Explaining Long COVID and Post-vaccine Syndrome: Exosomes, the Thymus and Immunosenescence

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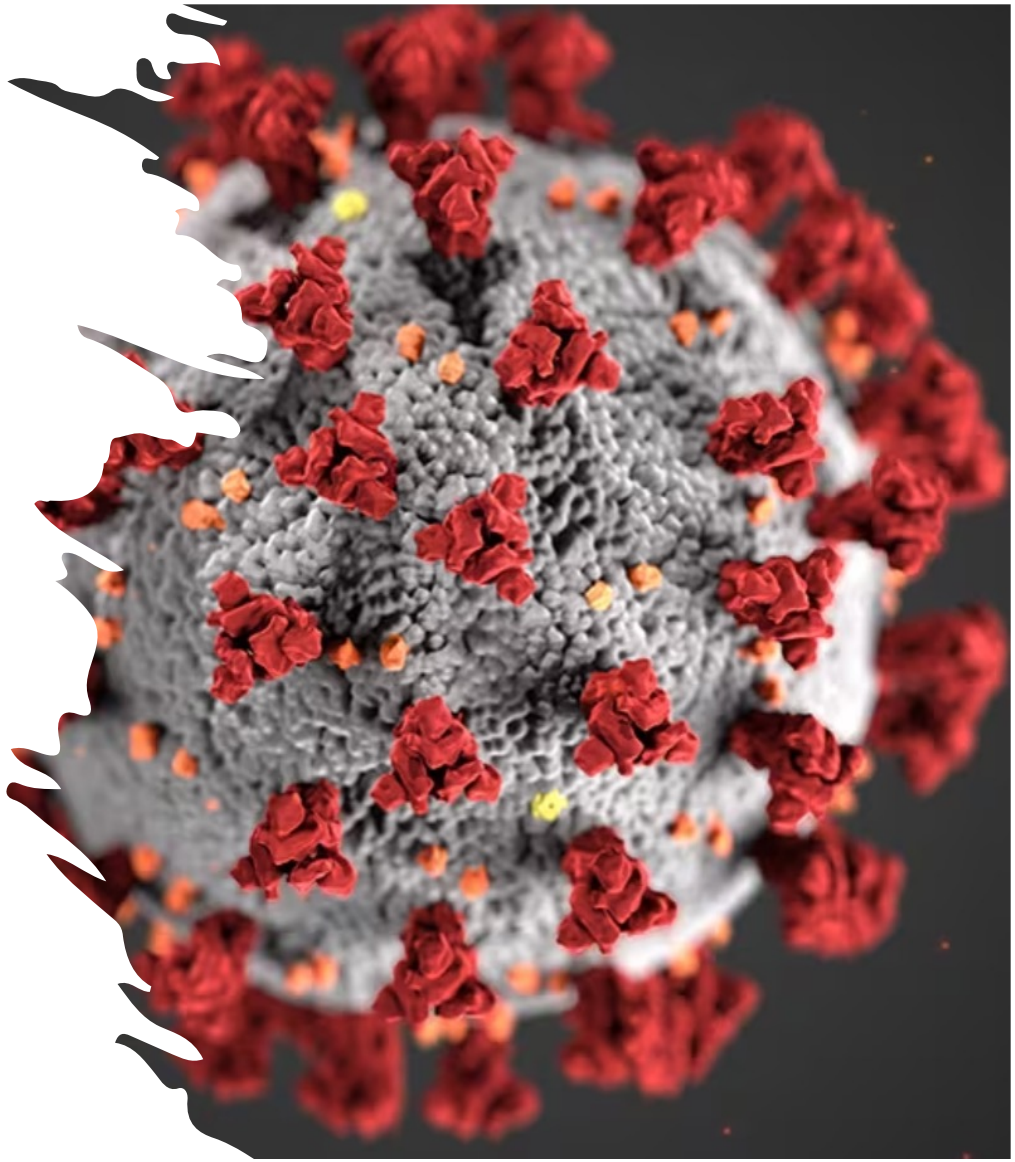


Outline

- Very brief introduction
- Exosomes
- Thymus
- Summary

Why the mRNA vaccines are more likely to cause damage to the organs than an infection

- SARS-CoV-2 infection begins in the lungs where most of the action is
  - The virus only escapes the lungs into the vasculature when the host is immune compromised
- The vaccine is injected into the arm muscle, past both the mucosal and the vascular barrier
- The vaccine mRNA is specially constructed to be very sturdy, resisting enzymatic breakdown and producing spike protein for a long time
- *Muscle cells take up the nanoparticles and synthesize large amounts of spike protein, releasing it, as well as the mRNA that carries the code, and the toxic cationic lipid, into exosomes that are dispersed throughout the body*
- The spike protein causes an inflammatory response wherever it goes, potentially leading to neurodegenerative disease and heart damage
- Much of the pathology may be related to antibodies to spike and molecular mimicry

Problems with the vaccine spike protein*

- "Is it possible the spike protein itself causes the tissue damage associated with Covid-19?”
- A “furin cleavage site” in the spike protein allows S1 subunit to be snipped off and released into circulation
- The S1 subunit localizes to the endothelia of microvessels in the mouse brain and is a potent neurotoxin."
- "So the spike S1 subunit of SARS-CoV-2 alone is capable of being endocytosed by ACE2 positive endothelia in both human and mouse brain, with a concomitant paucicellular microencephalitis that may be the basis for the neurologic complications of COVID-19."

*https://beta.regulations.gov/document/FDA-2020-N-1898-0246
Comment from J. Patrick Whelan MD PhD
Food and Drug Administration on Dec 8, 2020

Exosomes

The Big Picture

- Exosomes released by transfected muscle cells and immune cells circulate throughout the body delivering spike protein and spike mRNA to distant cells
- Exosomes can reach the brain directly from the deltoid muscle, via nerve fibers, never having to cross the blood-brain barrier
- The spike protein enters neurons and other cells via ACE2 receptors and induces senescence, leading to neurological disease, cardiovascular disease, diabetes, and vascular aging

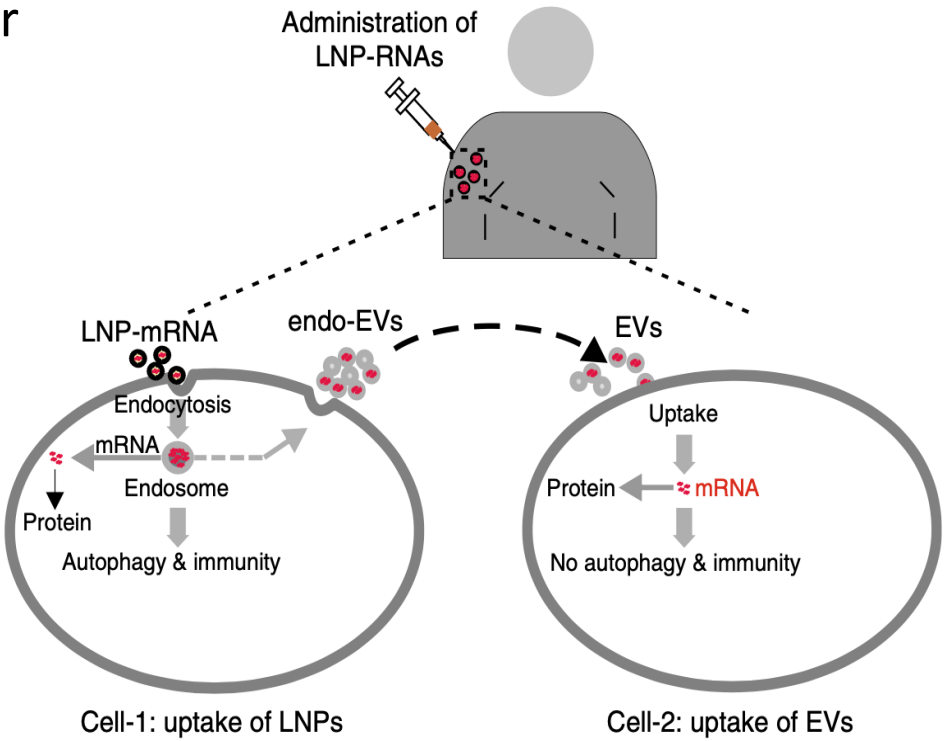
SARS-CoV-2 Spike Activates Human Microglia in the Brain via Exosomes Loaded with miRNAs*

- Exosomes are extracellular vesicles that are released by stressed cells and serve as a communication network throughout the body
- "SARS-CoV-2 spike transfected cells release a significant amount of exosomes loaded with microRNAs such as miR-148a and miR-590”
- "MicroRNAs get internalized by human microglia in the brain”
  - Induce a strong inflammatory response
- "These results uncover a bystander pathway of SARS-CoV-2 mediated CNS [central nervous system] damage through hyperactivation of human microglia"

*Ritu Mishra and Akhil C. Banerjea. Frontiers in Immunology 2021; 12:656700

mRNA Transfer to Other Cells via Exosomes*

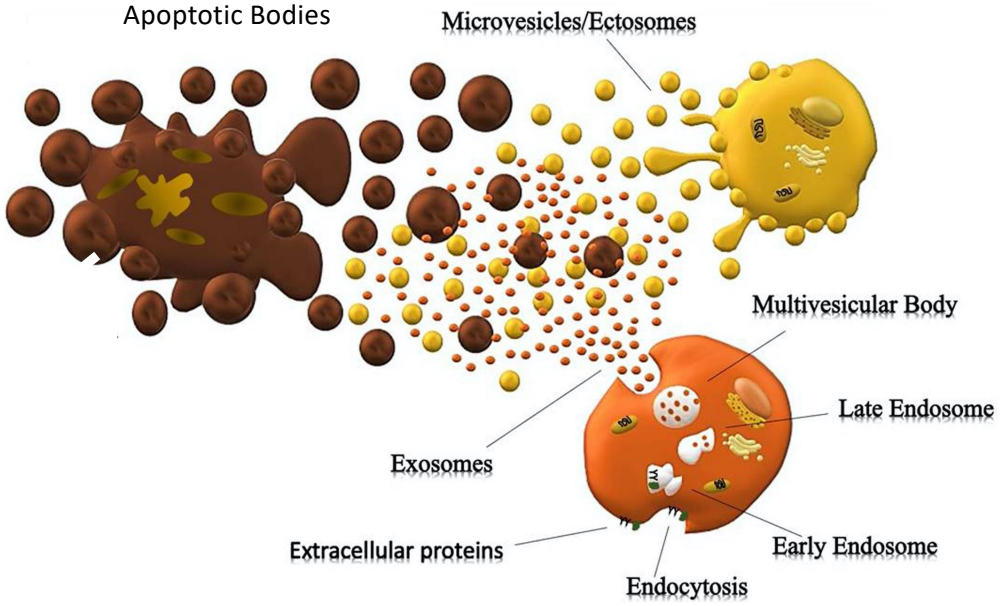
- Lipid nanoparticles containing mRNA coding for a specific protein are taken up by cells at the injection site and repackaged into endosomal vesicles that are then released into the circulation as exosomes
- *The cationic lipid is included in the exosomes*
- These exosomes can be taken up by other cells which then *translate the RNA into protein*
- EVs= extracellular vesicles = exosomes



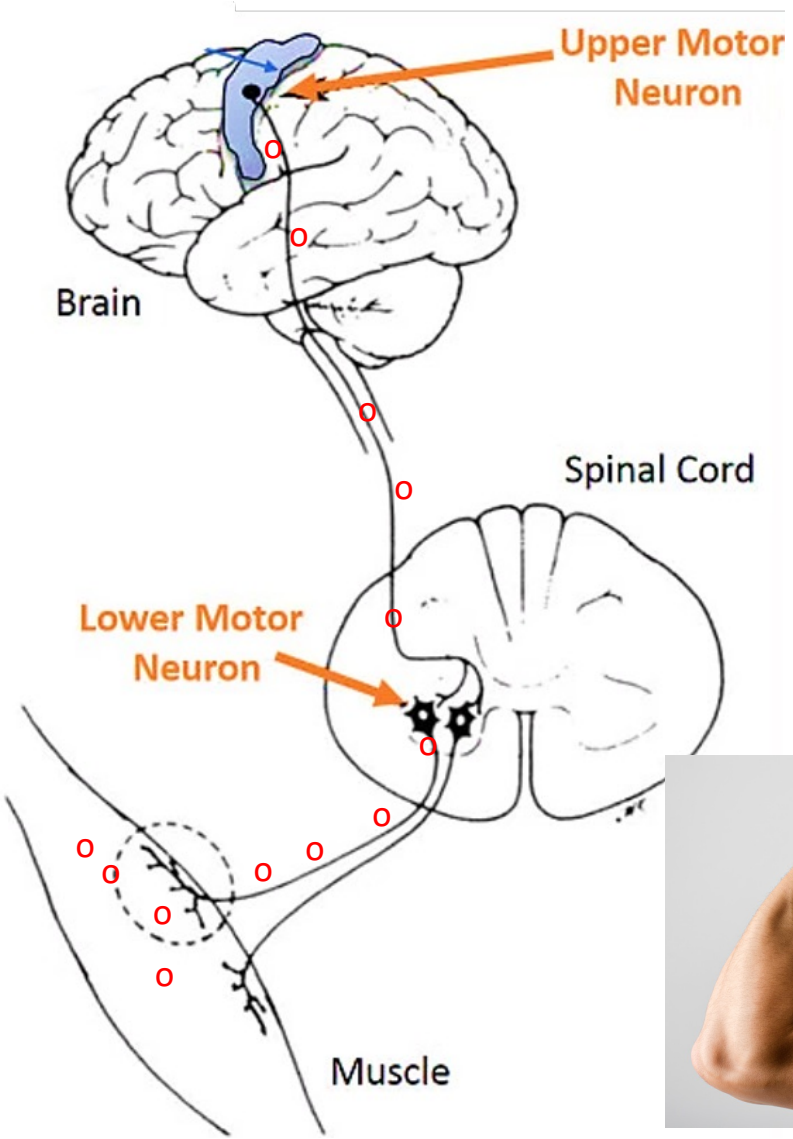
*Marco Maugeri et al. Nature Communications 2019; 10: 4333.

“Exosomes and Extracellular RNA in Muscle and Bone Aging and Crosstalk”*

- "EVs [extracellular vesicles] released by cells of one tissue or organ can travel in the circulation and may bind to cells of another tissue or organ through receptor-ligand interactions[14]."
- "Overall, evidence is accumulating that the cargo of muscle-derived exosomes can be changed under pathological conditions and that exosomes contribute to ... the propagation of pathogenic responses ... to distant cells.”



*Weiping Qin and Sarah L Dallas. Curr Osteoporos Rep. 2019; 17(6): 548–559.



Exosomal transport to the brainstem nuclei?

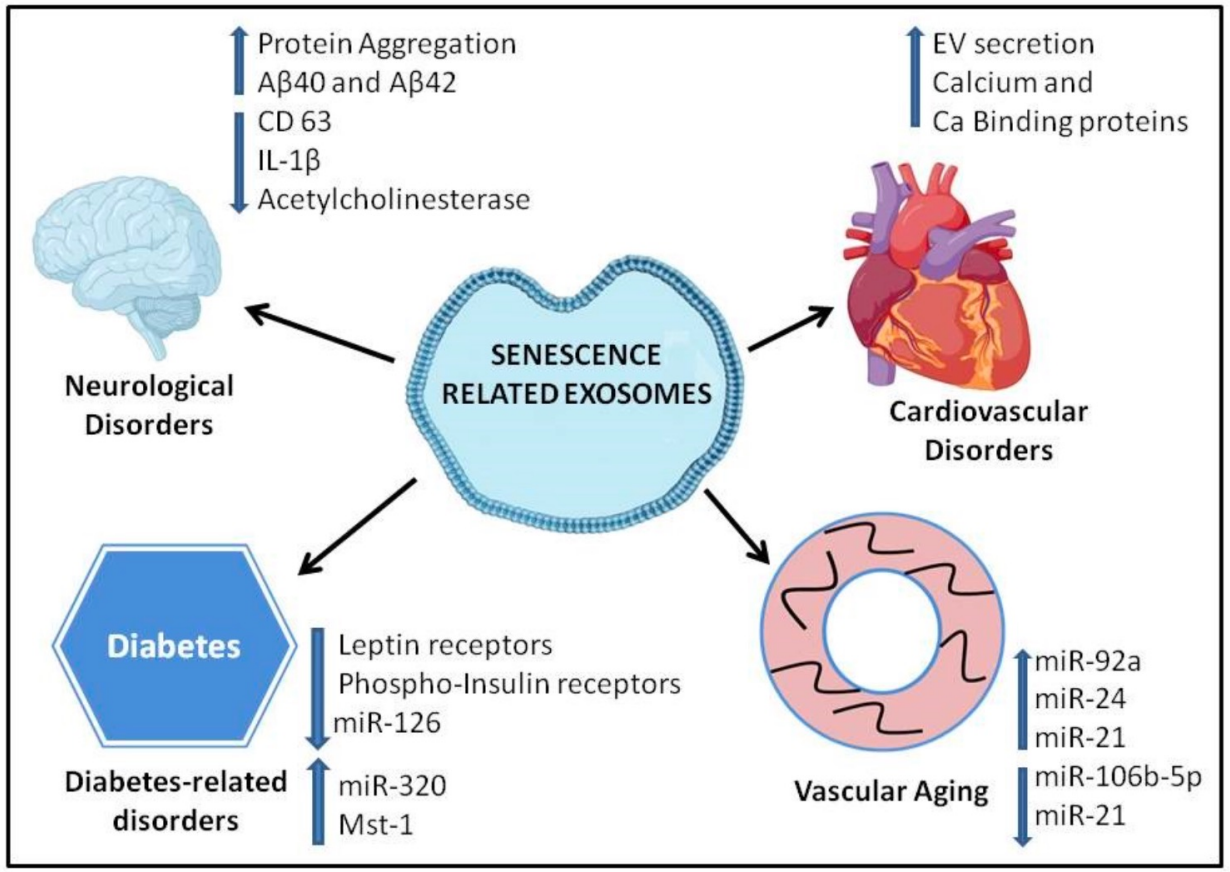
I hypothesize that exosomes released from the transfected deltoid muscles are actively transported by molecular motors along the axon of the lower motor neuron to the spinal cord, and then, relayed to the upper motor neurons in the brainstem nuclei in a second axonal pathway

SARS-CoV-2 causes senescence in human cells*

"S1-induced ACE2 stimulation, and increased ROS, could result in surpassing the senescent cell threshold, leading to feed-forward increases in senescent cell burden and resulting morbidity and mortality."

"Increased abundance of senescent cells might contribute to the brain fog/anxiety, physical inactivity/lethargy/muscle weakness/frailty, lung fibrosis/dyspnea, and arthritis/generalized pain symptoms that can persist after acute SARS-CoV-2 infection, the so-called post-acute sequelae of COVID-19."

*U Tripathi et al. Aging (Albany NY). 2021; 13(18): 21838-21854.



Senescence-related Exosomes*

"Extracellular vesicles (EVs) secreted from senescent cells have been implicated in cardiovascular diseases, diabetes, neurological disorders, and vascular aging."

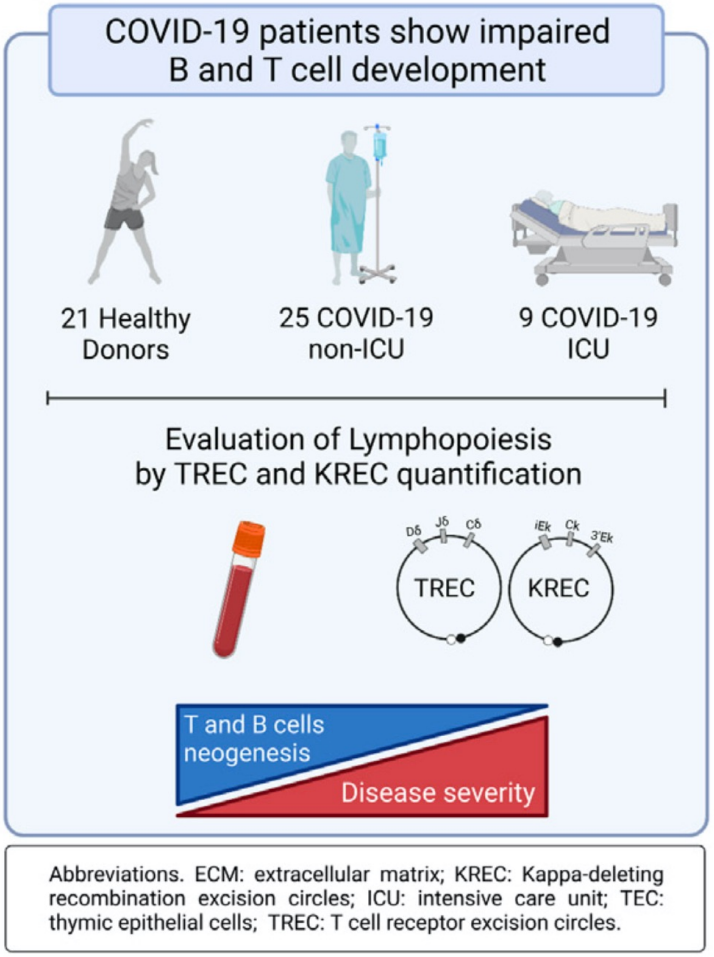
*Figure 2. Sherin Saheera et al. Cells 2020; 9: 1974.

Thymus

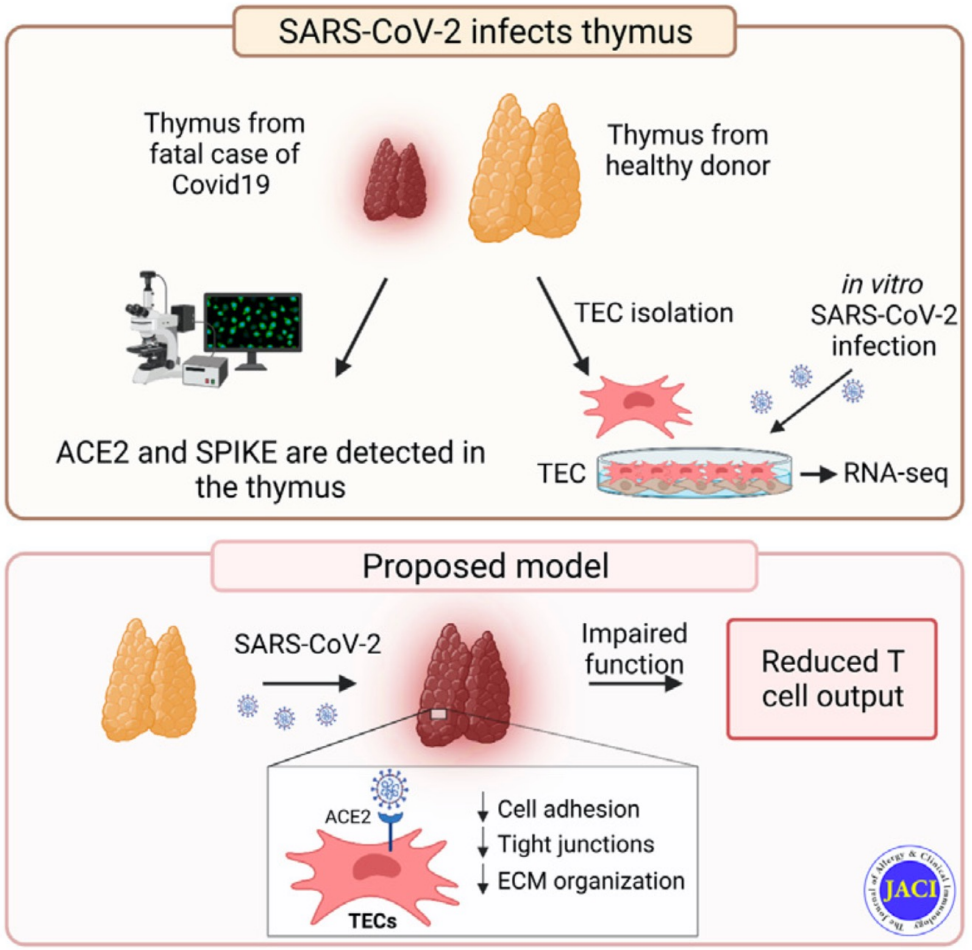
The Big Picture

- Activated dendritic cells (responding to spike) return to the thymus and promote thymic involution, a marker of biological aging
- There is an easy pathway from the axillary lymph nodes to the thymus via lymphatic vessels
- Thymic epithelial cells (TECs) express ACE2 and can be attacked by the spike protein, damaging them
- Damaged TECs are unable to prevent self-reactive T cells from escaping the thymus into the periphery
  - This leads to accelerated autoimmune disease
- Damaged TECs also promote loss of naïve T cells that can respond to new exposures (immune suppression)

SARS-CoV-2 infection of thymus induces loss of function which correlates with disease severity*



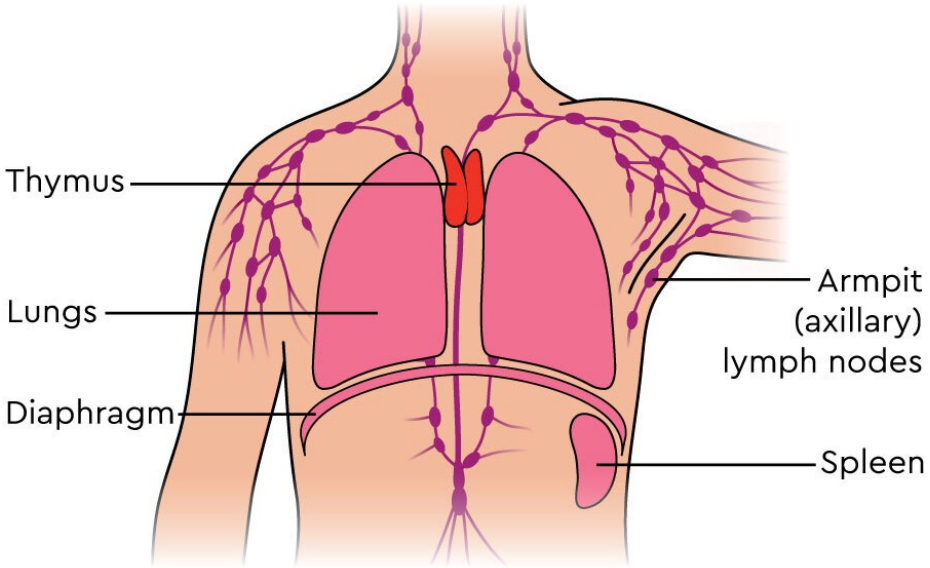
Abbreviations. ECM: extracellular matrix; KREC: Kappa-deleting recombination excision circles; ICU: intensive care unit; TEC: thymic epithelial cells; TREC: T cell receptor excision circles.



*Marco Rosichini et al. J Allergy Clin Immunol 2023; 151(4): 911-921.

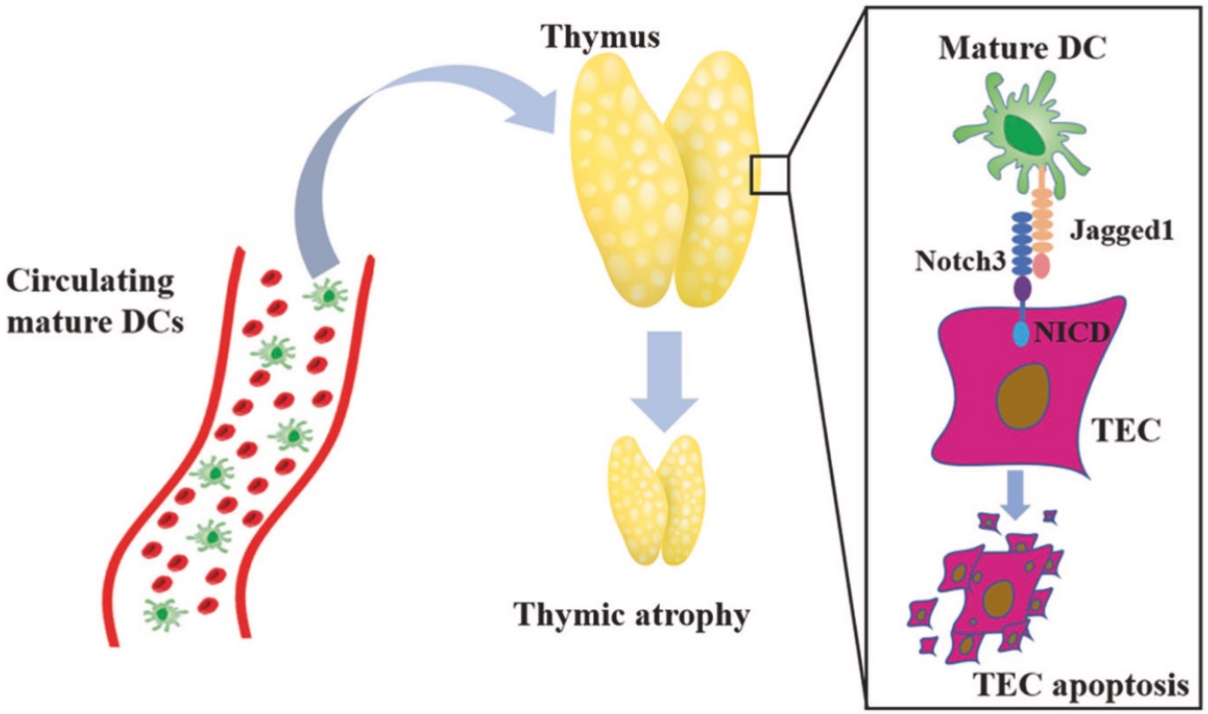
NLRP3 Inflammasome

- The ionizable cationic lipids in the vaccines can cause lysosomal rupture*
- Lysosomal rupture induces NLRP3 inflammasome**
- NLRP3 inflammasome causes accelerated thymic involution***
  - Thymic involution is a marker for biological aging
- Major cause of immunosenescence and inflammaging****



*J Forseter, III et al. Biomater Sci. 2022;10(19): 5566-5582.
**H Lima, Jr. et al. Cell Cycle. 2013; 12(12): 1868-78.
***Yun-Hee Youm et al. Cell Reports 2012; 1: 56-68.
****R Thomas et al. Immunity and Ageing 2020; 17: 2.

Thymic involution – immunosenescence*

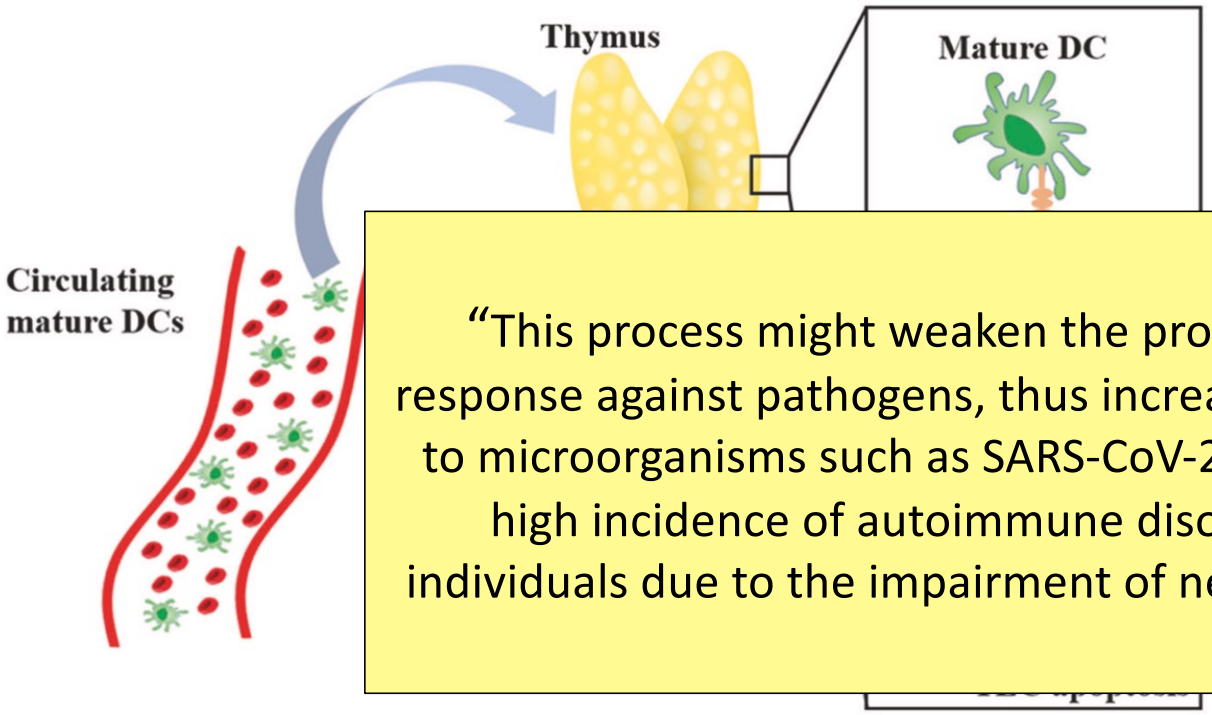


- In response to infection, some activated dendritic cells (DCs) return home to the thymus and expose the TECs to the offending antigen (e.g., spike)
- These activated DCs can induce TEC apoptosis by activating the Jagged1/Notch3 signaling pathway
- This results in acute atrophy of the thymus

DC = Dendritic Cell
TEC = Thymic Epithelial Cell

*Figure 7. Haojie Wu et al. Cell Death Discovery 2021; 7: 225.

Thymic involution – immunosenescence*



"This process might weaken the protective immune response against pathogens, thus increasing susceptibility to microorganisms such as SARS-CoV-2 and leading to a high incidence of autoimmune disorders in older individuals due to the impairment of negative selection."

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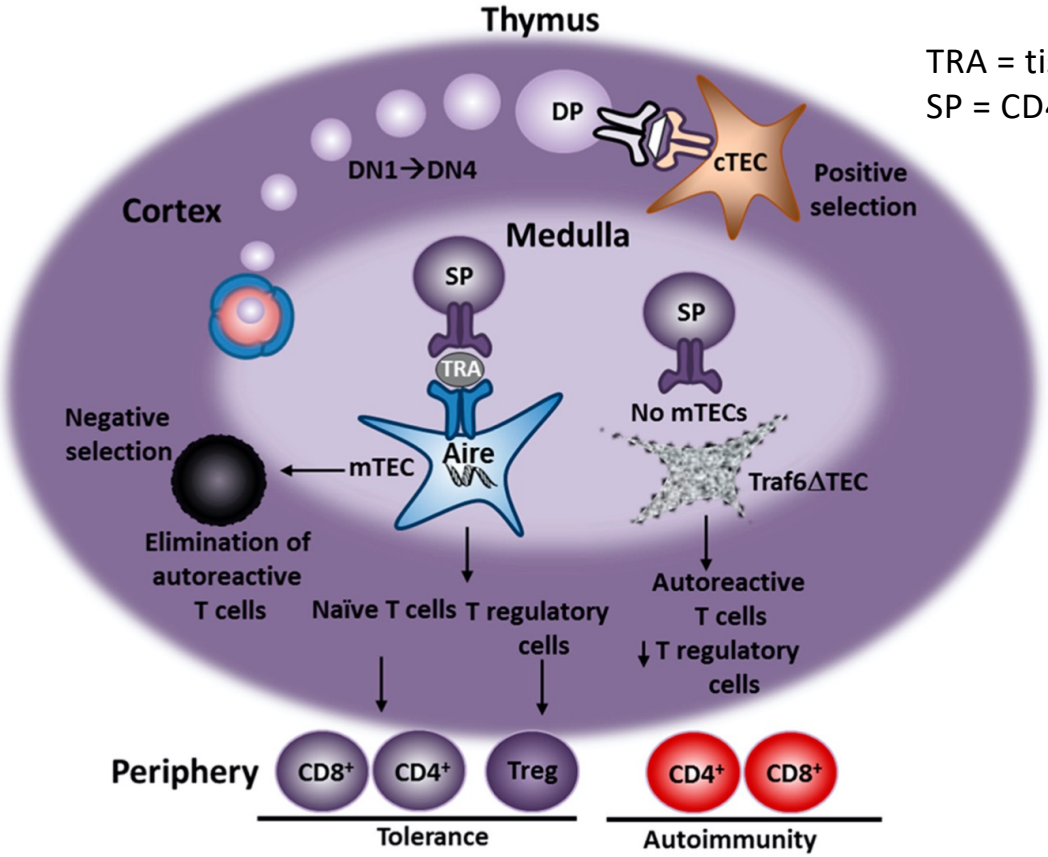
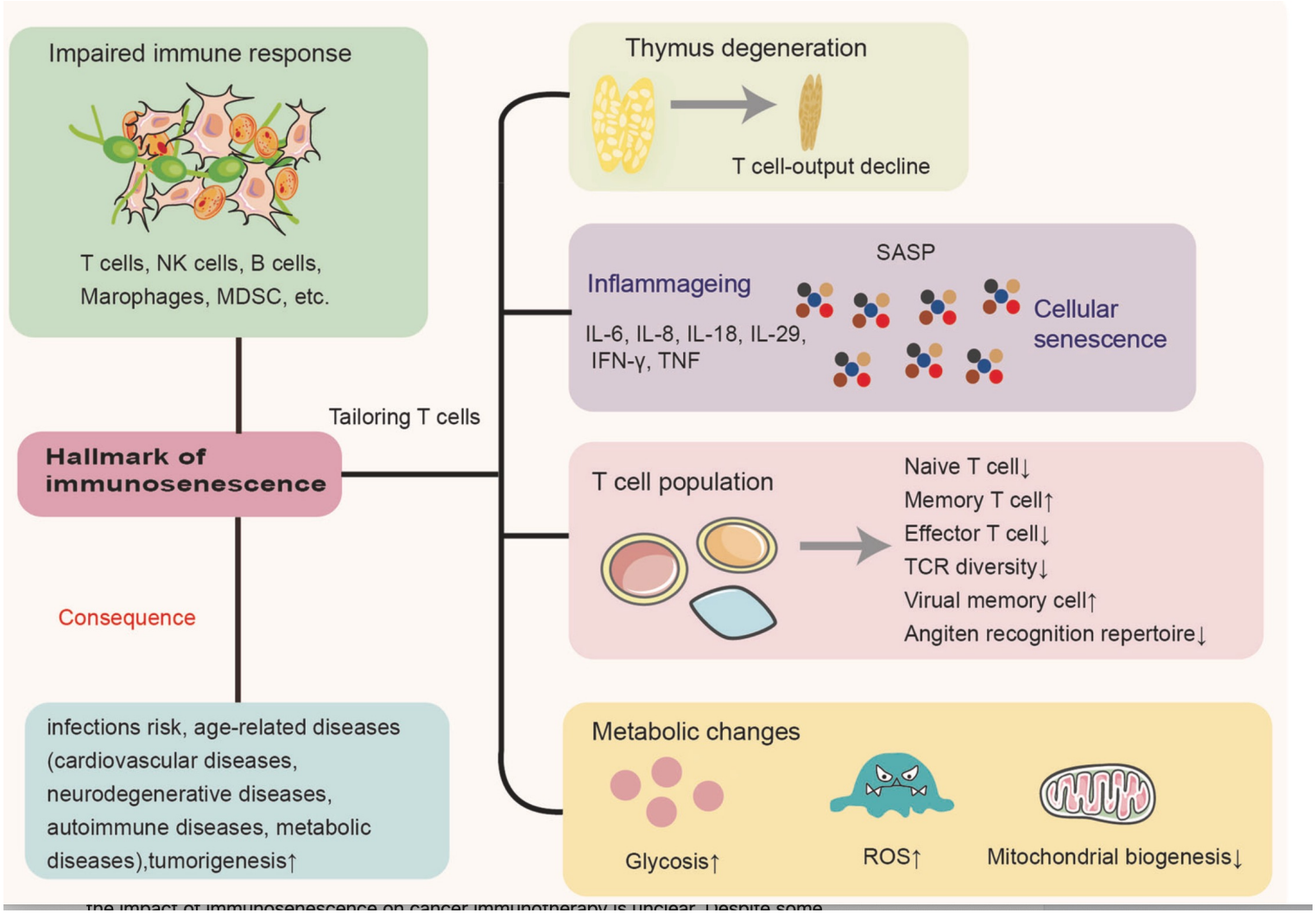
Mice Deficient in mTECs Develop Autoimmune Liver Disease*



TRA = tissue reactive antigens
SP = CD4+ or CD8+ "single positive" T cells

- Mice were engineered with a mutation that led to depletion of medullary thymic epithelial cells (mTECs)
- This resulted in an inability to remove self-reactive T cells and an inability to induce naïve T cells (protective)
- The result is immune suppression and autoimmune disease

*K Alexandropoulos et al. Int. J. Mol. Sci. 2015, 16, 1980-2000

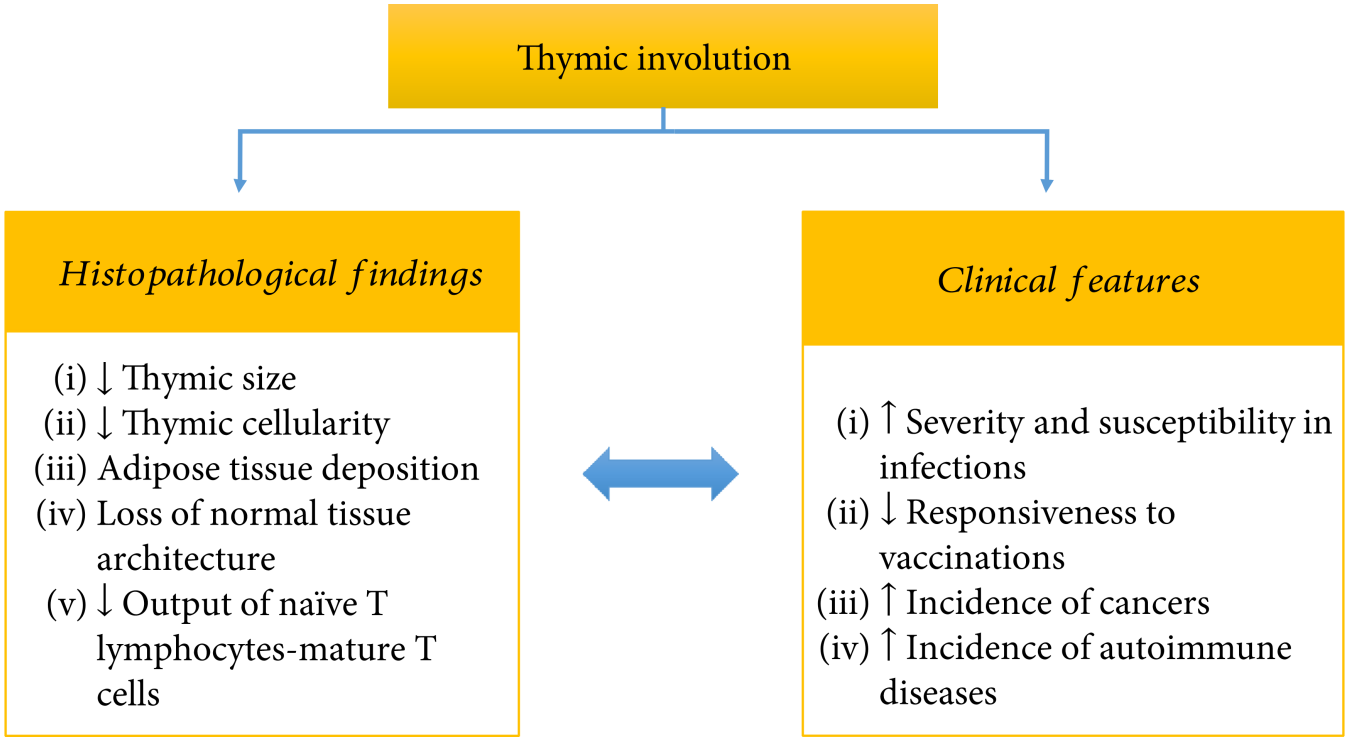


SASP = Senescence Associated Secretory Phenotype

Hallmarks of Immuno-senescence*

***Figure 2:** Z Liu et al. Sig Transduct Target Ther. 2023; 8: 200.

Thymic Involution and Aging*



*Alexandra Barbouti et al. Oxid Med Cell Longev. 2020; 2020: 7986071.

Summary

- Exosomes released by transfected muscle cells and immune cells may play a critical role in distributing the spike protein, spike mRNA and ionizable cationic lipid to distant sites
- Exosomal transport along nerve fibers to the brain stem nuclei is a direct path on the other side of the blood-brain barrier
  - Spike protein activates ACE2 receptors in the brain and causes senescence and neuronal injury
- Activated dendritic cells migrate to the thymus where the spike protein and the ionizable cationic lipid can be expected to be toxic to the thymic epithelial cells (TECs)
- Loss of TECs in the thymus is a direct pathway towards thymic involution, inflammaging and immunosenescence
  - Increased risk to infection, autoimmune disease and cancer