Molecular advances in cutaneous T-cell lymphoma

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■ **Abstract**

Cutaneous T-cell lymphoma (CTCL) is a group of malignancies derived from skin-homing T cells. Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common CTCL variants. In recent years, the genetic landscape of SS/MF has been characterized using genome-wide next-generation sequencing approaches. These studies have revealed that genes subjected to oncogenic mutations take part in cell cycle regulation, chromatin modification, Janus kinase (JAK)-signal transducer and activator of transcription protein (STAT) signaling, T-cell receptor (TCR)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, and microtubule associated protein kinase (MAPK) signaling, which suggests that deregulation of these cellular processes underlies lymphomagenesis. These studies provide the groundwork for functional and clinical studies that will lead to better risk assessment and more effective therapeutic approach in CTCL patients.

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Cutaneous T-cell lymphomas (CTCLs) are malignancies derived from skin-homing T cells. Mycosis fungoides (MF), the most common CTCL, typically presents with patches and plaques especially on sun-protected areas of the skin. The disease has an indolent clinical course with slow progression from patches to more infiltrated plaques and eventually to tumors. In a minority of patients, extracutaneous localization develops in later stages of the disease. The prognosis of MF patients depends on stage, in particular the type and extent of skin lesions and presence of extracutaneous disease.[1] While patients with early stages of disease have an excellent prognosis, the 10-year disease-specific survival of patients with tumor-stage disease and patients with histologically documented lymph node involvement is 42% and 20%, respectively.[2]

Sézary syndrome (SS), on the contrary, is a leukemic CTCL variant. SS presents with pruritic erythroderma, lymphadenopathy, and presence of tumor cells (known as Sézary cells) in skin, lymph nodes, and peripheral blood. Patients with SS have a poor prognosis, with a 5-year survival of 30%.[1,2]

The genetic alterations in CTCL, in particular SS and to a lesser extent MF, have been studied using cytogenetic and array-based methods. These studies identified extensive genetic instability with complex karyotypes but no highly recurrent translocations. In contrast, recurrent copy number alterations (CNAs) were identified, including deletion of *CDKN2A* in both SS and MF, deletion of *RB1* in SS, and gain of *MYC* in SS.[3,4]

In recent years, genome-wide studies using next-generation sequencing (NGS) have provided a more comprehensive picture of the genetic landscape of CTCL. Most of these studies have focused exclusively on SS (7 of 12),[5-11] while some others included MF samples together with SS samples (4 of 12),[12-15] and one study focused on MF only (Table).[16] Taken together, these studies include ~8 times more SS samples than MF samples, making the reported findings mostly a molecular representation of SS. Recently, all CTCL samples with publicly available sequencing data have been reanalyzed applying uniform methods and metrics to generate a more representative overview of point mutation frequencies in putative driver genes.[17] This article summarizes the most relevant findings in CTCL genetics derived from NGS studies and examines their therapeutic implications.

Next generation sequencing

NGS refers to a group of high-throughput technologies used to determine the order of nucleotides within nucleic acid molecules (ie, DNA and RNA). In cancer research, NGS is particularly suitable for the discovery of different types of genetic alterations ranging from pathogenic single nucleotide substitutions to large chromosomal aberrations in cancer genomes. The terms whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted sequencing (TS) refer to NGS approaches that characterize the entire genome, the complete set of coding genes (known as exome, <2% of the genome), or a defined group of individual genes, respectively.[18,19] Another NGS application, called RNA sequencing (RNA-seq), is used to characterize the collection of expressed genes in the cell known as the transcriptome, which makes possible the identification of abnormal gene expression patterns in malignancies when compared to healthy controls and the detection of expressed gene fusions derived from chromosomal rearrangements.[18] The large majority of studies reviewed in this article have made use of WES and/or TS to investigate SS/MF, whereas a minority of them opted for WGS or RNA-seq.

Discovery of molecular alterations in SS/MF using NGS

NGS data derived from the genome or transcriptome are analyzed using a variety of bioinformatic tools that allow the identification of genetic alterations or abnormal gene expression, respectively. In the case of SS/MF, these analyses have uncovered a distinctive mutational landscape and revealed that genes affected by point mutations and CNAs cluster mainly into 5 cellular processes: cell cycle regulation, Janus kinase (JAK)-signal transducer and activator of transcription protein (STAT) signaling, microtubule associated

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TABLE Next-generation sequencing studies on cutaneous T-cell lymphoma

Authors	Journal	Year	CTCL Variant (Number of samples)	WGS	WES	TS	RNA-seq
Lee et al[14]	*Blood*	2012	SS (3), MF (24)				27
Sekulic et al[7]	*Mol Genet Genomic Med*	2014	SS (1)	1			1
Vaqué et al[12]	*Blood*	2014	SS (4), MF (7)			11	
Choi et al[11]	*Nat Genet*	2015	SS (40)	2	40		
McGirt et al[16]	*Blood*	2015	MF (30)	5		25	
Ungewickell et al[13]	*Nat Genet*	2015	SS (32), MF (41)		11	73	
Kiel et al[9]	*Nat Comm*	2015	SS (66)	6	66		
Da Silva Almeida et al[15]	*Nat Genet*	2015	SS (25), MF (8), Other CTCLs (9)		42		
Wang et al[6]	*Nat Genet*	2015	SS (37)		37	37	32
Prasad et al[8]	*J Invest Dermatol*	2016	SS (12)		12		10
Woollard et al[5]	*Blood*	2016	SS (101)		10	101	
Izykowska et al[10]	*Oncotarget*	2017	SS (9)	9			9

NOTE: The majority of published studies used WES to characterize the mutational landscape of SS/MF genomes.
Abbreviations: CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; NGS, next-generation sequencing; RNA-seq, RNA sequencing; SS, Sézary syndrome; TS, targeted sequencing; WES, whole-exome sequencing; WGS, whole-genome sequencing.

protein kinase (MAPK) signaling, T-cell receptor (TCR)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, and chromatin modification (Figure). An overview of these findings is presented below.

The genomic landscape of SS/MF

The somatic mutation rate in SS (ie, average, 3.85 mutations/Mb) is similar to mutation rates observed in adult solid tumors.[6] The majority of somatic single nucleotide substitutions observed in SS/MF are C > T transitions (40%-75%),[6,16] which are much less common in other hematological cancers.[6] This mutational signature is regarded as caused by ultraviolet (UV) light exposure when occurring at NpCpG sites[6,11,16] or aging when occurring at NpCpC sites. In SS, both aging (43%) and UV radiation (30%) contribute to C > T transitions.[6,20] At present, it is unclear whether exposure to UV light plays a causative role in the onset of the disease.

The fact that oncogenic alterations in SS much more frequently result from CNAs rather than single nucleotide substitutions suggests that the former may play an important role in SS lymphomagenesis.[11] Choi and colleagues reported complex genomic rearrangements associated with deletion of tumor suppressors in SS, suggesting that phenomena such as chromothripsis or chromoplexy could be key events in the development of CTCL.[11] These authors proposed that deregulation of a group of DNA-cutting enzymes encoded by recombination activated genes may be implicated in the characteristic genomic instability of SS.[11]

Cell cycle and DNA repair

The cell cycle is a series of systematic events that regulate the correct division of a cell into 2 daughter cells. Although cyclins and cyclin-dependent kinases (CDKs) govern cell cycle progression, multiple other proteins participate indirectly in the regulation of the cell cycle.[21] For instance, ataxia telangiectasia mutated (ATM), retinoblastoma 1 (RB1), tumor protein 53 (TP53), and CDK inhibitors (CKIs) act on different signaling levels to ultimately induce cell cycle arrest in response to DNA damage. In SS, CKIs encoded by *CDKN1A* and *CDKN2A* are deleted in 11% and 40% of cases, respectively.[6,11] Deletions of *ATM* (30%), *RB1* (39%), and *TP53* (93%) are frequent as well.[6,11]

JAK-STAT signaling

Cytokines are small secreted proteins that mediate communication between cells. Receptors on T cells bind specific cytokines, become activated, and elicit changes in gene expression through intracellular signaling pathways. The JAK-STAT pathway is central to cytokine stimulation in T cells.[22] Cytokine-bound receptors activate JAK kinases, which then activate STAT proteins. Activated STAT proteins dimerize and translocate to the nucleus, where they induce expression of genes responsible for T-cell proliferation, differentiation, and apoptosis.[22]

Point mutations either predicted or confirmed to be gain-of-function are reported in *JAK1* (0.9% of cases), *JAK3* (2.7%), *STAT3* (0.9%), and *STAT5B* (3.6%; Figure).[17] Hyperactive JAK and STAT proteins often result from structural changes in their functional domains. For instance, amino acid substitutions in the pseudokinase domain of JAK proteins enhance their tyrosine kinase activity, while changes in the Src homology 2 (SH2) domain of STAT proteins are predicted to enhance dimerization. In addition, copy number gains of *JAK2* (13% of cases), *STAT3* (60%), and *STAT5B* (60%; Figure) are frequent and have been shown to correlate with increased expression.[17]

The existence of Food and Drug Administration (FDA)-ap-

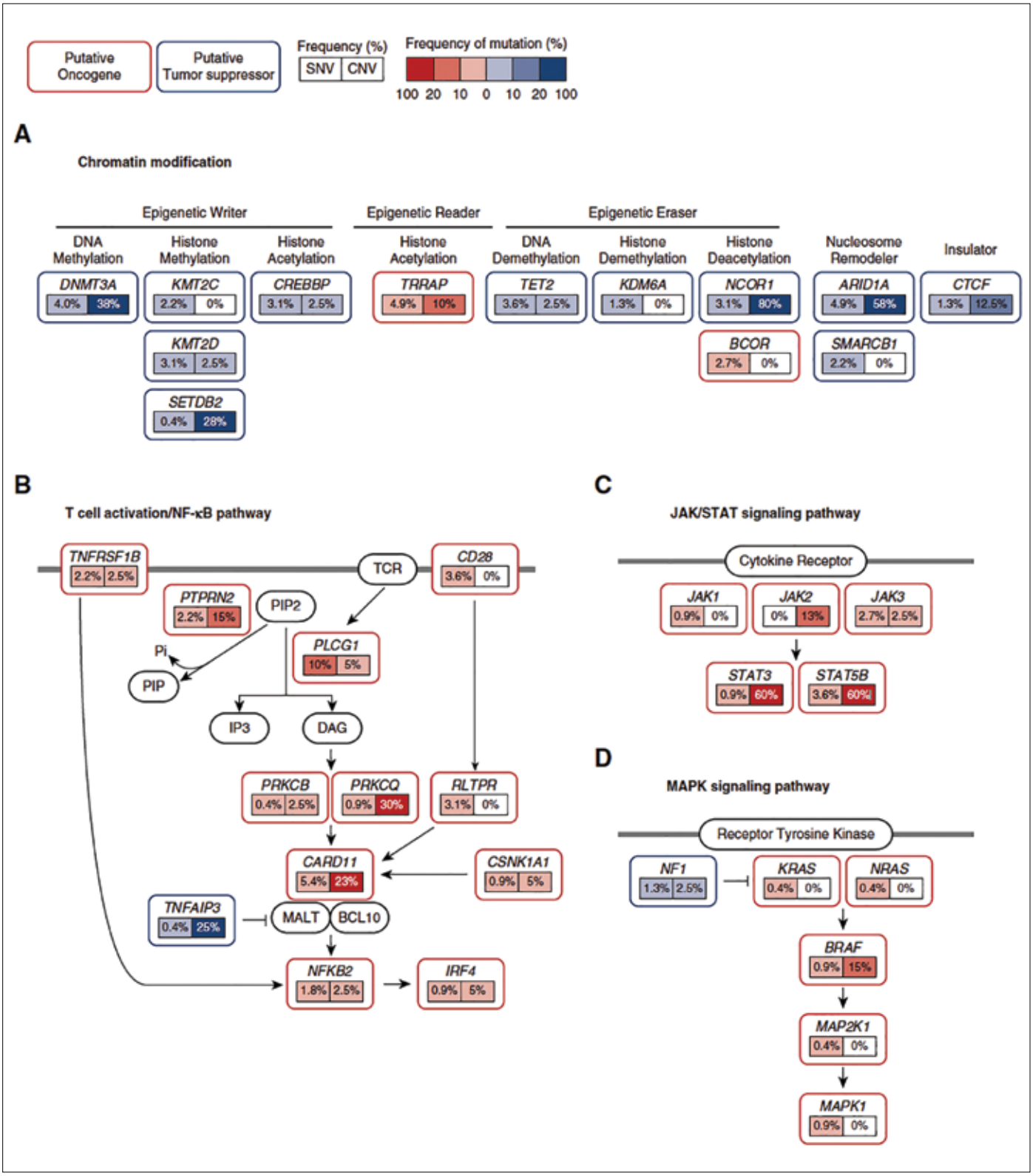

FIGURE Schematic of mutations in recurrently mutated signaling pathways in CTCL. CTCL harbors recurrent mutations that are predicted to affect **(A)** chromatin, **(B)** T-cell activation/NF-kB signaling, **(C)** JAK/STAT signaling, and **(D)** MAPK signaling. From: Park J, Yang J, Wenzel AT, et al. Genomic analysis of 200 CTCLs identifies a novel recurrent gain-of-function alteration in RLTPR (p.Q575E). Page 1433, *Blood*, 2017;130(12):1433. doi: 10.1182/blood-2017-02-768234. Used with permission from the American Society of Hematology.

proved JAK inhibitors such as Tofacitinib and Ruxolitinib makes the idea of targeting malignant T cells driven by hyperactive JAK kinases attractive. In 2 separate NGS studies, the authors demonstrated that CTCL cell lines bearing gain-of-function point mutations in *JAK3* are sensitive to these compounds, opening the possibility for their potential use in CTCL patients carrying JAK mutations.[15,16]

MAPK signaling

Similarly to the JAK-STAT pathway, the MAPK pathway propagates towards the nucleus extracellular signals received through cytokine receptors. These signals elicit cellular processes such as growth, proliferation, and apoptosis.[23] Subsets of SS/MF patients carry established gain-of-function mutations (<1%) in several members of this pathway such as *KRAS*, *NRAS*, *BRAF*, *MAP2K1*, and *MAPK1* (Figure).[17]

TCR/NF-κB signaling

Initiation of the adaptive immune response against pathogens relies on the activation of T cells capable of recognizing foreign antigens. Upon binding between the TCR and its cognate antigen, a series of signaling events leads to the expression of genes that promote T-cell survival, proliferation, and differentiation.[24] Activated T cells then orchestrate multiple immunological events directed at clearing the pathogen from the body.

In CTCLs, hyperactive TCR signaling might drive uncontrolled proliferation of malignant T cells. Genetic alterations reported in SS/MF target a variety of components of the TCR pathway.[6,11,13,15] CD28 is a costimulatory molecule of the TCR complex, which by engaging ligand B7 (CD80 and CD86) on antigen-presenting cells, cosignals for T-cell activation.[24] Increased affinity of CD28 for B7 due to amino acid substitutions or gene fusions results in augmented TCR signaling. Point mutations in CD28 occur in 3.6% of cases (Figure), while in-frame gene fusions (ie, *CD28*-inducible costimulatory [*ICOS*] and *CD28*-cytotoxic T lymphocyte-associated protein 4 [*CTLA4*]) have been observed in a small number of cases.[6,7,13,17]

Downstream to TCR activation, phospholipase C gamma 1 (PLCγ1) catalyzes the production of second messengers (ie, DAG and IP3), which in turn activate downstream kinases.[24] Point mutations in the catalytic core of PLCγ1 (10% of cases) and copy number gains (5%) increase second messenger production, which enhances antigen-dependent T-cell activation (Figure).[12,17] Furthermore, point mutations in DAG-activated kinases protein kinase C beta (PRKCB) and protein kinase C theta (PRKCQ) (<1% of cases) and amplification of the latter (30%) may contribute to TCR signaling deregulation (Figure).[17] However, the functional relevance of these alterations remains uncertain.

Gene expression changes triggered by TCR activation are effected through canonical NF-κB signaling and other downstream pathways.[24] *CARD11* encodes a scaffold protein needed for the activation of transcription factor complex NF-κB. In SS/MF, point mutations (5.4% of cases) and copy number gains (23%) involving *CARD11* lead to increased NF-κB activation (Figure).[13,15,17] In addition, recurrent deletions (2.5% of cases) of the C-terminal autoinhibitory IκB domain of NFKB2 are expected to render it constitutively active.[13,17]

Besides the TCR complex, other receptors can also elicit canonical NF-κB signaling in CTCL. Membrane receptor Tumor Necrosis Factor Receptor 2 (TNFR2; encoded by *TNFRSF1B*) initiates NF-κB signaling upon binding to ligand TNFα. Reported activating point mutations in *TNFRSF1B* enable constitutive NF-κB signaling without the need of a ligand.[13] Overall, point mutations and amplifications involving *TNFRSF1B* are reported in 2.2% and 2.5% of cases, respectively.[13,17] In addition, TNF alpha-induced protein 3 (*TNFAIP3*), which encodes an inhibitor of TNFα-induced NF-κB signaling, is deleted in 25% of SS cases (Figure).

In line with these studies, pharmacological inhibition of complex NF-κB decreased its DNA-binding ability and induced cell death of SS cells in vitro.[25,26] In a phase II study, the safety and efficacy of the NF-κB inhibitor bortezomib were evaluated in 10 MF patients.[27] The overall response rate for MF was 70%, and the complete response rate was 10%, suggesting the potential usefulness of NF-κB inhibitors in CTCL treatment.[27]

Chromatin modification

Chromatin consists of genomic DNA and associated proteins. Histone proteins, the main structural components of chromatin, form a protein core around which DNA winds called the nucleosome. Histones not only play roles in the packaging, replication, and repair of DNA but also regulate gene expression.[28,29] Both DNA and histones are subjected to chemical (known as epigenetic) modifications that direct changes in chromatin architecture. DNA methylation, histone methylation, and histone acetylation are epigenetic modifications with established effects on gene expression.[28,29]

Proteins that chemically alter chromatin, named epigenetic regulators, can be divided into 3 categories: writers, erasers, and readers. Writers are enzymes that add epigenetic marks to either DNA or histones, erasers reverse the action of writers, and readers interpret epigenetic marks to elicit downstream signals.[28,29] Epigenetic regulators are frequently mutated in CTCLs, particularly SS.

DNA methylation

In normal cells, widespread DNA methylation maintains chromosomal stability, whereas low methylation at gene promoters allows transcription. In cancer, this methylation pattern is typically inverted, promoting genome instability and transcriptional misregulation. Loss-of-function alterations in DNA methyltransferases (DNMT) can lead to global hypomethylation.[30] In SS, DNA methyltransferase DNMT3A is frequently deleted (38%) and mutated (4%; Figure). Opposing DNMTs, ten-eleven translocation (TET) enzymes demethylate DNA by oxidizing methylated cytosine residues in successive enzymatic steps. TET2 is often inactivated in hematological malignancies, though its role in cancer development is not clear.[31] In SS, *TET2* mutations (3.6% of cases) and deletions (2.5%) are reported too (Figure). In line with these results, it was shown that SS cells are characterized by widespread changes in DNA methylation, suggesting that SS could be amenable to treatment with demethylating agents.[32]

Histone methylation

Histone methyltransferases (HMTs) are enzymes that add 1, 2, or 3 methyl groups to specific lysine or arginine residues on histones,

while histone demethylases (HDMs) remove them. Histone methylation can signal either for gene activation or repression depending on the location of the epigenetic mark.[29] Aberrant methylation patterns on histones are extensively observed in malignancies and are likely to be a consequence of damaging mutations in HMTs and HDMs.[29] In SS, two HDMs, Lysine Methyltransferase 2C (KMT2C) and Lysine Methyltransferase 2D (KMT2D), are mutated in 2.2% and 3.1% of cases, respectively, while a third enzyme, SETDB2, is deleted in 28% of cases. In addition, mutations in histone demethylase Lysine Demethylase 6A (KDM6A) are also seen in 1.3% of SS cases (Figure).

Histone acetylation

Acetylation of lysine residues on histones activates gene expression by inducing chromatin relaxation. Acetyl groups neutralize the positive charge of lysine residues, which decreases the attraction between the nucleosome and the negatively charged DNA. The addition of acetyl groups is mediated by histone acetyltransferases (HATs). In SS, histone acetyltransferase CREB Binding Protein (CREBBP) can be mutated (3.1% of cases) or deleted (2.5%). By contrast, removal of acetyl groups is carried out by histone deacetylases (HDACs). Deletions involving histone deacetylase Nuclear Receptor Corepressor 1 (*NCOR1*) are frequent in SS/MF (80%), while point mutations are less common (3.1%; Figure). Another HDAC, BCL6 Corepressor (BCOR), is mutated in 2.7% of cases.[17] Finally, adapter protein TRRAP, which is part of various multiprotein complexes with HAT activity, is amplified in 10% of cases and mutated in 4.9% of cases (Figure).[17]

Two systemic HDAC inhibitors (HDACis), romidepsin (class I-specific HDACi) and vorinostat (pan-HDACi), are FDA approved for the treatment of CTCL. Trials with (novel) HDACis as single agents or in combinations are now underway in diverse cancer types, including hematologic and solid tumors, but have not yet reached the clinic.[33] However, insight in the mechanisms through which different HDACis suppress tumors is limited, and elucidation on how epigenetic drugs exert their anticancer effect will be crucial to further develop and optimize these therapies.

Chromatin remodeling

Chromatin remodelers are multiprotein complexes that change the degree of chromatin compaction and nucleosome position in response to upstream epigenetic signals. These changes in chromatin architecture regulate gene expression. Genetic alterations involving members of the switching defective/sucrose non-fermenting (SWI/SNF) family of chromatin remodelers are common in human cancers.[34] For instance, AT-Rich Interaction Domain 1A (*ARID1A*) and SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1 (*SMARCB1*) are frequently mutated in gastric and rhabdoid tumors, respectively.[34] In SS, deletion of *ARID1A* (58%), *ARID5B* (29%), and *SMARCC1* (21%) are the most frequent alterations involving chromatin remodeling genes (Figure).[9,17] Furthermore, *ARID1A* deletions have been shown to correlate with lower expression levels in SS.[11] Similarly, point mutations in chromatin remodeling genes *ARID2* and *SMARCB1* have been reported in subsets of MF patients.[16]

Conclusion and outlook

The combined results from recent NGS studies have uncovered extensive genetic changes in SS/MF, including recurrent CNAs and point mutations that affect key pathways that are likely of critical importance in driving the disease. In the forthcoming years, it will be essential to integrate genetic studies with transcriptional data and develop preclinical models to determine the functional consequences of the identified genetic alterations. These studies will guide the development of new therapeutic strategies including the targeting of frequently affected cellular processes, such as NF-κB and JAK-STAT signaling and chromatin regulation. Prospective studies on large numbers of CTCL patients, such as the Cutaneous Lymphoma International Consortium, will be essential to correlate specific genetic alterations with clinical course and response to therapy. It is hoped that ultimately these studies will lead to an individualized risk assessment and effective therapeutic approach.

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