Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease

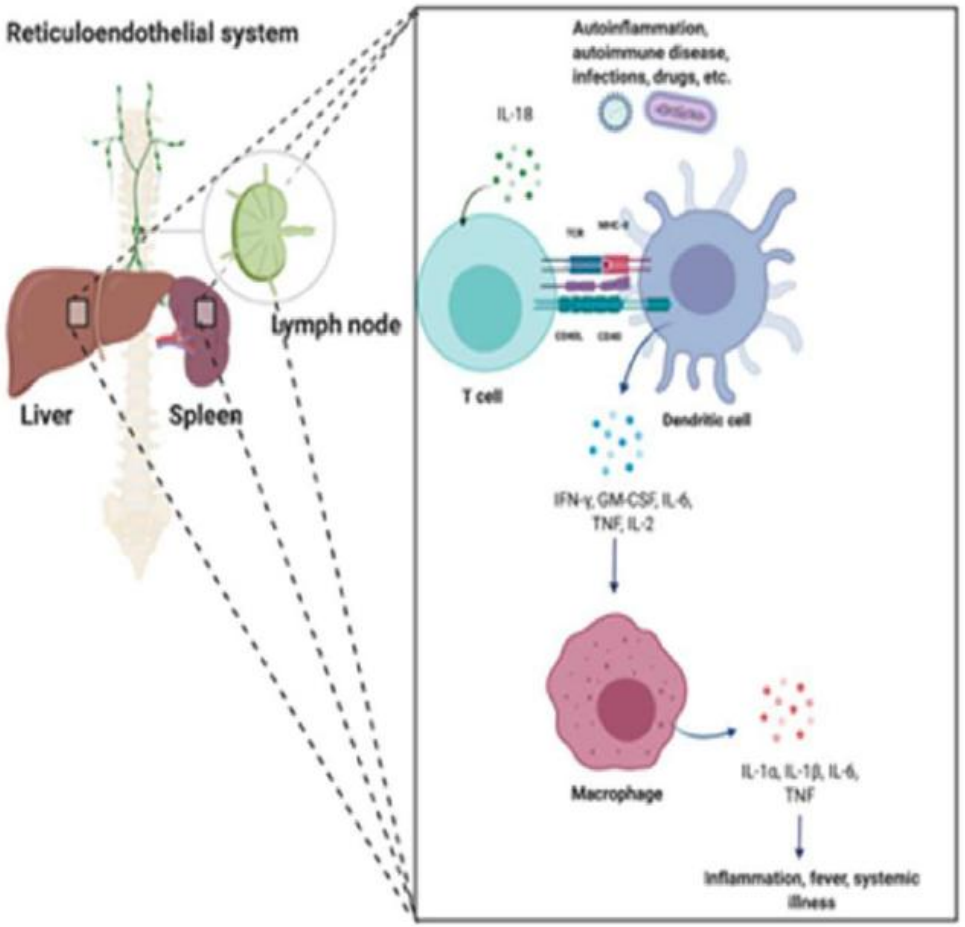
Dennis McGonagle[a,b,*], Kassem Sharif[a,c], Anthony O'Regan[d], Charlie Bridgewood[a]

[a] *Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM), University of Leeds, Leeds, UK*
[b] *National Institute for Health Research (NIHR) Leeds Biomedical Research Centre (BRC), Leeds Teaching Hospitals, Leeds, UK*
[c] *Sheba Medical Center, Tel Aviv, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[d] *National University of Ireland, Saolta University Healthcare Group, Galway, Ireland*

高雄長庚過敏免疫風濕科 何曉儒

Introduction

- Cytokine antagonism in non-immuno-deficient patients in children with systemic juvenile inflammatory arthritis (sJIA) (Still's disease): IL-6 or IL-1
- severe hyer-cytokinemic inflammatory state (**cytokine storm**, **macrophage activation syndrome** (MAS) , **secondary haemophagocytic lymphohistocytosis** (sHLH))
- Overzealous immune responses associated with MAS/sHLH → COVID-19 related ARDS ?



Classic MAS/sHLH picture:
most often occurs outside the lungs

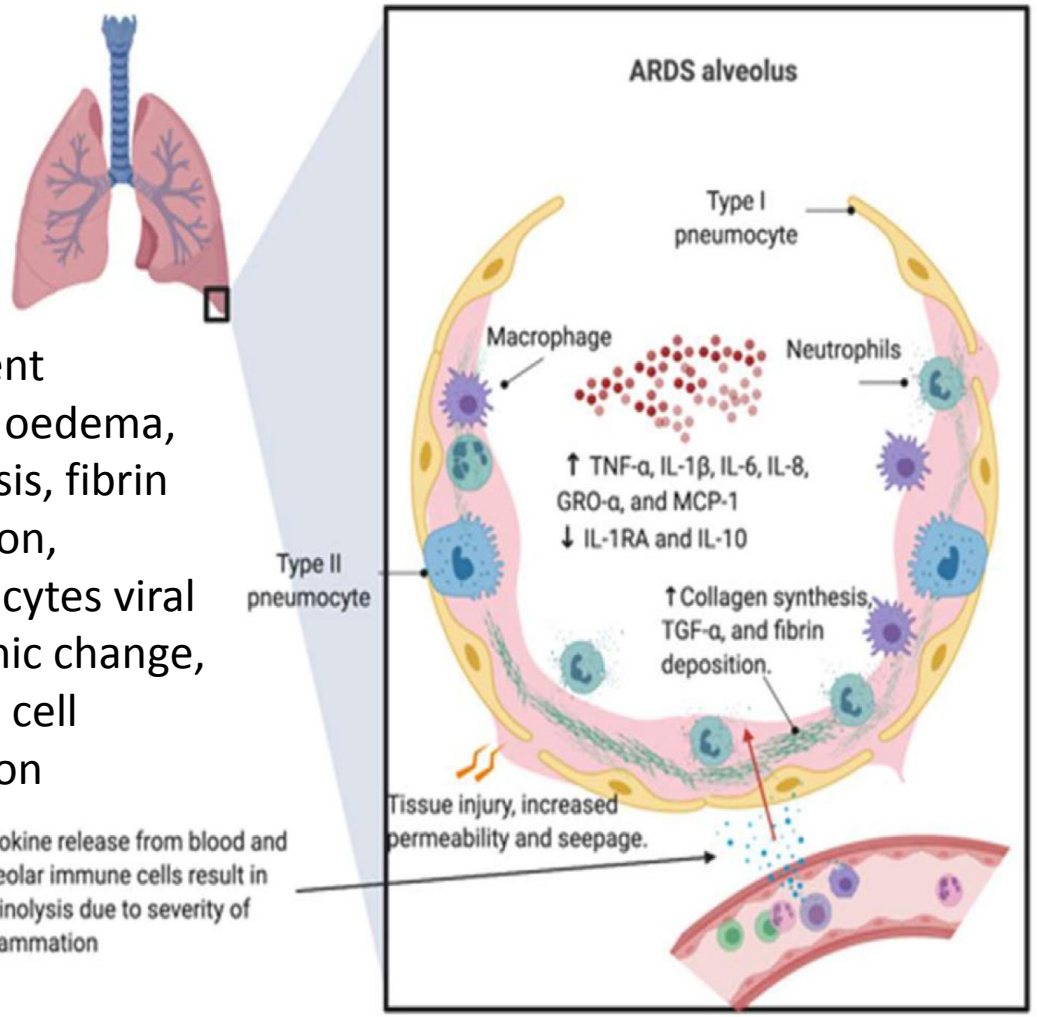
- fevers
- adenopathy
- hepatosplenomegaly
- anaemia
- cytopenias
- abnormal liver function
- deranged lipid profiles
- activation of intravascular coagulation cascades
  hypercytokinaemia

Macrophage activation syndrome in COVID-19 pneumonia?

- High CRP, ferritin, coagulopathy, abnormal liver function in many severe COVID-19 pneumonia
- Similar cytokine profile: ↑IL-1β, IL-2, IL-6, IL-17, IL-8, TNF, CCL2
- COVID-19: lung-centric immunopathology, absence of hepatosplenomegaly
- MAS/sHLH in SARS patients

Macrophage activation syndrome in COVID-19 pneumonia?

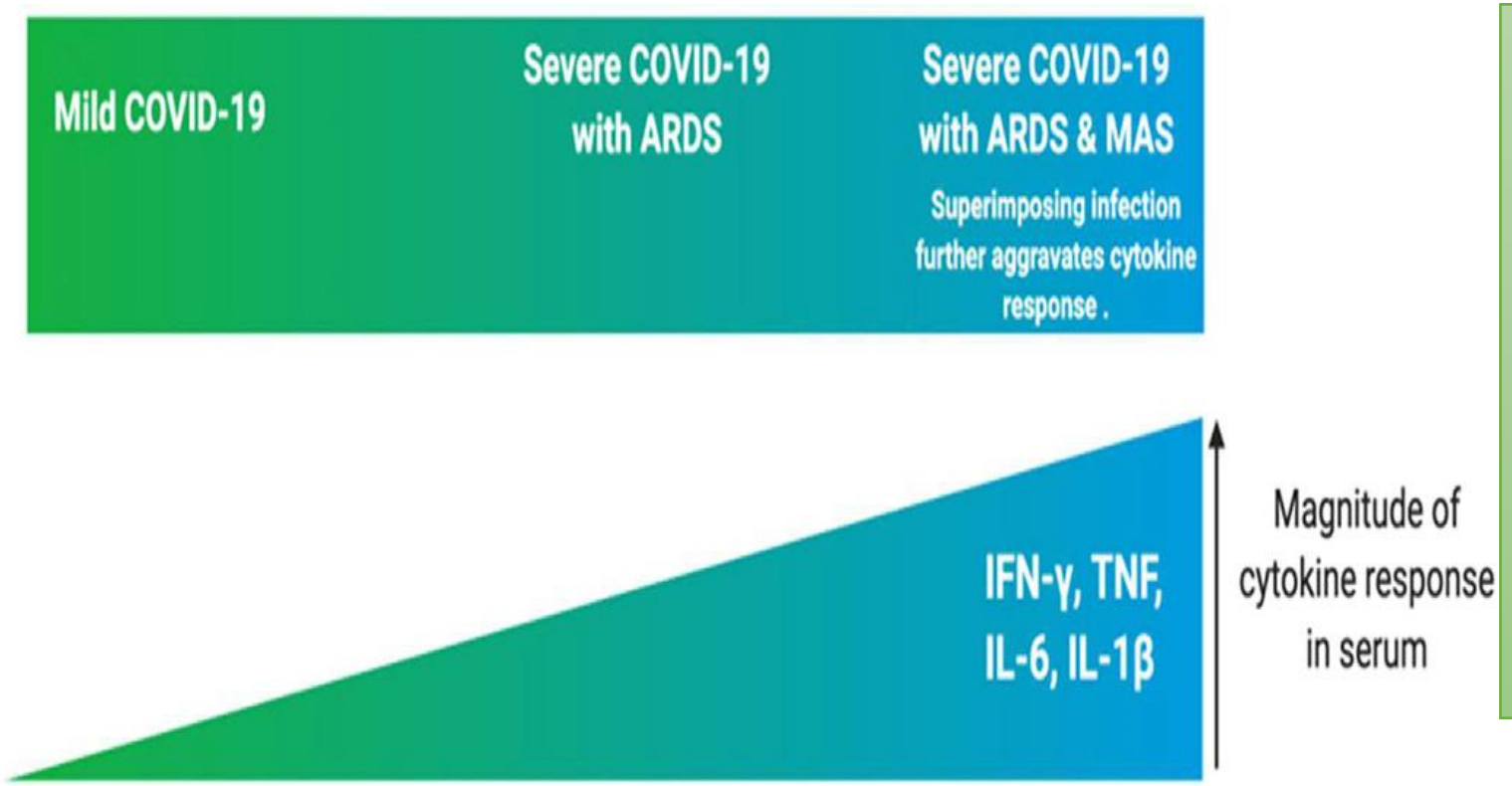
prominent alveolar oedema, hyalonosis, fibrin deposition, pneumocytes viral cytopathic change, immune cell infiltration



COVID-19: lung-centric

- high CRP, ferritin, coagulopathy, abnormal liver function
- cytokine profile: ↑IL-1β, IL-2, IL-6, IL-17, IL-8, TNF, CCL2
- **absence of hepatosplenomegaly**
- ↑D-dimer: pulmonary immunopathology to adjacent microcirculation → extensive secondary fibrinolytic activation

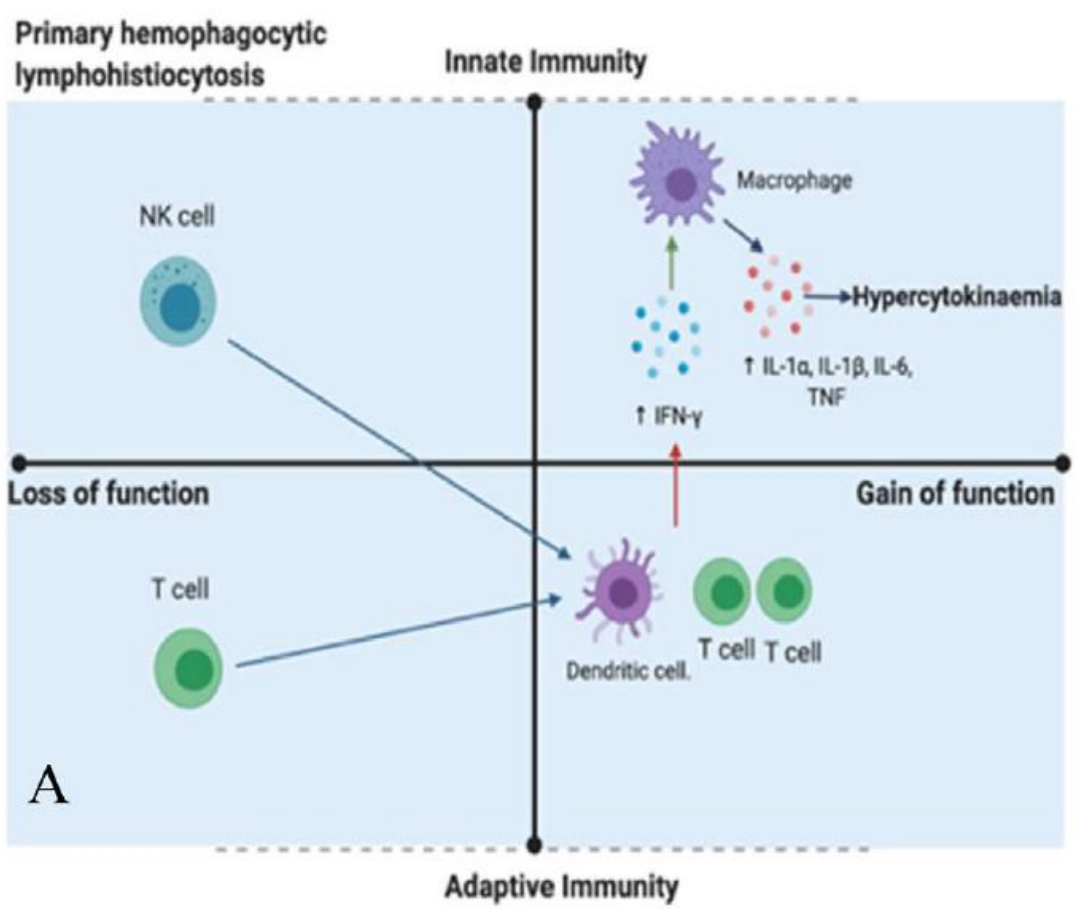
Hyper-cytokineaemia Overlaps between ARDS and MAS

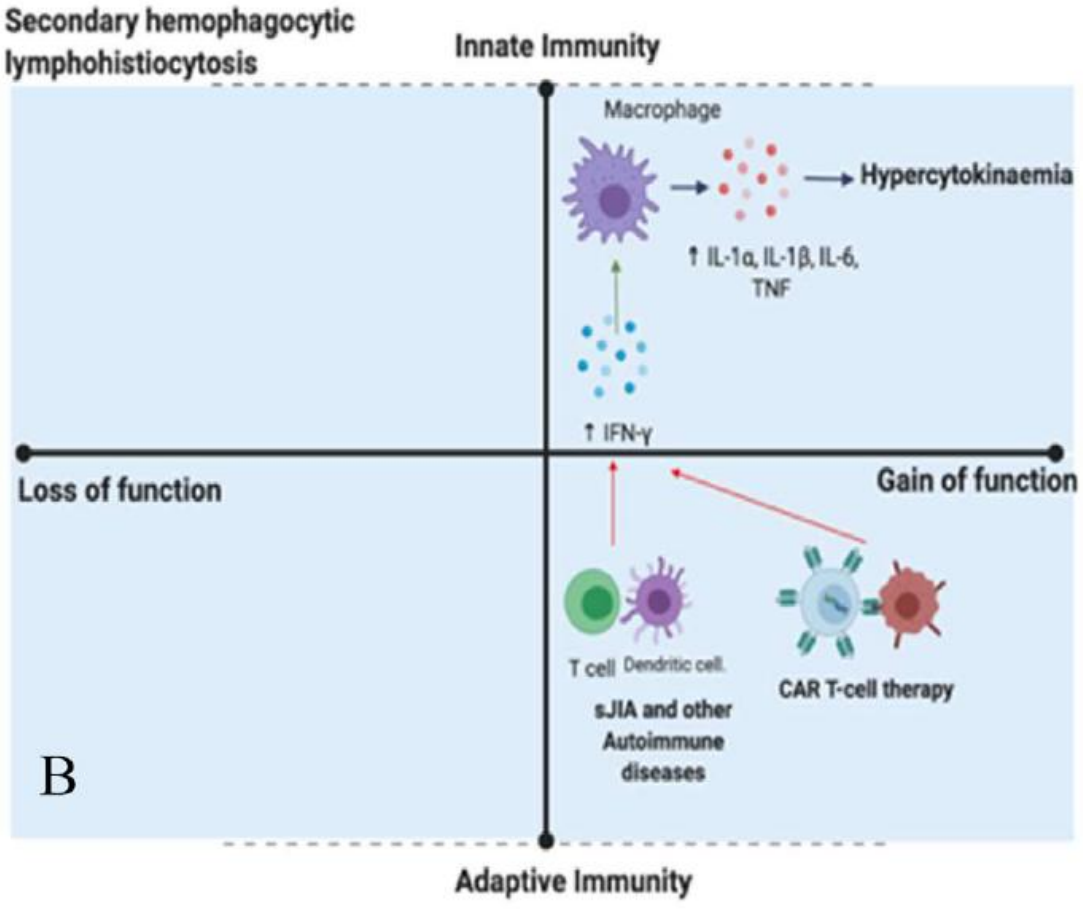


The magnitude of cytokine level changes may not be reliable in the differentiation from other cause of elevated cytokine levels including severe infection or tissue destruction and also no dependable cut-off values

A new proposed integrated innate and adaptive immune mechanisms in MAS/HLH

- Primary HLH: hyper-inflammation + immunodeficiency
- COVID-19 induction of a temporary immunodeficiency state (resembling primary HLH) & MAS/sHLH (may occur in immunocompetent states)

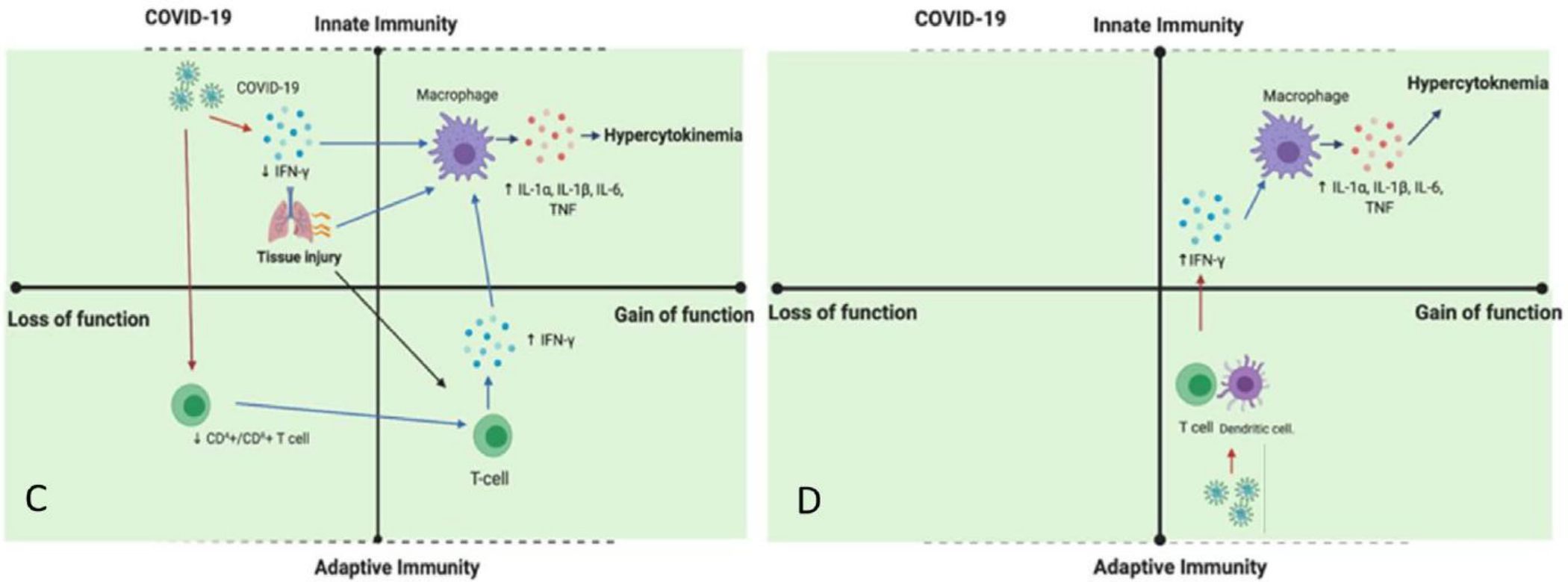




pHLH: genetic defect (NK and CD8+ T-cells) cannot be cured with anti-cytokine strategies

CAR-T cell therapy: hyper proliferating engineered T-cells may drive MAS/sHLH, only lasts during the presence of detectable tumor antigen

COVID-19 Immunodeficiency State Vs Immunocompetency State



Virally induced immunosuppression: low INFγ production by CD4+ T cell, lymphopenia→macrophage infiltration and the "second wave" of non-type-1 interferon pathway cytokines (IL-6, IL-1, IL-18, INFγ, GM-CSF...)

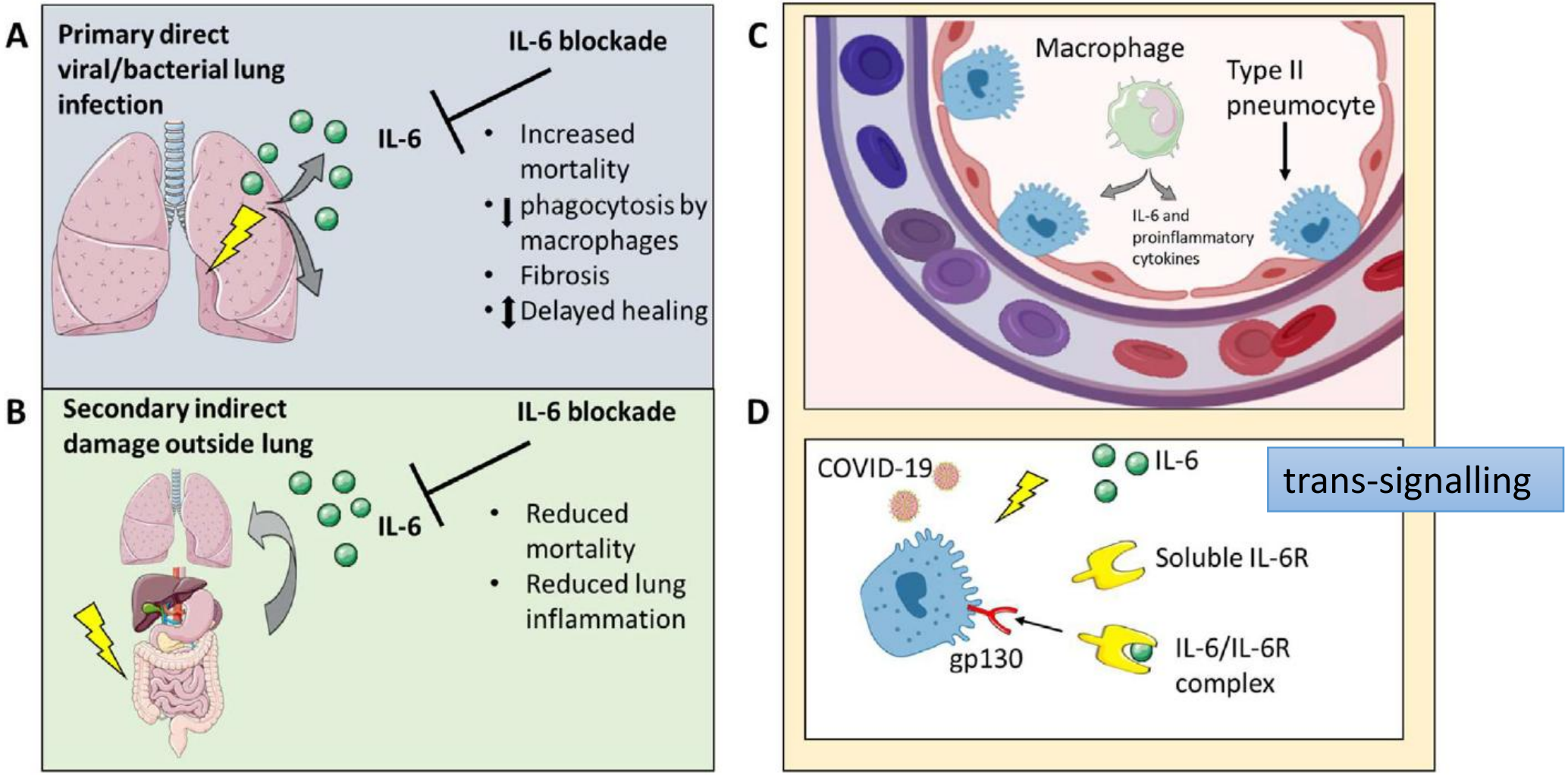
Exaggerated immune response including IFN driven and T-cell driven responses that clears the virus but induces pulmonary immune system collateral damage and ARDS

IL-6 and immune function in COVID-19 related pneumonia

Impact of Interleukin-6 on viral pneumonitis and lung Injury.

Experimental model	Key findings
Infection of human epithelial cells with SARS-CoV	• SARS-CoV induces greater IL-6 when compared to Influenza-A virus and human parainfluenza virus type 2
Infection of monocytes/macrophages with SARS-spike protein	• Upregulation of IL-6
Murine SARS-CoV model	• Disease dependent on infiltrating monocytes, which produced high levels of IL-6, IL-1β and TNF
Influenza infection with IL-6 KO mice	IL-6 KO mice show • Increased mortality • Reduced macrophage phagocytic function • Fibroblast proliferation, migration and collagen deposition • Prevents viral induced neutrophil death
HSV-1 respiratory infection with IL-6KO mice	• IL-6 KO mice show increased mortality
Experimental ARDS induced by the intratracheal instillation of bacterial endotoxin	• Reduced pulmonary inflammation by the addition of recombinant IL-6
Infectious models of tuberculosis, pneumococcal pneumonia and pulmonary aspergillosis	• IL-6 KO mice show increased mortality in all infectious models
Bleomycin lung injury model with IL-6 neutralization	IL-6 neutralization resulted in: • Accelerated type 2 pneumocyte apoptosis • Neutrophilic inflammation • Accelerated lung fibrosis
Rat model of bacterial sepsis remote from the lung with tocilizumab	Tocilizumab (anti-IL-6) resulted in: • Reduced sepsis-induced pulmonary and renal inflammatory • Decreased mortality

IL-6 in Viral Pneumonia and Potential Role in Type II Pneumocyte COVID-19 infection



Key messages and considerations for IL-6 for COVID-19 pneumonia, ARDS and MAS

Therapy considerations based on COVID-19 MAS-like picture.

	Primary HLH features	Secondary HLH pattern
Immune state	Viral induced immunodeficiency	Normal Immune response/ Hypersensitivity
Viral Load	Persistent Viral Shedding more likely	Initial Viraemia VViral shedding expected to disappear with vigorous T-cells responses to COVID-19 infected cells.
Progression rate	Unclear	Unclear Rapid deterioration 2nd week?
Resolution rate	Slower resolution	May quickly improve on viral load elimination?
CRP	Elevated + +	Elevated + + +
Ferritin	Elevated + +	Elevated + + (possible rapid rise)
Anti-viral therapy	Consider Anti-viral therapy	?
Corticosteroids	Caution (increase viraemia)	consider if viraemia cleared/clearing
Anti-IL-6R and biologics	Less likely to benefit (may cause harm)	More likely benefit
Frequency	Very common	Less common

Anti-IL-6R TOO EARLY: adversely affect viral clearance
Corticosteroid: not suggested based on the clinical experience in SARS-CoV, MER-CoV