiple cell types including embryonic stem cells, osteoblasts and immunocytes [20]. SATB2 is expressed in erythroid cells and activates γ-globin genes by binding to their promoters and recruiting the histone acetyltransferase PCAF [50]. SATB2 plays key roles in craniofacial patterning, osteoblast differentiation, cortical neuron differentiation and skeletal development [51–53]. Collectively, this affirms the role of higher-order chromatin organization and gene regulation mediated by SATB chromatin organizers towards governing diverse cellular functions.

Number of studies in the past decade have demonstrated strong association between expression of SATB1 with tumor aggressiveness in an array of cancer types including colorectal [54], breast [55], pancreatic [56], nasopharyngeal [57], bladder [58], prostate [59, 60], lung [61], ovarian [62], liver [63], glioma [64], lymphoma [35], cutaneous T cell lymphoma [65, 66], endometrial carcinoma [67] and kidney [68]. These studies suggest SATB1 as an ideal therapeutic target for cancer therapy; however, there are few contradictory reports in case of breast and colorectal cancer [69–71]. With respect to SATB2, its expression is correlated with aggressiveness of colorectal [72], bone [73], head and neck cancer [74] demonstrating its cancer specific role.

This review highlights the role of SATB1 towards tumor progression, metastasis, regulation switch between pluripotency and cellular differentiation and immunemodulatory functions. Current review uniquely delineates the importance of the cell-specific expression of SATB1 across tumor recruited dendritic cells (DC), cytotoxic T lymphocytes (CTL), T regulatory cells (Tregs) and tumor epithelial cells along with tumor microenvironment. This dynamic expression pattern of SATB1—upregulation in Tregs and DCs while downregulation in CTLs along with crosstalk of tumor niche leads to tumor progression and inflammation. Furthermore, comprehensive analysis of correlation of expression of the two members of SATB family chromatin organizers with patient survival for an array of tumor types clearly revealed their tissue-specific regulation. These correlations strongly suggest that status of expression of both SATB1 and SATB2 may serve as a highly reliable prognostic marker. Current review highlights the importance of balance between the expression of SATB chromatin organizers along with intratumoral cellular and molecular functions governed. We propose that the combined expression pattern of SATB1 and SATB2 provides improved insights towards understanding tumor progression and therefore establish them as reliable prognostic markers.

Molecular mechanisms of regulation of SATB chromatin organizers in cancer

Chromatin organizer proteins provide a structural network to regulate an array of genes, dysregulation of which could exert detrimental effects on the cellular phenotype. This presumably provides mechanistic clues towards how the aberrant expression of chromatin organizers might lead to accumulation of molecular events culminating in tumorigenesis. SATB1 regulates distant genes by selectively tethering specialized regions of the genome resulting in the formation of a characteristic 'cage-like' network [15, 29]. SATB1 provides a nuclear architectural platform that facilitates anchoring of an array of genes mediated via its interaction with specific genomic sequences [32, 75, 76]. SATB1 binds to the genomic regions outside heterochromatin, precisely at the base of chromatin loop domains suggesting its role in the positioning of genes in regions of the nucleus where their expression can be modulated [15]. In this manner SATB1 mediates expression of multiple genes which could be coordinately regulated, thereby enabling cells to alter their function in response to signals.

Chromosomes are organized into chromosome territories, largely separated from each other in the cell nucleus [77]. It has been proposed that chromatin, in chromosome territories, is folded into small-scale chromatin loops of ~50–200 Kb [78]. A recent report confirmed the existence of the chromosomal scaffold, loop organization and characterized the pathway of mitotic chromosome formation. This elegant study revealed that mitotic chromosomes fold as compact arrays of chromatin loops. During prophase, the interphase organization is rapidly lost in a condensin-dependent manner and arrays of consecutive 60 Kb loops are formed. Further, during prometaphase, ~80 Kb inner loops are nested within ~400 Kb outer loops [79]. The accessibility of chromatin modifiers along with chromatin domain architecture and spatial arrangement within the nucleus are determinants of gene expression [6, 80–82]. Chromatin is organized into a non-random 3D topology that is very essential for the establishment of the regulatory network for gene expression [76, 78, 83, 84]. Biological and biophysical principles governing the three-dimensional folding of chromatin are central to the understanding of epigenetic regulation during adaptive responses and in complex diseases, such as cancer [85]. Interestingly, in this context SATB1 is postulated to enhance transcription by

promoting the formation of small chromatin loops locally between regulatory elements, which would reduce the physical volume of within the gene cluster.

Global alterations in nuclear architecture and chromatin folding conspire with unstable epigenetic states of the primary chromatin fiber to drive the phenotypic plasticity of cancer cells [85]. Apart from the cellular transformation in cancer, it is established that SATB1 modulates the epigenetic and transcriptional pathways required for hematopoietic stem cell division, self-renewal, and lymphoid potential [86]. SATB1 acts as a 'docking site' for several chromatin modifiers including ACF, ISWI, and HDAC1 [28, 33] suggesting a molecular mechanism governing cellular plasticity. SATB1 recruits histone modifying enzyme p300 on promoters of tumor oncogenes and maintains histone activation mark such as histone H3K9/14 acetylation mark culminating in breast cancer progression. In contrast, SATB1 recruits HDAC1 on promoters of tumor suppressor genes, depletes the activation marks and thereby reducing their expression [18, 87]. SATB1 is speculated to affect histone modification states at the SATB1 binding sites and also at nearby genes [17, 88]. This presumably explains the dynamic molecular regulation mediated by SATB chromatin organizers towards tumor progression.

Multiple studies over the past decade have provided strong evidence implicating chromatin remodeling and regulatory elements in cancers. Chromatin remodeling machinery such as the SWItch/Sucrose Non-Fermenting (SWI/SNF) complex, also referred to as the BRG1-Associated Factor complex have been implicated in cancers [89, 90] wherein the core subunit SNF5 of the SWI/SNF complex acts as a tumor suppressor [91]. Cancers are associated with a specific alteration of the SWI/SNF subunit, which acts either as tumor suppressor genes or as oncogenes, and therefore constitute diagnostic or prognostic biomarkers [92]. Thus, dysregulation of epigenetic regulatory network presumably provides malignant cells an adaptive and selective advantage to escape homeostatic regulation [93–95].

SATB family chromatin organizers mediate higher-order chromatin organization thereby regulating gene expression [15, 27, 53]. Precisely, SATB1 might play role in specifying the nuclear location of specific genes thereby mediating other aspects of transcriptional control such as chromatin remodeling and access to transcription activators or repressors, to orchestrate gene expression [15, 29]. Depending on its interaction partners, SATB1 can either act as an activator or a repressor of transcription of multiple genes and mediate tissue-specific regulation [17]. In addition to the higher-order chromatin loop domain architecture, variety of histone modifications in chromatin also govern gene expression [96, 97]. SATB1 regulates gene expression by mediating histone modifications as it recruits histone-modifying enzymes on promoters of oncogenes and also recruits HDAC1 on promoters of tumor suppressor genes [18, 87]. Further SATB proteins also act as a 'docking site' for various chromatin remodelers [28, 33] and its post-translational modifications are important to regulate its functional role. Phosphorylation of SATB1 acts as a molecular switch regulating its transcriptional activity [33]. Although post-translational modifications of SATB2 have not been studied extensively so far, high extent of sequence homology and conservation of functional domains between SATB proteins indicate that SATB2 might exhibit similar functions. Together, these findings implicate SATB proteins as critical players in organizing nuclear structural framework required to establish the chromatin architecture to regulate global gene expression patterns. Further, their aberrant expression might lead to global transcriptional dysregulation leading to cancer progression (Fig. 1).

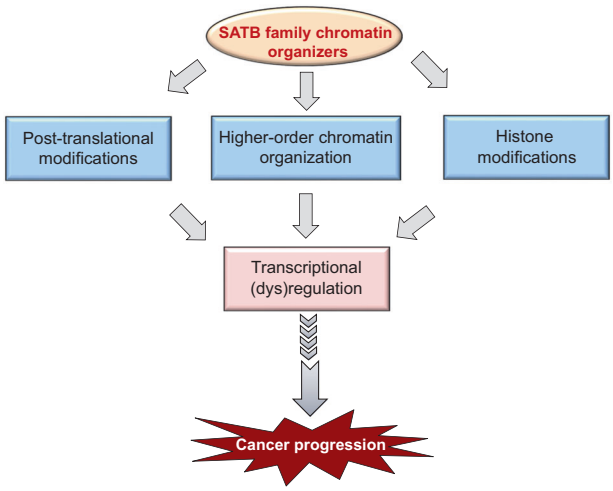

Fig. 1 Schematic representation of molecular mechanisms regulated by SATB family chromatin organizers leading to tumorigenesis and cancer progression. Tumor initiation is a multistep process triggered by series of changes in the genome. SATB family chromatin organizers modulate higher-order chromatin organization thereby reprogramming gene expression patterns leading to tumorigenesis and tumor progression. Along with regulation of higher-order chromatin organization, SATB proteins also mediate histone modifications which regulate gene expression leading to cancer progression. The accessibility of various transcription factors to chromatin is determined by post-translational modifications of histones and thereby regulates gene expression. Post-translational modifications of SATB1 is known to regulate gene expression. SATB1 is known to be involved in inactivation of tumor suppressors and activation of oncogenes thereby leading to tumor progression. Thus, aberrant expression of SATB family chromatin organizers alters gene expression patterns and mediates cancer progression

Dynamic expression patterns of SATB chromatin organizers governs stemness and differentiation

SATB1 is a major regulator involved in differentiation by opening the chromatin structure around cell-type specific genes to enable transcription factors and chromatin remodeling proteins to bind. Role of SATB1 is well established in the differentiation of T-cell lineage; [38, 43] mouse embryonic stem cells [98] epidermal differentiation [99, 100], wherein the absence of SATB1 marks differentiated cellular state. SATB1 is a regulator of hematopoiesis [46, 101] and drives early erythroid differentiation [102–104]. In contrast, presence of SATB2 denotes differentiated state for osteoblasts [20, 105], cortical neuron [106] and skeletal development [20]. SATB proteins promote trophoblast stem cell (TS) renewal and inhibit differentiation by physically associating with a regulatory site of the TS cell stem-associated transcription factor, EOMES [107]. It has now been well appreciated that tumors contain a rare population of the stem-like cells defined by the property of self-renewal, multi-lineage differentiation, tumor-initiating capacity and are capable of recapitulating the heterogeneity of primary tumors [108, 109]. This rare sub-population of cells termed as cancer stem cells (CSCs) or tumor-initiating cells are responsible for the generation of tumor heterogeneity by deriving tumor cell hierarchy with CSCs at the apex followed by progenitors and differentiated cells. CSCs are involved in the generation of chemo- and radio-resistance culminating in disease relapse [110–112]. Recently, the role of SATB1 in the maintenance of breast cancer stem cells [113] was elucidated along with esophageal cancer [114]. SATB1 is shown to regulate CSCs through activation of Notch signaling and further mediates EMT through Snail1 and Twist1 [113]. However, the understanding of regulatory mechanisms of CSCs and dissection of the relationship between CSCs and cancer metastasis requires further investigation.

SATB2 is proposed to serve as a diagnostic marker for CRC [115] and its expression was correlated with cancer-associated fibroblasts [116]. Role of SATB2 is speculated in the regulation of cancer stem cells in colorectal cancer [24], however, there is also a report stating SATB2 as a negative regulator of stemness in colorectal cancer [117] which might lead to its context-specific role. With the improved understanding of role SATB1 in metastasis and angiogenesis, elucidation of its role with respect to generation and maintenance of a stem or progenitor-like state is important since these are closely associated processes within a tumor.

SATB chromatin organizers modulate hallmarks of cancer

Aberrant expression of SATB1 and its association with an array of cancer types suggest its involvement in the modulation of higher-order chromatin organization leading to carcinogenesis. SATB1 mediated specific long-range chromosomal interactions between the mbr enhancer located within 3'-UTR of the BCL2 gene and the promoter regulate BCL2 expression during early apoptosis [118]. SATB1 is instrumental in regulating the dynamic equilibrium of apoptosis-controlling genes with antagonistic functions by modulating higher-order chromatin organization suggests that its aberrant expression might contribute to tumorigenesis by disrupting the co-regulated genes in apoptosis pathways [119]. Apart from disruption of apoptosis which is one of the hallmarks of cancer, SATB1 regulates estrogen signaling in breast cancer through miR-191 as the oncogenic player [120]. Knockdown of SATB1 is reported to inhibit angiogenesis, cell invasion, and metastasis in an array of cancer types thereby stating its role in governing hallmarks of cancer [64, 121]. Underlying these hallmarks is genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation. In this context, SATB1 expression is significantly associated with β-catenin overexpression and microsatellite stability [122]. Conceptual progress in the last decade has added two emerging hallmarks, namely reprogramming of energy metabolism and evading immune destruction to the previously established list [90]. In this context, SATB1 is speculated to be involved in the generation of hypoxia and metabolic stress in breast ductal carcinoma model [123], however, very little is known regarding the mechanistic details of the same.

SATB chromatin organizers act as key regulators of EMT–MET switch and metastasis

SATB1 overexpression is correlated with advanced stage, lymph node metastasis and distant metastasis in an array of cancer types including CRC [23], Prostate [124], esophageal squamous cell carcinoma [125], liver cancer [126], renal cell carcinoma [127], breast cancer [87], and pancreatic cancer [56]. In contrast, SATB2 acts as a negative regulator of Epithelial-Mesenchymal Transition (EMT) and metastasis in CRC [69, 128] and non-small-cell lung carcinoma (NSCLC) [25, 129]. Expression of SATB1 leads to upregulation of transcription factors associated with EMT such as Snail, Slug, Zeb1, and Zeb2 [130] and correspondingly downregulation of cell adhesion proteins such

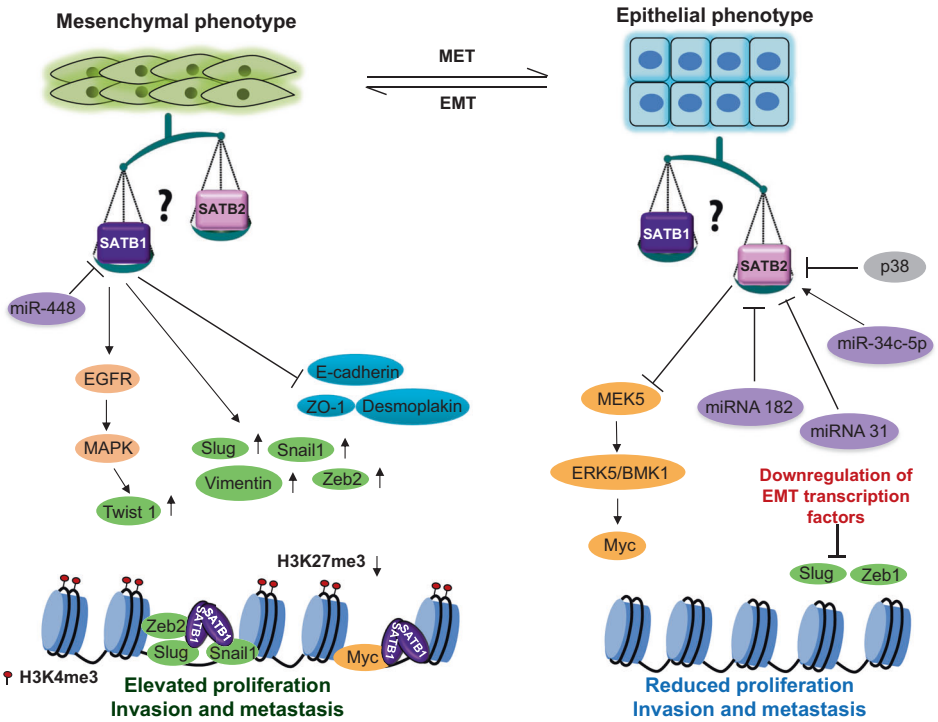

Fig. 2 Schematic representation of dynamic balance between expression patterns of SATB family chromatin organizers as regulators of EMT-MET cellular states during metastasis. Expression of SATB1 is positively correlated with upregulation of Epithelial-Mesenchymal Transition (EMT) associated transcription factors (Snail, Slug, Zeb1 and Zeb2) and negatively correlated with adhesion proteins (E cadherin, Desmoplakin, and ZO1) responsible for an epithelial phenotype (MET—mesenchymal-epithelial transition) of the cell. Higher expression of the respective SATB family member is schematically represented by the heavier pan of the balance. The microRNA miR-448 negatively regulates SATB1 leading to EMT through upregulation of Twist1. In contrast, increased expression of SATB2 leads to downregulation of EMT transcription factors and promotes epithelial phenotype. SATB2 is regulated negatively by miRNA-31, miRNA-182 and positively by miR-34c-5p, leading to downregulation of EMT related transcription factors. SATB1 promotes proliferation, invasion, and metastasis whereas SATB2 acts as a negative regulator of these processes. This suggests a state of dynamic balance between expression levels of SATB family chromatin organizers regulating cellular phenotypes involved in mediating EMT-MET during tumor invasion and metastasis

as E-cadherin, Desmoplakin, and ZO1 responsible for the epithelial phenotype of the cell [131]. SATB1 reprograms the expression of tumor growth and metastasis-associated genes to promote tumorigenesis and functionally overlaps with Wnt signaling critical for colorectal cancer tumorigenesis. An in-depth mechanistic investigation revealed that SATB1 shares a feedback regulatory network with TCF7L2/β-catenin signaling and is required for Wnt signaling-dependent regulation of β-catenin [54]. miR-448 suppression leads to enhanced SATB1 expression which initiates amphiregulin—epidermal growth factor receptor signaling towards Twist1 expression through mitogen-activated protein kinase leading to EMT [132]. In case of SATB2, microRNAs miR-182 and miR-31 directly target the 3′ untranslated region (3′ UTR) of its mRNA and subsequently repress the expression of SATB2 at both mRNA and protein levels to promote cancer cell proliferation and metastasis [133, 134]. Silencing of SATB2 mediated by methylated miR-34c-5p promoted the metastatic ability of CRC cells in vivo, enhancing the epithelial-mesenchymal transition (EMT) [135]. Interestingly, inhibition of p38 upregulated SATB2 expression and reversed epithelial-mesenchymal transition in NSCLC cells [25]. SATB1 promoted c-Myc expression leading to enhanced cell invasion and metastatic abilities while SATB2 mediated downregulation of c-Myc via inactivation of ERK5, suggesting a dynamic balance between SATB chromatin organizers as a major factor for cell migration and metastasis [136]. Further, genome-wide analysis identified association of SATB1 target genes, revealed upregulation of a long non-coding RNA UCA1 along with increased H3K4 trimethylation (H3K4me3) and decreased H3K27 trimethylation (H3K27me3) levels suggesting activation of genes involved in metastasis [137] (Fig. 2).

EMT is a prerequisite for invasion and migration for cancer cells, however after migration of cancer cells to secondary metastatic site cancer cells undergo Mesenchymal-Epithelial Transition (MET) required for colonization [138, 139]. EMT and MET constitute dynamic interchangeable cellular states required for migration,

invasion, and metastasis [140, 141]. This suggests a state of dynamic balance between expression levels of SATB chromatin organizers regulating cellular phenotypes involved in mediating EMT–MET during tumor invasion and metastasis (Fig. 2). Multiple studies demonstrate that SATB1 is critical for enhanced cell survival, cell invasion and cell migration properties suggesting that it might prime tumor cells for metastasis. In contrast, SATB2 typically acts as a negative regulator for migration, invasion, and metastasis. However, reports stating the role of SATB2 in regulating EMT and metastasis have contested the above notion [24, 142]. Nevertheless, it would be more pertinent to understand the mechanistic regulation of both SATB chromatin organizers with respect to tumor metastasis and whether their expression levels act as a molecular switch governing EMT and MET during metastasis.

Dynamic expression of SATB1 regulates tumor progression, immunity, and inflammation

Role of SATB1 during T cell development is well established wherein it acts as a critical regulator in $CD4^+CD8^+$ thymocytes and during activation of $CD4^+$ T cells [33, 36, 37, 143] and coordinates differentiation of specific T helper subtypes [38–40]. Strikingly, SATB1 is specifically downregulated in regulatory T cells [36, 43, 44]. SATB1 is required for normal T cell development as well as by activated tumor recruited cytotoxic T lymphocyte (CTL) to elicit active immune response [144]. However, its elevated expression in tumor epithelial cells marks tumor aggressiveness [54, 87]. Increased SATB1 expression in intratumoral Tregs [145] and dendritic cells (DCs) [146] mediates tumor inflammation (Fig. 3).

A recent report implicated SATB1 as an important player to avoid T cell exhaustion phenotype and elicit anti-tumor immune response [41]. Transfer of tumor-primed SATB1-deficient mixed population of T cells into the peritoneal cavity of mice bearing established orthotopic syngeneic ovarian tumors leads to accelerated tumor growth relative to the transfer of primed wild-type T cells. It is believed that SATB1 regulates T cells at multiple phases that would result in a "fixed" epigenetic landscape leading to an anti-tumor response [41]. Level of SATB1 is a critical mediator of the T cell exhaustion phenotype. Strikingly, a recent report indicated that PD1 signaling antagonizes CD28 costimulation, suggesting a feed-forward mechanism involving SATB1 whereby weak costimulation and/or signals from TGF-β from the tumor microenvironment that leads to downregulation of SATB1. Reduction in SATB1 results in elevated PD1 levels, thereby suppressing costimulation, and further locking the T cells into an exhausted state [144]. This important finding bolsters the role of cell type-specific expression of SATB1 in tumor recruited CTLs which could be explored to induce an anti-tumor response. Amongst tumor recruited immune cells, $FOXP3^+$ Tregs can markedly curtail host anti-tumor immune responses through inhibition of endogenous T cell response [147]. Intratumoral Tregs have a phenotype characterized by upregulated expression of FOXP3 mRNA and protein positively correlated with significantly increased expression of SATB1 as compared to normal Tregs where SATB1 is downregulated [44, 148, 149] (Fig. 3), suggesting SATB1 as an ideal target for antitumor Treg-based therapy [144].

Overexpression of the genome organizer SATB1 in tumor microenvironmental DCs drives genome-wide transcriptional program that globally transforms DCs. This leads to accelerated malignant tumor progression through an inflammatory axis that ablates anti-tumor immunity using the cytokine IL-6 and the immunosuppressive protein galectin-1 [145]. Galectin-1 secreted by inflammatory DCs inhibits T cell responses through multiple complementary mechanisms that affect DC immunocompetence [150]. Galectin-1 causes apoptosis in Th1 and Th71 cells [151], renders effector T cells unresponsive by cross-linking GM1 ganglioside [152], and promotes the differentiation of tumor-associated Foxp3 + Treg cells [153]. Immunosuppressive DCs can also produce cytokines such as IL-10 or TGF-β that directly inhibit the activity of anti-tumor T cells. Additionally, both IL-10 and TGF-β promote the conversion of CD4 T cells into Treg cells, as well as the immunosuppressive activity of natural Tregs [154–156] (Fig. 3). Collectively, this suggests $Dngr1^+$ DCs and galectin-1 that is secreted by inflammatory DCs could serve as an ideal target for cancer therapy.

Elevated levels of SATB1 are known to be associated with tumorigenesis, tumor metastasis and progression. SATB1 collaborates with loss of p16 in cellular transformation through Rb-E2F pathway [157]. SATB1 is known to play an oncogenic role mediated through FN1 and PDGFRB [114]. SATB1 regulates molecular changes required for epithelial to mesenchymal transition, an important phenotypic change essential for metastasis. SATB1 regulates expression of epithelial to mesenchymal transition (EMT) associated transcription factors slug, snail and twist [54, 113, 130]. SATB1 is necessary and sufficient to regulate the expression of β-catenin, TCF family members and multiple downstream effectors and mediators for regulation of the Wnt signaling pathway. Mir et al. recently elucidated the mechanism of regulation of SATB1 though Wnt/β-catenin signaling [54]. They demonstrated that TCF7L2 binds to the *Satb1* promoter and promotes H3K4 trimethylation, thereby directly regulates SATB1 expression. Hyperactivation of Wnt signaling induces occupancy of TCF7L2/β-catenin complex on *Satb1* promoter resulting

in induction of SATB1 expression. Further, knockdown of TCF7L2 and β-catenin and their subsequent loss of occupancy on *Satb1* promoter downregulated SATB1 as well as known downstream targets of Wnt signaling. Ectopic SATB1 expression in non-aggressive cells led to gene expression patterns consistent with aggressive-tumor phenotypes, acquiring metastatic activity in vivo. SATB1 delineates specific epigenetic modifications at target gene loci, directly upregulating metastasis-associated genes while downregulating tumor-suppressor genes [87]. Role of TGFβ in tumor cell migration and metastasis is well established and it is known to be secreted in the tumor microenvironment [158]. TGFβ secreted by tumor cells could downregulate SATB1 in CTLs leading to T cell exhaustion, transform SATB1 expressing immature DCs to inflammatory DCs which would inhibit tumor recruited CTLs and generate Tregs, thus, in turn, inhibiting CTLs. Therefore cell type-specific expression of SATB1 along with tumor microenvironment might act as primary determinants of tumor progression and tumor inflammation (Fig. 3). In vivo cell type-specific silencing of SATB1 specifically in tumor DCs and Tregs or neutralization of the immunosuppressive factors produced by SATB1 overexpressing DCs might emerge as promising immunotherapeutic alternatives in cancer therapy. Uncovering mechanisms to manipulate and increase SATB1 levels in CTLs might eventually enable new immunotherapies that would boost tumor immunity.

SATB chromatin organizers as biomarkers for cancer prognosis

To evaluate the association of SATB chromatin organizer expression within the tumor with the patient survival in an array of tumor types we used TCGA data [159]. Survival analysis was performed of TCGA dataset of patients from 14 cancer types in which gene expression obtained through RNA sequencing was correlated with patient survival data to evaluate the significance of the two members of the SATB family chromatin organizers towards cancer prognosis. Patients were sorted based on gene expression (read counts of RSEM RNAseqV2 normalized) from highest to least. Top 15–25% and bottom 15–25% patients based on SATB1 expression were characterized as $SATB1^{hi}$ and $SATB1^{low}$. Similarly, patients were sorted based on gene expression profiles as $SATB2^{hi}$ and $SATB2^{low}$. Statistical significance was calculated using log-rank p-value ≤ 0.05 considered as significant. However, those cancer types with lower patient numbers were considered for survival analysis (p-value ≤ 0.1) if they followed a survival trend since the increase in the number of patients would lead to the improved significance of the study. Survival analysis revealed that higher expression of both SATB1 and SATB2 was strongly correlated with poor patient survival for cervical squamous cell carcinoma, sarcoma, and stomach adenocarcinoma. Correlation of SATB1 is linked with aggressiveness in case of stomach adenocarcinoma and cervical squamous cell carcinoma, however, none of these studies had reported association of SATB2 [160, 161]. These findings are in agreement with earlier reports for sarcoma wherein expression of SATB1 and SATB2 was individually correlated to tumor aggressiveness in independent studies [162–164]. SATB1 expression correlated negatively with SATB2 which culminates in poor patient survival for colon adenocarcinoma, rectal adenocarcinoma, lung squamous cell carcinoma, uterine corpus endometrial carcinoma and liver hepatocellular carcinoma (Summarized in Table 1), which is well established in case of earlier two

Table 1 Correlation of expression of SATB family chromatin organizers with patient survival across cancer types

Cancer subtypes	Higher expression of SATB1 and SATB2 Poor prognosis	Higher expression of SATB1 and SATB2 Good prognosis	Higher expression of SATB1 and lower expression of SATB2 Poor prognosis	Higher expression of SATB2 and lower expression of SATB1 Poor prognosis
Urothelial bladder carcinoma				✓
Cervical squamous cell carcinoma	✓			
Kidney renal clear cell carcinoma		✓		
Acute meloid leukemia				✓
Low-grade glioma				✓
Liver hepatocellular carcinoma			✓	
Lung squamous cell carcinoma			✓	
Pancreatic adenocarcinoma				✓
Sarcoma	✓			
Stomach adenocarcinoma	✓			
Uterine corpus endometrial carcinoma			✓	
COAD			✓	
READ			✓	
Skin cutaneous melanoma				✓

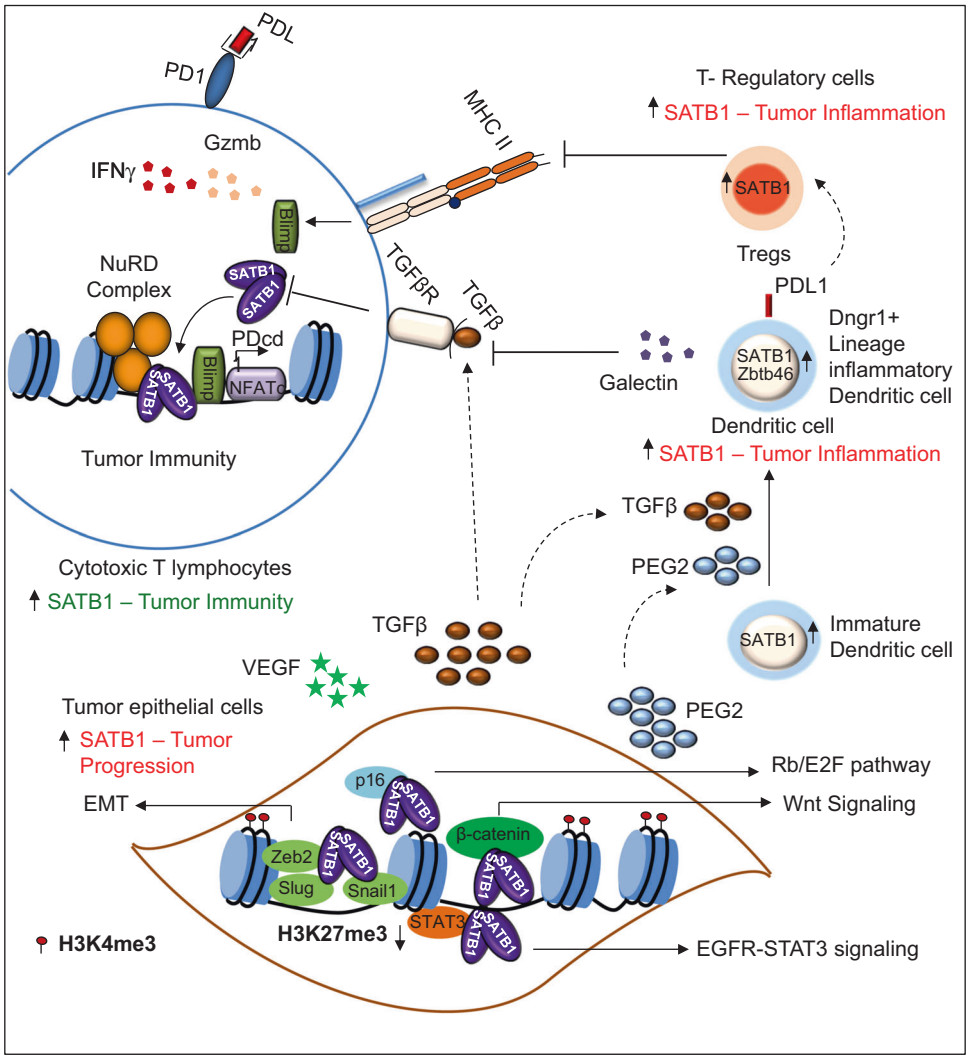

Fig. 3 Schematic representation of signaling pathways regulated by SATB1 in tumor epithelial cells, cytotoxic T lymphocytes (CTL), Dendritic cells (DC) and Tregs involved in tumor progression, tumor immunity, and inflammation respectively. Tumor microenvironment mediates cross-talk between the various cell types. TGFβ released in tumor niche downregulates SATB1 in CTLs due to which SATB1 is not available to interact with the NuRD complex required for transcription of *pdcd1* gene, which ultimately leads to T cell exhaustion. This explains the requirement of SATB1 expression for active CTL response against the tumor antigen. TGFβ is also responsible for differentiation of SATB1 expressing immature DCs to Dnrg1^{+} lineage inflammatory DCs that secrete galectin which inhibits CTLs. These DCs also lead to the generation of Tregs. Intratumoral Tregs are marked by upregulation of SATB1 and are responsible for tumor inflammation. SATB1 regulates tumor progression in epithelial cells via Wnt/β-catenin signaling and EGFR-STAT3 signaling. SATB1 mediates cellular transformation through the Rb-E2F pathway and promotes metastasis via the EMT associated transcription factors

cancer types [19, 138], whereas the correlation with latter types is novel. Survival analysis revealed that in case of acute myeloid leukemia, low-grade glioma, urothelial bladder carcinoma and pancreatic adenocarcinoma higher expression of SATB2 and lower expression of SATB1 were determinant of poor patient survival (Fig. 4; Fig. 5). However, a recent study exhibited a lack of clarity for the correlation of expression of SATB1 for urothelial bladder carcinoma [165]. Surprisingly, higher expression of both the SATB proteins conferred better patient survival for kidney renal clear cell carcinoma. Our analysis is in agreement with the established fact of downregulation of both SATB chromatin organizers in kidney renal clear cell carcinoma [125, 166]. Thus, the analysis presented here clearly indicates tissue-specific regulation of SATB chromatin organizers with respect to tumor aggressiveness (Fig. 4; Fig. 5). This comprehensive analysis across multiple tumor types strongly argues in favor of exploiting both members of the SATB family chromatin organizers to categorize cancer types, which can be effectively used to design molecularly targeted therapy.

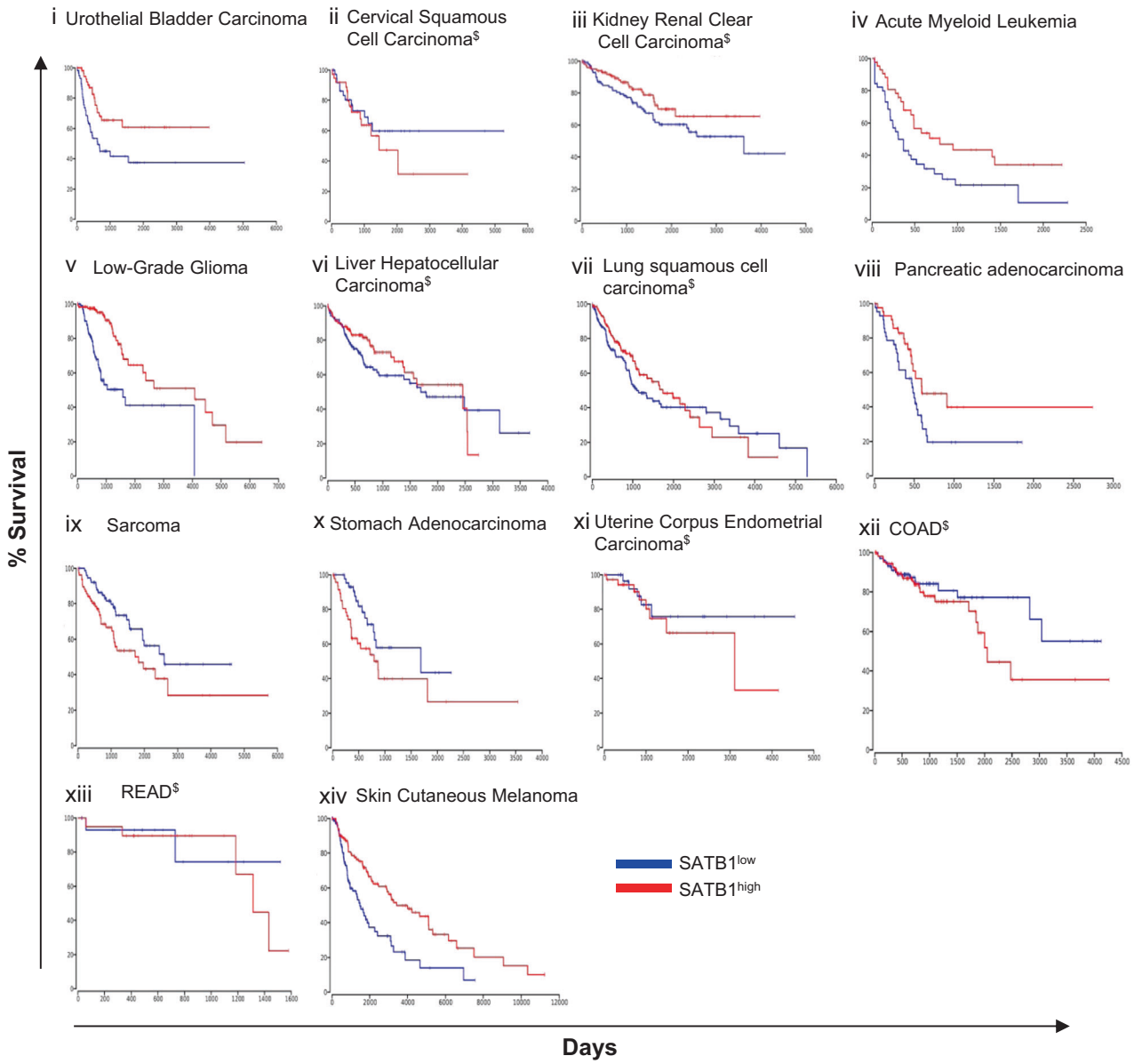

Fig. 4 Representative Kaplan Meier analysis plots for expression of SATB1 in various cancer types. TCGA gene expression data was downloaded for all available cancer types with patient clinical survival data (https://doi.org/10.7717/peerj-cs.67). Kaplan Meier survival analysis was performed with the correlation of expression of SATB1 with overall patient survival. The red line indicates higher expression of SATB1 whereas blue line indicates lower expression of SATB1. Data are plotted for Urothelial bladder carcinoma (N=60); cervical squamous cell carcinoma (N=39); kidney renal clear cell carcinoma (N=104); acute myeloid leukemia (N=45); low-grade glioma (N=127); liver hepatocellular carcinoma (N=126); lung squamous cell carcinoma (N=136); pancreatic adenocarcinoma (N=43); sarcoma (N=77); stomach adenocarcinoma (N=49); uterine corpus endometrial carcinoma (N=37); colon adenocarcinoma (N=110); rectal adenocarcinoma (N=19); skin cutaneous melanoma (N=114) where N represents number of patients of respective cancer type based on SATB1 expression each for $SATB1^{hi}$and $SATB1^{low}$. Statistical significance was calculated using log-rank p-value ≤ 00.5; $ indicates dataset with lower patient numbers with p-value ≤ 0.1

Future perspectives

SATB chromatin organizers have been actively involved in tumor progression and metastasis in an array of malignancies. Expression of SATB1/2 is also linked to clinicopathological outcome, with dynamic and tissue-specific expression pattern and correlation with patient survival indicating it as an ideal marker for disease prognosis.

Notably, despite the growing literature on SATB1 in cancer, the relevance of post-translational modifications has been poorly studied. Akt phosphorylates SATB1 at serine 47 and protects SATB1 from apoptotic cleavage [167] and

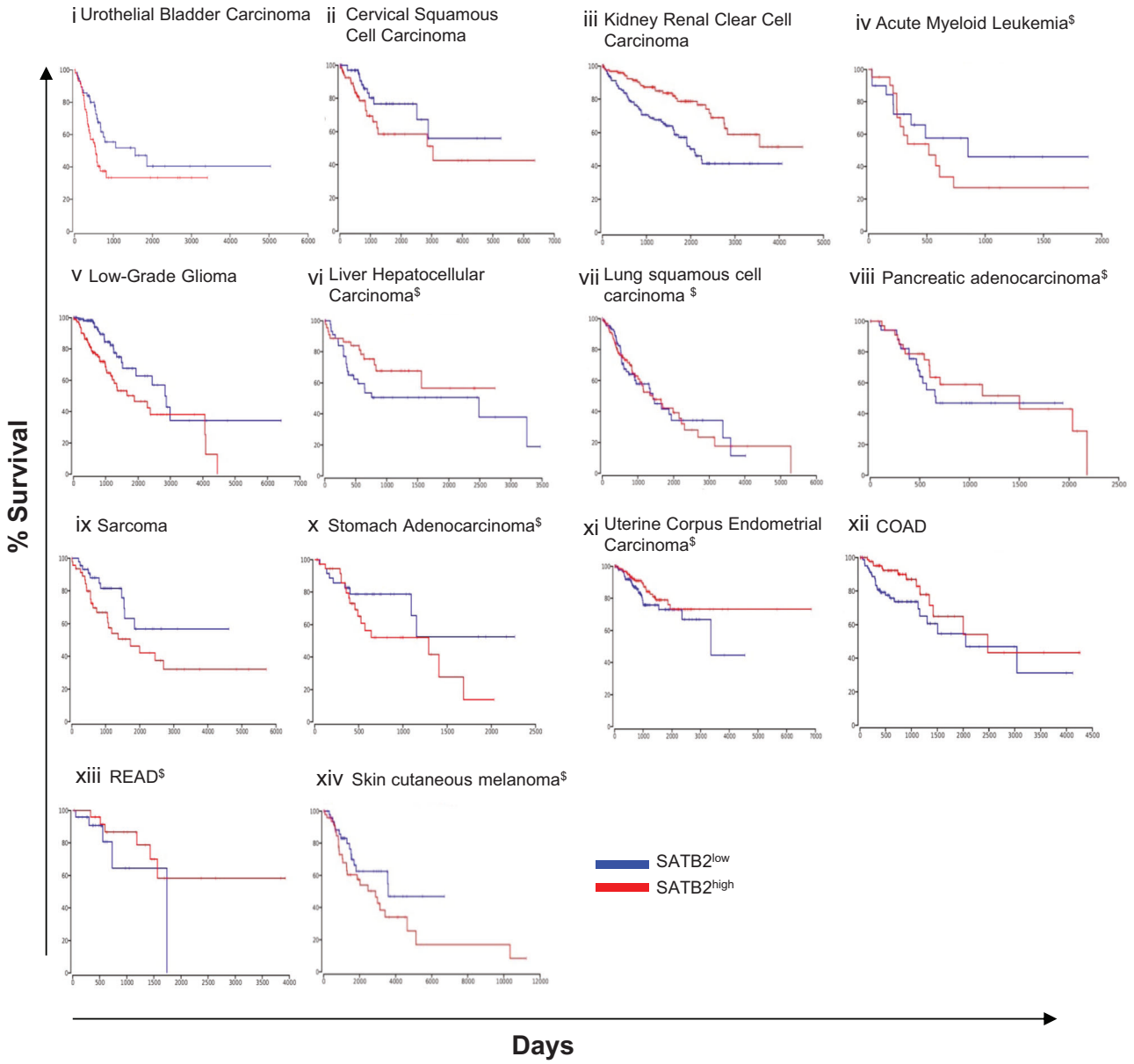

Fig. 5 Representative Kaplan Meier analysis plots for expression of SATB2 in cancer types. TCGA gene expression data was downloaded for all available cancer types with patient clinical survival data (https://doi.org/10.7717/peerj-cs.67). Kaplan Meier survival analysis was performed with the correlation of expression of SATB2 with overall patient survival. The red line indicates higher expression of SATB2 whereas blue line indicates lower expression of SATB2. Data are plotted for Urothelial Bladder Carcinoma (N=60); Cervical Squamous Cell Carcinoma (N=71); Kidney Renal Clear Cell Carcinoma (N=130); Acute Myeloid Leukemia (N=21); Low-Grade Glioma (N=127); Liver Hepatocellular Carcinoma (N=46); Lung squamous cell carcinoma (N=97); Pancreatic Adenocarcinoma (N=35); Sarcoma (N=46); Stomach Adenocarcinoma (N=37); Uterine Corpus Endometrial Carcinoma (N=135); Colon Adenocarcinoma (N=88); Rectal Adenocarcinoma (N=25); skin cutaneous melanoma (N=50), where N represents number of patients of respective cancer type based on SATB2 expression each for $SATB2^{hi}$ and $SATB2^{low}$. Statistical significance was calculated using log-rank p-value ≤ 00.5; $ indicates dataset with lower patient numbers with p-value ≤ 0.1

levels of phosphorylated SATB1 correlate with glioma prognosis [58]. The promyelocytic leukemia oncoprotein physically and functionally interacts with SATB1 to organize the major histocompatibility complex class I locus into distinct higher-order chromatin-loop structures [32]. Phosphorylation status of SATB1 at serine 185 governs its mutually exclusive association with HDAC1 and PCAF; whereas acetylation at lysine 136 impairs the DNA-binding activity of SATB1 [33]. Further, phosphorylation-dependent interaction of SATB1 and PIAS1 directs

SUMO-regulated caspase cleavage of SATB1 [168, 169]. Recently the role of sumoylation-deficient SATB1 has been implicated in cellular migration [170]. SUMO modification of SATB2 is known to modulate immunoglobulin mu gene expression [27]. However, its implications with respect to cancer are not studied so far. Therefore it is important to understand post-translational modifications such as phosphorylation, acetylation, and SUMOylation associated with SATB chromatin organizers that may contribute to reprogramming of gene expression patterns during tumor metastasis.

SATB1 is an attractive therapeutic target for cancer therapy and although a couple of drugs have been explored to exhibit anticancer activity via downregulation of SATB1, the underlying molecular mechanisms are still unclear. Baicalein has been shown to suppress SATB1 protein expression in a time- and dose-dependent manner, exerting anti-proliferative and anti-migratory effects [171]. At the molecular level, a decrease in EMT and cell cycle molecules has been found [172]. Likewise, hydrophobic statins such as simvastatin and fluvastatin have been shown to downregulate SATB1 possibly acting at the post-translational level [173]. Proteomic approaches should be employed to understand the repertoire of proteins interacting with SATB chromatin organizers. The interaction interface could be used for the development of small molecular weight inhibitors enabling targeted therapy.

Recently the role of SATB1 in hematopoiesis has been characterized. SATB1 regulates maintenance of hematopoietic stem cell (HSC) multipotency and leads to the generation of HSC heterogeneity [174]. More specifically, SATB1 is known to promote lymphoid differentiation from the hematopoietic stem-progenitor cell [103]. SATB1 conditional knockout mice in which *SATB1* gene is specifically deleted from hematopoietic cells, develop Sjögren's Syndrome suggesting the role of SATB1 dysregulation in HSCs driving diseased state [175]. Malignant cancer stage is characterized by altered hematopoietic differentiation resulting in an increase in myeloid output. Altered myelopoiesis along with SATB1 overexpression converge to transform DCs from an immunostimulatory to an immunosuppressive, tumor-promoting cell type [176].

Immunotherapy is recently much-appreciated treatment strategy in cancer therapy due to its least toxic nature. In this context, SATB1-derived epitope has been implicated as the immune target for cancer vaccine development [177]. In contrast, SATB1 overexpression has also been shown to act as a tumor promoter in cancer-associated dendritic cells [146]. By promoting the differentiation of dendritic cells, including inflammatory DCs infiltrating tumors, SATB1 has been shown in ovarian carcinoma to result in an immunosuppressive phenotype. Consequently, in vivo silencing of SATB1 in tumor-associated DCs was found to boost protective immunity. SATB1 regulates tumor progression by its downregulation in tumor recruited CTLs, and upregulation in tumor epithelial cells and tumor recruited Tregs. Thus SATB1 regulation is cell type-specific leading to aggressive phenotype and metastasis.

The availability of adequate tools for quantification and analysis, appropriate tumor models, novel therapeutic drugs that mediate tissue-specific knockdown of SATB family chromatin organizers will not only establish its utility as a prognostic marker, but also elucidate their possible use as a therapeutic target.

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Author contributions RN and SG conceived the ideas, analyzed the data and wrote the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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