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Is the epithelial-mesenchymal transition an ally or an enemy of cancer?

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Abstract

The cancer continues to be a leading cause of mortality in the world, the increment number of the cases has been correlated with the mechanisms that the tumoral cells have for growth and metastasis, there are some processes for the survival and resistance of cancer cells including epithelial-mesenchymal transition, metastasis, drug resistance and angiogenesis. The EMT is a biological process that allows cells of epithelial lineage undergo to a conversion to mesenchymal cell phenotype resulting in cells in intermediate states that have both, epithelial and mesenchymal characteristics. The ETM process induced pluripotent stem cell reprogramming and confers to the cancer cells tumor-initiating and metastatic potential. The development of metastatic process involves some proteins like E-cadherin, HLA-E, SPARC, TNS-4 and FN-1, each protein has an important role as check point of the metastasis and allow immune evasion and grows the seconds tumor.

Keywords: ETM; Metastasis; Immune evasion; E-cadherin; HLA-E; SPARC; TNS-4; FN-1.

Abbreviations: EMT: Epithelial-Mesenchymal Transition; PMN: Premetastatic Niche; TME: Tumoral microenvironment; CAFs: Cancer Associated Fibroblasts, TAMs: Immune Cells Like Tumor-Associated Macrophages; CTCs: Circulating tumor cells; BMDCs: Bone Marrow-Derived Cells; MHC: Major Histocompatibility Complex; CTL: Cytotoxic T lymphocyte; TILs: Tumor-Infiltrating Lymphocytes; NK: Natural Killer.

Introduction

Despite the continuous deployment of new diagnostic and treatment strategies, cancer continues to be a leading cause of mortality. Based on the GLOBOCAN 2020 dates, there were almost 10.0 million cancer deaths, 19,292,789 new cases in the world in 2020, and forecast almost 28.9 million new cases in 2040 [1].

The increment number of the cases has been correlated with the mechanisms that the tumoral cells have for growth and metastasis [2]. Recently evidence, have been identified common features involves in cancer development that have been dubbed hallmarks of cancer". These hallmarks are characteristics of the complex biological capabilities acquired during the development of tumors [3] and one of these hallmarks is the evasion of the immune response [4].

Tumor cells use diverse steps to avoid effectively the immune system [5]. One of these pathways is correlated with the inhibitory and stimulatory immune checkpoint molecules, the expression of these molecules in diverse tumor types (like melanoma, renal, ovarian and lung carcinoma [6-9] has been related to important processes for the survival and resistance of cancer cells including epithelial-mesenchymal transition, metastasis, drug resistance and angiogenesis [10].

Diverse studies have shown that epithelial-mesenchymal transition (EMT) is associated with a variety of immunosuppressive cells, and the expression of immune checkpoints, such as programmed cell death-ligand 1, in several cancer types [11-14]. Also, the epithelial-mesenchymal transition (EMT) tumor cells have a stretch crosstalk with the immune cells providing EMT cells promoting immune exclusion [15].

The EMT is a cellular program that confers to the cancer cells tumor-initiating and metastatic potential [16]. Furthermore epithelial-mesenchymal transition (EMT) [17] increased the success of immunotherapy [18,19].

Some proteins like as HLA-E and SPARC (secreted protein acidic and cysteine rich) recently have correlated with the immune evasion of tumoral cells [20,21], also proteins like E-cadherin have also been related to the EMT in different types of cancer [22,75,81,88]. Therefore, knowing about the mechanisms and the molecules implicated in the immune evasion and the EMT process are essential to ensure the most effective therapy, reduce the damaging effects of treatment, and direct the therapy to specific targets. In this article, we will briefly present an overview of how cancer evades immunity, the relation between the EMT and immune evasion, and how some proteins like E-cadherin, HLA-E, SPARC, TNS-4 and FN-1 have correlated with these processes.

Tumor immune evasion

The immune system is shaped by a variety of cells and molecular mechanisms [23] that are equilibrate for the recognition, elimination and memorize of harmful agents such as virus, bacteria, allergenic substance and even cellular alterations such as tumoral cells in the organism. However, this synchronized process of recognition to memorize has been altered by the cancer cells using the host immunity mechanisms to grow and disseminate in the organism even if the host has a functional immune system. This cancer activity had been studied for decades and receive the name of immunoediting [24,25].

The process of immunoediting is conformed for three stages: an initial one, knowing like -elimination- where the immune system can recognize and eliminate tumoral cells by innate and adaptive immune cells [26], the second one is equilibrium, where the malignant cells that could be destroyed remain and develop greater adaptation of the tumor-cells consequently for the pressure exercised by the immune system on the genetically and unstable highly heterogeneous cells in the tumor mass [27]. The final stage is escape or evasion, this happens when the selected cancer cells lack control thereby grow and disseminate in an immunocompetent environment [28].

Therefore tumors exploit several immunological processes such as the use of regulatory T cells (Tregs); CD4+CD25+ FoxP3+ for

the immune suppression [29]. Diverse studies have shown that tumor-derived Tregs have comparatively higher suppressive activity than naturally occurring Tregs [30,31] this is probably caused using multiple suppressive mechanisms to reduce tumor-associated antigen (TAA)-specific T-cell immunity [32]. The defective antigen presentation is another mechanism used by the tumoral cells and this occurs because of the affectation of the major histocompatibility complex (MHC) secondary to the down modulating antigen processing machinery. Therefore, the expression of tumor antigen is downregulated and has correlated with a cytotoxic T lymphocyte (CTL) with low capacity for recognition of target antigens on the tumor cells [33].

Another fundamental mechanism by which tumors can evade immune surveillance is by crippling CTL functionality via the production of immune-suppressive cytokines, especially by immune cells and epithelial cells [34]. For example, TFG- α which is the principal mediator of this activity has correlated with the inhibit maturation of dendritic cells (DC's) and cytokines like tumor necrosis factor (TNF- α), IL-1, IL-6, colony-stimulating factor (CSF)-1, IL-8, IL-10 can also significantly contribute to cancer growth [34,36,37] also studies had demonstrated that VEGF produced by tumors, inhibits the differentiation of progenitors into DC [38]. Pericyte are specialized cells that are in intimated contact with the basement membrane of capillaries, they coordinate intercellular signaling with the other components of the blood vessel [39], this cells also are implicated indirectly in tumor growth and metastasis tumor by diverse mechanisms for example the vasculature hyperstimulated by VEGF often has reduced pericyte coverage, its decrease facilitating metastatic spread [40].

Another component is the immune deviation produced by shifting the balance from Th1 to Th2 in a TGF- β - and IL-10-dependent manner [41], furthermore the expression of inhibitory molecules like programmed cell death (PD)-L1/B7H1 on tumor cells also has been associated with deletion or energy on tumor-reactive cells [42,43].

Epithelial-mesenchymal transition and immunity

The Epithelial-Mesenchymal Transition (EMT) is a biological process that allows cells of epithelial lineage undergo to a conversion to mesenchymal cell phenotype resulting in cells in intermediate states that have both, epithelial and mesenchymal characteristics [44]. This process occurs naturally during embryogenesis, and organ development [45] in adult life participates in diverse process like tissue regeneration and organ fibrosis but this reversible program reactivates during cancer pathogenesis [46-48].

During the EMT process, epithelial cells progressively lose their classic appearance by the disruption of cell-cell junctions, degradation of the underlying basement membrane, and reorganization of the extracellular matrix (ECM). After that, the cells adopt a mesenchymal morphology with the particularity of reverting back to an epithelial state using the reverse process, known as mesenchymal-epithelial transition (MET) [49]. Recently evidence showed that the reactivation of EMT in neoplastic cells is responsible for the malignant progression of possibly all types of cancer (pancreatic, hepatocellular, bladder, lung, colorectal carcinoma) [50-55].

These morphology changes are possible by the interaction of tumoral cells and diverse types of cells like angiogenic vascular cells, tumors, cancer-associated fibroblasts (CAFs) and immune cells like tumor associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), natural killer (NK) cells, and different T lymphocyte subpopulations, such as CD4+ T cells, CD8+ T cells, regulatory T cells (Tregs), and B lymphocytes mediated by signals pathways and transcription factors in the tumoral microenvironment (TME) [56,57].

The transcription factors (TFs) are involucrate in cellular functions such as cell proliferation, migration, apoptosis, and extracellular degradation, and their activation can occur by a variety of stimuli like extracellular signals, external agents, and pathologic intrinsic states [58-60]. TFs participate during the carcinogenesis process stimulate, tumor progression, angiogenesis, immunosuppression, invasion, and metastasis. In particular, has linked increased expression of EMT TFs such as TWIST1, SNAIL1, and ZEB1 with immune evasion during the EMT process. In the early stages of transformation, cytokines/chemokines (TGF β , IL-6, EGF, VEGF, and HGF) secreted by CAFs and TAMs attract various stromal and immune cells to the TME. These immune cells in turn provide a niche that facilitates the epithelial-mesenchymal transition, this occurs by the inhibition of effector immune cells and the accumulation of myeloid suppressive cells [61-64]. Another example of EMT TFs that recently have been associated with immune evasion is brachyury (T-box transcription factor T) which in a normal state is correlated with development pathways [65]. When is overexpressed by tumoral cells, upregulates levels of the transmembrane glycoprotein mucin-1 (MUC-1). Overexpression of MUC-1 led to reduced susceptibility to killing by tumor necrosis-related apoptosis-inducing ligand (TRAIL) and to CD8⁺ cytotoxic T cells (CTLs) lysis [66]. In addition, a study realized in diverse types of carcinomas demonstrates that high levels of brachyury reduce the susceptibility of carcinoma cells to either CTLs, NK, and lymphokine-activated killer (LAK) cells by decreasing the contribution to cell death of caspase-dependent pathways [67]. The phenotypic alterations that the tumoral cells suffer during the EMT process have significant consequences for the recognition by cells of the immune system and down or upregulation of cell surface molecules of immunological significance have been described [68]. In melanoma cells have been reported that EMT-like alterations reduce the expression of diverse tumor antigens allowing the escape from T cells specific for these antigens [69]. T cell-driven immunoediting of breast tumors in Neu-transgenic mice led to the emergence of antigen-loss variants that had undergone an EMT [70]. Furthermore, cells of non-small cell lung cancer (NSCLC) showed a significantly reduced expression of immunoproteasome components and their regulators [71]. The antigenic peptides are produced by the immunoproteasome and bind to human leukocyte antigen (HLA)-I molecules for recognition by CD8⁺ T cells. Consequently, the low expression of the immunoproteasome leads to decreased presentation of antigenic peptides. The reduction in antigen presentation and recognition by CTLs have been correlated with the downregulation of HLA-1 molecules demonstrated in epithelial cell lines of different tumors because of EMT [72,73]. The alteration in the levels of immune effectors like CTLs had clinical consequences, studies realized in mesenchymal subtype of ovarian cancer demonstrated worse prognosis and survival compared to other subtypes, this was correlated with a decreased number of CD8⁺ tumor-infiltrating lymphocytes (TILs) [74], other findings realized in an immunohistochemistry study performed in patients

with gastric cancer, had a high expression of EMT traits, the infiltration of TAMs, and the expression of TGF- β 1 were associated with a negative prognosis [75]. In a study of lung adenocarcinoma [76], EMT markers were associated with enhanced tumor infiltration of CD4⁺Foxp3⁺ Tregs and upregulation of inhibitory immune checkpoint molecules such as programmed cell death (PD)-ligand (L) 1, PD-L2, and CTLA-4, as well as a study in patients with adenocarcinoma of the lung, showed an association between EMT tumor cells and increased numbers of infiltrating PD-1⁺ cells [69]. Recent associations between autophagy and EMT resistance to immune effector mechanisms were made [69]. Studies realized in breast cancer cells showed that tumoral cells reduce the susceptibility to CTL-mediated lysis depending on upregulation of the stem cell marker Kruppel-like factor-4 (KLF-4) and miR-7 down regulation [77,78] also this type of tumoral cell that acquires an EMT phenotype had an increase resistance to CTL-mediated lysis, these resistant cells exhibited attenuation in the formation of an immunologic synapse with CTLs along with induction of autophagy [79]. Therefore, autophagy appeared to be critical to resistance to CTL-mediated lysis and a main process for EMT. Thereby, diverse studies had demonstrated that EMT is associated with the upregulation of inhibitory immune checkpoint molecules such as programmed cell death (PD)-ligand (L) 1, PD-L2. A study in patients with adenocarcinoma of the lung showed an association between EMT tumor cells and increased numbers of infiltrating PD-1⁺ cells [69]. Another study had demonstrated that CD4⁺ T cells are the main source of IL-6 in clear cell renal carcinoma cells can induce EMT-like features [80].

The role of proteins

The activity of diverse pathways and their transcription factors during the conservation of the tissues requires the function of a variety of proteins as shown in Table 1, because of the variety of activities of these proteins that are recently associated with the EMT process and the immune response, this is a recent area of research, and we will talk about this interaction:

E-cadherin: E-cadherin is a transmembrane glycoprotein and its main function is structural, maintaining cell-cell interactions and the polar orientation of cells [81]. Deletion and dysregulation of E-cadherin are correlated with alteration of intercellular junction, and subsequently, acquire a more mobile and invasive mesenchymal-like phenotype, this allows tumor invasion and metastasis [82,83]. In view of these facts, previously E-cadherin was considerate a cause of EMT [73], however, the abatement of E-cadherin is more a consequence of EMT than a cause [84,85].

In the normal tissues E-cadherin maintain intercellular union binding with β - and p120-catenins yielding a multiprotein complex, which interacts through α -catenin to actin filaments in the cell [86]. In normal cells, E-cadherin exerts its tumor-suppressing role mainly by sequestering β -catenin from its binding to LEF (lymphoid enhancer factor)/TCF (T cell factor) which has the function of transcribing genes of the proliferative Wnt signaling pathway [87].

Several studies have demonstrated that E-cadherin is involved in several signaling pathways, such as the Wnt/ β -catenin, Rho GTPase, and EGF/EGFR pathways [71,72,88] which are activated in carcinogenesis and play a role in many cancers. Therefore, alteration of these pathways had been correlated with the partial or complete loss of E-cadherin.

Also, CDH1, gen which codes for E-cadherin, is susceptible to a wide range of mutations that are related to the decrease of this protein [89-91]. The alterations on the expression of E-cadherin has big impact on the EMT process, thereby the mutations in CDH1 are also important, the alterations of this gene are implicated in hereditary carcinomas like the diffuse gastric and lobular breast cancer [92,93]. CDH1 repress the transcription of E-cadherin by specific molecules that bind to specific DNA sequences of the E boxes of CDH1 promoter, activating secondarily mesenchymal genes that promotes the EMT process. This process of losing epithelial gene expression and activation of mesenchymal genes involves the transcription factors SNAIL, ZEB, and TWIST [94-97]. Studies realized in breast carcinoma reported that silence SNAIL increases the expression of E-cadherin and decrease the expression of mesenchymal markers, also high levels of ZEB1 were associated with high aggressive carcinoma and advanced disease stage [98,99].

E-cadherin is considered as an invasion suppressor, and its deregulation is often found in advanced cases of some epithelial carcinomas [100]. The tumor microenvironment is also implicated in the dysregulation of E-cadherin by the NF- κ B pathway that mediates the activation of cytokines IL-1, IL-6, IL-8, MCP-1, apoptotic factors (Cip, c-FLIP, BCL-XL), vascular endothelial factor (VEGF) and matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9) in normal and malignant cells. The E-cadherin/catenin complex is known to decrease the activity of nuclear factor kappa B (NF- κ B) [101,102]. The signaling pathway that involves NF- κ B regulates the epithelial cell phenotype during inflammation, which is associated with carcinogenesis [103-105].

Fibronectin-1: Fibronectin 1 (FN-1) was originally described like a structural protein that is present on the cell surfaces [106]. We know that this protein is implicated in more processes such as wound healing, embryogenesis and blood coagulation [107].

Like other proteins, the expression of FN-1 is upregulated in several cancers (melanoma, ovarian, hepatocellular [108-112]) but interestingly the role of FN-1 is very variant. On the one hand is associated with a decrease level of E-cadherin and an increase in N-CAD, Vimentin, and other TFs associated with EMT and metastasis [113]. On the other side, FN-1 showed evidence of inhibiting tumor growth and metastasis. Glasner, A. et al. [114] showed that in an early pre-metastatic stage the tumor "prepares" itself for dissemination, this is detected by the NK cells via NCR1 mediated secretion of IFN- γ and FN-1 modifying tumor organization and consequently restricting metastasis [114].

The variability in FN-1 activity is also correlated with its ubiquity, evidence shows that endogenous FN-1 was associated with metastasis and poor prognosis in advanced stages [108-110] in contrast when is expressed in form of deposits into ECMs in the immunosuppressive tumor microenvironments (TIEMs) where promotes early tumor progression but curiously in these cases, the patients had a better prognosis [111,112].

The colony-stimulating factor 1 (CSF-1) has been shown to be a regulator of endogenous cellular FN expression [115, 116], also the activation of HIFs (HIF-1, HIF2) [117-119] have been correlated with the endogenous synthesis of FN-1 and as well-known HIFs has an important role as a stimulator for the tumor cells to change epithelial to a mesenchymal phenotype [120]. Thereby FN-1 can be overexpressed in tumor cells under hypoxic conditions. Meanwhile, SPARC that which is a protein implicated in the dormancy process was correlated with the

increased levels of periFN, therefore, the effect of SPARC on tumor dormancy may be due to the elevated level of periFN assembly [105].

The Programmed cell death protein 1 (PD-1) and their ligand, programmed cell death ligand 1 (PD-L1) which work as a co-inhibitory factor of the immune response, plays an important role in various malignancies where it can attenuate the host immune response to tumor cells [121]. miR200/ZEB1 axis-induced EMT pathways and regulates PD-L1 expression in CTS and FN expression is evidenced when miR200 is overexpressed or ZEB1 mRNA is stabilized [122-124], indicating the possibility that periFN on CTCs exerts PD-1/PD-L1-mediated immune checkpoint to escape T-cell-mediated cytotoxicity [125].

The expression of TFs like Prrx1, Snail 1 or Twist 1 enhances FN expression and promote metastasis [125]. In a study realized in Ovarian cancer was found that TWIST-1 promoted metastasis discoid in domain receptor, increase the activity of matrix modeling enzymes, and the cleavage of FN-1, leading to elevated migratory and invasive activities of tumor cells [113]. Snail1, p65NF- κ B, and PARP1 cooperate to activate the expression of FN-1 in cells undergoing EMT [126]. In a study realized in cells of thyroid cancer that shows increased levels of FN-1 expression in aggressive forms of this tumor, also have increased levels of Snail and p65NF- κ B [127].

SPARC: SPARC (secreted protein acidic and cysteine rich) is a multifunctional calcium-binding glycoprotein, the principal function of this matricellular molecule is regulate the interactions between cells and their surrounding extracellular matrix, is implicated in cell functions such as proliferation, migration and cell shape, SPARC also influence pathways associated with development, wound healing, tissue remodeling, angiogenesis, apoptosis, and regulation of the immune response [128-131]. SPARC could be expressed on the cell surface and within the intracellular compartment, when is expressed extracellular SPARC functions as a matricellular protein, while is intracellular and membrane-associated SPARC regulate cellular apoptotic pathways [132].

Dysregulation of SPARC has been found in the tumorigenesis process, thereby has correlated with the cell cycle progression, angiogenesis, apoptosis, EMT process, and metastasis [133-136]. SPARC works as a double agent in cancer; thus, increased or decreased levels of this protein have been found in diverse tumor. Higher levels of SPARC have been reported in breast cancer, hepatocellular and melanoma [137-139], however, lower levels of SPARC have been found in ovarian, prostatic, colorectal, and pancreatic cancers [140-142]. The function of SPARC is highly heterogeneous among tumor types, because SPARC has tissue specificity, and even in the same carcinoma as pancreatic cancer could act as a tumor suppressor or an oncogene [143-146], the overexpression of SPARC could act as a tumor suppressor gene, inhibiting proliferation, invasion and angiogenesis in cancers such as gastric and ovarian cancer [147]. On the other hand, low levels or absent expression of SPARC is correlated with bad prognosis and aggressive clinicopathological features for example in endometrial and colorectal carcinoma [148,149]. It has been demonstrated that low or absent expression of this protein is a consequence of the methylation of the gene promoter region [150].

The paradoxical role of SPARC as a tumor suppressor or promoter may be due to the specific microenvironment of each type of cancer [135]. The tumor associated stroma mainly ex-

press SPARC, predominantly in the cytoplasm and ECM of stromal fibroblasts. The high expression of SPARC on CAF supports the idea that stromal SPARC enhances tumor growth and tumor–stroma interactions, contributing to a more aggressive malignancy [151].

SPARC is also correlated with the TGF- β /Smad 2/3 pathway which regulates the synthesis of diverse ECM proteins. SPARC is a downstream mediator of the transcription factor SNAIL which is a regulator of TGF- β 1 [152]. By the way TGF- β 1 is implicated in the formation and dysregulation of EMT. SPARC stimulates the expression of TGF- β 1 in tumor cells such as the pancreatic cancer cells [153]. The SPARC-TGF β interaction affects negatively the expression levels of the epithelial markers such as: E-cadherin, Integrin β 1 and Focal Adhesion Kinase (FAK) and increases the expression of mesenchymal markers N-cadherin and vimentin, which facilitates the EMT and metastasis processes [154].

HLA-E: Major histocompatibility complex (MHC) class I molecules have main functions in both the innate and the adaptive immune system through the presentation of peptides from intracellular proteins to lymphocytes and by acting as ligands for NK cell receptors, this molecules can be classified in two groups, the non-classical HLA class Ib family (HLA-E,F,G and H) which are homologous to classical HLA Ia molecules (HLA-A,B,C) but their difference is the limited polymorphism, low cell expression, and limited tissue distribution [155].

The Human leukocyte antigen-E (HLA-E) belongs to a non-classical HLA class Ib group of molecules. In contrast to the other nonclassical class I molecules which are mainly restricted to specific tissues, e.g., placenta [156], expression of HLA-E is more ubiquitous and virtually every healthy cell in the body positive for HLA class I also expresses HLA-E but their expression levels are relatively low compared with class Ia. Other main differences of HLA-E is the least polymorphic of all the MHC class I molecules and can interact with inhibitory and activating receptors present in NK cells and T cells, having a dual function in the immune system [157,158].

The dual activity of HLA-E makes that the effect of this molecule and its alterations on the cellular immune response is too complex. The immune activation or suppression depends of the receptor and the responding cell, one of the most important receptor family interacting with HLA-E is the family of CD94/NKG2A which is expressed on NK cells. Two members of this family are NKG2A and NKG2C which forms a heterodimer with CD94. The interaction HLA-E and CD94/NKG2A provide an inhibitory signal to the NK cells meanwhile the binding of HLA-E and CD94/NKG2C delivers an activation signal to the NK cells. HLA-E has a major affinity for NKG2A which means a priority inhibitory function [159-161].

Usually, in cancer, HLA class Ia molecules are lost, this allows tumor cells to prevent T cell mediated recognition [162]. Studies had found that many tumors could maintain expression of HLA-E even in the absence of classical HLA class Ia molecules, suggesting a predominantly immunosuppressive role for HLA-E in anti-tumor immunity [163].

Some investigations had demonstrated high levels of HLA-E in various cancer types as gynecological cancers, renal, stomach and colorectal cancer [164-166] suggesting that this altered level functions as an acquired resistance mechanism after immune activation in the tumor microenvironment [167].

Recent findings associate HLA-E with a worse prognosis, for relapse-free survival in cancers like ovarian and breast carcinoma but interestingly only when the classical expression was lost [168,169]. On the other hand, retained expression of classical HLA class Ia was associated with a better prognosis for patients with cervical carcinoma and non–small cell lung carcinoma (NSCLC). However, this predictive value is abrogated when tumors display high HLA-E levels, suggesting that HLA-E mediates resistance against CD8 T-cell attack [170-172]. Therefore, HLA-E expression seems to be dependent on immune microenvironment.

C-terminal tensin-like (TNS4): C-terminal tensin-like (TNS4) is also known as COOH-terminus tensin-like molecule (CTEN) belong to the tensin gene family, which is formed by other 3 members (TNS1, TNS2 and TNS3) [173]. Tensins play important roles in various biological processes, such as cell adhesion, proliferation, migration invasion and apoptosis [174-176].

TNS4 promotes cell migration by triggering the uncoupling of integrins from the actin cytoskeleton [177], interestingly the expression of this protein is up-regulated or downregulated in different types of cancers, suggesting that alterations on TNS4 plays a critical role in tumorigenesis, even more important TNS4 could have both, oncogenic and tumor suppressor functions [178-180].

Up regulation of TNS4 was found in lung, colon, stomach, pancreatic and breast cancer and was also correlated with poor prognosis [181,182] on the other hand, downregulation of TNS4 was detected in the prostate (where normally is high expressed [183] and kidney cancers [184-186]. The specific mechanisms of this process of dysregulation are poorly described.

Evidence demonstrates that TNS4 bind with c-Cbl, a ubiquitin ligase that promotes the degradation of active β -catenin [187]. This protein forms part of the Wnt/ β -catenin signaling which is implicated in facilitates *cancer* stem cell renewal, cell proliferation and differentiation [188], β -Catenin indeed regulated the expression of VEGFA in colon cancer, VEGFA is an essential growth factor for vascular endothelial cells in normal and pathophysiological conditions [189]. Another study demonstrated protein expression levels of VEGFA were found to be upregulated in different subtypes of BRCA, inversely correlating with CTEN expression [190].

This activity may be related with the role of TNS4 as oncogene. Other studies had found that in invasive breast cancer TNS4 was associated with EGFR and HER2, also enhances the transcriptional activity of STAT3, contributed to the invasion and metastasis process of breast cancer cells [191]. Another study revealed that TNS reduces the E-cadherin levels enhanced EMT process [192].

Furthermore, investigations in non-small cell lung cancer shows that levels of TGF- β 1 are both significantly correlated with NSCLC tumor size, this study found that overexpression of CTEN promotes TGF- β 1 expression level and that overexpression of TNS4 promoted migration and invasion of human lung adenocarcinoma secondarily to TNS4 upregulated N-cadherin and Vimentin level while downregulated E-cadherin level [193]

In gastric cancer cells studies had found that tensin 4 can interact with PI3K through the SH2 domain to activate PI3K/AKT signaling pathways which produce p-GSK3 β , this increases the expression level of Snail by promoting its nuclear translocation [194,195]. Thus, TNS4 was closely associated with tumor

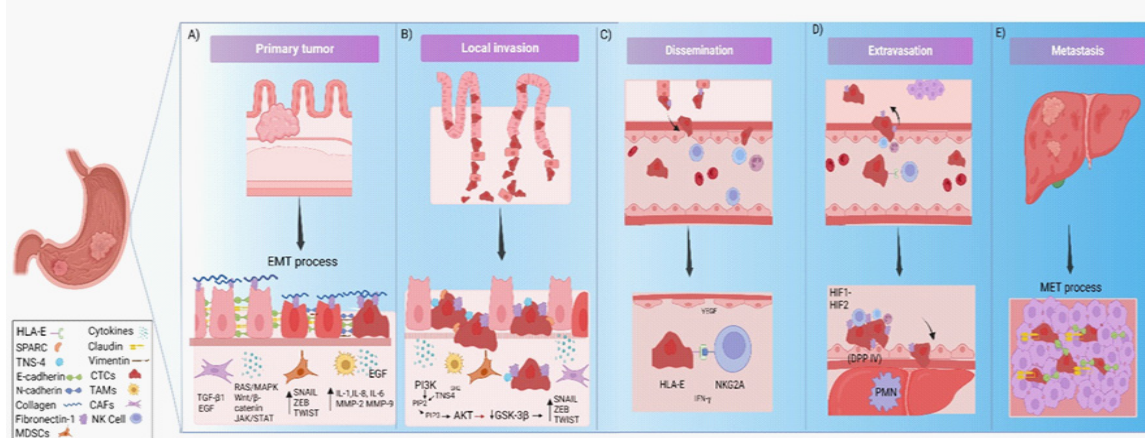


Figure 1: Hypothetic illustration of the metastasis process and the development of the EMT mechanism. **A)** The tumoral microenvironment (TME) of the primary tumor is implicated in the downregulation of diverse structural proteins such as E-cadherin and Claudin and the increase of N-cadherin and Vimentin by the activation of diverse pathways and increased transcription factors (SNAIL, ZEB, TWIST) which mediates the production of cytokines (IL-1,IL-8,IL-6) and matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9) by cancer associated fibroblasts (CAFs) and immune cells like Tumor-associated macrophages (TAMs) leading to elevated migratory and invasive activities of tumor cells. **B)** The accumulation of Myeloid-derived suppressor cells (MDSCs) and the immune cell of the TME provide a niche that facilitates the EMT process by the degradation and remodeling of ECM, SPARC stimulates the expression of TGF-β1 in tumor cells which has correlated with the inhibit maturation of dendritic cells, dysregulate the expression of epithelial and mesenchymal markers, also SPARC increase levels of FN1, the alteration of TNS4 promotes the degradation of active β-catenin that ligase that promotes the degradation of active β-catenin that forms part of the Wnt/β-catenin signaling, also there is represented the PI3K/AKT pathway which also interacts with TNS4. **C)** β-Catenin regulate the expression of VEGF and tumoral cells also produce increased VEGF which hyperstimulate the vasculature and consequently reduced pericyte coverage, this decrease facilitates the metastatic spread. The production of IFN-γ by the tumor-infiltrating T cells and NK cells significantly increases the surface expression of HLA-E in the Circulating tumor cells (CTCs), HLA-E interacts with NKG2A expressed on NK cells this interaction provides an inhibitory signal to the NK cells which might result in resistance and immune escape of cancer. **D)** Once the outgrown CTCs rich a certain size had hypoxic conditions, in response reexpress perFN1 as a consequence of activation of HIFs (HIF-1, HIF-2) the reexpression of FN1 helps to adhere CTCs to plaquettes macrophages or neutrophils to the endothelial cells via binding to dipeptidyl peptidase IV (DPP IV) facilitating their access to a secondary organ. With the growing of the primary tumor the hypoxia induces the expression of chemokines to drive bone marrow-derived cells (BMDCs) that are recruited in the distant organs to to establish premetastatic niche (PMN) where macrophages and CAFs are mainly responsible for the FN deposition in the ECM of PMN to prepare a suitable TMEs for the future extravasated metastatic cells. **E)** When the metastatic cells establish on the PMN reexpress epithelial markers for a better adhesion to the tissue, process knowing like mesenchymal-epithelial transition.

Table 1: The principal function of E-Cadherin, Fibronectin-1, Tensin-4, SPARC, HLA-E, and their principal sites of expression in normal conditions.

Protein	Function	Tissues with higger expression	Tissues with lower expression
E- cadherin	Cell-cell adhesión. Maintenance of normal tissue architecture.	Detected in many tissues. Enhanced in epithelial tissues.	Neuronal tissue.
Fibronectin-1	Cell adhesion, migration, growth, differentiation. Maintenance of cell shape. Wound healing.	Detected in many tissues. Enhanced liver and placenta.	Brain.
Tensin-4	Cell migration. Cartilage development. Glandular duct morphogenesis. Apoptosis. Linking signal transduction pathways to the cytoskeleton.	Detected in some tissues like skin and gastrointestinal tract.	Respiratory system. Connective and soft tissue.
SPARC	Regulate the interactions between cells and their surrounding extracellular matrix. Cell proliferation, migration and cell shape. Wound healing. Tissue remodeling. Regulation of the immune response.	Detected in all tissues, enhanced in placenta, brain and kidney.	Muscular tissues. Gastrointestinal tract.
HLA-E	Presentation of peptides from intracellular proteins to lymphocytes. Ligands for NK cell receptors.	Detected in many tissues, enhanced in lung, kidney, lymph nodes.	Muscular tissues (Heart muscle, Smooth muscle, Skeletal muscle) Adipose tissue.

infiltration depth, lymph node metastasis, and distal metastasis [196]. Tensin 4 may regulate EMT to promote invasion and migration of GC cells through the AKT/GSK-3β/Snail signaling pathway, providing a potential target for GC treatment [197] (Figure 1B).

Conclusion

We have discussed the fundamentals of immune evasion and the crosstalk between EMT tumor cells and immune cells, while this concept is quite clear, there remain important unresolved questions about their interaction. First, as already discussed, tumoral cells use diverse mechanisms to elucidate the immune response jointly known as immunoediting. Second, we presented the relationship between the EMT process and immune response, where the cyclical relationship is mediated by TFs such as TWIST, SNAIL1, and new ones like brachyury, the final products of these TFs are a reduced susceptibility to killing by CD8+ cytotoxic T cells lysis, reduction in antigenic presentation and recognition by CTLs, upregulation of inhibitory immune checkpoint molecules such as programmed cell death (PD)-ligand and stimulation of other mechanisms such as autophagy. Third, we do not know all the molecules that participate in this interaction, we present in this review the ones that are important in each stage of the EMT and immune evasion. We have seen that some of these proteins like FN-1 have different clinical result apparently on a level-dependent way, even in the same tissue, this could be mediated by the interaction between EMT, TME and immune response but this field have not been investigated so far. Much work remains to be done in this field, combined consideration of these processes might stimulate new studies and result in novel discoveries in the future.

Declarations

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