DATE: 25/02/22
PAGE:

CYTOKINES

Cytokines:-

- Low m.w proteins (<30kDa)
- Many are glycoproteins
- They have regulatory functions & help in communication b/w immune cells.
- They are secreted by cells other than immune cells as well.
- Other functions include ~~Stop~~ promoting growth & proliferation of immune effector cells, directing immune cells to site of infection.

- Chemokines: Class of cytokines that mobilize immune cells from one location to another. ← Type of chemoattractant
- Mode of Action-
  - Autocrine - Action on the same cell that secreted the cytokines
  - Paracrine - ~~Action of cy~~ Cytokines secreted by a cell acts on cells that are closely located.
  - Endocrine - The cytokine secreted by a cell act on a distant cell via the circulatory system.

- Properties: • Pleiotrophy — The same cytokine ~~ha~~ have diff. functions for diff. target cells.
  eg IL-4 → B cell: Activation, Proliferation, Differentiation
  Mast cell: Proliferation
  Thymocyte: Proliferation
  • Redundancy — Diff. cytokines have the same function.
  eg: IL-2, IL-4, IL-5 → B-cell: Proliferation
  • Synergy — when two cytokines have higher efficiency in its effect when combined.
  eg: IL-4, IL-5: Individual induce class switch to IgE
  IL-4 + IL-5: Class switch is more effective

DATE: / /
PAGE:

- Antagonism — Some cytokines will inhibit the functions of other cytokines.
  eg: IFN-γ inhibits class switching to IgE by IL-4
- Cascade induction — Property exhibited by cytokines which induce target cells to secrete other cytokines.
  eg: IFN-γ → Macrophage → IL-12 → Activated T_H cells → IFN-γ, TNF, IL-2

Classification -

6 families: 1) Interleukin 1 family
2) Hematopoietin Family (Class I)
3) Interferon Family (Class II)
4) Tumor Necrosis Factor Family
5) Interleukin 17 Family
6) Chemokine Family

(i) Interleukin 1 (IL-1) Family

→ These cytokines are usually Pro-inflammatory
basic property of infection
Dilation of blood vessels near site of infection causes redness of skin due to increased blood flow

Inflammation: Redness, swelling, Pain, Edema (Pus formation)
Due to increased Blood to site
caused due to penetration of immune cells through blood vessels to site of infection.
Later stage. immune cells dead.

→ Signals the liver to produce Acute Phase Proteins
Immediate-action Proteins

→ Receptors are often only expressed after exposure to antigens.

→ TIR domains: Cytoplasmic tail of the IL-1 receptors or toll-like receptors
Toll/Interleukin-1 Receptor

Adaptor protein [MyD88] binds to TIR domain upon binding of IL-1 to its receptor. Binding of Adaptor proteins induce recruitment of other proteins. These proteins can activate 2 cascades: MAP Kinase cascade, NF-KB Pathway.

DATE: 28/02/22
PAGE:

(ii) Hematopoietin (Class I) family

→ Onset of T-/B-cell proliferation
→ Onset of B-cell differentiation to plasma cells & Ab secretion
→ Onset of T-cell differentiation

(iii) Interferon (Class II) family

→ Types: Type I, Type II

- Secreted by activated Macrophages, dendritic cells & virally infected cells.
- Part of innate immune response
- [IFN α, IFN β]

- Secreted by activated T-cells, NK cells
- Part of Adaptive & Innate immune response
- [IFN-γ]
- very imp for T-cell activation

NOTE: Almost all IF work to neutralise viral infections.

JAK-STAT Pathway:

Signalling of Class I & Class II family of cytokines are very similar.

↳ Receptors for class I & class II family are present in dimeric form & after binding to cytokines.
↳ Dimerisation of receptors results in association of JAK [Janus Activated kinase] — type of tyrosine kinase. Results in Activation of JAK.
↳ Activation leads to Phosphorylation of receptor.
↳ Receptor Phosphorylation results in association of STAT (Transcription Factor)
↳ JAK Phosphorylates STAT. ~~STA Activati~~ Phosphorylation of STAT results in dimerisation of STAT — STAT Activation.
↳ Activated STAT translocates to nucleus.

DATE: / /
PAGE:

(iv) Tumor Necrosis Factor Family

→ Induces ~~immun~~ death in immune cells & Target cells.

→ Only class of cytokine that has soluble & membrane-bound cytokines.
TNF-α, TNF-β — soluble
CD40L, Fas Ligand (FasL) — membrane-bound

→ TNF-α, TNF-β : Receptors – TNF R1, TNF R2
↳ responsible for both life & death of an immune cell.

CD40L : Receptor – CD40

Fas Ligand : Receptor — FAS
↳ solely responsible for death signalling.

FAS Signalling –

- Fas induces cell death through the process of Apoptosis.
  Apoptosis — Process of cell death from within.
- FasL binds to Fas → induces Apoptosis → cell death
- Fas before binding to FasL is monomeric. Once Fas is bound, it undergoes trimerization.
- Fas has a domain in the cytoplasmic area called Death Domain. These domains interact with the Death domains of FADD [Homotrophic interaction].
- FADD also has a death effector domain which helps to recruit an inactive Protease (Cysteine Protease) called Procaspase 8 → it breaks peptide bonds after Aspartic acid.
  (has cysteine in active site)
- FADD effector domain helps recruit procaspase 8 which becomes active and ~~gives~~ becomes caspase 8 (caspase 8).
  caspase 8 is released into the cytoplasm.
- caspase 8 will proteolytically digest procaspase 3 and procaspase 7, making it active.
- caspase 3 and 7 will proteolytically digest apoptotic enzymes making it active and induces Apoptosis in the cell.

DATE: / /
PAGE:

TNF-R1 signalling –

TNF-R1 receptor induces two diff. signalling cascades in the cell: ~~Life, death~~ Life & Death of the cell.

Death signalling –

- TNF binds to TNF-R1 receptor — Receptor Trimerisation
- & Trimerisation of receptor ~~results in~~ brings together death domains (DD) to the receptor
- ~~The~~ Clustering of DD creates docking site for adaptor Protein : TRADD.
- TRADD recruits RIP1 & TRAF2.

  Complex 1 : RIP1 + TRAF2 + TRAAD
- As soon as complex 1 is formed. It dissociates & moves ~~in~~ to cytoplasm & associates with FADD.
- ~~FAD~~ FADD binding to Procaspase 8 (inactive) results in its activation and dissociation from complex 2.

  Complex 2 : Complex 1 + FADD + Procaspase-8
- Activated Caspase-8 induces Apoptosis in the cell

Life signalling –

- TNF binding to TNF R1 ~~rec~~ receptor — Receptor Trimerisation
- Trimerisation of receptor brings together death domains (DD) to the receptor.
- Clustering of DD creates docking site for adaptor Protein: TRADD
- TRADD recruits RIP1 & TRAF2

  complex 1: RIR 1 + TRAF2 + TRAAD
- If the signal is for survival, then complex 1 will recruit few more proteins instead of dissociating.
- & Ultimately induce NF-Kβ activation & MAP Kinase cascade. These Pathways induces gene expressions that promote cell survival.

DATE: / /
PAGE:

- NF-kβ will also activate the expression of a gene for protein ~~cFH~~ cFLIP. cFLIP will completely shutdown the death signalling pathways.

(v) Interleukin-17 Family

as a link

→ operates b/w innate & adaptive immunity

→ co-ordinates release of pro-inflammatory & Neutrophil-mobilizing cytokines eg: IL-17E → induces T_H2 response and supresses T_H17 response

04/03/2022

(vi) ~~Chemokines~~ Chemokine Family

Chemoattractants → Attract immune cells to site of infection

eg: CXCL9 (Ligand), CXCL10 (chemokine) ; Receptors: CXCR4 (Receptor)

Cytokine Antagonists :-

→ Inhibits Cytokines' function

→ Provided by the body as a counter measure to keep cytokines level in place. eg: IL-1RA → inhibits synthesis of IL-1R so that less Pro-inflammatory cytokines (IL-1) are ~~produced~~ released. hinder

→ Can be produced by Pathogens to ~~invade~~ the immune cells. function by interfering with ~~its~~ cytokine function.

- ~~eg~~ viruses can generate viral products that interfere with cytokine production eg: Rheumatoid Arthritis
  eg: Measles virus inhibits IL-12.
- Some viruses secrete cytokine homologues that compete with host's natural cytokine. ~~It~~
  eg: EBV ~~inhibi~~ secretes a cytokine called (viral) IL-10
  very imp. cytokine for Anti-viral response (signal T-cells to activate our immune cells) ← IL-10 homologue.

DATE: / /
PAGE:

Secretes soluble cytokine receptors that ~~cytokines that~~

- ~~Some~~ Some viruses binds to cytokines, ~~receptors~~ preventing cytokines from binding to its receptor.
  eg Variola virus secretes soluble IL-1 receptors that will go and bind to IL-1 cytokine preventing it from binding to its ~~or~~ own receptor. It also secretes a soluble TNF receptor that binds to TNF.

  eg Myxoma virus secretes soluble ~~IN~~ IFN-γ receptors

- Some viruses generate viral products that interferes with the cytokine signalling pathways.
  eg Adeno virus secretes a molecule that blocks IFN-induced JAK-STAT signalling Pathway.
- Some viral molecules induce the host cell to ~~induce~~ secrete cytokine inhibitors.
  eg Herpes simplex virus induces production of Type I interferon inhibitors

Cytokine-related Diseases:-

(i) Septic Shock - caused by pathogenic bacteria (Staphylococcus aureus mainly)
Overwhelming production of pro-inflammatory & fever inducing cytokines such as TNF-α & IL-1β

(ii) Bacterial Toxic Shock - can be fatal.
Caused due to presence of an antigen called Super Antigen. Super Antigen binds to MHC at a diff. location other than the Antigen-Presenting site. The super Antigen will interact with TCR ~~that~~ at a site diff. from its Antigen-binding site.

DATE: / /
PAGE:

This interaction (with TCR & MHC) is very strong. This leads to over-induction of T-cells (activation of all types of T-cells).

(iii) Lymphoid / Myeloid cancers – over production of IL-6 (thats responsible for lymphoids & Myeloids production).

(iv) Cytokine storm – caused by Spanish FLU, COVID-19 over-production of cytokines resulting in Prolonged inflammation.

Cytokine-based therapies :-

- Common cytokine-based therapy is against Rheumatoid Arthritis. (Inject Monoclonal Ab. against TNF-α.) It is caused due to prolonged inflammation.
- Injection of Abs against Pro-inflammatory cytokines.
- In several viral infections, interferons are administered.
- GM-CSF will stimulate the myloid progenitor cells, often used after bone-marrow transplatation.