IL-7 and IL-7R in Cancer

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Interleukin-7 (IL-7) is a multipotent cytokine that maintains the homeostasis of the immune system. IL-7 plays a vital role in T-cell development, proliferation, and differentiation, as well as in B cell maturation through the activation of the IL-7 receptor (IL-7R). IL-7 is closely associated with tumor development and has been used in cancer clinical research and therapy.

IL-7 IL-7R signal cancer immunotherapy

1. Introduction

Interleukin 7 (IL-7) is a cytokine necessary for the adaptive immune system, which is critical for B cell development [1][2][3] as well as proliferation and survival of memory and naive T cells, and T cell development in the thymus [4]. IL-7 performs its biological functions mainly through the activation of the IL-7 receptor (IL-7R) [5]. IL-7R is a heterodimer that is composed of the IL-7R α chain (CD127) and the common γ chain (CD132, IL-2Rγ) shared by multiple cytokines such as IL-2, IL-7, IL-4, IL-9, IL-15, and IL-21 [1]. IL-7 and IL-7Rα promote cell survival and inhibit cell apoptosis mainly by the activation of Janus kinase (JAK), signal transduction factor and transcription activator 5 (STAT5), and the phosphatidylinositol 3-kinase (PI3K)—protein kinase B (AKT)-mediated signal pathway [6][7][8]. IL-7 has strong immunomodulatory effects, which can directly or indirectly act on tumor cells and exert anti-tumor effects by enhancing tumor eradication or adoptive immunity [9]. Conversely, IL-7 also has potential pro-tumor effects via the activation of downstream JAK/STAT5 and PI3K–AKT pathways [10][11][12]. IL-7 is closely associated with tumor development and has been used in clinical research and treatment [5][13].

2. Biology and Functions of IL-7 and IL-7R

2.1. Biology and Functions of IL-7

IL-7 is widely expressed in many tissues, including lymphoid organs such as the bone marrow, thymus, lymph nodes, and spleen, as well as in non-lymphoid sites such as the skin, lung, intestine, and liver [14][15]. However, IL-7 is predominantly secreted by the bone marrow, thymus, and lymph nodes to maintain the body's immune self-stability [5]. The human IL-7 gene, located on chromosome 8, has 534 bp, contains 6 exons and 5 introns, and encodes a protein of 177 amino acids with a molecular weight of approximately 20 kDa. The active form of IL-7 encodes a 25 kDa, single-chain glycoprotein that is predicted to form a structure containing four α-helices with a hydrophobic core [2].

IL-7 can promote early B cell proliferation in mice, in vitro, and can also promote the growth of precursor B cells [16][17]. IL-7 knockout mice showed developmental retardation of bone marrow, inability to convert from pro-B cells to pre-B cells, lack of mature T cells and B cells, and a 20-fold reduction in thymic cells, indicating that IL-7 plays a crucial role in the development and maturation of the bone marrow, and the central T and B cells of the thymus [18]. Moreover, IL-7 could increase the viability of naive T cells in the absence of antigenic stimulation, suggesting that it plays an essential role in protecting the naive T cell repertoire [19][20][21]. It also plays a vital role in increasing memory T cell survival and expansion [22][23]. The deficiency of IL-7 and its receptor affects the development of B cells, T cells, natural killer (NK) cells, monocytes, macrophages, dendritic cells, and innate lymphoid cells, indicating that IL-7 plays crucial regulatory roles in the entire immune system [24].

2.2. Biology and Functions of IL-7Rα

IL-7 function is mediated by the IL-7R, a heterodimer consisting of the IL-7R α chain (CD127) and a common γ chain (CD132, IL-2Rγ). The human IL-7Rα gene, located on chromosome 5, contains 1380 bp, includes 8 exons and 7 introns, and encodes for a protein of 459 amino acids with a molecular weight of approximately 49.5 kDa [2]. IL-7Rα is expressed in hematopoietic cells, particularly the lymphoid lineage, including fetal NK/dendritic precursors, mature T cells and bone marrow macrophages, and developing T cells and B cells. Human marrow stromal cells [25], endothelial cells [26], normal human intestinal epithelial cells, and several malignant tumor cell lines containing breast cancer, melanoma, leukemia, lung cancer and cutaneous T cell lymphoma [27][28][29][30] were all found to express IL-7Rα. IL-7Rα has two forms, membrane-bound IL-7Rα and soluble IL-7Rα (sIL-7Rα), with different biological functions [31][32]. sIL-7Rα competes with membrane IL-7R to reduce excessive IL-7 consumption and antagonizes IL-7 signaling, hence enhancing the biological activity of IL-7 when cytokines are restricted [33]. In addition, sIL-7R directly bind to IL-2Rγ on membrane surface and inhibit IL-7 signaling in IL-2Rγ-positive cells [34]. Previous studies found that sIL-7Rα aggravate autoimmune diseases [33][35][36]. However, sIL-7Rα concentrations were demonstrated to be significantly enhanced in the serum of HIV-positive patients, and high concentrations of sIL-7Rα inhibit IL-7-mediated CD8+ T cell proliferation, indicating that sIL-7Rα may play dual regulatory roles in vivo [33][37][38]. Membrane-bound IL-7Rα promotes cell growth and proliferation, and it inhibits apoptosis by regulating the IL-7 signaling pathway [37]. During this process, IL-7 first binds to IL-7Rα and then recruits IL-2Rγ to form a ternary signaling complex [39], which activates two main downstream signaling pathways, the JAK/STAT5 and the PI3K–AKT signal pathways [6][7][8]. Furthermore, IL-7 also induces the activation of mitogen-activated protein kinases (MAPK) pathway [40] (**Figure 1**).

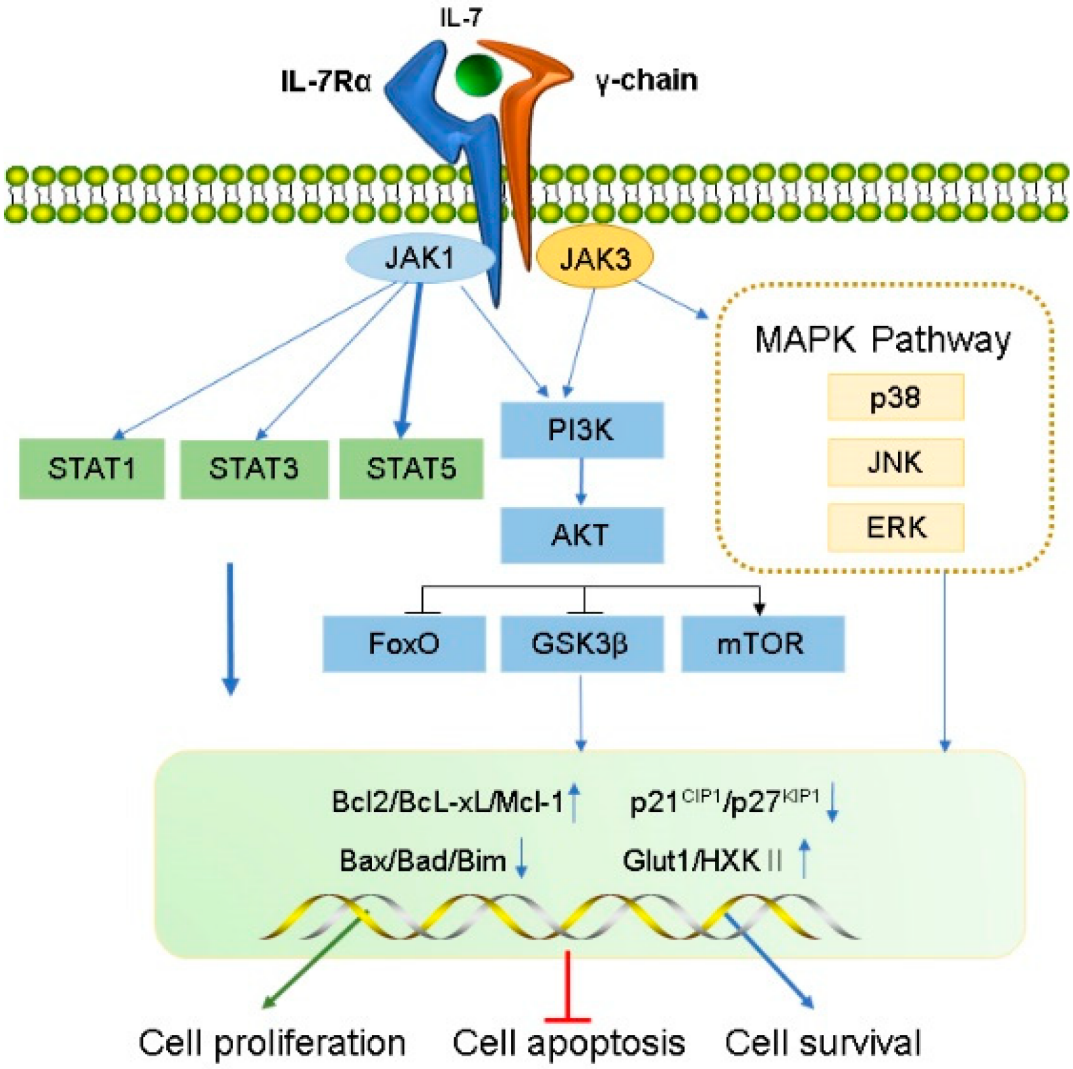

Figure 1. Transduction of IL-7 signaling pathway. IL-7 induces the activation of IL-7R downstream signaling pathway kinases, including JAK1 (linked to IL-7Rα) and JAK3 (linked to common γC), STAT1, STAT3, STAT5, PI3K, AKT, and MAPK. IL-7 signal transduction promotes cell proliferation and survival and inhibits apoptosis by regulating gene expression levels in the nucleus, including a decrease in pro-apoptotic factors (such as Bad and Bax) and cell cycle inhibitors ($p21^{CIP1}$ and $p27^{KIP1}$) and an increase in anti-apoptotic factors (such as Bcl-XL, Bcl-2, and McL-1) and glucose metabolism regulators (Glut1, HXKⅡ).

2.2.1. JAK/STAT5 Signaling Pathway

IL-7 binds to IL-7Rα, triggering activation of the IL-7Rα-associated tyrosine kinase, JAK 1 (linked to IL-7Rα), and JAK3 (linked to common γC). The activated JAK protein phosphorylates a specific motif on the IL-7Rα chain to form a binding site for STAT5 (a signaling molecule containing Src homologous 2 (SH2) domains), and then binds and phosphorylates STAT5, which forms a dimer and enters the nucleus.

During this process, a series of genes that modulate cell growth and survival in the nucleus is affected, as well as other pathways such as PI3K–AKT and MEK/extracellular signal-regulated kinase (ERK) are activated. For example, anti-apoptotic proteins Bcl-XL, Bcl-2, McL-1 belonging to the bcl-2 protein family are up-regulated, and

pro-apoptotic proteins (BAX, BAD) are down-regulated, which improve the survival of T cells in vivo [41]. IL-7 signaling can maintain survival of memory CD8 T cells by mediating STAT5 and STAT3 activation [42]. However, overexpression of Bcl-2 and Bcl-XL did not prevent effector cell death during lymphocytic choriomeningitis virus infection [43], suggesting that activation of other signaling pathways downstream of IL-7R are crucial for maintaining the survival of memory cell precursors. Correspondingly, basal levels of IL-7 can also regulate the number of memory CD8 T cells formed [44]. Furthermore, IL-7 mediates activation of STAT5 and is necessary for T cell proliferation [45], differentiation [46] and survival [47][48]. It also regulates T cell cytotoxicity [47] and drug resistance [49][50]. Additionally, IL-7 not only leads to IL-7-dependent activation of STAT1 and STAT5 in the presence of lymphopenia, but also enhances T cell response to type-I IFN by regulating STAT1 protein expression level [51][52]. In addition, STAT1 overexpression was related to reduce survival in CD4+ T cells undergoing lymphocytopenia-induced proliferation [52]. These results suggest that STAT1 is involved in the process by which IL-7 regulates T cell survival. IL-7 also activates STAT1 and STAT3 which promote B cell precursor acute lymphoblastic leukemia proliferation [53] and survival of B cell progenitors [54], respectively. Furthermore, The JAK/STAT pathway not only activates the family of cytokine signaling inhibitor proteins (SOCS) but can also be inhibited by them to form a negative feedback loop [55][56]. SOCS proteins inhibit cytokine signaling either by competing with STAT5 to inhibit JAK [57] or by proteasomal degradation of targeted signaling proteins [58][59][60].

2.2.2. PI3K/AKT/mTOR Signaling Pathway

Activated IL-7Rα stimulates JAK1/3, and then phosphorylates the P85 subunit of PI3K to activate PI3K and produces the second messenger phosphatidylinositol-(3,4,5)-trisphosphate (PIP3) on the plasma membrane. PIP3 binds to the signaling proteins AKT and (3-phosphoinositide-dependent protein kinase 1) PDK1 (containing Pleckstrin homology domain) and then promotes PDK1 to phosphorylate Ser308 of the AKT protein, thereby activating AKT. IL-7/IL-7R pathways mediate the main downstream targets of AKT such as glycogen synthase kinase (GSK, inhibited), forkhead box O (FoxO, inhibited), and mammalian target of rapamycin (mTOR, activated) [61]. AKT phosphorylates tuberous sclerosis complex 1/2 and prevents negative regulation of small GTP-binding proteins Rheb, resulting in enrichment of Rheb and activation of the mTOR complex (mTORC1) which promotes cell survival and proliferation by inhibiting Bad, Bim, Bax, $p21^{CIP1}$ and $p27^{KIP1}$ and activating Cdk2 [62][63]. Additionally, IL-7 increases the expression of glucose transporter 1 (Glut1) and glycolytic enzyme hexokinase II (HXKII), thereby increasing glucose uptake [64][65] and regulating glucose utilization depending on the PI3K/AKT signaling pathway [66]. IL-7 mediates the proliferation and activation of T cells in mice and is attenuated by PI3K inhibitors [67]. Furthermore, PI3K/AKT pathway is inhibited by PTEN; inhibitors of this pathway are critical for pro-B cell development [68]. IL-7 may promote adipose-derived stem cell differentiation by increasing AKT phosphorylation [69]. Therefore, the PI3K/AKT pathway is essential for powerful IL-7 signal transduction in the cell cycle.

2.2.3. MAPK Pathway

Early studies have shown that IL-7 activates MAPK, containing p38 kinase, c-Jun N-terminal kinase (JNK), and ERK [40]. IL-7-induced cell proliferation could be mediated by the inhibition of the downstream effector MAPK-

activated proteinase 2, further verifying that IL-7 activates this pathway [70]. Specific P38 inhibitors inhibit IL-7-induced T cell proliferation, suggesting that the P38 MAPK pathway plays a vital role in IL-7 signal transduction [70]. Additionally, IL-7 withdrawal blocks the activation of P38 and JNK kinases, leading to IL-7-dependent thymocyte death [71]. IL-7 rescues rapamycin-induced apoptosis of B-cell precursor acute lymphoblastic leukemia-acute lymphoblastic leukemia (ALL) cells by upregulating MEK/ERK [72]. Hence, the MAPK pathway may play a vital role in regulating cell development via IL-7-mediated signal transduction.

3. Effects of IL-7 and IL-7Rα in Cancer

3.1. Anti-Tumor Effects of IL-7 and IL-7Rα

IL-7 has a powerful immunomodulatory effect, which can directly or indirectly act on tumor cells and exert anti-tumor effects by enhancing tumor eradication or adaptive immunity. The expression levels of IL-7 and IL-7Rα are important for normal T cell development and sustaining the homeostasis of the immune system [18][73][74]. IL-7 enhances the cytotoxicity of NK, NKT, lymphokine-activated killer (LAK) cells, monocytes, and cancer-specific cytotoxic T lymphocytes (CTLs). It induces CTL to secrete perforin in a STAT5-dependent manner [47] and stimulates the expression of interferon-gamma (IFN-γ), mitogen-inducible gene (MIG), IL-12, and IFN-γ-induced protein 10 (IP-10) [75][76]. IL-7 can also increase the cytolytic functions of NK cells [77] and CTL [78] by increasing FasL mRNA and protein expression in the membrane. Furthermore, IL-7 increases the amount of CD4+, CD8+ T, cells and CD19+ B cells to promote antibody-dependent cell-mediated cytotoxicity; moreover, it also enhances the response of antigen-specific CD8+ T cells [79] and improve the recovery of CD4+ T cells after chemotherapy in solid tumors [80]. IL-7 inhibits melanoma growth by promoting the secretion of the cytokines IL-1β, IL-1α, and tumor necrosis factor-α (TNF-α) from monocytes [81]. IL-7 enhances the antitumor effect of IFN-γ in rat gliomas [9]. IL-7 restores the activity of CD8+ T cells by decreasing the expression of exhaustion marker PD- 1 [82][83]. Some tumors secrete TGF-β, which inhibits the proliferation of CD8+ T cells via SMAD proteins. IL-7 can reverse this inhibition by inducing the expression of SMAD ubiquitination regulatory factor 2 (SMURRF2) [82][83] (**Figure 2**).

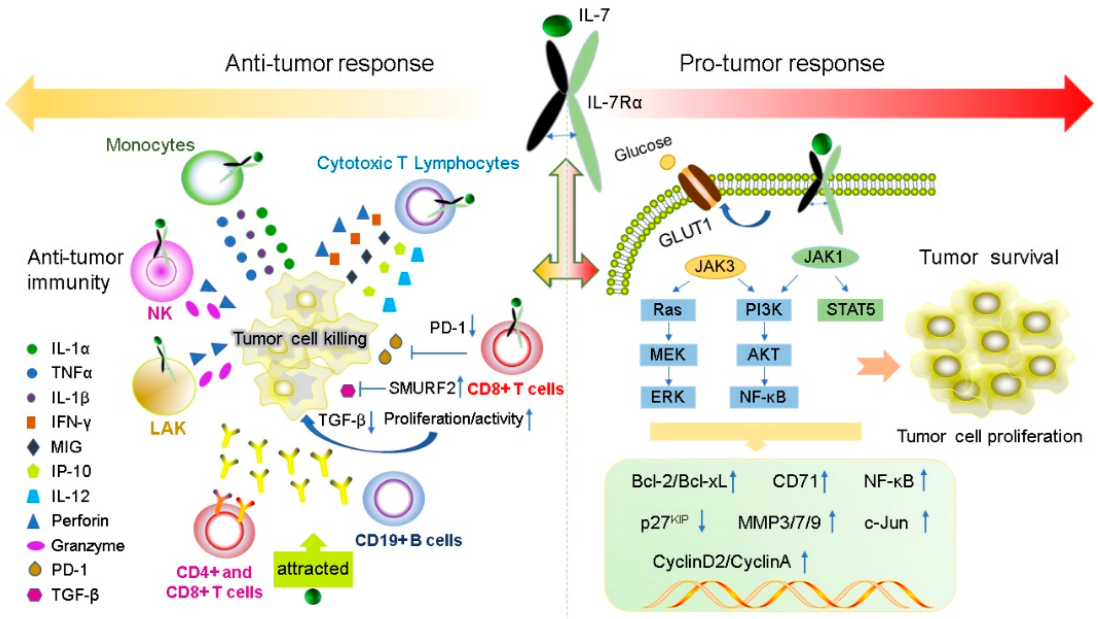

Figure 2. IL-7 and IL-7R have both pro- and anti-tumor functions. IL-7 plays anti-tumor roles by regulating immune cells to release cytokines such as IFN-γ, IL-1β, IL-1α and TNF-α. In contrast, IL-7 can promote the proliferation and survival of tumor cells by binding to the IL-7R to active JAK/STAT5, the PI3K/AKT and Ras/ERK signaling pathways to regulate gene expression levels of Bcl-2, Bcl-XL, CyclinA, CyclinD2, and $p27^{kip}$.

Recent studies suggest that IL-7Rα may be a beneficial prognostic marker for patients with lung adenocarcinoma (LUAD). Survival analysis showed that IL-7Rα expression is an independent prognostic factor for LUAD. IL-7Rα expression is positively correlated to the overall and progression-free survival in patients with LUAD, and negatively correlated to tumor size. IL-7Rα inhibits the growth of tumor cells by affecting the percentage of infiltrating cells in the tumor immune microenvironment. Thus, IL-7Rα may also be a possible therapeutic target for LUAD [84].

3.2. Pro-Tumor Effects of IL-7 and IL-7Rα

The expression levels of IL-7 and IL-7Rα are important for normal T cell development and preservation of homeostasis in the immune system [18][73][74]. IL-7 and IL-7Rα have bidirectional regulatory effects on tumors. IL-7 transgenic mice induced T cell dysplasia, characterized by decreased CD4+ CD8+ (double-positive) thymocytes and lymphoproliferative diseases such as B and T cell lymphoma [85]. Xenotransplant models of human T-ALL have shown that IL-7 promotes the formation of human T-ALL, providing a new method for the treatment of T-ALL by targeting IL-7/IL-7R signal transduction [86]. Moreover, during normal T-cell development, IL-7 exerts as an anti-apoptotic factor by upregulating the of Bcl-2 expression [24]. A similar situation appears in T-ALL cells, IL-7 not only upregulates the expression of Bcl-2 and down-regulates the cyclin-dependent kinase inhibitor $p27^{kip1}$ in T-ALL cells to avoid apoptosis, but also leads to continuing reaction of cyclin D2 and cyclin A during cell cycle progression [87][88]. All gamma-cytokines promote the proliferation of primary T-ALL cells, and IL-7 is the most potent cytokine that induces the proliferation of leukemia cells [89]. IL-7 mainly affects the proliferation and apoptosis of T-ALL cells by activating the JAK/STAT5 and PI3K/Akt/mTOR signaling pathways, leading to upregulation of transferrin receptor CD71, glucose transporter Glut1, glucose uptake and mitochondrial integrity [50][55][66][90][91]. In addition to its role in T-ALL formation, IL-7 also affects the invasion and growth of other tumor cells. For instance, expression of IL-7 is closely correlated with poor prognosis in prostate cancer (PCa) [92]. The IL-7/IL-7R pathway promotes the invasion and migration of PCa cells by activating the AKT/NF-κB pathway and regulating the expression of metalloproteinases (MMP 3 and 7), and it promotes the invasion and migration of bladder cancer cells via NF-KB-mediated upregulation of MMP-9 expression [12][93]. Furthermore, IL-7 can also induce the upregulation of cyclin D1 by modulating the c-FOS/c-Jun pathway, thereby promoting the proliferation of lung cancer cells [94]. Therefore, these studies also demonstrated the potential of IL-7 to promote cancer development.

Previous studies have shown that gain-of-function in IL-7R plays a key role in the generation of human T-ALL [95] and specific mutations in IL-7R specifically enhances steroid-resistance in T-ALL. Steroid resistance occurs due to mutations in IL-7R or other signaling molecules in this pathway which activate downstream MEK-ERK and AKT components, thereby upregulating the expression of MC1 and Bcl-XL, leading to a strong anti-apoptotic response. In addition, MEK-ERK and AKT signaling pathways also inhibit BIM, which is an important steroid-induced cell

death molecule, and GSK3B, which is an important regulator of pro-apoptotic BIM. However, IL-7R signaling inhibitors can restore steroid resistance [96]. In addition, the abnormal expression of wild-type IL-7R can lead to the occurrence of disease and even carcinogenesis. Insufficient IL-7R expression due to IL-7R gene polymorphism results in decreased T cells numbers; however, B cells numbers remain unaffected [97]. Overexpression of IL-7R also leads to potential thymocyte self-renewal and thymic hyperplasia related to proliferation of T cell precursors, which in turn infiltrates the lymph nodes, spleen, and bone marrow, ultimately resulting in fatal leukemia in a dose-dependent manner [98] (**Figure 2**).

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