

AADAC promotes therapeutic activity of cisplatin and imatinib against ovarian cancer cells

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Summary. Objective. To explore how AADAC functions in the malignant progression of ovarian cancer, and the effect of AADAC on drug therapeutic activity against ovarian cancer cells.

Methods. AADAC level in tumor and normal samples from TCGA-OV dataset and its survival significance were analyzed by bioinformatics methods. Signaling pathway enrichment analysis for the high- and low-AADAC patients was achieved by using GSEA software. AADAC expression in the cell lines with different treatments was evaluated via qRT-PCR. Cell proliferative ability was assessed via MTT assay Cell migratory and invasive abilities were evaluated via transwell assay. Angiogenesis assay was performed to examine the angiogenetic ability.

Results. AADAC was upregulated in ovarian cancer tissues, and patients with high expression of AADAC had favorable survival conditions compared to the low AADAC expression ones. Overexpression of AADAC inhibited the malignant progression of ovarian cancer cells. Both cisplatin and imatinib suppressed cancer cell malignant progression, while overexpressed AADAC synergistically enhanced such inhibition.

Conclusions. The study demonstrated that AADAC could somehow suppress the malignant progression of ovarian cancer, especially at the cellular level. In addition, synergic tumor-inhibitory effects between AADAC and the anti-cancer drugs were identified. All the above results proposed a novel idea and candidate biomarker for ovarian cancer therapy.

Key words: AADAC, Ovarian cancer, Cisplatin, Imatinib, Malignant progression

Introduction

The mortality of ovarian cancer ranks the highest in all gynecological malignancies (Li et al., 2019a,b). The five-year survival rate for advanced ovarian cancer cases was as low as 20% to 25% (Torre et al., 2015). In 2018, about 22,240 new cases were diagnosed with ovarian cancer in the United States and more than half of them succumbed to death (Torre et al., 2018). Although the treatment combining surgery and chemotherapy is effective for ovarian cancers to some degree, 50% of patients undergo recurrence and eventually die of this malignancy (Liao et al., 2016). Chemotherapy is crucial to treat ovarian cancer in clinical practice, however chemoresistance becomes a key obstacle for this therapy. Hence, factors involved in chemotherapy efficacy to ovarian cancer have been much considered and researched so far (Bandera et al., 2015; Kanlikilicer et al., 2018; Zuo et al., 2020). In addition, molecular targeted therapy has been widely studied and applied for years, and some targeted drugs such as bevacizumab, olaparib, and niraparib have been proven useful for treating ovarian cancer (Tomao et al., 2013; Walsh, 2018). Studies pointed out that the efficacies of chemotherapeutic and molecular targeted drugs are closely related to the expressions of certain genes (Shaw and Vanderhyden, 2007; Li et al., 2019a,b; Hao et al., 2021) in ovarian cancer, yet much about this phenomenon remains unknown.

Cisplatin and its analogues are first-line chemotherapeutic drugs for treating human ovarian cancer (Kelland, 2005; McKeage, 2005). Besides multiple anti-cancer effects, DNA damage to cancer cells is considered as the major mechanism that kills cancer cells (Ghosh, 2019). Similarly, Huang et al. (2018a,b) demonstrated that high expression of FOLR1 was conducive to an optimal outcome of cisplatin therapy in

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ovarian cancer.

Imatinib, as a tyrosine kinase inhibitor, is a commonly used targeted drug for ovarian cancer (Matei et al., 2004). This targeted drug can selectively inhibit tumor-promoting receptors (such as protein tyrosine kinase Bcr-Abl, platelet-derived growth factor receptors, KIT) blocking the signaling pathways involving in tumor aggressive phenotypes (Peng et al., 2005). As imatinib resistance is prevalently concerned when applying targeted drugs (Chen et al., 2005; Volpe et al., 2009; La Rosée and Deininger, 2010), seeking the involved genes and signaling pathways is urgently needed. For example, a latest study presented that TCF7 was a crucial factor in the formation of imatinib resistance in chronic myeloid leukemia (Zhang et al., 2021). By combining bioinformatics methods and regular cell function experiments, the authors of this study observed overexpression of TCF7 and much activated wnt/ β catenin/TCF7/ABC signaling pathway in the imatinib-resistant cells, and silencing TCF7 could enhance the sensitivity of the cancer cells to imatinib. As can be realized, screening the genes affecting drug sensitivity is an important point for cancer therapeutic strategy.

Serine hydrolase arylacetamide deacetylase (AADAC) (Jiang et al., 2017) expresses mainly in human intestine and liver, and accounts for hydrolyzing acetyl drugs like flutamide (Watanabe et al., 2009), phenacetin (Watanabe et al., 2010), rifampicin (Nakajima et al., 2011), prasugrel (Kurokawa et al., 2016), ketoconazole (Fukami et al., 2016) and indiplo (Shimizu et al., 2014). In previous studies, Watanabe et al. (2010) stated that AADAC is a major enzyme in hydrolyzing phenacetin, which was also identified from the phenomenon of reducing drug hydrolysis in the presence of tryptophan, an inhibitor of AADAC enzyme. AADAC is also associated with kidney failure and hepatotoxicity in some patients taking flutamide or phenacetin (Fukami and Yokoi, 2012). In addition, the average AADAC activity of smokers is significantly higher than that of non-smokers (Gabriele et al., 2019), which may be crucial to guiding the management of some cancers. Lots of work showed that AADAC was a vital regulator in development of cancer, and most present reports on the role of AADAC are related with digestive system tumors, and AADAC is considered as a potential biomarker gene. Liu et al. (2018) applied bioinformatics methods finding that AADAC expression level positively correlates with the overall survival (OS) status of gastric cancer patients. The researchers also suggested that AADAC could be a promising biomarker for the prognosis of gastric cancer patients. Yet, the involvement of AADAC in ovarian cancer remains unclear, for which we were planning to explore the effects of AADAC on ovarian cancer cell phenotypes and cancer drug efficacy.

In summary, this study aimed to clarify the effects of AADAC on the malignant progression of ovarian cancer cells as well as on the response of cisplatin and imatinib

in ovarian cancer cells. Our findings provided theoretical supports on developing biomarkers for cancer drug application.

Materials and methods

Bioinformatics analysis

Ovarian cancer related data (expression and clinical data) was assessed from TCGA database (<https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga>). By utilizing R package “survival”, overall and disease-free survival were analyzed on the basis of the downloaded TCGA data (Kumar et al., 2020). GSEA software was introduced to screen AADAC-involved significantly changed signaling pathways (Mootha et al., 2003). Briefly, for GSEA analysis, the patients were classified into the high- and low- AADAC expression groups according to the median of AADAC expression. Subsequently, the enrichment result of VEGF related signaling pathway could be calculated between the above two groups.

Cell culture

Human ovarian cancer cell lines HeyA8 (ZKCC-X2970) and OVCA420 (ZKCC-X2064) were obtained from Binsui Biotechnology Co., Ltd (Shanghai, China). Both cell lines were cultivated in Dulbecco's Modified Eagle's Medium (DMEM) (BNCC351841, BeNa Culture Collection, Shanghai, China) with 10% fetal bovine serum (FBS) in an incubator with 5% CO₂ at 37°C.

Cell transfection

pcDNA3.1-based AADAC overexpression plasmid (oe-AADAC) and the negative control (oe-NC) were purchased from RiboBio (Guangzhou, China). The two vectors were transfected into human ovarian cancer cell lines OVCA420 and HeyA8 by Lipofectamine 2000 kit (Invitrogen, Carlsbad, CA, USA). Cisplatin (5 μ M) (Abcam, Shanghai, China) and imatinib (10-15 μ M) (Cell Signaling Technology, Shanghai, China) were used to treat the transfected cells for 24 h. Then the cells were harvested for the subsequent experiments.

Real-time fluorescence quantitative PCR detection (qRT-PCR)

Total RNA isolation from the treated cells was conducted by TRIzol reagent (Life Technologies, Grand Island, NY, USA), followed by the determination of RNA concentration through NanoDrop 2000 system (Thermo Fisher Scientific, Inc., Waltham, MA, USA). The mRNA was transcribed into cDNA by PrimeScript RT Master Mix (Takara, P.R. China). qRT-PCR was performed on Applied Biosystems® 7500 Real-Time

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PCR Systems (Thermo Fisher Scientific, Waltham, MA) with SYBR[®] Premix Ex Taq TM II (Takara Bio Inc., Japan) to determine the mRNA level of AADAC. GAPDH was the internal reference for AADAC mRNA. Primer sequences are as follows: AADAC: F, 5'-TGCAGGAGGGAATTTAGCTG-3', R, 5'-TGACATC TGGGTCATCAAGG-3'; GAPDH: F, 5'-TGACTTCA ACAGCGACACCCA-3', R, 5'-CACCTGTGTC GTAGCCAAA-3'. By using the $2^{-\Delta\Delta C_t}$ method, the difference in the relative level of AADAC mRNA was compared between the control and experimental groups. Each experiment was performed three times.

Western blot assay

Western blot assay was performed as previously described (Wang et al, 2020). Antibodies included AADAC (Gene ID: 13) (Cat#: F49883, NSJ Bioreagents, USA), VEGFA (Gene ID: 7422) (Cat#: MA5-13182, Thermo Fisher Scientific, USA), β -actin (Cat#: ab115777, Abcam, UK), and IgG (Cat#: ab124055, Abcam, UK).

MTT assay

When cells reached 80% confluency, they were subjected to two washes with PBS, followed by cell digestion with 0.25% trypsin to produce single-cell suspension. Then, this suspension was introduced to a 96-well plate at $(3-6)\times 10^3$ cells/well with a volume of 0.2 ml/well. Six repetitions were performed for each group, and the cells were cultured for 24, 48, 72, and 96h. A fresh medium of 10% MTT solution (5 g/L) (GD-Y1317, Guduo Biotechnology, China) was the substitute for the previous medium for another 4h cell culture. After decanting the supernatant, 100 μ L dimethyl

sulfoxide (DMSO; D5879-100 ml, Sigma, USA) was introduced. The mixture was shaken softly for 10 min to dissolve the formazan crystals. Finally, the optical density was measured by a microplate reader at 490 nm (Nanjing DetieLab Experimental Equipment, China). As the mixture was performed at the maximum light absorption of 490 nm, we measured the OD values at this wavelength of the mixture to examine cell proliferative abilities. The stronger proliferation ability the cells performed, the higher OD value could be detected by a microplate reader at 490 nm. 3 repetitions were performed in each experiment.

Cell migration assay

Migration assay was performed within a 24-well transwell chamber (8 μ m pore diameter, BD Biosciences, USA). The upper side was introduced with roughly 2×10^4 cells per well. DMEM (Beijing Zhongke Quality Inspection Biotechnology, China) containing 5% FBS (Thermo Fisher Scientific, USA) was filled into the bottom side. After 48h incubation at 37°C in a humidity cell incubator, cells that did not pass through the membrane were removed with a cotton swab, and cells which passed to the bottom side were dyed using 0.1% crystal violet. The successfully migrated cells were counted, and the migratory ability was presented by normalizing the cell numbers. 3 repetitions were performed in each experiment.

Cell invasion assay

Invasion assay was performed within a 24-well transwell chamber (8 μ m pore diameter, BD Biosciences). The upper side, where Matrigel was coated, was introduced roughly with 2×10^5 cells. DMEM with

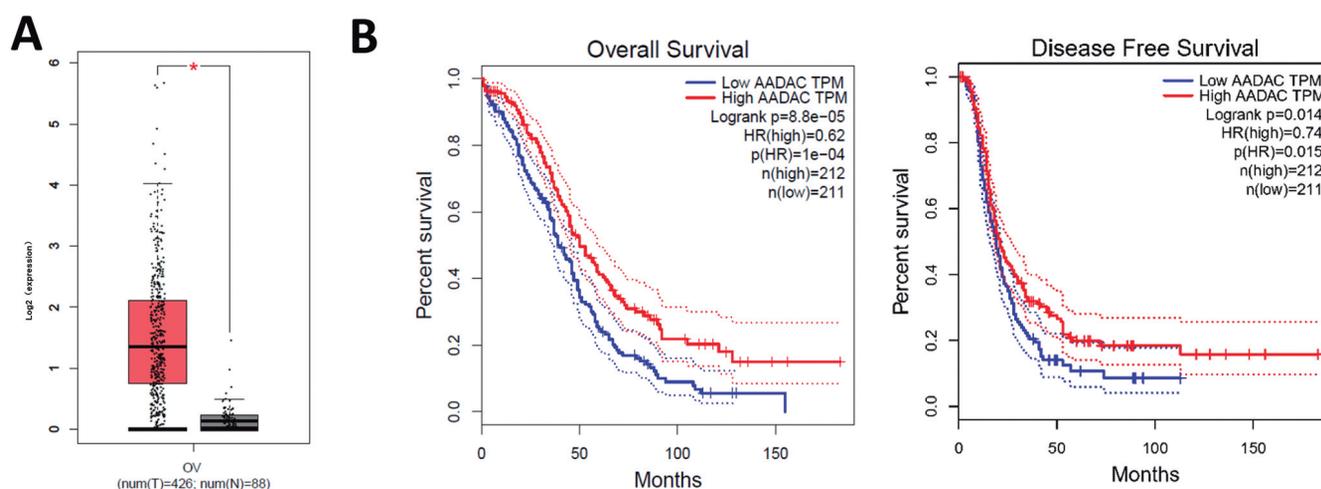


Fig. 1. Expression of AADAC in different tissue samples of ovarian cancer and its correlation with prognosis. **A.** Boxplot of AADAC expression in both normal (black) and ovarian cancer samples (red). **B.** Survival analysis between the patients with high AADAC level (red) and low AADAC level (blue). * $p<0.05$.

10% FBS (Thermo Fisher, USA) was applied to the lower chamber. After 48h of incubation at 37°C, cells that stayed at the original side of the membrane were removed with a cotton swab, and those passing through the membrane were dyed by introducing 0.1% crystal violet. The experiment was performed 3 times.

Angiogenesis assay

The angiogenesis of HUVECs was evaluated by adopting Matrigel. Pre-chilled 96-well plates were coated with 100 μ L Matrigel (BD Biosciences, USA) per well and cultured for polymerization at 37°C for 30 min. HUVECs were introduced to the culture medium which were then seeded on the polymerized Matrigel surface at a density of 4×10^5 cells/mL for 6h culture at 37°C. Three random areas were photographed. The number of vascular nodes was measured by ImageJ software. The specific operation steps refer to a previous article (Tang

et al., 2019).

Statistical analysis

Data of the study were processed using GraphPad Prism 6.0 (La Jolla, CA). The results are presented as mean \pm standard deviation, and the comparison between two groups was performed by using t-test.

Results

AADAC is upregulated in ovarian cancer tissue and is associated with patients' survival status

AADAC expression between ovarian cancer and normal samples was analyzed based on TCGA database, indicating that AADAC was upregulated in ovarian cancer (Fig. 1A). Also, by using bioinformatics methods, survival analysis was introduced, where the analysis

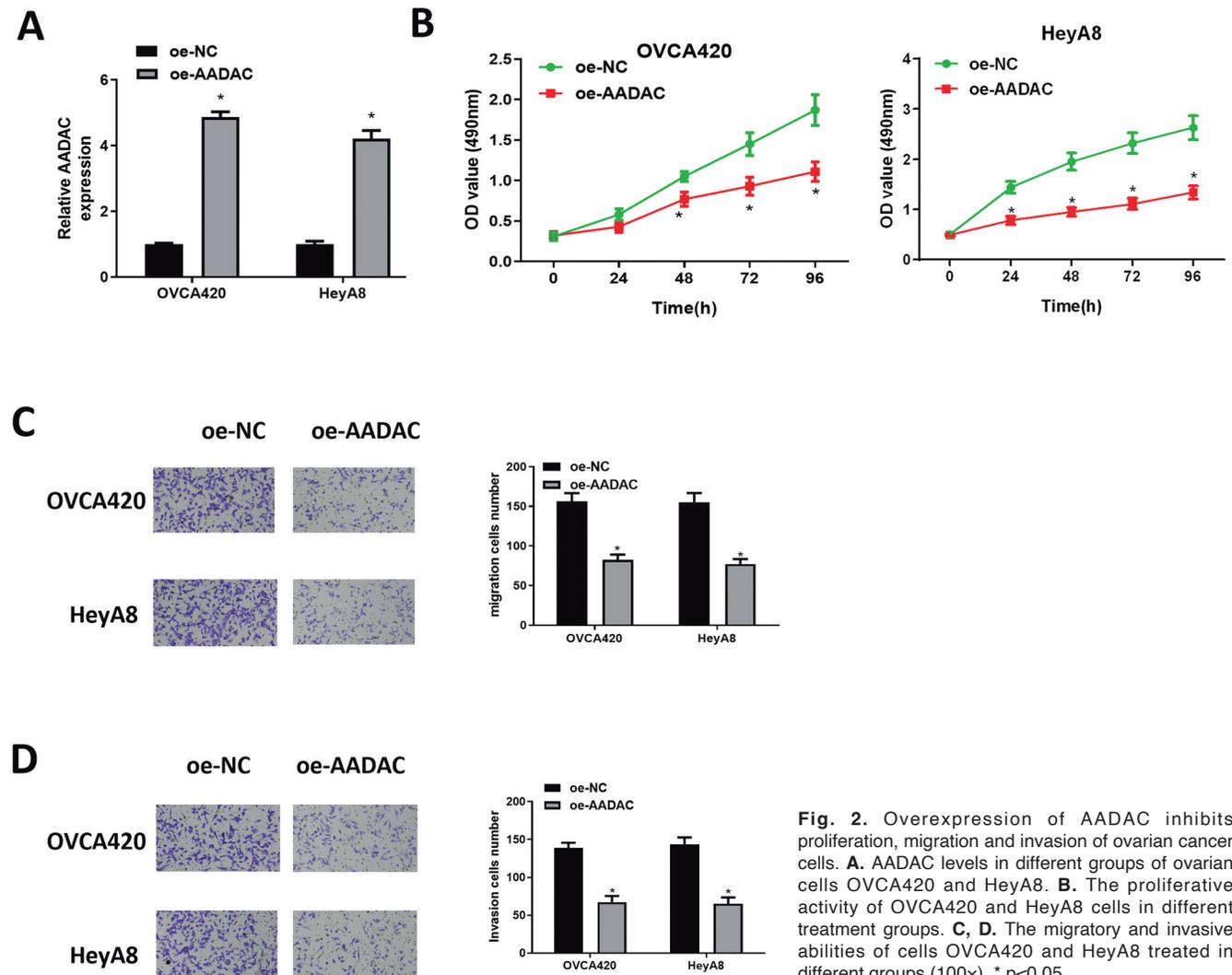


Fig. 2. Overexpression of AADAC inhibits proliferation, migration and invasion of ovarian cancer cells. **A.** AADAC levels in different groups of ovarian cells OVCA420 and HeyA8. **B.** The proliferative activity of OVCA420 and HeyA8 cells in different treatment groups. **C, D.** The migratory and invasive abilities of cells OVCA420 and HeyA8 treated in different groups (100 \times). * $p < 0.05$.

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illustrated that poor prognosis conditions were presented in the patients with low AADAC expression (Fig. 1B). Based on the results above, we assumed that AADAC, upregulated in ovarian cancer, may serve as a protecting

factor. To validate the hypothesis, two ovarian cancer cell lines (OVCA420 and HeyA8) were selected to study the effects of AADAC on the malignant progression of ovarian cancer cells.

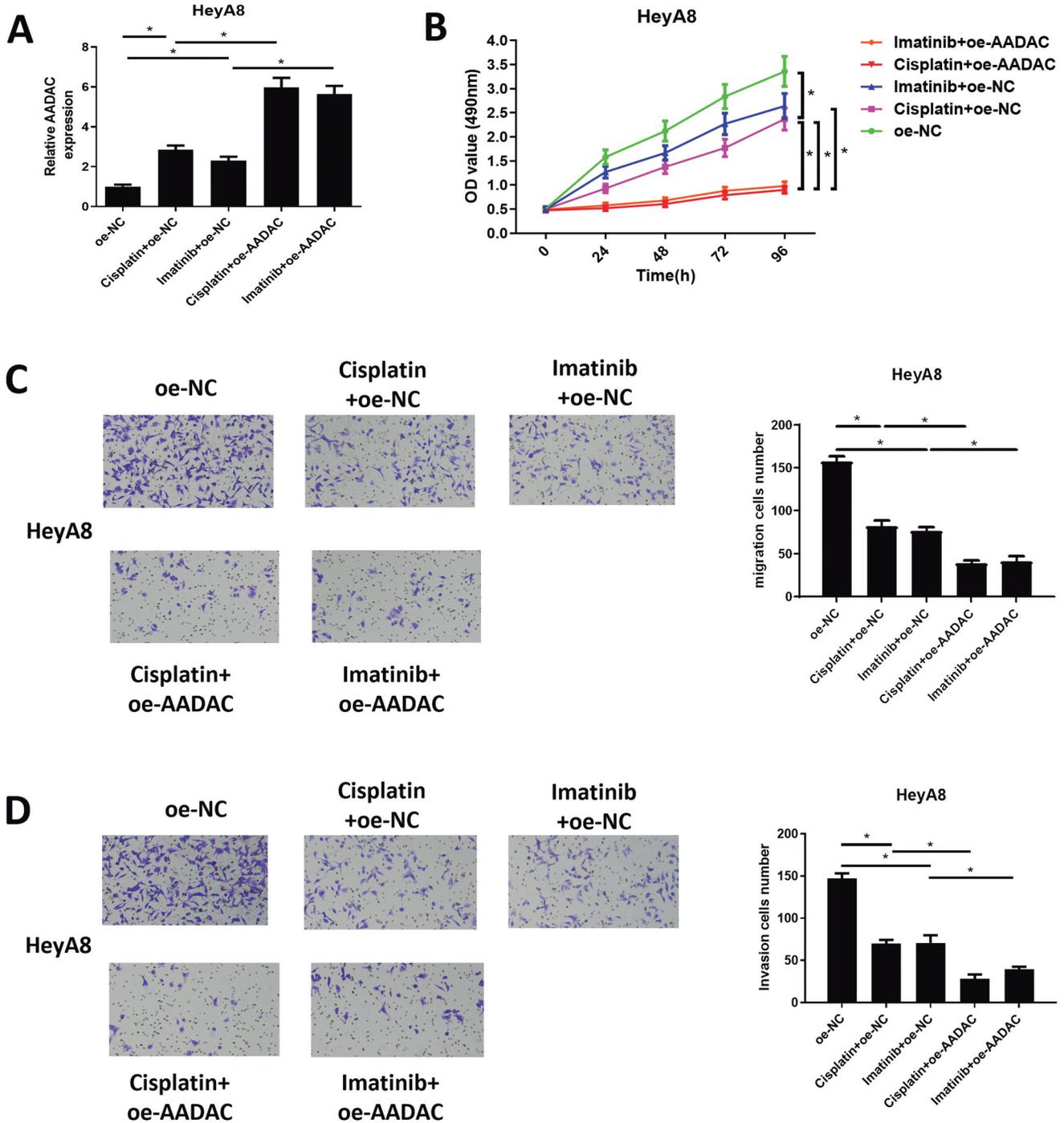


Fig. 3. AADAC synergistically enhances the inhibitory effects of cisplatin and imatinib on the proliferation, migration, and invasion of ovarian cancer cells. **A**. AADAC levels in ovarian cancer cells HeyA8 treated with cisplatin, imatinib, and overexpressed AADAC. **B**. The proliferative activity of HeyA8 cells treated with cisplatin, imatinib and overexpressed AADAC. **C**, **D**. The migratory and invasive abilities of HeyA8 cells in different treatment groups, x 100. * p<0.05.

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Overexpression of AADAC inhibits proliferation, migration, and invasion of ovarian cancer cells

We constructed AADAC overexpression cell line models based on OVCA420 and HeyA8 to investigate the biological function of AADAC in ovarian cancer.

The expression of AADAC in different groups detected by qRT-PCR was significantly up-regulated after the overexpression (Fig. 2A). Using MTT assay, the proliferative ability of ovarian cancer cells was observed to be remarkably inhibited in the overexpression group (Fig. 2B). Similarly, transwell assay revealed that

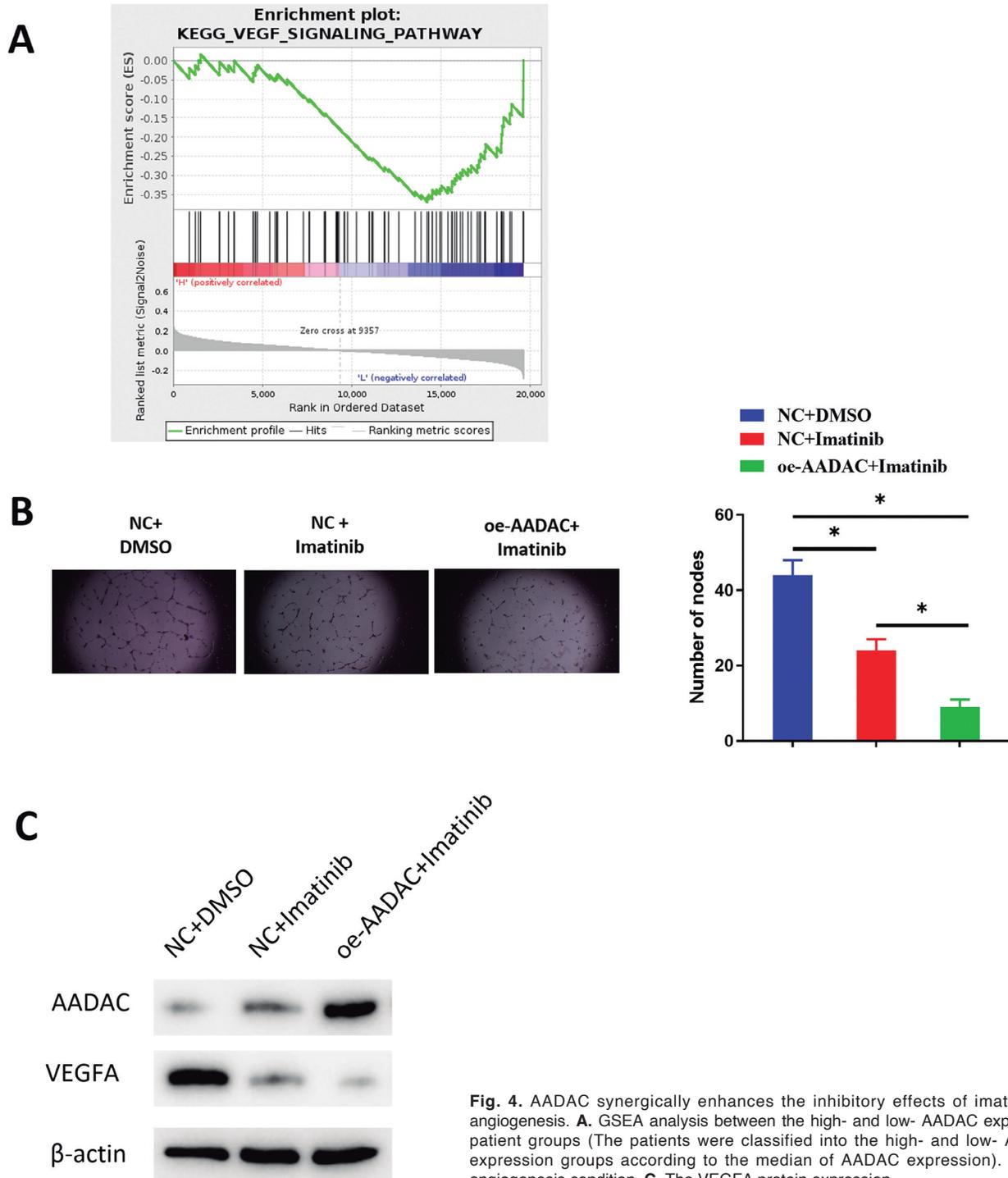


Fig. 4. AADAC synergically enhances the inhibitory effects of imatinib on angiogenesis. **A.** GSEA analysis between the high- and low- AADAC expression patient groups (The patients were classified into the high- and low- AADAC expression groups according to the median of AADAC expression). **B.** The angiogenesis condition. **C.** The VEGFA protein expression.

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overexpression of AADAC could notably hinder the migratory and invasive abilities of ovarian cancer cells (Fig. 2C,D). Collectively, it was indicated that overexpressing AADAC can exert tumor suppressing effects on ovarian cancer.

AADAC enhances the inhibiting effect of cisplatin and imatinib on the malignant progression of ovarian cancer cells

To verify whether AADAC expression could affect cisplatin and imatinib efficacy in ovarian cancer, we constructed 5 differently treated cell line models and conducted cell function experiments. We constructed the normal cell lines treated with cisplatin or imatinib (cisplatin+oe-NC and imatinib+oe-NC), and also constructed the AADAC overexpressed cell lines treated with cisplatin or imatinib (cisplatin+oe-AADAC and imatinib+oe-AADAC). The expression level of AADAC in different groups was tested by qRT-PCR. The results exhibited that AADAC was significantly up-regulated after cisplatin or imatinib was applied, and AADAC was much more upregulated in the cells co-treated with oe-AADAC and both drugs (Fig. 3A). Cell functional experiments were further implemented. From the MTT result, the proliferative ability of cells treated with cisplatin or imatinib was significantly decreased, while the reduction was greater under overexpressed AADAC (Fig. 3B). After that, the migratory and invasive abilities of different groups were detected via transwell assay. It was presented that there was a significant reduction in cell migration and invasion when cisplatin or imatinib exist, while these abilities were inhibited more greatly when AADAC was overexpressed (Fig. 3C,D). It can be concluded that there is a kind of synergy between the two anti-cancer drugs and AADAC expression.

AADAC suppresses angiogenesis in ovarian cancer synergistically with the treatment of imatinib

Previous research illustrated that the tumor-associated signaling pathways can be affected by the dysregulation of the gene expressions and imatinib response (Huang et al., 2018a,b). To investigate the potentially involved signaling pathways by the co-treatment of AADAC overexpression and the anti-cancer drugs, GSEA analysis was introduced. Through the GSEA analysis, it was understood that VEGFA related signaling pathway can be affected by the change of AADAC expression (NES=-1.490) (Fig. 4A). Also, imatinib was reported to affect VEGFA expression and angiogenesis (Raimondi et al., 2014), therefore we conducted angiogenesis and western blot assays to investigate the synergistic effect between AADAC expression and imatinib on VEGFA-dependent angiogenesis. Angiogenesis was significantly inhibited by imatinib treatment, and the inhibition was strengthened by overexpressing AADAC simultaneously (Fig. 4B). A similar trend was observed in the western

blot assay. VEGFA protein expression was inhibited to the most significant degree in the co-treated group (Fig. 4C). Concludingly, AADAC expression and imatinib are able to synergistically promote VEGFA-dependent angiogenesis.

Discussion

Though 80% of ovarian cancer patients have excellent response to first-line chemotherapy known as cell reduction and platinum chemotherapy, over 70% of the patients at advanced stage will relapse and develop resistance within five years (Kim et al., 2017). Therefore, more effective treatment strategies, especially reliable diagnosis, and the discovery as well as application of prognostic markers for ovarian cancer, are required to improve the survival rate and reduce the recurrence probability of ovarian cancer patients. We found that AADAC was upregulated in tumor tissue of ovarian cancer patients through bioinformatics analysis. Meanwhile, the OS and DFS rates of patients with upregulated AADAC were higher than those with low AADAC level. Therefore, we speculated that the elevated expression of AADAC could be a stress response induced by the tumor progression.

This study discovered that overexpression of AADAC in ovarian cancer can inhibit the malignant phenotypes of cancer cells. AADAC, a serine hydrolytic enzyme, mainly exists in human liver microsomes and plays a crucial part in hydrolyzing various drugs and allogenic substances (Ross and Crow, 2007; Tiwari et al., 2007). Several studies have reported the potential roles of AADAC in cancers so far, however, most of them are limited to bioinformatics prediction (Liu, 2018; Wu et al., 2020; Feng and He, 2022). Our study firstly reported the tumor suppressing role of AADAC in the ovarian cancer cell experiment.

This study also explored the synergic effects of AADAC expression and anti-cancer drugs (cisplatin and imatinib) on ovarian cancer progression. Simultaneous treatment of AADAC overexpression and drug treatment are found to perform the most significant tumor-suppressing effects. Though the underlying molecular mechanisms remain unclear yet, we did observe the synergic effects on suppressing angiogenesis in the co-treatment group of AADAC upregulation and imatinib. Claudio Raimondi previously reported the angiogenetic inhibiting role of Imatinib in endothelial cells, where neuropilin 1 was identified as the target of imatinib and the upstream activator of the VEGFA-dependent angiogenesis pathway (Raimondi, 2014). Similarly, some studies illustrated cisplatin induced VEGFA alteration. For example, Monique C.A. Duydam's team pointed out that HIF-1 could be inhibited by cisplatin in ovarian cancer cells, causing a subsequent downregulation of VEGFA (Duydam et al., 2007). Given that, we further clarified that AADAC upregulation could strengthen the effects of anti-VEGF with imatinib synergically. Based on the current

phenotype research, the underlying molecular mechanisms of the synergic effects could be investigated in further work. Collectively, the anti-cancer drugs (imatinib and cisplatin) may work more effectively for the ovarian tumor patients with high AADAC expression, indicating a potential capacity of AADAC as a biomarker for ovarian cancer therapy.

In summary, this study demonstrated that AADAC inhibited the cellular functions in ovarian cancer. This result provides a deeper understanding of AADAC functions in ovarian cancer and a guidance for further research on diagnostic and prognostic biomarkers, which is also helpful to promote targeted therapy for ovarian cancer. Moreover, AADAC was exhibited to enhance the inhibiting effect of cisplatin and imatinib on cellular functions in ovarian cancer. Also, the synergically inhibiting effects of AADAC and imatinib on angiogenesis were verified in our research. The above-mentioned findings collectively demonstrate the potential of AADAC as a prognostic marker in clinical drug therapy of ovarian cancer, which has guiding significance in the development of biological drugs and their application in the clinic.

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Consent for publication. All authors consent to submit the manuscript for publication.

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Conflict of Interest Statement. The authors declare that they have no potential conflicts of interest.

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Authors' contributions. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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