The EMT regulator slug and lung carcinogenesis

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Lung cancer is the leading cause of cancer death worldwide. Cancer metastasis and resistance to treatment (including radiotherapy, chemotherapy and targeted therapy) are two major causes for the poor survival of lung cancer patients. Epithelial–mesenchymal transition (EMT) is involved in cancer cell invasion, resistance to apoptosis and stem cell features. The process of EMT is controlled by a group of transcriptional factors, zinc finger proteins and basic helix-loop-helix factors. Signaling pathways activated by intrinsic or extrinsic stimuli converge on these transcriptional factors and regulated the phenotypic changes of cancer cells. These EMT regulators may play an important role in cancer progression. In lung cancer, Slug is the most thoroughly investigated EMT regulator. The expression of Slug is associated with lung cancer invasion and resistance to target therapy. In this review, we focus on the current understanding of the role of Slug in the carcinogenesis and progression of lung cancer.

Introduction

Currently, lung cancer remains as the leading cause of cancer-related mortality worldwide. More than 85% of lung cancer patients are diagnosed with non-small cell lung cancer (NSCLC); of these, ~70% present with unresectable disease, namely, stage IIIIB and IV NSCLC. Although there have been significant advances in cancer treatments owing to our knowledge in mechanisms in cell-signaling pathways. The prognosis of these patients with locally advanced or metastatic disease is ominous, with 5 years survival rates of <10% (1).

Even in those who receive surgically complete resection, lung cancer frequently relapses with metastasis. Several regimens of chemotherapy have been documented to improve survival (2); however, patients may not tolerate the adverse effects accompanying conventional chemotherapy. With the development of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, molecular-targeted therapy has established as an alternative treatment for patients with lung cancer. Recent research has indicated that patients with NSCLC with EGFR-activating mutations exhibit a dramatic clinical response to EGFR TKIs (3,4). In clinical practice, Asians, females, non-smokers and patients with adenocarcinoma respond preferentially to EGFR TKIs (5). These are also the patient groups with a high rate of EGFR mutations. Despite the dramatic initial responses to such inhibitors, most patients ultimately develop drug resistance and relapse.

Thus, the mechanisms of development of metastasis and resistance to therapy of lung cancer have been the most investigated fields. To circumvent these problems, we should have in-depth understanding of the molecular mechanisms of lung cancer dissemination and drug resistance.

Abbreviations: EGFR, epidermal growth factor receptor; EMT, epithelial–mesenchymal transition; ERK, extracellular signal-regulated kinase; GSK-3β, glycogen synthase kinase-3β; MDM2, murine double minute 2; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; TTF-1, thyroid transcription factor 1.

Epithelial–mesenchymal transition

Tumor dissemination is a complex process. The pathogenesis of cancer metastasis consists of a series of linked, sequential and selective steps involving processes such as migration, invasion, adhesion, proliferation and angiogenesis. Invasion, which is the most crucial step in the metastatic cascade, contains a series of biological activities involving the interaction of tumor cells with the surrounding environment (6). Tumors are a mass of heterogeneous neoplastic cells with different properties (7,8). During cancer progression, some tumor cells acquire new characters, as an expression of mesenchymal markers and loss of epithelial markers, and undergo profound morphogenetic changes, collectively referred to as epithelial–mesenchymal transition (EMT) (9,10).

EMT is originally described as a phenotypic conversion during embryonic development, such as gastrulation, as mesoderm is formed by invagination and during nervous system development, as cells emigrate from the neural crest (9). EMT (Figure 1) has also described in the process of re-epithelialization of wound healing and in the generating tissue fibroblast during the organ fibrosis process. The phenotypic changes are also observed in the process of cancer progression. While cancer progression, there is a movement toward a more aggressive behavioral pattern. These more aggressive cancer cells assume a spindled shape, lose desmosomes and adherens junctions, begin expressing vimentin and secrete increased amounts of proteolytic enzymes, such as matrix metalloprotease, to degrade the extracellular matrix and increase the movement ability. This is typified by the dissolution of cell–cell junctions, loss of apico-basolateral polarity and acquisition of front–rear polarization resulting in the formation of migratory mesenchymal cells with invasive properties. EMT also involves the reorganization of the cytoskeleton and changes in the interaction with the extracellular matrix. EMT is a key step in the progression of tumors toward metastasis and invasion (10). Moreover, the cancer cells undergoing an EMT have been found to show increased resistance to apoptosis and chemotherapeutic drugs and to acquire traits reminiscent of those expressed by stem cells (11).

EMT process can be controlled by intrinsic oncogenic activation, such as K-Ras mutation (12) or Her2 overexpression (13). EMT can also be triggered by external stimuli that emanate from microenvironment, which is composed of the extracellular matrix (such as collagen and hyaluronic acid), cancer-associated fibroblasts, myofibroblasts, immune cells and many secreted soluble factors, such as Wnt, transforming growth factor-β, Hedgehog, epidermal growth factor, hepatocyte growth factor and cytokines, such as tumor necrosis factor-α, interleukin-6 (14). These growth factors or inflammatory cytokines can exert through autocrine or paracrine manners. In addition, hypoxic environment can induce EMT of cancer cells (15). Cell–cell interaction, such as Notch signal, is the other mechanism to trigger EMT process (14,15). Interactions between the cancer cells and other local inflammatory cells or stromal cells may play an important role in the induction of EMT. Besides, intracellular interactions of those EMT-signaling pathways make the regulation of EMT more complex. Recent findings exemplify how the complex interplay between extra- and intracellular signals can trigger EMT and cancer progression (16). These signaling pathways orchestrate a concerted and elaborated gene program and protein network needed for the establishment of mesenchymal phenotypes.

Though the signaling pathways are complex, the hallmark of EMT in cancer is the downregulation of E-cadherin, which is also thought to be a repressor of invasion and metastasis (9). E-cadherin is a cell–cell adhesion molecule that participates in homotypic, calcium-dependent interactions to form epithelial adherent junctions and sequester β-catenin. Several transcription factors have been implicated in the
transcriptional repression of E-cadherin, including zinc finger proteins, Snail, Slug, Zeb1, Zeb2/SIP1, as well as the basic helix-loop-helix factors Twist and E47 (17,18). These transcriptional factors can suppress a subset of genes that encode cadherins, claudins, occludins, plakophilins, MUC1 and cytokeratins to induced EMT. These transcriptional factors can also repress the expression of proapoptotic genes such as PTEN, p53, Bid, PUMA or DFF40 and have been associated with resistance to radiotherapy, chemotherapy, endocrine therapy and targeted therapy (11,14). The transcriptional factors induce the expression of stemness-promoting genes, such as Sox2, Nanog, KLF4 and T cell factor-4, and are required for the synthesis of stem cell markers, such as aldehyde dehydrogenase 1 (19). Those EMT regulators act as a molecular switch of EMT process. In this review, we focus on our understanding of the role of Slug in the lung cancer carcinogenesis.

Snail family

The transcriptional factors of the Snail family have been associated with EMT during both embryonic development and cancer metastasis (17,18). The three members of the Snail family encode zinc finger type transcription factors and have been called Snail (Snai1), Slug (Snai2) and Smuc (Snai3). The most conserved feature of the Snail family proteins is the C-terminal domain, which contains four to six C2H2-type zinc fingers (Figure 2). These zinc fingers mediate sequence-specific interactions with DNA and bind to the E-box 5’-CAGGG-3’ (17–21). The other part of the protein is less well conserved in the family, but they contain the evolutionarily conserved SNAG domain at their extreme N-termini (17–22). The SANG domain is responsible for the suppressor function of these transcriptional factors and is required for the binding of corepressors. The SNAG domain of Slug interacts with CtBP-1, which recruits histone deacetylase to suppress expression of target genes (23).

The central region of the Snail family proteins is more divergent between Snail members. Slug has a unique conserved sequence motif near the zinc fingers, named Slug domain, which is absent in other members of the Snail family. The central part of the Snail protein has two functional domains: a regulatory domain containing a nuclear export signal and a destruction box domain, which are involved in the regulation of protein stability and localization. Snail and Slug are both unstable proteins with a half-life <1 h. The Snail stability is regulated by phosphorylation and dephosphorylation. Zhou et al. identify two consensus sites on Snail for glycogen synthase kinase-3β (GSK-3β). Firstly, in nucleus, GSK-3β phosphorylates four target serine residues, lying next to a nuclear export signal (24). Snail is exported into cytoplasm. Then, GSK-3β phosphorylates the other two serine residues that overlap with a destruction box recognized by β-TrCP1 ubiquitin ligase. Phosphorylated Snail binds to β-TrCP1, leading to its ubiquitination and degradation (24). FBXL14, another E3 ubiquitin ligase, also interacts with Snail and promotes its ubiquitination and proteasomal degradation but independently of phosphorylation by GSK-3β (25). Whether Slug also regulated by protein kinase and phosphorylation has been less studied and needs further investigation. Slug protein stability and degradation is modulated by FBXL14 ortholog Partner of Paired (26). Recently, we disclose that Slug protein is a target of the murine double minute 2 (MDM2) ubiquitin ligase (27). Slug interacts with MDM2 through amino acids 27–66 and is dependent on p53 that also associates to Slug through amino acids 21–27 (27). The details will be discussed in the latter section.

Slug and cancers

The Slug gene is located on human chromosome 8q11.21. Comparative genomic hybridization has shown an amplification of this region in many types of cancer (22). Slug protein consists of 268 amino acids and has a molecular weight of ~30 kDa (Figure 2). Slug contains five zinc finger domains in the C-terminus of the molecule. Slug was first identified to participate in mesoderm formation and neural crest cell formation in embryo (28). Slug is expressed in the craniofacial mesenchyme, developing bone, endocardial cushions and cardiac outflow tracts and mesenchymal components of the lungs, kidneys and gut of embryo (29). Slug-deficient mice are viable and have a white forehead blaze; patchy depigmentation of the ventral body, tail and feet; and macrocytic anemia and infertility, inferring an essential role for Slug in melanocyte stem cells, hematopoietic stem cells and germ cells (30). Transgenic mice overexpressing Slug are morphologically normal at birth and develop mesenchymal tumors (most leukemia and sarcomas) later demonstrating an oncogenic ability of Slug (31).

Slug has been shown to associate with a broad spectrum of biological functions such as cell movement, cell invasion, metastasis, cell cycle regulation, resistance to treatments and stem cell features in tumor cells. Slug is overexpressed in numerous cancers (32), including lung cancer, leukemia, esophageal cancer, gastric cancer, colorectal cancer, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, malignant meothelioma, cholangiocarcinoma, hepatocellular carcinoma and glioma. Elevated expression of Slug is associated with (i) reduced E-cadherin expression (ii) high histologic grade (iii) lymph node metastasis, (iv) postoperative relapse and (v) shorter patient survival of a variety of cancers (32–34).

Although the EMT regulators are thought to function in a redundant manner, several recent studies suggest unique function for Slug. It has been pointed out that Snail, Slug and E47 may differ in their respective target genes. Forced overexpression of each of these transcription...
factors induces EMT in cancer cell lines. A detailed analysis demonstrates that specific target genes, activated or suppressed, are significantly disparate even though similar mesenchymal phenotypes (19,35). Slug also reported to be more relevant for generating breast cancer cells with cancer stem cell phenotype than Snail (36).

Slug and lung cancer

We are interested in searching for novel genes associated with the invasion of lung cancer. We have previously established a panel of lung adenocarcinoma cell lines with increased invasiveness (CL1-0, CL1-1, CL1-5 and CL1-5-F4) from a parent lung adenocarcinoma cell line by repeated selection of more invasive cell lines (37). These selected sublines have shown greater invasive and metastatic potential compared with the parental cells. By using the complementary DNA microarray, we identify metastasis-associated genes on a genomewide scale in model lung cancer cell lines (38). Cluster analysis of the complementary DNA microarray data revealed that 589 (6.1%) genes were positively or negatively associated with cancer cell invasiveness. Moreover, most of these genes were involved in angiogenesis, cell motility, adhesion and proliferation.

Slug is one of the genes overexpressed in invasive cell lines by microarray. Overexpression of Slug suppressed the expression of E-cadherin and increased the invasive ability. A high expression of Slug messenger RNA in NSCLC tumor specimens was significantly associated with increased rate of cancer recurrence and decreased survival (36). The overexpression of Slug enhanced tumor growth and increased microvascular counts of xenograft. Matrix metalloproteinase-2 proteins and messenger RNA increased in Slug overexpressed cells and xenograft tumors. Our study showed that Slug is a metastasis-promoting gene in lung cancer through downregulated E-cadherin, upregulated matrix metalloproteinase-2 and enhanced angiogenesis (36).

From our previous microarray analysis, we found that expression of HLJ1 gene (Dnaj-like heat shock protein, also known as DNAJB4), was inversely associated with invasive ability. We prove that HLJ1 is an invasion suppressor as well as a tumor suppressor of NSCLC. Overexpression of HLJ1 in lung adenocarcinoma can reduce expression of the Slug and derepression of E-cadherin, effects that are associated with the inhibition of cell invasion and metastasis (39).

Thyroid transcription factor 1 (TTF-1) is an important transcription factor needed in lung morphogenesis. Amplification of TTF-1 gene is shown in lung adenocarcinoma. TTF-1 regulates gene expression in type II pneumocytes and Clara cells, which are found in terminal respiratory units. Expression of TTF-1 is a good prognostic marker in patients with NSCLC (40). Loss of TTF-1 expression is associated with poor differentiation of adenocarcinoma. Saito et al. reported that TTF-1 abrogated transforming growth factor-β-mediated induction of Slug and Snail. TTF-1 suppresses the expression of Slug and Snail and restores epithelial phenotypes in lung adenocarcinoma cells, leading to suppression of cell migration and invasion (41).

Several studies have suggested that Slug expression is associated with cancer stem cell properties. Oct4, a transcription factor, is essential to maintain self-renewal of stem cell features. Nanog is a downstream target of Oct4. Ectopic expressions of Oct4 and Nanog enhance the expression of Slug and Snail, increase tumor-initiating properties, induce drug resistance and promote metastasis in lung adenocarcinoma (42). Chen et al. used immunohistochemical staining of 118 lung adenocarcinoma specimens to demonstrate that patients with tumor of positive Slug stains have a worse survival prognosis, which is consistent with our report. Yang et al. (43) reported that in lung cancer cell lines, Slug but not Zeb1, binds to the promoter of 15-hydroxyprostaglandin dehydrogenase, an enzyme responsible for the degradation of prostaglandin E2. Prostaglandin E2 has been associated with increased tumor angiogenesis, metastasis, cell cycle regulation, and immune suppression. Slug suppresses the expression of 15-hydroxyprostaglandin dehydrogenase, resulting increased prostaglandin E2 level in NSCLC cell lines. This provides another mechanism for Slug to promote lung cancer carcinogenesis.

Idiopathic pulmonary fibrosis is an independent risk factor for lung cancer. It is an interstitial lung disease characterized by accumulation of activated fibroblasts and excessive extracellular matrix deposition in the destructed lung. Jayachandran et al. (44) analyzed the expression of Snail family transcription factors in human idiopathic pulmonary fibrosis tissue and found that Slug was the dominant transcription factor in the disease. Slug contributes to the formation of idiopathic pulmonary fibrosis and may predispose to the occurrence of lung cancer.

Transcriptional regulation of Slug

The fusion protein, E2A-HLF, acts as an inhibitor of apoptosis in lymphoid and myeloid cells and interferes with an early step in apoptotic signaling. Slug is a downstream target of the E2A-HLF, abnormally upregulated by this oncoprotein in certain leukemias and leads to increased cell survival (45). Slug is an essential mediator of BCR-ABL leukemogenesis. BCR–ABL oncogene induces Slug expression in blast cells of BCR–ABL transgenic mice and in blast cells from patients with Philadelphia chromosome-positive human leukemias. Slug-deficient mice are resistant to BCR–ABL-induced leukemogenesis (31). Slug is also a target of stem cell factor/c-kit pathway. Slug contributes to the stem cell factor-induced migration of c-kit+ cell and mediates the radioresistance of hematopoietic cells (46).

The promoter of Slug has been studied vigorously. Slug promoter shows the presence of consensus activator protein 1 sites, SMAD-binding elements, LEF1/T cell factor-binding sites and E-boxes (Figure 3). Slug is a downstream mediator of EGFR signaling. Epidermal growth factor-dependent expression of Slug is modulated via extracellular signal-regulated kinase (ERK) at wound healing and cancer migration. The Fra-1 is also regulated in an ERK-dependent manner. Chen et al. (47) showed that the expression of Slug is regulated by the ERK-Fra-1/c-jun signaling through the activator protein 1 site in the Slug promoter. Transforming growth factor-β-SMAD-signaling pathway induces SMAD complex binds to promoter of Slug and induces expression of Slug. Wnt signaling activates the T cell factor-β-catenin complex. This complex binds directly to the promoter of Slug and activates Slug expression. Interestingly, Slug can activate its own promoter by a direct binding to E-box (48). Therefore, Slug is not only a transcriptional repressor but also a transcriptional activator. Interestingly, Twist1 also directly binds to E-box on the Slug promoter, as a transcriptional activator to induce Slug transcription (49). Slug is essential for Twist1 to induce EMT. Knockdown of Slug completely blocks the ability of Twist1 to suppress E-cadherin transcription. Without Slug, Twist1 is not sufficient to induce cancer cell invasion and distant metastasis in mice.

There are two CSL consensus-binding sites in the human Slug promoter. Leong et al. (50) demonstrated that Slug is a direct target of Notch/C SL and Slug mediates the Notch-induced EMT. c-Myc induces transcriptional expression of Slug via Myb-binding sites in the promoter region and the first intron of the Slug gene (51). Slug can mediate the effect of oncogene c-Myc on migration, invasion and bone marrow homing of cancer cells.

In contrast to the above transcriptional factors, which induce the expression of Slug, the estrogen receptor-α directly represses transcription of Slug by the formation of a complex of ligand-activated estrogen receptor-α, histone deacetylase 1 and nuclear receptor co-repressor (N-CoR) that bound the Slug promoter in three half-site estrogen-response elements (52).

Posttranslational regulation of Slug

Slug and Snail are both labile proteins with a short half-life. Snail is degraded by proteasome after GSK-3β-dependent phosphorylation and β-TrCP-mediated ubiquitination. The phosphorylation by GSK-3β is counteracted by the action of the small C-terminal domain phosphatase, which stabilizes Snail in the nucleus (53). The tumor
necrosis factor-α/nuclear factor-kappaB pathway stabilizes Snail through the induction of COP9 signalosome 2 (CSN2), which blocks the phosphorylation and ubiquitination of Snail by disrupting its binding to GSK-3β and β-TrCP (54). Another mechanism to stabilize Snail is through the interaction with Lysyl oxidase-like 2 (LOXL-2), leading to blocking the interaction with GSK-3β (55). Growth factors are well known to inactivate GSK-3β through phosphorylation by the PI3K/Akt pathway. Canonical Wnt pathway leads to a PI3K-independent inhibition of GSK-3β. These signal pathways inactivate GSK-3β and induce nuclear accumulation of Snail, leading to EMT.

Our group found that Slug is also regulated by ubiquitination and degradation (27). Slug can bind wild-type p53 and MDM2 simultaneously. In NSCLC, wild-type p53 upregulates MDM2-ubiquitin ligase and forms a p53-MDM2-Slug complex that facilitates MDM2-mediated Slug degradation (Figure 3) and inhibits cancer cells invasion. In contrast, mutant p53 represses MDM2 expression, probably through interaction with p63 and p73 and inhibiting the transactivation of MDM2 and stabilizes Slug protein, which induces EMT. The N-terminal region (amino acids 21–66) of Slug is responsible for the binding of p53 and MDM2. The Slug-binding domain of p53 is located within its DNA-binding domain (residues 100–300). Both the DNA binding and transactivation activity of p53 is required for MDM2-mediated Slug degradation. Furthermore, in NSCLC tissue specimens, mutation of p53 correlates with low MDM2, high Slug and low E-cadherin expression and associated with poor overall survival and short metastasis-free survival of lung cancer patients. Recently, Lim et al. (56) also reported the physical interactions of p53/Slug and Snail/MDM2 and showed that p53 induces Snail degradation through MDM2-mediated ubiquitination in hepatocellular carcinoma cell lines.

**Slug confers resistance to EGFR tyrosine kinase inhibitor in NSCLC**

In addition to its effects on migration and metastasis, Slug confers the resistance to cell death induced by the withdrawal of survival factors. It regulates survival of cancer cells via direct or indirect transcriptional regulation of apoptosis-related genes (11). For instance, Slug exerts its protective role in DNA damage-mediated cell death by the direct repression of Puma, a key proapoptotic activator of p53 (57). Expression of Slug also contributes to the radioreistance through regulating stem cell factor–Kit-signaling pathway (46). Slug enhances chemoresistance of several types of cancer, including malignant mesothelioma and cholangiocarcinoma. Mancini et al. (58) have demonstrated that Slug overexpression contributes to apoptosis resistance in leukemic progenitors and Slug overexpression was involved in imatinib resistance of chronic myelocytic leukemia. Knockdown the expression of Slug increases the sensitivity of neuroblastoma cells to imatinib by downregulating Bcl-2 expression (59). These evidences suggest a crucial role of Slug in drug resistance.

Acquired resistance to EGFR TKIs is an important clinical problem in the field of target therapy for lung cancer. Yauch et al. (60) showed that E-cadherin expression can be a biomarker predicting clinical activity of the erlotinib in NSCLC patients. NSCLC cells become more aggressive and more resistant to gefitinib when undergone EMT. In contrast, ectopic expression of E-cadherin in NSCLC cells enhanced gefitinib sensitivity (61). These studies suggest EMT contributes to resistance of EGFR TKIs.

We are interested in studying the role of EMT in EGFR TKI resistance and found that the EMT regulator Slug contributes to the development of resistance to gefitinib in lung adenocarcinomas containing EGFR-activating mutations. The parental PC9 cell (gefitinib sensitive EGFR-mutant lung cancer cell) has epithelial phenotype, but the derived gefitinib-resistant cell line (PC9/geo) has mesenchymal phenotype and a higher invasive ability. We demonstrated that Slug but not other EMT regulators (Snail, Zeb1 or Twist) is overexpressed in PC9/geo than PC9 cells. Expression of Slug in PC9 induces EMT and also protects cells from gefitinib-induced apoptosis. Silencing of Slug in gefitinib-resistant cells restored gefitinib-induced apoptosis majorly through Bim upexpression and activation of caspase 9. In clinical samples, the expression of Slug is significantly higher in the cancer cells with resistance to EGFR TKIs than in the treatment-naive cancer cells (62).

Chung et al. used another EGFR-mutant lung cancer cell line (HCC827) model and also disclosed that EMT developed in acquired erlotinib resistance. The Slug and Twist were shown to be overexpressed in the resistant cells by microarray analysis (63).
Lung cancer cells with K-Ras mutations are resistant to EGFR TKI treatment. Wang et al. demonstrated that mutant Ras signaling causes an upregulation of the Slug compared with their isogenic counterparts with wild-type K-Ras in colorectal carcinoma cells (64). Slug is required for the survival of cells with mutant K-Ras but not otherwise isogenic cells harboring wild-type K-Ras. These data show that Slug as a possible target for the treatment of the broad spectrum of human cancers of epithelial origin with mutant Ras that have undergone EMT and are characterized by drug resistance.

Summary

In the past decade, the understanding of molecular mechanism of Slug in cancer progression has been greatly appreciated. Mounting evidence indicates that elevated expression of Slug promotes cancer cells in cancer progression has been greatly appreciated. Mounting evidence indicates that elevated expression of Slug promotes cancer cells to become motile and invasive by downregulating epithelial markers and upregulating mesenchymal markers. In addition to invasion and metastasis, Slug may play an important role in antiapoptosis and resistance to various kinds of therapy and maintenance of stem cell features.

Slug promotes invasion of lung cancer cells and overexpression of Slug is a biomarker to indicate poor overall survival in lung cancer patients. The degradation of Slug is controlled by p53 and MDM2. The expression of Slug confers resistance to EGFR TKI in lung cancer cells. Investigating the integrated and coordinated effort of molecular mechanisms of Slug may shed new light on the treatment of lung cancer. With the hope to suppress and intercept these processes, development of Slug-targeted drugs may be an effective approach for lung cancer therapy to revert the resistance to various treatments.

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