Interleukins in the treatment of melanoma

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Abstract

Interleukins (ILs) and associated cytokines serve as the means of communication for immune cells and non-immune cells. The use of ILs in harnessing the immune system to cancer treatment has been a promising approach. ILs not only nurture an environment enabling cancer growth but also simultaneously trigger a productive tumor-directed immune response. These properties of ILs are increasingly being explored as a strategy to improve the outcomes of cancer. Here, we describe recently innovative technological approaches that have been developed to improve the pharmacokinetics, safety, and efficacies of IL-2, 15, 10, and 18 in the treatment of melanoma. Furthermore, the combination of ILs and immune checkpoint inhibition may synergize to reshape the tumor environment, thus yielding better clinical benefits in the future.

Keywords: IL-2; IL-15; IL-10; IL-18; Melanoma; Immunotherapy

Introduction

The management of melanoma has undergone vast changes over the past two decades. From a disease with limited therapeutic options beyond surgical resection, treatment options for melanoma now encompass a multitude of approaches including molecularly targeted therapy, such as inhibition of the BRAF/MEK signaling pathway using either BRAF inhibitors or MEK inhibitors, chemotherapy, and immunotherapy.[1] Progress in tumor biology during the past years has demonstrated the essential interplay between the immune system and host cells. These insights laid the foundation for the concept of immunosurveillance: the ability of the immune system to recognize and eliminate abnormal cells.[2] In contrast, immunoediting describes the reciprocal interaction and shaping of the immune system and cancer cells, eventually culminating in cancer development. The resistance to immune attack and the presence of pro-tumoral inflammation are hallmarks of cancer.[3] Melanoma is often considered one of the most immunogenic human cancers because of the significant infiltration of lymphocytes and myeloid cells and a high tumor mutation burden.

In the tumor microenvironment (TME), cytokines mediate interactions between immune and non-immune cells, which regulate innate and adaptive immunity.[4] Interleukins (ILs) are a number of secreted molecules that first thought to be expressed by leukocytes alone but have later been found to be produced by various other cells, which modulate growth, differentiation, and activation upon immune responses. Among them, some ILs are particularly relevant in cancer development, progression, and control. The multitude of cellular sources, receptors, signaling pathways, and even concentrations define the pleiotropic role of ILs in biology, and thus promotes tumor progression or shrinkage in a cell-type-specific manner.[5] Recently, the therapeutic potential of ILs has been of great importance in both basic and translational cancer research.[6] Many clinical trials currently underway highlight its therapeutic value as a single agent or in combination with synthetic biology, gene, and cellular therapies. In this review, we will discuss the basic IL-related mechanisms in tumorigenesis and their therapeutic application in the treatment of melanoma. We also provide a current overview of newly approved therapeutic variants that have been engineered to improve the pharmacokinetics, safety, and efficacy of IL-2, 15, 10, and 18 (Table 1).

IL-2

IL-2 is a growth factor that promotes the activation and expansion of CD8+ T cells and natural killer (NK) cells. It can promote naive CD4+ T cell differentiation into T helper-1 (Th1) and T helper-2 (Th2) cells but inhibit T helper-17 (Th17) and T follicular helper cells differentiation.[7,8] There are three subunits of IL-2 receptor including IL-2Rα (encoded by *IL2RA*; also known as CD25),[9] IL-2Rβ

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Table 1: Clinical trials in melanoma patients with IL-2, 15, 10, and 18.

Category	Drug	Study population (*n*/*m*)	Outcomes	NCT number (Study phase)	References
IL-2	NKTR-214	7/28	Two PR and four SD in melanoma patients	NCT02869295 (Phase 1)	[17]
IL-2	NKTR-214 plus nivolumab	11/38	Four CR, three PR, and three SD in melanoma patients	NCT03635983 (Phase 3)	[17]
IL-2	NKTR-214 plus nivolumab	41/41	Seven CR, 13 PR, and three SD	NCT02983045 (Phase 1)	[18]
IL-2	NKTR-214 plus nivolumab *vs.* nivolumab	Estimated enrollment 764	Recruiting	NCT03635983 (Phase 3)	[19]
IL-15	rhIL-15	3/19	No objective responses	NCT01727076 (Phase 1)	[35]
IL-15	ALT-803	9/24	No objective responses	NCT01727076 (Phase 1)	[39]
IL-15	ALT-803 plus anti-PD-1 inhibitors	Estimated enrollment 145	Ongoing	NCT03228667 (Phase 2)	–
IL-15	NIZ985	Unknown/13	SD in one spindle cell ocular melanoma patients	NCT04261439 (Phase 1)	[36]
IL-15	NIZ985 plus spartalizumab	8/56	Three SD and one PR in CM, one SD in UM	NCT04261439 (Phase 1)	[36]
IL-10	Pegilodecakin	4/51	One PR in melanoma patients	NCT02009449 (Phase 1)	[44]
IL-10	Pegilodecakin plus anti-PD-1 inhibitors	37/111	Three SD in melanoma patients	NCT02009449 (Phase 1)	[46]
IL-18	Recombinant human IL-18	64/64	One PR, four SD	NCT00107718 (Phase 2)	[49]

CR: Complete response; CM: Cutaneous melanoma; IL: Interleukin; NK: Natural killer; *m* means number of cancer patients totally enrolled in the trial; *n* means number of melanoma patients in the trial; PR: Partial response; rhIL-15: Recombinant human IL-15; SD: Stable disease; UM: Uveal melanoma.

(encoded by *IL2RB*; also known as CD122),[10] and IL-2Rγ (encoded by *IL2RG*; also known as CD132).[11] IL-2 binds with low affinity to IL-2Rα, with intermediate affinity to IL-2Rβ and IL-2Rγ, or with high affinity to trimeric complex forms containing IL-2Rα, IL-2Rβ, and IL-2Rγ.[12] IL-2Rα initially binds IL-2, inducing a conformational change in IL-2, which then subsequently recruits IL-2Rβ and IL-2Rγ. The αβγ trimeric complex forms the high-affinity receptor, with signaling mediated by heterodimerization of the IL-2Rβ and IL-2Rγ cytoplasmic domains.[13,14] IL-2Rα is expressed by various immune cells including T regulatory cells (Treg), activated CD4+ and CD8+ T cells, B cells, mature dendric cells, endothelial cells, and NK cells. Memory CD8+ T cells express high levels of IL-2Rβ and IL-2Rγ and some NK cells can also express IL-2Rα after the stimulation by IL-2.[15] Group 2 innate lymphoid cells can also express IL-2Rα.[14] Of note, Tregs are very sensitive to IL-2 because these cells constitutively express high-affinity IL-2 receptors.

Based on the evidence from pre-clinical studies, IL-2 received U.S. Food and Drug Administration approval to treat melanoma in 1998 with a ~15% objective response rate (ORR).[6] Although high-dose IL-2 therapy induced durable complete responses (CRs) in some patients with melanoma and renal cell carcinoma (RCC), it also induced significant toxicity in multiple organs and tissues, limiting its clinical utility.[14] Therefore, low-dose IL-2 schedules were evaluated in clinical trials. However, low-dose IL-2 binds preferentially to its high-affinity receptor expressed on Treg cells, leading to immune evasion. Therefore, non-α IL-2 variants with increased affinity for the IL-2 receptor beta gamma (IL-2Rβγ) complex are in development.

A novel IL-2 variant that conjugated IL-2 with six releasable polyethylene glycol (PEG) chains, namely bempegaldesleukin (NKTR-214), was engineered.[16] In addition to an extended half-time, the PEG residues coupled to IL-2 block its binding site for the high-affinity IL-2Rα subunit. NKTR-214, therefore, promotes signaling predominately through the IL-2Rβγ, which preferentially increases the proliferation of CD8+ T cells and NK cells within the TME without expanding Tregs. In a mouse melanoma tumor model, it showed efficacy not only as a single agent but also provided durable immunity that was resistant to tumor progression in combination with anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody. NKTR-214 was further evaluated as a monotherapy in a phase I clinical trial in 28 patients with metastatic solid tumors including seven melanoma patients (NCT02869295). For melanoma patients, clinical responses included two partial response (PR) and four stable disease (SD) patients.[17] Nevertheless, NKTR-214 showed a good safety profile, encouraging its combination with immune-checkpoint inhibitors (ICIs).[16] Based on the non-overlapping toxicities with ICIs and well tolerability of NKTR-214, NKTR-214 in combination with nivolumab in 41 unresectable or metastatic melanoma patients was being evaluated in a phase I clinical trial

(NCT02983045). Preliminary results from the above study showed an ORR of 52.6% and a CR rate of 34.2% with an acceptable toxicity profile.[18] The combination had promising antitumor activity in metastatic melanoma, including an extended median progression-free survival. Increased polyfunctional responses in CD8+ and CD4+ T cells associated with better clinical response were observed.[18] A phase III clinical trial to test the effectiveness of NKTR-214 combined with nivolumab *vs.* nivolumab alone in participants with previously untreated melanoma or metastatic melanoma is currently ongoing (NCT03635983).[19] These findings suggest that NKTR-214 plus nivolumab treatment induced meaningful immunologic changes in the tumor tissue, and therefore explorations in larger population are warranted to determine whether these changes are predictive for ultimate clinical response.

ALKS 4230 is an engineered IL-2 variant comprised of a circularly permuted structure with the extracellular domain of IL-2Rα, which selectively activates effector lymphocytes bearing the intermediate-affinity receptors. ALKS 4230 induced greater activation and expansion of NK cells and lower expansion of Tregs compared with recombinant human IL-2 *in vitro* and *in vivo*.[20] Therefore, ALKS 4230 monotherapy in patients with advanced cutaneous melanoma (CM) or mucosal melanoma who have previously received anti-PD-1/PD-L1 is being tested in a phase II clinical trial (NCT04830124). Modified IL-2 formulations are also being developed in clinics. A monoclonal antibody (mAb) to human IL-2 named NARA1 was developed to act as a high-affinity CD25 mimic, thereby minimizing the association of its IL-2Rα.[21] IL-2/NARA1 complex immunotherapy resulted in efficient expansion of tumor-specific and polyclonal CD8+ T cells with robust IFNγ production and low expression levels of PD-1, lymphocyte activation gene-3, and T cell immunoglobulin and mucin domain-3. These data suggested that the IL-2/NARA1 complex may induce antitumor immune responses and thus prolonged survival in melanoma models. Based on the structure of the IL-2/NARA1 complex, a more stable molecule termed NARA1leukin was engineered. NARA1leukin is a fusion construct that consists of IL-2 engineered into the anti-IL-2 mAb NARA1. This mAb thereby permanently masks the CD25-binding site of human IL-2 and thus abolishes the CD25-mediated development of Treg cells. In comparison to IL-2/NARA1 complexes, NARA1leukin showed a longer half-life *in vivo* and more expansion of CD8+ T and NK cells, yet no association with IL-2Rα. These effects led to stronger antitumor responses in B16-F10 murine models, whereby NARA1leukin exceeded the efficacy of IL-2/NARA1 complexes in melanoma metastasis.[22] Collectively, these data demonstrate that engineered IL-2 variants, such as NARA1 or NARA1leukin, may reduce the toxicity and increase the efficacy of treatment in melanoma.

Computational approaches can design proteins that recapitulate the binding sites of ILs, which are unrelated in topology or amino acid sequence. Silva *et al*[23] used this strategy to design mimics of the central immune cytokine termed neoleukin-2/15 (Neo-2/15). Neo-2/15 is a hyperstable IL mimic that binds to the IL-2Rβγ but to neither IL-2Rα nor IL-15Rα, and mediates IL-2 and IL-15 signaling independently of IL-2Rα or IL-15Rα. Neo-2/15 has superior therapeutic activity to IL-2 in a mouse model of melanoma, with reduced toxicity and undetectable immunogenicity.[22] To our knowledge, Neo-2/15 was the first *de-novo* protein with immunotherapeutic potential designed by computational approach. *De-novo* protein design is being developed to treat diseases and its application in protein-based therapeutics is warranted in future clinical trials.

In addition, novel molecules in combination of other therapies have been generated according to the IL-2 system. A chimeric antigen receptor (CAR)-T cell-based method was used in which the cytoplasmic domain of the T cell receptor was engineered to contain a region from IL-2Rβ and a STAT3 binding motif, enhancing persistence and antitumor effects.[24] Treatment of melanoma patients with IL-2 to support adoptive cell therapy (ACT) has been studied with variable success in clinical trials. A phase II clinical trial of patients with metastatic melanoma with autologous tumor-infiltrating lymphocytes and low-dose IL-2 showed PRs in two of 12 patients (NCT01883323). These data indicate the potentiality of IL-2 in combination with tumor-infiltrating lymphocytes therapy in melanoma.[25] While some benefits were observed, this strategy still faced toxicity problems. An approach to reduce the toxic effect of systemic IL-2 treatment while retaining its ability to support ACT therapy was to build an orthogonal IL-2-IL-2R pair, where only the ACT product reacted to the orthogonal IL-2 treatment with systemic toxicity avoided. Orthogonal IL-2 already showed efficacy in a mouse melanoma model with the enhanced expansion of the orthogonal IL-2Rβ ACT product and limited toxic effects.[26] Also, IL-2 signaling can be inhibited by JAK1 and JAK3 inhibitors, which was not specific for IL-2 but nevertheless was effective.[27] ACT showed remarkable success in hematological malignancies but lacked efficiency in solid tumors due to poor infiltration and proliferation of the ACT product as well as a highly immunosuppressive TME. ILs may support ACT by overcoming those difficulties, and the number of clinical trials in melanoma patients may highlight the potential advantages for immunotherapy.

IL-15

IL-15 is an immune stimulatory cytokine with structural similarity to IL-2.[28] IL-15 is mainly produced by activated mononuclear phagocytes following infection by virus. Both IL-15 and IL-2 cytokines promote the activation and proliferation of cytotoxic lymphocytes and memory phenotype CD8+ T cells and help maintenance of NK cells.[29] Unlike IL-2, IL-15 lacks the capacity to consistently activate Tregs and to cause less capillary leak syndrome.[30] Studies in mice showed that IL-15 had a better safety profile than IL-2, with robust efficacy including induction of antitumor immunity.[31] Previous studies have highlighted the important role of IL-15 in NKT cell development and homeostatic maintenance.[32] Further study showed that co-expressing IL-15 with an optimized GD2-specific CARs enhanced the survival and

antitumor effector functions of NK cells in metastatic neuroblastoma models.[33] CAR-T cells can develop long-term persistence with abundance of T memory stem cells sustained by membrane-bound chimeric IL-15 signaling.[34]

The safety and efficacy of recombinant human IL-15 (rhIL-15) as a single agent was evaluated in a phase I clinical trial in patients with 11 metastatic melanoma patients and seven metastatic RCC patients (NCT01021059). So far, this first in-human phase I trial determined the safety and toxicity profile of rhIL-15, yet no response has been reported. SD was the best response, with one melanoma patient experiencing clearing of lung lesions. Nineteen refractory solid tumor patients including three melanoma patients were treated with subcutaneous rhIL-15 in outpatient phase I clinical trial (NCT01727076), in which the toxicity was well tolerated.[35] Despite the absence of objective response in this cohort, rhIL-15 showed clinical activities including disease stabilization. This study established a safe outpatient subcutaneous rhIL-15 to self-injection and its potential as a combination immunotherapy.

Since the published data on the monotherapy with IL-15 or engineered IL-15 variants in melanoma patients were seemingly ineffective, clinical trials may open to evaluate the safety and efficacy of combination therapies with IL-15 or its variants. NIZ985 is a soluble IL-15/IL-15 receptor α heterodimer that promotes expansion and activation of effector T cells and NK cells. A phase I study (NCT04261439) of NIZ985 with or without spartalizumab (anti-PD-1 antibody) in patients with metastatic solid tumors showed a well-tolerant safety. SD was observed in one patient with spindle cell ocular melanoma when NIZ985 was administrated as a single agent. Objective responses for NIZ985 plus spartalizumab (three SD and one PR in CM and one SD in uveal melanoma [UM]) occurred in eight melanoma patients.[36] This trial is still ongoing, and therefore more evidence is needed to address the potentiality of combination therapy with IL-15 in melanoma, even the rare type. BJ-001 is the first tumor-targeting IL-15 fusion protein, composed of an integrin-binding motif and a modified sushi domain. BJ-001 has shown an ability to activate NK cells and T cells in preclinical studies. The safety and tolerability of BJ-001 administered as a single agent or in combination with anti-PD-1/PD-L1 antibodies in adult patients with solid tumors including melanoma patients are currently under investigation (NCT04294576). According to the most recent data, the dosage of BJ-001 was well tolerated up to 6 μg/kg and the evaluation for 10 μg/kg is under investigation. A trend of increased NK cell counts was observed, whereas Treg counts remained stable as expected in this trial.

Of note, ALT-803 is an IL-15/IL-15Rα complex fused to an IgG1 Fc, in which an IL-15 mutant (asn72asp) was engineered to increase agonism of the IL-2 and IL-15βγ receptor. When administered to mice, ALT-803 could induce NK and CD8+ T cell proliferation and activation, and thereby promote potent antitumor responses. Combined ALT-803 and sunitinib inhibited tumor growth, and these effects were greater than sunitinib alone in melanoma mouse models.[37] Recently, ALT-803 has been proved to increase proliferation of hematopoietic progenitor cell derived-NK cells and production of IFNγ *in vitro* and *in vivo*.[38] To evaluate the safety and effective dose of ALT-803 as a monotherapy in patients with advanced solid tumors ($n = 24$) including nine melanoma patients, the clinical trial (NCT01946789) was investigated.[39] Intravenous and subcutaneous administration of ALT-803 was well tolerated and induced NK and CD8+ T cell proliferation and activation, which provided the rationale for combining ALT-803 with other agents.[39] To improve therapeutic efficacy, Tang *et al*[40] designed cell surface-conjugated nanogel proteins carrying an IL-15 superagonist complex, the delivery of which selectively expanded intratumor T cells and substantially increased tumor clearance by CAR-T cell therapy in B16-F10 murine models, which was a good example illustrating that ILs serve as a complement to ACT. Immunologic effects of ALT-803 in the application are complementary to other immunomodulators, including immune checkpoint blockade, vaccine strategies, and adoptive NK cell therapies for the treatment of cancer. For instance, Wrangle *et al*[41] reported data from a phase Ib clinical trial (NCT02523469) demonstrating that the combination of ALT-803 with nivolumab was safely administrated in an outpatient setting, with an ORR of 29% in refractory NSCLC patients. The median progression-free survival and overall survival was 9.4 months and 17.4 months, respectively. Of great importance, the ability of ALT-803 to reinduce responses in patients experiencing treatment failure with anti-PD-1 antibodies could have implications in more cancerous diseases. Based on these data, ALT-803 is being evaluated in an ongoing phase II trial combined with an anti-PD-1/PD-L1 checkpoint inhibitor in patients with solid tumor malignancies including melanoma (NCT03228667). The relatively large sample size in this trial may provide useful suggestions for melanoma treatment.

IL-10

IL-10 is an anti-inflammatory and CTL-stimulating cytokine predominantly produced by activated T cells and antigen-presenting cells.[42] So far, human recombinant IL-10 has been studied in inflammatory diseases, such as psoriasis and liver fibrosis.[42] The principal routine function of IL-10 appears to terminate inflammatory responses, while high-dose IL-10 activates the cytotoxicity and proliferation of CD8+ T cells, supporting the potential of an antitumor activity.[43] IL-10 was shown to stimulate the expansion and activation of tumor-infiltrating CD8+ T cells and to control tumor growth in mouse models.[44] Mechanically, pegilodecakin systemically induced Th1/Th2 immune activation and a reduction of Th17 inflammation, leading to the expansion of previously rare immune checkpoint-positive CD8+ T cells to become a sizable fraction of the T cell repertoire. This mechanism of action provides an opportunity for combinations of pegilodecakin with other immune therapies or chemotherapy.[45]

A pegylated formulation of recombinant IL-10 (AM0010, namely pegilodecakin) was developed to improve cytokine

half-lives and to allow sustained exposure.[44] Administration of pegilodecakin enhanced cytotoxicity and expansion of tumor-specific CD8+ T cells and resulted in tumor shrinkage in animal studies.[46] In a phase I clinical trial (NCT02009449), pegilodecakin monotherapy showed evidence of antitumor activity with an acceptable toxicity profile, particularly in RCC. In details, PRs were observed in four of 15 evaluable patients with RCC and one of four patients with UM.[44] Further analysis showed that pegilodecakin in combination with anti-PD-1 inhibitors in patients of RCC and NSCLC achieved objective responses of 40% (14/35) and 43% (12/18), respectively. For 31 melanoma patients in this cohort, ORR was only about 10%, lower than those in RCC and NSCLC.[47] In the same trial, pegilodecakin is being evaluated in combination with ICIs or chemotherapy in advanced solid tumors including melanoma.

IL-18

IL-18 is a member of the IL-1 cytokine family and triggers inflammation through its receptor highly expressed on NK cells. IL-18 stimulates innate lymphocytes and antigen-experienced T cells.[48] Its activity is moderated by IL-18-binding protein (IL-18BP), a receptor that acts as a decoy for IL-18. Although recombinant human IL-18 has a safety profile, little efficacy was observed as a single agent for metastatic melanoma patients in clinical trials.[49] This might be due to IL-18BP, which binds with high affinity to mature IL-18, preventing its interaction with IL-18R1. Therefore, recombinant IL-18 has been reported to synergize with ICIs and CAR-T cells in mouse models. In a mouse model of melanoma, a combination of the ICIs and IL-18 provided a much greater therapeutic benefit than ICIs alone. Mechanistically, IL-18 enhanced effects of immune checkpoint blockade through accumulation of precursor of mature NK and memory-type CD8+ T cells, and suppression of Tregs.[50] In an immune-competent B16-F10 murine model, Hu *et al*[46] reported IL-18-secreting CAR T cells to significantly boost CAR-T cell proliferation and antitumor activity. Recently, Zhou *et al*[51] engineered a "decoy-resistant" IL-18 (DR-18), which maintained IL-18 signaling potential by promoting the development of effector T cells, decreasing the prevalence of exhausted T cells, and enhancing the maturation of NK cells. DR-18 can also enhance NK cell activity and treat anti-PD-1 resistant tumors that have lost the expression of MHC class I. These results highlighted the potential of the IL-18 pathway for immunotherapeutic intervention and suggested a decoy-resistance cytokine variant as an effective way to enhance IL-18-based cancer immunotherapy. The efficacy and safety of DR-18 therapy need more evidence from clinical trials to confirm the conclusions that have been made on the basis of mouse genetics and pharmacologic studies with recombinant IL-18. Furthermore, ST-067 is an engineered variant of IL-18 developed by Simcha Therapeutics for cancer. The safety and efficacy of ST-067 as monotherapy in patients with relapsed or refractory solid tumors including melanoma are being evaluated in a phase Ia/II clinical trials (NCT04787042). Clinical activity of ST-067 administered subcutaneously as monotherapy in 28 melanoma patients may provide guidance on the means to better utilize IL-18 for patients with melanoma in the future.

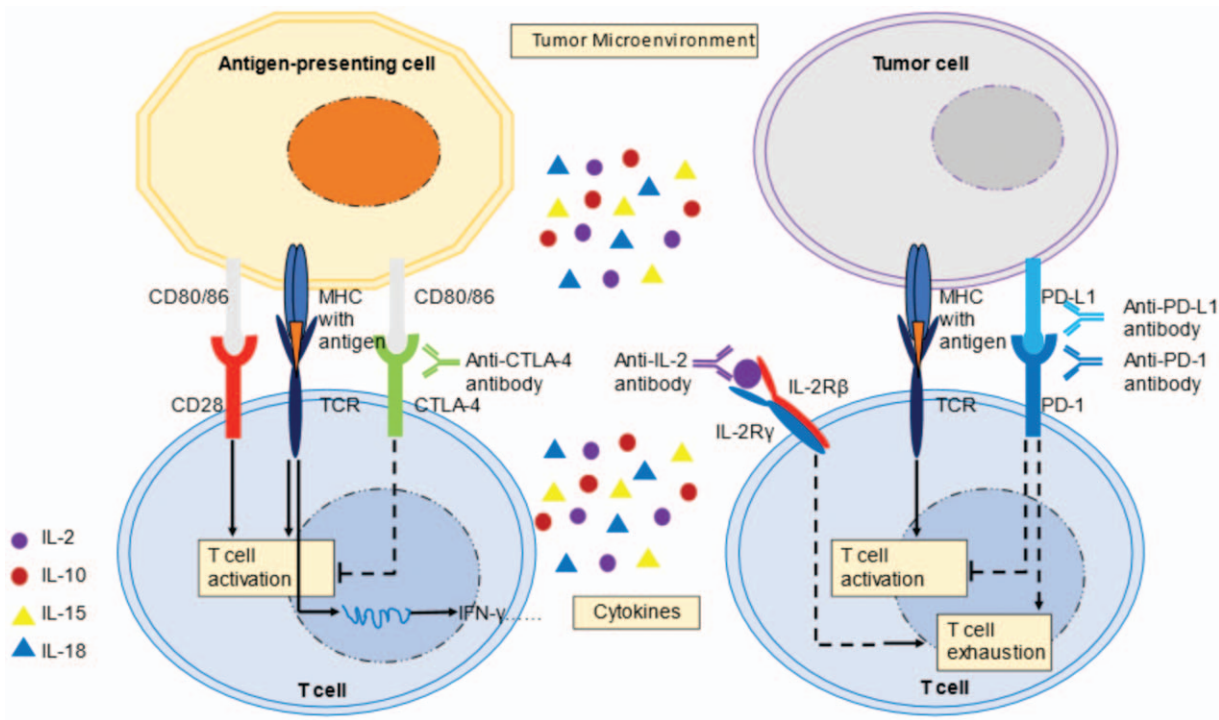

Figure 1: Interleukin-based immune control in melanoma. CTLA-4: Anticytotoxic T-lymphocyte-associated protein-4; IFN: Interferon; IL: Interleukin; MHC: Major histocompatibility complex; PD-L1: Programmed death-ligand 1; TCR: T-cell receptor.

Summary

IL-based therapy can elicit potential antitumor responses in melanoma. So far, as multiple side effects occurred, newly therapeutic strategies in the field of IL therapy for cancer treatment did not live up to the expectations concerning effectiveness.[5] In general, IL monotherapy still faces efficacy limitations; thus, the trend is moving from applying native forms of ILs to sophisticated engineered variants. To increase the efficacy and reduce toxicity, an increasing number of strategies, which involved altering the receptor affinity for the selected cell populations or designing tumor-targeting fusion constructs, were performed. In addition, combination with ICIs or other immunotherapeutic approaches are gaining great importance to improve better outcomes. Mechanical investigations into how ILs influence cancer progression and immune evasion will help to identify how ILs are involved in the resistance against established therapies.

In conclusion, ILs comprise key elements that orchestrate the TME and govern tumor-immune cell crosstalk as they are key players in larger cytokine networks [Figure 1]. Although ILs or IL-targeted therapy has difficulties to overcome on its avenue to the clinic, the foundational research being conducted on ILs in melanoma biology will help us to better understand the mechanisms of these newly engineered ILs together with combination agents, which may yield better clinical outcomes in the future.

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Conflicts of interest

None.

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