

# CANCER CONUNDRUM



## EPITHELIAL-MESENCHYMAL TRANSITION

Embryogenesis shows clearly that all the cells in the human body are generated by one cell, the fertilized zygote. A variety of cells and tissue are generated by this one cell.<sup>[1]</sup>

Developmental process generates the mesoderm and endoderm from the ectoderm. This involves a crucial and critical process called epithelial-mesenchymal transition (EMT).<sup>[2]</sup> In physiology, the role of EMT is seen at different time intervals. It is actually a series of events which is highly cell- and tissue-specific.<sup>[1,3]</sup>

The main event is when physiologic EMT is seen in gastrulation; formation and migration of neural crest cells.<sup>[3]</sup> The progression of EMT is further classified into primary (1°), secondary (2°) and tertiary (3°) EMT,<sup>[2]</sup> depending on the number or sequential sweeps of EMT and mesenchymal-epithelial transition (MET).<sup>[2]</sup> MET signifies the conversion of the mesenchymal phenotype back into the epithelial phenotype.

- 1° - Gastrulation, neural crest development
- 2° - Somite formation, palatogenesis, formation of liver, pancreas and reproductive tract
- 3° - Heart development.

EMT is defined as a biological process that allows a polarized epithelial cell, which normally interacts with

the basement membrane via its basal surface to undergo multiple biochemical changes that enable it to assume a mesenchymal cell phenotype (which includes enhanced migratory capacity, invasiveness, elevated resistance to apoptosis and greatly increased production of ECM components).<sup>[3]</sup>

EMTs are functional in different biological settings. Hence, EMT gets classified into three different biological subtypes:<sup>[2,4]</sup>

Type I – EMT associated with implantation and embryo formation, organ development and generation of diverse cell types.

Type II – EMT associated with wound healing, tissue regeneration and organ fibrosis. Type II EMTs are inflammation-driven and can lead to organ destruction and fibrosis.

Type III – Occurs in neoplastic cells responsible for invasion and metastasis.

## REGULATION OF EMT IN HEALTH AND DISEASE

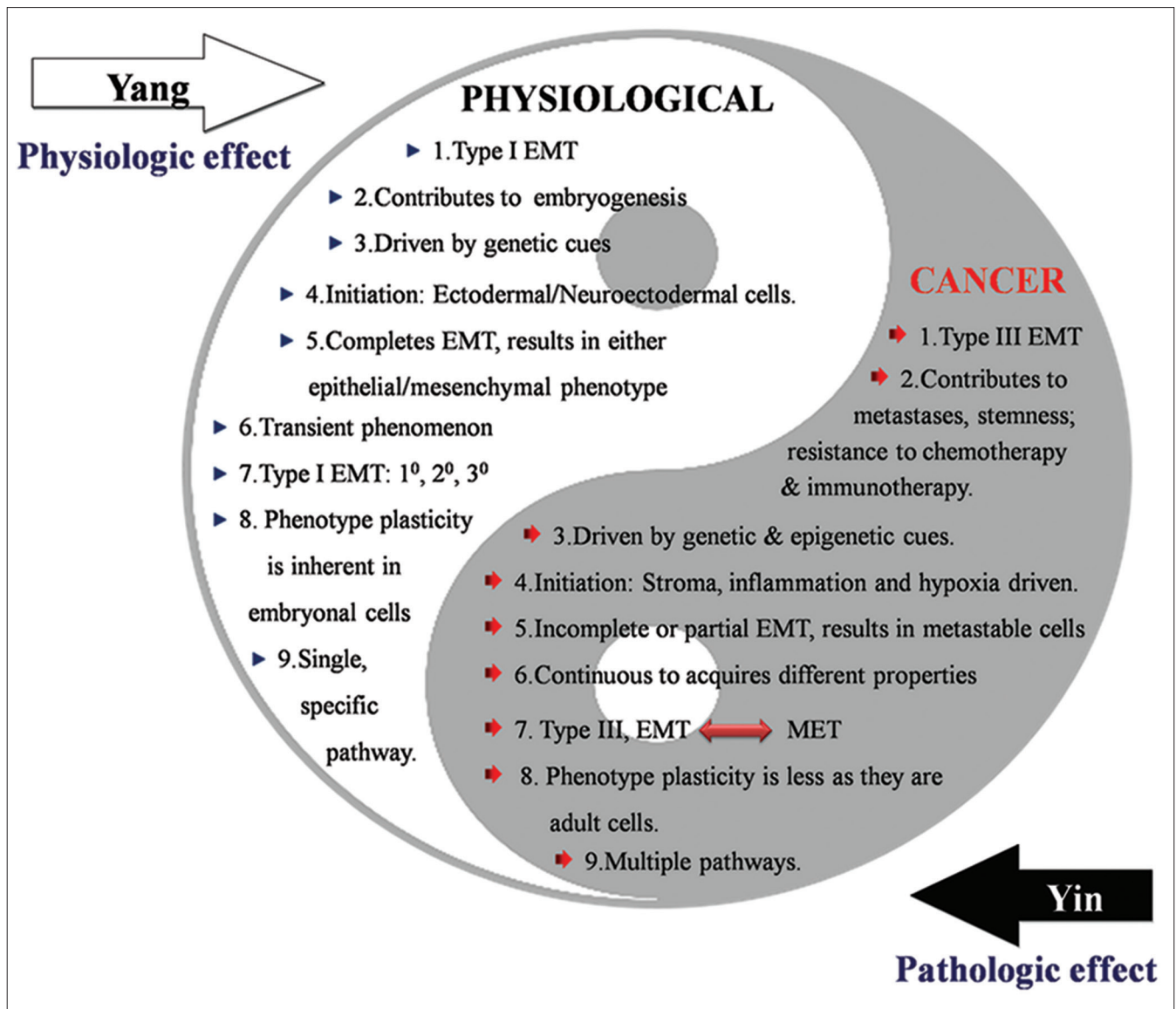
EMT associated with gastrulation follows canonical Wnt signaling. Transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily protein mediates the Wnt, leading to the expression of Wnt8c. EMT progresses with orchestrated

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**Figure 1:** Yin and Yang depicting the role of epithelial-mesenchymal transition in physiological and pathological (cancer) states

role of fibroblast growth factor (FGF), snail, crumbs and many more transcription factors. Similarly, during the neural crest cell migration, the genes expressed by the cells are sax, snail, slug and fork head.<sup>[5,6]</sup> EMT occurs by using signaling pathway mediated by Wnt, bone morphogenetic proteins, c-Myc and Msn-1.<sup>[3]</sup>

In Type II, EMT gets triggered frequently because of TGF- $\beta$ , platelet-derived growth factor (PDGF), epithelial growth factor (EGF) and FGF-2. Matrix metalloproteinases (MMPs) play an important role (especially MMP-2, 3 and 9). TGF- $\beta$  induces EMT via Smad 2 and/or mitogen-activated kinase-dependent pathway.<sup>[3]</sup>

Cancer EMT is induced mainly by the tumor-associated stroma, TGF- $\beta$ , hepatocyte growth factor and EGF,

while PDGF induces transcription factors snail, slug, ZEB1, twist, gooseoid and Foxc2. These transcription factors independently or with interlinked activity can also progress to EMT by the activation of several other signal transduction proteins, extracellular signal regulated kinases, HAPK, p13, Akt, smads, rheb, lymphocyte-enhancing factor (LEF), C-FOS,  $\beta$ -catenin,  $\beta_4$  integrin and  $\alpha v \beta 6$  integrin.<sup>[3,6]</sup>

TGF- $\beta$  can be an important contender to trigger EMT in cancer cells. Two important axes are known, one is the TGF- $\beta$ /Smad/LEF/PDGF axis and the other is TGF- $\beta$ /protein kinase B (APK)/p13k/Ras mutant.

The physiological and pathological roles of EMT are depicted through Yin and Yang [Figure 1].

## PROSPECTUS AND FUTURE OF EMT

EMT opens up new thoughts on understanding epithelial plasticity in development, health and disease. Occurrence of EMT in tumor pathology rekindles the development paradigm to be used by cancer cells to achieve fatal outcomes. EMTs in development and disease are very dynamic and complex, they also share a variety of genes, transcription proteins and pathways, making a clean distinction between the two types, i.e. EMT Type I and EMT Type III, very difficult.<sup>[1,2]</sup> Although it is now clear that EMT regulators and inhibitors can substantially play a solid role in tumor pathology, targetoid therapy can make tumors responsive to drugs, immunosurveillance, prevent invasion and metastasis and curb the stemness of tumor cells.<sup>[2,7]</sup>

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## Conflicts of interest

There are no conflicts of interest.

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