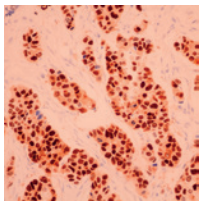
Breast Cancer

Major Finding: ARID1A is required for response of ER$^+$ breast cancer cells to tamoxifen and fulvestrant but not JQ1.

Mechanism: ARID1A, a BAF (mSWI/SNF) complex member, binds ER-target sites and recruits HDAC1 to deacetylate H4.

Impact: Twelve percent of metastatic breast cancers are *ARID1A*-mutant, so deeper knowledge of this pathway is critical.

mSWI/SNF COMPONENT ARID1A MEDIATES BREAST CANCER TREATMENT RESPONSE



Although most breast cancers are driven by estrogen receptor (ER) signaling and drugs targeting the ER pathway are often effective, *de novo* or acquired resistance is still problematic, prompting efforts to pinpoint factors that influence ER-related pathways. Using a genome-wide CRISPR screen in a breast cancer cell line, Nagarajan and colleagues found that *ARID1A*, encoding the BAF (also known as mSWI/SNF)-complex component AT-rich interactive domain-containing protein 1A, and some other BAF component–encoding genes were involved in response to treatment. Specifically, the results of the screen implied that the BAF complex was required for response to treatment with the ER modulator tamoxifen or the ER degrader fulvestrant, but that loss of the BAF complex sensitized cells to treatment with JQ1, which inhibits a potential therapeutic target (BRD4) in ER$^+$ breast cancer. Chromatin immunoprecipitation with sequencing analyses showed that more than 78% of ARID1A binding sites overlapped with those of ER, the pioneer transcription factor FOXA1, or both. Notably, the binding of ARID1A to these sites was not dependent on ligand-induced ER recruitment. Mouse xenograft experiments revealed that *ARID1A* knockout in tumor cells reduced the antitumor activity of tamoxifen and resulted in increased tumor growth even in the absence of treatment. Further experiments showed that ARID1A is able to regulate ER-target genes and may even be part of the ER transcriptional complex, and the role of FOXA1 in the process was revealed to be recruitment of ARID1A to chromatin. Mechanistically, ARID1A participated in recruitment of the histone deacetylase HDAC1 to target sites, resulting in decreased acetylation of H4 and restricted BRD4 recruitment, leading to decreased basal cell proliferation rates. These findings demonstrate how the BAF component ARID1A is recruited to ER-binding sites by FOXA1 prior to ER binding and that ARID1A contributes to transcriptional repression via recruitment of HDAC1. Because *ARID1A* mutations are present in approximately 5% of primary breast cancers and approximately 12% of metastatic breast cancers, deeper understanding of this pathway is needed. ■

Nagarajan S, Rao SV, Sutton J, Cheeseman D, Dunn S, Papachristou EK, et al. ARID1A influences HDAC1/BRD4 activity, intrinsic proliferative capacity and breast cancer treatment response. Nat Genet 2020 Jan 6 [Epub ahead of print].

Structural Biology

Major Finding: The structure of the chromatin-remodeling BAF complex provides molecular-scale mechanistic insight.

Approach: Cryo-electron microscopy was used for refinement to 3.7-Å resolution, enabling structural modeling.

Impact: This information has the potential to provide insight into the consequences of cancer-associated BAF-complex mutations.

CRYO-ELECTRON MICROSCOPY REVEALS ARCHITECTURE OF THE BAF COMPLEX

Mutations affecting protein subunits of the BAF and PBAF (also known as mSWI/SNF) complexes are present in up to 20% of cancers. Extensive research has been dedicated to the molecular characterization of these chromatin-remodeling complexes, but a lack of high-resolution structural information has hindered understanding of the spatial relationships among individual subunits and with the nucleosome. He, Wu, Tian, and colleagues used cryo-electron microscopy to determine the structure of a reconstituted human BAF complex bound to a nucleosome core particle (NCP) in the absence of ATP and ADP at a resolution of 3.7 Å, revealing previously elusive molecular details and providing mechanistic insights. The BAF complex was shown to bind NCPs differently than many other chromatin remodelers—instead of interacting with nucleosomal DNA or histone tails, the BAF complex envelops the entire NCP using the BAF complex's Base module (comprising approximately 80% of the total BAF complex by mass) and its ATPase module. The ATPase motor and nucleosomal DNA were in proximity to one another, and comparison of the BAF–NCP structure with a lower-resolution structure of the ADP-bound BAF–NCP complex suggested that ATP hydrolysis could result in interactions between the ATPase domain and nucleosomal DNA, effectively pushing DNA along the NCP. Four conserved arginine residues of the C-terminal alpha helix of SMARCB1, a protein essential for the structural integrity of the BAF complex, formed contacts with an acidic patch on the nucleosome; notably, these four residues are frequently mutated in human cancers. The structure further revealed that ARID1A, the largest BAF-complex subunit and one that is commonly mutated in human cancers, serves as a stable core of the Base module, and the Base module's two SMARCC subunits act as structural scaffolds. In summary, this study elucidated the long-awaited high-resolution structure of the NCP-bound BAF complex, which will provide a basis for further molecular characterization of this cancer-linked chromatin remodeler. ■

He S, Wu Z, Tian Y, Yu Z, Yu J, Wang X, et al. Structure of nucleosome-bound human BAF complex. Science 2020 Jan 30 [Epub ahead of print].

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