

Ulex europaeus agglutinin-I-binding alpha-1,2-fucosylated glycan is applicable for the diagnosis and treatment of meningioma

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Abstract

Meningiomas are the most common primary intracranial tumors, and improved diagnostic and therapeutic strategies are needed. Meningioma (MG) exhibits abnormal glycosylation, which can be used for diagnosis, prognosis, and treatment strategies. In this study, we use *Ulex europaeus* agglutinin-I (UEA-I) to develop an in-house enzyme-linked lectin assay for detecting meningioma (MG)-associated glycan in patient serum. The level of serum UEA-I binding glycan (UEAG) was significantly higher in MG and other brain tumors compared with healthy controls (HC). Moreover, we found that patients with a higher grade of MG (WHO Grade II) have a higher level of serum UEAG compared to those with Grade I. The functional analysis in MG cell lines showed that UEA-I can inhibit the migration and invasion of MG cells, with no effect on cell viability, suggesting the role of UEAG in MG progression. In conclusion, we have demonstrated the potential of UEAG as a serum glycobiomarker for diagnosis, and it may also serve as a target for MG treatment.

Introduction

Meningioma (MG) is the most common tumor arising from meningotheial cells in the arachnoid layer¹. According to the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS), MGs are classified into three grades. Grade 1 (low-grade MG) accounts for the majority of cases (80.1%), followed by grade 2 (high-grade MG, 18.3%), and grade 3 (anaplastic MG or malignant tumor, 1.5%)². The primary management of MG is surgical resection, often combined with radiotherapy or chemotherapy, such as hydroxyurea³. However, these treatments are not always effective for MG patients, and recurrence or progression of the tumor frequently occurs post-surgery⁴. The 10-year overall survival rates are approximately 81% for grade 1, 63% for grade 2, and only 15% for grade 3⁵. Moreover, MGs often grow slowly and remain asymptomatic for a long time; the imaging techniques are not able to detect tumors until they reach a certain size, which represents the major challenge in the early detection of MG⁶. Currently, no biomarkers are clinically approved for the diagnosis or prognosis of MG. Thus, identifying reliable biomarkers is essential for timely and effective clinical intervention.

Abnormal glycosylation was found in many types of cancer, such as cholangiocarcinoma, hepatocellular carcinoma, gliomas, and also MG^{7–10}. In MG, aberrant expression of tumor-associated glycans was detected using plant lectins—such as peanut agglutinin (PNA), soybean agglutinin (SBA), *Dolichos biflorus* agglutinin (DBA), wheat germ agglutinin (WGA), concanavalin A (Con A), and *Ulex europaeus* agglutinin I (UEA-I). Glycans play roles in progression and are associated with severity and meningioma subtype^{11,12}. Our previous study using serum dot blot analysis suggested the potential of lectins to detect serum glycobiomarkers for MG¹³. Among the tested lectins, UEA-I showed high reactivity with MG serum compared with healthy controls (HC). This information suggested the potential to use UEA-I to detect the MG-associated serum glycobiomarker.

In this study, we used UEA-I to develop an in-house enzyme-linked lectin assay (ELLA) to determine the level of UEA-I binding fucosylated-glycan (UEAG) in the serum of MG patients, compared with HC and other brain tumors (BT). Moreover, to elucidate the biological roles of UEAG and its potential as a therapeutic target of MG, we conducted functional analyses in MG cell lines. The information provided in our study highlight the significance of glycosylation in MG, suggesting the potential of MG-associated glycan to be a target for diagnosis and treatment of the disease.

Results

An in-house ELLA was developed to detect serum UEAG in MG patients ($n = 93$) compared with healthy controls (HC, $n = 100$). The data showed that serum UEAG in MG patients (46.9 ± 58.8 AU/ml) was significantly higher than that of HC (0.9 ± 3.2 AU/ml; Fig. 1A). The ROC analysis suggested the potential of using serum UEAG as a biomarker to distinguish between MG and HC, with an area under the curve (AUC) of 0.9093 ($P < 0.0001$; Fig. 1B). Moreover, we found that serum UEAG in MG patients was also significantly higher than in other benign ($n = 63$) and malignant ($n = 27$) brain tumors (BTs) as shown in Fig. 1C. The ROC analysis demonstrated the ability of serum UEAG to distinguish between MG and other BTs, with an AUC of 0.6266 ($P < 0.05$; Fig. 1D). In addition, among the MG patients, we found that patients with a higher grade of MG (WHO grade II, $n = 8$) have a higher level of serum UEAG, compared to those with Grade I patients ($n = 85$)(Fig. 1E).

(A) The scatter plot represents the level of UEAG in the serum of healthy controls (HC, $n = 100$) and meningioma patients (MG, $n = 93$). (B) ROC curve of serum UEAG compared between MG and HC. (C) The scatter plot shows the level of UEAG in the serum of meningioma patients (MG, $n = 93$) and other brain tumor patients (BT, $n = 90$). Other BTs consisted of benign ($n = 63$) and malignant ($n = 27$). (D) ROC curve of serum UEAG compared between MG and BTs. (E) Bar-graph comparing the level of serum UEAG between Grade I (MG-I, $n = 85$) and Grade II (MG-II, $n = 8$). Asterisk marks represent statistical significance (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$).

UEAG was differentially expressed in MG cell lines.

The expression level of UEAG in MG cell lines was examined using both non-permeabilized and permeabilized UEA-I cytofluorescent staining as shown in Fig. 2A. UEAG was strongly expressed on the cell membrane of HKBMM cells. In contrast, UEAG was negatively stained on the cell membrane of IOMM-Lee cells. However, permeabilized UEA-I cytofluorescent staining revealed that UEAG was positively stained in both HKBMM and IOMM-Lee cells, particularly strong signal in HKBMM compared with IOMM-Lee. Moreover, the UEAG is mainly localized in the cytoplasmic region of cells. Several studies demonstrated that UEA-I was specifically bind to α -L-fucose. To verify the specific interaction between UEA-I and α -L-fucose, sugar inhibition was performed. UEA-I was neutralized with fucose and galactose. The signals were inhibited in cells treated with UEA-I combined with fucose. On the other hand, the signal remained in those treated with UEA-I combined with galactose and PBS, which was used

as a positive control (Fig. 2B). These results demonstrated that UEA-I is differentially expressed in meningioma cell lines and recognized by UEAG with specific fucose glycan.

Table 1
Demographic data

Groups	n	Age [#] (Year)	Sex		Serum UEAG [#] (AU/ml)
			Male	Female	
Healthy	100	52.4 ± 11.4	40	60	0.9 ± 3.2
Meningioma (MG)	93	49.0 ± 7.3	23	70	46.9 ± 58.8
Other brain tumors	93	48.0 ± 17.0	45	48	18.9 ± 16.4
Pituitary tumors	27	51.3 ± 11.5	14	13	17.9 ± 13.0
Schwannoma	26	50.4 ± 12.8	5	21	18.1 ± 14.2
Craniopharyngioma	13	53.3 ± 12.4	8	5	17.9 ± 10.1
Medulloblastoma	10	14.1 ± 15.3	7	3	22.7 ± 25.3
Glioblastoma	12	54.9 ± 12.4	9	3	25.7 ± 28.4
Brain metastatic tumors	5	56.2 ± 8.8	2	3	13.2 ± 9.8
[#] The data was presented as an average level ± standard deviation (SD)					

Table 2
Correlation of serum UEAG with clinical parameters

Clinical parameter	n	Serum UEAG (AU/ml)		χ^2 (P-value)
		< 46.9	≥ 46.9	
Age				0.0850
< 49.0 years	45	33	12	
≥ 49.0 years	48	27	21	
Sex				0.9350
Male	23	15	8	
Female	70	45	25	
Blood group				0.721 ^{\$}
A	28	20	8	
B	21	12	9	
O	34	21	13	
AB	10	7	3	
Tumor grade				0.6130 [#]
I	89	58	31	
II	4	2	2	
^{\$} Likelihood ratio; [#] Fisher's Exact Test				

UEA-I differentially inhibited the viability of MG cell lines.

As lectin can cause cell aggregation, to acquire the appropriate concentration of UEA-I that it does not induce cell aggregation. The MG cells were treated with various concentrations of UEA-I (6.25 µg/ml to 100 µg/ml) for 1 h, and the formation of cell aggregation was observed under a microscope (Supplementary Fig.S1). The results showed that UEA-I does not generate cell aggregation in both HKBMM and IOMM-Lee at any concentration. As a result, the cytotoxic effect of UEA-I at 6.25 to 100 µg/mL on MG proliferation was subsequently determined using the MTT assay. UEA-I significantly reduced the cell viability of HKBMM from 12.5 to 100 µg/mL in a dose-dependent manner, with approximately a 50% decrease in cell viability when compared with the control observed at the highest concentration (Fig. 3A-D.) whereas the UEA-I treatment did not affect the viability of IOMM-Lee. These results were consequently due to the expression level of UEAG on the cell membrane of each cell line (Fig. 1A). The results suggested that UEA-I treatment significantly suppressed the viability of MG cell lines, depending on the expression level of UEAG on the MG cell membrane.

UEA-I potently inhibited the migration and invasion ability of MG.

The effect of UEA-I on the metastatic phenotype of MG cell lines was examined. Cells were treated with 6.25 and 50 µg/mL of UEA-I, and subsequently assessed their cell migration and invasion ability using the Boyden chamber. The results showed that UEA-I could significantly reduce both the migration and invasion ability of both MG cell lines to approximately 40% of the controls (Fig. 4A-B). This result suggests the potential effect of UEA-I on MG migration and invasion.

DISCUSSION

Meningiomas are the most common primary intracranial tumors, which exhibit a major challenge in the early detection of meningiomas. Finding a novel diagnostic, prognostic, and therapeutic approach is crucial for improving treatment strategies in MG. In this study, we used UEA-I to detect UEAG in clinical specimens of MG patients. Our data demonstrated that UEAGs are highly detected in MG and other brain tumors when compared with healthy controls. These results reveal its potential in diagnostics, therapeutic applications for MG.

This study demonstrated that MG exhibit altered glycosylation patterns compared to normal tissues. In previous studies, various lectins, such as wheat germ agglutinin (WGA), peanut agglutinin (PNA), *Bauhinia purpurea* agglutinin (BPA), *Helix pomatia* agglutinin (HPA), *Vicia fava* agglutinin (VFA) and Soyabean agglutinin (SBA), *Ulex europaeus* agglutinin type 1 (UEA-I), *Canavalia ensiformis* (Con A), *Dolichos biflorus* agglutinin (DBA), have revealed different binding affinities across meningioma subtypes^{12,14–16}. GalNAc-specific lectins were varied stained across meningioma tissues. WGA was strongly stained in all meningioma tissues, specifically in fibroblastic subtypes. PNA-binding glycan was associated with specific tumor growth patterns, such as syncytial lobules, whorled formations, or trabecular arrangements of meningioma cells. DBA predominantly labeled cellular nuclei, while SBA bound to psammoma bodies. Pseudopsammoma bodies were strongly stained with PNA, WGA, Con A), while with SBA and DBA. The selective reactivity of UEA-1 with endothelial cells of blood vessels enabled specific visualization of the vascular network in all histological subtypes of meningiomas. These findings highlight the heterogeneous glycosylation patterns in different meningioma subtypes and suggest that lectins can be valuable tools for evaluating the pluripotential differentiation of meningioma cells¹².

Moreover, Talabnin et. al. have demonstrated that benign meningiomas exhibit higher levels of terminal galactose and N-acetyl galactosamine compared to malignant forms, suggesting that altered glycosylation profiles may play a role in tumor progression, with specific glycosyltransferases being upregulated in malignant cases. This suggests that glycosylation not only serves as a marker but may also be involved in the tumor's biological processes¹¹. However, the interaction between meningiomas and UEA-I lectin has not been explored insight the mechanism for understanding tumor biology.

In our study, using the UEA-I immunofluorescent staining for the determination of UEAG in MG, we demonstrated that UEAG is highly expressed in MG cell lines (HKBMM and IOMM-Lee). Several studies

presented that UEA-I selectively and specifically binds to α -L-fucose, a common component of O- and N-linked type glycosylation¹⁷. We confirmed that the binding of UEA-I to MG cells is mediated specifically via α -L-fucose, as sugar inhibition assays revealed a complete loss of signal in the presence of fucose, suggesting the highly fucosylated glycan in MG. This observation agrees with the previous report that fucosylation of the mucin-type O-linked glycosylation is highly expressed in malignant meningioma cell lines when compared with benign meningiomas, as indicated by the upregulation of several fucosyltransferases (including FUT1, FUT2, FUT3, FUT6, FUT7, and FUT8)¹¹. Therefore, targeting fucosylation might be a therapeutic strategy for MG treatment. Herein, the masking of fucosylated glycan is achieved by treating the UEA-I on MG cell lines. Our data showed that UEA-I selectively inhibited the viability of HKBMM cells in a dose-dependent manner, with no effect on IOMM-Lee cells. This finding corresponds well with the presence of UEAG on the HKBMM cell membrane, supporting the notion that membrane-associated UEAG is critical for mediating UEA-I-induced cytotoxicity. Notably, this cytotoxic effect was observed at concentrations that did not induce cell aggregation, dismissing non-specific aggregation-mediated effects. These data suggest a potential glycan-targeted therapeutic role for UEA-I in UEAG-positive MG subtypes. Previously several lectins had been revealed to have anti-cancer activities via diverse mechanisms, including preferentially binding to cancer cell membranes or their receptors, resulting in activation of signaling pathways, autophagy, apoptosis, DNA damage, and inhibition of tumor growth¹⁸⁻²¹. Indeed, PNA lectin, which binds to galactose- β 1,3-N-acetylgalactosamine, inhibits breast cancer cell proliferation²². Moreover, PNA treatment induce cancer cell apoptotic and autophagic cell death via in activation of reactive oxygen species (ROS)²³. Medeiros et. al. revealed that *Myrsine coriacea* lectin (McL) strongly which binds to Tn antigen (GalNAc-O-Ser/Thr), exhibits in vitro inhibition of proliferation in several cancer cell lines²⁴. Although the anti-tumor activities of UEA-I (α -L-fucose specific) have not been explored yet. However, other L-fucose-binding lectins have been reported to exhibit anti-tumor activities. For instance, *Fenneropenaeus indicus* lectin induced apoptosis in breast cancer cells by increasing PARP cleavage and p21 level corresponding to cyclin D downregulation²⁵. *Aspergillus niger* lectin (ANL) induces the intrinsic apoptosis pathway in hepatocellular and colon cancer cells by interacting with cell-surface glycoproteins by via elevation of levels of cytochrome c, initiator caspase-9 and activation of caspase-3²⁶. Taken together suggest that UEA-I lectin can potentially be used as an anti-tumor agent in MG.

In addition to cell viability, we found that UEA-I significantly inhibited the migration and invasion of both MG cell lines, although these effects appeared independently to UEAG levels on the membrane, suggesting that the responsible signaling pathways or glycoproteins on the cell membrane of cell viability and migration-invasion are different. This may indicate a broader functional role of intracellular or low-abundance surface fucosylated glycans in modulating the cytoskeletal dynamics or adhesion molecules involved in cell motility, which need further investigation. Taken together, our findings reveal a novel association between UEAG expression and MG cell behavior, highlighting the significance of glycan-mediated interactions in tumor biology. Our data suggested that UEAG can be used as a functional biomarker and a possible therapeutic target for MG.

Materials and methods

Serum samples

Patient serum samples were obtained from the histological proven cases with meningioma (MG, n = 93), schwannoma (SCH, n = 26), pituitary adenoma (PT, n = 27), craniopharyngioma (CRA, n = 13), medulloblastoma (MDA, n = 10), and glioblastoma (GBM, n = 12), and brain metastatic tumors (n = 5) through the specimen bank of Mekong Health Science Research Institute and Faculty of Medicine, Khon Kaen University, Thailand. Healthy control sera (HC, n = 100) were obtained from asymptomatic individuals who visited Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand, for their annual check-up and presented with normal blood sugar levels, liver function (AST, ALT, and ALP), and a complete blood count. Informed consent was obtained from all subjects or their legal guardian(s). The study protocol was approved by the Khon Kaen University Ethics Committee for Human Research, in accordance with the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines (HE681088).

Cell lines and Cell culture

Meningioma cell lines: IOMM-Lee was obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA), and HKBMM was from the RIKEN cell bank, RIKEN BioResource Research Center (BRC), Japan. IOMM-Lee was maintained in Dulbecco's modified Eagle's medium (DMEM, Gibco; Paisley, Scotland, UK), and HKBMM was maintained in Ham's F-12 Nutrient Mixture (F-12) medium (HAM-F12, Gibco, Paisley, Scotland, UK), containing 1% antibiotic-antimycotic (Thermo Fisher Scientific, Waltham, MA, USA) and 10% fetal bovine serum (Gibco, Paisley, Scotland, UK). Cells were cultured at 37 °C in a humidified CO₂ incubator.

Enzyme-Linked Lectin Assay (SB)

An in-house enzyme-linked lectin assay (ELLA) was developed to detect serum UEAG in 100 healthy controls (HC), meningioma patients (MG), and patients with other brain tumors (BT). Serum samples were diluted 1:10 in 0.5% bovine serum albumin (BSA; Capricorn, Ebsdorfergrund, Germany) in phosphate-buffered saline (PBS; Gibco, Paisley, Scotland, UK). Fifty microliters (μL) of diluted serum were added to each well of a 96-well immunoplate (SPL, Florida, USA) and incubated overnight at 4°C. Plates were washed three times with PBS containing 0.05% Tween 20 (PBST), blocked with 3% BSA in PBS for 1 hour (hr). After washing, 50 μL of the mixture containing 0.25 μg/mL biotinylated UEA-I (bioWORLD, Ohio, USA) and 0.25 μg/mL horse radish peroxidase-conjugated streptavidin (streptavidin-HRP, Invitrogen, Carlsbad, CA) was then added and incubated at room temperature for 1 hour. After washing 5 times, 50 μL of TMB substrate (Thermo Fisher Scientific, Waltham, MA, USA) was added and incubated at room temperature for 30 minutes. The reaction was stopped with 25 μL of 2N H₂SO₄ solution, and absorbance was measured at 450 nm using a microplate reader (SpectraMax ABS, San

Jose, CA, USA). A pooled HC serum control and 0.5%BSA-PBS as background control were included in each plate. All serum samples were performed in duplicate.

Lectin cytofluorescence

MG cells (5×10^4 cell/well) were seeded into a 24-well plate and incubated at 37°C, 5% CO₂, for 72 h. MG cells were fixed with 4% ice-cold paraformaldehyde as a non-permeable staining and with 90% freeze ethanol as a permeable staining at room temperature for 15 min. The non-specific binding was blocked using 0.5% BSA for 1 h. Then, cells were incubated with 1:20 biotinylated UEA-I at 4°C, overnight, and with 1:500 streptavidin-conjugated Alexa Fluor 488 (Invitrogen, Carlsbad, CA) at room temperature for 1 h. at room temperature in the dark for 1 h. Nuclei were stained with 1 µg/mL of Hoechst 33342 (Molecular Probes; Oregon) for 15 min. The fluorescent imaging was examined using a fluorescence microscope (ECLIPSE Ti-U; Nikon, Tokyo, Japan) with Nikon NIS Bioinformatics analysis.

Cell aggregation assay

As lectin can cause cell aggregation, the appropriate UEA-I concentration was prior optimized. IOMM-Lee and HKBMM cells (5×10^4 cells/well each) were seeded in a 24-well plate and cultured with a two-fold dilution of 100 µg/ml unconjugated UEA-I (bioWORLD, Ohio, USA) in serum-free DMEM and Ham's F-12, respectively for 1 h. The aggregated cells were observed under light microscopy.

Cell viability assay

The IOMM-Lee and HKBMM cells were seeded into 96-well plates at 1×10^3 cells per well and cultured overnight at 37°C, 5% CO₂. The conditioned medium was replaced by a medium containing unconjugated UEA-I (bioWORLD, Ohio, USA) at concentrations of 6.25, 12.5, 25, 50, and 100 µg/ml, and cultured continuously for 72 h. The distilled water was used as a control condition. Cell viability was measured using the MTT assay (Molecular Probes, Eugene, OR, USA) at 0 and 72 h after treatment, according to the manufacturer's guidelines. Dimethyl sulfoxide (DMSO) was used to solubilize the formazan complexes and measure the absorbance at 540 nm. Cell viability was calculated as a percentage of control by [optical density (OD) of treatment $\times 100$]/mean OD of control. The presented data was the average from three experiments.

Cell migration and invasion assay

The IOMM-Lee and HKBMM cells were cultured for 72 h and harvested by trypsinization. After washing, the cells were counted and resuspended in a serum-free medium unconjugated UEA-I at concentrations of 6.25 and 50 µg/ml (bioWORLD, Ohio, USA) and in control condition, cells were treated with a serum-free medium instead of UEA-I. Cell migration ability was measured using the Boyden chamber followed the manufacturer's guidelines. For cell invasion assay, the chambers were coated with 0.4 mg/mL

Matrigel (Corning Incorporated, Corning, NY) and incubated overnight at 37°C. The 20,000 cells for both cell migration and invasion assay were seeded into the upper chamber of transwell inserts with 8.0-µm pore size (Corning Incorporated, Corning, NY, USA) and allowed the cells to migrate down into the lower chamber containing complete media for 6 h. The migrated cells were counted under a microscope and presented as a percentage of the control.

Statistical analysis

The statistical analysis was performed using IBM SPSS software version 29.0.2.0, and the graphical images were created with GraphPad Prism software version 10.6.1. The one-way ANOVA, Mann-Whitney U test, and Student's T-test were used to compare differences among the tested groups. Correlation between the level of serum UEAG and clinical parameters was analyzed using Chi-square (χ^2) or Fisher's Exact Tests.

Data availability

The datasets and materials used in this study are available upon reasonable request from the corresponding author.

Declarations

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Author contributions

O.P. contributed to the investigation, methodology, statistical analysis, and writing the original draft; P.P., N.K., N.M., S.P., P.P., S.L., and S.B. participated in the investigation and methodology; C.T., K.T., U.C., S.W., and N.A. provided materials. A.S. participated in conceptualization, methodology, and statistical analysis, supervised the work, and edited the manuscript. All authors reviewed the manuscript.

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Competing interests

The authors declare no competing interests.

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Figures

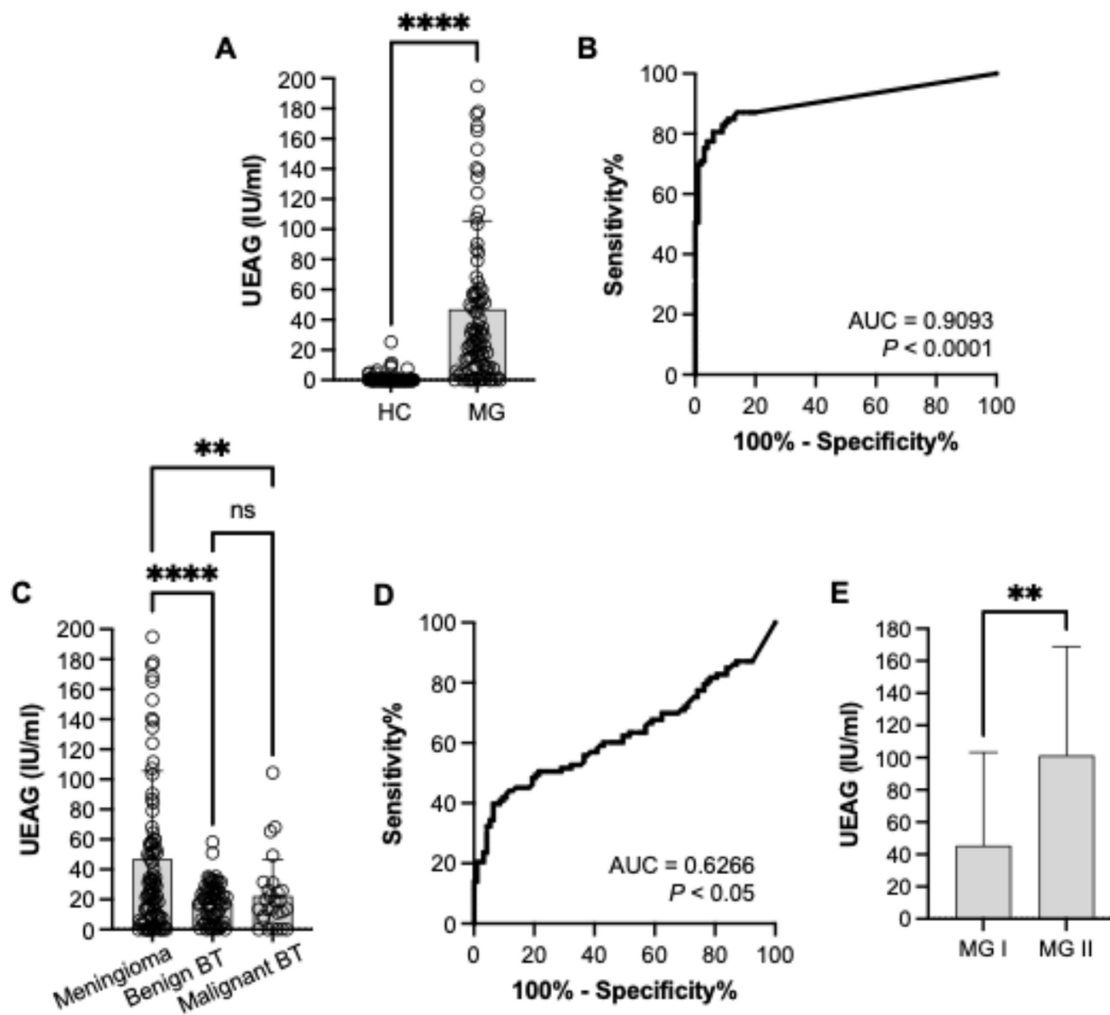


Figure 1

Serum UEA-1-binding glycan (UEAG)

(A) The scatter plot represents the level of UEAG in the serum of healthy controls (HC, n = 100) and meningioma patients (MG, n = 93). (B) ROC curve of serum UEAG compared between MG and HC. (C) The scatter plot shows the level of UEAG in the serum of meningioma patients (MG, n = 93) and other brain tumor patients (BT, n = 90). Other BTs consisted of benign (n = 63) and malignant (n = 27). (D) ROC curve of serum UEAG compared between MG and BTs. (E) Bar-graph comparing the level of serum UEAG between Grade I (MG-I, n = 85) and Grade II (MG-II, n = 8). Asterisk marks represent statistical significance (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$).

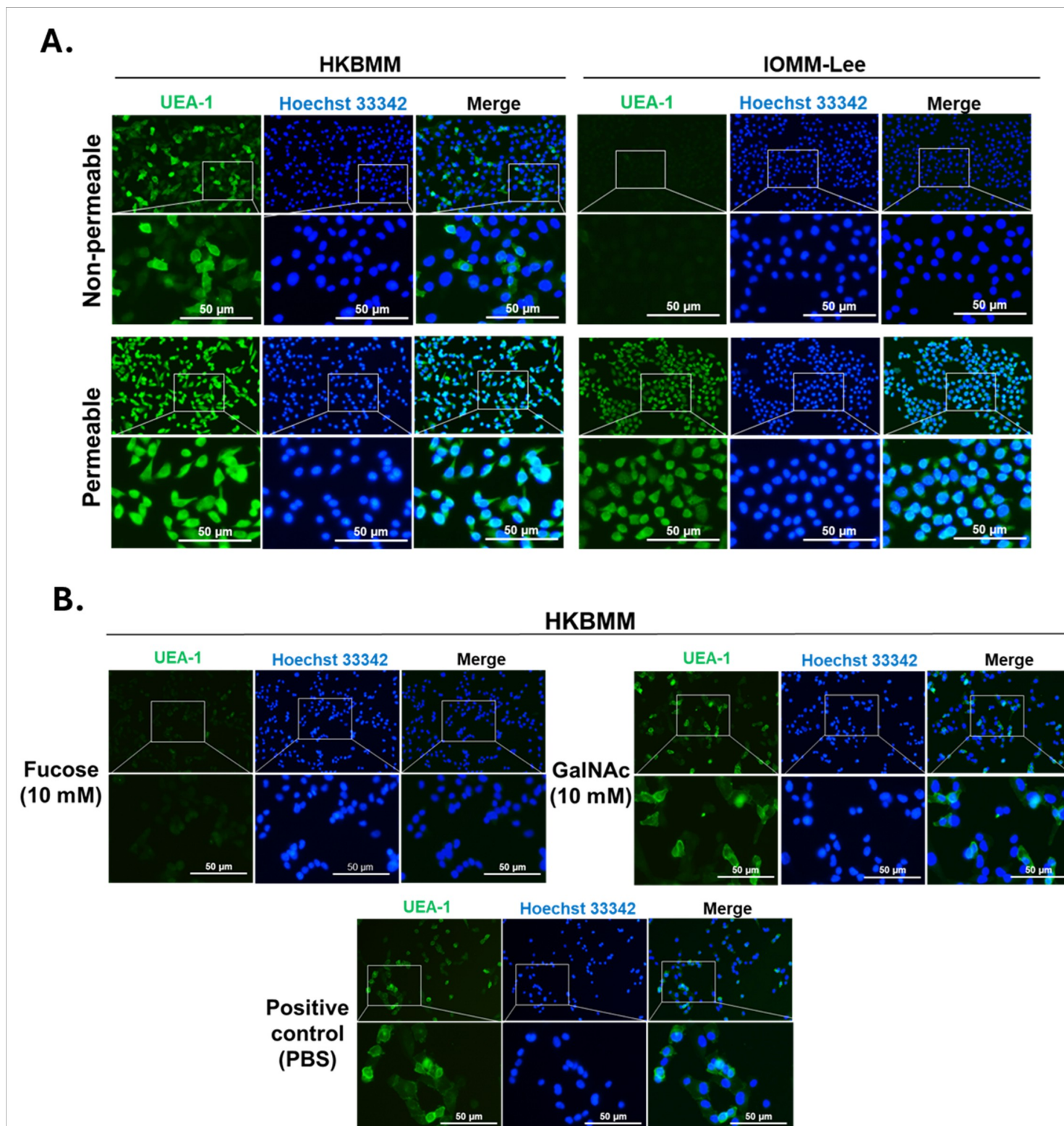


Figure 2

Expression of DBAG in MG cell lines (A) Expression of UEAG in HKBMM and IOMM-Lee was determined by lectin cytofluorescence using UEA-I (green) (B) The sugar neutralization of UEA-I with Fucose, GalNAc and PBS as a negative control was examined the specificity of UEA-I and UEAG. The nucleus was stained by Hoechst 33342 (blue). Scale bar equals 50 μ m.

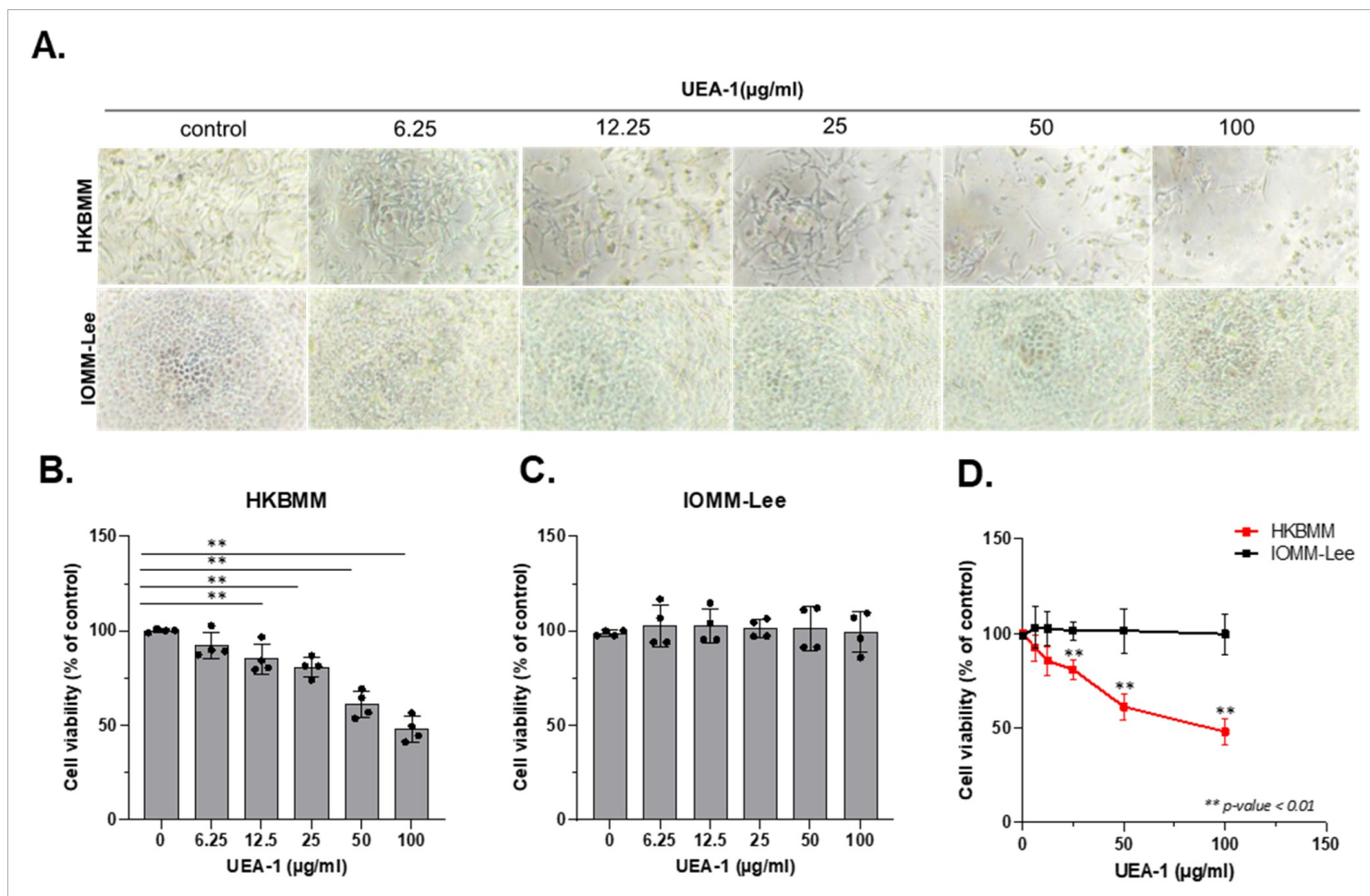


Figure 3

Effect of UEAG on MG cells. (A) Cell morphology of MG cells was observed after treatment with UEA-I 72 hr. Cell viability of (B) HKBMM and (C) IOMM-Lee was examined using MTT assay after treating with UEA-I 72 hr. (0 – 100 $\mu\text{g/ml}$). (D). The comparison of cell viability of HKBMM and IOMM-Lee. An asterisk mark (*) represents the statistically significant differences (*, $p < 0.05$; **, $p < 0.01$) with three independent experiments.

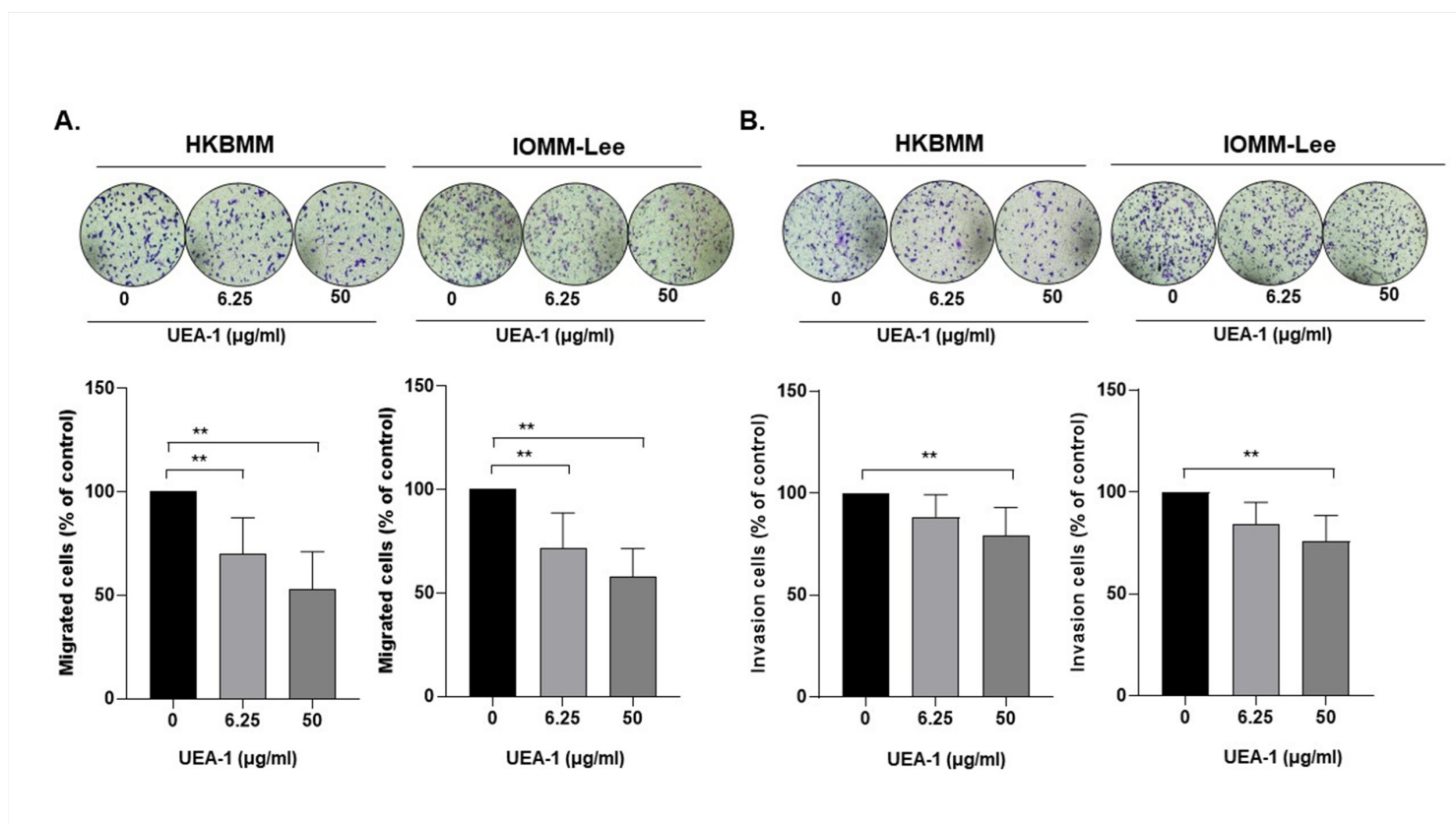


Figure 4

Effect of UEA-I on cell migration and invasion of MG cell. Cells were treated with UEA-I (6.25 and 50 µg/mL). After 6 h. the migrated and invaded cells were observed into the lower chamber. Cells without UEA-I treatment were used as a control. (A) Migrated cells and (B) invaded cells were stained with 0.5% (w/v) crystal violet and observed under a microscope compare with control. An asterisk mark (*) represents the statistically significant differences (*, $p < 0.05$; **, $p < 0.01$) with three independent experiments.

Supplementary Files

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