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Dysregulated myelopoiesis and hematopoietic function following acute physiologic insult

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Abstract

Purpose of review—The purpose of this review is to describe recent findings in the context of previous work regarding dysregulated myelopoiesis and hematopoietic function following an acute physiologic insult, focusing on the expansion and persistence of myeloid-derived suppressor cells, the deterioration of lymphocyte number and function, and the inadequacy of stress erythropoiesis.

Recent findings—Persistent myeloid-derived suppressor cell (MDSC) expansion among critically ill septic patients is associated with T-cell suppression, vulnerability to nosocomial infection, chronic critical illness, and poor long-term functional status. Multiple approaches targeting MDSC expansion and suppressor cell activity may serve as a primary or adjunctive therapeutic intervention. Traumatic injury and the neuroendocrine stress response suppress bone marrow erythropoietin receptor expression in a process that may be reversed by nonselective beta-adrenergic receptor blockade. Heparin-mediated iron-restricted anemia of critical illness requires further investigation of novel approaches involving erythropoiesis-stimulating agents, iron administration, and heparin modulation.

Summary—Emergency myelopoiesis is a dynamic process with unique phenotypes for different physiologic insults and host factors. Following an acute physiologic insult, critically ill patients are subject to persistent MDSC expansion, deterioration of lymphocyte number and function, and inadequate stress erythropoiesis. Better strategies are required to identify patients who are most likely to benefit from targeted therapies.

Keywords

emergency myelopoiesis; myeloid-derived suppressor cell; sepsis; stress erythropoiesis; trauma

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INTRODUCTION

Following an acute physiologic insult, granulocytes are mobilized to sites of injury, inflammation, and infection [1]. Increased T-cell apoptosis, reduced lymphopoiesis and expansion of T-regulatory population result in reduced effector cell function (ref). Simultaneously, innate immune cells have low proliferative capacity, and must be replenished by differentiation of hematopoietic stem and progenitor cells through the process of emergency myelopoiesis [2].

The above-said phenomenon has been demonstrated following intra-abdominal sepsis [2–5], hemorrhage [6], burn and soft-tissue injury [7–9], and bone marrow ablation [10], but not all injuries result in emergency myelopoiesis. Intraperitoneal lipopolysaccharide (LPS) injection causes emergency myelopoiesis in mice, but the combination of hypoxia and LPS may reduce myelopoiesis [4,5]. Chemical soft-tissue injury may also trigger emergency myelopoiesis, but the combination of tissue injury and hemorrhage reduces myelopoiesis [7]. The neuroendocrine stress response, which is common to many acute physiologic insults, potentiates myelopoiesis in a process that is reversed by chemical sympathectomy [8,9,11]. Aging is associated with reduced hematopoietic stem cell (HSC) proliferative capacity, and affects regulation of genes involved in granulocyte differentiation as well as lymphocyte and mononuclear cell activation [12]. Therefore, the nature of the injury and comorbidities of the host each affect emergency myelopoiesis.

Despite the dynamic nature of emergency myelopoiesis, several events occur with relative consistency and important clinical implications. This review will describe the pathophysiology and therapeutic targets for three such events: the expansion and persistence of myeloid-derived suppressor cells (MDSC), the deterioration of lymphocyte number and function, and the inadequacy of stress erythropoiesis.

MYELOID-DERIVED SUPPRESSOR CELL EXPANSION AND PERSISTENCE

Myeloid-derived suppressor cells are immature myeloid cells with simultaneous proinflammatory and immunosuppressive properties [13,14]. In addition to influencing tumor immunity, MDSCs play an important role in acute and chronic inflammatory processes [15]. MDSCs are characterized by suboptimal phagocytic and antigen-presenting functions, but are potent producers of TNF α , IL-10, TGFB, and reactive oxygen species [16–19]. Although an initial and proportionate expansion of MDSCs may be beneficial by potentiating the early innate immune response and pathogen surveillance, persistent MDSC expansion exerts harmful effects by propagating persistent inflammation while dampening the adaptive immune response via T-cell suppression and a shift toward the T_h2-adaptive immune response [1,20–22]. In a recent study of critically ill septic patients, persistent MDSC expansion was associated with T-cell suppression, nosocomial infection, chronic critical illness, and poor functional status at the time of discharge from the hospital [23^{***}].

MDSCs are intermediates in the generation of terminally differentiated myeloid populations. They originate from long-term hematopoietic stem cells (HSCs) that yield short-term HSCs with limited capacity for self-renewal, which become multipotent progenitors, then common

myeloid progenitors, and finally MDSCs [24]. Endogenous and exogenous granulocyte macrophage colony-stimulating factor (GM-CSF) has been shown to promote MDSC expansion and immunosuppressive activity [17,25]. High tyrosine-protein kinase Kit (c-Kit) activity promotes MDSC expansion and egress of immature myeloid cells from the bone marrow to peripheral blood [26,27]. Low bone marrow levels of stromal cell-derived factor one (SDF-1) are also associated with MDSC egress, and high peripheral SDF1-levels appear to have the same effect, which may be related to MDSC expression of the SDF-1 receptor, CXCR4 [28,29]. Upregulation of colony-stimulating factor one (CSF1) and its receptor, CSF1R, also appear to promote MDSC expansion and homing toward the CSF1–CSF1R axis [30,31]. Common to all of these pathways, MDSC expansion occurs whenever an acute insult prompts mobilization of mature leukocytes to peripheral sites of injury, infection, and inflammation, depleting bone marrow reserves and activating emergency myelopoiesis [24,32,33]. The degree of MDSC expansion observed following an acute physiologic insult, however, is proportionately greater than may be explained by emergency myelopoiesis alone [2,34].

MDSCs retain the capacity to differentiate into terminally differentiated populations [1,35]. Terminal differentiation of MDSCs, however, may be prevented by elevated levels of vascular endothelial growth factor (VEGF) [36,37]. As inflammatory stimuli persist, immature myeloid cell production persists as well, with increased expression of CD31 and decreased expression of MHC class II on splenocytes expressing GR-1 in models of prolonged sepsis or tumorigenesis [23[■],24,38]. Beyond these observations, factors influencing MDSC terminal differentiation are poorly understood. The degree to which MDSCs exert immunosuppressive effects, however, may be attenuated through several mechanisms, including inhibition of nitrosylation, blocking IL-10 and TGF β , and by inhibition of the negative costimulatory molecule-programmed cell death protein one (PD-1) and PD ligand 1 (PD-L1), which are upregulated following sepsis, traumatic injury, and burn injury [39–41].

The potential therapeutic value of PD-1 and PD-L1 inhibitors was demonstrated whenever sunitinib, a tyrosine kinase inhibitor, was shown to abrogate MDSC-associated immunosuppression by reducing PD-L1 expression on MDSCs [42]. The immunomodulating properties of PD-1 and PDL-1 appear to be conserved between rodents and humans. Among critically ill septic patients, high levels of PD-1 expression have been associated with nosocomial infection and increased mortality [43]. PD-1 and PD-L1 may also be therapeutic targets. In murine sepsis models, PD-1 and PD-L1 knockout and inhibition have been associated with improved survival [40,44,45[■],46[■]]. Among individuals with septic shock, in-vitro PD-1 and PD-L1 blockade has been associated with decreased T-cell apoptosis, decreased IL-10 production by monocytes, and restoration of normal function for neutrophils, monocytes, T cells, and natural killer cells [41,47[■]]. Most ongoing clinical trials using PD-1 and PD-L1 inhibitors are targeting cancer. It is, however, becoming increasingly apparent that PD-1 and PD-L1 modulation deserves further attention as a therapeutic strategy for critically ill septic patients. Recent evidence also suggests that high mobility group box 1 (HMGB1) blockade may improve neutrophil function and bacterial clearance following septic insult in mice and humans [48[■]].

LYMPHOPENIA AND LYMPHOCYTE DYSFUNCTION

Emergency myelopoiesis and granulocyte expansion may occur at the expense of common lymphoid progenitor production and lymphopoiesis. In addition, mature lymphocytes are adversely affected by T-cell exhaustion, increased regulatory T-cell activity, and apoptosis. The resulting lymphopenia and lymphocyte dysfunction place patients at increased risk for secondary infection following an acute physiologic insult.

Lymphopenia has been observed following human and murine sepsis, in proportion to illness severity [49–51]. Among critically ill septic patients, persistent lymphopenia and immunosuppression is associated with increased vulnerability to secondary infection with weak opportunistic pathogens and increased mortality [51,52]. T-cell exhaustion may contribute to this process. During persistent inflammation, T cells are continually exposed to antigenic and inflammatory signals, a state that is associated with deteriorating T-cell function [53,54]. Abrogating T-cell exhaustion has proven difficult. Although, there is experimental evidence to suggest that TGF β signaling is partially responsible for T-cell exhaustion [55], exogenous TGF β inhibitors have had little success [56,57]. Among mice with chronic lymphocytic choriomeningitis virus infections, the combination of PD-1 blockade and an agonistic antibody to CD137, a T-cell costimulatory molecule, was associated with expansion of viral-specific CD8⁺ T cells and decreased viral loads [58]. Blocking the immunosuppressive effects of hyperactive regulatory T cells has also been attempted in murine sepsis models by administering an herbal extract with potentially immunomodulating properties [59] and by neutralizing IL-10 and TGF β [60]. These approaches, however, require further preclinical investigation with consistent evidence of beneficial effects prior to clinical translation.

Blocking lymphocyte apoptosis has also been proposed as a therapeutic strategy [61]. This approach is supported by murine studies in which overexpression of Bcl-2, an antiapoptotic protein, is associated with improved survival following sepsis [62–64], and that blockade of the Fas/Fas ligand pathway has reduced mortality among septic mice [65,66]. In human and murine sepsis, endotoxin-stimulated monocytes have been shown to release caspase-1 and induce lymphocyte apoptosis in a process that is reversed by caspase-1 inhibition [67,68]. Unfortunately, the success of caspase blockade is hindered by incomplete caspase inhibition, as small amounts of uninhibited caspase are sufficient to damage deoxyribonucleic acid (DNA) and initiate cell death [69]. Nonselective caspase blockade may inhibit monocyte activation and inflammatory cytokine release, attenuating the early inflammatory response and potentially impacting the immune response to sepsis upstream of the effects of caspase blockade on lymphocyte populations [70[■]]. Therefore, the timing and selectivity of caspase inhibition for sepsis must be carefully considered and tailored to the therapeutic objective, recognizing that an effective host response to sepsis involves a robust early innate immune response, an effective late adaptive immune response, and downregulation of systemic inflammation and restoration of homeostasis after the infection is contained. A currently registered clinical trial is investigating caspase-4 and caspase-5 expressions in LPS-stimulated and nonstimulated monocytes from septic patients (NCT02539147). Monocyte apoptosis among septic patients is also being studied in the context of subcutaneous administration of thymosin α 1 (NCT02883595), an immunomodulating medication, which

has shown efficacy in improving survival among septic patients whenever administered in combination with ulinastatin [71[■]].

STRESS ERYTHROPOIESIS AND ANEMIA

An acute physiologic insult may be accompanied by increased oxygen demand, prompting increased erythrocyte production through stress erythropoiesis. Stress erythropoiesis, however, is often blunted by myeloid shifts away from erythrocyte production [72[■],73[■]]. This shift promotes granulocyte and monocyte production as part of the emergency myelopoiesis response at the cost of decreased erythropoiesis [74[■]]. Among critically ill patients, management of severe anemia often involves red blood cell transfusion, which is associated with immune suppression, infectious complications, and increased mortality [75–77]. Therefore, better strategies are needed to promote effective erythropoiesis among critically ill patients.

Iron dysregulation likely contributes to inadequate stress erythropoiesis. Bone marrow iron consumption and the rate of erythropoiesis may increase by as much as 10-fold and 5-fold, respectively [78,79]. Iron trafficking, however, is often dysregulated during systemic inflammatory states. Hepcidin and its receptor, ferroportin, are key regulators of iron trafficking. Ferroportin is present on enterocytes, macrophages, and hepatocytes, which are ideal locations to facilitate iron absorption, procurement from senesced erythrocytes, storage, and mobilization. Exogenous hepcidin and genetic upregulation of hepcidin are associated with decreased serum iron levels and iron-restricted erythropoiesis [80,81], whereas hepcidin gene inactivation is associated with iron overload [82,83]. Following an acute physiologic insult, elevated IL-6 levels and bone morphogenic protein (BMP) activation stimulate hepcidin production [84–86], potentiating an acute iron-restricted anemia. The hepcidin antagonist, lexatapid, has demonstrated efficacy in increasing serum iron levels in a recent randomized trial of endotoxin injection in healthy individuals, and appeared to be well tolerated [87]. The use of hepcidin antagonists in the ICU setting, however, has not yet been reported. Instead, management of severe anemia among critically ill patients often involves red blood cell transfusion, which is associated with immunomodulation, nosocomial infection, and increased mortality [75,88–90]. These effects are especially problematic for critically ill patients who are already at increased risk for secondary infection because of innate and adaptive immune dysfunction.

Anemic states also trigger extramedullary erythropoiesis in the spleen and liver, embryonic and fetal sites of erythropoiesis [91]. Extramedullary erythropoiesis is activated by global hypoxia, upregulation of BMP-4 [92,93], hedgehog signaling [94,95], and activation of the stem cell factor–c-Kit axis [96,97]. Extramedullary erythropoiesis is also upregulated by psychological stress alone, illustrating the importance of the neuroendocrine stress response in modulating erythropoiesis [11]. Following severe traumatic injury, erythroid progenitor growth in the spleen is significantly increased, though the magnitude of this increase may be insufficient to compensate for the degree of anemia [98[■]]. In addition, extramedullary hematopoiesis is associated with MDSC expansion [99[■]], suggesting that erythropoiesis in the spleen and liver are components of emergency myelopoiesis, wherein different

components of the granulocytic lineage respond to signaling pathways that are unique to the physiologic insult and host response.

Endogenous and exogenous erythropoietin potentiate stress erythropoiesis [100]. Erythropoietin binds to surface receptors on erythroid progenitor cells, activating several intracellular signaling pathways, including mitogen-activated kinase (MAPK), signal transducer and activator of transcription 5 (Stat5), and phosphoinositide-3 kinase–Akt pathways [101–103]. Although hypoxia, anemia, and stress upregulate erythropoietin, a pro-inflammatory state may render the bone marrow unable to respond to endogenous and exogenous erythropoietin. Heparin may play a key role in potentiating erythropoietin resistance [104[■]]. In rat models of severe traumatic injury and chronic activation of the neuroendocrine stress response, plasma erythropoietin is significantly elevated, but erythropoietin receptor expression is suppressed in the bone marrow and spleen [98[■],105[■]]. Likewise, severely injured trauma patients have elevated plasma erythropoietin, but decreased bone marrow expression of the erythropoietin receptor (unpublished observation). Abrogating the neuroendocrine stress response via nonselective beta-adrenergic receptor blockade or central nervous system-sympathetic inhibition may have the capacity to restore erythropoietin receptor expression and curtail persistent anemia following severe injury and chronic stress (manuscript under review).

In a randomized trial, nonselective beta-adrenergic receptor blockade administration to severely injured trauma patients was associated with increased bone marrow growth of erythroid progenitors, but did not significantly increase hemoglobin levels or decrease red blood cell transfusions [106]. This trial, however, may have been underpowered to detect differences in hemoglobin levels and transfusions. Nonselective beta blockade has also demonstrated efficacy in promoting erythroblast maturation following burn injury [72[■],73[■]]. In two multicenter randomized trials, administration of recombinant erythropoietin to critically ill medical and surgical patients increased hemoglobin and decreased red cell transfusions, without adverse effects [107,108]. In a subsequent multicenter randomized trial, exogenous erythropoietin administration was associated with increased incidence of thrombotic events and did not significantly decrease red cell transfusions, but was associated with lower mortality among trauma patients (hazard ratio 0.40, 95% CI 0.23–0.69) [109], which may be attributable to modulation of inflammation and apoptosis by erythropoietin.

Recent work has focused on the optimal approach to iron-restricted anemia of critical illness. In a recent multicenter randomized trial [110], iron supplementation to critically ill trauma patients was well tolerated, without increased risk for infection despite very high ferritin concentrations (>1000 ng/ml), but did not significantly increase hemoglobin levels or decrease red blood cell transfusion requirements. Critically ill trauma patients are being actively recruited to a randomized trial of intravenous iron administration with and without oral administration of oxandrolone, a commercially available anabolic steroid that may mitigate the effects of hepcidin (NCT02047552).

CONCLUSION

Following an acute physiologic insult, emergency myelopoiesis allows for mobilization of granulocytes to sites of injury, inflammation, and infection, and replenishes granulocyte populations by differentiation of hematopoietic stem and progenitor cells. Several phenomena may adversely affect the host response, including the expansion and persistence of MDSCs, the deterioration of lymphocyte number and function, and the inadequacy of stress erythropoiesis. Recent and ongoing studies are elucidating pathophysiology and identifying therapeutic targets to improve myelopoiesis and hemato-poietic function following trauma and sepsis. Future research should continue to investigate the safety and efficacy of PD-1 and PD-L1 inhibitors, caspase inhibitors, beta blockers, and combinations of iron, erythropoietin, and hepcidin modulators for critically ill patients with bone marrow dysfunction. As emergency myelopoiesis is a dynamic process with unique phenotypes for different injuries and host factors, better strategies are needed to determine which patients are most likely to benefit from targeted therapies.

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KEY POINTS

- Emergency myelopoiesis is a dynamic process with unique phenotypes for different physiologic insults and host factors.
- Following an acute physiologic insult, critically ill patients are subject to persistent MDSC expansion, deterioration of lymphocyte number and function, and inadequate stress erythropoiesis.
- Better strategies are needed to identify patients who are most likely to benefit from targeted therapies.