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Review

The Neuroendocrine Regulation of TGF-BETA ACTIVITY: Beyond the Opposition Between Immunostimulation and Immunosuppression in Human Systemic Diseases

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ABSTRACT

It is known that macrophage-mediated chronic inflammatory response may suppress the anticancer immunity and stimulate cancer progression. In fact, most inflammatory cytokines, including IL-6, IL-1 beta, and TNF-alpha, may suppress the anticancer immunity, whereas it is stimulated by IL-2 and IL-12, which may exert both inflammatory and anti-inflammatory effects. Because of its dual anti-inflammatory and immunosuppressive activities, TGF-beta, which is the main suppressive factor released from T reg cells, could play a fundamental role in the regulation of cytokine network involved in modulating the interactions between inflammatory and immune responses. Therefore, the control of TGF-beta could allow the possibility to modulate the whole cytokine network and the following immune reactions. Within the cytokine group, TGF-beta is stimulated by TGF-beta itself, IL-10 and IL-2, whereas both IL-12 and IL-17 play an inhibitory action. On the other side, from a neuroendocrine point of view, TGF-beta secretion is stimulated by corticosteroids, mu-opioid agonists and vitamin D3, it is inhibited by the pineal hormone melatonin and delta-opioid agonists, while cannabinoids may regulate TGF-beta secretion by indirectly acting in an inhibitory way on IL-17 release. Since the effects of TGF-beta depend on the concentrations of other cytokines, namely IL-6 and IL-17, it could be more easy to control TGF-secretion by acting on its central neuroendocrine regulation rather than on its cytokine modulation. The sense of the review is to understand the neuroendocrine regulation of TGF-beta in an attempt to clinically control its secretion in a more simple way than that with anti-TGF-beta monoclonal antibodies to either increase its secretion in auto-immunity and decrease its production in cancer.

Keywords: *Immunosuppression; Inflammatory Response; Neuroimmunomodulation; Transforming Growth Factor Beta.*

INTRODUCTION

Today, it is known the existence of reciprocal interactions between psychoneuroendocrine and immune systems.[1] Both cytokines and immunoreactive neuromodulators may influence the immune responses and the cytokine network by regulating the secretion of the various cytokines or their receptor expression. Moreover, some biological effects of cytokines may depend on their concentrations, with possibly different results with respect to the expected ones by considering the activity of every single cytokine. Then, some cytokines may exert opposite effects on immune cell proliferation and differentiation. One of the most ambiguous cytokines, namely in the anticancer immunity, is TGF-beta,[2] because of its concomitant antiproliferative and immune-stimulatory effects. While hormones and neurotransmitters tend to exert specific immune stimulatory or inhibitory effects, neurohormones, such as the pineal indole hormone melatonin (MLT),[3] neuropeptides, such as the opioid peptides[4] and neuromodulators, including the endogenous cannabinoids,[5] tend to exert both stimulatory and suppressive effects, depending on the functional status of the whole cytokine network, which is physiologically also under a neuroendocrine regulation. The existence of neuroendocrine regulation of the cytokine network would represent the mean reason to explain the different results observed in vitro and in vivo. The discovery of regulatory T lymphocytes(T reg; CD4+CD25+), which suppress the inflammatory response and T cell functions, has profoundly modified the interpretation of the immune system and its functionless,[6] also from a philosophic point of view. In fact, the immunosuppressive status of patients, occurring in the advanced neoplastic diseases, may be reinterpreted as the consequence of an excessive immunostimulation of T reg cell system. Therefore, within the great number of immune cell types with their specific subsets, including macrophages and lymphocytes, the modulation of T reg cell functions could constitute the most simple and direct strategy to regulate the functionless of the whole immune system. Then, since TGF-beta is the main anti-inflammatory and immunosuppressive cytokine released from T reg cells,[2] the control of TGF-beta secretion and activity may constitute a key-point to modulate the whole immune system. In fact, TGF-beta

has been proven to inhibit both TH1-dependent IL-2 secretion and dendritic cell (DC)-dependent IL-12 production.[2,6] Despite the complexity of cytokine clinical behavior in humans systemic diseases, the clinical studies have demonstrated that the activity of T reg cell system is abnormally enhanced in advanced cancer, and abnormally low in autoimmune diseases, namely during the phases of clinical exacerbation.[2,6,7] The main cytokine secreted by Treg cells is TGF-beta itself, which is under an immune cytokine and neuroendocrine regulation. The sense of the review is the exposition of the neuroendocrine control of TGF-beta secretion and activity in an attempt to clinically regulate its secretion in an easier manner with respect to those with other cytokines, or TGF-beta monoclonal antibodies

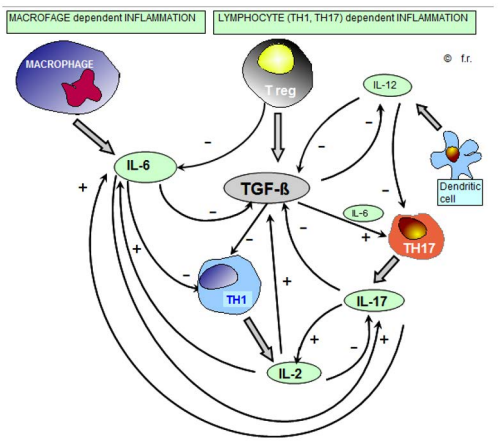
PHYSIOPATHOLOGY OF TGF-BETA AND T REG CELLS AND ITS INTERACTIONS WITH IL-2

T reg cell generation would be mainly induced by TGF-beta and IL-10 secreted by Myeloid Precursor Suppressor Cells (MSC) released from the bone marrow.[8] TGF-beta has been proven to be under complex cytokine, endocrine, and nervous regulation. T reg cells may suppress the immune functions by either a cell-cell contact mechanism, or secreting immunosuppressive cytokines, namely TGF-beta itself, as well as IL-10, IL-35, and IL-38, all provided by anti-inflammatory action.[8] While it is well known that the evidence of increased secretion of TGF-beta is associated with a more favorable prognosis in autoimmunity because of its immunosuppressive anti-inflammatory effects,[7] its role in cancer is still controversial because of its possible concomitant antitumoral action, due to inhibition of cancer cells proliferation.[9] In any case, the evidence of abnormally high levels of TGF-beta has appeared to be constantly associated with an enhanced T reg cell system activation, and poor prognosis in terms of both survival and response to treatments in cancer patients.[10] The effects of TGF-beta cannot be completely explained without taking into consideration its fundamental relation with IL-2,[11] which is, as well as TGF-beta, also provided by dual immunostimulatory and immunosuppressive effects. The immunostimulatory role of IL-2 is mainly due to a stimulation of T lymphocyte proliferation, namely of TH1 lymphocytes, with a following further production of IL-2, and self-expansion of TH1 cells.[11] On the other side, the immunosuppressive action of IL-2 is namely due to the stimulation of T reg cells and TGF-beta production.[12] Therefore, the interactions between TGF-beta and IL-2 may be interpreted in terms of an endocrine-like negative feedback system, with stimulatory action of IL-2 on TFG-beta, and with the inhibitory effect of TGF-beta on IL-2 release. On the contrary, IL-12 suppresses TGF-beta secretion.[13] The ambiguous effects of TGF-beta also regard its interactions with IL-17 secretion (14) from TH-17 lymphocytes, since TGF-beta alone tends to inhibit IL-17 secretion, whereas TGF-beta in association with IL-6, as well as IL-23, may stimulate TH-17 differentiation and IL-17 secretion. On the contrary, IL-17 suppresses T reg cell functions and TGF-beta production.[14] Therefore, TGF-beta and IL-17 secretions would also be connected by a negative feedback system, with inhibitory effects of IL-17 on TGF-beta and a preferential stimulatory action of TGF-beta on IL-17 production. Another fundamental cytokine interaction is that occurring between IL-6 and TGF-beta since IL-6 represents with IL-17 one of the main cytokines responsible for the inflammatory status. In fact, recent clinical studies have documented the existence of at least two independent origins of the inhibitor response, due to macrophage or TH17 lymphocyte systems, with high levels of IL6 or IL17, respectively.[15] IL-6 inhibits TGF-beta secretion,[15,16] which in turn may also inhibit IL-6 production.[16,17] Therefore, TGF-beta and IL-6 secretion would be connected by a reciprocal inhibitory action. Finally, IL-6 and IL-17, the two main inflammatory cytokines, would be connected by a reciprocal stimulatory action,[14] by suggesting the existence of interactions between IL-17- dependent and IL-6 dependent inflammatory responses. Then, it is possible to conclude that within the cytokine network, the immunobiological effects of TGF-beta, as well as those of IL-2, would primarily depend on the concentrations of other cytokines, namely IL-6 and IL-17, with also the possible existence with positive feedback systems, as well as that between IL-2 and IL-12, which are linked by a reciprocalstimulatory action.[13] Because of its inhibitory effect of IL-6 secretion[15] and its promoting effect on TH17 cell generation and IL-17 secretion,[14] TGF-beta would preferentially pilot the inflammatory response in a TH17 lymphocyte-dependent way rather than in the macrophage-dependent one. In the neoplastic diseases, it would be more active the IL-6-dependent inflammation, whereas in the autoimmune diseases – related inflammation would namely due to IL17 action.[15]

IL-2 AS THE KEY-CYTOKINE OF THE BALANCE BETWEEN IMMUNOACTIVATION AND IMMUNOSUPPRESSION

IL-2 has appeared to play a fundamental role in the regulation between inflammatory and anti-inflammatory responses of the biological life. At present IL-2 is the only cytokine, which has been proven to induce a clear lymphocytosis, not only in experimental conditions,[11,13,16] but also clinically in cancer patients with severe lymphocytopenia, by acting as the physiological T cell growth factor.[11,13] IL-2 secretion is namely connected to that of TGF-beta and IL-17 by feedback mechanisms, within the inhibitory effect of TGF-beta on IL-2 and the stimulatory effect of IL-2 on TGF-beta secretion, even though only in the presence of TGF-beta itself, and with stimulatory effect of IL-17 on IL-2 and an inhibitory one of IL-2 on IL-17 secretion.[13-16] These mechanisms are fundamental to explain the ambiguous behavior of IL-2 in both autoimmunity and cancer, whose clinical progression has appeared to be associated with a progressive decline in IL-2 secretion, and the following lymphocytopenia.[18,19] The dual effects of IL-2 are not surprising, since it may either immunostimulant by activating TH1 lymphocytes, or suppress the immune responses by activating T reg cell system.[13,20] Finally, there is a functional circuit between IL-2 and IL-6 secretions, with stimulatory action of IL-2 on IL-6 release and inhibitory effects of IL-6 on IL-2 secretion.[13] The interactions among TGF-beta, IL-2, IL-17, and IL-6 in the regulation of the inflammatory response are illustrated in Figure 1.

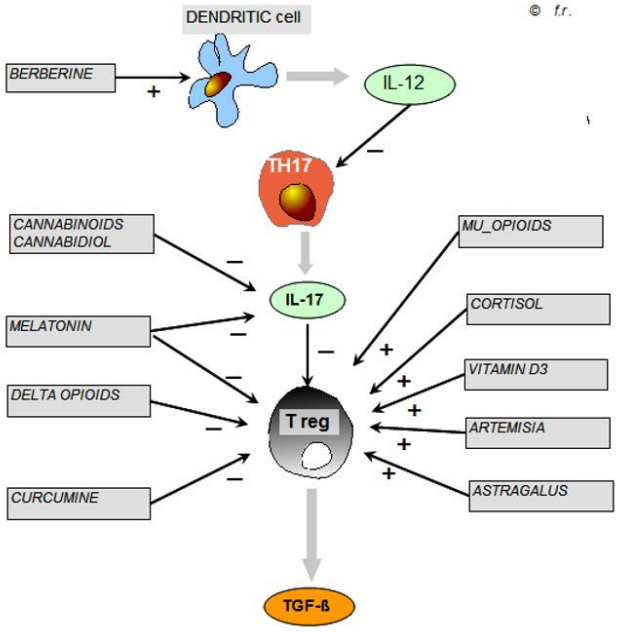
Figure 1. Cytokine regulation of macrofage-dependent and TH1 TH17 limphocyte dependent inflammation and the role opf TGF_beta



ENDOCRINE AND NEUROENDOCRINE REGULATION OF TGF-BETA SECRETION

In addition to the influence exerted by the other cytokines, TGF-beta has been proven to be also under a well defined neuroendocrine stimulatory and inhibitory regulation. While most cytokines and hormones may exert a specific effect on TGF-beta secretion, neurohormones and neuromodulators tend to exert both stimulatory and suppressive effects, depending on the functional status of T reg cell system itself, respectively with inhibitory or stimulatory effects in the presence of an excessive T reg system activation, as occurring in cancer, or in the presence of a diminished T reg cell activity, as in autoimmunity. The main hormones provided by stimulatory effects on TGF-beta secretion are the corticosteroids,[21] and this evidence would explain their anti-inflammatory immunosuppressive effects, due to T reg cell system activation. On the contrary, TGF-beta secretion is inhibited by the pineal hormone MLT,[22] whose biological effects are generally opposite with respect to those exerted by cortisol.[3] Even tough neuroactive and neuroendocrine agents may potentially influence the immune system, the neuroendocrine regulation of the cytokine network is mainly exerted by opioid and cannabinoid systems of brain, as well by the pineal gland,[23] because of its modulatory influence on both brain opioid and cannabinoid systems. Even though there are controversial results in the literature, at present it has been shown that the opioid system, namely the mu-agonist one, may play a major stimulatory role on T reg cell system and TGF-beta production,[24,25] whereas delta-opioid agonists would inhibit TGF-beta secretion.[26] On the contrary controversial results have been referred for the kappa-opioid agonists. On the other side, MLT, through its connection with the cannabinoid system, may inhibit TGF-beta secretion.[22] More controversial results are referred for the immunomodulating effects of CB1 and CB2 cannabinoid agonists.[5] The two main endogenous cannabinoids, Arachidonyl-Ethanol-Amide (AEA) and 2-Arachidonyl-Glycerol (2-AG), are both CB1 and CB2 agonists, and their biological effects are similar to those exerted by the psychoactive principle of marijuana, the tetrahydrocannabinol (THC), which also contains another neuro immunomodulating agent, the cannabidiol (CBD).[5] Even though CBD is not a cannabinoid agonist,[5] it may also influence the cannabinoid system by inhibiting the activity of Fatty Acid Amide Hydrolase (FAAH),[27] the enzyme involved in cannabinoid destruction, with the following increase in brain cannabinoid content. Cannabinoid agonists have been shown to inhibit in vitro lymphocyte proliferation and stimulate T reg cell differentiation,[28] but this finding was not confirmed by further studies.[29] At present, the most established immune effect of cannabinoids is the inhibition of IL-17 secretion.[30] This effect, exerted by both cannabinoid agonists and CBD, may already explain the anti-inflammatory action of cannabinoids and justify their therapeutic use in the treatment of autoimmune diseases, which have appeared to mainly depend on an exaggerated IL-17 production. Catecholamines may inhibit lymphocyte proliferation and induce apoptosis of lymphocytes,[31] namely by acting on a beta-adrenergic receptor. However, it has recently been shown that the effects of catecholamines on lymphocyte may change in relation to the different sub-sets, since TH1 and cytotoxic T lymphocyte inhibited by catecholamines, whereas Treg cells are stimulated.[32] The evidence of a different lymphocyte sensitivity to the action of beta-adrenergic agonist may explain the different effects of stress on the immune system. Finally, vitamin D3 has also appeared to stimulate TGF-beta secretion,[32] then it could be useful in the treatment of autoimmune diseases, whereas its administration to cancer patients could further enhance T reg cell-mediated immunosuppression.[33] By synthesizing, from a neuroendocrine point of view, TGF-beta secretion may be stimulated by corticosteroid, mu-opioid agonists and vitamin D, whereas it is inhibited by MLT. The neuroendocrine regulation of TGF-beta secretion is illustrated in Figure 2..

Figure 2. Neuroendocrine control of TGF_beta secretion and influence of some plant product



CHEMOTHERAPY AND PHYTOTHERAPY INFLUENCES ON TGF-BETA SECRETION

Both classical chemotherapy and complementary medicine may potentially act on TGF-beta secretion, even though their influence on TGF-beta endogenous production is not generally taken into consideration. In particular, it has been shown that metronomic low-dose chemotherapy may inhibit the angiogenic processes and induce different immune effects, consisting of selective depletion of T reg cells, with a consequent increase in the potency of the antitumor immunity.[34] Unfortunately, the influence of chemotherapy on TGF-beta secretion still remain to be analyzed. As far as Phytotherapy is concerned, most plants provided by potential anticancer properties have appeared to act by either inhibiting cancer cell proliferation, or inducing immunomodulating effects, which often are not taken into consideration by the complementary medicine of cancer. In particular, both astragaloside[35] and Artemisia compounds[36] have appeared to stimulate T reg cell system, whereas curcumin may inhibit TGF-beta secretion.[37] Artemisia may also inhibit IL-12 secretion (35), which in contrast is stimulated by berberine.[38] Therefore, the stimulatory effects of vitamin D3, astragaloside and artemisia extracts on T reg cell system may justify their use in the treatment of autoimmune diseases, being characterized by a diminished T reg cell function, whereas their use in advanced cancer patients, who are in contrast characterized by an enhanced T reg cell activity, cannot be generalized. Then, it has to be evaluated in relation to the single patient, and his immune status.

CONCLUSIONS

Because of its ambivalent anti-inflammatory and immunosuppres-

sive effects, as well as its complex interactions with IL-2, IL-12, and IL-17, the control of TGF-beta secretion could represent one of the most direct ways to modulate the whole cytokine network. TGF-beta is namely produced by T reg cells, then the control of TGF-beta secretion would correspond to the control of the T reg cell system itself. TGF-beta secretion, as well as that of the other cytokines, is influenced by both cytokines and neuroendocrine molecules. The control of the secretion of a single cytokine by using other cytokines with opposite or complementary effects may be more difficult from a clinical point of view, since every single cytokine may have important toxicity. Then, it would be easier to influence cytokine secretion by acting on its central neuroendocrine regulation. Therefore, a better knowledge of the neuroendocrine control of TGF-beta secretion may deserve important clinical benefits, because of the involvement of T reg cell system with a consequent altered TGF-beta secretion in the pathogenesis of most human systemic diseases, including cancer and autoimmunity, as well as in human severe diseases, whose pathogenesis has still to be better understood, such as the amyotrophic lateral sclerosis.[39] In fact, it has appeared to present a more aggressive behavior in the presence of a diminished T reg cell function. Even though cancer and autoimmunity are characterized by two opposite immune situations, respectively consisting of an abnormally high and low T reg cell activity, some neuroendocrine and neuroactive agents, namely the pineal hormone MLT, cannabinoid agents e CBD, would be therapeutically effective in both conditions of cancer and autoimmune. This finding could be due to their different immunomodulating effects, depending on the functional status of the immune system through a possible down- or up-regulation of cytokine receptors expression. On the contrary, opioids play a negative influence on the diagnosis of cancer[40] because of their immunosuppressive effects, whereas their immune effects in autoimmune diseases need to be further investigated.

CONFLICTS OF INTEREST

We have no conflicts of interest with nobody and have nothing to declare.

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