Prognostic role of CDX2 in Stage-II patients

Dalerba et al., NEJM, 374:211-222 (2016)
Predictive role of CDX2 expression on preferential benefit from adjuvant chemotherapy (Stage-II)

Dalerba et al., NEJM, 374:211-222 (2016)
Implications of the CSC model for the design and evaluation of anti-tumor treatments

Rajendran and Dalerba, Theoretical and experimental foundations of the “cancer stem cell” model. In: Cancer Stem Cells (ed. V.K. Rajasekhar) - Chapter 1 (2014)
“Stem Cell” working models to explain tumor resistance to classic anti-neoplastic agents (i.e. chemotherapy, radiotherapy)

Classical anti-tumor agents
(e.g. agents toxic to proliferating cells in the S or M phase of the cell cycle)

Examples:
- Vinca alkaloids
- Anti-metabolites
- Topo-isomerase inhibitors
- Ionizing radiation

Cancer Stem Cell (CSC)

a) multi-potent progenitors
   (not self-renewing)

b) mature - differentiated cancer cells

a) quiescent - G₀ state (leukemia)

b) high-level expression of:
   - drug pumps (leukemia)
   - enzymes for DNA repair (brain cancer)
   - scavengers of ROS (breast cancer)
   - anti-apoptotic pathways

a) multi-potent progenitors:
   - high proliferation rates

b) mature - differentiated cancer cells:
   - exposed to high intra-cellular concentrations of cytotoxic drugs
   - exposed to high levels of ROS ("reactive oxygen species")
   - vulnerable to extensive DNA damage
   - sensitive to apoptosis
Selective *in vivo* ablation of stem cell populations

Diphtheria Toxin Receptor
(mouse cells do not express this receptor, but are killed by the diphteria toxin if internalized)

Selective *in vivo* ablation of Lgr5+ stem cells does not appear to perturb intestinal homeostasis, and is followed by their rapid regeneration.
Selective *in vivo* ablation of Lgr5+ cancer cells can temporarily arrest intestinal tumor growth, but not eradicate malignant tissues.

Hierarchical models with one vs. multiple stem cell populations.

Evolutionary models suggested a “one stem cell” hierarchical structure...

... but are they correct?

Dalerba et al., Cell Stem Cell, 20:743-745 (2017)
Implications of multi-lineage differentiation for the design of synergistic drug combinations able to achieve “synthetic lethality” against the diversity of malignant cell types.

- Tumor composed of multiple cell types
  - Monotherapy with selective toxicity towards a single cell-type
    - Partial tumor regression
    - Relapse tumor regeneration
  - Multi-drug combination with toxicity towards multiple cell-types
    - Complete tumor eradication
Key points [summary #1]

1) Tumor tissues are frequently heterogeneous in cell composition; this diversity: a) is not only genetic, but also epigenetic in origin; b) it often mirrors the physiological diversity of specialized cell types found their normal counterparts; c) can arise as the result of a multi-lineage differentiation process, reminiscent of a stem cell hierarchical system;

2) In tumor tissues, the capacity to form tumors upon transplantation is frequently restricted to a subset of cancer cells, operationally defined as “cancer stem cells”; the precise molecular identity of “cancer stem cells” is still under study, and probably evolves over time, during disease progression;
3) analysis by gene-expression arrays of a bulk tumor’s transcriptional profile and the identification of a high degree of similarity with a gene-expression signature characteristic of “cancer stem cells” is usually associated with a more aggressive disease and, possibly, a differential response to anti-tumor drugs;

4) anti-tumor treatments unable to target and eradicate all “cancer stem cell” populations are likely unable to achieve long-term eradication of tumor tissues.
“Not everyone accepts the hypothesis of cancerous stem cells. Skeptics say proponents are so in love with the idea that they dismiss or ignore evidence against it. [...] the hypothesis was more akin to religion than to science.”

Gina Kolata
“Scientists Weigh Stem Cells’ Role as Cancer Cause”
Suggested readings

• Ramalho-Santos M. and Willenbring M. 
  On the origin of the term “stem cell”. 

• Weinberg R.A. 
  Multi-step Tumorigenesis 

• Rajendran P.S. and Dalerba P. 
  Theoretical and experimental foundations of the “cancer stem cell” model. 
  Chapter 1 - In: Cancer Stem Cells, 3-16 (2014)

• Dalerba P., Clarke M.F., Weissman I.L., Diehn M. 
  Stem Cells, Cell Differentiation and Cancer. 
  Chapter 7 - In: Abeloff’s Clinical Oncology (5th edition), 98-107 (2013)

• Dalerba P. 
  The dynamic identity of intestinal cancer stem cells. 
Conflict of interest (COI) disclosures [#1]

- Some of the “cancer stem cell” markers discussed in this presentation (e.g. CD44, CD166) have been described in a patent held by one of my former academic institutions (University of Michigan) and licensed to a start-up pharmaceutical company (OncoMed Pharmaceuticals Inc., now a fully owned subsidiary of the Mereo BioPharma Group). As a result of the licensing agreement negotiated by the University of Michigan, I receive royalties in recognition of my role as a co-inventor. Aside from this, I have no other financial interests in the company (e.g. no paid consultant agreements, no industry-sponsored research grants, no ownership of stock-options).

- Some of the “single-cell genomics” techniques described in this presentation have been described in a patent held by one of my former academic institutions (Stanford University) and licensed to a start-up pharmaceutical company (Quanticel Pharmaceuticals Inc., now a fully owned subsidiary of Celgene). As a result of the licensing agreement negotiated by Stanford University, I was awarded an aliquot of restricted stock in the company, and I receive royalties in recognition of my role as a co-inventor. Aside from this, I have no other financial interests in the company (e.g. no paid consultant agreements, no industry-sponsored research grants).

Piero Dalerba
• During my previous research at **Stanford University**, I contributed to develop methods to combine **anti-CD47 monoclonal antibodies** with **anti-EGFR monoclonal antibodies** (e.g. cetuximab, panitumumab) in order to increase their efficacy against colon cancer. The methods developed in these studies are described in a **patent application** that Stanford University licensed to a pharmaceutical start-up company (**Forty Seven Inc.**). As a result of the licensing agreement negotiated by Stanford University with Forty Seven Inc., **I own stock in the company** and receive **royalties**. Aside from this, I have no other financial interests in the company (e.g. no paid consultant agreements, no industry-sponsored research grants, no direct ownership of stock options).

• One of the **biomarkers** discussed in this presentation (**CDX2**) has been described in a **patent application** submitted by my current academic institution (**Columbia University**) to the **United States Patent and Trademark Office (USPTO)**. This patent application has not yet been licensed to any commercial entity.

Piero Dalerba
Conflict of interest (COI) disclosures [#3]

- My spouse was previously an employee of Amgen and Eli Lilly, two pharmaceutical companies which manufacture and sell anti-EGFR monoclonal antibodies (panitumumab, necitumumab) approved for the treatment of human cancer (colon, lung). As a result of her previous employment, my spouse owns stock in these companies. Aside from this, I have no other financial interests in these companies (e.g. no paid consultant agreements, no industry-sponsored research grants, no direct ownership of stock options).

- My spouse is currently an employee of Alexion, a pharmaceutical company develops, manufactures and sells drugs for the treatment of rare metabolic and immunological disorders (e.g. lipase deficiency, phosphatase deficiency, hemolytic syndromes caused by abnormal complement activation). As a result of her current employment, my spouse owns stock in the company. Aside from this, I have no other financial interests in the company (e.g. no paid consultant agreements, no industry-sponsored research grants, no direct ownership of stock options).

- My spouse owns stock in additional pharmaceutical companies, as part of her own diversified portfolio of investments, including Novartis and Teva Pharmaceuticals, which manufacture and/or develop anti-tumor drugs whose mechanism of action is investigated in my laboratory (but not discussed in this presentation). Aside from this, I have no other financial interests in these companies (e.g. no paid consultant agreements, no industry-sponsored research grants, no direct ownership of stock options).

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