

more than a marker for cancer stem cells

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INTRODUCTION

CANCER STEM CELLS (CSCs)...

- Are a small tumour cell subpopulation that can initiate and drive tumourigenic growth
- Carry out an asymmetric division: they are able to renew themselves and they can also differentiate

- Can arise from mutations in normal stem cells, progenitor or mature differentiated cells
- Are responsible for therapy failure, recurrence and metastasis
- Give another perspective in the treatment against cancer → Aldehyde dehydrogenase as a candidate target

1. CANCER STEM CELLS AND THEIR ORIGIN

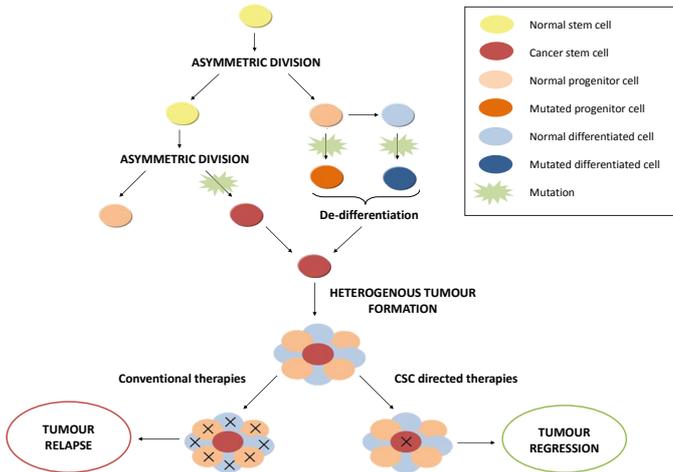
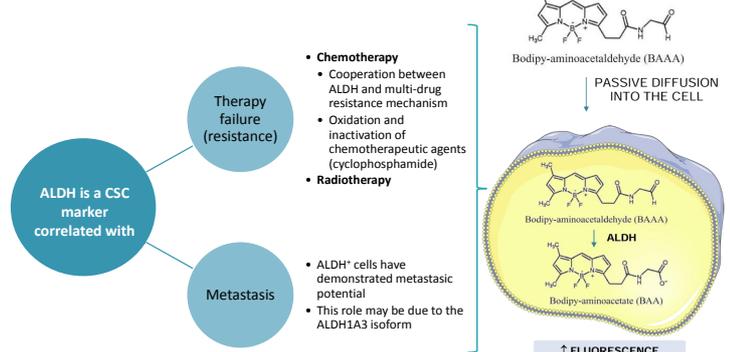


Figure 1 | Origin of cancer stem cells. CSCs can renew themselves to preserve the stem cell population and they can also differentiate to form various specialised cells in an asymmetric division. In fact, they can arise from mutations in normal stem cells, progenitor cells or differentiated cells, and they are responsible for tumour formation and growth. For this reason, CSC directed therapies would lead to tumour regression, whereas conventional therapies cause tumour relapse.

2. ALDEHYDE DEHYDROGENASE

- Aldehyde dehydrogenases (ALDH) are enzymes that catalyse the oxidation of aldehydes to their consequent acids by a NAD(P)⁺-dependent irreversible reaction
- This enzyme oxidises and detoxifies aldehydes that can be harmful to the organism
- ALDH is considered a marker for CSCs, identifiable by the Aldefluor assay



- **Chemotherapy**
 - Cooperation between ALDH and multi-drug resistance mechanism
 - Oxidation and inactivation of chemotherapeutic agents (cytotoxic phosphamide)
- **Radiotherapy**
 - ALDH⁺ cells have demonstrated metastatic potential
 - This role may be due to the ALDH1A3 isoform

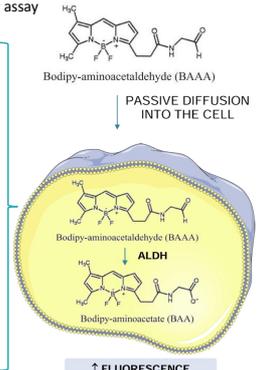


Figure 2 | Aldefluor Assay. BODIPY-aminooacetaldehyde can diffuse into the cell to be converted to a negatively charged fluorescent product named BODIPY-aminooacetate.

Figure was produced using Servier Medical Art (www.servier.com)

Existence of CSCs

Tumour initiation and growth

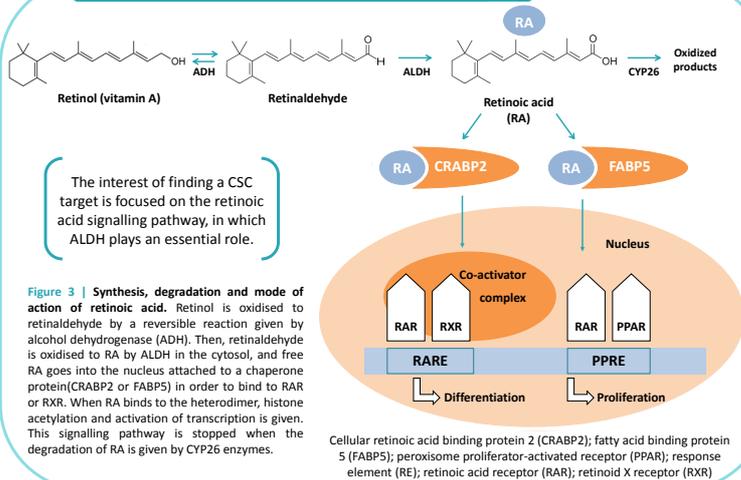
Conventional therapies failure

Tumour recurrence

Metastasis

Need for targeted therapies against CSCs

3. RETINOIC ACID SIGNALLING PATHWAY



4. THERAPIES THAT TARGET CSCs

METHOD	Targeting CSC-dependent of signalling pathways	Targeting the tumour microenvironment	Immunotherapy	Differentiation therapy
STRATEGY	Some specific signalling pathways (TGF-β, Wnt and Hedgehog) are involved in the maintenance of the cancer stem cell state	Affecting the microenvironment of the tumour, the maintenance of the stem cell state is lost and the EMT programme is altered	Activation of immune response against specific antigens in CSCs	This therapy induces the exit from the CSC state into a more differentiated state
EXAMPLES	PRI-724 is an inhibitor of Wnt signalling that blockades the β-catenin-CREB binding protein interaction ↓ proliferation	Elimination of signals that permit the 'stemness': inhibition of cytokines (such as IL-6) and growth factors	Cytotoxic T lymphocytes, natural killers and antibodies	All-trans retinoic acid (ATRA) treatment inhibits proliferation and invasion by activating retinoic acid pathway

5. CONCLUSIONS

1. CSCs open new frontiers in the treatment against cancer
2. ALDH is a good marker for CSCs because its identification and isolation is easier thanks to the Aldefluor Assay
3. Resistance to conventional therapies and metastasis can be explained by CSCs, where ALDH plays a valuable role on this matter
4. ATRA could be a novel cancer therapy by producing retinoic acid and causing differentiation, although non-CSCs also have to be eliminated to eradicate all the bulk of the tumour by conventional therapies



ALDH is not only a marker for cancer stem cells, and further studies are needed to resolve more questions about cancer

RELEVANT REFERENCES

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Molecules in Figure 2 are from: Stem Cell Technologies. Technical Bulletin - Identification of viable stem and progenitor cells with Aldefluor [Online]. France; 2009. [Consultation 7/4/2016]. Available in: https://www.stemcell.com/~media/Technical%20Resources/0/0/28728_aldefluor_July%202009.pdf?la=en