Introduction

EGFR alterations in non-small-cell lung cancer in brief

Epidermal growth factor receptor (EGFR) has tyrosine kinase activity and is a transmembrane glycoprotein. The EGFR and members of its family play a significant role in carcinogenesis through contribution into cell proliferation, apoptosis, cell motility, and angiogenesis. EGFR alterations are involved in the pathogenesis and progression of many malignancies including lung cancer [1–5].

One of the most common alteration in non-small-cell lung cancer (NSCLC) patients and cells is overexpression of EGFR, which is demonstrated in more than half cases of NSCLC and is associated with a poor prognosis and chemoresistance [6, 7]. Moreover, the expression of EGFR appears to be dependent on histological subtypes of NSCLC, and is most frequently expressed in squamous cell. In addition to EGFR overexpression, activating mutations of EGFR are observed in around 10% of all nonsquamous non-small-cell lung cancer patients [8].

Epidermal growth factor receptor mutations are significant predictors of treatment response to tyrosine kinase inhibitors (TKIs) in patients with non-small-cell lung cancer. However, according to researchers, diverse response to the treatment is common. Therefore, there are group of patients with mutations who do not show any response and some patients without mutations who can respond to the treatment. Moreover, other investigators [9] discovered additional alterations of EGFR in NSCLC patients (Table 1). Winter-Larsen et al. identified genetic polymorphism of the EGFR gene and expected it may be
important for prediction of clinical consequences in TKISs-treated advanced NSCLC patients [10]. Furthermore, increased EGFR copy numbers were described as a common modification in NSCLC. Altered EGFR copy numbers are present up to 59% of NSCLC [11–14]. According to Sholl et al. and other research groups [14, 16], gain of EGFR copy number is related to a positive effect after EGFR TKIs treatment; it has also been proposed to be a potential biomarker of TKIs responsiveness. Likewise, treatment with TKIs gives better results in positive EGFR samples [12, 15]. In addition to described alteration, EGFR methylation and phosphorylation might have strong impact on the clinical outcome of NSCLC. Thus, Li et al. discovered the importance of EGFR gene methylation, which was associated with malignancy of this type of cancer [17]. In other study, patients with phospho-EGFR-positive tumors demonstrated a longer survival [18]. On the other hand, Hijiya et al. investigated 21 cases of NSCLC to examine correlations between the existence of EGFR mutations and the EGFR phosphorylation grade by immunohistochemistry. Moreover, the mutation status of the EGFR gene was correlated with immunoreactivity for phosphor-EGFR and its immunoreactivity was significantly correlated with clinical responsiveness to one of the available drug—gefitinib [19]. Taking together, the alterations of EGFR are common condition in NSCLC patients and usually correlate with poor prognosis and resistance to chemotherapy.

**Notch in non-small-cell lung cancer in brief**

The Notch signaling pathway is conservative and plays an important role in the cellular proliferation, differentiation, and apoptosis. The human Notch family includes four receptors (Notch 1 through 4 in mammals) and five ligands (Jagged1, Jagged2, Dll1, Dll3, and Dll4) [20, 21]. Activation of Notch pathway depends on interaction between specific ligand and receptor; nevertheless different mechanisms are involved in this process. The canonical way occurs when NICD is released after enzymatic
intervention of ADAM family metalloprotease, which creates a substrate for a second cleavage by the γ-secretase complex, releasing the Notch intracellular domain (NICD). The intracellular domain is later moved into the nucleus where it cooperates with CBF-1 (transcription factor recombining binding protein suppressor of hairless). The noncanonical way can take place without γ-secretase cleavage and CBF-1 [20]. Although, the mechanisms of Notch activation are known in physiological conditions, the processes regulating this pathway in cancer are not so evident. It has been postulated that hypoxic tumor microenvironment may be crucial in regulation of Notch pathway in cancer. Moreover, evaluation of Notch pathway expression in cancer may not be related only to up- or down-regulation of this signaling, but may be determined by compound interactions with EGFR through activation of PI3K/AKT/mTOR cascade which in turn increases the translation of hypoxia inducible factors (HIF-1α). Therefore, according to some authors, hypoxia stabilizes NICD which can interact with hypoxia-inducible factor 1 alpha (HIF-1α) (Fig. 1) [22, 23].

There are some studies indicating Notch is highly activated in NSCLC [24, 25]. However, other studies demonstrated a reduced or undetectable Notch1 expression in NSCLC. This implies a supposed Notch1 tumor-suppressive role in these tumors and again gives a notion that Notch function in NSCLC is more complicated than predicted [26, 27].

On the other hand, altered Notch genes may influence the stabilization of Notch in NSCLC. Hence, two types of alterations were detected in NSCLC: heterozygous mutations of the Notch-1 locus in 10% of the cases, and loss of Numb expression in 30% of the cases of NSCLC [28].

Although, the role of Notch in non-small-cell lung cancer remains unclear, the observations reveal that Notch signaling in NSCLC depends on the specific tissue context, microenvironment, and crosstalk with other signaling pathways. Consequently, it might be important in development of tumor or can act as a tumor suppressor [24]. Although the mechanism of Notch signaling in lung cancer pathogenesis is not fully understood, most likely other factors are involved.

**Clinical relevance and therapeutic approaches aimed at targeting Notch and EGFR signaling in NSCLC**

Many research groups try to explain crosstalk between Notch and EGFR in order to understand the mechanism of this cooperation and to know how cancer cells use the Notch pathway to compensate for EGFR-targeted inhibition. Notch and epidermal growth factor receptor (EGFR) signaling are essential in cell proliferation, differentiation, and apoptosis, and thereby may contribute to the development of lung cancer.

It has been described that those pathways can cooperate in different mechanisms, either antagonistic or synergistic (Fig. 2), depending on tissue, developmental status, and microenvironment [29].

Although recent studies have shown that Notch and EGFR signaling are associated with drug resistance, antiangiogenic agent and EGFR tyrosine kinase inhibitors have been accepted for NSCLC treatment [30, 31].

Moreover, current clinical trials examine the efficacy and safety of antiangiogenic and anti-EGFR agents combinations, as well as additional agents such as multitargeted antiangiogenic tyrosine kinase inhibitors [32, 33].

The researchers revealed that the expression of Notch-1 was upregulated in EGFR-TKISs developed resistant lung cancer cells. Additional, Notch-1 contributed to the achievement of the epithelial–mesenchymal transition (EMT) phenotype, which was correlated with developed resistance to EGFR-TKIs [34].

Another study showed that while inhibition of EGFR leads to reduction in tumor cell number, it also leads to a potent activation of the Notch pathway. Combined

![Figure 2. Possible mechanisms of crosstalk between EGFR and Notch and clinical consequences: (A) EGFR cooperates with intracellular domain of Notch by enhancing its effect on tumor apoptosis, (B) EGFR overexpression downregulates Notch, (C) Notch upregulates EGFR expression through p53 as a mediator of the Notch-1. NICD, intracellular domain of Notch.](image-url)
inhibition of EGFR and Notch3 receptors significantly reduced the growth of stem-like cells. Taking together, investigators concluded that treatment of EGFR-mutated lung cancer cell lines with erlotinib enriched then stem-like cells with stem-like cell potential through EGFR-dependent activation of Notch3. Moreover, γ-secretase inhibitors could reverse this phenotype. Furthermore, the scientists noticed that phosphorylation of Notch3 can be linked to EGFR receptor, but no exact mechanism is known yet [35].

The crosstalk between Notch and EGFR pathway was also conducted by Konishi et al. and Kolev et al. The investigators demonstrated that the interaction between both pathways results in the inhibition of apoptosis [36, 37]. Although independent results presented in gliomas indicated that Notch may upregulate EGFR through p53 [38], another study showed that inhibition of Notch cleavage may not change cell number in the presence of EGFR mutations. Moreover, EGFR may affect Notch signaling suggesting that inhibition of both pathways could be promising in NSCLC. The researchers selected four NSCLC cell lines expressing different levels of NICD (intracellular domain of Notch) and EGFR protein levels and found that the cell lines exhibited different response to the γ-secretase inhibitor DAPT (N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester) and related this to EGFR status. DAPT was effective in proliferation of cells expressing wt EGFR (wild type), whereas it did not affect HCC827 cells expressing mutated EGFR. In addition, alterations were observed among the cells with wild-type EGFR [39]. Another groups of investigators focused on EGFR and Notch ligands. Correspondingly, Choi et al. examined Jag1 expression regulated by EGFR. Nevertheless, Jag2, which belongs to the same group of ligands, was not regulated by EGFR. To examine the role of EGFR using a different approach, wild-type EGFR H1299 cells, which indicated low levels of Jag1 and Jag2 expression, were treated with EGF or transfected with wild-type EGFR.

### Table 2. The most promising Notch and EGFR inhibitors list for targeted therapy of NSCLC.

| Targets | Notch inhibitors | EGFR inhibitors |
|---------|------------------|-----------------|
| Notch receptors and ligands | neutralizing monoclonal antibodies: OMP-59R5, OMP-21M18, NRR1, NRR2 | erlotinib, afatinib, gefitinib |
| Blocking proteolytic activation of Notch receptors | γ-secretase inhibitors: RO4929097, MRK-0752, PF-03084014, MRK-003, BMS-906024 | osimertinib, rociletinib, dacomitinib |
| EGFR gene mutations | anti-EGFR monoclonal antibodies: cetuximab, nimotuzumab, panitumumab |
| Cells with the T790M mutation | Three agents act on the same target (EGFR) |

### Table 3. Effectiveness of Notch- and EGFR-targeted therapies in NSCLC.

| Effectiveness of current Notch- and EGFR-targeted therapy in NSCLC | References |
|---------------------------------------------------------------------|------------|
| Inhibition of Notch signaling with available γ-secretase inhibitors, mAbs, arsenic trioxide (animal model) | Affect tumor cells survival, differentiation, angiogenesis; drawbacks—toxicity [42–44] |
| Inhibition of mutated EGFR with TKISs inhibitors | Efficient in NSCLC patients with mutated EGFR, effectiveness in the treatment of brain metastases from NSCLC; drawbacks—cancer cells develop new mutations in the EGFR gene [45–47] |
| Inhibition of mutated EGFR with mAbs | Used as chemotherapy as the first treatment in people with advanced squamous cell NSCLC inhibit tumor growth [48, 49] |
| Combined Notch-EGFR-targeted therapies | Combination of R and E is safe in patients with NSCLC; clinical trial information: NCT01193881 [50] |
| Combined Notch/EGFR therapy with γ-secretase inhibitor (DAPT) N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester and gefitinib (animal model) | Effective tumor growth inhibition, with decreased proliferative activity and increased apoptotic activity [34] |

mAbs, monoclonal antibodies; E, erlotinib; R, γ-secretase inhibitor RO4929097; TKISs, tyrosine kinase inhibitors; DAPT, N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester.
As a result, two of the transfected agents increased only the expression of Jag1 and gefitinib treatment abolished EGFR-induced Jag1 expression in H1299 cells [40]. The discovery of EGFR mutations in non-small-cell lung cancer initiated the personalized medicine in advanced NSCLC. During the last decade, different EGFR-TKIs have been developed. Three EGFR inhibitors, gefitinib, erlotinib, and afatinib, are already used in treatment for patients with NSCLC (Tables 2 and 3). Nevertheless, despite great advances have been made, novel treatment still should overcome the therapeutic challenges, such as resistance or metastases [41].

Conclusions

As researchers have developed knowledge about the alterations in lung cancer cells that help them grow, they have developed newer drugs that specifically target these changes. Despite of new drugs and therapeutic regiments, the prognosis for lung cancer patients has not significantly transformed in the last years. There is now overwhelming data on the prognostic and predictive value of each EGFR signaling in NSCLC. Although the role of EGFR signaling in the pathogenesis and progression of NSCLC is well recognized, the importance of Notch pathway and its correlation with EGFR in lung cancer is still under investigation. Notch may act as an oncogene or a tumor suppressor gene in lung cancer cells depending on tissue, developmental context, and microenvironment. However, recently agents targeting the fundamental molecular signaling pathways in lung cancer are already under clinical trials with more promising results. Thus, the mechanism(s) of crosstalk between EGFR and Notch in non-small-cell lung cancer need to be identified.

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Conflict of Interest

The author declares that there is no conflict of interests regarding the publication of this study.

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