REVIEW ARTICLE

The Negative Clinical Consequences Due to the Lack of the Elaboration of a Science of Cytokines in the Physiopathology and Treatment of Human Systemic Diseases

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ABSTRACT

Until a few years ago, the immune system was considered as responsible for the only defense against microbial infections and other external agents. On the contrary, the immune cells have been proven to be linked not only through cell-cell contact but also by releasing proteins capable of influencing the immune-inflammatory response, the so-called cytokines or interleukins. Moreover, the cytokines have appeared to play not only immune activities but also metabolic and systemic effects influencing the overall biological systems, including the nervous, the endocrine, and the cardiovascular systems, by representing the main endogenous molecules responsible for the maintenance of the unity of the biological life. Therefore, only the systematic clinical consideration of cytokine effects may allow the generation of real future holistic medicine.

Key words: Biological response, cytokines, cytokine network, inflammation, neuroimmunomodulation

INTRODUCTION

Despite the great number of experimental studies showing the fundamental role of cytokines in the pathogenesis of systemic inflammatory diseases, until now, human diseases depending on an altered host immunoinflammatory response, including cancer and autoimmune pathologies. It was necessary the dramatic evidence of Coronavirus disease-19 infection to rediscovery from a medical point of view the importance of the biological response of patients in determining the prognosis of the severe human diseases, as well as to understand that host biological response, namely consisting of the different types of cytokines produced by the patients during their disease. Then, because of the importance of cytokines to influence the prognosis of the different systemic pathologies, the human diseases may be classified in a new manner into two main classes, as follows: (1) Pathologies directly depending on the action of the various pathological causes, including toxic metals and microbes and (2) pathologies, whose prognosis is completely or at least in part due to host biological response, then to the different types of cytokines produced during the clinical course of the various diseases. At present, it is known the existence of more than 50 cytokines; the most relevant of them from a clinical point of view is generally defined as interleukins (IL). Unfortunately, because of the less clinical importance attributed to the IL in the past years, at present, it is not still possible to identify the pathogenesis of the various human systemic inflammatory diseases according to the behavior of some specific cytokines. In effect, the evidence of several cytokine alterations in the human inflammatory diseases, including autoimmunity and cancer, it is difficult to identify which may the main cytokine responsible for the alteration of several other cytokines. The difficulty is further enhanced by considering that most cytokines are connected among them by positive feedback mechanisms, then by a

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reciprocal stimulatory action, in respect to those presented by the endocrine system, whose hormone secretions are mainly under a negative feedback regulation.

CYTOKINE CLASSIFICATION IN RELATION TO THE INFLAMMATORY RESPONSE

The IL may be classified according to different criteria, including their family of origin, their action on the inflammatory response, and their effects on tumor development and growth. As far as the inflammatory response is concerned, cytokines and IL are generally classified into only two classes, consisting of inflammatory and anti-inflammatory factors. According to the most common classification, the main inflammatory cytokines include IL-1 beta, IL-6, tumor necrosis factor (TNF)-alpha, IL-2, IL-12 IL-4, IL-8, IL-13, IL-22, IL-23, and IL-17, while the clearly anti-inflammatory cytokines are substantially the only IL-10 and transforming growth factor (TGF)-beta, which are mainly released from both regulatory T lymphocytes (T reg) and macrophages. However, it is to be remarked that some IL, namely, IL-2[1] and IL-12,[2] may display both inflammatory and anti-inflammatory activities because of the great variety of their effects. The inflammatory action of IL-2 is mainly due to direct stimulation of the macrophage system, with a following increased production of IL-6, IL-1-beta, and TNF-alpha, whereas its inflammatory action is namely depending on a concomitant stimulation of TGF-beta secretion, which represents the most endogenous immunosuppressive factor, namely on the anticancer immunity.[3] More complex is the action of IL-12, which may be considered as the major connection between the innate and the acquired immunity, in other words, between the old and the new immunity.[4] In fact, IL-12 is namely produced by the dendritic cells, and it represents the main factor responsible for T helper (TH) differentiation into TH1 lymphocytes, with a following enhanced production of IL-2 and gamma-interferon.[4] Therefore, the pro-inflammatory action of IL-12 is primarily due to its stimulatory action on IL-2 release, as well as to its inhibitory activity on TGF-beta secretion.[5] On the other hand, the anti-inflammatory action of IL-12 is mainly depending on its inhibitory effect of IL-17 secretion, which, in contrast, is stimulated by IL-23.[6] Then, IL-12 and IL-23 would be connected by opposite effects on TH lymphocyte differentiation, consisting of the differentiation into TH1 or TH17 lymphocytes, respectively. However, at present, it is possible to recognize at least two different origins of the inflammation, consisting of macrophages and TH17 lymphocytes, respectively, characterized by enhanced production of IL-6 and IL-17,[7] but just at the beginning of the disease, since IL-17 and IL-6 are connected by a reciprocal stimulatory action.[8] Then, during its clinical course, each inflammatory disease tends to allow to an increase in blood concentrations of both cytokines.

CYTOKINE CLASSIFICATION IN RELATION TO THE ANTITUMOR IMMUNITY

The early stage of neoplastic diseases is generally characterized by normal levels of cytokines. On the contrary, patients with metastatic disease may present several cytokine alterations, with both enhanced productions of some cytokines and diminished production of other cytokines. In more detail, the advanced neoplastic disease has appeared to be characterized by low levels of IL-2 and IL-12, in association with abnormally high levels of IL-6, TNF-alpha, IL-10, and TGF-beta, while there is a controversial result about IL-17 and IL-18 concentrations.[9] This evidence is already enough to explain cancer-related immunosuppression since the only cytokines clearly provided by anticancer activity are IL-2 and IL-12,[9] as well as perhaps IL-15,[10] whereas most other cytokines would play a preferential stimulatory action on cancer growth by suppressing the anticancer immunity, particularly TGF-beta and IL-10, or by directly stimulating cancer cell proliferation, such as IL-17.[11] IL-2 plays its anticancer action by activating the antigen independent-antitumor immunity, which is mediated by natural killer-lymphokine-activated killer (LAK) cells cell system. NK cells may play a cytotoxic action only against artificial laboratory cell lines, but they may exert a cytotoxic activity also against fresh human cancer cells after their simulation by IL-2.[1] On the other hand, IL-12 exerts its anticancer action through several mechanisms, including stimulation of antigen-dependent anticancer cytotoxicity by activating cytotoxic T lymphocytes,[2] as well as by stimulating TH1 differentiation, with consequent enhanced production of IL-2,[2] and by inhibiting the production TGF-beta,[5] which represents the main endogenous immunosuppressive factor on the anticancer immunity.[3] IL-6 may play its suppressive action on the anticancer immunity by counteracting the evolution of NK cells into LAK cells under IL-2 stimulation,[9] while TGF-beta and IL-10 induce an immunosuppressive status by suppressing the immunostimulatory activity of both IL-2 and IL-12,[3] even though IL-10 could also exert some antitumor effects by promoting cytotoxic T cell-induced anticancer cytotoxicity. Other cytokines, namely IL-9[12] and IL-33,[13] would have controversial effects on anticancer immunity. In contrast, IL-35, namely released from T reg cells, would exert anti-inflammatory and immunosuppressive effects.[14] Then, it appears that the anti-inflammatory action, such as that played by IL-10, TGF-beta, and IL-35, is associated with concomitant immunosuppressive effects. Therefore, despite its great complexity, from a clinical point of view, it is possible to suggest that anticancer immunity may be considered as the end-result of the interactions between lymphocyte and macrophage systems, which are characterized by major preferential stimulatory and suppressive effects on the anticancer immunity, respectively, as confirmed by the fact

the cancer progression in mainly consisting of a progressive decline in lymphocyte-to-lymphocyte ratio (LMR),[15] which may be considered as a simple and less expensive biomarker to monitor the prognosis of the neoplastic diseases. Finally, it has been shown that some cancer progression-related symptoms, namely the so-called anemia of chronic diseases, would be due to IL-2 deficiency itself, since IL-2 immunotherapy of cancer has appeared to reduce ferritin levels with a consequent increase in hemoglobin level, by suggesting that liver iron accumulation is under an IL-2 control.[16]

CYTOKINE BEHAVIOR IN AUTOIMMUNITY AND ALLERGY

Like the advanced neoplasms, the autoimmune disease is also characterized by several alterations in cytokine secretion, namely consisting of abnormally high concentrations of the most common inflammatory cytokines, including IL-6, TNF-alpha, IL-17, and IL-1 beta, without any apparent relation with respect to the different autoimmune pathologies.[17] However, according to the more recent opinions, the main cytokine responsible for the onset of an autoimmune process would be represented by an abnormally high production of IL-17,[18] which allows to inhibition of T reg cell generation and activity, and the following enhanced immune reactions also against autoantigens. As far as the LMR in autoimmunity is concerned, it has appeared to be normal or high during the remission phase of the disease, whereas the acute phase is characterized by diminished LMR values.[17] This finding would seem to be paradoxical since we could expect an increase in LMR value because of the fundamental role of lymphocytes in determining autoimmunity related-tissue damage, but it would be only apparent since lymphocyte decline occurring during the exacerbate phases of the autoimmune pathologies could be simply due to the exit of lymphocytes from the blood circulation and the following tissue infiltration and damage.[17] On the other hand, because of their anti-inflammatory effects, the evidence of moderately high blood levels of TGF-beta ad IL-10 is associated with a remission phase and a better prognosis in the autoimmune pathologies.[4,5] IL-17 secretion is stimulated by IL-23, which is a release from several immune cell types, or by the association between TGF-beta plus IL-6 or IL-1, whereas TGF-beta alone may inhibit IL-17 production.[4,6,18] Then, autoimmune diseases are characterized by high blood levels of both IL-17 and IL-23. IL-23 would be mainly involved in the pathogenesis of autoimmune encephalomyelitis.[6] TH17 cells would be the main source of IL-22, which may also contribute to the induction of the acute phase of the inflammatory response.[18] IL-17 secretion is also inhibited by IL-2, whose secretion is in contrast stimulated by IL-17, as well as by IL-21,[19] a cytokine namely released from TH1 cells and provided by complex and controversial effects since it is also able to counteract T reg lymphocyte activity with a consequent possible promotion of the development of autoimmune processes, which are also promoted by IL-21-induced stimulation of the evolution of B lymphocytes into plasma cells[20] and a following possible increased autoantibody production. IL-21 production has been proven to be stimulated by estrogens, and this finding could contribute to explain the higher frequency of autoimmune diseases in female than in male subjects.[20] The behavior of the cytokine network in allergic pathologies has been less investigated and defined. However, according to the results available up to now, the main cytokines involved in the pathogenesis of the allergic diseases would consist of IL-18 and IL-12,[21] in any case with paradoxical results, since while IL-18 alone would stimulate the basophil production of IL-4 and the consequent increase in Immunoglobulin E (IgE) serum levels, the association between IL-18 and IL-12 has appeared to suppress IgE synthesis through gamma-interferon production.[21] At present, the most typical cytokine profile occurring in allergic diseases would consist of the association between increased secretions of IL-18 in association with a decline in gamma-interferon production.[22]

CYTOKINE SECRETION IN SEPTIC SHOCK AND RESPIRATORY DISTRESS

Today, it is known that both sepsis-related severe hypotension and acute respiratory distress syndrome (ARDS) are induced by an excessive endogenous release of inflammatory cytokines, including IL-6 and TNF-alpha. In more detail, the septic shock would be mainly due to the vasodilator action of IL-6,[23] while ARDS is preferentially determined by TNF-alpha-induced pulmonary tissue damage,[24] even though both cytokines would be involved, particularly in the case of coronavirus-related respiratory distress.[25] The enhanced secretion of TNF-alpha occurring in ARDS may be also counteracted by pentoxifylline.[26]

CYTOKINE PROFILE OF VIRAL INFECTIONS

The most known cytokine produced in response to viral infections is the interferon-alpha, which may act by inhibiting viral replication. However, several other cytokines are released during the viral infective diseases; some of them may protect against the infection, such as IL-21 and IL-22, whereas other cytokines, including IL-6 and TNF-alpha, may contribute to enhance the severity of the disease. Since the viral infection-related symptomatology depends also on the biological response of patients, a new approach in the treatment of virus infections could consist of the control of host biological response itself.

CYTOKINE PROFILE IN CARDIOVASCULAR DISEASES

Several cardiovascular pathologies have been proven to be due at least in part to an enhanced production of endothelin-1 (ET-1), which may be released by both heart itself and the endothelial cells, in particular during the myocardial infarction,[27] by allowing to a poor prognosis. The cardiac infarction is also associated with an enhanced secretion of several inflammatory cytokines, such as TNF-alpha.[28] Myocardial infarction-related inflammatory response would at least in part induced by ET-1 itself because of its stimulatory action on inflammatory cytokine secretion.[29] Finally, as in metastatic cancer and in the acute phase of the autoimmune diseases, the cardiac ischemia has also appeared to be characterized by a progressive decline in LMR values.[30] Therefore, the evidence of abnormally high values of LMR may predict a poor prognosis also in patients with myocardial infarction,[30] as well as in the metastatic neoplastic diseases[15] and in the exacerbation of the autoimmune pathologies.[18] ET-1 has also appeared to play a stimulatory role on cancer growth, by either acting as a tumor growth factor, or inducing suppression of the anticancer immunity.[29] On the contrary, the cardiac hormone atrial natriuretic peptide[31] and oxytocin[32] have been shown to inhibit cancer growth, to play an anti-inflammatory action, and to play a cardioprotective activity.

CYTOKINE SECRETION IN THE HEMOPHAGOCYTIC SYNDROME

The hemophagocytic syndrome, also called as a macrophage-activating syndrome (MAS), is a severe clinical complication, which may occur in neoplastic diseases, namely in lymphomas, infections, or autoimmune diseases,[21] whose pathogenesis is still poorly understood. MAS is consisting of excessive activation of the macrophage system, NK cells, and TH1 lymphocytes, and it is characterized by anemia, increased ferritin blood levels, and hypertriglyceridemia. From a cytokine point of view, MAS would be mainly due to an excessive secretion of IL-18, which may be produced by both macrophages and dendritic cells in association with diminished production of IL-18 binding protein (IL-18BP) and a consequent increase in biologically active free IL-18.[21]

THE NEUROENDOCRINE CONTROL OF THE CYTOKINE NETWORK

The secretion of cytokines depends not only on local factors but also a central regulation of cytokine network functionless, namely played by the pineal gland,[33] which has appeared to exert a fundamental immunoregulatory role in the control of the immune responses.[34] Unfortunately, most studies carried out to analyze the immunomodulatory role of the pineal gland have been limited to the only melatonin (MLT), which represents its most investigated hormone.[35] In more detail, MLT has appeared to stimulate IL-2 and IL-12 secretion[36] and to inhibit the release of most inflammatory cytokines, namely TNF-alpha.[37] MLT is the main pineal hormone produced during the night according to a well-defined light/dark circadian rhythm. On the contrary, during the light phase of the day, the pineal namely releases another indole hormone, the 5-methoxytryptamine (5-MTT), which is also provided by immunomodulating properties.[38] According to the data available up to now, it seems that MLT may preferentially act on the lymphocyte system by stimulating IL-2 release from TH1 cells, which have been proven to express MLT receptors,[36] while 5-MTT would mainly modulate the macrophage system by piloting its function in an antitumor way.[38] However, it has been demonstrated that the pineal gland, in addition to direct immunomodulating action through the release of its indole hormones, may also influence the immune functions by a regulation of the two major brain interneural immunoregulatory systems, consisting of brain cannabinoid and opioid systems. The functional status of the endogenous cannabinoid system may be simply evaluated by determining the blood levels of the main enzyme involved in the metabolic degradation of cannabinoids, the so-called fatty acid amide hydrolase (FAAH).[39] Then, the evidence of abnormally high blood concentrations of FAAH would reflect a condition of hypofunction of the endogenous cannabinoid system. Then, the biological response occurring during the inflammatory systemic diseases could be modulated and controlled by acting on the cannabinoid system through the administration of cannabinoid agonists, which may be considered as novel anti-inflammatory agents.[40] Cannabinoids may influence several cytokine secretions, but their main effect would consist of the inhibition of IL-17 secretion.[40] Then, since the enhanced IL-17 secretion would constitute the main autoimmunity-related cytokine alteration, the inhibitory effect of cannabinoids on IL-17 secretion justifies their use in the potential treatment of all autoimmune pathologies.[40] The pineal gland may modulate the cannabinoid system in an immunostimulatory way, then the pineal-brain cannabinoid system would constitute a fundamental functional axis responsible for the generation of an appropriate immune response.[41] The main endogenous cannabinoid agents are arachidonoyl-ethanolamide (AEA), also called anandamide, and 2-arachidonyl-glycerol (2-AG), and they are both characterized by a circadian rhythm in their secretion, with higher levels of AEA during the night and higher levels of 2-AG during the day.[42] On the contrary, brain opioid interneuron system would play a major immunosuppressive activity, particularly by acting on mu-opioid receptor.[43] The pineal-cannabinoid functional axis is in relation to both pleasure perception and spiritual sensitivity,[41] whereas brain opioid system is active in stress and depression conditions,[42]

by confirming that love and pleasure are fundamental to maintain the status of health. In fact, the pineal gland may be activated not only by a pharmacological approach but also by psychospiritual behavior, and particularly it has been shown that yoga practices may allow an increase in the endogenous secretion of MLT.[44] In addition, it has been shown that the occurred of alterations in MLT circadian secretion may negatively influence the prognosis of most systemic human diseases, including cardiovascular pathologies.[45] Each immune cell may be potentially influenced by hormones, neurotransmitters, and neuromodulators, but one of the main immune cells to be considered could be the T reg cell because of its fundamental role in the control of the immune reactions and the inflammatory biological response.[14] Then, the functional status of T reg cell system may influence the functionless of the whole immune system.[46] From this point of view, it is interesting to observe that beta-adrenergic agonists may allow apoptosis of all lymphocyte subsets, whereas the only T reg lymphocytes may be paradoxically stimulated in their functions.[47] On the same way, all lymphocyte subsets are inhibited by the mu-opioid agonists,[43] whereas T reg cells would be stimulated since the administration of the mu-opioid antagonist naloxone has been proven to inhibit T reg cell activity.[48] The cytokine network and the neuroendocrine system are connected by several links, and one of the main cytokines involved in realizing a connection between the cytokine network and the neuroendocrine system is IL-12 itself, which has appeared to inhibit FAAH activity, with a consequent increase in brain endogenous cannabinoid content.[48]

THE PHARMACOLOGICAL APPROACHES TO CONTROL CYTOKINE SECRETION AND ACTIVITY

At least from a theoretical point of view, the secretion of cytokines may be influenced by cytokines themselves, chemotherapeutic agents able to influence the cytokine network, endocrine and neuroactive substances provided by immunomodulating activity, monoclonal antibodies against cytokines, whose endogenous secretion may be abnormally enhanced, and potentially at least in part by the same different approaches of the complementary medicine. Within the neuroimmune approach, great importance would have to be attributed to MLT itself in the treatment of both cancer[35] and virus infections,[49] at least from an experimental point of view. Finally, as far as complementary medicine is concerned,[50] unfortunately, until a few years ago, the therapeutic use of plants and other vegetal products, namely mushrooms and algae extracts, was proposed on the only basis of empiric criteria, or on the only basis of their metabolic effects. On the contrary, because of the importance of cytokine secretions in influencing human systemic diseases, the therapeutic use of plants and other vegetal products as a complementary medicine would have to be reinterpreted in relation to their effects on the cytokine network.[48] At present, the most studied potential therapeutic vegetal products are those from Aloe (*Aloe arborescens* and *vera*), *Magnolia*, *Curcuma*, *Cannabis indica*, *Nelumbo nucifera* (Lotus) and *Annona muricata* for plants, *Agaricus blazei* Murril, *Ganoderma lucidum* (Reishi), *Lentinus edodes* (Shiitake), *Grifola frondosa* (Maitake), *Cordyceps sinensis*, Coriolus versicolor, Chaga and *Tremella* for mushrooms, and, while the most known algae extracts are those coming from *Aphanizomenon flos-aquae*, *Chlorella vulgaris*, and *Spirulina platensis* for algae extracts. Then, because of the importance of the various cytokine secretions in influencing the human systemic pathologies, the therapeutic action of plants and other vegetal products may be at present reinterpreted in relation to their effects on the cytokine network. Unfortunately, the few studies carried out to analyze the effects of mushrooms and algae extracts are still confusing and controversial since several stimulatory effects on the secretion of both inflammatory and anti-inflammatory cytokines have been reported for each single agent.

CONCLUSIONS

Today, most human systemic disease, whose pathogenesis is still unclear, may be reinterpreted in terms of the consequence of alterations involving the functionless of cytokine network itself. Therefore, medical sciences themselves may be founded in a new way in relation to the human systemic disease-related profile of cytokine secretion that we could call the science of cytokines, from either a diagnostic or a therapeutic point of view.

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How to cite this article: Lissoni P, Merli N, Lissoni A, Pelizzoni F, Messina G, Rovelli F, Sassola A, Galli C, Monzon A, Fede GD. The Negative Clinical Consequences Due to the Lack of the Elaboration of a Science of Cytokines in the Physiopathology and Treatment of Human Systemic Diseases. Clin Res Hematol 2020;3(2):1-7.