Published in final edited form as:

Curr Opin Hematol. 2021 July 01; 28(4): 251–261. doi:10.1097/MOH.0000000000000658.

The Nlrp3 inflammasome - the evolving story of its positive and negative effects on hematopoiesis

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Abstract

Purpose of review: Hematopoiesis is co-regulated by innate immunity, which is an ancient evolutionary defense mechanism also involved in the development and regeneration of damaged tissues. This review seeks to shed more light on the workings of the Nlrp3 inflammasome, which is an intracellular innate immunity pattern recognition receptor (PRR) and sensor of changes in the hematopoietic microenvironment, and focus on its role in hematopoeisis.

Recent findings: Hematopoietic stem progenitor cells (HSPCs) are exposed to several external mediators of innate immunity. Moreover, since hemato/lymphopoietic cells develop from a common stem cell, their behavior and fate are coregulated by intracellular innate immunity pathways. Therefore, the Nlrp3 inflammasome is functional both in immune cells and in HSPCs and affects hematopoiesis in either a positive or negative way, depending on its activity level. Specifically, while a physiological level of activation regulates the trafficking of HSPCs and most likely maintains their pool in the bone marrow, hyperactivation may lead to irreversible cell damage by pyroptosis and HSPC senescence and contribute to the origination of myelodysplasia and hematopoietic malignancies.

Summary: Modulation of the level of Nrp3 inflammasome activation will enable improvements in HSPC mobilization, homing, and engraftment strategies. It may also control pathological activation of this protein complex during HSPC senescence, GvHD, the induction of cytokine storms, and the development of hematopoietic malignancies.

Keywords

Hematopoietic stem cells; innate immunity; Nlrp3 inflammasome; hematopoietic stem cell trafficking

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Conflict-of-interest statement
The authors have no financial interests to disclose.

Introduction

The Nlrp3 inflammasome is, so far, the best-studied member of the inflammasome family, which consists of several members [1–6]. This intracellular protein complex is formed by multiprotein oligomers, each consisting of Nlrp3 protein, apoptosis-associated speck-like protein containing a CARD (ASC, also known as PYCARD), and pro-caspase 1 [7–11]. Upon activation, these multiprotein oligomers aggregate to form the inflammasome (also known as a speck complex). Nlrp3-mediated activation of caspase 1 promotes proteolytic cleavage and maturation of two pro-inflammatory cytokines, interleukin-1β (IL-1β) and interleukin 18 (IL-18), and cleavage of gasdermin D, which forms cell membrane pores involved in secretion of mature IL-1β and IL-18 [12–14]. Moreover, these pores secrete several danger-associated molecular pattern (DAMP) molecules [15,16]. Formation of gasdermin D pores may lead to irreversible leakage of cytoplasm content and a pro-inflammatory form of programmed cell death known as pyroptosis [17,18]. Recent results indicate that physiological activation of the Nlrp3 inflammasome is involved in *i)* mobilization of HSPCs from bone marrow (BM) into peripheral blood (PB), *ii)* HSPC homing to BM after transplantation, and *iii)* HSPC expansion and aging [19*, 20–25, 26*]. On the other hand, hyperactivation of the Nlrp3 inflammasome is involved in certain hematological pathologies, including *i)* myelodysplastic syndrome, *ii)* myeloproliferative neoplasms, *iii)* leukemia, and *iv)* post-transplantation graft-versus-host disease (GvHD) [27–37]. Thus, the biological impact of the Nlrp3 inflammasome on hematopoiesis depends on the overall level and timing of its activation [31*].

HSPCs require the Nlrp3 inflammasome for normal migration.

One of the essential features of HSPCs is their inborn ability to migrate, both during prenatal development and later on in the postnatal period of life. Based on reports that the Nlrp3 inflammasome is required for migration of T lymphocytes [38–40] and macrophages [41–44], we hypothesized that it could also be involved in the chemotactic responsiveness of HSPCs. In fact, by employing the Transwell migration system, we found that blockade of the Nlrp3 inflammasome by the small-molecule inhibitor MCC950 impaired migration of HSPCs in response to the major BM chemoattractant stromal-derived factor 1 (SDF-1) as well as two other supportive homing factors, namely, extracellular adenosine triphosphate (eATP) and sphingosine-1-phosphate (S1P) [19]. This finding has been subsequently reproduced with BMMNCs isolated from Nlrp3-KO mice, and we obtained similar results with human HSPCs exposed to MCC950 [19].

Overall, the migration of HSPCs in response to chemoattractants is regulated by membrane lipid rafts (MLRs), which are microdomains of cell membrane enriched in glycosphingolipids and cell-surface protein receptors [45,46]. As reported, HSPCs respond much more strongly to an SDF-1 chemotactic gradient if its specific receptor (CXCR4) is incorporated into the MLRs [47,48]. This association facilitates a stronger transduction between activated CXCR4 and the downstream signaling pathways involved in cell migration [49]. Our recent report revealed that activation of the Nlrp3 inflammasome in HSPCs enhances incorporation of CXCR4 into MLRs, resulting in better responsiveness of these cells to BM-expressed chemotactic factors [19].

These *in vitro* results inspired us to investigate the role of the Nlrp3 inflammasome in the trafficking of HSPCs in *i)* a murine model of HSPC mobilization into PB and *ii)* homing to BM after hematopoietic transplantation [19,20,27].

Nlrp3 inflammasomes expressed in the BM microenvironment and in HSPCs are required for proper mobilization of HSPCs.

HSPCs are retained in a quiescent state in stem cell niches spread throughout the BM microenvironment. Several mechanisms have been proposed that regulate their detachment and egress from these niches in response to a gradient of HSPC-specific chemotactic factors [50–56]. A crucial role in this process is the induction of a proteolytic and lipolytic microenvironment [57–62], which results from a state of sterile inflammation in the BM microenvironment in response to cues that promote egress of HSPCs from BM into PB [51,63,64]. From a clinical point of view, the forced release of HSPCs is observed after systemic administration of the cytokine granulocyte colony-forming factor (G-CSF) or the SDF-1 receptor (CXCR4) antagonist AMD3100. This process is employed in the clinic to harvest HSPCs from PB for transplantation and is called pharmacological mobilization [65*, 66*, 67–72].

Our recent results indicate that a crucial role in the initiation of the sterile inflammation state in BM, which promotes the mobilization process, is played by the activation of purinergic signaling and, in particular, the release of eATP [26,27]. In response to pro-mobilizing agents, a source of this extracellular signaling nucleotide is innate immunity cells, including granulocytes, monocytes, and dendritic cells [73–76]. It is well known that mice deficient in these cells are poor mobilizers [55,77,78].

eATP released in response to G-CSF or AMD3100 administration as one of the DAMPs that is secreted by pannexin 1 channels. It has been demonstrated that blockade of pannexin 1 channels by specific inhibitory peptides significantly decreases the pharmacological mobilization efficiency of HSPCs in mice [79]. Interestingly, our previously published results indicate that the pannexin 1 channel must be functional for optimal mobilization, not only in HSPCs but also in cells present in the hematopoietic microenvironment [80]. Supporting this finding, mice that were exposed to a pannexin-1-blocking peptide before mobilization mobilized poorly, which indicates a role for eATP in activating in this microenvironment pathways that are involved in HSPC egress into PB [80]. Based on this observation, we became interested in a potential link between eATP and intracellular activation of Nlrp3 inflammasomes.

The Nlrp3 inflammasome is activated in HSPCs and the BM microenvironment in an eATP–P2X4- and eATP–P2X7-dependent manner.

eATP is an activating ligand for several purinergic receptors from both the ionotropic P2X and metabotropic P2Y families, which consist of 7 and 8 receptors, respectively [81–83]. Our results indicate that the most important receptors in the mobilization of HSPCs are the ionotropic P2X4 and P2X7 receptors [79,84,85]. These receptors are highly expressed on the surfaces of both human and murine HSPCs. The importance of these receptors was confirmed by the finding that their blockade by small-molecule inhibitors, PSB12054 and

A438079, respectively, impaired the chemotactic responsiveness of murine and human HSPCs to SDF-1, eATP, and S1P gradients [84]. Moreover, like the blockade of pannexin 1 channels, the lack of functional P2X4 and P2X7 receptors on the surfaces of cells in the BM microenvironment also results in poor G-CSF- and AMD3100-induced mobilization in mice [84,85].

Explaining the role of eATP–P2X4 and eATP–P2X7 signaling in HSPC mobilization, both of these ligand–receptor axes are strong activators of the Nlrp3 inflammasome [86–88], which, as a component of innate immunity, functions as an intracellular pattern recognition receptor (PRR) for DAMPs [7,8,10]. eATP is the most important DAMP of the molecules in this functional category, such as high mobility group box 1 (HMGB1) and S100A9 immunoregulatory proteins. All these DAMPs are released in an Nlrp3 inflammasome-dependent manner, both from innate immunity cells and HSPCs, while eATP, by employing positive autocrine/paracrine feedback loop, maintains activation of this PRR [14,89,90]. At the same time other DAMPs, such as HMGB1 and S1009A, activate the complement cascade (ComC) [91], which has been reported to be crucial for optimal egress of HSPCs into PB [92]. Supporting this finding, mice that do not activate the ComC are normally poor mobilizers [78,93,94]. In addition to DAMPs, the Nlrp3 inflammasome may also be activated by reactive oxygen species (ROS)[95–97], and it is worth mentioning that ROS have been reported as important factors promoting the migration and mobilization of HSPCs [98–100]. This connection between the Nlrp3 inflammasome and ROS may explain why the biological effects of this PRR, like ROS, depend on the level of its expression (concentration) [12]. It is known that a balanced expression of ROS is crucial for maintaining the stem cell pool and host immunity, both under homeostatic steady-state conditions and during stress situations [98]. The same seems to be true for the Nlrp3 inflammasome.

Finally, very recently published results have demonstrated that when Nlrp3 inflammasome-associated caspase 1 is knocked out in mice, the resulting caspase-1-KO mice are poor mobilizers [101]. This finding has been explained by the role caspase 1 plays in the release of DAMPs, which promote mobilization (via eATP) and activate the ComC (via HMGB1 and S1009A). All these DAMPs together are required for normal egress of HSPCs from BM into PB.

Interestingly, the normal basic level of Nlrp3 inflammasome expression in HSPCs and innate immunity cells is regulated by intestinal Gram-negative bacteria-derived liposaccharide (LPS) [8,102–104]. By interacting with Toll-like receptor 4 (TLR4), LPS maintains expression of Nlrp3 inflammasome components in innate immunity cells and HSPCs. That LPS circulating in PB is derived from intestinal bacteria explains why mice depleted of this Gram-negative flora are poor mobilizers [105]. We propose that these results are most likely to be explained by the deficient expression of Nlrp3 inflammasome components in innate immunity cells and HSPCs.

Figure 1 illustrates all the major components of innate immunity that are part of the Nlrp3 inflammasome activation pathway and for which a deficiency results in poor mobilization.

Evidence that the Nlrp3 inflammasome directs homing and engraftment of transplanted HSPCs.

As presented above, the Nlrp3 inflammasome controls the normal chemotactic responsiveness of HSPCs to major BM chemoattractants. Therefore, besides its role in mobilization, we also became interested in the role of this PRR in the homing and engraftment of HSPCs. Again, we focused on Nlrp3 inflammasome expression, both directly in HSPCs, which must migrate to BM niches, and in cells in the BM microenvironment in transplantation recipients. As expected, we found that HSPCs from Nlrp3-KO mice show a decrease in homing (i.e., seeding efficiency) and engraftment in regular myeloablated hosts compared with normal control mouse HSPCs [19]. Since myeloablative conditioning for transplantation by lethal irradiation also induces a state of sterile inflammation in BM, in another set of experiments we studied the role of BM microenvironment-expressed Nlrp3 inflammasomes in facilitating the homing of transplanted BMMNCs. We found that Nrlp3-KO transplantation recipient mice engrafted poorly with normal BMMNCs compared with normal control animal recipients [19]. This finding indicates that the response of the Nlrp3 inflammasome to conditioning for transplantation here plays an important role in preparing the BM microenvironment to be seeded by HSPCs. Similarly, we recently demonstrated that the Nlrp3 inflammasome is highly activated in the BM of mice conditioned for transplantation by lethal irradiation and is involved in the regulation of SDF-1 expression and activation of the complement cascade, which has been demonstrated to promote optimal engraftment of HSPCs [78,92–94].

Moreover, in addition to Nlrp3 inflammasome deficiency, impaired homing and engraftment was also observed in animals deficient for other elements of purinergic signaling pathways related to Nlrp3 inflammasome activation (Figure 2). This again was observed both for transplanted cells and for animals that served as transplantation recipients. Supporting this finding, in addition to the abovementioned blockade of the pannexin 1 channel, poor homing and engraftment was observed following transplantations performed with P2X4 and P2X7 receptor-deficient BMMNCs [85,106]. We also observed poor homing and engraftment when transplanted recipient mice were deficient for P2X4 and P2X7 receptors [106] as well as caspase 1 [101**]. These findings support the role of Nlrp3 inflammasomes expressed in cells in the BM microenvironment in facilitating the seeding efficiency of transplanted HSPCs.

eATP and its extracellular metabolite adenosine (eAdo) regulate, in opposite ways, activation of Nlrp3 inflammasomes and cell migration.

In addition to eATP, another central mediator of purinergic signaling is its metabolite, extracellular adenosine (eAdo). As depicted in Figure 3, eATP released from stressed or activated cells is converted into eAdo in the extracellular space by two cell-surface ectonucleotidases, CD39 and CD73 [81,83]. This eATP-derived metabolite interacts with the P1 family of purinergic receptors, which consists of four G protein-coupled members. Of these four receptors, HSPCs positively express A_{2A} and A_{2B}, which after binding eAdo negatively affect migration of HSPCs [84,107,108].

Figure 3 also shows HSPCs migrating to BM after transplantation in response to SDF-1, S1P, and eATP gradients released from BM stroma conditioned for transplantation by myeloablative radio- or chemotherapy. HSPCs migrating in response to all these chemoattractants activate the Nlrp3 inflammasome, which initiates release from cells of several DAMPs, including eATP, HMGB1, and S1009A. While eATP, by employing P2X4 and P2X7 receptor autocrine loops, activates Nlrp3 inflammasomes to maintain the activity required for cell migration [85,106*,109], two other DAMPs activate the complement cascade, whose cleavage fragments, including anaphylatoxin C3a and C5a and non-lytic C5b-C9 (membrane attack complex), additionally stimulate Nlrp3 inflammasomes, both in migrating HSPCs and in the BM microenvironment [91,93].

As depicted in Figure 3, autocrine-secreted eATP promotes and maintains formation of MLRs. As reported these cell membrane microdomains incorporate CXCR4 and other homing receptors to connect them better with downstream signaling pathways. This facilitates optimal navigation of HSPCs to BM niches [47, 65*]. At the same time, eATP is processed by CD39 and CD73 to eAdo, which, by interacting with P1 receptors, activates intracellular heme oxygenase 1 (HO-1), which in turn has an inhibitory effect on Nlrp3 inflammasomes and MLR formation [19,110–112]. These are all coordinated processes that require both local cell migration-stimulating and cell migration-inhibiting mechanisms. Specifically, chemotactic factors, including CXCR4, $S1P_1R$, P2X4, and P2X7, are expressed at the leading surface of migrating cells, while the migration-inhibitory P1 receptors, $A2_A$ and/or $A2_B$, are expressed at the receding surface [75,113]. Thus, migration of HSPCs is balanced by eATP-, SDF-1-, and S1P-promoted chemotaxis and controlled negatively by eAdo.

The potential role of Nlrp3 inflammasomes in maintaining the pool of HSPCs and expanding these cells after transplantation into the recipient BM.

One of the challenging questions still to be answered is the potential effect of the Nlrp3 inflammasome on HSPC proliferation. Our recent results indicate that Nlrp3-KO mice have ~20% fewer Sca-1^+Kit$^+$Lin$^-$ (SKL) HSPCs in BM than do WT animals [19]. This raises the legitimate question of whether the Nlrp3 inflammasome affects the proliferation and expansion of these cells. In support of this possibility, it has been reported that in the developing murine embryo, the Nlrp3 inflammasome is involved in expansion of CD41$^+$ HSPCs [22]. Moreover, loss of Nlrp3 inflammasome components prevented the proliferation of embryonic HSPCs, and positive multilineage expansion results were obtained with human induced pluripotent stem cell-derived hemogenic cells in the presence of Nlrp3 inflammasome activators [114].

Another question is whether the proliferation of HSPCs is also affected by the eATP metabolite eAdo, which has an effect opposite to eATP on HSPC migration, as discussed above. Interestingly, in a zebrafish embryo model, somewhat surprisingly, eAdo has been proposed as a positive regulator of hematopoiesis [115]. However, in our hands, eAdo did not affect the proliferation of either murine or human HSPCs. This apparent discrepancy between zebrafish and human hematopoiesis can be explained by species differences. Nevertheless, the impact of the Nlrp3 inflammasome on proliferation of HSPCs needs

further study. This question could be addressed in a model of stress-induced hematopoiesis, for example, by evaluating hematopoietic recovery in sublethally irradiated Nlrp3-KO mice.

Hyperactivation of the Nlrp3 inflammasome as the culprit behind pyroptosis, senescence of HSPCs, induction of cytokine storms, GvHD, and the origin of hematopoietic malignancies.

While, as demonstrated above, the physiological level of Nlrp3 inflammasome activation regulates trafficking of HSPCs [19,20] and most likely maintains the pool of these cells in BM [116], hyperactivation in HSPCs may lead to several adverse effects, including irreversible cell damage through the mechanisms of pyroptosis and senescence and even contribute to the origin of hematopoietic malignancies [29–31,33,35,36,117–119]. On the other hand, uncontrolled hyperactivation of Nlrp3 inflammasomes in innate immunity cells may induce a cytokine storm [34] and initiate GvHD after hematopoietic transplantation (Figure 4). Moreover, while excessive hyperactivation of Nlrp3 inflammasomes in HSPCs may lead to cell death by pyroptosis, in a recent elegant paper it has been shown that Nlrp3 inflammasomes activated due to mitochondrial stress in aged HSPCs contribute to their aging [120**]. This process could be mediated by mitochondria-derived ROS, which, as mentioned above, are potent activators of Nlrp3 inflammasomes [96]. Another problem to consider is the involvement of Nlrp3 inflammasomes in myelodysplastic syndromes as part of aberrant activation of innate immunity and a “smoldering” pro-inflammatory state in the hematopoietic microenvironment [29,121]. This process potentiates BM inflammation and leads to hematopoietic cell damage, chromosomal abnormalities, expansion of BM myeloid-derived suppressor cells, and initiates myeloproliferative disorders and even leukemia. These effects are a consequence of inflammaging, which is driven, at least partially, by prolonged excessive activation of the Nlrp3 inflammasome [23–25,32].

Another complication of Nlrp3 hyperactivation in innate immunity cells is initiation of cytokine storms, as seen, for example, in COVID19-infected patients [122*–124*]. or patients undergoing CAR-T cell therapy [125,126]. Finally, the Nlrp3 inflammasome may be one of the contributing factors in initiating GvHD after hematopoietic transplantation [34,127]. Evidence indicates that these effects are regulated by modulating Nlrp3 inflammasome activity by positive and negative eATP- and eAdo- mediated signaling, respectively [128*].

Conclusions

The Nlrp3 inflammasome has recently become a “rising star” in studies on normal and pathological hematopoiesis. This popularity is reflected by the increasing number of publications related to the role of this exciting protein complex in maintaining BM homeostasis or its involvement in the pathogenesis of several disorders. It is expected that modulation of the level of Nrp3 inflammasome activation will allow for the development of better stem cell mobilization, homing, and engraftment strategies. On the other hand, controlling pathological activation of this protein complex may ameliorate HSPC senescence, GvHD, cytokine storms, and the development of hematopoietic malignancies. However, more investigation is still needed to elucidate the mechanistic aspects of Nlrp3

inflammasome action. Finally, in addition to the existing small-molecule inhibitor of the Nlrp3 inflammasome, MCC950, other potent new drugs are under investigation, and the first clinical trials to control activation of the Nlrp3 inflammasome in patients have been initiated. This progress is expected to lead to the application of these compounds in benign and malignant hematology.

Acknowledgments:

This work was supported by the NIH grants 2R01 DK074720, the Stella and Henry Hoenig Endowment, and the OPUS grant UMO-2018/29/B/NZ4/01470 to MZR.

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Key points

- Hematopoiesis is co-regulated by several innate immunity mediators and intracellular innate immunity pathways.
- Nlrp3 inflammasome is an innate immunity intracellular pattern recognition receptor that in addition to innate immunity cells is also functional in HSC and affects hematopoiesis in either a positive or negative way, depending on its activity level.
- Novel evidence demonstrates that physiological level of Nlrp3 inflammasome activation regulates the trafficking of HSC and most likely maintains their pool in the bone marrow.
- In contrast hyperactivation of Nlrp3 inflammasome may lead to irreversible cell damage by pyroptosis, HSC senescence, myelodysplasia and hematopoietic malignancies.

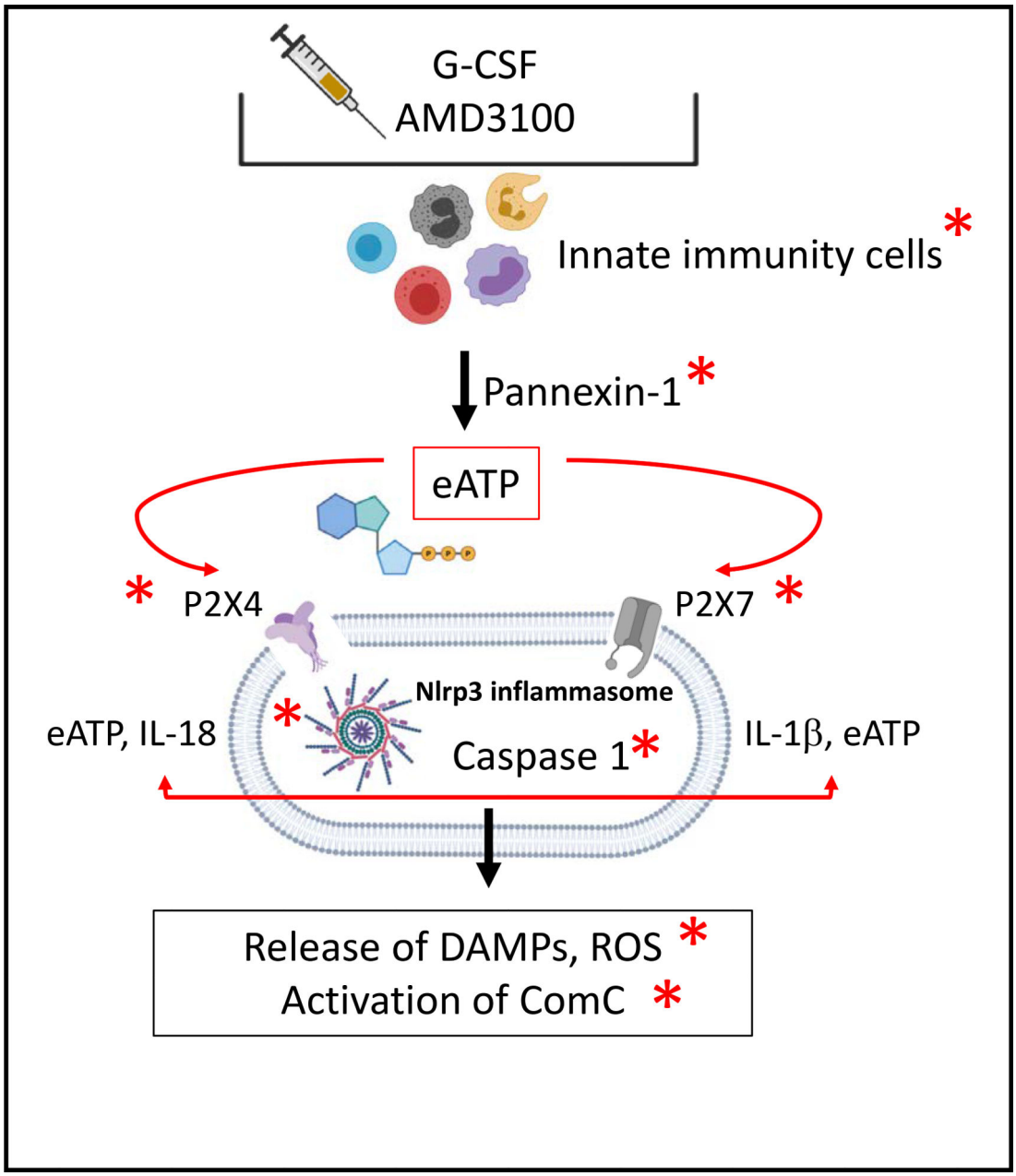

Figure 1. The elements of innate immunity involved in Nlrp3 inflammasome activation whose attenuation decreases HSPC mobilization.

Pro-mobilizing agents (G-CSF or AMD3100) stimulate the release of eATP from innate immunity cells (granulocytes, monocytes, and dendritic cells) in a pannexin-1-channel-dependent manner. Once released from these cells, eATP activates Nlrp3 inflammasomes in HSPCs via the P2X4 and P2X7 receptors, which subsequently activates caspase 1 to release active IL-1β and IL-18. Autocrine/paracrine stimulation of HSPCs, innate immunity cells, and cells in the BM microenvironment leads to a release of several types of DAMPs and activation of the complement cascade (ComC). Red asterisks indicate elements whose attenuation results in poor mobilization in our recently published or preliminary results.

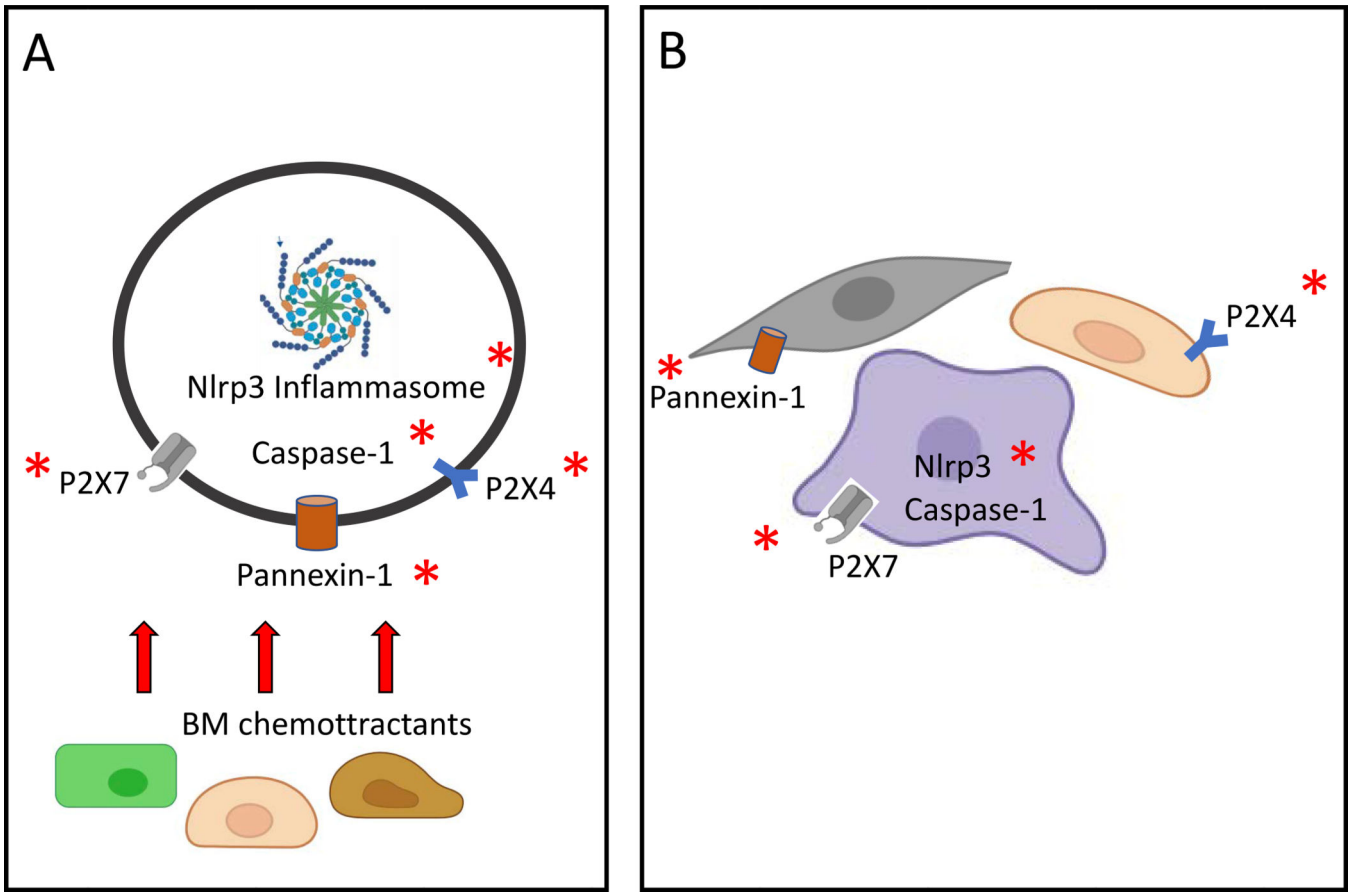

Figure 2.

A, The elements of innate immunity that are involved in Nlrp3 inflammasome activation and whose attenuation decreases HSPC migration after transplantation into recipient BM. Migration of transplanted HSPCs up a chemotactic gradient of BM chemoattractants is decreased by impaired Nlrp3 function as well as pannexin 1, P2X4, P2X7, and caspase 1 deficiency. B, The same effect is shown for Nlrp3 inflammasome activation components in the BM microenvironment of transplantation recipients. To home and engraft transplanted HSPCs, BM microenvironment cells require normal expression of the Nlrp3 inflammasome, pannexin 1, P2X4, P2X7, and caspase 1. Red asterisks indicate elements whose attenuation results in poor homing and engraftment in our recently published or preliminary results.

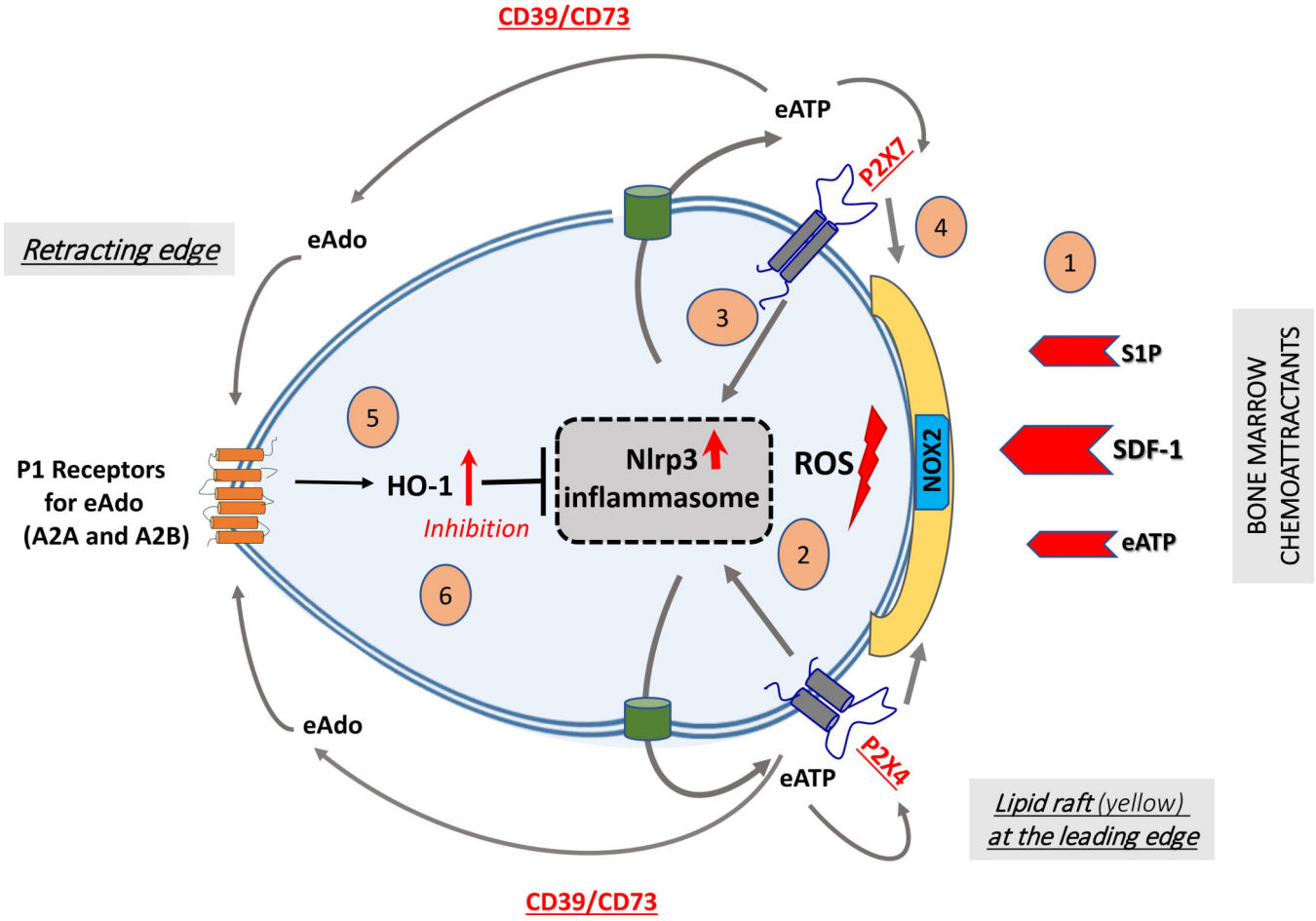

Figure 3. Cell migration-promoting mechanisms at the leading surface/edge and negative feedback mechanisms at the retracting surface/edge of migrating HSPCs.

We propose that, in response to BM chemoattractants, HSPCs activate Nox2 (shown as a green box in a membrane lipid raft [MLR], depicted in yellow), which is an MLR-associated enzyme and a source of ROS [1]. ROS activates the Nlrp3 inflammasome [2], which releases ATP into the extracellular space surrounding HSPCs [3]. In a positive-feedback mechanism, extracellular ATP (eATP) activates the Nlrp3 inflammasome and MLR formation so that cells respond more robustly to BM chemoattractants [4]. In a negative-feedback mechanism, eATP is converted by the cell surface-expressed ectonucleotidases CD39 and CD73 into extracellular adenosine (eAdo), which, via the P1 receptors (A2a, A2b), activates heme oxygenase 1 (HO-1) [5], a negative regulator of the Nlrp3 inflammasome [6]. (Modified from ref. 128).

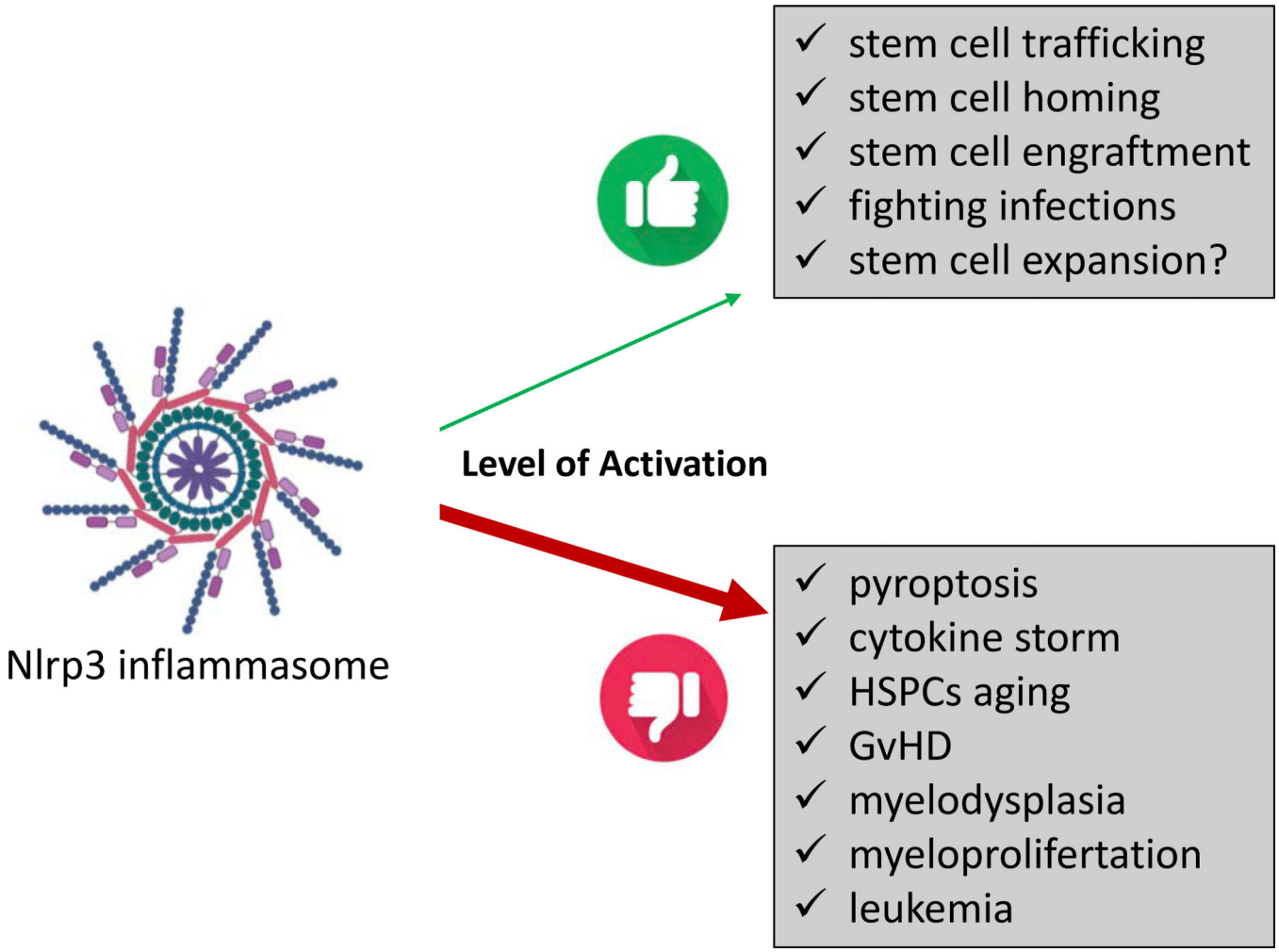

Figure 4. Positive and negative effects of the Nlrp3 inflammasome on hematopoiesis.

A physiologically low level of activation regulates stem cell trafficking, stem cell homing, stem cell engraftment, fighting infections, and, very likely, stem cell expansion. Hyperactivation is involved in hematopoietic cell pyroptosis, induction of cytokine storms, HSPC aging, induction of post-transplantation GvHD, myelodysplasia, and myeloproliferative disorders and may contribute to leukemia.