Recent advances in neutrophil chemotaxis abnormalities during sepsis

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A R T I C L E   I N F O

Article history:
Received 9 October 2021
Received in revised form 15 May 2022
Accepted 3 June 2022
Available online 13 June 2022

Keywords:
Sepsis
Neutrophil
Chemotaxis
Dysfunction
Migration

A B S T R A C T

Sepsis remains one of the leading causes of death globally, in spite of advanced developments in intensive care and better understandings of pathophysiology related to sepsis. There is no special treatment or drug available for sepsis, currently. Under normal circumstances, neutrophil is a major player in acute infection control. However, during sepsis, the migration abilities and antimicrobial functions of neutrophils are impaired, resulting in a dysregulated immune response. Recent studies have indeed demonstrated that blocking or reversing neutrophil migration and impaired antibacterial function can improve the outcomes in septic animal models. This article systematically synthesized information regarding related factors and signaling involved in the functions of neutrophils in sepsis. This review also discussed the possibility that neutrophils be used as a marker for specific diagnosis and/or prediction of the outcomes of sepsis.

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Introduction

Sepsis is often fatal with the mortality rate reaching as high as 30%–50%. In the United States, sepsis affects 1.7 million adult patients, and more than 250,000 deaths every year.1 Worldwide, sepsis is believed to affect 30 million people and cause 6 million deaths each year.2 Up to date, the existing epidemiologic studies suggest that sepsis remains a huge economic and health care burden across the world.

Sepsis is an uncontrolled response of the host to infected pathogens, accompanied by the life-threatening dysfunctions of one or more organs.3 In general, the occurrence mechanism of sepsis is complicated. Sepsis is a series of diseases caused by innate and adaptive immune response, with a prominent feature of activation of immune cells and release of various cytokines, including pro-inflammatory and anti-inflammatory factors. Cytokine storm is one of the important reasons why sepsis is difficult to control and the mortality remains high. Recently great progress has been made in our comprehension of the processes that trigger the production of magnanimous cell factors, but it is a pity that these findings have not been converted into serviceable treatment.4 A predominantly hyperinflammatory state caused by actions of pathogens on cells exists during the initial stage. The hyperinflammatory state is followed by a statute of immune hypo-responsivity in the later stage of sepsis. Therefore, fully understanding of the pathological mechanism of sepsis provides a better approach to diagnose and prevent sepsis.

Neutrophils account for 50%–70% of the total circulating white blood cells of human beings, which are a key member of the innate arm of immune system. Neutrophils have a hand in the initiation, spread, as well as regression of inflammation. Patients with congenital neutropenia are more sensitive to infection, and thus neutrophils are essential to fully protect against microbes in our environment.5 The three main mechanisms of neutrophil function have been proved to be changed: migration, phagocytosis and apoptosis. In addition, the delivery of neutrophil extracellular traps (NETs) is an important weapon for neutrophils to play their antibacterial role in sepsis. DNA, which carries histones and particles in the nucleus, is released into the extracellular space to capture and remove the germs. However, the accurate role of NETs in sepsis remains unknown. Studies on sepsis mouse models have shown that mosquito NETs cannot be generated to deal with infection.
leading to more serious insult and death. A growing body of evidence indicates that neutrophils play an integral role in the modulating of inflammatory response.

In the inception phase of infection, a series of events is ignited after the invasion of microorganisms. Neutrophils play a critical role in coordinating host defenses against infection. Emerging evidence suggests that neutrophils are a kind of critical cellular component that induces the innate immune response. Moreover, neutrophils have a more important effect on the site of infection through neutrophil migration. Neutrophils are the fastest cell type that migrates to infectious sites, where they kill infectious agents by releasing reactive oxygen and nitrogen species. However, some evidence indicates that the neutrophil response may be incompetent to control sepsis. Bacteria or bacterial components induce disseminated activation of Toll-like receptors (TLR), including TLR-2, TLR-4, and TLR-9. The activation of TLRs mediates exaggerated release of cytokines and chemokines into the circulation. These mechanisms result in inflammatory responses and changes in neutrophil function during sepsis. In spite of the mechanisms of impaired migration of neutrophils in sepsis that have been well studied, developing a comprehensive and incisive understanding of this pathophysiologic change is a formidable and resource-consuming task.

In this review, we discuss the chemotactic functions of neutrophils in sepsis and summarize mechanisms and results of these cellular and molecular dialogues, with the hope to provide a new therapeutic strategy for sepsis.

**Neutrophil dysfunction in sepsis**

Sepsis, which is an excessive host response caused by the invading microorganism, affects various organs as well as systems including the circulation, immune, coagulation, and/or neuroendocrine system. Neutrophils are the host's first line of defense against infection. The most important roles of neutrophils include migration, phagocytosis, and release of cytotoxic agents. Dysfunction of neutrophils in the infected sites have been well reported previously. Neutrophils originate from bone marrow, then leave the blood, recruit and migrate to inflammatory sites in the blood, and are finally cleared. However, during sepsis, these life processes undergo uncontrollable changes. The functions of neutrophils were changed in varying degrees during sepsis, including chemotactic ability, microbicidal efficacy (degranulation, reactive oxygen species, ROS, NETs). In the early stage of sepsis, mature neutrophils in bone marrow can migrate rapidly, and the number can increase 10 times in several hours compared with normal conditions. In addition, this neutrophil dysfunction is accompanied by abnormal accumulation of neutrophils, impaired recruitment of neutrophils to the infected foci, and impaired migration of neutrophils. In patients with sepsis, delayed apoptosis of neutrophils may lead to related tissue damage and multiple organ dysfunction syndrome. This variation has two sides: one conduces to combat against the damage induced by inflammation and the other facilitates the development of subsequent complications related to sepsis.

Infection is a troubling circumstance that leads to self-protection of the host. Neutrophils, as the earliest defenders against bacterial and fungal pathogens, are recruited to infected sites. The leukocyte recruitment process includes several steps: tether, rolling, adhesion, crawling, and finally reincarnation. This process is a continuous, multi-step and methodical adhesion cascade, in which various membrane molecules interact to each other. The abnormal accumulation of neutrophils, the damage of neutrophils to the infected foci, and the malfunction of neutrophil migration are related to poorly-regulated immune responses. Vascular endothelial cells and platelets are the main targets of inflammatory mediators and activated neutrophils, and other immune cells. In sepsis, endothelial cells interact with a large number of inflammatory mediators and coagulation factors of innate immunity and coagulation system. During septic shock, the barrier function of endothelial surface is almost uniformly damaged, which may lead to adverse consequences. Inflammation and coagulation are inseparable and an important part of the pathophysiology of sepsis. Platelet is the key component of thrombosis, and thrombocytopenia is a common complication in patients with sepsis and disseminated intravascular coagulation. Thrombocytopenia has been considered as a prognostic marker for mortality and incidence rate. Studies have shown that during sepsis, platelet mediated neutrophil recruitment to the vascular lumen. Platelet activating factor is produced by a variety of cells, especially those involved in host defense, such as neutrophils, monocytes and endothelial cells. Vascular endothelial cells, platelets and neutrophils are important components of the immune system and coagulation system. In sepsis, the immune system and coagulation system are disordered. At present, how they interact is not clear. Evidence indicates that neutrophil chemotaxis activity has the potential to be a prospective novel immunologic biomarker in predicting the clinical outcome in patients affected with severe sepsis and upregulation of cytokines, chemokines, and nitric oxide (NO), as neutrophil chemotaxis is a critical event that might result in dysfunction in neutrophil migration to the infection site observed in lethal microbial sepsis.

**Prolonged lifespan of circulating neutrophils in patients with sepsis**

Normally, neutrophils in the circulation have a short survival time, but their lifespan increases during sepsis. Expression of the anti-apoptotic protein Mcl-1, which inhibits neutrophil apoptosis, is elevated in neutrophils collected from patients affected by severe sepsis. Cherla et al. showed that nonmuscle myosin II inhibits neutrophil apoptosis by blocking caspase-3 cleavage and activating the mitogen-activated protein kinase (MAPK) survival pathway, which increases the expression of Mcl-1. Phoomvuthisarn et al. found that purvalanol A, a cyclin-dependent kinase-2 (CDK-2) inhibitor, mediates a prompt and extended promotion of human neutrophils apoptosis, which restrains the functions of the anti-apoptotic protein (granulocyte-macrophage colony stimulating factor) via increasing the turn round rate of Mcl-1. This effect of purvalanol A is dependent on the activation of p38-MAPK, as blocking of p38-MAPK signaling partly reverses the inhibitory effects of the CDK-2 on neutrophil apoptosis. These data unravel the regulation of CDK-2 in Mcl-1 expression.

During sepsis, proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-17, as well as bacterial products, increase the expression of granulocyte colony-stimulating factor (G-CSF). G-CSF induces the generation of immature and mature neutrophils. Recently, some newly discovered important chemokines are also involved in this process, which is mainly related to the retention of neutrophils in bone marrow. In addition, granulocyte colony stimulating factor indirectly mobilizes neutrophils by changing the balance between stromal cell-derived factor-1 and C-X-C chemokine receptor (CXCR) 2 ligands in bone marrow, triggering the release of neutrophils into the circulation. Decreased expression of CXCR chemokine ligand (CXCL)12 is seen in sepsis whereas CXCL1 is increased, the latter of which drives the release of neutrophils from the bone marrow into the blood. The migration process of neutrophil is composed of mobilization and release of neutrophils from the bone marrow, edge and scroll, stick, and loop. All of the four distinct phases, more or less, are impaired during sepsis. Margaria et al. demonstrated that the prognosis of experimental sepsis is associated with...
the degree of neutrophil migration disorder. Molecular patterns produced by bacteria can activate TLR, which is expressed on the surface of neutrophils to up-regulate the expression of G protein-coupled receptor kinase (GRK)2. Elevated GRK2 results in desensitization of CXCR2 expressed by neutrophils. The effects of GRK2 on CXCR2 expression can be reversed by IL-33, which drives neutrophil migration to the infected site. In addition, activation of TLRs can increase CC chemokine receptor (CCR)2 expressed by neutrophils, facilitating neutrophil recruitment to distal sites. 

**Impairment of neutrophil transmigration**

During sepsis, bacterial components and pro-inflammatory cytokines promote the shedding of L-selectin and increase the expression of β-integrins by neutrophils. Intercellular adhesion molecule-1 together with vascular cell adhesion molecule-1 mediates high-affinity adhesion between the endothelium and neutrophils. The failure of neutrophil migration seems to be due to the decrease of rolling and adhesion between neutrophils and endothelial cells. Neutrophil migration dysfunctions seem to be caused by TNF-α and IL-8, which induce the production of NO. Intravenous injection of these cytokines can reduce neutrophil migration mediated by various stimuli. At the same time, the concentrations of serum cytokines and chemokines are significantly elevated in severe sepsis, indicating the roles of these factors in neutrophil migration dysfunctions. Failure of neutrophil migration is TLR4-dependent, because TLR4 deficient mice do not show this phenomenon. In addition, circulating neutrophils from sepsis patients fail to respond to formyl-methionyl-leucyl-phenylalanine (fMLP), IL-8, and leukotriene B4 (LTB4), when elevated serum nitric oxide synthase (NOS) and cytokine concentrations is evident. In addition, failure of neutrophil migration or reduction in rolling and adhesion were not observed in inducible nitric oxide synthase (iNOS)−/− mice, which could be prevented by aminoguanidine.

In the early stages of sepsis, mature neutrophils in the bone marrow can be excreted quickly, increasing the number in the blood by 10 folds compared to normal in a few hours. Release of neutrophils from the bone marrow to the infection site has traditionally been regarded as the downstream events of increased chemokines, including leukotriene B4, C5a, IL-8, and bacterial components. CXCL-12, a newly discovered key chemokine that retains neutrophils in bone marrow, also participates in this process. Granulocyte colony-stimulating factor (G-CSF) indirectly mobilizes neutrophils by altering the balance between bone marrow stromal cell-derived factor (SDF)-1 and ligands of CXCR2, triggering release of neutrophils into the circulation. It has been well documented that neutrophil could migrate to the infected sites and arouse the first wave of host defence against infection or tissue damage (Fig. 1). However, dysfunction of neutrophil migration is directly correlated to mortality in those affected by severe sepsis. Mounting evidence suggests that neutrophils are critical during their migration to the infection sites.

**Sepsis-induced impairment of neutrophil chemotaxis**

Chemotaxis is defined as the tendency of cells to migrate toward the gradient direction of chemotactic stimulation, or away from a chemorepellent. The ability to fully sense chemotactic gradients is one of the most important features that neutrophils acquire to execute their immune functions. Chemotaxis is essential for the embryonic development. In embryonic development, chemotaxis boosts morphogenetic diversification via sensing the gradient of growth factors, which results in orienteering coordinated cell migration, for instance, the migration of neural crest cells. Neutrophils are very sensitive to stimuli, and can mobilize quickly and effectively to inflammatory areas within a few minutes. This process is called neutrophil chemotaxis. Studies have shown that chemotactic impairment is related to a spectrum of diseases with increased risk of infection, including diabetes, influenza, cyto-megalovirus, human immunodeficiency virus, and impaludism. In sepsis, the chemotaxis of neutrophils is impaired through various pathologic mechanisms. Increased levels of chemokines are detected at the site of infection in severe sepsis. However, evidence from experimental animals and individuals with severe sepsis indicates that neutrophil migration to the site of infection is inadequate compared to normal individuals. Neutrophil reverse migration is a special phenomenon in neutrophil migration. It describes the migration of neutrophils from inflammatory sites to vascular system after initial infiltration. The functional role of polymorphonuclear neutrophil (PMN) reverse migration in the inflammatory scene is unclear and needs to be further explored. Current evidence shows that PMN reverse migration can be either a protective response by promoting the effective solution of innate immune response or a tissue injury event in different environments. There has been a number of studies focusing on the mechanisms underlying the inability of neutrophils to migrate to infectious sites. Receptors on neutrophils recognize pathogenic molecular patterns and inflammatory environments, which leads to the activation of neutrophils. Hence, fully understanding expression and regulation of receptors on neutrophils and signal path to neutrophil chemotaxis may pave a way for prevention and early diagnosis of sepsis (Table 1).

CXCRs are members of the seven transmembrane domain chemokine receptor family. Neutrophils collected from mice and patients with severe sepsis express fewer CXCR2. Neutrophils collected from individuals with sepsis show attenuated chemotaxis towards fMLP, leukotriene B4 or IL-8. CXCR2 is restored slowly after sepsis-induced receptor internalization, which results in decreased CXCR2 expression on the neutrophils in septic individuals and mice, leading to inadequate chemotaxis. The activation of TLRs-2, 4 and 9 as well as the upregulation of NOS and TNF-α results in the induction of the expression of GRK2 and result in the subsequently desensitization and internalization of CXCR2.

Binding between complement factor 5a (C5a) and C5a receptor (C5aR) is critical in migration of neutrophils during sepsis. However, the chemotactic responsiveness of neutrophils to C5a is dysfunctional during sepsis. C5aR expressed on neutrophils reaches the peak at the first 24 h after sepsis initiation and gradually decline. Previous studies have shown that neutrophil chemotaxis and the innate immune reactions are suppressed during the later phases in sepsis by blocking extracellular signal-regulated kinase 1/2 signaling via C5a and its receptor (C5aR, C5L2). The levels of many factors involved in the cytokine storm are remarkably reduced up to 80% after cecal ligation and puncture (CLP) in C5aR−/− and C5L2−/− mice. More importantly, the survival is significantly improved in both C5aR−/− and C5L2−/− mice with severe or mild sepsis.

NO and its producer iNOS are also important in neutrophil migration disorders. Integrin, selectin and cellular adhesion molecule-1 can be inhibited by iNOS. Heme oxygenase-1, which can be reduced by NO as well, dampens neutrophil rolling and adhesion. In addition, elevated levels of carbon monoxide and bilirubin in the circulation and exhaled breath of patients with sepsis also suggest that heme oxygenase-1 pathway might have a role in this pathological process. Researchers investigated the effect of phosphatidylinositol–3–kinase (PI3K) in regulating the migration of neutrophils in sepsis, which are thought to be related to the dimerization of iNOS. Studies show that CXCR2 expression is increased while GRK2 expression is reduced in PI3Kc−/− mice with sepsis, which often brings a higher survival rates. In addition,
in vitro neutrophils without PI3Kc expression cultured with CXCL2 show downregulated internalization levels of CXCR2, indicating PI3K is a negative regulator of CXCR2 internalization.

Selectins are adhesion receptors on the neutrophil surface, which participate in the adhesion during migration of neutrophils. P-selectin glycoprotein ligand-1, endothelial surface layer, and CD44 have different contributions in complete identification of E-selectin ligand on neutrophils, which all participate in selectin-mediated neutrophil adhesion and signal transduction. It has been indicated that selectin ligand CD44 produced on neutrophils induces slow rolling in vivo, as well as neutrophil extravasation to inflamed sites together with P-selectin glycoprotein ligand-1. A number of studies have demonstrated that the interaction between a selectin and its ligand mediates many intracellular signaling pathways, such as tyrosine phosphorylation and P38 MAPK activation, which are necessary for neutrophil migration. Therefore, the interaction between selectins and neutrophil chemotaxis warrants future studies.

IL-33 binding to its heterodimer receptor complex signal transducer 2 inhibits TLR4-mediated internalization of CXCR2 via suppressing GRK2, which enhances the recruitment of neutrophils to the infection sites. Cystathionine B synthase together with cystathionine G lyase, which is involved in synthesizing hydrogen sulphide, act on CXCR2 which is expressed on neutrophils to modulate the process of sepsis.

**Neutrophil chemotaxis assays**

Improved technology in neutrophil chemotaxis assays, such as the Boyden chamber assay, the Dunn Zigmond assay, under-

| Table 1 | Common neutrophil chemoattractants and their receptors. |
|--------|---------------------------------------------------------|
| Receptor | Chemoattractant | Function |
| Chemokine receptors | CXCR2 | CXCL1 | Neutrophil recruitment and activation |
| | CXCR2 | CXCL2 | Neutrophil trafficking |
| | CXCR1 | CXCL8 | Neutrophil recruitment to sites of inflammation |
| | CXCR4 | CXCL12 | Bone marrow homing |
| Chemoattractant receptors | BLT1 (also known as fMLPR), FPR2 | LTB4 (leukotriene B4), Bacterial and mitochondrial formylated peptides, e.g. fMLP | Neutrophil recruitment and swarming |
| | C5aR | C5a | Neutrophil recruitment |
| | C3aR | C3a | Neutrophil recruitment (e.g. in autoantibody induced disease) |
| | ACKR1 (formerly Duffy antigen receptor) | Inflammatory CC chemokines | Inhibitor of neutrophil mobilization |
| Atypical chemokine receptors | ACKR2 (formerly D6) | Decoy/scavenger receptor | |

CXCRs: C-X-C chemokine receptors; CXCLs: C-X-C chemokine ligands; ACKRS: atypical chemokine receptors; BLTs: Leukotriene B4 receptors; LTB1: leukotriene B1; C5aR: complement factor 5a receptors; C5a: complement factor 5a; C3aR: complement factor 3a receptors; C3a: complement factor 3a; fMLP: formyl-methionyl-leucyl-phenylalanine; FPRs: formyl-peptide receptors.
agarose assay have improved our understanding of neutrophil chemotaxis mechanisms, despite their limitations. For example, the Boyden chamber is unable to develop stable chemical gradient profiles. Another limitation is that these assays require tens of milliliters of blood and complex cell purification protocols. Assessing neutrophil chemotaxis could be challenging for obtaining blood from infants or small animals. Sackmann et al. reported a microfluidic technique that distinguishes asthma from allergic rhinitis according to a patient’s neutrophil chemotaxis function. The whole blood was purified and chemotaxis neutrophils in a few minutes by the technique only using a microstraw. Microfluidic chemotaxis platforms can be deployed together with on-chip neutrophil purification, which shows benefits in terms of function, operability, and versatility of these assays. Moreover, the difficulties regarding long-term cell cultures, biological samples, as well as time-lapse microscopy have been reduced by the assay significantly.

Yang et al. developed a novel computer vision-based cellular chemotaxis analysis platform for dynamic assessments of neutrophils chemotaxis in those affected with severe infection. The platform is the first of the kind that can be used to assess the PMN chemotactic function. The chemotactic function of PMNs partially reflects the tune of the innate immune system in patients with infection, and indicates the severity of infection and organ functions. Whether the assay for PMN chemotactic function can be used in the diagnosis and treatment of infections warrants further investigations (Fig. 2).

**Neutrophil chemotaxis as biomarker during sepsis**

Timely and accurate diagnosis of sepsis is critical for therapy and an improved prognosis, so the diagnosis of sepsis has always been a cardinal concern. Studies show that increased mortality are an improved prognosis, so the diagnosis of sepsis has always been a cardinal concern. Another limitation is that these assays require tens of milliliters of blood and complex cell purification protocols. Assessing neutrophil chemotaxis could be challenging for obtaining blood from infants or small animals. Sackmann et al. reported a microfluidic technique that distinguishes asthma from allergic rhinitis according to a patient’s neutrophil chemotaxis function. The whole blood was purified and chemotaxis neutrophils in a few minutes by the technique only using a microstraw. Microfluidic chemotaxis platforms can be deployed together with on-chip neutrophil purification, which shows benefits in terms of function, operability, and versatility of these assays. Moreover, the difficulties regarding long-term cell cultures, biological samples, as well as time-lapse microscopy have been reduced by the assay significantly.

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receptor, CMRF-35-like molecule or myeloid related Ig like receptor. The inhibitory receptor CD300f contains two inhibitory motifs based on immune receptor tyrosine and one switching motif based on immune receptor tyrosine in the cytoplasmic region. CD300f is expressed in mast cells and neutrophils. Recent studies show clearly that particular lipids or lipid-binding proteins as ligands of CD300f. The concentrations of extracellular ceramides increased in the peritoneal cavity of mice treated with CLP, prompting that CD300f ligands play a probable role in controlling the congenital immune responses. CD300f is a magnetic target for the treatment of sepsis.

The exciting era lies ahead. With the improvement of our understanding of the intracellular mechanism regarding neutrophil migration, we are about to turn the new knowledge of in vivo research into new and effective treatments.

Conclusion

Sepsis usually occurs after traumatic bleeding, burns or major surgical procedures, which obtains interest from clinicians and researchers. Despite an enormous amount of time and energy, the pathophysiological mechanism is not fully understood, and many targeted therapies have not achieved a satisfying efficacy. This is mainly because that sepsis is a complex and dynamically changed disorder. Targeting neutrophil chemotaxis is a promising area in sepsis treatment. Understanding neutrophil chemotaxis in sepsis may offer significant opportunities to improve the prognosis of sepsis patients. In the near future, it can be predicted that this new strategy will be clinically evaluated in the treatment of sepsis.

Funding

This study was supported by the National Natural Science Foundation of China, No.82072217, 81772135 and U21A20370; by the Jiangsu Natural Science Foundation, No. BK20201178.

Ethical statement

This is a review article and thus ethical approval is not applicable.

Declaration of competing interest

The authors declare that they have no competing interests.

Author contributions

Bing-Wei Sun and Yu-Ying Zhou designed the manuscript sections and wrote paper. Yu-Ying Zhou performed collection of clinical and experimental data from published papers. All authors read and approved the final manuscript.
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