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Epithelial-Mesenchymal Transition as a Pathogenetic Mechanism of Sarcomatoid Carcinoma and Carcinosarcoma

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ABSTRACT

Epithelial-mesenchymal transition (EMT) is a phenotypic alteration that, in its most extreme form, involves the transformation of epithelium into mesenchymal cells. EMT is characterized by the loss of epithelial traits and the acquisition of mesenchymal characteristics, leading to increased cell motility. The tumor microenvironment, including cytokines, growth factors, extracellular matrix components, and hypoxia, significantly influences EMT, while key transcription factors such as the Snail, Zeb, and Twist families can trigger EMT in appropriate contexts. This process is relevant in various biological settings, including embryogenesis, wound healing, and fibrosis, as well as aspects of tumor progression such as invasion, metastasis, and acquisition of cancer stem cell-like properties. Although several studies in recent years have addressed the importance of EMT in these contexts, its role in the histogenesis of sarcomatoid carcinoma and carcinosarcoma has been less well recognized. Malignant tumors with a mixed phenotype featuring coexisting epithelial and mesenchymal-like tissues are a controversial area of pathology. They can occur in virtually any epithelial organ and display a wide range of microscopic appearances, depending on the degree of differentiation and the relationship between the two components. Morphological "transitional" zones between carcinomatous and sarcomatous tissue, along with the detection of intermediate epithelial-mesenchymal characteristics within the same cells by immunohistochemistry or electron microscopy, are distinctive features of these neoplasms, offering crucial insights into their histogenesis. Here, we propose a unifying histopathogenetic mechanism for sarcomatoid carcinoma and carcinosarcoma based on EMT, involving the conversion of carcinoma into sarcomatoid tissue. We review clinicopathologic evidence supporting this mechanism over alternative theories.

Keywords: Carcinosarcoma, EMT, Epithelial-mesenchymal transition, pluripotent stem cells, sarcomatoid carcinoma.

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INTRODUCTION

Epithelial-mesenchymal transition (EMT) is a complex biological program in which epithelial cells acquire mesenchymal properties to gain migratory capabilities, occurring in both embryonic morphogenesis and pathological conditions.[1–6] Epithelia are sheets of closely associated, largely

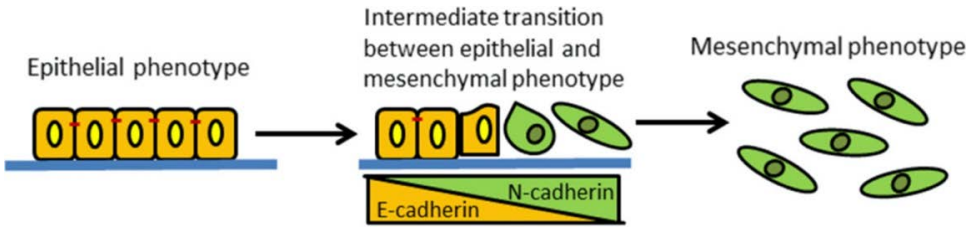

Figure 1. Highly schematic summary of the changes occurring during epithelial-mesenchymal transition (EMT). Epithelial cells (yellow) form a cohesive sheet of sedentary cells with apical-basal polarity, with their basal pole tethered to the underlying basement membrane. By contrast, mesenchymal cells (green) are unpolarized and motile. EMT-activating transcription factors, including the Snail, Zeb, and Twist families, are responsible for triggering the transition. The process of EMT is gradual and progressive, generating intermediate/hybrid forms between the epithelial and mesenchymal states (center). The E-cadherin to N-cadherin switch is indicative of ongoing EMT. However, EMT can be partial, and cells may remain in this intermediate state, maintaining characteristics of both epithelial and mesenchymal cells. This confers greater plasticity, adaptability to the changing environment, and thus an advantageous condition. (Kindly reprinted from Wu, Sarkissyan, and Vadgama,[5] modified).

stationary cells that line cavities and protect body surfaces. They reside above a basement membrane that separates them from the underlying interstitial tissues, exhibit apical-basal polarity, and have lateral surfaces tightly connected by cell-cell junctions. Mesenchymal tissue, by contrast, is composed of unpolarized, loosely associated cells surrounded by an extracellular matrix, capable of active migration. These cells typically do not form stable intercellular junctions and are often endowed with locomotory appendages such as actin-rich pseudopodia. Moreover, whereas epithelial cells are typically rich in cytokeratin intermediate filaments, mesenchymal cells possess a vimentin-based cytoskeleton.

EMT is not an all-or-nothing phenomenon, but rather a gradual, flexible, and reversible process primarily exploited to generate migrating cells (Fig. 1). In the embryo, EMT-generated cells can travel to distant locations and, upon reaching their final destination, re-aggregate through the reverse process of mesenchymal-epithelial transition (MET), which halts cell migration and promotes the formation of novel epithelial aggregates. Gastrulation, neural crest formation, and somitogenesis are examples of EMT/MET processes in embryogenesis, during which either EMT or rounds of reversible EMT and MET may occur.[1,6] The acquisition of mesenchymal properties during EMT takes place along a differentiation axis between epithelial and mesenchymal states, where fully epithelial and fully mesenchymal cells represent the extreme ends. However, the process is plastic and dynamic, comprising intermediate states with hybrid phenotypes in which cells concomitantly express both epithelial and mesenchymal features. Importantly, cells in these partial or hybrid EMT states play fundamental roles not only in embryogenesis but also in cancer progression.[1,3,4] Transient EMT occurs in a subset of cells at the invasive front of the primary carcinoma, where the neoplasm interacts closely with the host stroma. This enables peri-tumoral invasion, dissemination into the blood or lymphatic circulation, extravasation, and implantation at distant metastatic sites. Similar to embryonic development, tumor EMT is a reversible process, and the recovery of epithelial characteristics through MET occurs at the final metastatic site to form a secondary tumor colony.[1,3,4]

Sarcomatoid carcinoma and carcinosarcoma are unusual tumors arising in epithelial organs, characterized by a mixture of carcinomatous epithelial tissue and a mesenchymal-like component, resulting in a biphasic appearance. Tumors with such characteristics usually affect adults and the elderly, and have been reported in nearly every organ where carcinoma can occur. These neoplasms often present at an advanced pathological stage and, consequently, exhibit an aggressive clinical course.[6–12] They have been described under various names, including sarcomatoid carcinoma, carcinosarcoma, metaplastic carcinoma, spindle cell carcinoma, malignant mixed tumors, and others,[7] leading to uncertainty and debate regarding their classification and histopathogenesis. These lesions, regardless of their location, share many common features, making a general discussion of this topic appropriate. In this paper, the morphological and biological profiles of these neoplasms are briefly summarized, along with a critical review of the proposed histopathogenetic models. Although the pathological features of these tumors are well known, their pathogenesis requires reconsideration and reinterpretation within a modern conceptual framework. In recent years, accumulating evidence has suggested that these entities are closely comparable, with several lines of evidence indicating that the EMT process is involved in the genesis of the sarcomatous component.[8–18]

The idea that these lesions represent varying morphological expressions within a single pathological entity, characterized by different levels of EMT activation, has gained increasing acceptance. In the following article, a unifying concept of EMT-related pathogenesis is proposed for sarcomatoid carcinomas and carcinosarcomas (SC/CSs).

CLINICAL AND RESEARCH CONSEQUENCES

Basics of EMT

Epithelial-mesenchymal transition was formally recognized in the early 1980s by Elizabeth D. Hay.[19] She highlighted the formation mesenchymal cells from epithelial tissues in the primitive streak and neural crest, and demonstrated that even adult, differentiated epithelia are capable of transforming into mesenchyme *in vitro*, suggesting that the information necessary for this differentiation change is retained into adult life.[19,20] EMT was thus recognized as an important mechanism in embryogenesis, aimed at generating cells with the ability to migrate through the extracellular matrix and relocate within the embryo to form new tissues at distant sites. The first morphological change observed during EMT is typically the basal extension of pseudopodial protrusions through a disrupted basement membrane, followed by cell elongation and, ultimately, translocation into the interstitium. Meanwhile, intercellular junctions disassemble, promoting cell detachment and emigration from the parent epithelium. Molecular hallmarks of EMT include: up-regulation of EMT-inducing transcription factors, such as members of the Snail, ZEB, and Twist families; downregulation of E-cadherin, leading to loss of cell-cell adhesion and subsequent detachment from the epithelium; upregulation of matrix metalloproteinases, which degrade the epithelial basement membrane; loss of immunoreactivity for cytokeratin and other epithelial-associated markers; *de novo* expression of mesenchymal markers, such as vimentin, α-smooth muscle actin, fibronectin, N-cadherin, and fibroblast-specific protein 1 (FSP1); cytoskeletal reorganization, resulting in changes in cell shape and loss of apical-basal polarity; acquisition of motile and invasive properties (Table 1). The downregulation of E-cadherin accompanied by the upregulation of N-cadherin, referred to as the "E-cadherin to N-cadherin switch," is a hallmark of EMT.[3–6,20]

What triggers this complex array of changes is not yet fully understood, but molecules from the microenvironment, such as those involved in hypoxia and inflammation, acting on the cell surface seem to play important roles in facilitating EMT. In most systems, EMT is induced through growth factor-, cytokine-, or matrix-driven stimulation of cell surface receptors, or via activation of downstream signaling pathways. These include the transforming growth factor-beta (TGFβ)/Smads, Wnt/β-catenin, the Janus kinase/signal transducer and activator of transcription (JAK/STAT), Hedgehog, Notch, receptor tyrosine kinase-RAS/rapidly accelerated fibrosarcoma (RAF)/mitogen-activated protein kinase kinase (MEK)/mitogen-activated protein kinase (MAPK), and receptor tyrosine kinase-phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling cascades. All of these pathways ultimately lead to the upregulation of key molecules responsible for executing the transition program, specifically the EMT-activating Snail, ZEB, and Twist. These factors share the ability to repress the epithelial E-cadherin gene while concurrently activating genes associated with the mesenchymal phenotype.[3–5,19,21,22]

Table 1. Summary of the characteristics of epithelial and mesenchymal phenotypes

Epithelial phenotype	Mesenchymal phenotype
Cell-cell adhesion	Absence of cell-cell adhesion
Apical-basal polarity	Absence of apical-basal polarity
Stationary	Migratory
Basement membrane matrix	Interstitial-type matrix
Epithelial markers	Mesenchymal markers
E-cadherin	N-cadherin
Cytokeratin	Vimentin
ZO-1	α-smooth muscle actin
Claudins	Fibronectin
Occludin	Fibroblast-specific protein 1 (FSP-1)

Epithelial cells exhibit strong cell-cell adhesion mediated by E-cadherin-rich adherens junctions, ZO-1-, claudin-, and occludin-rich tight junctions, as well as desmosomes. They possess a laminin- and type IV collagen-rich basement membrane matrix, which supports cell attachment and establishes apical-basal polarity. Epithelial cells are generally non-motile. In contrast, mesenchymal cells are unpolarized and able to migrate, and their entire cell surface interacts via integrins with a fibronectin- and type I/III collagen-rich interstitial matrix. Furthermore, they are able to remodel the extracellular matrix both by producing it and, to facilitate locomotion, by degrading it through the release of metalloproteinases.

The Spectrum of Sarcomatoid Carcinoma and Carcinosarcoma

The terms sarcomatoid carcinoma and carcinosarcoma refer to closely related pathological lesions, believed to represent variants of the same tumor entity.[7] Traditionally, the term carcinosarcoma has been used in the presence of a connective tissue-specific sarcoma with little or no evidence of "transition" to carcinoma, while the term sarcomatoid carcinoma has usually been applied to tumors featuring non-specific mesenchymal spindle cells and evident morphological "transition" to carcinoma (Fig. 2a) or to tumors consisting predominantly or exclusively of elongated cells with a somewhat morphologically recognizable epithelial nature (the so-called "spindle cell carcinoma").[7] Alternatively, other authors have used the term sarcomatoid

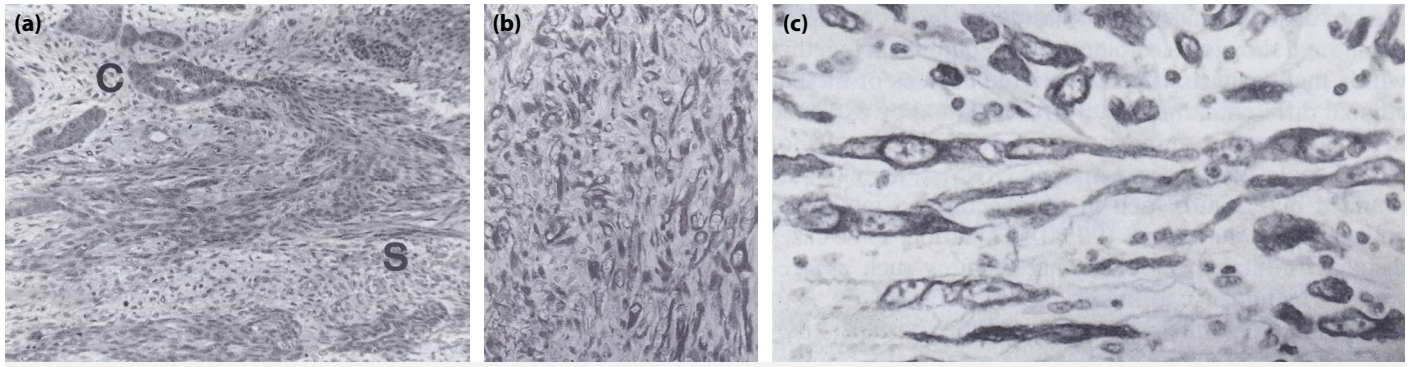

Figure 2. Microscopic features of a sarcomatoid carcinoma/carcinosarcoma (SC/CS) originating in the esophagus. **(a)** Histological section showing typical admixture of carcinomatous and sarcomatous tissues. The carcinomatous component is visible in the upper left corner (marked with C), characterized by well-circumscribed nests of cohesive epithelial cells embedded in sarcomatous tissue. At the bottom, a sarcomatous area (marked with S) is well represented, consisting of small spindle-shaped cells surrounded by an extracellular matrix. In the center, elongated but still largely cohesive intermediate cells can be observed, representing a "transitional" zone. (hematoxylin and eosin, original magnification ×100). **(b)** Sarcomatous spindle cells showing widespread immunoreactivity for vimentin, with fibrous extracellular matrix surrounding individual tumor cells (original magnification ×250). **(c)** The same spindle-shaped tumor cells also exhibit strong positivity for pan-cytokeratin antibodies. (original magnification ×400) (Reprinted from Guarino and Giordano,[20] by permission of Elsevier).

carcinoma for neoplasms with a sarcomatous component exhibiting epithelial features at the immunohistochemical and/or ultrastructural level, while designating as carcinosarcomas those tumors composed of epithelial and mesenchymal components distinguished by completely concordant and mutually exclusive expression of epithelial and mesenchymal markers.[23,24] SC/CSs arising in the female genital tract have interchangeably been called carcinosarcomas, malignant mixed Müllerian tumors, or malignant mixed mesodermal tumors. They have often been regarded as a specific tumor category occurring in Müllerian-derived organs and were historically classified either as sarcomas or true mixed tumors.[12,25]

Although often regarded as separate entities, growing evidence indicates that, despite their different denominations and somewhat differing histological appearances, these lesions are closely related and appear to be primarily carcinomatous in nature, as they exhibit clinicopathologic characteristics very similar to carcinoma.[7,12,17]

Pathologic Features and Histopathogenetic Theories

Sarcomatoid carcinoma/carcinosarcoma occurring in hollow organs often exhibit a distinctive polypoid macroscopic appearance,[7,13] likely related to the growth of the sarcomatous component and the associated production of abundant extracellular matrix. It has been suggested that the failure of sarcomatous cells to induce a desmoplastic reaction, and thus their inability to adhere to host tissues, favors the development of polypoid growth. Indeed, carcinoma cells rely on the host stromal matrix to support their growth, and a desmoplastic response is triggered as a result of carcinoma-host stroma interaction. In contrast, sarcomatous tissue produces its own matrix and does not induce desmoplasia.[7]

Histologically, SC/CSs present a mixed combination of carcinomatous and sarcomatous tissue, with a highly variable relative proportion between the two components. In some cases, the sarcomatous component is predominant, whereas the carcinoma may be very scant or present only in an situ form, requiring examination of multiple sections. When present, the invasive carcinomatous component is seen to merge imperceptibly with the sarcomatous tissue in at least some areas, giving rise to "transitional" images (Fig. 2a). Ultrastructural analyses have revealed intermediate cells with a hybrid epithelial-mesenchymal phenotype, showing both tonofilaments with desmosomal attachments typical of epithelia, and cytoplasmic actin filaments with focal densities and dilated rough endoplasmic reticulum, characteristic of mesenchyme.[16] Similarly, tumor cells of both components can coexpress cytokeratin and vimentin (Fig. 2b, c), The sarcomatous component is extremely variable, ranging from elongated, mesenchymoid cells that are still recognizable as epithelial in nature, through unspecified spindle cell sarcoma indistinguishable from a true mesenchymal neoplasm (Fig. 2b, c), to sarcomas with unquestionable connective tissue-type differentiation, sometimes unexpected based on location (so called "heterologous" differentiation), such as chondro-, osteo-, rhabdomyo-, or liposarcoma.

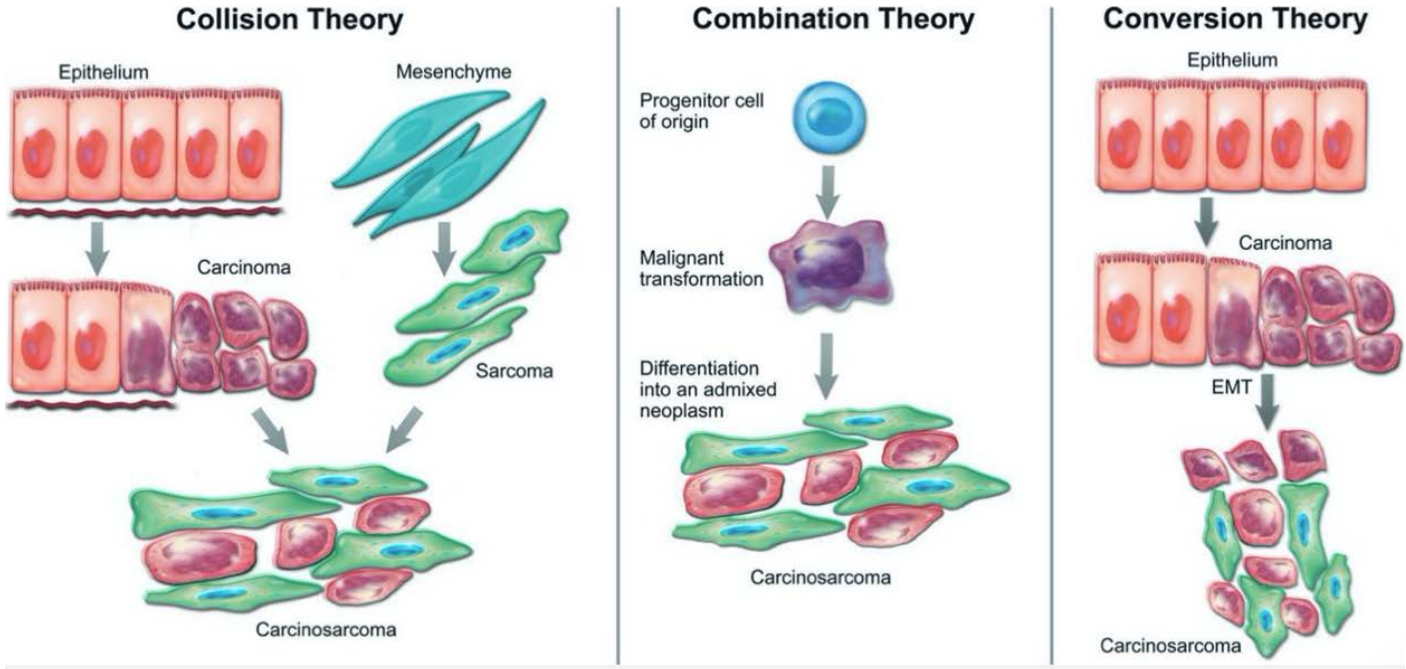

Figure 3. Highly schematic diagram depicting the theories proposed to explain the histopathogenesis of SC/CS. The collision theory assumes that SC/CSs are biclonal tumors, resulting from the oncogenic transformation of epithelial and mesenchymal cells that give rise to carcinoma and sarcoma, respectively; the two tumors subsequently collide and grow side by side. Both the combination and conversion theories are based on the postulate that SC/CSs are monoclonal tumors. In the combination theory, SC/CS is hypothesized to arise from a transformed multipotential progenitor cell, which subsequently diverges along two lines of differentiation, producing carcinomatous and sarcomatous components. The conversion theory is based on the assumption that transformed epithelial cells give rise to a carcinoma which, during its progression, may undergo conversion to sarcoma. As proposed in the text, this could occur through activation of an EMT program in a subset of tumor cells, generating an admixture of carcinomatous and sarcomatous tissues (from Somarelli et al.,[12] by permission of Histology and Histopathology).

SC/CSc arising in different anatomical sites are frequently associated with an immune infiltrate and exhibit immunohistochemical overexpression of programmed death-ligand 1 (PD-L1), especially in cancer cells of the sarcomatous component, suggesting that PD-L1 may represent an important predictive biomarker and that immune checkpoint-targeted therapy may be a treatment option for these patients.[9,13,18]

As mentioned, the histopathogenesis of SC/CS has been the subject of debate, and both biclonal and monoclonal theories have been proposed, including: (i) the biclonal collision theory, which assumes that two independently growing carcinoma and sarcoma components collide; (ii) the combination theory, which postulates that epithelial and mesenchymal components derive from a common pluripotent stem cell that diverges into two types of differentiation, epithelial and mesenchymal; and (iii) the transformation or conversion theory, which hypothesizes that a portion of carcinoma transforms into sarcoma (Fig. 3).[7,12] Collision tumors exist but are exceptionally rare and, by definition, are biclonal, consisting of two neighboring distinct neoplasms, carcinoma and sarcoma, that coexist in continuity with one another but show no or minimal intermingling between them.[26] These tumors are so rare as to be considered pathological curiosities and, moreover, are pathologically distinct from SC/CS, as they have clear boundaries without substantial intermixture. More importantly, this theory conflicts with several studies indicating that the two components of SC/CS share a monoclonal origin, as they harbor the same Kirsten rat sarcoma viral oncogene homolog (KRAS) or p53 mutations and/or immunoreactivity.[13,25,27] Therefore, the two proposed monoclonal models have received greater acceptance. To explain the development of SC/CS from a single cell clone, many authors have suggested an origin from a "pluripotent stem cell" that subsequently undergoes divergent differentiation along separate epithelial and mesenchymal lineages.[24,28–31] This concept implies that SC/CS may arise from a special type of primitive cell endowed with the inherent

potential to follow more than one differentiation pathway. Over the past 25 years, research into the generation and differentiation of pluripotent stem cells has gained enormous interest for its potential to revolutionize the treatment of tissue damage-related diseases. Indeed, a substantial body of knowledge has emerged regarding stem cell biology and their applications in regenerative medicine.[32,33] While a comprehensive overview of pluripotent stem cells is beyond the scope of this discussion, we briefly address the topic here. Pluripotent stem cells are undifferentiated cells characterized by their dual capacity to divide, and thus self-renew, while simultaneously generating progeny that differentiate into a variety of specialized cell types.[33] Harvested pluripotent stem cells can broadly be classified into basic categories depending on their tissue of origin, the isolation protocol employed, and their differentiation potential.[32] While the existence of adult, tissue-committed stem cells that generate new cells to replace those lost in order to maintain cell mass balance is widely accepted, a longstanding question in stem cell biology is whether pluripotent stem cells also exist in adult tissues. Recent evidence appears to confirm that adult organs harbor very rare populations of developmentally primitive stem cells committed to more than one lineage. These cells would therefore be developmental remnants deposited during embryogenesis that persist into adult life, implying that they may retain an "expanded" differentiation potential even postnatally.[33] However, it is not entirely clear whether they have the ability to cross ectodermal/endodermal boundaries and undergo mesodermal mesenchyme-type differentiation. Based on the above, the possibility that these rare primitive cells could undergo oncogenic transformation and subsequently give rise to a dual line of differentiation, one carcinomatous and the other sarcomatous, thereby resulting in SC/CS, appears to be an improbable occurrence. Although the theoretical possibility of such an event cannot be excluded, it would still represent an exceptional case. SC/CSs can arise in virtually any epithelial organ and are infrequent but not exceptionally rare. Therefore, it is reasonable to conclude that, to date, there is no substantial evidence supporting the theory that SC/CSs derive from "pluripotent stem cells." Instead, most current evidence supports the evolution of SC/CS from conventional carcinoma, with sarcomatoid transformation likely representing a progression from the original carcinoma.[34,35]

Stem Cell-Like Properties, Plasticity, and EMT

In addition to driving invasion and metastatic potential, EMT also plays pivotal roles in other important aspects of cancer, as it governs the acquisition of stemness and plasticity, cell quiescence and proliferation, tumor dormancy, and therapy resistance.[3] Indeed, although there is little evidence supporting the origin of SC/CS from pluripotent stem cells, the acquisition of stem cell-like characteristics is a consistent feature of cancer development and progression. Therefore, some aspects of SC/CS cells may actually relate to the stem cell-like properties intrinsic to the very nature of malignant tumors. Several studies have demonstrated a link between EMT, stemness, increased plasticity, and the potential for tumor progression. Induction of EMT-linked stemness in transformed epithelial cells has been shown to increase tumor-initiating capacity, enhance invasive and metastatic potential, and result in more aggressive tumor behavior.[36,37] Indeed, the prevailing model of metastasis suggests that a small subpopulation of cancer cells acquires cancer stem-like cell traits to increase their oncogenic potential and promote tumor progression.[1,22,36,37] This change in cancer cells is governed by EMT, resulting in motile cells that migrate away from the primary tumor and disseminate into circulation to distant metastatic sites, where they may then reform a secondary neoplastic growth via MET.[3–6] These EMT-derived cells express stem-like surface markers and exhibit increased plasticity, often displaying hybrid epithelial-mesenchymal characteristics.[5] Plasticity of tumor cells, a requirement for tumor progression that allows reversible adaptation to the ever-changing conditions of the microenvironment, is governed epigenetically by EMT, rendering the program reversible and highly dynamic.[4] The acquisition of stemness traits by cancer cells includes increased phenotype flexibility, which is necessary during invasion and metastasis when tumor cells must adapt to new environments. Gaining a hybrid epithelial-mesenchymal phenotype through EMT can serve this purpose.[1,36] Additionally, EMT-activating transcription factors are involved in DNA repair, escape from senescence and apoptosis, therapy resistance, and immune evasion, providing an advantage under stressful conditions.[4] Cancer stem cells are known to be quiescent and slow-cycling,[3] and a spatial relationship has also been identified between stemness, EMT, quiescence, and proliferative activity in tumors. EMT-derived mesenchymal cancer stem-like cells are primarily quiescent and localized at the tumor invasion front, while more epithelial cancer stem-like cells are proliferative and found more centrally within the tumor.[3,5] Similarly, dormancy, the phenomenon in which metastatic cells remain mitotically quiescent, may be linked to the persistence of the EMT-associated mesenchymal-like state, while cell proliferation and macrometastasis outgrowth are related to the epithelial-like state via MET.[3,38]

EMT, Invasion and Metastasis, and Development of SC/CS

There is consolidated evidence of a role of EMT in oncogenic progression, whereby EMT acts as a driver of invasion and metastasis in carcinomas. Progression of skin squamous cell carcinoma appears to be paralleled by increased acquisition of EMT traits, including a steady increase in EMT markers at each stage of progression, with β-catenin possibly providing

a mechanistic link between EMT, invasion, and stem-like traits. Cells positive for stem cell markers at the tumor invasion front display EMT characteristics, including downregulation of E-cadherin, disassembly of cell-cell junctions, and release of sequestered β-catenin from the cell membrane to the nucleus. This may lead to dysregulated Wnt/β-catenin signaling, an inducer of both cancer stem cell properties and EMT, and contribute to the development of cutaneous SC/CS.[39] Indeed, the same signaling networks involved in EMT during carcinoma invasion and progression may also be responsible for the development of SC/CS, whereby the sarcomatous component could derive from a carcinomatous tumor in which a subset of cells undergoes EMT, thus giving rise to a biphasic tumor.[12] Since EMT changes induced by invasion-related pathways lead to a transient, reversible, and partial-hybrid phenotype, it follows that a deeper and more lasting change must be required to generate a stable sarcomatous population in SC/CS. The development of SC/CS would therefore involve a permanent EMT, necessary for sustained repression of E-cadherin and continuous expression of mesenchymal markers.[35] Gaining a stable mesenchymal-like phenotype would require ongoing EMT-promoting signals; otherwise, the phenotype would revert to the epithelial state. Maintenance of the EMT phenotype could be accomplished through autocrine and/or continuous paracrine signaling pathways. Furthermore, the epigenetic landscape may govern EMT stability through DNA methylation and microRNAs (miRNAs).[5] miRNAs are critical regulators of EMT, with the miR-200 family being a well-known suppressor of EMT by negatively targeting ZEB1 and ZEB2, thereby maintaining the epithelial phenotype. In turn, ZEB1 and ZEB2 target and downregulate miR-200, resulting in a double negative feedback loop that provides an additional level of EMT regulation.[14] The resulting self-sustaining EMT changes in SC/CS would be variable, implying a spectrum of tissue alterations ranging from a hybrid epithelial-mesenchymal phenotype, through different degrees of transition to mesenchyme, to quasi-complete or even full EMT.[6] According to the EMT-based view, sarcomatoid carcinomas/carcinosarcomas could therefore be considered tumors exhibiting persisting or advanced features of EMT, extreme forms of carcinoma. In particular, carcinosarcoma, with its more clearly separated line of mesenchymal differentiation, appears to be even more advanced, suggesting a quasi-full EMT state.[39] Based on this, SC/CS may represent the best example in cancer pathology of the EMT concept,[8] constituting a stable change within the otherwise extremely dynamic and reversible EMT spectrum, the ultimate stage of EMT phenotypes.[17]

Uterine carcinosarcoma exhibits evidence of full EMT, with an S100A4/non-muscle myosin II signaling cascade underlying the establishment and maintenance of EMT and stem cell-like properties responsible for the transformation of carcinomatous tissue into sarcomatous tissue and the generation of a biphasic pattern.[15] Consistent with EMT activation, the sarcomatous component of uterine SC/CSs shows positivity for Snail, ZEB, and Twist; an E-cadherin to N-cadherin switch; and downregulation of miR-200s.[9,14] Therefore, uterine carcinosarcoma likely represents the end-stage evolution of carcinoma following the initiation of a stable EMT program, in which the interaction between various EMT-activating transcription factors and miR-200s may play an important role in fixing the mesenchymal phenotype. Furthermore, subsequent activation of specific transcriptional programs could induce various types of connective tissue-specific "heterologous" differentiation.[9]

In SC/CS of the bladder, the sarcomatous component is found to be immunoreactive for cytokeratin, p63, vimentin, and α-smooth muscle actin, coupled with an E-cadherin to N-cadherin switch and upregulation of Snail and ZEB. Patients often have a prior diagnosis of conventional carcinoma, suggesting that the sarcomatoid transformation is related to tumor progression.[11] Indeed, according to one study, SC/CS of the bladder evolves through progression from conventional carcinoma, involving mutations in TP53, RB1, and PIK3CA, and is driven by dysregulation of EMT networks.[18] This study also distinguishes between epithelial and mesenchymal SC/CS subtypes, resulting from partial and complete EMT, respectively. The epithelial type shows focal retention of p63 and E-cadherin, both involved in the maintenance of epithelial differentiation, whereas the purely mesenchymal SC/CS is negative for p63 and E-cadherin, exhibits downregulated miR-200s, and behaves more aggressively. P63 appears to play a central role in maintaining the epithelial phenotype, as it regulates cytokeratin expression and suppresses EMT.[18]

In a nutshell, the EMT hypothesis posits that SC/CSs arise from conventional carcinomas in which a subset of cells undergoes stable, self-sustaining EMT, giving rise to the sarcomatous component. The well-documented features of SC/CS, including the histological "transition" between carcinomatous and sarcomatous components (Fig. 2a), early expression of vimentin in the carcinomatous component, persistence of cytokeratin or other epithelial markers in the sarcomatoid component (Fig. 2c), mixed epithelial/mesenchymal ultrastructural features of tumor cells, frequent occurrence of SC/CS in organs where carcinomas are common, appearance of SC/CS in recurrences or metastases of carcinoma,[6,7,11,12] and sarcomatoid transformation following tyrosine kinase inhibitor treatment or neoadjuvant therapy of carcinomas,[10,13,40] are all consistent with an origin of SC/CS from conventional carcinoma through an EMT-based process. Therefore, it seems unnecessary to hypothesize an origin from "pluripotent stem cells" to explain

the expanded repertoire of differentiation in these tumors, as conventional carcinoma itself appears to possess a broader differentiation potential that is more than purely epithelial. Indeed, due to the acquisition of stem cell-like properties and increased plasticity, carcinoma cells gain the ability to respond to internal and microenvironmental EMT-promoting signals, thereby reprogramming their differentiation and giving rise to an unexpected sarcomatous component.

The importance of EMT involvement in SC/CS is significant for the broader study of EMT in cancer. Although EMT appears to be involved in various aspects of cancer, its transient and partial nature has long hindered its recognition. During tumor invasion and metastasis, epithelial neoplastic cells acquire some mesenchymal features, but they often regain a fully epithelial phenotype at metastatic sites. Therefore, a major challenge in conducting pathological studies to demonstrate the occurrence of EMT during invasion and metastasis lies in the difficulty of tracking individual cancer cells undergoing EMT in human tissues. Typically, on histopathological evaluation, the cell has either not yet undergone a morphologically detectable EMT or has already completed the process. In contrast, SC/CS cells acquire stable mesenchymal characteristics in their sarcomatous components—while often retaining expression of some epithelial markers—thus presenting a distinctly different scenario. SC/CS represents a true example of cancer featuring clear evidence of EMT, which can be readily observed in pathological studies, making it a straightforward case of this phenotypic transition.[15]

CONCLUSION

Epithelial-mesenchymal transition is recognized as an important mechanism in embryogenesis and also plays a pivotal role in cancer, where it contributes to various aspects of tumor aggressiveness. This article provides an overview of EMT, illustrates its involvement in cancer stemness and progression, discusses the proposition that SC/CSs can develop through an EMT-based mechanism. Patients with SC/CS respond poorly to conventional therapies, and the prognosis often remains unfavorable. As we have seen, SC/CSs often exhibit EMT-induced overexpression of PD-L1 in tumor cells, suggesting that immune checkpoint-targeted therapy may be a therapeutic option for these patients. A better understanding of the molecular mechanisms involved in EMT could inform the development of new targeted therapies that represent promising approaches to treatment. Since increased plasticity and stem cell-like features appear to underlie EMT-related processes, future agents that modulate epithelial-mesenchymal plasticity by targeting key mediators or molecular networks may prove effective in counteracting tumor growth in patients with SC/CS, thereby offering the potential to improve prognosis.

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