Review

Crosstalk between Dendritic Cells and Immune Modulatory Agents against Sepsis

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Abstract: Dendritic cells (DCs) play a critical role in the immune system which sense pathogens and present their antigens to prime the adaptive immune responses. As the progression of sepsis occurs, DCs are capable of orchestrating the aberrant innate immune response by sustaining the Th1/Th2 responses that are essential for host survival. Hence, an in-depth understanding of the characteristics of DCs would have a beneficial effect in overcoming the obstacle occurring in sepsis. This paper focuses on the role of DCs in the progression of sepsis and we also discuss the reverse sepsis-induced immunosuppression through manipulating the DC function. In addition, we highlight some potent immunotherapies that could be used as a novel strategy in the early treatment of sepsis.

Keywords: dendritic cells; immune modulatory agents; sepsis; innate and adaptive immune; immunosuppression

1. Introduction

Sepsis is still a life-threatening disease and a major contributor to the public health burden. It is characterized by a systemic inflammatory response syndrome (SIRS) which can lead to organ damage, organ failure, septic shock, and even death. The total burden of sepsis is high with an estimated 19 million clinical cases occurring each year. The annual actual incidence rate of sepsis is apparently far higher and most of these established cases occur in low-income areas. Moreover, due to the increased number of people with advanced age and improvements in the methods of detection, the incidence of sepsis was shown to gradually increase (8–13% per year) in high-income countries. In low-income countries, the mortality rate as a result of septic shock and severe sepsis is almost 60% [1]. Apart from the short-term mortality of patients with sepsis, septic patients undergo plenty of long-term complications which will affect the quality of life and increase the five-year risk of death from subsequent of acute events [2–4].

Sepsis is currently considered as a complex deregulation of the inflammatory processes, which lead to compromise the individual’s ability for the containment of infection. The high risk associated with sepsis can be only reduced through interventional therapies [5].

Dendritic cells (DCs) are key components of the innate immune system that are responsible for sensing bacteria or microbial products, processing the antigens, and priming the protective adaptive immune responses through antigen presentation to helper T lymphocytes [6]. The role of DCs has been
studied thoroughly in many human diseases, such as autoimmune diseases, while there is limited data on the DCs’ role in human sepsis. During the progression of sepsis, DCs can play a direct role in the aberrant immune response, and increasing the number of DCs or enhancing their functionality may lead to improve the outcome of disease [3,7]. Undoubtedly, understanding the mechanisms of DCs’ response during sepsis will be crucial for developing novel strategies for fighting this disease. Recent studies imply that some novel immunomodulatory agents, including IL-7, IL-15, GM-CSF, IFN-γ, and co-inhibitory molecule blockade can reduce the clinical morbidity associated with severe sepsis and septic shock [8–10].

2. DC Numbers, Subgroups and Immune Functions in Sepsis

DCs play an important role in the cross-link between innate and adaptive immunity to control microorganism infection. However, they have been shown to contribute to the development of immune suppression during sepsis. The DCs in septic patients undergo multiple alterations as follows: number of cells decreased, alteration of the DC subgroups, as well as alteration of their immune functions (Figure 1).

![Figure 1](attachment:image1.png)

Figure 1. The surface molecules associated with dendritic cell (DC) function are changed during sepsis, and the number of DCs will be decreased, resulting from apoptosis; moreover, the secretion of cytokines in DCs will be changed, which leads to immunological tolerance.

2.1. Sepsis can Lead to Reduction in DC Number

Previous studies of sepsis in animal models and in human patients have shown that the number of DCs was depleted in both lymph and non-lymphoid organs [11]. Using the cecal ligation and puncture (CLP) mouse model of sepsis, the number of CD11c+ DC was found to be lower in the spleen and lymph nodes than that in sham operation groups [12]. In peripheral organs of septic patients, clinical trials have shown that the number of interstitial DCs was remarkably lower than that in non-septic patients [13]. Moreover, it was demonstrated that the low DC count during the early stage of sepsis is closely related to the severity of sepsis. Therefore, the number of DCs can be a useful prognostic maker to evaluate the severity of disease and host response status against infection [14,15]. Sepsis can induce a numerical loss of DCs without significantly changing their maturation status, suggesting that the reduction of DC number may be mediated by an apoptosis process.
2.2. Alterations in the Composition of the DC Subgroups during Sepsis

DCs comprise two major distinct subsets: plasmacytoid DCs (pDCs) and myeloid DCs (mDCs), which are also called conventional or classical DCs (cDCs) [16]. The cDCs are professional antigen presenting cells characterized by an incredible ability to capture antigens and the expression of high levels of major histocompatibility (MHC) class II and co-stimulatory molecules which enables them to stimulate T cells [9].

Based on the surface expression of CD4 and CD8, DCs can be divided into three subgroups including CD4−CD8−, CD4+CD8−, and CD4−CD8+ [17]. Mice treated with CLP or sham operation for 36 h were used to count the number of the three major subpopulations of DCs. The control mice treated with sham operation exhibited the proportion of three DC subpopulations as follows: subpopulation CD4+CD8− (72%), CD4+CD8+ (11%), and CD4−CD8− (15%) [18]. In contrast, CLP-treated mice displayed a significant decrease in the number of CD4+CD8− DC and CD4−CD8+ DCs when compared with control groups. Meanwhile, in the spleen of both CLP and sham operation groups, the number of CD4−CD8− DCs remains unchanged. Therefore, the disappearance of splenic DCs during sepsis can account for a profound reduction of two special DC subgroups.

2.3. Sepsis can Lead to Functional Impairments in DCs

Sepsis is not only the cause of the decreased DC count, but it can also lead to functional limitation. These cells can lose their ability to produce inflammatory cytokines upon stimulation [19]. It was demonstrated that CD11c+ DCs harvested from the CLP model are impaired to expressed IL-12p40 and tumor necrosis factor-alpha (TNF-α) upon stimulation with lipopolysaccharide (LPS) or CpG, implying that sepsis has the ability to change DCs’ response to a Toll-like Receptor (TLR) agonist [20,21]. Similarly, splenic DCs from septic mice are unable to secrete IL-12, but they can release a significant amount of IL-10 compared with DCs obtained from control mice, suggesting that sepsis can abrogate DCs inducing Th1 cell polymerization [22]. However, DCs restore the capacity to promote the T cell proliferation during sepsis [23,24]. It was found that immature DCs from patients with sepsis and health donors have a similar ability to induce T cell proliferation, but the mature DCs did not [25]. Lastly, the expression levels of the B and T lymphocyte attenuator (BTLA), a co-inhibitory receptor, was found to be improved in immature and mature DCs in the peritoneum after CLP, which can result in an increased bacterial burden and severity of sepsis [26,27]. Therefore, BTLA may be considered as a potential therapeutic target, as it was shown that antibody blockade of BTLA can protect mice from LPS-induced septic shock [28,29].

3. Immunization of Sepsis with DC as the Target

3.1. Increasing the Number of DCs in Vivo

The reduction of DCs’ number is the dominant cause of immunosuppression and opportunistic infections during sepsis, which is closely related to an unsatisfactory prognosis. The lack of differentiation of peripheral blood mononuclear cells into DCs during sepsis can lead to the destruction of the dynamic balance between innate and acquired immunity. Therefore, increasing the number of DCs has potential as an immunoregulatory treatment for sepsis.

Fms-related tyrosine kinase 3 ligand (Flt3L) is a hemopoietic cytokine that serves as a DC growth factor, and can enhance the regeneration of DCs [30]. Flt3L receptor, named Flt3R, has also been shown to stimulate the expansion of progenitor cells and differentiation of both myeloid and lymphoid cells into DCs. It was also found that Flt3L treatment can augment DCs to release multiple cytokines, such as IFN-γ and IL-12 secretion, and to stimulate robust Th1 responses [31,32]. In vivo studies demonstrated that the administration of Flt3L can greatly increase the DCs’ number and promote mouse resistance to burn wound infection with *P. aeruginosa* [33,34]. In addition, Flt3L treatment can also prevent the decline of splenic CD4+ and CD8+ T cells, which has significantly improved the survival
rate of the septic mice [35,36]. These results suggested that amplification and functional enhancement of DC in vivo by Flt3L treatments can result in the enhancement of protective immune responses.

Complement protein C5a is a key component of proinflammatory mediators, which can induce IL-12+ DC migration from the peritoneal cavity to the peripheral blood and lymph nodes [37,38]. During sepsis, it was observed that the expression of C5a was excessively increased, which has harmful effects to the host [39]. Blockade of C5a can play a protective role against sepsis through increasing the amount of IL-12+ DCs in the peritoneal cavity [40].

3.2. Anti-DC Apoptosis

DC apoptosis plays a key role in the homeostasis process of the immune system during sepsis. Imbalance reducing in the number of DCs will decrease T lymphocyte proliferation and trigger the emergence of an immunosuppressive state [41,42]. Therefore, inhibition of DC apoptosis would improve the immune function and enhance the survival rate of septic patients. Some of the immune regulatory molecules such as cytokines, microRNAs (miRs), B cell lymphoma 2 (BCL-2), CD40 ligand (CD40L), TNF-related activation-induced cytokine (TRANCE), and histamine have been shown to negatively regulate DC apoptosis.

BCL-2 is an anti-apoptotic factor and key regulator of DC lifespan and immunogenicity. Bcl-2 transgenic mice exhibited limited number of DC apoptosis and improved their survivability during severe sepsis in comparison with wild type mice [43]. Overexpression of BCL-2 can increase DC survival and maintain the T cell activation and differentiation into the Th1 cell phenotype [44].

MiRs are short non-coding RNAs that regulate multiple biological processes via post-transcriptional regulation of gene expression. MiR-146a and miR-146b expression were found upregulated upon human monocyte differentiation into DCs. Silencing of miR-146a and/or miR-146b in immature DCs and mature DCs can dramatically block DC apoptosis and enhance proinflammatory cytokine production such as IL-12p70, IL-6, TNF-α, and IFN-γ [45].

CD40L is a transmembrane glycoprotein that is found on the surface of CD4+ T cells, which is crucial for CD4+ T cell activation when it binds with CD40 on the DC. It has been demonstrated to downregulate the expression of Bcl-2 in DCs and inhibit Fas-mediated apoptosis [46–48].

TRANCE, an apoptosis-inducing ligand of the TNF family, can augment the expression of Bcl-xL, leading to inhibition of murine DC apoptosis [49,50]. Inhibition of DC apoptosis by TRANCE can improve the immune function of the body and inhibit sepsis sequelae.

Histamine is a proinflammatory mediator that is found in performed state within the granules of basophils and mast cells. It was shown that histamine can abolish DC apoptosis by inhibition of caspase-3 cleavage through a mechanism dependent on protein kinase C activation [51].

3.3. Function Modification of DCs

DCs can secrete cytokines and manipulate lymphocyte function, which is an important manifestation of sepsis-associated immunosuppression (Figure 1). Therefore, the regulation and modification of DC impaired function would improve the immune function of sepsis. Some molecules have been shown to be hopeful targets for improving the function of DCs and prolonging their life during sepsis progression. These molecules include high mobility group protein 1 (HMGB1), CD155, toll-like receptor 4 (TLR4) and TLR2. In addition, phospholipase A2, miR-142-3p, SHARPIN, and glucocorticoids also possess the ability to correct impaired function of DCs (Table 1).

HMGB1 derived from DCs is a major regulator of late and sustained cytokine storm [52,53]. Administration of HMGB1 to mice can cause lethal organ damage similar to that seen in sepsis. Therefore, HMGB1 is a decisive inflammatory mediator and can be considered as a new target in the treatment of sepsis. Neutralization of HMGB1 with an antibody results in reduced mice succumbs during sepsis. Likewise, ablation of HMGB1 secretion in human DCs via siRNA, which targets the short acetylcholine receptor (ACHR) binding peptide, leads to decreased human cytokine storm...
and prevention of human lymphocyte apoptosis. Furthermore, silencing of HMGB1 expression can suppress CLP-induced humanized mice death [54].

The expression of CD155 on DCs was significantly boosted in septic mice. Administration of anti-CD155 antibody can reverse DC dysfunction and reduce morbidity of mouse sepsis models. Mechanistically, blockade of CD155 can efficiently increase the expression of pro-inflammatory molecules, such as TNF-α and IL-6, but it decreased the levels of anti-inflammatory IL-10. Nevertheless, the overexpression of CD155 can significantly increase the production of IL-10 and inhibit the production of IL-12P40 and IL-12P70, suggesting that the expression of CD155 on dendritic cells can promote immunosuppression by regulating the production of cytokines in sepsis [55].

TLR4, TLR2, and TLR9 play a central role in the response to intra-abdominal sepsis. TLR4 and TLR2 are involved in the control of splenic DC apoptosis during polymicrobial sepsis, suggesting that modulation of DC-specific TLR4/TLR2 signaling may be a new therapeutic strategy for the treatment of sepsis [56]. One of the TLR4 antagonists, named FP7, can inhibit LPS-induced cytokine production and DC maturation. In addition, blockade of TLR4 signaling can protect the mice from lethal viral sepsis [57,58]. However, activation of TLR2 signaling is crucial for improving the immune function during sepsis. Consistently, two TLR2 agonists, named MALP-2 and Pam3Cys, provoke the cytokine and chemokine secretion and prevent the sepsis-induced early depletion of splenic DC [59]. TLR2-derived peptides can also enhance antigen-induced DC maturation, IL-12 production, and differentially affect DC cytokine profile upon antigen stimulation [60,61]. Some studies reported that TLR9 is essential for the uptake and intracellular killing of the bacteria during infection with K. pneumonia. In addition, TLR9 can play a role in recruiting and activating DCs, which is required for the optimal activation of bactericidal activity [62].

Secretory phospholipase A2 (spla2) is an indispensable enzyme that catalyzes the production of lysophospholipids and free fatty acids by hydrolyzing phospholipids at the sn-2 site [63]. Administration of sPLA2 on DCs can result on activation of AP-1, NFAT, and NF-κB, which control the expression of multiple genes involved in immune regulation. Importantly, sPLA2 can bind to specific membrane receptors on DCs to mobilize lipid mediators and induce DC maturation [64].

MicroRNA can also be a potential target for the immunoregulation of DCs. For example, miR-142-3p was found to decrease LPS-induced death through targeting and inhibiting IL-6 expression [65].

SHANK-associated RH domain-interacting protein (SHARPIN) is an endogenous inhibitor of caspase-1 activation, and the interaction of SHARPIN–caspase-1 can lead to suppress the release of mature cytokines [66]. SHARPIN can also positively regulate NF-κB signaling, cytokine production, as well as the induction of Th1 differentiation by DCs [67,68].

Finally, glucocorticoids are an important member of steroid hormones which regulate various essential metabolic, cardiovascular, as well as homeostatic functions [69]. Mice with knockdown glucocorticoid receptor in DCs exhibited high susceptibility to endotoxin-induced septic shock and death. Endogenous glucocorticoids can blunt LPS-induced inflammation and promote tolerance by suppressing DC IL-12 production [70].

| Immunotherapy Agents            | Major Functions                          | Ref.       |
|----------------------------------|------------------------------------------|------------|
| FLT3L                            | Increasing the numbers of DCs            | [31,33,34,36,71,72] |
| BCL-2                            | Inhibiting Fas-mediated DC apoptosis     | [73]       |
| CD40L                            | Inhibiting Fas-mediated DC apoptosis     | [47,48]    |
| TRANCE                           | Inhibiting Fas-mediated DC apoptosis     | [50]       |
| Histamine                        | Inhibiting DC apoptosis                  | [51]       |
| Anti-HMGB1 antibody              | Reducing cytokine storm                  | [52–54]    |
| Anti-CD155 antibody              | Reverse DC dysfunction                   | [55]       |
| Anti-C5a antibody                | Improving survival of sepsis             | [37]       |
| TLR2-derived peptide            | Promoting DC maturation                  | [74]       |

Table 1. Immunization of sepsis with DCs as the target.
Table 1. Cont.

| Immunotherapy Agents | Major Functions | Ref. |
|-----------------------|-----------------|------|
| sPLA2                 | Increasing the IFN-γ secretion | [63,64,75] |
| miR-142-3p            | Promoting the expression of IL-6 and then reducing endotoxin-mediated mortality | [65] |
| SHARPIN               | Induction of Th1 differentiation by DCs | [67,68] |
| TLR4 agonist         | Inhibiting LPS-induced cytokine production | [57,59] |
| Glucocorticoids       | Reducing IL-12 production of DCs | [69,70] |
| CYT387               | Inhibiting LPS-induced cytokine production | [76] |

Ref.—Reference; FLT3L—Fms-related tyrosine kinase 3 ligand; BCL-2—B cell lymphoma 2; CD40L—CD40 ligand; TRANCE—TNF-related activation-induced cytokine; HMGB1—high mobility group protein 1; TLR2—toll-like receptor 2; TLR4—toll-like receptor 4; SHARPIN—SHANK-associated RH domain-interacting protein.

4. New Approaches: Immunotherapies in Sepsis

Sepsis is one of the main factors leading to death of critically patients in intensive care units (ICUs), and the hospitalization rate for sepsis have constantly increased, even though advances in supportive care mortality are still high. Therapy approaches developed against the pro-inflammatory stage have failed to show clinical efficacy [77–81]. Hence, new treatment strategies for sepsis targeting host immune response are urgently needed. The profound immunosuppression is one key factor in the sepsis pathophysiology, which often engenders secondary fungal, bacterial, or viral infections [82–85]. The following contents of this review will highlight the immunomodulators that improve T cell immune responses during sepsis, such as IL-7, PD1/PDL1-specific antibodies, IFN γ, G-CSF/GM-CSF, IL-15, IL-1ra, and anti-IL-6 antibody (Table 2).

4.1. Recombinant Human IL-7

IL-7, a pluripotent cytokine, is known as a master of the immune system because of its special role in immunotherapy [86]. IL-7 has a potent anti-apoptotic activity, which can abolish sepsis-induced apoptotic depletion of CD4+ and CD8+ T cells [87]. In a murine model of sepsis, IL-7 treatment resulted in the upregulation of the anti-apoptotic protein Bcl-2 and downregulation of pro-apoptotic proteins such as Bim and Puma [88]. IL-7 is also capable to prevent the sepsis-inducing depression of T-cell factors such as IFN-γ and enhance the expression of cell adhesion molecules, such as very late antigen (VLA)-4 and lymphocyte function-related antigen (LFA)-1 [89,90].

4.2. PD1/PDL1-Specific Antibodies

Programmed death-1 (PD-1), a co-inhibitory receptor with similarities to BTLA and T-lymphocyte antigen (CTLA)-4, exerts an inhibitory function by regulating the balance among T cell activation, tolerance, and immunopathology, which is often connected with the phenomenon of “T cell exhaustion” [91,92]. Blockade of PD-1 or its ligand PD-L1 hold great potential in reversing immunosuppression in sepsis via arresting lymphocyte apoptosis and preventing monocyte dysfunction [93,94]. Moreover, blockade of PD1–PDL1 or deficiency can significantly elevated the survival rate and reduced the mortality rate in animal models with sepsis caused by C. albicans [95]. It was noted that the decreased levels of MHC II expression in DC in the CLP model can be reversed by both anti-PD-1 and anti-PD-L1 treatments [96]. Importantly, PD-1/PD-L1 can be used as a candidate biomarker for monitoring the treatment of septic patients, as well as highly potential targets to maintain the normal function of adaptive immunity [97].

4.3. IFN-γ

IFN-γ is a decisive proinflammatory cytokine responsible for the activation of macrophages and monocytes, which play a key role in bacterial elimination during sepsis. Clinical studies demonstrated that the production of IFN-γ by T cells was decreased significantly during sepsis [98]. Moreover,
treatment with recombinant IFN-γ has been shown to reverse monocyte dysfunction and rescue the septic patients [99,100]. Although IFN-γ, as a potential immunotherapeutic agent, provides a real improvement for sepsis patients, it may be dangerous when administered in the pro-inflammatory phase of sepsis by exaggerating the stimulation of monocytes and forming a vicious inflammation cycle known as hyper-inflammation [101]. Thus, IFN-γ therapy can achieve better results with a time-dependent strategy and in combination with granulocyte–monocyte colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), or IL-7 and/or IL-15, which have the ability to enhance immune response, diminish secondary infections as well as improve long-term survival as sepsis recovery evolves [102].

4.4. G-CSF and GM-CSF

There are a few drawbacks in neutrophil function that occur in patients with sepsis resulting from hospital-acquired and community-acquired pneumonia. However, G-CSF has been shown to increase the number of neutrophils and modify their activity and function for better pathogen killing capacity, which will be instrumental in patients with neutropenia-related sepsis [103]. Additionally, G-CSF can also play a critical role in enhancing the activity of other immune cell functions, such as monocyte and macrophage. Meanwhile, a previous study demonstrated that intravenous administration of G-CSF was associated with long duration of survival rate in severe septic patients [104].

GM-CSF is a 23-kD heterodimer cytokine which can stimulate the stem cells to differentiate into neutrophils, monocytes, and macrophages [105]. Additionally, it has been shown that GM-CSF can modulate DC differentiation to reach the state of tolerance, which can boost regulatory T-cell number and function [106]. Recombinant GM-CSF therapy in immunosuppressed patients with sepsis can restore the HLA-DR expression and TNF production [107]. A meta-analysis study demonstrated that GM-CSF can reduce the rate of infection [108]. Furthermore, it was reported that at least two clinical trials of GM-CSF for the treatment of sepsis are currently enrolling patients (NCT01374711 and NCT01653665) [109].

4.5. IL-15

IL-15 is a pleiotropic cytokine that is closely correlated with IL-7. IL-15 plays a key role in the regulation of effector and memory T cells, natural killer (NK) cells, as well as natural killer T (NKT) cells. These properties make IL-15 an attractive candidate for immunotherapy in sepsis [110]. In mouse models of sepsis, administration of IL-15 can significantly inhibit sepsis-induced apoptosis of immune competent cells through boosting Bcl-2 expression [111]. However, it was shown that IL-15 has potential toxicity effects through causing liver injury and cachexia [112]. Therefore, IL-15 can be used in combination with other immunotherapeutic agents for sepsis treatment, such as antibodies that block PD-1 or CTLA-4, which have been found to diminish IL-10 production and PD-1 expression on CD8+ T cell [113].

4.6. IL-1ra

The IL-1 receptor antagonist (IL-1ra) is a competitive inhibitor that prevents IL-1 (including IL-1α and IL-1β) from interacting with the IL-1 receptor1 (IL-1R1) [114,115]. Silencing of IL-1ra can lead to numerous rampant inflammatory diseases including sepsis and Muckle–Wells syndrome. In septic mice, administration of IL-1ra could prevent IL-1β-induced septic shock [116]. Moreover, mice deficient in IL-1ra were more susceptible to endotoxemic death, while administration of recombinant human IL-1ra (rhIL-1ra) can significantly improve the survival of septic mice, providing evidence that IL-1 might be a promising therapeutic target against sepsis [117].

4.7. IL-6

IL-6 was determined to be implicated in the induction of thrombosis, vascular leakage, and multiple organ dysfunctions during severe sepsis [118]. In septic mice, IL-6 gene knockout can significantly
ameliorate pulmonary function, edema formation, and lung pathologies. The administration of anti-IL-6 antibody within 4 h after CLP was found to improve survival in a murine sepsis model. Moreover, the serum level of IL-6 is <4 pg/mL in healthy individuals, but it increases to >1000 pg/mL in severe sepsis, which indicated that IL-6 can serve as an excellent biomarker of severity and prognostic indicator of outcome for septic patients [119].

Table 2. New approaches: Immunotherapies in sepsis.

| Immunotherapy | Major Functions | Ref.       |
|---------------|-----------------|------------|
| GM-CSF        | Improving the production and function of neutrophils and monocytes. Inducing the proliferation of naive and memory T cells; reversing sepsis-induced depression of interferon γ | [120,121] |
| IL-7          | Decreasing Sepsis-induced lymphocyte apoptosis and increasing NK cell, T cell, NKT cell proliferation and activation | [89,122,123] |
| IL-15         | Increasing IL-17-expressing CD4⁺ T cells Reversing monocyte dysfunction; Increasing the numbers of IL-17-expressing CD4⁺ T cells | [99,124,125] |
| IFN-γ         | Inducing the proliferation of naive and memory T cells; decreasing Sepsis-induced lymphocyte apoptosis and reversing sepsis-induced depression of interferon γ | [89,122,123] |
| IgGAM         | Improving pathogen recognition and anti-apoptotic effects Augmenting bacterial clearance | [126,127,128] |
| Mesenchymal stem cells PDI/PDL1-specific antibodies IL-1ra anti-IL-6 antibody | Improving IFN-γ production and decreasing apoptosis of T cells Preventing IL-1β-induced septic shock Improving survival in sepsis model. | [96,111,122,123] |

5. Conclusions

DCs are defined as professional antigen-presenting cells of the immune network, and play a key proinflammatory role during sepsis. Strategies focused on inhibiting the dysfunction of DCs could increase survival in sepsis. Administration of DCs can efficiently arrest the induction of the immune suppression function of the residual DCs in septic mice, it diminished the proliferation and differentiation of Treg cells and suppressor T cells via a combination of factors like indoleamine 2,3 deoxygenase (IDO) and IL-10, enhanced the immune clearance of sepsis-causing pathogens, and eventually reduced organ damage, thereby improving the therapy effect [130,131]. A few immunotherapies that aimed to enhance DCs’ function have been shown to be capable of mitigating the disease symptoms. The effect of DC differentiation, maturation, migration, as well as information transfer through other cytokines during sepsis has yet to be further explored. Furthermore, the dose and safety aspects of DC treatment need further studies. Some recent reports also provide remarkable insights into novel strategies of immunotherapies contributing to alleviate the clinical morbidity associated with sepsis and septic shock.

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References
1. Cavaillon, J.M.; Singer, M.; Skirecki, T. Sepsis therapies: Learning from 30 years of failure of translational research to propose new leads. *EMBO Mol. Med.* 2020, e10128. [CrossRef] [PubMed]
2. Strother, R.K.; Danahy, D.B.; Kotov, D.I.; Kucaba, T.A.; Zacharias, Z.R.; Griffith, T.S.; Legge, K.L.; Badovinac, V.P. Polymicrobial Sepsis Diminishes Dendritic Cell Numbers and Function Directly Contributing to Impaired Primary CD8 T-Cell Responses in vivo. *J. Immunol.* 2016, 197, 4301–4311. [CrossRef] [PubMed]
3. Weber, G.F.; Maier, S.L.; Tina, Z.N.; Michael, B.; Therese, S.; Isabella, K.; Jürgen, W. Analysis of circulating plasmacytoid dendritic cells during the course of sepsis. *Surgery* 2015, 158, 248–254. [CrossRef] [PubMed]

4. Gnoni, A.; De Nitto, E.; Scarco, S.; Santacroce, L.; Palese, L.L. A New Look at the Structures of Old Sepsis Actors by Exploratory Data Analysis Tools. *Antibiotics* 2019, 8, 225. [CrossRef]

5. Rubio, I.; Osuchowski, M.F.; Shankar-Hari, M.; Skirecki, T.; Winkler, M.S.; Lachmann, G.; La Rosée, P.; Monneret, G.; Venet, F.; Bauer, M.; et al. Current gaps in sepsis immunology: New opportunities for translational research. *Lancet Infect. Dis.* 2019, 19, e422–e436. [CrossRef]

6. Darkwah, S.; Nago, N.; Appiah, M.G.; Myint, P.K.; Kawamoto, E.; Shimaoka, M.; Park, E.J. Differential Roles of Dendritic Cells in Expanding CD4 T Cells in Sepsis. *Biomedicines* 2019, 7, 52. [CrossRef]

7. Elsayh, K.I.; Zahran, A.M.; Mohamad, I.L.; Aly, S.S. Dendritic cells in childhood sepsis. *J. Crit. Care* 2013, 28, 881.e7–881.e13. [CrossRef]

8. Schraml, B.U.; Reis e Sousa, C. Defining dendritic cells. *Curr. Opin. Immunol.* 2015, 32, 13–20. [CrossRef]

9. Collin, M.; McGovern, N.; Haniffa, M. Human dendritic cell subsets. *Immunology* 2013, 140, 22–30. [CrossRef]

10. Vincent, J.L.; Mongkolpun, W. Non-antibiotic therapies for sepsis: An update. *Expert Rev. Anti-Infe.* 2019, 17, 169–175. [CrossRef]

11. Venet, F.; Monneret, G. Advances in the understanding and treatment of sepsis-induced immunosuppression. *Nat. Rev. Nephrol.* 2018, 14, 121–137. [CrossRef] [PubMed]

12. Li, P.; Zhao, R.; Fan, K.; Iwanowy, S.; Fan, H.; Li, Z.; Liu, B. Regulation of dendritic cell function improves survival in experimental sepsis through immune chaperone. *Innate. Immun.* 2019, 25, 235–243. [CrossRef] [PubMed]

13. Bouras, M.; Asehnoune, K.; Roquilly, A. Contribution of Dendritic Cell Responses to Sepsis-Induced Immunosuppression and to Susceptibility to Secondary Pneumonia. *Front. Immunol.* 2018, 9, 2590. [CrossRef] [PubMed]

14. Guisset, O.; Dilhuydy, M.S.; Thiebaut, R.; Lévéque, J.; Camou, F.; Sarrat, A.; Gabinski, C.; Moreau, J.F.; Blanco, P. Decrease in circulating dendritic cells predicts fatal outcome in septic shock. *Intensive Care Med.* 2007, 33, 148–152. [CrossRef]

15. Kumar, V. Dendritic cells in sepsis: Potential immunoregulatory cells with therapeutic potential. *Mol. Immunol.* 2018, 101, 615–626. [CrossRef]

16. Macri, C.; Pang, E.S.; Patton, T.; O’Keeffe, M. Dendritic cell subsets. *Semin. Cell Dev. Biol.* 2018, 84, 11–21. [CrossRef]

17. Sato, K.; Fujita, S. Dendritic Cells-Nature and Classification. *Allergol. Int.* 2007, 56, 183–191. [CrossRef]

18. Poehlmann, H.; Scheffold, J.C.; Zuckermann-Becker, H.; Volk, H.-D.; Meisel, C. Phenotype changes and impaired function of dendritic cell subsets in patients with sepsis: A prospective observational analysis. *Crit. Care* 2009, 13, R119. [CrossRef]

19. Huang, X.; Venet, F.; Chung, C.S.; Lomas-Neira, J.; Ayala, A. Changes in dendritic cell function in the immune response to sepsis. Cell- & tissue-based therapy. *Expert Opin. Biol. Ther.* 2007, 7, 929–938.

20. Nie, F.; Ding, F.; Chen, B.; Huang, S.; Liu, Q.; Xu, C. Dendritic cells aggregate inflammation in experimental osteoarthritis through a toll-like receptor (TLR)-dependent machinery response to challenges. *Life Sci.* 2019, 238, 116920. [CrossRef]

21. Zhang, Y.; Zhu, X.; Feng, Y.; Pang, W.; Qi, Z.; Cui, L.; Cao, Y. TLR4 and TLR9 signals stimulate protective immunity against blood-stage Plasmodium yoelii infection in mice. *Exp. Parasitol.* 2016, 170, 73–81. [CrossRef] [PubMed]

22. Flohe, S.B. Dendritic cells during polymicrobial sepsis rapidly mature but fail to initiate a protective Th1-type immune response. *J. Leukoc. Biol.* 2005, 79, 473–481. [CrossRef] [PubMed]

23. Appel, S.; Faivre, V.; Lukaszewicz, A.C.; Alves, A.; Charron, D.; Payen, D.; Haziot, A. Human Monocytes Differentiate into Dendritic Cells Subsets that Induce Anergic and Regulatory T Cells in Sepsis. *PLoS ONE* 2012, 7, e47209.

24. Wang, H.-W.; Yang, W.; Gao, L.; Kang, J.-R.; Qin, J.-J.; Liu, Y.-P.; Lu, J.-Y. Adoptive transfer of bone marrow-derived dendritic cells decreases inhibitory and regulatory T-cell differentiation and improves survival in murine polymicrobial sepsis. *Immunology* 2015, 145, 50–59. [CrossRef] [PubMed]

25. Faivre, V.; Lukaszewicz, A.C.; Alves, A.; Charron, D.; Payen, D.; Haziot, A. Accelerated in vitro differentiation of blood monocytes into dendritic cells in human sepsis. *Clin. Exp. Immunol.* 2007, 147, 426–439. [CrossRef]
26. Fan, X.; Liu, Z. Alterations of dendritic cells in sepsis: Featured role in immunoparalysis. *Genes* **2020**, *11*, 323. [CrossRef]

27. Shubin, N.J.; Chung, C.S.; Heffernan, D.S.; Irwin, L.R.; Monaghan, S.E.; Ayala, A. BTLA expression contributes to septic morbidity and mortality by inducing innate inflammatory cell dysfunction. *J. Leukoc. Biol.* **2012**, *92*, 593–603. [CrossRef]

28. Cheng, T.; Bai, J.; Chung, C.-S.; Chen, Y.; Biron, B.M.; Ayala, A. Enhanced Innate Inflammation Induced by Anti-BTLA Antibody in Dual Insult Model of Hemorrhagic Shock/Sepsis. *Shock* **2016**, *45*, 40–49. [CrossRef]

29. Kobayashi, Y.; Iwata, A.; Suzuki, K.; Sato, A.; Kawashima, S.; Saito, Y.; Owada, T.; Kobayashi, M.; Watanabe, N.; Nakajima, H. B and T lymphocyte attenuator inhibits LPS-induced endotoxic shock by suppressing Toll-like receptor 4 signaling in innate immune cells. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 5121–5126. [CrossRef]

30. Wolfran-Filipowicz, A. Flt3 Ligand: Role in Control of Hematopoietic and Immune Functions of the Bone Marrow. *Physiology* **2003**, *18*, 247–251. [CrossRef]

31. Li, J.; Chen, S.; Ge, J.; Lu, F.; Ren, S.; Zhao, Z.; Pu, X.; Chen, X.; Sun, J.; Gu, Y. A novel therapeutic vaccine composed of a rearranged human papillomavirus type 16 E6/E7 fusion protein and Fms-like tyrosine kinase-3 ligand induces CD8+ T cell responses and antitumor effect. *Vaccine* **2017**, *35*, 6459–6467. [CrossRef] [PubMed]

32. Ramos, M.I.; Tak, P.P.; Lebre, M.C. Fms-like tyrosine kinase 3 ligand-dependent dendritic cells in autoimmune inflammation. *Autoimmun. Rev.* **2014**, *13*, 117–124. [CrossRef] [PubMed]

33. Toliver-Kinsky, T.E.; Cui, W.; Murphey, E.D.; Lin, C.; Sherwood, E.R. Enhancement of Dendritic Cell Production by Fms-Like Tyrosine Kinase-3 Ligand Increases the Resistance of Mice to a Burn Wound Infection. *J. Immunol.* **2004**, *174*, 404–410. [CrossRef] [PubMed]

34. Bae, L.; Bohannon, J.K.; Cui, W.; Vinish, M.; Toliver-Kinsky, T. Fms-like tyrosine kinase-3 ligand increases resistance to burn wound infection through effects on plasmacytoid dendritic cells. *BMC Immunol.* **2017**, *18*, 9. [CrossRef]

35. Patil, N.K.; Bohannon, J.K.; Luan, L.; Guo, Y.; Fensterheim, B.; Hernandez, A.; Wang, J.; Sherwood, E.R. Flt3 Ligand Treatment Attenuates T Cell Dysfunction and Improves Survival in a Murine Model of Burn Wound Sepsis. *Shock* **2017**, *47*, 40–51. [CrossRef]

36. Hundeshagen, G.; Cui, W.; Musgrove, L.; Cherry, A.; Lee, S.-J.; Cox, R.A.; Toliver-Kinsky, T. Fms-Like Tyrosine Kinase-3 Ligand Attenuates Local and Systemic Infection in a Model of Post-Burn Pneumonia. *Shock* **2017**, *1*, 721–727. [CrossRef]

37. Grailer, J.J.; Fattahi, F.; Dick, R.S.; Zetouné, F.S.; Ward, P.A. Cutting Edge: Critical Role for C5aRs in the Development of Septic Lymphopenia in Mice. *J. Immunol.* **2015**, *194*, 868–872. [CrossRef]

38. Aballay, A.; Flierl, M.A.; Rittirsch, D.; Chen, A.J.; Nadeau, B.A.; Sarma, J.V.; Day, D.E.; Sarma, J.V.; Huber-Lang, M.S.; Ward, P.A. The Complement Anaphylatoxin C5a Induces Apoptosis in Adrenomedullary Cells during Experimental Sepsis. *PLoS ONE* **2008**, *3*, e2560. [CrossRef]

39. Rittirsch, D.; Flierl, M.A.; Nadeau, B.A.; Day, D.E.; Huber-Lang, M.; Mackay, C.R.; Zetouné, F.S.; Gerard, N.P.; Cianflone, K.; Köhl, J.; et al. Functional roles for C5a receptors in sepsis. *Nat. Med.* **2008**, *14*, 551–557. [CrossRef]

40. Ma, N.; Xing, C.; Xiao, H.; Wang, Y.; Wang, K.; Hou, C.; Han, G.; Chen, G.; Marrero, B.; Wang, Y.; et al. C5a regulates IL-12+ DC migration to induce pathogenic Th1 and Th17 cells in sepsis. *PLoS ONE* **2013**, *8*, e69779. [CrossRef]

41. Chen, M.; Wang, J. Programmed cell death of dendritic cells in immune regulation. *Immunol. Rev.* **2010**, *236*, 11–27. [CrossRef] [PubMed]

42. Bhan, C.; Dipankar, P.; Chakraborty, P.; Sarangi, P.P. Role of cellular events in the pathophysiology of sepsis. *Inflamm. Res.* **2016**, *65*, 853–868. [CrossRef] [PubMed]

43. Iwata, A.; Stevenson, V.M.; Minard, A.; Tasch, M.; Tupper, J.; Lagasse, E.; Weissman, I.; Harlan, J.M.; Winn, R.K. Over-Expression of Bel-2 Provides Protection in Septic Mice by a trans Effect. *J. Immunol.* **2003**, *171*, 3136–3141. [CrossRef] [PubMed]

44. Gautier, E.L.; Huby, T.; Saint-Charles, F.; Ouzilleau, B.; Chapman, M.J.; Lesnik, P. Enhanced Dendritic Cell Survival Attenuates Lipopolysaccharide-Induced Immunosuppression and Increases Resistance to Lethal Endotoxic Shock. *J. Immunol.* **2008**, *180*, 6941–6946. [CrossRef]

45. Park, H.; Huang, X.; Lu, C.; Cairo, M.S.; Zhou, X. MicroRNA-146a and MicroRNA-146b Regulate Human Dendritic Cell Apoptosis and Cytokine Production by Targeting TRAF6 and IRAK1 Proteins. *J. Biol. Chem.* **2015**, *290*, 2831–2841. [CrossRef]
46. Koppi, T.A.; Tough-Bement, T.; Lewinsohn, D.M.; Lynch, D.H.; Alderson, M.R. CD40 ligand inhibits Fas/CD95-mediated apoptosis of human blood-derived dendritic cells. *Eur. J. Immunol.* 1997, 27, 3161–3165. [CrossRef]

47. Michels, M.; Daneslki, L.G.; Vieira, A.; Florentino, D.; Dall’Igna, D.; Galant, L.; Sonai, B.; Vuolo, F.; Mina, F.; Pescador, B.; et al. CD40-CD40 Ligand Pathway is a Major Component of Acute Neuroinflammation and Contributes to Long-term Cognitive Dysfunction after Sepsis. *Mol. Med. (Camb. Mass.)* 2015, 21, 219–226. [CrossRef]

48. Sinistro, A.; Almerighi, C.; Ciaprini, C.; Natoli, S.; Sussarello, E.; Di Fino, S.; Calo-Carducci, F.; Rocchi, G.; Bergamini, A. Downregulation of CD40 Ligand Response in Monocytes from Sepsis Patients. *Clin. Vaccine Immunol.* 2008, 15, 1851–1858. [CrossRef]

49. Wong, B.R.; Josien, R.; Lee, S.Y.; Sauter, B.; Li, H.L.; Steinman, R.M.; Choi, Y. TRANCE (tumor necrosis factor [TNF]-related activation-induced cytokine), a new TNF family member predominantly expressed in T cells, is a dendritic cell-specific survival factor. *J. Exp. Med.* 1997, 186, 2075–2080. [CrossRef]

50. Cremer, I. Long-lived immature dendritic cells mediated by TRANCE-RANK interaction. *Blood* 2002, 100, 3646–3655. [CrossRef]

51. Alcain, J.; Podaza, E.; Gori, M.S.; Salamone, G.; Vermeulen, M. Modulation of Dendritic Cell Apoptosis and CD8+ Cytotoxicity by Histamine: Role of Protein Kinase C. *Mediat. Inflamm.* 2017, 2017, 1–12. [CrossRef] [PubMed]

52. Zhang, L.-T.; Yao, Y.-M.; Yao, F.-H.; Huang, L.-F.; Dong, N.; Yu, Y.; Sheng, Z.-Y. Association between High-Mobility Group Box-1 Protein Release and Immune Function of Dendritic Cells in Thermal Injury. *J. Interferon Cytokine Res.* 2010, 30, 487–495. [CrossRef] [PubMed]

53. Bae, J.-S. Role of high mobility group box 1 in inflammatory disease: Focus on sepsis. *Arch. Pharmacal Res.* 2012, 35, 1511–1523. [CrossRef] [PubMed]

54. Ye, C.; Choi, J.G.; Abraham, S.; Wu, H.; Diaz, D.; Terreros, D.; Shankar, P.; Manjunath, N. Human macrophage and dendritic cell-specific silencing of high-mobility group protein B1 ameliorates sepsis in a humanized mouse model. *Proc. Natl. Acad. Sci. USA* 2012, 109, 21052–21057. [CrossRef]

55. Meng, Y.; Zhao, Z.; Zhu, W.; Yang, T.; Deng, X.; Bao, R. CD155 blockade improves survival in experimental sepsis by reversing dendritic cell dysfunction. *Biochem. Biophys. Res. Commun.* 2017, 490, 283–289. [CrossRef] [PubMed]

56. Pene, F.; Courtine, E.; Ouaaz, F.; Zuber, B.; Sauneuf, B.; Sirgo, G.; Toubiana, J.; Balloy, V.; Chignard, M.; et al. Toll-Like Receptors 2 and 4 Contribute to Sepsis-Induced Depletion of Spleen Dendritic Cells. *Infect. Immun.* 2009, 77, 5651–5658. [CrossRef]

57. Perrin-Cocon, L.; Aublin-Gex, A.; Sestito, S.E.; Shirey, K.A.; Patel, M.C.; Andre, P.; Blanco, J.C.; Vogel, S.N.; Peri, F.; Lotteau, V. TL4 antagonist FP7 inhibits LPS-induced cytokine production and glycolytic reprogramming in dendritic cells, and protects mice from lethal influenza infection. *Sci. Rep.* 2017, 7, 40791. [CrossRef]

58. Deng, M.; Ma, T.; Yan, Z.; Zettel, K.R.; Scott, M.J.; Liao, H.; Frank, A.; Morelli, A.E.; Hodhi, C.P.; Hackam, D.J.; et al. Toll-like Receptor 4 Signaling on Dendritic Cells Suppresses Polymorphonuclear Leukocyte CXCR2 Expression and Trafficking via Interleukin 10 During Intra-abdominal Sepsis. *J. Infect. Dis.* 2016, 213, 1280–1288. [CrossRef]

59. Barrenschee, M.; Lex, D.; Uhlig, S. Effects of the TLR2 agonists MALP-2 and Pam3Cys in isolated mouse lungs. *PLoS ONE* 2010, 5, e13889. [CrossRef]

60. Raby, A.C.; Holst, B.; Le Bouder, E.; Diaz, C.; Ferran, E.; Conraux, L.; Guillemot, J.C.; Coles, B.; Kift-Morgan, A.; Colmont, C.S.; et al. Targeting the TLR Co-Receptor CD14 with TLR2-Derived Peptides Modulates Immune Responses to Pathogens. *Sci. Transl. Med.* 2013, 5, ra64–ra185. [CrossRef]

61. Baumann, C.L.; Aspalter, I.M.; Sharif, O.; Pichlmair, A.; Blüml, S.; Grebien, F.; Bruckner, M.; Pasierbek, P.; Aumayr, K.; Planyavsky, M.; et al. CD14 is a coreceptor of Toll-like receptors 7 and 9. *J. Exp. Med.* 2010, 207, 2689–2701. [CrossRef]

62. Atalan, N.; Acar, L.; Yapici, N.; Kudsioglu, T.; Ergen, A.; Yilmaz, S.G.; Isbir, T. The Relationship Between Sepsis-induced Immunosuppression and Serum Toll-like Receptor 9 Level. *Vivo* 2018, 32, 1653–1658. [CrossRef] [PubMed]
63. Eugenin, E.A.; Tan, T.L.; Goh, Y.Y. The role of group IIA secretory phospholipase A2 (sPLA2-IIA) as a biomarker for the diagnosis of sepsis and bacterial infection in adults—A systematic review. *PLoS ONE* 2017, 12, e0180554.

64. Perrin-Cocon, L.; Agaugué, S.; Coutant, F.; Masurel, A.; Bezzine, S.; Lambeau, G.; André, P.; Lotteau, V. Secretory phospholipase A2 induces dendritic cell maturation. *Eur. J. Immunol.* 2004, 34, 2293–2302. [CrossRef] [PubMed]

65. Sun, Y.; Varambally, S.; Maher, C.A.; Cao, Q.; Chockley, P.; Toubai, T.; Malter, C.; Nieves, E.; Tawara, I.; Wang, Y.; et al. Targeting of microRNA-142-3p in dendritic cells regulates endotoxin-induced mortality. *Blood* 2011, 117, 6172–6183. [CrossRef] [PubMed]

66. Wang, Z.; Potter, C.S.; Sundberg, J.P.; Hogenesch, H. SHARPIN is a key regulator of immune and inflammatory responses. *J. Cell. Mol. Med.* 2012, 16, 2271–2279. [CrossRef] [PubMed]

67. Ahuja, S.K.; Wang, Z.; Sokolovska, A.; Seymour, R.; Sundberg, J.P.; HogenEsch, H. SHARPIN Is Essential for Cytokine Production, NF-κB Signaling, and Induction of Th1 Differentiation by Dendritic Cells. *PLoS ONE* 2012, 7, e31809.

68. Nastase, M.-V.; Zeng-Brouwers, J.; Frey, H.; Hsieh, L.T.-H.; Poluzzi, C.; Beckmann, J.; Schroeder, N.; Pfeilschifter, J.; Lopez-Mosqueda, J.; Mersmann, J.; et al. An Essential Role for SHARPIN in the Regulation of Caspase 1 Activity in Sepsis. *Am. J. Pathol.* 2016, 186, 1206–1220. [CrossRef]

69. Marrack, P.; Li, C.C.; Munitic, I.; Mittelstadt, P.R.; Castro, E.; Ashwell, J.D. Suppression of Dendritic Cell-Derived IL-12 by Endogenous Glucocorticoids Is Protective in LPS-Induced Sepsis. *PLoS Biol.* 2015, 13, e1002269.

70. Robinson, R. Glucocorticoids Reduce Sepsis by Diminishing Dendritic Cell Responses. *PLoS Biol.* 2015, 13, e1002270. [CrossRef]

71. Bohannon, J.; Cui, W.; Cox, R.; Przkora, R.; Sherwood, E.; Toliver-Kinsky, T. Prophylactic Treatment with Fms-Like Tyrosine Kinase-3 Ligand after Burn Injury Enhances Global Immune Responses to Infection. *J. Immunol.* 2008, 180, 3038–3048. [CrossRef]

72. Beshara, R.; Sencio, V. Alteration of Flt3-Ligand-dependent de novo generation of conventional dendritic cells during influenza infection contributes to respiratory bacterial superinfection. *PLoS pathog.* 2018, 14, e1007360. [CrossRef]

73. Peck-Palmer, O.M.; Unsinger, J.; Chang, K.C.; McDonough, J.S.; Perlman, H.; McDunn, J.E.; Hotchkiss, R.S. Modulation of the Bcl-2 Family Blocks Sepsis-Induced Depletion of Dendritic Cells and Macrophages. *Shock (AugustaGa.)* 2009, 31, 359–366. [CrossRef]

74. Raby, A.C.; Labeta, M.O. Therapeutic Boosting of the Immune Response: Turning to CD14 for Help. *Curr. Pharm. Biotechnol.* 2016, 17, 414–418. [CrossRef] [PubMed]

75. Ramoner, R. Dendritic-cell activation by secretory phospholipase A2. *Blood* 2005, 105, 3583–3587. [CrossRef] [PubMed]

76. Lee, S.J.; Gharbi, A.; You, J.S.; Han, H.D.; Kang, T.H.; Hong, S.H.; Park, W.S.; Jung, I.D.; Park, Y.M. Drug repositioning of TANK-binding kinase 1 inhibitor CYT387 as an alternative for the treatment of Gram-negative bacterial sepsis. *Int. Immunopharmacol.* 2019, 73, 482–490. [CrossRef] [PubMed]

77. Peters van Ton, A.M.; Kox, M.; AbdO, W.F.; Pickkers, P. Precision Immunotherapy for Sepsis. *Front. Immunol.* 2018, 9, 1926. [CrossRef]

78. Watanabe, E.; Thampy, L.K.; Hotchkiss, R.S. Immunoadjuvant therapy in sepsis: Novel strategies for immunosuppressive sepsis coming down the pike. *Acute Med. Surg.* 2018, 5, 309–315. [CrossRef]

79. Oh, B.M.; Lee, S.J.; Park, G.L.; Hwang, Y.S.; Lim, J.; Park, E.S.; Lee, K.H.; Kim, B.Y.; Kwon, Y.T.; Cho, H.J.; et al. Erastin Inhibits Septic Shock and Inflammatory Gene Expression via Suppression of the NF-kappaB Pathway. *J. Clin. Med.* 2019, 8, 2210. [CrossRef]

80. Santacroce, L.; Charitos, I.A.; Bottalico, L. A successful history: Probiotics and their potential as antimicrobials. *Expert Rev. Anti-Infect. Ther.* 2019, 17, 635–645. [CrossRef]

81. Alkhateeb, T.; Kumbhare, A.; Bab, I.; Youssef, D.; Yao, Z.Q.; McCall, C.E.; El Gazzar, M. S100A9 maintains myeloid-derived suppressor cells in chronic sepsis by inducing miR-21 and miR-181b. *Mol. Immunol.* 2019, 112, 72–81. [CrossRef] [PubMed]

82. Seymour, C.W.; Rosengart, M.R. Septic Shock: Advances in Diagnosis and Treatment. *JAMA* 2015, 314, 708–717. [CrossRef] [PubMed]
83. Peake, S.L.; Delaney, A.; Bailey, M.; Bellomo, R.; Cameron, P.A.; Cooper, D.J.; Higgins, A.M.; Holdgate, A.; Howe, B.D.; Webb, S.A.; et al. Goal-directed resuscitation for patients with early septic shock. *N. Engl. J. Med.* 2014, 371, 1496–1506. [PubMed]

84. Leentjens, J.; Kox, M.; van der Hoeven, J.G.; Netea, M.G.; Pickkers, P. Immunotherapy for the Adjunctive Treatment of Sepsis: From Immunosuppression to Immunostimulation. Time for a Paradigm Change? *Am. J. Respir. Crit. Care Med.* 2013, 187, 1287–1293. [CrossRef]

85. Schrijver, I.T.; Theroude, C.; Roger, T. Myeloid-Derived Suppressor Cells in Sepsis. *Front. Immunol.* 2019, 10, 327. [CrossRef]

86. Venet, F.; Demaret, J.; Blaise, B.J.; Rouget, C.; Girardot, T.; Idealissoa, E.; Rimmelé, T.; Mallet, F.; Lepape, A.; Textoris, J.; et al. IL-7 Restores T Lymphocyte Immunometabolic Failure in Septic Shock Patients through mTOR Activation. *J. Immunol.* 2017, 199, 1606–1615. [CrossRef]

87. Mackall, C.L.; Fry, T.J.; Gress, R.E. Harnessing the biology of IL-7 for therapeutic application. *Nat. Rev. Immunol.* 2011, 11, 330–342. [CrossRef]

88. Hotchkiss, R.S.; Sherwood, E.R. Immunology. Getting sepsis therapy right. *Science* 2015, 347, 1201–1202. [CrossRef]

89. Chang, K.C.; Burnham, C.A.; Compton, S.M.; Rasche, D.P.; Mazuski, R.J.; McDonough, J.S.; Unsinger, J.; Green, J.M.; Hotchkiss, R.S. Interleukin-7 and Anti–Programmed Cell Death 1 Antibody Have Differing Effects to Reverse Sepsis-Induced Immunosuppression. *Shock (AugustaGa.)* 2015, 43, 334–343. [CrossRef]

90. Zhang, Y.; Zhou, Y.; Lou, J.; Li, J.; Bo, L.; Zhu, K.; Wan, X.; Deng, X.; Cai, Z. PD-L1 blockade improves survival in sepsis by inhibiting lymphocyte apoptosis and reversing monocyte dysfunction. *Crit. Care (Lond. Engl.)* 2013, 2013, 37, 4229–4232. [PubMed]

91. Monneret, G.; Gossez, M.; Venet, F. Sepsis in PD-1 light. *Crit. Care* 2016, 20, 186. [CrossRef] [PubMed]

92. Patera, A.C.; Drewry, A.M.; Chang, K.; Beiter, E.R.; Osborne, D.; Hotchkiss, R.S. Anti-PD-L1 peptide improves survival in sepsis. *J. Surg. Res.* 2017, 208, 33–39. [CrossRef] [PubMed]

93. Chang, K.C.; Burnham, C.A.; Compton, S.M.; Rasche, D.P.; Mazuski, R.J.; McDonough, J.S.; Unsinger, J.; Korman, A.J.; Green, J.M.; Hotchkiss, R.S. Blockade of the negative co-stimulatory molecules PD-1 and CTLA-4 improves survival in primary and secondary fungal sepsis. *Crit. Care (Lond. Engl.)* 2013, 17, R85. [CrossRef]

94. Brahnamdham, P.; Inoue, S.; Unsinger, J.; Chang, K.C.; McDunn, J.E.; Hotchkiss, R.S. Delayed administration of anti-PD-1 antibody reverses immune dysfunction and improves survival during sepsis. *J. Leukoc. Biol.* 2010, 88, 233–240. [CrossRef]

95. Jarvis, J.N.; Meintjes, G.; Rebe, K.; Williams, G.N.; Bicanic, T.; Williams, A.; Schutz, C.; Bekker, L.-G.; Wood, R.; Harrison, T.S. Adjunctive interferon-γ immunotherapy for the treatment of HIV-associated cryptococcal meningitis. *Aids* 2012, 26, 1105–1113. [CrossRef]

96. Kim, J.H.; Oh, S.J.; Ahn, S.; Chung, D.H. IFN-γ-producing NKT cells exacerbate sepsis by enhancing C5a generation via IL-10-mediated inhibition of CD55 expression on neutrophils. *Eur. J. Immunol.* 2014, 44, 2025–2035. [CrossRef]

97. Patil, N.K.; Bohannon, J.K.; Sherwood, E.R. Immunotherapy: A promising approach to reverse sepsis-induced immunosuppression. *Pharmacol. Res.* 2016, 111, 688–702. [CrossRef] [PubMed]

98. Delano, M.J.; Ward, P.A. Sepsis-induced immune dysfunction: Can immune therapies reduce mortality? *J. Clin. Invest.* 2016, 126, 23–31. [CrossRef] [PubMed]
103. Priyanka Gupta, R.S. Om Shankar Chaurasia, Anuj Sethi, Role of Granulocyte Colony Stimulating Factor (G-CSF) in Neonatal Sepsis with Neutropenia. *Peoples J. Sci. Res.* 2016, 9, 7-13.

104. Cheng, A.C.; Limmathurotsakul, D.; Chierakul, W.; Getchalarat, N.; Wuthiekanun, V.; Stephens, D.P.; Day, N.P.; White, N.J.; Chawagul, W.; Currie, B.J.; et al. A Randomized Controlled Trial of Granulocyte Colony-Stimulating Factor for the Treatment of Severe Sepsis Due to Melioidosis in Thailand. *Clin. Infect. Dis.* 2007, 45, 308–314. [CrossRef]

105. Becher, B.; Tugues, S.; Greter, M. GM-CSF: From Growth Factor to Central Mediator of Tissue Inflammation. *Immunology* 2016, 45, 963–973. [CrossRef]

106. Bhattacharya, P.; Budnick, I.; Singh, M.; Thiruppathi, M.; Alharshawi, K.; Elshabrawy, H.; Holtermann, M.J.; Prabhakar, B.S. Dual Role of GM-CSF as a Pro-Inflammatory and a Regulatory Cytokine: Implications for Immune Therapy. *J. Interferon Cytokine Res.* 2015, 35, 585–599. [CrossRef]

107. Marlow, N.; Morris, T.; Brocklehurst, P.; Carr, R.; Cowan, F.; Patel, N.; Petrou, S.; Redshaw, M.; Modi, N.; Priyanka Gupta, R.S. Om Shankar Chaurasia, Anuj Sethi, Role of Granulocyte Colony Stimulating Factor (G-CSF) in Neonatal Sepsis with Neutropenia. *Peoples J. Sci. Res.* 2011, 32, 14 of 15.

108. Bo, L.; Wang, F.; Zhu, J.; Li, J.; Deng, X. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) for sepsis: A meta-analysis. *Crit. Care* (Lond. Engl.) 2011, 15, R58. [CrossRef]

109. Fink, M.P.; Warren, H.S. Strategies to improve drug development for sepsis. *Nat. Rev. Drug Discov.* 2014, 13, 741–758. [CrossRef]

110. Guo, Y.; Luan, L.; Patil, N.K.; Wang, J.; Bohannon, J.K.; Rabacal, W.; Fensterheim, B.A.; Hernandez, A.; Sherwood, E.R. IL-15 Enables Septic Shock by Maintaining NK Cell Integrity and Function. *J. Immunol.* 2017, 198, 1320–1333. [CrossRef]

111. Inoue, S.; Unsinger, J.; Davis, C.G.; Muenzer, J.T.; Ferguson, T.A.; Chang, K.; Osborne, D.F.; Clark, A.T.; Coopersmith, C.M.; McDunn, J.E.; et al. IL-15 Prevents Apoptosis, Reverses Innate and Adaptive Immune Dysfunction, and Improves Survival in Sepsis. *J. Immunol.* 2009, 184, 1401–1409. [CrossRef][PubMed]

112. Hall, M.W.; Knatz, N.L.; Vetterly, C.; Tomarello, S.; Wewers, M.D.; Volk, H.D.; Carcillo, J.A. Immunoparalysis of IL-6 and IL-8 and support HSP10 in an in vitro sepsis model. *PLoS ONE* 2016, 11, e0148452.

113. Malik, A.; Kanneganti, T.D. Function and regulation of IL-1alpha in inflammatory diseases and cancer. *Immunol. Rev.* 2018, 281, 124–137. [CrossRef]

114. Benjamin, J.T.; Moore, D.J.; Bennett, C.; van der Meer, R.; Royce, A.; Loveland, R.; Wynn, J.L. Cutting Edge: IL-1alpha and Not IL-1beta Drives IL-1R1-Dependent Neonatal Murine Sepsis Lethality. *J. Immunol.* 2018, 199, 585–599. [CrossRef] [PubMed]

115. Ge, Y.; Huang, M.; Yao, Y.M. Recent advances in the biology of IL-1 family cytokines and their potential roles in development of sepsis. *Cytokine Growth Factor Rev.* 2019, 45, 24–34. [CrossRef]

116. Hall, M.W.; Knatz, N.L.; Vetterly, C.; Tomarello, S.; Wewers, M.D.; Volk, H.D.; Carcillo, J.A. Immunoparalysis and nosocomial infection in children with multiple organ dysfunction syndrome. *Intensive Care Med.* 2010, 36, 525–532. [CrossRef] [PubMed]

117. Mei, C.; Schefold, J.C.; Pschowski, R.; Baumann, T.; Hetzger, K.; Gregor, J.; Weber-Carstens, S.; Hasper, D.; Keh, D.; Zuckermann, H.; et al. Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: A double-blind, randomized, placebo-controlled multicenter trial. *Am. J. Respir. Crit. Care Med.* 2009, 180, 640–648. [CrossRef][PubMed]

118. Hotchkiss, R.S.; Monneret, G.; Payen, D. Immunosuppression in sepsis: A novel understanding of the disorder and a new therapeutic approach. *Lancet Infect. Dis.* 2013, 13, 260–268. [CrossRef]
123. Unsinger, J.; Burnham, C.A.; McDonough, J.; Morre, M.; Prakash, P.S.; Caldwell, C.C.; Dunne, W.M., Jr.; Hotchkiss, R.S. Interleukin-7 ameliorates immune dysfunction and improves survival in a 2-hit model of fungal sepsis. *J. Infect. Dis.* 2012, 206, 606–616. [CrossRef] [PubMed]

124. Venet, F.; Lukaszewicz, A.-C.; Payen, D.; Hotchkiss, R.; Monneret, G. Monitoring the immune response in sepsis: A rational approach to administration of immunoadjuvant therapies. *Curr. Opin. Immunol.* 2013, 25, 477–483. [CrossRef] [PubMed]

125. Marciano, B.E.; Wesley, R.; De Carlo, E.S.; Anderson, V.L.; Barnhart, L.A.; Darnell, D.; Malech, H.L.; Gallin, J.I.; Holland, S.M. Long-Term Interferon- Therapy for Patients with Chronic Granulomatous Disease. *Clin. Infect. Dis.* 2004, 39, 692–699. [CrossRef]

126. Kalvelage, C.; Zacharowski, K.; Bauhofer, A.; Gockel, U.; Adamzik, M.; Nierhaus, A.; Kujath, P.; Eckmann, C.; Pletz, M.W.; Bracht, H.; et al. Personalized medicine with IgGAM compared with standard of care for treatment of peritonitis after infectious source control (the PEPPER trial): Study protocol for a randomized controlled trial. *Trials* 2019, 20, 156. [CrossRef]

127. Schlosser, K.; Wang, J.P.; Dos Santos, C.; Walley, K.R.; Marshall, J.; Fergusson, D.A.; Winston, B.W.; Granton, J.; Watpool, L.; Stewart, D.J.; et al. Effects of Mesenchymal Stem Cell Treatment on Systemic Cytokine Levels in a Phase 1 Dose Escalation Safety Trial of Septic Shock Patients. *Crit. Care Med.* 2019, 47, 918–925. [CrossRef]

128. Steinhagen, F.; Schmidt, S.V.; Schewe, J.C.; Peukert, K.; Klinman, D.M.; Bode, C. Immunotherapy in sepsis—Brake or accelerate? *Pharmacol. Ther.* 2020, 107476. [CrossRef]

129. Tanaka, T.; Narazaki, M.; Kishimoto, T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. *Immunotherapy* 2016, 8, 959–970. [CrossRef] [PubMed]

130. Wu, D.-D.; Li, T.; Ji, X.-Y. Dendritic Cells in Sepsis: Pathological Alterations and Therapeutic Implications. *J. Immunol. Res.* 2017, 2017, 1–9. [CrossRef] [PubMed]

131. Kolling, Y.; Salva, S.; Villena, J.; Alvarez, S. Are the immunomodulatory properties of Lactobacillus rhamnosus CRL1505 peptidoglycan common for all Lactobacilli during respiratory infection in malnourished mice? *PLoS ONE* 2018, 13, e0194034. [CrossRef] [PubMed]

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