Role of SWI/SNF chromatin remodelling genes in lung cancer development

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Abstract

SWI/SNF family of chromatin remodelling complexes uses the energy of ATP to change the structure of DNA, playing key roles in DNA regulation and repair. It is estimated that up to 25% of all human cancers contain alterations in SWI/SNF, although the precise molecular mechanisms for their involvement in tumor progression are largely unknown. Despite the improvements achieved in the last decades on our knowledge of lung cancer molecular biology, it remains the major cause of cancer-related deaths worldwide and it is in urgent need for new therapeutic alternatives. We and others have described recurrent alterations in different SWI/SNF genes in nearly 20% of lung cancer patients, some of them with a significant association with worse prognosis, indicating an important role of SWI/SNF in this fatal disease. These alterations might be therapeutically exploited, as it has been shown in cellular and animal models with the use of EGFR inhibitors, DNA-damaging agents and several immunotherapy approaches. Therefore, a better knowledge of the molecular mechanisms regulated by SWI/SNF alterations in lung cancer might be translated into a therapeutic improvement of this frequently lethal disease. In this review, we summarize all the evidence of SWI/SNF alterations in lung cancer, the current knowledge about the potential mechanisms involved in their tumorigenic role, as well as the results that support a potential exploitation of these alterations to improve the treatment of lung cancer patients.

1. Introduction

Chromatin remodelling complexes are key components that modulate chromatin landscape. They use the energy provided by ATP hydrolysis to disrupt nucleosome-DNA contacts, move nucleosomes along DNA and catalyze its ejection, insertion or exchange [1,2]. Consequently, they modify the accessibility of specific regions of DNA to the enzymatic transcriptional machinery, as well as different DNA-binding proteins, cofactors and regulators, playing important roles in gene expression regulation and DNA repair.

According to their subunit composition and biochemical activity, chromatin remodelling complexes can be divided in four major families: SWI/SNF, INO80/SWR1, ISWI and NURD/CHD, being SWI/SNF complex the most clearly implied in tumor development [1].

SWI/SNF complexes are complicated macromolecular assemblies consisting of many diverse and variable subunits. They are evolutionary conserved from yeast to mammals [1]. Mammalian SWI/SNF complexes are currently divided in three broad subfamilies: canonical BAF (cBAF); polybromo-associated BAF (PBAF) and the recently described non-canonical BAF (ncBAF) [3].

All complexes contain a group of the so-called core subunits, which are highly conserved and always include SMARCC1/BAF155, SMARCC2/BAF170 and either one of the two

mutually exclusive ATPases subunits (SMARCA2/BRM or SMARCA4/BRG1), but they also contain numerous accessory subunits that provide each of the complexes with a distinct identity. Thus, SMARCB1/BAF47/SNF5 and SMARCE1/BAF57 are common to cBAF and PBAF families, whereas ARID1A and ARID1B subunits are specific for cBAF family and ARID2, PBRM1 and BRD7 are specific for PBAF. Finally, ncBAF complexes utilize instead BRD9, GLTSCR1 and GLTSCR1L subunits for their core assembly [1,3,4]. Accessory subunits are thought to contribute to the targeting, assembly and regulation of lineage-specific gene networks [1,4].

Some common subunits of the SWI/SNF complex are encoded by genes that produce different isoforms by alternative splicing. Moreover, they belong to gene families that often display differential lineage-restricted expression, what means that some subunits are only expressed in some specific tissues [4]. It is therefore likely that a large number of different SWI/SNF complexes exist in mammals, which in turn control distinct set of genes and signalling pathways in different cellular contexts.

Mammalian SWI/SNF complexes have broad roles in transcriptional regulation. Essential roles for these complexes have been identified during neurogenesis, myogenesis, adipogenesis, osteogenesis and hematopoiesis [1]. The precise mechanism behind the role of SWI/SNF complexes in transcriptional regulation is not fully understood, but recent reports indicate that they are highly enriched in enhancers, modulating their accessibility to different transcription factors and opposing to the inactivation mediated by polycomb repressive complexes [5,6]. In particular, in a rhabdoid tumor cell model, loss of *SMARCB1* alters SWI/SNF complex integrity and its targeting to enhancers implied in cell differentiation, while keeping SWI/SNF binding to super-enhancers required for tumor survival [5]. In agreement with this observation, as a result of *SMARCB1* re-expression in *SMARCB1*-deficient sarcoma cell lines, there is an increase in genome-wide BAF complex occupancy, which mediates enhancer activation and opposes to the polycomb-mediated repression at bivalent promoters [6].

Large genome sequencing studies have evidenced a prominent role of chromatin structure in cancer development. The catalytic and accessory subunits of the complex have been found recurrently mutated in several tumor types and their alteration has been associated with tumor progression [4–9], whereas core components in general present a very low mutation rate. One significant exception to this is *SMARCB1,* which is inactivated via biallelic mutations in 98% of malignant rhabdoid tumors (MRT) (rare and aggressive childhood cancers) [10,11].

Regarding accessory and catalytic subunits, *PBRM1* is inactivated in 41% of clear cell renal cell carcinoma patients [12,13]. *ARID1A*, which is probably the most broadly mutated subunit, is altered in 50% of ovarian clear cell carcinomas (one of the most lethal subtypes of ovarian cancer), in 35% of endometroid carcinomas [14,15], in 9.4% of colorectal and in 8.2% of lung cancers [7]. It is estimated that more than 90% of ovarian small-cell carcinoma hypercalcaemic type patients harbor biallelic inactivating mutations in *SMARCA4* [16]. *SMARCA2* is epigenetically silenced or transcriptionally inactivated in rhabdoid tumors [17] and ovarian small-cell carcinoma hypercalcaemic type [18]. In non-small cell lung cancer (NSCLC) SMARCA2 and/or SMARCA4 expressions are frequently lost and they are associated with worse prognosis [8,19]. Lastly, *ARID2* expression is lost in approximately 20% of NSCLC [9], has been found inactivated in 18.2% of hepatocellular carcinomas [20] and it is also a significantly mutated gene in melanoma [21].

Overall, genes encoding subunits of the SWI/SNF chromatin remodelling complex are collectively mutated in almost 25% of all human cancers, what places SWI/SNF as the second most frequent alteration in cancer, just after *TP53* [4–7].

2. SWI/SNF complex disruption in lung cancer

Lung cancer remains the major cause of cancer-related deaths worldwide, with an average 5-year survival rate bellow 20%, irrespective of the subtype [22]. Large genomic projects have facilitated the identification of major players in this tumor type: small cell lung cancer (SCLC, 15% of cases) is mainly driven by mutations in *TP53* and *RB1*, in lung adenocarcinoma (LUAD, 40% of cases) *KRAS, EGFR, ALK, ROS1* and *BRAF* are the main recurrently altered genes, while squamous cell carcinoma (LUSC) is genetically more heterogenous [23].

In the last two decades, several studies provided many evidences of an important role of SWI/SNF complexes alterations in lung cancer development. Thus, in 2003 Reisman and coworkers sequenced a total of 20 non-small cell lung cancer (NSCLC) cell lines and observed loss of SMARCA2 and SMARCA4 expression in 30% of the cases. In addition to this, when they compared the survival of SMARCA2/SMARCA4-negative against SMARCA4-positive patients, they show a significant higher survival in the second group, highlighting the role of these genes as tumor suppressors [8]. Ten years afterwards, Matsubara and coworkers confirmed the prognostic role of SMARCA2/SMARCA4 expression by comparing the survival of 442 primary lung adenocarcinomas, which were divided in three groups according to their expression of SMARCA2 and SMARCA4. In this study, they observed that the high expression of both catalytic subunits correlated with better prognosis [24]. Soon afterwards, Bell and coworkers validated in a large cohort of 440 human NSCLC that decreased expression of SMARCA4 was associated with worse prognosis [25].

Similar observations have been done in other accessory subunits of the complex. For instance, Zhang and coworkers analyzed the expression of ARID1A in 106 NSCLC and reported almost a 35% decreased staining, which significantly correlated with a poor differentiated stage, a higher TNM score and nodal metastasis [26]. Additionally, Manceau and coworkers found *ARID2* loss-of-function mutations in 5% of NSCLC [27].

In line with this, our group has recently analyzed ARID2 expression in a cohort of 139 lung cancer patients and has shown loss or low/heterogeneous ARID2 production in nearly 20% of the cases [9]. What is more, we have proved that *ARID2* deficiency in lung cancer cellular models is accompanied by a decrease in chromatin accessibility around enhancers, which is associated with a pro-tumoral transcriptional program in these cells. These results are in agreement with an increased proliferative and metastatic potential both *in vitro* and *in vivo* [9].

Finally, among NSCLC, SWI/SNF mutations occur more frequently in lung adenocarcinoma (LUAD) than in squamous cell carcinoma. According to the currently available LUAD data deposited on TCGA portal, SWI/SNF genes are collectively mutated in around 20% of the cases, with *SMARCA4* (8%), *ARID1A* (6%), *ARID2* (6%) and *SMARCA2* (3%) being the most commonly altered subunits (Figure 1). Consequently, SWI/SNF alteration might constitute a new molecular mechanism of vital importance in lung cancer progression. A better understanding of the gene networks regulated by each SWI/SNF subcomplex can unravel new opportunities for the management of lung cancer patients.

SWI/SNF-mutated patients show *TP53* and *KRAS* mutations in similar ratios to no-mutated patients. Nevertheless, *SWI/SNF*-mutant patients show a lower *EGFR* mutation ratio (9/115 ~ 7.8%) than the 12% observed in the complete cohort, although this difference is not statically significant (P value=0.0797, one-tailed Fisher's exact test). This bias is mainly the result of *SMARCA4* mutations showing significant mutual exclusivity with *EGFR* mutations in this dataset, as only 2% of *SMARCA4*-mutated patients show *EGFR* mutations versus the 12% that would be expected by chance (P value=0.0151, one-tailed Fisher's exact test). This observation extends previous results [24] and suggests the existence of either synthetic lethality relationships or redundant tumor progression promoting activities.

3. Potential pro-tumoral mechanisms associated with SWI/SNF alterations

Despite the clear role of SWI/SNF alterations in the development of different types of cancer, the molecular pathways behind its contribution to tumorigenesis still remain elusive [1–4].

There is a considerable amount of scientific evidence that links SWI/SNF with different DNA repair mechanisms, which suggests that a potential mechanism of tumorigenesis in *SWI/SNF*-deficient cells is through the promotion of genomic instability.

In particular, SMARCA4 is able to bind to γ-H2AX nucleosomes through its bromodomain, facilitating double-strand break (DSB) repair [27]. Similarly, SMARCB1 promotes nucleotide excision repair (NER) by interacting with UV damage recognition factor XPC at DNA damage sites [28]. Our laboratory described that ARID2 colocalizes with γ-H2AX and 53BP1 at the DNA-repair foci and its loss in human lung cancer cell lines is associated with a delay in the resolution of DNA damage foci, which in turn sensitizes cells to DNA-damaging agents (such as, cis-platin, etoposide and PARP inhibitors) [9]. Supporting the role of SWI/SNF complexes in DNA repair, Shen and coworkers reported a higher sensitivity to DNA-damaging agents in *ARID1A*-deficient cells [29]. Similarly, *SMARCA4*-mutated cell lines showed an increase in DNA damage foci and an activation of the ATR pathway [30]. Finally, it has been described that mutations in *ARID1A* are mutually exclusive with the ones in *TP53*, that could suggest redundant functions [31].

SWI/SNF complex is able to interact with canonical cancer associated genes, such as *RB1*, *TP53* and *MYC* [32,33], suggesting that defects in these chromatin remodelling complexes could promote cancer through the activation of canonical cancer pathways. Regarding this, it has been demonstrated that *SWI/SNF* and *TP53* or *PTEN* mutations do not usually concur in the same colorectal tumor neither in the same ovarian clear-cell carcinoma [7,30]. In the context of lung cancer, *SMARCA4* downregulation does not occur simultaneously with *EGFR* mutations [32,33], neither with *MYC* amplification [34].

Important relationships between the catalytic subunit of the complex SMARCA4 and critical molecular pathways have also been reported, which might provide molecular clues for its role in tumorigenesis. Thus, in NSCLC *SMARCA4* loss is synthetic lethal with CDK4/6 inhibition both *in vitro* and *in vivo* [35]. Additionally, in a murine mouse model of LUAD where *SMARCA4* is ablated, there is enhanced oxygen consumption [36], what suggests that *SMARCA4*-deficient cell lines rely on this metabolic process to sustain their high metabolic rate. Supporting this idea, derived tumor cells are more sensitive to OXPHOS inhibition. Moreover, it is known that *SMARCA4* regulates the expression of *MAX* and it is also required to activate neuroendocrine transcriptional programs and to upregulate *MYC* target genes, such

as the ones implicated in glycolysis. In agreement with this observation, *SMARCA4* alterations do not concur with *MAX* inactivation in SCLC cell lines [32].

Additionally, we reported that the accessory subunit ARID2 is necessary to keep an open chromatin structure around the enhancers of the metastasis inhibitor *MTSS1* and the adhesion molecule *SDK1*, allowing its expression [9]. This might explain the observed increased migration and invasion capabilities of these cells *in vitro*.

Finally, alterations in any of the catalytic subunits of the complex (SMARCA2 or SMARCA4) correlates with a loss of bronchial epithelial phenotype, low E-cadherin and high vimentin expression, what supports an enhanced epithelial to mesenchymal transition as a result of the loss of SWI/SNF function [24].

4. Impact of *SWI/SNF* mutations in current lung cancer treatments

Due to the recurrency of SWI/SNF alterations in different tumor types, any new knowledge about how to exploit these alterations for therapy could improve the treatment of many cancer patients. According to current available NSCLC treatments, several studies have provided very interesting data.

Firstly, due to its role in DNA repair, many authors reported that lack of some accessory subunits of the SWI/SNF complex sensitizes tumor cells to therapeutic strategies aimed at promoting genomic instability. For instance, *SMARCA4* [25], *ARID1A* [29] and *ARID2* [9] alterations have been linked to a higher sensitivity to platinum-based chemotherapy or treatments based on the inhibition of PARP. Moreover, *SMARCA4* [30] and *ARID1A* [37]-mutated lung cancer cell lines are more sensitive to ATR inhibition. Additionally, *SMARCA4*-mutant NSCLC cell lines are also more sensitive to aurora kinase inhibition [36]. Therefore, loss of any of the above-mentioned accessory subunits might be used as biomarkers in lung cancer patients that could benefit from therapeutic strategies that exploit defects in the DNA repair machinery of tumor cells (Figure 2).

Secondly, it has been described that loss of *SMARCE1* subunit gives rise to an enhanced resistance to MET and ALK inhibitors in NSCLC cell lines, which is restored by the use of EGFR inhibitors [38]. It is thought that this resistance relies on AKT and ERK activation. If these results are consistent in human patients, *SMARCE1* expression might emerge as a potential predictive marker for drug response to MET and ALK inhibitors and *SMARCE1*-mutated tumors may benefit from treatments based on EGFR inhibition (Figure 2).

Finally, another strategy that has been proved successful in many cancer types, including lung cancer, is the boost of the proper immune response of the patient against its tumor cells. Regarding this, in 2018 Pan and coworkers reported that the murine melanoma cell line B16F10 increased its sensitivity to T cell-mediated cytotoxicity after mutating different subunits of the PBAF complex (in particular, *Arid2, Pbrm1* and *Brd7* [39]). These results seem to indicate that tumors harboring mutations in the SWI/SNF complex might respond better to immunotherapy. In agreement with this hypothesis, mice bearing tumors induced with *Pbrm1*-deficient B16F10 cells were more strongly infiltrated by cytotoxic T cells, developed smaller tumors and had an improved survival in comparison with control cells. In accordance with this result, Miao and coworkers performed a whole exome sequencing of human metastatic clear cell renal carcinomas and verified that *PBRM1* inactivation is associated with better clinical outcome from immune checkpoint inhibitor (ICI) therapy [40]. Finally, a recent study published by Zhu and coworkers in 2021 performed on NSCLC

patients has extended this observation to other accessory subunits of the complex, such as *ARID1A* and *ARID1B* [41] (Figure 2). However, the precise mechanism that explains why *ARID1A*, *ARID1B* or *ARID2*-mutated tumors are more likely to benefit from ICI therapy has not been elucidated.

5. New therapeutic opportunities for *SWI/SNF*-mutated patients

SWI/SNF complexes exist in multiple compositions since several subunit positions can be occupied alternatively by proteins encoded from different genes. According to that, many authors have reported a dependency on the remaining functional alternative subunit in cells with alterations in specific SWI/SNF components. That is the case of SMARCA2 in *SMARCA4*-deficient cells [42,43] or ARID1B in *ARID1A*-deficient cells [44,45]. Similar synthetic lethality relationships have been described among SMARCA4 and ARID2, SMARCA4 and ACTB, as well as SMARCC1 and SMARCC2 [46]. Consequently, it has been postulated that this dependency could be therapeutically exploited. According to that, it has been demonstrated that SMARCA2/4 specific protein degraders or ATP inhibitors impair the proliferation in *SMARCA4*-deficient lung cancer cellular models [47,48].

Lastly, another proposed alternative is based on the previously reported antagonistic role between polycomb repressive complex 2 (PRC2) and SWI/SNF [49,50]. According to this dependency, EZH2 (catalytic subunit of PRC2) inhibition has shown very promising anti-tumoral activity in a variety of *SWI/SNF*-deficient cell lines (highlighting *SMARCB1* and *ARID1A*) of different tumor types and could suppose a future treatment opportunity for *SWI/SNF*-deficient lung tumors [49,50]. In agreement with these promising results, an specific inhibitor of EZH2, tazemetostat, has been approved for the treatment of epithelioid sarcoma and MRT [51], constituting the first target therapy described for *SWI/SNF*-mutant tumors.

6. Concluding remarks

In the last decade, an overwhelming amount of data supporting an important role of SWI/SNF alterations in human cancer has been generated. This is especially interesting in the case of lung cancer, the first cause of cancer-related deaths worldwide, in urgent need for the discovery of new molecular pathways to be therapeutically exploited. Thus, in this tumor type at least four different SWI/SNF genes, *SMARCA4*, *ARID1A*, *ARID2* and *SMARCA2*, are found recurrently mutated with what it seems an exclusion pattern with other highly recurrently mutated cancer genes, such as *EGFR*. This opens at least two potential alternatives: either *SWI/SNF*-mutated patients constitute a biologically different group that deserve special consideration; or SWI/SNF alterations constitute an alternative way of activating EGFR pathway. In any case, further research on the molecular pathways affected by SWI/SNF alterations could have a great impact in the treatment of lung cancer patients.

It is estimated that around 25% of all cancer patients contain SWI/SNF alterations. Thus, any new knowledge of how to exploit these alterations for therapy could have a huge impact in the treatment of multiple cancer types. In this context, it is especially remarkable the last reports linking SWI/SNF alterations with a higher sensitivity to immunotherapy. This strategy has been incorporated into the therapeutic portfolio of many malignancies and besides its great efficacy in many cases, it is still not fully understood why many patients are refractory

to this treatment. Therefore, understanding the molecular pathways by which SWI/SNF alterations modulate the immune response is key to improve the efficiency of immunotherapy strategies in cancer patients.

7. Perspectives

- SWI/SNF is collectively mutated in almost 20% of lung cancer patients, which offers a new opportunity to improve our molecular knowledge, as well as the therapeutic opportunities in the first cause of cancer-related deaths worldwide.
- SWI/SNF deficiency can be therapeutically exploited with currently available treatments used in lung cancer, such as those based on the promotion of genomic instability or immunotherapy; as well as with new strategies exploiting synthetic lethal relationships among SWI/SNF components and with other epigenetic systems.
- A better knowledge of the molecular mechanisms regulated by SWI/SNF alterations could be translated into better treatments for lung cancer patients.

8. Figures and tables

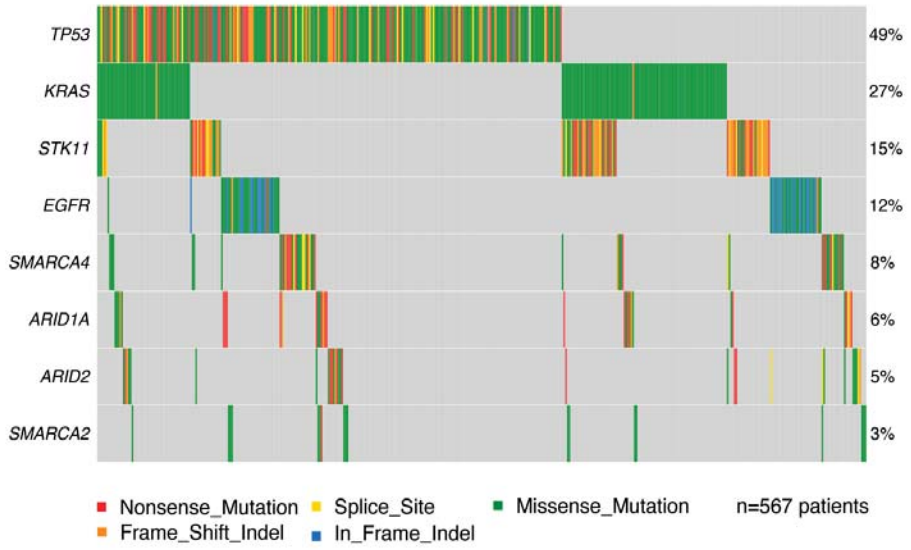

Figure 1. Mutual exclusivity between SWI/SNF and canonical pathways altered in lung adenocarcinoma. Oncostrip representation of the non-synonymous mutations found by MuTect2 [52] in patients with lung adenocarcinoma (LUAD) extracted from the TCGA-LUAD project dated March 2022 (*maftools* R library was used to create the maf object and to plot the somatic variants). For each gene (rows), the presence of mutations in each of the 567 patients (columns) is represented in different colors according to the mutation predicted functional consequence.

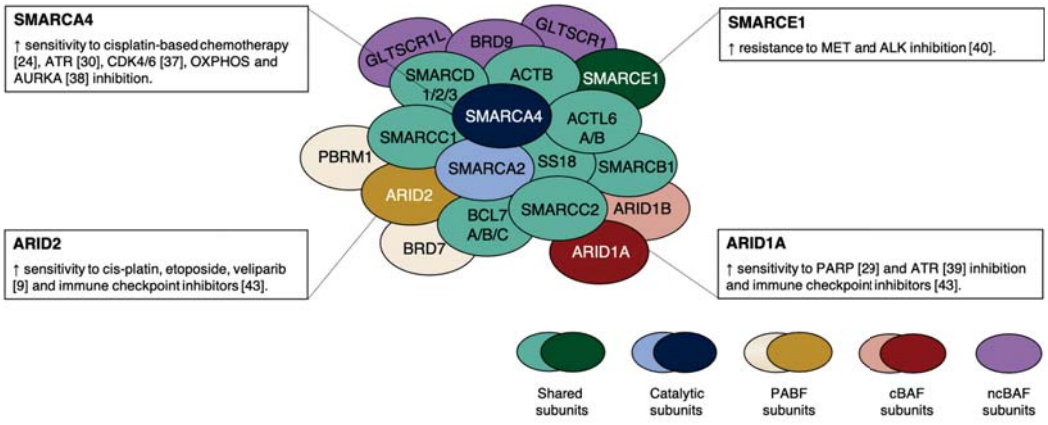

Figure 2. Therapeutic implications of SWI/SNF altered lung tumors. The most commonly mutated subunits of the complex and its association with different sensitivities to lung cancer treatments are depicted in blue or orange, depending on whether they are currently available or under development. Shared subunits of SWI/SNF complexes are represented in green. The catalytic subunits of the complex (SMARCA2 and SMARCA4) appear in blue. The accessory subunits that define PBAF, cBAF and ncBAF families are represented in yellow, red and purple, respectively. The bibliographic references supporting SWI/SNF alteration and its response to different treatments are indicated in brackets.

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10. Author contributions, conflicts of interest, acknowledgments and funding

Author contributions

B. M. performed the literature review, wrote the first draft of the manuscript and performed suggested modifications in further versions. I. V. performed a literature review, proposed the first review schema, proposed modifications to early versions and performed the final modifications to the manuscript.

Declaration of interest

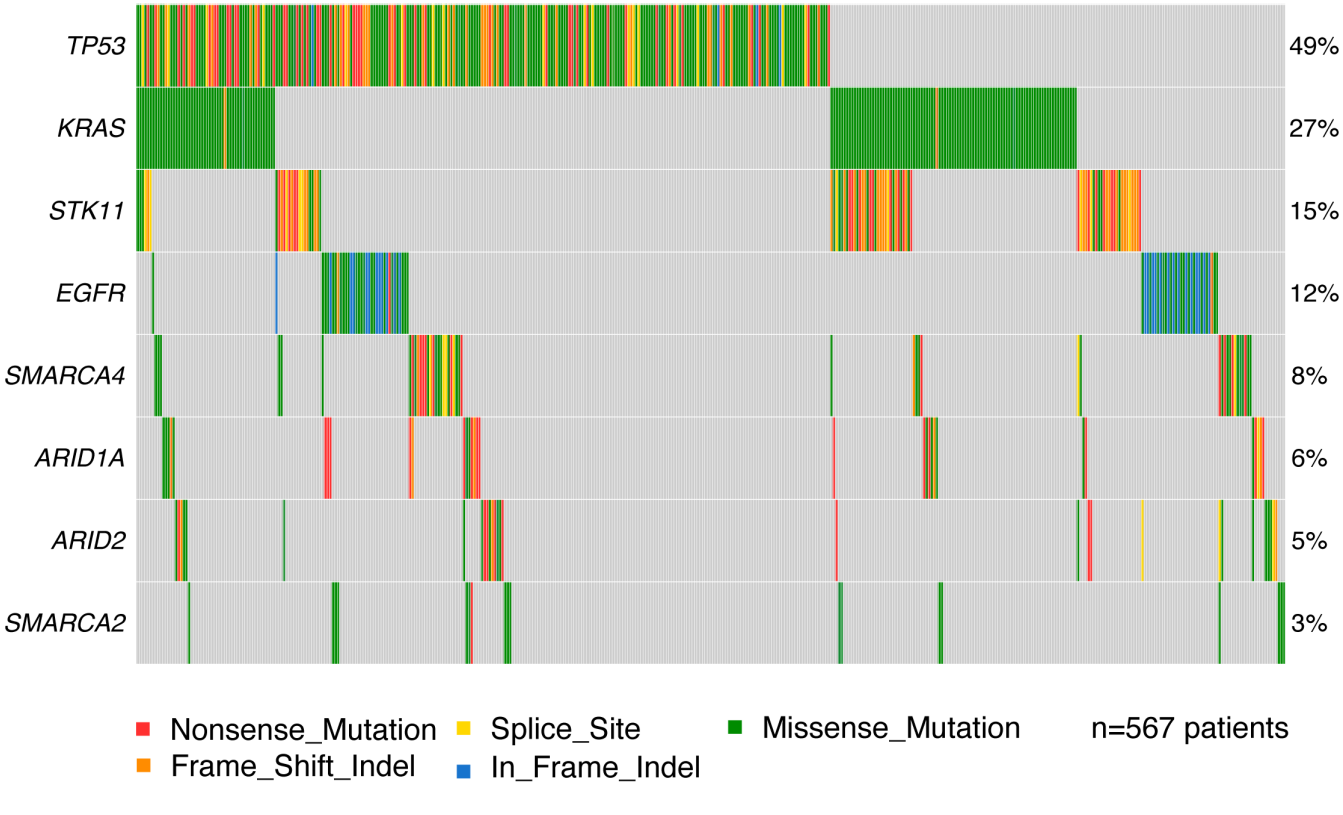
The authors declare that there are no competing interests associated with the manuscript.

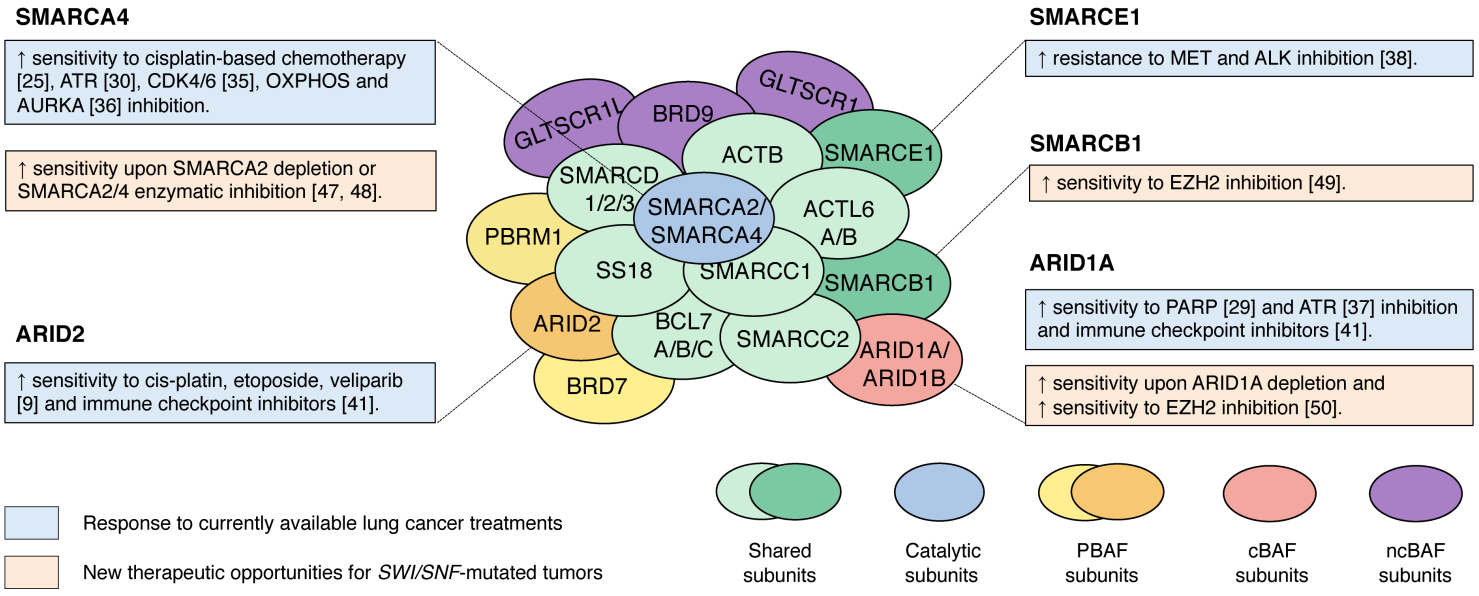
Acknowledgements

We would like to thank the staff members of the Biobanco Valdecilla (Tissue Node, PT13/0010/0024), as well as to Dr. Javier Freire, Dr. Javier Gómez-Román and Dr. Eduardo Salido for their exceptional advice in the management of lung cancer patients.

Funding

This work is supported by the Spanish Ministerio de Ciencia e Innovación (MCIN/ AEI /10.13039/501100011033. ref PID2020-117539GB-I00). B.M is awardee of the Ayudas para la formación de profesorado universitario (FPU, Ministerio de Ciencia, Innovación y Universidades, Spain).


TP53
KRAS
STK11
EGFR
SMARCA4
ARID1A
ARID2
SMARCA2
49%
27%
15%
12%
8%
6%
5%
3%
Nonsense_Mutation
Frame_Shift_Indel
Splice_Site
In_Frame_Indel
Missense_Mutation
n=567 patients


SMARCA4
↑ sensitivity to cisplatin-based chemotherapy [25], ATR [30], CDK4/6 [35], OXPHOS and AURKA [36] inhibition.
↑ sensitivity upon SMARCA2 depletion or SMARCA2/4 enzymatic inhibition [47, 48].
ARID2
↑ sensitivity to cis-platin, etoposide, veliparib [9] and immune checkpoint inhibitors [41].
GLTSCR1L
BRD9
GLTSCR1
ACTB
SMARCE1
SMARCD 1/2/3
SMARCA2/ SMARCA4
ACTL6 A/B
PBRM1
SS18
SMARCC1
SMARCB1
ARID2
BCL7 A/B/C
SMARCC2
ARID1A/ ARID1B
BRD7
SMARCE1
↑ resistance to MET and ALK inhibition [38].
SMARCB1
↑ sensitivity to EZH2 inhibition [49].
ARID1A
↑ sensitivity to PARP [29] and ATR [37] inhibition and immune checkpoint inhibitors [41].
↑ sensitivity upon ARID1A depletion and ↑ sensitivity to EZH2 inhibition [50].
Response to currently available lung cancer treatments
New therapeutic opportunities for SWI/SNF-mutated tumors
Shared subunits
Catalytic subunits
PBAF subunits
cBAF subunits
ncBAF subunits