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EGFR Transactivation is Regulated by Neurotensin Receptors in Cancer

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Abstract

The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase (RTK) which regulates the proliferation of cancer cells especially non-small cell lung cancer (NSCLC). NSCLC growth is inhibited by EGFR tyrosine kinase inhibitors (TKI) such as erlotinib or gefitinib. Gefitinib is used to treat NSCLC patients who have EGFR mutations. EGFR tyrosine phosphorylation is regulated by G protein-coupled receptors (GPCR) such as the neurotensin (NTS) receptor. EGFR transactivation caused by NTS addition to NSCLC cells is inhibited by SR48692 (*NTSR1* antagonist) or gefitinib. SR48692 and gefitinib are synergistic at inhibiting NSCLC proliferation. The results indicate that GPCR antagonists can potentiate the effects of TKI in cancer.

Keywords: Neurotensin; *NTSR1* antagonist; SR48692; Epidermal growth factor receptor; Gefitinib; Non-small cell lung cancer

Abbreviations CNS: Central Nervous System; EGF: Epidermal Growth Factor; GPCR: G Protein-Coupled Receptor; HB: Heparin Binding; MMP: Matrix Metalloprotease; MAPK: Mitogen Activated Protein Kinase; NTS: Neurotensin; NSCLC: Non-small Cell Lung Cancer; PM: Plasma Membrane; PI: Phosphatidyl Inositol; PK: Protein Kinase; ROS: Reactive Oxygen Species; RTK: Receptor Tyrosine Kinase; SCLC: Small Cell Lung Cancer; TGF: Transforming Growth Factor; TM: Transmembrane; TKI: Tyrosine Kinase Inhibitor

Introduction

High concentrations of receptor tyrosine kinases (RTK) such as the Epidermal Growth Factor Receptor (EGFR, *erbB1*) are present in certain cancers such as non-small cell lung cancer (NSCLC) [1]. After binding ligands such as EGF, heparin binding (HB-EGF), transforming growth factor (TGF α) or amphiregulin, the EGFR can form homodimers with itself or heterodimers with other receptor tyrosine kinases (RTK) such as *HER2* (*erbB2*) [2]. This increases tyrosine phosphorylation of protein substrates such as the mitogen activated protein kinase (MAPK) or phosphatidylinositol-3 kinase (PI3K) leading to increased cancer cellular proliferation and survival [3].

NSCLC, which kills approximately 130,000 citizens annually in the USA, is traditionally treated with combination chemotherapy; however, the 5-year survival rate is only 16% [1]. Approximately 13% of the NSCLC patients have mutated EGFR due to exon 19 deletions or exon 21 mutations such as L858R [4]. The mutated EGFR has increased tyrosine kinase activity resulting in the tyrosine phosphorylation of the EGFR. The patients with mutated EGFR can be treated with tyrosine kinase inhibitors (TKI) such as gefitinib or erlotinib, but after a year secondary EGFR mutations can occur such as T790 M resulting in TKI resistance [4]. There is a need to increase the sensitivity of NSCLC patients to TKI.

The phosphorylation of the EGFR is regulated by G protein-coupled receptors (GPCR) for neurotensin (NTS) within minutes after addition of ligand to NSCLC cells [5]. The expression of RTK such as ErbB1, ErbB2 or ErbB3 is increased by NTS days after addition to NSCLC cells [6]. The tyrosine phosphorylation of the EGFR caused by NTS addition to NSCLC cells is impaired by the *NTSR1* antagonist SR48692 and the TKI gefitinib. In this communication, the mechanism by which NTS causes EGFR transactivation is reviewed.

NTS ligand

Neurotensin (NTS) is a 13 amino acid peptide which is biologically active in the central nervous system (CNS). When released from hypothalamic brain neurons, NTS causes analgesia, hypothermia and modulates dopamine signaling in the CNS [7]. NTS may be a neuromodulator in the CNS whereby it is released from brain neurons and activates receptors in adjacent cells. In cancer, NTS is an autocrine growth factor. NTS is abundant in small cell lung cancer (SCLC) [8] and medullary thyroid carcinoma [9]. NTS is secreted from SCLC and binds with high affinity to SCLC cells [10]. The action of NTS is mediated by *NTSR1* in cancer cells and NTS stimulates the growth of SCLC cells. SR48692 is a non-peptide *NTSR1* antagonist [11] which inhibits the proliferation of pancreatic, prostate and SCLC cells in vitro and in vivo [12-14].

NTS is synthesized as a 170 amino acid precursor protein (prepro-NTS) which lacks biological activity [15]. A signal protease cleaves prepro-NTS to pro-NTS (147 amino acids) which is inactive. A proprotein convertase enzyme and carboxypeptidase cleaves pro-NTS to NTS (13 amino acids) which is biologically active and Neuromedin N (5 amino acids). Table 1 show that the C-terminal hexapeptide of NTS (NTS8-13) is biologically active. Degradation of NTS at the *Arg8-Arg9* or *Pro10-Tyr11* amide bonds by endopeptidases leads to inactive products [16]. NTS is secreted from the SCLC cells when the cellular cAMP is elevated [8]. The secreted NTS binds to cell surface receptors causing an autocrine SCLC proliferation.

NTS receptors

NTS binds with high affinity (Kd=4 nM) to NSCLC cells which have 1500 receptors/cell [5]. Table 1 shows that Ac-NTS8-13, NTS8-13 and SR48692 inhibit specific 125I-NTS binding with high affinity (IC50=7, 10 and 205 nM, respectively); acetylation of the N-terminal of

NTS8-13 increases its potency. In contrast, NTS1-8 and levocabastine (NTSR2 agonist) were inactive with IC50 values greater than 2000 nM. Reubi et al. [17] found a high density of specific (125I-Tyr3) NTS binding sites in Ewing's sarcoma and medullary thyroid cancers using autoradiographic techniques. In NSCLC, NTS and *NTSR1* immunoreactivity are present in approximately 60% of lung adenocarcinoma biopsy specimens [18]. *NTSR1* is present in numerous cancers.

The human *NTSR1* contains 418 amino acids and 7 transmembrane (TM) domains. Asn at positions 4, 37 and 41 of the *NTSR1* extracellular N-terminal can be N-glycosylated whereas Cys at positions 381 and 383 of the *NTSR1* intracellular C-terminal can be S-palmitoylated. SR48692 binds to a deep protein binding pocket anchored by *TM6* and *TM7* and numerous amino acids are essential for high affinity SR48692 binding e.g. Tyr319, Arg323, Phe326, Tyr346, Thr349, Phe353 and Tyr354 [19]. In contrast, the *NT8-13-NTSR1* complex has been crystalized and NT8-13 sits on top of the *NTSR1* binding pocket and binds with high affinity to Asn360, Pro361 and Tyr364 [20]. The greatest number of contacts between *NTS8-13* and *NTSR1* occur at extracellular loops 2 and 3 and TM domains 6 and 7. When *NTSR1* is occupied by SR48692, NTS cannot bind and cause signal transduction.

NTS signal transduction

When activated the *NTSR1* interacts with a G protein (Gq) causing phosphatidylinositol (PI) turnover in a phospholipase C dependent manner [21]. PI-4,5-bisphosphate is metabolized to inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) which elevates cytosolic Ca2+ [22] and activates protein kinase (PK)C, respectively [23]. The PKC can cause phosphorylation of ERK, PKD, focal adhesion kinase and Src [24-27]. In a ligand independent mechanism, Src can directly phosphorylate the EGFR at Tyr845 [28]. In the triple membrane passing signal pathway, *NTSR1* activation causes shedding of EGFR ligands from the plasma membrane (PM). Matrix metalloproteases (MMP) of the disintegrin and metalloproteinase (ADAM) family cleave inactive precursors e.g. the 160 amino acid prepro-TGFα in the PM into biologically active TGFα (50 amino acids) which is secreted into the extracellular fluids. The EGFR has a 621 amino acid extracellular N-terminal and subdomains II and IV are structural in nature and enriched in Cys amino acids. Subdomains I and III bind EGF, TGFα, amphiregulin or HB-EGF with high affinity. The EGFR has a single TM domain (24 amino acids) and an intracellular tyrosine kinase domain (541 amino acids) and C-terminal. The EGFR kinase domain binds ATP at Lys721 and transfers the phosphate to tyrosine amino acids on proteins such as PI-3-kinase (K), Phospholipase C and the EGFR. When gefitinib blocks the catalytic site of the EGFR, ATP cannot bind and cause the phosphorylation of Tyr992, Tyr1045, Tyr1068, Tyr1086, Tyr1148 or Tyr1173 of the EGFR. The EGFR interacts with the adapter proteins GRB2 and SHC. This activates the SOS protein leading to the metabolism of GTP by RAS. RAS activates the kinase RAF leading to the activation of MEK which phosphorylates ERK. Phosphorylated ERK enters the nucleus and increases expression of the nuclear oncogenes *c-fos* and *c-jun* after 1 hour. NTS addition to glioblastoma cells up-regulates *c-myc* but down regulates miR-29b-1 and miR-129-3p [29]. The *c-fos* and *c-jun* form heterodimers and increase expression of growth factor genes such as neurotensin/neuromedin N [30].

RTK transactivation

NTS analogs were added to NCI-H1299 NSCLC cells and the tyrosine phosphorylation of the EGFR determined by Western blot. (Figure 1A and 1B) shows that addition of NTS to NSCLC cells increases P-EGFR significantly after 0.5 min and the effect is maximal after 2 min. In contrast, NTS has no effect on total EGFR after 2 min. The effect of NTS on P-EGFR is dose-dependent and half-maximal tyrosine phosphorylation of the EGFR occurs using 5 nM NTS (Figure 1C and 1D). Structure-activity studies showed that NTS, Ac-NTS8-13, NTS8-13 but not NTS1-8 increase phosphorylation of the EGFR (Figure 1E and 1F). Addition of NTS to NSCLC cells for 2 min increased tyrosine phosphorylation of the EGFR 3-fold which was inhibited by SR48692, siRNA for *NTSR1* and gefitinib [5]. Addition of JMV449, a NT8-13 analog, to NSCLC cells for 48 hours increased expression of EGFR, HER2 and HER3 approximately 2-fold [6]. Also, JMV449 increased P-EGFR, P-HER2 and P-HER3 which was reversed by SR48692. JMV449 increased MMP1 resulting in elevated HB-EGF and Neuregulin-1 which activate the EGFR and HER3, respectively.

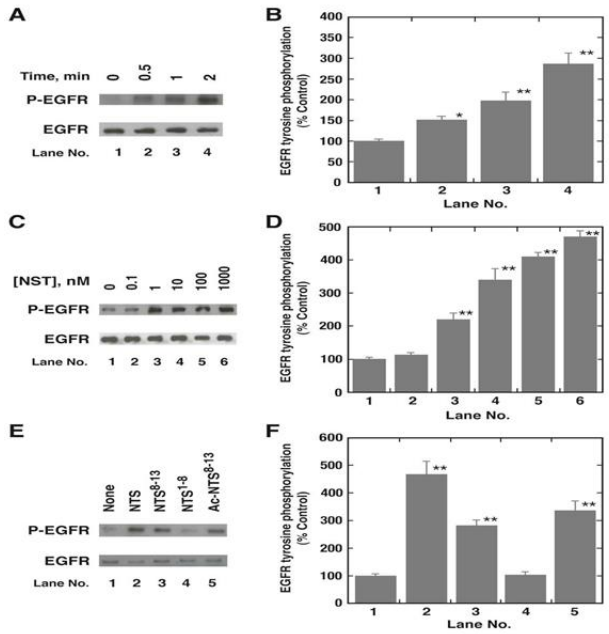

Figure 1: Regulation of EGFR transactivation by *NTSR1*. (A) The ability of 100 nM NTS to increase tyrosine phosphorylation of the EGFR in NSCLC cells was investigated as a function of time. Total EGFR was unaltered. (B) The mean P-EGFR+S.D. of 3 determinations is indicated; $p<0.05^{*}$, $p<0.01^{**}$ by ANOVA. (C) The ability of NTS to increase tyrosine phosphorylation of the EGFR in NSCLC cells at 2 min was investigated as a function of dose. Total EGFR was unaltered. (D) The mean P-EGFR+S.D. of 3 determinations is indicated; $p<0.01^{**}$ by ANOVA. (E) The ability of 100 nM NTS, NTS8-13, NTS1-8 or Ac-NTS8-13 to increase tyrosine phosphorylation of the EGFR in NSCLC cells was investigated after 2 min. Total EGFR was unaltered. (F) The mean P-EGF+S.D. of 3 determinations is indicated; $p<0.01^{**}$ by ANOVA.

Reactive oxygen species (ROS) are essential for NTS to cause EGFR transactivation. GPCR may cause p-47phox phosphorylation leading to the activation of NADPH oxidase increasing ROS [31]. The ROS

may oxidize protein tyrosine phosphatases reducing catalytic activity resulting in a transient increase in EGFR tyrosine phosphorylation [28]. The transactivation of the EGFR regulated by *NTSR1* is impaired by Tiron (superoxide scavenger) and diphenyleneiodonium (NADPH oxidase inhibitor) [5].

NTS causes EGFR transactivation in numerous cancers including prostate cancer, colon cancer and foregut neuroendocrine tumors [23,32,33]. Gastric cancer patients whose tumors had high levels on *NTSR1* immunoreactivity had poor patient survival [34]. Addition of NTS to NSCLC cells caused tyrosine phosphorylation of the EGFR, Src and β-catenin in a PKC-dependent manner [5]. When β-catenin is phosphorylated, it dissociates from E-Cadherin and enters the nucleus altering gene expression of the *NTSR1*. In hepatocellular carcinoma, *NTS/NTSR1* co-expression is activated the Wnt/β-catenin signaling pathway enhancing epithelial to mesenchymal transitions promoting tumor metastasis [35].

Proliferation

The *NTSR1* regulates the proliferation of NSCLC cells. Addition of NTS stimulated the proliferation of NSCLC cells whereas SR48692 inhibits the proliferation of NSCLC cells in a cytostatic manner (Table 1). SR48692 potentiated the cytotoxicity of gefitinib in a synergistic manner [5]. Breast cancer tumors grew faster in nude mice if they had high levels of NTS [36]. Tumors with high levels of NTS had elevated EGFR, HER2 and HER3 and their phosphorylated derivatives. The high levels of P-EGFR, P-HER2 and P-HER3 were reversed if the mice were treated with SR48692. The breast tumors with elevated NTS had increased MMP9 resulting in increased secretion of HB-EGF and Neuregulin-2. Approximately 43% of the biopsy specimens from NSCLC patients had immunostaining for *NTSR1*. The survival of NSCLC patients who had high *NTSR1* levels was significantly reduced relative to NSCLC patients whose tumor had low levels of *NTSR1* [6]. It remains to be determined if SR48692 will potentiate the effects of TKI in NSCLC patients. The *NTSR1* gene is present in many colon cancer biopsy specimens. Methylation of the *NTSR1* gene is associated with increased patient survival [37]. *NTSR1* expression is reduced by histone deacetylase inhibitors in colorectal cancer cell lines resulting in decreased proliferation [38]. These results indicate that *NTSR1* levels can be regulated by epigenetic mechanisms.

Ligand	IC50, nM	% Proliferation
NTS	4+1	176+19**
Ac-NTS8-13	7+1	157+16*
NTS8-13	10+3	143+18*
SR48692	205+31	48+7*
NTS1-8	>2000	103+11
Levocabastine	>2000	102+12
Gefitinib	>2000	62+8*
None	ND	100+7
SR4869+Gefitinib	ND	23+5**

Table 1: Effect of ligands on NSCLC cells The IC50+S.E. of 3 determinations to inhibit specific 125I-NTS binding to NSCLC cells are indicated. The % mean colony number+S.E. of 3 determinations is indicated using NSCLC cells; $P<0.05^{*}$, $P<0.01^{**}$ by ANOVA. The ligand structures are shown below: (1) NTS: Pyr-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu. (2) SR48692: 2{[1-(7-chloro-4-quinolinyl)-5-(2,6)-dimethoxyphenyl]-1H-pyrazole-3-yl-carbonyl}amino)tricycle[3,3,1,13]decane-2-carboxylic acid. (3) Gefitinib N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazoline-4-amine.

Conclusion

Gefitinib and erlotinib are used currently to treat NSCLC patients who have failed chemotherapy and have EGFR mutations. Due to low potency TKI are not used in patients with wild type EGFR. The potency of gefitinib can be increased in cells with wild type EGFR using GPCR antagonists such as SR48692 [5]. The *NTSR1* is an excellent molecular target in cancer and its expression in NSCLC, breast and gastric tumors is associated with poor patient survival.

There are multiple GPCR in cancer cells which can regulate RTK transactivation. Peptide GPCR include angiotensin, bombesin, bradykinin, cholecystokinin, endothelin, pituitary adenylate cyclase activating peptide and substance P, all of which interact with Gq and cause PI turnover [39]. RTK which can be transactivated include erbB1, erbB2, erbB3, platelet derived growth factor receptor and Trk. There are numerous GPCR antagonists which may potentiate the ability of TKI to inhibit the growth of cancer cells.

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