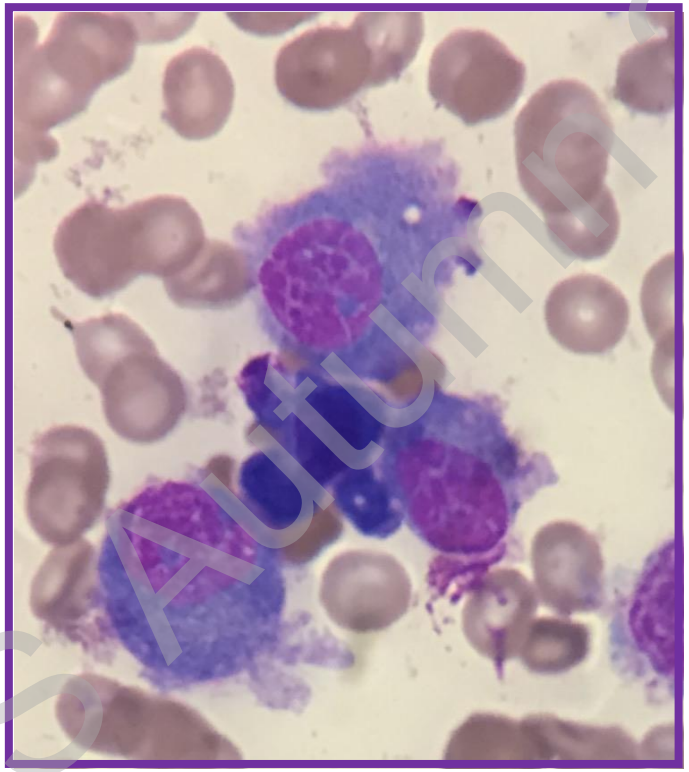
Anaemia and the ageing bone marrow



Simona Deplano
Imperial College Healthcare NHS Trust
simona.deplano@nhs.net

Disclosure

I have no conflicts of interest to declare

Introduction

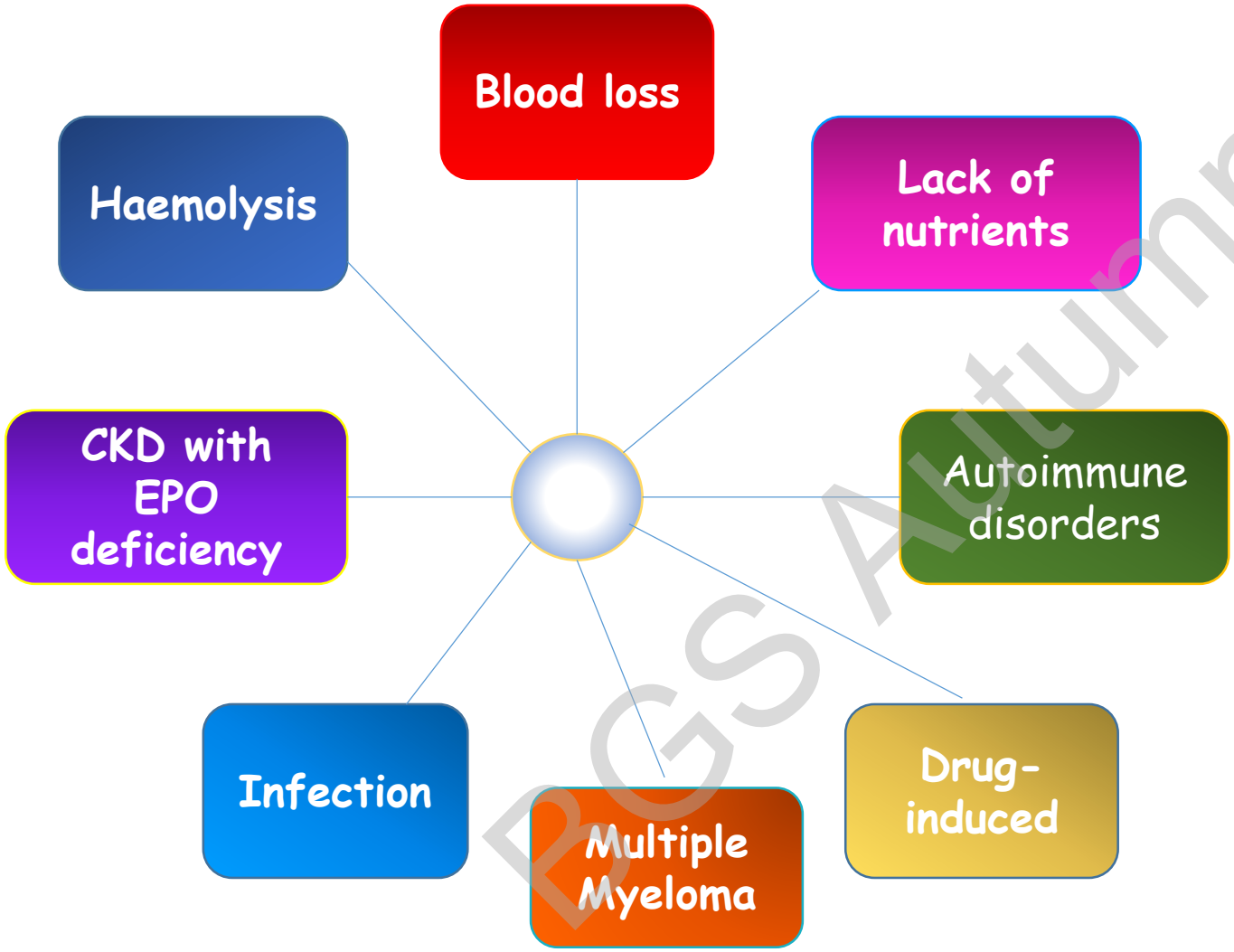
- Anaemia is a frequent finding in older patients and has been shown to be associated with:

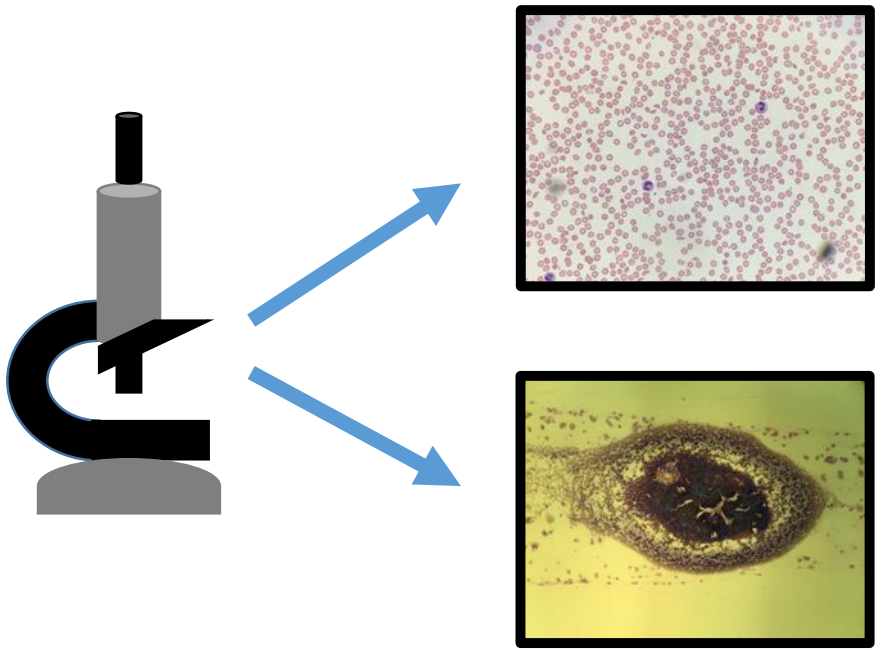
- Reduced quality of life
- Increased physical impairment
- Depression
- Cognitive decline
- Mortality

- The etiology is often complex and multifactorial.

Balducci L. Transfus Clin Biol. 2010;17(5-6):375-381
Riva E. Haematologica.2009;94(1):22-28
Den Elzen WP CMAJ.2009;181(3-4):151-157

Diagnostic approach





Idiopathyc Cytopenia of Undetermined Significance (ICUS)

- In up to one third of older adults with anaemia no clear-cut cause is identified upon routine evaluation.

- Patients with ICUS are not known to have clonal disorders

<u>ICUS may take one or several courses over time:</u>

- Spontaneous resolution of cytopenia
- Diagnosis of MDS or other haematological malignancy
- Persistent cytopenia that lasts for years

Guralnik JM. Blood. 2004;104(8):2263
Valent P. Leuk Res. 2012 Jan;36(1):1-5.

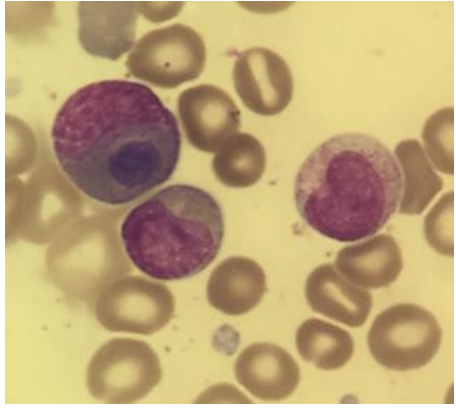
Clonal hematopoiesis of indeterminate potential (CHIP)

- Recent genetic studies have demonstrated that at least 10% of patients older than 70 have somatic mutations in genes involved in RNA splicing, DNA methylation, DNA repair and transcription regulation.

- CHIP confers a risk of subsequent diagnosis of overt haematologic malignancy of 0.5-1% per year and is associated with increased all-cause mortality.

Steensma DP et al. Blood 2015;126:9-16

Myelodysplastic syndromes



- Clonal stem cell disorders characterized by ineffective hematopoiesis, cytopenias in peripheral blood and increased risk of progression to acute myeloid leukemia.
- Median age at diagnosis ranges between 71 and 76 years.
- Allogeneic stem cell transplant is the only curative treatment.
- Only a minority of patients with MDS are eligible for transplant due to age, and comorbidities.

Gurion R Haematologica 2010;95(2)

Anaemia and transfusion dependence in MDS

- Anaemia is the most frequent cytopenia in MDS.
- 80-90% of patients with MDS develop anaemia during the course of their disease.
- The majority of patients with MDS become transfusion-dependent and develop iron overload with an increased risk of associated comorbidity and mortality.
- Anaemic MDS patients have been shown to have a higher mortality rate than non anaemic MDS patients.

Mitchell et al. Expert Rev Hematol. 2013 August; 6(4): 397-410

Challenges in diagnosing MDS in the elderly

- Dysplastic changes, mainly in megakaryocytes and erythroblasts are observed frequently in elderly patients without haematological disease.

- According to WHO criteria, MDS is diagnosed when patients exhibit at least one of the following:

- Extensive cellular dysplasia (> 10% of bone marrow cells)
- Increased number of blasts
- MDS-associated karyotypic abnormality

Girodon F. et al. Clin Lab Haematol. 2001;23(5):297-300
Valent P. Eur J Clin Invest. 2009;39(7):548

Patients fate in MDS

- 1/3 has a stable, non-progressive course (patients predominantly die from cardiac causes)
- 1/3 dies from cytopenic complications (i.e. infections, bleedings)
- 1/3 dies from acute myeloid leukemia

Progression markers

- worsening of cytopenias
- increase in blasts
- clonal evolution

Aul C, et al. Haematologica. 1998;83:71-86.
Giagounidis A, Haase D. Best Pract Res Clin Haematol. 2013;26:337-53.

Genetic profile of MDS clones changes

Process is driven by:

- **karyotype evolution**
  normal karyotype ➔ gain of clonal abnormalities
  abnormal karyotype ➔ additional abnormalities

- **molecular evolution**
  subclonal mutations in addition to pre-existing gene mutations and/or chromosomal abnormalities

Consequences of clonal evolution

- accumulation of abnormalities
- increasing genetic instability
- increasing disturbance of normal cellular function (differentiation, apoptosis, cell-cycle control)
- resistance to therapy ➔ multiple escape routes

Giagounidis A, Haase D. Best Pract Res Clin Haematol. 2013;26:337-53.

How does the hematopoietic system change with age?

How does this lead to MDS or other haematological malignancies?

Is there anything we can do to stop this process?

Age-related changes in the bone marrow

- Like every organ system, the bone marrow undergoes changes with age.
- The most apparent change is decreased cellularity.
- By age 65, bone marrow cellularity is approximately 30% with a corresponding increase in marrow fat.
- Imbalanced bone remodelling and osteoporosis result in decreased trabecular bone which itself may contribute to reduced hematopoiesis.

Prabhakar M. Aging health. 2009 Jun 1; 5(3): 385–393

Hematopoiesis

- All blood cells arise from a small population of hematopoietic stem cells (HSCs) that have two unique properties:

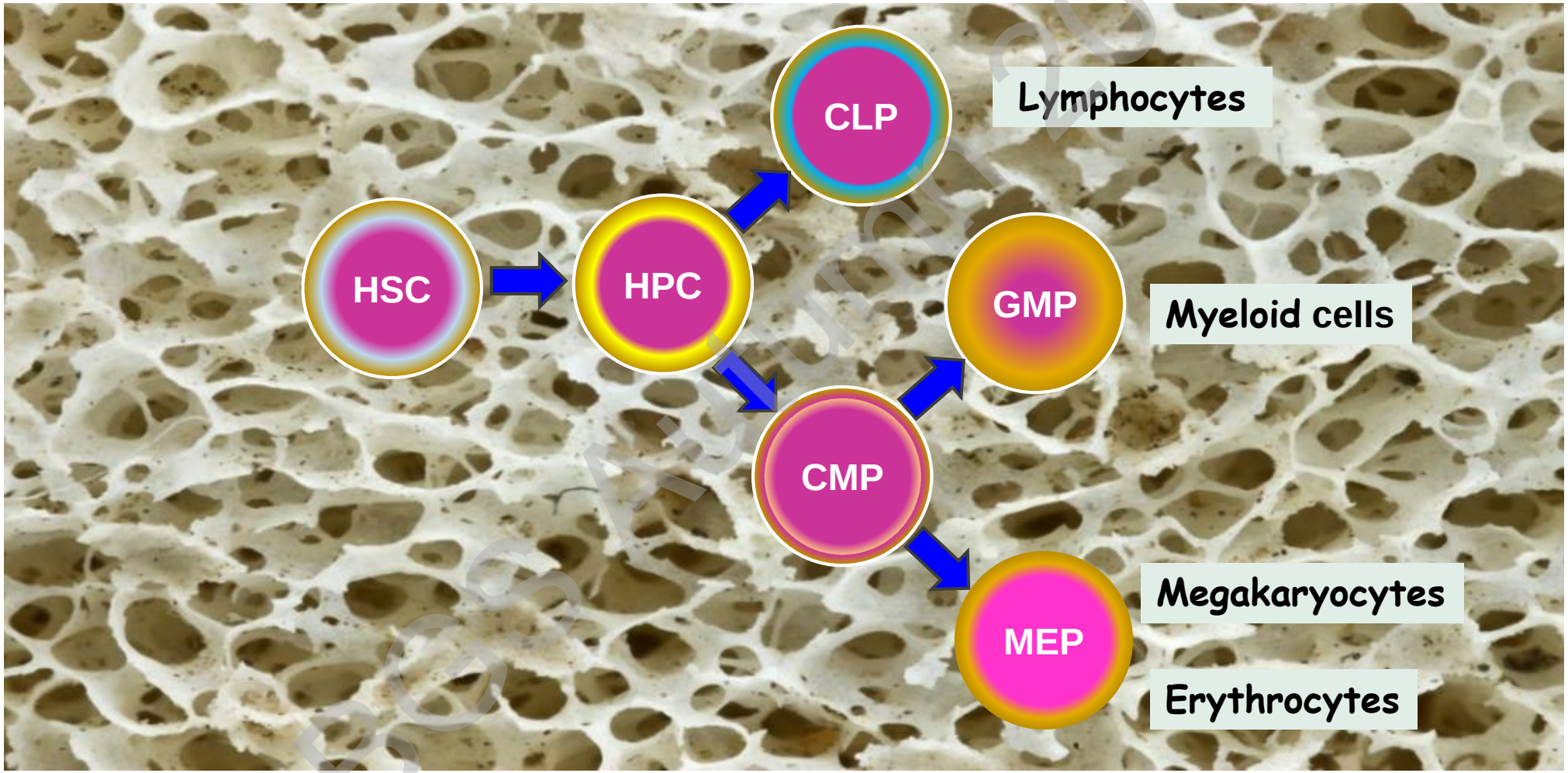
- Self-renewing capacity
- Multi-lineage differentiation capacity

- During steady-state conditions, most HSCs are quiescent and divide rarely.

- Daily hematopoietic production is mainly sustained by highly proliferative downstream hematopoietic progenitor cells (HPCs).

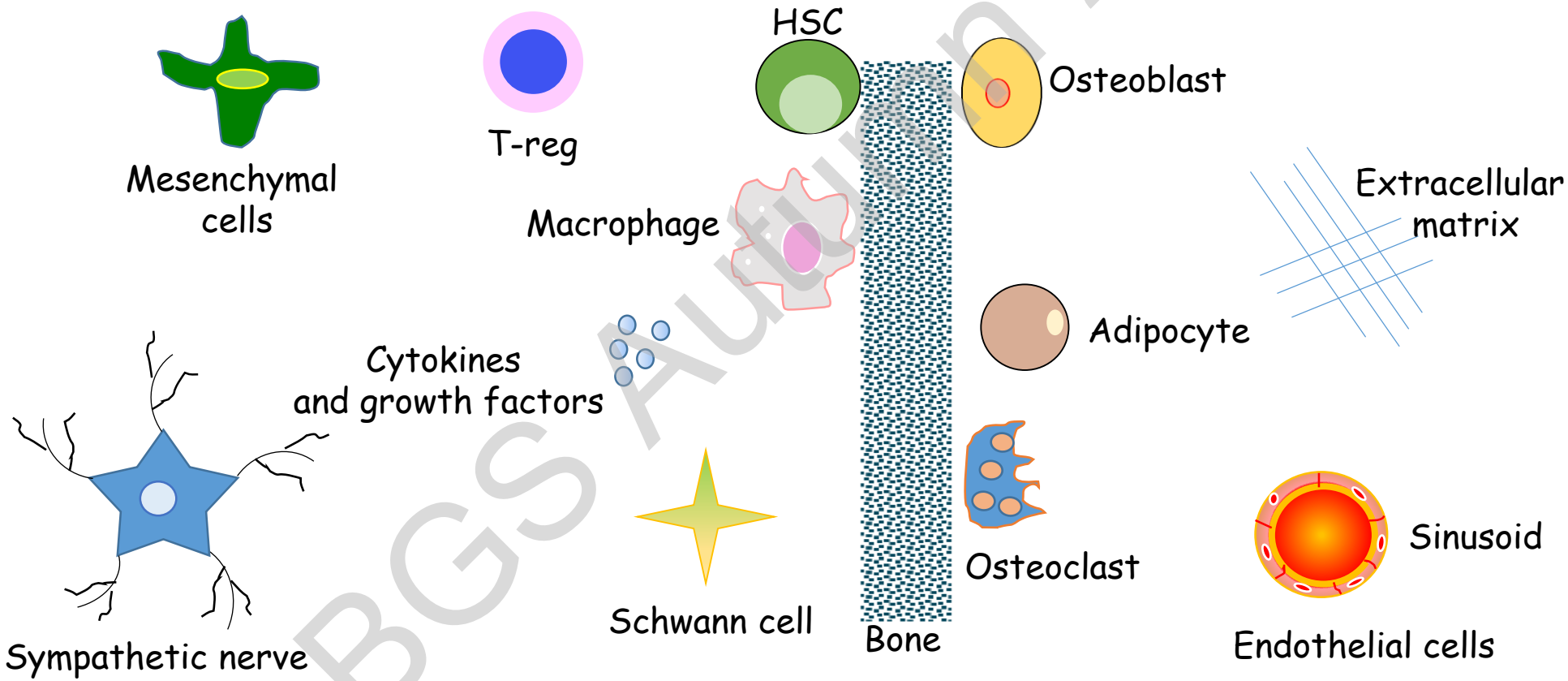
Sun J. Nature (2014) 514:322-7

Hematopoiesis



HSC, hematopoietic stem cell; **HPC** hematopoiet**i**c progenitor cell; **CLP**, common lymphoid progenitors;
CMP, common myeloid progenitor; **GMP**, granulocyte/monocyte progenitor;
MEP, megakaryocyte/erythrocyte progenitor.

The hematopoietic niche



Adapted from Nature Reviews.Immunology;Vol.13,Iss.5 (May 2013):376-89

What changes occur in the ageing Hematopoietic Stem Cell compartment?

Increased HSCs numbers and decreased regenerative potential

- Unexpectedly, the number of HSCs increase by two to tenfold with ageing.
- However, under conditions of stress, aged HSCs exhibit several functional defects including a diminished regenerative potential.
- The increase in the number of HSCs does not compensate for their loss in function, and this leads to an overall reduction in the regenerative capacity.

Geiger H. Nature Reviews Immunology 13, 376-389 (May 2013)
De Haan G. Blood 89,1543–1550 (1997)
Chambers S. Stem Cell Rev. 3, 201–211 (2007)

Skewed differentiation potential

- HSCs are a heterogeneous population of cells with distinct lineage differentiation potential:

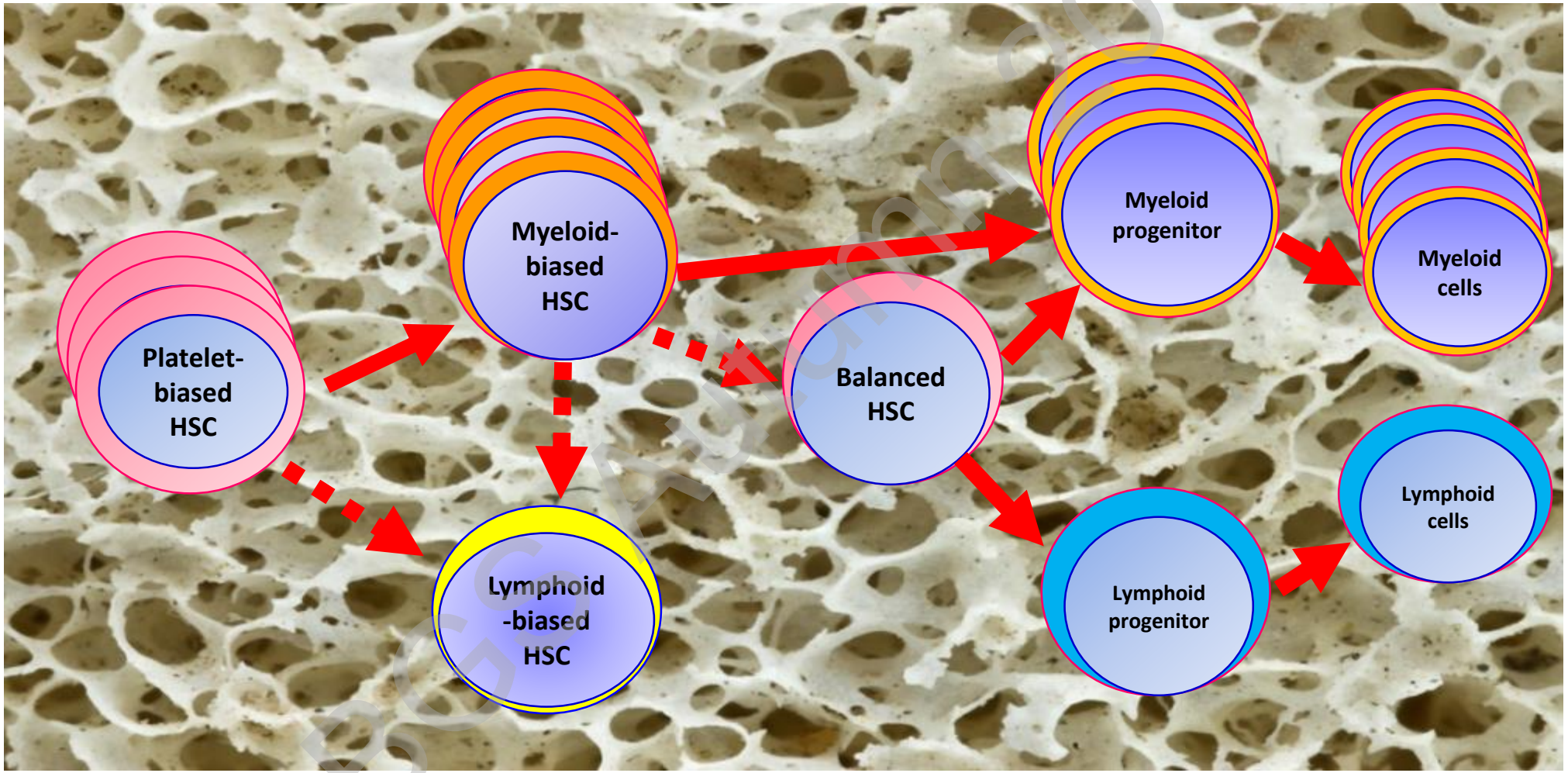
  - Myeloid-biased HSCs
  - Lymphoid-biased HSCs
  - Platelet-biased HSCs

- Functional hierarchy

- Platelet-biased HSCs appear to be to be positioned at the apex of the hematopoietic hierarchy.

Morita Y. J Exp Med (2010) 207:1173–82
Sanjuan-Pla A. Nature (2013) 502:232–6.

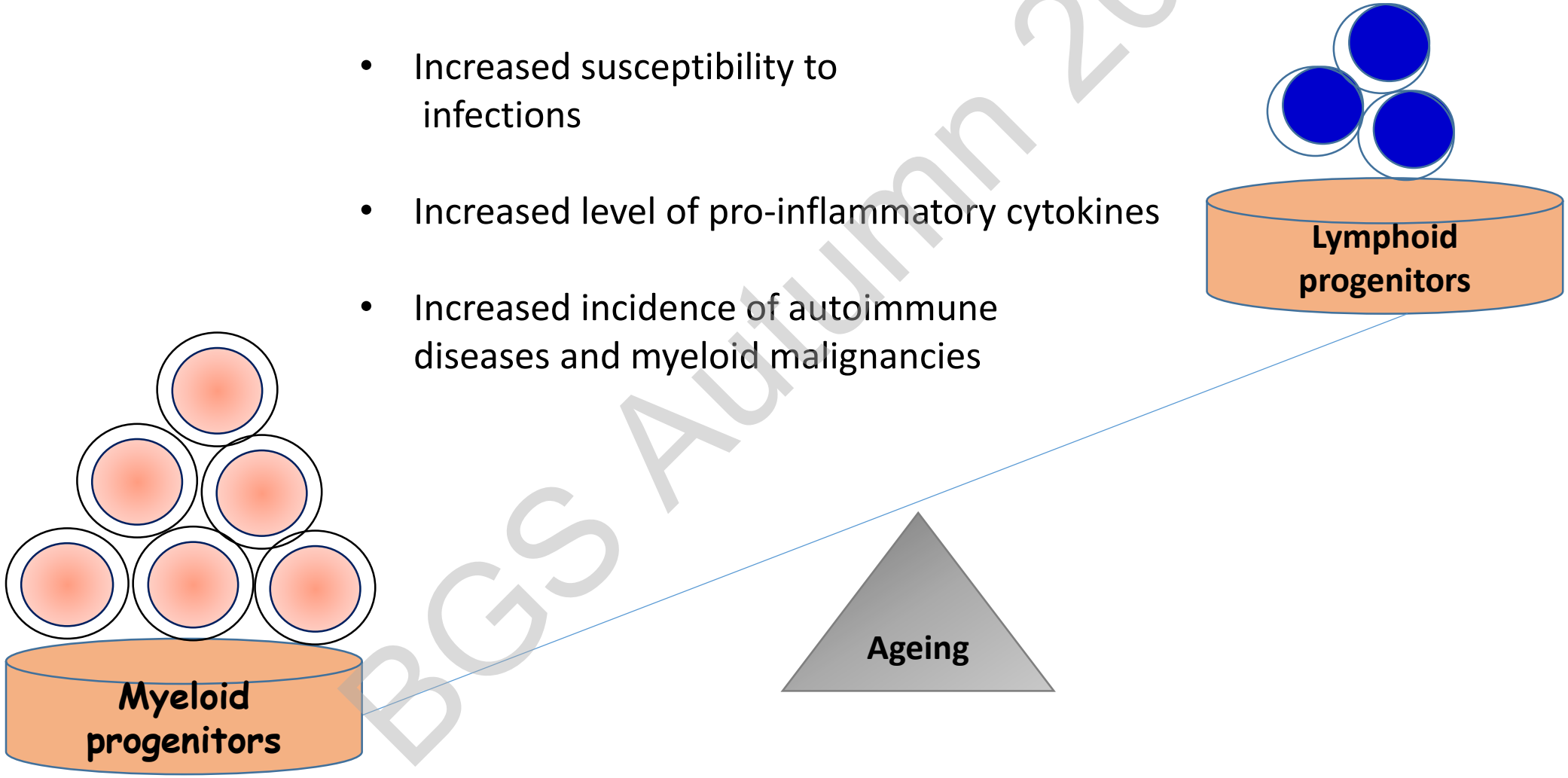
Ageing hematopoiesis



Adapted from Kovtonyuk L. Front Immunol. 2016 Nov 14;7:502

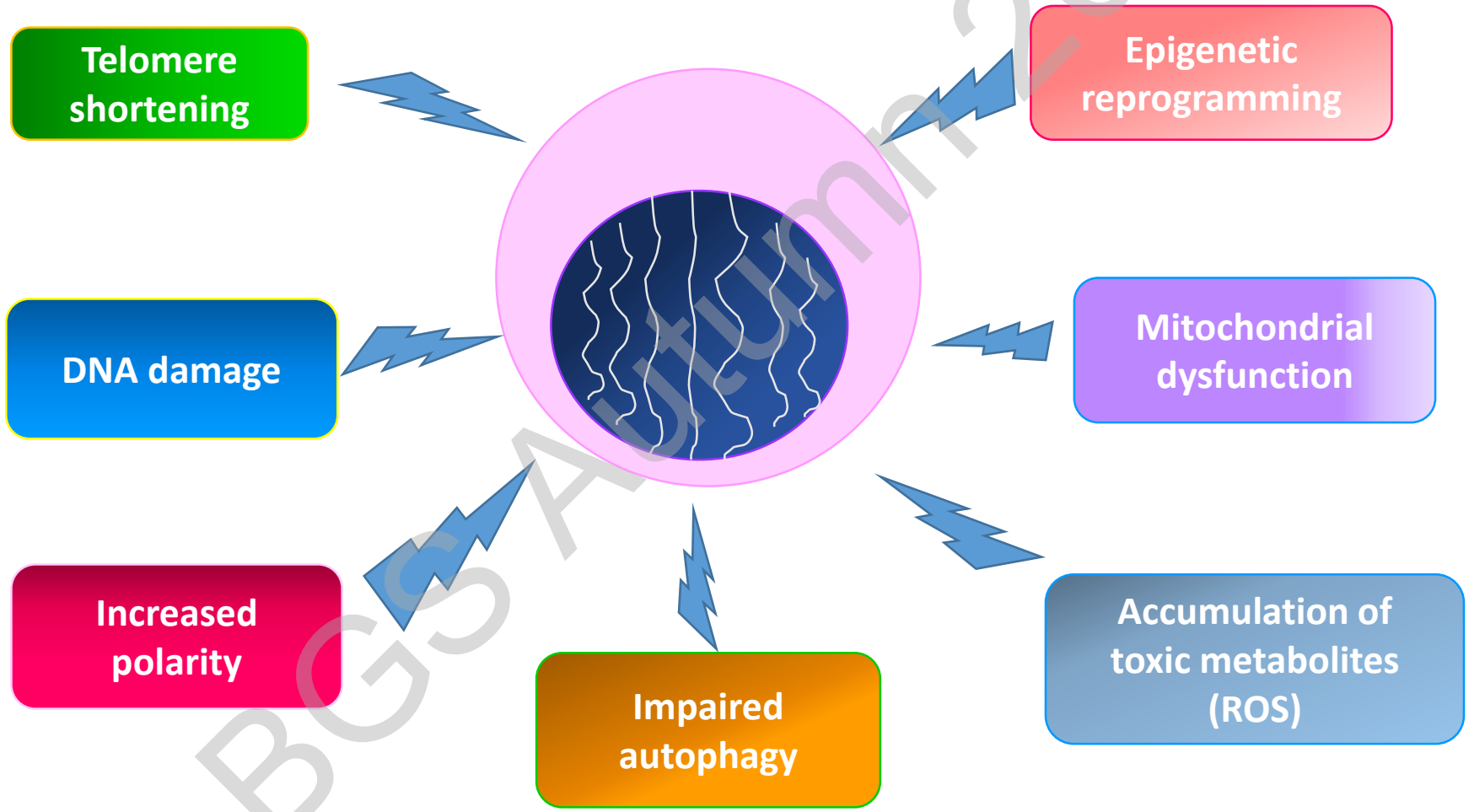
Consequences of myeloid skewing

- Increased susceptibility to infections
- Increased level of pro-inflammatory cytokines
- Increased incidence of autoimmune diseases and myeloid malignancies



Adapted from Kovtonyuk L. Front Immunol. 2016 Nov 14;7:502

Cell-intrinsic mechanisms of HSC ageing

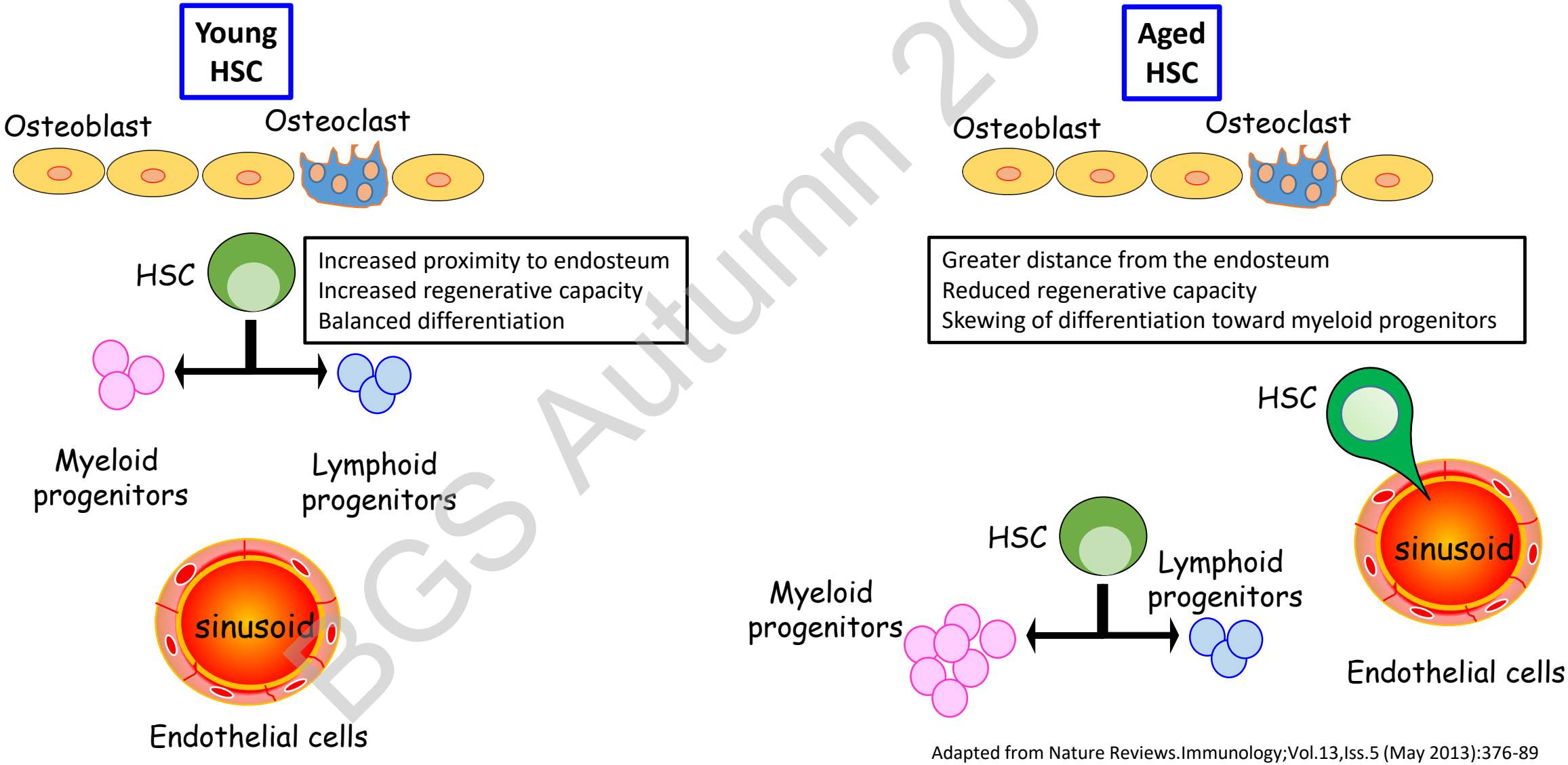


Cell-extrinsic mechanisms involved in HSC ageing

The hematopoietic niche undergoes several changes with ageing:

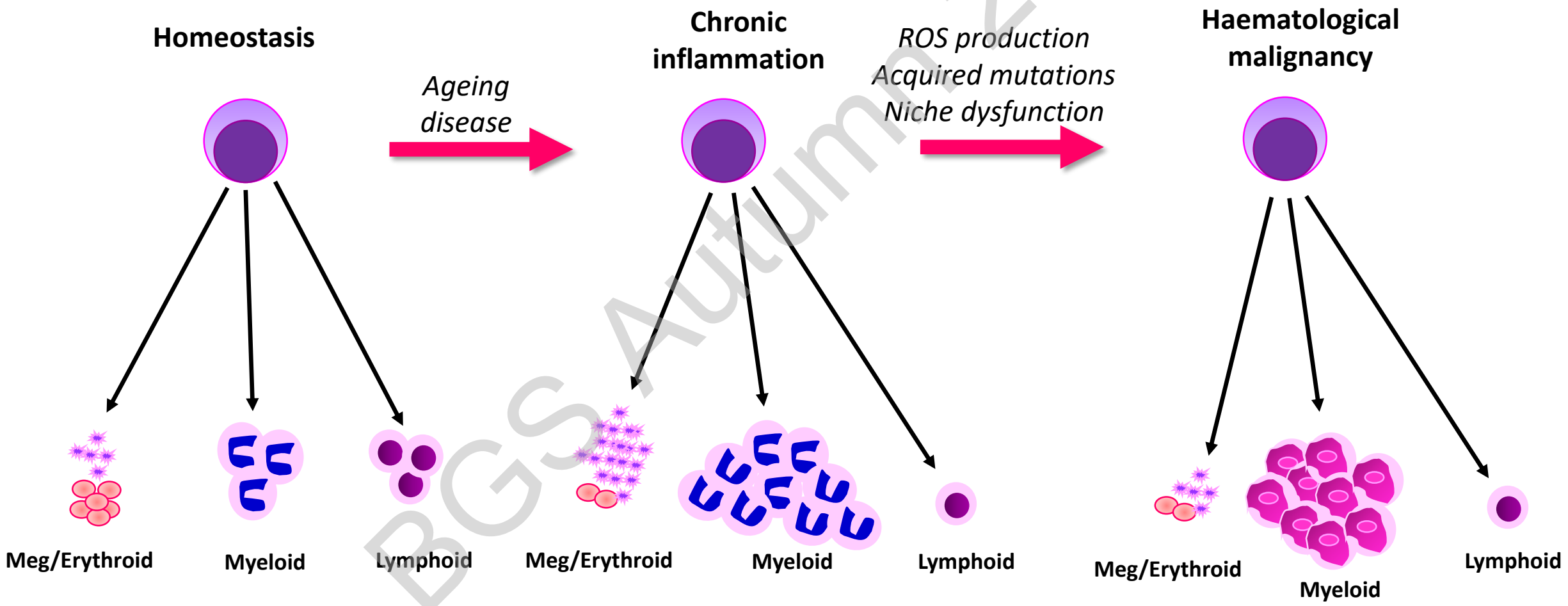
- The number of osteoblasts decreases.
- The number of adipocytes increases.
- The composition of the extracellular matrix changes.
- Increased ROS levels and activation of MAPK signalling pathway.
- Increased levels of cytokines such as CCL5.

Changes in HSCs upon ageing



Adapted from Nature Reviews.Immunology;Vol.13,Iss.5 (May 2013):376-89

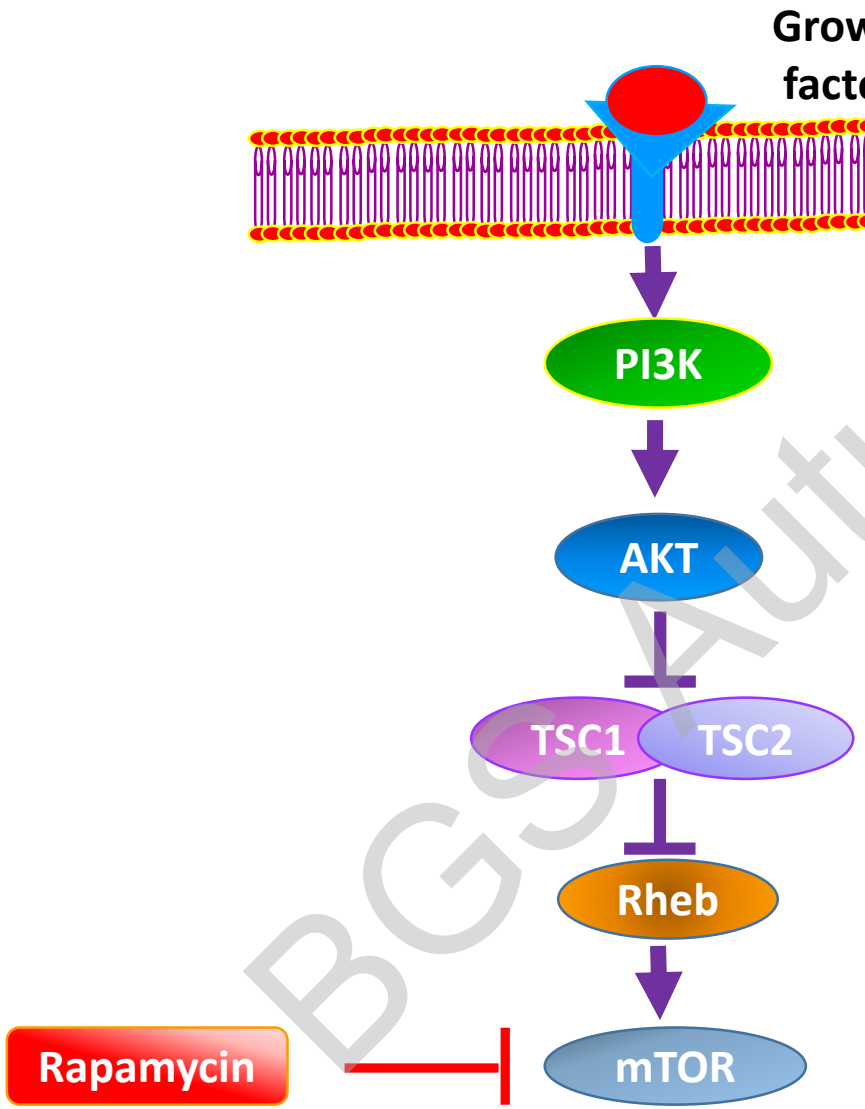
Links between inflammation, ageing and cancer



Adapted from Pietras E. M. Blood 2017 130:1693-1698

Can we reverse HSC ageing?

mTOR is a key regulator of HSC ageing



- Protein synthesis and cell growth
- Cell cycle progression/proliferation
- Inhibition of apoptosis/cell survival

Effects of mTOR inhibition on aged HSCs

- mTOR activity is increased in HSCs from old mice compared to those from young mice.
- Inhibition of mTOR by Rapamycin rescues HSC function in aged mice.
- Inhibition of mTOR by Rapamycin increases life span in mice.
- Inhibition of mTOR stimulates immune function in aged mice.

Chen C. Sci Signal. 2009 Nov 24;2(98):ra75

CDC42 activity and HSC ageing

- Cdc42 belongs to the family of small Rho-GTPase and cycles between an active (GTP-bound) and an inactive (GDP-bound) state.
- Cdc42 is known to regulate actin and tubulin organization, cell-cell and cell-extracellular matrix adhesion and cell-polarity in distinct cell types.
- Constitutively increased Cdc42 activity results in ageing of young HSCs.
- Inhibition of Cdc42 is able to reverse most of the aged HSCs phenotypes.

Florian MC. Cell Stem Cell. 2012 May 4; 10(5): 520–530.

Conclusions

- Our knowledge on HSC ageing has greatly increased in the last decade.
- HSC ageing appears to be driven by both intrinsic and extrinsic factors.
- Studies conducted on murine models have shown that at least some aspects of HSC aging can be reversed.
- Further studies are required to identify key regulators of human HSC ageing to eventually design appropriate rejuvenation approaches.

Thank you for your attention