ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

Downregulation of MGAT3 Promotes Benzo[*a*]pyrene-Mediated Lung Carcinogenesis by Regulating Cell Invasion and Migration Activity

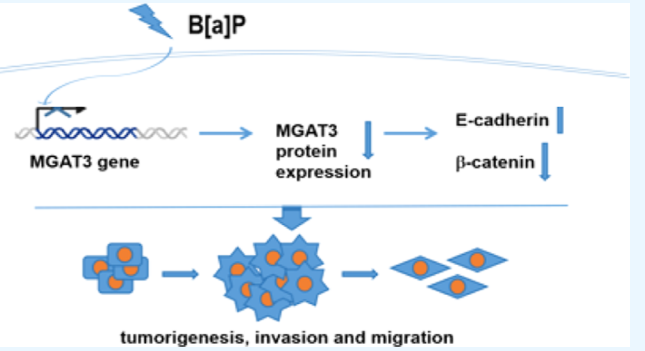
Su Zhang, Xia-Yan Zhang, Xiao-Chun Zheng, Xiao-Lan Ye, Ping Huang, Wen-tong Liu, and Hong-juan Jiang*

Cite This: *ACS Omega* 2025, 10, 17404−17415

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Environmental chemical carcinogens are major factors in the induction of lung cancer, with benzo[*a*]pyrene (B[*a*]P) being one of the most widespread and highly carcinogenic among them. Although studies have reported that B[*a*]P exerts its carcinogenic effects by causing mutations, inducing cytotoxicity, and inhibiting DNA synthesis, the early molecular regulatory events and mechanisms involved in B[*a*]P-induced tumor initiation remain unclear. This study found that the MGAT3 gene was significantly downregulated in B[*a*]P-induced mouse lung tumorigenesis, suggesting its important tumor-suppressive function. Further investigation revealed that suppression of MGAT3 expression promoted the invasion and migration abilities of lung cancer cells, while overexpression of MGAT3 in these cells inhibited these effects. Western blot analysis also showed that MGAT3 regulated the expression of epithelial-mesenchymal transition markers, thereby affecting the motility of lung cancer cells. Xenograft assay also confirmed the inhibitory effect of MGAT3 overexpression on tumor proliferation. Analysis of lung cancer tissue expression further validated that MGAT3 is significantly downregulated in lung cancer tissues, and this decrease in expression is associated with a poor prognosis in lung cancer patients. Our research indicates that the suppression of MGAT3 expression and its downstream regulatory molecules plays a crucial role in lung cancer development induced by environmental chemical carcinogens.



INTRODUCTION

Lung cancer, one of the most noteworthy causes of cancer-related mortality globally, represents a significant health burden that continues to escalate despite advances in medical research and treatment modalities.[1,2] Despite significant advances in early detection and therapies, the poor prognosis of lung cancer patients still persists, highlighting the necessity for a more comprehensive understanding of the molecular mechanisms underlying the initiation and progression. Among various environmental carcinogens, polycyclic aromatic hydrocarbons (PAHs) have garnered substantial attention due to their ubiquitous presence and well-documented carcinogenic potential.[3,4] PAHs are particularly noteworthy due to their prevalence in tobacco smoke and environmental pollution.[3,4] These compounds have been extensively studied for their carcinogenic properties, yet the precise molecular pathways through which they contribute to lung cancer development remain a focal point of ongoing research.

Benzo[*a*]pyrene (B[*a*]P), a well-studied PAH, is classified as a group 1 human carcinogen by the International Agency for Research on Cancer. It is widely found in industrial waste gas, motor vehicle exhaust, soot, tar, cigarette smoke, household exhaust smoke, and other outdoor and indoor pollutants. It can directly lead to skin cancer, gastric cancer, digestive tract cancer, and other epithelial tissue malignancies, particularly lung cancer.[5,6] B[*a*]P plays an important role in both initiating and promoting lung tumorigenesis.[6,7] It undergoes metabolic activation in the body, leading to the formation of highly reactive intermediates capable of forming DNA adducts.[6,7] The metabolic activation of B[*a*]P by cytochrome P450 enzymes converts it to its ultimate carcinogenic form, benzo[*a*]pyrene diol epoxide (BPDE). BPDE is notorious for its ability to form covalent bonds with DNA, leading to bulky adducts that interfere with DNA replication and repair processes.[8,9] The persistence of these adducts can result in mutations, particularly in genes that regulate cell proliferation and

Received: November 24, 2024
Revised: April 13, 2025
Accepted: April 17, 2025
Published: April 23, 2025

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415

division, such as the tumor suppressor gene TP53 and the oncogene KRAS.[10,11]

In the early stages of lung cancer progression, B[*a*]P plays a critical role in the malignant transformation of lung epithelial cells.[12] This process is driven by the deregulation of gene expression including both oncogenes and tumor suppressor genes. For example, B[*a*]P-mediated gene mutations of TP53 can induce the loss of its tumor-suppressive functions, such as cell cycle regulation, DNA repair, and apoptosis, thereby enabling the uncontrolled proliferation of cells with damaged DNA.[9] Additionally, B[*a*]P has been shown to upregulate the expression of oncogenes such as KRAS, which promotes cancer cell proliferation and survival by the activation of its downstream signal pathways like MAPK/ERK and PI3K/AKT.[11,13] B[*a*]P has also been implicated in the promotion of malignant phenotypes such as enhanced proliferation, angiogenesis, and metastasis. These effects are mediated by various cellular signaling pathways, including NF-κB, STAT3, and HIF-1α.[14−16] Moreover, chronic exposure to B[*a*]P can lead to a pro-inflammatory microenvironment, further facilitating tumor progression and resistance to therapy.[16,17] Although these findings enhance our understanding of B[*a*]P-induced carcinogenesis, pinpointing the molecular dysregulation underlying lung tumorigenesis and discovering novel therapeutic targets remain formidable challenges.

Recent research has prominently underscored the pivotal role of glycosylation enzymes, particularly β-1,4-*N*-acetylglucosaminyltransferase III (MGAT3), in the progression of various cancers.[18−22] MGAT3 is involved in the modification of *N*-glycans, a process that can influence various cellular functions including cell adhesion, migration, and signal transduction. Emerging evidence suggests that MGAT3 functions as a tumor suppressor gene, and its expression is often downregulated in various cancers, including lung cancer.[20,23−25] The loss of MGAT3 expression has been associated with enhanced tumor growth, metastasis, and resistance to chemotherapy.[20,21] In the context of chemical carcinogenesis, including PAH-induced lung cancer, MGAT3 may play a critical role in counteracting the oncogenic effects of these compounds by maintaining proper glycosylation patterns that suppress malignant transformation.[26] Understanding the interplay between PAH exposure and MGAT3 expression could yield valuable insights into the mechanisms underlying lung cancer progression, potentially revealing new targets for therapeutic intervention.

Our study revealed a significant reduction in MGAT3 gene expression in lung tumorigenesis following B[*a*]P exposure in AJ mice, A similar trend was observed in the context of microRNA expression changes. Furthermore, the suppression of MGAT3 expression has been shown to promote the migration of lung cancer cells and to increase the expression of markers associated with the epithelial-mesenchymal transition (EMT). This study suggests a potential role for MGAT3 inhibition in lung tumorigenesis, specifically through modulation of cellular invasion and metastasis in response to environmental carcinogen exposure.

MATERIALS AND METHODS

Cell Lines. BEAS-2B and HBE, human bronchial normal epithelium cell line, and lung cancer cells H1975, A549, CALU6, HCC2279, HCC827, H1299, H1651, H226, H460, and H520 were purchased from the Cell Bank of the Chinese Academy of Science (Xiangya and Shangai, China). The authenticity of the cell lines in our study had been verified by DNA sequencing using an Applied Biosystems AmpF/STR Identifier kit. Cells were cultured in RPMI 1640 (Gibco, Grand Island, NY, USA.) supplemented with 10% fetal bovine serum (Gibco), streptomycin (100 g/mL), and penicillin (100 U/mL) at 37 °C and 5% CO_2.

Animal Studies. Female A/J mice 4 weeks of age (Model Animal Research Center, Nanjing, China and SLAC Laboratory Animal, Shanghai, China) were used in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals. A/J female mice were randomly divided into two groups (12/group): one for B[*a*]P treatment and the other used as a control. Mice were exposed to B[*a*]P (25 mg/kg, dissolved in tricaprylin solvent) via intraperitoneal injection. The intraperitoneal injection was repeated weekly for 8 weeks. Then A/J mice were sequentially raised for 4 months. Control groups received tricaprylin solvent of the same amount.[12]

Balb/c nude mice (4 weeks) were subcutaneously injected with 5×10^6 lung cancer cells with stable overexpressed MGAT3 or negative control. The tumor size was measured every 5 days. After 25 days, the mice were sacrificed and the tumor tissues were obtained and weighed. The volume (V) of the tumors was calculated using the formula $V = 1/2 \times a \times b^2$. The protocol of animal experiments has been reviewed and approved by the Laboratory Animal Management and Ethics Committee of Zhejiang Provincial People's Hospital (No. 20240403142656742501). The two-tailed Student's *t*-test was used for statistical data analysis; $p < 0.05$ were considered to be statistically significant.

Immunoblot Analysis. Cell lysates were collected and separated using 10% SDS-PAGE gels. Subsequently, they were transferred onto a nitrocellulose membrane (Whatman, Maidstone, UK). Following the transfer, the membrane was blocked with 5% skim milk solution for 1 h and incubated with the primary antibody at 4 °C overnight. IRDye 800CW- or IRDye 680-conjugated secondary antibodies (LI-COR Biosciences, Lincoln, NE, USA No. 925-32221) were used to incubate the membrane for detecting by an Odyssey infrared imaging system. Primary antibodies E-cadherin (ab40772), β-catenin (ab223075), and glyceraldehyde-3-phosphate dehydrogenase (GADPH) (ab8245) were purchased from Abcam.

RT-PCR Analysis. The lung cancer cells and tumor-normal samples were collected and lysated for extracting total RNA with TRIzol reagent (Invitrogen No. 15596026). Total RNA was reverse transcribed by the Prime-Script RT reagent Kit (TaKaRa No. RR037A). QRT-PCR was performed for RNA expression and carried out with a SYBR Premix Ex Taq instrument (TaKaRa No. RR820A). Experimental results were repeated in triplicate, and values were normalized to GAPDH using the $2(-\Delta\Delta Ct)$ method for gene expression analysis. The primers information is listed in Table 1. One-way analysis of variance was used for statistical data analysis; $p < 0.05$ were considered to be statistically significant.

RNA-seq Analysis. Total RNA was extracted from normal, paraneoplastic, and tumor lung tissues (5 independent replicates per group) from the B[*a*]P-induced mice model, utilizing the TRIzol reagent (Invitrogen). The RNA gene expression profiling of each sample was used for RNA-seq performed by the Novogene Corporation. HT Seq v0.6.1 was used to count the read numbers mapped for each gene, and RPKM (reads per kilo bases per million reads) was calculated based on the length of the gene and reads count mapped for the genes.[12] In RNA-seq differential expression analysis, a

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415

Table 1. Primers for RT-PCR

gene name	primer sequences
NDRG2-F	5′-GGGGACAGGGATGGAAAATGG-3′
NDRG2-R	5′-CAGAGCCGTATGGTGTCTCC-3′
MGAT3-F	5′-CCACCACATTGTCCAGCAAGG-3′
MGAT3-R	5′-CGGGGGAAGGTGACATAGGA-3′
ASCL1-F	5′-TCTGATTCCGCGACTCCTTG-3′
ASCL1-R	5′-CGTTTGCAGCGCATCAGTTC-3′
GSTA3-F	5′- TCAGGAGGTGGCCTTGAGAA-3′
GSTA3-R	5′-CTGCCCCGTCCATTGAAGT-3′
FMO3-F	5′-AAGTGGCCATCATTGGAGCTG-3′
FMO3-R	5′-GTGGCAAGACCCCTCTTGTA-3′
INMT-F	5′-ATTCGCCTGTGAGCTGGAAG-3′
INMT-R	5′-ATCAAGGCTACAGCAGGCAC-3′
GAPDH-F	5′-ACATCGCTCAGACACCATG-3′
GAPDH-R	5′-TGTAGTTGAGGTCAATGAAGGG-3′

corrected q-value threshold of 0.05 and a log2 fold change threshold of 1 are commonly set to identify genes that are significantly differentially expressed thresholds for significant differential gene expression. The normal lung tissue mRNA was used as the control.

Scratch Test. Lung cancer cells were transfected with empty vector or MGAT3 constructed plasmid and plated with 90% confluence in 6-well plates. The monolayer was scratched with a sterile 10 μL pipet tip. To determine the rate of wound closure, images were taken directly after scratching (0 h) and after 24 h. ImageJ software was used to analyze the percentage of wound closure. The cells transfected with empty vector were used as negative control (NC).[12] The two-tailed Student's t-test was used for statistical data analysis; $p < 0.05$ were considered to be statistically significant.

Transwell Assay. Cell invasion assay was performed in 24-well transwell plates with 8 μm pores (Costar, Cambridge, MA, USA). Lung cancer cells (2×10^4) were added to the upper chambers with matrigel in serum-free medium after transfection with empty vector or MGAT3 constructed plasmid, whereas the complete RPMI 1640 medium was added to the lower chambers. After 48 h incubation at 37 °C, the cells invaded through the filters were stained with 0.5% crystal violet after fixing with 4% paraformaldehyde at room temperature. Finally, the filter membrane was analyzed and photographed with microscopes. The cells transfected with empty vector were used as NC.[12] The two-tailed Student's t-test was used for statistical data analysis; $p < 0.05$ were considered to be statistically significant.

RNA Interference (RNAi) and Gene Transfection. The small interfering RNA (siRNA) targeting human MGAT3 (sense strand sequence 5′-3′:GAGUCCAACUUCACGG-CUUAU; antisense strand sequence 5′-3′:AUAAGCCGU-GAAGUUGGACUC; GenePharma, Shanghai, China) were transfected into cells by Lipofectamine RNAiMAX (Invitrogen No. 13778150) according to the manufacturer's instruction. The siRNA targeting luciferase was used as a NC.

Overexpression of MGAT3 constructed plasmid and empty vector in cells was performed with X-tremeGENE HP DNA Transfection Reagent (Roche No. 04476093001) according to the manufacturer's instruction. The empty vector was used as the NC.

Patient Samples. A total of 38 nonsmall-cell lung cancer (NSCLC) clinical samples of the Zhejiang Provincial People's Hospital, Affiliated People's Hospital were used in this study. The study was approved by the ethics committee of the hospital (Approval No. 2025-005). The clinical characteristics of these samples are listed in Table S1. The cancer tissues were formalin-fixed and paraffin-embedded for immunohistochemistry (IHC).

Statistical Analysis. The two-tailed Student's t-test and one-way analysis of variance were used for statistical data analysis. Data from three independent experiments were presented as mean standard deviation (SD); $p < 0.05$ were considered to be statistically significant. * represents $p < 0.05$, **represents $p < 0.01$.

RESULT

MGAT3 is Significantly Downregulated in the Benzo[*a*]pyrene-Induced Mouse Lung Cancer Model. To investigate the key molecular events and regulatory functional genes in the early stages of B[a]P-induced lung carcinogenesis, we first established an A/J mouse model of lung cancer induced by B[a]P exposure. Figure 1a,b presents a schematic illustration of the strategy employed to induce B[a]P-mediated tumorigenesis in a mouse model. The HE stained images of lung tissues confirmed the carcinogenicity of B[a]P exposure. Tumor tissues and adjacent normal lung tissues from the treated group were collected, and solvent control lung tissues were used as controls. Key regulatory functional genes were then analyzed using RNA-seq experiments. Heatmap analysis revealed that, in comparison to the control group, the B[a]P-exposed group displayed a significant downregulation of 15 genes and upregulation of 10 genes. Interestingly, the same gene expression changes were also observed in adjacent normal lung tissues, suggesting that these abnormal gene expression changes are likely key driving factors in lung carcinogenesis and that expression changes occur early in tumorigenesis (Figure 1c). The expression changes of genes altered during B[a]P-induced lung tumorigenesis were validated through RT-PCR. The results further confirmed the changes in these genes and revealed that MGAT3 was the most significantly downregulated gene (Figure 1d).

MGAT3 is Strongly Downregulated in Both BPDE-Induced Malignant Transformed Cells and Lung Cancer Cells. It is well-known that the suppression of tumor suppressor gene expression is a critical initiating event in tumorigenesis. To gain deeper insights into the pivotal regulatory mechanisms underlying B[a]P-mediated lung carcinogenesis, we conducted a comprehensive analysis of the expression alterations in the six most prominently downregulated genes. These genes were meticulously identified via rigorous screening procedures in BPDE-exposed human lung epithelial cells undergoing malignant transformation (specifically, BPDE 0.2 and 0.5 μM) as well as in lung cancer cells. The results revealed that all six genes (NDRG2, MGAT3, ASCL1, GSTA3, FMO3, and INMT) were significantly downregulated. MGAT3 exhibited the most pronounced suppression in both BPDE-induced malignant transformed cells and lung cancer cells (Figure 2a–f). Moreover, we found that the expression of MGAT3 was downregulated after exposure to other environmental chemical carcinogens, such as N-nitroso compounds (MNNG, MNU) (Figure 2h), suggesting that MGAT3 inhibition may be a common molecular event after environmental carcinogens treatment. We also analyzed the MGAT3 expression in lung cancer tissues at the different time points during B[a]P-induced carcinogenesis (Figure 2g). The results showed that

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415

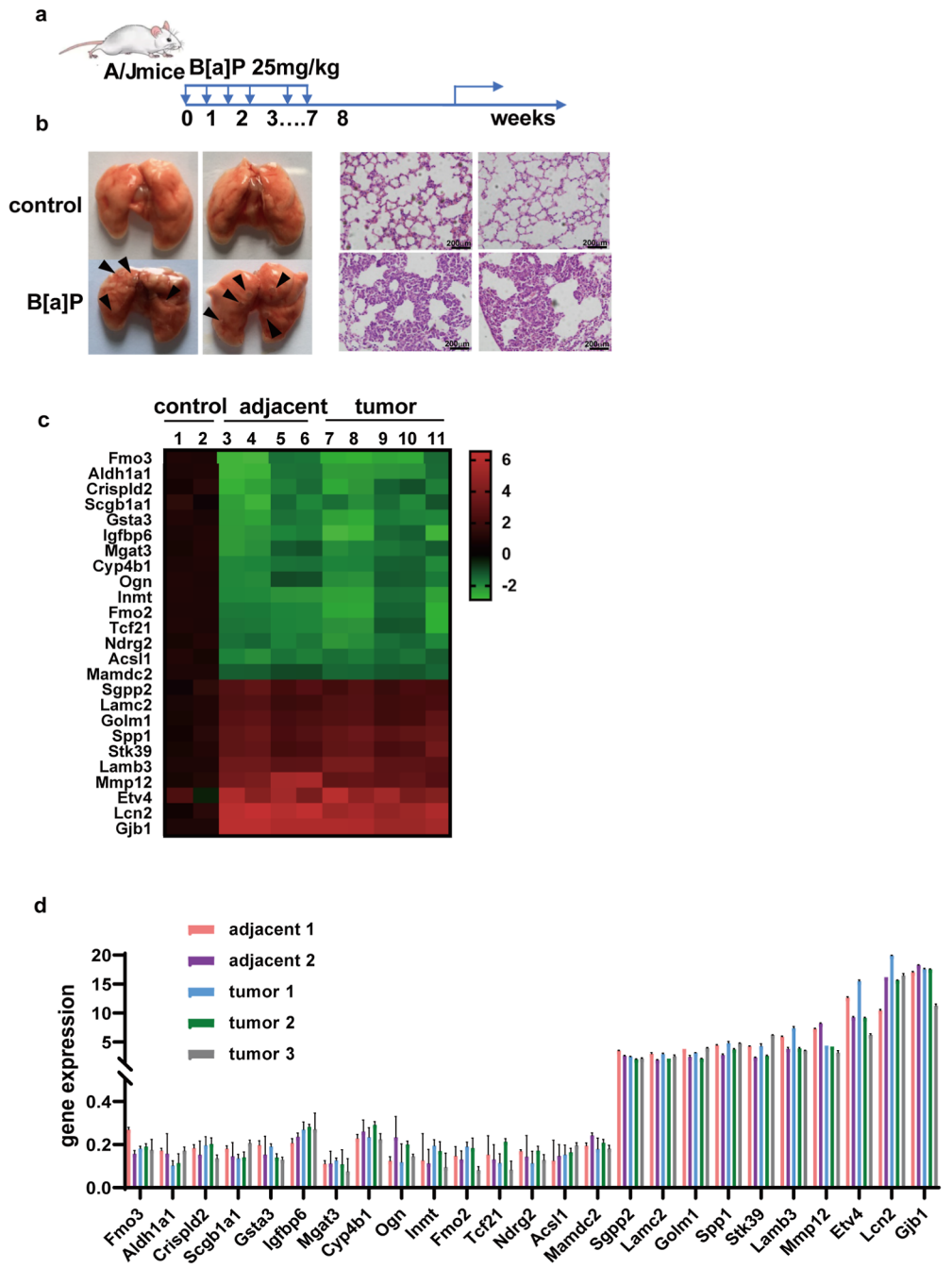


Figure 1. MGAT3 was downregulated in B[*a*]P-induced lung carcinogenesis. (a) Schematic map of B[*a*]P-induced lung carcinogenesis mice model. (b) Left, representative images of lung primary tumor in mice with or without B[*a*]P treatment; right, representative images of HE staining. (c) Heatmap of the mRNA expression of different genes by RNA-sequencing in different lung tissues from mice treated with or without carcinogens. Control: normal lung tissue samples from the mice without B[*a*]P treatment; adjacent: paraneoplastic tissue samples from the mice with B[*a*]P treatment; cancer: neoplastic tissue samples from the mice with B[*a*]P treatment. (d) Expressions of mRNA levels of different genes selected by RNA-sequencing were analyzed by RT-PCR and normalized with normal lung tissues mRNA expression in paraneoplastic and neoplastic lung tissue samples from the mice with B[*a*]P treatment. The analyses were repeated three times, and the results were expressed as mean ± SD.

MGAT3 was downregulated in the pretumor formation stage, and the reduced expression of MGAT3 persisted until tumor formation. Furthermore, the downregulation of the above six genes expression was also observed in lung cancer cells compared to the normal epithelium cells. MGAT3 was showed as the most downregulated gene (Figure 3a–f). To further validate the downregulation of MGAT3 expression in tumor cells, we analyzed the expression of MGAT3 in different tumor cells from the CCLE database (Figure 3g). The results showed that the expression of MGAT3 was downregulated in most tumor cells. RT-PCR analysis also confirmed the downregulation of the MGAT3 gene expression in lung cancer cells (Figure 3h). Our data indicate that MGAT3 may be the common molecular target of environmental chemical carcinogens and could play an important role in suppressing environmental carcinogens-induced carcinogenesis.

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415

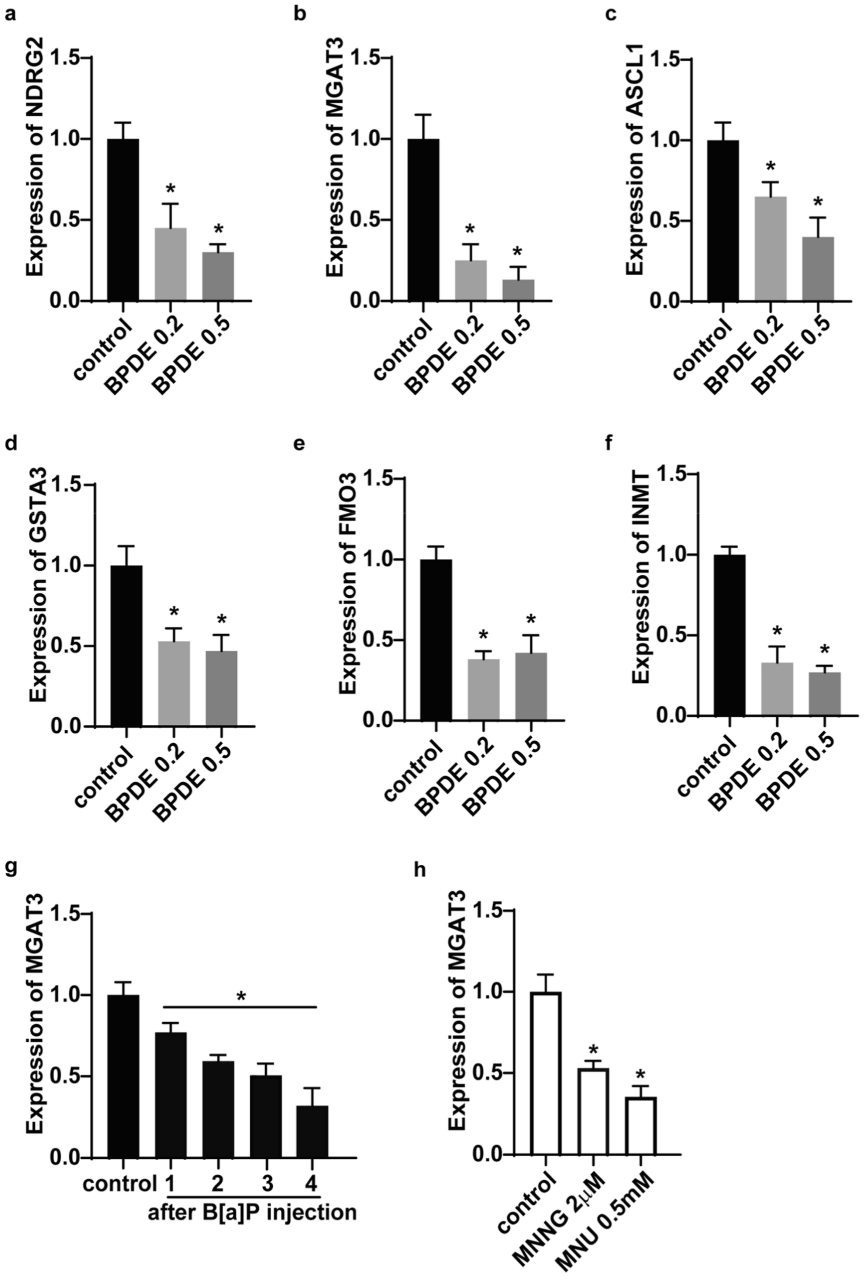


Figure 2. MGAT3 was downregulated in BPDE-induced malignant transformed lung cells. (a–f) Expressions of mRNA levels of different genes selected by RNA-sequencing were analyzed by RT-PCR in BPDE-induced malignant transformed lung cells. The cell without BPDE treatment was used as control. (g) mRNA expression of MGAT3 at the different time points during the B[*a*]P-induced carcinogenesis. Control: the sample without B[*a*]P treatment. 1,2,3,4: the samples after B[*a*]P injection for 8 weeks and raised in different months. (h) MGAT3 gene expression after chemical carcinogen *N*-nitroso compounds exposure. The analyses were repeated three times, and the results were expressed as mean ± SD $*p < 0.05$.

Overexpression of MGAT3 Inhibits the Invasion and Migration of Lung Cancer Cells. To further elucidate the tumor-suppressive function of the MGAT3 gene, we conducted wound healing and transwell assays to assess the migration and invasion abilities of lung cancer cells after the overexpression of MGAT3. The experimental results showed that overexpression of MGAT3 significantly inhibited the migration and invasion capabilities of lung cancer H1975 and A549 cells (Figure 4), suggesting that MGAT3 may participate in lung cancer development by modulating cell motility. Notably, EMT markers play a crucial role in cell invasion and migration, such as E-cadherin and *β*-catenin. We further investigated the impact of MGAT3 on the changes of EMT markers. Western blot analysis revealed a significant upregulation of E-cadherin expression and a downregulation of *β*-catenin expression in lung cancer cells upon MGAT3 overexpression. Conversely, the RNAi-mediated knockdown of MGAT3 expression suppressed E-cadherin expression and upregulated *β*-catenin expression. However, changes in MGAT3 expression exerted minimal effects on the expression of EMT markers in normal lung epithelial cells (Figure 5a). RT-PCR results also demonstrated similar expression changes (Figure 5b,c). Gene set enrichment analysis (GSEA) revealed significant alterations in a large fraction of EMT pathway

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415

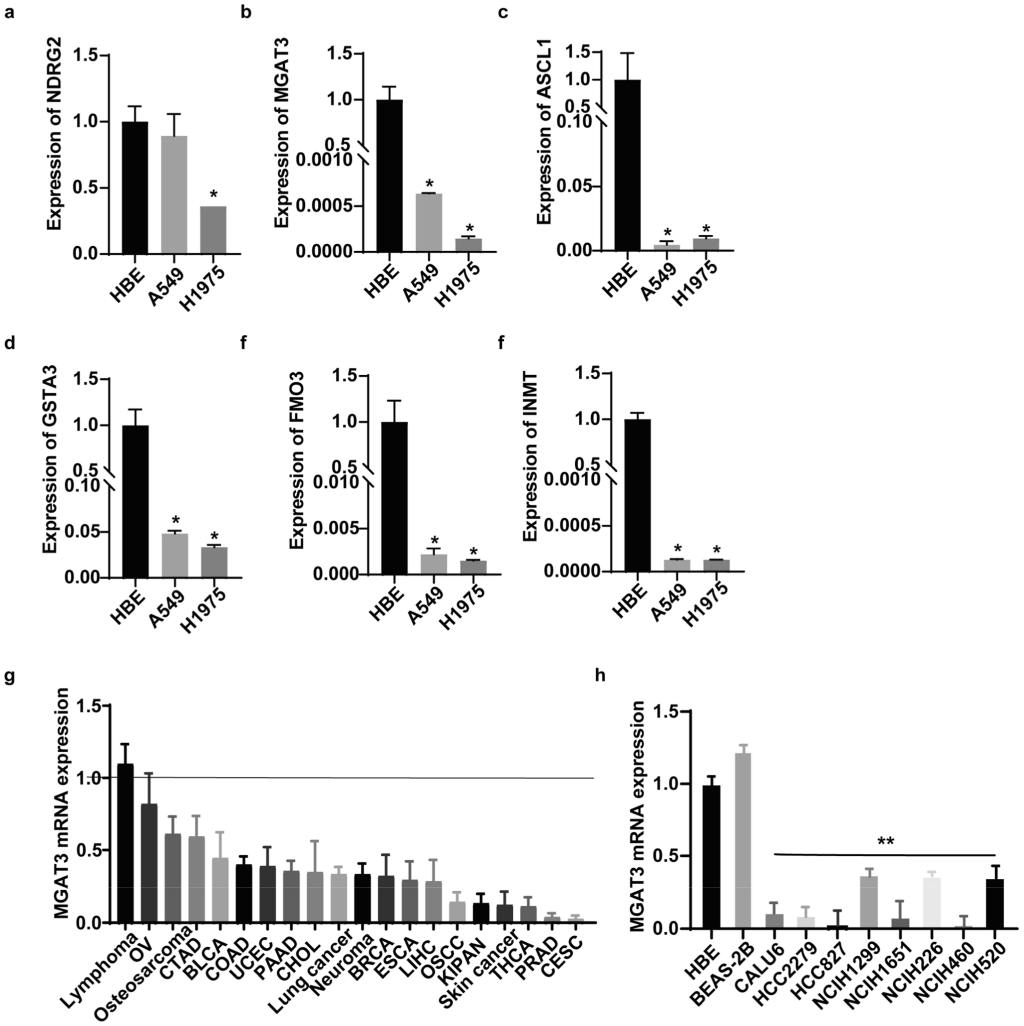


Figure 3. MGAT3 was downregulated in lung cancer cells. (a−f) Expression of mRNA levels of different genes selected by RNA-sequencing was analyzed by RT-PCR in lung cancer cells (H1975 and A549) and normal lung epithelial cells (HBE). (g) MGAT3 mRNA expression in different cancer cell lines by CCLE database. (h) Expression of mRNA of MGAT3 was analyzed by RT-PCR in different lung cancer cells. Normal lung epithelial cells HBE and BEAS-2B were used as control. The analyses were repeated three times, and the results were expressed as mean ± SD $*p < 0.05$, $**p < 0.01$.

downstream genes from the Proteomic Data Commons database (PDC000219) (Figure 5d). Moreover, protein−protein interaction network analysis using the STRING database showed that MGAT3 could interact with different genes, including EMT marker genes (Figure 5e).

MGAT3 Has an Onco-Suppressive Effect in Lung Cancer. To validate the tumor-suppressive function of the MGAT3 gene in lung cancer, we performed a xenograft assay. The results showed that overexpression of MGAT3 gene significantly inhibited the proliferation of lung cancer cells (Figure 6a−c). In addition, we analyzed lung cancer tissue expression profiles using the TCGA and PDC databases to assess the changes in MGAT3 expression. MGAT3 mRNA and protein expression were significantly reduced in lung cancer tissues compared to the normal tissues (Figure 6d,e). The expression of MGAT3 in lung adenocarcinoma based on individual cancer stages also showed a significant inhibition by TCGA and CPTAC databases (Figure 6f,g). Immunohistochemical staining assay confirmed that downregulation of MGAT3 was accompanied by reduced E-cadherin expression and increased β-catenin expression in lung cancer compared to normal tissue samples (Figure 6h). Moreover, analysis of the lung cancer single-cell RNaseq data set (35027529) for lung adenocarcinoma and squamous lung cancer and paracancerous samples, with cell type and MGAT3 expression visualized, revealed that MGAT3 was significantly downregulated in suprachiasmatic cells and monocytes of both lung adenocarcinoma and squamous lung cancer (Figure S1). Clinical prognosis data analysis further revealed that low MGAT3 expression was associated with worse overall survival and disease-free survival in lung cancer patients (Figure 6i,j), suggesting that the suppression of MGAT3 expression in lung cancer tissues is associated with a poor prognosis. Moreover, the MGAT3 expression level was positively correlated with that of E-cadherin (Figure 6k), indicating that MGAT3 may exert its tumor-suppressive effect by regulating EMT in lung cancer cells.

DISCUSSION

B[*a*]P primarily induces lung carcinogenesis by causing DNA mutations and activating cell signaling cascades that contribute to the regulation of the cell cycle. Numerous studies have exhaustively described the DNA binding and damage-inducing activities of B[*a*]P and its active form BPDE. Current research

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415

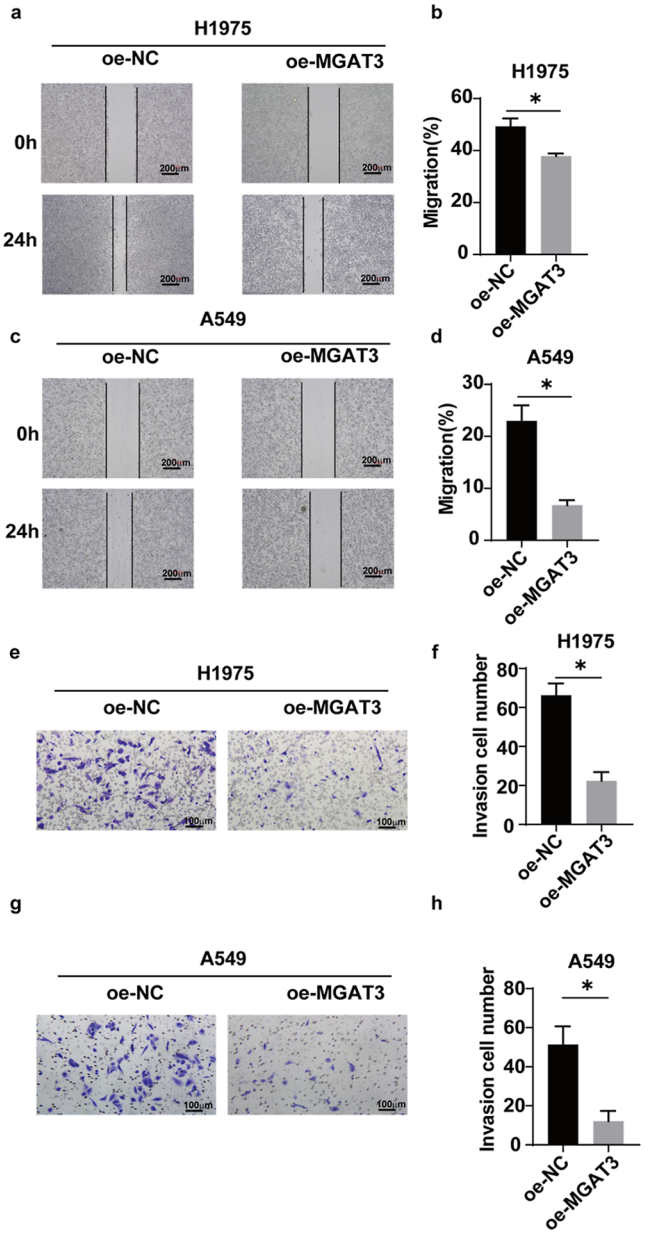


Figure 4. MGAT3 inhibited the invasion and migration of lung cancer cells. (a–d) Left, representative images of wound healing assays; right, relative percentage wound closure after treatment. (e–h) Left, representative images of transwell invasion; right, relative percentage of numbers of transwell invasion after treatment. The cell transfected with empty vector was used as the NC. The analyses were repeated three times, and the results were expressed as mean ± SD $*p < 0.05$.

focuses on uncovering the specific mechanisms by which B[*a*]P exposure leads to the regulation of gene expression involved in lung carcinogenesis.[6−8,27,28] Our study identified that B[*a*]P treatment led to MGAT3 downregulation, which regulated cell migration and invasion ability and EMT marker gene expression, subsequently contributing to lung tumorigenesis. These data have identified MGAT3 as a novel target gene involved in the carcinogenic effects of lung cancer, particularly in the tumor initiation process induced by B[*a*]P.

Dysregulation of *N*-glycan branching is a hallmark of cancer progression. Aberrant glycosylation has been implicated in various aspects of tumor biology, including cancer progression, metastasis, immune evasion, and chemoresistance.[18,19,29,30] MGAT3, an enzyme of *N*-glycan modification, catalyzes the formation of bisecting GlcNAc structures that inhibit cancer cell migration, invasion, and metastasis. Recent studies demonstrate that MGAT3 expression is regulated both by transcription factors and epigenetic mechanisms including DNA methylation and miRNAs.[18,31−34] HIF-1a transcriptionally represses MGAT3 expression, thereby promoting breast cancer metastasis.[31] In hepatocellular carcinoma cells, 5-aza treatment reduces MGAT3 promoter methylation levels, consequently suppressing malignant progression.[32] The miRNAs miR-199-5p, miR-633b, and miR-188-5p directly target MGAT3 to inhibit its expression, contributing to invasion and metastasis across multiple tumor types.[18,33,34] Notably, environmental chemical carcinogenesis is frequently accompanied by the dysregulation of epigenetic modifiers and transcription factor networks, which subsequently modulate downstream effector genes involved in tumor initiation and progression. Our current study reveals that benzo[*a*]pyrene exposure downregulates MGAT3 expression to facilitate lung cancer invasion and metastasis. Although the precise molecular mechanisms underlying MGAT3 suppression require further elucidation, these findings collectively suggest that epigenetic regulation likely plays a pivotal role in benzo[*a*]pyrene-induced MGAT3 downregulation.

Recent studies have demonstrated that MGAT3 is generally considered a tumor suppressor. Downregulation of MGAT3 is frequently observed in various cancers, including lung, liver, and breast cancer, and is associated with poor prognosis.[24] However, in some tumor types, MGAT3 exhibits a dual role, functioning as either a tumor suppressor or promoter, depending on the cellular context.[20,21,35] For example, studies have shown that MGAT3 expression is associated with reduced invasiveness in cancer cells by stabilizing E-cadherin, a key molecule in maintaining epithelial integrity.[20,35] Conversely, in hepatocellular carcinoma, MGAT3 expression has been linked to enhanced tumorigenic potential and poor prognosis, suggesting that its role in cancer is highly context-dependent.[21] Emerging evidence supports a tumor-suppressive role of MGAT3 in lung cancer.[18,20,36,37] The present study has reported that MGAT3 was significantly downregulated in lung cancer cells compared with normal epithelial cells. Clinical analysis also confirmed the downregulation of MGAT3 expression in cancer tissues compared with normal tissues, and its downregulation was associated with poor clinical outcomes. Functional studies in lung cancer cell lines demonstrated that overexpression of MGAT3 significantly inhibited cell proliferation, invasion, and migration, suggesting its tumor-suppressive role in lung cancer. Proteomic Data Commons database analysis also showed the negative correlation of MGAT3 and EMT pathway downstream genes. Interestingly, protein−protein interaction assays revealed that MGAT3, in addition to interacting with the EMT marker molecules, also strongly interacted with another glycosylation regulator enzyme, MGAT1. Moreover, previous findings demonstrate that MGAT3 forms distinct molecular assemblies with the central hub protein Golgi a-mannosidase IIX (MAN2A2), along with MGAT1, MGAT2, and MGAT4B, to efficiently orchestrate the biosynthesis of complex *N*-glycans in vivo. Notably, during EMT in tumor cells, MGAT3 cooperates with MGAT5 and FUT8 to coordinately regulate the glycosylation of EMT marker molecules and the extracellular-matrix-degrading enzymes, collectively driving tumor invasion and metastasis. These results underscore that

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415

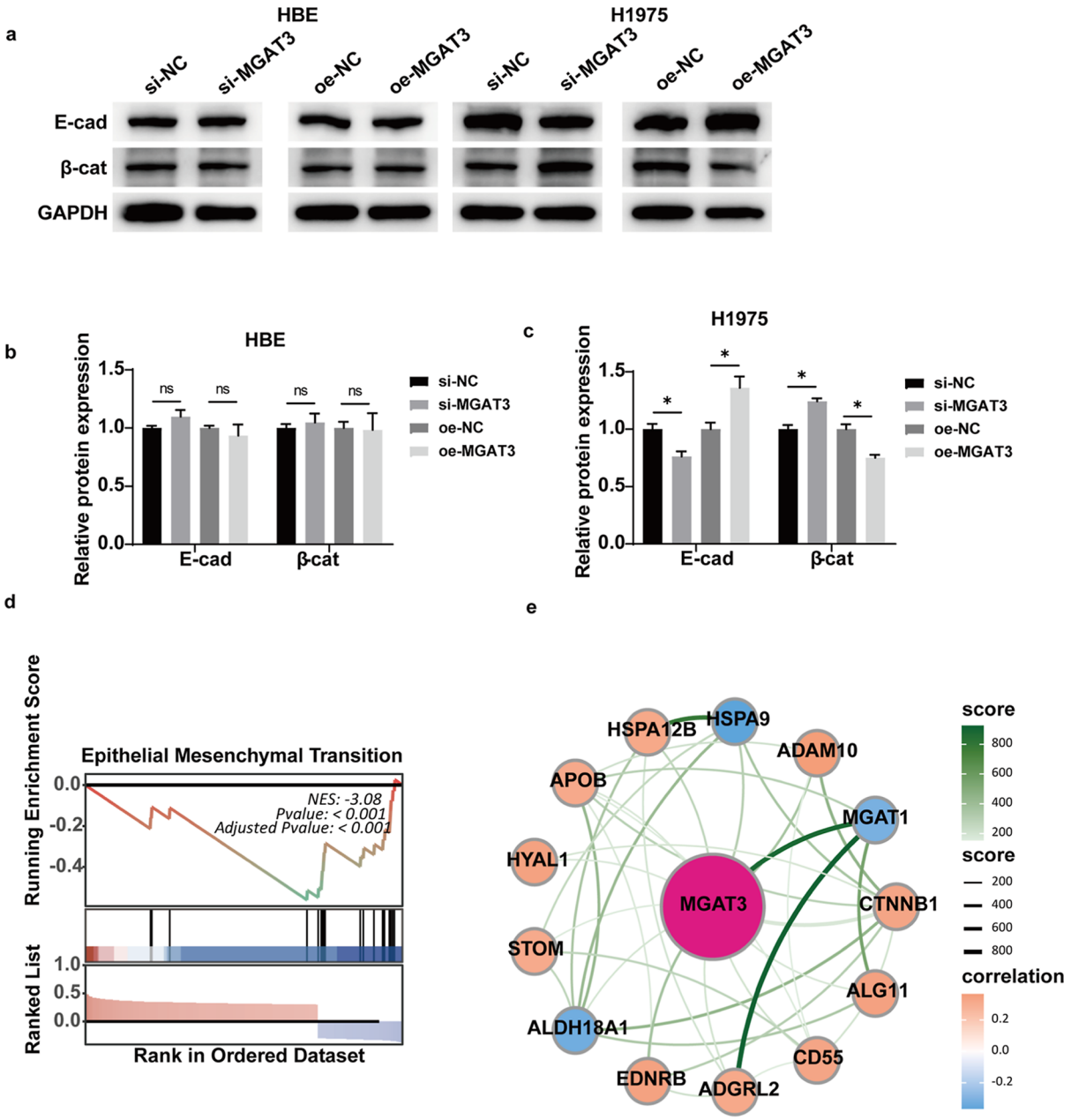


Figure 5. MGAT3 regulated the expression of EMT marker genes. (a) Protein levels of E-cadherin and β-catenin in lung cancer cells and normal lung epithelial cells after transfection with MGAT3 siRNA and MGAT3 overexpressed plasmid by Western blot. (b,c) E-cadherin and β-catenin mRNA expression in lung cancer cells and normal lung epithelial cells after transfection with MGAT3 siRNA and MGAT3 overexpressed plasmid. The cell transfected with empty vector or scramble siRNA was used as NC. The analyses were repeated three times, and the results were expressed as mean ± SD $*p < 0.05$. (d) Gene set enrichment plots of differentially expressed genes belonging to the EMT pathway in MGAT3 downregulated cells. (e) MGAT3 and the proteins included in the GSEA analysis were explored for protein−protein interaction network analysis with STRING database. Node colors represents the correlation values and line colors represents the strength of protein−protein interaction action, except for MGAT3.

protein glycosylation during tumorigenesis and progression is coregulated by multiple glycosyltransferases, with MGAT3 playing a pivotal role. Mechanistically, MGAT3 modulates intracellular glycosylation patterns by forming multienzyme complexes with distinct glycosyltransferases, thereby influencing oncogenic processes, suggesting that the inhibition of their corresponding genes would also be desirable in therapeutics.[38−40] However, the interactive effects of MGAT family members, especially MGAT1 and MGAT3, on tumors remain to be further revealed.

Moreover, PAHs, as the most widespread tumor-triggering environmental chemicals, have been extensively studied for their molecular regulatory mechanisms in carcinogenesis. However, the relationship between changes in glycosylation levels and chemical carcinogenesis has faced many unknown challenges. Recent studies have begun to elucidate the role of glycosylation in the carcinogenic process triggered by PAHs.[41] Among them, MGAT3, as an important glycosylation modification enzyme, can also mediate DNA damage-related signaling pathways involved in tumor progression.[41] Our study demonstrated that MGAT3 expression was significantly

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415

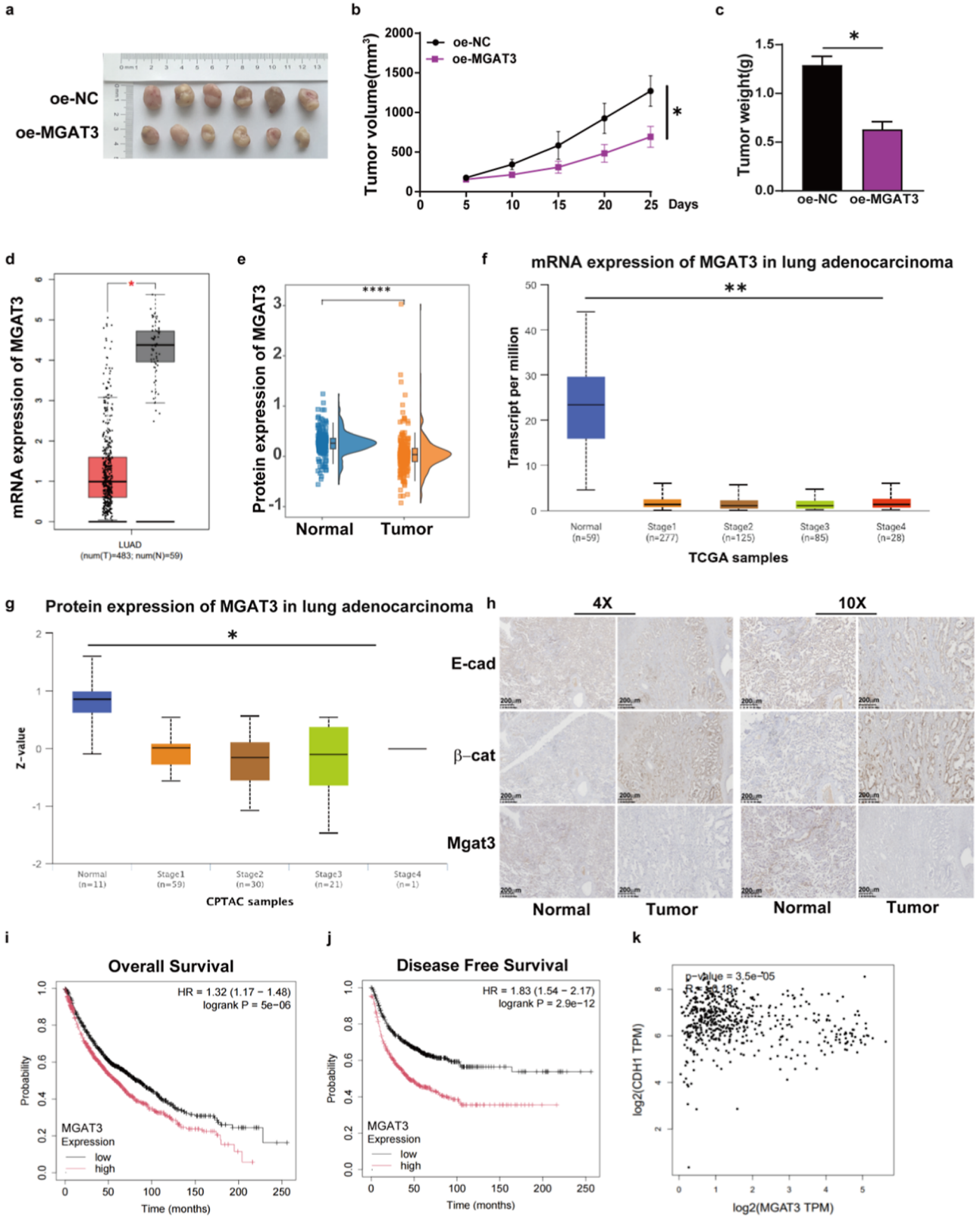


Figure 6. MGAT3 has an onco-suppressive effect in lung cancer. (a−c) Xenograft tumor growth assay of lung cancer cells after empty vector and MGAT3 overexpression. Photos of tumors, tumor growth curves, and tumor weight are shown. Empty vector was used as NC. (d,e) Qualification of MGAT3 mRNA and protein expression in lung cancer and normal tissues by TCGA and PDC database. (f,g) Expression of MGAT3 mRNA and protein levels in clinical lung adenocarcinoma tissue samples of different stages by TCGA and CPTAC database. (h) Representative image of IHC staining of MGAT3, E-cadherin, and β-catenin in human lung normal and tumor tissues. (i,j) Correlation analysis of MGAT3 expression and the clinical prognostic indicators of lung cancer patients. (k) Correlation of MGAT3 and E-cadherin expression in lung cancer tissues. The analyses were repeated three times, and the results were expressed as mean ± SD *p < 0.05, **p < 0.01.

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415

downregulated during the early stages of lung cancer development in B[*a*]P-induced carcinogenesis, indicating a potential mechanism through which environmental carcinogens can modulate glycosylation patterns, subsequently altering cellular behavior. This downregulation may contribute to the loss of cell adhesion and the acquisition of a more migratory and invasive phenotype, which are hallmarks of malignancy. Additionally, MGAT3's role in modulating the activity of key signaling pathways, such as Wnt/β-catenin and EGFR/Erk, which are often dysregulated in PAH-induced lung cancers,[12,42,43] highlights its importance in this context. The data can help to better reveal the important role of glycosylase-modifying enzyme molecules in B[*a*]P-induced tumorigenesis, which is conducive to the in-depth exploration of the molecular regulatory mechanisms of this class of molecules in environmental chemical carcinogenesis and provide new potential therapeutic targets for intervening in chemical carcinogenesis.

In addition, we identified the significantly decreased expression of other tumor suppressor genes, such as NDRG2, ASCL1, GSTA3, FMO3, and INMT[44−48] in B[*a*]P and BPDE-induced tumorigenesis. Further studies on the mechanism of the abnormal expression of these genes in the tumorigenesis induced by B[*a*]P will help to comprehensively reveal the role and mechanism of the complex gene coregulatory network in environmental carcinogenesis. The suppression of MGAT3 together with other downregulated genes by PAHs could be a critical step in the disruption of normal cellular processes, facilitating tumor initiation and the progression of early-stage lung cancers. However, The specific regulatory mechanisms by which MGAT3, along with other downregulated genes, collaboratively contribute to B[*a*]P-induced lung carcinogenesis remain to be further elucidated.

CONCLUSIONS

In conclusion, MGAT3 plays a crucial role in lung cancer development and progression, particularly in the context of environmental carcinogens such as B[*a*]P. Its downregulation is associated with increased tumor aggressiveness and poor clinical outcomes. Future research should focus on the mechanisms regulating MGAT3 expression and its potential as a therapeutic target. Understanding the regulatory mechanisms underlying MGAT3 expression in lung cancer could provide new avenues for therapeutic intervention, which leads us to uncover new strategies for diagnosis, prognosis, and treatment, particularly for cancers associated with environmental exposures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c10682.

Clinic pathological characteristics of lung cancer tissues and analysis of the lung cancer single-cell RNaseq data set (PDF)

AUTHOR INFORMATION

Corresponding Author

Hong-juan Jiang − *Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou 310014 Zhejiang, China;* orcid.org/0000-0002-6083-0730; Email: tigergirl@126.com

Authors

Su Zhang − *Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou 310014 Zhejiang, China*

Xia-Yan Zhang − *Department of Pharmacy, the Fifth Affiliated Hospital of Wenzhou Medical University, Lishui 323000 Zhejiang, China*

Xiao-Chun Zheng − *Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou 310014 Zhejiang, China*

Xiao-Lan Ye − *Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou 310014 Zhejiang, China*

Ping Huang − *Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou 310014 Zhejiang, China*

Wen-tong Liu − *School of Pharmacy, Hangzhou Normal University, Hangzhou 311121 Zhejiang, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c10682

Author Contributions

H.-j.J. and S.Z. designed the research, performed experiments, prepared the figures and wrote the main text of the manuscript. X.-Y.Z., X.-C.Z., X.-L.Y., and W.-t.L. analyzed the data. P.H. supervised the study. All authors reviewed and approved the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by Zhejiang Medical and Health Science and Technology Project (no. 2022KY024, 2024KY754, 2024KY761, 2025KY641). Zhejiang Province traditional Chinese medicine research project (no. 2025ZR078). The authors are grateful to Zhejiang Provincial People's Hospital.

REFERENCES

(1) International Agency for Research on Cancer, World Health Organization. *World Cancer Report*, 2014. http://globocan.iarc.fr (accessed Feb 3, 2014).

(2) IARC. IARC monographs on the evaluation of carcinogenic risks to humans. *Outdoor Air Pollution*; IARC, 2013; Vol. *109*.

(3) Chen, W.; Padilla, M. T.; Xu, X.; Desai, D.; Krzeminski, J.; Amin, S.; Lin, Y. Quercetin Inhibits Multiple Pathways Involved in Interleukin 6 Secretion from Human Lung Fibroblasts and Activity in Bronchial Epithelial Cell Transformation Induced by Benzo[a]-pyrene Diol Epoxide. *Mol. Carcinog.* **2016**, *55* (11), 1858−1866.

(4) Mallah, M. A.; Changxing, L.; Mallah, M. A.; Noreen, S.; Liu, Y.; Saeed, M.; Xi, H.; Ahmed, B.; Feng, F.; Mirjat, A. A.; Wang, W.; Jabar, A.; Naveed, M.; Li, J. H.; Zhang, Q. Polycyclic Aromatic Hydrocarbon and Its Effects on Human Health: An Overview. *Chemosphere* **2022**, *296*, 133948.

(5) Wogan, G. N.; Hecht, S. S.; Felton, J. S.; Conney, A. H.; Loeb, L. A. Environmental and Chemical Carcinogenesis. *Semin. Cancer Biol.* **2004**, *14* (6), 473−486.

(6) Bukowska, B.; Mokra, K.; Michałowicz, J. Benzo[a]pyrene-Environmental Occurrence, Human Exposure, and Mechanisms of Toxicity. *Int. J. Mol. Sci.* **2022**, *23* (11), 6348.
(7) Tung, E. W.; Philbrook, N. A.; Belanger, C. L.; Ansari, S.; Winn, L. M. Benzo[a]pyrene Increases DNA Double Strand Break Repair in Vitro and in Vivo: A Possible Mechanism for Benzo[a]pyrene-Induced Toxicity. *Mutat. Res., Genet. Toxicol. Environ. Mutagen.* **2014**, *760*, 64−69.
(8) Abd El-Fattah, E. E.; Abdelhamid, A. M. Benzo[a]pyrene Immunogenetics and Immune Archetype Reprogramming of Lung. *Toxicology* **2021**, *463*, 152994.
(9) Moorthy, B.; Chu, C.; Carlin, D. J. Polycyclic aromatic hydrocarbons: from metabolism to lung cancer. *Toxicol. Sci.* **2015**, *145* (1), 5−15.
(10) Chandrashekar, N.; Subramanian, R.; Thiruvengadam, D. Baicalein inhibits cell proliferation and enhances apoptosis in human A549 cells and benzo(a)pyrene-induced pulmonary carcinogenesis in mice. *J. Biochem. Mol. Toxicol.* **2022**, *36* (7), No. e23053.
(11) Cheng, T.; Chaousis, S.; Kodagoda Gamage, S. M.; Lam, A. K.; Gopalan, V. Polycyclic Aromatic Hydrocarbons Detected in Processed Meats Cause Genetic Changes in Colorectal Cancers. *Int. J. Mol. Sci.* **2021**, *22* (20), 10959.
(12) Ke, X.; He, L.; Wang, R.; Shen, J.; Wang, Z.; Shen, Y.; Fan, L.; Shao, J.; Qi, H. miR-377−3p-Mediated EGR1 Downregulation Promotes B[a]P-Induced Lung Tumorigenesis by Wnt/Beta-Catenin Transduction. *Front. Oncol.* **2021**, *11*, 699004.
(13) Huang, G.; Feng, H.; Zhou, Y.; Cao, B.; Zan, Z.; He, Z.; Huang, H.; Luo, X.; Wei, Q. Estradiol and Benzo[a]pyrene Co-Exposure Contributes to Lung Cancer Cell A549 Proliferation through AHR/AKT/ERK1/2 Pathway. *Ann. Clin. Lab. Sci.* **2023**, *53* (6), 872−880.
(14) Shi, Q.; Godschalk, R. W. L.; van Schooten, F. J. Inflammation and the Chemical Carcinogen Benzo[a]pyrene: Partners in Crime. *Mutat. Res., Rev. Mutat. Res.* **2017**, *774*, 12−24.
(15) Li, E.; Xu, Z.; Zhao, H.; Sun, Z.; Wang, L.; Guo, Z.; Zhao, Y.; Gao, Z.; Wang, Q. Macrophages Promote Benzopyrene-Induced Tumor Transformation of Human Bronchial Epithelial Cells by Activation of NF-κB and STAT3 Signaling in a Bionic Airway Chip Culture and in Animal Models. *Oncotarget* **2015**, *6* (11), 8900−8913.
(16) Gao, M.; Zheng, A.; Chen, L.; Dang, F.; Liu, X.; Gao, J. Benzo(a)pyrene affects proliferation with reference to metabolic genes and ROS/HIF-1α/HO-1 signaling in A549 and MCF-7 cancer cells. *Drug Chem. Toxicol.* **2022**, *45* (2), 741−749.
(17) Malik, D. E.; David, R. M.; Gooderham, N. J. Mechanistic Evidence That Benzo[a]pyrene Promotes an Inflammatory Microenvironment That Drives the Metastatic Potential of Human Mammary Cells. *Arch. Toxicol.* **2018**, *92* (10), 3223−3239.
(18) You, X.; Wang, Y.; Meng, J.; Han, S.; Liu, L.; Sun, Y.; Zhang, J.; Sun, S.; Li, X.; Sun, W.; Dong, Y.; Zhang, Y. Exosomal miR-663b exposed to TGF-β1 promotes cervical cancer metastasis and epithelial-mesenchymal transition by targeting MGAT3. *Oncol. Rep.* **2021**, *45* (4), 12.
(19) Ding, Z.; Xiao, X.; Fan, L.; Mao, Z.; Sun, C.; Li, N.; Zhang, Q. Circ_0070934 Promotes MGAT3 Expression and Inhibits Epithelial-Mesenchymal Transition in Bronchial Epithelial Cells by Sponging miR-199a-5p. *Allergy, Asthma, Clin. Immunol.* **2024**, *20* (1), 23.
(20) Krug, J.; Rodrian, G.; Petter, K.; Yang, H.; Khoziainova, S.; Guo, W.; Bénard, A.; Merkel, S.; Gellert, S.; Maschauer, S.; Spermann, M.; Waldner, M.; Bailey, P.; Pilarsky, C.; Liebl, A.; Tripal, P.; Christoph, J.; Naschberger, E.; Croner, R.; Schellerer, V. S.; Becker, C.; Hartmann, A.; Tüting, T.; Prante, O.; Grützmann, R.; Grivennikov, S. I.; Stürzl, M.; Britzen-Laurent, N. N-glycosylation Regulates Intrinsic IFN-γ Resistance in Colorectal Cancer: Implications for Immunotherapy. *Gastroenterology* **2023**, *164* (3), 392−406e5.
(21) Li, J.; Xu, J.; Li, L.; Ianni, A.; Kumari, P.; Liu, S.; Sun, P.; Braun, T.; Tan, X.; Xiang, R.; Yue, S. MGAT3-mediated glycosylation of tetraspanin CD82 at asparagine 157 suppresses ovarian cancer metastasis by inhibiting the integrin signaling pathway. *Theranostics* **2020**, *10* (14), 6467−6482.
(22) Wang, B.; He, X.; Zhou, Y.; Tan, Z.; Li, X.; Guan, F.; Lei, L. Proximity Labeling-Based Identification of MGAT3 Substrates and Revelation of the Tumor-Suppressive Role of Bisecting GlcNAc in Breast Cancer via GLA Degradation. *Cells* **2025**, *14* (2), 103.
(23) Kumar, K.; Verma, R.; Manjit; Priya; Mishra, M.; Mishra, M.; Rani, V.; Chawla, R. In Vivo Cancer Microenvironment Responsive Glycan Receptor-Targeted Nanoparticles for Gemcitabine Delivery to Benzo[a]pyrene-Induced Lung Cancer Model. *AAPS PharmSciTech* **2023**, *25* (1), 2.
(24) Taniguchi, N.; Kizuka, Y. Glycans and cancer: role of N-glycans in cancer biomarker, progression and metastasis, and therapeutics. *Adv. Cancer Res.* **2015**, *126*, 11−51.
(25) Zhao, L.; Liu, H.; Luo, S.; Moorman, P. G.; Walsh, K. M.; Li, W.; Wei, Q. Associations between Genetic Variants of KIF5B, FMN1, and MGAT3 in the Cadherin Pathway and Pancreatic Cancer Risk. *Cancer Med.* **2020**, *9* (24), 9620−9631.
(26) Vergara, A. G.; Watson, C. J. W.; Chen, G.; Lazarus, P. UDP-Glycosyltransferase 3A Metabolism of Polycyclic Aromatic Hydrocarbons: Potential Importance in Aerodigestive Tract Tissues. *Drug Metab. Dispos.* **2020**, *48* (3), 160−168.
(27) Wang, A.; Gu, J.; Judson-Kremer, K.; Powell, K. L.; Mistry, H.; Simhambhatla, P.; Aldaz, C. M.; Gaddis, S.; MacLeod, M. C. Response of Human Mammary Epithelial Cells to DNA Damage Induced by BPDE: Involvement of Novel Regulatory Pathways. *Carcinogenesis* **2003**, *24* (2), 225−234.
(28) Li, W.; Hu, J.; Adebali, O.; Adar, S.; Yang, Y.; Chiou, Y. Y.; Sancar, A. Human Genome-Wide Repair Map of DNA Damage Caused by the Cigarette Smoke Carcinogen Benzo[a]pyrene. *Proc. Natl. Acad. Sci. U.S.A.* **2017**, *114* (26), 6752−6757.
(29) Tan, Z.; Ning, L.; Cao, L.; Zhou, Y.; Li, J.; Yang, Y.; Lin, S.; Ren, X.; Xue, X.; Kang, H.; Li, X.; Guan, F. Bisecting GlcNAc modification reverses the chemoresistance via attenuating the function of P-gp. *Theranostics* **2024**, *14* (13), 5184−5199.
(30) Li, J.; Ren, X.; Cao, L.; Min, K.; Wang, M.; Lin, S.; Lei, L.; Tan, Z.; Cheng, X.; Li, X.; Guan, F. Bisecting GlcNAc modification of vesicular GAS6 regulates CAFs activation and breast cancer metastasis. *Cell Commun. Signaling* **2025**, *23* (1), 39.
(31) Tan, Z.; Wang, C.; Li, X.; Guan, F. Bisecting N-Acetylglucosamine Structures Inhibit Hypoxia-Induced Epithelial-Mesenchymal Transition in Breast Cancer Cells. *Front. Physiol.* **2018**, *9*, 210.
(32) Klasić, M.; Krištić, J.; Korać, P.; Horvat, T.; Markulin, D.; Vojta, A.; Reiding, K. R.; Wuhrer, M.; Lauc, G.; Zoldoš, V. DNA hypomethylation upregulates expression of the MGAT3 gene in HepG2 cells and leads to changes in N-glycosylation of secreted glycoproteins. *Sci. Rep.* **2016**, *6*, 24363.
(33) Ding, Z.; Xiao, X.; Fan, L.; Mao, Z.; Sun, C.; Li, N.; Zhang, Q. Circ_0070934 promotes MGAT3 expression and inhibits epithelial-mesenchymal transition in bronchial epithelial cells by sponging miR-199a-5p. *Allergy, Asthma, Clin. Immunol.* **2024**, *20* (1), 23.
(34) Niu, H.; Qu, A.; Guan, C. Suppression of MGAT3 expression and the epithelial-mesenchymal transition of lung cancer cells by miR-188−5p. *Biomed J.* **2021**, *44* (6), 678−685.
(35) Wang, Y.; Li, Q.; Niu, L.; Xu, L.; Guo, Y.; Wang, L.; Guo, C. Suppression of G6PD Induces the Expression and Bisecting GlcNAc-branched N-glycosylation of E-Cadherin to Block Epithelial-Mesenchymal Transition and Lymphatic Metastasis. *Br. J. Cancer* **2020**, *123* (8), 1315−1325.
(36) Klasić, M.; Krištić, J.; Korać, P.; Horvat, T.; Markulin, D.; Vojta, A.; Reiding, K. R.; Wuhrer, M.; Lauc, G.; Zoldoš, V. DNA Hypomethylation Upregulates Expression of the MGAT3 Gene in HepG2 Cells and Leads to Changes in N-Glycosylation of Secreted Glycoproteins. *Sci. Rep.* **2016**, *6*, 24363.
(37) Niu, H.; Qu, A.; Guan, C. Suppression of MGAT3 Expression and the Epithelial-Mesenchymal Transition of Lung Cancer Cells by miR-188−5p. *Biomed. J.* **2021**, *44* (6), 678−685.
(38) Kizuka, Y. Regulation of intracellular activity of N-glycan branching enzymes in mammals. *J. Biol. Chem.* **2024**, *300* (7), 107471.
(39) Taniguchi, N.; Ohkawa, Y.; Maeda, K.; Harada, Y.; Nagae, M.; Kizuka, Y.; Ihara, H.; Ikeda, Y. True significance of N-

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415

acetylglucosaminyltransferases GnT-III, V and α1,6 fucosyltransferase in epithelial-mesenchymal transition and cancer. *Mol. Aspects Med.* **2021**, *79*, 100905.
(40) Khoder-Agha, F.; Sosicka, P.; Escriva Conde, M.; Hassinen, A.; Glumoff, T.; Olczak, M.; Kellokumpu, S. N-acetylglucosaminyltransferases and nucleotide sugar transporters form multi-enzyme-multi-transporter assemblies in golgi membranes in vivo. *Cell. Mol. Life Sci.* **2019**, *76* (9), 1821−1832.
(41) Pinho, S. S.; Reis, C. A. Glycosylation in Cancer: Mechanisms and Clinical Implications. *Nat. Rev. Cancer* **2015**, *15* (9), 540−555.
(42) Vergara, A. G.; Watson, C. J. W.; Watson, J. M.; Chen, G.; Lazarus, P. Altered Metabolism of Polycyclic Aromatic Hydrocarbons by UDP-Glycosyltransferase 3A2Missense Variants. *Chem. Res. Toxicol.* **2020**, *33* (11), 2854−2862.
(43) Cheng, L.; Cao, L.; Wu, Y.; Xie, W.; Li, J.; Guan, F.; Tan, Z. Bisecting N-Acetylglucosamine on EGFR Inhibits Malignant Phenotype of Breast Cancer via Down-Regulation of EGFR/Erk Signaling. *Front. Oncol.* **2020**, *10*, 929.
(44) Ma, Z.; Ma, Y.; Feng, J.; Xu, Z.; Cheng, C.; Qin, J.; Li, S.; Jiang, J.; Kong, R. NDRG2 acts as a negative regulator of the progression of small-cell lung cancer through the modulation of the PTEN-AKT-mTOR signalling cascade. *Toxicol. Appl. Pharmacol.* **2024**, *485*, 116915.
(45) Olsen, R. R.; Ireland, A. S.; Kastner, D. W.; Groves, S. M.; Spainhower, K. B.; Pozo, K.; Kelenis, D. P.; Whitney, C. P.; Guthrie, M. R.; Wait, S. J.; Soltero, D.; Witt, B. L.; Quaranta, V.; Johnson, J. E.; Oliver, T. G. ASCL1 Represses a SOX9+ Neural Crest Stem-like State in Small Cell Lung Cancer. *Genes Dev.* **2021**, *35* (11−12), 847−869.
(46) Zhou, X.; Zou, B.; Wang, J.; Wu, L.; Tan, Q.; Ji, C. Low expression of INMT is associated with poor prognosis but favorable immunotherapy response in lung adenocarcinoma. *Front. Genet.* **2022**, *13*, 946848.
(47) Bae, S. Y.; Choi, S. K.; Kim, K. R.; Park, C. S.; Lee, S. K.; Roh, H. K.; Shin, D. W.; Pie, J. E.; Woo, Z. H.; Kang, J. H. Effects of Genetic Polymorphisms of MDR1, FMO3 and CYP1A2 on Susceptibility to Colorectal Cancer in Koreans. *Cancer Sci.* **2006**, *97* (8), 774−779.
(48) Li, W.; Qiu, C.; Wang, S.; Wu, L.; Zhao, T. Inhibitory Effect of Glutathione S-Transferase A3 in the Progression of Cutaneous Squamous Cell Carcinoma. *J. Cosmet. Dermatol.* **2021**, *20* (7), 2287−2295.

https://doi.org/10.1021/acsomega.4c10682
ACS Omega 2025, 10, 17404−17415