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International Journal of Innovative Research in Technology, Science & Engineering (IJIRTSE)
ISSN: 2395-5619, Volume – 1, Issue – 5. July 2015

A REVIEW ON STRUCTURE, FUNCTION AND IMMUNOTHERAPY OF INTERLEUKIN-2 AND ITS RECEPTOR

[1]Sasi Devi D, [2]Sivanandham M
Department of Biotechnology, Sri Venkateswara College of Engineering, Sriperumbudur, India
[1]msiva@svce.ac.in

Abstract— **In this review article, the structure, function and immunotherapy of interleukin-2 and its receptor are detailed. Interleukin-2 is a pleiotropic cytokine produced by antigen activation through antigen presenting cells. It plays a very important role in the human immune responses. Interleukin-2 also determined as T- cell growth factor, functions in the proliferation and differentiation of T lymphocytes and also B lymphocytes. It plays a vital role in immunotherapy in most of the infectious diseases and major role in Renal Cell Carcinoma (RCC) and Melanoma and also in HIV- infection.**

Keywords: Interleukin-2, T lymphocytes, RCC, Melanoma.

I. INTRODUCTION

Interleukin-2 (IL-2) was discovered in the year 1975 in the activated human T cells. The activated T cells mediate T cell growth and proliferation (Morgan *et al*., 1976). This was the first type I cytokine (Bazan, 1990) to be cloned (Taniguchi *et al*., 1983). IL-2 was the first type I cytokine whose receptor component was cloned (Leonard *et al*., 1984; Nikaido *et al*., 1984). The proliferation of natural killer (NK) cells was induced by the IL-2 molecule and it also augments their cytolytic activity (Siegel *et al*., 1987). It also promotes the production of antibody and B cell proliferation (Mingari *et al*., 1984). The IL-2 also promotes the differentiation of T helper 1 cells (Th1) (Liao *et al*., 2011; Shi *et al*., 2008) and T helper 2 (Th2) cells (Cote-Sierra *et al*., 2004; Liao *et al*., 2008). IL-2 also plays a major role in the production of Interleukin-9 (IL-9) (Schmitt *et al*., 1994). Thus, IL-2 has broad immunological actions. The potentially dangerous autoimmune reactions were also limited by the IL-2 molecule. Herein, we discuss the molecular structure and cellular biology of IL-2 and its function in immune response. Finally, we also discuss IL-2 as an immunotherapeutic agent.

A. Interleukin-2

Interleukin-2 (IL-2) was first discovered in the year 1975 in the supernatants of activated human T- Cells that helps the growth and proliferation of human T lymphocytes (Morgan *et al*., 1976). It was the first cytokine to be characterized at the molecular level. IL-2 originally identified as T cell growth factor for its ability to sustain the continuous proliferation of T-lymphocytes (Gillis *et al*., 1978). It is a globular protein, similar in structure to Interleukin-4 (IL-4) and granulocyte- macrophage colony stimulating factor (GM-CSF) (Bazan., 1992).

IL-2 is a type 1 four alpha-helical bundled cytokine molecule of 15.5 kDa size produced primarily by CD4+ T cells following antigen stimulation by the APC's (Leonard, 2001). It is also produced in a lesser amount by CD8+ cells (Paliard *et al*., 1988), NK cells (Yui *et al*., 2004), activated dendritic cells (DC's) (Granucci *et al*., 2001). It consists of 133 amino acid residues (Theze *et al*., 1996). IL-2 is capable of supporting long term T lymphocyte proliferation (Robb and Smith., 1981). It was the first protein molecule in the class of cytokine to be purified to homogeneity by immunoaffinity chromatography (Smith *et al*., 1984).
IL-2 promotes the proliferation and differentiation of T lymphocytes, B lymphocytes and natural killer (NK) cells. The IL-2 stimulated expansion of antigen selected T cells determines the effect of antigen specific immune responses and it forms the cellular basis for immunologic memory.

B. Structure of Interleukin-2:

IL-2 is a monomeric secreted glycoprotein that exerts in a globular structure with four α-helices folded in a confirmation that is typical to the type I cytokine family (Malek *et al*., 2010).

The IL-2 gene is located in the mid portion of the long arm of human chromosome 4, at band q26-28 (Seigel *et al*., 1984). It exists as a single copy per haploid human genome, is 5040 base pairs (bps) long and consists of four exons (Fujita *et al*., 1983 and Holbrook *et al*., 1984). A promoter sequence TATAAA and a CAT homology region are situated 77bp and 104bp upstream (5') from the translational initiation site.

A single disulphide bond between cysteine residues 58 and 105 connects the second helix to the inner - helical region between the third and fourth helices. This provides the essential stability of IL-2.

C. Interleukin-2 Receptor

The interaction between the IL-2 and the activated T cells is a classic polypeptide hormone- receptor system (Robb *et al*., 1983). The Early studies on the IL-2 binding with its receptor revealed the existence of three classes of IL-2 binding complexes and that exhibited low, intermediate and high affinities for ligand. The three classes of cell surface receptors formed by various combinations of three IL-2R subunits: IL-2Rα, IL-2Rβ and IL-2Rγ (Kim *et al*., 2006; Lin and Leonard, 2000; Malek and Castro, 2010) (Robb *et al*., 1981).

IL-2Rα (CD25) was originally identified as Tac antigen due to blockage of the binding of IL-2 (Leonard *et al*., 1982) by the anti-Tac monoclonal antibody (mAb) (Uchiyama *et al*., 1981). IL-2Rβ (CD122) (Sharon *et al*., 1986; Teshigawara *et al*., 1987; Tsudo *et al*., 1986) is also present in the receptor complex of IL-15 molecule (Giri *et al*., 1994). IL-2Rγ (CD132) (Takeshita *et al*., 1992) is the common cytokine receptor γ chain, γc (Leonard *et al*., 1995; Noguchi *et al*., 1993a; Russell *et al*., 1993). The common gamma chain, γc, is also common in the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptor molecules (Leonard, 2001; Rochman *et al*., 2009).

IL-2Rα is either absent or minimally expressed on resting T-lymphocytes and NK cells, but its transcription is potently induced on T cells stimulated through the TCR or IL-2 molecule (Depper *et al*., 1984, 1985; Leonard *et al*., 1985) or on NK cells stimulated with the IL-2 (Siegel *et al*., 1987). The IL-2Rβ chain expression level is low on T cells but it can be induced by certain stimuli, including IL-2 (Siegel *et al*., 1987). The γc is also expressed on these cell surfaces but is less inducible than IL- 2Rα or IL-2Rβ (Cao *et al*., 1993).

The three receptor subunits: alpha, beta and gamma common chain, together form the high-affinity IL-2 receptor (Takeshita *et al*., 1992), and the structure has also been identified (Stauber *et al*., 2006; Wang *et al*., 2005). The receptors with the intermediate affinity are present on resting T lymphocytes (Zhang *et al*., 1998) and NK cells (Siegel *et al*., 1987). The high-affinity receptors are expressed by activated T lymphocytes (Robb *et al*., 1981). The interaction of the IL-2 to intermediate affinity receptors induces cell growth and cytolytic activity (Siegel *et al*., 1987) and the transcription of IL-2Rα (Depper *et al*., 1985).

After the activation of T cells, IL-2Rα is induced rapidly and high-affinity receptors are activated to the IL-2 molecules. IL-2 primarily acts as a soluble factor via intermediate and high-affinity receptors, like IL-15, IL-2 can be presented in trans, where IL-2 molecule bound to IL-2Rα on one cell surface stimulates another cell that expresses IL-2Rβ and γc (Wuest *et al*., 2011). In addition to cell surface IL-2Rα, the αR can also exist in a soluble form (sIL-2Rα) that can be released from the cell surface, including in infectious disorders, transplantation rejection, and autoimmune inflammatory states, with an elevated amount of sIL-2Rα being detected in certain hematologic malignancies.

The multiple lymphohematopoietic populations of cells, including NK cells, resting T cells, monocytes, and neutrophils also express the IL-2Rβ. Upon the T cells, TCR stimulation, IL-2, and IL-4 each augments IL-2Rβ expression via both transcriptional and posttranscriptional regulation (Kim *et al*., 2006). IL-2Rγ is also constitutively expressed on the cell surfaces and mainly restricted to lymphohematopoietic cells like IL-2Rβ (Cao *et al*., 1993).

D. IL-2 Receptor mechanism

After the binding of the IL-2 molecule to the receptor, the IL-2 receptor complex is rapidly internalized, with IL-2Rα located in early transferrin+ endosomes will recycle to the plasma membrane, whereas IL-2Rβ and γc are targeted to the nucleus and degraded (He´ mar *et al*., 1995). Following the binding with the receptor complex, IL-2 molecule activates multiple signaling pathways.

Heterodimerization of IL-2Rβ and γc cytoplasmic domains leads to activation of Janus family tyrosine kinases, JAK1 and JAK3, with JAK1 associating with IL-2Rβ and JAK3 with γc (Boussiotis *et al*., 1994; Miyazaki *et al*., 1994; Russell *et al*., 1994). The JAK kinases activate each other and phosphorylate key residues in IL-2Rβ. The phosphorylation of JAK Kinase induces the activation of Ras-MAP kinase and promotes the cell growth. After the Phosphorylation of above two, the STAT1, STAT3, STAT5A, and STAT5B were activated, with most potent and sustained activation of STAT5 proteins (Friedmann *et al*., 1996; Lin *et al*., 2012). IL-2 also activates the phosphoinositol 3-kinase (PI 3-kinase) signalling pathway (Lin and Leonard, 2000; Malek and Castro, 2010), which promotes cell growth and survival (Franke *et al*., 1997).

E. Immunotherapy of IL-2

IL-2 has been employed in the immunotherapy for many years. It's been used for the treatment of metastatic renal cell carcinoma (RCC) with FDA approval in 1992 and for metastatic melanoma in 1998. The patients with these diseases can have a complete remission of 5%–10% with the IL-2 treatment, with lack of recurrence for as long as 25 years. The IL-2 treatment potentially cures of 70% of these individuals, with complete tumor regression (Rosenberg, 2012). IL-2 can also have clinical use as an immune therapy in patients with HIV infection (Sarah *et al*., 2004). In patients with HIV infection, IL-2 therapy leads to an increased number of CD4+ T lymphocytes (Sereti *et al*., 2002 and Natrajan *et al*., 2002).

F. IL-2 Toxicity

In the early clinical trials, administration of IL-2 led to significant toxicity (Rosenberg et al., 1987 and Rosenberg et al., 1985). It may be mostly due to an inflammation response mediated by the exogenously administered IL-2, leading to systemic inflammatory response syndrome. The toxicity of IL-2 causes hypotension, nausea, vomiting, diarrhea, confusion, shortness of breath, pulmonary edema, abnormal liver function tests, renal failure, rash, fever. Chills and malaise and infection (Atkins *et al*., 1999, Fyfe *et al*., 1995, Kovacs *et al*., 1996 and Rosenberg *et al*., 1994). The long term therapy with IL-2 causes both hypo- and hyperthyroidism (Krouse *et al*., 1995). But the effects are not clear whether it is due to the effects of IL-2 on the thyroid gland or production of anti-thyroid antibodies. However, there is no predictive relationship between thyroid dysfunction and response to therapy (Kruit *et al*., 1993).

G. Recombinant human IL-2 (rIL-2)

The commercially available preparation (Aldesleukin, Chiron Corp) is a recombinant protein with a single amino acid modification at residue 125. The chemical name is desalanyl-1, serine-125 human interleukin-2. It is a highly purified protein molecule of molecular weight 15,300 daltons. It is a biologic response modifier and has the same action as native IL-2 in the treatment of renal cell carcinoma and melanoma. It is produced by the mutation done at position 125 from cysteine to serine. It is a non-glycosylated molecule because it is derived from *E.Coli* strain. No N-terminal alanine was present. It is given intravenously with a recommended dose of 600,000 IU/kg over 15 minutes for every 8 hours upto14 doses followed by 9 days of rest and then another 14 doses. Its volume of distribution is 0.18 l/kg.

II. DISCUSSION

The molecular structure and the function of interleukin-2 were studied and the signalling mechanisms involved in binding of the IL-2 molecule with its heterotrimer receptor. Also, there are many toxic side effects of IL-2 therapy, the most common of which are fevers, chills gastrointestinal problems. In addition, there is an increase in vascular permeability and a decrease in systemic vascular resistance, resulting in hypotension that requires fluid replacement and a common effect is an increase in body weight of up to 10%. To overcome all such side effects the immunotherapeutic value of the IL-2 should be increased through mutations.

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