Cancer Stem Cells and Tumor Population Dynamics

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Overview

Biology of cancer

- TNM
- Oncogene
- cancer cell structure:

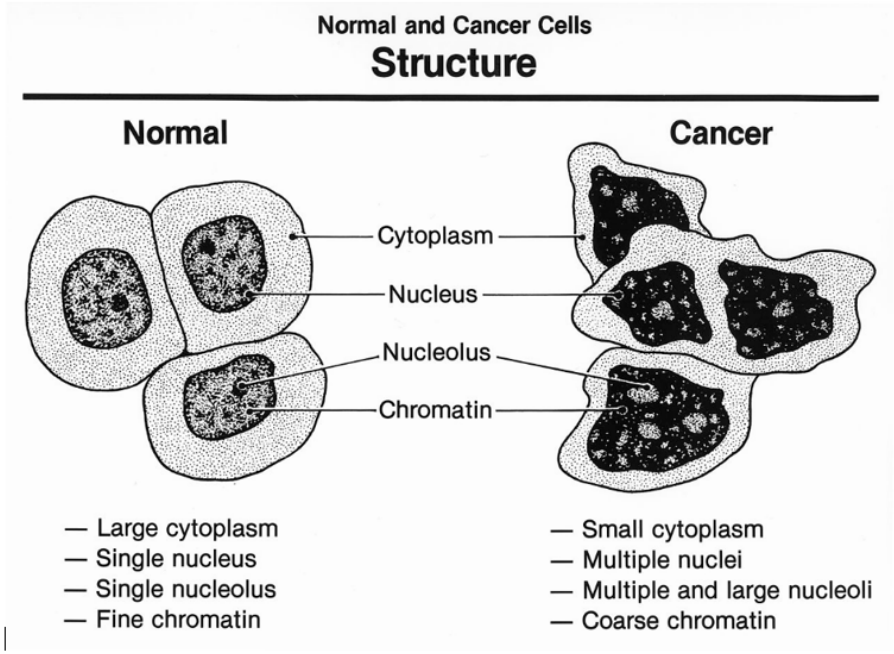

Figure: cancer cell structure

Core Hypothesis

- Tumors driven by small subpopulation: **Cancer Stem Cells (CSCs)**
- Key properties:
  - Self-renewal capability
  - Differentiation into heterogeneous cancer cells
- Cancer stem cells were first identified by John Dick in acute myeloid leukemia in the late 1990s.

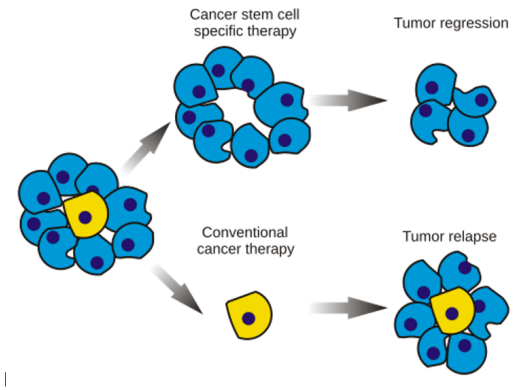

Figure:

Identification Protocol

Standard approach:

1. Sort cells via FACS using surface markers (e.g., CD44+/CD24-)
2. Transplant sorted cells into immunocompromised mice
3. Observe tumor formation
4. Re-isolate marker-positive cells from new tumor
5. Repeat transplantation (serial passaging)

Key evidence: Tumor formation exclusively by marker-positive cells

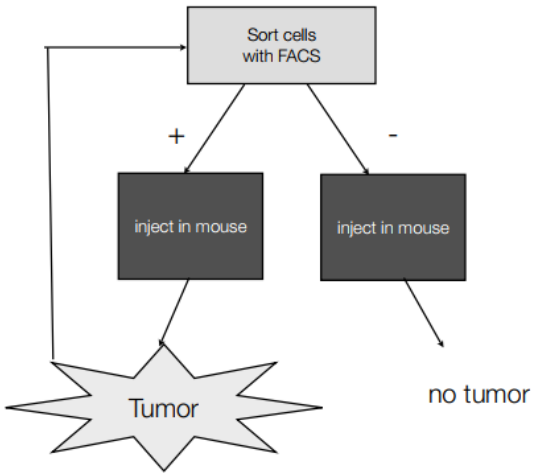

Figure: protocol used to identify CSCs

Challenges and Limitations

- **Transplantation artifacts:**
  - Xeno/syngeneic grafts miss tumor microenvironment (fibroblasts, cytokines)
- **Marker reliability issues:**
  - No universal marker (e.g., ALDH works in breast cancer but not melanoma)
  - Marker expression may be reversible
- **Model dependence:**
  - Tumor-initiating cell fraction varies with mouse strain
- **Therapeutic complications:** Targets like Notch pathway cause high toxicity

Branching Process Model

Cell types:

- CSCs: Unlimited divisions
- Cancer Cells (CCs): Finite divisions (M generations)
- Senescent cells: Death rate q

CSC division probabilities:

- Symmetric: $\text{CSC} \xrightarrow{p_2} \text{CSC} + \text{CSC}$
- Asymmetric: $\text{CSC} \xrightarrow{p_1} \text{CSC} + \text{CC}$
- Symmetric differentiation: $\text{CSC} \xrightarrow{p_0} \text{CC} + \text{CC}$

Key parameter: $\epsilon = p_2 - p_0$ (net CSC increase/generation)

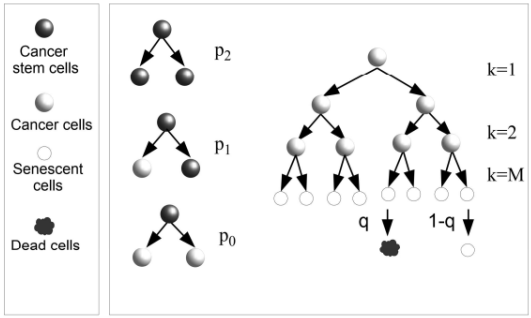

Figure: branching process for cancer stem cells

Dynamics Equations

Recursion relations (S^N: CSCs at gen. N; C_k^N: CCs of "age" k):

$$S^N = (1+\epsilon)S^{N-1}$$
$$C_1^N = (1-\epsilon)S^{N-1}$$
$$C_k^N = 2C_{k-1}^{N-1} \quad (k \geq 2)$$
$$D^N = (1-q)D^{N-1} + 2C_M^{N-1}$$

Eq. 5.2 - Only CSCs ($C_k^0 = D^0 = 0$)

$$S^N = (1+\epsilon)^N S^0$$
$$C_k^N = \begin{cases} S^N \left(\frac{2}{1+\epsilon}\right)^{k-1} \frac{1-\epsilon}{1+\epsilon} & N > k \\ 0 & N \leq k \end{cases}$$
$$D^N = \begin{cases} S^N \frac{1-\epsilon}{\epsilon+q} \left(\frac{2}{1+\epsilon}\right)^M \left(1 - \left(\frac{1-q}{1+\epsilon}\right)^{N-M}\right) & N > M \\ 0 & N \leq M \end{cases}$$

Dynamics EquationsII

Eq. 5.3 - Non-CSC Dynamics ($S^0 = 0, C_k^0 = D^0 = c$)

$$\hat{S}^N = 0$$

$$\hat{C}_k^N = \begin{cases} 2^k c & N < k \\ 0 & N \geq k \end{cases}$$

$$\hat{D}^N = \begin{cases} c(1-q)^N + c\frac{2}{1+q}(2^N - (1-q)^N) & N \leq M \\ c(1-q)^N \left(1 + \frac{2}{1+q}\left(\left(\frac{2}{1-q}\right)^M - 1\right)\right) & N > M \end{cases}$$

Complete Solution (Eq. 5.4)

$$n_{\text{tot}}^N = \underbrace{S^N}_{\text{CSCs}} + \hat{S}^N + \sum_{k=1}^{M} \left(\underbrace{C_k^N}_{\text{CSC-derived}} + \underbrace{\hat{C}_k^N}_{\text{non-CSC}} \right) + \underbrace{D^N}_{\text{CSC-senescent}} + \underbrace{\hat{D}^N}_{\text{non-CSC senescent}}$$

Biological Predictions

Senescent cell fraction: $f_{SC}^{\infty} = \dfrac{1-\epsilon}{1+q}$

CSC fraction: $f_{CSC}^{\infty} = \dfrac{q+\epsilon}{1+q}\left(\dfrac{1+\epsilon}{2}\right)^{M}$

Interpretation:

- Normal tissue ($\epsilon = 0$): High senescence, low CSCs
- Tumors ($\epsilon > 0$): Reduced senescence, increased CSCs
- Aggressive tumors: High $\epsilon \Rightarrow$ high CSC fraction

Experimental validation: Matches melanoma growth curves (ABCG2+ vs. ABCG2- cells)

Phenotypic Switching

Mathematical models predict that depletion of CSCs induces a rapid return to the CSC state through phenotypic switching, with an overshoot effect.

Model Equations

$$\frac{dS}{dt} = R_d\left(\epsilon S + p(\mu)(C + D)\right)$$
$$\frac{dC}{dt} = R_d(1-\epsilon)S - C(1 + p(\mu))$$
$$\frac{dD}{dt} = R_d(2C - p(\mu)D)$$

Where:

S = CSC population, C = cancer cells, D = senescent cells, and $p(\mu)$ = switching probability influenced by miRNAs.

Overshoot in CSC population

The model indicates that once the CSC population is depleted, an overshoot occurs due to a feedback mechanism in the miRNA network.

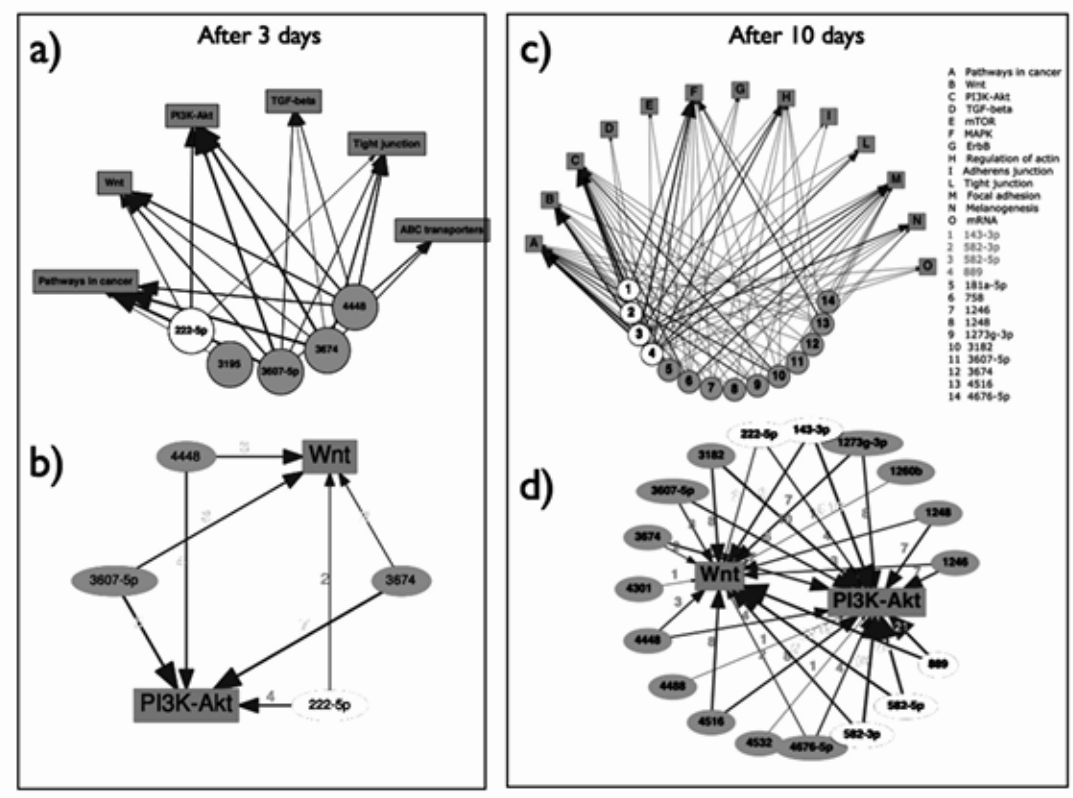

Figure: Interaction network between miRNAs and pathways during CSCswitch in melanoma

Key Takeaways

- CSCs are essential for tumor growth, but their identification and quantification remain challenging.
- Population dynamics models help explain CSC-driven tumor growth.
- Experimental and theoretical models must account for complex phenomena like phenotypic switching, which is influenced by both environmental factors and genetic regulation.

References

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