The SWI/SNF complex, transcription-replication conflicts and cancer: A connection with high therapeutic potential

Aleix Bayona-Feliu[1,2] * and Andrés Aguilera[1,2,]

[1] *Centro Andaluz de Biología Molecular y Medicina Regenerativa CABIMER, Universidad de Sevilla-CSIC-Universidad Pablo de Olavide, Sevilla 41092, Spain*

[2] *Departamento de Genética, Facultad de Biología, Universidad de Sevilla, Seville 41012, Spain*

* *Corresponding author. E-mail:* aleix.bayona@cabimer.es

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ABSTRACT

Genome instability is a hallmark of cancer. ATP-dependent chromatin remodelers are frequently altered in cancer. We have recently reported that the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex protects the genome by limiting R-loop-mediated genome instability, mainly that caused by transcription-replication conflicts. Here we discuss the significance and biomedical applications of this finding.

Abstract: 50 words

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AUTHOR'S VIEW

In addition to the transcription machinery, non-B DNA structures generated by transcription may pose an obstacle to replication fork (RF) progression. Co-transcriptional R-loops, three-stranded nucleic acid structures composed of a DNA-RNA hybrid plus a displaced single strand DNA (ssDNA), may occur naturally to serve a physiological role but its unscheduled formation have been shown to menace genome integrity (1). Avoidance of such situations is achieved thru multiple mechanisms, also involving the chromatin network.

Genome instability is a hallmark of cancer cells. Well-known cancer-associated factors such as Breast cancer type 1/2 susceptibility proteins (BRCA1/2) have been demonstrated to impact R-loop homeostasis (1). ATP-dependent chromatin remodelers are frequently altered in cancer, with the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex genes accumulating mutation at frequencies close to those of the Tumor Protein P53 (TP53) gene (2). SWI/SNF's contribution to transcription had been extensively studied, but little was known about its impact on genome integrity. Our recently published work (3) unveils a novel role for SWI/SNF in preventing DNA replication stress by helping solve transcription-replication conflicts (TRCs), which may be an important source of DNA damage and genome instability. In particular, SWI/SNF mutations effect in genome instability was found epistatic to *Fanconi Anemia Complementation Group D2 (FANCD2)*, a member of the Fanconi Anemia pathway of repair accumulating at sites of RF stalling, directly linking SWI/SNF to TRC resolution rather than prevention.

A major contribution of SWI/SNF-related Matrix-associated Actin-dependent Regulator of Chromatin subfamily A (SMARCA), member 4 (SMARCA4), best known as Brahma-related gene 1 (BRG1), but not SMARCA member 2 (SMARCA2), also named Brahma (BRM), the two ATPase subunits of the human SWI/SNF, was shown to play a central role in TRC resolution. Consistently, BRG1 generally associates with proliferative tissues with DNA replication rates, whereas BRM is mostly linked to differentiated tissues with low replication (4,5). SWI/SNF may exist in several complex subtypes including canonical BRG1-associated factor (cBAF), non-canonical BAF (ncBAF) and polybromo BRG1-associated factor (PBAF) with subunits specific to each subtype. Interestingly, a major contribution of cBAF complex subtype to TRC outcome was evidenced by the observation that AT-Rich Interaction Domain 1A (ARID1A) also accumulates at TRC and its depletion results in R-loop-dependent DNA damage. Polybromo 1 (PBRM1), a member of the PBAF complex subtype, also influences R-loop homeostasis, but to a lesser extent. Consistently, *ARID1A* and *PBRM1* inactivation also induces R-loops (6,7). Interestingly, *BRG1*, *ARID1A* and *PBRM1* are

among the ATP-chromatin remodeling subunit genes most frequently altered in cancer (2), suggesting a direct connection between their recurrent mutation in malignant cells and their function preventing TRC-derived genome instability, and highlighting their importance as putative tumor suppressors. *BRM*, which does not impact TRCs, present much lower mutation rates in transformed cells.

Defining the origin and cause of malignancies is crucial to understand the disease and to generate new therapeutic approaches. According to the *Integrative Onco Genomics (Intogen)* database, *BRG1*, *ARID1A* and *PBRM1* act as cancer-drivers in several cancer types (8). In these cases, malignancy could be mediated by a sustained R-loop-induced genome instability eventually leading to cell transformation. Nevertheless, this process would imply that pre-malignant and/or malignant cells develop additional mechanisms to deal with DNA replication stress and genome instability to proliferate (Figure 1a). Indeed, sustained genome instability prior to malignant transformation might promote mutations that could increase cell fitness and malignant cell proliferation in contrast to other cells presenting genome instability. The same rational would apply when malignancy is acquired, since cancer cells able to deal with its inherent genome instability would proliferate better.

BRG1 is overexpressed in a wide range of cancers (9). It is possible that under DNA replication stress higher levels of BRG1 confer a cell proliferation advantage given its role in TRC resolution and genome integrity (Figure 1b). If so, the use of BRG1-targeting drugs would be a plausible approach to limit cancer cell proliferation, by restoring the high genome instability, thus affecting cell fitness. A similar mechanism has been suggested for Inositol requiring 80 (INO80) complex, which also impacts on R-loop homeostasis (10). INO80 depletion inhibits cell growth in PC3 (prostate cancer), MCF7 (breast cancer) and WM1361 (melanoma) cancer cells, but co-depletion of INO80 and ribonuclease H1 (RNase H1), which degrades the RNA moiety from DNA-RNA hybrids, restores cell proliferation.

Therefore, even though dysfunction of SWI/SNF triggers genome instability and might promote cell transformation, different survival mechanisms can be used in some cancer types with high genome instability. Unveiling the contribution of the chromatin-remodeling network is vital to understand how cells proliferate under DNA replication stress. Identifying the chromatin activities used by SWI/SNF-deficient cancer cells to grow despite its high R-loop-dependent genome instability could serve to design new drugs targeting specifically such activities. The combined use of such drugs with DNA replication stress-inducing drugs could block cell proliferation in malignancies with up-regulated SWI/SNF levels. In support of this possibility, PBRM1 deficiency was found

to be synthetic lethal with Poly(ADP-Ribose) Polymerase (PARP) and Ataxia Telangiectasia And Rad3-Related (ATR) inhibitors (7).

In conclusion, identification of the cause-effect relationship of SWI/SNF alterations in several cancer types could permit designing new strategies to specifically target malignant cells. The identification of R-loop-mediated replication stress may suppose a step forward in this direction.

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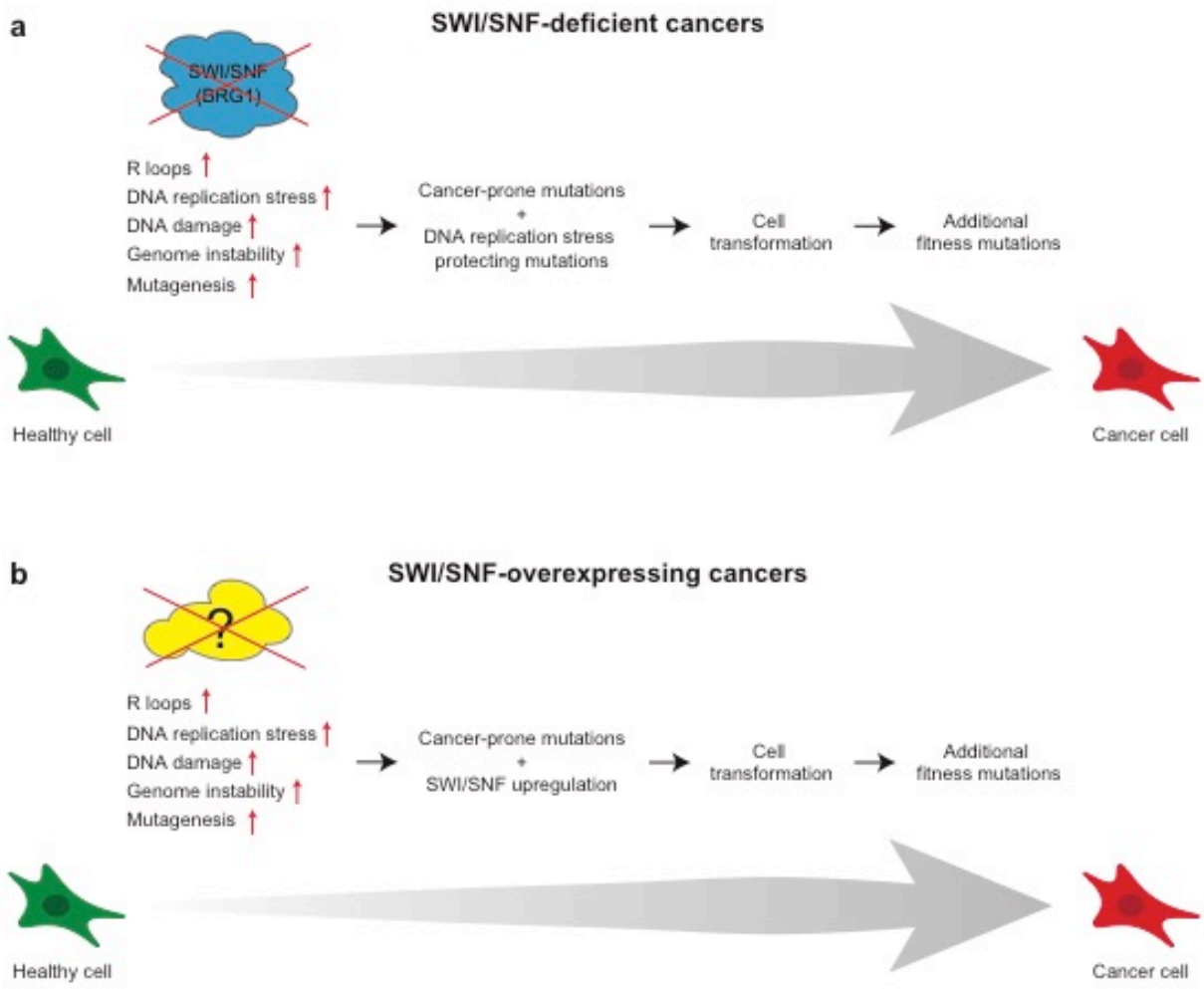

Figure 1. Potential impact of SWI/SNF complexes on DNA replication stress-mediated cancer-driving mechanisms.
SWI/SNF complex influences malignancy acquisition under high genome instability scenarios. **a**, In SWI/SNF-deficient cells, strong unscheduled R loop formation causes DNA replication stress, DNA damage and genome instability. Under these conditions, mutagenesis increases and results in accumulation of cancer-prone alterations. Its co-occurrence with DNA replication stress safeguarding alterations may permit cell survival and eventually lead to cell transformation. **b**, Deficiencies in molecular activities leading to high R loop-mediated genome instability scenarios may increase mutagenesis and promote cell transformation if cancer-prone alterations are combined with SWI/SNF upregulation, given its role at TRCs. Additional mutations after transformation may further increase cell fitness.