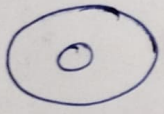
Stem cell signaling

→ Self renewal and differentiation potential

→ Yamanaka factor – Sox-2, Oct 4, Klf-4, & C-Myc.

i) Octamer binding transcription factor-4 (Oct 4)
ii) Sex determining region Y box-2
iii) Kruppel-like factor-4. (Klf-4)
iv) c-myelocytomatosis (c-Myc)

plays key role in maintainence of pluripotency.


Stem cell

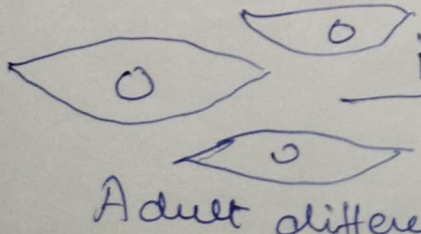
→ Terminally differentiated cell → Yamanaka factors

30/09/22

Yamanaka factors

Takahashi and Yamanaka → maintenance of Pluripotency

→ induced pluripotent stem cell were produced by exogenous expression of transcriptional pluripotency program in adult differentiated cell

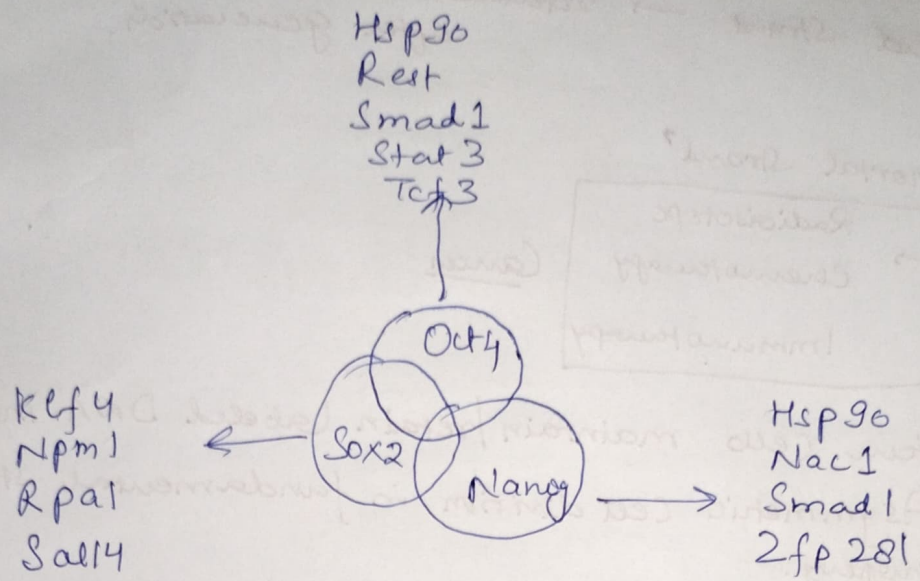

Adult differentiated cell

incubated in Oct4; Sox2; Nanog Klf4

Process was known as induced Pluripotency

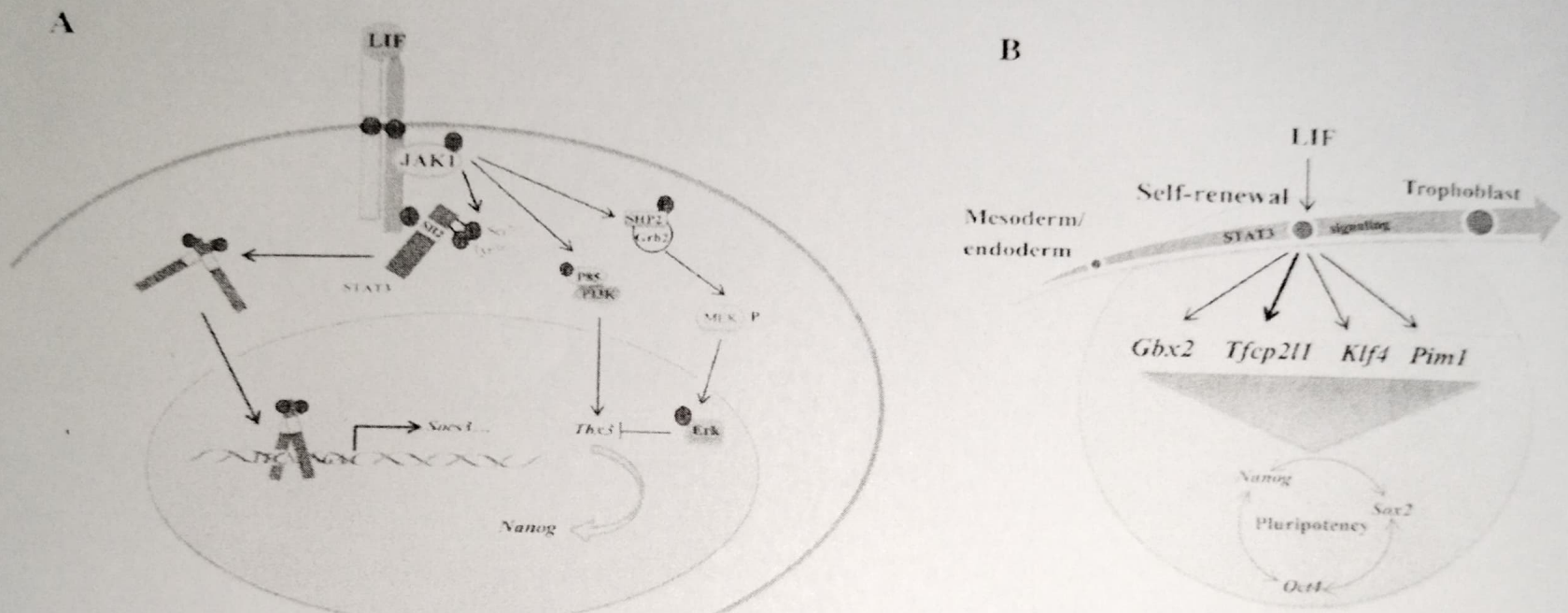
Stem cell

Pluripotent like ESC.



Core pluripotency TF's interact ē each other and also interact with many transcriptional regulators to maintain stem cell pluripotency.

Oct4 — Core factor
Sox2 — Core factor
Nanog — Core factor
~~Klf 2/4/5~~ — self renewal
c-myc — "
Tbx3 — "
~~Esrrb~~ — "
Tcf-211 — "
Tfe-3 — "
Zscan — Genomic stability.
Mbd3 — Differentiation
Tcf3 "
Cdx2 "
Gata 4/6 "
Tfap2C "
Sox17 "



LIF/JAK/STAT3 signaling pathway in mouse ESC self-renewal. a Binding of LIF to its membrane receptor results in recruitment of JAKs and phosphorylation of STAT3 at Tyrosine 705. Activated STAT3 dimerizes and translocates into nucleus to activate transcription. LIF also activates PI3K/AKT and SHP2/MAPK pathways that are not essential for mouse ESC self-renewal. b STAT3 activation level is critical for maintaining mouse ESC self-renewal. Multiple downstream target genes have been identified to connect STAT3 signaling to core pluripotency network

④ WNT - Involved in cellular proliferation; adhesion; migration.

WNT sig → Stabilization of β-Catenin

↓

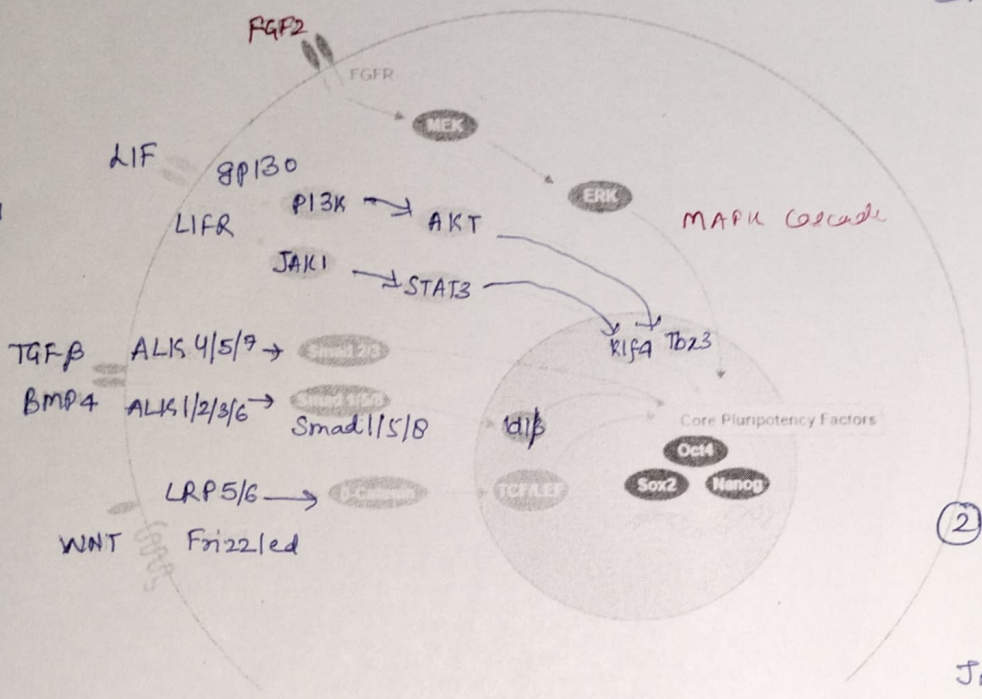
β-Catenin + T-cell factor / Lymphoid enhancer factor (TCF/LEF)

↓

Oct4 & Nanog

mESCs

hESCs



① FGF2 :- regulates various cellular process Cell proliferation; mig; diff & survival

ERK/MAPK → FGF2 / Tyrosine Kinase receptor

↓

involved in the maintenance of hESC pluripotency.

ERK/MAPK — not required for mESC maintenance

ERK/MAPK → activated → Differentiation.

② LIF Sig → Simultaneous activation of JAK/STAT3 & PI3K/AKT

Imp. role in murine ESC pluripotency

JAK/STAT3 * → Ind^{n}. of Klf4 → Sox2 Act^{n}. of PI3K/AKT → Tbx3 Nanog

Kinase Modulating Pathways

Several kinase signal transduction pathways modulate the core pluripotency transcription factors in response to both intrinsic and extrinsic stimuli, preserving stem cell self-renewal and differentiation potential. Synergy between these pathways ensures the maintenance of pluripotency.

③ * TGF-β pathway → 1) Differentiat^{n}; proliferation; programmed cell death 2) Imp. for maintenance of self-renewal and differentiation potential of mESCs and hESCs.

i) TGF-β + BMP4 → Smad 1/5/8 act^{n}. → Induction of Inhibitor of DNA-binding/differentiation (Id) protein for maintenance of mESCs.

ii) TGF-β + Activin → Smad2 for maintenance of hESCs.

Mesenchymal Stem Cells (MSCs)

HSCs ; MSCs ⟶ multipotent ⟶ Mesenchymal Stromal Cells

↓

MSCs ⟶ Adult Stem Cells.

Properties of MSCs

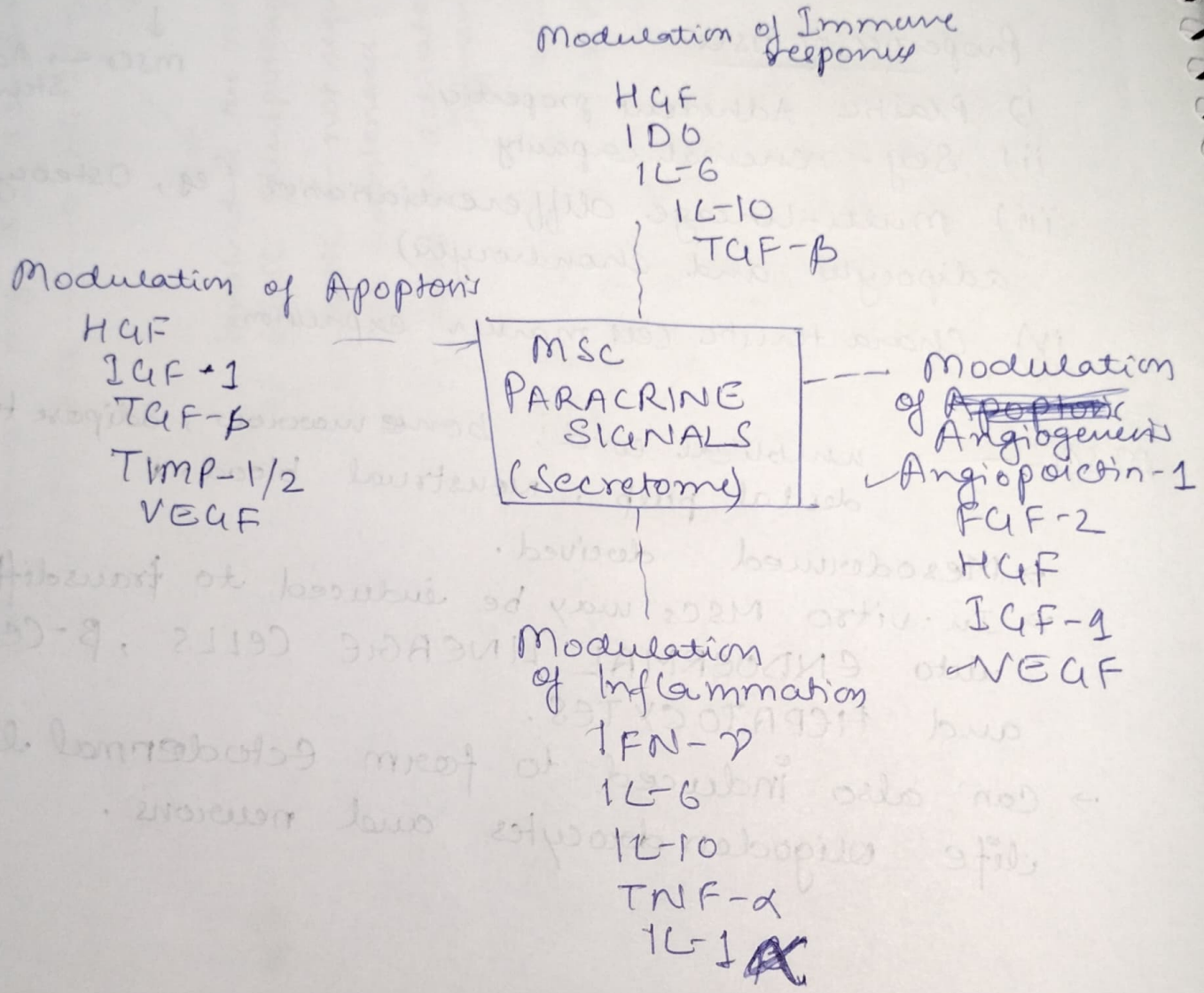
i) Plastic Adherent properties
ii) Sey-renewal capacity
iii) Multi-lineage differentiation (eg., Osteocytes, adipocytes and chondrocytes)
iv) Characteristic cell marker expression.

MSCs ⟶ umbilical cord; bone marrow, adipose tissue dental pulp, menstrual blood, &

→ Mesodermed derived.
→ In-vitro MSCs may be induced to transdifferentiate into ENDOERMAL LINEAGE CELLS, β-CELLS and HEPATOCYTES.
→ Can also induced to form ectodermal lineage like oligodendrocytes and neurons.

Functions Of MSCs.

→ Tissue maintance and repair
→ The potential for differentiantion provides the mechanism for tissue self repair following injury, disease or absence.
→ They also contribute to homeostatic functions they regulate immune responses through various regulation involving cell contact, and secreted factors involving both innate and adaptive immunity.
→ MSCs release a variety of bioactive molecule referred as "SECRETOME" including GFs, enzymes, adhesion protein & cytokines.


Modulation of Immune Response
HGF
IDO
IL-6
IL-10
TGF-β
Modulation of Apoptosis
HGF
IGF-1
TGF-β
TIMP-1/2
VEGF
MSC PARACRINE SIGNALS (Secretome)
Modulation of Angiogenesis
Angiopoietin-1
FGF-2
HGF
IGF-1
VEGF
Modulation of Inflammation
IFN-γ
IL-6
IL-10
TNF-α
IL-1