Review Article

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Wrong place, wrong time: Runt-related transcription factor 2/SATB2 pathway in bone development and carcinogenesis

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Abstract:

Upregulation or aberrant expression of genes such as special AT-rich sequence-binding protein 2 (SATB2) is necessary for normal cell differentiation and tissue development and is often associated with carcinogenesis and metastatic progression. SATB2 is a critical transcription factor for biological development of various specialized cell lineages, such as osteoblasts and neurons. The dysregulation of SATB2 expression has recently been associated with various types of cancer, while the mechanisms and pathways by which it mediates tumorigenesis are not well elucidated. Runt-related transcription factor 2 (RUNX2) is a master regulator for osteogenesis, and it shares common pathways with SATB2 to regulate bone development. Interestingly, these two transcription factors co-occur in several epithelial and mesenchymal cancers and are linked by multiple cancer-related proteins and microRNAs. This review examines the interactions between RUNX2 and SATB2 in a network necessary for normal bone development and the circumstances in which the expression of RUNX2 and SATB2 in the wrong place and time leads to carcinogenesis.

Keywords:

Carcinogenesis, microRNA, osteogenesis, Runt-related transcription factor 2, SATB2

Introduction

Special AT-rich sequence-binding protein 2 (SATB2) is a nuclear matrix-associated protein that regulates gene transcription by binding to the nuclear matrix-attachment regions and altering organization of eukaryotic chromosomes. It is an important regulator of the osteoblastic, craniofacial, and nervous system development.[1-3] SATB2 was identified at locus 2q32, in which the chromosomal changes contributed to the pathogenesis of isolated cleft palate.[2,3] SATB2-knockout mice presented a similar phenotype as observed in humans, such as delayed bone formation and mineralization, resulting in death shortly after birth.[1] Further examination of SATB2-knockout mice during embryonic development showed that the observed cleft palate malformation was caused by a defect in skeletal patterning,[1] which suggested failure to form areas of condensed mesenchymal progenitor cells or improper differentiation of chondrocytes or osteoblasts.

While SATB2 has been identified mainly as a gene contributing to embryonic development, it was recently found expressed in adenocarcinomas, as well as in many other tumors, such as breast, ovarian, lung, and sinonasal carcinomas.[4] Recent studies have revealed an important role of SATB2 in mediating heavy metal-induced cell transformation.[5,6] SATB2 plays an important role in the cell development and differentiation, while its pathway and mechanisms in cancers are not well understood. Thus, this review aims to

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explore a potential signaling pathway in which SATB2 and Runt-related transcription factor 2 (RUNX2) cooperate to promote carcinogenesis.

Runt-related Transcription Factor 2 and SATB2 in Bone Development

RUNX2 is another important regulator in the bone development. RUNX2 expression establishes commitment to the osteoblast lineage and is necessary for proliferation of osteoprogenitors and immature osteoblasts, as well as upregulation of the bone matrix molecules needed for differentiation into mature osteoblasts.[7] Like SATB2-knockout mice, mice lacking RUNX2 exhibited an absence of mature osteoblasts and ossification and neonatal mortality.[8,9] If RUNX2 is a master switch for inducing osteoblast differentiation, then SATB2 is believed to be a molecular node in the transcriptional network regulating osteoblast differentiation.[10] SATB2 is not considered as a direct interacting transcription factor with RUNX2, but the connection between RUNX2 and SATB2 through their participation in the bone development and formation has been described.[11] The interaction between RUNX2 and SATB2 is supported by pathway analysis.[12] As shown in the Gene Oncology Study of String (https://string-db.org), a potential SATB2/RUNX2 pathway is mainly involved in osteoblast differentiation and development, and bone morphogenetic protein (BMP) signaling pathway, as well as many other cancer-associated pathways, such as extracellular matrix organization, epithelial–mesenchymal transition (EMT), cell proliferation, and cell death signaling pathways [Table 1].

Common Upstream Regulators

RUNX2 and SATB2 share common upstream regulators during osteoblast differentiation, such as BMP-2 and SMAD pathways. While BMP-2 is not required for RUNX2 to induce the expression of osteoblast genes, the formation of RUNX2–SMAD complex is necessary for BMP-2 to transduce osteoblastogenic signals and to complete osteogenic processes.[13] A study also found that BMP-2 activated RUNX2 in the early osteogenesis mediated by two homeodomain proteins Dlx3 and Dlx5, which are essential mechanisms in the commitment to osteogenic lineage, and in later stages, BMP-2 facilitated RUNX2 in cell differentiation.[14] BMP-2 also stimulated SATB2 expression in a time- and concentration-dependent manner in C2C12 cells, a mouse myoblast cell line used to study the differentiation of myoblasts and osteoblasts under expression of various target proteins, which was mediated through SMAD1/5 by directly binding and activating SATB2 promoter to mediate myoblast/osteoblast transdifferentiation.[15]

Table 1: Runt-related transcription factor 2 and SATB2 are correlated in many biological processes as supported by string gene oncology study analysis

Biological process	*P*
Osteoblast differentiation	6.32E-09
Osteoblast development	4.82E-08
BMP signaling pathway	4.80E-06
Positive regulation of extracellular matrix organization	5.32E-06
Positive regulation of epithelial to mesenchymal transition	3.46E-05
Regulation of epithelial cell proliferation	0.0002
Apoptotic process	0.0054
Stress-activated MAPK cascade	0.0059
Negative regulation of cell death	0.0061
Notch signaling pathway	0.0067

BMP: Bone morphogenic protein, MAPK: Mitogen-activated protein kinase

Mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) is the upstream of RUNX2 and phosphorylates and activates RUNX2, promoting osteoblast differentiation.[16-19] MAPK/ERK was reported to participate in SATB2-mediated osteogenesis,[20] and many downstream microRNAs (miRNAs) targeted by SATB2 in mouse bone mesenchymal stem cells (BMSCs) were also involved in MAPK/ERK signaling as determined by pathway analysis.[21] In contrast, continuous activation of ERK by extracellular stimuli had a negative effect in BMP-2 induction of osteoblast genes and an inhibitory effect on osteogenesis.[22,23] It was pointed out that ERK phosphorylated BMP-associated SMAD1/5/8 and mediated degradation of SMAD proteins in a cell-specific manner.[22] ERK inhibited SATB2 activity,[23] supporting the role of MAPK/ERK signaling in osteoblast differentiation showing that SATB2 was downstream of MAPK/ERK pathway.

Common Downstream Targets

Genes regulated by RUNX2 and SATB2 individually have been identified, and there are also genes controlled by both of these transcription factors.[1] RUNX2 was found to directly target many osteoblast-specific genes. The osteoblast-specific cis-acting element 2 (OSE2, ACCACA) is a binding site for RUNX2, and it has been characterized in the promoters of many osteo-specific genes: osteocalcin (OCN), bone sialoprotein (BSP), COL1A1, osterix (OSX), and osteopontin (OPN).[24] SATB2 is also found to target a few genes regulated by RUNX2, such as BSP, COL1A1, and OCN.[1,25] BSP is an essential component of bone extracellular matrix and an important protein for bone development.[26] Several studies have demonstrated that SATB2 regulated BSP by binding to its promoter.[1,10,27] Microarray analysis indicated COL1A1 as a downstream of SATB2.[1] COL1A1 is another osteomarker gene

induced by RUNX2 during osteoblast development that encodes fibrillar collagen in connective tissues.[24,28] One study found that lower RUNX2 level failed to decrease COL1A1 expression in mature osteoblast,[29] indicating that the expression of COL1A1 can be maintained through other pathways independent of RUNX2 and may be a compensatory pathway aided by SATB2.

SATB2 can act as a protein scaffold to enhance the activity of other DNA-binding proteins. Although SATB2 was shown to directly bind to the promoter of OCN, OCN was activated by SATB2 binding and promoting the activity of RUNX2.[1] It was suggested that the interaction of SATB2 with RUNX2 occurs at the 108 N-terminal residues of RUNX2, where a QA domain is present to mediate this activation.[1] QA domain of RUNX2 was believed to be responsible for preventing the heterodimerization with core-binding factor (CBF)-β, a co-factor for RUNX2 transactivity.[30,31] SATB2 may have compromised the function of the QA domain of RUNX2, promoting RUNX2 binding with CBF-β, thereby stimulating the transcription of genes controlled by the RUNX2/CBF-β complex, e.g., OCN, and other targets necessary for bone development.

Intermediate Genes between Runt-related Transcription Factor 2 and SATB2

RUNX2 and SATB2 are also connected by osteomarkers. OSX is a critical transcription factor in osteoblast differentiation and is downstream of RUNX2 regulated by an OSE2 element that binds RUNX2.[32-34] OSX was reported to regulate SATB2 expression in C2C12 cells by promoter activation.[27] Another study reported that SATB2 increased RUNX2 transactivity on OSX promoter and SATB2 also increased OSX expression independent of RUNX2.[10] This indicates a positive feedback signal in the RUNX2/OSX/SATB2 pathway and suggests SATB2 also functions independently of RUNX2, to regulate OSX expression.

Although many studies placed SATB2 downstream of RUNX2 during osteogenesis, SATB2 can also regulate upstream. HOXA2 is a direct target of SATB2 and a negative regulator of RUNX2.[1,35] HOXA2 was upregulated in SATB2$^{-/-}$ embryos and osteoblasts, and SATB2 was able to bind to the EII enhancer of HOXA2 *in vivo* and decrease H3K4me at the endogenous HOXA2 promoter.[1] HOXA2 inhibits skeletal formation,[35,36] and inactivation of the HOXA2 gene in SATB2$^{-/-}$ embryos rescues the delay in calvarial bone formation.[1] RUNX2 expression was found increased in the HOXA2-mutated embryos,[35] indicating that HOXA2 might modulate SATB2 and RUNX2 signaling by SATB2-repressing HOXA2, activating RUNX2 expression. In fact, studies reported that overexpression of SATB2 in the BMSCs rapidly induced osteogenic differentiation with increased expression of RUNX2 as well as other osteo-specific markers such as BSP, OSX, and ALP.[37] Another study suggested that SATB2 interacted and upregulated RUNX2 in the early stages of osteoblast differentiation.[38] During craniofacial development, SATB2 was activated early, allowing the induction of RUNX2 by inhibiting HOXA2.[38] SATB2-induced RUNX2 was reported by Mi *et al*., although it was not clear whether the induction was a direct interaction between SATB2 and RUNX2 or mediated through other factors. The authors suggested that SATB2 might be involved in the BMP-2/RUNX2 pathway with BMP-2–activating SATB2, which then induces RUNX2 to mediate osteoblast differentiation.[39]

miRNAs are short noncoding RNA molecules that target mRNA degradation, inhibiting protein translation and altering chromatin structure to repress gene expression.[40-43] A group of miRNAs associated with osteogenic lineage commitment in the mesenchymal stem cells (MSCs) has been characterized and termed osteo-miRNA,[44] many of which are involved in RUNX2/SATB2 network during osteogenesis. miR-31 and miR-23a~27a~24-2 are negatively regulated by RUNX2 to suppress SATB2 expression in osteogenesis.[45-47] SATB2 was found to control the expression of many miRNAs that negatively correlated with the expression of SATB2, including miR-125b, miR-132, miR-128, miR-127, miR-143, and miR-22,[48] many of which also target RUNX2 as confirmed by the TargetScan (http://www.targetscan.org). Some miRNA downstream of RUNX2, such as miR-690 and miR-185, was found to target SATB2.[49,50] A list of miRNAs involved with SATB2 and RUNX2 is shown in Table 2 along with their role in osteogenesis.

An illustration of SATB2 and RUNX2 network in the bone development is shown in Figure 1. In total, SATB2 and RUNX2 function in the same network but have independent roles in osteoblast differentiation. In addition, SATB2 induces expression of factors that limit osteoblast differentiation, such as ATF3 and AP2-β,[10,27] indicating that RUNX2 and SATB2 might act to balance differentiation at certain stages. Considering this intricate interaction between RUNX2 and osteoblast differentiation during normal bone development, it is important to consider the conditions in which they are aberrantly expressed and the targets they induce to initiate cancer and promote disease progression.

Runt-related Transcription Factor 2 and SATB2 in Carcinogenesis

Transitioning from a normal cell to a cancer cell occurs through germline mutations or epigenetic alterations caused by exposure to carcinogens. These

Table 2: The microRNAs cooperating with Runt-related transcription factor 2 and SATB2 in osteogenesis

Genes	Target gene	Regulator	Study model	Function
miR-31[45,46]	SATB2*	RUNX2*	Rat BMSC; Human primary dental follicle cell	Inhibit osteogenic transcription factors; Regulate matrix remodeling and osteoclast activity
miR-23a~27a~24-2[47]	SATB2*	RUNX2*	ROB, MC3T3-E1	Suppress osteogenic differentiation
miR-690[49]	SATB2	RUNX2*	C2C12	Suppress osteogenic differentiation
miR-185[50]	SATB2	RUNX2*	MC3T3-E1	Suppress amelogenesis and osteogenesis
miR-205[51]	RUNX2, SATB2*		Rat BMSC	Suppress osteogenic differentiation
miR-127[48,52]	RUNX2*	SATB2	Rat BMSC	Promote chondrogenic and cartilage differentiation
miR-128[48,53]	RUNX2*	SATB2	Human MSCs	Promote osteogenic differentiation
miR-132[48,54]	RUNX2*	SATB2	Human osteoblast	Suppress osteoblast differentiation
miR-22[48,55]	RUNX2*	SATB2	Mouse pre-osteoblast	Stimulate osteoblast differentiation; Suppress adipogenic differentiation
miR-218[48,56]	RUNX2*	SATB2	MEC3T3-E1	Suppress osteoblast differentiation
miR-103a[48,57]	RUNX2*	SATB2	hFOB 1.19	Inhibit bone formation
miR-125b[48,58]	RUNX2*	SATB2	Human BMSC	Suppress osteogenic differentiation

*Experimentally confirmed. BMSC: Bone mesenchymal stem cell, ROB: Rat primary osteoblasts, MC3T3-E1: Mouse pre-osteoblast cell line, C2C12: Myogenic progenitor cell, MSCs: Mesenchymal stem cells; hFOB 1.19: Human osteoblast

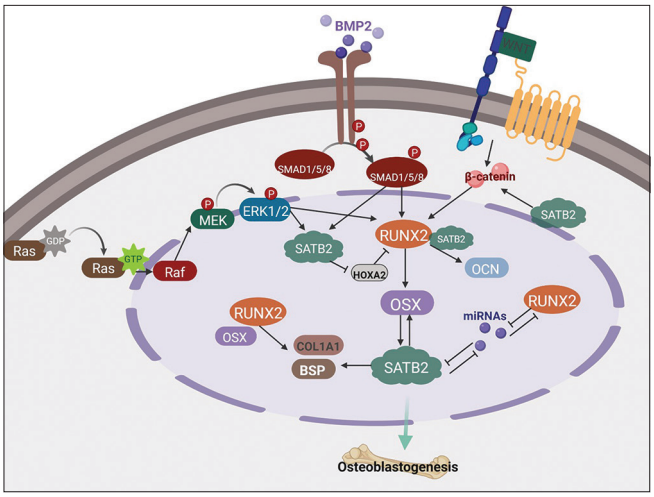

Figure 1: An illustration of SATB2 and Runt-related transcription factor 2 network in bone development. Runt-related transcription factor 2 and SATB2 share common upstream regulators such as MAPK/ERK pathway and bone morphogenetic protein/SMAD pathway, and they have overlapping downstream genes such as osteocalcin, bone sialoprotein, and COL1A1 in osteogenesis. They are connected by HOXA2, osterix, and various microRNAs in either direction, allowing Runt-related transcription factor 2 and SATB2 to act as an upstream regulator for one another. Among the microRNAs connecting SATB2 and Runt-related transcription factor 2, miR-31 and miR-23-27a ~24-2 have solid evidence supporting the pathway axis in osteoblast differentiation. In addition, SATB2 also displays physical interaction with Runt-related transcription factor 2 to regulate its transcription activity and induce the expression of osteocalcin

germline mutations or epigenetic changes may result in haploinsufficiency of tumor suppressors or increased expression of oncogenes. Tumor suppressors activate pathways that limit cell proliferation, promote contact inhibition, prevent cell migration and invasion, and support normal autophagy and apoptosis. Oncogenes, however, activate pathways that increase cell proliferation, migration, and invasion while preventing contact inhibition and programmed cell death. It is important to understand the roles of RUNX2 and SATB2 as either tumor suppressors or oncogenes as they cooperate or antagonize one another in promoting cancer progression.

Runt-related transcription factor 2 and SATB2 as tumor suppressor

The role of SATB2 in cancers has been reviewed by Chen *et al*., suggesting that SATB2 can function either as an oncogene or tumor suppressor.[59] For example, SATB2 is recognized as a biomarker for colorectal cancer (CRC). However, in some studies, CRC cells exhibit low SATB2 mRNA expression; however, when SATB2 expression was turned on, cancer cell proliferation was reduced.[60] RUNX2 also exerts paradoxical effects in carcinogenesis, acting as a tumor suppressor or oncogene.[61] RUNX2 serves as a regulator for cell cycle and inhibits cell proliferation during osteogenesis.[62] RUNX2 can arrest the cell cycle in the G1 phase, allowing cells to exit the cell cycle and avoid abnormal cell proliferation.[63] A loss of RUNX2 function was related to enhanced *in vitro* growth potential in RUNX2-deficient osteoblasts.[64]

Runt-related transcription factor 2 and SATB2 as oncogene

On the other hand, RUNX2 and SATB2 are well-known oncogenes. While SATB2 expression is associated with normal embryonic development, its expression in cancers, however, determines overall progression and patient prognosis. SATB2 was first reported to mediate head and neck squamous cell carcinoma (HNSCC) as a novel binding partner for p63 and p73 promoting chemoresistance, and its expression was associated with advanced-stage HNSCC.[65] SATB2 was also a diagnostic marker for CRC.[66] Increased expression of SATB2 has been observed in many other cancers such as osteosarcoma,[67] pancreatic cancer,[68] breast cancer,[69,70] endometrial cancer,[71] and cancer stem cells (CSCs).[64] In addition, many downstream targets of SATB2 such as B-cell lymphoma 2 (BCL-2), BSP, c-MYC, KLF-4, HOXA2, and NANOG are key regulators of cell pluripotency and survival.[68]

RUNX2 is expressed only in a limited number of nonosseous tissues, including testis,[72,73] mammary epithelium,[74,75] thymus,[75] endothelial cells,[76] and transformed cells.[64] Aberrant expression of RUNX2 has been described in the progression and metastasis of several human cancers, including pancreatic cancer,[77] thyroid cancer,[78] bone cancer,[79] breast cancer,[80] and prostate cancer.[81] RUNX2 promoted cell proliferation and inhibited cell death by repressing transcription of p21/CDKN1A in fibroblasts and osteosarcoma cells, which act to arrest in the G1 phase.[82] RUNX2 activated Gpr30 expression and reduced Rgs2 level to increase mitogenic signaling through cAMP and G-protein–coupled receptors.[83] Moreover, downstream genes of RUNX2, such as MMPs, vascular endothelial growth factor (VEGF), BSP, and c-MYC, are involved in promoting cancer cell metastasis.[74,84-86] RUNX2-regulated genes such as SOX9, SNAI2, SNAI3, TWIST1, and SMAD3 are potential inducers of cell invasion.[87,88]

Runt-related transcription factor 2/SATB2 in osteosarcoma

Osteosarcoma is an aggressive bone cancer with poor clinical outcome. It was conventionally believed that osteosarcoma originated from osteoblasts due to the presence of the bone matrix osteoid, whereas it was later found that it can originate from the differentiation of MSCs to a mature osteoblasts.[89] RUNX2 and SATB2 are both key transcription factors in osteoblast lineage commitment and development; thus, cell transformation and metastasis would be supported by aberrant expression of these proteins during osteogenesis.

Improper expression of the development-related genes, at the wrong time, contributed to carcinogenesis. The expression level of RUNX2 was dynamic from pre-osteoblast to immature osteoblasts, and finally to the maturation of osteoblast.[90] Early onset of RUNX2 expression in MSCs may direct the cells to osteoblast progenitors, which is required for their expansion.[91] The expression of RUNX2 increases in immature osteoblast, regulating the expression of many bone matrix proteins.[92] However, in the late stage of osteogenesis, RUNX2 was largely decreased to allow maturation of osteoblasts.[93] RUNX2 was not required for the expression of major bone matrix genes in mature osteoblast, and continuous expression of RUNX2 at high levels was found to inhibit and impair bone formation in immature mouse osteoblasts.[90,93] RUNX2 overexpression was confirmed in osteosarcomas and associated with poor tumor response to chemotherapy.[94] A frequent amplification and rearrangement where the RUNX2 gene is located (6p12–p21) was found in osteosarcoma.[94] Deregulation of cell cycle control might be a factor promoting osteosarcoma mediated by RUNX2, since studies had reported that high levels of RUNX2 in SAOS-2, a human osteogenic sarcoma cell line, lost cell cycle control.[95] Further studies indicated that the function of RUNX2 in osteosarcoma was related to pRB and p53.[96] Activation signaling pathways for RUNX2, such as PI3K/Akt, Wnt, BMP/TGF-β, MAPK/ERK, and Notch, were all found turned on in osteosarcoma,[97-100] indicating that increased expression of RUNX2 at the wrong time, e.g., final stage of osteogenesis, caused formation of too many immature osteoblast cells, resulting in osteosarcoma.

SATB2 was also found commonly expressed in osteosarcoma and has been suggested as a sensitive marker for this cancer.[67] However, SATB2 expression was not specific for osteosarcoma since it was also expressed in other types of bone sarcomas, such as undifferentiated pleomorphic sarcoma and bone fibrosarcoma, and high-grade chondrosarcomas.[101] It is a marker for osteoblast differentiation in both benign and malignant bone tumors. One study reported that SATB2 enhanced osteosarcoma stem cell-like characteristics through the induction of N-cadherin and NF-κB signaling, and knockdown of SATB2 repressed these genes, leading to impaired osteosarcoma sphere formation and tumor cell proliferation.[102] In normal cells, NF-κB is activated by host defense mechanisms in response to inflammation, but this pathway activates osteosarcoma tumorigenesis.[103] However, NF-κB is an inhibitor for RUNX2 in osteoblasts since induced expression of NF-κB was found to repress the binding of RUNX2 with β-catenin and with the downstream target genes such as BSP and OCN, leading to decreased expression of matrix protein and bone formation.[104] Although NF-κB failed to affect RUNX2 expression, considering the transactivity of RUNX2 can be mediated by co-factors, a compensation of RUNX2 expression would be possible by prolonged inflammation. In addition, SATB2 is an activator of β-catenin,[105] allowing a counteracting effect with NF-κB on RUNX2, which contributes to SATB2-driven osteosarcoma.

c-MYC is a transcription factor that plays an important role in cell proliferation, apoptosis, and metabolism.[106] It is involved in cancers such as ovarian, breast, pancreatic, gastric, and uterine cancer and CRC.[107,108] It was also found overexpressed in osteosarcoma and this was related with metastasis.[109] MYC promoted OS cell invasion by MEK/ERK pathway.[110] c-MYC was a target for RUNX2, and it was overexpressed in human and mouse OS cells compared to MSCs. RUNX2 promoted c-MYC expression by recruiting the COMPASS-like complex to the promoter of c-MYC, and RUNX2/c-MYC pathway contributed to survival of OS cells. Although RUNX2 is required to maintain the expression of c-MYC, in OS cells, c-MYC can be induced through other factors.[111] In fact, c-MYC is also a downstream

target for SATB2. It was found that SATB2 can directly target c-MYC promoter and regulate its transcription in CSCs.[70] Ectopic expression of c-MYC in mature fibroblasts inhibited cell differentiation and promoted formation of multifunctional progenitor cells. SATB2 alone increased expression of c-MYC as well as other pluripotency factors such as Oct-4, SOX-2, and KLF-4, to induce de-differentiation and transformation of human mammary epithelial cells (HMEGs) into progenitor cells.[70]

Runt-related Transcription Factor 2 and SATB2 in Other Cancers

A search of the cBio genomic cancer portal (http://www.cbioportal.org) for RUNX2 and SATB2 in the Cancer Genome Atlas database found expression of these two transcription factors in cancers, including testicular, bladder, and lung squamous carcinoma, HNSCC, melanoma, CRC, and prostate, breast, papillary thyroid, and cervical cancer [Table 3].

Lung squamous cell carcinoma is a major subtype of nonsmall cell lung cancer (NSCLC) and accounts for about 25%–30% of all lung cancers. RUNX2 was suggested as a novel prognostic marker in NSCLC since its expression correlated with tumor size, tumor stage, and lymph node metastasis.[112] Although SATB2 has been characterized as a tumor suppressor for NSCLC,[113] SATB2 mediated Beas2B cell transformation by metal carcinogens.[5] Inhibition of SATB2 in transformed Beas2B cells reduced cell proliferation and anchorage-independent growth.[6] SATB2 was induced by arsenic exposure in Beas2B by the downregulation of miR-31, following induction of RUNX2 during cellular transformation.[114] miR-31 was implicated as an important negative regulator in osteogenesis with RUNX2 and SATB2 in an osteoblast differentiation pathway.[45,46] MiRNA-31 is a pleiotropically acting miRNA involved in CRC,[115-117] squamous cell carcinoma,[118] and breast,[119] gastric,[120] and pancreatic cancer.[121] Two binding sites for miR-31 were characterized in the 3′UTR of SATB2 and identified as a direct target for miR-31 in cancer-associated fibroblasts.[122] The miR-31/SATB2 axis was also active in CRCs in which upregulated miR-31 reduced SATB2 level promoting cell proliferation, invasion, and metastasis.[117]

Table 3: SATB2 and Runt-related transcription factor 2 co-occurred in cancers as in the cBio genomic cancer portal queried Cancer Genome Atlas Database

Cancer type	Log2 OR	*P*	*Q*	Tendency
Testis cancer	>3	0.002	0.002	Co-occurrence
Head and neck squamous cancer	>3	0.002	0.002	Co-occurrence
Bladder cancer	>3	<0.001	0.005	Co-occurrence
Melanoma	2.47	0.006	0.14	Co-occurrence
Lung squamous cell carcinoma	1.846	0.026	0.219	Co-occurrence
Colorectal adenocarcinoma	2.409	0.087	0.087	Co-occurrence
Prostate cancer	0.129	0.618	0.658	Co-occurrence
Breast cancer	0.879	0.249	0.358	Co-occurrence
Papillary thyroid cancer	2.338	0.085	0.312	Co-occurrence
Cervical cancer	2.249	0.247	0.829	Co-occurrence

OR: Odds ratio

Wnt/β-catenin pathway plays an important role in SATB2-induced CRC,[123,124] while RUNX2 is known to be downstream of Wnt/β-catenin pathway in osteogenesis.[125] An increased level of RUNX2 was found in CRC cells, confirming its function in CRC metastasis, TMN stages, and prognosis.[126-128] SATB2 was suggested to be a diagnostic marker for CRCs since SATB2 stained positively in 71%–97% of primary and metastatic CRCs biopsies with immunohistochemistry. Reduced expression of SATB2 in colon cancer was associated with poor prognosis, while increased expression enhanced therapeutic sensitivity.[66,129-132] One study found that SATB2 induction and subsequent transformation of colon epithelial cells (CRL-1831) were mediated through Wnt/β-catenin/TCF/LEF pathway.[105] Many downstream genes of the pathway have been associated with cell transformation, including c-MYC, cyclin, and VEGF.[105] Many studies have indicated the role of VEGF in colon cancer.[133] VEGF is an important factor during osteogenesis in directing the invasion of blood vessels into cartilage, and it is also a shared downstream target by SATB2 and RUNX2.[10,134] However, VEGF was not directly targeted by SATB2. As a target of Wnt/β-catenin signaling, RUNX2 is very likely involved in the SATB2-induced VEGF via Wnt/β-catenin pathway in CRC carcinogenesis. The HDAC4/RUNX2/VEGF pathway was investigated in chondrosarcoma, suggesting that reduced HDAC4 induced expression of RUNX2 and thereby increased VEGF to enhance angiogenesis, tumor growth, and metastasis.[86]

RUNX2 level was found aberrantly increased in pancreatic cancer, and its expression was associated with poor prognosis.[77] SATB2 was also found highly expressed in pancreatic CSCs causing cell proliferation and EMT by inducing the expression of many pluripotency and stem cell markers such as NANOG, OCT-4, CD24, CD44, as well as BCL-2.[68] BCL-2 regulates cell apoptosis and is a pluripotency-maintaining factor directly targeted by SATB2.[68] However, in osteoblasts, deficient in BCL-2 was associated with increased expression of RUNX2 and other osteogenic markers such as OSX, COL1A1, OCN, and OPN, indicating a negative relationship between BCL-2 and osteoblast differentiation.[135,136] In MG-62, nitric oxide induced expression of BCL-2 by

inducing RUNX2 and promoted cancer cell survival under oxidative stress conditions.[137] Hypoxia-induced expression of RUNX2 increased cell viability by inducing the cell apoptosis-associated factor, BCL-2, resulting in apoptosis resistance in prostate cancer cells.[81]

RUNX2 was upregulated in the HNSCC with lymph node metastasis and was identified as a key transcription factor in promoting HNSCC progression and metastasis. RUNX2 level was found negatively regulated by miR-376c, which mediated cell metastasis via the RUNX2/inhibin subunit beta A axis.[138] SATB2 was highly expressed in advanced HNSCC enhancing resistance to chemotherapy and radiation-induced cell death by promoting the dominant-negative p63a level and subsequently inhibiting proapoptotic Tap73b and p53 signaling.[65] SATB2 is also a direct target of miR-376c (http://www.targetscan.org), indicating that RUNX2 and SATB2 could be co-regulated in HNSCCs.

RUNX2 expression is increased in bladder cancers (compared to noncancerous bladder tissue/cells), and it has been suggested that RUNX2 level in bladder cancer cells was regulated by miRNAs such as miR-217 and miR-154.[139,140] Calcification is one of the symptoms of papillary thyroid carcinoma (PTC), and RUNX2 when induced by HOXA9 was associated with PTC calcification and invasiveness.[78] An increased expression of RUNX2 was observed in melanoma cells, and RUNX2 regulated expression of matrix metalloproteases implicated in tumor invasion and metastasis, which furthers the conclusion that regulated RUNX2 expression is important to maintain specialized mesenchymal lineages.[141] A Runt domain of RUNX2 was necessary for melanoma cell proliferation and cell migration,[134] and RUNX2 may probably mediate cell malignancy by regulating downstream genes such as BSP, MMPs, and COL3.[141] SATB2 was also found increased by an unknown mechanism in PTC, breast cancer (BC), and melanoma cancer cells as shown in the Human Protein Atlas Database. A summary of RUNX2 and SATB2 in various cancers is listed in Table 4.

MicroRNAs in Runt-related transcription factor 2/SATB2 network in carcinogenesis

Both SATB2 and RUNX2 have been implicated in the regulation of miRNA in cancers.[59,140] MiRNAs connecting them with osteogenesis might also be important in RUNX2/SATB2-mediated carcinogenesis. miR-31 not only links RUNX2 and SATB2 with osteogenic differentiation but also negatively regulates SATB2 in mediating lung and colon cancer.[114,117] miR-23a connects RUNX2 and SATB2 in osteoblasts, and it is also targeted by RUNX2 in mouse liver cancer cells to increase metastatic potential.[142] A summary of miRNAs involved in RUNX2/SATB2 pathway and carcinogenesis is listed in Table 5.

miR-127 is an upstream regulator of RUNX2 in rat BMSCs (bone mesenchymal stromal cells).[52] Osteosarcoma cells had reduced miR-127 level, while the restoration of miR-127 inhibited cell migration, invasion, and increased apoptosis.[146] An inverse expression level between miR-153 and RUNX2 was observed in breast cancers and RUNX2 overexpression reversed cell proliferation, migration, and invasion of breast cancer cells which was suppressed by miR-153.[145] miR-103 inhibited bone formation by acting as a mechanosensitive miRNA and directly targeting RUNX2 at its 3'UTR.[57] It also prolonged the Wnt signaling and promoted CRC stemness along with miR-107 pathway.[142] miR-34c downregulated RUNX2 in OS cells and was negatively regulated by p53, creating a novel network p53-miR-34c-RUNX2 in osseous cells and osteosarcoma (OS) cells.[147] SATB2 was found upregulated when miR-34c was silenced by DNA methylation increasing cell metastasis and EMT in the CRC cells.[148] miR-211 significantly reduced SATB2 level in hepatocellular carcinoma, resulting in the reduction of cell proliferation and migration.[149] miR-211 with its homologous miR-204 negatively regulated RUNX2 to inhibit osteogenesis and promoted adipogenesis in mesenchymal progenitor cells and BMSCs.[150] miR-205 was found to target RUNX2 in inhibiting pancreatic cancer progression.[143] Together, this suggests that SATB2-driven miRNA expression may alter RUNX2 activity and that epigenetic alterations of SATB2 may affect normal osteogenesis or cell differentiation, thereby resulting in bone dysmorphia, osteosarcoma, or other cancers. Additional evidence is required to confirm the axis connected by miRNA under different cell context.

In addition, many downstream miRNAs regulated by SATB2 are also potential regulators for CBF-β with its 3'UTR directly targeted by miR-143, miR-128, miR-124, miR-125a, miR-381, and miR-326, as searched on the TargetScan.[48] Other than by physically interacting with RUNX2 domains, this provides a new potential mechanism for SATB2 affecting CBF-β binding and cooperating with RUNX2 to regulate downstream genes [Figure 2].

Conclusion

It is known that both RUNX2 and SATB2 are key regulators of osteoblast differentiation and development. While many studies tend to place RUNX2 upstream of SATB2, the interaction between the two transcription factors is complex. They are linked by common upstream regulators and osteo-specific markers as well as multiple miRNAs, allowing them to act upstream or

Table 4: Runt-related transcription factor 2 and SATB2 in cancers

Cancer type	Gene	Author	Year	Significant finding and conclusion
Osteosarcoma	SATB2	Davis and Horvai[67]	2016	SATB2 is a sensitive marker for osteosarcoma
		Machado *et al*.[101]	2016	SATB2 immunoexpressing can help to distinguish osteosarcoma from its mimickers, except between chondroblast osteosarcoma and high-grade chondrosarcoma
		Xu *et al*.[102]	2017	SATB2 plays an important role in regulating osteosarcoma stem cell-like properties and tumor growth, while metformin reduces the cancer-like phenotypes and tumor growth via inhibition of N-cadherin/NF-kB signaling
	RUNX2	Westendorf *et al*.[82]	2002	RUNX2 promotes cell proliferation and inhibits cell death by interacting with HDAC6 and repressing p21 promoter in osteosarcoma cells
		Sadikovic *et al*.[94]	2010	RUNX2 is significantly overexpressed in osteosarcoma and is associated with poor chemotherapy response
		Galindo *et al*.[95]	2005	RUNX2 level is not regulated by cell proliferation and remained high in osteosarcoma cells
		Pereira *et al*.[96]	2009	pRB, p53, and RUNX2 form a bone-specific regulatory network that controls normal cell cycle progression in osteoblasts and that is deregulated in osteosarcoma cells
CRC	SATB2	Dragomir *et al*.[66]	2014	SATB2 can be a diagnostic marker for primary and metastatic CRCs
		Yu *et al*.[105]	2017	SATB2/β-catenin/TCF-LEF pathway induces cellular transformation by generating cancer stem cells in colorectal cancer
		Yang *et al*.[117]	2013	miR-31 mediates colorectal cancers progression by directly inhibiting SATB2 level
		Eberhard *et al*.[129]	2012	SATB2 expression level can be a prognosis marker for colon cancer
		Lin *et al*.[130]	2014	SATB2 and cadherin-17 are sensitive and specific immunomarkers for colorectal carcinomas
		Moh *et al*.[131]	2016	High SATB2 expression can distinguish ovarian metastasis of colorectal origin from primary ovarian tumors
		Zhang *et al*.[132]	2018	SATB2 can be a promising biomarker for identifying a colorectal origin from liver metastatic adenocarcinomas
	RUNX2	Wen *et al*.[126]	2017	Inhibiting RUNX2 by miR-539 can repress colorectal cancer progression and can be a potential therapeutic approach
		Wang *et al*.[127]	2016	CBX4 can suppress metastasis of colorectal carcinoma via inhibiting RUNX2 promoter
		Ji *et al*.[128]	2019	MALAT1 elevates RUNX2 expression in CRC cells, and they are two biomarkers for predicting the recurrence and metastasis of CRC
Breast cancer	SATB2	Yu *et al*.[70]	2017	SATB2 is highly expressed in human breast cancer cell lines and may have a role in regulation of pluripotency, cell survival, and proliferation
		Patani *et al*.[69]	2009	SATB2 mRNA expression is significantly associated with increasing tumor grade and poorer overall survival in breast cancer
	RUNX2	Zuo Z, *et al*.[142]	2019	Inhibition of RUNX2 by miR-153 can reverse breast tumor growth and metastasis, and miR-153/RUNX2 axis may be used as a potential therapeutic target in breast cancer treatment
		Barnes *et al*.[80]	2003	RUNX2 expression in metastatic breast cancer cells and may explain the metastasize to the bone
HNSCC	SATB2	Chung *et al*.[65]	2010	SATB2 expression positively correlates with HNSCC chemoresistance, and knockdown of SATB2 resensitizes HNSCC to chemotherapy- and γ-irradiation-induced apoptosis
	RUNX2	Chang *et al*.[138]	2016	RUNX2 is widely upregulated in HNSCC and downregulation of RUNX2 by miR-376c will suppress metastatic capability
Pancreatic cancer	SATB2	Yu *et al*.[68]	2016	SATB2 can induce dedifferentiation by inducing stemness and may have a role in pancreatic carcinogenesis and can be used as a diagnostic biomarker
	RUNX2	Kayed *et al*.[77]	2007	RUNX2 is overexpressed in pancreatic cancer cells and is regulated by cytokines such as TGF-1 and BMP-2 to modulate the expression of extracellular matrix modulators
		Zhuang *et al*.[143]	2019	miR-205 is a tumor suppressor by targeting RUNX2 in pancreatic cancer to inhibit cell proliferation and migration
NSCLC	SATB2	Ma *et al*.[113]	2018	SATB2 suppressed lung cancer cell invasion and metastasis and regulated the expression of EMT-related proteins and histone methylation by G9a
		Clancy *et al*.[5]	2012	SATB2 is a commonly increased gene during metal-induced bronchial epithelial cell transformation
		Wu *et al*.[6]	2016	SATB2 plays a pivotal role in Ni-induced bronchial epithelial cell transformation
		Chen *et al*.[114]	2018	SATB2 plays an important role in arsenic-induced bronchial epithelial cell transformation

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Table 4: Contd...

Cancer type	Gene	Author	Year	Significant finding and conclusion
	RUNX2	Li *et al*.[112]	2013	RUNX2 may play an important role in NSCLC tumorigenesis and it might serve as a novel prognostic marker in NSCLC
Thyroid cancer	RUNX2	Niu *et al*.[78]	2012	Enhanced RUNX2 is functionally linked to tumor invasion and metastasis of thyroid carcinoma by regulating EMT-related molecules, matrix metalloproteinase, and angiogenic/lymphangiogenic factors
Prostate cancer	RUNX2	Browne *et al*.[81]	2012	Increased expression of RUNX2 modulates the expression of apoptosis-associated factors, specifically Bcl-2, serves as a contributing mechanism for progression of prostate cancer cells to a malignant phenotype
Bladder cancer	RUNX2	Zhao *et al*.[139]	2017	Inhibition of RUNX2 by miR-154 in bladder cancer cells can inhibit cellular malignancy
		Huang *et al*.[140]	2018	RUNX2 expression induced by has_circ_0000144 is critical for its oncogenic role, while inhibition of RUNX2 by miR-217 suppresses bladder cancer cell proliferation and invasion
Melanoma	RUNX2	Riminucci *et al*.[141]	2003	The expression of RUNX2 may control the BSP expression and invasive behavior in malignant melanoma cells
		Deiana *et al*.[134]	2018	RUNT domain is important in melanoma metastasis and cell migration, and RUNX2 may serve as a prospective target in malignant melanoma therapy
Endometrial cancer	SATB2	McCluggage and Van de Vijver[71]	2019	Increased expression of SATB2 in modular metaplasia is associated with the endometrioid histotype of endometrial

HNSCC: Head and neck squamous cell carcinoma, CRC: Colorectal cancer, NSCLC: Nonsmall cell lung cancer, BMP: Bone morphogenic protein, TGF: Transforming growth factor, EMT: Epithelial–mesenchymal transition, RUNX2: Runt-related transcription factor 2, NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells, TCF-LEF: T-cell factor/lymphoid enhancer factor

Table 5: The microRNAs connecting Runt-related transcription factor 2 and SATB2 in carcinogenesis

miRNA	Target gene	Regulator	Cancer type	Function/activity
miR-31[114,117]	SATB2*	RUNX2	Lung cancer, CRC	Inhibition of lung epithelial cell transformation induced by arsenic; regulate CRC cell proliferation, invasion, and metastasis
miR-23a[144]	SATB2	RUNX2*	Liver cancer	Increase the metastatic potential of mouse liver cancer cell
miR-153[145]	RUNX2*	SATB2	Breast cancer	Suppress breast cancer cell proliferation, migration, and invasion
miR-127[146]	RUNX2*	SATB2	Osteosarcoma	Inhibit osteosarcoma cell migration, invasion, and induced cell apoptosis
miR-103[142]	RUNX2*	SATB2	CRC	Promote CRC stemness
miR-34c[147]	RUNX2*		Osteosarcoma	Regulate cell proliferation
miR-34c[148]	SATB2*		CRC	Regulate cell metastasis
miR-205[143]	RUNX2*	SATB2	Pancreatic cancer	Inhibit pancreatic cancer progression
miR-211[149]	SATB2*/RUNX2		Liver cancer	Reduce cell proliferation and migration

*Experimentally confirmed. CRC: Colorectal cancer, miRNA: MicroRNA, RUNX2: Runt-related transcription factor 2

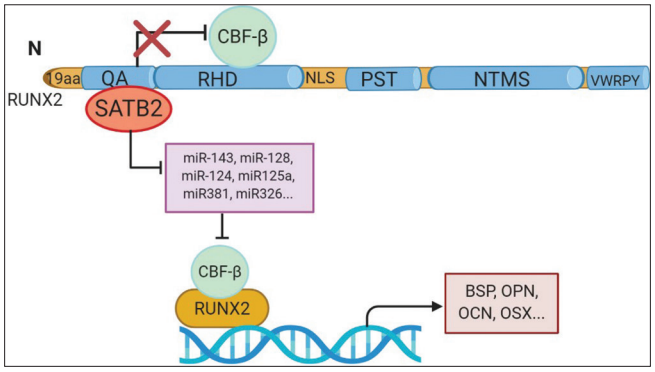

Figure 2: An illustration of a potential pathway that SATB2 mediated core-binding factor-β binding with Runt-related transcription factor 2 by inhibiting QA domain and microRNAs that target core-binding factor-β to induce the expression of Runt-related transcription factor 2 downstream genes

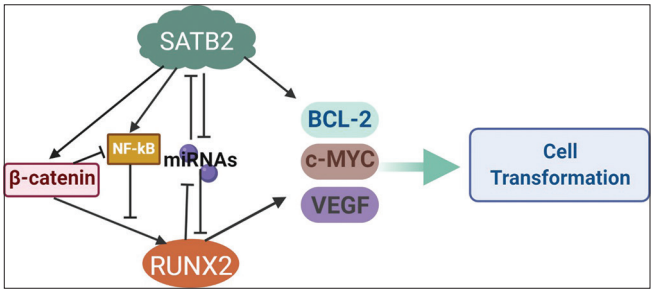

Figure 3: An illustration of a possible SATB2 and Runt-related transcription factor 2 network in carcinogenesis. SATB2 and Runt-related transcription factor 2 are linked by multiple microRNAs in the pathways of carcinogenesis. Improper activation of Runt-related transcription factor 2 might also be induced by SATB2 via β-catenin/NF-kB pathway under a prolonged inflammation condition. Runt-related transcription factor 2 and SATB2 also share many downstream targets such as B-cell lymphoma 2, c-MYC, and vascular endothelial growth factor in mediating cell transformation

downstream of each other, or function in concert in the network that orchestrates osteogenesis. In this review, we describe how RUNX2 and SATB2 were involved in many cancers and improper expression of these proteins at a wrong time during osteogenesis or wrong place in other organs contributes to tumorigenesis. However, the exact pathway between the two proteins has not been well studied as these bone regulators act

in concert, independently, or in opposition depending on cellular conditions and context. This review provides a comprehensive summary of the current studies addressing the relationship between RUNX2 and SATB2 in osteogenesis and sheds lights on their roles in carcinogenesis. A summary of RUNX2/SATB2 network in carcinogenesis is shown in Figure 3. Some potential mechanisms and pathways between RUNX2 and SATB2 have also been proposed, to involve CBF-β, miRNAs, and β-catenin. In the end, more studies are needed to clarify the relationship between SATB2 and RUNX2, such as the mechanism of their physical interaction between the two proteins, promoter-binding possibilities between the two transcription factors, and roles of different miRNAs in their regulation under different cell context.

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Conflicts of interest

There are no conflicts of interest.

References

1. Dobreva G, Chahrour M, Dautzenberg M, Chirivella L, Kanzler B, Fariñas I, *et al*. SATB2 is a multifunctional determinant of craniofacial patterning and osteoblast differentiation. Cell 2006;125:971-86.
2. Rosenfeld JA, Ballif BC, Lucas A, Spence EJ, Powell C, Aylsworth AS, *et al*. Small deletions of SATB2 cause some of the clinical features of the 2q33.1 microdeletion syndrome. PLoS One 2009;4:e6568.
3. FitzPatrick DR, Carr IM, McLaren L, Leek JP, Wightman P, Williamson K, *et al*. Identification of SATB2 as the cleft palate gene on 2q32-q33. Hum Mol Genet 2003;12:2491-501.
4. Magnusson K, de Wit M, Brennan DJ, Johnson LB, McGee SF, Lundberg E, *et al*. SATB2 in combination with cytokeratin 20 identifies over 95% of all colorectal carcinomas. Am J Surg Pathol 2011;35:937-48.
5. Clancy HA, Sun H, Passantino L, Kluz T, Munoz A, Zavadil J, *et al*. Gene expression changes in human lung cells exposed to arsenic, chromium, nickel or vanadium indicate the first steps in cancer. Metallomics 2012;4:784-93.
6. Wu F, Jordan A, Kluz T, Shen S, Sun H, Cartularo LA, *et al*. SATB2 expression increased anchorage-independent growth and cell migration in human bronchial epithelial cells. Toxicol Appl Pharmacol 2016;293:30-6.
7. Komori T. Regulation of proliferation, differentiation and functions of osteoblasts by runx2. Int J Mol Sci 2019;20(7):1694.
8. Komori T, Yagi H, Nomura S, Yamaguchi A, Sasaki K, Deguchi K, *et al*. Targeted disruption of Cbfa1 results in a complete lack of bone formation owing to maturational arrest of osteoblasts. Cell 1997;89:755-64.
9. Otto F, Thornell AP, Crompton T, Denzel A, Gilmour KC, Rosewell IR, *et al*. Cbfa1, a candidate gene for cleidocranial dysplasia syndrome, is essential for osteoblast differentiation and bone development. Cell 1997;89:765-71.
10. Zhang J, Tu Q, Grosschedl R, Kim MS, Griffin T, Drissi H, *et al*. Roles of SATB2 in osteogenic differentiation and bone regeneration. Tissue Eng Part A 2011;17:1767-76.
11. Zhao X, Qu Z, Tickner J, Xu J, Dai K, Zhang X. The role of SATB2 in skeletogenesis and human disease. Cytokine Growth Factor Rev 2014;25:35-44.
12. Yu L, Xu Y, Qu H, Yu Y, Li W, Zhao Y, *et al*. Decrease of MiR-31 induced by TNF-α inhibitor activates SATB2/RUNX2 pathway and promotes osteogenic differentiation in ethanol-induced osteonecrosis. J Cell Physiol 2019;234:4314-26.
13. Javed A, Bae JS, Afzal F, Gutierrez S, Pratap J, Zaidi SK, *et al*. Structural coupling of Smad and Runx2 for execution of the BMP2 osteogenic signal. J Biol Chem 2008;283:8412-22.
14. Hassan MQ, Tare RS, Lee SH, Mandeville M, Morasso MI, Javed A, *et al*. BMP2 commitment to the osteogenic lineage involves activation of Runx2 by DLX3 and a homeodomain transcriptional network. J Biol Chem 2006;281:40515-26.
15. Bonilla-Claudio M, Wang J, Bai Y, Klysik E, Selever J, Martin JF. Bmp signaling regulates a dose-dependent transcriptional program to control facial skeletal development. Development 2012;139:709-19.
16. Lou J, Tu Y, Li S, Manske PR. Involvement of ERK in BMP-2 induced osteoblastic differentiation of mesenchymal progenitor cell line C3H10T1/2. Biochem Biophys Res Commun 2000;268:757-62.
17. Franceschi RT, Ge C. Control of the osteoblast lineage by mitogen-activated protein kinase signaling. Curr Mol Biol Rep 2017;3:122-32.
18. Costessi A, Pines A, D'Andrea P, Romanello M, Damante G, Cesaratto L, *et al*. Extracellular nucleotides activate Runx2 in the osteoblast-like HOBIT cell line: A possible molecular link between mechanical stress and osteoblasts' response. Bone 2005;36:418-32.
19. Franceschi RT, Xiao G. Regulation of the osteoblast-specific transcription factor, Runx2: Responsiveness to multiple signal transduction pathways. J Cell Biochem 2003;88:446-54.
20. Hu N, Feng C, Jiang Y, Miao Q, Liu H. Regulative effect of mir-205 on osteogenic differentiation of bone mesenchymal stem cells (BMSCs): Possible role of SATB2/Runx2 and ERK/MAPK pathway. Int J Mol Sci 2015;16:10491-506.
21. Gong Y, Xu F, Zhang L, Qian Y, Chen J, Huang H, *et al*. MicroRNA expression signature for Satb2-induced osteogenic differentiation in bone marrow stromal cells. Mol Cell Biochem 2014;387:227-39.
22. Osyczka AM, Leboy PS. Bone morphogenetic protein regulation of early osteoblast genes in human marrow stromal cells is mediated by extracellular signal-regulated kinase and phosphatidylinositol 3-kinase signaling. Endocrinology 2005;146:3428-37.
23. Zuo C, Zhao X, Shi Y, Wu W, Zhang N, Xu J, *et al*. TNF-α inhibits SATB2 expression and osteoblast differentiation through NF-κB and MAPK pathways. Oncotarget 2018;9:4833-50.
24. Ducy P, Zhang R, Geoffroy V, Ridall AL, Karsenty G. Osf2/Cbfa1: A transcriptional activator of osteoblast differentiation. Cell 1997;89:747-54.
25. Xu J, Wang L, Li H, Yang T, Zhang Y, Hu T, *et al*. Sho×2 regulates osteogenic differentiation and pattern formation during hard palate development in mice. J Biol Chem 2019;294:18294-305.
26. Fisher LW, McBride OW, Termine JD, Young MF. Human bone sialoprotein. Deduced protein sequence and chromosomal localization. J Biol Chem 1990;265:2347-51.
27. Tang W, Li Y, Osimiri L, Zhang C. Osteoblast-specific transcription factor Osterix (Osx) is an upstream regulator of Satb2 during bone formation. J Biol Chem 2011;286:32995-3002.
28. Xiao Z, Awad HA, Liu S, Mahlios J, Zhang S, Guilak F, *et al*. Selective Runx2-II deficiency leads to low-turnover osteopenia in adult mice. Dev Biol 2005;283:345-56.
29. Liu W, Toyosawa S, Furuichi T, Kanatani N, Yoshida C, Liu Y, *et al*. Overexpression of Cbfa1 in osteoblasts inhibits osteoblast maturation and causes osteopenia with multiple fractures. J Cell Biol 2001;155:157-66.
30. Kagoshima H, Shigesada K, Satake M, Ito Y, Miyoshi H, Ohki M, *et al*. The Runt domain identifies a new family of heteromeric transcriptional regulators. Trends Genet 1993;9:338-41.

31. Golling G, Li L, Pepling M, Stebbins M, Gergen JP. Drosophila homologs of the proto-oncogene product PEBP2/CBF beta regulate the DNA-binding properties of Runt. Mol Cell Biol 1996;16:932-42.
32. Nakashima K, Zhou X, Kunkel G, Zhang Z, Deng JM, Behringer RR, *et al*. The novel zinc finger-containing transcription factor osterix is required for osteoblast differentiation and bone formation. Cell 2002;108:17-29.
33. Nishio Y, Dong Y, Paris M, O'Keefe RJ, Schwarz EM, Drissi H. Runx2-mediated regulation of the zinc finger Osterix/Sp7 gene. Gene 2006;372:62-70.
34. Artigas N, Urena C, Rodriguez-Carballo E, Rosa JL, Ventura F. Mitogen-activated protein kinase (MAPK)-regulated interactions between Osterix and Runx2 are critical for the transcriptional osteogenic program. J Biol Chem 2014;289:27105-17.
35. Kanzler B, Kuschert SJ, Liu YH, Mallo M. Hoxa-2 restricts the chondrogenic domain and inhibits bone formation during development of the branchial area. Development 1998;125:2587-97.
36. Creuzet S, Couly G, Vincent C, Le Douarin NM. Negative effect of Hox gene expression on the development of the neural crest-derived facial skeleton. Development 2002;129:4301-13.
37. Gong Y, Qian Y, Yang F, Wang H, Yu Y. Lentiviral-mediated expression of SATB2 promotes osteogenic differentiation of bone marrow stromal cells *in vitro* and *in vivo*. Eur J Oral Sci 2014;122:190-7.
38. Zhang P, Men J, Fu Y, Shan T, Ye J, Wu Y, *et al*. Contribution of SATB2 to the stronger osteogenic potential of bone marrow stromal cells from craniofacial bones. Cell Tissue Res 2012;350:425-37.
39. Mi W, Shi Q, Chen X, Wu T, Huang H. MiR-33a-5p modulates TNF-α-inhibited osteogenic differentiation by targeting SATB2 expression in hBMSCs. FEBS Lett 2016;590:396-407.
40. Li Z, Hassan MQ, Volinia S, van Wijnen AJ, Stein JL, Croce CM, *et al*. A microRNA signature for a BMP2-induced osteoblast lineage commitment program. Proc Natl Acad Sci U S A 2008;105:13906-11.
41. Li Z, Hassan MQ, Jafferji M, Aqeilan RI, Garzon R, Croce CM, *et al*. Biological functions of miR-29b contribute to positive regulation of osteoblast differentiation. J Biol Chem 2009;284:15676-84.
42. Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell 2004;116:281-97.
43. Pawlicki JM, Steitz JA. Nuclear networking fashions pre-messenger RNA and primary microRNA transcripts for function. Trends Cell Biol 2010;20:52-61.
44. Bakhshandeh B, Soleimani M, Paylakhi SH, Ghaemi N. A microRNA signature associated with chondrogenic lineage commitment. J Genet 2012;91:171-82.
45. Deng Y, Wu S, Zhou H, Bi X, Wang Y, Hu Y, *et al*. Effects of a miR-31, Runx2, and Satb2 regulatory loop on the osteogenic differentiation of bone mesenchymal stem cells. Stem Cells Dev 2013;22:2278-86.
46. Ge J, Guo S, Fu Y, Zhou P, Zhang P, Du Y, *et al*. Dental follicle cells participate in tooth eruption via the RUNX2-MiR-31-SATB2 loop. J Dent Res 2015;94:936-44.
47. Hassan MQ, Gordon JA, Beloti MM, Croce CM, van Wijnen AJ, Stein JL, *et al*. A network connecting Runx2, SATB2, and the miR-23a ~ 27a ~ 24-2 cluster regulates the osteoblast differentiation program. Proc Natl Acad Sci U S A 2010;107:19879-84.
48. Jaitner C, Reddy C, Abentung A, Whittle N, Rieder D, Delekate A, *et al*. Satb2 determines miRNA expression and long-term memory in the adult central nervous system. Elife 2016;5:e17361.
49. Yu S, Geng Q, Pan Q, Liu Z, Ding S, Xiang Q, *et al*. MiR-690, a Runx2-targeted miRNA, regulates osteogenic differentiation of C2C12 myogenic progenitor cells by targeting NF-kappaB p65. Cell Biosci 2016;6:10.
50. Chang H, Wang Y, Liu H, Nan X, Wong S, Peng S, *et al*. Mutant Runx2 regulates amelogenesis and osteogenesis through a miR-185-5p-Dl×2 axis. Cell Death Dis 2017;8:3221.
51. Hu Z, Wang Y, Sun Z, Wang H, Zhou H, Zhang L, *et al*. miRNA-132-3p inhibits osteoblast differentiation by targeting Ep300 in simulated microgravity. Sci Rep 2015;5:18655.
52. Xue Z, Meng Y, Ge J. miR-127-5p promotes chondrogenic differentiation in rat bone marrow mesenchymal stem cells. Exp Ther Med 2017;14:1481-6.
53. Wang C, Qiao X, Zhang Z, Li C. MiR-128 promotes osteogenic differentiation of bone marrow mesenchymal stem cells in rat by targeting DKK2. Biosci Rep 2020;40(2): BSR20182121.
54. Qu X, Chen Z, Fan D, Sun C, Zeng Y. MiR-132-3p Regulates the Osteogenic Differentiation of Thoracic Ligamentum Flavum Cells by Inhibiting Multiple Osteogenesis-Related Genes. Int J Mol Sci 2016;17:1370.
55. Huang S, Wang S, Bian C, Yang Z, Zhou H, Zeng Y, *et al*. Upregulation of miR-22 promotes osteogenic differentiation and inhibits adipogenic differentiation of human adipose tissue-derived mesenchymal stem cells by repressing HDAC6 protein expression. Stem Cells Dev 2012;21:2531-40.
56. Zhang Y, Xie RL, Croce CM, Stein JL, Lian JB, van Wijnen AJ, *et al*. A program of microRNAs controls osteogenic lineage progression by targeting transcription factor Runx2. Proc Natl Acad Sci U S A 2011;108:9863-8.
57. Zuo B, Zhu J, Li J, Wang C, Zhao X, Cai G, *et al*. microRNA-103a functions as a mechanosensitive microRNA to inhibit bone formation through targeting Runx2. J Bone Miner Res 2015;30:330-45.
58. Wang H, Xie Z, Hou T, Li Z, Huang K, Gong J, *et al*. MiR-125b regulates the osteogenic differentiation of human mesenchymal stem cells by targeting BMPR1b. Cell Physiol Biochem 2017;41:530-42.
59. Chen QY, Des Marais T, Costa M. Deregulation of SATB2 in carcinogenesis with emphasis on miRNA-mediated control. Carcinogenesis 2019;40:393-402.
60. Mansour MA, Hyodo T, Ito S, Kurita K, Kokuryo T, Uehara K, *et al*. SATB2 suppresses the progression of colorectal cancer cells via inactivation of MEK5/ERK5 signaling. FEBS J 2015;282:1394-405.
61. Blyth K, Cameron ER, Neil JC. The RUNX genes: Gain or loss of function in cancer. Nat Rev Cancer 2005;5:376-87.
62. Mukherjee A, Wilson EM, Rotwein P. Selective signaling by Akt2 promotes bone morphogenetic protein 2-mediated osteoblast differentiation. Mol Cell Biol 2010;30:1018-27.
63. Martin JW, Zielenska M, Stein GS, van Wijnen AJ, Squire JA. The Role of RUNX2 in Osteosarcoma Oncogenesis. Sarcoma 2011;2011:282745.
64. Blyth K, Terry A, Mackay N, Vaillant F, Bell M, Cameron ER, *et al*. Runx2: A novel oncogenic effector revealed by *in vivo* complementation and retroviral tagging. Oncogene 2001;20:295-302.
65. Chung J, Lau J, Cheng LS, Grant RI, Robinson F, Ketela T, *et al*. SATB2 augments ΔNp63α in head and neck squamous cell carcinoma. EMBO Rep 2010;11:777-83.
66. Dragomir A, de Wit M, Johansson C, Uhlen M, Ponten F. The role of SATB2 as a diagnostic marker for tumors of colorectal origin: Results of a pathology-based clinical prospective study. Am J Clin Pathol 2014;141:630-8.
67. Davis JL, Horvai AE. Special AT-rich sequence-binding protein 2 (SATB2) expression is sensitive but may not be specific for osteosarcoma as compared with other high-grade primary bone sarcomas. Histopathology 2016;69:84-90.
68. Yu W, Ma Y, Shankar S, Srivastava RK. Role of SATB2 in human pancreatic cancer: Implications in transformation and a promising biomarker. Oncotarget 2016;7:57783-97.
69. Patani N, Jiang W, Mansel R, Newbold R, Mokbel K. The mRNA expression of SATB1 and SATB2 in human breast cancer. Cancer Cell Int 2009;9:18.
70. Yu W, Ma Y, Ochoa AC, Shankar S, Srivastava RK. Cellular transformation of human mammary epithelial cells by SATB2. Stem Cell Res 2017;19:139-47.

71. McCluggage WG, Van de Vijver K. SATB2 is Consistently expressed in squamous morules associated with endometrioid proliferative lesions and in the stroma of atypical polypoid adenomyoma. Int J Gynecol Pathol 2019;38:397-403.
72. Lengner CJ, Drissi H, Choi JY, van Wijnen AJ, Stein JL, Stein GS, *et al*. Activation of the bone-related Runx2/Cbfa1 promoter in mesenchymal condensations and developing chondrocytes of the axial skeleton. Mech Dev 2002;114:167-70.
73. Ogawa S, Harada H, Fujiwara M, Tagashira S, Katsumata T, Takada H. Cbfa1, an essential transcription factor for bone formation, is expressed in testis from the same promoter used in bone. DNA Res 2000;7:181-5.
74. Inman CK, Shore P. The osteoblast transcription factor Runx2 is expressed in mammary epithelial cells and mediates osteopontin expression. J Biol Chem 2003;278:48684-9.
75. Satake M, Nomura S, Yamaguchi-Iwai Y, Takahama Y, Hashimoto Y, Niki M, *et al*. Expression of the Runt domain-encoding PEBP2 alpha genes in T cells during thymic development. Mol Cell Biol 1995;15:1662-70.
76. Sun L, Vitolo M, Passaniti A. Runt-related gene 2 in endothelial cells: Inducible expression and specific regulation of cell migration and invasion. Cancer Res 2001;61:4994-5001.
77. Kayed H, Jiang X, Keleg S, Jesnowski R, Giese T, Berger MR, *et al*. Regulation and functional role of the Runt-related transcription factor-2 in pancreatic cancer. Br J Cancer 2007;97:1106-15.
78. Niu DF, Kondo T, Nakazawa T, Oishi N, Kawasaki T, Mochizuki K, *et al*. Transcription factor Runx2 is a regulator of epithelial-mesenchymal transition and invasion in thyroid carcinomas. Lab Invest 2012;92:1181-90.
79. Pratap J, Lian JB, Javed A, Barnes GL, van Wijnen AJ, Stein JL, *et al*. Regulatory roles of Runx2 in metastatic tumor and cancer cell interactions with bone. Cancer Metastasis Rev 2006;25:589-600.
80. Barnes GL, Javed A, Waller SM, Kamal MH, Hebert KE, Hassan MQ, *et al*. Osteoblast-related transcription factors Runx2 (Cbfa1/AML3) and MSX2 mediate the expression of bone sialoprotein in human metastatic breast cancer cells. Cancer Res 2003;63:2631-7.
81. Browne G, Nesbitt H, Ming L, Stein GS, Lian JB, McKeown SR, *et al*. Bicalutamide-induced hypoxia potentiates RUNX2-mediated Bcl-2 expression resulting in apoptosis resistance. Br J Cancer 2012;107:1714-21.
82. Westendorf JJ, Zaidi SK, Cascino JE, Kahler R, van Wijnen AJ, Lian JB, *et al*. Runx2 (Cbfa1, AML-3) interacts with histone deacetylase 6 and represses the p21(CIP1/WAF1) promoter. Mol Cell Biol 2002;22:7982-92.
83. Teplyuk NM, Haupt LM, Ling L, Dombrowski C, Mun FK, Nathan SS, *et al*. The osteogenic transcription factor Runx2 regulates components of the fibroblast growth factor/proteoglycan signaling axis in osteoblasts. J Cell Biochem 2009;107:144-54.
84. Akech J, Wixted JJ, Bedard K, van der Deen M, Hussain S, Guise TA, *et al*. Runx2 association with progression of prostate cancer in patients: Mechanisms mediating bone osteolysis and osteoblastic metastatic lesions. Oncogene 2010;29:811-21.
85. Papachristou DJ, Papachristou GI, Papaefthimiou OA, Agnantis NJ, Basdra EK, Papavassiliou AG. The MAPK-AP-1/-Runx2 signalling axes are implicated in chondrosarcoma pathobiology either independently or via up-regulation of VEGF. Histopathology 2005;47:565-74.
86. Sun X, Wei L, Chen Q, Terek RM. HDAC4 represses vascular endothelial growth factor expression in chondrosarcoma by modulating RUNX2 activity. J Biol Chem 2009;284:21881-90.
87. Baniwal SK, Khalid O, Gabet Y, Shah RR, Purcell DJ, Mav D, *et al*. Runx2 transcriptome of prostate cancer cells: Insights into invasiveness and bone metastasis. Mol Cancer 2010;9:258.
88. Yuen HF, Kwok WK, Chan KK, Chua CW, Chan YP, Chu YY, *et al*. TWIST modulates prostate cancer cell-mediated bone cell activity and is upregulated by osteogenic induction. Carcinogenesis 2008;29:1509-18.
89. Yang Y, Yang R, Roth M, Piperdi S, Zhang W, Dorfman H, *et al*. Genetically transforming human osteoblasts to sarcoma: Development of an osteosarcoma model. Genes Cancer 2017;8:484-94.
90. Komori T. Regulation of osteoblast differentiation by Runx2. Adv Exp Med Biol 2010;658:43-9.
91. Enomoto H, Furuichi T, Zanma A, Yamana K, Yoshida C, Sumitani S, *et al*. Runx2 deficiency in chondrocytes causes adipogenic changes *in vitro*. J Cell Sci 2004;117:417-25.
92. Komori T. Regulation of bone development and extracellular matrix protein genes by RUNX2. Cell Tissue Res 2010;339:189-95.
93. Maruyama Z, Yoshida CA, Furuichi T, Amizuka N, Ito M, Fukuyama R, *et al*. Runx2 determines bone maturity and turnover rate in postnatal bone development and is involved in bone loss in estrogen deficiency. Dev Dyn 2007;236:1876-90.
94. Sadikovic B, Thorner P, Chilton-Macneill S, Martin JW, Cervigne NK, Squire J, *et al*. Expression analysis of genes associated with human osteosarcoma tumors shows correlation of RUNX2 overexpression with poor response to chemotherapy. BMC Cancer 2010;10:202.
95. Galindo M, Pratap J, Young DW, Hovhannisyan H, Im HJ, Choi JY, *et al*. The bone-specific expression of Runx2 oscillates during the cell cycle to support a G1-related antiproliferative function in osteoblasts. J Biol Chem 2005;280:20274-85.
96. Pereira BP, Zhou Y, Gupta A, Leong DT, Aung KZ, Ling L, *et al*. Runx2, p53, and pRB status as diagnostic parameters for deregulation of osteoblast growth and differentiation in a new pre-chemotherapeutic osteosarcoma cell line (OS1). J Cell Physiol 2009;221:778-88.
97. Bailey JM, Singh PK, Hollingsworth MA. Cancer metastasis facilitated by developmental pathways: Sonic hedgehog, Notch, and bone morphogenic proteins. J Cell Biochem 2007;102:829-39.
98. Rubin EM, Guo Y, Tu K, Xie J, Zi X, Hoang BH. Wnt inhibitory factor 1 decreases tumorigenesis and metastasis in osteosarcoma. Mol Cancer Ther 2010;9:731-41.
99. Engin F, Bertin T, Ma O, Jiang MM, Wang L, Sutton RE, *et al*. Notch signaling contributes to the pathogenesis of human osteosarcomas. Hum Mol Genet 2009;18:1464-70.
100. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene 2007;26:3279-90.
101. Machado I, Navarro S, Picci P, Llombart-Bosch A. The utility of SATB2 immunohistochemical expression in distinguishing between osteosarcomas and their malignant bone tumor mimickers, such as Ewing sarcomas and chondrosarcomas. Pathol Res Pract 2016;212:811-6.
102. Xu HY, Fang W, Huang ZW, Lu JC, Wang YQ, Tang QL, *et al*. Metformin reduces SATB2-mediated osteosarcoma stem cell-like phenotype and tumor growth via inhibition of N-cadherin/NF-kB signaling. Eur Rev Med Pharmacol Sci 2017;21:4516-28.
103. Mori T, Sato Y, Miyamoto K, Kobayashi T, Shimizu T, Kanagawa H, *et al*. TNFα promotes osteosarcoma progression by maintaining tumor cells in an undifferentiated state. Oncogene 2014;33:4236-41.
104. Tarapore RS, Lim J, Tian C, Pacios S, Xiao W, Reid D, *et al*. NF-κB has a direct role in inhibiting bmp- and wnt-induced matrix protein expression. J Bone Miner Res 2016;31:52-64.
105. Yu W, Ma Y, Shankar S, Srivastava RK. SATB2/β-catenin/TCF-LEF pathway induces cellular transformation by generating cancer stem cells in colorectal cancer. Sci Rep 2017;7:10939.
106. Dang CV. c-Myc target genes involved in cell growth, apoptosis, and metabolism. Mol Cell Biol 1999;19:1-1.
107. Ross JS, Ali SM, Wang K, Palmer G, Yelensky R, Lipson D, *et al*. Comprehensive genomic profiling of epithelial ovarian cancer by next generation sequencing-based diagnostic assay reveals new routes to targeted therapies. Gynecol Oncol 2013;130:554-9.
108. Chen Y, McGee J, Chen X, Doman TN, Gong X, Zhang Y, *et al*.

Identification of druggable cancer driver genes amplified across TCGA datasets. PLoS One 2014;9:e98293.
109. Gamberi G, Benassi MS, Bohling T, Ragazzini P, Molendini L, Sollazzo MR, *et al*. C-myc and c-fos in human osteosarcoma: Prognostic value of mRNA and protein expression. Oncology 1998;55:556-63.
110. Han G, Wang Y, Bi W. C-Myc overexpression promotes osteosarcoma cell invasion via activation of MEK-ERK pathway. Oncol Res 2012;20:149-56.
111. Shin MH, He Y, Marrogi E, Piperdi S, Ren L, Khanna C, *et al*. A RUNX2-mediated epigenetic regulation of the survival of p53 defective cancer cells. PLoS Genet 2016;12:e1005884.
112. Li H, Zhou RJ, Zhang GQ, Xu JP. Clinical significance of RUNX2 expression in patients with nonsmall cell lung cancer: A 5-year follow-up study. Tumour Biol 2013;34:1807-12.
113. Ma YN, Zhang HY, Fei LR, Zhang MY, Wang CC, Luo Y, *et al*. SATB2 suppresses non-small cell lung cancer invasiveness by G9a. Clin Exp Med 2018;18:37-44.
114. Chen QY, Li J, Sun H, Wu F, Zhu Y, Kluz T, *et al*. Role of miR-31 and SATB2 in arsenic-induced malignant BEAS-2B cell transformation. Mol Carcinog 2018;57:968-77.
115. Wang CJ, Zhou ZG, Wang L, Yang L, Zhou B, Gu J, *et al*. Clinicopathological significance of microRNA-31, -143 and -145 expression in colorectal cancer. Dis Markers 2009;26:27-34.
116. Slaby O, Svoboda M, Fabian P, Smerdova T, Knoflickova D, Bednarikova M, *et al*. Altered expression of miR-21, miR-31, miR-143 and miR-145 is related to clinicopathologic features of colorectal cancer. Oncology 2007;72:397-402.
117. Yang MH, Yu J, Chen N, Wang XY, Liu XY, Wang S, *et al*. Elevated microRNA-31 expression regulates colorectal cancer progression by repressing its target gene SATB2. PLoS One 2013;8:e85353.
118. Wong TS, Liu XB, Wong BY, Ng RW, Yuen AP, Wei WI. Mature miR-184 as potential oncogenic microRNA of squamous cell carcinoma of tongue. Clin Cancer Res 2008;14:2588-92.
119. Valastyan S, Reinhardt F, Benaich N, Calogrias D, Szasz AM, Wang ZC, *et al*. A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis. Cell 2009;137:1032-46.
120. Guo J, Miao Y, Xiao B, Huan R, Jiang Z, Meng D, *et al*. Differential expression of microRNA species in human gastric cancer versus non-tumorous tissues. J Gastroenterol Hepatol 2009;24:652-7.
121. Papaconstantinou IG, Manta A, Gazouli M, Lyberopoulou A, Lykoudis PM, Polymeneas G, *et al*. Expression of microRNAs in patients with pancreatic cancer and its prognostic significance. Pancreas 2013;42:67-71.
122. Aprelikova O, Yu X, Palla J, Wei BR, John S, Yi M, *et al*. The role of miR-31 and its target gene SATB2 in cancer-associated fibroblasts. Cell Cycle 2010;9:4387-98.
123. Suzuki H, Masuda N, Shimura T, Araki K, Kobayashi T, Tsutsumi S, *et al*. Nuclear beta-catenin expression at the invasive front and in the vessels predicts liver metastasis in colorectal carcinoma. Anticancer Res 2008;28:1821-30.
124. Rawson JB, Mrkonjic M, Daftary D, Dicks E, Buchanan DD, Younghusband HB, *et al*. Promoter methylation of Wnt5a is associated with microsatellite instability and BRAF V600E mutation in two large populations of colorectal cancer patients. Br J Cancer 2011;104:1906-12.
125. Gaur T, Lengner CJ, Hovhannisyan H, Bhat RA, Bodine PV, Komm BS, *et al*. Canonical WNT signaling promotes osteogenesis by directly stimulating Runx2 gene expression. J Biol Chem 2005;280:33132-40.
126. Wen D, Li S, Jiang W, Zhu J, Liu J, Zhao S. miR-539 inhibits human colorectal cancer progression by targeting RUNX2. Biomed Pharmacother 2017;95:1314-20.
127. Wang X, Li L, Wu Y, Zhang R, Zhang M, Liao D, *et al*. CBX4 suppresses metastasis via recruitment of HDAC3 to the Runx2 promoter in colorectal carcinoma. Cancer Res 2016;76:7277-89.
128. Ji Q, Cai G, Liu X, Zhang Y, Wang Y, Zhou L, *et al*. MALAT1 regulates the transcriptional and translational levels of proto-oncogene RUNX2 in colorectal cancer metastasis. Cell Death Dis 2019;10:378.
129. Eberhard J, Gaber A, Wangefjord S, Nodin B, Uhlén M, Ericson Lindquist K, *et al*. A cohort study of the prognostic and treatment predictive value of SATB2 expression in colorectal cancer. Br J Cancer 2012;106:931-8.
130. Lin F, Shi J, Zhu S, Chen Z, Li A, Chen T, *et al*. Cadherin-17 and SATB2 are sensitive and specific immunomarkers for medullary carcinoma of the large intestine. Arch Pathol Lab Med 2014;138:1015-26.
131. Moh M, Krings G, Ates D, Aysal A, Kim GE, Rabban JT. SATB2 expression distinguishes ovarian metastases of colorectal and appendiceal origin from primary ovarian tumors of mucinous or endometrioid type. Am J Surg Pathol 2016;40:419-32.
132. Zhang YJ, Chen JW, He XS, Zhang HZ, Ling YH, Wen JH, *et al*. SATB2 is a promising biomarker for identifying a colorectal origin for liver metastatic adenocarcinomas. EBioMedicine 2018;28:62-9.
133. Ellis LM, Takahashi Y, Liu W, Shaheen RM. Vascular endothelial growth factor in human colon cancer: Biology and therapeutic implications. Oncologist 2000;5 Suppl 1:11-5.
134. Deiana M, Dalle Carbonare L, Serena M, Cheri S, Parolini F, Gandini A, *et al*. New insights into the runt domain of RUNX2 in melanoma cell proliferation and migration. Cells 2018;7(11):220.
135. Moriishi T, Maruyama Z, Fukuyama R, Ito M, Miyazaki T, Kitaura H, *et al*. Overexpression of Bcl2 in osteoblasts inhibits osteoblast differentiation and induces osteocyte apoptosis. PLoS One 2011;6:e27487.
136. Moriishi T, Kawai Y, Komori H, Rokutanda S, Eguchi Y, Tsujimoto Y, *et al*. Bcl2 deficiency activates FoxO through Akt inactivation and accelerates osteoblast differentiation. PLoS One 2014;9:e86629.
137. Ho WP, Chan WP, Hsieh MS, Chen RM. Runx2-mediated bcl-2 gene expression contributes to nitric oxide protection against hydrogen peroxide-induced osteoblast apoptosis. J Cell Biochem 2009;108:1084-93.
138. Chang WM, Lin YF, Su CY, Peng HY, Chang YC, Lai TC, *et al*. Dysregulation of RUNX2/Activin-A Axis upon miR-376c downregulation promotes lymph node metastasis in head and neck squamous cell carcinoma. Cancer Res 2016;76:7140-50.
139. Zhao X, Ji Z, Xie Y, Liu G, Li H. MicroRNA-154 as a prognostic factor in bladder cancer inhibits cellular malignancy by targeting RSF1 and RUNX2. Oncol Rep 2017;38:2727-34.
140. Huang W, Lu Y, Wang F, Huang X, Yu Z. Downregulation of circular RNA hsa_circ_0000144 inhibits bladder cancer progression via stimulating miR-217 and suppressing RUNX2 expression. Gene 2018;678:337-42.
141. Riminucci M, Corsi A, Peris K, Fisher LW, Chimenti S, Bianco P. Coexpression of bone sialoprotein (BSP) and the pivotal transcriptional regulator of osteogenesis, Cbfa1/Runx2, in malignant melanoma. Calcif Tissue Int 2003;73:281-9.
142. Zuo Z, Ye F, Liu Z, Huang J, Gong Y. MicroRNA-153 inhibits cell proliferation, migration, invasion and epithelial-mesenchymal transition in breast cancer via direct targeting of RUNX2. Exp Ther Med 2019;17:4693-702.
143. van der Deen M, Taipaleenmäki H, Zhang Y, Teplyuk NM, Gupta A, Cinghu S, *et al*. MicroRNA-34c inversely couples the biological functions of the runt-related transcription factor RUNX2 and the tumor suppressor p53 in osteosarcoma. J Biol Chem 2013;288:21307-19.
144. Chen HY, Lang YD, Lin HN, Liu YR, Liao CC, Nana AW, *et al*. miR-103/107 prolong Wnt/β-catenin signaling and colorectal cancer stemness by targeting Axin2. Sci Rep 2019;9:9687.
145. Huang H, Liu Y, Yu P, Qu J, Guo Y, Li W, *et al*. MiR-23a transcriptional activated by Runx2 increases metastatic potential

of mouse hepatoma cell via directly targeting Mgat3. Sci Rep 2018;8:7366.

146. Gu J, Wang G, Liu H, Xiong C. SATB2 targeted by methylated miR-34c-5p suppresses proliferation and metastasis attenuating the epithelial-mesenchymal transition in colorectal cancer. Cell Prolif 2018;51:e12455.
147. Jiang G, Cui Y, Yu X, Wu Z, Ding G, Cao L. miR-211 suppresses hepatocellular carcinoma by downregulating SATB2. Oncotarget 2015;6:9457-66.
148. Huang J, Zhao L, Xing L, Chen D. MicroRNA-204 regulates Runx2 protein expression and mesenchymal progenitor cell differentiation. Stem Cells 2010;28:357-64.
149. Zhuang L, Guo J, Yao Y, Li Z. miR-205 targets runt-related transcription factor 2 to inhibit human pancreatic cancer progression. Oncol Lett 2019;17:843-8.
150. Wang D, Tang L, Wu H, Wang K, Gu D. MiR-127-3p inhibits cell growth and invasiveness by targeting ITGA6 in human osteosarcoma. IUBMB Life 2018;70:411-9.