Immunology lecture: 14

Cytokines:

1)Interferons"IFN" : 2 types

Type 1 :

- **IFN-Alpha :**

  Main source: Macrophages

- **IFN-Beta**:

  Main source: Fibroblast, but actually it can be produced by other types of cells

  **There are few types of IFN-alpha , but one type of IFN beta , but they all interact with one cell receptor

  Q1: what induce the production of IFNs?

  Viral infections are the primary inducers of their production

  Plus activation of cells by bacterial infections but again the main driving force of activation is the viral infections .

  Q2: what are their main actions ?

  Protect the cells from the virus i.e. by arresting the metabolism of the cell so the virus doesn't use the cellular machinery to replicate and increase in number also these **IFNs can pass from the cell to neighboring cells to give them protection**, also it will **increase the expression of MHC 1 on the infected cells** as the cytotoxic T-cells that kill the virally infected cells recognize viral antigens in conjunction with MHC 1 molecule, so these are the main function of IFN alpha and Beta .

Now we will move to type 2 IFN which is IFN gamma...

IFN gamma:

- it does have some antiviral activity but not that important .
- its main Source: is TH1 cells, when you get activation of TH1 cells they will produce IFN-gamma also it can be produced by CD8 T-cells as well as NK cells.
- **Main function:**

Activation of macrophages, neutrophils, **as well as activation of the respiratory burst** which play a role in the cell mediated immunity (macrophage the most imp. In this).. **it also increase induction of MHC 1 and 2 on the surface of the cells** so in fact it play role in better antigen presentation.. it also **contribute in presentation of MHC 2 on surface of**

Non- APC cells such as endothelial cells which can express MHC 2 molecules because of the effect of IFN-gamma

infection >>activation of many TH1 cells>> release of IFN-gamma so you may get this phenomenon **"expression of MHC molecule on Non-APC such as endothelial cells " at the site of infection leading to abnormal APCs which may develop abnormal results , because some people believe that Autoimmunity can result sometimes from chronic infection by abnormal antigen presentation on NON-APCs by the effect of IFN-gamma.

In Addition, IFN-gamma can:

-stimulate cytotoxic Tcells ,and NK cells

-It **encourage** TH1cells profileration

-It **suppress** TH2 cells proliferation

(process of immune deviation by cytokines)

-also, it **suppress cytokines** produced by TH2 cells such as : IL-4,5,10.

-it is believed to be involved in switching in Rats to IgG, in humans possibly to IgG3.

-it inhibit switching to IgE as its induced by IL-4 produced by TH2 cells.

#It promotes switching to IgG , inhibit switching to IgE.

**Other cytokines: ((Interleukins))

A) IL-1

Main source: Macrophages

Many cells in the body can produce IL-1 but the main source is **activated macrophage** which is activated by foreign material such as bacteria which has been ingested and then, macrophage will produce IL-1.

****Main activator of Macrophages**: is the **lipopolysaccharide** (LPS) which has a Toll like receptor on the macrophage which will lead to activation of macrophage and the Release of IL-1.

IL-1 work on macrophages in **Autocrine fashion, so it makes it more active and it promote its activity .

IL-1 also can interact with B &T-cells to enhance their activation in a **Paracrine fashion.

Also IL-1 has **Endocrine action on distant places :

1) such as on hypothalamus and this will result in **Pyrexia** " increase in the body temperature".

2)It can go to the Liver, act on hepatocytes and make them **produce Acute phase proteins**.

-it is believed that also it can produce coagulation" clotting of the blood" in **conjunction of TNF**.

-also it can **suppress Appetite**

-The prolonged production of IL-1 for long period of Time it can produce **Cachexia "weight loss"** (الهزال)

(some chronic infections like tuberculosis can produce cachexia, as well as some cancers)

IL-1 is similar in action to **TNF** but **IL-1 doesn't produce septic shock.**

B)IL-2:

Main source: Helper T-cells, it can be produced by cytotoxic, NK cells but not in sufficient amounts.

Function: go to the receptors and stimulate maturation and proliferation of helper T cells **so it's considered as a growth factor for Helper T-cell ,Cytotoxic T-cells ,NK cells ,B cells**.

NK cells are activated very much by IL-2 and do their job much better and sometime it is used for **Treatment of Cancers**.

By : taking NK cells from the body and treat them with IL-2 and then they become bigger and expand to clone, and these cells are known as **LAK (Lymphokine Activated Killer cells)** , lymphokine is a cytokine produced by lymphocyte and a monokine is cytokine produced by a monocyte and these LAK cells are injected back to the body and suppress Tumors hopefully to kill them.

The **receptor for IL-2 actually is made from **three chains**

(alpha ,Beta ,Gamma) but **normally** only two are expressed and the **Alpha is not expressed** so it's not complete as 2 out of three chains are expressed.

****Activation Of T-cell involve** expression Of IL-2 Receptor, which means it involve expression of the third chain and this **third chain is known as CD25** (this is the newly expressed chain) , this process involve Naïve T cells **except** T- Regulatory cell as they **always have CD25** " they are CD25 +ve " , so this is how we can differentiate between T-regulatory cells and unstimulated Naïve T-cells.

****More explanation** : about IL-2 receptor , **normally** 2 chains are expressed on T cells but **Upon activation** there will be expression of the third chain which is CD25 chain and now we have a **complete receptor** that can receive IL-2 but the regulatory T cells express this chain "CD25" **constitutively** and that's why it is called **"CD25 +ve " cells.**

C)IL-4:

Source:TH2 cells ,some **mast cells** can produce IL-4, some(**NK-T Cell**)

Functions:

-encourage activation of B cells to produce Antibodies

-encourage **switching to IgE**

-produce **immune deviation** toward TH2 Cell

-**suppression** of TH1 Cells

-**antagonize** the effect of IFN gamma

D) IL-5:

Source: TH2 cells

Function: Growth factor for **eosinophils** with IL-4

(**IL-4,IL-5** are involved in parasitic diseases and allergic reactions)

E)IL-6:

Source: TH2 cells

Function: **potentiate** the action of other cytokines such as IL-4,IL-5 , so it promote the growth and proliferation of B cells , also it produce induction of Acute phase proteins.

F)IL-8:

-is a **chemokine**, which attract polymorphonuclear neutrophils and other cells to the site of infection.

G)IL-10:

-**Suppressing cytokine**, so far the above mentioned cytokines are **proinflammatory cytokines** they promote activation and proliferation of cells and induction of inflammation. On the other hand, we have cytokines that are really **suppressors of inflammation** and **IL-10** is one of them.

- **source**: by TH2 cells, some of the regulatory T cells especially the induced one of the T regulatory cells or the TH3 cells, as we have **three types of T-regulatory cells:**

1-natural regulatory cells

2-induced regulatory cells

3-TH3 cells

(All of these are suppressive)

So **IL-10 is **suppressive to inflammatory cells,** and it produce **Tolerance**.

_It is believed to be a **switching factor to IgG4** so it inhibit TH1 cells, NK cells

H)IL-12:

Source: **Activated Macrophage**, during phagocytosis of bacteria by macrophage it start producing IL-12, and upon stimulation of T-helper cells, **IL-12** will **deviate the immune response toward TH1 cells response** ,so it will enhance production of TH1 cells,CD8 cells, as well as NK cells .

**NK cells are involved in cell mediated immunity.

****IL-12** is the **most potent stimulator of NK cells**

TNF

-also called **TNF-alpha**, **Cachectin** and as the name implies it will produce cachexia as IL-1.

-Why it's Called TNF?

Because when it was discovered it did actually produce necrosis in some Tumors.

-How does it do that?

It can kill some cells directly just like (FAS-FASL) so cells that express FAS can be killed by FAS ligand ,as well as (CD-40 –CD-40L)

***TNF**, **FAS-FASL**, **CD40-CD40L** >> all of them belong to the same family which is **TNF family.**

*TNF has got a **death domain** on its receptor, so it **send signal of apoptosis** to the cell and the cell dies.

*it also **produce coagulation** and this can block of blood vessels ,so it **can block blood vessels of Tumors** and kills them and that's why it was called TNF.

***Main source**: activated macrophages especially when activated By LPS.

*TNF activates macrophages, other cells as well ,**it has similar functions to IL-1** also it produce cachexia as it suppress appetite , it also produce fever, also it interfere with fat metabolism that's why it produce suppression of appetite and cachexia, it also reduce Myocardial contractility and decrease smooth muscle contraction(dilatation of smooth

muscle) so you will get low cardiac output as well as increase peripheral resistance and low blood pressure and **that's what is really responsible for producing Septic shock** .

(LPS Can cause septic shock, as LPS stimulate macrophages to produce lots of TNF and this will cause septic shock which is a very serious condition which-if not treated – can lead to death.

*__TNF__ cause suppression of bone marrow, and that's why when a Patient got chronic inflammation he **will develop anemia**, that's because the bone marrow is suppressed.

*__TNF__-contribute in acute phase response by acting on hepatocytes and increase their synthesis of certain proteins , and it's pyrogenic just like IL-1.

*Another cytokine which is **Lymphotoxin** "TNF –Beta" it is called like this because its similar to TNF but its produced by lymphocytes, it has similar effect as TNF but very much milder than TNF it actually potentiate the effect of TNF .

**__TGF-Beta__ (Transforming Growth Factor –Beta):

-it is produced by **fibroblasts and many other cells**

-it is involved in **healing of Tissues** so it is considered as **Positive type of cytokines** as it is involved in repair.

-It has effects on B&T- cells: it is produced by **T-regulatory cells** and they are **suppressive cytokines** just like IL-10 and its not proinflammatory , it suppress T&B-cells and its found a lot in GI tract along with TH3 cells which produce a lot of TGF-Beta

#**TGF-Beta as well as IL-10** suppress B&T-cells and produce self-Tolerance.

-TGF-Beta is involved in isotype switching to IgA, and that's presented within T-cells in the GI tract so you produce IgA which is a secretory Antibody and it is not really proinflammatory as it doesn't activate complement but it gets rid of aggregates of immune reactants.

*In fact you need some suppressive cytokines in your GI tract so you will not get allergic upon any single protein in your GI tract as GI tract is full of proteins and peptides so in order not to get inflammation from a single component of GI tract.
