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Diverse compositions and functions of chromatin remodeling machines in cancer

Cigall Kadoch^{1,2}

¹Department of Pediatric Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA 02215, USA.

²Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA.

Abstract

Human cancer genetics power biochemical and functional interrogation of chromatin remodeling complexes, informing therapeutic opportunities

Dynamic regulation of genomic architecture is required for timely and appropriate gene expression in nearly every cellular context, serving critical roles across a range of developmental, cell differentiation, and disease processes. Recent exome- and genome-wide sequencing studies have unmasked a major, previously unexpected contribution of chromatin regulatory factors to human disease (1). One class of genes in particular, which had taken a backseat role for decades, has now jumped to the forefront of attention: the genes encoding the mSWI/SNF (mammalian switch/sucrose nonfermentable) family of adenosine triphosphate (ATP)-dependent chromatin remodeling complexes, which are mutated in over 20% of human cancers.

mSWI/SNF complexes, which represent one family of ATP-dependent chromatin remodeling complexes encoded in the mammalian genome, use the energy of ATP hydrolysis to mobilize nucleosomes, thereby modulating chromatin architecture. These ~1.0- to 1.5-MDa-sized, 10- to 15-subunit macromolecular assemblies are pieced together combinatorically from the products of 29 total genes, producing hundreds of possible combinations that play specialized, instructive roles in tissue-specific development and differentiation. Our work has revealed that in specific disease contexts, these remodelers themselves, in essence, become “remodeled,” providing opportunities to discover how changes in protein complex topology and histone landscape interactions yield both tumor-suppressive and oncogenic outcomes. Taken collectively, mutations in mSWI/SNF complex subunit genes are broad-spanning in human cancer, much like mutations in long-standing tumor suppressor culprits such as *TP53* (1). Importantly, in certain cancers, particularly rare pediatric tumor types, mutations in mSWI/SNF complex subunits are found in a large majority—even 100%—of cases with few to no other mutations present, strongly

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cigall_kadoch@dfci.harvard.edu.

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implicating their causative roles (2–5). Our group has leveraged such cancer settings extensively to gain insights into the many different routes by which chromatin remodeling machines can become perturbed—much like the array of issues that can underlie malfunction of a car or any other intricate machine—and the severity and implications of each. Further, extending beyond the bona fide subunits themselves, we have identified specific transcription factor families that transiently, but specifically, tether to mSWI/SNF complex surfaces to direct their genome-wide chromatin remodeling activities (6, 7). These discoveries underscore the need to achieve a precise structural and functional understanding of this class of macromolecular complexes in both normal and disease settings and to advance these emerging insights into therapeutic strategies for a broad range of indications.

Despite breakthrough disease genetics, a comprehensive translation of underlying mutations to targetable molecular mechanisms rooted in three-dimensional (3D) protein complex structure and biochemical properties has not been achieved. Our research laboratory aims to systematically interrogate the contribution of each protein subunit, domain, and interaction surface to complex function, genomic targeting, enzymatic activity, and resultant chromatin topology and gene transcription. Among our recent efforts applying multidisciplinary approaches, from biochemistry and structural studies to high-throughput functional genomics and epigenomics, systems biology, and combinations thereof, we highlight select works of particularly broad relevance and impact.

ASSEMBLY, MODULAR ORGANIZATION, AND CHROMATIN INTERACTIONS

A major barrier to our understanding of the normal functions, the tissue-specific roles, and, importantly, the diverse impacts of mutations on mSWI/SNF complex mechanisms lies in the lack of information regarding subunit organization, assembly, and 3D structure. Studying individual domains in isolation can often present limitations in determining the roles of interfacial surfaces, ordered series of reactions, and allosteric modulatory relationships that govern chromatin engagement and activity. Using strategies to capture endogenous complexes and subcomplexes with minimal heterogeneity and high purity, coupled with density gradient mass spectrometry, cross-linking mass spectrometry (CX-MS), systematic genetic manipulation of subunits and paralog families, evolutionary analyses, and human disease genetics, we found that mSWI/SNF complexes unexpectedly exist in three distinct, functionally nonredundant final form assemblies: canonical BAF (cBAF), polybromo-associated BAF (PBAF), and a recently discovered non-cBAF (ncBAF), for which we established the order of assembly and modular organization (8, 9). We defined the full spectrum of endogenous combinatorial possibilities and the impact of individual subunit deletions as well as disease-associated recurrent missense and frameshift mutations on complex assembly and architecture. Bringing these biochemical complex properties to the level of chromatin, we then mapped the localization of all three complex types genome wide, resolving both shared and complex-specific targeting proclivities. This collection of studies potentiates the ability to dissect complex and subcomplex functions and interactions with specific genomic and histone landscape features, as well as to develop physiologically meaningful strategies for small-molecule discovery.

RARE DISEASES INFORM mSWI/SNF COMPLEX MECHANISMS

Using proteomic mass spectrometric analyses and biochemical studies of endogenous complexes across cell types, we previously identified a protein called SS18 (among others) as a stable and dedicated component of the BAF subgroup of mSWI/SNF complexes (2). This was particularly exciting in that, in 100% of cases of a rare soft-tissue malignancy known as human synovial sarcoma, the t(X;18) chromosomal translocation results in the production of a fusion oncoprotein, SS18-SSX. This is the hallmark molecular aberration in this disease, which spans both pediatric and adult patients, and is pathognomonic for its diagnosis. As a result of the fusion event, precisely 78 amino acids are added to the C terminus of SS18 in every case—a small 78-amino acid tail with major consequences to the assembly, genomic targeting, and downstream gene regulatory effects of BAF chromatin remodeling complexes. We demonstrated that, in a gain-of-function manner, SS18-SSX globally “hijacks” mSWI/SNF complexes to sites that are normally repressed, resulting in cancer-specific oncogenic gene activation (4). Further studies will be needed to characterize the interaction between the SSX 78-amino acid fusion partner and chromatin that dictates site-specific hijacking, as well as to define the structural basis for SS18-SSX-directed mSWI/SNF biochemical properties.

In parallel, we have found that other rare diseases are uniformly or near-uniformly driven by perturbations in subunits that are part of the mSWI/SNF “core functional module,” which we recently defined using large-scale functional genomic fitness screens (5). Particularly, loss of ARID1A/ARID1B, SMARCB1, SMARCE1, and SMARCA4/SMARCA2 (ATPase) subunits, which inactivate cBAF subcomplex-mediated nucleosome remodeling activities via distinct mechanisms, results in convergent loss-of-function phenotypes and, at the cellular level, a halt in normal cell differentiation (3, 5, 8, 9). Further, we identified ncBAF complex components as synthetic lethal targets in cancers driven by these core functional module perturbations, such as in malignant rhabdoid tumors (>98% of which are characterized by biallelic inactivation of SMARCB1), opening potential avenues for therapeutic intervention in diseases characterized by BAF subunit gene loss-of-function events (10).

TRANSCRIPTION FACTOR–mSWI/SNF COMPLEX INTERACTIONS: IMPLICATIONS IN DEVELOPMENT, DIFFERENTIATION, IMMUNE MODULATION, AND CANCER

Inspired by the “one-off” gain-of-function mechanism we had identified in one rare cancer, synovial sarcoma, and turning to the idea that nature tends to use cellular mechanisms more than once, we sought to identify whether other proteins may interact with and similarly retarget or “hijack” mSWI/SNF complex activities. Using proteomic mass spectrometry and biochemical methods, we identified a set of lineage- and disease-associated transcription factors that selectively bind mSWI/SNF complexes in solution. These data suggested that tethering of transcription factors to specialized mSWI/SNF surfaces can actively reposition chromatin remodeling activities to new genomic sites to generate de novo accessibility and gene activation, further extending the collection of cancers as well as other disease and developmental settings in which altered mSWI/SNF function is implicated (6, 7).

Importantly, because small-molecule inhibition of high-affinity transcription factor–DNA interactions has been a recalcitrant challenge not overcome for decades by either academia or the pharmaceutical industry, these results suggest that targeting low-affinity (albeit necessary) interactions between transcription factors and chromatin remodeling complex surfaces may represent viable therapeutic approaches.

Over the coming years, continued development of strategies to navigate the complexities of macromolecular chromatin regulatory complex assembly, structure, histone landscape interactions, and activity will be required to traverse the bottleneck of cancer genetics into the, to date, unfilled space of therapeutic identification and development (Fig. 1). Underlying disease genetics will continue to serve as a powerful guide in advancing a comprehensive biologic, chemical, and physical understanding of chromatin remodeling machines of broad-spanning importance in health and disease.

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Fig. 1. mSWI/SNF ATP-dependent chromatin remodeling complexes: Unmasking diverse oncogenic mechanisms.

Summary of key studies to define biochemical properties, chromatin interactions, structure, and gene regulatory functions of mSWI/SNF chromatin remodeling complexes. The three mSWI/SNF family complexes (cBAF, PBAF, and ncBAF) are drawn as one for simplicity.