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Clinical and Experimental Sepsis Impairs CD8 T-Cell-Mediated Immunity

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Abstract

Septic patients experience chronic immunosuppression resulting in enhanced susceptibility to infections normally controlled by T cells. Clinical research on septic patients has shown increased apoptosis and reduced total numbers of CD4 and CD8 T cells, suggesting contributing mechanism driving immunosuppression. Experimental models of sepsis, including cecal ligation and puncture, reverse translated this clinical observation to facilitate hypothesis-driven research and allow the use of an array of experimental tools to probe the impact of sepsis on T-cell immunity. In addition to numerical loss, sepsis functionally impairs the antigen-driven proliferative capacity and effector functions of CD4 and CD8 T cells. Sepsis-induced impairments in both the quantity and quality of T cells results in reduced protective capacity and increased susceptibility of mice to new or previously encountered infections. Therefore, the combined efforts of clinical and experimental sepsis research have begun to elucidate the impact of sepsis on T-cell-mediated immunity and potential T-cell-intrinsic and -extrinsic mechanisms driving chronic immunosuppression. Future work will explore the impact of sepsis on the recently appreciated tissue-resident memory (T_{RM}) T cells, which provide robust protection against localized infections, and dendritic cells, which are needed to activate T cells and promote effective T-cell responses.

Keywords

sepsis; CD4 and CD8 T cells; apoptosis; circulatory and tissue-resident memory; cecal ligation and puncture; dendritic cells

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I. INTRODUCTION

Sepsis is the result of an exaggerated immune response to a systemic infection that leads to damage or death of the host. Recent population-level studies have estimated the global burden of sepsis to be 31.5 million cases annually, with a death toll of 5.3 million individuals.[1] In the United States, hospitalizations due to sepsis accounted for over $20 billion in total healthcare costs in 2007.[2] A study investigating readmission rates of academic medical center-affiliated hospitals in the United States found that 20% of patients diagnosed with severe sepsis were readmitted to the hospital within 30 days of discharge, with over 60% of these readmissions due to secondary infection.[3] The outcome of these studies, coupled with increases in the incidence of sepsis, underscore the need for further investigation into the possible deficits of T-cell-mediated immunity that lead to increased susceptibility to infection after a septic event.[4]

A variety of immunologic insults have the potential to precipitate a septic event. Pulmonary infections are the most common site of primary infection, whereas infections of the abdomen (e.g., those arising from a perforated or ischemic bowel), soft tissues, and the urinary tract are also common primary infection loci in adult septic patients.[5,6] Causative microorganisms include both gram-positive (*Staphylococcus aureus* and *Streptococcus pneumoniae*) and gram-negative bacteria (*Escherichia coli* and *Klebsiella* species), with some patients experiencing polymicrobial infections.[7] In addition, the number of sepsis cases caused by fungal organisms has increased substantially.[8] However, as noted in a recent study, a pathogen may be unable to be isolated and identified in up to 30% of septic patients.[9] The pathogen-specific biology of sepsis is an important parameter that influences host responses after a septic event, as well the efficacy of therapeutic interventions. This idea is highly relevant to the study of the immune system and to T-cell responses in particular.

After the initial septic insult, the immune system simultaneously produces both pro-inflammatory and anti-inflammatory cytokines, resulting in a “cytokine storm.”[10] Although both pro-inflammatory and anti-inflammatory mediators are present, the pro-inflammatory response, hallmarked by increased levels of tumor necrosis factor-alpha (TNF-α) and interleukin 1-beta (IL-1β) in the serum of septic patients, is predominant very early after a septic event.[10–12] This increase in pro-inflammatory cytokines leads to increased gene expression of inducible nitric oxide synthase (iNOS), type II phospholipase (PLA_2), and cyclooxygenase-2 (COX-2), which produce NO, leukotrienes, and prostanoids.[13,14] Depending on the health status of the host, the systemic effects of these pro-inflammatory cytokines and their small-molecule mediators may result in the manifestation of early clinical signs such as hypotension, shock, fever, and death.[10,13,14]

Septic patients that survive the initial phase dominated by pro-inflammatory mediators transition to a state of immunoparalysis and have increased susceptibility to opportunistic secondary infections.[15–19] In addition to secondary infections, a high frequency of septic patients experience reactivation of latent viral infections such as cytomegalovirus (CMV), as detected by viral copy number in the plasma, or herpes simplex virus (HSV), as detected by HSV nuclear inclusions from pulmonary samples.[17,20,21] Furthermore, sepsis survivors have an increased risk of death from non-septic events that extends 5 years beyond the initial

septic insult, suggesting that septic patients suffer from long-term impairments.[22] Despite these prolonged deficits, studies investigating the long-term consequences of a septic event in survivors are lacking.

Opportunistic secondary infections and viral reactivation indicate that septic patients may have a defect in T-cell-mediated immunity. T cells are divided into conventional CD4 and CD8 populations and provide important regulatory and effector immune functions during infection. The composition of the naive pathogen-specific CD8 T-cell repertoire is important in both the clearance of infection and the generation of memory CD8 T cells in response to infection and/or vaccination. Upon interaction with their cognate antigen (Ag) in the presence of co-stimulatory molecules and appropriate cytokines, naive Ag-specific CD8 T cells undergo vigorous proliferative expansion in numbers (Fig. 1A, model).[23–25] This expanding pool gains effector functions characterized by the production of cytokines [e.g., interferon-gamma (IFN-γ) and TNF-α] and the ability to lyse infected host cells, thus providing the host with increased protection from the pathogen.[25–29] Depending on the type of pathogen and pathogen biology, the peak number of Ag-specific effector CD8 T cells is achieved days to weeks after the initial infection. At this point, 95–98% of the expanded pool of Ag-specific CD8 T cells is eliminated during the programmed contraction (death) phase, with the surviving fraction encompassing a memory CD8 T-cell population with a protective capacity upon Ag re-encounter (re-infection) that depends on both the quantity and functional fitness of the CD8 T cell memory pool.[25,30–34] These long-lived memory CD8 T cells undergo proliferative expansion upon pathogen re-encounter and provide increased protection after re-infection (Fig. 1B).[25,35,36]

After recognition of cognate Ag expressed by antigen-presenting cells (APCs), naive CD4 T cells are polarized to different phenotypes [T-helper 1 (Th1), Th2, Th17, regulatory T cells (T_{reg})] in part due to environmental cytokines.[37–43] Th1 CD4 T cells serve important roles in the activation of cytotoxic CD8 T cells and the formation of memory CD8 T cells via IL-2 secretion.[44–49] Th2 CD4 T cells mediate class switching of B cells via the production of IL-4 and IL-5.[43,50,51] Th17 CD4 T cells, which are effector CD4 T cells that produce IL-17, IL-22, and TNF-α, are important in immunity to extracellular fungal and bacterial pathogens (especially at mucosal surfaces[52]) through the recruitment and activation of neutrophils.[53] T_{reg} play a vital role in the maintenance of immune homeostasis, serving to limit host immune responses after infection to prevent host tissue damage.[54] Due to the importance of T cells in controlling and eradicating infection, further examination into the impact of sepsis on the number, phenotype, and function of T cells is clearly warranted.

II. CLINICAL SEPSIS INDUCES T-CELL APOPTOSIS

Apoptosis, or programmed cell death, is important in the development and homeostasis of the immune system; however, it also plays a detrimental role in disease pathology, with septic patients showing increased presence of apoptotic lymphocytes in the spleen.[55–58] *Post mortem* samples of septic intensive care unit patients within 90 minutes of death show increased signs of apoptosis (pyknosis and karyorrhexis) compared with critically ill, non-septic controls.[57] In addition, immunohistochemistry stains from septic patients demonstrate increased levels of activated caspase 3, a protease in the common apoptotic pathway,

compared with non-septic patients.[57–59] An increase in apoptotic markers has also been observed in the spleens of pediatric patients, suggesting that lymphocyte apoptosis during sepsis is a universal phenomenon.[60]

Increased frequency of apoptotic CD4 and CD8 T cells has also been detected in the peripheral blood of septic patients, which corresponds to persistent lymphopenia, compared with other non-septic, critically ill patients.[61,62] Furthermore, T cells isolated from septic patients had increased levels of caspase 8 and caspase 9, suggesting that apoptosis of blood lymphocytes associated with sepsis occurs by both intrinsic and extrinsic apoptotic pathways.[62] In addition to observing increased apoptosis of CD4 and CD8 T cells in septic patients, Weber et al. found that septic patients have increased expression of mRNA encoding for the pro-apoptotic proteins Bim, Bid, and Bak in the peripheral blood and down-regulate the anti-apoptotic protein Bcl-2 in CD4 T cells of the blood compared with their non-septic, critically ill counterparts.[63] The apoptosis of T cells and increased expression of mRNA encoding pro-apoptotic proteins in septic patients is consistent with the state of chronic immune suppression after a septic event and suggests a possible mechanism for the observed susceptibility to opportunistic secondary infections and the reactivation of latent viral infections in sepsis survivors.

III. EXPERIMENTAL SEPSIS MODELS FACILITATE HYPOTHESIS-DRIVEN RESEARCH

Clinical observations of septic patients with enhanced T-cell apoptosis and chronic immunosuppression offers valuable insight to how sepsis impairs T-cell-mediated immunity. However, limiting factors of hypothesis-driven research in humans, including biological heterogeneity and imperfect control cohorts, has led to the necessity of an experimental sepsis model. Cecal ligation and puncture (CLP) represents a widely used model of polymicrobial sepsis that induces T-cell apoptosis. This model has many advantages, such as controllable sepsis severity by adjusting cecal ligation length and/or number of punctures,[64,65] and, analogous to clinical scenarios, CLP mice receiving fluid resuscitation or broad-spectrum antibiotics have improved prognosis.[66,67] With clinical observations of T-cell apoptosis during sepsis reverse translated in an experimental mouse model of sepsis, researchers are able to use additional experimental techniques to perform hypothesis-driven experiments. Ultimately, validated hypotheses using mouse models will be translated to human patients to encompass a wide array of biological and pathological heterogeneity to further test these hypotheses (Fig. 2).[68]

Mouse models are essential for the study of both general sepsis biology, as well as for dissecting immunological changes associated with the immunosuppression phase of sepsis. One key advantage of mouse models is the generation of highly reproducible conclusions due to the ability to control experimentally the severity, timing, and nature of the septic insult. In addition to these parameters, a wide array of cutting-edge experimental techniques are possible with the use of inbred mice. Unlike human patients, *a priori* knowledge of major histocompatibility complex (MHC) restriction and pathogen-derived T-cell epitopes in inbred mice permits precise *in vivo* assessment of endogenous Ag-specific T-cell responses

and the role of sepsis in the development, function, and maintenance of T-cell immunity. For instance, the use of peptide: MHC I tetramer-based enrichment technology has permitted enumeration of the relatively low number of naive Ag-specific CD4 and CD8 T cells, enabling analysis of primary T-cell responses in the context of sepsis.[69] One way that we have used the power of cutting-edge immunological techniques to explore specific hypotheses about sepsis-induced immune suppression is to adoptively transfer T-cell receptor-transgenic (TCR-tg) T cells into mice before or after the induction of sepsis. Adoptive transfer of such T cells, followed by infection with recombinant pathogens expressing cognate Ag, permits analyses of the impact of sepsis on a defined Ag-specific T-cell population during distinct phases of the CD8 T-cell responses. In contrast, clinical studies of septic patients typically examine the impact of sepsis on the bulk T-cell pool, which is composed of a heterogeneous population of mixed Ag specificity and unknown stimulation history. Last, an additional benefit of mouse models is the large assortment of gene knock-out mice that have proven useful in probing the contribution of individual molecules (e.g., inflammatory mediators) in the context of sepsis. In addition, gene knock-out mice were pivotal in elucidating that T-cell-sufficient hosts have higher levels of IL-6 during the acute phase of sepsis, suggesting that this subset of leukocytes plays a role in exacerbating the cytokine storm that develops during a septic event.[70–72] Therefore, inbred mice generate highly reproducible results and permit an array of experimental techniques that make them valuable tools for pursuing hypothesis-driven research. Undoubtedly, a shortcoming of sepsis research utilizing inbred mice is the lack of biological heterogeneity associated with human populations. However, the use of outbred mice provides a middle ground between the biological homogeneity of inbred mice and septic patients. Some reports have recently elucidated the potential of using outbred mice (e.g. Swiss Webster) as an additional experimental tool in the context of sepsis research.[73–77]

However, the usefulness of some animal models of sepsis has been recently called into question with reports elucidating the discrepancies between human and mouse immune cell subset composition, TCR signaling, and surface molecule expression,[78] as well as the fact that laboratory mice housed under “specific-pathogen-free” conditions have a CD8 T-cell phenotype and distribution pattern that more closely resemble human newborns.[79] One critical report by Seok et al. compared the genomic responses of human and animal models of inflammatory diseases and concluded that animal models poorly mimic their human counterparts.[80] However, Takao et al. re-analyzed these genomic responses of inflammatory diseases using a different analysis approach and came to the opposite conclusion: that mouse models of inflammatory diseases do highly recapitulate the human disease, which suggests the benefit of mouse models as a research tool.[81] Ultimately, all models mentioned will be critical to further elucidate the impact of sepsis on T-cell-mediated immunity that leads to enhanced susceptibility of septic patients to new or previously encountered infections.

IV. ROLE OF SEPSIS IN SHAPING T-CELL RESPONSES TO NEWLY ENCOUNTERED INFECTIONS

Although a relatively small number of naive CD8 T cells specific for any particular pathogen-derived Ag exist *in vivo*, newly encountered infections have the capacity to trigger

a substantial number of pathogen-specific naive CD8 T-cell precursors, promoting their numerical expansion, gain in effector function, and pathogen clearance.[82–84] Importantly, the magnitude of the primary Ag-specific CD8 T-cell response correlates with the dose of the infection and duration of inflammation,[30,85] as well as with the number of naive CD8 T-cell precursors recruited into the response.[86] Therefore, sepsis-induced alterations in the number of naive T cells have the potential to compromise the ability of the host to mount effective primary T-cell responses. The first reports examining the impact of sepsis on T cells determined that sepsis-induced apoptosis of thymocytes[87–89] and T-cell apoptosis was observed in nearly all tissues examined, including the spleen, lung, and colon.[90] Direct examination of naive CD4 and CD8 T cells based on phenotype or using TCR-tg T cells further confirmed that T cells are highly susceptible to sepsis-induced apoptosis.[69,91–93] These results show that sepsis-induced naive T-cell apoptosis and numerical loss is a phenomenon that occurs in an array of host tissues. Subsequent studies using caspase inhibitors or overexpression of the anti-apoptotic protein Bcl-2 confirmed that apoptosis was the primary mechanism driving sepsis-induced numerical loss of T cells.[94,95] Interestingly, using the state-of-the-art techniques to count naive CD8 T-cell precursors specific for defined pathogen-derived antigens, we were able to show that sepsis-induced apoptosis has the capacity to change the composition of naive CD8 T-cell repertoire, leading to sustained and incomplete recovery of naive CD8 T-cell precursors and contributing to impaired CD8 T-cell responses to new infections (Fig. 3).[69,74] The data also suggested that, due to the stochastic nature of the sepsis-induced changes in the composition of naive CD8 T cells, potential “holes” in the CD8 T-cell repertoire can be formed, further contributing to the reduction in primary CD8 T-cell responses to new infections in sepsis survivors.[69,96] Attempts to reverse the sepsis-induced reduction in the number of naive T cells has used exogenous addition of the prosurvival cytokines IL-7 and IL-15, which enhances T-cell expression of Bcl-2 and demonstrates some efficacy in experimental models.[91,97] Therefore, sepsis can result in substantial and long-lasting changes in the available T-cell repertoire, affecting the capacity of the host to respond to subsequent infections.

Beyond sepsis-induced numerical changes, CD8 T cells from septic patients undergo phenotypic alterations that reduce the quality (functional capacity) of CD8 T cells upon stimulation.[98] Therefore, sepsis-induced changes in the quality of CD8 T cells also likely contribute to the enhanced susceptibility of septic patients to both new and previously encountered infections. The numerical loss of all lymphocytes subsets, including T cells, as a result of sepsis generates a lymphopenic environment that has the capacity to initiate homeostatic proliferation of naive T cells and their numerical recovery.[99] Homeostatic proliferation, however, results in naive T cells adopting an “Ag-experienced” or “memory-like” T-cell phenotype in naive CD4 ($CD11a^{hi}$ $CD49d^{+}$) and CD8 ($CD8\alpha^{lo}$, $CD11a^{hi}$) T cells, even in the absence of cognate Ag recognition.[69,93,99–101] This suggests that sepsis induces long-term phenotypic alterations of the surviving naive T-cell pool. It remains to be determined whether naive CD8 T cells express additional “memory-like” markers that could alter their migratory or proliferative capacity and how naive CD8 T-cell acquisition of this phenotype alters their response to new infections. Coinciding with this phenotypic change, sepsis-induced homeostatic proliferation alters the TCR clonotype composition of an Ag-specific CD4 T-cell population.[93] Due to this finding, it is speculated sepsis-induced

homeostatic proliferation of naive T cells condenses the clonal diversity of the naive T-cell pool, potentially reducing the breadth of Ag that the host can recognize.[102] Importantly, over 30 days after sepsis induction in mice, not all Ag-specific naive T cells undergo complete numerical recovery as a result of homeostatic proliferation, which suggests long-term numerical impairments of the naive T-cell pool.[69,93] Therefore, sepsis shapes the composition and the phenotype of the naive T-cell pool, which could impair the effectiveness of subsequent T-cell responses. Additional inquiry into the extent to which sepsis-induced alterations of the T-cell pool reduces their overall quality and affects subsequent T-cell responses is warranted. This future work will be critical to further understanding septic patients' enhanced susceptibility to newly encountered pathogens.

The extent to which sepsis-induced alterations to the naive T-cell compartment impairs subsequent T-cell responses is important to further understanding the enhanced susceptibility of septic patients to primary infections. Specifically, septic patients may have enhanced susceptibility to either acute (short-term) or chronic (persistent) infections. Septic hosts that acquired an acute infection had impaired T-cell responses, resulting in a reduced number of effector CD8 T cells producing effector cytokines (IFN-γ, TNF-α, and IL-2).[69,103] Similar impairments in the magnitude of expansion and effector functions of CD4 T cells have been seen after sepsis[92,93] and be a result of sepsis impairing CD4 Th lineage commitment due to repressive histone methylation marks in the promoter regions associated with Th1 and Th2 lineages.[92] Interestingly, amelioration of the deleterious effects of sepsis on the primary expansion of CD8 T cells could be achieved by administering α-TNF-related apoptosis-inducing ligand (TRAIL) antibody.[104] Therefore, sepsis-induced dysfunction of memory T-cell expansion is in part TRAIL mediated.[96,105] Furthermore, chronically infected septic hosts generate a primary CD8 T-cell response with impaired cytokine production and enhanced expression of inhibitory molecules (e.g. PD-1 and LAG-3), leading to increased viral burden.[74] Importantly, the impairments in the CD8 T-cell response to chronic infections were seen long after the initial septic event resolved.[74] Amelioration of the sepsis-enhanced CD8 T-cell exhaustion and improved control of chronic infection could be achieved in mice that received therapeutic blockade of PD-1 and LAG3.[74] This report suggests that septic hosts exposed to chronic infections have an enhanced rate of CD8 T-cell exhaustion, resulting in an impaired T-cell response to chronic infections. Attempts to reduce T-cell exhaustion in clinical settings with therapeutic administration of anti-PD-1 has shown some efficacy in reducing CD4 and CD8 T-cell apoptosis and restoring effector cytokine production in septic patients.[98] In short, sepsis-induced alterations in the composition of the naive T-cell pool results in increased susceptibility to new infections.

V. ROLE OF SEPSIS IN SHAPING INFECTION AND/OR VACCINE-INDUCED MEMORY T-CELL RESPONSES

The increased susceptibility to previously encountered infections and latent viral reactivation exhibited by septic patients suggests impairments in previously generated memory T-cell responses. Some of the first reports of impaired T-cell immunity in septic patients described the reduction of delayed-type hypersensitivity reactions, even to Ags known to have been encountered previously.[106] Because the quantity (number) and quality (functional capacity)

of memory T cells at the time of re-infection affects directly the degree of T-cell-mediated protection, the impact of sepsis on these parameters will be discussed.[30,31,34]

Sepsis reduces the number of memory CD4 and CD8 T cells in a variety of tissues (e.g., blood and spleen).[73,91,104,107] Similar to naive T cells, numerical alterations of memory T cells are driven by sepsis-induced apoptosis, which is facilitated by cell expression of LFA-1 (CD11a).[73,91,108] Reductions in the quantity of memory T cells suggest a mechanism for septic patients enhanced susceptibility to previously encountered pathogens. Upon re-infection, sepsis impairs the magnitude of secondary expansion due to a reduced number of memory T cells and impairs the proliferation capacity on a per-cell basis (Fig. 3).[73,92,104] Importantly, sepsis-induced impairments in the secondary expansion of T cells results in a higher pathogen burden.[73,104] However, therapeutic administration of the prosurvival cytokine IL-7 after sepsis restores the number of central and effector memory CD4 and CD8 T cells.[91,109] In short, vaccination or infection-generated memory T cells are numerically susceptible to sepsis-induced apoptosis and, upon re-infection, results in a reduced magnitude of secondary expansion and impaired pathogen clearance.

Beyond numerical alterations, sepsis also reduces the functional quality of memory T cells, which contributes to the impairments in the T-cell response. Sepsis reduces the ability of memory CD8 T cells to produce IFN-γ upon encountering cognate Ag (functional avidity), suggesting that sepsis induces memory CD8 T-cell-intrinsic dysfunction on a per-cell basis.[73] In addition, memory CD8 T cells do not require Ag to participate during infection because inflammatory cytokines (e.g. IL-12 and IL-18) are sufficient to drive Ag-independent activation, also known as bystander activation.[110–115] Importantly, we showed recently that sepsis impairs bystander activation of memory CD8 T cells *in vivo* in mice.[73] Experimental bystander activation was performed using lymphocytic choriomeningitis virus (LCMV)-immune mice that subsequently received *Listeria monocytogenes* (LM) as a heterologous infection. There is no known cross-reactivity between LCMV and LM from the CD8 T-cell perspective, so LCMV-specific memory CD8 T-cell production of effector cytokines (e.g., IFN-γ) is due to bystander activation. This impairment of memory CD8 T cells to sense and respond to heterologous infection in a bystander manner after sepsis was evident in both inbred and outbred (Swiss Webster) mice.[73] However, memory CD8 T cells from septic hosts regained bystander activation capacity *in vitro* when cultured with the appropriate inflammatory cytokines.[73] This suggests the exciting possibility that impairments in bystander activation of memory T cells was due to a T-cell-extrinsic factor, possibly due to sepsis-induced impairments in the function of innate immune cells ability to provide inflammatory cytokines (e.g., IL-12) upon heterologous infection. Together, these results suggest that sepsis-induced impairments of T-cell-mediated immunity could be the result of dysfunction in both T-cell-intrinsic and -extrinsic factors, a notion that warrants further investigation.

VI. FUTURE DIRECTIONS

A. Impact of Sepsis on Tissue-Resident Memory T-Cell-Mediated Immunity

This review, and in fact the majority of the sepsis literature, has probed the impact of sepsis on T-cell-mediated immunity by examining T cells from secondary lymphoid organs and

peripheral blood. This subset of circulating memory T cells (T_{CIRM}) migrate passively in search of their cognate Ag due to the chemotactic influence of sphingosine-1-phosphate (S1P) and/or the CCR7 ligands CCL19 and CCL21.[116] Paradigmatically, it was thought the memory T-cell pool had the capacity to circulate throughout host tissues and lymphoid organs in search for cognate Ag after vaccination or infection. However, Masopust et al. discovered that memory CD8 T cells could position themselves within non-lymphoid barrier tissues (e.g., lung and small intestine) after infection, with these cells possessing enhanced cytolytic capacity compared with their splenic T-cell counterparts.[117] Teologically, it was predicted that memory CD8 T cells within barrier tissues could provide protection rapidly upon homologous infection compared with their T_{CIRM} counterparts. Subsequently, it was determined that effector CD8 T cells seed non-lymphoid tissue after vaccination or infection and generate tissue-resident memory CD8 T cells (T_{RM}).[118] Further exploring the phenotype of T_{RM} provided insight into their tissue-resident mechanism: constitutive expression of CD69 and CD103, which interfere with S1PR1 function and tether T_{RM} to E-cadherin expressed on epithelial cells, respectively.[116,119] Much work in the memory CD8 T-cell field is now focused on elucidating the importance of T_{RM}. The numerical appreciation of T_{RM} was determined by enumerating P14 memory CD8 T cells generated after LCMV infection and greater than 90% of memory P14 within non-lymphoid tissue were T_{RM}.[120] In response to infection, T_{RM} activation promotes pathogen clearance of the tissues by orchestrating innate and adaptive immune systems rapidly to provide robust protection against an array of viral and parasitic infections.[121–128] As a result of T_{RM} robust protective capacity, research effort is now focused on modifying vaccine formulations to generate site-specific T_{RM}.[129]

As discussed in this review, T_{CIRM} are susceptible to sepsis-induced apoptosis; however, it is unclear to what extent T_{RM}s are similarly affected. We hypothesize that the distinct position of T_{RM} within tissue parenchyma could confer some protection against the deleterious effects of sepsis. Differential survival of T_{CIRM} and skin T_{RM} has been observed in cutaneous T-cell lymphoma patients receiving alemtuzumab (αCD52) to deplete T cells.[130,131] Further appreciation of this concept is that transplantation recipients on immunosuppressive drugs can have protracted disease-free periods that are perhaps due to the persistence of T_{RM}.[132,133] The distinction between circulation and parenchyma is seen in the experimental technique that distinguishes T_{CIRM} from T_{RM}. Intravenous injection of a fluorescently conjugated mAb labels T_{CIRM} but leave T_{RM} unlabeled due to their position outside of the circulation.[134] The impact of sepsis on vascular endothelial cells, providing the biological barrier between circulation and parenchyma, will be pivotal in these pursuits. It has been speculated that severe sepsis has negative impacts on endothelial cell integrity, specifically, lipopolysaccharides and extracellular histones can induce endothelial cells apoptosis.[135–139] In addition to conventional CD4 and CD8 T_{RM}, γδ T cells and invariant natural killer tissue-resident T-cell subsets have been characterized.[140] The impact of sepsis on the number, function, and protective capacity of T_{RM} remains to be determined, as well as how the severity of sepsis dictates the susceptibility of this population. Due to the importance of T_{RM} in providing rapid protection during localized infections and the chronic immunosuppression seen in septic patients, the impact of sepsis on T_{RM} will be critical to further understanding sepsis-induced dysfunction of T-cell-mediated immunity.

B. Contribution of T-Cell-Extrinsic Factors Leading to Deficits in T-Cell-Mediated Immunity

As discussed previously in this review, septic survivors enter a state of chronic immunosuppression associated with increased susceptibility to secondary infections normally controlled by T-cell-mediated immunity.[15–19] This immune suppression has been recapitulated in mouse models of sepsis, with septic mice showing similar immune suppression and increased susceptibility to secondary infection.[74,104] Our recent work has demonstrated that septic mice have a prolonged impairment in the ability to mount primary CD8 T-cell responses (resulting from infection/vaccination) upon Ag encounter; however, the mechanism of this deficit (CD8 T-cell-intrinsic and/or -extrinsic) is not well defined.[69,73,74] Primary CD8 T-cell expansion upon newly encountered infection or vaccination is reliant on CD8 T-cell-extrinsic factors (Fig. 4). These extrinsic factors, which can be provided by APCs such as dendritic cells (DCs), include the presence of Ag:MHC complex (signal 1), co-stimulatory ligands (signal 2), and appropriate cytokines such as IL-12 (signal 3).[23–25,141–143] A sepsis-induced lesion in the quantity (numbers) or quality (ability to provide signals 1–3) of DCs could be an important extrinsic factor contributing to suboptimal CD8 T-cell immunity after sepsis.

Investigations into the effect of sepsis on DCs have shown that splenic DCs decline in number after a septic event in both septic patients and experimental models of sepsis.[144–147] Furthermore, previous work has demonstrated that post-septic DCs produce less IL-12 and more IL-10 upon TLR stimulation than sham controls.[146–148] These observed lesions in DC number and IL-12 (signal 3) production provide support for a possible T-cell-extrinsic lesion; however, further queries into the effects of sepsis on DCs are warranted. Specifically, the status of DCs in the context of impaired CD8 T-cell immunity after sepsis has not been elucidated. Future investigations will examine the manner in which DC lesions may impair CD8 T-cell responses to pathogens and probe whether recovery in the quantity and quality of DCs may help to ameliorate impairments in CD8 T-cell immunity. Moreover, there has been little investigation into the potential therapeutic benefit of DC-mobilizing cytokines such as FMS-like tyrosine kinase 3 ligand (Flt3L)[149] after a septic event with the idea of restoring T-cell immunity through boosting DC numbers. The key point here is that only targeting the “T-cell side” of the equation by bolstering numbers with cytokines (e.g., IL-7) or improving function with checkpoint inhibitors may not be sufficient to fully restore T-cell immunity after a septic event if the APCs, which are required for T-cell activation, are also reduced in number/function during sepsis.

VII. CONCLUSIONS

Septic patients that survive the cytokine storm experience long-term pathological consequences, including chronic immunosuppression. Therefore, further understanding of the immunological modifications associated with sepsis-induced chronic immunosuppression is an important research goal. Clinical studies of sepsis revealed that CD4 and CD8 T cells undergo apoptosis, leading to appreciable numerical decline. Experimental models of sepsis, such as CLP, recapitulated these clinical observations. In addition, sepsis experimental models have facilitated researchers to ask hypothesis-driven questions to further probe the impact of sepsis on T-cell-mediated immunity. As discussed in

this review, surviving T cells exposed to the septic environment are affected functionally in a number of ways. Sepsis-induced impairments in the quantity and quality of T cells give insight into sepsis-induced impairments of T-cell immunity. Both clinical and experimental approaches have been critical in understanding changes in T-cell-mediated immunity that help to explain septic patients' susceptibility to infections normally controlled by T cells. However, many experimental questions still exist regarding the impact of sepsis on T-cell-mediated immunity. For example, CD4 and CD8 T_{RM} are critical mediators of pathogen clearance but, to our knowledge, little data have been published determining the impact of sepsis on CD8 T_{RM}. In addition, CD8 T-cell-extrinsic factors, such as DC participation in providing the appropriate signals for proper T-cell activation and function, require additional examination to further understand the changes in CD8 T-cell-mediated immunity during the immunosuppression phase of sepsis.

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ABBREVIATIONS

Ag	antigen
APC	antigen-presenting cell
CD	cluster of differentiation
CLP	cecal ligation and puncture
DC	dendritic cell
IFN	interferon
IL	interleukin
TCR-tg	T-cell receptor-transgenic
TNF	tumor necrosis factor

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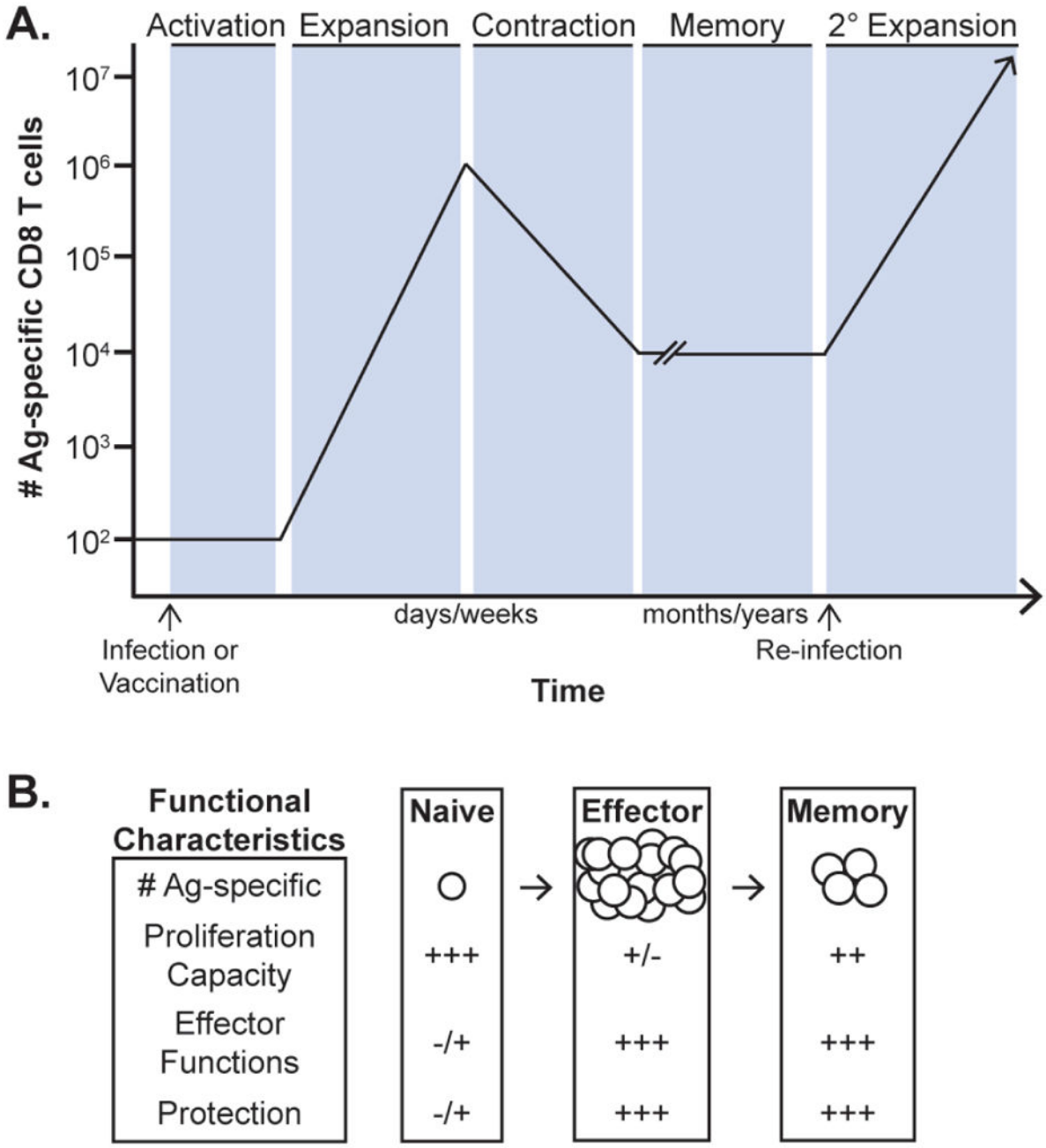

FIG. 1.

Distinct phases of the primary CD8 T-cell responses upon antigen encounter. **A,** Naive CD8 T cells encounter cognate Ag and appropriate signals and promote their activation and accumulation during the vigorous primary expansion phase. Upon completion of the expansion, effector CD8 T cells undergo a programmed contraction (death) phase, which leaves a stable number of memory CD8 T cells that can be maintained for the life of the host and rapidly undergo secondary expansion upon Ag re-encounter. **B,** Functional properties of naive, effector and memory CD8 T cells. Naive CD8 T cells do not possess effector functions, but, upon exposure to cognate Ag, this population has the capacity to undergo

proliferative expansion in numbers. Effector and memory CD8 T cells possess effector functions (cytokine secretion and cytolytic capacity) that mediate host protection. Vaccination or infection-generated memory CD8 T cells exposed to cognate Ag possess the capacity to undergo proliferative expansion and gain effector functions, providing rapid protection to the host upon re-infection. (Figure adapted with permission from Badovinac et al, 2006.[35]).

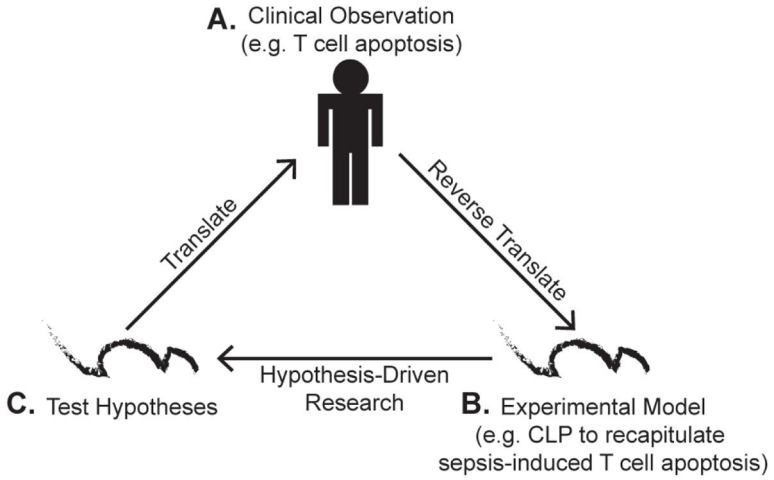

FIG. 2.

Proposed interplay of clinical and experimental research to elucidate the impact of sepsis on T-cell-mediated immunity. **A,** Clinical research on septic patients has shown increased apoptosis and reduced numbers of CD4 and CD8 T cells. **B,** Clinical observations of sepsis-induced apoptosis were successfully reverse translated in an experimental model (e.g., CLP). **C,** Experimental models could allow sepsis researchers to pursue hypothesis-driven research and utilize an array of experimental tools that are not feasible with human patients. The ultimate goal of experimental models is to translate hypotheses to human septic patients to further test hypotheses incorporating an array of biological and pathological heterogeneity. (Figure adapted with permission from Efron et al, 2015.[68]).

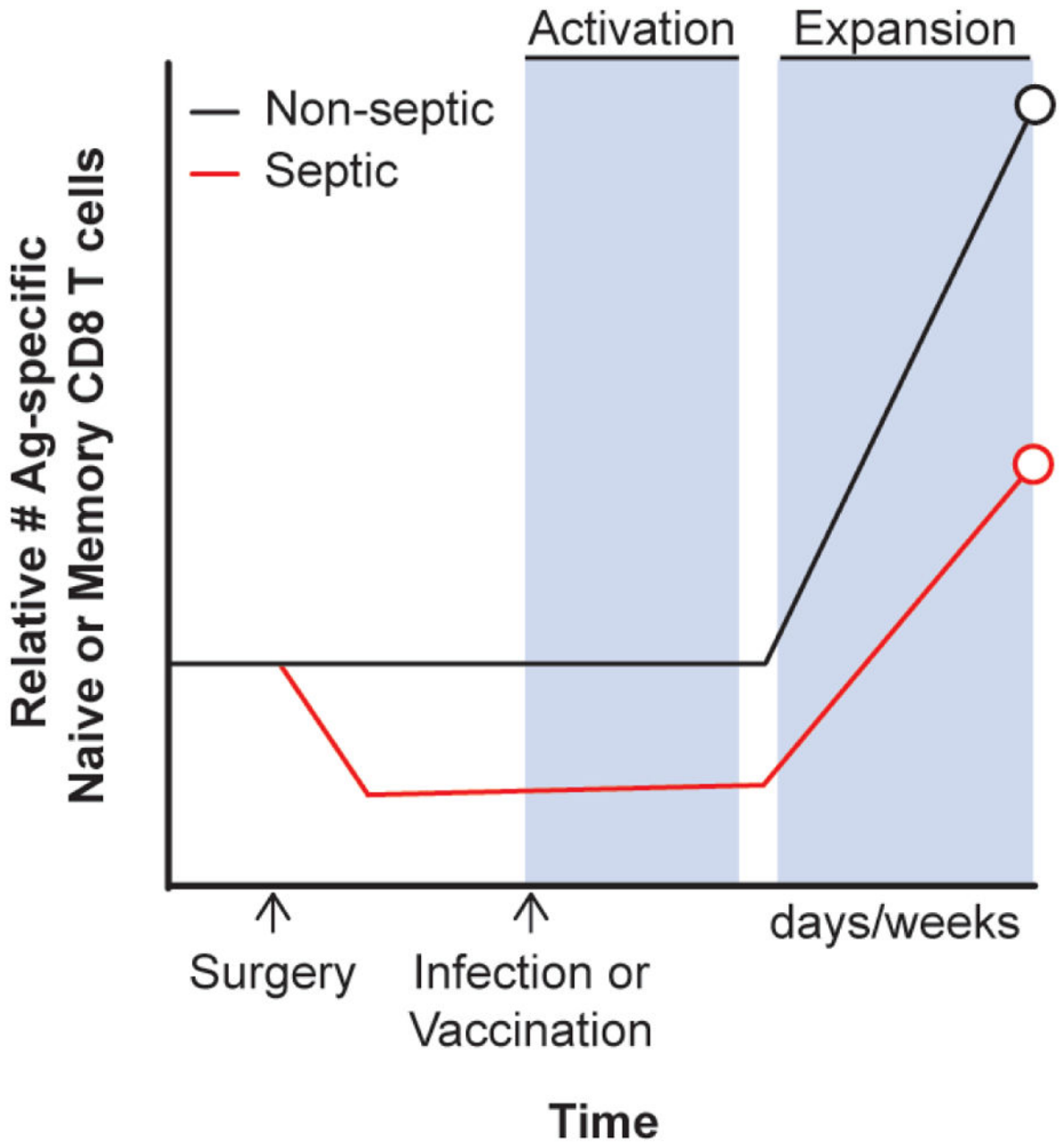

FIG. 3.

Sepsis affects the number of naive and memory CD8 T cells, influencing their ability to respond to secondary infection. Naive and primary memeory Ag-specific CD8 T cells undergo numerical loss shortly after sepsis induction. Due to their decreased numbers and/or impaired per-cell functionality, the magnitude of primary and secondary CD8 T-cell expansion is diminished in the septic host after secondary infection.

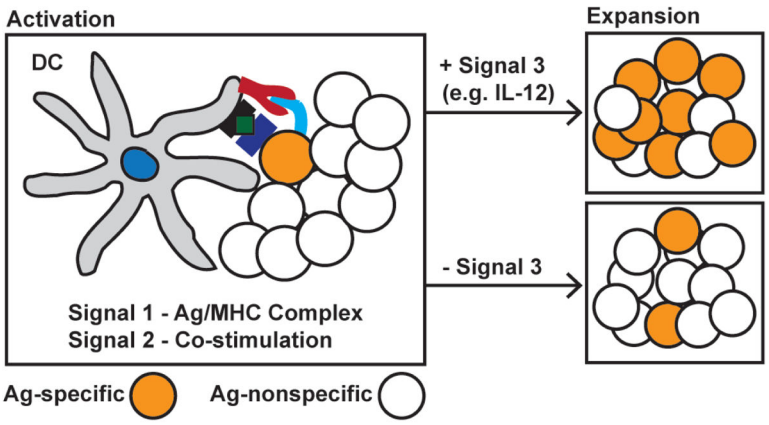

FIG. 4.

T-cell-extrinsic factors mediate effective CD8 T-cell responses. The expansion of Ag-specific CD8 T cells is dependent on APCs (DCs) providing Ag:MHC (signal 1), co-stimulation (signal 2), and signal 3 cytokines (e.g. IL-12). Lack of signal 3 cytokine will lead to suboptimal CD8 T-cell expansion, reducing the effectiveness of the T-cell response. Sepsis-induced impairments of DCs' ability to provide signals 1–3 could be an important mechanism behind the observed deficits in CD8 T-cell immunity after a septic event. (Figure adapted with permission from Haring et al., 2006.[23]).