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Unit-III

TOPIC: HISTORY OF THE CANCER STEM CELL

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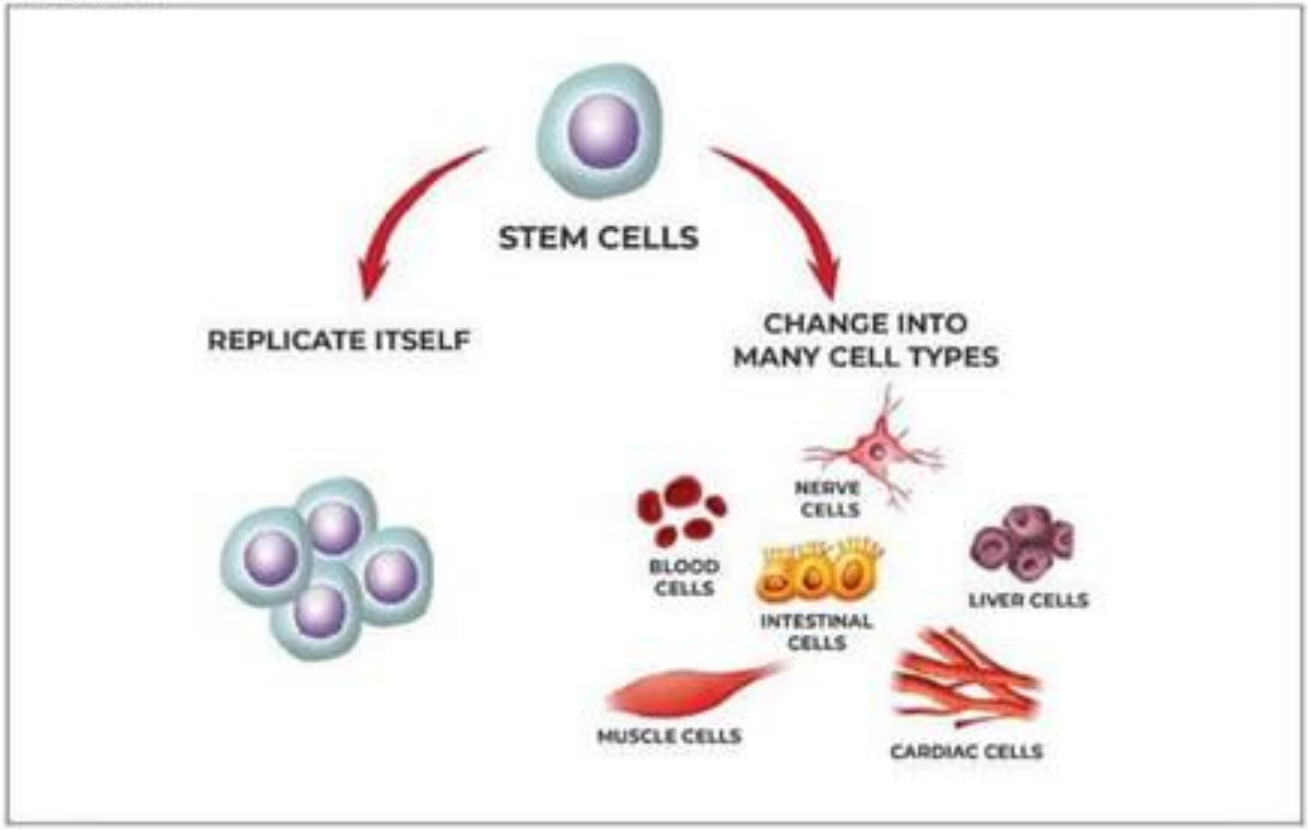
HISTORY OF THE CANCER STEM CELL

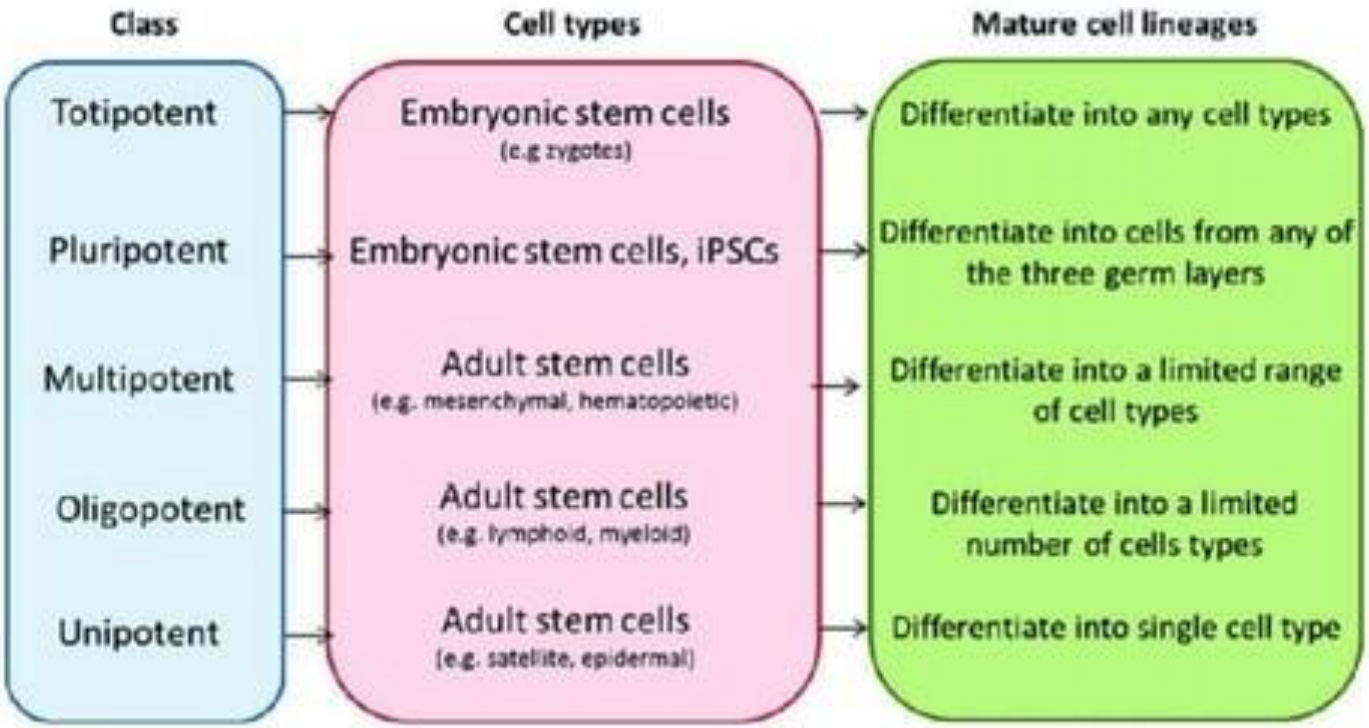
Overview

- Cancer Stem cells (CSCs) - Introduction
- Models of Carcinogenesis
- Origin of CSCs
- Examples of CSCs
- Isolation & Identification of CSCs
- Regulation of CSCs by tumor micro-environment
- EMT/MET and CSCs
- Signal transduction pathways involved in CSCs and their therapeutic targeting
- Future Perspective

STEM CELLS

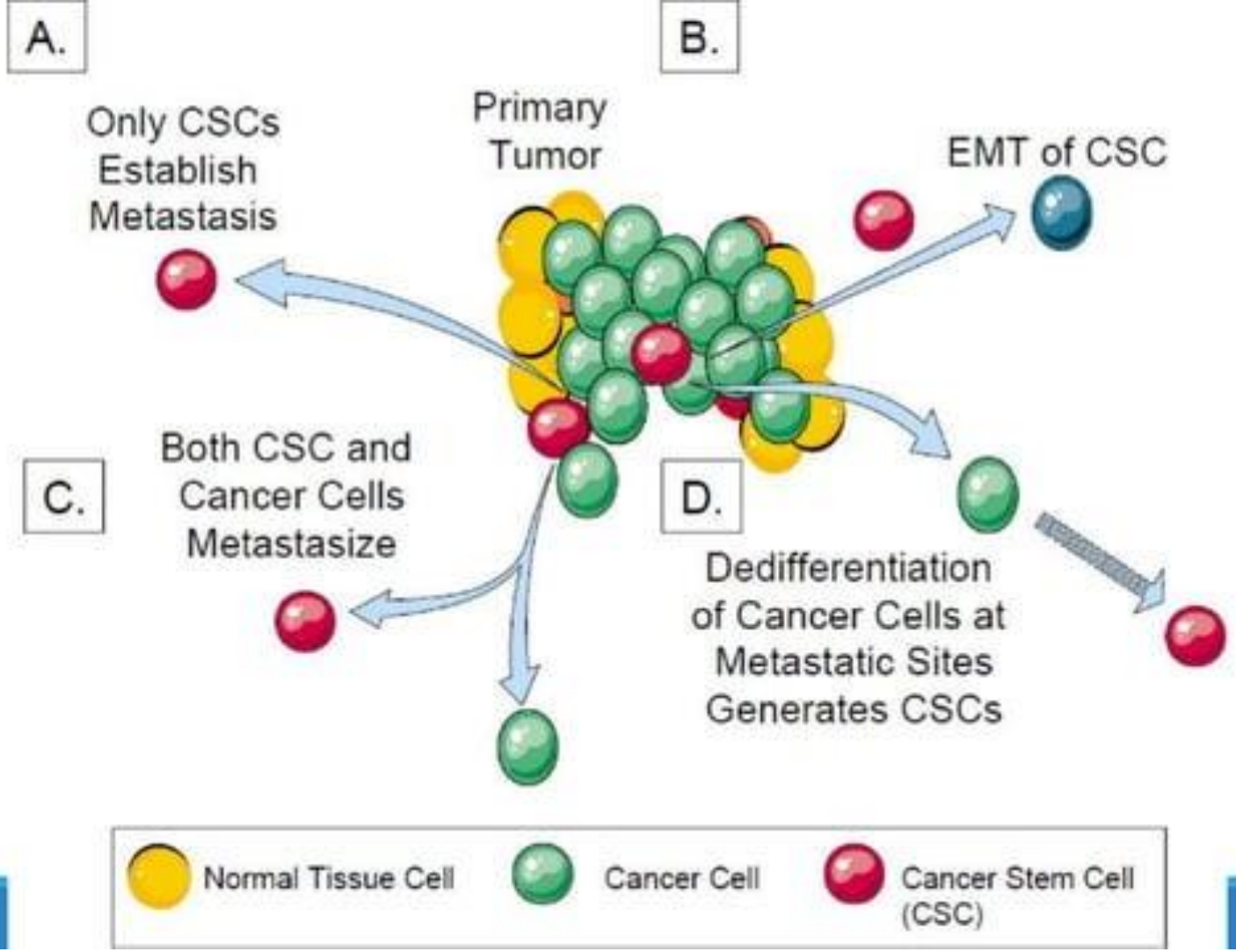

STEM CELLS
REPLICATE ITSELF
CHANGE INTO
MANY CELL TYPES
NERVE
CELLS
BLOOD
CELLS
INTESTINAL
CELLS
LIVER CELLS
MUSCLE CELLS
CARDIAC CELLS

STEM CELLS CLASSIFICATION



Introduction

- Sub-population of tumor cells with stem cell properties
  - **Self renewal**
  - **Lineage differentiation**
- Isolated from numerous human malignancies using **cell surface markers** & **enzymatic activity of cytoplasmic proteins**
- Mediate **metastasis**
- Contribute to **treatment resistance** and **relapse**
- Recent studies – CSCs are regulated by component of **tumor microenvironment** through complex network of cytokines and growth factors
- Future prospects – attractive targets for development of novel therapeutics

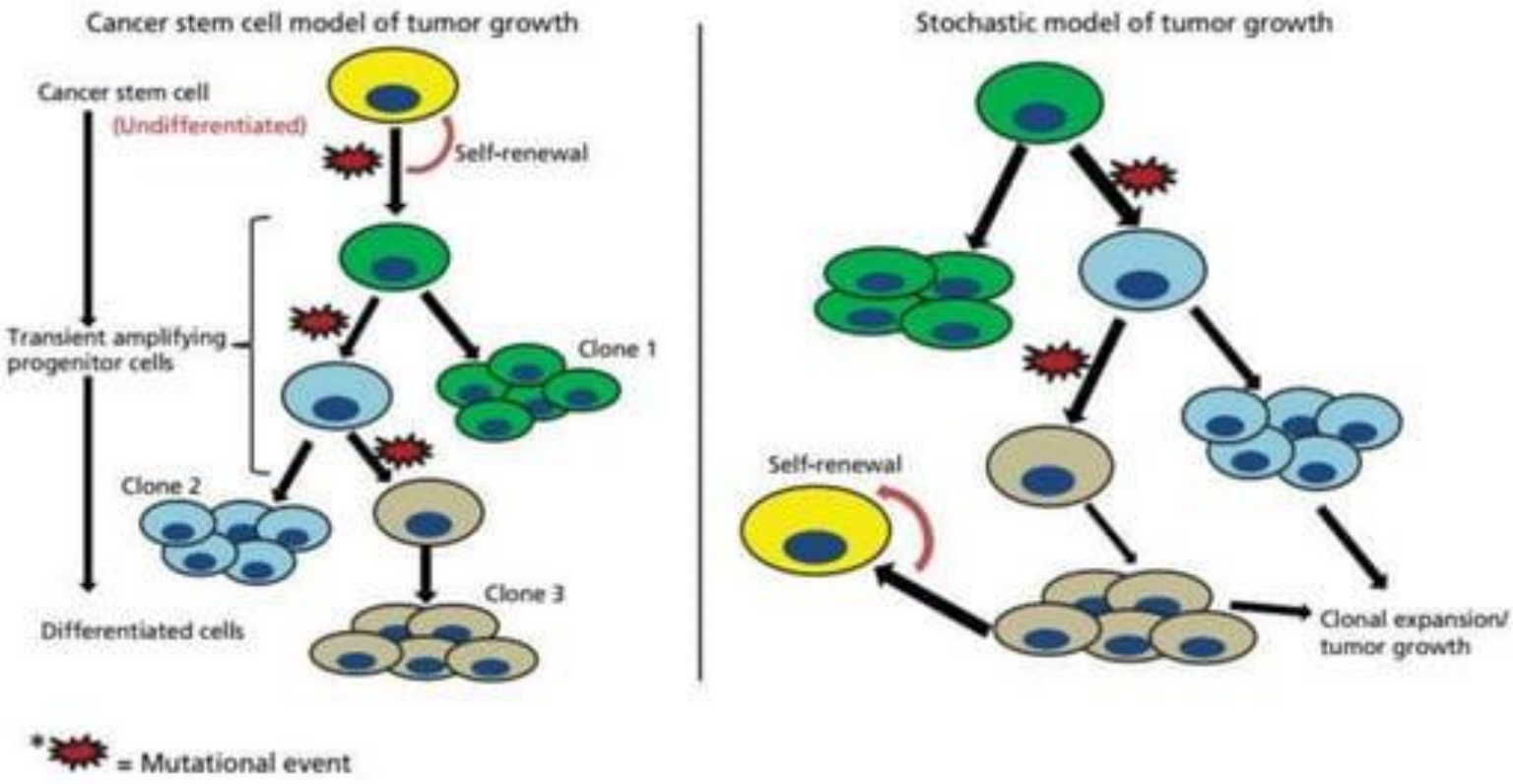

A.
B.
Only CSCs Establish Metastasis
Primary Tumor
EMT of CSC
C.
Both CSC and Cancer Cells Metastasize
D.
Dedifferentiation of Cancer Cells at Metastatic Sites Generates CSCs
Normal Tissue Cell
Cancer Cell
Cancer Stem Cell (CSC)

Models of Carcinogenesis

Models of carcinogenesis

- classical "**STOCHASTIC**" model:
  - Cancer may arise from **any cell**
  - Carcinogenesis evolves through **random** process of mutation f/b clonal selection
  - Disease development is driven by **Darwinian selection** of fittest clones of cancer cells

- **CSC model**:
  - Process originates in cells that acquire **stem cell** property of self-renewal
  - Tumors display a degree of **hierarchical** organization
  - Apex of this hierarchy are CSCs
  - Vogelstein et al – incidence of cancer is directly proportional to number of tissue stem cell divisions


Cancer stem cell model of tumor growth
Cancer stem cell
(Undifferentiated)
Self-renewal
Transient amplifying
progenitor cells
Clone 1
Clone 2
Clone 3
Differentiated cells
Stochastic model of tumor growth
Self-renewal
Clonal expansion/
tumor growth
= Mutational event

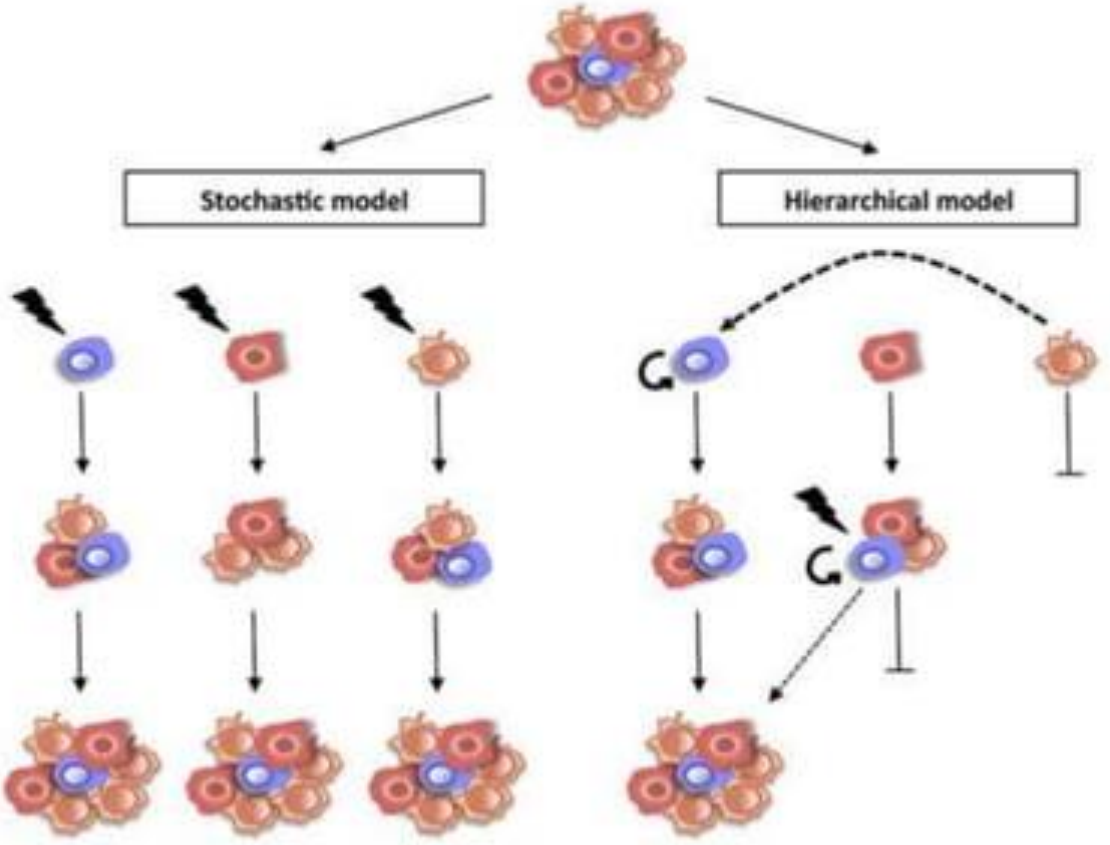


FIGURE 2.1 Different models of tumorigenesis.

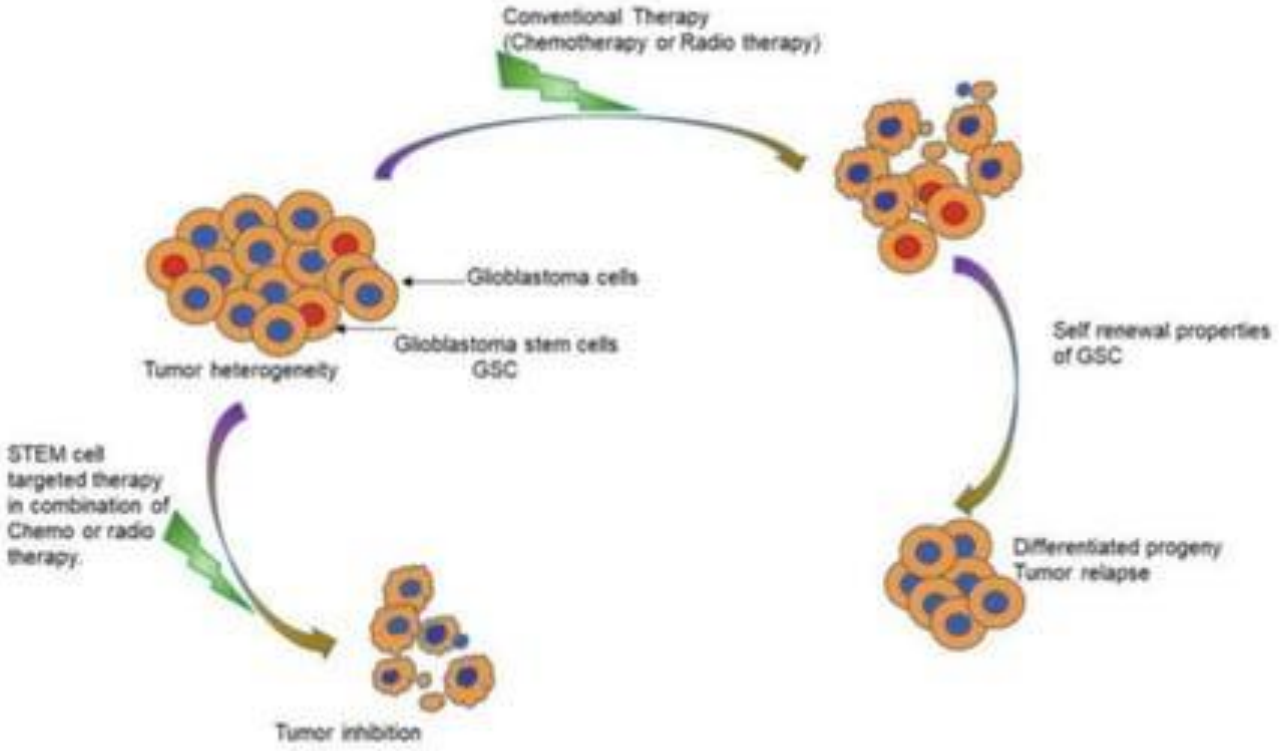
Origin of CSCs

CSCs – unifying concept in multiple cancers

- First identified in Human Leukemia in 1997 by John Dick et al
- A small fraction of cell were capable of regenerating leukemia in NOD/SCID mice
- Specific phenotype **CD34+/CD38-** (resembling normal hematopoietic stem cell)
- Subsequently, CSC were identified in breast, brain, prostate, colon, pancreas, liver, lung, melanoma and head & neck malignancies

Origin of CSCs

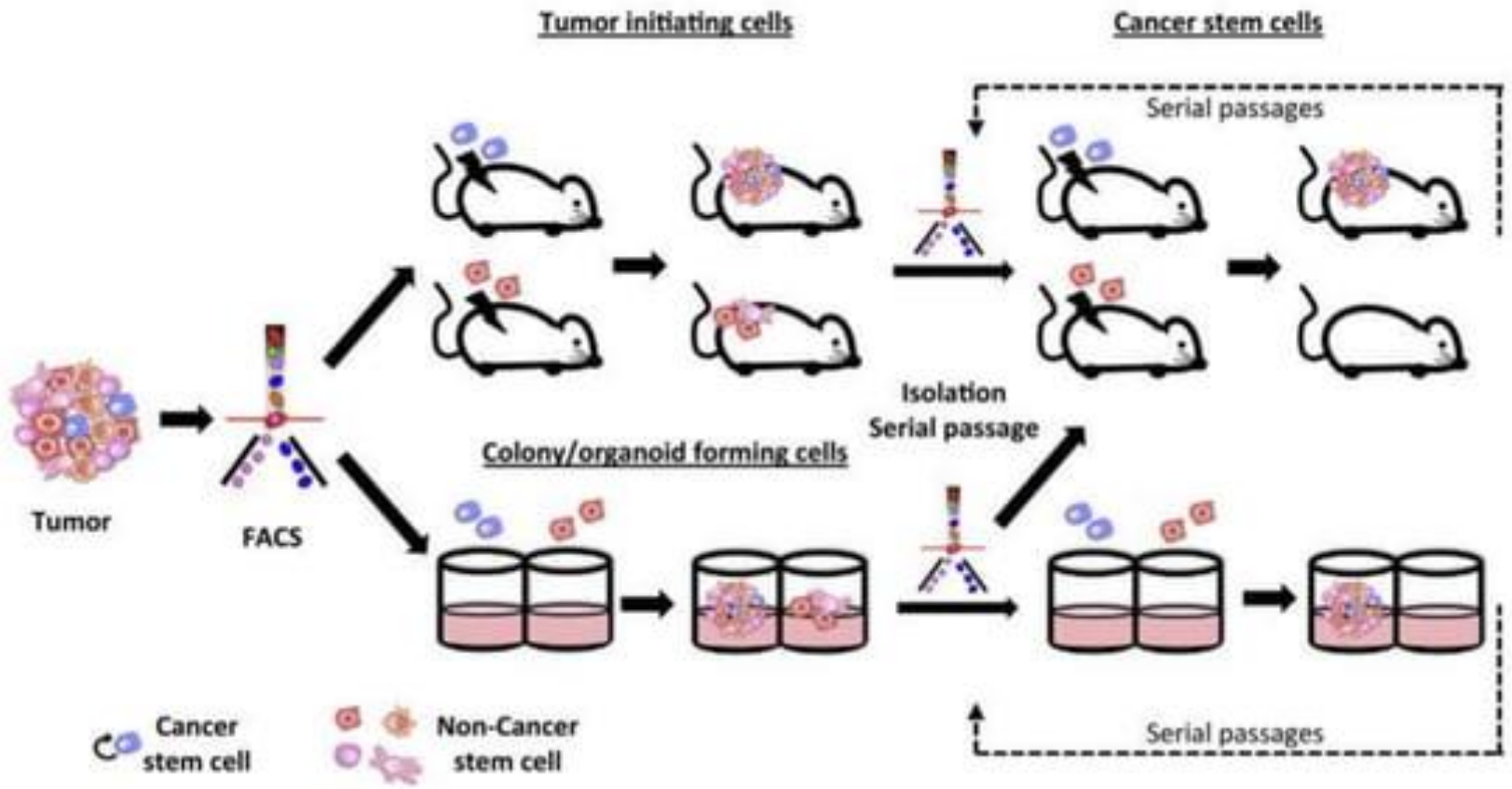
- Expression of Wnt target Lgr5 – intestinal stem cells
  - Schepers et al. demonstrated that Lgr5+ cells : ability of forming adenoma in mice
- Driessens et al – similar genetic lineage tracing studies to mark skin papilloma cells which self renewed in mouse models
- Patients with glioblastoma – median survival of 1 yr
  - Mainly because of therapeutic resistance and recurrence after resection
  - Chen and colleagues : genetically engineered mouse model – repopulating cells were nestin + CSCs located in subventricular zone
- These studies – strong support to CSC model of tumorigenesis


Conventional Therapy
(Chemotherapy or Radio therapy)
Glioblastoma cells
Glioblastoma stem cells
GSC
Tumor heterogeneity
Self renewal properties
of GSC
Differentiated progeny
Tumor relapse
STEM cell
targeted therapy
in combination of
Chemo or radio
therapy.
Tumor inhibition

Examples of CSCs

- Uchida et al – **CD113+/CD34-/CD45-** : expression of cell surface Ag – PROMININ -1
  - Cells were able to form Brain tumors in NOD-SCID mice and neurospheres in vitro cultures
- **EpCam+/CD44+/CD24-/Lin-** : breast cancer in NOD-SCID mice
- **CD44+/α2β1^{hi} /CD133+** : prostate CSCs
- **Sca1+/CD34+/CD45-/Pecam-** : pulmonary CSCs
- Ricci and O'Brien et al – isolated **CD133+** human colon CA cells and injected S/C in NOD-SCID mice – generated tumor in them, CD133- cells failed to do so
- Pancreatic carcinoma – **CD44+/CD24+/ESA+** phenotype 100 fold more tumorigenic
- Human Liver CSCs – **CD133+** demonstrated self renewal potential, colony forming ability and tumor formation in mouse xenografts

Isolation and Identification of CSCs


Tumor initiating cells
Cancer stem cells
Serial passages
Tumor
FACS
Isolation
Serial passage
Colony/organoid forming cells
Cancer
stem cell
Non-Cancer
stem cell
Serial passages

Isolation & Identification of CSCs

CSC marker expression:

- First solid tumor CSC – Breast carcinoma
- Phenotype: CD44+/CD24-
- CD 113 – brain and lung cancer
- ALDH – another CSC marker
  - Involved in oxidation of retinol to retinoic acid
  - Readily determined by commercially available Aldefluor assay
  - Useful marker in CA breast, colon, ovary, head&neck, and recently melanoma

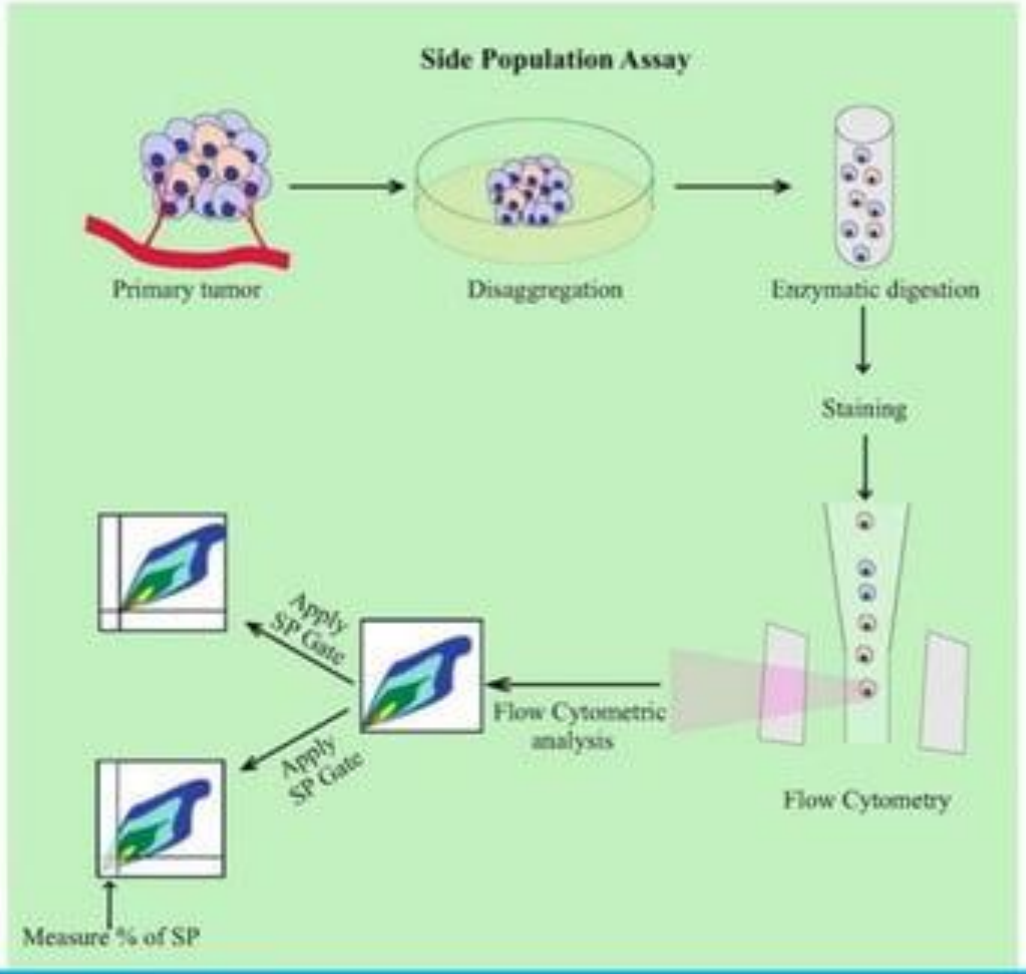
Table 1.1 Verified Cancer Stem Cell Populations and Their Corresponding Markers in Various Cancers

Cancer Class	Markers (eg)
Leukemia/Lymphoma	CD34$^+$, CD47$^+$, CD96$^+$, CD25$^+$, CCL-1$^+$ CD38$^-$
Head and neck squamous cell carcinoma	CD44$^+$, BMI 1$^+$, CD24$^+$, CD133$^+$
Glioblastoma multiforme	CD133$^+$, CD49f$^+$, JAM-A, HER2$^+$, EGFRvIII$^+$
Lung	CD44$^+$ CD133$^+$
Breast	ESA$^+$CD44$^+$/CD24$^{-/low}$ Lin$^-$, ALDH1$^+$, CD133$^+$, CD61$^+$
Ovarian	CD44$^+$, CD117$^+$
Pancreas	CD44$^+$, CD24, ESA$^+$
Gastric	CD44$^+$, CD133$^+$, ABCB1$^+$, ABCG2$^+$
Colorectal	CD44$^+$, CD133$^+$, CD166$^+$, CD24$^+$
Prostate	CD44$^+$, CD133$^+$, ALDH$^+$
Bladder	CD44$^+$, CD90$^+$, CD49f$^+$
Melanoma	CD20$^+$, CD271$^+$, ABCB5$^+$

Isolation & Identification of CSCs

Dye exclusion assays:

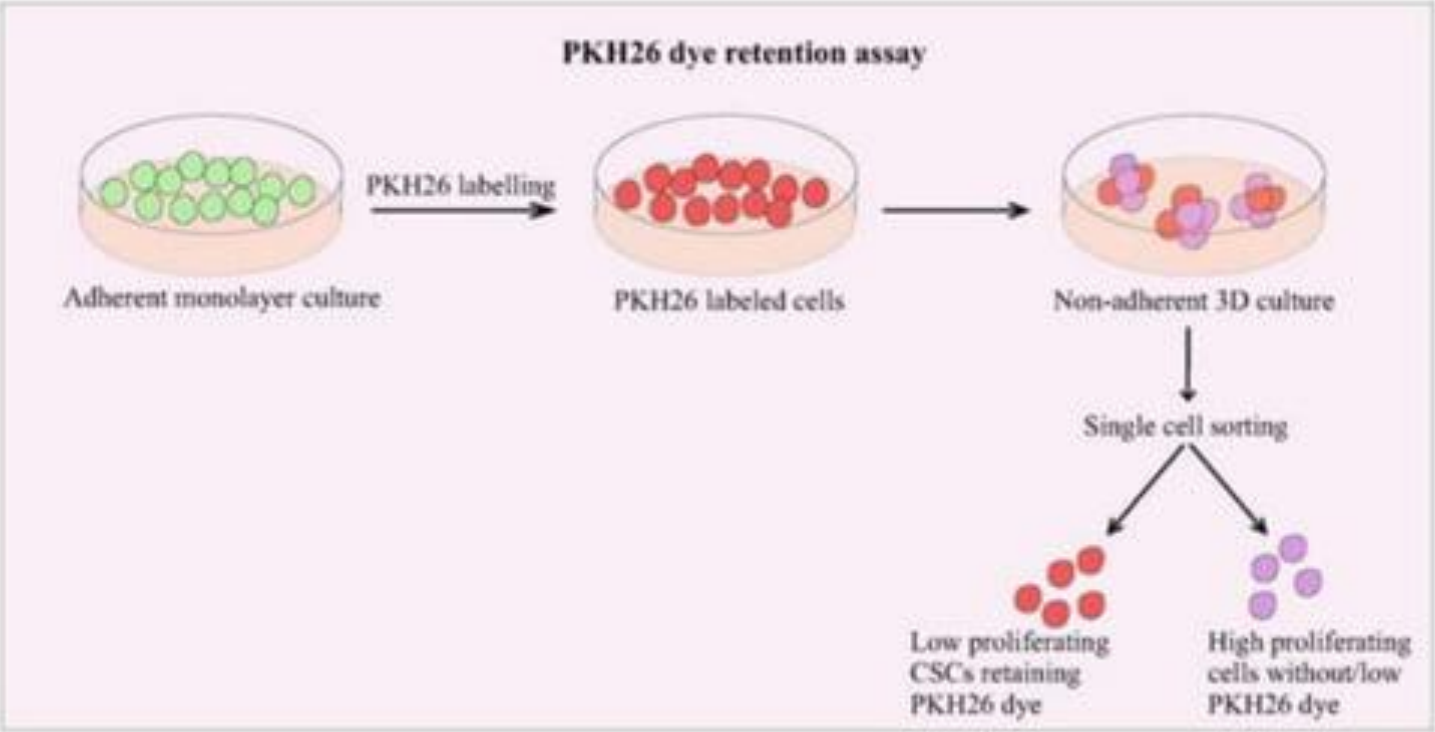
- Ability of stem cells to efflux lipophilic dyes, such as Rhodamine
- High expression - ATP-binding cassette transporter proteins ABCG2/BCRP1
- Flow cytometry analysis, cells that do not retain dye are observed as a side population
- This side population cells are enriched with tumor stem cells – capable of generating heterogenous tumor cell populations
- Cellular toxicity of dye – limited role in functional tests


Side Population Assay
Primary tumor
Disaggregation
Enzymatic digestion
Staining
Flow Cytometry
Flow Cytometric analysis
Apply SP Gate
Apply SP Gate
Measure % of SP

Isolation & Identification of CSCs

Label retention:

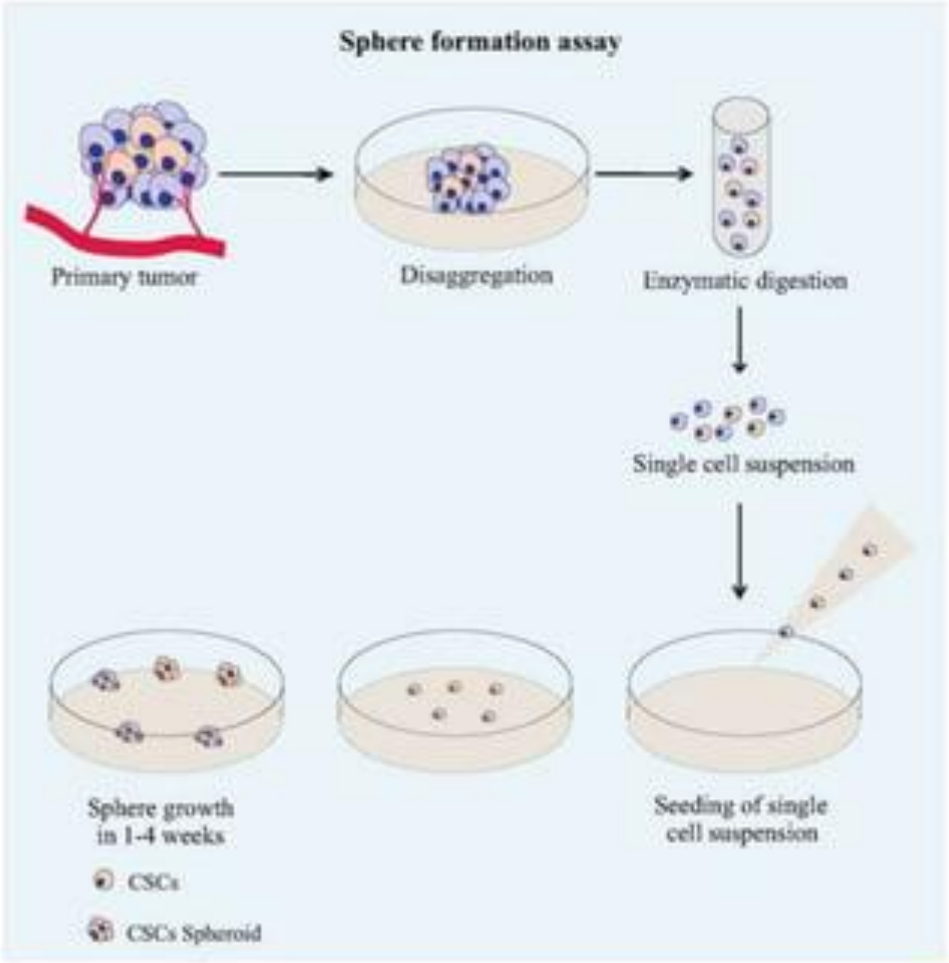
- Another dye based in vitro test
- Cell membrane assay using **fluorescent PKH dye**
- Dye consists of a fluorophore that binds to the cell membrane **lipid bilayer**
- On cell division – dye gets equally distributed into daughter cells
- Stem cells undergo asymmetric cell renewal process generating stem cells and daughter cell
- Generated stem cells are quiescent and thus **retains the dye longer**
- Recently – CSCs are reported to demonstrate auto-fluorescence in presence of riboflavin
- These cells had increased chemo-resistance, highly metastatic, long term in vivo tumorigenicity


PKH26 dye retention assay
PKH26 labelling
Adherent monolayer culture
PKH26 labeled cells
Non-adherent 3D culture
Single cell sorting
Low proliferating
CSCs retaining
PKH26 dye
High proliferating
cells without/low
PKH26 dye

Isolation & Identification of CSCs

Sphere formation assays:

- Another in vitro assay
- Based on a property shared by both normal and malignant stem cells:
  "survival when cultured in suspension and generation of spheroids at clonal density"
- These spheres can be serially passaged and display stem cell properties with each passage
- Possible to combine different in vitro assays like:
  - addition of PKH dye during sphere formation

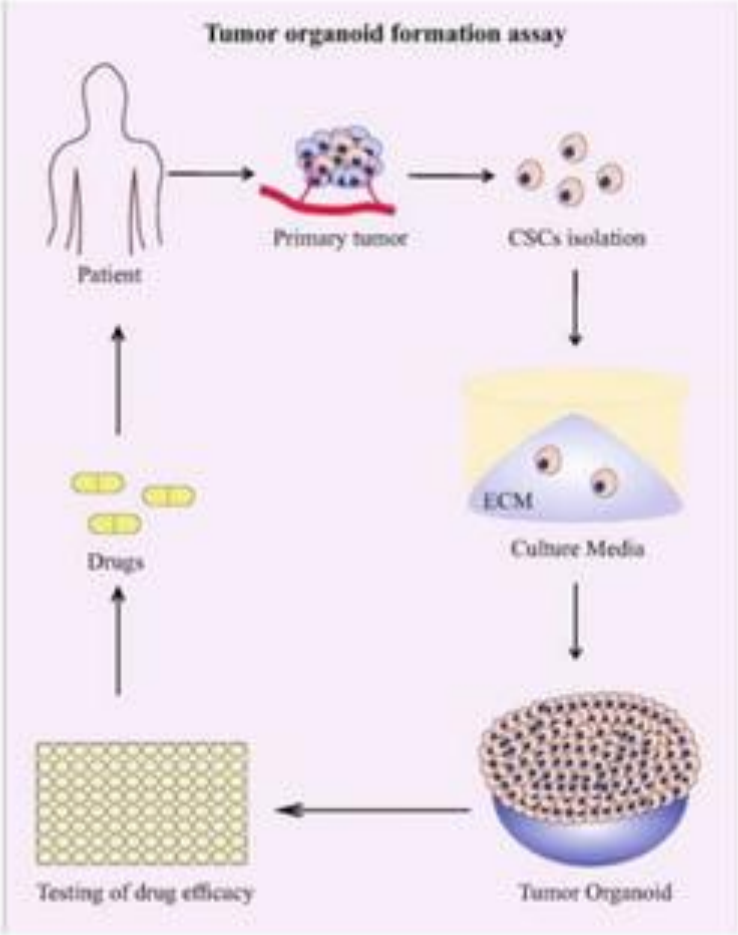

Sphere formation assay
Primary tumor
Disaggregation
Enzymatic digestion
Single cell suspension
Seeding of single cell suspension
Sphere growth in 1-4 weeks
CSCs
CSCs Spheroid

Isolation & Identification of CSCs

In vivo serial dilution CSC assays:

- Limitation of in vitro assays:
  - expression of CSC markers can be variable
  - influenced by tumor micro-environment
  - sphere formation assay not correlate with tumor forming capacity

- **Gold standard:** initiation of tumor when injected into SCID mice
- immunosuppressed mouse models also have limitations
- immune system play an important role in CSC regulation


Tumor organoid formation assay
Patient
Primary tumor
CSCs isolation
ECM
Culture Media
Tumor Organoid
Testing of drug efficacy
Drugs

Regulation of CSCs population

Regulation of CSCs by tumor micro-environment

- Tumors are "**ORGAN-like**" structures – different cell types – interact to drive and promote growth and metastases
- cells of tumor micro-environment include:
  - MSCs (mesenchymal stem cells)
  - Tissue fibroblasts
  - Endothelial cells
  - Immuno-modulatory cells – T cells and Macrophages
- Interact with tumor CSCs via growth factors and cytokines
- Inflammatory cytokines – IL-1, IL-6, IL-8 regulate CSCs during carcinogenesis

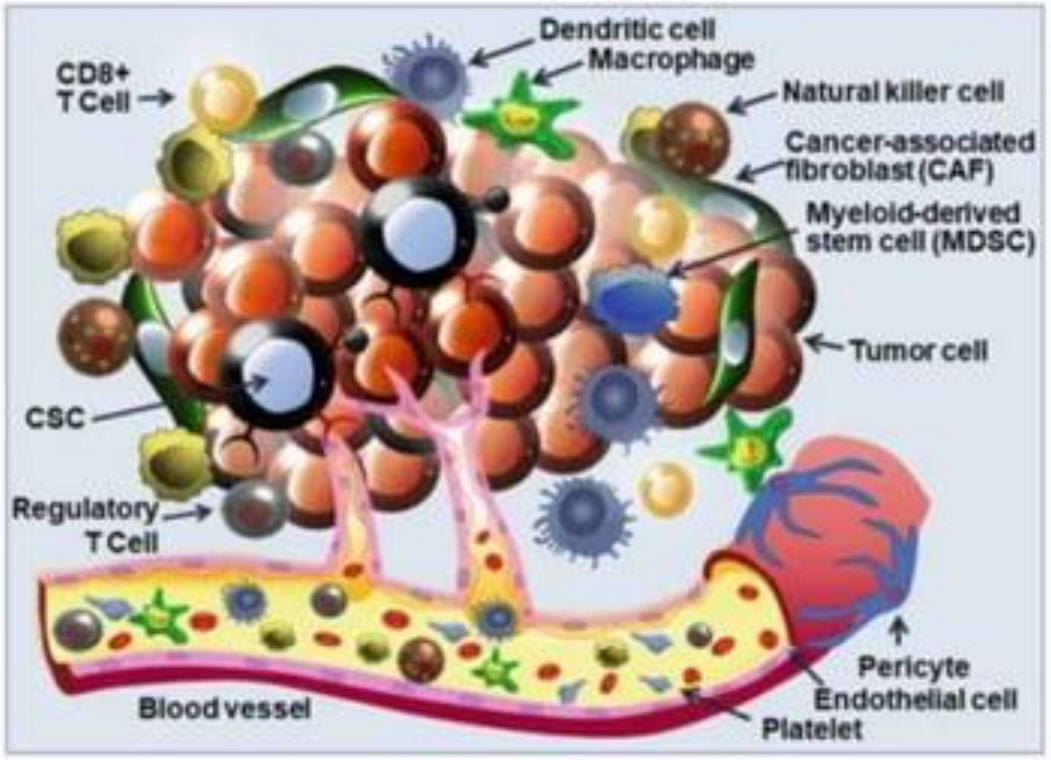


Fig. 16.5 Cancer stem cells and the tumor microenvironment (TME). TME-associated important cell types and their spatial localizations are shown

Regulation of CSCs by tumor micro-environment

- Epigenetic and genetic changes during carcinogenesis modulate these regulatory signals
- commonly dysregulated signals include:
  - NOTCH
  - HH
  - Wnt
  - PI-3k
  - NFκB
  - Jak/STAT pathways

Regulation of CSCs by tumor micro-environment

- Many of these pathways resemble those in normal wound healing – including cytokine loops regulated by transcription factor NFκB
- activation of fibroblasts and myofibroblasts – Gabbiani and Majno – similarities in wound healing and tumorigenesis
- Malignant tumors are "wounds that never heal"

Regulation of CSCs - fibroblasts

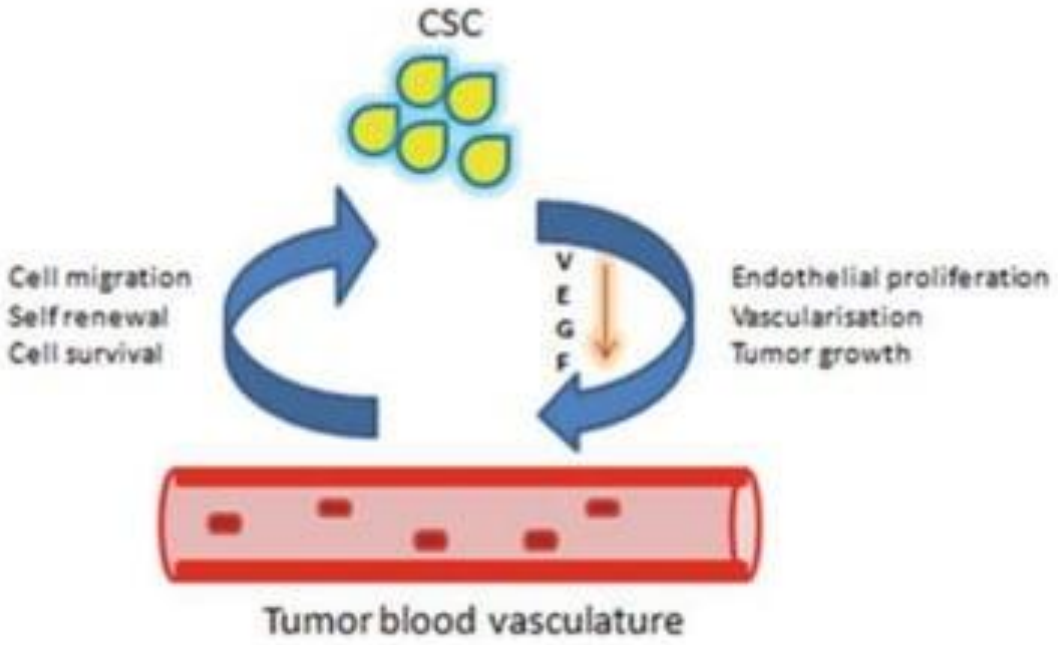
- Growth factors : TGF-β involved in epigenetic changes – activation of fibroblasts
- Cytokines: SDF-1 (CXCL-12) produced by breast CA associated fibroblasts – promote tumor cell proliferation
- High SDF-1 expression in serum : indicator of poor survival
- Hepatocyte growth factor (HGF) – produced by mammary stromal cells – induces stem cell activation
- HGF co-stimulates Wnt signal during colon carcinogenesis
- CSCs use oxidative stress – drive stromal fibroblasts to activate various signaling pathways
- Estrogen regulates breast CSC population – paracrine mechanism involving FGF9

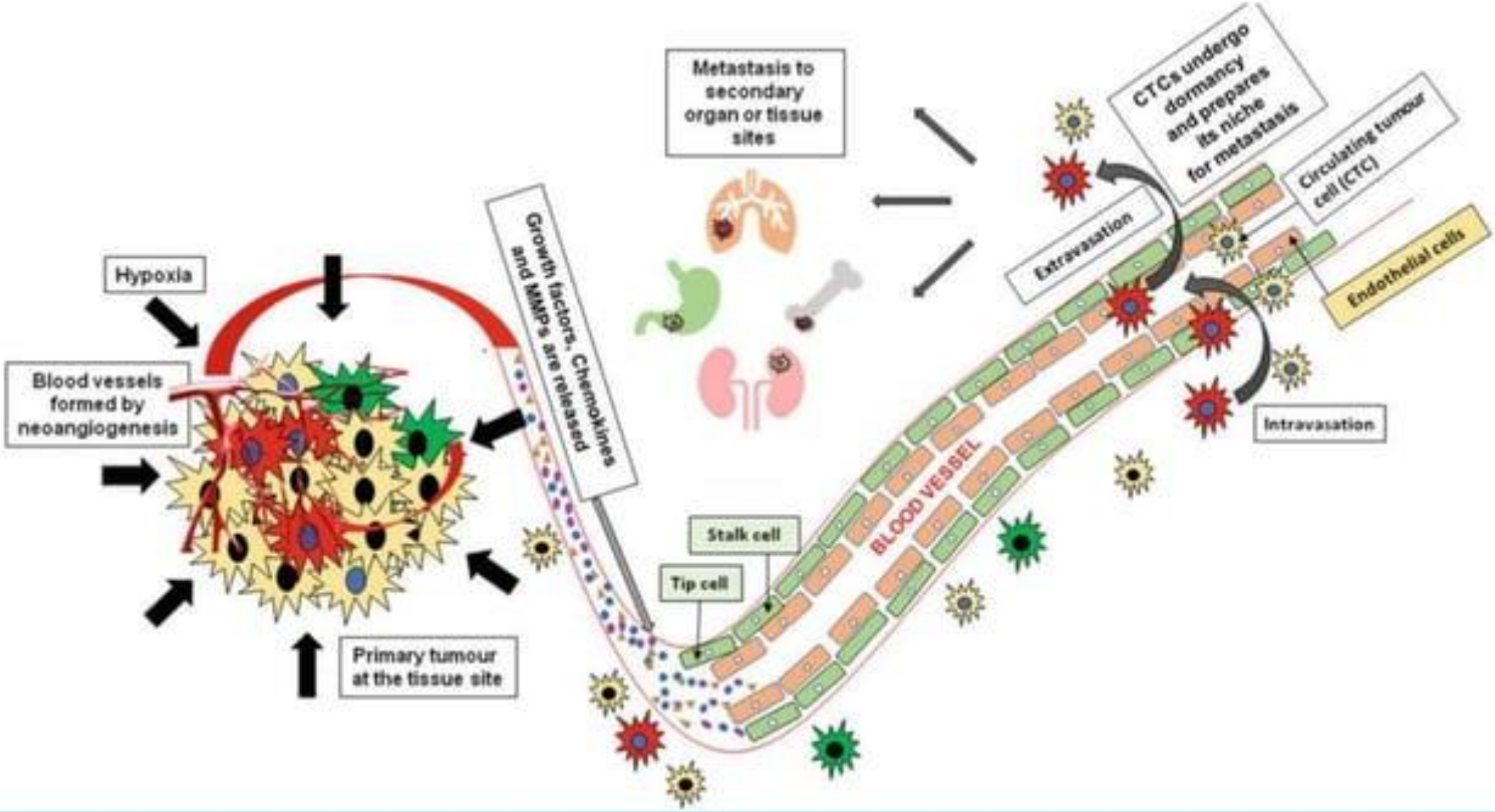
Regulation of CSCs - T cells and macrophage

- Exert both stimulatory and inhibitory effects on CSCs
- Recent studies in leukemia & lymphoma – tumor cells express Ag CD47+
- This serves as "don't eat me" signal to tumor macrophages
- Also they express "Calreticulin": serve as "eat me" signals
- Administration of CD47 blocking Ab – induced tumor macrophage induced phagocytosis
- CD47 widely expressed in several solid tumor CSCs.
- Targeting this molecule – suppresses tumor growth and metastases in mouse models

Regulation of CSCs - endothelial cells

- Directly interact with tumor cells as well as role in blood vessel formation
- Judah Folkmann proposed 40 yrs back – angiogenesis – tumor growth and mets
- Bone marrow derived endothelial progenitor cells – attracted to tumors – differentiate into mature endothelial cells and capillaries
- Carry oxygen and nutrients to growing tumors
- CSCs – vasculogenic mimicry – stem cells transdifferentiate into endothelial like cells
- VEGF – primary mediator of this process
- Targets: Bevacizumab, multikinase VEGF i: Sorafenib and Sunitinib – FDA approved


CSC
Cell migration
Self renewal
Cell survival
VEGF
Endothelial proliferation
Vascularisation
Tumor growth
Tumor blood vasculature


Metastasis to secondary organ or tissue sites
CTCs undergo dormancy and prepares its niche for metastasis
Circulating tumour cell (CTC)
Extravasation
Endothelial cells
Hypoxia
Blood vessels formed by neoangiogenesis
Growth factors, Chemokines and MMPs are released
Stalk cell
Tip cell
BLOOD VESSEL
Intravasation
Primary tumour at the tissue site

Role of cytokines in CSCs renewal

- Link between inflammation and cancer – Virchow – 1864
- He observed inflammatory cells infiltrated tumor stroma
- also examples of Ulcerative colitis, Hepatitis C and chronic pancreatitis in respective cancers
- chronic inflammation mediated by IL-1β, IL-6, and IL-8
- mesenchymal cells, macrophages and immune cells – secrete both IL6 and IL8
- elevated levels in advanced breast cancer – poor outcome
- IL-6:
  - Direct regulator of BCSCs self renewal – mediated by IL-6 receptor/GP-130 complex – via activation of STAT3
  - Sethi et al. – IL6 mediated Jagged1/NOTCH signaling in breast CA bone metastases

Role of cytokines in CSCs renewal

- IL-8:
  - IL-8 receptor CXCR1 – highly expressed in BCSCs
  - CXCR1 inhibitor : REPARAXIN – reduced CSC in breast CA xenografts
- NF-KB:
  - Induces transcription of IL-6 and IL-8
  - Positive feedback loop maintains chronic inflammatory state in tumor cells
  - Involves microRNA let7 and Lin 28 – factors involved in embryonic stem cell self renewal
  - This feedback loop is maintained by IL-6 through activation of STAT-3 – which activates NF-KB
  - Her-2 neu mouse model of mammary carcinogenesis – suppression of NF-KB reduced stem cell population

EMT/MET and CSCs

EMT/MET and CSCs

- **EMT** – physiological process during embryogenesis where epithelial cells acquire mesenchymal properties
- Characterised by **loss of CAMs** (E- Cadherin) and acquisition of **invasive properties**
- In cancer – EMT associated with process of metastasis where primary tumor cells acquire mesenchymal phenotype and invade cells
- EMT is regulated by microenvironmental factors –
  - Tissue hypoxia
  - TGF- β
  - Transcription factors like: TWIST1, TWIST2, SNAI1, SNAI2, ZEB1, and ZEB2
  - Other inflammatory cytokines
- Several studies suggest EMT generates CSC like cells

EMT/MET and CSCs

- Overexpression of SNAI1 or TWIST1 - induce EMT in MCF10A and immortalized human mammary epithelial cells
- Increased expression of stem cell marker CD44 and a decrease in CD24 expression (CD44+/CD24-) suggests induction of CSC-like phenotype
- TWIST1 - increased ability of breast cancer cells to form mammospheres and secondary tumors
- basal subtype breast CA, particularly claudin-low
  - possess an EMT-like gene expression signature
  - high proportion of CD44+/24− cells
  - highly aggressive behavior with greater propensity to develop metastasis

Role of EMT in breast cancer

- CSC possesses alternative phenotypes
  - one involved in tumor invasion and metastasis
  - another maintains the bulk of the tumor
- recent study comparing ALDH+ and CD44+/24− BCSCs isolated from different subtypes of breast cancer
  - ALDH+ CSCs - interior of the tumors - self-renewed and proliferated at a higher rate, E-cadherin +
  - CD44+/24− CSCs - mesenchymal, located on the tumor margins, and were more quiescent, Vimentin +

    More potential to invade blood vessels when triggered by stromal factors
- The plasticity of BCSCs from a quiescent mesenchymal state to a proliferative epithelial-like state is critical for formation of tumor metastases

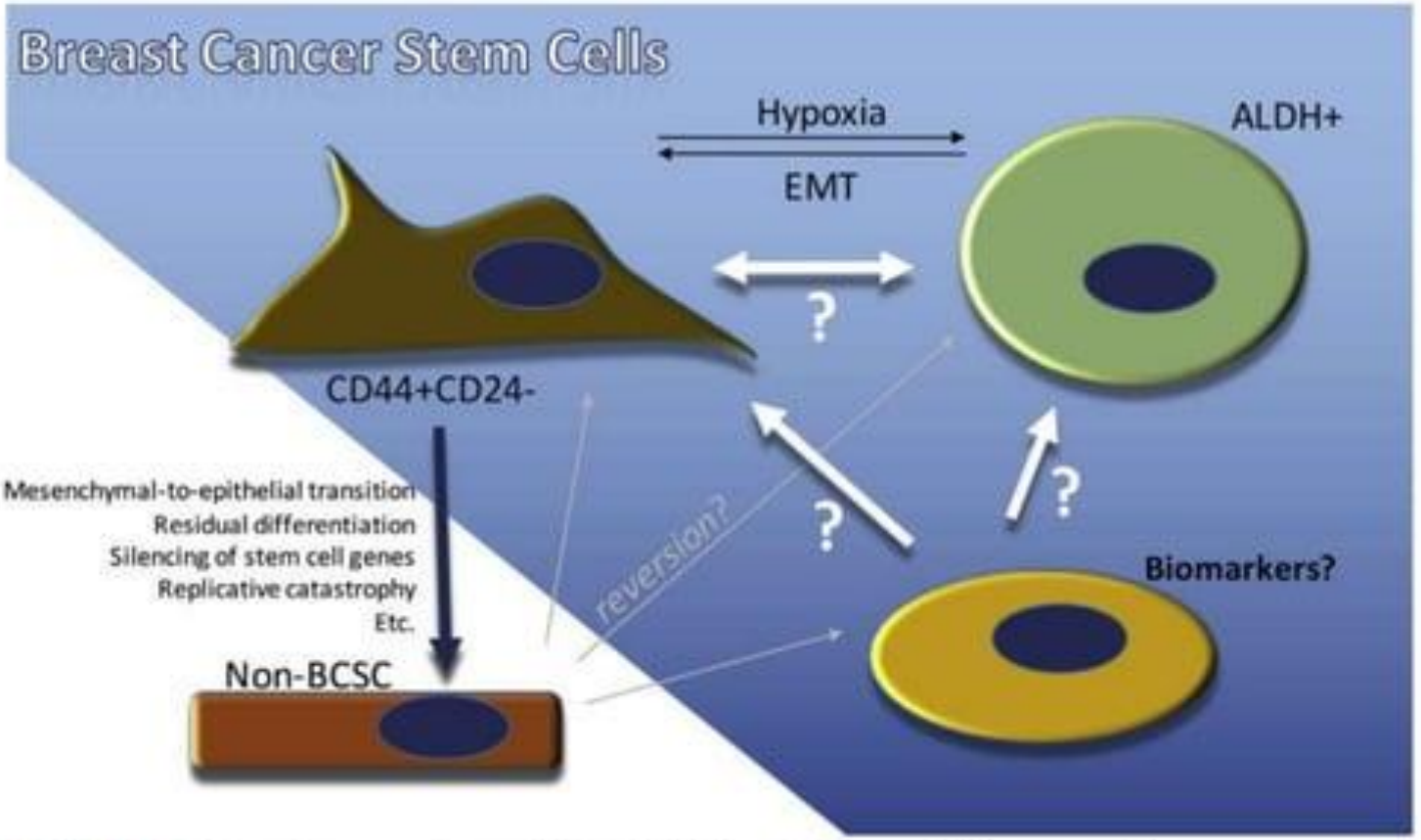


FIGURE 5.1 Breast cancer stem cell (BCSC) differentiation and interconversion.

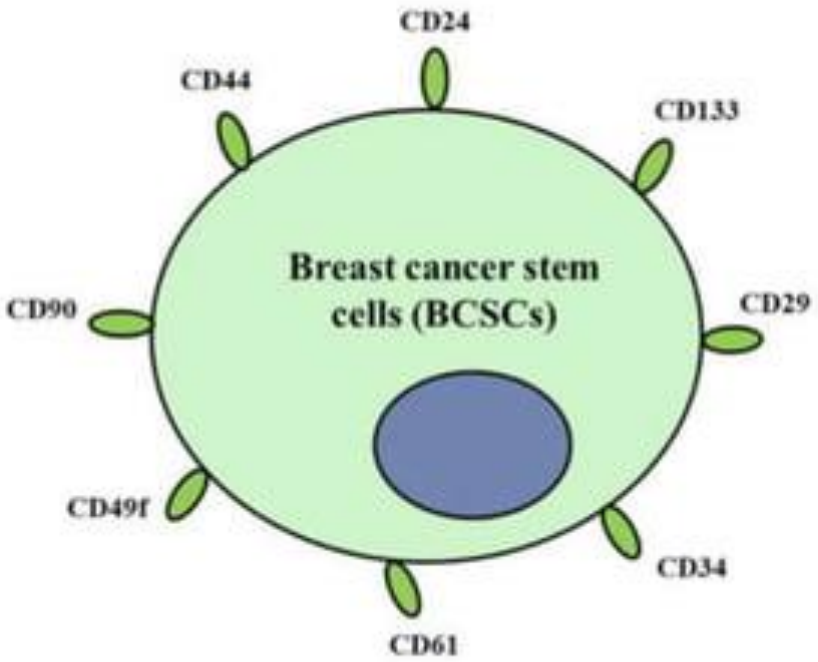


Fig. 5.1 Different cell surface breast cancer stem cell (BCSC) markers

Signal transduction pathways and CSCs

1. HEDGEHOG
2. NOTCH
3. WNT

Signal transduction pathways in CSCs and their therapeutic targeting

Hedgehog signaling:

- Hedgehog family of proteins control cell growth, survival and stem cell maintenance
- Three ligands: Sonic (SHH), Indian (IHH), desert hedgehog (DHH)
- Aberrant activation of HH signaling linked to BCC, medulloblastoma, RMS, glioma and others
- HH proteins bind to PTCH receptor – upregulation of GLI1-3 transcription factors
- Normal mammary stem cells demonstrate PTCH1, GLI1 and GLI2
- High expression of SHH, PTCH1, and GLI1 in invasive breast cancer suggest a role of this pathway
- Linked to early bone metastasis (secretion of HH ligand by tumor cells activates transcription of Osteopontin by bone osteoclasts)

Signal transduction pathways in CSCs and their therapeutic targeting

Hedgehog signaling:

- Commonly used antagonist of HH signalling: plant based alkaloid – **CYCLOPAMINE**
- Downregulates GLI1
- Other antagonists: SANTs 1-4; KAAD-cyclopamine; Compound 5 and Z; and Cur-61414
- Recent: 5E1 monoclonal Ab targeting SHH in small cell lung carcinoma
- GDC – 0449 (**vismodegib**) : first HH pathway inhibitor FDA approved – experimental clinical trials

Signal transduction pathways in CSCs and their therapeutic targeting

NOTCH signaling:

- Regulation of cell fate determination, proliferation and differentiation
- Ligands: Delta like (DLL-1,3, and 4), JAG1 and2, NOTCH1-4
- Oncogenic role of NOTCH 1 – first described in T-ALL
- Overexpression of NOTCH 4 – poorly diff mammary and salivary adenoCA
- CD44+/24- breast CSCs – display NOTCH pathway activation
- NOTCH 4 – most important regulator of BCSCs
- Activation of NOTCH – early event in breast cancer, observed in DCIS
- Co-expression of JAG1 and NOTCH1 – poor overall survival

Signal transduction pathways in CSCs and their therapeutic targeting

NOTCH signaling:

- variety of agents inhibiting NOTCH signaling – early phase clinical trials
- **γ – secretase inhibitors** block NOTCH processing (begacestat)
- Antibodies against specific NOTCH receptors (ARP39295_P050)
- Antibodies against NOTCH ligand DLL4 (ab183532)

Signal transduction pathways in CSCs and their therapeutic targeting

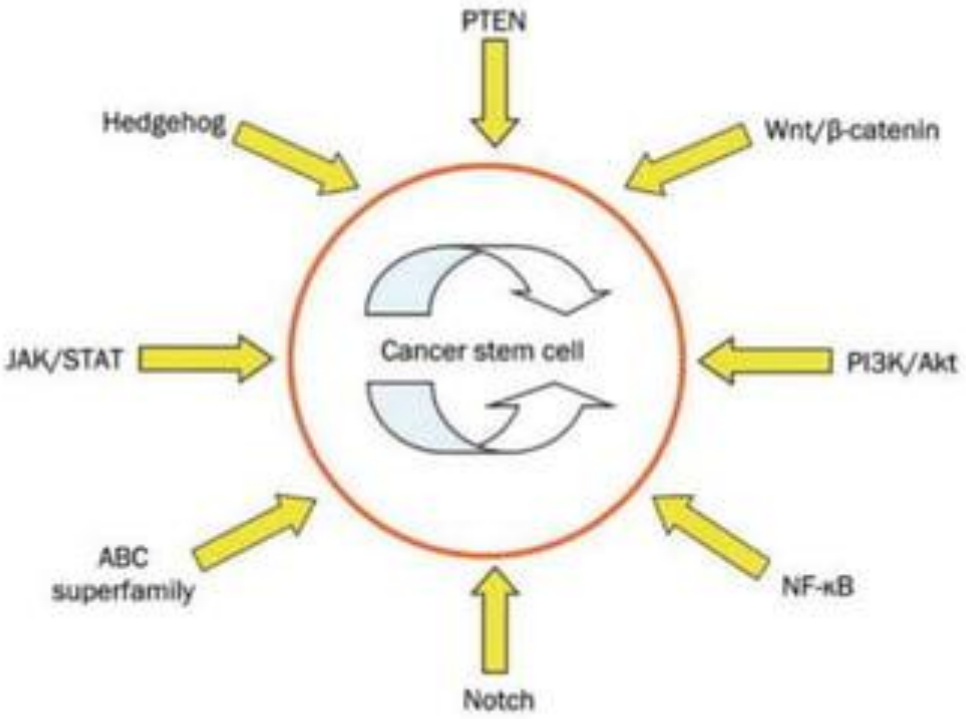
Wnt signalling:

- Wnt/β-catenin/TCF pathway: maintenance of adult tissue homeostasis, cell proliferation, differentiation, migration, apoptosis
- Also regulates self renewal and maintenance of embryonic and tissue specific stem cells
- Canonical Wnt pathway – mutation of APC - activation of β-catenin/TCF complex – upregulation of c-myc and Cyclin D1 – majority of sporadic colorectal cancer
- Germline APC mutation – FAP
- Other cancers involving β-catenin mutation: melanoma, thyroid and ovarian
- Epigenetic silencing through methylation of Wnt antagonist gene (SFRP) – colon, breast, prostate, lung and other cancers

Signal transduction pathways in CSCs and their therapeutic targeting

Wnt signaling:

- Wnt/ β-catenin signaling – EMT regulation (downregulation of E-cadherin and upregulation of SNAIL and TWIST)
- Wnt signaling – stem cell expansion induced by Hif 1-α
- Drugs:
  - **NSAIDS – Sulindac and Celecoxib** (phase II trials)
  - antibodies targeting Wnt signaling
  - Wnt3A neutralizing Ab – reduces proliferation and enhances apoptosis in prostate cancer
  - Monoclonal Ab – **OMP54F28**: early phase clinical trials


PTEN
Hedgehog
Wnt/β-catenin
JAK/STAT
Cancer stem cell
PI3K/Akt
ABC
superfamily
NF-κB
Notch

Clinical significance of CSC and future perspective

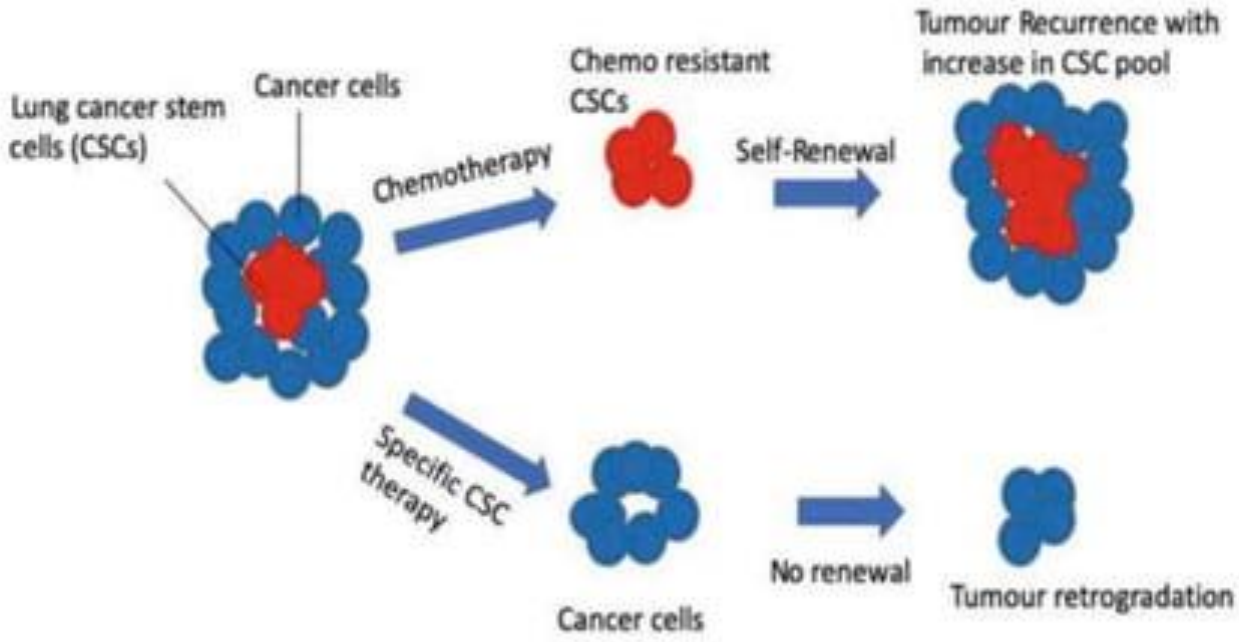
- Substantial evidence that CSC plays role in:
  - Treatment resistance to CT and RT*
  - Tumor propagation
  - Distant metastasis

- *Mechanisms:
  - Alteration in cell cycle kinetics
  - Increased expression of anti-apoptotic proteins
  - Increase in cellular transporters
  - Increased efficacy in DNA repair

Future perspective

Clinical significance of CSC and future perspective

- Currently, tumor shrinkage is accessed by RECIST criteria
- However, it poorly correlates with patient survival
- Tumor shrinkage is measure of effects of treatment on tumor bulk, but CSC constitute a minority of tumor bulk
- Current approach for CSC drug development :
  - Assessing toxicity in Phase I trials
  - Combining CSC targeting drugs with traditional agents that targets bulk population
- Preliminary data suggest that these agents are well tolerated at doses that reduce CSC number in serial biopsies
- CSC targeted therapies should have greatest effect in adjuvant setting (target potential of CSC to self renew into clinically significant disease from micrometastasis)

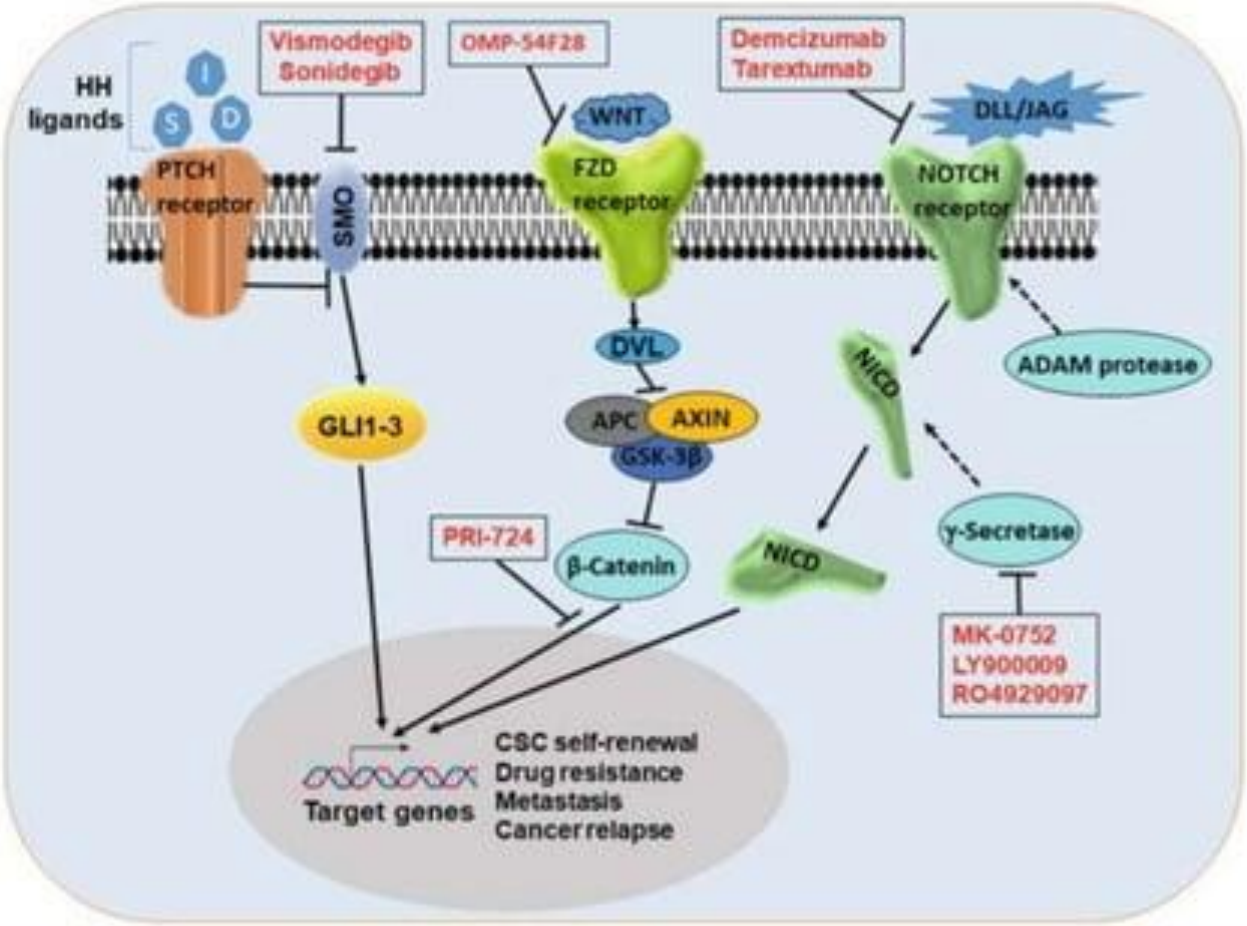

Lung cancer stem cells (CSCs)
Cancer cells
Chemotherapy
Chemo resistant CSCs
Self-Renewal
Tumour Recurrence with increase in CSC pool
Specific CSC therapy
Cancer cells
No renewal
Tumour retrogradation

Clinical significance of CSC and future perspective

- Trastuzumab – targets Her-2 : prevent recurrence when utilised in adjuvant setting
- Development of cancer immunotherapies – immune checkpoint blockers
- CSCs are particularly competent in evading immune surveillance – high expression of PDL1 or secretion of immunosuppressive TGF-β
- CSC based vaccines and peptides – under development
- Worldwide over 70 clinical trials utilising novel CSC targeting agents – most in their early stages
- Comprehensive RCTs will be required to conclusively determine whether targeting CSCs improves patient outcome

Novel CSC Targets


Targeting surface markers
•Targeting CD44
•Targeting CD90
•Targeting CD133
•Targeting CD33
Targeting signal cascades
•Notch
•Hedgehog
•Wnt
•NF-κB
Targeting cancer stem cells
•Verapamil
•MS-209
•VX-710
•Tariquidar
Targeting ABC cassette
•CXCL12/CXCR4
•VEGF/VEGFR
•Weakly acidic pH
Targeting microenvironment


HH ligands
I
S
D
PTCH receptor
SMO
Vismodegib
Sonidegib
OMP-54F28
WNT
FZD receptor
Demcizumab
Tarextumab
DLL/JAG
NOTCH receptor
ADAM protease
DVL
APC
AXIN
GSK-3β
GLI1-3
β-Catenin
PRI-724
NICD
NICD
γ-Secretase
MK-0752
LY900009
RO4929097
Target genes
CSC self-renewal
Drug resistance
Metastasis
Cancer relapse

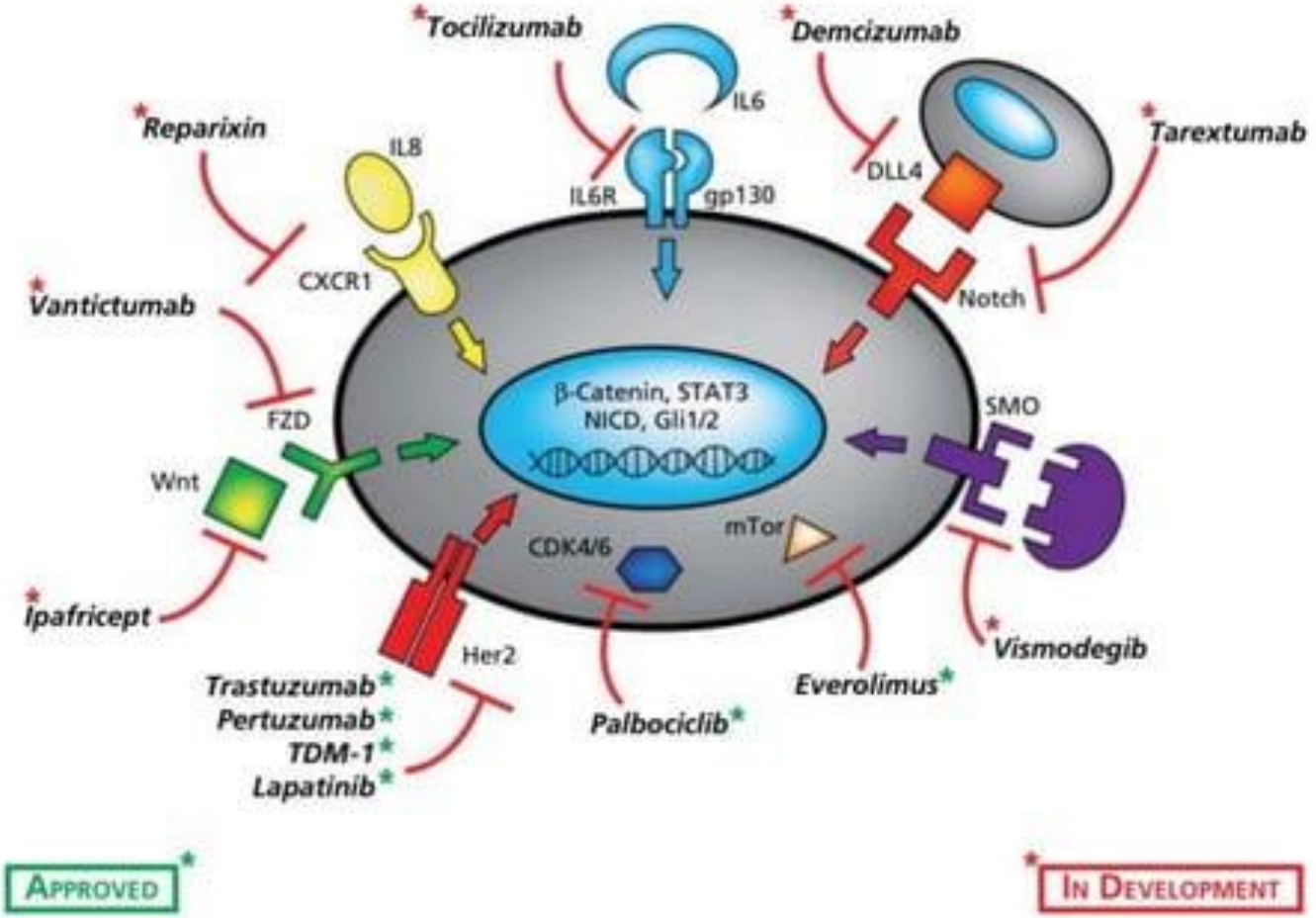
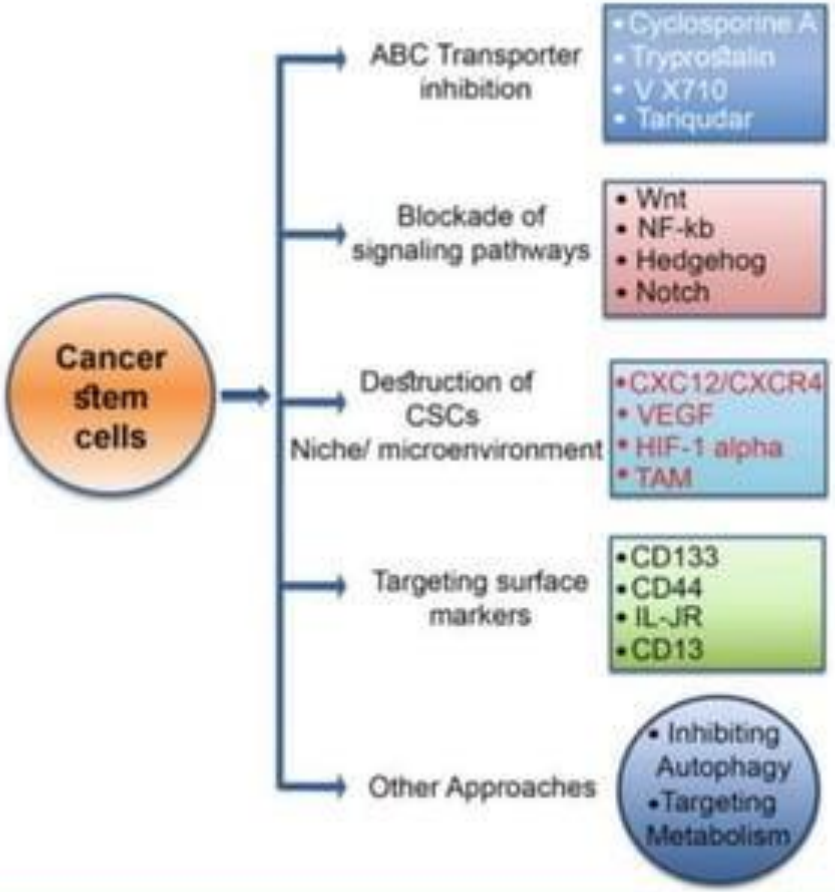


Figure 2 Cancer stem cell-targeted drugs and their cellular targets currently being evaluated in early phase clinical trials or FDA approved for other purposes.

Targeting CSCs by Nano enabled drug delivery

- **Nanobots**: self driven, submicron dimension biodegradable devices, deliver cargo at target sites
  - PEDOT/Zn micromotor
  - DNA origami based nanobots
  - Nano-swimmers – swim in blood stream to deliver the targets
- **Nanoneedles / Nanoclusters / Nanobubbles**:
  - facilitate drug delivery directly into cell cytoplasm
  - nanoclusters: 10nm size, self assembly of polymeric substance cross linked with Au/Ag/magnetic nanoparticles
  - nanobubbles: spherical gas filled structures stabilised using polymeric/lipid shells
- **Dendrimers**
- **Graphene and Carbon nanotubes**
- **Nano-diamonds / exosomes** as drug cargo


Cancer stem cells
ABC Transporter inhibition
• Cyclosporine A
• Tryprostatin
• V X710
• Tariqudar
Blockade of signaling pathways
• Wnt
• NF-kb
• Hedgehog
• Notch
Destruction of CSCs Niche/ microenvironment
•CXC12/CXCR4
• VEGF
• HIF-1 alpha
• TAM
Targeting surface markers
•CD133
•CD44
• IL-JR
•CD13
Other Approaches
• Inhibiting Autophagy
•Targeting Metabolism

Take home message

- Despite considerable progress in molecular underpinning of cancer, this understanding is yet to be translated into significant improvement in patient survival
- Substantial evidence that many cancer are hierarchically organised and driven by cells having stem cell properties
- Ability to self renew and differentiate, forming the cells that constitute the tumor bulk
- Tumor initiating cells or CSC may mediate tumor metastasis and contribute to treatment resistance
- Additional therapies targeting CSC population may be required to limit metastasis and significantly improve patient survival
- Preclinical models – targeting regulatory pathways IL-6. IL-8 and NFKB can effectively reduce CSC population in breast cancer

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THANK YOU