

The fantastic Interleukins

Role in health and disease



Juan Carlos Aldave, MD
Allergy and Clinical Immunology

Chapters 1 - 12

The fantastic Interleukins

Role in health and disease

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First Edition E-book: December 2015

December 2015.

Since we are born, many dangerous microbes and malignant cells threaten our life. Therefore, we need to have powerful cells and molecules capable of defending us. We will call **immune system** to our body defenses, and **immunocytes** to the immune cells that protect us.

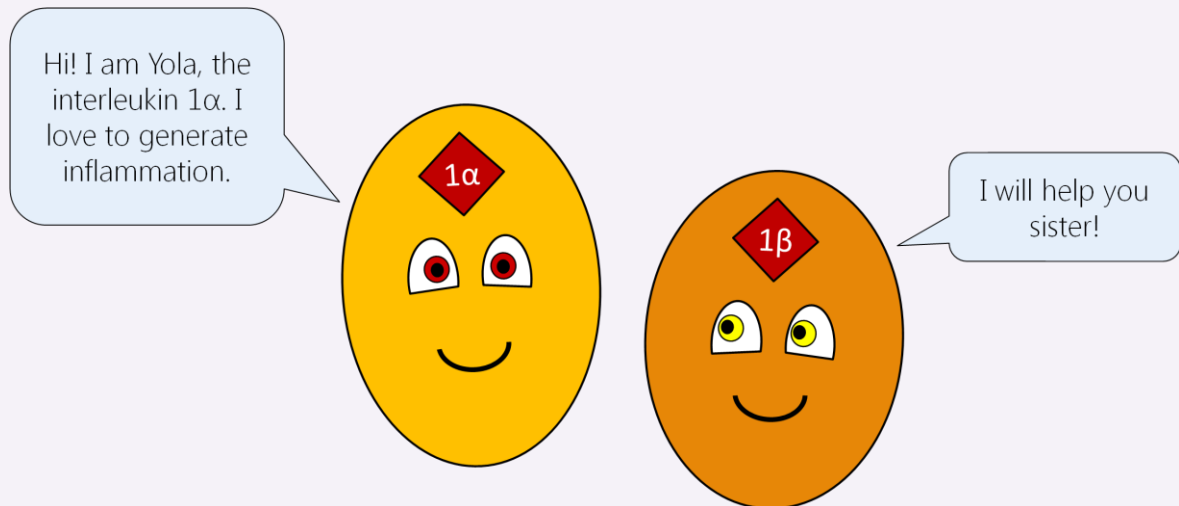
Our immunocytes are very strong to attack threatening organisms and cells. However, they tolerate certain molecules such as self proteins, good microbes, food and harmless substances.

Immunocytes communicate between them and with other cells through proteins called **interleukins**. In this book we will learn in a very simple and didactic way about our 38 interleukins and their role in health and disease.

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Yola and Tola, IL-1 α and IL-1 β

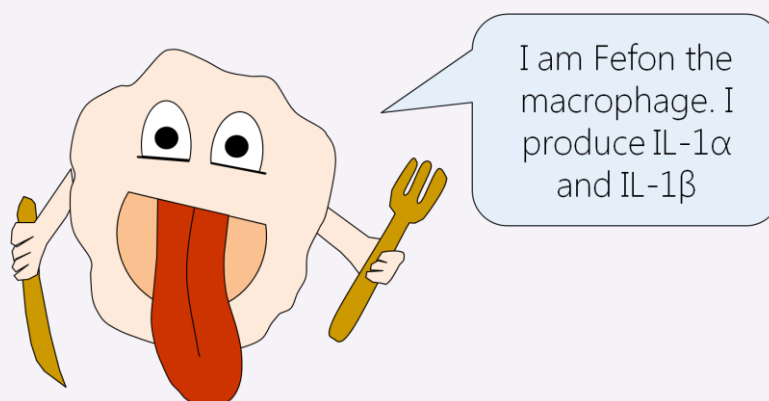


The family of interleukin 1 is composed of eleven cytokines: seven are inflammatory (IL-1 α , IL-1 β , IL-18, IL-33, IL-36 α , IL-36 β , IL-36 γ) and the other 4 are antiinflammatory (IL-1Ra, IL-36Ra, IL-37, IL-38).

IL-1 α and IL-1 β have potent inflammatory activity. Their natural antagonist is the protein IL-1Ra (interleukin 1 receptor antagonist).

Where are they produced?

Yola and Tola are produced primarily by activated macrophages. Their actions are proinflammatory and pyrogenic. IL-1 β also favors the differentiation of TH17 lymphocytes.



Are there people who cannot produce IL-1 α or IL-1 β ?

So far there are no reports of subjects with pathogenic mutations in the genes encoding IL-1 α and IL-1 β .

However, there are patients who cannot synthesize the antagonist molecule IL-1Ra. The resulting disease is called DIRA (Deficiency of the Interleukin 1 Receptor Antagonist), characterized by multifocal osteomyelitis, periostitis and pustulosis of neonatal onset.

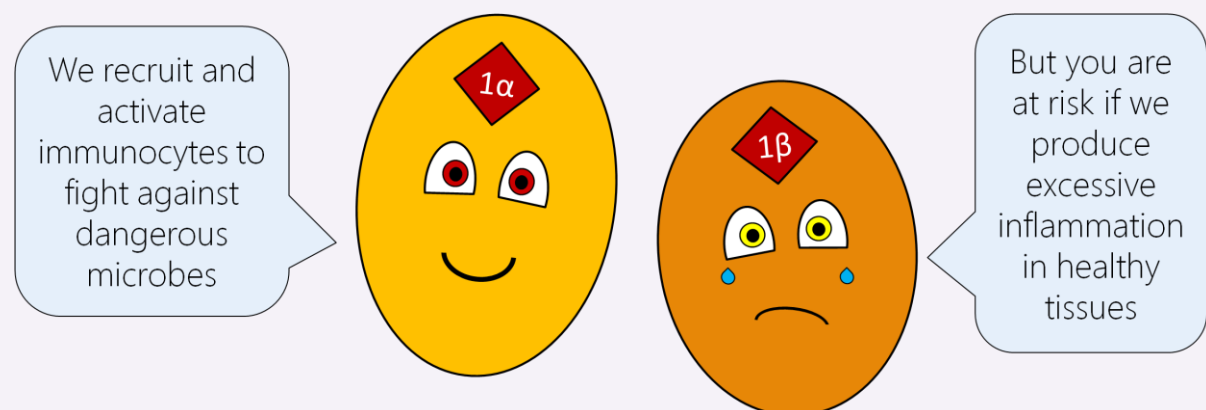
Are there people who produce IL-1 α or IL-1 β in excess?

Yes, excessive production of IL-1 α and IL-1 β occurs in:

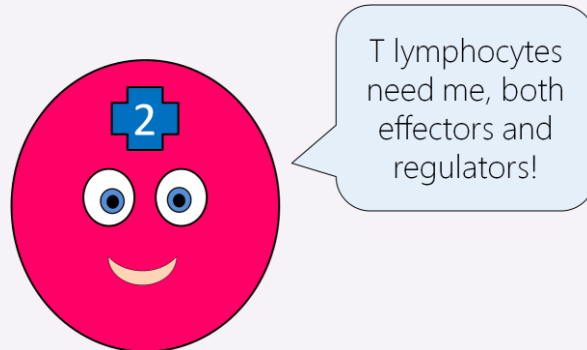
- Many autoimmune diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel disease.
- Several autoinflammatory disorders (genetic defects that generate disproportionate activation of innate immunity), such as Familial Mediterranean fever and Muckle-Wells syndrome.

In patients with these diseases both cytokines become therapeutic targets. For example:

- The drug Anakinra is a synthetic antagonist of IL-1.
- The monoclonal antibody Canakinumab traps IL-1 β .



Elva, the interleukin 2

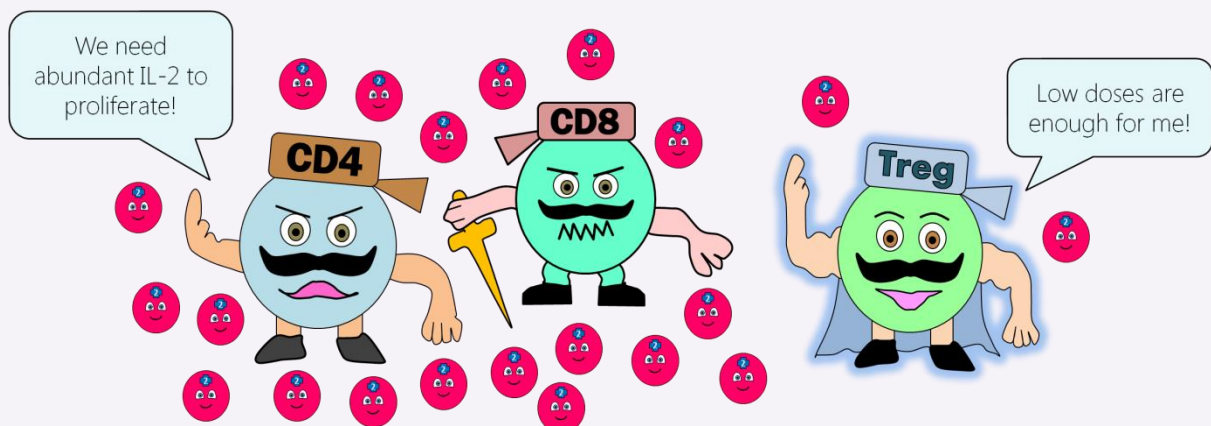


Elva is an essential protein for T lymphocytes. Its receptor (IL-2R) is formed by 3 chains: IL-2R α (CD25), IL-2R β and IL-2R γ (CD132, γ c or gamma common chain). γ c is also part of the receptors of interleukins 4, 7, 9, 15 and 21.

Where is Elva produced?

IL-2, fabricated initially by dendritic cells, stimulates the activation of T lymphocytes. Activated T cells synthesize more IL-2 and IL-2R, amplifying their proliferation in an autocrine fashion.

On the other hand, IL-2 at low doses is essential for the development of regulatory T lymphocytes. Elva also participates in the activation of innate lymphoid cells, B lymphocytes and NK cells.



Are there people who cannot produce IL-2 or its receptor?

γc deficiency causes an absence of T lymphocytes (lack of response to IL-2 and IL-7) and NK cells (lack of response to IL-15), giving rise to severe combined immunodeficiency. Affected patients are susceptible to infections by all kinds of microbes.

The absence of IL-2Rα prevents the activation of effector and regulatory T cells, favoring infectious and autoimmune processes.

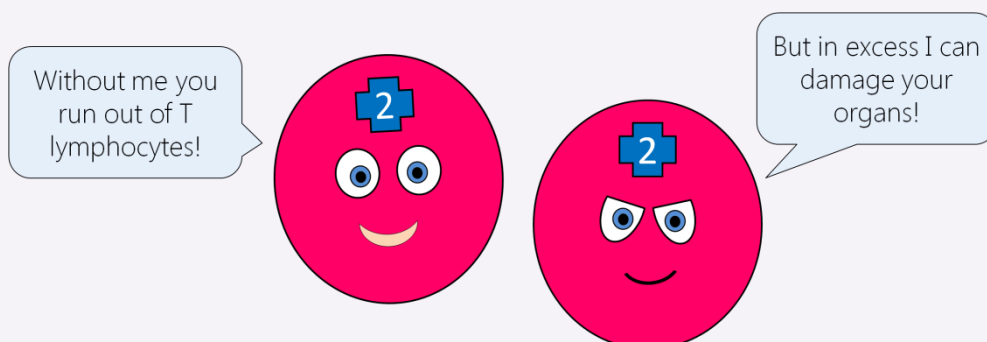
High-dose recombinant IL-2 can potentiate effector T lymphocytes in subjects with immunodeficiencies, cancer, or chronic infections. At low doses, IL-2 could attenuate autoimmunity by promoting differentiation of regulatory T lymphocytes.

Are there people who fabricate IL-2 in excess?

Excessive IL-2 activity may favor the development of autoimmune diseases such as multiple sclerosis.

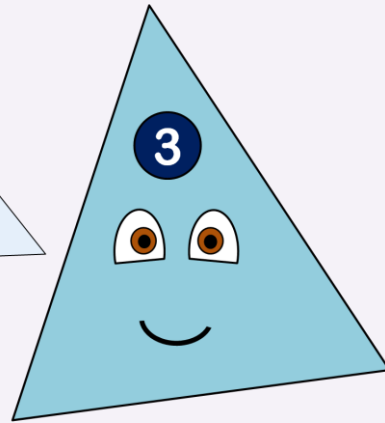
IL-2 activates T lymphocytes in patients receiving an allogeneic transplant, favoring the rejection of foreign tissue. In this context, anti-IL2Rα monoclonal antibodies (e.g. daclizumab, basiliximab) reduce rejection risk.

Denileukin diftitox (recombinant IL-2 joined to Diphtheria toxin) is a compound that can be useful in T cell neoplasms.



Mili, the interleukin 3

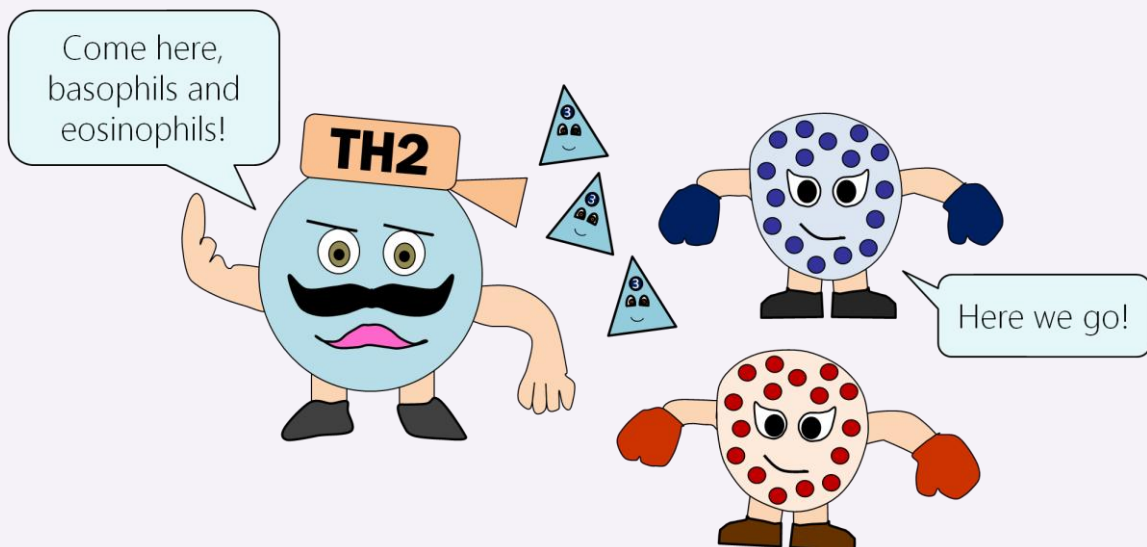
You want to call basophils and eosinophils? I have that ability! In addition, I help to produce several hematopoietic cells.



IL-3 is a hematopoietic growth factor that stimulates the production of several blood cell lineages. It also has the ability to activate basophils and eosinophils.

Where is Mili produced?

Mili is produced by T lymphocytes, especially TH2 cells, macrophages, NK cells, certain stromal cells, mast cells and eosinophils.



Are there people who cannot produce IL-3?

So far, human beings with clinically relevant mutations in the IL-3 gene have not been described

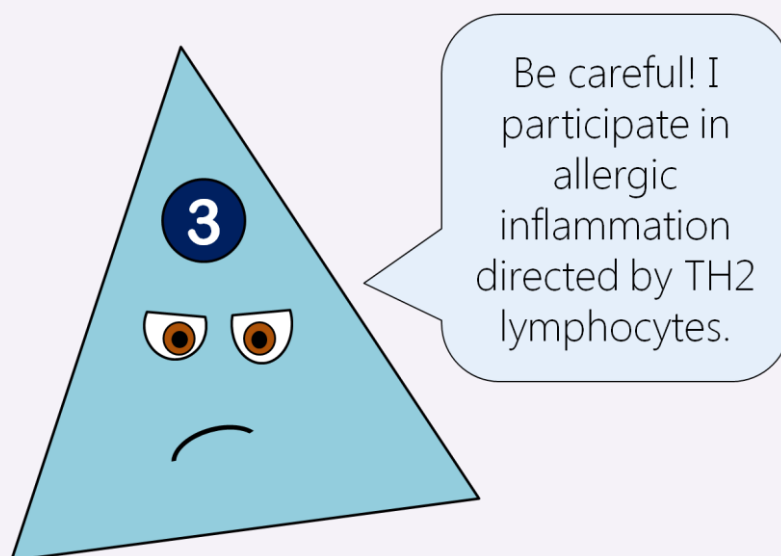
However, genetically modified mice deficient in IL-3 could have a reduction in the number of mast cells and basophils, as well as a decreased immune response to helminth parasites (e.g. *Strongyloides venezuelensis*).

In patients with cancer-related myelosuppression, the application of IL-3 as a stimulant of hematopoiesis has been investigated.

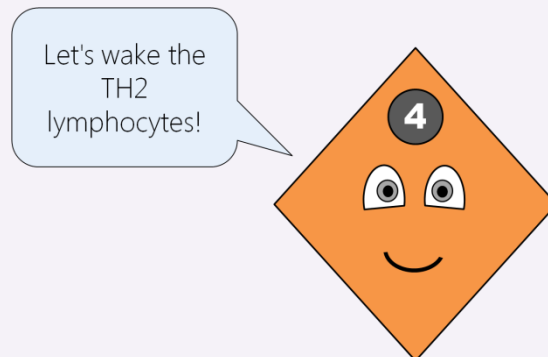
Are there people who fabricate IL-3 in excess?

Yes. In individuals with IgE-mediated allergic diseases (e.g. allergic rhinitis, bronchial asthma), TH2 lymphocytes recruit inflammatory basophils and eosinophils through the production of IL-3 and other cytokines.

Currently, IL-3 is not considered a therapeutic target for allergic diseases.



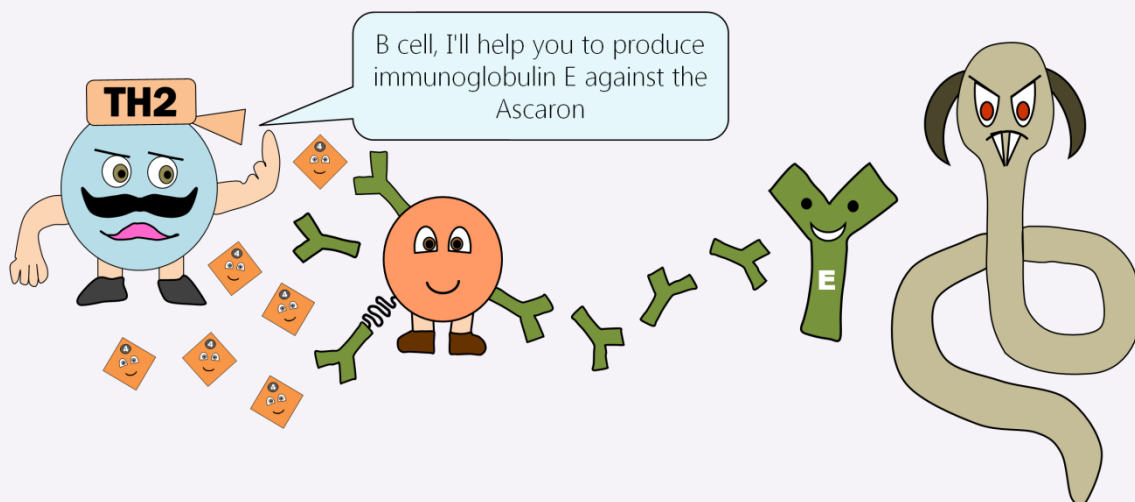
Sabri, the interleukin 4



Sabri is a cytokine that induces TH2 immunity through 2 receptors:
a) type 1 receptor, formed by IL-4R α chain and the common gamma chain;
b) type 2 receptor, formed by IL-4R α chain and IL-13R α chain (IL-13 also signals through this type 2 receptor).

Where is Sabri produced?

The main sources of IL-4 are TH2 lymphocytes, type 2 innate lymphoid cells (ILC2), basophils, mast cells and eosinophils. Sabri strengthens our TH2 army against helminths and other extracellular parasites by inducing the development of TH2 lymphocytes and the secretion of IgE from B lymphocytes.



Are there people who cannot produce IL-4?

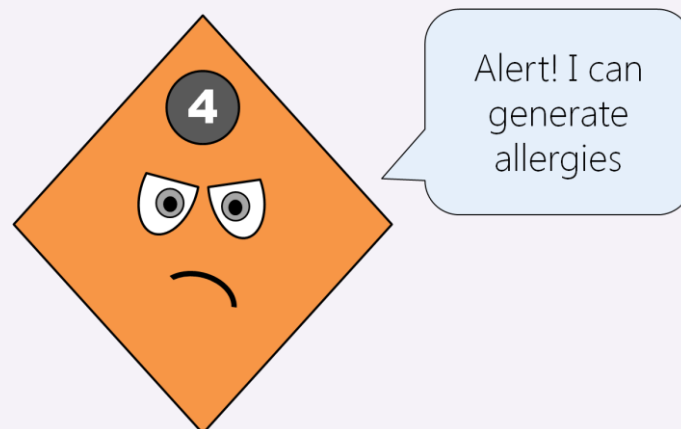
No human immunodeficiencies have been described because of the absence of IL-4.

Are there people who fabricate IL-4 in excess?

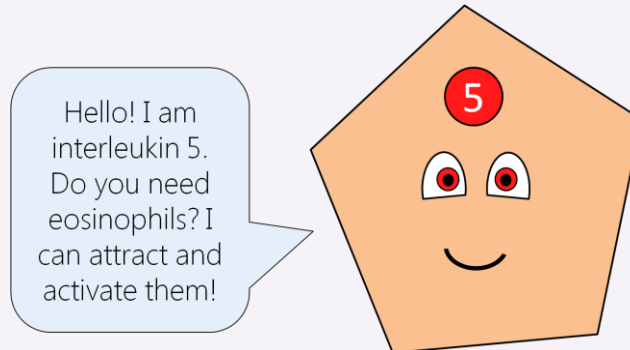
Yes, excessive production of IL-4 against molecules that should be tolerated favors the development of TH2 allergic diseases, such as allergic bronchial asthma, allergic rhinitis and atopic dermatitis.

In patients with these diseases, IL-4 and its receptor are therapeutic targets for novel drugs. For example:

- The drug Pitrakinra is a mutated recombinant version of IL-4 that binds to the IL-4R α subunit, thereby blocking the action of interleukins 4 and 13.
- Pascolizumab is a humanized anti-IL-4 monoclonal antibody investigated as an asthma therapy.
- The monoclonal antibody Dupilumab is directed against the IL-4R α subunit of the IL-4 receptor. It blocks the activity of IL-4 and IL-13, becoming one of the most promising drugs for the treatment of TH2 allergies.



Ale, the interleukin 5

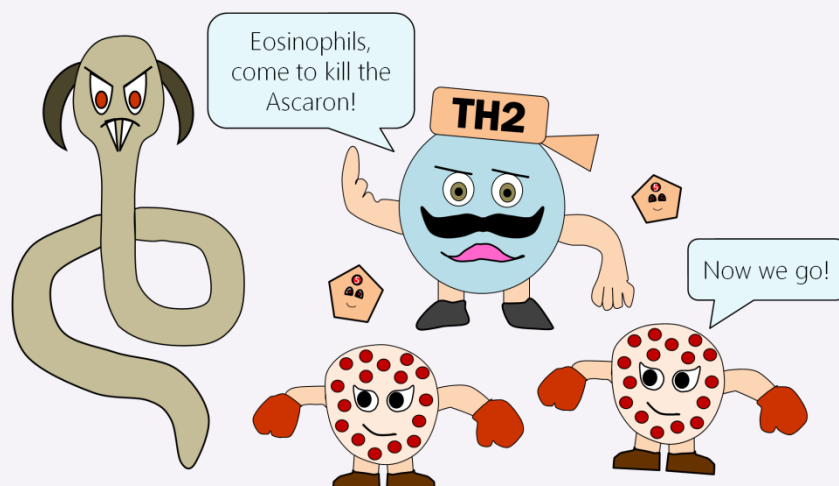


IL-5 belongs to the group of TH2 cytokines. Its receptor is a heterodimer formed by an alpha chain (IL-5R α) and a beta chain (β c). β c is also part of the IL-3 and GM-CSF receptor.

IL-5 is produced during the TH2 immune response against worms such as the Ascaron (*Ascaris lumbricoides*). This cytokine promotes the proliferation, activation, survival and adhesion of eosinophils. It also participates in tissue remodeling and repair.

Where is Ale produced?

Ale is produced mainly by CD4 TH2 lymphocytes, type 2 innate lymphoid cells (ILC2), activated eosinophils and mast cells.



Are there people who cannot produce IL-5?

Human immunodeficiencies due to the absence of IL-5 have not been described yet.

IL-5-deficient mice are more resistant to asthma induction and less able to expel the helminth *Nippostrongylus brasiliensis*.

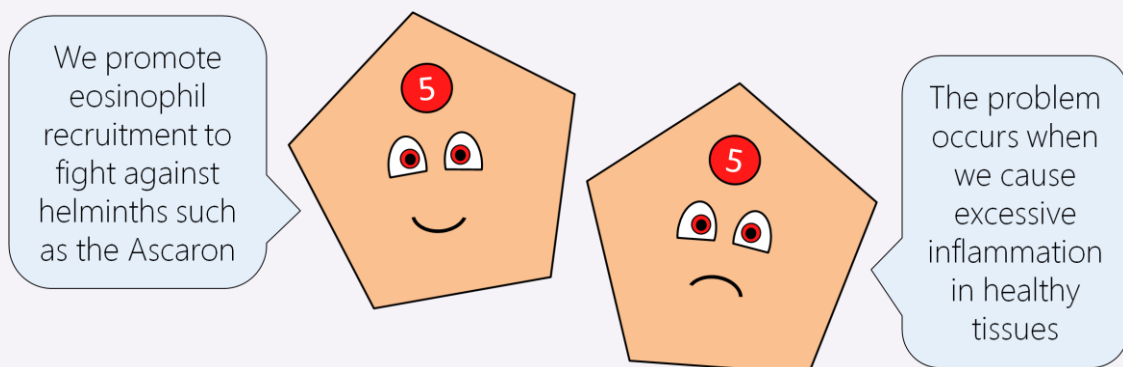
Are there people who fabricate IL-5 in excess?

Yes, excessive producción of IL-5 occurs in patients with:

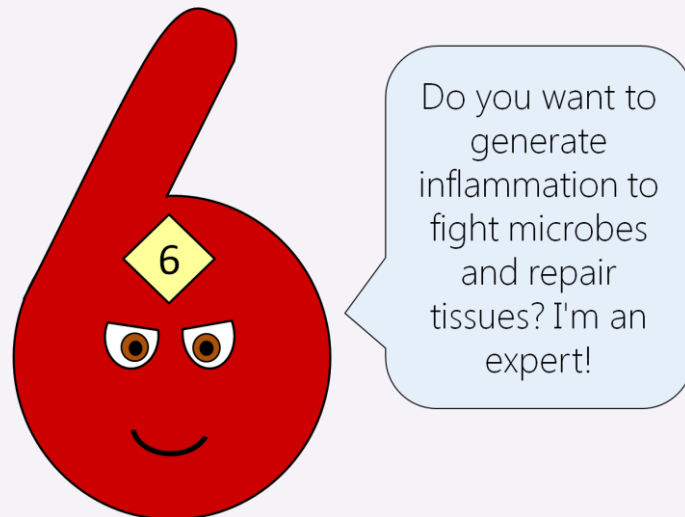
- Eosinophilic asthma, where eosinophils contribute to airway inflammation as well as tissue destruction and remodeling.
- Other eosinophilic diseases, such as eosinophilic esophagitis and gastroenteritis, hypereosinophilic syndromes, etc.).

In these inflammatory diseases, IL-5 becomes a therapeutic target. For example:

- Anti-IL-5 monoclonal antibodies (Mepolizumab and Reslizumab) are potentially beneficial for patients with eosinophilic diseases.
- Benralizumab, a monoclonal antibody directed against IL-5R α , has the same potential.



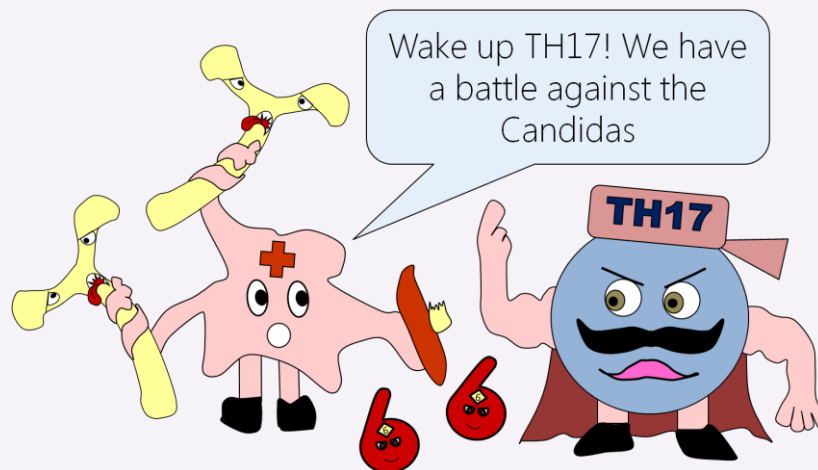
Lucy, the interleukin 6



Lucy belongs to the family of cytokines 'IL-6-type', which includes leukemia inhibitory factor, ciliary neurotrophic factor and oncostatin M. Its receptor consists of an IL-6 binding chain (IL-6R α) and the signaling component gp130.

Lucy is a multifunctional cytokine with essentially inflammatory actions:

- Stimulates hepatic production of acute-phase reactants.
- Induces hematopoiesis.
- Recruits and activates phagocytes.
- Induces the differentiation and activation of T and B cells.
- Promotes the differentiation of T CD4 lymphocytes into TH17 lymphocytes, the commanders of our immune army against extracellular fungi and bacteria such as *Candida albicans* and *Staphylococcus aureus*.



Where is Lucy produced?

Lucy is produced by macrophages, endothelial cells and fibroblasts.

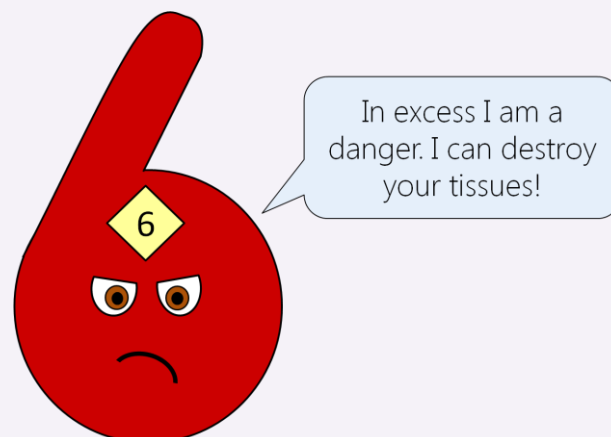
Are there people who cannot produce IL-6?

Some individuals produce neutralizing antibodies against IL-6, becoming susceptible to infections by *Staphylococcus aureus*.

Are there people who fabricate IL-6 in excess?

Yes, excess production of IL-6 occurs in patients with certain autoimmune or autoinflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus.

Patients affected by these diseases may improve with Tocilizumab, a monoclonal antibody against the IL-6 receptor.



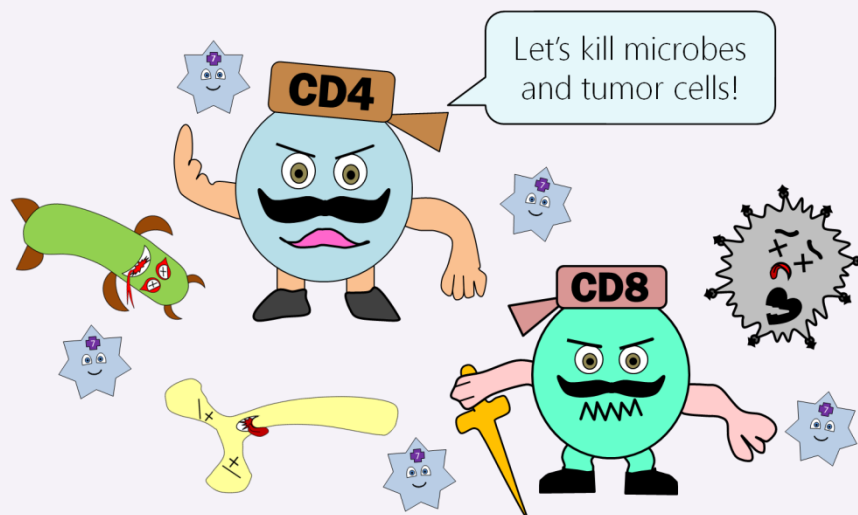
Betsy, the interleukin 7



The main function of IL-7 in humans is to activate T lymphocytes. Betsy acts through its receptor composed of an alpha chain (IL-7R α or CD127) and the common gamma chain (γ c or CD132).

Where is Betsy produced?

IL-7 is synthesized by dendritic cells, B lymphocytes, monocytes/macrophages and epithelial cells including keratinocytes. Betsy induces the development, proliferation and survival of T lymphocytes. It also favors the development and maintenance of innate lymphoid cells (ILCs).



Are there people who cannot produce IL-7?

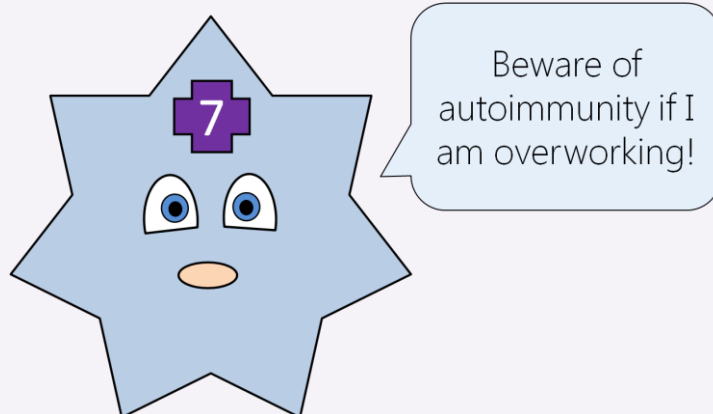
Patients with genetic defects in IL-7R α cannot fabricate T lymphocytes, resulting in severe combined immunodeficiency (SCID) with susceptibility to all types of infections. The problem is even greater in children with genetic mutations in γc , who cannot produce NK cells neither. Children with SCID need urgently a hematopoietic stem cell transplant or gene therapy to survive.

Human recombinant IL-7 can empower T lymphocytes in patients with cancer, AIDS, chronic viral infections, or post-transplant immunodeficiency.

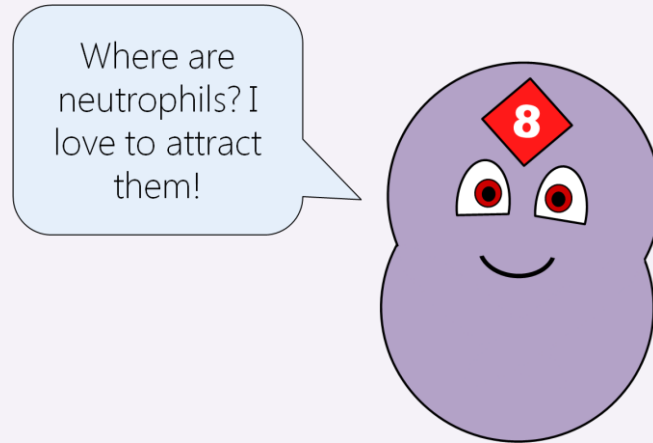
Are there people who fabricate IL-7 in excess?

Excessive activation of T lymphocytes induced by IL-7 can occur in several autoimmune and inflammatory diseases such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis, sarcoidosis or graft-versus-host disease.

Could IL-7 be a therapeutic target in these diseases? Probably yes. The problem would be the immunodeficiency generated by blocking the action of IL-7.



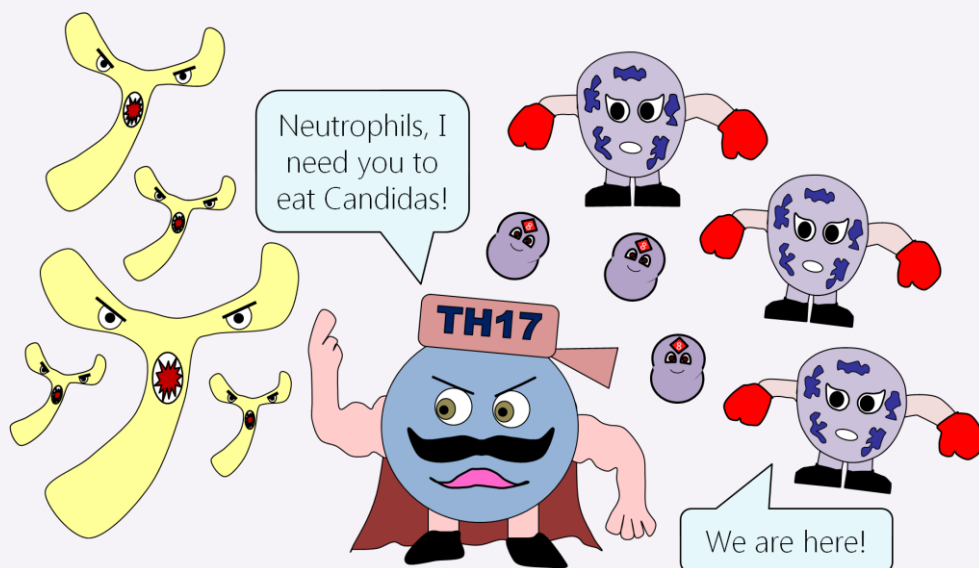
Silvia, the interleukin 8



Silvia belongs to the CXC chemokine family. It acts through its receptors CXCR1 (IL-8RA) and CXCR2 (IL-8RB).

Where is Silvia produced?

Several cells make IL-8 (macrophages, lymphocytes, neutrophils, endothelial and epithelial cells), especially after stimulation with IL-1 α , IL-1 β , IL-17 or TNF- α . Its main function is to recruit neutrophils to sites of infection or damage. It can also attract T and NK lymphocytes, basophils and eosinophils. It promotes angiogenesis.



Are there people who cannot produce IL-8?

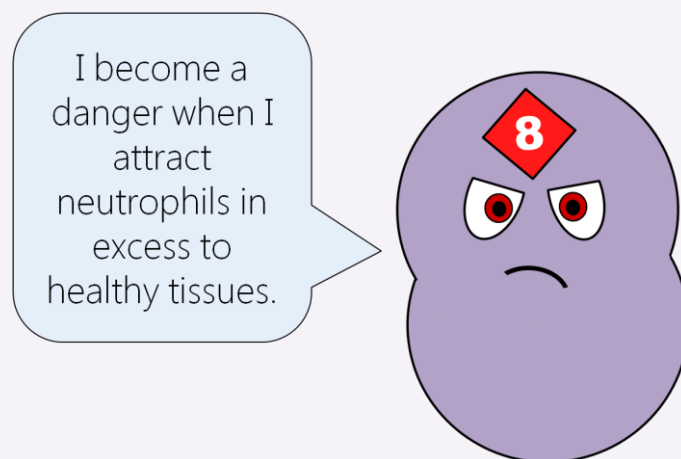
Genetic defects affecting TH17 immunity (e.g. STAT1 gain-of-function, CARD9 deficiency) reduce the ability to synthesize IL-8 and recruit neutrophils, leading to increased susceptibility to infections by extracellular fungi and bacteria.

Are there people who fabricate IL-8 in excess?

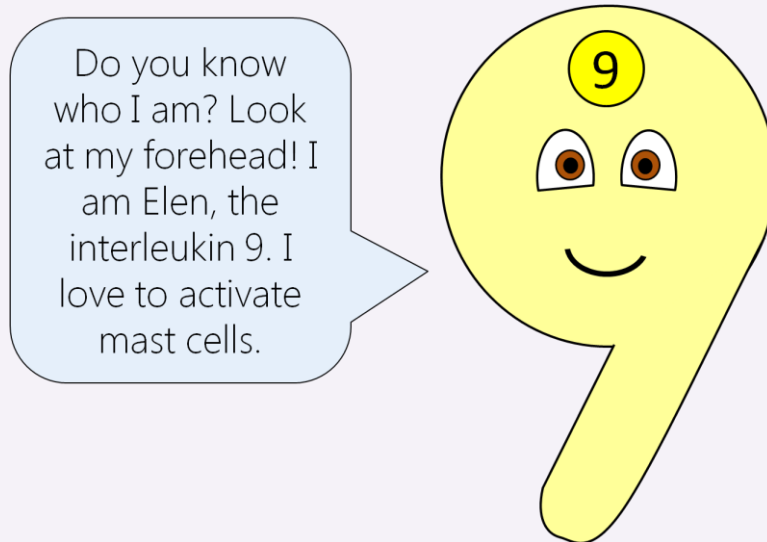
Yes. Excessive production of IL-8 generates damage. This occurs in chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, chronic obstructive pulmonary disease (COPD), neutrophilic asthma and various neoplasms.

Clinical trials with anti-IL-8 monoclonal antibodies (HuMax-IL-8, ABX-IL-8) have been performed in inflammatory diseases such as palmoplantar pustulosis, COPD and cancer. Theoretically, any disease where tissue damage is caused by neutrophils could improve antagonizing the action of IL-8.

Polymorphisms in the IL-8 gene may increase the risk of atrophic gastritis and gastric cancer caused by a local excess of IL-8 and neutrophilic infiltration.



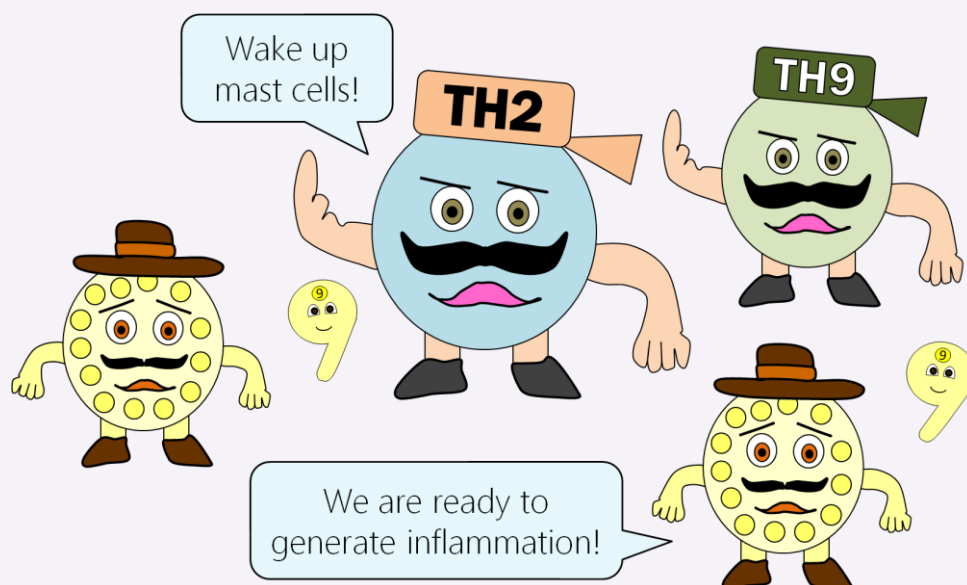
Elen, the interleukin 9



IL-9 is a proinflammatory cytokine whose receptor is formed by an IL-9R α chain and the common gamma chain (γ c).

Where is Elen produced?

Elen is mainly synthesized by TH2 and TH9 lymphocytes, type 2 innate lymphoid cells (ILC2), mast cells and eosinophils.



The main action of IL-9 is to stimulate the production and activation of mast cells. In addition, it increases secretion of mucus by epithelial cells and favors IgE synthesis.

Physiologically, these actions promote immediate inflammation and activation of our TH2 army to combat helminth parasites.

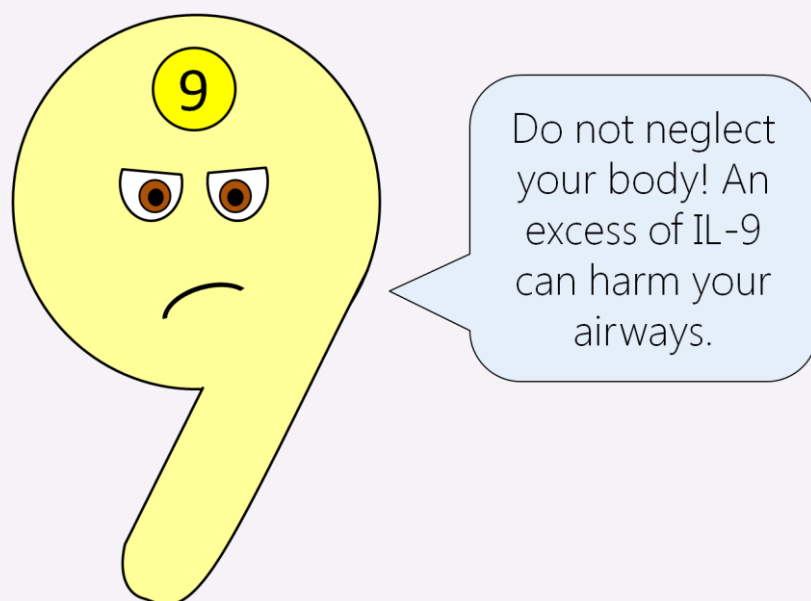
Are there people who cannot produce IL-9?

Patients with clinically significant defects in the IL-9 gene have not been described.

Are there people who fabricate IL-9 in excess?

Unfortunately yes. In patients with IgE-mediated allergic diseases (eg, allergic rhinitis, bronchial asthma), TH2 and TH9 lymphocytes, as well as ILC2, activate mast cells through IL-9 and other related cytokines.

The therapeutic effect of an anti-IL-9 monoclonal antibody is being investigated in patients with bronchial asthma.



Ruth, the interleukin 10

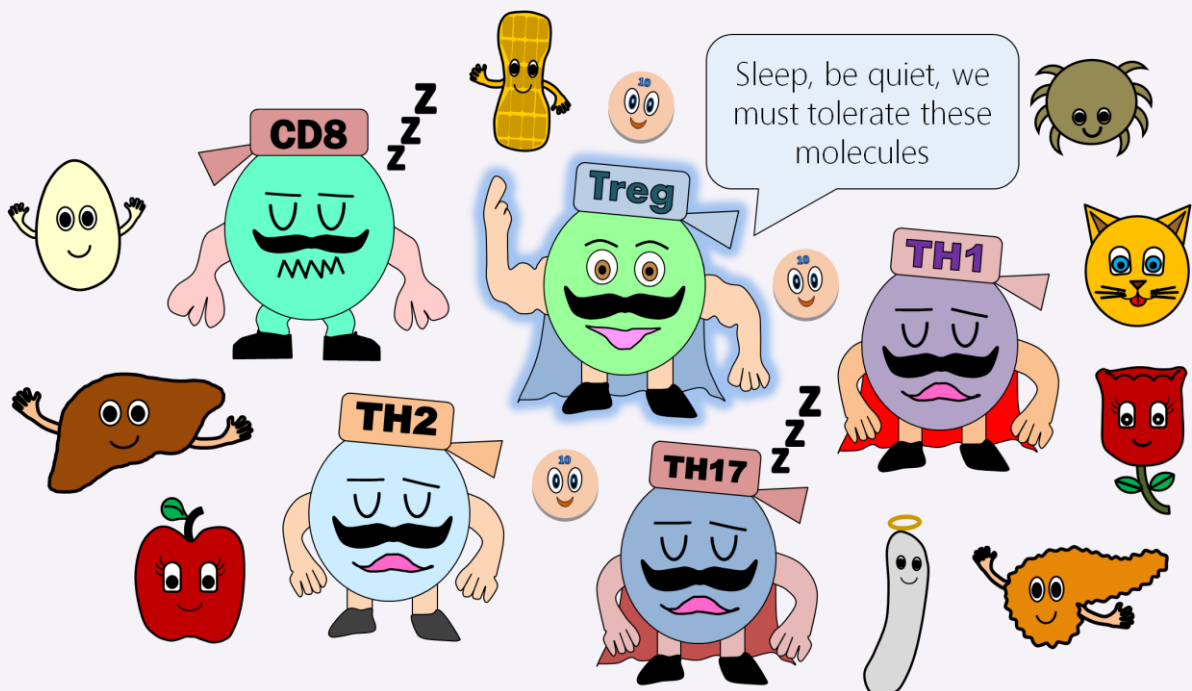
I am Ruth,
interleukin 10. I
protect you from
inflammation and
induce immune
tolerance



IL-10, acting on its IL-10R1/IL10R2 receptor, is an anti-inflammatory and regulatory cytokine. Together with other cytokines (IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, IL-29), they compose the IL-10 family.

Where is Ruth produced?

IL-10 is synthesized by monocytes, dendritic cells and lymphocytes, particularly by the regulatory cells TR1 and B10.



Ruth has several immunoregulatory actions. For example:

- Induces dendritic cells to a tolerogenic phenotype (↓ HLA class II molecules, ↓ proinflammatory cytokines, ↓ costimulatory molecules CD80 and CD86).
- Promotes the differentiation of T regulatory lymphocytes (TR1) and inhibits T effector lymphocytes (TH1, TH2, TH17).
- Stimulates synthesis of IgG4 by B lymphocytes.

Are there people who cannot produce IL-10?

Children with genetic defects in IL-10 or its receptor (IL-10R1/IL-10R2) suffer severe early-onset inflammation (inflammatory bowel disease with perianal fistulas, folliculitis, arthritis).

A local defect in IL-10 expression may favor the development of intestinal inflammation, autoimmunity (e.g. rheumatoid arthritis, lupus), allergies (e.g. allergic rhinitis), and neoplasms. The effect of recombinant IL-10 on these pathologies is being tested.

Are there people who fabricate IL-10 in excess?

Theoretically, local excess of IL-10 would facilitate the spread of infections and cancer. However, in real life, recombinant IL-10 appears to be useful for the treatment of malignancies.



People who can not fabricate me are predisposed to severe inflammatory processes

Julia, the interleukin 11

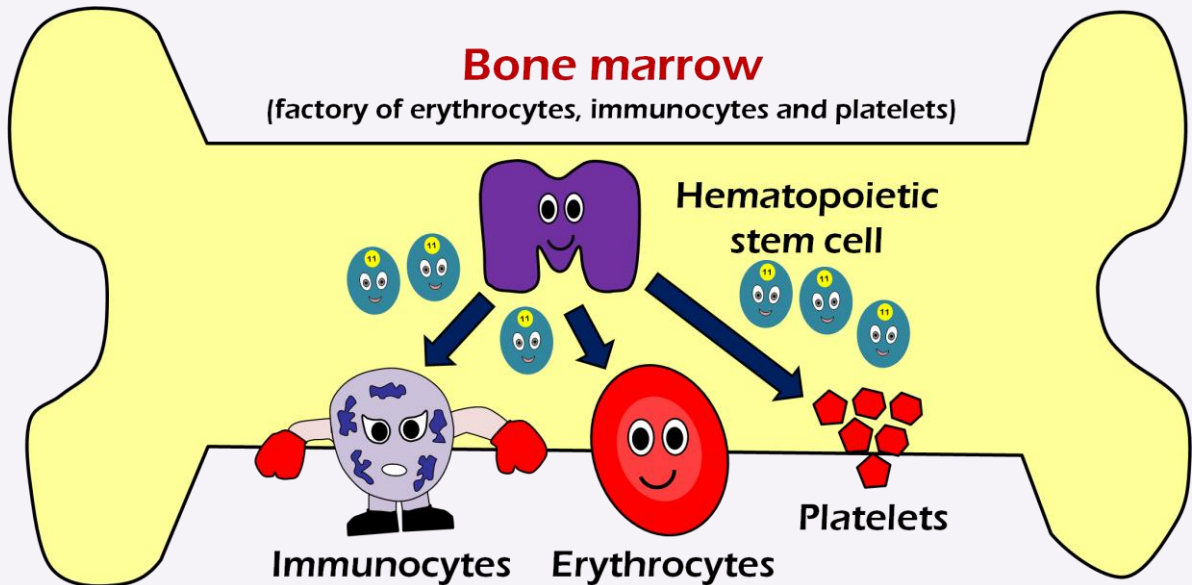


The IL-11 receptor is made up of 2 subunits: IL-11R α and gp130. Remind that gp130 is also part of the receptors of IL-6 and other proteins (ciliary neurotrophic factor, leukemia inhibitory factor, oncostatin M and cardiotrophin-1).

Where is Julia produced?

Various cells can make IL-11, such as stromal cells of the bone marrow, fibroblasts, epithelial cells, endothelial cells, synoviocytes and osteoblasts.

The main function of Julia, in synergy with IL-3, is to stimulate hematopoiesis, fundamentally platelet production. Other functions are: protection of epithelial cells and connective tissue, induction of acute phase proteins, neuronal development, bone remodeling by stimulating osteoclasts and inhibiting osteoblasts, and activation of B lymphocytes.



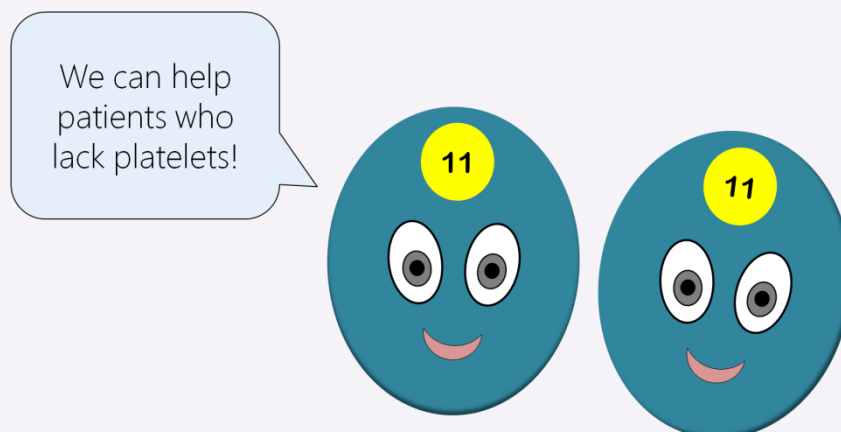
Are there people who cannot produce IL-11?

So far there are no reports of genetic diseases caused by the absence of IL-11.

Recombinant human IL-11 (Oprelvekin) stimulates platelet production and may be useful for patients with thrombocytopenia (e.g. post-chemotherapy).

Are there people who fabricate IL-11 in excess?

Certain polymorphisms in the IL-11 gene have been associated with ulcerative colitis and chronic obstructive pulmonary disease.



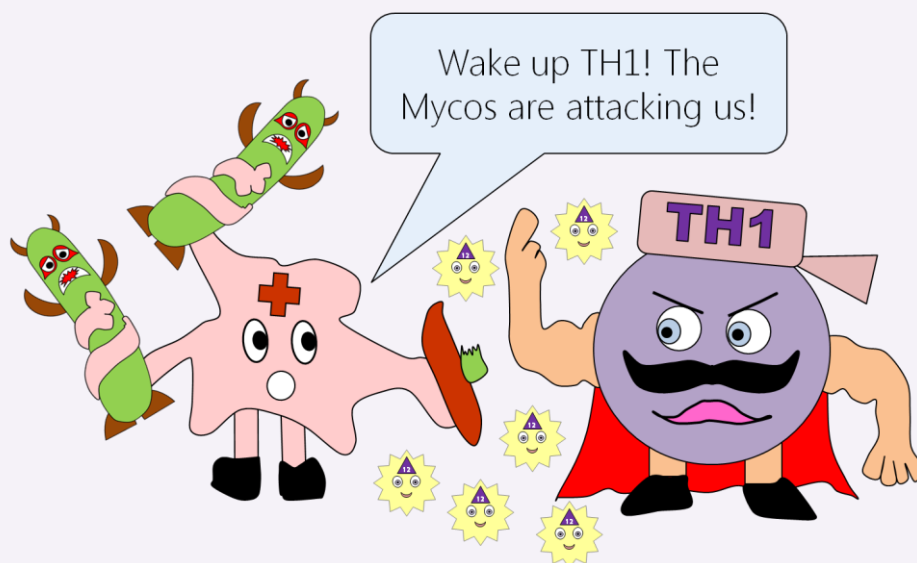
Bolli, the interleukin 12



The bioactive form of IL-12 (IL-12p70) has 2 subunits: p35 and p40. The p40 subunit is also part of IL-23. The IL-12 receptor has 2 chains: IL-12R β 1 (also makes up the IL-23 receptor) and IL-12R β 2 (is also part of the IL-35 receptor).

Where is Bolli produced?

IL-12 is mainly synthesized by monocytes, macrophages and dendritic cells. Its major function is to activate our TH1 army against intracellular microbes (e.g. mycobacteria, *Salmonella spp*, *Histoplasma spp*, virus, etc.) and tumor cells.



In addition to inducing the differentiation and maintenance of TH1 lymphocytes, Bolli is able to activate NK lymphocytes and type 1 innate lymphoid cells (ILC1). Activated TH1 and NK lymphocytes synthesize interferon-gamma (IFN- γ), thus enhancing the attack against intracellular microbes and malignant cells (IL-12/IFN- γ axis).

Are there people who cannot produce IL-12?

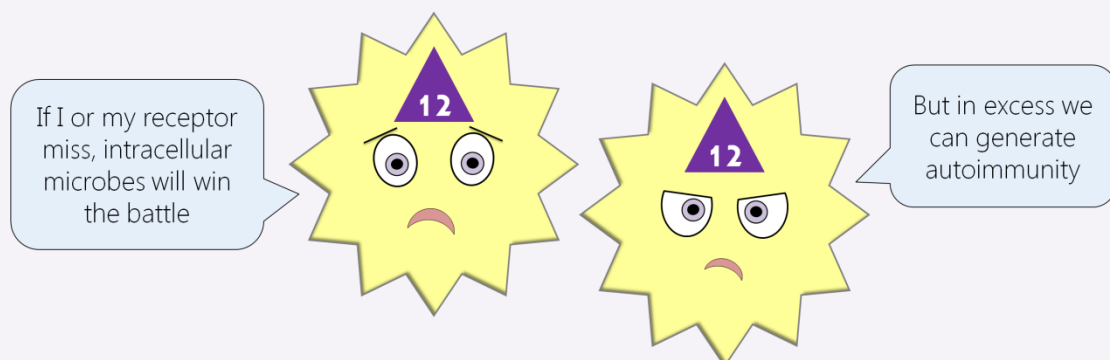
Yes. Patients with primary immunodeficiencies due to absence of IL-12p40 or IL-12R β 1 are susceptible to infections by intracellular microbes such as mycobacteria or Salmonella (Mendelian susceptibility to mycobacterial diseases). The same problem affects subjects with deficiency of IFN- γ or its receptor.

By enhancing TH1 immunity, recombinant IL-12 is a potential treatment for subjects with immunodeficiencies or cancer.

Are there people who fabricate IL-12 in excess?

Yes. Excessive activity of our TH1 army against self molecules can lead to the onset of autoimmune diseases.

Ustekinumab is a monoclonal antibody that neutralizes the p40 subunit of IL-12 and IL-23, thereby inhibiting the activation of TH1 and TH17 immunity, respectively. Therefore, this biologic drug has therapeutic potential for autoimmune diseases such as psoriasis.



In this book we have learned about the role of interleukins in the normal function of our immune system and in distinct immunological diseases (immunodeficiencies, autoimmunity, allergies, autoinflammation and cancer).

Do not miss our next educational books, where we will continue learning on the fantastic world of Immunology.

Juan Carlos Aldave, MD

Allergy and Clinical Immunology



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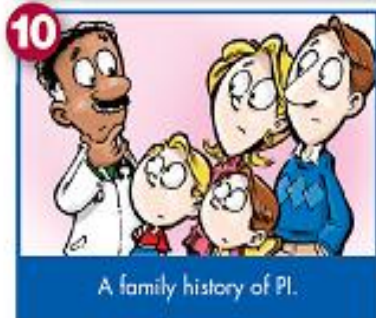
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"For God so loved the world that he gave his one and only Son, that whoever believes in him shall not perish but have eternal life". John 3:16

10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. **If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.**



"These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested. ©2013 Jeffrey Modell Foundation"

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Juan Carlos Aldave, MD

Allergy and Clinical Immunology

"Proper functioning of our immune system is essential for life. The purpose of this book series is to introduce everyone into the fantastic world of Immunology".

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- Book 3: The TH1 army against Mycobacteria
- Book 4: The TH2 army against worms
- Book 5: The battle against Pneumococcus
- Book 6: Los Inmunocitos contra el cáncer
- Book 7: T regs: controlling the immune army
- Book 8: When the Immunocytes get sick...
- Book 9: When the Immunocytes go crazy...
- Book 10: The Immunocytes and transplantation
- Book 11: The armor of the Immunocyte Felix
- Book 12: The fantastic Interleukins

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