# IL-6 Cytokines and EMP

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Epithelial–mesenchymal plasticity (EMP) plays critical physiological roles during embryonic development, postnatal growth and epithelial homeostasis, but it is also involved in a number of pathological conditions, including wound repair, fibrosis, inflammation and cancer. EMP has been intimately linked with most, if not all, of the steps during cancer development and progression (e.g., migration, invasion, immune escape, drug resistance and metastatic dissemination). Cytokines from the interleukin 6 (IL-6) family play fundamental roles in mediating tumour-promoting inflammation within the tumour microenvironment. In general, IL-6 cytokines activate EMP processes, fostering the acquisition of mesenchymal features in cancer cells. Here, we will summarise all the relevant literature related to all members of the IL-6 family and EMP.

Keywords: cancer ; epithelial–mesenchymal transition ; epithelial–mesenchymal plasticity ; cytokines ; IL-6 ; oncostatin M (OSM) ; invasion ; migration

## 1. Introduction

Epithelial–mesenchymal transition (EMT) is a dynamic process in which epithelial cells reorganize their cytoskeleton, lose apical–basal polarity, cell–cell adhesions and acquire mesenchymal phenotypes with increased migration and invasion capacities [1]. In the opposite process, mesenchymal–epithelial transition (MET), motile, spindle-shaped mesenchymal-like cells reorganize their cytoskeleton, resulting in an organized epithelium [1]. Both EMT and MET are key processes during physiological (embryonic development, regeneration) and pathological processes, such as cancer and fibrosis [1].

Epithelial–mesenchymal transition (EMT) has been a controversial concept in the last years. The criteria to define EMT have been based on context-specific or even research-community-specific observations, leading to discrepancies in data interpretation and persistent disagreements about whether the process studied in vivo could be considered EMT or not [2][3][4][5][6][7][8][9]. Besides, increasing evidence supports that the complexity, plasticity and diversity of EMT manifestations have been underestimated or oversimplified, and that cells can adopt various degrees of mixed epithelial and mesenchymal features, leading to a continuum of intermediate hybrid phenotypes known as “partial” EMT, which is a heterogeneous, dynamic and reversible process [10][11][12]. Those partial EMT states have been reported to be more relevant to cancer metastasis than the mesenchymal phenotype itself [13], and multiple partial EMT states have been proposed and verified to coexist in the same tumour. Moreover, it was recently suggested that the number of potential intermediate EMT states within a tumour can be an indicator of malignancy [14]. Therefore, the EMT International Association (TEMTIA) has recently published a consensus statement to avoid misinterpretations of the generated research data and encourage scientists to adhere to the term EMP instead of the traditional EMT [1].

Epithelial–mesenchymal plasticity (EMP) plays critical physiological roles during embryonic development, postnatal growth and epithelial homeostasis, but it is also involved in a number of pathological conditions, including wound repair, fibrosis, inflammation and cancer. EMP has been intimately linked with most, if not all, of the steps during cancer development and progression (e.g., migration, invasion, immune escape, drug resistance and metastatic dissemination), and these links have been extensively reviewed [15][16][17][18][19][20][21].

During cancer progression, tumour cells and the surrounding tumour microenvironment (TME) components (e.g., immune cells, fibroblasts, endothelial cells) secrete a variety of inflammatory mediators (including cytokines, chemokines, matrix metalloproteinases (MMPs)) that can foster the acquisition of mesenchymal features in cancer cells by fuelling the EMP-promoting inflammation [22][23][24]. Tumour microenvironment-associated inflammation, mainly regulated by cytokines, has been long described to contribute to every stage of cancer progression [25][26][27][28]. Pro-inflammatory cytokines alert the immune system to potential threats, playing a fundamental role in the body’s immune defence. However, dysregulated cytokine production can result in harmful responses to the body and consequent development of pathological conditions, including cancer [29].

The interleukin 6 (IL-6) cytokine family plays important physiological roles in inflammation, immune responses and haematopoiesis [30]. Deregulation of IL-6 signalling has been associated with chronic inflammation, autoimmunity, infectious diseases and cancer, where it often acts as a diagnostic or prognostic indicator of disease activity and response to therapy [31][32]. IL-6 has been considered a keystone cytokine in the link between inflammation and cancer, and has received a lot of attention as a potential therapeutic target [33].

The IL-6 cytokine family includes IL-6, IL-11, IL-27, IL-31, ciliary neurotrophic factor (CNTF), leukaemia inhibitory factor (LIF), cardiotrophin 1 (CT-1), cardiotrophin-like cytokine (CLC) and oncostatin M (OSM), all sharing the common glycoprotein 130 (gp130, IL6ST) receptor signalling subunit. Cytokine specificity is dependent on its unique cell-surface receptor, which shows a restricted expression pattern and dimerises with the ubiquitously expressed gp130 subunit. This restricted pattern is what makes some cells more responsive to certain cytokines than others [31]. All IL-6-related cytokine receptor complexes transduce intracellular signals via the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, but they can also activate the mitogen-activated protein kinase (MAPK)–extracellular signal-regulated kinase (MAPK/ERK) and phosphoinositide 3-kinase (PI3K)–protein kinase B (PKB or Akt) pathways [34]. Activated STATs enter the nucleus and activate context dependent genes [35]. STAT3 signalling is considered a major pathway for cancer inflammation due to its frequent activation in malignant cells and key role in regulating many crucial genes associated with inflammation in the tumour microenvironment [36]. STATs also induce the suppressors of cytokine signalling (SOCS) [37][38], which bind to tyrosine-phosphorylated JAK and tyrosine-phosphorylated gp130 [39], respectively, to stop IL-6 family signalling by means of a negative feedback loop. Interestingly, the IL-6 family has been described to have a great deal of promiscuity, with some members presenting affinity to more than one specific receptor and being able to induce the same or different physiological outcomes [31].

## 2. Role of IL-6 and OSM in Epithelial–Mesenchymal Plasticity

The reciprocal causative link between EMP and IL-6 family has been supported by a large number of independent studies. The experimental evidence linking OSM and EMP is less, but it is still supported by a considerable number of scientific reports. The main effects of IL-6 and OSM in EMP and the signalling pathways involved are summarised in Figure 1. In general, IL-6 and OSM induce EMP in cancer cells by favouring the acquisition of mesenchymal traits and cancer stem cell (CSC) associated features. They also promote stemness, migration, invasion and metastasis in different in vitro and in vivo experimental settings of several cancer types including breast, head and neck, lung and gastric cancers.

The STAT3 transcription factor is the leading EMP effector upon activation of IL-6 receptor (IL-6R) and OSM receptor (OSMR) [40][41], although the involvement of other downstream effectors cannot be disregarded. There is strong experimental evidence supporting the role of the transcription factor STAT3 as the main mediator of EMP induction by IL-6 and OSM in cancer [40][41][42][43]. STAT3 can cooperate with other signalling nodules (mainly Src, SMAD and c-Myc) to mediate IL-6 and OSM promotion of EMP in cancer cells [42][44][43][45][46][47][48][49][50]. Interestingly, a few reports have described anti-EMP and anti-metastatic effects of OSM mediated by STAT1 [51][52][53]. It is widely accepted that activation of STAT3 by IL-6 related cytokines leads to EMP while activation of STAT1 leads to anti-tumorigenic and anti-EMP effects.

Transcription factors involved in EMP (EMT-TFs) have been recently classified as core and non-core EMT-TFs [1]. IL-6 is able to induce the expression of EMT-TFs in a wide variety of cancer types. It is widely accepted that Snail is increased after OSM exposure in many cancer types, including prostate [30], pancreatic [31], cervical [32] and breast cancers [33][34][35][36]. In addition, OSM has been described to increase the Zeb1 protein levels in PDAC [31] and breast cancer [36] and Zeb2 in cervical cancer [32].

Apart from the transcriptional regulation, EMT-TFs levels can be altered by a variety of post-transcriptional, translational and post-translational regulatory networks including micro-RNAs (miRNAs). The list of miRNAs directly or indirectly associated with EMP is extensively increasing [54]. So far, miR200 [55][56] and miR34 [57][58] families are the best characterized, being both miRNA families strong protectors of the epithelial phenotype in different cellular systems and positively regulated by the tumour suppressor p53 [57][59][60]. Both miRNA families have been shown to be modulated by IL-6 and OSM in cancer cells.

Most of the scientific evidence point to similar molecular and functional consequences of IL-6 and OSM-induced EMP in cancer cells. Both IL-6 and OSM induce E-cadherin repression, increase the expression of mesenchymal markers, promote mesenchymal/ fibroblastic morphology, stemness and migration, as well as invasion in vitro and in vivo. In addition, IL-6 has been reported to induce resistance to cancer therapies and anoikis. Although most of the evidence is derived from studies performed in cancer cell lines, the pro-EMT and pro-invasive effects of IL-6 and OSM have been proved in vivo in animal models of breast, lung, gastric, cervical, and head and neck cancers, among others.

Despite some controversy regarding the direct effect of EMP on cancer metastasis, EMP related features have been associated with aggressiveness and worse prognosis [2][3][4][5][6][7][8][9]. Similarly, IL-6 and OSM are linked to decreased overall and disease-free survival in various cancer types, in part due to their role in EMP and metastasis [61]. The association between IL-6, OSM and EMP observed in cancer cell lines and animal models is relevant in the clinical setting.

## 3. Role of LIF on Epithelial-Mesenchymal Plasticity

The relevance of the leukaemia inhibitory factor (LIF) in stem cell maintenance and development is well described [37]. However, its role in cancer-related epithelial–mesenchymal plasticity is less clear, as both pro- and anti-EMP functions have been reported.

In nasopharyngeal carcinoma, LIF reprograms the cancer cell invasive mode from collective to mesenchymal migration via acquisition of EMP, as shown by increased expression of N-cadherin, vimentin and IQ motif-containing GTPase-activating protein 1 (IQGAP1) concomitant with a decreased expression of E-cadherin [38]. In those cancer cells, LIF promoted invadopodia-associated characteristics and markers, such as tyrosine kinase substrate with five SH3 domains (TKS5), cortactin (CTTN), matrix metallopeptidase 2 (MMP2) and SRC proto-oncogene (SRC). Furthermore, LIF induced fibroblastic morphology with enhanced vascular dissemination and local invasion through modulation of the YAP1-FAK/PXN signalling in 3D gels and xenografts [38]. These results are relevant in the clinical setting, as higher levels of LIF and LIF receptor (LIFR) correlated with poorer metastasis/recurrence-free survival [38].

Other studies have also associated LIF signalling with EMP features such as increased cell migration, invasion, CSC properties and metastasis, reporting both promoting and inhibitory roles, despite not always showing a direct link between LIF and EMP. In gastric cancer, LIF promoted proliferation, colony formation, invasion, migration and tumour growth by inhibiting the Hippo pathway, resulting in increased YAP nuclear translocation and transcriptional activity, giving rise to cancer cells with decreased E-cadherin and increased MMP7 protein levels [39]. Interestingly, LIF promoted mesenchymal epithelial transition in lung cancer cells through the LIF/LIFR/p-ERK/pS727-STAT3 signalling pathway leading to increased metastasis [40].

Intriguingly, in breast cancer, anti-metastatic potential has been attributed to LIFR [41][62], as LIFR downregulation was responsible for the pro-metastatic effect of the E-cadherin suppressor miR-9 [41]. Additionally, in the TNBC cell line MDA-MB-231, LIFR overexpression did not alter vimentin protein levels in vitro but reduced vimentin positive metastatic foci in vivo [41]. The anti-tumorigenic roles of LIF in gastric CSCs also have been described, where it decreased the CSC properties and population in both cell lines and a patient-derived xenograft (PDX) [42]. Both in breast and in gastric cancer cells, the anti-metastatic role of LIF-LIFR was mediated through the activation of Hippo tumour suppressor kinases (MST1/2 and LATS1/2), with the consequent inhibition of the YAP/TAZ/TEAD oncogenic effector activity. It would be interesting to know if STAT1 is involved in the anti-metastatic effect of LIF, as has been described for other cytokines of the family [44].

## 4. Role of IL-11 on Epithelial–Mesenchymal Plasticity

Interleukin-11 (IL-11) is known to participate in osteoclast-mediated bone remodelling together with TGFβ, and both have been associated with increased bone metastasis [63][64]. However, reports linking IL-11 and EMP are limited, as far as we know, with few exceptions supporting a positive contribution of IL-11 to EMP features.

IL-11 is increased by HIF1α in hypoxia and induces EMP via the PI3K/Akt/GSKβ3/Snai1 pathway in anaplastic thyroid carcinoma cells, as demonstrated by reduced ZO-1 and E-cadherin and increased vimentin and Snail protein levels, ultimately improving their migratory and invasive potential [43]. IL-11 treatment also promoted EMP in different in vivo NSCLC models, via AKT and STAT3, leading to increased levels of mesenchymal markers, such as Snail, Slug, Twist1, vimentin and N-cadherin, and downregulation of E-cadherin, claudin-1 and ZO-1 expression [65][45]. One of these studies reported that IL-11 treatment promoted lung adenocarcinoma cell growth and EMT through activation of the STAT3/HIF-1α/EMT signalling pathway [65]. In TNBC cells, IL-11 cooperated with its upstream regulator twinfilin 1 in promoting EMT and chemoresistance. In addition, knockdown of IL-11 favoured a mesenchymal-to-epithelial transition phenotype as demonstrated by rearranged actin filaments and increased vinculin-stained focal adhesions [46]. The relevance in the clinical setting was demonstrated as low IL-11 correlated with relapse-free survival in breast cancer patients [46]. Additionally, the IL-11/STAT3 pathway, activated by the oncogene HMGA2, has been shown to facilitate the migratory and invasive capacities of colorectal cells in vitro together with increased vimentin and decreased E-cadherin levels, and to promote tumorigenesis and distant metastasis in vivo [66]. Of interest, the oncogene HMGA2 is also a master regulator of OSM-induced epithelial plasticity in breast cancer and can be induced by OSM [36], as we described in previous sections.

A recent study has shown that, in PDAC cells, IL-6 and IL-11 stimulated the expression of most S100 proteins regulating epithelial/mesenchymal features [67]. Even if IL-11 treatment alone did not induce EMP by itself in this study, it synergised with IL-6 to activate STAT3, which cooperated with ZEB1 to upregulate the mesenchymal S100A4/A6 proteins, nullify the effect of epithelial S100A14 expression and promote an invasive phenotype [67].

In conclusion, the available literature supports the role of IL-11 as a pro-EMP and pro-tumorigenic factor in anaplastic thyroid, lung, breast, colorectal and pancreatic cancer, mainly through activation of the STAT3 and PI3K/Akt pathways [67][43][65][45][46][66].

## 5. Conclusions

IL-6 family cytokines share many similarities as they have the potential to activate the same signalling pathways (e.g., JAK/STATs, MAPK/ERK and PI3K/AKT), but play different roles and are involved in different physiological and pathological processes as it is evidenced in the case of EMP. IL-6 and OSM are clear EMP promoters and their role in tumour progression and metastasis is widely accepted. IL-11 and LIF seem to promote EMP in some cancer types, even if the mechanisms are not as thoroughly described. However, the implication of LIF is less clear as it can exert both pro and anti-metastatic functions and their link with EMP is less studied. IL-27 is the unique strong EMP inhibitor of the family by a dominant STAT1 activation, while, interestingly, its subunit p28 (IL-30) has been suggested to favour an invasive phenotype in breast cancer cells.

Although it is widely accepted that IL-6 and OSM promote EMP in many cancer types, the data gathered in this review further suggest that both promote different EMP programmes depending on the cancer type and the experimental setting, giving rise to cells with intermediate phenotypes within the epithelium-mesenchymal spectrum rather than generating complete mesenchymal cells with no epithelial features. Repression of E-cadherin and increased Snail levels seem to be common features of the EMP programmes activated by IL-6 and OSM, while there is more discrepancy in the mesenchymal markers and other core EMT-TFs induced by those cytokines. The tumorigenic properties of IL-6 and OSM are principally mediated by STAT3, while few anti-EMP functions of OSM have been described by a dominant STAT1 activation in specific contexts.

Even if the EMP process induced by IL-6 and OSM has been shown to be reversible, there are several autocrine and paracrine positive feedback loops leading to long term pro-EMP signalling. In addition, both cytokines are required for the initiation and maintenance of transdifferentiated/ mesenchymal and CSC-like populations, supporting a role in the acquisition of therapy resistance [44][68][69][70][61][71][72]. In conclusion, the data presented here, obtained from in vitro and in vivo experiments and from clinical samples, strongly supports the role of IL-6 and OSM on EMP promotion and suggests that both cytokines could be potential therapeutic targets to halt tumour progression by blocking EMP.

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