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Sepsis and multiple sclerosis: causative links and outcomes

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Abstract

Sepsis is a life-threatening condition characterized by an acute cytokine storm followed by prolonged dysfunction of the immune system in the survivors. Post-septic lymphopenia and functional deficits of the remaining immune cells lead to increased susceptibility to secondary infections and other morbid conditions causing late death in the patients. This state of post-septic immunoparalysis may also influence disorders stemming from inappropriate or overactive immune responses, such as autoimmune and immunoinflammatory diseases, including multiple sclerosis. In addition, ongoing autoimmunity likely influences the susceptibility to and outcome of sepsis. This review article addresses the bidirectional relationship between sepsis and multiple sclerosis, with a focus on the immunologic mechanisms of the interaction and potential directions for future studies.

Keywords

Sepsis; multiple sclerosis; gut microbiota

1. Sepsis

The devastating immune response that develops following disseminated infection leads to a life-threatening organ dysfunction called sepsis [1]. Approximately 50 million individuals

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developed sepsis and 11 million sepsis-related deaths were reported worldwide in 2017, which accounted for almost 20% of all global deaths [2]. Although 85% of sepsis cases and sepsis-related deaths occur in low- and middle-income countries, wealthy societies are not spared from this devastating disorder. For example, nearly 2 million people in the United States develop sepsis each year and it is the most expensive hospital-treated condition in the U.S., with >$23 billion spent on hospital treatment of sepsis annually [3]. Sepsis is characterized by the overproduction of both pro- and anti-inflammatory cytokines leading to temporary and severe lymphopenia [4–6] (Fig 1A). Sepsis survivors (~ 75% survival rate [7]) progress into a state of prolonged immunoparalysis [8], where they become susceptible to secondary infections and viral reactivation, and have decreased 5-year survival, relative to matched individuals who did not have sepsis [9–11] (Fig 1B, C).

The number of peripheral blood leukocytes fluctuates significantly during the course of sepsis [12]. While a noticeable increase in neutrophil and monocyte populations is observed in the first 2–4 days from septic onset, the lymphopenic state quickly follows the resolution of the cytokine storm [13]. The marked decrease in the number of B cells, $CD4^+$ and $CD8^+$ T cells, and NK cells following sepsis onset is the result of apoptotic loss [12–14]. Lymphocyte numbers normalize within a month in sepsis survivors, but the functionality of the immune cells is reduced for an extended period [15] (Fig 1C). Failure to regulate either leukocytosis or lymphopenia in the early stages of sepsis correlates with increased mortality in patients [16]. Yet, it is the previously septic individual's increased susceptibility to secondary infections and viral reactivation, due to long-lasting functional impairments, that leads to shortened life expectancy [9–11]. Experimental therapies targeting sepsis-induced immunoparalysis are thus focused not only on preventing cell loss and potentiating recovery of lymphocyte number, but also restoring function to the repopulating immune cells [17].

2. Multiple sclerosis

Multiple sclerosis (MS) is an incurable chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS) that affects more than 2.8 million individuals worldwide [18]. Current drugs target the autoimmune response that initiates and propagates CNS tissue destruction during MS [19]. Indeed, the autoimmune response during MS is initiated by $CD4^+$ T cells specific for CNS antigens, which in turn orchestrate the activity of macrophages, $CD8^+$ T cells, B cells and other immune cells against myelin and other structures within the CNS [20]. $CD4^+$ T cells (*i.e.,* T helper (Th) cells) are the accepted initiators of MS pathogenesis following recognition and activation by CNS antigens or microbial mimics of CNS antigens. These cells differentiate towards Th1 and Th17 cells and then migrate into the CNS where they are re-activated to initiate inflammation within the CNS [21]. Meanwhile, $CD8^+$ T cells and B cells dominate the inflammatory reaction in the CNS, while macrophages and other innate immune cells are prominent contributors to the tissue damage observed in MS [20, 22, 23].

Characteristically, the disease evolves into a relapsing-remitting course where activation of the autoimmune response happens periodically provoking neurological deficits in patients. The autoimmune responses then resolve either spontaneously or after glucocorticoid therapy. However, a proportion of patients develop progressive forms of the disease, either from the

start of MS manifestation (primary progressive) or following a period of relapsing-remitting course (secondary progressive). Current therapeutic strategies available for the treatment of MS are meant to modulate the immune system, thereby slowing disease progression and preventing relapses. Since demyelination and neurodegeneration are consequent to autoimmune activity, remyelination and neuroprotection are the ultimate goals of current studies in MS [24].

3. Sepsis – MS relations

As previously stated, septicemia induces long-lasting changes in the immune system. Specifically, these changes include: an altered TCR repertoire (notably including a decreased diversity of TCR Vβ [25]), incomplete recovery of some epitope specificities [26], and antigen-dependent homeostatic proliferation of T cell clones specific for gut microbiota [27]. Additionally, T cells sustain functional deficits, reflected by impaired delayed-type hypersensitivity responses and higher viral reactivation [28–30] as well as global anergy mirrored in reduced ability to produce cytokines [31–37], impaired proliferative capacity [31, 38, 26], and increased expression of inhibitory receptors [39–46]. Further, there are changes in subset representation, including decreased transcript levels of major Th transcriptional factors Tbet, GATA-3, RORγt [47], repressive histone methylation at *Ifnγ* and *Gata3* promoter regions [38], an increased representation of Foxp3-expressing $CD4^+$ Tregs [35, 48–50] with a corresponding decrease in the representation of Th1, Th2, Th17 and Tfh subsets [35, 50–52]. All of these changes have the potential to affect the process of MS pathogenesis (Fig 2).

In agreement with this idea, sepsis was recently shown to impede experimental autoimmune encephalomyelitis (EAE) development in mice [53]. EAE, the most commonly used animal model in the study of MS, is induced in susceptible rodent strains by peripheral injection of CNS proteins or peptides emulsified in complete Freund's adjuvant (CFA). The effect of sepsis on EAE was mediated through reduction in myelin oligodendrocyte protein (MOG)-specific encephalitogenic $CD4^+$ T cell numbers in the CNS during effector phase and lymph nodes draining the site of immunization in the inductive phase of EAE. This numeric deficit even preceded immunization to induce EAE, wherein septic (cecal ligation and puncture, CLP-treated) hosts had a reduced number of naïve MOG-specific $CD4^+$ T cells. Importantly, transfer of naïve encephalitogenic $CD4^+$ T cells after resolution of the cytokine storm, to replace those lost during sepsis-induced lymphopenia, was able to re-establish the development of EAE disease (Fig 3). Interestingly, those MOG-specific cells that were primed and expanded in CLP hosts were not functionally impaired. Further, naïve encephalitogenic cells transferred after resolution of the cytokine storm were capable of proliferating equivalently to those in control (sham surgery-treated) counterparts suggesting the post septic environment was not limiting functionality of these cells. This observation is in stark contrast to infection scenarios after sepsis wherein the post-septic environment may limit T cells expansion and function through impairment of other cells (including dendritic cells and endothelia) [54, 55]. Yet, this may in part be the result of the substantial antigen and inflammatory bolus utilized in EAE immunization that is not present under infection conditions.

Limited epidemiological data, however, do not support the notion that sepsis would impair subsequent autoimmune development. Specifically, Taiwanese septicemia patients had approximately 3-fold higher risk to develop MS [56], and more severe septicemia was associated with an increased risk to develop MS. It is, however, important to note that this study did not address whether the patient cohorts had differential HLA expression, which is strongly associated with development of MS. Further, while the selection criteria identified patients that had not presented with clinical signs prior to the septic insult, it remains formally possible that subclinical autoimmune activity may have occurred and even potentially contributed to elaboration of the septic event. Similar results were observed for non-MS demyelinating syndromes, such as neuromyelitis optica spectrum disorders, transverse myelitis, and acute disseminated encephalomyelitis [57], yet the same limitations apply. It is also notable that both of these studies were limited to Taiwanese cohorts, which may not be representative of the broad range of patients who may either experience a septic event or develop MS. Thus, more robust interrogation of the association of sepsis with subsequent autoimmune development in patient cohorts is required.

Consecutively, the discrepancy between MS and EAE sepsis-related data could be attributed to imperfections in the translational capacity of the model. Indeed, several differences in the pathogenesis of MS and EAE exist that prevent direct translation of data obtained in the model for the benefit of the patients [22, 58]. $CD4^+$ T cells are the initiators of autoimmune response both in MS and EAE, and contribute to the disease pathogenesis in humans and experimental animals alike. Still, the immune response within the CNS is dominated by $CD8^+$ T cells and B cells in MS, but not in EAE [22, 23]. Additionally, the use of complete CFA and pertussis toxin in EAE immunization biases the initiated immune response. Notably, CFA stimulates the immune response against non-CNS antigens on its own [59], skewing the immune response to be Th1-driven [60], and induces pain, thereby inducing glial activation and production of inflammatory mediators in the spinal cord [61]. However, novel varieties of EAE that overcome the obstacles of the classical EAE have subsequently been developed [62]. For instance, EAE models in which $CD8^+$ T cells and B cells, in conjunction with $CD4^+$ T cells, have a dominant role in disease pathogenesis are available for study [63, 64]. EAE can also be induced without the use of CFA in Dark Agouti rats [65]. We have also recently investigated the cellular components of CFA-free EAE in detail [66] and found there is a lower total number of cells, including $CD4^+$ T cells in SCH-immunized rats in the inductive phase of EAE. Interestingly, $CD8^+$ macrophages were identified as one of the leading CNS-infiltrating populations at the peak of the disease in CFA-free model of EAE. Our novel results suggest a resemblance of this model pathogenesis to that of MS. These and other non-classical varieties of EAE may assist in further elucidation of the interplay between sepsis and MS.

Alternately, the influence of ongoing autoimmunity on sepsis outcomes is also worthy of study. Yet, as with the influence of sepsis on the development of autoimmunity, epidemiological data evaluating the influence of autoimmunity on sepsis are scarce. MS patients enrolled in three studies in the U.S. had a higher overall mortality rate and increased predisposition to serious infections and sepsis than matched control individuals; this was true both with regard to controls that did not have autoimmune disease and controls with other autoimmune conditions [67–69]. Further, sepsis was identified as one of the

leading reasons for MS patients' readmission to hospitals in the U.S. [70]. An increased predisposition for serious infection and sepsis mortality was also observed for MS patients in two studies in Canada [71, 72]. Similarly, a study performed in Basque Country, Spain showed respiratory infection and sepsis were the most frequent MS-related causes of death among the examined individuals [73]. Obviously, additional epidemiological data is needed to garner insight into the relationship between sepsis and MS.

It is also important to consider the potential effects of disease-modifying drugs that are widely used in the treatment of MS on the epidemiological results. These drugs have general immunomodulatory properties, including a profound effect on peripheral leukocytes [74]. Indeed, one epidemiological study showed the disease modifying therapeutics natalizumab, fingolimod and dimethyl fumarate, unlike beta-interferon and glatiramer acetate, increased risk to infections in MS patients [75]. On the other hand, studies on animal models of sepsis showed beneficial effects of fingolimod, dimethyl fumarate, and glatiramer acetate [76–78]. Thus, it is plausible that MS drugs could influence the immune response in sepsis. This could be either to limit the ability of an individual to control an infection, which may not have otherwise become septic, or by dampening the cytokine storm to reduce the septic burden. To the best of our knowledge there has been no study conducted to date dedicated to the relationship between the risk of sepsis and specific treatment in MS. There is only one report showing slightly, yet statistically insignificant, lower risk for sepsis in the group of MS patients treated with various disease-modifying drugs [79]. It will be important to address this point in the forthcoming studies, as well. Animal models will surely be helpful in resolving the influence of the CNS autoimmunity on sepsis. Induction of sepsis during ongoing CNS inflammation or after the resolution of EAE, in appropriate EAE varieties, may be informative and hopefully opens additional angles for therapeutic intervention in patients.

4. Gut microbiota link

Considering the increasing interest in the contribution of gut microbiota to the pathogenesis of MS, it will be of utmost importance to determine to what extent the effects of sepsis on the CNS autoimmunity might be attributed to the changes in the gut microbiota composition and activity. Indeed, MS pathogenesis has been indirectly associated with altered gut microbiota composition [80, 81], while the importance of gut microbiota for the pathogenesis of EAE has been demonstrated in numerous studies. Notably, gut microbiota composition changes during the course of EAE and varies between the different stages and clinical subtypes of the disease [82–84]. The importance of gut microbiota in EAE was recently revealed in data showing germ-free mice did not develop disease in a model of spontaneous EAE, but disease was initiated once the mice were colonized with human gut microbiota [85]. Importantly, a higher proportion of mice developed EAE in response to MS twin-derived faecal samples than to healthy twin-derived samples. Similar results were obtained in another study, where transfer of gut microbiota from MS patients to germ-free C57Bl/6 mice increased their susceptibility to the induction of active EAE to greater extent than transfer of gut microbiota from healthy subjects [86]. These studies clearly imply the gut microbiota of MS patients is in state of dysbiosis that can be associated with disease pathogenesis (Fig 4). Indeed, reduced diversity of gut microbiota

in MS patients correlated with increased abundance of $CXCR3^+$ T cells expressing the gut-homing α4β7 integrin receptor in the peripheral blood [87]. Further, MS gut microbiota might contain microorganisms able to provoke or promote CNS autoimmunity, as elevated levels of *Akkermansia muciniphila*-specific IgG were present in the cerebrospinal fluid of MS patients [88]. Moreover, a $CD4^+$ T cell clone that was clonally expanded in MS brain lesions was shown to recognize guanosine diphosphate (GDP)-l-fucose synthase, an enzyme expressed by gut microorganisms [89]. Accordingly, a recent EAE study has identified specific gut microorganisms involved in the reactivation of MOG-specific T cells [90]. Namely, peptides originating from *Lactobacillus reuteri* mimic MOG, while *Erysipelotrichaceae* can act as an adjuvant to enhance the responses of encephalitogenic Th17 cells. Thus, the observation that proliferation of lymphocytes after the acute sepsis phase can be driven in part by gut microbiota antigens [27], implies that some of the proliferating clones may also have specificity for the CNS antigens. Activation of T cell clones specific for MOG peptides in response to some gut bacterial mimic is one of the plausible explanations for the observation of Jensen et al. [53], based on data showing the numerical recovery and acquisition an activated phenotype (*i.e.*, increased expression of CD44) of MOG-specific $CD4^+$ T cells in some hosts with time after sepsis. Alternately, that MOG-specific cells could encounter CNS antigen as a consequence of sepsis-induced damage or are potentially acquiring an activated phenotype via homeostatic proliferation [15, 91, 92]. Regardless of the mechanism behind the acquisition of the activated phenotype, these MOG-specific $CD4^+$ T cells may now have the potential to begin exerting their effector function within these hosts. This could explain the increased risk for sepsis survivors to develop CNS autoimmunity, but we acknowledge the possibility that other impairments to the immune system may also exist in an individual after sepsis that may temper the magnitude of the autoimmune response. It is also possible that the mechanisms by which sepsis influences subsequent autoimmunity may change with time and depend on the composition of the host gut microbiome.

Another important point that should be addressed is the consequence of antibiotic use in sepsis and its impact on susceptibility to MS. Broad spectrum antibiotics are routinely used as the initial treatment of sepsis, and they have beneficial effects in EAE through modulation of murine gut microbiota composition [93–95]. Conversely, EAE aggravation as the consequence of broad-spectrum antibiotic application has been observed in rats [83]. The results of a recent study in spontaneous EAE clearly indicate the timing of gut microbiota perturbation by antibiotics is crucial for the consequent effects on the CNS autoimmunity. Namely, prophylactic, but not therapeutic, application of antibiotics and subsequent modulation of gut bacteria was effective in restraining CNS autoimmunity [96]. Additionally, studies on mice showed development of the regulatory arm of the gut immune system was acquired in a narrow period between the second and fourth weeks of life [97]. This “weaning reaction” of the gut immune system developed under the influence of gut microbiota and was essential for prevention of the future inflammatory pathologies in the adult organisms. Thus, the use of antibiotics in the early childhood to treat sepsis could be a predisposing factor for development of autoimmunity, particularly MS. It will be important to examine available epidemiological data on the association between childhood sepsis and development of MS later in life.

Finally, GM-CSF-producing $CD4^+$ T cells have recently been defined as a distinct population in humans [98]. These cells were identified as the major encephalitogenic cells in EAE [99–102]. An increased proportion of $GM\text{-}CSF^+$ $CD4^+$ T cells was also observed in individuals with sepsis [103] and were proportionally increased in non-survivors relative to survivors. Given that the gut microbiota is essential for Th differentiation in EAE [104] and encephalitogenic T cells migrate to the gut where they can undergo re-differentiation [105, 106], it is tempting to speculate that the gut microbiota has a decisive role in GM-CSF-producing $CD4^+$ T cell origin and function (Fig 4). Thus, tracing the gut microbiota-related fate of GM-CSF-producing $CD4^+$ T cells in animals that survive sepsis and are subsequently immunized to develop EAE (or vice versa) seems an important direction for future study.

5. Conclusions

Sepsis and MS are devastating disorders that inflict enormous physiological and economic burdens for the society. Thus, studies on the pathogenesis of sepsis and MS are needed for the design of novel therapeutics to diminish the effects of each of these disorders. Although different in their initiation and clinical manifestation, these disorders have a common characteristic: inappropriate activity of the immune system. Given the complexity of the immune system and the numerous connections among its cellular constituents, it is logical to assume that the disbalance of the immune system imposed by one of the disorders will impact the other one. Currently, there are limited epidemiological and experimental data on the links between sepsis and MS, though they are indicative of causal interplay. Thus, novel studies on animal models, as well as novel analyses of the patient records are warranted.

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Highlights

- Potential interplay between sepsis and multiple sclerosis (MS) is reviewed
- Immunological mechanism(s) governing sepsis/MS interactions are proposed
- The role of gut microbiota influencing the sepsis/MS interaction is discussed

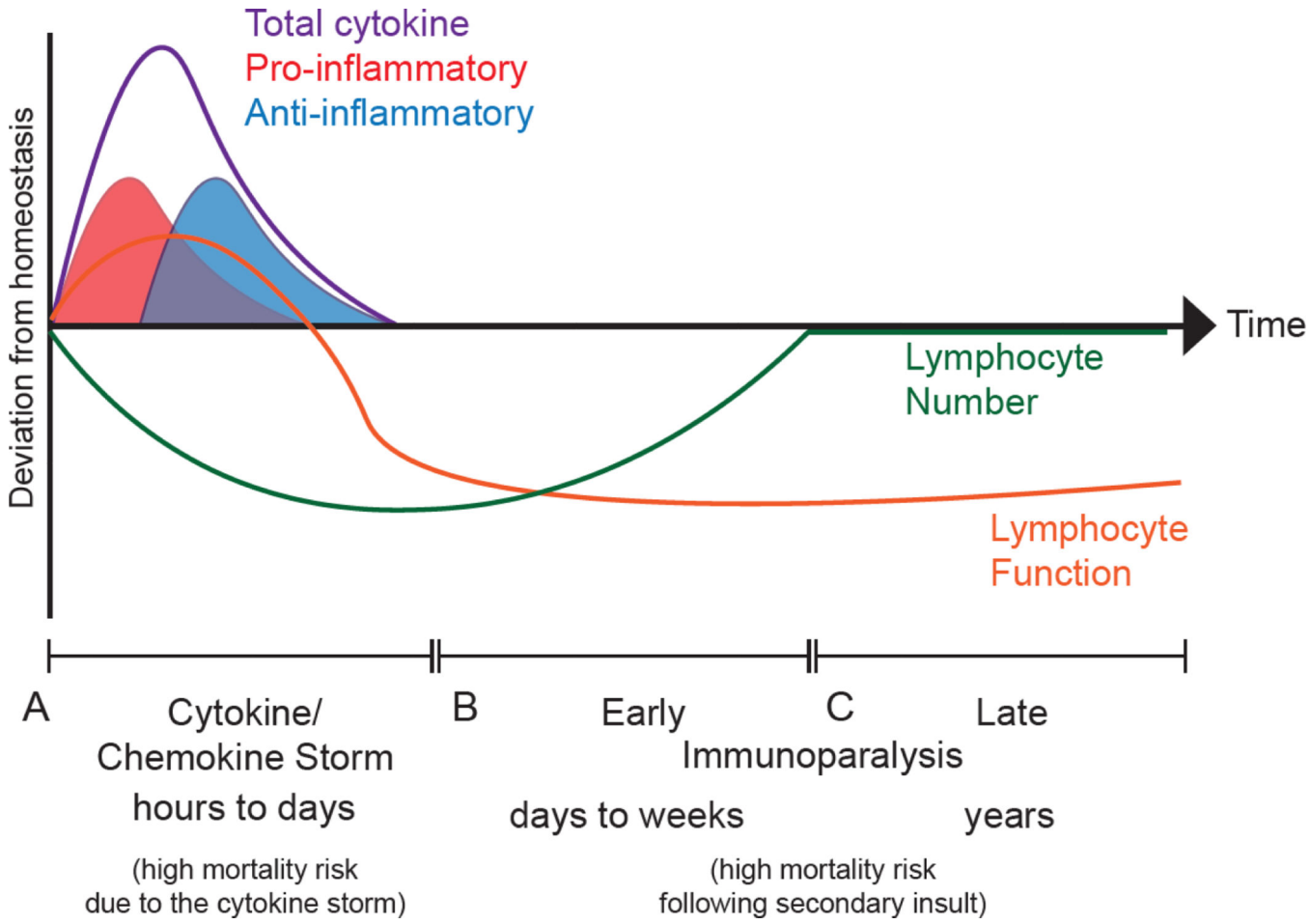

Figure 1: Influence of the sepsis-induced cytokine storm and immunoparalysis state on host immune response.

A) In the first several hours to days following a septic insult, lymphocytes become activated and begin contributing pro-inflammatory cytokines [4–6]. As the infection begins to become mismanaged lymphocytes begin to undergo apoptosis and produce anti-inflammatory cytokines to counterbalance the pro-inflammatory cytokines and limit immunopathology. The culmination of the pro- and anti-inflammatory cytokine responses is termed the cytokine storm. **B)** If the host survives the cytokine storm, then as the inflammation subsides the host is left with a substantially reduced number of lymphocytes and these surviving lymphocytes exhibit functional impairment. This defines the early immunoparalysis state that may last for days to weeks after the septic insult wherein hosts are now more susceptible to secondary pathogenic insults (i.e., infection or cancer). [8–11] **C)** With time the number of total lymphocytes recovers, however, these lymphocytes continue to exhibit functional impairment years after the septic insult due to sepsis-induced cell-intrinsic and -extrinsic changes [15]. This defines the late immunoparalysis state that is also associated with increased susceptibility to secondary pathogenic insults.

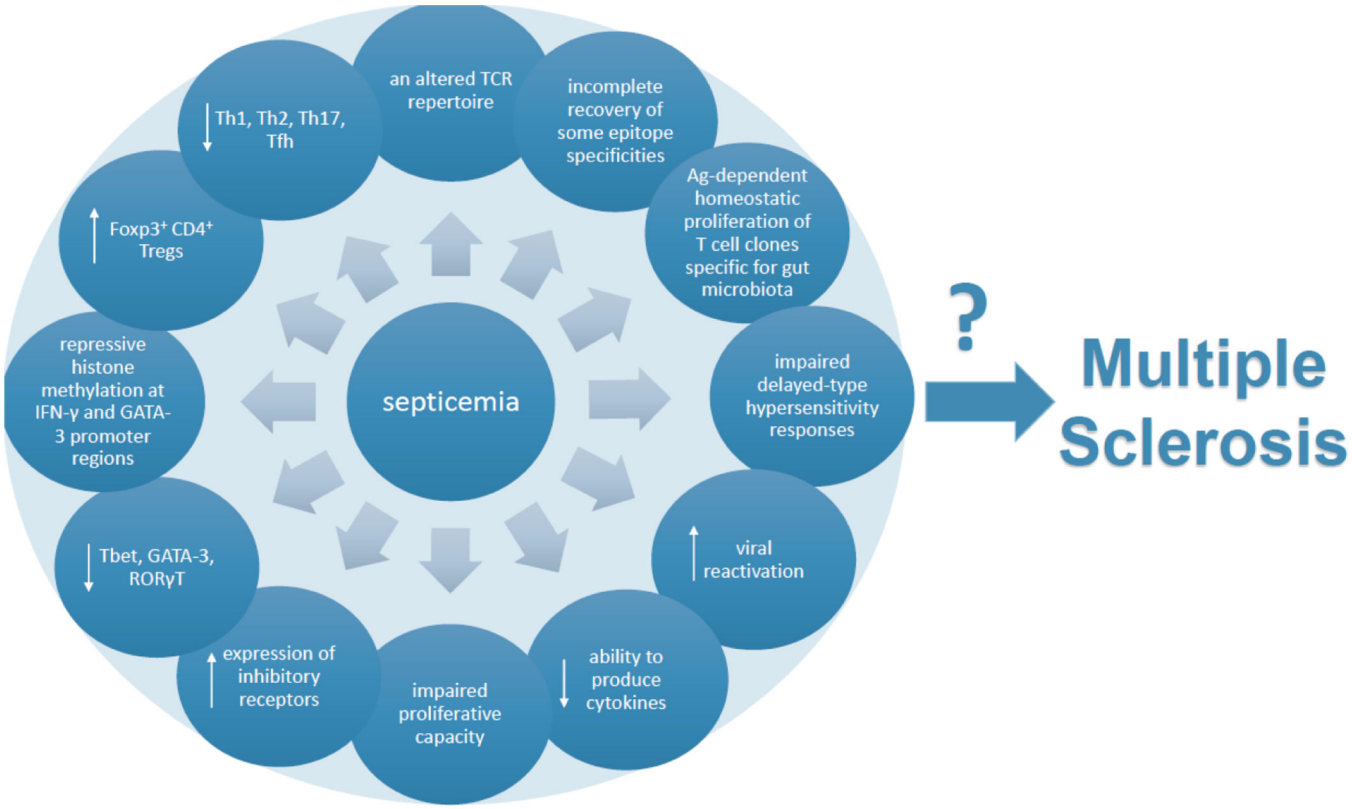

Figure 2: Effects of sepsis on T cells that are relevant for MS pathogenesis.

Septicemia induces various changes in T cell activity that could have profound influence on MS pathogenesis. [23–50]

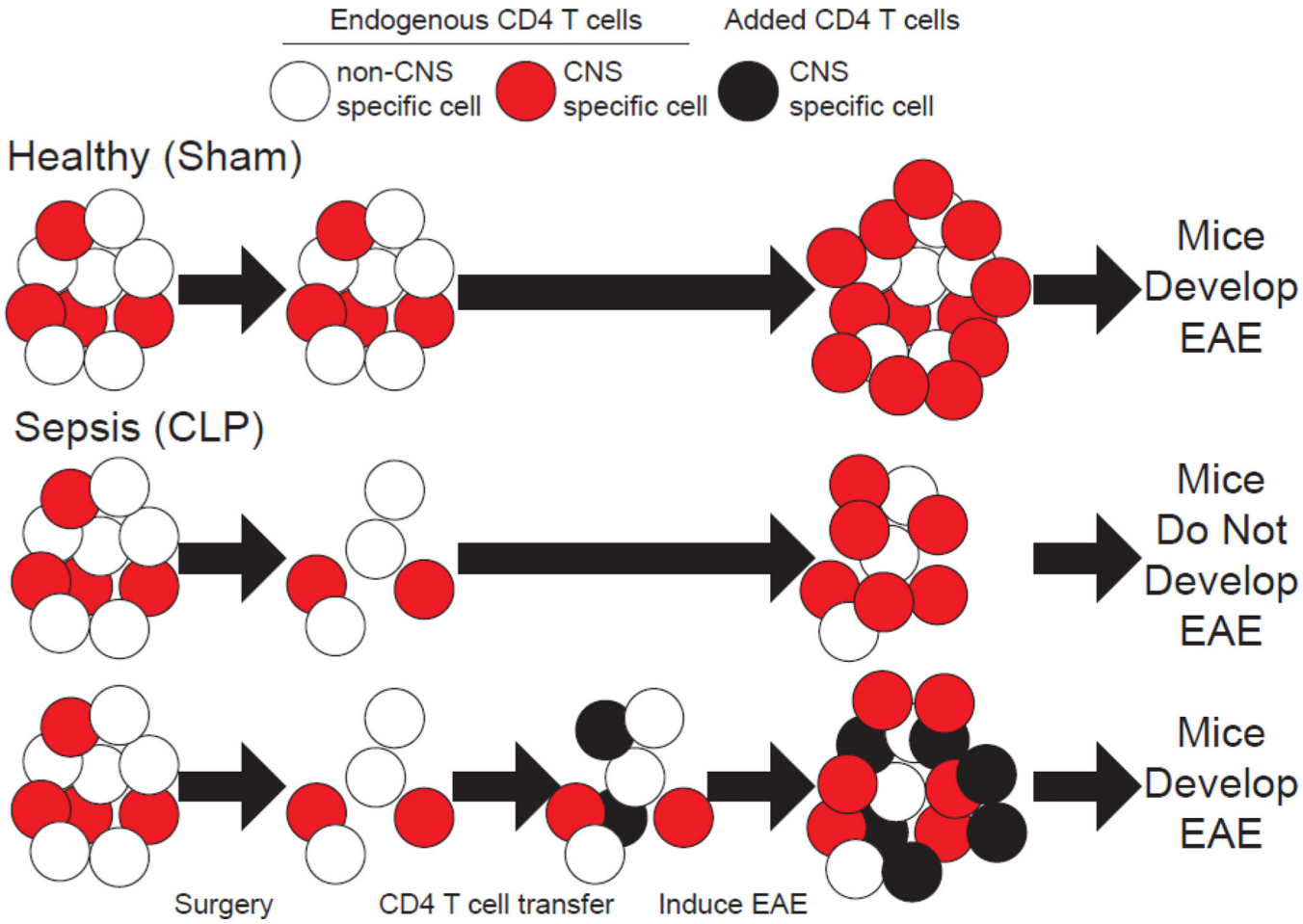

Figure 3: Sepsis ablates EAE development by reducing the number auto-antigen specific CD4$^+$ T cells.

CLP (sepsis) induces numeric loss of CD4$^+$ T cells, including autoantigen-specific CD4$^+$ T cells that target the brain and spinal cord (CNS). Thus, when the autoantigen-specific cells respond following EAE induction there is reduction in the number of autoantigen-specific effectors thereby ablating EAE disease development. However, if these autoantigen specific cells are supplemented through an add back experiment, CLP hosts re-acquire the ability to develop EAE, demonstrating that the numeric deficit in autoantigen-specific CD4$^+$ T cells is causal in the impaired capacity of septic hosts to develop EAE. [51]

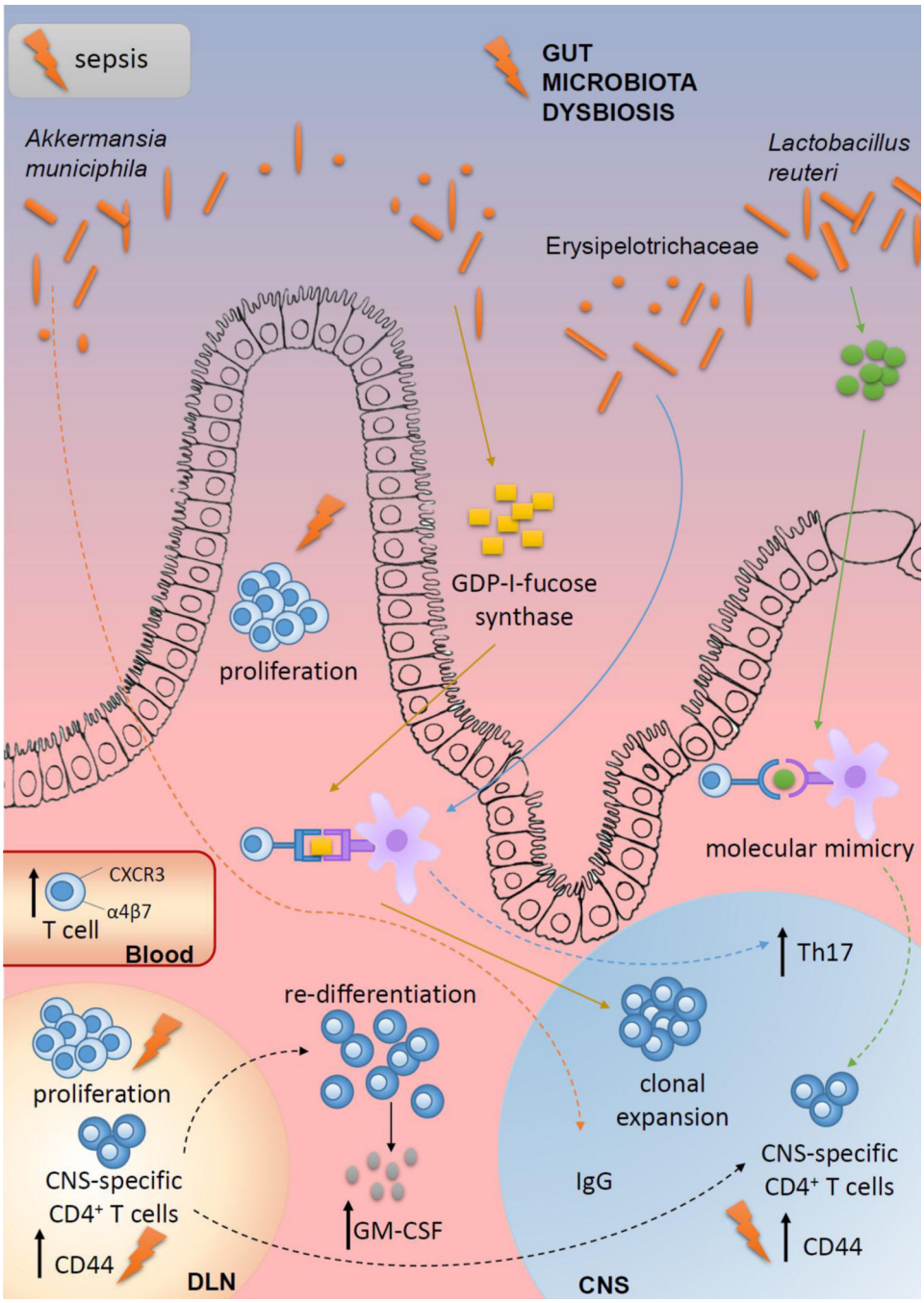

Figure 4: Convergent contribution of sepsis and gut microbiota dysbiosis to MS pathogenesis.

Dysbiosis of gut microbiota in MS patients correlates with increased abundance of $CXCR3^+$ T cells expressing the gut-homing α4β7 integrin receptor in the peripheral blood [87]. Elevated levels of *Akkermansia muciniphila*-specific IgG are present in the cerebrospinal fluid of MS patients [88]. $CD4^+$ T cell clone that is clonally expanded in MS brain lesions is shown to recognize GDP-l-fucose synthase, an enzyme expressed by gut microorganisms [89]. Peptides originating from *Lactobacillus reuteri* mimic MOG, while *Erysipelotrichaceae* can act as an adjuvant to enhance the responses of encephalitogenic Th17 cells [27].

Gut dysbiosis increases abundance of GM-CSF-producing $CD4^+$ T cells that are among the major encephalitogenic cells in EAE [99–102]. CNS-specific T cells migrate to the gut where they can undergo re-differentiation into potent encephalitogenic cells under the influence of gut microbiota dysbiosis [105, 106]. Sepsis (lightning symbol) can influence many of these processes, thus cooperating with gut microbiota dysbiosis in MS pathogenesis.