The emerging role of ISWI chromatin remodeling complexes in cancer

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Abstract
Disordered chromatin remodeling regulation has emerged as an essential driving factor for cancers. Imitation switch (ISWI) family are evolutionarily conserved ATP-dependent chromatin remodeling complexes, which are essential for cellular survival and function through multiple genetic and epigenetic mechanisms. Omics sequencing and a growing number of basic and clinical studies found that ISWI family members displayed widespread gene expression and genetic status abnormalities in human cancer. Their aberrant expression is closely linked to patient outcome and drug response. Functional or componential alteration in ISWI-containing complexes is critical for tumor initiation and development. Furthermore, ISWI-non-coding RNA regulatory networks and some non-coding RNAs derived from exons of ISWI member genes play important roles in tumor progression. Therefore, unveiling the transcriptional regulation mechanism underlying ISWI family sparked a booming interest in finding ISWI-based therapies in cancer. This review aims at describing the current state-of-the-art in the role of ISWI subunits and complexes in tumorigenesis, tumor progression, immunity and drug response, and presenting deep insight into the physiological and pathological implications of the ISWI transcription machinery in cancers.

Keywords: ISWI family, Cofactors, Transcription complexes, Tumor immunology, Inhibitors

Background
Normal gene transcription is fundamental for cell physiology. The gene transcription program is executed by transcription complexes (TCs). Chromatin remodeling complexes (CRCs) are multisubunit TCs containing a series of ATP-dependent remodeling enzymes, which act as ‘molecular motors’ that couple ATP hydrolysis to the perturbation of histone-DNA contacts with respect to individual nucleosome core particles [1]. Based on the sequence homology of the catalytic ATPase and the accessory subunits, CRCs are divided into four main subfamilies: switch/sucrose nonfermentable (SWI/SNF), chromodomain-helicase DNA-binding protein (CHD), inositol-requiring mutant 80 (INO80) and imitation switch (ISWI) [1–3]. Generally, ISWI complexes help the initial histone–DNA complexes (pre-nucleosomes) to mature into canonical octameric nucleosomes and spacing of nucleosomes at relatively fixed distances [4, 5], and are involved in multiple aspects of cell physiology, such as transcriptional regulation [6–9], DNA damage response, repair and recombination [10–13].

To date, a growing number of preclinical and clinical studies have highlighted that ISWI complexes play critical pathological roles in tumorigenesis, tumor development, tumor immunity and drug response. ISWI subunits display multiple functions in affecting tumor cell phenotypes via regulation of oncogenic gene transcription. Somatic mutations, copy number changes or translocations have been identified that may produce gain/
loss-of-function properties of ISWI subunits. Deregu-
lation of ISWI complexes by abnormal expression or act-
ivity disrupts the normal interplay between ISWI subunits
and TFs or facilitates the activity of oncogenic ISWI-con-
taining TCs, which is expected to upset gene regulatory
networks. Here, we provide unique insight into the impli-
cations of ISWI complexes and subunits in cancer.

The ISWI complex: types and composition
ISWI family is one of the best conserved ATPase families.
It possesses highly conserved SWI2/SNF2 family ATPase
domain, belonging to the superfamily of DEAD/H-heli-
cases, that provides the motor for chromatin remodeling
and a characteristic HAND-SANT-SLIDE domains with
DNA binding activity [4]. Chromatin remodeling complexes
containing the ISWI ATPase, including NURF, CHRAC
and ACF, were, originally identified in Dros-
ophila homologs, and later shown to be highly conserved
in many other organisms, such as yeast and mammals
[14]. In general, the CHRAC and ACF complexes seem to
function in assisting nucleosome sliding [15]. NURF acts
particularly in the epigenetic regulation, such as the regu-
lation of higher-order chromatin structure [4]. The ISWI
complexes display various variants over different species.
For example, there are two ISWI catalytic subunit vari-
ants (Isw1 and Isw2) in Saccharomyces cerevisiae, form-
ing 4 different complexes via association with different
subunits [16]. Isw1 forms an Isw1a complex with loc3,
which prevents the binding of basal Pol II transcription
machinery to the promoter and inhibits transcription
initiation [16]. In addition, Isw1 forms an Isw1b com-
plex together with loc2 and loc4 subunits, which play a
regulatory role in Pol II transcription elongation and ter-
mination [4]. Isw2 forms a complex with Itcl, Dpb4 and
Dls1, which regulates the spacing of nucleosome series
and play a remodeling function [4]. In Drosophila, it
contains only one ISWI ATPase, which is a constituent
of three complexes: dNURF, dACF and dCHRAC [17].
dNURF promotes H1 loading onto chromosomes in vivo
and directly facilitated some genes-mediated transcrip-
tion from chromatin templates, such as GAL4 [4, 18].
dNURF can be recruited by the transcriptional repressor
dKen to repress STAT responsive-genes, blocking activa-
tion until signal thresholds are reached [19]. dACF is able
to assist the assembly of chromatin with regular nucleo-
some spacing and is capable of catalyzing considerable
ACF-dependent motility of entire chromatosomes within
fully loaded arrays [20]. In mammals, a specific ISWI
complex is composed of one ATPase subunit (SMARCA5
or SMARCA1) and one to three noncatalytic subunits
[21]. Specially, both human ATPases, SMARCA1 and
SMARCA5, form stable complexes with all regulatory
subunits, which expands the ISWI complex members up
to 16, including RSF-1/RSF-5 (SMARCA1/5 and RSF1),
ACF-1/ACF-5 (SMARCA1/5 and BAZ1A), CHRAC-1/
CHRAC-5 (SMARCA5/1, BAZ1A, CHRAC1 and
POLE3), WICH-1/WICH-5 (SMARCA1/5 and BAZ1B),
NoRC-1/NoRC-5 (SMARCA1/5 and BAZ2A), NuRF-1/
NuRF-5 (SMARCA1/5, BPTF, RBBP7 and RBBP4),
CERF-1/CERF-5 (SMARCA1/5 and CECR2) and BRF-1/
BRF-5 (SMARCA1/5, BAZ2B) [14, 22] (Fig. 1A). Differ-
ent subunits possess different functional domains and
play distinct roles in complexes, which is summarized in
Fig. 1B and Table 1.

Genetic alterations in ISWI members are common in cancer
and correlated with prognosis
The pan-cancer analysis of TCGA dataset and a grow-
ing number of studies revealed that ISWI subunits are
abnormally expressed in human cancers (Fig. 2A and
B). Whole genome, exome and transcriptome sequenc-
ing identified aberrant genetic states for ISWI subunits,
including somatic mutations, abnormal copy numbers
and gene fusions in various tumor types (Tables 2, 3 and
4). The genetic abnormality is a main factor determining
the levels of some ISWI subunits in a particular type of
cancer, and contributing to tumor phenotypes. For exam-
ple, BPTF gene copy number is frequently amplified in
human tumors, particularly in melanoma [23], neuro-
blastosomas and lung cancers [24]. Specifically, in 67% of
the BPTF-positive lung tumors cases, gain of the 17q24.3
locus was associated with poor prognosis (grade III).
Knock-down of excessive BPTF negates the pre-malign-
ant phenotype of highly proliferating lung embryonic
fibroblasts cells [24].

Some ISWI subunits have been found to be closely
related to patient prognosis. For example, serum RSF1
DNA levels are obviously upregulated in lung cancer
patients and closely associated with TNM stage and
lymph node metastasis [25]. In HER2+ breast tumors,
high levels of BAZ1A are associated with detrimental
relapse-free survival (RFS) and extremely poor overall
survival (OS) [26]. The BAZ1A gene within the 14q12-q13
amplicon is frequently amplified in esophageal squamous

(See figure on next page.)

**Fig. 1** Classification of ISWI family. Molecular components, functional domains, subcellular localization and targeting inhibitors for the ISWI family. A Sixteen different types of ISWI complexes are shown [14, 22, 48]. They harbor either SMARCA1 or SMARCA5 as ATPase subunits and 1–3 noncatalytic subunits. B Schematic representation of functional domains, protein subcellular localization, number of nucleotides and targeting inhibitors for each ISWI protein member.
Fig. 1 (See legend on previous page.)
cell carcinoma (ESCC), while this region harbors some oncogenic genes whose amplification leads to the development and progression of various types of tumors, such as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [27]. The levels of BAZ2A are upregulated and associated with poor prognosis and recurrence in various tumors, such as prostate cancer [28]. Interestingly, high levels of BAZ2A correlate with the deletion of the PTEN gene in primary prostate cancer, which can be an indicator of poor prognosis [29]. BPTF is suggested to be a pan prognostic marker in various cancers. BPTF, which is highly expressed in NSCLC tumor tissues, is positively associated with advanced clinical stage, more lymph nodes and distant metastasis [30, 31]. In particular, it is strongly relevant to the risk for lung adenocarcinoma (LUAD) with EGFR mutations [32]. Moreover, BPTF, amplified in human breast tumors, is linked to shorter metastasis-free survival (MFS) [33, 34].

Roles of ISWI subunits and ISWI-containing transcription complexes in cancer development

The ATPase subunit of the major mammalian ISWI complex interacts with different proteins, forming multiprotein complexes that in some cases have many subunits. ISWI ATPases also interact with a variety of DNA-binding factors and cofactors, which are involved in malignant transformation and tumor progression. In contrast, noncatalytic subunits are critical for the functional diversity of ISWI complexes and perform specialized functions in cancers.

**SMARCA1**

SMARCA1 is broadly expressed in primary human tissues. However, multiple types of genetic abnormalities, including mutation, amplification and deletion lead to changes in SMARCA1 expression in tumors (Tables 2, 3 and 4). SMARCA1 plays an oncogenic or a tumor suppressor role, depending on tumor type. In breast, lung and cervical cancer, the oncogenic effects of SMARCA1 involve cell survival and cell cycle progression [35]. Inhibition of SMARCA1 increases the activity of caspase 9 by upregulating the expression of Apaf-1, which subsequently activates the caspase cascade [35]. In contrast, as a tumor suppressor, SMARCA1 is frequently silenced in gastric cancer due to aberrant DNA methylation. SMARCA1 knockdown promotes the growth of gastric tumor cells, accompanied by downregulation of genes related to cellular homeostasis [36]. Similarly, SMARCA1 is strongly expressed in normal melanocytes but is widely absent in malignant melanoma. Forced expression of SMARCA1 in melanoma cells inhibits cell proliferation and metastasis by attenuating Wnt/β-catenin signaling [37].

### Table 1 Functional domains of ISWI proteins

| Domain                        | Functions                                                                                                                                 |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| ATP binding domain            | ATP binding domain, an autonomous nucleosome remodeling machine, interacts with the super helical location 2 (SHL2) of the nucleosomal DNA, with the N-terminal tail of H4 and with the α1 helix of H3 |
| C-terminal NegC domain        | The C-terminal NegC domain is involved in binding to the core2 domain and functions as an allosteric element for ISWI to respond to the extranucleosomal DNA length |
| SANT domain                   | SANT domain has a central role in chromatin remodeling by functioning as a unique histone-interaction module that couples histone binding to enzyme catalysis, and it is important for nucleosome sliding activity, such as the regulation of nucleosome spacing |
| WAC domain                    | WAC domain is involved in the interaction of ACF with chromatin and the binding of other ACF-related factors to DNA                               |
| DDT domain                    | DDT domain associates with the histone modifications H3K4me3 and H4K16ac and facilitates DNA binding                                          |
| Bromodomain                   | Bromodomain is a conserved motif, which recognizes acetylated lysine residues of histones or interacting proteins                           |
| MBD domain                    | The MBD (methyl-CpG-binding) domain specifically recognizes and binds to methylated CpGs. This binding allows it to trigger methylation of H3K9 and results in transcriptional repression |
| PHD-type zinc finger domain   | PHD-type zinc finger domain binds specific epigenetic marks on histone tails to recruit transcription factors and nucleosome-associated complexes to chromatin. For example, it resides in the BPTF subunit of NURF, interacts directly with H3K4me3, stabilizes association of BPTF/NURF with chromatin |

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(Fig. 2) Gene expression analysis of ISWI family members in human cancers. A. Fold changes in gene expression of ISWI members across a variety of tumor types compared to the normal control, based on the TCGA dataset (only tumor types with more than 10 normal samples and tumor samples were selected). FPKM data were used as the expression profile, and the R language limma package was used to conduct variance analysis. Red indicates upregulation, and blue indicates downregulation (P<0.05 after correction) in tumors. LogFC = log2 (average (tumor)/average (normal)). Full names for cancer abbreviations are shown in the abbreviation table. B. A schematic diagram shows the most significant change in the mRNA expression levels of ISWI member genes in different types of cancer based on TCGA dataset analysis or literature summaries. The most significantly upregulated or downregulated genes are marked in red and in blue, respectively.
Fig. 2 (See legend on previous page.)
| Tumor                              | Gene      | Mutation number | Case number with mutation | Percentage (total number) |
|------------------------------------|-----------|-----------------|----------------------------|----------------------------|
| Acinar Cell Carcinoma of the Pancreas | RBBP4     | 2               | 2                          | 8.6%(23)                  |
|                                    | BPTF      | 4               | 3                          | 13%(23)                   |
| Acral Melanoma                     | RSF1      | 1               | 1                          | 10%(10)                   |
| Adenoid Cystic Carcinoma           | BAZ2B     | 2               | 2                          | 5.3%(38)                  |
| Angiosarcoma                       | BPTF      | 3               | 3                          | 3.6%(83)                  |
| Basal Cell Carcinoma               | BAZ2B     | 15              | 15                         | 5.1%(293)                 |
|                                    | BAZ2A     | 18              | 14                         | 4.8%(293)                 |
|                                    | BAZ1A     | 14              | 13                         | 4.4%(293)                 |
|                                    | BAZ1B     | 13              | 13                         | 4.4%(293)                 |
|                                    | RSF1      | 9               | 9                          | 3.1%(293)                 |
| Bladder Cancer                     | BAZ2B     | 29              | 25                         | 6.1%(412)                 |
|                                    | BPTF      | 26              | 24                         | 5.1%(474)                 |
|                                    | RSF1      | 18              | 17                         | 4.1%(412)                 |
|                                    | BAZ2A     | 17              | 16                         | 3.9%(412)                 |
| Cervical Squamous Cell Carcinoma   | BPTF      | 13              | 12                         | 4.1%(291)                 |
| Cholangiocarcinoma                 | SMARCA1   | 1               | 1                          | 12.5%(8)                  |
| Colon Cancer                       | BPTF      | 9               | 9                          | 8.5%(106)                 |
|                                    | SMARCA1   | 30              | 26                         | 4.9%(534)                 |
| Colorectal Adenocarcinoma          | SMARCA1   | 30              | 26                         | 4.9%(534)                 |
|                                    | BPTF      | 26              | 26                         | 4.2%(619)                 |
|                                    | BAZ2B     | 26              | 20                         | 3.7%(534)                 |
|                                    | RSF1      | 29              | 19                         | 3.6%(534)                 |
|                                    | BAZ1A     | 25              | 19                         | 3.6%(534)                 |
|                                    | BAZ1B     | 22              | 19                         | 3.6%(534)                 |
|                                    | BAZ2A     | 21              | 19                         | 3.6%(534)                 |
|                                    | RBBP7     | 18              | 16                         | 3.0%(534)                 |
| Cutaneous Squamous Cell Carcinoma  | BAZ2B     | 14              | 13                         | 33.3%(39)                 |
|                                    | BAZ2A     | 8               | 8                          | 20.5%(39)                 |
|                                    | BAZ1A     | 8               | 5                          | 12.8%(39)                 |
|                                    | SMARCA1   | 4               | 3                          | 7.7%(39)                  |
|                                    | SMARCA5   | 3               | 3                          | 7.7%(39)                  |
|                                    | RSF1      | 4               | 3                          | 7.7%(39)                  |
|                                    | BAZ1B     | 3               | 3                          | 7.7%(39)                  |
| Desmoplastic Melanoma              | BPTF      | 3               | 3                          | 15%(20)                   |
| Esophageal Carcinoma               | BPTF      | 36              | 35                         | 6.8%(518)                 |
|                                    | BAZ2B     | 25              | 22                         | 4.2%(518)                 |
|                                    | BAZ2A     | 20              | 18                         | 3.5%(518)                 |
|                                    | SMARCA1   | 103             | 56                         | 10.8%(517)                |
| Gallbladder Carcinoma              | BAZ2B     | 2               | 2                          | 6.3%(32)                  |
|                                    | BPTF      | 2               | 2                          | 6.3%(32)                  |
| Gastric Cancer                     | CECR2     | 3               | 3                          | 3.8%(78)                  |
|                                    | BAZ2B     | 5               | 5                          | 3.4%(147)                 |
| Head and Neck Squamous Cell Carcinoma | BAZ2B   | 18              | 17                         | 3.3%(515)                 |
| Intrahepatic Cholangiocarcinoma    | BPTF      | 7               | 7                          | 6.8%(103)                 |
| Liver Hepatocellular Carcinoma     | BAZ2B     | 3               | 3                          | 6.5%(46)                  |
|                                    | BPTF      | 12              | 12                         | 3.2%(173)                 |
Data come from the TCGA database

| Tumor                                | Gene  | Mutation number | Case number with mutation | Percentage (total number) |
|--------------------------------------|-------|-----------------|---------------------------|--------------------------|
| Lung Adenocarcinoma                  | BAZ2B | 13              | 12                        | 6.7%(179)                |
|                                       | BAZ1A | 11              | 9                         | 5.0%(179)                |
|                                       | BAZ2B | 11              | 11                        | 4.8%(230)                |
|                                       | BPTF  | 9               | 8                         | 4.4%(183)                |
|                                       | SMARCA1| 7               | 7                         | 3.9%(179)                |
|                                       | SMARCA1| 21              | 20                        | 3.5%(566)                |
|                                       | BAZ1B | 7               | 6                         | 3.4%(179)                |
| Lung Squamous Cell Carcinoma         | BAZ2B | 28              | 27                        | 5.6%(484)                |
|                                       | BPTF  | 21              | 19                        | 3.9%(484)                |
|                                       | BAZ1B | 16              | 15                        | 3.1%(484)                |
| Lung Squamous Cell Carcinoma         | SMARCA1| 9               | 9                         | 3.9%(179)                |
| Mantle Cell Lymphoma                 | BPTF  | 1               | 1                         | 3.4%(29)                 |
| Metastatic Melanoma                  | BPTF  | 22              | 17                        | 11.8%(144)               |
|                                       | BAZ2A | 14              | 14                        | 9.7%(144)                |
|                                       | BAZ1A | 8               | 8                         | 5.6%(144)                |
| Non-Hodgkin Lymphoma                 | RBBP4 | 1               | 1                         | 7.1%(14)                 |
|                                       | BPTF  | 18              | 18                        | 3.6%(500)                |
| Pleural Mesothelioma                 | BPTF  | 1               | 1                         | 4.5%(22)                 |
| Primary Central Nervous System Lymphoma| SMARCA5| 1               | 1                         | 10%(10)                  |
| Prostate Cancer                      | CHAC1 | 1               | 1                         | 3.3%(30)                 |
| Skin Cutaneous Melanoma              | BPTF  | 52              | 48                        | 10.9%(440)               |
|                                       | BAZ2A | 47              | 40                        | 9.1%(440)                |
|                                       | BAZ1A | 36              | 26                        | 5.9%(440)                |
|                                       | RSF1  | 26              | 25                        | 5.7%(440)                |
|                                       | SMARCA1| 23              | 23                        | 5.2%(440)                |
|                                       | BAZ1B | 20              | 20                        | 4.5%(440)                |
|                                       | RBBP4 | 15              | 13                        | 3%(440)                  |
| Small-Cell Lung Cancer               | BPTF  | 9               | 9                         | 7.5%(120)                |
|                                       | RSF1  | 7               | 7                         | 5.8%(120)                |
| Stomach Adenocarcinoma               | BPTF  | 34              | 30                        | 7.6%(395)                |
|                                       | BAZ1A | 16              | 16                        | 4.1%(395)                |
|                                       | RSF1  | 16              | 15                        | 3.8%(395)                |
|                                       | BAZ2A | 14              | 14                        | 3.5%(395)                |
| Urothelial Carcinoma                 | BPTF  | 5               | 5                         | 6.9%(72)                 |
|                                       | RSF1  | 1               | 1                         | 6.3%(16)                 |
| Uterine Clear Cell Carcinoma         | BAZ1B | 1               | 1                         | 6.3%(16)                 |
|                                       | CECR2 | 3               | 3                         | 4.2%(72)                 |
| Uterine Corpus Endometrial Carcinoma | SMARCA1| 103             | 56                        | 10.8%(517)               |
|                                       | BPTF  | 93              | 52                        | 10.1%(517)               |
|                                       | BAZ1A | 70              | 46                        | 8.9%(517)                |
|                                       | SMARCA5| 64              | 42                        | 8.1%(517)                |
|                                       | BAZ2A | 62              | 40                        | 7.7%(517)                |
|                                       | RSF1  | 56              | 38                        | 7.4%(517)                |
|                                       | BAZ1B | 68              | 38                        | 7.4%(517)                |
|                                       | RBBP7 | 30              | 23                        | 4.4%(517)                |
|                                       | RBBP4 | 18              | 16                        | 3.1%(517)                |
Table 3  ISWI subunits with high frequency of abnormal copy numbers in malignancies

| Tumor                              | Gene    | Cytoband | Type of CNA | Case number with CNA | Percentage (total number) |
|------------------------------------|---------|----------|-------------|-----------------------|---------------------------|
| Acral Melanoma                     | RSF1    | 11q14.1  | AMP         | 6                     | 15.8%(38)                 |
|                                    | BAZ2A   | 12q13.3  | AMP         | 2                     | 5.3%(38)                  |
| Adenoid Cystic Carcinoma           | BAZ2A   | 12q13.3  | HOMDEL      | 6                     | 10%(60)                   |
|                                    | BAZ1A   | 14q13.1-q13 | HOMDEL  | 4                     | 6.7%(60)                  |
| Adrenocortical Carcinoma           | BAZ2A   | 12q13.3  | AMP         | 3                     | 3.3%(90)                  |
|                                    | POLE3   | 9q32     | AMP         | 3                     | 3.3%(90)                  |
| Adult Soft Tissue Sarcomas         | CHRC1   | 8q24.3   | AMP         | 9                     | 4.4%(206)                 |
| Angiosarcoma                       | RBBP4   | 1p35.1   | AMP         | 3                     | 3.6%(83)                  |
|                                    | BPTF    | 17q24.2  | AMP         | 3                     | 3.6%(83)                  |
|                                    | CHRC1   | 8q24.3   | AMP         | 3                     | 3.6%(83)                  |
| Bladder Cancer                     | CHRC1   | 8q24.3   | AMP         | 21                    | 5.1%(408)                 |
|                                    | RSF1    | 11q14.1  | AMP         | 16                    | 3.9%(408)                 |
|                                    | BAZ2B   | 2q24.2   | AMP         | 5                     | 1.1%(442)                 |
| Brain Lower Grade Glioma           | CHRC1   | 8q24.3   | AMP         | 18                    | 3.5%(511)                 |
| Breast Cancer                      | CHRC1   | 8q24.3   | AMP         | 449                   | 20.7%(2173)               |
|                                    | RSF1    | 11q14.1  | AMP         | 204                   | 9.4%(2173)                |
|                                    | BPTF    | 17q24.2  | AMP         | 167                   | 7.7%(2173)                |
|                                    | BAZ1A   | 14q13.1-q13  | AMP      | 10                    | 4.2%(237)                 |
|                                    | CECR2   | 22q11.1-q11.21 | HOMDEL | 10                  | 4.2%(237)                 |
|                                    | RBBP4   | 1p35.1   | AMP         | 7                     | 3%(237)                   |
| Colorectal Adenocarcinoma          | CHRC1   | 8q24.3   | AMP         | 21                    | 3.5%(592)                 |
| Esophageal Carcinoma               | CHRC1   | 8q24.3   | AMP         | 21                    | 11.5%(182)                |
|                                    | RSF1    | 11q14.1  | AMP         | 18                    | 4.8%(378)                 |
|                                    | SMARCA5 | 4q31.21  | AMP         | 6                     | 3.3%(182)                 |
|                                    | BPTF    | 17q24.2  | AMP         | 12                    | 3.2%(378)                 |
|                                    | BAZ2B   | 2q24.2   | AMP         | 2                     | 1.1%(184)                 |
| Gastric Cancer                     | SMARCA1 | Xq25-q26.1 | HOMDEL  | 106                   | 98.1%(108)                |
|                                    | RBBP7   | Xp22.2   | HOMDEL      | 105                   | 97.2%(108)                |
|                                    | CHRC1   | 8q24.3   | AMP         | 22                    | 20.4%(108)                |
|                                    | BAZ1B   | 7q11.23  | AMP         | 7                     | 6.5%(108)                 |
|                                    | BPTF    | 17q24.2  | AMP         | 5                     | 4.6%(108)                 |
|                                    | RSF1    | 11q14.1  | AMP         | 5                     | 4.6%(108)                 |
|                                    | POLE3   | 9q32     | AMP         | 4                     | 3.7%(108)                 |
| Head and Neck Squamous Cell Carcinoma | CHRC1   | 8q24.3   | AMP         | 41                    | 7.9%(517)                 |
|                                    | RSF1    | 11q14.1  | AMP         | 18                    | 3.5%(517)                 |
| Liver Hepatocellular Carcinoma     | CHRC1   | 8q24.3   | AMP         | 60                    | 16.2%(370)                |
|                                    | BPTF    | 17q24.2  | AMP         | 16                    | 4.3%(370)                 |
|                                    | BAZ2B   | 2q24.2   | AMP         | 4                     | 1.1%(370)                 |
| Lung Adenocarcinoma                | BAZ1A   | 14q13.1-q13 | AMP      | 60                    | 11.6%(516)                |
|                                    | CHRC1   | 8q24.3   | AMP         | 15                    | 5.0%(302)                 |
|                                    | RSF1    | 11q14.1  | AMP         | 20                    | 3.9%(516)                 |
|                                    | BPTF    | 17q24.2  | AMP         | 19                    | 3.7%(516)                 |
| Tumor                                | Gene    | Cytoband | Type of CNA | Case number with CNA | Percentage (total number) |
|--------------------------------------|---------|----------|-------------|-----------------------|--------------------------|
| Lung Squamous Cell Carcinoma         | CHRAC1  | 8q24.3   | AMP         | 36                    | 7.2%(501)                |
|                                      | BPTF    | 17q24.2  | AMP         | 18                    | 3.6%(501)                |
|                                      | BAZ2B   | 2q24.2   | AMP         | 4                     | 1.1%(370)                |
|                                      |         | 2q24.2   | HOMDEL      | 8                     | 1.6%(501)                |
| Melanoma                             | CHRAC1  | 8q24.3   | AMP         | 17                    | 26.6%(64)                |
|                                      | BAZ1B   | 7q11.23  | AMP         | 11                    | 17.2%(64)                |
|                                      | BPTF    | 17q24.2  | AMP         | 5                     | 7.8%(64)                 |
|                                      | RSF1    | 11q14.1  | AMP         | 4                     | 6.3%(64)                 |
|                                      | SMARCA5 | 4q31.21  | AMP         | 2                     | 3.1%(64)                 |
|                                      | BAZ2A   | 12q13.3  | AMP         | 2                     | 3.1%(64)                 |
|                                      |         | 12q13.3  | HOMDEL      | 2                     | 3.1%(64)                 |
|                                      | POLE3   | 9q32     | AMP         | 2                     | 3.1%(64)                 |
|                                      |         | 9q32     | HOMDEL      | 3                     | 4.7%(64)                 |
|                                      | BAZ2B   | 2q24.2   | AMP         | 3                     | 4.7%(64)                 |
|                                      |         | 2q24.2   | HOMDEL      | 1                     | 1.6%(64)                 |
| Mesothelioma                         | BPTF    | 17q24.2  | AMP         | 5                     | 5.7%(87)                 |
| Ovarian Serous Cystadenocarcinoma    | CHRAC1  | 8q24.3   | AMP         | 156                   | 27.3%(572)               |
|                                      | RSF1    | 11q14.1  | AMP         | 57                    | 10%(572)                 |
|                                      | RBBP4   | 1p35.1   | AMP         | 27                    | 4.7%(572)                |
| Pancreatic Cancer                    | CHRAC1  | 8q24.3   | AMP         | 14                    | 12.8%(109)               |
|                                      | BAZ1B   | 7q11.23  | AMP         | 7                     | 6.4%(109)                |
|                                      | RBBP4   | 1p35.1   | HOMDEL      | 6                     | 5.5%(109)                |
|                                      | SMARCA5 | 4q31.21  | HOMDEL      | 6                     | 5.5%(109)                |
|                                      | BPTF    | 17q24.2  | HOMDEL      | 4                     | 3.7%(109)                |
|                                      | BAZ2B   | 2q24.2   | AMP         | 2                     | 1.8%(109)                |
| Pediatric Neuroblastoma              | BPTF    | 17q24.2  | AMP         | 2                     | 3.4%(59)                 |
| Prostate Cancer                      | CHRAC1  | 8q24.3   | AMP         | 87                    | 19.6%(444)               |
|                                      | RBBP7   | Xp22.2   | AMP         | 47                    | 10.6%(444)               |
|                                      | BAZ1B   | 7q11.23  | AMP         | 25                    | 5.6%(444)                |
|                                      | BPTF    | 17q24.2  | AMP         | 22                    | 5%(444)                  |
|                                      | POLE3   | 9q32     | AMP         | 21                    | 4.7%(444)                |
|                                      | BAZ1A   | 14q13.1-q13.2 | AMP     | 18                    | 4.1%(444)                |
|                                      | SMARCA1 | Xq25-q26.1 | AMP       | 16                    | 3.6%(444)                |
|                                      | BAZ1B   | 7q11.23  | AMP         | 5                     | 3.3%(150)                |
|                                      | RBBP4   | 1p35.1   | AMP         | 1                     | 3.3%(30)                 |
| Stomach Adenocarcinoma               | CHRAC1  | 8q24.3   | AMP         | 32                    | 7.3%(441)                |
|                                      | RSF1    | 11q14.1  | AMP         | 16                    | 3.6%(441)                |
| Urothelial Carcinoma                 | BPTF    | 17q24.2  | AMP         | 13                    | 24.5%(53)                |
|                                      | CHRAC1  | 8q24.3   | AMP         | 8                     | 15.1%(53)                |
|                                      | CECR2   | 22q11.1-q11.21 | AMP | 3 | 5.7%(53) |
|                                      | RSF1    | 11q14.1  | AMP         | 3                     | 5.7%(53)                 |
|                                      | BAZ1A   | 14q13.1-q13.2 | AMP     | 3                     | 5.7%(53)                 |
|                                      | BAZ1B   | 7q11.23  | AMP         | 2                     | 3.8%(53)                 |
|                                      | BAZ2B   | 2q24.2   | AMP         | 3                     | 5.7%(53)                 |
It has been found that SMARCA1 regulates normal stem cell or cancer stem cell (CSC) characteristics by interplaying with other types of cofactors. For example, WASH, an actin nucleating factor of the WASP family, assists the recruitment of SMARCA1-NURF complex to the \( c-Myc \) promoter and enhances gene transcription through VCA domain-dependent nuclear actin nucleation, which maintains the differentiation potential of long-term hematopoietic stem cells (LT-HSCs) to mature blood lineages [38] (Fig. 3A). Additionally, the SMARCA1-NURF complex was recruited to the \( OCT4 \) promoter by TF ZIC2 and initiated \( OCT4 \) transcription via elevated chromatin accessibility and H3K4 me3 levels of the \( OCT4 \) locus, which maintained the self-renewal of…

| Tumor                                | Gene  | Cytoband | Type of CNA | Case number with CNA | Percentage (total number) |
|--------------------------------------|-------|----------|-------------|-----------------------|---------------------------|
| Uterine Carcinosarcoma               | CHRAC1| 8q24.3   | AMP         | 5                     | 8.9%(56)                  |
|                                      | BPTF  | 17q24.2  | AMP         | 3                     | 5.4%(56)                  |
|                                      | SMARCA1| Xq25-q26.1| HOMDEL     | 2                     | 3.6%(56)                  |
|                                      | BAZ2B | 2q24.2   | AMP         | 1                     | 1.8%(56)                  |
| Uterine Corpus Endometrial Carcinoma | CHRAC1| 8q24.3   | AMP         | 24                    | 4.5%(539)                 |
|                                      | BAZ2B | 2q24.2   | AMP         | 6                     | 1.1%(539)                 |
| Uveal melanoma                       | CHRAC1| 8q24.3   | AMP         | 14                    | 17.5%(80)                 |
| Invasive ductal cancer               | BAZ1A | 14q12-q13| AMP         | 7                     | 5.74%(122)                |

All data come from the TCGA database

| Table 4 | ISWI subunits with abnormal gene fusions in malignancies |
|---------|------------------------------------------------------------|
| Tumors  | Gene  | Fusion number | Case number with fusion | Percentage (total number) |
|---------|-------|---------------|--------------------------|---------------------------|
| Adrenocortical Carcinoma              | BAZ1A | 1             | 1                        | 1.1%(90)                  |
| Bladder Urothelial Carcinoma          | SMARCA5| 1         | 1                        | 0.2%(408)                 |
| Brain Lower Grade Glioma              | RSF1  | 8             | 8                        | 0.8%(1070)                |
| Breast Invasive Carcinoma             | RSF1  | 2             | 2                        | 0.2%(1070)                |
|                                       | RBBP7 | 1             | 1                        | < 0.1%(1070)              |
|                                       | BAZ2B | 1             | 1                        | < 0.1%(1070)              |
|                                       | RBBP4 | 1             | 1                        | < 0.1%(1070)              |
| Prostate                              | SMARCA1| 2           | 2                        | 0.2%(494)                 |
| Lung Adenocarcinoma                   | BPTF  | 1             | 1                        | 0.2%(511)                 |
| Metastatic Solid Cancers              | SMARCA1| 2           | 2                        | 0.4%(500)                 |
| Ovarian Serous Cystadenocarcinoma     | RBBP4 | 2             | 2                        | 0.4%(523)                 |
|                                       | RSF1  | 1             | 1                        | 0.2%(523)                 |
| Pancreatic Adenocarcinoma             | BPTF  | 1             | 1                        | 0.6%(183)                 |
|                                       | CHRAC1| 1             | 1                        | 0.6%(179)                 |
| Prostate                              | SMARCA1| 2           | 2                        | 0.2%(494)                 |
| Sarcoma                               | RSF1  | 2             | 2                        | 0.8%(253)                 |
| Skin Cutaneous Melanoma               | RBBP7 | 4             | 4                        | 0.9%(440)                 |
| Small-Cell Lung Cancer                | RSF1  | 1             | 1                        | 0.2%(500)                 |
| Uterine Corpus Endometrial Carcinoma  | BAZ1B | 2             | 2                        | 0.4%(500)                 |

All data come from the TCGA database
liver CSCs [39]. Correspondingly, high expression of the SMARCA1-NURF complex, ZIC2 and OCT4 are positively correlated with the clinicopathological stages of hepatocellular carcinoma (HCC) [39] (Fig. 3B).

**SMARCA5**

SMARCA5 and SMARCA1 share a high degree of amino acid sequence homology but appear to have different functions, as judged, for example, by their expression profiles and involvement in structurally and functionally different remodeling complexes [40]. SMARCA5 is frequently overexpressed in breast cancer [41], ovarian cancer [42], HCC [43] and acute myeloid leukemia (AML) [44, 45]. In breast cancer, the SMARCA5 expression level is positively correlated with tumor size, TNM stage and poor overall survival. Knockdown of SMARCA5 inhibits
cell proliferation by arresting the G1 to S phase transition and suppresses MMP2-mediated invasion [41]. In ovarian cancer, the interplay between Rsf-1 and SMARCA5 contributes to tumor cell survival and growth. As a partnership of SMARCA5, induction of Rsf-1 expression not only facilitates translocation of SMARCA5 into nuclei where it colocalizes with Rsf-1 but also enhances SMARCA5 protein expression [42]. In HCC, SMARCA5 is able to promote cell survival and proliferation by increasing the protein level of β-catenin and enhancing its nuclear accumulation [43]. SMARCA5-containing fusion proteins caused by chromosomal translocations also contribute to carcinogenesis. For example, Sumegi et al. identified that a chromosomal translocation t(4;22) (q31;q12) causes an in-frame fusion of the first 7 exons of EWSR1 to the last 19 exons of SMARCA5 in extraskelatal Ewing sarcoma/primitive neuroectodermal tumors. NIH3T3 cells expressing the EWSR1–SMARCA5 fusion exhibited anchorage-independent growth and formed colonies in soft agar, indicating this chimeric protein has tumorigenic potential [46].

SMARCA5 plays an important role in hematological malignancies. SMARCA5 was upregulated in CD34+ AML progenitors, and loss of SMARCA5 inhibited AML cell proliferation [44, 45]. Moreover, the binding site of SMARCA5-CTCF complex at the key hematopoietic regulator PLL1 was methylated in AML, which blocked the complex binding. Upon demethylation by 5-azacytidine (AZA) treatment, the occupancy of SMARCA5-CTCF complex was partly restored, which led to the downregulation of PLL1 transcription and induced myeloid differentiation, indicating that the occupancy of the SMARCA5-CTCF complex at the specific hematopoietic gene is critical for normal hematopoiesis [45] (Fig. 4A).

It should be noted that although SMARCA5 and SMARCA1 have overlapping expression patterns in some cases, the activities of SMARCA1- and SMARCA5-containing complexes likely are not fully redundant. For instance, the spatial and temporal expression patterns of SMARCA1 and SMARCA5 are distinct throughout murine development and in the adult animals, indicating that they may have non-overlapping functions [40]. Through analysis of TCGA database, the SMARCA5 and SMARCA1 gene have divergent patterns of expression in cancers, such as colon adenocarcinoma (COAD), LUAD and stomach adenocarcinoma (STAD) (Fig. 2A), suggesting that they have differential roles or even opposing roles. Indeed, SMARCA5-null embryos die during the peri-implantation stage due to hypoproliferation of the inner cell mass and trophoectoderm, while SMARCA1-null mice survive normally, but show hyperproliferation of cortical progenitors, resulting in an enlarged brain [47]. Therefore, changing the balance of SMARCA5 and SMARCA1 levels could be a potential therapeutic strategy after confirming their opposing expression levels and functions in one given tumor.

RSF complex
RSF1 functions as a nuclear protein with histone chaperon function and interacts with SMARCA5 or SMARCA1 to form RSF complexes that is involved in nucleosome assembly and ATPase-dependent chromatin remodeling [48] (Fig. 1A). The formation of RSF-5 complex is conducive to the nuclear import of SMARCA5, and stabilize SMARCA5 levels through preventing SMARCA5 protein degradation [49]. RSF1 is overexpressed in various tumor tissues based on recent studies and the TCGA database, including breast cancer, HCC, Glioma, etc. [50–55] (Fig. 2A). Meanwhile, overexpression of it is associated with poor overall survival, advanced clinical features and drug resistance in many types of cancer [50–57]. Mutations and abnormal copy numbers have also been found in a variety of tumors, such as acral melanoma, STAD, bladder cancer, etc. (Tables 2 and 3). As a binding partner, SMARCA5 is also overexpressed in the above-mentioned RSF1-overexpressing tumors, as reflected by recent reports [42, 50, 55] and the TCGA database analysis (Fig. 2A).

RSF1 was identified as an amplified gene that activated NF-κB–dependent gene expression such as XIAP (anti-apoptotic gene) and PTGS2 (anti-inflammatory gene) for paclitaxel resistance by functioning as a coactivator for the NF-κB-SMARCA5 complex in ovarian tumor cells [56] (Fig. 4B). In some case, the functional characteristics of RSF1 for malignant transformation are associated with p53 expression or its mutation status. For example, in non-transformed cells, upregulation of RSF1 induces an ATM/p53-dependent DNA damage response, which leads to growth arrest and apoptosis in cells with wild-type p53. Inactivation of p53 by knockout of p53 alleles or p53 mutation reverses the growth inhibitory effects of RSF1 and favors outgrowth of cell clones [48, 58]. In contrast, upregulation of an cyclin E1-RSF1-SMARCA5 complex promotes tumorigenicity in the presence of p53mut RK3E cells, while tumorigenesis was not detected if they were expressed in a p53wt background [59]. In addition, Sehdev et al. found that p53 mutations probably represent a very early molecular genetic change in the development of high-grade serous carcinoma, which initiates a cascade of molecular changes, including upregulation of RSF1 [60]. These studies suggest that RSF1 may act as a driver gene for tumorigenesis, confer on cells with a p53 mutation background certain selective advantages with respect to neighbouring cells.
Fig. 4 ISWI proteins mediate the chemotherapy response and chemical resistance. Some chemotherapy response- and chemoresistance-related genes are regulated by ISWI complexes. The transition of ISWI occupancy by changing DNA methylation levels or targeting ISWI protein/TF interactions may be two treatment strategies for pharmacological intervention. A In AML, the binding of the SMARCA5-CTCF complex at the PU.1 gene is blocked due to DNA methylation. Upon treatment by AZA-mediated DNA demethylation, the SMARCA5-CTCF complex is recruited to the enhancer of the PU.1 gene and inhibits its expression [45]. B The RSF1-SMARCA5 complex functions as a coactivator for NF-κB, consequently augmenting the expression of NF-κB-dependent chemoresistance-related genes, further resulting in paclitaxel resistance in ovarian cancer cells [56]. C Breast cancer cells with estrogen receptor positivity. After EB1089 (vitamin D analog) treatment, the occupancy of vitamin D receptor (VDR) and BAZ1B on CYP19A1 (encoding the enzyme aromatase, which can catalyze the conversion of androgens to estrogens) promoter are altered with the recruitment of VDR and dissociation of BAZ1B, which results in the inhibition of CYP19A1 transcription and contributes to the EB1089 treatment response by arresting the transformation of androgens to estrogens [70, 71]. D In HCC, the recruitment of the NuRD complex by SALL4 to the promoter of some tumor suppressors via an interaction of SALL4 with RBBP4. FFW (a highly potent SALL4-RBBp4 antagonist peptide) treatment abolishes the binding of SALL4 to RBBP4, which leads to the reactivation of tumor suppressors [111].
ACF complex

BAZ1A forms ACF complexes together with SMARCA1/5 or CHRAC complexes with SMARCA1/5, CHRAC1 and POLE3 (Fig. 1A). The ACF complex catalyzes both the relaxation of chromatin structure and the deposition of histones into extended periodic nucleosome arrays [61]. Within the ACF complex, BAZ1A stimulates SMARCA5 activity, regulates SMARCA5 remodeling properties and enhances the efficiency of nucleosome sliding during DNA replication and transcription, while SMARCA5 maintains the stability of the BAZ1A protein [11, 62]. Furthermore, CHRAC1 and POLE3 interaction facilitates nucleosome sliding and assembly mediated by the BAZ1A-CHRAC complex [63].

In normal cells, BAZ1A is involved in DNA double-strand breaks (DSBs) and DSB repair. Upon DNA damage, BAZ1A and SMARCA5 accumulate rapidly at DSBs and contribute to nonhomologous end-joining (NHEJ) repair of DSBs via recruitment of the KU70/80 complex and formation of the CHRAC complex. Inhibition of BAZ1A or SMARCA5 causes cells to become extremely sensitive to X-rays and chemical treatments with unrepaired DSBs [62]. The ACF complex is also associated with cellular senescence. Li et al. found that disruption of the ACF complex either by inhibition of BAZ1A or SMARCA5 resulted in the upregulation of the target gene SMAD3, which in turn activated p21 gene transcription and senescence-associated phenotypes of tumor cells [64].

Through TCGA database analysis, we found that BAZ1A, CHRAC1 and POLE3 are simultaneously upregulated in a variety of tumors, such as esophageal carcinoma (ESCA), liver hepatocellular carcinoma (LIHC), STAD, breast invasive carcinoma (BRCA), etc. (Fig. 2A). Specially, various kinds of tumors, such as adrenocortical carcinoma, gastric cancer, melanoma, etc. display high frequency of abnormal copy numbers in at least two components of CHRAC complexes (Table 3). These data suggest that CHRAC complexes potentially play a driving role in cancers. Indeed, studies found that the BAZ1A gene within the 14q12-q13 amplicon is frequently amplified in cancers. Indeed, studies found that the BAZ1A gene, amplified on chromosome 8q24.3, is confirmed to be a driver gene regulating the proliferation/survival of clonogenic breast cancer cells [65]. In prostate cancer, POLE3 is upregulated by aberrant copy number amplification in cisplatin-resistant testicular germ cell tumors harboring the 9q32-q33.1 gain [66]. Knockout of the POLE3 gene increased the sensitivity of cells to an ATR inhibitor, a PARP inhibitor, and camptothecin [67].

BAZ1B

BAZ1B, a tyrosine-protein kinase belonging to the bromodomain family, was originally identified as a hemizygously deleted gene in Williams syndrome [68]. BAZ1B interacts with SMARCA1/5 to form WICH complexes (Fig. 1A). BAZ1B binds specifically to acetylated histones and plays a critical role in chromatin assembly, RNA polymerase I and III gene regulation, vitamin D metabolism, and DNA repair. Acetylation or phosphorylation (S158) of BAZ1B increases intrinsic kinase activities [69]. BAZ1B is overexpressed in breast and colorectal carcinoma cancer tissues, as well as in ESCA, STAD, etc. from TCGA database (Fig. 2A). Moreover, BAZ1B possesses high frequency of mutation in cutaneous cancer and lung carcinoma as well as high frequency of copy numbers amplification in breast cancer, gastric cancer and etc. (Tables 2 and 3).

In breast cancer, BAZ1B acts as an activator of a CYP19A1 gene that encodes the enzyme aromatase and ERα genes [70]. Treatment with the vitamin D analog EB1089 effectively inhibits aromatase-dependent growth of breast cancer cells by dissociating BAZ1B from the CYP19A1 promoter in a vitamin D receptor (VDR)-dependent manner, suggesting that BAZ1B is a potential drug target in breast cancer [70, 71] (Fig. 4C). In lung cancer, Meng et al. found that BAZ1B acts as an oncogene to promote tumor aggressiveness by inducing epithelial–mesenchymal transition (EMT) via activation of the PI3K/Akt and IL-6/STAT3 pathways [72].

BAZ1B functions not only in intranuclear transcription regulation but also in intercellular communication. Liu et al. found that the KRASG12 mutant induces the release of BAZ1B into the extracellular space by activating NRG3 transcription that can transport BAZ1B [73]. A BAZ1B-NRG3 complex in the extracellular space activates a series of oncogenic pathways such as the RAS-MAPK, NOTCH1 and JAK pathways, in normal colon cells carrying KRASWT and etc. (Tables 2 and 3).

In breast, prostate and bone tumor cells, BAZ1B, INTS3 and RUNX2 form UV-responsive complexes with the serine-139-phosphorylated isoform of H2AX (γH2AX). This complex supports histone displacement, DNA unwinding and stabilization of single-stranded DNA to mount an integrated response to DNA damage [76]. Like BAZ1A, BAZ1B has high-frequency mutations in skin melanoma cells (Table 2), which provides an intriguing link to UV-sensitivity. Upregulation of BAZ1B by imatinib is involved
in apoptosis of CML cells by phosphorylation of H2AX at Tyr142 [77]. Moreover, BAZ1B acts as a key mediator that connects Ras/ERK signaling and phosphorylation of H2AX (H2AXY142ph). Ras-ERK1/2 induces BAZ1B degradation by increasing MDM2 expression to downregulate H2AXY142ph, which promotes cell growth and metastasis in gastric cancer [78].

NORC complex

NORC complexes, composed of BAZ2A and SMARCA1/5, recruit promoter-bound TTF-I, pRNA, and acetylated H4K16 to ribosomal DNA (rDNA) through BAZ2As TAM bromodomain domain [79, 80]. In human, rDNA instability is observed in cancers and premature aging syndromes. The NORC complex is critical for preventing cellular senescence through interaction with SIRT7, which maintains rDNA heterochromatin [81]. Depletion of BAZ2A unleashes rDNA instability, with excision and loss of rDNA gene copies, which in turn induced acute senescence [82].

BAZ2A are up-regulated in multiple tumors, such as prostate cancer, HCC, and chronic lymphocytic leukaemia (CLL) [28, 83, 84]. Moreover, BAZ2A are over-expressed in ESCA and STAD with high frequency of mutations according to TCGA database (Fig. 2A and Table 2). BAZ2A has been found to act as an oncogenic partner of TFs [85–87]. Upregulation of BAZ2A in HCC promoted the EMT progression of HCC cells by enhancing the interaction between β-catenin and TCF7L2 through its interaction with TCF7L2 [83]. Moreover, a fusion of ETV6 with the BAZ2A intron sequence generated by a cytogenetically cryptic rearrangement between 12p13 and 12q13 occurred in a pediatric case of pre-B acute lymphoblastic leukemia (ALL), which encodes a truncated form of ETV6 that leads to a pathogenic effect [88]. In a mouse prostate cancer organoid model, high BAZ2A expression is critical for the initiation of prostate cancer of luminal origin mediated by Pten-loss whereas it is dispensable once Pten-loss mediated transformation is established, which suggest that BAZ2A-mediated epigenetic second events sensitize for key genetic events that drive tumor development [89]. Mechanismly, BAZ2A binds to a class of inactive enhancers that are marked by H3K14ac via its bromodomain and represses the expression of genes implicated in aggressive and dedifferentiated prostate cancer [90].

CERF complex

The CERF complex remodels chromatin via nucleosome-dependent ATPase activity and is involved in DNA double strand break repair [91, 92]. Recently, CECR2 together with nine other genes, including ARHGAP21, ENSA, GPATCH8, KIAA1109, MGMT, PCDHB13, SELM, SPAG9 and WDR6, have been reported to be selected as the optimal gene combination that could be associated with the prognosis of patients with glioma [93]. Furthermore, a non-BET BRD inhibitor, NVS-CECR2–1, is able to kill SW48 colon tumor cells by targeting CECR2, suggesting that it may be an oncogene in some types of tumors [94]. However, the molecular and clinical implications of CECR2 in cancer remain largely unknown.

NURF complex

The NURF complex catalyzes ATP-dependent nucleosome sliding. Within the complex, BPTF, recognizes histone loci of methylation (H3K4me2/3) and acetylation (H4K12/16/20) by its PHD finger domain and bromodomain, respectively, and thus promotes gene transcription [31]. RBBP4 and RBBP7 are members of the WD-40 protein family and originally found associated with retinoblastoma proteins [95]. Both proteins are components of several multi-protein complexes that contain histone deacetylases (HDACs) and are involved in chromatin remodeling, histone post-translational modifications and regulation of gene expression, suggesting diverse functions for RBBP4/7 [95, 96].

BPTF

Genetic disorders of the BPTF gene are commonly seen in various cancer tumors. According to TCGA database, BPTF is upregulated in STAD, ESCA, LIHC, LUAD and downregulated mainly in kidney Chromophobe (KICH), thyroid carcinoma (THCA), kidney renal clear cell carcinoma (KIRC), prostate adenocarcinoma (PRAD), etc. (Fig. 2A). Moreover, BPTF possess both high frequency of mutation and abnormal copy number in angiosarcoma, COAD, ESCA, LIHC, LUAD, melanoma and urothelial carcinoma (Tables 2 and 3) [23, 24]. Particularly, BPTF was found to be the most frequently mutated gene observed (28.6%) in whole exome sequencing of Lacrimal Gland Adenoid Cystic Carcinoma (LGACC) [97]. Moreover, a NUP98-BPTF gene fusion in which a C-terminal chromatin recognition module of BPTF is fused to the N-terminal moiety of NUP98 has been identified in primary refractory acute megakaryoblastic leukemia (AMKL) that contributes to refining the NUP98 rearrangement subgroup of pediatric AMKL [98]. BPTF functions as a cofactor of oncogetic TFs. For example, BPTF-NURF complex is essential for c-MYC recruitment, chromatin accessibility and remodeling [99–101] (Fig. 3C). Knockdown of BPTF impairs tumor development with inactivation of the c-MYC and/or c-Myc target genes transcriptional program in preneoplastic pancreatic acinar cells and high-grade glioma [99, 101]. Correspondingly, BPTF expression is positively correlated with c-MYC gene signatures [99–101].
Particularly, the epigenetic environment is important for the genomic locations of BPTF. In bladder cancer, H2A.Z nucleosomes are enriched for the active histone modification H3K4me2/me3, which facilitates to recruit BPTF to H2A.Z target genes [102, 103]. The BPTF-c-Myc signaling axis is suggested to be a driving factor. For example, in the Eμ-Myc transgenic mouse model of aggressive B-cell lymphoma, BPTF allele is sufficient to delay lymphomagenesis, which display decreased c-MYC levels and pathway activity [104], suggesting that interruption of the c-Myc-BPTF-NURF complex interaction is a potential strategy for the treatment of c-Myc driven tumors.

**RBBP7**

Through the TCGA database analysis, RBBP4/7 and BPTF is simultaneously overexpressed in ESCA, LIHC, STAD etc. and downregulated in KIRC, KICH, kidney renal papillary cell carcinoma (KIRP) and prostate adenocarcinoma (PRAD) (Fig. 2A). RBBP4/7 expression were also consistent with HCC severity and prognosis together with BPTF [39]. Moreover, RBBP4 or RBBP7 and BPTF possess high frequency of abnormal copy number in angiosarcoma, breast cancer, pancreatic cancer, prostate cancer and gastric cancer (Table 3), and are mutated in colorectal adenocarcinoma, lymphoma, melanoma, etc. (Table 2).

A dual role of RBBP7 in tumor metastasis has been found to be closely related to recruitment of different RBBP7-containing complexes to EMT-related genes. For example, in cervical cancer, RBBP7 and BAF155 can be differentially recruited by NKX6.1 to suppress the *vimentin* gene and activate the *E-cadherin* gene, thus suppressing the EMT program [105] (Fig. 5A). In lung cancer, the region between −428 and −377 of the *E-cadherin* promoter contains a binding site for RBBP7, where RBBP7 functions as a transcriptional activator of the *E-cadherin* gene by binding to its promoter region, thereby repressing EMT progression [106] (Fig. 5B). Furthermore, RBBP7, as a corepressor, interacts normally with HNF1B to repress the *SLUG* gene and EMT program. However, in prostate cancer, upregulation of EZH2 suppresses the levels of the RBBP7/HNF1B transcriptional complex via direct inhibition of HNF1B expression, promoting *SLUG* transcription [107] (Fig. 5C). Additionally, in breast cancer, the transcription factor TWIST recruits an RBBP7/4-MTA2/Mi-2/HDAC1/HDAC2 complex to the proximal regions of the *E-cadherin* promoter for transcriptional repression via an interaction with RBBP7, which promotes breast cancer cell invasion and metastasis [108] (Fig. 5D).

**RBBP4**

RBBP4-containing complexes are involved in drug resistance. RBBP4 interacts with CBP/p300 to form a chromatin modifying complex that binds to MGMT, RAD51 and selected DNA repair genes. RBBP4 deletion enhanced temozolomide (TMZ) sensitivity, induced synthetic lethality to PARP inhibition and increased DNA damage signaling in response to TMZ in glioblastoma [109]. Release of RBBP4 complex occupancy or targeting the interactions between RBBP4 and oncogenic TFs provides increased opportunities for tumor intervention. For example, a BCL11A peptide inhibitor that blocks the recruitment of RBBP4-BCL11A complexes to BCL11A-targeted genes decreases aldehyde dehydrogenase-positive breast cancer stem cells (BCSCs) [110]. FFW functions as a specific SALL4–RBBP4 inhibitory peptide by targeting RBBP4 in HCC, releasing the expression of tumor suppressor PTEN [111] (Fig. 4D). In neuroblastoma cells, RBBP4 interacts with ARMC12 to facilitate the enrichment of PRC2 and H3K27me3 on tumor suppressive genes such as *CADM1, EGLN3* and *SMAD9*, resulting in transcriptional repression. While a cell-penetrating inhibitory peptide blocks the interaction between ARMC12 and RBBP4, inhibiting aggressive cell behaviors [112].

However, although some ISWI dependent functions of RBBP4/7 as components of NURF complexes have been uncovered [38, 39, 113–118]. It should be noted that RBBP4 and RBBP7 not only participate in ISWI complexes, but also in several multi-protein transcription complexes [95, 110, 119]. Specially, ISWI participates in different larger protein complexes [120–122]. At present, a large proportion of studies mentioned above focus on the biological functions and/or mechanisms of RBBP4 and RBBP7 alone, which can not make a conclusion that RBBP4 or RBBP7 play those roles in some given tumors in a ISWI or non-ISWI dependent manners. It is possible that both ISWI or non-ISWI dependent mechanisms simultaneously contribute to the whole impact of RBBP4 or RBBP7.

**BRF complexes**

BAZ2B interacts with SMARCA1/5 to form BRF-1 and BRF-5 complexes, which induces remodeling of the DNA-bound mononucleosomes [22]. Crystal structure studies of purified BAZ2B protein show that its PHD domain interacts with unmodified histone H3K4 while the bromodomain interacts with the acetylated histone H3K14 and H3K16 [123]. According to the TCGA database, BAZ2B is down-regulated in a variety of tumors, such as KICH, lung squamous cell carcinoma (LUSC), BRCA, etc. (Fig. 2A). Moreover, BAZ2B...
possess highly frequency mutations and abnormal copy number in some tumors, such as melanoma, bladder cancer, COAD, HCC, etc. (Table 2 and Table 3) However, its pathogenic mechanisms still remain unclear, and need to be further explored.

The ISWI and non-coding RNA functional connection
Recent studies showed that non-coding RNAs regulate chromatin modification and gene expression through their interactions with the ISWI complexes, which affect tumorigenesis and development in different ways. Non-coding RNAs can directly bind to the subunit of the ISWI complexes and serve as a guide to anchor the ISWI complexes. Moreover, Non-coding RNAs can be incorporated into the ISWI complexes and function as a scaffold to assemble the complex for chromatin remodeling. For example, in gastric tumor cells, the circ-DONSON recruits the SMARCA1-NURF complex to the SOX4 promoter by directly interacting with SMARCA1, which facilitates tumor cell development via enrichment of the
active markers H3K27ac and H3K4me3 on the promoter and activation of \textit{SOX4} transcription [115] (Fig. 6A). In colorectal cancer, the \textit{SMARCA1}-NURF complex is recruited by lnc-DLEU1 to the \textit{KPNA3} promoter and initiates \textit{KPNA3} expression via H3K27ac enrichment, which promotes tumor cell proliferation and migration [116] (Fig. 6B). \textit{SMARCA1}-noncoding RNA complexes also play a vital role in tumor-initiating cells (TICs) and their properties. lncHOXA10 recruits the \textit{SMARCA1}-NURF complex to the \textit{HOXA10} promoter and activates gene transcription, promoting the self-renewal of liver TICs [117] (Fig. 6C). Similarly, lncGata6 guides the localization of the \textit{SMARCA1}-NURF complex to the \textit{Ehf} promoter, which subsequently induces Lgr4/5 expression and activation of Wnt signaling in intestinal stem cells (ISCs) [118] (Fig. 6D). ISWI proteins are also involved in the noncoding RNA regulatory network. For example, RSF1 functions as an effector in lncRNA-induced drug resistance. In NPC, NEAT1/let-7a-5p axis regulates the cisplatin resistance by targeting RSF1 [124]. In ESCC, NSUN2-methylated lncRNA (NMR) directly bind to BPTF and potentially elevate MMP3 and MMP10 expression by the ERK1/2 pathway by recruiting BPTF to chromatin [125].

In particular, recent studies found that circRNAs transcribed from the ISWI genes were involved in the etiology of cancer. cSMARCA5, a circRNA derived from exons 15 and 16 of the \textit{SMARCA5} gene (hsa_circ_0001445) was upregulated in prostate cancer. Knockdown of cSMARCA5 significantly repressed the cell cycle and promoting tumor apoptosis [126]. The presence of cSMARCA5 inhibits the growth and metastasis of HCC by acting as a sponge of miR-17-3p and miR-181b-5p to upregulate TIMP3 [127, 128]. Interestingly, cSMARCA5 and SMARCA5 displayed opposite expression in HCC. Both products of the \textit{SMARCA5} gene and cSMARCA5 are associated with poor prognosis, synergistically promoting the progression of HCC [43, 127, 128]. Circ-BPTF

![Fig. 6](image)

**Fig. 6** Representative models of ISWI-noncoding RNA interplay in cancer. ISWI family proteins are implicated in the regulation of oncogene transcription involving their interplay with noncoding RNAs. Generally, noncoding RNA recruits ISWI proteins to alter the chromatin environment and histone modification, thereby affecting oncogene transcription. A In gastric tumors, circ-DONSON recruits the SNF2 L-NURF complex to the \textit{SOX4} promoter by interacting with \textit{SMARCA1}, which enriches the transcriptionally active markers H3K27ac and H3K4me3 and increases \textit{SOX4} promoter accessibility and transcription [115]. B In colorectal cancer, lncRNA DLEU1 recruits the SNF2 L-NURF complex to the \textit{KPNA3} promoter and promotes gene expression through the enrichment of histone modification H3K27ac, which further facilitates malignant behaviors [116]. C LncHOXA10 guides the localization of the SNF2 L-NURF complex to the \textit{HOXA10} promoter by directly interacting with \textit{SMARCA1}, which further activates \textit{HOXA10} transcription and promotes liver tumor-initiating cell self-renewal [117]. D LncGata6 recruits the NURF complex to the \textit{Ehf} promoter and induces gene expression by directly binding with \textit{SMARCA1}, which further promotes Lgr4/5 (ISC cell-specific marker) expression and activation of Wnt signaling and thus maintains ISC stemness or promotes tumorigenesis [118].
also plays an important role in tumor progression. For example, a circular RNA (hsa_circ_0000799) derived from BPTF exons attenuates the anti-oncogenic effect of miR-31-5p and consequently enhances RAB27A expression in bladder cancer [129].

**Impact of ISWI proteins on tumor immunity**

The levels of tumor-infiltrating immune cells within the tumor microenvironment (TME) and immune checkpoints on immune cells and tumor cells are two key factors determining the antitumor immune response. A correlation analysis in 33 tumor types based on the TCGA database showed that the gene levels of some ISWI members are strongly correlated with immune checkpoint gene levels and/or the tumor-infiltrating immune cell ratio within the TME, suggesting that ISWI members play a key role in the transcriptional regulation of immune-related genes and pathways (Fig. 7). To date, BPTF, POLE3, RSF1, BAZ1B and CECR2 have been found to be involved in immune cell development and activity and the regulation of immune-related genes.

The BPTF-NURF complex plays vital roles in normal thymocyte development. This complex facilitates the differentiation of CD4+ and CD8+ cells to mature T cells by activating the transcription of key thymocyte maturation-specific genes (e.g., Egr1, Ikaros, IL-2, and IL7ra) in a T-cell antigen receptor signaling-dependent manner [130]. For example, BPTF facilitates the recruitment of the NURF complex to the promoter region of the Egr1 gene via interaction with TF SRF [2, 130]. Aberrantly high levels of the BPTF/NURF complex are supposed to promote cancer immune escape by impacting multiple types of immune cell activity. Deletion of BPTF activates a stimulatory molecule and inhibits an inhibitory antigen on the surface of mouse breast cancer and skin melanoma cells, inducing a T-cell-mediated immune response [131]. In BPTF knockout mouse models of breast cancer and melanoma, BPTF depletion enhances antigen processing and CD8+ T cell cytotoxicity [131]. Mechanistically, BPTF knockout promotes the expression of the immunoproteasome subunits Psmb8 and Psmb9 and the antigen transporters Tap1 and Tap2, resulting in enhanced antigenicity and T-cell antitumor immunity [131]. Tumor cells with BPTF deficiency display increased CD8+ cell infiltration and CD8+ cell cytotoxicity, including the release of perforin, granzyme and IFN-γ and subsequent induction of the JAK/STAT and Fas/TRA1 pathways [132]. BPTF also stimulates hep-aranase expression, which reduces cell surface heparan sulfate proteoglycan and natural cytotoxicity receptor co-ligand abundance, therefore inhibiting NK cell antitumor activity in breast cancer cell lines [33]. Moreover, BPTF is vital for self-tolerance and immune homeostasis by stabilizing Treg function and Foxp3 expression in a cell-intrinsic manner [133]. Lack of BPTF in Foxp3-expressing Treg cells caused defective suppressive function of Treg cells, reduced Foxp3 expression, and increased lymphocyte infiltration in the nonlymphoid organs, ultimately leading to aberrant immune activation and an autoimmune syndrome [133].

In addition to BPTF, POLE3, RSF1 and BAZ1B also play vital roles in T-cell-mediated immunity via regulation of cell cycle progression, antigen-specific cytotoxic T lymphocyte (CTL) responses and metabolic pathways. C-terminal mutants of POLE3 cause a cell-autonomous, stage-specific interruption of T and B cell development and interfere with the S-phase of cell cycle progression in lymphocytes, leading to severe peripheral lymphopenia [134]. RSF1-transduced dendritic cells induced a CTL response to produce IFN-γ and IL-12 against ovarian cancer cells in vitro, suggesting that RSF1-transduced dendritic cells may be a potential adjuvant immunotherapy [135]. BAZ1B functions as an amino acid sensor to modulate T cell antitumor immunity, cytokine production and survival [136]. Upregulated L-arginine levels have been reported to induce global metabolic changes, including a conversion from glycolysis to oxidative phosphorylation in activated T cells, and increase the generation of central memory-like cells with higher survival capacity and antitumor activity [136]. Interestingly, BAZ1B, PSIP1, and TSN could sense and modulate the L-arginine-dependent reprogramming of T cells toward increased survival capacity during the above process [136–138].
Fig. 7 (See legend on previous page.)
CECR2 has been found to be involved in the regulation of tumor immunity via macrophages. In this respect, upregulation of CECR2 in metastatic breast cancer is positively related to M2 macrophages and increases tumor metastasis by promoting M2 macrophage polarization to create an immunosuppressive microenvironment [139]. Mechanically, CECR2 formed a complex with p65 through its bromodomain to activate the expression of the NF-kB target genes CSF1 and CXCL1, which are critical for macrophage-mediated immune suppression at metastatic sites [139]. Correspondingly, the inhibition of CECR2 by targeting bromodomain arrests immunosuppression by macrophages and inhibits breast cancer metastasis [139].

**ISWI complexes as potential targets for cancer therapy**

The emergence of ISWI members as oncology targets has spurred significant drug discovery efforts with the goal of identifying small molecule inhibitors that target their functional domains for therapeutic applications [140]. The bromodomain of ISWI is an attractive target for drug design. Bromodomains are readers of acetyl marks in histone tails or nonhistone proteins. From the perspective of bromodomain structure, the bromodomain structure possesses a hydrophobic acetylated lysine-binding pocket, which is optimal for the interaction of the charge-neutralized acetylated lysine and has comparatively low strength of protein-protein interaction, thus making this domain particularly targetable by small molecules that interfere with this interaction [141]. Several potent inhibitors are being developed for bromodomains present in the ISWI complexes. NVS-CECR2–1, the first selective inhibitor targeting the CECR2 bromodomain, inhibits chromatin binding of CECR2 bromodomain and displaces CECR2 from chromatin within cells. NVS-CECR2–1 exhibits cytotoxic activity against various human cancer cells mainly through inducing cell apoptosis [94]. GSK2801 is a selective and cell-active acetylatedlysine competitive inhibitor of BAZ2A/B bromodomains. Although GSK2801 has little effect on growth arrest as a single agent, it shows a strong synergistic effect on triple-negative breast cancer (TNBC) in combination with the BET bromodomain inhibitor (BETi) JQ1 [142]. Their synergistic inhibition on bromodomains induces apoptosis of TNBC by a combinatorial suppression of ribosomal DNA transcription and ETS-regulated genes. Arylurea (AU1) was the first small molecule selective inhibitor of the BPTF bromodomain and was selective for BPTF over BRD4 with moderate potency in an in vitro assay. AU1 treatment alters chromatin accessibility, decreases target gene c-MYC chromatin occupancy, weakens proliferative capacity, and leads to G1 arrest in mouse breast cancer cells [143].

The availability of crystal structures of ISWI subunits provided a unique strategy to develop their selective antagonists. To date, the crystal structures of ISWI subunits in some species have been elucidated to different resolution [144–147]. For example, Yan et al. crystallized a construct of ISWI containing the catalytic core from *M. thermophila* called MtISWI with 2.4 Å resolution, whose sequence is about 68, 68, and 58% identical to those of ISW1 and ISW2 of *Saccharomyces cerevisiae* and human SNF2h, respectively [148]. Besides, Chittori et al. determined a cryo-EM structure of the complex formed between nucleosome and the ATPase domain of the Chaetomium thermophilum ISWI [149]. In human, Armache et al. presented cryo-EM structures of the full-length form of the human ISWI remodeler at 3.4 Å, showing structures of SNF2h-nucleosome complexes with ADP-Befx [150]. Tallant C et al. identified the high-resolution crystal structures of PHD zinc finger and BRD from of human BAZ2A and BAZ2B in complex with H3 and/or H4 histones from 1.6 Å to 1.99 Å [79].

**Conclusions and perspectives**

As key chromatin remodeling complexes, ISWI variably functions as a part of different larger protein complexes, and different kinds of tumor cells have diverse expression arrays of ISWI components, each with discrete functions. Different ISWI subunits have unique regulatory roles and determine ISWI complex functions, which confer a complex ability to regulate a variety of cellular events in normal and malignant cells (Table 5). ISWI actions in cancer are gene- or context-dependent, while cooperation with different TFs or TCs may produce distinct tumor properties. The abnormal activity and expression of ISWI subunits or the occurrence of aberrant composition in ISWI-containing complexes could lead to malignant phenotypes by upsetting gene regulatory networks. In some cases, the function of oncogenic TFs and fusion proteins is reliant on direct interactions with ISWI-containing complexes, where the ISWI family is critical for the optimal oncogenic activity of the complexes. Many factors, such as mutation, copy number variations (CNVs) or aneuploidy, induce imbalances in ISWI subunit stoichiometry in cancers. In general, too few of any one subunit limits the number of assembled complexes that can satisfy biological functions. Conversely, excess subunits outside their designated complexes are often nonfunctional and may have adverse effects. Therefore, stoichiometric imbalances of key “driver” components of ISWI complexes in a given tumor may be a key etiology. Balancing or restoring the normal expression levels and/or function of components within ISWI complex or between ISWI and other protein complexes promises...
### Table 5  ISWI-containing complexes in cancer and their functions

| Complex components | Cell types or tumors | Functions |
|--------------------|----------------------|-----------|
| SNF2L-NURF complex-Circ-DONSON | GC cell lines (BGC-823, AGS, MGC-803, MKN74, HGC-27 and SGC-7901) | Activating SOX4 transcription, which leads to the proliferation, migration and invasion of GC cells |
| SNF2L-NURF complex-LncRNA DLEU1 | Human colorectal cell lines (HCT8 and SW480 cell) | Initiating KPNA3 expression and promoting cell proliferation, migration and invasion |
| SNF2L-NURF complex-LncHOXA10 | Primary liver TICs | Activating HOXA10 transcription to promote the self-renewal of liver tumor initiating cells (TICs) |
| SNF2L-NURF complex-LncGata6 | Mouse intestinal stem cells | Promoting Ehf transcription, which subsequently induces Lgr4/5 expression and activation of Wnt signaling in intestinal stem cells (ISCs) |
| SNF2L-NURF complex-WASH | Mouse long-term hematopoietic stem cells | WASH assists the NURF complex in the c-Myc promoter and enhances gene transcription, which maintains the differentiation potential of long-term hematopoietic stem cells (LT-HSCs) to mature blood lineages |
| SNF2L-NURF complex-ZIC2 | Primary liver CSCs and Hep3B cell lines | Initiating OCT4 activation to maintain the self-renewal of liver CSCs |
| SNF2H-CTCF complex | MEL and OCI-M2 cells | Being recruited to the enhancer of PU.1 gene and blocking gene expression |
| RSF1-cyclin E1 | Renal epithelial cells | Contributing to neoplastic transformation in the presence of TP53 mutations |
| SNF2H-RSF1-NF-κB | Ovarian cancer cell lines (SKOV3, OVCAR3, and A2780) | Activating NF-κB-dependent gene expression, contributing to the development of chemoresistance |
| SNF2H-ACF1-CHRAC15-CHRAC17-KU70/80 | U2OS/TRE/I-SceI-19 cells | Playing important roles in double-strand break repair |
| WSTF-RUVBL2-INTS3-RUNX2 | Breast, prostate, and bone cancer cell lines (Saos2, U2OS, MDA-MB-231 and PC3) | Mounting an integrated response to DNA damage through supporting histone displacement, DNA unwinding, and stabilization of single-stranded DNA |
| WSTF-NRG3 | Colon cancer cell line (SW48) | Activating oncogenic pathways of the surrounding normal colon cells through mediating cell-cell communication |
| TIPS-EZH2 | Prostate cancer cell line (PC3) | Participating in epigenetic silencing of AOX1, FBN1, FHL2 and HOMER2 genes |
| BPTF-c-Myc | Pre-neoplastic pancreatic acinar cells | Increasing c-MYC recruitment to target genes and regulating chromatin accessibility at promoters, thus increasing target genes' transcription |
| BPTF-P50-NF-κB | Lung cancer cell lines (A549 and NCI-H460) | Increasing COX-2 expression by binding to COX-2 promoter region, promoting tumor cell growth |
| BPTF-WDR5 | Bladder cancer cell line (LD611) | Promoting the expression of tumorigenic genes |
| RBP7-NKX6.1 | Cervical cancer cell line (HeLa) | Serving as a repressor to bind to vimentin promoter, thus suppressing its transcription |
| RBP7-HNF1B | Prostate cancer cell line (DU145) | Repressing SLUG expression and EMT phenotype |
| RBP7/4-MTA2/Mi-2/HDAC1/2-TWIST | Human and mouse breast cancer cells (MDA-MB-435 and T1) | Suppressing E-cadherin transcription, inducing EMT program |
| RBP4-BCL11A | Breast cancer cell line (SUM149) | The recruitment of RBP4-BCL11A complexes to BCL11A-targeted genes decreases aldehyde dehydrogenase-positive breast cancer stem cells (BCSCs) and their mammosphere formation capacity |
| RBP4-ARM12 | Neuroblastoma cell lines (SH-SYSY, BE(2)-C and IMR32) | Facilitating the formation of PRC2 in neuroblastoma, resulting in transcriptional repression of tumor suppressive genes |
| RBP4-CBP/p300 | Glioblastoma cell line (T98) | Promoting DNA repair genes expression, which influences the survival against temozolomide (TMZ) therapy |
| RBP4-LncRNA LCPAT1 | Breast cancer cell lines (MCF-7 and MDA-MB-231) | Activating MAF2 transcription and promoting breast cancer progression |
exciting therapeutic insights. ISWI bromodomain inhibitors have shown synergistic or additive effects with numerous chemotherapeutic agents. In preclinical and clinical settings, ISWI subunits have recently emerged as immunoregulators that modulate immune cell phenotypes or the expression of immune checkpoints. Therefore, the combination of ISWI inhibitors with immune checkpoint inhibitors may be considered a major breakthrough in the treatment of malignancies.

Given that epigenetic regulation of the ISWI family globally affects the gene regulatory network, an ensemble of key cancer-driving ISWI subunits has been identified. Future studies need to identify more regulatory factors that dysregulate ISWI family expression and determine how their misexpression contributes to the pathogenesis of malignancies. Identification of more crystal structures of ISWI subunits and epigenetic mechanisms, thereby targeting specific ISWI domains, ISWI-mediated pathways and the TF/ISWI interface, may contribute to the development of novel inhibitors in ISWI-associated malignancies.

**Abbreviations**

AZA: 5-azacytidine; ALL: Acute lymphoblastic leukemia; AMKL: Acute megakaryoblastic leukemia; AML: Acute myeloid leukemia; AU1: Arylurea; BETi: BET bromodomain inhibitors; BCCA: Breast invasive carcinoma; BRD: Bromodomain; CSCs: Cancer stem cells; CRCs: Chromatin remodeling complexes; CHD: Chromodomain-helicase DNA-binding protein; CLL: Chronic lymphocytic leukemia; COAD: Colon adenocarcinoma; CTL: Cytotoxic T lymphocytes; DSBs: Double-strand breaks; EMT: Epithelial–mesenchymal transition; ESCA: Esophageal carcinoma; ESCC: Esophageal squamous cell carcinoma; HCC: Hepatocellular Carcinoma; ISWI: Imitation switch; INO80: Inositol-requiring mutant 80; ICSs: Intestinal stem cells; KICH: Kidney Chromophobe; KIRC: Kidney renal clear cell carcinoma; LADC: Lung adenocarcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MFS: Metastasis-free survival; NPC: Nasopharyngeal carcinoma; NRG3: Neuregulin 3; NHEJ: Nonhomologous end-joining; NSCLC: Non-small cell lung cancer; OS: Overall survival; PDAC: Pancreatic ductal adenocarcinoma; PRAD: Prostate adenocarcinoma; RFS: Relapse free survival; RCC: Renal cell carcinoma; SCLC: Small cell lung cancer; STAD: Stomach adenocarcinoma; SWI/SNF: Switch/sucrose non-fermentable; TMZ: Temozolomide; THCA: Thyroid carcinoma; ISWI-mediated pathways and the TF/ISWI interface, may contribute to the development of novel inhibitors in ISWI-associated malignancies.

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**Authors’ contributions**

ZW designed this study. ZW, PL, YL, PH, and YZ drafted the manuscript. JL and HP revised this manuscript. YL, YZ, YC, and HL drew the figures. All authors read and approved the final manuscript.

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All of the authors are aware of and agree to the content of the paper and their being listed as a co-author of the paper.

**Competing interests**

The authors declare that they have no competing interests.

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