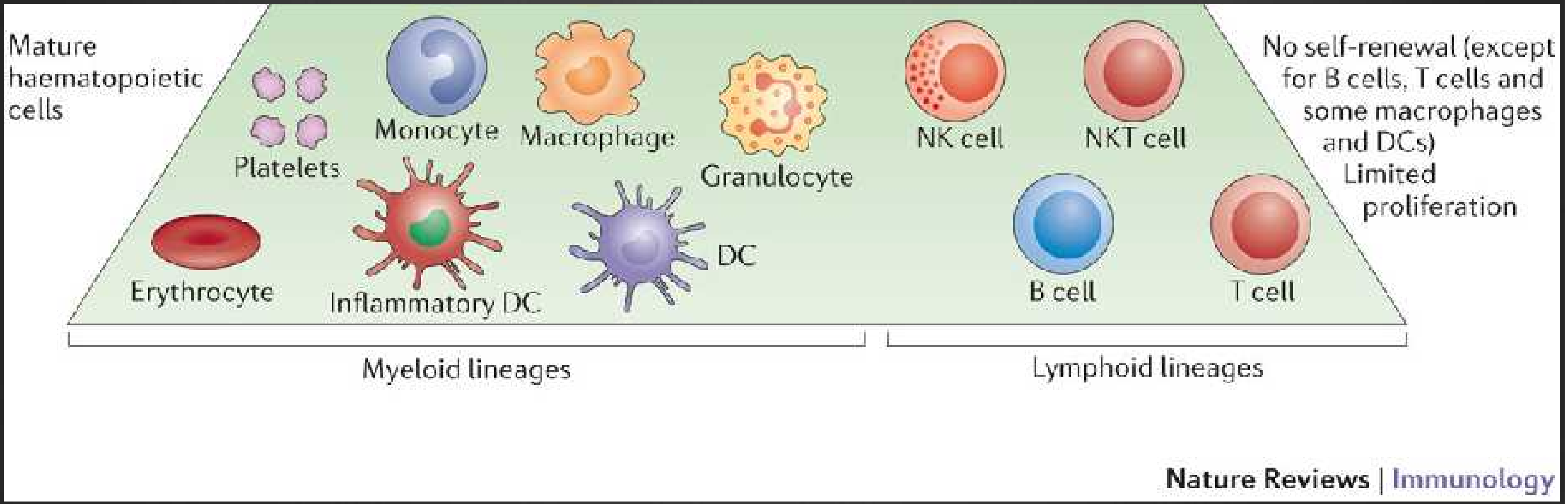
Συμμετοχή μυελού των οστών σε φλεγμονώδεις απαντήσεις

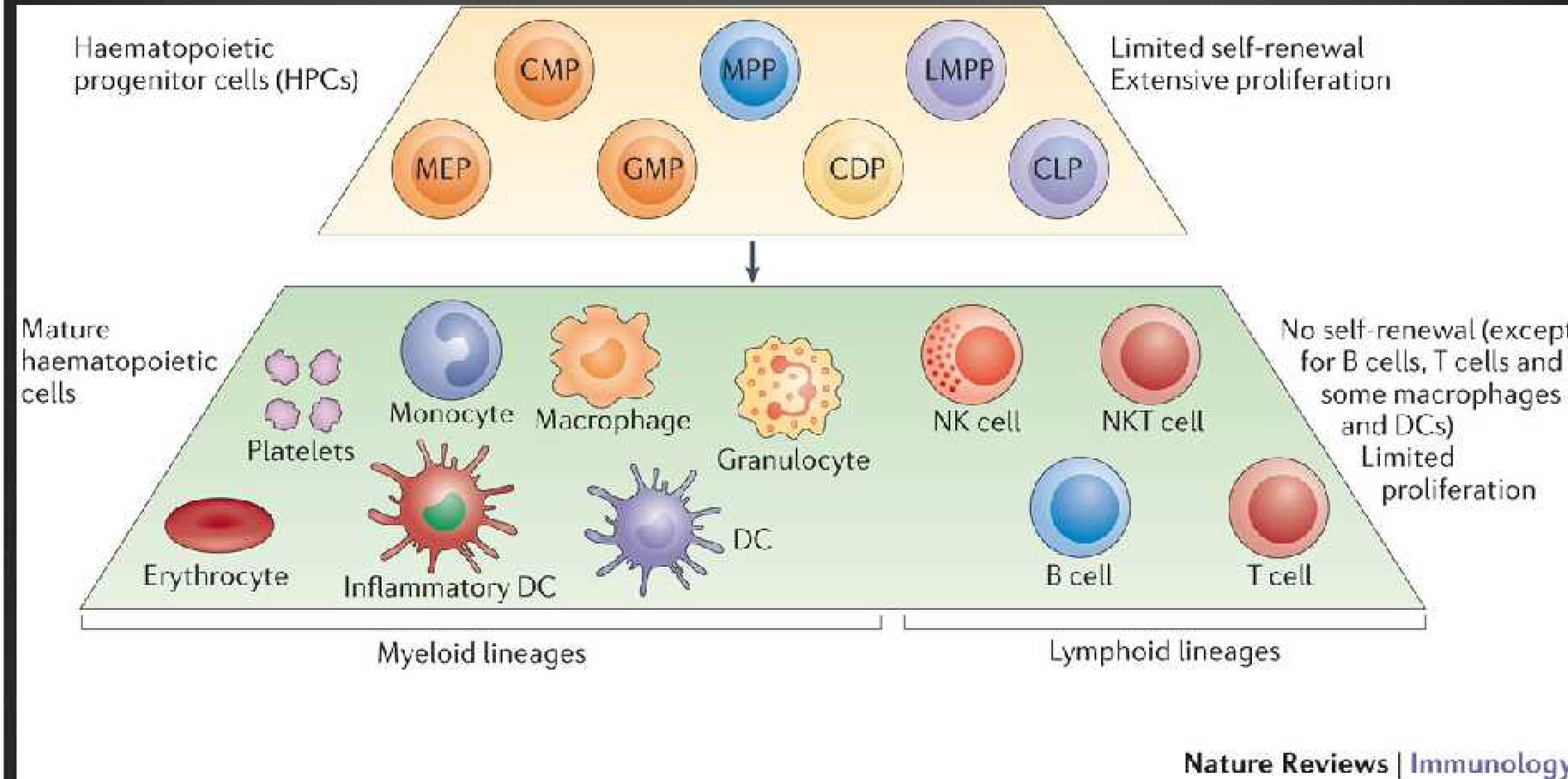
Ιωάννης Μητρούλης
Επικ. Καθ. Παθολογίας ΔΠΘ

HSCs at the top of immune system



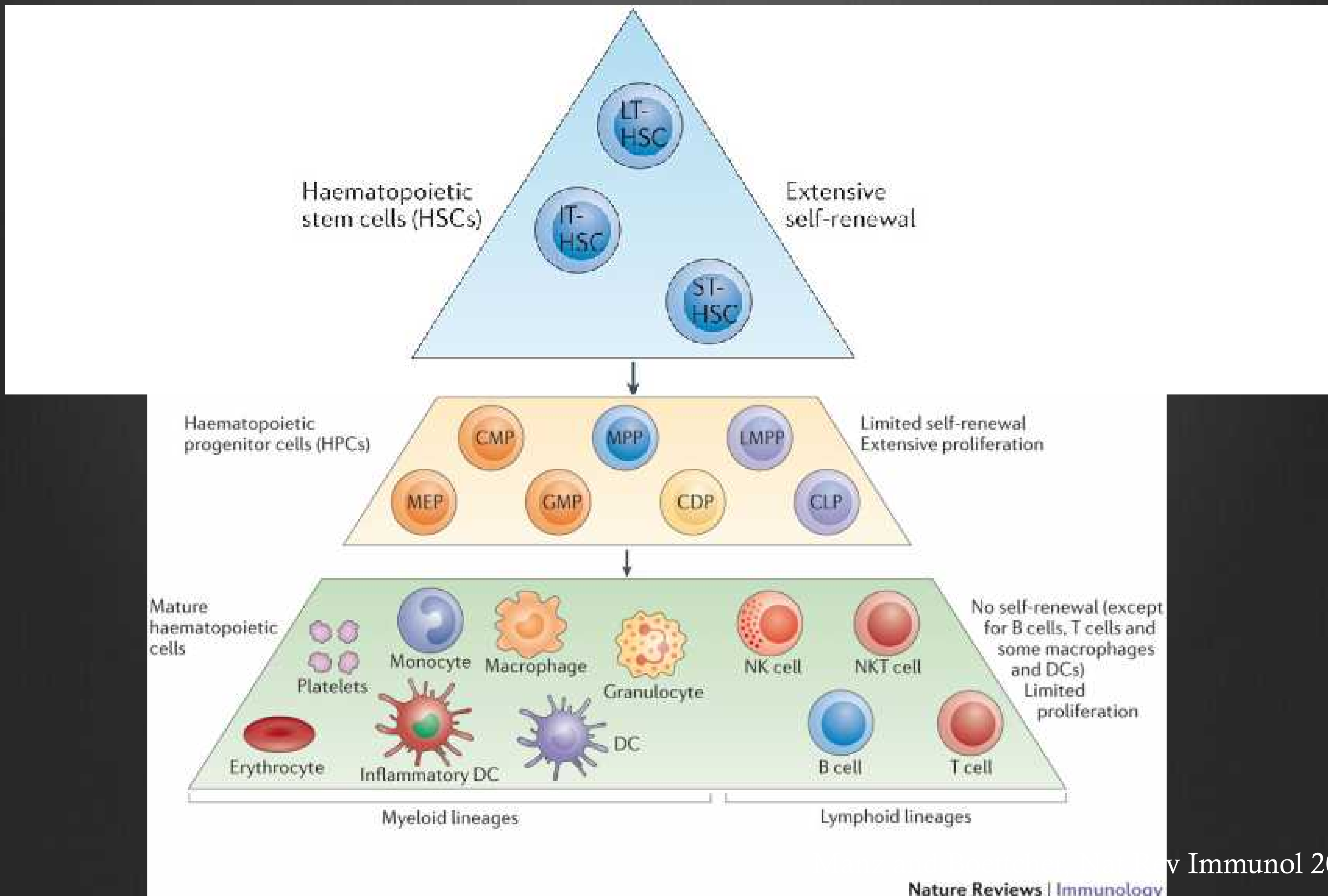
Manz and Boettcher, Nat Rev Immunol 2014

HSCs at the top of immune system



Manz and Boettcher, Nat Rev Immunol 2014

HSCs at the top of immune system



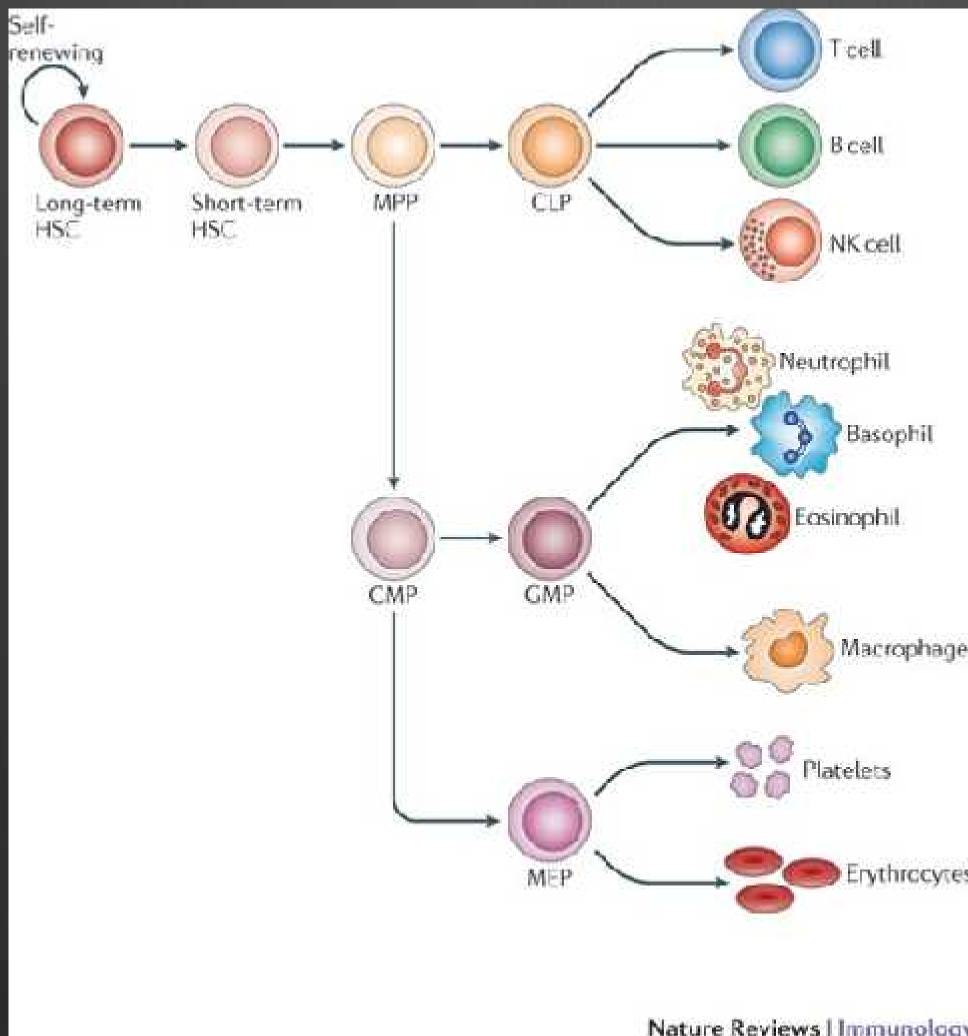
v Immunol 2014

Characteristics

- Self-renewal
- Multi-lineage differentiation

Designation	Differentiation potential implied by designation	Examples of Stem/Progenitors with these Properties
Toti-potent	All embryonic and extraembryonic tissues	zygote
Pluri-potent	All embryonic tissues	ICM, ES cell, iPS cell
Multi-potent	All lineages of a tissue/organ	HSC, NSC
Oligo-potent	Several but not all lineages of a tissue/organ	CMP, CLP
Uni-potent	Single lineage of a tissue/organ	Macrophage progenitor

HSC lineage differentiation

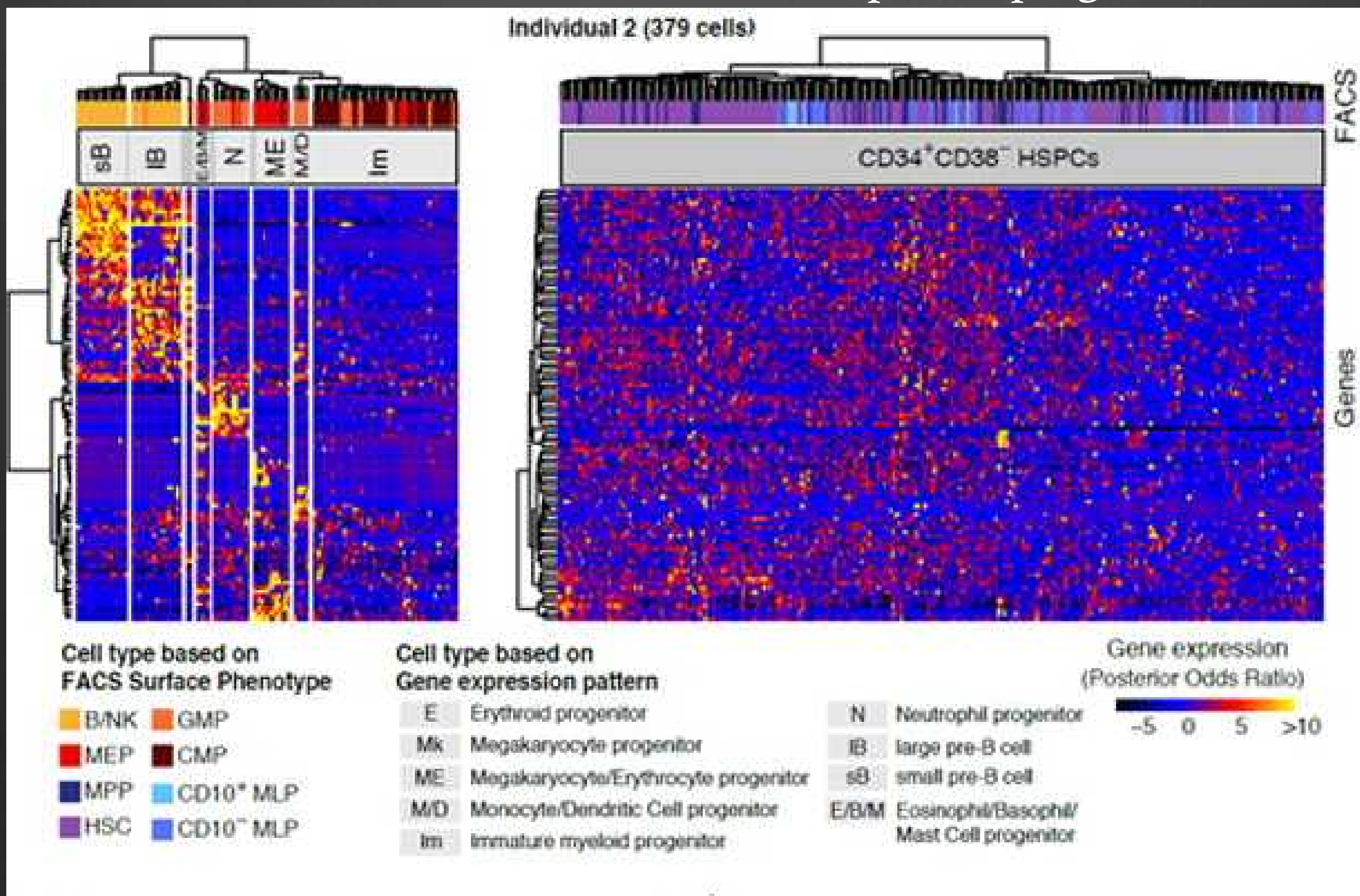


King KY and Goodell MA, Nature Reviews Immunology, 2014

Transcriptional regulation of cell commitment in human CD34+ cells

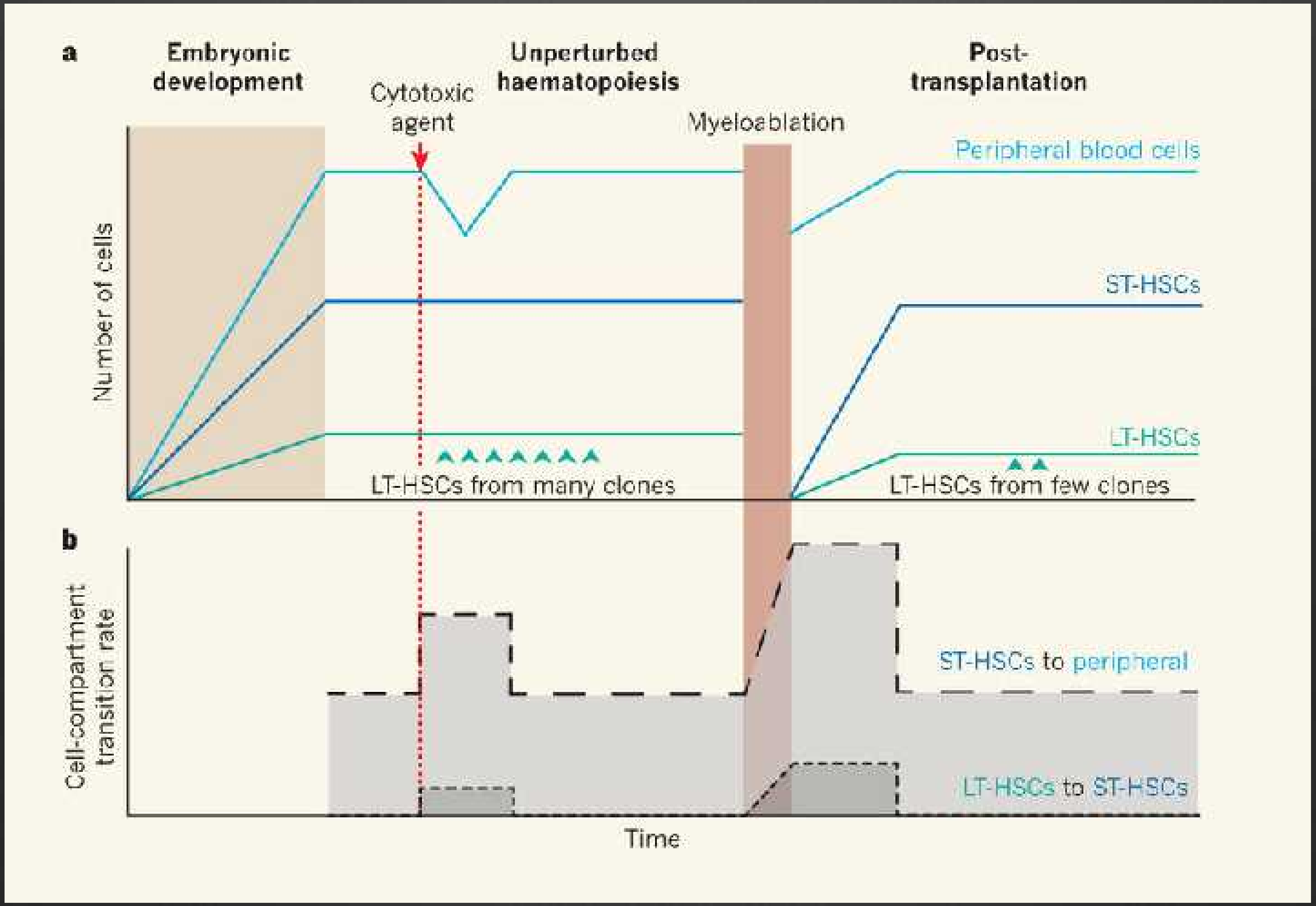
Myeloid progenitors

Hematopoietic progenitors



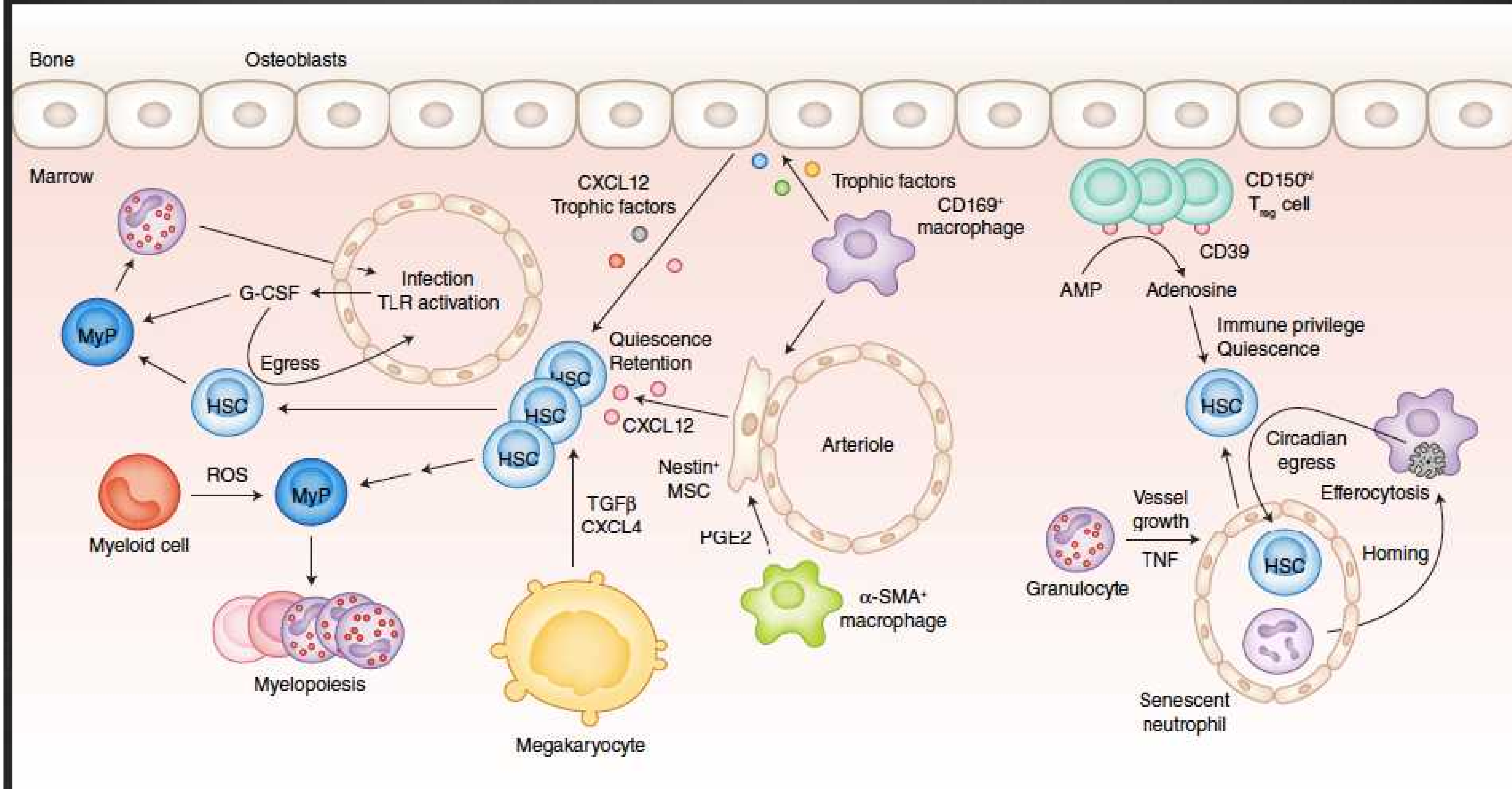
Velten et al, Nat Cell Biol, 2017

HSC in steady state vs stress hematopoiesis



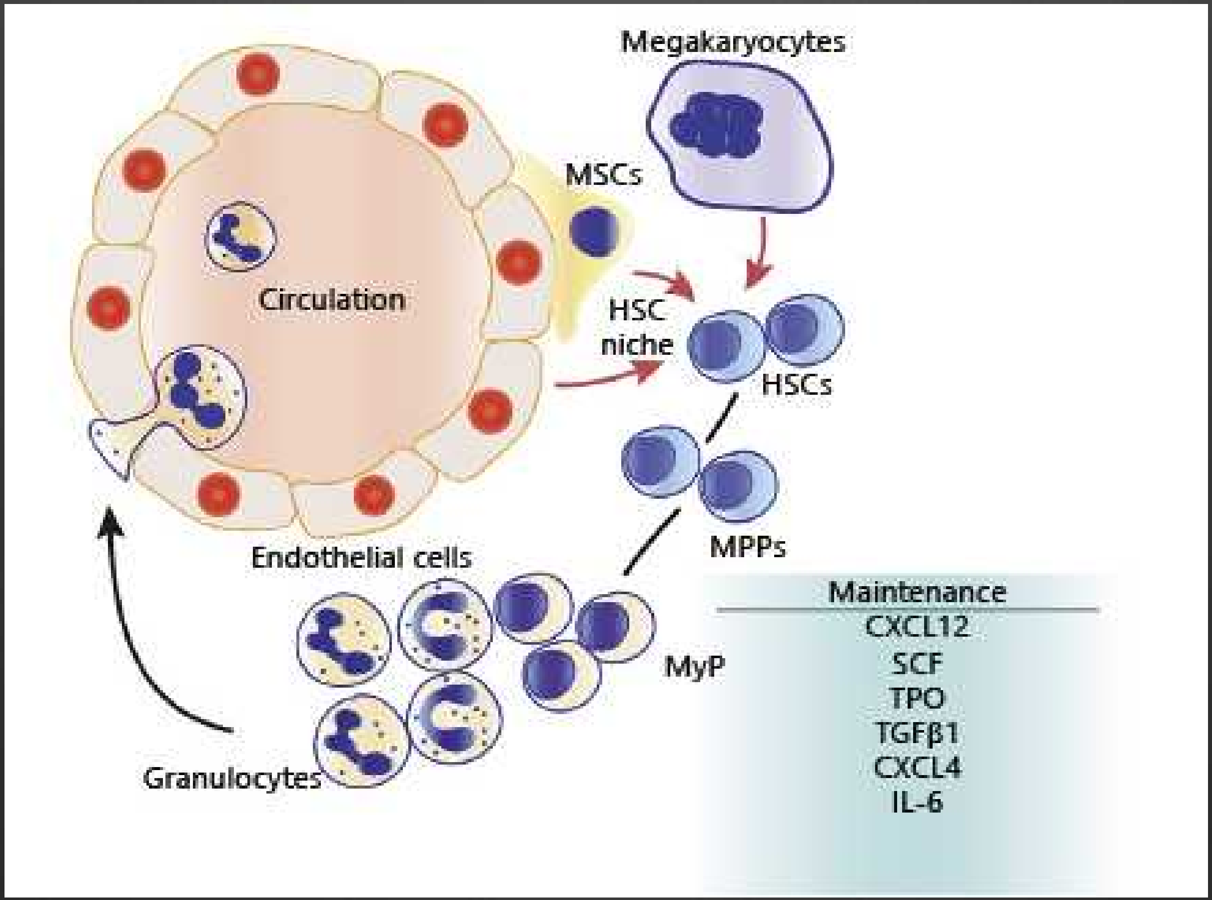
Busch et al, Nature 2014

The adult bone marrow HSC niche.



Chavakis, Mitroulis, Hajishengallis, Nat Immunol, 2019

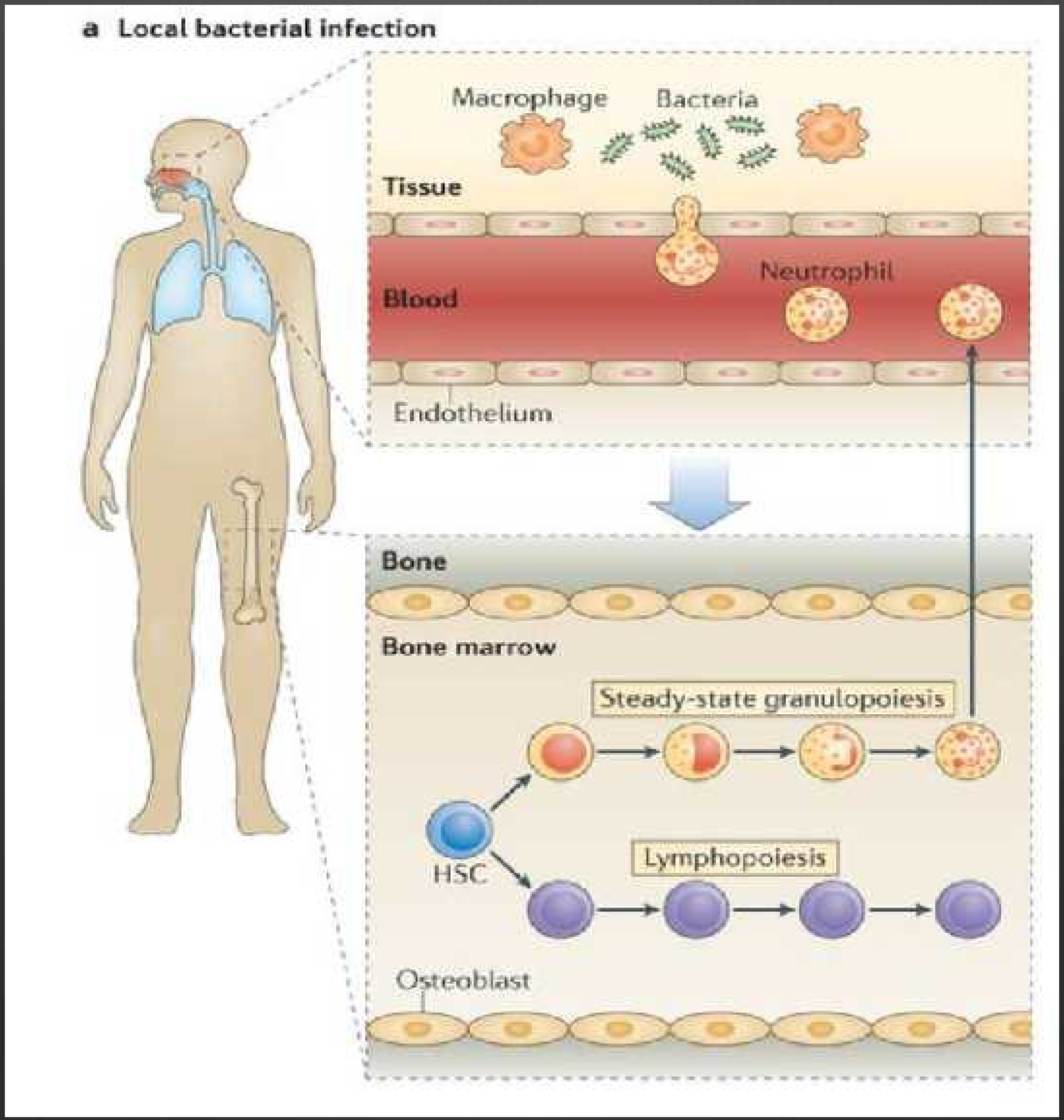
Regulation of steady state myelopoiesis



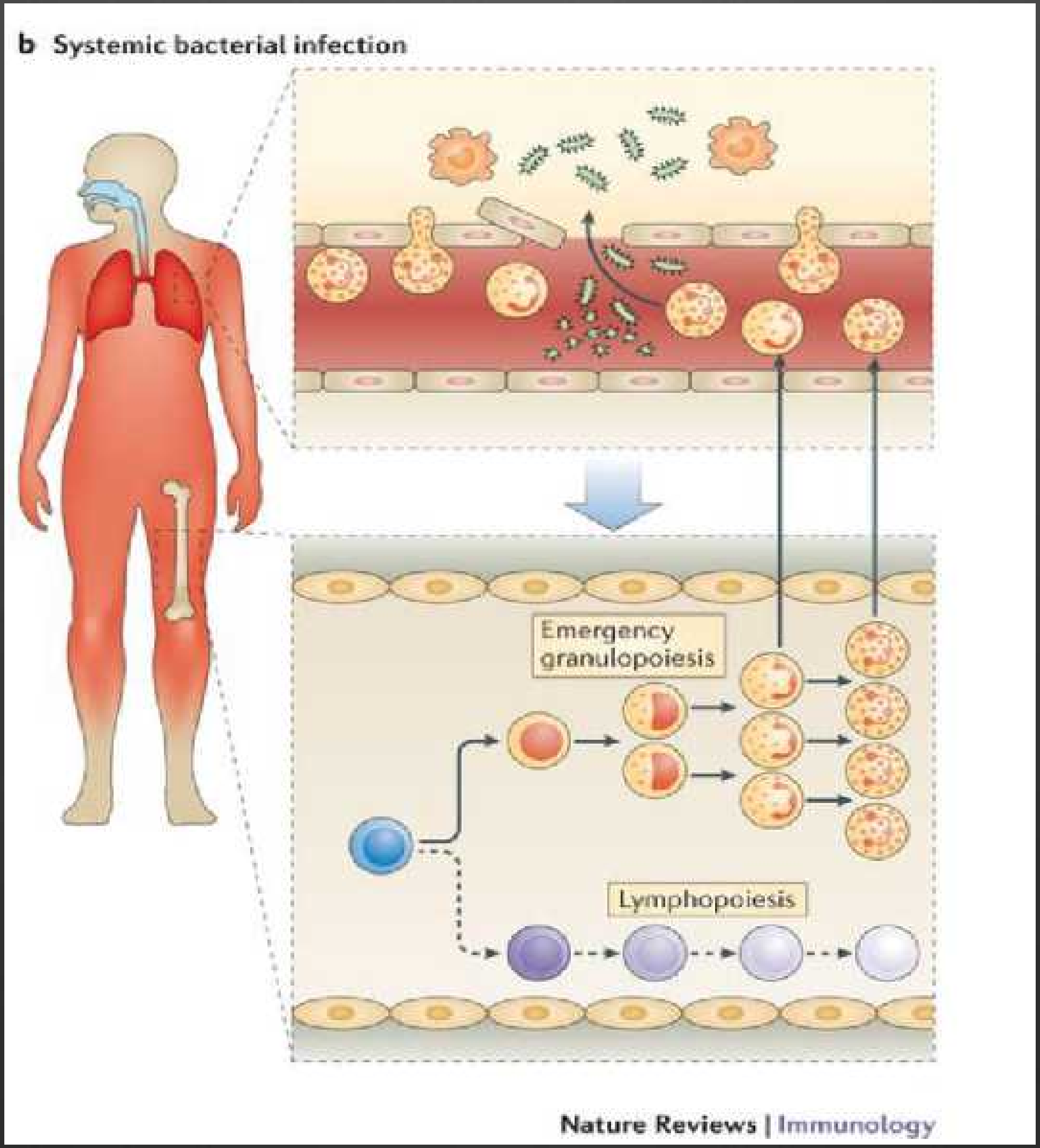
Mitroulis et al, J Innate Immunity, 2018

HSCS in acute inflammation/infection

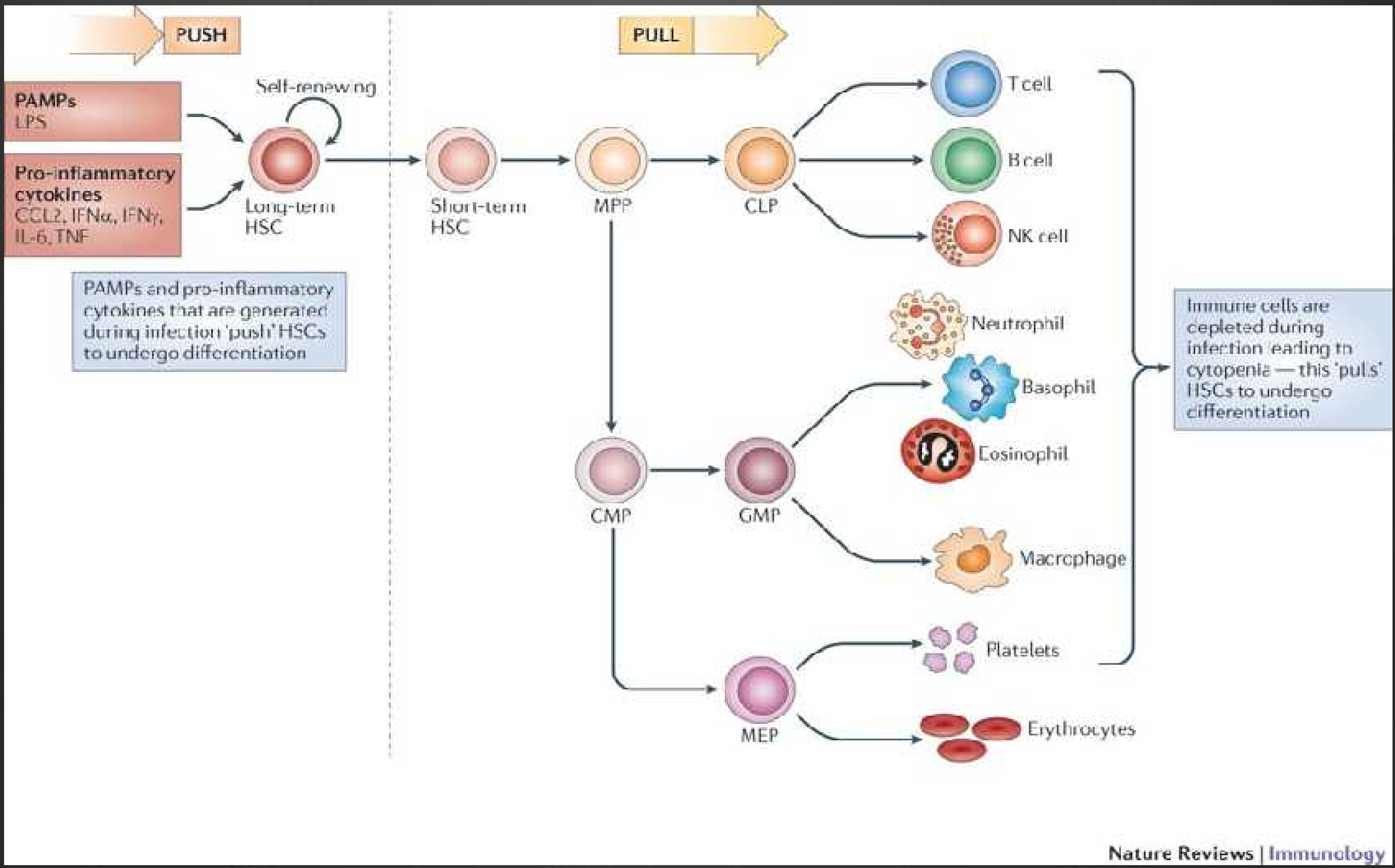
HSCs in infection



HSCs in systemic infection

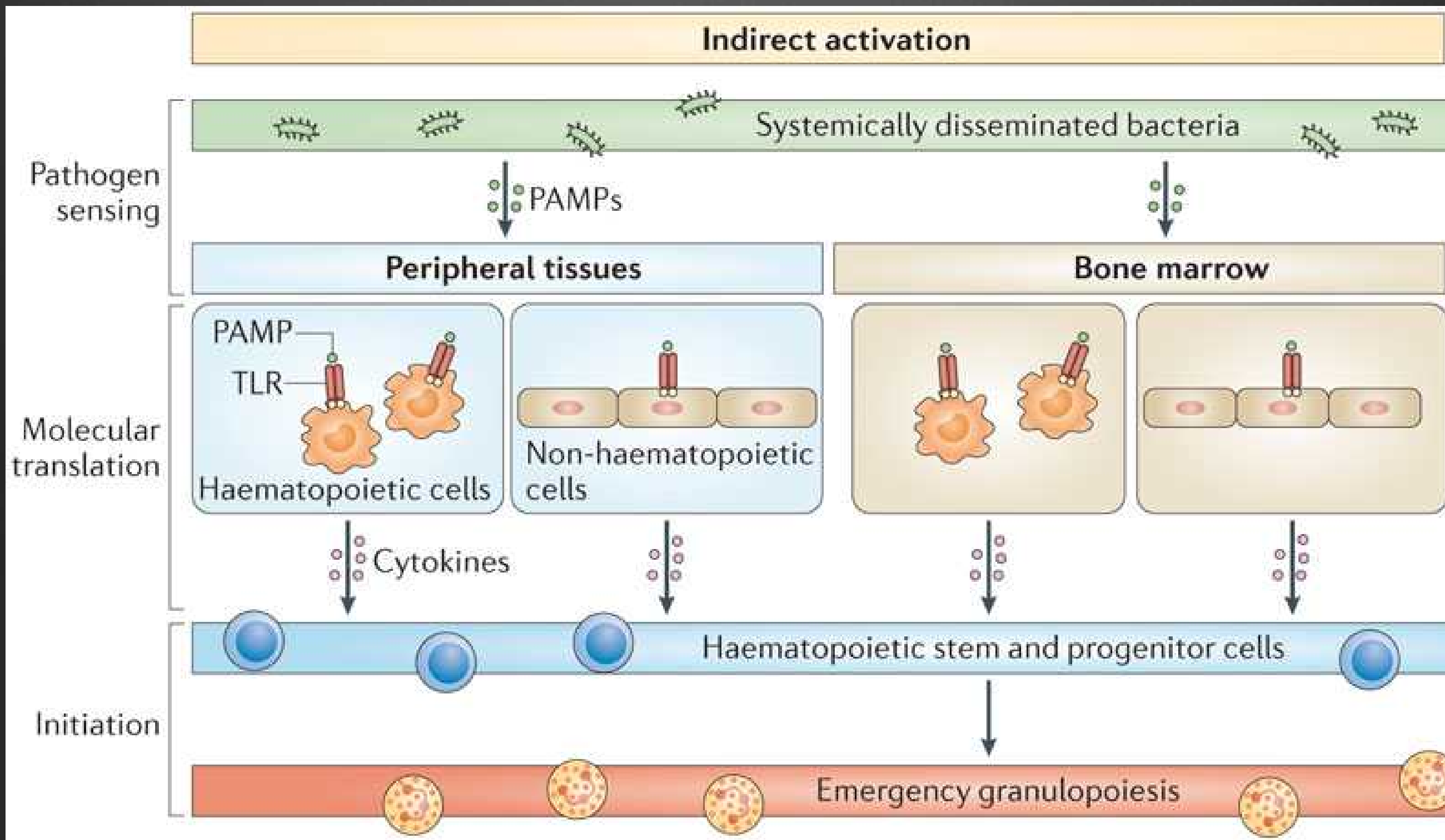


Direct activation vs depletion of mature cells



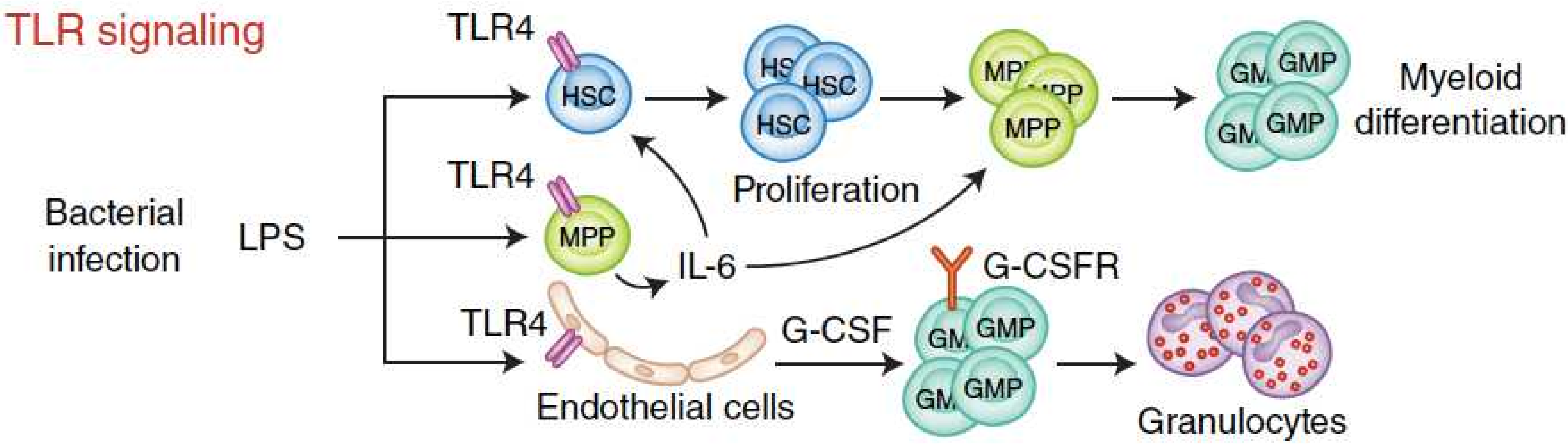
King KY, Goodell MA, Nature Reviews Immunology (2014)

HSCs in systemic infection



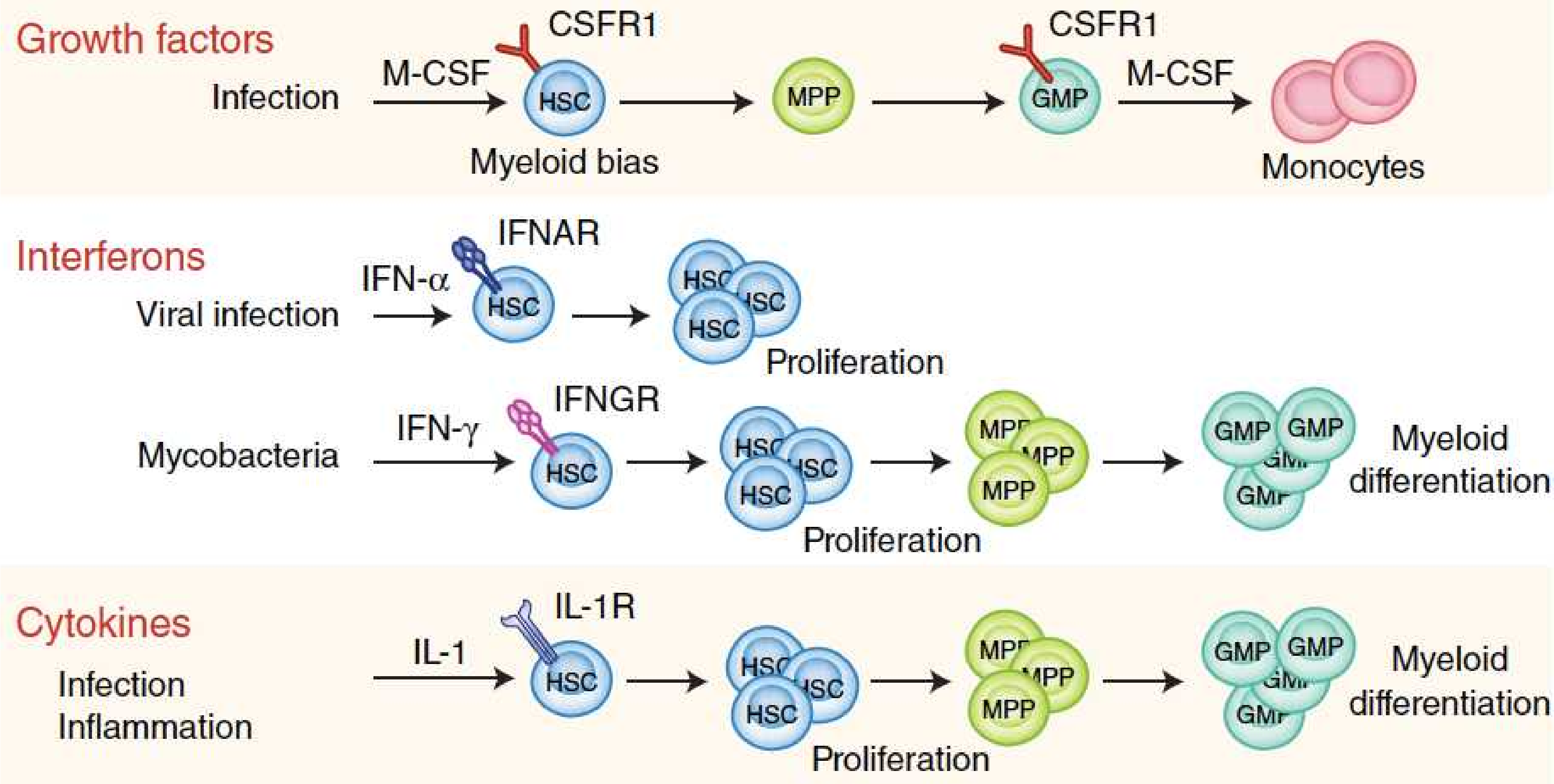
King KY and Goodell MA, Nature Reviews Immunology, 2014

Regulation of hematopoiesis by pathogen-derived signals



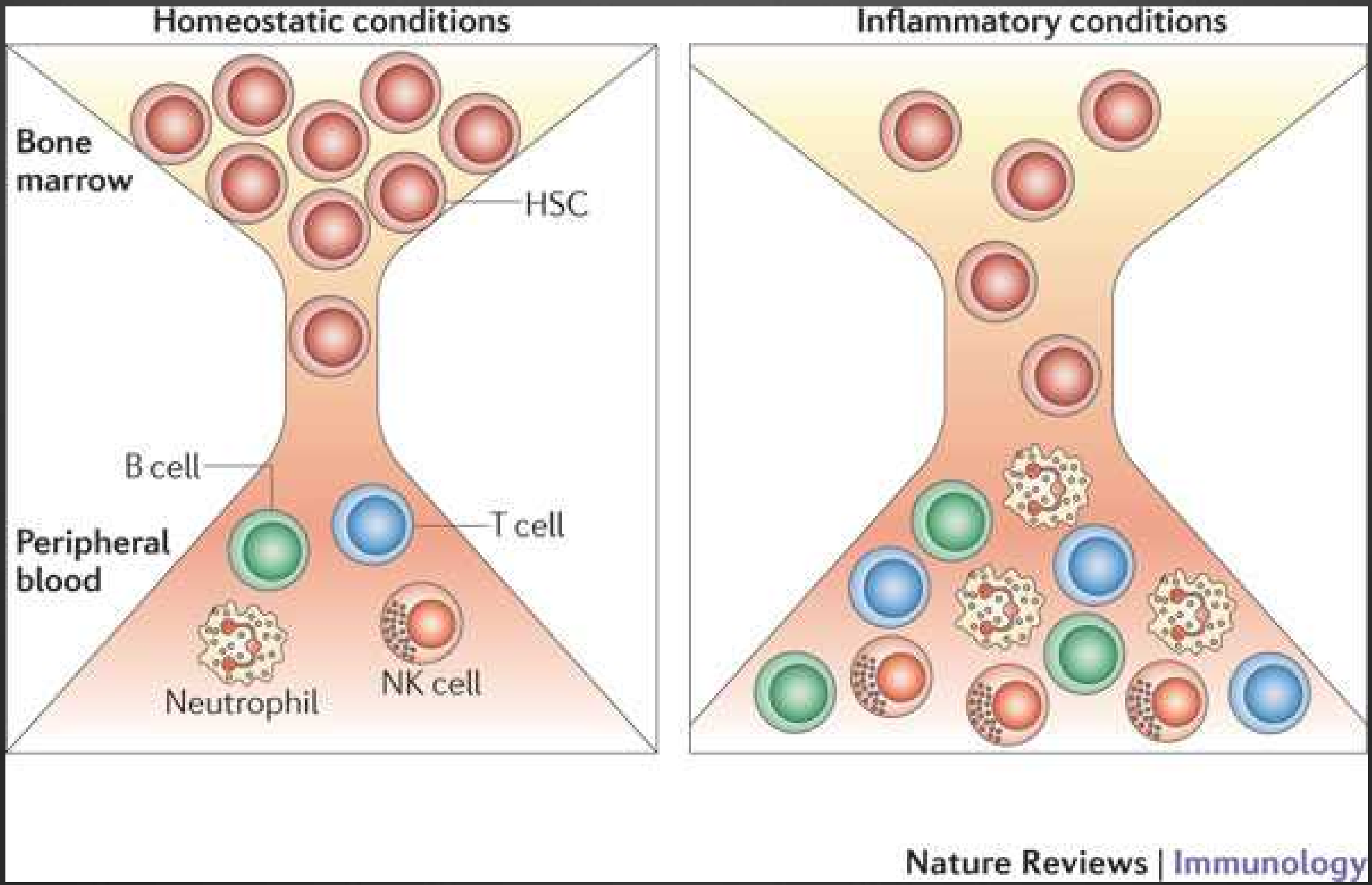
Chavakis, Mitroulis, Hajishengallis, Nat Immunol, 2019

Regulation of hematopoiesis by inflammatory signals



Chavakis, Mitroulis, Hajishengallis, Nat Immunol, 2019

HSCs attrition and inflammation

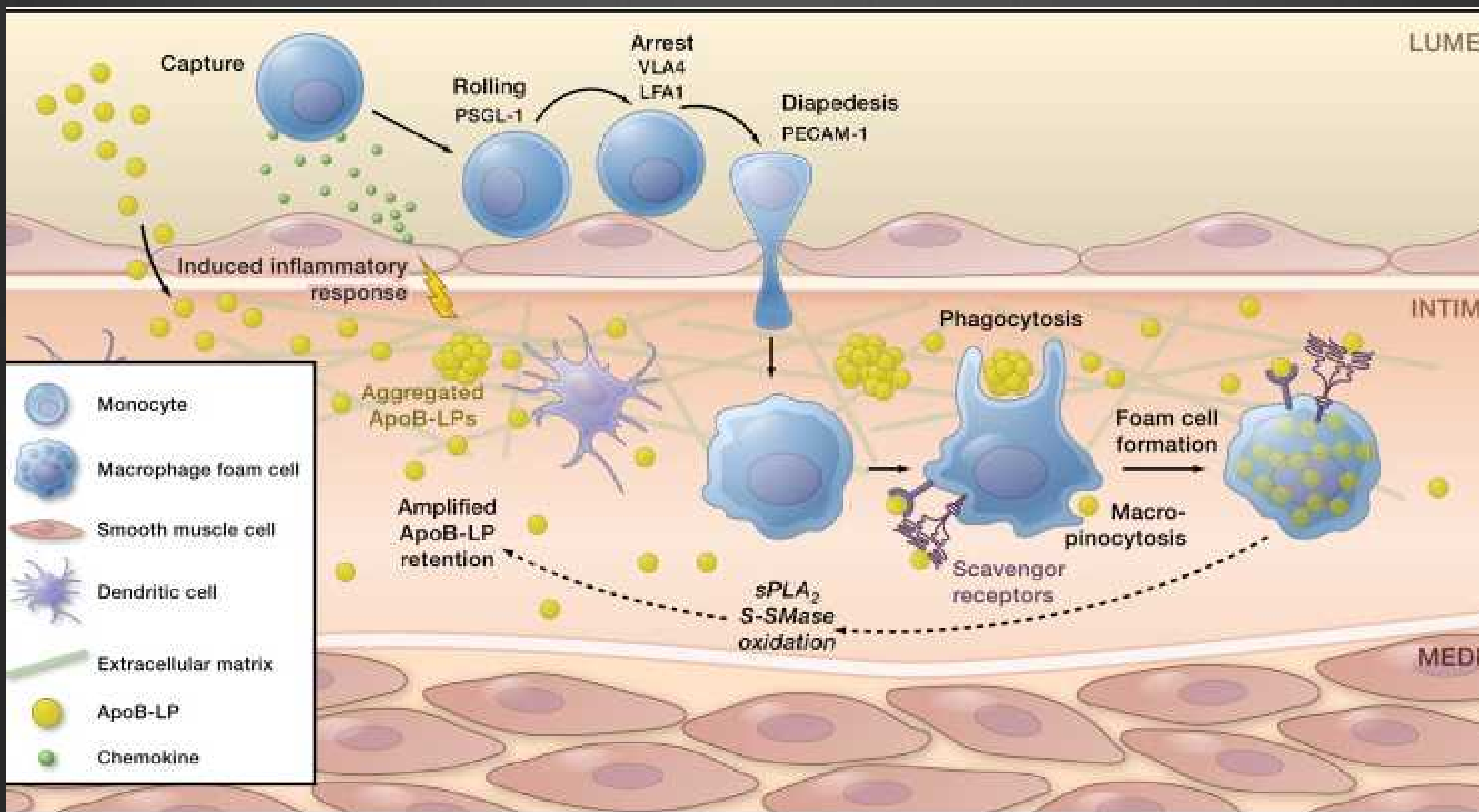


King KY and Goodell MA, Nature Reviews Immunology, 2014

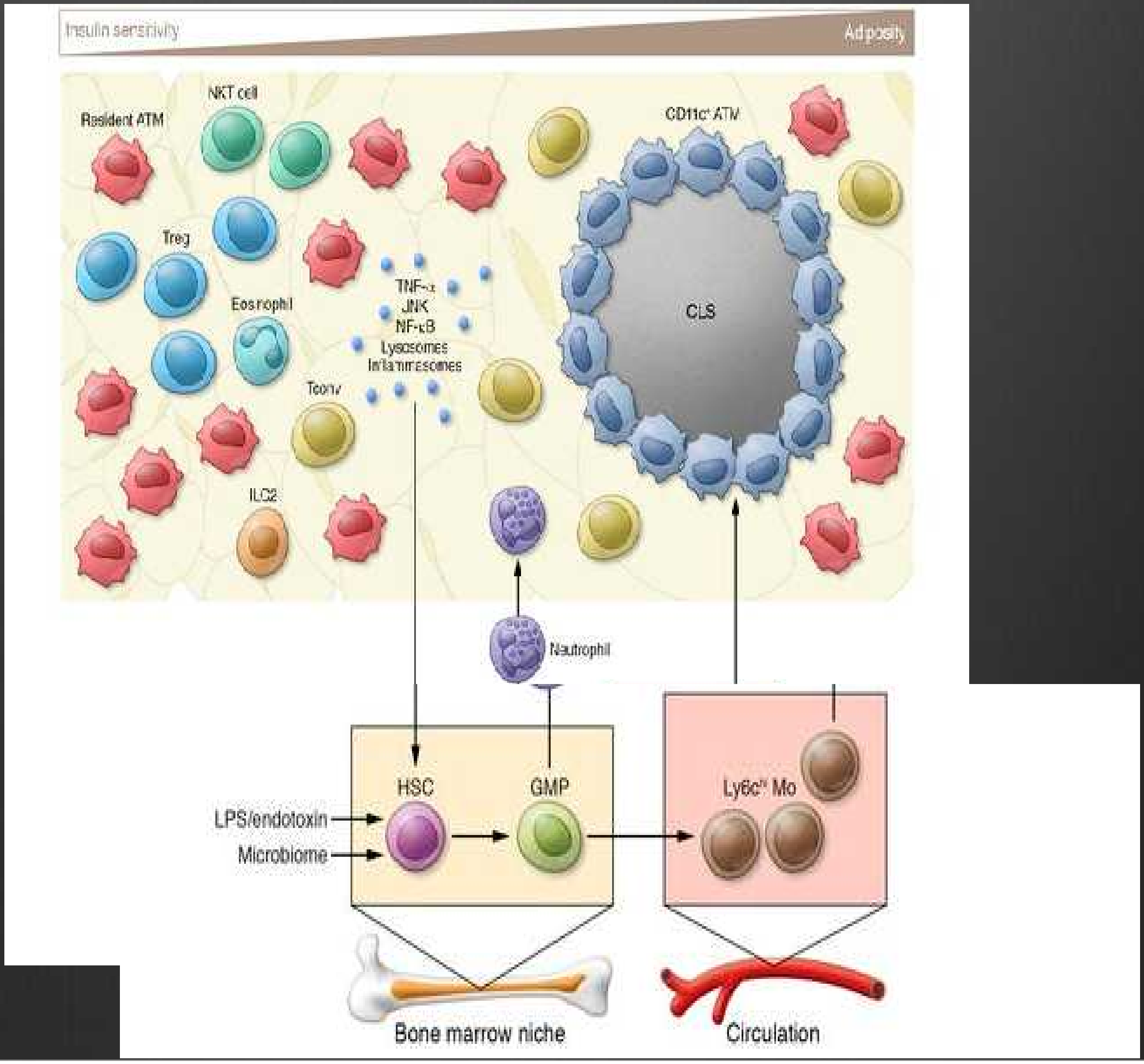
HSCs sense acute inflammation and replenish the pool of inflammatory cells

Hematopoietic progenitors and atherothrombosis

Macrophages in atherosclerosis

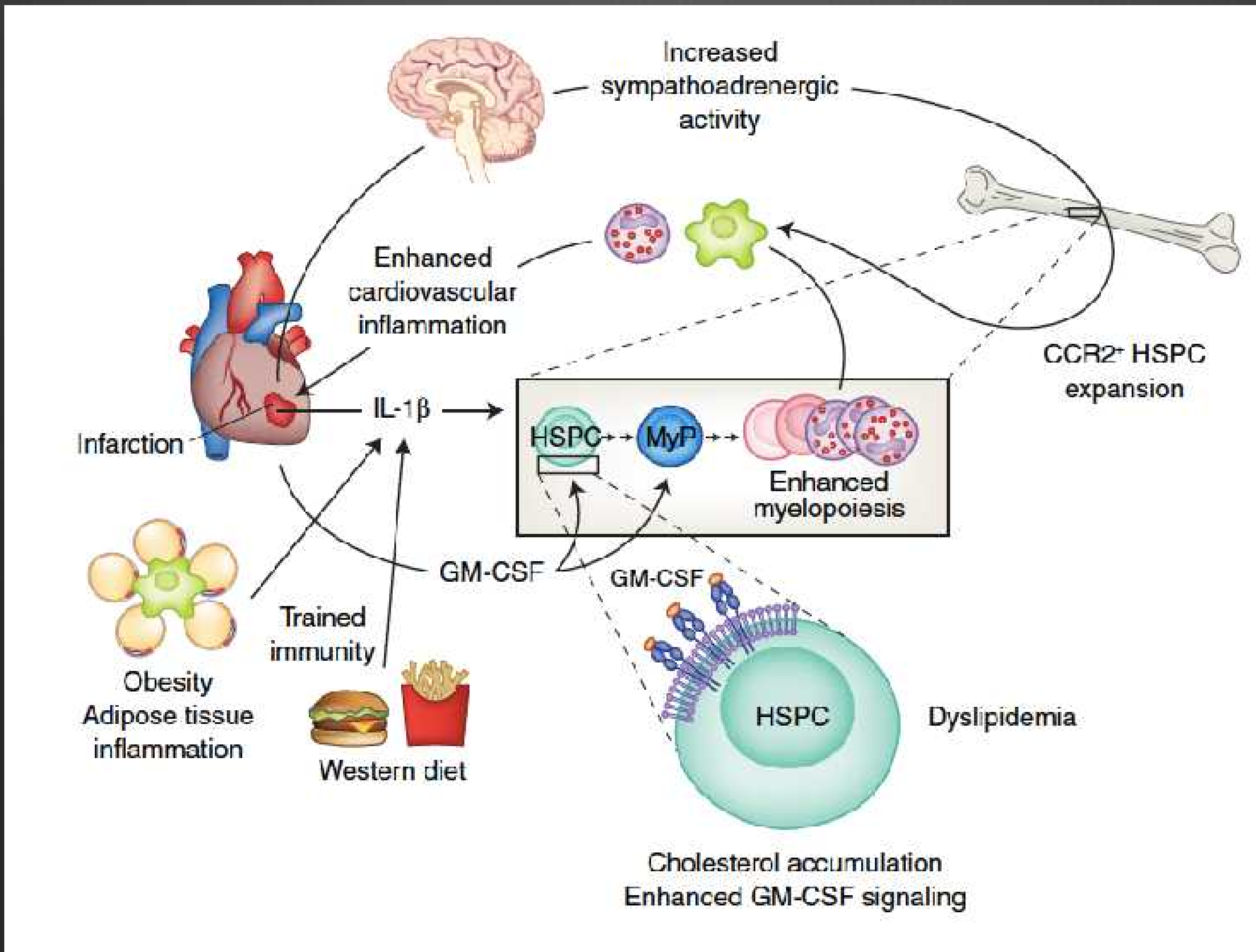


The initiation of inflammation in metabolic syndrome



J Clin Invest DOI: 10.1172/JCI88882

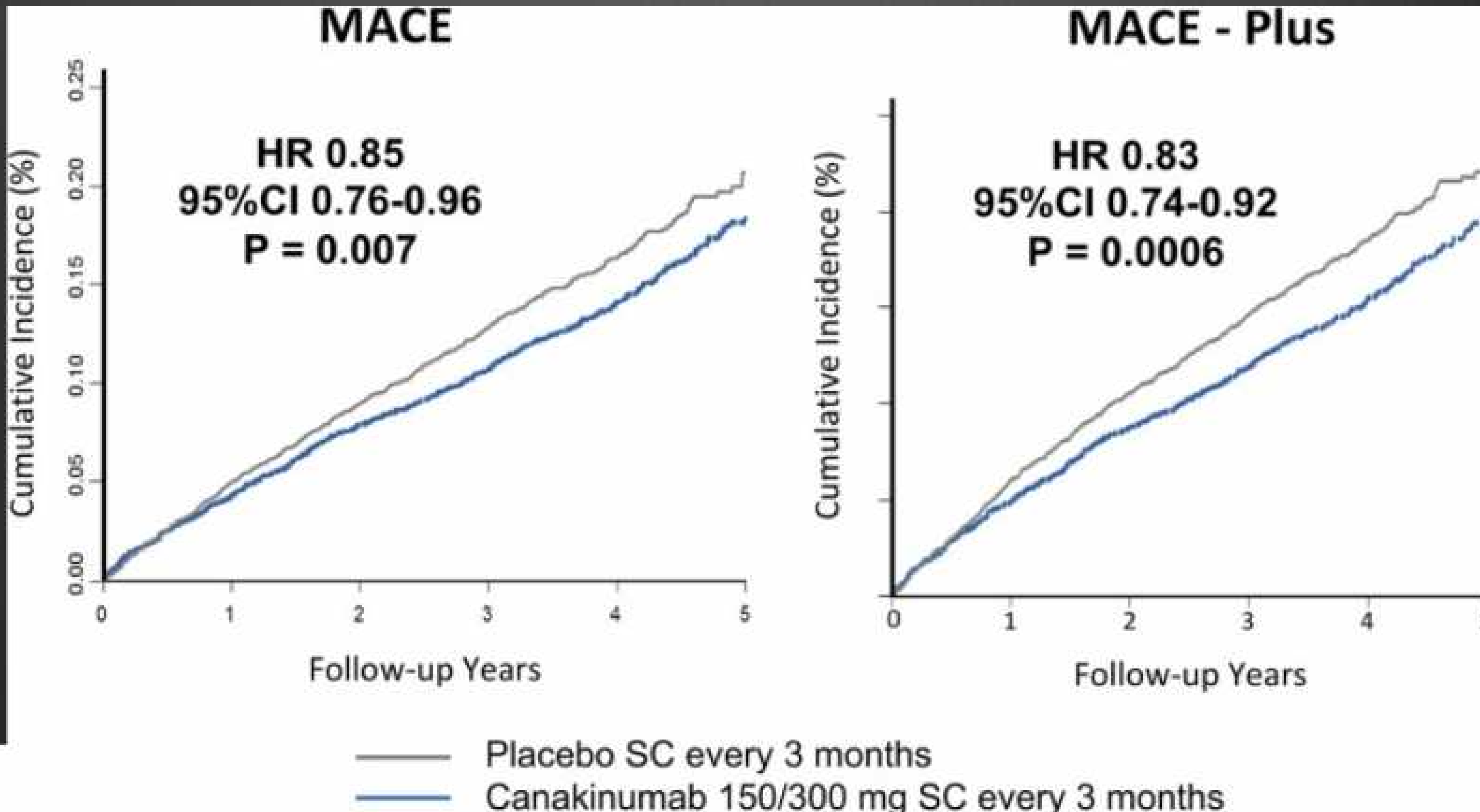
Adaptation of hematopoietic progenitors to cardio-metabolic disease



Chavakis, Mitroulis, Hajishengallis, Nat Immunol, 2019

Low dose inflammation in obesity drives expansion of myeloid biased HSC, which results in the generation of inflammatory macrophages

CANTO trial

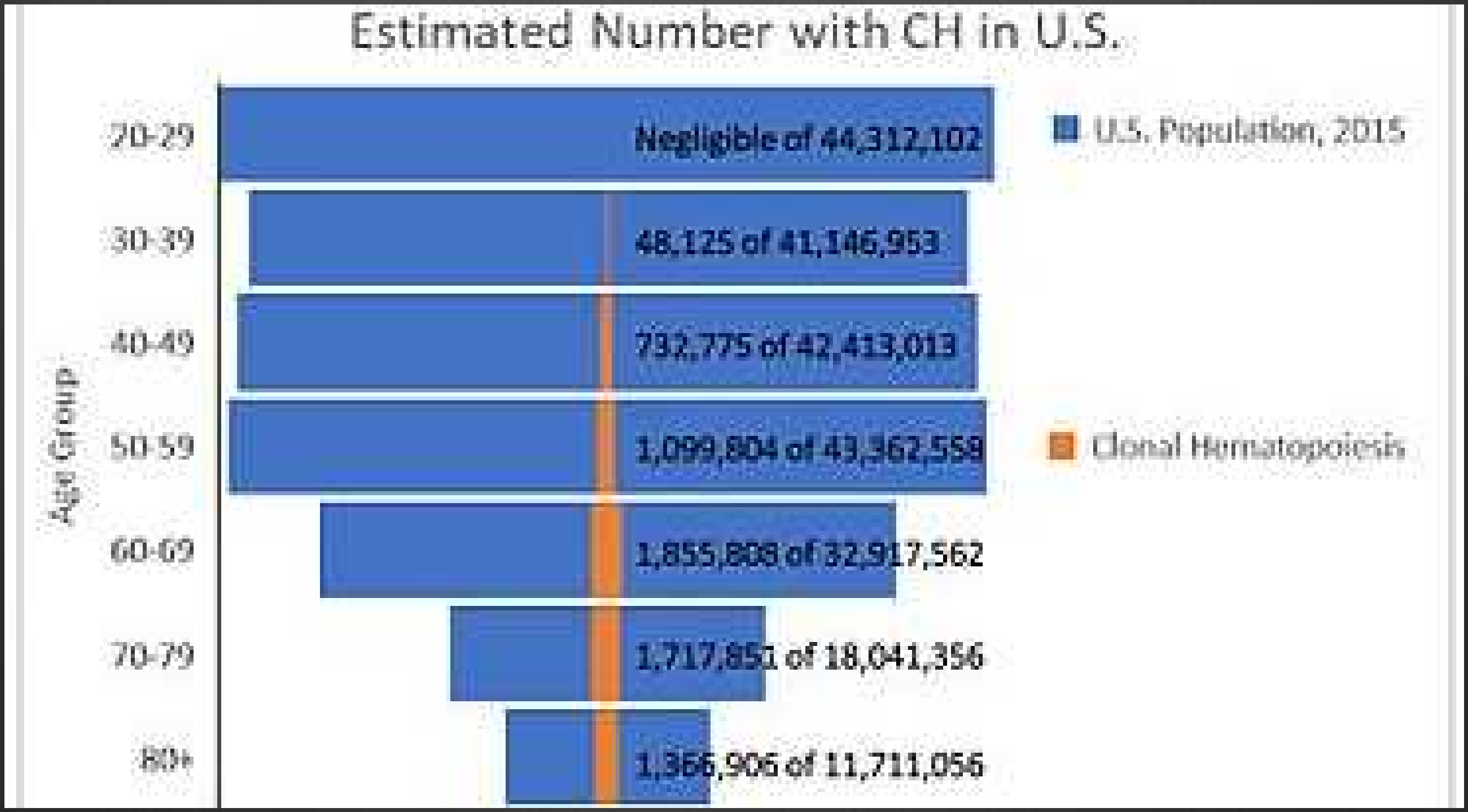


ORIGINAL ARTICLE

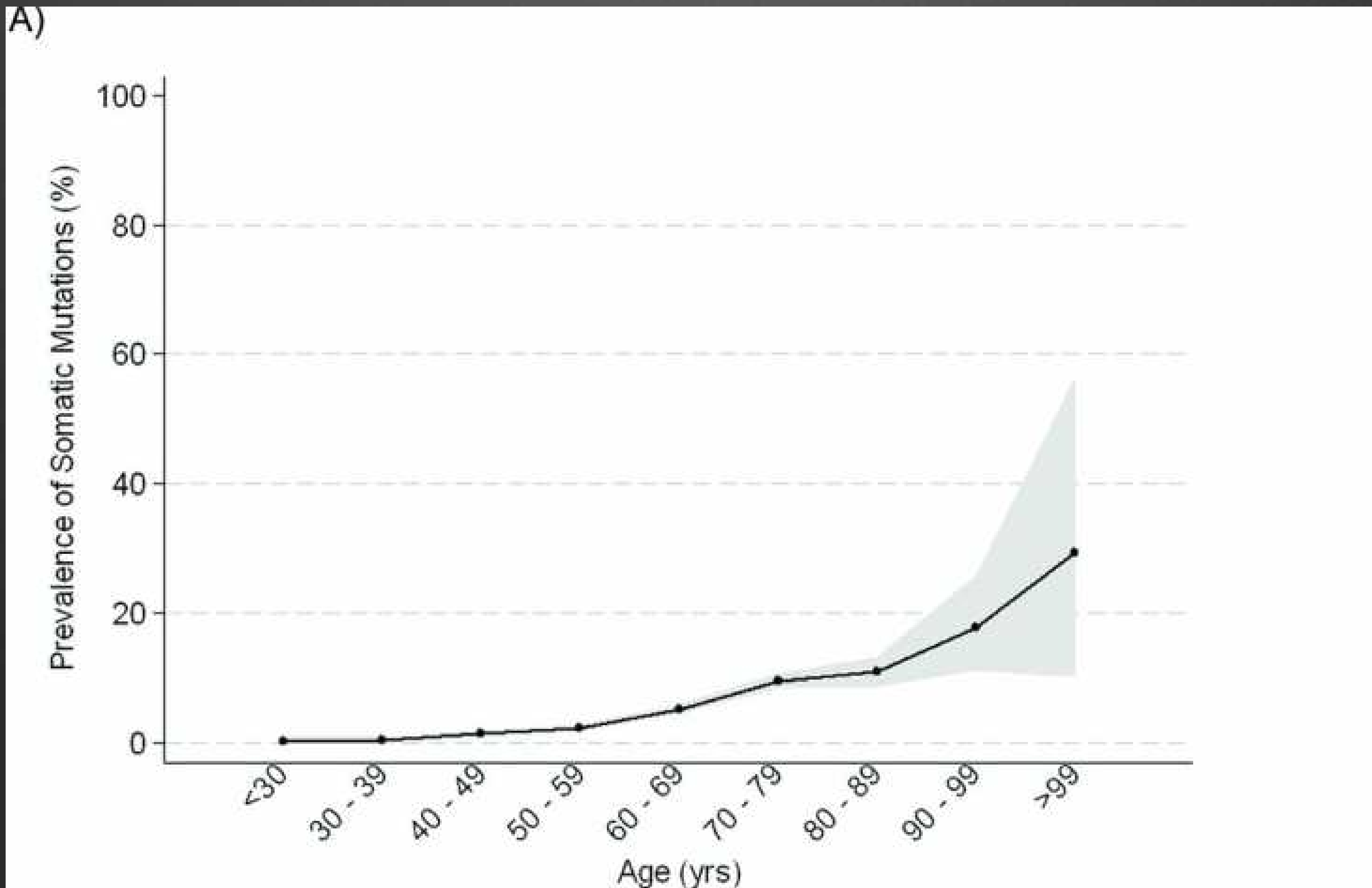
Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

Clonal hematopoiesis and cardiovascular risk



Prevalence of somatic mutations according to age and risk of development of a hematologic cancer among persons with somatic mutations.



Luca Malcovati, and Mario Cazzola Hematology 2015;2015:299-307

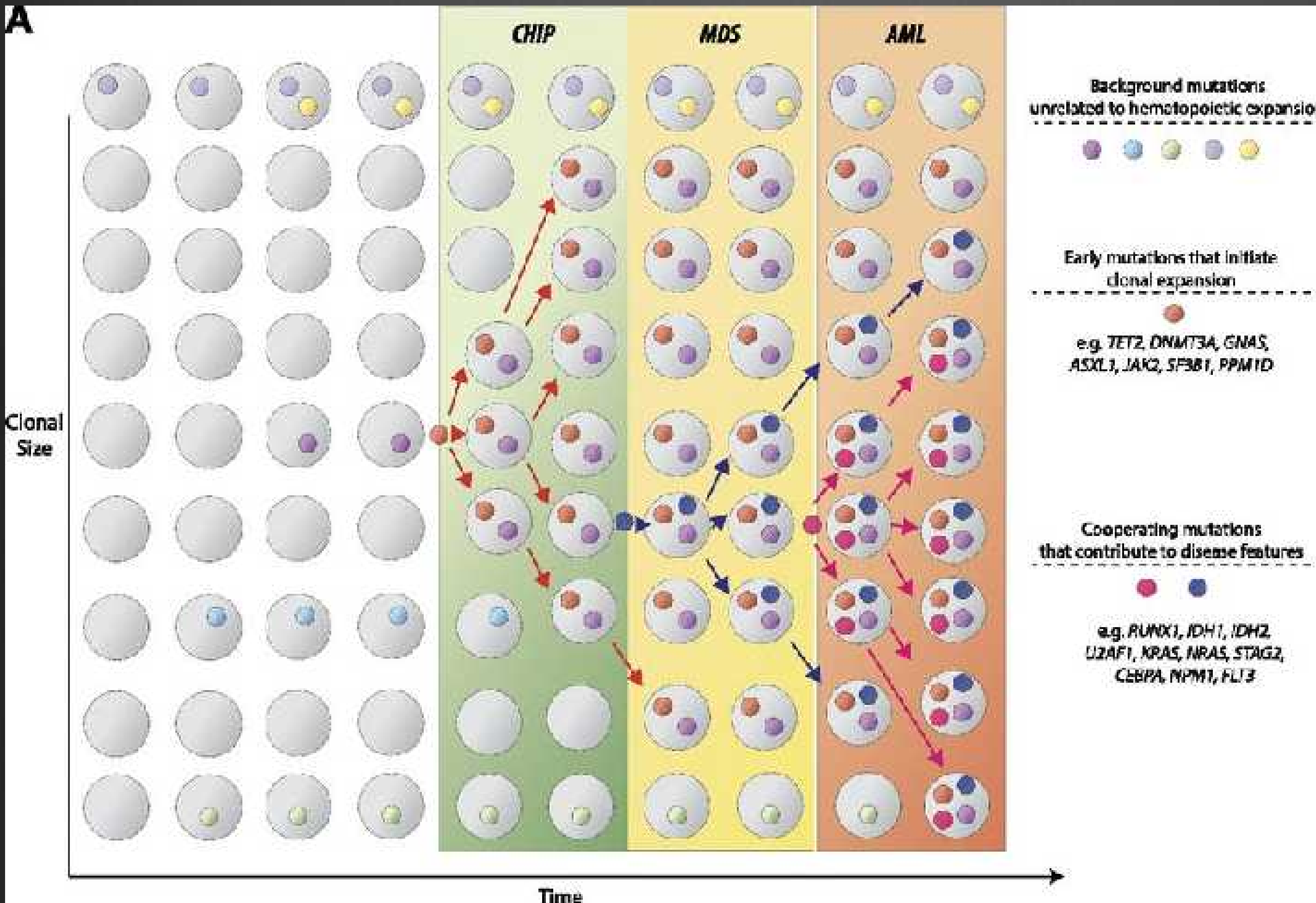
Definition of CHIP and its distinction from MDS and non-clonal cytopenic states.

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- Features:
  - Absence of definitive morphological evidence of a hematological neoplasm
  - Does not meet diagnostic criteria for PNH, MGUS or MBL
  - Presence of a somatic mutation associated with hematological neoplasia at a variant allele frequency of at least 2% (e.g., *DNMT3A, TET2, JAK2, SF3B1, ASXL1, TP53, CBL, GNB1, BCOR, U2AF1, CREBBP, CUX1, SRSF2, MLL2, SETD2, SETDB1, GNAS, PPM1D, BCORL1*)
  - Odds of progression to overt neoplasia are approximately 0.5-1% per year, similar to MGUS

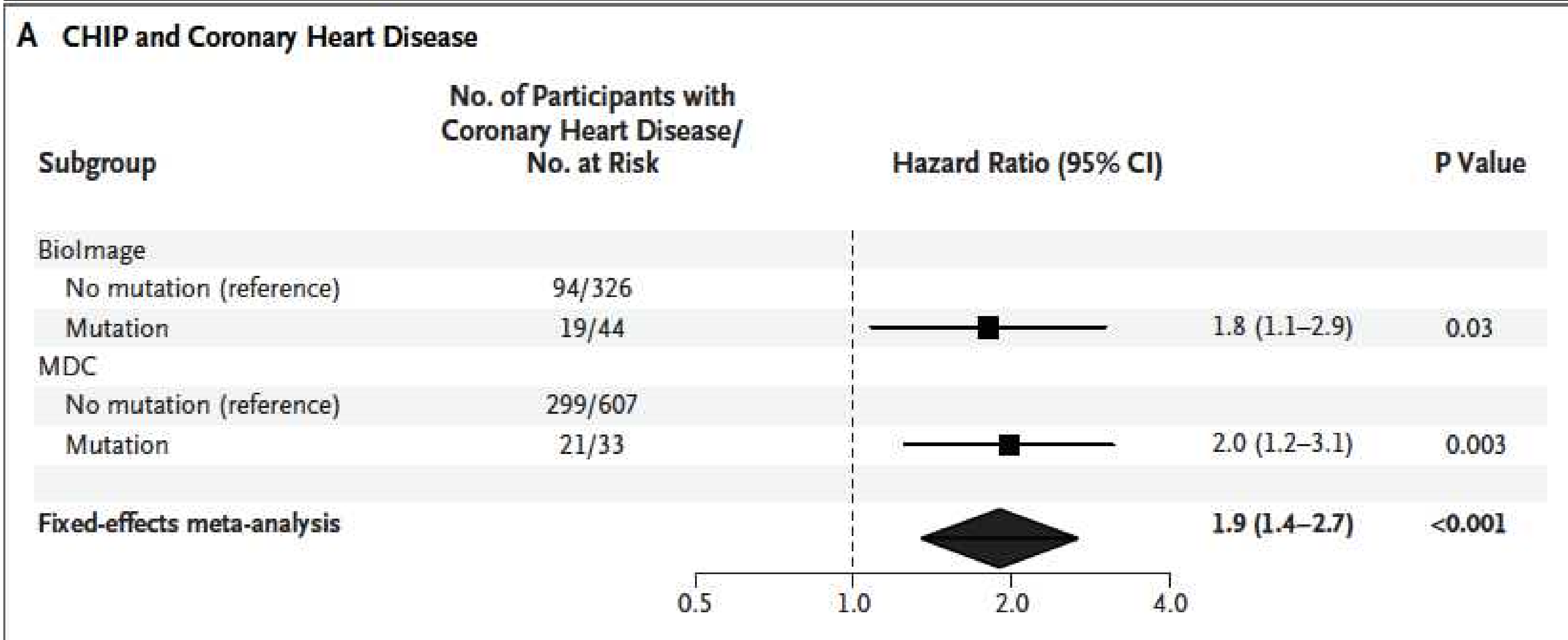
David P. Steensma et al. Blood 2015;126:9-16

CHIP as a precursor state for hematological neoplasms.



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

Clonal hematopoiesis and cardiovascular risk

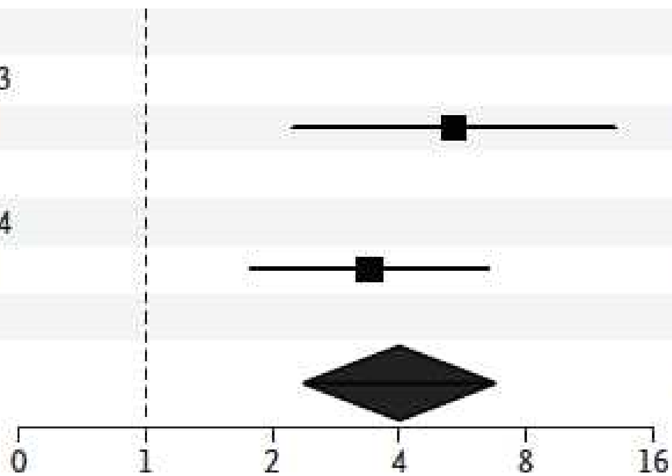


Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease

S. Jaiswal, P. Natarajan, A.J. Silver, C.J. Gibson, A.G. Bick, E. Shvartz, M. McConkey, N. Gupta, S. Gabriel, D. Ardissino, U. Baber, R. Mehran, V. Fuster, J. Danesh, P. Frossard, D. Saleheen, O. Melander, G.K. Sukhova, D. Neuberg, P. Libby, S. Kathiresan, and B.L. Ebert

B CHIP and Early-Onset Myocardial Infarction

Subgroup	No. of Participants with Myocardial Infarction/ No. at Risk	Odds Ratio (95% CI)	P Value
ATVB			
No mutation (reference)	1716/3293		
Mutation	37/43	5.4 (2.3–13.0)	<0.001
PROMIS			
No mutation (reference)	2488/3844		
Mutation	52/65	3.4 (1.8–6.5)	<0.001
Fixed-effects meta-analysis		**4.0 (2.4–6.7)**	**<0.001**



Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease

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B CHIP and Myocardial Infarction, According to Mutated Gene

ATVB and PROMIS	No. of Participants with Myocardial Infarction/No. at Risk	Odds Ratio (95% CI)	P Value
DNMT3A	31/46	1.4 (0.7–2.8)	0.29
TET2	12/13	8.3 (1.2–357.5)	0.02
ASXL1	8/8	Undefined	0.02
JAK2	16/16	Undefined	<0.001
Other	20/22	6.9 (1.7–61.6)	0.001

Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease

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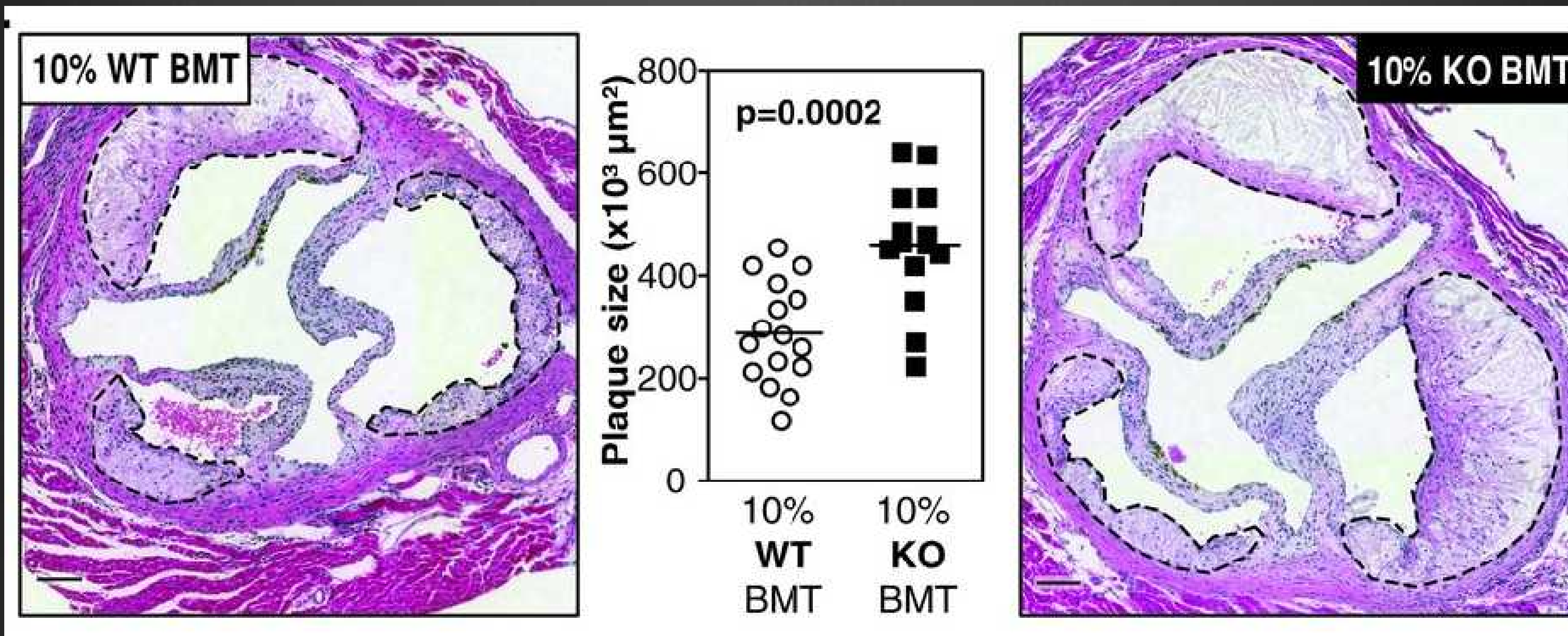
Clonal expansion of TET2-deficient cells accelerates atherosclerosis in Ldlr−/− mice.



José J. Fuster et al. Science 2017;355:842-847

Science
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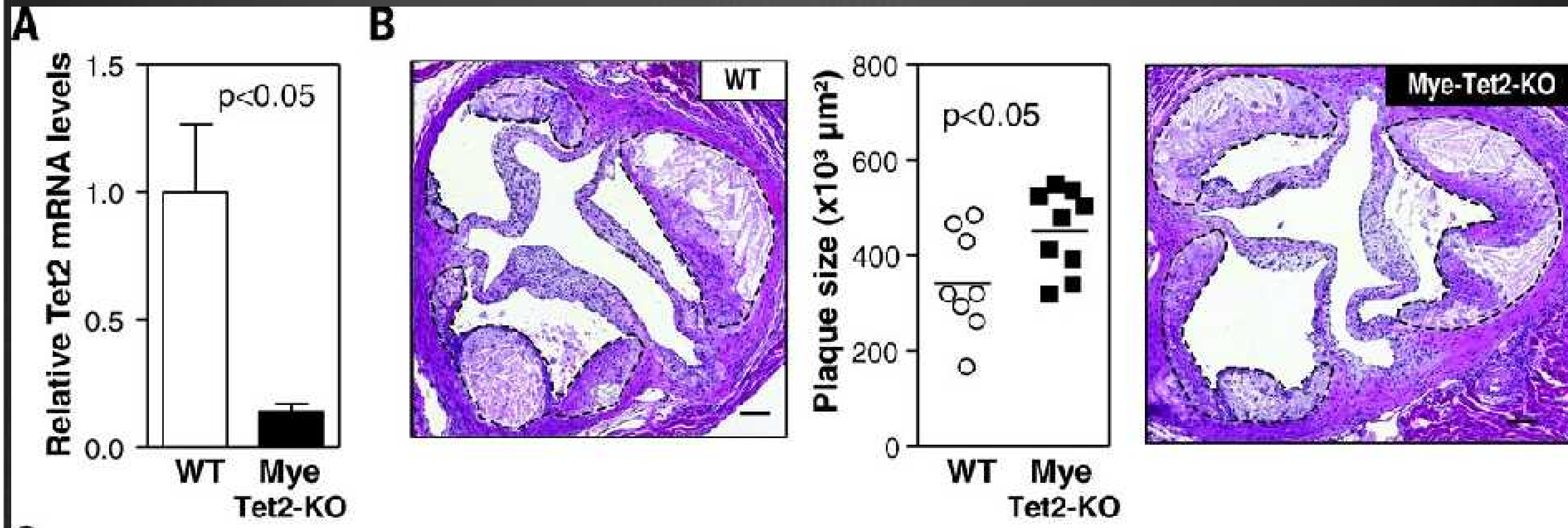
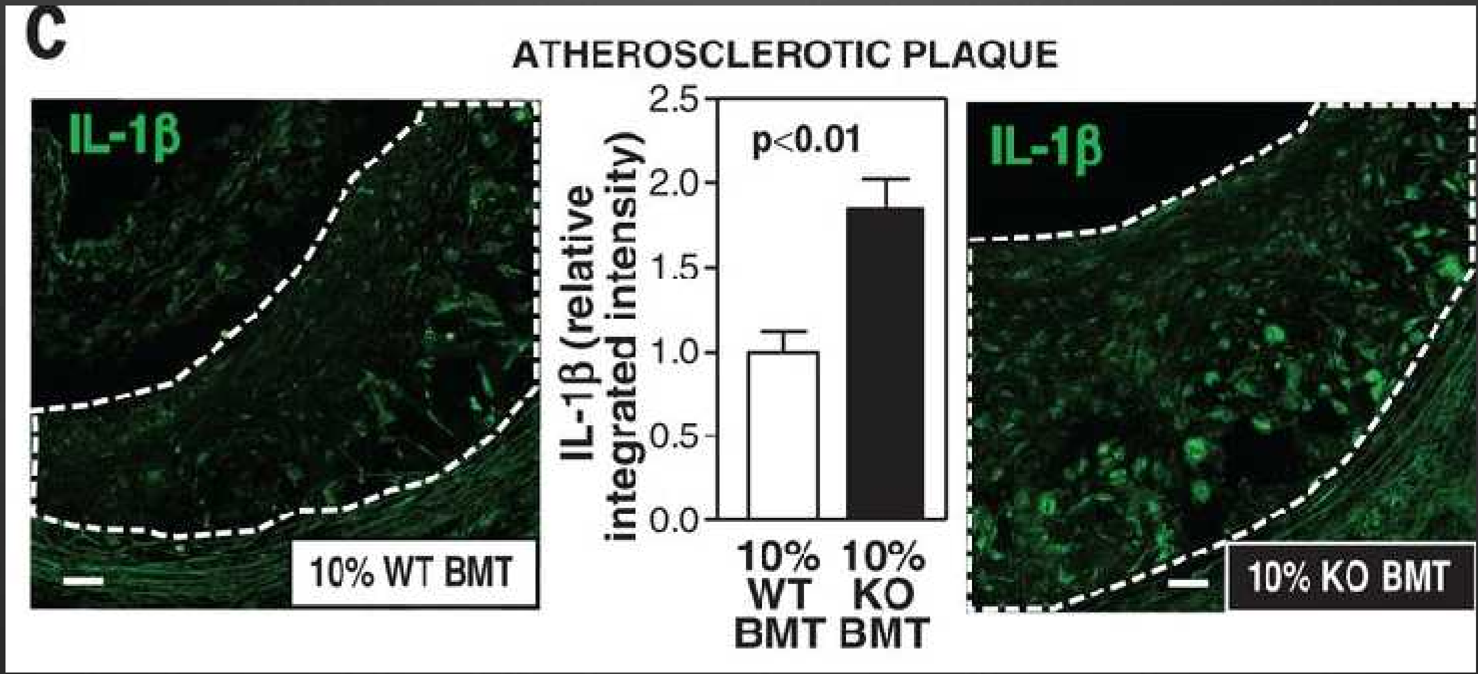


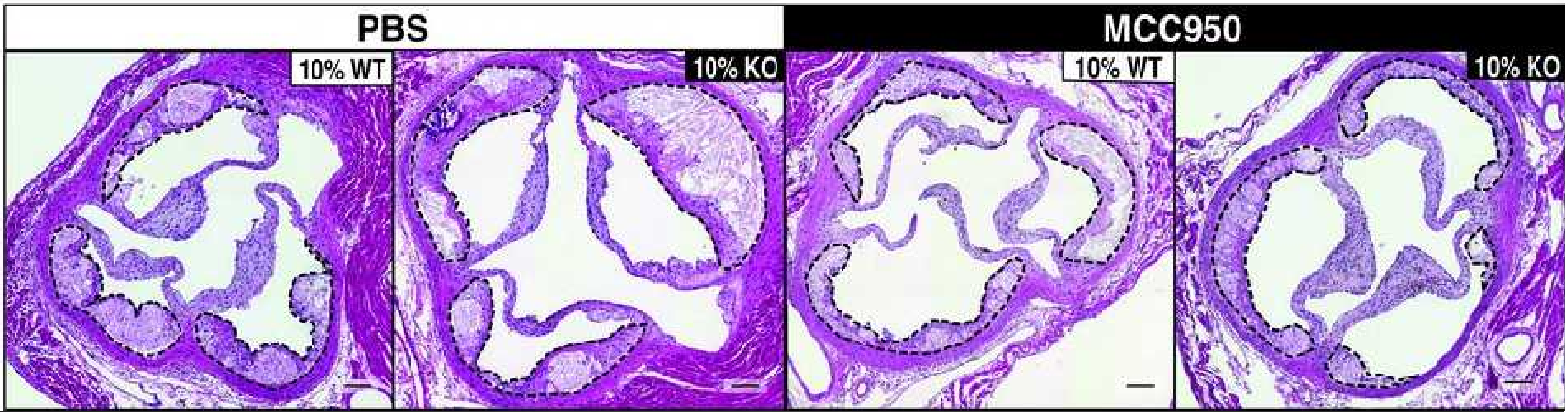
José J. Fuster et al. Science 2017;355:842-847

TET2 regulates IL-1β expression in macrophages.



José J. Fuster et al. Science 2017;355:842-847

The NLRP3 inflammasome is essential for the exacerbated atherosclerosis associated with clonal expansion of TET2-deficient hematopoietic cells.



José J. Fuster et al. Science 2017;355:842-847

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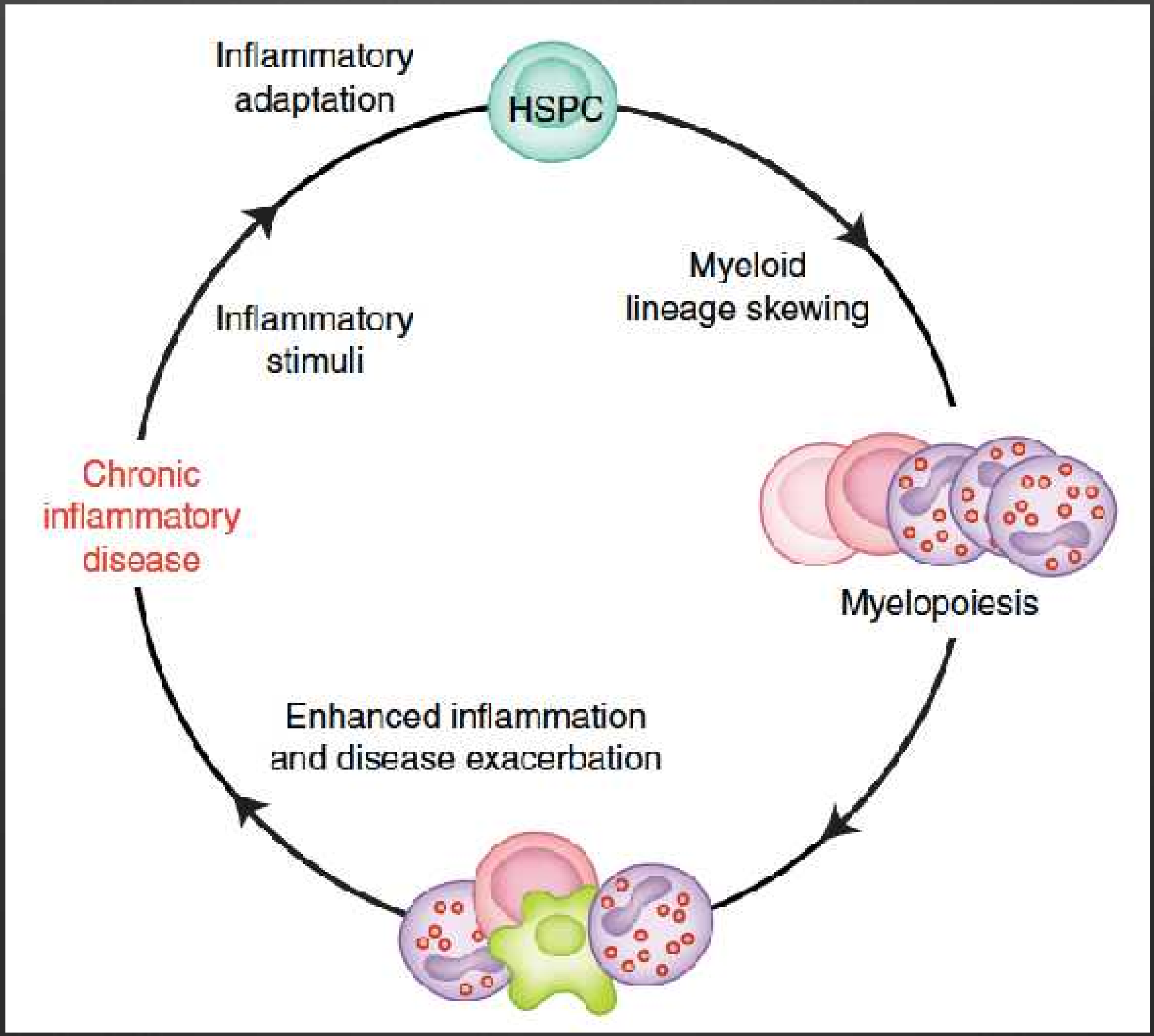
Clonal HSCs (Tet2 Ko) generate pro-inflammatory macrophages

Is cardiovascular disease a clonal hematopoietic disorder?

Feed-forward loop that links the adaptation of HSPCs to inflammation with chronic inflammatory disease



Chavakis, Mitroulis, Hajishengallis, Nat Immunol, 2019

Thank you for your attention