

BRG1 and Ep300 as a Transcriptional Regulators of Breast Cancer Growth

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Abstract : Brg1, a member of SWI/SNF complex, plays a role in chromatin remodeling, therefore, regulates expression of many genes. Brg1 is an ATPase of SWI/SNF complex, thus its activity requires ATP. Through its bromodomain recognizes acetylated histone residues and evicts them, thus promoting transcriptionally active state of chromatin. One of the enzymes that is responsible for acetylation of histone residues is Ep300. It was previously shown in the literature that cooperation of Brg1 and Ep300 occurs at the promoter regions that have binding sites for E2F-family transcription factors as well as CpG islands. According to literature, approximately 20% of human cancer possess mutation in Brg1 or any other crucial SWI/SNF subunit. That phenomenon makes Brg1-Ep300 a very promising target for anti-cancer therapy. Therefore in our study, we investigated if physical interaction between Brg1 and Ep300 exists and what impact those two proteins have on key for breast cancer cells processes such as DNA damage repair and cell proliferation. Bioinformatical analysis pointed out, that genes involved in cell proliferation and DNA damage repair are overexpressed in MCF7 and MDA-MB-231 cells. Moreover, promoter regions of these genes are highly acetylated, which suggests high transcriptional activity of those sites. Notably, many of those gene possess within their promoters an E2F, Brg1 motives, as well as CpG islands and acetylated histones. Our data show that Brg1 physically interacts with Ep300, and together they regulate expression of genes involved in DNA damage repair and cell proliferation. Upon inhibiting Brg1 or Ep300, expression of vital for cancer cell survival genes such as CDK2/4, BRCA1/2, PCNA, and XRCC1 is decreased in MDA-MB-231 and MCF7 cells. Moreover, inhibition or silencing of either Brg1 or Ep300 leads to cell cycle arrest in G1. After inhibition of BRG1 or Ep300 on tested gene promoters, the repressor complex including Rb, HDAC1, and EZH2 is formed, which inhibits gene expression. These results highlight potentially significant target for targeted anticancer therapy to be introduced as a supportive therapy.

Keywords : brg1, ep300, breast cancer, epigenetics

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