IL15 and T-cell Stemness in T-cell-Based Cancer Immunotherapy

Karolina Pilipow1, Alessandra Roberto2, Mario Roederer3, Thomas A. Waldmann4, Domenico Mavilio2,5, and Enrico Lugli1

Abstract

Preclinical models revealed that the immune system can mediate rejection of established tumors, but direct evidence in humans has been limited to largely immunogenic tumors, such as melanoma. The recent success of immune checkpoint inhibitors and adoptive T-cell transfer immunotherapy in clinical trials has instilled new hope for the use of T-cell immunotherapy in the treatment of cancer. IL15, a potent immunostimulatory cytokine, both potentiates host T-cells and natural killer (NK) cell immune responses and promotes the generation of long-lived memory T cells with superior functional capacity, with potential use in adoptive T-cell transfer protocols. IL15 has been recently tested in the clinic and showed dramatic effects at the level of responding NK and CD8+ memory T cells. The recent advances in the knowledge of IL15-dependent regulation of T-cell responses, gene expression, and metabolic adaptation have important implications for the use of IL15 in T-cell–based immunotherapy of cancer. Cancer Res; 75(24); 5187–93. ©2015 AACR.

Introduction

The immune system can prevent cancer formation and dissemination. Immune effector cells potentially infiltrate the tumor but, when the disease is established, their activity is inhibited by the presence of suppressor cells and metabolites in the tumor microenvironment, thus favoring evasion of the antitumor immune response. New therapeutic solutions, mainly based on immune checkpoint inhibitors anti–CTLA-4 and anti–PD-1/PD-1-I monocolonal antibodies, have proven efficacious in stimulating T-cell immune responses to reject established tumors and resulted in extended survival in a subset of patients with cancer (1). Recent preclinical data indicate that these strategies when combined with additional immunotherapies or anti–PD-L1 antibodies, cancer vaccines or adoptive cell transfer (ACT) of T cells redirected with tumor-specific T-cell receptors (TCR) or chimeric antigen receptors (CAR) may result in improved efficacy. IL15, a potent immunostimulatory cytokine, both potentiates host T and natural killer (NK) cell immune responses and promotes the generation of memory T cells with superior functional capacity with potential use in ACT protocols (2). IL15 recently entered clinical trials in patients with metastatic melanoma and renal cell carcinoma and showed a dramatic capacity to expand effector T and NK cells (3). We discuss the potential applications of IL15 in T-cell–based cancer immunotherapy and the current strategies that are being adopted to reduce toxicity while improving efficacy in vivo.

Basic Biology of IL15

IL15 is a 4-$\alpha$-helix bundle cytokine playing a pivotal role in stimulation of both innate and adaptive immune cells. IL15 induces the activation, the proliferation, and the survival of T cells and contributes to generation and maintenance of high avidity, antigen-specific CD8+ memory T cells in the long term. In addition, IL15 is involved in the development, the persistence, and the activation of NK and NKT as well as γ/δ T cells (2).

The IL15 receptor (IL15R) is composed of three different molecules, better known as the α (CD215; unique to the IL15R), the β (CD122), and the γ (CD132) chains. In particular, CD122 is also a component of the IL2R, whereas CD132, also known as the common γ chain (γc), is shared with different cytokines, including IL2, IL4, IL7, IL9, and IL21 (2). While the IL15Rβγ complex is present on target cells, IL15Rα can be expressed as a membrane-bound complex with IL15 on the surface of many cell types, including activated monocytes, dendritic cells (DC), and endothelial cells. Such a heterodimer is presented in trans to neighboring α/β, γ/δ T or NK cells (2, 4). Alternatively, it can be shed and released as a soluble factor. Recent evidence indicates that virtually all circulating IL15 in human and mouse serum is complexed with IL15Rα (5). Triggering of the receptor activates downstream signaling pathways that include JAK1 and JAK3 as well as STAT3 and STAT5, followed by the recruitment of the PI3K/AKT/mTOR and RAS/RAF/MAPK–ERK cascades. By inducing FOS/JUN, MYC, NF-$\kappa$B, and BCL2 genes expression and by decreasing the expression of BIM and PUMA, IL15 has a stimulating effect on T-cell proliferation and survival (2).
Because sharing the β and γ components of the receptor, IL2 and IL15 exert similar functions on T cells. Indeed, both stimulate the proliferation of T cells, facilitate the differentiation of cytotoxic T lymphocytes (CTL), and induce the generation and maintenance of NK cells. Nevertheless, mice deficient in IL2 or IL15 have different phenotypes, and administration of IL2 and IL15 to mice, primates, or humans leads to distinct effects on cells of the immune system (2, 3, 6–8). As regards to antigen-activated effector cells, while IL2 promotes terminal differentiation and, eventually, their elimination by activation-induced cell death (AICD), IL15 inhibits AICD and promotes the generation of long-lived memory T cells as well as their maintenance by homeostatic proliferation (Fig. 1A). Notably, IL2, but not IL15, is involved in the prevention of autoimmunity due to the maintenance of CD4+CD25+Foxp3+ regulatory T (Treg) cells that also inhibit antitumor immunity. This observation raised concerns on the therapeutic use of IL2 as an immunotherapeutic agent as promotion of effector T cell functions could be hampered by Treg expansion (9, 10).

IL15 and Tumor-Specific T Cells in ACT

Understanding the biologic basis of IL2 and IL15 signaling on T-cell subsets has tremendous implications for expansion of tumor-specific T cells to be used in ACT immunotherapy. Historically, tumor-infiltrating lymphocytes (TIL) have been isolated from tumor resections (mostly melanoma), expanded \textit{in vitro} with polyclonal stimuli and high doses of IL2, selected for antigen reactivity and reinfused into the patients (11). Despite the fact that this approach led to objective clinical responses in a number of trials, exhaustion and terminal differentiation of the infused cells contributed, at least in part, to the limited therapeutic efficacy (11). IL2 infusions in humans could ameliorate persistence and ability of adoptively transferred T cells only marginally, whereas preclinical studies demonstrated the superior \textit{in vivo} antitumor capacity of T cells either cultured in IL15 or expressing IL15 as a transgene (2, 12). A major breakthrough came from the observation that increased levels of IL15 and IL7 caused by chemotherapy-induced lymphodepletion prior to ACT effectively supports the function of transferred cells (13, 14).

Extensive research in the field of T-cell differentiation has revealed that the peripheral T-cell compartment is organized in subsets that are endowed with specialized effector capacities. The analysis of surface and intracellular markers by polychromatic flow cytometry allows the discrimination and purification of such subsets for further analysis (15, 16). Current models support the concept that memory T-cell differentiation progresses linearly in mice, nonhuman primates, and humans and that T cells gradually lose some abilities while maturing, including the capacity to self-renew, expand, and persist \textit{in vivo}. In parallel, they gain others, such as effector functions and tropism to peripheral tissues (11, 15). In the context of ACT, it is worth noting that early-differentiated memory T cells, despite not showing immediacy of killing capabilities directly \textit{ex vivo}, can differentiate to potent effectors \textit{in vivo} following encounter with the cognate antigen (17). These cells are thought to maintain T-cell memory in a stem cell-like fashion, that is, to self-renew while simultaneously generating more differentiated progeny (15, 18). Exploiting these properties in the context of ACT proved effective in ameliorating antitumor T-cell responses at the preclinical level and, indirectly, in humans. ACT of TCR- or CAR-transduced T cells resulted in increased persistence compared to TILs, possibly due to the presence of early-differentiated T-cell precursors in the infusion product (11, 19–21). By analyzing retroviral integration sites, Biasco and colleagues demonstrated that adoptively transferred CD8+ T memory stem cells (TSCM), the earliest differentiated circulating memory T-cell population possessing superior stem cell–like qualities identified thus far, preferentially survived \textit{in vivo} compared with more differentiated central memory (Tcm) or effector memory T (Tem) cells in patients treated with genetically modified lymphocytes (22).

The TSCM seem therefore the ideal subset to exploit to induce long-lasting antitumor T-cell responses. These cells are identified by the coexpression of multiple naïve-associated markers by flow cytometry, including CD45RA, CCR7, CD27, and IL7Rα (also known as CD127), among others, but simultaneously overexpress the memory antigens CD95, CD122, and CD58 and share properties with conventional memory cells. IL15-dependent signals seem pivotal to generate the murine TSCM (defined as CD44hiCD62LhiCD122hiSca-1hi) as originally shown in the context of experimentally induced graft-versus-host disease (23). In particular, in combination with appropriate stimulations, IL15 has been exploited to uncouple T-cell proliferation from differentiation, with the final aim to expand the tumor-specific T-cell pool while promoting and maintaining the stem cell–like state. Indeed, stimulation of human naïve T (T0) cell precursors with anti-CD3/CD28 antibody–conjugated beads in the presence of IL15 and IL7 induces T cells with stem cell–like properties (Fig. 1A; ref. 24). In \textit{vivo}, TSCM develop from Tcm cell precursors following transfer in lymphodepleted hosts harboring increased levels of plasma IL15 and IL7 (25, 26). Importantly, IL15 also mediates self-renewal of polyclonal and antigen-specific TSCM (17, 27). When redirected to recognize a specific antigen of mesothelioma through CAR transduction, these cells also displayed enhanced functional capacity in preclinical models of tumor xenografts (17). After adoptive transfer in immunodeficient NOD/SCID/γ chain−/− mice, TSCM cell properties of CAR-CD19-transduced human T cells were maintained by culturing with IL15 and IL7 as opposed to IL2 and correlated with improved survival and durability of the response \textit{in vivo} (28).

It is not entirely clear how IL2 and IL15 signaling through the same IL2R/IL15Rβ receptor complex leads to opposing differentiation programs in antigen-activated T cells. Recent results obtained on murine T cells suggest that metabolic reprogramming, downstream gene expression and, at a lesser extent, the dose of the cytokine may play a critical role in this regard. Differential gene expression could be observed when sub saturating doses of cytokines were used. However, these differences were nearly abrogated at very high doses. Interestingly, IL2 and IL15 bind their receptor complex in almost identical ways as revealed by X-ray crystal structures, thus leading the authors to conclude that differences in downstream signaling and mRNA transcripts could be explained by differential receptor affinities and cytokine interaction kinetics, mostly regulated at the level of the IL2Rα and IL15Rα chains transpresenting their related cytokines (29). Notably, CD8+ memory T cells generated from antigen-activated effectors in response to IL15 display a different metabolic response compared with effectors maintained in IL2 (Fig. 1A) (30). The former mostly rely on oxidative phosphorylation (OXPHOS, taking place in the mitochondria) to support their metabolic demand for long-term survival. Conversely, the latter...
preferentially use glycolysis to support effector functions such as rapid IFNγ production. Specifically, IL15 regulates oxidative metabolism in murine CD8+ memory T cells by promoting mitochondria biogenesis and expression of carnitine palmitoyltransferase 1A (CPT1A), a fatty acid transporter located in the mitochondria favoring fatty acid oxidation (FAO; ref. 30). Given that TSCM share multiple features with conventional human and murine memory T cells, it is likely, yet to be demonstrated formally, that TSCM preferentially engage OXPHOS over glycolysis for their metabolic demand. Should this hypothesis be confirmed,
we speculate that modulation of T-cell metabolism rather than differential cytokine stimulation could be exploited to regulate T-cell fate and thus generate more potent T cells to be used in ACT.

Preclinical and Clinical Evaluation of IL15 in the Therapy of Cancer

Although IL2 has been approved by the FDA, IL15 may be superior in the therapy of cancer, as it has no major effect on Tregs, does not promote AICD, and expands effector cells with an antitumor potential, mostly NK and CD8\(^+\) memory T cells. IL15 showed efficacy in a plethora of murine models of cancer as a single agent alone or in combination with monoclonal antibodies or ACT (2).

In analysis of IL15 in rhesus macaques when administered by bolus infusions, subcutaneously, or by continuous intravenous infusion (CIV), the only toxicity was redistribution of neutrophils from circulation to tissues. Twelve-day bolus intravenous administrations of 20 μg/kg/d of IL15 to rhesus macaques was associated with 4- to 8-fold increases in the numbers of circulating NK and CD8\(^+\) memory T cells (6). Administration of IL15 by CIV at 20 μg/kg/d for 10 days led to 10-fold increases in numbers of circulating NK cells, 15-fold increases in monocytes, and 80- to 100-fold increases in circulating TEM (31).

Several clinical trials have been opened using IL15 in cancer treatment (summarized in Table 1). In a phase I study of recombinant human IL15 administered by bolus infusions daily for 12 days, there was a constant temporal pattern of posttreatment adverse events in patients given 3 μg/kg doses of IL15, with fever and rigors beginning at 2 to 4 hours after infusion initiation (3). These changes were concurrent with the maximum of 50-fold elevations of serum concentrations of IL6 and IFN\(\gamma\). The maximum tolerated dose of IL15 was 0.3 μg/kg/d. Polychromatic flow cytometry of peripheral blood lymphocytes revealed margination or efflux of NK as well as of multiple subsets of memory T cells from circulating blood within minutes upon IL15 administration, which protracted for a few hours (3). Notably, NK and TEM\(_{EM}\) tended to disappear faster than less differentiated memory T cells, likely due to the higher expression of IL15R\(\alpha\) on their surface. Early lymphopenia was followed by influx and hyperproliferation, leading to 10-fold expansions of NK, γδ T cells, and CD8\(^+\) memory T cells that ultimately returned to baseline. Therefore, rapidity of efflux from the peripheral blood seemed to predict subsequent expansion. Previous studies in rhesus macaques showed that IL15 targeted CD4\(^+\) and CD8\(^+\) T cells systemically, with the vast majority of these cells displaying markers of proliferation and activation in both lymphoid and nonlymphoid tissues (6). In the first-in-human phase I trial involving individuals with metastatic melanoma and renal cell carcinoma, 5 patients manifested decreases between 10% and 30% of their marker lesions and two patients had clearing of lung lesions (3). Daily IL15 IV at the dose of 0.25 and 0.50 μg/kg replaced IL2 in a recent trial to favor the persistence and function of adoptively transferred TILs in patients with metastatic melanoma (Table 1). However, the trial was stopped because of autoimmune toxicity seen in one patient that, according to the promoters of the study, was probably related to the IL15 injection. These data underline the potential proinflammatory effect of IL15 on cells of the immune system. To avoid toxicities associated with high IL15 C\(_{max}\) levels following bolus infusions, IL15 was administered subcutaneously on days 1 to 5 and 8 to 12 or by continuous intravenous infusion for 10 days. A dose of 2 μg/kg/d was well tolerated (T.A. Waldmann, unpublished observation).

Although IL15 may show efficacy in treatment of metastatic malignancy it is not optimal, as there is only a low level of IL15R\(\alpha\) expression on resting DCs. In addition, the biochemical instability of the soluble molecule, that undergoes rapid renal clearance, may result in reduced therapeutic potential (3). The IL15 cytokine may be the IL15R\(\alpha\)/IL15 heterodimeric cytokine (32) that is naturally present in the serum of mice and in humans (5). IL15 within the heterodimer has increased half-life and greater biologic activity determined by the increased affinity for the IL15R\(\beta\) complex (29). The enhanced biologic antitumor activity of cross-linked IL15 protein has been tested in several metastatic preclinical models, such as B16OVA melanoma and MC38 colon cancer. Reduced metastatic foci were attributed to the increased numbers of NK and CD8\(^+\) T cells within spleen, lung, and liver (33). In preclinical trials, IL15 preassociated with IL15R\(\alpha\) or with IL15R\(\alpha\) IgG1-Fc had improved pharmacokinetics and increased efficacy in increasing circulating numbers of NK and CD8\(^+\) T cells (32). Clinical trials involving the IL15/IL15R\(\alpha\) IgG1-Fc heterodimer (ALT-803, from Altor Bioscience Corporation) have currently been initiated in the United States in patients with different types of cancer (Table 1).

Tumor delivery of IL15 instead of systemic administration would be optimal to decrease toxicity and increase efficacy. To this end, multiple approaches were conceived. In mouse models, the presence of IL15 in the tumor favored tumor rejection through T-cell infiltration in a non–antigen-specific manner (34) and rendered adoptively transferred NK cells resistant to suppression (35). More recently, an IL15 transgene resistant to the suppressive activity of tumor-associated macrophages was shown to be more effective than monotherapy (36). Importantly, patients bearing colorectal cancer metastasis with no deletion of the IL15 gene had better prognosis compared with those who had gene deletion: the presence of IL15 in the tissue was associated with increased T-cell proliferation at the tumor-invasive margin (37), thereby supporting a role for IL15-mediated T-cell immune responses in inhibition of cancer growth. However, it should be noted that injection in the tumor mass directly or incorporation of IL15 as a transgene in adoptively transferred cells is difficult to implement on a practical level: the presence of multiple metastatic sites or the excessive growth and potential leukemic transformation of the transduced cells, respectively, may in fact limit therapeutic relevance.

Future Directions: Combination Therapies

Despite the increased immune functional capacity observed following monotherapy, it is probable that in the future IL15 will be used in combination therapy (Fig. 1B). Recent use of immune checkpoint inhibitors anti–CTLA-4 and anti–PD-1/PD-L1 monoclonal antibodies confirmed that the immune system can reject established tumors. These two molecules target two nonoverlapping inhibitory pathways and proved more effective than monotherapy when tested in combination therapy in metastatic melanoma (1). Similarly, an approach combining the immunostimulatory cytokine granulocyte macrophage colony-stimulating factor (GM-CSF) with IL15 and IL24 would provide a strong basis to target the IL15R\(\beta\) complex. The combination of IL15 with the IL15R\(\beta\) complex provided promising results in studies of colorectal tumor xenografts. However, the limited half-life of IL15 may also benefit from the IL15R\(\alpha\)/IL15R\(\beta\) complexes, which have increased stability and have demonstrated antitumor activity (29, 32, 33). The addition of IL15 to the IL15R\(\alpha\)/IL15R\(\beta\) complex would provide a large number of IL15R\(\alpha\)/IL15R\(\beta\) complexes and permit the use of therapeutic doses of IL15R\(\alpha\) that are not currently achievable.
<table>
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<th>Clinical ID</th>
<th>Phase</th>
<th>Aim</th>
<th>Study period</th>
<th>Tumor type</th>
<th>Patients, n</th>
<th>Age of patients (min–max)</th>
<th>Treatment</th>
<th>IL15/ALT-803 (dose, µg/kg)</th>
<th>Principal investigator</th>
<th>Responsible party</th>
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<td>Safety/Efficacy</td>
<td>Terminated</td>
<td>Metastatic melanoma</td>
<td>3</td>
<td>18–66</td>
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<td>≥18</td>
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<td>Estimated 61</td>
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<td>2–25</td>
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<td>NA</td>
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| Abbreviations: ALL, acute lymphoblastic leukemia; ALT-803, IL15 super agonist complex; AML, acute myelogenous leukemia; BCG, Bacillus Calmette-Guérin; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndromes; NA, not available. |
factor (GM-CSF, also known as sargramostim) in combination with the anti–CTLA-4 antibody ipilimumab improved overall survival and was associated with reduced side effects compared with ipilimumab alone in a similar cohort of patients (38). To date, combination therapies with IL15 have been tested only in preclinical models. The simultaneous addition of antibodies to two checkpoints CTLA-4 and PD-L1 in association with IL15 yielded additivity/synergy in three murine tumor models (39).

Furthermore, coadministration of an agonistic anti-CD40 antibody with IL15 was valuable in avoiding “helpless” CD8+ T cells that were not tumor-specific. In particular, the administration of the combination of IL15 plus the agonistic anti-CD40 antibody was associated with a meaningful increase in the number of TRAMP-C2–specific SPAS-1/SNC9-HA tetramer CD8+ T cells, which depended on the increased expression of IL15Rα on dendritic cells, possibly promoting transpresentation of the high-affinity heterodimer. Combination therapy resulted in the protection from tumor development on rechallenge (40). Recently, a trifunctional antibody fusion protein composed of the IL15/IL15Rα, a tumor-specific recombinant antibody, and a ligand targeting the costimulatory molecule 4-1BB (also known as CD137) was shown to be effective in reducing metastasis in a melanoma (B16-FAP) tumor mouse model (41). This fusion protein was able to increase the proliferation and specifically activation of tumor-specific CD8+ memory T cells.

Concluding Remarks

The predominant approaches involving IL15 discussed above are based on the hypothesis that the host is making an immune response albeit inadequate to the tumor that can be augmented by administration of IL15. TILs are found in the tumor site, but their activity is inhibited by multiple types of suppressor cells present in the tumor microenvironment. IL15 seems to not inactivity is inhibited by multiple types of suppressor cells present in. It is also worth noting that suppressive cells in the tumor microenvironment along with additional components such as cancer-associated fibroblasts and the extracellular matrix physically inhibit the direct contact of T cells with the tumor itself, hence generating a site of immune privilege (43). In this context, IL15–induced expansion of local T cells as well as the infiltration of long-lived memory T cells may be of limited value. It could thus be hypothesized, yet to be demonstrated experimentally, that IL15 in combination with therapies capable of disrupting physical barriers may promote cancer regression. These along with other studies revealing the signaling pathways at the basis of IL15–mediated antitumor activity, T-cell self-renewal, and enhanced effector functions will make it possible to conceive more effective strategies of T-cell–based cancer immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors apologize to colleagues whose work could not be cited because of space limitation. They thank Dr. Luca Gattinoni (National Cancer Institute, NIH, Bethesda, MD) for critical reading of the manuscript.

Grant Support

This work was supported by grants from the Fondazione Cariplo (Grant Ricerca Biomedia 2012/0683 to E. Lugli), the Italian Ministry of Health (Bando Giovani Ricercatori GR-2011-02347324 to E. Lugli), the Associazione Italiana per la Ricerca sul Cancro (IG 14687 to D. Mavilio), the Intramural Research Program of the National Institutes of Allergy and Infectious Diseases (M. Roederer), and of the National Cancer Institute (T.A. Waldmann). E. Lugli is an International Society for the Advancement of Cytometry (ISAC) scholar and is a recipient of the European Union Marie Curie Career Integration Grant 322093. A. Roberto is a recipient of the Guglielmina Lucatello e Gino Mazzega Fellowship from the Fondazione Italiana per la Ricerca sul Cancro.

Received May 31, 2015; revised July 24, 2015; accepted July 27, 2015; published OnlineFirst December 1, 2015.

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Cancer Res 2015;75:5187-5193. Published OnlineFirst December 1, 2015.

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