Journal of Pharmaceutical Care & Health Systems
ISSN: 2376-0419

Gomes et al., J Pharma Care Health Sys 2016, 3:3
DOI: 10.4172/2376-0419.1000166

Review Article Open Access

Anti-Inflammatory Cytokines in Sepsis: Immunological Studies and *In Silico* Investigation

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Received date: Jun 10, 2016; **Accepted date:** July 28, 2016; **Published date:** Aug 12, 2016

Abstract

The pathophysiology, diagnosis, treatment and prognosis of sepsis remain major challenges for contemporary clinical practice. In this sense, efforts to broaden the knowledge about the mechanisms involved in systemic inflammation and to identify new methods for detecting sepsis in the early stages and the stratification of patients are extremely important. The purpose of this paper is to review the role of the anti-inflammatory cytokines in sepsis and present perspectives on the *in silico* investigation of the role of these mediators in this nosological entity, using the computational system *AutoSimmune*.

Keywords: Cytokines, Inflammation, In silico research, Sepsis.

Introduction

Cytokines are low molecular weight proteins (polypeptides) or glycoproteins secreted by leukocytes and by various other cells in the organism, in response to diverse stimuli [1]. The function of these molecules is to mediate the interactions between the cells of the affected organism in order to establish an effective immune response [2].

These substances are often named according to their cellular sources and their action in other cells. Thus, for example, those produced by leukocytes and which act on other leukocytes are called interleukins (IL) [1]. It is also important to note that other compounds are known by common names unassociated with their functionality, such as tumor necrosis factor and the interferons. There is yet another group of cytokines, the chemokines, which are thus named due to their effect on leukocyte chemotaxis and behavior [3].

The clinical importance of these substances is mostly related to their function in inflammatory processes and their ability to generate immune responses to external stimuli [2]. There are cytokines that function primarily as inductors of inflammation - pro-inflammatory cytokines -, while others act in counter regulation processes - the anti-inflammatory cytokines [4]. The inflammatory response is controlled by both groups of cytokines. Examples of markedly pro-inflammatory cytokines include tumor necrosis factor (TNF), interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 8 (IL-8), and interleukin 17 (IL-17) [4]. On the other hand, the principal cytokines possessing an anti-inflammatory effect, known to date, include the interleukins IL-4, IL-10, IL-22, IL-13, IL-1RA, and transforming growth factor β (TGF-β) [3]. It is known that the action of IL-10, IL-1AR, and TGF-β takes place, primarily in the innate immune response, while anti-inflammatory action on specific immunity is mediated by IL-4 and IL-13. It is important to note that the action of the cytokines is directly linked to some of their properties, as summarized in Table 1.

Properties of the Cytokines
Rapid and self-limiting secretion
Not stored as pre-formed molecules
Are able to act in different cell types (pleiotropism)
Are redundant (several cytokines with the same effect)
Influence the synthesis of other cytokines
Local and/or systemic action
Able to bind to membrane-specific receptors
May stimulate proliferation and new functions of target cells
Action on mRNA synthesis processes

Table 1: General properties of the cytokines in human immunological system. **Source:** Material elaborated by the authors based on references 1 and 2.

The role of the cytokines in human medicine has been amply studied over the past years, and, especially in the context of sepsis, deserve notice for their central role in the pathophysiology of this disease. Sepsis, before 2016 had been defined as a systemic inflammatory response due an infection [5-6]. However, now we have to define sepsis as a life-threatening organ dysfunction caused by infection. For clinical operationalization sepsis defined by a clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less by a dysregulated host response to infection [7]. The rate of occurrence is high, with over 1665 cases of sepsis occurring yearly in

the United States, reaching a lethality rate of 20–50 percent [8]. It is also important to note that, even with ideal treatment, the possibility of death is approximately 40 percent and can be greater than 50 percent in the most severe cases [9-12].

It is known that in sepsis, the widespread participation of pathogen-responsive cells evolves with the production and secretion of several pro-inflammatory cytokines. However, in addition to this intense pro-inflammatory activity, anti-inflammatory cytokines are also produced, which are implicated in the development of anergia and in the slowed response to etiologic agents. Regulation of this anti-inflammatory response is associated with the progression of the sepsis state, whether to resolution or death, and is carried out by a complex web of mediators [13-14].

Simulations of the immune system have been used in the study of certain clinical situations in order to better understand the pathophysiological aspects of disease in humans [15-16]. In this sense the use of multi-agent systems is interesting, in which cells of the organism, their products (e.g., cytokines, antibodies, etc.) and the antigens can be implemented as independent agents that interact amongst themselves, following a specific set of rules for each of these agents, for different contexts [15,17].

The implementation of the cytokines in *AutoSimmune* (immune system simulator) is performed as values scattered in arrays of data parallel to the agent interaction environment [18].

Thus, in this paper, we present the principal aspects of the pathogenesis of the anti-inflammatory response in sepsis. We, also, highlight the main anti-inflammatory cytokines. which can be used like biomarkers in the clinical setting. In addition, we argue about the new perspectives for in silico investigation of sepsis, using the *AutoSimmune* computer system.

Methods

The research methodology that was used for the text making based on a PubMed search, using the fixed descriptor sepsis, always in association with one of the anti-inflammatory cytokines under investigation, including interleukin 1-RA (IL-1RA), interleukin 4 (IL-4), interleukin 10 (IL-10), interleukin 13 (IL-13), interleukin 22 (IL-22) and transforming growth factor β (TGF-β).

Among the results of the searches described in Table 2 during the process of choosing papers, we focused on the text that best correlated the role of the anti-inflammatory cytokines in the context of sepsis and its possible etiologies. Thus, 1,651 citations were obtained, from which 21 papers were selected. After reading the papers, the material was organized in four sections (1) The anti-inflammatory cytokines, and (2) The anti-inflammatory cytokines in the context of sepsis and a brief commentary was made on the perspectives for scientific investigation using *in silico* experimentation the section *AutoSimmune*: overall characteristics and anti-inflammatory cytokines emphasizing the use of the *AutoSimmune* computational system.

Strategies	Number of Citations Obtained
Sepsis+"interleukin 4"	210
Sepsis+"interleukin 10"	1273
Sepsis+"interleukin 22"	7
Sepsis+"interleukin 13"	30
Sepsis+"interleukin 1RA"	3
Sepsis+"TGF beta"	128
Total	1651

Table 2: Distribution of the number of citations obtained following the search strategy up to 31/12/2015.

Anti-Inflammatory Cytokines

The cytokines IL-4, IL-10, IL-22, IL-13, IL-1RA and TGF-β have known anti-inflammatory roles and will be addressed in this section (Table 3).

Cytokines	Secreted by	Sites of Action and Biological Effects
Interleukin-1 receptor antagonist (IL-1Ra)		Inhibits the pro-inflammatory action of IL-1α and IL-1β in order to maintain the equilibrium of the inflammatory response.
Interleukin-4 (IL-4)	Mast cells, T cells, and stomatal cells from bone marrow	Promotes the growth and development of B and T cells and monocytic lineage cells; also affects cells external to the immune system, including endothelial cells and fibroblasts.
Interleukin-10 (IL-10)	Subgroup of activated T CD4+ and CD8+ cells	Stimulates proliferation of B cells, thymocytes, and mast cells; stimulates, together TGF-β, synthesis and secretion of IgA by human B cells; antagonizes generation of the TH1 subgroup of helper T cells.
Interleukin-13 (IL-13)	Activated T cells, mast cells, and NK cells	Role in TH2 responses; increases IgE synthesis and suppresses inflammatory responses; involved in the pathology of asthma and some allergic conditions.
Interleukin-22 (IL-22)	Primarily T CD4+ cells.	Member of the IL-10 family, inhibits epidermal differentiation; induces acute phase responses, activates pancreatitis-associated protein 1 (PAP1) and osteopontin; like IL-19 and IL-20 shown to alter the TH1/TH2 equilibrium.
Transforming growth factor beta (TGF-β)	Multiple types of nucleated cells and also found in platelets	Inhibits growth of various cell types; affects tissue remodeling, lesion repair, development and hematopoiesis; exerts suppressive effect on the expansion of certain immune populations; IgA exchange factor.

Table 3: Principal pro-inflammatory cytokines, their sources and their biological functions. **Source:** Material elaborated by the authors based on references 1 and 2.

IL-10 is an unglycosylated polypeptide, with approximately 18 kDa, synthesized in inflammatory cells as well as neuroendocrine and neural tissues. The anti-inflammatory action of this cytokine limits excessive tissue damage in infectious conditions be they viral or bacterial. It is responsible for establishing control of the inflammatory activity mediated by Th1 cells inhibiting pro-inflammatory cytokines – especially tumor necrosis factor (TNF), IL-1, and IL-6 – produced by macrophages and activated monocytes, stimulating the endogenous production of anti-inflammatory cytokines [19].

IL-22 is an anti-inflammatory cytokine with similar activity to that of IL-10, is produced and released exclusively by leukocytes – CD4 T lymphocytes (especially Th17), natural killer (NK) cells, LTi and LTi-like cells – and its primary site of activity is epithelial tissue. Although it has known inflammatory action in chronic diseases – such as psoriasis and rheumatoid arthritis – its protective is also fundamental. As a result of the inflammatory/anti-inflammatory duality, its function is determined according to its concentration, duration time of the process, and affected tissues. It is an important protective molecule during the inflammatory process, acting by activation of the Stat3 cascade that induces anti-apoptotic and proliferative cell activities and AIDS in the prevention and repair of tissue damage. This interleukin presented a protective effect in cases of hepatitis, inhibiting apoptosis of hepatocytes and later stimulating the process of hepatic regeneration [20].

IL-4 is a 15 kDa glycoprotein with action on mast cells, T and B lymphocytes, NK cells, synoviocytes, and endothelial cells through the JAK/STAT pathway [19]. This cytokine plays a fundamental role in cell growth and survival, with regulating action on T lymphocyte differentiation - especially during the immune response - in addition to having been shown to function as a factor in the differentiation of B cells. It is produced and regulated mainly by Th2 cells, mast cells, and basophils. In vitro experiments have shown that IL-4 acts on monocytes, inhibiting production of inflammatory cytokines, such as TNF-a, IL-1a, IL-1b, IL-6, and IL-8 [21]. Its protective anti-inflammatory effect in chronic illness - such as diabetes mellitus and rheumatoid arthritis - is being investigated, opening possibilities for its role as a potential factor in the treatment of auto-immune diseases [21-22].

IL-13 is an anti-inflammatory cytokine produced mainly by T-CD4 cells of the Th2 subtype [19]. It has a dominant role in parasite immunity, asthma mediation, and resistance to intracellular microorganisms [23]. It acts by inhibiting the production of nitric oxide and various other cytokines produced by B lymphocytes and monocytes. It has stimulating action on the production of IL-1RA [19]. It also has an important function in inhibiting monocyte production of IL-1, IL-6, IL-8, and TNF-α, via the IL-1 receptor antagonist [23]. It has strong inhibitory action on the lipopolysaccharide induced secretion of IL-6 by monocytes [24].

TGF-β is an anti-inflammatory cytokine that acts in the innate immune response, with an important function in aiding tissue repair. It is a suppressor of differentiation and proliferation, for both B and T lymphocytes as well as antigen-presenting cells. Its function in tissue reconstitution occurs in two forms (1) through production of protease inhibitors, and (2) reduction of protease synthesis. In the context of human pathology, TGF-β has been associated as a promoter of pulmonary fibrosis, and may be associated with acute adult respiratory distress syndrome (ARDS) [25].

IL-1RA, a interleukin 1-receptor antagonist, is a 17 kDa protein of the IL-1 family, which inhibits the pro-inflammatory action of IL-1α and IL-1β in order to maintain the equilibrium of the inflammatory response [26-27]. In humans, under physiological conditions, it is detected in synovial fluid, tears, blood, and cerebrospinal fluid [27].

Anti-Inflammatory Cytokines in the Context of Sepsis

Severe sepsis remains one of the greatest causes of morbimortality of individuals hospitalized with severe illness in intensive care units. Actually, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [7,28]. For clinical operationalization, the organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone [28].

It is a syndrome that generally begins with a pro-inflammatory state, evolving later to immunological non-responsiveness. The balance between the inflammatory and anti-inflammatory cytokines is probably a central part of the pathophysiology of this process. There is evidence demonstrating that the catecholamines and glycocorticoids have an important role in the regulation of cytokine production, inhibiting the production of pro-inflammatory substances – such as IL-12, TNF-α, and INF-γ – and stimulating production of anti-inflammatory substances – such as IL-10, IL-4, and TGF-β [29]. However, under circumstances associated with stress exacerbation – such as in the case of acute or chronic disease, intense exercise, pregnancy and immediately *postpartum* -, the balance between the cytokines may be altered and consequently influence the progression or development of autoimmune diseases [30,31].

During infectious processes, the initial response to microbial penetration is, generally, mediated by production of inflammatory cytokines that will modulate the immune response to the pathogenic agents. The principal cytokines involved in the pro-inflammatory process are tumor necrosis factor alpha (TNF-α), IL-1β, IL-12, IL-6, and interferon γ (INF-γ). Following an exacerbated inflammatory response, usually with elevated production of pro-inflammatory cytokines, septic shock ensues. In an attempt to maintain organic homeostasis in sepsis, there is an increase of the anti-inflammatory mediators [32]. It is currently proposed that the anti-inflammatory cytokines are promptly produced in counterbalance to the onset of an exacerbated systemic immune response [25].

Studies with septic shock patients show that during follow-up, survivors present higher serum levels of INF-ɣ when compared with those who did not survive hospitalization. Among the deceased, significant quantities of TNF and IL-1 antagonist anti-inflammatory cytokines were found, such as IL-1RA [32].

The significant increase in IL-22 among patients with abdominal sepsis was described for the first time in a study performed at the University of Frankfurt [33]. This cytokine stood out as an important factor to be evaluated in infectious processes, given that reports of its activity in response to pneumonias by *Klebsiella pneumoniae* infection and, likewise, as a protective factor in gastrointestinal infections by *Citrobacter rodentium* and *Salmonella enterica* [33-34]. Because IL-22 has potentially damaging activity in circumstances such as psoriasis and arthritis, it is supposed that substantially elevated levels are

responsible for altering its activity, initially anti-inflammatory, to pro-inflammatory activity [33].

The TGF-β cytokine is an important factor in the inflammatory and anti-inflammatory balance. On the other hand, a study of a model of pulmonary fibrosis induced by bleomycin found that the TGF-β isoforms present a crucial factor in the pathogenesis of the lung damage. Given this, subsequent investigations on the influence of the production of this cytokine on patients presenting ARDS associated with sepsis showed significant elevation in serum levels of the TGF-β1 subtype in individuals with fatal outcome [25].

It is known that IL-10 is a potentially anti-inflammatory cytokine, such that excessive production can induce immunosuppression and increase lethality. Studies comparing the IL-10 genotypes AA, AG, and GG – of severely ill patients – having sepsis as the principal cause – showed that there was a statistically significant association of the G allele to higher lethality rates [26]. Upon analysis of the influence of lipopolysaccharide (LPS) desensibilization on IL-10 production, it was noticed that this process causes a reduction in the production of this cytokine. Faced with the fact that macrophages and monocytes present high sensitivity to LPS – a substance frequently released by pathogenic microorganisms -, it can be perceived that the fatal cases of sepsis, generally, were associated with a monocyte state of lower responsiveness to LPS occurring in conjunction with a reduction of IL-10 synthesis and consequent fatal outcome [35].

Currently, knowledge about the endogenous and exogenous activity of IL-4 in the inflammatory process in living beings remains imprecise. Endogenous IL-4 is thought to inhibit development of arthritis, but it has not been proven to present this effect [21]. Studies performed with a group of trauma victims showed a possible correlation between IL-4/-589 polymorphism and its stimulating action on the Th2 immune response, with development of a severe picture of systemic inflammatory response in these subjects. In combination with the role of IL-4 in the pathogenesis of sepsis, this polymorphism may come to be considered a risk factor for the development of post-traumatic sepsis in this research group [36].

Given the knowledge that IL-13 represents an important factor in the pathogenesis of allergic asthma – inducing proliferation of mucous and the hyper-responsiveness of the airways – studies have sought to investigate its influences on children with sepsis, who, generally evolve to multiple organ failure and death. In this study, a correlation was found between an unfavorable outcome (death) among the individuals admitted with sepsis and low levels of IL-13. This, on the other hand, represents a divergent result from other studies, which makes it impossible to predict an association of this cytokine with patient outcome in sepsis [37].

While many studies are currently being developed – both *in vitro* and *in vivo* –, different gaps remain in relation to understanding the role of the anti-inflammatory cytokines in sepsis. In this sense, as an additional strategy for the study of the human immune system, computer systems have been developed for the simulation of cells and mediators, which permit the development of numerous assays – in silico experimentation – with the potential use in the study of sepsis, as we will briefly comment on.

AutoSimmune: Overall Characteristics and Anti-Inflammatory Cytokines

AutoSimmune is the name given to the immune system Simulator implemented at the Universidade Federal de Viçosa, originally for the study of autoimmunity. Proposed by Possi (2012) [38], the Simulator is based on the concept of multi-agent systems.

The computational tool was implemented using the Rephast Simphony framework, and assumes as agent all components of the immune response that possess recognition patterns. In this way, the cells of the immune system, the antibodies, and the etiologic agents – bacteria, protozoa, and viruses -are implemented as agents, which, in turn are simulated in an environment where they interact over time in accordance with previously defined rules, based on the behavior of these same components in a living organism, in accordance with the literature [15-16].

The substances that participate in the immune responses, such as the cytokines, for instance, are implemented as data matrixes parallel to the agent interaction environment. Each agent has access to the concentration of each substance dispersed in that instant, to its position, through these matrixes, as well as, to secrete more substances [18].

Currently, the implemented substances are divided in two major groups defined as pro- and anti-inflammatory, identified in the system by the termination 1 and 2, respectively. The pro-inflammatory cytokines include PK1 (stress factors released by tissues that are undergoing damage as a result of infection or immunologic response), MK1 (a group of pro-inflammatory substances present in innate immune responses), and CK1 (a group of pro-inflammatory substances present in adaptive immune responses).

The anti-inflammatory cytokines include: (1) CK2: a group of anti-inflammatory substances present in adaptive immune responses; representing the substances TGF-β, IL-4, IL-5, IL-6, IL-10, and IL-13;

(2) MK2: a group of anti-inflammatory substances present in innate immune responses; representing the substances IL-10, CCL1, CCL17, CCL22, CCL11, CCL24, and CCL26 [15, 38, 39, 40].

The current work is focused on separating the CK2 and MK2 cytokines in the different molecules that make them up, thus increasing the computational complexity of the system. Once these changes have been implemented, it will be possible for focused studies on the role of these substances in the immune response, in silico, of sepsis [38,41].

With this, we hope to aid in the identification of the relationships of the anti-inflammatory cytokines in the pathophysiology of sepsis, as well as try to direct future research for the definition of diagnostic and prognostic markers for this morbid condition. Furthermore, in silico experiments may provide important result in the elaboration and validation of new hypotheses, which, in conjunction with other analysis, such as those involving proteomics and transcriptomics, may provide important tools for understanding the mechanisms related to sepsis [15].

Final Considerations

In a general assessment, the anti-inflammatory cytokines, with their diverse functionalities and importance in the context of sepsis, present as potentially related factors to the outcome of affected patients. However, there is still a need for more studies able to evaluate the real

influence of each of them on individuals with sepsis, and consequently, to assess whether these substances can be used routinely to evaluate the evolution of these individuals. This in turn, would allow for early intervention in an attempt to recover the normal state of the individual's immune response and proceed with a favorable outcome.

Conflict of interest:

None

Acknowledgments:

The authors are grateful to FAPEMIG for financial support.

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