Breast cancer stem cells generated through the epithelial mesenchymal transition

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1. INTRODUCTION

Epithelial mesenchymal transition consists in the loss of apico-basal polarity and epithelial markers as E-cadherin or integrins and acquisition of mesenchymal migratory phenotype with markers vimentin, fibronectin and N-cadherin. During tumor progression EMT results in the acquisition of invasive properties such as high resistance to apoptosis, properties of stem cells and the ability to migrate allowing them to move and integrate into nearby tissue.

There is a large number of genes and signaling pathways involved including TGF-β, Wnt, Notch, and ERK/MAPK pathways that allows the upregulation of transcriptional repressors of E-cadherin expression like Snail or Twist. It has been seen that it is a small heterogeneous population of cancer stem cells responsible for the initiation and metastatic growth of breast cancer. The main objective will be to identify their markers and signaling pathways responsible for maintenance of this BCSCs.

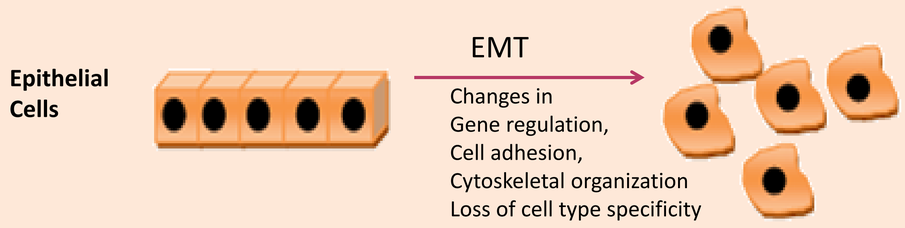

Figure 1: Modified from "Breast Cancer Stem Cells, Pathways and Therapeutic Perspectives 2011" (2012).

2. TGF-β IS THE MAIN INDUCER OF EMT

The transforming growth factor beta is overexpressed in many human cancers. Cooperates with Wnt, Ras, Hedgehog and Notch pathways to induce a complete EMT.

TGF-β activates multiple signaling pathways through TGF-βRI and TGF-βR II that activate and phosphorylate effector molecules as Smad2 and Smad3. These phosphorylated form trimers with Smad4 to enter the nucleus and bind to transcription factors thereby promoting the expression of target related with proliferation, differentiation, apoptosis and cell migration.

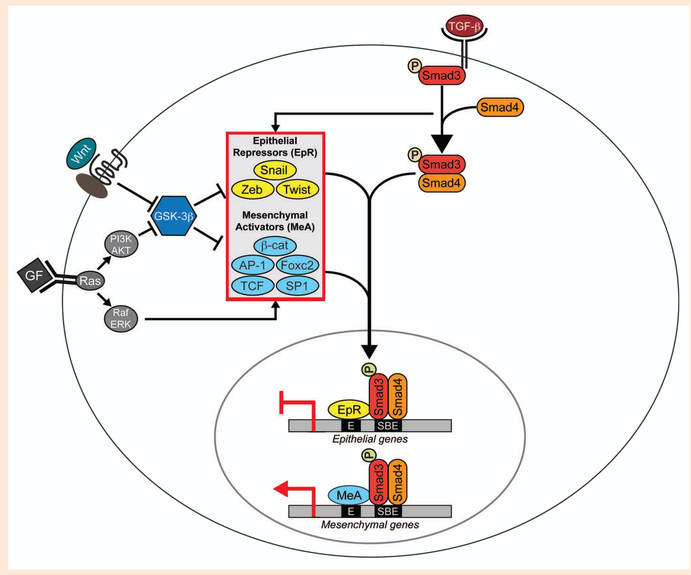

Figure 2: Modified from "Transcriptional crosstalk between TGFβ and stem cell pathways in tumor cell invasion: Role of EMT promoting Smad complexes" (2010).

3. BREAST CANCER STEM CELLS (BCSCs)

Their most important features are the ability to self-renewal and regulating the balance between self-renewal and differentiation. They also have a great migratory and proliferative potential and express high levels of ABC transporters and thus, it has been suggested to be responsible for the development of drug resistance.

BCSCs marker
CD44+/CD24-/loLin- phenotype
HER2 overexpression
Mammosphere formation
Exclusion of fluorescent dye by a side population
Transforming growth factor-β (TGF-β)
BMP-7 expression
microRNAs
CXCR4 (Chemokine receptor)
CSCL12 expression
ESA, CK5, and α6- integrin
Aldehyde dehydrogenase-1 (ALDH1) activity
CD44

Table 1: Modified from "Breast Cancer Stem Cells, Pathways and Therapeutic Perspectives 2011" (2012).

CD44 is a target gene of β-catenin / TCF4. It is a membrane receptor that recognizes ligands of the extracellular matrix, whose expression has been linked to aggressive behavior and tumor metastasis.

CD24 can regulate cell adhesion by reducing CXCR4.

ALDH1 is responsible for the intracellular oxidation of aldehydes; thus confers resistance to alkylating agents. It may have a role in self-renewal of the cells oxidizing retinol to retinoic acid. It also increases the ability to form mamospheres.

CXCR4 is a receptor driving stem cells and tumor metastasis. CSCL12 is a chemokine that promote induction and migration of immune cells to the site of infection. CXCL12 interacts with CXCR4 inducing migration and survival of neoplastic cells.

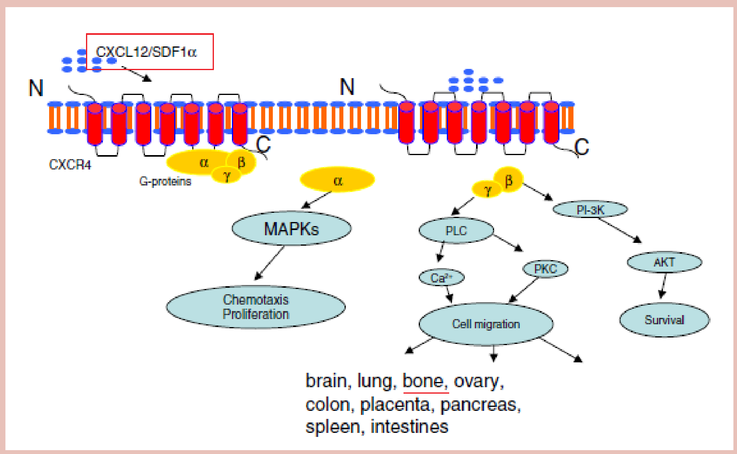

Figure 3: Modified from "Role of the CXCR4/CXCL12 signaling axis in breast cancer metastasis to the brain" (2010).

4. PATHWAYS RESPONSIBLE FOR THE MAINTENANCE OF BCSCs

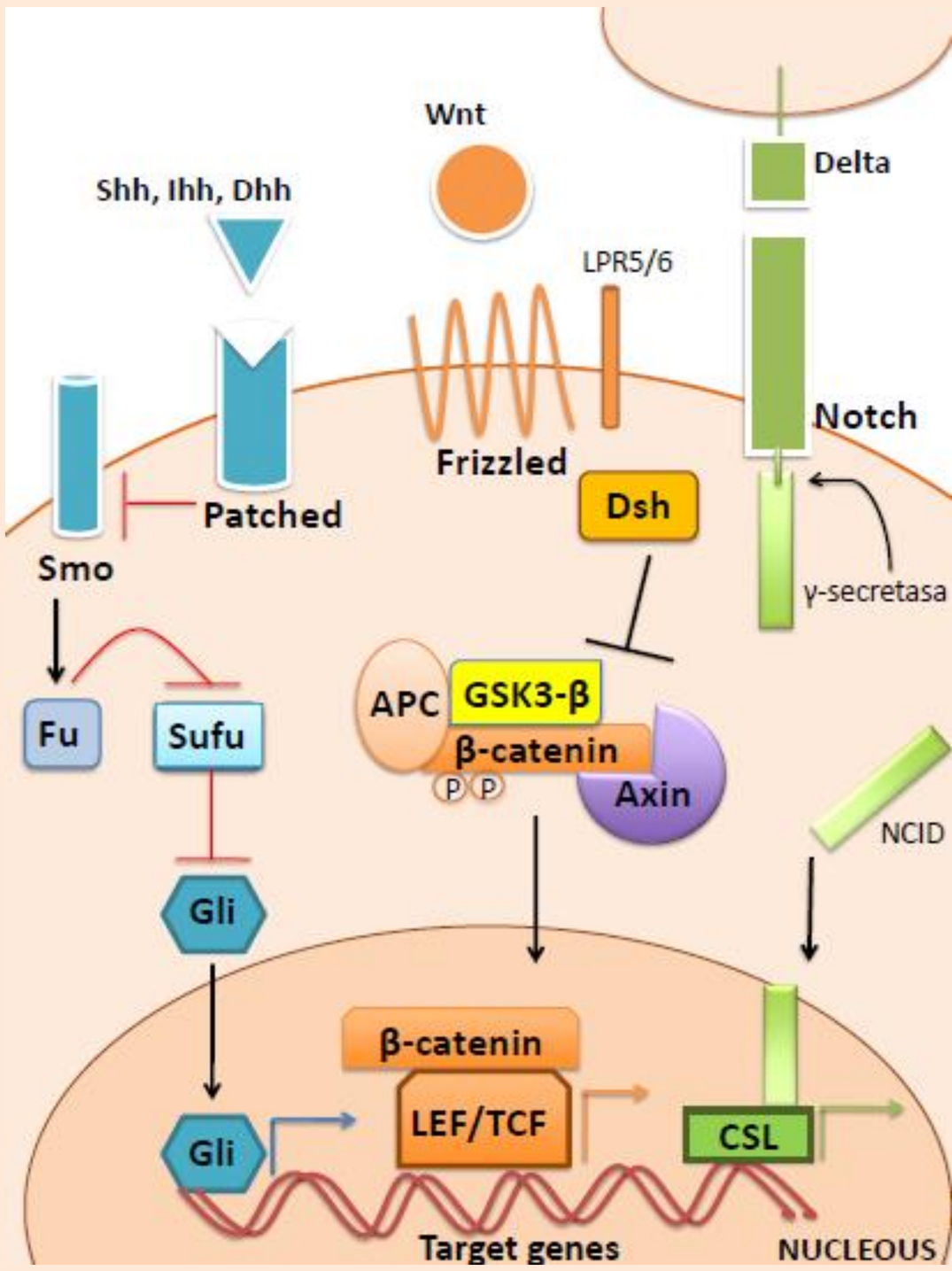

Figure 4: Wnt, Hedgehog and Notch signaling pathways regulate the maintenance of breast cancer stem cells controlling the transcription of various target genes associated with EMT and repression of E-cadherin.

5. THERAPY

❖One of them would be directed to resistance to chemotherapy of this stem cells: inhibitors of these transporters ABCG2 and ABCB1, ex. Nilotinib.

❖Remove cancer stem cells, ex. trastuzumab led to ErbB2.

❖Inhibition of the pathways involved in self-renewal: cyclopamina to inhibit Smo in the Hedgehog pathway, imatinib that negatively regulate β-catenin in the Wnt signaling and Notch-4 blocking antibody.

❖Therapies targeting chemoreceptors using these breast cancer stem cells to migrate and proteins necessary for integration with the microenvironment for example using CXCR4 antagonists.

❖ Inducing differentiation of breast cancer stem cells.

6. CONCLUSIONS

❖Epithelial mesenchymal transition generates cells with stem cell properties with phenotype CD44+/CD24- or activity ALDH1 and these cells are enriched with tumor-initiating cells.

❖These cells are responsible for the resistance to treatment of this cancer.

❖There is strong evidence that the crosstalk of the Hedgehog, Notch, Wnt and other keys signaling pathways and their role in the regulation of tumor-initiating cells, can promote tumorigenesis in breast cancer.

❖Regarding the treatment, the better would be the combination of different therapies aimed at eliminating breast cancer stem cells responsible of the invasive progression tumor.

7. REFERENCES

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