CANCER STEM CELL (CSC)

What are stem cells?

** Stem cells are unspecialized immature cells that can renew themselves through cell division for long periods of time.

** They are necessary for our survival. Skin stem cells renew and repair our skin. Cells in our bone marrow generate the different cell types in our blood.

** Under specific conditions, physiological or experimental, stem cells can differentiate along distinct lineages through systemic differentiation steps generating progenitors to the final stage of differentiation: Muscle cells, nerve cells, bone cells… etc

** The blood system has the best described normal stem cells.

Normal stem cells

Rare cells within organs with the ability to self-renew and give rise to all types of cells within the organ to drive organogenesis

Cancer stem cells

Rare cells within tumors with the ability to self-renew and give rise to the phenotypically diverse tumor cell population to drive tumorigenesis

Properties shared by normal stem cells and cancer stem cells

- Assymetric Division:
  - Self renewal –
    - Tissue-specific normal stem cells must self-renew throughout the lifetime of the animal to maintain specific organs
    - Cancer stem cells undergo self-renewal to maintain tumor growth
  - Differentiation into phenotypically diverse mature cell types –
    - Give rise to a heterogeneous population of cells that compose the organ or the tumor but lack the ability for unlimited proliferation (hierarchical arrangement of cells)
- Regulated by similar pathways
  - Pathways that regulate self-renewal in normal stem cells are dys-regulated in cancer stem cells

Types of stem cells

Embryonic stem cells (pluripotent):

** They have the potential to generate all cell types in any organ or tissue in the body

** They come from a blastocyst, a small sphere of cells that results from cell division in a fertilized ovum.

** For research purposes, cells are harvested from the inner cell mass of the blastocyst when it is approximately six days old and consists of around 200 cells

Types of stem cells

Adult stem cells (multipotent stem cells):

- They are postembryonic stem cells required for normal cellular turnover and repair
- The best example is the hematopoietic stem cell but they are found in nearly every major organ
- They are relatively undifferentiated cells that are able to maintain their own numbers for life through continuous division
- Their progeny can differentiate into various cell lineages
- They divide slowly and this reduces the rate at which stem cells acquire DNA mutations

Cancer stem cell theory

- The idea of cancer cells arising from a common origin has been thoroughly explained and published as the Unitarian or Trophoblastic theory of cancer in 1950.
- It states that cancer--differentiated trophoblast proliferation-- is part of the healing process, and the disease only manifests if its control (immune response and nutrition) are impeded.

Cancer stem cell theory

There are two competing visions of tumors.

Old cancer model:

1) All tumor cells can form new tumors and are therefore equally tumorigenic.
2) Unregulated growth is due to serial acquisition of genetic events leading to the expression of genes that promote cell proliferation with concomitant silencing of growth inhibitory genes and blunting of cell death.
3) Cancer is a proliferative disease.

Cancer stem cell theory

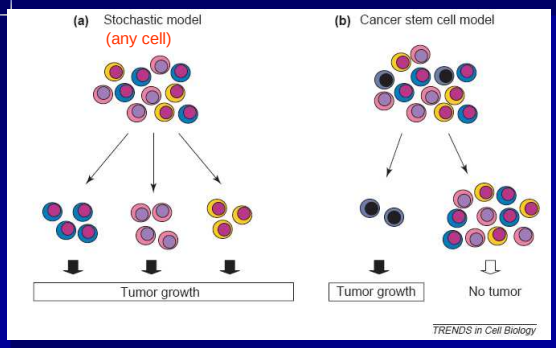
New cancer model:

1) Tumors arise from cells termed cancer stem cells that have properties of normal stem cells, particularly self-renewal and multipotentiality (a minority) of tumor cells.

2) Unregulated cell growth is due to a disruption in the regulatory mechanism in stem cell renewal.

3) Cancer is a stem cell disorder and not a simple mechanism whereby cell proliferation is disrupted.

Cancer Stem Cell-Models



Trends in Cell Biology 2005;15:494-501

Cancer stem cell theory

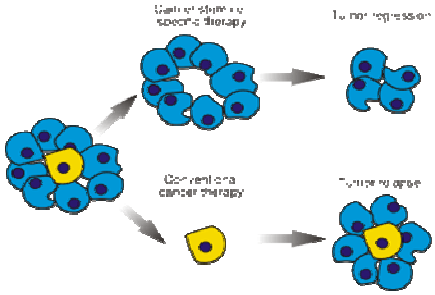
- These CSCs cells persist in tumors as a distinct population that likely causes relapses and metastasis.
- This theory explains why are many cancers so difficult to treat.

Cancer stem cell theory

Why stem cells?

- Only stem cells have the ability to self renew and neoplasia is essentially dysregulated self renewal
- Stem cells are long-lived cells which can acquire the necessary number of sequential mutations to convert a normal cell into a malignant one.

WRONG TARGET. Traditional cancer therapies (top) kill rapidly dividing tumor cells (blue) but may spare stem cells (yellow) that can give rise to a new tumor. In theory, killing cancer stem cells (bottom) should halt a tumor's growth lead to its disappearance.



Self-renewal of stem cells

1) Provides the cell with the ability to undergo infinite cellular divisions with only few of the stem cells dividing at a particular time.

2) The doubling time of most stem cells is relatively long, as compared to their immediate progenitors, which replicate with shorter doubling times (Repair of DNA damage).

3) In some stem cells at division the `mother' cell retain the original chromosome while providing the daughter with the newly formed chromosome (Chromosomal preservation) ⟶ minimizes mutation in the mother cell.

Normal Stem Cells vs. Cancer Stem Cells

- The stem cells in tumors (CSCs) are not the same type of stem cells being explored as potential therapies to treat degenerative diseases.
- But they develop because of mutations that accumulate over years and often decades. The mutations are thought to promote the tumor stem cells' ability to proliferate, eventually leading to cancer

Evidence for the presence of CSC

1) In exp. Animal research, efficient tumor formation to establish a tumor. This was formerly explained by:

** Poor methodology (loos of cell viability during transfer).

** The critical importance of the microenvironment.
** The particular biochemical surroundings of the injected cells.

According to CSC theory

only a small fraction of the injected cells, the CSC, have the potential to generate a tumor. In human AML the frequency of these cells is less than 1 in 10,000.

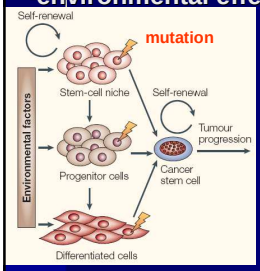
Evidence for cancer stem cells

2) Tumor heterogeneity: Most umors are very heterogeneous and heterogeneity is commonly retained by tumor metastases.

This implies that the cell that produced them had the capacity to generate multiple cell types (have a multidifferentiative potential), a classical hallmark of stem cells.

Origin of Cancer Stem Cell

-environmental effect



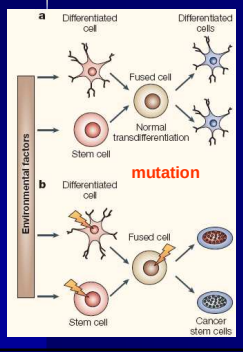
- Environmental factors in cancer initiation
  - Gastric cancer originating from BMDCs -Houghton J.
- Possible origins of cancer stem cells
  - Convergent mechanisms governing terminal differentiation and transformation along the neural stem cell to astrocyte axis -Bachoo, R. M

Nature Review Cancer 2005;5:899-904

Cancer Cell 1,269–277 (2002)
Science 306, 1568–1571 (2004)
Cancer Cell 1,269–277 (2002)

Origin of Cancer Stem Cell

-cell-cell fusion



- Mammalian fusogenic factors
  - CD44, CD47 (macrophage)
  - macrophage fusion receptor MFR/PTPNS1 (macrophage)
  - IL-4 (myoblast)
  - CXCR4/SDF1 (osteoblast)

Stem Cells 23, 879–894 (2005)
Science 308, 369–373 (2005)
Nature Review Cancer 2005;5:899-904

Cancer Stem Cell

-Breast Cancer

- Al-Hajj first provided the evidence of breast cancer stem cells.
- They are $CD44^{+}/CD24^{-/low}/$ lineage^{-}
- These population has a 10–50-fold increase in ability to form tumors in xenografts compared with the bulk of breast tumor cells.

Nature Reviews Cancer 2003;3:832-844

CSC- PATHWAYS

- **A normal stem cell may be transformed into a cancer stem cell through disregulation of the proliferation and differentiation pathways controlling it.**
- **The first findings in this area were made using haematopoietic stem cells (HSCs) and their transformed counterparts in leukemia.**
- **However, these pathways appear to be shared by stem cells of all organs.**

Stem Cell Pathways

- WNT: APC/axin/GSK3-β/Dsh; β-catenin; LEF/LCF
- Hedgehog: sonic(Shh), Desert(Dhh), Indian(Ihh); patched, smoothened, Fused (Fu), SuFu, Gli
- Bmi-1: INK4a, ARF, MDM2, Cyclin D, CDK4
- Notch: SHARP, HDAC, SKIP, CBF-1
- PTEN: PI3K, AKT, mTOR

CSC- PATHWAYS

Bmi-1

This group of transcriptional repressor was discovered as a common oncogene activated in lymphoma and later shown to specifically regulate HSCs and neural stem cells. This pathway appears to be active in CSC of pediatric brain tumors and CRC

CSC- PATHWAYS

Bmi-1

**** In normal cells BMI-1 inhibits the transcription of CDNK2A which encodes two cyclin dependent kinase inhibitors, INK4A and ARF.**

**** Cell cycle progression is promoted in the absence of INK4A and pro-apoptotic genes are inhibited in the absence of ARF. Hence, BMI-1 promotes proliferation and inhibits apoptosis.**

****In the case of cancer, BMI-1 is circumvented and CDNK2A is no longer inhibited, thereby resulting in unregulated proliferation and self-renewal.**

CSC- PATHWAYS

Notch

- The Notch pathway has been known to developmental biologists for decades.
- Its role in control of stem cell proliferation has now been demonstrated for several cell types including haematopoietic, neural and mammary stem cells.
- Components of the Notch pathway have been proposed to act as oncogenes in mammary and other tumors.

CSC- PATHWAYS

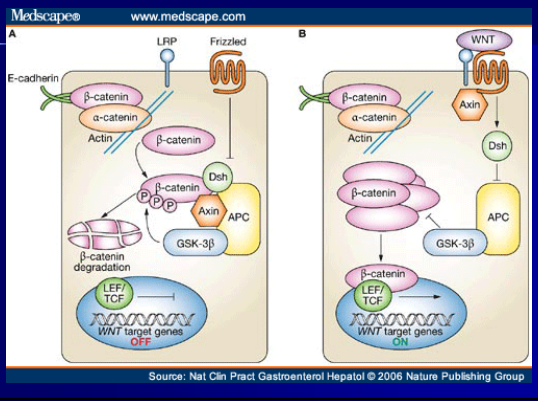
Wnt/β-catenine

- This pathway is strongly implicated as stem cell regulators.
- It is commonly hyperactivated in tumors and is required to sustain tumor growth.
- Their role has been illustrated especially in gliomas (the Gli transcription factors), CRC and mammary tumors.

The Wnt-B-catenine pathway

- In the normal Wnt pathway the levels of the transcription factor ß-catenin mediates self-renewal.
- ß-catenin could be turned off by a destruction complex as a feedback mechanism.
- However, in cancer the control process is circumvented and ß-catenin levels constantly thrive, hence causing continual proliferation and self- renewal.

The Wnt-B-catenine pathway



Source: Nat Clin Pract Gastroenterol Hepatol © 2006 Nature Publishing Group

Summary of Pathways

Pathway	Stem cell	Cancer
WNT	Haematopoietic stem cells[31,32] Intestinal epithelial stem cells[47] Keratinocyte stem cells[30,85] Cerebellar granule-cell progenitors[86*] CNS stem cells[43]	Lymphoblastic leukaemia[60,61] Colorectal cancer[49] Pilomatricoma[45,46] Medulloblastoma[44] Gliomas?
SHH	Hair-follicle progenitors[87,88*] Cerebellar granule-cell progenitors[33*] CNS stem cells[35]	Basal-cell carcinoma[89–91] Medulloblastoma[34,92–94] Gliomas[95]
BMI1	Haematopoietic stem cells[13]	B-cell lymphomas[71] AML[14]
Notch	Haematopoietic stem cells[38] Mammary epithelial stem cells[96]	Lymphoblastic leukaemia[37] Breast cancer[97]
PTEN	Neural stem cells[41]	Gliomas[98]

Nat Rev Cancer 2003;3:895-902

CONCLUSION

- Stem cells are immature cells that can replicate, or renew themselves, and are able to differentiate into all cells types.
- mutations and rearrangements of the genomes of stem cells give rise to CSCs. These changes could underlie the development of cancers in many tissues.
- Stem cells are more difficult to kill. Because they are so important throughout a person's lifetime, they have developed mechanisms that protect themselves. Therefore, tumor stem cells are able to resist toxic substances, such as cancer drugs.

CONCLUSION

- The next step is to figure out what makes the CSC different from the other cells in the tumor.
- DNA microarrays could be used to identify genes that are active in the cancer-causing cells (CSCs) compared to other tumor cells. Some of these genes might control the cell's ability to replicate and metastasize.
- Identifying these genes may suggest new drug targets that could selectively kill the cancer cells