# Cancer and development: Epithelial mesenchymal transition in terminal end buds of the mammary gland

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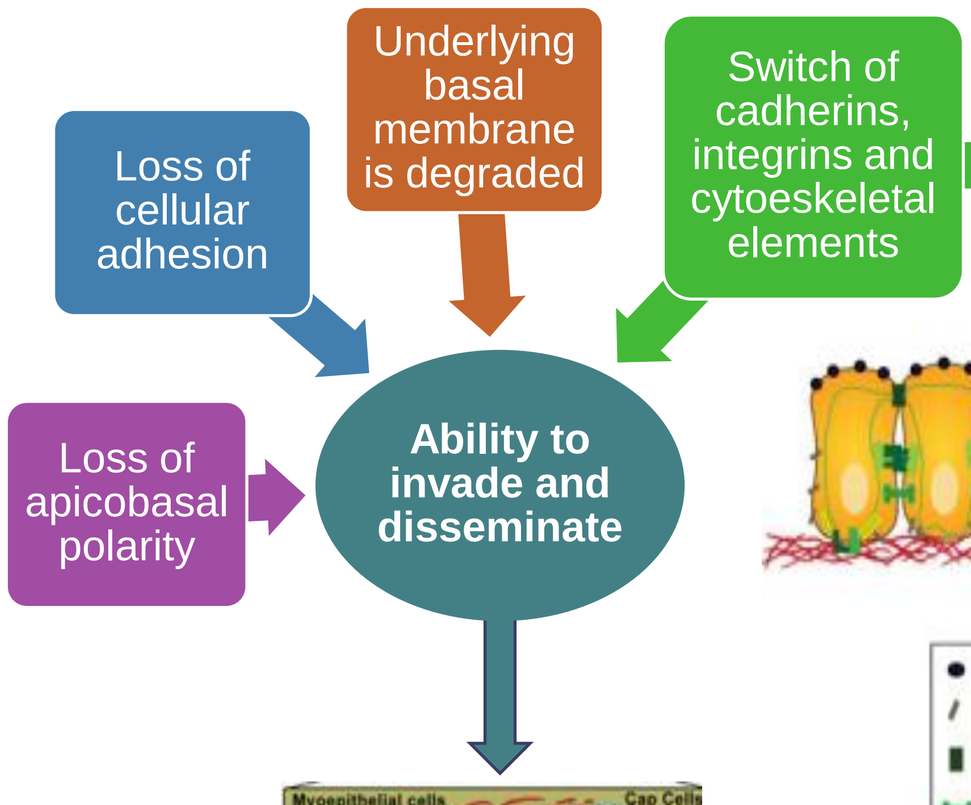
## Introduction

Several embryonic mechanisms have been described to be reactivated during tumour progression to serve cancer purposes. For example, **epithelial-mesenchymal transition (EMT)** allows cancer cells to invade, inducing metastasis. It is like disggregate epithelial structure in order to cells acquire the capacity of movement.

| HALLMARK | CANCER | DEVELOPMENT |
|---|---|---|
| *Sustaining Proliferative Signalling* | Oncogens | Morphogens |
| *Evading Growth Suppressors* | Tumour suppressor genes (TSG) | Morphogens |
| *Resisting Cell Death* | No functional p53 | p53 is dispensable |
| *Enabling Replicative Immortality* | Telomerase activation | Telomere elongation |
| *Inducing Angiogenesis* | Leaking and aberrant vessels, erratic blood flow | Controlled, closed and correct blood flow |
| *Activating Invasion and Metastasis* | EMT | EMT |

Table 1. It shows proposed correspondences or relation of hallmarks of cancer with development processes




**Functional loss of E-cadherin** is considered a hallmark of EMT and TGF-beta signalling pathway the primary inducer of EMT, as it induces E-cadherin repressors (Snail, Slug, SIP1).

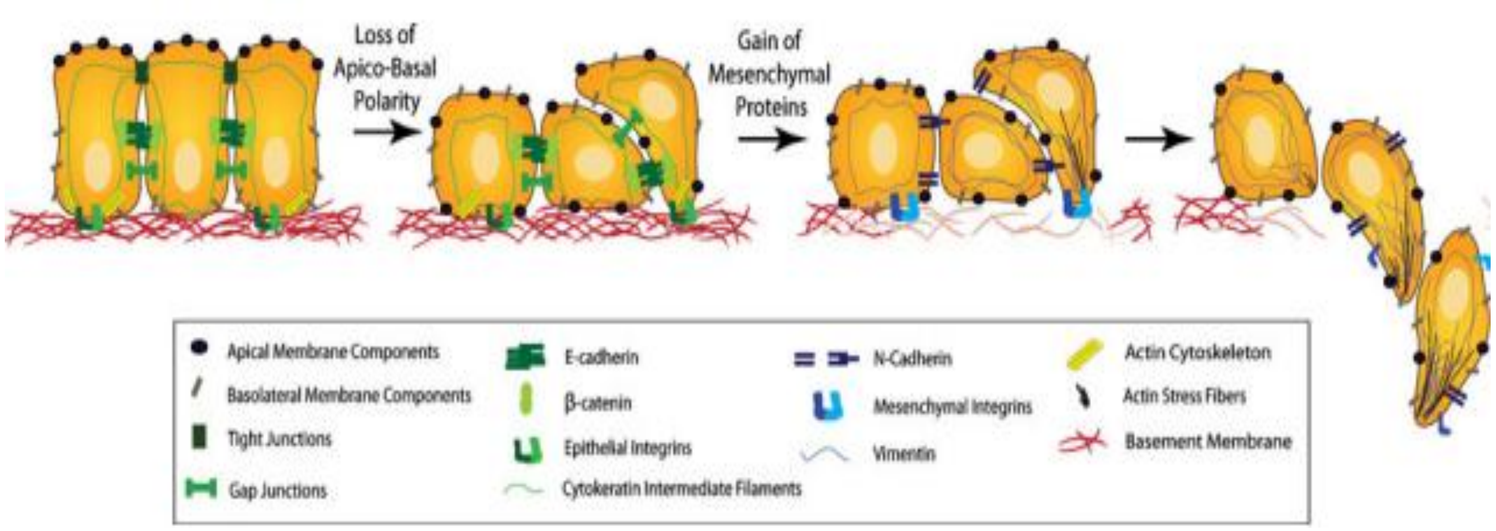



**Figure 1. Epithelial Mesenchymal Transition.** More relevant changes in features and molecules are shown, displaying the conversion from epithelial to mesenchymal phenotype. Ref.(1)

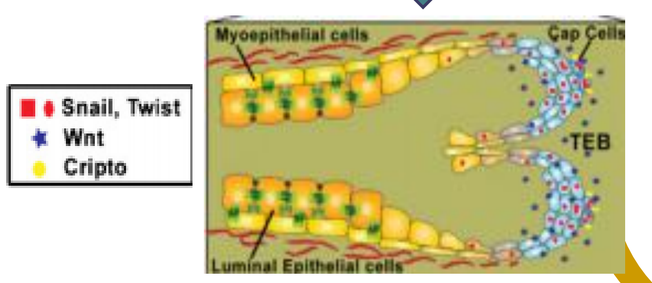



**Figure 2. TEB structure.** At the onset of puberty, at the end of mammary gland ducts terminal end buds (TEB) are stablished, showing a multilayered epithelial structure. Ref. (1)

**TEB**

- Multilayered epithelial structure: luminal (polar), basal (myoepithelial) and internal
- Give rise to the bilayered mammary ducts (lobuloalveolar units, LAU)
- Elongation of the ducts depends on proliferation within the TEB, where cells exhibit mesenchymal characteristics (epithelial plasticity): lacking contact with lumen or basal membrane, cell adhesion and apicobasal polarity

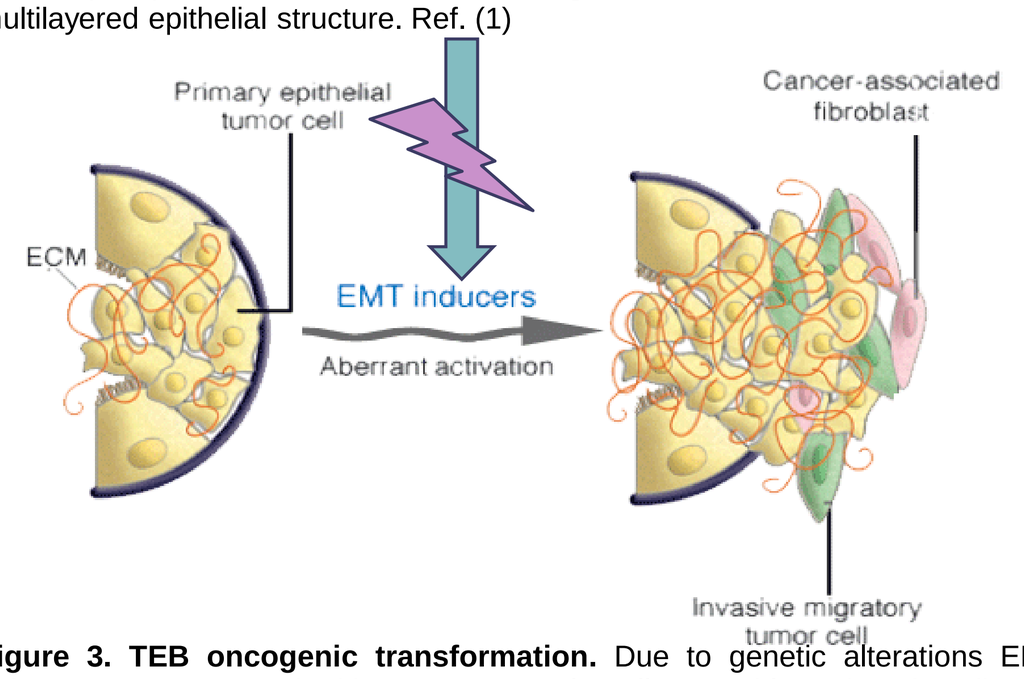



**Figure 3. TEB oncogenic transformation.** Due to genetic alterations EMT inducers are expressed without any control. Cells are able to invade adjacent stroma and disseminate to spread throughout the body by blood vessels. Ref. (2)

- Induced by steroids at puberty; RTK signalling – shared with EMT
- High proliferation rate → high probability of mutations and more sensitive to carcinogens → sites of malignization in breast cancer

## Conclusions

Genetic instability → activation of EMT inducers
Even CIS but already EMT → implications not just for metastasis
Quicker dissemination as they are already motile when basal membrane is disrupted → prediction of agresiveness
New insight in cancer = developmental point of view
Reactivated developmental mechanisms → molecules or pathways implicated are possible target for novel therapies (highly specifics)

**References**

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(2) Acloque H, Adams MS, Fishwick K, Bronner-Fraser M, Nieto MA. Epithelial-mesenchymal transitions: the importance of changing cell state in development and disease. J Clin Invest . 2009 Jun 1;119(6):1438–49.