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Review

Compartmentalization of the inflammatory response during bacterial sepsis and severe COVID-19

Jean-Marc Cavaillon[1,*], Benjamin G. Chousterman[2,3], Tomasz Skirecki[4]

[1] Institut Pasteur, Paris, France
[2] Department of Anesthesia and Critical Care, Lariboisière University Hospital, DMU Parabol, APHP Nord, Paris, France
[3] Inserm U942, University of Paris, Paris, France
[4] Department of Translational Immunology and Experimental Intensive Care, Centre of Postgraduate Medical Education, Warsaw, Poland

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ABSTRACT

Acute infections cause local and systemic disorders which can lead in the most severe forms to multi-organ failure and eventually to death. The host response to infection encompasses a large spectrum of reactions with a concomitant activation of the so-called inflammatory response aimed at fighting the infectious agent and removing damaged tissues or cells, and the anti-inflammatory response aimed at controlling inflammation and initiating the healing process. Fine-tuning at the local and systemic levels is key to preventing local and remote injury due to immune system activation. Thus, during bacterial sepsis and Coronavirus disease 2019 (COVID-19), concomitant systemic and compartmentalized pro-inflammatory and compensatory anti-inflammatory responses are occurring. Immune cells (e.g., macrophages, neutrophils, natural killer cells, and T-lymphocytes), as well as endothelial cells, differ from one compartment to another and contribute to specific organ responses to sterile and microbial insult. Furthermore, tissue-specific microbiota influences the local and systemic response. A better understanding of the tissue-specific immune status, the organ immunity crosstalk, and the role of specific mediators during sepsis and COVID-19 can foster the development of more accurate biomarkers for better diagnosis and prognosis and help to define appropriate host-targeted treatments and vaccines in the context of precision medicine.

Introduction

Bacterial sepsis has been recognized by the World Health Organization (WHO) as a global health priority.[1] The current estimates of 47–50 million episodes and nearly 11 million deaths per year, many of them children, come from a systematic review of data collected in 2017.[2] The number of cases during the pandemic due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is impressive (estimated to be 676,609,955 on March 10, 2023, https://gisanddata.maps.arcgis.com/apps/dashboards/bda7594740fd40299423467b48e9ecf6) while the total number of deaths might be higher than the official figures (i.e., close to 18 million by December 31, 2021 *vs.* 5.9 million reported by authoritative sources).[3] The flop to develop new drugs to address the sepsis challenge is a consequence of the failure of translational research, as well as a simplistic approach to sepsis that does not consider the great complexity of the syndrome and the great diversity of the patients.[4] To address Coronavirus disease 2019 (COVID-19), many therapeutic approaches have been inspired by the previous studies performed in bacterial sepsis, but a concomitant and dual inflammatory response with an immunosuppressive phase, in addition to an under-recognition of immune and inflammatory compartmentalization, has made the topic more critical[4,5] (Figure 1).

New tools, including -omic approaches and artificial intelligence (AI), are expected to enable the development of modern precision medicine aimed at improving early diagnosis, clinical management, patient prognostication, and clinical outcomes.

Severe COVID-19 has been classified as a viral sepsis[6] and it meets the sepsis definition as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[7] Indeed, a recent meta-analysis revealed that 77.9% of adult patients and 67% of the children hospitalized in the intensive

* Corresponding author: Jean-Marc Cavaillon, Jean-Marc Cavaillon, Institut Pasteur, Paris 75015, France.
E-mail address: jean-marc.cavaillon@pasteur.fr (J.-M. Cavaillon).

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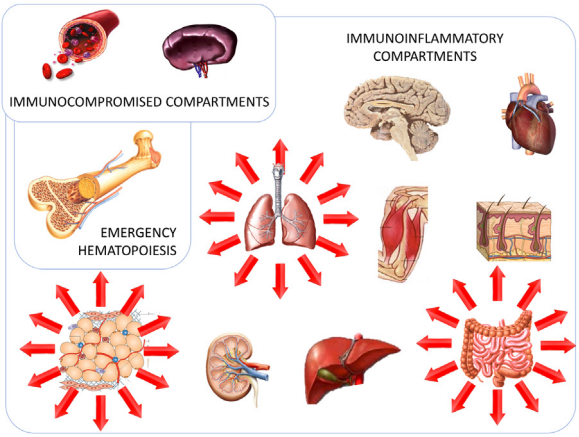

Figure 1. Compartmentalization. In contrast to the hematopoietic compartments (blood, spleen) where immune cells are essentially immunosuppressed, leukocytes within the other organs are rather activated. While a crosstalk perpetuates the inflammatory process, some tissues are more prone to propagate the systemic inflammation. This is particularly the case of the lungs and adipose tissue during severe acute respiratory syndrome coronavirus 2 infection or the gut during bacterial sepsis. The role of bone marrow and the emergency hematopoiesis appears ambiguous.

care unit (ICU) for SARS-CoV-2 infection met the sepsis 3.0 criteria.[8] Pulmonary thrombosis,[9] high levels of circulating D-dimer,[10] and transcriptional profile showing involvement of coagulation pathways in nasopharyngeal swabs[11] are reminiscent of the disseminated intravascular coagulation (DIC) encountered in bacterial sepsis. The altered immune status of the circulating leukocytes, particularly in terms of *ex vivo* cytokine production observed in COVID-19 patients,[12,13] is similar to that reported in bacterial sepsis.[14,15] Furthermore, long-term sequelae have been observed post both bacterial sepsis and severe COVID-19.[16] Mortality related to COVID-19 occurs following life-threatening complications, including cardiac and renal failure, cerebrovascular disease, and acute respiratory distress syndrome (ARDS). However multiple differences exist between COVID-19 and bacterial sepsis.[16] ARDS was first defined in 1967 as an acute onset of tachypnea, hypoxemia, and loss of lung compliance.[17] Among hospitalized COVID-19 patients, 33% develop ARDS, and 75% of those are admitted to ICU,[18] for whom the mortality rate is extremely high.[19] The incidence of ARDS among bacterial sepsis patients is lower, ranging from 6%[20] to 34%,[21] depending on the studies. Multi-omic comparison between COVID-19 ARDS and bacterial sepsis-induced ARDS identified in plasma 706 molecules (metabolites, lipids, proteins) differently abundant between the two ARDS etiologies, revealing more than 40 biological processes differently regulated between the two groups.[22] Similarly, a urine-based multi-omic comparative analysis identified 150 metabolites and 70 proteins that were differentially abundant between the two ARDS etiologies.[23] Despite the early papers claiming that COVID-19 was associated with a cytokine storm within the bloodstream as in bacterial sepsis, we and others refuted this idea.[24–26] In contrast, transcriptomic and proteomic analyses of bronchoalveolar lavage (BAL) fluid cells revealed a robust innate immune response with overexpression of genes involved in inflammation illustrating an excessive local pro-inflammatory cytokine release.[27,28] Such an observation is a hallmark of the concept of compartmentalization, defined as an inflammatory reaction that we postulated to occur in organs of sepsis patients concomitantly with the altered immune status that can be identified within the systemic circulation.[29]

The concept of compartmentalization of the inflammatory response: the precursor works

The idea of a specific immune response within the lungs emerged in 1972 when a distinct humoral and cellular immune response was observed in guinea pigs immunized either systemically or locally with the influenza virus vaccine[30]. The following year, it was similarly reported in humans that cell-mediated immunity in the lower respiratory tract was best stimulated by aerosol immunization, while subcutaneous immunization stimulated primarily a systemic immune response.[31] The concept of compartmentalization later appeared in a review published in 1977 by Johnson and Philp[32] who reported that the amplitude of the local and systemic immune responses initiated by a nasal vaccination was distinct from that following a systemic delivery of the antigen. In 1986, Fels et al.[33] compared intraperitoneal *vs.* intrapleural injection of *Cryptosporidium parvum*. They showed that the alteration of arachidonic acid metabolism in murine peritoneal or pleural macrophages was only observed in those cells derived from the injected cavity. The concept of compartmentalization in terms of cytokine production was first illustrated in rats that were systemically or intratracheally challenged with bacterial endotoxin lipopolysaccharide (LPS): increase in tumor necrosis factor (TNF) levels was confined to the LPS-challenged compartment.[34] In humans, the natural occurrence of compartmentalized cytokines was reported by Brandtzaeg et al.[35] studying patients with meningococcal meningitis and septic shock/bacteremia. They reported that TNF and interleukin-6 (IL-6) were localized to the subarachnoid space in patients with meningitis, but patients with septic shock tended to have elevated cytokines in both serum and cerebrospinal fluid.[35,36] Similarly, intravenous injection of LPS in human volunteers led to the detection of IL-8 in serum but not in BAL fluid.[37] However, such a discrepancy is not universal, and it may depend on the nature of the studied chemokine. For example, it was shown that intraperitoneal injection of LPS in mice can lead to the induction of high levels of RANTES (chemokine CC-ligand [CCL] 5) within the lungs.[38] The variations may also be due to different doses of LPS injected. Systemic reaction is not an all-or-nothing process and is probably a continuum related to the site and intensity of local insult. During bacterial peritonitis, not surprisingly, a major intraperitoneally compartmentalized cytokine response occurs in humans.[39] In patients undergoing appendectomy, TNF was present in peritoneal fluid but not in plasma, and IL-6 levels were very high in peritoneal fluids but low in plasma.[40] Of note, the plasma levels of cytokines may be misleading and reflect neither their tissue concentration nor their local biological activity. This remark also concerns patients suffering from pneumonia or ARDS for whom significant levels of cytokines, such as IL-6 and IL-8, were found in the BALs but also in serum.[41] A crosstalk between compartments was strongly suggested by the correlation between the levels of soluble IL-6 receptor and soluble TNF receptors I and II found in plasma and in pleural effusion and by the correlation observed between the levels of transforming growth factor-β (TGF-β) in pleural effusion and in BAL in septic patients.[42] The

differential location of the highest concentration of some mediators, either in plasma or in the pleural cavity, argues in favor of both a systemic and a compartmentalized response. The idea is that systemic features result both from the draining of the local reaction into the circulation and from the generalized response due to circulating cells and the vascular endothelium. For example, a relocation of inflammatory cells in the serosal cavities during acute inflammation such as the pleura or the peritoneum has been observed during pneumonia.[43]

Because cytokines can be trapped by the surrounding cells in their environment, measurable levels of cytokines in biological fluids represent the "tip of the iceberg."[44] In addition to cytokines, other inflammatory players, such as inducible nitric oxide synthase (iNOS), have been shown to be compartmentalized in severe sepsis: NOS activity was increased in putrescent areas in muscle and in fat tissues.[45] Another hallmark of compartmentalization is the status of leukocytes which can vary depending upon their localization. In murine models of hemorrhagic shock and endotoxemia, the transcriptional regulatory factors NF-κB and cAMP response element binding protein (CREB) as well as the extracellular regulated kinase 2 (ERK2) and the mitogen-activated protein kinase1/2 were activated in the lung neutrophils but not in peripheral blood neutrophils.[46,47] Most interestingly, the immune status of cells from different compartments can be fully different. For example, neutrophils isolated from the sputum of subjects with chronic bronchial sepsis fail to respond to IL-10, in contrast to their blood neutrophils.[48] In contrast to the circulating monocytes from sepsis patients, which have been shown to be reprogramed toward a reduced capacity to release inflammatory cytokines, macrophages derived from inflammatory foci can be more responsive in terms of IL-1 release upon *ex vivo* activation than normal cells as reported in patients with ARDS[49] or peritonitis[50] In 2001, one of us,[29] Munford and Pugin[51] came to a similar conclusion: during systemic inflammation, the immune response is compartmentalized. In other words, despite the systemic nature of the host's response in sepsis, the events observed within the bloodstream may not reflect events occurring within the tissues. Importantly, the plasma from septic patients was considered to be an immunosuppressive milieu[52] as was illustrated by the presence of certain anti-inflammatory cytokines such as IL-10 in plasma which was shown to contribute to the intracellular sequestration of human leukocyte antigen (HLA)-DR in monocytes during septic shock, a hallmark of the altered immune status of these patients.[53]

Immune cells differ from one compartment to another

Sender et al.[54] have revealed the total number (1.8×10^{12}) of immune cells in all compartments of the human body. The bone marrow and the lymphatic tissue host the greatest number of immune (7×10^{11} each). This analysis reminds us that the nature of immune cells varies greatly from one compartment to another while they are present in the gastrointestinal tract, lungs, skin, adipose tissue, skeletal muscles, kidneys, and blood. For example, the number of immune cells in the skin is twice that in the blood. Therefore, the analysis of blood leukocytes to monitor the whole body's immune status can be questioned.

Most animal studies on immunity investigate tissue-harvested cells (e.g., splenocytes, lung, bone marrow, and peritoneal cavity). In contrast, most studies in humans are performed on circulating cells from the blood samples due to their availability, even though immune processes usually take place in both lymphoid and non-lymphoid tissues. However, even in animal studies, immune cells of the same origin are rarely compared at different sites. Nevertheless, multiple lines of evidence indicate that the immune cells of the same origin differ depending on their localization in different tissues. For example, in mice, macrophages from the spleen, the lungs, the peritoneal cavity, and the brain each exhibit different cell surface markers (e.g., CD11a, CD93, VCAM-1, and CX3CR1) and express different gene profiles.[55] Murine tissue-resident macrophages (microglia, Kupffer cells, spleen macrophages, lung macrophages, peritoneal macrophages, gut macrophages, and monocytes) display a distinct epigenetic landscape.[56] It was elegantly demonstrated that differentiated tissue-resident macrophages could be reprogrammed when transferred into a new microenvironment. Most interestingly, the capacity to release cytokines (IL-1, IL-6, TNF, and IL-8) which is very pronounced for human monocytes in response to *Staphylococcus aureus*, interferon-γ (IFN-γ) or phorbol myristate acetate, is nil for intestinal macrophages.[57] On the other hand, murine alveolar macrophages have specific properties as they do not express toll-like receptor (TLR) 9 in contrast to peritoneal macrophages and bone marrow-derived macrophages,[58] and they do not produce IFN-β in response to TLR3- and TLR4-agonists, in contrast to peritoneal macrophages.[59] On the contrary, TLR9 expression has been observed on human alveolar macrophages[60] which do produce type I IFN in response to viruses.[61] In mice, it was shown that the TNF production in response to *S. aureus* is particularly dependent on the phagocytic process of the bacteria and on the phagosome maturation for murine monocytes, while this is not the case for peritoneal macrophages and to a limited extent for alveolar macrophages.[62] This heterogeneity is further complicated by the existence of different macrophage subsets within the murine heart, liver, lung, kidney, and brain, as revealed by single-cell transcriptomics.[63] This has been nicely demonstrated in the analysis of the mouse kidney-resident macrophages[64]: the transcriptomic analysis revealed seven distinct macrophage subpopulations, which are organized into zones corresponding to regions of the nephron. Each subpopulation was identifiable by a unique transcriptomic signature, suggesting distinct functions. Following ischemic kidney injury, the original localization of each subpopulation was lost, either from changing locations or transcriptomic signatures. The original spatial distribution of kidney macrophages was not fully restored for at least 28 days after injury. Recently, metabolic differences, specifically dependence on the oxidative phosphorylation of macrophages residing at different sites, were shown in both humans and mice.[65] The existence of monocyte subsets has also been demonstrated within the blood compartment. For example, it was reported in humans that following an insult such as severe surgery, the reduced expression of HLA-DR occurs within a few hours among the $CD14^{HIGH}$ $CD16^{-}$ monocyte subset when a similar reduction of HLA-DR expression needed 1 day to be observed on $CD14^{LOW}$ $CD16^{+}$ monocytes.[66] Another degree of complexity is added by the fact that circulating monocytes can be recruited to the inflammatory

focus, and once differentiated into macrophages, they can display inflammatory signatures different from that of resident macrophages as illustrated in the murine model of experimental autoimmune encephalomyelitis when comparing monocyte-derived macrophages and microglia-derived macrophages in brains and spinal cords.[67]

The recruitment of neutrophils (polymorphonuclear [PMN] cells) is another hallmark of inflammation. A local insult results in their local recruitment; for example, the combination of mechanical ventilation and bacteria significantly increased the influx of neutrophils into the BAL fluid in a murine model of mechanical ventilation.[68] Interestingly, still in a mouse model, PMN recruitment can occur in different tissues during a systemic insult such as sepsis, as illustrated by the presence of infiltrating PMN within the myocardium resulting in cardiac dysfunction.[69] In human peritonitis, recruited PMN in the abdominal cavity have increased levels of IL-8 mRNA as compared to circulating neutrophils.[70]

Similarly, in patients with cystic fibrosis, a distinct profile of expressed cytokines has been reported for blood and sputum PMN, while the responsiveness of the latter to anti-inflammatory signals such as glucocorticoids or IL-10 appeared impaired.[71,72] In patients with ARDS, blood and alveolar neutrophils were distinct from circulating cells of healthy subjects, with increased CD11b and reduced CD62L expression, primed oxidase responses, resistance to phosphoinositide 3-kinase inhibition, and delayed constitutive apoptosis.[73]

A sequential characterization of natural killer (NK) cell responses in the spleen, lungs, bone marrow, peritoneum, and blood in mice injected with endotoxin revealed that the expression of activation markers (CD69 and CD25) and effector molecules (IFN-γ, granzyme B, and IL-10) displayed an organ-specific expression.[74] Adoptive transfers of spleen and lung NK cells proved that these cells have the capacity to quickly adapt to their new environment and adjust their response levels to that of resident NK cells.[74] This investigation supports the concept of compartmentalization of human NK cells responses during systemic inflammation, associated with the extravasation of NK cells into the sites of inflammation.[75] The characteristics of NK cells reflect their compartmentalization with different surface markers expression and transcriptomes depending on whether they are present in human blood, spleen, or lungs.[76,77]

Data from human transplant donor studies showed that the majority of mucosal, lymphoid, and non-lymphoid tissue T cells are tissue-resident cells (usually with the expression of CD103 marker), while half of the blood T cells have an effector memory phenotype.[78,79] Importantly, even the tissue-resident T cells have a differential transcriptomic profile depending on the tissue of residency.[80] Also, memory B cells have a tissue-dependent transcriptomic profile.[81] Importantly, such differences are preserved in both humans and mice, enabling animal model studies.[82] It should be emphasized that the tissue-resident lymphoid cells develop and seed the distal tissues upon activation by pathogens or commensals, and the specific-pathogen-free mice present poor occurrence of these cells.[83,84] One possibility to overcome this critical caveat is the generation of the so-called “dirty mice” by co-housing laboratory mice with wild or pet shop animals.[85,86] Dirty mice show an abundance of tissue-resident T cells and mimic the immune response to sepsis better than the “clean” laboratory mice.[86]

Immune response differs from one compartment to another

There are not many studies that simultaneously compared the immune cells from different compartments during experimental or clinical sepsis. The most demonstrative investigation was performed by the team of Irshad Chaudry, the “father” of the cecal ligature and puncture (CLP) murine model of sepsis.[87] They compared the *ex vivo* production of IL-2, IL-6, TNF, and IFN-γ by activated peripheral blood mononuclear cells (PBMCs), spleen macrophages, alveolar macrophages, and Kupffer cells following CLP or CLP preceded by trauma-hemorrhage. The *ex vivo* LPS-induced production of IL-6 and TNF by PBMCs and spleen macrophages was reduced as compared to sham animals, whereas those by alveolar macrophages and Kupffer cells were enhanced. While an alteration of the immune status of circulating human blood monocytes has been regularly reported during sepsis,[14,88] it should be emphasized that the bone marrow-resident monocytes are primed for regulatory function prior to their bone marrow egress and ahead of the development of systemic inflammation during murine acute intestinal parasitic infection.[89] Most interestingly, the hemophagocytosis syndrome, which is characterized by the activation of inflammatory processes in the bone marrow, is a hallmark of a subset of sepsis patients.[90–92] An aggressive immunosuppressive therapy has been suggested to be beneficial for those patients.[93] Indeed, in COVID-19, the use of recombinant interleukin-1 receptor antagonists (rIL-1Ra; Anakinra®) has been suggested to be beneficial in patients with such hemophagocytosis syndrome.[94] Because the immune status of leukocytes varies greatly depending on the compartment from where they are derived it would be inappropriate to describe the sepsis patients as unequivocally immunosuppressed.[95] Multiple examples illustrate that within tissues, immune cells could be pre-activated while those within the bloodstream or in the spleen are rather de-activated. In mice injected with LPS, alveolar macrophages do not undergo endotoxin tolerance as do blood monocytes or peritoneal macrophages.[96,97] Similarly, in humans intravenous LPS injection suppresses the *ex vivo* PBMC response to LPS[98] but primes that of alveolar macrophages[99] as does an LPS instillation.[100] Similarly, in mice receiving an LPS pre-conditioning 18 h before a second LPS challenge, TNF levels were lower in plasma but higher in the renal cortex as compared to control mice.[101] In the brain, a similar observation was made: microglial cells ($CX3CR^+CCR2^-$) isolated from sepsis survivor mice 5 days post–CLP produce increased TNF compared to sham-operated animals upon *ex vivo* stimulation with LPS.[102] One of the most extensive characterizations of the response of macrophages residing in different organs in response to sepsis and sterile injuries (myocardial infarction and stroke) showed that the specific tissue residence was a more important factor determining the response of these cells than the trigger of the major injury in mice.[103]

In healthy human blood neutrophils, CD24 ligation induces cell death through depolarization of the mitochondrial membrane in a manner dependent on caspase-3 and caspase-9 and reactive oxygen species. A decreased CD24 expression observed on blood neutrophils from sepsis patients was associated with

a lack of functionality of the molecule because cross-ligation of CD24 failed to trigger apoptosis.[104] Furthermore, populations of immunosuppressive mature and immature neutrophils are found in the blood of sepsis patients. In co-culture, CD66b$^+$ sepsis neutrophils inhibit the proliferation and activation of CD4$^+$ T cells.[105] In contrast, lung mature neutrophils of sepsis and COVID-19 patients are continuously recruited from circulation and progress toward a hyperinflammatory state driven by TNF and IL-1β. Upon recruitment, likely via the IL-8/CXCR2 axis, airway neutrophils acquire a distinct phenotype and produce inflammatory cytokines dominated by IL-8, IL-1β, IL-6, and CCL3/4, along with elevated levels of neutrophil elastase and myeloperoxidase, the hallmarks of transcriptionally active and pathogenic airway neutrophilia.[106] The presence of neutrophil extracellular traps (NETs) was found in the airway compartment and neutrophil-rich inflammatory areas of the interstitium in the lungs of COVID-19 patients, while NET-prone primed neutrophils were present in arteriolar microthrombi. These results support the hypothesis that NETs may represent drivers of severe pulmonary complications of COVID-19.[107] Accordingly, targeting lung neutrophilia and NETosis-associated lung impairment in sepsis and COVID-19 patients is highly desirable.[108]

An increased IL-17 production by $\gamma\delta$ T lymphocytes has been observed in the lungs of mice exposed to CLP.[109] In the skin of mice who underwent CLP, resident memory CD8$^+$ T-cells maintain antigen-dependent "sensing and alarming" function, analyzed in terms of IFN-γ production, whereas spleen CD8 T-cells produce less IFN-γ as compared to sham animals.[110] In the lungs, the CLP-induced sepsis did not influence the number of CD4$^+$ and CD8$^+$ T cells while the number of liver CD8$^+$ T cells increased.[111] Also, the CD4$^+$ T cells residing in the bone marrow of septic mice showed preserved ability to cytokine production together with a lower apoptosis rate in comparison to splenic T cells.[112]

The same receptors or the same mediators can play different roles depending upon the compartment

It has been reported that depending upon the localization of the insult, the same cell surface receptors, or even the same cytokines, can have opposite effects. A very elegant demonstration of this phenomenon was achieved with mice in which TLR4 was specifically deleted either in myeloid cells or in hepatocytes. In the mice undergoing CLP, TLR4 in hepatocytes was required for efficient LPS clearance from the circulation, and its deletion was associated with enhanced macrophage phagocytosis, lower bacterial levels, and improved survival in CLP without antibiotics, suggesting that TLR4 on hepatocytes is rather deleterious. In contrast, the absence of TLR4 in myeloid cells was associated with greater mortality as compared to wild-type mice, illustrating that TLR4 expression in myeloid cells is rather protective.[113] The role of different pattern recognition receptors (PRRs), was assessed in peritoneal or pulmonary *S. aureus* infection models. Using scavenger receptors-deficient mice (CD36 KO; Scavenger receptor-A [SR-A] KO; MARCO KO) and TLR2 KO mice, it was shown that these PRRs play opposite roles, being protective during lung infection but deleterious during peritoneal infection.[114] A similar dichotomy was reported for IL-10. Using IL-10 receptor-deficient mice and comparing cutaneous infection *vs.* pulmonary infection by *Francisella tularensis*, it was shown that IL-10 was deleterious in cutaneous infection but protective in pulmonary infection.[115] Of note, the respective role of a given innate immune player may vary depending on the nature of the infectious agent. It was reported that CD137, a member of the TNF receptor family, was protective during Gram-positive peritoneal infection (*S. aureus*; *Streptococcus pneumoniae*; *Enterococcus faecalis*) but deleterious during Gram-negative peritoneal infection (*Escherichia coli*; *Pseudomonas aeruginosa*; *Salmonella enterica* serovar *Typhimurium*).[116] Other examples are given when comparing the responsiveness of monocytes to that of monocytes-derived macrophages. IL-10 behaves as an anti-inflammatory cytokine when added to adherent monocytes but primes non-adherent monocytes.[117] Similarly, the anaphylatoxin C5a enhances monocytes responsiveness to LPS[118] but decreases that of M-CSF or GM-CSF-derived macrophages.[119]

Heterogeneity of organ-specific endothelium

Not only do immune cells vary from organ to organ, but the endothelium displays major differences depending on the tissues.[120–124] The endothelium plays a critical role being at the interface between the bloodstream and organs. Particularly during inflammation, it orchestrates cell adherence and recruitment as well as the coagulation process. Endothelial cells throughout the body are heterogeneous, and this is tightly linked to the specific functions of organs and tissues. Organ-specific endothelial cell signatures are determined from development onwards and conditioned by their microenvironments during adulthood. Microvascular endothelial cells have distinct morphological characteristics reflecting the permeability control required to exert their physiological function. Vascular permeability and leukocyte recruitment are predominantly regulated at the level of the capillaries and postcapillary venules, which show organ-specific structural differences based on inter-endothelial connections. There are three main types of capillaries. Non-fenestrated continuous capillaries, characterized by low permeability and a high abundance of tight junctions and caveolae, allowing the most controlled passage of blood and soluble components in the blood, are found in the heart, lungs, and brain. Discontinuous capillaries allowing free passage are found in the spleen, liver, and bone marrow. Fenestrated endothelium has an intermediate permeability and is characterized by sparse tight junctions to ensure proper filtration and transendothelial transport. It is found in the microvasculature of the kidney, gastric endocrine glands, and intestinal mucosa. The intestinal-specific endothelial identity has been recently reviewed.[125] These endothelial cells are specialized for gut nutrient absorption and are critical for the recruitment of enterotropic lymphocytes and gut immunosurveillance. Furthermore, cell surface receptors of endothelial cells, their secretory profile and their metabolism vary from organ to organ. The tissue-specific diversity of endothelial cells is reflected by their expression of genes characteristic for a given site and maintained during inflammatory response.[126] This specificity influences leukocyte trafficking and activation.[126,127] Accordingly, the heterogeneity of tissue endothelial cells can be perceived as a key orchestrator of the compartmentalization of immune response.

Specific local microbiota influences tissue and systemic response

A relationship was established between the local mucosal microbiota and the systemic viral load, spike-specific antibody responses, and inflammatory cytokine levels.[128] Local microbiota is another player that varies between compartments. Gut microbiota is well-known to be required not only for the development of local immunity but also for physiological and emergency hematopoiesis.[129,130] For years, the gut has been claimed to be the motor of multiple organ failure.[131] Emerging evidence displays an important role of gut micro-organisms (including bacteria, fungi, eukaryotic viruses, and bacteriophages) and their derived metabolites in both the susceptibility to as well as outcomes of sepsis.[132] The gut microbiome becomes pathologically altered in sepsis (so-called "pathobiome"), which likely contributes to the development of sepsis-associated encephalopathy.[133] Disruption of the microbiome while treating sepsis with antibiotics can itself result in immune dysregulation. Alterations in the gut microbiome resulting from sepsis and its treatment have been implicated in organ dysfunction typical of sepsis.[134] The gut virobiome that partly consists of bacteriophages is also detectable in gut contents that might be different between sepsis and normal hosts.[135]

The cutaneous microbiome also plays a role in the establishment and maintenance of skin immunity. Importantly, the infant skin flora and common causative pathogen(s) both contribute to neonatal sepsis.[136] Similarly, respiratory tract microbiota shape local immune responses.[137] Sepsis alters the pulmonary microbiota by enrichment with the gut microbiota, which correlates with local inflammation.[138] Investigations of the respiratory microbiome led to the identification of three- and four-factor signatures that predicted ARDS, hospital-acquired pneumonia, and prolonged mechanical ventilation with relatively high accuracy.[139] A role for the nasopharyngeal microbiome in regulating local and systemic immunity that determines COVID-19 clinical outcomes has also been reported by Smith et al.[140] Their study illustrates that during severe COVID-19, microbial dysbiosis and high levels of IL-33, IFN-λ3, and IFN-γ in the nasal mucosa associated with a distinct pattern of inflammatory cytokines in the bloodstream are a testimony of the importance of microbiota and compartments during COVID-19.[141] Multiple microbiota-directed interventions are currently under investigation in the setting of sepsis, including fecal transplant, the administration of dietary fiber, and the use of antibiotic scavengers that attenuate the effects of antibiotics on the gut microbiota while allowing them to concentrate at the primary sites of infection.[135]

Lungs are the site of immune activation during sepsis and COVID-19

Before it acquired its new definition,[7] sepsis was previously defined as a systemic inflammatory response to infection.[142,143] This old definition is fully illustrated by the fact that independent of the site of infection, a major modification of gene transcripts can be monitored within the blood leukocytes. For example, in patients with peritonitis or with pneumonia, 3437 genes were similarly modulated, although 113 were specific to community-acquired pneumonia and 1454 were specific to fecal peritonitis.[144] A comparison of the gene expression profile within the blood revealed an unexpectedly low number of 307 genes common to sepsis and COVID-19 when 3839 were specific to severe COVID-19 and 125 to bacterial sepsis.[145] Most interestingly, a comparison of differentially expressed gene transcripts in tissue samples (lungs, heart, kidneys, liver, and spleen) from meningococcal septic shock patients revealed a great number of genes specific to each organ: 827 out of 2039 in the lungs, 982 out of 2029 in the heart, 837 out of 2231 in the kidneys, 559 out of 1531 in the liver, while surprisingly, the spleen expressed the lowest number of modulated genes, 435 of which 182 were specific to this organ.[146] A similar study included transcriptomic analysis of the cortex and hippocampus of patients who died of septic shock.[147] The study reveals that the brain also displays a specific pattern of activated and repressed genes.

While the altered immune status of circulating cells reflects systemic aggression, also revealed by increased levels of circulating cytokines,[148] many organ analyses in humans demonstrated a major perturbation of homeostasis which could lead to organ dysfunction and damage, as illustrated within the liver,[149] the kidneys,[150] the muscle,[151] the heart,[152] the adipose tissue,[153] the bone marrow,[154] and the brain.[155] Indeed, neuroinflammation is a major life-threatening event occurring in COVID-19 patients associated with immune activation within the central nervous system,[156] leading to encephalopathy that is well recognized in sepsis patients.[157]

Frequently altered lung function and ARDS are a hallmark of severe COVID-19 and bacterial sepsis. Depending on the studies, up to 44% of the patients with bacterial sepsis developed acute lung injury.[158] Nevertheless, post-mortem analysis of sepsis patients revealed that lung pathology was detected in 90% of the studied subjects.[159] The frequency of ARDS is great among hospitalized COVID-19 patients, reaching up to 75% among the most severe patients admitted to ICU.[18] In a murine model of sepsis, it was elegantly demonstrated, using transfection of antisense oligonucleotides (ODN), that sepsis-induced gene overexpression of iNOS, cyclooxygenase-2, histamine H1-receptor, platelet-activating factor receptor, and bradykinin B1 and B2 receptors in lung tissues was significantly inhibited by NF-κB decoy ODN, thereby illustrating that NF-κB is a central transcription factor during sepsis.[160] Among the other molecules and molecular platforms that orchestrate the inflammatory response during sepsis and COVID-19, the inflammasome plays a central role.[161,162] Indeed, preventing the action of IL-1β released after inflammasome activation by its natural antagonist (rIL-1Ra) was reported to be beneficial in severe COVID-19.[163]

Comparison of biomarkers, cell content, and cell surface markers in the alveolar space and in the peripheral blood illustrates the local inflammatory process during sepsis. Among the cytokines, IL-8 is particularly elevated in the BAL of patients with ARDS as compared to serum levels.[164] In a murine experimental model, intranasal instillation of LPS in mice that survived sepsis led to higher levels of MIP-2 and S100A8/A9 in the BAL as compared to control, with enhanced lung injury, increased alveolar permeability, increased neutrophil recruitment, illustrating that sepsis could predispose to enhanced LPS-induced lung injury.[165] In agreement with this experimental model, it was noticed that the pulmonary source of the initial septic shock was an independent risk factor for subsequent ICU-

acquired pneumonia.[166] In a porcine endotoxin shock model, the expression of major histocompatibility complex class II was lower on blood CD14$^+$ CD163$^+$ monocytes as compared to BAL monocytes.[167] This observation was in conformity with a similar analysis performed in patients with septic shock[168] or in patients with pneumonia-related ARDS.[169] Furthermore, in the later patients, there was a lower PD-L1 expression on the alveolar than on blood monocytes of ARDS (when expressed in mean fluorescence intensity).

As previously mentioned, a major cytokine storm is occurring within the lungs of the COVID-19 patients as revealed by transcriptomic analysis.[27,28] The intensity of the inflammatory process within the tissues associated with the development of organ dysfunction is a hallmark of sepsis and to a lesser extent of COVID-19[170–173] (Figure 2). Concomitantly, the coagulation and complement systems are activated, further contributing to the local inflammatory process.[24] In addition, alveolar macrophage activation, NETosis, anti-Type I IFN auto-antibodies, DAMPs release (e.g., S100A8), and viral cytopathogenicity contribute to the alteration of pulmonary function. The role of the coagulation process is illustrated by significantly increased levels of d-dimers, thrombin-antithrombin complexes, soluble tissue factor, C1-inhibitor antigen, tissue-type plasminogen activator, and plasminogen activator inhibitor type I in the bronchoalveolar compartment.[174] The high levels of inflammatory cytokines (IL-1Ra, IL-6, IL-8, IL-10, chemokine CXC-ligand −10, IFN-γ, and TNF) in endotracheal aspirates as compared to serum suggests local production.[175] Of note, among the inflammatory cytokines present in bronchial aspirates obtained during invasive mechanical ventilation of COVID-19 patients, IL-1α, oncostatin M, and tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL) showed the strongest association with in-ICU mortality.[176] Among the players that could contribute to lung tissue injury, a protease-anti-protease imbalance (neutrophil elastase *vs.* alpha-1 antitrypsin) has been reported in the airways of SARS-CoV-2-ARDS patients.[177] In contrast, some markers are particularly abundant within the bloodstream of COVID-19 patients, such as vascular endothelial growth factor (VEGF) and several vasoactive eicosanoids.[178] In addition to soluble mediators which locally contribute to the alteration of the lung tissues, activated immune cells, particularly T lymphocytes and myeloid cells in the respiratory tract perpetuate lung pathology and disease pathogenesis. Through longitudinal profiling of paired airways and blood from patients, Szabo et al.[179] revealed many important features of severe COVID-19. They confirmed that COVID-19 airways contain elevated levels of myeloid and T cell-derived cytokines (i.e., Granzyme B, CCL2 (monocyte chemoattractant protein-1) CCL3 (MIP-1α) CCLL4 (MIP-1β), IL-7, and lymphotoxin). They showed that airway T cells in COVID-19 are dominated by tissue-resident memory T cells expressing higher levels of T cell activation markers (HLA-DR and programmed cell death protein 1) as compared to blood T-cells. Similarly, HLA-DR expression is higher among airway myeloid cells as compared to those in the blood. Furthermore, inflammatory gene signatures of T cells and myeloid cells are enriched in the airways of COVID-19 patients. Finally, COVID-19 lung autopsies exhibit specific and extensive accumulation of monocytes and macrophages relative to control lungs. A crosstalk between pro-inflammatory macrophages and IFN-γ producing cytotoxic lymphocytes is associated with severe tissue damage.[180] Indeed, in COVID-19, there is a positive feedback loop between macrophages and T cells inside the lung that produces a prolonged and destructive inflammation. In the majority of patients with SARS-CoV-2 infection, the alveolar space was persistently enriched in T cells and monocytes. SARS-CoV-2 infects alveolar macrophages, which in turn respond by producing T cell chemoattractants. These T cells produce IFN-γ that induces inflammatory cytokine release from alveolar macrophages and further promotes T cell activation.[181] In contrast, sepsis mainly causes immune cell activation and burst, and inflammation tends to resolve rapidly.[182]

The inflammatory process is perpetuated by a crosstalk between compartments—a major contribution of the bone marrow

The crosstalk between organs during sepsis has been well described and documented.[24] For example, a crosstalk between the gut and brain has been suggested in a rat model of sepsis,[183] and an acute kidney injury can affect distant organs, including heart, lung, spleen, brain, liver, and gut.[184] However, the way each organ contributes to propagating the inflammatory process remains poorly understood, and feedback loops between injured tissues are not fully deciphered. Among the compartments, the bone marrow plays a central role by delivering throughout the whole organism the innate and adaptive immune cells needed to address the infectious process. Sepsis induces a similar expansion and proliferation of early hematopoietic stem and progenitor cells (HSPC) while committed progenitors decrease. It was suggestive that the Notch pathway contributed to this effect in a humanized mice model of sepsis and endotoxemia.[185] More recently, it was reported that the deubiquitinase ubiquitin-specific peptidase 22 which regulates the levels of mono-ubiquitinated histone H2B was an intracellular regulator of this process.[186] The phenomenon, known as “emergency hematopoiesis,” aims to provide urgently needed leukocytes[187] (Figure 3). The boosting of hematopoiesis is triggered by the pathogen-associated molecular patterns (PAMPs) provided by the infectious agents, the damage-associated molecular patterns (DAMPs) released by altered host cells and damaged tissues during the infectious process and by hematopoietic cytokines (macrophage-colony stimulating factor [M-CSF], granulocyte CSF [G-CSF], GM-CSF, and IL-3). Concomitantly, chemokine CXC-ligand 12 (stromal cell-derived factor-1), the main chemokine that regulates the homing and maintenance of HSPC in this niche, is downregulated during inflammation, allowing the mobilization of HSPC to the periphery.[187,188] Furthermore, IL-1 was initially recognized as a factor boosting hematopoiesis, acting in synergy with the hematopoietic factors and was early named “hemopoietin-1.”[189] IL-1 can be induced by PAMPs and favors the release of IL-3.[190] Within an amplification loop, IL-3 potentiates the inflammatory response by favoring inflammatory cytokines production by mouse macrophages.[191] Accordingly, IL-3, which is a cytokine involved in early differentiation and proliferation of the bone marrow cell, fuels the cytokine storm and amplifies the inflammatory process during murine sepsis.[192] Thus, emergency hematopoiesis associated with myeloid priming, innate and adaptive immunity, and inflammation could contribute to the pathobiology of sepsis and COVID-19.[187] The presence of immature neutrophil populations indicating the occur-

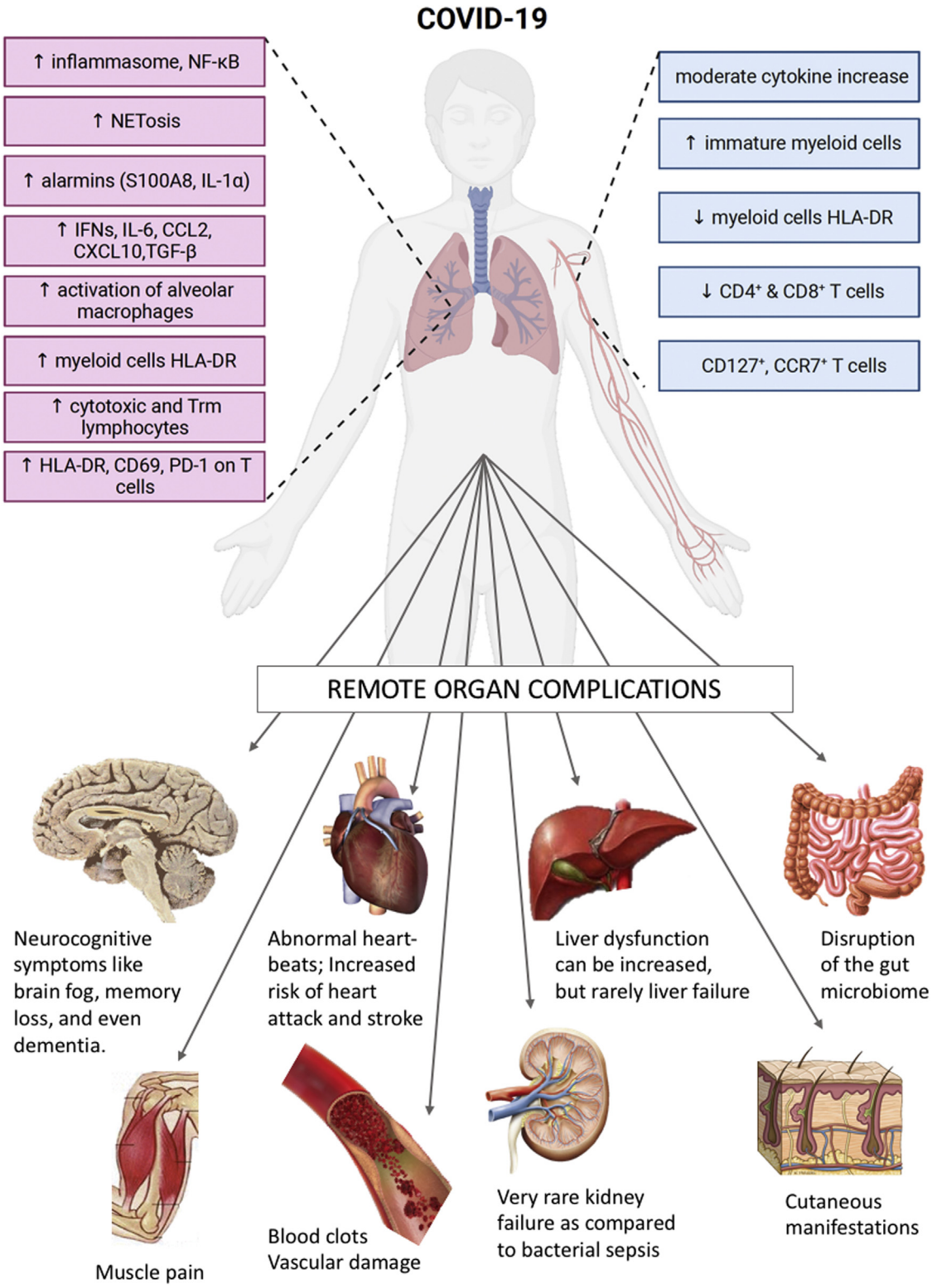

Figure 2. Lung *vs.* systemic immune responses in COVID-19 and remote organ injury.
CCL: Chemokine CC-ligand; CXCL: Chemokine CXC-ligand; HLA: Human leukocyte antigen; IFN: Interferon; IL: Interleukin; NET: Neutrophil extracellular trap; NF-κB: Nuclear factor κB; PD-1: Programmed cell Death protein 1; TGF: Transforming growth factor.

rence of emergency granulopoiesis in the bone marrow has been linked to a potential immunosuppressive role of neutrophils during SARS-CoV-2 infection.[193,194] A comparison of the immune profile of severe COVID-19 with non-SARS-CoV-2 pneumonia ICU patients showed that increased emergency myelopoiesis and adaptive immune paralysis were observed in both clinical settings. Of note, pathological immune signatures suggestive of T-cell exhaustion were exclusive to COVID-19.[195] Similarly, T-cell exhaustion has been regularly reported in bacterial sepsis.[196,197] Most importantly, the inflammatory environment

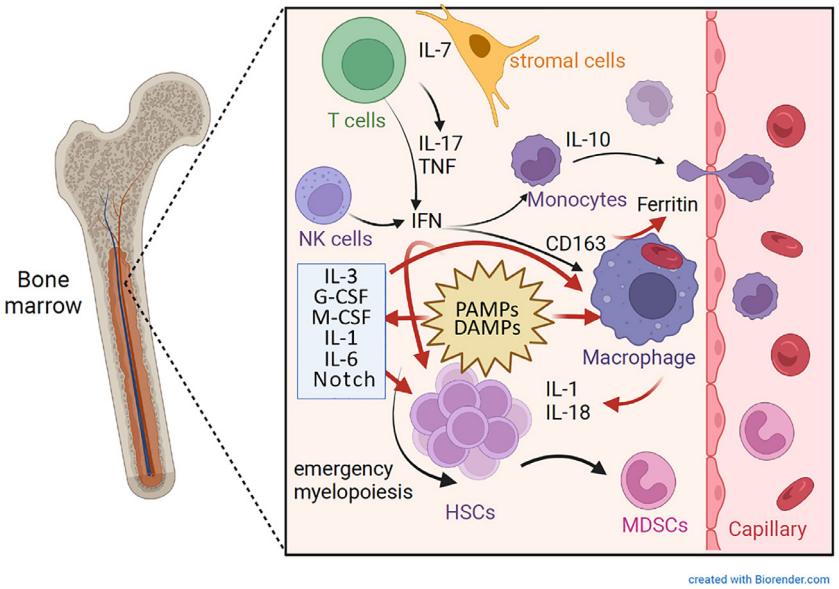

Figure 3. The bone marrow in sepsis. During systemic infection PAMPs and cytokines enter bone marrow where they are sensed by both stromal and hematopoietic cells (including mature cells as macrophages and stem and progenitor cells). Induction of G-CSF, IL-1, IL-3, IFN, and Notch boost proliferation and myeloid differentiation of HSCs. HSCs also egress from the bone marrow due to altered chemokine gradients and proteolytic milieu. Massive inflammation leads to the generation of myeloid-derived suppressor cells which contribute to immunocompromised systemic response. Bone marrow macrophages not only sense PAMPs but also can bind haptoglobin via CD163 which activates them and, in some patients, lead to features of MAS. Macrophage-derived cytokines also modulate hematopoiesis. Tissue-resident T cells and NK cells reside in the bone marrow and are not paralyzed in sepsis as their splenic counterparts. NK cells are the source of IFN which induces anti-inflammatory phenotype of emigrating monocytes.
DAMPs: Damage-associated molecular patterns; G-CSF: Granulocyte-colony stimulating factor; HSCs: Hematopoietic stem cells; IFN: Interferon; IL: Interleukin; MAS: Macrophage Activating Syndrome; M-CSF: Macrophage-colony stimulating factor; MDSCs: Myeloid-derived suppressor cells; NK: Natural killer; PAMPs: Pathogen-associated molecular patterns; TNF: Tumor necrosis factor.

related to emergency hematopoiesis can reprogram the differentiation of granulocytes. In septic mice, Wang et al.[198] identified stressed granulocytes with innate immune memory. Those leukocytes pose an amplified immune response, specifically causing lung injuries and increasing mortality during secondary infections. Additionally, the bone marrow is the primary site of $CD4^+$ memory T cell homing and proliferation after sepsis-induced lymphopenia. These cells have the capacity to migrate outside the bone marrow niche and engraft murine secondary lymphoid organs.[112] Of note, hematopoietic factors have been suggested to be of putative interest to boost the altered immune status of circulating cells.[199] Noteworthy, systemic inflammation can stimulate extramedullary hematopoiesis, particularly in the spleen and the liver. Macrophages maintain the bone marrow hematopoietic stem cells niche and regulate HSPC activity by supplying various cytokines and retention factors.[200] Endothelial cells and mesenchymal stromal cells also secrete factors that promote hematopoietic stem cell maintenance in these niches.[201] During a murine model of sepsis and in humans, the spleen has been identified as a major site of megakaryopoiesis and platelet production, and spleen-derived protective platelets may be broadly immunomodulatory in acute inflammatory states such as sepsis.[202]

Taking into account the compartmentalized immune response for improved COVID-19 vaccination

During bacterial sepsis, adaptive immunity has been regularly reported to be suppressed as a reflection of lymphopenia and up-regulation of programmed cell death protein 1/PDL-1 interaction between regulatory T cells and antigen-presenting cells. The adaptive immunity plays a limited role during the early phase of sepsis and the proposal of vaccines as prevention of sepsis has been rarely put forward, except in a few cases, such as meningococcemia[203] *S. pneumoniae*,[204] *P. aeruginosa*, *Klebsiella pneumoniae*, and *E. coli* infections.[205,206] After Chedid et al.[207] offered the basis for a universal anti-endotoxin antibody, it has been attempted to address Gram-negative sepsis with passive therapy using anti-LPS antibodies. Anti-endotoxin vaccines have been proposed to cope with the increasing occurrence of antimicrobial-resistant Gram-negative bacteria, but they would merit further studies.[208] In the case of COVID-19, the induction of a compartmentalized adaptive immunity could be considered by mucosal vaccination. Because of the mode of contamination by SARS-CoV-2 through the nose and the throat, natural infection initiates both local and systemic immunity. However, an analysis addressing both plasma and nasopharyngeal swabs revealed two types of responses.[140] Some patients had IgA and IgG antibodies in both compartments while others had antibodies only present in plasma. Natural infection allows the maintenance of SARS-CoV-2-specific immune memory within tissues.[209] Up to 6 months after infection, SARS-CoV-2-specific $CD4^+$ T, $CD8^+$ T (in lower frequency than $CD4^+$T cells), and B cells were predominantly localized in the lung and lung-associated lymph nodes. Based on the natural immune response to SARS-CoV-2 infection, mucosal vaccination could be supported to provide a suitable local and systemic immune response.[210] Furthermore, while intra-muscular vaccination did not prevent the vaccinated subject from being a carrier of the virus once naturally infected and spreading the virus, a stronger local immunity could limit the contamination process and be an appropriate approach for preventing

future pandemics. As recently reported respiratory mucosal immunization with a next-generation adenoviral-vectored trivalent COVID-19 vaccine expressing spike induces protective mucosal immunity against SARS-CoV-2 via induction of systemic and local antibodies, lung-tissue-resident memory T cells, and trained alveolar macrophages.[211] Another approach would be to use mucosal vaccination to boost a previous systemic delivery of the vaccine.[212] Thus, the compartmentalized immune response should be seen as an advantage in proposing new vaccination strategies, but should also be carefully considered when immunotherapies are proposed in order to avoid an undesirable boosting effect of the inflammatory response.

Precision medicine and compartmentalization

Efforts to transfer to the bedside the therapies that had been successful in pre-clinical murine models of sepsis have failed, as most of the clinical trials included a heterogenous sepsis population, without taking into account the site of infection, the nature of the infectious agent, the failed organ or any biological parameters that would allow to identify the subset of patients who may benefit from a given treatment.[4] For example, a re-analysis of the rIL-1Ra (anakinra) sepsis trial indicated that a subgroup of patients with features of the hemophagocytosis-like syndrome (i.e., based on the presence or the absence of concurrent hepatobiliary dysfunction and disseminated intravascular coagulation) might benefit from the IL-1 blockade.[93] A similar beneficial effect was reported in COVID-19 patients with secondary hemophagocytic lymphohistiocytosis[94] and subsequent meta-analysis suggested that rIL-1Ra could reduce the mortality risk in patients with signs of hyperinflammation such as C-reactive protein concentrations higher than 100 mg/L.[163] Interestingly, re-analysis of the trials of activated protein C led to the identification of subsets of patients who respond differently to activated protein C.[213] High ferritin levels can also enrich the selection of therapy-responsive patients.[214] While the benefit of glucocorticoids in sepsis remains debatable, and only a subset of septic shock patients could benefit from the treatment,[215] their use in a homogenous group of patients with severe community-acquired pneumonia or oxygen-dependent COVID-19 was shown to be beneficial.[216] Even more benefits can be obtained by patients who present specific endotypes, and this example highlights the importance of defining endotypes in sepsis and COVID-19.[217]

Sepsis or COVID-19 patients can display an immunosuppressed status, as revealed by the analysis of plasma markers and circulating blood leukocytes. Accordingly, for the introduction of biological therapies, it is critical to identify patients who may benefit from either immunostimulatory or immunosuppressive treatment.[218] However, during sepsis and COVID-19, the concomitant expression of tissue inflammation and immunosuppression has been regularly reported.[179,219,220] Thus, immunosuppressive or immunostimulant therapies should precisely target different compartments.

IL-7 has been shown to reverse the lymphopenia associated with human sepsis and to restore the peripheral T-lymphocytes function,[221] and GM-CSF to upregulate the HLA-DR expression on monocytes in septic patients with multi-organ dysfunction and to concomitantly increase of the *ex vivo* whole blood TNF response.[222] Both recombinant G-CSF and GM-CSF have pleiotropic immunomodulatory action during sepsis.[223] The compartmentalization process illustrates that the altered immune status is not a global defect[95] and the ambiguous behavior of GM-CSF questions the systemic or local administration of this cytokine in sepsis and COVID-19.[95,224]

Of note, the use of IFN-γ to boost the immune status among mechanically ventilated patients with acute organ failure, compared with placebo neither significantly reduced the incidence of hospital-acquired pneumonia nor the occurrence of death on day 28. But most importantly, and in agreement with our concerns,[225] the trial had to be discontinued early due to a higher rate of respiratory complications in patients receiving the treatment. The poor lung tolerance of IFN-γ in critically ill patients suggests a specific immune response to treatment in this compartment.[226]

As a consequence of these heterogeneous behaviors of immune cells depending on their organ localization, targeted approaches to deliver drugs aimed to specifically address immune cell functions in tissues appear as the most promising strategy.[227–229] For example, it was recently demonstrated that a phosphoinositide 3-kinase-γ inhibitor specifically targeted toward hepatic parenchymal cells without compromising other cells could be beneficial in restoring organ function in sepsis.[230]

The lungs are the organs most easily targeted, using direct drug delivery by aerosol therapy.[227] The other organs require passage through different biological barriers, but several targeting strategies have been developed, including small molecules (e.g., peptides, nucleic acids), large molecules (e.g., antibodies), or nanoparticles.[228,229] By tailoring the properties of nanoparticles, including size, shape, surface chemistry, and site-specific drug delivery in organ, cellular, and subcellular levels could be achieved.[231] Thus, the systemic administration of a drug for local delivery or a local effect is now achievable.[229,232]

The comprehensive research on the different compartments of immune response requires proper analytical tools. Furthermore, as high-throughput molecular techniques, including multi-omics, are producing gigabytes of data, only approaches leveraging AI and machine learning can boost the discoveries of proper biomarkers and pathophysiological crosstalks. Then, at the bedside, both of these techniques are believed to be helpful in the prediction, diagnosis, subphenotyping, prognosis assessment, and clinical management of sepsis.[233–237] Whether the use of AI will appropriately address compartmentalization remains an open question.

Conclusions and Perspectives

The numerous failures of the development of host-targeting treatments in sepsis clearly indicate the need for a change in the research paradigm.[4] The phenomenon of the compartmentalization of the immune response in the course of sepsis was under-recognized for a long time despite clear signs of its presence.[29] In agreement with our review questioning the validity of analysis performed on circulating blood leukocytes to define the global immune status of patients,[225] Conway Morris et al.[238] pointed out that mechanisms that predominate in one tissue may not dominate or even be relevant in other tissues. Only recently did the progress in large-scale immunological methods together with the focus on the comparison be-

tween immune cells from different organs bring a broader attention of researchers to this issue. Because of the specific lung pathology observed in severe COVID-19 patients, this viral sepsis has offered an opportunity for the scientific community to focus on local immunopathology to emphasize the importance of the concept of compartmentalization.[5,29] Understanding the tissue-specific responses of the immune cells during severe infections should enable a more precise selection of therapeutic targets and appropriate biomarkers. As a consequence, this could increase the specificity and safety of novel therapies aimed to favor precision medicine.

While performing the proofreading of this manuscript, an important contribution was published by Takahama et al.[239] supporting the concept of compartmentalization. Measuring dynamic changes in genes expression across organs, the authors beautifuly established the specific responsiveness of different tissues and cell types in a murine CLP model, and upon LPS injection. A pairwise cytokines injection mirrors the various impacts of sepsis across tissues.

Author Contributions

Jean-Marc Cavaillon: Writing – original draft, Writing – review & editing. **Benjamin G. Chousterman:** Writing – review & editing. **Tomasz Skirecki:** Writing – review & editing.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Not applicable.

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