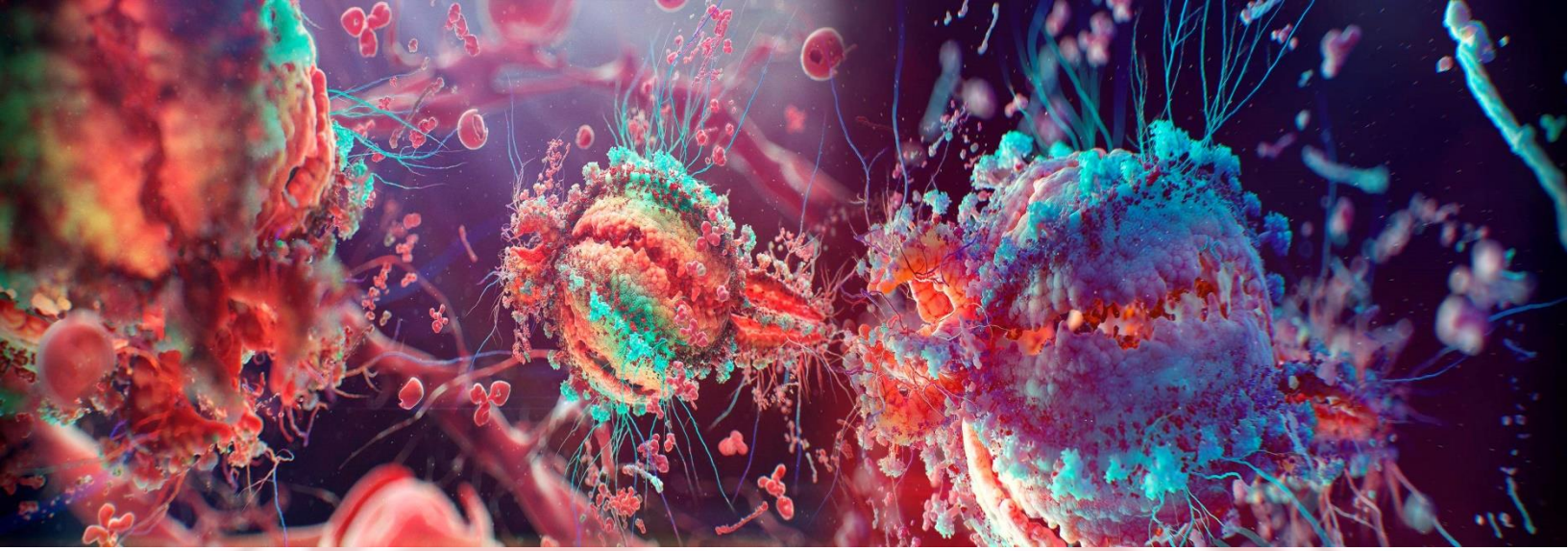


Immunology

Lecture (10)

Done by:
Ala Alrwashdeh

Today we will revise cytokines and talk about their functions because it is an important part of the immune system, when we talk about the innate there were cytokines, in inflammation there are cytokines, B and T cells there are cytokines, sp today we will talk about the function of cytokines in the immune system.

Definition

A group of low molecular weight polypeptides or proteins which are secreted by activated immunocytes or some matrix cells and possess high activity and various functions.
So let's focus in each word of this definition
So firstly we talked that it is a low molecular weight, so it has a small size.
And we said that it is a polypeptide or proteins, so its structure is a polypeptide or protein
Its usually secreted by immunocytes or some matrix cells.
It has a small size but it has a strong effect and it usually has multifunctions.
So can we have one cytokine with more than one function?

- **Yes**

Cytokine or immunocytokine is a generic name used to describe a diverse group of soluble proteins and peptides which act as humoral regulators at the nano- to- picomolar concentrations.

So, for cytokines, they can do their function with a very small concentration.

Their major functions are to mediate and regulate immune response and inflammatory reactions.

So cytokines regulate the immune system response, they can activate or inhibit it.

General Properties

Most cytokines are low molecular weight polypeptides or glycoprotein (8~80 KD), and most of them are monomers.

Natural cytokines are secreted by activated cells such as activated immune cells, matrix cells and tumour cells.
Even some viruses can secrete cytokines, so the original place for the secretion of cytokines in the immune cell (innate/adaptive), also other cells like matrix cells, tumour cells and viruses.

Why do the matrix cells and tumour cells secrete cytokine?

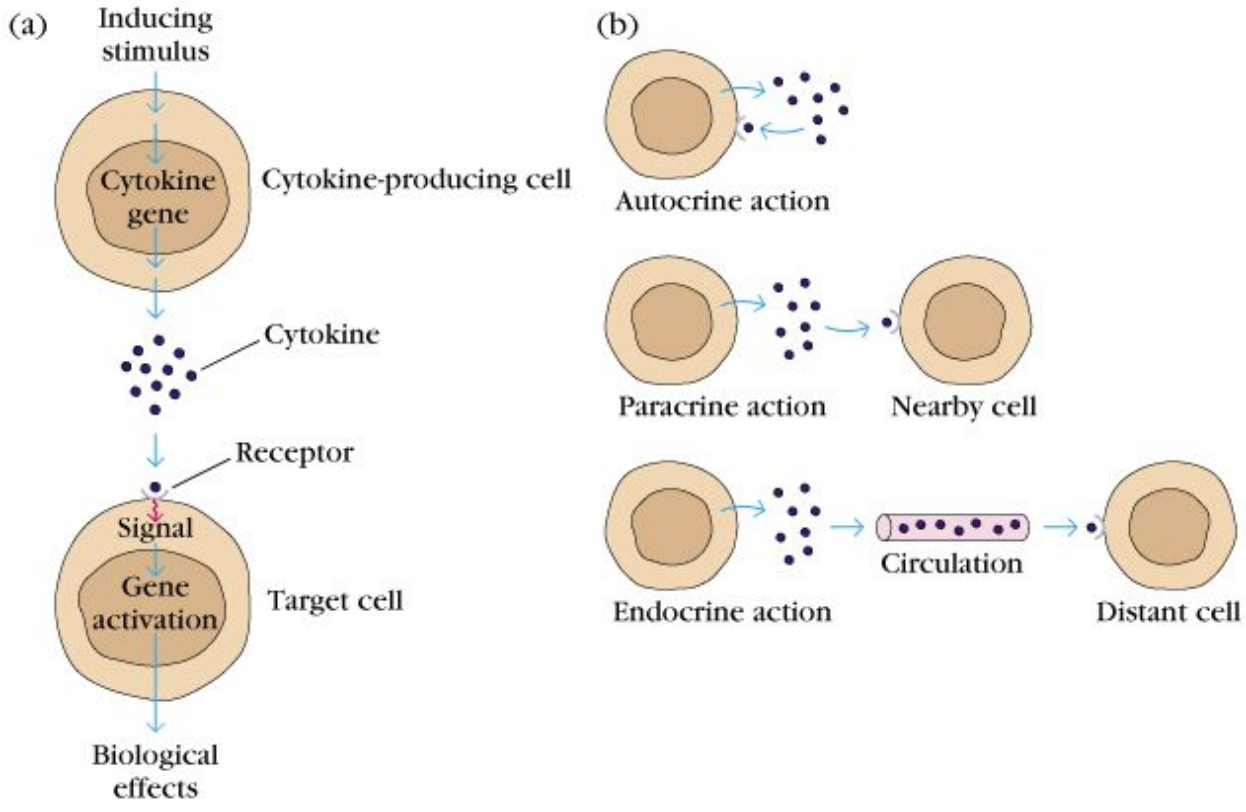
Matrix cells and tumour cells want to inhibit the immune system to protect themselves, so they use cytokines to inhibit the immune system.
For example, we can take Epstein–Barr virus (which cause infectious mononucleosis, Burkitt's lymphoma, Hodgkin's lymphoma, stomach cancer, nasopharyngeal carcinoma, multiple sclerosis, and lymphomatoid granulomatosis) his target cell is B cell, so the immune cells try to kill him, so he secretes IL-10 which is an inhibitory cytokine (shut down the immune system).

One kind of cytokines can be produced by different cells. One kind of cells can secrete different cytokines.
Cytokines initiate their actions by binding to specific membrane receptors on target cells.
So cytokines bind with their receptor and this will lead to signalling and activation.

Cytokines can act on the cells that produce them (autocrine), on other cells in the immediate vicinity (paracrine), or on cells at a distance (endocrine) after being carried in blood or tissue fluids.
1-cytokines can act on their own cell, we mean that cell secretes the cytokines and those cytokines bind to this cell receptor, we call this autocrine. IL-2 by T cell (its receptor is CD25)

2-Cytokine can also bind to the near cells and we call this paracrine.

3-Cytokines bind to cells at a long distance, (like hormones) and we call this endocrine.



Cytokines names

Interleukins - produced exclusively by leukocytes (interleukins leukocytes)

Lymphokines - produced by lymphocytes(lymphokines lymphocytes)

Monokines - produced exclusively by monocytes

Interferons - involved in antiviral responses (it is secreted mainly by DCs, NKs, etc)

Colony Stimulating Factors - support the growth of cells in semisolid media. (it makes bone morrow produce specific cells) such as erythropoietin

Chemokines - promote chemotaxis (we talked about it previously)

Effects of Cytokines

- **<u>Pleiotropism</u> refers to the ability of one cytokine having multiple effects on diverse cell types.**

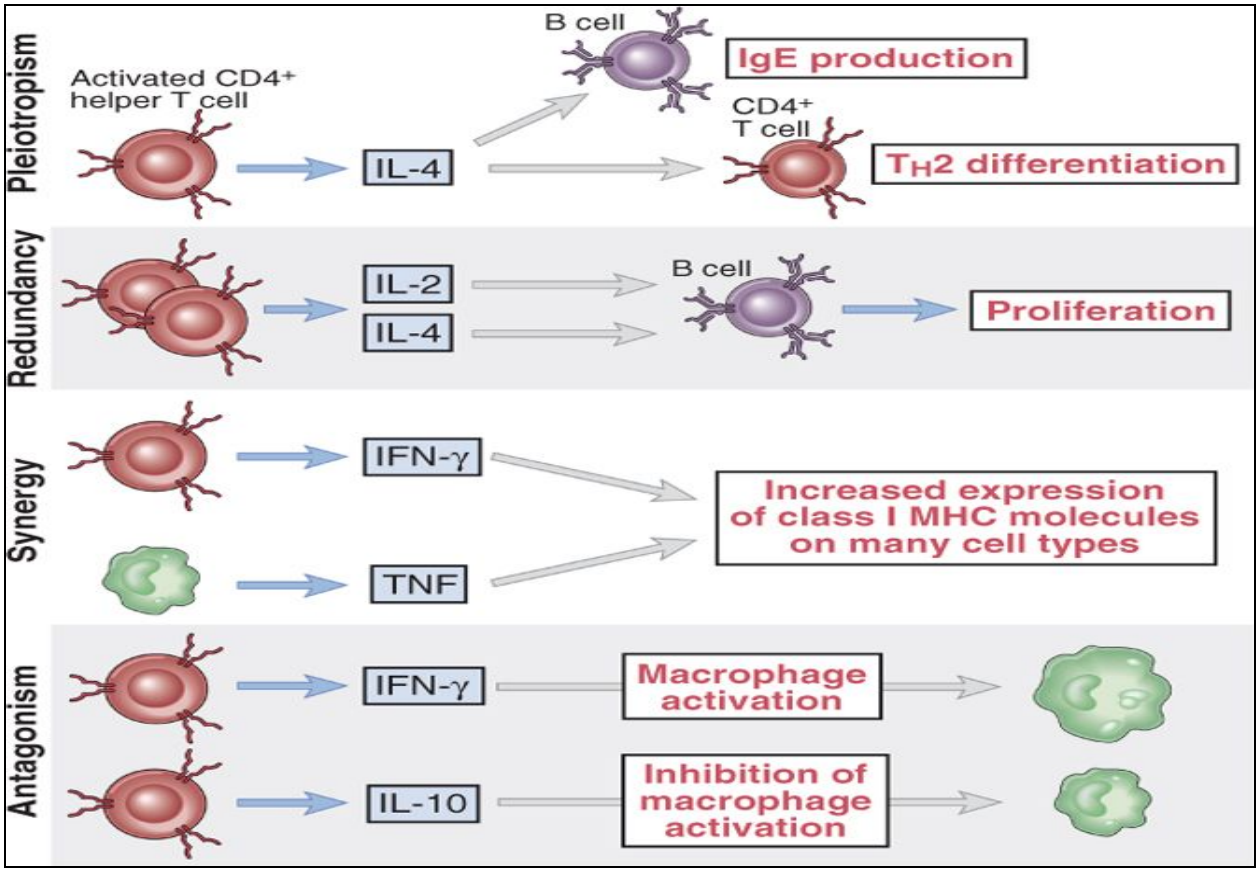
We mean by this that we have one cytokine but can do multiple effects.

- **<u>Redundancy</u> refers to the property of multiple cytokines having the same or overlapping functional effects.**
- **<u>Synergy</u> refers to the property of two or more cytokines having greater than additive effects.**

We remember what synergy means, (1+1=3)

- **<u>Antagonism</u> refers to the ability of one cytokine inhibiting the action of another.**

Example:IL10: Suppresses inflammatory responses



Cytokine General Actions

Can anyone remember what are the cells that play a role in the inflammation?
TNF IL1/IL6/IL8
Can anyone remember what are the cells that play a role in the innate immune system?
IL2/IL4/IL5/IFN-γ
Can anyone remember what are the cells that play a role in B cell activation?
IL1/IL2/IL4
Can anyone remember what are the cells that play a role in T cell activation?
IL2/IL4/IL5

- **Development of cellular and humoral immune responses. (B and T)**
- **Induction of inflammation**
- **Regulation of hematopoiesis (IL3/ IL7/CSF)**
- **Control of cellular proliferation and differentiation (IL2)**
- **Induction of wound healing**
- **Chemotaxis**

Classification of cytokines

- **Interleukin, IL secreted by leukocytes**
- **Interferon, IFN**
- **Tumour necrosis factor, TNF**
- **Colony-stimulating factor, CSF**
- **Chemokine**
- **Transforming growth factor**

Interleukins IL

They are a large group which contains more than 33 types, but we will focus on the main types.

Cytokines secreted by leukocytes that have the ability to act as signal molecules between the different population of leukocytes.

IL1-IL29

Th1 secrete IL-2

Th2 secrete IL-4,IL-5

Th3/Treg secrete IL-10

Th17 secrete IL17

Th1 it initiates inflammation by bringing macrophages and neutrophil usually mediated by IFN-γ

Th2 bring mast cell and basophil (allergy cells)

Th17 it is for extracellular and fungi

So why we put 17 in this Th? Because it secretes IL17

Interferon (IFN)

A group of glycoproteins produced by human or animal cells following the infection of virus and exposure to various inducing agents.

They are divided into

IFN-α produced by leukocyte

IFN-β produced by Fibroblasts, the fibroblast is not an immune cell, so IFN-β is an example for cytokine produced by non-immune cell

IFN-γ type 2 produced by T cells (TH1, CD8+ T cells), NK cells

Alfa and beta are from the same type (type 1)

Their function

Alfa: anti-virus, immune regulation, when we say immune regulation in alfa we mean activation.

Beta: antitumour

Gama: weak anti-virus effect, stronger immune regulation effect (activation) and antitumour

What is the most powerful one against viruses? Alfa

What is the most powerful one against tumour? Beta

What is the most powerful in the regulation of the immune system? Gama

	Types	Produced cells	Main functions
IFN-α	Type I	leukocyte	anti-virus, immune regulation
IFN-β	Type I	fibroblast	anti-tumour
IFN-γ	Type II	Th1, NK	weaker anti-virus effect, stronger immune regulation effect, anti-tumour

Tumour Necrosis Factor (TNF)

We can figure out its function from its name, necrosis for tumour tissues.

TNFs were originally thought of as selective antitumour agents, but are now known to have a multiplicity of actions.

TNF-α is produced mainly by LPS activated monocytes and macrophages.

LPS=lipoploysaccharide is secreted by the gram-negative bacteria, we said that gram-negative bacteria is worse than other types because of many reasons one of them is secretion of LPS, so LPS activate TNF-alfa which cause a shock-like state.and this cause fatigue and high temperature and other symptoms, for that we see the fatigue and fever symptoms in the infection of gram-negative bacteria, gram-positive bacteria infection doesn't contain these symptoms because it doesn't produce LPS.

TNF-β is produced mainly by activated Th0 and Th1.(we have already taken this in the last lectures)

Colony-Stimulating Factors (CSF)

Cytokines that stimulate proliferation or differentiation of pluripotent hematopoietic stem cell and different progenitors.

- **Multi-CSF (IL-3), we call (multi) because it can stimulate many cells, such as (IL-3).**
- **Granulocyte macrophage-CSF (GM-CSF), activation of macrophages.**
- **monocyte -CSF (M-CSF), activation of monocytes.**
- **Granulocyte-CSF (G-CSF), activation of granulocyte.**
- **Stem cell factor (SCF), activation of stem cells.**
- **erythropoietin (EPO), activation of bone marrow to produce RBCs.**

Chemokine

Chemokines are cytokines which recruit monocytes, granulocytes and lymphocytes in the blood to the sites of inflammation.
We call them chemoattractants

They are divided into 4 groups:
C=Cystine X=other amino acids

- **CXC chemokines (α subgroup)**

2 Cystines with 1 other amino acid

- **CC chemokines (β subgroup)**

2 Cystines

- **C chemokines (γ subgroup)**

1 Cystine

- **CX*3C chemokines (δ subgroup)**

2 Cystines and 3 other amino acids

Transforming Growth Factor

Growth-factor is cytokines which stimulate the growth of their target cells.

- **Transforming growth factor-β (TGF- β) increase the growth of all cells even tumour cells.**
- **Epithelial growth factor (EGF)**
- **Vascular endothelial cell growth factor (VEGF)**
- **fibroblastic growth factor (FGF)**

CK receptor

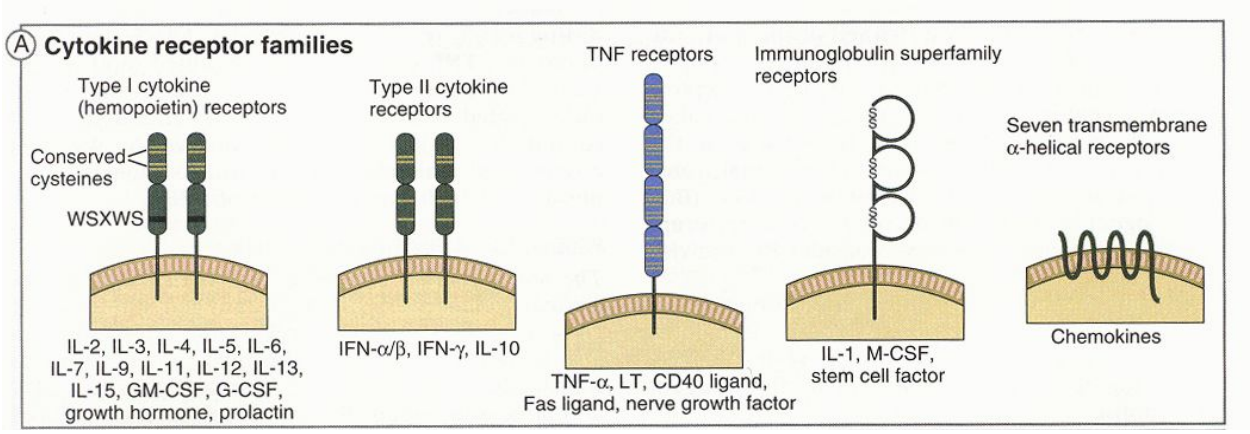
We said that cytokines work by binding to its receptor which is called Membrane-binding cytokine receptor.
The receptor consists of the extracellular region, trans-membrane region and cytoplasmic region.

What is the function of the extra-cellular region?
Binding
What is the function of the trans-membrane region?
Hold the cytokine
What is the function of the cytoplasmic region?
Signalling

CK receptors can be grouped into five families according to structure and function:

- **Ig receptor superfamily**
- **Type I cytokine receptor superfamily**

- **Type II cytokine receptor superfamily**
- **Type III cytokine receptor superfamily**
- **G protein-linked receptor superfamily**



حبايبي لازم تحفظوا الcytokines تحت كل receptor, مهمين كتيييير.

Look at Ig receptor superfamily, it is similar to antibody shape it has circles.

We have a specific type for the chemokines, we should remember how the cytokines structure is, its structure has cystines so this will fit the chemokines.

Functional Categories

- **Mediate/regulate innate immunity**

TNF, IL-1, IL-12, IFN type1, IL-10

- **Mediate/regulate adaptive immunity**

IL-2, IL-4, IFN-γ, TGF-β

- **Stimulate hematopoiesis**

IL-3, IL-7

Specific Interleukins Functions

- **IL1: Play a role in inflammation, binds with Ig receptor superfamily**
- **IL2: Growth factor for B and T cells (clonal expansion)**
- **IL3: Haematopoetic growth factor which stimulates colony formation of blood cells**
- **IL4: help in the development of Th2 cells from naïve Th cell. Stimulates Ig class switch from IgG1 to IgE.**
- **IL5 Produced by Th2 cells and aids in the growth and differentiation of eosinophils. (in the past lecture we didn't talk about IL5 role in the differentiation of eosinophils.**
- **IL6: (inflammation) acute phase response, what we mean by acute phase response?**

It initiates a systemic effect and stimulates the liver to produce inflammatory markers such as CRP.

- **IL10: Suppresses inflammatory responses and Inhibits production of IFN-γ, IL-2, IL-3, TNFα, GM-CSF**

We need all of this information to know the cytokines, and it is not an easy thing, what the importance of knowing the function and the structures for the cytokines?

1- we need it in drugs, to stop the inflammation we can give the patient anti IL1.

2- to stimulate the killing of the viruses, I give him IFN-alfa

3- if I want to work on a tumour, I give him IFN-beta

4- if the patient has an autoimmune disease, I give him IL10

5- if the patient's white bone marrow doesn't produce WBC, I give him IL3

But unfortunately all of these uses we can't use them in real life, because of many circumstances:

1- receptors need to activation. Such as IL2 and its receptor CD25

2- the similarities in the function between ILs, so if we give the patient anti IL1 to stop the inflammation there are other inflammatory ILs such as IL6.

3- the environment of the immune system.

4- until now, there is no disease caused by the absence of one cytokine because of redundancy.

so, we said that we can't diagnose disease by the cytokines, so how can we know their function by knock-out mouse or immunological blocking (block receptors).

However, there are many functions for cytokines in the treatment of some diseases, such as:

- **Erythropoietin (EPO): anaemia associated with kidney disease.**
- **In chemotherapy, we shut down the bone marrow because we have a genetic issue in the bone marrow which cause to produce abnormal cells, so we shut it down for a while to produce a new generation of normal cells.**

When do we decide to do a bone marrow transplant?

- **When we have leukaemia (its origin from bone marrow)**

What is a bone marrow transplant?

We need a similar doner and take a sample and to give it to the patient (IV route) its effect from 5-10 years.

We have other uses for cytokines such as:

IFN-α: antiviral therapy (chronic Hepatitis B and C)

IFN-β: multiple sclerosis

IFN-γ: chronic granulomatous disease (CGD)

IL-2: kidney cancer, melanoma.

tolerance and autoimmunity

Now we will we talk about tolerance and autoimmunity

What do we mean by tolerance?
Normalize the relationship between the immune system and some factors.

What is the importance of regulation of the immune system?

- **To avoid excessive lymphocyte activation and tissue damage during normal protective responses against infections**

- **To prevent inappropriate reactions against self antigens ("self-tolerance")**

- **Failure of control mechanisms is the underlying cause of immune-mediated inflammatory diseases (autoimmune diseases)**

General principles of controlling immune responses

- **Responses against pathogens decline as the infection are eliminated**
  - **Apoptosis of lymphocytes that lose their survival signals (antigen, etc)**
  - **Memory cells are the survivors**

- **Active control mechanisms may function to limit responses to persistent antigens (self-antigens, possibly tumours and some chronic infections)**
  - **Often grouped under "tolerance"**

Continuous exposure to chronic infection will produce tolerance.

- **Immunological tolerance: specific unresponsiveness to an antigen that is induced by exposure of lymphocytes to that antigen (tolerogen vs immunogen)**

- **Autoimmunity: immune response against self (auto-) antigen, by implication pathologic**
  - **Disorders are often classified under "immune-mediated inflammatory diseases"**

so, tolerance good or bad?

- **Against body antigen, it is very good**
- **Against tumour and chronic infection, it is very bad**

Tolerogen versus Immunogen

- **Tolerogen: antigen that induces tolerance**
- **Immunogen: antigen that induces an immune response**
- **The same chemical compound can be an immunogen or tolerogen depending on how it is presented to the immune system**
- **Factors promoting tolerance rather than stimulation of the immune system include:**

1. **High dose of antigen**
2. **Persistence of antigen in the host**
3. **Intravenous or oral introduction**
4. **Absence of adjuvents**
5. **Low level of costimulation**

Thank you,

طبعا يا حلوين انا اضفت كل السلايدات وكلام الدكتور الي حكاه كامل بدون نقصان اخر شي يعني من عند الدكتور tolerance بس قرأ السلايدات وما اضاف شي كثير واتوقع انه يعيد الكلام في المحاضرة الجاي, موفقين يا اصدقاء.