Cancer stem cells, reason of the failure of conventional cancer treatments

Anna Pérez Martín. Grau de Biotecnologia. Universitat Autònoma de Barcelona

OBJECTIVES

- To understand the properties and the role within tumors of cancer stem cells
- To know cancer stem cells origin
- To study different signalling pathways implied in cancer stem cells maintenance
- To understand why current therapies fail in front of cancer stem cells

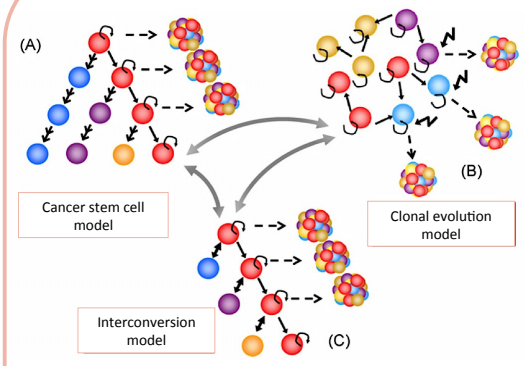
CANCER STEM CELLS

Definition Cancer stem cells (CSCs) are cancer pluripotent initiating cells that are present within tumors in a low percentage.

Properties CSCs have been defined on the basis of their ability to self-renew (dividing itself into two identical daughter CSCs), to expand the tumor, to migrate and form new tumors, to avoid antigrowth signals, to evade apoptosis, to replicate limitless and to resist conventional therapies.

Inconvenient Because of their high resistance, cancer stem cells are a reason of the failure of conventional therapies, which are not targeting CSCs. New therapies are being developed, not focused on reducing the tumor mass, but in targeting CSCs.

THE ROLE OF CSCs IN CANCER PROPAGATION



Cancer stem cell model

Only CSCs have the ability to generate the tumor, being progenitors cells unable to generate it

Clonal evolution model

All tumor cells have the aptitude to form new tumors

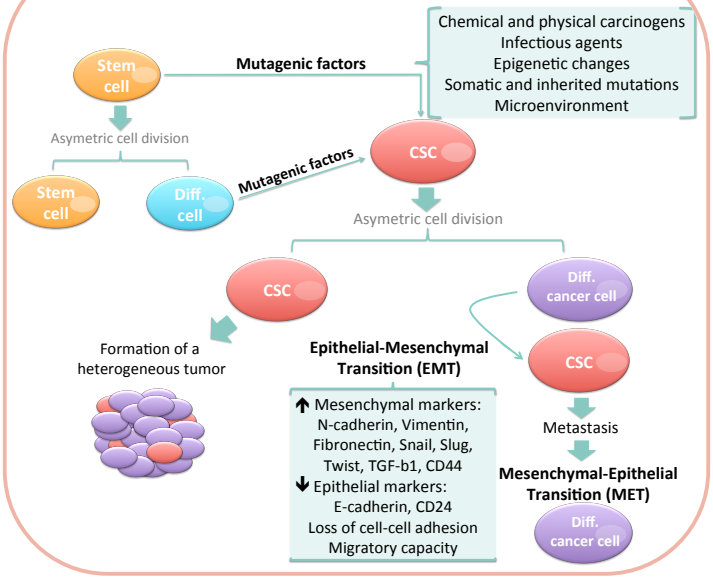
Interconversion model

Cancer cells will always return to a equilibrium of cell-state proportions, due to a bidirectional interconversion between CSC and non-CSC states

Models are not mutually exclusive

Shackleton, M. et *al* . Semin. Cancer Biol. **20**, 85–92 (2010)

ORIGIN OF CANCER STEM CELLS



↑ Mesenchymal markers: N-cadherin, Vimentin, Fibronectin, Snail, Slug, Twist, TGF-b1, CD44
↓ Epithelial markers: E-cadherin, CD24
Loss of cell-cell adhesion
Migratory capacity

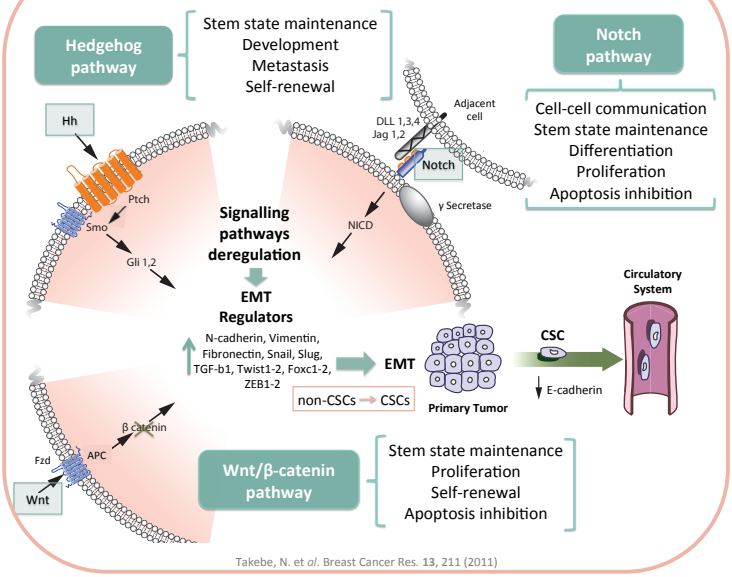
SIGNALLING PATHWAYS IMPLIED IN CSCs

Hedgehog pathway

Stem state maintenance
Development
Metastasis
Self-renewal

Notch pathway

Cell-cell communication
Stem state maintenance
Differentiation
Proliferation
Apoptosis inhibition



Wnt/β-catenin pathway

Stem state maintenance
Proliferation
Self-renewal
Apoptosis inhibition

Takebe, N. et *al*. Breast Cancer Res. **13**, 211 (2011)

CANCER TREATMENT

Conventional therapies

Chemotherapy
Radiotherapy
Surgery

CSCs present genetic and cellular adaptations

High capacity for DNA repair
High resistance to drug penetration
Resistance to apoptosis
Microenvironment
Dormancy/Slow cell cycle kinetics
High metastatic potential
Epithelial-Mesenchymal transition

Therapy failure

Cancer stem cells therapies

A successful therapy must eliminate the tumor bulk cells and induce the differentiation or elimination of CSCs

Being necessary to combine traditional chemotherapy and radiotherapy with new strategies targeting CSCs

Differentiation therapy

Must force CSCs

to differentiate terminally
to lose self-renewal property
to lose progression property

Retinoic acids
Drugs targeting tumor epigenetic changes

Elimination therapy

Transplanting hematopoietic stem cells with allogeneic inserts
Therapies against the self-renewal
Modelling the mechanism of resistance
Therapies based in antigens
Hypoxia-induced anti-cancer agents
Epigenetic therapies

Nanomedicine
Gene therapy
Drugs

CONCLUSIONS

- Knowledge of cancer stem cells leads to another point of view against the treatment of cancer.
- Cancer stem cells properties help us to understand conventional therapies failure.
- Combination therapies are needed to destroy CSCs, through differentiation or elimination, but also to avoid Epithelial-mesenchymal transition.

RELLEVANT REF.

- Takebe, N., Warren, R. Q. & Ivy, S. P. Breast cancer growth and metastasis: interplay between cancer stem cells, embryonic signalling pathways and epithelial-to-mesenchymal transition. *Breast Cancer Res.* **13,** 211 (2011).
- Han, L., Shi, S., Gong, T., Zhang, Z. & Sun, X. Cancer stem cells: therapeutic implications and perspectives in cancer therapy. *Acta Pharm. Sin. B* **3,** 65–75 (2013).
- Zhao, Y., Alakhova,D.Y.,.Can nanomedicines kill cancer stem cells? *Adv. Drug Deliv. Rev.* **65**, 1763-1783 (2013).
- Shackleton, M. Normal stem cells and cancer stem cells: similar and different. *Semin. Cancer Biol.* **20,** 85–92 (2010).

UAB
Universitat Autònoma de Barcelona