讀書分享會

Cytokine Release Syndrome in Severe COVID-19

Lessons from arthritis and cell therapy in cancer patients point to therapy for severe disease

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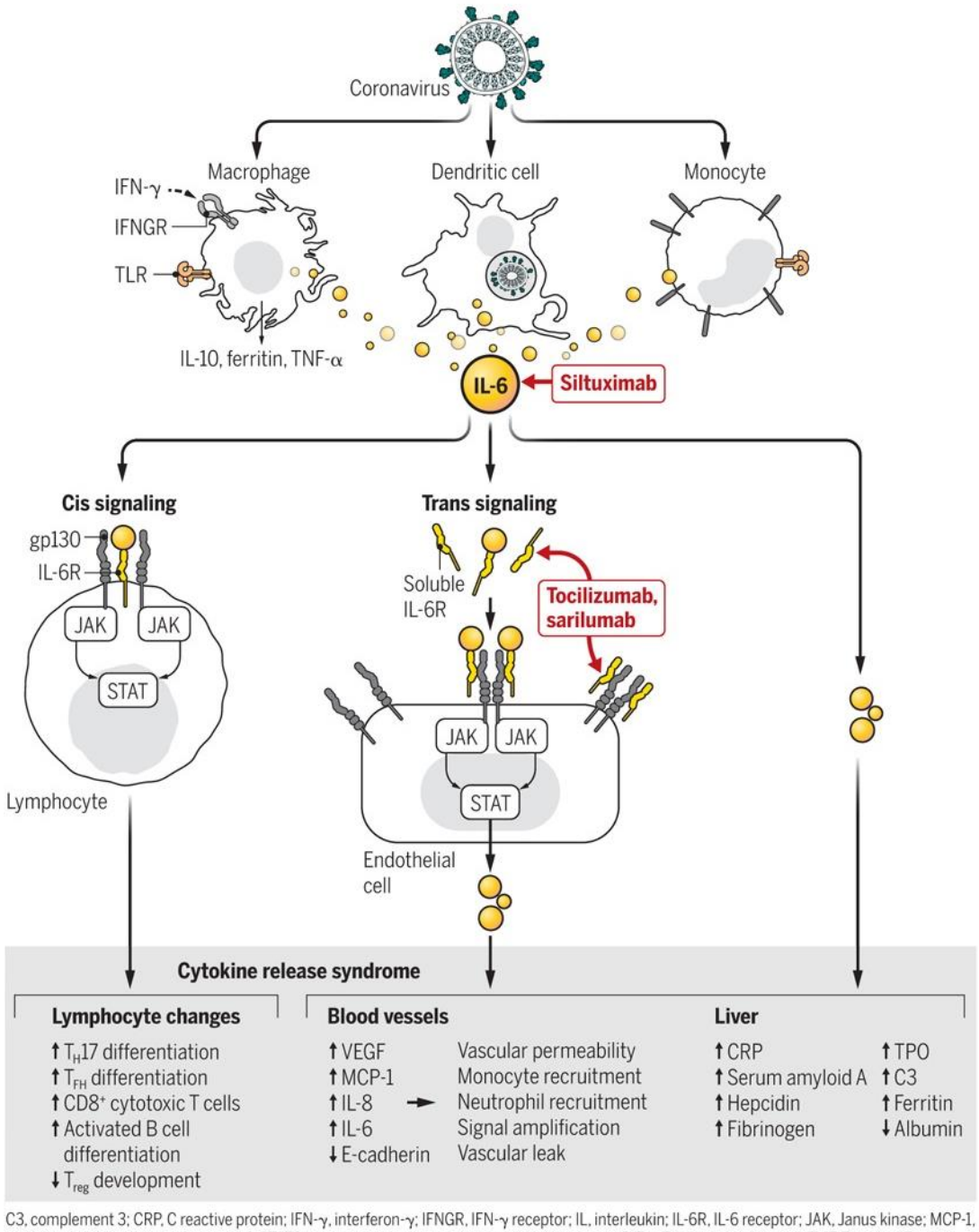
Severe Disease of Coronavirus Disease 2019 (COVID-19)

- **Fever**, **pneumonia**, and **acute respiratory distress syndrome (ARDS)**
- Reminiscent of **cytokine release syndrome (CRS)-induced ARDS** & **secondary hemophagocytic lymphohistiocytosis (sHLH)**
  - Seen in SARS-CoV & MERS-CoV
  - In leukemia patients receiving engineered T cell therapy

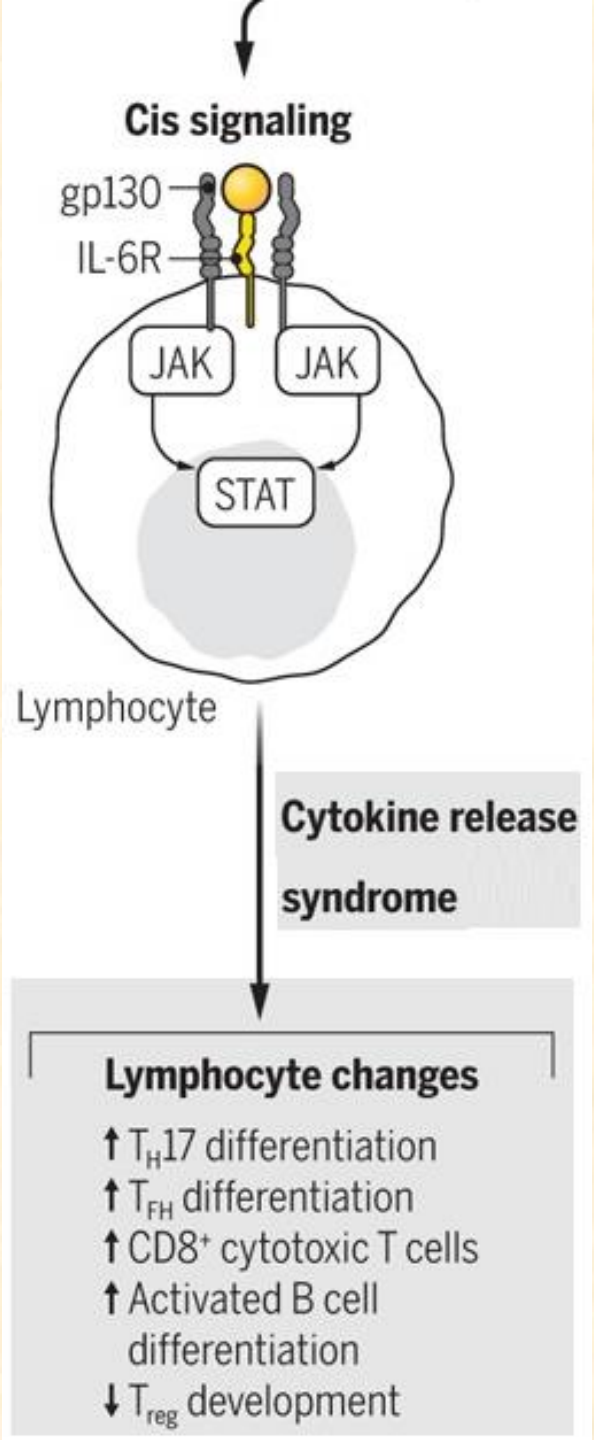
CRS was found to be the major cause of morbidity in patients infected with SARS-CoV and MERS-CoV.



C3, complement 3; CRP, C reactive protein; IFN-γ, interferon-γ; IFNGR, IFN-γ receptor; IL, interleukin; IL-6R, IL-6 receptor; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein–1; STAT3, signal transducer and activator of transcription 3; T_{FH}, T follicular helper cell; T_H17, T helper 17 cell; TNF-α, tumor necrosis factor–α; TLR, Toll-like receptor; TPO, thrombopoietin; T_{reg}, T regulatory cell; VEGF, vascular endothelial growth factor.

Interleukin-6 (IL-6):

- Implicated in the pathogenesis of many diseases, such as autoimmune diseases, multiple myeloma and prostate cancer.
- **Proinflammatory** properties
- Two main signal pathways: **cis signaling** & **transsignaling**
- Result in systemic cytokine storm
- Elevated serum IL-6 in COVID-19 **correlates with respiratory failure, ARDS, and adverse clinical outcomes**.



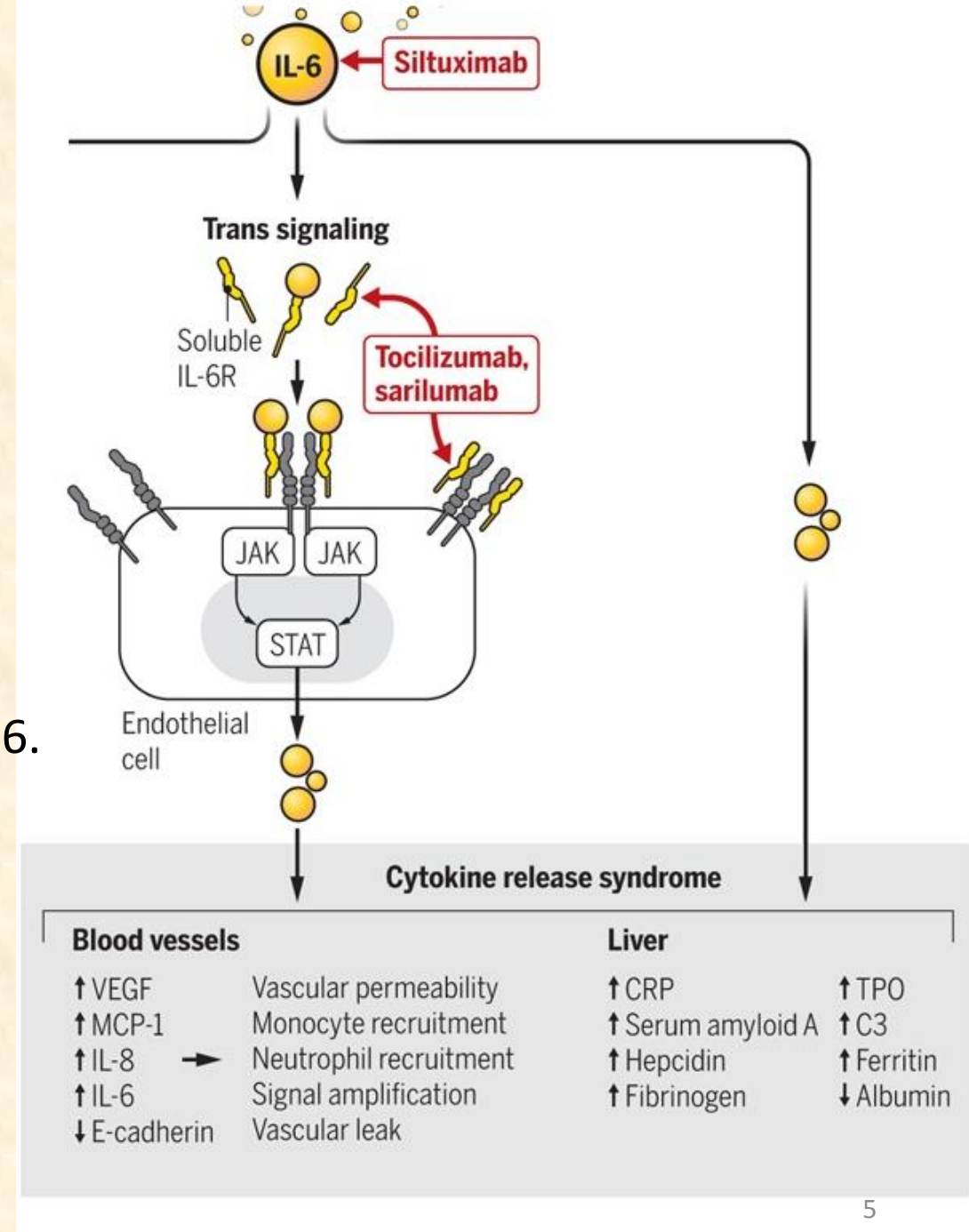
Cis signaling:

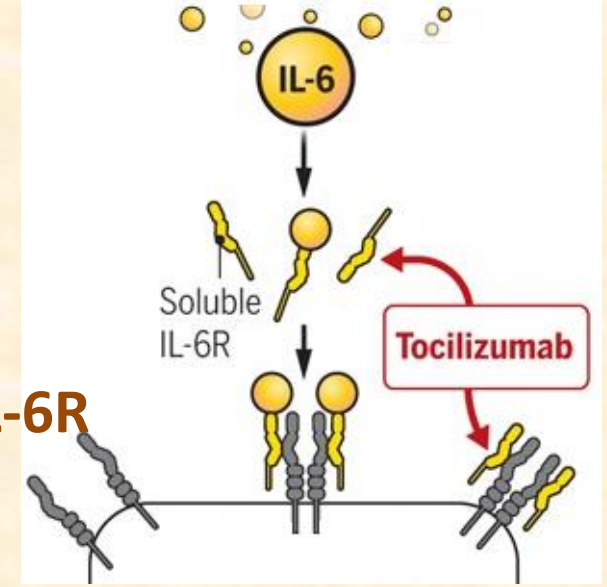
- IL-6 binds to membrane-bound IL-6 receptor (mIL-6R) in a complex with gp130.

- Cis signaling results in effects on the **acquired immune system** (B and T cells) **as well as the innate immune system** [neutrophils, macrophages, and natural killer (NK) cells], which can contribute to CRS.

Trans signaling:

- Circulating IL-6 molecules bind to the soluble form of IL-6R (sIL-6R), forming a complex with a gp130 dimer on potentially all cell surfaces, such as **endothelial cells**.
- Secretion of vcular endothelial growth factor (VEGF), monocyte chemoattractant protein–1 (MCP-1), IL-8 and IL-6.
- **VEGF** and **reduced E-cadherin** expression contribute to **vascular permeability** and leakage → **hypotension** and **pulmonary dysfunction** in ARDS





Tocilizumab:

- A **humanized monoclonal antibody against IL-6R**
- An immunosuppressive drug, mainly for treatment of rheumatoid arthritis
- Approved by the U.S. Food and Drug Administration (FDA) for the treatment of CAR T cell–induced CRS
- Clinical trials to treat COVID-19
  - Result of a preliminary open study of 21 patients with COVID-19 in China was encouraging. (Fever subsided in all patients within the first day. Oxygen requirements were reduced in 75% of the patients.) [China XiV 202003 (5 March 2020)]

Corticosteroid use in SARS and MERS patients:

- did not improve mortality
- resulted in **delayed viral clearance**

The expert consensus from infectious disease authorities is to avoid systemic corticosteroids in COVID-19 patients.

Theoretical possibility:

IL-6/IL-6R antagonism delays viral clearance**?**

Another concern:

The complication of IL-6 antagonists, ex. fungal infections or osteonecrosis

- The complications usually occurred in patients dosed monthly on these drugs for chronic conditions such as rheumatoid arthritis.
- One or two doses are unlikely to result in complications.

- Tocilizumab was first approved for rheumatic conditions, then for CRS in patients receiving CAR T cell therapy, and is now being repurposed for the COVID-19 pandemic. It is possible that it will be used in future pandemics involving other viruses such as influenza and Ebola.

- The immediate goal of IL-6 antagonism is to **ameliorate severe COVID-19** cases. The long-term goal should include a focus on the development of antivirals and vaccines.

thank you!

謝謝聆聽

THANK YOU FOR YOUR ATTENTION