The psychoneuroimmunotherapy of human immune-mediated systemic diseases, including cancer and autoimmune diseases

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Abstract

Until few years ago, the *in vivo* immune responses were considered to be identical to the reactions occurring *in vivo*, but the recent discoveries in the Psychoneuroendocrinoimmunology (PNEI) area have demonstrated that the immune system is under a psychoneuroendocrine regulation, which represents the biochemical mediation of the influence of emotions and consciousness states on the immune system, by allowing the possibility to modulate the immune functions by acting on their neuroendocrine control rather than directly on the immune cells. The immune responses are inhibited by the opioid system, mainly by acting on mu-opioid receptors, whereas they are stimulated by the pineal-cannabinergic system functional axis. The metastatic cancer is characterized by low blood concentrations of IL-2 and IL-12, in association with abnormally high levels of TGF-beta, IL-10 and IL-6, with a following decline in TH-1 lymphocytes and an increase in T regulatory (T reg) cell count. The autoimmune diseases are characterized also by enhanced levels of proinflammatory cytokines, namely IL-17, in association with low values of TGF-beta and IL-10 as the consequence of a decline in T reg cell count. Cancer progression is associated with a progressive decline in the endocrine function of the pineal gland, which may release at least three molecules provided by antitumor activity: melatonin, 5-methoxytryptamine and pinealine. The inhibitory effects of opioids on the anticancer immunity may be abrogated by the administration of the long-acting mu-opioid antagonist naltrexone. The deficiency of pineal indole hormones, which play a fundamental anticancer activity, as well that of the main antitumor cytokines, including IL-2 and IL-12, may be simply corrected by their exogenous administration. Finally, IL-17-induced immunoinflammatory response occurring in the autoimmune diseases may be counteracted by cannabinoid agonists, which may inhibit IL-17 secretion. The pineal hormones also may contribute to inhibit the chronic inflammatory response.

Keywords: Autoimmunity; Cancer; Cannabinergic system; Neuroimmunomodulation; Opioid system; Pineal gland; Psychoneuroendocrinoimmunology.

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Introduction

Until about 30 years ago, it was common opinion that the hormonal molecules may exert only endocrine effects, and the immune substances may induce only immune activities. In contrast, several successive studies have demonstrated that the hormones may also be able to induce immunomodulatory effects and at the other side that the immune cells may influence the endocrine secretions through the release of less characterized substances, which were identified as cytokines [1]. Two experimental studies had in particular a great relevance to understand the human systemic diseases as a consequence of alterations in the immune neuroendocrine interactions, consisting of the evidence that the surgical removal of the pineal gland may induce an immunosuppressive status [2] and the demonstration of a stimulatory effect on the hypothalamic-pituitary-adrenal (HPA) axis by the pro-inflammatory cytokines, including IL-1 beta, IL-2, IL-6, IL-12 and TNF-alpha [1,3]. The evidence that the immune system is physiologically under a modulatory control played by the endocrine and the nervous systems allowed the onset of the Psychoneuroendocrinoimmunology (PNEI) as the medical psychological branch, which studies the interactions between immune and neuroendocrine systems [4]. The clinical PNEI is simply consisting of the clinical application of PNEI knowledgements, in an attempt to put into evidence that the human chronic immune-mediated systemic diseases, namely cancer and autoimmune diseases, as the consequence of PNEI disorders, consisting of an altered regulation of the immune system [4]. Then, on the basis of PNEI discoveries, it is now possible to affirm that the subjective psychological and spiritual behaviour may influence the status of health through a chemical psychoneuroendocrine modulation of the immune system, in an attempt to maintain a perfect equilibrium between the auto-reactivity of the autoimmune diseases and the lack of an effective reaction against cancer cell proliferation sand dissemination. Almost all hormones, neurotransmitters and neuromodulators may potentially exert immunomodulatory effects, but the most important endocrine anatomic structures influencing the immune system are represented by the pineal and adrenal glands, which are provided respectively by immunostimulating and immunoinhibitory effects of the antitumor response [5], as well as brain opioid [6] and

cannabinergic [7] systems for the nervous system, which constitute two fundamental neuro-endocrine functional units, consisting of the opioid system-pituitary axis and the later the cannabinoid-pineal axis. In fact, brain opioid system is mainly functionally associated with the pituitary and the adrenal glands, and it exerts an immunosuppressive action mainly on the anticancer immunity [6], whereas the cannabinergic system is namely linked to the pineal gland, by representing a functional unit stimulating the immune system [8], and by playing a fundamental role in the maintenance of the natural immuno-biological resistance against cancer development. Then, the major limit of the ancient Immunology, preceding the discovery of cytokines, is to consider the *in vivo* immune reactions as identical to the same immune reactions observed *in vitro*, by completely excluding the *in vivo* existence of a psychoneuroendocrine modulation of immune response themselves, which may either amplify or counteract the same *in vitro* immune reactions by influencing the functional status of the immune cells. The *in vivo* existence of a psychoneuroendocrine control of the immunity would represent the main reason for the differences existing between the *in vivo* immune responses with respect to the same reactions *in vitro* [9].

The Cytokine Bases of the Immune System

The two main immune cells, from whose interactions would depend the whole immune functionless, are consisting of T helper-1 (TH1) lymphocytes (CD4+), which activate the immune system through the production of IL-2 (10) by representing the main growth factor for T lymphocytes, and T regulatory (T reg) lymphocytes (CD+CD25+), which on the contrary suppress the immune responses, including the anticancer immunity, through the release of immunosuppressive substances, the most active of them is TGF-beta [11,12]. A fundamental role in the interactions between TH1 and T reg lymphocytes is played by IL-12 [13], which stimulates T helper differentiation into TH1 instead of TH2 lymphocytes and to counteract T reg cell generation and activation. On the other hand, IL-17, produced by TH 17-lymphocytes, would constitute the main cytokine in the induction of the inflammatory response and in the inhibition of T reg cell functions, with a consequent predisposition to the onset of autoimmune diseases [14], due to the potential activation of auto-reactive T lymphocyte clones. The immune effects of the main cytokines.

The Chemical Bases of the Neuroimmunomodulation

Despite the great complexity of the neuroendocrinoimmune interactions, the two main nervous structures responsible for the Neuroimmunomodulation (NIM) are the opioid [6] and the cannabinergic systems of the brain [7]. The opioid system produces three major endogenous opioids, consisting of endorphins, enkephalins and dinorphins , which mainly act on mu-, delta- and kappa-opioid receptors, respectively. At the other side, the cannabinergic system produces two main cannabinoid molecules, the arachidonyl-ethanol-amide, also called anandamide, and the 2-arachidonyl-glicerol , which exert immunmodulatory effects by mainly acting on the macrophage system through an inhibition of macrophage-mediate inflammatory and immunosuppressive events, as well as on Th-17 lymphocytes by inhibiting the secretion of IL-17 [15], whose fundamental role in the induction of the inflammatory response and macrophage activation is well known [14]. The immunomodulatory effects of both opioids and cannabinoids may be simply explained by considering their action on T helper-1 (TH1) lymphocytes and T reg lymphocytes, as well as on their interactions. The opioid system may stimulate T reg cell generation by acting on mu-opioid receptor, whereas it plays an inhibitory role of TH1 cell functions, with a consequent decline in the endogenous production of IL-2 [16]. On the contrary, the cannabinoid system stimulates TH1 cell functions and counteract T reg cell activation [17] by acting in connection with the pineal gland [8]. Moreover, it has to be taken into consideration within the complex neuroimmune interactions that some endocrine feedback mechanisms are under an immune modulation mediated by specific cytokines, the most important of them is the circuit existing between pro-inflammatory cytokines and the HPA-axis, which is essential in the control of the intensity of the immuno-inflammatory responses. The inflammatory cytokines produced in a non-specific manner during the immune response may stimulate cortisol production [1,3], which in turn inhibits the proliferation of lymphocytes non-specifically activated by a specific antigen, including potential auto-reactive lymphocyte clones. Then, in the presence of an eventual deficiency of the HPA-axis- immune cell circuit, cortisol response to the action of the inflammatory cytokines would be absent or abnormally low, and this finding could predispose to the onset of autoimmune diseases. Finally, the complex interactions between opioid and cannabinergic systems are regulated by the pineal gland [18].

The Pineal Gland and the PNEI

Since PNEI may be defined as the study of the interactions between psycho-spiritual status and neuroimmune systems, the main anatomic structure responsible for the modulation of the interactions between immune and neuroendocrine systems is the pineal gland [4,5,8,18], which represents on the same time the most important endogenous anticancer organ. Then, the pineal gland has been proven to play a fundamental role in maintaining the natural resistance against tumor onset and dissemination by acting as a central regulator of the cytokine network [18], since the pineal endocrine functions are at least in part under an immune regulatory control. The pineal endocrine activity is generally inhibited by the action of the inflammatory cytokines, such as IL-6 and IL-1 beta, and at the other side it exerts important immunomodulatory effects through the release of its indole hormones, the most investigated of them is melatonin (MLT) [19]. However, MLT is not the only anticancer pineal indole, since at least another pineal indole, the 5-metoxytryptamine (5-MTT), has appeared to exert *in vitro* antitumor effects superior to MLT itself [20]. Moreover, the pineal gland produces anticancer molecules other than the indole hormones, including less characterized

antitumor peptides, such as the epithalamin [21], and the wide group of beta-carbolines, which are provided by both antitumor and psychedelic effects of mind expansion, the most active of them is the 6-methoxy-1, 2, 3, 4-tetrahydro-beta carboline, also called pinoline or pinealine [22]. Therefore, through the release of anticancer indole hormones and beta-carbolines, the pineal gland plays an essential role in the modulation of emotions and consciousness states, and in mediating their influence on the biological body namely through the immune system, by constituting the main structure responsible for the natural resistance against cancer development. The fundamental anticancer role of the pineal gland is also suggested by the fact that all environmental and psychosocial conditions characterized by an enhanced risk of cancer development, including stress, changes in light/dark circadian rhythm and exposure to constant light or to magnetic fields, despite their differences, may present as a common finding the evidence of alterations of MLT light/dark rhythm [19]. Another demonstration of the anticancer role of the pineal gland in influencing the prognosis of the neoplastic diseases is the evidence that cancer progression is associated with a progressive decline in the nocturnal production of MLT, with a consequent loss of its physiological light/dark rhythm [19]. Then, because of its antitumor property, cancer progression-related pineal endocrine deficiency would not a simple epiphenomenon, but it could play a role in cancer progression itself. Therefore, the occurrence of pineal deficiency in cancer patients would constitute the primary sign of a progressive decline in the natural anticancer biological resistance.

PNEI Pathogenesis of Cancer and Autoimmune Diseases

Systemic disease may be considered each human pathology, whose pathogenesis cannot be explained as a simple consequence of organ-limited disturbances, but only as the expression of alterations involving the mechanisms responsible for the neuroendocrine and immune regulation of the whole living organism. The two major still untreatable immune dysfunction-related human systemic chronic diseases, consisting of metastatic tumors and autoimmune diseases would be due, at least of the beginning of disease to an altered psychoneuroendocrine control of the immune functions rather than to a primary alteration of immune cells themselves, as well as during the successive phases of disease. Today it is known that the main immune alterations in the anticancer cytokine network occurring during cancer progression are substantially consisting of hyperactivity of macrophage and T regulatory lymphocyte (T reg) systems, with a consequent abnormally enhanced production of IL-6, IL-1 beta, IL-10 and TNF-alpha by macrophages and TGF-beta by T reg cells. At the other side, the most important immune cytokine alterations of autoimmune diseases are represented by an enhanced production of IL-17 by TH-17 lymphocytes, with a consequent induction of the inflammatory response [14], as well as of IL-6, IL-1 beta, IL-2, IL-12 and TNF-alpha, with some preferential cytokine profiles in relation to the different types of autoimmune disease, such as the abnormal production of TNF-alpha in the rheumatoid arthritis. On the contrary, the autoimmune diseases tend to be characterized by a reduced production of IL-10 and TGF-beta [23], with a consequent deficiency in the mechanisms responsible for the inhibition of the immune responses. In any case, at present no autoimmune disease has appeared to be characterized by a specific cytokine profile, but only by a general nonspecific enhanced production of inflammatory cytokines. IL-18, which is mainly released from the endothelial cells, would also play an important role in the pathogenesis of the autoimmune diseases [24]. In addition, from a psycho-neuroendocrine point of view, cancer onset would be mainly promoted by a hyper-function of brain mu-opioid system, as well as in stress conditions [25], with a consequent progressive immunosuppression of the anticancer immunity due to mu-opioid-induced inhibition of TH-1-dependent IL-2 production and stimulation of T reg system, with a consequent enhanced TGF-beta production, which is the most potent endogenous immunosuppressive agent in humans [12]. Cancer-related brain opioid hyperactivity may be simply abrogated by the administration of long-acting mu-opioid antagonists, such as naltrexone (NTX), which in fact has been proven to exert antitumor effects [25]. Moreover, cancer-related increased brain opioid activity has appeared to be constantly associated with a progressive decline in the pineal function [24], which in turn allows a concomitant progressive decline in the activity of brain cannabinergic system [7] because of the reciprocal stimulatory interactions between pineal gland and cannabinergic system [8]. In fact, histological damages of the pineal gland have been observed in patients died from cancer [26]. Then, it is probable that cancer progression may be associated with a whole pineal endocrine deficiency rather than the only MLT secretion [24], even though at present there are no data about the endogenous secretion of pineal indoles other than MLT, as well as that of pineal beta-carbolines in cancer patients. MLT has been proven to act as an anticancer molecule by either a direct antiproliferative cytotoxic activity through the induction of apoptosis of cancer cells, or stimulating the anticancer immunity through a promoting effect of the secretion of the two main antitumor cytokines in humans, consisting of IL-2 from TH1-lymphocytes and IL-12 from dendritic cells [5,27]. Moreover, also considering the only anticancer cytotoxic action, MLT would represent at present the only known molecule existing in the nature, which may be potentially effective in counteracting the all six main phases of the clinical history of the neoplastic disease, consisting of : 1) stress-induced immunosuppression, which would constitute the main mechanism responsible for the evolution of the single transformed malignant cell into a clinically evident tumor mass; 2) spontaneous or carcinogen-induced cancer cell transformation; 3) intercellular junction alterations; 4) neo-angiogenesis induced by changes in the intercellular matrix following intercellular junction alterations; 5) cancer cell proliferation and production of immunosuppressive molecules, such as TGF-beta and IL-10; 6) Fas-L expression by cancer cells as the last terminal event of cancer dissemination because of the occurrence of apoptosis of Fas-expressing T H1 and T cytotoxic lymphocytes in the case of cell contact with cancer cells expressing Fas-L on their cell surface [5,27]. From a biochemical point of view, MLT may exert cytotoxic effects on

cancer cells by inducing their apoptosis through an inhibition of bcl-2 expression and EGF-R enhanced activation. Finally, MLT has appeared to act as an immunomodulating agent to stimulate the anticancer immunity by inducing the secretion of IL-2 from TH1 lymphocytes and IL-12 by dendritic cells through a direct action of specific MLT receptors expressed by both TH1 and dendritic cells [28]. Then, the progressive decline in the pineal endocrine function would represent the most important hormonal failure responsible for cancer onset and progression, since pineal deficiency may allow a loss of several endogenous anticancer molecules, including pineal indoles and beta-carbolines. The anticancer activity of the other pineal molecules, including the indole 5-MTT [20] and beta-carbolines [22], would mainly depend on antiproliferative cytotoxic action, while few data only are available about their possible immunomodulating effects, which have to be better investigated. On the other hand, from a neuroendocrine point of view, the autoimmune diseases would mainly depend on a hypo-activity of brain cannabinergic system, with a consequent possible enhanced production of IL-17, which is under a central inhibitory regulation exerted by the cannabinoid system and which plays a fundamental role in the induction of autoimmune response by activating the inflammatory response and by inhibiting T reg generation control [15]. As far as the pineal function in the autoimmunity is concerned, at present only few and controversial data are available, since both enhanced and diminished MLT secretion have been reported in association with alterations of its light/dark circadian rhythm [29]. Alterations of other endocrine and neuroendocrine circadian rhythms, namely that of cortisol, have been also observed in both metastatic cancer and autoimmune diseases [30] as a consequence of the increased secretion of pro-inflammatory cytokines, which stimulate HPA-axis [1,3]. By synthetizing, both cancer and autoimmune diseases are characterized by an enhanced chronic inflammatory response, which would be mainly generated by the macrophage system in cancer, and by TH 17-lymphocytes in the autoimmune diseases. In addition, both cancer and autoimmune diseases may be characterized by a deficiency involving brain cannabinoid system, which would be associated with a concomitant hyperfunction of brain opioid system in cancer and on the contrary with a brain opioid system deficiency in the autoimmune diseases [5-7].

Neuroimmunotherapy of Human Systemic Diseases

The approach to the treatment of human systemic diseases, which may be also defined in a more simple way as neuroimmunotherapy (NIT) is consisting of a pharmacological modulation of the immune responses by acting not only directly on the immune cells. Moreover, on its neuroendocrine regulation, in an attempt to replace the neuroimmune biochemistry of the status of health by pharmacologically correcting the main neuroendocrine and immune alterations occurring during the clinical course of the various diseases. Substantially, consisting of IL-2, IL-12 and MLT deficiencies in advanced cancer [5,19] and IL-10 and TGF-beta diminished production in autoimmunity [24], and on the other hand to inhibit the exaggerated secretion of those cytokines, whose production is abnormally high, namely TGF-beta in cancer [12] and pro-inflammatory cytokines, including IL-6, IL-1 beta and TNF-alpha in both cancer and autoimmune diseases.

Neuroimmunotherapy of Cancer

Because of its immunostimulatory and anticancer activity [5,19], the administration of the only MLT may be already just considered as a PNEI therapy of cancer. In fact, from a historical point of view, PNEI therapy of human neoplasms was started several years ago with the administration of MLT alone as a palliative therapy of untreatable metastatic cancer patients, for whom no other standard effective anticancer therapy was available and with life expectancy generally less than 6 months, by obtaining a prolongation of survival and an improvement in the clinical conditions [31-34]. Moreover, MLT at mild pharmacological doses ranging from 20 to 100 mg/day in the evening, has been proven to enhance the efficacy of cancer chemotherapy and to reduce some chemotherapy-induced side-effects, namely cachexia, thrombocytopenia, asthenia and cardiotoxicity, whereas no efficacy was seen in the prevention of chemotherapy-induced alopecia and neutropenia [5,19,35,36]. Finally, the anticancer activity of MLT has appeared to be a dose-dependent phenomenon [37]. Cancer-associated hyper-activity of brain opioid system, also related to stress and chronic pain, which may induce a suppression of the anticancer immunity by stimulating T reg lymphocyte system and promote cancer cell proliferation [38], may be blocked by the simple administration of the mu-opioid antagonist NTX at a dose of about 50 mg/day [25,39]. At the other side, cancer-related pineal endocrine deficiency may be simply treated by an endocrine replacement therapy with MLT alone [31-35] or in a more complete manner with MLT plus other pineal anticancer indoles, namely 5-MTT [20], and beta-carbolines, such as the beta-carboline pinealine [40]. On the same way, cancer-related brain cannabinergic system failure with a consequent progressive decline in the perception of pleasure, including appetite and sexual interest [7], which would depend on cancer-related pineal deficiency because of the reciprocal stimulatory interactions between pineal and cannabinergic system [8], may be treated by the simple administration of both natural and synthetic cannabinoid agonists. Finally, the main cancer-related alterations in the antitumor cytokine network, consisting of IL-2 and IL-12 deficiency, may be corrected by their exogenous administration through subcutaneous low-dose injections, because of the lower toxicity with respect to the intravenous route of administration [37,38]. In more detail, in addition to the correction of its possible endogenous deficiency, IL-12 administration has been proven to be also able to counteract T reg lymphocyte activation and TGF-beta production [13], which in contrast are stimulated by IL-2 [41], and to promote IL-2 production by stimulating T H1 cell differentiation [42]. Therefore, because of the stimulatory role of IL-2 on lymphocyte proliferation [10] and the ability of IL-12 to counteract T reg cell functions and IL-2-induced T reg activation [13] and to promote TH1 differentiation [41], at least from a theoretical point of view the immunotherapy with IL-2

plus IL-12 could represent the best cancer immunotherapy, because of its potential ability to correct the two major cancer-related immune dysfunctions, consisting of TH1 cell and dendritic cell deficiencies in association with enhanced activity of T reg and macrophage systems. In fact, the maximal lymphocytosis, which represents the most important favourable prognostic factor to predict the efficacy of cancer immunotherapies [43], has been obtained by an association with IL-2 plus IL-12 [44,45]. Same results in the control of T reg cell activation may be artificially obtained by anti-immune checkpoint monoclonal antibodies, including Nivolumab and Ipilimumab [46]. Cancer immunotherapy with cytokines, namely IL-2 and IL-12, may be also improved in its efficacy by a concomitant MLT administration [45]. Then, the simple administration of MLT in association with anticancer cytokines is already sufficient to transform the immunotherapy of cancer into a neuroimmunoterapy (NIT) of cancer, consisting of a possible amplification of the therapeutic effect of the anticancer cytokines by a concomitant administration of the same molecules physiologically involved in the neuroendocrine control of the immune system, namely MLT itself [5]. In fact, preliminary clinical studies have shown that the concomitant administration of MLT may enhance the therapeutic efficacy of IL-2 cancer immunotherapy in several tumor histotypes [47], as well the immunobiological effects of IL-12 [45]. Further promising results may be achieved by blocking the opioid system through NTX administration [39], in an attempt to counteract opioid-induced T reg cell activation. In fact, according to the recent advances in the knowledge of the mechanisms involved in the anticancer immunity, at present it is possible to conclude that the main problem of cancer immunotherapies is to stimulate TH-1 lymphocyte functions without a concomitant excessive activation of T reg lymphocytes. Finally, MLT anticancer activity may be further enhanced by the concomitant administration of antitumor plants, namely Aloe, Myrrh, Magnolia and Boswellia, which also play immunomodulating and antitumor effects. In the case of Cannabis plant [7], the most anticancer agent is the same psychoactive molecule tetra-hydro-cannabinol (THC). The rationale of cannabinoid agents in cancer therapy is justified by both curative and palliative effects [7], since they may exert direct cytotoxic anticancer effects and be effective in the treatment of several cancer-related symptoms, including anorexia, vomiting, pain, cachexia, pleasure deficiency and depression.

Table 1: Main immune effects and alterations of the most important cytokines involved in the pathogenesis of cancer and autoimmune diseases.

Cytokines	Immune effects	Cytokine blood levels	
		Cancer	Autoimmune diseases
IL-2	Stimulation of TH-1 and T reg cells Suppression of T reg generation	Low	High
IL-12	Macrophage-induced inflammation	Low	High
IL-1 beta	Inhibition of NK cells	High	High
IL-6	Inhibition of Th-1 and T cytotoxic cells	High	High
IL-10	TH-17-induced inflammation	High	Low
Il-17	Inhibition of TH-1 and T cytotoxic cells	High/normal	High
TGF-beta	Inhibition of lymphocytes and cachexia	High	Low
TNF-alpha		High	High

Neuroimmunotherapy of Autoimmune Diseases

At present, there is no specific PNEI therapy for the autoimmune disease, since no clinical study has been carried out to explore the efficacy of a neuroimmune regimen to control their clinical progression, and in particular the possible therapeutic role of MLT still remains controversial, because of its potential immune-stimulatory action, even though it namely involves the cellular immunity rather than the humoral immunity, which represents the immune response most involved in the autoimmune diseases, since they are mainly due to an abnormal auto-antibody production. In any case, at present MLT has appeared to induce some therapeutic benefits in the treatment of bowel inflammatory diseases and some forms of systemic lupus erythematosous, whereas both improvement or worsening have been reported in MLT therapy of rheumatoid arthritis [29]. However, according to previous data concerning the pathogenesis of the autoimmune diseases, they could achieve some benefits from cannabinoid therapy, because of the inhibitory effects of cannabinoid agonists on IL-17 secretion, whose enhanced production plays a fundamental role in the induction of autoimmune disease-related inflammatory response [7]. Vitamin D therapy may be also potentially effective in the treatment of autoimmune disease because of its stimulatory action of T reg cell generation [48,49], whose activity is abnormally reduced in the presence of autoreactive reactions and whose stimulation may allow a suppression of autoreactive lymphocyte clones. Anti-inflammatory plants, such as Aloe and Myrrh, may be potentially effective in the palliative therapy of autoimmune disease, because of their inhibitory effects on macrophage-mediated inflammatory response.

Conclusions

The dream of the historical beginning of PNEI to treat the human immune-mediated systemic diseases, due to a reduced or to an exaggerated immune reactivity by acting not only directly on the immune system, but also on the neuroendocrine regulation of the immune system in an attempt to perfectly reproduce the psychoneuroendocrine and immune biochemistry of the status of health, seems really to become

clinically possible, at least in terms of modulation of the two main brain areas of the neuroimmunomodulation, the opioid and the cannabinoid systems. In any case, from a clinical point of view, the main problem to realize a real evaluation of the immune status of cancer patients is to identify a possible surrogate inexpensive biomarker capable to investigate the anticancer immunity in a similar manner with respect to that shown by more sophisticate and expensive immune evaluations, such as lymphocyte subset detection and cytokine blood concentrations. Recently, however, it has been shown that the simple lymphocyte-to-monocyte ratio (LMR) has appeared to reflect the relation between lymphocyte-mediated anticancer immune reaction and its macrophage-mediated suppression, as well as that the evidence of an abnormally low LMR may predict a poor prognosis in human neoplasms [50]. Therefore, LMR could constitute a simple inexpensive and adequate biomarker to evaluate the antitumor immune-neuroendocrine status of cancer patients.

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