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Commentary

ADNP (Activity Dependent Neuroprotector Homeobox): A novel oncogene driving poor prognosis in high-grade serous carcinoma

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In this issue of EBioMedicine, Gatza and colleagues show through an integrative proteogenomic analysis of publicly available datasets that amplification and overexpression of ADNP (Activity Dependent Neuroprotector Homeobox) are associated with poor prognosis in high-grade serous carcinoma (HGSC), and further demonstrate its oncogenic potential via *in vitro* studies [1].

HGSC is the most common histologic subtype of ovarian carcinoma typically presenting at advanced stage and accounting for most deaths from ovarian cancer [2]. Nearly all HGSCs exhibit TP53 mutations, DNA copy number alterations and multiple subchromosomal aberrations, most frequently MYC, PIK3CA, AKT1 and NOTCH3 amplification, and dysregulation of Rb/E2F, Ras/PI3K and FoxM1 pathways [3,4]. Unfortunately, inhibition of these pathways has not been effective in clinical trials [5], and there are conflicting results for the prognostic significance of molecular subtypes of HGSC [3,6,7]. Therefore, identification of novel oncogenes such as ADNP is essential in the discovery of much needed new prognostic and predictive markers in HGSC.

The Gatza group applied the Poor Prognosis Signature (PPS) by the Cancer Genome Atlas (TCGA) Project [3] to three independent datasets [3,7,8] to identify the top 10 signaling pathways associated with the PPS signature. The authors used a 3-step approach to identify functionally significant alterations. First, samples were scored to detect copy number changes associated with a high PPS score. Secondly, the correlation between mRNA or protein expression and the PPS score was assessed to determine the functional relevance of genes/proteins in each amplicon. Finally, the statistically significant candidates were compared to identify genes amplified and overexpressed at the mRNA and protein level. Of 131 genes, 39 were reproducibly correlated with the PPS score. Finally, to prioritize these 39 genes for functional studies, the Achilles RNAi proliferation screen data was assessed. By examining the essentiality of the ~9000 genes profiled in this screen relative to PPS score in a panel of 29 ovarian cell lines, ADNP and AKAP8K were identified as genes with a high PPS transcriptome profile. Given the association of ADNP copy number status with poor prognosis, the authors focused on this gene.

ADNP is a Homeobox transcription regulator which includes nine zinc-fingers essential in chromatin remodeling, microtubule/autophagy regulation, cell growth and proliferation, modulation of E2F-regulated genes and p53, SWI/SNF and PI3K/AKT signaling. ADNP has been implicated in intestinal cell growth, neurological development, autism spectrum disorders, Alzheimer's disease and cancers including sarcomas [9,10]. Gatza and colleagues demonstrated strong associations between ADNP loss and decreased expression of cell cycle genes resulting in cell cycle inhibition following ADNP silencing, as well as between ADNP overexpression and activation of these pathways in three datasets. Importantly, ADNP mRNA expression was predictive of poor overall survival.

Several questions remain unresolved. The PPS signature does not contain ADNP, and it is unclear if a pathway-based analysis would identify amplification and/or overexpression of ADNP; however, Gatza and colleagues demonstrated that ADNP mRNA expression consistently corresponds with a panel of proliferation and proliferation-associated gene expression signatures and cell cycle proteins. Furthermore, despite the strong association of ADNP expression with cell cycle alteration, effects of ADNP silencing varied among ovarian cancer cell lines: ADNP loss led to G1/S checkpoint arrest in OVCAR3 and G2/M checkpoint arrest in OVCAR5. Given that ADNP loss results in decreased expression of CDC25A which regulates CDK2/Cyclin E activity at the G1/S checkpoint and CDK1/Cyclin B activity at the G2/M checkpoint, the authors speculate that CDC25A activation in combination with other co-factors may be important in ADNP-mediated regulation of the cell cycle.

Additionally, some of the findings of the study are somewhat contradictory to the existing literature. ADNP has been suggested to act as a tumor suppressor in triple-negative breast cancer, and either tumor suppressor or oncogene in colorectal cancer. Although Gatza and colleagues show that ADNP is an oncogenic mediator of cell cycle progression in HGSC, it is certainly plausible that ADNP may have a tissue-specific or dichotomous role in carcinogenesis. It is even possible that modulating the ADNP expression level in ovarian cancer cell lines changes the functional properties of these cells simply because the ADNP gene product is involved in the cell cycle.

Nevertheless, *in silico* and *in vitro* data by Gatza and colleagues support an oncogenic role and prognostic potential of

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ADNP in HGSC. Additional studies are warranted to determine the effect of targeting ADNP in normal cell lines to determine the transformative capacity of ADNP, and to elucidate the mechanisms and context of ADNP-mediated tumor cell growth and survival in HGSC.

Declaration of Competing Interest

The author declares no conflict of interest.

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