Preclinical Development

Activation of the Insulin-like Growth Factor-1 Receptor Induces Resistance to Epidermal Growth Factor Receptor Antagonism in Head and Neck Squamous Carcinoma Cells

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Abstract

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) have poor efficacy in head and neck squamous carcinoma cells (HNSCC). Because the IGF-1 receptor (IGF1R) generates potent prosurvival signals and has been implicated in therapeutic resistance, its ability to induce resistance to EGFR-TKIs was studied in vitro. Five HNSCC cell lines showed reduced sensitivity to the EGFR-TKI gefitinib when the IGF1R was activated. In SCC-25 and Cal27 cells, gefitinib inhibited basal and EGF-stimulated EGFR, extracellular signal–regulated kinase (Erk), and Akt phosphorylation and reduced cell number. This correlated with initiation of apoptosis based on a 4-fold increase in PARP cleavage and a 2.5-fold increase in Annexin V positivity. The apoptotic response and reduction in cell number were blocked by IGF1R activation, which resulted in phosphorylation of both Erk and Akt. In both the cell lines, IGF1R-induced Erk, but not Akt, activation was eliminated by gefitinib. IGF1R-induced gefitinib resistance was unaffected by MAP/Erk kinase inhibition with U0126 but was partially impaired by inhibition of phosphoinositide-3-kinase with LY294002. The IGF1R-TKI PQ401 inhibited growth of SCC-25 and Cal27 cells alone and also acted synergistically with gefitinib. Thus, the IGF1R can make HNSCC cells resistant to EGFR-TKI treatment via a prosurvival mechanism. Of the 8 HNSCC tumor samples studied, all samples expressed the IGF1R and 5 showed detectable IGF1R phosphorylation, suggesting that this receptor may be relevant in vivo, and thus, combined EGFR/IGF1R inhibition may be necessary in some patients for effective targeted molecular therapy.

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Introduction

In head and neck squamous carcinoma cells (HNSCC), the epidermal growth factor receptor (EGFR) has emerged as a potential therapeutic target; more than 90% of HNSCCs overexpress the EGFR and elevated EGFR expression predicts decreased survival. Several targeted anti-EGFR agents have been developed, but their efficacy in HNSCC has been limited, showing both intrinsic (low initial response rate) and acquired (short duration of benefit) resistance. Phase II clinical trials with single-agent EGFR-tyrosine kinase inhibitors (TKI) showed response rates of only 5% to 15% (1, 2). Treatment failures do not result from lack of EGFR expression or inability to block receptor activation in vivo, and EGFR expression level does not predict effectiveness. To date, molecular markers that predict response or resistance in HNSCC have not been identified (3).

IGF-1 and IGF-2 are ubiquitously produced protein hormones that interact with the IGF-1 receptor (IGF1R) to regulate growth, differentiation, and survival. The IGF1R activates both Ras/Erk- and PI3K/Akt-related signal transduction pathways, which act to promote proliferation and prevent apoptosis (4). The IGFs are regulated extracellularly by 6 IGFBP-binding proteins (IGFBP) that buffer receptor activation. Thus, dysregulation of IGF production, IGF1R expression, or IGFBP secretion can alter growth regulation.

There is substantial evidence that the IGF1R plays a central role in cancer development and tumor cell growth. The IGF1R is expressed by nearly all tumor types studied and is activated in an autocrine or paracrine fashion when tumor or stromal cells secrete IGFs (5, 6). In certain settings, the IGF1R is required for transformation by other agents (including the EGFR; ref. 7), and the IGF1R encourages and supports properties of the transformed phenotype. In addition, IGF-1 is also involved in other aspects of cancer progression such as angiogenesis and inflammation (8). Recent studies have shown that elevated serum IGF-1 levels are associated with increased risk of...
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a variety of epithelial cancers (9–12) and that reduced IGF-1 levels may be protective (13). Thus, it has been proposed that reduction of IGF signaling in some cancer types may have therapeutic benefit (4, 14). Augmenting this concept is the recent demonstration that the IGF1R can promote therapeutic resistance to multiple treatment approaches including radiation, cytotoxic chemotherapy, and molecular targeted therapy (15–18). The significance of these findings in HNSCC is, as yet, unknown.

In the present study, we show that activation of the IGF1R in HNSCC cells can overcome growth inhibition caused by EGFR-TKIs via a primarily antiapoptotic mechanism. This validates the concept that, in the context of EGFR blockade, an alternate growth factor can continue to sustain tumor cell growth and suggests that IGF1R signaling may be a mechanism of resistance to targeted anti-EGFR therapy in vivo. Thus, coinhibition of the EGFR and the IGF1R may lead to increased clinical response rates.

Materials and Methods

Reagents
Recombinant human IGF-1 was obtained from Santa Cruz Biotechnology, des-[1-3]IGF-1 from GroPep, EGF from Sigma, and FBS from Invitrogen. U0126, PD158780, and LY294002 were obtained from EMD Biosciences; gefitinib and erlotinib from LC Laboratories; and PQ401 from Tocris Bioscience. Anti-IGF1Rα was acquired from Santa Cruz Biotechnology; anti-p-Erk from Sigma; anti-p-Tyr and anti-PARP from BD Biosciences; and anti-Akt, anti-p—Akt (S473), anti-Erk, anti-p-IGF1R, and anti-p-EGFR from Cell Signaling Technology.

Tissue culture and human tissue specimens
HNSCC cell lines included SCC-25, SCC-9, Cal27, and FaDu cells obtained from American Type Culture Collection, and SCC-61 and UNC—7 cells were kindly provided by Dr. Wendell Yarbrough (Vanderbilt University, Nashville, TN). These were selected to evaluate a variety of anatomic sites in the upper aerodigestive tract and because they exhibit a wide range of IGF1R expression. None of these cell lines had detectable basal IGF1R activation. They were grown in Dulbecco’s Modified Eagle’s Media/F12 supplemented with 400 ng/mL hydrocortisone and 5% FBS at 37°C and 5% CO2. In vitro, cells were histopathologically consistent with HNSCC on standard hematoxylin and eosin staining and were positive for cytokeratin. Rat1 cells overexpressing the IGF1R (RIG) cells were kindly provided by Dr. Michael Weber (University of Virginia). They were grown in Dulbecco’s Modified Eagle’s Media and 5% FBS at 37°C and 5% CO2. Monolayers were starved in no or very low (0.5%) serum. Monolayers were starved in no or very low (0.5%) serum at 37°C and 5% CO2.

CellTiter 96 aqueous cell proliferation assay
Cells were plated at 5,000 cells per well in a 96-well plate, grown for 24 hours, and serum-starved for 24 hours. Cells were washed with PBS, incubated for 2 hours with inhibitor, and stimulated for 48 hours with growth factor. MTS and phenazine methosulfate were added to each well was collected; cell monolayers were trypsinized, resuspended in the corresponding medium, centrifuged at 1,000 × g for 7 minutes at 4°C, washed once with cold PBS, and resuspended in Annexin V-fluorescein isothiocyanate (FITC) and propidium iodide according to the manufacturer’s instructions. Proteins were visualized by reaction with Immobilon Western Chemiluminescent Horseradish Peroxidase Substrate (Millipore).
well according to the manufacturer’s protocol (Promega). Cells were incubated for 4 hours at 37°C and the absorbance at 490 nm was recorded, correcting for background absorbance. Control studies were conducted to show the linearity of this assay at the cell densities used.

**alamarBlue assay**

Cells were prepared and treated as for the MTS assay above. alamarBlue (Invitrogen) was added to each well according to the manufacturer’s protocol. Cells were incubated for 3 to 4 hours at 37°C and the fluorescence at 540 nm was recorded.

**Drug combination analysis**

Growth inhibition data resulting from coinhibition of both the EGFR and the IGF1R were assessed by median-effect analysis as described by Chou and Talalay (19) using CalcuSyn version 2.0 (Biosoft). The combination index was calculated, and an isobologram was plotted for multiple dose combinations. Combination index values of <1, 1, and >1 indicated synergism, additivity, and antagonism, respectively.

**Results**

**IGF1R-induced resistance to EGFR-TKIs**

PD158780, gefitinib, and erlotinib are well-characterized EGFR-TKIs; treatment of HNSCC cell lines with these compounds caused growth inhibition. Activation of the IGF1R was tested for its ability to alter HNSCC sensitivity to EGFR-TKIs (Fig. 1). IGFBP-2 and IGFBP-3 are secreted at high levels by some HNSCC cells (20) and can interfere with activation of the IGF1R by exogenously added free IGF-1. Because of its dramatically reduced affinity for the IGFBPs, des[1-3]IGF-1 was used to activate the IGF1R.

The original observation of IGF1R-induced resistance to EGFR inhibition was made in SCC-25 cells treated with PD158780 (Fig. 1A). PD158780 reduced cell number by 66% at 48 hours. Addition of exogenous EGF caused a 40% increase in cell number; this effect was abolished by PD158780. Activation of the IGF1R with des[1-3]IGF-1 caused a similar increase in cell number that was only minimally affected by PD158780. Stimulation with FBS resulted in an 86% increase in cell number; this was partially blocked by PD158780 (Fig. 1A). These results show that activation of the IGF1R in SCC-25 cells confers resistance to the growth-inhibitory effects of EGFR inhibition. The protective effect of IGF1R activation was measurable across a range of doses for multiple EGFR-TKIs including PD158780, gefitinib, and erlotinib (Fig. 1B). Because it is most likely to have clinical applicability for HNSCC, gefitinib was tested in 4 additional HNSCC cell lines (Fig. 1C); activation of the IGF1R reduced gefitinib sensitivity in all 4 cell lines.

**Erk and Akt activation by the IGF1R**

The effect of gefitinib and IGF1R activation on extracellular signal–regulated kinase (Erk) and Akt phosphorylation was assessed in SCC-25 and Cal27 cells by immunoblot (Fig. 2). A small amount of Erk and Akt phosphorylation were present in unstimulated cells. Whereas EGF caused a large increase in p-Erk with little change in p-Akt, treatment with des[1-3]IGF-1 stimulated a modest increase in p-Erk and a large increase in p-Akt. Addition of gefitinib eliminated baseline p-Erk and p-Akt, confirming that their constitutive phosphorylation depends primarily on EGFR activity. Treatment with gefitinib eliminated EGFR- and des[1-3]IGF-1–induced Erk activation, suggesting that phosphorylation of Erk downstream of the IGF1R is EGFR dependent; this has been reported in other HNSCC cell lines (20, 21). Notably, des[1-3]IGF-1–induced Akt phosphorylation was unaffected by gefitinib in both cell lines, indicating that the IGF1R is capable of providing a persistent prosurvival signal in the presence of an EGFR-TKI.

**IGF1R inhibition of PD158780-induced apoptosis**

Cleavage of PARP, a DNA repair enzyme, occurs in response to caspase-3 activation, serving as an early marker of apoptosis. Figure 3A shows an immunoblot analysis of SCC-25 cell lysates using an anti-PARP antibody that detects the initial PARP cleavage product (c-PARP). Treatment with gefitinib caused a dose-dependent increase in c-PARP that was completely blocked by IGF1R activation. Addition of exogenous EGF did not counteract gefitinib-induced PARP cleavage (Fig. 3B). The densitometric analysis in Fig. 3B confirms that IGF1R activation in SCC-25 cells inhibits gefitinib-induced apoptosis. These data are in keeping with the understanding that the IGF1R can act as a potent prosurvival agent. A similar response to gefitinib and IGF1R activation was also noted in 3 other HNSCC cell lines (Fig. 3C).

Florescence-activated cell sorting was used in conjunction with Annexin V–FITC and propidium iodide staining to identify cells in early and late apoptosis (Fig. 3D). As shown in the quantitative analysis in Fig. 3D, the basal rate of early apoptosis plus late apoptosis (necrosis) was 11% at 48 hours. Addition of gefitinib increased total apoptosis to 28%. Although activation of the IGF1R had little effect on the basal apoptotic rate (10%), it dramatically inhibited the gefitinib-induced apoptosis rate to 13%. The effect of exogenous des[1-3]IGF-1 was blocked by addition of the IGF1R-TKI PQ401 (22, 23).

**Prosurvival signaling from the IGF1R**

The MAP/ERK kinase (MEK) inhibitor U0126 and the phosphoinositide-3-kinase (PI3K) inhibitor LY294002 were used to assess the roles of the Erk and Akt pathways in the antiapoptotic response to IGF1R activation. U0126 and LY294002 treatment resulted in highly selective inhibition of Erk and Akt, respectively (Fig. 4A). U0126 augmented gefitinib-induced PARP cleavage, but des[1-3]IGF-1 still eliminated PARP cleavage in the presence of both inhibitors (gefitinib and U0126; Fig. 4B), showing that...
IGF1R-induced resistance to gefitinib is not MEK/Erk dependent. Addition of LY294002 augmented gefitinib-induced PARP cleavage and reduced, but did not completely eliminate, the ability of des[1-3]IGF-1 to block PARP cleavage (Fig. 4B). Although these data imply incomplete inhibition of PI3K by LY294002, activation of Akt by an alternate (non-PI3K) pathway, or participation of additional signaling pathways in the prosurvival activity of the IGF1R, they strongly suggest involvement of the PI3K/Akt pathway rather than the MEK/Erk pathway in this process.

**EGFR and IGF1R coinhibition**

To determine the utility of IGF1R blockade, SCC-25 and Cal27 cells were treated with PQ401, an IGF1R-TKI (22, 23). PQ401 had an IC50 value of approximately 4 to 5 μmol/L (Fig. 5A). Although p-IGF1R could not be detected in unstimulated cells, PQ401 inhibited des[1-3]IGF-1–stimulated IGF1R phosphorylation and downstream Akt phosphorylation in a dose-dependent manner (Fig. 5B). In SCC-25 cells, PQ401 was shown to reduce basal Akt phosphorylation at lower concentrations (Fig. 5C), suggesting that some basal Akt phosphorylation.
phosphorylation may be due to low-level constitutive IGF1R activity. Figure 5D shows the effect of combined EGFR and IGF1R inhibition with gefitinib and PQ401. For these studies, PQ401 and gefitinib were combined in several ratios (1:1, 2:1, 1:2, and 1:4). On the basis of the combination indices and isobologram analyses, the 2 drugs are synergistic at IC50 levels.

**IGF1R expression in HNSCC tumors**

Figure 6 shows immunoblot analysis of human HNSCC tumor specimens. The tumor specimens used represent small biopsies of solid tumor tissue and the surrounding tissue was shown to be predominantly squamous carcinoma cells by standard clinical histopathology. When lysates of these specimens were immunoblotted, IGF1R was detectable in all tumors, and p-IGF1R was detectable in 5 of 8 specimens. IGF-1-stimulated RIG cells (24) were used as a positive control. These data indicate that the IGF1R is present in HNSCC and often constitutively phosphorylated, providing preliminary data that the IGF1R may have an important clinical role.

**Discussion**

In HNSCCs, EGFR—TKIs can induce tumor regression or stabilization and may augment the antitumor activity of radiotherapy and cytotoxic chemotherapy, but the proportion of responsive tumors is small, and the response is generally not sustained (2). Thus, clinical targeted anti-EGFR therapy yields disappointing results due to both intrinsic and acquired resistance. While EGFR mutations impact sensitivity to EGFR-TKIs in other tumor types, their role in HNSCC is not yet clear (25–27). Because EGFR-TKIs may impact their function, expression of other HER family members may also play an important role in sensitivity to EGFR inhibition. Gefitinib is more than 100-fold less potent at inhibiting HER2 (IC50 > 3.7 μmol/L) than EGFR (IC50 = 0.033 μmol/L) in vitro kinase assays, but it is not known that how important the effect of gefitinib on HER2 is in relation to growth inhibition. The expression and function of HER family members in HNSCC is even less well studied than in other epithelial tumors but could be of significant consequence for EGFR-TKI therapy.

Signaling from other receptor tyrosine kinases can effectively substitute for EGFR activity; these may be constitutively active redundant pathways (intrinsic resistance) or compensatory responses (acquired resistance). The first well-described example of this was c-Met (28), and other receptor tyrosine kinases, including the IGF1R, have since been implicated. In non-HNSCC cell lines, IGF1R activation has been shown to inhibit the apoptosis
induced by cetuximab (29) and by the EGFR-TKI AG1478 (30). After long-term gefitinib exposure, HN11 HNSCC cells showed elevated levels of activated IGF1R and Akt and increased sensitivity to IGFBP-3 (17). These findings support an important EGFR-IGF1R interaction, and, although the mechanism is not fully understood, the prosurvival activity of the IGF1R appears to be crucial.

Chakravarti and colleagues (30) showed that resistance of a glioblastoma cell line to EGFR-TKIs was mediated by increased IGF1R expression with persistent PI3K signaling. In multiple breast cancer cell lines, IGF1R inhibition synergistically increased apoptosis when combined with gefitinib; in these cell lines, inhibition of Akt activity required combined EGFR/IGF1R inhibition (31). Similarly, in A431 cells with induced resistance to gefitinib, Guix and colleagues (17) showed that elimination of persistent

Figure 3. Effect of gefitinib on apoptosis. After 2 hours of treatment with vehicle or gefitinib, cells were incubated for 6 hours (A–C) or 48 hours (D) with growth factors and harvested. A–C, cells were lysed and immunoblotted for PARP. Band density vs. gefitinib only (%) was quantified by densitometry (c-PARP density/total PARP density) and is shown as average percentage of maximal (gefitinib alone) ± SEM for 3 independent experiments. D, cells were treated with Annexin V-FITC and propidium iodide (PI) and assessed by flow cytometry. The average percentage of Annexin V-positive/PI-negative cells ± SEM is shown for 3 similar experiments. Early apoptosis, Annexin V-positive/PI-negative; late apoptosis/necrosis, Annexin V-positive/PI-positive; gefitinib, 5 μmol/L gefitinib; IGF, 10 nmol/L des[1-3]IGF-1; PQ401, 5 μmol/L PQ401. *P < 0.05 versus uninhibited (the Student’s t test).
IGF1R-induced Akt activity was required to reestablish gefitinib sensitivity. On the basis of these findings, persistent IGF1R activity may predict resistance to anti-EGFR therapy. More broadly, IGF1R inhibition also increases apoptosis in response to cytotoxic agents (32, 33), and thus IGF1R activity may also impact the effectiveness of non-targeted chemotherapeutics.

Constitutive activation of the IGF1R in human HNSCC tumor specimens (Fig. 6) suggests the existence of an autocrine or paracrine loop. This is consistent with other studies showing the production of IGF-1 and/or IGF-2 by head and neck tumor cells (20). However, IGF production by epithelial tumor cells may not be necessary to activate the IGF1R; IGF-1 and/or IGF-2 produced by nearby stromal cells could serve as a paracrine growth stimulator. These data establish an important distinction between in vitro studies and the in vivo situation: While in vitro evaluation suggests no IGF1R phosphorylation in the absence of exogenous IGF, there is a high likelihood that HNSCC tumors in vivo are exposed to IGF-1 and/or IGF-2 and that the IGF1R exhibits some degree of constitutive activation. Combined with our findings of IGF1R-induced resistance to EGFR inhibition in multiple HNSCC cell lines in vitro, this would predict potential widespread resistance to EGFR-TKIs in vivo. Because HNSCC are highly heterogeneous tumors, a method for predicting IGF1R-based resistance to anti-EGFR therapy in the clinical setting will be crucial to evaluate the relevance of this mechanism in patients with HNSCC.

Accurate predictors of response to EGFR-TKIs in HNSCC have not been identified. A recent assessment by Rogers and colleagues (34) of a panel of 18 HNSCC cell lines showed a correlation between sensitivity to gefitinib and degree of EGFR phosphorylation. Although Met expression predicted response, Met knockdown had no effect on gefitinib sensitivity. In their study, neither IGF1R expression level nor degree of phosphorylation predicted response to gefitinib (34). However, there was no assessment of downstream targets in this study and thus no indication of the net impact of IGF1R level/activity. Unfortunately, it is unlikely that IGF1R-based resistance will correlate simply with IGF1R expression; in addition to the level and affinity of the IGF1R, the degree of IGF1R activation is dependent on the abundance of IGF ligands and IGFBPs, and the impact of IGF1R activity is highly context sensitive. For example, IGF1R activation can have a greater impact on cell growth when the EGFR is inhibited (Fig. 1C). In addition, the mechanism(s) of interaction between the HER and IGF systems may be complex. A recent study showed that, in breast cancer, trastuzumab regulates IGFBP-2 and IGFBP-3 expression, which impacts IGF1R downstream signaling (35). Cytotoxic agents can also regulate IGFBP secretion: Increased secretion of IGFBP-3 in prostate cancer cells treated with 5-fluorouracil plays an important role in its proapoptotic effect (36). Thus, because of the complexities of the IGF system and its regulation, further investigation will be required to identify a reliable marker of IGF1R-based resistance to therapy.

In general, the effectiveness of EGFR-TKIs in vivo has been based on assessment of EGFR phosphorylation. In SCC-25 and Cal27 cells treated with des[1-3]IGF-1, we detected persistent downstream signaling even when EGFR phosphorylation was undetectable (Fig. 2). Residual downstream target phosphorylation may be due to incomplete EGFR blockade or the activity of other receptors such as the IGF1R. Janmaat and colleagues (37) have shown that failure of gefitinib to inhibit cell growth is correlated with persistent Erk and Akt activity. Therefore, complete assessment of the effectiveness of EGFR-TKIs both in vitro and in vivo requires analysis of phosphorylation of downstream targets.

SCC-25 and Cal27 cells exhibit high EGFR and IGF1R expression and constitutive EGFR, Erk, and Akt phosphorylation. Gefitinib induced apoptosis in a dose-dependent fashion; this was eliminated when IGF1R was inhibited by U0126 or LY294002 (Fig. 4). These data establish an important distinction between in vitro and in vivo assessment of the effectiveness of EGFR-TKIs. More broadly, IGF1R inhibition also increases apoptosis in response to cytotoxic agents (32, 33), and thus IGF1R activity may also impact the effectiveness of non-targeted chemotherapeutics.

Figure 4. Role of MEK and PI3K in gefitinib-induced apoptosis and rescue by IGF1R activation. After 24 hours of serum starvation, SCC-25 cells were incubated for 5 minutes (A) or 48 hours (B) with inhibitors with or without growth factor. Cell lysates were immunoblotted. A, average PARP cleavage (c-PARP density/total PARP density) ± SEM is shown relative to gefitinib alone (100%) for 3 independent experiments.
activated. On the basis of inhibitor studies, this effect is at least partially related to persistent Akt signaling, which is consistent with the well-established role of Akt as a prosurvival effector of the IGF1R. Addition of the PI3K inhibitor LY294002 reduced, but did not eliminate, IGF1R-based resistance to gefitinib-induced apoptosis suggesting incomplete PI3K inhibition, PI3K-independent Akt activation, or an alternate (Akt-independent) prosurvival
In addition to these predictable off-target effects, there may be unexpected and as-yet unknown effects resulting from interactions with unrelated proteins. Future studies should more extensively evaluate the impact of these inhibitors on a broad range of molecular targets in HNSCC.

Our data showing augmented growth inhibition of SCC-25 and Cal27 cells with PQ401 provide preliminary evidence that combined EGFR/IGF1R inhibition may be an effective treatment approach to HNSCCs. Other authors have used combined EGFR/IGF1R inhibition in limited in vivo models of HNSCC (39) but were unable to show a synergistic effect of the 2 inhibitors. Wilsbacher and colleagues (40) showed that inhibition of EGFR and IGF1R acts synergistically in A431 cells; only the combination eliminated Akt phosphorylation and introduction of constitutively active Akt resulted in resistance to the drug combination. Erlotinib and the IGF1R-TKI PQIP were noted by Buck and colleagues (41) to be synergistic in a range of epithelial tumors. Their data suggested that coinhibition was necessary due, at least in part, to increased activation of the reciprocal receptor when either drug was used alone.

It seems clear that, in most cancers, effective targeted therapy will involve blockade of multiple targets. There is now mounting evidence that the IGF1R and/or its downstream signaling pathways will be of key importance in conjunction with the EGFR-TKIs. The most important element of attempting new combinations of targeted therapies will be tumor/patient selection. Thus, correlative evidence is needed that shows biomolecular markers predictive of IGF1R-based EGFR-TKI resistance. It is currently unclear whether unique IGF system molecules (IGF1R, IGF-1 or IGF-2, IGFBP-1 through IGFBP-6) or downstream signaling molecules, such as Akt or others, will be the most significant markers for exploitation and continued evaluation is warranted.

Conclusion

The present study clearly shows that the IGF1R can act as a mechanism of resistance to EGFR-TKIs in an in vitro model of HNSCC and highlights the potential utility of coinhibition of the EGFR and IGF1R.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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