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Review Article

Interleukins in Therapeutics

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ABSTRACT

Interleukins are a subset of a larger group of cellular messenger molecules called cytokines, which are modulators of cellular behaviour. On the basis of their respective cytokine profiles, responses to chemokines, and interactions with other cells, these T-cell subsets can promote different types of inflammatory responses. During the development of allergic disease, effector TH2 cells produce IL-4, IL-5, IL-9, and IL-32. IL-25, IL- 31, and IL-33 contributes to TH2 responses and inflammation. These cytokines have roles in production of allergen-specific IgE, eosinophilia, and mucus. ILs have role in therapeutics as well as diagnosis and prognosis as biomarker in various conditions. Therapeutic targeting of the IL considered to be rational treatment strategy and promising biologic therapy.

Keywords: Interleukins, cytokines, Interleukin Inhibitors, Advances

INTRODUCTION

Interleukins are group of cytokines that were first seen to be expressed by leucocytes and they interact between cells of the immune systems. It is termed by Dr. Vern Paetkau (University of Victoria) in1979.Interleukins (IL) are able to promote cell growth, differentiation, and functional activation. The question of how diverse cell types communicate with each other, had led to the discovery of interleukins. The name interleukin was chosen because it reflected the basic property of these mediators to serve as communication links between leukocytes. [1,2] Effects of ILs has greatly increased since the discoveries of monocyte IL (called IL-1) and lymphocyte IL (called IL-2); more than 40 cytokines are now designated as ILs. [3]

Cytokines are low molecular weight regulatory proteins or glycoproteins secreted by white blood cells & other cells in the body in response to various stimuli. Cytokine is a word that comes from cyto meaning “cell” and kinin meaning ‘hormones’. It was Stanley Cohen in 1974 who for the first time introduced the term ‘‘cytokine’’. It includes lymphokines, monokines, interleukins, and colony stimulating factors (CSFs), interferons (IFNs), tumor necrosis factor (TNF) and chemokines. The majority of interleukins are synthesized by helper CD4 T lymphocytes as well as through monocytes, macrophages, and endothelial cells. They promote the development and differentiation of T, B, and hematopoietic cells. [1,2,3]

Properties of cytokines: Based on function[1,3]

Hormone like action: autocrine, paracrine, endocrine

One cytokine can affect more than one type of cells – Pleiotropism

Different cytokines can perform some similar functions - Redundancy

One cytokine can influence the function(s) and/or production of other cytokines- Multifunctional

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Classification of Cytokines: Based on principal action[2,3]

Principal action	Mediators of innate immunity	Mediators of specific immunity	Stimulate growth of BM progenitors
Source	Mononuclear phagocytes	Ag stimulated T lymphocytes	BM cells, T cells
Cytokines	IL1 IL6 IL10 IL12 IL15 Type I IFN Chemokines	IL2 IL4 IL5 TGF ß IFN α TNF	IL3 IL7 GM-CSF M-CSF G-CSF

Classification of interleukins: Based on shared structural characteristics, and/or shared receptor subunits and/or shared chromosomal locations[2,3,4,5]

Family	Interleukins	Functions
IL-1 family	IL-1α, IL-1β, IL-18 , IL-33	Co-stimulation of T helper cells; Maturation and proliferation of B cells; Activation of NK cells; Role in inflammation acute phase reactions and fever.
IL-2 family	IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-21	Stimulates growth and differentiation of cell response; IgG and IgE synthesis (important in allergic response); Used as Immunotherapy to treat cancer or suppressed for transplant patients; Used in clinical trials to raise CD4 counts in HIV positive patients
IL-10 family	IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, IL-29	Cytokine production; Histamine release; Inhibits Th1 cytokine production (IFN gamma, TNF-beta, IL-2); Osteoclast formation
IL-12 family	IL-12, IL-23, IL-27	Differentiation into cytotoxic T cells with IL-2; Increase IFN-gamma and TNF-alpha, Decrease IL-10; iincrease TNF-alpha and IFN-gamma
IL-17 family	IL-17A–F, IL-25	Angiogenesis; Increase inflammatory cytokines; Pro inflammatory role in asthma; Induces production of IL-4, IL-5 and IL-13, which stimulate eosinophil expansion
Family of 'Like' cytokines	IL-3, IL-5 ,IL-6 and IL-11	Differentiation of activated B cells into plasma cell; Antibody secretion; Osteoclast formation; Acute phase reaction, hematopoiesis, differentiation, inflammation, etc.

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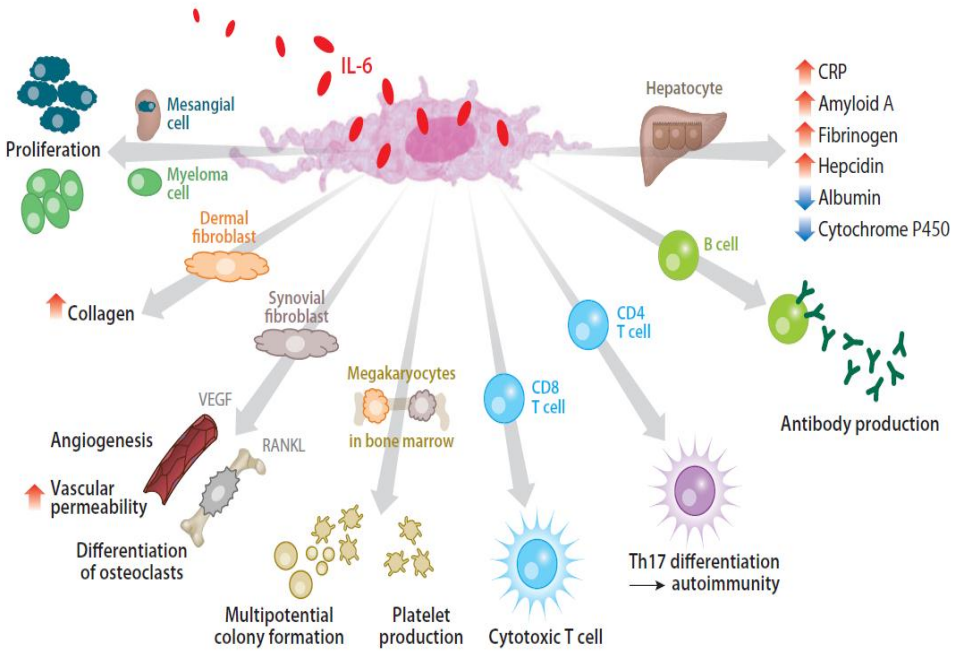

Fig: Interleukin-6 as multifunctional interleukins[3,8]

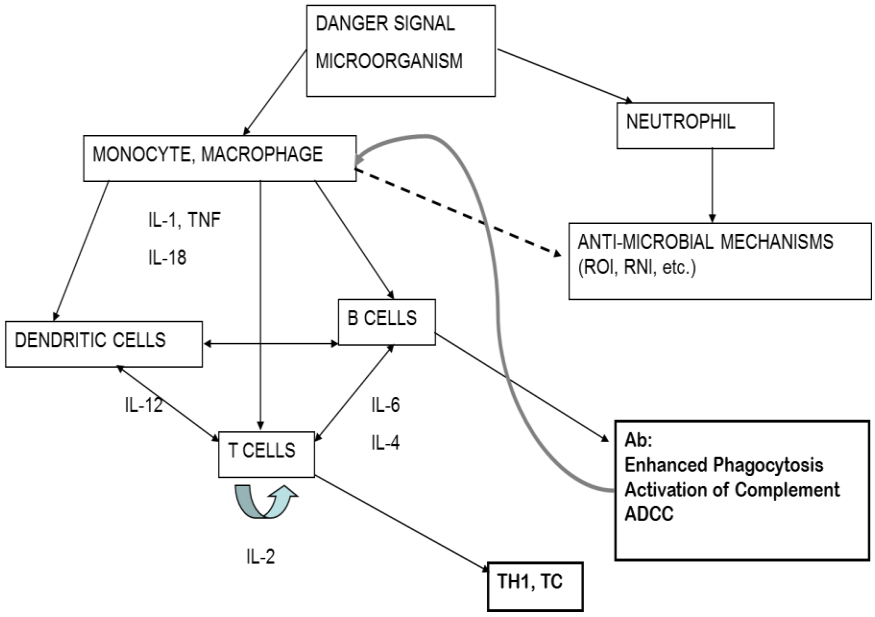

Fig: Cytokine cascade links inflammatory and immune responses[3,8,9]

ROLE OF INTERLEUKINS AND THEIR INHIBITORS IN THERAPEUTICS

Aldesleukin is proleukin, a lymphokine, human recombinant interleukin-2. It stimulates the growth of IL-2 dependent cells, triggers natural killer (NK) and lymphokine-activated killer (LAK) cell activity. It Induces production of interferon gamma, and increases lymphocyte cytotoxicity.

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It is used for treatment of adults with metastatic renal cell carcinoma, melanoma and bone tumour. [3,10,11,12]

Interleukin Inhibitors

1. TNF-alpha inhibitors: Etanercept, Infliximab, Adalimumab
2. IL-1 receptor antagonist: Anakinra, Rilonacept, Canakinumab, Endogenous IL1RA
3. IL-2 receptor antagonist (Anti CD25): Daclizumab, Basiliximab
4. IL-4 antagonist: Pascolizumab
5. IL-4 and IL-13 antagonist: Pitrakinra
6. Anti IL-5: Mepolizumab
7. Anti IL-6: Ruxolitinib, Tocilizumab, Bevacizumab, Cucurbitacin, Siltuximab
8. IL-13 inhibitors: Tralokinumab, Lebrikizumab
9. IL-17 inhibitors: Vidofludimus, Ustekinumab

Anakinra is a recombinant, IL-1 receptor antagonist. It is used as single daily subcutaneous injection at recommended fixed daily dose of 100 mg. it has been approved for use in rheumatoid arthritis and neonatal onset multisystem inflammatory disease. Neutrophil counts prior and while receiving anakinra, monthly for 3 months, and thereafter quarterly for a period up to 1 year is required. [3,12,13]

Daclizumab is a therapeutic humanized monoclonal antibody to IL-2R. It is used to prevent rejection in organ transplantation, especially in kidney transplants. Its recommended dose is 1.0 mg/kg and given in multiple doses, the first 1 hour before the transplant operation and 5 further doses given at two week intervals after the transplant. Phase II clinical trial has been completed for its possible use in Multiple Sclerosis. [3,8,14]

Basiliximab is chimeric mouse-human monoclonal antibody IL-2R. It is used to prevent rejection in organ transplantation, especially in kidney transplants. Its dose is 20 mg two times 4 days apart -given in two doses, the first within 2 hours of the start of transplant operation and the second 4 days after the transplant. Lichen planus have been successfully treated with basiliximab as an alternative therapy to cyclosporine, with a dose of 20 mg every 4 days. [3,6,8,15]

Tocilizumab is a humanized anti-interleukin-6 receptor antibody of IgG 1 class. It has been used invarious conditions like autoimmune diseases (SLE, RA, Systemic sclerosis, Polymyositis , Takayasu arteritis and giant cell arteritis, Crohns' disease), chronic inflammatory conditions (Castleman's disease, Systemic juvenile idiopathic arthritis and adult onset still's disease, Amyloid A Amyloidosis, Bechet syndrome) and malignant diseases (Gliobastoma multiforme, renal cell carcinoma, prostate cancer, mesothelioma, multiple myeloma). [3,10,17,19]

Newer Interleukin inhibitors

Pitrakinra is a IL-4 and IL-13 antagonist in phase IIa studies for asthma
Mepolizumab is a humanized monoclonal antibody that recognizes IL-5 and used to treat asthma, white blood cell diseases and hypereosinophilic syndrome.
Tralokinumab is a human monoclonal antibody which targets interleukin 13 and is designed for treatment of asthma. Phase II trial is undergoing to evaluate in patients with active, moderate-to-severe ulcerative colitis.
Lebrikizumab is a humanized monoclonal antibody and used as experimental immunosuppressive drug for the treatment of asthma that cannot be adequately controlled with inhalable glucocorticoids (successful Phase II clinical trial). [3,10]

Miscellaneous agents

- Cyclosporin inhibits IL-1 and IL-2 receptor production.
- Auranofin inhibits release of IL-1 and TNF-alpha.

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- Raloxifene inhibits IL-6 production by human trabecular osteoblast.
- Clarithromycin inhibits IL-13 induced goblet cell hyperplasia in human airway cells.
- Methylprednisolone inhibits IL-8 and IL-6 during open heart surgery.
- Simvastatin inhibits IL-6 release in human monocytes stimulated by C-reactive protein and lipopolysaccharide.
- Testosterone inhibits IL-6 production of normal and gingival fibromatosis.

Interleukins in pregnancy

TNF-α has a characteristic inflammatory action, and it is an additional diabetogenic factor in pregnancy. The loss of the control of the production of these cytokines, with increase of TNF-α, is related to the risk for developing obstetric complications, particularly recurrent fetal loss, GDM, hypertensive syndromes, and fetal growth restriction**.** IL-10 is an important cytokine for pregnancy maintenance and development. During this specific period, its immunosuppressive action plays a key role in regulating the balance of pro- and anti-inflammatory signs that orchestrate the adequate development of pregnancy and in placental growth and remodeling, which are also important for a favorable pregnancy outcome. [3,13,14,15]

Interleukins as bio-markers

IL-6 provides a promising serum marker for the nonsurgical prediction of endometriosis.IL-8 is a promising marker for many clinical conditions such as chronic prostatitis, acute pyelonephritis, non-Hodgkin's lymphoma, urinary bladder cancer, therapeutic target to control cancer growth and metastasis, nosocomial bacterial infections in neonatal intensive care unit (NICU), vesicoureteral reflux (VUR), Detection of pulmonary infections and osteomyelitis. BothIL-6 and IL-8 are used as marker for acute pyelonephritis, early biomarker of acute kidney injury and predict prolonged mechanical ventilation. Il-13 is used as biomarker for asthma. [3,10,16,17,18]

RECENT ADVANCES IN INTERLEUKINS

IL-2 acts as novel targets for several autoimmune diseaseIL-1B converting enzyme inhibitors decreases death rate in severe acute experimental pancreatitis- promising future studies.IL-1R antagonist appear as new therapy in type 2 diabetes mellitus. DIRA-Deficiency of IL-1 receptor antagonist is a new autoimmune disease related to skin disruption manifests in first 3 weeks of life as fetal distress, joint swelling, oral mucosal lesions and painful movement.Interleukin-10 may protect against progressing injury during the acute phase of ischemic stroke. [3,6,7,9,17,19,20]

CONCLUSION

IL contributes to host defense against pathogens. Dysregulation of IL production plays a significant pathological role in various autoimmune, inflammatory diseases and malignancy. Therapeutic targeting of the IL considered tobe rational treatment strategy and promising biologic therapy. Research is continuing with an aim to develop new therapies and refine those already in use.

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