Cancer stem cells, evolution of the concept and therapeutic perspectives

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INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality worldwide. Since the identification of **cancer stem cells (CSCs)**, plenty of studies have suggested that this small subpopulation of cancer cells with tumour-initiating capability is the core origin of the tumorigenesis and intra-tumour heterogeneity. CSCs are also thought to be responsible for the conventional therapy-resistance and tumour relapse, thus being one of the most promising therapeutic targets.

OBJECTIVES

1. To stablish CSCs characteristics.
2. To understand CSCs role in tumour growth and heterogeneity by the evolution of the concept in the last 20 years.
3. To determine the possible therapeutic strategies targeting CSCs to prevent tumour relapse.

METHODS

Bibliography obtained from **PubMed** and **Scopus** data bases with the following searching criteria:

Keywords: cancer stem cells, tumour evolution, clonal evolution, plasticity, model, heterogeneity tumour niche, etc.
Publication dates: last 5 years for therapies, no limit for CSCs basic information.
Article types: Reviews, Classical articles, Clinical Trials.

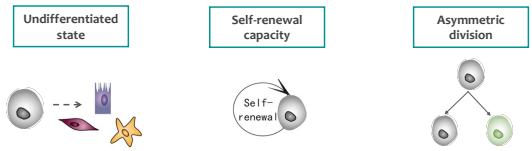
Other materials: books, web pages, scientific posters.

Extensive analysis of bibliography and merging of information. Citations management by **Mendeley.**

RESULTS

CANCER STEM CELLS

CSCs share common features with normal stem cells:

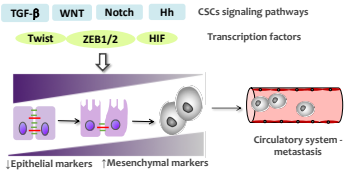


There are 3 possible origins for CSCs:

1. Normal stem cells.

2. Differentiated cell that express reprogramming factors.

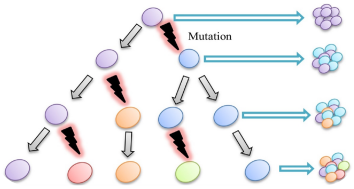
3. Differentiated cell that suffers epithelial-to-mesenchymal transition (EMT).



MODELS FOR TUMOUR HETEROGENEITY

1 Stochastic model

According to stochastic model, all tumour cells are biologically equivalent and the multiple cell populations forming the tumour are a result of genetic mutations which appear by a stochastic manner. The progression of tumour follows the clonal evolution, in which some clones have an increased survival advantage and outcompete the other tumour cells.

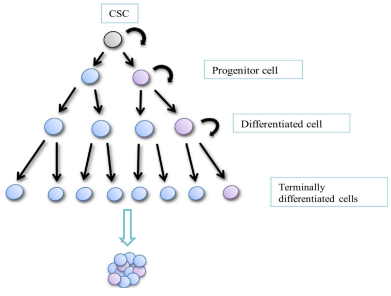


CONTRADICTIONS

- Cancers whose incidence is higher depending on the age.
- Differentiated cells lifespan prevents the accumulation of enough mutations to become neoplastic.

2 CSCs model

The CSCs model postulates the existence of biologically and functionally distinct classes of cells in a tumour. CSCs are in the apex of the hierarchy and undergo asymmetrically to give rise to more CSCs and to non-CSCs that will form the bulk of the tumour. In this case, only a subset of cells present in a low frequency in the tumour are able to initiate tumour growth.



CONTRADICTIONS

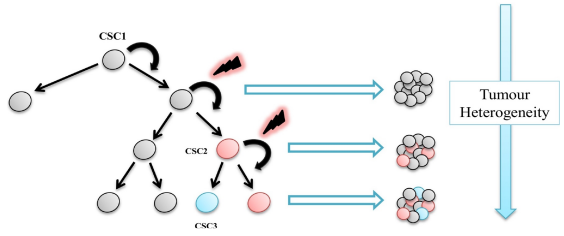
- CSCs, as proliferating cells, shouldn't be resistant to conventional therapies.

CANCER STEMLOIDS
(dormant CSCs populations)

- Recent studies demonstrate that CSCs may not necessary to be in a low frequency in tumours.

3 Dynamic model

Tumours are initiated by a CSCs (CSC1), but during the progression of the disease different clones of CSCs (CSC2, CSC3) can appear due to stochastic mutations either in CSCs existing clones or even in differentiated-non-tumorigenic cells which provide them with reprogramming capacities. The more aggressive CSC clones will become dominant and drive tumour growth.



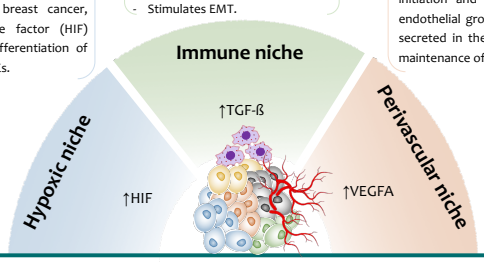
CANCER STEM CELL NICHE

CSCs have been suggested to require their CSC niche to maintain stem cell properties and to favour the reprogramming process by which non-CSCs are converted into CSCs.

In leukaemia brain, pancreatic and ER-positive breast cancer, hypoxia inducible factor (HIF) induces the dedifferentiation of non-CSCs into CSCs.

Macrophages recruited into the tumour tissue secrete TFG-ß which:
- Supress immunosurvillance.
- Stimulates EMT.

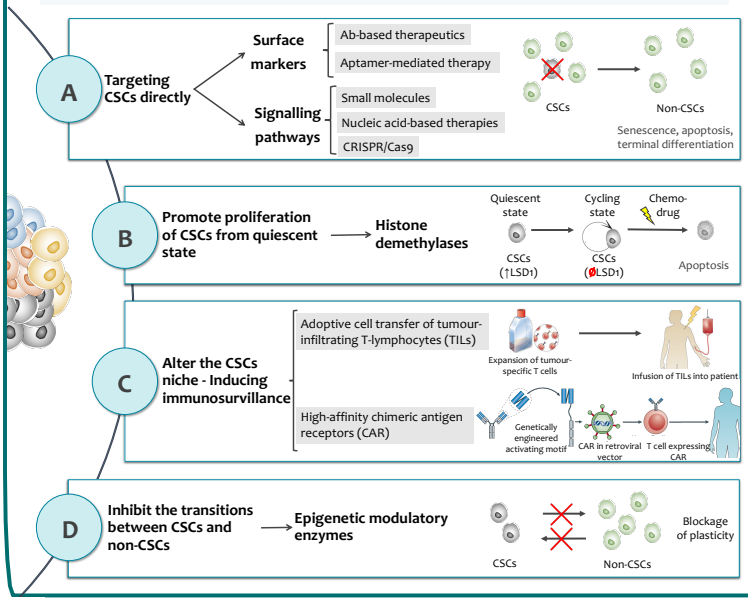
Angiogenesis has key roles in cancer initiation and progression. vascular endothelial growth factor A (VEGFA) secreted in the vascular niche helps maintenance of glioblastoma CSCs



CANCER STEM CELL TARGETING

Cancer stem cells (CSCs) therapy-resistance strategies

- Stemloids dormancy
- Altered metabolism
- High capacity for DNA repair
- Cell plasticity
- Microenvironmental factors
- Reactive oxygen species
- ATP binding cassette (ABC)-related transporters
- Noisy gene expression



CONCLUSIONS

- CSCs, similarly as normal stem cells, possess the ability to divide asymmetrically giving rise to daughter cells that will differentiate into the neoplastic cells forming the bulk of the tumour as well as daughter cells that will remain as CSCs.
- The dynamic model of tumour heterogeneity explains that some tumours may not follow a clear hierarchy and that CSCs might not necessarily have to be rare.
- Although the elimination of CSCs offers an exciting potential to cure cancer, it may be not enough as many cancers show dynamic stemness. Therefore, it is necessary to combine therapy approaches to first eliminate CSCs populations that already reside in the tumour and to secondly control a variety of reprogramming mechanisms either by blocking cell-signalling pathways or niche-specific signals.

RELEVANT BIBLIOGRAPHY

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