SYLLABUS “SWI/SNF-dependent tumors”

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Since the seminal description in 1999 of recurrent inactivation of SMARCB1- which encodes a subunit of SWI/SNF complexes- in malignant rhabdoid tumors, experimental evidence has consistently demonstrated that most subunits of the SWI/SNF complexes act as tumor suppressor genes. We review herein the functions of these complexes and discuss the main types of sarcomas which have been linked to their alteration.

SWI/SNF (BAF) complexes basics

SWI/SNF (Switch/Sucrose Non Fermentable) complexes were initially purified from yeast. Their human orthologs are called hSWI/SNF or hBAF (standing for human brahma associated factors) complexes. They are assembled in evolutionarily conserved multiprotein complexes, belonging to the Snf2 family of ATP-dependent helicases. They are made of 8 to 14 subunits which specific assortment provides functional diversity\(^1\). They regulate gene expression through the modification of nucleosomes composition or position across the genome. The complexes are anchored to the nucleosome and DNA, regulating the access of transcription factors to the regulatory regions of target genes\(^2\).

BAF complexes and cancer

The complexes are frequently targeted in cancer through inactivating mutations of the genes encoding its subunits with an estimated overall frequency of 19.6% in human cancer\(^3\). This broad mutation pattern is similar to that of TP53, suggestive of the major tumor suppressor role played by the complexes. However, these mutations are recurrent in only a few tumor types, a finding suggestive of the driving role that inactivation of BAF complexes play in these subsets of tumors. This review will focus on these entities with a special emphasis on sarcomas.

Malignant rhabdoid tumor (MRT)

MRT were the first malignancies to be linked to BAF complexes dysfunction. They are underlined by inactivating mutations of SMARCB1 located in 22q11, which gene encodes a key subunit of the BAF complex\(^4\). Clinically, these tumors may locate in central nervous system, referred as atypical rhabdoid/teratoid tumors (AT/RT) or in kidney and soft tissue where they are classically called malignant rhabdoid tumors (MRT). A constitutional mutation is present in 30% of cases\(^5\). This constitutional setting is referred to as rhabdoid predisposition syndrome 1 (OMIM 609322). Schwannomatosis represents another inherited (OMIM 162091) related to SMARCB1 mutations predisposing to the development of schwannomas and meningiomas which display loss of SMARCB1 expression in this setting.

A genetic variant of AT/RT and MRT has been described in 2011, which is underlined by SMARCA4 inactivation\(^6\). SMARCA4 is located in 19p13.2 and encodes one of the ATPase subunit of the BAF complexes, functionally related to SMARCB1.

Epithelioid sarcoma
Epithelioid sarcomas (ES) display a loss of SMARCB1 expression in 90% of cases. This immunohistochemical feature is now acknowledged as a mandatory criteria to render the diagnosis of ES. SMARCB1 loss is primarily underlined by genomic deletions in ES while inactivation result from more diverse mechanisms in MRT (mostly inactivating mutation combined with copy neutral-loss of heterozygosity or deletions). Although a unique case of epithelioid sarcoma with constitutional SMARCB1 alteration has been described, this association is probably rare.

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT)

Next generation sequencing studies of series of SCCOHT have recently evidenced recurrent SMARCA4 inactivation. This finding combined with the rhabdoid appearance displayed by these tumors and their clinical features (dismal prognosis and frequent association with germline mutation) led to the speculation that SCCOHT represent « malignant ovarian rhabdoid tumors ». This hypothesis is supported by transcriptomic studies emphasizing the close vicinity of their transcriptomes with those of SMARCB1 and SMARCA4-inactivated rhabdoid tumors. These malignancies are listed along with SMARCA4-mutated MRT in the spectrum of rhabdoid predisposition syndrome 2 (OMIM 613325).

SMARCA4-deficient thoracic sarcoma (SMARCA4-DTS)

This new tumor subtype consists in mediastino-pulmonary malignancies typically affecting 30-35 years old male adults (median age: 39 yo). These tumors grow rapidly, displaying an aggressive behaviour with a median survival of 7 months. They consist in sheets of epithelioid to rhabdoid tumor cells expressing at least focally AE1/E3 or EMA, along with diffuse expression of CD34 and SOX2. They are underlined by SMARCA4 mutations and display constant loss of SMARCA4 nuclear expression. Preliminary data do not suggest SMARCA4-DTS are associated with constitutional alterations. Although their genomic background is more complex than those of MRT and SCCOHT, their transcriptomes cluster closely together suggesting that common mechanisms are involved in the development of these groups of tumors.

Epithelioid malignant peripheral nerve sheet tumors (eMPNST)

The epithelioid variant of MPNST display SMARCB1 loss in up to 50% of cases while this feature is not seen in conventional MPNST. This loss occurs secondarily to genomic deletions.

Myoepithelial carcinoma

Myoepithelial carcinoma loose SMARCB1 expression in 10% of cases which loss is underlined by genomic deletions. Additionally, a series of SMARCB1-lost neoplasms of vulvar location has been described compiling cases of myoepithelial carcinomas, epithelioid sarcomas as well as tumors with intermediate features. However, these cases presumably represent classical cases of these entities rather than a specific entity.

The concept of composite rhabdoid tumors

It has been hypothesized that rhabdoid microscopic features may represent a surrogate of BAF complex dysfunction. While initial studies conducted with SMARCB1 immunohistochemistry dismissed this hypothesis, other investigators reported variants of
carcinomas harbouring SMARCB1 loss such as SMARCB1-deficient sinonasal carcinoma\textsuperscript{13,14}. Furthermore, SMARCB1 and SMARCA4 inactivations have also been described in dedifferentiated variants of carcinomas in the endometrium\textsuperscript{15}, the GI tract\textsuperscript{16}, lung\textsuperscript{17} and pancreas\textsuperscript{18}. These findings suggest that BAF complexes alterations may contribute to dedifferentiation in tumors. The term of « composite rhabdoid tumor » previously proposed to describe tumors which display focal rhabdoid features intermingled with well differentiated areas but is of no practical use.

Conversely, tumors may display recurrent loss of expression of BAF complex subunits although they do not display rhabdoid features. Two of them involve original mechanisms. First, synovial sarcomas have long been shown to harbour frequent loss or attenuated expression of varied BAF complexes subunits\textsuperscript{19}. This peculiar immunophenotype is secondary to the ejection of SMARCB1 subunit from BAF complexes caused by the incorporation of the SS18-SSX fusion protein\textsuperscript{20}. Renal medullary carcinoma. Second, renal medullary carcinomas (RMC) are aggressive kidney malignancies affecting sickle cell disease patients. RMC display loss of SMARCB1 expression related to a translocation involving \textit{SMARCB1}, resulting in a truncated non functional protein\textsuperscript{21}.

References


