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Crosstalk between G-protein-coupled receptors and Epidermal growth factor receptor in cancer

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1. ABSTRACT

EGFR and its respective ligands are overexpressed in various tumors and this over-expression correlates with poor prognosis in selected cancers. In addition to direct activation by EGFR autocrine ligands, the large family of G-protein-coupled receptors (GPCRs) has been reported to transactivate EGFR via both ligand-dependent and independent mechanisms. GPCRs can induce the cleavage of membrane-bound EGFR-ligand precursors or directly activate the juxtamembrane tyrosine kinase domain of EGFR. Due to the heterogenous expression of GPCRs in tumors, this form of receptor crosstalk may contribute to the modest clinical responses to EGFR-targeted therapies observed to date. Studies, so far, have indicated that the signaling mechanisms involved in transactivation are specifically influenced by the activated GPCR and the tumor type in question. The progression of colon, lung, breast, head and neck, prostate and ovarian cancers have all been reported to be mediated, at least in part, by GPCR-EGFR crosstalk. Increased understanding of the specific signaling pathways involved in EGFR transactivation by GPCR will facilitate the identification of new biomarkers for molecular targeting strategies.

2. INTRODUCTION

Cancer cells harness multiple signaling pathways to proliferate, invade, and resist the cytotoxic effects of therapy, thereby contributing to tumor invasion and metastasis. Elucidation of these signaling pathways has enabled the identification of molecular targets that can be used for cancer therapy. Among the molecular targets discovered to date, growth factor receptors have been most amenable to the design of targeting strategies including monoclonal antibodies and kinase inhibitors. Growth factor receptors that are implicated in cancer development and/or progression include the epidermal growth factor receptor (EGFR), insulin-like growth factor receptor (IGF-R), fibroblast growth factor receptor (FGF-R) and platelet-derived growth factor receptor (PDGFR).

EGFR is frequently overexpressed in epithelial tumors including those arising in the colon, lung, breast and head and neck where expression levels correlate with decreased five year survival rates (1). These tumors also express high levels of EGFR ligands such as transforming growth factor alpha (TGF-alpha), amphiregulin, and

Table 1. GPCR Ligands reported to activate EGFR and tumorigenesis according to tumor type

Malignancy	GPCR Ligands	References
Colon Cancer	Thrombin	41, 74
	Prostaglandin E2	35
	Lysophosphatidic Acid	37, 75
	Endothelin-1	36
Non-small cell lung cancer	Gastrin-releasing peptide	46, 47
	Prostaglandin E2	48
	Interleukin-8	45
Head and neck squamous cell carcinoma	Lysophosphatidic Acid	24
	Thrombin	24
	Gastrin-releasing peptide	22, 51
	Prostaglandin E2	54
	Bradykinin	54
Pancreatic cancer	Cholecystokinin	61
	Vasopressin	59
	Bradykinin	59

heparin-binding EGF (HB-EGF), implicating autocrine regulatory pathways. Autocrine and paracrine activation of EGFR results in the activation of the intracellular tyrosine kinase domain and the consequent recruitment of docking proteins that mediates downstream signaling. There are currently several EGFR inhibitors that are either FDA approved for cancer therapy or are under active clinical development. These inhibitors target the tyrosine kinase domain (e.g. erlotinib or gefitinib) or the extracellular ligand-binding domain (e.g. cetuximab or pamitumimab).

Despite the widespread overexpression of EGFR in these tumors and the correlation of EGFR levels with survival, targeting strategies that have demonstrated efficacy in preclinical models have proven effective in only a subset of cancer patients. One possible explanation for this low response rate is the interaction of EGFR with other cell surface receptors that mediate multiple signaling pathways. Several reports have indicated that interaction between IGF-1R and EGFR contributed to the increased proliferation and metastasis of pancreatic and breast cancer (2, 3). EGFR was also reported to transactivate PDGFR in vascular smooth muscle cells (VSMC) and interact with Fas death receptor to affect cellular survival (4, 5). GPCRs, the family of heptahelical receptors, have been shown to activate EGFR and play an integral role in cancer progression. GPCRs activate EGFR via two possible mechanisms: 1) increased EGFR ligand production; and 2) intracellular tyrosine kinase domain activation.

Studies on the GPCR-mediated activation of EGFR have implicated distinct signaling pathways, depending on the specific GPCR and cell type under investigation. Over 50% of the drugs that are currently developed target GPCRs due to the relative ease of inhibiting these receptors and their role in many diseases, in addition to cancer (6). However, the heterogenous nature of tumors suggests that a single GPCR cannot be responsible for activating EGFR and contributing to cancer progression. The identification of heterotrimeric G-protein inhibitors (7) and common signaling intermediates among various GPCRs will allow for the development of targeting strategies that block this process in general. In addition, reports indicating that GPCRs can mediate mitogenic signaling independent of EGFR activation suggest that combined targeting of EGFR and GPCRs may be an effective therapeutic strategy.

In this review, we will focus on tumors that are currently being treated with FDA approved EGFR inhibitors (Table 1), although GPCR-EGFR crosstalk has been reported in other malignancies. The similarities and differences in the signaling mechanisms among the specific GPCRs and tumor types will be highlighted.

3. EPIDERMAL GROWTH FACTOR RECEPTOR

EGFR or HER1 is a member of the ErbB family of cell surface tyrosine kinase receptors, which includes HER2/neu, HER3 and HER4. With the exception of HER2/neu, the other ErbB members are activated in a ligand-dependent manner. There are eight known ligands for EGFR including EGF, TGF-alpha, amphiregulin, HB-EGF, betacellulin, epiregulin, epigen and crypto (8, 9). The ligands for HER3 and HER4 are a group of proteins known as neuregulins (10). Unlike HER2, HER3 contains an extracellular binding domain but has an inactive kinase domain. HER2 has a functional kinase domain, therefore HER2 and HER3 generate strong downstream signaling via heterodimerization with each other or with EGFR (11-13). EGFR ligand binding induces homo- and/or hetero-dimerization of the ErbB receptors and phospho-tyrosine recruitment of proteins to docking sites on the intracellular portion of the receptor that mediate downstream signaling cascades (1, 14). Heterodimers between EGFR and HER2 or HER3 result in more potent signaling cascades compared with EGFR homodimers, which include the MAPK, JNK and PI3K pathways. These signaling cascades have pleiotropic effects on cellular behavior. EGFR activation in cancer cells results in increased DNA synthesis, proliferation, metastasis and angiogenesis (15). Overexpression of EGFR in cancer has been correlated with poor prognosis in cancer patients (16). There are several FDA approved EGFR inhibitors for specific cancer types and a large number of ongoing clinical trials using EGFR inhibitors in combination with other agents, including chemotherapy, radiation and/or molecular targeting strategies.

4. G-PROTEIN-COUPLED RECEPTORS

GPCRs are seven transmembrane receptors that mediate their signaling via a heterotrimeric G-protein complex. They comprise a large family of receptors that play critical roles in a wide variety of processes including sight, smell, cardiovascular health, and cancer progression (17). GPCRs signal via a heterotrimeric small G-protein complex, G alpha beta gamma. Agonist binding to GPCRs results in the exchange of GDP for GTP on the G alpha subunit and its dissociation from the tightly bound G beta gamma dimer (6, 18). The G alpha and G beta gamma subunits mediate their own signaling cascades that are GPCR and cell type-specific. The G alpha subunit is further divided into other subtypes including Gi, Gq, Gs and G12/13. The Gi and Gs subunits couple to the second messenger protein adenyl cyclase leading to inhibition and

Table 2. Preclinical studies of combined inhibition of GPCR and EGFR in different tumor types

Malignancy	Clinical Trials	References
Colon Cancer	Sulindac and EKI-569	76
Non-small cell lung cancer	CU201 and gefitinib	77
	sc58236 and erlotinib	48
Head and neck squamous cell carcinoma	CU201 and gefitinib	54
	Sulindac and erlotinib	54
	PD176252 and erlotinib	65
	Celecoxib and gefitinib	78, 79
Pancreatic Cancer	Celecoxib and erlotinib	80

activation of adenyl cyclase and cAMP generation respectively. The Gq subunit activates phospholipaseC-beta (PLC-beta) and calcium signaling cascades while G12/13 activates the guanine exchange factor, Rho. Recent studies on G beta gamma have suggested that these subunits play a role in the activation of PLC, PI3K and adenyl cyclase (17). Young *et al* identified the first oncogene that was a member of the GPCR family of receptors called MAS (19). Following the identification of MAS in 1986, further investigation showed that overexpression of GPCRs and their respective ligands led to cancer phenotypes in breast and oral squamous cell carcinoma (20, 21).

5. TRANSACTIVATION OF EGFR

Daub *et al* published the first report on the activation of EGFR by GPCRs in Rat-1 fibroblasts (22). Stimulation of these cells with the GPCR ligands, lysophosphatidic acid (LPA), endothelin-1 (ET-1), and thrombin induced phosphorylation of EGFR and its downstream target Erk1/2. Following this discovery, the Ullrich group and others demonstrated that this transactivation phenomenon occurred in different cell types including vascular smooth muscle cells (VSMC), keratinocytes, PC-12 cells and multiple cancer cell lines (23-25). Activation of EGFR following GPCR stimulation is mediated by both ligand-dependent and ligand-independent mechanisms. Ligand-independent activation of EGFR was shown to occur via Src-dependent activation of the intracellular tyrosine kinase domain of EGFR (26, 27). Another possible ligand-independent mechanism of GPCR activation of EGFR may be via inactivation of protein tyrosine phosphatase (PTP) by NADPH-mediated release of reactive oxygen species (ROS). Fisher *et al* reported the LPA-induced activation of the RTK c-Met via NADPH-mediated release of ROS (28). The role of ROS in GPCR-mediated activation of EGFR in cancer is incompletely understood. Matrix metalloprotease (MMP) inhibitors abrogated GPCR-mediated EGFR activation in some cell systems leading to the development of the "triple membrane pass system" (TMPS) model where GPCRs mediated the cleavage of EGFR proligands in a MMP-dependent manner (29, 30). Further investigation demonstrated that the MMP involved in this process was from the ADAM (a disintegrin and metalloprotease) family of metalloproteases. ADAM family members 10, 12 and 17 have been reported to be responsible for the cleavage of TGF-α, AR and HB-EGF in a GPCR ligand and cell-type specific manner (24, 31, 32). With respect to cancer, ADAM17 overexpression was observed and shown to mediate GPCR-induced ligand-dependent activation of EGFR in colon cancer (33, 34). Along with colon cancer, GPCR-EGFR crosstalk in non-small cell lung cancer, HNSCC and pancreatic cancer will be addressed in this article.

5.1. Colon Cancer

In the United States, colon cancer is the second leading cause of cancer. Crosstalk between GPCRs and EGFR play a critical role in the activation of the Wnt signaling pathway. In human colon cancer cell lines, the GPCR ligand prostaglandin E2 (PGE2) transactivates both EGFR and c-met-R and results in the increased nuclear accumulation of β-catenin and cellular invasion. Inhibition of EGFR abrogated PGE2- mediated invasion *in vitro* (35). Endothelin-1 (ET-1) has been shown to promote tumorigenesis in colorectal cancer via the upregulated Endothelin A (ETA) receptor. In the HT29 colon cancer cell line, ET-1 stimulation induced increased proliferation and DNA replication. The ET-1 mediated effects were dependent on PI3K, protein kinase C (PKC) and EGFR. Inhibition of EGFR resulted in a significant decrease on ET-1 stimulated proliferation (36). Lysophosphatidic Acid (LPA) was reported to activate EGFR and induce the expression of cyclooxygenase-2 (COX-2) in colon cancer cells (37). LPA can interact with three GPCRs, LPA1, LPA2 and LPA3, although LPA2 is primarily overexpressed in colon cancer (38, 39). The induction of COX-2 was shown to be dependent on the presence of EGFR and resulted in increased mitogenesis. This observation has therapeutic implications since COX-2 is responsible for the production of PGE2. Therefore, crosstalk between LPA and EGFR can further potentiate EGFR activation via PGE2. There is a report indicating that the pan-COX inhibitor Sulindac decreased EGFR activation and expression in HT-29 cells (40).

Metastatic colon cancer has been correlated with the expression of the protease-activated receptors (PAR1). PAR1 is one of three PARs that are the cognate receptors for thrombin. Darmoul et.al reported that thrombin-mediated colon cancer cell proliferation resulted via crosstalk between PAR1 and EGFR. The activation of EGFR was also shown to be dependent on Src and MMP-mediated release of the EGFR ligand TGF- alpha (41). Antibody-based neutralization of TGF- alpha and tyrosine kinase inhibition of EGFR completely reverted the thrombin-induced increase in colon cancer cell proliferation *in vitro*. Unlike thrombin, interleukin-8 (IL-8) was shown to transactivate EGFR via the release of HB-EGF and promote Caco-2 proliferation and migration (42). Combined inhibition of EGFR, HB-EGF and MMPs completely blocked IL-8 mediated proliferation. Thus, there are multiple GPCRs that are overexpressed in colon cancer that promote tumor progression via the activation of EGFR where EGFR activation is dependent on MMP/ADAM-mediated cleavage of different EGFR proligands. Therefore, inhibition of MMP, Src and COX-2

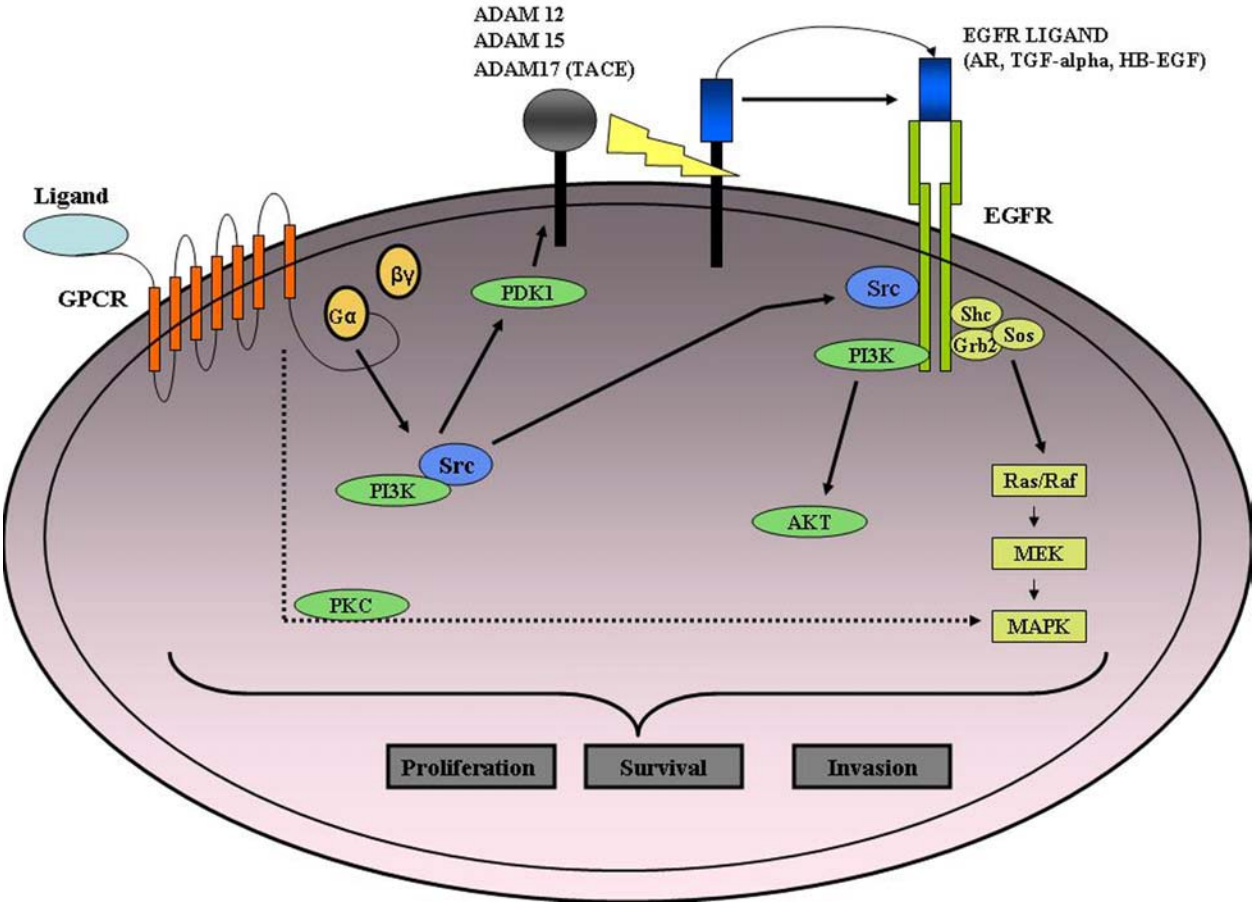

Figure 1. Model of GPCR-EGFR crosstalk in Cancer. Black unbroken arrows indicate GPCR-mediated activation of EGFR via both ligand-dependent and independent mechanisms. The broken Arrow indicates GPCR-mediated EGFR-independent activation of mitogenic signaling. Model illustrates key signaling intermediates involved in GPCR-EGFR crosstalk, which includes Src, PDK1 and ADAMs. GPCR, G-protein-coupled receptor; EGFR, epidermal growth factor receptor; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphatidylinositol-3 kinase; ADAM, a disintegrin and metalloprotease; AR, amphiregulin; TGF-alpha, transforming growth factor alpha; HB-EGF, heparin binding-epidermal growth factor.

may be effective therapeutic options for colon cancer patients.

The role of COX-2 and IL-8 in colon cancer emphasizes the link between cancer and inflammation. For example, COX-2 expression has been reported to play a significant role in ulcerative colitis- associated colon cancer (43). The contribution of inflammatory mediators in bridging inflammatory disease to cancer is an expanding field of study. Crosstalk of GPCRs with EGFR in inflammatory diseases may reflect an early event in colon carcinogenesis that can be exploited for diagnostic purposes.

5.2. Non-Small Cell Lung Cancer (NSCLC)

In comparison to other malignancies, lung cancer results in the highest number of deaths (44). Hiemstra *et al* showed that the cytokine interleukin-8 (IL-8) mediated the proliferation of NSCLC. Inhibition of EGFR with the tyrosine kinase inhibitor AG1478 and an EGFR blocking antibody decreased IL-8-mediated proliferation of A549 *in vitro*. The mechanism for IL-8-induced EGFR activation was shown to be MMP-dependent. The specific MMP or MMP family molecule responsible for EGFR activation is unknown, but IL-8 has been reported to activate the extracellular release of EGFR proligands (45). Another G-protein coupled receptor that is aberrantly expressed in NSCLC is the gastrin releasing protein receptor (GRPR). Treatment of NSCLC cells with gastrin releasing peptide (GRP) was shown to activate EGFR and phosphorylation of Erk where Erk activation induced NSCLC proliferation (46, 47). The activation of EGFR by GRP was also shown to be sensitive to MMP inhibition and HB-EGF and TGF-alpha neutralization.

GPCRs that activate EGFR have also been described to activate proliferative signals independent of EGFR. PGE2 was reported to activate EGFR, however in the presence of EGFR inhibition MAPK was still activated in NSCLC cell lines. The activation of MAPK was also reported to be resistant to Src and MMP-inhibition. The key finding in this report showed that PGE2-mediated

activation of MAPK in NSCLC was dependent on PKC (48). Combined inhibition of EGFR and COX-2 had a significant effective on decreasing proliferation.

5.3. Head and Neck Squamous Cell Carcinoma (HNSCC)

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy worldwide and over 90% of HNSCC tumors overexpress EGFR (49). Similar to NSCLC, GRPR is overexpressed in HNSCC compared to the normal mucosa (50). Lui *et al* reported that GRP induced the activation of EGFR and its mitogenic surrogate MAPK in HNSCC cells (51). Further investigation indicated that the activation of EGFR was dependent on Src, ADAM17 (TACE) and extracellular release of amphiregulin. A novel role for phosphoinositide-dependent kinase 1 (PDK1) was also discovered to induce phosphorylation of TACE following GRP stimulation (52, 53). In addition, PDK1 downmodulation and EGFR inhibition significantly decreased HNSCC proliferation *in vitro*. Two other GPCR ligands, PGE2 and bradykinin (BK) have been shown to activate EGFR and promote HNSCC proliferation and invasion *in vitro* (54). Activation of EGFR by PGE2 and bradykinin was reported to be dependent on Src, ADAM17 and TGF- alpha release. In addition to EGFR activation, PGE2 and BK were reported to activate MAPK in the presence of EGFR tyrosine kinase inhibition (54). Combined inhibition of the PGE2 and BK pathways and EGFR resulted in significant decreases in HNSCC proliferation and invasion *in vitro*. Three other GPCR ligands, LPA, thrombin and carbachol were reported to activate EGFR in HNSCC cell lines, however their influence on a HNSCC phenotype were not investigated (24). With respect to signaling mechanisms, LPA-mediated activation of EGFR was reported to be MMP-dependent.

5.4. Pancreatic Cancer

Pancreatic cancer is one of the deadliest cancers of the digestive system. In 2004, approximately 31,000 new cases and deaths were recorded (55). Pancreatic tumors overexpress EGFR and their respective ligands (14, 56, 57) which also correlates to chemotherapeutic resistance (58). Pancreatic cell lines have also been shown to respond to multiple GPCR agonists including cholecystokinin (CCK), bradykinin, vasopressin and neurotensins (59, 60). Piiper *et al* reported that CCK and gastrin activated EGFR in the AR42J pancreatic cell line (61). CCK and gastrin-mediated activation of EGFR was also shown to be dependent on the Src family kinase, Yes. The co-immunoprecipitation of Yes to EGFR indicated that CCK and gastrin mediated a ligand-independent activation of EGFR and its downstream effector MAPK. However, CCK also activated MAPK by another pathway, which was PKC-dependent and EGFR-independent (61). Another report showed that neurotensins activated MAPK independent of EGFR via the PKC-dependent pathway also (59). PKC has been reported to activate MAPK following GPCR activation through the direct activation of Ras (62).

Src, PKC and Ras have been shown to play critical roles in GPCR-mediated activation of EGFR and MAPK in pancreatic cancer cell lines (59, 61). In contrast to the colon, NSCLC and HNSCC, GPCR-EGFR crosstalk in pancreatic cancer has been reported to be primarily an intracellular process. Inhibition of these intracellular molecules in combination with erlotinib, which is FDA approved for pancreatic cancer (63), may be an efficacious therapeutic strategy.

6. SUMMARY

Despite the widespread overexpression of EGFR in most epithelial malignancies, EGFR targeting alone has not resulted in dramatic clinical responses in the absence of EGFR activating mutations in selected NSCLC. Transactivation of EGFR by GPCRs may contribute to the continued growth of cancers in the setting of EGFR blockade. In addition, GPCRs have been shown to mediate mitogenic signaling pathways independently of EGFR (48, 54, 59, 61). Both PGE2 and bradykinin have been shown to induce cancer cell proliferation in an EGFR-independent fashion in NSCLC and HNSCC. CCK and neurotensin were also shown to activate MAPK via a PKC-Ras interaction that is EGFR-independent. The EGFR-independent activation of ERK by GPCRs has been called multi-track signaling, where EGFR may effect a dual function by activating signaling components via its kinase domain or functioning as a scaffold to Ras/Raf/MEK complex which is necessary for Erk activation independent of its kinase function (64). Preclinical studies have shown that combined inhibition of GPCR pathways and EGFR results in additive or synergistic growth inhibition in HNSCC and NSCLC (48, 54, 65). Therapeutic strategies that inhibit both GPCR and EGFR pathways may prove effective as cancer treatment.

Preclinical studies inhibiting GPCR and EGFR pathways have been reported in colon, HNSCC, NSCLC and pancreatic cancer (Table 2). These studies have primarily utilized non-steroidal anti-inflammatory agents such as celecoxib or sulindac to inhibit the BK and PGE2 GPCR signaling modalities. Combined inhibition of COX-2 and EGFR has shown additive or synergistic effects in colon, NSCLC, HNSCC and pancreatic cancer models. Clinical trials to evaluate the efficacy of COX inhibitors in combination with EGFR inhibitors are underway in several cancers. There were two clinical trials that combined the COX-2 inhibitor celecoxib with the EGFR inhibitors erlotinib and gefitinib in NSCLC (66, 67). HNSCC and colon cancer patients are currently being enrolled on phase I/II studies using COX and EGFR inhibitors (www.clinicaltrials.gov).

In the absence of clinical inhibitors to other GPCRs such as thrombin, IL-8 and CCK, inhibition of proteins implicated in the transactivation mechanism may prove beneficial. For example, Src family kinases and TNF-alpha converting enzyme (TACE) have been consistently been identified to mediate the activation of EGFR by a variety of GPCRs in several tumor systems. The Src family kinase inhibitor dasatanib (Sprycel) is FDA approved for the treatment of chronic myelogenous leukemia (CML) and selected leukemias and is under early

stage investigation in solid tumors (68). Because Src mediates both ligand-dependent and – independent GPCR-mediated activation of EGFR, dasatinib in combination with an EGFR inhibitor may have significant anti-tumor effects. TACE may be another key target in abrogating the effects of GPCR-EGFR crosstalk in tumors. The TACE inhibitor INCB3619 in combination with gefitinib decreased NSCLC proliferation both *in vitro* and *in vivo* (69). Two other TACE inhibitors, TMI-2 and Ro-32-7315, have shown to be potent in the treatment of preclinical arthritis models (70, 71). Both orally administered TACE inhibitors also lower associated toxicities compared to clinical grade broad range MMP inhibitors. The efficacy of TMI-2 and Ro-32-7315 are yet to be tested in a tumor model. Furthermore, TACE inhibition not only abrogates EGFR ligand production but HER3 ligand production also (69, 72, 73). Therefore, targeting TACE may be an effective treatment strategy in tumors that are driven by GPCR-EGFR crosstalk and HER3 signaling (73). However, it is unknown whether GPCRs can transactivate HER3 in a ligand-dependent manner independently of EGFR. Gschwind *et al* reported that LPA induced the EGFR-dependent phosphorylation of HER2 in HNSCC, indicating the LPA induced EGFR homodimer and EGFR/HER2 heterodimer formation (24). Future investigation of GPCR-mediated HER2/HER3 dimerization in tumor types driven by HER3 signaling is needed.

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Abbreviations: GPCR: G-protein-coupled receptor; EGFR: Epidermal growth factor receptor; TACE: TNF-alpha converting enzyme; ADAM: a disintegrin and metalloprotease; PGE2: Prostaglandin E2; LPA: Lysophosphatidic Acid; ET-1: Endothelin-1; GRP: Gastrin releasing peptide; IL-8: interleukin-8; BK: Bradykinin; CCK: cholecystokinin

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