



**University of  
Zurich**<sup>UZH</sup>

**Zurich Open Repository and  
Archive**

University of Zurich  
Main Library  
Strickhofstrasse 39  
CH-8057 Zurich  
[www.zora.uzh.ch](http://www.zora.uzh.ch)

---

Year: 2021

---

## **Inflammation as a regulator of hematopoietic stem cell function in disease, aging, and clonal selection**

Caiado, Francisco ; Pietras, Eric M ; Manz, Markus G

**Abstract:** Inflammation is an evolutionarily selected defense response to infection or tissue damage that involves activation and consumption of immune cells in order to reestablish and maintain organismal integrity. In this process, hematopoietic stem cells (HSCs) are themselves exposed to inflammatory cues and via proliferation and differentiation, replace mature immune cells in a demand-adapted fashion. Here, we review how major sources of systemic inflammation act on and subsequently shape HSC fate and function. We highlight how lifelong inflammatory exposure contributes to HSC inflamm-aging and selection of premalignant HSC clones. Finally, we explore emerging areas of interest and open questions remaining in the field.

DOI: <https://doi.org/10.1084/jem.20201541>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-207126>

Journal Article

Published Version



The following work is licensed under a Creative Commons: Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0) License.

Originally published at:



Caiado, Francisco; Pietras, Eric M; Manz, Markus G (2021). Inflammation as a regulator of hematopoietic stem cell function in disease, aging, and clonal selection. *Journal of Experimental Medicine*, 218(7):e20201541.

DOI: <https://doi.org/10.1084/jem.20201541>

REVIEW

Hematopoietic Stem Cells Focus

# Inflammation as a regulator of hematopoietic stem cell function in disease, aging, and clonal selection

Francisco Caiado<sup>1,2</sup> , Eric M. Pietras<sup>3\*</sup> , and Markus G. Manz<sup>1,2\*</sup> 

**Inflammation is an evolutionarily selected defense response to infection or tissue damage that involves activation and consumption of immune cells in order to reestablish and maintain organismal integrity. In this process, hematopoietic stem cells (HSCs) are themselves exposed to inflammatory cues and via proliferation and differentiation, replace mature immune cells in a demand-adapted fashion. Here, we review how major sources of systemic inflammation act on and subsequently shape HSC fate and function. We highlight how lifelong inflammatory exposure contributes to HSC inflamm-aging and selection of premalignant HSC clones. Finally, we explore emerging areas of interest and open questions remaining in the field.**

## Introduction

The hematopoietic system is responsible for lifelong blood cell production and downstream primary functions, including oxygen transportation (erythrocytes), hemostasis (platelets), and host defense (leukocytes: myeloid and lymphoid cells). Recent estimations suggest that adult bone marrow (BM) produces  $2\text{--}6 \times 10^{10}$  cells/kg/d in mice and  $5\text{--}7 \times 10^{10}$  cells/kg/d in humans under homeostatic conditions (steady-state hematopoiesis), which can increase several fold upon stress demands, e.g., infection (demand-adapted or “emergency” hematopoiesis; [Nombela-Arrieta and Manz, 2017](#); [Sender and Milo, 2021](#)). To replenish high cellular consumption while preserving its function and preventing potentially debilitating conditions derived from hematopoietic failure or excess (e.g., aplasia or leukemia, respectively), the hematopoietic system is tightly regulated and characterized by a hierarchical cellular differentiation system sustained by rare stem cell populations kept in protective BM niches coupled to sensing mechanisms that connect the stress-exposed periphery to the BM tissue.

Hematopoietic stem cells (HSCs; also termed long-term [LT] HSCs) reside at the top of the hematopoietic hierarchy and have two unique properties: self-renewal (ability to generate a daughter cell that retains HSC activity) and multilineage differentiation capacity (ability to produce all blood cell types). HSCs differentiate into multipotent progenitors (MPPs), which together are defined as hematopoietic stem and progenitor cells (HSPCs) and in mice

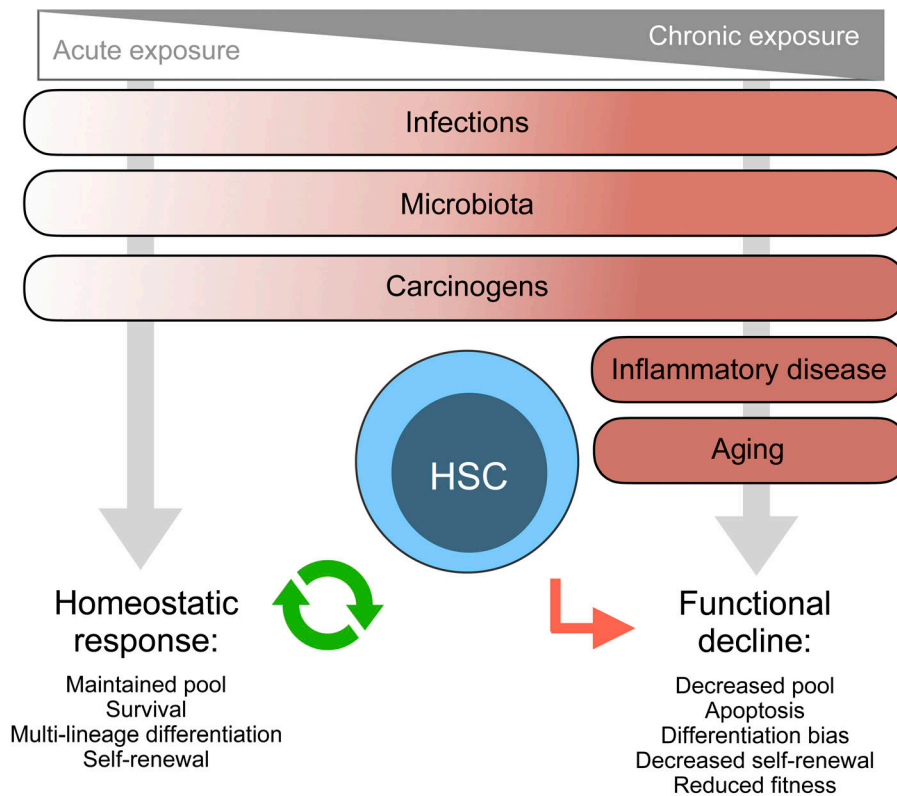
share Lin<sup>−</sup>Sca-1<sup>+</sup> and c-Kit<sup>+</sup> marker expression. MPPs subsequently differentiate to increasingly lineage-restricted progenitor cells that undergo terminal differentiation into mature blood cells. MPPs and their progeny are termed hematopoietic progenitor cells (HPCs; [Wilson et al., 2008](#); [Manz and Boettcher, 2014](#)). Under steady-state conditions, most adult HSCs are quiescent, residing in the G<sub>0</sub> phase of the cell cycle. Highly quiescent HSC fractions have an estimated turnover rate of months (in mice) to years (in humans; [Takizawa et al., 2011](#); [Trumpp et al., 2010](#)). Thus, daily hematopoietic production is primarily sustained by highly proliferative HPCs ([Sun et al., 2014](#); [Busch et al., 2015](#)). However, HSCs can sense environmental cues and depending on the type, duration, and concentration of the signal(s), initiate demand-adapted hematopoiesis by exiting quiescence, proliferating and differentiating, and/or self-renewing.

Inflammation, generally defined as a protective immune response to infection and tissue damage, is mediated by proinflammatory cytokines and chemokines that are produced by stressed or damaged cells and sensed by effector cells that orchestrate a systemic and/or local response ([Medzhitov, 2008](#)). It has now become well recognized that HSCs are key players in systemic inflammatory responses capable of integrating external inflammatory cues into cellular responses and establishing a demand-adapted axis between peripheral stresses and hematopoietic responses in the BM ([Takizawa et al., 2012](#)). In recent years, a wealth of new investigations has probed more deeply into how HSC function is impacted by inflammation and how

<sup>1</sup>Department of Medical Oncology and Hematology, University Hospital Zürich, Zürich, Switzerland; <sup>2</sup>University of Zürich, Comprehensive Cancer Center Zürich, Zürich, Switzerland; <sup>3</sup>Division of Hematology, University of Colorado Anschutz Medical Campus, Aurora, CO.

\*E.M. Pietras and M.G. Manz contributed equally to this paper; Correspondence to Markus G. Manz: [markus.manz@usz.ch](mailto:markus.manz@usz.ch); Eric M. Pietras: [eric.pietras@CUAnschutz.edu](mailto:eric.pietras@CUAnschutz.edu).

© 2021 Caiado et al. This article is distributed under the terms of an Attribution–Noncommercial–Share Alike–No Mirror Sites license for the first six months after the publication date (see <http://www.rupress.org/terms/>). After six months it is available under a Creative Commons License (Attribution–Noncommercial–Share Alike 4.0 International license, as described at <https://creativecommons.org/licenses/by-nc-sa/4.0/>).



**Figure 1. Causes and consequences of inflammation on HSC functionality.** Schematic representation of current understanding in the field on the major causes of systemic inflammation known to impact HSC biology in mouse models (infection, microbiota, carcinogens, inflammatory diseases, aging). Each cause is distributed in a gradient regarding the duration of inflammation: acute to chronic. HSC properties during homeostatic responses (more frequently associated with acute inflammation) or functional decline (more frequently associated with chronic inflammation) are depicted.

such responses may contribute to HSC aging and oncogenesis (Fig. 1). Here, we summarize current knowledge in the field with an emphasis on highlighting new themes and ambiguities emerging in the current literature.

**Main causes of inflammation and their impact on HSC biology**  
**Infectious diseases**

King and Goodell (2011) previously defined four different mechanisms by which infections can influence HSC biology. The first two mechanisms act via direct effects on HSCs: (1) direct infection or (2) direct recognition of a pathogen. The other two mechanisms are indirect: (3) via proinflammatory cytokines released by other cells or (4) through changes in the cellular BM microenvironment. Here, we focus on and dissect mechanism 3, particularly in the context of in vivo mouse infection models. Table 1 summarizes the major sources of infection-derived inflammation (viral, bacterial, protozoan, and fungal infections), their associated inflammatory pathways, and consequent biological impacts on HSCs. Despite the significant variability among the different infection models, there are some conserved features: (a) Infection-derived inflammation leads frequently to HSC functional decline, including reduced repopulating capacity and increased proliferation associated with a myeloid lineage bias; (b) HSC functional decline is most commonly associated with chronic infection, which suggests that prolonged inflammation and the resultant demand may exert cumulative effects on HSC function; (c) inflammatory cytokines can act both directly on HSCs and indirectly, leading to secondary inflammatory signal production by BM niche cells, such as mesenchymal stromal cells (MSCs), endothelial cells, and mature

hematopoietic cells. Overall, the studies presented in Table 1 indicate that infection-derived inflammation is a significant source of BM inflammation with the potential to establish long-term functional impairment on HSCs (Binder et al., 1997; de Bruin et al., 2013; Matattal et al., 2014; Schürch et al., 2014; Isringhausen et al., 2020 Preprint; Hirche et al., 2017; Scumpia et al., 2010; Burberry et al., 2014; Shi et al., 2018; Baldrige et al., 2010; Matattal et al., 2016; Florez et al., 2020; Choi et al., 2011; Khan et al., 2020; MacNamara et al., 2011; Smith et al., 2018; Vainieri et al., 2016; Haltalli et al., 2020; Martínez et al., 2018; Mitroulis et al., 2018).

**Microbiota**

The intestinal bacterial microbiome is emerging as a key regulator of hematopoiesis (Tada et al., 1996; Deshmukh et al., 2014; Balmer et al., 2014; Khosravi et al., 2014; Lee et al., 2011; Staffas et al., 2018). Concerning the effects of microbiota on HSPC pool size, Balmer et al. (2014) showed that germ-free (GF) mice (mice lacking microbiota) or antibiotic-treated specific pathogen-free (SPF) mice (carrying a full microbiota of >100 bacterial species, but free of known mouse pathogens) have lower steady-state HSPC numbers compared with untreated SPF mice. Interestingly, colonization of GF mice with a defined, low-complexity microbiota led to an intermediate expansion of the HSPC pool to levels still below that of SPF mice. This suggests that HSPC pool size is governed by the strength of microbiota-associated signals and/or the presence of a complex microbial milieu. Later, Josefsdottir et al. (2017) further demonstrated that antibiotic-treated mice show microbiota depletion (but unaltered serum levels of IFNs, IL-6, TNF, G-CSF) and a decrease in HSPC pool

Table 1. Summary of mouse studies describing the contribution of different infection-derived inflammatory sources to HSC biology

Source	Inflammatory pathway	Molecular mechanism	Effect on HSCs	Reference
<b>Viral</b>				
Lymphocytic choriomeningitis virus	IFN- $\alpha/\beta$ -IFNAR	ND	30-fold reduction on CFU (at infection day 3)	Binder et al. (1997)
	IFN- $\gamma$ -IFNGR	IFN- $\gamma$ -induced SOCS1 inhibits TPO-induced STAT5 phosphorylation and leads to decreased/increased cyclin D1/Cdkn1C	Decreased pool recovery and self-renewal capacity (at infection days 4–12)	de Bruin et al. (2013)
	IFN- $\gamma$ -IFNGR	IFN- $\gamma$ -induced <i>Cebpb</i> in high IFNGR-expressing myeloid-biased HSCs	Increased proliferation and myeloid bias associated to decreased self-renewal (at infection day 6)	Matatall et al. (2014)
	IFN- $\gamma$ -IFNGR-IL-6	Cytotoxic CD8 <sup>+</sup> T cell-produced IFN- $\gamma$ activates IL-6 production by BM MSCs, leading to reduced <i>Runx-1</i> and <i>Cebpa</i> expression	Increased myeloid-differentiation bias on HSPCs	Schürch et al. (2014)
	IFN- $\alpha/\beta$ -IFNAR and IFN- $\gamma$ -IFNGR	Persistent destruction of CARC networks by virus-specific IFN-producing CD8 <sup>+</sup> T cells—loss of HSC quiescence-enforcing niche	Increased proliferation, decreased pool size, and decreased repopulating capacity	Isringhausen et al., 2020 Preprint
Murine cytomegalovirus	Increased IFN- $\gamma$ , IL-17, and CCL12 levels	Inflammatory milieu associates in an IFNAR-independent manner with increased <i>Sca-1</i> and <i>Evi1</i> gene expression in HSCs	Decreased repopulating capacity and increased myeloid differentiation, after BM viral clearance (at infection day 21)	Hirche et al. (2017)
<b>Bacterial</b>				
Polymicrobial sepsis using cecal ligation and puncture model	ND	HSC expansion associates with reduced BM cellularity but is independent from MyD88, TRIF, IFNAR, TNF- $\alpha$ , IL-1, IL-6, prostaglandins, oxidative stress, and super antigen signaling	Increased pool size	Scumpia et al. (2010)
<i>Escherichia coli</i>	G-CSF/CXCL12	Dual stimulation of NOD1 and TLR4 leads to increased G-CSF and decreased CXCL12 production in radioresistant endothelial cells	Increased mobilization of BM-expanded HSCs, reduced repopulating capacity, and increased myeloid-differentiation	Burberry et al. (2014)
	SHH-GLI	ERK1/2-SPI-mediated increased SHH expression in Lin <sup>+</sup> BM cells leads to higher GLI levels in HSCs	Proliferation and myeloid differentiation	Shi et al. (2018)
	IFN- $\gamma$ -IFNGR	ND	Increased proliferation and decreased repopulating capacity (4 wk after single bacterial inoculation)	Baldridge et al. (2010)
<i>M. avium</i>	IFN- $\gamma$ -IFNGR	IFN- $\gamma$ -induced <i>Batf2</i> leading to HSPC terminal differentiation	Decreased pool size, repopulating capacity, and increased myeloid differentiation (after six monthly inoculations)	Matatall et al. (2016)
	IFN- $\gamma$ -IFNGR	IFN- $\gamma$ -induced expression of BST2 (noncanonical E-selectin ligand) displaces HSCs from quiescence-enforcing CARC niche to an activating E-selectin-positive vascular niche	Increased proliferation, terminal differentiation, and decreased pool size (after four monthly inoculations)	Florez et al. (2020)
<i>Mycobacterium tuberculosis</i>	TNF- $\alpha$ /IL-6	TLR2 and MyD88 bacterial sensing dependent	Increased HSPC pool and myeloid differentiation	Choi et al. (2011)
	IFN- $\alpha/\beta$ -IFNAR	IFNAR-dependent reprogramming of HSCs leading to dysregulated iron metabolism, depolarized mitochondrial membrane, and necrosis in myeloid progenitors	Decreased pool and reconstitution capacity (up to 1 yr after infection)	Khan et al. (2020)

Table 1. Summary of mouse studies describing the contribution of different infection-derived inflammatory sources to HSC biology (Continued)

Source	Inflammatory pathway	Molecular mechanism	Effect on HSCs	Reference
<i>Ehrlichia muris</i>	IFN- $\gamma$ -IFNGR	ND	Decreased pool and reconstitution capacity, and increased myeloid differentiation bias (at infection day 8)	MacNamara et al. (2011)
<b>Protozoan</b>				
<i>Plasmodium berghei</i>	IFN- $\alpha/\beta$ -IFNAR	Direct sensitization of HSPCs to RIPK1-dependent death and increased HSC proliferative arrest	Decreased pool and reconstitution capacity (at infection day 7)	Smith et al. (2018)
	ND	ND	Increased proliferation and pool size (at infection days 7–10)	Vainieri et al. (2016)
	IFN- $\gamma$ -IFNGR	Loss of BM niche osteoblasts and endothelial cell properties	Increased turnover leading to decreased functionality and transcriptional identity	Haltali et al. (2020)
<b>Fungal</b>				
<i>Candida albicans</i>	ND (TNF- $\alpha$ )	TLR2/MyD88 and dectin-1 fungal sensing dependent	Increased proliferation and pool size	Martínez et al. (2018)
	IL-1 $\beta$ and GM-CSF/CD131	$\beta$ -glucan-mediated IL-1 $\beta$ and GM-CSF production by BM cells leads to increased glycolytic pathways and proliferation in HSCs	Increased proliferation, pool size, and myeloid differentiation bias (at 7 d after exposure)	Mitroulis et al. (2018)

size to levels similar to those of *Stat1*<sup>-/-</sup> mice. These data suggest that cytokine-dependent STAT1 signaling, stimulated by the microbiome, is required for maintenance of normal BM HSPC numbers. In agreement, Iwamura et al. (2017) showed that NOD1 ligand administration to GF mice activates BM MSCs to produce key hematopoietic factors, including IL-7, Flt3L, stem cell factor, thrombopoietin (TPO), IL-6, and TNF, which restored HSPC pool size to levels equivalent to SPF mice. Furthermore, Lee et al. (2019) revealed that microbiome-derived molecules, including bacterial DNA, reach the BM via systemic blood circulation and are sensed by CX3CR1<sup>+</sup> mononuclear cells via a TLR-dependent mechanism, resulting in the production of inflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6) that regulate the HSPC pool size and their differentiation potential toward myeloid lineages. Along these lines, unpublished data from our laboratory suggest that upon aging, the levels of continuously circulating microbiota-derived molecules (e.g., TLR4 and 8 agonists) increase. High abundance of these molecules leads to enhanced myeloid-derived systemic IL-1 production, causing HSC pool expansion and increased myeloid differentiation bias. Overall, these studies suggest that tonic, microbiota-associated inflammatory signaling is essential to maintain HSPC pool size and myelopoiesis in steady-state conditions but can potentially become detrimental in the context of an aged hematopoietic system. Furthermore, whether signaling via multiple pathways (e.g., STAT1, NOD1, TLRs) are all required in concert to effectively govern HSPC pool size and myelopoietic activity or whether requirements for these signaling pathways may reflect differences in microbial communities established in different SPF mouse colonies remains to be rigorously addressed.

### Carcinogens

Carcinogens include any substance, radionuclide, or radiation that promotes cancer formation. Long-term BM injury mediated by carcinogens, like ionizing radiation (IR) and chemotherapy (CT), is attributed to direct effects on HSCs as well as on the BM environment. These effects include induction of apoptosis, differentiation, senescence, and/or damage to BM HSC niche (reviewed in Shao et al., 2013). Additionally, IR and CT (doxorubicin, 5-fluorouracil [5-FU], cisplatin, paclitaxel) are known to induce a rapid and dynamic production of multiple proinflammatory cytokines and chemokines, including IL-1 $\alpha/\beta$ , IL-6, IL-8, IFN- $\alpha/\beta$ , TNF- $\alpha$ , CXCL9, CCL2, CCL3, and GM-CSF, within the first 1–2 wk following exposure (Citrin and Mitchell, 2017; McKelvey et al., 2018; Zhang et al., 2012; Vyas et al., 2014; Pietras et al., 2016). However, the effects of IR- and CT-mediated inflammation are difficult to dissociate from the direct effects of IR and CT on the metabolic and genomic integrity of HSCs themselves (Mohrin et al., 2010). Analysis is further confounded by the complexity of the systemic “storm” of cytokines and damage-associated molecular patterns produced in response to these insults in addition to other effects, including loss of gut integrity, which can release inflammatory microbial products into the bloodstream. These confounders have been partially addressed by transplanting cytokine or chemokine receptor-null HSCs into IR- or CT-treated animals and following the kinetics by which they regenerate the blood system. Interestingly, most primary

receptor-null mice do not have a clear HSC phenotype, suggesting a redundant role of cytokines in HSC regulation in steady state. On the other hand, HSCs from these mice often show improved long-term repopulating capacity compared with their WT counterparts upon transplantation into irradiated recipients, including *Tnfrsfla*<sup>-/-</sup> and *Tnfrsflb*<sup>-/-</sup> (Pronk et al., 2011), *Ifnar*<sup>-/-</sup> (Essers et al., 2009), and *Ifngr*<sup>-/-</sup> (Matatall et al., 2014). This suggests that IR- and CT-mediated inflammation restricts HSC self-renewal and repopulating capacity, particularly in the context of serial transplantation. Besides IR and CT, cigarette smoke is one of the most widespread carcinogens (containing at least 98 hazardous components; Talhout et al., 2011), yet its impact on hematopoiesis may be overlooked. Mice exposed to cigarette smoke exhibited increased extramedullary hematopoiesis, decreased MSCs and HSCs, and increased expression of pro-proliferation genes that lead to the expansion of HSPCs (Khaldoyanidi et al., 2001; Pandit et al., 2006; Siggins et al., 2014). Cigarette smoke extract also inhibits osteogenic differentiation and increases expression of proinflammatory markers (Cyprus et al., 2018). Furthermore, in the context of human hematopoiesis, individual smoking status associates with *ASXL1* loss-of-function-driven clonal hematopoiesis (Dawoud et al., 2020). While cigarette smoke elicits a similar hematopoietic phenotype as many inflammatory challenges, the contribution of inflammation and identity of elicited inflammatory factors, such as cytokines in this context, remains elusive. Altogether, similar to infection, carcinogen exposure can induce inflammatory stresses that negatively impact HSC function, particularly in contexts where IR or CT induces myeloablation and subsequent replicative “aging” of HSCs that degrades their function (Beerman et al., 2014; Bernitz et al., 2016). Nonetheless, it should be noted that highly quiescent and drug-resistant “reserve” HSC fractions have been identified (Zhao et al., 2019; Wilson et al., 2008) that retain HSC activity following exposure to CT challenges, such as 5-FU. Hence, not all HSCs respond uniformly to the inflammatory, cytotoxic, and replicative challenges associated with carcinogen exposure. This feature is likely a significant contributor to hematopoietic recovery following induction CT and/or HSC transplantation in the context of hematological malignancy.

### Inflammatory diseases

Inflammatory diseases are a diverse group of conditions resulting from dysregulated immune responses that lead to a deleterious state of chronic inflammation and/or periodic inflammatory “flares” that potentially affect HSC function. Broadly speaking, BM failure is rare in such “sterile” inflammatory contexts, although cytopenias, anemia, overproduction of myeloid cells, immunosenescence, and other hematologic comorbidities have been documented in patients who suffer from rheumatoid arthritis (RA) and juvenile idiopathic arthritis, systemic lupus erythematosus (SLE), colitis, and various auto-inflammatory conditions such as gout where IL-1 is the primary pathogenic factor (Colmegna and Weyand, 2011; Papadaki et al., 2002; Pascual et al., 2005; Chalayer et al., 2017; Gasche et al., 2004). Many of these diseases have been modeled in the mouse. Using an IL-23-driven chronic intestinal inflammation model,

Griseri et al. (2012) showed an IFN- $\gamma$ -dependent increase in HSC proliferation, leading to an eightfold expansion of the HSC pool. This effect was associated with GM-CSF-dependent myeloid differentiation bias and extramedullary hematopoiesis in colitic mice (Griseri et al., 2012). Chronic granulomatous disease (CGD) is a primary immunodeficiency characterized by dysfunctional microbicidal activity and chronic inflammation, often related to deficiency in the *NOX* genes. In mice with CGD, increased cycling of HSCs, expansion of HPCs, and impaired long-term engraftment capacity were associated with high concentrations of proinflammatory cytokines, including IL-1 $\beta$ . Interestingly, treatment of WT mice with IL-1 $\beta$  mimicked these effects, while inhibition of IL-1 signaling (using IL-1R1 antagonist Anakinra and anti-inflammatory steroid dexamethasone) in CGD mice reduced HPC numbers but had only minor effects on the repopulating ability of HSCs (Weisser et al., 2016). RA is a debilitating autoimmune disease characterized by chronic inflammation and progressive destruction of joint tissue. Using a collagen-induced arthritis mouse model, Hernandez et al. (2020) identified systemic inflammation (increased serum levels of TNF, IFN- $\gamma$ , G-CSF) and myeloid overproduction associated with activation of a myeloid differentiation gene program in HSCs. Myeloid overproduction has been characterized in a genetic RA model as well (Oduro et al., 2012). In a similar vein, using an experimental spondyloarthritis mouse model that generates systemic and local inflammation, Regan-Komito et al. (2020) documented an IL-33-GM-CSF axis that promotes HSC myeloid differentiation bias and a GM-CSF-dependent accumulation of granulocyte/macrophage progenitors at extramedullary sites that leads to severe symptoms in spondyloarthritis mice. Likewise, using a genetic mouse model of SLE, Niu et al. (2013) showed an intrinsic and extrinsic (increased serum levels of IL-6, IL-10, TNF- $\alpha$ , and IFN- $\alpha/\beta$ ) inflammatory-dependent expansion and mobilization of HSCs with myeloid lineage differentiation bias. While the cytokine milieu induced by these diseases overlap with those observed in the chronic infection models described above, disruption of HSC repopulating function is generally much less significant. Indeed, HSCs from collagen-induced arthritic mice activate a proliferation arrest gene program associated with maintenance of quiescence and reconstitution capacity, despite ongoing inflammation. Furthermore, treatment with the IL-1R1 antagonist Anakinra reverted myeloid overproduction and associated gene programs in these HSCs (Hernandez et al., 2020), suggesting that disease has an impact on the hematopoietic system, including HSCs themselves, and can be at least partially reversed following inflammatory challenge. Likewise, HSCs from the genetic SLE model retained robust self-renewal capacity and, in fact, exhibited a repopulating advantage over WT HSCs, which resulted from a single nucleotide polymorphism in the *cdkn2c* gene that causes reduced p18INK4c expression (Niu et al., 2013). Unpublished data from our laboratory using a pristane-induced model of chronic SLE confirm the absence of HSC pool attrition despite ongoing IFN signaling, and HSCs from these mice exhibit only a moderate defect in long-term repopulating activity. These data raise the interesting question as to why some chronic infections may impart a more severe

impact on HSC pool size and function than the sterile inflammation models described above, despite inducing similar cytokine milieus. Possibilities include differences in cytokine levels, increased hematopoietic demands caused by active turnover of immune cells during infection, and/or direct effects of pathogens on HSCs (including direct infection or recognition). Overall, chronic inflammatory disease can significantly impact HSC function; key next steps are to assess the extent to which anti-inflammatory therapies, including cytokine blockade approaches currently in clinical use, reverse these phenotypes and to address the impact of recently characterized “immune training” on long-term HSC and blood system function in this context.

### Aging

Aging is associated with chronic low-grade inflammation (i.e., a two- to fourfold increase in IL-1, IL-6, TNF, and C-reactive protein serum levels; [Vasto et al., 2007](#)), a state often referred to as inflamm-aging. This phenotype, observed in both mice and humans, is attributed to a cumulative lifetime exposure to infectious and noninfectious agents and/or senescence-associated cytokines that leads to a self-sustained, vicious proinflammatory cycle (reviewed in [Baylis et al., 2013](#); [Kovtonyuk et al., 2016b](#); [Fulop et al., 2018](#)). Aging also associates with functional changes in both mature and immature hematopoietic cells. Aged HSCs show increased pool size and quiescence, reduced self-renewal capacity, increased myeloid/megakaryocytic-differentiation bias, accumulated DNA damage and proliferative stress marks, increased resistance to apoptosis, epigenetic and transcriptional alterations, loss of autophagy capacity, decreased homing capacity, and increased expression of adhesion molecules (reviewed in [Geiger et al., 2013](#); [Kovtonyuk et al., 2016a](#)). The contribution of inflamm-aging to HSC dysfunction has been addressed in multiple studies. [Ergen et al. \(2012\)](#) performed heterochronic BM transplantation and BM cytokine profiling to identify RANTES (Regulated And Normal T cell Expressed and Secreted)/Ccl5 as a driver of HSC myeloid differentiation bias during aging. Using RANTES overexpression and *Rantes* KO mice, the HSC myeloid bias phenotype was mechanistically linked to increased *Gata2* (promyeloid transcription factor), decreased *Gata3* and *Ikaros* (lymphoid-associated transcription factors) expression, and increased mTOR activity (previously implicated in HSC aging; [Saxton and Sabatini, 2017](#)). [Frisch et al. \(2019\)](#) showed that impaired neutrophil efferocytosis (specialized phagocytosis that minimizes the inflammatory consequences of apoptosis; [Arandjelovic and Ravichandran, 2015](#)) and increased caspase-1 activity in old BM macrophages associates with increased BM levels of IL-1 $\beta$  and with enhanced HSC megakaryocytic differentiation bias (associated with expression of CD41 and CD61). In another study, aged BM stromal cells showed enhanced IL-6 and TGF- $\beta$  signaling. While IL-6 inhibition led to improved erythroid progenitor function in aged mice, TGF- $\beta$  neutralization resulted in reversal of age-associated HSC megakaryocytic differentiation bias, increased generation of lymphoid progenitors, and rebalanced HSC lineage output in transplantation assays ([Valletta et al., 2020](#)). [Pioli et al. \(2019\)](#) suggested that plasma cells from old mice accumulate in the BM where they display increased TLR-driven

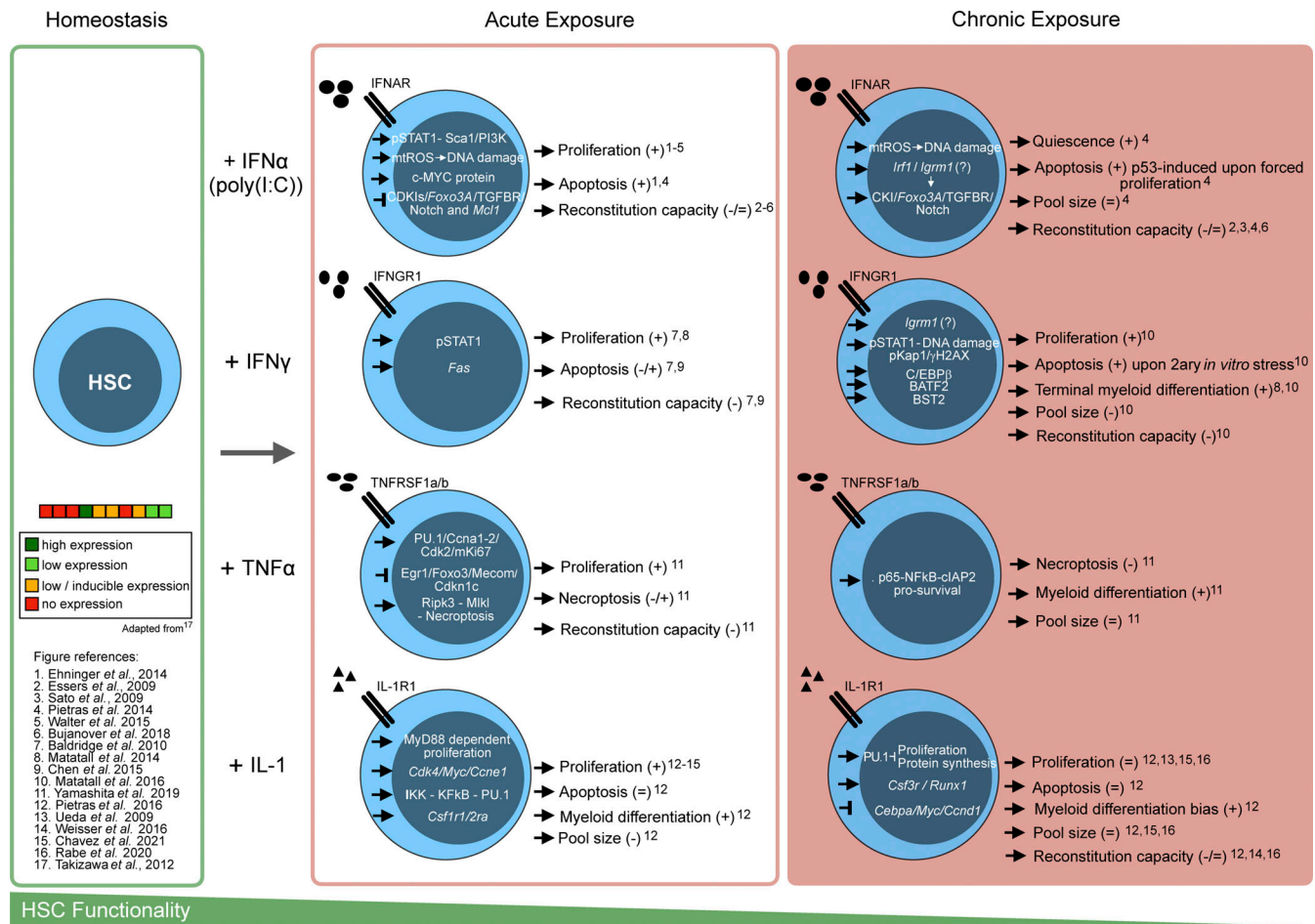
activation and produce (together with stromal cells) a positive feedback network of proinflammatory cytokines (including IL-1, TNF- $\alpha$ , and M-CSF) that promote HSC myeloid differentiation bias. In overall agreement, work by [Helbling et al. \(2019\)](#) from our laboratory demonstrated that the BM stromal compartment (particularly CXCL12-abundant reticular cells [CARC]) contributes significantly to IL-1- and IL-6-mediated inflamm-aging. Furthermore, transcriptomic pathways induced during aging were largely recapitulated by in vivo administration of prototypic microbial molecules, thereby supporting an inflammatory basis of age-related alterations to HSC function. Collectively, these studies indicate that inflamm-aging is a key, and at least to some extent reversible, mediator of age-associated HSC myeloid/megakaryocyte differentiation biases, while having as-yet undetermined impacts on other aging-associated HSC impairments. Further disentangling the respective contributions of accumulated replicative history, age-related alterations in BM niche function, and inflamm-aging to impaired HSC function and oncogenesis could provide a basis for improving blood system function and health span in old age.

### Role of key cytokines on HSC biology: New concepts and ambiguities

HSCs are exposed to multiple and diverse inflammatory milieus during their lifetime. A large body of work using models of single-cytokine stimulation in mice has demonstrated both unique and overlapping impacts of these factors on HSC function independently of the inflammation source. The most commonly studied factors include type I and II IFNs, TNF- $\alpha$ , IL-1, and G-CSF. In this section, we dissect the direct consequences of in vivo administration of these key cytokines on HSC biology and provide a critical review of insights and limitations emerging from mouse models of acute and chronic cytokine exposure ([Fig. 2](#)).

#### Type I IFN

Acute exposure of type I IFN inducer polyinosinic:polycytidylic acid (polyI:C) or IFN- $\alpha$  itself can drive proliferation of dormant HSCs through a pathway dependent on the IFN- $\alpha/\beta$  receptors IFNAR and STAT1 ([Essers et al., 2009](#); [Pietras et al., 2014](#)) that associate with increased MYC protein levels ([Ehninger et al., 2014](#)), decreased expression of quiescence-enforcing genes, and increased mitochondrial ROS-induced DNA damage ([Walter et al., 2015](#)). Interestingly, work by [Haas et al. \(2015\)](#) indicated a stronger type I IFN-induced proliferation in CD41<sup>hi</sup> HSC-like megakaryocytic progenitors within the phenotypic SLAM (Signaling Lymphocytic Activation Molecule) gate. Notably, this effect is transient, as the compartment returns to a quiescent state under continued IFN- $\alpha$  administration ([Pietras et al., 2014](#)). Effects of type I IFNs are negatively regulated by Irf2, as HSC deficiency in this transcription factor exhibits significantly impaired function ([Sato et al., 2009](#)). The overall impact of type I IFNs on HSC function remains an area of continued interest. HSCs remain protected from the p53-dependent proapoptotic effects of type I IFNs so long as they remain quiescent; however, forced entry of HSCs into the cell cycle by culture and/or 5-FU induces apoptosis and rapid depletion of HSCs ([Pietras et al.,](#)



**Figure 2. Effects of acute and chronic inflammatory signaling in HSC biology.** Schematic representation of the antagonizing effects of acute or chronic in vivo cytokine exposure on murine HSC functions. Here, acute is defined as exposure of the indicated cytokine in one to three consecutive single daily doses, while chronic represents more than three consecutive daily exposures (in agreement with classic definitions in the field). The left panel depicts HSCs in homeostatic state and the published expression levels of cytokine receptors. Acute and chronic exposures panels depict the pathways and the respective cellular effects of the exposure to the indicated cytokines. The bottom scheme shows loss of HSC functionality from homeostasis to acute to chronic inflammatory exposure. 2ary, secondary.

2014). Along these lines, transplantation assays using SLAM cells and/or unfractionated BM have suggested that acute and chronic exposures to type I IFNs impair HSC function (Essers *et al.*, 2009; Pietras *et al.*, 2014). On the other hand, recent work has shown that long-term HSCs, prospectively isolated based on an HSC-specific *Fgd5* reporter, do not exhibit impaired reconstitution activity following acute type I IFN exposure (Bujanover *et al.*, 2018). Hence, the effect of type I IFNs on HSC reconstitution activity appears to vary significantly based on the phenotypic definition used to prospectively identify HSCs, calling into question the fidelity of commonly used surface marker definitions such as the SLAM code or Sca-1 expression levels (discussed in King and Goodell, 2011; Kanayama *et al.*, 2020) under nonhomeostatic conditions.

### Type II IFN

Acute IFN- $\gamma$  exposure drives HSC proliferation via IFNGR and STAT1; associates with Fas-mediated apoptosis (Chen *et al.*, 2015); and, like type I IFNs, is associated with reduced repopulation capacity (Baldridge *et al.*, 2010; Matatall *et al.*, 2014).

Chronic IFN- $\gamma$  exposure (via chronic *Mycobacterium avium* infection) results in increased proliferation stress, potentially resulting from an override of *Irgm1*-dependent cell-cycle and IFN response suppression (King *et al.*, 2011). Like type I IFNs, IFN- $\gamma$  primes HSCs to undergo apoptosis upon secondary stress (in vitro culture). Impaired HSC function has also been attributed to enhanced *Batf2*-dependent terminal myeloid differentiation that depletes the HSC pool and severely impairs self-renewal capacity (Matatall *et al.*, 2016). Notably, surface expression of IFNGR is heterogeneous in the phenotypic HSC compartment, and IFNGR<sup>+</sup> HSCs exhibit myeloid bias and reduced repopulating activity, further confirming the importance of direct IFNGR signaling in eliciting reduced HSC function (Matatall *et al.*, 2014) as well as the inherent heterogeneity contained within the phenotypic HSC compartment.

### TNF- $\alpha$

The role of TNF- $\alpha$  in HSC function remains an area of significant interest and open questions. Work by Pronk *et al.* (2011) demonstrated that TNF- $\alpha$  signaling restricts HSC proliferative and



reconstitution activity via both TNFRI and TNFRII pathways. On the other hand, recent work by [Yamashita and Passegué \(2019\)](#) showed that the duration of TNF- $\alpha$  stimulation is an essential variable that determines HSC responses. Accordingly, acute TNF- $\alpha$  exposure leads to HSC proliferation and a transient activation of the canonical NF- $\kappa$ B pathway, which maintains HSC survival during proliferation. Interestingly, 48 h later, the initial TNF- $\alpha$  exposure no longer sustains NF- $\kappa$ B pathway activity, resulting in Ripk3-Mlkl-mediated necroptosis associated with reduced HSC repopulating capacity. During chronic TNF- $\alpha$  exposure, there is a sustained p65-NF- $\kappa$ B-mediated prosurvival signaling activity that prevents necroptosis and poises HSCs to undergo myeloid differentiation by inducing *Pu.1* expression ([Etzrodt et al., 2019](#)). This potentially further contributes to the reestablishment of HSC quiescence by inhibiting cell-cycle activators ([Staber et al., 2013](#)), thus protecting HSCs from necroptosis while terminating the regenerative response ([Yamashita and Passegué, 2019](#)). Hence, TNF signaling may exert distinct effects based on context and dose. It remains to be addressed whether the capacity of TNF to induce PU.1, which can promote terminal differentiation and restrict HSC cell-cycle activity (see below), may provide insight into the seemingly paradoxical capacity of TNFR signaling to restrict HSC proliferation and reconstitution activity while promoting HSC survival and expansion in other contexts.

### IL-1

HSCs exposed to acute IL-1 $\beta$  appear to exhibit *Myd88*-dependent proliferation and myeloid differentiation through activation of the transcription factor PU.1 (downstream of NF- $\kappa$ B activation) without losing self-renewal capacity ([Ueda et al., 2009](#); [Pietras et al., 2016](#); [Weisser et al., 2016](#)). Indeed, short-term or low-dose administration of IL-1 $\alpha$ /IL-1 $\beta$  prevents IR- or CT-induced myelosuppression and protects mice with cyclophosphamide-induced neutropenia against sepsis ([van der Meer et al., 1988](#); [Damia et al., 1992](#); [Pietras et al., 2016](#)). Likewise, IL-1R1-deficient mice exhibit slowed myeloid recovery following 5-FU administration, further supporting a nonredundant role for IL-1 in hematopoietic regeneration ([Pietras et al., 2016](#)). On the other hand, chronic IL-1 $\beta$  exposure results in a profound, yet reversible reduction in long-term repopulating activity in the phenotypic SLAM HSC compartment ([Pietras et al., 2016](#); [Weisser et al., 2016](#)). However, more recent work has shown that the long-term impact of chronic IL-1 $\beta$  exposure on HSC reconstitution activity might in fact be minimal if stringent phenotypic definitions (ECPR<sup>+</sup>/CD34<sup>-</sup> SLAM cells or Fgd5<sup>+</sup> SLAM cells) are used to prospectively isolate HSCs ([Rabe et al., 2020](#)). These data suggest that like type I IFNs, the impact of IL-1 signaling on long-term HSC function may be relatively small. Indeed, IL-1 triggers only limited proliferative activity in vivo within the ECPR<sup>+</sup>/CD34<sup>-</sup> long-term HSC compartment following acute IL-1 treatment, and quiescence is quickly reestablished during chronic exposure ([Rabe et al., 2020](#); [Chavez et al., 2021](#)). Along these lines, IL-1 rapidly induces repression of *Myc* and numerous protein synthesis genes within the first day of exposure, an effect that is sustained with chronic stimulation. Interestingly, IL-1-induced activation of PU.1 is a proliferation-limiting mechanism,

as IL-1 triggers aberrant protein synthesis activity, proliferation, and HSC pool expansion in PU.1-deficient HSC ([Chavez et al., 2021](#)). These findings are consistent with previous characterizations of PU.1 as a cell-cycle inhibitor ([Staber et al., 2013](#); [Kueh et al., 2013](#)) that facilitates myeloid differentiation by promoting intracellular PU.1 accumulation. Furthermore, recent work has identified IL-1 as a key player in HSC immune training, suggesting that IL-1 and other proinflammatory cytokines can induce heritable, long-term effects on HSC function ([Mitroulis et al., 2018](#)). Taken together, these results illustrate an ongoing redefinition of how IL-1 impacts HSC function in contexts such as regeneration versus chronic inflammation and the extent to which prospective HSC isolation strategies can affect experimental results and their interpretation.

### G-CSF

G-CSF administration in vivo results in transient HSC proliferation ([Wilson et al., 2008](#)), peripheral mobilization, and expansion of the HSC pool within the central but not endosteal BM region ([Grassinger et al., 2012](#)). However, chronically G-CSF-treated HSCs have an overall loss of repopulating and self-renewal activity ([Kovtonyuk et al., 2016b](#)) that associates with enhanced TLR/MyD88 signaling ([Schuettpelez et al., 2014](#)). Interestingly, work from [Cain et al. \(2011\)](#) suggested that transient IL-1-mediated HSPC proliferation may be indirectly regulated by IL-1R1-dependent G-CSF production. These data are consistent with prior BM chimera studies from the same group, showing that alum-induced HSPC proliferation requires IL-1R1 expression in the radioresistant (nonhematopoietic) compartment ([Ueda et al., 2009](#)), which aligns with our finding that direct IL-1 signaling triggers a PU.1-mediated proliferation-limiting mechanism in HSCs instead. Interestingly, later work from [Bernitz et al. \(2017\)](#) suggested that like type I IFNs, G-CSF-induced proliferation is limited to CD41<sup>hi</sup> SLAM cells based on H2B-GFP dilution studies. Hence, as with IL-1 and type I IFNs, the precise functional impacts of G-CSF on HSC function remain to be fully clarified.

Taken as a complete body of work, it is clear that proinflammatory cytokines can exert significant effects on HSCs. Strikingly however, and perhaps contrary to initial published characterizations, most cytokines directly elicit only transient, if any, proliferative activity in true long-term HSCs. Moreover, the mechanisms underlying these activities require revisiting, as with PU.1 and IL-1. Importantly, limitations imposed by established experimental model setups need scrutiny. In particular, standard definitions of inflammatory stimulus duration (i.e., acute and chronic) often lack consistency; do not align with established clinical definitions of acute and chronic disease; and thus, represent a significant source of noise in the field. In addition, time points after inflammatory stimulus at which hematopoietic outcomes are analyzed are of key importance. As perturbed biological systems tend to return to a homeostatic state over time, it is likely that analysis closer to inflammatory stimulation associates with stronger phenotypes. Finally, as discussed above, the phenotypic definition of HSCs needs to be updated and systematized in order to accommodate the growing evidence of molecular heterogeneity within this compartment.

In spite of these limitations, the totality of evidence suggests that chronic exposure to individual cytokines exerts fairly mild effects on HSC function. Such results are again in contrast to chronic infection models where the HSC compartment exhibits more profound changes in proliferation and functional decline. Hence, individual proinflammatory cytokines on their own (alongside any secondary signals they induce) may not be sufficient to severely degrade HSC function. On the other hand, they may trigger much more significant impairment of HSC and blood system function in the context of ongoing hematopoietic demand, such as during exposure to combined IFN-1 and 5-FU challenge or complex “cytokine storms.” Furthermore, while the majority of experimental systems address acute and chronic exposures, the impact of serial inflammatory episodes on HSC function is less well studied. This further highlights the fact that HSC responses to inflammatory cytokines are the result of biological processes that are highly dependent on the (path) physiological context in which the inflammatory signals are produced as well as on cytokine doses and duration of exposure. Care must therefore be taken not to derive broad generalizations about HSC responses to inflammation based on the results of individual studies using specific cytokines and/or experimental models.

#### Inflammation as a driver of somatic evolution in BM

Chronic inflammation and/or tonic levels of inflammatory signaling sustained over time and combined with aging-associated declines can have deleterious impacts on overall blood system function. This includes multiple HSC properties, such as survival, proliferation, differentiation, self-renewal, and genomic integrity (see previous sections). While HSCs are clearly capable of adapting to inflammatory signals necessary for hematopoietic regeneration and blood system maintenance without incurring dramatic functional costs, the extent to which chronic or even punctuated inflammatory insults degrade HSC function over time and contribute to morbidities, such as BM failure and/or myeloid oncogenesis, remains an area of active investigation. Indeed, there is an association between inflammatory burden, preleukemic states, and full-blown leukemia development (reviewed in Craver et al., 2018). Along these lines, revised models of cancer development, such as the theory of adaptive oncogenesis, implicate inflammation as a crucial driver of hematological and other malignancies by impairing the fitness (defined as capacity to generate progeny) of normal cells, thereby altering the tissue fitness landscape to favor cells harboring oncogenic mutations (Laconi et al., 2020). Here, we summarize multiple studies that have suggested that selective pressure imposed by chronic inflammation on the HSC pool might drive genetic mutations and/or selection/expansion of inflammation-adapted mutant clones, leading to a preleukemic state and, potentially, evolution to leukemia (Fig. 3).

#### Inflammation and DNA damage in HSCs

Cellular mutation occurrence probability is defined by the product of the mutation rate per division per DNA base pair (defined as  $3 \times 10^{-9}$ ) and the cellular division rate (Rozhok et al., 2014, 2016). Therefore, accelerated inflammation-induced HSC

cycling can enhance mutational occurrence. Indeed, in vivo cell-cycle induction using IFN- $\alpha$ , G-CSF, TPO, serial bleeding, or chronic polyI:C regimens leads to increased mitochondrial ROS-induced DNA damage in WT HSCs and results in HSC depletion and BM failure in mice with a nonfunctional Fanconi anemia DNA repair pathway (*Fanca*<sup>-/-</sup>; Walter et al., 2015). Work from our laboratory further established that HSCs exposed to prolonged bacterial LPS stimulation or *Salmonella typhimurium* infection exhibit elevated proliferative stress and DNA damage formation mainly via TLR4-TRIF signaling (Takizawa et al., 2017). Importantly, these effects are amplified in genetic contexts associated with defective DNA repair. Zhang et al. (2007) showed that TNF- $\alpha$ -induced senescence in WT HSPCs correlates with the accumulation of ROS-mediated DNA damage and leads to increased chromosomal aberrations (in Lin<sup>-</sup> cells), which are further enhanced in *Fancc*<sup>-/-</sup> mice. This strongly suggests that inflammatory exposure leads to increased mutagenesis in Lin<sup>-</sup> cells; however, direct evidence in HSCs remains to be established (Fig. 3 A). Along these lines, HSPCs with compound loss of single-stranded DNA-binding proteins Ssb1 and Ssb2 rapidly induce type I IFNs associated with replication stress and depletion of HSC (Shi et al., 2017). Indeed, BM failure syndromes are commonly associated with chronic production of TNF and IFNs (Hara et al., 2004; Chen et al., 2015), reinforcing the pathogenic role of inflammation in this context. Finally, it is worth noting that genotoxin exposure can trigger DNA breaks in quiescent HSCs, which are repaired by nonhomologous end joining, leading to acquisition of chromosomal aberrations (Mohrin et al., 2010). The extent to which inflammation can induce somatic mutations in quiescent HSCs via induction of nonhomologous end joining and other proliferation-independent DNA modification or repair mechanisms remains an important question. Altogether, inflammation functions as both a cause and an effect of DNA damage. Defining the extent to which inflammation directly induces mutations that lead to hematological malignancy, as opposed to serving as a selective mechanism for mutated HSC clones, remains an important frontier of investigation in the field.

#### Inflammation-adapted mutant HSCs

Inflammatory milieus are associated with hematological malignancies, such as myelodysplastic syndromes (reviewed in Sallman and List, 2019), myeloproliferative neoplasms (reviewed in Lussana and Rambaldi, 2017), chronic myeloid leukemia (reviewed in Hoermann et al., 2015), and acute myeloid leukemia (AML; reviewed in Binder et al., 2018). Again, whether inflammation is a cause or consequence (or both) of these established malignancies remains to be determined. In healthy, young tissue systems, mutated cell clones often exhibit low relative fitness levels and are routinely eliminated via apoptosis, terminal differentiation, immune system surveillance, and/or entry into a senescent state (Laconi et al., 2020). However, the proinflammatory stimuli discussed above are capable of inducing these processes in normal HSCs, thereby reducing their relative fitness. Indeed, as we describe above, IFNs can induce p53-dependent apoptosis and/or cell-cycle arrest, whereas IL-1 and TNF can activate PU.1 and promote

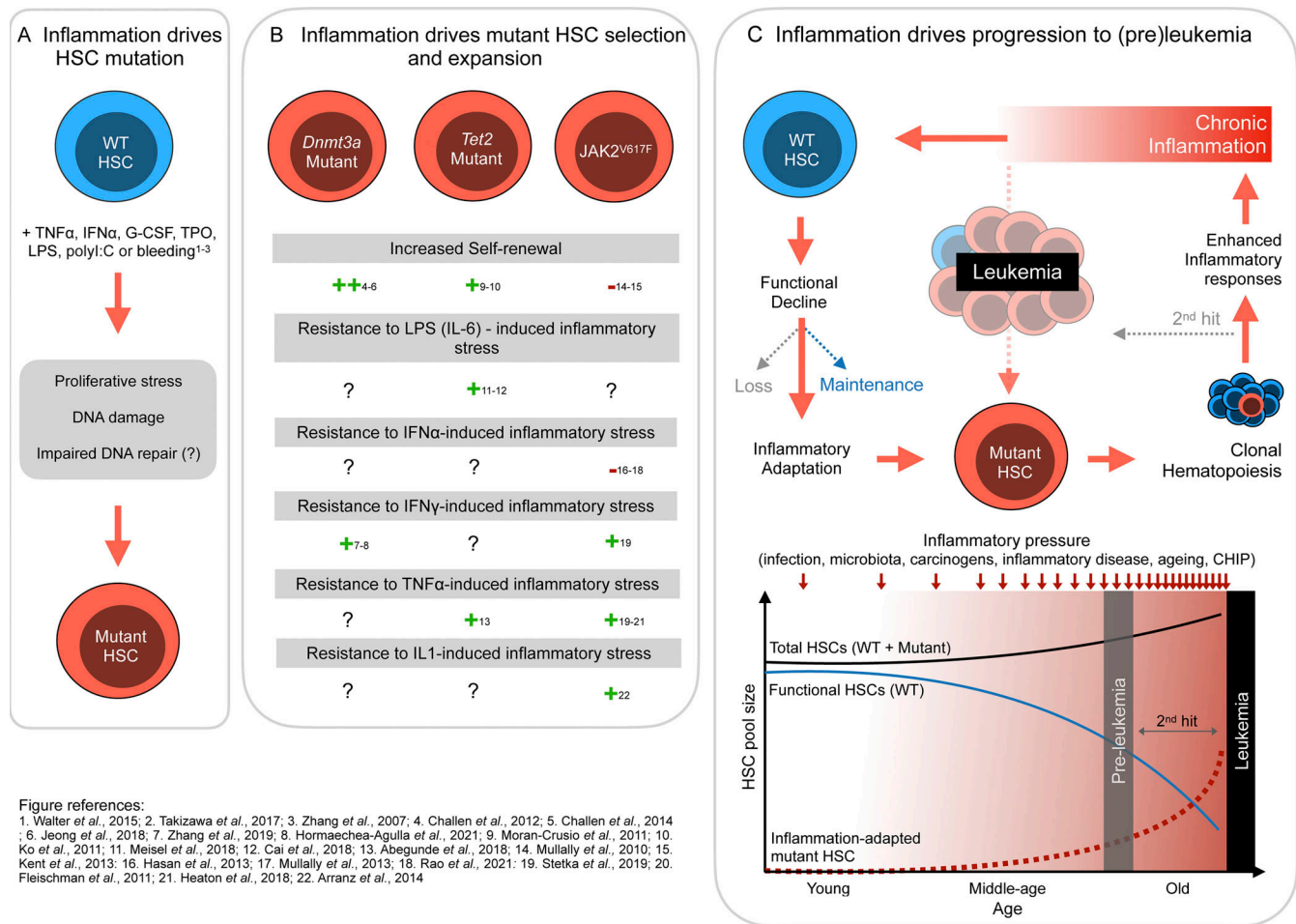


Figure references:

1. Walter *et al.*, 2015; 2. Takizawa *et al.*, 2017; 3. Zhang *et al.*, 2007; 4. Challen *et al.*, 2012; 5. Challen *et al.*, 2014; 6. Jeong *et al.*, 2018; 7. Zhang *et al.*, 2019; 8. Hormaechea-Agulla *et al.*, 2021; 9. Moran-Crusio *et al.*, 2011; 10. Ko *et al.*, 2011; 11. Meisel *et al.*, 2018; 12. Cai *et al.*, 2018; 13. Abegunde *et al.*, 2018; 14. Mullally *et al.*, 2010; 15. Kent *et al.*, 2013; 16. Hasan *et al.*, 2013; 17. Mullally *et al.*, 2013; 18. Rao *et al.*, 2021; 19. Stetka *et al.*, 2019; 20. Fleischman *et al.*, 2011; 21. Heaton *et al.*, 2018; 22. Arranz *et al.*, 2014

Figure 3. **Proposed mechanisms of HSCs inflammation-driven evolution.** Schematic representation of the three main processes by which sustained inflammation drives HSC somatic evolution. **(A)** Inflammation as a driver of mutation incidence in HSC by inducing increased proliferation stress and DNA damage. Impact of inflammation on DNA repair efficiency is unknown. **(B)** Inflammatory pressure leads to the selection and expansion of HSC-carrying mutations (in *DNMT3A*, *TET*, and *JAK2*). Depicted are the published adaptations of each mutation to inflammatory stress (++ strongly present, + present, - absent, ? unknown). **(C)** Speculative role of inflammation on establishment of clonal hematopoiesis and its progression to leukemia. Lifelong inflammatory exposure leads to functional decline of WT HSCs and selects inflammatory-adapted mutant HSCs that expand, leading to a preleukemic stage. Enhanced cytokine production by mutant myeloid cells further increased the systemic-inflammatory load, leading to inflammatory-adapted mutant HSC clonal expansion and increasing the risk of secondary hit mutations and potential leukemia transformation.

terminal differentiation and/or enforce quiescence, altogether limiting proliferative activity. Mutations that render HSCs insensitive to these effects can thus confer a relative fitness advantage in an inflammatory environment, leading to an altered tissue landscape that now selects for such mutations. Indeed, a wide variety of mutations associated with myeloid malignancy interfere with the normal expression and/or function of proinflammatory cytokine targets, such as *PU.1*, *C/EBP $\alpha$* , and *p53*, and/or lead to increased activation of survival and proliferation pathways, such as *Flt3* and *Ras* (Gerloff *et al.*, 2015; McKenzie *et al.*, 2019; Mueller *et al.*, 2006; Noguera *et al.*, 2016; Vangala *et al.*, 2003; Yang *et al.*, 2012; Kaasinen *et al.*, 2019; Henry *et al.*, 2015). Along these lines, we recently showed that IL-1 rapidly suppresses HSC expression of *Myc*, a key player regulating relative cell fitness in many tissues, including HSCs (Laurenti *et al.*, 2008; Scognamiglio *et al.*, 2016; Wilson *et al.*, 2004). On the other hand, *PU.1*-deficient HSCs are largely

insensitive to this effect of IL-1, fail to repress *Myc*, and instead continue to proliferate and expand in the BM (Chavez *et al.*, 2021) during IL-1 exposure. Likewise, *Cebpa*-deficient MPPs can outcompete their WT counterparts in vivo when exposed to chronic IL-1 (Higa *et al.*, 2021). Strikingly, both *PU.1*- and *Cebpa*-deficient HSPCs are not selected for in the absence of the inflammatory signal, providing important evidence that the loss of these factors alone is not sufficient to promote their expansion.

Preleukemic states where founding mutations are present but where the hematopoietic system is still uncompromised (reviewed in Corces-Zimmerman and Majeti, 2014), constitute an ideal system to address how inflammatory pressure acts on a genetically heterogeneous HSC pool to select for clones carrying specific mutations. Clonal hematopoiesis of indeterminate potential (CHIP) is a hematological condition first characterized in humans by the presence of an expanded somatic blood cell clone carrying a mutation in leukemia driver genes (e.g., *DNMT3A*,

*TET2*, *ASXL1*, *TP53*, *JAK2*, and *SF3B1*) at a variant allele frequency of at least 2% in the absence of any other hematological abnormalities. CHIP incidence increases with age (and is thus sometimes also termed age-related clonal hematopoiesis, ARCH) and associates with an increased risk of hematological malignancies, cardiovascular disease, and all-cause mortality (Boettcher and Ebert, 2019; Jaiswal et al., 2014; Genovese et al., 2014; Shlush et al., 2014), which is attributed to increased inflammatory responses from mutant immune cells (reviewed in Cook et al., 2020). Indeed, individuals with CHIP have higher serum IL-6, TNF- $\alpha$ , IL-1 $\beta$ , and IL-18 levels than those without (Cook et al., 2019; Bick et al., 2020). Furthermore, enhanced inflammatory responses have been described in *DNMT3A* (Leoni et al., 2017; Sano et al., 2018a), *TET2* (Sano et al., 2018b; Fuster et al., 2017; Zhang et al., 2015; Cull et al., 2017), and *JAK2* mutant myeloid cells (Wang et al., 2018). Importantly, multiple studies in mice and humans have suggested that CHIP-mutant HSPCs, contrary to their WT counterparts, have developed molecular mechanisms that potentially allow adaptation to the sustained inflammatory cues present in CHIP individuals (Fig. 3 B). Here, we summarize the main inflammatory adaptation mechanisms observed in *DNMT3A*, *TET2*, and *JAK2* mutant HSPCs.

***DNMT3A*.** Mutations in *DNMT3A*, which encodes a DNA methyltransferase enzyme responsible for establishing de novo DNA methylation patterns during stem cell differentiation (Okano et al., 1999), are the most common CHIP mutations and are detectable in Lin<sup>-</sup>CD34<sup>+</sup>CD38<sup>-</sup> HSCs. These mutations are heterozygous, occur in structural and functional domains, and are thought to lead to loss of protein function (Arends et al., 2018). HSCs from *Dnmt3a*<sup>-/-</sup> mice show enhanced self-renewal and reduced differentiation efficiency, which results from biased HSC fate decisions (Challen et al., 2012; Jeong et al., 2018; Challen et al., 2014) and has been partially attributed to hypomethylation-mediated increased expression of self-renewal genes (Jeong et al., 2014). In the context of inflammation, a higher frequency of *DNMT3A* (and *PPM1D*) mutations in ulcerative colitis patients was recently described, possibly related to higher IFN- $\gamma$  serum levels in patients with *DNMT3A* mutations (Zhang et al., 2019). In agreement, it was also shown that chronic mycobacterial infection as well as chronic IFN- $\gamma$  administration drive the expansion of *Dnmt3a*<sup>-/-</sup> HSCs over WT HSCs. Mechanistically, this associated with hypermethylation of prodifferentiation genes (Jun/Fos gene family members and *Batf2*) in *Dnmt3a*<sup>-/-</sup> HSCs, rendering them more resistant to pool exhaustion via infection-mediated terminal differentiation and secondary stress-induced apoptosis (Hormaechea-Agulla et al., 2021).

***TET2*.** The *TET2* gene encodes a dioxygenase that promotes DNA demethylation via the conversion of 5-methylcytosine to 5-hydroxymethylcytosine and other oxidized derivatives (Ito et al., 2010). *TET2* mutations are the second most common in CHIP, are detectable in Lin<sup>-</sup>CD34<sup>+</sup>CD38<sup>-</sup> HSCs, and are also loss of function (Arends et al., 2018). HSCs from *Tet2*<sup>-/-</sup> mice (or with targeted disruption of the catalytic domain) also show increased self-renewal, impaired differentiation, and a predisposition to hematological malignancy development (Moran-Crusio et al., 2011; Ko et al., 2011). In the context of inflammation, *Tet2*-

deficient murine and human HSCs have a strong proliferative and antiapoptotic advantage compared with WT cells when exposed in vitro to TNF- $\alpha$  (Abegunde et al., 2018). Murine *Tet2*-deficient HSPCs further show enhanced proliferation and myeloid differentiation in response to microbial-induced IL-6 (Meisel et al., 2018). Moreover, *Tet2*<sup>-/-</sup> HSPCs maintain a repopulation advantage after a chronic inflammatory insult (LPS), which is related to hyperactivation of the IL-6/Shp2/Stat3/lncRNA-*Morbid* axis, resulting in reduced apoptosis compared with WT cells (Cai et al., 2018). *Tet2*-deficient HSPCs also exhibit a competitive advantage over WT cells during low-grade inflammation in a manner associated with increased TLR-TRAF6 and noncanonical NF- $\kappa$ B activation (Muto et al., 2020), confirming their enhanced fitness in inflammatory contexts.

***JAK2*.** *JAK2* is a member of the JAK family of nonreceptor protein tyrosine kinases involved in cytoplasmic signaling components of cytokine receptors. The *JAK2*<sup>V617F</sup> variant can be found in 3% of individuals with CHIP (Cordua et al., 2019). *JAK2*<sup>V617F</sup> reduces the self-renewal capacity of individual HSCs but leads to expansion of downstream progenitor cells (Mullally et al., 2010; Kent et al., 2013). *JAK2*<sup>V617F</sup> HSPCs proliferate and exhaust after IFN- $\alpha$  treatment, losing disease initiation capacity in secondary transplantation (Hasan et al., 2013; Mullally et al., 2013). In agreement, *JAK2*<sup>V617F</sup> megakaryocyte-biased CD41<sup>hi</sup> HSCs were recently shown to exhaust after IFN- $\alpha$  treatment (Rao et al., 2021). On the other hand, *JAK2*<sup>V617F</sup> HSCs exhibit increased IL-1 $\beta$  secretion, which induces MSC death, resulting in mutant HSC expansion and accelerated myeloproliferative neoplasm progression (Arranz et al., 2014). Furthermore, *JAK2*<sup>V617F</sup> HSPCs exposed to IFN- $\gamma$ , TNF- $\alpha$ , and TGF- $\beta$ 1 treatment show a DUSP1-dependent proliferation and protection against DNA damage accumulation and inflammatory stress (Stetka et al., 2019). Additionally, TNF- $\alpha$  drives *JAK2*<sup>V617F</sup> HSPC expansion (Fleischman et al., 2011) in an autocrine Tnfr2-NF- $\kappa$ B-dependent fashion that downregulates XIAP and MAPK8, leading to increased survival compared with WT progenitors (Heaton et al., 2018). Altogether, these studies provide compelling evidence that inflammatory alterations to the BM fitness landscape can activate a process of somatic evolution that favors oncogenic mutations. Notably, many of these studies rely on generation of BM chimeras using lethal irradiation, which imparts lasting effects on BM integrity, including increased ROS (Rodrigues-Moreira et al., 2017), which could accelerate and/or alter selection processes in the BM. The use of nonconditioned recipients (Wang et al., 2020); less-inflammatory methods of BM conditioning, such as low-dose CT (Henry et al., 2015; Higa et al., 2021); or genetic mosaic approaches may provide more faithful readouts of selective processes triggered by inflammation and assist in the development of novel therapies to address BM oncogenesis.

### **Inflammation as a driver of CHIP-mutant HSC malignant transformation**

CHIP increases the risk of hematologic malignancy (in aggregate) by 0.5–1% per year (Jaiswal et al., 2014). Subsequent studies indicate that the type of mutation, higher number of mutations, and higher mutational variant allele frequencies

Table 2. Summary of human studies describing the effects of different inflammatory sources and pathways on phenotypically defined HSC

Source	Inflammatory pathway	Effect on HSCs	HSC phenotype	Reference
<b>Viral</b>				
HIV patients	Not direct infection	Decreased pool	CD34 <sup>+</sup> CD38 <sup>-</sup>	Marandin et al. (1996)
	TNF- $\alpha$ -induced Fas	Apoptosis	CD34 <sup>+</sup>	Isgro et al. (2004)
	IL-18 increase; stem cell factor decrease	Decreased pool	Circulating Lin <sup>-</sup> CD34 <sup>+</sup> CD45RA <sup>+</sup> CD10 <sup>+</sup> CD117 <sup>-</sup>	Bordoni et al. (2018)
HIV humanized mice	pDCs (via IFN- $\alpha$ / $\beta$ ?)	Decreased pool and colony formation	CD34 <sup>+</sup> CD38 <sup>-</sup>	Li et al. (2017)
<b>Bacterial</b>				
Sepsis patients	Increased CXCL12 and decrease SIP at day 1 after septic shock	Increased mobilization and proliferation at day 3 after septic shock	Circulating Lin <sup>-</sup> CD133 <sup>+</sup> CD45 <sup>+</sup> and CD34 <sup>+</sup> CD38 <sup>-</sup>	Skirecki et al. (2019)
	ND	Minor increase mobilization at days 4 and 7 after septic shock	Circulating CD34 <sup>+</sup> CD38 <sup>-</sup> CD90 <sup>+</sup> CD45RA <sup>-</sup>	Wang et al. (2021)
Sepsis humanized mice	Increased TLR4 and CXCR4 expression/notch-1 Jagged1 signaling	Increased pool and proliferation	CD34 <sup>+</sup> CD38 <sup>-</sup>	Skirecki et al. (2015)
Inflammatory disease	Increased proinflammatory milieu (IL-1 $\beta$ , according to mouse model)	Decreased pool	Lin <sup>-</sup> CD34 <sup>+</sup> CD38 <sup>-</sup>	Weisser et al. (2016)
CGD patients	Exhausted after in vitro culture	Exhausted after in vitro culture	G-CSF-mobilized CD34 <sup>+</sup> CD38 <sup>-</sup> CD90 <sup>+</sup>	
RA patients	Increased TNF- $\alpha$	Decreased pool and increased apoptosis	CD34 <sup>+</sup>	Papadaki et al. (2002)
	ND/premature telomere shortening	Decreased pool	Circulating CD34 <sup>+</sup>	Colmegna et al. (2008)
		Impaired proliferative potential		
	Increased TNF- $\alpha$	Decreased pool and colony formation	CD34 <sup>+</sup>	Porta et al. (2004)
SLE patients	Increased Fas (via TNF- $\alpha$ ?)	Decreased pool and colony formation	CD34 <sup>+</sup> CD38 <sup>-</sup>	Papadaki et al. (2001)
	Enhanced CD40-CD40L	Decreased pool and increased apoptosis	CD34 <sup>+</sup>	Pyrovolaki et al. (2009)
	ND	Increased pool	CD34 <sup>+</sup> CD38 <sup>-</sup>	Taraldsrud et al. (2009)
	ND	Increased pool	CD34 <sup>+</sup> CD38 <sup>-</sup>	Kuranda et al. (2011)
		Decrease in myeloid lineage bias in vivo (NSG mice) and in vitro		
	Increased ERK/MAPK and GM-CSF signaling (transcriptomics)	Increased pool and reduced quiescence	Lin <sup>-</sup> CD34 <sup>+</sup> CD38 <sup>-</sup> CD90 <sup>+</sup> CD45RA <sup>-</sup>	Pang et al. (2011)
<b>Aging</b>				
Elderly individuals		Reduced in vitro plating efficiency and increased myeloid bias		
		Reduced in vivo (NSG mice) engraftment and increased myeloid bias		
	ND	Increased pool	CD34 <sup>+</sup>	Woolthuis et al. (2014)
		Impaired reconstitution capacity at 1 yr after autologous stem cell transplantation		
	ND	Increased pool	Lin <sup>-</sup> CD34 <sup>+</sup> CD123 <sup>low</sup> CD90 <sup>+</sup> CD45RA <sup>-</sup>	Rundberg Nilsson et al. (2016)
	ND	Reduced in vitro plating efficiency and colony size		
		Intrinsic megakaryocytic/ erythroid bias (transcriptomics)		

pDC, plasmacytoid dendritic cells.

predict which CHIP-carrying individuals are more likely to progress to AML (Desai et al., 2018; Abelson et al., 2018). Thus, identifying the factors leading to expansion of CHIP mutant clones and to acquisition of secondary mutations is key to understanding leukemia pathogenesis. Based on evidence discussed here, we propose that lifelong chronic inflammation derived from cumulative sources (infection, microbiota, inflammatory diseases, aging, and CHIP) might be a driver of AML progression in CHIP carriers, particularly in the ones carrying inflammation-adapted mutant clones (*TET2*<sup>+/-</sup>, *DNMT3A*<sup>+/-</sup>, *JAK2*<sup>V617F</sup>). Accordingly, selection and expansion of inflammation-adapted CHIP mutant over WT HSPCs will generate an increasingly larger mutant HSC-derived allele fraction in mature cells that further contributes to systemic inflammation. With time, this proinflammatory cycle can facilitate the acquisition of secondary mutations, increasing the potential for leukemia development (Fig. 3 C). Continued effort into developing in vivo models that can report and/or replicate how sequential mutations lead to malignant transformation (Loberg et al., 2019) will provide opportunities for important advancement in this area. Moreover, whether lifelong proinflammatory stress is also a relevant driver of clonal evolution in nonhematopoietic tissues (e.g., skin, colon, liver; Martincorena et al., 2015; Blokzijl et al., 2016; Brunner et al., 2019) remains to be determined.

### Concluding remarks

At least three decades' worth of work and resultant literature have sought to address the functional and mechanistic impacts of inflammatory challenges on HSCs (Fig. 1 and Tables 1 and 2). This process has been greatly accelerated over the past decade by advances in HSC isolation and functional profiling as well as by development of advanced mouse models of disease and infection. Considering these investigations as a whole, it is now clear that in the absence of defects in DNA repair or other HSC maintenance systems, the hematopoietic system (and the HSC pool in particular) is sufficiently robust to withstand inflammatory challenges, respond to them, and restore homeostasis without incurring immediate dramatic functional costs. On the other hand, in extreme circumstances, inflammatory responses can break this homeostatic buffer and compromise the hematopoietic system, as observed in some infection models or in the context of BM failure. Second, models used to study the impact of inflammation on HSCs vary considerably in terms of the content of the inflammatory milieu, the relative quantities of cytokines, damage-associated molecular patterns, metabolites, and other factors; the duration of the inflammatory stimuli; the extent to which supportive niches are disrupted; and, finally, the proliferative demands exerted upon HSCs. Direct comparisons between models and even to human biology (which is analyzed using a substantially different time frame), must be made cautiously and with due consideration of these confounding factors. Third, it has become clear that as methods for prospective isolation of HSCs improve alongside advanced technologies that allow for interrogation of molecular state and clonal dynamics at the single-cell level, we will be required to revisit, refine, and perhaps discard elements of current dogma related to how

inflammation shapes the HSC pool and alters its functional properties. Finally, it is also important for the field to consider the cumulative impact on HSCs of a lifetime of inflammatory challenges and exposure to tonic inflammatory signals generated by the microbiome and other environmental factors. The extent to which "normal" levels of inflammation or serial exposures to inflammatory signals contribute to eventual HSC decline in the context of aging remains a fertile area of investigation, with the potential for significant impact on human health span and risk for hematological malignancy. As the field further clarifies the contribution of inflammation to oncogenesis (Fig. 3), significant opportunities will arise to translate this knowledge into potential novel strategies that prevent and/or redirect somatic evolution to reduce the risk of malignancy, cardiovascular disease, and other comorbidities. Taken together, it is clear that the study of inflammation and HSC biology remains an exciting and active topic replete with ambiguities, evolving concepts, and new opportunities to address key problems in human health.

### Acknowledgments

This work was supported by National Institutes of Health grant R01 DK119394 and the Cleo Meador and George Ryland Scott Endowed Chair in Hematology (to E.M. Pietras), a Comprehensive Cancer Center Zurich fellowship (to F. Caiado), and the Swiss National Science Foundation (310030B\_166673/1 to M.G. Manz).

Author contributions: F. Caiado, E.M. Pietras, and M.G. Manz researched and wrote the paper.

Disclosures: The authors declare no competing interests exist.

Submitted: 29 March 2021

Revised: 19 May 2021

Accepted: 19 May 2021

### References

- Abegunde, S.O., R. Buckstein, R.A. Wells, and M.J. Rauh. 2018. An inflammatory environment containing TNF $\alpha$  favors Tet2-mutant clonal hematopoiesis. *Exp. Hematol.* 59:60–65. <https://doi.org/10.1016/j.exphem.2017.11.002>
- Abelson, S., G. Collord, S.W.K. Ng, O. Weissbrod, N. Mendelson Cohen, E. Niemeyer, N. Barda, P.C. Zuzarte, L. Heisler, Y. Sundaravadanam, et al. 2018. Prediction of acute myeloid leukaemia risk in healthy individuals. *Nature.* 559:400–404. <https://doi.org/10.1038/s41586-018-0317-6>
- Arandjelovic, S., and K.S. Ravichandran. 2015. Phagocytosis of apoptotic cells in homeostasis. *Nat. Immunol.* 16:907–917. <https://doi.org/10.1038/ni.3253>
- Arends, C.M., J. Galan-Sousa, K. Hoyer, W. Chan, M. Jäger, K. Yoshida, R. Seemann, D. Noerenberg, N. Waldhueter, H. Fleischer-Notter, et al. 2018. Hematopoietic lineage distribution and evolutionary dynamics of clonal hematopoiesis. *Leukemia.* 32:1908–1919. <https://doi.org/10.1038/s41375-018-0047-7>
- Arranz, L., A. Sánchez-Aguilera, D. Martín-Pérez, J. Isern, X. Langa, A. Tzankov, P. Lundberg, S. Muntión, Y.S. Tzeng, D.M. Lai, et al. 2014. Neuropathy of haematopoietic stem cell niche is essential for myelo-proliferative neoplasms. *Nature.* 512:78–81. <https://doi.org/10.1038/nature13383>
- Baldrige, M.T., K.Y. King, N.C. Boles, D.C. Weksberg, and M.A. Goodell. 2010. Quiescent haematopoietic stem cells are activated by IFN- $\gamma$  in response to chronic infection. *Nature.* 465:793–797. <https://doi.org/10.1038/nature09135>

- Balmer, M.L., C.M. Schürch, Y. Saito, M.B. Geuking, H. Li, M. Cuenca, L.V. Kovtonyuk, K.D. McCoy, S. Hapfelmeier, A.F. Ochsenbein, et al. 2014. Microbiota-derived compounds drive steady-state granulopoiesis via MyD88/TICAM signaling. *J. Immunol.* 193:5273–5283. <https://doi.org/10.4049/jimmunol.1400762>
- Baylis, D., D.B. Bartlett, H.P. Patel, and H.C. Roberts. 2013. Understanding how we age: insights into inflammaging. *Longev. Healthspan.* 2:8. <https://doi.org/10.1186/2046-2395-2-8>
- Beerman, I., J. Seita, M.A. Inlay, I.L. Weissman, and D.J. Rossi. 2014. Quiescent hematopoietic stem cells accumulate DNA damage during aging that is repaired upon entry into cell cycle. *Cell Stem Cell.* 15:37–50. <https://doi.org/10.1016/j.stem.2014.04.016>
- Bernitz, J.M., H.S. Kim, B. MacArthur, H. Sieburg, and K. Moore. 2016. Hematopoietic stem cells count and remember self-renewal divisions. *Cell.* 167:1296–1309.e10. <https://doi.org/10.1016/j.cell.2016.10.022>
- Bernitz, J.M., M.G. Daniel, Y.S. Fstikchyan, and K. Moore. 2017. Granulocyte colony-stimulating factor mobilizes dormant hematopoietic stem cells without proliferation in mice. *Blood.* 129:1901–1912. <https://doi.org/10.1182/blood-2016-11-752923>
- Bick, A.G., J.S. Weinstock, S.K. Nandakumar, C.P. Fulco, E.L. Bao, S.M. Zekavat, M.D. Szeto, X. Liao, M.J. Leventhal, J. Nasser, et al. NHLBI Trans-Omics for Precision Medicine Consortium. 2020. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature.* 586:763–768. <https://doi.org/10.1038/s41586-020-2819-2>
- Binder, D., J. Fehr, H. Hengartner, and R.M. Zinkernagel. 1997. Virus-induced transient bone marrow aplasia: major role of interferon- $\alpha/\beta$  during acute infection with the noncytopathic lymphocytic choriomeningitis virus. *J. Exp. Med.* 185:517–530. <https://doi.org/10.1084/jem.185.3.517>
- Binder, S., M. Luciano, and J. Horejs-Hoeck. 2018. The cytokine network in acute myeloid leukemia (AML): A focus on pro- and anti-inflammatory mediators. *Cytokine Growth Factor Rev.* 43:8–15. <https://doi.org/10.1016/j.cytogfr.2018.08.004>
- Blokzijl, F., J. de Lig, M. Jager, V. Sasselli, S. Roerink, N. Sasaki, M. Huch, S. Boymans, E. Kuijk, P. Prins, et al. 2016. Tissue-specific mutation accumulation in human adult stem cells during life. *Nature.* 538:260–264. <https://doi.org/10.1038/nature19768>
- Boettcher, S., and B.L. Ebert. 2019. Clonal hematopoiesis of indeterminate potential. *J. Clin. Oncol.* 37:419–422. <https://doi.org/10.1200/JCO.2018.79.3588>
- Bordoni, V., D. Viola, A. Sacchi, C. Pinnetti, R. Casetti, E. Cimini, N. Tumino, A. Antinori, A. Ammassari, and C. Agrati. 2018. IL-18 and Stem Cell Factor affect hematopoietic progenitor cells in HIV-infected patients treated during primary HIV infection. *Cytokine.* 103:34–37. <https://doi.org/10.1016/j.cyto.2017.12.033>
- Brunner, S.F., N.D. Roberts, L.A. Wylie, L. Moore, S.J. Aitken, S.E. Davies, M.A. Sanders, P. Ellis, C. Alder, Y. Hooks, et al. 2019. Somatic mutations and clonal dynamics in healthy and cirrhotic human liver. *Nature.* 574:538–542. <https://doi.org/10.1038/s41586-019-1670-9>
- Bujanover, N., O. Goldstein, Y. Greenspan, H. Turgeman, A. Klainberger, Y. Scharff, and R. Gazit. 2018. Identification of immune-activated hematopoietic stem cells. *Leukemia.* 32:2016–2020. <https://doi.org/10.1038/s41375-018-0220-z>
- Burberry, A., M.Y. Zeng, L. Ding, I. Wicks, N. Inohara, S.J. Morrison, and G. Núñez. 2014. Infection mobilizes hematopoietic stem cells through cooperative NOD-like receptor and Toll-like receptor signaling. *Cell Host Microbe.* 15:779–791. <https://doi.org/10.1016/j.chom.2014.05.004>
- Busch, K., K. Klapproth, M. Barile, M. Flossdorf, T. Holland-Letz, S.M. Schlenner, M. Reth, T. Höfer, and H.R. Rodewald. 2015. Fundamental properties of unperturbed haematopoiesis from stem cells in vivo. *Nature.* 518:542–546. <https://doi.org/10.1038/nature14242>
- Cai, Z., J.J. Kotzin, B. Ramdas, S. Chen, S. Nelanuthala, L.R. Palam, R. Pandey, R.S. Mali, Y. Liu, M.R. Kelley, et al. 2018. Inhibition of inflammatory signaling in Tet2 mutant preleukemic cells mitigates stress-induced abnormalities and clonal hematopoiesis. *Cell Stem Cell.* 23:833–849.e5. <https://doi.org/10.1016/j.stem.2018.10.013>
- Cain, D.W., P.B. Snowden, G.D. Sempowski, and G. Kelsø. 2011. Inflammation triggers emergency granulopoiesis through a density-dependent feedback mechanism. *PLoS One.* 6:e19957. <https://doi.org/10.1371/journal.pone.0019957>
- Chalayer, E., N. Costedoat-Chalumeau, O. Beyne-Rauzy, J. Ninet, S. Durupt, J. Tebib, B. Asli, O. Lambotte, M. Ffrench, C. Vasselon, and P. Cathébras. 2017. Bone marrow involvement in systemic lupus erythematosus. *QJM.* 110:701–711. <https://doi.org/10.1093/qjmed/hcx102>
- Challen, G.A., D. Sun, M. Jeong, M. Luo, J. Jelinek, J.S. Berg, C. Bock, A. Vasanthakumar, H. Gu, Y. Xi, et al. 2012. Dnmt3a is essential for hematopoietic stem cell differentiation. *Nat. Genet.* 44:23–31. <https://doi.org/10.1038/ng.1009>
- Challen, G.A., D. Sun, A. Mayle, M. Jeong, M. Luo, B. Rodriguez, C. Mallaney, H. Celik, L. Yang, Z. Xia, et al. 2014. Dnmt3a and Dnmt3b have overlapping and distinct functions in hematopoietic stem cells. *Cell Stem Cell.* 15:350–364. <https://doi.org/10.1016/j.stem.2014.06.018>
- Chavez, J.S., J.L. Rabe, D. Loeffler, K.C. Higa, G. Hernandez, T.S. Mills, N. Ahmed, R.L. Gessner, Z. Ke, B.M. Idler, et al. 2021. PU.1 enforces quiescence and limits hematopoietic stem cell expansion during inflammatory stress. *J. Exp. Med.* 218:e20201169. <https://doi.org/10.1084/jem.20201169>
- Chen, J., X. Feng, M.J. Desierto, K. Keyvanfar, and N.S. Young. 2015. IFN- $\gamma$ -mediated hematopoietic cell destruction in murine models of immune-mediated bone marrow failure. *Blood.* 126:2621–2631. <https://doi.org/10.1182/blood-2015-06-652453>
- Choi, H.H., K.K. Kim, K.D. Kim, H.J. Kim, E.K. Jo, and C.H. Song. 2011. Effects of mycobacterial infection on proliferation of hematopoietic precursor cells. *Microbes Infect.* 13:1252–1260. <https://doi.org/10.1016/j.micinf.2011.08.001>
- Citrin, D.E., and J.B. Mitchell. 2017. Mechanisms of normal tissue injury from irradiation. *Semin. Radiat. Oncol.* 27:316–324. <https://doi.org/10.1016/j.semradonc.2017.04.001>
- Colmegna, I., and C.M. Weyand. 2011. Haematopoietic stem and progenitor cells in rheumatoid arthritis. *Rheumatology (Oxford).* 50:252–260. <https://doi.org/10.1093/rheumatology/keq298>
- Colmegna, I., A. Diaz-Borjon, H. Fujii, L. Schaefer, J.J. Goronzy, and C.M. Weyand. 2008. Defective proliferative capacity and accelerated telomeric loss of hematopoietic progenitor cells in rheumatoid arthritis. *Arthritis Rheum.* 58:990–1000. <https://doi.org/10.1002/art.23287>
- Cook, E.K., T. Izukawa, S. Young, G. Rosen, M. Jamali, L. Zhang, D. Johnson, E. Bain, J. Hilland, C.K. Ferrone, et al. 2019. Comorbid and inflammatory characteristics of genetic subtypes of clonal hematopoiesis. *Blood Adv.* 3:2482–2486. <https://doi.org/10.1182/bloodadvances.2018024729>
- Cook, E.K., M. Luo, and M.J. Rauh. 2020. Clonal hematopoiesis and inflammation: Partners in leukemogenesis and comorbidity. *Exp. Hematol.* 83:85–94. <https://doi.org/10.1016/j.exphem.2020.01.011>
- Corces-Zimmerman, M.R., and R. Majeti. 2014. Pre-leukemic evolution of hematopoietic stem cells: the importance of early mutations in leukemogenesis. *Leukemia.* 28:2276–2282. <https://doi.org/10.1038/leu.2014.211>
- Cordua, S., L. Kjaer, V. Skov, N. Pallisgaard, H.C. Hasselbalch, and C. Ellervik. 2019. Prevalence and phenotypes of JAK2 V617F and *calreticulin* mutations in a Danish general population. *Blood.* 134:469–479. <https://doi.org/10.1182/blood.2019001113>
- Craver, B.M., K. El Alaoui, R.M. Scherber, and A.G. Fleischman. 2018. The Critical role of inflammation in the pathogenesis and progression of myeloid malignancies. *Cancers (Basel).* 10:104. <https://doi.org/10.3390/cancers10040104>
- Cull, A.H., B. Snetsinger, R. Buckstein, R.A. Wells, and M.J. Rauh. 2017. Tet2 restrains inflammatory gene expression in macrophages. *Exp. Hematol.* 55:56–70.e13. <https://doi.org/10.1016/j.exphem.2017.08.001>
- Cyprus, G.N., J.W. Overlin, K.M. Hotchkiss, S. Kandalam, and R. Olivares-Navarrete. 2018. Cigarette smoke increases pro-inflammatory markers and inhibits osteogenic differentiation in experimental exposure model. *Acta Biomater.* 76:308–318. <https://doi.org/10.1016/j.actbio.2018.06.018>
- Damia, G., K.L. Komschlies, H. Futami, T. Back, M.E. Gruys, D.L. Longo, J.R. Keller, F.W. Ruscetti, and R.H. Wiltrott. 1992. Prevention of acute chemotherapy-induced death in mice by recombinant human interleukin 1: protection from hematological and nonhematological toxicities. *Cancer Res.* 52:4082–4089.
- Dawoud, A.A.Z., W.J. Tapper, and N.C.P. Cross. 2020. Clonal myelopoiesis in the UK Biobank cohort: ASXL1 mutations are strongly associated with smoking. *Leukemia.* 34:2660–2672. <https://doi.org/10.1038/s41375-020-0896-8>
- de Bruin, A.M., Ö. Demirel, B. Hooibrink, C.H. Brandts, and M.A. Nolte. 2013. Interferon- $\gamma$  impairs proliferation of hematopoietic stem cells in mice. *Blood.* 121:3578–3585. <https://doi.org/10.1182/blood-2012-05-432906>
- Desai, P., N. Mencia-Trinchant, O. Savenkov, M.S. Simon, G. Cheang, S. Lee, M. Samuel, E.K. Ritchie, M.L. Guzman, K.V. Ballman, et al. 2018. Somatic mutations precede acute myeloid leukemia years before diagnosis. *Nat. Med.* 24:1015–1023. <https://doi.org/10.1038/s41591-018-0081-z>
- Deshmukh, H.S., Y. Liu, O.R. Menkiti, J. Mei, N. Dai, C.E. O’Leary, P.M. Oliver, J.K. Kolls, J.N. Weiser, and G.S. Worthen. 2014. The microbiota regulates neutrophil homeostasis and host resistance to *Escherichia coli* K1 sepsis in neonatal mice. *Nat. Med.* 20:524–530. <https://doi.org/10.1038/nm.3542>

- Ehninger, A., T. Boch, H. Uckelmann, M.A. Essers, K. Müdder, B.P. Sleckman, and A. Trumpp. 2014. Posttranscriptional regulation of c-Myc expression in adult murine HSCs during homeostasis and interferon- $\alpha$ -induced stress response. *Blood*. 123:3909–3913. <https://doi.org/10.1182/blood-2013-10-531038>
- Ergen, A.V., N.C. Boles, and M.A. Goodell. 2012. Rantes/Ccl5 influences hematopoietic stem cell subtypes and causes myeloid skewing. *Blood*. 119:2500–2509. <https://doi.org/10.1182/blood-2011-11-391730>
- Essers, M.A.G., S. Offner, W.E. Blanco-Bose, Z. Waibler, U. Kalinke, M.A. Duchosal, and A. Trumpp. 2009. IFN $\alpha$  activates dormant haematopoietic stem cells in vivo. *Nature*. 458:904–908. <https://doi.org/10.1038/nature07815>
- Etzrodt, M., N. Ahmed, P.S. Hoppe, D. Loeffler, S. Skylaki, O. Hilsenbeck, K.D. Kokkaliaris, H.M. Kaltenbach, J. Stelling, C. Nerlov, and T. Schroeder. 2019. Inflammatory signals directly instruct PU.1 in HSCs via TNF. *Blood*. 133:816–819. <https://doi.org/10.1182/blood-2018-02-832998>
- Fleischman, A.G., K.J. Aichberger, S.B. Luty, T.G. Bumm, C.L. Petersen, S. Doratotaj, K.B. Vasudevan, D.H. LaTocha, F. Yang, R.D. Press, et al. 2011. TNF $\alpha$  facilitates clonal expansion of JAK2V617F positive cells in myeloproliferative neoplasms. *Blood*. 118:6392–6398. <https://doi.org/10.1182/blood-2011-04-348144>
- Florez, M.A., K.A. Matatall, Y. Jeong, L. Ortinau, P.W. Shafer, A.M. Lynch, R. Jaksik, M. Kimmel, D. Park, and K.Y. King. 2020. Interferon gamma mediates hematopoietic stem cell activation and niche relocalization through BST2. *Cell Rep*. 33:108530. <https://doi.org/10.1016/j.celrep.2020.108530>
- Frisch, B.J., C.M. Hoffman, S.E. Latchney, M.W. LaMere, J. Myers, J. Ashton, A.J. Li, J. Saunders II, J. Palis, A.S. Perkins, et al. 2019. Aged marrow macrophages expand platelet-biased hematopoietic stem cells via Interleukin1B. *JCI Insight*. 5:e124213. <https://doi.org/10.1172/jci.insight.124213>
- Fulop, T., A. Larbi, G. Dupuis, A. Le Page, E.H. Frost, A.A. Cohen, J.M. Witkowski, and C. Franceschi. 2018. Immunosenescence and inflammation as two sides of the same coin: friends or foes? *Front. Immunol*. 8:1960. <https://doi.org/10.3389/fimmu.2017.01960>
- Fuster, J.J., S. MacLachlan, M.A. Zuriaga, M.N. Polackal, A.C. Ostriker, R. Chakraborty, C.L. Wu, S. Sano, S. Muralidharan, C. Rius, et al. 2017. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science*. 355:842–847. <https://doi.org/10.1126/science.aag1381>
- Gasche, C., M.C.E. Lomer, I. Cavill, and G. Weiss. 2004. Iron, anaemia, and inflammatory bowel diseases. *Gut*. 53:1190–1197. <https://doi.org/10.1136/gut.2003.035758>
- Geiger, H., G. de Haan, and M.C. Florian. 2013. The ageing haematopoietic stem cell compartment. *Nat. Rev. Immunol*. 13:376–389. <https://doi.org/10.1038/nri3433>
- Genovese, G., A.K. Kähler, R.E. Handsaker, J. Lindberg, S.A. Rose, S.F. Bakhoun, K. Chambert, E. Mick, B.M. Neale, M. Fromer, et al. 2014. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N. Engl. J. Med*. 371:2477–2487. <https://doi.org/10.1056/NEJMoa1409405>
- Gerloff, D., R. Grundler, A.A. Wurm, D. Bräuer-Hartmann, C. Katzerke, J.U. Hartmann, V. Madan, C. Müller-Tidow, J. Duyster, D.G. Tenen, et al. 2015. NF- $\kappa$ B/STAT5/miR-155 network targets PU.1 in FLT3-ITD-driven acute myeloid leukemia. *Leukemia*. 29:535–547. <https://doi.org/10.1038/leu.2014.231>
- Grassinger, J., B. Williams, G.H. Olsen, D.N. Haylock, and S.K. Nilsson. 2012. Granulocyte colony stimulating factor expands hematopoietic stem cells within the central but not endosteal bone marrow region. *Cytokine*. 58:218–225. <https://doi.org/10.1016/j.cyto.2012.01.014>
- Griseri, T., B.S. McKenzie, C. Schiering, and F. Powrie. 2012. Dysregulated hematopoietic stem and progenitor cell activity promotes interleukin-23-driven chronic intestinal inflammation. *Immunity*. 37:1116–1129. <https://doi.org/10.1016/j.immuni.2012.08.025>
- Haas, S., J. Hansson, D. Klimmeck, D. Loeffler, L. Velten, H. Uckelmann, S. Wurzer, Á.M. Prendergast, A. Schnell, K. Hexel, et al. 2015. Inflammation-induced emergency megakaryopoiesis driven by hematopoietic stem cell-like megakaryocyte progenitors. *Cell Stem Cell*. 17:422–434. <https://doi.org/10.1016/j.stem.2015.07.007>
- Haltall, M.L.R., S. Watcham, N.K. Wilson, K. Eilers, A. Lipien, H. Ang, F. Birch, S.G. Anton, C. Pirillo, N. Ruivo, et al. 2020. Manipulating niche composition limits damage to haematopoietic stem cells during Plasmodium infection. *Nat. Cell Biol*. 22:1399–1410. <https://doi.org/10.1038/s41556-020-00601-w>
- Hara, T., K. Ando, H. Tsurumi, and H. Moriwaki. 2004. Excessive production of tumor necrosis factor- $\alpha$  by bone marrow T lymphocytes is essential in causing bone marrow failure in patients with aplastic anemia. *Eur. J. Haematol*. 73:10–16. <https://doi.org/10.1111/j.1600-0609.2004.00259.x>
- Hasan, S., C. Lacout, C. Marty, M. Cuingnet, E. Solary, W. Vainchenker, and J.L. Villeval. 2013. JAK2V617F expression in mice amplifies early hematopoietic cells and gives them a competitive advantage that is hampered by IFN $\alpha$ . *Blood*. 122:1464–1477. <https://doi.org/10.1182/blood-2013-04-498956>
- Heaton, W.L., A.V. Senina, A.D. Pomicter, M.E. Salama, P.M. Clair, D. Yan, R.N. Bell, J.M. Gililand, J.T. Prchal, T. O'Hare, and M.W. Deininger. 2018. Autocrine Tnf signaling favors malignant cells in myelofibrosis in a Tnfr2-dependent fashion. *Leukemia*. 32:2399–2411. <https://doi.org/10.1038/s41375-018-0131-z>
- Helbling, P.M., E. Piñero-Yáñez, R. Gerosa, S. Boettcher, F. Al-Shahrour, M.G. Manz, and C. Nombela-Arrieta. 2019. Global transcriptomic profiling of the bone marrow stromal microenvironment during postnatal development, aging, and inflammation. *Cell Rep*. 29:3313–3330.e4. <https://doi.org/10.1016/j.celrep.2019.11.004>
- Henry, C.J., M. Casás-Selves, J. Kim, V. Zaberezhnyy, L. Aghili, A.E. Daniel, L. Jimenez, T. Azam, E.N. McNamee, E.T. Clambey, et al. 2015. Aging-associated inflammation promotes selection for adaptive oncogenic events in B cell progenitors. *J. Clin. Invest*. 125:4666–4680. <https://doi.org/10.1172/JCI83024>
- Hernandez, G., T.S. Mills, J.L. Rabe, J.S. Chavez, S. Kuldaneck, G. Kirkpatrick, L. Noetzli, W.K. Jubair, M. Zanche, J.R. Myers, et al. 2020. Pro-inflammatory cytokine blockade attenuates myeloid expansion in a murine model of rheumatoid arthritis. *Haematologica*. 105:585–597. <https://doi.org/10.3324/haematol.2018.197210>
- Higa, K.C., A. Goodspeed, J.S. Chavez, M. De Dominicis, E. Danis, V. Zaberezhnyy, J.L. Rabe, D.G. Tenen, E.M. Pietras, and J. DeGregori. 2021. Chronic interleukin-1 exposure triggers selection for Cebpa-knockout multipotent hematopoietic progenitors. *J. Exp. Med*. 218:e20200560. <https://doi.org/10.1084/jem.20200560>
- Hirche, C., T. Frenz, S.F. Haas, M. Döring, K. Borst, P.K. Tegtmeier, I. Brizic, S. Jordan, K. Keyser, C. Chhatbar, et al. 2017. Systemic virus infections differentially modulate cell cycle state and functionality of long-term hematopoietic stem cells in vivo. *Cell Rep*. 19:2345–2356. <https://doi.org/10.1016/j.celrep.2017.05.063>
- Hoermann, G., G. Greiner, and P. Valent. 2015. Cytokine regulation of microenvironmental cells in myeloproliferative neoplasms. *Mediators Inflamm*. 2015:869242. <https://doi.org/10.1155/2015/869242>
- Hormaechea-Agulla, D., K.A. Matatall, D.T. Le, B. Kain, X. Long, P. Kus, R. Jaksik, G.A. Challen, M. Kimmel, and K.Y. King. 2021. Chronic infection drives Dnmt3a-loss-of-function clonal hematopoiesis via IFN $\gamma$  signaling. *Cell Stem Cell*. S1934-5909(21)00108-9. <https://doi.org/10.1016/j.stem.2021.03.002>
- Isgrò, A., I. Mezzaroma, A. Aiuti, A. Fantauzzi, M. Pinti, A. Cossarizza, and F. Aiuti. 2004. Decreased apoptosis of bone marrow progenitor cells in HIV-1-infected patients during highly active antiretroviral therapy. *AIDS*. 18:1335–1337. <https://doi.org/10.1097/00002030-200406180-00013>
- Isringhausen, S., L. Kovtonyuk, U. Suessbier, N.J. Kraeutler, A. Gomariz, P.M. Helbling, H.C. Wong, T. Nagasawa, M.G. Manz, A. Oxenius, et al. 2020. CD8 T cells induce destruction of bone marrow stromal niches and hematopoietic stem cell dysfunction in chronic viral infections. *bioRxiv*. (Preprint posted May 8, 2020) <https://doi.org/10.1101/2020.05.07.076083>
- Ito, S., A.C. D'Alessio, O.V. Taranova, K. Hong, L.C. Sowers, and Y. Zhang. 2010. Role of Tet proteins in 5mC to 5hmC conversion, ES-cell self-renewal and inner cell mass specification. *Nature*. 466:1129–1133. <https://doi.org/10.1038/nature09303>
- Iwamura, C., N. Bouladoux, Y. Belkaid, A. Sher, and D. Jankovic. 2017. Sensing of the microbiota by NOD1 in mesenchymal stromal cells regulates murine hematopoiesis. *Blood*. 129:171–176. <https://doi.org/10.1182/blood-2016-06-723742>
- Jaiswal, S., P. Fontanillas, J. Flannick, A. Manning, P.V. Grauman, B.G. Mar, R.C. Lindsley, C.H. Mermel, N. Burt, A. Chavez, et al. 2014. Age-related clonal hematopoiesis associated with adverse outcomes. *N. Engl. J. Med*. 371:2488–2498. <https://doi.org/10.1056/NEJMoa1408617>
- Jeong, M., D. Sun, M. Luo, Y. Huang, G.A. Challen, B. Rodriguez, X. Zhang, L. Chavez, H. Wang, R. Hannah, et al. 2014. Large conserved domains of low DNA methylation maintained by Dnmt3a. *Nat. Genet*. 46:17–23. <https://doi.org/10.1038/ng.2836>
- Jeong, M., H.J. Park, H. Celik, E.L. Ostrander, J.M. Reyes, A. Guzman, B. Rodriguez, Y. Lei, Y. Lee, L. Ding, et al. 2018. Loss of Dnmt3a immortalizes hematopoietic stem cells in vivo. *Cell Rep*. 23:1–10. <https://doi.org/10.1016/j.celrep.2018.03.025>



- Josefsdottir, K.S., M.T. Baldrige, C.S. Kadmon, and K.Y. King. 2017. Antibiotics impair murine hematopoiesis by depleting the intestinal microbiota. *Blood*. 129:729–739. <https://doi.org/10.1182/blood-2016-03-708594>
- Kaasinen, E., O. Kuusimäki, K. Rajamäki, H. Ristolainen, M. Aavikko, J. Kondelin, S. Saarinen, D.G. Berta, R. Katainen, E.A.M. Hirvonen, et al. 2019. Impact of constitutional TET2 haploinsufficiency on molecular and clinical phenotype in humans. *Nat. Commun.* 10:1252. <https://doi.org/10.1038/s41467-019-09198-7>
- Kanayama, M., Y. Izumi, Y. Yamauchi, S. Kuroda, T. Shin, S. Ishikawa, T. Sato, M. Kajita, and T. Ohteki. 2020. CD86-based analysis enables observation of bona fide hematopoietic responses. *Blood*. 136:1144–1154. <https://doi.org/10.1182/blood.2020004923>
- Kent, D.G., J. Li, H. Tanna, J. Fink, K. Kirschner, D.C. Pask, Y. Silber, T.L. Hamilton, R. Sneade, B.D. Simons, and A.R. Green. 2013. Self-renewal of single mouse hematopoietic stem cells is reduced by JAK2V617F without compromising progenitor cell expansion. *PLoS Biol.* 11:e1001576. <https://doi.org/10.1371/journal.pbio.1001576>
- Khaldoyanidi, S., L. Sikora, I. Orlovskaya, V. Matrosova, V. Kozlov, and P. Sriramarao. 2001. Correlation between nicotine-induced inhibition of hematopoiesis and decreased CD44 expression on bone marrow stromal cells. *Blood*. 98:303–312. <https://doi.org/10.1182/blood.V98.2.303>
- Khan, N., J. Downey, J. Sanz, E. Kaufmann, B. Blankenhaus, A. Pacis, E. Pernet, E. Ahmed, S. Cardoso, A. Nijnik, et al. 2020. M. tuberculosis reprograms hematopoietic stem cells to limit myelopoiesis and impair trained immunity. *Cell*. 183:752–770.e22. <https://doi.org/10.1016/j.cell.2020.09.062>
- Khosravi, A., A. Yáñez, J.G. Price, A. Chow, M. Merad, H.S. Goodridge, and S.K. Mazmanian. 2014. Gut microbiota promote hematopoiesis to control bacterial infection. *Cell Host Microbe*. 15:374–381. <https://doi.org/10.1016/j.chom.2014.02.006>
- King, K.Y., and M.A. Goodell. 2011. Inflammatory modulation of HSCs: viewing the HSC as a foundation for the immune response. *Nat. Rev. Immunol.* 11:685–692. <https://doi.org/10.1038/nri3062>
- King, K.Y., M.T. Baldrige, D.C. Weksberg, S.M. Chambers, G.L. Lukov, S. Wu, N.C. Boles, S.Y. Jung, J. Qin, D. Liu, et al. 2011. Irgm1 protects hematopoietic stem cells by negative regulation of IFN signaling. *Blood*. 118:1525–1533. <https://doi.org/10.1182/blood-2011-01-328682>
- Ko, M., H.S. Bandukwala, J. An, E.D. Lamperti, E.C. Thompson, R. Hastie, A. Tsangaratou, K. Rajewsky, S.B. Koralov, and A. Rao. 2011. Ten-Eleven-Translocation 2 (TET2) negatively regulates homeostasis and differentiation of hematopoietic stem cells in mice. *Proc. Natl. Acad. Sci. USA*. 108:14566–14571. <https://doi.org/10.1073/pnas.1112317108>
- Kovtonyuk, L.V., K. Fritsch, X. Feng, M.G. Manz, and H. Takizawa. 2016a. Inflamm-aging of hematopoiesis, hematopoietic stem cells, and the bone marrow microenvironment. *Front. Immunol.* 7:502. <https://doi.org/10.3389/fimmu.2016.00502>
- Kovtonyuk, L.V., M.G. Manz, and H. Takizawa. 2016b. Enhanced thrombopoietin but not G-CSF receptor stimulation induces self-renewing hematopoietic stem cell divisions in vivo. *Blood*. 127:3175–3179. <https://doi.org/10.1182/blood-2015-09-669929>
- Kueh, H.Y., A. Champhekar, S.L. Nutt, M.B. Elowitz, and E.V. Rothenberg. 2013. Positive feedback between PU.1 and the cell cycle controls myeloid differentiation. *Science*. 341:670–673. <https://doi.org/10.1126/science.1240831>
- Kuranda, K., J. Vargaftig, P. de la Rochere, C. Dosquet, D. Charron, F. Bardin, C. Tonnelle, D. Bonnet, and M. Goodhardt. 2011. Age-related changes in human hematopoietic stem/progenitor cells. *Aging Cell*. 10:542–546. <https://doi.org/10.1111/j.1474-9726.2011.00675.x>
- Laconi, E., F. Marongiu, and J. DeGregori. 2020. Cancer as a disease of old age: changing mutational and microenvironmental landscapes. *Br. J. Cancer*. 122:943–952. <https://doi.org/10.1038/s41416-019-0721-1>
- Laurenti, E., B. Varnum-Finney, A. Wilson, I. Ferrero, W.E. Blanco-Bose, A. Ehninger, P.S. Knoepfler, P.F. Cheng, H.R. MacDonald, R.N. Eisenman, et al. 2008. Hematopoietic stem cell function and survival depend on c-Myc and N-Myc activity. *Cell Stem Cell*. 3:611–624. <https://doi.org/10.1016/j.stem.2008.09.005>
- Lee, Y.K., J.S. Menezes, Y. Umesaki, and S.K. Mazmanian. 2011. Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. *Proc. Natl. Acad. Sci. USA*. 108(Suppl 1):4615–4622. <https://doi.org/10.1073/pnas.1000082107>
- Lee, S., H. Kim, G. You, Y.M. Kim, S. Lee, V.H. Le, O. Kwon, S.H. Im, Y.M. Kim, K.S. Kim, et al. 2019. Bone marrow CX3CR1+ mononuclear cells relay a systemic microbiota signal to control hematopoietic progenitors in mice. *Blood*. 134:1312–1322. <https://doi.org/10.1182/blood.2019000495>
- Leoni, C., S. Montagner, A. Rinaldi, F. Bertoni, S. Polletti, C. Balestrieri, and S. Monticelli. 2017. Dnmt3a restrains mast cell inflammatory responses. *Proc. Natl. Acad. Sci. USA*. 114:E1490–E1499. <https://doi.org/10.1073/pnas.1616420114>
- Li, G., J. Zhao, L. Cheng, Q. Jiang, S. Kan, E. Qin, B. Tu, X. Zhang, L. Zhang, L. Su, and Z. Zhang. 2017. HIV-1 infection depletes human CD34+CD38- hematopoietic progenitor cells via pDC-dependent mechanisms. *PLoS Pathog.* 13:e1006505. <https://doi.org/10.1371/journal.ppat.1006505>
- Loberg, M.A., R.K. Bell, L.O. Goodwin, E. Eudy, L.A. Miles, J.M. SanMiguel, K. Young, D.E. Bergstrom, R.L. Levine, R.K. Schneider, and J.J. Trowbridge. 2019. Sequentially inducible mouse models reveal that Npm1 mutation causes malignant transformation of Dnmt3a-mutant clonal hematopoiesis. *Leukemia*. 33:1635–1649. <https://doi.org/10.1038/s41375-018-0368-6>
- Lussana, F., and A. Rambaldi. 2017. Inflammation and myeloproliferative neoplasms. *J. Autoimmun.* 85:58–63. <https://doi.org/10.1016/j.jaut.2017.06.010>
- MacNamara, K.C., M. Jones, O. Martin, and G.M. Winslow. 2011. Transient activation of hematopoietic stem and progenitor cells by IFN $\gamma$  during acute bacterial infection. *PLoS One*. 6:e28669. <https://doi.org/10.1371/journal.pone.0028669>
- Manz, M.G., and S. Boettcher. 2014. Emergency granulopoiesis. *Nat. Rev. Immunol.* 14:302–314. <https://doi.org/10.1038/nri3660>
- Marandin, A., A. Katz, E. Oksenhendler, M. Tulliez, F. Picard, W. Vainchenker, and F. Louache. 1996. Loss of primitive hematopoietic progenitors in patients with human immunodeficiency virus infection. *Blood*. 88:4568–4578. <https://doi.org/10.1182/blood.V88.12.4568.bloodjournal88124568>
- Martincorena, I., A. Roshan, M. Gerstung, P. Ellis, P. Van Loo, S. McLaren, D.C. Wedge, A. Fullam, L.B. Alexandrov, J.M. Tubio, et al. 2015. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. *Science*. 348:880–886. <https://doi.org/10.1126/science.aaa6806>
- Martínez, A., C. Bono, J. Megías, A. Yáñez, D. Gozalbo, and M.L. Gil. 2018. Systemic candidiasis and TLR2 agonist exposure impact the antifungal response of hematopoietic stem and progenitor cells. *Front. Cell. Infect. Microbiol.* 8:309. <https://doi.org/10.3389/fcimb.2018.00309>
- Matatall, K.A., C.-C. Shen, G.A. Challen, and K.Y. King. 2014. Type II interferon promotes differentiation of myeloid-biased hematopoietic stem cells. *Stem Cells*. 32:3023–3030. <https://doi.org/10.1002/stem.1799>
- Matatall, K.A., M. Jeong, S. Chen, D. Sun, F. Chen, Q. Mo, M. Kimmel, and K.Y. King. 2016. Chronic infection depletes hematopoietic stem cells through stress-induced terminal differentiation. *Cell Rep.* 17:2584–2595. <https://doi.org/10.1016/j.celrep.2016.11.031>
- McKelvey, K.J., A.L. Hudson, M. Back, T. Eade, and C.I. Diakos. 2018. Radiation, inflammation and the immune response in cancer. *Mamm. Genome*. 29:843–865. <https://doi.org/10.1007/s00335-018-9777-0>
- McKenzie, M.D., M. Ghisi, E.P. Oxley, S. Ngo, L. Cimmino, C. Esnault, R. Liu, J.M. Salmon, C.C. Bell, N. Ahmed, et al. 2019. Interconversion between tumorigenic and differentiated states in acute myeloid leukemia. *Cell Stem Cell*. 25:258–272.e9. <https://doi.org/10.1016/j.stem.2019.07.001>
- Medzhitov, R. 2008. Origin and physiological roles of inflammation. *Nature*. 454:428–435. <https://doi.org/10.1038/nature07201>
- Meisel, M., R. Hinterleitner, A. Pacis, L. Chen, Z.M. Earley, T. Mayassi, J.F. Pierre, J.D. Ernest, H.J. Galipeau, N. Thuille, et al. 2018. Microbial signals drive pre-leukaemic myeloproliferation in a Tet2-deficient host. *Nature*. 557:580–584. <https://doi.org/10.1038/s41586-018-0125-z>
- Mitroulis, I., K. Ruppova, B. Wang, L.S. Chen, M. Grzybek, T. Grinenko, A. Eugster, M. Troullinaki, A. Palladini, I. Kourtzelis, et al. 2018. Modulation of myelopoiesis progenitors is an integral component of trained immunity. *Cell*. 172:147–161.e12. <https://doi.org/10.1016/j.cell.2017.11.034>
- Mohrin, M., E. Bourke, D. Alexander, M.R. Warr, K. Barry-Holm, M.M. Le Beau, C.G. Morrison, and E. Passegué. 2010. Hematopoietic stem cell quiescence promotes error-prone DNA repair and mutagenesis. *Cell Stem Cell*. 7:174–185. <https://doi.org/10.1016/j.stem.2010.06.014>
- Moran-Crusio, K., L. Reavie, A. Shih, O. Abdel-Wahab, D. Ndiaye-Lobry, C. Lobry, M.E. Figueroa, A. Vasanthakumar, J. Patel, X. Zhao, et al. 2011. Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. *Cancer Cell*. 20:11–24. <https://doi.org/10.1016/j.ccr.2011.06.001>
- Mueller, B.U., T. Pabst, J. Fos, V. Petkovic, M.F. Fey, N. Asou, U. Buerger, and D.G. Tenen. 2006. ATRA resolves the differentiation block in t(15;17) acute myeloid leukemia by restoring PU.1 expression. *Blood*. 107:3330–3338. <https://doi.org/10.1182/blood-2005-07-3068>

- Mullally, A., S.W. Lane, B. Ball, C. Megerdichian, R. Okabe, F. Al-Shahrour, M. Paktinat, J.E. Haydu, E. Housman, A.M. Lord, et al. 2010. Physiological Jak2V617F expression causes a lethal myeloproliferative neoplasm with differential effects on hematopoietic stem and progenitor cells. *Cancer Cell*. 17:584–596. <https://doi.org/10.1016/j.ccr.2010.05.015>
- Mullally, A., C. Bruedigam, L. Poveromo, F.H. Heidel, A. Purdon, T. Vu, R. Austin, D. Heckl, L.J. Breyfogle, C.P. Kuhn, et al. 2013. Depletion of Jak2V617F myeloproliferative neoplasm-propagating stem cells by interferon- $\alpha$  in a murine model of polycythemia vera. *Blood*. 121:3692–3702. <https://doi.org/10.1182/blood-2012-05-432989>
- Muto, T., C.S. Walker, K. Choi, K. Hueneman, M.A. Smith, Z. Gul, G. Garcia-Manero, A. Ma, Y. Zheng, and D.T. Starczynowski. 2020. Adaptive response to inflammation contributes to sustained myelopoiesis and confers a competitive advantage in myelodysplastic syndrome HSCs. *Nat. Immunol.* 21:535–545. <https://doi.org/10.1038/s41590-020-0663-z>
- Niu, H., G. Fang, Y. Tang, L. Xie, H. Yang, L. Morel, B. Diamond, and Y.R. Zou. 2013. The function of hematopoietic stem cells is altered by both genetic and inflammatory factors in lupus mice. *Blood*. 121:1986–1994. <https://doi.org/10.1182/blood-2012-05-433755>
- Noguera, N.I., M.L. Piredda, R. Tauli, G. Catalano, G. Angelini, G. Gaur, C. Nervi, M.T. Voso, A. Lunardi, P.P. Pandolfi, and F. Lo-Coco. 2016. PML/RARa inhibits PTEN expression in hematopoietic cells by competing with PU.1 transcriptional activity. *Oncotarget*. 7:66386–66397. <https://doi.org/10.18632/oncotarget.11964>
- Nombela-Arrieta, C., and M.G. Manz. 2017. Quantification and three-dimensional microanatomical organization of the bone marrow. *Blood Adv.* 1:407–416. <https://doi.org/10.1182/bloodadvances.2016003194>
- Oduro, K.A. Jr., F. Liu, Q. Tan, C.K. Kim, O. Lubman, D. Fremont, J.C. Mills, and K. Choi. 2012. Myeloid skewing in murine autoimmune arthritis occurs in hematopoietic stem and primitive progenitor cells. *Blood*. 120:2203–2213. <https://doi.org/10.1182/blood-2011-11-391342>
- Okano, M., D.W. Bell, D.A. Haber, and E. Li. 1999. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell*. 99:247–257. [https://doi.org/10.1016/S0092-8674\(00\)81656-6](https://doi.org/10.1016/S0092-8674(00)81656-6)
- Pandit, T.S., L. Sikora, G. Muralidhar, S.P. Rao, and P. Sriramarao. 2006. Sustained exposure to nicotine leads to extramedullary hematopoiesis in the spleen. *Stem Cells*. 24:2373–2381. <https://doi.org/10.1634/stemcells.2005-0447>
- Pang, W.W., E.A. Price, D. Sahoo, I. Beerman, W.J. Maloney, D.J. Rossi, S.L. Schrier, and I.L. Weissman. 2011. Human bone marrow hematopoietic stem cells are increased in frequency and myeloid-biased with age. *Proc. Natl. Acad. Sci. USA*. 108:20012–20017. <https://doi.org/10.1073/pnas.1116110108>
- Papadaki, H.A., D.T. Boumpas, F.M. Gibson, D.R. Jayne, J.S. Axford, E.C. Gordon-Smith, J.C.W. Marsh, and G.D. Eliopoulos. 2001. Increased apoptosis of bone marrow CD34(+) cells and impaired function of bone marrow stromal cells in patients with systemic lupus erythematosus. *Br. J. Haematol.* 115:167–174. <https://doi.org/10.1046/j.1365-2141.2001.03076.x>
- Papadaki, H.A., H.D. Kritikos, V. Valatas, D.T. Boumpas, and G.D. Eliopoulos. 2002. Anemia of chronic disease in rheumatoid arthritis is associated with increased apoptosis of bone marrow erythroid cells: improvement following anti-tumor necrosis factor- $\alpha$  antibody therapy. *Blood*. 100:474–482. <https://doi.org/10.1182/blood-2002-01-0136>
- Pascual, V., F. Allantaz, E. Arce, M. Punaro, and J. Banchereau. 2005. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J. Exp. Med.* 201:1479–1486. <https://doi.org/10.1084/jem.20050473>
- Pietras, E.M., R. Lakshminarasimhan, J.M. Techner, S. Fong, J. Flach, M. Binnewies, and E. Passegué. 2014. Re-entry into quiescence protects hematopoietic stem cells from the killing effect of chronic exposure to type I interferons. *J. Exp. Med.* 211:245–262. <https://doi.org/10.1084/jem.20131043>
- Pietras, E.M., C. Mirantes-Barbeito, S. Fong, D. Loeffler, L.V. Kovtonyuk, S. Zhang, R. Lakshminarasimhan, C.P. Chin, J.M. Techner, B. Will, et al. 2016. Chronic interleukin-1 exposure drives hematopoietic stem cells towards precocious myeloid differentiation at the expense of self-renewal. *Nat. Cell Biol.* 18:607–618. <https://doi.org/10.1038/ncb3346>
- Pioli, P.D., D. Casero, E. Montecino-Rodriguez, S.L. Morrison, and K. Dorshkind. 2019. Plasma cells are obligate effectors of enhanced myelopoiesis in aging bone marrow. *Immunity*. 51:351–366.e6. <https://doi.org/10.1016/j.immuni.2019.06.006>
- Porta, C., R. Caporali, O. Epis, I. Ramaioli, R. Invernizzi, B. Rovati, G. Comolli, M. Danova, and C. Montecucco. 2004. Impaired bone marrow hematopoietic progenitor cell function in rheumatoid arthritis patients candidated to autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 33:721–728. <https://doi.org/10.1038/sj.bmt.1704407>
- Pronk, C.J.H., O.P. Veiby, D. Bryder, and S.E.W. Jacobsen. 2011. Tumor necrosis factor restricts hematopoietic stem cell activity in mice: involvement of two distinct receptors. *J. Exp. Med.* 208:1563–1570. <https://doi.org/10.1084/jem.20110752>
- Pyrovolaki, K., I. Mavroudi, P. Sidiropoulos, A.G. Eliopoulos, D.T. Boumpas, and H.A. Papadaki. 2009. Increased expression of CD40 on bone marrow CD34+ hematopoietic progenitor cells in patients with systemic lupus erythematosus: contribution to Fas-mediated apoptosis. *Arthritis Rheum.* 60:543–552. <https://doi.org/10.1002/art.24257>
- Rabe, J.L., G. Hernandez, J.S. Chavez, T.S. Mills, C. Nerlov, and E.M. Pietras. 2020. CD34 and EPCR coordinately enrich functional murine hematopoietic stem cells under normal and inflammatory conditions. *Exp. Hematol.* 81:1–15.e6. <https://doi.org/10.1016/j.exphem.2019.12.003>
- Rao, T.N., N. Hansen, J. Stetka, D. Luque Paz, M. Kalmer, J. Hilfiker, M. Ende, N. Ahmed, L. Kubovcakova, M. Rybarikova, et al. 2021. JAK2-V617F and interferon- $\alpha$  induce megakaryocyte-biased stem cells characterized by decreased long-term functionality. *Blood*. 137:2139–2151. <https://doi.org/10.1182/blood-2020005563>
- Regan-Komito, D., J.W. Swann, P. Demetriou, E.S. Cohen, N.J. Horwood, S.N. Sansom, and T. Griseri. 2020. GM-CSF drives dysregulated hematopoietic stem cell activity and pathogenic extramedullary myelopoiesis in experimental spondyloarthritis. *Nat. Commun.* 11:155. <https://doi.org/10.1038/s41467-019-13853-4>
- Rodrigues-Moreira, S., S.G. Moreno, G. Ghinatti, D. Lewandowski, F. Hoffschir, F. Ferri, A.S. Gallouet, D. Gay, H. Motohashi, M. Yamamoto, et al. 2017. Low-dose irradiation promotes persistent oxidative stress and decreases self-renewal in hematopoietic stem cells. *Cell Rep.* 20:3199–3211. <https://doi.org/10.1016/j.celrep.2017.09.013>
- Rozhok, A.I., J.L. Salstrom, and J. DeGregori. 2014. Stochastic modeling indicates that aging and somatic evolution in the hematopoietic system are driven by non-cell-autonomous processes. *Aging (Albany NY)*. 6:1033–1048. <https://doi.org/10.18632/aging.100707>
- Rozhok, A.I., J.L. Salstrom, and J. DeGregori. 2016. Stochastic modeling reveals an evolutionary mechanism underlying elevated rates of childhood leukemia. *Proc. Natl. Acad. Sci. USA*. 113:1050–1055. <https://doi.org/10.1073/pnas.1509333113>
- Rundberg Nilsson, A., S. Soneji, S. Adolfsson, D. Bryder, and C.J. Pronk. 2016. Human and murine hematopoietic stem cell aging is associated with functional impairments and intrinsic megakaryocytic/erythroid bias. *PLoS One*. 11:e0158369. <https://doi.org/10.1371/journal.pone.0158369>
- Sallman, D.A., and A. List. 2019. The central role of inflammatory signaling in the pathogenesis of myelodysplastic syndromes. *Blood*. 133:1039–1048. <https://doi.org/10.1182/blood-2018-10-844654>
- Sano, S., K. Oshima, Y. Wang, Y. Katanasaka, M. Sano, and K. Walsh. 2018a. CRISPR-mediated gene editing to assess the roles of TET2 and DNMT3A in clonal hematopoiesis and cardiovascular disease. *Circ. Res.* 123:335–341. <https://doi.org/10.1161/CIRCRESAHA.118.313225>
- Sano, S., K. Oshima, Y. Wang, S. MacLauchlan, Y. Katanasaka, M. Sano, M.A. Zuriaga, M. Yoshiyama, D. Goukassian, M.A. Cooper, et al. 2018b. Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1 $\beta$ /NLRP3 inflammasome. *J. Am. Coll. Cardiol.* 71:875–886. <https://doi.org/10.1016/j.jacc.2017.12.037>
- Sato, T., N. Onai, H. Yoshihara, F. Arai, T. Suda, and T. Ohteki. 2009. Interferon regulatory factor-2 protects quiescent hematopoietic stem cells from type I interferon-dependent exhaustion. *Nat. Med.* 15:696–700. <https://doi.org/10.1038/nm.1973>
- Saxton, R.A., and D.M. Sabatini. 2017. mTOR signaling in growth, metabolism, and disease. *Cell*. 168:960–976. <https://doi.org/10.1016/j.cell.2017.02.004>
- Schuettel, L.G., J.N. Borgerding, M.J. Christopher, P.K. Gopalan, M.P. Romine, A.C. Herman, J.R. Woloszynek, A.M. Greenbaum, and D.C. Link. 2014. G-CSF regulates hematopoietic stem cell activity, in part, through activation of Toll-like receptor signaling. *Leukemia*. 28:1851–1860. <https://doi.org/10.1038/leu.2014.68>
- Schürch, C.M., C. Riether, and A.F. Ochsenbein. 2014. Cytotoxic CD8+ T cells stimulate hematopoietic progenitors by promoting cytokine release from bone marrow mesenchymal stromal cells. *Cell Stem Cell*. 14:460–472. <https://doi.org/10.1016/j.stem.2014.01.002>
- Scognamiglio, R., N. Cabezas-Wallscheid, M.C. Thier, S. Altamura, A. Reyes, Á.M. Prendergast, D. Baumgärtner, L.S. Carnevalli, A. Atzberger, S. Haas, et al. 2016. Myc depletion induces a pluripotent dormant state mimicking diapause. *Cell*. 164:668–680. <https://doi.org/10.1016/j.cell.2015.12.033>

- Scumpia, P.O., K.M. Kelly-Scumpia, M.J. Delano, J.S. Weinstein, A.G. Cuenca, S. Al-Quran, I. Bovio, S. Akira, Y. Kumagai, and L.L. Moldawer. 2010. Cutting edge: bacterial infection induces hematopoietic stem and progenitor cell expansion in the absence of TLR signaling. *J. Immunol.* 184: 2247–2251. <https://doi.org/10.4049/jimmunol.0903652>
- Sender, R., and R. Milo. 2021. The distribution of cellular turnover in the human body. *Nat. Med.* 27:45–48. <https://doi.org/10.1038/s41591-020-01182-9>
- Shao, L., Y. Wang, J. Chang, Y. Luo, A. Meng, and D. Zhou. 2013. Hematopoietic stem cell senescence and cancer therapy-induced long-term bone marrow injury. *Transl. Cancer Res.* 2:397–411.
- Shi, W., T. Vu, D. Boucher, A. Biernacka, J. Nde, R.K. Pandita, J. Straube, G.M. Boyle, F. Al-Ejeh, P. Nag, et al. 2017. Ssb1 and Ssb2 cooperate to regulate mouse hematopoietic stem and progenitor cells by resolving replicative stress. *Blood.* 129:2479–2492. <https://doi.org/10.1182/blood-2016-06-725093>
- Shi, X., S. Wei, K.J. Simms, D.N. Cumpston, T.J. Ewing, and P. Zhang. 2018. Sonic hedgehog signaling regulates hematopoietic stem/progenitor cell activation during the granulopoietic response to systemic bacterial infection. *Front. Immunol.* 9:349. <https://doi.org/10.3389/fimmu.2018.00349>
- Shlush, L.I., S. Zandi, A. Mitchell, W.C. Chen, J.M. Brandwein, V. Gupta, J.A. Kennedy, A.D. Schimmer, A.C. Schuh, K.W. Yee, et al. HALT Pan-Leukemia Gene Panel Consortium. 2014. Identification of pre-leukaemic haematopoietic stem cells in acute leukaemia. *Nature.* 506: 328–333. <https://doi.org/10.1038/nature13038>
- Siggins, R.W., F. Hossain, T. Rehman, J.N. Melvan, P. Zhang, and D.A. Welsh. 2014. Cigarette smoke alters the hematopoietic stem cell niche. *Med. Sci. (Basel).* 2:37–50. <https://doi.org/10.3390/medsci2010037>
- Skirecki, T., J. Kawiak, E. Machaj, Z. Pojda, D. Wasilewska, J. Czubak, and G. Hoser. 2015. Early severe impairment of hematopoietic stem and progenitor cells from the bone marrow caused by CLP sepsis and endotoxemia in a humanized mice model. *Stem Cell Res. Ther.* 6:142. <https://doi.org/10.1186/s13287-015-0135-9>
- Skirecki, T., M. Mikaszewska-Sokolewicz, M. Godlewska, B. Dołęgowska, J. Czubak, G. Hoser, J. Kawiak, and U. Zielińska-Borkowska. 2019. Mobilization of stem and progenitor cells in septic shock patients. *Sci. Rep.* 9:3289. <https://doi.org/10.1038/s41598-019-39772-4>
- Smith, J.N.P., Y. Zhang, J.J. Li, A. McCabe, H.J. Jo, J. Maloney, and K.C. MacNamara. 2018. Type I IFNs drive hematopoietic stem and progenitor cell collapse via impaired proliferation and increased RIPK1-dependent cell death during shock-like ehrlichial infection. *PLoS Pathog.* 14:e1007234. <https://doi.org/10.1371/journal.ppat.1007234>
- Staber, P.B., P. Zhang, M. Ye, R.S. Welner, C. Nombela-Arrieta, C. Bach, M. Kerényi, B.A. Bartholdy, H. Zhang, M. Alberich-Jordà, et al. 2013. Sustained PU.1 levels balance cell-cycle regulators to prevent exhaustion of adult hematopoietic stem cells. *Mol. Cell.* 49:934–946. <https://doi.org/10.1016/j.molcel.2013.01.007>
- Staffas, A., M. Burgos da Silva, A.E. Slingerland, A. Lazrak, C.J. Bare, C.D. Holman, M.D. Docampo, Y. Shono, B. Durham, A.J. Pickard, et al. 2018. Nutritional support from the intestinal microbiota improves hematopoietic reconstitution after bone marrow transplantation in mice. *Cell Host Microbe.* 23:447–457.e4. <https://doi.org/10.1016/j.chom.2018.03.002>
- Stetka, J., P. Vyhliadalova, L. Lanikova, P. Koralkova, J. Gursky, A. Hlusi, P. Flodr, S. Hubackova, J. Bartek, Z. Hodny, and V. Divoky. 2019. Addiction to DUSP1 protects JAK2V617F-driven polycythemia vera progenitors against inflammatory stress and DNA damage, allowing chronic proliferation. *Oncogene.* 38:5627–5642. <https://doi.org/10.1038/s41388-019-0813-7>
- Sun, J., A. Ramos, B. Chapman, J.B. Johnnidis, L. Le, Y.J. Ho, A. Klein, O. Hofmann, and F.D. Camargo. 2014. Clonal dynamics of native haematopoiesis. *Nature.* 514:322–327. <https://doi.org/10.1038/nature13824>
- Tada, T., S. Yamamura, Y. Kuwano, and T. Abo. 1996. Level of myelopoiesis in the bone marrow is influenced by intestinal flora. *Cell. Immunol.* 173: 155–161. <https://doi.org/10.1006/cimm.1996.0261>
- Takizawa, H., R.R. Regoes, C.S. Boddupalli, S. Bonhoeffer, and M.G. Manz. 2011. Dynamic variation in cycling of hematopoietic stem cells in steady state and inflammation. *J. Exp. Med.* 208:273–284. <https://doi.org/10.1084/jem.20101643>
- Takizawa, H., S. Boettcher, and M.G. Manz. 2012. Demand-adapted regulation of early hematopoiesis in infection and inflammation. *Blood.* 119: 2991–3002. <https://doi.org/10.1182/blood-2011-12-380113>
- Takizawa, H., K. Fritsch, L.V. Kovtonyuk, Y. Saito, C. Yakkala, K. Jacobs, A.K. Ahuja, M. Lopes, A. Hausmann, W.D. Hardt, et al. 2017. Pathogen-induced TLR4-TRIF innate immune signaling in hematopoietic stem cells promotes proliferation but reduces competitive fitness. *Cell Stem Cell.* 21:225–240.e5. <https://doi.org/10.1016/j.stem.2017.06.013>
- Talhout, R., T. Schulz, E. Florek, J. van Benthem, P. Wester, and A. Opperhuizen. 2011. Hazardous compounds in tobacco smoke. *Int. J. Environ. Res. Public Health.* 8:613–628. <https://doi.org/10.3390/ijerph8020613>
- Taraldsrud, E., H.K. Grøgaard, S. Solheim, K. Lunde, Y. Fløisand, H. Arnesen, I. Seljeflot, and T. Egeland. 2009. Age and stress related phenotypical changes in bone marrow CD34+ cells. *Scand. J. Clin. Lab. Invest.* 69:79–84. <https://doi.org/10.1080/00365510802419447>
- Trumpp, A., M. Essers, and A. Wilson. 2010. Awakening dormant haematopoietic stem cells. *Nat. Rev. Immunol.* 10:201–209. <https://doi.org/10.1038/nri2726>
- Ueda, Y., D.W. Cain, M. Kuraoka, M. Kondo, and G. Kelsoe. 2009. IL-1R type I-dependent hematopoietic stem cell proliferation is necessary for inflammatory granulopoiesis and reactive neutrophilia. *J. Immunol.* 182: 6477–6484. <https://doi.org/10.4049/jimmunol.0803961>
- Vainieri, M.L., A.M. Blagborough, A.L. MacLean, M.L.R. Haltalli, N. Ruivo, H.A. Fletcher, M.P.H. Stumpf, R.E. Sinden, and C.L. Celso. 2016. Systematic tracking of altered haematopoiesis during sporozoite-mediated malaria development reveals multiple response points. *Open Biol.* 6: 160038. <https://doi.org/10.1098/rsob.160038>
- Valletta, S., A. Thomas, Y. Meng, X. Ren, R. Drissen, H. Sengül, C. Di Genua, and C. Nerlov. 2020. Micro-environmental sensing by bone marrow stroma identifies IL-6 and TGFβ1 as regulators of hematopoietic ageing. *Nat. Commun.* 11:4075. <https://doi.org/10.1038/s41467-020-17942-7>
- van der Meer, J.W.M., M. Barza, S.M. Wolff, and C.A. Dinarello. 1988. A low dose of recombinant interleukin 1 protects granulocytopenic mice from lethal gram-negative infection. *Proc. Natl. Acad. Sci. USA.* 85:1620–1623. <https://doi.org/10.1073/pnas.85.5.1620>
- Vangala, R.K., M.S. Heiss-Neumann, J.S. Rangatia, S.M. Singh, C. Schoch, D.G. Tenen, W. Hiddemann, and G. Behre. 2003. The myeloid master regulator transcription factor PU.1 is inactivated by AML1-ETO in t(8;21) myeloid leukemia. *Blood.* 101:270–277. <https://doi.org/10.1182/blood-2002-04-1288>
- Vasto, S., G. Candore, C.R. Balistreri, M. Caruso, G. Colonna-Romano, M.P. Grimaldi, F. Listi, D. Nuzzo, D. Lio, and C. Caruso. 2007. Inflammatory networks in ageing, age-related diseases and longevity. *Mech. Ageing Dev.* 128:83–91. <https://doi.org/10.1016/j.mad.2006.11.015>
- Vyas, D., G. Laput, and A.K. Vyas. 2014. Chemotherapy-enhanced inflammation may lead to the failure of therapy and metastasis. *Oncotargets Ther.* 7:1015–1023. <https://doi.org/10.2147/OTT.S60114>
- Walter, D., A. Lier, A. Geiselhart, F.B. Thalheimer, S. Huntscha, M.C. Sobotta, B. Moehrle, D. Brocks, I. Bayindir, P. Kaschnig, et al. 2015. Exit from dormancy provokes DNA-damage-induced attrition in haematopoietic stem cells. *Nature.* 520:549–552. <https://doi.org/10.1038/nature14131>
- Wang, W., W. Liu, T. Fidler, Y. Wang, Y. Tang, B. Woods, C. Welch, B. Cai, C. Silvestre-Roig, D. Ai, et al. 2018. Macrophage inflammation, erythrophagocytosis, and accelerated atherosclerosis in JAK2<sup>V617F</sup> mice. *Circ. Res.* 123:e35–e47. <https://doi.org/10.1161/CIRCRESAHA.118.313283>
- Wang, Y., S. Sano, Y. Yura, Z. Ke, M. Sano, K. Oshima, H. Ogawa, K. Horitani, K.D. Min, E. Miura-Yura, et al. 2020. Tet2-mediated clonal hematopoiesis in nonconditioned mice accelerates age-associated cardiac dysfunction. *JCI Insight.* 5:e135204. <https://doi.org/10.1172/jci.insight.135204>
- Wang, P., J. Wang, Y.H. Li, L. Wang, H.C. Shang, and J.X. Wang. 2021. Phenotypical changes of hematopoietic stem and progenitor cells in sepsis patients: correlation with immune status? *Front. Pharmacol.* 11:640203. <https://doi.org/10.3389/fphar.2020.640203>
- Weisser, M., U.M. Demel, S. Stein, L. Chen-Wichmann, F. Touzot, G. Santilli, S. Sujer, C. Brendel, U. Siler, M. Cavazzana, et al. 2016. Hyperinflammation in patients with chronic granulomatous disease leads to impairment of hematopoietic stem cell functions. *J. Allergy Clin. Immunol.* 138:219–228.e9. <https://doi.org/10.1016/j.jaci.2015.11.028>
- Wilson, A., M.J. Murphy, T. Oskarsson, K. Kaloulis, M.D. Bettess, G.M. Oser, A.C. Pasche, C. Knabenhans, H.R. Macdonald, and A. Trumpp. 2004. c-Myc controls the balance between hematopoietic stem cell self-renewal and differentiation. *Genes Dev.* 18:2747–2763. <https://doi.org/10.1101/gad.313104>
- Wilson, A., E. Laurenti, G. Oser, R.C. van der Wath, W. Blanco-Bose, M. Jaworski, S. Offner, C.F. Dunant, L. Eshkind, E. Bockamp, et al. 2008. Hematopoietic stem cells reversibly switch from dormancy to self-renewal during homeostasis and repair. *Cell.* 135:1118–1129. <https://doi.org/10.1016/j.cell.2008.10.048>
- Woolthuis, C.M., N. Mariani, R.N. Verkaik-Schakel, A.Z. Brouwers-Vos, J.J. Schuringa, E. Vellenga, J.T.M. de Wolf, and G. Huls. 2014. Aging impairs

- long-term hematopoietic regeneration after autologous stem cell transplantation. *Biol. Blood Marrow Transplant.* 20:865–871. <https://doi.org/10.1016/j.bbmt.2014.03.001>
- Yamashita, M., and E. Passegué. 2019. TNF- $\alpha$  Coordinates Hematopoietic Stem Cell Survival and Myeloid Regeneration. *Cell Stem Cell.* 25: 357–372.e7. <https://doi.org/10.1016/j.stem.2019.05.019>
- Yang, H., H. Liang, J.S. Yan, R. Tao, S.G. Hao, and L.Y. Ma. 2012. Down-regulation of hematopoiesis master regulator PU.1 via aberrant methylation in chronic myeloid leukemia. *Int. J. Hematol.* 96:65–73. <https://doi.org/10.1007/s12185-012-1106-x>
- Zhang, X., D.P. Sejas, Y. Qiu, D.A. Williams, and Q. Pang. 2007. Inflammatory ROS promote and cooperate with the Fanconi anemia mutation for hematopoietic senescence. *J. Cell Sci.* 120:1572–1583. <https://doi.org/10.1242/jcs.003152>
- Zhang, M., L. Yin, K. Zhang, W. Sun, S. Yang, B. Zhang, P. Salzman, W. Wang, C. Liu, S. Vidyasagar, et al. 2012. Response patterns of cytokines/chemokines in two murine strains after irradiation. *Cytokine.* 58: 169–177. <https://doi.org/10.1016/j.cyto.2011.12.023>
- Zhang, Q., K. Zhao, Q. Shen, Y. Han, Y. Gu, X. Li, D. Zhao, Y. Liu, C. Wang, X. Zhang, et al. 2015. Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. *Nature.* 525:389–393. <https://doi.org/10.1038/nature15252>
- Zhang, C.R.C., D. Nix, M. Gregory, M.A. Ciorba, E.L. Ostrander, R.D. Newberry, D.H. Spencer, and G.A. Challen. 2019. Inflammatory cytokines promote clonal hematopoiesis with specific mutations in ulcerative colitis patients. *Exp. Hematol.* 80:36–41.e3. <https://doi.org/10.1016/j.exphem.2019.11.008>
- Zhao, M., F. Tao, A. Venkatraman, Z. Li, S.E. Smith, J. Unruh, S. Chen, C. Ward, P. Qian, J.M. Perry, et al. 2019. N-cadherin-expressing bone and marrow stromal progenitor cells maintain reserve hematopoietic stem cells. *Cell Rep.* 26:652–669.e6. <https://doi.org/10.1016/j.celrep.2018.12.093>