Lec3\ Hematopoietic stem cell transplantation

اعداد

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رمز الصف :

Definition of Hematopoietic Stem Cells (HSCs)

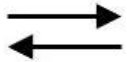
All lineage blood cells are produced by a rare population of multipotent HSC, which can proliferate by self-renewal and differentiate to accomplish the functional maturation. From HSC to mature cells, there are several intermediate progenitor cells.

These cells can display both functional multipotent and lineage-committed properties simultaneously or separately prior to complete maturation and bone marrow (BM) supports the dynamic movement of diverse cells to maintain homeostasis of blood cells. Approximately, one trillion cells are generated daily to compensate apoptotic cells in human BM, suggesting rapid circulation of blood cells.

Types of HSC

HSC can be divided into LT-HSC, ST-HSC, and multipotent progenitor (MPP) in terms of duration of repopulation . In normal physiological conditions, rare HSC populations such as LT-HSC can develop into all lineage blood cells in the BM. However, HSC populations in the PB tend to be higher in myelosuppressive conditions caused by drug and granulocyte colony-stimulating factor (G-CSF), and rapidly migrate from the BM, suggesting different properties. HSC/progenitor cells in the PB are ST-HSC, which might directly contribute to recovering damaged tissues, and these are regarded as optimal curative cell sources in regenerative medicine.

Long-term HSC (LT-HSC)



Short-term HSC (ST-HSC)

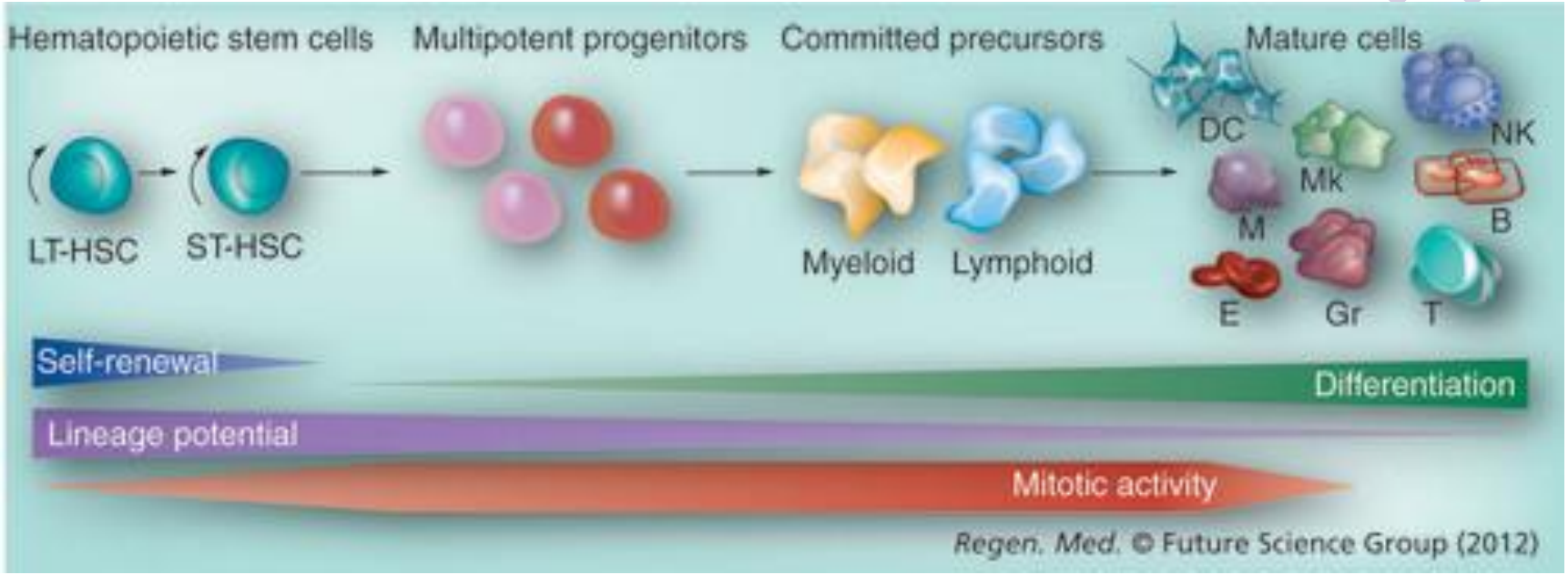
Human Markers	$lin^-/CD34^+/CD38^-/CD45RA^-/CD49f^+/CD90^+$ and $lin^-/CD34^-/CD38^-/CD93^{hi}$	$lin^-/CD34^+/CD38^-/CD45RA^-/CD49f^+/CD90^+$
Mouse Markers	$CD48^-/CD150^+/CD34^{-/low}$ and $CD135^-/CD201^+$	$CD48^{-/low}/CD150^-/CD135^-/CD201^-$

Differentiation of HSC :

Blood cells from HSCs are divided into two lineages: lymphoid cells and myeloid cells .

The lymphoid branch consists of T, B, and natural killer (NK) cells, which are relevant to innate and adaptive immune cells. This process is known lymphopoiesis. Myeloid lineage cells include all blood cells except lymphoid cells. There are several types of cells including monocytes from monoblasts, erythrocytes from erythroblasts, platelets from megakaryocytes, and granulocytes, which consist of neutrophils, eosinophils, and basophils, and are from myleoblasts. Lineage committed progenitor cells are specified for cell fate and develop into mature cells through myelopoiesis. In myeloid lineage cells, committed myeloid progenitors can be converted into mature types of myeloid cells.

Lymphoid cells also have a similar process as the myeloid cells for generating progenitor cells and lymphoblast are from committed lymphoid progenitor cells. These blood cells are affected by dynamic niche composition including hormone and pericytes in BM. Similar to stem cells, progenitor cells in each step can also function as a strong cell source in regenerative medicine (Fig. 1). Thus, understanding HSC/progenitor cells is important to apply these cells in regenerative medicine depending on the **disease type and severity.**


Hematopoietic stem cells
Multipotent progenitors
Committed precursors
Mature cells
LT-HSC
ST-HSC
Myeloid
Lymphoid
DC
Mk
NK
M
B
E
Gr
T
Self-renewal
Differentiation
Lineage potential
Mitotic activity
Regen. Med. © Future Science Group (2012)

Because rare populations of HSC can lead the entire hematopoiesis, knowing the properties of HSC is very important to enhance therapeutic effects in clinical application. Recently, aging is emerging as an issue in HSC biology. Since Morrison et al. mentioned homing and engraftment of HSCs based on aging, many papers have demonstrated the relevance of aging by DNA damage in HSC and molecules such as ATR gene and Cdc42 are pivotal to maintain phenotypes without HSC loss and back to rejuvenation.

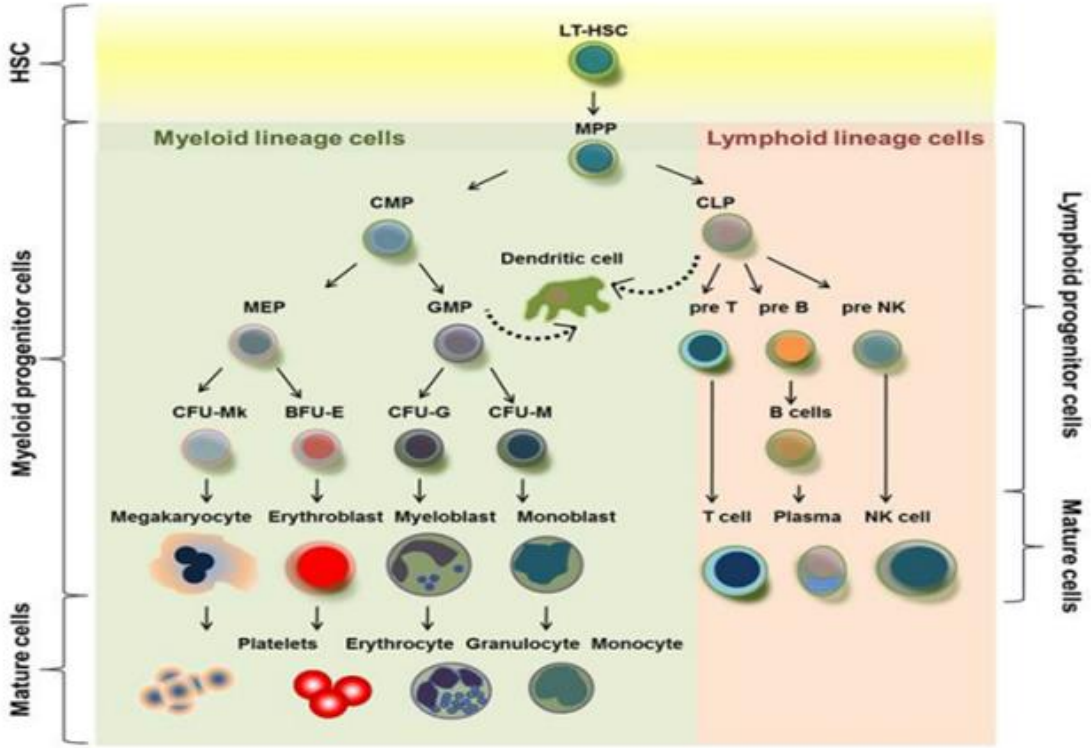
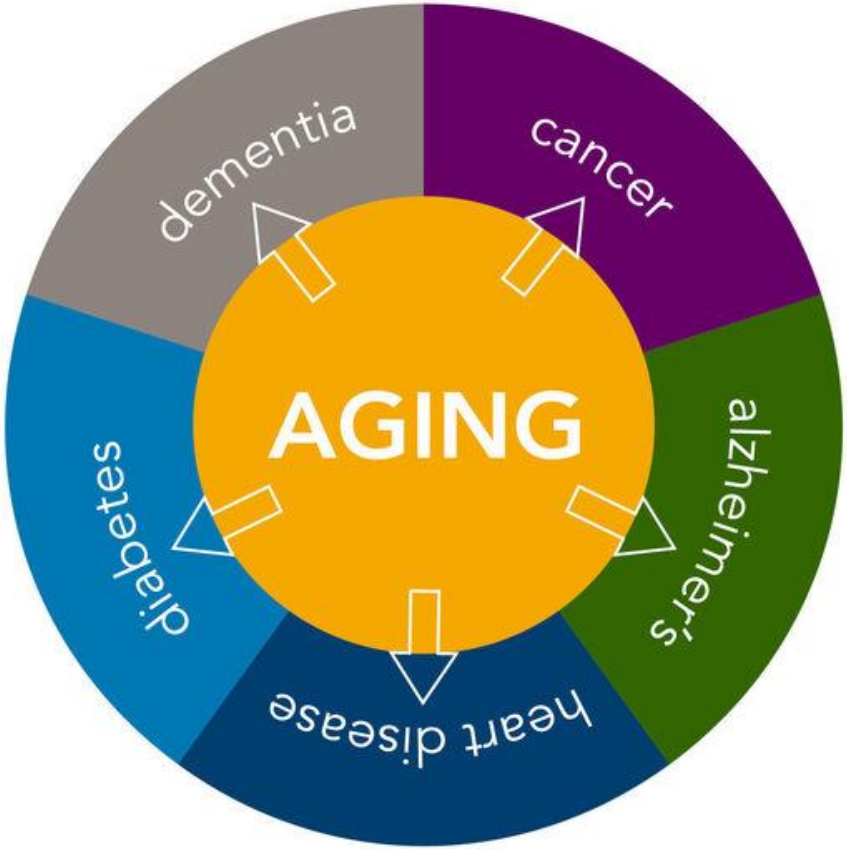


Fig. 1. Schematic illustration showed hematopoiesis in adult BM. HSCs have self-renewal activity and differentiation capability into blood cell lineages. LT-HSCs are quiescent and sustained by arrested cell division in endosteal niche, whereas ST-HSCs are promptly differentiated into myeloid and lymphoid lineage cells in vascular niche, and then lineage cells exit into periphery.

Aging factors

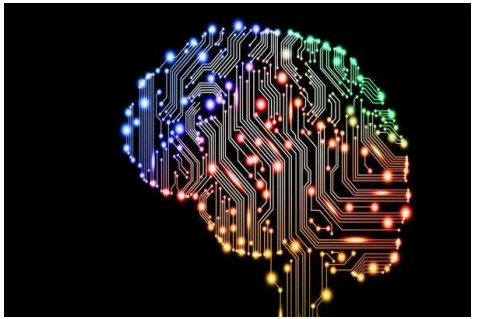
there are several emerging intrinsic factors such as increased polarity, reactive oxygen species, and injured autophagy and mitochondria metabolism as ample evidence of aging of HSCs , which show the main features of aged HSCs compared to that of young HSCs. contributing factor, deregulation of a UPR(mt)-mediated metabolic checkpoint, in HSC aging, which suggested that mitochondria metabolism may play a role to govern juvenescence of HSCs. Although these evidence remain unclear, pharmacological and metabolic interventions in these pathways may be continuously exploited to restore function in aged HSCs.


dementia
cancer
AGING
diabetes
alzheimers
heart disease

Epigenetic reprogramming

as a part of intrinsic regulation is one of the main factors in aging of HSCs. Although epigenetic abnormality is easily detected, correlation between aged HSC and epigenetic aberrancy is unreadable due to the slow loss of normal stem cell potential. Epigenetic regulation by TET2, DNMT3, and EZH2 led to hematologic malignant transformation, implying the faithful role of epigenetic control in the aging of HSCs.

Epigenetic fidelity in a normal stem cell niche is required to maintain normal HSCs, because aging of HSCs is driven by a strong contribution of aged niche . Multiple myeloma (MM) is a clonal plasma cell malignancy from BM failure by epigenetic defects . Thus, an epigenetic modulating agent such as decitabine is used to enhance therapeutic efficacy in MM.



Regardless of aberrant epi-genetic defects in the niche as well as autonomous HSCs, gene mutations may ultimately alter the epigenetic memory of HSCs, and then clonally expand with mutant epigenetic memory leading to abnormal hematopoiesis. It shows that modulation of epigenetic agents synergistically enhances clinical drug responses and normalization of abnormal mutation from aging status.

إعادة البرمجة اللاجينية

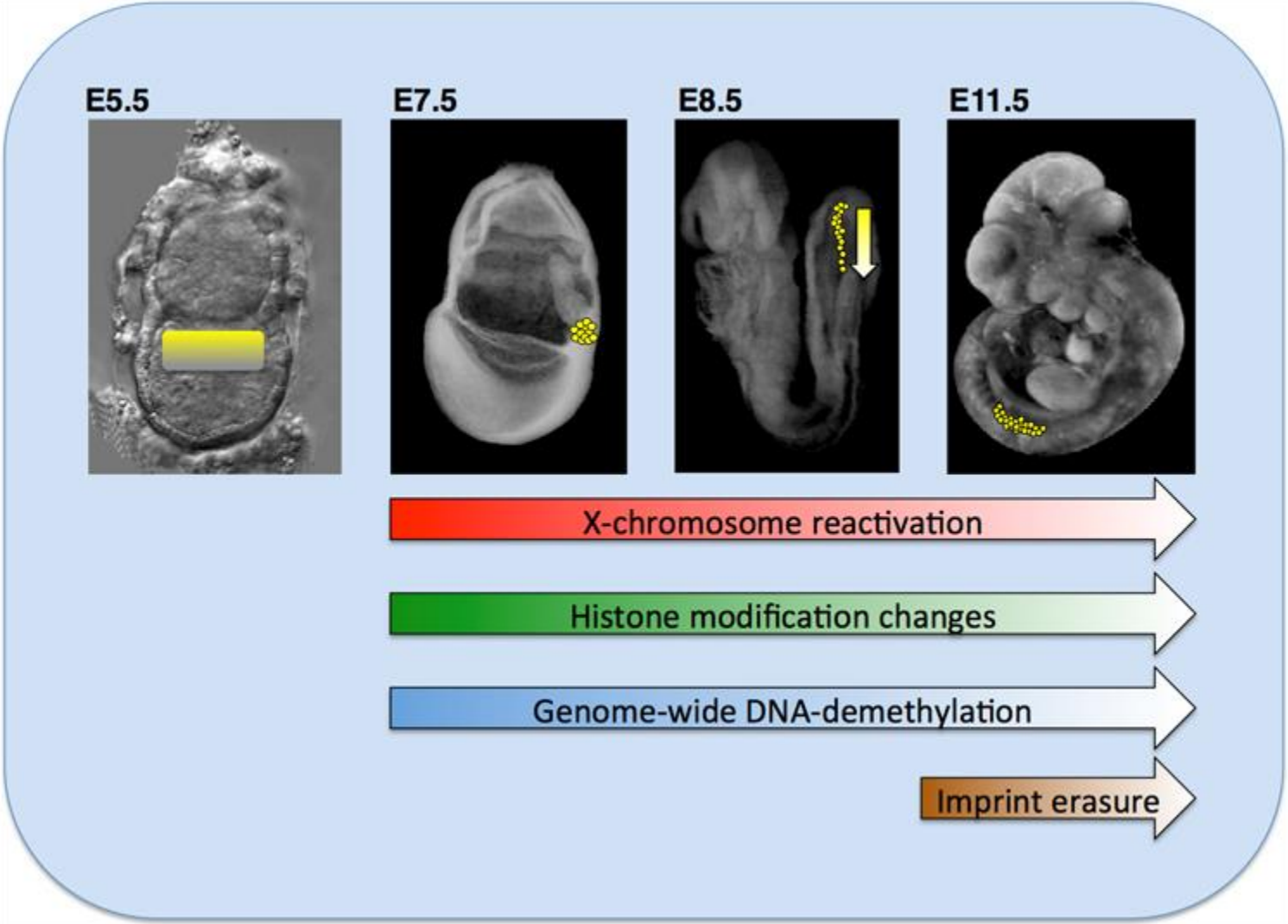
1 إطالة التيلومير

2 عكس الشيخوخة

3 تعزيز الميتوكوندريا

4 علاجات الخلايا الجذعية

The aging of HSCs depends on cellular changes, such as epigenetic factors, telomere and genomic damage, and molecular damage, including DNA damage, and finally resulting in dysfunctional HSCs . As previously mentioned, there is some debate regarding the properties of aged HSCs in humans, and analysis of HSC characteristics during aging remains inconclusive. Thus, the identification and isolation of bona fide HSCs are required prior to investigating aging HSCs, which can be achieved by applying recently developed advanced isolation techniques that ensure high purity, and using improved HSC-specific markers.


E5.5
E7.5
E8.5
E11.5
X-chromosome reactivation
Histone modification changes
Genome-wide DNA-demethylation
Imprint erasure