Epithelial-mesenchymal transition in cancer: Role of the IL-8/IL-8R axis (Review)

ZHIWEI ZHAO[1*], SHICHAO WANG[1,2*], YINGBO LIN[3], YALI MIAO[4], YE ZENG[1], YONGMEI NIE[2], PENG GUO[1], GUANGYAO JIANG[5] and JIANG WU[1,2]

[1]West China Medical Center, Sichuan University, Chengdu, Sichuan 610041; [2]School of Basic Medicine, Xinjiang Medical University, Urumqi, Xinjiang 830011, P.R. China; [3]Department of Oncology and Pathology, Karolinska Institute, Cancer Centre Karolinska, SE-171 76 Stockholm, Sweden; [4]West China Second University Hospital, Sichuan University; [5]Outpatient Building, West China Fourth Hospital, Sichuan University, Chengdu, Sichuan 610041, P.R. China

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Abstract. Epithelial-mesenchymal transition (EMT) is a biological process that is associated with cancer metastasis and invasion. In cancer, EMT promotes cell motility, invasion and distant metastasis. Interleukin (IL)-8 is highly expressed in tumors and may induce EMT. The IL-8/IL-8R axis has a vital role in EMT in carcinoma, which is regulated by several signaling pathways, including the transforming growth factor β-spleen associated tyrosine kinase/Src-AKT/extracellular signal-regulated kinase, p38/Jun N-terminal kinase-activating transcription factor-2, phosphoinositide 3-kinase/AKT, nuclear factor-κB and Wnt signaling pathways. Blocking the IL-8/IL-8R signaling pathway may be a novel strategy to reduce metastasis and improve patient survival rates. This review will cover IL-8-IL-8R signaling pathway in tumor epithelial-mesenchymal transition.

Contents

Correspondence to: Dr Jiang Wu, West China Medical Center, Sichuan University, 17 Section 3 Renmin South Road, Chengdu, Sichuan 610041, P.R. China
E-mail: jw@scu.edu.cn

Dr Guangyao Jiang, Outpatient Building, West China Fourth Hospital, Sichuan University, 18 3rd Section, Renmin Nanlu Road, Chengdu, Sichuan 610041, P.R. China
E-mail: 502422662@qq.com

*Contributed equally

Abbreviations: EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition; IL-6, interleukin-6; IL-8, interleukin-8; VEGF, vascular endothelial growth factor; TGFβ, transforming growth factor β; MMP, matrix metalloprotease; TNFα, tumor necrosis factor-α; PTEN, phosphatase and tensin homolog; PI3K, phosphatidyl inositol 3-kinase; JNK, Jun N-terminal kinase; ATF-2, activating transcription factor-2; NF-κB, nuclear factor-κB

Key words: interleukin-8, C-X-C motif chemokine receptor 1, C-X-C motif chemokine receptor 2, epithelial-mesenchymal transition, metastasis, prognosis

1. Introduction

Epithelial-mesenchymal transition (EMT) is a crucial process that promotes cell motility, wound healing, tissue regeneration, fibrogenesis and tumor metastasis (1). EMT has been reported to be implicated in multiple steps of several developmental processes involved in tumor progression (2). It can lead to a loss of cell-cell junctions in tumor cells and a decrease in the expression of E-cadherin in the epithelium (3). EMT can also lead to an increase in expression of vimentin (4), a marker of mesenchymal-derived cells. Notably, EMT facilitates cancer cells to initiate distant metastasis and is able to increase motility of cancer cells at the leading tumor edge and cell invasion (5). EMT is an important process in cancer cell migration and invasion. Thus, manipulating the EMT process *in vivo* may be a useful strategy to prevent tumor metastasis. Notably, the cytokine interleukin (IL-8) is important for EMT, and it is highly expressed in the cancer microenvironment (6). Although IL-8 has a pro-inflammatory role, cancer cells are able to evade host immune defense mechanisms (7). The chemokine IL-8 is secreted by fibroblasts, endothelial and immune cells. IL-8 expression is closely associated with cancer (6). Furthermore, the involvement of IL-8 in angiogenesis (8), and cancer cell invasion and metastasis has been previously

reported (9). A previous study has indicated that in cancer patients, increased expression of IL-8 in tumor tissues may be associated with EMT (10).

2. EMT and tumorigenesis

It has been previously demonstrated that EMT in tumors can be induced by the secretion of specific factors, including IL-6, IL-8, vascular endothelial growth factor (VEGF), transforming growth factor β (TGFβ), SNAIL, matrix metalloprotease (MMP), tumor necrosis factor α (TNFα) and TWIST (2,11-14). The secretion of pro-inflammatory cytokines (TNFα and IL-6), chemokine IL-8 and growth factors (TGFβ and VEGF) has also been reported in A549 cells, and may have important associations with cancer (2). IL-8 is able to promote cell motility, cancer metastasis and cell invasion (15) following EMT. Tumor cells are able to secrete IL-8 via an autocrine mechanism, which can promote EMT. A previous study revealed that knockdown of IL-8 suppressed the level of phosphorylated AKT in S18 cells (4). IL-8 knockdown may lead to upregulation of the epithelial marker E-cadherin as well as downregulation of the mesenchymal markers vimentin and fibronectin (4). Additionally, IL-8 has been closely associated with EMT (16) and may promote tumor metastasis and cell invasion.

Cancer cells undergo a reversal of EMT, termed mesenchymal-epithelial transition (MET) (17), to invade multiple organs until they migrate to their final destination for colonization. In contrast to EMT, MET is associated with colonization at the metastatic site (18). Once mesenchymal cells reach their destination, the cell phenotype changes to an epithelial phenotype via MET to colonize the organs (19). These changes involve the loss of cell-cell junctions, and cells acquire motility and invasive capabilities (3). Cancer cells must undergo the MET process to migrate to their destination. Furthermore, MET is closely associated with cancer cells, which may acquire a second colonization (otherwise termed metastasis).

A vital characteristic of cancer metastasis is induction of EMT, which is associated with interaction with the extracellular matrix (20). In the extracellular matrix, the role of the cellular factors is to communicate with the intracellular matrix and a number of these factors have been reported to be associated with EMT, including IL-6, IL-8, VEGF, TGFβ, SNAIL, MMP, TNFα and TWIST. The mechanism underlying the interaction between these factors and EMT is complicated. Notably, the dramatic phenotypic change in EMT is coupled with motility and metastasis (21). Understanding the underlying mechanisms involved in normal morphogenesis and designing treatment strategies to reduce EMT is vital (17).

During the EMT process, cancer cells lose cell polarity and adhesion. The cancer cells acquire increased migratory and invasive capabilities. The EMT process is regulated by several signaling pathways (22,23), which lead to cancer cell migration and invasion. In breast cancer, cancer cells penetrate and transmigrate into the basement membrane barriers, causing angiogenesis and invasion (24) into the circulation. It has been observed that when EMT was activated by epithelial cells in the epithelium constituent of carcinosarcomas, the cells exhibited epithelial and mesenchymal phenotype (25). Furthermore, the study was able to directly assess epithelial plasticity and EMT reversal.

The EMT in carcinoma allows cancer cells to gain increased motility and invasiveness. EMT involves a change in phenotype from epithelial to mesenchymal, thereby allowing cells to invade and colonize nearby tissues. Disseminated cancer cells need to transmigrate the epithelial status during the period of metastatic colonization. These cancer cells have high proliferative potential, allowing the formation of secondary tumors. The normal cellular junctions consist of specific epithelial splicing and epigenetic mechanisms to maintain epithelial homeostasis (25). In summary, EMT is regulated by many factors in the extracellular and intracellular matrix. It has a vital role in regulating cancer cell motility, metastasis, invasion, reverse transition and establishment of a secondary tumor.

3. Regulation of EMT

Transforming growth factor β (TGFβ). E-cadherin and vimentin are markers of epithelial and mesenchymal cells, respectively (6). It has been previously demonstrated in A549 human lung carcinoma cell line that a number of cytokines are associated with EMT, including IL-8, VEGF, TGFβ and TNFα (26). It has also been reported that TGFβ is able to induce EMT in multiple cell lines via activation of the E-cadherin repressor (19). Bone morphogenetic protein 7 is a member of the transforming growth factor-β family and serves an important role in kidney development (27). TGFβ has an important role in cell migration and is a tumor-promoting factor. It has also been reported that TGFβ is able to upregulate MMP expression in A549 lung cancer cells. TGFβ is able to induce EMT to promote metastasis (28). Other studies have also revealed that TGFβ is able to induce EMT by upregulating the expression of zinc finger E-box binding homeobox 1 (ZEB1) in renal tubular epithelial cells (29). Epstein-Barr virus-induced TGFβ-spleen associated tyrosine kinase (Syk)/Src AKT/extracellular signal-regulated kinase (ERK) signaling may also be able to promote malignant and invasive potential in human corneal epithelial cells by inducing EMT, and thus may be an effective therapeutic target for the treatment of ocular disease (30). Therefore, the TGFβ signaling pathway may have an important role in advancing tumor progression and metastasis.

MMPs. The role of MMPs in cell invasion and tumor metastasis has been well established. MMPs are able to remodel the cell cytoskeleton in tumor cells to induce EMT. It has been demonstrated that MMP-2 is able to facilitate tumor metastasis and cell invasion. MMP-2 may therefore be a sensitive predictor of lung tumor progression (31). Furthermore, MMPs released by tumor-associated neutrophils, may facilitate tumor progression, leading to cytoskeleton remodeling and promotion of tumor metastasis (32). Therefore, MMPs may have an important role in tumor metastasis and thus may provide a novel target for cancer therapeutics.

SNAIL. Previous studies have suggested that SNAIL has an important role in EMT in cancer cells, particularly in epithelial tumor cells (33,34). SNAIL is able to reduce the number of cell-cell junctions in cancer tissue and alter the cell

cytoskeleton (35). SNAIL, vimentin and TWIST are upregulated in human hepatic cells, and these changes are associated with EMT (13). It has also been demonstrated that SNAIL is able to directly activate IL-8 via binding with the IL-8 receptor (36). EMT is promoted by the expression of Notch, which leads to E-cadherin activation via SNAIL (37-39). Additionally, a previous study suggested that high expression of Notch leads to EMT (40). Notably, SNAIL-induced EMT can be eliminated by anti-IL-8 receptor B neutralizing antibodies, suggesting that IL-8 has an effective role in mediating SNAIL-induced EMT and in advancing carcinoma development (41). Targeting IL-8 may provide a novel strategy for the treatment of cancer. Previous studies have also revealed close associations between EMT and SNAIL in tumor metastasis (42-44). ZEB1, TWIST and SNAIL have also been implicated in carcinoma via the phosphatidyl inositol 3-kinase (PI3K) (45,46) and glycogen synthase kinase 3β signaling pathways (42).

VEGF. A previous study demonstrated that IL-6 (47) and VEGF (48) cytokines are secreted by neoplastic cells undergoing EMT. Furthermore, it has been reported that these two cytokines can co-operate to induce EMT (2) in prostate intraepithelial neoplasia-like cells via an autocrine loop (48). MCF7 breast cancer cells are also able to undergo EMT via TWIST overexpression, and this was associated with increased synthesis of the angiogenic factor VEGF (49). VEGF has an important role in angiogenesis, thus VEGF and microvessel density may be useful biomarkers for predicting outcomes for colorectal cancer patients (50). In summary, VEGF has a vital role in cancer progression by promoting EMT via angiogenesis.

IL-8 and IL-8R. It has been reported that the levels of IL-8 and IL-8 receptor type 1 (CXCR1) and 2 (CXCR2) increase due to the inhibition of phosphatase and tensin homolog (PTEN) in prostate carcinoma (51,52). Overexpression of CXCR1 and CXCR2 has been detected in prostate cancer tissue and promotes tumor progression by contributing to cell proliferation and angiogenesis (52). Furthermore, overexpression of IL-8 and CXCR2 has been closely associated with tumor progression and metastasis in esophageal squamous cell carcinoma (53). IL-8 may induce tumor progression, metastasis and angiogenesis via CXCR2 (54). The role of microRNA-200 in inhibiting angiogenesis via downregulation of IL-8 and CXCR1 in ovarian cancer cell lines has also been reported (55). The expression of CXCR1 and CXCR2 was not affected by chemotherapy in breast cancer where there was increased expression of IL-8, thus CXCR may be desensitized prior to and following chemotherapy (56). IL-8 and CXCL1 can affect angiogenesis via endothelial CXCR2 receptors (57). In summary, IL-8 and its receptors are closely associated with tumor progression, angiogenesis and metastasis, which may promote EMT in tumor cells.

Blocking IL-8 signaling is a potential strategy to inhibit EMT and thus reduce tumor progression, metastasis and angiogenesis, which may lead to improvements in 5-year disease-free survival and overall survival rates (11). There is increased expression of IL-8 in the tumor microenvironment. IL-8 secretion may be mediated via fibroblasts, endothelial cells and immune cells, which may promote EMT in cancer (11).

4. Signaling pathways associated with IL-8

The p38/Jun N-terminal kinase (JNK)-activating transcription factor-2 (ATF-2) signaling pathway serves a vital role in cell invasion and EMT, which is mediated by autocrine IL-8 in A549 lung cancer cells (2). Previous studies have demonstrated that ATF-2 is able to promote tumorigenesis, and has been observed to be upregulated in various types of carcinoma, including mouse skin tumors (58), human neuroblastoma (59) and prostatic neoplasia (60). Notably, ATF-2 can be activated by IL-8 transcription (61). IL-8 is able to induce the JNK/p38-ATF-2 signaling pathway and promote invasion in A549 lung cancer cells (2). Furthermore, ATF-2 is a potential therapeutic target for inhibiting tumor metastasis (2).

The PI3K/AKT signaling pathway has an important role in promoting cell proliferation and survival. Inhibiting the AKT signaling pathway can lead to a decrease in cell motility, which is induced by IL-8 stimulation. AKT is an important signaling pathway for modulating IL-8-induced cell motility and invasion (62). PTEN can result in dysregulation of the PI3K/AKT signaling axis in pancreatic ductal adenocarcinoma (63). Furthermore, loss of PTEN induces the upregulation of IL-8 signaling in prostate carcinoma (51). A previous study has demonstrated that there is high expression of phosphorylated AKT when cells are treated with recombinant human netrin-1 in a human hepatocellular carcinoma cell line (64). The role of AKT in activating nuclear factor (NF)-κB signaling has been well established (65). Additionally, the NF-κB signaling pathway has been associated with IL-8, which has an important function in regulating tumor invasion (66). Therefore, cell motility can be promoted by IL-8 via the AKT signaling pathway. It has also been reported that AKT signaling can lead to EMT in breast cancer cells (67).

Several signaling pathways have been associated with EMT, including the PI3K and Wnt signaling pathways (68). The Wnt signaling pathway can be activated via overexpression of IL-8 (69). Previous studies have also indicated that the Wnt signaling pathway serves an important role in mediating cell-cell adhesion and beta-catenin self-phosphorylation in tumor cells (70,71). Therefore, the PI3K/AKT, NF-κB and Wnt signaling pathways are closely associated with IL-8 and EMT (62,72). The signaling pathways and factors associated with EMT in tumor cell proliferation, metastasis, invasion and angiogenesis are displayed in Table I (11,12,14,73-83).

5. Effects of IL-8 on EMT in the tumor microenvironment

The cytokine IL-8 is a potential therapeutic target for treating inflammatory diseases (84,85) and inhibiting carcinoma angiogenesis (86). A previous study has demonstrated that IL-8 mRNA expression has a role in EMT and tumor progression (87). In prostate carcinoma cells, increased expression of IL-8 promotes cancer progression, but the expression of E-cadherin is reduced. In addition, IL-8 has an important role in cancer cell proliferation, invasion and metastasis (62). Cancer cells secrete IL-8, and promote angiogenesis, cell proliferation, metastasis and invasion (62). Under hypoxic conditions, cancer cells are able to secrete IL-8 (78). Additionally, the

Table I. Epithelial-mesenchymal transition in tumors is closely associated with several cytokines.

Factors	Associated signaling pathways	Associations with tumor
IL-8	p38/JNK-ATF-2 (2) PI3K/AKT (73) NF-κB (66,74) Wnt (69)	Induction of EMT (11) Angiogenesis (75) Promotion of cancer cell proliferation, invasion and metastasis (76) Lung cancer risk marker (77) IL-8 secretion by tumor cells (78) Induced by TGFβ or SNAIL overexpression (36,79)
TGFβ	Syk/Src-AKT/ERK (30)	Induction of EMT (12) Inhibition of E-cadherin (19) Tumor cell migration (30)
MMP	NF-κB (80)	Induction of EMT (14) Tumor cell metastasis (31) Cytoskeleton remodeling (32)
SNAIL	PI3K (46) GSK 3β (42)	EMT progression (25) Changes in cytoskeleton (81) Activation of IL-8 (36)
VEGF	PI3K/AKT (82)	Promotion of EMT (2) Angiogenesis (83)

ATF-2, activating transcription factor-2; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; GSK 3β, glycogen synthase kinase 3β; IL-8, interleukin-8; PI3K, phosphatidyl inositol 3-kinase; JNK, Jun N-terminal kinase; NF-κB, nuclear factor-κB; MMP, matrix metalloprotease; Syk, spleen associated tyrosine kinase; TGFβ, transforming growth factor β; VEGFR, vascular endothelial growth factor receptor.

expression of IL-8 in various types of carcinoma tissues, including breast, colon, gastric, lung and ovarian cancer has also been reported (88). IL-8 secretion is induced by TGFβ stimulation (79) and SNAIL overexpression (36), which can lead to EMT in colorectal cancer cells.

IL-8 can induce and maintain the mesenchymal phenotype to facilitate metastatic carcinoma progression. Previous studies have reported that IL-8 secreted by the tumor stroma is able to induce cell proliferation (89), migration, invasion and EMT (11,79,90). These factors may enable cancer cells to evade apoptosis, and thus promote cell survival (91). IL-8 is also able to induce angiogenesis (92-94), and facilitate cancer progression and metastasis in melanoma and ovarian cancer (95,96). Increased serum levels of IL-8 are associated with the risk of lung cancer, which precedes diagnosis (77). Furthermore, a previous study has demonstrated that the blockade of CXCR1 with a CXCR1-specific blocking antibody or repertaxin, the small-molecule inhibitor of IL-8, was able to inhibit angiogenesis, invasion, metastasis and tumor progression in xenograft tumor models (97,98). IL-8 is able to promote cell migration, invasion, and metastasis (72). IL-8 also serves a vital role in EMT and can regulate the tumor microenvironment (6). In summary, there are close associations between IL-8 and EMT in cancer. A list of the signaling pathways and factors associated with IL-8, including PI3K/AKT, NF-κB, p38/ATF-2, JNK, MMP and Wnt signaling pathways are displayed in Fig. 1.

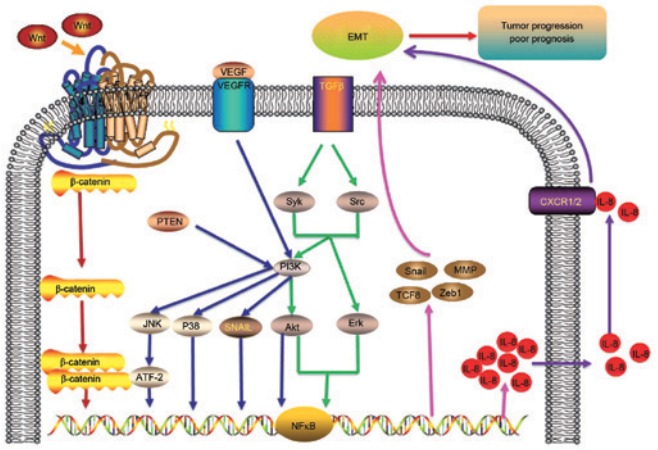

Figure 1. IL-8/IL-8R axis. IL-8 is able to induce EMT and promote tumor progression. There are important associations between IL-8/IL-8R and EMT in cancer patients. The IL-8/IL-8R signaling pathway is able to induce IL-8 overexpression, which is closely correlated with poor prognosis. ATF-2, activating transcription factor-2; CXCR1/2, IL-8 receptor type 1/2; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; IL, interleukin; NF-κB, nuclear factor-κB; JNK, Jun N-terminal kinase; MMP, matrix metalloprotease; PI3K, phosphatidyl inositol 3-kinase; PTEN, phosphatase and tensin homolog; Syk, spleen associated tyrosine kinase; TGFβ, transforming growth factor β; VEGFR, vascular endothelial growth factor receptor; ZEB1, zinc finger e-box binding homeobox 1.

Increased expression of IL-8 in the tumor microenvironment is associated with cell invasion and metastasis. IL-8 may have an important role in ovarian cancer metastasis and induces EMT (99). Another study also reported the important role of a number of cytokines including IL-8 in tumor metastasis (100).

Furthermore, invasive tumor cells have increased expression of IL-8 compared with non-cancerous tissue cells (101). Tumor cells can promote cell motility when there is an increased expression of IL-8 in the tumor microenvironment, thus promoting cancer cell migration and metastasis (102). The expression of the brachyury gene is positively associated with IL-8 and negatively associated with E-cadherin. This may lead to induction of EMT and tumor metastasis in primary lung cancer (103). Studies generally have reported that EMT can be induced by IL-8, which promotes cancer metastasis and angiogenesis (6,11). However, IL-8 secretion in the tumor microenvironment can also be induced by EMT.

6. Prognosis

Researchers have observed that IL-8 serves an important role in the prognosis of several types of carcinoma, including breast, colorectal, lung, gastric and prostate cancer (77,104-108). Increased levels of IL-8 and MMP-3 are indicators of poor prognosis in triple-negative breast carcinomas (109). A study demonstrated that NF-κB upregulates IL-8, which led to tumor progression and poorer outcomes in a pancreatic cancer model (100). Brachyury mRNA is able to induce the secretion of IL-8 and reduce the 5-year disease-free survival and overall survival rates (103). Additionally, the levels of IL-8 and its receptor may be employed as an indictor to predict prognosis and survival rate. Increased levels of IL-8 in ovarian, lung, renal and breast cancer have been reported, and this was associated with poor prognosis (55). Therefore, inhibiting IL-8 may be a potential strategy to control cancer cell migration, invasion and metastasis. Furthermore, IL-8 is able to induce EMT and this leads to a poor outcome in hepatocellular cancer patients (10). In summary, IL-8 has an important association with EMT and prognosis in cancer patients.

7. Conclusion

EMT has an important role in the progression of cancer metastasis. Induction of EMT is closely associated with distant metastasis and cell invasion in tumor progression, and indicates a poor prognosis. A number of studies have reported that multiple factors can affect EMT in cancer, including IL-6, IL-8, VEGF, TGFβ, SNAIL, MMP, TNFα and TWIST (30,110,111), which can enhance cell motility and promote tumor metastasis. EMT in cancer cells involves loss of cell-cell junctions and the acquisition of cell motility and invasion factors. Multiple signaling pathways are closely associated with EMT in tumors, including TGFβ-Syk/Src-AKT/ERK, p38/JNK-ATF-2, PI3K/AKT, NF-κB and Wnt signaling pathways (2,30,112-114). Additionally, IL-8 and its receptors have associations with EMT in cancer patients, thus blocking the IL-8/IL-8R axis may have be a potential strategy to improve prognosis for cancer patients.

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