Cancer stem cells: a possible target for new cancer therapies

Lorena García Martinez – Grau en Biologia

Role of CSC in cancer

- CSCs are proposed to be exclusively capable of driving tumorigenesis because of:
  - Their ability for long-term self-renewal
  - Their capacity to differentiate into tumor bulk populations devoid of CSC features
  - Their unlimited potential for proliferation and tumorigenic growth
- CSC can arise from mutations of normal stem cells, progenitor cells or more differentiated cells
- Dysregulation of microenvironmental factors can contribute to the carcinogenic process
- CSC exhibit increased resistance to chemotherapeutic agents
- CSC are likely to drive tumor progression, tumor recurrence and metastasis

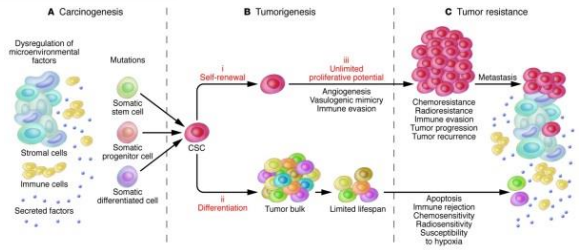

Image from Frank et al., *J Clin Invest*. Jan 4, 2010; 120(1): 41–50.

Models of tumor heterogeneity

- Tumors are composed of heterogeneous cell populations
- According to the **stochastic model**, all tumor cells are biologically equivalent, but their behavior is influenced by extrinsic and intrinsic factors. So, tumor-initiating activity can not be given to a specific group of cells
- According to the **hierarchy model**, there are distinct classes of cells with different behavior in a tumor. Only a subset of them (CSCs) has the ability to initiate tumor growth

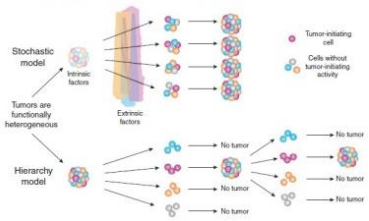

Image from Dick et al., *Nature Biotechnology* **27**, 44 - 46 (2009)

CSC and metastasis

- Metastasis is the final step in the progression of malignancies
- It is though that CSCs drive metastasis, as they are thought to be the unique cells with tumor-initiating ability:
  - CSCs of the primary tumor enter to the circulation trough EMT process (epithelial – mesenchymal transition), becoming circulating tumor cells (CTC) with stem cells features
  - These CTC remain in the circulation until they go to another organ and seed a new tumor

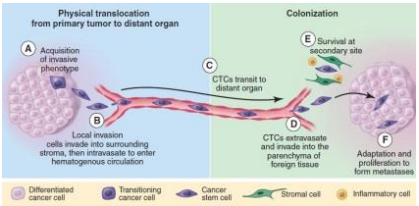

Image from Chaffer et al., *Science* **331**, 1559 (2011).

Therapies

- Current anticancer therapies are directed to proliferating cells assuming that all cells within a tumor have equal malignant potential
- Cancer stem cells are not eradicated because of their chemoresistance and radioresistance
- After therapy, CSCs survive and can reestablish the tumor
- If therapies were directed against CSCs, then the other tumor cells will be unable to maintain the tumor, and it will degenerate
- Several novel therapeutic strategies directed to CSCs are beginning to emerge, and are summarized in the following table:

Type of strategy		Tumor in which has been proven
Direct strategies	CSC ablation	Experimental models melanoma, liver cancer, glioma, breast cancer, human leukemia and bladder cancer
	Reversal of resistance of CSCs	In vitro melanoma, CD133+ glioma CSC and breast cancer
	Differentiation therapy	Experimental models of human glioma, breast cancer, acute myeloid leukemia
Indirect strategies	Antiangiogenic therapy	Xenogratfs of human CD133+ glioma CSC
	Immunotherapetic approaches	None at the moment

Future views

CSCs represent novel relevant targets for clinical cancer therapies, and the knowledge about this cells is still limited. It seems that patients cure without the efficient eradication of CSCs seems unreachable. Further research is needed, and if therapies were effective, they would be much mess toxic and more effective than current treatment modalities

For more information

- Frank, N. Y., Schatton, T., & Frank, M. H. (2010). The therapeutic promise of the cancer stem cell concept. *The Journal of clinical investigation*, *120*(1), 41.
- Reya, T., Morrison, S. J., Clarke, M. F., & Weissman, I. L. (2001). Stem cells, cancer, and cancer stem cells. *Nature*, *414*(6859), 105-111.

Universitat Autònoma de Barcelona