The Role of IL-15 in Human Cancer: Friend or Foe?

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Abstract— IL-15 is a member of the family of IL-2 cytokines. This family of cytokines activates signaling pathways leading to cellular activation, proliferation and survival. IL-15 exhibits broad activity and induces the differentiation and proliferation of NK, T and B cells. Furthermore, IL-15 protects T-effector cells from the action of T Regulatory cells and reverses tolerance to tumor associated antigens. Thus, IL-15 potentiates the immune system which is important in immunosurveillance against cancer. However, IL-15 may be also involved in the pathogenesis of hematological malignancies and mediates the processes of tumor progression and metastasis, becoming a growth factor for cancer cells. In preclinical studies, administration of IL-15 in several tumors potentiated antitumor effects alone or in combination with other anti-cancer treatments. To date, there are some phase I clinical trials to test the effective role of IL-15 in human cancer. Thus, according to its pleiotropic and wide involvement in human cancer pathogenesis, it is still under discussion if IL-15 will be friend or foe. The discussion of these issues is the aim of the present review.

Index Terms— IL-15, In innate immunity, adaptive immunity, Celiac Disease, Inflammatory Bowel Diseases, Hematological Malignances, Solid tumors.

I. BIOLOGY OF IL-15

IL-15 is a member of the family of IL-2 cytokines. This family of cytokines activates signaling pathways leading to cellular activation, proliferation and survival [1]. It includes: IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 [1-3]. IL-15 was co-discovered by two different laboratories in 1994 and characterized as a T cell growth factor. IL-15 displays pleiotropic functions in homeostasis of both innate and adaptive immune system [4]. IL-15 receptor is a heterotrimeric receptor composed of three subunits: alpha is specific for IL-15, while beta (CD122) and gamma (CD132) are shared with the IL-2 receptor. The common receptor components determine the sharing of the JAK1/JAK3/STAT5 signalling pathway. The similar structure of their receptors explains partial functional redundancy among γc-chain cytokines [3].

The IL-2R/IL-15Rβγc complex binds to IL-15 with high affinity (Kd > 10^{-11} M) and retains IL-15 on the cell surface. This high affinity along with the co-expression of IL-15Ra and IL-15 produced in the same cell, allows intracellular binding of IL-15 to IL-15Ra, which is then shuttled to the cell surface as a complex. Once on the cell surface, the IL-15Ra/IL-15 complex can stimulate IL-15Rγc in an opposing cell during a cell–cell interaction. This mechanism of cytokine delivery has been referred to as trans-presentation [2] and leads the formation of the so called immunological synapse [5].

The prevalent mechanism of IL-15 action seems to be by trans-presentation (juxtacrine signalling), IL-15 may also acts by intracrine, autocrine, paracrine and endocrine signalling [6]. Cis-presentation, when IL-15 form autocrine is presented by IL-15Ra to IL-15R on the same cell, is also possible [7]. IL-15 is produced by several cell types, but the higher production is observed in dendritic cells, monocytes and macrophages. Then, the IL-15Ra of these cells is able to trans-present IL-15 to IL-15Rβγc of CD8 T cells, NK cells, and NK-T cells, that do not express IL-15 [8]. This effects induces the formation of the immunological synapse [9, 10]. In addition to these studies that show the hematopoietic cells that trans-present IL-15, other studies show also that IL-15 has effects on non-hematological cells including myocytes, adipocytes, fibroblast, epidermal skin cells, endothelial, kidney, placenta, lung, heart and neural cells [2, 8] and also cancer cells [6].

There are numerous cells that trans-present IL-15, but their ability depends on the biological status of the responding lymphocyte, the residence tissue, and the stage of lymphocyte differentiation. Castillo et al. showed that the developmental and homeostatic niche of NK cells is not only driven by IL-15 but by also by distinct IL-15R on different cell types that may be tightly regulated by tissue microenvironment [8]. Several authors have demonstrated that murine and human IL-15Ra, exists both in membrane bound, and also in a soluble form [4]. Soluble IL-15Ra (sIL-15Ra) is constitutively generated from the transmembrane receptor through proteolytic cleavage. The constitutive and inducible shedding of IL-15Ra involves the activity of Tumor necrosis factor-Alpha-Converting Enzyme (TACE/ADAM17), and is blockaded by appropriate metalloproteinase inhibitors [4]. In physiological and/or pathological conditions, the proteolytic release of IL-15Ra could be of functional importance, and could affect the signalling properties of IL-15. The presence of sIL-15Ra in biological fluids may negatively affect the...
availability of free IL-15, first by competing for the cytokine with cognate membrane-bound receptors, thereby countering the IL-15-induced signalling. Thus, sIL-15Ra may represent an important protective mechanism against excessive IL-15 activity [4, 6].

II. PHYSIOLOGICAL FUNCTIONS OF IL-15

IL-15 acts preventing apoptosis and stimulating activation, proliferation and survival of target cells that express IL-15-receptor complex. Throughout the mechanism of trans-presentation, IL-15 mediates an intracellular signalling pathway leading to the activation of anti-apoptotic genes, such as Bcl-2, and regulatory genes, such as Myc, Fos/Jun and NF-kB. IL-15 bound to IL-15Ra can also recycle through endosomal vesicles for many days (endosomal recycling) resulting in the persistence of membrane-bound IL-15 [9].

IL-15 plays a pleiotropic role in the interface between innate and adaptive immunity. IL-15 exhibits broad activity and induces the differentiation and proliferation of NK, NK-T, T and B cells. It also enhances the cytolytic activity of CD8 T cells and induces long-lasting antigen-experienced CD8 memory T cells [2] and makes both CD4 and CD8 T cells resistant to the action of Treg cells [11].

IL-15 is a cytokine of IL-2 family. So, IL-2 and IL-15 cytokines, sharing two receptor subunits (IL-2/IL-15Rβ and γc), have several similar functions [5]. These functions include stimulating the proliferation of activated CD4 and CD8 T cells. Furthermore, these two cytokines facilitate the induction of CTLs, and they induce the proliferation of B cells and also induce immunoglobulin synthesis by B cells. Moreover, IL-2 and IL-15 stimulate the generation and proliferation of NK cells. In addition to these similarities, there are distinct differences between the function of IL-2 and IL-15, and these differences are crucial in the homeostasis of adaptive immune response [5].

Unlike IL-2 which is required to maintain FoxP3-expressing CD4⁺CD25⁺ Tregs and for the retention of these cells in the periphery, IL-15 has little and controversial effects on Tregs [12]. On the one hand IL-15 induces the expression of FoxP3 on Tregs [13], but on the other hand it renders effector T-cell resistant to the regulatory action of Tregs [11]. So, the fact that IL-15 doesn’t result as a growth factor Tregs is important because IL-15 protects T-effector cells from the action of T Regulatory cells and reverse tolerance to tumor associated antigens (TAAs) [7], that are the main mechanisms which tumor may escape from immune system [14, 15].

Furthermore, IL-2 has also a crucial role in initiating activation-induced cell death (AICD), a process that leads to the elimination of self-reactive T cells, whereas IL-15 is an anti-apoptotic factor for T cells [16], thus contributing to the maintenance and potentiating of immune response in infections such as in cancer. Notably, the IL-15-mediated inhibition of AICD may be responsible for the induction of autoimmunity, considered as a possible side effect of clinical administration of IL-15.

III. ROLE OF IL-15 IN CANCER

According to its functions on adaptive immunity, IL-15 can potentiate immune system. For this activity, while IL-15 has a deleterious effect in the pathogenesis of inflammation and autoimmunity, it also may play a role in enhancing the response to cancer [17].

The most important cells engaged in IL-15 antitumor activity are T cells, in particular CD8 T cytotoxic cells (CTLs) and NK cells. Both of them can kill tumor cells by granule- or FAS-mediated pathways [7]. So, IL-15 can reverse unresponsiveness of CD8 T cells against tumor cells and abrogate tolerance to TAAs. Furthermore, IL-15 renders T effector cells resistant to the immunosuppressive action of Tregs [11]. Moreover, the ability of IL-15 to stimulate NK cell cytotoxicity as a result of enhanced expression of the activating NKG2D receptor present on NK and T cells is another mechanism of interference with tumor evasion strategies [7].

To date, IL-2 is the only cytokine approved for cancer treatment. Some clinical trials using IL-15 are being performed. In fact, IL-2 has been approved by US Food and Drug Administration for the treatment of patients with metastatic renal cell carcinoma and malignant melanoma [18, 19]. However, the early enthusiasm associated with the use of IL-2 in tumor therapy has diminished, as durable complete responses were achieved in only a small percentage of patients given high-dose IL-2 therapy [14]; application of high dose of IL-2 is plagued by severe toxicity [7, 20]. Moreover, IL-2 is not optimal for inhibiting tumor growth, because in the presence of IL-2, the generated cytotoxic lymphocytes might recognize cancer cells as self and thus undergo AICD In addition, under IL-2 treatment, the immune response to cancer may be inhibited by activation and proliferation of IL-2-dependent Tregs. By contrast IL-15, it has been claimed that IL-15 with its ability to activate T and NK cells, its inhibition of AICD and its role in the persistence of CD8-memory T cells might be a better choice than IL-2 for the treatment of cancer [21].

However, in the lack of clear cut experimental data, the effective role of IL-15 in cancer remains still controversial. In fact, on one hand, several data suggest that IL-15 may improve immune response in cancer, but on the other hand, other data IL-15 has been associated to inflammation, which is linked to cancer pathogenesis, particularly to lymphomagenesis [22]. In fact, some ex vivo studies have revealed a controversial role of IL-15 in human cancer. Thus., although we have described the positive immune-stimulatory role of IL-15 in cancer, this cytokine may play also opposite effects in promoting the growth of cancer cells and the progression of tumor and metastases. In particular, according to its ability in preventing apoptosis of blood cells, IL-15 is reported to be implicated in the pathogenesis of hematological malignancies.

a. Hematological malignancies and hematological Celiac Disease-related complications.
IL-15 stimulates the proliferation and maintenance of NK, T and B cells, favouring the development of oligo- monoclonal T cell populations; for this activity, it may play a role in the pathogenesis of some haematological malignancies [17]. In fact, IL-15 and IL-15 pathway are over-expressed in patients with acute lymphocytic leukemia (ALL), human T cell lymphotrophic virus (HTLV-1)-associated Adult-T-cell leukemia, and Sezary’s syndrome and in the leukemic form of mycosis fungoides [17].

In addition, it has been suggested that IL-15 participate in the pathogenesis of the main hematological complications of Celiac Disease (CD), such as Refractory Celiac Disease (RCD) and Enteropathy-Associated T-cell Lymphoma (EATL) [23]. RCD is a severe complication of CD that occurs in approximately 5% of celiac patients. RCD is defined by persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet for at least 6-12 months in the absence of other causes of non-responsive treated CD and overt malignancy. Symptoms are often severe and required additional therapeutic intervention besides dietary treatment [24]. RCD can be classified as type I, defined by normal polyclonal IEL (Intra Epithelial Lymphocytes) phenotype, or type II, defined by the emergence of a population of abnormal aberrant IELs within the epithelium, which are characterized by a clonal rearrangement of the TCR [25], by loss of surface expression of CD3 and CD8 and very stereotypical phenotype anomalies. Type II RCD is considered as an equivalent of intrapitithelial T lymphoma known as low-grade [26]. Enteropathy associated T lymphoma (EATL) is a rare and aggressive non-Hodgkin lymphoma of T-cell origin showing varying degrees of transformation but usually presenting as a tumor composed of a large lymphoid cell, often with an inflammatory background [27].

Several mechanisms have been implicated in the increased risk of malignancies in CD. Firstly, the augmented proportions of peripheral and tissue infiltrating Tregs could justify the improved global risk of malignancy in CD population and support the efficacy of lifelong gluten-free diet in the overall reduction of cancer risk [15, 28]. Moreover, as a result of tissue chronic inflammation there is a continued antigen presentation at tissue level in duodenal mucosa of CD patients [29].

The proinflammatory cytokine IL-15, that is over-expressed both in lamina propria and in the intestinal epithelium of CD patients [30], plays a major role in these cellular interactions and thus it has been considered as a crucial element that orchestrates intestinal inflammation and T-cell mediated autoimmune tissue destruction [31].

IL-15 induces upregulation of anti-apoptotic genes, such as Bcl-xL and Bcl-2, helping effector lymphocytes to escape AICD. The IL-15-related upregulation of antiapoptotic genes promote the proliferation of IELs. Thus, in CD protracted production of IL-15 might result in accumulation of proinflammatory and/or autoreactive lymphocytes sustaining chronic inflammation, autoimmunity and might lead to the development of oligoclonal and/or monoclonal T cell proliferations [32]. In summary, IL-15 induced IELs proliferation and apoptosis resistance might be a factor involved in the development of T-cell lymphoma in the CD mucosa [33]. Furthermore, human studies are needed to demonstrate if targeting IL-15 may have a valuable impact in the treatment of these disorders.

Several strategies have been proposed to block IL-15 pathways to obtain clinical benefits in diseases where IL-15 may have a role. For example, Yokoyama et al. [34] in a transgenic mouse model studied the effect of the monoclonal antibodies TM-β1 blocking IL-15 receptor complex to reverse the autoimmune intestinal damage associated to overexpression of IL-15 in enterocytes.

In addition, a monoclonal antibody, MiK-(β1), directed against the human CD122 (IL-2Rβ) that blocks IL-15 activity is already in Phase I trials for evaluation in the treatment of T cell LGL leukemias [35, 36].

On data based in the animal model [22, 37], it can be hypothesized that blocking IL-15 might prove a useful therapeutic approach in CD complications, such as type II RCD and EATL which are the most severe diseases resistant to currently available treatments. However, anti-IL-15 therapy warrants further investigation in patients with CD, because none of these experimental approaches has resulted in an effective drug to treat CD complications.

Although we have discussed on the role of IL-15 in stimulating the development of EATL of gut mucosa, there are several observations suggesting that IL-15 may have also a potential anticancer effect on B-cell lymphoma [38]. The anticancer action on B-cell lymphoma is possible because IL-15 is a key activator of NK cell function. In fact, NK cells are the most important effectors cell in the mechanism of antibody-dependent cellular cytotoxicity (ADCC) in which tumor-targeting antibodies participated in mediating cancer cells death.

It has been demonstrated that IL-15 is able to potentiate Rituximab-mediated ADCC against B-cell lymphoma [38], and might improve therapeutic effects of other tumor-targeting monoclonal antibodies [7]. The same result that IL-15 have in potentiating Rituximab-mediated ADCC against B-cell lymphoma has more recently demonstrated also in the case of Chronic Lymphocytic Leukemia (CLL) [39].

Finally, IL-15 has a role also in other hematological malignancies, such as large granular lymphocytes leukemia. The lymphoproliferative disorder of large granular lymphocytes leukemia (LDGL) is a disease that was originally characterized in the last decades of the previous century [40]. It consists of an abnormal proliferation of large granular lymphocytes (LGL): CD3 positive or negative or NK-cells. Several cases represent self limiting leukemoid reactions in response to infections or autoimmune diseases, but in other patients clonality can be demonstrated and the disease represent a true leukemia [41].

In T-cell LGL leukemia IL-15 and IL-15R alpha levels are increased and PBMCs of some T-LGL patients proliferated at higher levels in response to exogenously added IL-15 compared with those of normal donors. Thus suggesting a role for IL-15 in the pathogenesis of these diseases [42]. More recently it has been demonstrated that in leukemias of both T and NK cells, STAT3 is mutated and STAT3 abnormal signaling induced by cytokines may contribute to disease
pathogenesis [43]. Moreover, STAT3 inhibitors have a beneficial role in this disease [44].

b. Solid tumors

In non-hematological malignancies there is little evidence that IL-15 plays some direct role in the development of solid cancers, but instead there is evidence suggesting that it may play a role in immunosurveillance and protection from tumor formation [17].

Several experiments, both in animal and ex vivo models, have been performed to tested the clinical efficacy of IL-15 in the treatment of cancer. For example, pre-clinical studies have demonstrated potentiated antitumor effects of IL-15 following pre-association with IL-15Rα, or when used in combination with chemotherapy, adoptive therapy, monoclonal antibodies and tumor vaccines [7]. Even, the direct administration of IL-15 has shown anti-tumor effects in numerous preclinical mice models [21, 45]. In a recent study, Yu et al. have demonstrated that IL-15 prolongs the survival of mice with metastatic CT26 colon cancer [45].

However, in this experiment, in addition to having shown the positive action of IL-15 in cancer, it has been demonstrated also that IL-15 may participate in activating immune-system negative regulatory checkpoints that might also dampen the immune response. In fact, IL-15 induced the expression of the immunosuppressive receptor programmed death-1 (PD-1), and increased the secretion of the immunosuppressive cytokine IL-10 by CD8 T cells. Thus, the greatest therapeutic effect have been achieved with combination modality treatment based on application of IL-15 and blockade of both anti-programmed death-1 ligand (PD-L1) and anti-cytotoxic lymphocyte antigen 4 (CTLA-4) [45]. Co-administration of PD-L1 and CTLA-4 monoclonal antibodies reduced PD-1 and IL-10 expression and resulted in greater anti-tumor responses than did IL-15 alone [15, 45]. However, this inhibition of negative regulators of the immune response can induce serious autoimmune reactions inducing colitis, dermatitis and hypophysitis [7].

Various other preclinical approaches have been explored to increase the efficacy of IL-15 immunotherapy, including coadministration of anti-CD40 to induce and enhance IL-15Rα expression [17]. Zhang et al. using a mouse model of colon cancer demonstrated that the administration of the anti-CD40 antibody was associated with increased expression of IL-15Rα on DCs and an increased concentration of released IL-15Rα in the serum; thus, these authors demonstrated that the combination therapy with IL-15 and anti-CD40 antibody is able to prolong survival of those tumor-bearing mouse models [21]. In addition to its therapeutic benefit, this combination therapy resulted also in a specific biological effect; in fact, it was also associated with increased NK cell cytotoxic activity [21]. Yet, in mice bearing renal adenocarcinoma, a combination of IL-15 and agonistic anti-CD-40 antibody induced reduction of both Treg and myeloid-derived suppressor cells in the tumor microenvironment [46].

The diverse functions of IL-15 facilitate the development of both innate and durable adaptive immunity making it an ideal agent to be used either alone or in combination with other treatment modalities in tumor therapy [7]. In fact, although IL-15 administration may show efficacy in the treatment of metastatic malignancy in human clinical trials, it doesn’t seem to be optimal as a single agent [21]. Thus, using a tumor-bearing rat model, it has been demonstrated that IL-15 administration is useful to improve of the therapeutic index of 5-Fluorouracil alone and in combination with Leucovorin [47]. This co-administration of IL-15 to the other chemotherapy drugs active in colorectal cancer is also able to protect from chemotherapy-induced toxicities, but at the same time is able to increase the proportion of complete tumor regression induced by chemotherapy [47].

To date, there are some phase I clinical trials to test the effective role of IL-15 in human cancer. These trials use recombinant human IL-15 (rhIL-15) protein alone or combined with the administration of patient-derived tumor infiltrating lymphocytes (TILs) [15, 17, 48]. Clinical trials using IL-15 have been begun in human are: in phase I using intravenous rhIL-15 in adults with refractory metastatic malignant melanoma and metastatic renal cell cancer, a use of IL-15 after chemotherapy and TILs transfer in metastatic melanoma, a IL-15 DCs vaccine for patients with resected stage IIIc and stage IV melanoma and haploidentical stem cells transplantation and a IL-15 NK cell infusion for pediatric refractory solid tumors [17].

The capacity of IL-15 to potentiate activation of NK cells, NK-T cells and CD8 T cells has been exploited to make a mouse model in which an IL-15 superagonist was delivered in hepatocellular cancer (HCC) tissue. In this model [49], authors employed hepatotropic adeno-associated virus serotype 8 (AAV8) to deliver the IL-15 superagonist, consisting of IL-15 covalently linked to the N-terminal domain of the IL-15 receptor α chain (IL-15-IL-15RαS). This experiment has demonstrated that a single injection of AAV8 expressing IL-15-IL-15RαS, but not IL-15 alone, greatly expanded the number of intra-hepatic mononuclear cells, mainly NK cells. So, in this liver metastatic murine HCC model AAV8/ IL-15-IL-15RαS treatment generated potent antitumor activity and significantly prolonged the survival time of treated animals [49].

Further evidence confirmed the involvement of IL-15 in HCC. In fact, it has been demonstrated that type I IFN therapy of hepatitis C-related HCC induced IL-15 production and also suggested that IL-15 may be associated with type I IFN-induced immune response [50].

Moreover, IL-15 has been also found to potentiate the effectiveness of tumor chemotherapy [7]. For example, IL-15 prolonged remission induced by cyclophosphamide in rhabdomyosarcoma- and lung- bearing mice with participation of Tqβ, Tyβ cells, and NK cells [51, 52]. Similarly, the coadministration of other cytokines such as IL-21 has augmented the anti-tumor efficiency of IL-15 in animal tumor models [53]. Thus, in clinical practice IL-15 is
not only used as a single agent therapy but it can be used in combined treatment with other cytokines. For example, IL-15 combined with IL-21 synergistically expanded CD8 T cells and CD8 T memory cells, and such co-cultures contained a lower proportion of the immunosuppressive Tregs [7]. Therefore, a combination therapy with IL-15 and IL-7 has been experimented in breast carcinoma models in mice: combining radiofrequency thermal ablation of breast tumors with intra-lesional administration of IL-15 and IL-7 induced tumor-specific immune response and inhibited tumor growth and formation of lung metastases [54]. Then, in a melanoma model in mice has been demonstrated that a combined treatment with IL-15 and IL-12 produced synergistic anti-tumor effects, which probably resulted from potentiated activation by these cytokines of both NK and CD8 T cells [55]. The anti-cancer effect of IL-15, is probably connected with the ability of this cytokine to improve immune-surveillance to cancer. However, there are controversial data on the direct role of IL-15 on cancer cells deriving from experimental evidences. In fact, it has been demonstrated that IL-15 can act as growth factor not only for immune cells but also for cancer cells. In example, it has been demonstrated that IL-15 may have biological effects also on colon cancer cells. The group of Kuniyasu has shown that the IL-15 produced by metastatic colon carcinoma cells can induce hyperplasia in the mucosa adjacent to colon cancer, thus contributing to angiogenesis and progression of the disease [56]. In this ex vivo experiment, IL-15 has been shown to promote the proliferation, motility and invasiveness of colon cancer cells as well as increase their tolerance resistance to apoptosis, suggesting that IL-15 expression is closely related to the production of metastasis. IL-15 also increases the production of angiogenic factors by intestinal epithelial cells, which suggest that IL-15 can contribute to both mucosal hyperplasia and angiogenesis and, hence, to tumor progression and metastasis [56]. Finally, the safety of IL-15 administration in vivo has been evaluated in mice and in non-human primates. IL-15 seems to have a good toxicology pattern, lacking from the most common adverse affects of IL-2 infusion, such as the vascular leak syndrome (VLS), caused by an altered vascular permeability [17]. Further characterization of associated adverse effects of IL-15 administration must await the completion of human Phase I trials. However, before beginning each clinical trial based on application of IL-15 in tumor patients, it is important to be aware of its potential side effects, including induction of pro-inflammatory cytokines, induction of autoimmunity, atherogenic effects and promotion of proliferation, survival and dissemination of some tumor cells [5, 7].

IV. CONCLUSIONS

According to its functions on adaptive immunity, IL-15 potentiates immune system. For this, while IL-15 has a deleterious effect in the pathogenesis of inflammation and autoimmunity, this cytokine may play a positive role in the response to cancer [17]. The ability of IL-15 to activate many immune antitumor mechanisms, as widely discuss in this review coupled with an apparent lack of toxicity, makes it a good candidate for application in tumor immunotherapy. Unfortunately, although IL-15 can be regarded as a good candidate for tumor therapy, used alone or in combination with other treatment modalities, it can also demonstrate the opposite effects on tumor development. In fact, IL-15 has been found to participate in the development of some leukemias and solid tumors, to inhibit apoptosis of tumor cells and support their survival, and to promote their proliferation, migration, epithelial-to-mesenchymal transition, invasion and metastasis [7]. In hematological malignancies, IL-15 has a dual role: on the one hand it participates in their development, being a growth factor for blood cells and favouring oligo- mono- clonal T cell proliferation, but on the other hand IL-15 may be used as adjuvant in the treatment of B-cell lymphoma to potentiate Rituximab-mediated ADCC. In solid tumors, IL-15 seems to be a good agent for immunotherapy, alone or in combination with other chemoterapics, adoptive therapy, monoclonal antibodies and tumor vaccines. However, IL-15 can act as growth factor not only for immune cells but also for cancer cells leading to tumor progression and metastasis. Thus, the use of IL-15 in tumor immunotherapy should always be considered with caution and should be preceded by a careful examination of its effects on the appropriate tumor cells in vitro.

Finally, in this review we have described the involvement of IL-15 in some hematological and solid tumors, according to the experimental and clinical evidences present in scientific literature. However, although our knowledge on IL-15 function in cancer is increasing, a more complete and wide study of its action in other tumors is required before it could be proposed for application in human cancer immunotherapy. In summary, our emerging understanding of the IL-15-IL-15R system is providing the scientific basis for the development of rational approaches that use IL-15 for cancer immunotherapy as single therapeutical agent or in combination therapy. However, more investigation about the precise role and the clinical effect of this cytokine in cancer are required. Thus, according to its pleiotropic and wide involvement in human cancer, only after a depth study of the role of IL-15 for each specific tumor it would be possible predict if it will be friend or foe.

REFERENCES


