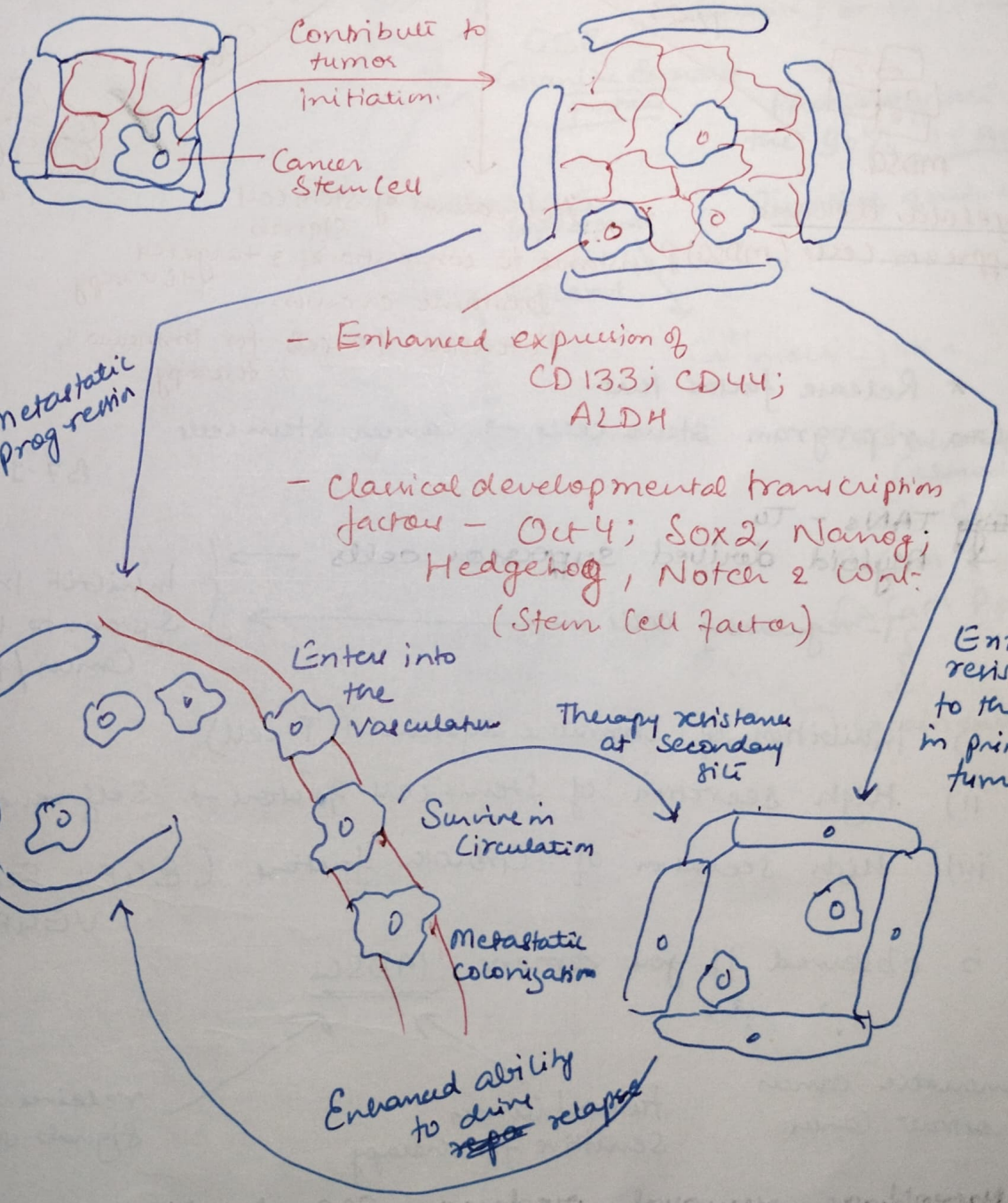
02/09/22

Microenvironment remodelling

If some cells ⇒ Physiological reason
Genetic reason
Environmental tissue
Combination
→ Cells become Cancerous
↓
remodel the microenvironment
↓
- Inflammatory
- protumorigenic



Tumor associated macrophages

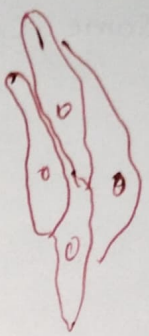
TAMs

Cancer associated fibroblast cell

CAF

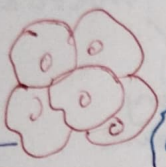
IL-6; EGF

make CSC resistant to Braf and MEK Inhibitors



Stromal Signals

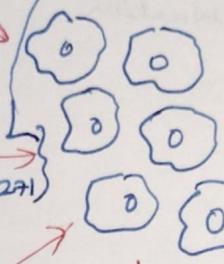
IL-6; IL-8; FGF



B-cell

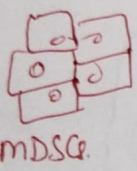
IGF-1

(CD20; CD133; CD274)

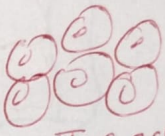


IL-23

PDL-1; CD80



MDSCs



T-cells

Myeloid derived Suppressor cells (MDSCs)

Activation of stem cell Signals

Resistance to conventional & targeted therapy

Immune evasion

Potential targets for Immuno therapy

* Release factors that can reprogram stem cells → Cancer stem cells

B7-1 (CD80)

→ ~~Eggs~~ TANs – Tu

→ Myloid derived suppressor cells →

T-regulatory cells →

} Inhibit Immune System to kill Cancer/tumor cell.

i) Inhibition of Immune System (T-cell)

ii) High secretion of Stem-cell factor → Self renewal

iii) High secretion of Growth factors (EGF; FGF; VEGF)

It is observed if you remove MDSCs

Pancreatic cancer
Prostate Cancer.

tumor/cancer sensitive for therapy

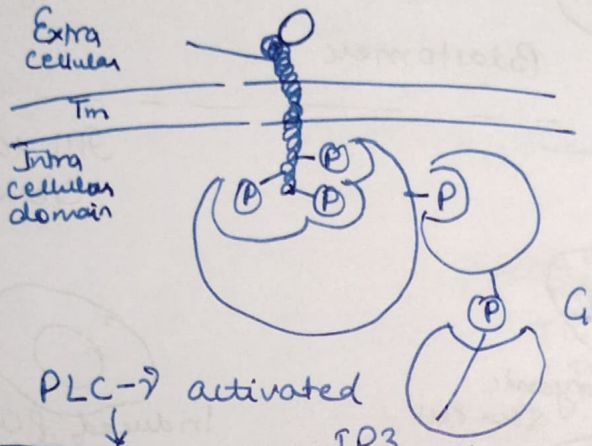
releases suppressive signals on T-cells

- Macrophage removal reduce CSCs fraction → Cancer stem cell.
  making it more sensitive for chemotherapy.

oB-cell are also implicated to target therapy.

Signal transduction Cascade

- Signal (Ligand / hormone / factor)
- Receptor
- TFs



factor binding triggers conformational change

↓

triggers protein kinase Associated c cytoplasmic domain / or on co receptor.

↓

Phosphorylate the Go% ITAM

Tyrosine amino acid

GEFs
Guanine Exchange Factors

PLC-γ activated

PIP3 → IP3 — Inositol 1,4,5 triphosphate

DAG — Diacyl glycerol

Ca^{++} mobilization

NF-κB – IκB (P)
Inhibitor of κ-B

Protein kinase-C

NF-κB

Ca^{++} binding protein
Calmodulin
Ca-Cam*
CaCam PKs
CaCam Pphosphatase

NF-AT (P)
Inactive

Calcineurin

NF-AT - active

GEFs
↓
Ras - Raf
↓
MEKs
↓
MAPs
↓

CFos
CMyc
CJun
→ GE

GE