EPITHELIAL TO MESENCHYMAL TRANSITION IN MAMMARY TISSUE AND ANTI METASTASIS THERAPY

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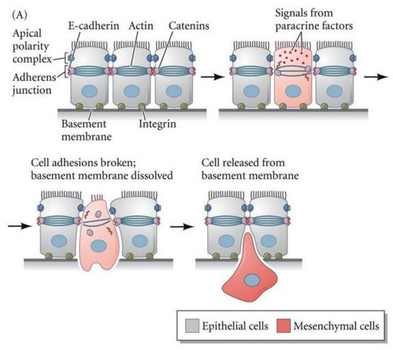
The aim of this literature review is to make known the EMT phenomenon in mammary tissue and its importance in the development, wound healing and cancer. In addition, evidence of possible anti metastasis therapies which could reverse EMT is given.

INTRODUCTION

The topic was chosen due to the importance of EMT over an individual's lifetime, and specifically in mammary tissue for the incidence of breast cancer nowadays. To make known the possible anti metastasis therapies, could give an encouraging view to keep investigating in this field.

The mammary tissue is an epithelial tissue in which the cells are in contact with each other and with the ECM. It is very important to maintain these contacts for the integrity of the tissue. If by different mechanisms these contacts are lost, cells acquire a migratory capacity with an invasion of other tissues.

The EMT phenomenon is a process that allows the cells to lose their contacts. Therefore, the epithelial cells become mesenchymal cells.



Epithelial Mesenchymal Transition phenomenon. (From Scott F. Gilbert, 2010 [2])

MATERIALS AND METHODS

Breast cell cultures, murine models, mutant constructs and Breast cancer cell lines have been used to achieve the results exposed.

High quality journals and books have also been used as reference for this literature review. The articles and reviews related to the EMT in the mammary tissue have been selected to give a general view of the processes involved.

DEVELOPMENT TYPE I EMT

- Epithelial cells in the epiblast layer express E-cadherin and exhibit apical basal polarity.
- During mammary development Wnt, Notch and Hedgehog pathways are activated.
- The epithelial cells that line the mammary gland establish an AB axis with apical and basal surface and specialized junctions are formed along the lateral membrane. The junctional localization of E-cadherin and β-catenin is crucial for the cell-cell and ECM-cell contacts.
- The sustained balance of polarity signaling is crucial for the continued maintenance of AB polarity.

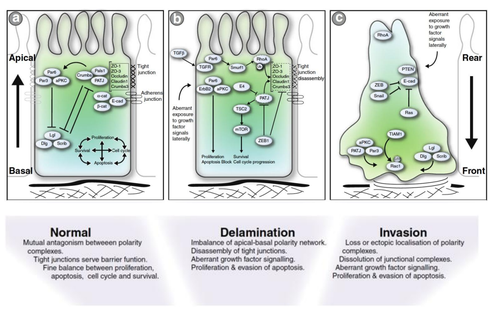
REGENERATION TYPE II EMT

- The process of wound healing involves the orchestred activities of cell types to facilitate the re-epithelization of denuded areas.
- The key cells involved in the repair of damaged epithelium are myofibroblasts, and signaling by TGF-β and ECM are essential in promoting the activation and differentiation of myofibroblasts.
- The completion of EMT is typically assessed by α-SMA expression in fully transitioned cells and its expression is indicative of a fibrotic state. α-SMA expression is induced by TGF-β and integrin activation cooperates with TGF-β to induce EMT and myofibroblasts activation.
- TGF-β signaling supports chronic inflammatory reactions that promote fibroproliferative disorders in humans.

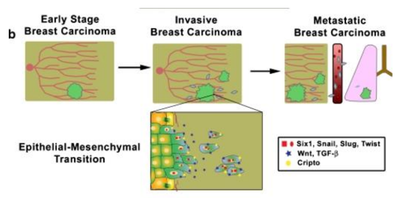
RESULTS AND DISCUSSION

EMT IN BREAST CANCER

In breast cancer progression, imbalances in the AB polarity network weaken tight junctions. There are several pathways, such as TGF-β which promotes survival and cell cycle progression destabilizing the contacts between cells. Transcription Factor ZEB1 activates the mTOR pathway which is deregulated in breast cancer.



Polarity switching in breast cancer development. (From Goode NJ et al. 2010 [1]).



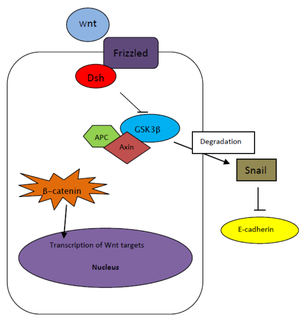
Genes and pathways missexpressed in breast cancer include Cripto-1, Snail/Slug/Twist, Wnt and TGF-β signaling. Collective migration of the tumor cells sets the stage for metastatic dissemination to distant organ sites in late stage breast cancer. (From Micalizzi DS, et al. 2010 [3]).

A central target to the EMT signaling pathway is E-cadherin, the main protein involved in adherens junctions, classified as a tumor suppressor. It can be perturbed at multiple levels and this is central to polarity changes associated with EMT. Snail is the first direct transcriptional repressor of E-Cadherin, but Slug and Twist are also EMT inducers in cancer cells. The expression of these three correlates with aggressive disease, reinforcing the effects of an oncogenic EMT.

Developmental EMT signaling pathways reactivated in Breast Cancer

Notch signaling pathway

The Notch signaling pathway plays an important role in maintaining the progenitor cell population. This pathway is coordinated with others to regulate EMT such as TGF-β pathway. Elevated Jagged 1(Notch ligand) and Notch promote Slug expression, thereby repressing E-cadherin. Moreover, there is a crosstalk between Notch and Wnt pathways. Wnt1 transforms primary human mammary epithelial cells, and these cells have Delta ligand expression.



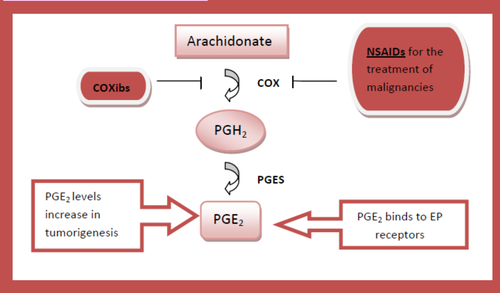
Wnt signaling pathway reactivated in Breast Cancer

Wnt signaling pathway

In the presence of Wnt ligands, β-catenin translocates into the nucleus regulating the transcription of Wnt target genes. GSK3β not only regulates β-catenin but also mediates proteosomal degradation of Snail. Inhibition of GSK3β leads to accumulation of Snail which represses E-cadherin. Therefore, Wnt can stabilize the levels of Snail and β-catenin.

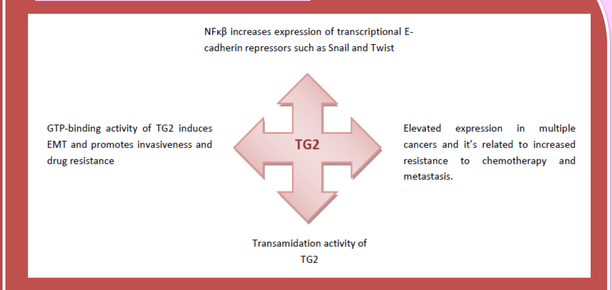
ANTI METASTASIS THERAPY

PROSTAGLANDIN



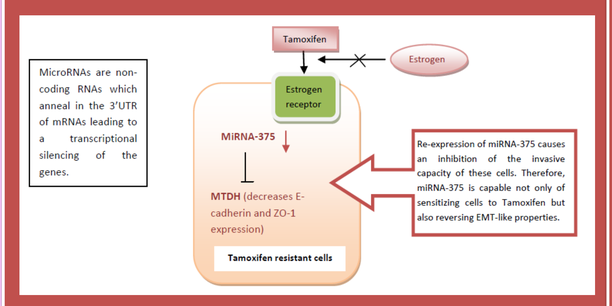
There are 4 types of EP receptors with different intracellular signaling pathways, so some receptors contribute to tumor progression and others may be protective. As the role of each receptor in cancer grows, selective EP agonists and antagonists could be exploited as therapeutic targets.

TRANSGLUTAMINASE 2



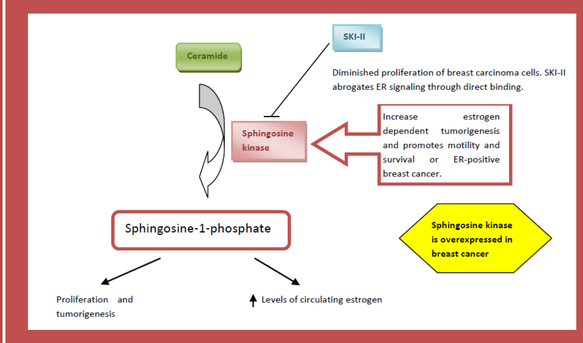
Inhibition of TG2 by small-molecule inhibitors, antisense RNA or siRNA could render cancer cells sensitive to chemotherapeutic drugs.

miRNA-375



Re-expression of miRNA-375 or inhibition of MTDH might be potential therapeutic approaches for the treatment of Tamoxifen-resistant breast cancer in future.

SPHINGOSINE KINASE



SKI-II can be an effective ER antagonist in the setting of Tamoxifen resistance making SKI-II an attractive therapeutic candidate for the treatment of ER-positive breast cancer.

CONCLUSIONS

- The epithelial mesenchymal transition phenomenon is crucial for the embryonic developmental processes as well as wound healing and cancer.
- It is very important for the cells that undergo an EMT to lose cell-cell and ECM-cell contacts in order to establish the mesenchymal phenotype that allows them to migrate and expand within distant tissues.
- Studies reveal several anti-metastatic therapies that could reverse the epithelial mesenchymal transition. The molecules involved are Prostaglandin E2, Transglutaminase 2, microRNA-375 and sphingosine kinase.

REFERENCES

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