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Golgi phosphoprotein-3 (GOLPH3) promote metastasis of nasopharyngeal carcinoma through regulating E-cadherin

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Abstract. – OBJECTIVE: The purpose of this study was to investigate GOLPH3 expression in nasopharyngeal carcinoma (NPC) and its influence on the metastatic ability of NPC cells; meanwhile, the underlying mechanism of GOLPH3 promoting the malignant progression of NPC was also explored.

PATIENTS AND METHODS: In this study, quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was performed to examine the expression of GOLPH3 in 34 pairs of tumor tissue and paracancerous tissue specimens collected from NPC patients, and the interplay between GOLPH3 expression and clinical indicators was analyzed, as well as the prognosis of NPC patients. Meanwhile, GOLPH3 expression in NPC cell lines was further verified by qRT-PCR assay. Furthermore, GOLPH3 knockdown model was constructed in NPC cell lines, including SUNE2 and CNE. Then, cell counting kit-8 (CCK-8), transwell invasion, and cell wound healing assays were applied to analyze the effect of GOLPH3 on the biological function of NPC cells. In addition, an in-depth study of the relationship between GOLPH3 and E-cadherin was conducted.

RESULTS: QRT-PCR results indicated that the expression level of GOLPH3 in NPC was remarkably higher than that in adjacent tissues, and the difference was statistically significant. Compared with patients with low expression of GOLPH3, those with high expression of GOLPH3 had a higher incidence of lymph node metastasis. Compared with sh-NC group, the proliferation and invasive ability of NPC cells decreased remarkably after knockdown of GOLPH3. Subsequently, E-cadherin expression was found to be remarkably reduced and negatively correlated with GOLPH3 in NPC cell lines and tissues. Finally, the recovery experiment demonstrated that GOLPH3 might have a mutual regulatory relation with E-cadherin, both of which jointly affect the malignant progression of NPC.

CONCLUSIONS: GOLPH3 expression is remarkably associated with lymph node metastasis and poor prognosis of NPC patients; in addition, it may promote the proliferation and metastatic ability of NPC cells by regulating E-cadherin.

Key Words:
GOLPH3, E-cadherin, NPC, Metastasis.

Introduction

Nasopharyngeal carcinoma (NPC) is a common tumor of the head and neck, which mainly occurs in southeast Asia and is closely related to EB virus infection[1-3] Due to its special anatomical position and relative sensitivity to radiotherapy, radiotherapy has become the main treatment for nasopharyngeal carcinoma. However, recurrence and metastasis are the main causes of treatment failure[4-6]. With the advancement of radiotherapy equipment and treatment technology, three-dimensional intensity modulated radiotherapy become the mainstream clinical treatment technology, with the local control rate up to over 90%; however, the incidence of distant metastasis is not remarkably improved compared with the past 2D ordinary radiotherapy, which has become the bottleneck restricting the further improvement of survival rate[6,7]. Currently, it has entered the era of precision medicine, molecular mechanism research on malignant progression such as tumor development, invasion and metastasis, and early diagnosis and individualized precision treatment have become the focus of research in nasopharyngeal carcinoma[8-10].

Golgi phosphoprotein 3 (GOLPH3) and its interacting proteins are a hotspot in tumor research[11,12]. GOLPH3, also known as GMx33 or GPP34, is a highly conserved Golgi transmembrane protein, which is also an important protein for recycling, glycosylation and protein communication with plasma matrix in the Golgi body[12,13]. Buschman et al[14] and Li et al[15] found that GOLPH3 not only plays a role in morphology and trans-

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port of Golgi body, but also acts as a tumor gene, whose abnormal expression usually promotes the formation and metastasis of tumor. It has been reported[15-18] that the tumor gene GOLPH3 promotes tumor metastasis and proliferation by activating the Wnt pathway, BF-kB pathway, mTOR pathway or up-regulating the expression of MMP2 and MMP9. Zhang et al[19] demonstrated that high expression of GOLPH3 can promote tumor proliferation and metastasis in patients with bladder cancer, which is also found in lung cancer, rectal cancer, prostate cancer, ovarian cancer, liver cancer, and renal epithelial cancer. High expression of GOLPH3 is also found in breast cancer tissues, thus promoting the metastasis and proliferation of breast cancer[20-23] .

Epithelial cadherin (E-cadherin) is a transmembrane glycoprotein with molecular weight of 124 kD, which belongs to the classic calcium-dependent calcium adhesive subgroup. The lack of E-cad protein is associated with high mitotic index[24,25]. At present, the pathogenesis of NPC still remains elusive, and the role of GOLPH3 protein and E-cad protein in the occurrence and development of NPC has not been clearly reported in China. Therefore, in this study, the possible roles of GOLPH3 and E-cadherin in the malignant progression of NPC and their molecular regulatory mechanisms were explored, respectively, which may bring new ideas for the diagnosis and treatment of NPC.

Patients and Methods

Patients and NPC Samples

NPC tumor tissues and paracancerous tissues of 34 patients undergoing radical resection were collected. All patients underwent no radiotherapy or chemotherapy before surgery. The pathological classification and staging of NPC were based on the International Association of Cancer (UICC) staging criteria for NPC. Patients and their families had been fully informed and informed consent had been signed. The collection of clinical specimens was approved by the Ethics Committee of Caoxian People's Hospital.

Cell Lines and Reagents

Human NPC cell lines HNE1, SUNE2, HONE1, CNE2, and 6-10B cells and human nasopharyngeal immortalized epithelial cell line NP460 were purchased from American Type Culture Collection (ATCC; Manassas, VA, USA), and cultured in Roswell Park Memorial Institute-1640 (RPMI-1640; HyClone, South Logan, UT, USA) containing 5% fetal bovine serum (FBS) medium. Dulbecco's Modified Eagle's Medium (DMEM) and FBS were purchased from Life Technologies (Gaithersburg, MD, USA). All cell lines were cultured with high-glucose DMEM containing 10% FBS, penicillin (100 U/mL) and streptomycin (100 μg/mL) in an incubator with 5% CO_2 at 37°C.

Transfection

The control group (sh-NC) and the lentivirus containing the GOLPH3 knockdown sequence (sh-GOLPH3) were purchased from Shanghai Jima Company (Shanghai, China). Cells were plated in 6-well plates and cultured up to 40% cell density, followed by transfection according to the manufacturer's instructions. After 48 h, cells were collected for quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) analysis and cell function experiments.

Cell Counting Kit-8 (CCK-8) Assay

After 48 h of transfection, cells were collected and plated into 96-well plates at 2000 cells per well. The cells were cultured for 6 h, 24 h, 48 h, and 72 h respectively, and then added with CCK-8 (Dojindo Molecular Technologies, Kumamoto, Japan) reagent. After incubation for 2 h, the optical density (OD) value of each well was measured at an absorption wavelength of 490 nm using a microplate reader.

Cell Wound Healing

After transfection for 48 hours, the cells were digested, centrifuged, and resuspended in medium without FBS to adjust the density to 5 x 105 cells/mL. The density of the plated cells was determined according to the size of the cells (the majority of the number of cells plated was set to 50000 cells/well), and the confluency of the cells reached 90% or more the next day. After the stroke, cells were rinsed gently with phosphate-buffered saline (PBS) for 2-3 times and observed again after incubation with low-concentration serum medium for 24 h.

Transwell Cell Invasion Assay

When the density of NPC cell lines (SUNE2 and CNE2) reached 3×10^5/well, they were seeded in a 6-well plate. Liposomal transfection experiments can be performed when cell fusion reaches 80%. Positive clones were selected for expanded culture for subsequent transwell experiments, and the

transwell chamber containing Matrigel (Corning, Corning, NY, USA) and no Matrigel was placed in a 24-well plate. 200 μL of the cell suspension was added in the upper chamber, while 500 μL of a medium containing 10% FBS was added to the lower chamber. After incubation in the incubator at 37°C for 48 h, the chamber was removed, fixed with 4% paraformaldehyde for 30 min, and stained with crystal violet for 15 min. Subsequently, cells were washed with PBS, and the inner surface of the basement membrane of the chamber was carefully cleaned to remove the inner layer cells. The perforated cells stained in the outer layer of the basement membrane of the chamber were observed in 10 randomly selected fields of view under the microscope (Olympus, Tokyo, Japan).

QRT-PCR

The expression of E-cadherin, β-actin, GOLPH3, and U6 mRNA in NPC tissues and cells was detected by qRT-PCR. Total RNA was extracted in one step by TRIzol reagent (Invitrogen, Carlsbad, CA, USA), reversely transcribed into the first strand of complementary deoxyribose nucleic acid (cDNA) using PrimeScript RT Reagent (TaKaRa, Otsu, Shiga, Japan) reverse transcription kit, and primers were designed using Primer 5.0 software. The qRT-PCR was performed using SYBR® Premix Ex Taq™ (TaKaRa, Otsu, Shiga, Japan) and StepOne Plus Real-time PCR System (Applied Biosystems, Foster City, CA, USA). The following primers were used for qRT-PCR reaction: GOLPH3: forward: 5'-GGGCGACTCCAAGGAAAC-3', reverse: 5'-CAGCCACGTAATCCAGATGAT-3'; E-cadherin: forward: 5'-CGGGATCCATGGATGAAAACCTGAAGGCAGCCGAC-3', reverse: 5'-CCATCGATTGTCGTCCTCGCCACCGCCG-3'; β-actin: forward: 5'-CCTGGCACCCAGCACAAT-3', reverse: 5'-GCTGATCCACATCTGCTGGAA-3'. With replicates set for each sample, the assay was repeated twice. The Bio-Rad PCR instrument (Bio-Rad, Hercules, CA, USA) was used to analyze and process the data. β-actin and U6 genes were used as internal parameters, and the gene expression was calculated by the 2-ΔΔCt method.

Western Blot Assay

The tissue or cells to be analyzed were collected, and the tissue lysate pre-cooled on ice was added, shaken vigorously, and placed on ice for lysis for 30 min. After the protein concentration was determined by the Bradford method, the protein sample was denatured in a water bath at 100°C for 5 min and added with an appropriate amount of the loading buffer (Beyotime, Shanghai, China). The denatured protein sample was pipetted to the sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) gel, transferred to polyvinylidene difluoride (PVDF) membrane (Roche, Basel, Switzerland), and blocked with 5% skim milk powder for 1 h at room temperature, followed by incubation with primary antibodies against GOLPH3 (1:1500) and E-cadherin (1: l500) overnight at 4°C in a shaker. On the next day, the membrane was rinsed 3 times with Tris-Buffered Saline and Tween-20 (TBST) and incubated with second antibody (concentration: 1:1000) for 1 h at room temperature. After that, the protein samples on the membrane were finally semi-quantitatively analyzed by Alpha Innotech Digital Imaging System (Bosch Institute, University of Sydney, Australia).

Statistically Analysis

Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) 22.0 statistical software (IBM Corp., Armonk, NY, USA). The *t*-test was used to compare the measurement data, and the categorical variables were analyzed by χ^2-test or Fisher's exact probability method. Survival analysis was performed using the Kaplan-Meier method and survival curves were plotted. Data were expressed as mean ± standard deviation ($\bar{x}\pm s$), and $p<0.05$ was considered to be statistically significant.

Results

GOLPH3 Was Highly Expressed in NPC Tissues and Cell Lines

GOLPH3 expression was remarkably enhanced in NPC tumor tissue specimens compared to paracancerous ones, and the difference was statistically significant (Figure 1A and 1B). Similarly, compared with NP460, GOLPH3 was highly expressed in NPC cell lines, especially in the SUNE2 and CNE2 cell lines, the two of which were therefore selected for subsequent cell experiments (Figure 1C).

GOLPH3 Expression Was Correlated With Lymph Node Metastasis and Prognosis of NPC

We subsequently analyzed the relationship between the expression of GOLPH3 in tumor tissues of 34 patients with NPC and their clinical indica-

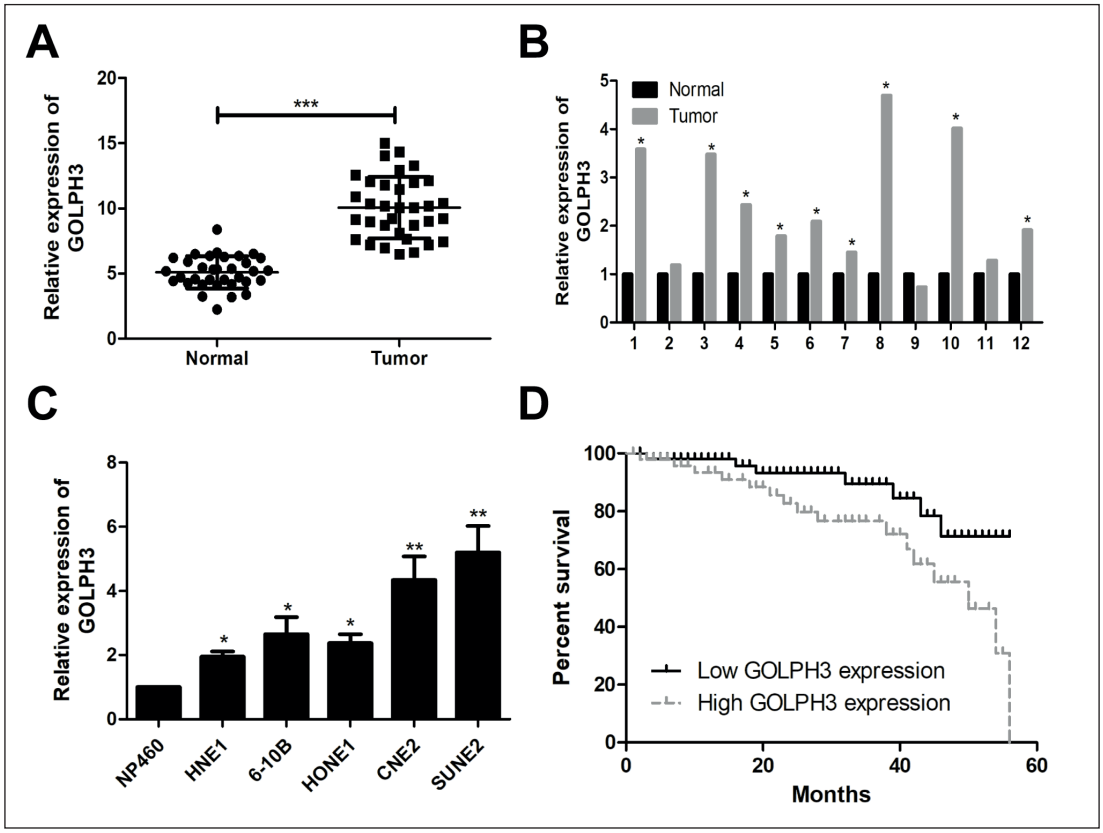

Figure 1. GOLPH3 is highly expressed in nasopharyngeal carcinoma tissues and cell lines. **A**, **B**, QRT-PCR was used to detect the difference in expression of GOLPH3 in tumor tissues and paracancerous tissues of patients with nasopharyngeal carcinoma. **C**, QRT-PCR was used to detect the expression level of GOLPH3 in nasopharyngeal carcinoma cell lines. **D**, Kaplan Meier survival curve of patients with nasopharyngeal carcinoma was plotted based on GOLPH3 expression; the prognosis of patients with high expression was significantly worse than that of low expression group. Data are mean ± SD, *p<0.05, **p<0.01, ***p<0.001.

tors such as age, sex, pathological stage, and the condition of lymph node metastasis. As shown in Table I, high expression of GOLPH3 was positively correlated with the incidence of lymph node metastasis, but not with other parameters. In addition, relevant follow-up data were collected to explore the association between GOLPH3 expression and the prognosis of NPC patients. Kaplan-Meier survival curves indicated that high expression of GOLPH3 was conspicuously associated with poor prognosis of NPC (p<0.05; Figure 1D).

Knockdown of GOLPH3 Inhibited Cell Proliferation Ability and Invasion in NPC

To explore the influence of GOLPH3 on the function of NPC cells, the GOLPH3 knockdown expression model was first constructed and verified successfully by qRT-PCR (Figure 2A). Cell proliferation, cell wound healing, and transwell assays were subsequently performed in the SUNE2 and CNE2 cell lines, respectively. CCK-8 result revealed that the proliferation rate of NPC cells in the GOLPH3 knockdown group was remarkably lower than that in sh-NC group, and the difference was statistically significant (Figure 2B). In addition, cell wound healing test revealed that the crawling ability of NPC cells in the GOLPH3 knockdown group was attenuated compared with the sh-NC group (Figure 2C). Meanwhile, the transwell invasion assay also showed a significant decrease in the number of membrane-penetrating nasopharyngeal carcinoma cells in the transwell chamber of the GOLPH3 knockdown group, suggesting that the cell invasive ability was inhibited (Figure 2D).

E-cadherin was Lowly Expressed in NPC Tissues and Cell Lines

Bioinformatics studies have been used to predict that GOLPH3 and E-cadherin may have some association in NPC. It was found by Western Blot that knockdown of GOLPH3 remark-

Table I. Association of GOLPH3 expression with clinicopathologic characteristics of nasopharyngeal carcinoma.

Parameters	Number of cases	GOLPH3 expression		*p*-value
		Low (%)	High (%)	
Age (years)				0.311
<50	18	11	7	
≥50	16	7	9	
Gender				0.746
Male	16	8	8	
Female	18	10	8	
T stage				0.800
T1-T2	22	12	10	
T3-T4	12	6	6	
Lymph node metastasis				0.038
No	23	15	8	
Yes	11	3	8	

ably increased the expression level of E-cadherin protein, indicating a close relationship between GOLPH3 and E-cadherin-related proteins (Figure 3A). Subsequently, qRT-PCR experiment also showed that downregulation of GOLPH3 elevated the mRNA level of E-cadherin (Figure 3B). In addition, NPC tissue verification revealed a significant decrease in E-cadherin expression in tumor tissue samples of NPC patients compared to paracancerous ones (Figure 3C). At the same time, E-cadherin was also remarkably lower in NPC cell lines than that in NP460 cells, and the difference was also statistically significant (Figure 3D). Therefore, we detected the mRNA expression of GOLPH3 and E-cadherin in above NPC tissue samples using qRT-PCR and found that there was a negative correlation between the two genes (Figure 3E).

GOLPH3 Modulated E-Cadherin Expression in Human NPC Cells

To further explore how GOLPH3 and E-cadherin work together to regulate the malignant progression of NPC, we simultaneously knocked down GOLPH3 and E-cadherin in SUNE2 and CNE2 cell lines, and the transfection efficiency was verified by qRT-PCR (Figure 4A). Subsequently, CCK-8 and transwell invasion experiments demonstrated that knockdown of E-cadherin remarkably increased the number of transmembrane NPC cells in the GOLPH3 knockdown group, thereby counteracting the effect of down-regulation of GOLPH3 on invasion and metastasis of NPC cells (Figure 4B and 4C).

Discussion

NPC is a malignant head and neck tumor with high incidence in southern China, with an increasing incidence year by year[1-3]. Liu et al[4] and Holliday et al[5] have shown that NPC is more likely to occur in middle-aged and elderly people, and its incidence gradually increases with the increase of age, reaching its peak at the age of 45-60 years. Its pathogenesis is highly correlated with EB virus, genetic susceptibility, environmental factors, dietary habits, and other factors. Like other tumors, the occurrence and development of NPC is a complex process involving multiple genes, pathways, and steps[3-7]. In recent years, GOLPH3 has been increasingly known as an oncogene[11-13]. GOLPH3 in serum can be used as a tumor marker for the diagnosis of ovarian cancer, which, combined with traditional tumor markers including CA125 and CA199, can improve the diagnostic accuracy of ovarian cancer patients[26]. After clarifying the clinical diagnostic value of GOLPH3, current studies[14-16] are focusing on the effect of GOLPH3 on tumor biological characteristics. GOLPH3 can promote the formation and proliferation of esophageal cancer through the mTOR and the Wnt pathway[15-18], while Wu et al[21] found that overexpression of GOLPH3 can promote the proliferation of rectal cancer cells and lead to poor prognosis. Therefore, GOLPH3 is a factor that plays a pivotal role in tumor biological behavior and is involved in regulating cell proliferation, cell cycle, apoptosis, and cell invasion[17-23]. We found that GOLPH3 is an oncogene with high expres-

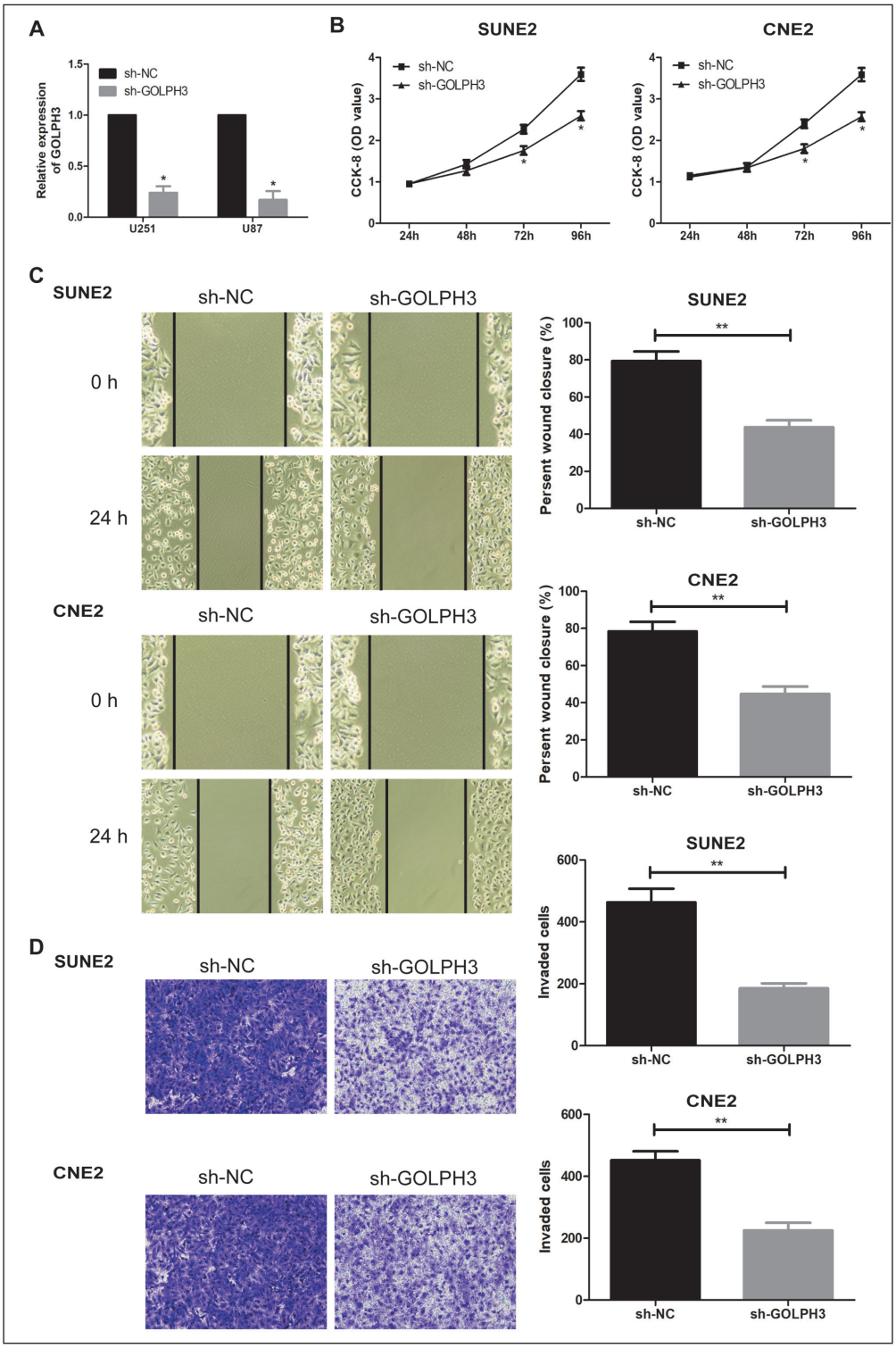

Figure 2. Knockdown of GOLPH3 inhibits the proliferation and invasion of nasopharyngeal carcinoma cells. **A**, QRT-PCR verified the interference efficiency of GOLPH3 after transfection of GOLPH3 knockdown vector in nasopharyngeal carcinoma SUNE2 and CNE2 cell lines. **B**, CCK-8 assay was used to detect the proliferation ability of nasopharyngeal carcinoma cells after knockdown of GOLPH3 in nasopharyngeal carcinoma SUNE2 and CNE2 cell lines. **C**, Cell wound healing assay was used to detect the crawling ability of nasopharyngeal carcinoma cells after knockdown of GOLPH3 in nasopharyngeal carcinoma SUNE2 and CNE2 cell lines (magnification: 40×). **D**, Transwell invasion assay was used to detect the invasion and migration ability of nasopharyngeal carcinoma cells after knockdown of GOLPH3 in nasopharyngeal carcinoma SUNE2 and CNE2 cell lines (magnification: 40×). Data are mean ± SD, *p<0.05, **p<0.01.

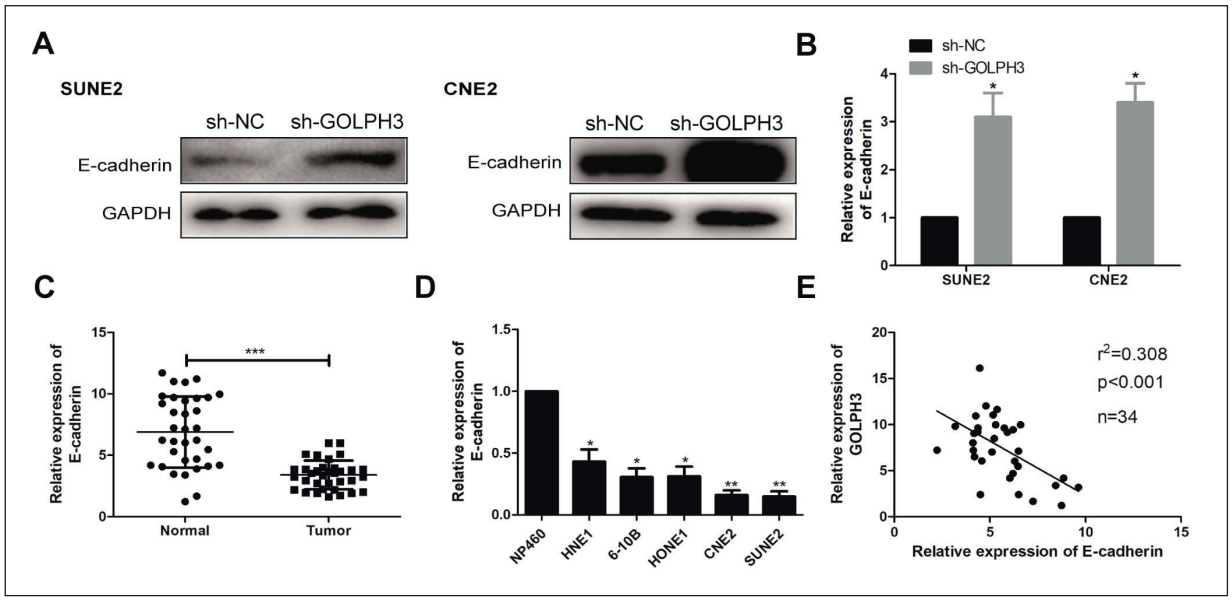

Figure 3. E-cadherin is underexpressed in nasopharyngeal carcinoma tissues and cell lines. **A**, Western blot verified the expression level of E-cadherin after transfection of GOLPH3 knockdown vector in nasopharyngeal carcinoma SUNE2 and CNE2 cell lines. **B**, QRT-PCR verified the expression level of E-cadherin after transfection of GOLPH3 knockdown vector in nasopharyngeal carcinoma SUNE2 and CNE2 cell lines. **C**, QRT-PCR was used to detect the difference of E-cadherin expression in tumor tissues and paracancerous tissues of patients with nasopharyngeal carcinoma. **D**, QRT-PCR was used to detect the expression level of E-cadherin in nasopharyngeal carcinoma cell lines. **E**, There was a significant negative correlation between the expression levels of GOLPH3 and E-cadherin in nasopharyngeal carcinoma. Data are mean ± SD, *p<0.05, **p<0.01, ***p<0.001.

sion in NPC tissues, which is valuable for early diagnosis. Moreover, high GOLPH3 expression was indicated to be positively correlated with the incidence of lymph node metastasis, suggesting that GOLPH3 may play a pivotal role in the metastasis of NPC.

GOLPH3 knockdown vector was constructed using lentivirus and transfected into NPC cell lines including SUNE2 and CNE2, and the interference efficiency was verified by qRT-PCR. Transwell invasion assay revealed that the invasion ability of NPC cells was remarkably attenuated after down-regulation of GOLPH3. Therefore, it was concluded that knockdown of GOLPH3 can remarkably reduce the invasion ability of NPC cell lines, resulting in increased lymph node metastasis in patients with NPC.

To clarify the biological function of GOLPH3 in NPC, we further searched for its target gene and explored the effect of its interaction with target gene on the process of tumor genesis and development. Subsequently, qRT-PCR and Western blot results revealed that the expression of E-cadherin in NPC tumor tissues was remarkably down-regulated compared with the matched adjacent tissues. In addition, it was found by qRT-PCR that the expression level of E-cadherin was the lowest in SUNE2 and CNE2 cell lines, laying a foundation for the subsequent experiments. Furthermore, it was verified that knockdown of GOLPH3 remarkably upregulated mRNA and protein expression of E-cadherin. Finally, the recovery assay verified that silencing E-cadherin remarkably elevated the number of transmural NPC cells in the transwell compartment of the GOLPH3-knockdown group, thereby counteracting the effect of GOLPH3 on the invasion and metastasis of NPC cells. Therefore, GOLPH3 may promote malignant progression of NPC *via* regulating E-cadherin.

Conclusions

In summary, GOLPH3 expression is remarkably associated with the incidence of lymph node metastasis and poor prognosis of NPC patients; in addition, GOLPH3 may promote the invasion of NPC by regulating E-cadherin.

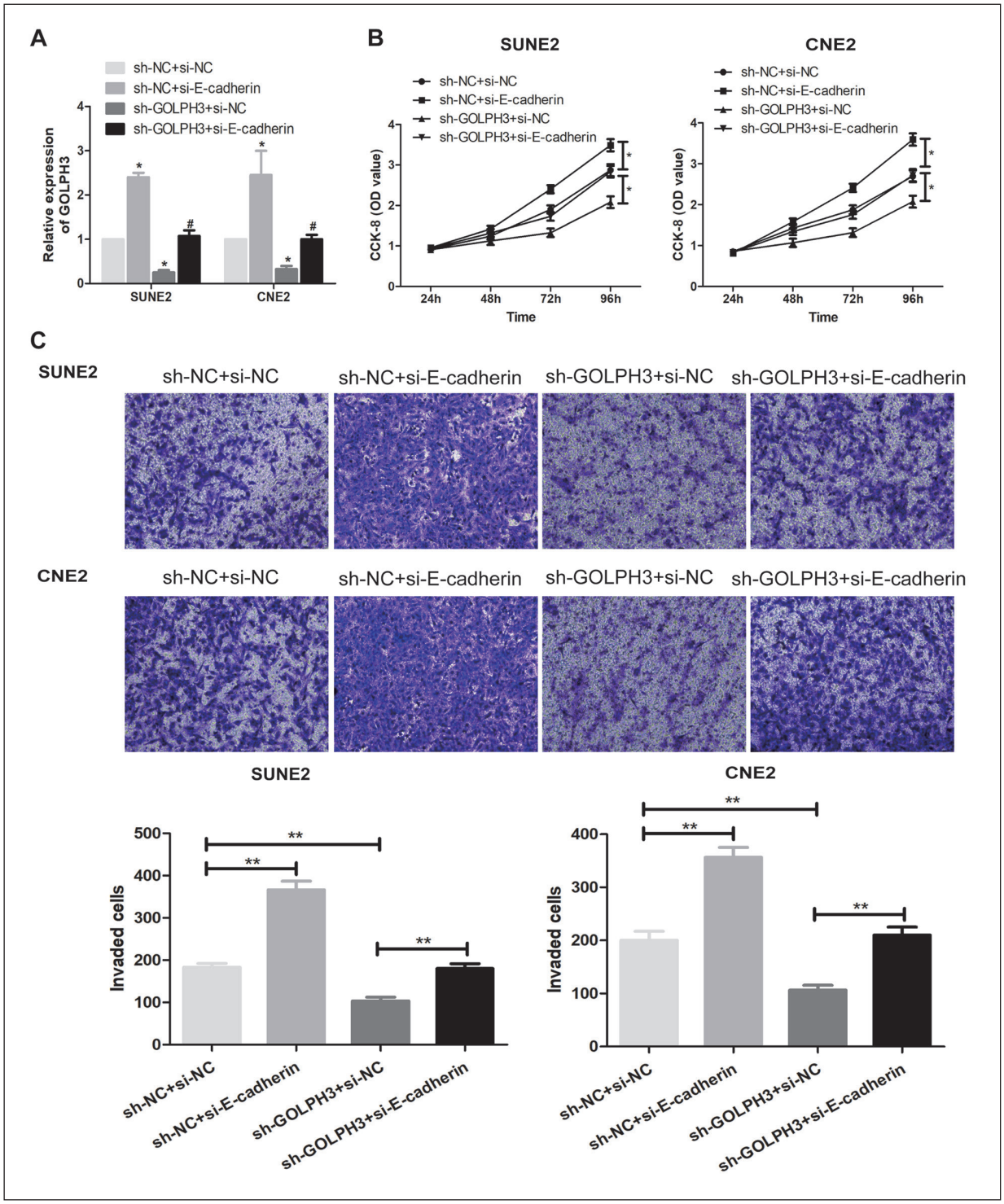

Figure 4. GOLPH3 regulates the expression of E-cadherin in nasopharyngeal carcinoma cell lines. **A**, GOLPH3 expression levels in nasopharyngeal carcinoma cell lines co-transfected with GOLPH3 and E-cadherin were detected by qRT-PCR. **B**, CCK-8 assay was used to detect the proliferation ability of nasopharyngeal carcinoma cells after co-transfection of GOLPH3 and E-cadherin. **C**, Transwell invasion assay was used to detect the invasion ability of nasopharyngeal carcinoma cells after co-transfection of GOLPH3 and E-cadherin (magnification: 40×). Data are mean ± SD, *p<0.05, **p<0.01.

Conflict of Interests

The authors declare that they have no conflict of interests.

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