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4

Cell Signalings and the Communications in Head and Neck Cancer

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1. Introduction

HNSCC (head and neck squamous cell carcinoma) is the sixth most common neoplasm worldwide (Cripps et al., 2010). Approximately 600,000 new cases are reported each year (Cripps et al., 2010), and in the past 30 years recurrent and/ or metastatic HNSCC has had a poor prognosis (Forastiere et al., 2001; Khuri et al., 2000). More than 50% of newly diagnosed patients do not achieve complete remission, and in approximately 10% of HNSCC cases relapse with metastasis to distant organs has been reported (van Houten et al., 2000). Therefore, research focused on gaining a better understanding of this disease and the development of novel treatment strategies is required.

Epidermal growth factor receptor (EGFR), a ubiquitously expressed transmembrane glycoprotein belonging to the ErbB/HER family of receptor tyrosine kinases (TK), is composed of an extracellular ligand-binding domain, a hydrophobic transmembrane segment and an intracellular TK domain. When ligands bind to EGFR the receptor undergoes a conformational change that promotes homo- or hetero-dimerization with other members of the ErbB/HER family of receptors; subsequent autophosphorylation and activation of the TK domain ensues (Ciardiello & Tortora, 2003). Activation of EGFR leads to activation of intracellular signaling pathways that regulate cell proliferation, invasion, angiogenesis and metastasis.

EGFR is expressed at high levels in the majority of epithelial malignancies including HNSCC. Elevated expression of EGFR in HNSCC correlates with poor prognosis, and it has long been a target of anticancer treatments owing to its critical role in cell survival and proliferation. Numerous tyrosine kinase inhibitors with the Food and Drug Administration (FDA) approval have been developed to target EGFR including gefitinib, erlotinib and lapatinib (Carter et al., 2009). These molecules are reversible competitors, competing with ATP for the tyrosine kinase binding domain of EGFR. By inhibiting receptor activation, downstream signaling pathways are inhibited, leading to a decrease in cell proliferation and survival. EGFR signaling activates a number of downstream effectors including the phosphatidylinositol-3-kinase (PI3Kinase)/Akt pathway.

2. Rare EGFR mutations in HNSCC

Somatic mutations in the TK domain of the *EGFR* gene (in-frame deletion in exon 19, L858, G719X and L861Q) are associated with increased sensitivity to EGFR tyrosine kinase inhibitors (TKIs) and are present in 10~30% of non-small cell lung carcinoma (NSCLC) cases depending on ethnic origin. These mutant EGFRs selectively activate signal transduction and activator of transcription (STAT) signaling pathways and Akt, which promote cell survival. However, they have no effect on extracellular signal-regulated kinase signaling, which induces proliferation. Furthermore, mutant EGFRs selectively transduce survival signals, and inhibition of those signals by TKIs could contribute to the efficacy of a drug used to treat NSCLC (Sordella et al., 2004). However, molecular analysis of HNSCC tumor samples has not revealed the same spectrum of mutations (Loeffler-Ragg et al., 2006; Ozawa et al., 2009; Taguchi et al., 2008).

A resistance mutation has emerged in EGFR and is known as T790M. It is a missense mutation in the kinase domain that could help to explain resistance to TKIs in NSCLCs exhibiting L858R (Wong, 2008). However, we did not detect this mutation in 86 HNSCC tumor samples (Baba et al., 2011).

3. Inhibition of PI synthesis in HNSCC

3.1 Anti-proliferation

An imbalance between G1 cyclin and CDK (cyclin-dependent kinase) inhibitors (CKIs) contributes to tumorigenesis and tumor progression. Cyclin D1/PRAD1 acts as a positive regulator of the cell cycle via phosphorylaton of pRB (Rb protein), and the formation of a cyclin D1-CDK4 complex. When pRB is hyperphosphorylated by CDKs, pRB release E2F, and E2F is necessary for the activation of a gene expression network that regulates entry and progression through S phase.

CKIs are classified into two groups: members of the Ink4 family (p15, p16, p18, and p19) for cyclin D/CDK4 or cyclin D/CDK6, and the cip/kip family (p21, p27, and p57) for cyclin D/CDK4 and cyclin E/CDK2 (Baba et al., 2000a). Over-expression of cyclin D1 in HNSCC is an important prognostic marker, predicting sensitivity to chemotherapy and radiotherapy (Fujii et al., 2001; Ishiguro et al., 2003; Nishimura et al., 1998). Furthermore, imbalance between cyclin D1 and its inhibitors (p16 and p27) could be critical in the development of HNSCC (Baba et al., 1999, 2001a). Strategies to block cyclin D1 function have been studied extensively; for example, Nakashima et al. (Nakashima & Clayman, 2000) reported that introduction of an antisense cyclin D1 expression vector into cells reduced their growth rate *in vitro* and decreased tumorigenicity in athymic nude mice. We have previously reported that inhibition of PI synthesis caused G1 arrest of HNSCC accompanied by decreased levels of cyclin D1, cyclin E and phosphorylated pRB (Baba et al., 2001b).

3.2 Inhibition of matrix metalloproteinase (MMP) production/ activity

Tumor metastasis is a complex multistep process including growth at the primary site, entry into the circulation (intravasation), adhesion to the basement membranes (BM) of target organs, extravasation and growth at secondary sites. Among these steps, the intravasation and extravasation processes involve degradation of the BM by proteinases, such as some

MMPs. MMP-9/gelatinase B and MMP-2/gelatinase A have specificity for type IV collagen, which acts as the backbone of BM, and therefore probably play a major role in degrading the BM. In HNSCC, MMP-2 and MMP-9 are associated with metastatic potential. Indeed, inhibition of MMP-2 and MMP-9 production lead to repress invasive activity of HNSCC cells (Baba et al., 2000b). Therefore, MMPs are attractive therapy targets and many drugs have been developed to prevent their extracellular matrix-degrading activities during metastasis and angiogenesis.

3.3 Anti-angiogenesis

Angiogenesis, the formation of new blood vessels from pre-existing capillaries or incorporating bone marrow-derived endothelial precursor cells into growing vessels, is associated with the malignant phenotype of cancer. In addition, it also plays a role in diverse diseases such as diabetic retinopathy, age-related macular degeneration, rheumatoid arthritis, psoriasis, atherosclerosis and restenosis (Cherrington et al., 2000). Clinical association of tumor vascularity with tumor aggressiveness has been demonstrated in a wide variety of tumor types including HNSCC. Therefore, determining microvessel density in tumor tissues can be useful in the estimation of a patient's prognosis. Inhibition of angiogenesis can repress the growth rate of tumor cells and lead to cell death resulting from reduced nutrition and oxygen supply to the tumor. VEGF (vascular endothelial growth factor), which plays a major role in many angiogenic processes, binds to its receptor Flk-1/KDR in order to stimulate endothelial cell (EC) proliferation through the phospholipase Cγ-protein kinase C-ERK (extracellular signal-regulated kinase) pathway, but not via Ras (Takahashi et al., 1999). In addition, VEGF stimulates EC migration through p38 MAPK (mitogen-activated kinase) independently of ERK (Rousseau et al., 1997). Therefore, these two major MAPK pathways are eligible targets for therapeutic reduction of angiogenesis in HNSCC.

Most clinical trials concerning anti-angiogenic agents have been conducted in patients with advanced disease that had become resistant to conventional therapies. Phase III trials of these agents have compared the efficacy of standard chemotherapy alone and in combination with an experimental angiogenesis inhibitor (Gotink & Verheul, 2010). The results of some studies were negative or controversial, but several recent clinical trials in which VEGF signaling was blocked demonstrated a significant clinical benefit (Ho & Kuo, 2007). SU11248, a tyrosine kinase inhibitor of the Flk-1/KDR receptor (VEGF receptor) and bevacizumab, a monoclonal antibody to VEGF, have been approved by FDA (Ho & Kuo, 2007). Furthermore, we have demonstrated that the inhibition of PI abrogated stimulation by VEGF on the growth and migration of human umbilical vein ECs through the ERK-cyclin D1 and p38 pathways, respectively (Baba et al., 2004). Because increased PI synthase expression is an early event in HNSCC (Kaur et al., 2010), inhibition of PI synthesis could be a potent therapeutic strategy for HNSCC (Baba et al., 2010).

4. Resistance to EGFR TKIs

In a phase II trial gefitinib was administered to patients with recurrent or metastatic HNSCC and the overall response rate was 11% (Cohen et al., 2003). Furthermore, in a similar study carried out on patients with recurrent and /or metastatic HNSCC, the response rate to

erlotinib was 4% (Soulieres et al., 2004). This is suggesting that multiple intracellular signaling pathways are involving to associate tumor survival, growth, and the other malignant phenotype.

4.1 Ras mutations

Previous reports have indicated that activating K-ras mutations could induce activation of the Ras/mitogen activated protein kinase (MAPK) pathway independent of EGFR, which in turn induces resistance to TKIs (Eberhard et al., 2005). The data suggest that K-ras mutation causes insensitivity to TKIs. In HNSCC, H-ras mutations are more common than K-ras mutations and may play an important role in resistance to EGFR-targeted therapies (Anderson et al., 1994).

4.2 Epithelial-Mesenchymal Transition (EMT)

EMT, a change in the morphology and motility of cells that is indicated by increased vimentin expression, decreased expression of E-cadherin and increased expression of claudins 4 and 7, has been associated with gefitinib resistance in HNSCC (Frederick et al., 2007).

4.3 Upregulation of cyclin D1

Upregulation of cyclin D1 in HNSCC cell lines is specifically associated with resistance to gefitinib; retinoblastoma protein (pRb) is hyperphosphorylated by cyclin D1-cyclin dependent kinase 4 (CDK4) (Kalish et al., 2004).

4.4 Cortactin

Recently, increased expression of cortactin, a protein that increases the formation of actin networks critical to cell motility and receptor-mediated endocytosis, has been associated with gefitinib resistance and increased metastasis in HNSCC (Timpson et al., 2007).

Akt has been implicated in EMT by integrin-linked kinase (ILK). The PI3Kinase/Akt pathway not only regulates the transcriptional activity of cyclin D1, but also increases its accumulation by inactivating glycogen synthase kinase-3 (GSK3), which targets cyclin D1 for proteasomal degradation. The effect of cortactin on cancer cell proliferation is associated with increased activation of Akt (Timpson et al., 2007). Therefore, factors related to resistance to EGFR TKIs are associated with the PI3kinase/Akt pathway.

5. PI3kinase/Akt pathway

5.1 Activation of the PI3kinase/Akt pathway

Signaling through the PI3kinase/Akt pathway can be initiated by several mechanisms, all of which increase activation of the pathway in cancer cells. Once activated, the PI3kinase/Akt pathway can be propagated to various substrates including mTOR, a master regulator of protein translation. The pathway is initially activated at the cell membrane, where the signal for activation is propagated through class IA PI3kinase. Activation of PI3kinase can occur through tyrosine kinase receptor for EGF and insulin-like growth factor-1 (IGF-1). Integrins and G-protein-coupled receptors (GPCRS) are also known to activate it. PI3kinase catalyzes

phosphorylation of the D3 position on phosphoinositides to generate the biologically active moieties phosphatidylinositol-3,4,5-triphosphate (PI(3,4,5)P3) and phosphatidylinositol-3,4-bisphosphate (PI(3,4)P2). PI(3,4,5)P3 binds to the pleckstrin homology (PH) domains of PDK-1 (3'-phosphoinositide-dependent kinase 1) and Akt, resulting in the proteins being translocated to the cell membrane where they are subsequently activated. The tumor suppressor PTEN (phosphatase and tensin homolog deleted on chromosome ten) antagonizes PI3kinase by dephosphorylating PI (3,4,5)P3 and (PI(3,4)P2), thereby preventing activation of Akt and PDK-1. Akt exists as three structurally similar isoforms, Akt1, Akt2 and Akt3, which are expressed in most tissues. Activation of Akt1 occurs through two crucial phosphorylation events. The first, carried out by PDK-1, occurs at T308 in the catalytic domain. Full activation requires a subsequent phosphorylation at S473 in the hydrophobic motif, which can be mediated by several kinases including PDK-1, ILK, Akt itself, DNA-dependent protein kinase and mTOR; phosphorylation of homologous residues in Akt2 and Akt3 occurs by the same mechanism. Phosphorylation of Akt at S473 is controlled by a recently described phosphatase, PHLPP (PH domain leucine-rich repeat protein phosphatase), that has two isoforms that preferentially decrease activation of specific Akt isoforms (Brognard et al., 2007). Amplification of Akt1 has been described in human gastric adenocarcinoma, and amplification of Akt2 has been described in ovarian, breast and pancreatic carcinoma (Bellacosa et al., 1995; Cheng et al., 1996). Although Akt mutations are rare, Carpten *et al.* (Carpten et al., 2007) recently described somatic mutations occurring in the PH domain of Akt1 in a small percentage of human breast, ovarian and colorectal cancers.

5.2 Downstream substrates of activated Akt

Akt recognizes and phosphorylates the consensus sequence RXRXX (S/T) when it is surrounded by hydrophobic residues. This sequence is present in many proteins resulting in numerous Akt substrates being identified and validated. These substrates control key cellular processes such as apoptosis, cell cycle progression, transcription and translation. For example, Akt phosphorylates the FoxO subfamily of forkhead family transcription factors, inhibiting transcription of several pro-apoptotic genes including Fas-L, IGF Binding Protein1 (IGFBP1) and Bim. Additionally, Akt can directly regulate apoptosis by phosphorylating and inactivating pro-apoptotic proteins such as BAD, which controls the release of cytochrome c from mitochondria, and apoptosis signal-regulating kinase-1 (ASK1), a mitogen-activated protein kinase kinase involved in stress- and cytokine-induced cell death. In contrast, Akt can phosphorylate IkappaBalpha kinase (IKK), which indirectly increases the activity of nuclear factor kappa B (NFκB) and stimulates the transcription of pro-survival genes. Cell cycle progression can also be affected by Akt; inhibitory phosphorylation of the cyclin-dependent kinase inhibitors p21 and p27, and inhibition of GSK3β by Akt, stimulates cell cycle progression by stabilizing cyclin D1 expression. A novel pro-survival Akt substrate, PRAS40 (proline-rich Akt substrate of 40kDa), has been described recently (Vander Haar et al., 2007). Phosphorylation of PRAS40 by Akt attenuates its ability to inhibit mTORC1 kinase activity. It has been suggested that PRAS40 could be a specific substrate of Akt3 (Madhunapantula et al., 2007). Therefore, Akt inhibition could have pleiotropic effects on cancer cells that contribute to an anti-tumor response. The most-studied downstream substrate of Akt is the serine/threonine kinase mTOR (mammalian

target of rapamycin). Akt can directly phosphorylate and activate mTOR, and indirectly activate it by phosphorylating and inactivating TSC2 (tuberous sclerosis complex 2, also called tuberin), which normally inhibits mTOR through the GTP binding protein Rheb (Ras homolog enriched in brain) (Inoki et al., 2003). When TSC2 is inactivated by phosphorylation, the GTPase Rheb is maintained in its GTP-bound state, allowing increased activation of mTOR (Inoki et al., 2005). mTOR exists in two complexes: the TORC1 complex, in which mTOR is bound to Raptor; and the TORC2 complex, in which mTOR is bound to Rictor. In the TORC1 complex, mTOR signals to its downstream effectors S6 kinase/ribosomal protein and 4EBP-1/eIF-4E, to control protein translation (Inoki et al., 2005). mTOR is generally considered to be a downstream substrate of Akt, but it can phosphorylate Akt when bound to Rictor in TORC2 complexes (Sarbassov et al., 2005), and this could provide positive feedback in the pathway. In addition, the downstream mTOR effector S6 kinase-1 (S6K1) can regulate the pathway by catalyzing an inhibitory phosphorylation on insulin receptor substrate (IRS) proteins. This prevents IRS proteins from activating PI3kinase, thereby inhibiting activation of Akt (Harrington et al., 2004).

5.3 Rationale for targeting the PI3kinase/Akt pathway

In addition to preclinical studies, clinical observations support the targeting of the PI3kinae/Akt/mTOR pathway in human cancer (Vogt et al., 2009). Immunohistochemical studies using antibodies that recognize Akt phosphorylated at S473 have demonstrated that activated Akt is detectable in cancers including head and neck cancer (Gupta et al., 2002). Tsurutani *et al.* (Tsurutani et al., 2006) recently extended these studies using antibodies against S473 and T308, two sites of Akt phosphorylation. This study demonstrated that Akt activation is selective for NSCLC versus normal tissue, and that phosphorylation of Akt at both sites is a better predictor of poor prognosis in NSCLC than phosphorylation of S473 alone. In addition, amplification of Akt isoforms has been observed in some cancers, albeit at a lower frequency. Another frequent genetic event occurring in human cancer is loss of function of the tumor suppressor PTEN. PTEN normally suppresses activation of the PI3kinase/Akt/mTOR pathway by functioning as a lipid phosphatase. Loss of PTEN function in cancer can occur through mutation, deletion or epigenetic silencing. In tumor types where PTEN mutations are rare such as lung cancer, epigenetic silencing can occur (Forgacs et al., 1998). Several studies have demonstrated the prognostic significance of PTEN loss in multiple human cancers where mutation, deletion or epigenetic silencing of PTEN correlates with poor prognosis and reduced survival (Bertram et al., 2006). Collectively, these studies have established that the loss of PTEN is a common mechanism for activation of the PI3kinase/Akt/mTOR pathway and led to poor prognostic factor in human cancer. Activation of PI3Kinase has been described in human cancers. It can result from amplification, over-expression, or mutations in the p110 catalytic or p85 regulatory subunits. Amplification of the 3q26 chromosomal region, which contains the gene PI3KCA that encodes the p110α catalytic subunit of PI3K, occurs in 40% of ovarian and 50% of cervical carcinomas (Ma et al., 2000; Shayesteh et al., 1999). Somatic mutations of this gene have been detected in several cancer types and result in increased kinase activity of mutant PI3K relative to wild-type PI3K (Samuels & Ericson, 2006). Mutations in the regulatory p85 subunit have also been

detected. Any of the aforementioned alterations in individual components would result in activation of the PI3 kinase/Akt pathway, and studies suggest that pathway activation is one of the most frequent molecular alterations that occur in cancer (Samuels & Ericson, 2006).

6. Cross talk between the IGF1 receptor (IGF1R) and EGF receptor (EGFR) pathways through PI3 kinase/Akt

The phenomenon of growth factors switching from one pathway to another has an adaptive component, which could be induced by blocking the dominant growth factor receptor pathway. Blockade of EGFR signaling has been demonstrated to result in the enhancement of the growth promoting effects of the peptide growth factor ligands basic fibroblast growth factor and IGF-1 in DU145 and PC-3 human prostate cancer cells, respectively (Jones et al., 1997). More recently, the substantial growth inhibitory effects of the EGFR-selective tyrosine kinase inhibitor gefitinib on EGFR-positive MCF-7-derived tamoxifen-resistant breast cancer cells, has been demonstrated. Furthermore, this effect can be subverted by additionally exposing cells to non-EGF ligands such as heregulin-β and IGF-II (Knowlden et al., 2005). The reversal of the anti-tumor effects of gefitinib by IGF-II, acting through the IGF-1R, is accompanied by a reactivation of the previously reduced activity of Akt and extracellular-regulated kinase (ERK); ERK signaling contributes to the re-establishment of tumor cell growth. Therefore, in the presence of a dominant growth pathway, cancer cells are capable of responding to other growth factors that are present, thereby compromising the anti-tumor activity of agents designed specifically to inhibit EGFR. Importantly, a previous study demonstrated that following blockade of EGFR signaling, switching to the IGF-1R pathway is a common mechanism used to promote resistance to anti-EGFR treatment (Choi et al., 2010). For example, gefitinib initially inhibited the growth of the EGFR-positive cell lines DU145 (prostate cancer cells) and MCF-7-derived tamoxifen- and fulvestrant resistant breast cancer cell lines, but chronic challenge with the inhibitor resulted in the development of gefitinib-resistant variant sub-lines, all of which presented with up-regulation of multiple IGF-1R signaling components when compared with the parental cell lines (Jones et al., 2004). This resulted in increased production and elevated expression of the IGF-1R ligand IGF-II, increased activity of IGF-1R and increased levels of Akt activity. In addition, the A549 lung cancer cell line, which displays a partial sensitivity to gefitinib, was chronically challenged with the inhibitor; the resistant variant that emerged presented with a marked adaptive increase in the activity of elements of the IGF-1R pathway. The importance of IGF-1R signaling in these various cell types with acquired gefitinib resistance was further supported by the observation that they demonstrated an enhanced dependency on IGF-1R signaling; they were subsequently more sensitive to growth inhibition by IGF-1R-selective tyrosine kinase inhibitors (Jones et al., 2004). Therefore, the dominance of the EGFR pathway in parental cells is replaced by the elevated use of the IGF-1R in gefitinib resistant cells. However, such growth factor pathway switching can not only result from changes occurring during the development of acquired resistance, but also, critically, can occur rapidly and modulate initial sensitivity to EGFR-blockade resulting in *de novo* or intrinsic resistance to anti-EGFR agents such as gefitinib. Indeed, although the EGFR and

IGF-1R pathways are classically regarded as separate entities, promoting growth utilizing overlapping downstream signal transduction molecules indicates that these receptors can affect each other's signaling abilities, although the precise mechanisms involved in this crosstalk have not been fully elucidated. For example, gefitinib only partially blocks EGFR activity in A549 lung cancer cells and this is accompanied by a dramatic increase in the activity but not the expression of IGF-1R. Moreover, in these cells IGF-1R can transphosphorylate EGFR, maintaining EGFR activity in the presence of gefitinib. Therefore, gefitinib limits its own efficacy by facilitating IGF-1R activity in these cells. Interestingly, it was observed that in de novo gefitinib-resistant LoVo colorectal cancer cells, which are defective in terms of ability to produce mature IGF-1R and predominantly express insulin receptor-isoform A (InsR-A), a close family member of the IGF-1R, insulin receptor activity is increased and downstream activated Akt levels are elevated in the presence of gefitinib (Jones et al., 2006). Furthermore, InsR can modulate and maintain EGFR phosphorylation in these cells. Such rapid and dynamic interplay between EGFR and IGF-1R or InsR could play an important role in limiting the anti-tumor activity of gefitinib; partial and de novo resistance to the inhibitor has been demonstrated in A549 and LoVo cells, respectively.

In HNSCC, it has been found that the use of the combination of both IGF-1R and EGFR antibodies was more effective than either single agent alone at reducing cancer cell growth (Barnes et al., 2007). There may be a potential benefit in the use of combined anti-tyrosine kinase receptor directed therapies to treat HNSCC. Slomiany *et al.* also demonstrated the potential for the co-targeting of both IGF-1R and EGFR signaling in HNSCC (Slomiany et al., 2007). Furthermore, Rebucci *et al.* reported that the combination of cetuximab with a PI3K inhibitor could be a good therapeutic option in HNSCC (Rebucci et al., 2011).

7. Cross talk between the NFκB and STAT3 signaling pathways

Of interest, whereas the activation of EGFR leads to the rapid tyrosine phosphorylation of STAT3 in tyrosine705 and the consequent activation of STAT3-dependent gene expression, it was observed that STAT3 tyrosine phosphorylation and the formation of active STAT3 DNA-binding complexes are insensitive to the inhibition of EGFR in a large fraction of HNSCC cell lines (Sriuranpong et al., 2003). Indeed, 9 of 10 cell lines form a representative panel of HNSCC-derived cells showing increased tyrosine phosphorylation and activity of STAT3, but constitutive activity of EGFR was present in only 3 of them (Sriuranpong et al., 2003). In search for the mechanism responsible for the EGFR-independent activation of STAT3 in HNSCC cells, it was observed that the activation of the gp130 cytokine receptor subunit promoted the phosphorylation of STAT3 in tyrosine 705 through the activation of intracellular tyrosine kinases of the JAK family. Suprisingly, the activation of gp 130 was found to be primarily initiated by IL-6, which, on its secretion and release on the cell surface of HNSCC cells in an autocrine fashion. These findings suggest that the persistent activation of STAT3 in HNSCC can result from the deregulated activity of EGFR or from the autocrine activation of STAT3 by tumor-released cytokines in an EGFR-independent fashion. Furthermore, it was found that overexpression of IL-6 in HNSCC cells involves increased transcription from the IL-6 promoter, which is dependent

on the presence of an intact NFκB response element located 63 to 75 bp upstream of the IL-6 transcriptional initiation site. Furthermore, inhibition of NFκB led to a remarkable downregulation of IL-6 gene and protein expression, concomitant with a decreased release of other inflammatory cytokines, such as IL-8, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF). Surprisingly, the blockade of NFκB led also to a drastic inhibition of the constitutive STAT3 activity in HNSCC cells, as reflected by the reduced tyrosine phosphorylation of STAT3. Interestingly, interfering with NFκB function also prevented the autocrine/paracrine activation of STAT3 in HNSCC cells (Squarize et al., 2006). These findings support a cross-talk between the NFκB and the STAT3 signaling systems. This cross-talk is initiated by the release of IL-6 as a consequence of the NFκB-dependent activation of the IL-6 promoter, and the subsequent tyrosine phosphorylation of STAT3 by the autocrine/paracrine activation of IL-6 receptors in tumor cells.

8. Future prospects

Signaling of multiple receptor tyrosine kinases (RTKs) is propagated through Akt. Therefore, simultaneous inhibition of EGFR with pathway components such as Akt or mTOR could circumvent the feedback activation observed with either approach alone. The most extensive data concerning proximal and distal signaling inhibition relates to combining PI3kinase/Akt/mTOR pathway inhibitors with EGFR antagonists. Several PI3kinase inhibitors can restore sensitivity to EGFR inhibitors. For example, the selective pI3kinase inhibitor PX-866 and p110α can abolish gefitinib resistance in NSCLC xenografts (Ihle et al., 2005). Synergistic effects of rapamycin and EGFR TKIs have been observed in several *in vitro* systems including glioblastoma multiforme, prostate cancer, pancreatic cancer, squamous cell carcinoma, renal cell carcinoma, leukemia, cervical carcinoma and NSCLC (Birle & Hedley, 2006; Buck et al., 2006; Costa et al., 2007; Hjelmeland et al., 2007; Jimeno et al., 2007; Mohi et al., 2004). Several studies extended efficacy of these combinations in the xenograft experiments. Buck *et al.* (Buck et al., 2006) showed re-sensitization and synergistic growth inhibition with the combination of rapamycin and erlotinib in cell lines that were previously resistant to erlotinib. Li *et al.* noted significant regression of lung tumors in transgenic mice possessing the secondary resistance mutation T790M when treated with a combination of rapamycin and the irreversible EGFR TKI, HKI-272 (Li et al., 2007). In human glioma cell lines with mutant PTEN, addition of the dual PI3kinase/mTOR inhibitor PI-103 to erlotinib was necessary to induce growth arrest (Fan et al., 2007), suggesting that activation of the PI3kinase/Akt/mTOR pathway by EGFR-independent mechanisms confers resistance to EGFR inhibitors, which can nonetheless be overcome by the addition of pathway inhibitors. Collectively, these data suggest that the use of EGFR antagonists with PI3kianse/Akt pathway inhibitors could be beneficial to patients that have developed resistance to EGFR TKIs.

However, we think that the use of EGFR antagonists with PI3kinase/Akt pathway inhibitors might allow the activation of TNFR and/or IL-1R-NFκB-IL6-STAT3 signaling (Fig1). Therefore, we recommend the use of EGFR antagonists with PI3kinase/Akt pathway inhibitors and NFκB-IL6-STAT3 pathway inhibitors.
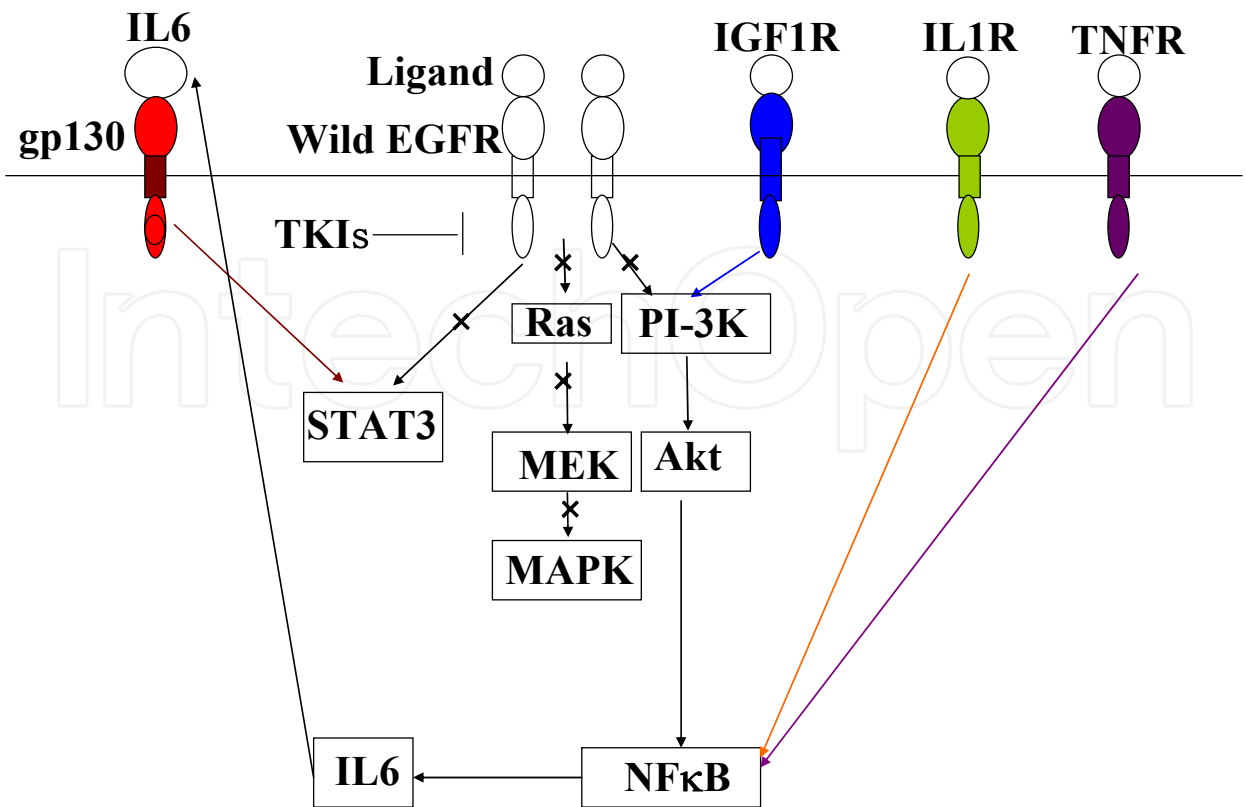
Fig. 1. Cell signalings and the communications in head and neck cancer.

9. Conclusions

EGFR is expressed at a high level in HNSCC but EGFR inhibitor monotherapy has limited success. Previous studies have demonstrated that EGFR mutations are extremely rare inHNSCC; inhibition of PI synthesis provides anti-proliferative, anti-invasive and anti-angiogenesis effects on HNSCC. The PI3kinase/Akt pathway is responsible for cellular survival and there is molecular cross-talk between EGFR and IGF1R signaling through PI3kinase/Akt in HNSCC. Furthermore, there is molecular cross-talk between the NFκB and STAT3 signaling pathways. Therefore, combination therapy targeting PI3kinase/Akt, NFκB/STAT3, and EGFR signaling pathways should provide clinical benefit for patients suffering with HNSCC (Fig. 1). Although various Akt and/or NFκB specific inhibitors have been developed, we recommend using a combination of an EGFR antagonist with numerous chemo-preventive compounds that inhibit the activation of both Akt and NFκB , as natural compounds have little side effect. Resveratrol, trans-3,5,4′-trihydroxystibene, was first isolated in 1940 as a constituent of the root of white hellebore (Veratrum grandiflorum O. Loes), but has since been found in various plants including grapes, berries and peanuts. In addition to cardioprotective effects, resveratrol exhibits anticancer properties as suggested by its ability to suppress proliferation of a wide variety of tumor cells. The growth-inhibitory effects of resveratrol are mediated through cell-cycle arrest: up-regulation of p21, p53 and Bax, and down-regulation of survivin, cyclin D1, cyclin E, Bcl-2, Bcl-xl and cIAPs, and activation of caspases. Resveratrol suppresses the activation of several protein kinases including Akt (Banerjee et al., 2010), and limited data from

humans suggest that it is pharmacologically safe. Furthermore, resveratrol suppresses TNF-induced activation of NFκB (Manna et al., 2000). Another chemopreventive agent whose effects on Akt signaling have been studied in some detail is the rotenoid deguelin. Deguelin is a rotenoid from the African plant Mundulea sericea (Leguminosae), which was identified as a potent chemopreventive agent on the basis of its action against chemically induced preneoplastic lesions in a mammary organ culture, and its inhibition of papillomas in a two-stage mouse skin carcinogenesis model (Nair et al., 2006). Furthermore, deguelin suppresses the formation of carcinogen-induced aberrant crypt foci in mouse colon (Murillo et al., 2003). More recently, this rotenoid was shown to suppress cigarette smoke-induced lung carcinogenesis (Lee et al., 2005), and it enhances the sensitivity of leukemia cells to chemotherapeutic agents (Bortul et al., 2005). How deguelin mediates its chemopreventive and chemosensitizing effects is not yet fully understood, but various mechanisms have been proposed including suppression of the PI3kinase/Akt pathway (Chen et al., 2009). In Akt-inducible transgenic mice, deguelin was competent at suppressing Akt activation in the lung. At doses achievable in vivo, it reduced pAkt levels, induced apoptosis and suppressed proliferation of premalignant and malignant human bronchial epithelial cells; minimal effects were observed in normal bronchial cells (Chun et al., 2003). Blockade of Akt activation is likely to contribute to the pro-apoptotic actions of deguelin in breast cancer cell lines and anti-angiogenic effects in vitro. Deguelin inhibited formation of murine lung tumors in conjunction with suppression of Akt activation in vivo (Hecht, 2005). Furthermore, deguelin suppresses NFκB activation induced by various carconogens and inflammatory stimuli including TNF and IL-1β (Nair et al., 2006). The cruciferous vegetable component indole-3-carbinol has chemopreventive activity that could be associated with down-regulation of Akt signaling (Chinni & Sarkar, 2002). Furthermore, indole-3-carbinol suppresses NFκB activation induced by various carconogens and inflammatory stimuli including TNF and IL-1β (Takada et al., 2005). Honokiol, used as a muscle relaxant, is derived from the stem and bark of the plant Magnolia officinalis, which is used in traditional Chinese and Japanese medicine. Extensive research has demonstrated that honokiol inhibits skin tumor promotion, nitric oxide synthesis, TNF expression and inhibits invasion. Furthermore, it down-regulates the anti-apoptotic protein bcl-xl, inhibits angiogenesis and tumor growth *in vivo*, induces caspase-dependent apoptosis in B-cell chronic lymphocytic leukemia cells through down-regulation of the anti-apoptotic protein Mcl-1, and overcomes drug resistance in multiple myeloma. Honokiol blocks TNF-induced NFκB activation (Ahn et al., 2006). Indeed, Honokiol inhibits EGFR signaling involving Akt and STAT3, and enhances the antitumor effects of EGFR inhibitors (Leeman-Neill et al., 2010). In conclusion, the combination of an EGFR antagonist with these chemo-preventive compounds that inhibit the activation of both Akt and NFκB may overcome the resistance to EGFR antagonist in HNSCC.

10. Acknowledgement

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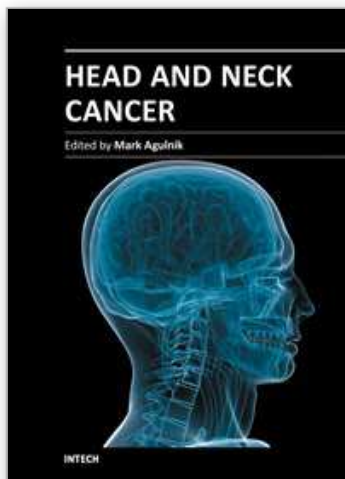
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