

Dysregulated Immune Response in Sepsis

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Sepsis

: *Dysregulated host response to infection*

Sepsis and Septic Shock

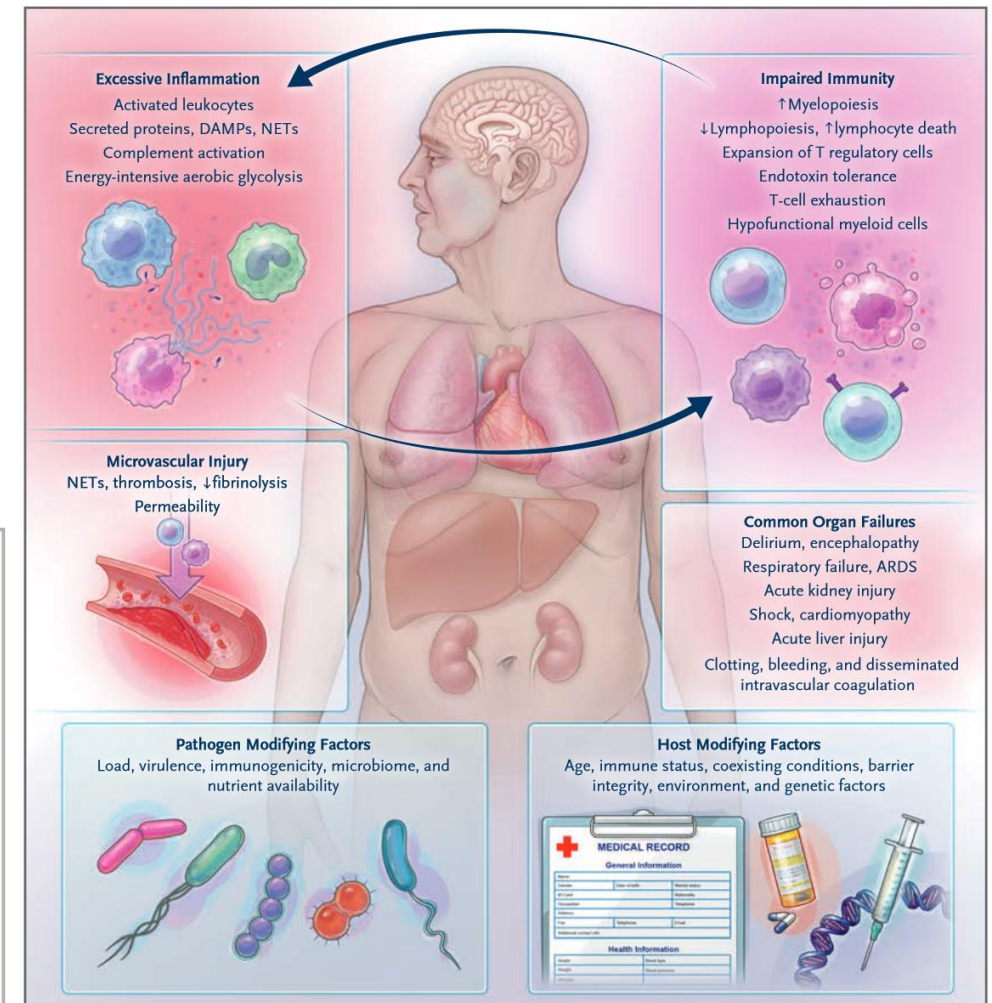
Nuala J. Meyer, M.D., and Hallie C. Prescott, M.D.

SEPSIS, A SYNDROME OF LIFE-THREATENING, ACUTE ORGAN DYSFUNCTION due to a dysregulated response to infection, is a major global health burden. Worldwide, an estimated 48.9 million cases of sepsis and 11 million related deaths occur annually.¹ In the United States, more than one third of in-hospital deaths are attributed to sepsis,² at costs exceeding \$38 billion in 2017, which makes sepsis both the most common cause of in-hospital death and the most expensive cause of hospitalization.³

KEY POINTS

SEPSIS AND SEPTIC SHOCK

- Sepsis is a syndrome of life-threatening acute organ dysfunction due to bacterial, fungal, parasitic, or viral infection.
- Factors that affect the risk of sepsis include age, immune status, pathogen virulence, and pathogen burden.
- Sepsis is associated with long-term complications among survivors.
- Biologic features of sepsis include dysregulated inflammation, immunosuppression, and vascular injury.
- Management of sepsis focuses on prompt infection control and hemodynamic resuscitation.
- Research is ongoing to determine whether and how to modulate the host immune response in order to improve outcomes.



Immunopathophysiology of sepsis

- Extensive research has emphasized the *role of dysregulated immune responses* in sepsis pathophysiology,
 - but only a few immunoadjuvant treatments have shown signals of efficacy and robust positive findings have yet to be produced for clinical endpoints
- The **heterogeneity** *of immune dysregulation* in patients with sepsis explains the many failed attempts to target the dysregulated immune response in clinical trials

Sepsis: *A complex and heterogeneous state*

- Concurrent **proinflammatory** and **anti-inflammatory** responses
- The heterogeneity of the immune response can be ascribed to
 - **Age** (very old over 70 YRs and very young less than 1 YR)
 - Different **infectious causes**
 - **Sites** of infection
 - Host **genetics**
 - Applied **treatments**
 - Rapidly **changing illness dynamics** of sepsis

Profiling the dysregulated immune response in sepsis

- “Precision Medicine”

Review > Lancet Respir Med. 2024 Apr;12(4):305-322. doi: 10.1016/S2213-2600(23)00330-2. Epub 2023 Dec 21.

Profiling the dysregulated immune response in sepsis: overcoming challenges to achieve the goal of precision medicine

Sara Cajander¹, Matthijs Kox², Brendon P Scicluna³, Markus A Weigand⁴, Raquel Almansa Mora⁵, Stefanie B Flohé⁶, Ignacio Martin-Loeches⁷, Gunnar Lachmann⁸, Massimo Girardis⁹, Alberto Garcia-Salido¹⁰, Frank M Brunkhorst¹¹, Michael Bauer¹², Antoni Torres¹³, Andrea Cossarizza¹⁴, Guillaume Monneret¹⁵, Jean-Marc Cavaillon¹⁶, Manu Shankar-Hari¹⁷, Evangelos J Giamarellos-Bourboulis¹⁸, Martin Sebastian Winkler¹⁹, Tomasz Skireckj²⁰, Marcin Osuchowski²¹, Ignacio Rubio¹², Jesus F Bermejo-Martin²², Joerg C Scheffold²³, Fabienne Venet²⁴

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Abstract

Sepsis is characterised by a dysregulated host immune response to infection. Despite recognition of its significance, immune status monitoring is not implemented in clinical practice due in part to the current absence of direct therapeutic implications. Technological advances in immunological profiling could enhance our understanding of immune dysregulation and facilitate integration into clinical practice. In this Review, we provide an overview of the current state of immune profiling in sepsis, including its use, current challenges, and opportunities for progress. We highlight the important role of immunological biomarkers in facilitating predictive enrichment in current and future treatment scenarios. We propose that multiple immune and non-immune-related parameters, including clinical and microbiological data, be integrated into diagnostic and predictive combitypes, with the aid of machine learning and artificial intelligence techniques. These combitypes could form the basis of workable algorithms to guide clinical decisions that make precision medicine in sepsis a reality and improve patient outcomes.

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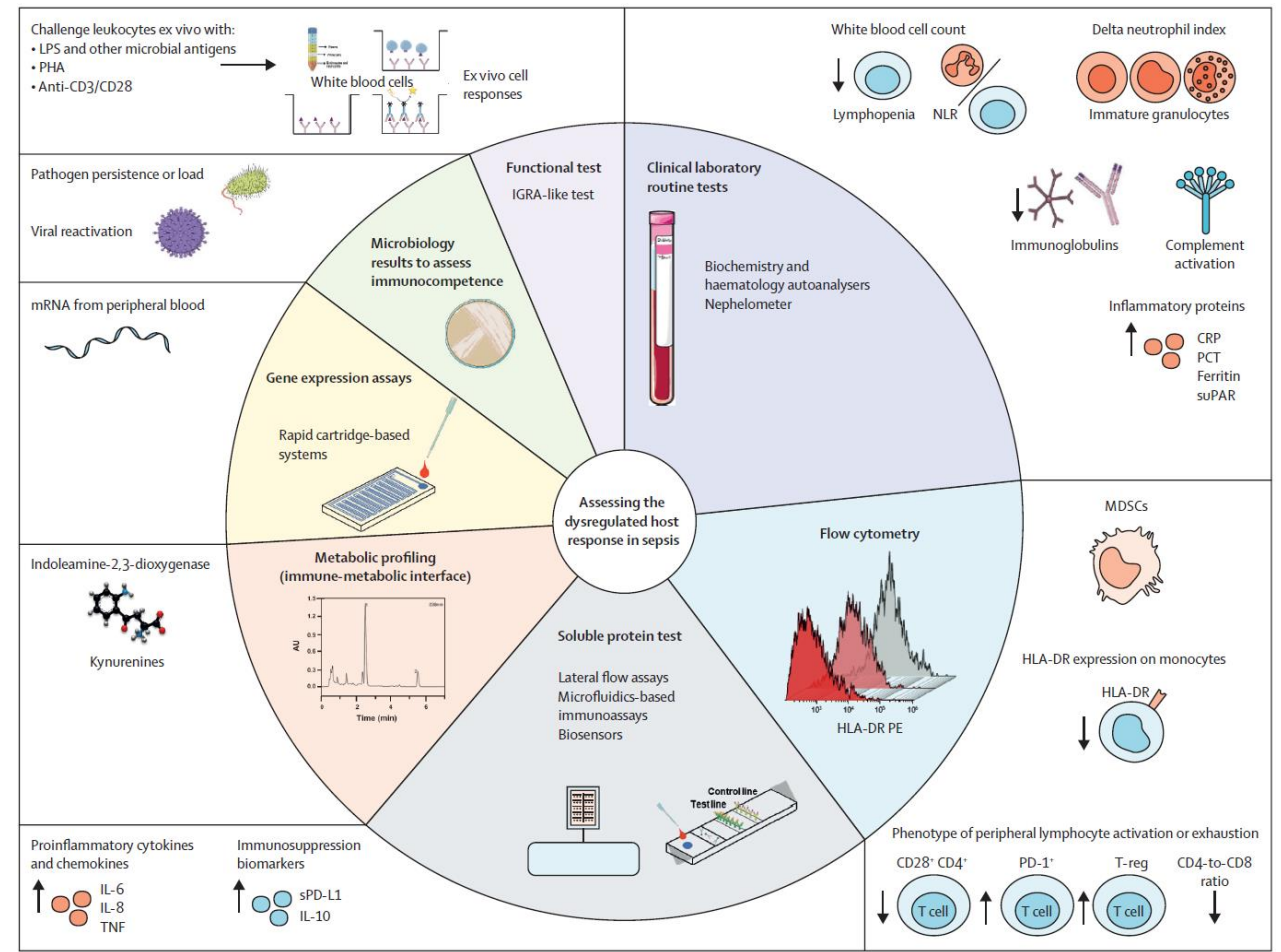
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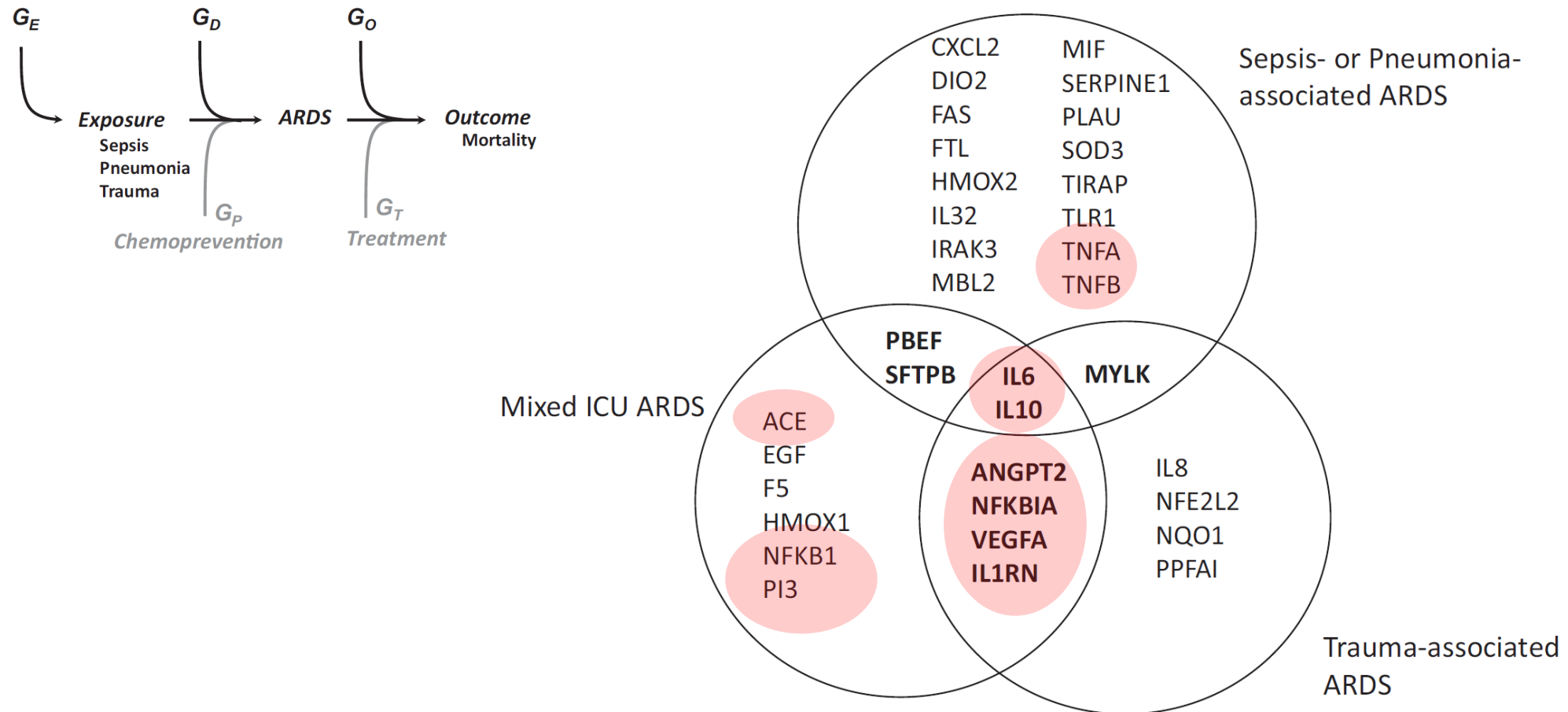
MeSH terms

Related information



Cajander S, et al. Lancet Respir Med. (2024)

Immune pathology associated with “*dysregulated inflammation*” in the resp. tract

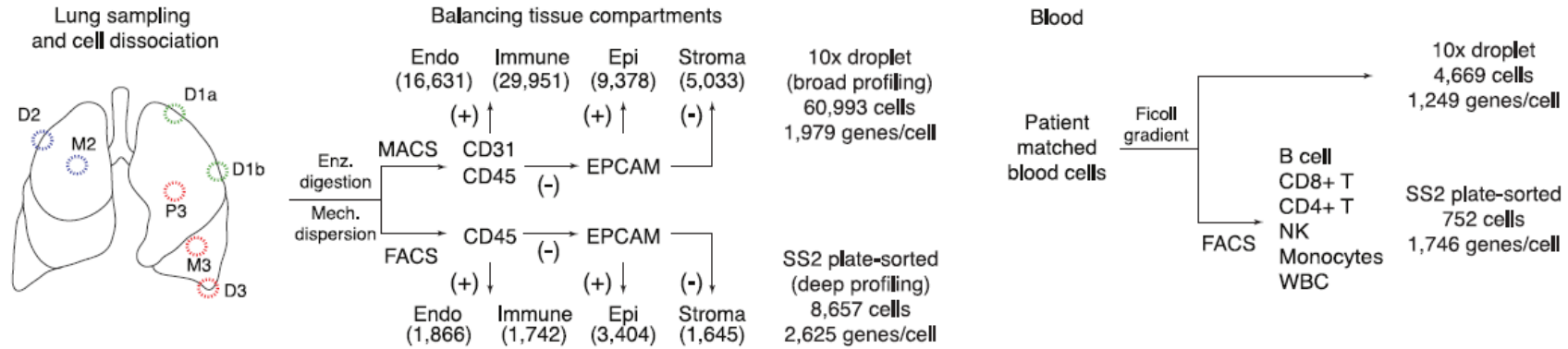


Immune/inflammation process

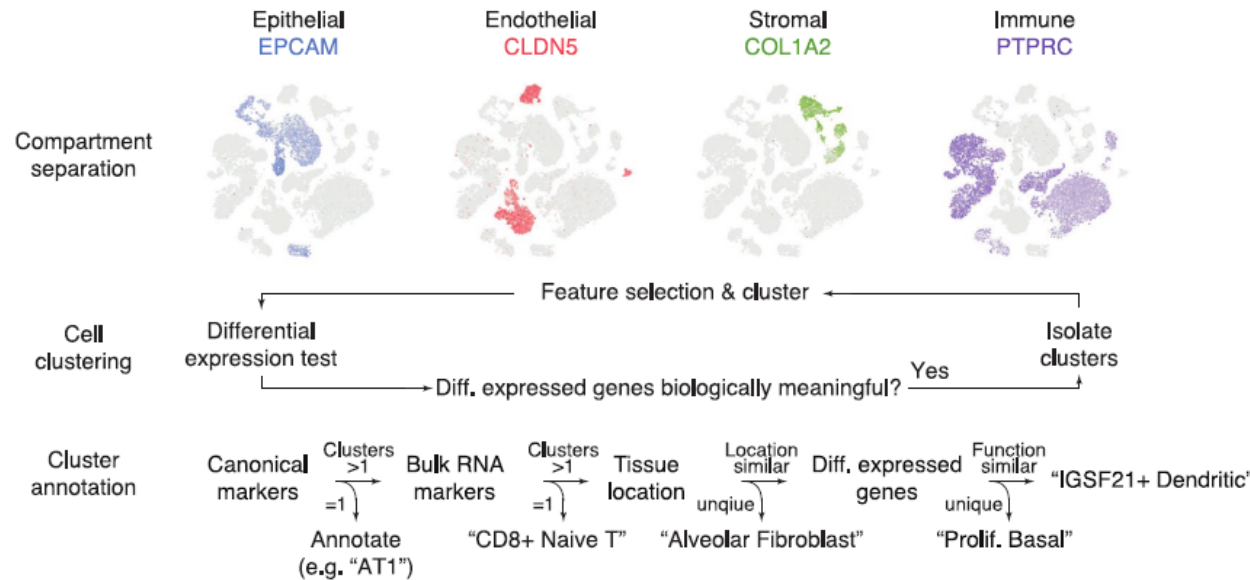
*“How many **functionally independent cell subtypes** exist in the tracheobronchial trees and lungs?”*

A *molecular cell atlas* of the human lung

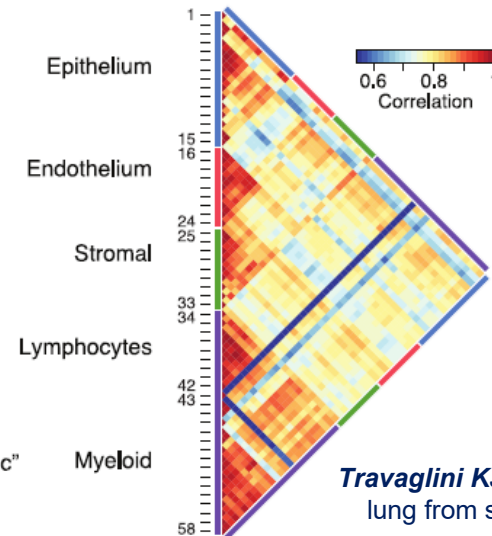
a Cell isolation, balancing, and sequencing



b Cell clustering and annotation

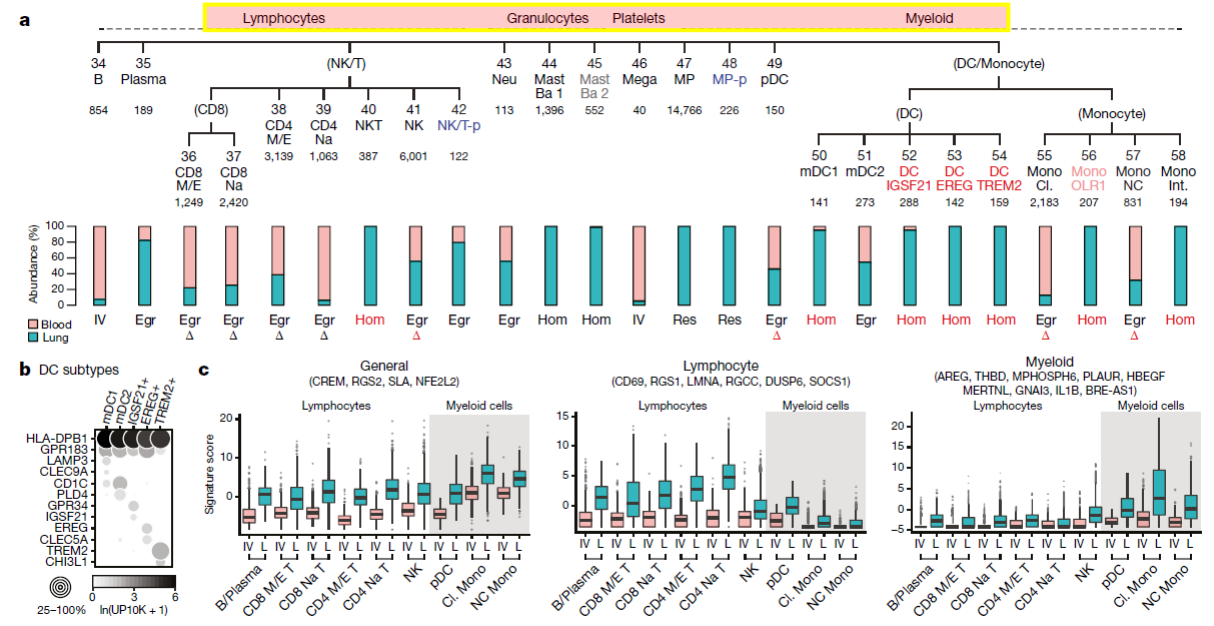
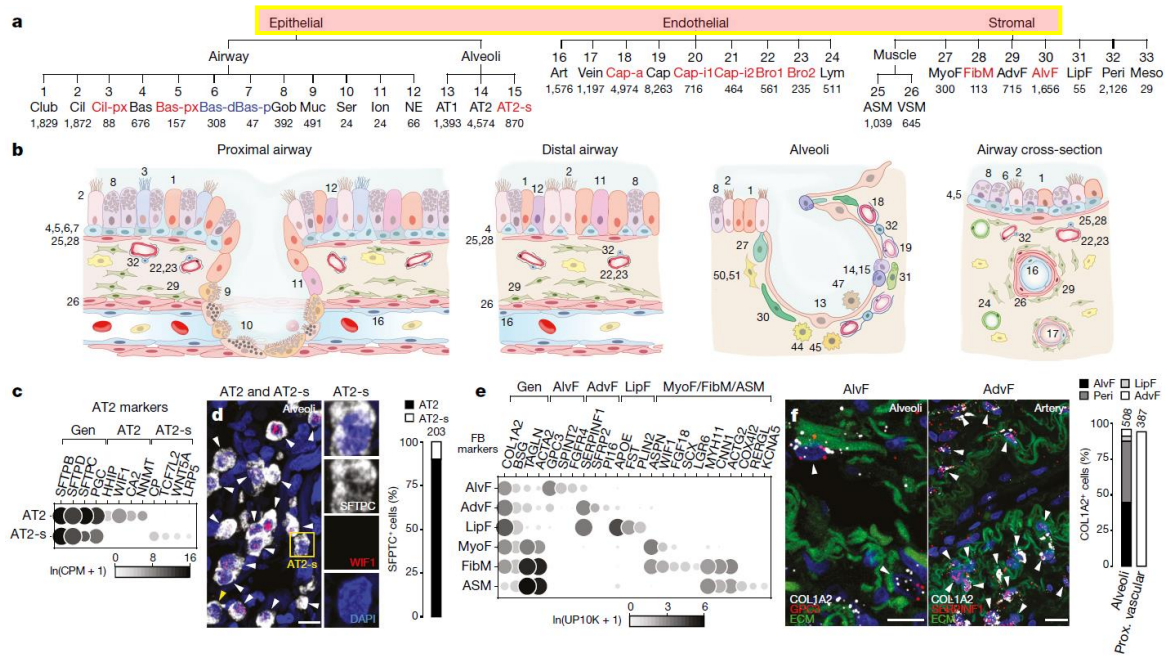


c Cell clusters



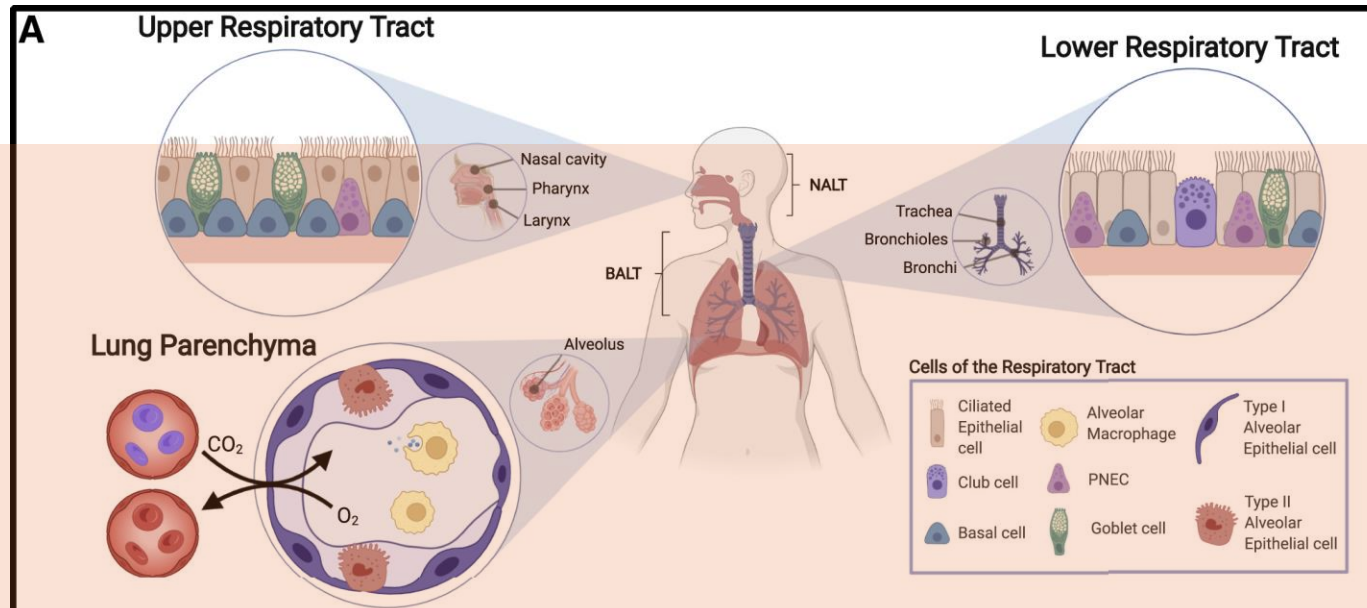
Travaglini KJ, et al. A molecular cell atlas of the human lung from single-cell RNA sequencing. *Nature*. (2020)

A *molecular cell atlas* of the human lung

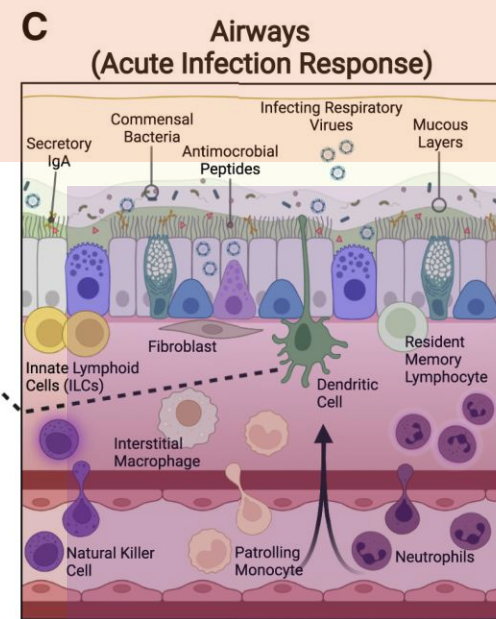
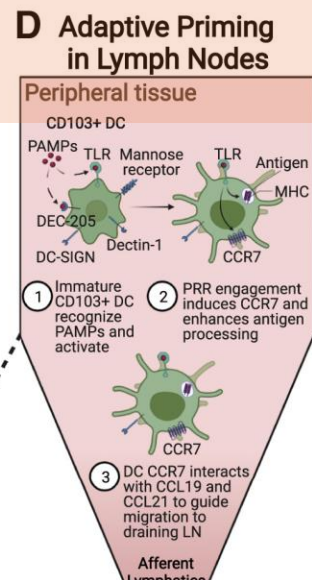
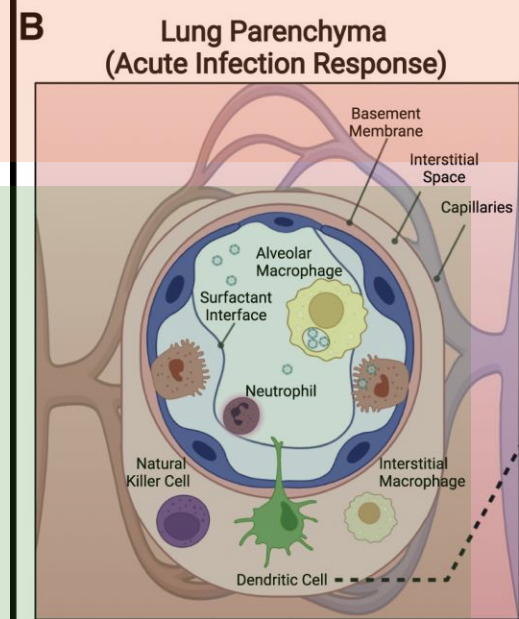


Travaglini KJ, et al. A molecular cell atlas of the human lung from single-cell RNA sequencing. *Nature*. (2020)

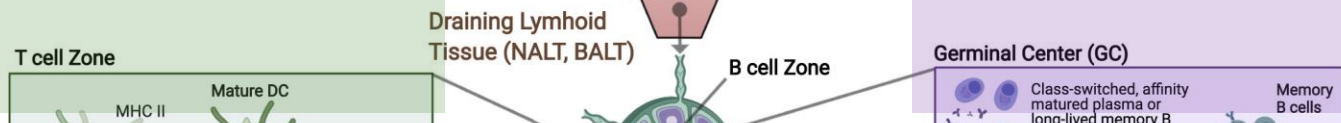
Innate immunity



T cell immunity

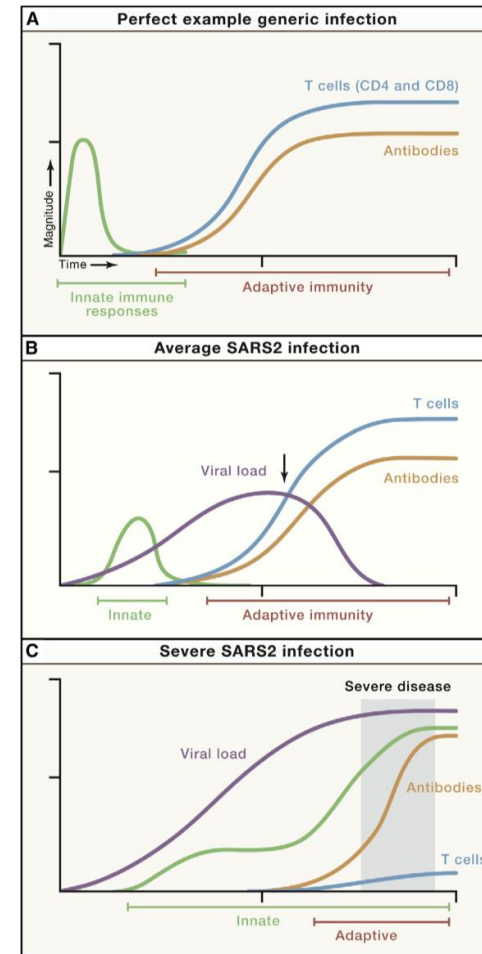
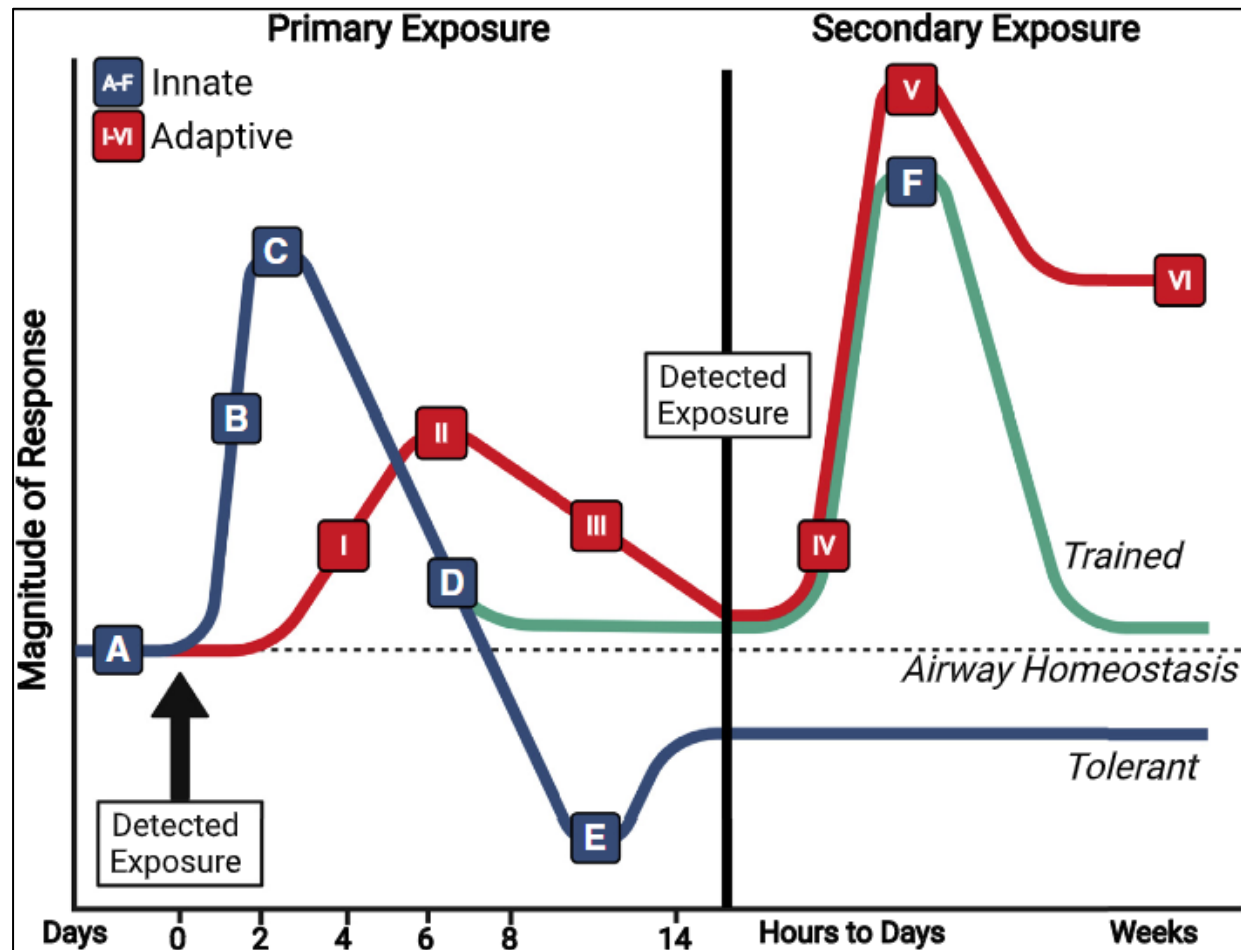


B cell immunity



Mucosal immune responses to infection and vaccination in the respiratory tract. *Immunity*. (2022)

Innate and adaptive immune response magnitude dynamics *over time*

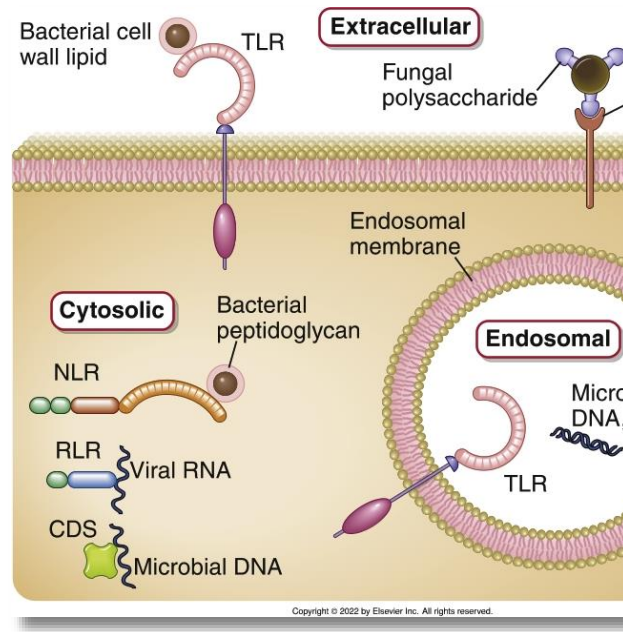


Mettelman, RC, et al. Mucosal immune responses to infection and vaccination in the respiratory tract. *Immunity*. (2022)

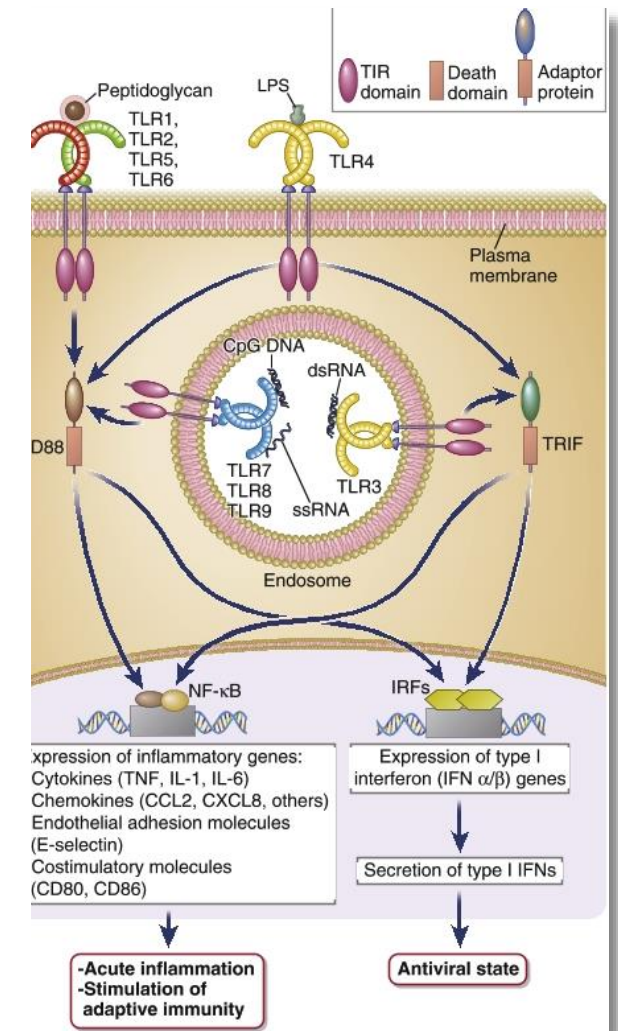
Sette A, et al. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell*. (2021)

Innate Immune Cell-Mediated Pathogenesis

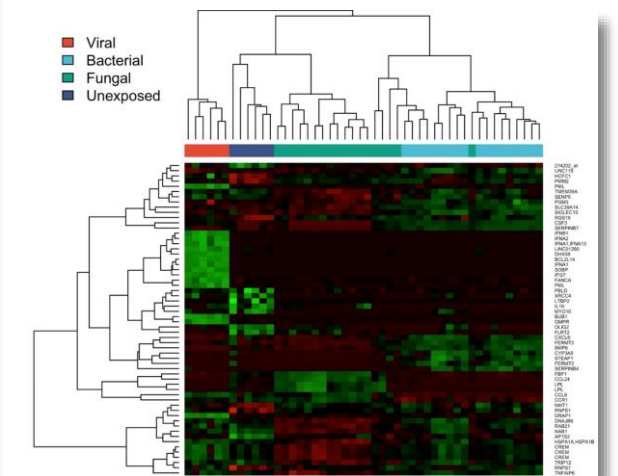
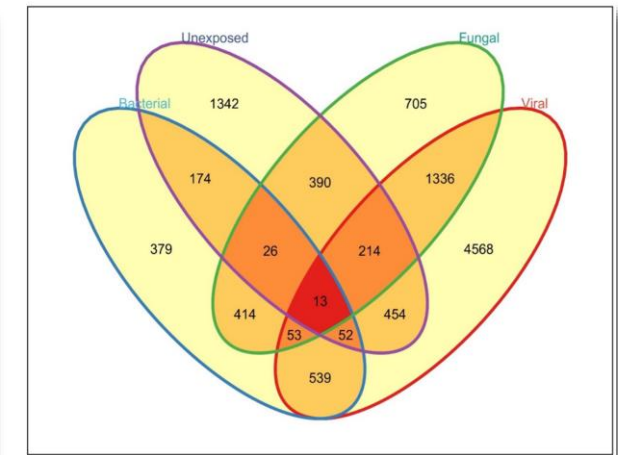
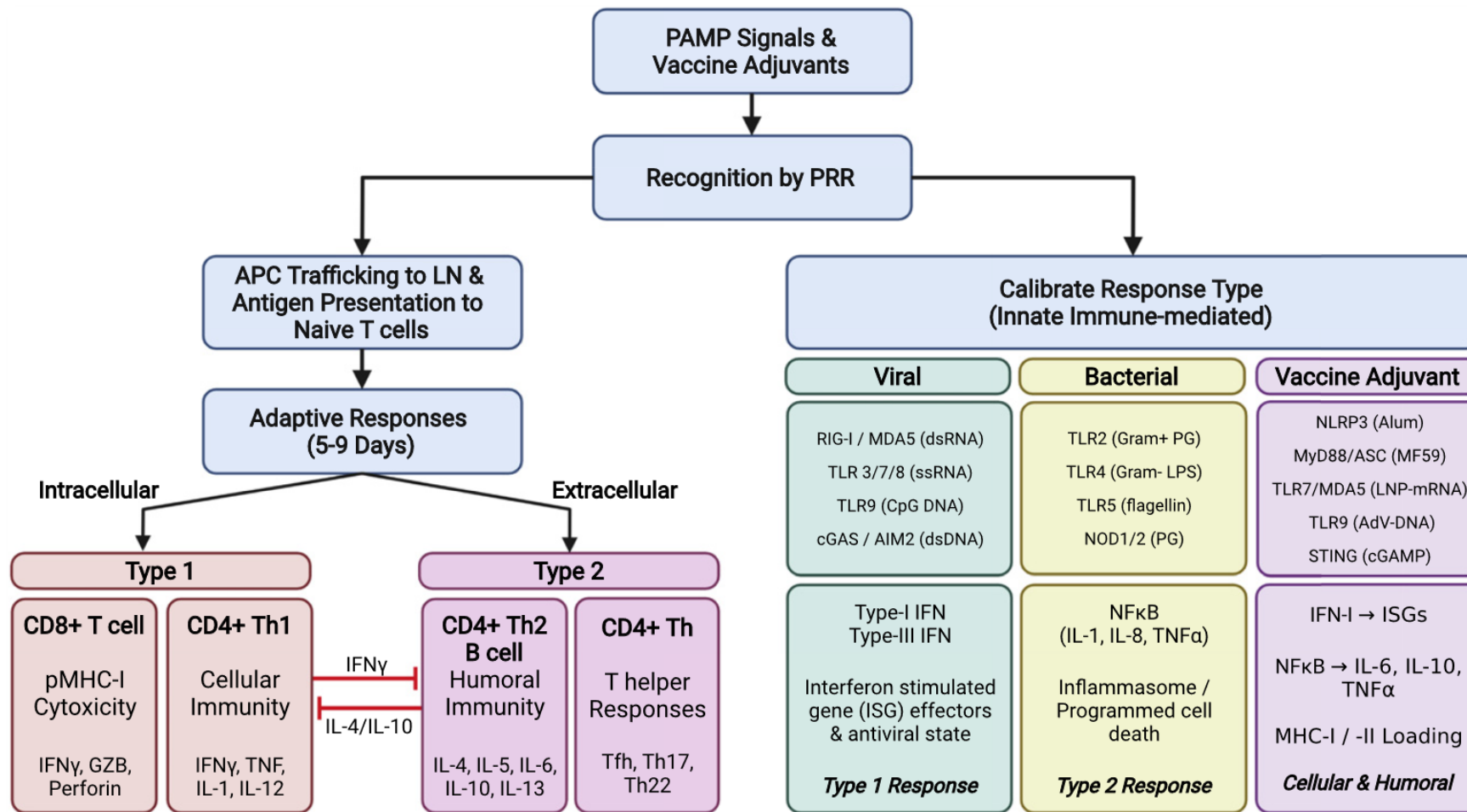
Pattern Recognition Receptors (*PRRs*)



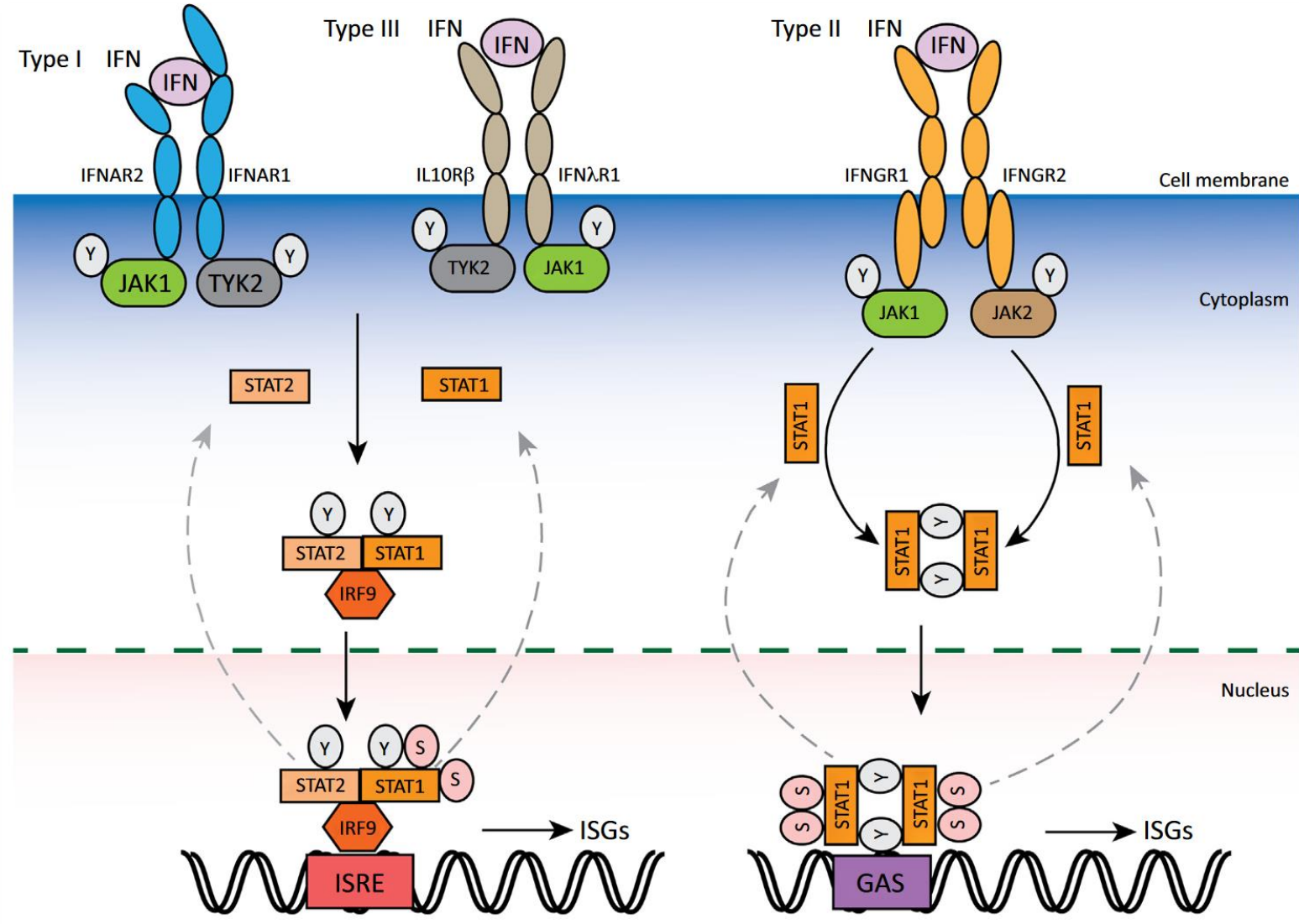
Feature	Innate immunity	Adaptive immunity
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns)	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens
Microbial molecules recognized	About 1000 molecular patterns (estimated); essential for survival of microbes; usually cannot be mutated	>10 ⁷ antigens; most are nonessential and can be mutated to evade immunity
Receptors	Located in plasma membrane, endosomal membrane, cytosol	Located only in plasma membrane
Number and types of receptors	About 100 different types of invariant receptors	Only 2 types of receptors (Ig and TCR), with millions of variations of each
Distribution of receptors	Nonclonal: identical receptors on all cells that express the receptors	Clonal: clones of lymphocytes with distinct specificities express different receptors
Genes encoding receptors	Germline encoded, in all cells	Formed by somatic recombination of gene segments only in B and T cells
Discrimination of self and nonself	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on elimination or inactivation of self-reactive lymphocytes; may be imperfect (hence the possibility of autoimmunity)



Acute pulmonary inflammation and downstream responses



Interferons (*IFNs*)



IFNs and interferon-stimulated genes (ISGs)

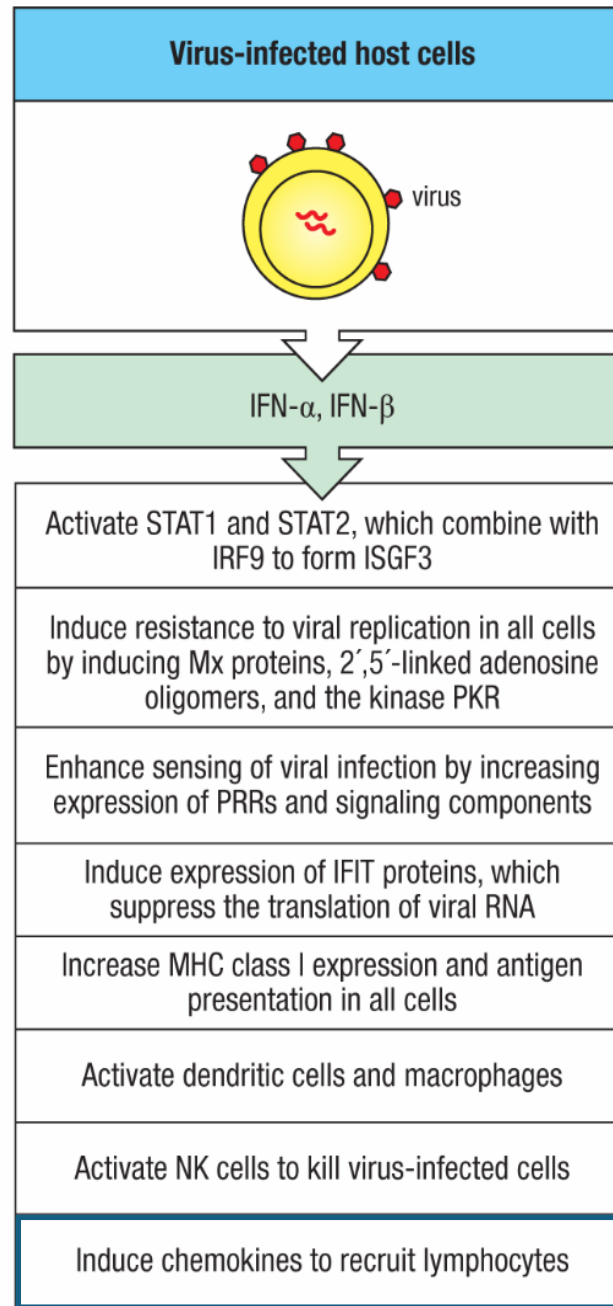
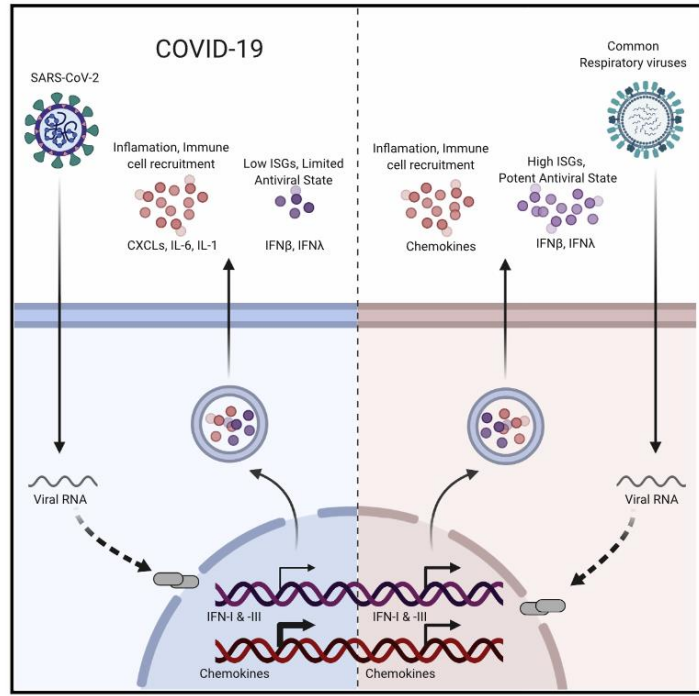


Table 1

Antiviral interferon-stimulated genes

Gene symbol	Targeted viruses	Viral life cycle	Mechanism related to antiviral activity
ADAR	HCV(r), HDV [enhances CHIKV, HIV-1, MV, VEEV, VSV, WNV, YFV]	replication	viral RNA editing, suppress PKR
APOBEC3	HIV-1, other retroviruses	replication	cytidine deamination of viral genome
BST2 (tetherin)	filovirus, FLUAV, HIV-1, LASV, VSV	egress/budding	block release of nascent virions
C6orf150 (MB21D1)	CHIKV, VEEV, WNV, YFV	translation	unknown
CD74	HIV-1	replication	unknown
DDIT4	HCV	translation	unknown
DDX58 (RIG-I)	numerous RNA and DNA viruses	translation, replication	viral sensing, activation of IRFs
DDX60	HCV, PV, VSV	translation (HCV)	promote RIG-I-like receptor signaling
EIF2AK2 (PKR)	numerous RNA and DNA viruses	translation	targets EIF2A
GBP1, GBP2	EMCV, HCV(r), VSV	replication	unknown
HPSE	CHIKV, VEEV, WNV, YFV	unknown	unknown
IFI44L	HCV	translation	unknown
IFI6/G1P3	HCV(r), YFV	unknown	unknown, possibly antiapoptotic
IFIH1 (MDA5)	numerous RNA and DNA viruses	translation, replication	viral sensing, activation of IRFs
IFIT1/2/3/5	FLUAV, HPV, MHV', RVFV, SINV, VSV, WNV'	translation, replication	target EIF3 subunits, target HPV helicase, bind 5'-triphosphate RNA
IFITM1/2/3	DENV, filovirus, FLUAV, HIV-1, SARS-CoV, VSV, WNV, YFV	entry	unknown, possibly target endocytic pathway
IRF1	numerous RNA and DNA viruses	similar to IFN	IFN induction, direct ISG induction
IRF7	numerous RNA and DNA viruses	similar to IFN	IFN induction, direct ISG induction
ISG15	FLUAV, HIV-1, HSV-1, JEV, MHV-68, SINV, VV Δ E3L	various	modulate protein function by ISGylation
ISG20	BVDV, DENV, EMCV, FLUAV, HCV, SINV, VSV, WNV(v), YFV	viral RNA synthesis	exonuclease activity
MAP3K14 (NIK)	HCV	translation	unknown, possibly NF- κ B activation
MOV10	HIV-1, HCV	post-entry (HIV-1)	unknown
MS4A4A	HCV	translation	unknown
MX1 (MxA)	CVB, FLUAV, HCV(r), HPIV3, LACV, MV, SFV, THOV, VSV, others	primary transcription, nucleocapsid shuttling	formation of highly ordered oligomers
MX2 (MxB)	HIV-1, HNTV, LACV, RVFV, VSV	unknown	unknown
NAMPT (PBEF1)	VEEV, WNV	unknown	unknown
NT5C3	HCV	translation	unknown
OAS1/2/3	CHIKV, DENV, EMCV, HCV(r), SFV, SINV, WNV	replication	activate RNaseL to degrade viral genome
OASL	HCV, HCV(r)	translation	unknown
P2RY6	CHIKV	unknown	unknown
PHF15	WNV	unknown	unknown
PML (TRIM19)	numerous RNA and DNA viruses	various	organize multiprotein nuclear bodies
RSAD2 (viperin)	DENV, DENV(v), FLUAV, HCMV, HCV(r), SINV, WNV(v)	egress (FLUAV)	perturb lipid rafts (FLUAV), promote TLR7/9 signaling
RTP4	YFV	unknown	unknown
SLC15A3	CHIKV	unknown	unknown
SLC25A28	CHIKV	unknown	unknown
SSBP3	HCV	translation	unknown
TREX1 (AGS1)	YFV	unknown	unknown
TRIM5	HIV-1, other retroviruses	before reverse transcription	target incoming capsids, promote innate signaling
TRIM25	FLUAV, VSV	similar to IFN	activate RIG-I via ubiquitination
SUN2 (UNC84B)	HIV-1	unknown	unknown
ZC3HAV1 (ZAP)	EBOV, FLUAV, MBGV, NDV, retrovirus, SINV	post-entry, translation	target viral RNA, promote RIG-I signaling

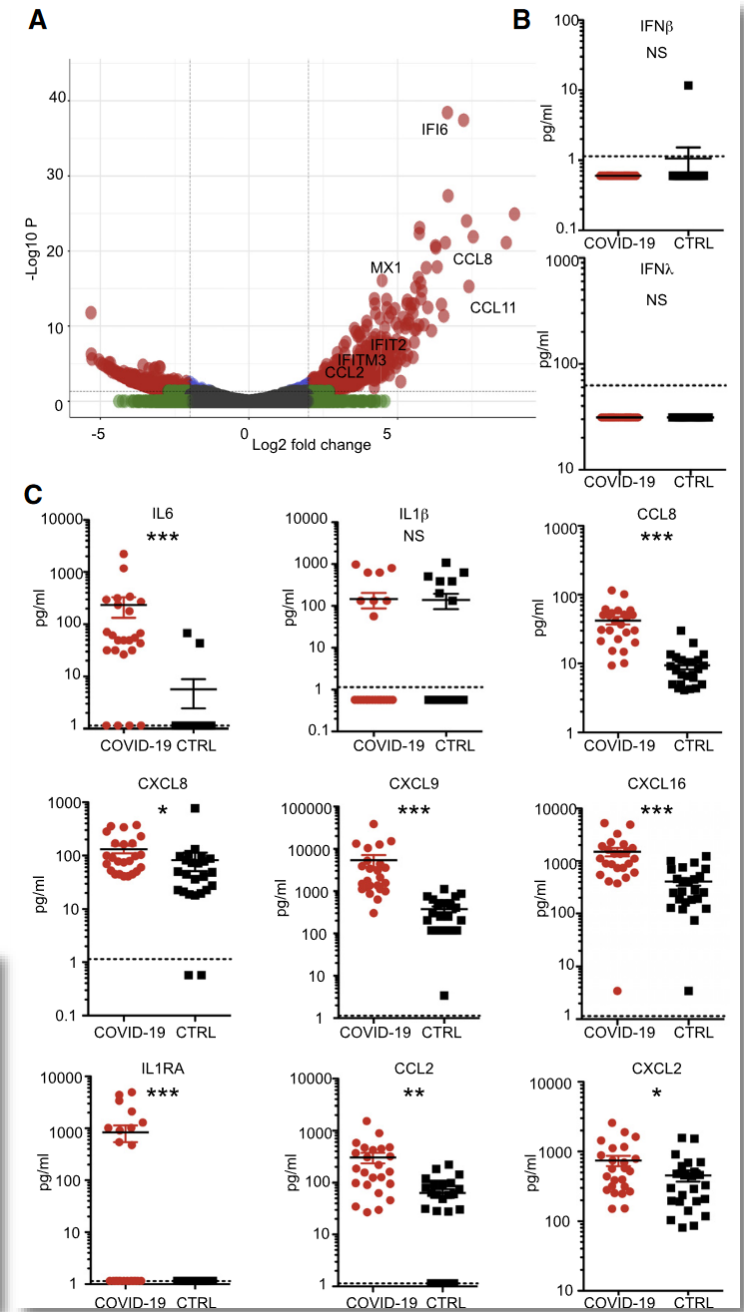
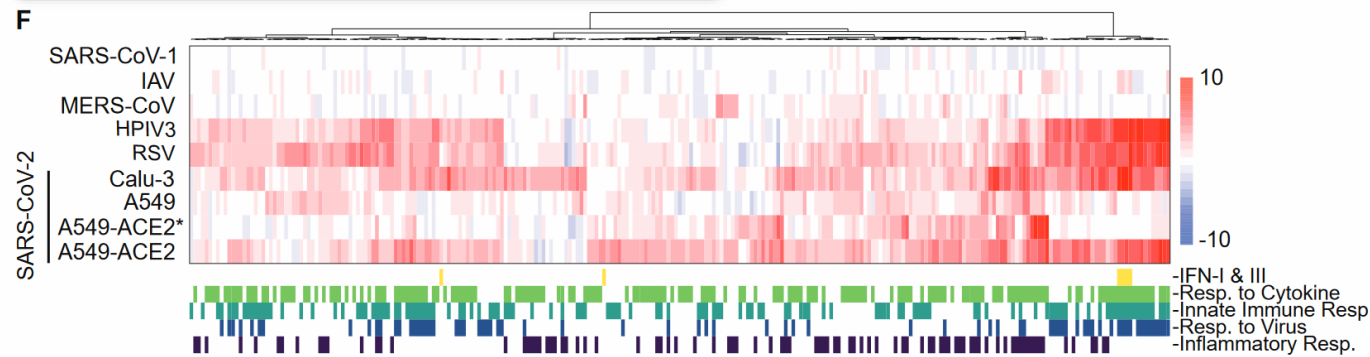
Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19

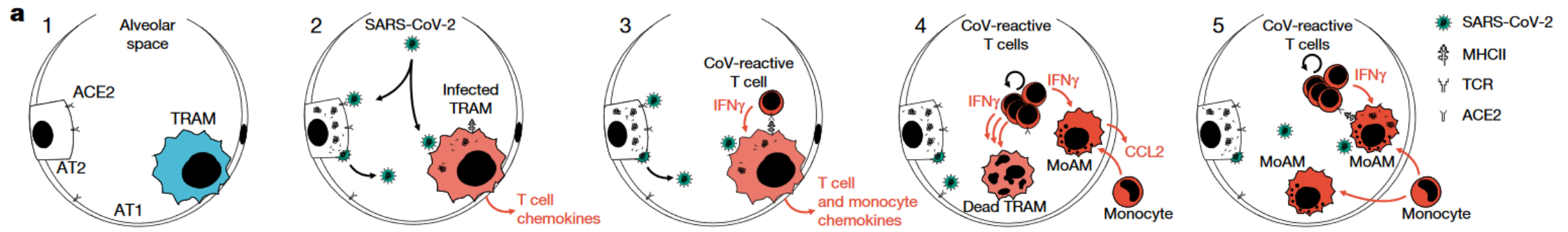


Clinical Samples (PBMCs) & *In vitro* Models: Cell lines (Epithelium)

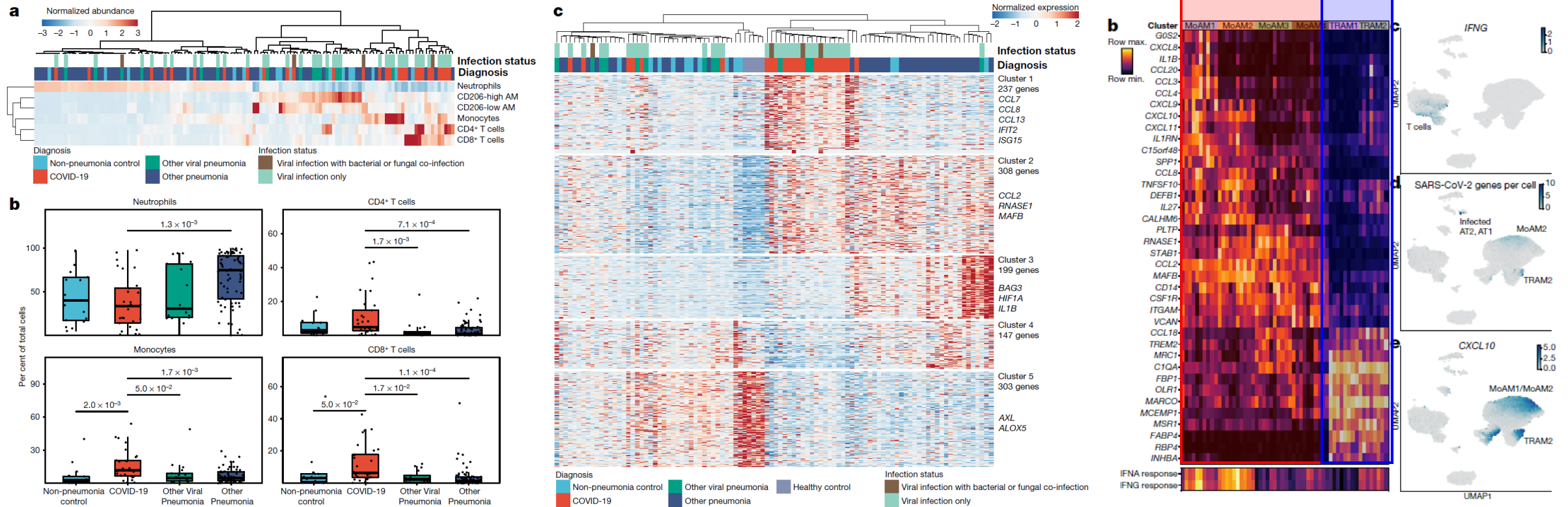
In Brief

In comparison to other respiratory viruses, SARS-CoV-2 infection drives a lower antiviral transcriptional response that is marked by low IFN-I and IFN-III levels and elevated chemokine expression, which could explain the pro-inflammatory disease state associated with COVID-19.





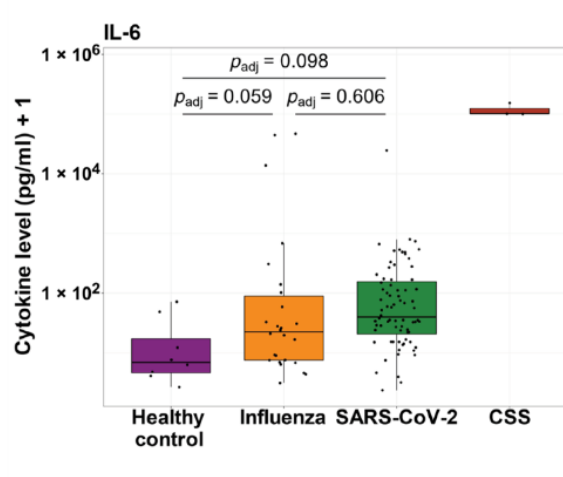
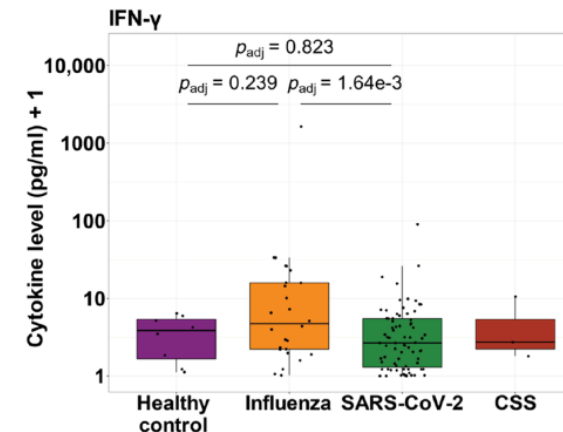
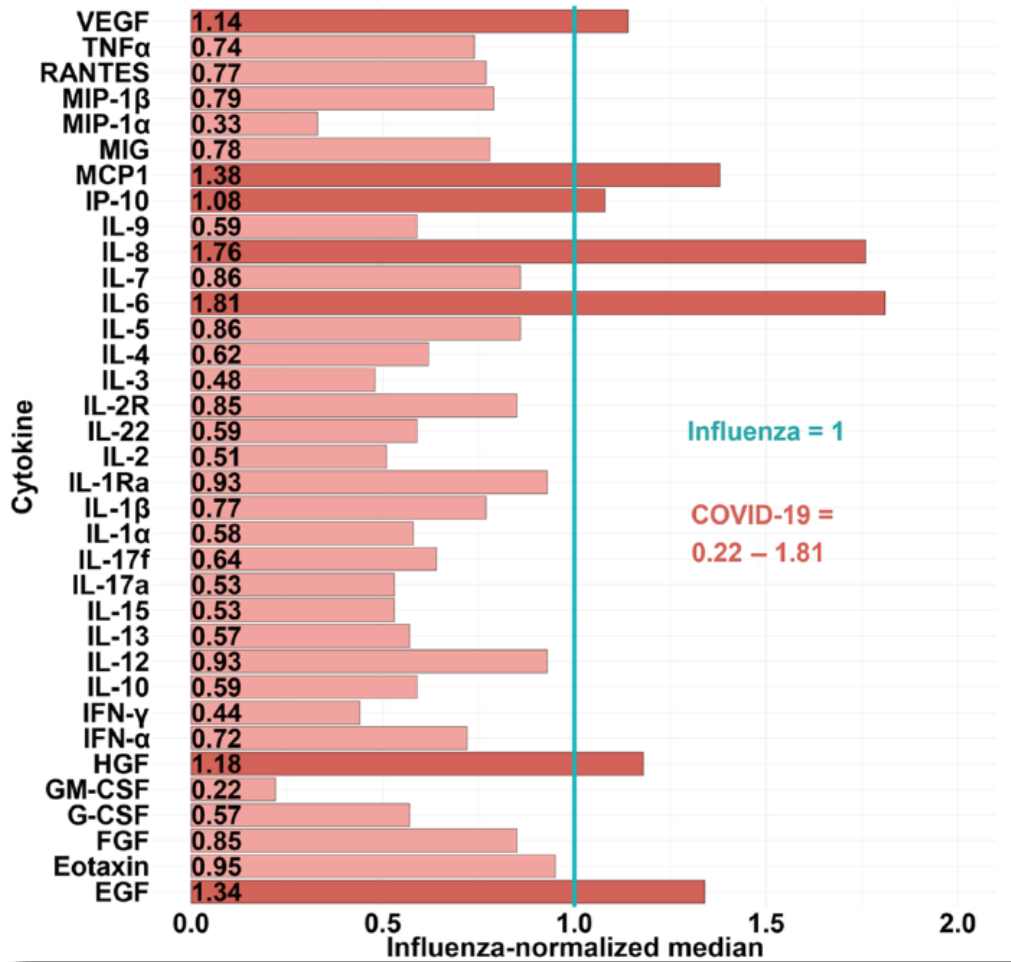
Bronchoalveolar lavage Fluids



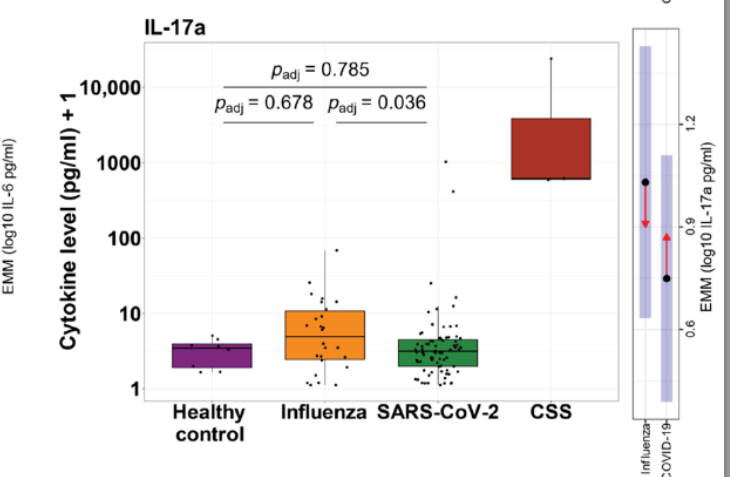
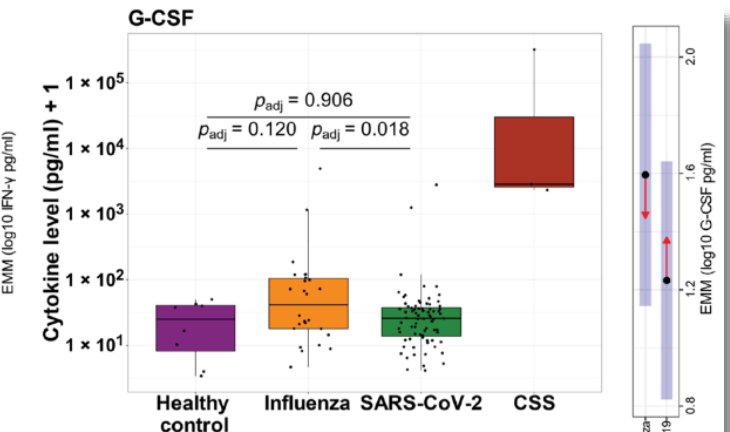
Grant RA, et al. NU SCRIPT Study Investigators. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. *Nature*. (2021)

Pathogen level differences in immune dysregulation

: Influenza vs. SARS-CoV-2 infections

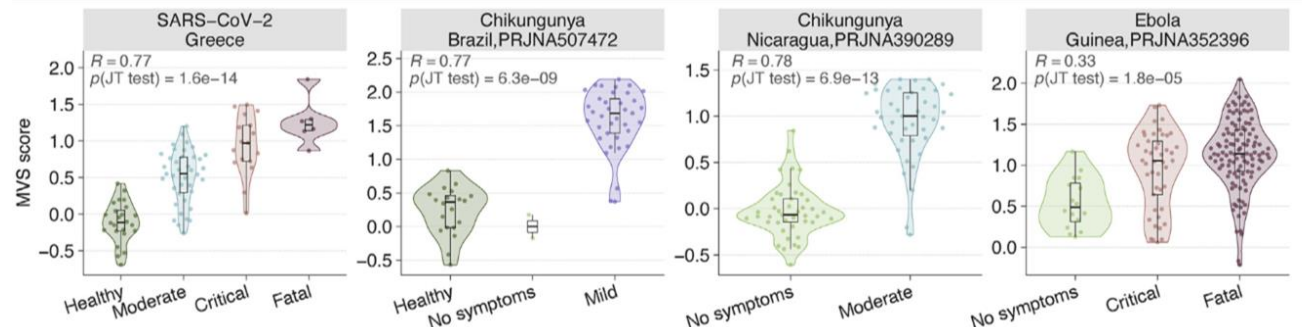
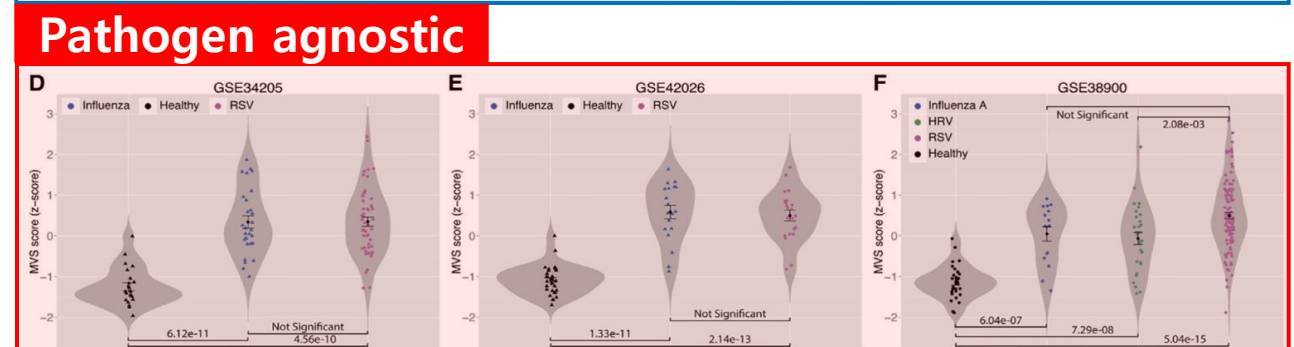
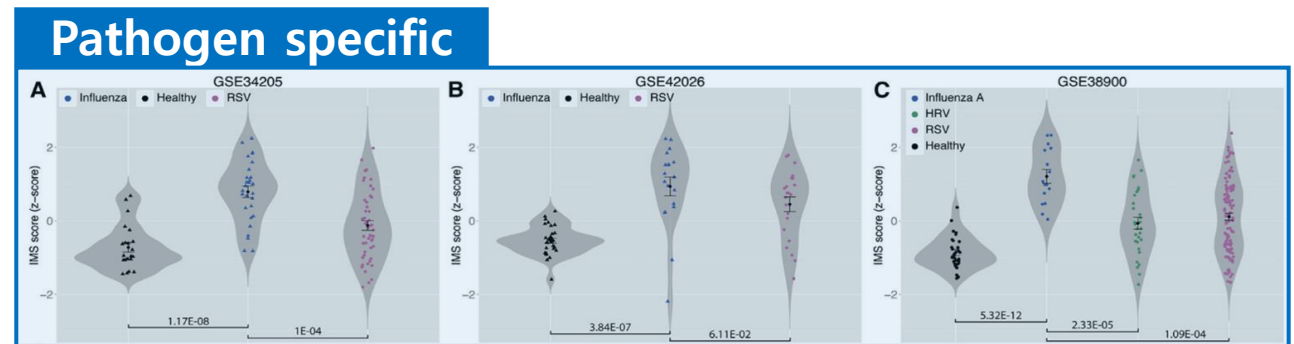
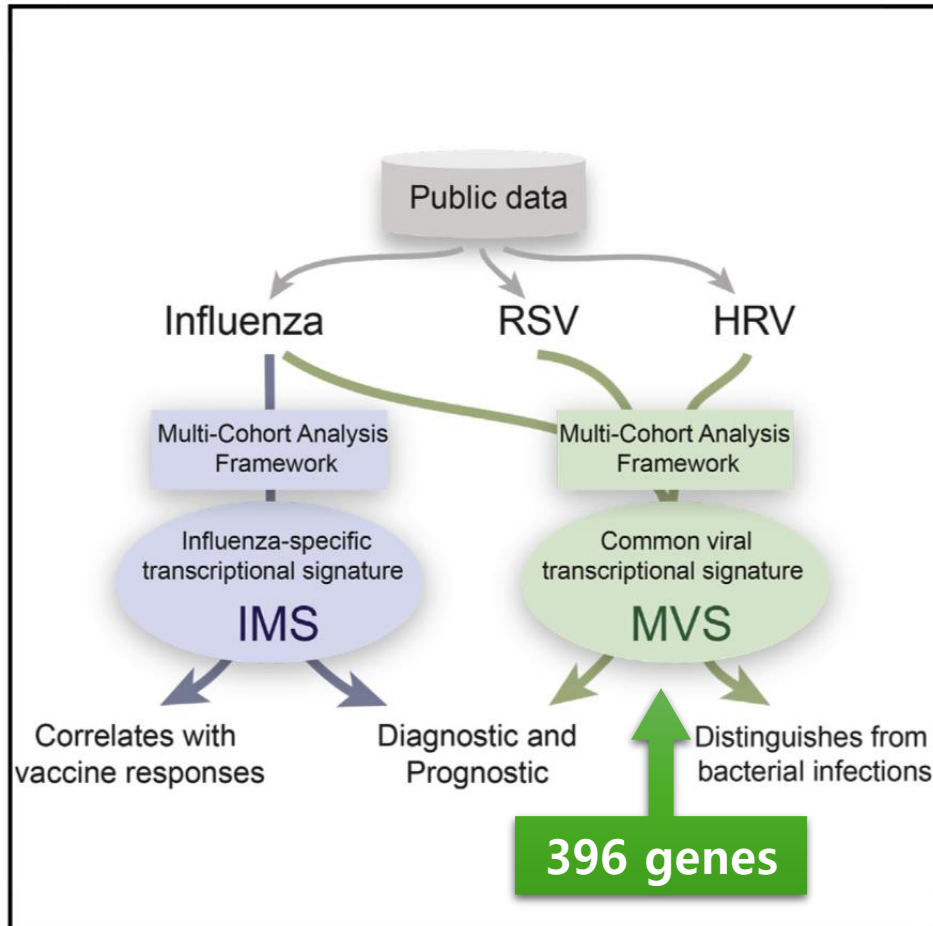


Blood Samples (PBMCs)

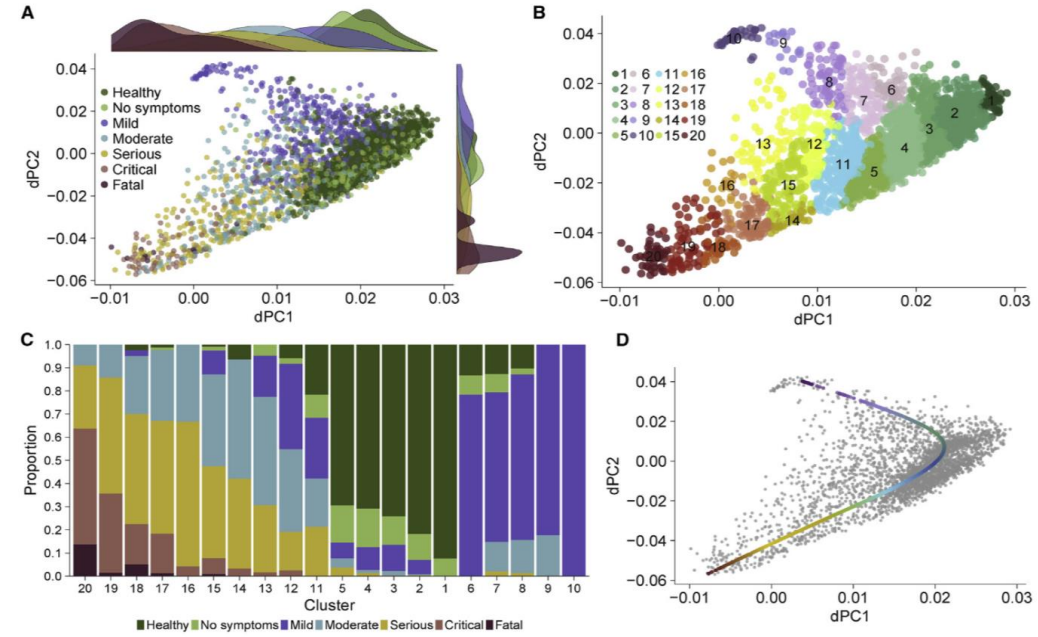
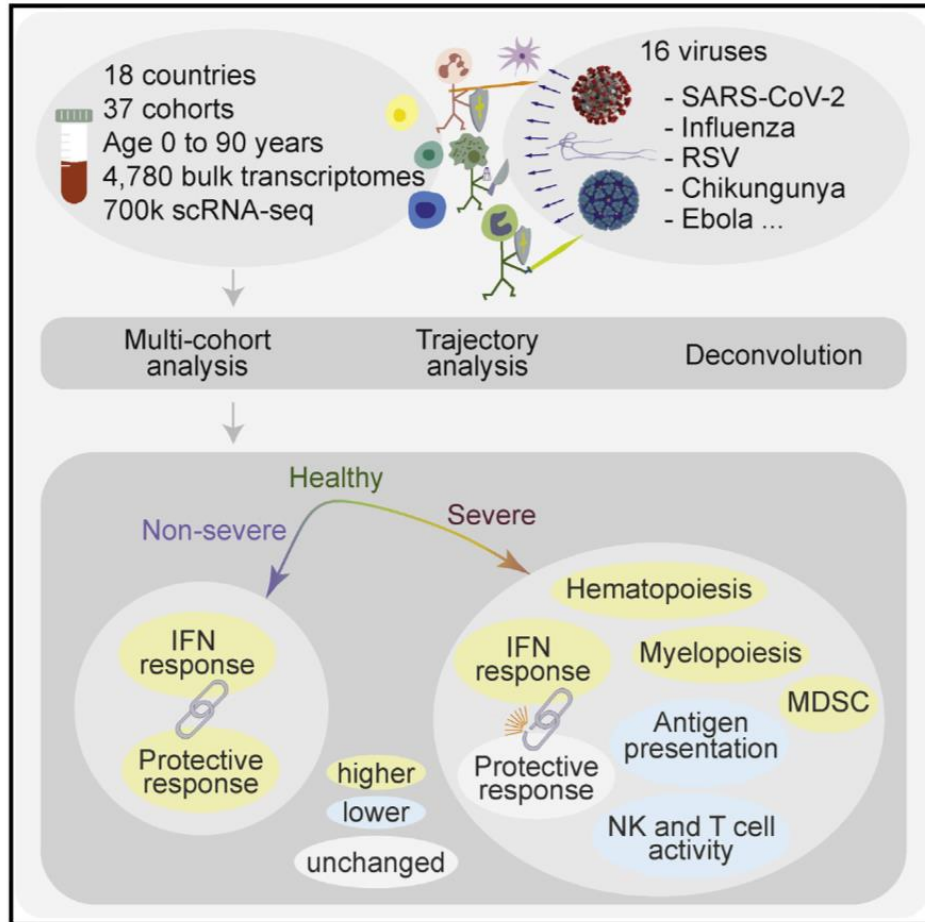


Genomic signature of viral infection

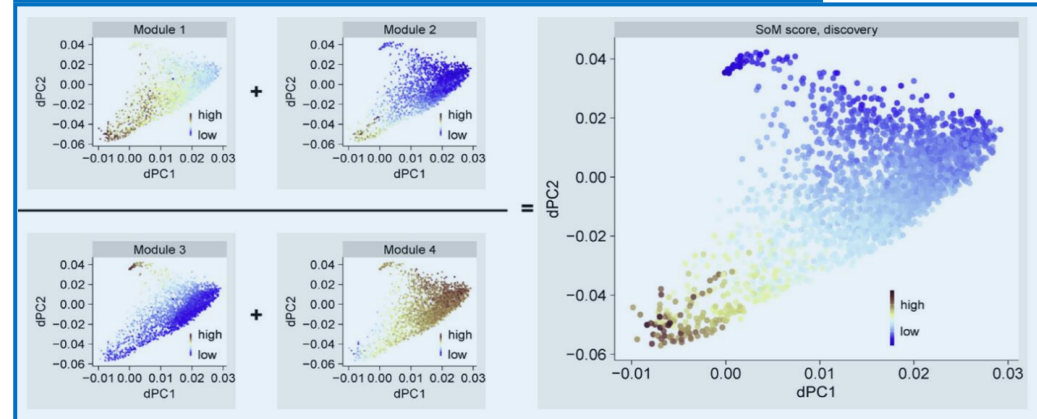
: pathogen specific / pathogen agnostic signature



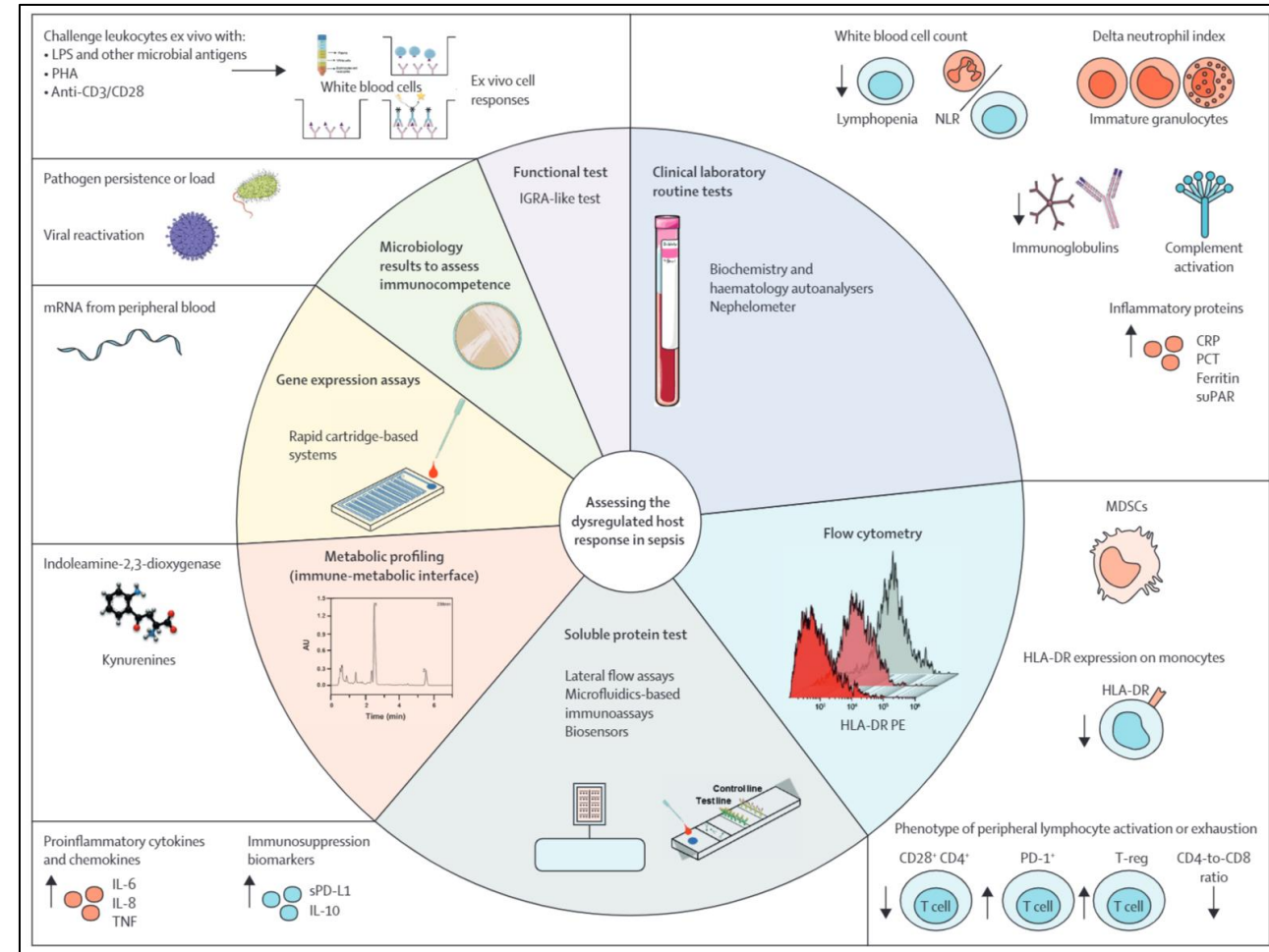
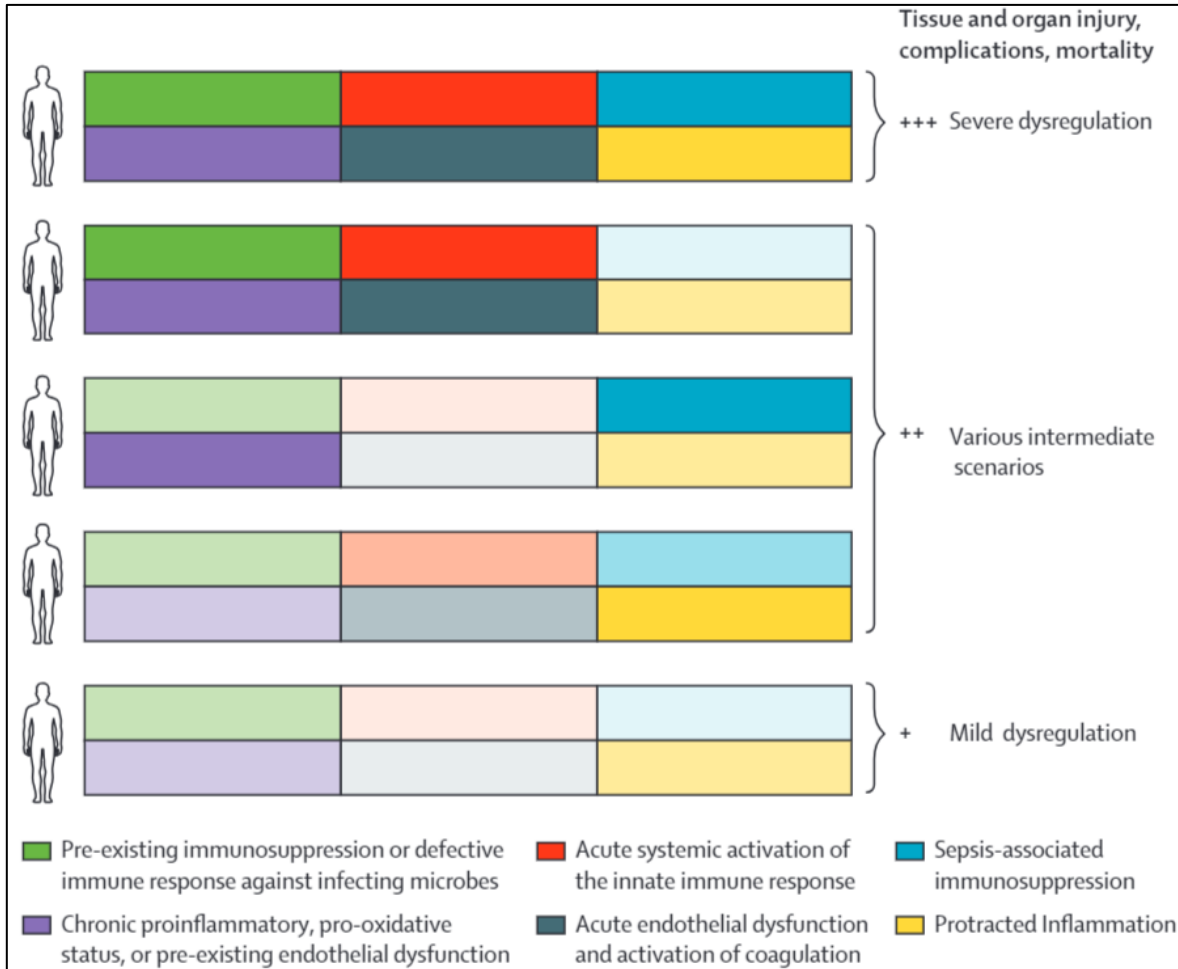
Conserved host response : *“Pan-viral trajectory”*”



SOM score (Severe Or Mild score)

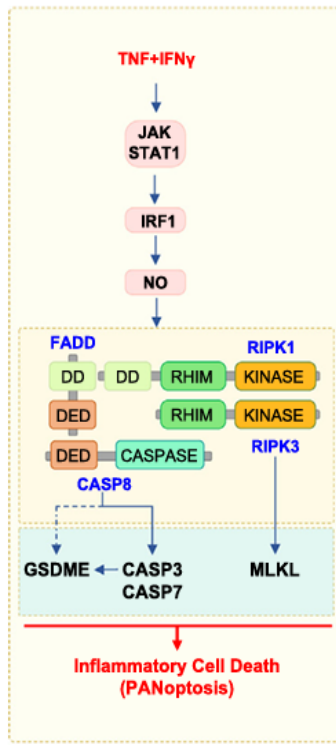


Profiling the dysregulated immune response

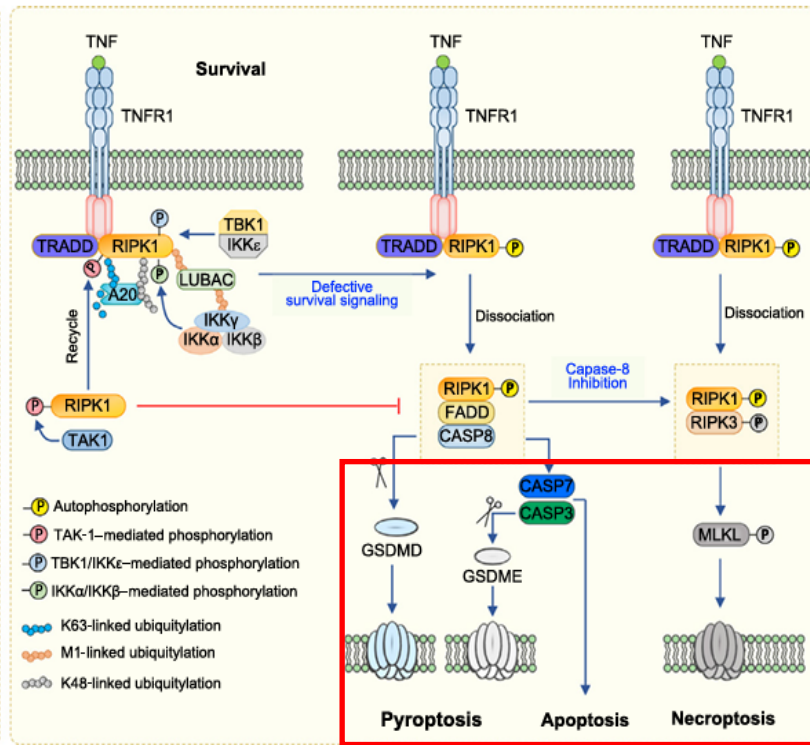


Inflammatory Cell Death & Cytokine Storm Synd.

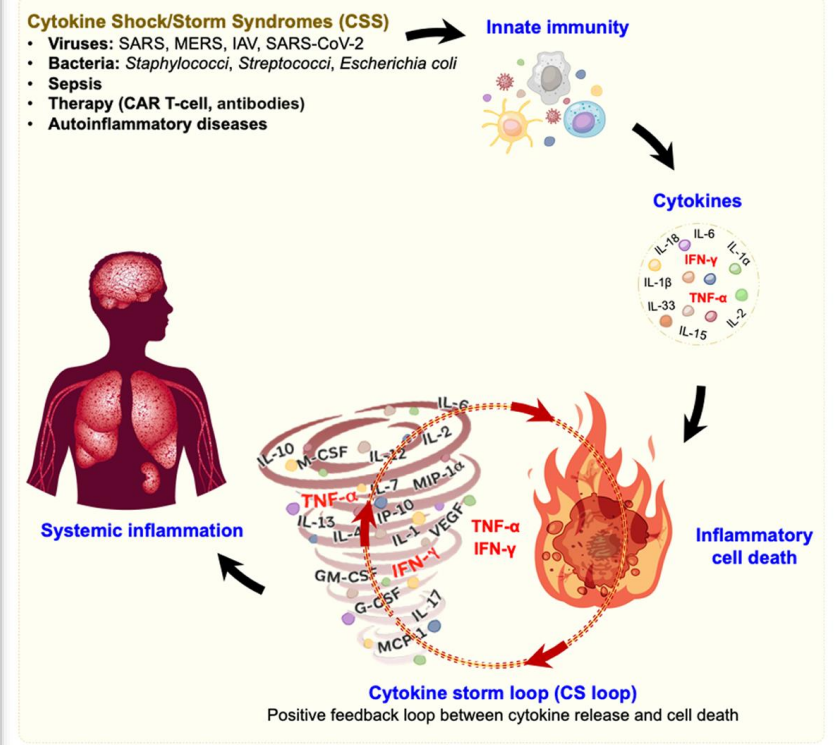
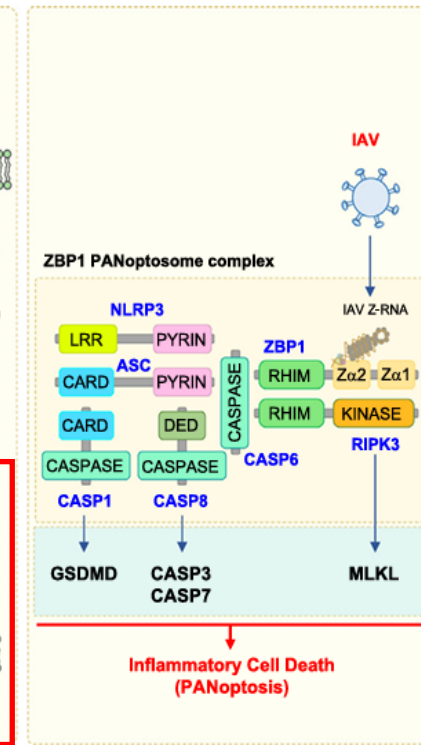
(A) Cytokine-induced inflammatory cell death



(B) TNF and RIPK1 signaling in inflammatory cell death



(C) IAV-mediated inflammatory cell death



Regulated Cell Death in the Immune System

Cell Death Pathway	Plasma Membrane Rupture	Cell Types	Triggers	Receptors (Sensors)	Signaling Pathway	Immunogenicity	Physiological Examples	Pathological Role
Extrinsic apoptosis	Not always or late	All cells, death receptor expression required	Death receptor ligands	Death receptors	FADD, caspase-8, caspase-3, caspase-7	No, immunologically silent	AICD, cytotoxic T cells	Failure to induce extrinsic apoptosis (especially by Fas/CD95) results in ALPS
Intrinsic apoptosis	Yes, late	All cells	Various: eg. DNA damage, ER stress, growth factor withdrawal	Bcl-2 family	Cytochrome c, APAF1, caspase-9, caspase-3, caspase-7	Mostly immunologically silent, immunogenic apoptosis can occur under special circumstances	AICD, T cell and B cell development, development of the nervous system	Failure in intrinsic apoptosis can contribute to development of cancer
Necroptosis	Yes, early	All cells, death receptor or TLR expression required	Death receptor ligands, TLR ligands, Z-nucleic acids	Death receptors TLRs (via TRIF), ZBP1	RIPK1, RIPK3, MLKL (inhibited by caspase-8)	Yes	Organ development, clearance of virus infected cells	Possible role in organ damage after ischemia reperfusion injury. Failure to engage the necroptosis pathway can sensitize for lethal virus infection
Pyroptosis	Yes, early	Predominantly myeloid, endothelial, and epithelial cells	Various cytosolic PAMPs and DAMPs, eg. dsDNA, uric acid crystals, bacterial toxins, flagellin	NLRs and ALRs	Caspases-1, caspase-11 in mice; caspase-1, caspase-4, and caspase-5 in humans; and gasdermin D	Yes	Clearance of virus or bacteria infected cells, attraction of neutrophils and other immune cells	Excess pyroptosis leads to organ failure during sepsis. Pyroptosis-associated IL-1 cytokines promote joint inflammation in rheumatoid arthritis
NETosis	Not always	Neutrophils	Extracellular PAMPs or DAMPs	Unknown	Gasdermin D	Unknown	Killing of extracellular bacteria	Failure to clear NETs can induce autoimmunity
Ferroptosis	Yes, early	Variable, although many transformed cells are sensitive	Cysteine deprivation, inhibition of system X_c^- , inhibition of GPX4	None	Fenton reaction	No	Response to pharmacologic inhibitors of system X_c^- , GPX4, possibly killing of tumor cells by cytotoxic lymphocytes	Possible role in ischemia reperfusion injury

AICD, activation-induced cell death; ALPS, autoimmune lymphoproliferative disease; ALR, AIM-like receptor; APAF1, apoptosis protease activating factor 1; DAMP, danger-associated molecular pattern; FADD, Fas-associated protein with death domain; GPX4, glutathione peroxidase 4; IL-1, interleukin-1; MLKL, mixed lineage kinase domain-like pseudokinase; NET, neutrophil extracellular trap; NLR, NOD-like receptor; PAMP, pathogen-associated molecular pattern; RIPK, receptor-interacting serine/threonine protein kinase 1; TLR, Toll-like receptor; TRIF, TIR domain-containing adapter-inducing interferon-beta; ZBP1, Z-DNA binding protein 1.

Dysregulated immune response from recruited cells

: Neutrophil (NETosis)

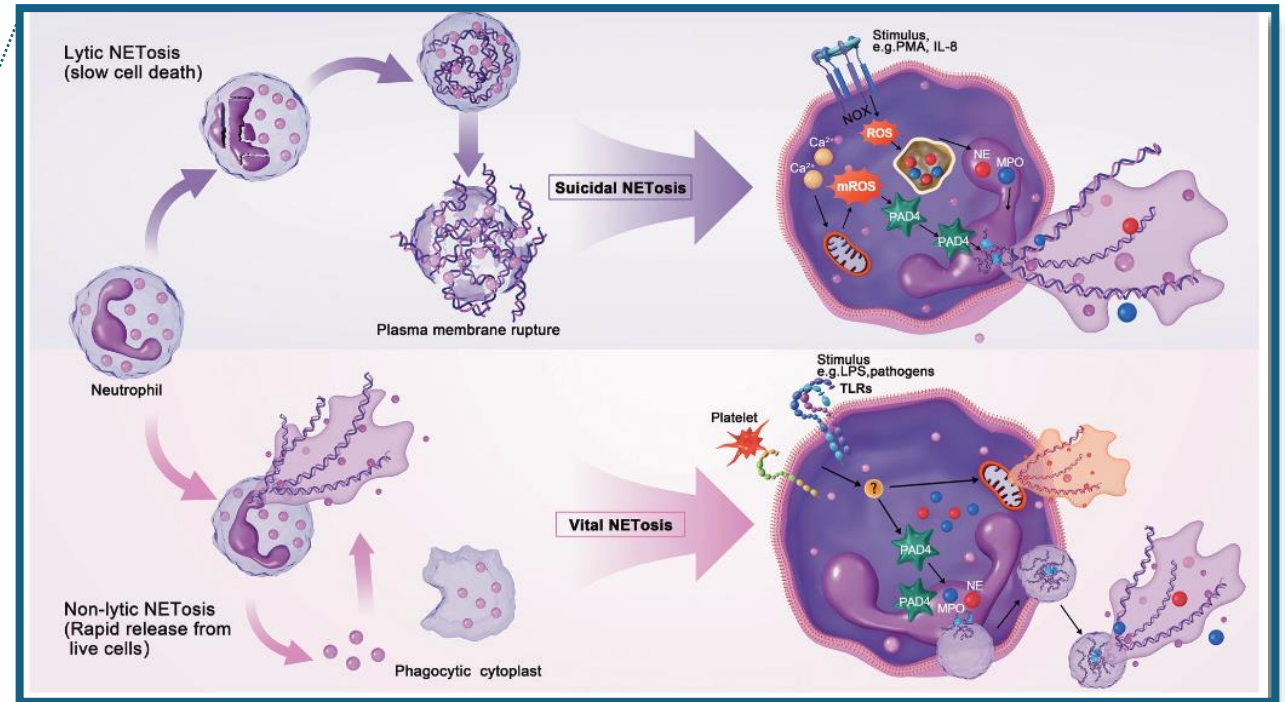
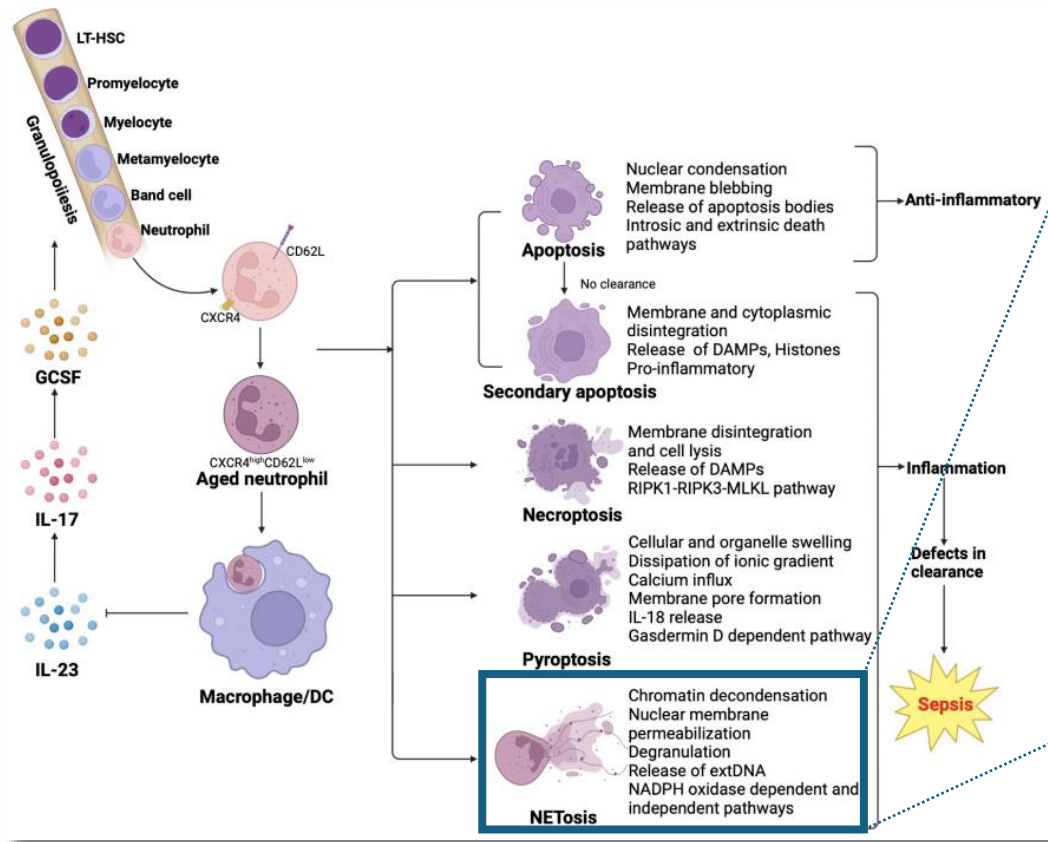
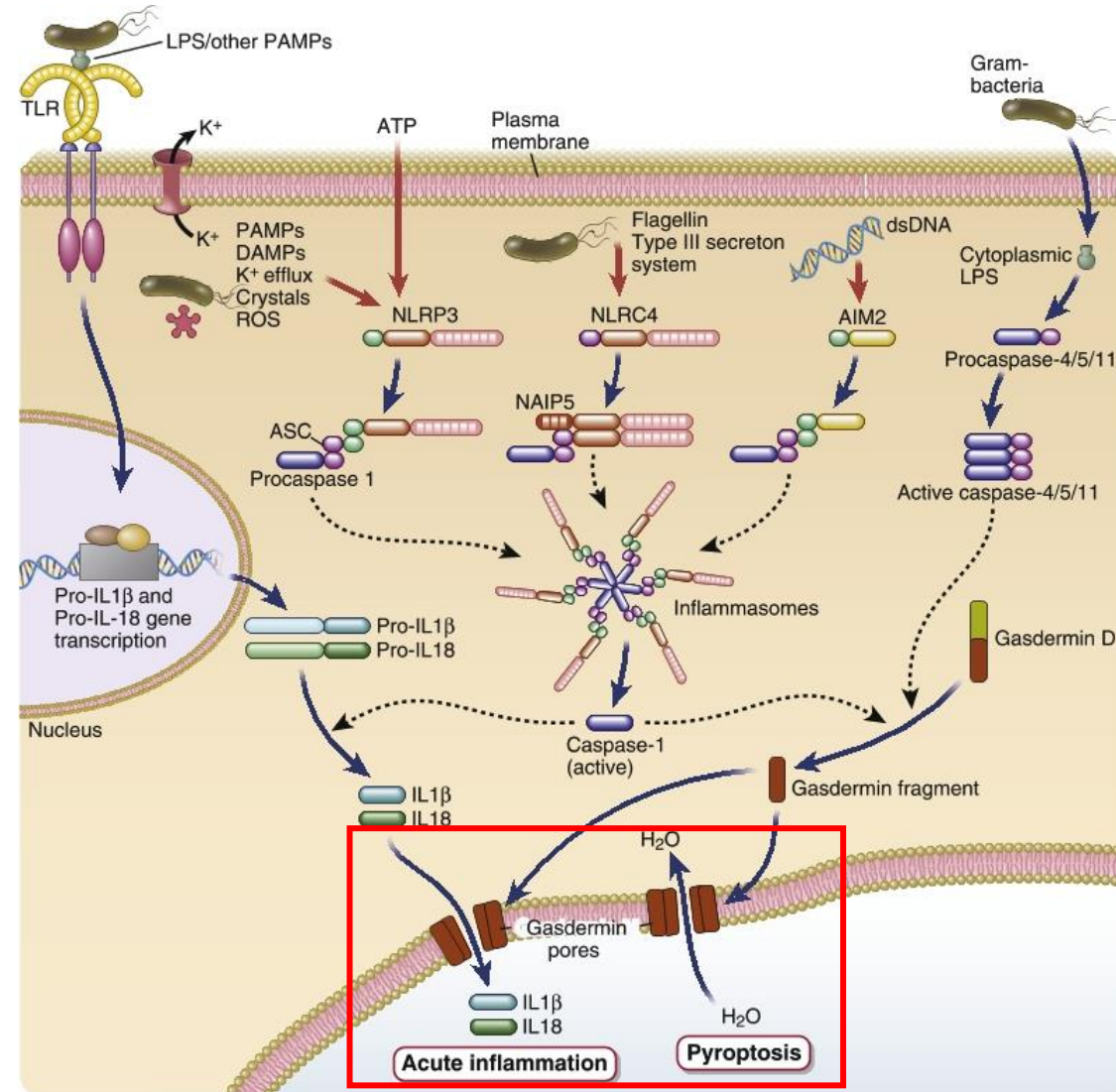


Fig. 2 NET formation pathways. NET formation can be categorized into two main pathways. The first type is the classic pathway known as NETosis, which initiates with nuclear lobulation, followed by disassembly of nuclear membranes, loss of cellular polarization, chromatin decondensation, and eventual rupture of plasma membranes. An alternative pathway is termed non-lytic NETosis which can occur without cell death, where chromatin expulsion is accompanied by the release of granular proteins. These components are formed extracellularly, leaving behind active anucleate phagocytes with capabilities for microbial phagocytosis and chemotaxis. This figure was created by Adobe Photoshop CS6 (Adobe Systems, USA)

Inflammasomes



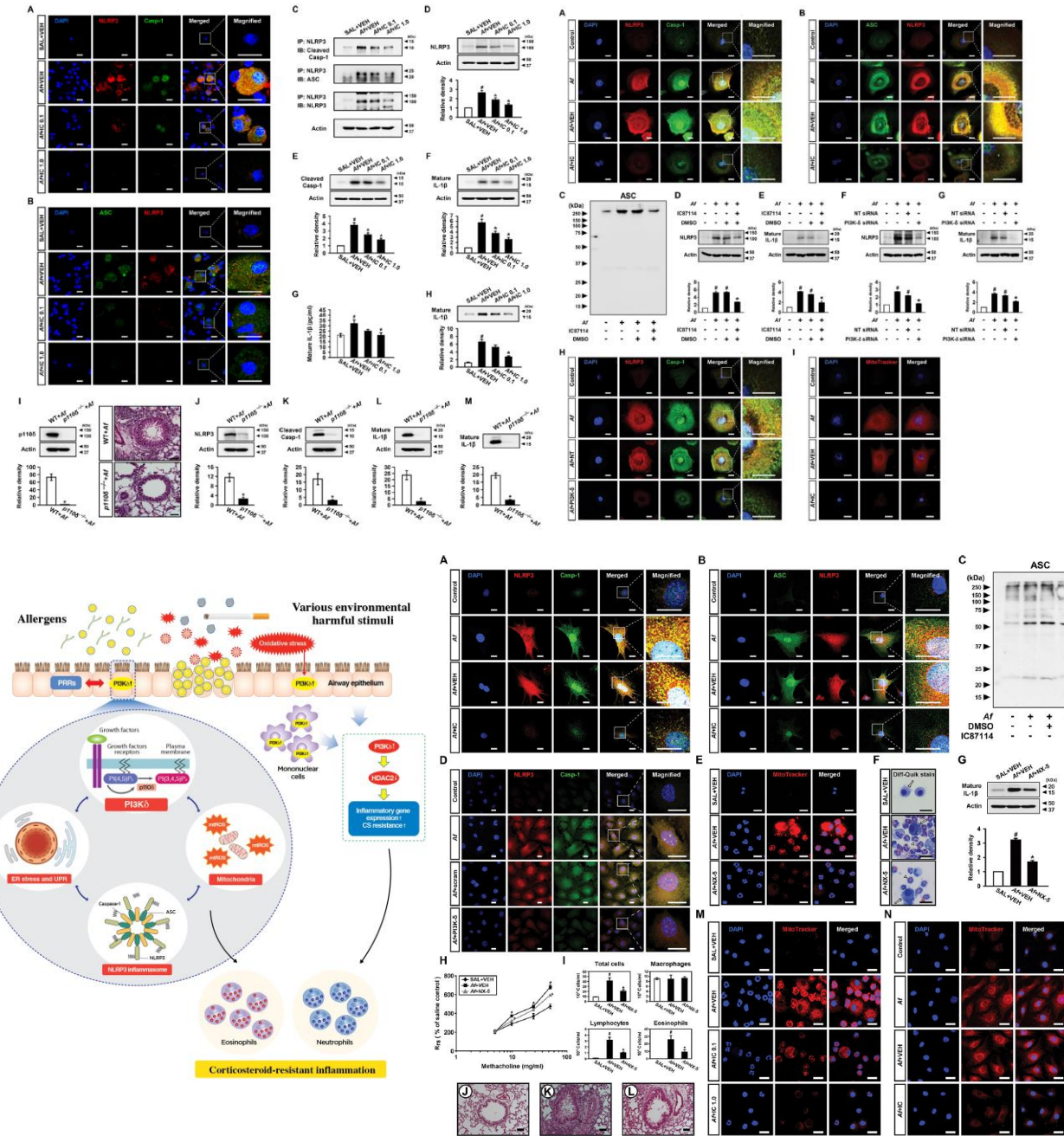
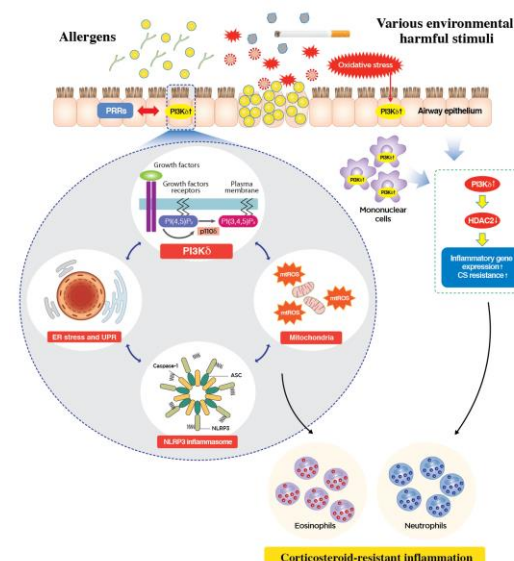
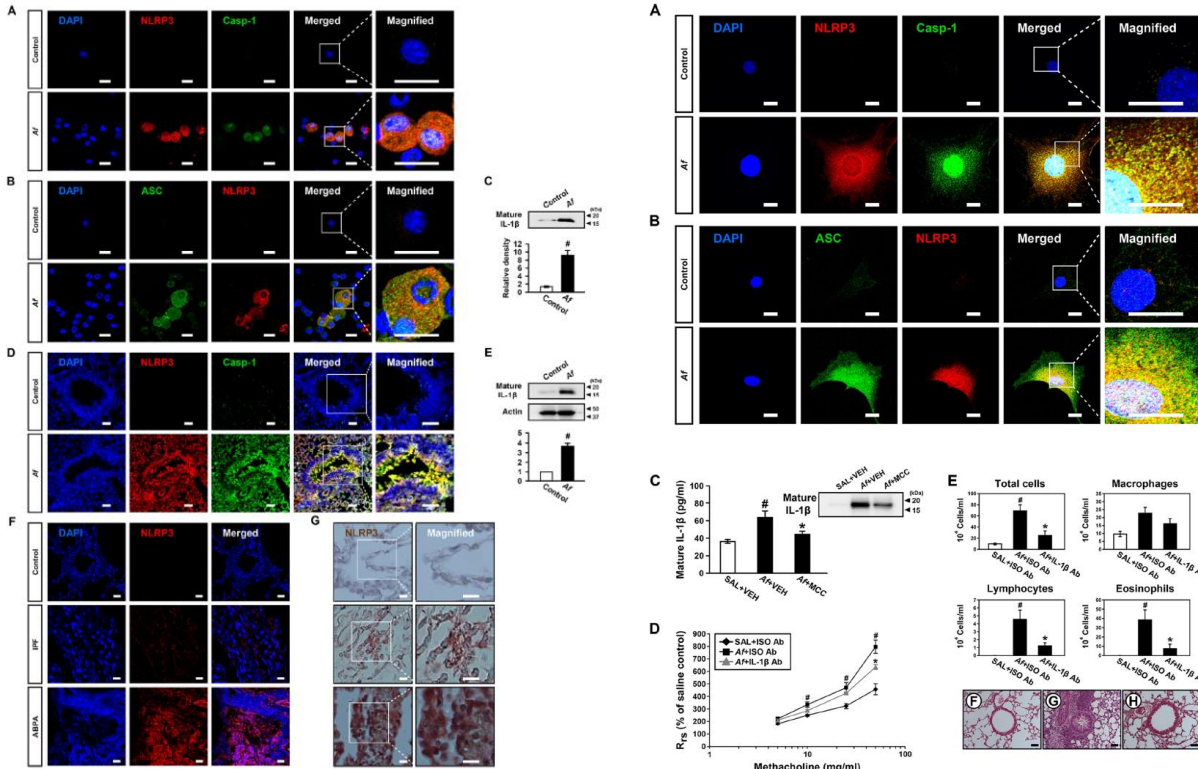
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ORIGINAL ARTICLE

Airway epithelial phosphoinositide 3-kinase- δ contributes to the modulation of fungi-induced innate immune response

Jae Seok Jeong,¹ Kyung Bae Lee,¹ So Ri Kim,^{1,2} Dong Im Kim,¹ Hae Jin Park,¹ Hern-Ku Lee,³ Hyung Jin Kim,^{2,4} Seong Ho Cho,⁵ Narasaiah Kolliputi,⁵ Soon Ha Kim,⁶ Yong Chul Lee^{1,2}



Viral Infection-Induced *Ferroptosis*

Syrian hamsters as a model of lung injury with SARS-CoV-2 infection: Pathologic, physiologic, and detailed molecular profiling

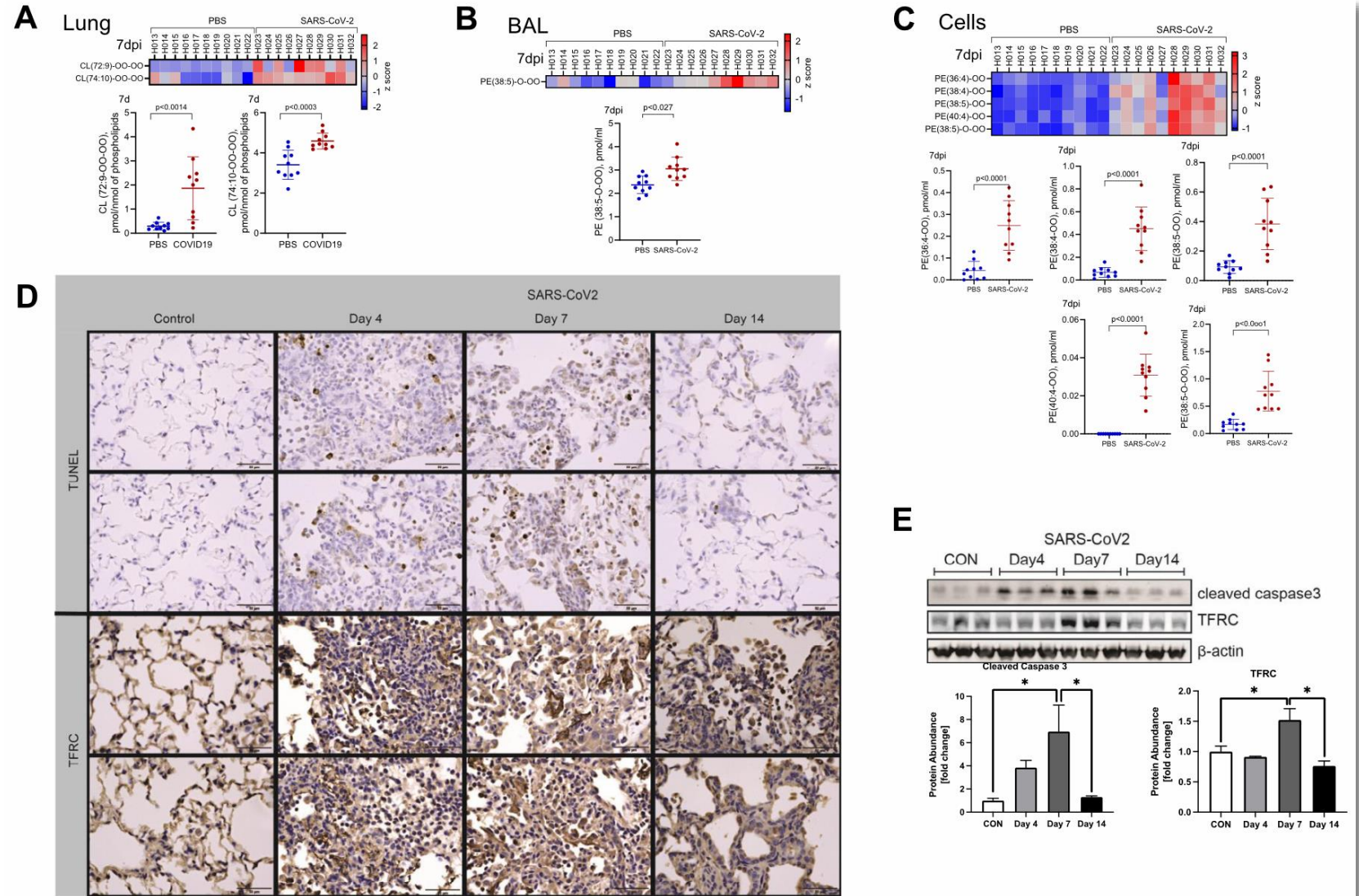
AT A Glance Commentary
Bednash JS, et al.

Background

The acute respiratory distress syndrome (ARDS) is a common complication of severe COVID-19. Animal models of SARS-CoV-2 ARDS are crucial to understanding molecular mechanisms driving disease.

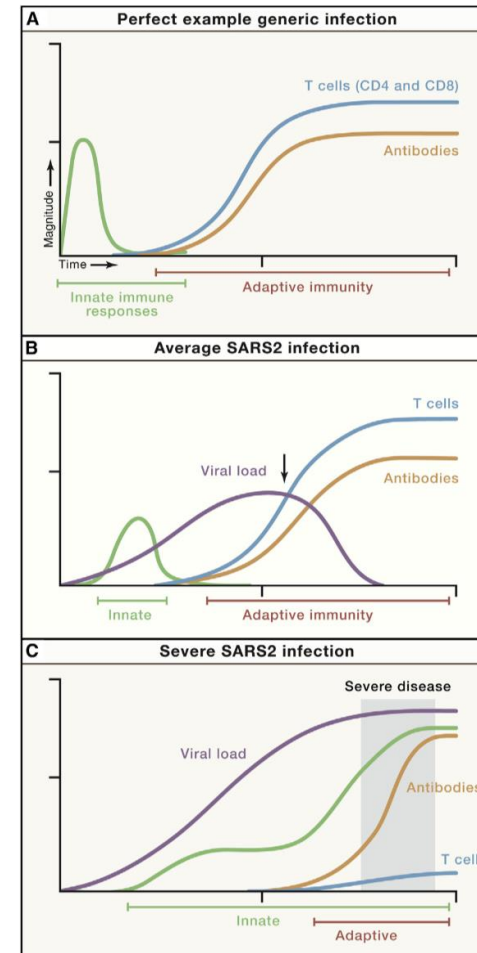
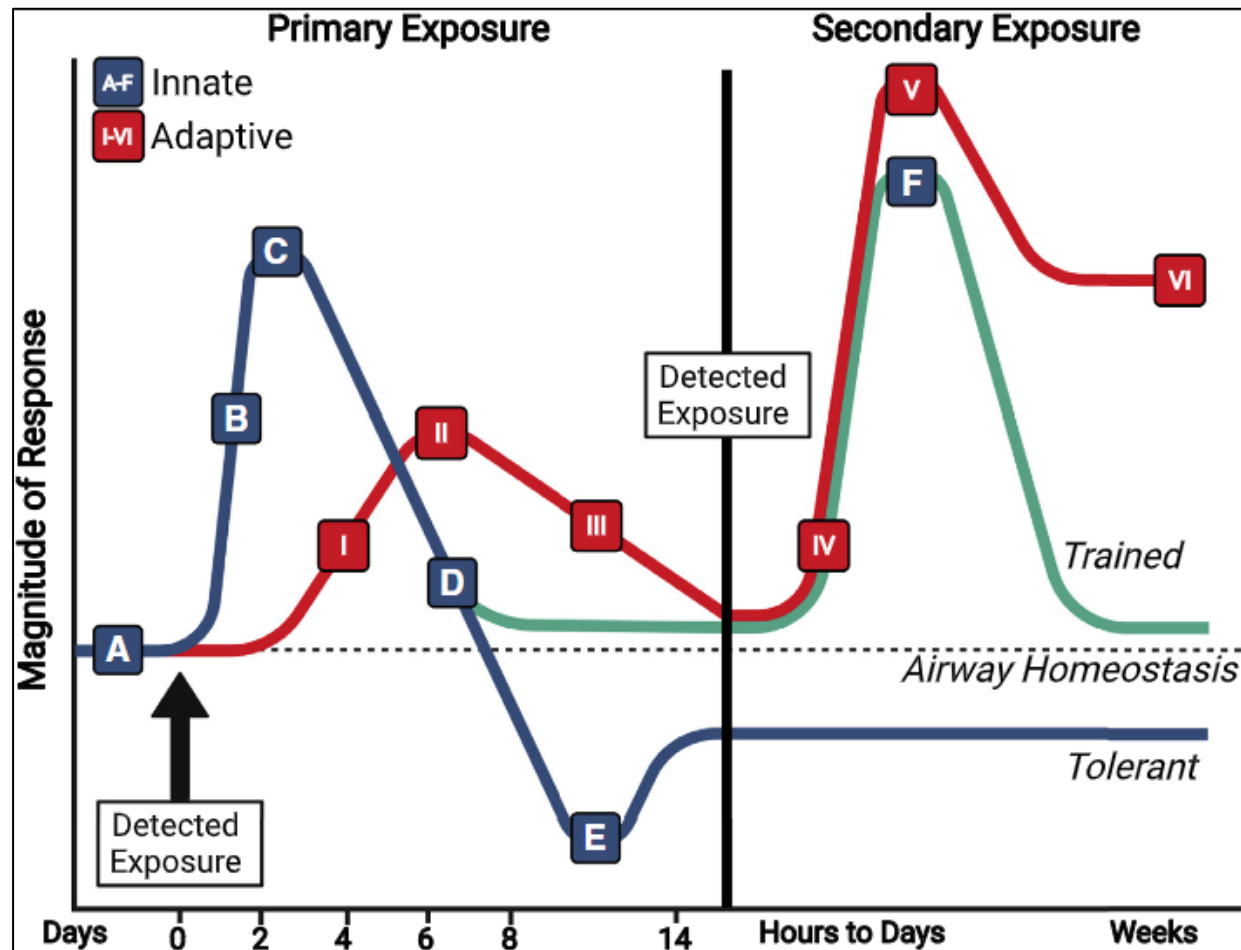
Translational Significance

We systematically evaluated Syrian golden hamsters as an experimental model of SARS-CoV-2 ARDS, based on biophysical, transcriptomic, and lipidomic data. Hamsters demonstrate key features of ARDS, including hypoxemia. Detailed molecular analysis demonstrates upregulation of interferon signaling, recapitulating findings of human illness. We also present the first and most robust lipidomic analysis in an animal model of SARS-CoV-2 infection. These findings demonstrate utility of hamsters as an experimental model of COVID-19 ARDS.



Adaptive Immune Cell-Mediated Pathogenesis

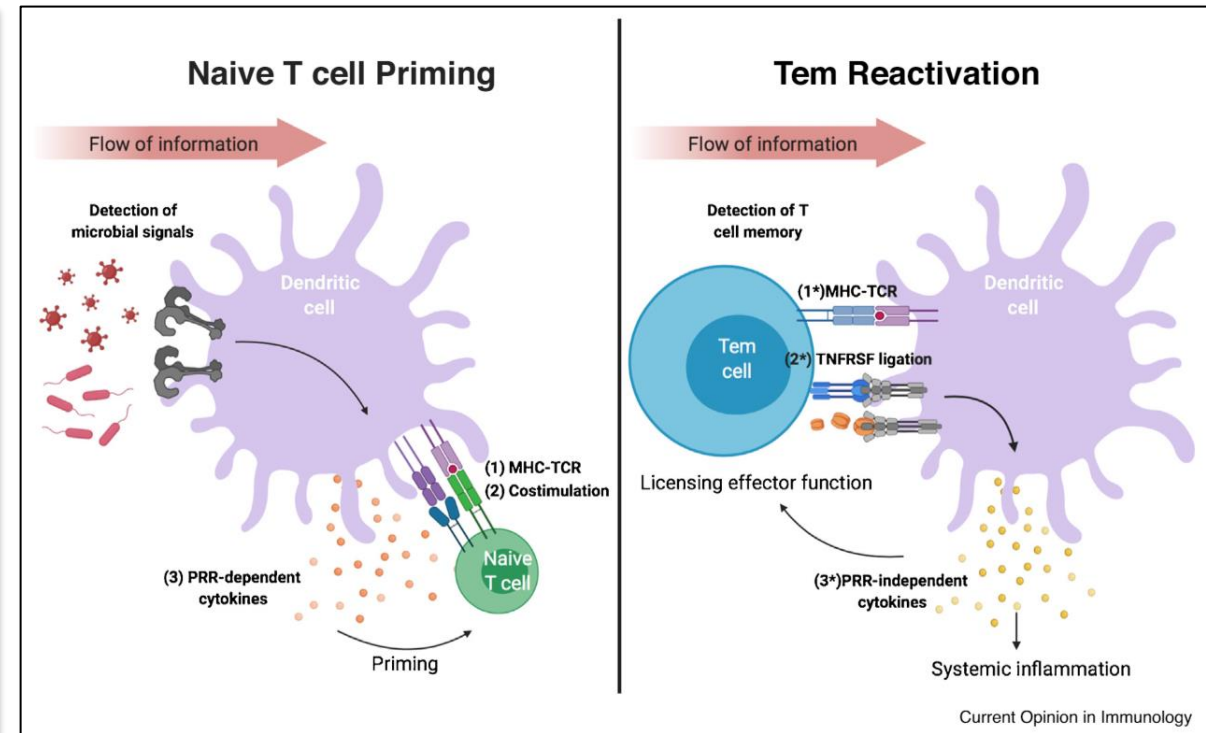
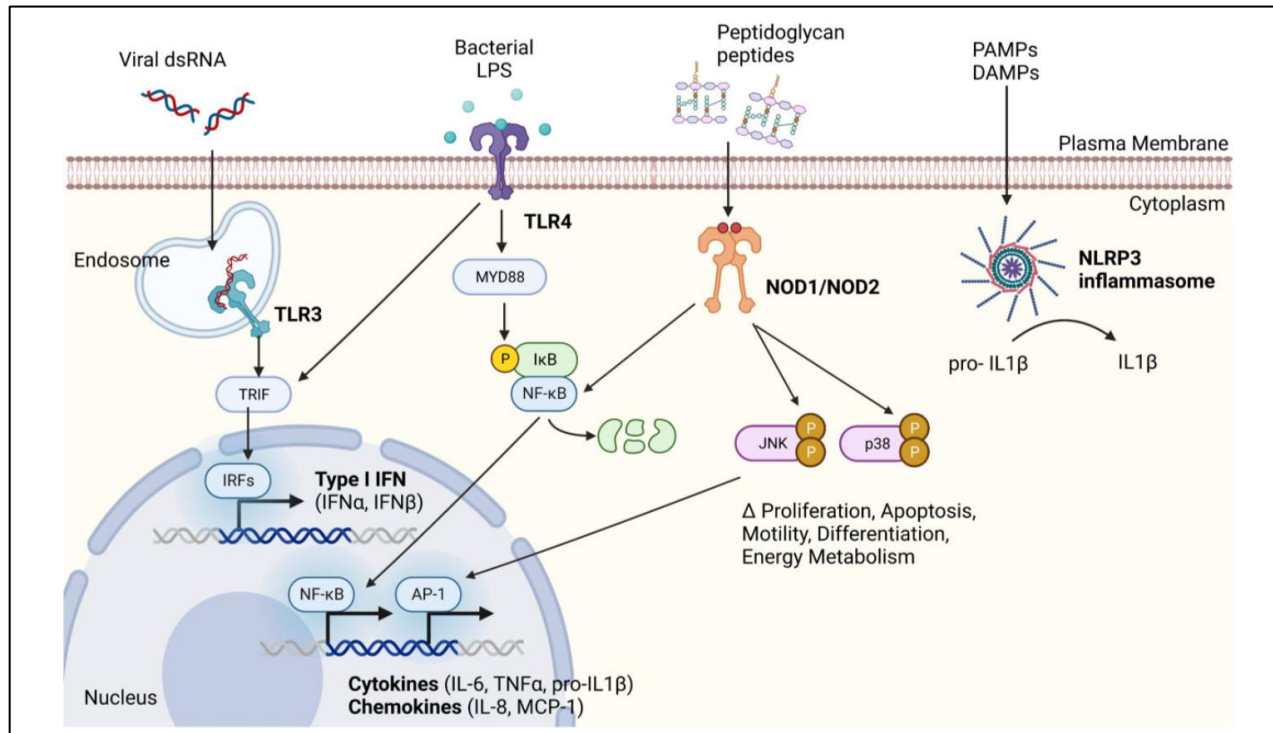
Innate and adaptive immune response magnitude dynamics *over time*



Mettelman RC, et al. Mucosal immune responses to infection and vaccination in the respiratory tract. *Immunity*. (2022)

Sette A, et al. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell*. (2021)

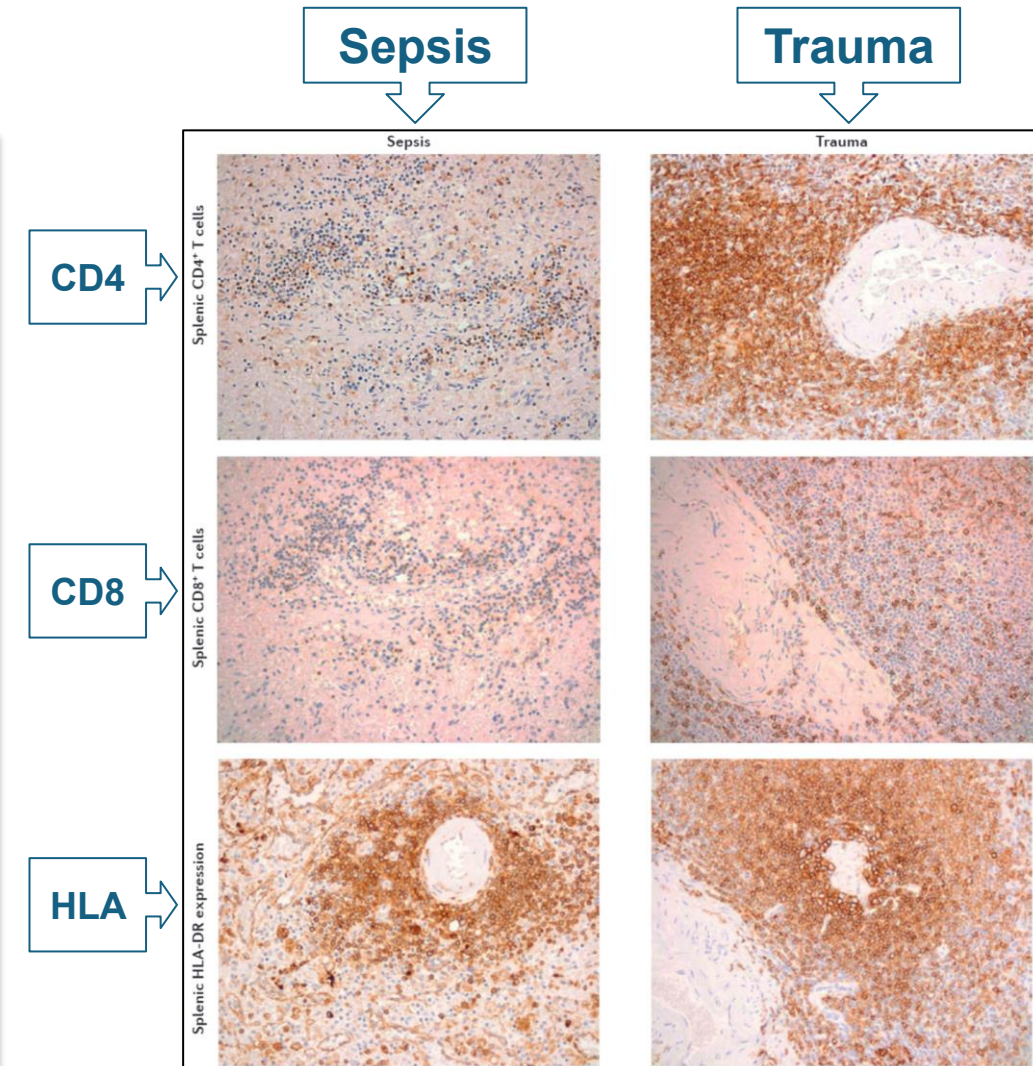
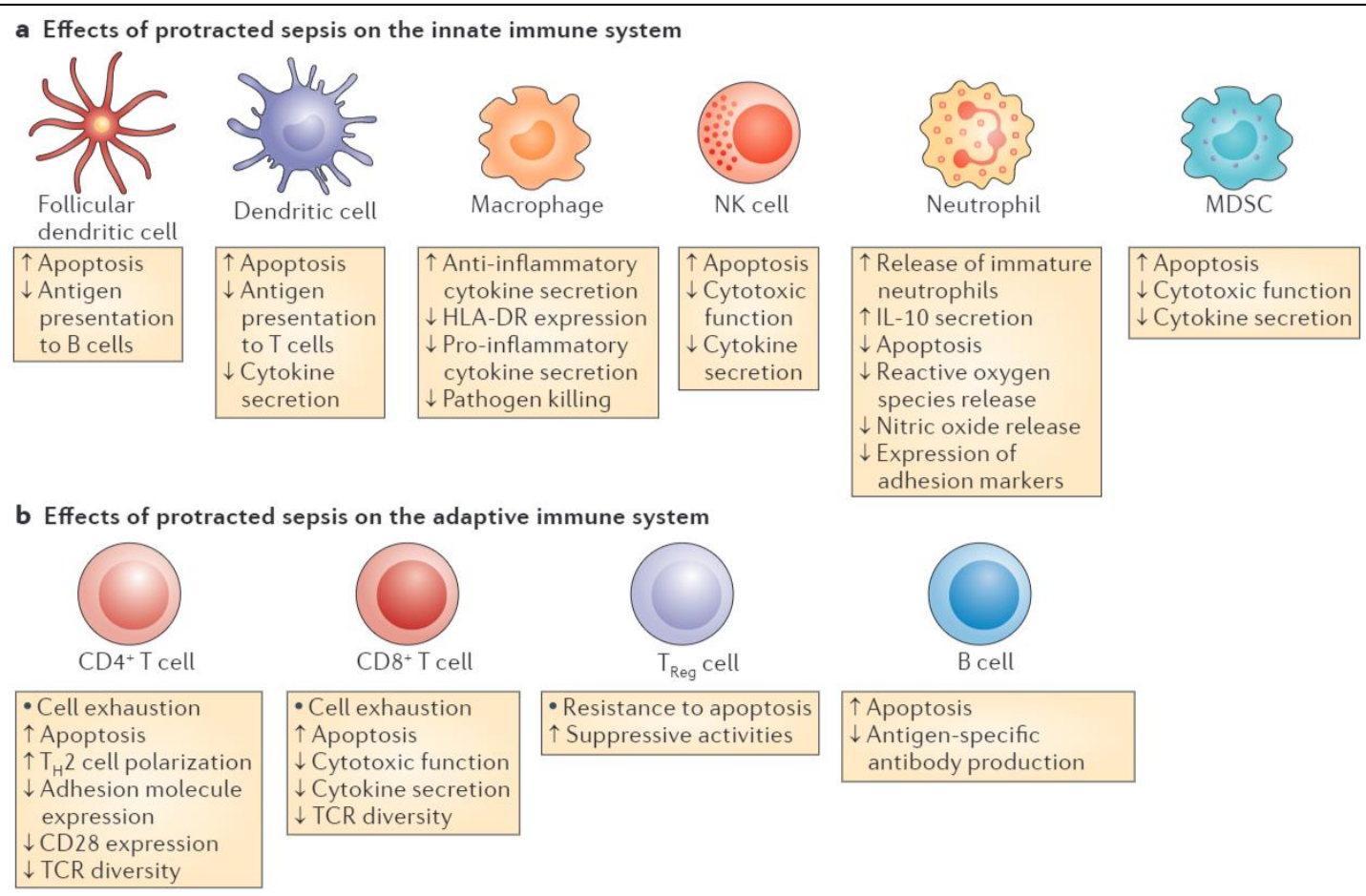
Crosstalk between Innate & adaptive immunity



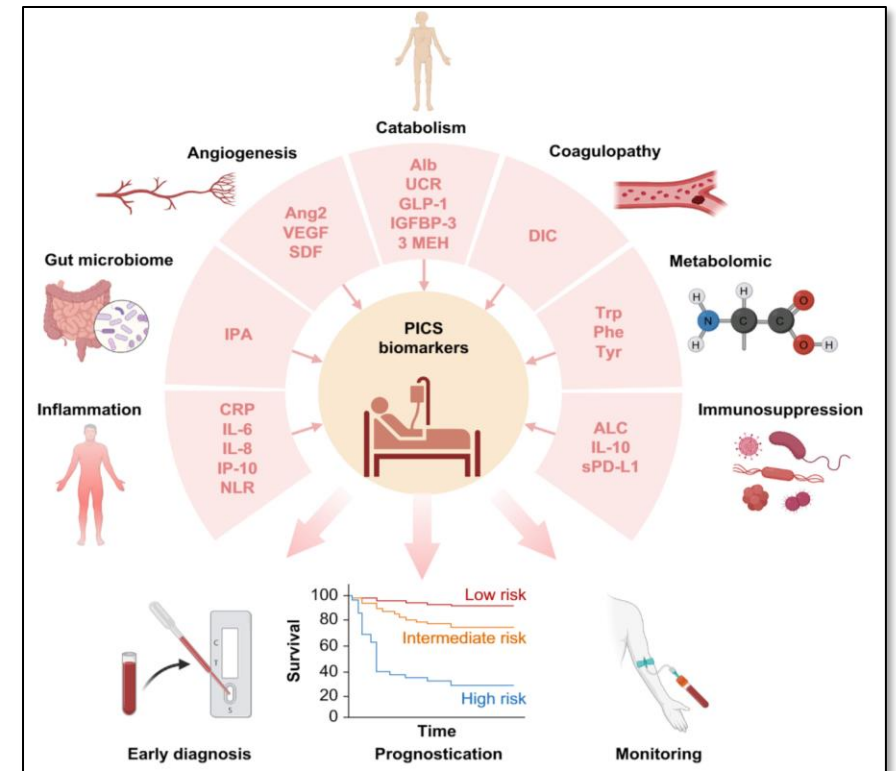
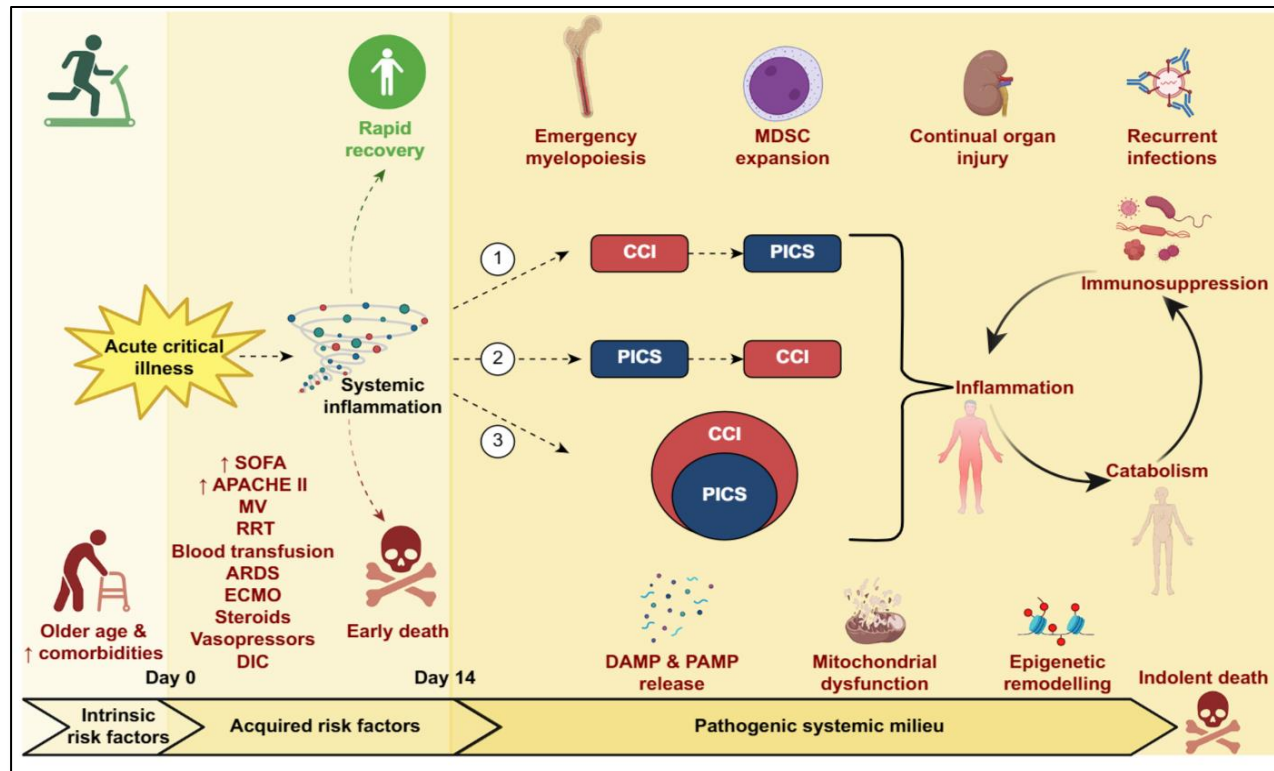
Lindsay CV, et al. Endometrial responses to bacterial and viral infection: a scoping review. *Hum. Reprod. Update.* (2023)

McDaniel MM, et al. Innate control of adaptive immunity and adaptive instruction of innate immunity: bi-directional flow of information. *Curr. Opin. Immunol.* (2021)

Protracted sepsis : *Immunosuppression*

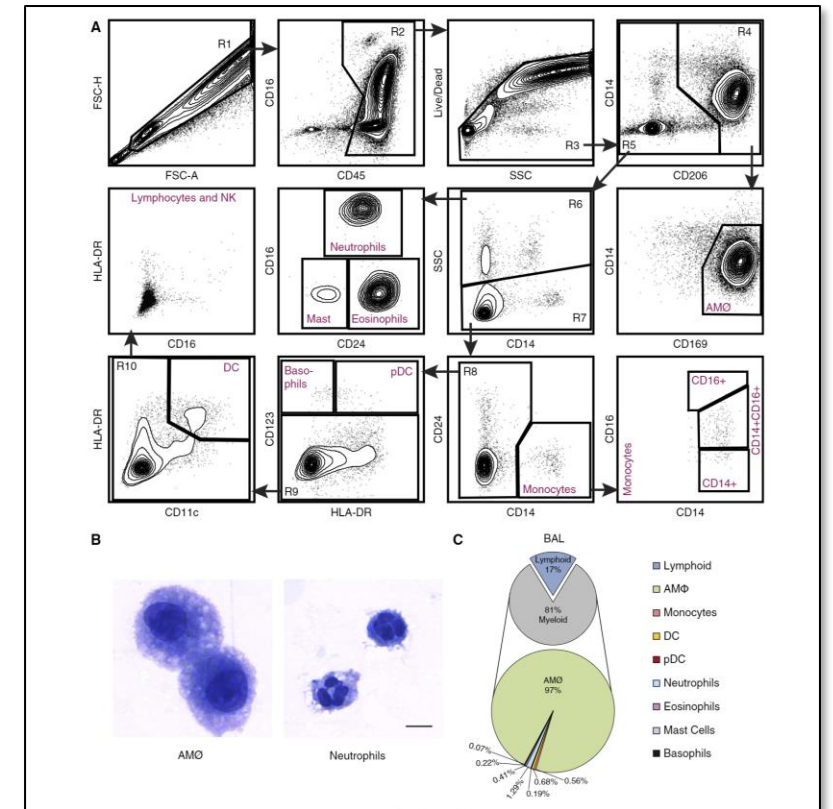
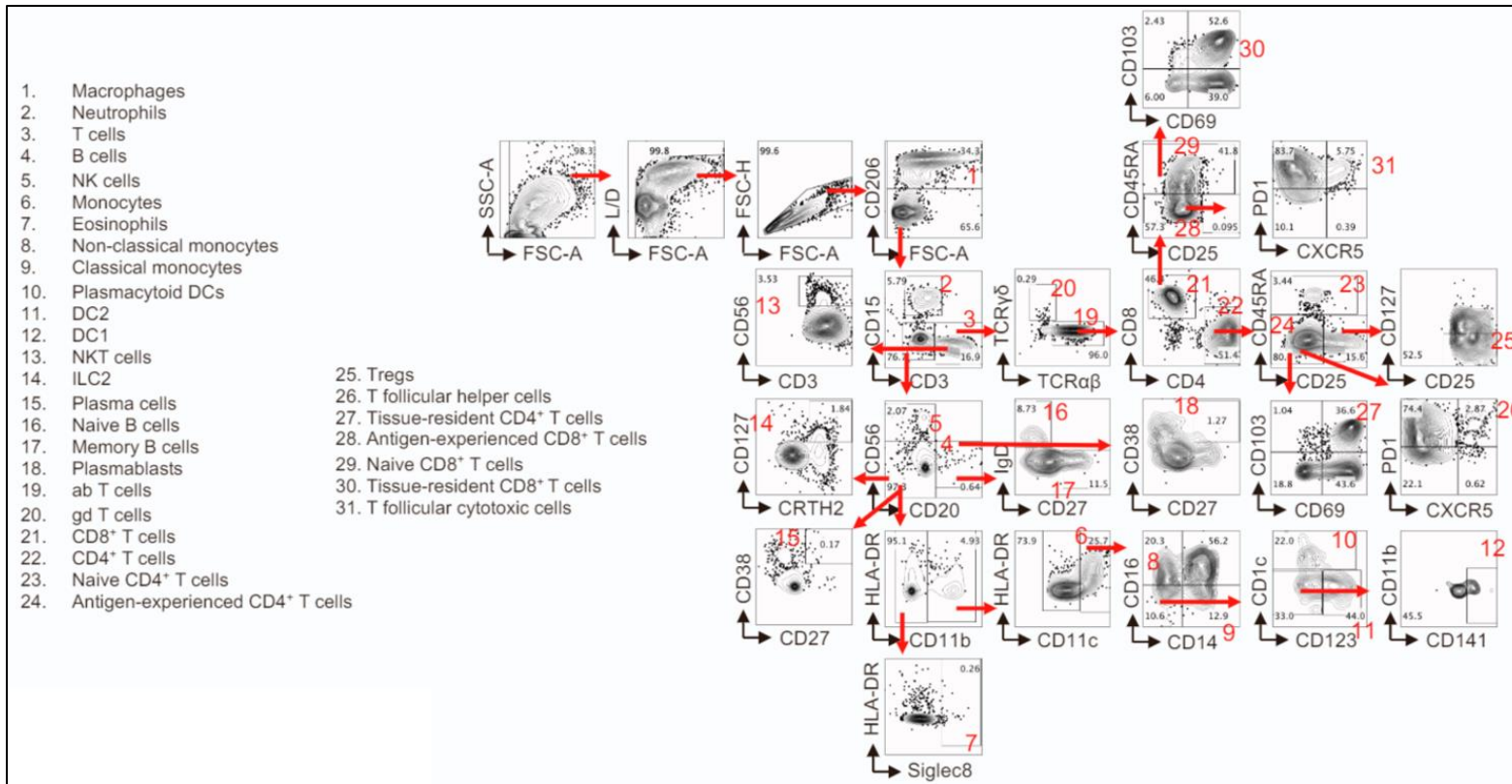


Persistent inflammation, Immunosuppression, and Catabolism syndrome (PICS)



PICS: persistent inflammation, immunosuppression, and catabolism syndrome, DAMP: danger associated molecular pattern, PAMP: pathogen-associated molecular pattern, MDSC: myeloid-derived suppressor cell, IGFBP-3: insulin-like growth factor binding protein 3, IP-10: interferon gamma-induced protein, IPA: indole-3-propionate, sPD-L1: soluble programmed death ligand-1, SDF: stromal cell derived factor, VEGF: vascular endothelial growth factor, GLP-1: glucagon-like peptide-1, Ang2: angiotensin 2, DIC: disseminated intravascular coagulation, ECMO: extracorporeal membrane oxygenation, UCR: urea: creatinine ratio, CCI: chronic critical illness

Spectral flowcytometry (다중 형광 유세포 분석)

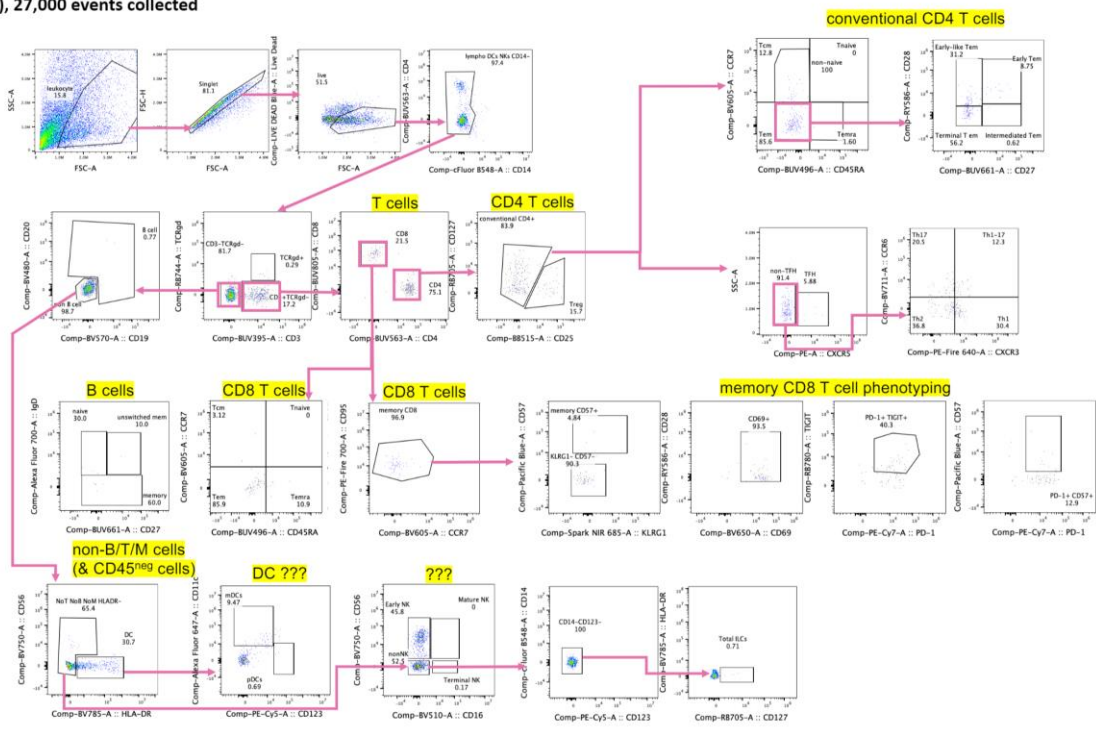


Vijayakumar B, et al. Immuno-proteomic profiling reveals aberrant immune cell regulation in the airways of individuals with ongoing post-COVID-19 respiratory disease. *Immunity*. (2022)

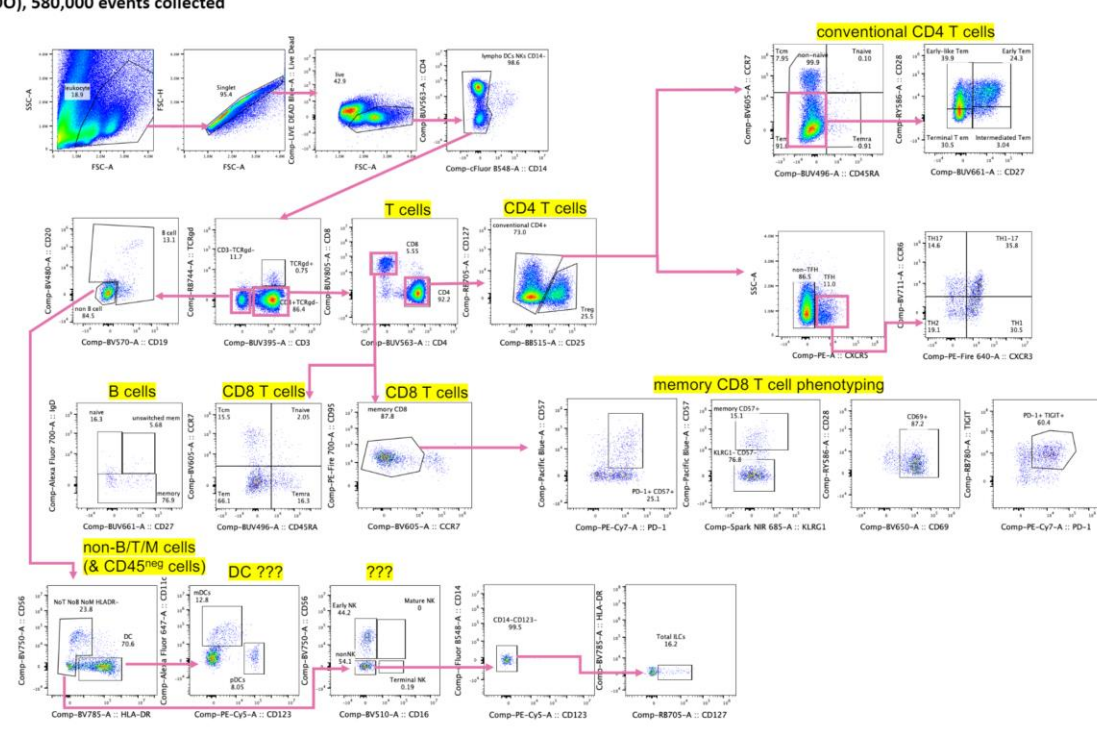
Yu Y-R A, et al. Flow cytometric analysis of myeloid cells in human blood, bronchoalveolar lavage, and lung tissues. *Am. J. Respir. Cell Mol. Biol.* (2016)

Examples for immune phenotyping (BALF)

Sample 1 (0|00), 27,000 events collected



Sample 3 (0|00), 580,000 events collected



Extension of MVS Score

: Inclusion of many Infectious disease with Neutrophil Signature

Immunity

A conserved immune dysregulation signature is associated with infection severity, risk factors prior to infection, and treatment response

In brief

The impact of risk factors for severe infections (being old, male, obese, and having comorbidities) on immune dysregulation prior to infection remains understudied. Using 12,026 blood

samples, Ganesan et al. showed that their previously described 42-gene SoM signature is conserved across risk factors and predicts response to corticosteroid treatment and all-cause mortality.

Authors

Ananthakrishnan Ganesan, Andrew R. Moore, Hong Zheng, ..., Andrew T. Magis, James R. Heath, Purvesh Khatri

Bulk transcriptome

9,346 samples
63 datasets
26 countries

scRNA-seq

584,260 cells
223 samples
4 datasets

Proteomics

2,487 samples
Arivale Cohort

42-gene Severe-or-Mild Signature

Detrimental modules (higher = worse)

24 genes:
Neutrophils

Protective modules (higher = better)

18 genes:
Monocytes, T, NK

Quantify Immune Dysregulation

Prior to infection

Risk factors for severe infection



Age, sex, BMI, smoking, asthma

Acute infection

Severity of infection



Response to treatment



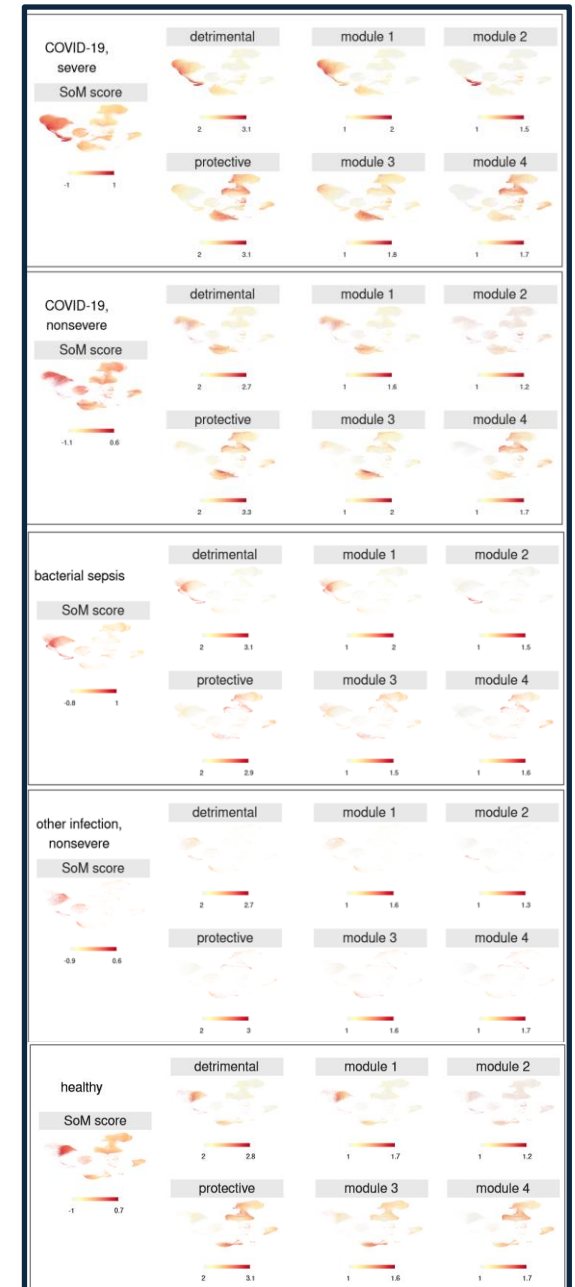
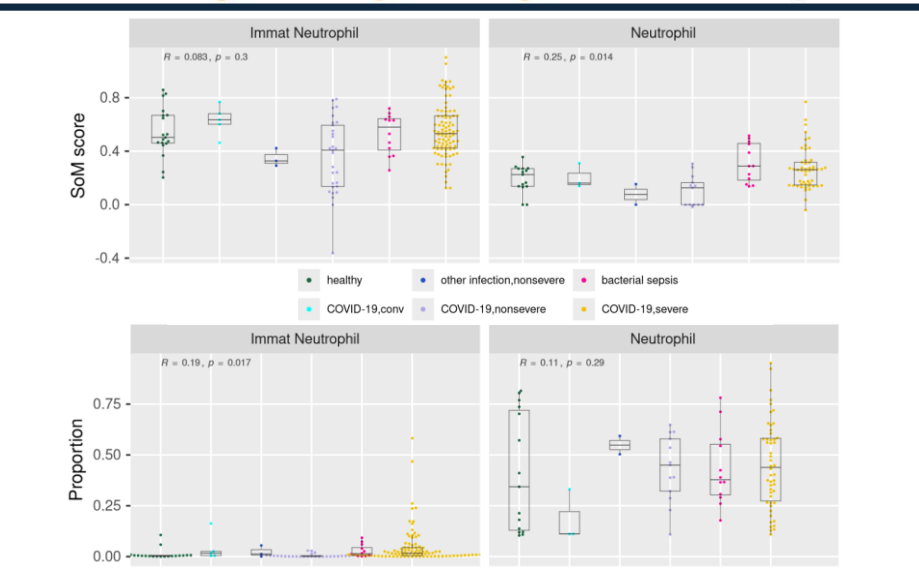
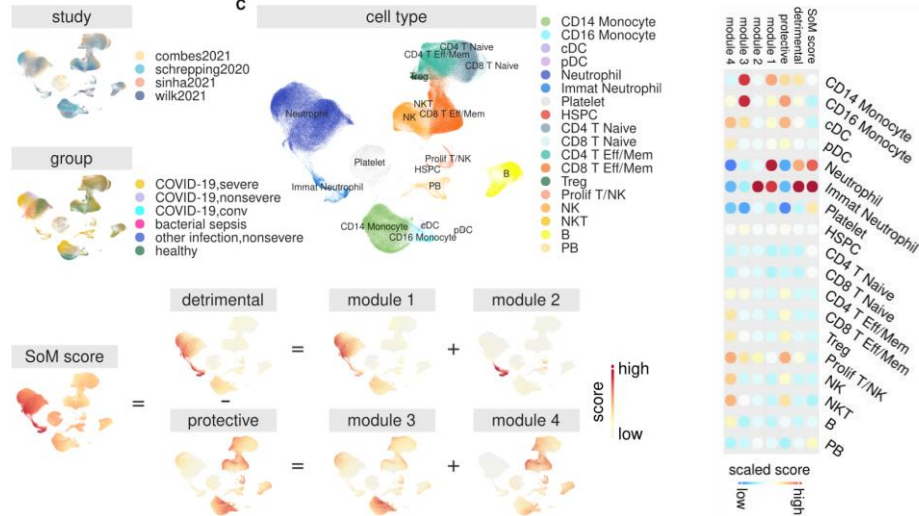
Long-term health

All-cause mortality



Conserved Consensus Immune Dysregulation in Health and Disease

Gene modules in SoM signatures are cell type-specific



Conserved Immune Dysregulation

: Risk factor including host factor, treatment, and lifestyle

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A conserved immune dysregulation signature is associated with infection severity, risk factors prior to infection, and treatment response

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Quantify Immune Dysregulation

Prior to infection

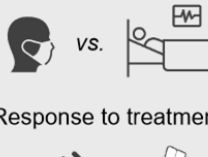
Risk factors for severe infection



Age, sex, BMI, smoking, asthma

Acute infection

Severity of infection



Response to treatment

Long-term health

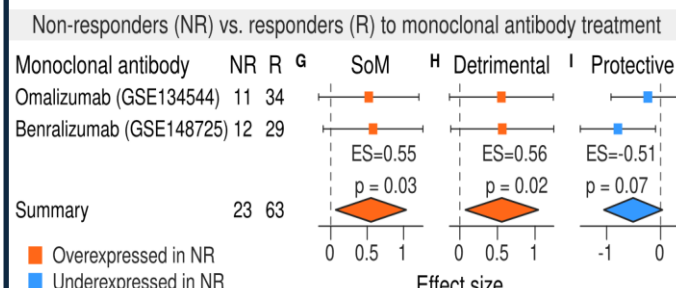
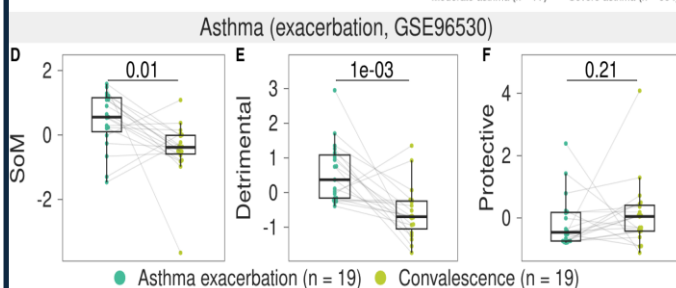
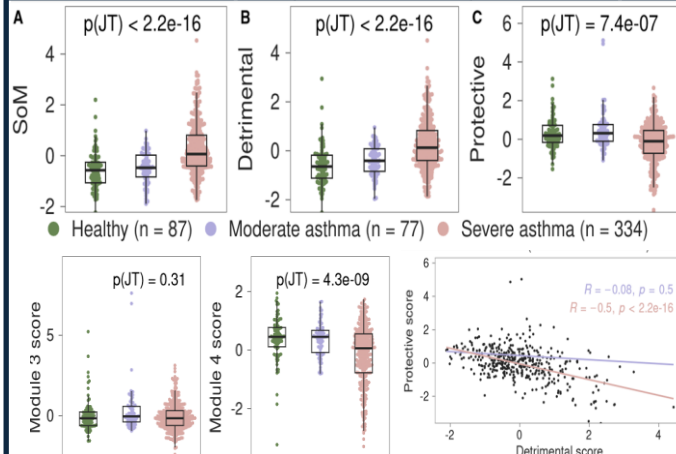
All-cause mortality



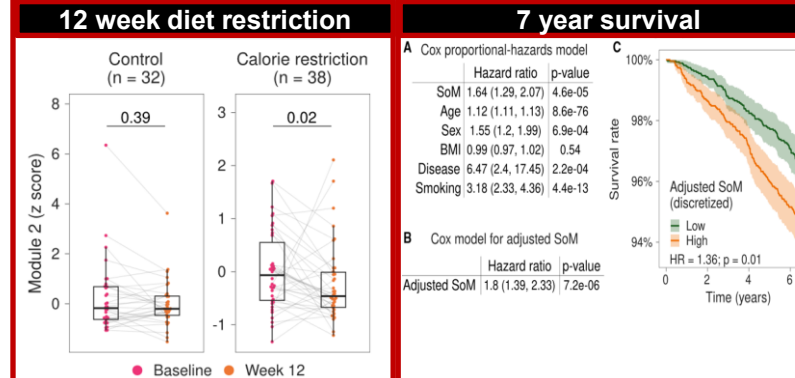
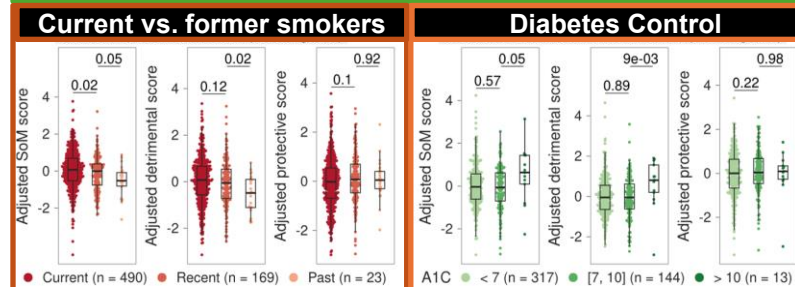
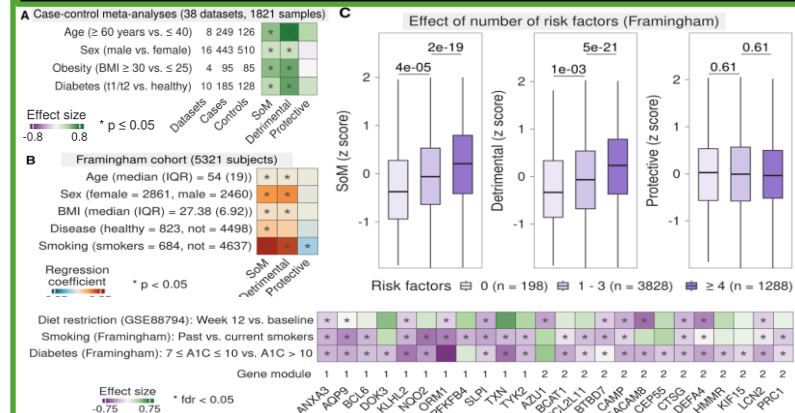
vs.

Conserved Consensus Immune Dysregulation in Health and Disease

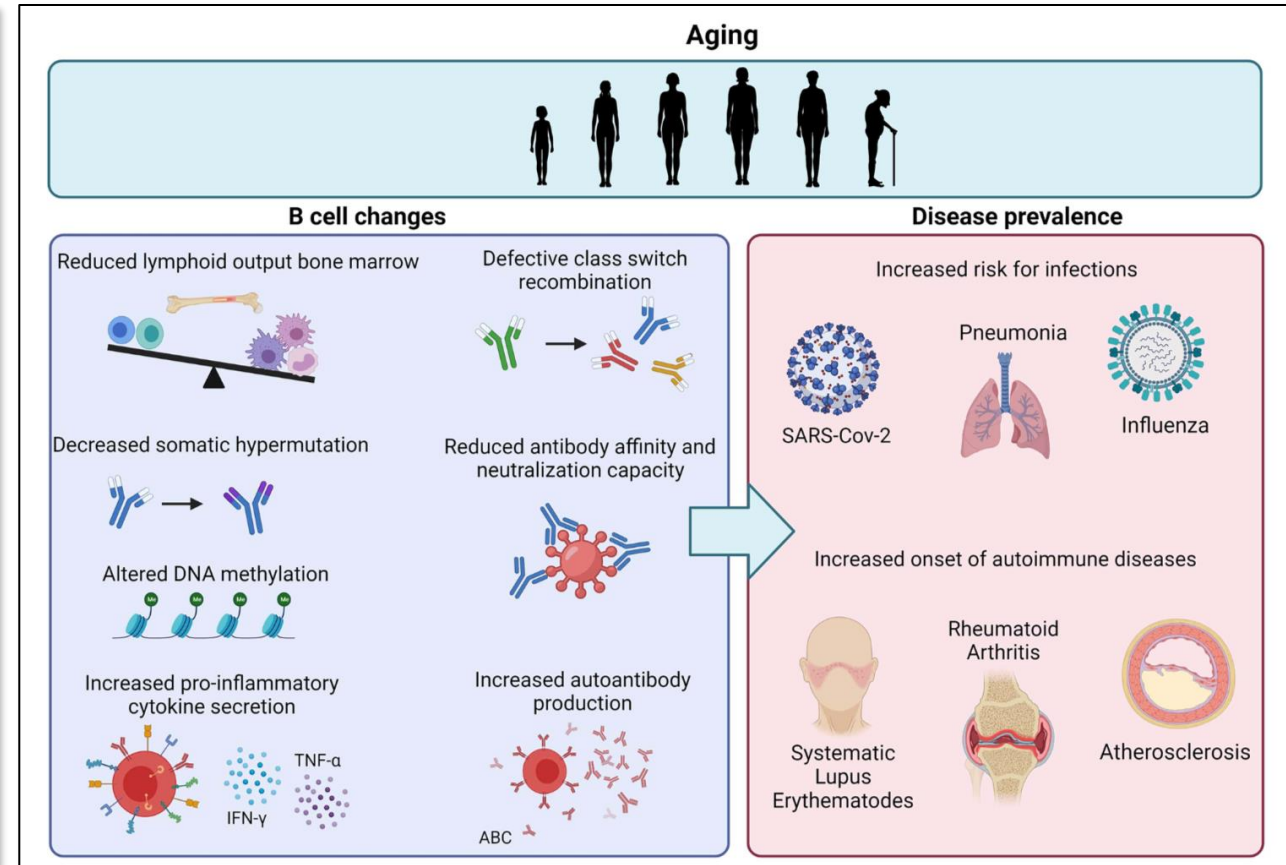
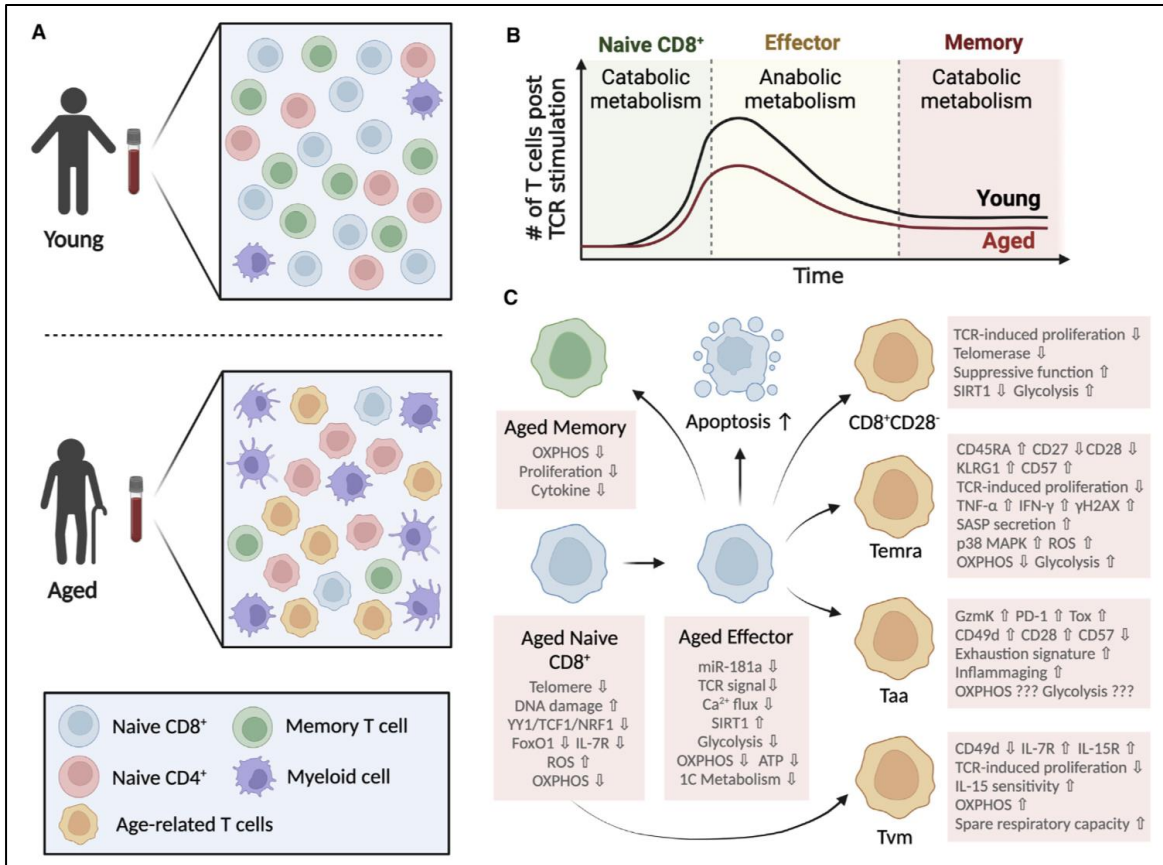
Asthma (baseline, GSE69683)



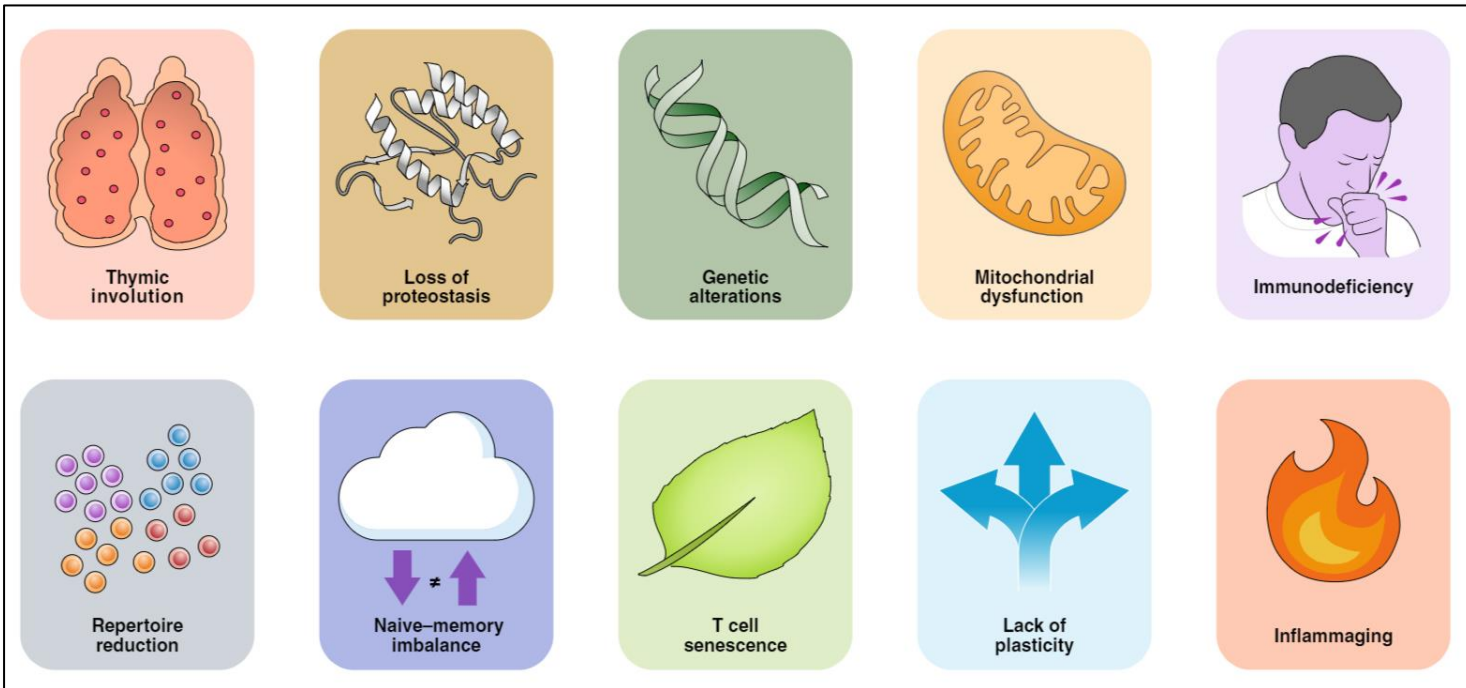
Multifactorial Risk Factor



Aging and immunosenescence

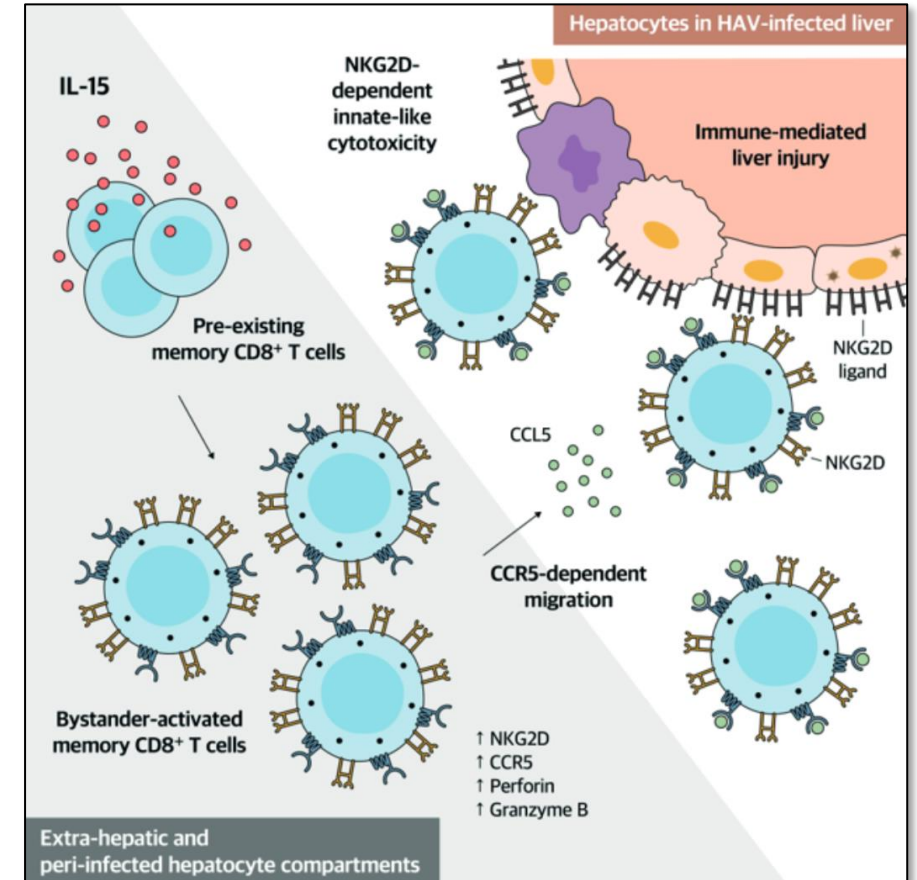
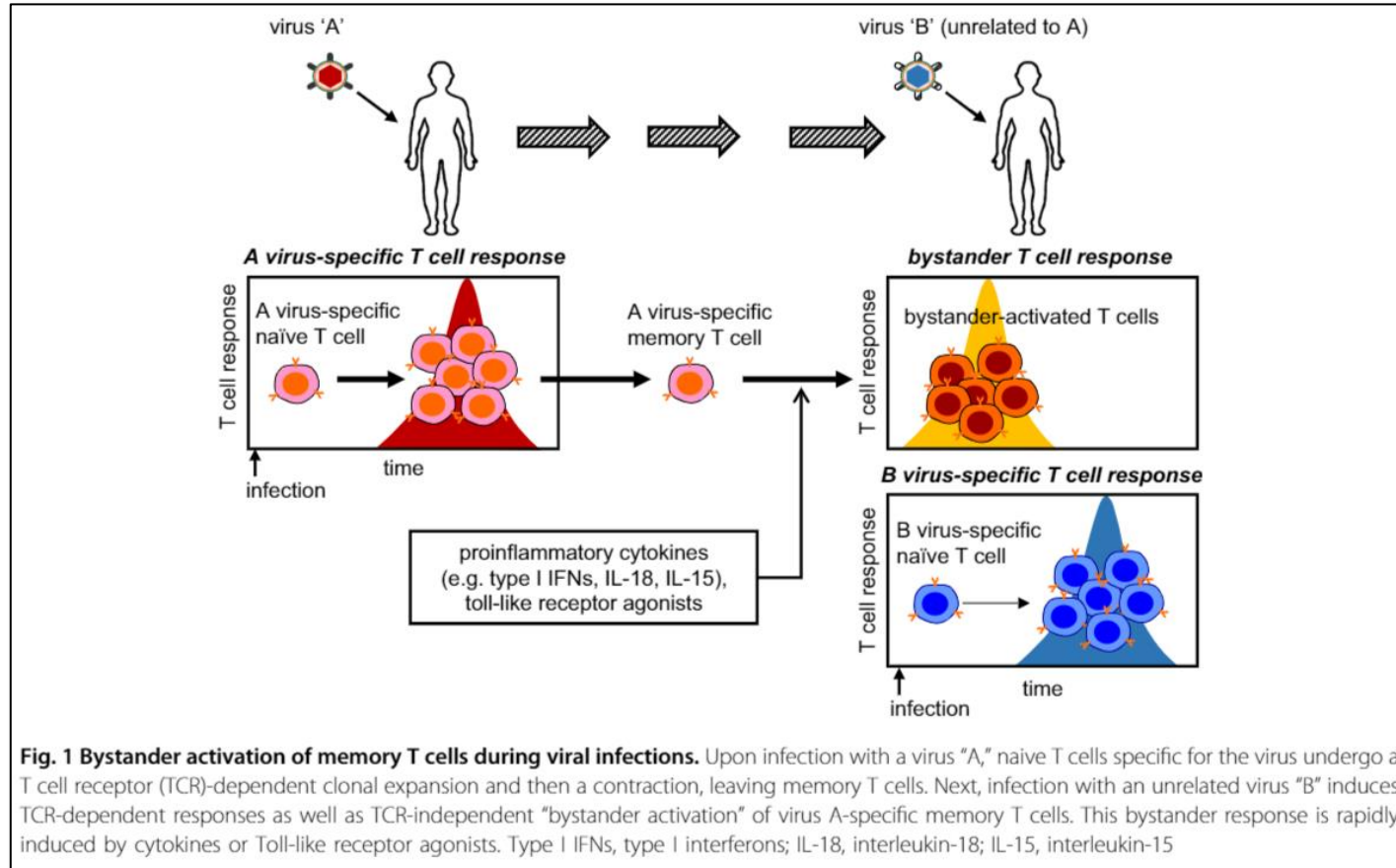


Hallmarks of T cell aging



1. ↓ **Peripheral T cell** (말초 T 세포 감소)
2. ↓ **Activation and proliferation**
(활성화 및 증식 감소)
3. ↓ **Naïve T** vs. ↑ **Memory T**
(naive T 세포 감소, memory T 세포 증가)
4. ↑ **SA-βGal** 증가
5. ↑ **CD27 Shedding** 증가
6. ↑ **Senescence pathway markers** 증가
(노화 경로 지표들)
7. ↑ **SASP** 증가
8. ↑ **DNA damage** 증가 (DNA 손상)
9. ↓ **TCR downstream molecules** 감소
(TCR 하위 분자들)
10. ↑ **Mitochondrial dysfunction** 증가
(미토콘드리아 기능 장애)

Altered immune interaction and pathology



Neutrophil-lymphocyte ratio (NLR) in sepsis

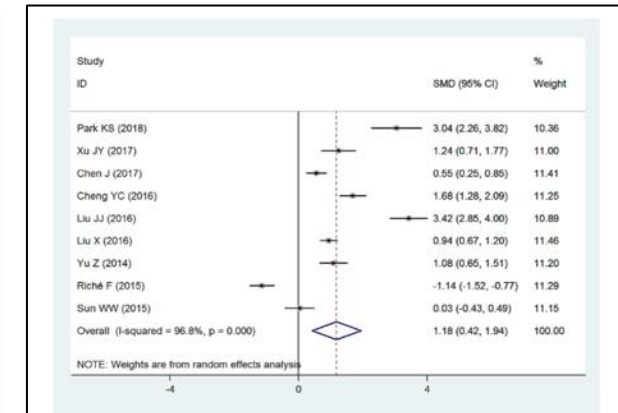
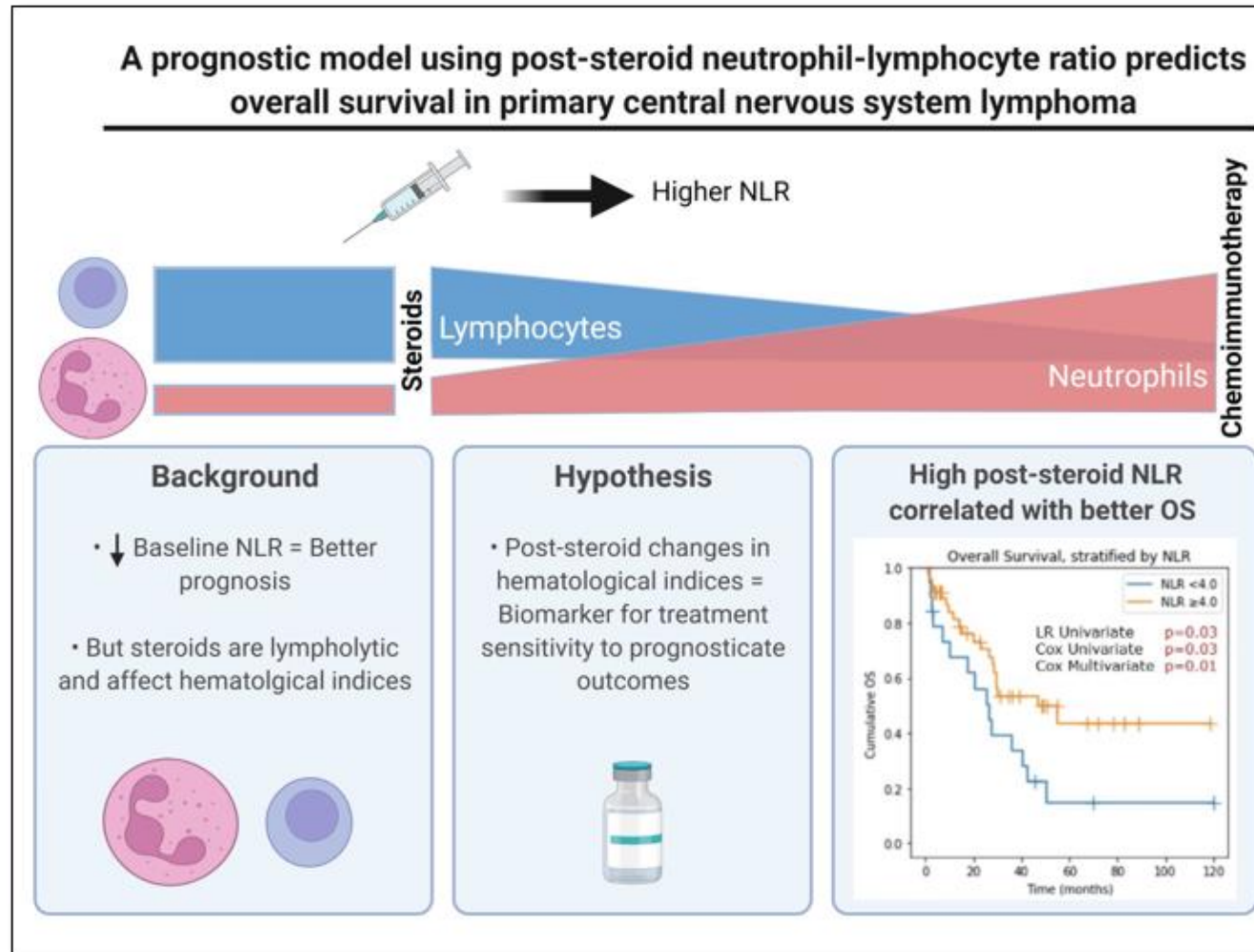
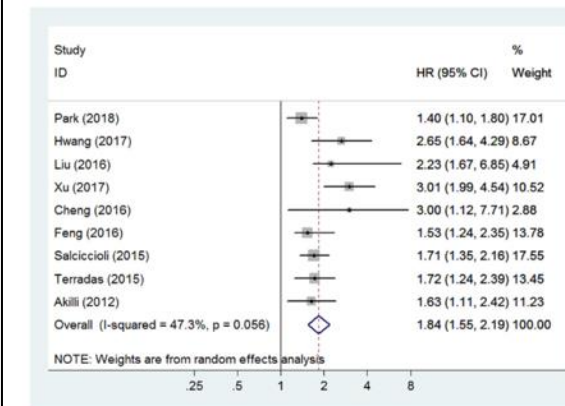
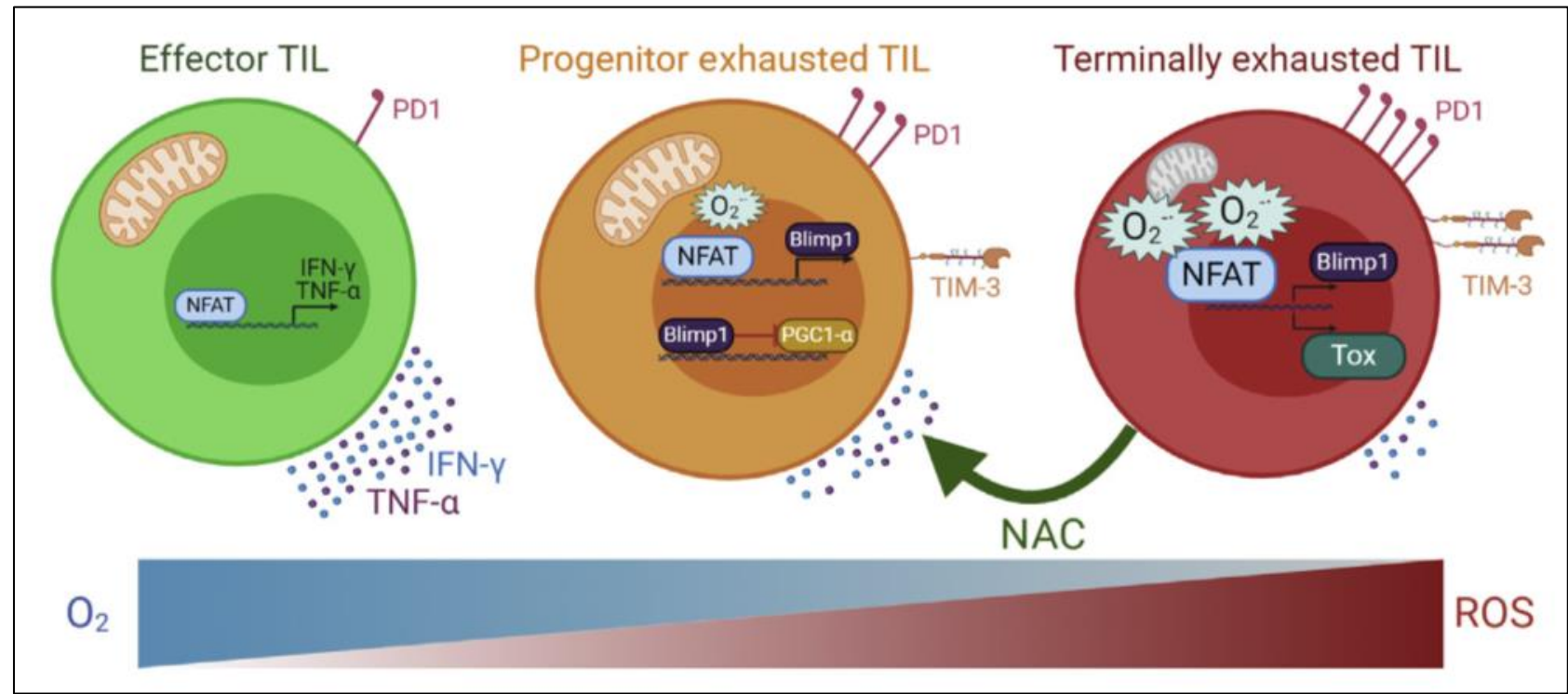
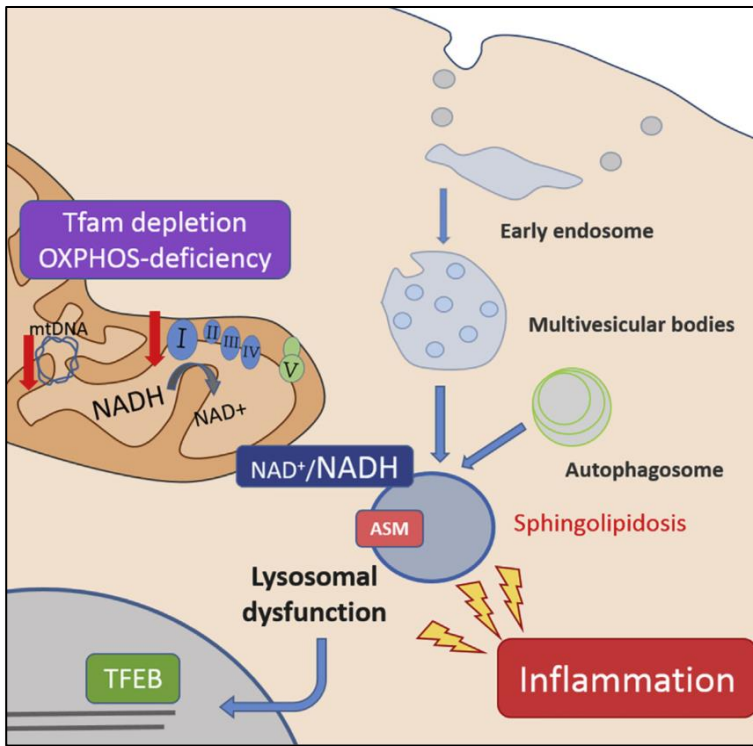


Fig. 2. Forest plot diagrams of neutrophil-to-lymphocyte ratios (NLR) in survivors and non-survivors among patients with sepsis. The squares and horizontal lines correspond to study-specific standard mean differences (SMDs) and 95% confidence intervals (CIs).



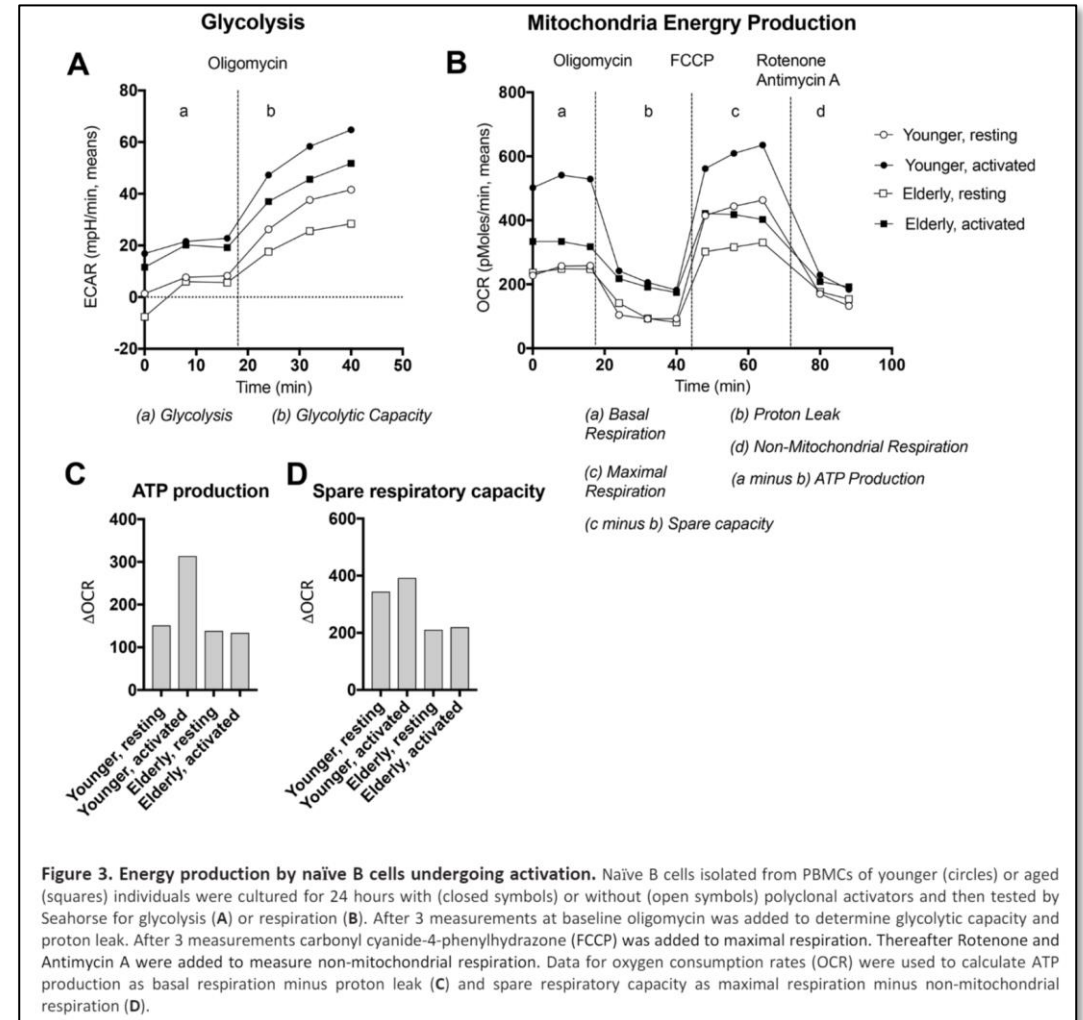
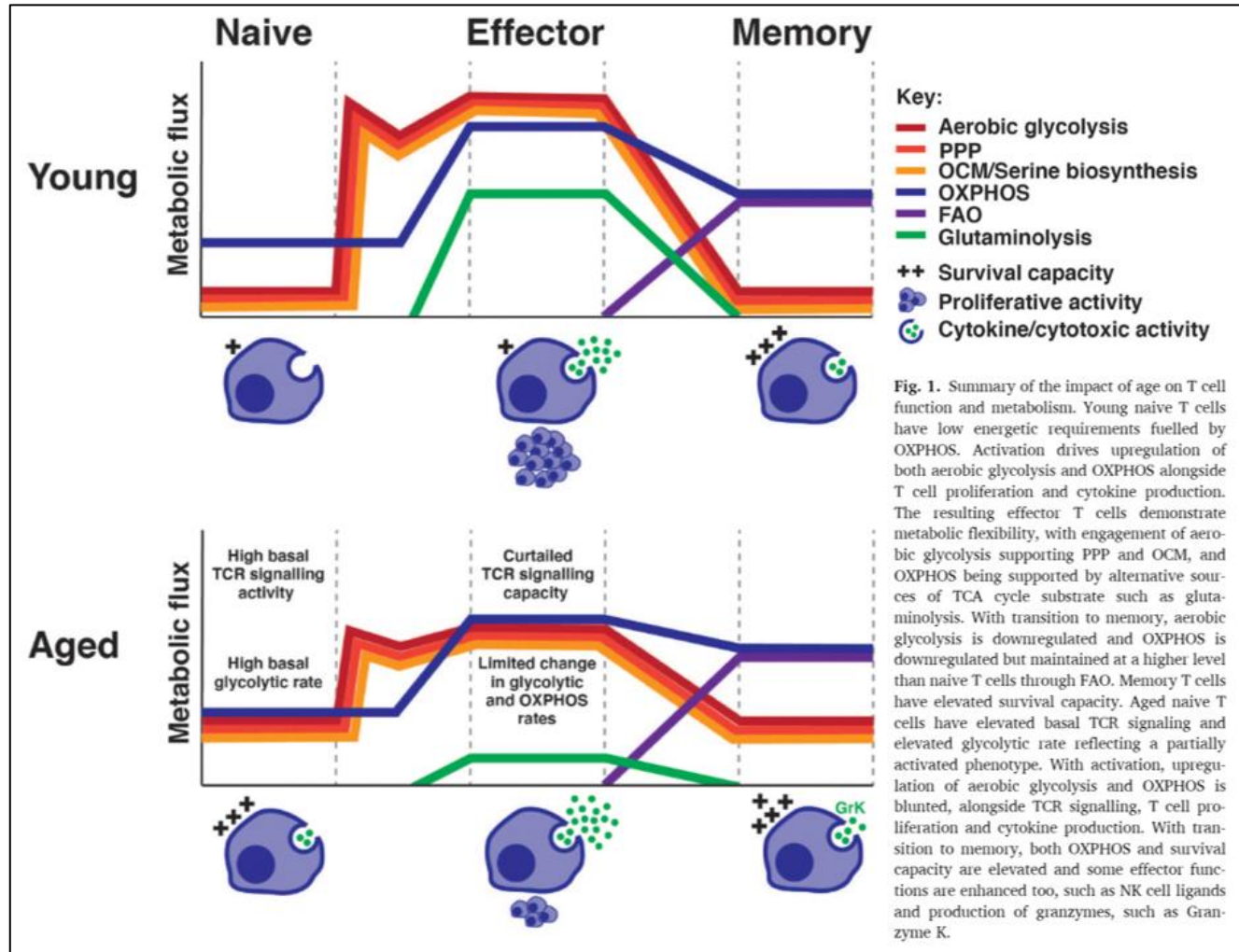
Mitochondrial Dysfunction & T Cell Aging



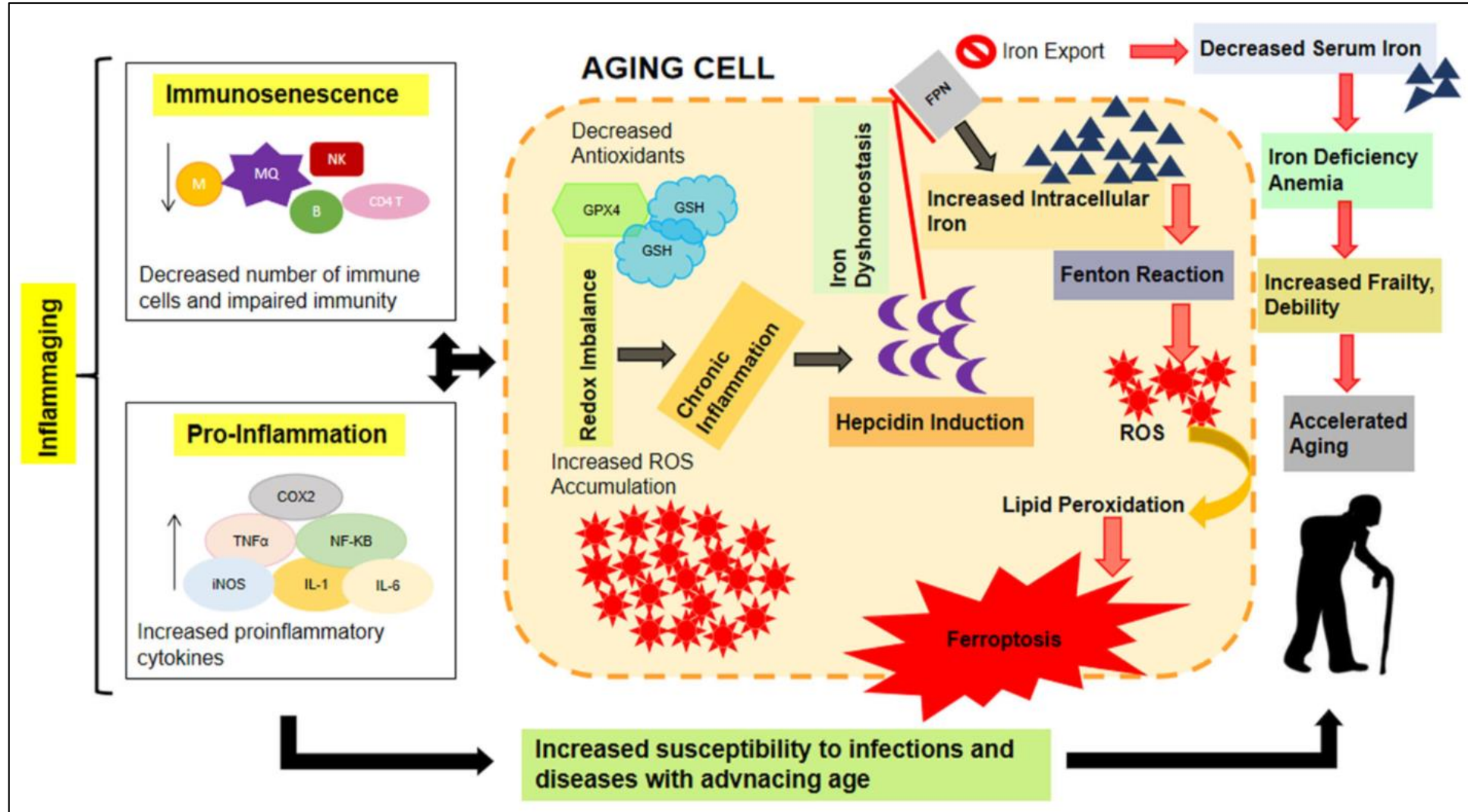
Baixauli F, et al. Mitochondrial respiration controls lysosomal function during inflammatory T cell responses. *Cell Metab.* (2015)

Soto-Herederó G, et al. Mitochondrial dysfunction defines T cell exhaustion. *Cell Metab.* (2021)

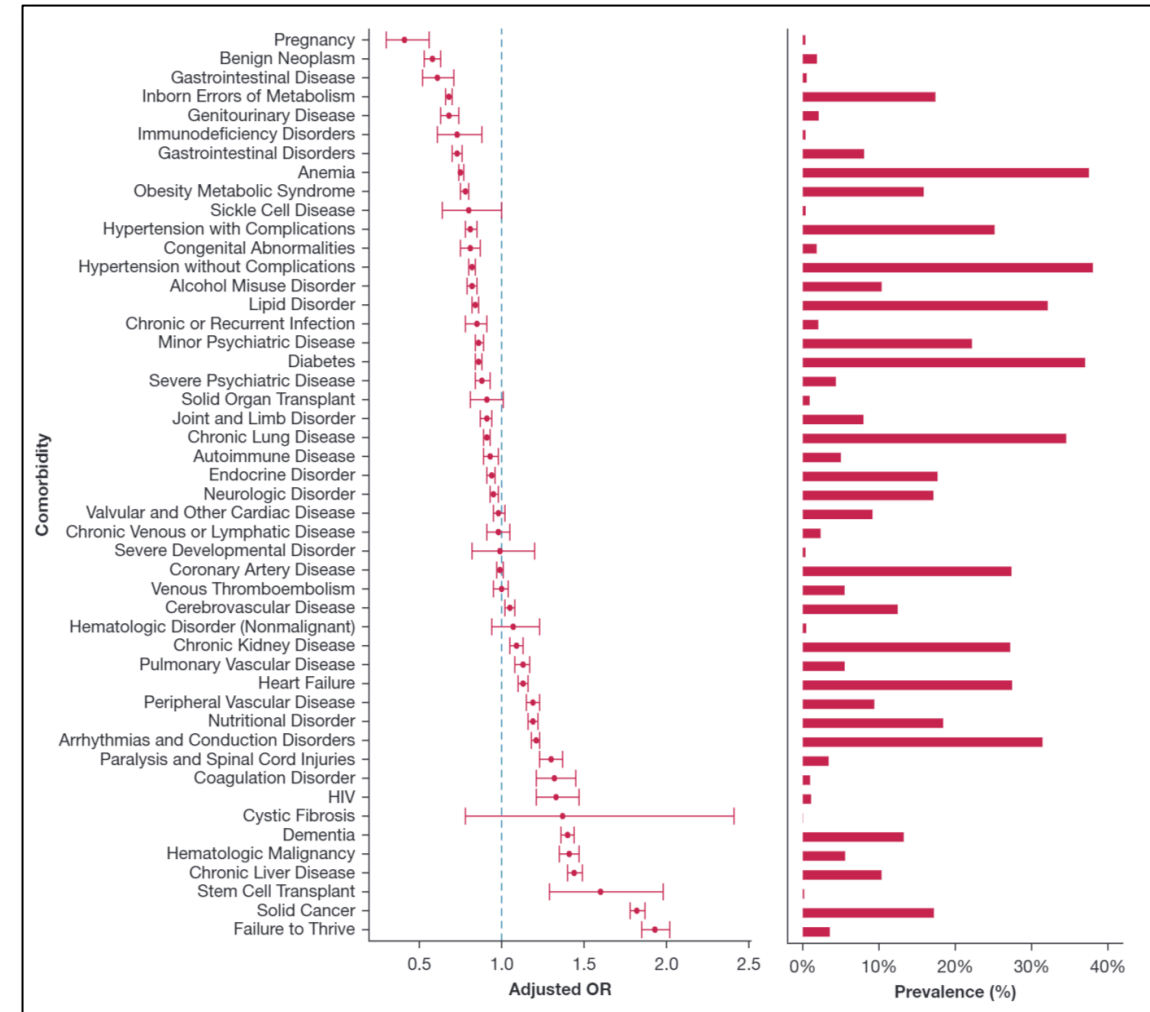
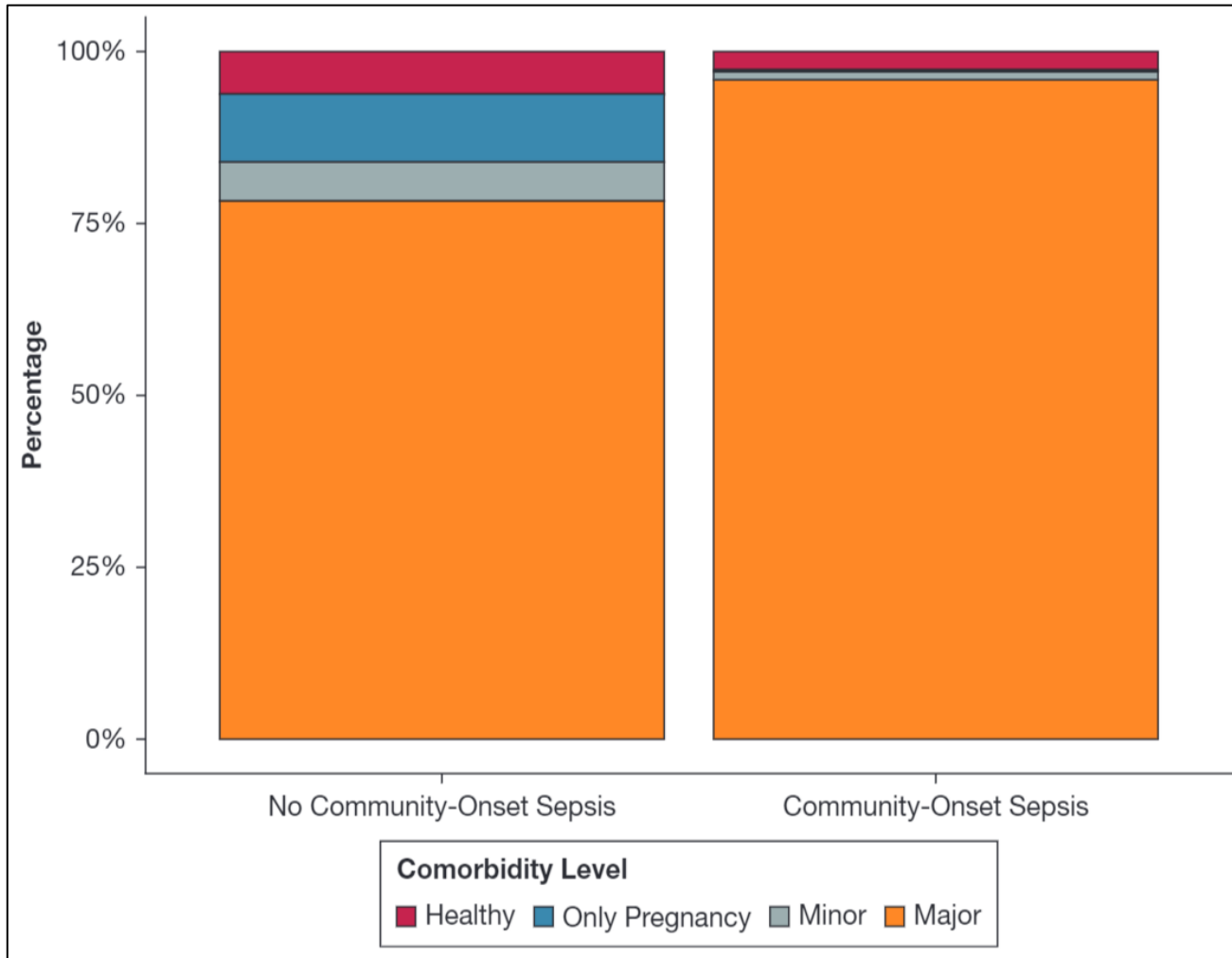
Metabolic senescence



Ferroptosis and Aging

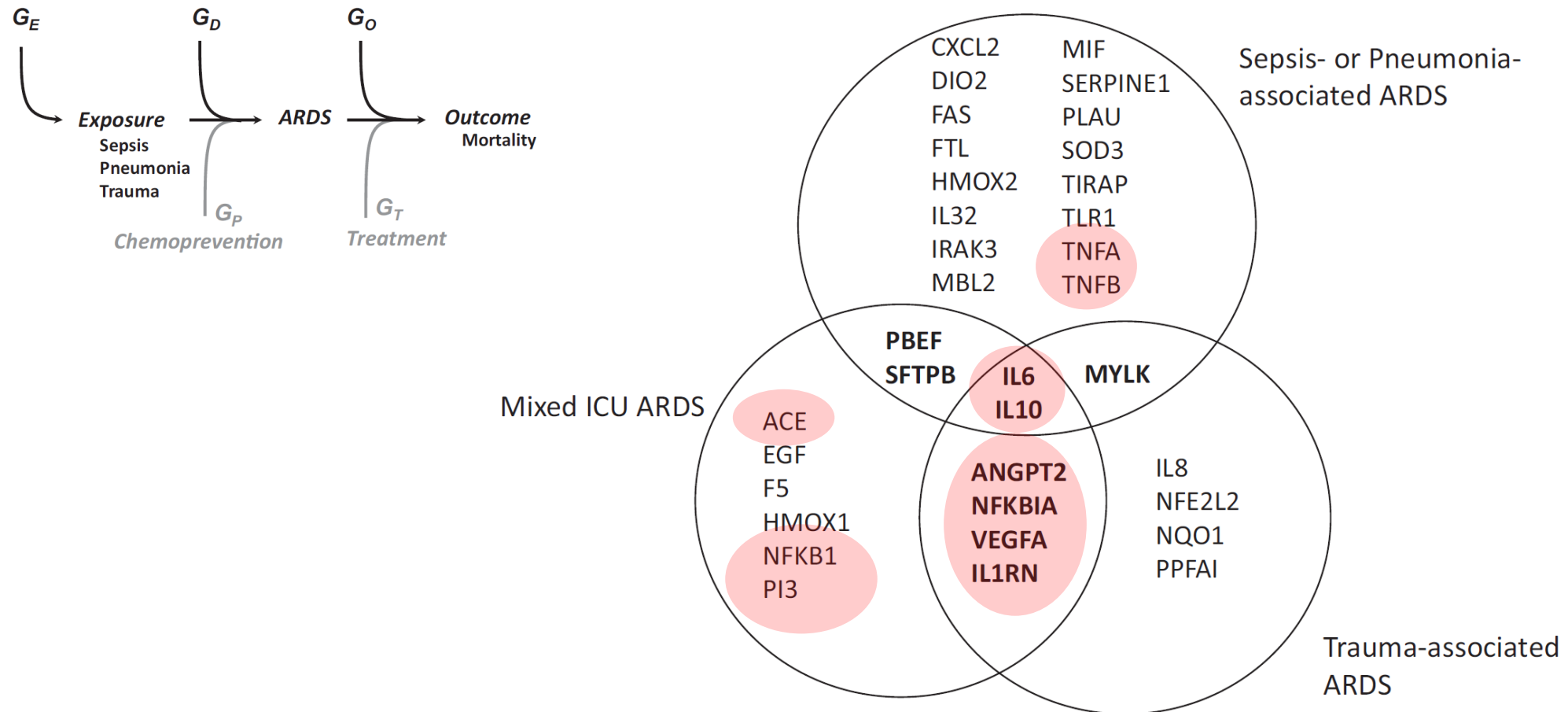


Host factors such as co-morbidities



Endothelial Injury

Immune pathology associated with “*dysregulated inflammation*” in the resp. tract



Loss of ACE2 Homeostatic Regulation : *Dysregulation of the Renin-Angiotensin System*

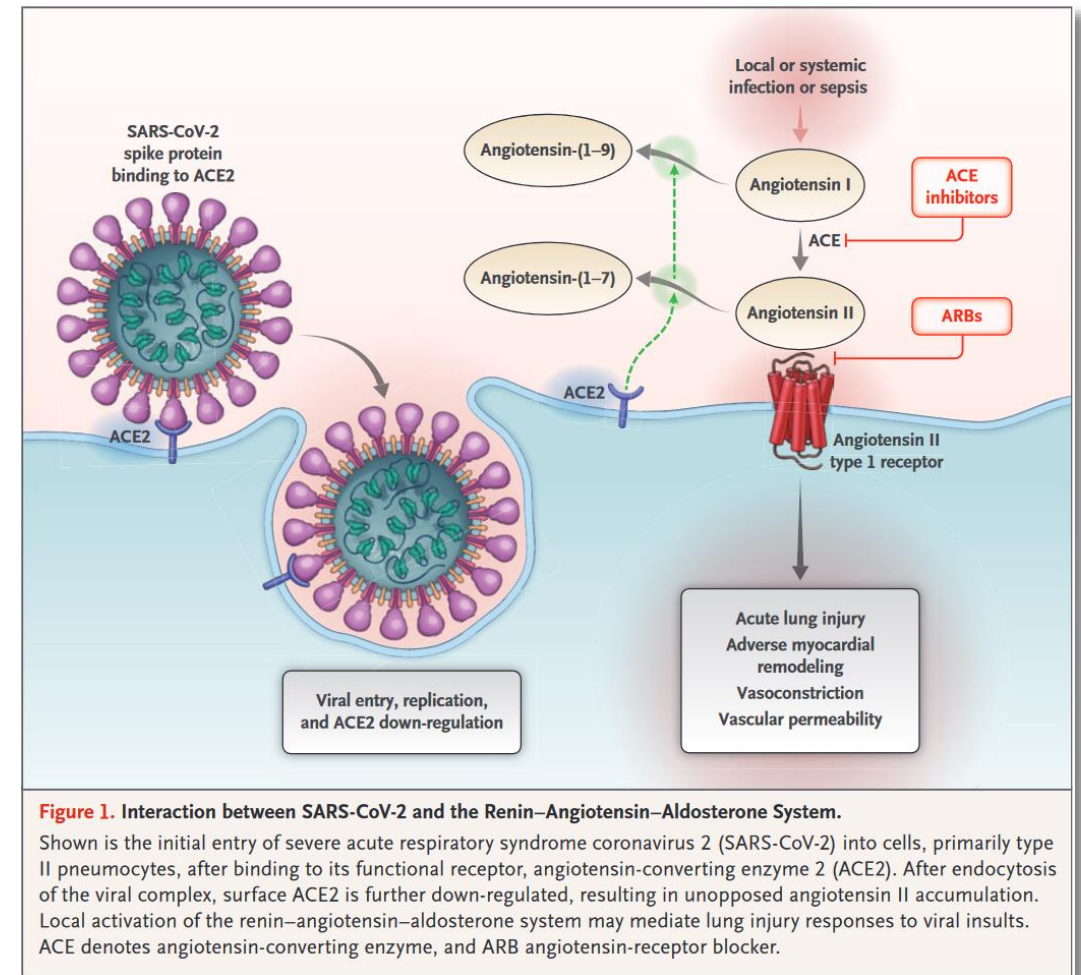
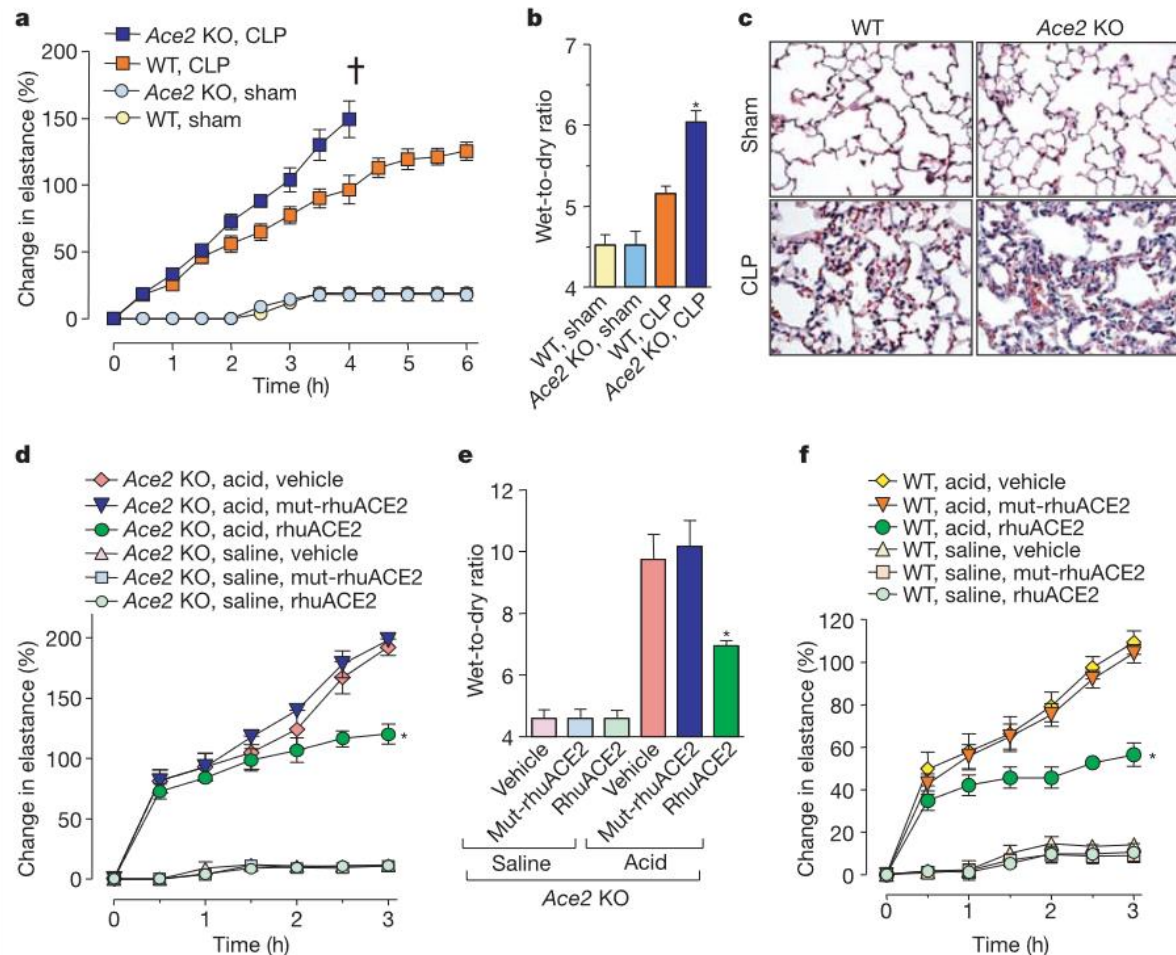
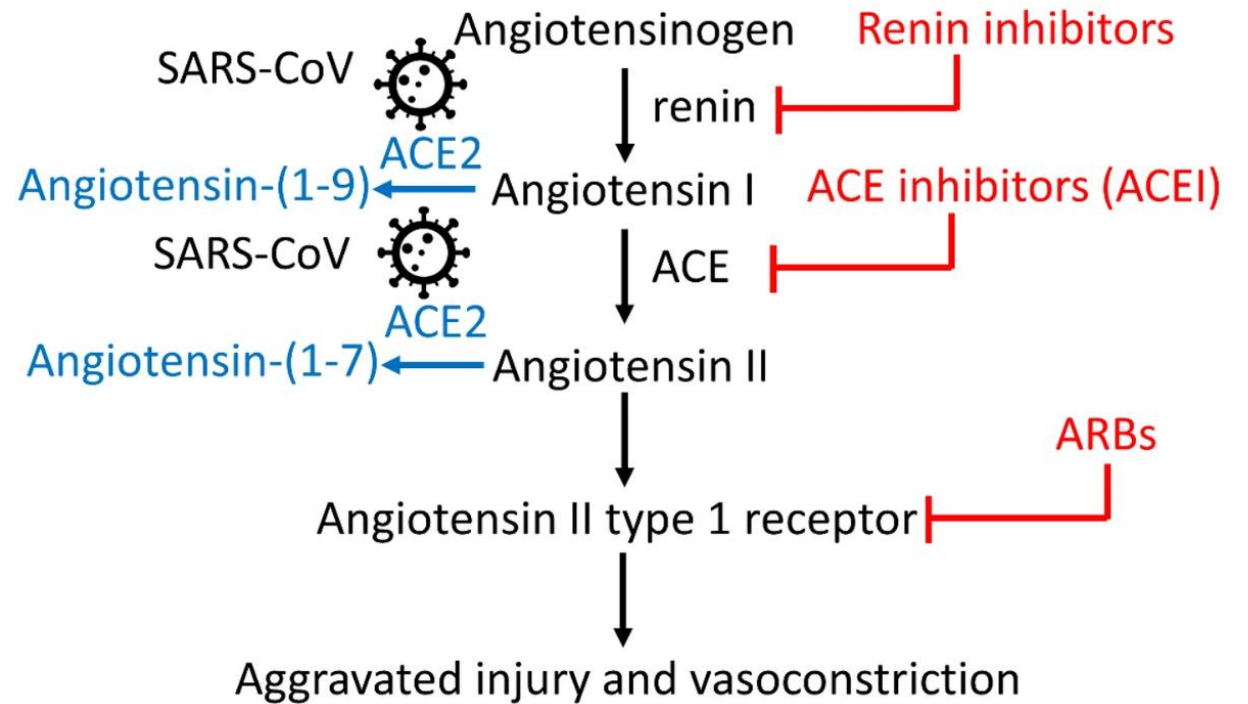
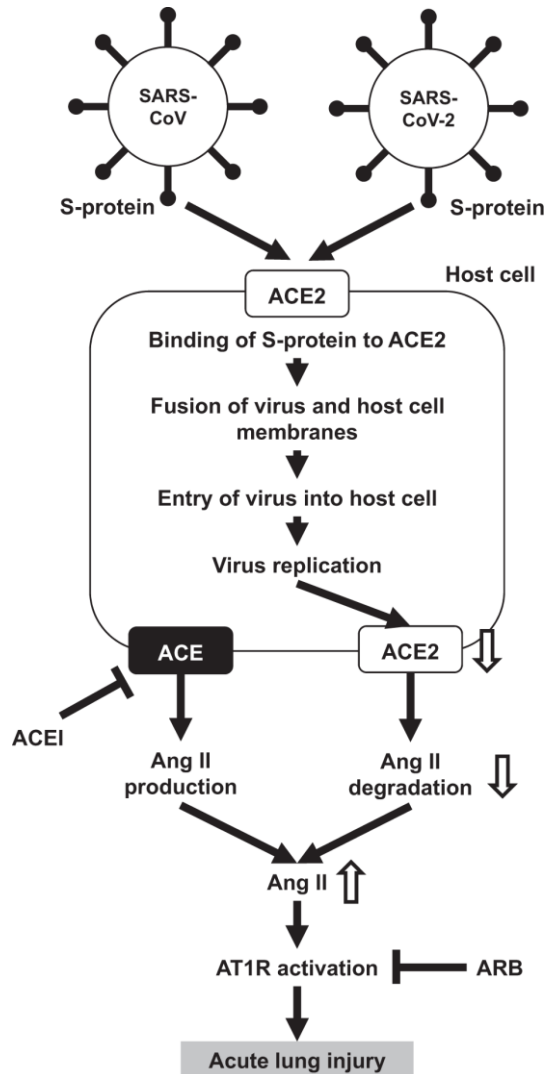


Figure 1. Interaction between SARS-CoV-2 and the Renin-Angiotensin-Aldosterone System. Shown is the initial entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells, primarily type II pneumocytes, after binding to its functional receptor, angiotensin-converting enzyme 2 (ACE2). After endocytosis of the viral complex, surface ACE2 is further down-regulated, resulting in unopposed angiotensin II accumulation. Local activation of the renin-angiotensin-aldosterone system may mediate lung injury responses to viral insults. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

Renin-angiotensin system (RAS) in ARDS



Kim GJ, et al. The effect of renin-angiotensin-aldosterone system inhibitors on organ-specific ace2 expression in zebrafish and its implications for COVID-19. *Sci Rep.* (2021)

Kai H, Kai M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors-lessons from available evidence and insights into COVID-19. *Hypertens Res.* (2020)

Systemic Cascade

: Endothelial Damage, Inflammation, and Hypercoagulability

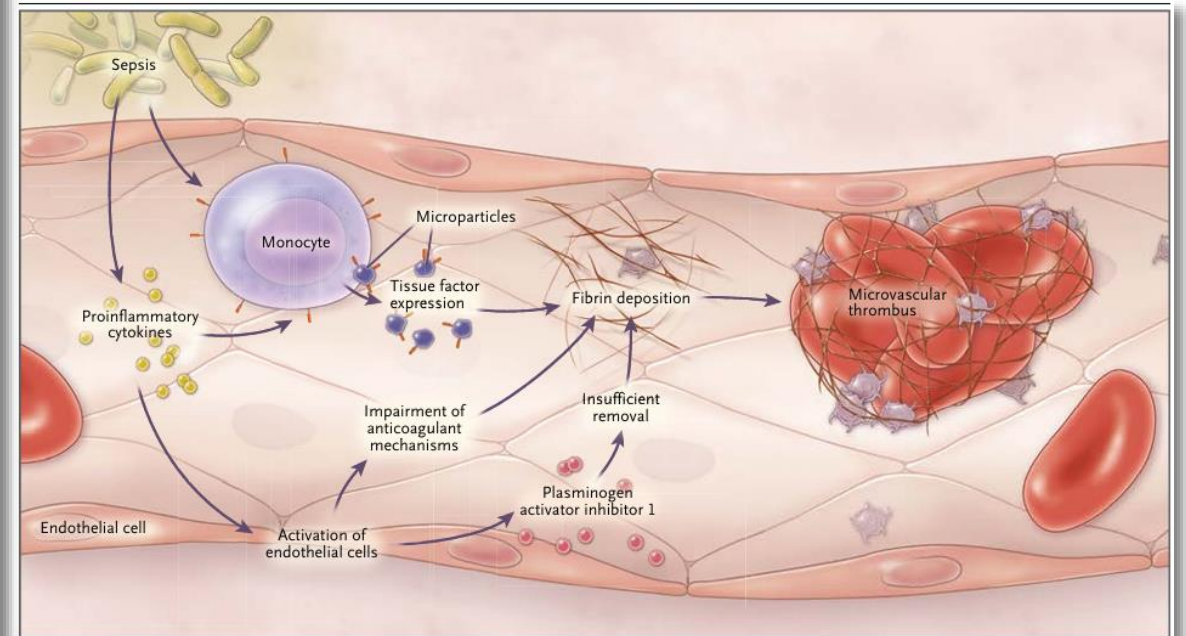
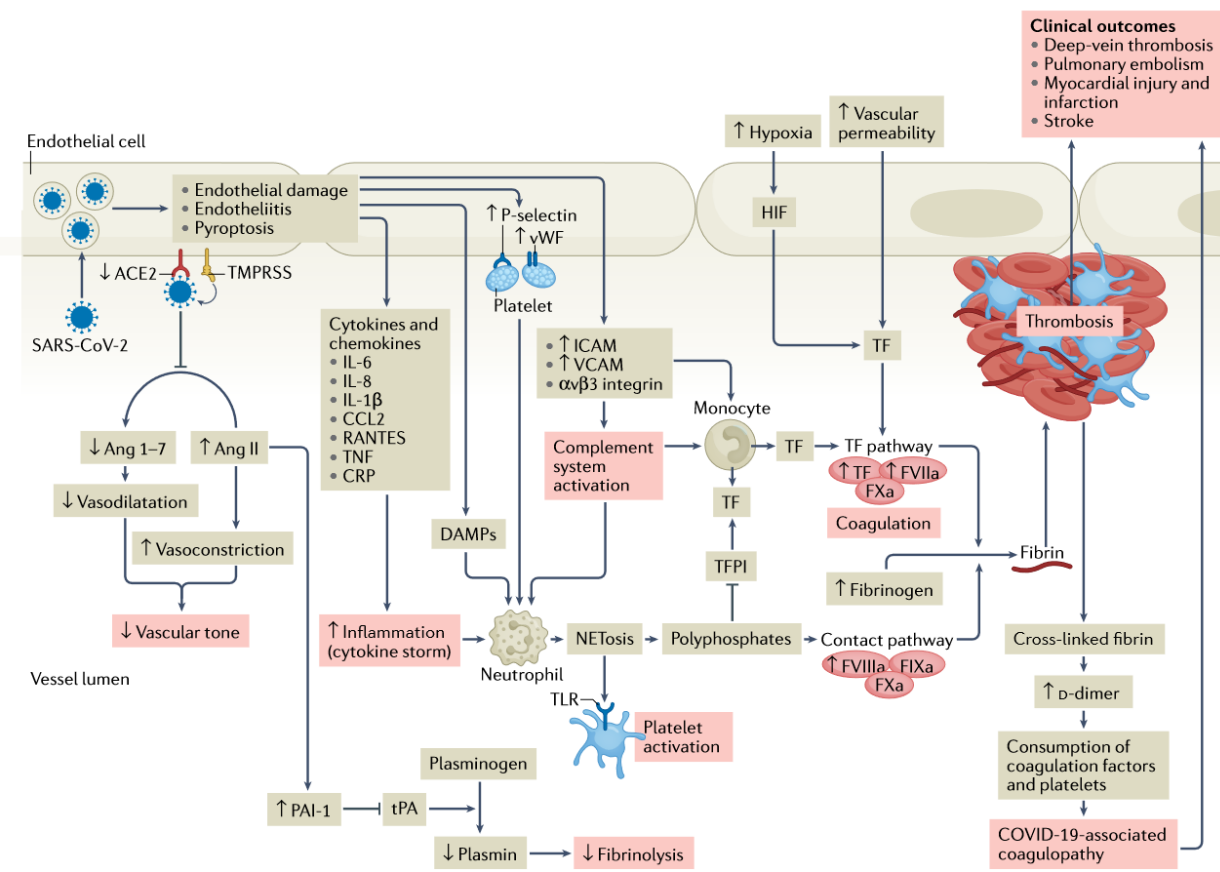
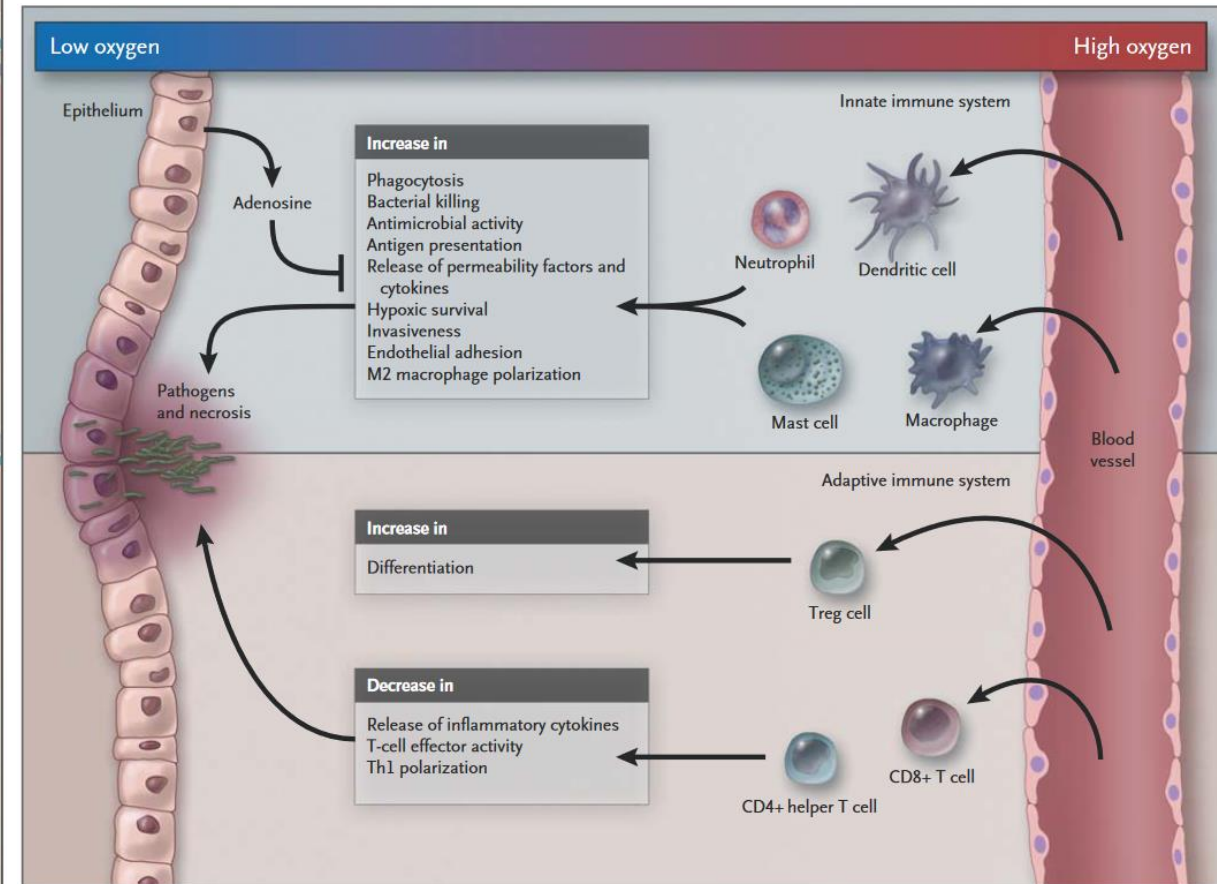
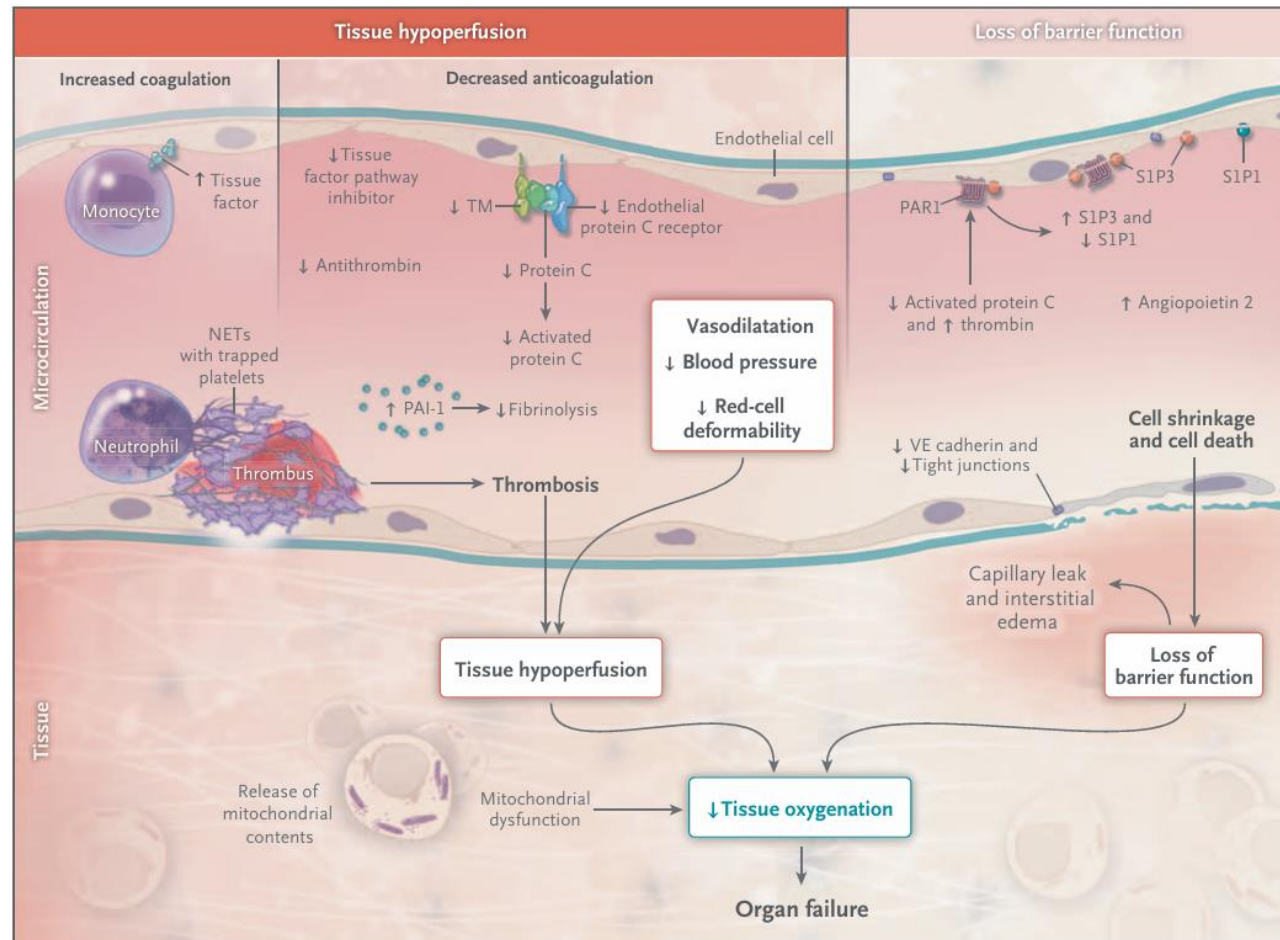


Figure 2. Pathogenesis of Disseminated Intravascular Coagulation in Sepsis.

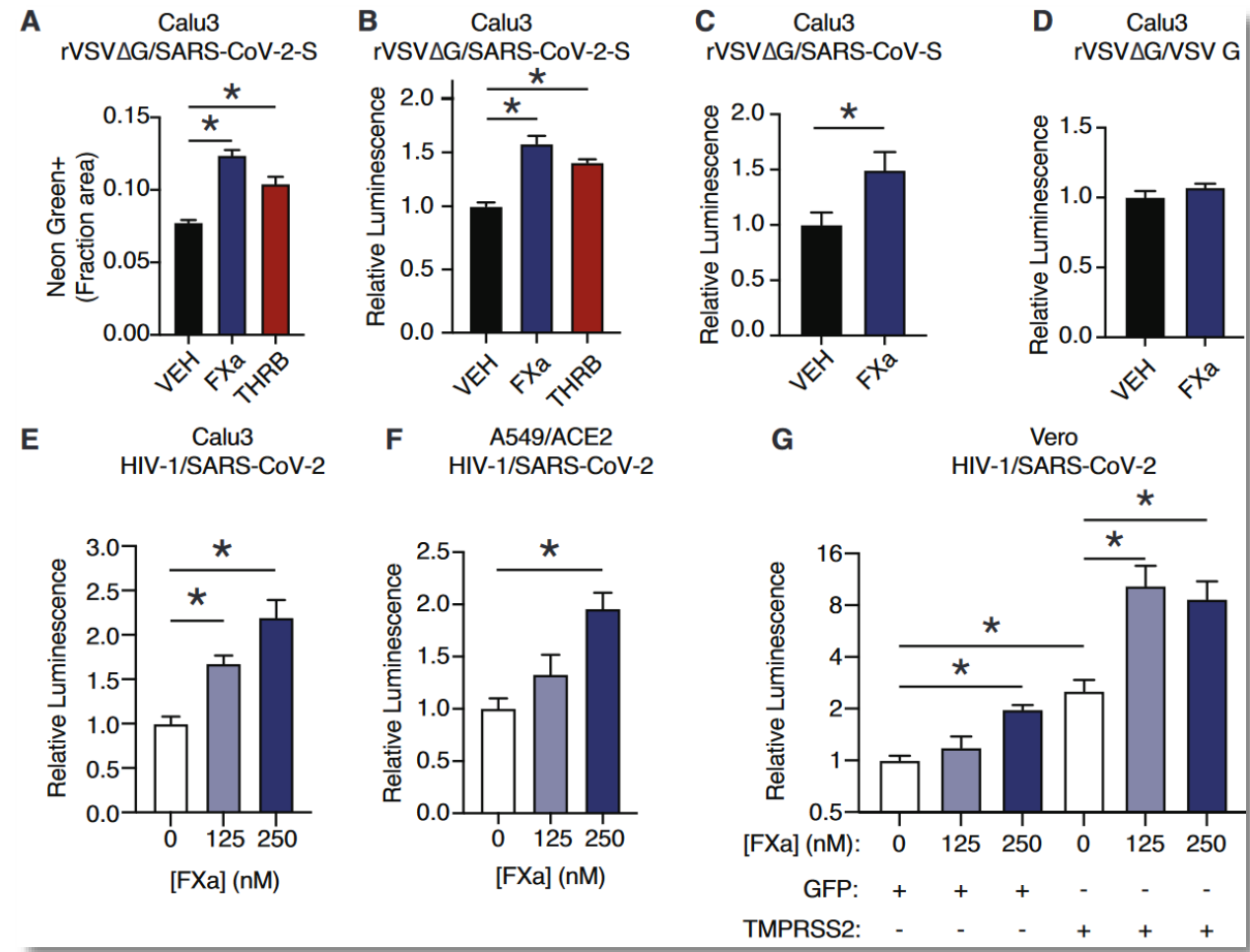
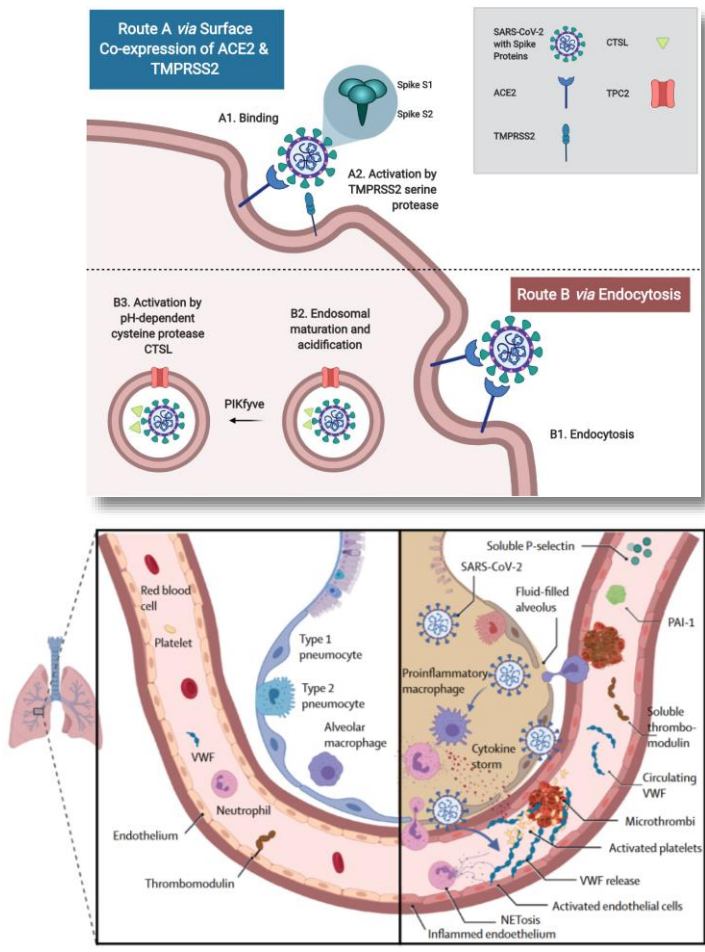
Through the generation of proinflammatory cytokines and the activation of monocytes, bacteria cause the up-regulation of tissue factor as well as the release of microparticles expressing tissue factor, thus leading to the activation of coagulation. Proinflammatory cytokines also cause the activation of endothelial cells, a process that impairs anticoagulant mechanisms and down-regulates fibrinolysis by generating increased amounts of plasminogen activator inhibitor.

Lethal Culmination: : Hypoperfusion and Multi-Organ Failure



SARS-CoV-2 Host Cell Entry

: *The Dual Role of ACE2 and the Coagulation System*

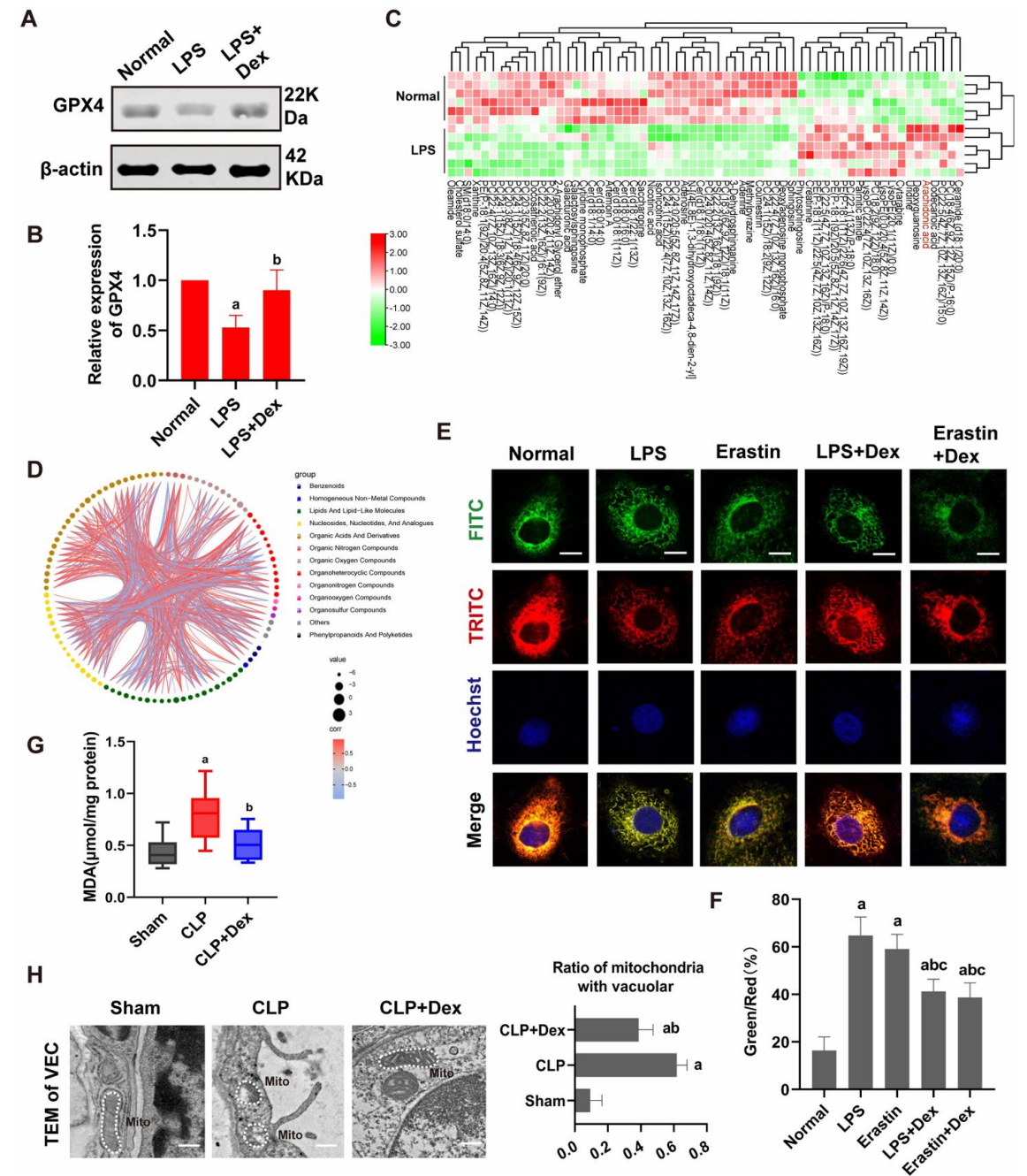
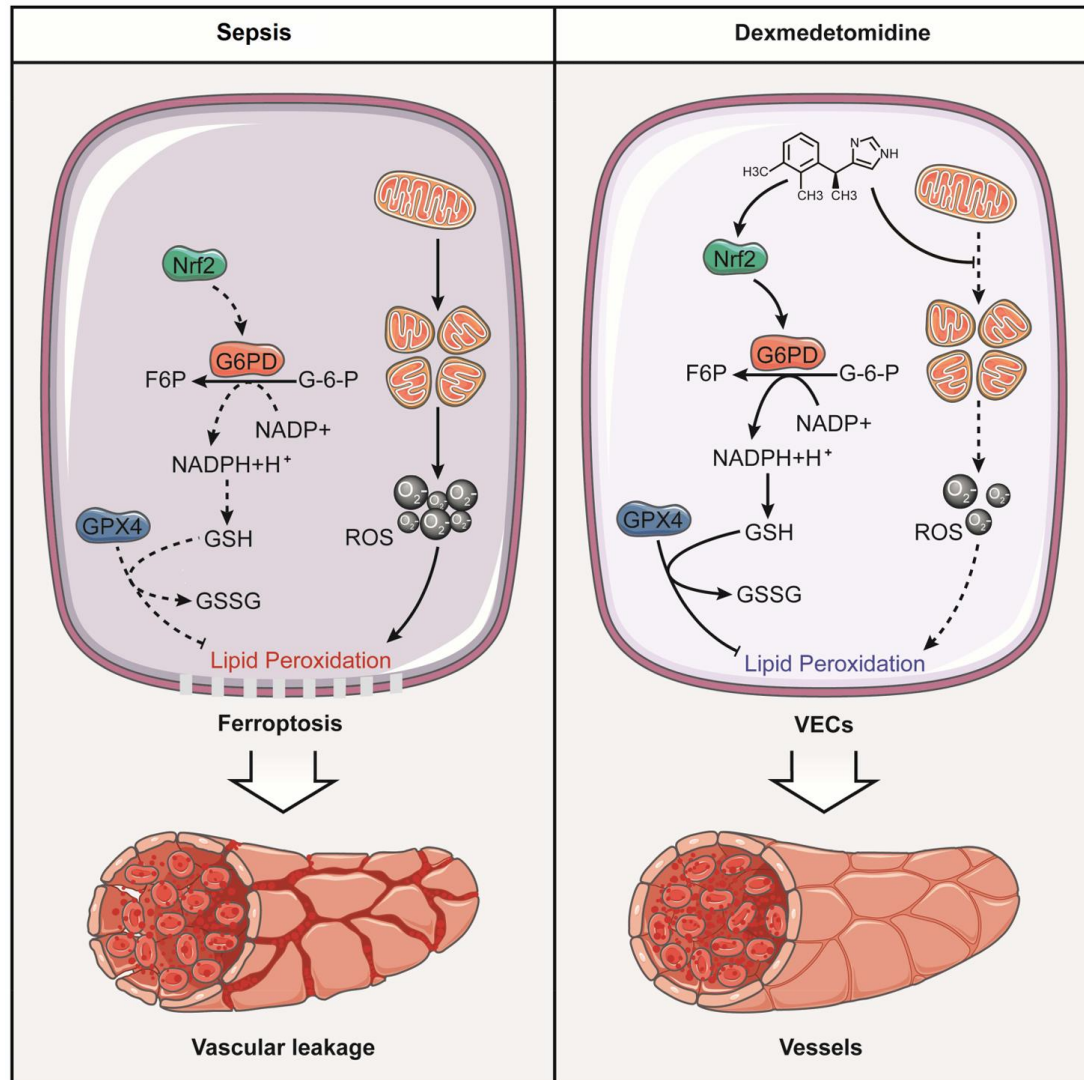


Kwan JYY, et al. Elevation in viral entry genes and innate immunity compromise underlying increased infectivity and severity of COVID-19 in cancer patients. *Sci Rep.* (2021)

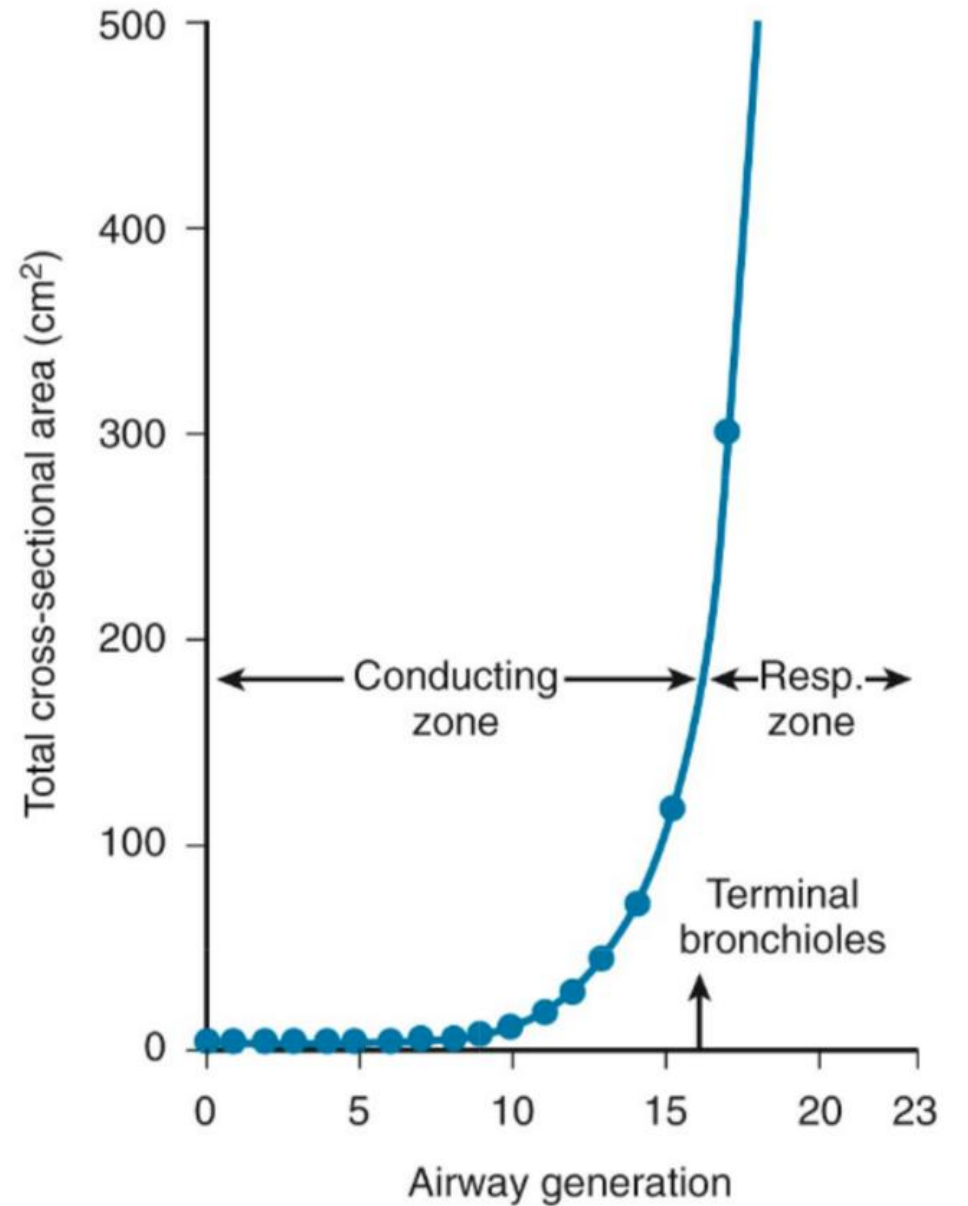
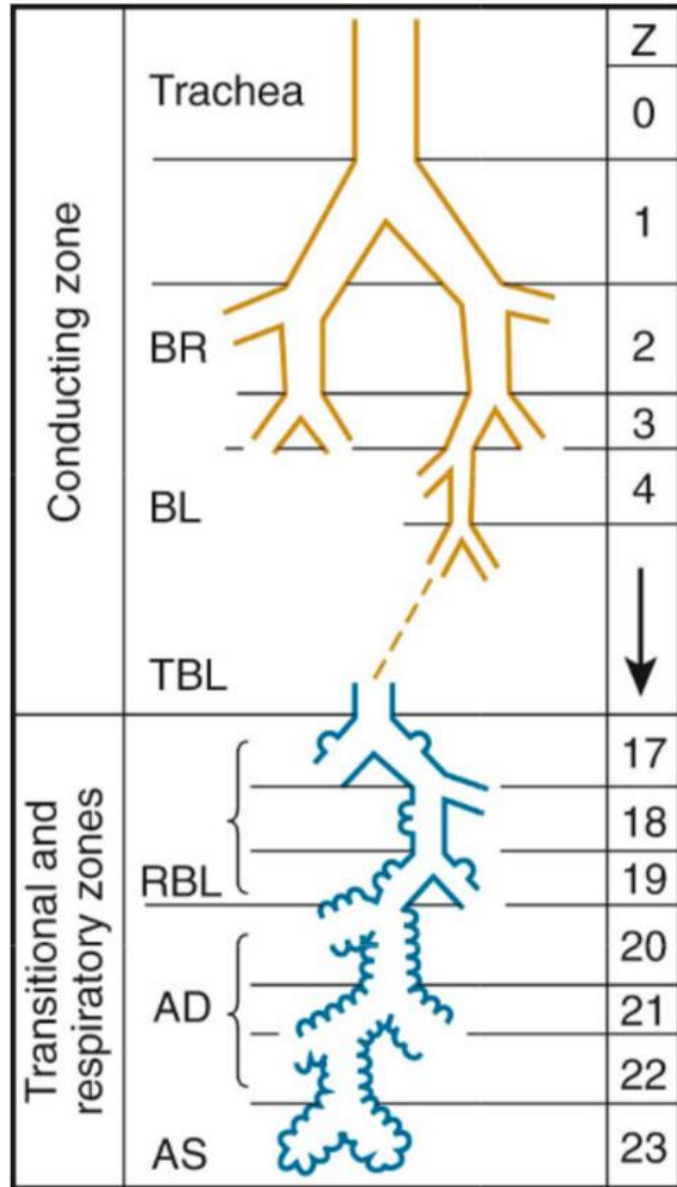
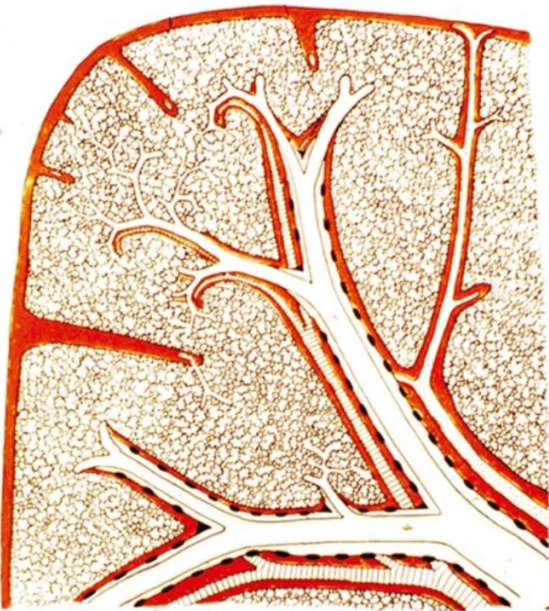
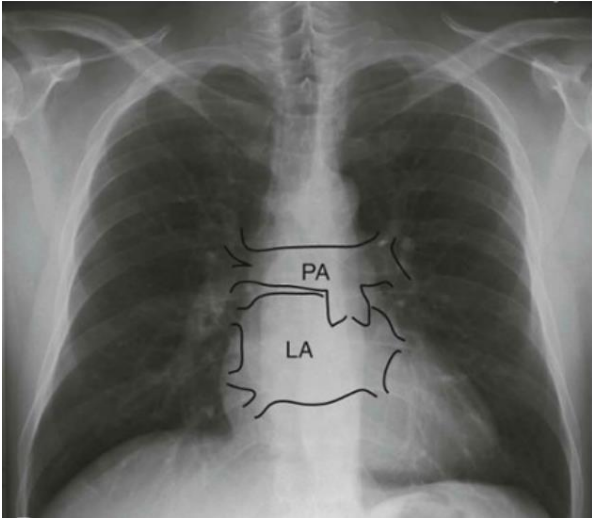
O'Sullivan JM, et al. Endothelial cells orchestrate COVID-19 coagulopathy. *The Lancet Haematology.* (2020)

Kastenhuber ER, et al. Coagulation factors directly cleave SARS-CoV-2 spike and enhance viral entry. *eLife.* (2022)

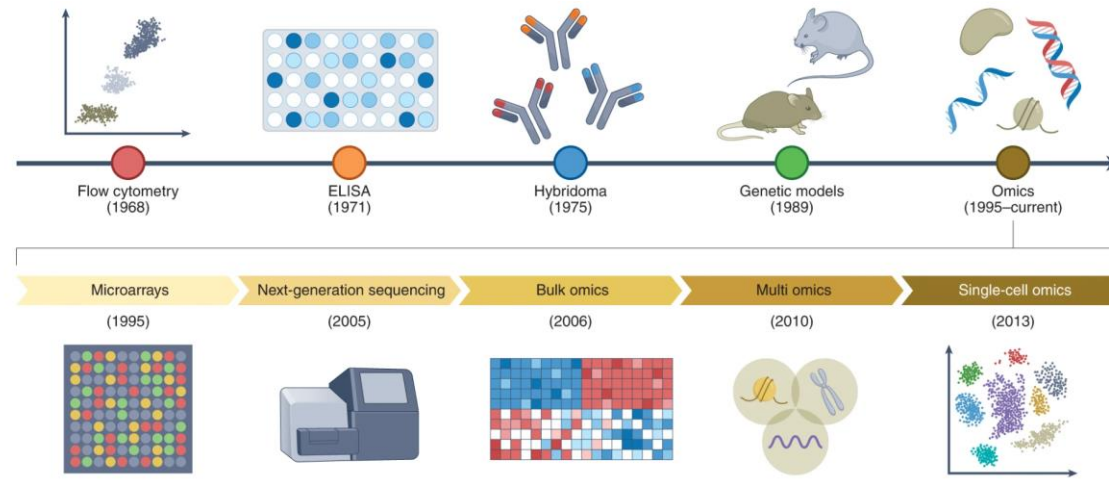
Protective Effects of Dexmedetomidine on Sepsis-Induced Vascular Leakage by Alleviating Ferroptosis via Regulating Metabolic Reprogramming



Epithelial Injury

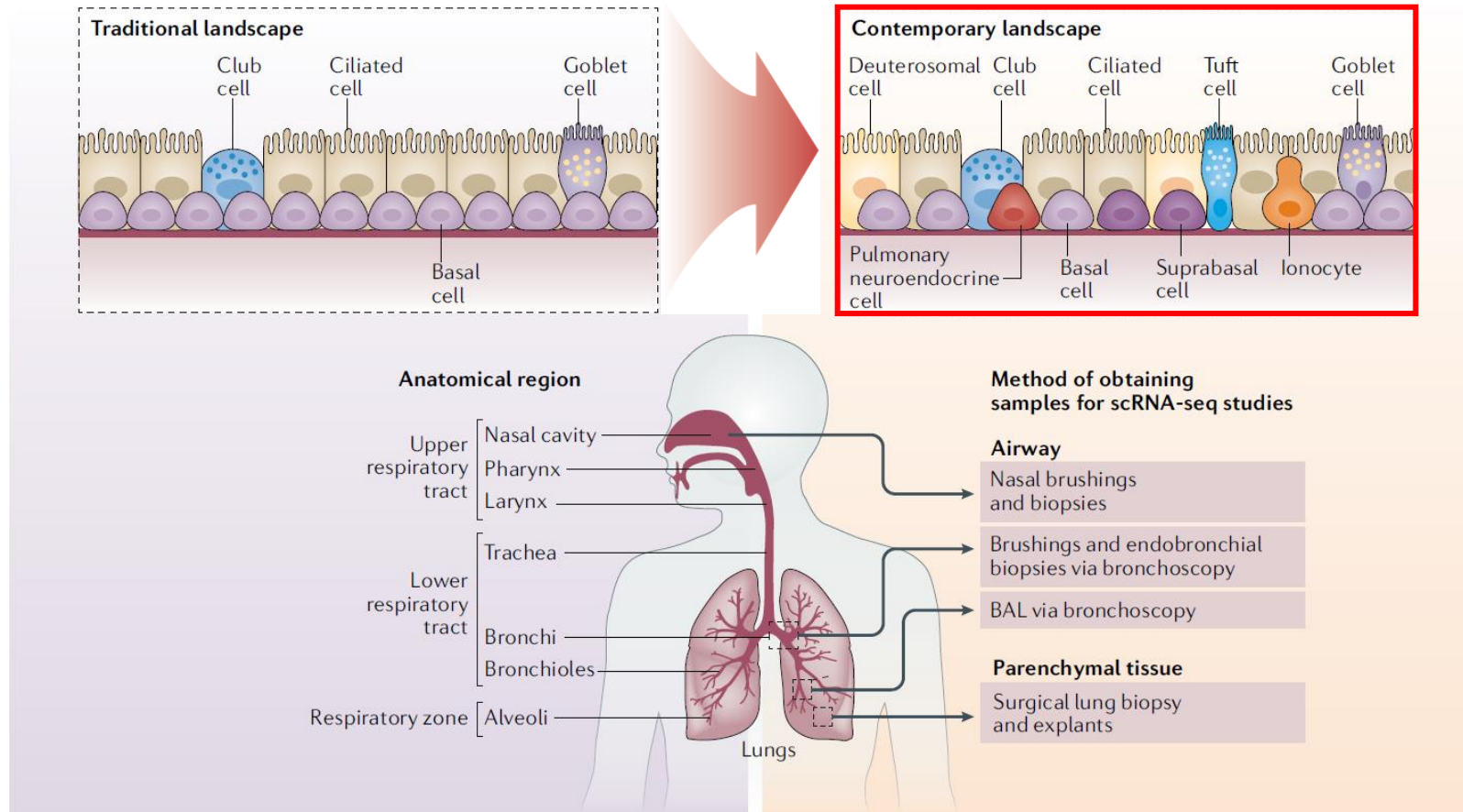


Benefits of utilizing *scRNA-seq*.



- Deconstructing **airway and/or lung tissues into their component cells** provides a unique lens into the cellular ecosystem of human airway inflammatory conditions, helping us to
 - Characterize each major cell type *without the biases* that are typically introduced by pre-selection of markers
 - Evaluate cell types and/or states with *disease-associated transcriptional* differences
 - Reconstruct *tissue-level dynamics*
 - *Computationally interrogate cell-cell interactions using known ligand-receptor interactions*

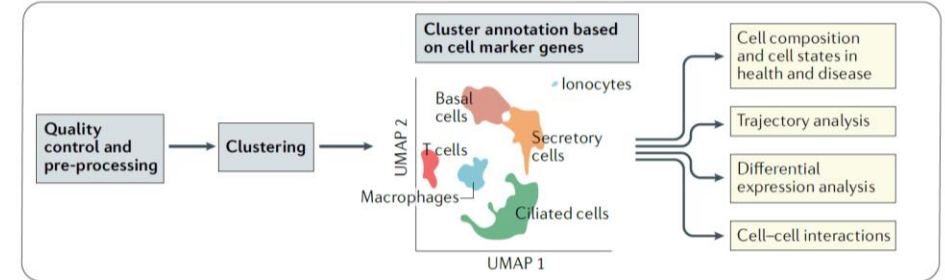
Revised cell repertoire of *human airway epithelium* captured by single-cell RNA sequencing (scRNA-seq.)



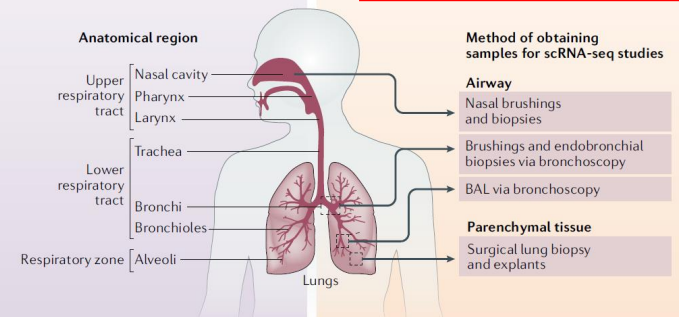
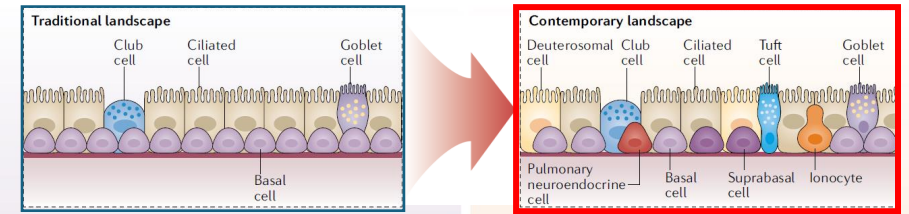
“Respiratory epithelium”

: More than just a barrier !!

- This collection of specialized epithelial cells lining the airways,
 - **Responds to microbes and noxious stimuli** that overcome the mucociliary barrier
 - **Vital component of host defence, interacting with cells of the immune system**
- Epithelial dysfunction is a driver of numerous chronic diseases affecting the lungs.



a wide range of highly specialized cells !!



... Noteworthy is the ***inconsistent annotation of secretory cell types, including club cells and goblet cells***, between single-cell studies due to overlapping gene expression signatures....!!

Cell type	Selected human marker genes	Proposed function
Basal cells	<i>KRT5, TP63, KRT14, PDPN, NGFR, LGALS1, ITGA6, ITGB4, LAMA3, LAMB3, KRT15, S100A2, NPPC, BCAM, DST</i>	Main airway stem cells — regeneration, repair of epithelial lining
Suprabasal cells	<i>KRT5, TP63 low, KRT19, NOTCH3</i>	Intermediate between basal and club cells
Secretory — club and goblet cells	<i>SCGB1A1 (club cells), MUC5AC (goblet cells), MUC5B, TFF3, SCGB3A1, BPIFB1, MSMB, SLPI, WFDC2</i>	Secretion of mucus, antimicrobial and anti-inflammatory peptides
Deuterosomal cells	<i>DEUP1/CCDC67, FOXJ1, FOXN4, CDC20B</i>	Precursor of ciliated cell characterized by genes critical to centriole amplification
Ciliated cells	<i>FOXJ1, PIFO, TPPP3, SNTN, FAM183A, LRR1Q1, DNAH12, C20orf85, SNTN, CAPS, TUBB4B, DNAH5, TSPAN1</i>	Clearance of mucus and debris
Mucous-ciliated cells	<i>FOXJ1, MUC5AC</i>	Differentiation intermediate between goblet and ciliated cells in homeostatic and diseased airways
Rare cell types		
Ionocyte	<i>FOXI1, CFTR, ASCL3, RARRES2</i>	Ion transport, fluid and pH regulation
Pulmonary neuroendocrine cells	<i>ASCL1, CHGA, CGRP, INSM1, HOXB5</i>	Environmental sensor — signals to CNS
Tuft/brush cells	<i>DCLK1, RGS13, POU2F3, ASCL2, LRMP,</i>	Immune and taste sensor, leukotriene synthesis, links to type 2 immunity
'Hillock' cells	<i>KRT13, KRT4</i>	Transitional cell type between basal and secretory; located in stratified, non-ciliated structures with high cell turnover; postulated to play a role in squamous barrier function and immunomodulation

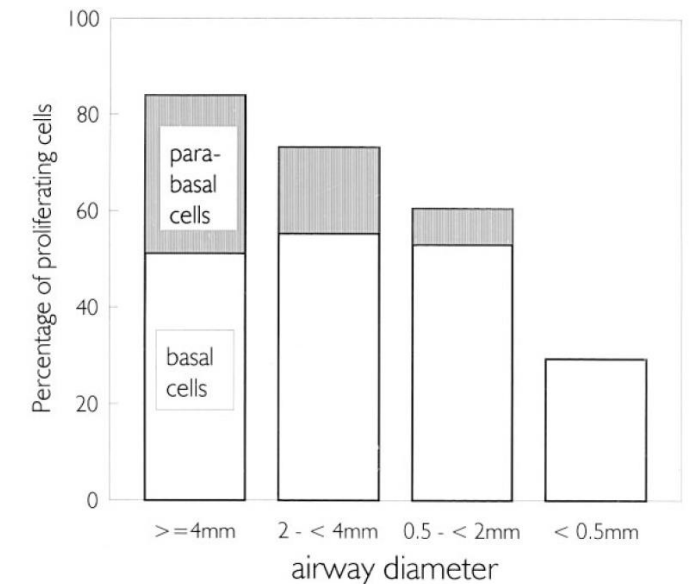
CNS, central nervous system; scRNA-seq, single-cell RNA sequencing. Selected marker genes used to assign a cell type to clusters in single-cell transcriptomic studies. Derived from REFS^{10,19,22–24,30,67}.

The contribution of *basal cells* to the proliferation compartment per airway-diameter group

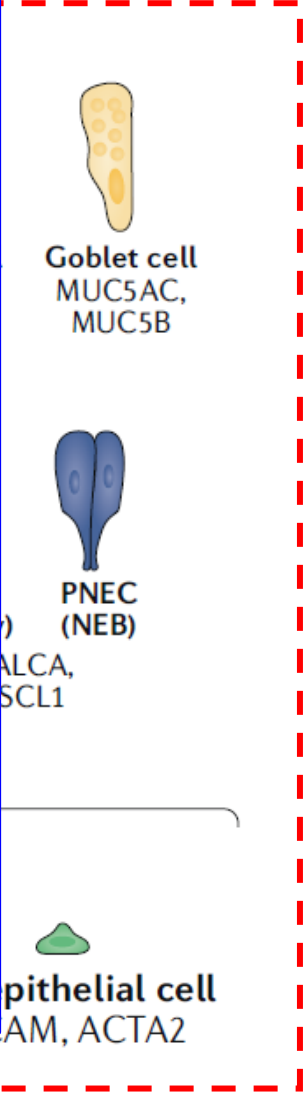
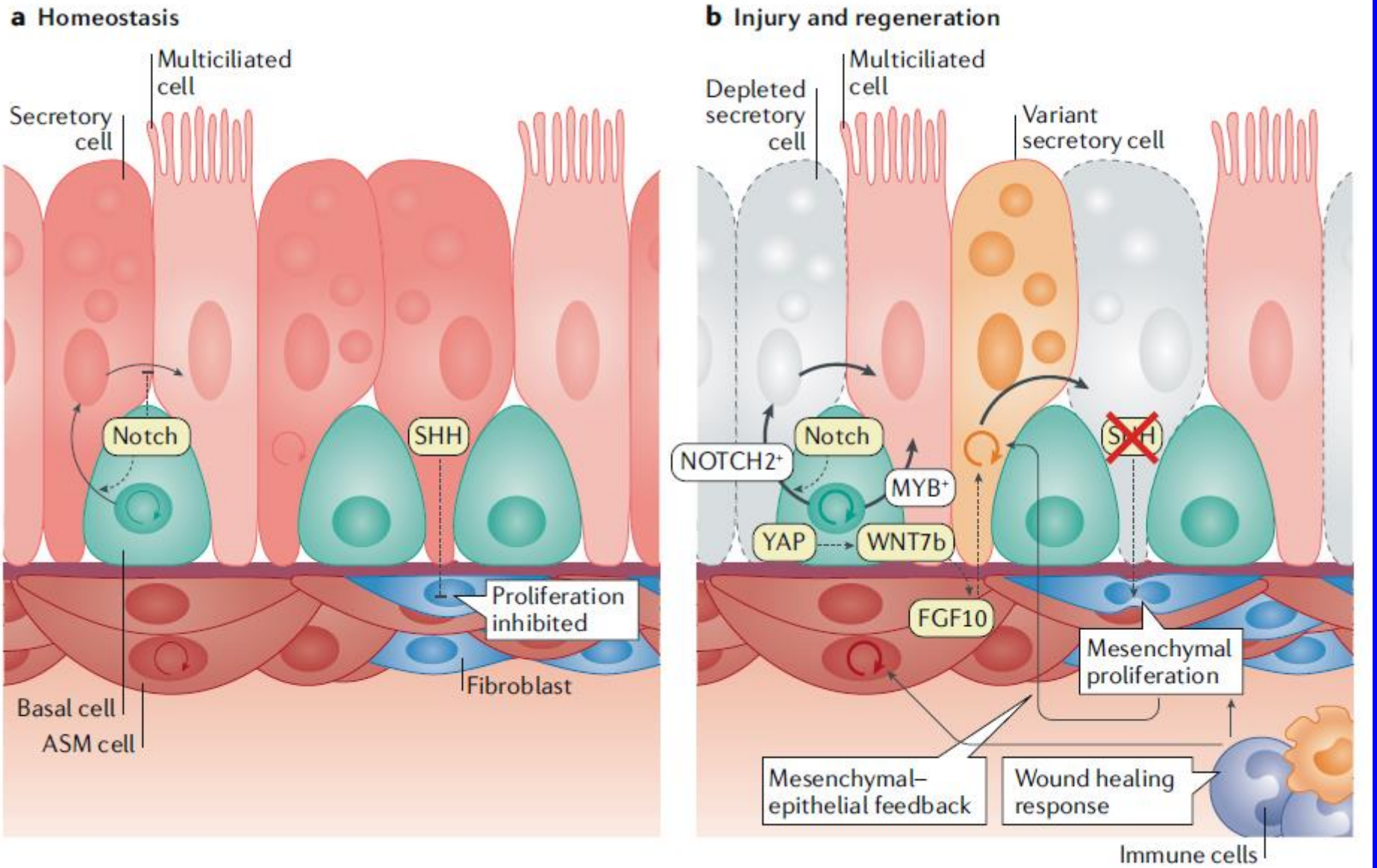
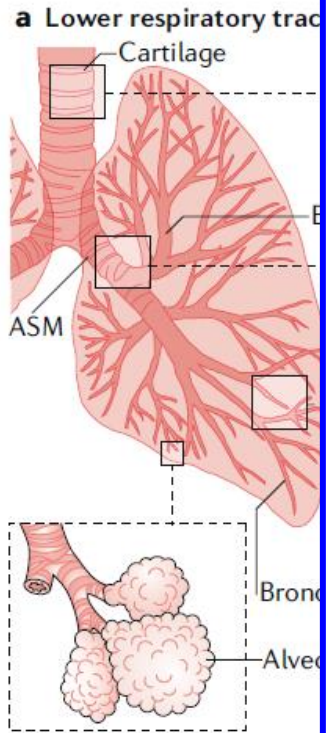
TABLE 2
NUMBER OF ASSESSED AIRWAYS, TOTAL NUMBER OF EPITHELIAL CELLS
PER MILLIMETER OF BASEMENT MEMBRANE*

	Airway diameter				Total or Mean
	≥ 4 mm	≥ 2 mm, < 4	≥ 0.5 mm, < 2	< 0.5 mm	
Number of assessed airways	24	24	23	21	92
Number of assessed epithelial cells	36,093	30,619	19,011	16,117	101,800
Mean number of epithelial cells/mm basement membrane	338	271	223	173	266
Basal cells, mean ± SD %	31 ± 7	30 ± 7	23 ± 7	6 ± 4	23 ± 5
Parabasal cells, mean ± SD %	7 ± 4	3 ± 2	1 ± 2	0	3 ± 1
MIB-1-positive cells, mean ± SD %	1.02 ± 0.41	0.85 ± 0.50	0.87 ± 0.43	1.01 ± 0.98	0.87 ± 0.30
MIB-1-positive basal cells, mean ± SD % of proliferation fraction	51 ± 9	55 ± 7	53 ± 15	30 ± 9	48 ± 26
MIB-1-positive parabasal cells, mean ± SD % of proliferation fraction	33 ± 6	18 ± 11	8 ± 7	0	15 ± 14

* Basal, parabasal, and MIB-1-positive cells are expressed as percentage of epithelial cells per airway-diameter group. MIB-1-positive basal and parabasal cells are expressed as percentage of the proliferation fraction (i.e., all MIB-1-positive epithelial cells).



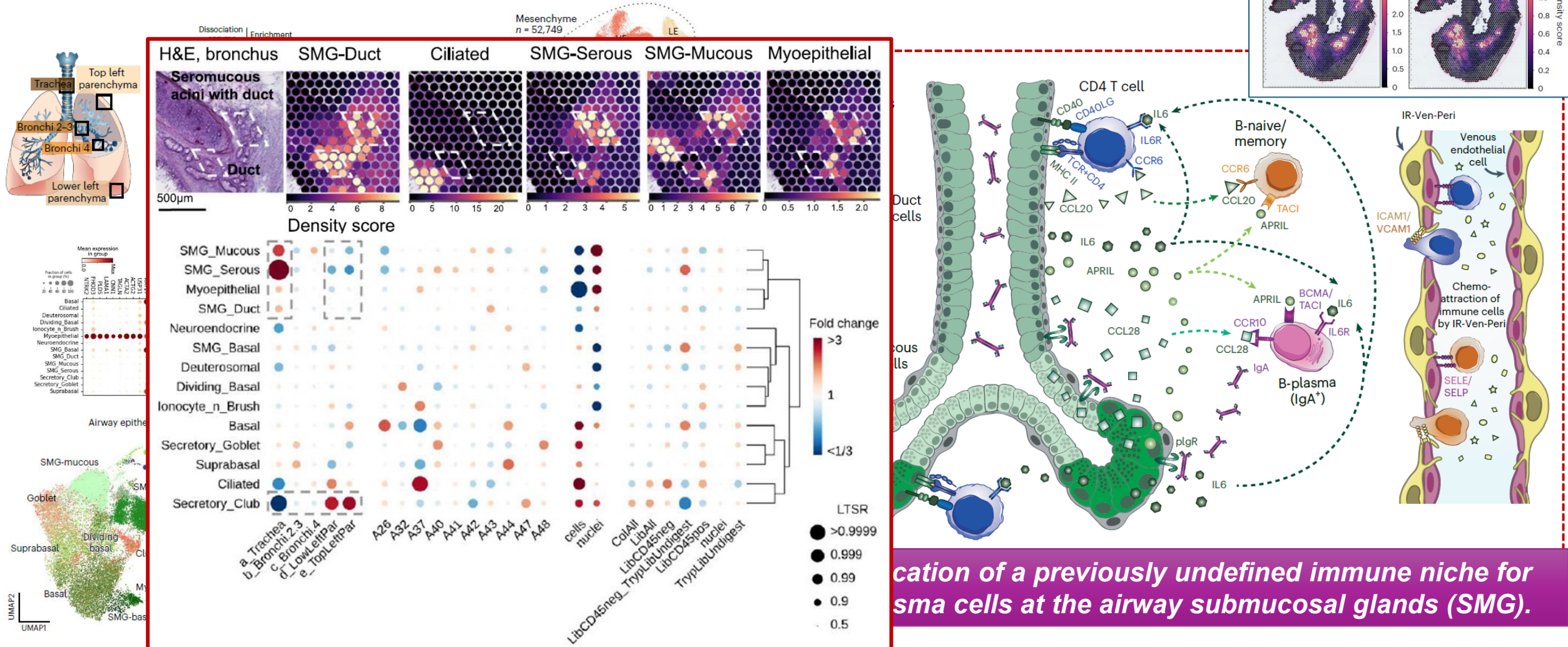
Human



Zepp JA, Morrisey EE. Cell fate and the respiratory system. *Nat Rev Mol Cell Biol.* (2019)

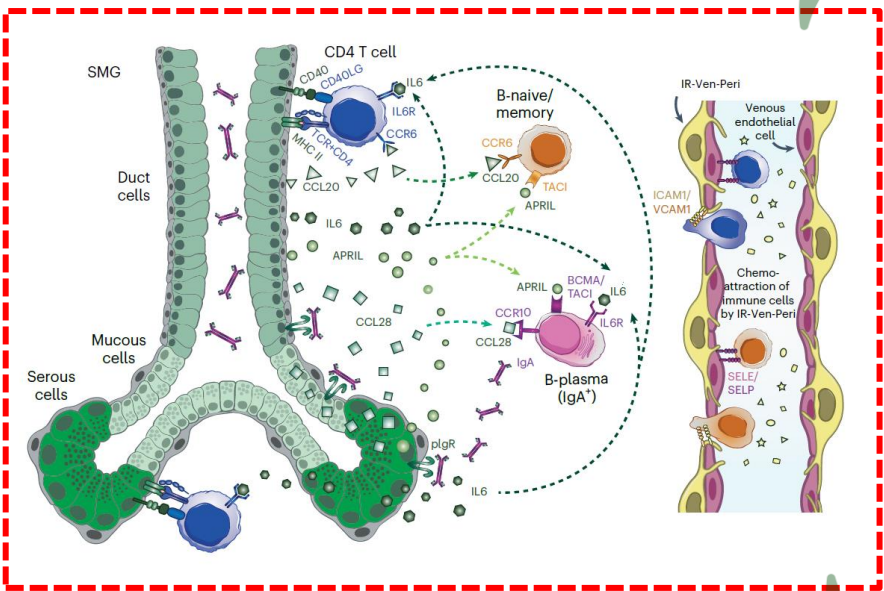
ACTA2, LGR6 GLI1, AXIN2 EPCAM, ACTA2

Gland-associated immune niche (GAIN) : Lower respiratory tract

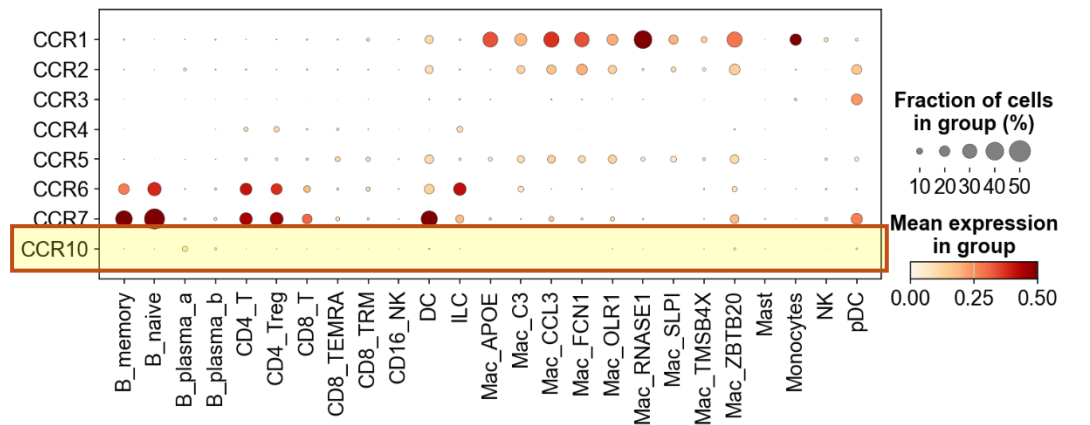
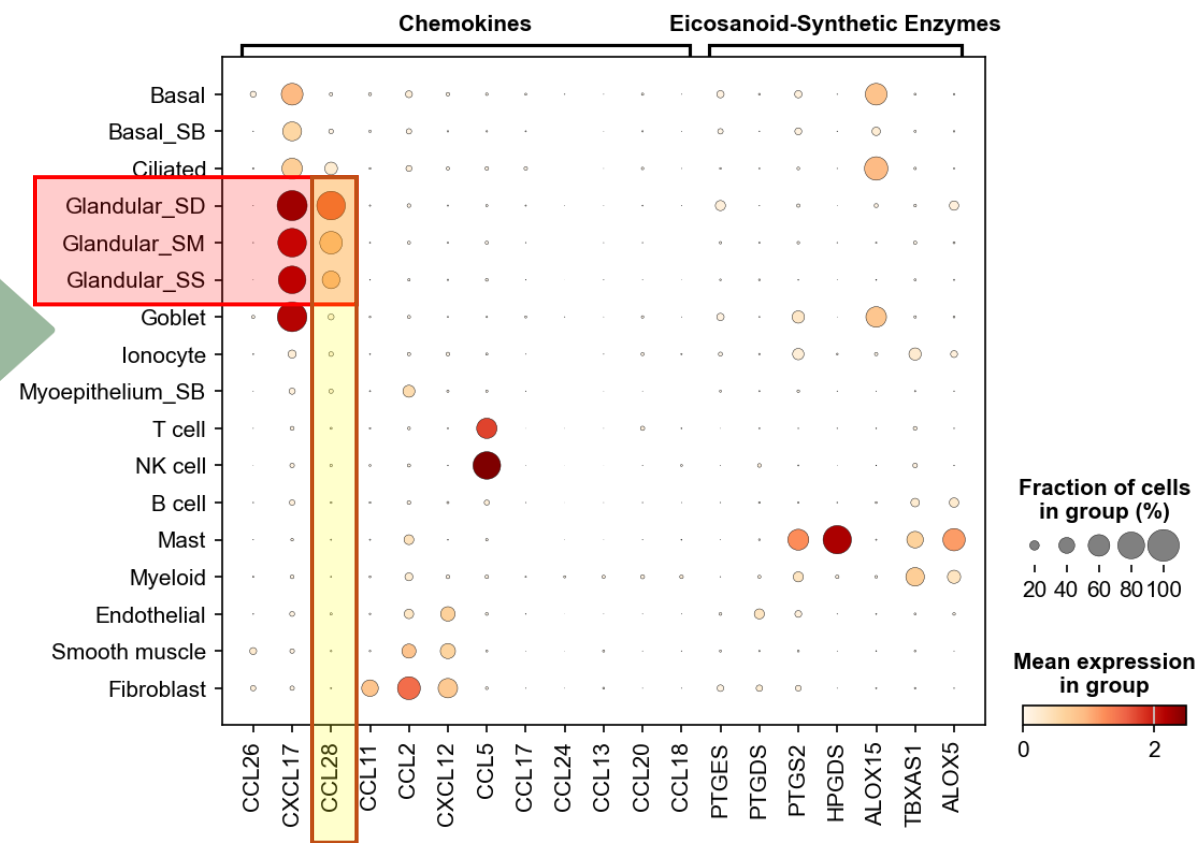


Characterization of a previously undefined immune niche for plasma cells at the airway submucosal glands (SMG).

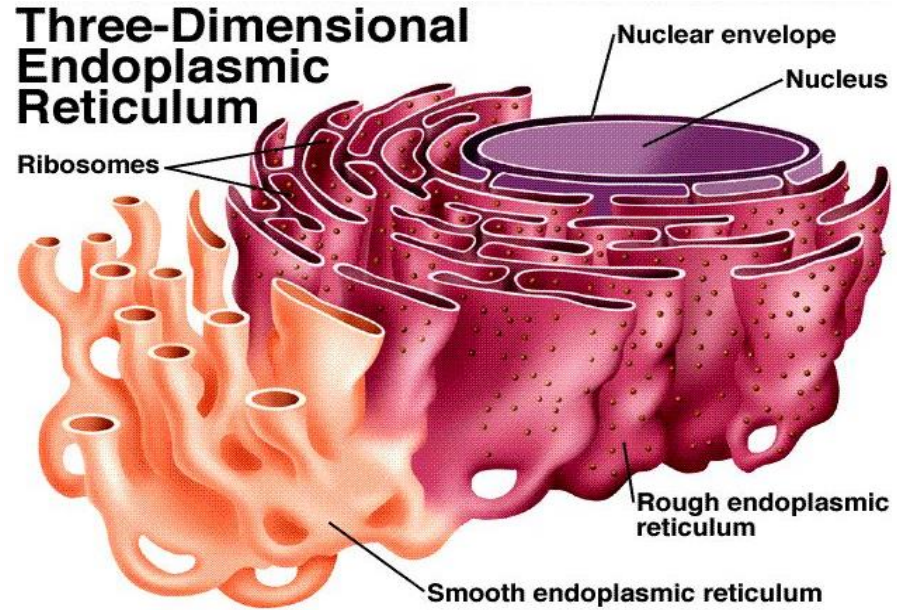
Potential *GAIN* in SN cavity



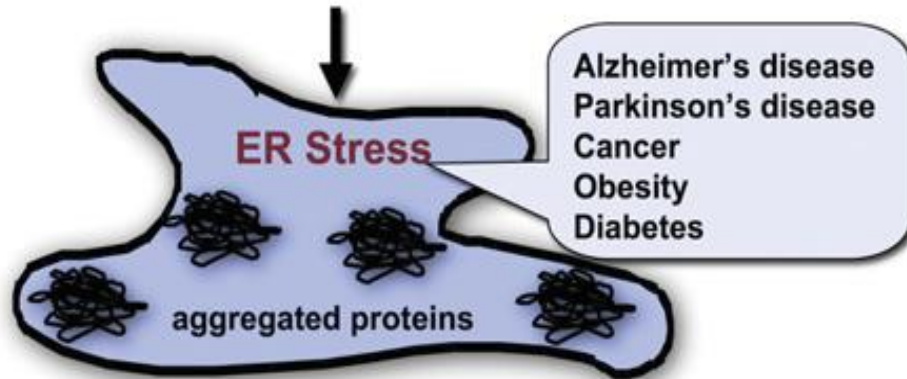
Madisson E, et al. A spatially resolved atlas of the human lung characterizes a gland-associated immune niche. Nat Genet. (2023)



What is an endoplasmic reticulum (ER) and ER stress?



Environmental or genetic factors



Endoplasmic reticulum (ER)

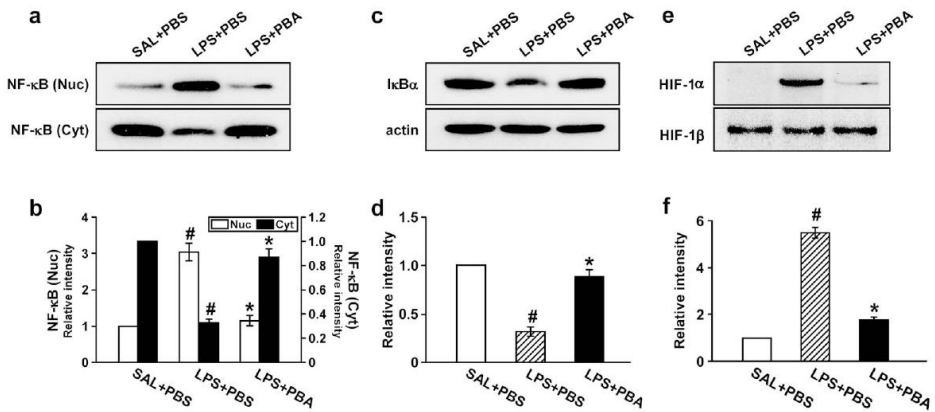
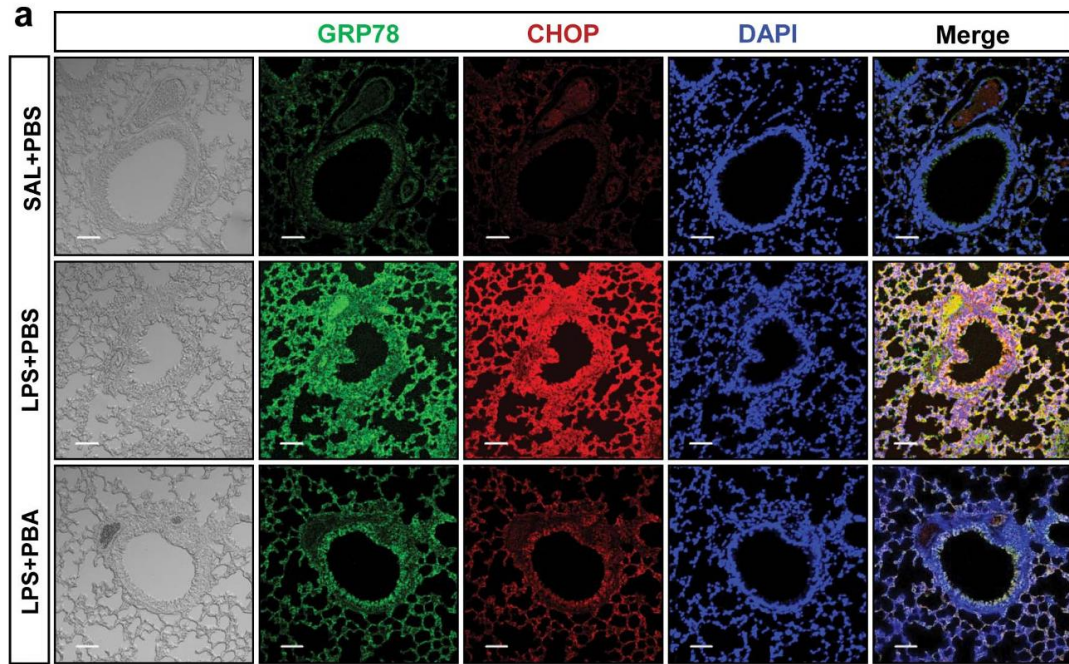
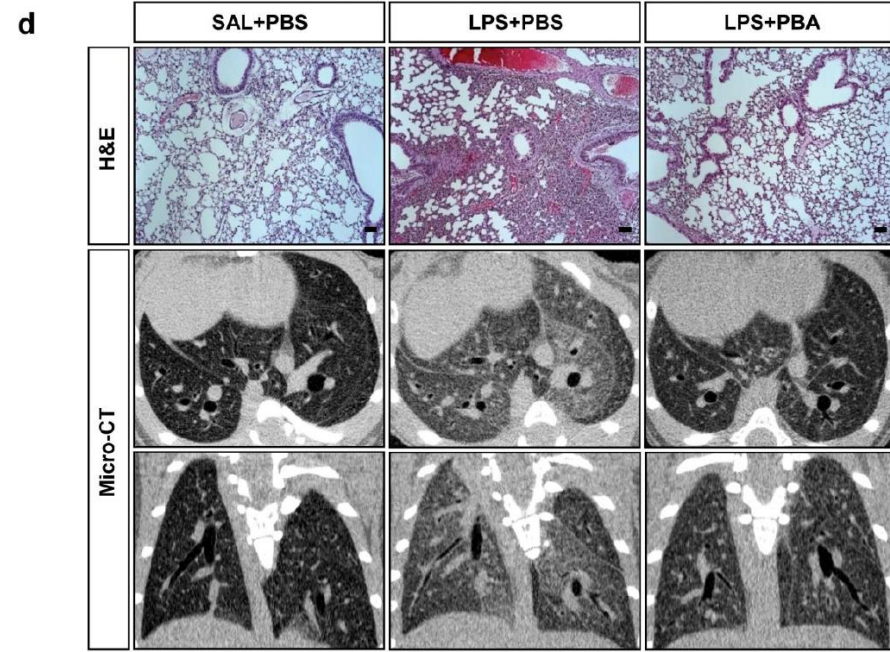
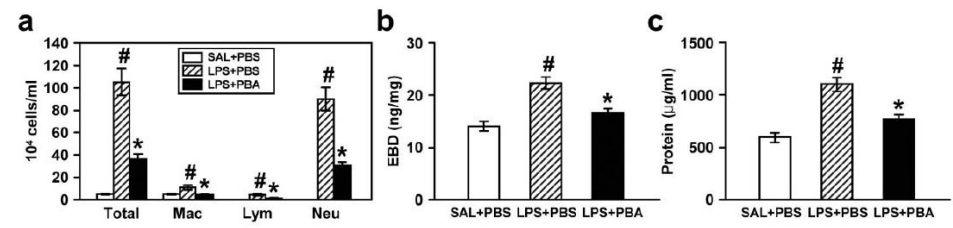
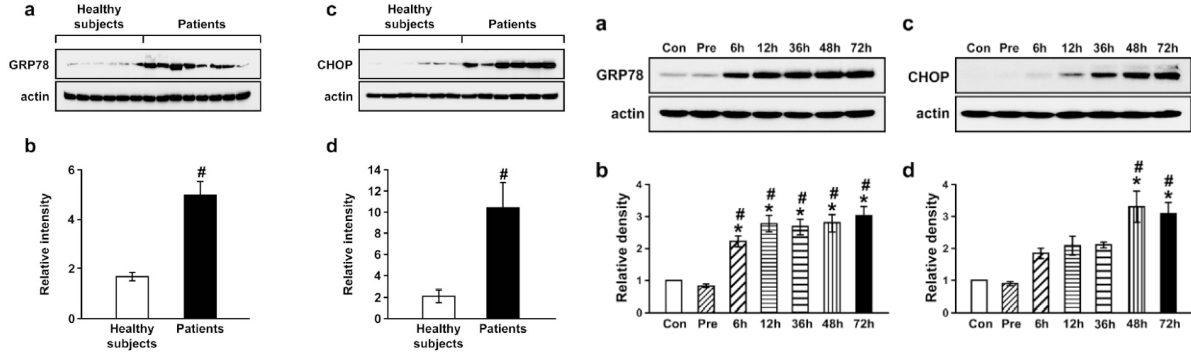
- ◆ A specialized organelle that plays a central role in the biosynthesis, correct folding, and post-translational modifications of **secretory and membrane proteins**.
- ◆ Highly **sensitive to stresses** that perturb cellular energy levels, redox state, or Ca^{2+} concentration.

...Stress reduces protein folding capacity of the ER, resulting in the accumulation and aggregation of unfolded proteins, which is referred to as “**ER stress**”...

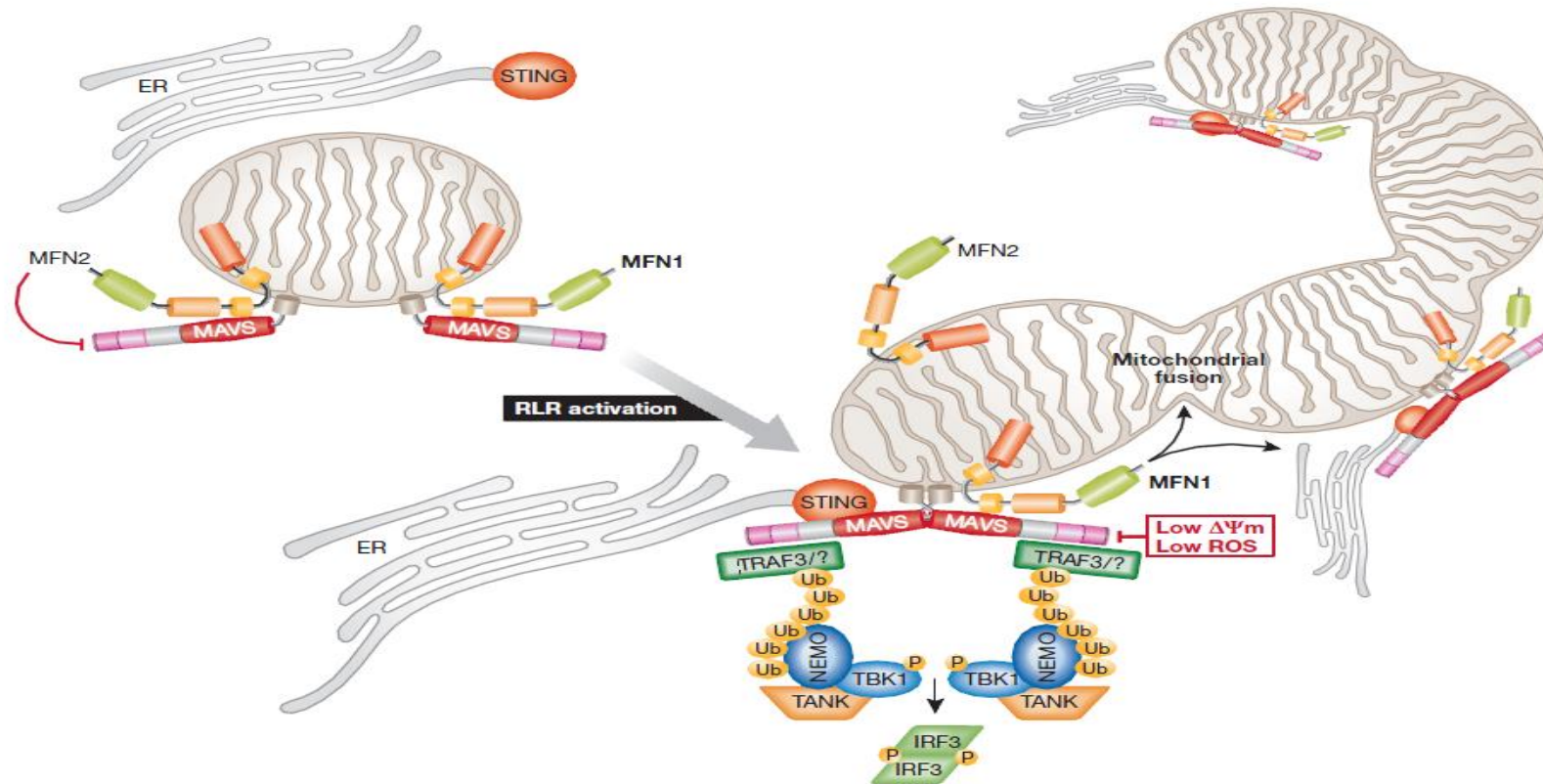


Inhibition of endoplasmic reticulum stress alleviates lipopolysaccharide-induced lung inflammation through modulation of NF- κ B/HIF-1 α signaling pathway

SUBJECT AREAS:
ACUTE INFLAMMATION
TRANSCRIPTION
INFECTION
TARGET IDENTIFICATION

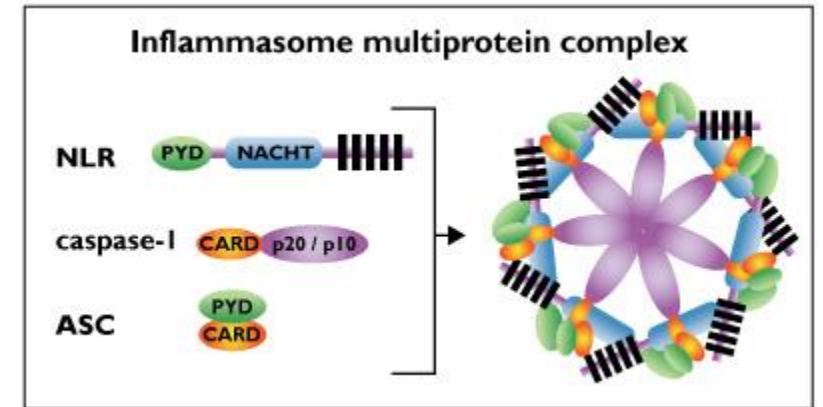
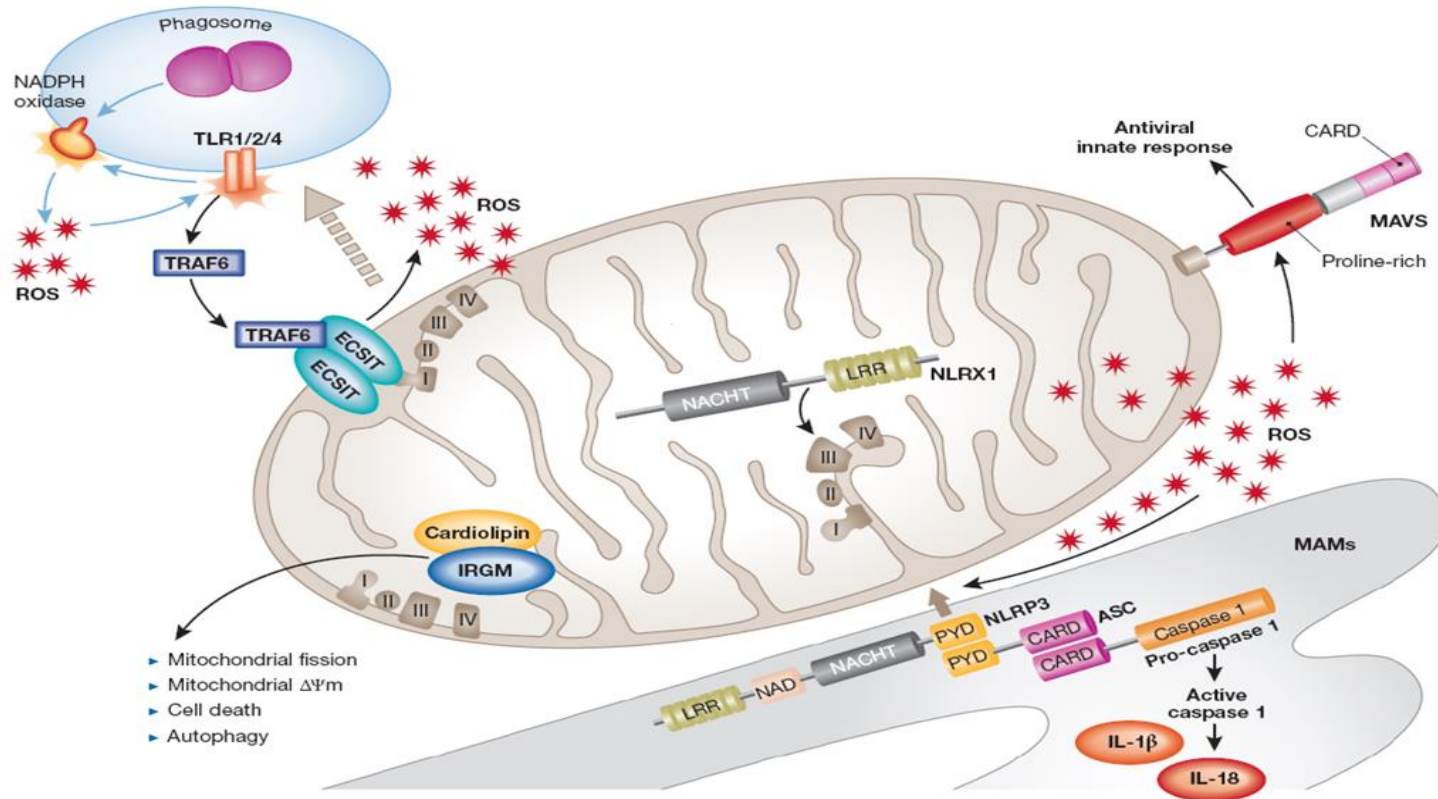


Mitochondria and ER in innate immune response



Both *PAMPs and DAMPs* trigger innate immunity following detection by PRRs. PRR activation leads to ER-Inflammasome-Mitochondrial fusion.

Mitochondria and ER in innate immune response



On induction of mitochondrial ROS, NLRP3 localizes to the mitochondrial-associated ER membrane (MAM) with ASC and pro-caspase 1, inducing caspase-1 activation and the production of IL-1 β and IL-18.



Phosphoinositide 3-kinase- δ regulates fungus-induced allergic lung inflammation through endoplasmic reticulum stress

Kyung Sun Lee,¹ Jae Seok Jeong,² So Ri Kim,^{1,3} Seong Ho Cho,⁴ Narasaiah Kolliputi,⁴ Yun Hee Ko,^{1,3} Kyung Bae Lee,^{1,3} Suk Chul Park,^{1,3} Hae Jin Park,^{1,3} Yong Chul Lee

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2015-207096>).

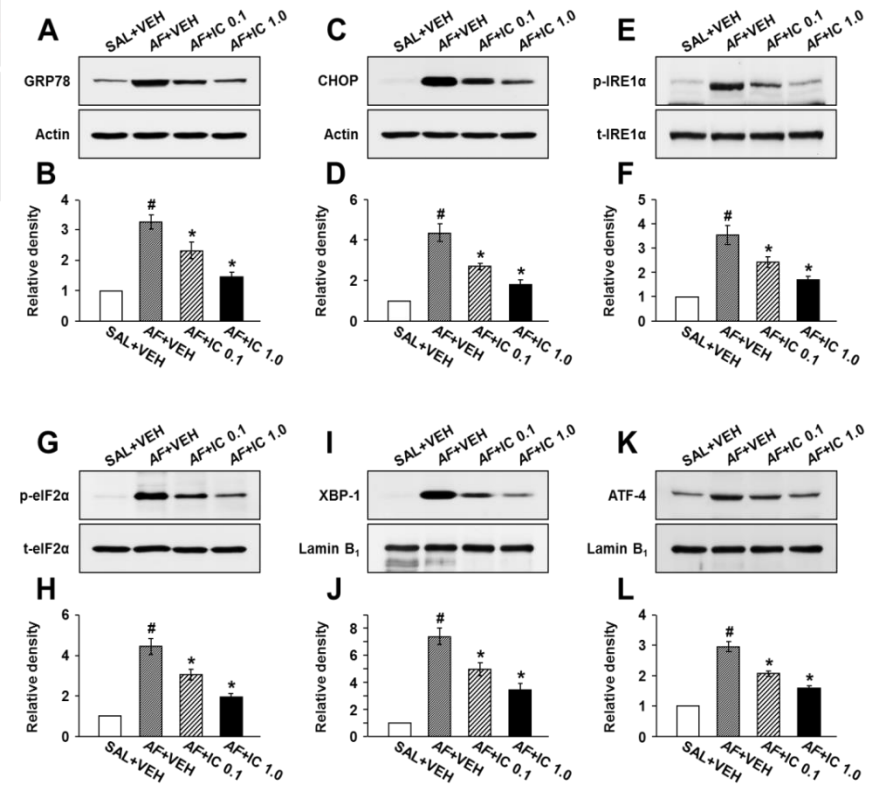
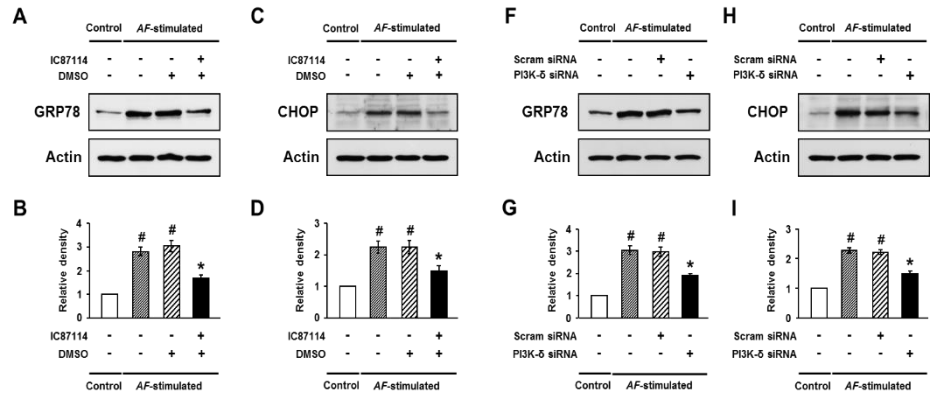
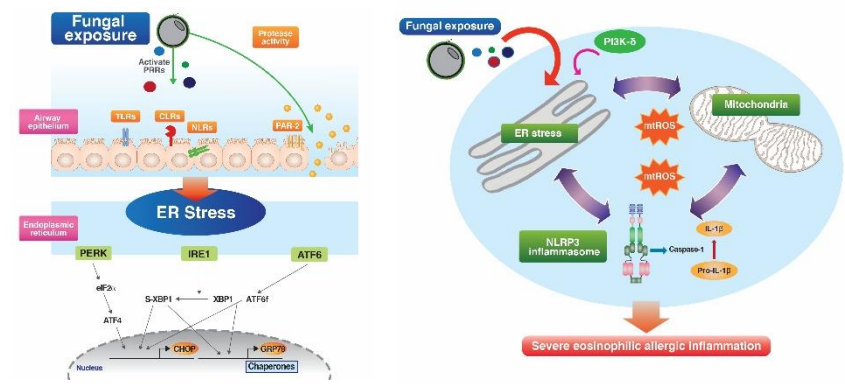
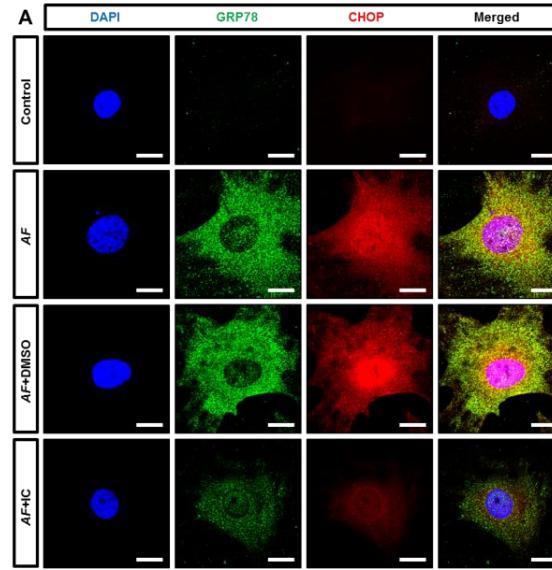
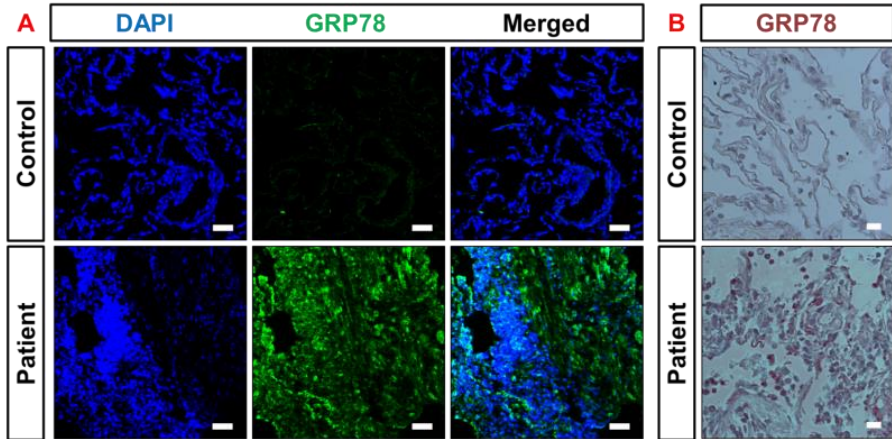
ABSTRACT

Background Sensitisation with *Aspergillus fumigatus* (Af) is known to be associated with severe allergic lung inflammation, but the mechanism remains to be clarified. Phosphoinositide 3-kinase (PI3K)- δ and

Key messages

What is the key question?

Corticosteroid-resistant severe eosinophilic asthma



Fungus-induced steroid-resistant severe asthma murine model

Thorax cover image (January 2016, Volume 71, Issue 1)



ORIGINAL ARTICLE

Phosphoinositide 3-kinase- δ regulates fungus-induced allergic lung inflammation through endoplasmic reticulum stress

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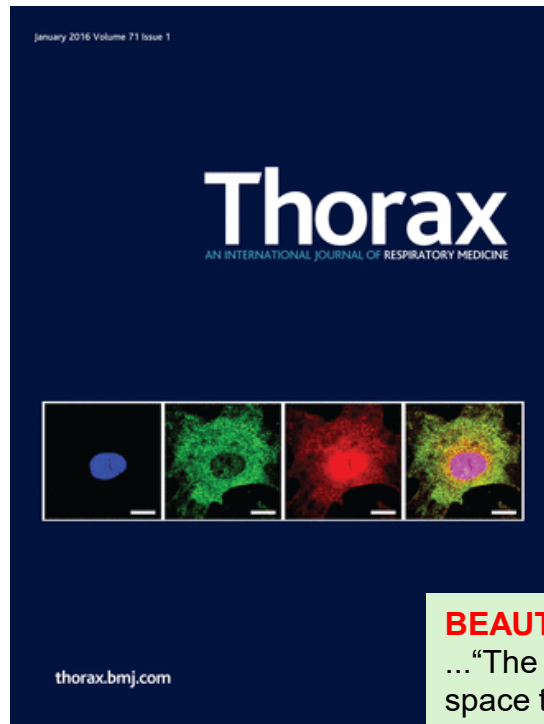
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속보 IC참간열려 소발다 하보나, 5월부터 보일 적중

학회·학술 전북대병원 이용철 교수, Thorax 신년표지 장식
중증천식기관지 세포 - 우주 망원경을 통해 관찰한 듯 아름다워
차원준 기자 (chamed7@bosa.co.kr) [다른 기사 보기](#)

송고시간 : 2016-01-04 12:16

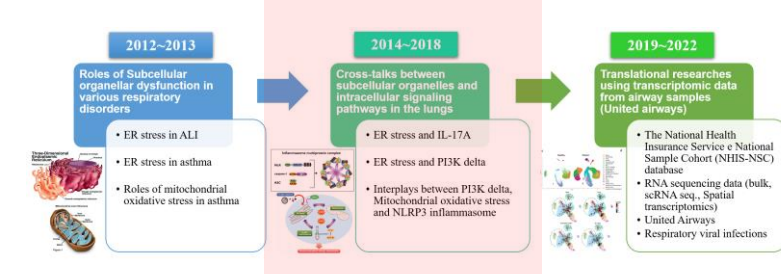
“이 이미지는 허블 우주 망원경을 통해 얻은 소행성과 주변의 위성인 것처럼 보이지만 사실은 중증 천식 동물 모델의 기관지 세포를 공초점 레이저 현미경으로 관찰한 형광 사진이다.”

이 사진은 전북대학교병원 호흡기전문질환센터 이용철 교수팀의 연구 결과가 세계적인 학술지인 흉부학 저널 'Thorax'의 2016년 1월 신년호 표지를 장식하고 'Thorax' 지 편집위원이 설명한 내용이다.

기초의학 결과는 어렵고 말개만 느껴왔던 사람들에게도 표지 사진 속 이미지는 실제 우주 여행 중 한 장면처럼 기억되기에 충분히 아름답고 생생해 보인다.

이 이미지는 이용철 교수팀의 새로운 논문 연구 결과로 중증 천식 환자에게서 생체 내 발현이 증가되는 소포체 스트레스 (Endoplasmic Reticulum Stress, ER stress)의 표지자에 결합 발색을 일어나게 처리하고 이를 공초점 레이저 현미경을 이용해 촬영한 사진이다.

▲ 'Thorax' 신년호 표지
녹색 또는 붉게 발색되어 빛나는 부분이 바로 소포체 스트레스가 중증 천식 동물 모델의 기관지 세포 내부에 비 사체질을 보여 주



“Journal articles read most by allergists & immunologists last month” by Medscape Allergy

Medscape ALLERGY Top Journal Articles

Journal articles read most by Allergists & Immunologists last month:

1. Phosphoinositide 3-Kinase-Delta Regulates Fungus-Induced Allergic Lung Inflammation Through Endoplasmic Reticulum Stress
Thorax. 2016;71(1):52-63. © 2016 BMJ Publishing Group Ltd & British Thoracic Society
2. New Inhaled Formulations for the Treatment of Asthma in Children and Adolescents
Pediatr Pharm. 2015;21(12) © 2015 University of Virginia
3. Pathogenesis and Prevention Strategies of Severe Asthma Exacerbations in Children
Curr Opin Pulm Med. 2016;22(1):25-31. © 2016 Lippincott Williams & Wilkins
4. Prenatal Tobacco Smoke Exposure Increases Hospitalizations for Bronchiolitis in Infants
Respiratory Research. 2015;16(152) © 2015 BioMed Central, Ltd.
5. The Pregnant Patient With Asthma
J Nurs Pract. 2016;12(1):1-6. © 2016 Elsevier Science, Inc.

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6. Genome-Wide Significant Association With Seven Novel Multiple Sclerosis Risk Loci
J Med Genet. 2015;52(12):848-855. © 2015 BMJ Publishing Group

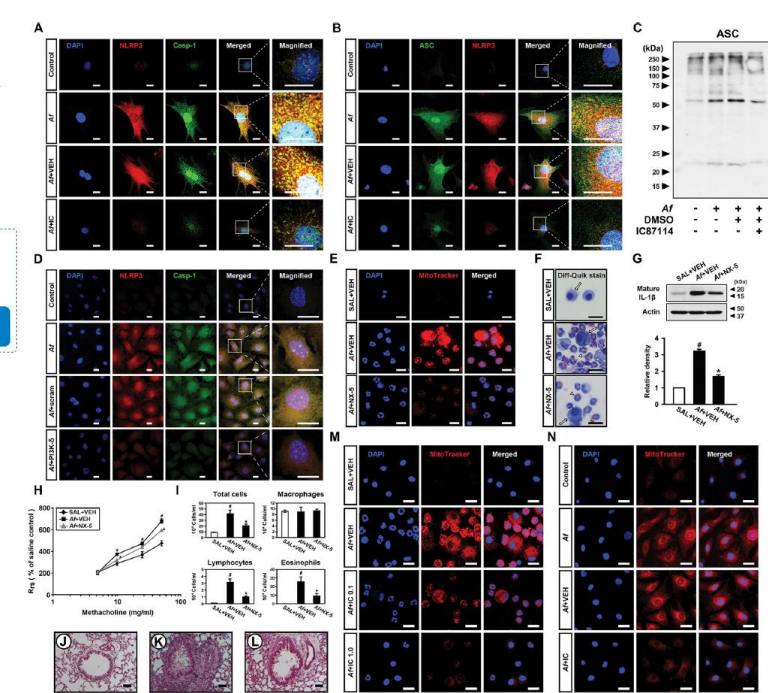
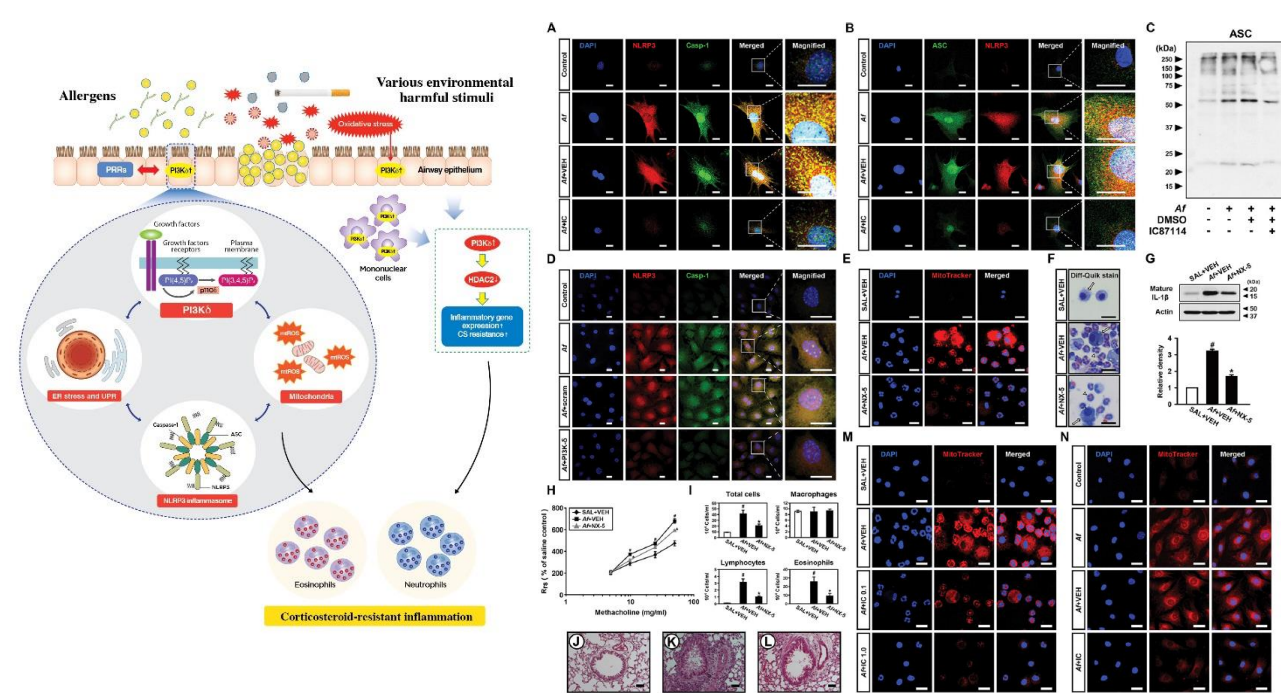
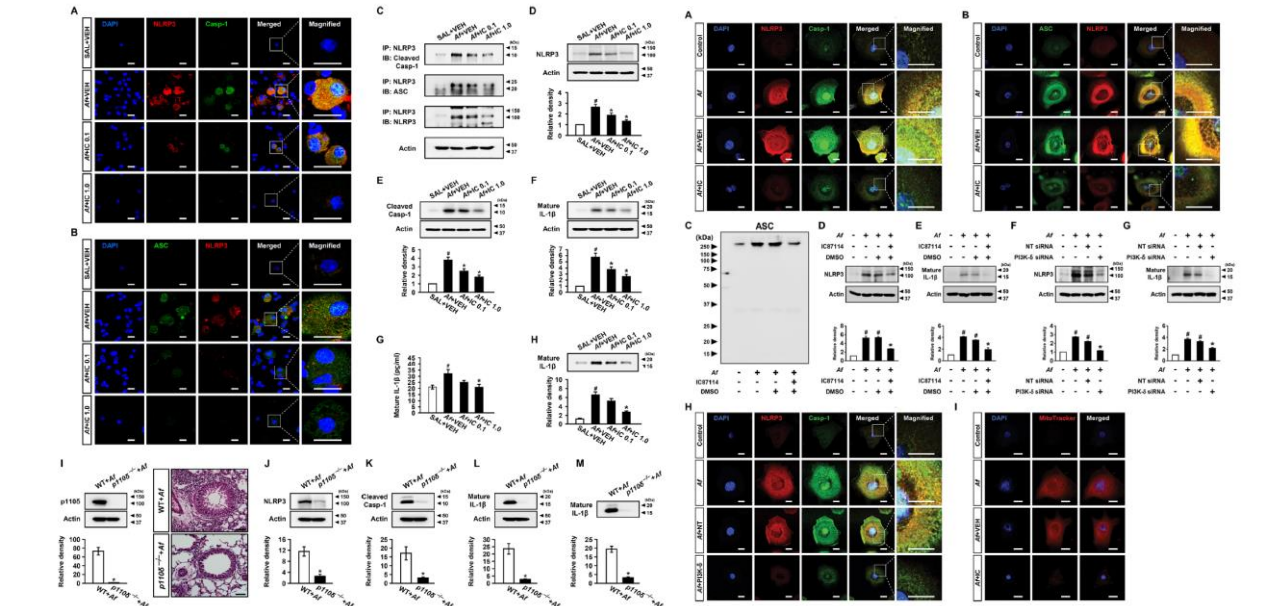
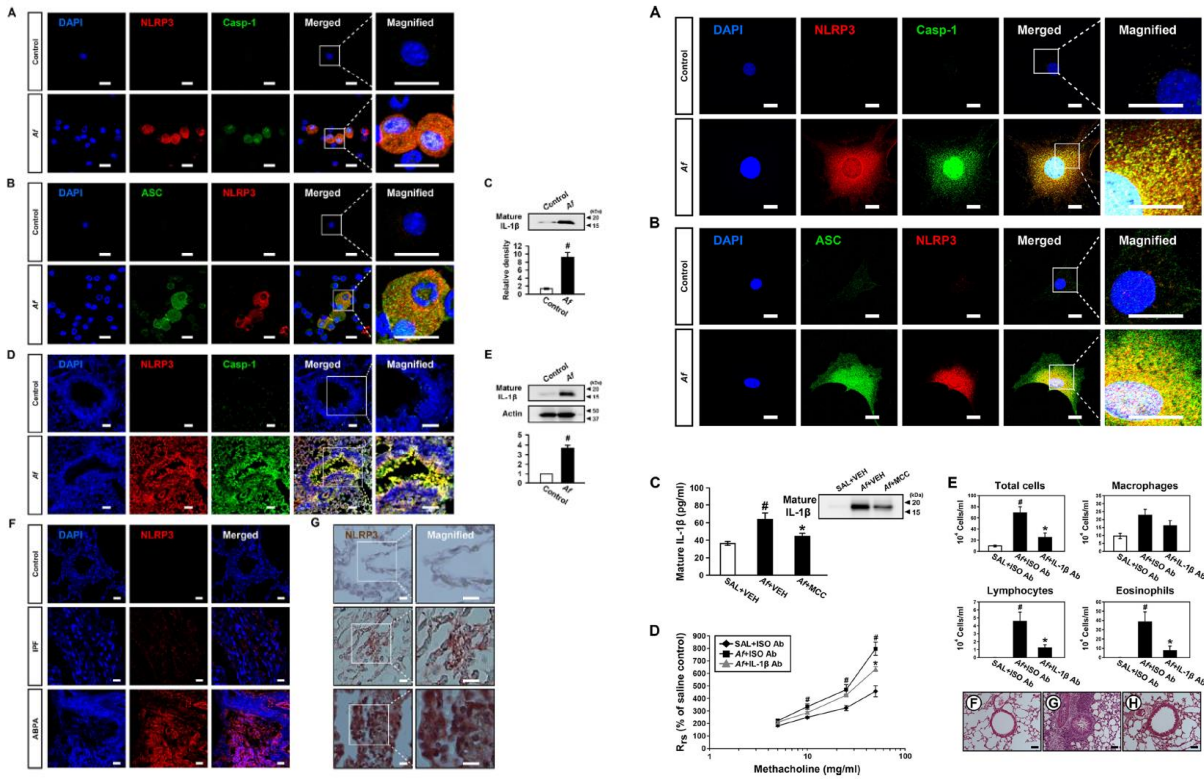
BEAUTIFUL IMAGES OF ALLERGIC INFLAMMATION
 ...“The elegant images in figures 2 and 6 could be from the Hubble space telescope but are in fact confocal laser immunofluorescence photomicrographs”...
 Editors-in-chief, *Highlights from this issue*



ORIGINAL ARTICLE

Airway epithelial phosphoinositide 3-kinase- δ contributes to the modulation of fungi-induced innate immune response

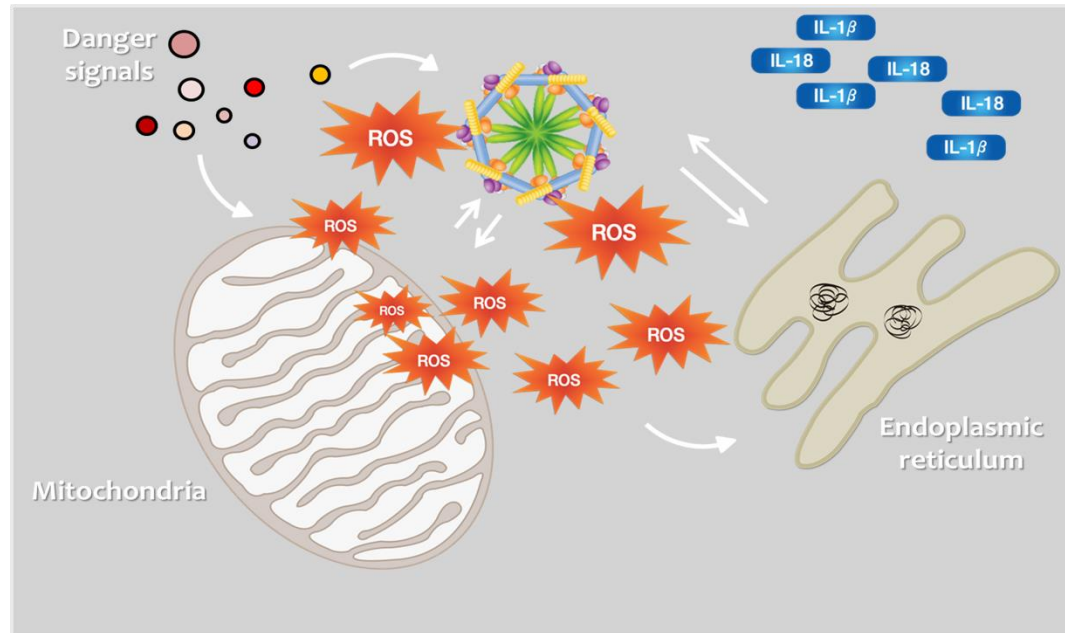
Jae Seok Jeong,¹ Kyung Bae Lee,¹ So Ri Kim,^{1,2} Dong Im Kim,¹ Hae Jin Park,¹ Hern-Ku Lee,³ Hyung Jin Kim,^{2,4} Seong Ho Cho,⁵ Narasaiah Kolliputi,⁵ Soon Ha Kim,⁶ Yong Chul Lee^{1,2}



Roles of subcellular organellar complex for severe asthma

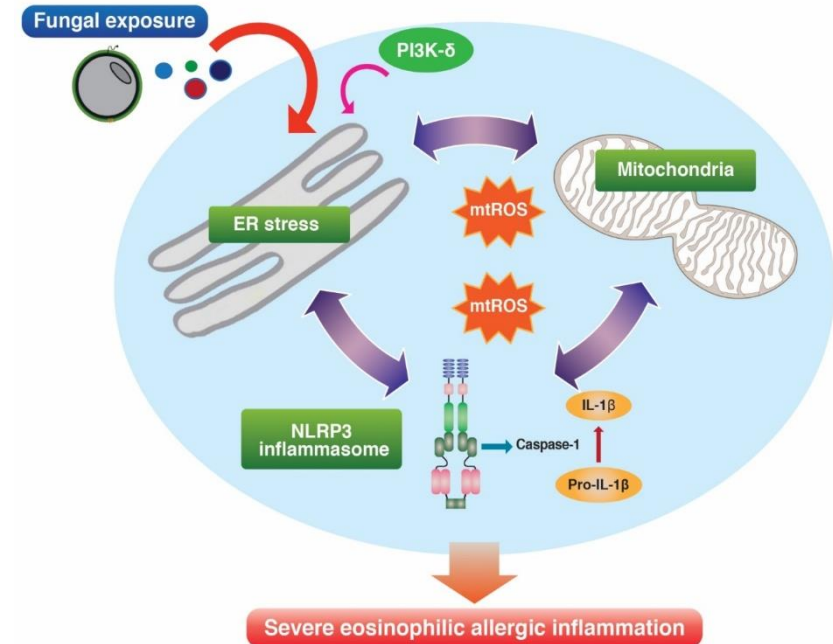
- ER stress/mtROS/NLRP3 inflammasome

Both *eosinophilic* and *neutrophilic* severe asthma

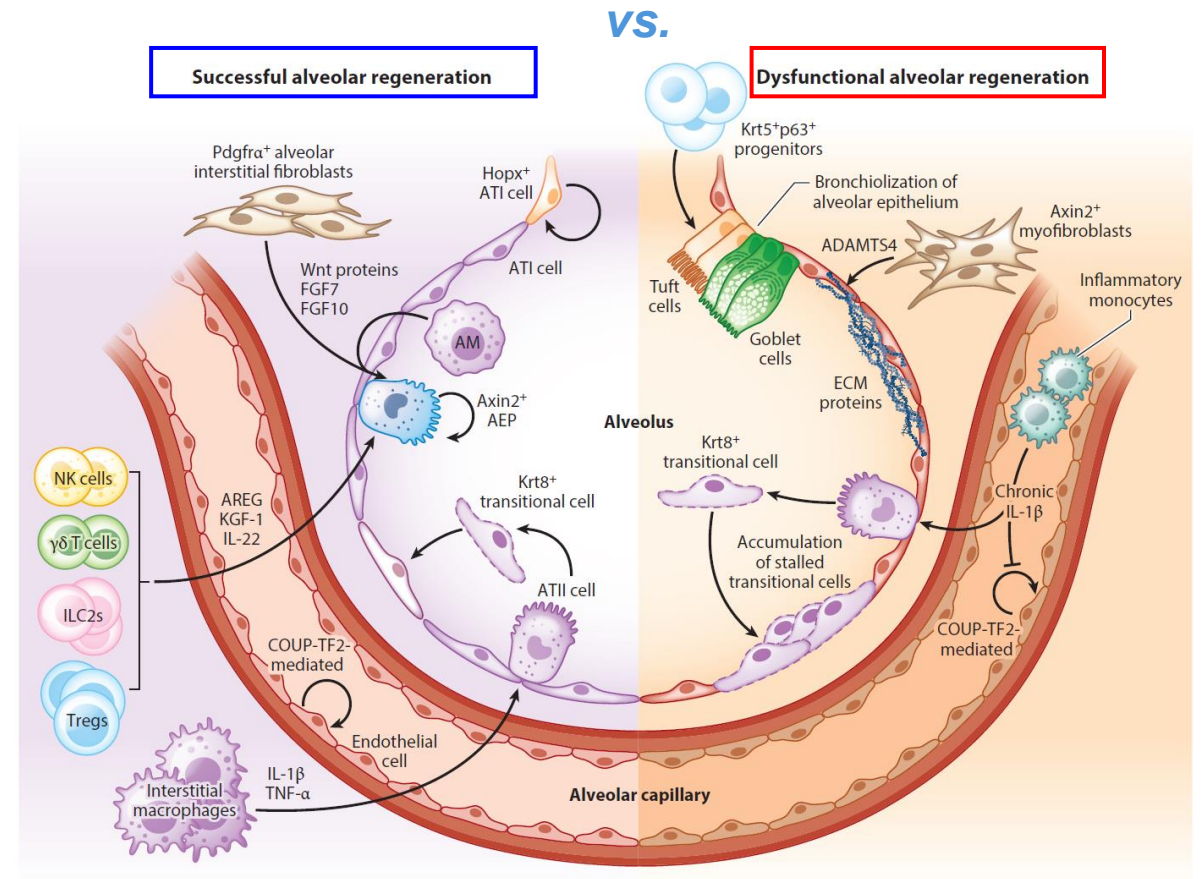
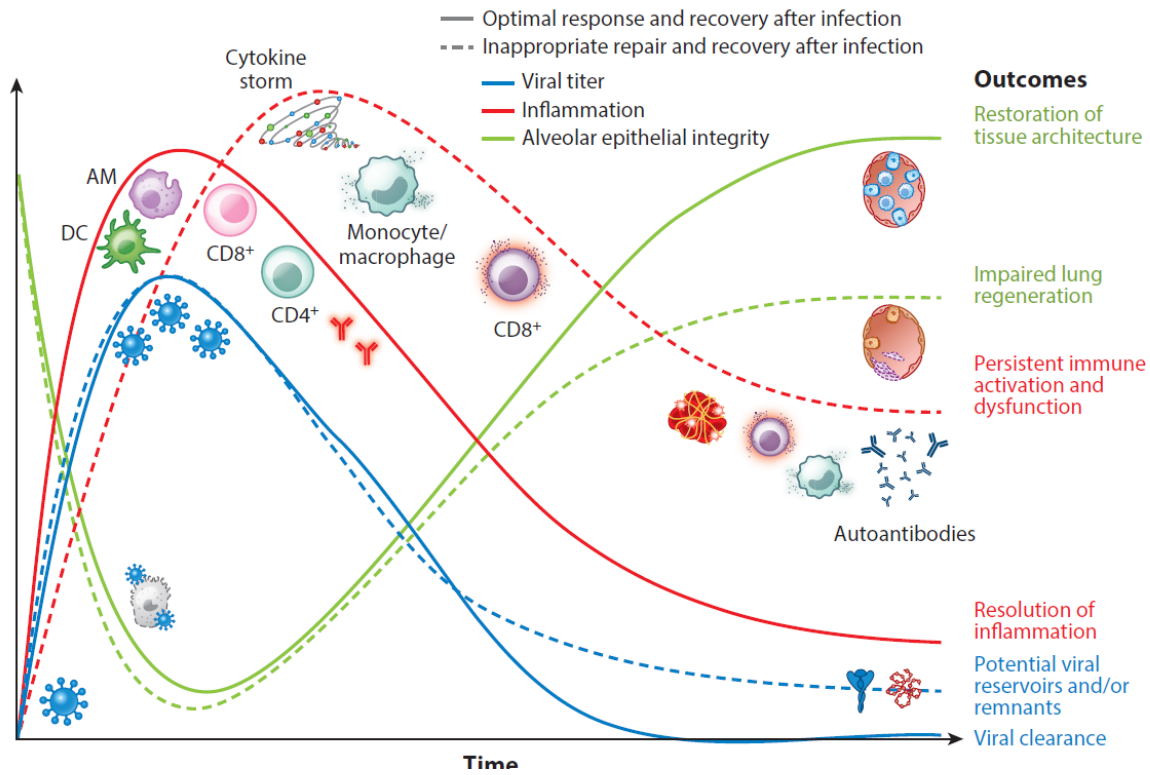


- PI3K-δ isoform

Eosinophilic severe asthma (in association with cytoplasmic organellar complex)



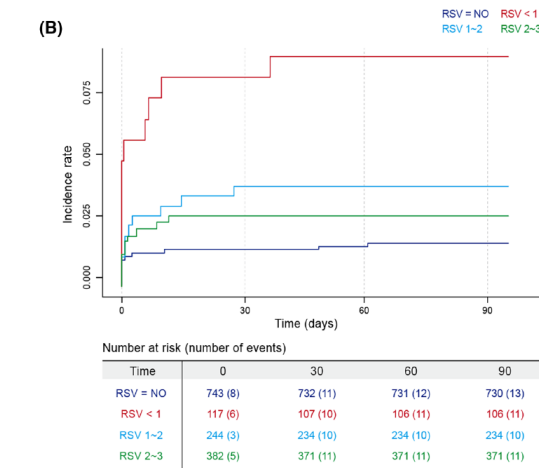
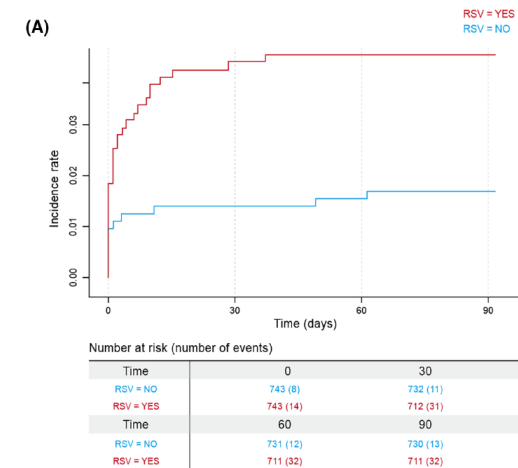
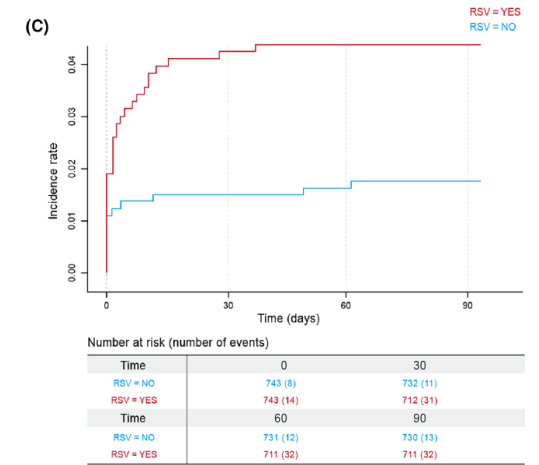
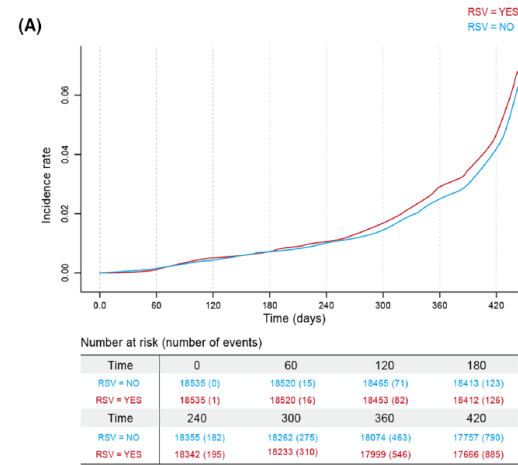
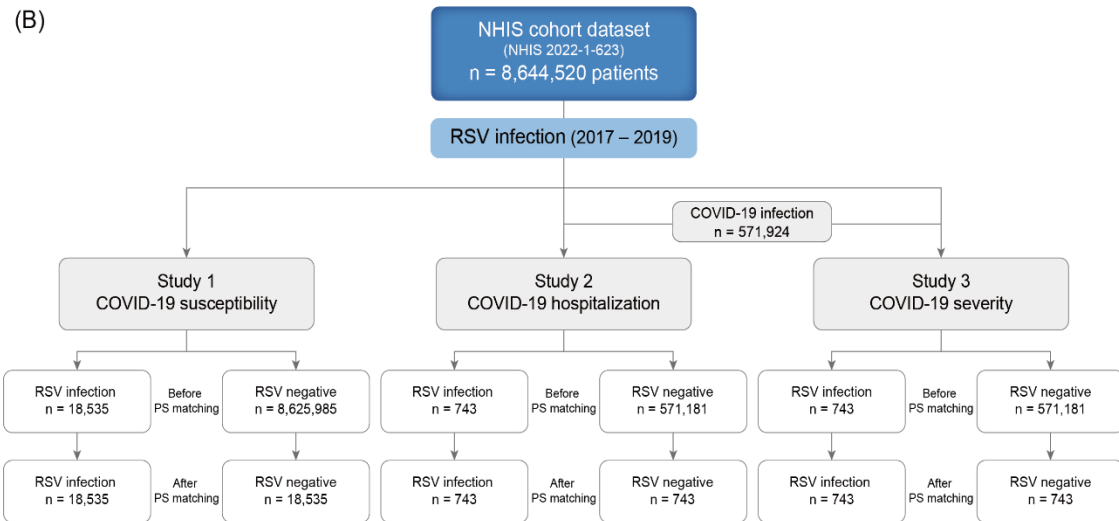
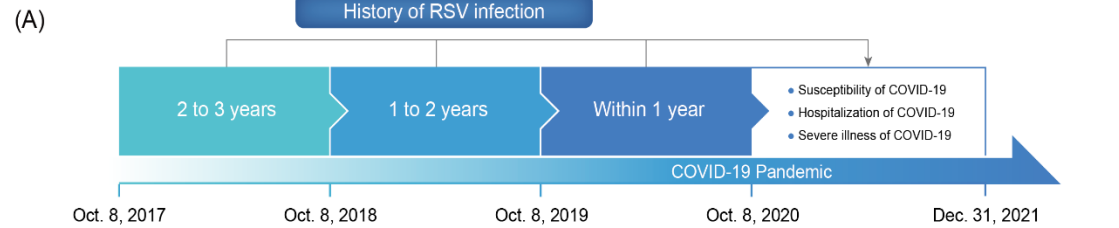
An overview of the pulmonary milieu during an “*acute respiratory viral infection*”



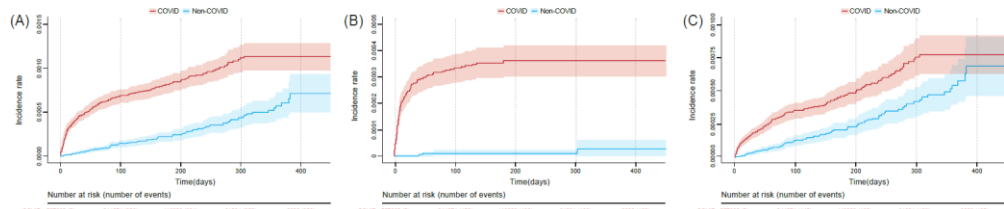
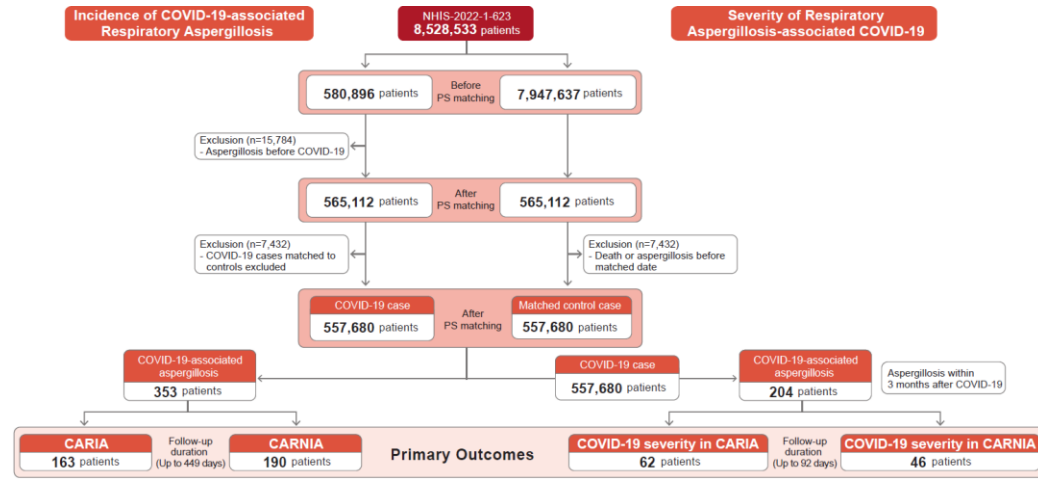
Potential impact of previous RSV infection on the severity of COVID-19

: “Chronic pulmonary sequelae”

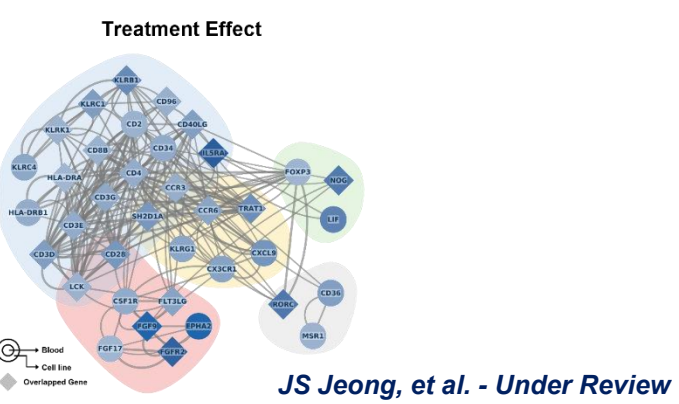
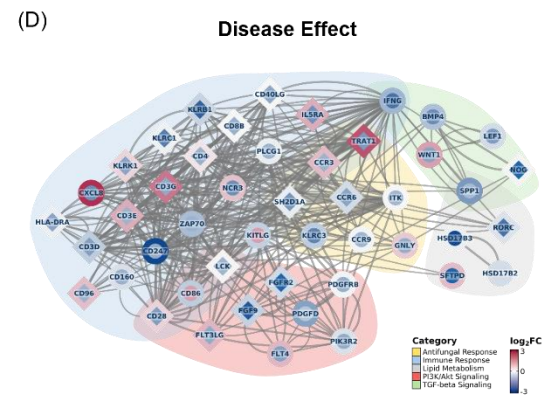
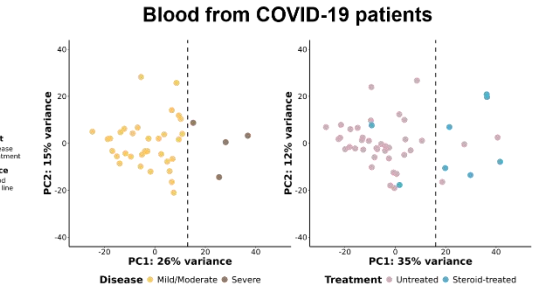
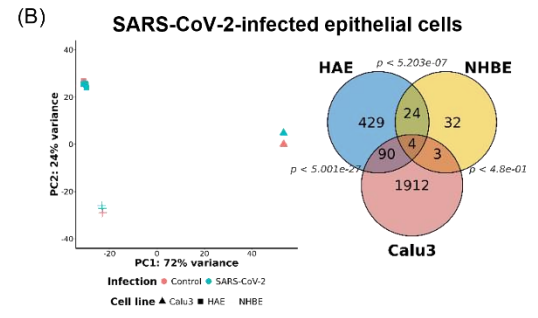
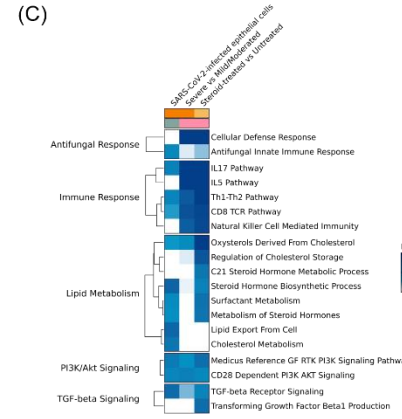
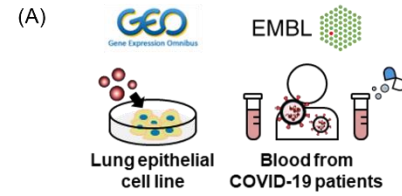
Prior respiratory syncytial viral infection contributes to severe COVID-19 illness: A nationwide cohort study



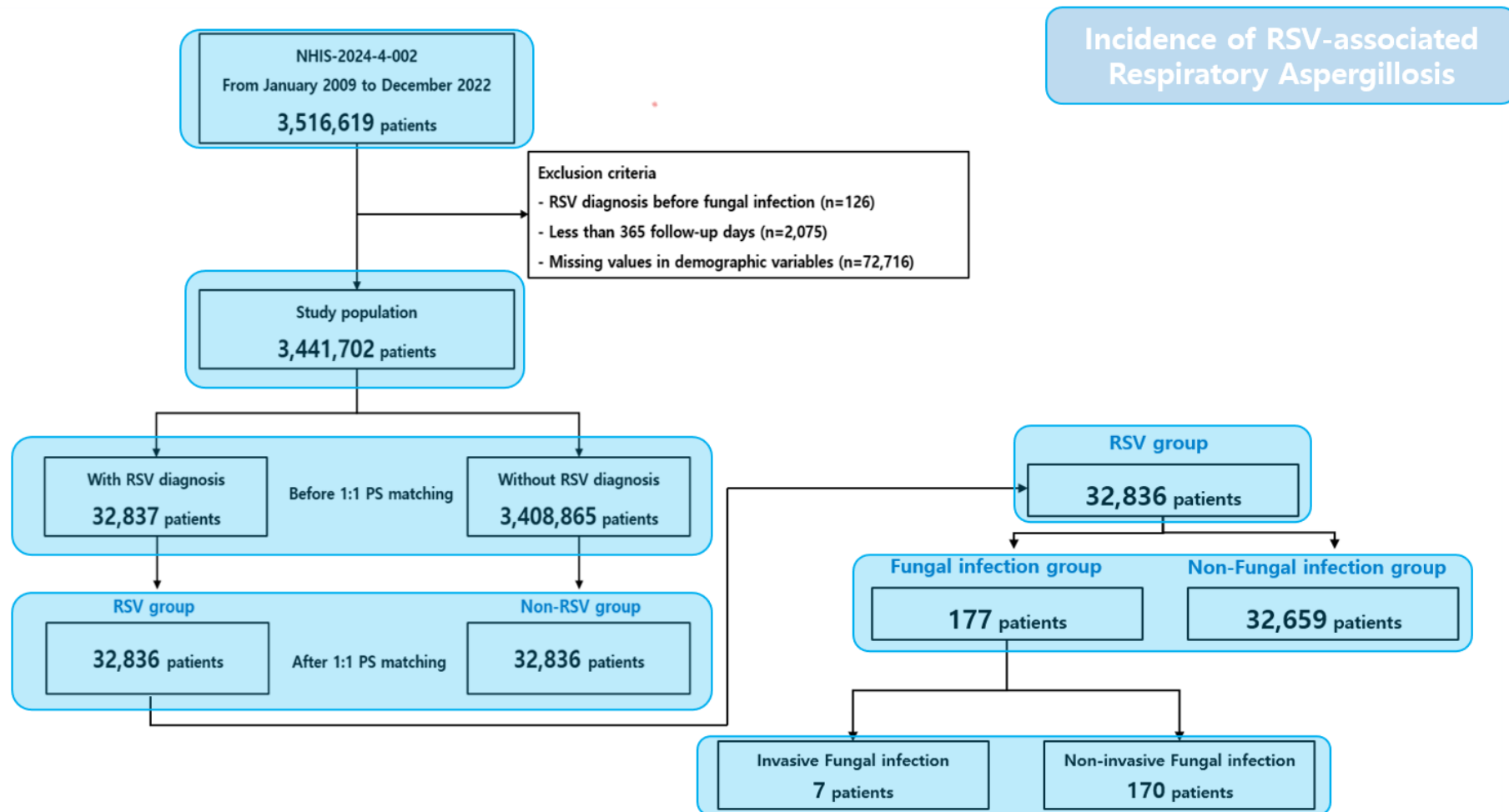
Potential impact of COVID-19 on the incidence of the “subsequent fungal infection”



Outcome	Total number	Cases	Adjusted hazard ratio (95% CI)	P Value
Susceptibility for Aspergillosis				
COVID-19 after 2020-10-08	557,680	353	3.81 (3.03 - 4.78)	<0.001
Using systemic steroids	43,178	197	15.68 (12.21 - 20.14)	<0.001
Not using systemic steroids	514,502	156	1.95 (1.51 - 2.51)	<0.001
Demography				
Male	575,302	262	1.34 (1.09 - 1.60)	0.004
Age Young	547,387	88	0.58 (0.43 - 0.80)	0.001
Age Old	232,810	261	1.81 (1.42 - 2.31)	<0.001
SES High	352,615	148	0.99 (0.81 - 1.20)	0.009
Metropolitan Area	602,778	232	0.96 (0.80 - 1.14)	0.073
Comorbidity				
HTN	252,292	267	1.26 (0.98 - 1.61)	0.073
DM	191,882	254	2.89 (2.14 - 3.90)	<0.001
CHD	12,283	42	1.94 (1.38 - 2.72)	<0.001
CNF	68,670	127	1.68 (1.32 - 2.14)	<0.001
CVD	64,652	94	1.20 (0.94 - 1.54)	0.147
Cancer	141,204	149	1.34 (1.09 - 1.66)	0.006
MI	29,007	46	1.17 (0.85 - 1.62)	0.341
Asthma	75,466	31	0.89 (0.60 - 1.31)	0.057
COVID	36,077	35	2.36 (1.62 - 3.37)	<0.001



Potential impact of RSV infection on the incidence of the “*subsequent fungal infection*”



[Confidential]

Different points of immune dysregulation in ARDS

1. Immune/inflammation processes

- Cell-intrinsic anti-microbial responses and different shaping of immune responses
 - PRRs: Characteristic pro-inflammatory/IFNs balance (bacteria, viral, fungal, etc.)
- Dysregulated immune response by recruited cells (e.g. NETosis)
- Dysregulated cell death in CSS
- Dysregulated adaptive responses: Protracted immune response and immunosuppression
 - Immune senescence, potential implication of bystander cell activation

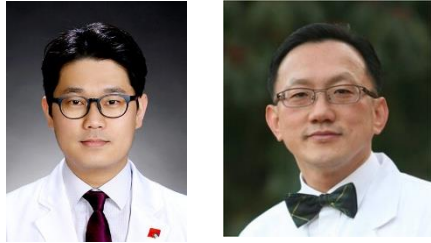
2. Endothelial injury

- Dysregulated RAAS with inflammation: Increased permeability and vasoconstriction
- NETosis and ferroptosis: Platelet accumulation, clotting, coagulation

3. Epithelial injury

- Secretory cells: Immunomodulatory and regenerative roles
 - Rely on proper ER and mitochondrial function, Susceptibility for ferroptotic cell death?
- Chronic pulmonary sequelae with long-term effects: Subsequent infections (virus, fungi, etc.)

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: Ferroptosis와 미토콘드리아-소포체의 상호관련성 기반의 중증 호흡기계 손상 제어기술 개발

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: 혁신형 의사과학자 양성을 통한 융합 연구 개발



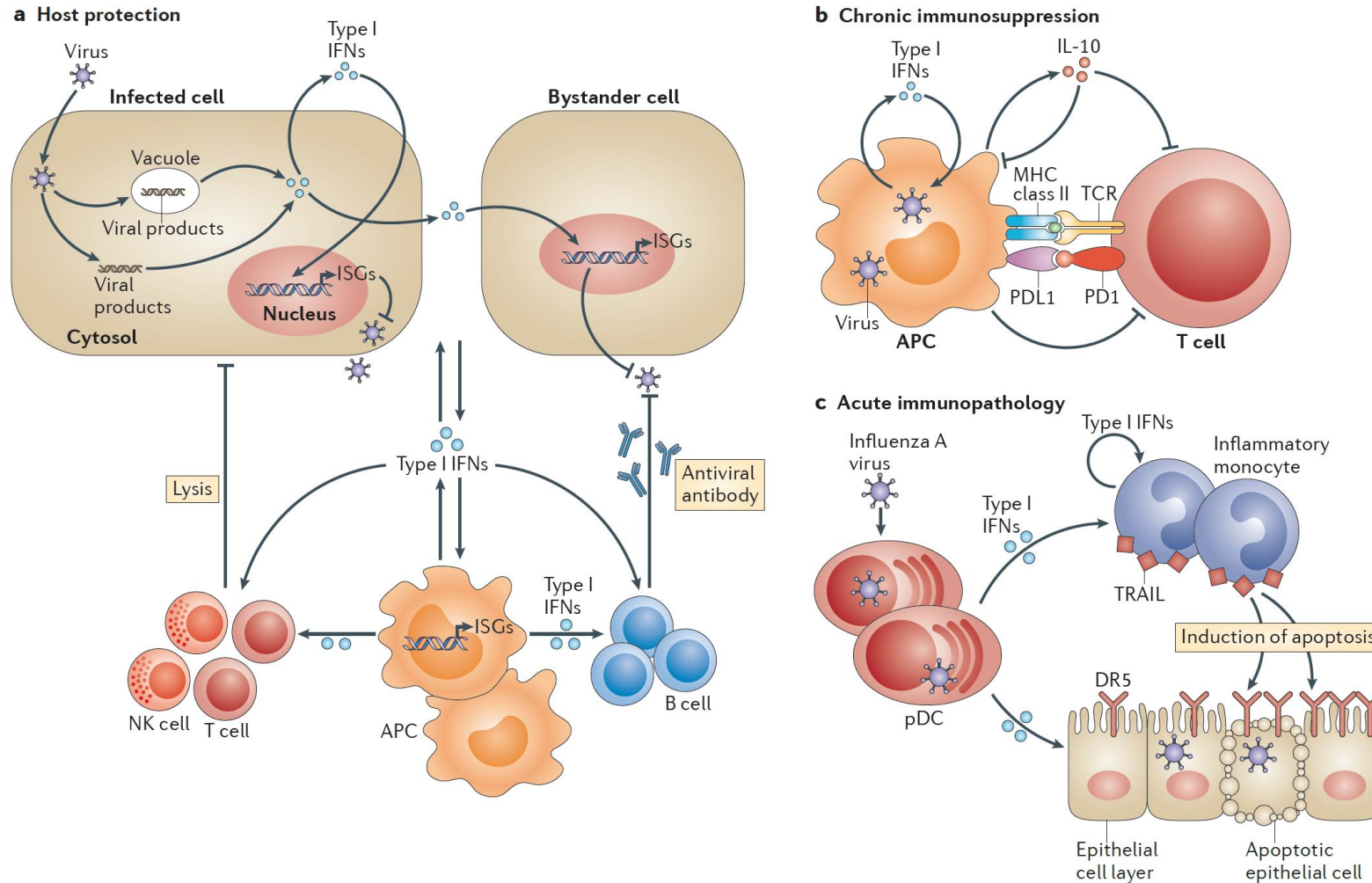
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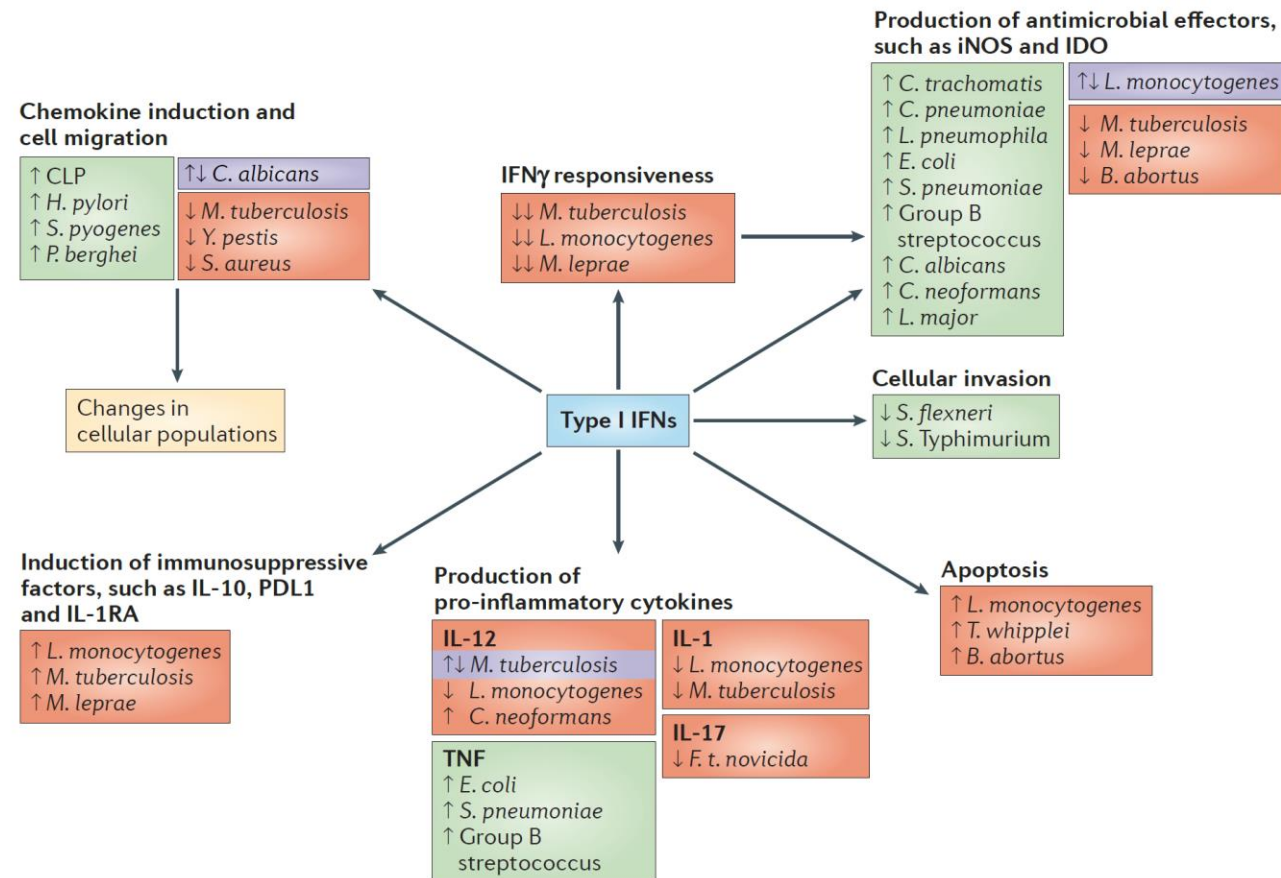
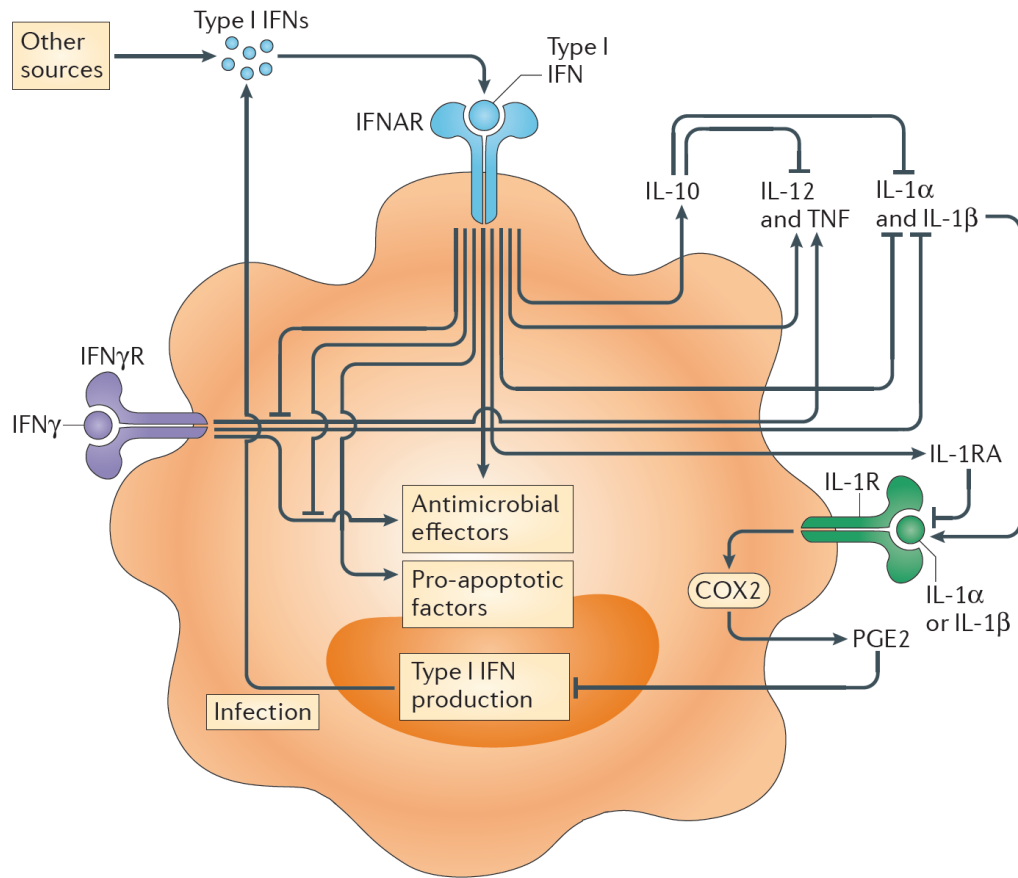
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* 보건복지부 2024년도 글로벌 의사과학자 양성사업 (RS-2024-00440408; JS, Jeong)
: 식물 유래 저항원성 세포외소포체를 이용한 중증천식의 만성염증 제어 기술 개발

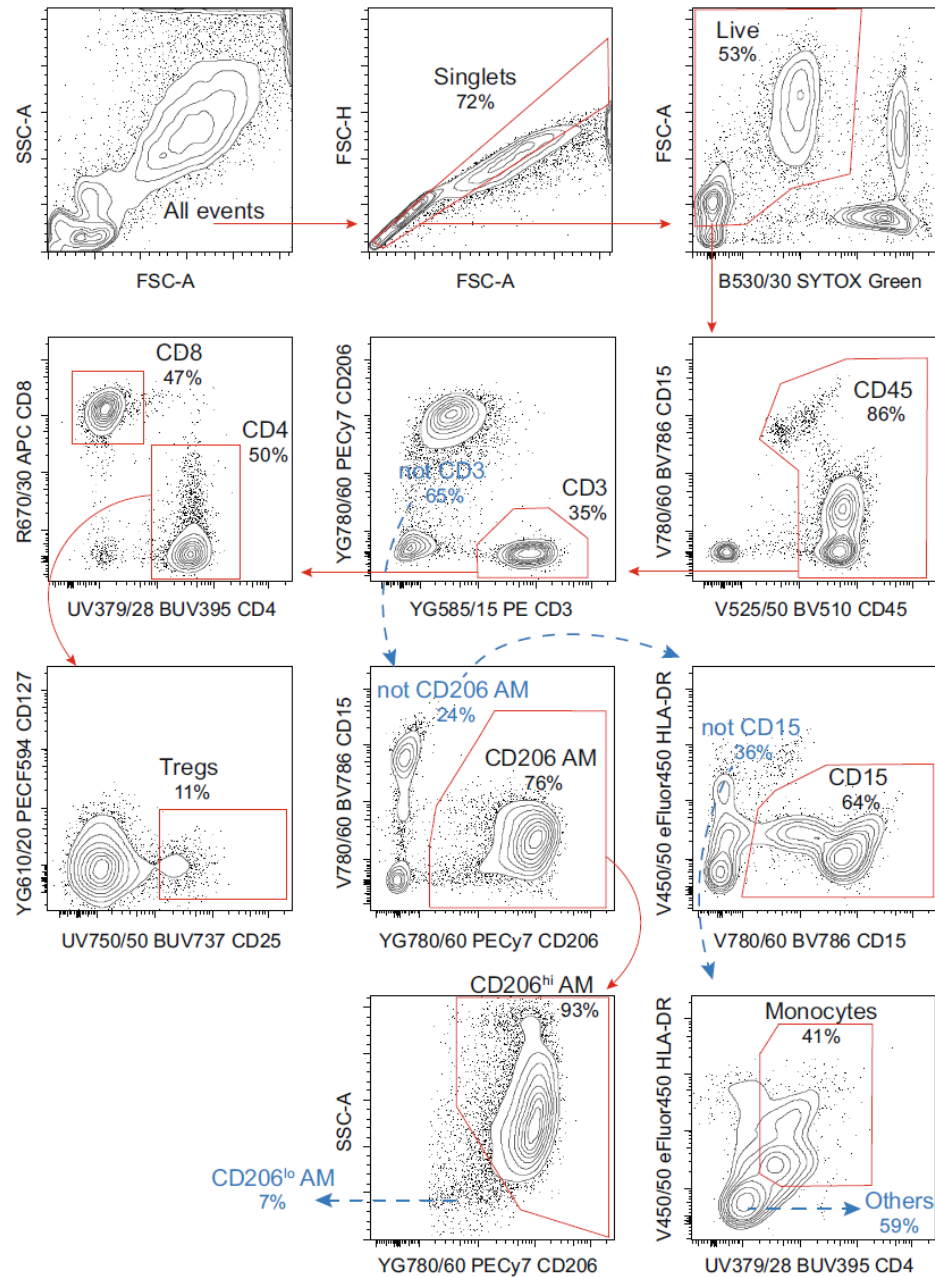
Type I interferons during “*viral infection*”



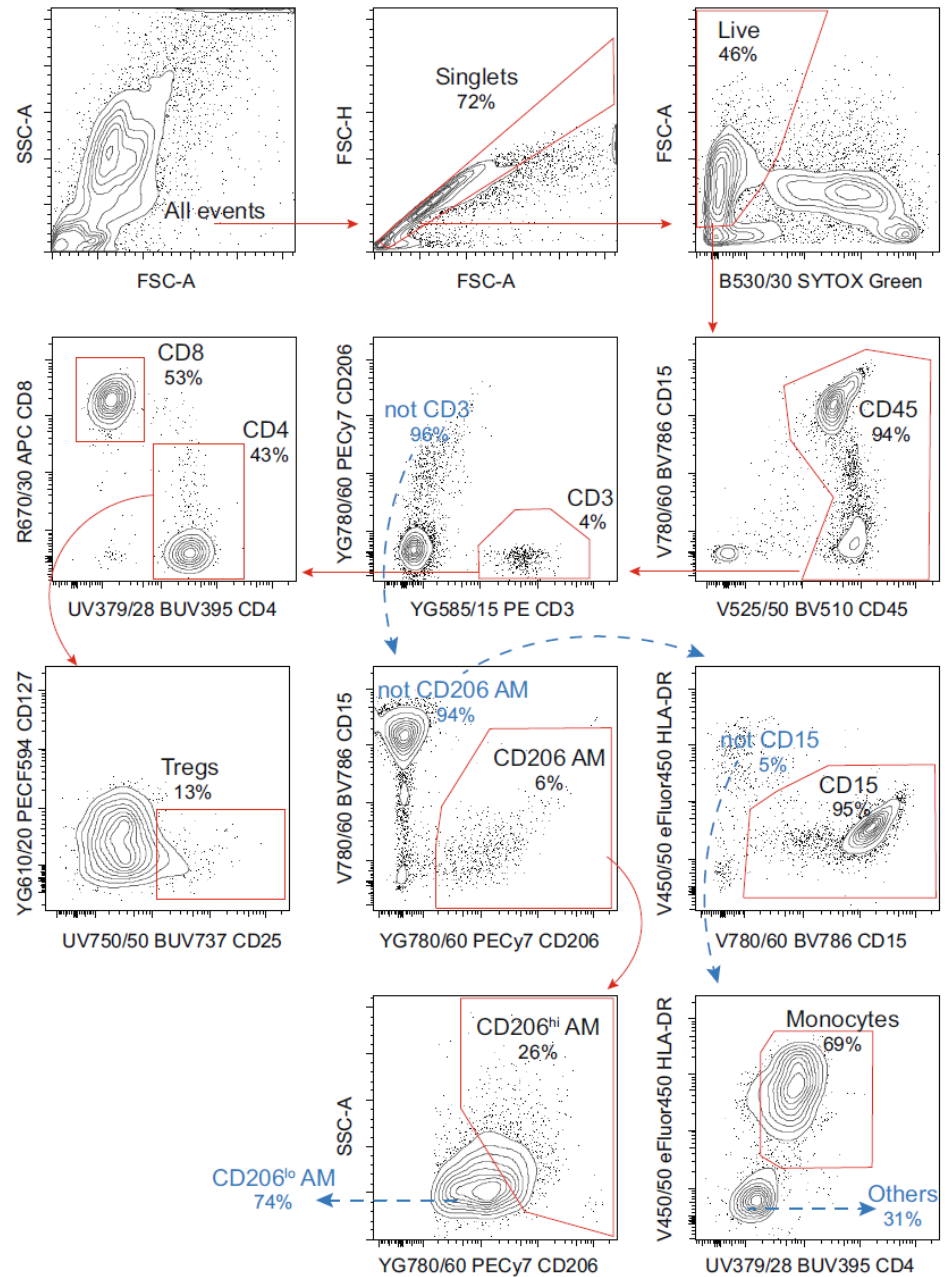
Mechanisms of interferon action in “non-viral infections”



a Gating strategy for representative “non-neutrophilic” sample



b Gating strategy for representative “neutrophilic” sample



Dysregulated bronchoalveolar immune landscapes in patients with “*severe COVID-19*” infection

