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EGF-receptor signaling and epithelial-mesenchymal transition in human carcinomas

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1. ABSTRACT

The epidermal growth factor receptor (EGF-R) signaling pathway maintains a balance between cell proliferation, differentiation and apoptosis, and thus it is believed that EGF-R signaling pathways play an important role in the development and progression of several human carcinomas. Epithelial-mesenchymal transition (EMT) describes the dedifferentiation switch between polarized epithelial cancer cells and contractile and motile mesenchymal (invasive) cells during cancer progression and metastasis. Activation of EGF-R signaling regulates EMT-associated invasion and migration in normal and malignant epithelial cells. In contrast, blocking EGF-R and consequently its pathways, by a monoclonal antibody (mAb) or a tyrosine kinase inhibitor (TKI), inhibit cellular migration and invasion, suggesting an essential role for EGF-R inhibitors in the control of cancer metastasis. The purpose of this review is to summarize current information regarding the role of EGF-R signaling on EMT during human cancer progression and metastasis.

2. INTRODUCTION

Carcinomas are tumors of epithelial origin and represent over 90% of human cancers; metastatic carcinomas are responsible for the majority of cancer-related deaths, either directly due to tumor involvement of critical organs or indirectly due to complications of therapy to control tumor growth and spread. The epidermal growth factor receptor (EGF-R) is a receptor tyrosine kinase that is over-expressed in a wide variety of human carcinomas, including non-small cell lung, breast, head and neck, bladder, ovarian and prostate cancer, and it has been associated with a number of studies of advanced disease and poor prognosis (1,2). In addition, it is well known that EGF-R is not only important in cell proliferation, but in a number of varied processes likely to be significant for carcinomas progression such as cell adhesion, cell motility and invasion which are major steps in the epithelial-mesenchymal transition (EMT) event (3,4). The EMT is a highly conserved cellular program that allows polarized, immotile epithelial cells to convert to motile mesenchymal

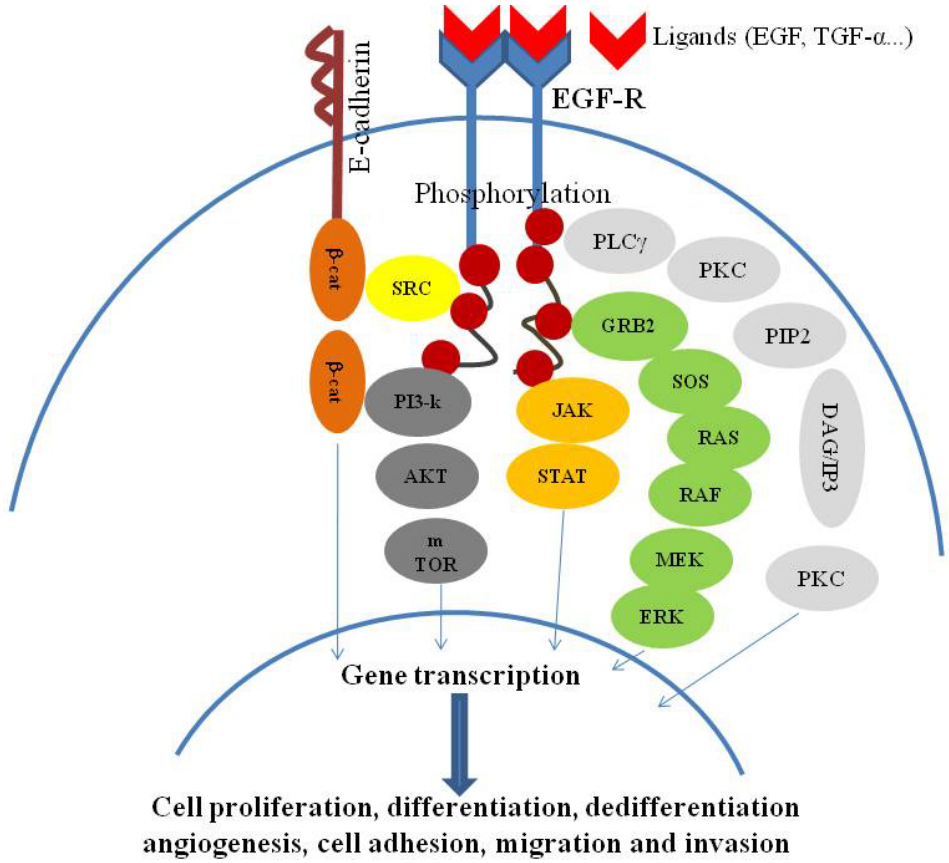

Figure 1. EGF receptor signaling pathways. Ligands of the EGF family bind to the EGF-R and incite homo or hetero-dimerization that causes phosphorylation of distinct tyrosine residues. Afterwards, the receptor homo or hetero-dimers activate downstream-signaling pathways including JAK, PI3 kinase, SRC kinase, PLCy and the ERK pathway. These pathways ultimately alter the activity of multiple nuclear transcription factors. The EGF-R network initiates diverse cellular mechanisms that lead to cell proliferation, differentiation, dedifferentiation, angiogenesis, cell adhesion, migration and invasion.

cells (4,5). This important process was initially recognized during several critical stages of embryonic development and has more recently been implicated in promoting carcinomas invasion and metastasis. In this review, we discuss the role of EGF-R signaling in human carcinomas progression through its regulation of the EMT process.

3. EPIDERMAL GROWTH FACTOR RECEPTOR SIGNALING

The epidermal growth factor receptor (EGF-R) is a 170-kd, 1186–amino acid long transmembrane receptor belonging to a family of receptor tyrosine kinases that includes, in addition to EGF-R, three other members (ErbB2/HER-2, ErbB3/HER-3, and ErbB4/HER-4) (6,7,8). These four receptors share a common structure that is composed of an extracellular domain with binding site for specific ligands, a short transmembrane region, and an intracellular tyrosine kinase domain. A number of ligands can bind to EGF-R such as epidermal growth factor (EGF), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin (AR), betacellulin (BTC) and transforming growth factor-alpha (TGF-α) (9,10,11,12). Binding these ligands to the extracellular domain of the receptor results in receptor conformational changes, which facilitate the receptor homo- or heterodimerization (13,14), followed by autophosphorylation of key tyrosine residues within the COOH-terminal portion of EGF-R, which can act as specific docking sites for specific proteins containing Src homology 2 and phosphotyrosine binding domains (15,16,17). The activation of EGF-R initiates intracellular signaling via several pathways including Ras/ MAPK, Akt, Src family of kinases, Jak-Stat and the phospholipids metabolism enzymes, phospholipase C-c (PLC- c), phosphatidylinositol 3-kinase (PI3K), and phospholipase D pathways (15,18,19,20,21). The activation of these pathways initiate the transcription of several genes involved in cell proliferation, survival, differentiation, apoptosis and adhesion (22,23,24,25,26,27,28) (Figure 1). More specifically, Ras/MAPK pathway regulates cell proliferation, transformation, and metastasis development, while, the Akt pathway is involved in cell survival processes, apoptosis resistance, invasion and migration (26,27,29). In addition to ligand binding, EGF-R can be activated by phosphorylation of specific amino acid residues as a result of trans-activation by G-protein coupled receptors (30). Phosphorylation of receptor can also occur in response to nonspecific stimuli, including exposure to

ionizing radiation, UV radiation, hypoxia, hyperthermia and oxidative stress (31,32,33,34). Given the significant role of EGF-R signaling in all aspects of cell growth and survival (Figure 1), the alterations in the function of EGF-R are expected to play a crucial role in the development and progression of some pathological conditions including cancer.

Accumulating evidence supports the key role of EGF-R in the development and progression of many human tumors. For example, EGF-R mutations are found in most of human tumors such as head and neck squamous cell carcinomas (HNSCC), glioblastoma, NSCL, breast, colorectal, bladder, prostate and ovarian carcinomas (35,36,37,38,39,40,41,42,43). A strong correlation has been found between EGF-R mutations and tumor aggressiveness (44), decreased overall survival (45), poor prognosis (46), treatment resistance (47), disease recurrence (48), and increased risk of metastasis (49,50,51). EGF-R abnormalities within detected cancer types include gene amplification (40), protein over-expression and aberrant activation (51,52,53,54). Gene amplification of EGF-R has been shown to especially occur in epithelial cancers, and it was presumed to play a central role in the early pathogenesis and progression of these tumors (35,40,55,56,57). Over-expression of EGF-R has been detected in squamous cell carcinomas and to a lesser extent in adenocarcinomas (39,58,59).

Mutations in the EGF-R kinase domain have been often diagnosed in a number of carcinomas such as HNSCC, colorectal and NSCLC (38,60,61). EGF-R mutations were also reported in atypical adenomatous hyperplasia, which is considered to be a precursor lesion of lung adenocarcinomas (62,63), suggesting that EGF-R mutations are also involved in the early stage of lung cancer progression. Moreover, several studies have shown that mutations in the tyrosine kinase domain of the EGF-R gene strongly correlate with ethnicity (64,65), and the clinical responses to EGF-R inhibitors such as gefitinib (66,67,68,69). The majority of EGF-R mutations occurs in exons 18–21, the first four exons encoding tyrosine kinase domain, and the most prevalent mutations consist of in-frame deletions in exon 19 *(*45.7%). Over 20 variant types of mutations have been detected (70,71). The mutation in exon 21, which leads to L858R substitution, accounts for 43% of EGF-R mutations. Less frequent, point mutations, such as G719C and G719S in exon 18, account for 3.5% of EGFR mutations. There are occasional in-frame insertion mutations in exon 20 (72,73,74).

In spite of many proposed hypotheses, the mechanisms of how the mutations affect EGF-R function and what role they play in the oncogenic processes require further investigations. It is proposed that mutations spread along the kinase-coding regions (exons 19- 21) result in constitutive autophosphorylation, leading to the stimulation of the basal kinase activity, and thus activation of EGF-R. These mutations also appear to enhance sensitivity to cancer treatment by TKIs (75). It has been hypothesized that EGF-R mutations in cancer cells (deletion in exon 19 and L858R mutation in exon 21) lead to a selective activation of PI3K/Akt and Jak/Stat signaling pathways that inhibit apoptosis and promote cell survival with less effect on the mitogen-activated protein kinase (MAPK) pathway that induces cell proliferation (76,77). In contrast, over-expression of EGF-R in different tissues including urothelium, glial cells or esophageal keratinocytes was found to increase proliferation, migration, and aggregation (78). Deletion of exon 19 appears to confer higher malignant transforming ability than exon 21-point mutation (L858R), and this difference is believed by some researchers to reflect patient survival (48,79). Finally, it has been shown that the EGF-R gene intron 1 has a polymorphic region of CA dinucleotide repeats, ranging from 9 to 26 repeats, and these repeats are proposed to affect *EGF-R* transcription efficiency, influence clinical prognosis, and modulate anti-EGF-R drug sensitivity in colorectal, head and neck, lung and breast cancers (80,81). The aforementioned pathways are often associated with the implication of cancer progression in accordance with EGF-R in homo or hetro-dimerization with ErbB family members. Next, we will discuss the critical involvement of EGF-R pathways in human carcinomas progression through its regulation of epithelial-mesenchymal transition phenomena and E-cadherin expression.

4. EPITHELIAL-MESENCHYMAL TRANSITION AND E-CADHERIN EXPRESSION

Epithelial-mesenchymal transition (EMT) is an evolutionary conserved developmental process (82) that plays a critical role in the embryonic development, cancer progression and metastasis. It is probable that a common molecular mechanism is shared by these processes (4,83,84). EMT is a multi-step process in which cells acquire molecular alterations that facilitate dysfunctional cell–cell adhesive interactions (4), loss of cell–cell junctions (83) and reorganization of the cytoskeleton (85), all of which result in the loss of apical polarity and the acquisition of a more spindle-shaped morphology (4,82) (Figure 2). Most cancer cells, like epithelial cells during embryonic development, undergo physical and biochemical changes that enable them to interact with the surrounding microenvironment, thus facilitating their migration from the site of origin and dissemination to distant tissues and organs (4,82). Moreover, similar to normal development, epithelial-like cancer cells in the primary tumor can initiate a multi-step process whereby cells down-regulate the expression of intracellular proteins, such as E-cadherin, occludin and claudins and up-regulate signaling pathways and proteins, such as N-cadherin and vimentin (86) associated with a more motile, mesenchymal-like phenotype. Such changes lead to alterations in cell polarity and cell–cell adhesion as the epithelial cells transition to a mesenchymal-like phenotype (4,87). These changes are hallmark feature of EMT (87); this incites to a reduction in cell-cell adhesion and enhances migratory capacity (4,82,88).

Several genes including ErbB family are involved directly and/or indirectly in the initiation of the EMT phenomenon and consequently cancer progression and

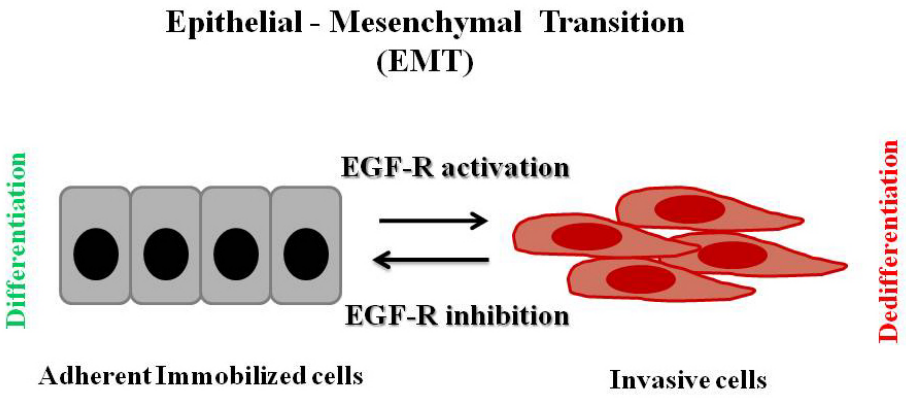

Figure 2. Epithelial-mesenchymal transition (EMT) event and EGF-R modulation. The EMT is a multi-step process which allows cells migration and invasion through dysfunctional cell–cell adhesive interactions, loss of cell–cell junctions and reorganization of the cytoskeleton; these procedures result in the loss of apical polarity and the acquisition of a more spindle-shaped morphology. Activation of EGF-R induces dedifferentiation EMT which is accompanied by over-expression of mesenchymal markers such as vimentin, fibronectin and N-cadherin. In contrast, EGF-R inhibition, by a TKI or antibody, provokes differentiation MET which is escorted by markers such as E-cadherin and ZO-1.

metastasis. For example, EGF-R activity has been shown to induce tumor cell motility and invasion by regulating the activity of downstream signaling molecules, such as FAK, β-catenin, Ras, Raf, MAPK, and PI3K/Akt (89). The activation of different pathways including ErbB signaling can result in increased activity of transcriptional repressors, such as Snail, Zeb, and Twist, which repress expression of cell adhesion molecules like E-cadherin (90). On the other hand, EGF-R signaling can induce EMT, invasion, and metastasis in several different types of rodent and human cancer cells including human breast cancer, which can be mediated via STAT3-dependent Twist up-regulation (91) or by inducing the expression of Snail and Zeb (90,82).

The E-cadherin expression in normal cells is thought to stabilize the cell architecture, and as such its expression is an indispensible element of epithelial differentiation (3). More importantly, its reduced expression has been associated with the induction of EMT, which is instrumental in pathologies such as carcinomas invasion (92,83). In addition, earlier studies have described the EMT signature of decreased E-cadherin expression and increased vimentin and N-cadherin expression in mammary gland hyperplasia's and tumors from transgenic mice over-expressing human Cripto-1 (93). An increase in migration and invasion of cervical and breast cancer cells has been associated with Cripto-1 over-expression (94,95). These findings support the significant role of Cripto-1 in the induction of EMT in cancer cells which may explain, in part, why Cripto-1 expression has been associated with more aggressive behavior in several human carcinomas including breast cancer and colon cancer (95,96).

Further, previous studies reported that E-cadherin expression can be regulated by the deregulation of Cox-2 and Pge-2 in human lung carcinomas (97,98). Cox-2 and Pge-2 expression resulted in a significant reduction in E-cadherin via Zeb-1 and Snail transcriptional factor mediated mechanism, and inhibition of Cox-2 resulted in the rescue of E-cadherin expression (97). This newly defined pathway for transcriptional regulation of E-cadherin has important implications on chemoprevention and treatment of human carcinomas especially lung metastatic cancer using Cox-2 inhibitors through the inhibition of EMT progression. Moreover, the ectopic expression of Snail or Slug has resulted in EMT-associated enhanced motility, invasiveness, and tumorigenicity in ovarian cancer cells (99); while, activation of these transcriptional factors by hypoxia revealed immediate up-regulation of Slug expression with consequent down-regulation of Snail and E-cadherin expression (100) thus stimulating EMT progression. Further evidence of EMT in ovarian cancer is supported by a recent study which demonstrated that 17b-estradiol increased Snail expression with subsequent increase in the MMP-2 expression and decrease in E-cadherin expression in estrogen receptor positive and estrogen receptor negative ovarian cancer cell lines (101).

The coupled expression of E-cadherin and β-catenin has been shown to be critical for the stable assembly of a cytoskeleton structure, and maintenance of cell-cell contact in epithelial cells (102). In colon cancer, constitutive activation of the Wnt signaling pathway is a key contributor to tumorigenesis (103). Accumulation of nuclear β-catenin was observed at the invasive front and in tumor cells migrating into stroma (104,105), consistent with an EMT. In contrast, in the remainder of the primary tumor, and in metastases, heterogeneous intracellular distribution of β-catenin was detected (103,106).

The role of EMT in prostate cancer progression has emerged from studies using *in vitro* and *in vivo* models. Various factors appear to be altered in the prostate cancer microenvironment through increased production of tumor cells or the cancer-associated stroma these changes appear to be associated with EMT (107). Many of these factors have also been shown to cause EMT in other systems (107-

109). For example, the transcription factor Twist similarly represses E-cadherin expression as well as up-regulates N-cadherin levels in prostate cancer cells (110,111). In contrast, loss of prostate-derived ETS factor (PDEF), which is down-regulated by TGF-β, induces EMT in PC3 cells (112). In addition, over-expression of prostate specific antigen (PSA) and kallikrein-related peptidase 4 (KLK4), both potential activators of pro-EGF and latent TGF-β2, results in EMT in PC3 cells (113,114). On the other hand, PSA and KLK4 which are part of normal prostatic secretions, leak into the tumor microenvironment due to the disruption of glandular architecture during cancer progression, suggesting a link between tissue architecture and EMT.

Earlier study indicates that EMT of tumor cells not only causes increased metastasis, but also contributes to drug resistance (115). This implies that treatments that target cell growth pathways might not be effective in killing these cells. Indeed, increasing amount of data relate drug resistance of tyrosine kinase inhibitors to the existence of EMT. For instance, epithelial but not mesenchymal gene signature has been associated with sensitivity to the small molecule-EGF-R-inhibitor erlotinib (Tarceva) (116). Clinical trials confirmed this relationship in several carcinomas; significant benefits were observed in lung carcinoma patients with high expression of E-cadherin who were treated with erlotinib, contrarily to the E-cadherin-negative patients this was also found in xenografts of lung carcinoma cells (117) as well as in other types of tumors such as head and neck squamous cell carcinomas and hepatocellular carcinomas (115). Other EGF-R inhibitors exhibited the same affect, such as gefitinib (Iressa) (118) and cetuximab (119). In parallel, gemcitabine-resistant pancreatic cells with increased invasive capacities, oxaliplatin-resistant colorectal cancer cells and post-ionizing radiation related tumor distant metastasis in patients with advanced lung cancer, have all been associated with EMT (120-122). In addition, an EMT implication in therapeutic drug resistance was recently increased with Lapatinib resistance in breast cancer (123) and paclitaxel resistance in epithelial ovarian carcinomas (124). In fact**,** empirical reports connecting EMT to the emergence of stem cells has recently been reported (125).

To conclude, progression of human carcinomas involves spatial and temporal occurrences of EMT, whereby tumor cells acquire a more invasive and metastatic phenotype. Subsequently, the disseminated mesenchymal tumor cells must undergo the reverse transition, MET, at the site of metastases, as metastases recapitulate the pathology of their corresponding primary tumors. Initiation of tumor growth at the secondary site is the rate-limiting step in metastasis. This suggests that cellular plasticity and the ability to undergo from EMT to MET in the appropriate microenvironments are key features for a successful cancer treatment (Figure 2). Thus, targeting EMT and/or its regulators may provide a novel strategy to inhibit cancer progression and metastasis by trapping disseminated tumor cells in a state of micro- metastasis.

5.EPITHELIAL-MESENCHYMAL TRANSITION/EPIDERMAL growth factor receptor interaction

It is known that epithelial and mesenchymal tissues are endowed with different adhesion systems that have to be modulated in order to allow cells to move. Normal epithelial cells adhere to the basement membrane matrix and to each other by the E-cadherin/catenin complex (3). Mesenchymal cells, that generally do not establish significant cell–cell adhesions, are characterized by dynamic cell–matrix adhesions present on the entire cell surface which allows them to move individually within the ECM (3-5) (Figure 2). In addition to regulating cell–matrix adhesion, EGF-R can also influence cell–cell adhesion. Indeed, there is strong evidence that the altered balance between the two adhesion systems can contribute to invasion and cancer progression (4,126) (Figure 2). It is well documented that EGF-R activation causes disruption of cell–cell junctions and promotion of invasiveness through the phosphorylation of the E-cadherin/catenin complex thus resulting in dissociation of the latter and functional loss of E-cadherin; these events releases β-catenin into the cytoplasm and then into the nucleus, which stimulates transcriptional activity (3,127,128,129). β-catenin-regulated genes, such as Myc, Snail-family members, cyclin D1, vimentin, and matrix-degrading proteases, are involved in EMT, invasion and tumor progression (128,130).

In order to investigate the role of EGF-R activation in human lung carcinomas EMT and consequently cell motility and invasion in these cancer cells, we examined the effect of a ligand-blocking mAb against the EGF-R, LA1, in three human lung cancer cell lines H322, A549 and H661 as well as human normal bronchial epithelial (HNBE) cells. We found that the LA1 mAb inhibits cell growth, induces differentiation to a more epithelial phenotype and up-regulates E-cadherin protein expression in H322, A549 and HNBE cells. In contrast, LA1 had no effect on H661 cells, which do not express detectable levels of EGF-R (3,131,132). Furthermore, we investigated the effect of LA1 mAb on the E-cadherin/catenin complex in H322 and A549 cell lines. Inhibition of EGF-R was associated with re-localization of E-cadherin, α-catenin and β-catenin, but not γ-catenin. Moreover, we demonstrated that mAb LA1 induces up-regulation of the E-cadherin/catenin complex and inhibits cell motility of both cell lines. In contrast, EGF and HB-EGF lignads induce cell proliferation and the epithelial-like to fibroblastoid (mesenchymal) conversion of H322, A549 and HNBE cells, slightly reduces the expression of E-cadherin and β-catenin, but not α- and γ-catenins, and stimulates cell motility (3,131,132,133). More interestingly, we found that amphiregulin, another lignad of EGF-R, stimulates cell proliferation but not the epithelial-like to fibroblastoid conversion of H322, A549 and HNBE cell lines. This is a very important issue for different aspects of human health especially in skin restoration where we can provoke normal epithelial cell proliferation without any modification in their phenotype [Al Moustafa *et al.*, unpublished data]. Nevertheless, these studies demonstrate that EGF-R

modulation regulates the E-cadherin/catenin complex and consequently cell motility and invasion of human lung carcinoma cells.

In order to develop new strategies in the treatment of human prostate and lung carcinomas, we investigated the effect of *Teucrium polium* (*TP*) medicinal plant extract on two human prostate and lung cancer cell lines, PC3 and DU145 and A549 and H322, respectively; we found that *TP* plant extract inhibits cell proliferation and induces cell apoptosis in these cell lines (134,135). More importantly, we demonstrated that *TP* plant extract induces differentiation (fibroblast-like to epithelial transition) and blocks cell invasion ability of PC3 and DU145 prostate cancer cells though the restoration of E-cadherin/catenin complex via Src dephosphorylation which is an important pathway of EGF-R activation (134); Our recent results revealed that *TP* plant extract blocks cell invasion through the inactivation of EGF-R which in turn dephosphorylates Src in human prostate and lung cancer cells (134). Activation of several different cell signaling pathways regulated by EGF-R stimulates the induction of EMT (136,137). Chronic stimulation with EGF can result in activation of Snail and EMT in several human carcinomas including breast (131,136,138). Blocking EGF-R signaling inhibits alcohol-stimulated Snail mRNA expression which play an important role in EMT (139) and Snail mediated colon cancer metastases in mice (140). EMT in cervical cancer is also correlated with EGF-R and Snail over-expression (141). Moreover, cigarette smoke exposure activates EGF-R which can contribute to prolonged downstream signaling through the activation of Akt and extracellular signal regulated kinases (ERK1/2)-survival, proliferation and cell adhesion pathways and consequently the EMT process in human lung cancer (142,143). Meanwhile and as we mentioned above, it has been reported that EMT plays an important role in resistance to EGF-R TKIs, during which cancer cells lose their epithelial marker, such as E-cadherin (116,117,118). In contrast, strong expression of E-cadherin enhances gefitinib sensitivity in lung carcinomas with a mesenchymal phenotype (116). Although EMT can predict resistance to gefitinib or erlotinib (117,118,144), nevertheless the molecular mechanisms are still unknown.

Src kinases are transducers of signals activated by many different classes of cell-surface receptors. More specifically, Src can be activated by growth factor receptors including EGF-R and Met-receptors, cytokine receptors, protein tyrosine phosphatase 1B, CAS, and focal adhesion kinase (FAK). Src interacts with a network of intracellular signaling pathways, including the integrin/FAK pathway, β-catenin/Wnt, RAS-MEK, phosphatidylinositol-3-OH kinase–AKT and Janus-activated kinase–STAT pathways (145,146,147). These complex interactions explain why Src is involved in a large number of cellular functions. In order to determine the role of Src , as an important pathway of EGF-R and a major target in the treatment of several human carcinomas, we examined the effect of Src/Abl inhibitor, SKI-606 on cell proliferation, cell cycle progression, mesenchymal-epithelial transition and finally invasion and motility in numerous human carcinoma cell lines including lung, breast and cervical. The Src/Abl inhibitor induces mesenchymal-epithelial transition and consequently up-regulates E-cadherin expression and inhibits cell invasion ability of human lung, breast and cervical cancer cells. This effect occurs through the conversion of β–catenin's role from a transcription regulator to a cell-cell adhesion molecule via Src dephosphorylation (148,149). Collectively, these data suggest the concept that EGF-R and/or its pathways inactivation play an important role in the regulation of cell invasion and metastasis of human carcinoma cells through MET (Figure 2). Therefore, EGF-R-targeted therapies using new specific molecule of one and/or two pathways of EGF-R and/or mAbs against EGF-R are important strategies to treat several human carcinoma patients.

6. SUMMARY AND PERSPECTIVES

The EMT is a process that plays essential roles in epithelial cancer metastasis that is characterized by loss of homotypic adhesion, cell polarity, increased invasion and migration. On the other hand, the EMT process has provided insight into the mechanisms that are implicated in the migration, invasion, and metastatic spread of cancer cells. Indeed, this review has highlighted the importance of the EGF-R alteration in regulating epithelial plasticity and EMT during human carcinomas progression. Understanding and defining the initial molecular signals leading to the EMT switch in tumor cells would undoubtedly contribute to earliest clinical detection and intervention strategies. Although the use of inhibitors delivered individually to EGF-R targets appears rational, however, limited efficacy suggests that a combinatorial approach would offer improved clinical outcome. Therefore, it should be promising to identify new molecules that selectively target cancer cells via more than one EGF-R pathway. Overall, understanding how EGF-R actuation controls EMT and in particular cancer cell motility should greatly facilitate the design of more successful, personalized cancer therapies.

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Abbreviations: AR: Amphiregulin; BTC: Betacellulin; CAS: Crk-associated substrate; COX2: Cyclooxygenase-2; E-cadherin: Epithelial-cadherin; ECM: Extracellular matrix; EGF-R: Epidermal growth factor-receptors; EMT: Epithelial-mesenchymal transition; EPR: Epiregulin; ERK: Extracellular signal regulated kinases; ETS: E26 transformation specific; FAK: Focal Adhesion protein; HB-EGF: Heparin-binding EGF like growth factor; HNSCC: Head and neck squamous cell carcinomas; JAK: Janus protein tyrosine kinase; KLK: Kallikrein-related peptidase; mAbs: Monoclonal Antibodies; MAPK: Mitogen-activated protein kinases; Met: MNNG HOS Transforming gene; MMP: Matrix metalloproteinase; N-cadherin: Neural-cadherin; NRG: Neuregulin; NSCL: Non-small cell lung cancer; P-cadherin: Placental-cadherin; PDEF: Prostate-derived ETS factor; Pge-2: Prostaglandin E2; PI3K: phosphatidylinosital 3-kinase; PKC: Atypical protein kinase C; PLCc: Phospholipase C-c; PLCγ: Phopholipase C γ; PSA: Prostate-specific antigen; RAS: RAt Sarcoma; SRC: Sarcoma; STAT: Signal transducers and activators of transcription; TGF-α: Transforming growth factor- alpha; TGF-β: Transforming growth factor- beta; TKIs: Tyrosine kinase inhibitor; TP: Teucrium polium; UV: Ultra-violet

Key Words: EGF-receptor, Epithelial-Mesenchymal Transition, Human Cancer Progression, Review

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