

In the name of God

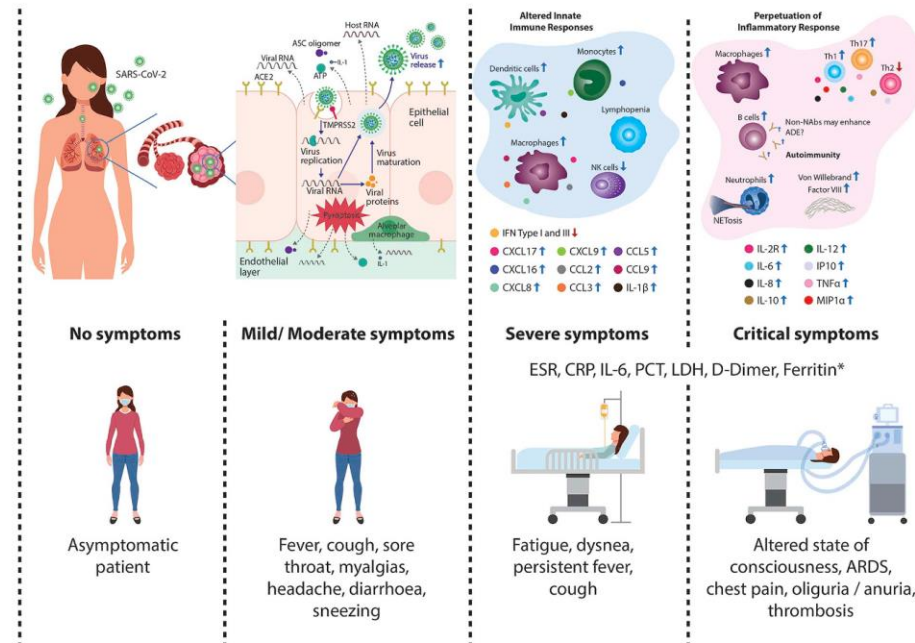
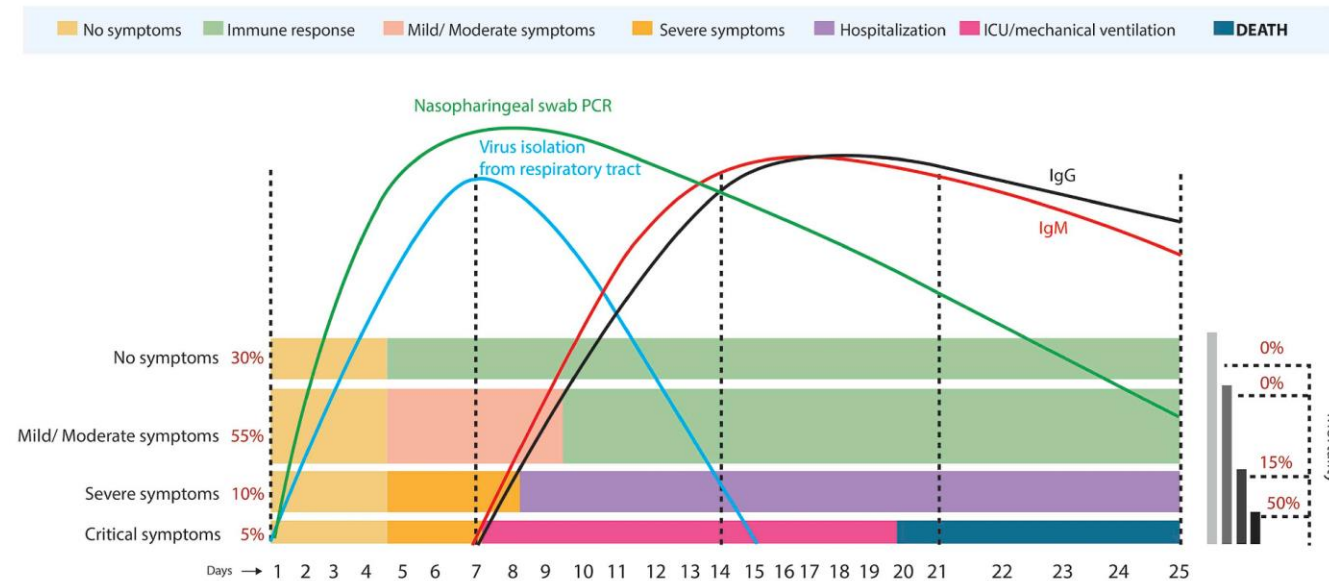


Immune responses during COVID-19 infection

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Alborz University of Medical Sciences, Karaj, Iran

Translational overview of COVID-19

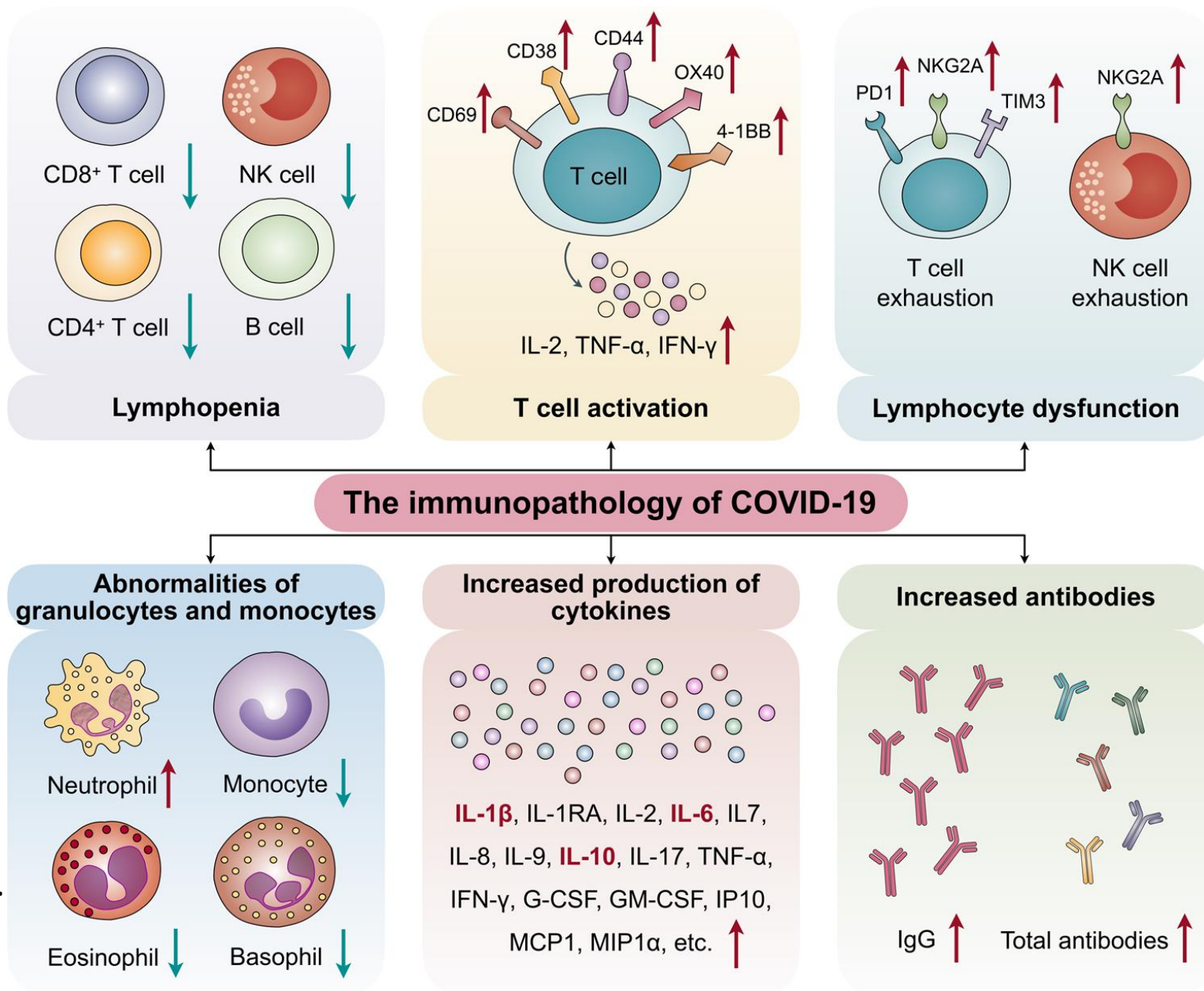


Rodríguez, Y, J Autoimmun.
2020 Nov;114:102506

The immunopathology of COVID-19

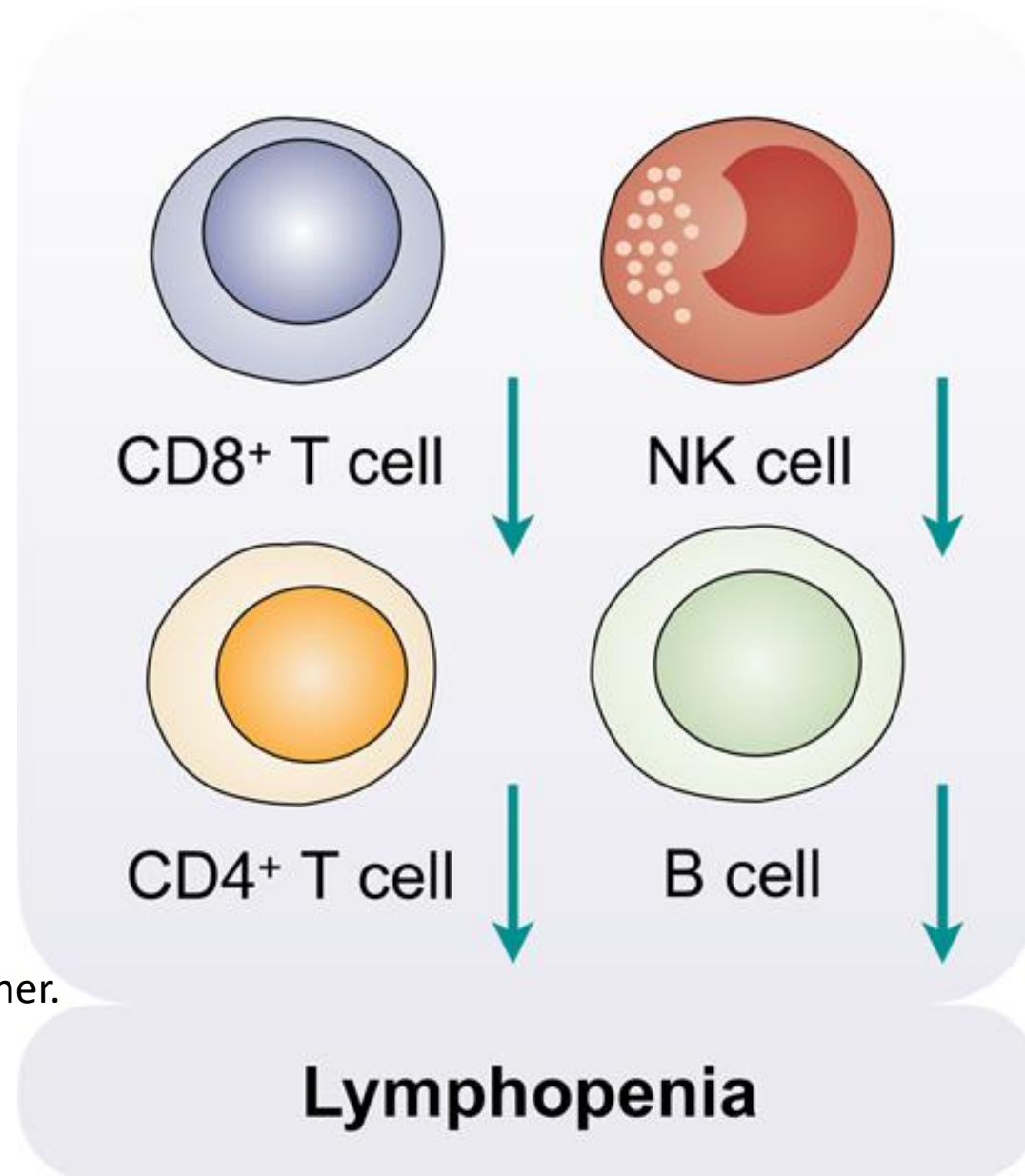


دانشگاه علوم پزشکی و خدمات بهداشتی درمانی همدان



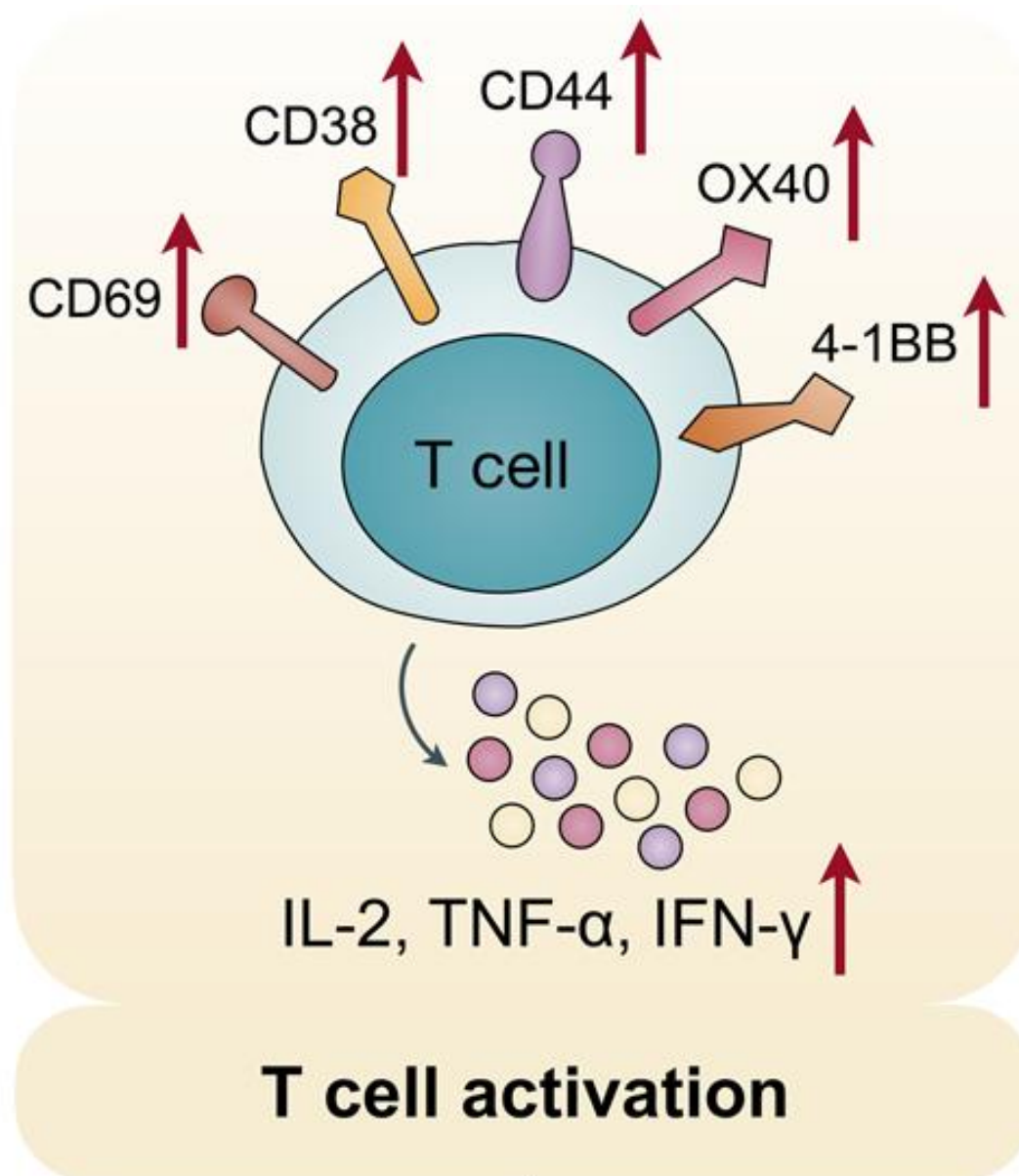
Yang, L, Signal
Transduct Target Ther.
2020 Jul 25;5(1):128

A. Lymphopenia



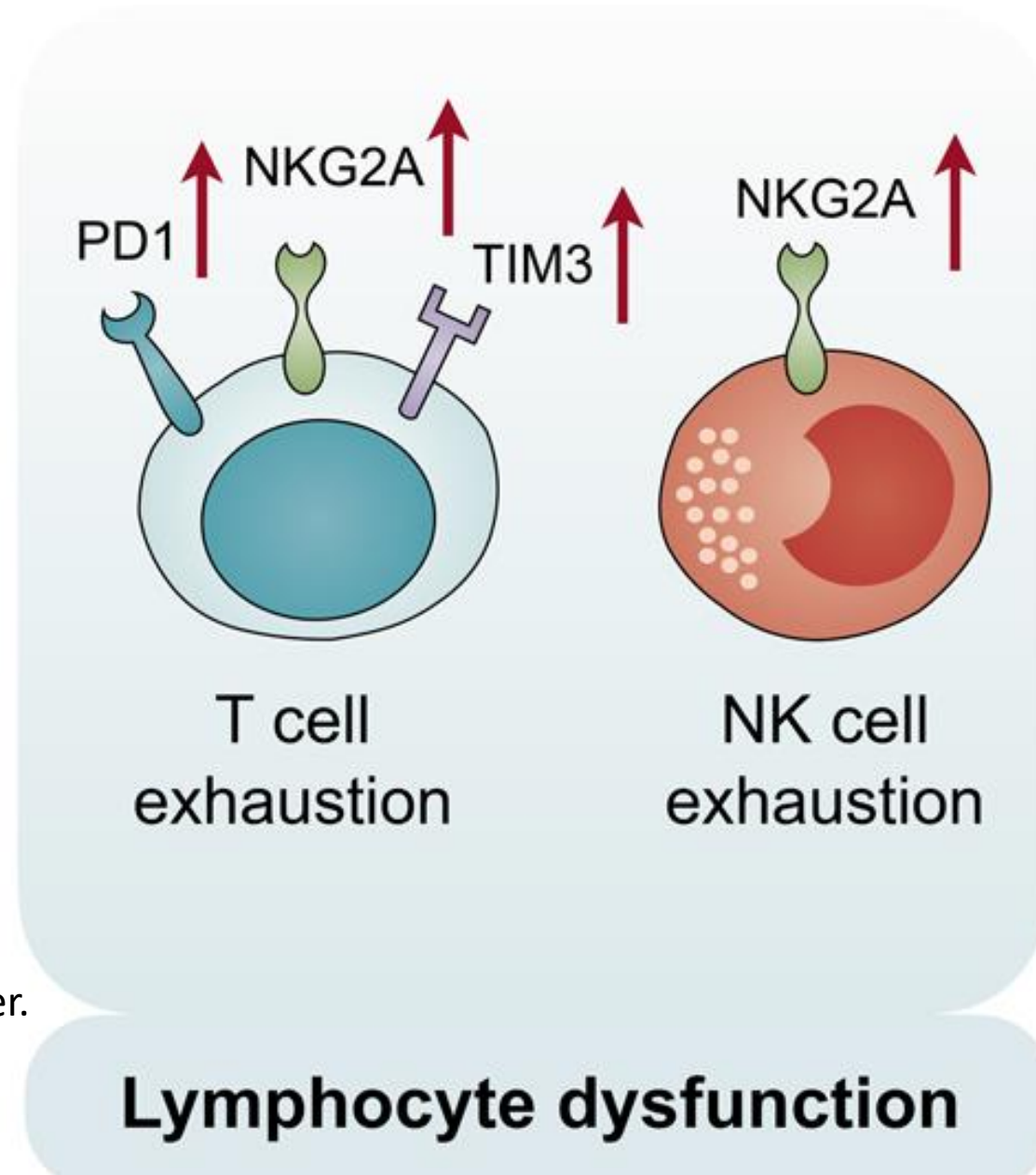
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B. T cell activation



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C. Lymphocyte dysfunction



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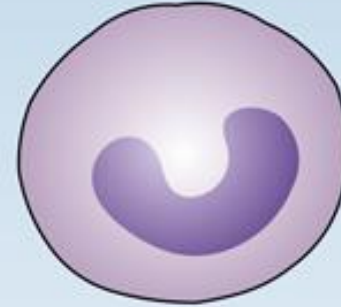
D. Abnormalities of granulocytes and monocytes



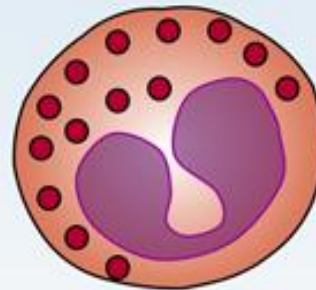
Abnormalities of granulocytes and monocytes



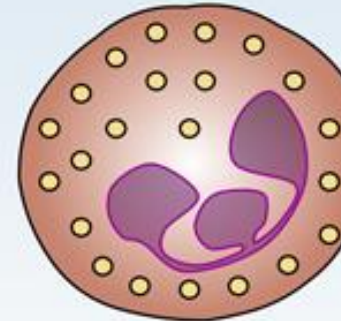
Neutrophil



Monocyte



Eosinophil



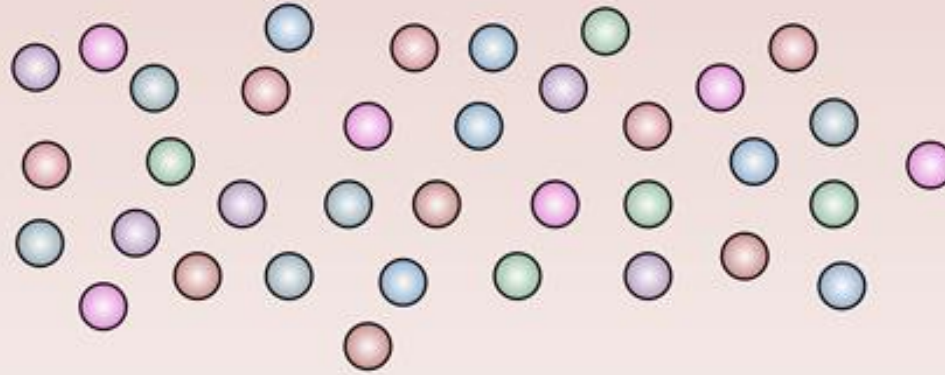
Basophil



E. Increased production of cytokines



Increased production of cytokines

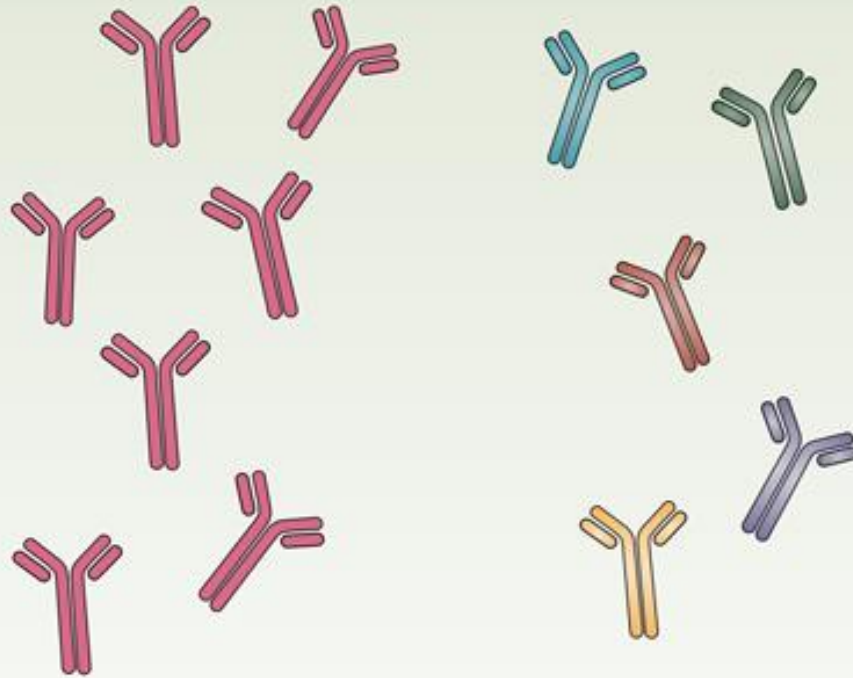


IL-1 β , IL-1RA, IL-2, **IL-6**, IL7,
IL-8, IL-9, **IL-10**, IL-17, TNF- α ,
IFN- γ , G-CSF, GM-CSF, IP10,
MCP1, MIP1 α , etc.

F. Increased antibodies

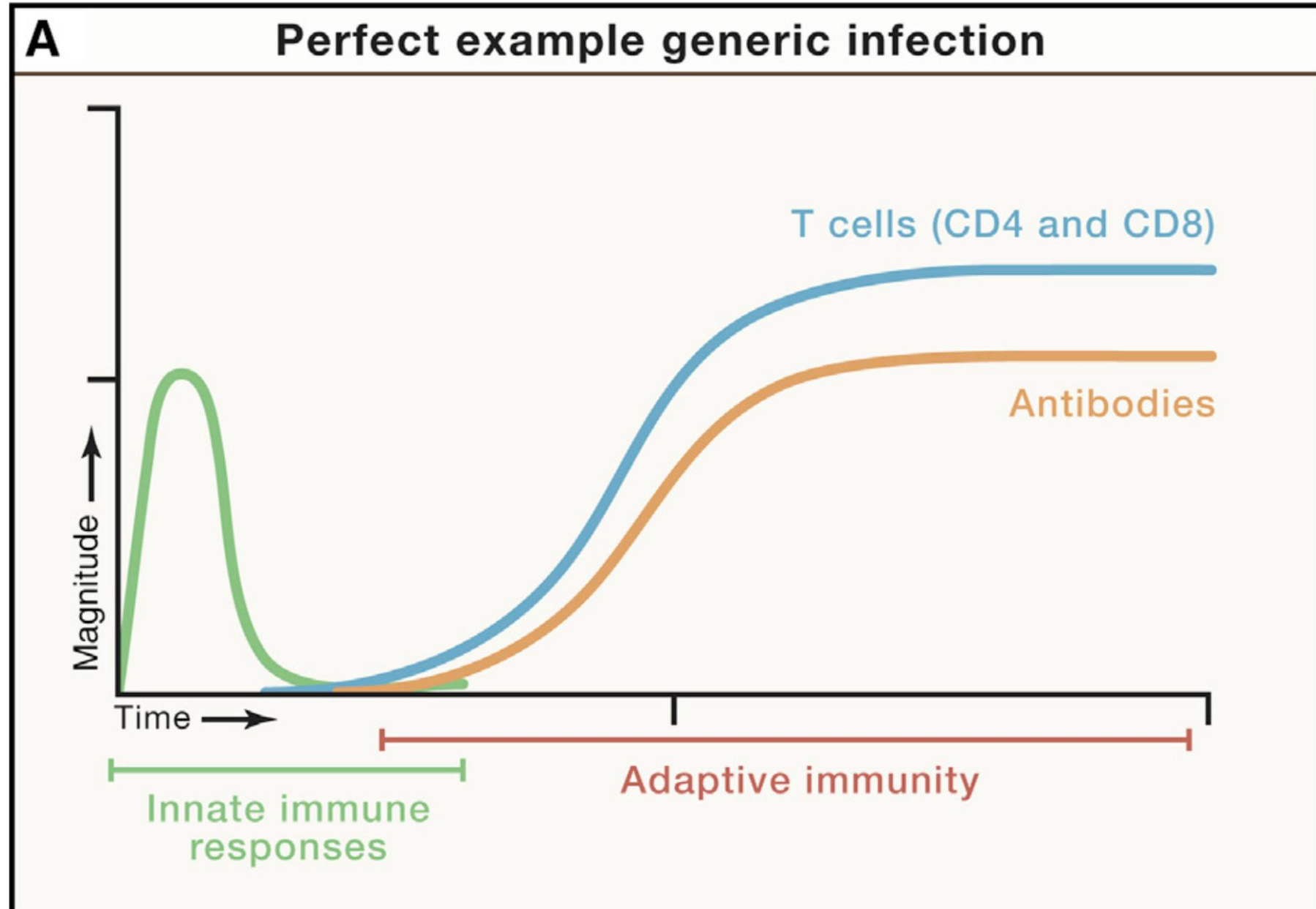


Increased antibodies



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An integrated working model of COVID-19 immunology and disease severity

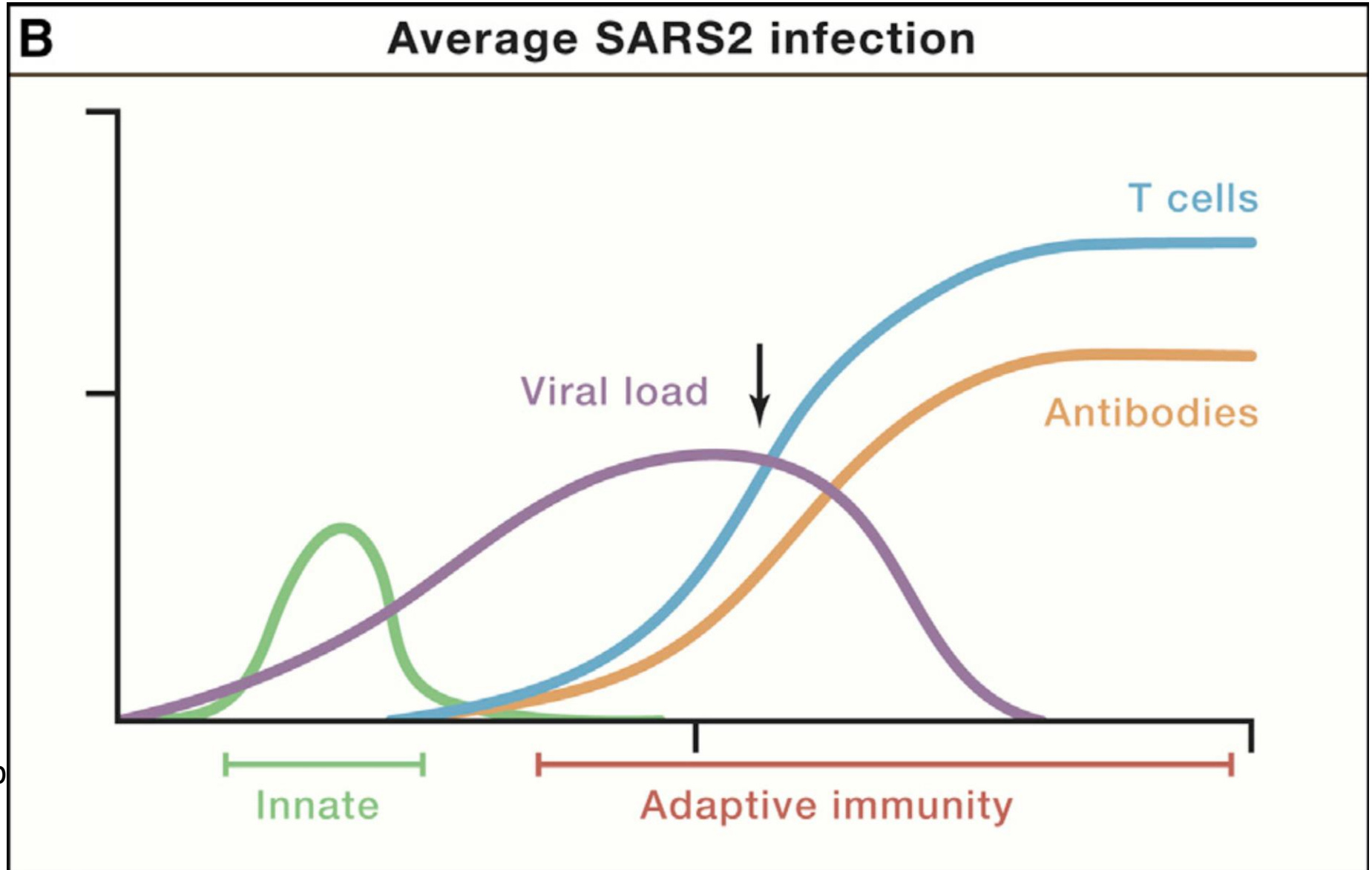


Sette, A, Cell. 2021 Feb
18;184(4):861-880

An integrated working model of COVID-19 immunology and disease severity

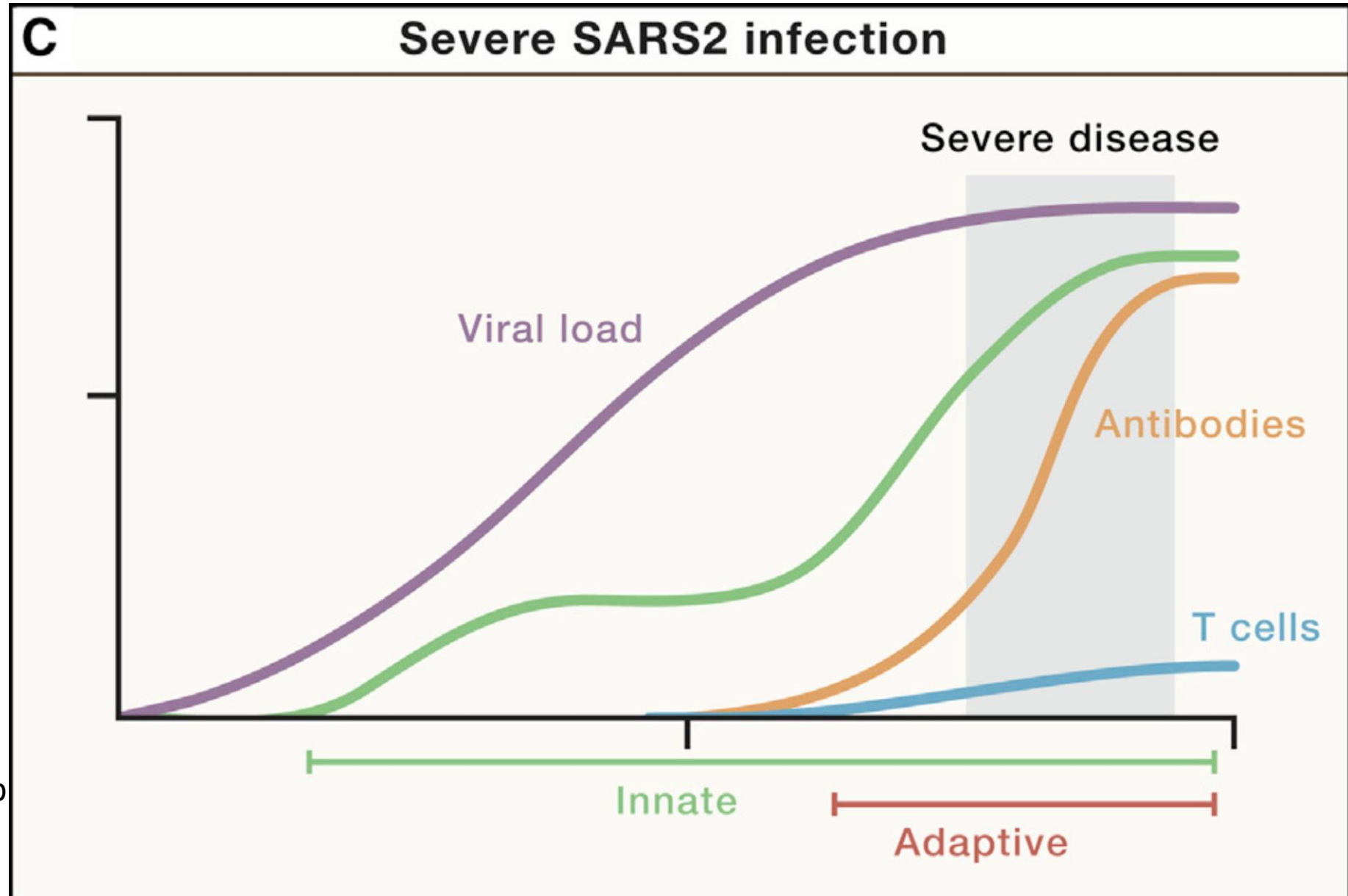


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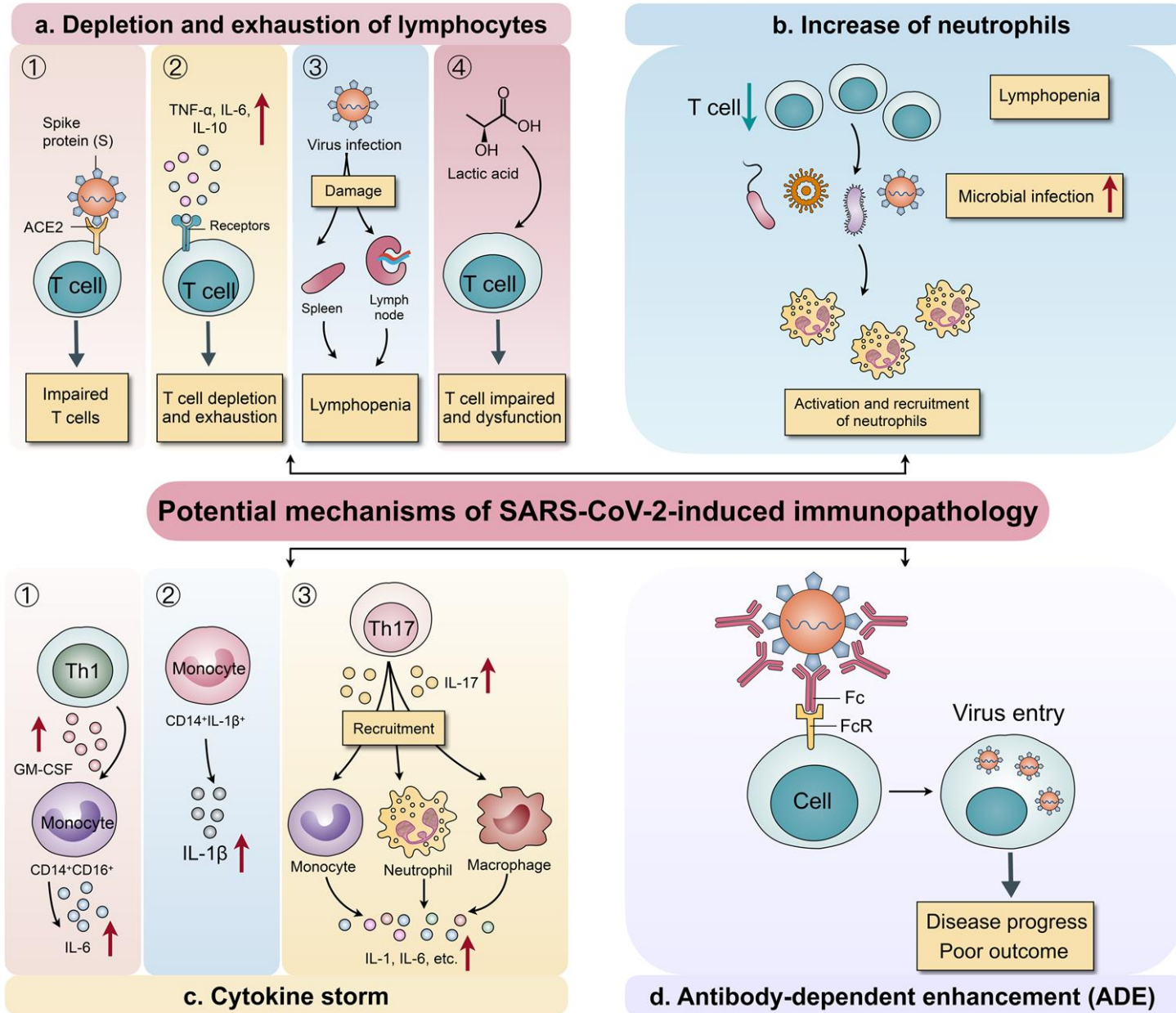
Sette, A, Cell. 2021 Feb
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An integrated working model of COVID-19 immunology and disease severity



Sette, A, Cell. 2021 Feb
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Potential mechanisms of SARS-CoV-2-induced immunopathology

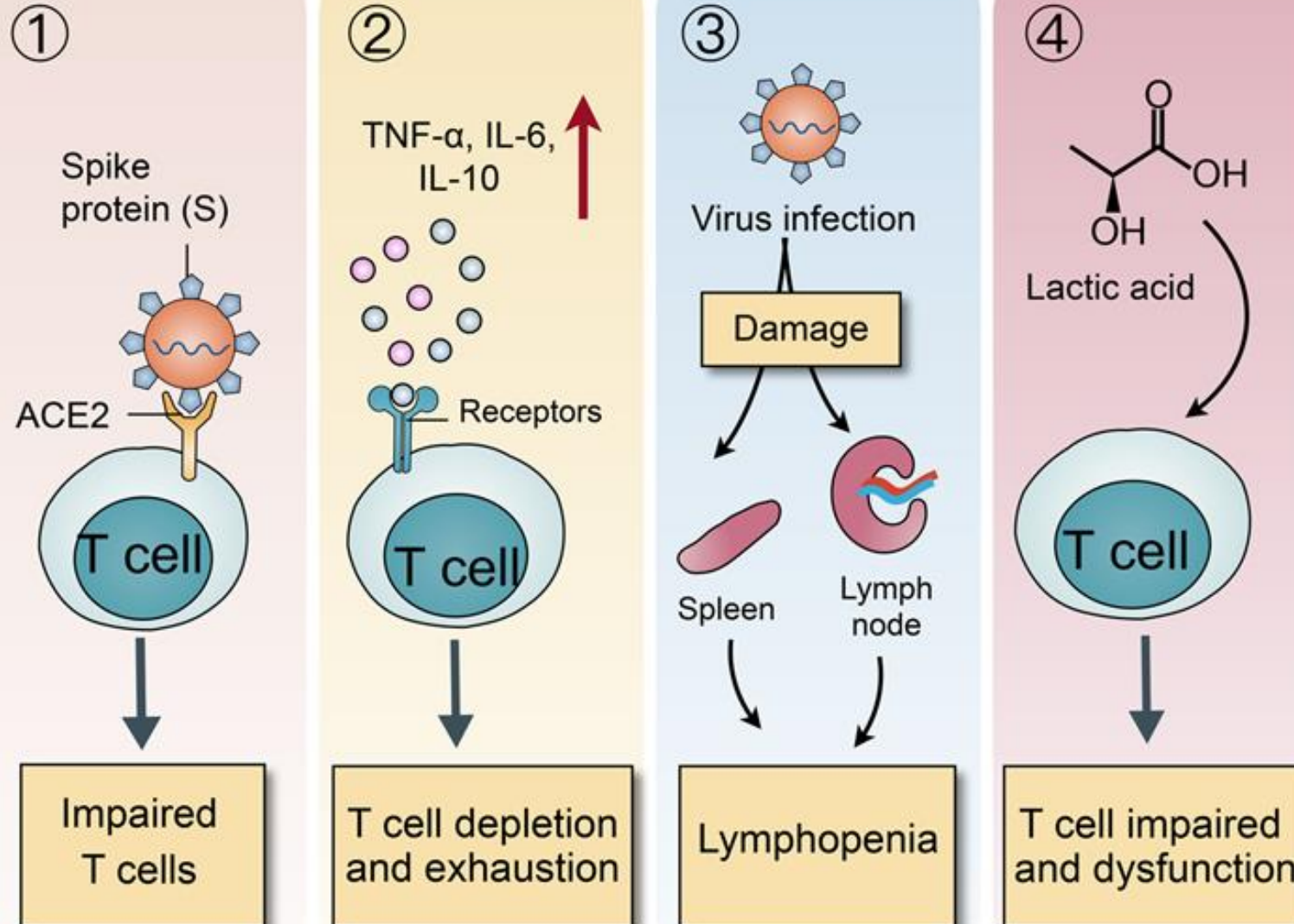


Yang, L, Signal Transduct
Target Ther. 2020 Jul
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A. Potential mechanisms of depletion and exhaustion of lymphocytes

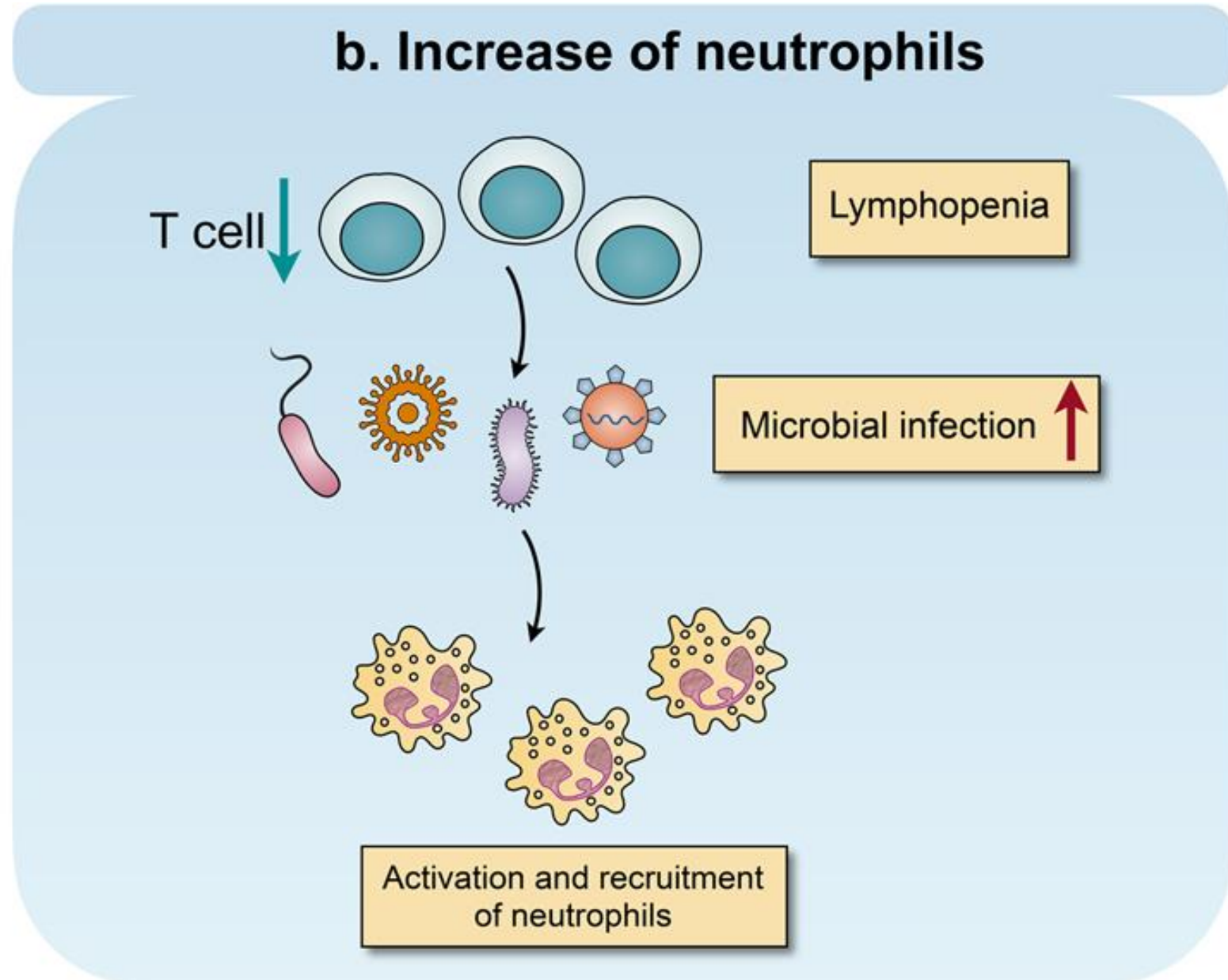


a. Depletion and exhaustion of lymphocytes



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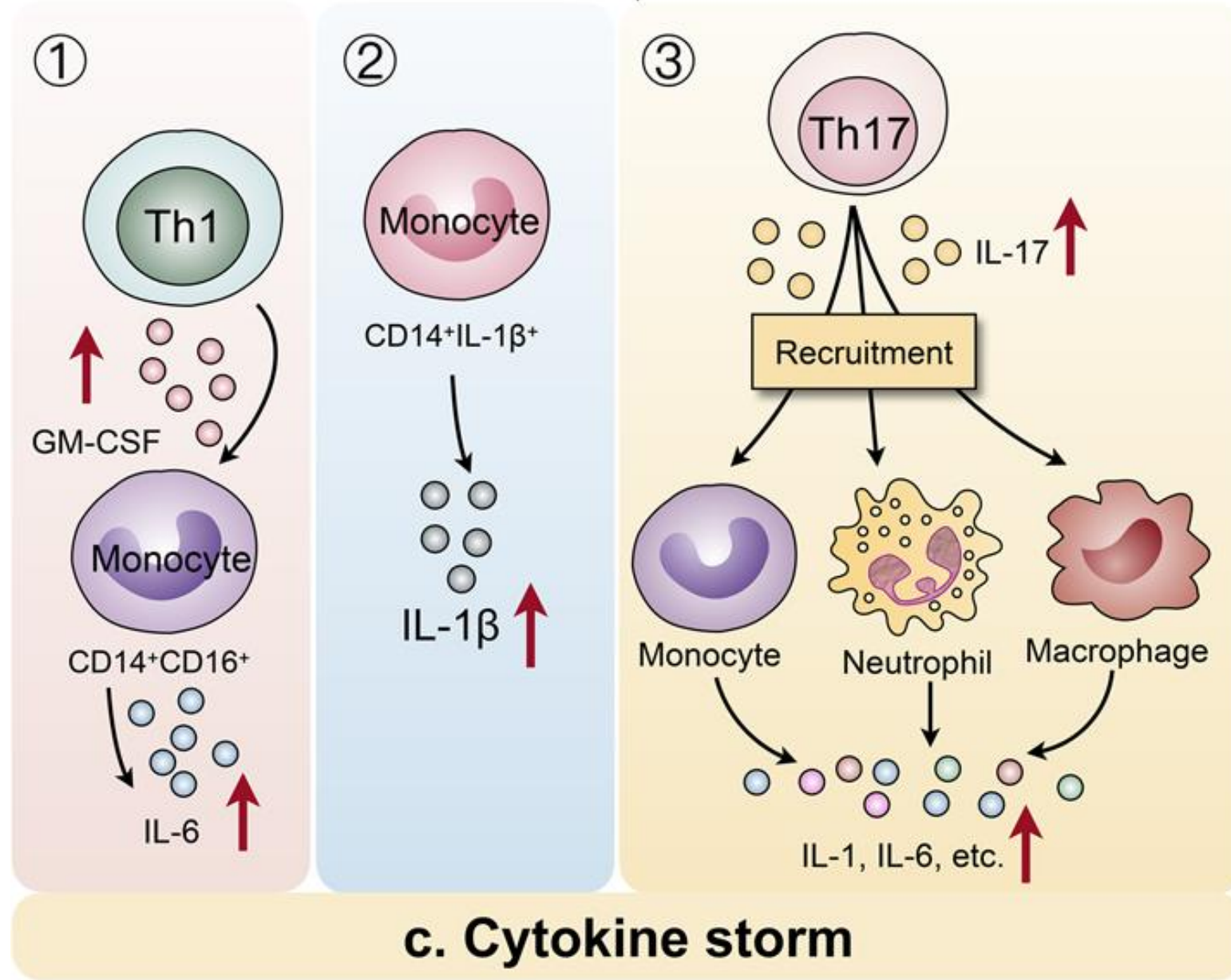
B. Increase of neutrophils



C. The potential mechanisms of cytokine storm induction

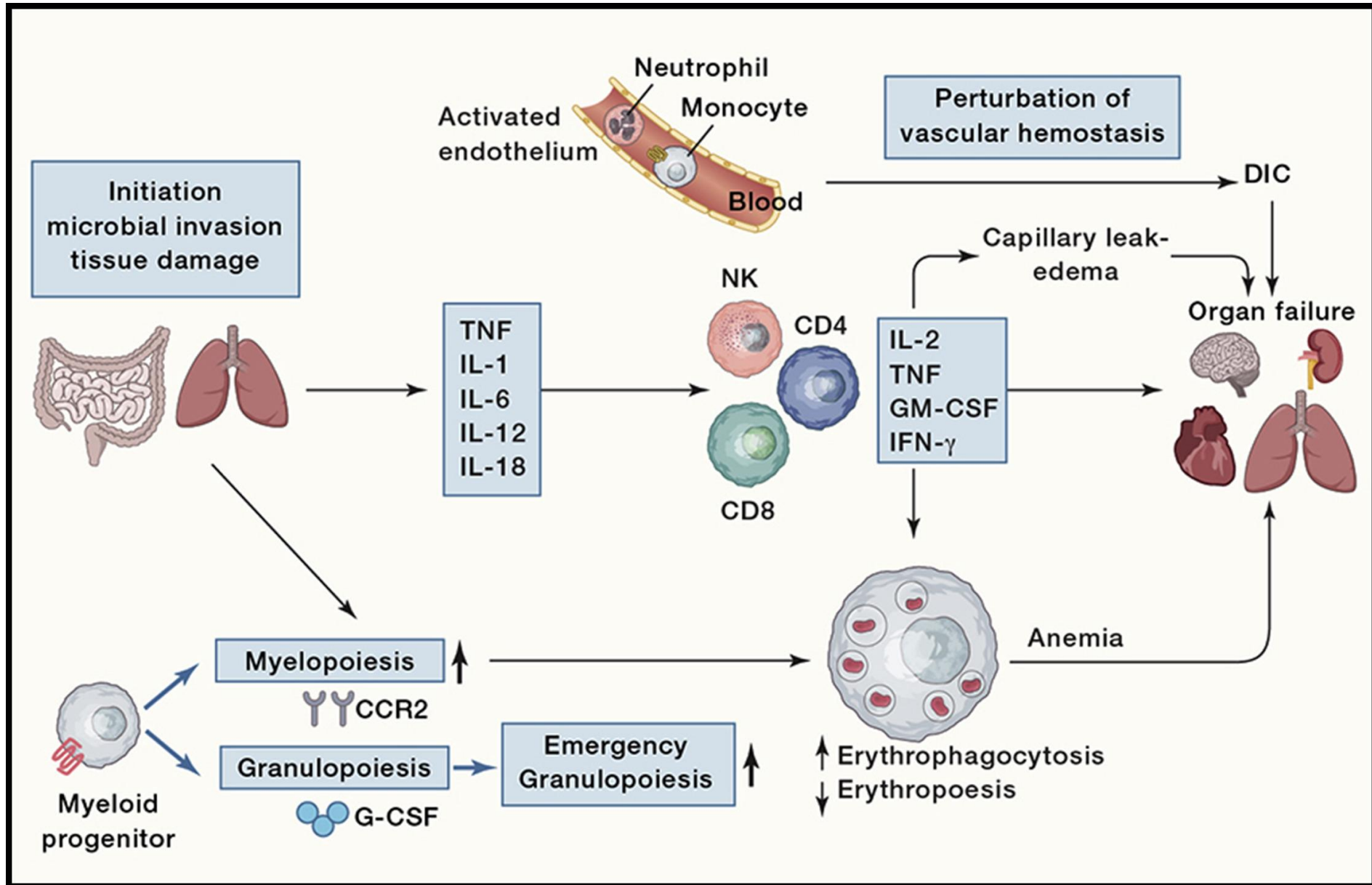


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Yang, L, Signal Transduct
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Pathophysiology of a Cytokine Storm

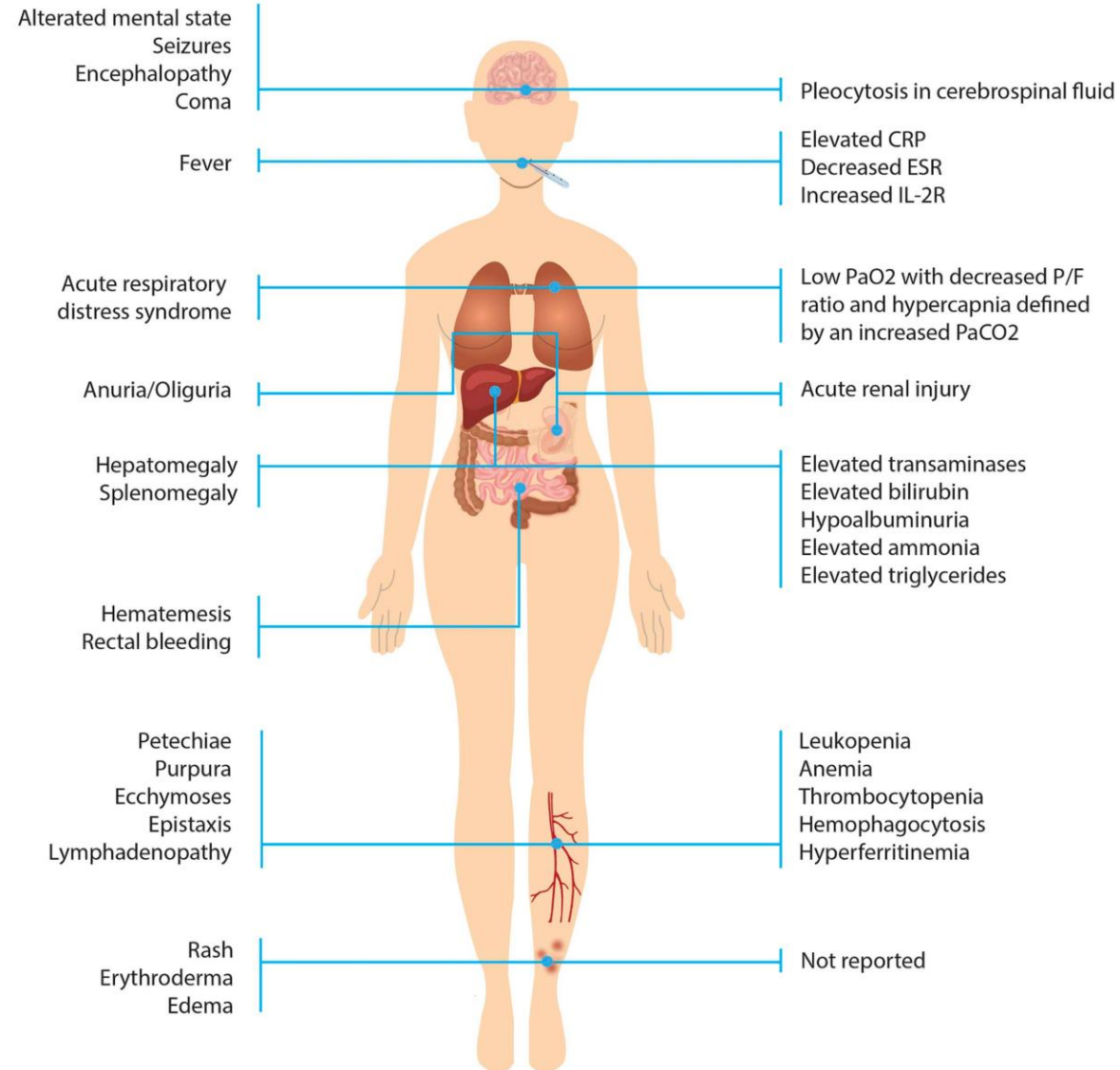


Clinical manifestations in the cytokine storm syndrome



Clinical manifestations

Laboratory findings

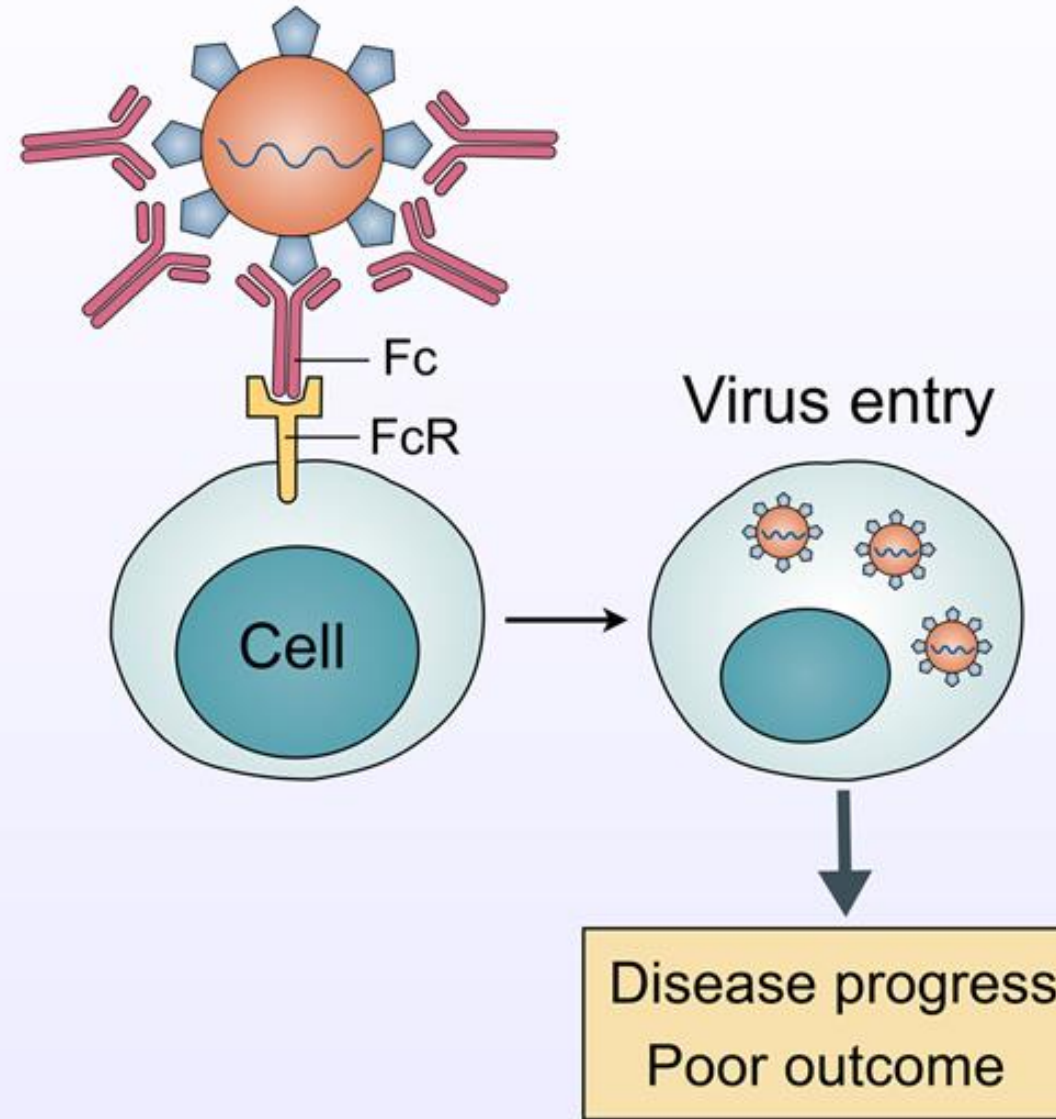


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D. Antibody-dependent enhancement



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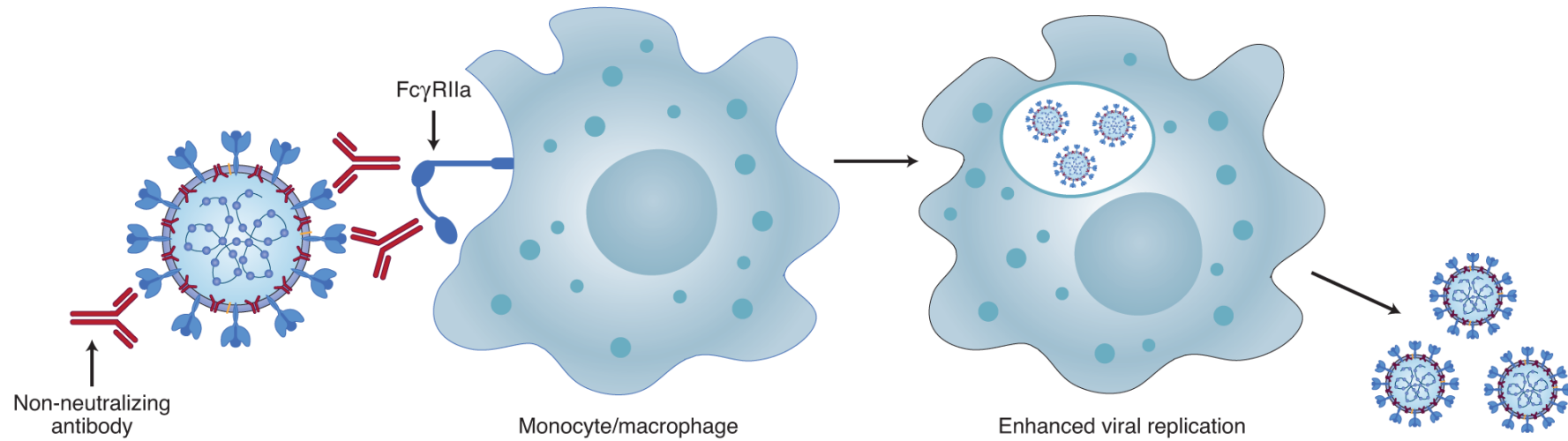


d. Antibody-dependent enhancement (ADE)

Two main ADE mechanisms in viral disease

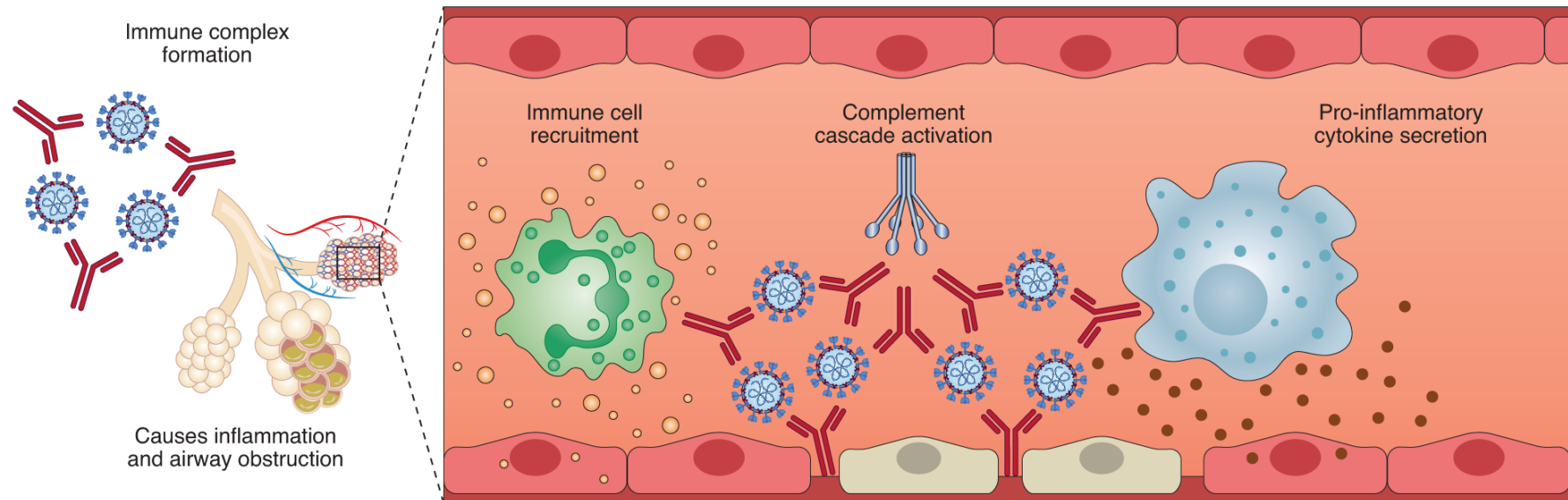
a

Macrophage-tropic viruses: dengue virus, FIPV



b

Respiratory viruses: RSV, measles



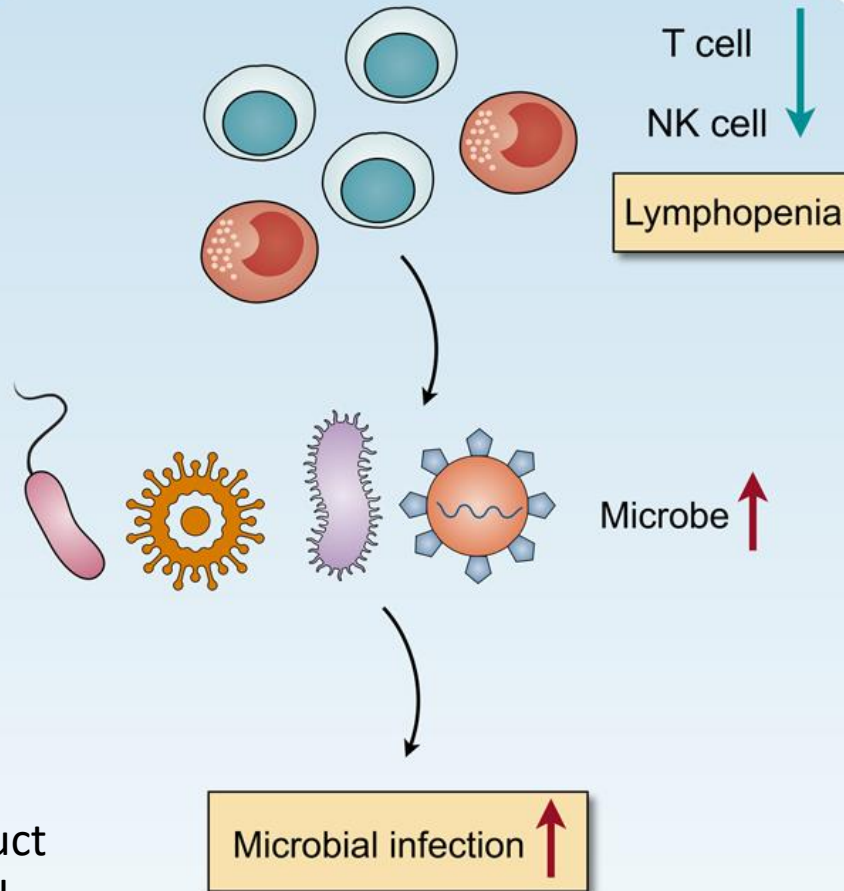
Lee, W.S, Nat
Microbiol.2020 May,
1185–1191

Clinical implications of SARS-CoV-2-induced immunopathology

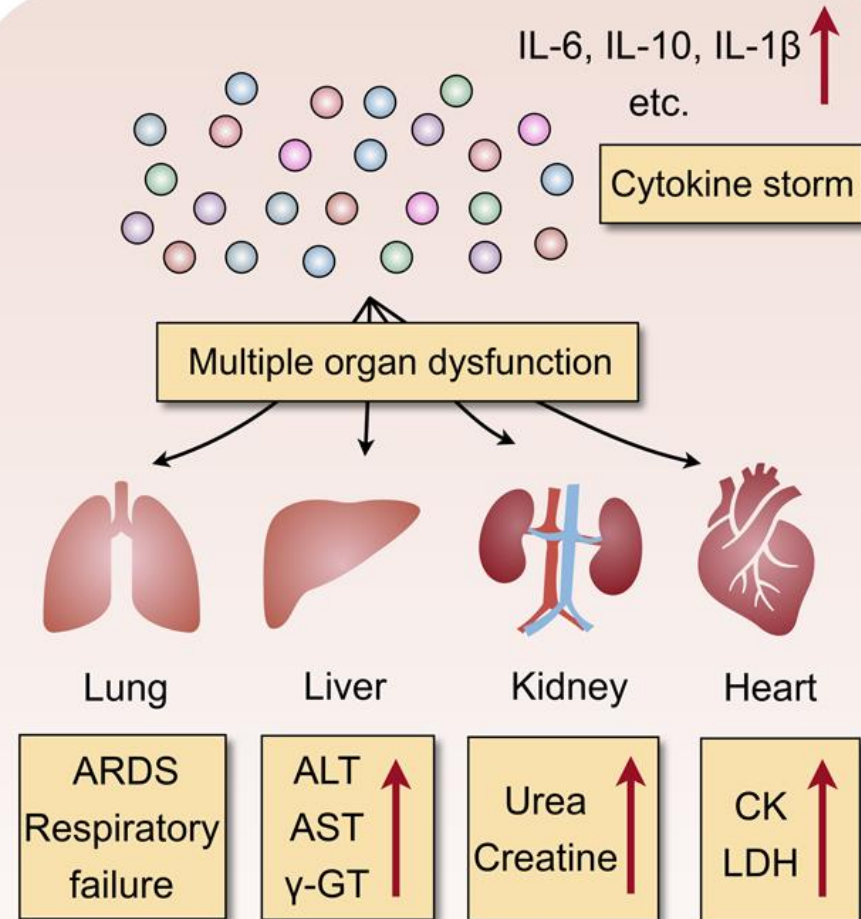


دانشگاه علوم پزشکی خدمات بهداشتی درمانی همدان

The effect of lymphopenia on microbiota infection

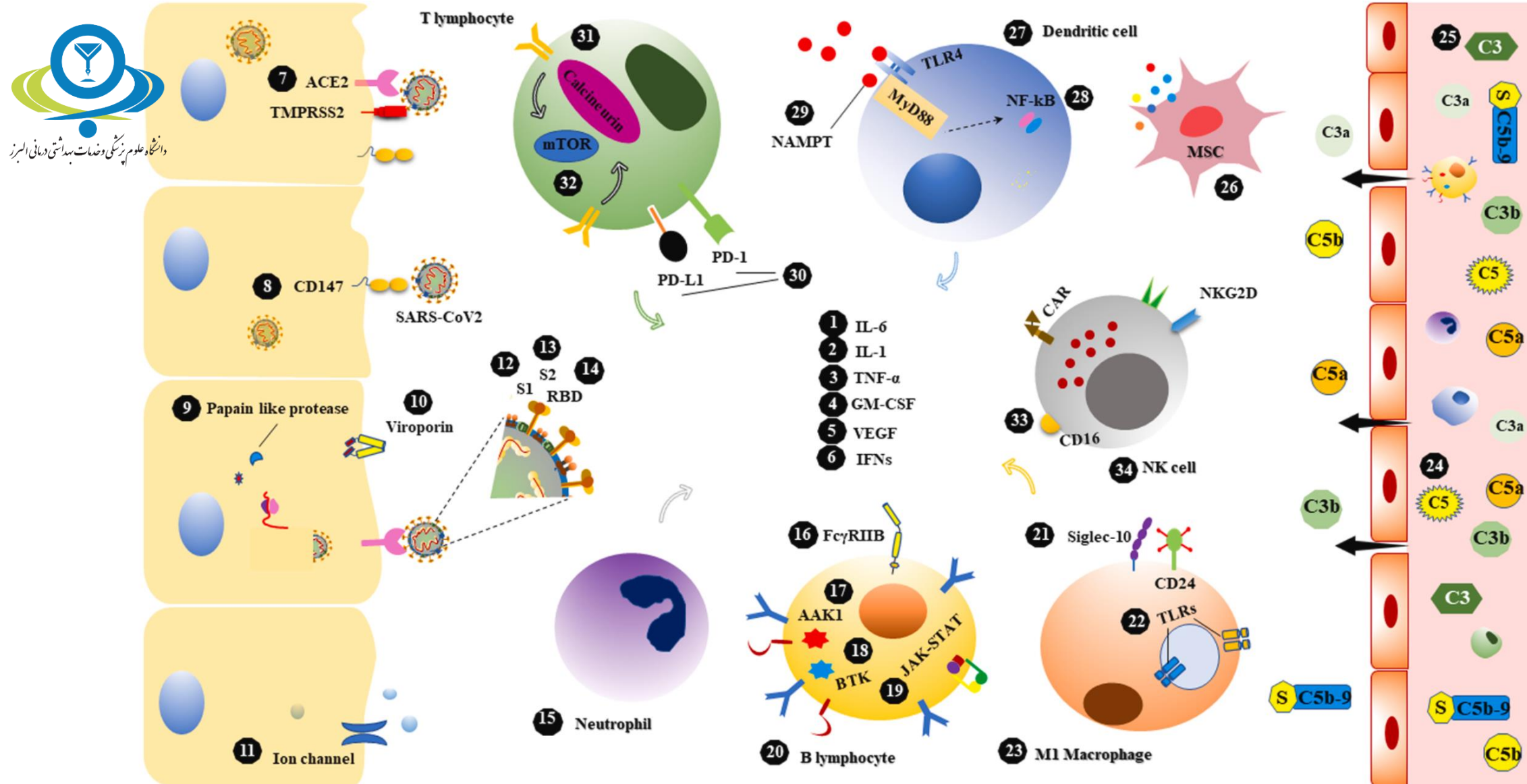


The effect of elevated cytokine production on severe syndromes



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Potential immunotherapeutic strategies for COVID-19



key immunotherapeutic approaches against COVID-19



Therapy	Example	Potential target	Mechanism of action
Passive immunotherapy	Convalescent plasma (CP) & hyperimmune globulin (H-IG)	Viral proteins (S, nucleocapsid, RBD, etc.), immune components (complement (C3a, C5a), proinflammatory cytokines, autoantibodies (FcRn & FcγR), DC (MHC II, IL-12, IL-10, IL-4, IL-1RA, CD80/CD86, endocytosis), Th1 (IL-6), Th2 (IL-4 & IL-5), Th17 (IL-17 A & F, CCL20 & IL-21), CD8 ⁺ T cell (cytotoxicity & proliferation), Treg (IL-10), B cell (FcγRIIB, proliferation and apoptosis)), M1 macrophage (migration)	Viral neutralization & clearance (opsonization, phagocytosis, ADCC, complement fixation), immunomodulation, ↓ inflammation, ↓ thrombotic problems
	Intravenous immunoglobulin	Immune components similar to CP & H-IG	Immunomodulation, ↓ inflammation, ↓ thrombotic problems
	Monoclonal antibody (CR3022, m396, F26G19, 1G10, 1A9, 2B2, 4B12, S309, dewetting antibodies)	Viral proteins (S, RBD, HR1), NAMPT, ion channels, ACE2, viroporins, CD147, CCR5, CD16, TLR3, G-CSF, MCP-1, IL-4, IL-10 & ITAM	↓ viral infection & spread, ↓ inflammation and tissue fibrosis
Kinase inhibitor	Fedratinib	JAK2	Block viral trafficking, mitigating cytokine storm (Th17 suppression, ↓ IL-22, IL-17 & GM-CSF), Slight noise in B cell & innate immunity
	Baricitinib	cyclin G-related kinases (JAK1 & JAK2), AAK1	Block viral membrane trafficking, ↓ pulmonary failure, immunomodulation
	Ruxolitinib	JAK1 & JAK2	Improving lung & kidney activity, ↑ hemodynamic balance, ↓ tissue inflammation (↓ CD8 ⁺ T cell proliferation via STAT1 blocking)
	Ibrutinib, acalabrutinib & zanubrutinib	BTK	Block B cell proliferation & cytokine release
	Sunitinib	RTK	Block viral membrane trafficking
	Erlotinib	EGFR	Block viral membrane trafficking

key immunotherapeutic approaches against COVID-19



Kinase inhibitor	Fedratinib	JAK2	Block viral trafficking, mitigating cytokine storm (Th17 suppression, ↓ IL-22, IL-17 & GM-CSF), Slight noise in B cell & innate immunity
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	Erlotinib	EGFR	Block viral membrane trafficking
Cytokine therapy	IL-6 inhibition (tocilizumab, sarilumab, siltuximab, sirukumab, clazakizumab)	IL-6, soluble and membrane bound IL-6R	Block proinflammatory downstream JAK-STAT signaling, ↓ cytokine storm, ↓ inflammation
	IL-1 inhibition (anakinra)	IL-1R	↓ cytokine storm, ↓ inflammation, ↓ lung injury
	TNF-α inhibition (etanercept)	TNF-α	Mitigating cytokine storm, ↓ inflammation, ↓ lung injury
	GM-CSF inhibition (mavrilimumab, TJ003234, gimsilumab, lenzilumab)	GM-CSFR & GM-CSF	↓ inflammation, ↓ lung injury
	VEGF inhibition (bevacizumab)	VEGF	↓ lung injury
	IFNs prescription	IFN-β-1b, IFN-λ	↑ antiviral defense, immunomodulation

key immunotherapeutic approaches against COVID-19



Complement inhibition	Eculizumab	C5	↓ inflammation, recovery of lymphocytopenia & thrombocytopenia, blocking C3 & C5 convertases, ↓ lung injury, reducing vascularization & microvascular injury, ↓ aberrant thrombosis & NETosis
	AMY-101	C3	
Engineered product	CD24-Fc	Siglec10	B cell tolerance, ↓ DC-mediated tissue inflammation, immunomodulation, recovery of T cell number & activity, ↓ leukocyte infiltration
	ACE2 blocking agents (soluble RBD, RBD-Fc, scFV, nanobodies, VHH domain)	ACE2	↓ viral infection, antiviral response induction (Fc-mediated phagocytic & NK cell activation)
	S protein blocking agents (OC43-HR2P, EK1, soluble ACE2, ACE2-Fc, hrACE2)	S protein (HR1, HR2)	↓ viral infection, antiviral response induction (Fc-mediated phagocytic & NK cell activation)
Cell-based therapy	NK cell supply (CYNK-001, NKG2D-ACE2 CAR-NK, bystander activation of self NK cell)	Self or non-self NK cell	Recovery of NK cell homeostasis & activity, ↑ antiviral defense
	MSC adoption	MSC	Immunomodulation, ↓ inflammation, ↓ viral replication, immunosuppression, tissue repair, lymphocyte recovery, ↑ tDC & Treg

key immunotherapeutic approaches against COVID-19



Immune potentiator	Immune checkpoint inhibitor	PD-1, PD-L1, TIM3	Recovery of NK & T cell activity & number, ↑ antiviral defense
	Tissue fibrosis blocker (pirfenidone)	TGF-β1, PDGF	↓ tissue fibrosis & EM formation, antioxidant, ↓ inflammation
	Growth factor	Thymosin, IL-7	↑ proliferation & differentiation of B, NK & T cells, ↑ NK & T survival, ↑ B cell maturation and immune homeostasis
Nonspecific therapy	PRR ligands (viral ds & ssRNA, CpG, PUL-042)	TLR3, TLR7, TLR9, TLR 2/6	↑ IFNs response & viral eradication
	Antimicrobial peptide (defensin)	Viruses, bacteria & fungi	↑ viral defense, altering the cytokine milieu of the lung
	Calcineurin inhibitor (tacrolimus, cyclosporine)	Calcineurin, viral reproduction	Immunosuppression, ↓ inflammation & cytokine storm, ↓ viral replication
	Corticosteroid (dexamethasone, ciclesonide)	IL-1, TNF-α, PG, NO & ROS	↓ lung injury & inflammation, ↓ ARDS, immunosuppression
	NSAID (indomethacin, ibuprofen, naproxen)	Cyclo-oxygenase, viral reproduction	↓ inflammation, ↓ viral replication
	mTOR inhibitors (rapamycin, sirolimus)	mTOR, memory B cell, viral reproduction	↓ ADE, ↓ viral replication & spread
	Metabolic enzyme blockers (6-mercaptopurine, mycophenolate mofetil, 6-thioguanine)	WBC proliferation, DNA, guanine nucleotide, Papain-like protease	Immunosuppression, ↓ T cell progenitor proliferation, ↓ inflammation, DNA methylation/alkylation, block guanine synthesis, ↓ viral replication & spread

*Thank You
For Your Attention*

