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Tumor Inflammatory Microenvironment in EMT and Metastasis

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1. Introduction

Approximately 90% of cancer-related death is caused by metastasis. The increased motility and invasiveness of metastatic tumor cells is reminiscent of events that occur at the epithelial-mesenchymal transition (EMT), which is a characteristic that occurs during embryonic development, tissue remodeling, wound healing and metastasis. Interestingly, EMT is a dynamic process and mainly occurs at the edges of wounds during healing and at the invasive fronts of metastatic tumors, which suggest that EMT is influenced by stimuli that emanate from the inflammatory microenvironment. The tumor microenvironment consists of many kinds of cells including infiltrated inflammatory cells, such as neutrophils, lymphocytes, macrophages and myeloid derived suppressor cells (MDSC). These infiltrated immune cells secrete cytokines, chemokines and growth factors, such as TNF-α, TGF-β, IL-6, fibroblast growth factor (FGF) and epidermal growth factor (EGF). These growth factors contribute significantly to the invasive and metastatic traits of cancer cells by inducing EMT. Here, we discuss new insights into the molecular pathways and key regulators that link inflammatory tumor microenvironment to EMT and metastasis.

2. Cancer and immunity: Immunity's roles in tumor suppression and promotion

One of the most challenging questions in immunology is to understand how the immune system affects cancer development and progression. In recent years, after a long eclipse, different lines of work have lead to a renaissance of the inflammation-cancer connection (Balkwill and Mantovani 2001; Coussens and Werb 2002; Mantovani, Allavena et al. 2008). It is now believed that the immune system plays a dual role in cancer: on one hand , it can function as an extrinsic tumor suppressor (Dighe, Richards et al. 1994; Kaplan, Shankaran et al. 1998; Smyth, Thia et al. 2000; Girardi, Oppenheim et al. 2001; Shankaran, Ikeda et al. 2001; Street, Trapani et al. 2002) by destroying cancer cells or inhibiting their outgrowth; on the other hand, the immune system can also promote tumor progression by establishing conditions within the tumor microenvironment that facilitate tumor outgrowth (Schreiber, Old et al.). Inflammatory responses play decisive roles at different stages of tumor

development, including initiation, promotion, malignant conversion, invasion, and metastasis (de Visser, Eichten et al. 2006; Grivennikov, Greten et al. 2010).

3. EMT and metastasis

Epithelial-mesenchymal transition (EMT) is a phenotypic conversion during embryonic development when tissue remodeling and cell migration shape the future organism, such as in embryonic development and wound healing. During EMT, epithelial cells lose the adherent junctions that keep them in contact with their neighbors. They gain a mesenchymal cell phenotype that enables them to break through the basal membrane and migrate over a long distance, a result of profound changes in their cytoskeleton architecture and gene expression profile (Kalluri and Neilson 2003). This concept was pioneered by the seminal study from Elizabeth Hay using chick primitive streak formation as a model in 1967 (Hay 1995). Hay realized that an epithelial phenotypic conversion was of crucial importance during gastrulation and cell migration in the early vertebrate embryo. She proposed that differentiated epithelial cells could undergo a dramatic "transformation" into mesenchymal cells (Greenburg and Hay 1988; Hay 1995). However, this "transformation" is reversible: mesenchymal cells can revert back to epithelial cells through a reverse process called mesenchymal-epithelial transition (MET). As a result, the term "transition" is now used.

EMT does not only occur during embryonic development or as a physiological response to injury. It is also an important element in cancer progression and other pathologies that involve organ degeneration, such as fibrosis. At the cellular level, pathological EMTs are very similar to physiological EMTs in that they are governed by similar signaling pathways, regulators, and effective molecules.

From a clinical perspective, metastasis is the most critical aspect of tumorigenesis: we have already addressed that more than 90% of cancer mortality is caused by metastasis. Aberrant control of epithelial proliferation and angiogenesis underlie the initiation and growth of primary carcinomas (Hanahan and Weinberg 2011). However, additional steps must be completed before a metastatic tumor is successfully established. The spread of malignant cells consists of a series of steps, all of which are thought to be important for metastatic outgrowth in different organs. Basically, these steps include local invasion toward and entry into blood vasculature (intravasation), survival within the circulation system, arrest in distant capillary beds or "homing" to distal organs, exit from blood vasculature (extravasation), and eventual outgrowth and re-establishment of malignant growths in secondary locations (Woodhouse, Chuaqui et al. 1997; Chambers, Naumov et al. 2001; Fidler 2003; Hanahan and Weinberg 2011).

3.1 Classification of EMT into three different subtypes

Based on recent intensive study in this field, EMT can be divided into three subtypes, which have different biological functional consequences (Kalluri 2009; Kalluri and Weinberg 2009; Zeisberg and Neilson 2009). Type 1 EMT occurs during implantation, embryo formation, gastrulation, and neural crest migration, which describes the transition of epithelial cells to generate diverse mesenchymal cell types. These primary mesenchymal cells can revert back to form secondary epithelia in mesodermal and endodermal organs through MET. Type 2 EMT occurs during wound healing, tissue regeneration and organ fibrosis, which is usually

associated with injury and chronic inflammation. Type 2 EMT ceases once inflammation is attenuated, but if inflammation persists, this type of EMT will eventually lead to tissue fibrosis and organ destruction. Unlike Type 1 EMT, these mesenchymal cells have no potential to undergo MET and turn back to epithelial cells. Type 3 EMT occurs during tumor progression, which describes how neoplastic cells at the invasive front of primary tumors undergo a transition to acquire increased motility and invasive ability, enabling them to invade and metastasize through the blood stream or lymph node system, eventually generating life-threatening metastatic lesions at distant organs.

Because studies of EMT often involve various model systems ranging from different epithelial cell types to assorted stimulations, it is important to use validated biomarkers to examine the phenotypic conversion during all three classes of EMT. Common biomarkers include cell-surface and extracellular molecules, cytoskeletal proteins and specific transcription factors. For example, down-regulation of E-cadherin is a hallmark of EMT, and loss of E-cadherin expression facilitates the induction of EMT (Huber, Kraut et al. 2005). E-cadherin is a cell-cell adhesion molecule that participates in homotypic, calcium-dependent interactions to form epithelial adherent junctions (Cowin, Rowlands et al. 2005; Junghans, Haas et al. 2005). In addition, E-cadherin repressors, such as Snail, Slug, Twist and ZEB1/2, are commonly used as EMT markers. Snail is the first described E-cadherin repressor and is also the common downstream target of various signaling pathways that lead to EMT. Vimentin, an intermediate filament mainly expressed in fibroblasts, endothelial cells and hematopoietic cells, is also commonly used as an indicator for Type 3 EMT, since expression of vimentin in tumor cells correlates with their invasiveness and metastatic potential. Furthermore, differential expression of integrin is also used as a biomarker of EMT, since integrins modulate the interaction of cells with extracellular matrix (ECM). For example, increased expression of α5 integrin is commonly found in Type 2 and Type 3 EMT (Qian, Zhang et al. 2005; Davidson, Marsden et al. 2006; White, Blanchette et al. 2007).

3.2 Type1 EMT in the formation of mesoderm and neural crest

EMT is crucially important to tissue morphogenetic events during embryonic development, such as the mesoderm formation, neural crest formation, heart valve development, and secondary palate formation. Without EMT, development cannot proceed through the blastula stage. Mesoderm formation and neural crest development represent the major EMT programs that occur during early embryonic development; the resulting mesenchymal and neural crest cells act as progenitors and further differentiate into various cell types via MET. For example, gastrulation EMT produces the mesoderm, giving rise to muscle, bone and connective tissues, whereas neural crest delamination EMT gives rise to glial and neuronal cells, adrenal glandular tissues, pigment-containing cells of the epidermis and skeletal and connective tissues. The heart valve development and secondary palate formation occur in relatively well-differentiated epithelial cells that are destined to become defined mesenchymal cells types.

The formation of mesoderm from the primitive ectoderm during gastrulation is the classic example of EMT. Gastrulation, observed in all metazoans, is accompanied by drastic morphogenic changes from a single epithelial layer (the epiblast) into three embryonic germ layers, the ectoderm, mesoderm, and endoderm, to form a complex three-dimensional multilayered embryo (Shook and Keller 2003). In chicken and mouse embryo, Wnt and TGF-

β signaling provide the initial induction signals for EMT, while the FGF signal is necessary to maintain the EMT regulatory network during mesoderm formation. All these signaling events activate the expression of Snail, which represses the expression of E-cadherin and other tight junction components (such as claudins, occludins, and Crumbs) and promotes cell migration. In Snail knock-out mice the cells that form are unable to migrate, although mesoderm specification is not affected.

Neural crest formation is another example of Type 1 EMT in embryogenesis where premigratory neural crest cells form at the border of the neural plate and non-neural ectoderm as a result of signals emanating from these two tissues. Interestingly, similar signaling pathways operating during EMT at gastrulation are used in the neural crest formation. Indeed, a combination of Wnt, FGF, and TGF-β (mainly BMP) induce the expression of Snail, Sox and forkhead box D3 transcription factors (Villanueva, Glavic et al. 2002). In addition, experimental evidence shows that Notch signalling pathway plays an important role in neural crest formation through induction of Slug in frog and chick embryo (Nieto 2002). The combination of these transcription factors generates the full spectrum of phenotypic changes associated with EMT and primes the precursor cells to become migratory neural crest cells. These neural crest cells are equipped with the ability to migrate over extraordinarily long distances in the embryo, prior to their reaggregation via MET for further differentiation.

3.3 Type 2 EMT in tissue and organ fibrosis

3.3.1 Implications of EMT in fibrosis

Re-epithelization, tissue regeneration and organ fibrosis constitute Type 2 EMT. Organ fibrosis is mediated by inflammatory cells and fibroblasts, which deposit collagens, elastin, tenacin and other matrix molecules. Fibrosis-associated Type 2 EMT specifically occurs in kidney, liver, lung and intestine (Zeisberg, Tarnavski et al. 2007). A series of typical experiments has shown that EMT is an important process during tissue injury that leads to organ fibrosis. In terms of EMT proteomes, fibroblast-specific protein 1 (FSP1, also known S100A4 and MTS-1), α-SMA (smooth muscle actin) and collagen I are reliable markers to characterize the mesenchymal products generated by EMTs in the development of fibrosis in various organs. TGF-β1, as the major pro-fibrotic cytokine, induces many of the central processes involved in fibrosis, including differentiation of fibroblast to myfibroblasat, ECM deposition and EMT. TGF-β not only contributes to pulmonary and hepatic fibrosis, but also plays a key role in cardiac fibrosis (Gressner, Weiskirchen et al. 2002; Willis and Borok 2007; Zeisberg, Tarnavski et al. 2007). TGF-β induces EMT via both a Smad2/3-dependent pathway and a MAPK-dependent pathway. The relevance of TGF-β-induced EMT for progression of organ fibrosis was recently further elucidated using BMP-7 as an intracellular competitor of TGF-β signaling in mouse models of kidney, liver, billiard tract, lung and intestinal fibrosis (Zeisberg, Bottiglio et al. 2003; Zeisberg, Hanai et al. 2003). The function of TGF-β in fibrosis is highlighted by the finding that Smad3-/- mice are resistant to the induction of several fibrotic diseases (Flanders 2004). TGF-β levels are also over-produced and are associated with functional impairment in patients with fibrotic pulmonary diseases such as idiopathic pulmonary fibrosis (Salez, Gosset et al. 1998). Clinical studies have also demonstrated the correlation between fibrosis and EMT (Rastaldi, Ferrario et al. 2002). Using immunohistochemistry and in situ hybridization, an EMT was demonstrated with the

expression of several markers of tubular phenotype transition, such as cytokeratin, vimentin, α-SMA and zona occludens (ZO-1) in 133 kidney biopsies (Rastaldi, Ferrario et al. 2002). Similarly, an expression pattern of EMT was found in areas of fibrosis in the colon in patients with Crohn's disease (Bataille, Rohrmeier et al. 2008).

3.3.2 Re-epithelialization of wounded skin

Re-epithelialization recapitulates several aspects of EMT. Re-epithelialization requires epithelial cells at the edge of wounded tissue to loosen their cell–cell and cell–ECM contacts and assume a migratory phenotype, reminiscent of EMT. Slug has a crucial role in wound-healing, which is expressed in keratinocytes at the boundary of wounds. Importantly, epithelial cell outgrowth from skin explants was markedly reduced in Slug knockout mice, whereas overexpression of Slug in cultured human keratinocytes result in increased cell spreading and desmosomal disruption (Savagner, Kusewitt et al. 2005). Arnoux et al further found that EGF can activate Erk5, which specifically enhances Slug promoter activity and controls wound healing in keratinocyte-derived HacaT cells in vitro (Arnoux, Nassour et al. 2008). However, it should be noted that not all features of EMT are seen. First, the migrating keratinocytes remain part of a cohesive cell sheet since they retain some intercellular junction. Second, the epithelial cells do not actually become mesenchymal (i.e., interstitial) cells. They retain epithelial characteristics. Once wound closure is complete, the involved epithelial cells revert to their tissue-specific, differentiated state.

3.4 Type 3 EMT in cancer metastasis

Cancer metastasis is believed to consist of four distinct steps: invasion, intravasation, extravasation and metastatic colonization (Chambers, Groom et al. 2002; Pantel and Brakenhoff 2004). During invasion, tumor cells lose cell-cell adhesion, gain mobility and leave the site of the primary tumor to invade adjacent tissues. In intravasation, tumor cells penetrate through the endothelial barrier and enter systemic circulation through blood and lymphatic vessels. In extravasation, cells that survive anchorage-independent growth conditions in the bloodstream attach to vessels at distant sites and leave the bloodstream. Finally, in metastatic colonization, tumor cells form macrometastases in the new host environment (Chambers, Groom et al. 2002; Pantel and Brakenhoff 2004). All of these steps, from initial breakdown of tissue structure through increased invasiveness, and ultimately distribution and colonization throughout the body, are characteristics of the developmental process at EMT/MET. The similarity of genetic controls and biochemical mechanisms underlying the acquisition of the invasive phenotype, and the subsequent systemic spread of the cancer cells, highlights that tumor cells usurp this developmental pathway for their metastatic dissemination. We will further discuss this type of EMT, with more detail on how it is regulated by different signaling pathways and molecular in various tumor microenvironments.

3.5 Molecular regulation of EMT

The hallmark of EMT is the loss of E-cadherin expression, an important caretaker of the epithelial phenotype. Loss of E-cadherin expression is often correlated with the tumor grade and stage, because it results in disruption of the cell-cell adhesion and an increase in nuclear

β-catenin (Cowin, Rowlands et al. 2005; Junghans, Haas et al. 2005). Several transcription factors have been implicated in the regulation of EMT, including zinc finger proteins of the Snail/Slug family, the basic helix-loop-helix factor Twist, E12/E47, Goosecoid, δEF1/ZEB1 and SIP1 (Nieto 2002; Yang, Mani et al. 2004; Hartwell, Muir et al. 2006). These factors act as a molecular switch of EMT program by repressing a subset of common genes that encode cadherins, claudins, integrins, mucins, plakophilin, occludin and ZO1 to induce EMT. For example, Snail expression is associated with E-cadherin repression in metastasis; it also correlates with tumor recurrence and poor prognosis in various cancers (Elloul, Elstrand et al. 2005; Moody, Perez et al. 2005; Bruyere, Namdarian et al. 2009). In addition, extensive crosstalk among these transcription factors forms a signaling network that is responsible for establishing and maintaining mesenchymal cell phenotypes. Furthermore, some of these transcription factors, including Snail, play an important part in overcoming oncogene-induced senescence (Ansieau, Bastid et al. 2008), inhibiting tumor immunosuppression (Kudo-Saito, Shirako et al. 2009) and generating tumorigenic cancer stem cells (Mani, Guo et al. 2008). These transcription factors communicate and respond to extracellular signals such as growth factors, cytokines and hypoxia from their microenvironment to induce EMT.

Many signaling pathways trigger EMT in both embryonic development and in normal and transformed cell lines. The signaling pathways include those triggered by different members of the TGF-β superfamily, Wnts, Notch, EGF, FGF and many others (Fig.1).
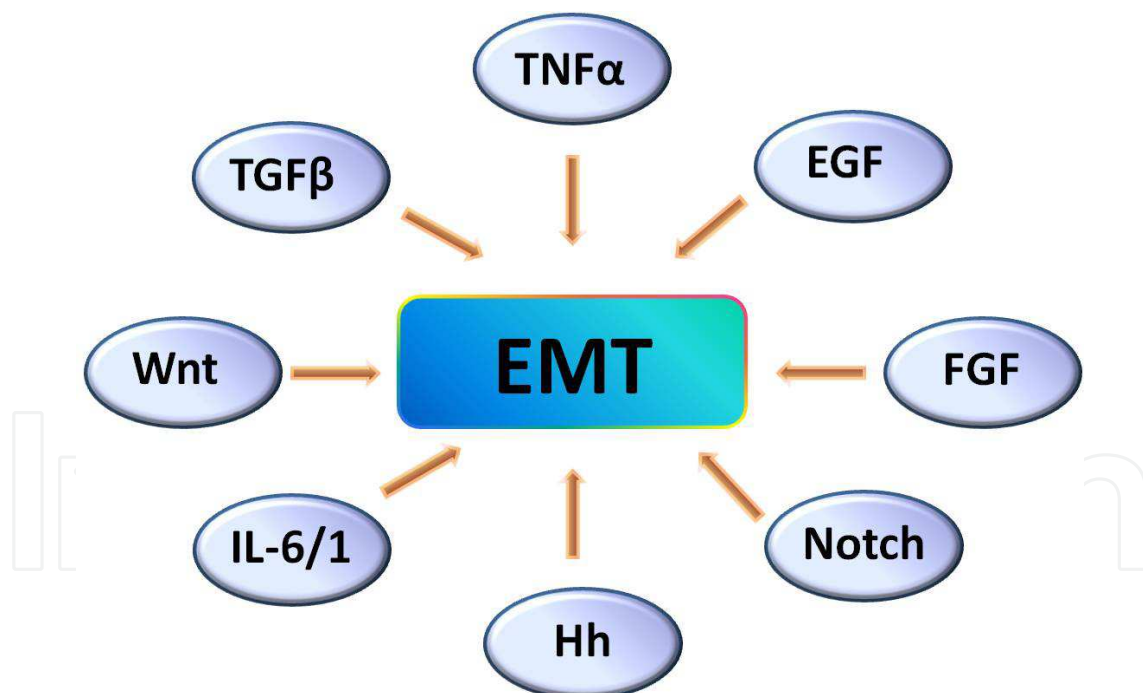

Fig. 1. Overview of the Molecular regulation of EMT.

TGF-β is a primary inducer of EMT. It not only contributes to EMT during embryonic development, but also induces EMT during tumor progression in vivo (Zavadil and Bottinger 2005). Overexpression of Smad2 and Smad3 result in increased EMT in a mammary epithelial

model (Valcourt, Kowanetz et al. 2005). Knockout of Smad3 blocks TGF-β-induced EMT in primary tubular epithelial cells; the reduction of Smad2 and Smad3 function is associated with the decreased metastatic potential of breast cancer cell lines in a xenograft model (Zavadil, Cermak et al. 2004). It is interesting that SMAD3 and SMAD4 interact and form a complex with Snail, targeting the promoters of CAR (a tight-junction protein) and E-cadherin during TGF-β-inducing EMT in breast epithelial cells (Vincent, Neve et al. 2009). Bos et al identified that TGF-β primed cancer cells for lung metastasis through angiopoietin-like 4 via Smad signaling pathway (Bos, Zhang et al. 2009). In contrast, inhibition of TGF-β or TGF-β receptor reduces the invasive and metastatic activities of cancer cells. TGF-β can also downregulate various epithelial molecules, including E-cadherin, ZO-1 and several specific keratins; it also upregulates certain mesenchymal proteins such as fibronectin, fibroblast specific protein 1, α-smooth muscle actin and vimentin. In addition, TGF-β cooperates with numerous kinases such as RAS, MAPK, and p38MAP, to promote EMT (Zavadil and Bottinger 2005; Buijs, Henriquez et al. 2007). More specifically, p38 MAPK and RhoA mediate an autocrine TGF-β-induced EMT in NMuMG mouse mammary epithelial cells (Bhowmick, Ghiassi et al. 2001). ECM molecules, such as integrin β1 and Fibulin-5, augment TGF-β-induced EMT in a MAPK-dependent mechanism (Bhowmick, Ghiassi et al. 2001; Lee, Albig et al. 2008). Constitutive activation of Raf enhances the function of TGF-β in inducing EMT via MAPK in MDCK cells (Janda, Lehmann et al. 2002). TGF-β also induces EMT through changes in the expression of certain cell polarity molecules. For example, TGF-β can induce phosphorylation of Par6, which in turn stimulates binding of Par6 to E3 ligase Smurf1. The Par6-Smurf1 complex then mediates the localized ubiquitination of RhoA to disrupt tight junctions during EMT (Ozdamar, Bose et al. 2005). TGF-β can also downregulate Par3 expression to destroy cell polarity (Wang, Nie et al. 2008). It is interesting to note that Abl can inhibit TGF-β-mediated EMT in normal and metastatic mammary epithelial cells (MECs) (Allington, Galliher-Beckley et al. 2009). Furthermore, TGF-β can cooperate with other oncogenic pathways, such as Notch, Wnt/β-catenin and NF-κB, to maintain the mesenchymal phenotype of invasive/metastatic tumor cells (Nawshad, Lagamba et al. 2005; Zavadil and Bottinger 2005; Neth, Ries et al. 2007).

The Wnt/β-catenin pathway has a particularly tight link with EMT (Li, Hively et al. 2000). On one hand, β-catenin is an essential component of adherent junctions, where it provides the link between E-cadherin and α-catenin and modulates cell-cell adhesion and cell migration. On the other hand, β-catenin also functions as a transcription cofactor with T cell factor (TCF). Nuclear translocation of β-catenin can activate expression of Slug, thus inducing EMT. Expression of β-catenin in oocyte induces a premature EMT in the epiblast, concomitant with Snail transcription. Interestingly, Snail is a highly unstable protein and is dually regulated by protein stability and cellular location. We showed that GSK-3β binds and phosphorylates Snail at two consensus motifs to dually regulate the function of this protein: phosphorylation at the first motif regulates its ubiquitination mediated by β-Trcp, and phosphorylation at the second motif controls its subcellular localization (Zhou, Deng et al. 2004). Thus, Wnt can suppress the activity of GSK-3β, and it stabilizes the protein level of Snail and β-catenin to induce EMT and cancer metastasis (Yook, Li et al. 2005; Yook, Li et al. 2006). Meanwhile, Snail can functionally interact with β-catenin to increase Wnt-dependent target gene expression, promoting EMT (Stemmer, de Craene et al. 2008). Increasing evidence indicates that Wnt signaling is strongly associated with human basal-like breast cancer. Inhibiting Wnt signaling through LRP6 reduces the capacity of cancer cells to self-renew and colonize in vivo. It also results in the re-expression of breast epithelial markers

and repression of EMT transcription factors Slug and Twist (DiMeo, Anderson et al. 2009). How the synergistic activation of Snail and β-catenin by the Wnt signaling pathway, enhancing EMT and metastasis, remains to be further defined.

Notch is an evolutionarily conserved signaling pathway that regulates cell fate specification, self-renewal and differentiation in embryonic and postnatal tissues. Four Notch (Notch 1−4) and five ligands (Jagged1, 2 and Deltalike1, 3, 4) have been identified. Notch signaling is normally activated followed by ligand-receptor binding between two neighboring cells. Notch undergoes intramembrane cleavage by γ-secretase, and its intracellular domain (NICD) is released and translocates to the nucleus to activate gene transcription by associating with Mastermind-like 1 (MAM) and histone acetyltransferase p300/CBP. Alteration of Notch signaling has been associated with various types of cancer in which Notch can act as an oncogene or as a tumor suppressor, depending on the cellular context. The first observation that Notch pathway is required for EMT was derived from cardiac valve and cushion formation at heart development (Timmerman, Grego-Bessa et al. 2004). This implies that Notch, acting through a similar mechanism, induces EMT during tumor progression and converts polarized epithelial cells into motile and invasive ones (Grego-Bessa, Diez et al. 2004). Indeed, overexpression of Jagged1 and Notch1 induces the expression of Slug and correlates with poor prognosis in various human cancers (Leong, Niessen et al. 2007). Slug is essential for Notch-mediated EMT by repressing E-cadherin expression, which results in β-catenin activation and resistance to anoikis. Inhibition of Notch signaling in xenografted, Slug-positive/E-cadherin-negative breast tumors promotes apoptosis and inhibits tumor growth and metastasis (Leong, Niessen et al. 2007). In addition, Notch signaling deploys two distinct mechanisms that act in synergy to control the expression of Snail (Sahlgren, Gustafsson et al. 2008). First, Notch directly upregulates Snail expression by recruiting the Notch intracellular domain to the Snail promoter. Second, Notch potentiates hypoxia-inducible factor 1α (HIF-1α) recruitment to the lysyl oxidase (LOX) promoter and elevates the hypoxia-induced upregulation of LOX, which stabilizes the Snail protein. Thus, Notch signaling is required to convert the hypoxic stimulus into EMT, and it increases the invasiveness of tumor cells. In addition, the Notch signaling pathway is involved in the acquisition of EMT phenotype of gemcitabine-resistant (GR) cells in pancreatic cancer (Wang, Li et al. 2009). Down-regulation of Notch signaling is associated with decreased invasive behavior of GR cells. Moreover, Notch signaling leads to the increased expression of vimentin, ZEB1, Slug, Snail, and NF-κB, and it results in EMT. Thus, inhibition of Notch signaling by novel therapeutic strategies can be clinically important in overcoming drug resistance and EMT phenotype of tumor cells.

The Hedgehog (Hh) signaling pathway was first identified in a large screen for Drosophila genes required for patterning of the early embryo (Hooper and Scott 2005; Jacob and Lum 2007). The Hh ligands, Sonic-, Desert-, and Indian Hh in vertebrates and Hh in Drosophila, are secreted proteins that undergo several posttranslational modifications to gain full activity. Key effectors of Hh signaling include zinc-finger proteins of the Gli1-3 transcription factors. Hh signaling can initiate cell growth, cell division, lineage specification and axon guidance and can also function as a survival factor. Activation of Hh signaling also leads to EMT. In mouse epidermal cells or in rat kidney epithelial cells immortalized with adenovirus E1A, Gli1 rapidly induces transcription of Snail and promotes EMT (Li, Deng et al. 2006; Li, Deng et al. 2007). Targeted expression of Gli1 in the epithelial cells of mammary gland of mice induces the expression of Snail, resulting in the disruption of the mammary

epithelial network and alveologenesis during pregnancy (Fiaschi, Rozell et al. 2007). In addition, Hedgehog signals induce JAG2 up-regulation for Notch-CSL-mediated Snail expression; on the other hand, Hedgehog induces TGF-β1 secretion to induce ZEB1 and ZEB2 expression through TGF-β and NF-κB pathways. Conversely, blocking Hedgehog signaling by inhibitor cyclopamine suppresses pancreatic cancer invasion and metastasis by inhibiting EMT (Feldmann, Dhara et al. 2007). The crosstalk between the Hh and EMT also presents in human esophageal squamous cell carcinoma (ESCC) (Isohata, Aoyagi et al. 2009). Hh and EMT signaling genes are co-expressed on the undifferentiated esophageal epithelial cells and in most ESCCs. These findings suggest that mesenchymal gene expression is maintained or strengthened through Hh signaling in cancer cells.

3.6 Microenvironmental regulation of EMT/metastasis

Metastasis is a multi-step process that requires cancer cells to escape from the primary tumor, survive in circulation, seed at distant sites and grow. Each of these processes involves rate-limiting steps influenced by non-malignant cells of the tumor microenvironment (Joyce and Pollard 2009), composed of multiple cell types, such as stroma fibroblasts, epithelial cells, and a variety of bone marrow-derived cells (BMDCs) including macrophages, myeloid-derived suppressor cells (MDSCs), and so on. In this surrounding environment, a variety of stromal cells are recruited to tumors, not only enhance growth of the primary tumor, but also to facilitate its metastatic dissemination to distant organs (Tse and Kalluri 2007; Lunt, Chaudary et al. 2009).

Recent work has indicated that EMT is a dynamic process controlled by signals that cells receive from their microenvironment. By adopting a mesenchymal phenotype through EMT, individual carcinoma cells can infiltrate adjacent tissues, cross endothelial barriers, and enter the circulation through blood and lymphatic vessels. Once the tumor cells reach their secondary tissues or organs, they no longer encounter the signals they experienced in the primary tumor, and they can revert to an epithelial state via a mesenchymal-epithelial transition (MET). Consistent with this notion, EMT commonly occurs at the invasive front (tumor-stromal boundary) of many invasive carcinomas (Christofori 2006; Franci, Takkunen et al. 2006). These observations indicate that EMT is triggered by cellular signals from microenvironment. These immune and inflammatory cells secrete cytokines, chemokines, and growth factors, which play essential roles for supporting tumor progression and metastasis. Because it is analogous with the role of inflammation in mediating wound healing, we hypothesize that the migratory and invasive ability of tumor cells at the invasive front is initiated and propelled by an inflammatory microenvironment through the induction of EMT.

4. The role of inflammatory cells and cytokines in EMT/metastasis

4.1 Tumor-Associated Macrophages (TAMs)

Consistent with our hypothesis, a high content of inflammatory cells, particularly tumor-associated macrophages, is commonly found at the invasive fronts of advanced carcinoma (Condeelis and Pollard 2006). Macrophages are key cells in chronic inflammation. M1 macrophages are involved in Type 1 reactions and are classically activated by microbial products, killing microorganisms and producing reactive oxygen and nitrogen

intermediates. In contrast, M2 cells (tumor associated macrophage; TAM) are important components of infiltrated leukocytes in most malignant tumors. They are involved in Type 2 reactions, tune inflammation and adaptive immunity, promote cell proliferation by producing growth factors and enhance angiogenesis, tissue remodeling, and repair. Macrophage directly influences the behavior and function of tumor cells and has been regarded as an "obligate partner for tumor-cell migration, invasion and metastasis" (Condeelis and Pollard 2006). Clinical studies indicate a correlation between TAM density and poor prognosis (Pollard 2004). For example, in PyMT-induced mammary tumors, macrophages are present in the areas of basement membrane breakdown during the development of "early-stage" metastatic lesions and systemic depletion of macrophages results in reduced formation of lung metastasis (Lin, Nguyen et al. 2001). TAMs produce a wide variety of growth factors (such as FGF, HGF, EGF, PDGF and TGF-β and cytokines [such as TNFα, interleukin-6, interleukin-1, and interferons]) to stimulate the growth, motility, and invasiveness of tumor cells. TAMs also produce many proteases, ranging from uPA to a variety of matrix metalloproteinases, to degrade the basement membrane in order to create a channel for tumor cell invasion. In our recent study, we found that the EMT/invasiveness of tumor cells was dramatically enhanced when they were co-cultured with macrophages or macrophage-conditioned medium (Wu, Deng et al. 2009). We showed that this effect, mainly mediated by the secretion of TNFα from macrophages as neutralization of TNFα by TNFα antibody, greatly suppressed macrophage-mediated tumor cell invasion and metastasis(Wu, Deng et al. 2009). Consistent with our finding, Hagemann et al found that co-culturing macrophages with tumor cells enhanced their invasive ability in a manner dependent on TNFα and matrix metalloproteinases (MMP)(Hagemann, Wilson et al. 2005). Interestingly, expression of Snail in the non-metastatic breast cancer cell lines MCF7 and T47D, which contain little endogenous Snail, greatly increased the invasiveness of these cells by inflammation, indicating that Snail, through the induction of EMT, is critical for mediating inflammation-induced invasion/metastasis of breast cancer cells. Knockdown Snail expression significantly inhibited cell migration and invasion induced by inflammatory cytokines; it also suppressed inflammation-mediated breast cancer metastasis in animal model. Thus, macrophages, the major inflammatory component of the stroma in malignancies, facilitate angiogenesis, extracellular matrix breakdown, invasion, and metastasis through multiple mechanisms.

4.2 T-reg cells

Regulatory T cells (Treg), which include many populations that differ in phenotype, cytokine secretion profile and suppressive mechanism (Maloy and Powrie 2001; Shevach 2002; Wood and Sakaguchi 2003), were reported to interact with tumor cells, promoting rather than inhibiting cancer development and progression. High Treg levels have been found in peripheral blood, lymph nodes, and tumor specimens from patients with different types of cancer (Wang 2008). Treg have been characterized by the constitutive expression of Forkhead box P3 (FoxP3), glucocorticoid-induecd THFR family-related receptor (GITR), cytotoxic T lymphocyte associated antigen 4 (CTLA-4), and high levels of the alpha chain of the IL-2 receptor (CD25). It was found that Treg numbers were significantly higher in patients with metastatic cancer compared to healthy donors (Audia, Nicolas et al. 2007; Watanabe, Oda et al. 2010).

The level of FoxP3, an indicator of Treg activity, might also be an indicator of breast tumorigenesis (Gupta, Joshi et al. 2007). It has been demonstrated that high numbers of FoxP3-positive Tregs were present in high-grade tumors, increasing the risk of relapse/metastasis (Bates, Fox et al. 2006). Interestingly, the FoxP3 transcription factor, recently found to be expressed in tumor cells, can regulate a large number of genes. Besides, FoxP3 binds to the gene region upstream of the transcriptional start site of CCR7 and CXCR4 (Zheng and Rudensky 2007), two chemokine receptors recently reported to play an important role in cancer invasion and metastasis (Kodama, Hasengaowa et al. 2007; Pitkin, Luangdilok et al. 2007). Thus, FoxP3 expressed in breast cancer cells might influence metastasis by modulating the expression of these chemokine receptors or other genes, which encode cell surface or secrete molecules that regulate the response of tumor cells to the microenvironment (Merlo, Casalini et al. 2009).

Recently, it has been demonstrated that pulmonary metastasis of breast cancer requires recruitment and expansion of Treg that promote escape from host protective immune cells. Arya Biragyn's group reported that the primary role of tBregs (tumor-evoked Bregs) in lung metastases of breast cancer in the mouse 4T1 model is to induce TGF-β–dependent conversion of FoxP3+ Tregs from resting CD4+ T cells. In the absence of tBregs, 4T1 tumors cannot metastasize into the lungs efficiently due to poor Treg conversion, which suggest that tBregs must be controlled to interrupt the initiation of a key cancer-induced-immunosuppressive event that is critical to support cancer metastasis.(Olkhanud, Damdinsuren et al. 2011)

Tregs were selectively recruited within lymphoid infiltrates and activated by mature dendritic cells likely through the recognition of tumor-associated antigen presentation, which result in the prevention of effector T cell activation, immune escape, and ultimately, tumor progression (Gobert, Treilleux et al. 2009). Treg depletion may become a successful anticancer strategy, and Treg manipulation in terms of frequency and functional activity should be added to the therapeutic regimen to enhance tumor immunity in humans (Wolf, Wolf et al. 2003).

4.3 Myeloid-Drived Suppressor Cells (MDSC) and others

Myeloid-derived suppressor cells (MDSC) are present in many cancer patients and mice with transplanted or spontaneous tumors (Young and Lathers 1999; Almand, Clark et al. 2001). MDSC, characterized as CD11b+ Gr-1+ in mice, can be recruited and activated by multiple factors, such as VEGF, IL-1β and IL-6, many of which are associated with chronic inflammation (Gabrilovich and Nagaraj 2009). Recent studies indicated that these cells also have a crucial role in tumor progression. MDSCs can directly incorporate into tumor endothelium. They secret many pro-angiogenic factors as well. In addition, they play an essential role in cancer invasion and metastasis through inducing the production of matrix metalloproteinases (MMPs), chemoattractants and creating a pre-metastatic environment. Recruitment of MDSCs further produces pro-inflammatory factors, resulting in the amplification of the pro-inflammatory response. MDSCs not only suppress the adaptive immune responses but also regulate innate immune responses by modulating the cytokine production of macrophages (Sinha, Clements et al. 2007), thus directly facilitating metastasis. Recent studies have shown a close correlation between the level of MDSCs and cancer stage, metastatic tumor burden, and responsiveness to chemotherapy (Diaz-Montero,

Salem et al. 2009). MDSCs from mammary carcinoma can promote tumor invasion and metastasis (Bunt, Yang et al. 2007). In Tgfbr2-deficient mice, MDSCs are concentrated at the invasive tumor front and facilitate tumor cell invasion and metastasis through chemokine receptors CXCR2 and CXCR4 (Yang, Huang et al. 2008). It has been recently found that MDSCs accumulated in pregnant mice and exerted an inhibitory effect on NK cell activity, and decreased NK cell activity is responsible for the observed increase in metastasis during murine gestation, providing a candidate mechanism for the enhanced metastatic tumor growth observed in gestant mice.(Mauti, Le Bitoux et al. 2011)

In addition to macrophages and MDSC, fibroblasts/myofibroblasts comprise another major component of tumor stroma. These cancer-associated fibroblasts (CAF) share a lot of characteristics with activated fibroblasts in wound healing and promote tumor progression. Recent studies have demonstrated that CAF are important in tumor cell migration and metastasis. CAF isolated from metastatic breast cancer produce elevated levels of IL-6 and enhance cancer cell invasiveness (Studebaker, Storci et al. 2008). Similarly, De Wever et al found that the invasive growth of breast and colon cancer cells could be stimulated using myofibroblasts isolated from surgical colon cancer specimens (De Wever, Westbroek et al. 2004). In addition, CAF in pancreatic ductal adenocarcinoma are responsible for a poorly vascularized architecture that imposes a barrier for drug delivery and spurs metastasis (Olive, Jacobetz et al. 2009). Furthermore, fibroblasts promote tumor cell proliferation and metastasis through the production of several growth factors, cytokines, chemokines, and matrix metalloproteinases (MMPs). MMPs derived from tumor cells and stromal components are regarded as major players in assisting the metastasis of tumor cells. For example, transgenic expression of MMP3 stimulates expression of Snail through the increased cellular reactive oxygen species, inducing down-regulation of E-cadherin and increased tumor progression (Radisky, Levy et al. 2005). Besides, Reisfeld's group demonstrated recently that CAF are key modulators of immune polarization in the tumor microenvironment of a 4T1 murine model of metastatic breast cancer. Elimination of CAF in vivo by a DNA vaccine targeted to fibroblast activation protein results in a shift of the immune microenvironment from a Th2 to Th1 polarization. This shift is characterized by increased protein expression of IL-2 and IL-7, suppressed recruitment of tumor-associated macrophages, myeloid derived suppressor cells, T regulatory cells, and decreased tumor angiogenesis and lymphangiogenesis. (Liao, Luo et al. 2009)

Neutrophils are also noted as important cells in the tumor inflammatory microenvironment. CXCR2 can induce the expression of matrix metalloproteinase 9 (MMP9) and vascular endothelial growth factor (VEGF) to recruit neutrophils (Albini, Mirisola et al. 2008). This subsequently leads to endothelial cell invasion and blood vessel formation. On the other hand, there are reports demonstrated that neutrophils accumulate in the lung prior to the arrival of metastatic cells in mouse models of breast cancer. Those tumor entrained neutrophils (TENs) inhibit metastatic seeding in the lungs by generating H_2O_2. TENs are present in the peripheral blood of breast cancer patients prior to surgical resection but not in healthy individuals. Thus, whereas tumor-secreted factors contribute to tumor progression at the primary site, they concomitantly induce a neutrophil-mediated inhibitory process at the metastatic site. These neutrophils acquire a cytotoxic phenotype and provide anti-metastatic protection by eliminating disseminated tumor cells. Although the neutrophils are eventually outcompeted by continued influx of metastatic cells, infusion of exogenous neutrophils effectively blocks metastasis and therefore represents a potential therapeutic strategy for management of micro-metastatic disease.(Granot, Henke et al. 2011)

Taken together, all of these infiltrated inflammatory cells secret different cytokines, chemokines, and other factors to influence the tumor cell migration and invasion and contribute to inflammation-mediated metastasis.

4.4 Cytokines

TNF-α, a key inflammatory cytokine, plays a central role in tumor progression. Constitutive expression of TNF-α from the tumor microenvironment is a characteristic of many malignant tumors and its presence is often associated with poor prognosis. Several lines of evidence point to the tumor-promoting effects of TNF-α in inflammation-driven tumorigenesis. First, overexpression of TNF-α confers migratory and invasive properties of many tumor cell lines (Rosen, Goldberg et al. 1991). Second, TNF-α and TNF-α receptor 1 (TNFR1) knock-out mice are resistant to chemical-induced-carcinogenesis in skin and liver metastasis in an experimental colon cancer model (Knight, Yeoh et al. 2000; Arnott, Scott et al. 2004). Third, various tumor-promoting effects of TNF-α are further confirmed in enhancing tumor cell motility, activating oncogenic pathways, and triggering EMT. TNF-α can also promote breast cancer cell migration through up-regulating LOX (Liang, Zhang et al. 2007). Endogenous TNFα contributes to the growth and invasiveness of primary pancreatic ductal adenocarcinoma, and anti-TNFα inhibit metastasis of these tumors (Egberts, Cloosters et al. 2008). Using RNA interference technology, Kulbe et al demonstrated that tumor growth and dissemination were significantly inhibited when TNFα production was blocked (Kulbe, Thompson et al. 2007). In addition, TNF-α can up-regulate SELECTIN and VCAM1 on endothelial cells that promote tumor cell adhesion and migration (Mannel, Orosz et al. 1994; Stoelcker, Hafner et al. 1995). Furthermore, TNF-α enhances the invasive property of cancer cells by inducing EMT through Snail or ZEB1/ZEB2 (Chua, Bhat-Nakshatri et al. 2007; Chuang, Sun et al. 2008). In our recent study, we found that inflammatory cytokine TNF-α is the major signal to induce Snail stabilization and EMT induction (Wu, Deng et al. 2009). We showed that TNF-α greatly enhanced the migration and invasion of tumor cells by inducing EMT program through NF-κB-mediated Snail stabilization. Knockdown of Snail expression not only inhibits TNF-α-induced cancer cell migration and invasion in vitro but also suppresses LPS-mediated metastasis in vivo. Furthermore, knockdown of Snail expression not only blocks metastasis that is intrinsic to the metastatic breast cancer cells but also greatly suppresses inflammation-accelerated metastasis. Collectively, our study indicates that Snail stabilization and EMT induction mediated by the inflammatory cytokine TNF-α are critical for metastasis. Our study provides a plausible molecular mechanism for tumor cell dissemination and invasion at the tumor invasive front.

In fact, under hypoxic and inflammatory conditions, the tumor microenvironment generates and sustains a tumor-promoting cytokine network for facilitating tumor growth and metastasis. For example, the production of TGF-β from myeloid cells, mesenchymal cells, and cancer cells is significantly enhanced in a hypoxic or inflammatory state. TGF-β is a multifunctional growth factor with a complicated dual role in tumorigenesis(Leivonen and Kahari 2007). At the early stages of tumor formation, TGF-β acts as a tumor suppressor by inhibiting proliferation and inducing apoptosis of tumor cells. At the later stages of tumorigenesis, TGF-β functions as a tumor promoter by increasing tumor growth, survival, motility, and invasion. TGF-β has also been shown to induce EMT in normal mammary

epithelial cells and breast cancer cell lines (Miettinen, Ebner et al. 1994) (Forrester, Chytil et al. 2005). As we mentioned in part-2.5 (Molecular regulation of EMT), TGF-β plays an important role in the process of EMT.

IL-6 is another important inflammatory cytokine linking inflammation and cancer. IL-6 transmits its signal through a common signaling receptor, gp130, expressed in many cell types. IL-6 binds to the sIL-6R receptor (gp80, present either on the cell surface or in solution), which then induces dimerization of gp130 chains, resulting in activation of the associated Janus kinases (JAKs). JAKs phosphorylate gp130, leading to the recruitment and activation of the STAT3 and STAT1 transcription factors, as well as other molecules (SHP2, Ras-MAPK, and PI3K) (Mumm and Oft 2008). The role of IL-6 in accelerating tumorigenesis is becoming clear as exogenous administration of IL-6 to mice during tumor initiation results in an increase in tumor burden and multiplicity (Grivennikov, Karin et al. 2009). IL-6 also enhances tumor proliferation in tumor-initiating intestinal epithelial cells (IECs) through NF-κB-IL-6-STAT3 cascade (Bollrath, Phesse et al. 2009; Bromberg and Wang 2009; Grivennikov, Karin et al. 2009). IL-6 can also act as an inducer of EMT in breast cancer cells. Ectopic expression of IL-6 in breast adenocarcinoma cells exhibits an EMT phenotype characterized by suppressing E-cadherin expression and inducting vimentin, N-cadherin, Snail and Twist (Sullivan, Sasser et al. 2009). In addition, IL-6 also synergizes with EGF in inducing EMT through the activation JNK2/STAT3 in ovarian carcinomas (Colomiere, Ward et al. 2009).

The interleukin-1 (IL-1) also promotes inflammatory processes and augments metastasis. There are two forms of IL-1 protein, IL-1α and IL-1β, and one antagonistic protein IL-1 receptor antagonist (IL-1ra). IL-1β is active solely in its secreted form, whereas IL-1α is active mainly as an intracellular precursor. IL-1 is abundant at tumor sites, where it affects the process of carcinogenesis, tumor growth and invasiveness, and the patterns of tumor-host interactions (Apte, Krelin et al. 2006). Genetic ablation of IL-1β in mice results in the absence of metastatic tumors in vivo (Voronov, Shouval et al. 2003). Liver metastasis can be almost completely inhibited in mice with deletion of the interleukin-1β converting enzyme, which is required for the processing of IL-1β (Vidal-Vanaclocha, Fantuzzi et al. 2000). IL-1β also directly induces uPA expression and NF-κB activation, which results in the migration of A549 cells (Cheng, Hsieh et al. 2009).

Together with chemotaxis, chemokines, a family of inducible chemo-attractant cytokines that regulate the chemotaxis of tumor cells and other cell types, are thought to be involved in every crucial step of tumor cell dissemination (Roussos, Condeelis et al. 2011). Chemotaxis of carcinoma cells and tumor-associated inflammatory and stromal cells is mediated by chemokines, chemokine receptors, growth factors and growth factor receptors. Chemotaxis helps to shape the tumor microenvironment. Directional migration to a chemokine source is evident both in vitro and in vivo for most cells of the tumor microenvironment. The most common chemokine receptor detected in cancer cells is CXCR4; another common one is CCR7 (Muller, Homey et al. 2001; Lazennec and Richmond 2010). In standard chemotaxis assays in vitro, CXCR4-positive cancer cells can migrate in a directional manner toward CXCL12, whereas CCR7-expressing cancer cells can migrate towards CCL21 (Kodama, Hasengaowa et al. 2007; Pitkin, Luangdilok et al. 2007). Recently, it has been reported that the recruitment of inflammatory monocytes, which express CCR2,

is dependent on CCL2 synthesized by both the tumor and the stroma, facilitating breast-tumor metastasis; the same is true for the subsequent recruitment of metastasis-associated macrophages and their interaction with metastasizing tumor cells (Qian, Li et al. 2011).

5. Summary

Every year about 500,000 people in the United States die as a result of cancer, among which 90% exhibit systemic disease with metastasis. That's why it is so important to understand the mechanism behind EMT and metastasis. Based on thousands of studies in this field in recent years, significant progress has been made regarding our understanding of EMT and metastasis, which point out that EMT is the most critical mechanism implicated in tumor metastasis and recurrence. It is now quite clearly that solid tumors are not simply clones of cancer cells. A variety of stromal cells in the surrounding environment are recruited to tumors, which including mesenchymal supporting cells (e.g. fibroblasts), cells of the vascular system, and cells from immune system, such as TAMs, Treg, MDSC, Neutrophils and so on. The dynamic interaction which exists between cancer cells and the inflammatory microenvironment not only enhances growth of the primary cancer but also facilitates its metastatic dissemination to distant organs. There are many evidences show that the induction of EMT is dependent on the signals that cells received from their microenvironment, and the crosstalk between inflammation and metastasis has an un-replaceable role in each step for the successful establishment of a metastatic tumor (Fig. 2).
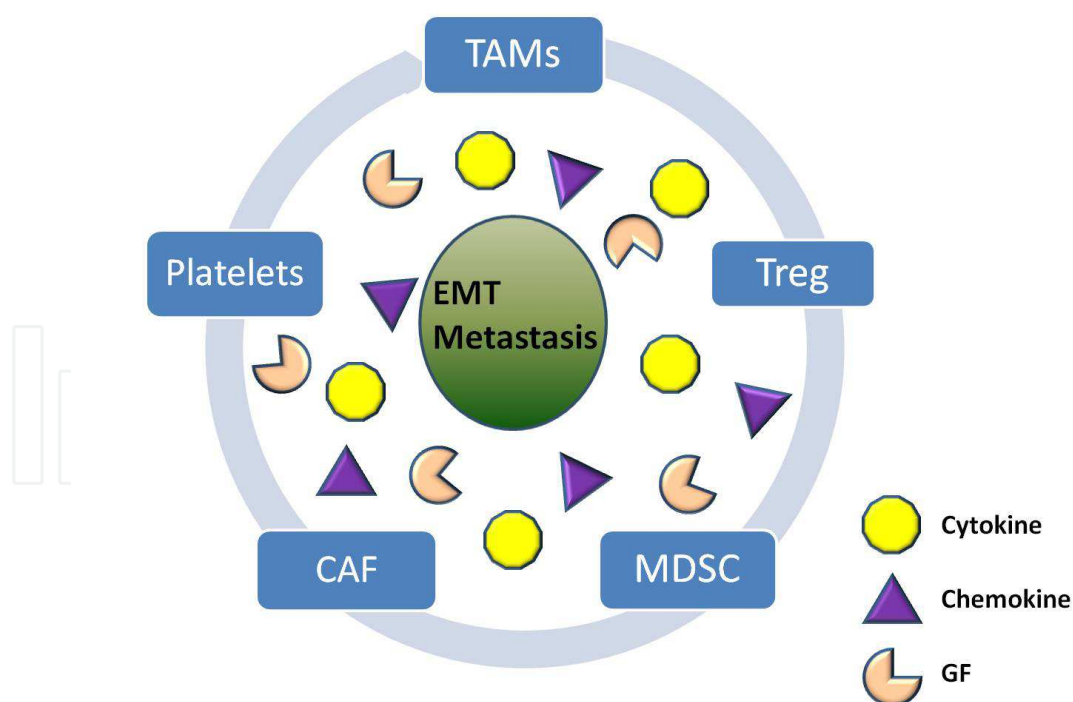

Fig. 2. Tumor Inflammatory Microenvironment in EMT and Metastasis.

Understanding how inflammatory microenvironment is maintained and how it contributes to the tumor progression and metastasis will be crucial for understanding tumor biology as

well as the development of new effective cancer prevention and therapy. Hopefully, with recent research illuminating the involvement of infiltrated inflammatory cells and many kinds of cytokines in tumor progression and EMT/Metastasis, a more comprehensive view of how cancer cells spreads to different organs in a specific manner will emerge in the near future. However, we have to realize that several challenges still need to be addressed about how to translate these basic findings into clinical practice and find novel treatment strategies targeting the inflammatory microenvironment which could efficiently kill both primary and metastatic tumor cells.

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7. References

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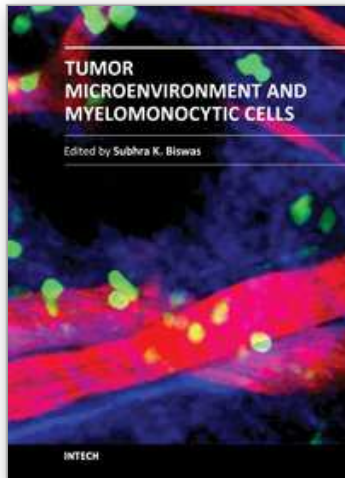
Tumor Microenvironment and Myelomonocytic Cells

Edited by Dr. Subhra Biswas

Tumor microenvironment represents an extremely dynamic niche shaped by the interplay of different cell types (e.g. tumor cells, stromal cells), their soluble products (e.g.cytokines, chemokines and growth factors) and varied physico-chemical conditions (e.g low oxygen concentration or hypoxia). Recent studies have identified myelomonocytic cells as key players in regulating the tumor microenvironment and hence, tumor progression in a variety of cancers. In view of these findings, the present book attemps to provide a comprehensive account of the diversity of tumor microenvironment across different cancers and how myelomonocytic cells have taken the center-stage in regulating this niche to direct cancer progression. A better understanding of the myelomonocytic cells and the mechanisms by which they regulate cancer progression will open new vistas in cancer therapeutics.

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