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The Involvement of IL-17 – ACE-ACE2 System Connections in the Pathogenesis of Cancer

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Abstract

Until few years ago, TGF-beta was considered one of the main pro-tumoral endogenous molecules, because of its immunosuppressive activity, due to an inhibitory effect on the secretion of both IL-2 and IL-12, the two major anticancer cytokines in humans. IL-17, which was considered the main cytokine responsible for the pathogenesis of the autoimmune diseases because of its inhibitory action on T reg cells and TGF-beta secretion, has recently appeared to play a major pro-tumoral role, due to several mechanisms, including a direct stimulation of cancer cell proliferation, neo-angiogenesis and macrophage system-induced immunosuppression of the anticancer immunity. Moreover, IL-17 has also appeared to induce an unbalanced ACE-to-ACE2 ratio by stimulating ACE expression, which in addition to its hypertensive action has been proven to exert inflammatory, pro-fibrotic and pro-tumoral effects, whereas ACE2 expression plays hypotensive, anti-inflammatory, anti-fibrotic and antitumoral antiproliferative properties. Therefore, the inhibition of IL-17 secretion and activity could constitute a new way in cancer therapy. At present, it is known that IL-17 secretion may be physiologically inhibited by IL-2, IL-12, and even though in a less manner by cannabinoid agonists and the pineal hormone melatonin. On the same way, anti-IL-17 monoclonal antibodies may also block IL-17 secretion. Therefore, the antitumor therapy with anti-IL-17 monoclonal antibodies might represent a new strategy in cancer immunotherapy. In addition, IL-2 cancer immunotherapy could be reintroduced in the clinical oncology with a new ratio, that of suppressing IL-17 secretion and/or activity.

Keywords: ACE; ACE2; Cancer; Cannabinoid agonists; Immunotherapy; IL-2; IL-12; IL-17; TGF-beta

Introduction

The activation of an effective antitumor immune response represents the best way to win cancer. Today, it is known that there are two fundamental immune-mediated anticancer cytotoxic mechanisms, which consist of antigen-independent and antigen-independent cytotoxicity. The antigen-dependent cytotoxicity is mediated by the cytotoxic T lymphocytes (CD8+), while the antigen-independent one is realized by the NK-LAK cell system. The cytotoxic T lymphocytes are mainly activated by IL-12 released from the dendritic cells [1]. On the other side, NK cells are activated by IL-2 secreted by T helper-1 (Th1) lymphocytes [2], which stimulates NK cells evolution into LAK cells. NK cells play a cytotoxic activity only against laboratory artificial cancer cell lines, whereas LAK cells may destroy fresh human cancer cells drawn from cancer patients themselves [2]. Moreover, Th1 differentiation is promoted by IL-12 itself [1]. Then, IL-2 and IL-12 would represent the two main antitumor cytokines in humans. On the contrary, the antitumor immunity is suppressed by two other major systems, consisting of regulatory T (T reg) lymphocytes [3] and monocyte-macrophage system [4]. T reg cells exert their immunosuppressive activity on the antitumor immunity by releasing some immunosuppressive cytokines, mainly TGF-beta, IL-10, and IL-35. In more detail, TGF-beta has been proven to suppress the anticancer immunity by inhibiting the secretion of both IL-2 and IL-12 [5]. Macrophages may also inhibit the anticancer immunity through the production of several immunosuppressive cytokines, including IL-6, IL-1beta, TNF-alpha and TGF-beta itself [6]. The secretion of IL-6 is determined by IL-1beta itself. IL-6 has appeared to counteract IL-2-induced transformation of NK into LAK cells, while TNF-alpha may exert a direct lymphocytolytic activity. Moreover, it has been shown that T reg cell generation

is promoted by TGF-beta and IL-10 released from some myeloid cell precursors [3-5]. Therefore, the inhibition of TGF-beta secretion and activity could represent a new approach in cancer immunotherapy to enhance the efficacy of the antitumor immunity [5]. Until few years ago, TGF-beta was considered the main endogenous immunosuppressive factor. Moreover, the antitumor efficacy of IL-2 has appeared to be limited by its potential stimulatory role on T reg system and TGF-beta secretion [7], at least in some experimental conditions. IL-2-induced stimulation of T reg lymphocytes may be abrogated by the concomitant administration of IL-21 [7]. However, more recently another cytokine has been proven to play a fundamental role in the control of cancer growth, the IL-17, which is mainly produced by Th17 lymphocytes [8], because of its complex influence on the whole cytokine network.

The Physiology of IL-17

IL-17 is present in several isoforms, the most biologically active of them is IL-17A [8]. IL-17 secretion is inhibited by both IL-12 [9] and IL-2 [10]. IL-17 secretion would be also inhibited by IL-21 [7]. On the contrary, IL-17 secretion is stimulated by IL-1beta produced by macrophages [11], whose production is promoted by IL-17 itself. Therefore, there is a positive feedback mechanism with reciprocal stimulatory effects between IL-17 and IL-1beta, by realizing a connection between macrophage- and Th17 lymphocyte-mediated inflammatory response. Finally, IL-17 secretion is inhibited by TGF-beta, which in contrast stimulates Th17 cell differentiation and IL-17 secretion in association with IL-6 [12] or IL-23 [13]. However, IL-17 secretion has also appeared to be under a central neuroendocrine regulation, since it may be inhibited by the cannabinoid agonists [14] and the pineal immunomodulating hormone melatonin (MLT) [15], whereas it is stimulated by the mu-opioid agonists [16]. The main endogenous cannabinoid agonists are represented by arachidonyl-ethanol-amide (AEA) and 2-arachidonyl-glycerol (2-AG), while the most known exogenous cannabinoid is tetrahydrocannabinol (THH) from Cannabis Indica (14). IL-17 secretion may be also counteracted by inhibitors of the fatty acid amide hydrolase (FAAH), the enzyme involved in cannabinoid degradation [17], with the following increase in the endogenous content of cannabinoids. An inhibitory action on FAAH may be exerted by the endogenous palmitoyl-ethanol-amide (PEA) [18] and by the non-psychoactive component of Cannabis cannabidiol (CBD) [14], even though they are not cannabinoid agonists. The most relevant biological action of IL-17 consists of the inhibition of T reg cell system [8], with the following promotion of the development of possible autoimmune processes. In fact, IL-17 has been proven to play a fundamental role in the pathogenesis of the autoimmune diseases [19]. Therefore, from a physio-pathological point of view, until few years ago IL-17 was thought to be substantially involved in the only onset of autoimmune diseases. In contrast, recent experimental and preliminary clinical observations have demonstrated the involvement of IL-17 also in the onset and progression of cancer, even though controversial results have been reported in the literature [20,21].

The Effects of IL-17 on Cancer Growth and Antitumor Immunity

Abnormally high blood levels of IL-17A and enhanced IL-17A have been observed in several solid tumor histotypes, consisting of lung cancer, including small cell and non-small cell lung cancer [22], gastric cancer [23], colorectal cancer [24], biliary tract carcinoma [25], hepato-carcinoma [26], pancreatic cancer [27], uterine cervix carcinoma [28] and triple negative breast cancer (TNBC) [29]. Moreover, the evidence of an enhanced IL-17 expression and secretion has appeared to predict a poor prognosis and to be associated with a greater tumor extension and a lower survival in most solid tumor histotypes, including the TNBC [20-28]. On the contrary, few authors only have described a positive prognostic significance of an enhanced IL-17 expression and secretion, and substantially for the only esophageal cancer [21]. Finally, Th17 lymphocyte infiltration into tumour mass has appeared to stimulate cancer cell proliferation and to suppress the antitumor immunity [20-29]. Moreover, intratumor IL-17-positive mast cells have been proven to be one of the main sources for IL-17 itself [30,31]. The controversial results concerning IL-17 significance in cancer might be simply due to the ability of IL-17 to potentially exert both pro-tumoral and antitumoral effects. However, most data agree with the evidence that the pro-tumoral activity of IL-17 is superior with respect to its potential anticancer action [20-29]. In fact, the possible antitumor effects of IL-17 are limited to its stimulatory action of cytotoxic T lymphocytes [20,21], and to its inhibitory activity on T reg lymphocytes (8), which in contrast suppress the antitumor immunity [3]. On the other hand, the fundamental pro-tumoral activity of IL-17, mainly of IL-17A, is related to multiple biological mechanisms [20,21,30], including direct stimulatory effect on cancer cell proliferation, stimulation of tumour angiogenesis by inducing VEGF secretion, which represents the main endogenous angiogenic factor, induction of neutrophil attraction to tumor sites, and activation of macrophage system, which suppresses the antitumor immunity by the release of inflammatory immunosuppressive cytokines, particularly IL-6 and TNF-alpha. Therefore, the potential antitumor properties of IL-

17 would by abrogated by its more pronounced pro-tumoral effects. The recent cancer immunotherapies with anti-immune checkpoint monoclonal antibodies, including anti-CTLA-4 and anti-PD-1, have appeared to increase IL-17 levels [32]. Then, checkpoint inhibitor-induced enhanced IL-17 secretion could represent one of the possible mechanisms responsible for the lack of efficacy of immunotherapies themselves. Finally, IL-17 would be also involved in the pathogenesis of some advanced cancer-related severe clinical complications. including the acute respiratory distress syndrome (ARDS) [33]. The importance of IL-17 in the pathogenesis of ARDS is also confirmed by the evidence that the blockade of IL-17 activity may be effective in the treatment of ARDS [33].

Interactions Between IL-17 and ACE -ACE2 System

Until few years ago, renin-angiotensinogen- angiotensin converting enzyme (ACE) was considered as involved in the only control of blood pressure and cardiac activity. ACE transforms angiotensin (AT)- I into AT-II, responsible for the hypertensive status because of its vasoconstrictor property. Successively, it has been demonstrated the existence of another ACE, the ACE2, which transforms AT-I into AT 1-7, that in contrast exerts a vasodilator action [34]. More recently, it has been shown that ACE – ACE2 system is not involved in the only cardiovascular regulation, but also in the control of the main biologic functions, including inflammatory response, cell proliferation, and postinjury- or age-related fibrotic processes [35]. ACE activation through its product AT-II may induce hypertension, and exert a stimulatory effect on the inflammatory response, organ fibrosis, and cell proliferation, with a following potential pro-tumoral role. On the contrary, ACE2 through its product AT 1-7 plays a vasodilator action, an anti-inflammatory activity and inhibitory effects on the fibrotic processes and cell proliferation, including that of malignant cells [35]. ACE-2 has been proven to be expressed by most tissues, including lung, heart, brain, endothelium, liver, kidney, and intestine. In addition, ACE – ACE2 system has appeared to be under an immunoregulatory control played by IL-17, which may enhance ACE expression and reduce that of ACE-2 [36]. Then, IL-17-induced enhanced ACE expression could be responsible for cardiac and vascular dysfunctions caused by IL-17 itself [36]. Moreover, age-related diminished expression of ACE-2 [37] could depend at least in part on the increase in the endogenous production of IL-17 with age [38]. In addition, because of the anti-inflammatory and anticancer activity of ACE2 [39], a decline in ACE2 expression caused by cancer-relatedenhanced production of IL-17 may furtherly stimulate cancer progression. Finally, ACE allows a stimulation of the cardiovascular secretion of endothelin-1 [34,35], which exerts pro-tumoral and

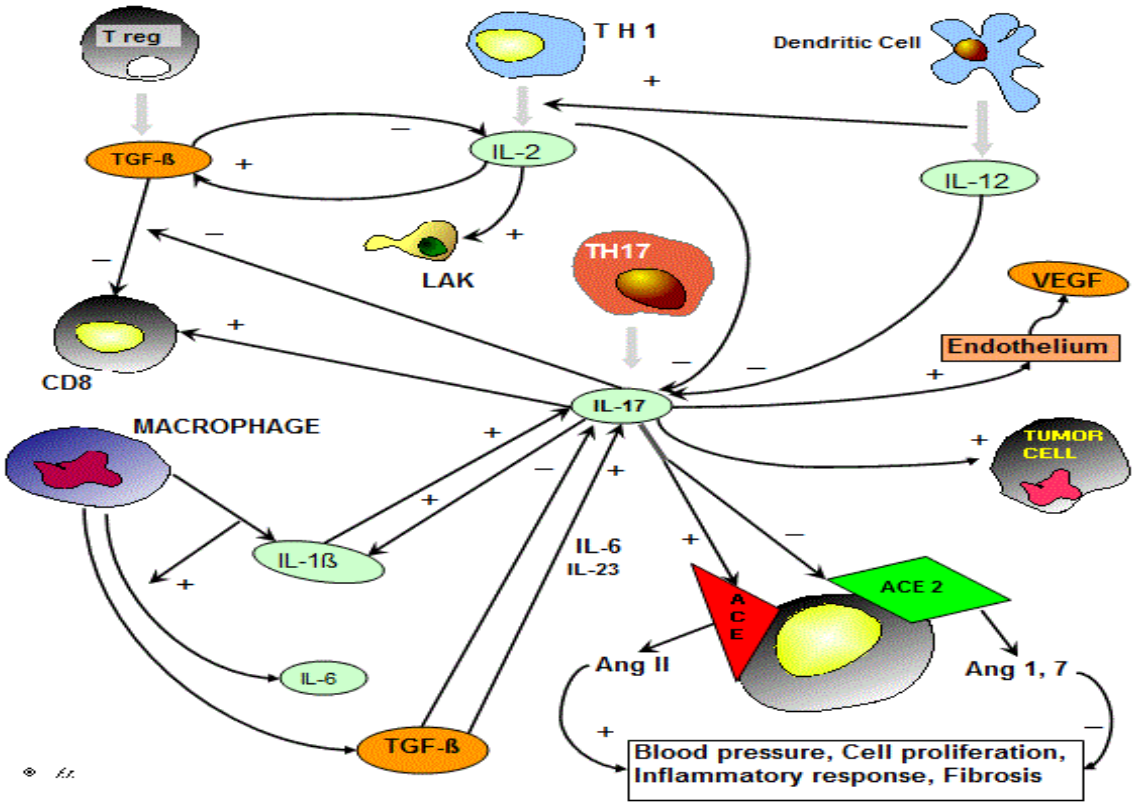

Fig. 1 The role of IL-17 in the antitumor immunity

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inflammatory activities [40]. On the contrary, ACE2 induces the cardiac secretion of atrial natriuretic peptide (ANP), which plays antitumoral and anti-inflammatory effects [41]. Covid-19 infection-induced ARDS would be also determined by an unbalance between ACE and ACE2 expression [42, 43], probably promoted by the enhanced secretion of IL-17A, which could constitute the main cytokine involved in Covid-19 infection-induced severe respiratory failure [44]. The interactions between ACE-ACE2 system and IL-17 secretion are illustrated in Figure 1.

Therapeutic Implications

According to the results available up to now on the role of IL-17 in human tumours, an inhibition of IL-17 secretion and activity could counteract at least in part cancer growth, irrespectively of the histotype of cancer. A direct inhibition of IL-17 may be achieved by the administration of specific anti- IL-17 monoclonal antibodies, such as the already available secukinumab. IL-17 secretion is also inhibited by IL-12 [9] and IL-2 [10]. IL-12 cancer immunotherapy is still experimental [1], while that with IL-2 has been proven to induce objective tumor regressions, namely in renal cancer and melanoma [6]. Unfortunately, cancer immunotherapy was clinically abandoned by the Oncologists because of its potential stimulatory action of T reg cells [7], which in contrast suppress the antitumor immunity [3-5]. However, IL-2-induced stimulation of T reg cell system may be simply due at least in part on its inhibitory action on IL-17 secretion [10], which in contrast inhibit T reg cell functions and TGF-beta release [8]. Then, cancer immunotherapy with IL-2 could be reintroduced into the clinical oncology with the aim of blocking IL-17 secretion and its pro-tumoral activity [10]. In any case, cancer immunotherapies with IL-2 and anti-CTLA-4 and anti-PD-1 monoclonal antibodies may be proposed for the metastatic disease. On the contrary, in the presence of locally limited neoplasms, it could be enough as an adjuvant therapy to counteract IL-17 secretion by acting on its central neuroendocrine inhibitory regulatory control, which is mainly mediated by the pineal gland through MLT and brain endocannabinoid system [14-18], then by the exogenous administration of MLT itself, cannabinoids agonists and FAAH inhibitors, including PEA and CBD, which have been proven to inhibit IL-17 secretion.

Conclusion

If successive experimental and clinical studies will confirm the clear pro-tumoral activity of IL-17 and its negative prognostic significance in cancer patients, each molecule provided by an inhibitory action on IL-17 secretion or activity could have to be considered as a potential anticancer agent.

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