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Sepsis induced T cell immunoparalysis: the ins and outs of impaired T cell immunity[1]

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Abstract

Sepsis results in a deluge of both pro- and anti-inflammatory cytokines leading to lymphopenia and chronic immunoparalysis. Sepsis induced long-lasting immunoparalysis is, in part, defined by impaired CD4 and CD8 αβ T cell responses in the post-septic environment. The dysfunction in T cell immunity affects naïve, effector, and memory T cells, and is not restricted to classical αβ T cells. While the 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 both classical and non-classical T cell subsets and discuss current therapeutic approaches being developed to boost the recovery of T cell immunity post sepsis induction.

Introduction

Sepsis is characterized by an exaggerated host response, involving both 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 (>$20B/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

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sepsis-induced cytokine storm as the mortality rate is currently ~25% (compared to ~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-year survival compared to control cohorts (4–6). This inability to mount/support effective immune responses is termed immunoparalysis, and while 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 make 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 utilization 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 (SPF) mice have an immune system resembling that of newborn infants, due to limited history of pathogen exposures (11–13). In contrast, use of ‘dirty mice’ (i.e., mice purchased from pet stores or inbred mice co-housed 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). While ‘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, IV bacterial injection, pneumonia, fecal slurry injection, colon ascendens stent peritonitis (CASP), and cecal ligation and puncture (CLP) to induce polymicrobial sepsis (14–20). TLR agonist models elicit different inflammatory profiles between mice and human; however, they do elicit cell loss similar to other sepsis models (7, 21). Additionally, ‘two-hit’ models have been approached 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 (22–26).

While there is debate regarding the utility 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 (15, 27–31). Here, 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 naïve, effector, and memory αβ T cells (defined in Figure 1) with a brief discussion of non-classical T cell subsets (i.e. γδ, NKT, MAIT, and IEL), and a description of current therapeutic strategies

being evaluated for accelerating the numerical and/or functional recovery of T cells in the survivors of sepsis.

Sepsis and naïve T cells: The Mandela Effect and a “hole” other repertoire

Sepsis-induced lymphopenia invariably affects the naïve, ‘antigen (Ag)-inexperienced’ T cell pool in humans and experimental mouse models. In SPF mice, naïve T cells remaining in the periphery after the 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: $CD8\alpha^{lo}CD11a^{hi}$; CD4 T cells: $CD44^{hi}CD11a^{hi}CD49d^{hi}$) and even effector functionality (Figure 2A), in a potentially Ag-independent manner (32, 33). Although numerical recovery of T cells in sepsis survivors can occur in thymectimized animals, sepsis also reduces the number of newly generated naïve T cells by affecting thymic output (32, 34–36). In addition, homeostatic proliferation in the lymphopenic environment likely selects those T cell specificities with the highest precursor frequencies resulting in “holes” in the naïve T cell compartment and an inability to mount effective primary T cell responses to particular Ag/pathogens (Figure 2A) (33, 37). With these issues in mind, the likelihood of fully regenerating a diverse naïve T cell pool becomes doubtful. This is especially true for elderly septic patients whose naïve T cell pool represent only a small portion of their total T cell repertoire (35, 38). In addition to a changing composition of the T cell compartment, sepsis increases inhibitory receptor (e.g. 2B4 and PD-1) expression on surviving naïve T cells (in both human and animal models), which can be associated with increased mortality (39, 40). 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) (32, 33). The full extent of the intrinsic impairments in naïve T cells that occur as a result of sepsis, however, is not known or well defined. This could include reduced responsiveness to TCR stimulation, changes in co-stimulatory molecule expression, cytokine responsiveness, and even metabolic functionality. As such, sepsis-induced changes within the naïve T cell repertoire have the potential to lead to lackluster effector and memory T cell generation or even inappropriately tolerizing to some Ag.

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

Effector T cell function in the post-septic environment can be viewed in response to the pathogen(s) that precipitated the 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 the changes in composition of T cell compartment, in a host recovering from the CLP-induced sepsis (Figure 2A). Using inbred C57Bl/6 (B6) mice obtained from different vendors naturally colonized or devoid of commensal segmented filamentous bacteria (SFB), Cabrera-Perez et al. demonstrated acquisition of a memory phenotype and proliferative expansion of SFB-specific CD4 T cells in mice undergoing CLP with SFB as a part of gut microbiome (41). Intriguingly, no such

Ag-specific responses have been observed for CD8 T cells. Whether Ag-specific responses to microbial commensals are restricted to CD4 T cells or not, a response to gut-resident commensals may skew host immunity long-term as a result of immune-mediated dysbiosis at epithelial surfaces (42, 43). This immune-mediated dysbiosis may in part result in the sepsis associated 'pathobiome' which develops in patients (44–46), which is subsequently associated with an elevated inflammatory state of the host and has the capacity to impact T cell response to Ag (47). In the case of intestinal dysbiosis, this can affect nutrient acquisition and an individual's long-term health (48). Additionally, chronically elevated local inflammation, because of inappropriate responses to gut commensals, can lead to increased barrier permeability that may potentiate another septic event as a result of bacterial translocation (43, 48–52). This represents a seemingly paradoxical outcome where functional normalcy of a T cell response may be detrimental or have long-lasting effects in modulating the composition of CD4 and CD8 T cells in the post-septic environment.

Effector T cell responses to newly introduced pathogens will be influenced by the status of the host post-sepsis. The reduced number of naïve Ag-specific T cell precursors early after sepsis induction will contribute to suboptimal generation of primary effector T cells; however, the extent to which T cell intrinsic impairments further compromise effective T cell immunity (even in scenarios when numerical recovery is achieved) are currently ill defined. Interestingly, Markwart et al. did not observe TCR signaling defects in naïve T cells following CD3/CD28 stimulation in a TLR agonist injection mouse model (53). In fact, Borken et al. 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 (54). These data suggest 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 (DC) (55). Additionally, changes in the metabolic state of T cells impair their capacity to expand and perform effector function (56–58), and sepsis affects the metabolism of a variety of cells, including T cells (59–62). These metabolic changes likely have a direct association with the impaired accumulation and decreased functionality of T cells *in vivo* in the post-septic environment and will require further interrogation (Figure 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 are likely to be a focus of future studies.

Under normal conditions, the priming of naïve 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 naïve 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 (63–65). The instructional programming that occurs within CD8 T cells helped by CD4 T cells prevents TNF-related apoptosis-inducing ligand (TRAIL)-mediated activation-induced cell death of the CD8 T cells (66, 67). The numerical and functional deficits in CD4 T cells during sepsis creates 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 sepsis impairs T cell effector responses during early immunoparalysis state (in part) in a TRAIL-dependent

manner (68–70). 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 (69).

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 (71), which even extended to an impairment in naïve CD8 T cells from non-septic mice transferred into CLP-treated recipients. Interestingly, post-sepsis 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 both T cells and supporting innate cells (such as DC) 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 (72–75). Although memory CD8 T cells are more resistant to radiation-induced apoptosis than their naïve counterparts, a sepsis-induced decline in existing circulatory memory (T_{CIRCM}) CD8 T cell numbers are equal to those observed for the naïve CD8 T cell pool (Figure 2B) (76–80). Interestingly, some data suggest different subsets of CD8 T_{CIRCM} (e.g. $CD62L^{-}CCR7^{-}$ ‘effector’ and $CD62L^{+}CCR7^{+}$ ‘central memory’) are similarly susceptible to sepsis-induced apoptosis suggesting a stochastic and/or non-discriminatory nature of CD8 T_{CIRCM} decline in septic hosts (VPB unpublished data and (76)). Similarly, memory CD4 T cells experience a numerical loss following sepsis (36, 81, 82). Proportionally, however, CD4 T cell subsets shift to a higher frequency of $FoxP3^{+}$ regulatory T (T_{reg}) cells, due to preferential loss of other subpopulations (e.g. T_H1, T_H2, T_H17, and T_{FH}) (36, 82–84). In mouse models this population shift can be abrogated by the transfer of BMDC and is associated with decreased PD-1 expression by CD4 T cells (40, 85, 86). Additionally, recent data suggest IL-33 plays a role in promoting T_{reg} expansion and immunoparalysis up to 15 d post-infection (87). The relevance of this population shift continues to be debated as contrasting associations have been made based on timing of analyses, among other considerations (88–92). But the potential for this increased prevalence to impair immunity to new or re-encountered infection remains open.

In both CD4 and CD8 T cells, existing memory shows impaired Ag-specific expansion and effector functionality in the post-septic environment (Figure 2) (69, 71, 76, 77, 81). 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 re-infections (77). 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 (as measured by IFN-γ production) to heterologous infection/cytokine stimulation are mainly intact (77). Moreover, memory CD8 T cells obtained from a septic animal can respond to secondary Ag-stimulation when transferred to a normal (non-septic) host. Together, these findings suggest the functional impairments observed in memory CD8 T cell responses are also influenced by the post-septic environment. The nature of the extrinsic factors controlling T cell immunity, the extent to which CD8 T_{CIRCM} numerically recover and their ability to differentiate into long-term memory CD8 with defined phenotype and function (93, 94) are, though, a metaphoric black box (Figure 2B), but critical for our understanding of sepsis-induced long-lasting impairments observed in sepsis survivors.

In contrast to CD8 T_{CIRCM}, tissue resident memory CD8 (T_{RM}) T cells are necessary and sufficient (in some cases) to provide robust protection to localized pathogen re-encounter (95–98). Interestingly, in direct contrast to CD8 T_{CIRCM} of the same Ag-specificity, CD8 T_{RM} remain numerically intact after moderate CLP sepsis (76). Moreover, the sensing and alarming functions (e.g., production of IFN-γ in response to cognate Ag injection or pathogen re-infection) of CD8 T_{RM} are maintained after sepsis induction (Figure 3A–B) (76, 96). Sepsis does, however, 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_{RM}–derived sensing and alarming signals, resulting in increased susceptibility to re-infection (Figure 3C–D) (76). In this setting, local endothelial cells cannot detect T_{RM}-produced IFN-γ and subsequently upregulate CXCL9/10 and VCAM to permit entrance of recruited cells into the infected tissue (76). Thus, sepsis has the capacity to influence the host response to pathogen re-infection either by directly influencing memory CD8 T cell populations (e.g. number and function of CD8 T_{CIRCM}) and/or by preventing other cell types from properly recognizing localized pathogen-induced alarming signals delivered by CD8 T_{RM}. It is yet to be determined to what extent CD4 T_{RM} (compared to CD4 T_{CIRCM}) are affected by sepsis. Given their differential localization within some tissues (e.g., CD8 T cells reside predominately in the epidermis while CD4 T cells are preferentially in the dermis), CD4 T_{RM} may be more affected by sepsis (99, 100).

Memory T cell formation post-sepsis

Post-sepsis primary memory T cell formation faces the same environmental conditions that impair the naïve 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 (76). The extent to which sepsis influences naïve to memory CD4 and CD8 T cell differentiation in response to acute infections/vaccinations is unknown and critical for defining immunity in post-septic environment. However, not all infections encountered will be acute in nature as chronic/latent infection may exist prior to the initiation of sepsis or established in the post-septic 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, 101–104). LCMV clone 13 infection of the septic hosts results in exacerbated exhaustion of CD8 T

cells (based on increased PD-1 and LAG-3 expression and decreased Ag-driven cytokine production) and increased viral burden compared to non-septic controls (105). Similarly, recent clinical data show reduced poly-functionality of T cells from patients with CMV reactivation after sepsis (106). CD8 T cells from these patients also exhibited enhanced PD-1 expression, highlighting the relevance of animal models for studying sepsis-induced impairments (105, 106). In contrast to these data, Choi et al. did not observe increased PD-1 and 2B4 on CD4 T cells and the effect of sepsis on CD4 T cell exhaustion has yet to be evaluated in mouse models (106), nor has the effect of sepsis on previously established chronic viruses been modeled. Taken together, this information highlights how sepsis impairs T cell immunity at multiple junctures. However, additional investigation is required to address several biologically relevant questions regarding how sepsis affects existing memory T cells long-term (Figure 2B).

Sepsis and non-conventional 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 other T cell populations, both variant and invariant in nature, exist in humans and mice (107–110). Unfortunately, very little is known about these non-conventional T cell subsets in the post-septic environment. Clinically, circulating γδ T cells numerically decline in the post-septic environment (111); however, in contrast to their αβ counterparts, murine γδ T cells (especially Vγ4) accumulate and have increased intracellular IL-17 in the lungs post-sepsis (112). Additionally, $FoxP3^+$ Vδ1 T cells are increased in frequency in patients after sepsis (113). The parallel with conventional $CD4^+$ T_{reg} reveals an important aspect of non-conventional T cells in sepsis that remains to be studied. Intriguingly, γδ T cells from septic patients stimulated with PMA and Ionomycin show reduced capacity to upregulate CD69 and produce IFN-γ (114), suggesting cell intrinsic impairment. Thus, it is pertinent to understand this impairment as it is likely distinct 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 glycolipids presented by CD1d) with characteristics of both natural killer and T cells, have shown conflicting results when using different models of sepsis (36, 115, 116). There was no numerical loss of NKT cells in the liver in a burn wound model (116), but a loss in both the number and frequency of NKT cells was noted after CLP (36). The timing of these observations may be a determining factor in the data, as the CLP assessment occurred 20 h post-surgery while the burn wound observation occurred 4 days after burn induction. Our own data show a numerical reduction of NKT cells two days after CLP, but they also represented a larger proportion of lymphocytes in the liver (VPB unpublished observation). An additional factor to consider is the proximity of the site of evaluation to the nidus of the septic event, as the numerical loss of NKT cells in the liver occurred during CLP – an event proximal to the liver, while the burn wound – an event distal to the liver – did not. The differences in NKT cell frequency in the liver between the two CLP experiments indicates that NKT cell redistribution of these cells may occur following

the 20 h time point (36). This would be consistent with the results of Heffernan et al., who clinically observed an increased frequency of circulating NKT cells after sepsis (115). As such it is important to clarify how sepsis may be affecting the distribution 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, respectively, present distinct aspects of immunity whose impairment by sepsis has yet to be understood.

Mucosal associated invariant T cells (MAITs) and intraepithelial lymphocytes (IELs) represent the most understudied T cell populations in sepsis. Circulating MAITs numerically decline in patients early after sepsis, though it remains to be determined to what extent this is apoptosis-induced reduction or relocation as a result of infection (117, 118). IELs have a reduced frequency in the small intestine after CLP, coinciding with an increased frequency of apoptotic IELs (119). The commonality among these subsets is that they largely exist at epithelial surfaces which are often the site of sepsis initiation (118, 120–124). Given the unique distribution and distinct Ag repertoires of these cell subsets a more thorough numerical and functional evaluation in the post-septic environment should be approached.

Sepsis and immune targeting therapies: Making more and making them better

Several commonalities have arisen across all T cell subsets during sepsis, and each in turn have 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 (BTLA), T cell Membrane Protein-3 (TIM-3), Lymphocyte Activation-Gene-3 (LAG-3), and 2B4] to allow for cell proper activation (125–128). 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 (33, 66, 68–70, 129–131). 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 processing of cytokines (e.g., IL-1β) into their mature forms (132). 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 siRNA to inhibit the caspase production (133–135). 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 timeframes to have a clinical benefit.

The next strategy, and 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 – namely, IL-2, IL-7, and IL-15 (79, 116, 136–139). 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 (62). 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 (57, 62, 140, 141). However, T cell expansion induced by these cytokines in a post-septic host is generally reduced relative to non-septic mice (62, 79, 137), suggesting a cell intrinsic impairment(s) exists and cytokine administration may only result in expansion of a functionally impaired population. Additionally, lymphocyte numbers typically drop after therapy is halted (142). 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 (137, 142). The therapeutic benefit of exogenous IL-7 administration has also been evaluated in parallel clinical trials in the U.S. (NCT02640807) and France (NCT02797431). The purpose of these double-blinded, placebo-controlled trials was to evaluate the ability of recombinant IL-7 (CYT107) to restore absolute lymphocyte counts in sepsis patients. These U.S. and French trials are active, but not accruing patients, or have been terminated, respectively. 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 which address other aspects of sepsis induced impairment. Shindo et al. recently demonstrated the combination IL-7 and anti-PD-1 mAb, following the two-hit model, yielded improved functionality, IFN-γ production, over monotherapy (127). In addition to therapies directly targeting T cells, additional 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 twofold 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 (71). Flt3L therapy has been tested in a number of clinical settings, but has yet been evaluated in sepsis patients. Other potential therapies include administration of chemokines following re-admittance with secondary infection to assist in the recruitment and migration of T cells to sites of infection in the post-septic environment, such as the CXCL9/10 used by Danahy et al. (76). 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, production of other chemokines during sepsis may be detrimental during sepsis. Ramonell and colleagues recently showed CXCR4 antagonism, which prevented the binding of CXCL12, lead to a decrease in sepsis-induced mortality (143).

The explosion in the past 15–20 years in the use of biologics targeting components of the immune system 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 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, BTLA, TIM-3, LAG-3, and 2B4 on T cells or in the plasma from septic hosts (39, 125, 144–146). Generally speaking, interaction among these immune cell checkpoint receptors with their cognate ligands inhibits T cell function, and it has been hypothesized such interactions contribute to the immune

dysfunction seen during sepsis. Data showing 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 both CD4 and CD8 T cells – especially when used in combination with immunostimulatory cytokines (40, 127, 139). One important benefit when considering checkpoint blockade in the treatment of sepsis is that a number of mAb 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 in regard to safety and efficacy. As such, the safety, tolerability, and PK/PD 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 here 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 (125, 147). 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 both 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 also exhibit prolonged functional impairment. This impairment is multifactorial driven by both cell intrinsic and extrinsic factors. Many of the impairments highlighted throughout this review indicate T cell-extrinsic impairments being a major factor in impaired T cell immunity. Additionally, while 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 either CD4 or CD8 T cells but not both. The distinctions between CD4 and CD8

T cells are important as impairment of functional and interdependent mechanisms of these T cells will shape our understanding of how sepsis affects T cell immunity. To compound this further many of these evaluations are completely lacking for non-conventional 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 post-septic environment, it would seem the therapeutic strategies that bolster multiple aspects of T cell immunity would best alleviate the sepsis-induced immunoparalysis. Yet, some underlying T cell-intrinsic impairments may remain. As such further interrogation 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 where 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 the exciting advances being made now in regard to immune system knowledge and manipulation will only be the beginning of a wave of future findings to expand our arsenal of weapons used in our fight against sepsis.

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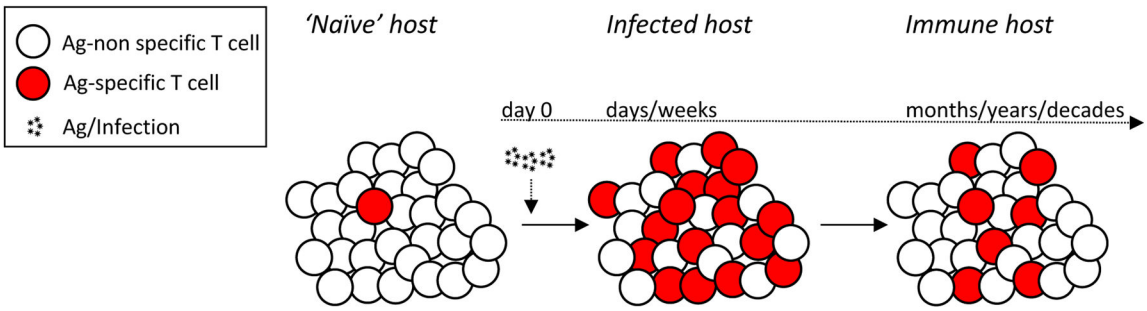

Ag-specific T cell	**Naive**	**Effector**	**Memory[1]**
Numbers	+	+++	++
Persistence/survival	+++	+	+++
Proliferation capacity	+++	+/-	++
Effector functions	+/-	+++	+++
Protection	+/-	+++	+++

Figure 1. Naïve, effector, and memory T cells generated after acute infection/vaccination

Naïve T cells, of a given Ag-specificity, exist at low numbers with minimal on-per-cell basis functionality and protective capacity. They are long-lived cells able to vigorously proliferate upon cognate Ag-stimulation, generating a sizable effector pool with ample functionality (cytotoxicity and cytokine production) and protective capacity. However, the vast majority of effector T cells have a limited life-span with diminished Ag-driven proliferative capacity. Those effector T cells that survive the contraction phase will form a long-lived memory T cell pool maintaining their effector functionality and protective capability.

[1]Of note - memory T cells represent a heterogeneous population of cells with defined phenotype, function, and localization that constantly changes with time after initial antigen encounter (93, 94). It is interesting to posit that memory T cell subsets might have differential susceptibility to sepsis-induced apoptosis and ability to recover in numbers and function in post-septic environment.

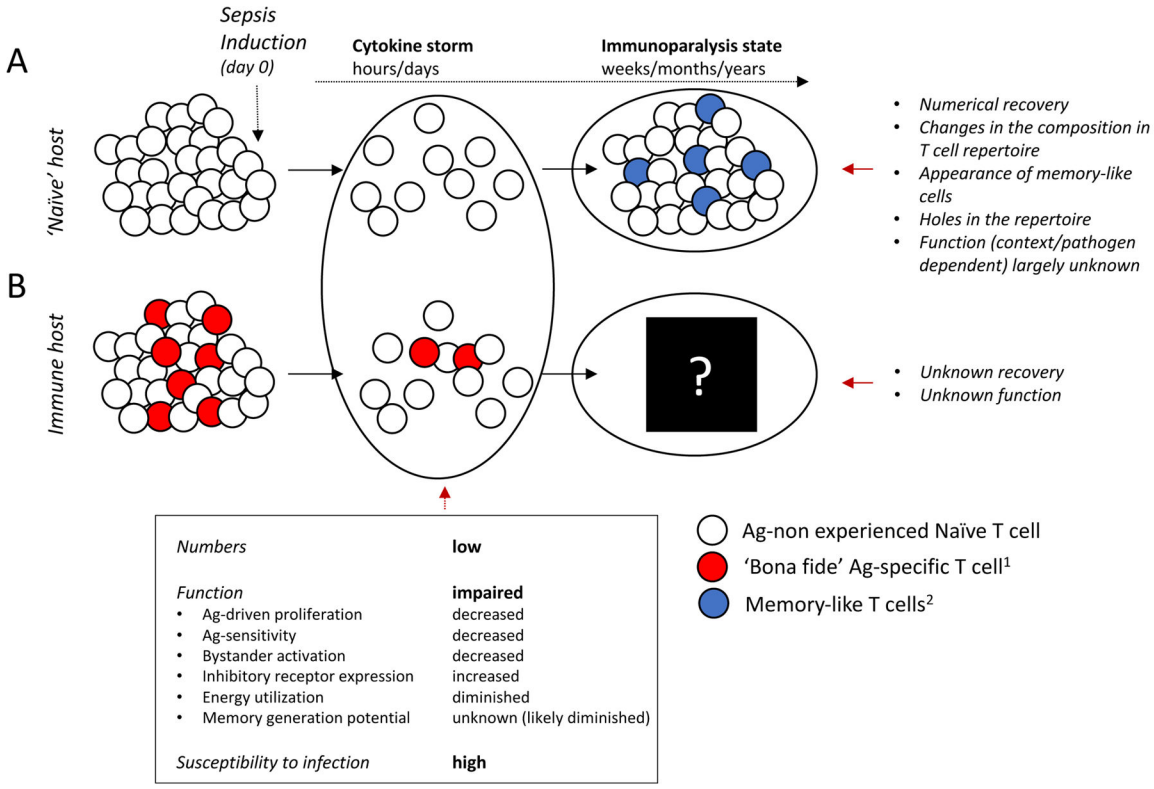

Figure 2. Sepsis-induced changes in naïve and memory T cells

Sepsis induces rapid and vigorous apoptosis of **A)** naïve (Ag-non experienced CD11a^{low}/CD8α^{high} CD8 or CD11a^{low}/CD49d^{low} CD4 T cells) T cells creating a lymphopenic environment supporting homeostatic proliferation (HP) of T cells that survive early 'cytokine storm' phase of sepsis. As a consequence of HP and in response to microbes that evoke sepsis, numerical recovery of 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, making their subsequent T cell responses to newly encountered pathogens potentially impaired. Similarly, **B)** pre-existing memory T cells (here, 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 currently unknown but critical for our understanding of the sepsis-induced long-lasting immunoparalysis state. Of note, naïve 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 both populations of CD4 and CD8 T cells simultaneously present.

[1]Memory T cell responses of defined Ag-specificity generated after primary infection and/or vaccination that exist prior to septic insult;

[2]Memory-like cells (defined as CD11a^{high}/CD8α^{low} CD8 or CD11a^{high}/CD49d^{high} CD4 T cells) are those which acquire memory characteristics as a result of the septic event and potentially include both Ag-independent (HP) and Ag-dependent (pathogens that induce sepsis) T cell responses.

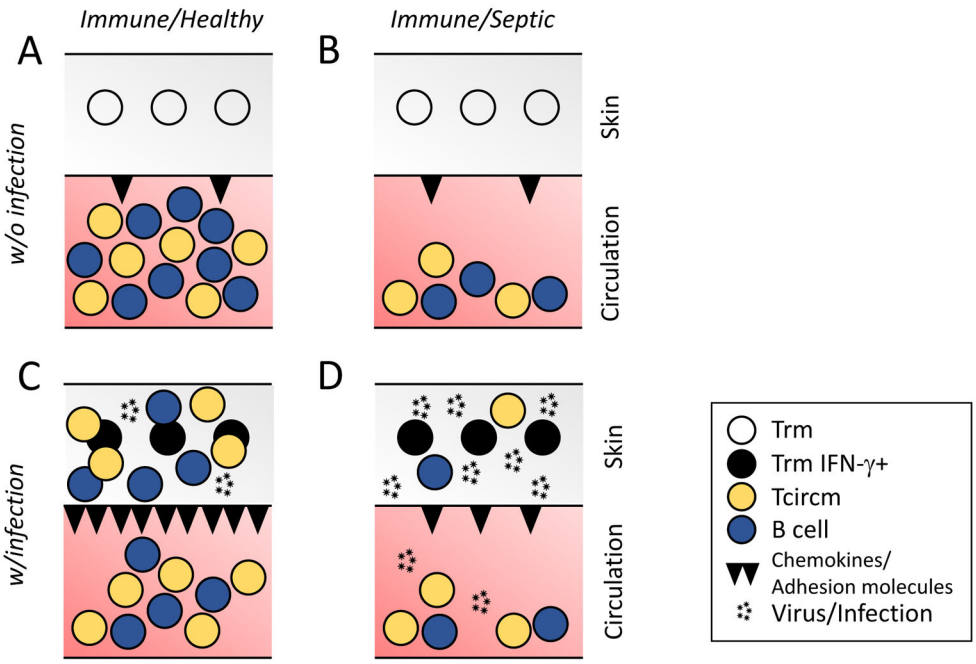

Figure 3. CD8 T cell-mediated immunity to localized re-infection diminished after sepsis in a multifactorial manner

A) Tissue resident memory CD8 T cells (T_{RM}) and circulating memory (T_{CIRCM}) CD8 T and B cells are evoked upon primary infection/immunization. **B)** 'Moderate' sepsis (that leads to 90%+ long-term survival) induces dramatic numerical loss of circulating but not resident CD8 T cell populations. **C)** Localized pathogen re-infection (or cognate Ag-encounter) of the healthy host induces the 'sensing and alarm' function of T_{RM}. As a consequence, the IFN-γ produced by T_{RM} acts on the local endothelium to upregulate chemokines and adhesion molecules (e.g., CXCL9 and VCAM1, respectively) promoting the influx of memory T and B cells from circulation and facilitating clearance of the pathogen *in situ*. **D) '**Moderate' sepsis does not significantly impact the number and/or function of pre-existing T_{RM} responding to pathogen re-infection. However, endothelial cells are unable to respond to the IFN-γ signal and upregulate chemokines and adhesion molecules. Consequently, there is a dramatically reduced number of effector cells recruited from the circulation and pathogen clearance is significantly impaired.