Stem Cells and Cancer

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1. the concept of "stem cells"
2. the concept of "cancer stem cells"
3. biological implications of the "cancer stem cell" model
4. clinical implications of the "cancer stem cell" model
Historical origins of the word “stem cell” [#1]

Ernst Haeckel is famous for having introduced the concept: “Ontogenesis recapitulates phylogenesis”

Ernst Haeckel, Anthropogenie, 1874

The early stages of embryonic development are very similar across species.
Historical origins of the word “stem cell” [#2]

Historically, Ernst Haeckel first used the word “stem cell” to identify an ancestor/progenitor cell that stands at the “stem” of a genealogic tree, used to depict either evolutionary (i.e. phylogenetic) or developmental (i.e. ontogenetic) processes.

Phylogenetic tree of life (i.e. evolution of life on Earth)

Ontogenetic tree of life (i.e. embryonic development)
Current use of the word “stem cell”

The meaning remains essentially intact today, where it is mainly used in developmental biology, to identify a cell capable to generate and sustain over time a specific set of diversified cell populations whose aggregate interaction leads to the formation of either:

a) an entire living organism:
   - the zygote (totipotent capacity)
   - embryonic stem cells (pluripotent capacity)

b) a specific subset of its organs and tissues:
   - adult stem cells (oligopotent or multipotent capacity)
Many tissues have a “hierarchical” organization and undergo a continuous process of cell turnover.

- Long-term self-renewing stem cells
- Short-term multipotent progenitors
- Oligolineage precursors
- Mature cells

Specialized cell types often short-lived undergo turnover during lifetime (with variable kinetics)
Stem Cell Properties

Stem cells are defined by three key properties:

1) The ability **to give rise to a functionally heterogeneous progeny of cells**, which progressively specialize according to a **hierarchical process (differentiation)**;

2) The ability **to form new stem cells** with identical, intact differentiation potential, thus maintaining the stem cell pool (**self-renewal**);

3) The ability to modulate the two previous properties according to environmental stimuli and genetic constraints (**homeostatic control**).
Examples of normal tissues that are sustained by adult stem cell populations [#1].

**Hematopoietic system**

Examples of normal tissues that are sustained by adult stem cell populations [#2].

Intestinal epithelium

Tumors are histological “caricatures” of corresponding normal tissues

Dalerba et al., Nature Biotechnology, 29:1120-1127, 2011
Tumors are histological “caricatures” of their corresponding normal tissues.

von Hansemann, Die mikroskopische Diagnose der bösartigen Geschwülste [The microscopic diagnosis of malignant tumors] (1897)

Figure 7. Rectal Cancer [...] Great similarity with the normal mucosa. Goblet cells.

Images from: Historic Book Collection, Humboldt Universität, Berlin
Tumor tissues act as “histological caricatures” of their normal counterparts.

The three-dimensional architecture and cell composition of neoplastic tissues usually mirrors that of the corresponding normal tissues of origin, and includes a variety of cell types.

Rajendran and Dalerba, Theoretical and experimental foundations of the “cancer stem cell” model. In: Cancer Stem Cells (ed. V.K. Rajasekhar) - Chapter 1 (2014)
Key points [#1]

- cancer tissues are frequently heterogeneous in cell composition; this diversity often mirrors the repertoire of specialized cell types found in normal counterparts;
- thus, in many instances, cancer tissues are not simply amorphous collections of transformed cells, but complex three-dimensional structures that retain architectural features of their parent tissues;

amorphous tumor mass vs. architecturally complex tumor mass
The “Cancer Stem Cell” hypothesis

If tumor tissues are “caricatures” of normal ones (and retain many of their architectural features), then do they also contain a pathological (e.g. mutated) stem cell population that sustains their long-term growth?

In other words, are malignant tissues the product of pathological stem cells?

If this hypothesis is correct, what are its biological implications and how can we test it?
Sources of cell heterogeneity in cancer tissues [#1]

"stochastic" model (random mutation)

differences between various types of cancer cells are caused by differences in the repertoire of genetic mutations (i.e. co-existence of different genetic sub-clones);

the heterogeneity is genetic

"cancer stem cell" model (multi-lineage differentiation)

differences between various types of cancer cells are caused by differential activation of specialized gene-expression programs that "enforce" specific cell identities (i.e. differentiation);

the heterogeneity is epigenetic