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Epithelial-mesenchymal transition in cancer: An overview

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Abstract

Epithelial-mesenchymal transition (EMT) is a complex developmental program that enables carcinoma cells to suppress their epithelial features changing to mesenchymal ones. This change allows cells to acquire mobility and the capacity to migrate from the primary site. EMT provides a new insight for understanding the several steps of the metastatic process, from dedifferentiation to a more aggressive phenotype. In this review, we provide a summary of the historical and recent insights into the role of EMT in cancer metastasis, including the main biomarkers already described, the new potential biomarkers, as well as the role of EMT for resistance to therapies.

From transformation to transition

Our body is formed by cells of different types and functions. In this review, we will approach a phenomenon that occurs between two specific types, epithelial and mesenchymal. Epithelial cells are highly adhered by intercellular adhesion complexes differing from mesenchymal ones, which are nonpolar and have junctions that allow for greater mobility between cells [1]. These two types of cells are involved in the process known as epithelial-mesenchymal transition (EMT), which is a normal phenomenon that occurs mainly in the embryonic stage [2]. Elizabeth Hay (1985) made the first descriptions of the process more than 40 years ago in studies *in vivo* with chickens; she observed the transformation of epithelial into mesenchymal cells. Later, this phenomenon ceased to be considered exclusively embryonic, as it was also present in other processes that required greater cellular mobility and thus increased migratory capacity, such as the healing process and even the progression of cancer [3]. The term transition started to be used due to the reversibility of the process (EMT-MET). EMT can be classified in three types according to the process involved: type 1 for gastrulation and embryogenesis, type 2 for regeneration and wound healing and type 3 for carcinogenesis (metastasis, malignancy and invasion) [4].

Cell plasticity and EMT

Cell plasticity is observed to be a collective migration process, in which epithelial cells move in a connected way both physically and functionally [5]. This phenomenon has been identified as a critical process especially during the embryogenesis of the mammary gland [6], intestinal differentiation [7] and the healing process [8]. Cellular plasticity that occurs in development processes suggests that differences between epithelial and mesenchymal cells are more likely to be a continuum spectrum than two different cell states. In mammals, EMT and metaplasia are targets of epithelial cell plasticity studies [9]. Metaplasia is a spontaneous process in which a particular differentiated cell type converts into another without the need of cell division. The term transdifferentiation is used by cell biologists and, in spite of being more common in amphibians, it has also been observed in mammals among islet cells, hepatocytes, lactotrophs and pneumocytes [9].

EMT and the metastatic process

Metastasis is a process defined when cells of the primary tumor break off, entering the bloodstream and/or lymph vessels and settling at a secondary site. EMT is paramount for this phenomenon, being considered a promoter of metastasis, due to the transformations through which cells acquire mobility, a mesenchymal feature. The metastatic process associated with mesenchymal features are displaying in a huge variety of cancers, including the most aggressive cancer subtypes [10]. This association is corroborated by many reports linking EMT and disease progression [11-14].

Metastasis is a complex process and many points are still not well understood but it is well-recognized that it consists in several steps [15]. Detachment is the first step in metastasis, in which the cells of the primary tumor lose contact with each other and become mobile owing to the mesenchymal acquisition triggered by EMT. Subsequently, the cells are able to invade neighboring tissues and the basal membrane (invasion phase) reaching the blood and lymphatic vessels, thus characterizing the stage of intravasion where no more epithelial characteristics are observed. Some cells exit the vessels by the process of extravasation, reaching other organs called secondary sites. Not all the cells go through these stages, but those that are fixed can proliferate in this new environment, reaching the stage of colonization and forming micrometastases; this may give rise to the secondary tumor [16]. Some studies demonstrated that cells from the primary and secondary tumors share a similar epithelial nature and that in many tumors such as breast, prostate, colorectal and lung, the cells from the secondary tumor were less differentiated than their counterparts [16]. This observation was incompatible with the EMT theory and a reverse process (MET) was suggested as part of the metastatic tumor formation [17].

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Some hypotheses try to explain the relationship between EMT and metastasis. One of the strongest hypotheses is that tumor cells are in different stages, and consequently cells at different stages can enter into EMT, evolving to more advanced degrees of the tumor.

Tumor microenvironment involved in EMT

The tumor microenvironment comprises several cell types, such as inflammatory and immune cells, extracellular matrix components (ECM), cancer associated fibroblasts (CAFs), endothelial and epithelial cells, pericytes, mesenchymal stem cells, etc. It plays an important role in tumor progression, induction of EMT, and cancer metastasis. The alteration of phenotypes that occur in EMT in tumor cells involves several extracellular signaling such as TGF-β, NF-kB and Wnt [18]. Cellular plasticity of tumor cells is important for its adaptation to the microenvironment changes between the primary site and the site of colonization. Therefore, heterotypic interactions are established to determine the course of tumor progression and metastasis [19-21].

Immune cells derived from bone marrow are able to infiltrate the primary tumor, inducing EMT by TFG-β, EGF and HGF from several signaling pathways [22]. Platelet-derived TFG-β and direct contact of immune cells with tumors synergistically activate two signaling pathways in cancer cells, TFG-β/Smad and NF-kB, leading to an alteration of the mesenchymal phenotype and to the initiation of the metastatic process *in vivo*. Inhibition of NF-kB signaling in cancer cells or ablation of the expression platelet TFG-β1 expression may promote protection against the development of lung metastasis *in vivo* [22].

In co-culture of breast tumor cells with bone marrow-derived mesenchymal stem cells (MSCs) a significant positive regulation of specific EMT markers such as N-cadherin, Vimentin, Twist and Snail and negative regulation of E-cadherin expression was observed [23]. Thus, this group of cells can promote metastasis in breast cancer through the facilitation of the EMT process. Another cell type that may contribute to tumor progression through EMT induction is tumor associated macrophages (TAM). Bonde *et al.* [24] demonstrated that through the signaling of TFG-β and activation of the β-catenin pathway these cells can induce EMT in the intra-tumor environment. When the gene and protein expressions associated with EMT and macrophages were analyzed, these authors found a positive correlation between TAM density and expression of mesenchymal markers, activation of β-catenin pathway, increase of mesenchymal markers expression, decrease of E-cadherin expression, and an invasive phenotype. Other components such as CAFs have also been shown to participate in EMT. CAFs can be activated by interleukin 6 (IL-6) and, through secretion of metalloproteinases, they induce EMT in tumor cells being related to aggressiveness [25]. IL-6 is considered to be an inducer of EMT phenotype in breast cancer cells, with the cells exhibiting increased levels of Interleukin- 6 (IL-6) according to the increase in tumor grade and poor survival of the patient [25]. In addition, Sullivan *et al.* [26] have observed E-cadherin repression by IL-6 in positive estrogen receptor (ER+) breast cancer cells, corroborating the findings of IL6 as an EMT inducer.

The identification of specific mediators that act in signaling pathways inducing EMT helps to elucidate the triggering of this process. Consequently, many of these molecules have been used as biomarkers.

The main biomarkers for EMT

Biomarkers are widely used in EMT studies to characterize the state in which cells are found. In addition to the level of expression, the distribution and function of proteins can also be altered, allowing them to be used as biomarkers. Some are already well-related to this process, such as growth factors (TFG-β and Wnts), transcription factors (SNAIL and TWIST), adhesion molecules (cadherins) and molecules present in the cytoskeleton (vimentin) [17].

TGF-β is considered one of the first inducers of EMT and an important suppressor of epithelial cells [27]. It stimulates cells to lose epithelial markers, such as E-cadherin, and also to gain mesenchymal markers, such as vimentin. TGF-β is related to cell proliferation, and when this growth factor is mutated it contributes to the uncontrolled proliferation of cancer cells [28]. Another important transcription factor for EMT called Snail, which is induced by TGF-β, controls the expression of proteins with the mesenchymal phenotype and represses epithelial proteins such as E-cadherin; its overexpression may induce to the transition process. Snail also has other targets that are related to cell polarity, cell cycle and apoptosis [29]. In addition, this protein is able to promote the migration and differentiation of epithelial cells, and in the embryonic stage it promotes mesoderm formation [30]. Like Snail, Twist (also a transcription factor) is related to the migration and differentiation of epithelial cells into the mesenchymal phenotype. The phenomenon known as "cadherin exchange" is influenced by Twist, in which it regulates the shift from E-cadherin to a less adhesive N-cadherin; though E-cadherin production is repressed while N-cadherin is stimulated. N-cadherin also acts on the intracellular adhesion system and is a characteristic cadherin in mesenchymal cells [31].

In addition, the expression of β-catenin and the loss of *CDH1* expression are also associated with the mesenchymal stages [30,32,33]. The levels of cadherins (E-cadherins and N-cadherins) are commonly evaluated to monitor EMT, and the reduction or even loss of their function is widely used in monitoring the evolution of the mesenchymal stage of cancer cells [34]. The gene encoding E-cadherin (*CDH1*) usually has its expression diminished by epigenetic factors such as repression of transcription factors and methylation of the CpG islands [35]. *CDH1* can also be mutated and present a nonfunctional protein [36].

In breast cancer, alterations such as loss of differentiation characteristics, tumor grade, metastasis, poor prognosis and invasiveness are inversely correlated with the levels of E-cadherin [37,38], so that changes in expression of E-cadherin have been used as a tumor progression monitor. It is also possible that it has a more significant role in the MET process due to the transition between E-cadherin and N-cadherin [39].

E-cadherin expression is also affected by the Wnt signaling pathway that regulates the transcription of genes that control cell proliferation, differentiation and migration, and its expression is identified by high β-catenin concentrations. The presence of Wnt/β-catenin signaling is observed in more advanced cases with worse prognoses [40].

Some biomarkers help identify the EMT phases. The acquisition of mesenchymal markers such as vimentin, the collagen-specific tyrosine kinase receptor, tyrosine kinase 2 receptor discoidin domain (DDR2) and fibroblast-specific protein 1 (S100A4) by epithelial cells have been described well [41,42]. Vimentin is an intermediate filament, usually found in migratory processes and expressed in several cell types [43,44]. The increased expression of vimentin has already been observed in several carcinomas such as breast, prostate, colon and oral mucosa, associated with increased invasiveness and metastasis [44,45]. For example, when analyzed in patients with breast cancer in advanced disease stage (Bloom Richardson scores 8 and 9) and with negative progesterone receptors (PR-), vimentin showed a significantly increased expression [44]. Studies in breast cancer cell lines displaying

different degrees of invasiveness demonstrated the expression of vimentin being regulated by Smad interacting protein 1 (SIP1), revealing a new pathway that may contribute to metastatic progression [46]. These results demonstrate that the vimentin expression may be used as a biomarker to predict factors such as disease-free survival and overall survival in breast cancer [44].

Attempt to explain reversible EMT through microRNAs and epigenetics

One of the main paradigms of the evolution of carcinogenesis is that metastasis is originated from irreversible mutations. Some researchers propose that the processes of carcinogenesis may be derived from reversible epigenetic processes [47,48]. These epigenetic changes involve DNA methylation, histone modifications, and changes in the expression of microRNAs (miRNAs) – small molecules of non-coding RNA that act as a post-transcriptional mechanism in the expression of genes, blocking translation or promoting mRNA degradation.

Many miRNAs are located in regions more susceptible to deletions, amplifications and recombination. These changes correlate miRNAs with processes that regulate cell division, apoptosis, angiogenesis; factors directly linked to the development and progression of cancer [49]. Many miRNAs have been described as tumor suppressors and oncogenes depending on the target mRNA. Several types of EMT regulation are studied, but in recent years, with the observation of the association of tumor transition and progression, miRNAs have gained importance because they are described as agents capable to influence the mesenchymal and epithelial phenotypes [50].

Many miRNAs are related as important regulators of EMT. The miR-200 family (miR-200a, miR-200b, miR-141 and miR-429) have been described as epithelial markers with important function in this process by suppressing the change of epithelial cells to mesenchymal by targeting the *ZEB1* and *ZEB2* mRNAs, thus changing their expression. ZEB1 and ZEB2 proteins are members of the zinc-finger family E-box-binding homeobox factor (ZEB) and are characterized as being transcriptional repressors. These repressors induce EMT by repressing the expression of E-cadherin, contributing to tumor progression [51]. The variation in miR-200 expression directly influences TGF-β, and the expression ratio between them is inversely related. The high expression of miR-200 has the ability to block TGF-β, which in turn does not induce EMT. The miR-200 family also influences the concentrations of markers such as vimentin, where its inhibition increases the levels of the mesenchymal marker [50]. Hsa-mir-9 shows a strong relationship with EMT markers, mainly targeting the *CDH1* gene, which encodes E-cadherin [49]. Mir-9 can reduce E-cadherin expression by up to 70% and at the same time it increases the expression of vimentin by inducing EMT. In primary breast tumors, mir-9 is overexpressed when there is presence of metastasis [50]. Inhibition of miR-9 resulted in low migration and invasion into M12 cell lines, as well as low tumor growth and metastatic indices in male mice, indicating that mir-9 acts as an oncomiR [51]. According to Li Ma *et al.* [52], miR-9 activates β-catenin signaling that contributes to vascular endothelial growth factor (VEGF) expression in SUM149 and not SUM159 cell lines. In the MCF7-RAS line, miR-9 inhibited E-cadherin expression and induced VEGF-induced tumor angiogenesis, indicating the ability of miRNA to modulate E-cadherin expression. Another miRNA that is overexpressed in the presence of metastasis is the miR-10b identified by microarray in mammary carcinomas [53]. Inhibition of miR-10b in rodents decreased invasiveness, and its high expression promoted mobility in non-invasive cells. One of the most described miRNAs in several tumors is miR-21, which is also correlated with the metastatic process. Its inhibition decreases the invasiveness of cells *in vitro* and in lung tissues with metastasis in rats [50]. The miR-30 family is often found in several tumors with low expression and miR-30a has the *VIM* gene as a target in which it binds the 3'UTR region. In the study by Cheng *et al.* [54], the high expression of miR-30a is related to a decrease in migration and invasiveness of breast neoplastic cells. The high expression of miR-30a has recently been described as being related to the inhibition of the mobility of lung tumor cells because there is a decrease in the expression of Snail, a transcriptional regulator that represses E-cadherin expression during EMT [54].

MiR-155 is commonly found with a high expression in several cancers [55,56]. The study made by He *et al.* [57] found miR-155 inversely correlated with HER2 expression in breast tumors. *HER2*, in turn, is a gene that plays an important role in malignant tumor progression and may be inhibited by miR-155 expression in breast cancer cells.

Other epigenetic mechanisms, such as CpG promoter methylation and histone modification, also play a role in the regulation of EMT as main regulators of several transcription factors linked to EMT program, including Twist, Snail, Slug and target genes such as *CDH1* [58]**.** The hypermethylation of the *CDH1* promoter has been observed in mammary carcinomas leading to a decrease in E-cadherin expression favoring the mesenchymal phenotype [59].

Treatment with demethylating agents causes the re-expression of E-cadherin [60]. Another important example is the polycomb group (PcG) proteins PCR1 and PCR2. They are epigenetic regulators that act as repressors and have a key role in regulating the expression of E-cadherin and a variety of proteins [60]. During cancer evolution, the elevated expression of certain PRC2 subunits is thought to drive malignant progression through an EMT program [61] by repressing key genetic targets, including *CDH1*. Therefore, PcG proteins can drive tumor development controlling the different phenotypic states of cancer cells.

EMT and resistance to therapies

EMT is clearly associated with therapy resistance and metastasis. The role of EMT is evident in several tumors, including prostate [62] and pancreas tumors [63]. The stem cell features acquired in EMT processes are an important focus of current research and must be considered when choosing therapeutic intervention [64]. Several lines of research try to target the aggressive traits of the dedifferentiated cells, including strategies designed to reverse the program by inducing a MET [65]. The idea behind this strategy is the reestablishment of the epithelial state with the consequent loss of stem-like properties. Molecules involved in the maintenance of cell adhesion, polarity and the interaction with the basal membrane are good candidates as targets [66-68].

Several efforts have been made to better understand the signaling pathways involved in the maintenance of cancer cells in the stem cell state and to directly target them. Factors such as prostaglandin 2 (PGE2) secreted by mesenchymal stem cells, together with cytokines, induce a stem cell state and create a favorable niche [69]; canonical pathways such as NF-κB and PI3K-AKT also contribute to reveal new targets including the trophoblast cell surface antigen 2 (TROP2), which regulate the PI3K-AKT pathway, thus inducing EMT in gallbladder cancer [70]. In breast cancer, the expression of Twist has been shown to be related to drug resistance. Twist transcriptionally upregulates AKT2 which increases migration, invasiveness and paclitaxel resistance. When AKT2 was silenced, the resistance of paclitaxel was reduced [71].

Also, the overexpression of Twist promotes hormone resistance to the estrogen receptor modulator (SERM) tamoxifen and to the selective estrogen receptor down-regulator [72]. Breast cancer ER-positive cell line MCF-7 became resistant to tamoxifen when the EMT morphology was induced (loss of cell-cell junctions and change in the morphology) [73]. Furthermore, the EMT-like phenotype with HER2 overexpression is resistant to trastuzumab [74].

In summary, the disruption of these paracrine and autocrine signaling pathways can induce a more differentiated and susceptible-to-therapy epithelial state.

Conclusion

Our understanding of the role of EMT/MET-related processes in cancer evolution has dramatically increased, with several studies strongly supporting the notion that EMT is a key mechanism for effective metastatic dissemination. Many main factors that driven EMT are now recognized, as reviewed in this article, but further research is necessary to identify all the components of this complex program. This knowledge will have a huge impact on the identification of new markers for disease severity and potential for recurrence. Another aspect of great importance is the development of new therapies, based on the notion by targeting the EMT-related mechanisms one can hold the cells in an epithelial state that is unfavorable for tumor progression.

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