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Chromatin remodeling and SWI/SNF2 factors in human disease

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1. ABSTRACT

Chromatin structure and its changes or maintenance throughout developmental checkpoints play indispensable role in organismal homeostasis. Chromatin remodeling factors of the SWI/SNF2 superfamily use ATP hydrolysis to change DNA-protein contacts and their loss-of-function or inappropriate increase leads to distinct human pathologic states. In this review, we focus on the translational view of human pathologic physiology involving SWI/SNF2 superfamily combining latest findings from basic and clinical research. We discuss in mechanistic terms the consequences resulting from dose alteration of the SWI/SNF2 superfamily ATPases and emphasize the necessity of future human subject-based studies.

2. INTRODUCTION

Probably all functional transactions of DNA wrapped around a histone octamer in a nucleosome require precise regulation of its complex tertiary structure referred to as chromatin. This review summarizes the published work on chromatin remodeling proteins of the SWI/SNF2 superfamily and their emerging role in human pathologies including tumorigenesis and developmental syndromes. SWI/SNF2 proteins (mating type switch/sucrose non-fermenting), identified first through yeasts two-hybrid system, use the energy from ATP hydrolysis to perturb histone-DNA contacts and to change the position of histone octamers on DNA resulting in either a nucleosome-free region or a densely packed array of nucleosomes.

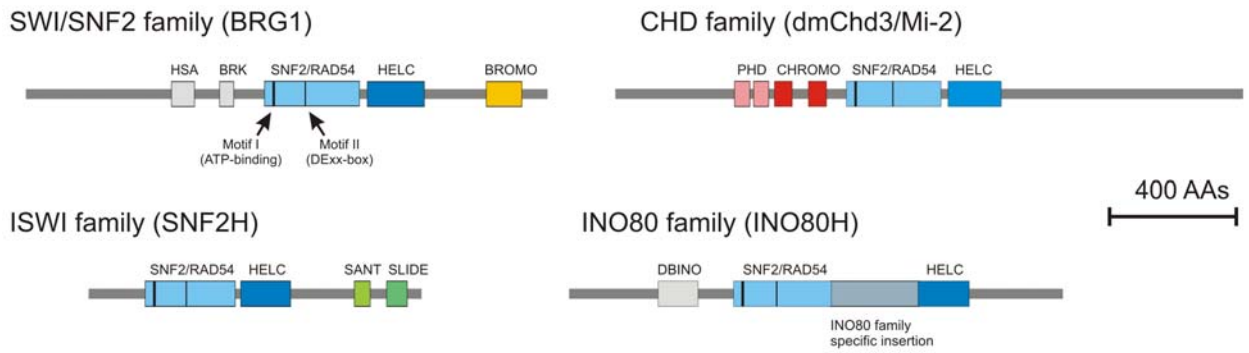

Figure 1. SWI/SNF2 superfamily of helicases consists of the SWI/SNF2, ISWI, CHD, and INO80 subfamilies. Primary protein structure of SWI/SNF2 proteins is shown relative to their molecular size. Individual domains are shown in color boxes representing their homology within SWI/SNF2 superfamily. HSA = helicase/SANT-associated domain, BRK = BRM and KIS domain, SNF2/RAD54 = helicase N-terminal domain, HELC = helicase C-terminal domain, BROMO = bromodomain, SANT = Swi3, Ada2, NCoR, TFIIIB domain, SLIDE = SANT-like domain, PHD = (Plant homeodomain)-type zinc finger domain, CHROMO = chromodomain, DBINO = DNA binding domain of INO80. Helicase motifs I (Walker A) and II (Walker B) of the SNF2/RAD54 domain are indicated by arrows.

Remodeling of the nucleosomal structure and position influences both specific and global transcription, replication and gene repair, regulating thus cell specific differentiation, proliferation and survival (reviewed in (1)). ATP-dependent chromatin-remodeling protein complexes contain a highly conserved ATPase that belongs to the SWI/SNF2 superfamily of helicases consisting of the SWI/SNF2 and the ISWI subfamilies and also of the less known CHD and INO80 subfamilies (summarized in Figure 1). SWI/SNF2 proteins or their interacting partners contain specific protein domains that can directly interact with chromatin, especially with covalently modified histone residues (reviewed in (1) and Figure 1). Human SWI/SNF2 complexes contain either BRG1 or BRM catalytic ATPase subunits that are present in several separate complexes containing up to 11 subunits, and well studied examples include BAF170, BAF155, BAF60 and BAF47/INI1. Human ISWI complexes contain either SNF2H/SMARCA5 or closely related SNF2L/SMARCA1 ATPase in the oligosubunit complexes with bromodomain-containing protein ACF/BAZ1A or its homologues WSTF/BAZ1B or TIP5/BAZ2A (reviewed in (2), (3)). Non-catalytic subunits of both SWI/SNF2 and ISWI complexes and the variations in their composition presumably assist in directing specificity of the complexes. However, the exact mechanisms of how they regulate chromatin remodeling activities are not well understood.

Numerous examples document specific roles of the histone modifying proteins in cancer (reviewed in (4)). Recent emerging evidence supports the role of SWI/SNF2 superfamily of helicases in oncogenesis (reviewed in (5)). SWI/SNF2 proteins are recruited onto chromatin to regulate transcription and nucleosome remodeling in an ATP-dependent fashion. There are currently four concepts of how the SWI/SNF2 superfamily of complexes regulates the nucleosome structure and position including nucleosome sliding and disruption (ejection), and histone dimer H2A-H2B removal and replacement (reviewed in (6)). Some differences exist between SWI/SNF2 and ISWI subfamilies in the sliding mechanism: most ISWI complexes equally space nucleosomes whereas SWI/SNF2 randomize position of a nucleosome on the template. In addition SWI/SNF2 remodelers can eject nucleosomes. Both subfamilies are capable of histone dimer ejection whereas solely the INO80 remodeler can reverse this reaction presumably involved in DNA repair (reviewed in (6)). SWI/SNF2 complexes alter the nucleosomal structure and each probably recognizes particular epitopes on the nucleosome through specific domains including the bromodomain or chromodomain. Current research is focused on identifying the mechanisms of recognition of individual covalently modified histone residues during progression through specific developmental checkpoints in normal and pathologic states (reviewed in (7)). Another line of research also aims to determine the particular role/s of the SWI/SNF2 superfamily proteins in this process.

The roles of the SWI/SNF2 superfamily of proteins in disease pathogenesis are reviewed below in the contexts of developmental disorders, solid tumors and hematologic malignancies. Specific disease characteristics are compared with available animal models and potential mechanisms of disease pathogenesis are discussed (summarized in Table 1).

3. THE SWI/SNF2 SUPERFAMILY AND HEREDITARY SYNDROMES

Several examples document a relationship between chromatin remodeling proteins and developmental disorders, such as SNF2H and Williams syndrome, SMARCAL1 and Schimke immuno-osseous dysplasia, and CHD7 and CHARGE syndrome. Williams syndrome transcription factor (WSTF/BAZ1B) is invariably deleted in the haploinsufficiency Williams-Beuren Syndrome (reviewed in (8)). Williams syndrome is characterized by a striking cognition and behavior phenotype with moderate mental retardation, severe visuospatial construction deficit and learning difficulties contrasting with a relative strength in verbal short term memory and language, high sociability

Table 1. Selected examples of human diseases associated with dysregulation of SWI/SNF2 superfamily proteins

ATPase	Complexes	Molecular composition	Molecular function	Associated diseases
BRG1/BRM*	SWI/SNF BAF Complex* and Tissue specific variants	BAF250A (ARID1A), BAF250B (ARID1B), BAF170 (SMARCC2), BAF155 (SMARCC1), BAF60A (SMARCD1), BAF60B (SMARCD2), BAF60C (SMARCD3), BAF57 (SMARCE1), BAF53A (ACTL6A), BAF47 and (SMARCB1/SNF5/INI1), BAF53B (ACTL6B), BAF45A (PHF10), BAF45B (DPF1), BAF45C (DPF2), BAF45D (DPF3)	Transcriptional activation	Rhabdoid tumors Atypical teratoid tumors Familial posterior fossa tumors of infancy Familial Schwannomatosis Prostate cancer Breast cancer Colonic carcinomas Pancreatic carcinoma Uteral cervix cancer Neuroendocrine carcinomas Lung adenocarcinomas Squamous cell lung carcinoma Nonsmall lung cancer Small cell lung carcinomas Primary gastric carcinomas Cervical carcinomas Neuroblastomas Prostate carcinomas Melanomas Epithelioid sarcomas Polycythemia vera with transformation to acute leukemia Williams-Beuren Syndrome (?)
	SWI/SNF PBAF Complex	BAF200 (ARID2), BAF180 (PBR1), BAF170, BAF155, BAF60A, BAF60B, BAF60C, BAF57, BAF53A, BAF47	Transcriptional activation	
	WINAC complex	BAZ1B (WSTF), BAF250A, BAF250B, BAF170, BAF155, BAF60A, BAF60B, BAF60C, BAF57, BAF53A, BAF47, TOPO2, FACT140 (SUPT16H), CHAF1A (CAF1P150)	Transcriptional activation	
	NUMAC complex	BAF250A, BAF250B, BAF170, BAF155, BAF57, BAF47, CARM1, BAF42 (ACTB)	Transcriptional activation	
	NCoR complex	BAF170, BAF155, BAF47, HDAC3, KAP1	Transcriptional repression, gene silencing	
	mSin3A/HDAC complex	BAF250A, BAF250B, BAF170, BAF155, BAF60A, BAF60B, BAF57, BAF53A, BAF47, SIN3A, PRMT5, HDAC1, HDAC2	Transcriptional repression, gene silencing	
SNF2H/SNF2L**	ACF	BAZ1A (ACF1)	Chromatin assembly	Acute myeloid leukemia Prostate adenocarcinoma Williams-Beuren Syndrome (?)
	CHRAC	BAZ1A (ACF1), CHRAC15, CHRAC17	Chromatin assembly	
	WICH**	BAZ1B (WSTF)	Nucleosome assembly and transcriptional repression of rRNA genes	
	NORC	BAZ2A (TIP5)	Transcriptional repression of rRNA genes	
	RSF	RSF1 (HBXAP)	Nucleosome spacing	
	SNF2H-Cohesin complex	CHD3/4, RAD21, HDAC1,HDAC2, SMC1, SMC3, MBD2, MBD3, MTA1, MTA2, RBAP46, RBAP48	Chromosome segregation	
	NURF**	BPTF, RBAP46, RBAP48	Transcriptional activation	
	CERF**	CECR2	Transcriptional activation	
CHD1				
CHD1L				
CHD2				
CHD3, CHD4	NuRD complex	CHD3/CHD4, MTA2, MBD2, MBD3, MTA1L1, HDAC1, HDAC2, RBBP4 and RBBP7	Transcriptional repression by histone deacetylation and nucleosome remodeling	Hodgkin's lymphoma
CHD5				Neuroblastoma
CHD6				
CHD7				CHARGE syndrome Idiopathic scoliosis type 3
CHD8	CTCF-CHD8	CTCF	Insulation and epigenetic regulation at active insulator sites	
CHD9			Transcriptional coactivator for NRs	
INO80H	INO80 complex	BAF53A (ARP4), ARP5, ARP8, TIP49A, TIP49B, PAPA1, IES6/IES2 and YY1, NFRKB, TFPT (Amida), FLJ90652 (CCDC95), UCH37, FLJ20309 (LOC54891), MCRS1	DNA repair and histone dimer exchange	

and empathy for others. Williams syndrome is also accompanied by growth retardation and cardiovascular abnormalities in approximately 80% of patients. Williams syndrome is caused by a hemizygous deletion of 1.6 Mb DNA region containing 28 genes on chromosome 7q11.23. Targeted gene inactivation mouse models linked specific phenotypes with symptomatology of Williams syndrome patients and associated several genes with Williams syndrome pathogenesis including *Limk1* and *Fzd9* with visuospatial deficit and *Cyln2* with coordination deficit. *WSTF* is located in central portion of the deletion in direct vicinity of *FZD9* on centromeric site whereas *CYLN2* and *LIMK1* are located on the telomeric site. *Wstf* -null mice are needed to improve our understanding of Williams syndrome. WSTF-SNF2H complex (WICH) has been recently associated with several biological processes that can play a role in Williams syndrome, mainly by maintenance of chromatin fluidity (9) that can influence both developmental and postnatal phenotypes. WSTF in WICH complex has been suggested to restrict SNF2H nucleosome assembly activity while stimulating nucleosome mobility, global transcription and chromatin remodeling shortly after DNA replication (9). WICH complex has another proposed role in the RNA Polymerase I-directed transcription, similarly to another SNF2H-containing complex NoRC consisting of transcription factor TIP5/BAZ2A and SNF2H (reviewed in (10)). More studies using patient-derived chromatin are needed to understand the exact role of WSTF in Williams syndrome and whether the associated haploinsuficiency facilitates an increased heterochromatin formation due to elevated WICH-free SNF2H contents. Alternatively, the Williams syndrome symptomatology may also result from the composition defect in the WICH and the NoRC complexes that are involved in repression mechanism of rRNA genes (reviewed in (10)).

SNF2H is an ISWI ATPase highly homologous to another closely related ISWI ATPase SNF2L, with 81% cDNA and 87% amino acid homology. The co-expression of SNF2H and SNF2L occurs in testes, brain, and liver whereas SNF2H but not or very little of SNF2L is

expressed in all types of hematopoietic cells (11), (12). The interactions of Snf2l and Snf2h with their binding partners within ACF and WICH complexes, Acf1 and Wstf respectively, were studied in detail (13). At least in embryonic stem cells Snf2l and Snf2h are co-immunoprecipitated with an antibody against Acf1. However, only Snf2h and not Snf2l was detected in the immunoprecipitate of the antibody against Wstf. These results indicate that while both Snf2h and Snf2l are found in ACF complexes, Snf2h is the predominant isoform of ISWI with which Wstf interacts (13). It would be of interest to determine whether there are any functional differences between Snf2h-Acf1 and Snf2l-Acf1. One of the potentially valuable methods might be the template commitment assays during ACF-mediated chromatin assembly (14). Studies using *Snf2h* knockout mice indicate that Snf2l cannot sufficiently substitute for Snf2h at early stages of development (15). *Snf2h*-null homozygous mice die around day E5, early during gastrulation and after embryonic implantation. *In vitro* outgrowth studies of *Snf2h*-null cells implicate proliferation arrest and apoptosis of both inner cell mass and trophoblast-like structures (15) and *Snf2h*-heterozygous mice exhibit a postnatal growth delay (16). In addition, SNF2H knock down in hematopoietic progenitors inhibited cytokine-induced proliferation *in vitro* (15). These findings argue against a possibility that at later stages of development Snf2l is capable of replacing Snf2h, *e.g.* in the ACF complex. It seems however plausible that Snf2h substitutes for Snf2l in the developing embryo, as indicated by currently undertaken studies using mouse Snf2h and Snf2l models.

SWI/SNF2 superfamily genes regulate relatively large cohorts of mRNA transcripts and thus their mutations can lead to the phenotypes that one would expect to be a result of extensive gene loss. Such example represents the CHARGE syndrome that displays **C**oloboma, **H**eart Defect, **A**tresia choanae, **R**etarded Growth and Development, **G**enital Hypoplasia, **E**ar Anomalies/Deafness. It has been recently found that patients diagnosed with CHARGE syndrome (also Hall-Hittner Syndrome) are characterized by haploinsufficiency of *CHD7* (17), a chromatin remodeling chromodomain-containing ATPase expressed predominantly in the brain, kidney, and skeletal muscle. It should be noted that two of the patients in the study carried a 2.3 Mb deletion (17). The CHARGE syndrome is autosomal dominant and can be inherited in rare cases of missense mutations or mosaicism in one of the parents (18), (19). Genetic association of the CHARGE syndrome with the mostly truncating mutations of *CHD7* appears throughout the gene in 40% of cases (18). There are ten known CHD genes characterized by two chromodomains, a centrally located SNF2 helicase domain, and a C-terminal DNA binding domain. Mouse mutagenesis models of *Chd7* displayed craniofacial defects, vestibular dysfunction, and abnormalities of the ear and the heart (20). Knockout of *Chd7* in mice is embryonic lethal, around day E10.5 and both homozygotes and heterozygotes display histological defects in the ear, eye, pituitary, heart, brain, and craniofacial structures (21). Thus single allele mutations of *Chd7* gene in mice are able to produce phenotype resembling CHARGE syndrome. However, it remains to be determined if the defects in CHARGE pathology is caused by defects in CHD7-dependent transcriptional guidance of gene expression, or by CHD7-dependent defects in chromatin structure, or both. Data from mouse models indicate that levels of CHD7 are very important in human developmental pathogenesis and that slight decreases in CHD7 function have global effect on multiple organismal functions. This notion is further supported by findings of CHD7 gene variations that are associated with the most common spinal deformity in children idiopathic scoliosis type 3 (22).

Mutations in SWI/SNF2 proteins were also found in autosomal recessive Schimke immuno-osseous dysplasia (SIOD) with predominant biallelic mutations of SWI/SNF2 ATPase SMARCAL1 (23). SIOD exhibits multiple phenotypic features including T-cell deficiency, renal disease, spondyloepiphyseal dysplasia, and characteristic dysmorphic features. SIOD is a genetically heterogeneous disease with a marked variation in severity and onset of symptoms, often accompanied by other developmental features including cerebral arteriosclerosis, migraine-like headaches, blood lineage deficiency, hypothyroidism, corneal and retinal defects, dental anomalies, autoimmune enteropathy, pulmonary hypertension and opportunistic infections (reviewed in (24)). Diagnostic criteria of patients and their relatives must rich 4 points and include childhood growth failure (1 point), renal failure (1), lymphopenia (1), recurrent infections (1), cerebral ischemia (1), death before (2) or after age of 10 (1). The analysis of SMARCAL1 involvement in SIOD focuses on the detection of biallelic mutations in SMARCAL1 gene. In case of heterozygous mutations in SMARCAL1, the fibroblast or EBV-transformed lymphocytic cell lines are isolated from patients and SMARCAL1 levels of both mutant and normal gene products are determined (24). Less than half of SIOD patients have normal structure and expression of SMARCAL1, marked by a slightly favorable prognosis. The exact roles of SMARCAL1 mutation/s in SIOD pathogenesis remain to be determined.

The hereditary syndromes reviewed in this part display complex phenotypic features and several genetic studies indicate that levels of the chromatin remodeling proteins regulate expression of relatively large set of genes.. Further studies are however required to identify disease-associated mechanisms as they are needed for designing future therapeutic approaches.

4. THE SWI/SNF2 SUPERFAMILY IN SOLID TUMORS AND LEUKEMIA

Significant progress in connecting the SWI/SNF2 superfamily with cell proliferation and tumorigenesis was initiated by gene inactivation studies of *Brm* and *Brg1* in mice. *Brm* null mice display a mild phenotype of ~15% increase of body weight and *ex vivo* isolated Brm deficient cells exhibit a defect in the G0/G1 cell cycle arrest followed by the induction of cell confluence or DNA damage (25). In contrast, *Brg1* null mice die early in development at periimplantation stage and *Brg1* heterozygous mice display exencephaly and solid epithelial

tumors (26). Co-immunoprecipitation studies indicate that Brg1 can substitute for Brm in SWI/SNF2 complexes isolated from *Brm* null mice (25). As described above BRG1 and BRM complexes in humans share some of the interacting partners including INI1 (also known as *BAZ47/SNF5/SMARCB1)*. *Ini1* null mice die around implantation stage, analogously to *Brg1* knockout mice (27). *Ini1* heterozygous mice develop rhabdomyosarcomas at craniocervical location, due to a loss-of-function (loss of heterozygosity, LOH) mechanism (27).

Further studies using *Brg1, Brm* and *Ini1* knockout mice identified at least two different mechanisms for oncogenesis mediated by the protein components of murine SWI/SNF2 complexes. Mammary epithelial tumors observed in *Brg1* heterozygous mice arise because of haploinsufficiency with increased genomic instability rather than LOH (26). In contrast, *Ini1* haploinsufficiency increases rates of proliferation and cell immortalization, while its biallelic inactivation gives rise to rhabdoid tumors (28). *Ini1* loss results in concomitant dysregulation of E2F targets and increased levels of p53 that are accompanied by apoptosis, polyploidy, and G2 growth arrest (29). Co-inactivation of p53 but not pRb or $p16^{Ink4a}$ resulted in dramatic acceleration of tumor onset in the *Ini1* knockout mice (29). Another report indicated that pRb and Ini1 may possess mutually redundant tumor-suppressing capabilities (28). Tumor formation in *Rb*-heterozygous mice (due to an LOH mechanism) was not affected by the presence of one or two copies of functional *Ini1*, and most pituitary adenomas lost functional *Rb*. However, some atypical cells displayed LOH for the functional *Ini1* allele while retaining the heterozygous state of *Rb* (28).

Multiple analyses identified a large spectrum of mutations or dysregulation of the SWI/SNF2 superfamily in the cell lines derived from human solid tumors. Global screen in 268 human tumor cell lines identified biallelic mutations of BRG1 in the prostate, breast, pancreas, uterine cervix, and in neuroendocrine and lung carcinoma cell lines (30), (31). Cell lines from other tumors including colon carcinoma exhibited monoallelic *BRG1* point mutations and subsequent studies indicated that the expression levels of BRG1 mRNA and/or composition of SWI/SNF2 complexes was found defective in these cells (30). Reintroduction of BRG1 into *BRG1*-deficient tumor cell lines induced G1 cell cycle arrest, however dependent on pRb co-expression (30). This demonstrates that in the absence of pRb the SWI/SNF2 complex cannot efficiently control the G1/S transition in tumor cells, presumably by inefficient co-regulation of E2F transcription factors. It is of interest that BRG1 cooperates with other two tumor-related components, BRCA1 and p53, by directly interacting with BRCA1 in regulation of p53-mediated transcription (32). The mutation and dysregulation of SWI/SNF2 superfamily proteins in cancer cell lines constituted a basis for further research in patients with solid tumors.

Studies of *BRG1* mutations in non-small lung cancer indicate that BRG1 regulates a set of disease-associated target genes. Reintroduction of BRG1 into *BRG1*-defficient lung cancer cells resulted in the upregulation of expression of 43 genes. In addition, the regulatory regions of the selected genes were shown to be directly occupied by BRG1 (33). This observation was confirmed for the BRG1 targets ZNF185 and CYP3A4 in more than half of the primary tumor samples (33), using lung cancer cell lines and 27 primary lung cancer samples. Furthermore, levels of BRG1 were decreased in 15% of the primary tumor samples that did not display *BRG1* mutation (33). Another studies identified SWI/SNF2 target genes of neuronal origin, *Synaptophysin and SCG10*, to be differentially expressed in non-small cell lung carcinoma and their expression negatively correlates with BRM and BRG1 expression (34). Expression and localization of BRG1 and BRM may also have significant prognostic value in both adenocarcinoma and squamous cell lung carcinoma as nuclear co-expression of both BRG1 and BRM predicts favorable prognosis (overall 5-year survival 72 v.s. 33.6%) compared to lung tumors positive for either or negative for both markers (35).

In contrast, BRG1 expression may have different prognostic significance when considered in different types of solid tumor, as is the case for prostate cancer. In prostate cancer, the occurrence of biallelic BRG1 mutations is a rare event. Increased BRG1 protein expression and downregulation of BRM in malignant tissues compared to the benign compartments indicated tumor development and progression (36). In addition, increased BRM expression in the tumor tissue was associated with low grade tumors, suggesting different functions of BRM- and BRG1-containing complexes in prostate cancer subtypes (36). Expression of other SWI/SNF2 protein from the ISWI subfamily, SNF2H, and several known histone H3 modifications were determined in large patient cohorts diagnosed with prostate pathologic states including benign prostatic hyperplasia (BPH), low and high grade prostatic intraepithelial neoplasia (PIN), and the prostate adenocarcinoma. SNF2H nuclear protein expression was strongly increased in all PIN and adenocarcinoma samples and lower in BPH. Thus expression of the SWI/SNF2 and ISWI ATPases reflects oncogenic transformation in prostate and their levels appear important for disease progression. Currently, more experiments on prostate cancer patient samples are needed to identify tumorigenic SWI/SNF2 and ISWI target genes to identify prostate-specific disease mechanisms.

BRG1 and BRM proteins do not substitute each other in the SWI/SNF2 complexes in cancer cells, revealing thus different specificities of these complexes in respect to the composition. Recent report using gastric cancer cell lines identified frequent loss of BRM expression in 67% of the major types of primary gastric carcinomas including tubular and poorly differentiated gastric carcinoma (37). In contrast, BRG1 expression is retained in most cases, while a concomitant loss is rarely observed (37). Moreover, one of predicted intestinal metaplasia-associated markers, *Villin*, was also downregulated in BRM-negative gastric carcinoma cell lines and its expression was induced by ectopic BRM expression. Furthermore, BRM occupancy at *Villin* regulatory region was clearly detected by chromatin immunoprecipitation (37). Downregulation of BRM is not

observed during early stages of carcinogenesis including chronic atrophic gastritis and intestinal metaplasia, BRM loss may thus represent an event associated with later stages of gastric carcinogenesis.

Several genes, linked with tumor progression and metastasis, are targets of BRG1. One such example represents widely distributed transmembrane glycoprotein CD44 that is overexpressed in some carcinomas and reduced in others including cervical carcinomas, neuroblastomas, prostate carcinomas, melanomas, and small cell lung carcinomas (38), (reviewed in (39)). In a large cervical cancer patient cohort, the BRG1 and CD44 expression was determined in neuroendocrine, squamous carcinoma and adenocarcinoma samples. The data clearly indicate that 70.59% of neuroendocrine carcinomas stained negative for BRG1 and CD44 (39). Overexpression of BRG1 in BRG1-negative cancer cell lines restored CD44 expression whereas the dominant negative mutant of BRG1 inhibited CD44 expression in BRG1-expressing cancer cell lines (40). In contrast, CD44 expression is increased in cervical squamous cell carcinoma (39). It suggests levels of BRG1 and its target gene CD44 associate with some cervical tumor subtypes. Further identification of more cancer type-specific BRG1 gene targets can be an effective tool for identification of markers of cervical tumor progression and metastasis.

Several gene-inactivation models in mice resemble human pathologic states with high fidelity. Examples include malignant rhabdoid tumors observed in pediatric patients carrying aberrations of *INI1* gene (41). Moreover, INI1 targets presumably in SWI/SNF2 complex the *MyoD1* gene and thus MyoD1 expression in the malignant rhabdoid tumor serves independently as control for INI1 function (41). Other tumor cell lines (N=34) and fresh tumor samples (80) did not show *INI1* mutation (41). Recently, however, rare soft tissue neoplasm, epithelioid sarcoma, was associated with *INI1* mutations (42). Breakpoint at chromosome 22q11 was identified near the region containing the *INI1* gene that was found biallelically deleted in a half of the epithelioid sarcomas (42). Another recent report suggests a germ line mutation of *INI1* gene in Familial Schwannomatosis, in one family case where both father and daughter were diagnosed with schwannomas and carried mutation in exon 1 of *INI1* gene (43). Development of schwannomas clearly associate with the LOH mechanism as another mutation in exon 5 of *INI1* gene was detected in these tumors (43).

Beside carcinomas and sarcomas, hematologic malignancies are also strongly associated with SWI/SNF2 gene dysregulation. Study of hematopoietic progenitors in acute leukemia identified an increase in SNF2H expression that correlated with status of the disease and decreased after the patients achieved complete therapy-induced hematologic remission (44). Data of increased SWI/SNF2 function in hematologic malignancies are supported by study of myeloproliferative stem cell disorder, polycythemia vera with transformation to acute leukemia, identified several regions with amplification of the locus at 9p22 –p24.3 containing BRM gene (45). Another data from Hodgkin's lymphoma cells found increased expression CHD3-interacting partner Ki-1/57 in Reed-Sternberg cells (46). CHD3 homologue CHD5 is in turn found consistently mutated in neuroblastoma patients carrying deletions of the corresponding allele (reviewed in (47)). The understanding of detailed involvement of the SWI/SNF2 proteins in hematologic malignancies however needs to be supported by additional translational research and mouse model-based studies.

5. PERSPECTIVE

The chromatin remodeling SWI/SNF2 superfamily plays important role in normal organism development (reviewed in (1)) and this review attempted to summarize examples of human diseases that are either caused or strongly associated with dysregulation or mutations of SWI/SNF2 proteins. Multiple studies of SWI/SNF2 proteins in mice and human disease implement both non-targeted chromatin structure maintenance as well as transcription factor-targeted distinct changes at specific regulatory regions on DNA. Consequent and biologically informative array of histone modifications (reviewed in (48)) and SWI/SNF2-dependent distinct changes of nucleosomal structure are critical parameters of transcription, replication and gene repair in cancer (reviewed in (49)). In addition, the SWI/SNF2 proteins are involved in reprogramming during development in gametes and are thought to be involved together with DNA methyl transferases among genes that provide epigenetic memory (16). The validation of emerging concepts of causative roles of precise regulation of chromatin structure during normal development and of its perturbations in hereditary syndromes and acquired malignancies will require a combination of both basic and clinical research approaches.

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Abbreviations: SNF2H: Sucrose nonfermenting-2 (yeast) homolog, SNF2L: Sucrose nonfermenting-2 (yeast) homolog-like, NuRD: Nucleosome remodeling and histone deacetylation complex, ARID: AT-rich interaction domain, BAF: BRG1/hBrm-associated factors, BRG1: Brahma-related gene-1, BRM: Brahma homolog, HDAC: Histone deacetylase, MBD: Methyl CpG-binding protein, NR: Nuclear receptor, PBAF: Polybromo-associated BAF, REST: Repressor element 1-silencing transcription factor, RSC: Remodeling the structure of chromatin, SWI/SNF: Mating-type switching and sucrose non-fermenting, WINAC: WSTF including nucleosome assembly complex, WSTF: Williams syndrome transcription factor, NCoR: Nuclear receptor corepressor,

CTCF: CCCTC-binding factor, INO80: Inositol-requiring protein 80, WINAC: WSTF Including Nucleosome Assembly Complex, NUMAC: Nucleosomal methylation activator complex, ACF: ATP-utilizing chromatin assembly and remodelling factor, CHRAC:Chromatin accessibility complex, RSF: Remodelling and spacing factor, NURF: Nucleosome-remodelling factor, CERF: CECR2-containing remodelling factor, BAZ: Bromodomain adjacent to zinc finger domain protein, WICH: WSTF-ISWI chromatin remodelling complex, NoRC: Nucleolar remodelling complex

Key Words: SWI, SNF2, ISWI, SNF2H, SMARCA5 BRG1, BRM, Chromatin Remodelling, Hereditary Syndromes, Tumors, Leukemia, Review

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