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The role of IL-17 secretion in mediating the influence of stress on cancer and other human systemic diseases

Abstract

It is known that stress may predispone to both cancer and autoimmunity. Moreover, it has also been shown that stress-induced immune changes may mainly depend on the activation of both HPA-axis and brain opioid system, since the negative immune effects of stress have appeared to be abrogated by the administration of mu-opioid antagonists. Mu-opioid agents have been shown to stimulate both T reg lymphocytes and the secretion of IL-17, which in turn may inhibit T reg cell generation. The preferential stimulatory role of opioid agents on IL-17 secretion or on T reg cell activation would depend on the interactions with the other main brain neuroregulatory system, represented by cannabinergic-pineal axis, which in contrast may counteract IL-17 secretion and T reg cell activation. Then, the possibility to control IL-17 secretion, which is involved in the pathogenesis of both autoimmunity and cancer, by acting on its neuronedocrine regulation could consitute a new immunotherapeutic strategy in the treatment of human systemic diseases.

Keywords: cannabinoid system, cytokines, IL-17, melatonin, opioid system, neuroimmunomodulation, pineal gland, stress, lymphocytes

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Paolo Lissoni, Giusy Messina, Vezika Cenaj, Franco Rovelli, Giorgio Porro, Arianna Lissoni, Tiziana Aymerich, Giuseppe Di Fede

Institute of Biological Medicine, International Institute of PNEI, Milan, Italy

Correspondence: Paolo Lissoni, Institute of Biological Medicine, International Institute of PNEI, Milan, Italy, Email paolo.lissoni@gmx.com

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Introduction

Several experimental and clinical investigations have shown that stress may predispose to the most severe systemic illnesses, including cancer and autoimmune diseases.[1] According to the recent discoveries of the Psycho-neuroendocrino-immunology (PNEI),[2] cancer-and autoimmunity-related immune alterations may depend at least at the beginning of disease on an altered psychoneuroendocrine regulation of the immune responses. From an immune point of view, despite the great complexity of immune interactions involved in the onset of human systemic diseases, cancer and autoimmunity may be considered as the result of two opposite manners of immune reaction, consisting of a deficiency in the immune response in cancer and an exaggerated reaction in the autoimmunity, which allows a consequent reaction also against self-antigens. More in detail, the differences in the immune behavior occurring in cancer and in autoimmune diseases would synthetically depend on the different interactions among the three main subsets of CD4+T lymphocytes, consisting of T helper (TH) (CD4+CD25-CD17-), regulatory T lymphocytes (T reg) (CD4+CD25+) and TH-17 lymphocytes (CD4+CD17+).[3–5] In particular, T reg cell number and function have been shown to be abnormally high in cancer and abnormally low in the autoimmunity.[3–6]

Then, since stress has been proven to predispose to both cancer and autoimmunity,[1,2] it remains still unclear how the same stress condition may induce two opposite types of immune reaction. The opposite behavior of T reg cells occurring in cancer and in autoimmunity could probably depend on the different behavior of the cytokines involved in the regulation of T reg cellsthemselves, one of the most important of them isIL-17, produced by TH17 lymphocytes, which constitutes one of the main inhibitory factors for T reg cell generation and activation.[7] The behavior of the cytokine network occurring in stress conditions is also influenced by the activation of the hypothalamic-pituitary-adrenal (HPA) axis,[8] which plays an inhibitory effect on the immune responses. On the other hand, the immune system is also under a neuroendocrine stimulatory regulation, mainly mediated by the functional axis constituted by the pineal gland and braincannabinergic system.[9–10] The activation of the HPA axis allows an enhanced production of both cortisol and adrenaline, respectively produced by the cortical and the medullary adrenal gland. Stress is also characterized by a general stimulation of the sympathetic system, with a following enhanced noradrenaline release. The activation of both HPA axis and sympathetic system is due to the same mechanism, consisting of an enhanced hypothalamic release of CRH.[8] Both cortisol and cathecolamines have appeared to exert lymphocytolitic effects and to induce a suppression of lymphocyte functions. From a psychoneuroendocrine point of view, stress biochemistry is mainly characterized by changes in the interactions between the two major brain systems responsible for the neuroendocrine modulation of the immune responses, which consist of brain opioid system and brain cannabinergic system-pineal axis, respectively involved in the inibition or stimulation of the immune system, namely of the antitumor immunity.[9–13] In fact, the pineal gland has been shown to play an essential role in the stimulation of the immune system, namely of the antitumor immune response, through the release of its most investigated in dole hormone, melatonin (MLT).[9–11] On the contrary, even though their acute administration may stimulate some immune functions, such as NK cells activity, the opioid peptides, mainly the mu-opioid agonists such as beta-endoprhin, would play a major immunosuppressive effect, in particular on the antitumor immunity by stimulating T reg cell system and by concomitantly inhibiting IL-2 production from TH1 lymphocytes and IL-12 secretion from dendritic cells.[12,13]

The stimulation of T reg cell system allows an enhanced production of TGF-beta, which represents one of the main endogenous immunosuppressive factors of the antitumor immunity.[14] In fact, it has been shown that stress-related tumor development is mainly mediated by an enhanced brain opioid system activation, as confirmed by the fact that the concomitant administration of mu-opioid antagonists, such as naltrexone (NTX), may abrogate stress-induced promoting

effect on tumor onset and dissemination.[14] The antitumor immunity is mainly inhibited by T reg cell system and by the chronic inflammatory response, which is mainly mediated by the macrophage system.[15] The link between T reg cell and macrophage systems would be mainly mediated by IL-17, since IL-17 has been proven to either inhibit T reg cells generation and activation, or to induce macrophage-mediated inflammatory response.

The neuroendocrine regulation of IL-17 secretion

According to the results available up to now, IL-17 secretion is under a major stimulatory and inhbitory control, respectively exerted by brain opiod system[16] and cannabinergic system through its connection with the pineal gland. [17–21] Therefore, since the opioid agents, namely the mu-agonists ones, have been proven to stimulate both T reg cell activation[12,13] and IL-17 secretion,[16] the in vivo immune end result of the mu-opioid agonists could depend on the balance between their concomitant stimulatory effects on both T reg cells and IL-17 secretion, as well as on their interaction with the cannabinergic system in the brain. If the preferential stimulatory effect of stress-induced brain opiod system activation is that of the stimulation of IL-17 secretion, which in turn plays an inhibits T reg cell system, stress would mainly predispose to the onset of an autoimmune disease. On the contrary,if the preferential effect of stress is the stimulation of T reg cell system, stress would mainly predispose to cancer development, because of the inhibitory action of T reg lymphocytes on the antitumor immunity.[14,15]

In any case, to understand the neuro-immuno-modulation (NIM) of stress, it is alsonecessary to evaluate the functional status of the other major neuroendocrine system involved in the neuroendocrine control of the immune system, represented by brain cannabinoid system and pineal gland, which constitute a fundamental functional immunostimulatory neuroendocrine axis, being connected by reciprocal stimulatory links.[17–20] In contrast to the stimulatory action of brain opioid system on IL-17 secretion,[16] pineal-cannabinergic functional axis has been shown to inhibit IL-17 production and secretion by TH17 lymphocytes. In more detail, the pineal hormone MLT has been proven to play a central regulatory role on the whole cytokine network,[9] with inhibitory effects on TNF-alpha, IL-1-beta, IL-6, and IL-10 secretion, and stimulatory activity on IL-2 and IL-12 release secretion,[11] while its effects on IL-17, IL-18 and TGF-beta are still controversial.

MLT would exert a modulatory regulation on TGF-beta secretion, with both inhibitory and stimulatory effects, depending on the different experimental conditions.[11] On the same way, MLT may promote IL-17 secretion,[17] but in contrast it is also able to inhibit IL-17-mediated inflammatory response.[18] The controversial results of MLT on IL-17 secretion and activity could also depend on the existence of several IL-17 isoforms,[7] one of the most active of them is IL-17 A, with possible different responses to MLT action.MLT has been also shown to inhibit the inflammatory action induced by IL-18,[19] which may further enhance IL-17-induced inflammatory response.[20] Finally, the cannabinoid system has appeared to inhibit macrophage-induced inflammatory response and IL-17 secretion from TH17 lymphocytes,[21] while it has no relevant effect on TH and T reg lymphocyte differentiation and activity. Brain opioid system has been shownto be constantly activated during stress conditions,[2] while the behavior of pineal and brain cannabinergic system in stress conditions is still less investigated and controversial, probably depending on the duration of stress. If acutely both pineal and cannabinoid system may be stimulated by stress, a chronic condition of stress would allow a progressive decline in pineal and brain cannabinoid system activity.[11,22] Therefore, in the presence of a concomitant reduced activity of brain cannabinoid-pineal axis, opioid system-induced immune effects of stress would mainly allow an enhanced production of IL-17, because of the lack of cannabinoid-mediated inhibitory action on IL-17 production,[21,22] with a following major predisposition to the autoimmune diseases, because of the well documented fundamental role of IL-17 in the induction of the autoimmune dynamics.[7]

On the other hand, in the presence of a normal cannabinoid function, which inhibits IL-17 secretion, the major immune effect of opioids in stress conditions would consist of a stimulation of T reg cell system, with a consequent major predisposition to the neoplastic diseases, because of the inhibitory action of T reg cells on the antitumor immunity. Therefore, the determination of IL-17 blood concentrations could differentiate two different kinds of stress from an immunological point of view, mainly characterized by an enhanced IL-17 production or by an enhanced T reg cell activity, with a consequent enhanced secretion of TGF-beta and IL-10 and a diminished production of IL-2 and IL-12, the two main antitumor cytokines in humans, with a consequent major predisposition to the autoimmune or to the neoplastic diseases, respectively. The fundamental role of IL-17 in promoting the onset of autoimmune diseases[7,23] and the enhanced T reg cell activity in promoting the development of cancer[3–6] have been confirmed by several experimental and clinical studies. Brain opioid system has appeared to be involved in the regulation of the unconscious life, anxiety and depression, whereas pineal-cannabinoid axis has been proven to be involved in the mediation of both pleasure perception and spiritual expansion of mind. Then, the great complexity of the neuroimmune interactions would simply represent the chemical mediation of the psycho-spiritual life of humans, whose knowledge could allow us to treat cancer and autoimmune diseases by acting not only on the immune system, but also on the psycho-neuroendocrine regulation of the immune functionless.

Cytokine network of the inflammatory response

From a phylogenetic point of view, the inflammatory response represents the most ancient and non-specific immunobiological response. The discovery of cytokines has allowed to understand the chemical mechanisms responsible for the inflammatory response, whereas in the past years it was belived to depend only on the action of local inflammatory substances, such as prostaglandins and leukotrienes. The cytokine network may be considered as an endocrine system within the immune system, since the different immunobiological responses would simply depend on complex negative and positive feed back mechanisms operating among the different cytokines. However, to understand the immunobiological responses occurring in vivo, including the inflammatory reaction, it is not sufficient to consider the only secretion of cytokines and their interactions, since the in vivo activity of the various cytokines is physiologically under a modulatory contyrol exerted by the neuroendocrine system, as confirmed by the recent advances in PNEI knowledgements.[1,2]

At present, it is known that the inflammatory response may be generated by three different fundamental origins, consisting of macrophage system through the release of IL-1 beta, IL-6 , IL-8 and TNF-alpha, TH17 lymphocytes through the secretion of IL-17,[7] and the same endothelial cells, namely by producing IL-18.[21] Obviously, the three different mechanisms are connected among them, but on

the same time it is possible to suggest that the inflammatory response occurring in the autoimmune diseases is mainly mediated by TH17-lymphocytes by releasing IL-17,[23] cancer-related chronic inflammation is mainly induced by the activation of the macrophage system,[15] and allergy-related inflammatory status is namely induced by IL-18.[21] In any case, stress conditions, being characterized by an enhanced brain opioid activity, would progressively determine a chronic status of inflammation induced by the increased IL-17 secretion, which stimulates the secretion of other inflammatory cytokines, including IL-1 beta and IL-6.[7]

Inflammatory cytokine-hpa axis connections

The first historical demonstration of the existence of interactions between endocrine secretions and the immune response was that concerning the stimulatory action on cortisol secretion induced by the supernatant of in colture activated immune cells, due to their cytokine content.[24] Further studies have demonstrated that the pro-inflammatory cytokines, including IL-1 beta, IL-6, TNF-alpha, IL-2 and IL-12, may stimulate the HPA axis by acting either on hypothalamic-pituitary sites, or directly on adrenal gland itself.[25] It is known that cytokines production induced by antigen-activated lymphocytes may stimulate in a non-specific way classes of lymphocytes other than those specifically activated by the antigen, including the potentially auto-reactive ones, and that the inhibitory effect of cortisol on lymphocytes is more pronounced on non-specifically antigen-activated lymphocytes than on specifically antigen-activated lymphocytes.[11] Then, the significance of the stimulatory effect of cytokines produced by antigen-activated lymphocytes on cortisol secretion in the presence of an immunoinflammatory response would consist of the prevention of a possible induction of autoimmune reactions through a more selective inhibitory action lymphocytes activated by cytokines in a non-specific manner. Therefore, the existence of a reduced response of cortisol to the stimulatory action of the pro-inflammatory cytokines could predipose to the onset of autoimmune diseases under some viral or bacterial infections. Unfortunately, at present no clinical test has been standardized to investigate the sensititivy of the HPA axis to the action of pro-inflammatory cytokines, even though preliminary clinical studies have been already proposed the evaluation of cortisol response to subcutanoeus low-dose IL-2 to explore the functional status of inflammatory cytokines- HPA axis relations.[25]

Clinical investigation of the neuroendocrine control of inflammation

Despite its complexity potentially involving all neurohormones and neuromodulators, the central neuroendocrine control of the inflammatory response and most in general of the immune responses is substantially mediated by the opioid system, the cannabinoid system and the pineal gland. Then, it becomes clinically important to evaluate the functional status of these neuoendocrine structures either in cancer, or in autoimmune diseases. The endocrine function of the pineal gland may be evaluated by measuring at least the light/dark circadian rhythm of its most investigated hormone, MLT, which in normal conditions is characterized by highest levels during the dark period of the day, or the urinary excretion of its main metabolite, the 6-sulphatoxy-melatonin (6-MTS).[26] The cannabinoid system may be clinically investigated by measuring the blood concentrations of its two main molecules, anandamide and 2-arachidonyl-glicerol.[21,22] Finally, the functional status of the opioid system may be simply clinically explored by evaluating the endocrine response of LH and cortisol to a standard dose of a mu-opioid antagonist, such as naloxone or naltrexone, which in normal conditions consists of an increase in both cortisol and LH concentrations, whereas a lack of response or an exaggerated response would reflect an increased or a decreased brain opioid tone, respectively.[2,13]

Future therapeutic strategies of the inflammation

The most suitable way to control the inflammatory processes in a next futurecould consists of a direct modulation of the cytokine network through a neuroendcorine approach. The action of the single cytokine may be artificially blocked by using specific monoclonal antibodies, or in a new way by acting on the neuroendocrine control of cytokine secretion. Unfortunately, PNEI knowledgements still substantianlly remain only experimental evidences, since very few clinical studies have been performed up to now to monitor and treat the human systemic diseases on the basis of PNEI point of view. However, according to the data available up to now, it is already known the possibility to neuro-endocrinologically control the secretion of most cytokines, including IL-1 beta, IL-2, IL-6, IL-10, IL-12, IL-17, IL-18, TNF-alpha and TGF-beta. In more detail, IL-1 beta, IL-6, TNF-alpha, IL-10 and TGF-beta secretions may be inhibited by the pineal hormone MLT.[9,11,26] IL-17 secretion may be blocked by the cannabinoid agents[21] and by MLT itself,[18] which may also counteract IL-18 activity.[19] IL-2 and IL-12 secretions may be stimulated by MLT[11] and inhibited by the mu-opioid agonists.[2,12,13] Finally, IL-10 secretion may be stimulated by cortisol itself.[8]

Obvioulsy, the possibility to regulate the inflammatory response and most in general the immune responses by acting on the neuroendocrine control of the cytokine network from a clinically point o f view would require to monitor the blood concentrations of the main cytokines and the main neuroendocrine molecules involved in the NIM, including the pineal hormone MLT, the endogenous cannabinoids and opioids, either in basal conditions and during the clinical course of the various human systemic diseases characterized by a chronic inflammatory status. This statement is justified by the evidences that the prognosis of the neoplastic diseases has been shown to be more negative in the presence of low levels of IL-2 and IL-12 in association with high concentrations of TGF-beta and IL-,[10] as well in the presence of a diminished pineal function,[11] and that the prognosis of autoimmune disease is better in the presence of high levels of IL-10 and TGF-beta in association with low levels of IL-17, IL-18, IL-1 beta, IL-6 and TNF-alpha, despite the existence of some differences in cytokine secretion in relation to the different autoimmune pathologies.[23] In other words, in the presence of an abnormal cytokine secretion, it would be required to clinically investigate the functional status of the neuroendocrine structures involved in the control of the immune system, in an attempt to establish whether the altered cytokine secretion may depend on a primary immune cell anomaly of its production, or on its abnormal neuroendocrine control. Then, the future immunotherapies of the main human systemic diseases could probably namely consist of the modulation of the cytokine network by the administration of both cytokine, neurohormones and neuropetides involved in the NIM processes, including the pineal hormone MLT,[9,11,26] the cannabinoid agents[21,22] and the opioid agonists.[12,13]

Conclusion

According to the recent knowledgements in the areas of Immunology and PNEI, all human systemic diseases may be reinterpretated as depending on alterations of cytokine secretions,

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which in turn could be the consequence of an altered neuroendocrine control of cytokine network itself. In addition to the well known role exerted by the activation of HPA-axis, stress-induced promoting effect on the onset of systemic diseases, including cancer and autoimmunity, would mainly depend on an enhanced activity of brain opioid system, which allows a stimulation of both T reg cell system and IL-17 secretion.[27] Opioid-induced stimulation of T reg cells could predispose to cancer, whereas the promoting effet of opioids on IL-17 secretion could predispose to the autoimmune diseases, because of its fundamental role in the pathogenesis of the autoimmunity due to an inhibition of T reg cell system activation. In contrast, IL-17 secretion may be inhibited by the cannabinoid agents,[21] and the pineal hormone MLT.[11,18] Obviously, the evolution of PNEI is depending on each single new discovery on the neuroendocrine regulation of the cytokine network, but on the same time on the elaboration of a systemic vision of the immuno-neuroendocrine interactions, even though to be modified in relation to the occurrence of possible new discoveries on the relation between immune system and its psycho-neuro-endocrine regulation.

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Conflict of interest

Author declares there is no conflict of interest.

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