FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Clinica e Terapia delle Sindromi Mielodisplastiche

28 maggio 2022

La nicchia emopoietica nelle MDS: aspetti clinico-biologici e potenziali targets terapeutici

Giuseppe A. Palumbo

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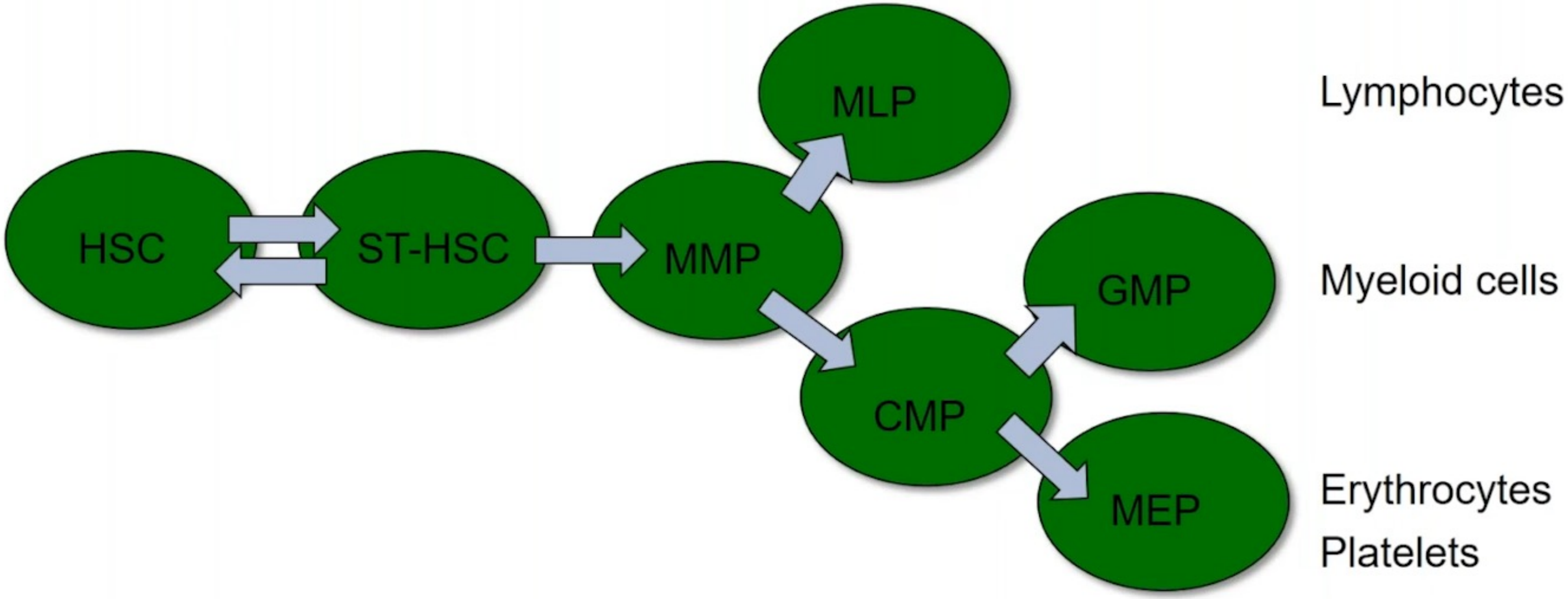
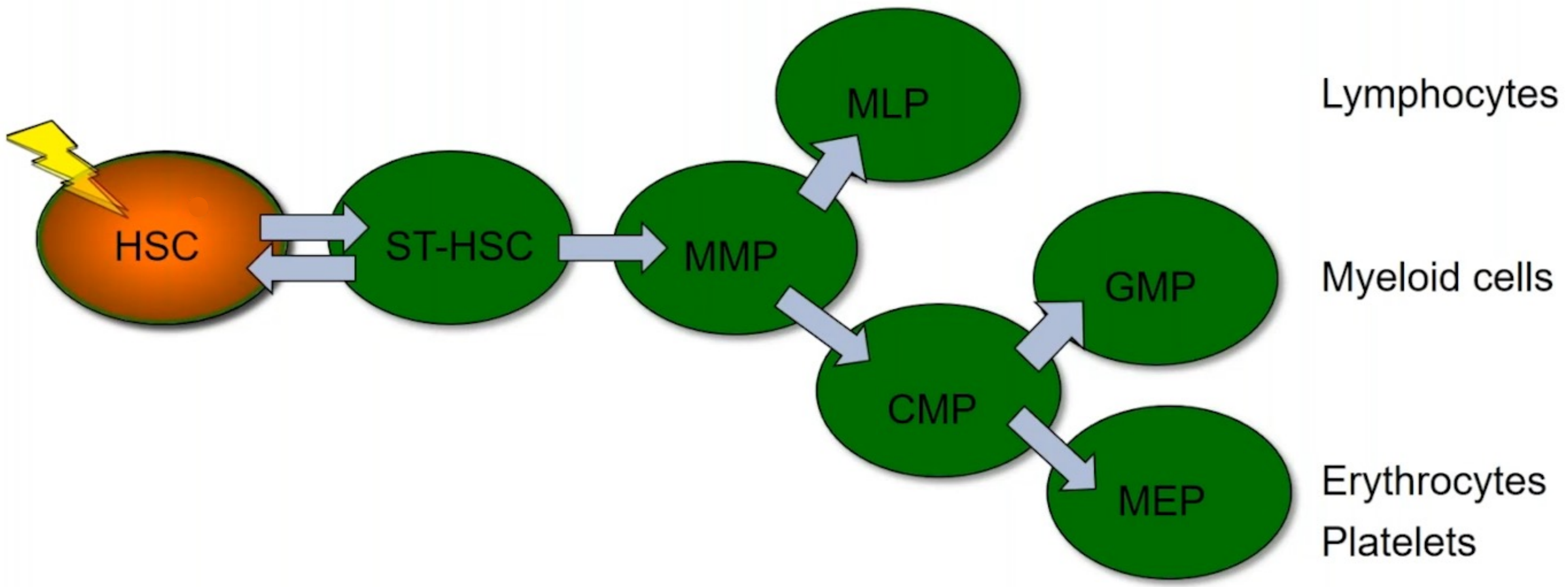
Hematopoiesis and clonal evolution



Adapted from The niche in MDS: Inflammation driving evolution?
Raaijmakers Marc H.G.P. at ESH Translational Research Conference on MDS 2021

Hematopoiesis and clonal evolution



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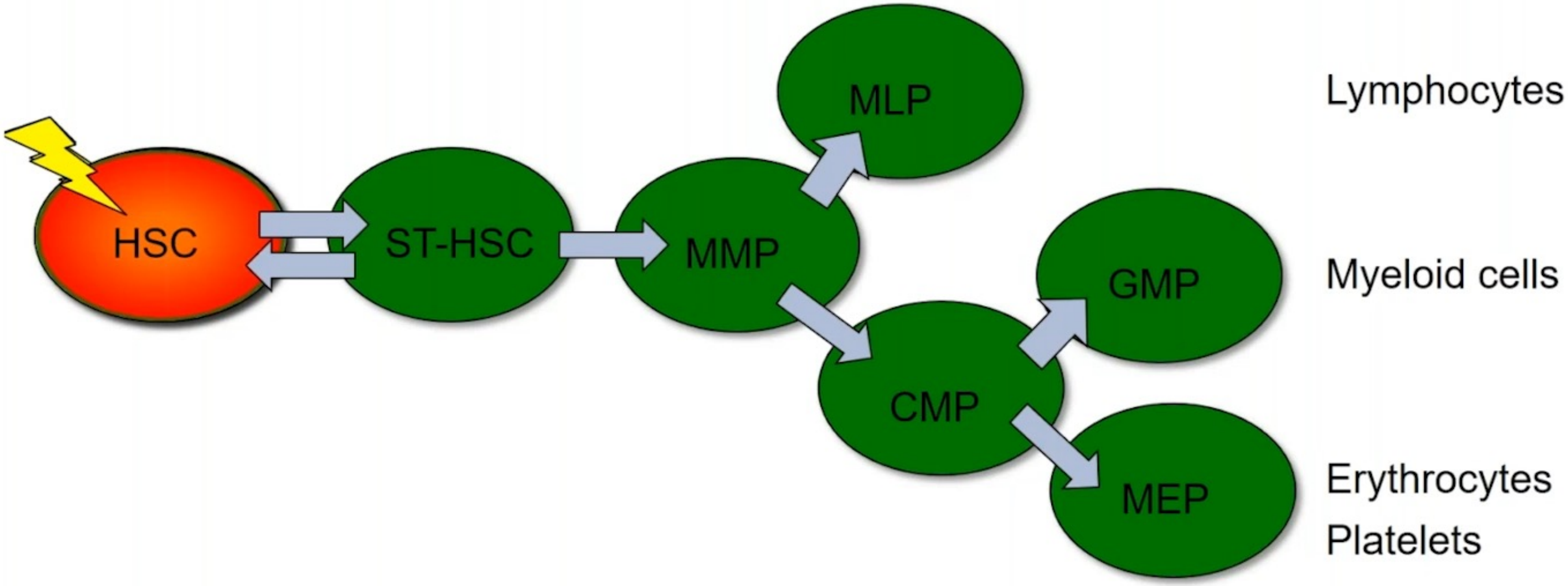

What drives the evolution of mutational clones?

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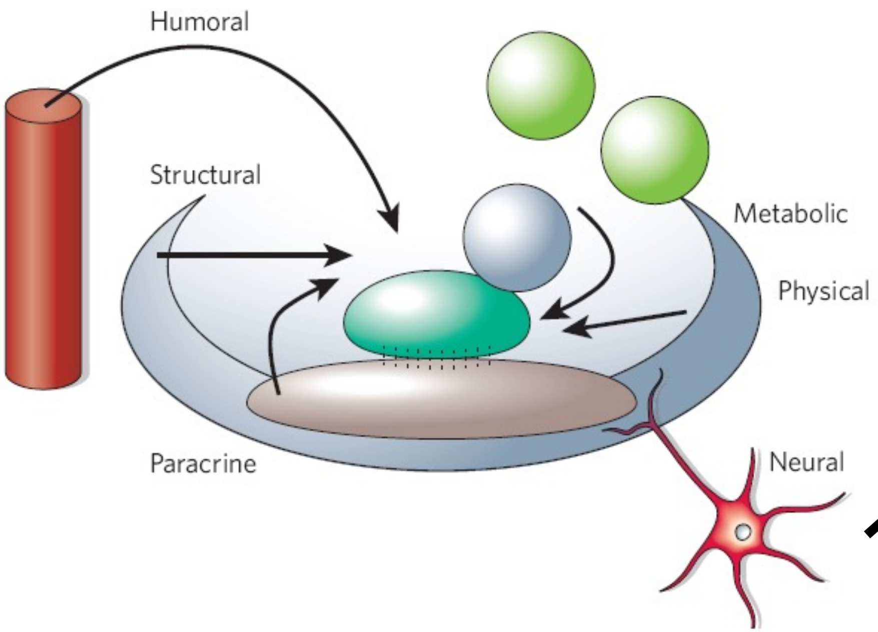
La nicchia è un'entità strutturale e biochimica nella quale vengono integrati i segnali regolatori ambientali e il programma genetico delle SSC

Informazioni attraverso ormoni



Le connessioni neurali portano informazioni (di ferite, danni) da grandi distanze

Durante lo sviluppo si ha la colocalizzazione di cellule endoteliali e cellule progenitrici di diversi tessuti

Le SSC nelle nicchie sono spesso associate a microvascolatura

La nicchia fornisce un microambiente protetto

- Impedisce alle cellule staminali ospiti di venire in contatto con stimoli al differenziamento o all'apoptosi

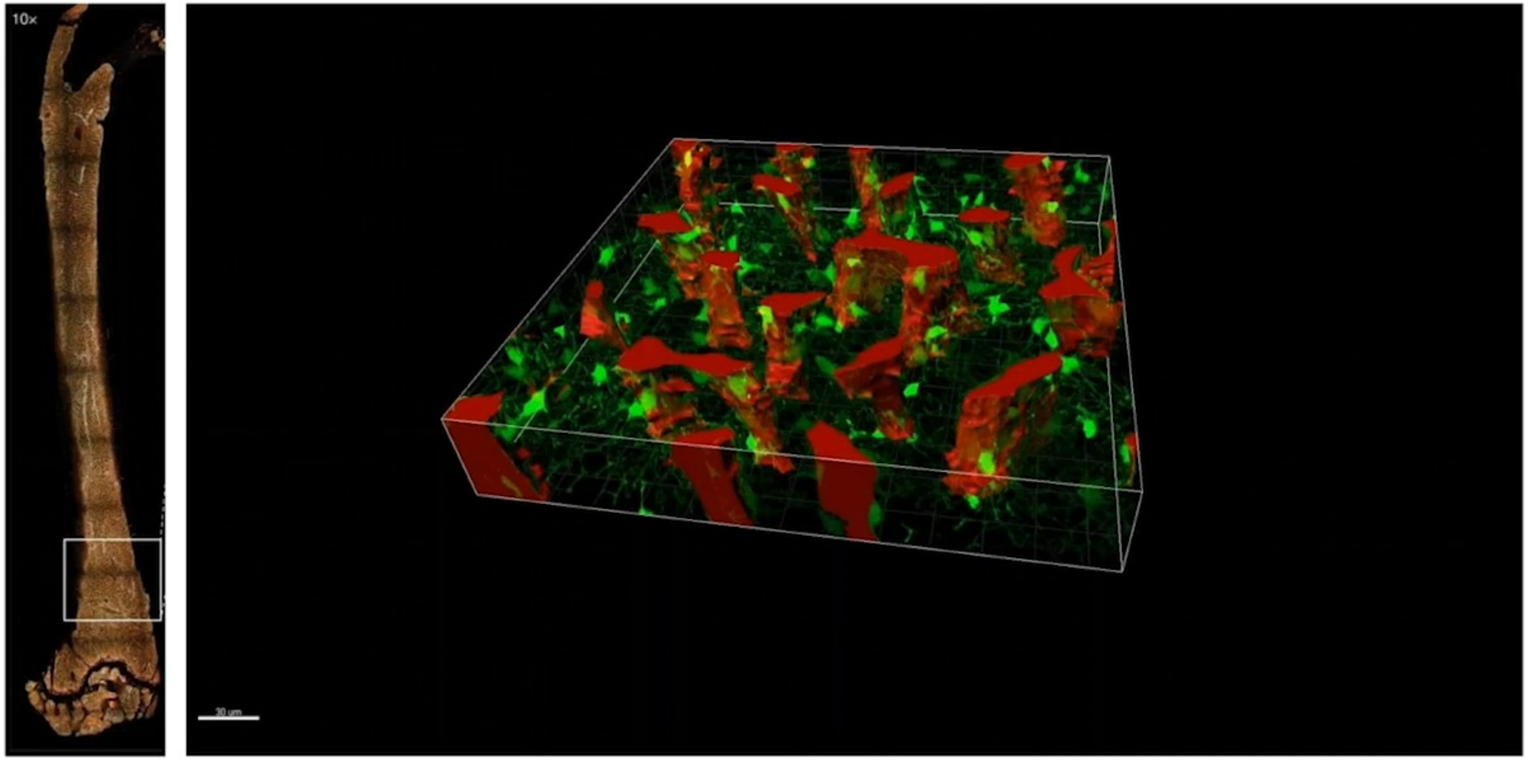
- Regola la proliferazione degli elementi staminali

↓

Impedisce la formazione di ”tumori”

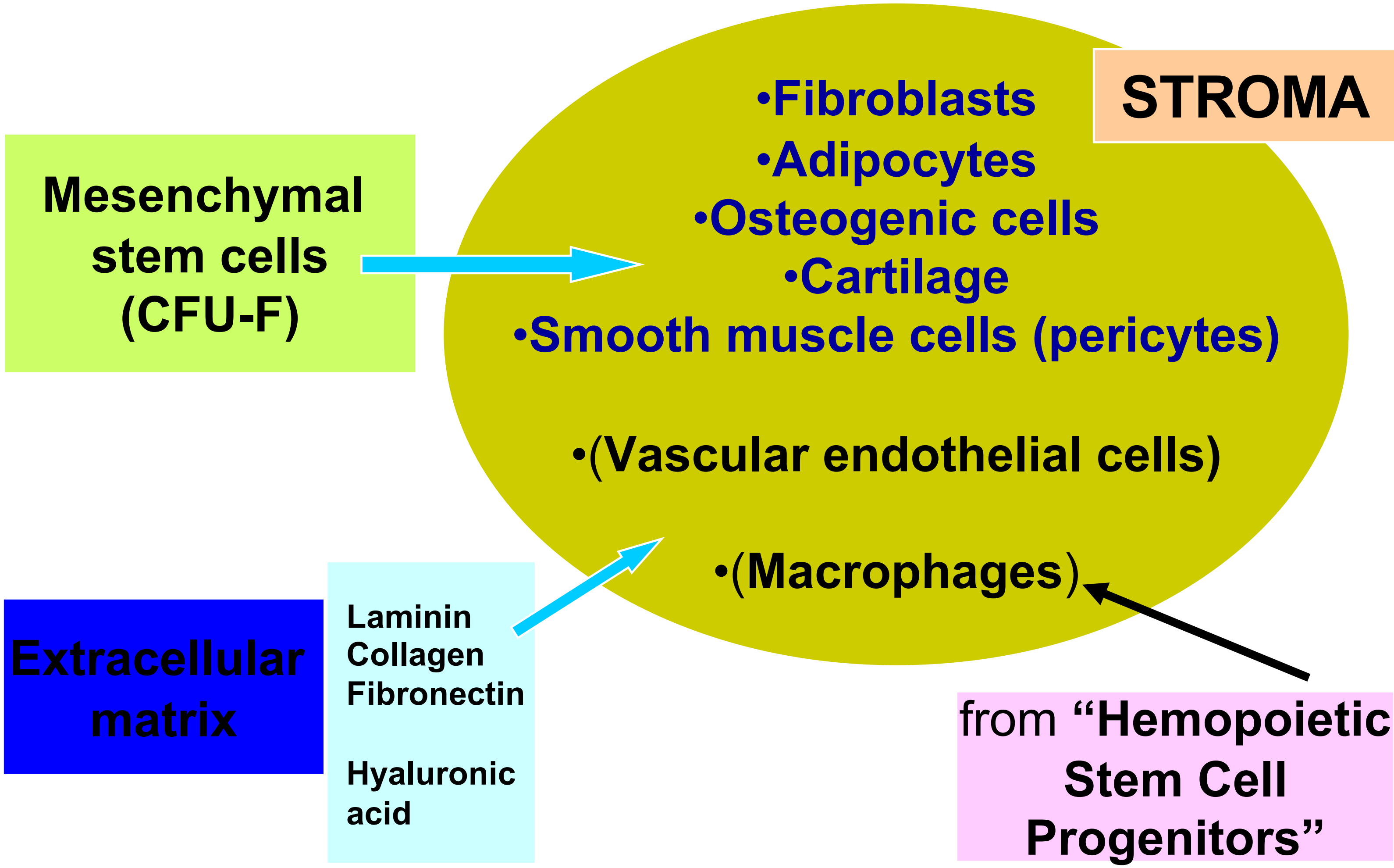
- Si può quindi ipotizzare che una delle differenze tra cellule staminali normali e cancerose sia proprio la perdita da parte di queste ultime della dipendenza dai segnali della nicchia

Stromal cells in the bone marrow



A. Gomariz et al. Nature Communications 9: 2532 (2018)

MARROW STROMA : A HETEROGENEOUS POPULATION OF CELLS



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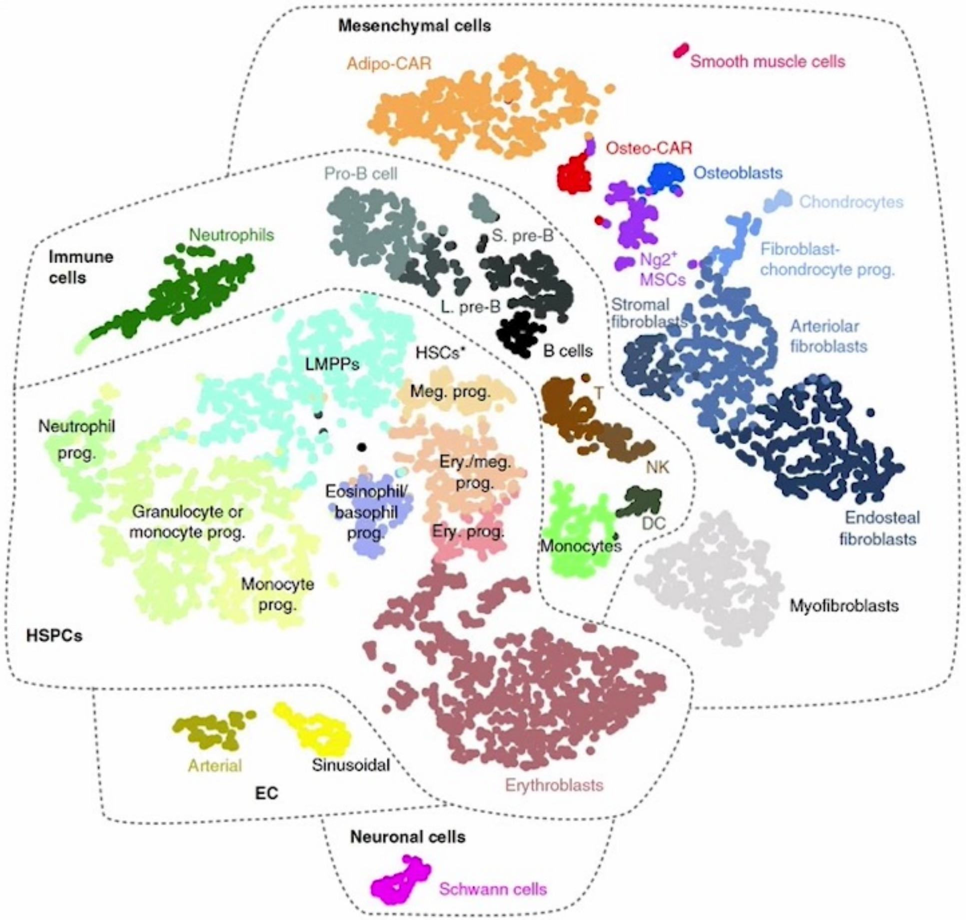
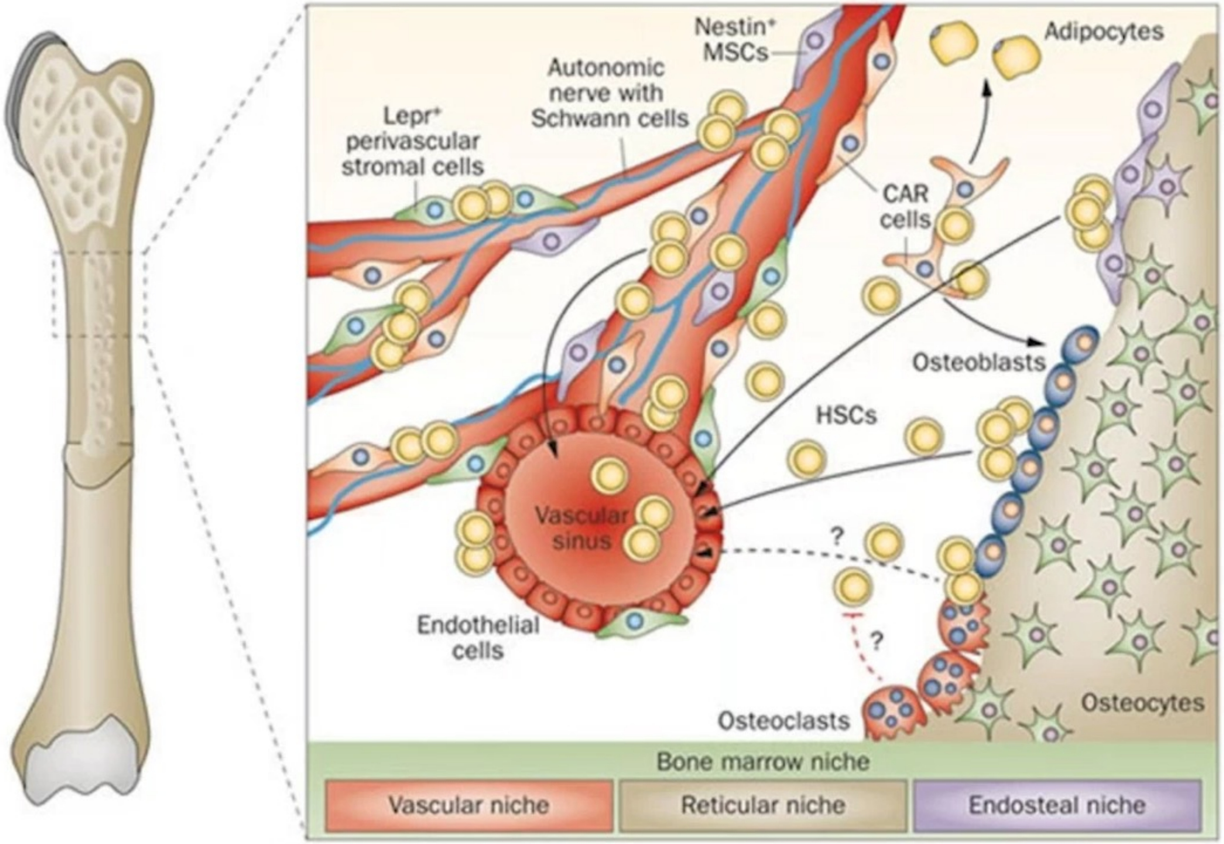
ARTICLES
https://doi.org/10.1038/s41556-019-0439-6
nature cell biology

Combined single-cell and spatial transcriptomics reveal the molecular, cellular and spatial bone marrow niche organization

Chiara Baccin[1,2,10], Jude Al-Sabah[3,4,10], Lars Velten[1,9,10,11*], Patrick M. Helbling[5], Florian Grünschläger[3,4], Pablo Hernández-Malmierca[3,4], César Nombela-Arrieta[5], Lars M. Steinmetz[1,6,7,11*], Andreas Trumpp[3,4,8,11*] and Simon Haas[3,4,11*]

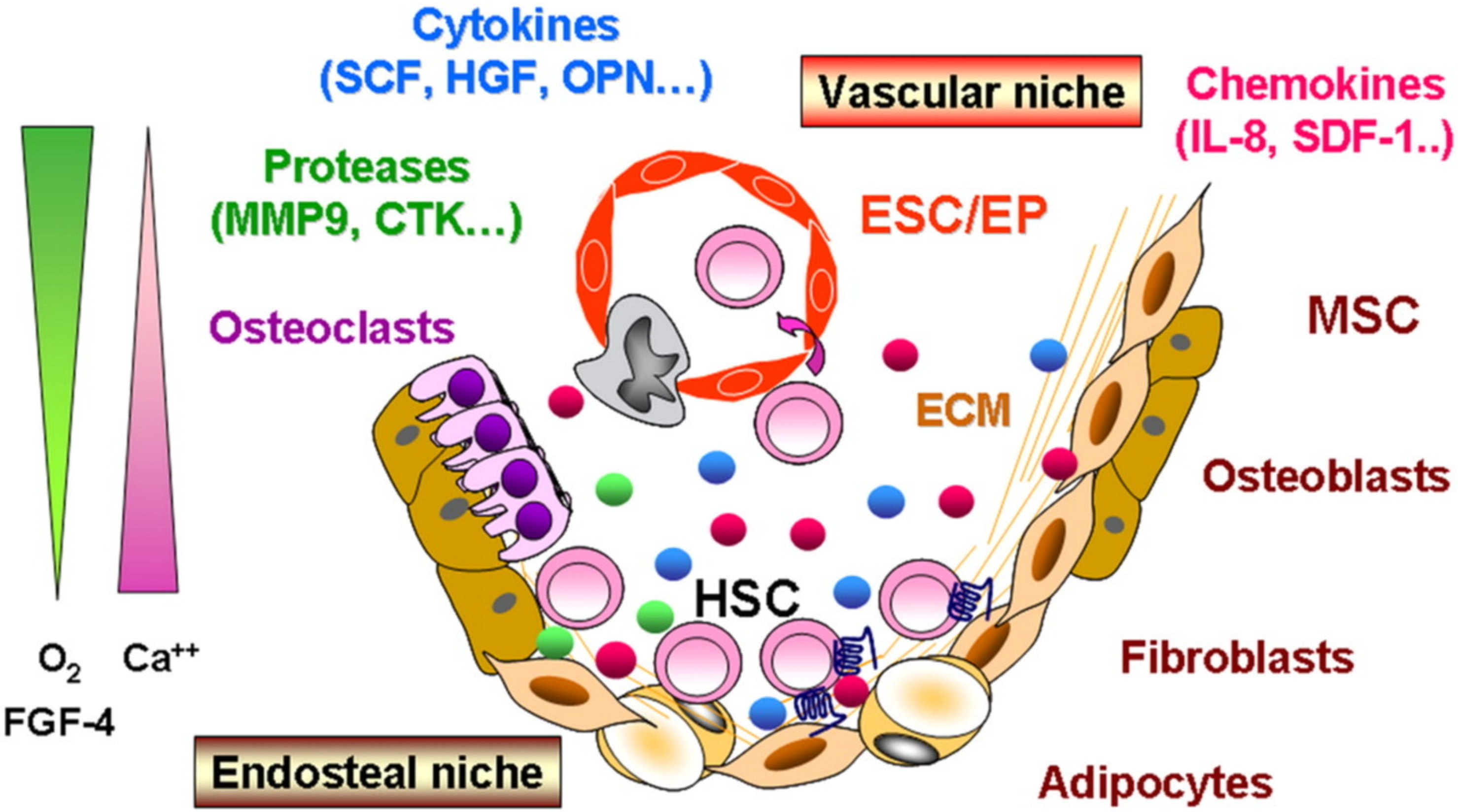


Osteohematopoietic niche

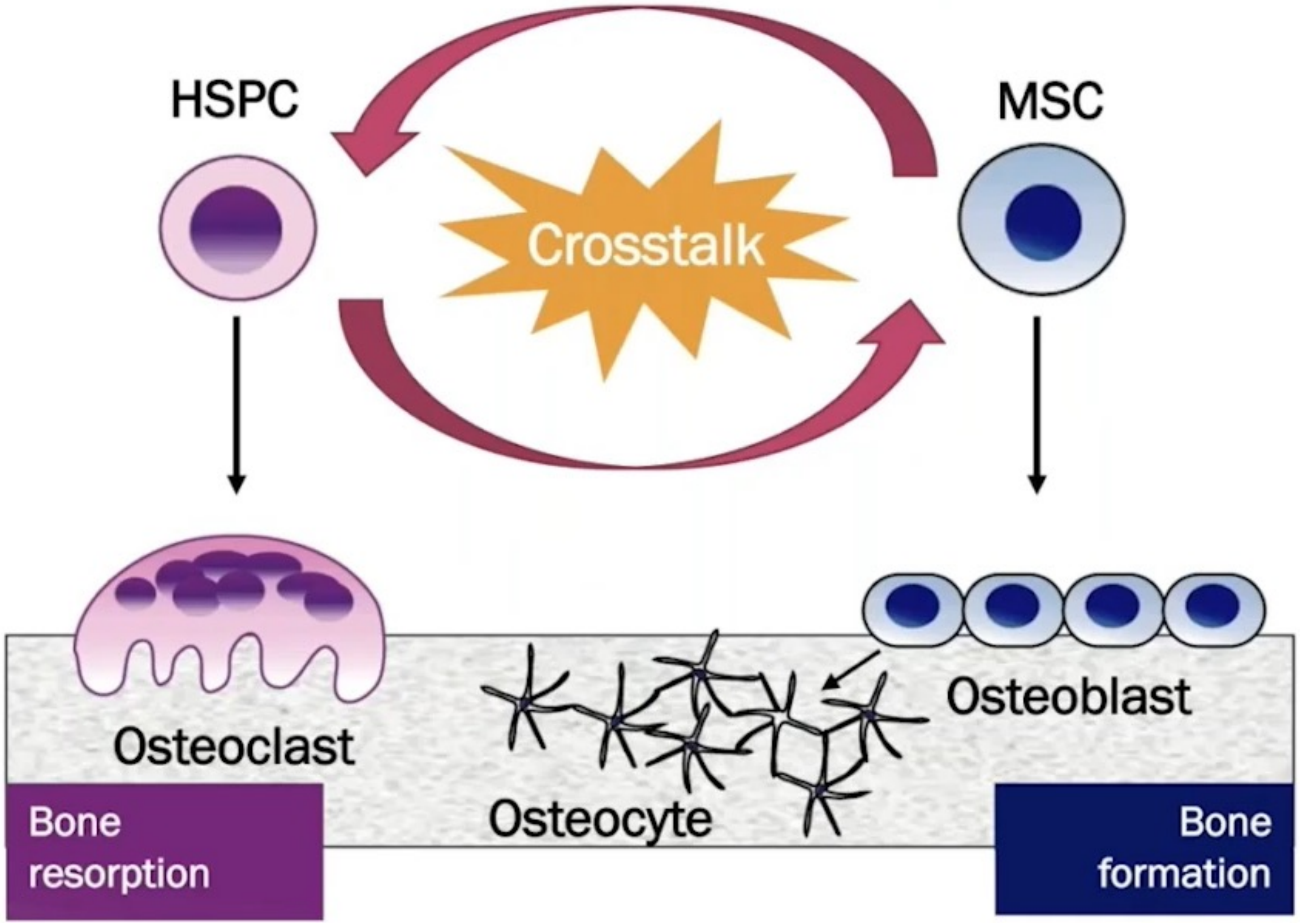


Takayanagi. Reviews Reumatology 2012, 8: 684

Microambiente midollare



Lataillade J et al. Blood 2008;112: 3026-3035

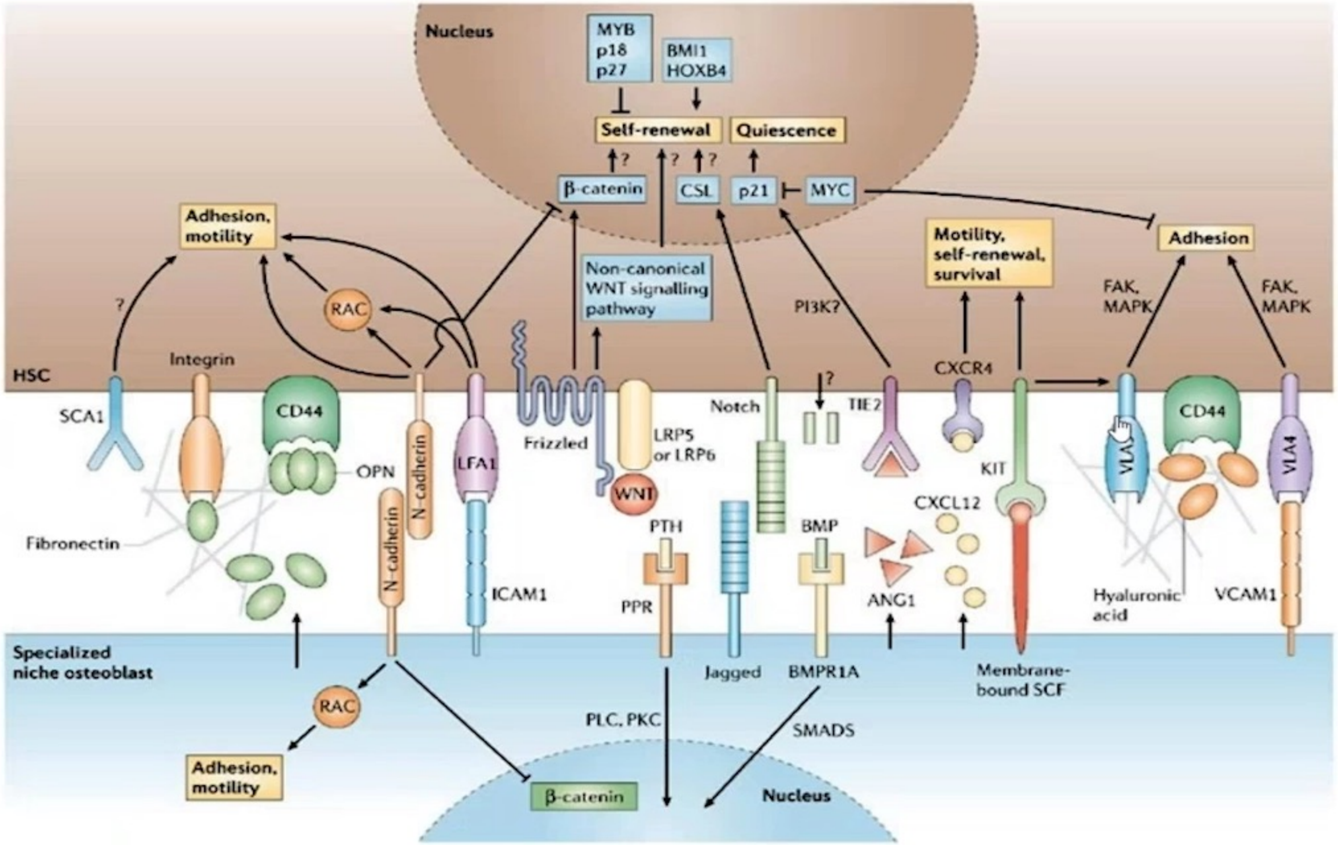


Bulycheva E et al. Leukemia 2015; 29: 259-68

Osteoblast-HSC interactions

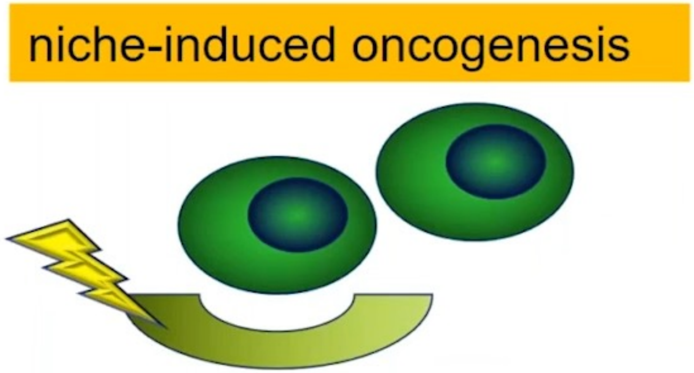
HSC

Osteo-
blast



Wilson & Trumpp. Nature Reviews Immunology 2006, 6: 93-106

Niche contributions to hematopoietic neoplasm



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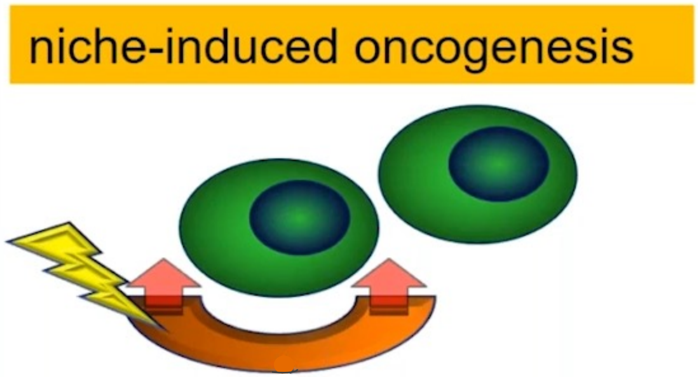

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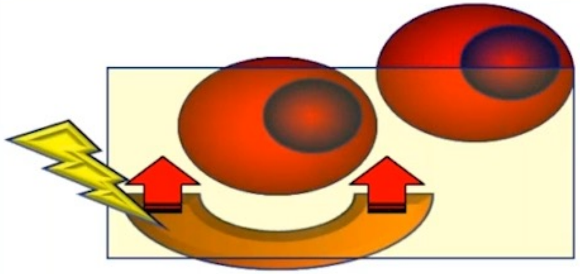
Niche contributions to hematopoietic neoplasm

niche-induced oncogenesis



Walkley et al, *Cell* 2007 (MPN)
Raaijmakers et al, *Nature* 2010 (MDS)
Kode et al, *Nature* 2014 (MDS/AML)
Dong at al, *Nature*, 2016 (JMML/MPN)
Xiao et al, *Blood Adv* 2018 (MDS/MPN)

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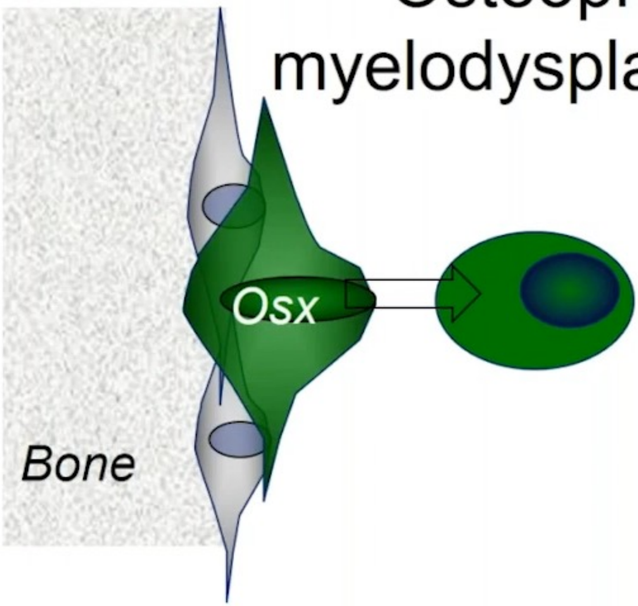
Osteoprogenitor cell dysfunction induces myelodysplasia and secondary leukemia in mice



Raaijmakers M, Mukherjee S, et al. Nature 2010 8;464(7290):852-7

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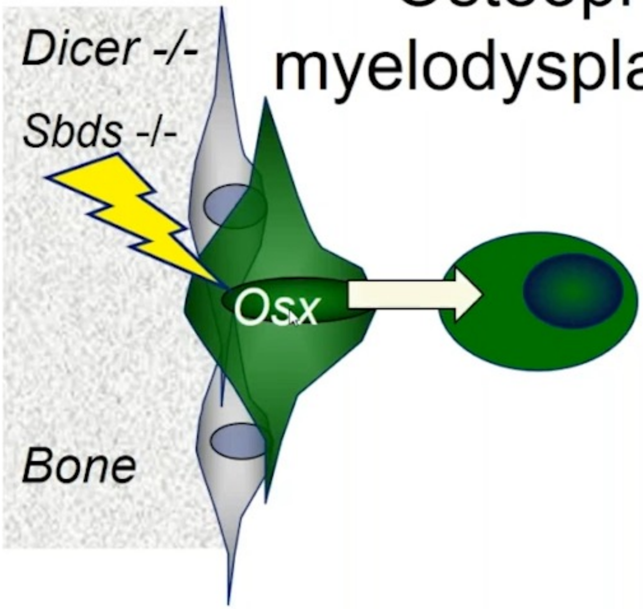

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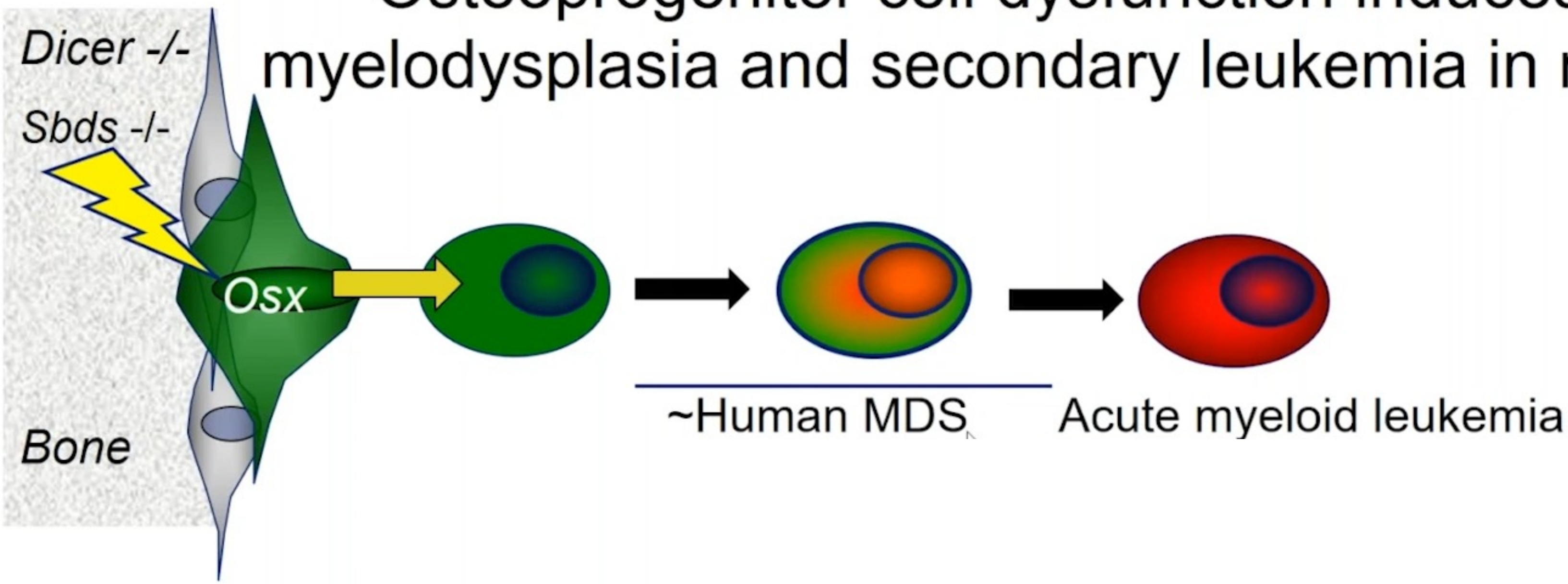
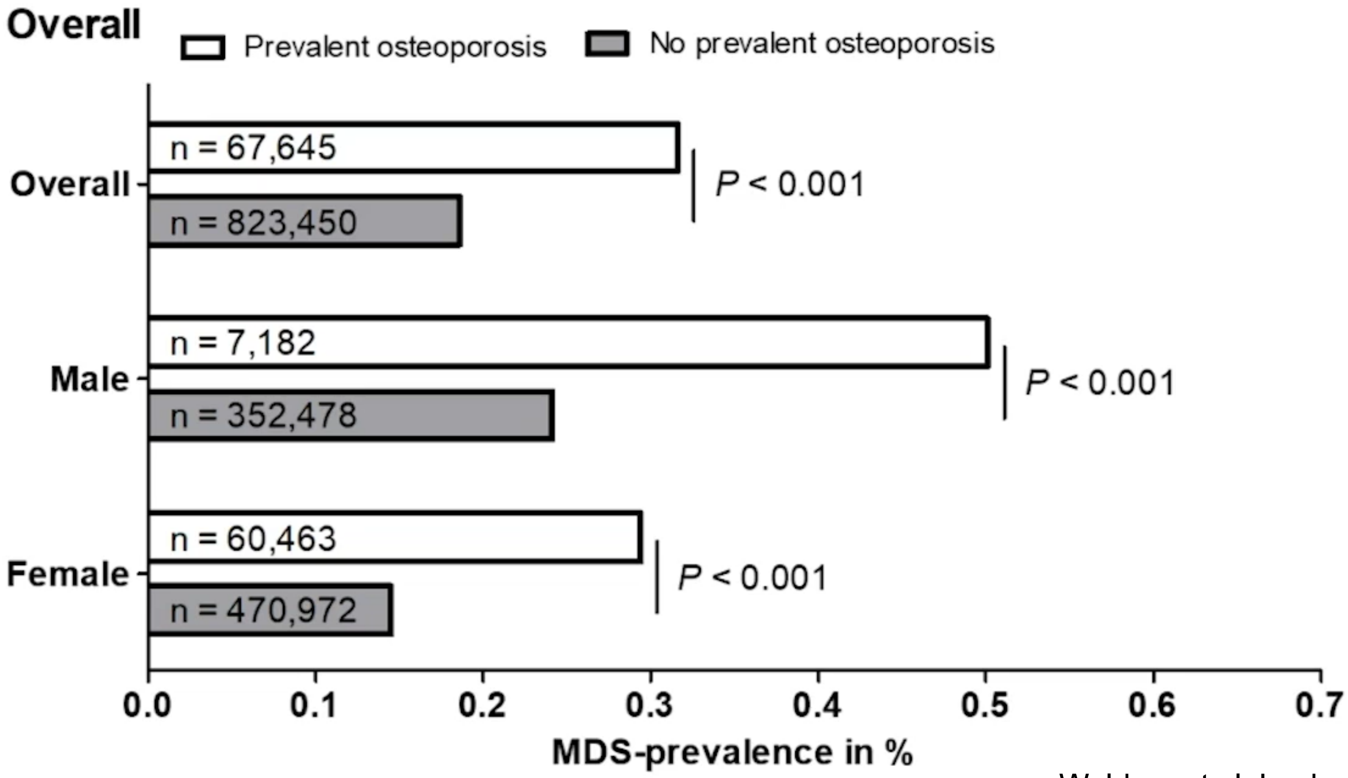


Raaijmakers M, Mukherjee S, et al. Nature 2010 8;464(7290):852-7

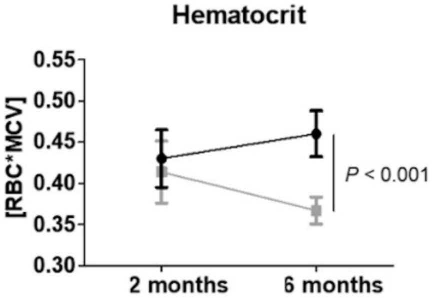
Patients with MDS frequently develop osteoporosis

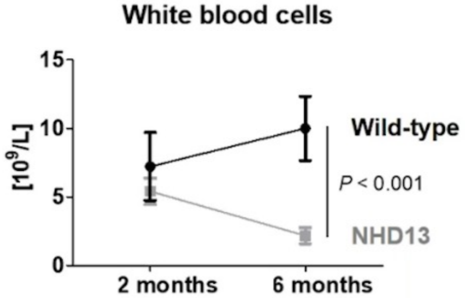


Weldner et al. Leukemia 2017; 31: 1003-1007

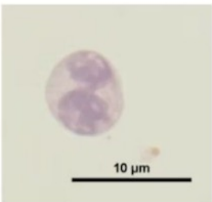
NHD13 mouse as a model for MDS

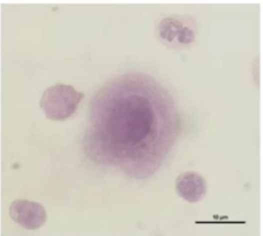
- Overexpress the NUP98/HOXD13 fusion protein in hematopoietic cells (vav1-promoter)
- NUP98/HOXD13 fusion protein is commonly found in MDS





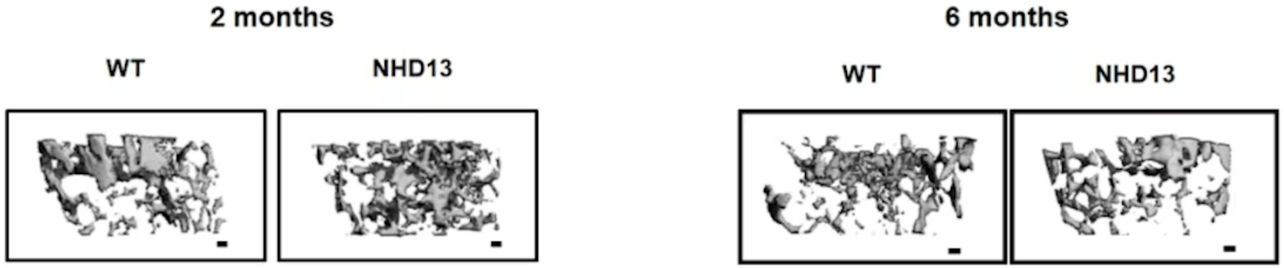
Bone marrow

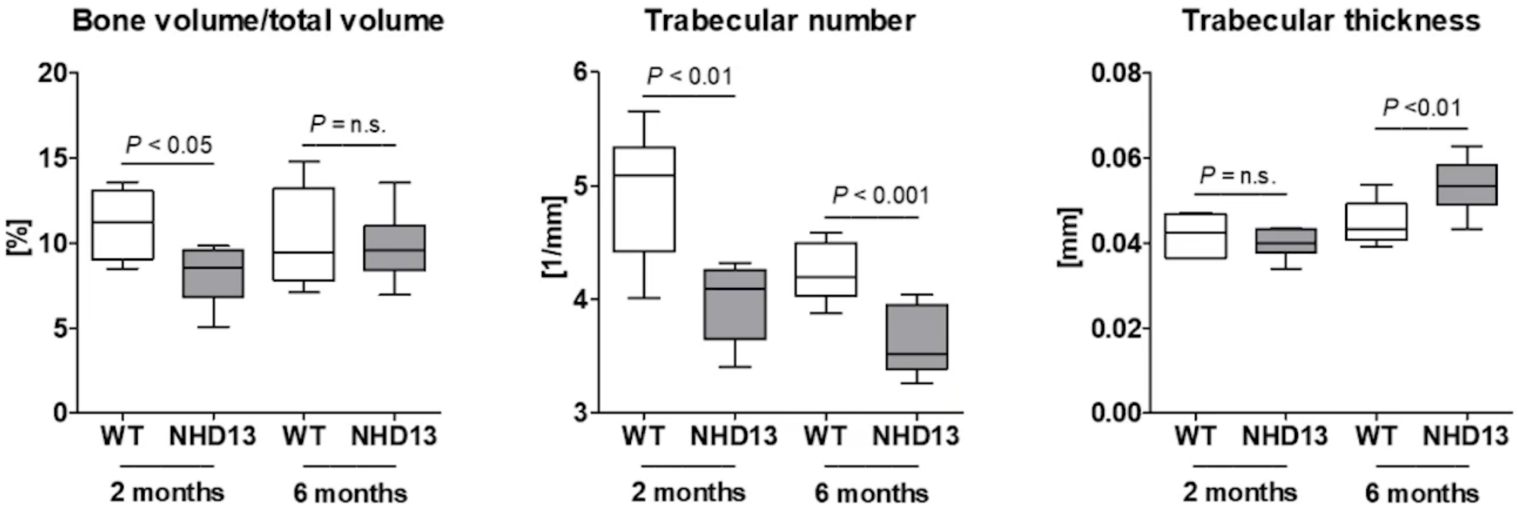


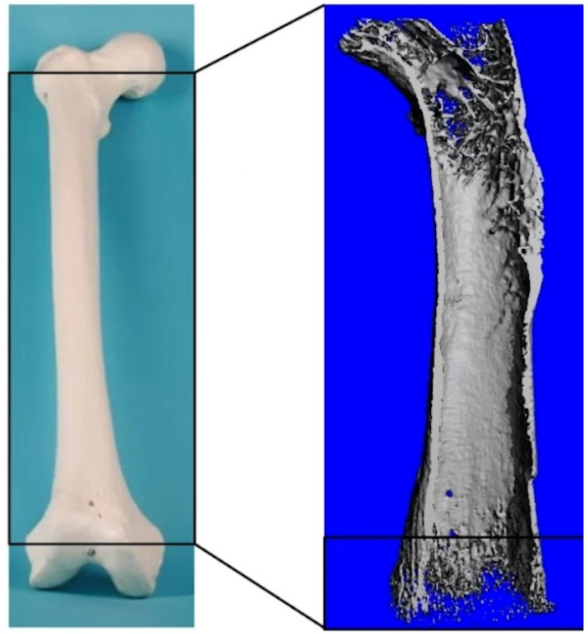


Weldner et al. Leukemia 2017; 31: 1003-1007

Altered bone microarchitecture in MDS mice

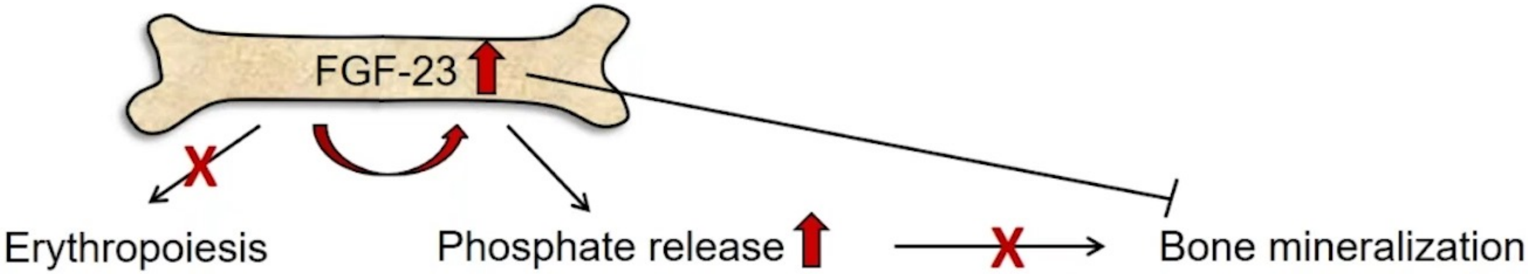


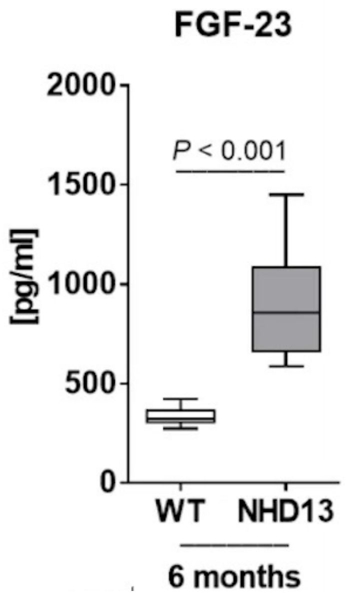




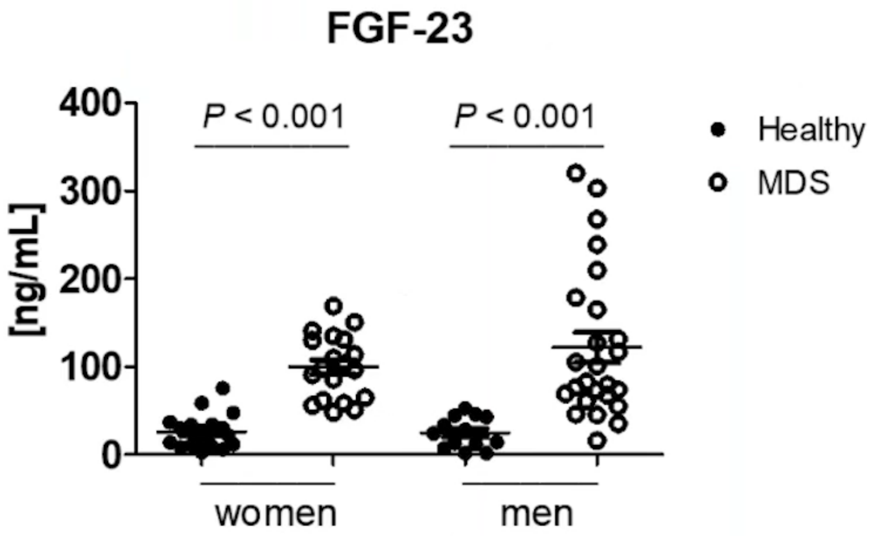
Weldner et al. Leukemia 2017; 31: 1003-1007

Levels of FGF-23 in MDS mice





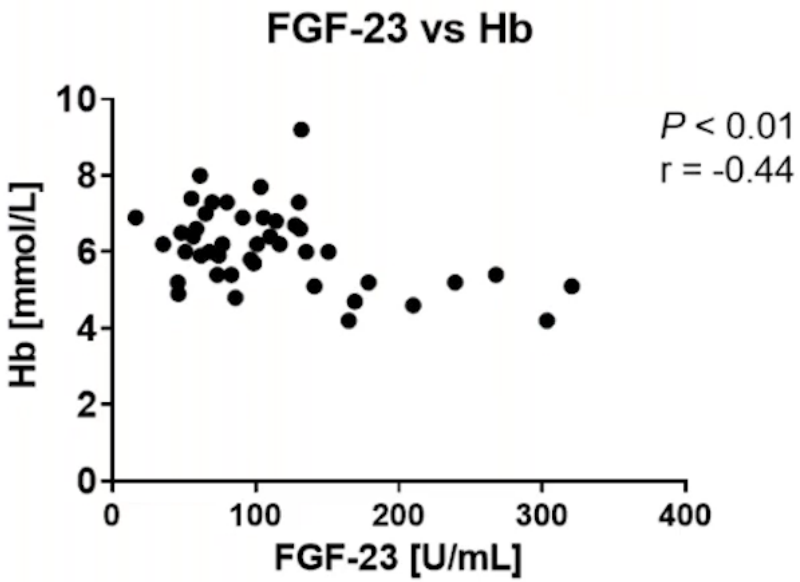
Increased serum concentrations of FGF-23 in patients with MDS

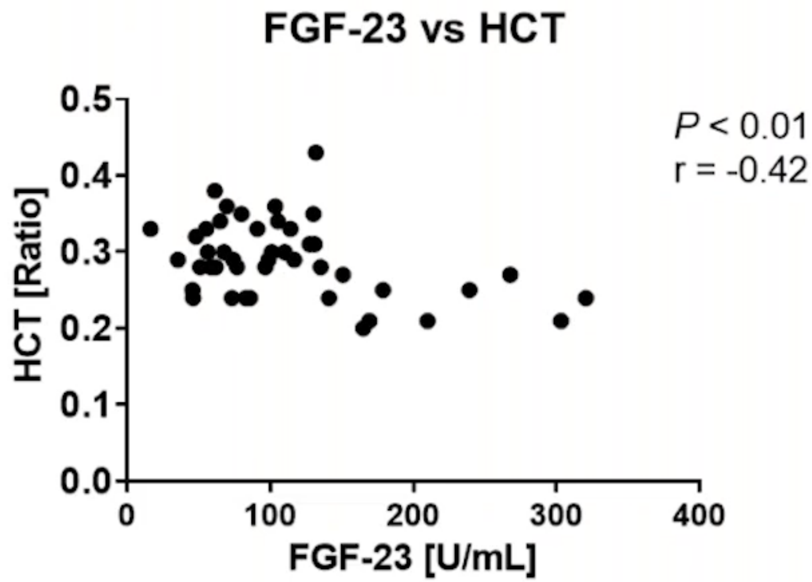


Healthy donor:	women	n = 19	[median: 76 years]
	men	n = 13	[median: 65 years]
MDS patient:	women	n = 19	[median: 70 years]
	men	n = 25	[median: 69 years]

Weldner et al. 2020

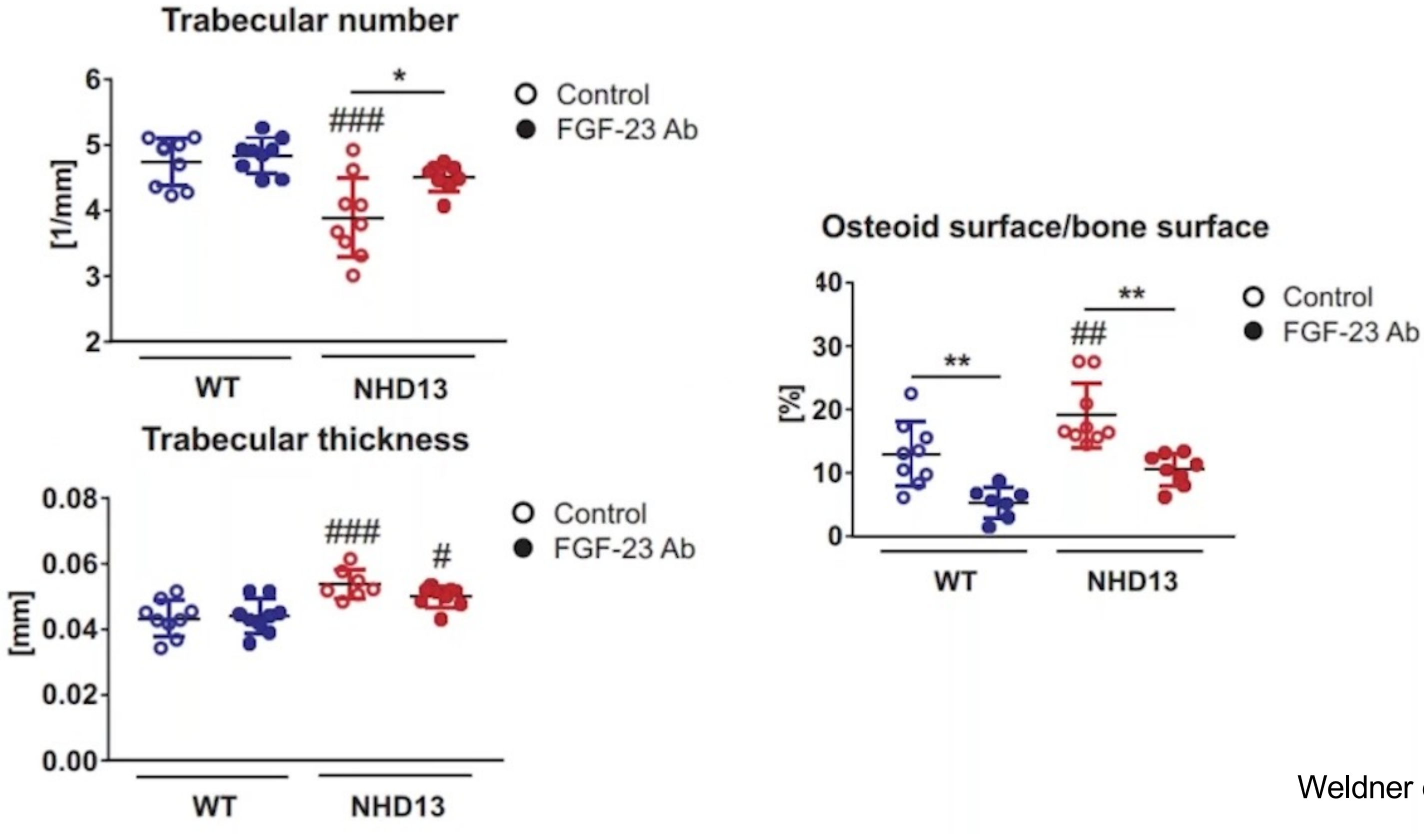
FGF-23 negatively correlates with RBC parameters





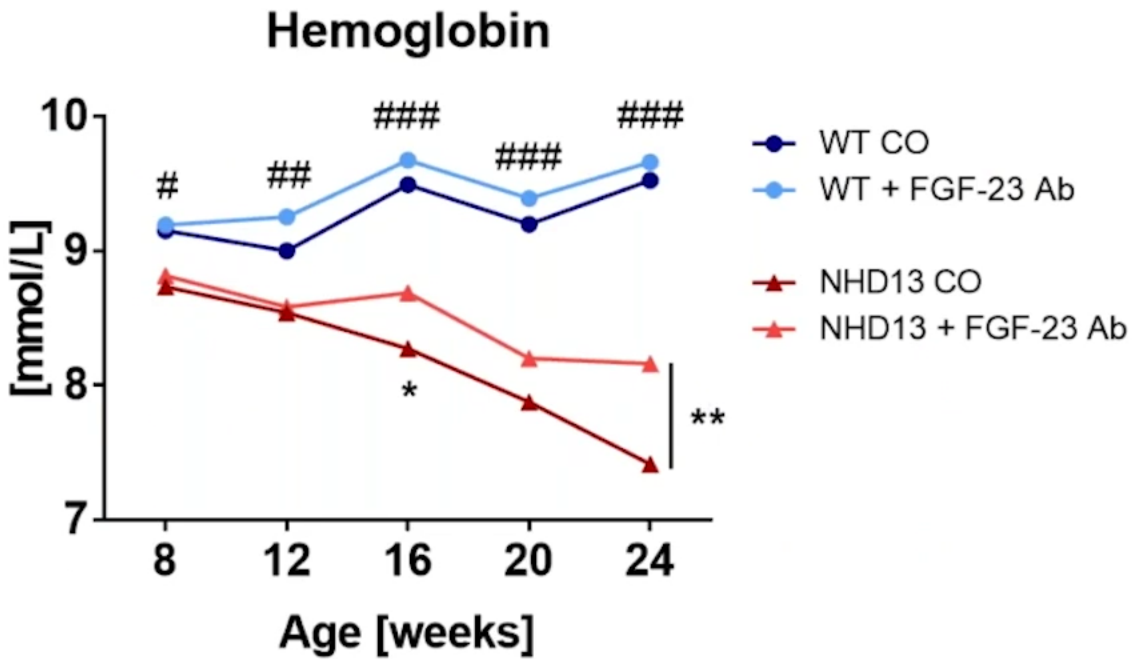
Weldner et al. 2020

Blocking FGF-23 restores the osteoid phenotype



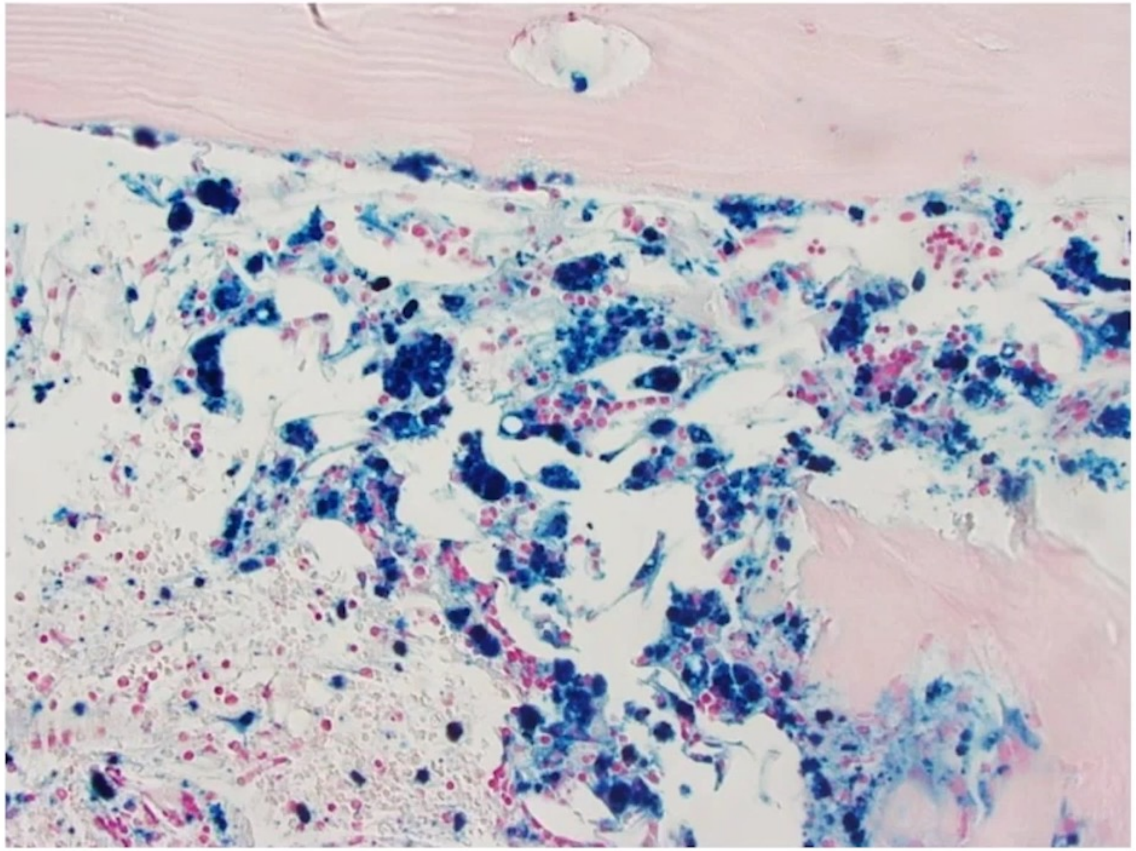
Weldner et al. 2020

Blocking FGF-23 delays anemia development



Weldner et al. 2020

Iron overload in the osteohematopoietic niche



Prussian blue staining

Dysregulations of iron homeostasis are detrimental for bone

Anemia and osteoporosis

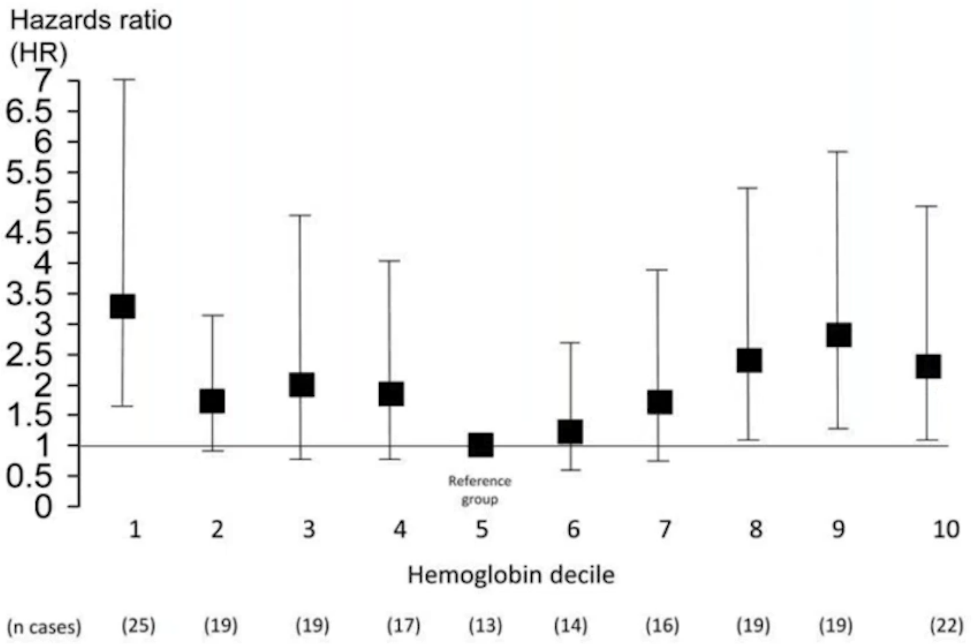
- Anemia (Hb) frequently does not correlate with BMD
- Associations of Hb with change of BMD over time was observed
- Hb appears to positively correlate with bone quality measurements and fractures

Outcome	Age group, years	Hemoglobin concentration			Anemia		
		ß	std err	p	ß	std err	p
Speed of Sound	20-39 (n=1,181)	1.713	1.096	0.118	-1.785	4.408	0.686
	40-59 (n=2,336)	**3.274**	**0.763**	**<0.001**	**-6.561**	**3.330**	**0.049**
	60-90 (n=1,648)	**2.927**	**0.772**	**<0.001**	**-6.830**	**2.882**	**0.018**

Hanneman et al. JCEM 2020

Associations of iron with bone

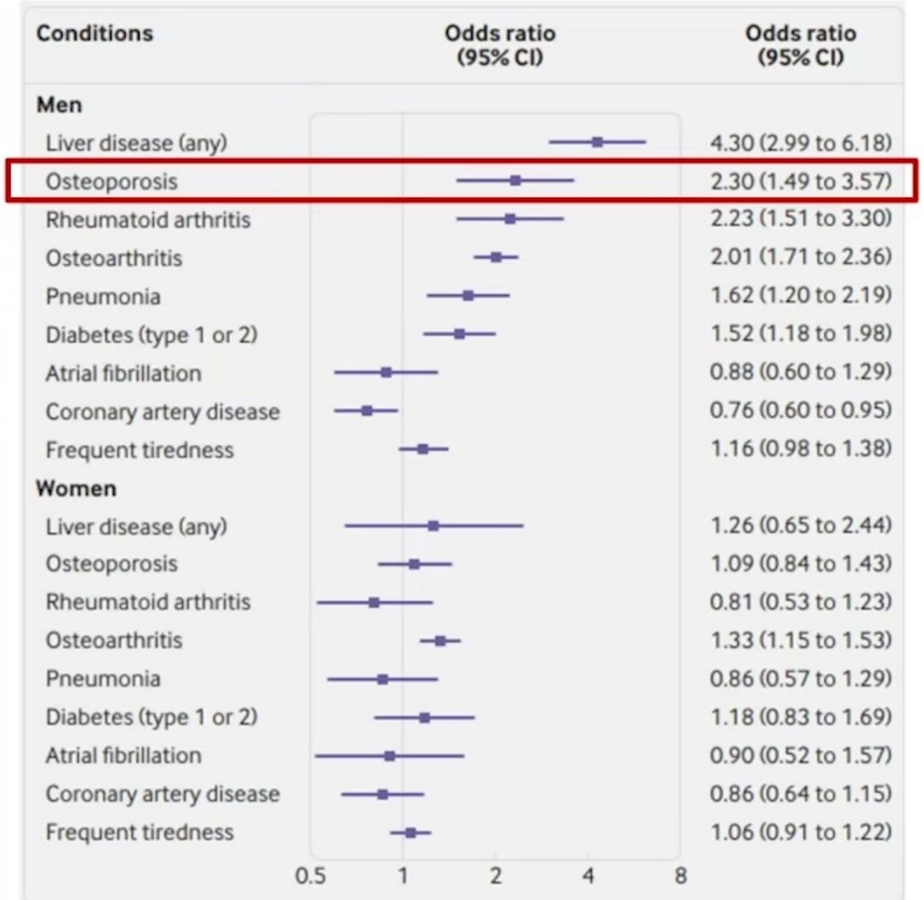
- Anemia is associated with low bone mass/fractures
- NHANES III study: >2,200 individuals aged 65+



Looker. Osteoporosis Int 2014

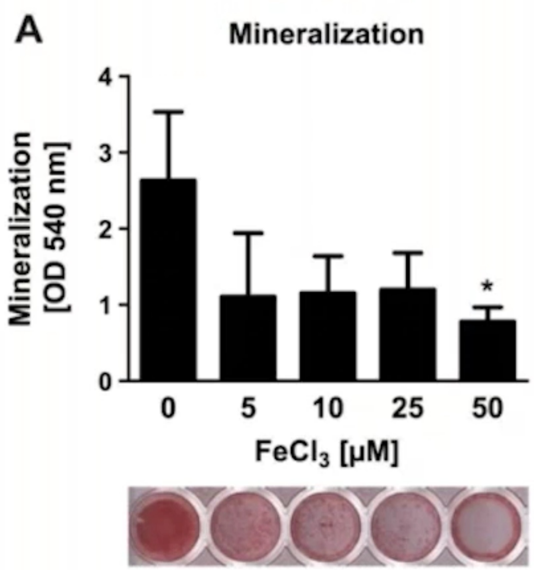
Dysregulations of iron homeostasis are detrimental for bone

Hereditary hemochromatosis and osteoporosis



Pilling et al. BMJ 2019

Iron inhibits, iron chelation stimulates osteoblastogenesis



Baschant et al. Haematologica 2012

Extrinsic contributions to MDS pathogenesis?

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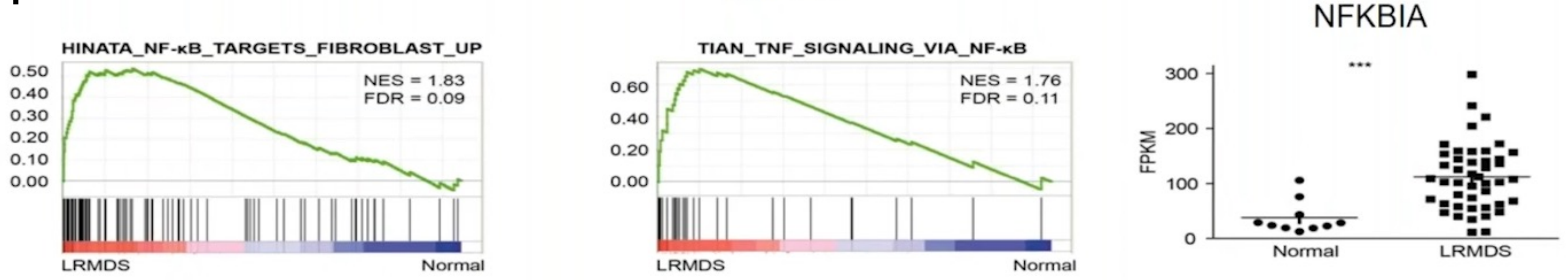
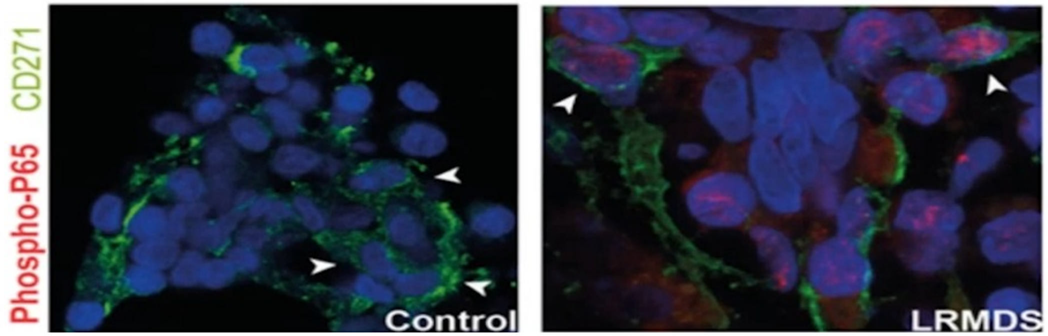
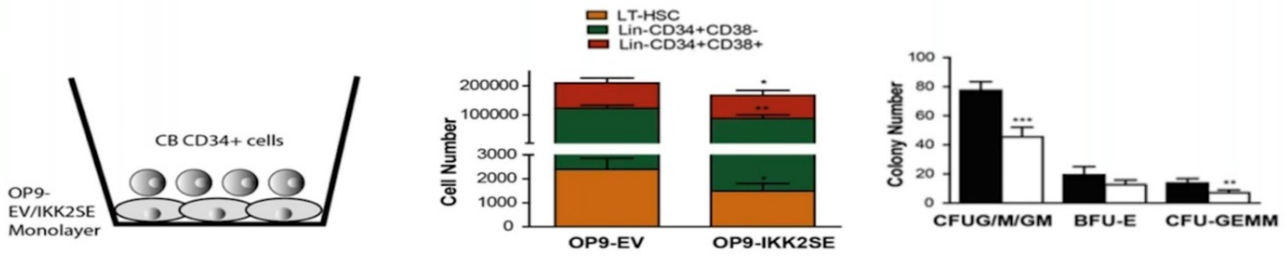
Mesenchimal activation of NF-kB signaling is common in LR-MDS and impairs hematopoiesis







Ping Z et al. Leukemia 2019; 33: 536-541

MDS mutations induce activation of innate immune signaling

MDS mutation

⇩

Activation innate immune signaling

Genetic abnormality	Gene class	Mutant gene/ Chromosome alteration	Innate immune-signaling effect*
Somatic mutations	Epigenetic modifiers	*TET2*	↑ IL-6 production via ↓ HDAC2 recruitment; ↑ IL-1β
		DNMT3A	↑ Type 1 IFN production via ↑ HDAC9 expression
		ASXL1	↑ NADPH oxidase ROS; ↑ TLR4, TICAM2
		EZH2	↑ S100A8/A9 via NF-κB derepression
	Spliceosomes	*SF3B1*	↑ NF-κB activation via ↓ MAP3K7
		SRSF2	↑ S100A8 and S100A9, DNA-RNA hybrids; ↑ NF-κB activation via caspase 8 isoform
		U2AF1	↑ DNA-RNA hybrids, ATG7 alternate splicing impairing autophagy
Chromosomal abnormality	N/A	Deletion 5q	Haploinsufficiency: RPS14 ↑ S100A8/A9; miR-145/146 + TIFAB ↑ TRAF6/IRAK1

Sallman and List, Blood 2019

Cull AH et al. Exp Hematol. 2017;55:56-70.

Molly A et al. Nature Cell Biology 21, 640–650(2019)

Pollyea DA et al. Haematologica. 2019

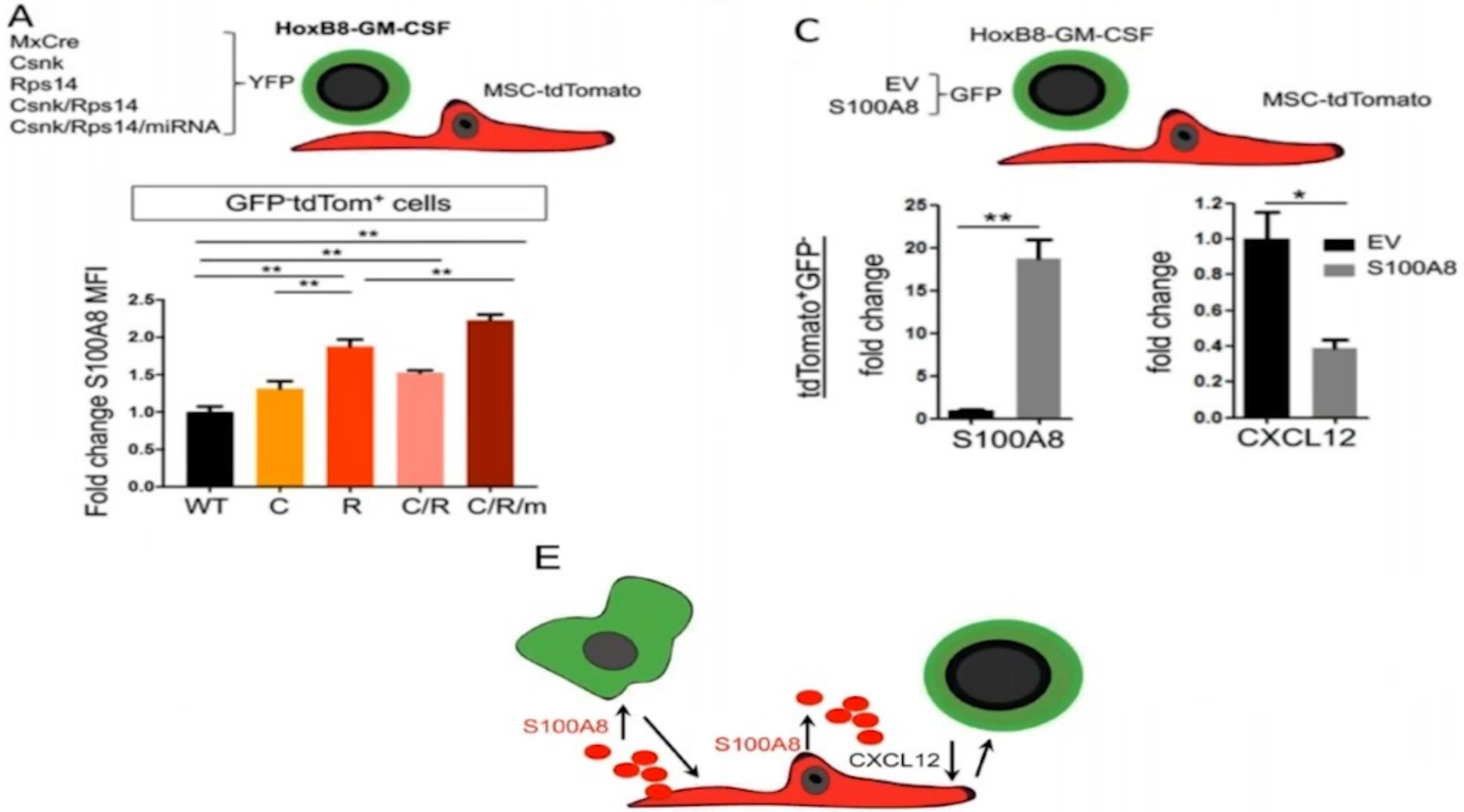
Niche contributions to hematopoietic neoplasm: Chicken or egg?

S100A8/A9 as a driver of MDS

Genetic event in HSPC
(*SF3B1*, *TET2*, del5q)

Zambetti N et al. Cell Stem Cell 2016
Basiorka AA et al. Blood. 2016 Dec 22;128(25):2960-2975
Schneider RK et al. Nat Med. 2016 Mar;22(3):288-97

5q- macrophages induce overexpression of S100A8 in the mesenchymal niche



Ribezzo F et al. Leukemia. 2019

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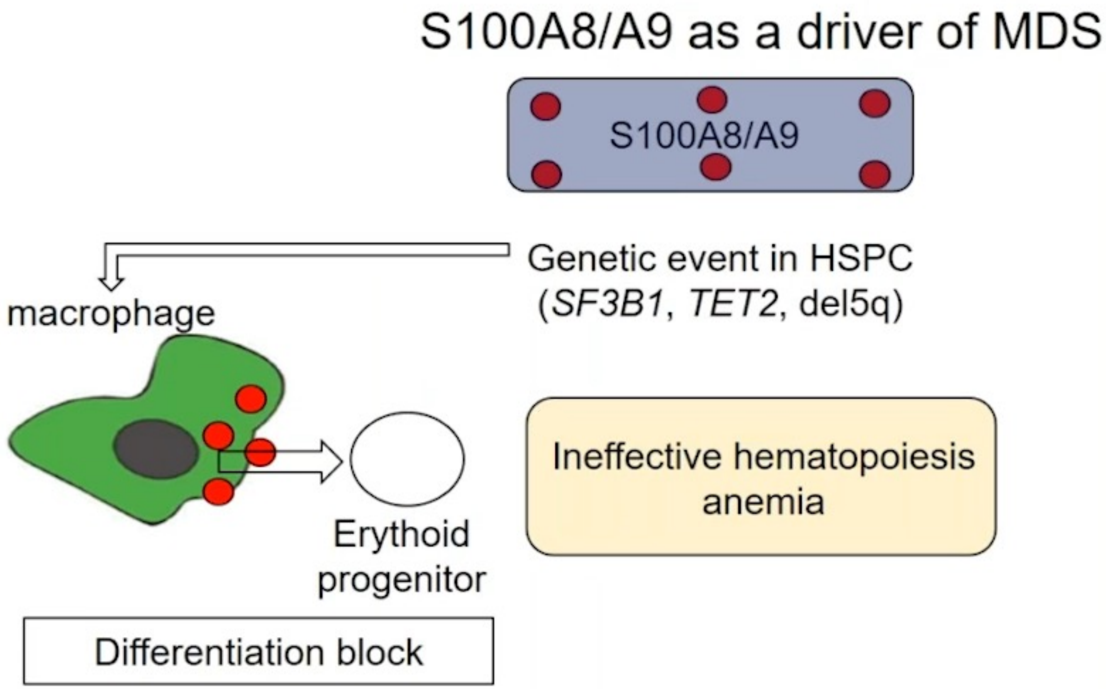
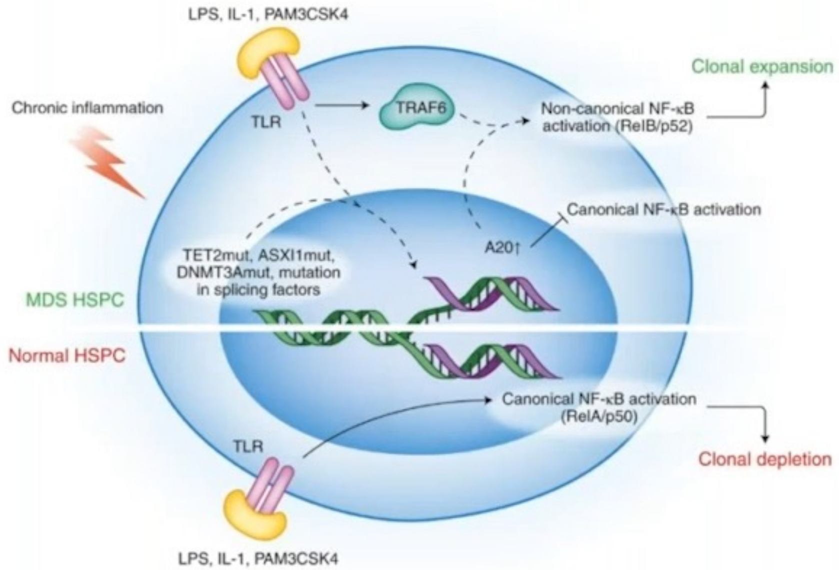


Zambetti N et al. Cell Stem Cell 2016
Basiorka AA et al. Blood. 2016 Dec 22;128(25):2960-2975
Schneider RK et al. Nat Med. 2016 Mar;22(3):288-97

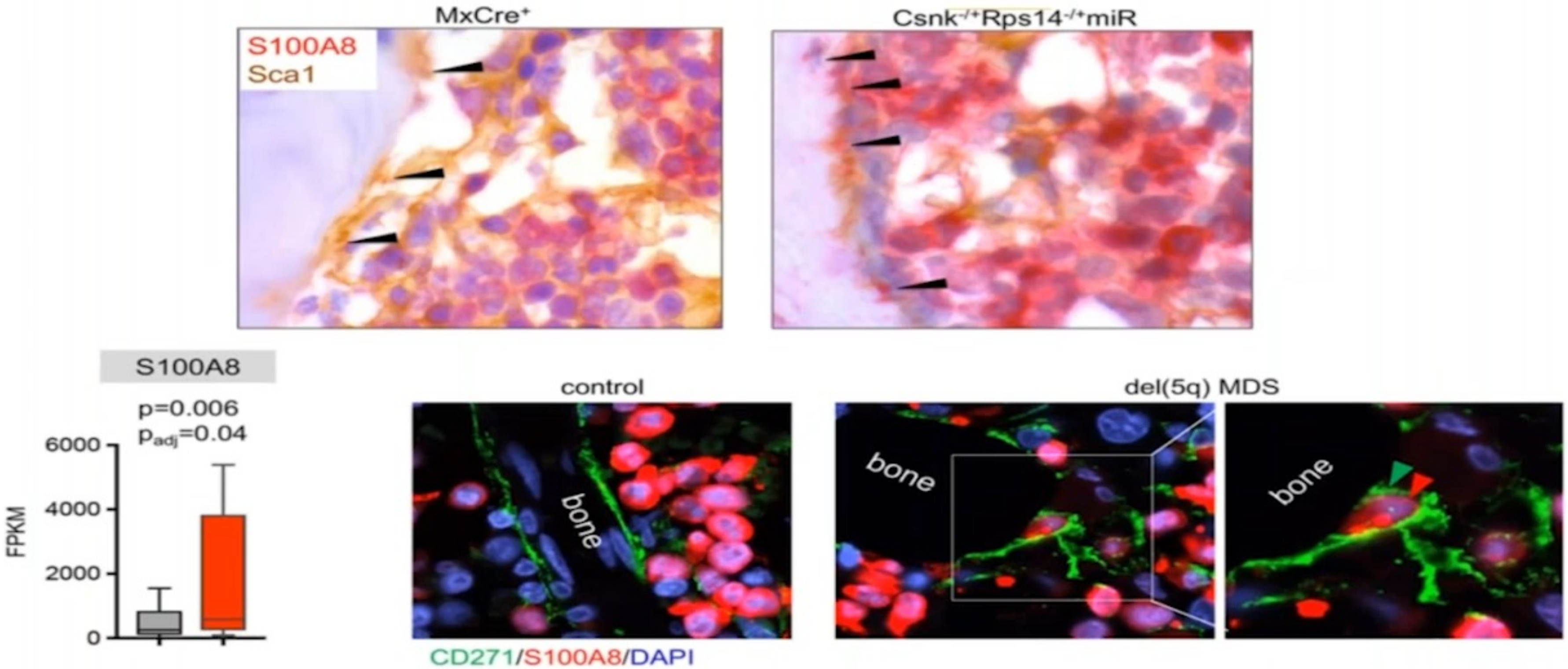
Chronic inflammation confers a competitive advantage in MDS HSPCs



- ❑ TRAF6 overexpressed in 40% of MDS
- ❑ Competitive advantage of TLR-TRAF6 primed HSPCs in inflammatory (LPS) environment
- ❑ Switch from canonical to non-canonical NFkB signaling
- ❑ TLR-TRAF mediated activation of A20
- ❑ Restored by inhibition A20/ noncanonical NFkB signaling

Muto et al. Nature Immunology 2020;21(5):535-545 (Figure: Ueda et al.)

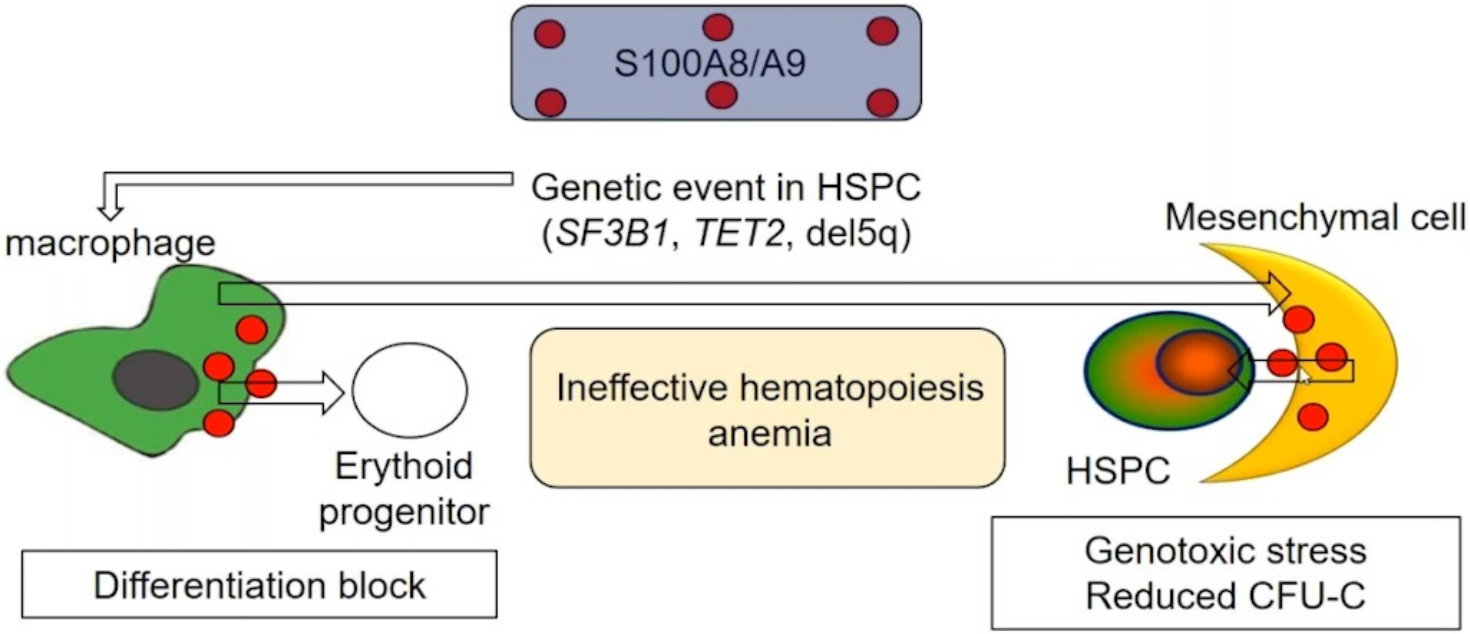
Aberrant hematopoietic cells induce S100A8 expression in the mesenchymal niche in 5q- MDS



Ribezzo F et al. Leukemia. 2019

Niche contributions to hematopoietic neoplasm: Chicken or egg?

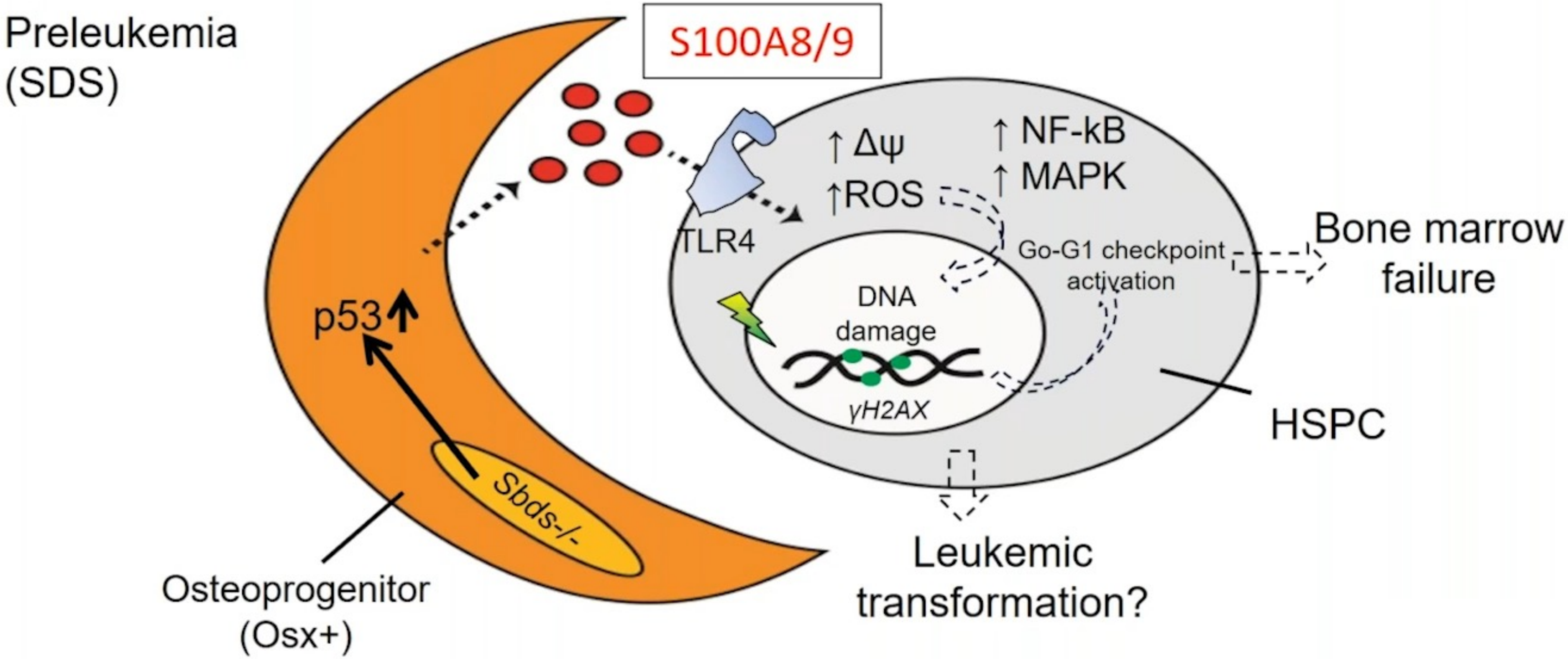
S100A8/A9 as a driver of MDS



Specific niches contribute to specific aspects of the disease phenotype

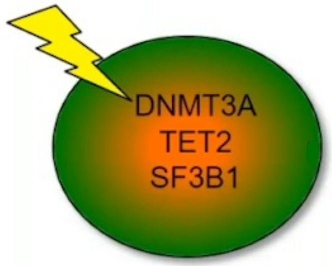
Zambetti N et al. Cell Stem Cell 2016
Basiorka AA et al. Blood. 2016 Dec 22;128(25):2960-2975
Schneider RK et al. Nat Med. 2016 Mar;22(3):288-97

Mesenchymal inflammation drives genotoxic stress in hematopoietic stem cells



Zambetti, Ping, Chen et al, *Cell Stem Cell*, 2016

A model of 'mesenchymal niche inflammation facilitated' clonal evolution in MDS



The mesenchymal niche in MDS. Pronk E, Raaijmakers MHGP. *Blood 2019 7;133(10):1031-1038* 2019

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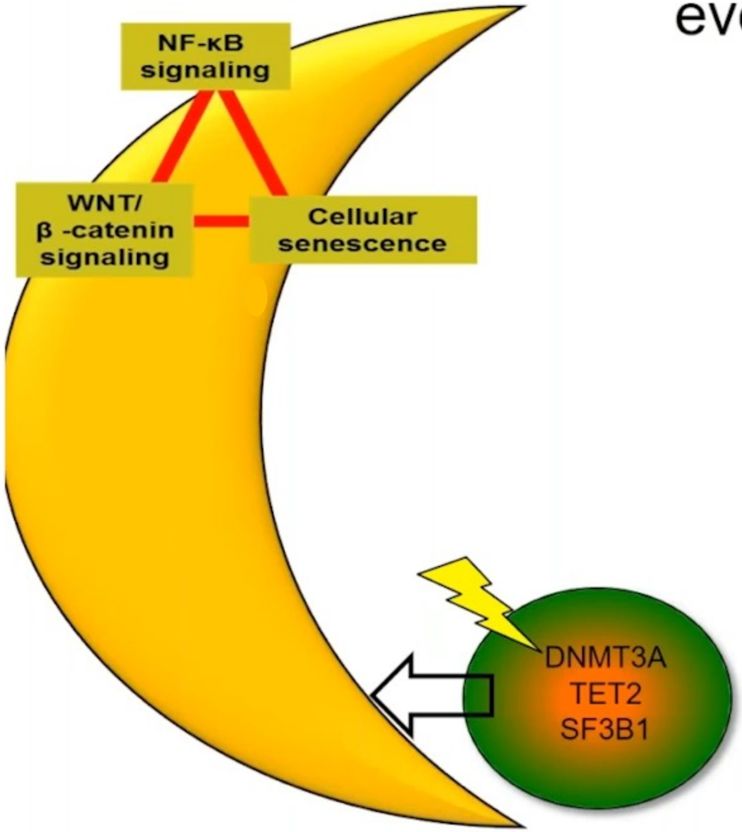

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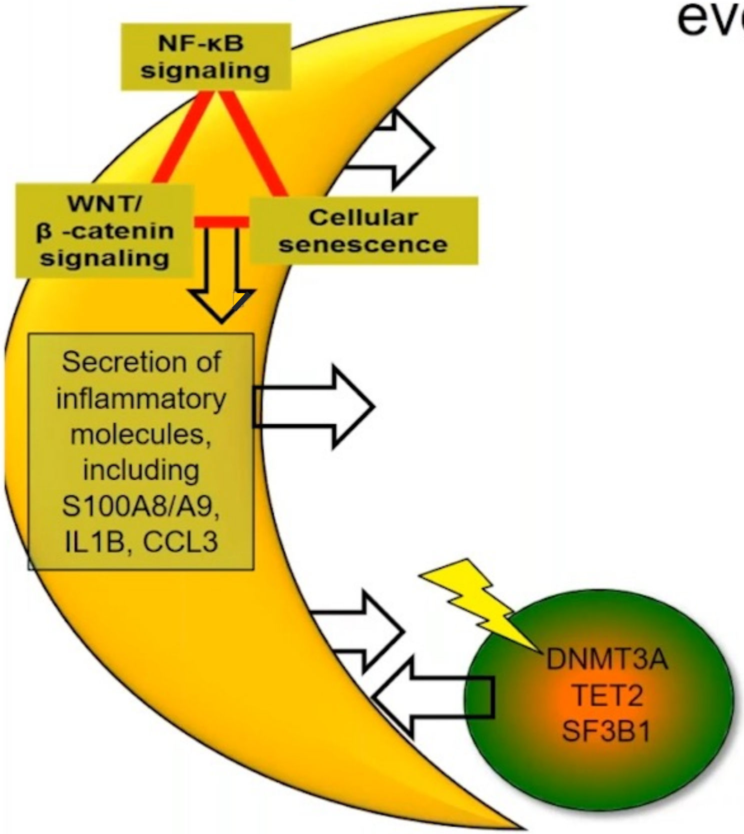
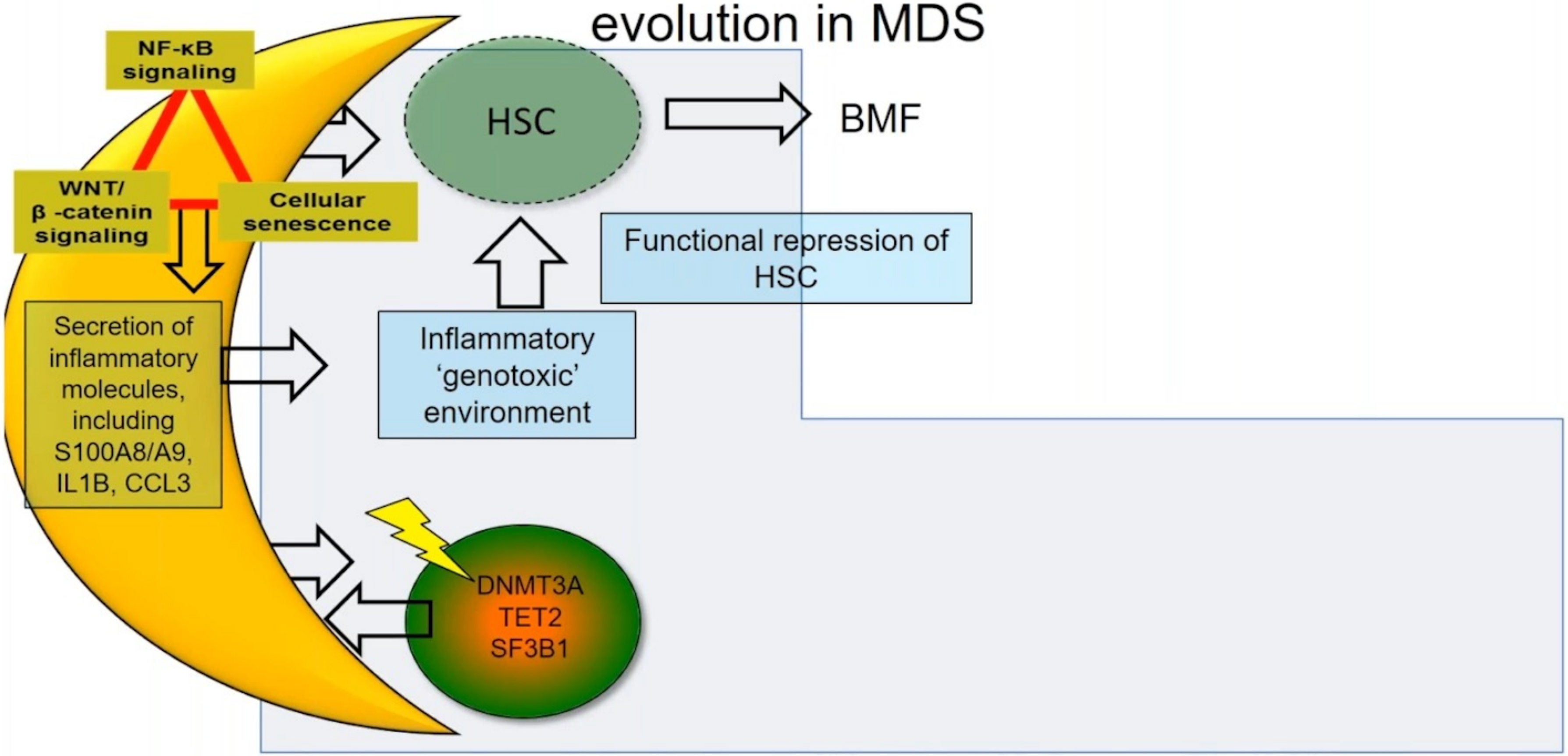


The mesenchymal niche in MDS. Pronk E, Raaijmakers MHGP. *Blood 2019 7;133(10):1031-1038* 2019

A model of ‘mesenchymal niche inflammation facilitated’ clonal evolution in MDS



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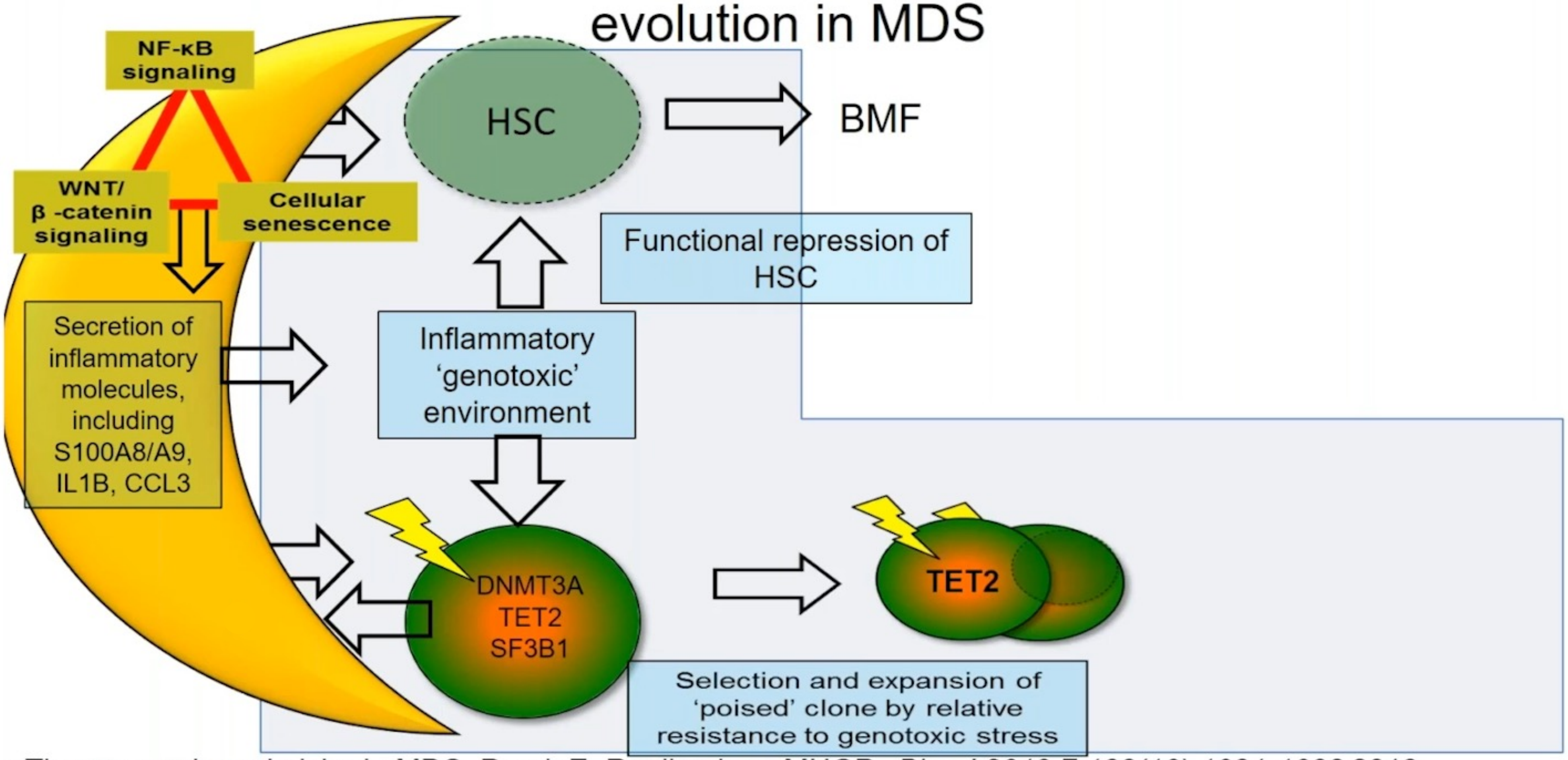

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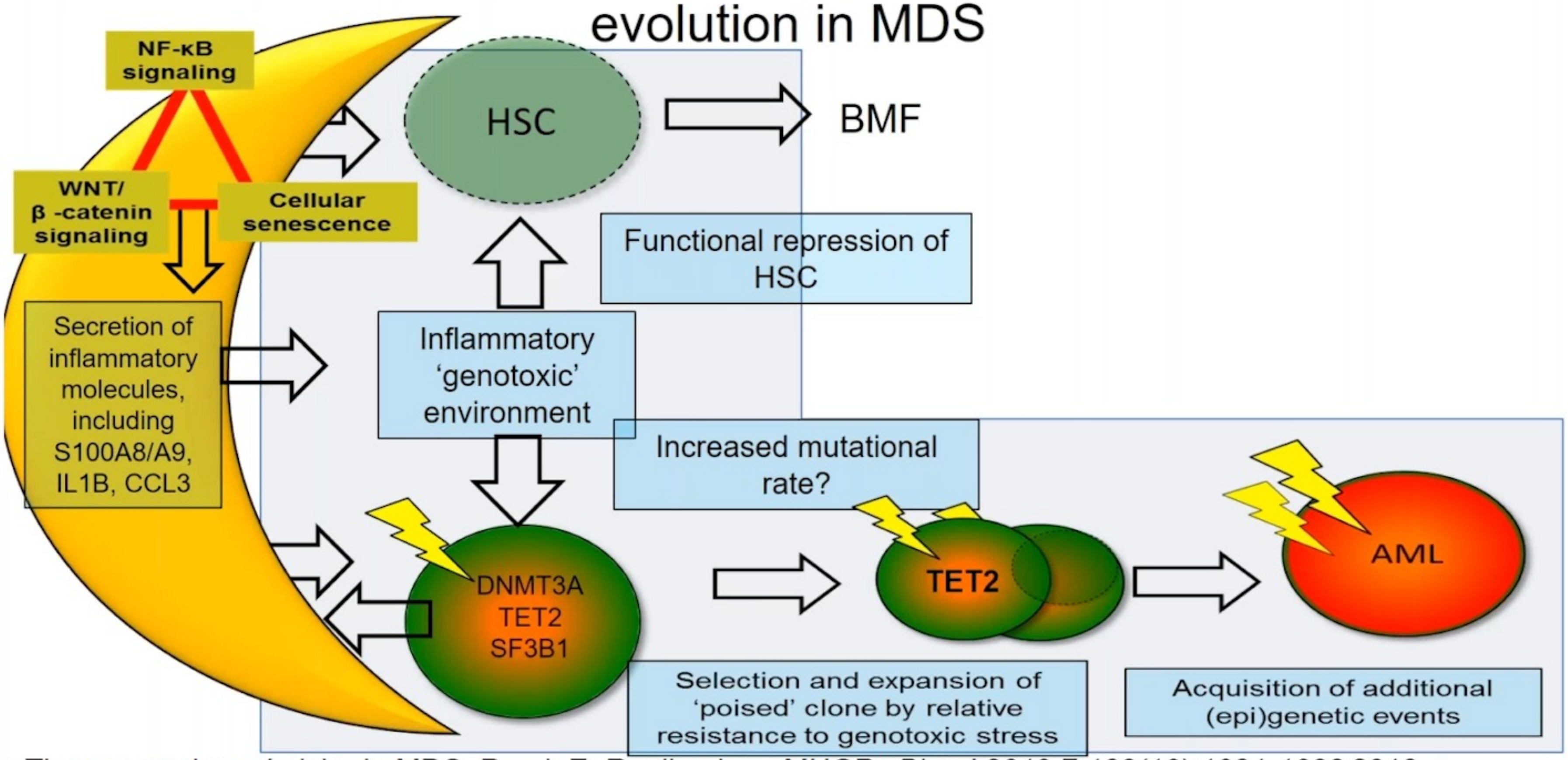

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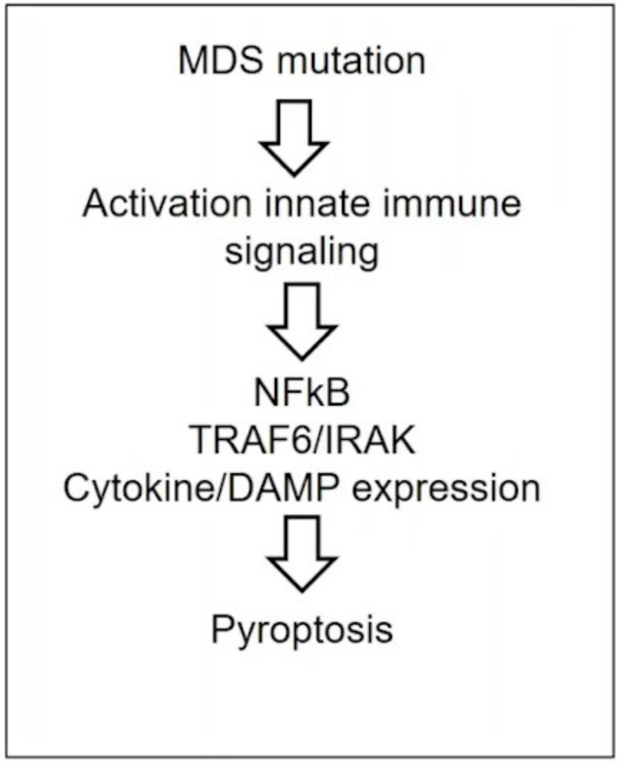
MDS mutations induce activation of innate immune signaling



Genetic abnormality	Gene class	Mutant gene/ Chromosome alteration	Innate immune-signaling effect*	Inflammasome-signaling effect†
Somatic mutations	Epigenetic modifiers	*TET2*	↑ IL-6 production via ↓ HDAC2 recruitment; ↑ IL-1β	↑ Pyroptosis and β-catenin signaling
		DNMT3A	↑ Type 1 IFN production via ↑ HDAC9 expression	
		ASXL1	↑ NADPH oxidase ROS; ↑ TLR4, TICAM2	↑ Pyroptosis and β-catenin signaling
		EZH2	↑ S100A8/A9 via NF-κB derepression	
	Spliceosomes	*SF3B1*	↑ NF-κB activation via ↓ MAP3K7	↑ Pyroptosis and β-catenin signaling
		SRSF2	↑ S100A8 and S100A9, DNA-RNA hybrids; ↑ NF-κB activation via caspase 8 isoform	↑ Pyroptosis and β-catenin signaling
		U2AF1	↑ DNA-RNA hybrids, ATG7 alternate splicing impairing autophagy	↑ Pyroptosis and β-catenin signaling ; impaired autophagy leading to NLRP3 activation
Chromosomal abnormality	N/A	Deletion 5q	Haploinsufficiency: RPS14 ↑ S100A8/A9; miR-145/146 + TIFAB ↑ TRAF6/IRAK1	↑ Pyroptosis and β-catenin signaling

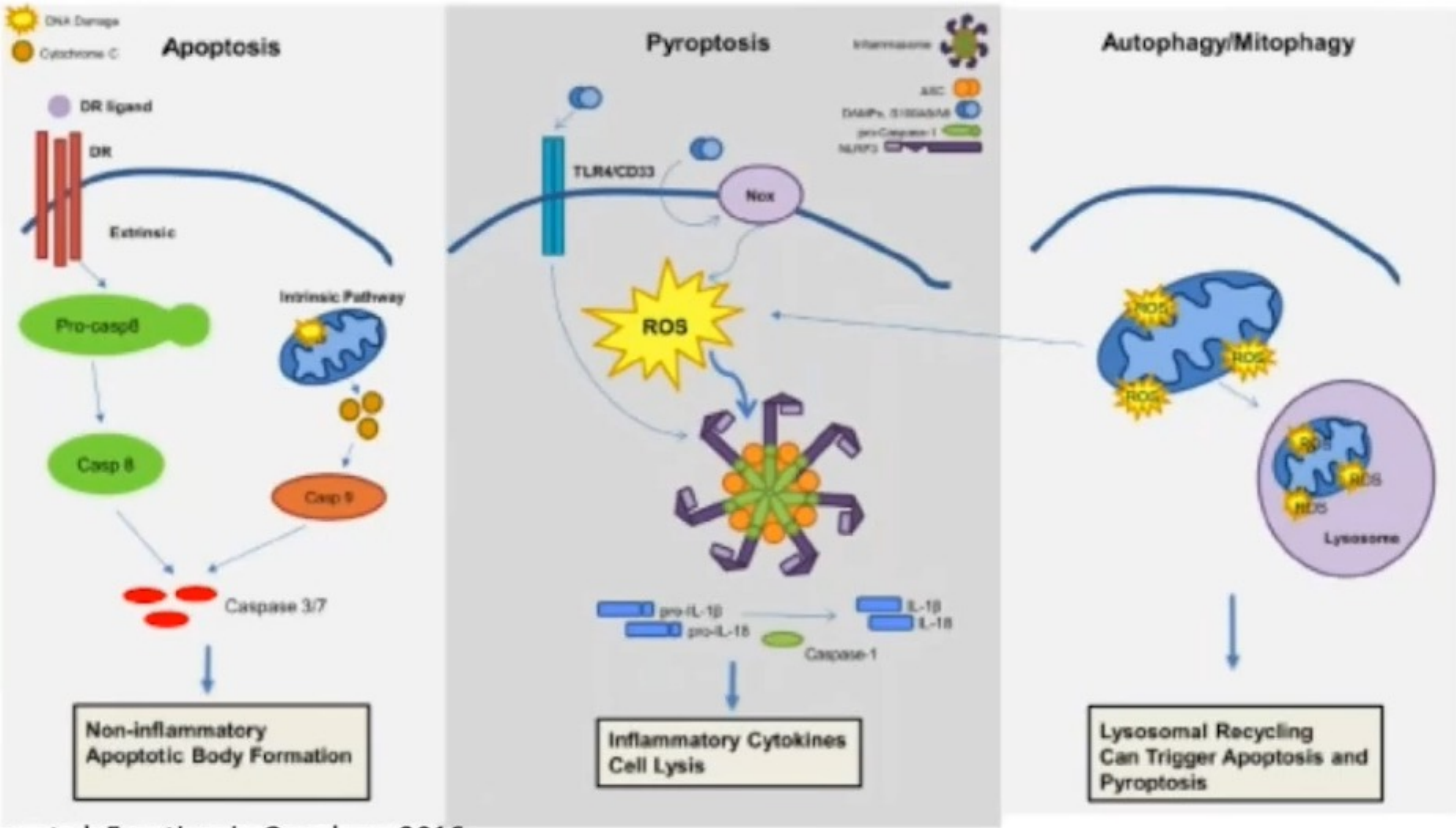
Sallman and List, Blood 2019

Cull AH et al. Exp Hematol. 2017;55:56-70.

Molly A et al. Nature Cell Biology 21, 640–650(2019)

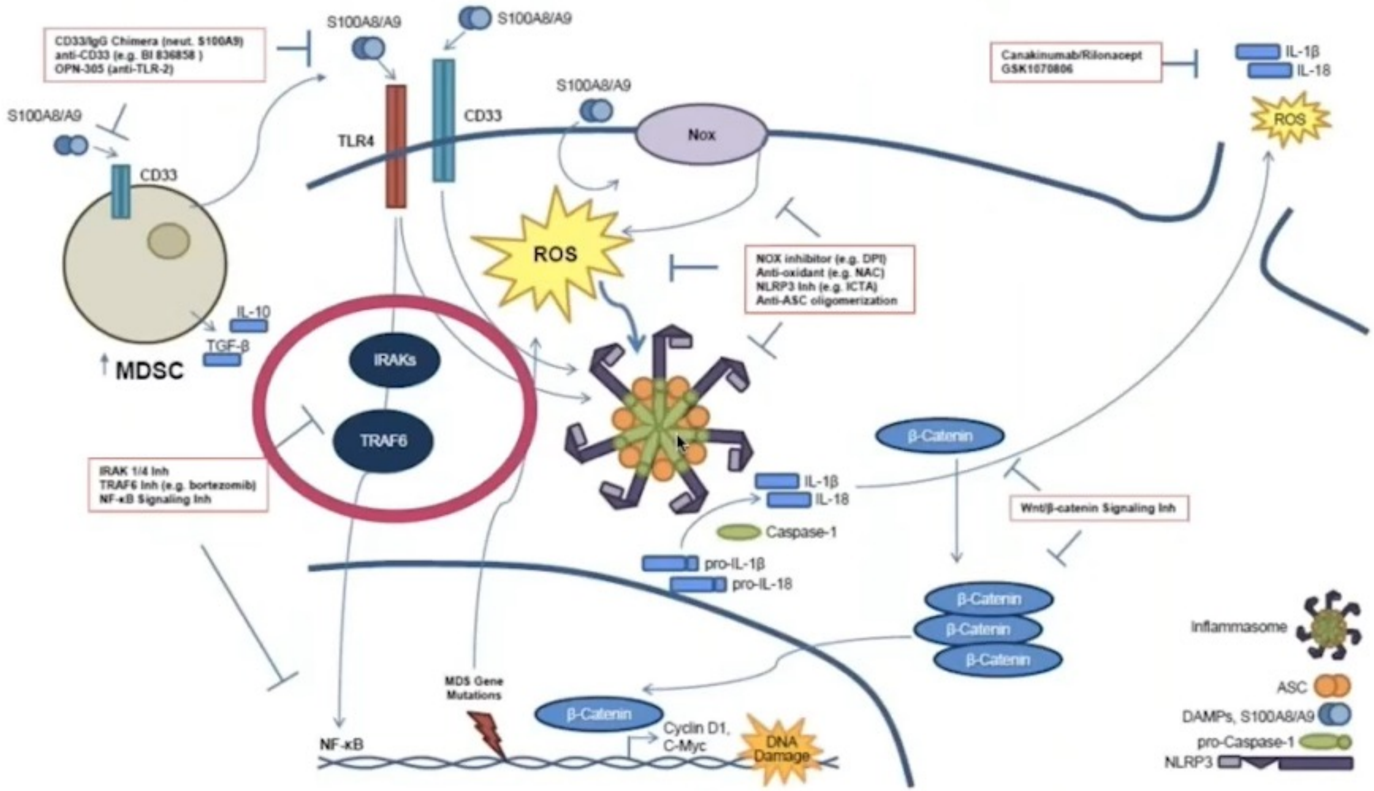
Pollyea DA et al. Haematologica. 2019

Mechanisms of cell death in the pathogenesis of MDS



Sallman et al, Frontiers in Oncology, 2016
Basiorka et al, Blood 2016

Targeting the “Inflammasome”

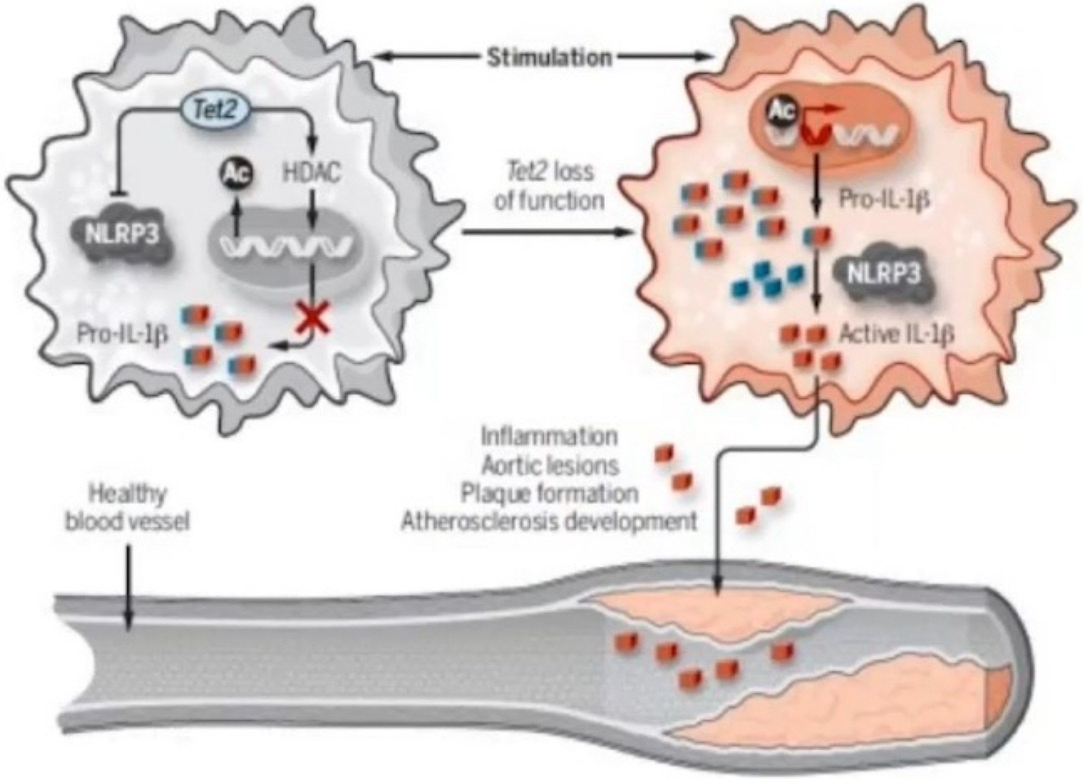


Canakinumab, rilonacept, and bortezomib are not yet licensed for MDS indications in Europe or Israel.
ASC, associated speck-like protein containing a caspase-recruitment domain; IL, interleukin; IRAKs, IL-1 receptor-associated kinases; Inh, inhibitor; neut., neutrophil; NOX, dihydronicotinamide-adenine dinucleotide phosphate oxidase; TGF-β, transforming growth factor-b; TLR, toll-like receptor; TRAF6, tumour necrosis factor receptor-associated factor 6.

Sallman DA et al.
Clin Lymphoma Myeloma Leuk 2017; 17: 613-620

Enigma of TET2 unravelled?

- HSPC differentiation and expansion of macrophage pool
- Increased production of pro-infl IL-1β and NLRP3
- Changes abrogated by treating with NLRP3 inhibitor

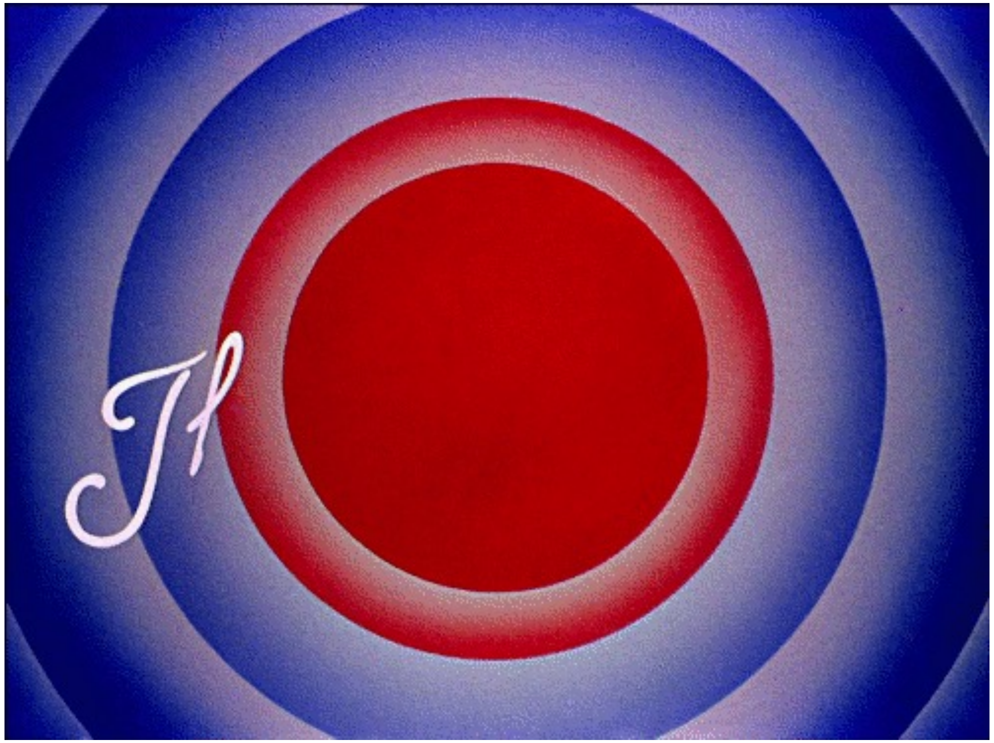


- IL-1 neutralising antibodies
- Hypomethylating agents
- NLRP3 inhibitor

Zhu et al, Science
Fuster, et al, Science, 355, 842, 2017

Take home messages

- La nicchia emopoietica gioca un ruolo chiave nella patogenesi delle MDS
- Le mutazioni (driver e subclonali) supportano l'esistenza di un microambiente infiammatorio
- L'infiammazione può a sua volta provocare instabilità genomica che porta a progressione di malattia
- Impairment osseo nelle MDS, da monitorare anche nella pratica clinica
- Numerosi target terapeutici dallo studio del microambiente
  - ✓ **Ferrochelazione**
  - ✓ **FGF-23**
  - ✓ **Inflammasoma**
    - NF-kB
    - WNT/Beta-catenin
    - S100A8/A9, ROS, NLRP3
    - IRAKs, TLRs, TRAF6
    - IL-1, IL-18, TGF-beta



Thank you!

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