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MINI-SYMPOSIUM: When Genetics Meets Epigenetics—A New Option for Therapeutic Intervention in Brain Tumors?

Rhabdoid Tumors: An Initial Clue to the Role of Chromatin Remodeling in Cancer

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Abstract

The discovery of biallelic, inactivating *SMARCB1* mutations in rhabdoid tumors (RTs) over a decade ago represented the first recognized link between chromatin remodeling and tumor suppression. SMARCB1 is a core subunit of the SWI/SNF chromatin remodeling complex, and the recent emergence of frequent mutations in genes that encode subunits of this complex across a wide variety of cancers suggests that perturbation of this chromatin remodeling complex constitutes a key driver of cancer formation. Despite the highly aggressive nature of RTs, they are genetically simple cancers that appear to lack chromosomal instability and contain very few mutations. Indeed, the mutation rate in RTs is among the lowest of all cancers sequenced, with loss of *SMARCB1* as essentially the sole recurrent event. Given the genetic simplicity of this disease, understanding the chromatin dysregulation caused by *SMARCB1* loss may provide more general insight into how epigenetic alterations can contribute to oncogenic transformation and may reveal opportunities for targeted therapy not only of RT but also the variety of other SWI/SNF mutant cancers.

CHROMATIN AND CANCER

History has revealed a theme that genes mutated in early onset pediatric cancers and familial cancer predisposition syndromes are often of fundamental importance to cancer in general. For example, retinoblastoma is a rare pediatric cancer but served as the initial clue to the importance of the *RB* gene in tumor suppression. In 1998, the causative mutation of rhabdoid tumors (RTs) was identified as biallelic inactivation of the gene *SMARCB1* (*SNF5*/*INI1*/*BAF47*) (5, 6, 71). *SMARCB1* encodes a core subunit of SWI/SNF chromatin remodeling complexes (53, 76). This finding represented the first identified link between ATPase chromatin remodeling complexes and tumor suppression—a link that has since blossomed with findings of SWI/SNF subunit mutations in many types of cancer, both pediatric and adult. Indeed, recent cancer genome sequencing efforts have further highlighted the role of chromatin regulators in cancer as a variety of genes whose products covalently modify histones and chromatin have also been found to be mutant in cancer. Here we review and discuss RT and describe mechanistic and potential therapeutic insights that have resulted from subsequent studies.

RTs are aggressive pediatric cancers that arise most frequently in the brain, where they are referred to as atypical teratoid/rhabdoid tumor (AT/RT), and the kidney, but can also arise in soft tissues throughout the body (3, 8, 59, 78). These tumors tend to have a very early onset, with roughly half of cases arising in children less than 1 year of age and the large majority of cases occurring in children under the age of 3 (3). These tumors are highly malignant and confer a particularly poor prognosis, although the recent use of highly intensive multimodality therapeutic regimens may offer some improvement in outcome (14). Although an origin from neural progenitors has been hypothesized, analyses of gene expression have yielded conflicting conclusions, and the cell(s) of origin remains unclear (11, 20).

After cytogenetic analysis identified the deletion of chromosome 22q11.2 region as the only frequent copy number change in RT cell lines and primary tumors, further mapping showed that the gene *SMARCB1* was almost universally missing in these cancers (4, 6, 31, 71). These findings provided the first clear evidence that AT/RT, renal RT and soft-tissue RT are all genetically related (6, 64). Analogous to retinoblastoma, germ line mutations in *SMARCB1* strongly predispose to RTs and the rare cases of familial rhabdoid predisposition syndrome are predominantly due to inherited heterozygous mutations in *SMARCB1* (65, 68). Indeed, biallelic loss of *SMARCB1*, particularly as evidenced by negative immunostaining with the INI1 antibody, is now used in the diagnosis of RT (3). It should be noted, however, that in a very small percentage of RT cases, the tumors lack *SMARCB1* mutations but carry mutations in another SWI/SNF subunit, *SMARCA4* (*BRG1*/*SNF2-beta*) (24, 61), further establishing mutation of the SWI/SNF complex as a signature event of RT.

SWI/SNF COMPLEX SUBUNITS ARE FREQUENTLY AND WIDELY MUTATED IN CANCER

SWI/SNF complexes were originally characterized in yeast as factors being essential for mating type switching (SWI) or for

sucrose metabolism (mutants were sucrose non-fermenting, SNF). Mammalian versions of these complexes consist of 10–12 subunits and are transcriptional modulators that possess ATP-dependent nucleosome remodeling activity (9, 16). SWI/SNF complexes are comprised of one of two ATPase subunits (SMARCA4 or SMARCA2/BRM), a set of highly conserved "core" subunits (SMARCB1, SMARCC1/BAF155 and SMARCC2/BAF170), and variant subunits thought to contribute to lineage-specific functions of the complexes (26, 27, 36, 51, 53, 75). While SMARCB1 is constitutively present in SWI/SNF complexes, its biochemical contribution remains unclear.

Although SWI/SNF complexes were first linked to cancer when *SMARCB1* was found to be recurrently mutated in RT, recent findings from cancer genome sequencing studies reveal that at least seven SWI/SNF subunits are mutated, often at high frequency, across a wide variety of cancers (Table 1) (82). For example, the *ARID1A* (*BAF250a*) subunit is mutated in 50% of ovarian clear cell carcinomas, 30% of endometrioid carcinomas, 27% of gastric cancers, 13% of bladder carcinomas, 10% of colorectal and lung adenocarcinomas, 10% of hepatocellular carcinomas, and occasionally in breast, pancreatic, and prostate cancers and neuroblastomas (10, 15, 19, 29, 30, 34, 35, 54, 62, 66, 80, 84). The *PBRM1* (*BAF180*) subunit is mutated in 40% of renal carcinomas, as well as occasionally in breast, gastric and pancreatic cancers (18, 52, 66, 70, 85). The *BRD7* subunit is lost in up to 20% of *p53* wild-type breast cancers (17), and the *ARID2* (*BAF200*) subunit is mutated in 18% of hepatitis C-associated hepatocellular carcinomas, 7% of melanomas, and occasionally in some pancreatic cancers (19, 28, 43, 46). The *SMARCA4* subunit is mutated in 35% of non-small cell lung cancers and in medulloblastomas, particularly the WNT (26%) and group 3 (11%) subtypes (44, 49, 50, 54, 55, 58). Finally, mutations in SWI/SNF subunits were identified in one-third of pancreatic cancers (2, 66). It remains unclear why different SWI/SNF subunits are mutated in different cancers, although it raises the possibility of lineage-specific contributions of individual subunits. Collectively, a broad role for the SWI/SNF complex as a tumor suppressor has recently emerged, suggesting substantial relevance for this complex in tumor suppression beyond RT.

RT: REMARKABLY SIMPLE GENOMES

Since first being linked to RT, studies have sought to identify additional genetic mechanisms and mutations that cooperate with *SMARCB1* loss to drive RT. While SMARCB1 was initially implicated in DNA repair (72), a subsequent evaluation found no clear role and further found that 16 out of 18 primary RT samples were diploid and indistinguishable from normal peripheral blood DNA by SNP array, other than *SMARCB1* loss, suggesting an unusual degree of genomic stability in RT (47). To characterize the genomes of RT and search for genetic mutations that cooperate with *SMARCB1* loss to drive RT formation, SNP analysis and exome sequencing were recently performed on 32 frozen primary RT samples paired with matched normal genomic DNA. RT genomes were found to be remarkably simple with no recurrent copy number variations other than focal deletions of the *SMARCB1* locus or monosomy of chromosome 22, where *SMARCB1* is located (42, 47). Whole exome sequencing revealed a particularly low mutation rate, with an average of four non-synonymous somatic mutations detected per tumor exome (42). This mutation rate is among the lowest of all sequenced cancer genomes, and indeed two tumors contained no somatic mutations other than biallelic loss of *SMARCB1*. Across the 32 samples, *SMARCB1* was the only gene found to have significant recurrent mutations. Two additional studies focused upon known cancer-related genes also found an essential absence of cooperating mutations (25, 39). Collectively, these data raise the possibility that, at least within the protein coding exome, *SMARCB1* loss might be the sole genetic driving event in RT, although it remains possible that germ line variants or mutations located outside the exome could be required to cooperate with *SMARCB1* loss to drive RT tumor formation.

The surprisingly low mutation rate seen in RT suggests that widespread genomic instability might not be a necessary hallmark for the genesis of even highly aggressive cancers such as RT. Rather, at least in certain contexts, perhaps only a few, or one, genetic perturbation can be sufficient to drive cancer formation. Other pediatric cancers such as infant leukemia, neuroblastoma and retinoblastoma have also been found to possess mutation rates several log-fold lower than highly mutagenic adult cancers such as melanoma (28, 60, 87). Some adult cancers, such as acute myeloid leukemia (AML), have also been found to have low mutation rates, and occasional individual cases of most common cancer types also have very low mutation rates (79). While 5–15 somatic driver mutations had been predicted as being essential for the genesis of cancer (7), it now appears that substantially lower numbers are required, at least in some contexts. But how could a single genetic lesion be sufficient for cancer? The mathematics would seem to suggest, were this true, that everyone would develop cancer at a young age. This raises the possibility that cooperating events, rather than being genetic mutations, might occur as epigenetic chromatin alterations.

FUNCTIONAL INSIGHTS INTO SMARCB1

Insights come from studies regarding the normal function of SMARCB1 and the mechanisms by which its loss drives cancer formation. Several mouse models of *Smarcb1* inactivation have been developed (22, 40, 56, 57, 69). Homozygous deletion of *Smarcb1* results in early embryonic lethality while heterozygous knockout mice develop tumors comparable to human RT (22, 40, 56). Analysis revealed that these tumors have spontaneously lost the second *Smarcb1* allele, a requirement that likely explains the 30% penetrance and 11-month median onset. In comparison, in conditional mice in which *Smarcb1* is inducibly inactivated in some cells, 100% of mice develop lymphomas or RTs with a median onset of only 11 weeks, markedly faster than that occurs following inactivation of tumor suppressors such as p53, p16 or p14 (37, 57, 63, 81). Of note, as cancers driven by *Smarcb1* loss occur in multiple genetic backgrounds, this could suggest that a specific germ line variant is not essential for the genesis of cancers driven by *Smarcb1* loss. Collectively, these experiments demonstrated a potent and bona fide role for *Smarcb1* as a tumor suppressor.

Providing important insight into transformation driven by *Smarcb1* loss, while *Smarcb1* inactivation results in rapid cancer onset, its loss is detrimental to the vast majority of cells. Inactivation

Table 1. SWI/SNF subunits are mutated in a wide variety of cancers. Selected studies revealing SWI/SNF subunit mutations in cancer.

Common SWI/SNF subunit mutations discovered by cancer genome sequencing					
SWI/SNF complex subunit	Cancer type	Cell line or primary tumor	Mutation type	% Mutated	Reference
SMARCB1	Rhabdoid tumor	Primary tumors	Deletions and copy neutral loss of heterozygosity	94	(25)
		Primary tumors	Homozygous inactivation: deletions, nonsense and other null mutations	100	(42)
		Primary tumors	Homozygous inactivation: deletions, nonsense and other null mutations	98	(31)
SMARCA4	Medulloblastoma	Primary tumors	Missense mutations	4	(54)
		Primary tumors	Null and missense mutations	5	(33)
	Lung adenocarcinoma	Both	Unknown point mutation	32	(44)
		Primary tumors	Null and missense mutations	11	(30)
	Pancreatic ductal adenocarcinoma	Both	Heterozygous deletions	9.6	(66)
SMARCA2	Pancreatic ductal adenocarcinoma	Both	Heterozygous deletions	2.6	(66)
PBRM1	Renal clear cell carcinoma	Primary tumors	Null mutations	53	(52)
		Both	Null mutations	60	(18)
		Primary tumors	Null and missense mutations	21	(23)
		Primary tumors	Truncating mutations	41	(70)
	Pancreatic ductal adenocarcinoma	Both	Null mutations and deletions	9.6	(66)
		Cell lines	Truncating mutations	27	(74)
ARID2	Hepatocellular carcinoma	Primary tumors	Indel, nonsense and null mutations	5.8	(19)
		Primary tumors	Truncating mutations	14–18	(43)
	Non-small cell lung carcinoma	Both	Homozygous deletions, null mutations	7.3	(46)
	Pancreatic ductal adenocarcinoma	Primary tumors	Null and missense mutations, copy number changes	12	(2)
	Melanoma	Primary tumors	Null and missense mutations	9	(28)
ARID1A	Ovarian clear cell carcinoma	Both	Null and missense mutations	46	(80)
		Primary tumors	Null mutations	57	(35)
	Endometrioid carcinoma	Primary tumors	Null and missense mutations	30	(80)
	Gastric adenocarcinoma	Primary tumors	Null mutations	8	(86)
		Both	Indel, missense and nonsense mutations	10	(34)
		Primary tumors	Truncating mutations	29	(73)
	Bladder transitional cell carcinoma	Primary tumors	Null and missense mutations	13	(21)
	Colorectal carcinoma	Primary tumors	Indel and nonsense mutations	10	(10)
		Both	Indel and nonsense mutations	10	(34)
	Hepatocellular carcinoma	Primary tumors	Indel, missense and nonsense mutations	13	(29)
		Primary tumors	Indel, missense and nonsense mutations	10	(19)
	Pancreatic ductal adenocarcinoma	Primary tumors	Indel and nonsense mutations	10	(2)
		Both	Null mutations and deletions	8.3	(66)
		Both	Indel and nonsense mutations	8	(34)
	Neuroblastoma	Primary tumors	Null and missense mutations	6	(60)
	Lung adenocarcinoma	Primary tumors	Indel, missense and nonsense mutations	8	(30)
		Both	Indels	2	(34)
	Breast cancer	Primary tumors	Indel, missense and nonsense mutations	4	(67)
		Primary tumors	Deletions (point mutations)	37 (3)	(15)
		Both	Indel, missense and nonsense mutations	4	(34)
		Primary tumors	Deletion	13	(45)
	Prostate cancer	Both	Indels	8.7	(34)
ARID1B	Neuroblastoma	Primary tumors	Deletions, null and missense mutations	7	(60)
	Breast cancer	Primary tumors	Indel, missense and nonsense mutations	5	(67)
	Pancreatic ductal adenocarcinoma	Both	Null mutations and deletions	3.9	(66)
	Hepatocellular carcinoma	Primary tumors	Indel, missense and nonsense mutations	6.7	(19)

in embryonic stem cells blocks development and causes arrest at the blastocyst stage (40). Deletion of *Smarcb1* in primary fibroblasts results in cell cycle arrest and a block in proliferation (41). Indeed, even in a T-cell lymphoma model where *Smarcb1* deletion *in vivo* results in rapid cancer onset in all mice (57), the vast majority of T cells do not tolerate *Smarcb1* loss, resulting in markedly reduced T-cell numbers in these animals. From this aberrant T-cell environment, cancer arises like a phoenix from the ashes. As the human

tumor data suggest that this phenotypic variation is not explained by the acquisition of genetic mutations, epigenetic differences and alterations likely play a key role in determining susceptibility to transformation upon *SMARCB1* loss. Notably, while SWI/SNF subunit mutations are collectively found in a wide variety of cancers, *SMARCB1* loss itself has only been associated with RT and a few other rare cancers—it is not generally mutated in common adult cancers. In mouse lymphomas, *Smarcb1* loss drives lymphoma formation from mature CD8+ memory-like T cells, but not from immature T cells or B cells (77). Collectively, this suggests that only certain cell types, or epigenetic states, are susceptible to *SMARCB1* loss. Other cell types/states might be susceptible to the loss of other specific SWI/SNF subunits.

Alterations of the epigenetic landscape caused by *SMARCB1* loss affect several pathways that might be important in the genesis of RT in susceptible cell types. Studies of mouse models and human tumors revealed the existence of epigenetic antagonism between SMARCB1 and the Polycomb repressor complex subunit EZH2, such that the loss of *SMARCB1* results in unopposed activity of EZH2 that serves an essential role in tumor formation (38, 83). In addition, the loss of *SMARCB1* in RT has been found to have effects upon a wide spectrum of cellular processes. SMARCB1 and SWI/SNF complexes appear to modulate the cell cycle through transcriptional regulation of the $p16^{INK4a}$-cyclinD/CDK4-pRb-E2F mitotic checkpoint (1, 13, 72). Similarly, the absence of SMARCB1 increases cell motility by posttranslational deregulation of RhoA, possibly through epigenetically driven changes in expression of G-protein guanine exchange factors and activating proteins (12). These various effects might be modulated by adaptor proteins such as BIN1 (48). Evidence has also linked SMARCB1 directly to GLI1, an effector in the hedgehog signaling pathway (32). While it remains unknown whether these same pathways are activated in cancers linked to mutations in other SWI/SNF subunits, the understanding gleaned from studying RT suggests that *SMARCB1* loss results in the deregulation of multiple pathways that contribute to oncogenesis in a lineage-specific fashion.

Understanding the mechanisms by which epigenetic changes contribute to oncogenesis offers the promise of informing development of therapeutics. Recent sequencing efforts have revealed a theme that genes encoding chromatin modifiers, not just SWI/SNF, are recurrently mutated across a wide spectrum of cancer types, suggesting that changes in chromatin structure might be important in oncogenesis. Indeed, epigenetic alterations have been implicated in many cancer types, although it has often been challenging to define potential epigenetic contributions when they occur in the setting of high mutation rates and genomic instability. Perhaps in part due to a low incidence of age-related and environmentally induced passenger mutations, early onset pediatric cancers such as RT often have simpler genomes. Consequently, these cancers might constitute outstanding models with which to mechanistically characterize the roles of chromatin-based changes in driving cancer growth and, potentially, with which to identify specific mutation-driven therapeutic susceptibilities.

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