Notes

Stem cells

Stem cells are defined as cells with self-renewal and multipotent differentiation ability.
Thus, stem cells are functionally defined.
Why do we need stem cells: For repair and regeneration and regeneration is limited in higher organisms. Stem cells can be transplanted from one individual to the other.

Loss of stem cells: Degenerative diseases – neurodegenerative diseases, muscular degenerative diseases, macular degeneration, etc

Cells that can undergo unlimited population doublings without oncogenic transformation. Can be tested in the lab where the cells show extensive population doublings, commonly seen in embryonic stem cells. No replication arrest or senescence.

Telomere: How is it maintained- through telomerase-how is the gene activated?
Proliferation of adult stem cells are tested in vivo in experimental animal models by serial transplantation.
Has clonal propagation capacity.
Progenitor cells have differentiation capacity with limited proliferation ability
Differentiation ability: multiple lineages or multiple cell types of a lineage
Stem cells can be totipotent (?), pluripotent or multipotent
Stem cells can be isolated from embryonic, fetal or adult stage or iPSC

Thus, stem cells have a different set of gene activation mechanisms and gene expression profile. Molecular signature of stem cells

What is the origin of stem cells:

i. Uncommitted cells during development – occupy a niche to become stem cells
ii. Committed cells occupy a particular niche to become stem cells

Stem cell niche might impose a lineage restriction on the stem cells

Stem cells identification:
Stem cells are identified based on their characteristics: that is, the functional characteristics
Embryonic stem cells: derived from the inner mass of the blastocyst
Self-renewal, multilineage differentiation in vitro and in vivo, clonogenicity, normal karyotype
Ability to give rise to all lineages including germ line
Teratoma formation, embryoid bodies formation, chimera formation after transplantation into non-human blastocyst
Expression of molecular markers of pluripotent stem cells
Adult stem cells
Clonal cell that self-renewes and has ability to differentiate
transdifferentiation abilities (?)
Reconstitution in the in vivo assay

Characteristic features common to stem cells:

- Gene expression profile
- Signal transduction pathways
- Cell cycle regulators
- Telomerase maintenance
- Epigenetic profile
- Transcriptional regulatory mechanisms
- Multidrug resistance
- Protein folding machinery
- Ubiquitin system

Quiescence
Hierarchical arrangement
Asymmetric/symmetric cell division

Long-Term Control of HIV by CCR5 Delta32/ Delta32 Stem-Cell Transplantation

HIV-1 positive patient treated with HARRT for 10 years developed acute myeloid leukemia (AML)

Treated with chemotherapy but relapsed after 7 months.

An allogenic stem cell transplantation was performed with CD34+ cells from a donor who was $CCR5^{\Delta 32/\Delta 32}$

($CCR5^{\Delta 32/\Delta 32}$ patients are immune to HIV infection that uses CCR5 as a co-receptor since these patients have a 32bp deletion in CCR5 gene – so that the virus cannot bind and enter the CD4+ T cells.)

HAART was stopped after transplantation but no rebound of virus occurred.

AML relapsed after 332 days of transplantation. Second transplantation was performed with the same donor – resulting in complete engraftment and no virus presence even without HAART treatment.

Thus, a case study to show that stem cells can be used to cure AML (reported in many cases) and also HIV-1 infection.