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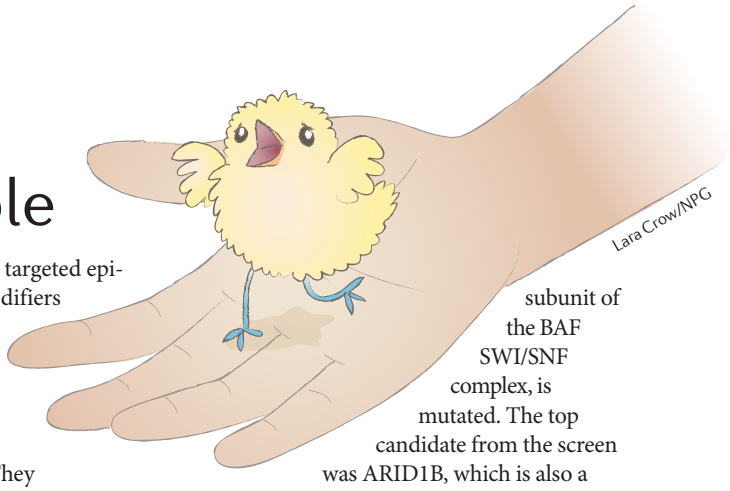
CHROMATIN REMODELLING

# Looking vulnerable




Four recent papers have highlighted the importance of the disruption of the chromatin-modifying SWI/SNF axis in human cancer and how this might prove to be a widespread Achilles heel.

Montse Sanchez-Cespedes and colleagues investigated which genetic alterations can promote the development of small-cell lung cancer (SCLC) and found that approximately 6% of SCLCs have lost the expression of MYC-associated factor X (MAX). The binding of the SWI/SNF ATPase subunit BRG1 (also known as SMARCA4), which is present in both BRM/BRG1-associated factor (BAF) and polybromo BRG1-associated (PBAF) SWI/SNF complexes, to the *MAX* promoter was required for the increased expression of MAX in response to glucocorticoids. Further experiments indicated that BRG1 is required for MYC–MAX induction of target genes, such as those involved in glycolysis, and for the MAX-mediated expression of neuroendocrine factors. These results suggest that an aberrant SWI/SNF–MYC network is required for lung cancer development and are consistent with the mutually exclusive mutation of *MYC*, *MAX* and *BRG1* in lung cancer. The loss of *BRG1* in cells in which *MAX* is inactive resulted in cell death, which suggests a synthetic lethal interaction and underlines the importance of this network in lung cancer development.

A synthetic lethal interaction involving BRG1 was also found by Frank Stegmeier, Zainab Jagani and colleagues. They used a deep coverage short hairpin RNA (shRNA) screen that targeted epigenetic modifiers to identify epigenetic dependencies in 58 cancer cell lines. They found that in cell lines that have loss-of-function mutations in *BRG1*, expression of BRM (also known as SMARCA2; a mutually exclusive ATPase subunit of BAF SWI/SNF complexes) is essential for cell survival. Depletion of BRM in *BRG1*-deficient cells resulted in cell cycle arrest and senescence *in vitro* and reduced growth of tumour xenografts *in vivo*. Immunoprecipitation of two core subunits of the SWI/SNF complex indicated that knockdown of BRM in *BRG1*-mutant cells did not lead to dissociation of the complex, thereby suggesting that the synthetic lethality that was evident in this screen was not due to dissociation of the SWI/SNF complex, but was more the result of loss of the ATPase subunits. These findings were echoed by Charles Roberts and colleagues, who showed that loss of BRG1 activity results in SWI/SNF complexes that contain BRM, which are required for tumorigenesis. Moreover, data from a loss-of-function screen in 165 cancer cell lines indicated that *BRM* is an essential gene in *BRG1*-mutant cancer cell lines.

Roberts and colleagues also screened for mutations that compromised the viability of cancer cell lines in which AT-rich interactive domain 1A (*ARID1A*), a variant subunit of the BAF SWI/SNF complex, is mutated. The top candidate from the screen was ARID1B, which is also a BAF SWI/SNF variant subunit that is mutually exclusive with ARID1A (ARID1A and ARID1B are not present in the same complex). Further investigations showed that BAF SWI/SNF complexes can contain ARID1B in both wild-type and *ARID1A*-mutant cells and that knockdown of ARID1B using shRNAs in *ARID1A*-mutant cells prevented the formation of intact SWI/SNF complexes. Interestingly, mutations in *ARID1A* and *ARID1B* can co-occur in human cancers, but an intact allele of either *ARID1A* or *ARID1B* is retained, which suggests that a functional SWI/SNF complex is required for cell survival.

All four studies indicate that targeting the SWI/SNF complexes might prove to be clinically useful in several cancer types.

*Nicola McCarthy*

> “in cell lines that have loss-of-function mutations in *BRG1*, expression of BRM … is essential for cell survival”

**ORIGINAL RESEARCH PAPERS** Romero, O. A. *et al.* *MAX* inactivation in small cell lung cancer disrupts MYC–SWI/SNF programs and is synthetic lethal with BRG1. *Cancer Discov.* **4**, 292–303 (2014) | Hoffman, G. R. *et al.* Functional epigenetics approach identifies BRM/SMARCA2 as a critical synthetic lethal target in BRG1-deficient cancers. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1316793111 (2014) | Wilson, B. G. *et al.* Residual complexes containing SMARCA2 (BRM) underlie the oncogenic drive of *SMARCA4* (*BRG1*) mutation. *Mol. Cell Biol.* **34**, 1136–1144 (2014) | Helming, K. C. *et al.* ARID1B is a specific vulnerability in *ARID1A*-mutant cancers. *Nature Med.* http://dx.doi.org/10.1038/nm.3480 (2014)