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Review Article

The role of IL-21 in hematological malignancies

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ABSTRACT

IL-21, the newest member of the common γ-chain family of cytokines, has pleiotropic biological effects through regulating a variety of immune cells. Recently, the role of IL-21 in the treatment of cancers has been widely investigated. Conducted phase I trials in metastatic malignant melanoma and renal cell carcinoma have shown that rIL-21 has a favorable antitumor activity. Expression of IL-21 and IL-21R has also been found in many types of hematological malignancies, such as chronic lymphocytic leukemia (CLL), multiple myeloma (MM) and lymphoma. Through binding with IL-21R, IL-21 induces activation of different JAK/STAT signal transduction pathways and regulates proliferation or apoptosis of tumor cells. In this review, we will discuss the expression of IL-21/IL-21R and its effect in different types of hematological malignancies.

1. Introduction

IL-21, the most recently identified member of the type I cytokine family, was initially discovered by functional cloning after expression of the IL-21R α-chain in BaF3 cells and a library from activated T cells to screen for ligands. IL-21 production was originally thought to be restricted to CD4+ T cells, a major source of IL-21 is T-follicular helper cells found in the B-cell areas of secondary lymphoid tissue, but it is now clear that IL-21 also is produced by Th17 cells and by natural killer T (NKT) cells, and IL-21 mRNA expression has also been reported in stromal cells in lymph nodes, indicating roles for IL-21 in innate as well as adaptive immune responses [1–3].

The IL-21 receptor (IL-21R) was first discovered by genomic and cDNA sequencing projects in 2000 as a putative type I family receptor bearing close resemblance to the IL-2 receptor β chain, moreover, IL-21R was located immediately downstream of IL-4Rα on human chromosome 16p11 [1,4], the full-length cDNA sequence for IL-21R encodes a 538 amino acid cytokine receptor, most similarly to IL-4Rα, with an extracellular domain consisting of one copy of the conserved WSXWS-containing cytokine-binding domain, followed by a transmembrane domain and a relatively long cytoplasmic domain [5]. There are 6 tyrosines in the human IL-21R cytoplasmic domains, Y281, Y361, Y369, Y397, Y317 and Y510. Simultaneous mutation of all 6 tyrosines greatly diminishes IL-21-mediated proliferation, whereas retention of Y510 allows full proliferation [6]. Binding to the IL-21R expressed on cells lacking the γc, IL-21 is unable to transduce any intracytoplasmic signals, while in γc-transfected cells, IL-21 binds to the IL-21R and then activates signals downstream, moreover, the chemical cross-linking study reveals the direct binding of IL-21 to the γc, all these data demonstrated that the functional receptor for IL-21 exists as a heterodimer that comprises IL-21R and the common gamma chain (γc; CD132) [7]. γc is mutated in humans with X-linked severe combined immunodeficiency (XSCID) and results in a failure to generate T cells, NK cells, and a functional B cell population [8]. Expression of the IL-21R complex is detected in lymphoid tissues, including spleen, thymus, and peripheral blood cells. It is also expressed on resting and activated B cells, T cells, NK cells, dendritic cells (DCs), macrophages and keratinocytes. Among T cells, the IL-21R complex is expressed on both CD4+ and CD8+ subsets and upregulated upon T-cell receptor (TCR) activation. Moreover, expression of the IL-21R complex is detected in a variety of B, T, and NK cell lines including IM-9, Jurkat, EL-4, NK-92 and others [3].

Driving the antitumor activity of CD8+ T cells is a well-known role of IL-21. The ability of IL-21 to promote CD8+ T-cell-dependent tumor responses against solid tumors has been shown in mice depleted of CD8+ T cells. IL-21 therapy in mice increases

Abbreviations: IL-21, interleukin-21; rIL-21, recombinant IL-21; IL-21R, IL-21 receptor; JAK/STAT, Janus-activated kinase/signal transducer and activator of transcription; CpG, cytosine-phosphate-guanosine; ODN, oligodeoxynucleotide; anti-BCR, anti-B-cell-receptor antibody; HMCL, human myeloma cell lines; IGF-1, insulin-like growth factor-1; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; MIP-3α, macrophage-inflammatory protein-3α; Gal1, glycan-binding protein galectin-1; NF-kappaB, nuclear factor-kappaB; EBV, Epstein-Barr virus; HTLV-I, human T-cell leukemia virus type I.

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Table 1
Effects of IL-21 on different hematological neoplastic cell type.

Hematological malignancy	Mechanism and effects	Ref.
Chronic lymphocytic leukemia		
Human primary B-CLL cells	Expression of granzyme-B and CD107a Induction of apoptosis Increased IL-21R expression (by CpG-ODN triggering)	[11]
Human primary B-CLL cells	Signaling via JAK1, JAK3 and STAT1, STAT3 and STAT5 Activation of caspase-8 and cleavage of Bid to t-Bid Activation of caspase-3 and cleavage of p27Kip-1 and PARP Inhibition of CD23 expression Induction of apoptosis Increased IL-21R expression (by CD40 triggering) Inhibition of IL-15-triggered proliferation	[17]
Human primary B-CLL cells	Signaling via STAT1 and STAT3 Upregulation of BH3 domain protein BIM Induction of apoptosis	[18]
Human primary B-CLL cells	Signaling via JAK1, JAK3 and STAT1, STAT3 Induction of apoptosis Counteraction the antiapoptotic effect of IL-15	[21]
Multiple myeloma		
$CD45^-$ human myeoloma cell lines	Signaling via STAT1, STAT3 and Erk1/2 Autocrine IGP-1 secretion Stimulation of clonogenicity of human myeloma cells Induction of myeloma cell growth	[26]
Human primary myeloma cells IL-6-dependent human myeloma cell lines ANBL-6, IH-1 and OH-2	Signaling via JAK1, STAT3 and Erk1/2 Induction of proliferation and inhibition of apoptosis Increased IL-21R expression Increased DNA synthesis in primary myeloma cells	[27]
Hodgkin lymphoma		
Primary HL cells HL cell lines L428, HDLM-2, L1236, KM-H2, L591, L540 and L540Cy	Signaling via STAT3 Increased expression of IL-6 and MCL1 Upregulation of MIP-3alpha and attraction of CCR6+CD4+CD25+FoxP3+CD127lo Treg cells Protection of HDLM-2 cells from CD95-induced apoptosis Induction of proliferation Mediation of immune escape	[19]
HL cell lines L428, L1236 and L591	Signaling via STAT3 and STAT5 Activation of the NF-kappaB pathway Immortalization of B cells resembled HL cells (through expression of CA-STAT5) Induction of proliferation	[33]
Follicular lymphoma		
Primary FL cells FL cell line SUDHL4	Signaling via JAK1, JAK3 and STAT1, STAT3, STAT5 Activation of caspase-3, -8 and -9 Decreased expression of Bcl-2 and Bcl-XL, and increased expression of Bax Induction of SOCS3 gene expression Induction of apoptosis	[23,37]
FL cell lines DOHH2, KARPAS-422, RL, DB, LY8 and WSUFSCCL Diffuse lymphomas evolved from previous FL	Signaling via JAK1 Low IL-21R expression Resistance to IL-21-mediated apoptosis	[37]
Diffuse large B cell lymphoma		
Primary DLBCL cells DLBCL cell line CRL-2632 with t(14;18)(q32;q21)	Signaling via JAK1, JAK3 and STAT1, STAT3 Upregulating expression of c-Myc Induction of apoptosis	[19,38]
Mice harboring xenograft DLBCL tumors	Promotion of tumor regression and prolonged survival	
Mantle cell lymphoma		
MCL cell lines Mino, SP53 and Rec-1	Signaling via STAT1 Upregulation of BIK, NIP3 and HARAKIRI Downregulation of Bcl-2, Bcl-XL/S and TNF-alpha Downregulation of DNA-binding ability of NF-kB Induction of apoptosis	[40]
Burkitt's lymphoma/leukemia		
EBV-transformed B cells BL lines Ramos, Namalwa, and Daudi	Expression of granzyme-B Induction of apoptosis	[11]
BL cell line Ramos	Signaling via JAK1, JAK3 and STAT1, STAT3 Enhancement of proliferation	[23]
Adult T-cell leukemia/lymphoma		
Primary ATL cells ATL-43T and ED-40515(+) cell lines	Signaling via STAT3 and STAT5 Induction of proliferation Induction of DNA synthesis	[46,47]