



The Physiopathology of Cytokine Secretion in Severe Acute Respiratory Distress

Lissoni P*, Rovelli F, Fumagalli L, Monzon A, Messina G and Di Fede G

Institute of Biological Medicine, Milan, Italy

*Corresponding author: Lissoni P, Institute of Biological Medicine, Milan, Italy; E-mail: paolo.lissoni@gmx.com

Abstract

Irrespectively of its specific cause, ARDS represents one of the most severe complications, and it has been proven to be due to an absolute profound alteration involving several cytokine secretions, which are depending on an exaggerated immunoinflammatory biological response of patients rather than on the direct action of pathogenic agent itself. The most common ARDS-related cytokine profile is consisting of abnormally high blood levels of TNF-alpha, IL-6, and IL-17A, by realizing a concomitant occurrence of both macrophage- and TH17-mediated inflammatory processes. The abnormal cytokine secretions could be potentially controlled through three essential strategies, represented by the administration of monoclonal antibodies against some specific cytokines, the administration of other cytokines with antagonistic effects, and in a new manner a pharmacological neuroimmune manipulation of the cytokine network. Because of their fundamental physiological role in the neuroimmunomodulation and their complete lack of toxicity, the pineal hormone melatonin and cannabinoid agents could constitute the more appropriate drugs.

Keywords: ARDS; Cannabinoids; Coronavirus; COVID-19; Melatonin; Pineal gland; SARS

Introduction

The recent advances in the knowledge of the physiopathology of human systemic diseases have demonstrated that the immunoinflammatory biological response is under a central regulation [1], which is mediated by a great number of proteins, the so-called cytokines, namely released from the activated immune cells. Most cytokines have received the definition of interleukins (ILs), and at present the number of proteins classified as interleukins is 40 [2]. In addition to the proteins defined as interleukins, we have to consider at least some other cytokines provided by a fundamental role in the regulation of the biological response, namely TNF-alpha [3] and TGF-beta [4], respectively characterized by an inflammatory, or an anti-inflammatory activity, even though they are both provided by a common immunosuppressive action, atleast in the anticancer immunity. The secretion of the different types of cytokines substantially depends on the interaction between macrophage and lymphocyte systems, particularly by the T lymphocytes. Several T lymphocyte subsets have been discovered, but from a clinical point of view

the regulation of the immune system would mainly depend on three fundamental subpopulations of T cells, which may be recognized on the basis of the different types of molecules expressed on their cell surface, the so-called clusters of differentiation (CDs), and which consist of T helper (TH) lymphocytes (CD4+), regulatory T (T reg) lymphocytes (CD4+CD25+), and TH17 lymphocytes (CD4+CD17+). TH cells may be furtherly classified into TH1 and TH2 cells, not in relation to a different CD expression, but only in relation to the different type of cytokines produced by them. TH1 cells release IL-2, gamma-interferon (IFN) and IL-21, whereas TH2 mainly produced IL-4, IL-5, IL-6, IL-10 and IL-13. T reg cells may secrete TGF-beta, IL-10, IL-22, and IL-35, while TH17 have been proven to secrete IL-17, which exists in six isoforms; the most biologically active of them is IL-17A [5]. On the other side, the classification of macrophages is more undefined, even though they are generally subdivided into M1 and M2 macrophages, respectively characterized by a major inflammatory and anti-inflammatory activity [6]. As far as the biological function of

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interleukins is concerned, it has been shown that most of them are characterized by an inflammatory activity, which, however, has appeared to be due to different mechanisms. The group of cytokines provided by inflammatory activity includes IL-1 beta, IL-6, IL-17, IL-18, IL-20, IL-22, IL-23, IL-24, IL-32, IL-36, and IL-38 [2]. Moreover, it has been demonstrated that some interleukins generally classified as anti-inflammatory cytokines on the basis of their *in vitro* effects [2], have appeared *in vivo* to induce an inflammatory status, such as IL-4 and IL-13, because their stimulatory effect on histamine release, with a consequent possible development of a capillary leak syndrome [7]. Other interleukins, namely IL-2, IL-12, IL-15, and IL-21, may exert both inflammatory and anti-inflammatory effects, depending on their dosage and on the different experimental and clinical conditions [8]. On the other side, the number of interleukins provided by a clear anti-inflammatory effect is very low, and it is substantially limited to IL-10 [9], IL-30, IL-35, and IL-37 [2]. IL-10 is namely produced by T reg lymphocytes, as well as TGF-beta [4,9]. In addition, more recently it has been identified the existence of at least two different origins of the inflammatory status [10], represented by the macrophage system namely through the release of IL-1 beta, IL-6, IL-18, and TNF-alpha, and by the lymphocyte system, due to TH-17 cells through the secretion of IL-17 [5]. Obviously, lymphocyte-related inflammation is a more recent form of inflammation with respect to that mediated by the macrophage system from a phylogenetic point of view. Macrophage-mediated inflammatory status is more typical of the advanced metastatic diseases [11], while that induced by TH17 lymphocytes would represent the type of inflammation characterizing the autoimmune diseases [12]. IL-2 has appeared to counteract TH-17 differentiation and IL-17 production, and this IL-2 activity is inhibited by IL-1 beta [12]. Then, IL-1 beta, as well as IL-6 and IL-23, contributes to stimulate TH17 cell functions. Therefore, at present it is known that the inflammatory status, which characterizes each severe systemic human disease would be due to different types of interaction occurring between macrophage and lymphocyte systems, since the dysfunction of immune system itself may be synthetically interpreted as the end-result of macrophage-lymphocyte relationships. The whole system of cytokines constitutes the cytokine network, whose great complexity is mainly depending on the fact that several cytokines are connected among them by positive feedback mechanisms, then by reciprocal stimulatory circuits. The systemic human diseases would be substantially due to unbalanced ratios among the three major T cell subsets, consisting of TH1-to-T reg cell ratio [13], TH17-to-T reg cell ratio [14], and, even though with less importance, TH1-to-TH17 cell ratio. The metastatic cancer is characterized by a progressive decrease in TH1-to-T reg cell ratio [13], while the autoimmune diseases are characterized by an abnormally high

TH17-to T reg cell ratio [14]. Macrophage-related chronic inflammation, which characterizes the advanced neoplastic diseases [15], may be clinically identified by the evidence of abnormally high blood levels of TNF-alpha and IL-6, as well as by an abnormally low lymphocyte-to-monocyte ratio (LMR) [16]. On the other side, TH17 lymphocyte-related inflammation, which is responsible for the pathogenesis of the autoimmune diseases, is clinically recognized by the occurrence of abnormally high blood concentrations of IL-17 [17], as well as by a normal or enhanced LMR, at least during the remission phase of disease [16]. Finally, it has been well documented that the cytokine network is physiologically under a central neuroendocrine regulation, which is the expression of the psychospiritual life [18], namely realized by the pineal gland [19,20] through the circadian light/dark release of several indole and beta-carboline neurohormones, the most investigated of them is the indole hormone melatonin (MLT) [19,21]. The pineal gland plays its immunostimulatory and immunoregulatory role namely in connection with brain cannabinoid system [22], while the brain mu-opioid system would exert a major immunosuppressive activity [23].

The Acute Respiratory Distress

The acute respiratory distress syndrome (ARDS), which includes the severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV, represents one of the most severe clinical complications, which may occur during lung injury, disseminated cancer, or coronavirus infection. Despite the different causes, ARDS would be due to similar mechanisms, consisting an abnormal and excessive inflammatory cytokine endogenous secretion, namely that of TNF-alpha [24] and IL-6 [25]. Then, ARDS would mainly depend on host biological immunoinflammatory response, namely mediated by the macrophage system, rather than to a direct action of some specific cause. In any case, more recently it has been shown that TH-17-related inflammation is also involved in ARDS [26]. In more detail, it has been shown that the concomitant occurrence of a TH-17 lymphocyte-related inflammation in patients with ARDS, as shown by the evidence of abnormally high blood concentrations of IL-17A, as well as by an evident increase in TH17-to-T reg cell ratio (TH17/T reg), may allow a more severe and often lethal prognosis [26]. This evidence may be simply explained by the fact that a decline in the functionless of T reg cell system would allow a more severe host inflammatory reaction. Then, if we consider that macrophage-related inflammation is more typical of the metastatic tumours [11,15], while TH-17-related inflammation is namely involved in the autoimmune diseases [12,14], it appears that ARDS-related inflammatory status could be imaginatively considered as the synthesis of the clinical complications of both metastatic cancer and autoimmune disorders in their exacerbation phase. Therefore,

the clinical evolution of ARDS would have to be monitored by detecting LMR values, TH17/T reg cell ratio, and blood levels of TNF-alpha, IL-6, IL-10, and IL-17A. The histopathological examination of lungs in patients with coronavirus-induced ARDS shows oedema, proteinaceous exudate with globules patchy inflammatory cellular infiltration and formation of hyaline membranes, diffuse alveolar damage, and pneumocyte desquamation [27]. The clearly higher mortality of aged patients during viral infections, including the COVID-19 one, could be namely due to age-decline in the functionless of the immune system, consisting of progressive increase in TH17 cell [28] and decline in T reg cell counts [29], with a following increase in TH17/T reg cell ratio, which allows a greater risk of ARDS in the case of lung injury or lung viral infections. On the contrary, children are less resistant to ARDS development at least in part because of their higher blood levels of MLT itself [21].

Possible New Strategies in the Treatment of ARDS

Being due to a profound alteration in the endogenous production of cytokines, it is obvious that the cure of ARDS would have to consist of a modulation of the cytokine network. One way is represented by the administration of monoclonal antibodies against those cytokines, whose secretion are abnormally increased, such as Certolizumab for TNF-alpha, and Tocilizumab for IL-6, but the complexity of cytokine alterations makes as difficult a similar approach. ARDS-related TH17 cell abnormal activation could be counteracted by IL-2 itself, since IL-2 has been proven to inhibit TH17 cell system [12], but its potential inflammatory action could furtherly negatively influence the clinical course of ARDS, even though low-dose IL-2, which may be well tolerated [8], might allow a decline in TH17/ T reg cell ratio by activating T reg cell system and inhibiting TH17 cell hyperfunction, with a consequent possible improvement of the prognosis of ARDS itself. Another simple and non-toxic strategy to modulate host immunoinflammatory reactivity in an inhibitory way may be drawn from the recent advances in the psycho-neuro-endocrine-immunology (PNEI) [18]. In fact, it has been shown that the inflammatory status induced by both macrophage and TH17 cell system hyperactivation may be blocked through a neuroendocrine approach, with a consequent possible inhibition at least in part of TNF-alpha, IL-6 and IL-17 secretions. In more detail, according to the knowledgements of PNEI, the secretion of both TNF-alpha and IL-6 may be counteracted by the pineal hormone MLT [30,31], while that of IL-17 may be blocked by the non-psychotic agent of Cannabis, the cannabidiol (CBD) [32], or by its endogenous equivalent palmitoyl-ethanol-amide (PEA) [33]. CBD is not a CB1-CB2 agonist, but it may inhibit the activity of the main enzyme involved in cannabinoid destruction, the fatty acid amide hydrolase (FAAH), with a following possible increase in brain cannabinoid endogenous content [34,35]. In

addition, MLT has also been proven to reduce the clinical severity of most viral infections in experimental conditions, including various encephalitis viruses, Ebola virus, and COVID-19 itself [31,36]. Finally, MLT has also appeared to counteract TGF-beta - induced fibrosis following tissue damage [37]. The clinical advantage of MLT is in its completely lack of toxicity even at very high pharmacological doses, corresponding to 1mg/day in healthy subjects [38] and 100 mg/day in very compromised metastatic cancer patients [39]. Obviously, dosage and schedule of treatment may be established only by clinical investigations. Finally, the ARDS-related cardiopathy could achieve some benefits from oxytocin therapy, because of its cardioprotective activity and its important role in heart regeneration either alone, or by stimulating atrial natriuretic peptide (ANP) secretion, which is also provided by cardioprotective effects [40].

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