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Sepsis-induced T cell immunoparalysis: The ins and outs of impaired T cell immunity

Isaac J. Jensen,* Frances V. Sjaastad, † Thomas S. Griffith, ‡§¶ and Vladimir P. Badovinac*¶‖

Sepsis results in a deluge of pro- and anti-inflammatory cytokines, leading to lymphopenia and chronic immunoparalysis. Sepsis-induced long-lasting immunoparalysis is defined, in part, by impaired CD4 and CD8 αβ T cell responses in the postseptic environment. The dysfunction in T cell immunity affects naïve, effector, and memory T cells and is not restricted to classical αβ T cells. Although sepsis-induced severe and transient lymphopenia is a contributory factor to diminished T cell immunity, T cell–intrinsic and -extrinsic factors/mechanisms also contribute to impaired T cell function. In this review, we summarize the current knowledge of how sepsis quantitatively and qualitatively impairs CD4 and CD8 T cell immunity of classical and non-classical T cell subsets and discuss current therapeutic approaches being developed to boost the recovery of T cell immunity postsepsis induction. The Journal of Immunology, 2018, 200: 1543–1553.

Sepsis is characterized by an exaggerated host response, involving pro- and anti-inflammatory cytokines, to a disseminated infection, followed by severe transient lymphopenia and immunological dysregulation. Sepsis is the most expensive clinical condition treated in the United States (> $20 billion per year) and affects 1.5 million Americans annually. Additionally, one third of the patients who die in the hospital have sepsis (1). Advances in medical technology and practice have resulted in increased survival from the sepsis-induced cytokine storm, because mortality is currently ∼25% (compared with ∼45% in 1993) (2, 3). However, long after the cytokine storm has resolved, patients continue to demonstrate increased susceptibility to secondary infection, increased viral reactivation, and decreased 5-y survival compared with control cohorts (4–6). This inability to mount/support effective immune responses is termed immunoparalysis; although this immunoparalysis affects multiple aspects of innate and adaptive immunity, its effect on αβ T cells is particularly pronounced.

The combination of sepsis-induced quantitative and qualitative impairments to the T cell compartment and our in-depth understanding of T cell biology makes these cells prime candidates to assess the overall fitness of the immune system in experimental model(s) and/or clinical setting of sepsis. Animal models present an invaluable array of tools, including a priori knowledge of MHC restriction of T cells, for performing directed hypothesis interrogation. However, recent work has established that the genetically inbred aspects of many mouse models do not always accurately recapitulate what is observed in genetically outbred patients (7). As such, validating results in outbred animals, such as Swiss Webster mice, and the use of reverse translational approaches becomes necessary as the field progresses (8–10). In addition, the immunological status of the host can have a big impact on the responsiveness to inflammatory events. Specifically, conventionally housed specific pathogen–free mice have an immune system resembling that of newborn infants, due to the limited history of pathogen exposures (11–13). In contrast, the use of “dirty mice” (i.e., mice purchased from pet stores or inbred mice cohoused with or exposed to the bedding of feral mice) allows for analysis of animals with an immune system that more closely recapitulates the immune system of an adult human because of multiple pathogen exposures (11, 13). Although dirty mice have yet to be used in sepsis research, they could represent a model with the capacity to further bridge animal and human research.

Sepsis has been modeled in multiple fashions to encompass the broad etiology of the disease. These models include, but are not limited to, TLR agonist (e.g., LPS) injection, i.v. bacterial injection, pneumonia, fecal slurry injection, colon ascendens stent peritonitis, and cecal ligation and puncture (CLP) to induce polymicrobial sepsis (10, 14–19). TLR agonist models elicit different inflammatory profiles between mice and humans; and 5 T32 CA09138 (to F.V.S.) and by a U.S. Department of Veterans Affairs Merit Review Award (to T.S.G.).

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Abbreviations used in this article: CLP, cecal ligation and puncture; DC, dendritic cell; Flt3L, Flt3 ligand; IEL, intraepithelial lymphocyte; LAG-3, lymphocyte activation gene-3; MAIT, mucosal-associated invariant T; SFB, segmented filamentous bacteria; TCIRG1, circulatory memory T cell; Treg, regulatory T cell; TRES, tissue-resident memory T cell.

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however, they do elicit cell loss similar to other sepsis models (7, 20). Additionally, “two-hit” models have been utilized in an effort to recapitulate septic outcomes as a result of secondary nosocomial infection. Often the first “hit” involves an injury-related induction, such as CLP or burn wound, followed by a secondary infection model, typically pneumonia, a common secondary infection of immunosuppressed septic patients (21–25).

Although there is debate regarding the usefulness of each animal model, the clinical parameters of lymphopenia (including diminished T cell numbers) and induction of immunoparalysis are found (to varying degrees) in each of these models, effectively enabling a reverse translational approach to connect clinical and experimental research (10, 26–30). In this article, we will synthesize our current understanding of how sepsis, across model systems, impairs primary and secondary T cell responses. The major focus will be on naive, effector, and memory αβ T cells (defined in Fig. 1), with a brief discussion of nonclassical T cell subsets (i.e., γδ, NKT cells, mucosal-associated invariant T [MAIT] cells, and intraepithelial lymphocyte [IELs]), and a description of current therapeutic strategies being evaluated for accelerating the numerical and/or functional recovery of T cells in survivors of sepsis.

Sepsis and naive T cells: the Mandela Effect and a “hole” other repertoire

Sepsis-induced lymphopenia invariably affects the naive Ag-inexperienced T cell pool in humans and experimental mouse models. In specific pathogen–free mice, naive T cells remaining in the periphery after septic lymphopenia undergo homeostatic proliferation to compensate for the imposed numerical reduction and acquire memory-like characteristics, including memory phenotype marker expression (e.g., CD8 T cells: CD8αloCD11ahi; CD4 T cells: CD44hiCD11ahiCD49dhi) and even effector functionality (Fig. 2A), in a potentially Ag-independent manner (31, 32). Although numerical recovery of T cells in sepsis survivors can occur in thymectomized animals, sepsis also reduces the number of newly generated naive T cells by affecting thymic output (31, 33–35). In addition, homeostatic proliferation in the lymphopenic environment likely selects those T cell specificities with the highest precursor frequencies, resulting in holes in the naive T cell compartment and an inability to mount effective primary T cell responses to particular Ag/pathogens (Fig. 2A) (32, 36). With these issues in mind, the likelihood of fully regenerating a diverse naive T cell pool becomes doubtful. This is especially true for elderly septic patients whose naive T cell pool represents only a small portion of their total T cell repertoire (34, 37). In addition to a changing composition of the T cell compartment, sepsis increases inhibitory receptor (e.g., 2B4 and PD-1) expression on surviving naive T cells (in human and animal models), which can be associated with increased mortality (38, 39). Invariably, this change in repertoire/composition and expression of inhibitory receptors expression contributes to the increased susceptibility of the host to unrelated secondary infection(s) (31, 32). However, the full extent of the intrinsic impairments in naive T cells that occur as a result of sepsis is not known or well defined. This could include reduced responsiveness to TCR stimulation, changes in costimulatory molecule expression, cytokine responsiveness, and even metabolic functionality. As such, sepsis-induced changes within the naive T cell repertoire have the potential to lead to lackluster effector and memory T cell generation or even inappropriate tolerance to some Ags.

Sepsis and effector T cells: too hot or too cold but nothing just right

Effector T cell function in the postseptic environment can be viewed in response to the pathogen(s) that precipitated the
A septic event or in response to a newly introduced secondary infectious pathogen. With widespread inflammation and bacterial translocation occurring in most sepsis models, it is reasonable to posit that multiple Ag-specific responses to the polymicrobial infection occur, even with the concurrent sepsis-induced lymphopenia. The acquisition of Ag-specific effector CD4 T cell responses to microbes present in the gut can indeed be detected, further contributing to overall changes in the composition of T cell pools, potentially impairing their subsequent T cell responses to newly encountered pathogens. The Journal of Immunology 1545

**FIGURE 2.** Sepsis-induced changes in naive and memory T cells. (A) Sepsis induces rapid and vigorous apoptosis of naive (Ag-nonexperienced CD11alo/CD8a
t CD8 or CD11alo/CD49dlo CD4 T cells) T cells, creating a lymphopenic environment supporting homeostatic proliferation (HP) of T cells that survive the early “cytokine storm” phase of sepsis. As a consequence of HP and in response to microbes that evoke sepsis, numerical recovery of the T cell compartment is accompanied by phenotypic/functional changes (memory-like T cells) on a sizeable fraction of T cells. Sepsis can induce holes in the T cell repertoire, further contributing to overall changes in the composition of T cell pools, potentially impairing their subsequent T cell responses to newly encountered pathogens. (B) Similarly, pre-existing memory T cells (we are considering circulatory memory CD8 T cells) are also susceptible to sepsis-induced apoptosis, leaving the host susceptible to pathogen re-encounter. The extent to which “bona fide” memory T cell responses recover numerically and/or functionally is unknown but critical for our understanding of the sepsis-induced long-lasting immunoparalysis state. Naive and pre-existing memory T cell responses were modeled separately in (A) and (B) for clarity; however, the T cell compartment in any host experiencing sepsis will have populations of CD4 and CD8 T cells present simultaneously. 1Memory T cell responses of defined Ag specificity generated after primary infection and/or vaccination that exist prior to septic insult. 2Memory-like cells (defined as CD11ahi/CD8a
t CD8 or CD11ahi/CD49dhi CD4 T cells) are those that acquire memory characteristics as a result of the septic event and potentially include Ag-independent (HP) and Ag-dependent (pathogens that induce sepsis) T cell responses.
Alterations to existing memory T cells.

In fact, Borken et al. (52) observed enhanced proliferation of T cells from septic patients after CD3/CD28 cross-linking, but they were unable to identify any changes in proximal TCR signaling events to account for this difference. These data suggest that impairments in T cells from sepsis patients can be overcome with strong TCR stimulation. However, impairment may still be relevant at a lower stimulation threshold achieved in vivo during T cell stimulation by Ag-presenting dendritic cells (DCs) (53). Additionally, changes in the metabolic state of T cells impair their capacity to expand and perform effector functions (54–56), and sepsis affects the metabolism of a variety of cells, including T cells (57–60). These metabolic changes likely have a direct association with the impaired accumulation and decreased functionality of T cells in vivo in the postseptic environment and will require further interrogation (Fig. 2). The extent to which those intrinsic impairments are transient and recover with time, or are reversible and could be sped up with intervention to enable recovery, is likely to be a focus of future studies.

Under normal conditions, the priming of naive CD8 T cells is done in a highly controlled manner, largely to prevent the generation of responses to normal healthy tissues, under the assumption that a mixture of cell-intrinsic and -extrinsic factors is needed for the proper expansion and functionality of naive CD8 T cells. Among the various extrinsic factors, CD4 T cell help is a key feature in the formation of a primary CD8 T cell response (61–63). The instructional programming that occurs within CD8 T cells helped by CD4 T cells prevents TRAIL-mediated activation-induced cell death of CD8 T cells (64, 65). The numerical and functional deficits in CD4 T cells during sepsis create the potential for a number of CD8 T cell responses to proceed without the necessary CD4 T cell help. The combination of these facts led to data suggesting that sepsis impairs T cell effector responses during the early immunoparalysis state (in part) in a TRAIL-dependent manner (66–68). The importance of TRAIL in sepsis-induced immunosuppression was exemplified with the therapeutic use of a blocking anti-TRAIL mAb, which restored CD8 T cell responses and improved the control of a secondary bacterial infection following a CLP model (67). Sepsis-induced numerical loss and compositional changes within the DC compartment were also recently found to directly contribute to the impaired pathogen-specific primary CD8 T cell responses (69), which even extended to an impairment in naive CD8 T cells from nonseptic mice transferred into CLP-treated recipients. Interestingly, postsepsis Flt3 ligand (Flt3L) treatment increased the number of DCs and improved DC function, including the ability to sense inflammation and produce cytokine IL-12, leading to improved primary CD8 T cell responses to newly introduced Ag. Thus, a direct link between sepsis-induced deficiencies in T cell–intrinsic and -extrinsic factors has been established, and therapeutic approaches designed to target T cells and support innate cells (such as DCs) at the same time might further benefit the host recovering from the septic incident.

Sepsis and memory T cells: retrograde and anterograde amnesia

Alterations to existing memory T cells. As humans and mice age, their pool of memory T cells expands to become the major population in the total T cell repertoire due (in part) to well-defined age-related changes and a history of pathogen encounters and/or vaccinations (70–73). Although memory CD8 T cells are more resistant to radiation-induced apoptosis than their naive counterparts, the sepsis-induced decline in existing CD8 circulatory memory T cell (T_{circ}) numbers is equal to that observed for the naive CD8 T cell pool (Fig. 2B) (74–78). Interestingly, some data suggest that different subsets of CD8 T_{circ} (e.g., CD62L$^*$CCR7$^*$ “effector” and CD62L$^*$CCR7$^*$ “central memory”) are similarly susceptible to sepsis-induced apoptosis, suggesting a stochastic and/or nondiscriminatory nature of the CD8 T_{circ} decline in septic hosts (V.P. Badovinac, unpublished observations) (74). Similarly, memory CD4 T cells experience a numerical loss following sepsis (35, 79, 80). Proportionally, however, CD4 T cell subsets shift to contain a higher frequency of Foxp3$^*$ regulatory T cells (T_{reg}), due to preferential loss of other subpopulations (e.g., T_{H1}, T_{H2}, T_{H17}, and T follicular helper cells) (35, 80–82). In mouse models, this population shift can be abrogated by the transfer of bone marrow–derived DCs and is associated with decreased PD-1 expression by CD4 T cells (39, 83, 84). Additionally, recent data suggest that IL-33 plays a role in promoting T_{reg} expansion and immunoparalysis up to 15 d postinfection (85). The relevance of this population shift continues to be debated, because contrasting associations have been made based on the timing of analyses, among other considerations (86–90), but the potential for this increased prevalence to impair immunity to new or re-encountered infection remains a possibility.

In both CD4 and CD8 T cells, existing memory populations show impaired Ag-specific expansion and effector functionality in the postseptic environment (Fig. 2) (67, 69, 74, 75, 79). For CD8 T cells, this includes decreased Ag sensitivity (functional avidity) and Ag-driven secondary expansion, directly contributing to the diminished memory CD8 T cell–mediated immunity (“retrograde amnesia”) to bacterial or viral reinfections (75). Moreover, inflammation-induced Ag-independent bystander activation of memory CD8 T cells in response to heterologous infection is also significantly impaired in vivo early after sepsis induction. When analyzed on a per-cell basis, the sensitivity of pre-existing memory CD8 T cells to respond to heterologous infection/cytokine stimulation (as measured by IFN-γ production) is mostly intact (75). Moreover, memory CD8 T cells obtained from a septic animal can respond to secondary Ag stimulation when transferred to a normal (nonseptic) host. Together, these findings suggest that the functional impairments observed in memory CD8 T cell responses are also influenced by the postseptic environment. The nature of the extrinsic factors controlling T cell immunity, the extent to which CD8 T_{circ} numerically recover, and their ability to differentiate into long-term memory CD8 with defined phenotype and function (91, 92) are a metaphoric black box (Fig. 2B) but are critical for our understanding of the sepsis-induced long-lasting impairments that are observed in sepsis survivors.

In contrast to CD8 T_{circ}, CD8 tissue-resident memory T cells (T_{Rm}) are necessary and sufficient (in some cases) to provide robust protection against localized pathogen re-encounter (93–96). Interestingly, in direct contrast to CD8 T_{circ}, the same Ag specificity, CD8 T_{Rm} remain numerically intact after moderate CLP sepsis (74). Moreover, the sensing and alarming functions (e.g., production of IFN-γ in
response to cognate Ag injection or pathogen reinfec-
tion) of CD8 T\textsubscript{TRM} are maintained after sepsis induction (Fig. 3A, 3B) (74, 94). However, sepsis does dramatically change the ability of the host to recruit bystander immune cells (i.e., B cells, Ag-experienced T cells) to sites of localized Ag encounter in response to the CD8 T\textsubscript{TRM}-derived sensing and alarming signals, resulting in increased susceptibility to reinfection (Fig. 3C, 3D) (74). In this setting, local endothelial cells cannot detect T\textsubscript{TRM}-produced IFN-γ and subsequently upregulate CXCL9/10 and VCAM to permit entrance of recruited cells into the infected tissue (74). Thus, sepsis has the capacity to influence the host response to pathogen reinfec-
tion by directly influencing memory CD8 T cell populations (e.g., number and function of CD8 T\textsubscript{TRM}) and/or by preventing other cell types from properly recognizing localized pathogen-induced alarming signals delivered by CD8 T\textsubscript{TRM}. It is yet to be determined to what extent CD4 T\textsubscript{TRM} (compared with CD4 T\textsubscript{CIRC}) are affected by sepsis. Given their differential localization within some tissues (e.g., CD8 T cells reside predominantly in the epidermis, whereas CD4 T cells are preferentially found in the dermis), CD4 T\textsubscript{TRM} may be more affected by sepsis (97, 98).

Memory T cell formation postsepsis. Postsepsis, primary memory T cell formation faces the same environmental conditions that impair the naive T cell pool and existing memory T cell responses, which potentially culminates in T cells exhibiting a type of “anterograde amnesia”: the impaired ability to generate new CD4 and CD8 T cell memory (74). The extent to which sepsis influences naive to memory CD4 and CD8 T cell differentiation in response to acute infections/ vaccinations is unknown and critical for defining immunity in the postseptic environment. However, not all infections encountered will be acute in nature, because chronic/laten
t infection may exist prior to the initiation of sepsis or be established in the postseptic environment.

When considering chronic infection, memory T cell responses acquire functional defects over time as a result of constant stimulation (i.e., T cell “exhaustion”) (5, 6, 99–102). LCMV clone 13 infection of the septic hosts results in exacerbated exhaustion of CD8 T cells (based on increased PD-1 and lymphocyte activation gene-3 [LAG-3] expression and decreased Ag-driven cytokine production) and increased viral burden compared with nonseptic controls (103). Similarly, recent clinical data show reduced polyfunctionality of T cells from patients with CMV reactivation after sepsis (104). CD8 T cells from these patients also exhibited enhanced PD-1 expression, highlighting the relevance of animal models for studying sepsis-induced impairments (103, 104). In contrast to these data, Choi et al. (104) did not observe increased PD-1 or 2B4 on CD4 T cells, and the effect of sepsis on CD4 T cell exhaustion has yet to be evaluated in mouse models; also, the effect of sepsis on previously established chronic viruses has not been modeled. Taken together, this information highlights how sepsis impairs T cell immunity at multiple junctures. However, additional investigation is required to address several biologi-
cally relevant questions regarding how sepsis affects existing memory T cells long-term (Fig. 2B).

Sepsis and nonconventional T cells: in need of an unconventional perspective

We have focused our discussion on the consequences of sepsis on conventional αβ T cells to this point, but we recognize that other T cell populations, both variant and invariant in nature, exist in humans and mice (105–108). Unfortunately, very little is known about these nonconventional T cell sub-
sets in the postseptic environment. Clinically, circulating γδ T cells numerically decline in the postseptic environment (109); however, in contrast to their αβ counterparts, murine γδ T cells (especially Vvγ) accumulate and have increased intracellular IL-17 in the lungs postsepsis (110). Additionally, FOXP3\textsuperscript* Vδ1 T cells are increased in frequency in patients after sepsis (111). The parallel with conventional CD4\textsuperscript* T\textsubscript{reg} reveals an important aspect of nonconventional T cells in sepsis that remains to be studied. Intriguingly, γδ T cells from septic patients stimulated with PMA and ionomycin show a reduced capacity to upregulate CD69 and produce IFN-γ (112), suggesting cell-intrinsic impairment. Thus, it is perti-
nent to understand this impairment, because it is likely dis-
tinct from any changes occurring in αβ T cells and may require different therapeutic strategies to resolve.

Interestingly, NKT cells, a T cell population (often expressing a semi-invariant TCR Vα14i, which recognize lipids and gly-
colipids presented by CD1d) with characteristics of NK and T cells, have shown conflicting results when using different models of sepsis (35, 113, 114). There was no numerical loss of NKT cells in the liver in a burn wound model (114), but a loss in the number and frequency of NKT cells was noted after CLP (35). The timing of these observations may be a deter-
mining factor in the data, because the CLP assessment occurred 20 h postsurgery, whereas the burn wound observation oc-
curred 4 d after burn induction. Our own data show a nu-
merical reduction in NKT cells 2 d after CLP, but they also repre-
sented a larger proportion of lymphocytes in the liver (V.P. Badovinac, unpublished observations). An additional factor to consider is the proximity of the site of evaluation to the naidus of the septic event; the numerical loss of NKT cells in the liver occurred during CLP, an event proximal to the liver, whereas during the burn wound, an event distal to the liver, loss did not occur. The differences in NKT cell frequency in the liver between the two CLP experiments indicate that NKT cell redistribution of these cells may occur following the 20-h time point (35). This would be consistent with the results of Heffernan et al. (113), who clinically observed an increased frequency of circulating NKT cells after sepsis. As such, it is im-
portant to clarify how sepsis may be affecting the distribu-
tion of NKT cells and how this affects host immunity. The recognition of distinct Ag repertoires by αβ T cells and NKT cells/γδ T cells, proteins and glycoproteins/lipids, re-
spectively, represents distinct aspects of immunity whose im-
pairment by sepsis has yet to be understood.

MAIT cells and IELs represent the most understudied T cell populations in sepsis. Circulating MAIT cells numerically decline in patients early after sepsis, although it remains to be de-
termined to what extent this is an apoptosis-induced reduction or relocation as a result of infection (115, 116). IELs have a reduced frequency in the small intestine after CLP, coinciding with an increased frequency of apoptotic IELs (117). The commonality among these subsets is that they largely exist at epithelial surfaces that are often the site of sepsis initiation (116, 118–122). Given the unique distribution and distinct Ag repertoires of these cell subsets, a more thorough num-
beral and functional evaluation in the postseptic environment should be undertaken.
Several commonalities have arisen across all T cell subsets during sepsis, and each, in turn, has been targeted by therapeutic interventions to alleviate sepsis-induced immunoparalysis. These strategies include limiting cell death, expanding the surviving cells, expanding DC populations, and blocking inhibitory ligand expression (e.g., PD-1/PD-L1, CTLA-4, B and T lymphocyte attenuator, T cell membrane protein-3, LAG-3, and 2B4) to allow for cell proper activation (123–126). Limiting cell death by blocking apoptotic pathways was originally approached as a method of reducing the severity of the cytokine storm, induced by various sepsis models, by preventing the release of additional danger-associated molecular patterns (32, 64, 66–68, 127–129). Among the proteins targeted in the apoptosis signaling pathway, caspase inhibition seemed to have great promise when initially investigated. Caspases are involved in the apoptotic process responsible for the loss of lymphoid cells (among the many dying cells found during a septic event) but are also necessary in the response to endotoxin and the processing of cytokines (e.g., IL-1β) into their mature forms (130). As such, a number of approaches have been tested in preclinical models to block apoptosis as a means of ameliorating the progression of sepsis, including the administration of caspase inhibitors to block caspase activation or small interfering RNA to inhibit caspase production (131–133). Unfortunately, the idea of targeting caspases as a sepsis treatment failed to gain traction because of the importance of caspases in a number of other physiological events and the difficulties in delivering inhibitors in sufficient amounts and time frames to have a clinical benefit.

The next strategy, and the most common for T cell impairment, is to drive the expansion of the remaining cells by administration of cytokines that promote T cell survival, proliferation, and/or function (i.e., IL-2, IL-7, and IL-15) (77, 114, 134–137). Additionally, treatment with these cytokines promotes mTOR activation, which is an aspect of oxidative phosphorylation and an important metabolic aspect in the maintenance of memory T cells (60). As a result, treatment with IL-2/7/15 may have the additional benefit of resolving the metabolic deficits of memory T cells imposed by sepsis (55, 60, 138, 139). However, endothelial cells are unable to respond to the IFN-γ signal and upregulate chemokines and adhesion molecules. Consequently, a dramatically reduced number of effector cells is recruited from the circulation, and pathogen clearance is significantly impaired.
after therapy is halted (140). Of the candidate cytokines tested to date, IL-7 seems to be the best tolerated and, importantly, improved host immunity and survival when given to CLP-treated mice that also received a secondary heterologous infection (135, 140). The therapeutic benefit of exogenous IL-7 administration has also been evaluated in parallel clinical trials in the United States (NCT02640807) and France (NCT02797431). The purpose of these double-blinded, placebo-controlled trials was to evaluate the ability of rIL-7 (CYT107) to restore absolute lymphocyte counts in sepsis patients. The United States trials are active but are not accruing patients, whereas the French trials have been terminated. Data describing the outcomes of these studies will likely be published in the near future. Another therapeutic strategy using IL-2/7/15 has been to administer them in tandem with therapies that address other aspects of sepsis-induced impairment. Shindo et al. (125) recently demonstrated that the combination IL-7 and anti–PD-1 mAb, following the two-hit model, yielded improved functionality and IFN-γ production compared to monotherapy. In addition to therapies directly targeting T cells, supportive therapies boosting the recovery of T cell–extrinsic factors should be considered. For example, the administration of Flt3L to expand DC populations would have the 2-fold effect of promoting more effective T cell priming and re-establishing a population of immune cells normally responsible for the production of “signal 3” cytokines (IL-12 and IFN-γ) needed for optimal T cell activation (69). Flt3L therapy has been tested in a number of clinical settings but has not yet been evaluated in sepsis patients. Other potential therapies include administration of chemokines following readmittance to the hospital with secondary infection to assist in the recruitment and migration of T cells to sites of infection in the postseptic environment, such as CXCL9/10 used by Danahy et al. (74). The use of chemokines like CXCL9/10 during secondary infection is meant to overcome impairments as a result of the septic environment and is unlikely to resolve cell-intrinsic defects. In contrast, the production of other chemokines during sepsis may be detrimental during sepsis. Ramonell et al. (141) recently showed that CXCR4 antagonism, which prevented the binding of CXCL12, led to a decrease in sepsis-induced mortality.

The explosion in the use of biologics targeting components of the immune system in the past 15–20 y has given researchers and clinicians another set of powerful reagents to treat a variety of diseases. Among these, immune checkpoint inhibitors have revolutionized the way in which cancer is treated, and checkpoint blockade is also proving to be a means to remove some of the sepsis-imposed limitations on the immune system. A number of publications have reported the increased expression of PD-1, CTLA-4, B and T lymphocyte attenuator, T cell membrane protein-3, LAG-3, and 2B4 on T cells or in the plasma from septic hosts (38, 123, 142–144). Generally speaking, interaction between these immune cell checkpoint receptors and their cognate ligands inhibits T cell function, and it has been hypothesized that such interactions contribute to the immune dysfunction seen during sepsis. Data showing that T cell function is improved (mostly in in vitro assays) with inclusion of mAb to these inhibitory receptors support this hypothesis. For example, disruption of the PD-1/PD-L1 pathway has demonstrated some effect in correcting septic impairment of T cells, including increased CD28 expression and IFN-γ production by CD4 and CD8 T cells, especially when used in combination with immunostimulatory cytokines (39, 125, 137). One important benefit when considering checkpoint blockade in the treatment of sepsis is that a number of mAbs targeting these molecules (i.e., PD-1, PD-L1, and CTLA-4) have been and are currently being evaluated in other clinical (primarily oncology) settings, thus providing a large information base with regard to safety and efficacy. As such, the safety, tolerability, and pharmacokinetic/pharmacodynamic modeling of an anti–PD-L1 mAb was recently evaluated in a phase 1b/2a trial in patients with severe sepsis (NCT02576457). This was a randomized double-blinded placebo-controlled study measuring a variety of clinical and immunological parameters in these patients, but it also gave the investigators the opportunity to determine the therapeutic potential of ameliorating mortality and restoring immune function in these patients after blocking PD-1 signaling. The study was completed in early 2017, but the results of the trial are yet to be made public. Positive findings (i.e., improved survival and/or immune function) could provide an important new means of treating patients with sepsis.

The therapies described in this article have demonstrated success in various preclinical sepsis models, but their clinical potentials are only beginning to be evaluated. Most (if not all) sepsis therapeutics targeting the immune system have generally not been as effective in the clinical setting as in preclinical models, but the positive preliminary reports coming from trials testing IL-7 and checkpoint inhibitors may be reversing this negative trend (123, 145). A number of reasons for the limited clinical effect in the past have been posited, but the complex etiology of sepsis and range of immunological impairments observed suggest the possibility that monotherapy targeting a single cell type or pathway is unlikely to be effective. Rather, integrative therapeutic strategies that engage multiple aspects of T cell biology are more likely to benefit most patients. However, understanding how sepsis affects other arms of the immune system, for their distinct and T cell supportive roles, is crucial to developing strategies to reverse immunoparalysis.

Conclusions

The massive attrition of lymphocytes during sepsis has detrimental effects on multiple aspects of T cell immunity. In addition to the sepsis-induced T cell apoptosis, most of the remaining T cells exhibit prolonged functional impairment. This impairment is multifactorial and is driven by cell-intrinsic and -extrinsic factors. Many of the impairments highlighted throughout this review indicate that T cell–extrinsic impairments are a major factor in impaired T cell immunity. Additionally, although several intrinsic changes occur, including altered TCR repertoires and increased inhibitory receptor expression, much remains to be understood about the extent to which/how sepsis affects TCR signaling. Further, an understanding of the effect of sepsis on T cell metabolic activity is likely to reveal important aspects about how functional impairment manifests in these cells.

Other questions regarding the effect of sepsis on T cell immunity have been partially answered in CD4 or CD8 T cells but not both. The distinctions between CD4 and CD8 T cells are important, because impairment of functional and
interdependent mechanisms of these T cells will shape our understanding of how sepsis affects T cell immunity. To complicate this further, many of these evaluations are completely lacking for nonconventional T cell subsets. Finally, the question of resolving the sepsis-induced quantitative and/or qualitative changes in T cells is becoming more investigated as the mechanisms responsible for suboptimal T cell immunity in the septic host are being better defined. Given the variety and nature of the impairments observed in the postseptic environment, it would seem that therapeutic strategies that bolster multiple aspects of T cell immunity would best alleviate the sepsis-induced immunomodulation. Yet, some underlying T cell–intrinsic impairments may remain. As such, further interpretation into how sepsis affects the inherent functionality of T cells is required if this is to be overcome. Improved knowledge of T cell biology is driving the development of new therapies for clinical settings in which the number and/or function of T cells is abnormal, and many of these new drugs have the potential for use across multiple disease platforms (e.g., use of checkpoint inhibitors for improved T cell activity in cancer or sepsis patients). We can only hope that the exciting advances being made with regard to immune system in cancer or sepsis patients). We can only hope that the ex-

References


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