Mechanism of the GALNT family proteins in regulating tumorigenesis and development of lung cancer (Review)

CHANGCHUN MIAO, RONGGUI SUN, DEYU JI, MIN WU, QIGUI FU, LIANGLIANG MEI and ZHIYONG WU

Department of Cardiothoracic Surgery, Mingguang People's Hospital, Mingguang, Anhui 239400, P.R. China

Received September 11, 2024; Accepted February 20, 2025

DOI: 10.3892/mco.2025.2832

Abstract. Lung cancer is one of the most common and lethal malignant tumors. Currently, surgical resection is the most effective treatment for early-stage lung cancer, and often results in favorable recovery outcomes. Therefore, early detection and control of lung cancer occurrence, invasion and metastasis are crucial for improving patient survival rates. Identifying tumor markers for lung cancer plays a vital role in facilitating early detection and control of its progression. The GALNT family proteins are enzymes that regulate the initial step in mucin O-glycan synthesis. It has been revealed that the expression of polypeptide N-acetyl-galactosamine-transferase (GALNT) family members is dysregulated in various tumors, and is closely associated with tumorigenesis, tumor cell growth, metastasis, adhesion, and serves as an important early indicator of tumor development. The present review compiles and analyzes findings concerning the role of GALNT family proteins in regulating lung cancer, with the goals of elucidating their mechanisms in lung cancer occurrence and progression and providing insights for improving the prognosis and therapeutic treatment of patients with lung cancer.

Contents

1. Introduction

In recent years, due to factors such as increased environmental pollution, the incidence of lung cancer has been increasing, and it now occupies first place in cancer incidence (1). According to its pathological type, lung cancer can be divided into categories of small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC accounts for 85% of lung cancers and is the most common type of lung cancer. It mainly includes lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD) (2,3). Among NSCLCs, LUAD is the main manifestation, and accounts for >85% of NSCLCs (4). It is known that tumor markers are helpful for detecting the early onset of cancer and treating the disease. Existing serum tumor molecular markers, including carcinoembryonic antigen and neuron specific enolase have been widely used in the diagnosis of lung cancer. However, their diagnostic sensitivity and specificity in lung cancer are very limited, and especially for early-stage lung cancer. Therefore, early detection and control of the occurrence, invasion and metastasis of LUAD are of great significance for improving the survival of patients with that disease. With the advancement of molecular medicine, our understanding of lung cancer now extends to the genetic level, and especially our understanding of LUAD, for which treatment plans can be detailed to specific target genes (for example, *EGFR*, *ROS1* and *ALK*). However, numerous patients with advanced LUAD still lack detectable genetic mutations, and some develop drug resistance or experience side effects following targeted therapy. Therefore, exploring novel genes associated with the occurrence and progression of LUAD and identifying tumor markers with greater specificity and sensitivity are crucial for optimizing treatment strategies for this disease.

Glycosylation is a widespread type of protein post-translational modification, of which N-glycosylation and O-glycosylation are the two most important examples (5). N-glycosylation regulates protein folding, secretion and stability. When N-glycosylation is abnormal, the endoplasmic reticulum stress response and apoptosis become activated. O-glycosylated proteins are found on the cell surface, serum and extracellular matrix (ECM). Changes in O-glycoproteins on the cell surface are usually associated with uncontrolled proliferation, invasion and metastasis. O-glycosylated ECM proteins are associated with various pathological changes (6). Abnormal forms of O-glycans are found in different solid tumors, including ovarian, bladder, breast, cervical, colon and lung cancers (7-9). O-glycosylation is initiated by polypeptide-N-acetyl-galactosamine-transferase (GALNT enzyme family), which covalently combines the GalNAc group of the glycoside donor UDP-GalNAc with the side chain

Correspondence to: Professor Zhiyong Wu, Department of Cardiothoracic Surgery, Mingguang People's Hospital, 379 Mingguang Avenue, Mingguang, Anhui 239400, P.R. China
E-mail: mgsrmyywzy@163.com

Key words: lung adenocarcinoma, N-acetyl-galactosamine-transferase family proteins, tumor microenvironment, early diagnosis, cell adhesion, invasion and metastatic capacity

hydroxyl group of a protein serine or threonine residue (10). The GalNAc-α-Ser/Thr structure is formed, also known as the Tn antigen structure. Members of the GALNT enzyme family are type II transmembrane proteins. During development and differentiation, the expression of various GALNT genes is highly restricted to cells and tissues (11). In recent years, numerous studies have shown that GALNT family proteins play an important role in the development of lung cancer. Therefore, the mechanism by which abnormal expression of GALNT family proteins regulates the occurrence and development of lung cancer is reviewed.

2. GALNT proteins

GALNT2 protein. The GALNT2 protein is overexpressed in lung cancer and regulated by microRNA (miR)-30a-5p (Fig. 1). A proteomics search for differentially expressed proteins in lung cancer tissues and normal lung tissues, plus an analysis of RNA sequencing data for lung cancer tissues and corresponding paracancerous tissues in The Cancer Genome Atlas (TCGA; https://www.cancer.gov/ccg/research/genome-sequencing/tcga), Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) and Oncomine (https://www.oncomine.com/) databases, among others, revealed that GALNT2 protein is involved in NSCLC. GALNT2 expression is significantly increased in NSCLC, and GALNT2 is positively correlated with the poor prognosis for NSCLC (12-15). A high level of GALNT2 expression in lung cancer is related to the low methylation level in the promoter region of the gene. Expression of the GALNT2 protein is also regulated by miR-30a-5p (16). Induction of miR-30a-5p expression in lung cancer cell lines was found to reduce GALNT2 mRNA and protein levels in LUAD.

It has been reported that GALNT2 promotes cell proliferation, migration and invasion by activating the Notch/Hes1-PTEN-PI3K/Akt signaling pathway (Fig. 1) (12). Using small interfering RNA (siRNA) to interfere with GALNT2 protein expression in lung cancer cells can lead to decreased levels of Notch1/3, Hes1, p-AKT, t-AKT and p-mToR, and increased expression of the tumor suppressor gene, *PTEN*. The Notch signaling pathway regulates several cancer-related processes, including proliferation, metastasis, epithelial-to-mesenchymal transition (EMT), angiogenesis, and the stemness of cancer cells (17,18). Notch1 and Notch3 promote LUAD, while Notch2 inhibits LUAD. A meta-analysis (including 19 articles with a total of 3,663 cases) showed that overexpression of Notch1 or Notch3 significantly reduced the overall survival (OS) of patients with NSCLC (19). Results of another NSCLC study showed that GALNT2 mediates the development of lung cancer by regulating the O-glycosylation of ITGA5, leading to activation of the PI3K/Akt and MAPK/ERK pathways (Fig. 1) (14). ITGA5 belongs to the integrin alpha chain family. Integrins are heterodimeric integral membrane proteins composed of α and β subunits that play roles in cell surface adhesion and signaling. The ITGA5 subunit and ITGB1 subunit combine to form fibronectin receptors. This integrin may promote tumor invasion, and high expression of this gene may be associated with a shorter survival time for patients with lung cancer (20). The AKT and ERK signaling pathways are closely related to the occurrence and development of tumors. It has been reported that ERK1/2 and p-ERK1/2 expression are associated with low survival rates among patients with lung cancer (21).

The GALNT2 protein is also a key regulator of radioresistance in n NSCLC, and the insulin-like growth factor 1 receptor (IGF1R) may be an important effector protein downstream of the GALNT2 signaling pathway (16). IGF1R is a ubiquitously expressed membrane-bound tyrosine kinase receptor that recognizes its two major ligands, IGF1 and IGF2, and controls a variety of basic cellular functions (22). IGF1R signaling is a key factor in cancer cell proliferation, survival, migration and resistance to anticancer therapy, and plays an important role in lung cancer (23).

In addition, GALNT2 can also regulate immune cell infiltration in lung cancer (13,15). Single sample Gene Set Enrichment Analysis (ssGSEA) was used to analyze the correlation between GALNT2 expression and immune cell infiltration in LUAD, and it was found that GALNT2 expression was negatively correlated with activated B cells, activated CD8 T cells, immature B cells and eosinophil infiltration (all $P<0.001$). Further research found that PD-L1 expression was positively correlated with GALNT2 expression, suggesting that GALNT2 could serve as a predictive biomarker for the therapeutic effect of immunotherapy drugs.

GALNT3 protein. When compared with normal lung tissues, the levels of GALNT3 mRNA and protein in NSCLC tissues are significantly increased (24,25). GALNT3 protein expression in LUAD is regulated by the LINC02535/miR-30a-5p axis (Fig. 2) (26). LINC02535 is significantly upregulated in LUAD, resulting in a downregulation of miR-20a-5p. Downregulation of miR-20a-5p results in increased GALNT3 protein expression. In addition, it has been revealed that abnormal expression of the GALNT3 protein is related to abnormal promoter methylation (27).

GALNT3 protein can promote the proliferation, migration and invasion of LUAD cells, activate the NF-κB signaling pathway by affecting glycosylation of the MUC1 protein, and promote the malignant progression of LUAD cells (Fig. 2). MUC1 is a mucin-like type I transmembrane glycoprotein (28) that plays an important role in the renewal and differentiation of epithelial cells, maintenance of epithelial cell integrity, as well as tumor occurrence and metastasis (29). In numerous malignant tumors, changes in MUC1 glycosylation lead to its highly abnormal expression (30). The transmembrane C-terminus of MUC1 (MUC1-C), as an oncoprotein, can affect the NF-κB signaling pathway and promote the occurrence and development of various malignant tumors (31).

Overexpression of GALNT3 mRNA is associated with immune cell infiltration and a poor prognosis in cases of LUAD, and patients with high GALNT3 mRNA expression have a higher survival rate (24). The level of GALNT3 expression in LUAD is closely related to the Th2 cell immune marker genes *STAT6*, *CCR8* and *HAVCR1*. The aforementioned study also found that in LUAD cases with high levels of macrophages, regulatory T cells, and type 2 T helper cell infiltration, high GALNT3 expression was most closely related to a poor prognosis. There are also studies showing completely contradictory conclusions regarding the role of GALNT3 in lung cancer. A previous study showed that GALNT3 inhibited the

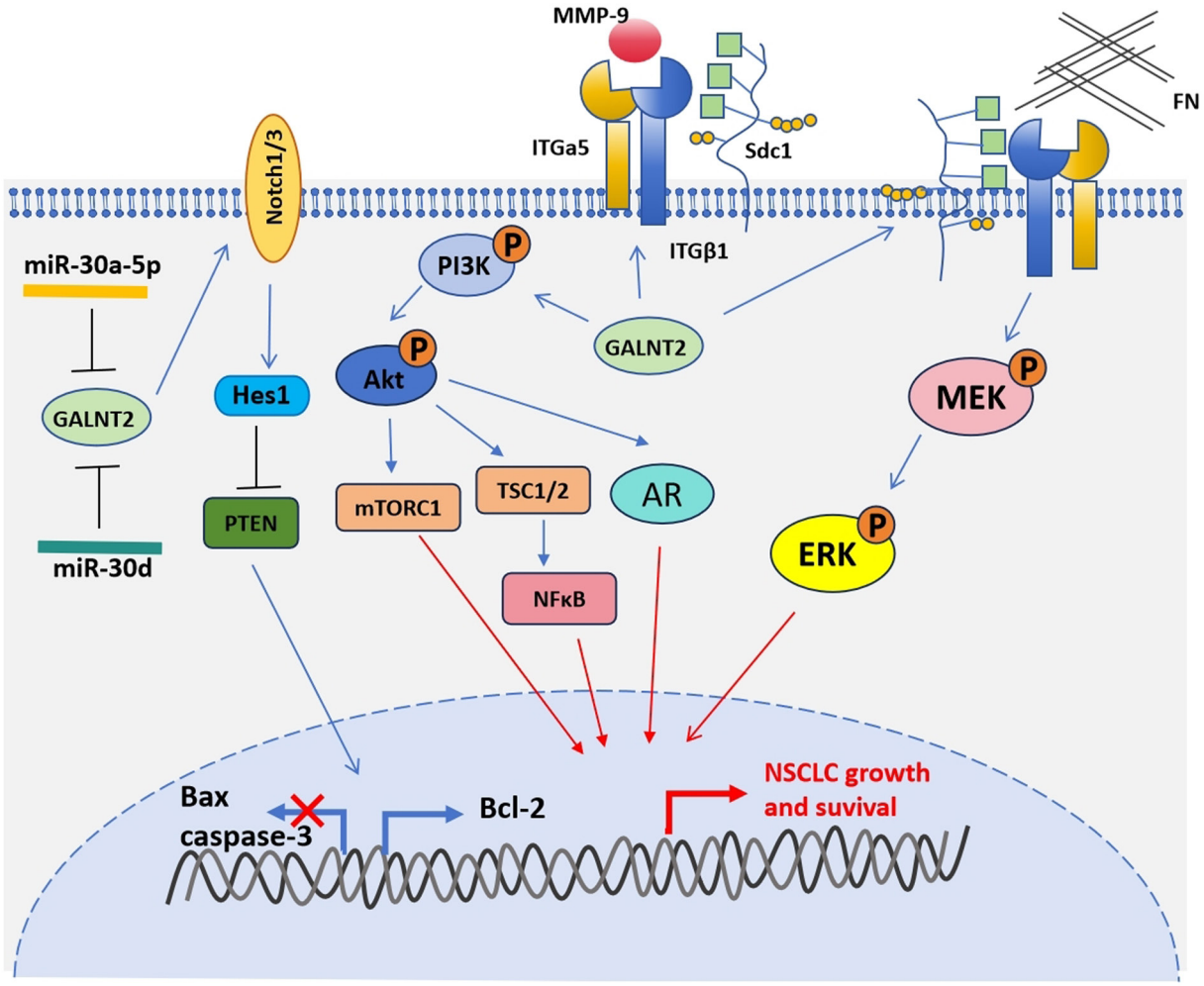

Figure 1. Mechanism by which the GALNT2 protein regulates the occurrence and development of lung cancer. GALNT, N-acetyl-galactosamine-transferase; NSCLC, non-small cell lung cancer; miR, microRNA.

development of lung cancer in both xenograft and syngeneic mouse models, where it inhibited lung cancer by reducing myeloid-derived suppressor cell infiltration and angiogenesis in a TNFR- and c-MET pathway-dependent manner (32). Additionally, it has been shown that the abnormally high expression of GALNT3 in LUAD is promoting tumor growth. However, it has also been reported that abnormally high expression of GALNT3 can decelerate lung cancer growth by disrupting the tumor microenvironment (TME), which may be achieved through different signaling pathways. Notably, these results need to be verified by more powerful biological experiments. Therefore, a hypothesis was proposed by the authors: Abnormally high expression of GALNT3 protein in the early stage of lung cancer promotes tumor growth, and when the expression reaches a certain threshold, it destroys the TME and thus decelerates the tumor progression, and serves to inhibit tumor growth.

GALNT4 protein. GALNT4 protein can promote the proliferation and invasion of NSCLC cells and inhibit tumor cell apoptosis (33). In the H1299 cell line, using siRNA to reduce the expression level of GALNT3 protein also reduced the proliferation rate of tumor cells, the number of clones formed, and increased the proportion of apoptotic cells. In NSCLC, GALNT4 protein expression is regulated by miR 365b. The levels of miR-365b are significantly downregulated in NSCLC cells, and the reduced binding to the GALNT4 mRNA 3'-untranslated region induces a high level of GALNT4 mRNA expression, thereby promoting the development of lung cancer.

GALNT4 protein can be used to predict the prognosis of LUAD. One group of researchers constructed a model to predict the prognosis of patients with LUAD. The model included SMCO2, SATB2, HAVCR1, GRIA1 and GALNT4 protein expression, as well as TP53 mutations (34). A patient's risk score was derived from those indicators, and calculated as follows: Risk score=0.737888 x Exp SMCO2 + 0.357248 x Exp SATB2 + 0.061489 x Exp HAVCRI-0.72351 x Exp GRIA1 + 0.43393 x Exp GALNT4 + 0.14491 x mut TP53. Patients with high risk scores had lower survival rates, while patients with low risk scores had a greater likelihood of survival.

GALNT6 protein. The upregulated expression of GALNT6 protein in LUAD is associated with lymph node metastasis and a poor prognosis (35). In LUAD cells, GALNT6 overexpression was found to promote EMT, wound healing and invasion, while reducing GALNT6 protein expression significantly reversed those effects. Furthermore, reducing GALNT6 expression alleviated LUAD metastasis and prolonged the

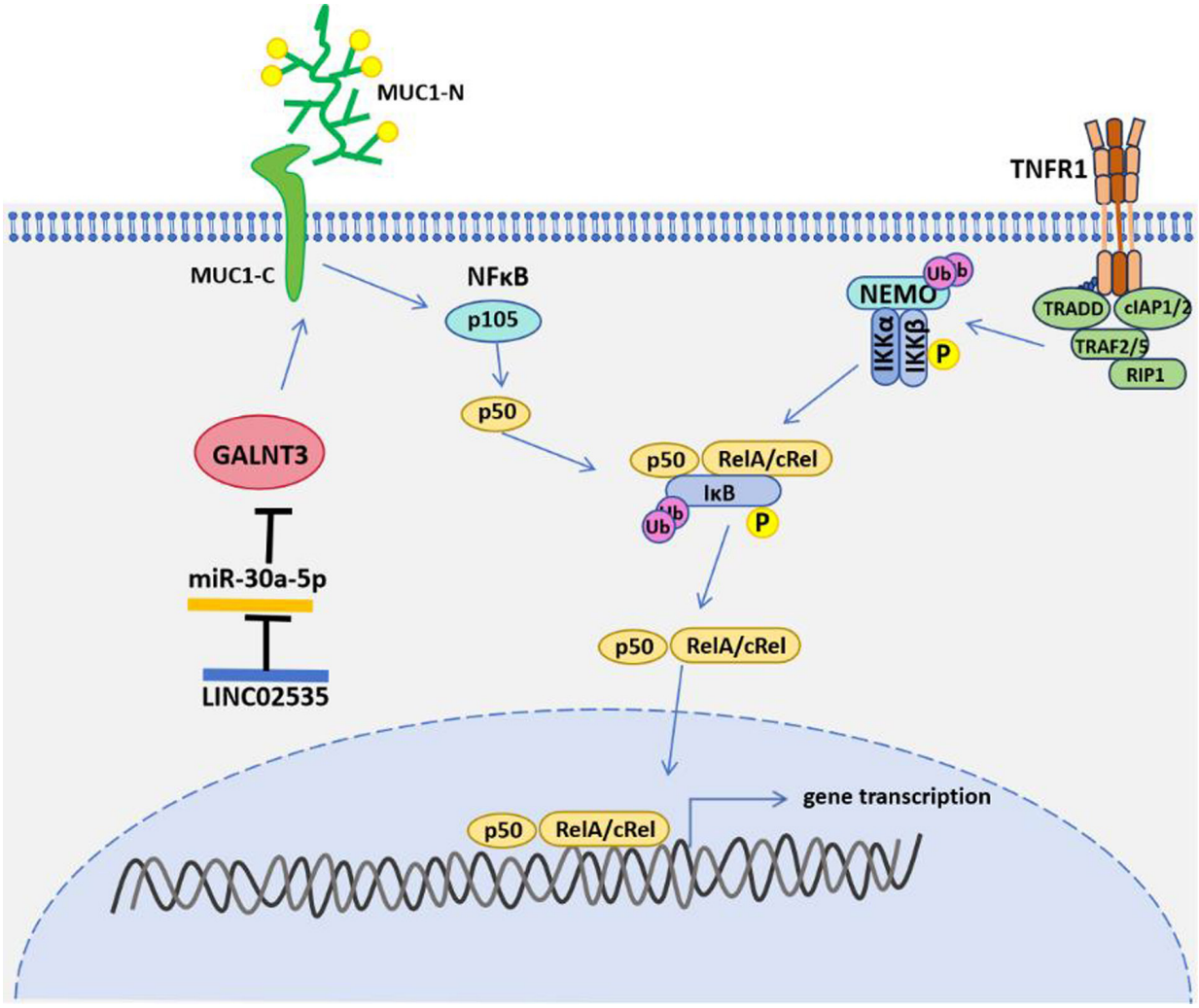

Figure 2. Mechanism by which the GALNT3 protein regulates the occurrence and development of lung cancer. GALNT, N-acetyl-galactosamine-transferase; miR, microRNA.

survival times of mice with xenograft tumors. Mechanistic studies indicate that GALNT6 directly interacts with the glycosylation chaperone GRP78, and GRP78 promotes EMT by enhancing the MEK1/2/ERK1/2 signaling pathway in lung cancer cells (Fig. 3). GALNT6-induced O-glycosylation is critical for the stability of GRP78, its subcellular localization in the endoplasmic reticulum, and its anti-apoptotic function. O-glycosylation stabilizes GRP78 protein, and high levels of GRP78 protein can drive the relocation of GALNT6 from the Golgi apparatus to the endoplasmic reticulum. Loss of O-glycosylation also results in the translocation of GRP78 protein from the endoplasmic reticulum to the cytoplasm. Furthermore, O-glycosylation of the GRP78 protein is critical for cell survival under conditions of nutrient deprivation. Therefore, GALNT6 is becoming recognized as a new type of positive regulatory factor for human LUAD malignancy, and targeting of GALNT6-GRP78-MEK1/2/ERK1/2 may become a new strategy for preventing lung cancer metastasis. Similar to GALNT3 protein, GALNT6 protein can also regulate the glycosylation of MUC1 protein. Blocking the O-glycosylation of MUC1-N and its subsequent MUC1-C/p120ctn interaction with GALNT6 shRNA can prevent the initiation of EMT and reduce the viability of lung cancer cells (36).

GALNT13 protein. GALNT13 protein can promote lung cancer metastasis. It was first discovered that the GALNT13 protein was upregulated in the highly metastatic subline of the mouse Lewis lung cancer cell line (37). In an analysis of the mechanism of cancer metastasis, it was found that reduced levels of ganglioside GM1 lead to increased invasion and metastasis potential (38). In the mouse Lewis lung cancer cell line, reduced GM1 protein expression induces an upregulation of GALNT13 expression (Fig. 4). Stable overexpression of the GALNT13 protein enhances the invasiveness and motility of Lewis lung cancer cells and induces the formation of trimeric Tn antigen on Syndecan 1. In C57BL/6 mice, injection of the GALNT13-silenced Lewis lung cancer cell line produced primary tumors that were less integrated with fascia and peritoneum and had significantly fewer lung metastases. Further research on the mechanism of action of the trimeric Tn antigen formed by Syndecan 1 during lung cancer metastasis revealed that it enhances cell adhesion to fibronectin by forming a complex with integrin α 5β1. It also enhances invasion and metastasis activity by recruiting MMP-9 to GEM/rafts, and increases the phosphorylation levels of FAK and paxillin (39). These results provide a convincing basis for explaining the mechanistic role of GALNT13 protein in lung cancer metastasis.

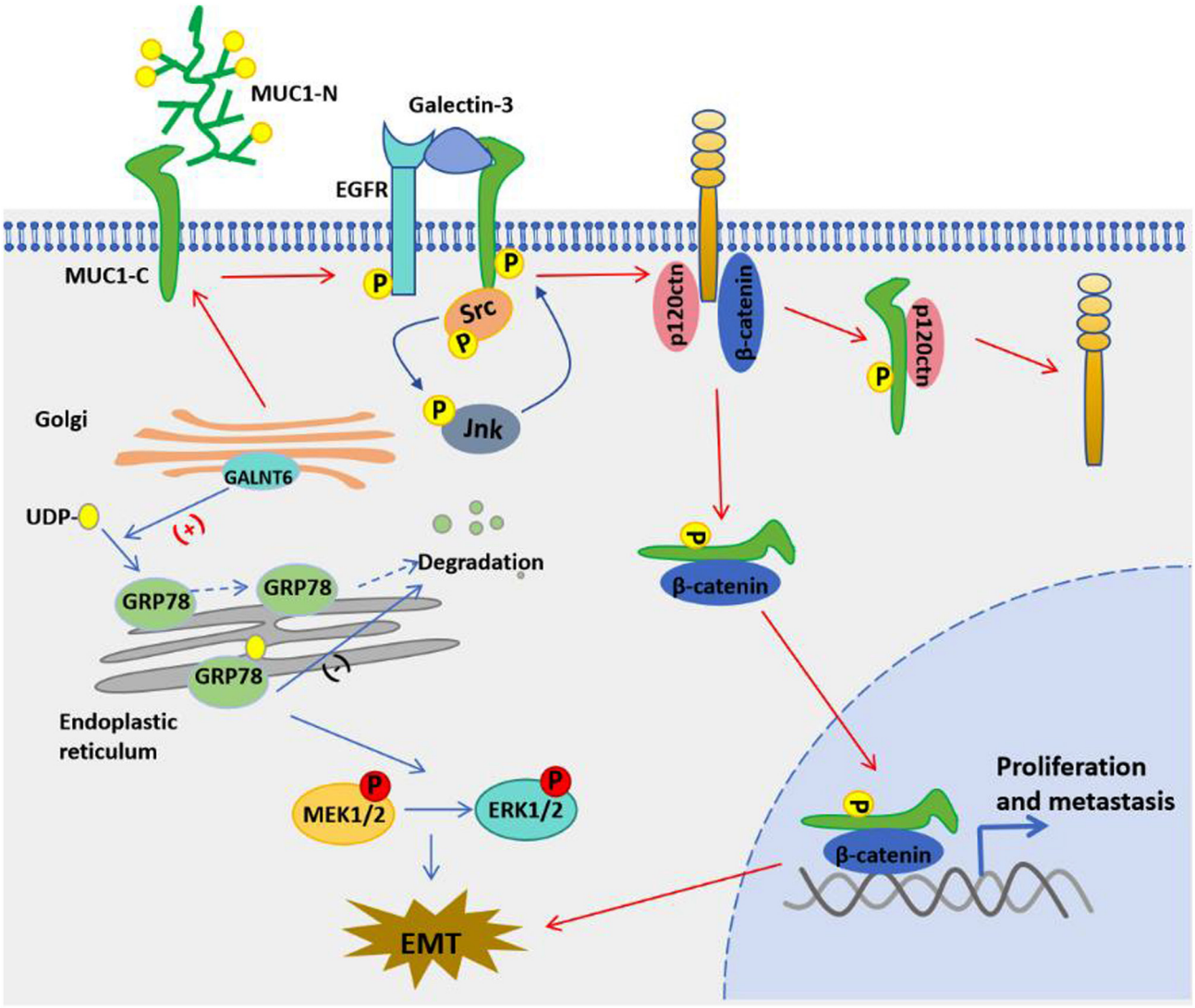

Figure 3. Mechanism by which the GALNT6 protein regulates the occurrence and development of lung cancer. GALNT, N-acetyl-galactosamine-transferase; EMT, epithelial-to-mesenchymal transition.

Overexpression of GALNT13 protein is associated with a poor prognosis in patients with lung cancer. Reverse transcription-quantitative PCR was used to analyze the expression levels of GALNT13 mRNA and the use of its variant exons in 91 surgical specimens of lung cancer; after which, the correlation with clinical data was evaluated. It was found that a high level of GALNT13 mRNA significantly shortened the recurrence-free survival (RFS) time of patients with lung cancer (P=0.045) (40). There are different transcriptional variants of GALNT13 mRNA; the E13 positive expression group is significantly correlated with a poor OS prognosis. On the contrary, when compared with a negative group, the E14 positive expression group had a significantly longer RFS time. In the aforementioned study, immunohistochemistry was used to detect GM1 and evaluate the expression of ppGalNAc-T13 and trimeric Tn antigen as prognostic factors (40). The results identified that among 35 patients with lung cancer, GALNT13 and trimeric Tn antigens were associated with a poor prognosis.

GALNT14 protein. GALNT14 can promote the sensitivity of lung cancer cells to Apo2L/TRAIL ligands by regulating the glycosylation of apoptosis receptors, DR4 and DR5 (Fig. 5A). Apo2L/TRAIL stimulates cancer cell death via the pro apoptotic receptors, DR4 and DR5. When studying the mechanism of tumor cell susceptibility to this ligand, researchers found that the levels of GALNT14 mRNA were correlated with the sensitivity of Apo2L/TRAIL in pancreatic cancer, NSCLC and melanoma (41). RNA interference with GALNT14 expression reduces cell sensitivity to Apo2L/TRAIL, while overexpression produces the opposite effect. GALNT14 mRNA is overexpressed in >30% of NSCLC cells. Further research has shown that GALNT14 can regulate the O-glycosylation of DR4 and DR5 proteins. O-glycosylation promotes the aggregation of ligand-stimulated DR4 and DR5, which mediates the recruitment and activation of apoptosis initiated by protease caspase-8. GALNT14 expression in NSCLC cell lines can strongly predict the efficacy of the pro-apoptotic receptor agonist dulanermin, the *in vitro* sensitivity of rhApo2L/TRAIL, and the efficacy of drozitumab monoclonal antibodies (DR5 agonist antibodies) (42). Those findings revealed a new connection between death receptor O-glycosylation and apoptosis signaling pathways, and suggest predictive biomarkers for cancer treatment strategies based on Apo2L/TRAIL.

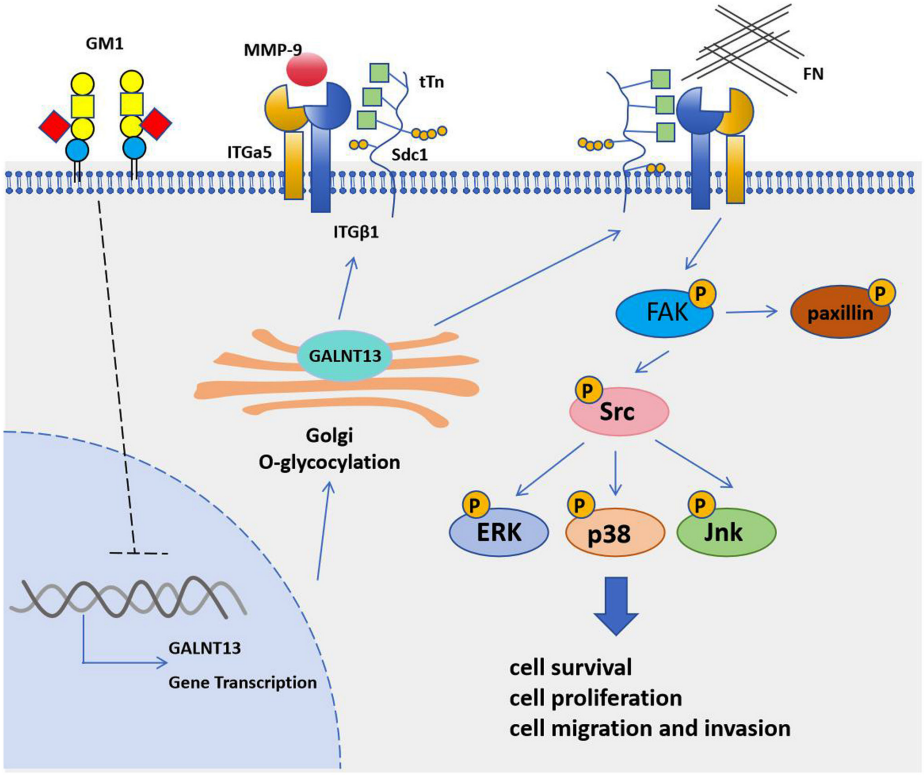

Figure 4. Mechanism by which the GALNT13 protein regulates the occurrence and development of lung cancer. GALNT, N-acetyl-galactosamine-transferase.

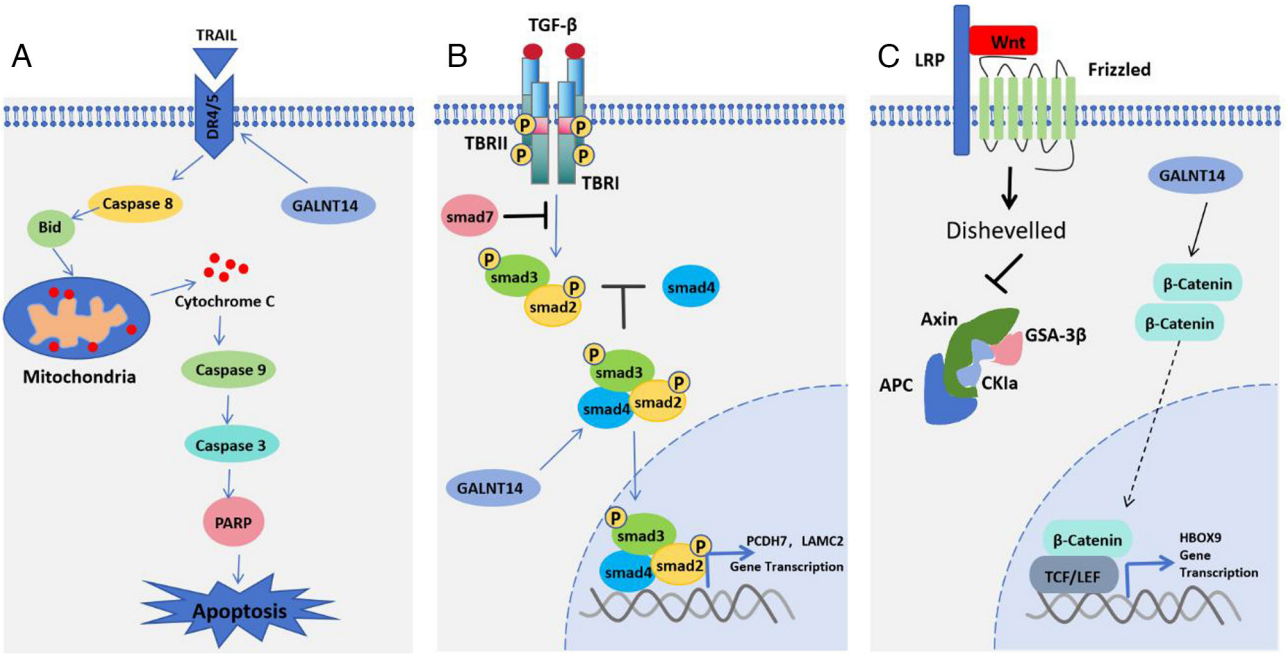

Figure 5. Mechanism by which the GALNT14 protein regulates the occurrence and development of lung cancer. (A) GALNT14 promotes mitochondrial apoptosis by regulating apoptosis receptors DR4 and DR5. (B) GALNT14 promotes the activation of the SMAD heterotrimeric complex in the nucleus of the TGF-β signaling pathway. (C) GALNT14 promotes the WNT response by improving the stability of β-catenin protein. GALNT, N-acetyl-galactosamine-transferase; PARP, poly (ADP-ribose) polymerase.

Overexpression of GALNT14 is associated with a poor prognosis for patients with NSCLC. In a clinical genomics study involving 138 patients with NSCLC, GALNT14 expression was highly correlated with shorter RFS times (43). GALNT14 can also regulate lung cancer metastasis. An analysis of RFS and differentially expressed genes in 516 cases of LUAD in the TCGA database revealed 7 genes (*GALNT14*, *9COL7A1*, *GPR115*, *C1QTNF6*, *KRT16*, *INHA* and *TNFSF11*) that were significantly correlated with cancer progression and recurrence, suggesting those genes as predictive factors

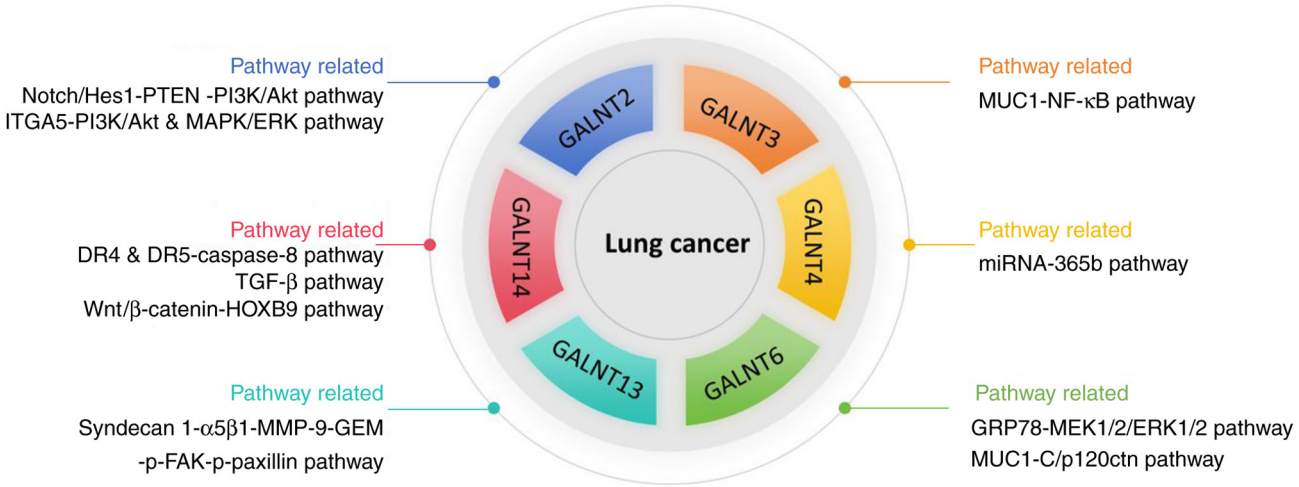

Figure 6. GALNT proteins involved in lung cancer and pathway related. GALNT, N-acetyl-galactosamine-transferase; miRNA, microRNA.

for a poor prognosis (44). In a group of patients that highly expressed all 7 genes, both the metastatic and tumor features showed positive enrichment, which was very significant in the high GALNT14 gene expression group. In patients with lung cancer, GALNT14 expression is significantly and negatively correlated with local RFS, distant metastasis-free survival and OS rate.

GALNT14 protein regulates the occurrence and development of lung cancer via multiple pathways (Fig. 5B and C) (44,45). GALNT14 protein promotes tumor metastasis and SOX4 expression. The expression levels of AREG and VCAN proteins are related. In lung cancer, the GALNT14 protein also affects the TGF-β signaling pathway, which has been widely studied as a tumor suppressor, tumor promoter and promoter of metastasis (46-48). GALNT14 can also enhance the sensitivity to WNT signals, increase the stability of β-catenin, and thereby induce the expression of HOXB9 and promote development of an invasive phenotype (47). A meta-analysis of clinical genomics data showed that overexpression of GALNT14 or HOXB9 was closely related to a decrease in RFS time and an increase in HR, suggesting that targeting the GALNT14/WNT/HOXB9 axis may be a new therapeutic approach for inhibiting NSCLC metastasis.

The *GALNT14* gene is associated with paclitaxel resistance in lung cancer (48). Gene methylation and expression differences between paclitaxel resistant and sensitive lung cancer cells have been studied using methylation chip analysis and transcriptome sequencing. A total of 43,426 differentially methylated genes and 2,870 differentially expressed genes were identified, including 6 genes (*KANK1 ALDH3A1*, *GALNT14*, *PIK3R*3, *LRG*1 and *WEE2*) that may be related to paclitaxel resistance in LUAD. *GALNT14* was one of those genes.

In addition, GALNT14 can also regulate immune cell infiltration in lung cancer (13). The correlation between GALNT14 expression and immune cell infiltration in LUAD was analyzed using ssGSEA, and it was observed that f GALNT14 expression was negatively correlated with immature B cells and eosinophil infiltration (all $P<0.01$). Further research has found that PD-L1 expression is positively correlated with GALNT14 expression, which suggests that GALNT14 protein expression could be used for predicting the efficacy of immunotherapy.

Other GALNT family proteins. Researchers have conducted studies using Oncomine database. The NSCLC data from TCGA, UALCAN (https://ualcan.path.uab.edu/), GTEx (https://www.gtexportal.org/home/) and Kaplan Meier plotter (https://kmplot.com/analysis/) databases were analyzed, and the differential expression of mRNA for GANLT family proteins in NSCLC was systematically examined (14). In addition to the GALNT family proteins related to lung cancer aforementioned, the expression levels of GALNT7 mRNA in LUAD and LUSC were higher than those in normal tissues. Furthermore, the expression levels of GALNT5/15/16/18/20 mRNA in LUAD and LUSC were lower than those in normal tissues; the expression levels of GALNT8/9/11/17/19 in LUAD and LUSC were basically consistent with those in normal tissues; the expression levels of GALNT10/12 mRNA in LUSC were lower than those in normal tissues, and the expression levels in LUAD were consistent with those in normal tissues. A high level of GALNT 9 expression was associated with a decrease in the OS rate of patients with lung cancer, and a high level of GALNT16 expression was associated with poor disease-free survival in patients with lung cancer. At present, the role of these GALNT family members in lung cancer has not been reported.

Limitations and outlook. It is necessary to acknowledge the limitations of the present review. The generalizability of our findings may have been affected by the small sample size of the study, which sought to investigate the mechanisms of lung cancer occurrence and development in a specific population. Additional studies with larger sample sizes will be needed to confirm the present results. Moreover, the similar mechanism of action of the important members of the GALNT protein family and the interaction network between the proteins need to be explored in depth in the future.

Despite some limitations, we remain confident that we can carry out ambitious research in the field. Regarding the GALNT family proteins, it is hoped that progress can be made

in the following areas: i) determine whether GALNT family proteins can be used as predictive markers for early-stage lung cancer; ii) explore GALNT family proteins as biomarkers for predicting the efficacy of lung cancer drugs; iii) investigate the role of other GALNT family proteins in lung cancer; iv) investigate the relationship between members of the GALNT family and the immune microenvironment, as well as the efficacy of immunotherapy; v) investigate the regulatory mechanism of GALNT family proteins in lung cancer, with the goal of developing new strategies for lung cancer treatment based on O-GalNAc glycosylation.

3. Summary

In summary, the high expression of numerous members of the GALNT family in lung cancer is closely related to the occurrence, development, and a poor prognosis for those tumors. The abnormal expression of GALNT family members is usually caused by abnormal methylation of gene promoters, and upstream regulatory gene changes caused by changes in miRs. GALNT family proteins generally exert their effects by regulating the O-glycosylation of proteins that play a crucial role in the occurrence and development of lung cancer; however, the mechanisms of action of different members vary. The main signaling pathways involved in regulating lung cancer occurrence and development by members of the GALNT family include Notch/Hes1-PTEN-PI3K/Akt, GRP78-MEK1/2/ERK1/2 and TGF-β (Fig. 6). Another study has found that GALNT3 exerts inhibitory effects in lung cancer, and indicate that the mechanism by which the GALNT proteins regulate the occurrence and development of lung cancer is complex (36). The positive and negative regulation of GALNT3 protein in lung cancer requires further exploration. Among the GALNT family proteins, GALNT2/3/14 can affect immune cell infiltration in lung cancer, suggesting that members of the GALNT family may serve as biomarkers for predicting the therapeutic effect of immunotherapy drugs. The GALNT family proteins are also used to construct predictive models for patient prognosis, but they are usually combined with other indicators to construct predictive models. A single GALNT family protein indicator predictive model has not yet emerged. There is relatively little research on the relationship between GALNT family proteins and the drug sensitivity of tumors. Only GALNT 14 has been found to be associated with lung cancer resistance to paclitaxel, and be a potential predictive biomarker for Apo2L/TRAIL-based cancer treatment strategies.

Briefly, the present review summarizes the abnormal expression and important roles of GALNT family protein members (2-4,6,13,14) in lung cancer. The sensitivity and specificity of GALNT family proteins will be an important direction for future exploration, and the correlation between the expression of GALNT family proteins for drug efficacy monitoring in lung cancer and immunotherapy is also worth exploring. Moreover, the role of other GALNT family proteins (except 2-4,6,13,14) in lung cancer and the research on the molecular mechanisms by which GALNT family proteins regulate the development of lung cancer will provide new ideas for the diagnosis and treatment of lung cancer.

Acknowledgements

The authors would like to thank Dr Xiaofeng Wan from the Hefei Cancer Hospital of the Chinese Academy of Sciences for her pertinent comments on this manuscript.

Funding

The present study was supported by the Chuzhou Health Research Program (grant no. 2022008).

Availability of data and materials

Not applicable.

Authors' contributions

CM wrote the original draft, conducted investigation and methodology. RS conceptualized the study. DJ performed software analysis. LM conducted visualization. QF performed literature review. MW revised the manuscript. ZW supervised the study and polished the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A and Siegel RL: Breast cancer statistics, 2019. CA Cancer J Clin 69: 438-451, 2019.
2. Jiang JJ, Li YQ and Gu YY: Clinical and histopathological features of immune checkpoint inhibitor-related myositis in patients with advanced non-small cell lung cancer. Zhonghua Jie He He Hu Xi Za Zhi 45: 47-52, 2022 (In Chinese).
3. Duma N, Santana-Davila R and Molina JR: Non-small cell lung cancer: Epidemiology, screening, diagnosis, and treatmen. Mayo Clin Proc 94: 1623-1640, 2019.
4. Broderick SR: Adjuvant and neoadjuvant immunotherapy in non-small cell lung cancer. Thorac Surg Clin 30: 215-220, 2020.
5. Hussain MR, Hoessli DC and Fang M: N-acetylgalactosaminyltransferases in cancer. Oncotarget 7: 54067-54081, 2016.
6. Hollingsworth MA and Swanson BJ: Mucins in cancer: Protection and control of the cell surface. Nat Rev Cancer 4: 45-60, 2004.
7. Ohyama C: Glycosylation in bladder cancer. Int J Clin Oncol 13: 308-313, 2008.
8. Langbecker D and Janda M: Systematic review of interventions to improve the provision of information for adults with primary brain tumors and their caregivers. Front Oncol 5: 1, 2015.
9. Stowell SR, Ju T and Cummings RD: Protein glycosylation in cancer. Annu Rev Pathol 10: 473-510, 2015.
10. Peng C, Togayachi A, Kwon YD, Xie C, Wu G, Zou X, Sato T, Ito H, Tachibana K, Kubota T, *et al*: Identification of a novel human UDP-GalNAc transferase with unique catalytic activity and expression profile. Biochem Biophys Res Commun 402: 680-686, 2010.

11. Gomes J, Mereiter S, Magalhães A and Reis CA: Early GalNAc O-glycosylation: Pushing the tumor boundaries. Cancer Cell 32: 544-545, 2017.
12. Wang W, Sun R, Zeng L, Chen Y, Zhang N, Cao S, Deng S, Meng X and Yang S: GALNT2 promotes cell proliferation, migration, and invasion by activating the Notch/Hes1-PTEN-PI3K/Akt signaling pathway in lung adenocarcinoma. Life Sci 276: 119439, 2021.
13. Yu Y, Wang Z, Zheng Q and Li J: GALNT2/14 overexpression correlate with prognosis and methylation: Potential therapeutic targets for lung adenocarcinoma. Gene 790: 145689, 2021.
14. Hu Q, Tian T, Leng Y, Tang Y, Chen S, Lv Y, Liang J, Liu Y, Liu T, Shen L and Dong X: The O-glycosylating enzyme GALNT2 acts as an oncogenic driver in non-small cell lung cancer. Cell Mol Biol Lett 27: 71, 2022.
15. Alghamdi RA and Al-Zahrani MH: Integrated bioinformatics analyses identifying key transcriptomes correlated with prognosis and immune infiltrations in lung squamous cell carcinoma. Saudi J Biol Sci 30: 103596, 2023.
16. Dong X, Leng Y, Tian T, Hu Q, Chen S, Liu Y and Shen L: GALNT2, an O-glycosylating enzyme, is a critical regulator of radioresistance of non-small cell lung cancer: Evidence from an integrated multi-omics analysis. Cell Biol Toxicol 39: 3159-3174, 2023.
17. Baumgart A, Mazur PK, Anton M, Rudelius M, Schwamborn K, Feuchtinger A, Behnke K, Walch A, Braren R, Peschel C, *et al*: Opposing role of Notch1 and Notch2 in a Kras(G12D)-driven murine non-small cell lung cancer model. Oncogene 34: 578-588, 2015.
18. Zheng Y, de la Cruz CC, Sayles LC, Alleyne-Chin C, Vaka D, Knaak TD, Bigos M, Xu Y, Hoang CD, Shrager JB, *et al*: A rare population of CD24(+)ITGB4(+)Notch(hi) cells drives tumor propagation in NSCLC and requires Notch3 for self-renewal. Cancer Cell 24: 59-74, 2013.
19. Yuan X, Wu H, Xu H, Han N, Chu Q, Yu S, Chen Y and Wu K: Meta-analysis reveals the correlation of Notch signaling with non-small cell lung cancer progression and prognosis. Sci Rep 5: 10338, 2015.
20. Zheng W, Jiang C and Li R: Integrin and gene network analysis reveals that ITGA5 and ITGB1 are prognostic in non-small-cell lung cancer. Onco Targets Ther 9: 2317-2327, 2016.
21. Zhang YL, Wang RC, Cheng K, Ring BZ and Su L: Roles of Rap1 signaling in tumor cell migration and invasion. Cancer Biol Med 14: 90-99, 2017.
22. Girnita L, Worrall C, Takahashi S, Seregard S and Girnita A: Something old, something new and something borrowed: emerging paradigm of insulin-like growth factor type 1 receptor (IGF-1R) signaling regulation. Cell Mol Life Sci 71: 2403-2427, 2014.
23. Alfaro-Arnedo E, López IP, Piñeiro-Hermida S, Canalejo M, Gotera C, Sola JJ, Roncero A, Peces-Barba G, Ruíz-Martínez C and Pichel JG: IGF1R acts as a cancer-promoting factor in the tumor microenvironment facilitating lung metastasis implantation and progression. Oncogene 41: 3625-3639, 2022.
24. Luo D, Fang M, Shao L, Wang J, Liang Y, Chen M, Gui X, Yan J, Wang W, Yu L, *et al*: The EMT-related genes GALNT3 and OAS1 are associated with immune cell infiltration and poor prognosis in lung adenocarcinoma. Front Biosci (Landmark Ed) 28: 271, 2023.
25. Pucci M, Duca M, Malagolini N and Dall'Olio F: Glycosyltransferases in cancer: Prognostic biomarkers of survival in patient cohorts and impact on malignancy in experimental models. Cancers (Basel) 14: 2128, 2022.
26. Li Y, Zhao J, Zhang W, Wang A, Jiao M, Cai X, Zhu J, Liu Z and Huang JA: LINC02535/miR-30a-5p/GALNT3 axis contributes to lung adenocarcinoma progression via the NF-κB signaling pathway. Cell Cycle 21: 2455-2470, 2022.
27. Vojta A, Samaržija I, Bočkor L and Zoldoš V: Glyco-genes change expression in cancer through aberrant methylation. Biochim Biophys Acta 1860: 1776-1785, 2016.
28. Chen W, Zhang Z, Zhang S, Zhu P, Ko JK and Yung KK: MUC1: Structure, function, and clinic application in epithelial cancers. Int J Mol Sci 22: 6567, 2021.
29. Supruniuk K, Czarnomysy R, Muszyńska A and Radziejewska I: Combined action of anti-MUC1 monoclonal antibody and pyrazole-platinum(II) complexes reveals higher effectiveness towards apoptotic response in comparison with monotherapy in AGS gastric cancer cells. Pharmaceutics 13: 968, 2021.
30. Hagiwara M, Fushimi A, Yamashita N, Bhattacharya A, Rajabi H, Long MD, Yasumizu Y, Oya M, Liu S and Kufe D: MUC1-C activates the PBAF chromatin remodeling complex in integrating redox balance with progression of human prostate cancer stem cells. Oncogene 40: 4930-4940, 2021.
31. Ahmad R, Raina D, Trivedi V, Ren J, Rajabi H, Kharbanda S and Kufe D: MUC1 oncoprotein activates the IkappaB kinase beta complex and constitutive NF-kappaB signalling. Nat Cell Biol 9: 1419-1427, 2007.
32. Park MS, Yang AY, Lee JE, Kim SK, Roe JS, Park MS, Oh MJ, An HJ and Kim MY: GALNT3 suppresses lung cancer by inhibiting myeloid-derived suppressor cell infiltration and angiogenesis in a TNFR and c-MET pathway-dependent manner. Cancer Lett 521: 294-307, Aug 17, 2021 (Epub ahead of print).
33. Xing L, Hong X, Chang L, Ren P and Zhang H: miR-365b regulates the development of non-small cell lung cancer via GALNT4. Exp Ther Med 20: 1637-1643, 2020.
34. Chen X, Yu L, Zhang H and Jin H: Identification of new prognostic genes and construction of a prognostic model for lung adenocarcinoma. Diagnostics (Basel) 13: 1914, 2023.
35. Song J, Liu W, Wang J, Hao J, Wang Y, You X, Du X, Zhou Y, Ben J, Zhang X, *et al*: GALNT6 promotes invasion and metastasis of human lung adenocarcinoma cells through O-glycosylating chaperone protein GRP78. Cell Death Dis 11: 352, 2020.
36. Zhang L, Gallup M, Zlock L, Chen YT, Finkbeiner WE and McNamara NA: Pivotal role of MUC1 glycosylation by cigarette smoke in modulating disruption of airway adherens junctions in vitro. J Pathol 234: 60-73, 2014.
37. Matsumoto Y, Zhang Q, Akita K, Nakada H, Hamamura K, Tokuda N, Tsuchida A, Matsubara T, Hori T, Okajima T, *et al*: pp-GalNAc-T13 induces high metastatic potential of murine Lewis lung cancer by generating trimeric Tn antigen. Biochem Biophys Res Commun 419: 7-13, 2012.
38. Zhang Q, Furukawa K, Chen HH, Sakakibara T, Urano T and Furukawa K: Metastatic potential of mouse Lewis lung cancer cells is regulated via ganglioside GM1 by modulating the matrix metalloprotease-9 localization in lipid rafts. J Biol Chem 281: 18145-18155, 2006.
39. Matsumoto Y, Zhang Q, Akita K, Nakada H, Hamamura K, Tsuchida A, Okajima T, Furukawa K, Urano T and Furukawa K: Trimeric Tn antigen on syndecan 1 produced by ppGalNAc-T13 enhances cancer metastasis via a complex formation with integrin α5β1 and matrix metalloproteinase 9. J Biol Chem 288: 24264-24276, 2013.
40. Nogimori K, Hori T, Kawaguchi K, Fukui T, Mii S, Nakada H, Matsumoto Y, Yamauchi Y, Takahashi M, Furukawa K, *et al*: Increased expression levels of ppGalNAc-T13 in lung cancers: Significance in the prognostic diagnosis. Int J Oncol 49: 1369-1376, 2016.
41. Wagner KW, Punnoose EA, Januario T, Lawrence DA, Pitti RM, Lancaster K, Lee D, von Goetz M, Yee SF, Totpal K, *et al*: Death-receptor O-glycosylation controls tumor-cell sensitivity to the proapoptotic ligand Apo2L/TRAIL. Nat Med 13: 1070-1077, 2007.
42. Stern HM, Padilla M, Wagner K, Amler L and Ashkenazi A: Development of immunohistochemistry assays to assess GALNT14 and FUT3/6 in clinical trials of dulanermin and drozitumab. Clin Cancer Res 16: 1587-1596, 2010.
43. Lee ES, Son DS, Kim SH, Lee J, Jo J, Han J, Kim H, Lee HJ, Choi HY, Jung Y, *et al*: Prediction of recurrence-free survival in postoperative non-small cell lung cancer patients by using an integrated model of clinical information and gene expression. Clin Cancer Res 14: 7397-7404, 2008.
44. Kwon OS, Lee H, Kong HJ, Kwon EJ, Park JE, Lee W, Kang S, Kim M, Kim W and Cha HJ: Connectivity map-based drug repositioning of bortezomib to reverse the metastatic effect of GALNT14 in lung cancer. Oncogene 39: 4567-4580, 2020.
45. Derynck R, Akhurst RJ and Balmain A: TGF-beta signaling in tumor suppression and cancer progression. Nat Genet 29: 117-129, 2001.
46. Padua D and Massagué J: Roles of TGFbeta in metastasis. Cell Res 19: 89-102, 2009.
47. Kwon OS, Oh E, Park JR, Lee JS, Bae GY, Koo JH, Kim H, Choi YL, Choi YS, Kim J and Cha HJ: GalNAc-T14 promotes metastasis through Wnt dependent HOXB9 expression in lung adenocarcinoma. Oncotarget 6: 41916-41928, 2015.
48. Pu J, Shen J, Zhong Z, Yanling M and Gao J: KANK1 regulates paclitaxel resistance in lung adenocarcinoma A549 cells. Artif Cells Nanomed Biotechnol 48: 639-647, 2020.