Park 7: A Novel Therapeutic Target for Macrophages in Sepsis-Induced Immunosuppression

Yanwei Cheng [1,2], Tony N. Marion [3,4], Xue Cao [2,3], Wanting Wang [1] and Yu Cao [1,2]*

[1] West China Hospital Emergency Department, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, and Collaborative Innovation Center of Biotherapy, Chengdu, China, [2] Disaster Medicine Center, Sichuan University, Chengdu, China, [3] Department of Rheumatology and Immunology, West China Hospital, Sichuan University, Chengdu, China, [4] Department of Microbiology, Immunology, and Biochemistry, The University of Tennessee Health Science Center, Memphis, TN, United States

Sepsis remains a serious and life-threatening condition with high morbidity and mortality due to uncontrolled inflammation together with immunosuppression with few therapeutic options. Macrophages are recognized to play essential roles throughout all phases of sepsis and affect both immune homeostasis and inflammatory processes, and macrophage dysfunction is considered to be one of the major causes for sepsis-induced immunosuppression. Currently, Parkinson disease protein 7 (Park 7) is known to play an important role in regulating the production of reactive oxygen species (ROS) through interaction with p47^{phox}, a subunit of NADPH oxidase. ROS are key mediators in initiating toll-like receptor (TLR) signaling pathways to activate macrophages. Emerging evidence has strongly implicated Park 7 as an antagonist for sepsis-induced immunosuppression, which suggests that Park 7 may be a novel therapeutic target for reversing immunosuppression compromised by sepsis. Here, we review the main characteristics of sepsis-induced immunosuppression caused by macrophages and provide a detailed mechanism for how Park 7 antagonizes sepsis-induced immunosuppression initiated by the macrophage inflammatory response. Finally, we further discuss the most promising approach to develop innovative drugs that target Park 7 in patients whose initial presentation is at the late stage of sepsis.

Keywords: Park 7, sepsis-induced immunosuppression, inflammation, macrophages, ROS, p47^{phox}, NADPH, crystal structure

INTRODUCTION

Sepsis is a common clinical disease with high morbidity and mortality. Annually, ∼30 million (1) people are affected by sepsis and more than 6–8 million (2) of those affected die. Despite significant advances in treatment, sepsis is still a major clinical problem and remains the leading cause of death in the critically ill patient population (3, 4) with an associated severe cost burden (5). In 2013, sepsis was responsible for more than $23 billion (6) of hospital costs in the USA alone. Thus, sepsis has been described as "the quintessential medical disorder of the twenty-first century." On 26 May 2017, the World Health Organization listed sepsis as a global health priority by adopting a resolution to improve the prevention, diagnosis and management of this deadly disease (7).

In the recent "sepsis-3" consensus (8), sepsis is defined as a life-threatening, multiorgan dysfunction caused by a dysregulated host response to infection, which is primarily caused by Gram-negative bacteria. However, a global study of 14,000 critically ill patients found that 47% of isolates were Gram-positive, indicating that more patients currently become septic from Gram-positive infections (9). Even after an inciting infection has been resolved, septic patients continue to mount an excessive inflammatory response (10) that leads to tissue damage and organ failure. Key advances have made earlier recognition and treatment of sepsis feasible with the result that some patients can restore immune homeostasis, completely clear infection, and achieve complete recovery (11). Otherwise, patients progress into late stage sepsis and suffer from severe immunosuppression characterized by an impaired activation of the immune response and a hypo-inflammatory response (12), resulting in more difficult recovery and poor long-term outcomes with risk of cognitive and physical impairments, even an increased incidence of delayed death due to the lack of effective treatment for sepsis-induced immunosuppression (13). At present, immunosuppression in septic patients constitutes an important focus of research. Thus far, various interrelated, non-mutually exclusive mechanisms have been proposed to explain sepsis-induced immunosuppression, including cellular apoptosis (14), autophagy (15, 16), regulation by the central nervous system (17, 18), metabolic reprogramming (19), epigenetic regulation (20–22), and endotoxin tolerance (23–25). The immunopathogenesis of sepsis-induced immunosuppression is a very complex process that involves both innate and adaptive immune cells. In fact, it is at least partially caused by the dysfuction of macrophages.
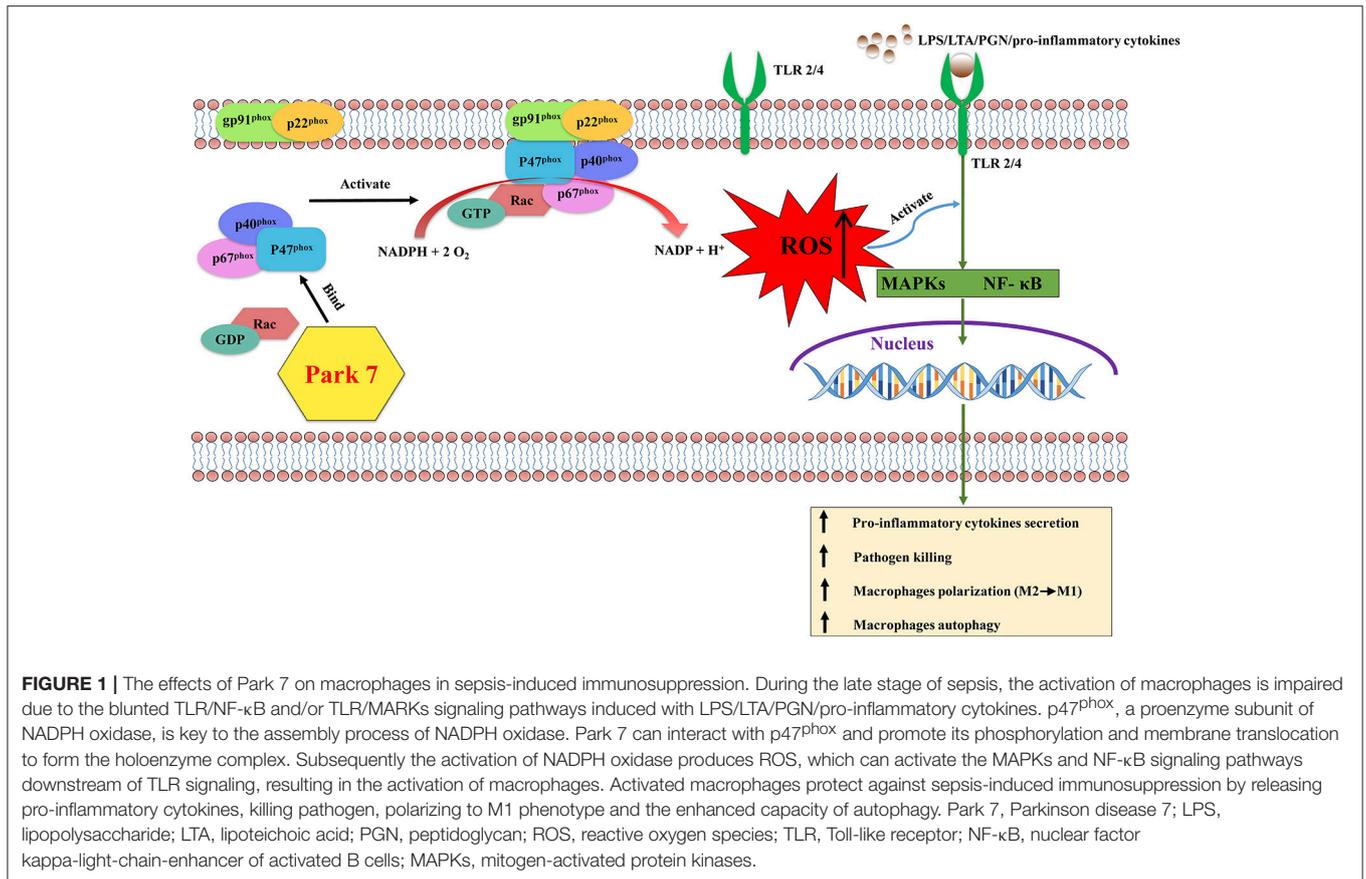
MACROPHAGES AND SEPSIS-INDUCED IMMUNOSUPPRESSION

Macrophages play essential roles throughout all phases of sepsis with their ubiquitous presence and comprehensive effects on immune homeostasis and inflammatory process. After infection, macrophage is activated through Toll-like receptor (TLR) that recognizes pathogen-associated molecular patterns (PAMPs) of the invading pathogen, such as lipopolysaccharide (LPS) in Gram-negative bacteria and lipoteichoic acid (LTA)/peptidoglycan (PGN) in Gram-positive bacteria (26). In the early stage of sepsis, macrophages undergo M1 differentiation and promote host defense by eliminating invading pathogens or damaged tissues and releasing massive amounts of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-a), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-8 (IL-8) (27). However, macrophages may be excessively activated during the early phase and produce excessive pro-inflammatory cytokines (28), which have been identified as one of the major causes for the high mortality rate in the early stage of sepsis (29). If macrophage-mediated pro-inflammatory responses cannot be adequately regulated, a cytokine storm may emerge (30) with the pro-inflammatory response becoming pathogenic and eventually

immunosuppressive in late stage sepsis (31–33). As activated pro-inflammatory macrophages undergo apoptosis and/or polarize to the M2 phenotype that dampens the pro-inflammatory response, they may contribute to immunosuppression. Due to the cytokine storm, a large number of apoptosis-inducing factors are generated and released, including TNF-a, high mobility group box-1 protein (HMGB1) (34), thereby inducing and promoting macrophage apoptosis (35). Previous studies (36, 37) have determined the presence of an excessive level of macrophages apoptosis in human autopsies and animal models of sepsis. However, escaped M1 macrophages from apoptosis convert into M2 macrophages, showing downregulated inflammatory cytokines but upregulated anti-inflammatory cytokines (38). Certain cytokines (i.e., TNF-a, IL-13, IL-4, IL-10 etc.) can stimulate the polarization of macrophages toward M2 phenotype (39–41). Porta et al. (42) found that LPS-tolerant macrophages have the same characteristics as M2 macrophages. When a gram-negative infection persists, long-term accumulation of LPS can reprogram inflammatory responses (43) from activation to suppression leading to decreased production of inflammatory cytokines (44). The affected host may present a LPS-tolerant state, and macrophages also display the phenomenon of LPS-tolerance (45–47). In addition, M2 phenotype macrophages also accelerate T cell apoptosis and suppress Th1 cell responses (48). Collectively, this "dysfunctional" macrophage plays a key role in the pathogenesis of sepsis-induced immunosuppression because their pro-inflammatory cytokine secretions to support effective immune reactivity against primary or secondary pathogens is compromised. Therefore, modulating homeostasis of pro- and anti-inflammatory responses and functional stabilities of macrophages can be of great benefits for sepsis-induced immunosuppression.

REACTIVE OXYGEN SPECIES (ROS) AND MACROPHAGES

In addition to its cytotoxic function, reactive oxygen species (ROS) can initiate multiple signal transduction cascades to modulate macrophage function and are critical to the regulation of immune responses against pathogens (49). Previous studies have shown that ROS have an established role in regulating TLR signaling pathways, such as TLR/NF-κB and TLR/MARKs pathways (50–52). In LPS-tolerant macrophages, LPS tolerance blunts the TLR4 signaling, inhibiting the activation of the NF-κB signaling pathway downstream of TLR4, resulting in reduced production of inflammatory cytokines in response to LPS challenge (53–55). ROS can modulate the production of pro-inflammatory cytokines from LPS-tolerant macrophages by activating TLR4/NF-κB and TLR/MARKs pathways (49) mainly by accelerating the phosphorylation of IκBα and MAPK phosphatases (56, 57), respectively. In addition, it has been reported that TLR2-deficient macrophages lacked the response to Gram-positive LTA and PGN (58, 59), which can interact with TLR2, leading to NF-κB activation and induction of proinflammatory mediators in macrophages (59, 60). Rajamani (61) also demonstarted that high glucose mediated ROS could

FIGURE 1 | The effects of Park 7 on macrophages in sepsis-induced immunosuppression. During the late stage of sepsis, the activation of macrophages is impaired due to the blunted TLR/NF-κB and/or TLR/MARKs signaling pathways induced with LPS/LTA/PGN/pro-inflammatory cytokines. p47^{phox}, a proenzyme subunit of NADPH oxidase, is key to the assembly process of NADPH oxidase. Park 7 can interact with p47^{phox} and promote its phosphorylation and membrane translocation to form the holoenzyme complex. Subsequently the activation of NADPH oxidase produces ROS, which can activate the MAPKs and NF-κB signaling pathways downstream of TLR signaling, resulting in the activation of macrophages. Activated macrophages protect against sepsis-induced immunosuppression by releasing pro-inflammatory cytokines, killing pathogen, polarizing to M1 phenotype and the enhanced capacity of autophagy. Park 7, Parkinson disease 7; LPS, lipopolysaccharide; LTA, lipoteichoic acid; PGN, peptidoglycan; ROS, reactive oxygen species; TLR, Toll-like receptor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPKs, mitogen-activated protein kinases.

induce TLR-2 activation and downstream NF-κB signaling mediating increased inflammation during diabetic retinopathy. TLR4/NF-κB pathway also plays a central role in the regulation of macrophage polarization (48). M1 macrophage polarization is related to the activation of the TLR4/NF-κB pathway (62), whereas M2 macrophage polarization is associated with the down-regulatation of NF-κB pathway (63). A recent study has confirmed that the p50 subunit of NF-κB inhibits the NF-κB pathway and M1 polarization (42). Kuchler et al. (64) reported that impaired ROS formation contributed to an M2 phenotype shift of macrophages in sepsis by inhibiting NF-κB signaling. Consequently, increased ROS formation may reduce the M2 polarization of macrophages and protect against sepsis-induced immunosuppression.

The TLR4/MARKs pathway is also involved in regulating the LPS/pro-inflammatory cytokines-induced autophagy (65). Autophagy can induce cell death but can also be a cytoprotective process. Deficient autophagy suppresses the immune response in sepsis and increases mortality (15, 16, 66). Macrophage autophagy is considered an important part of the host immune defense, eliminating intracellular pathogens through heterophagy. It has been reported that ROS can influence the MAPK pathways to activate macrophage autophagy. In hepatoma cells, migration inhibitory factor, produced by many cells including macrophages, induced autophagy via ROS generation (67). Likewise, autophagy also participates in

regulating functions of macrophages and affects their ability to defend and clear pathogens through activating NF-κB pathway (68) and enhancing phagocytic capacity of macrophages (69). All of this suggests that ROS can activate macrophages to improve bactericidal and autophagy and increase production of pro-inflammatory cytokines, thereby helping to maintain immune homeostasis. Thus, a novel approach to improve ROS production in macrophages may be a useful therapy for sepsis-induced immunosuppression.

PARKINSON DISEASE 7

Parkinson disease 7 (Park 7), also known as DJ-1 (70), is highly conserved in almost all organisms and is ubiquitously expressed in all tissues and organs (71). Park 7 was initially discovered as a novel oncogene product (72) and is considered as a major causal factor for the early onset of Parkinson's disease (73). In the past two decades, Park 7 has been intensely studied in many diseases including cancer (74), neurodegenerative disorderes (75) and stroke (76). Among these diseases, Park 7 not only serves as a reliable predictor of auxiliary diagnosis, but also is a useful therapeutic target. Park 7 is a multi-functional protein with transcriptional regulation, protein chaperone, protease, and antioxidative stress functions (77). At present, increasing evidence has demonstrated that Park 7 plays

important functions in protecting neurons (78), astrocytes (79), cardiomyocytes (80, 81), and renal proximal tubule cells (82) against oxidative stress-induced cell injury. In addition, Park 7 played an important role in restoring impaired autophagy and ameliorated phenylephrine-induced cardiac hypertrophy in a repression of cardiac hypertrophy model (83). Oxidative stress is strongly related to inflammation and is thought to be involved in the processes of many diseases, including sepsis (84). Recently, accumulating lines of evidence for Park 7 in activating the inflammatory response through modulating ROS regulating oxidative stress have also been reported (53, 85). As an antioxidant, Park 7 helps to limit to cell and tissue injury in a number of diseases by removing accumulated ROS (82, 86–89). However, studies had shown that Park 7 surprisingly seems to be required for high intracellular ROS production (85, 90). Therefore, Park 7 plays a dual role in buffering cellular ROS levels: functions as a scavenger in high ROS levels, whereas helps ROS production when essential ROS are required. In view of the hypo-inflammation characteristics of sepsis-induced immunosuppression and the critical role of Park 7 in modulating ROS production and initiating an inflammatory response, recently it has been reported that Park 7 can protect against sepsis-induced immunosuppression.

PARK 7 PROTECTS AGAINST SEPSIS-INDUCED IMMUNOSUPPRESSION (FIGURE 1)

In a park 7 knock-out (KO) mouse injected with LPS, Liu et al. (53) found that park 7 KO mice present immunosuppression phenotypes similar to the late stage of sepsis but not acute inflammation state, suggesting that park7 KO mice could serve as an animal model of sepsis-induced immunosuppression. In this model, Park 7 absence led to macrophage paralysis that resulted in increased abdominal bacterial burdens, reduced local and systemic inflammation, and impaired pro-inflammatory cytokines induction, eventually leading to high susceptibility to LPS. Neutrophil paralysis, similar to macrophage paralysis described above, was described in experimental studies of patients and sepsis animal models and was associated with decreased production of ROS in neutrophils (91, 92). In a liver fibrosis model, Park 7 deficiency inhibited ROS production in macrophages (93). Similarly, Liu et al. also observed greatly reduced ROS production in macrophages from park 7 KO mice (53). Macrophages with Park 7 deficiency showed downregulation of NF-κB and MAPK signaling pathways downstream of TLR suggesting that Park 7 deficiency can reduce the ROS production to limit TLR signaling and impair the activation of macrophages. Restoration of Park 7 expression with an inducible Park7 transgene restored the production of ROS in Park 7 KO macrophages to subsequently restore TLR signaling, pro-inflammatory cytokine production, bactericidal function, and eventually improve survival of the Park 7 KO mice in the late stage of sepsis. However, immunosuppressive IL-10 was not simultaneously enhanced after restoration of Park7 expression. During the late stage of sepsis, Park 7 may

also enhance the macrophage functions by restoring impaired macrophages autophay through increased ROS and TLR/MARK signaling. Macrophage autophagy can affect cell death via complex pathways involving crosstalk with apoptosis, which may also partly attenuate immunosuppression (94). Moreover, Park 7 may contribute to the M1 macrophages polarization and inhibit the M2 macrophages polarization by the increased ROS.

Although there are many sources of ROS within macrophages, NADPH oxidase-derived ROS are critical in host defense. When macrophages are stimulated by an extracellular stimulus such as hormones, cytokines, and other inflammatory factors, the six proenzyme subunits of NADPH oxidase (95), including p22^{phox}, gp91^{phox}, GTPase Rac, p40^{phox}, p47^{phox}, and p67^{phox}, form the holoenzyme complex that catalyzes the transfer of NADPH electrons to oxygen molecules to produce ROS (96). Key to the assembly process of the holoenzyme complex is p47^{phox} (97, 98). After macrophages are stimulated extracellularly, p47^{phox}, which resides in the cytosol during the resting state (95), is phosphorylated and translocated to the plasma membrane together with the remaining proenzyme subunits and activation of NADPH oxidase (99, 100). Consistent with Liu's study (53), by interacting with p47^{phox} and modulating phosphorylation and membrane translocation of p47^{phox}, Park7 promoted NADPH oxidase assembly and induced the production of ROS in macrophages. This mechanism supports the hypothesis that Park 7-targeted therapy maybe useful in the future in the treatment of sepsis-induced immunosuppression.

IS PARK 7 A POTENTIAL TARGET FOR DRUG TREATMENT IN THE FUTURE?

In this decade, many reports have shown the therapeutic potency of Park 7 and Park 7-targeting molecules/compounds in treating several neurodegenerative disorders (101–103). Can Park 7 be a potential target for drug treatment for sepsis-induced immunosuppression in the future? Structure-based drug design (SBDD) (104), as a valuable pharmaceutical lead discovery tool, opens up new opportunities for drug design for the patient with sepsis-induced immunosuppression. A typical example is the successful design of many valuable drugs by SBDD based on the crystal structure of Class B G-protein-coupled receptors (105). As noted above, the interaction of Park 7 and p47^{phox} is a decisive factor in activating macrophages to ameliorate sepsis-induced immunosuppression, suggesting that the interaction between Park 7 and p47^{phox} may be an ideal target for drug design. Single crystal structures of Park 7 and p47^{phox} have been determined. Human Park 7 consists of 189 amino acids from N-terminus to C-terminus, which folds into a helix-strand-helix sandwich structure (106). The C-terminal domain (CTD) of Park 7 physically interacts with p47^{phox} in vitro (53). In addition, the C106 and L166 residues in the CTD of Park 7 are important for its functions (107, 108), suggesting the two residues might play a key role in Park 7 interacting with p47^{phox}. However, the details of the interaction depend on the crystal structure of the Park7-p47^{phox} complex. Therefore, determing Park7-p47^{phox} complex structure should be an urgent issue for future research.

With regard to a potential drug treatment based on Park 7 in the future it might be important to discuss three relevant points here. (1) It would be necessary to detect/diagnose the immune status of the patient in sepsis-induced immunosuppression. (2) In line with this it would be crucial to find the right timing to start drug treatment to overcome sepsis-induced immunosuppression. (3) Considering the complexity of the host response during sepsis and the variety of pathophysiological pathways involved, it is unlikely that the current "one-target" and "one-size-fits-all" approach will ever be successful. To date, absolute lymphocyte count and decreased expression of HLA-DR by monocytes seem to be the most robust markers for patient stratification in multicenter clinical trials (109–112). Measurement of soluble mediators such as IL-6, IL-10, and TNF-a can also help detect immune status. However, a convenient, faster detection protocol and other effective drugs are extremely necessary. These are interesting issues that are worth pursuing in the future.

CONCLUSION

In summary, macrophages, as one of the most important cells of the innate immune system, play an important role in inflammatory and immune processes. In the early stage of sepsis, macrophages usually have a pro-inflammatory phenotype, whereas the excessive inflammatory macrophage response can lead to macrophages apoptosis and change macrophage polarization contributing to the immunosuppression. ROS have the capacity to initiate many TLR signaling pathways and in turn modulate macrophage functions and are produced by the activation of NADPH oxidase. Park 7 has been extensively studied in many diseases and can serve as an effective therapeutic target. For research on sepsis in the late stage, Park7 KO mice can be an ideal model. The interaction of Park7 and p47^{phox} can activate NADPH oxidase and subsequently increase ROS in macrophages to initiate TRL signaling to in turn, reinforce macrophage functions to protect against sepsis–induced immunosuppression. In light of this understanding, the Park 7/p47^{phox}/ROS axis may become an effective therapeutic target for sepsis induced immunosuppression.

AUTHOR CONTRIBUTIONS

YaC wrote the first draft of this article. XC and WW designed the figure. YC and TM critically revised the manuscript for important intellectual content. All authors approved the final version.

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