Chapter 2

The Crosstalk of c-MET with Related Receptor Tyrosine Kinases in Urothelial Bladder Cancer

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1. Introduction

RTKs are often deregulated in human malignancies, contributing to cancer development and progression. Deregulation of RTKs leads to aberrant receptor activity resulting in increased cell proliferation, inhibition of apoptosis, invasion, and enhanced tumor metastases. Because RTKs are membrane proteins, they represent attractive targets for cancer therapy, with a number of agents already approved for clinical use.

c-MET gene, located on chromosome 7q21-q31, encodes a single precursor protein and is post-transcriptionally digested and glycosylated. The mature receptor is composed of a 50 kDa extracellular α-chain and a transmembrane 140 kDa β-chain, which are linked by disulfide bonds [1]. The MET β-chain contains homologous domains that shared with other proteins, including a semaphorin (Sema) domain, a PSI domain (in plexins, semaphorins and integrins), four IPT repeats (in immunoglobulins, plexins and transcription factors), a transmembrane domain, a juxtamembrane domain, a tyrosine kinase domain and a carboxy-terminal tail region [2, 3].

The transforming property of c-MET was initially described in a human osteosarcoma cell line after chemically induced mutagenesis [4]. In this *in vitro* model, c-MET was found to be constitutively activated by translocation at (1;7), resulting in fused sequences of c-MET gene on chromosome 7q31 to the translocated promoter region on chromosome 1q25 [5]. Since then, support for c-MET signaling in human carcinogenesis comes from data of the cell culture [6], mice [7, 8], and sporadic and hereditary forms of renal carcinoma, where germline and somatic missense mutations were identified in c-MET's kinase domain [9, 10]. Furthermore, c-MET activity plays a significant role in promoting tumor invasion and metastasis

[11, 12]. In summary, c-MET regulates embryonic development and play important roles in the carcinogenesis, tumor progression, and a variety of cellular processes, including migration, proliferation, morphogenesis, and angiogenesis [13, 14].

HGF is predominantly secreted by mesenchymal cells, and c-MET is widely expressed on the surface of epithelial cancer cells [15]. Homodimerization of c-MET after binding to HGR leads to transphosphorylation of cytoplasmic tyrosine kinase domain at two specific sites (Y1234 and Y1235) and activation of down-stream signaling [16]. These events are essential during embryogenesis, and also play a critical role in normal tissue homeostasis of the hepatocytes, renal tubule cells, and myoblasts [17].

The phosphorylation of two tyrosine residues within COOH terminus (Y1349 and Y1356) is necessary and sufficient to mediate biological effects induced by of the c-MET activation [18]. These two residues recruit a number of adapter proteins, including Gab1, Grb2, Shc and the p85 subunit of phosphatidylinositol-3 kinase (PI3K) [17]. The involvement of diverse effectors allows the activation of different downstream pathways, including PI3K-Akt signaling, Ras-mitogen-activated protein kinase (MAPK) pathways, signal transducer and activator of transcription proteins (STATs) and the nuclear factor-kB (NF-kB) complex [17]. These signaling pathways are important during embryogenesis and in normal tissue homeostasis, such as cell proliferation, differentiation, transformation, migration and apoptosis.

Accumulating data have demonstrated that crosstalk between c-MET and other RTKs may contribute to tumor progression in some of human cancers [19-21]. As a result, evaluation of c-MET expression status and its crosstalk partners of RTKs may identify a subset of c-MET-positive cancer patients who may require co-targeting therapy.

2. Role of c-MET in human cancers

Overexpression of c-MET has been reported in different subtypes of lung cancer, including adenocarcinoma (67%), carcinoid (60%), large cell carcinoma (57%), squamous cell carcinoma (57%), and small cell lung cancer (SCLC) (25%) [22]. In terms of functional activity, positive staining could be demonstrated in the subtypes of adenocarcinoma (44%), large cell carcinoma (86%), squamous cell carcinoma (71%), carcinoid (40%), and SCLC (100%), respectively, using antibody for phospho-c-MET at the Y1003 (c-Cbl binding site). On the other hand, positive staining was observed in 33% of adenocarcinomas, 57% of large cell carcinoma and 50% of SCLCs using antibody for autophosphorylation of c-MET at the Y1230/1234/1235 site [22]. Importantly, missense germ-line mutations in the tyrosine kinase domain of c-MET have been described in patients with hereditary papillary renal carcinoma [9]; whereas sporadic mutations in the tyrosine kinase, juxtamembrane, or semaphorin domains of c-MET have been detected in gastric cancer, HCC and SCLCs [23-25]. Concerning biologic significance, activation of HGF/MET signalling pathway was shown to promote cell invasiveness *in vivo* and trigger tumor metastases through angiogenic pathways [26]. In addition, amplification of c-MET has been detected in the carcinomas of the stomach, esopha-

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gus, and colorectum, non–small-cell lung cancer, and glioblastoma, and is usually associated with acquired resistance to anticancer drugs-gefitinib or erlotinib [27-32].

Altered HGF secretion was reported in both solid and hematologic malignancies. Both tumor and mesenchymal cells are responsible for increased HGF production, leading to paracrine and/or autocrine activation of c-MET by HGF [33, 34, 35]. The enhanced c-MET signaling is tumorigenic and could induce tumor metastasis in athymic nude mice [11]. As a result, HGF and/or c-MET overexpression were suggested to be a prognostic biomarker for cancer patients [36-38], although not all studies got the same conclusion [39, 40].

3. Role of c-MET-related RTKs in cancer

In addition to c-MET, coexpression of c-MET and related RTKs was shown to have prognostic relevance in some human cancers [41-45]. For example, RON and MET were overexpressed in 55 % and 56 % of human ovarian cancer, respectively, and 42 % of them have coexpression of RON and MET ($P < 0.001$) [41]. Coexpression of RON/MET was associated with more aggressive phenotype of node-negative breast cancer patients. The 10-year disease-free survival in RON-/MET- breast cancer is significantly higher than that of RON +/MET+ group (79.3 % vs. 11.8 %) [42]. Furthermore, both MET and EGF family receptors are overexpressed in different human cancers. Coexpression of c-MET and HER2 were observed in breast cancer and cholangiocarcinoma, and is usually associated with poor prognosis [43]. Similarly, coexpression of c-MET and HER2 could be detected in gastric cancer, and activation of c-MET further increases the resistance to EGFR inhibitor-Lapatinib [44, 45].

4. Overexpression of c-MET as a prognostic indicator for urothelial carcinoma of the bladder

High levels of c-MET expression have been correlated with metastatic progression of tumors and poor survival in patients with carcinomas of the breast, extrahepatic biliary tract, stomach, endometrum, liver, colorectum, and kidney [46-53]. c-MET was also reported to play a positive role in the tumorigenesis of human bladder [54, 55]. For example, expression of c-met mRNA tended to positively correlate with differentiation of cancer cell lines in the absence of point mutation [55]. Expression of Met was positively associated with histologic grade, stage classification, tumor size, and nodular tumor growth ($P < 0.05$, respectively), and is an independent indicators for poor long-term survival ($P = 0.04$) [55]. Furthermore, pY1349 c-Met was found to be a prognostic marker in predicting metastasis-free and survival of bladder cancer in a large cohort study of 133 non-metastatic specimens of bladder cancer [56]. Taken together, c-met proto-oncogene plays an important role in the progression of bladder carcinogenesis. Evaluation of Met expression could identify a subset of bladder cancer patients who may require a more intensive treatment targeting strategy.

5. The signaling pathway of c-MET

5.1. c-MET-related signaling pathways

The signaling for growth depends on RAS-MAPK signaling pathway and plays an essential role in morphogenesis and epithelial-to-mesenchymal transition that results from loss of intracellular adhesion via cadherins, focal adhesion kinase, and integrins, in association with alteration of cell shape [57]. Activation of HGF/c-MET axis prevents cell apoptosis through PI3 kinase and subsequent Akt signaling events [58-60]. The crosstalk of c-MET and PI3K-Akt pathway with RAS-MAPK pathway has been implicated in patient survival [61, 62].

5.2. Crosstalk with other membrane proteins or receptor tyrosine kinases

c-MET is known to interact with other membrane proteins on the cell surface [63], including laminin receptor-α6β4 integrin, semaphorin receptors of plexin B family, and v6 splice variant of hyaluronan receptor-CD44 [63, 64]. The crosstalk between c-MET and membrane proteins modulates the activation of both c-MET and its partners and allows for integration of signals present in the extracellular environment [65]. Crosstalk between c-MET and epidermal growth factor receptor (EGFR) has been implicated in several biological systems [66]. Furthermore, the crosstalk of c-MET with other RTKs regulates different physiological and/or pathological situations additively or synergistically. This interaction promotes transphosphorylation of kinase of each other by directly binding or transducing through their downstream signaling pathways indirectly. We review the potential role of c-MET and related RTKs, including RON, EGFR, Axl and platelet derived growth factor receptor-alpha (PDGFR-α), in urothelial carcinoma of the bladder, either independently or in combination in vivo (crosstalk) (Fig. 1).

6. RON

Recepteur d'Origine Nantais (RON) is a MET RTK subfamily member. Its ligand is macrophage-stimulating protein (MSP) which is expressed by renal tubular cells [67-69]. Activation of RON induces apoptotic resistance, superoxide anion production, and phagocytosis of macrophages through different molecules and related signaling pathways, *i.e.* Src, ERK, p38 and PI3K/AKT, which are related to tumorigenesis [70-72]. The crosstalk between c-MET and RON has been reported in different *in vitro* experimental models, and has been confirmed in the human cancers of the liver, ovary, breast and urinary bladder.

Heterodimerization plays a pivotal role in initiating the crosstalk and activation of related signal transduction pathways. Follenzi *et al.*, showed that activated c-MET directly cross-phosphorylates RON, and c-MET/RON heterodimmer activates the catalytic region of c-MET at Y1234/Y1235 and RON at Y1238/Y1239, respectively (Figure 1A). Moreover, both signal transducer docking sites of c-MET at Y1349/Y1356 and RON at Y1353/Y1360 are generated for downstream signaling molecules. Mutation of RON suppresses the transforming

phenotype induced by c-MET [73]. In contrast, RON is specifically trans-phosphorylated by MET, but not by EGFR or HER2; and MET-specific kinase inhibitors also suppress the phosphorylation of RON [41]. In addition to HGF, other cytokines, including EGF, interleukin-1, interleukin-6 and tumor necrosis factor alpha (TNF- α), are able to induce the expression of both MET and RON in HCC, suggesting that MET and RON are regulated by similar cytokine networks [42].

Overexpression of RON increases the growth, motility and anti-apoptosis of cancer cells *in vitro* [74]. In primary human bladder cancer, overexpression of RON is detected in 32.8 % of the tumors, and 23.3 % of these positive tumors also showed high levels of MET expression as well. In addition, co-expressed RON and MET was significantly associated with decreased overall survival (P= 0.005) or metastasis-free survival (P = 0.01) [74]. Overexpression of RON and MET seems to be a universal event in uroepithelial cells [75]. These data support the potential significance of RON/MET crosstalk, and the occurrence as a biomarker in selection of appropriate treatment strategy for cancer patients.

7. EGFR

The EGFR (HER1 or ErbB-1 in humans) belongs to RTKs of ErbB family which consists of EGFR, HER2/c-neu (ErbB-2), Her3 (ErbB-3) and Her4 (ErbB-4) four subfamily members. EGF is the ligand of EGFR [76]. EGFR signaling pathway participates in the growth and progression of urothelial cancers. Mutations affecting EGFR expression or activity may initiate a cascade of events leading to autonomous cell proliferation, migration, invasion and apoptosis inhibition, leading to tumor progression [77, 78].

The crosstalk between EGFR and MET has been reported during development and tumorigenesis. Cooperative action of MET and EGFR controls the number of nephron (the functional unit of the kidney) and maintains the duct morphology during kidney development [79]. Three underlying mechanisms of crosstalk between MET and RTK have been reported: (1) Trans-phophorylation and activation: Both RON and EGFR can bind with MET, and form heterodimeric receptor complex to activate both tyrosine kinases through trans-phosphorylation. The crosstalk of EGFR or RON with c-MET was confirmed by co-immunopreciptation assay (Figure 1A) [66, 80]; (2) c-MET activates EGFR through transcriptional activation of the ligand EGF: c-MET increases the production of EGF through Ras/Erk signaling-mediated promoter activation. EGF then is transported out of the cell to bind with EGFR in an autocrine or paracrine manner (Figure 1B) [81]; (3) EGFR activates c-MET through Ras/Erk MAPK signaling pathway to activate metalloproteinasea (TIMP)-3 which then cleavages the c-MET at ectodomain (Figure 1C). The truncated c-MET protein promotes the proliferation and cell transformation [82, 83].

Naik *et al*., reported that positive staining for EGFR, HER2 and EGF could be detected in 23%, 60% and 47% of primary bladder cancer specimens, respectively [84]. The HER2/neu gene amplification and protein overexpression were demonstrated in high grade, invasive bladder cancer [85]. Overexpression of EGFR/ERBB2 correlates with higher tumor grading/

stage and poorer clinical outcome in bladder cancer patients [86, 87]. These evidences support the selection of EGFR as a molecular marker for diagnosis and/or prognosis of bladder carcinoma [88, 89]. Recently, EGFR inhibitor Iressa has shown a strong protective efficacy through cell cycle regulation in carcinogen induced rat bladder cancer model [90]. Therefore, EGFR, vascular endothelial growth factor (VEGF), mTOR and their-related signaling molecules are excellent therapeutic targets, in combination with cytotoxic chemotherapy, in the design of bladder cancer treatment [91]. Overexpression of RON and EGFR, as well as their crosstalk, has been reported in various human bladder cancer cell lines [74, 92]. It is noteworthy to clarify the potential of RTK co-targeting in the application of EGFR inhibitors in bladder cancer therapy.

8. AXL

AXL is a member of TAM RTK family, including AXL, Tyro3 and Merk. It has a unique structure of extracellular region that juxtaposes IgL and FNIII repeats [93, 94]. The protein S and Gas6 (growth-arrest-specific protein 6) are ligands for TAM receptor [95]. Gas6/AXL controls diverse cellular functions, including proliferation, survival, migration and anti-inflammation through different signaling pathways [96]. Gas6/AXL stimulates cell proliferation through MEK/Erk signaling pathway [97]. Gas6/AXL activates the PI3K/AKT and p38 signaling pathways to enhance the cell survival and migration, respectively [98, 99]. Gas6/AXL also suppresses Toll-like receptor and cytokine receptor signaling in innate immune cells through regulation of STAT1 [100, 101]. Overexpression of AXL has been reported in mesothelioma, NSCLC, breast carcinoma, and bladder cancer [20, 96, 102]. However, AXL can be activated by a ligand-independent manner when AXL interacts with adjacent cells in which AXL was overexpressed, suggesting that overexpression of AXL may be activated *per se* through auto-activation [103].

9. PDGFR-α

PDGF, a ligand of PDGFR-α and -β, results in auto-phosphorylation and signaling transduction of PDGFR [104]. PDGF/PDGFR signaling is involved in the development of various tissues, and is essential for epithelial-mesenchymal interaction during metamorphic skin remodeling, mesenchymal cell migration and proliferation [105]. In PDGF-α knock-out mice, neural tube and brain are abnormally accompanied by defect of the nervous system [106]. PDGF contributes to the development and progression of cancer by autocrine or paracrine signaling, and further promotes tumorigenesis through proliferation, angiogenesis and tumor stromal interaction [107].

In huamn uroepithelial cells, c-MET is frequently co-expressed with AXL, PDGFR-α, discoidin domain receptor tyrosine kinase 2 (DDR2), and/or insulin-like growth factor I receptor (IGF1R). Overexpression of AXL and PDGFR-α has been detected in various human cancers,

and is associated with invasiveness and/or metastasis of carcinoma of the breast, kidney and bladder [20, 108, 109]. Overexpression of c-MET/PDGFR-α was demonstrated in all of 9 human bladder cancer cell lines tested [110]. We identified that both AXL and PDGFR may be c-MET related RTKs in a cDNA microarray analysis [20]. In sharp contrast to crosstalk between c-MET and RON or EGFR, both AXL and PDGFR do not directly bind with c-MET, and is transcriptionally activated by mitogen activated protein kinase/extracellular signal-regulated kinase (MEK/Erk) signaling pathway (Figure 1B) [20].

9.1. The relationship among environmental carcinogens, c-MET and RTKs

The environmental carcinogens, mainly from cigarette smoking, play important roles in the bladder cancer development, specifically urothelial carcinoma [111, 112]. Cigar smoking, pipe smoking, and secondhand smoke are implicated as risk factors for urothelial carcinoma. The incidence of urothelial cancer is approximately 4 times higher in smokers compared with non-smokers [113]. It is also reported that 50 % of all bladder cancers in men and 30 % in women are due to cigarette smoking [114]. All these evidences suggest that smoking is the most important risk factor for bladder cancer development. Genetic damage is the major cause of smoking-related cancer induction by which normal cellular pathways are altered to trigger cell growth and induce tumor formation [115]. In addition to bladder cancer, lung cancer formation is also induced by genetic modifications mostly caused by tobacco smoking [116]. Genetic mutations and amplifications in RTK related signaling, such as c-MET, EGFR, ErbB2, c-Kit, VEGFR, PI3K, and PTEN, contribute to lung cancer development by escaping from normal growth control and transforming into a malignant phenotype [117, 118]. Several autocrine loops, including stem cell factor (SCF)/c-Kit, IGF-I/IGF-IR, and HGF/c-MET, lead to the activation of PI3K/Akt signaling pathway and promote the cell growth, survival, and chemotherapy resistance in lung cancer. During lung cancer development, RTKs and their downstream effectors are selectively up-regulated. It is intriguing to clarify whether crosstalk of c-MET with RTKs in bladder cancer is also related to smoking. Altogether, it is noteworthy to clarify the relationship among smoking, c-MET, RTKs and bladder cancer development in the further study.

10. Conclusion and future direction

Overexpression of multiple RTKs has been reported in many human cancers, including bladder cancer. Cross-connection among individual signaling pathway activated by each RTK forms the signaling networks, which may complicate the development of anticancer strategies. With discussion above, more attention is focused to identify the prognostic targets and development of the targeted therapy for bladder cancer. In this review, we describe the current knowledge of interaction between c-MET and related RTKs. On the basis of complicated signaling network, the multimodal strategies should include systemic chemo- or biological therapies in combination with surgery and/or radiation applicable for invasive/metastatic bladder cancers [91]. Diverse therapeutic strategies have been developed to inhibit the HGF/c-MET signaling, including anti-HGF antibodies, HGF antagonists, anti-c-MET

antibodies, and c-MET tyrosine kinase inhibitors. The c-MET pathway inhibitors have been reported to block the activities of other related tyrosine kinases. For example, MP470, a RAD51 inhibitor, suppresses the activity of c-MET and PDGFR [119]. MK-2461 suppresses the activity of both c-MET and RON [120]. BMS-777607 inhibits the activity of c-MET, RON and AXL [119, 121]. Furthermore, Foretinib, an oral multi-kinase inhibitor, inhibits the c-MET activity and its related RTKs (RON, EGFR, AXL and PDGFR) [122, 123]. Altogether, these inhibitors have potential to be used for bladder cancer therapy in the future. Cooperative action of c-MET with RON, EGFR, AXL and PDGFR-α has been reported to play important roles in bladder cancer progression, and thus deserves further investigation as the co-targeting therapy candidates. Understanding of the mechanisms underlying crosstalk of c-MET with RTKs is indispensible in the development of novel strategies against urothelial bladder cancer.

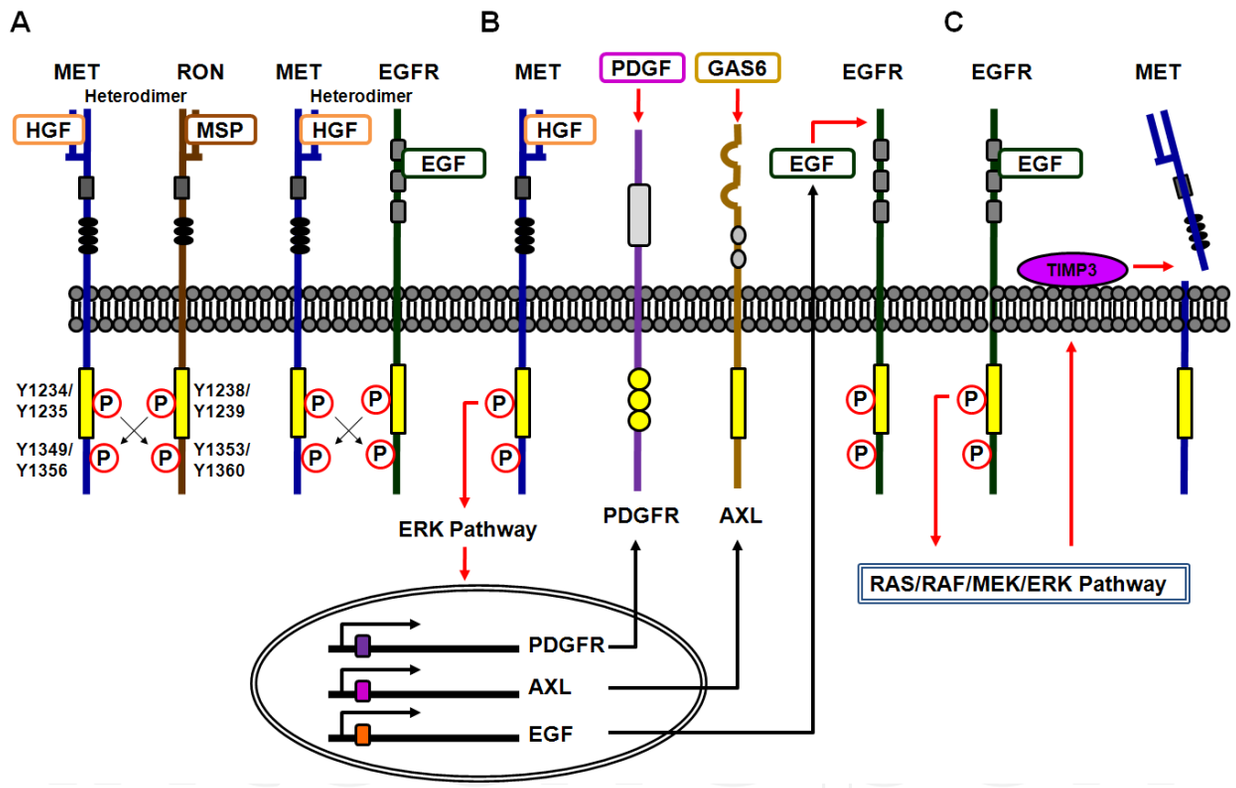

Figure 1. The crosstalk between c-MET and related receptor tyrosine kinases

A. Trans-phosphorylation by other RTKs. The ligands, such as HGF, MSP and EGF, activate the MET, RON and EGFR, respectively, through tyrosine phosphorylation. The activated receptors (MET, RON or EGFR) cross talk with other RTKs through trans-phosphorylation. B. Activation of other RTKs by c-MET through transcriptional regulation. HGF activates the c-MET and downstream Ras/Erk signaling pathway through tyrosine phosphorylation. Expression of PDGFR, AXL and EGF was enhanced through transcriptional regulation. Overexpression of PDGFR and AXL enhances their binding with cognate ligands (PDGF

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and GAS6) and activation of their downstream signaling pathways. Overexpression of EGF further enhances the activity of EGFR in an autocrine or paracrine manner. C. Metalloproteinase cleavage regulates c-MET activation. EGF induces the phosphorylation of EGFR and activation of Ras/Erk signaling, and promotes the MET ectodomain shedding by cleavage of TIMP3 sensitive metalloproteinase.

Abbreviations

DDR2 (Discoidin domain receptor tyrosine kinase 2)

EGF (Epidermal growth factor)

EGFR (Epidermal growth factor receptor)

HCC (Hepatocellular carcinoma)

HGF (Hepatocyte growth factor)

HGFR (Hepatocyte growth factor receptor)

IGF1R (Insulin-like Growth Factor I Receptor)

IL-1 (Interleukin-1)

IL-6 (Interleukin-6)

MAPK (Mitogen-activated protein kinase)

MSP (Macrophage-stimulating protein)

NF-κB (Nuclear factor-κB)

PI3K (Phosphatidylinositol-3 kinase)

PDGFR (Platelet-derived growth factor receptor)

PTKs (Protein tyrosine kinases)

RON (Recepteur d'Origine Nantais)

RTKs (Receptor tyrosine kinases)

SCLCs (Small cell lung cancer cells)

STATs (Signal transducer and activator of transcription proteins)

TCC (Transitional cell carcinoma)

TIMPs (Tissue inhibitors of metalloproteinases)

TNF- α (Tumor necrosis factor alpha)

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