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

Canitrot Regueira, Lucía

Bioscience Faculty
Universitat Autònoma de Barcelona 2014/2015

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 disintegrate epithelial structure in order to cells acquire the capacity of movement.

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 established, showing a multilayered epithelial structure. Ref. (1)

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)

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).

• 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

• 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 aggressiveness
New insight in cancer = developmental point of view
Reactivated developmental mechanisms → molecules or pathways implicated are possible target for novel therapies (highly specifics)

References