CYTOKINES

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How do Innate Immune Cells Communicate?

- Surface receptors
- Soluble factors (cytokines/chemical messengers)

What are cytokines?

- Soluble proteins
- Low molecular mass (around 8-25 kDa).
- Secreted by a large number of different cell types.
- They regulate many important biological processes
- Mediators of cell – cell communication in the immune response
- They regulate the intensity and duration of the immune response
- They are NOT hormones!!!

What are cytokines?

- **Low molecular weight, soluble proteins** that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems.
- Cytokines are **pleiotropic** (act on different cell types), **redundant** (different cytokines carry out the same function), and **multifunctional** (same cytokine is able to regulate a number of different functions).
- **Three functional categories** of cytokines:

  a) cytokines that regulate innate immune responses,

  b) cytokines that regulate adaptive Immune responses, and

  c) cytokines that stimulate hematopoiesis.

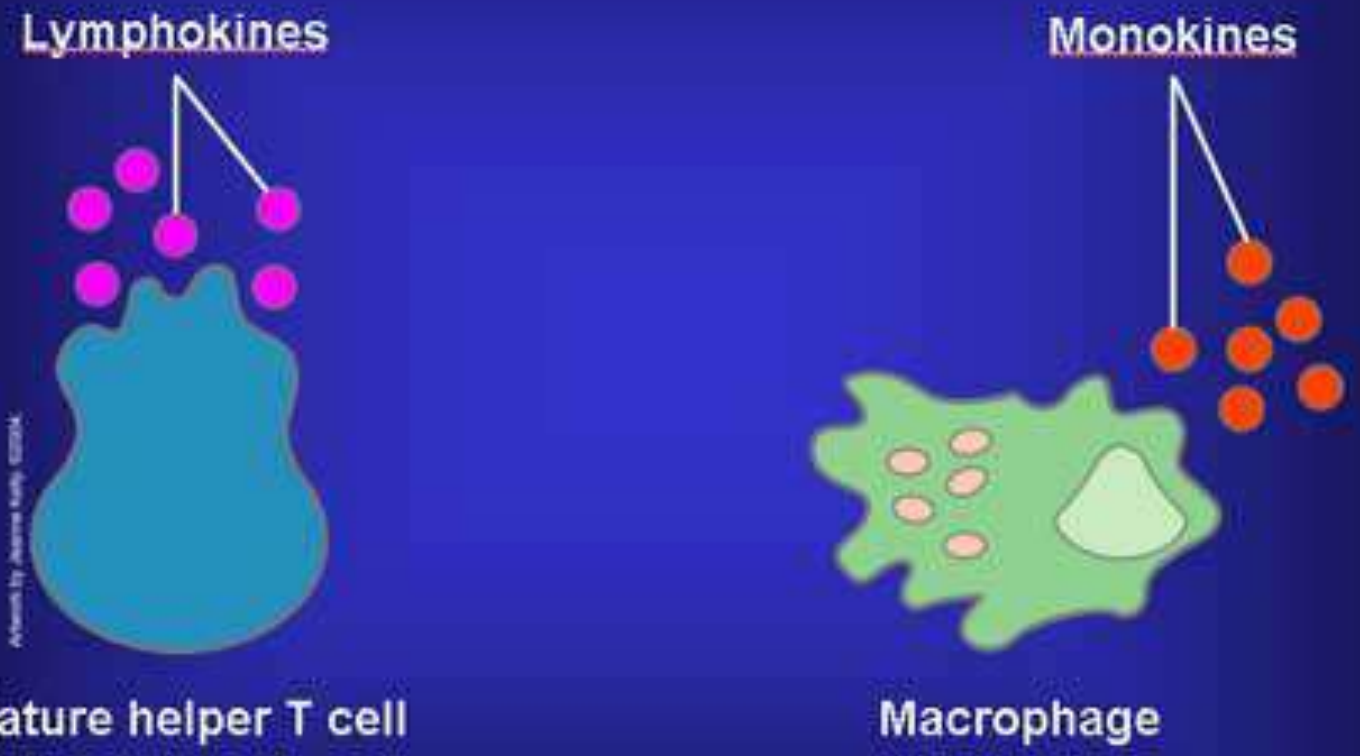
What are cytokines?

Nomenclature

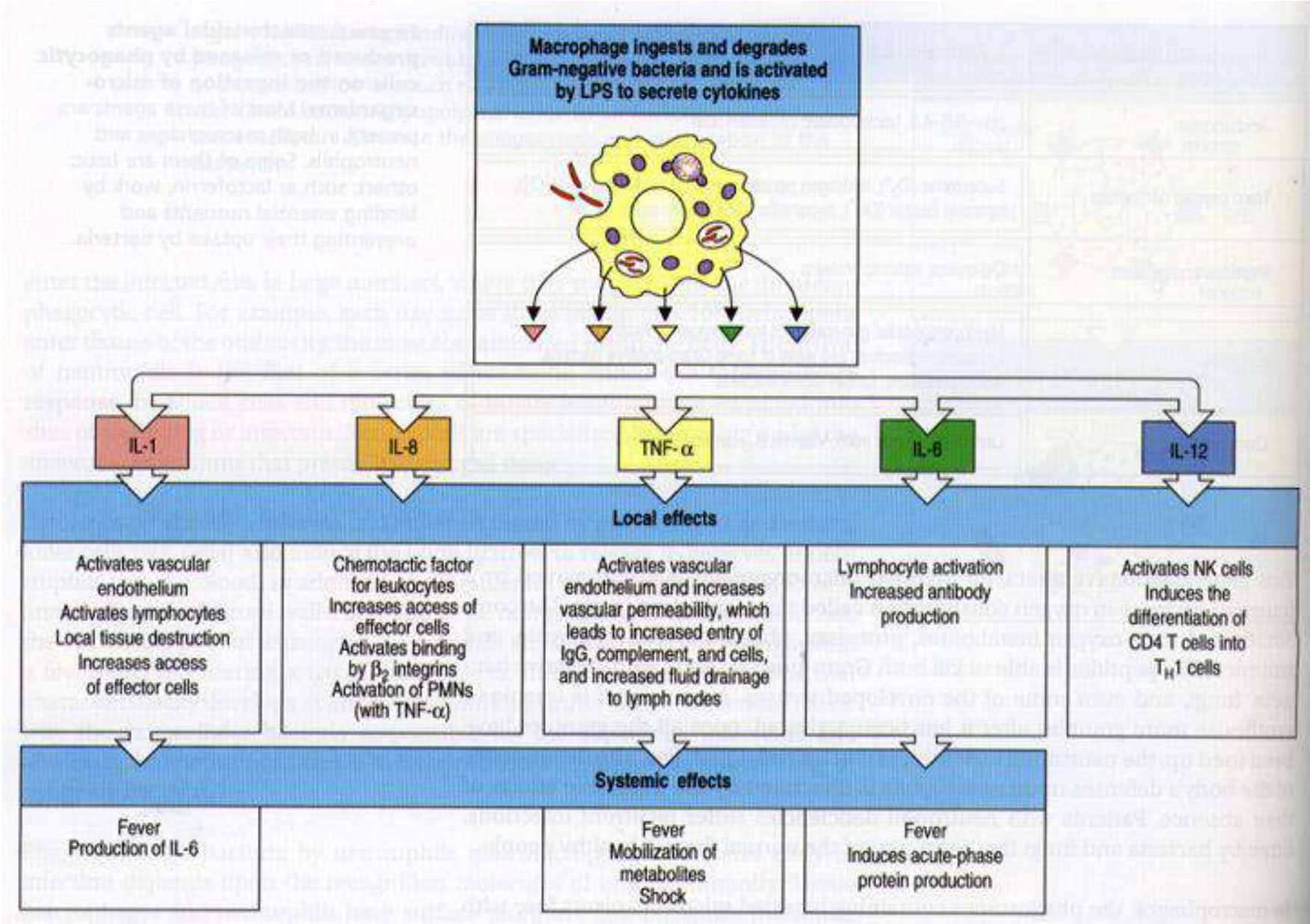
Cytokines released by

- lymphocytes are also called LYMPHOKINES
- monocytes and macrophages are also called MONOKINES
- leukocytes that act on other leukocytes are referred to as INTERLEUKINS
- Cytokines with chemotactic activity are also called CHEMOKINES

Cytokines



Some important cytokines



SUPPLEMENTARY TABLE 5. KEY FUNCTIONS OF SELECTED CYTOKINES

Cytokine	Phase	Source	Target/effects
IL-1	Innate	Myeloid cells; epithelial/endothelial cells	Inflammation, fever, cell activation
IL-2	Adaptive	T cells	Proliferation of T and B cells; activation of NK cells and innate T cells
IL-4	Adaptive	Th2 cells; mast cells	Promotion of Th2 bias; class switching to IgE
IL-5	Adaptive	Th2 cells	Activation of eosinophils
IL-6	Innate	Myeloid cells; epithelial/endothelial cells; fibroblasts	Inflammation; proliferation of B cells, promotion of antibody secretion
IL-12	Innate	Macrophages, DC	Promotion of Th1 bias; activation of NK cells/innate T cells
IL-17: six isoforms, all from different genes	Adaptive	Subsets of T cells; other leukocytes; skeletal muscle; nervous tissue	Stimulation of inflammatory cytokines; angiogenesis; affects endothelial and epithelial cells
IL-21	Innate and adaptive	Subsets of T cells	Regulation of NK cells and cytotoxic T cells; promotes cell division/proliferation
TNFα	Innate	Myeloid cells	Inflammation, fever, activation of neutrophils, apoptosis
IFNα	Innate	Plasmacytoid DC; fibroblasts	Promotes MHC I expression; activation of NK cells; promotes $CD8^+$ T cell response
IFNβ	Innate	Fibroblasts	Promotes MHC I expression; activation of NK cells
IFNγ	Adaptive	Th1 cells; $CD8^+$ T cells; NK cells; innate T cells	Activation of macrophages/DC, promotes expression of MHC II, promotes antigen presentation
TGFβ	Adaptive	T cells; macrophages	Inhibition of T cells, inhibition of B-cell proliferation, class switching to IgA, inhibition of macrophages

IL, interleukin; NK, natural killer; Th, T helper; Ig, immunoglobulin; DC, dendritic cell; TNF, tumour necrosis factor; IFN, interferon; MHC, major histocompatibility complex; CD, cluster of differentiation; TGF, transforming growth factor.

Cytokine Storm

What is cytokine storm?

- The **cytokine storm** (hypercytokinemia) is the systemic expression of a severe immune reaction resulting in the release of more than 150 known inflammatory mediators (pro-inflammatory **c**ytokines, oxygen free radicals, and coagulation factors) into the blood too quickly.
- Cytokines play an important role in normal immune responses, but having a large amount of them released in the body all at once can be harmful.
- A cytokine storm can occur as a result of an infection, autoimmune condition, or other disease.
- Signs and symptoms include high fever, inflammation (redness and swelling), and severe fatigue and nausea. Sometimes, a cytokine storm may be severe or life threatening and lead to ARDS, SIRS and MOSF.

Normal tissue response to an injury

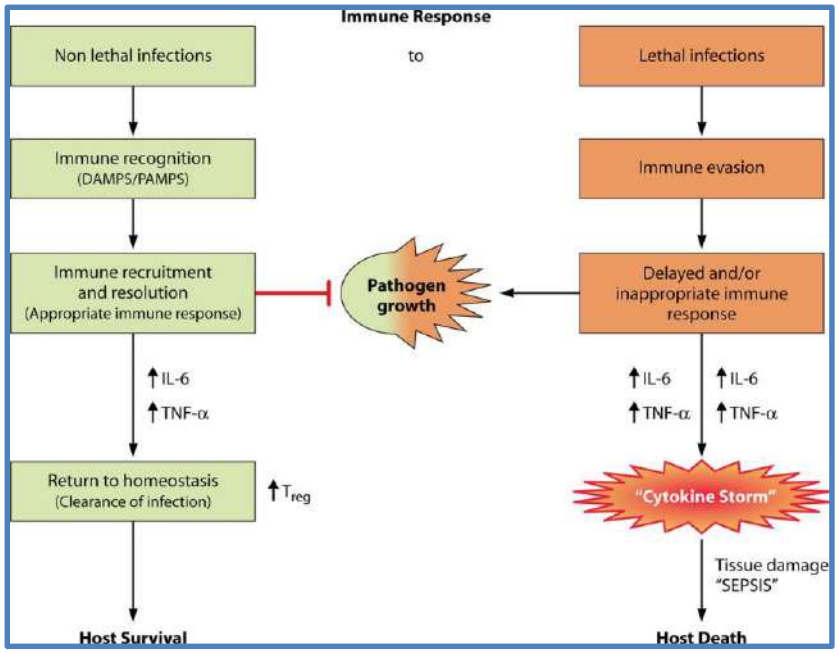
- In the event of tissue damage, whether caused by injury or infection, inflammation is the body's first coordinated line of defense.
- It is responsible for activating both innate and adaptive immune responses so that the damage can be resolved and homeostasis restored.
- There are four stages to a classical self-limiting inflammatory response: (i) recognition of the problem, (ii) recruitment of leukocytes and other immune system components, (iii) elimination of the threat, and (iv) resolution of the inflammatory state (i.e., a return to homeostasis).

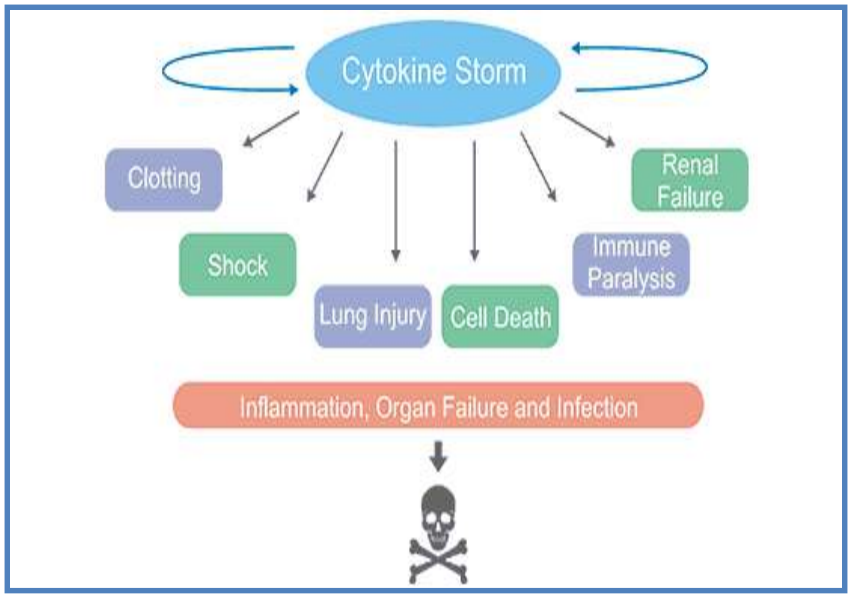
Resolution of inflammation

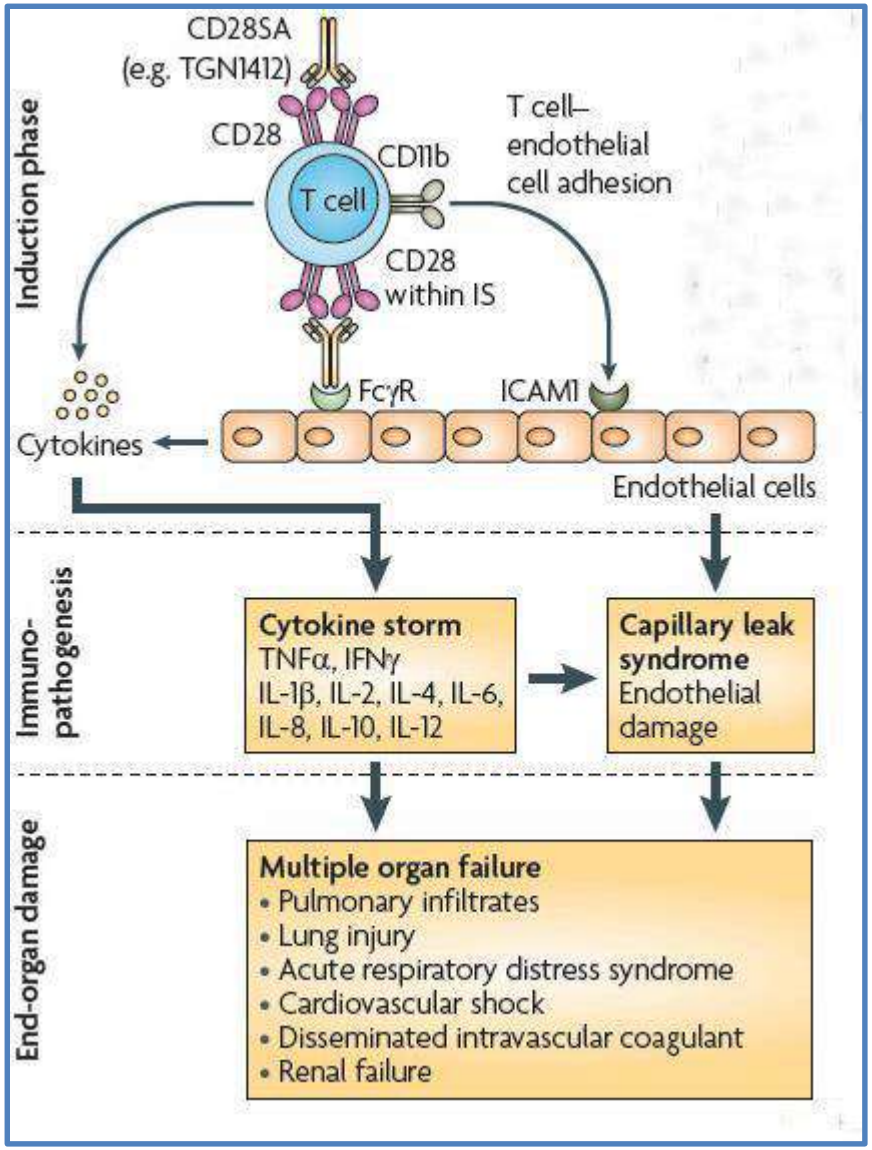
- The cytokines induced by PAMPs and produced by leukocytes are proinflammatory cytokines and include tumor necrosis factor alpha (TNF-α), IL-6, and members of the IL-1 family.
- TNF-α and IL-1β induce vasodilation and permeability, allowing immune cells to reach the site of damage
- IL-β and IL-6 iactivate complement and opsonization
- Proinflammatory cytokines can affect the brain, inducing behavioral and physiological symptoms such as fever, nausea, and anorexia.
- Finally following recruitment of immune cells to the site of inflammation, resolution of the damage begins.

Pathogenesis of cytokine storm

- Diverse pathogenic viruses (e.g., influenza A, SARS CoV-2) and bacteria (e.g., *Francisella tularensis, Pesudomonas*) have been found to induce cytokine storms or hypercytokinemia.
- These pathogens disrupt the delicate balance of a suitable inflammatory response, tipping it from being beneficial to destructive by causing large amounts of positive feedback in immune cells
- This results in exaggerated immune response and upregulation of proinflammatory cytokines, in particular TNF-α, IL-1β, IL-8, and IL-6.
- Results in symptoms such as hypotension, fever, edema, respiratory distress, intravascular blood coagulation , increased viscosity of blood, thrombosis and hypotension eventually causing ARDS and organ dysfunction and death.

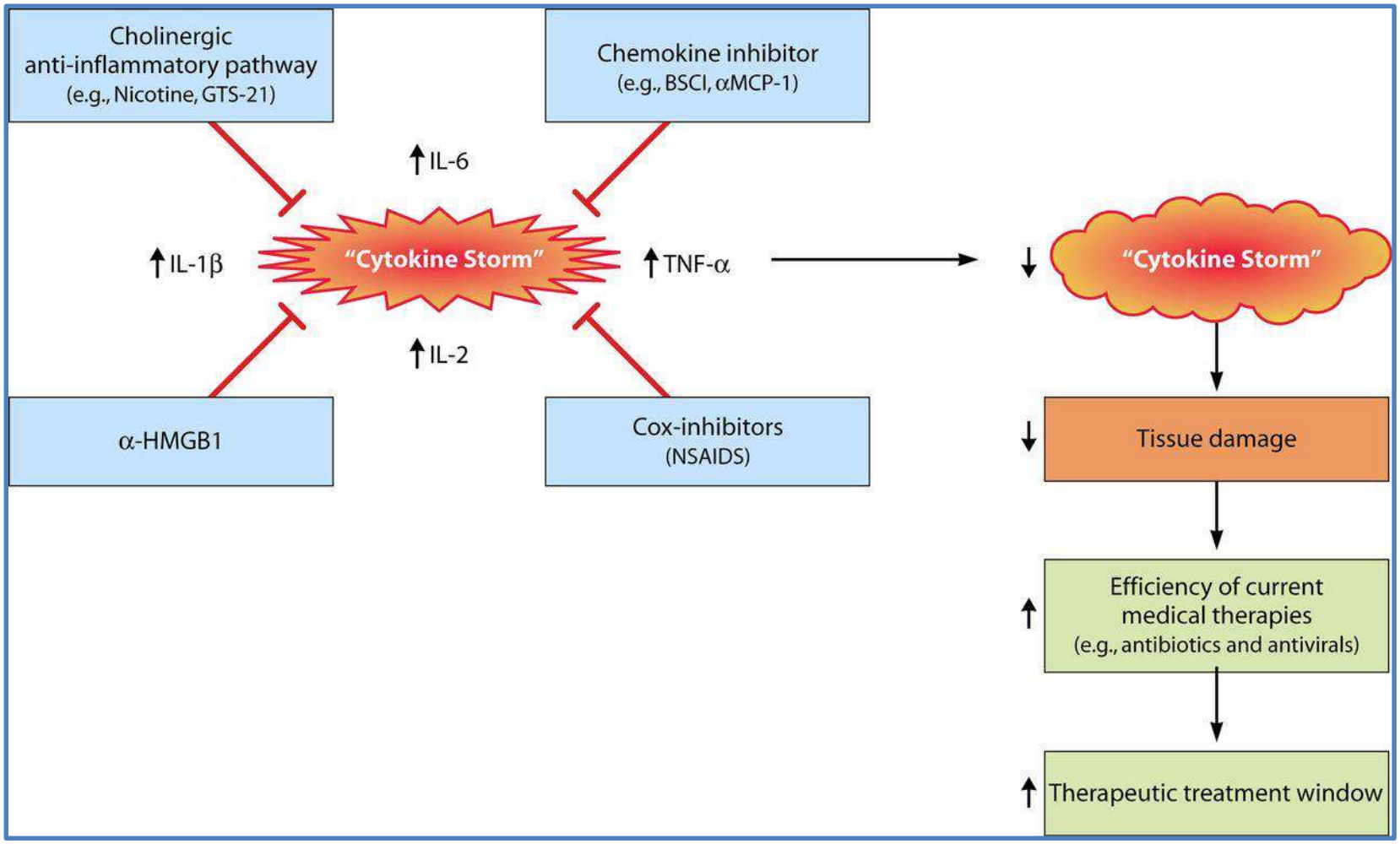

Immune Response
to
Non lethal infections
Lethal infections
Immune recognition
(DAMPS/PAMPS)
Immune evasion
Immune recruitment
and resolution
(Appropriate immune response)
Pathogen
growth
Delayed and/or
inappropriate immune
response
↑IL-6
↑TNF-α
↑IL-6
↑TNF-α
↑IL-6
↑TNF-α
Return to homeostasis
(Clearance of infection)
↑Treg
"Cytokine Storm"
Tissue damage
"SEPSIS"
Host Survival
Host Death

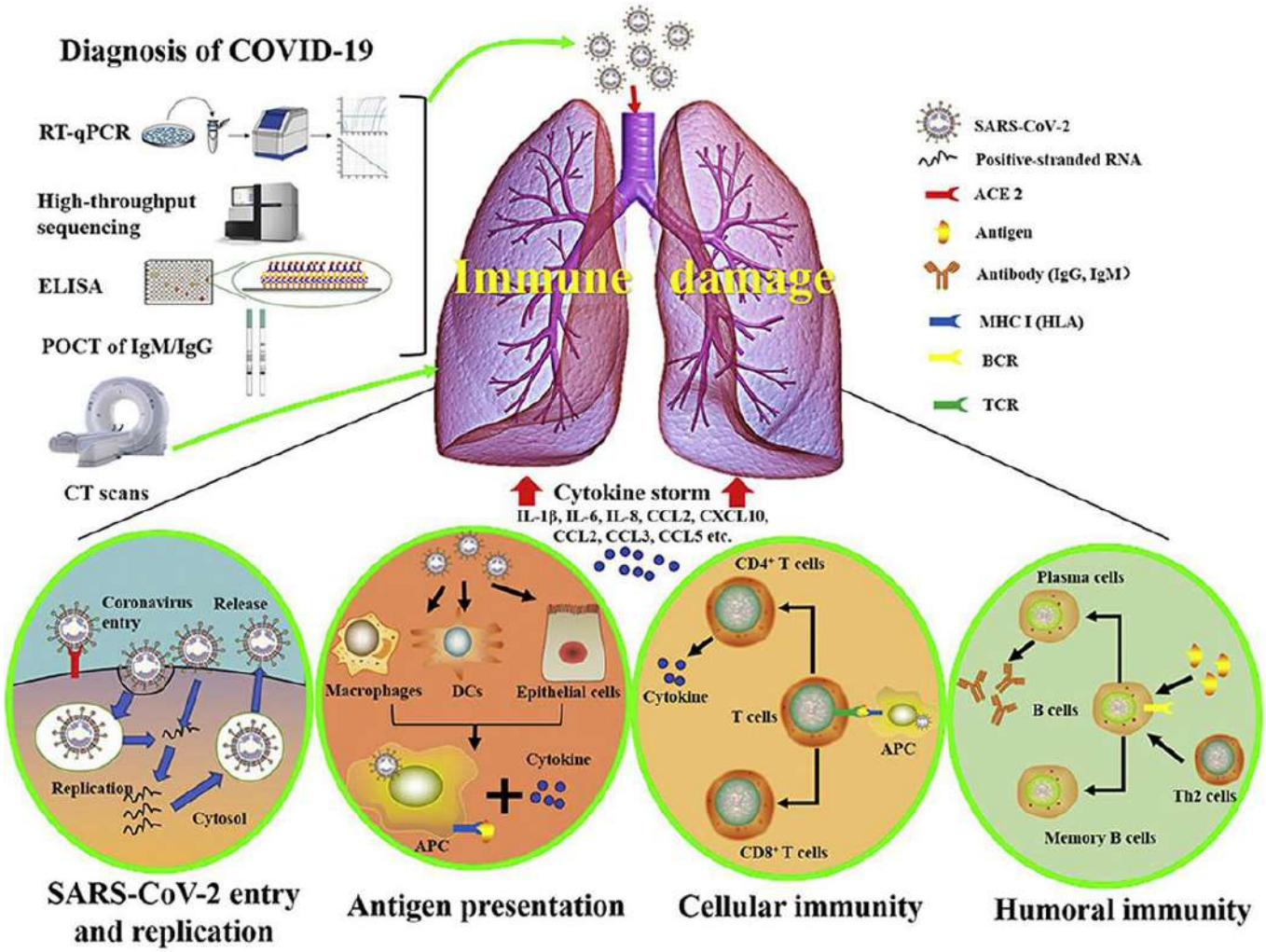

Cytokine Storm
Clotting
Renal
Failure
Shock
Immune
Paralysis
Lung Injury
Cell Death
Inflammation, Organ Failure and Infection


CD28SA
(e.g. TGN1412)
CD28
CD11b
T cell
T cell–
endothelial
cell adhesion
CD28
within IS
Induction phase
FcγR
ICAM1
Cytokines
Endothelial cells
Immuno-
pathogenesis
Cytokine storm
TNFα, IFNγ
IL-1β, IL-2, IL-4, IL-6,
IL-8, IL-10, IL-12
Capillary leak
syndrome
Endothelial
damage
End-organ damage
Multiple organ failure
• Pulmonary infiltrates
• Lung injury
• Acute respiratory distress syndrome
• Cardiovascular shock
• Disseminated intravascular coagulant
• Renal failure

Management of cytokine storm

- Strategies to combat cytokine storm include compounds that target fundamental immune pathways, such as the chemokine network and the cholinergic anti-inflammatory pathway,
- Specific strategies - HMGB1 antibodies and COX-2 inhibitors.
- All these lead to a downregulation of the cytokine storm, reducing the risk of tissue damage and allowing time for conventional therapies to target the pathogen directly.
- Cytosorb - CytoSorb blood purification technology is indicated for treating cytokine storm
- Auronafin
- Anti-cytokine MAbs – e.g Infliximab (anti-TNFα MAb), Sarilumab (anti IL6 Mab)


Cholinergic anti-inflammatory pathway (e.g., Nicotine, GTS-21)
Chemokine inhibitor (e.g., BSCI, αMCP-1)
↑IL-6
↑IL-1β
"Cytokine Storm"
↑TNF-α
↑IL-2
α-HMGB1
Cox-inhibitors (NSAIDS)
↓
"Cytokine Storm"
↓
Tissue damage
↑
Efficiency of current medical therapies (e.g., antibiotics and antivirals)
↑
Therapeutic treatment window


Diagnosis of COVID-19
RT-qPCR
High-throughput sequencing
ELISA
POCT of IgM/IgG
CT scans
Immune damage
Cytokine storm
IL-1β, IL-6, IL-8, CCL2, CXCL10, CCL2, CCL3, CCL5 etc.
SARS-CoV-2
Positive-stranded RNA
ACE 2
Antigen
Antibody (IgG, IgM)
MHC I (HLA)
BCR
TCR
Coronavirus entry
Release
Replication
Cytosol
SARS-CoV-2 entry and replication
Macrophages
DCs
Epithelial cells
Cytokine
APC
Antigen presentation
CD4+ T cells
Cytokine
T cells
APC
CD8+ T cells
Cellular immunity
Plasma cells
B cells
Th2 cells
Memory B cells
Humoral immunity