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REVIEW ARTICLE

Epithelial Mesenchymal Transition: The dancing from Embryonic Development to Cancer metastasis

Shaheen Sameerah*

Anatomy Department and Stem Cell Unit, College of Medicine, King Saud University, Riyadh, Saudi Arabia

***Corresponding Author:** Shaheen Sameerah, Anatomy Department and Stem Cell Unit, College of Medicine, King Saud University, Riyadh, Saudi Arabia, Tel.: 504885084, E-mail: sshahee@ksu.edu.sa

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Abstract

Epithelial-mesenchymal transition (EMT) is a pivotal biological phenomenon that underpins critical events in embryonic development and is reactivated in pathological conditions, including cancer metastasis and tumorigenesis. Despite being a well-studied topic, recent technological advancements and discoveries have shed new light on the intricacies of EMT regulation. EMT involves a multifaceted system of transcriptional and translational regulators, coupled with post--transcriptional and post-translational modifications that amplify initial indications. This review comprehensively examines key aspects of EMT research, spanning from its role during embryonic development, its implications in cancer biology, and the regulatory molecular pathways governing this process. Firstly, we delve into EMT during embryonic development, exploring the signaling pathways in gastrulation and neural crest formation, which highlight the conservation of EMT mechanisms across diverse biological contexts. Shifting focus to its connection with cancer, we elucidate the impact of EMT on disruption of cell junctions, cancer cell survival and polarity, the emergence of cancer stem cells, circulating tumor cells, and the development of drug resistance. Furthermore, we discuss the intricate regulatory pathways involved in EMT, encompassing gene expression alterations, the complexity of signaling cascades, the role of microRNAs, and the intriguing intersection with autophagy. Lastly, we address the critical role of EMT in cancer metastasis, emphasizing its significance in driving the invasive and migratory behavior of cancer cells. In conclusion, this review integrates historical insights with recent breakthroughs, providing a comprehensive understanding of the multifaceted role of EMT in both development and cancer biology, and highlighting its potential as a therapeutic target in cancer management.

Keywords: Epithelial-Mesenchymal Transition (EMT); Cancer Metastasis; Embryonic Development; Regulatory Networks; Signaling Pathways; Molecular Pathways

Introduction

Epithelial-mesenchymal transition (EMT) plays an essential part in various physiological and pathological events, as highlighted by Kim. This process, originally observed in embryonic development, is often rebooted in pathological situations like tumor formation and metastasis, as discussed by Huang. EMT involves a complex interplay of factors, signaling pathways, mediators and molecules as noted by Chen.

The recognition of epithelial and mesenchymal cell types dates back to the late 19th century, based on cell organization and shape for the period of embryonic growth. Frank Lillie's observations in 1908 marked the early understanding of the inter-conversion between mesenchymal and epithelial cells. However, the concept of EMT as a discrete cellular method did not emerge until the 1980s, introduced by Greenburg and Hay. Subsequently, the significance of EMT has been widely acknowledged, with implications spanning various biological processes, including stem cell differentiation, embryonic development, pluripotency induction, wound healing, tissue repair, and stem cell performance, as well as its involvement in pathological conditions like cancer development, cancer stem cell performance, and tissue/organ.

Notably, EMT is a reversible biological process Sato, characterized by the transition between the mesenchymal and epithelial phenotypes. This transformation involves the conversion of tightly bound, apical-basal differentiated epithelial cells into motile, migrating, and hostile mesenchymal phenotype cells. This transition is facilitated by membrane projections such as lamellipodia, filopodia, and invadopodia, as documented in studies by Loboda, Liu, Steinestel.

The objective of this review article is to comprehensively study the multifaceted role of epithelial-mesenchymal transition (EMT) in various biological contexts, ranging from embryonic development to its involvement in cancer-related processes, particularly metastasis. We aim to elucidate the regulatory networks governing EMT, encompassing genetic and protein-level mechanisms, and how they underpin both physiological and pathological events. This review seeks to bridge historical insights with recent advancements, shedding light on key concepts and emerging discoveries in the EMT research field. Our focus encompasses EMT during embryonic development, emphasizing critical signaling pathways during gastrulation and neural crest formation. Furthermore, we delve into the intricate relationship between EMT and cancer, exploring its implications in cancer cell survival, perturbation of cell junctions and polarity, cancer stem cell dynamics, circulating tumor cells, and resistance to cancer therapies.

Moreover, we aim to elucidate the central regulatory molecular pathways involved in EMT, including gene expression alterations, the complexity of signaling cascades, the role of microRNAs, and their intersection with autophagy. Ultimately, our review addresses the profound impact of EMT on cancer metastasis, providing a comprehensive understanding of its role in driving invasive and migratory behavior in cancer cells. In essence, this study aims to unravel the intricate interplay of EMT in various biological processes, serving as a valuable resource for researchers and clinicians seeking the latest insights into EMT and its implications in cancer metastasis and beyond.

Notions and EMT Characteristics

EMT is a living procedure during which cells undergoing dramatic changes, where the epithelial cells loss the epithelial traits completely and converting into mesenchymal-phenotype cells. More particularly, while experiencing cytoskeleton re-arrangement the layers of polarized epithelial cell lose their polarity, cell to cell bond as well as cell to extracellular matrix (ECM) adhesions. This allows the cells to detach and separate from the surrounding tissues in order to invade and migrate (ECM) as single cells and that is the hallmark of the EMT process. The converse/contrary process to EMT is named as mesenchymal–epithelial transition (MET), where the mesenchymal cells (migratory cells) return to epithelial cells at their destination via an MET. Therefore, and because this process is reversible or transition back to epithelial cells, the most appropriate and favored word to describe the EMT and its reverse process MET was “Transition” term instead of other terms that have been used in the past to

describe EMT eg. “transformation”, “interaction” or “trans-differentiation”.

Over the previous 20 years the EMT investigation field has full-fledged and in the past 6 years alone the majority of all EMT articles have been published Yang. Fifty percent of those articles have stated on investigations of EMT in the situation of cancer biology. However, the rising variety of the EMT writings and the increasing intricacy of EMT proceedings and officials have caused confusion and often imprecise descriptions of EMT certainly in cancer. As this complexity converts to be valued progressively guidelines Yang therefore, an explanation of EMT related phenomena as well as a explanation of the diverse types of EMT that can occur in dissimilar settings need to be decided by the society of EMT researcher experts.

The occurrence of an EMT can manifest within three distinct biological settings, each leading to markedly different outcomes. Although the precise signaling pathways that govern EMT remain incompletely elucidated, it is widely acknowledged that the functional consequences of EMT are context-dependent, varying according to the biological setting. Table 1 categorizes EMT into three discrete subtypes based on the specific biological context in which the EMT process takes place.

Conversely, there is an opposite method known as Mesenchymal-Epithelial Transition (MET), where mesenchymal cells, which are migratory in nature, degenerate to an epithelial cell state upon reaching their destination. MET is essentially the opposite of EMT and is a reversible transition.

Table 1: Three categories of the epithelial mesenchymal transition

Types of EMT	Functions	Features	Consequences
1	Implantation, organ development and embryogenesis	Generates a variety of cell types that have the potential to undergo a Mesenchymal-to-Epithelial Transition (MET), ultimately forming secondary epithelial cells during embryogenesis.	No invasion; No fibrosis
2	Wound healing, organ fibrosis and tissue restoration	Generates fibroblasts and further associated cells to rebuild tissues succeeding inflammatory injury and trauma	No invasion; fibrosis
3	Malignant conversion of cancer cells	Generates cancer cells that retain numerous epithelial characteristics while also exhibiting some mesenchymal traits or gives rise to cancer cells that undergo a complete transition to a mesenchymal state	Metastasis and invasion

The EMT process is inherently dynamic and context-dependent, characterized by cells oscillating within a spectrum of transitional states, ranging from a fully epithelial to a fully mesenchymal phenotype. This dynamic nature of EMT poses challenges in definitively classifying cancer cells as either fully epithelial or fully mesenchymal. Instead, cancer cells often exhibit a range of intermediate or "partial" EMT states, where they may display a combination of both epithelial and mesenchymal characteristics or lose some of their typical traits. Consequently, EMT is not a binary process but exists in various states of transition, from partial to complete, and is inherently reversible. This active reversibility, often termed "EMT-MET," underscores the plasticity exhibited by certain embryonic and adult cells implicated in disease contexts. Recently, this phenomenon has been termed epithelial-to-mesenchymal plasticity (EMP) or epithelial plasticity, further emphasizing the dynamic nature of EMT.

Intermediate stages of EMT, commonly referred to as hybrid EMT or partial EMT (pMET), exhibit the potential to acquire stem cell characteristics, including self-renewal ability, which plays a crucial role in tumor propagation. However, the extreme EMT states, characterized by a fully mesenchymal phenotype, tend to lose stemness, plasticity, and tumor-initiating potential. An intermediate epithelial/mesenchymal (E/M) phenotype has been reported to possess tumor-initiating capabilities and cellular plasticity, enabling differentiation into various cell lineages.

Given the plasticity and heterogeneity of EMT, variations in data interpretation and ongoing debates about whether a specific

process qualifies as EMT have emerged. The use of the term EMT spans research areas as diverse as developmental biology, cell biology, tissue homeostasis, and diseases like cancer and fibrosis. During the progression of these conditions, EMT can be activated to various degrees, ranging from partial to full EMT, and it is often a reversible process, resulting in cells residing within a spectrum of states, which can be considered as the endpoints of EMT. This diversity and plasticity of EMT programs pose a significant challenge for the research community, emphasizing the need to comprehend the full spectrum of EMT in various biological contexts. Intermediate states, as demonstrated by the identification of transitioned or "EMTed" phenotypes (either partial or complete) in circulating tumor cells, play a crucial role in this context. These cells, arrested in or transitioning through intermediate or metastable states of EMT, are often referred to as "fused cells" due to their possession of attributes from both epithelial and mesenchymal phenotypes, along with exhibiting stem cell-like properties. These "fused cells" demonstrate a high degree of plasticity between epithelial and mesenchymal phenotypes, which is critical for cancer metastasis.

A noteworthy characteristic of in vivo EMT, whether occurring during normal development or in pathological contexts, is that the transition from an epithelial to a mesenchymal state is often incomplete. This results in cells residing in intermediate states that retain characteristics of both epithelial and mesenchymal states. Importantly, these intermediate states can be highly diverse, referred to as incomplete or partial EMT phenotypes, particularly within the context of cancer, depending on specific biological guidelines.

Partial EMT appears to confer tumor cells with enhanced epithelial-mesenchymal plasticity, which is crucial for processes such as metastasis, tumor recurrence, and resistance to therapy (Figure 1). Consequently, it is imperative to recognize and investigate the diverse ways in which tumor cells traverse the EMT spectrum, especially when addressing clinical implications.

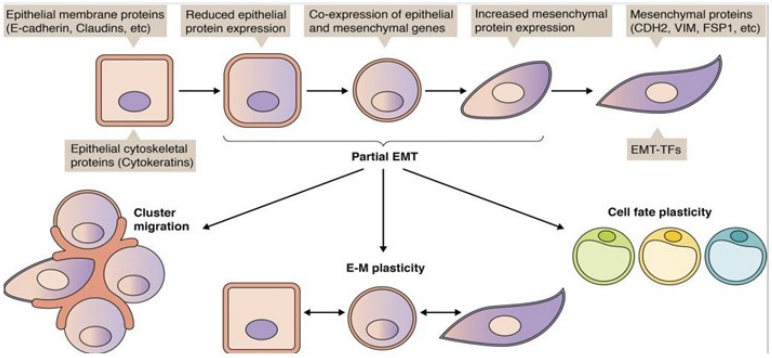

Figure 1: Partial EMT: Heterogeneity and functional consequences.

EMT (Epithelial-Mesenchymal Transition) represents a range of phenotypic conditions in cancer cells. Partial EMT, characterized by a combination of both epithelial and mesenchymal gene expression, plays a significant part in cancer biology. It enables the potential for cells to change their fate, such as transdifferentiating into adipocytes, flexibility between epithelial and mesenchymal states and even cluster migration.

A study reported that the KPCY mouse model of PDAC, particularly the classic subtype, predominantly displayed a partial EMT phenotype. Interestingly, in vitro experiments showed that partial EMT tumor cell lines involved in combined migration, whereas full EMT tumor lines dispersed as solitary cells. Furthermore, partial EMT cells produced more circulating tumor groups in vivo. The partial EMT phenotype was not limited to this model but was also experiential in numerous human cancer cell lines from breast, pancreatic and colon carcinomas, suggesting its prevalence across different cancer types.

In a separate study, demonstrated that breast cancer cells in a partial EMT state could transdifferentiate into adipocytes. They achieved this conversion by using a mixture conduct concerning rosiglitazone (a peroxisome proliferator-activated receptor-γ agonist inducing adipocyte distinction) and trametinib (a kinase inhibitor blocking TGF-β signaling). This approach significantly reduced lung metastasis, indicating the therapeutic potential of targeting partial EMT.

Partial EMT is developing as a mutual feature in cancer, granting cancer cells increased plasticity. This plasticity opens up new

therapeutic possibilities for managing cancer by exploiting the transitional nature of these cells.

In the context of cancer, full EMT is a rare occurrence, and partial EMT is further commonly observed, with cancer cells existing beside a spectrum of epithelial and mesenchymal characters. The molecular mechanisms that lead a cell down the path to EMT and the factors that halt this process partially likely involve a mixture of cell-autonomous and non-cell-autonomous cues. These factors may include microenvironmental signals, the cell's transcriptomic landscape, or chromatin availability, which can be influenced by the cell's source. The practical significances of partial EMT include promoting collective migration of cells. However, the association concerning partial EMT and other aspects of the EMT platform, such as stemness, is not fully understood.

Partial EMT has functional consequences that include driving collective cell migration. However, its relationship with other aspects of the EMT program, for example stemness, remains incompletely understood. Current research has begun to rise the significance of EMT dynamics in influencing metastasis and stemness. Epithelial-mesenchymal plasticity, prominently represented by partial EMT, appears crucial for cancer cells to acclimatize to constantly altering microenvironments, whether encountered in distant organs or in response to various therapies. Notably, recent findings indicate that partial EMT equips tumor cells with remarkable plasticity, enabling them to Trans segregate into completely dissimilar cell forms. Pointing partial EMT, and thereby cellular elasticity, holds therapeutic promise, but elucidating the precise molecular mechanisms governing partial EMT is a prerequisite.

In cancer, each cell can adopt one of 3 phenotypic states: epithelial (E), mesenchymal (M), or the hybrid epithelial/mesenchymal (E/M) state. The E/M hybrid state has been considered a transient phenotype during the EMT process. However, certain transcription factors like OVOL and GRLH2, known as phenotypic constancy aspects, could soothe the hybrid phenotype. Recent experiments have demonstrated the occurrence of the E/M hybrid state during EMT but not during the reverse MET process.

Partial EMT is likely the utmost applicable form in cancer, as it places cancer cells in an active state that confers the plasticity necessary for metastasis and tumor progression. This plasticity endows cancer cells with attributes such as tumorigenicity, stemness, motility, and resistance to therapy. However, the face of EMT-related factors is often transient and partial, reflecting the fact that stemness linked and EMT associated features may not be advantageous at all phases of tumor development. This underscores the prevalence of partial EMT initiation in cancer, relatively than the full implementation of the EMT program. Additionally, partial EMT plays essential roles in adult tissue homeostasis and repair practices, such as epithelial regeneration and wound curing. In tumors, these features are frequently expressed transiently and at varying levels, leading to the emergence of partial EMT phenotypes.

In the pathogenesis of fibrosis and cancers, EMT can be stimulated to varying grades, from partial to full activation, and it is often alterable, demonstrating a remarkable flexibility that results in cells adopting a range of states between a completely epithelial and a completely mesenchymal phenotype, which are reflected the endpoints of EMT. Therefore, EMT does not lead to an only mesenchymal state but somewhat yields several transitional states with differing amounts of epithelial and mesenchymal characteristics. This plasticity and diversity of EMT programs across different biotic circumstances pose a significant challenge for researchers seeking to understand and characterize them effectively.

Cells that stimulate EMT programs often direct groupings of both epithelial and mesenchymal indicators in adult muscles under pathological circumstances and infrequently complete the whole EMT process, indicating that "partial EMTs" are the rule relatively than the exclusion. The behavior of carcinoma cells transitioning to impermanent epithelial/mesenchymal states (E/M states), which are indicative of partial EMTs, parallels the performance of epithelial cells for the period of usual growth. Furthermore, it has been observed that carcinoma cells experiencing partial EMT can decrease their epithelial phenotype through post-translational mechanisms, creating it puzzling to understand studies that depend on exclusively on the perturbation of transcriptomes by EMT-TFs (Transcription Factors). This context-dependent variability of EMT programs and the

roles of EMT-TFs further complicates our understanding of EMT. In addition to their implication with canonical EMT regulation, EMT programs have also been connected to other traits not traditionally associated with EMT, such as cell survival, stemness, drug resistance, and metabolic changes in cancer cells.

To better encompass the capability of cells to accept assorted epithelial and mesenchymal features and to interconvert among intermediate E/M phenotypic situations that cannot be easily distinguished based on present facts, the term "epithelial-mesenchymal plasticity" (EMP) is recommended. EMP represents the capacity of cells to transition among these situations, though the permanency of these states can vary in dissimilar biological circumstances. EMP is commonly experiential in various processes, including cancer, wound healing and development. It also accounts for the reversibility of the EMT suite, as epithelial cells experiencing EMT can provide increase to cell populations that can move in numerous states with dissimilar extents of epithelial and mesenchymal features. EMP is believed to deliver cells with the flexibility and fitness needed to meet the different supplies during both pathological and developmental methods.

EMT during Embryonic Development

During the first eight weeks of human development, cells undergo progressive transformations, transitioning from epithelial to mesenchymal states to form the initial organ or tissue structures known as primordia. Throughout embryonic development and cell specialization, a series of EMT-MET cycles occur, stated as primary EMT, secondary EMT, and tertiary EMT.

Primary EMT occurs early in embryogenesis, such as during parietal endoderm formation in mice. After implantation, the first primary EMT event involves the development of mesoderm from embryonic ectoderm by gastrulation, followed by the delamination of neural crest cells from the dorsal neural tube. These processes result in the generation of mesenchymal cells and neural crest cells, both maintaining multipotentiality and the capability to distinguish into several cell types.

In the primary EMT, the epithelial morphogenesis directs the EMT method, leading to the de-epithelialization of the epithelial cell layer, followed by ingression of epithelial cells. This transition ultimately outcomes in the establishment of early mesenchymal cells with fundamental mesenchymal characteristics, including cell motility and migration. Subsequent events in embryonic growth, such as neural crest formation and gastrulation, necessitate EMT processes. Mesenchymal cells generated during these events contribute to the formation of the three germ coats. Following primary EMT, the secondary EMT takes place, allowing potentially restricted mesenchymal cells to discriminate into numerous cell forms. After gastrulation, early mesodermal cells segment into axial, paraxial, intermediate, and lateral plate mesodermal cells. These cells then undergo MET to condense into transient epithelial structures, forming structures such as the notochord, somites, somatopleure, and splanchnopleure.

Migratory neural crest cells discriminate into neurons, cartilage, or bone cells, following a conventional pathway to their final endpoints. These temporary assemblies subsequently experience secondary EMT, leading to the creation of mesenchymal cells that further distinguish into definite cell forms. Additionally, endodermal tissues like the pancreatic liver and bud diverticulum experience morphological variations significant of secondary EMT, facilitating the detachment of hepatoblasts and endocrine cells from their individual epithelial primordia.

EMT is a crucial biological procedure in which epithelial cells undergo a transformation to acquire mesenchymal characteristics. This transition involves the loss of cell polarity, cell-cell adhesion and the acquisition of invasive and migratory properties. EMT plays vital roles in embryonic development, including neural crest formation and gastrulation, and is also involved in secondary EMT events that promote the differentiation of various tissues, such as somites, palate, pancreas, liver, and reproductive tracts. The hallmark molecular variations related with EMT comprise reduced communication of E-cadherin and amplified communication of mesenchymal indicators like vimentin. These EMT events are closely associated to metastasis and cancer invasion.

MET represents the reverse method of EMT, where mesenchymal cells degenerate to an epithelial phenotype. MET is crucial

during normal development, including the development of reproductive tracts and secondary palate. After the fusion of the palatal splits, it is quiet unclear whether the involved cells experience EMT, travel to the voiced epithelium, or undergo apoptosis. In masculine reproductive areas, the Mullerian duct reverts following EMT induced by the Mullerian-inhibiting material.

Snail genes, including Snail1 and Snail2 (SNAI1 and SNAI2 in humans), play a crucial role in EMT. They are brought by members of the transforming growth factor beta (TGFβ) superfamily, and fibroblast growth factors (FGF) signaling is essential to sustain their appearance during processes like gastrulation. Embryos deficient in Snail genes fail to gastrulate, leading to the gathering of "mesodermal" cells unable to downregulate E-cadherin.

Throughout embryonic development and in cancer metastasis, cycles of EMT and MET occur, allowing for cell form concentration as cells reach their final destinations. These dynamics are important for tissue development and metastatic processes.

So, EMT and MET are fundamental procedures in biology, playing pivotal roles in both cancer progression and embryonic development. Understanding the molecular mechanisms behind these transitions is critical for deciphering their roles in various biological contexts.

EMT and Signaling Pathways in Gastrulation

Gastrulation is a pivotal event in embryonic development that marks the establishment of the three fundamental germ layers: ectoderm, mesoderm, and endoderm, from the primary epithelial embryonic layer recognized as the epiblast. During gastrulation, the embryo undergoes a spatial reorganization, positioning the ectoderm as the outer layer, the mesoderm in the middle layer, and the endoderm as the innermost layer. The process by which the mesoderm and endoderm relocate to their respective positions is referred to as "ingression," a fundamental step in gastrulation characterized by Epithelial-Mesenchymal Transition (EMT), where individual cells detach from the outer epiblast and undergo internalization through a structure named the primitive streak.

In invertebrate gastrulation, key transcription factors Snail and Twist play a pivotal role by initiating apical contraction, leading to the construction of ventral channels and subsequent cell ingression. In contrast, during mouse gastrulation, the signaling molecules Nodal and fibroblast growth factor (FGF) induce EMT as cells ingress through the embryonic streak. Mutations in Nodal result in incomplete gastrulation, a defect that can be rescued by transplanting a small number of Nodal-expressing cells. The coordinated action of Nodal and Vg1 leads to the formation of the embryonic streak and subsequent cell ingression, following Wnt signaling, which renders the epiblast proficient to undergo gastrulation. The FGF receptor (FGFR) signaling pathway sustains the leading network governing EMT during gastrulation. In mice deficient in FGFR, the embryonic streak and mesodermal cell formation initiate but then arrest.

Therefore, gastrulation is a difficult and extremely controlled process involving the repositioning of germ layers within the developing embryo. The interplay of various signaling pathways and transcription factors, such as Nodal, Snail, FGF, and Twist, orchestrates this intricate developmental event.

EMT and Signaling Paths during Neural Crest Construction

Following gastrulation in vertebrates, neural crest cells undergo a well-defined migratory process, characterized by a classical EMT event within the neural tube. Throughout this procedure, neural crest cells within the neural tube transition from an epithelial phenotype to a traveling mesenchymal phenotype. Subsequently, these neural crest cells delaminate from the neural doublings and disperse to various areas within the embryo before undergoing a Mesenchymal-Epithelial Transition (MET), leading to the formation of various neural crest-derived structures such as the peripheral nervous system ganglia and adrenal medulla chromaffin cells.

The molecular signaling pathways involved in neural crest cell formation exhibit similarities to those active during gastrulation at the embryonic streak. These pathways include retinoic acid, FGF, Wnt, and bone morphogenetic protein (BMP) signaling, all of which are essential for neural crest cell initiation. The established Wnt signaling pathway plays a vital role in the delamination, stabilization, and induction of neural crest cell precursors, while the non-established Wnt way contributes to contact inhibition of directional movement and locomotion of neural crest cells.

Within the TGF-β superfamily, BMPs, in particular BMP4, are convoluted in neural crest cell development. BMP4 appearance within the neural pleats triggers the transition of epithelial cells into migratory neural crest cells through the activation of transcription factors, including Snail 2 and msh homeobox 1 (Msx1). BMPs may also modify the timing of neural crest cell movement, as demonstrated by the inhibition of migration when BMP activity is blocked by Noggin. Additionally, Cv-2, a vertebrate homologue of Drosophila crossveinless, adjusts the BMP signaling pathway, so governing the initiation of neural crest cell movement, particularly in the trunk section.

Several key transcription factors, including Sox E genes (Sox8, Sox9, and Sox10), Rhob, Foxd3, and Snail2, play vital roles in neural crest formation. While these factors are essential, it's important to note that they may not individually suffice to persuade a whole EMT in neural crest cells. Instead, a coordinated action involving multiple transcription factors is necessary to orchestrate the full EMT process and subsequent migration of neural crest cells from the neural tube.

Consequently, the migration of neural crest cells is a highly regulated and intricate process in vertebrate improvement. It involves a series of cellular transitions, including EMT and MET, guided by the activation of specific signaling pathways and the action of transcription factors to ensure the proper formation and distribution of neural crest-derived structures.

MET and Embryonic Development

MET is a living process categorized by the reverse of Epithelial-Mesenchymal Transition (EMT). Numerous studies have demonstrated that ectopic appearance of the E-cadherin gene can induce mesenchymal cells to conversion into an epithelial phenotype. For example, the transfection of invasive corneal fibroblasts with the E-cadherin gene leads to a remarkable transition from a mesenchymal phenotype to an epithelial phenotype, specifically resulting in the formation of a stratified epithelium with desmosomes.

One of the well-studied instances of MET during embryonic expansion is observed in the development of the nephron epithelium within the kidney. In this MET process, nephric mesenchymal cells combined around individual branches of the ureteral bud, polarize, express laminin, establish cell-cell adhesions, and eventually discriminate into epithelial cells that contribute to the formation of renal tubules. This phenomenon highlights the plasticity of cells, where mesenchymal cells can transition back to an epithelial phenotype, not only in non-pathological conditions but also under pathological conditions.

Furthermore, it's worth noting that certain adult neoplastic tissues, such as pleomorphic adenomas of the parotid gland, and synovial sarcomas, exhibit features of both MET and EMT phenotypes. In the case of pleomorphic adenomas, the expression profiles of matrix genes have been used as important criteria to demonstrate unequivocal differentiation amongst epithelial and mesenchymal situations.

Therefore, MET represents a dynamic process where mesenchymal cells can undergo a reversal to an epithelial phenotype, and this phenomenon has been detected in various developmental and pathological contexts. E-cadherin, among other factors, plays an essential role in mediating this conversion.

EMT and Cancer

EMT and Cancer Cell Survival

Epithelial cancers, which represent the predominant category of cancer types, are characterized by a critical phase in their progression. During the change from benign adenoma towards malignant carcinoma, and subsequently during metastasis, epithelial tumor cells undergo a profound transformation in their behavior.This transformation is associated with a process called Epithelial-Mesenchymal Transition (EMT), which entails a series of substantial changes in cellular morphology, the restoration of cell-cell and cell-matrix linkages, and the achievement of invasive and migratory abilities.

EMT is a multifaceted and multistage method characterized by significant cellular plasticity and a multitude of epigenetic and genetic modifications. It involves the alteration of fully distinguished epithelial cells into poorly distinguished invasive, and migratory, mesenchymal cells. Over the years, numerous genes critical for metastasis formation and EMT have been identified. Remarkably, the EMT process not only enhances cancer cell invasiveness and motility but also provides cancer cells with mechanisms to evade various physiological barriers, including apoptosis, anoikis (cell death triggered by loss of cell-matrix adhesion), cellular senescence, oncogene addiction, and immune defense mechanisms. Additionally, EMT appears to play a pivotal role in the maintenance and generation of cancer stem cells, aligning with the notion that metastatic cells possess the capability to start new tumors.

EMT and Disruption of Cell Junctions and Polarity

One of the promises of EMT is the disruption of cell junctions and polarity, which are critical for maintaining epithelial integrity. In epithelial cells, specialized cell surface protein complexes establish essential cell-cell junctions, including tight junctions, adherens junctions, gap junctions, and desmosomes. However, upon the beginning of EMT, these junctions undergo significant changes, including deconstruction and the relocalization and/or degradation of junction proteins.

Tight junctions, for instance, experience dissolution during EMT, supplemented by reduced appearance of key components like claudin and occludin, along with the distribution of zonula occludens 1 (ZO1) from cell-cell contacts. Adherens junctions, characterized by epithelial cadherin (E-cadherin), are disrupted during EMT. E-cadherin is slashed at the plasma membrane and afterward despoiled, leading to the damage of interactions with β-catenin. Consequently, β-catenin is either degraded or protected from degradation, depending on signaling pathways such as WNT, enabling its involvement in transcriptional processes. The nuclear accumulation of p120 catenin is another consequence of decreased E-cadherin levels, contributing to altered transcription.

EMT also impacts desmosomes, leading to their disruption, and compromises the integrity of gap junctions by reducing connexin levels. As EMT progresses, the repression of junction protein expression occurs at the transcriptional level, further solidifying the loss of epithelial junctions.

In addition to junction disruption, EMT disrupts the apical-basal and planar polarity of epithelial cells, which are typically organized by polarity complexes combined with the cell junction construction. In vertebrate cells, these polarity complexes include Crumbs and Partitioning-defective (PAR) complexes that define apical compartments, as well as Scribble complexes that define basolateral compartments.

During EMT, the termination of epithelial junctions results in the damage of apical-basal polarity. For instance, decreased E--cadherin expression in tumor cells avoids the contact of Scribble (SCRIB) with the lateral plasma membrane, thereby reducing adhesion and increasing cell motility. Furthermore, EMT leads to the repression of polarity complex proteins, such as LGL2 and CRB3, which further disrupts the polarized phenotype.

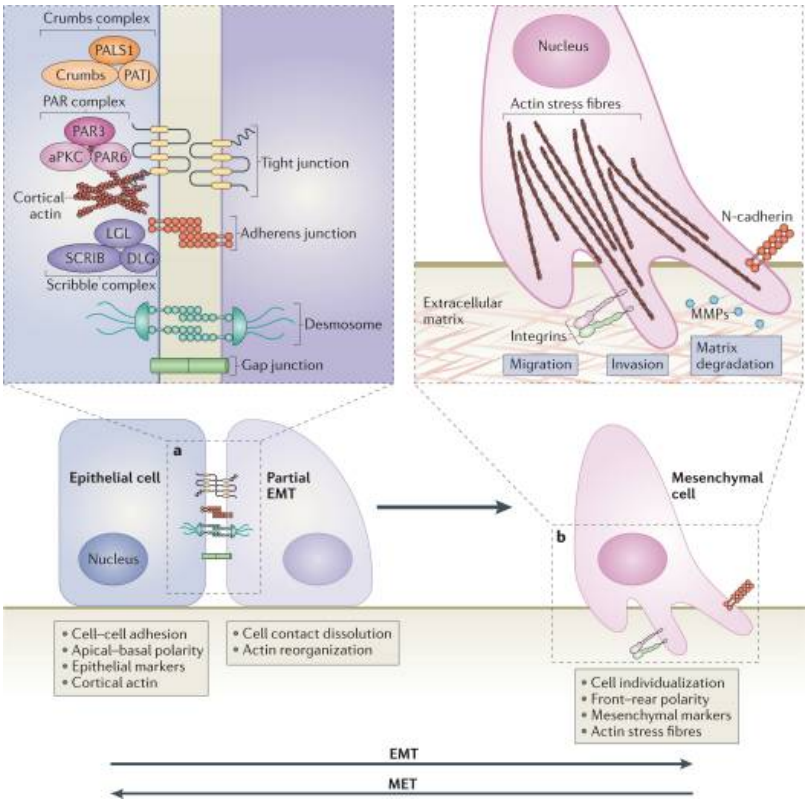

Figure 2: Epithelial-Mesenchymal Transition (EMT) Cellular Events.

Schematic representation illustrating the key cellular events during EMT. Epithelial cells undergo a phenotypic shift characterized by loss of cell-cell adhesion, cytoskeletal reorganization, and acquisition of mesenchymal features, facilitating enhanced motility and invasion. Thereby, transitioning from static epithelial states to dynamic, migratory mesenchymal phenotypes and vice versa.

EMT and Cancer Stem Cell

EMT is recognized as a phenomenon linked to cancer stemness, categorized by an augmentation in the population of cancer stem cells (CSCs). CSCs represent a subset of cells within tumor tissues that acquire stem cell-like properties. These cells possess the ability for self-renewal, maintain tumor-initiating potential, and can distinguish into various cell types to support tumor growth, making them a significant source of relapse, metastasis, and tumorigenesis. Notably, CSCs are strongly linked with resistance to chemotherapy. Even if conventional chemotherapy eliminates the majority of tumor cells, if CSCs persist, the risk of relapse, metastasis, and resistance to treatment remains prevalent. Most CSCs, akin to normal stem cells, are dormant and exhibit slow growth, rendering them resistant to many anticancer drugs.

Previous research has proposed that cells undertaking EMT acquire stem cell-like characteristics, and tumor cells with stemness often express markers associated with EMT. Nevertheless, conflicting findings have emerged, with some studies proposing that stemness is more closely associated with Mesenchymal-Epithelial Transition (MET) rather than EMT, suggesting that the instruction of EMT and stemness is distinctive. Consequently, the precise correlation between EMT and CSCs has remained unclear.

Recent advancements have led to the characterization of EMT as a dynamic, hybrid state that encompasses both epithelial and mesenchymal features. This hybrid state represents a coexistence of epithelial and mesenchymal phenotypes rather than a simple transition between separate phenotypes, and the term "epithelial-mesenchymal plasticity" has been employed to define this phenomenon during EMT. Significantly, epithelial-mesenchymal plasticity has been implicated in cancer development and is related with stem cell-like traits, potentially shedding light on the intricate association between EMT and CSCs.

Moreover, emerging evidence proposes that epithelial-mesenchymal plasticity is involved in the improvement of CSCs. The co-existence of CSCs and epithelial-mesenchymal plasticity has been linked to poor prognosis and resistance to therapy. Furthermore, recent studies have shown that targeting CSCs induced by epithelial-mesenchymal plasticity can efficiently standardize tumor development and mitigate drug resistance. For instance, metformin has been established to prevent enzalutamide-resistant prostate cancer by reducing cells exhibiting a hybrid E/M status, thus limiting the establishment of CSCs.

EMT and Circulating Tumor Cells

The formation of Circulating Tumor Cells (CTCs) encompasses a series of critical steps, including detachment from the primary tumor mass, incursion through the surrounding tissues and basal membrane, entry into the bloodstream, and the ability to survive in the peripheral circulatory system. Notably, EMT and the linked regulatory networks play a central role in promoting CTC generation through three fundamental mechanisms (Figure 3).

1. Enhanced Tumor Cell Invasiveness: Epithelial cells are typically immovable due to the exact regulation of robust cell-cell and cell-extracellular matrix bonds, which include tight junctions, adherent junctions, and desmosomes, coupled with a well-organized cytoskeleton. However, during EMT, critical components of intercellular connections, such as occludins, claudins, desmosomes, and E-cadherin, are straight down-regulated by EMT transcription elements (EMT-TFs) like Slug, Snail, and SIP1. Research utilizing cell and animal assays has shown that the reformation of bonding agent molecules is related with amplified intrusiveness. Moreover, the transition from an epithelial to a mesenchymal state during EMT involves a reshaping of the cytoskeleton, facilitating a spindle-like morphology appropriate for relocation. Additionally, EMT-TFs can encourage the appearance of matrix metalloproteinases (MMPs), which play a vital part in degrading the basal membrane and surrounding tissues, further promoting invasiveness. It is noteworthy that extracellular factors like FGF, TGF-β,and Wnt contribute in this governing network by encouraging both EMT and MMP expression. Hypoxia also influences this regulatory network in a manner akin to extracellular factors.

2. Promotion of Tumor Cell Intravasation: The EMT governing system contributes to angiogenesis and enables cancer cell intravasation into blood vessels. EMT-TFs, such as Snail and Slug, have been shown to encourage the development of blood vessels by inducing the appearance of vascular endothelial growth factor A (VEGF-A). Other factors within this regulatory network, including Notch and HGF, also contribute to angiogenesis through similar mechanisms. Notably, VEGF and HIF1-α have been detected on CTCs. Furthermore, TGF-β-induced and EMT-induced proteases, particularly MMPs, can endorse both intravasation and angiogenesis. Importantly, recently formed tumor-associated blood vessels often exhibit abnormalities and leakiness, which enables the invasion of tumor cells. Specifically, EMT-related and EMT-TFs factors have been displayed to increase transendothelial movement, additional supporting the role of EMT in tumor cell intravasation.

3. Facilitation of Tumor Cell Survival in the Peripheral System: CTCs encounter significant challenges in the peripheral circulatory system, including potential signals for anoikis (cell death due to loss of cell adhesion) and exposure to chemotherapy or radiotherapy. Nevertheless, EMT plays a critical role in enhancing tumor cell survival in this hostile environment. EMT-TFs, such as Twist, Slug, Snail, and SIP1, defend CTCs from anoikis by disrupting usual resisting senescence, apoptotic pathways, and collaborating with factors like TrkB. Additionally, EMT-TFs confer struggle to chemotherapy and radiotherapy in various cancer types. For instance, Snail and Slug have been directly implicated in cisplatin resistance in ovarian cancer. Importantly, the inhibition of EMT has been shown to restore chemosensitivity, suggesting that targeting EMT-TFs may hold promise as a therapeutic strategy to counteract treatment resistance.

Intriguingly, numerous governing loops happen within the mechanisms of the EMT regulatory system, highlighting the complexity of their interactions. For instance, EMT-TFs can bring the expression of MMPs, while certain proteases can converse EMT. VEGF-A plays a similar role within the context of EMT. In instant, the EMT-related regulatory network is a highly interactive and intricately regulated network that involves hypoxia, extracellular factors (FGF, TGF-β, Notch, etc.), and EMT —each playing a vital role in cancer development. Serving as the central component of this regulatory network, EMT, in concert with

related factors and pathways, significantly contributes to the generation of CTCs by promoting angiogenesis, cell invasion, therapy resistance, intravasation, and survival.

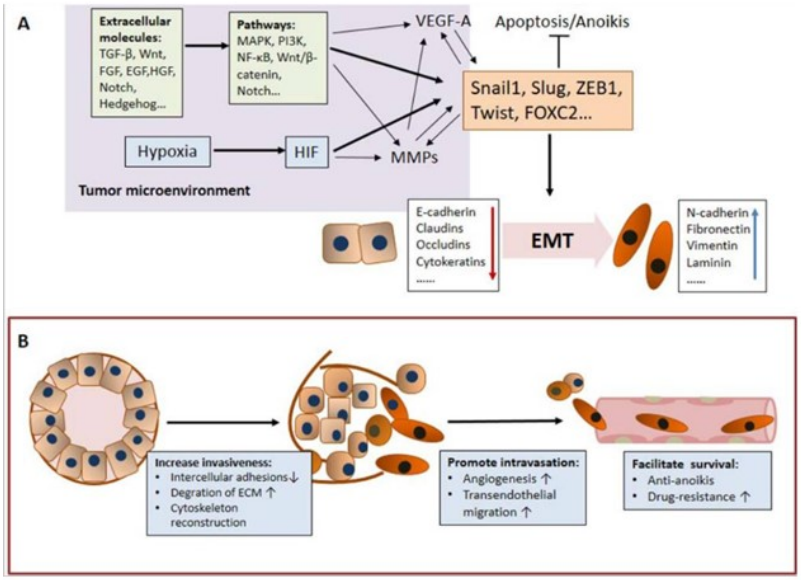

Figure 3: (A) The EMT-Related Regulatory Network

This panel illustrates the comprehensive regulatory network linked with Epithelial-Mesenchymal Transition (EMT). Central to this network are EMT-inducing transcription factors (EMT-TFs) such as ZEB1, Snail1, Snail2 (Slug), and Twist, which exert control over molecular changes during the EMT process. Additionally, key extracellular molecules found in the tumor microenvironment, including HGF, FGF, TGFβ, Notch, and Wnt, interact with their individual receptors to initiate EMT. Hypoxia, a significant factor in cancer progression, can trigger EMT and is integrated into this regulatory network. Importantly, this EMT regulatory network operates as an interconnected and precisely regulated system, contributing significantly to the generation of Circulating Tumor Cells (CTCs). (B) EMT Promotes CTC Generation: This panel highlights the primary roles of EMT in promoting the formation of Circulating Tumor Cells (CTCs). EMT contributes to CTC generation by enhancing tumor cell invasiveness, facilitating tumor cell intravasation into blood vessels, and promoting the survival of tumor cells in the peripheral system. These critical processes collectively play a pivotal role in cancer development. Adapted from.

EMT and Drug Resistance to Cancer Therapy

The association between Epithelial-Mesenchymal Transition (EMT) and drug resistance in cancer has been recognized since the early 1990s. Notably, studies by Sommers observed that certain drug-resistant cancer cell lines, such as adriamycin-resistant vinblastine-resistant ZR-75-B cells and MCF-7 cells, displayed EMT characteristics. For instance, adriamycin-resistant MCF-7 cells exhibited increased expression of vimentin and a decrease in the development of tight junctions and desmosomes, hallmark features of EMT. Importantly, it was noted that not all drug-resistant MCF-7 cells exhibited EMT traits, suggesting that within heterogeneous cancer cell populations, EMT cells may possess a discriminating growth benefit in the occurrence of drugs.

Subsequently, numerous studies have reported a frequent relationship between drug resistance and EMT in various cancer types, including breast cancer bladder cancer, and pancreatic cancer. Recent research using genetically-engineered mouse models has further substantiated the causal link between cancer drug resistance and EMT. Fischer documented an EMT lineage--tracing arrangement in mice to display transient and reversible EMT processes. This system allowed the tracking of cancer cells that underwent EMT, even after subsequent reversion and metastasis to an epithelial phenotype (MET). Upon management with the chemotherapy drug cyclophosphamide, the primary tumor's development was abridged, but GFP-positive EMT cells within the tumor exhibited resistance to apoptosis initiation and maintained their cell numbers, in contrast to the epithelial--

type cancer cells. Remarkably, lung metastases in chemotherapy-treated mice had a significantly higher number of EMT cancer cells compared to the control group, suggesting that EMT plays a pivotal part in cancer drug resistance and donates to post-chemotherapy metastasis.

Several signaling pathways associated with EMT have been identified as contributors to drug resistance. For instance, TGFβ, a well-known EMT linked cytokine, has been linked to drug resistance since the 1990s, with TGFβ-neutralizing antibodies shown to restore drug consideration in resistant cancers. It has been confirmed that TGFβ induces EMT, leading to drug resistance. Additionally, the Wnt and Hedgehog pathways have also been involved in drug resistance. Overexpression of Wnt3 activates the Wnt/β-catenin pathway, promoting trastuzumab-resistant phenotypes and EMT in breast cancer cells. Initiation of the Hedgehog pathway has been connected with EGF receptor tyrosine kinase inhibitor (EGFR-TKI) resistance in lung tumor cells. EMT-TFs, such as Snail, Slug, Twist, and ZEB, have also been linked to drug resistance in various cancer categories.

Key Regulatory Molecular Pathways of EMT

EMT is a complex biological method regulated through a series of intricate molecular mechanisms, including gene expression modulation, signaling pathways, and various layers of regulation. EMT proceeds in a well-defined and sequential manner, with cells transitioning through multiple stages, beginning at the epigenetic level and progressing through post-translational modifications.

The EMT gene program is under the governor of a sophisticated network involving transcription factors, lengthy non-coding RNAs, microRNAs (miRNAs), exterior microenvironmental indicators and epigenetic modulators. Eventually, the paths triggering EMT join to destroy the expression of epithelial genes, with E-cadherin being a hallmark molecule of the epithelial state. One potent inducer of EMT is transforming growth factor-beta (TGF-β), which signs through the TGF-β receptor-Smad path to upregulate master transcriptional controllers of EMT, such as ZEB1, SNAI1, and a zinc-finger transcriptional repressor of E--cadherin. Moreover, ZEB1 inhibits the expression of the miR-200 family of miRNAs, which, in turn, mutually suppress TGF-β and ZEB1/2 construction. The miR-200s/ZEBs undesirable response loop is known to sustain epithelial homeostasis when miR-200 levels are high. This loop is also the most significant response mechanism in supporting the mesenchymal state when Zeb1/2 are highly communicated. Intriguingly, bioinformatics studies have suggested non-linear multistable EMT dynamics, primarily based on response loops at the core of the EMT governing system, particularly the damaging response loops involving miR-200/ZEB1 and miR-34/SNAI1. These interrelated bistable modifications play a critical role in EMT regulation.

Gene Expression Changes in EMT

Tumor metastasis is a multifaceted procedure initiated by EMT, where epithelial cells experience a transformation into a more mobile and invasive mesenchymal phenotype. EMT is characterized by the loss of the epithelial marker E-cadherin and an up-regulation of mesenchymal markers. This transition empowers principal epithelial-like tumor cells to obtain offensive mesenchymal traits, a pivotal step in metastatic progression. As a result, these cells gain increased motility and invasiveness, enabling their dissemination from the major tumor into the bloodstream or lymphatic vessels. Consequently, genes associated with EMT represent potential markers and therapeutic targets in the context of osteosarcoma treatment.

Recent investigations have illuminated a connection between EMT and the immune response in human cancers. Elevated expression of EMT markers within breast tumors has been linked to increased immune infiltration within the tumor microenvironment. The presence of immune cells in this microenvironment subsequently fosters immune elusion by cancer cells, a phenomenon linked with metastasis and tumor progression. In non-small-cell lung cancer, EMT status has been strongly correlated with an inflammatory cancer microenvironment. Comprehensive pan-cancer analyses have further highlighted a robust association between immune activation and EMT.

Complexity in EMT Signaling Pathways

Various stimuli trigger numerous signal transduction paths that ultimately converge into a central regulatory network comprising transcription factors (e.g., ZEB1/2, SNAIL1/2, TWIST) and miRNAs (e.g., miR200 and miR34 families). These regulatory elements further interrelate with other components to guide a cell towards one of numerous promising cellular fates. For instance, SNAIL1 can bind to P53, a pivotal regulatory protein responsible for initiating apoptosis or senescence, effectively sequestering P53 in the cytosol. Consequently, SNAIL1 prevents the cellular choice between apoptosis or senescence. Subsequently, the determination of cell fate is executed by initiating the matching gene expression suite and further reinforced through various events, including epigenetic modifications and the engagement of multiple feedback loops. Importantly, this movement of material is not unidirectional; at each stage, both positive and negative feedback mechanisms interplay with preceding stages, collectively forming a closed and intricate network. Figure 4 presents a schematic overview of the intricate cellular methods involved in sensing, transmitting, and responding to various stimulating signals.

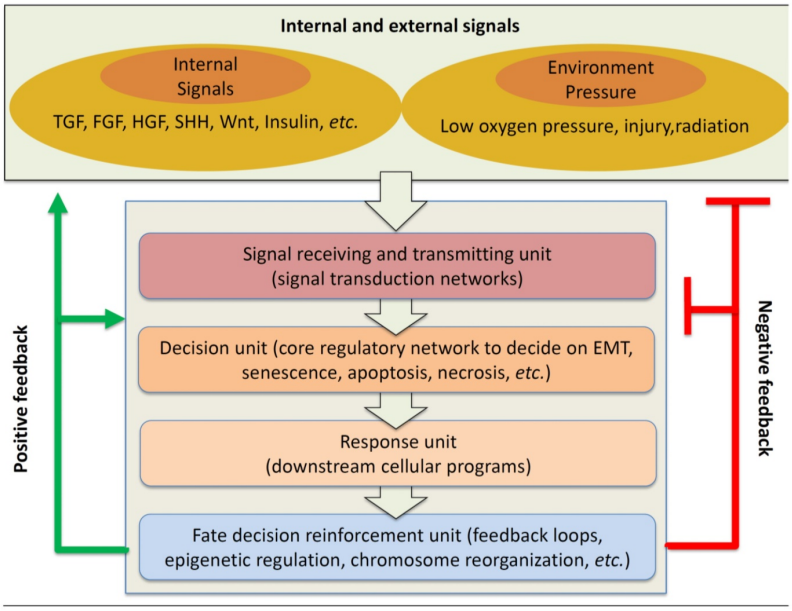

Figure 4: This schematic diagram outlines the intricate process of signal reception, transduction, and cellular response during the phenomenon of epithelial-mesenchymal transition (EMT). Multiple intracellular and extracellular signals are relayed and integrated through four fundamental functional units. These signaling events are subject to both negative and positive feedback loops, contributing to the regulation of EMT process.

EMT and MicroRNAs

A multitude of microRNAs (miRNAs) play a pivotal role in the intricate regulation of EMT by directly targeting EMT transcription factors and connected molecules, thereby exerting their regulatory influence on this cellular process. For instance, miR-205 collaborates synergistically with miR-200 family associates to defeat the expression of EMT-inducing transcription factors like ZEB, consequently promoting the reversal of EMT, known as mesenchymal-epithelial transition (MET). In mammary gland cells, miR-205 plays a crucial role in maintaining epithelial differentiation. In the context of prostate cancer, miR-29b functions as a suppressor of metastasis by regulating signaling pathways associated with EMT. Moreover, researches have revealed that miR-30a experiences downregulation during EMT in murine hepatocytes. Furthermore, in non-small-cell lung cancer (NSCLC), Snail1, a key EMT transcription factor, is post-transcriptionally directed by miRNA-30a. In hepatoma cells, miR-148a has been recognized as an adverse controller of Met/Snail signaling, effectively preventing EMT and subsequent metastasis.

A captivating double-feedback loop exists between Snail and miR-34, in which Snail binds to E-boxes contained by the promoter region of the miR-34 gene, leading to the transcriptional suppression of miR-34. In the situation of TGF-β-induced EMT, increased Snail expression suppresses miR-34. Another intriguing miRNA feedback loop, miR-203/SNAI1, has been stated in

breast melanoma. These intricate double-feedback loops play a vital role in enhancing the initiation of EMT and maintaining the equilibrium between the two cellular states, epithelial and mesenchymal.

Recent research has proposed a unique EMT system that integrates undesirable response loops, namely miR-200/ZEB and miR-203/SNAI1, to function as a switch controlling the malleability of epithelial cells during variation and cancer development. In metastatic breast cancer cells, transcription factor Twist brings the appearance of miR-10b, which directly targets the mRNA encoding homeobox D10, leading to amplified expression of RHOC, a well-known pro-metastatic gene.

Some miRNAs exert their regulatory influence on EMT by pointing either the receptors that receive signals from EMT inducers or various EMT/MET mechanisms. Notably, miR-204 directly targets TGF-βRII and Snail2, contributing to the regulation of EMT by modulating claudin expression levels. miR-204 possesses a dual role in maintaining epithelial integrity, as it can also target Snail, which is quickly prompted by TGF-β signaling through EMT.

The Eph tyrosine kinase receptor A4 (EphA4) plays a dire role in MET during somite morphogenesis and facilitates cell relocation and proliferation through the EphA4-FGFR1 signaling path. In hepatocellular carcinoma (HCC), miR-10a targets EphA4 and modulates the metastatic possessions of cancer cells. EphA4 knockdown mimics the effects of miR-10a, and its ectopic expression restores the impact of miR-10a on invasion, migration, and linkage in HCC cells.

EMT and Autophagy

The termination of intercellular connections and the subsequent attenuation of apical-basal polarity constitute critical processes that instigate the reorganization of the cytoskeleton, ultimately fostering cellular motility and invasion through the development of specialized membrane structures known as lamellipodia, filopodia, and invadopodia. EMT represents a profound biological phenomenon that orchestrates a remarkable cellular metamorphosis, shifting cells from their tightly bound, polarized epithelial state into motile, migratory, and invasive mesenchymal-phenotype cells (Figure 2). EMT manifests not only through embryonic growth but also in various normal and pathological contexts, encompassing tissue repair, organ fibrosis, wound healing, and cancer progression. Notably, EMT stands as one of the defining hallmarks of human cancer, playing a pivotal role in initiating metastasis, as it endows cancer cells with the capacity for heightened motility following their achievement of a mesenchymal phenotype, facilitating their movement to detached anatomical sites.

The downregulation of E-cadherin, a prominent epithelial marker recognized as the "gatekeeper" of EMT, culminates in the dismantling of adherens desmosomes, junctions, gap junctions and tight junctions. This interference of intercellular junctions, coupled with the loss of apical-basal polarization, initiates a profound restructuring of the cytoskeleton, fostering cellular motility and invasiveness through the development of specialized membrane protrusions, including filopodia lamellipodia and invadopodia. Concomitantly, the promotion of mesenchymal gene expression, including genes encoding proteins such as N-cadherin, Vimentin, fibronectin, and matrix metalloproteinases (MMPs), contributes to heightened cellular migratory capabilities and empowers cells with the ability to evade apoptosis and facilitate metastasis. These mesenchymal cells can subsequently degenerate to a more epithelial state through a process known as mesenchymal-epithelial transition (MET).

With mounting evidence highlighting the role of EMT in fostering drug resistance and stemness in colorectal cancer (CRC) cells and giving rise to a cancer stem cell (CSC)-like phenotype, it develops apparent that EMT represents a process through which epithelial cells adopt the attributes of mesenchymal stem cells. Additionally, EMT significantly influences tumor cell proliferation, drug resistance, and overall tumor growth. Of particular significance, a considerable body of literature firmly establishes the integral involvement of EMT in tumor cell metastasis (Figure 5). Particular its pivotal part in metastasis, EMT has garnered considerable consideration among scientists.

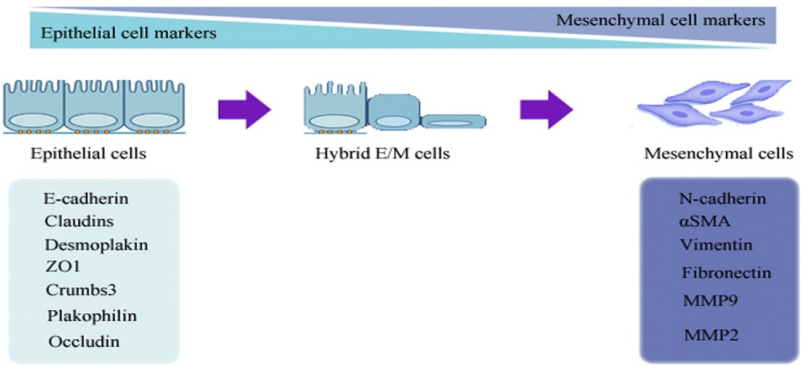

Figure 5: Molecular Landscape of EMT Induction: the epithelial marker declines in this process, the mesenchymal marker upsurges, driving the transition and the cells miss their polarization and are transformed to the motile cells.

Impact of EMT on Cancer metastasis

EMT-inducing transcription factors (EMT-TFs) can be classified into two distinct groups based on their mechanism of E-cadherin transcriptional suppression. The first group comprises EMT-TFs that unswervingly attach to the E-cadherin promoter and physically interact with E-cadherin. This group includes zinc finger proteins from the SNAIL family (SNAIL1, SLUG or SNAIL2, and SMUC or SNAIL3), ZEB1, ZEB2 (SIP1), and KLF8. In contrast, the second group consists of EMT-TFs that indirectly repress E-cadherin. This group encompasses basic helix-loop-helix (bHLH) proteins belonging to the TWIST family (TWIST1 and TWIST2) and the forkhead box protein FOXC2.

Regulation of EMT-TFs occurs through various signaling pathways operating at different stages of RNA metabolism. These pathways encompass TGFβ, Wnt, NOTCH, MAPK, FGF, EGF, and the miR-200 family. It's noteworthy that both mesenchymal cells during embryonic development and metastatic cancer cells during malignant progression share common features, such as the loss of cellular acquisition and the polarity of motile characteristics. Importantly, these attributes are also ascribed to cancer stem cells (CSCs) and common stem cells.

Several studies have unveiled a durable relationship among EMT and CSCs, with EMT frequently coinciding with an upsurge in CSC populations. Furthermore, CSCs, which drive carcinogenesis and metastasis, often originate from cells undergoing EMT. EMT confers upon cancer cells an invasive, migratory, drug-resistant, stem-like, and metastatic phenotype, as substantiated by in vitro studies conducted on colorectal carcinoma (CRC) and ovarian carcinoma cell lines.

It is largely acknowledged that EMT plays a pivotal part in the initiation of drug resistance, as substantial evidence supports their interrelation across different malignancies. Moreover, numerous anti-cancer drugs have been found to induce EMT in numerous tumor types. This induction is reinforced by the observation that the loss of E-cadherin expression during EMT contributes to chemoresistance. For instance, conventional chemotherapy agents commonly employed in CRC treatment, such as Oxaliplatin or 5-fluorouracil (5-FU), have been revealed to induce EMT by upregulating the expression of the transcription factor Snail. Consequently, Snail-mediated downregulation of E-cadherin expression ensues, leading to augmented chemoresistance.

Notably, EMT is not the sole determinant of cellular chemoresistance. Conversely, MET, characterized by the upregulation of E-cadherin and the silencing of EMT master regulators, can restore drug sensitivity and enhance cancer cell susceptibility to a variety of cytotoxic agents in specific scenarios, such as in CRC cells. An accumulating body of research has illuminated the involvement of NANOG in mediating both EMT and drug resistance in numerous human cancers. A recent study conducted by Liu and colleagues on ovarian cancer cells postulated that NANOG overexpression facilitates drug resistance and EMT through the STAT3 pathway. Concerning drug resistance, NANOG conferred chemoresistance upon ovarian cancer cells, as evidenced by the downregulation of chemoresistance-associated genes like MDR genes (MDR1) and GST-π following NANOG downregu-

lation. Regarding EMT, cells transfected with si-NANOG and treated with a STAT3 inhibitor (WP1066) exhibited the highest E-cadherin expression and the lowest Vimentin expression profile.

A research conducted by Meng and associates reported that NANOG not only functions as an EMT inducer but is also subject to EMT in CRC tumor progression. NANOG plays an important part in promoting the transcription of major EMT regulators, Slug and Snail. Notably, Snail exerts control over NANOG expression, indicating the presence of a positive feedback mechanism between NANOG and Snail in CRC. Furthermore, recent research has demonstrated that NANOG mediates both EMT and CSC stemness in CRC. Insulin-like growth factor II (IGF-II) induces NANOG-mediated CSC self-renewal through a STAT3-dependent mechanism. NANOG facilitates the activation of EMT by binding to its binding sites in the Slug promoter region, thereby promoting Slug transcriptional activity in CRC cells.

Concluding Remarks

In conclusion, the intricate procedure of epithelial-to-mesenchymal transition (EMT) plays a pivotal role in a myriad of physiological and pathological events, ranging from embryonic growth to organ fibrosis and cancer progression. EMT, categorized by the transformation of epithelial cells into motile, invasive mesenchymal-like cells, is an essential mechanism underpinning metastasis, a hallmark of advanced malignancies. This dynamic process is orchestrated by a multitude of transcription factors, miRNAs, and signaling pathways, culminating in the repression of epithelial markers like E-cadherin and the stimulation of mesenchymal genes.

Crucially, EMT is closely intertwined with cancer stem cells (CSCs), adding an additional layer of complexity to tumor progression. Emerging evidence substantiates the notion that EMT and CSCs are invariably linked, with EMT often coinciding with an expansion of the CSC pool. The acquisition of EMT attributes confers upon cancer cells a spectrum of aggressive traits, including invasiveness, stem-like properties, resistance to therapy, and the potential to seed metastatic colonies.

Drug resistance, a formidable challenge in cancer therapy, frequently emerges as a consequence of EMT. Many conventional chemotherapeutic agents have been shown to induce EMT, driving chemoresistance and complicating treatment strategies. Therefore, understanding the intricate regulatory networks governing EMT and its crosstalk with CSCs is of paramount importance in devising innovative therapeutic approaches to combat metastatic cancer.

Furthermore, the role of NANOG, a pluripotency-associated transcription factor, in mediating both EMT and drug resistance underscores its significance as a potential therapeutic target. NANOG exhibits a multifaceted role in modulating EMT, CSC self-renewal, and chemoresistance in various cancer types. Targeting NANOG and its associated pathways may hold promise for disrupting the EMT-CSC axis and sensitizing cancer cells to conventional treatments.

In light of these observations, future research endeavors should focus on unraveling the intricacies of EMT and its interplay with CSCs, with a view to identifying novel therapeutic strategies that can effectively impede metastasis and enhance the efficacy of anti-cancer therapies.

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