Small molecules targeting ARID1A in the MDA-MB-231 cell line revealed by hub gene analysis of SWI/SNF chromatin remodeling complex in along with structure-based virtual screening and *in vitro* confirmation.

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Abstract

Molecular heterogeneity of Triple-negative breast cancer (TNBC) contributes to its high mortality rate. The SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex plays a crucial role in regulating gene expression and acts as a tumor suppressor; however, its disruption is observed approximately in 20-25% of cancers. ARID1A (AT-rich interactive domain-containing protein 1A), a critical component of SWI/SNF primarily acts as a tumor suppressor in various cancers, and its loss of function contributes to the activation of PI3K/AKT/mTOR signaling can promotes tumor proliferation, and highlighting its potential as a therapeutic target. In this study, the ARID1A protein was modeled and subjected to a 500 ns MD simulation to assess it structural stability. Subsequently, structure-based virtual screening was performed using the ChemBridge database to identify potential small molecule modulators. Top ranked hits were validated for binding strength through additional MD simulations, Prime MM GBSA, and DFT analyses, followed by comparison with RosettaFold all-atom predictions. Computational analysis revealed that ChemBridgeID:61952109 [Hit-1] and ChemBridgeID:33541564 [Hit-2]can effectively boost ARID1A expression. Both compounds showed strong anti-cancer effects in TNBC cells, inducing DNA damage, promoting apoptosis, generating reactive oxygen species, impairing mitochondrial function, and inhibiting cell growth and migration. Furthermore, treatment with these compounds restored ARID1A expression, which leads to PTEN upregulation, PI3K/AKT pathway suppression, and G1 phase cell-cycle arrest. Among the two potent compounds, Hit-2demonstrated superior anti-cancer activity, making it a promising candidate for TNBC to overcome chemoresistance by targeting ARID1A and the SWI/SNF network.

Keywords: SWI/SNF complex, hub genes analysis, ARID1A, structure-based virtual screening, Molecular dynamic simulation, in vitro evaluation, MDA-MB-231 cell line.