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REVIEW

During Sepsis and COVID-19, the Pro-Inflammatory and Anti-Inflammatory Responses Are Concomitant

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Abstract
The most severe forms of COVID-19 share many features with bacterial sepsis and have thus been considered to be a viral sepsis. Innate immunity and inflammation are closely linked. While the immune response aims to get rid of the infectious agent, the pro-inflammatory host response can result in organ injury including acute respiratory distress syndrome. On its side, a compensatory anti-inflammatory response, aimed to dampen the inflammatory reaction, can lead to immunosuppression. Whether these two key events of the host inflammatory response are consecutive or concomitant has been regularly depicted in schemes. Initially proposed from 2001 to 2013 to be two consecutive steps, the concomitant occurrence has been supported since 2013, although it was proposed for the first time in 2001. Despite a consensus was reached, the two consecutive steps were still recently proposed for COVID-19. We discuss why the concomitance view could have been initiated as early as 1995.

Keywords Compensatory anti-inflammatory response syndrome (CARS) · Cytokines · Immunosuppression · SARS-CoV-2 · Systemic inflammatory response syndrome (SIRS) · Trauma

COVID-19 Allowed Rediscoveries of Well-Established Knowledges Characteristic of Bacterial Sepsis

The zoonotic severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused COVID-19 pandemic of which severe cases most commonly involve respiratory manifestations. COVID-19 includes dysregulation of the host response, triggering wide-ranging immuno-inflammation, thrombotic, and parenchymal derangements. Complement system activation, activation of alveolar macrophages, NETosis, alarmin release, anti-interferon auto-antibodies, coagulation, viral cytopathogenicity, obesity, and old ages are among the aggravating players. Evidence for many distinctive mechanistic features indicates that COVID-19 constitutes a new disease entity [1]. Modeling approaches suggest that by the end of 2021, some 18 million people had died because of the pandemic, a greater number than the official figures [2]. Sepsis has been defined as a life-threatening organ dysfunction caused by dysregulated host response to infection [3], and severe COVID-19 is considered to be a viral sepsis [4]. A recent meta-analysis revealed that indeed 77.9% of adult patients and 67% of the children hospitalized in intensive care unit (ICU) for SARS-Cov-2 infection met the sepsis 3.0 criteria [5]. Thus, not surprisingly, many features and parameters reported for bacterial sepsis were recovered in COVID-19 [6]. Unfairly, the publications in high impact factor journals rarely mentioned the precursors' works. For example, the contribution of the C5a/C5aR axis found in COVID-19 [7] had been reported 21 years earlier for bacterial sepsis [8]. Similarly, the synergy between gamma-interferon (IFNγ) and tumor necrosis factor (TNF) resulting in cell death, tissue damage, and mortality in COVID-19 [9] had been demonstrated 29 years earlier in the endotoxin shock model [10].

A Compartmentalized Cytokine Storm

The earlier publications claimed that COVID-19 was associated with a cytokine storm [11, 12]. But soon, a careful analysis of the exact levels of circulating cytokines within the blood stream revealed that there was not such a peripheral storm [13–15], and Dan Remick's team rather proposed

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the term "cytokine drizzle" [16]. Nevertheless, circulating cytokines represent the tip of the iceberg [17], meaning that even low levels suggest an involvement of cytokines in the pathological process. Of note, both pro-inflammatory and anti-inflammatory cytokines were reported in the blood of COVID-19 patients [18]. In contrast, the investigations performed within the respiratory tract of severe COVID-19 patients revealed a robust innate immune response, a chemokine-dominant hypercytokinemia, high expression of IFN-inducible genes, and an overrepresentation of genes involved in inflammation [19]. The cytokine expression profile in bronchoalveolar lavage fluids (BALF) suggests excessive pro-inflammatory cytokine release as a hallmark of COVID-19 patients [20]. SARS-CoV-2 virus infection stimulates a unique transcriptome profile in COVID-19 patients' BALF. This specificity of severe COVID-19 patients was confirmed by the analysis of 72 plasma biomarkers when compared with other community-acquired pneumonia consecutive to either *Streptococcus pneumoniae* or influenza infections [21]. The major lung inflammation in severe COVID-19 is a clear example of what was claimed early in the field of bacterial sepsis, i.e., the compartmentalization of the host response recognized in 2001 [22, 23] with the blood stream as a testimony of an immunosuppressive milieu [24].

The Story of a Theoretical Scheme

Sepsis went through different definitions. Initially, sepsis was defined as a systemic inflammatory response syndrome (SIRS) associated with infection [25]. While the notion of SIRS has not been further supported by intensive care doctors, it re-emerged with COVID-19 [26, 27]. In 1997, Roger Bone coined a new concept, the compensatory anti-inflammatory response syndrome (CARS) [28]. In other words, inflammation is associated with a regulatory mechanism aimed to dampen the inflammatory process. But CARS has a side effect, i.e., the suppression of the immune system. We revisited the idea and considered that CARS should be considered as an adapted compartmentalized response with the aim to silence some acute pro-inflammatory genes and to maintain the possible expression of certain genes involved in the anti-infectious process [29]. Then, from 2001 to 2013, a theoretical figure was proposed by different authors providing schemes displaying a two-step process with two waves of events: first the pro-inflammatory response and then followed by the anti-inflammatory response [30–37] (Fig. 1A). This vision of the inflammatory response was extended to other clinical settings than sepsis such as trauma [38, 39] and pancreatitis [40]. By 2013, some authors accompanied their two-step scheme with a contradictory comment: "rigorous examination of previous studies provides evidence that both pro-inflammatory and opposing anti-inflammatory response(s) occur concomitantly in sepsis" [37]. Indeed, as early as 2001, we claimed that both phases were concomitant and published a figure illustrating the simultaneity of the two processes [23]. In fact, in 1995, three different groups reported significant correlations ($0.57 \leq r \leq 0.87$) between the levels of circulating IL-10 with those of IL-6, IL-8, and TNF [41–43]. Not only these results illustrated that both pro-inflammatory and anti-inflammatory cytokines were present at the same time but also that the intensity of the anti-inflammatory response is proportional to that of the pro-inflammatory response [44] (Fig. 1B). IL-10, a well-known anti-inflammatory cytokine (although this

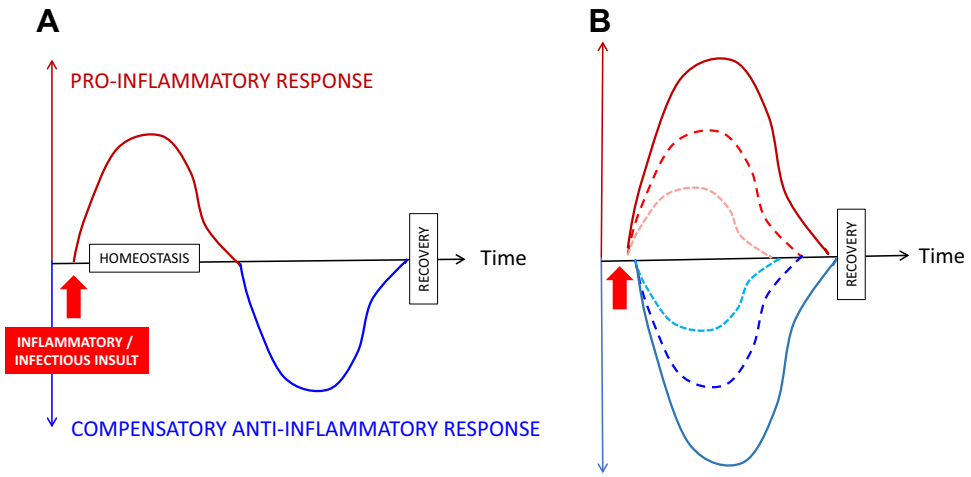

Fig. 1 **A** To characterize the host response to sterile or infectious insult, a two-step event has been regularly proposed from 2001 to 2013, suggesting that following any severe insult (trauma, surgery, pancreatitis, infection…), the host response is characterized by a pro-inflammatory reaction reflecting a systemic inflammatory syndrome (SIRS) and then followed by a compensatory anti-inflammatory syndrome (CARS). **B** From 2013, although already proposed in 2001, a consensus was reached agreeing on a concomitant pro-inflammatory and anti-inflammatory response. Importantly, the intensity of both responses is proportional

statement is a bit too simplistic [45]!), is present very early after any insults (e.g., major trauma and resuscitation after cardiac arrest) and is a marker of severity [46, 47]. The arbitrary distinction of separating sepsis into pro-inflammatory and anti-inflammatory phases was not supported by gene expression data [48, 49]. Furthermore, pro- and anti-inflammatory responses were shown to be regulated simultaneously from the first moments of septic shock [50]. Indeed, in a murine model of sepsis, levels of both pro-inflammatory markers and anti-inflammatory markers (including soluble TNF receptors) are predictive of early mortality [51]. The consequences of the CARS on the immune system are observed extremely rapidly. A decrease of HLA-DR expression on monocytes, a recognized marker of immunosuppression, was observed to occur during surgery [52]. In sepsis, IL-10 was shown to be responsible for the sequestration of surface HLA-DR by monocytes [53]. The reduction of the ex vivo cytokine production upon activation of blood leukocytes also takes place while the patients are still under surgery [54]. Similarly, a decreased ex vivo cytokine production was observed soon after admission of patients with severe multiple injury [55]. Peter Pickkers' team sampled patients on the site of car accident and reported the early presence of danger-associated molecular patterns (DAMPs), the early decreased HLA-DR expression, and the early reduced ex vivo cytokine production [56]. In agreement with these reports was this conclusion on CARS in sepsis patients: "We found no evidence to support a two-phase model of sepsis pathophysiology or any immunological changes related to higher risk of secondary infections" [57]. In this context, the scientific and medical community reached a consensus, and since 2013, reviews have been regularly published [58–65] that provide schemes supporting a concomitant occurrence of SIRS and CARS in full agreement with the concept we introduced in 2001 [23], also applicable to trauma [66, 67] and COVID-19 [63]. Thus, it was most surprising to read a recent paper on COVID-19 [68] with a figure very similar to that published 14 years earlier (and in which the original source of the figure was not cited) providing the successive two-step process [35]. While in our Fig. 1 we depicted a happy ending with a recovery and a return to homeostasis, a persistent inflammation—immune suppression catabolism syndrome (PICS)—can occur associating a persistent low-grade inflammation with defects in innate and adaptive immunity [69]. These patients may lately return to functional life, or can be discharged to long-term acute care facilities, or may suffer prolonged decline and end with indolent death.

Conclusion

The story of this theoretical scheme illustrates that thinking out of the box may only lead to consensual agreement once the tenors in the field will have made the idea their own. But even if a consensus has been reached and a common vision has been shared, some are not immune to retrograde ideas.

Author Contributions I wrote the whole manuscript.

Declarations

Competing Interests I declare no competing interests.

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