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Interleukin 15 as a promising candidate for tumor immunotherapy

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ABSTRACT

Interleukin 15 participates in the development of important immune antitumor mechanisms. It activates $CD8^+$ T cells, natural killer (NK) cells, NK T cells, and can promote the formation of antitumor antibodies. IL-15 can also protect T effector cells from the action of T regulatory cells and reverse tolerance to tumor-associated antigens. In pre-clinical studies IL-15 has been found to demonstrate potentiated antitumor effects following pre-association with IL-15Rα, or when used in combination with chemotherapy, adoptive therapy, monoclonal antibodies, and tumor vaccines. Although a clinical trial based on application of IL-15 in tumor patients has already begun, it is important to be aware of its potential side effects, including induction of autoimmunity and promotion of proliferation, survival, and dissemination of some tumor cells.

1. Introduction

Interleukin 15 (IL-15) was discovered as another T cell growth factor [1] and belongs to the family of the common gamma chain (γc) or four-helix-bundle cytokines, which includes IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. IL-15 displays pleiotropic functions in homeostasis and activation of both innate and adaptive immunity. Receptors for these cytokines share the common γc chain and have unique α chains. IL-2R and IL-15R have additional identical IL-2/15Rβ chains (reviewed in [2]); the similar structure of their receptors explains partial functional redundancy among γc chain cytokines. These cytokines nonetheless display unique features even if IL-2 is compared with IL-15, which shares two out of three chains in their receptors. Until recently, IL-2 has attracted the attention of oncologists as the only interleukin approved for tumor immunotherapy in the treatment of metastatic melanoma and renal cell carcinoma since 1992 [3]. 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 [4]. Application of high doses of IL-2 is also accompanied by severe toxicity [5,6]. Furthermore, although IL-2 stimulates proliferation and differentiation of effector T cells, memory $CD8^+$ T cells and natural killer (NK) cells (reviewed in [7]), strengthening the antitumor immune response, it may also limit the effectiveness of antitumor immunity because of its critical role in the differentiation and maintenance of regulatory T (Treg) cells [8] and the induction of activation-induced cell death of effector T lymphocytes [9]. As oncologists' interest in IL-2 has waned, IL-15, another member of the γc chain family of cytokines, has proven significant as a cytokine with strong antitumor activity. Advantages of IL-15 in tumor immunotherapy result from its unique ability to activate important mechanisms of antitumor immunity, including development and activity of both NK cells [10–12] and $CD8^+$ T cells [13–16], and promoting a persistent immune response through its action on memory T cells [16–20]. What is more, IL-15 is less toxic [21] and less effective in inducing Treg cell activity, as compared with IL-2 [22], and in certain circumstances it can even protect human effector T cells from the action of Treg cells [23] (see below). IL-15 is at the top of the National Cancer Institute's list of agents with the greatest potential use in tumor immunotherapy [24], and the first clinical study of recombinant human IL-15 in adults with refractory metastatic melanoma and metastatic renal cell cancer is currently recruiting patients (http://clinicaltrials.gov/ct2/show/NCT01021059). Although 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, it is important to

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; JAK, Janus kinase; LPS, lipopolisaccharide; NK, natural killer; NKT, natural killer T cell; PD-1, programmed death-1; STAT, signal transducer and activator of transcription; TAAs, tumor-associated antigens; TCR, T-cell receptor; TGF-β, transforming growth factor β; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α.

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examine the peculiarities of its activity and be aware of the potential drawbacks and side effects of its application.

2. Expression of IL-15

The human IL-15 gene was mapped to chromosome 4 region q25–35 [25]. Although IL-15 mRNA can be found in many tissues and cells, including fibroblasts, muscle cells, keratinocytes, kidney cells, lymphocytes, mast cells, and tumor cells (reviewed in [26]), this four-helix-bundle cytokine is produced as a mature protein mainly by dendritic cells, monocytes, macrophages, and stromal cells, but not T cells ([27,28] and reviewed in [24]). The discrepancy between the broad appearance of IL-15 mRNA and the limited production of IL-15 protein might be explained by the presence of upstream AUG codons in mRNA that can repress translation (reviewed in [29]). Translationally inactive IL-15 mRNA is stored in the cell, ready to be rapidly translated upon specific signals [30]. Expression of IL-15 is stimulated by cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interferons, and agonists of Toll-like receptors (TLRs) including LPS, double-stranded RNA, and unmethylated CpG oligonucleotides [31–33], and is regulated at the level of translation, intracellular trafficking, and secretion [34–36]. IL-15 pre-mRNA is alternatively spliced to yield two IL-15 mRNA and ultimately two precursor (pre-IL-15) isoforms, which differ in the N-terminal portion of their signal peptides, containing either a 21-aa short or 48-aa long signal peptide [34,37]. It has been proposed that IL-15 associated with short signal peptide plays a role in the negative feedback control of IL-15 expression and/or activity either inhibiting its transcription [38] or competing for binding to IL-15Rα [39]. Following removal of signal peptide, mature IL-15 proteins are identical [34].

3. IL-15 trans-presentation and signaling

The prevailing mechanism of IL-15 action seems to be trans-presentation (juxtacrine signaling) (Fig. 1), although it also includes intracrine, autocrine, paracrine, and endocrine signaling ([40,41] and reviewed in [26]). *Cis*-presentation, when IL-15 from autocrine or other sources is presented by IL-15Rα to IL-15R on the same cell, is also possible [42]. IL-15-producing cells, monocytes and dendritic cells in particular, simultaneously express the IL-15Rα chain, which, in contrast to IL-2Rα, binds IL-15 with high affinity ($K_a \sim 10^{-11}$ M) [43] and can mediate signal transduction [44]. Binding of IL-15 with sushi domain of IL-15Rα [42] occurs intracellularly, and IL-15Rα chaperons and shuttles IL-15 from the endoplasmic reticulum to the cell membrane [45]. IL-15 autocrine signaling can occur intracellularly (intracrine mechanism) [40] or at the level of the cell membrane in *cis* [42]. However, the IL-15/IL-15Rα complex is mostly trans-presented to the responding cells, which express IL-2/15Rβγc (or possibly also IL-2/15Rβαγc) in their cell membranes [46]. IL-15 binds to IL-2/15Rβγc with intermediate affinity ($K_a \sim 10^{-9}$ M) (reviewed in [47]), and, unexpectedly, IL-15Rα joining IL-2/15Rβγc complex does not further increase this affinity [43,48]. Trans-presentation (juxtacrine signaling) enables IL-15-producing cells to direct IL-15 more precisely to responding cells. This mode of IL-15 presentation is supported and characterized by the following observations:

- IL-15 is not usually secreted in a soluble form [49] and is rarely found in tissue fluids (reviewed in [50]);
- Expression of IL-15 and IL-15Rα seems to overlap [46];
- Both IL-15 and IL-15Rα have to be expressed by the same cells in order to activate IL-15-responsive cells [22,51];
- IL-15Rα or its fragment complexed to IL-15 prolongs its half-life, increases its binding to and biological effects through IL-2/15Rβγc membrane receptors [45,52,53];

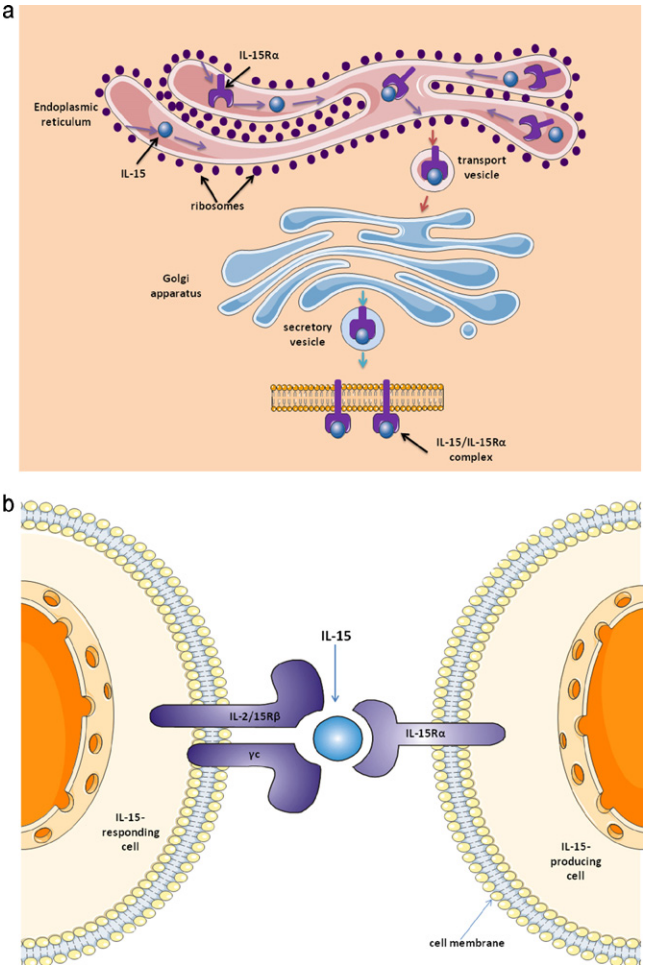

Fig. 1. Trans-presentation of IL-15 to IL-15-responding cell. A. Synthesis of IL-15 and IL-15Rα in trans-presenting cell. IL-15Rα combines with IL-15 in endoplasmic reticulum and transports IL-15 through Golgi network to the cell membrane [45]. B. IL15-Rα can now trans-present IL-15 to responding cells displaying IL-2/15Rβγc receptor. Although some signaling properties have been assigned to IL-15Rα [70] and it may be present in the IL-15 receptor, the affinity of IL-2/15Rβγc is not further increased by the presence of IL-15Rα [43,48] and it is dispensable for cell response to IL-15 [43].

- IL-15 alone does not form a stable complex with IL-2/15Rβγc [54]; and
- Expression of IL-15Rα cytoplasmic domain in IL-15 responding cells seems to be dispensable for IL-15 action on these cells [43].

Thus, IL-15 seems to function under normal circumstances as a cell-bound cytokine and is trans-presented to responding cells together with co-stimulatory signals ([46] and reviewed in [55]), although the dominance of trans-presentation of IL-15 to $CD8^+$ T cells has recently been called into question [56]. It can be hypothesized that following administration of soluble IL-15 it mostly undergoes association with IL-15Rα before being presented efficiently to cells responding to this cytokine [2]. Another interesting phenomenon concerning IL-15/IL-15Rα complexes is their recycling between cell membrane and endosomes [46]. Internalized IL-15/IL-15Rα complexes, owing to high-affinity IL-15/IL-15Rα binding, do not undergo separation and eventual degradation during their sojourn in endosomes but reappear in the cell membrane, resulting in prolonged presentation of IL-15 to neighboring IL-2/15Rβγc-expressing cells. Soluble complexes of IL-15 bound to fragments of IL-15Rα containing sushi domain could appear in mouse serum following alternative splicing of IL-15Rα primary transcript [57]. These isoforms display potentiated