https://www.cytojournal.com/

CytoJournal

Editor-in-Chief:
Miaoqing Zhao, PhD., MD (Shandong First Medical University, Jinan, China)
He Wang, MD, PhD (Yale University School of Medicine, New Haven, Connecticut, USA)
Founding Editor & Editor-in-chief Emeritus:
Vinod B. Shidham, MD, FIAC, FRCPath (WSU School of Medicine, Detroit, USA)

OPEN ACCESS

Review Article

Aberrations in the glycosylation of receptor tyrosine kinases: A focus on lung adenocarcinoma

Anna M. Dmitrieva, PhD,[1] Ilayda G. Kocak, MS,[1] Lydia Meder, PhD,[1]*

[1]Department of Experimental Medicine I, Medical Faculty, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.

***Corresponding author:**

Prof. Lydia Meder, PhD, Department of Experimental Medicine I, Medical Faculty, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.

lydia.meder@fau.de

Received: 31 January 2025
Accepted: 17 April 2025
Published: 14 June 2025

DOI
10.25259/Cytojournal_21_2025

Quick Response Code:

ABSTRACT

Lung cancer is the leading cause of cancer-related deaths worldwide, with genetic- and protein-based diagnostics playing a crucial role in disease detection and improving patient outcomes. Glycosylation, a major post-translational modification, has recently emerged as a factor influencing cancer progression, immune evasion, and therapeutic resistance. Aberrant glycosylation patterns, particularly among receptor tyrosine kinases (RTKs), have been shown to modulate oncogenic signaling pathways and influence tumor growth. This review provides a comprehensive overview of how glycosylation alterations affect the stability, function, and therapeutic targeting of key RTKs relevant in lung adenocarcinoma: Epidermal growth factor receptor, human epidermal growth factor receptor 2, and cellular mesenchymal-epithelial transition factor, rearranged during transfection, anaplastic lymphoma kinase, and ROS proto-oncogene 1 receptor tyrosine kinase. Despite substantial advances in targeted therapies, initial and acquired resistance remain a major challenge in the treatment of lung cancer. There is growing evidence that strategies targeting glycosylation can be combined with established treatment protocols to help overcome resistance. Finally, we propose future directions for the advancement of glycosylation-based approaches to improve precision medicine.

Keywords: Glycosylation, Lung cancer, Receptor tyrosine kinase

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths globally, with significant incidence and mortality rates. It accounts for approximately 2 million new diagnoses and 1.8 million deaths annually, making it the most common cause of cancer-related mortality worldwide.[1] Adenocarcinoma and squamous cell carcinoma are the two most common subtypes of non-small cell lung cancer (NSCLC), accounting for about 50% and 20-30% of lung cancer cases each year, respectively. Notably, the patient's smoking history and histological subtype frequently correlate; for example, adenocarcinoma is more prevalent in patients with a history of never or light smoking. Furthermore, both types are linked to targetable genomic alterations.[2-4]

Over the past two decades, significant advancements in understanding the molecular biology of lung cancer have led to the identification of various oncogenic driver mutations that can be targeted with specific therapies. The majority of therapeutically significant oncogenic drivers are kinases that are activated by mutation, amplification, or by constitutively activating the kinase domain in fusion proteins. In NSCLC, the key receptor tyrosine kinases (RTKs) identified include epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER-2), cellular mesenchymal-epithelial transition factor (c-MET), rearranged during

transfection (RET), anaplastic lymphoma kinase (ALK), and ROS proto-oncogene 1, receptor tyrosine kinase (ROS1). Oncogene addiction, the cancer cell's dependence on specific oncogenes for survival, has led to the development of targeted treatments, primarily tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs), which attach to the active kinase domain's ATP-binding pocket or block ligand-receptor binding, respectively.[5,6]

Although targeted treatments against RTKs have improved survival rates, resistance often develops, necessitating ongoing research into next-generation inhibitors and combination therapies to overcome this phenomenon. Post-translational modifications such as glycosylation of RTKs play a significant role in modulating signaling pathway activation status and are also associated with therapy resistance.[7] For example, inhibition of N-glycosylation disrupts RTK signaling in tumor cells.[8] This disruption can reduce RTK activity and radiosensitize tumor cells, suggesting a therapeutic approach to target primary and redundant RTK signaling.[7] This review highlights how glycosylation may interfere with the regulatory mechanisms of RTKs and modulate their ability to promote oncogenic signaling.

GLYCOSYLATION IN CANCER

Glycosylation is a critical post-translational modification involving the addition of carbohydrate chains, or glycans, to proteins and lipids. This process is essential for various physiological and pathological cellular functions by influencing cell signaling and cellular interactions.[9,10] In the context of cancer, glycosylation plays a significant role in tumor progression and immune modulation.[11,12] Changes in glycosylation may occur through genetic mutations or can be induced within the tumor microenvironment by factors such as hypoxia and inflammation that drive the activity of glycosyltransferases. Glycoproteins are proteins that have carbohydrate chains covalently attached to their polypeptide backbones, and these chains can constitute 1-80% of the total protein weight.[9,10] These structures are crucial for various biological functions, including cell-cell recognition and protein stability. Common sugars in glycoproteins include galactose, mannose, glucose, N-acetylglucosamine, and sialic acids.[10]

N- and O-linked glycans are the two types of glycosylation that occur in the endoplasmic reticulum (ER) and Golgi apparatus.[13,14] While N-glycosylation [Figure 1] always involves the same core glycan being attached to the amide nitrogen of asparagine (Asn) residue, O-glycosylation can take many different forms: Intracellular O-GlcNAc modification of nuclear and cytosolic proteins; O-xylose-linkage of glycosaminoglycans; O-mannosylation of dystroglycan, cadherins, and protocadherins; O-fucosylation and O-glucosylation of surface receptors; O-galactosylation of collagen; and the linkage of O-acetylgalactosamine (GalNAc) glycans, also known as mucin-type O-glycans.[13]

The main principle of O-glycosylation is that sugars are attached to the oxygen atom of serine (Ser) or threonine (Thr) residues in proteins. This process is tissue-specific and depends on the protein's structure. The elongation and termination of O-glycans are regulated by specific transferases.[15] O-glycosylation has many functions, such as regulating immune responses, and it can modulate enzyme and signaling molecule activities by altering protein stability and facilitating functional recognition.[13] O-glycosylation is further regulated by exon shuffling and alternative splicing which can result in proteins differing in their presence or absence of Ser/Thr (/Proline)-rich domains.

Aberrant O-glycosylation is also linked to cancer metastasis. For instance, in pancreatic cancer, the loss of core1 β1,3-galactosyltransferase (C1GALT1) leads to immature O-glycosylation and truncation of CD44, resulting in Tn-antigen enrichment.[16] This, in turn, drives tumorigenesis, metastasis, and stemness properties. Little is known about the functional consequences of O-glycosylation alterations in lung cancer, but recent glycoproteomic studies have identified aberrantly glycosylated proteins in this disease.[17]

N-glycosylation is a highly conserved process and involves the attachment of an oligosaccharide precursor to the Asn residue of a protein within the consensus sequence Asn-X-Ser/Thr (NXS/T), where X represents any amino acid except proline. This NXS/T motif is essential for the addition of glycans and is commonly found in extracellular and luminal regions of glycoproteins.[18] The mechanism of N-glycosylation begins with the synthesis of a lipid-linked oligosaccharide precursor on the ER membrane, which is subsequently transferred altogether as a group to the nascent polypeptide chain by the enzyme oligosaccharyltransferase (OST). Once the oligosaccharide is attached, it undergoes a series of modifications, including trimming and processing by glycosidases and glycosyltransferases in the ER and Golgi.[14,18,19] These modifications generate complex, hybrid, or high-mannose glycan structures that influence protein folding, trafficking, and function.[20] Proper N-glycosylation ensures correct protein conformation and prevents premature degradation, while dysregulated N-glycosylation in cancer cells can lead to altered receptor activity, increased proliferation, and enhanced metastatic potential.[21] In cancer cells, alterations in NXS/T motifs, such as mutations, can disrupt normal glycosylation patterns. This may result in misfolded proteins, impaired cell signaling, and enhanced tumor progression.[22] Studies have shown that the strategic targeting of N-glycosylation sites in key oncogenic proteins, such as RTKs, could provide new therapeutic avenues by modulating receptor activity and downstream signaling pathways.[23] For example, in prostate cancer, N-glycosylation

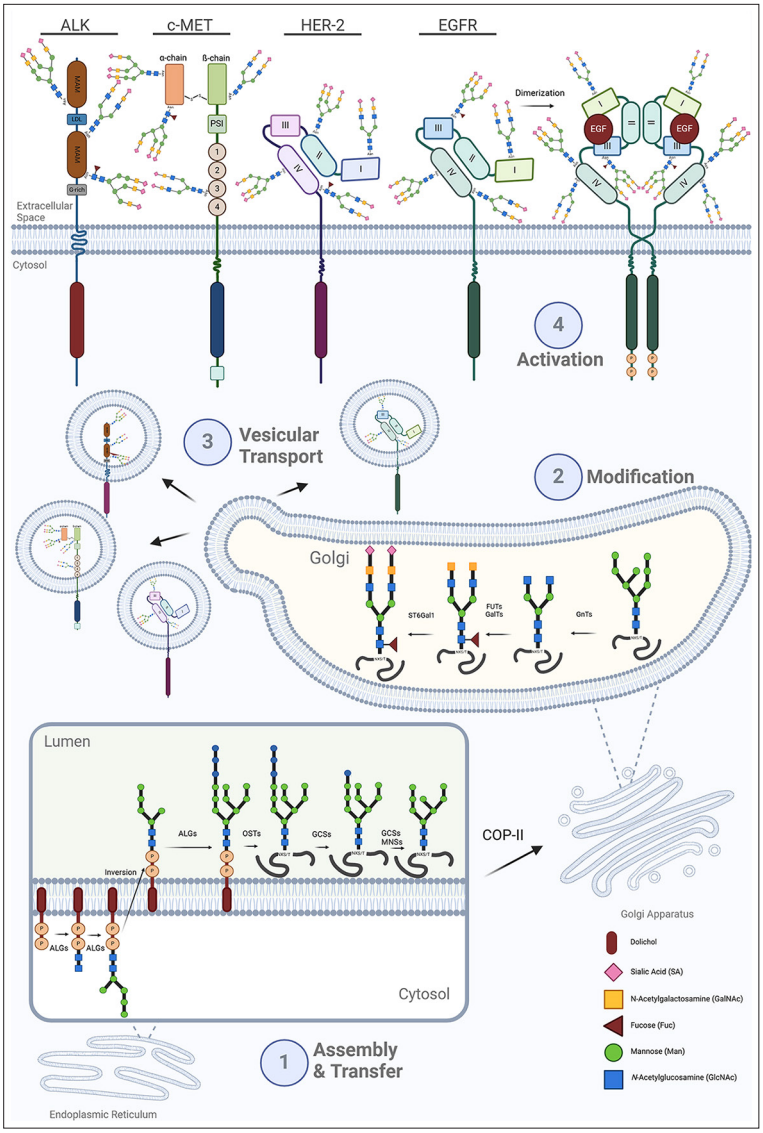

Figure 1: N-glycosylation of receptor tyrosine kinases. N-glycosylation begins in the endoplasmic reticulum (ER) with (1) assembly of an oligosaccharide precursor which is linked to the Asn residue of a protein. Correctly folded proteins are then transported from the ER to the Golgi apparatus through coat protein complex II (COP-II) vesicles, where (2) N-glycans are trimmed and extended by glycosyltransferases. Finally, proteins are transported (3) directly to the plasma membrane through transport vesicles where they can be activated through dimerization and ligand binding (4). ALGs: Mannosyltransferases, ALK: Anaplastic lymphoma kinase, c-MET: Cellular mesenchymal-epithelial transition factor, EGF: Epidermal growth factor, EGFR: Epidermal growth factor receptor, Fuc: Fucose, FUTs: Fucosyltransferases, GalTs: Galactosyltransferases, GalNAc: N-Acetylgalatosamine, GCSs: Glucosidases, GlnNAc: N-Acetylglucosamine, GnTs: N-acetylglucosaminyltransferases, G-rich: Glycine-rich, HER-2: Human epidermal growth factor receptor 2, LDL: Low-density lipoprotein class motif, MAM: Meprin, A5 protein and receptor protein tyrosine phosphatase mu domain, Man: Mannose, MNSs: Alpha-mannosidases, OSTs: Oligosaccharyltransferases, P: Protein-residue for post-translational modification, PSI: Plexin-semaphorin-integrin homology domain, SA: Sialic acid, ST6GAL1: ST6 beta-galactoside alpha-2,6-sialyltransferase 1, Created in BioRender. Meder, L. (2025) https://BioRender.com/s89u633.

supports cross-talk between RTKs and the androgen receptor, thereby influencing cell viability and receptor activation.[24]

Recently, there has been a growing focus on the role of glycosylation in cancer progression, particularly in lung cancer. Notable examples include the use of fluorinated monosaccharides, which have demonstrated promising preclinical efficacy as potential cancer therapeutics.[25] In addition, targeting N-glycosylation has emerged as a strategy for cancer treatment, such as the application of 2-deoxy-D-glucose to inhibit N-glycosylation in chimeric antigen receptor T cells. This approach reduces their binding affinity to immune-inhibitory molecules within the tumor microenvironment, thereby enhancing their cytotoxic activity against lung cancer cells expressing the cancer-testis antigen FMR1NB.[26] The use of 2-fluorofucose in cancer treatment trials has shown promising results in both human and animal studies, particularly in inhibiting protein and cellular fucosylation.[27] Glycosylation, particularly N-glycosylation, affects the function and stability of RTKs. These modifications play significant roles in various cellular processes, including signal transduction, protein folding, and cellular localization, which are crucial for both normal cellular functions and pathological conditions such as cancer. Inhibiting N-glycosylation has emerged as a potential therapeutic strategy to disrupt RTK signaling in cancer.[7] In lung cancer cells, alteration of glycosylation in RTKs such as EGFR, HER-2, c-MET, RET, ALK, and ROS1 can significantly impact their function and disease progression. This review summarizes the current advancements in our understanding of RTK glycosylation in cancer cells and its implications for treatment strategies that focus on lung cancer.

THE ROLE OF GLYCOSYLATION IN RTK SIGNALING

EGFR

EGFR, encoded by *ERBB1*, is a critical RTK involved in the regulation of cell growth and survival. EGFR mutations are found in a significant proportion of NSCLC cases, with frequencies varying by region and population. EGFR mutations are more prevalent in females, Asian populations, and non-smokers, while smoking history inversely correlates with mutation frequency.[28-30] EGFR is structurally composed of three key domains: An extracellular domain (ECD) for ligand binding, a transmembrane domain for membrane anchoring, and an intracellular cytoplasmic domain containing catalytic tyrosine kinase activity.[31] In its inactive state, EGFR primarily exists as an auto-inhibited monomer. However, upon ligand binding, EGFR changes to a conformation that enables it to form either homodimers or heterodimers with HER-2 or other receptors. Receptor activation is possible upon the establishment of an asymmetric dimer configuration of the kinase domains, wherein one domain allosterically potentiates the activity of the other.[32] The EGFR ECD, which has a complex, heart-shaped structure, comprises 4 subdomains. Domain I (L1), with a leucine-rich repeat structure, is involved in ligand binding, as is Domain III (L2), which also has a leucine-rich repeat structure. Domain II (CR1) and Domain IV (CR2), which are cysteine-rich domains, contribute to the dimerization of the receptor. The entire ECD adopts a tethered conformation in the absence of a ligand, preventing spontaneous activation by keeping L1 and L2 in a compact state.[31,32] The intracellular domain of EGFR comprises a juxtamembrane region involved in tyrosine kinase domain regulation and function. It is a bilobal structure encompassing the ATP binding site (in the N-terminal lobe), the activation loop, and a substrate binding site (both in the C-terminal lobe). A C-terminal tail, rich in tyrosine residues, undergoes autophosphorylation and serves as a platform for interaction with downstream signaling proteins.[31,32] Oncogenic EGFR mutants induced by amplification of activating mutations exhibit functional characteristics similar to those of the ligand-activated wild-type receptor. Tumors with EGFR mutations often present with specific imaging features such as ground-glass opacity and histological patterns such as lepidic growth. These features can help predict genetic changes and guide treatment decisions.[33,34] The most prominent *EGFR* lesions involve the L858R point mutation in exon 21 and deletions within exon 19, often grouped as classical mutations that comprise 85-90% of EGFR kinase domain mutations.[35] In general, *EGFR* mutations and extensive rearrangements observed across solid cancer entities frequently cause dysregulation of receptor endocytosis, which, in turn, enhances the receptor's signaling potential.[36]

EGFR is a heavily glycosylated protein and carbohydrate chains constitute approximately 25% of the 180 kDa mass of the receptor. This post-translational modification plays a fundamental role in various receptor processes, such as ligand-independent activation, growth factor binding affinity, and dimerization. Moreover, significant alterations in glycosylation are observed in various cancers, including NSCLC.[31] N-glycosylation is crucial for the proper folding, stability, and function of EGFR. Disruption of this process can lead to altered receptor activity and localization, which may enhance cancer cell proliferation and survival [Figure 2]. The absence of N-glycosylation can lead to increased dimerization of EGFR, even in the absence of ligands, which promotes spontaneous activation of the receptor. This can result in the activation of downstream signaling pathways that drive cancer cell proliferation and survival. EGFR-targeted therapies such as erlotinib can sensitize cancer cells, suggesting that targeting N-glycosylation could be a strategy to overcome drug resistance in EGFR-mutant cancers. Disruption of N-glycosylation in cancer cells can

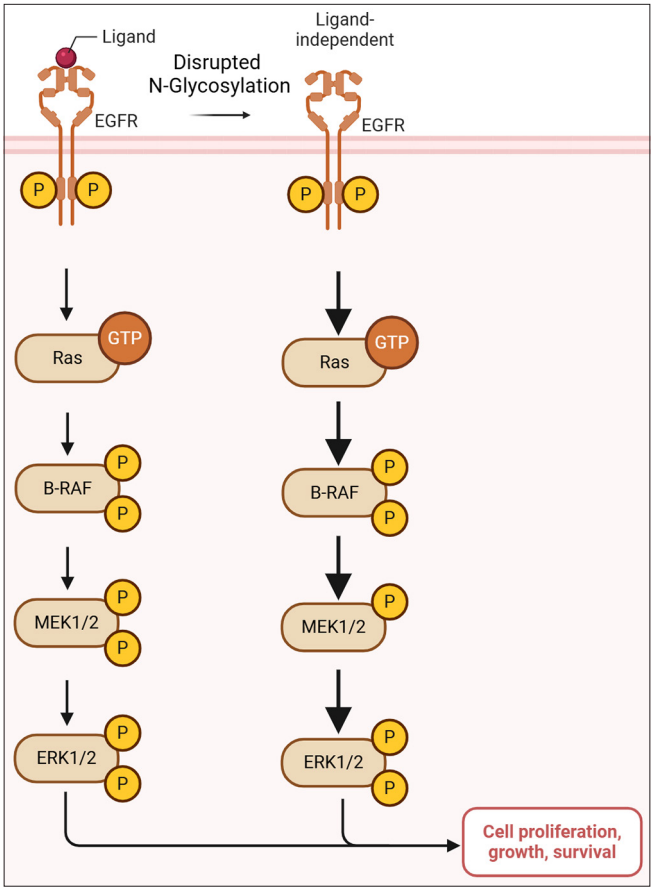

Figure 2: Epidermal growth factor receptor (EGFR) signaling upon disrupted N-glycosylation. EGFR dimerization and downstream signaling occur upon proper glycosylation of EGFR and ligand binding. This leads to EGFR pathway activation through Rat sarcoma (Ras), V-Raf Murine Sarcoma Viral Oncogene Homolog B (B-RAF), mitogen-activated extracellular signal-regulated kinase 1/2 (MEK1/2), and extracellular signal-related kinase 1/2 (ERK1/2) activation resulting in cell proliferation, growth, and cell survival. Disruption of EGFR N-glycosylation enables ligand-independent dimerization and activation. P: Phospho; GTP: Guanosine triphosphate. Created in BioRender. Meder, L. (2025) https://BioRender.com/8rqpbva.

lead to uncontrolled receptor activation by promoting spontaneous oligomerization, ultimately contributing to increased proliferation, survival, and drug resistance.[37,38] It may also impair receptor maturation by altering subcellular localization.[39]

The ECD of EGFR is heavily modified post-translationally by the addition of sugar, which influences receptor activity.[40] GlyGen, a web-based platform that integrates glyco-conjugate-related information from publicly available databases, shows 17 sites for N-glycosylation and 6 sites for O-linked glycans, but not all have been verified to be related to cancer.[41]

Glycosylation of the EGFR ECD occurs at Asn residues that fit the NXS/T consensus motif, including an atypical site at Asn32, which is located within a unique Asn-Asn-Cys sequence.[40,42,43] This atypical site has been shown to undergo both N-glycosylation and O-fucosylation. Experimental and computational analyses have demonstrated that glycosylation is essential for maintaining both the structural integrity and stability of the protein.[40] Through recent molecular dynamic simulations, the study of a complete monomeric glycosylated EGFR structure situated in a membrane bilayer has highlighted the critical role of N-glycosylation in enabling the EGFR ECD to adequately interact with the membrane, a prerequisite for maintaining its proper structural conformation.[42] Specific glycosylation sites, such as N361 in Domain III and N579 in Domain IV, are critical for EGFR dimerization. Mutations at N361A increase dimerization and alter ligand sensitivity, impacting cell viability and response to inhibitors.[44] Glycosylation at N579 affects the receptor's conformation, influencing its dimerization state. The N579Q mutation, which prevents glycosylation, results in a higher fraction of receptors in a high-affinity state and alters phosphorylation patterns.[45] In total, 4 glycosylation sites are located in Domain III, where the monoclonal antibody cetuximab (an anti-EGFR targeted therapy) binds to its target epitope.[46] In addition, inhibition of N-glycosylation using OST inhibitors can overcome resistance to EGFR TKIs by disrupting EGFR signaling and reducing tumor cell viability. For instance, NGI-1, which is an OST inhibitor, was able to restore sensitivity to osimertinib, a first-generation TKI, by inducing G1 arrest and apoptosis in resistant NSCLC cells.[47] To date, O-glycosylation in EGFR signaling has not been studied in lung cancer so far. However, C1GALT1, which is responsible for elongation of GalNAc-type O-glycosylation, and N-acetylgalactosaminyltransferase 2 (GALNT2), which regulates the early steps of mucin O-glycosylation, have been shown to enhance oncogenic EGFR signaling in brain cancers and oral squamous cell carcinomas. Both glycosyltransferases trigger EGFR terminal O-glycosylation and promote EGFR phosphorylation and downstream signaling.[48,49]

In general, since EGFR-mutated cancer cells frequently develop resistance to EGFR blockade, attenuating the glycosylation of EGFR has emerged as a promising therapeutic approach for NSCLC. It may counteract dimerization and activation of overexpressed EGFR or can enable mAb binding. Therefore, exploring the inhibition of glycosylation as a complementary approach holds potential as a strategy to enhance therapeutic outcomes and possibly address drug resistance.

HER-2

HER-2 is an extensively studied member of the EGFR family of receptors in cancer research and is encoded by the *ERBB2* gene. It is a transmembrane RTK that, when overexpressed or amplified, contributes to aggressive tumor behavior and poor prognosis.[50] HER2 mutations are identified in

approximately 2% of NSCLC, with a notable prevalence in lung adenocarcinomas. These mutations are often found in specific subgroups such as females, non-smokers, and those with adenocarcinoma histology.[51]

HER-2 is a type I transmembrane growth factor RTK and exhibits significant structural similarity to other EGFR family receptors.[52] This class of receptors comprises an extracellular N-terminal domain that serves as the ligand-binding site, a transmembrane domain, and an intracellular region that includes a juxtamembrane domain, a kinase catalytic domain, and a carboxy-terminal domain. In contrast to other receptors, HER-2 lacks confirmed ligands for binding; its activation occurs through heterodimerization with other EGFR family receptors bound to their respective ligands or through homodimerization.

Amplification of *ERBB2* and overexpression of HER-2 are well-established characteristics in breast, gastric, and lung cancers, serving as predictive markers for therapeutic approaches aimed at HER-2.[53] The most frequently observed and extensively studied alterations of HER-2/*ERBB2* in tumor cells include protein overexpression as well as gene mutations and amplifications.[52-55] *ERBB2* mutations are independent of amplification, indicating that they represent a separate biological entity and a potential therapeutic target.[55,56] *ERBB2* overexpression or gene mutations result in an elevated presence of HER-2 on the cell surface and enhanced activation. This activation drives the uncontrolled proliferation of tumor cells.[50,53]

The percentage of NSCLC patients with *ERBB2* mutations is approximately 1-4%, while *ERBB2* gene amplification occurs in 2-5% of cases and protein overexpression in 2-30% of cases. This overexpression can be induced by cytotoxic drugs through downregulation of microRNAs miR-125a and miR-125b which normally suppress HER-2 expression. The majority of patients harboring *ERBB2* mutations have a history of never smoking and present with adenocarcinoma histology.[57] The most frequent *ERBB2* mutations are in-frame insertions within exon 20 (ex20ins), notably the A775_G776insYVMA insertion/duplication. These mutations are typically found to be mutually exclusive with *EGFR* mutations and *ALK* rearrangements.[58]

The most common treatments for cancer patients with *ERBB2* mutations and/or HER-2 overexpression involve a range of targeted therapies, including pan-HER-2 inhibitors (such as afatinib and neratinib) and targeted mAbs and antibody-drug conjugates such as trastuzumab and trastuzumab emtansine (T-DM1), respectively.[59] Trastuzumab, often used in combination with chemotherapy, has been utilized in treating HER-2-positive NSCLC. However, its efficacy as a monotherapy is limited, with a progression-free survival of about 5.1 months.[57,60] T-DM1 has shown superior activity against HER-2-expressing tumors compared to unconjugated trastuzumab, with improved efficacy and safety.[61]

There are studies suggesting that post-translational modifications of the HER-2 protein, rather than its overexpression, have a pivotal role in regulating endocytosis and determining the effectiveness of anti-HER-2 therapies in lung cancer cell lines and patient-derived xenograft models.[60] A recent study that utilized mass spectrometry to create a comprehensive glycosylation profile of HER-2 showed site-specific modifications and their impact on receptor stability and activity. HER-2 has 8 identified N-glycosylation sites in its ectodomain that can interfere with trastuzumab binding to its target epitope.[62] GlyGen references 6 sites for N-glycosylation: Asn124, Asn187, Asn259, Asn530, Asn571, and Asn629 and two sites for O-glycosylation: Thr127 and Ser998.[41] The effectiveness of trastuzumab in treating HER-2-positive gastric cancer is significantly challenged by molecular resistance, which is influenced by extensive N-glycosylation of the HER-2 receptor. Through mass spectrometry analysis, it was found that galactose α-2,6-sialyltransferase 1 (ST6Gal1) modifies specific N-glycosylation sites within the trastuzumab-binding domain of HER-2, affecting receptor stability and therapeutic response. Inhibiting ST6Gal1 expression altered glycosylation patterns, increased HER-2 stability, and enhanced sensitivity to trastuzumab by reducing HER-2 and EGFR activation.[63] Another way HER-2 targeting was used in the context of glycosylation, was coupling trastuzumab with a sialidase. The targeted sialidase activity toward breast cancer cells using antibody-enzyme conjugates led to desialylation of the cancer cell surface accompanied by increased NK cell killing by antibody-dependent, cell-mediated cytotoxicity.[64]

Taken together, these findings suggest a potential new area of investigation for HER-2 and other RTK modifications in tumor cells, focusing on the role of surface receptor glycosylation across various cancer types. Altered glycosylation patterns of HER-2, including modifications in the trastuzumab-binding domain, can significantly influence receptor stability and activity as well as impact the efficacy of targeted therapies. In addition, directing de-glycosylating enzymes to RTKs might indicate a novel approach to improve immunotherapeutic approaches in cancer treatment in the future, including lung cancer treatment.

c-MET

c-MET mutations occur in approximately 3-5% of NSCLC cases, with a higher prevalence in adenocarcinoma and a notable enrichment in the sarcomatoid subtype. In addition, *de novo* c-MET amplifications are observed in 1-5% of NSCLC, primarily affecting adenocarcinoma.[65] c-MET is an RTK, and its active form is a disulfide-linked heterodimer, which includes an extracellular α-subunit and

a single-pass transmembrane β-subunit. The extracellular portion of c-MET features a large N-terminal semaphorin (SEMA) domain, an integrin PSI domain, along with transcription factor IPT domains. The intracellular portion of c-MET consists of three main segments: a juxtamembrane region, a tyrosine kinase domain, and a C-terminal docking site.[66] c-MET activation occurs when it forms a homodimer in response to binding with a ligand. This binding involves high-affinity sites located within the IPT3 and IPT4 domains, as well as low-affinity sites within the SEMA domain.[67] Hepatocyte growth factor (HGF) is the only known true endogenous ligand for c-MET.[68] Human c-MET contains several reported glycosylation sites: 10 N-linked and three O-linked sites, according to GlyGen.[41]

Some findings suggest that the N-glycans of the SEMA domain positively regulate HGF signaling, whereas the N-glycans of the other regions negatively regulate signaling.[69] Specific N-glycans on c-MET regulate its proteolytic processing and HGF-induced signaling in a site-specific manner. Deletion of these N-glycans affects c-MET's status and function. c-MET is initially synthesized as a partially glycosylated single-chain precursor (pro-MET) in the ER. Pro-MET undergoes disulfide bond formation, post-translational glycosylation, and endoproteolytic cleavage to produce the mature heterodimeric form.[70] During receptor homodimerization and autophosphorylation, the activation of several downstream signaling pathways occurs, including the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) and RAS/extracellular signal-regulated kinase (RAS/ERK) pathways. These signaling pathways drive various cellular processes, such as cell proliferation, migration, differentiation, and morphogenesis.[69]

Dysregulation of c-MET, resulting in aberrant signaling, can occur through various mechanisms such as gene amplification, overexpression, activating mutations, increased autocrine or paracrine ligand stimulation, HGF overexpression, formation of abnormal autocrine signaling, and interaction with other active cell-surface receptors.[71] Elevated c-MET expression has been observed in multiple cancers, including lung, breast, ovarian, kidney, colon, thyroid, liver, and gastric carcinomas.[68] Approximately 3-5% of NSCLC patients have c-MET dysregulation, including splice site mutations in METex14 that have been reported in about 4% of NSCLC patients.[68,71,72] Recent advancements have led to the development and approval of several c-MET TKIs, such as capmatinib and tepotinib.[73-75] Drug resistance is an unavoidable challenge in targeted therapies. The presence of *MET* amplification can lead to short-lived and heterogeneous responses.[76] *MET* amplification is a well-established mechanism of acquired resistance to EGFR TKIs in NSCLC patients. It often occurs alongside secondary *EGFR* mutations, contributing to the complexity of resistance.[77]

Since both transcriptional and post-translational mechanisms control the expression and activity of c-MET, NSCLC treatment may benefit from a combination of c-MET TKIs with drugs that influence c-MET maturation in cancer cells. C1GALT1 controls the formation of mucin-type O-glycans, including O-glycosylation of c-MET, thereby enhancing HGF-induced dimerization and activation.[78] GALNT2, an enzyme involved in the first step of mucin-type O-glycosylation, inhibits malignant characteristics in gastric adenocarcinoma by modulating the activity of the c-MET receptor. Knocking down GALNT2 significantly increased c-MET phosphorylation, especially in response to HGF stimulation, and reduced lectin binding to c-MET O-glycans, indicating that GALNT2 plays a role in modifying c-MET O-glycans in gastric cancer cells.[79]

Taken together, specific N-glycans in the SEMA domain enhance HGF signaling, while those outside of this domain suppress it. O-glycosylation, particularly mediated by C1GALT1 and GALNT2, influences c-MET dimerization, activation, and downstream signaling pathways. These modifications suggest that targeting glycosylation could become a novel therapeutic option for NSCLC. Combining c-MET inhibitors with drugs targeting c-MET maturation, such as glycosylation modulators, could enhance treatment efficacy and might improve outcomes for NSCLC patients with c-MET-driven tumors.

RET

RET rearrangements occur in approximately 1.2-2.2% of NSCLC cases, with a slightly higher prevalence in adenocarcinomas.[80,81] RET is distinguished from other RTKs by its extracellular region. This domain is characterized by 4 cadherin-like structures and a segment of 120 amino acids containing 16 cysteine residues.[82] It is activated by glial cell line-derived neurotrophic factor (GDNF) ligands binding to GDNF family receptor alphas, leading to RET dimerization and activation. This activation triggers downstream signaling pathways such as PI3K/AKT, mitogen-activated protein kinase, and phospholipase C gamma (PLCγ), promoting cell proliferation, growth, and survival.[82,83] Overexpression and rearrangements of RET have been identified as potential oncogenic drivers, leading to increased interest in targeted therapies. RET rearrangement is observed in approximately 1-2% of lung adenocarcinomas, with reports indicating that activating EGFR mutations can also co-exist.[84,85] RET is also known for its fusions, such as kinesin family member 5B (KIF5B)-RET, which are found in about 1.7% of lung adenocarcinomas and often associated with younger, non-smoking patients and poorly differentiated tumors.[86] Targeted therapies, such as RET TKIs selpercatinib and pralsetinib, show antitumor activity in lung tumors with high RET expression. Vandetanib, a multikinase inhibitor, may overcome resistance

to EGFR-TKIs in RET-overexpressing lung adenocarcinomas, suggesting its potential use in combination therapies.[87]

At present, there is a lack of studies specifically addressing the glycosylation of RET in cancer and the potential functional consequences. However, GlyGen identifies 4 reported N-glycosylation sites of RET: Asn343, Asn554, Asn763, and Asn975.[41]

ALK and ROS1

ALK rearrangements occur in approximately 3.8-6.3% of NSCLC cases, with a higher prevalence in adenocarcinomas. ALK-positive NSCLC is more common in younger patients, women, and never-smokers. The mean age difference between ALK-positive and -negative patients is significant, with ALK-positive patients being younger by about 7 years.[88] ALK is a receptor transmembrane protein tyrosine kinase and is involved in various signaling pathways that regulate cell growth, survival, and differentiation by its activation through binding of the extracellular ligands ALKAL1 and ALKAL2.[89,90] Like many RTKs, ALK is structured with three distinct regions: an extra-cellular domain that binds to ligands, a single-transmembrane segment that anchors the protein, and an intracellular cytoplasmic tyrosine kinase domain critical in the development of diseases.[91] ROS1 is also an RTK that has been implicated in various cancers, but its exact function in healthy cells remains unknown. ROS1 and ALK share significant structural similarities, particularly in their kinase domains, which have 49% amino acid sequence homology. This substantial overlap contributes to their functional similarities.[92,93]

ALK fusions, generated by chromosomal rearrangements, can signal continuously without the normal regulatory controls. The first alteration of the *ALK* gene identified in human cancers was the nucleophosmin-1 (NPM1)-ALK fusion gene.[89] In the presence of NPM1-ALK fusions, a number of interconnected pathways are activated, such as RAS/ERK, janus kinase 3 - signal transducer and activator of transcription 3, PLCγ, and PI3K/AKT, which results in cellular proliferation, survival, and phenotypic changes.[91] Echinoderm microtubule-associated protein-like 4 (EML4)-ALK is another well-studied fusion gene that is considered to be one of the key pathogenic drivers identified in NSCLC and the most common variant in NSCLC.[94] Beyond EML4, less common yet important ALK fusion partners in NSCLC include KIF5B, a motor protein for intracellular transport, TFG, involved in membrane trafficking, KLC1, another motor protein, and STRN, a scaffolding protein, thus demonstrating a diversity of involved proteins.[89] ALK fusions occur in approximately 3-7% of lung cancers.[95] EML4-ALK fusion variants arise from variable breakpoints during chromosomal rearrangements, leading to fusion proteins of differing sizes; the ALK gene frequently breaks at exon 20 and less commonly at exon 19, while the EML4 breakpoint is more variable, thus generating various fusion proteins with Variants 1 and 3 as the most common.[96]

ROS1 rearrangements are found in a small subset of NSCLCs, with prevalence rates ranging from 0.5% to 2.6% in various studies.[97] ROS1 also forms fusions, which are significant oncogenic drivers in various cancers, including NSCLC, glioblastoma, and others. The fusion proteins resulting from these genetic rearrangements lead to constitutive activation of the ROS1 kinase, promoting cancer cell proliferation and survival.[98] There are at least 26 known genes that can fuse with ROS1, including cluster of differentiation 74, syndecan 4, and solute carrier family 34 member 2, among others. ROS1 fusions in NSCLC are more common in younger, non-smoking patients and these fusions are mutually exclusive with other common mutations like EGFR and Kirsten rat sarcoma viral oncogene homolog.[98]

ROS1 and ALK have a high degree of similarity at the ATP binding site, with about 77% identity. This similarity is crucial because it allows certain inhibitors, such as crizotinib, to target both kinases effectively.[93] Both ROS1 and ALK can develop resistance to inhibitors through similar mechanisms, such as mutations in the kinase domain. For example, ROS1 S1986Y/F and ALK C1156Y mutations are homologous and exhibit similar resistance patterns to certain TKIs. Kinase domain mutations are a major mechanism of acquired resistance in both ROS1- and ALK-positive NSCLC.[99]

Inhibition of N-glycosylation impairs ALK phosphorylation and disrupts downstream pro-survival signaling pathways such as AKT, ERK1/2, and STAT3 in neuroblastoma cell lines. This suggests that glycosylation is essential for ALK's role in promoting cell survival and proliferation.[100] However, no reported glycosylation sites in ALK have been identified thus far. GlyGen lists only 18 predicted sites with 16 N- and two O-glycosylation sites.[41] For ROS1, GlyGen shows three reported O-glycosylation sites in close proximity, namely Ser1570, Ser1577, and Ser1581, suggesting a functional relevance.[41] Collectively, glycosylation in the context of ALK or ROS1 aberrations remains largely unexplored. Given the structural similarities between ALK and ROS1, it is plausible that glycosylation findings in one of these RTKs can be extrapolated to the other.

SUMMARY

Glycosylation plays a very important role in the regulation of RTKs relevant to solid cancers, particularly in lung cancer, and these post-translational modifications influence protein stability and function as well as therapeutic targeting. This review highlights the significance of aberrant glycosylation patterns in the key RTKs: EGFR, HER-2, ALK, ROS1, RET, and c-MET, and their potential impact on cancer treatment strategies.

N- and O-glycosylation in key domains of RTKs serve as crucial protein modifications that affect receptor activity, ligand binding, and downstream signaling pathways. EGFR, HER-2, ALK, and c-MET have been studied to some extent, and insights from their glycosylation patterns have already led to potential therapeutic interventions. For example, targeting specific glycan structures has shown promise in enhancing the efficacy of EGFR and HER2 inhibitors, possibly helping to alleviate drug resistance and improving patient responses. Furthermore, ALK glycosylation affects receptor activation and contributes to resistance mechanisms, emphasizing the need for further exploration of the role of glycosylation in fusion-driven lung cancers. On the other hand, ROS1 and RET remain relatively unexplored in terms of functional glycosylation in cancer. Their structural and functional similarities to more well-characterized RTKs provide a strong rationale for investigations to narrow our gap in understanding glycan-mediated regulatory mechanisms of RTKs in cancer.

Despite significant progress, challenges remain in translating glycosylation-based insights into clinical applications. The complexity of glycosylation patterns and their dynamic nature necessitate advanced analytical tools and comprehensive studies to identify specific glycan structures that could serve as biomarkers or therapeutic targets. In addition, understanding the interplay between glycosylation and genomic alterations is critical to developing personalized treatment strategies. Future research should focus on the integration of large-scale glycoproteomics into routine cancer diagnostics to identify additional glycosylation sites relevant to lung cancer and acquired therapy resistance. The development of glycan-targeting therapeutics and monoclonal antibodies targeting aberrantly glycosylated proteins will be critical in combined therapy regimens. In addition, fine-tuning of antibody-enzyme conjugates leading to tumor cell-specific targeted de-glycosylation activity will be necessary for enhanced personalized treatment approaches. By advancing our understanding of the role of glycosylation in lung cancer, we can lay the foundation for more precise and effective diagnostic and therapeutic approaches and ultimately improve patient outcomes.

AVAILABILITY OF DATA AND MATERIALS

Glyco-conjugate-related data have been accessed through GlyGen at https://www.glygen.org/, an international data source integrating and harmonizing publicly available data.

ABBREVIATIONS

ALG: Mannosyltransferase
ALK: Anaplastic lymphoma kinase
Asn: Asparagine
C1GALT1: Core1 β1,3-galactosyltransferase
c-MET: MET proto-oncogene RTK
ECD: Extracellular domain
EGF: Epidermal growth factor
EGFR: Epidermal growth factor receptor
EML4: Echinoderm microtubule-associated protein-like 4
EMT: Epithelial-mesenchymal transition
ER: Endoplasmic reticulum
ERBB2: v-erb-b2 erythroblastic leukemia viral oncogene homolog 2
FUT: Fucosyltransferases
GalNAc: N-Acetylgalactosamine
GALNT2: N-Acetylgalactosaminyltransferase 2
GalT: Galactosyltransferase
GCS: Glucosidase
GDNF: Glial cell line-derived neurotrophic factor
GFRα: GDNF family receptor alpha
GnT: N-acetylglucosaminyltransferase
HER-2: Human epidermal growth factor receptor 2
HGF: Hepatocyte growth factor
mAb: Monoclonal antibody
MNS: Alpha-mannosidase
NPM1: Nucleophosmin-1
NSCLC: Non-small cell lung cancer
OST: Oligosaccharyltransferase
PFS: Progression-free survival
RET: Rearranged during transfection receptor tyrosine kinase
ROS1: ROS proto-oncogene 1 receptor tyrosine kinase
RTK: Receptor tyrosine kinases
SEMA: Semaphorin
Ser: Serine
ST6GAL1: ST6 beta-galactoside alpha-2,6-sialyltransferase 1
T-DM1: Trastuzumab emtansin
Thr: Threonine
TKI: Tyrosine kinase inhibitors

AUTHOR CONTRIBUTIONS

AMD: Contributed to the study design and literature research and wrote the original draft; IGK: Contributed to manuscript editing and visualization; LM: Contributed to the study concept and literature research, visualization, manuscript editing, and supervision. All authors read and approved of the final manuscript. All authors meet ICMJE authorship requirements.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study does not involve any human or animal experiments, therefore ethics approval and consent to participate are not applicable.

ACKNOWLEDGMENT

The figures have been created in BioRender. Meder, L. (2025) https://BioRender.com/s89u633 and Meder, L. (2025)

https://BioRender.com/8rqpbva. This review has utilized AI language tools to enhance readability and clarity. Generative AI or AI-assisted tools to create or alter images have not been used. The author retains full responsibility for the content and interpretations presented.

FUNDING

LM is supported by the Hightech Agenda Bavaria. The work was supported by funds from the Interdisciplinary Center for Clinical Research (IZKF) (Grant No. N11 [LM]).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

EDITORIAL/PEER REVIEW

To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a **double-blind model** (authors are blinded for reviewers and vice versa) through an automatic online system.

REFERENCES

1. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung cancer. Lancet 2021;398:535-54.
2. Nicholson AG, Tsao MS, Beasley MB, Borczuk AC, Brambilla E, Cooper WA, *et al*. The 2021 WHO classification of lung tumors: Impact of advances since 2015. J Thorac Oncol 2022;17:362-87.
3. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, *et al*. International Association for the Study of Lung Cancer/American Thoracic Society/European respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-85.
4. Devarakonda S, Li Y, Martins Rodrigues F, Sankararaman S, Kadara H, Goparaju C, *et al*. Genomic profiling of lung adenocarcinoma in never-smokers. J Clin Oncol 2021;39:3747-58.
5. Fois SS, Paliogiannis P, Zinellu A, Fois AG, Cossu A, Palmieri G. Molecular epidemiology of the main druggable genetic alterations in non-small cell lung cancer. Int J Mol Sci 2021;22:612.
6. Saraon P, Pathmanathan S, Snider J, Lyakisheva A, Wong V, Stagljar I. Receptor tyrosine kinases and cancer: Oncogenic mechanisms and therapeutic approaches. Oncogene 2021;40:4079-93.
7. Contessa JN, Bhojani MS, Freeze HH, Rehemtulla A, Lawrence TS. Inhibition of N-linked glycosylation disrupts receptor tyrosine kinase signaling in tumor cells. Cancer Res 2008;68:3803-9.
8. Onglao W, Khew-Goodall Y, Belle L, Lonic A. Aberrant post-translational modifications in endosomal trafficking are potential therapeutic targets to avert therapy resistance in solid cancers. BioEssays [Internet]. 2021 Dec 16;44(2). Available from: http://dx.doi.org/10.1002/bies.202100192
9. Oliveira-Ferrer L, Legler K, Milde-Langosch K. Role of protein glycosylation in cancer metastasis. Semin Cancer Biol 2017;44:141-52.
10. Mereiter S, Balmaña M, Campos D, Gomes J, Reis CA. Glycosylation in the era of cancer-targeted therapy: Where are we heading? Cancer Cell 2019;36:6-16.
11. Pinho SS, Reis CA. Glycosylation in cancer: Mechanisms and clinical implications. Nat Rev Cancer 2015;15:540-55.
12. Reily C, Stewart TJ, Renfrow MB, Novak J. Glycosylation in health and disease. Nat Rev Nephrol 2019;15:346-66.
13. Wandall HH, Nielsen MAI, King-Smith S, de Haan N, Bagdonaite I. Global functions of O-glycosylation: Promises and challenges in O-glycobiology. FEBS J 2021;288:7183-212.
14. Aebi M. N-linked protein glycosylation in the ER. Biochim Biophys Acta 2013;1833:2430-7.
15. Magalhães A, Duarte HO, Reis CA. The role of O-glycosylation in human disease. Mol Aspects Med 2021;79:100964.
16. Leon F, Seshacharyulu P, Nimmakayala RK, Chugh S, Karmakar S, Nallasamy P, *et al*. Reduction in O-glycome induces differentially glycosylated CD44 to promote stemness and metastasis in pancreatic cancer. Oncogene 2022;41:57-71.
17. Balbisi M, Sugár S, Turiák L. Protein glycosylation in lung cancer from a mass spectrometry perspective. Mass Spectrom Rev 2024. Available from: http://dx.doi.org/10.1002/mas.21882.
18. Ramírez AS, Locher KP. Structural and mechanistic studies of the N-glycosylation machinery: From lipid-linked oligosaccharide biosynthesis to glycan transfer. Glycobiology 2023;33:861-72.
19. Ahangama Liyanage L, Harris MS, Cook GA. *In vitro* glycosylation of membrane proteins using N-glycosyltransferase. ACS Omega 2021;6:12133-42.
20. Schwarz F, Aebi M. Mechanisms and principles of N-linked protein glycosylation. Curr Opin Struct Biol 2011;21:576-82.
21. Christiansen MN, Chik J, Lee L, Anugraham M, Abrahams JL, Packer NH. Cell surface protein glycosylation in cancer. Proteomics 2014;14:525-46.
22. Vasconcelos-Dos-Santos A, Oliveira IA, Lucena MC, Mantuano NR, Whelan SA, Dias WB, *et al*. Biosynthetic machinery involved in aberrant glycosylation: Promising targets for developing of drugs against cancer. Front Oncol 2015;5:138.
23. Rodrigues JG, Duarte HO, Reis CA, Gomes J. Aberrant protein glycosylation in cancer: Implications in targeted therapy. Biochem Soc Trans 2021;49:843-54.
24. Itkonen HM, Mills IG. N-linked glycosylation supports cross-talk between receptor tyrosine kinases and androgen receptor. PLoS One 2013;8:e65016.
25. Costa AF, Teixeira A, Reis CA, Gomes C. Novel anticancer drug discovery efforts targeting glycosylation: The emergence of fluorinated monosaccharides analogs. Expert Opin Drug Discov 2025;20:193-203.
26. Toyofuku T, Ishikawa T, Nojima S, Kumanogoh A. Efficacy against lung cancer is augmented by combining aberrantly N-glycosylated T cells with a chimeric antigen receptor targeting fragile X mental retardation 1 neighbor. J Immunol 2024;212:917-27.

27. Do KT, Chow LQ, Reckamp K, Sanborn RE, Burris H, Robert F, *et al.* First-in-human, first-in-class, phase I trial of the fucosylation inhibitor SGN-2FF in patients with advanced solid tumors. Oncologist 2021;26:925-e1918.
28. Shi Y, Li J, Zhang S, Wang M, Yang S, Li N, *et al*. Molecular epidemiology of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology - Mainland China subset analysis of the PIONEER study. PLoS One 2015;10:e0143515.
29. Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, *et al.* A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014;9:154-62.
30. Auliac JB, Thomas PA, Bylicki O, Guisier F, Curcio H, AlainVegnenègre, *et al*. Resected EGFR-mutated non-small-cell lung cancers: Incidence and outcomes in a European population (GFPC Exerpos Study). Ther Adv Med Oncol 2024;16:17588359241236451.
31. Martin-Fernandez ML, Clarke DT, Roberts SK, Zanetti-Domingues LC, Gervasio FL. Structure and dynamics of the EGF receptor as revealed by experiments and simulations and its relevance to non-small cell lung cancer. Cells 2019;8:316.
32. Uribe ML, Marrocco I, Yarden Y. EGFR in cancer: Signaling mechanisms, drugs, and acquired resistance. Cancers (Basel) 2021;13:2748.
33. Qiu J, Ma Z, Li R, Qu C, Wang K, Liu B, *et al.* Distinguishing EGFR mutant subtypes in stage IA non-small cell lung cancer using the presence status of ground glass opacity and final histologic classification: A systematic review and meta-analysis. Front Med (Lausanne) 2023;10:1268846.
34. Suda K, Mitsudomi T, Shintani Y, Okami J, Ito H, Ohtsuka T, *et al.* Clinical Impacts of EGFR mutation status: Analysis of 5780 surgically resected lung cancer cases. Ann Thorac Surg 2021;111:269-76.
35. Vyse S, Huang PH. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Signal Transduct Target Ther 2019;4:5.
36. Sigismund S, Avanzato D, Lanzetti L. Emerging functions of the EGFR in cancer. Mol Oncol 2018;12:3-20.
37. Ma Y, Zhang F, Li J, Li J, Li Y. Diverse perspectives on proteomic posttranslational modifications to address EGFR-TKI resistance in non-small cell lung cancer. Front Cell Dev Biol 2024;12:1436033.
38. Lin Y, Lubman DM. The role of N-glycosylation in cancer. Acta Pharm Sin B 2024;14:1098-110.
39. Klaver E, Zhao P, May M, Flanagan-Steet H, Freeze HH, Gilmore R, *et al.* Selective inhibition of N-linked glycosylation impairs receptor tyrosine kinase processing. Dis Model Mech 2019;12:dmm039602.
40. Azimzadeh Irani M, Kannan S, Verma C. Role of N-glycosylation in EGFR ectodomain ligand binding. Proteins 2017;85:1529-9.
41. York WS, Mazumder R, Ranzinger R, Edwards N, Kahsay R, Aoki-Kinoshita KF, *et al.* GlyGen: Computational and informatics resources for glycoscience. Glycobiology 2020;30:72-3.
42. Taylor ES, Pol-Fachin L, Lins RD, Lower SK. Conformational stability of the epidermal growth factor (EGF) receptor as influenced by glycosylation, dimerization and EGF hormone binding. Proteins 2017;85:561-70.
43. Takahashi M, Hasegawa Y, Maeda K, Kitano M, Taniguchi N. Role of glycosyltransferases in carcinogenesis; growth factor signaling and EMT/MET programs. Glycoconj J 2022;39:167-76.
44. Whitson KB, Whitson SR, Red-Brewer ML, McCoy AJ, Vitali AA, Walker F, *et al.* Functional effects of glycosylation at Asn-579 of the epidermal growth factor receptor. Biochemistry 2005;44:14920-31.
45. Lam D, Arroyo B, Liberchuk AN, Wolfe AL. Effects of N361 glycosylation on epidermal growth factor receptor biological function. bioRxiv [Preprint]; 2024. doi: 10.1101/2024.07.12.603279.
46. Rodrigues JG, Duarte HO, Gomes C, Balmaña M, Martins ÁM, Hensbergen PJ, *et al.* Terminal α2,6-sialylation of epidermal growth factor receptor modulates antibody therapy response of colorectal cancer cells. Cell Oncol (Dordr) 2021;44:835-50.
47. Lopez Sambrooks C, Baro M, Quijano A, Narayan A, Cui W, Greninger P, *et al.* Oligosaccharyltransferase inhibition overcomes therapeutic resistance to EGFR tyrosine kinase inhibitors. Cancer Res 2018;78:5094-106.
48. Su Y, Ao X, Long Y, Zhang Z, Zhang M, Zhang Z, *et al.* C1GALT1 high expression enhances the progression of glioblastoma through the EGFR-AKT/ERK cascade. Cell Signal 2025;125:111513.
49. Lin MC, Huang MJ, Liu CH, Yang TL, Huang MC. GALNT2 enhances migration and invasion of oral squamous cell carcinoma by regulating EGFR glycosylation and activity. Oral Oncol 2014;50:478-84.
50. Weinberg F, Peckys DB, de Jonge N. EGFR Expression in HER2-Driven breast cancer cells. Int J Mol Sci 2020;21:9008.
51. Mazières J, Peters S, Lepage B, Cortot AB, Barlesi F, Beau-Faller M, *et al.* Lung cancer that harbors an HER2 mutation: Epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013;31:1997-2003.
52. Vathiotis IA, Charpidou A, Gavrielatou N, Syrigos KN. HER2 Aberrations in non-small cell lung cancer: From pathophysiology to targeted therapy. Pharmaceuticals (Basel) 2021;14:1300.
53. Yu X, Ji X, Su C. HER2-Altered non-small cell lung cancer: Biology, clinicopathologic features, and emerging therapies. Front Oncol 2022;12:860313.
54. Yagishita S, Fujita Y, Kitazono S, Ko R, Nakadate Y, Sawada T, *et al.* Chemotherapy-regulated microRNA-125-HER2 pathway as a novel therapeutic target for trastuzumab-mediated cellular cytotoxicity in small cell lung cancer. Mol Cancer Ther 2015;14:1414-23.
55. Suzuki M, Shiraishi K, Yoshida A, Shimada Y, Suzuki K, Asamura H, *et al.* HER2 gene mutations in non-small cell lung carcinomas: Concurrence with Her2 gene amplification and Her2 protein expression and phosphorylation. Lung Cancer 2015;87:14-22.
56. Li BT, Ross DS, Aisner DL, Chaft JE, Hsu M, Kako SL, *et al.* HER2 Amplification and HER2 mutation are distinct molecular targets in lung cancers. J Thorac Oncol 2016;11:414-9.
57. Mazières J, Barlesi F, Filleron T, Besse B, Monnet I,

Beau-Faller M, *et al.* Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: Results from the European EUHER2 cohort. Ann Oncol 2016;27:281-6.
58. Zhang X, Lv J, Wu Y, Qin N, Ma L, Li X, *et al.* HER2 Exon 20 insertion mutations in lung adenocarcinoma: Case series and response to pyrotinib. Front Oncol 2020;10:1162.
59. Zhao J, Xia Y. Targeting HER2 alterations in non-small-cell lung cancer: A comprehensive review. JCO Precis Oncol 2020;4:411-25.
60. Rolfo C, Russo A. HER2 Mutations in non-small cell lung cancer: A Herculean effort to hit the target. Cancer Discov 2020;10:643-5.
61. Huang CS, Yang Y, Kwong A, Chen SC, Tseng LM, Liu MC, *et al.* Trastuzumab emtansine (T-DM1) versus trastuzumab in Chinese patients with residual invasive disease after neoadjuvant chemotherapy and HER2-targeted therapy for HER2-positive breast cancer in the phase 3 KATHERINE study. Breast Cancer Res Treat 2021;187:759-68.
62. Schettini F, Prat A. Dissecting the biological heterogeneity of HER2-positive breast cancer. Breast 2021;59:339-50.
63. Duarte HO, Rodrigues JG, Gomes C, Hensbergen PJ, Ederveen AL, de Ru AH, *et al.* ST6Gal1 targets the ectodomain of ErbB2 in a site-specific manner and regulates gastric cancer cell sensitivity to trastuzumab. Oncogene 2021;40:3719-33.
64. Xiao H, Woods EC, Vukojicic P, Bertozzi CR. Precision glycocalyx editing as a strategy for cancer immunotherapy. Proc Natl Acad Sci U S A 2016;113:10304-9.
65. Friedlaender A, Drilon A, Banna GL, Peters S, Addeo A. The METeoric rise of MET in lung cancer. Cancer 2020;126:4826-37.
66. Hu X, Tang F, Liu P, Zhong T, Yuan F, He Q, *et al.* Structural and functional insight into the glycosylation impact upon the HGF/c-met signaling pathway. Front Cell Dev Biol 2020;8:490.
67. Fu J, Su X, Li Z, Deng L, Liu X, Feng X, *et al.* HGF/c-MET pathway in cancer: From molecular characterization to clinical evidence. Oncogene 2021;40:4625-51.
68. Sierra JR, Tsao MS. c-MET as a potential therapeutic target and biomarker in cancer. Ther Adv Med Oncol 2011;3 (1 Suppl):S21-35.
69. Saitou A, Hasegawa Y, Fujitani N, Ariki S, Uehara Y, Hashimoto U, *et al.* N-glycosylation regulates MET processing and signaling. Cancer Sci 2022;113:1292-304.
70. Dai R, Li J, Fu J, Chen Y, Yu L, Zhao X, *et al.* Disturbance of Ca2+ homeostasis converts pro-Met into non-canonical tyrosine kinase p190MetNC in response to endoplasmic reticulum stress in MHCC97 cells. J Biol Chem 2012;287:14586-97.
71. Titmarsh HF, O'Connor R, Dhaliwal K, Akram AR. The emerging role of the c-MET-HGF axis in non-small cell lung cancer tumor immunology and immunotherapy. Front Oncol 2020;10:54.
72. Jamme P, Fernandes M, Copin MC, Descarpentries C, Escande F, Morabito A, *et al.* Alterations in the PI3K pathway drive resistance to MET inhibitors in NSCLC harboring MET exon 14 skipping mutations. J Thorac Oncol 2020;15:741-51.
73. Mathieu LN, Larkins E, Akinboro O, Roy P, Amatya AK, Fiero MH, *et al.* FDA Approval summary: Capmatinib and tepotinib for the treatment of metastatic NSCLC harboring MET exon 14 skipping mutations or alterations. Clin Cancer Res 2022;28:249-54.
74. Wolf J, Hochmair M, Han JY, Reguart N, Souquet PJ, Smit EF, *et al.* Capmatinib in MET exon 14-mutated non-small-cell lung cancer: Final results from the open-label, phase 2 GEOMETRY mono-1 trial. Lancet Oncol 2024;25:1357-70.
75. Wu YL, Guarneri V, Voon PJ, Lim BK, Yang JJ, Wislez M, *et al.* Tepotinib plus osimertinib in patients with EGFR-mutated non-small-cell lung cancer with MET amplification following progression on first-line osimertinib (INSIGHT 2): A multicentre, open-label, phase 2 trial. Lancet Oncol 2024;25:989-1002.
76. van Veggel B, de Langen AJ, Hashemi S, Monkhorst K, Rosenberg EH, Heideman DA, *et al.* Crizotinib treatment for patients with EGFR mutation positive NSCLC that acquire cMET amplification after EGFR TKI therapy results in short-lived and heterogeneous responses. Lung Cancer 2018;124:130-4.
77. Moores SL, Chiu ML, Bushey BS, Chevalier K, Luistro L, Dorn K, *et al.* A Novel bispecific antibody targeting EGFR and cMet is effective against EGFR inhibitor-resistant lung tumors. Cancer Res 2016;76:3942-53.
78. Wu YM, Liu CH, Huang MJ, Lai HS, Lee PH, Hu RH, *et al.* C1GALT1 enhances proliferation of hepatocellular carcinoma cells via modulating MET glycosylation and dimerization. Cancer Res 2013;73:5580-90.
79. Liu SY, Shun CT, Hung KY, Juan HF, Hsu CL, Huang MC, *et al.* Mucin glycosylating enzyme GALNT2 suppresses malignancy in gastric adenocarcinoma by reducing MET phosphorylation. Oncotarget 2016;7:11251-62.
80. Feng J, Li Y, Wei B, Guo L, Li W, Xia Q, *et al.* Clinicopathologic characteristics and diagnostic methods of RET rearrangement in Chinese non-small cell lung cancer patients. Transl Lung Cancer Res 2022;11:617-31.
81. Michels S, Scheel AH, Scheffler M, Schultheis AM, Gautschi O, Aebersold F, *et al.* Clinicopathological characteristics of RET rearranged lung cancer in European patients. J Thorac Oncol 2016;11:122-7.
82. Regua AT, Najjar M, Lo HW. RET signaling pathway and RET inhibitors in human cancer. Front Oncol 2022;12:932353.
83. Kawai K, Takahashi M. Intracellular RET signaling pathways activated by GDNF. Cell Tissue Res 2020;382:113-23.
84. Servetto A, Esposito D, Ferrara R, Signorelli D, Belli S, Napolitano F, *et al.* RET rearrangements in non-small cell lung cancer: Evolving treatment landscape and future challenges. Biochim Biophys Acta Rev Cancer 2022;1877:188810.
85. Tang Z, Zhang J, Lu X, Wang W, Chen H, Robinson MK, *et al.* Coexistent genetic alterations involving ALK, RET, ROS1 or MET in 15 cases of lung adenocarcinoma. Mod Pathol 2018;31:307-12.
86. Wang R, Hu H, Pan Y, Li Y, Ye T, Li C, *et al.* RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. J Clin Oncol 2012;30:4352-9.
87. Russo A, Cardona AF, Caglevic C, Manca P, Ruiz-Patiño A, Arrieta O, *et al.* Overcoming TKI resistance in fusion-driven NSCLC: New generation inhibitors and rationale for combination strategies. Transl Lung Cancer Res 2020;9:2581-98.

88. Fan L, Feng Y, Wan H, Shi G, Niu W. Clinicopathological and demographical characteristics of non-small cell lung cancer patients with ALK rearrangements: A systematic review and meta-analysis. PLoS One 2014;9:e100866.
89. Roskoski R Jr. Anaplastic lymphoma kinase (ALK): Structure, oncogenic activation, and pharmacological inhibition. Pharmacol Res 2013;68:68-94.
90. De Munck S, Provost M, Kurikawa M, Omori I, Mukohyama J, Felix J, *et al.* Structural basis of cytokine-mediated activation of ALK family receptors. Nature 2021;600:143-7.
91. Ducray SP, Natarajan K, Garland GD, Turner SD, Egger G. The Transcriptional roles of ALK fusion proteins in tumorigenesis. Cancers (Basel) 2019;11:1074.
92. Ou SH, Tan J, Yen Y, Soo RA. ROS1 as a 'druggable' receptor tyrosine kinase: lessons learned from inhibiting the ALK pathway. Expert Rev Anticancer Ther 2012;12:447-56.
93. Tian Y, Yu Y, Shen Y, Wan H, Chang S, Zhang T, *et al.* Molecular simulation studies on the binding selectivity of Type-I inhibitors in the complexes with ROS1 versus ALK. J Chem Inf Model 2017;57:977-87.
94. Lei Y, Lei Y, Shi X, Wang J. EML4-ALK fusion gene in non-small cell lung cancer. Oncol Lett 2022;24:277.
95. Wu W, Haderk F, Bivona TG. Non-canonical thinking for targeting ALK-fusion onco-proteins in lung cancer. Cancers (Basel) 2017;9:164.
96. Elshatlawy M, Sampson J, Clarke K, Bayliss R. EML4-ALK biology and drug resistance in non-small cell lung cancer: A new phase of discoveries. Mol Oncol 2023;17:950-63.
97. Yang X, Tang Z, Li J, Jiang J, Liu Y. Progress of non-small-cell lung cancer with ROS1 rearrangement. Front Mol Biosci 2023;10:1238093.
98. Facchinetti F, Rossi G, Bria E, Soria JC, Besse B, Minari R, *et al.* Oncogene addiction in non-small cell lung cancer: Focus on ROS1 inhibition. Cancer Treat Rev 2017;55:83-95.
99. Facchinetti F, Loriot Y, Kuo MS, Mahjoubi L, Lacroix L, Planchard D, *et al.* Crizotinib-resistant ROS1 mutations reveal a predictive kinase inhibitor sensitivity model for ROS1- and ALK-rearranged lung cancers. Clin Cancer Res 2016;22:5983-91.
100. Del Grosso F, De Mariano M, Passoni L, Luksch R, Tonini GP, Longo L. Inhibition of N-linked glycosylation impairs ALK phosphorylation and disrupts pro-survival signaling in neuroblastoma cell lines. BMC Cancer 2011;11:525.

How to cite this article: Dmitrieva AM, Kocak IG, Meder L. Aberrations in the glycosylation of receptor tyrosine kinases: A focus on lung adenocarcinoma. CytoJournal. 2025;22:62. doi: 10.25259/Cytojournal_21_2025

HTML of this article is available FREE at:
https://dx.doi.org/10.25259/Cytojournal_21_2025