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Loss of Immune Tolerance in Long COVID

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ABOUT

Jamie Kunkle, ND
Tickborne Illness & Lyme Disease | Autoimmunity | TCM | Environmental Medicine | Long Covid

Dr. Kunkle has a diverse skill set including (but not limited to): Lyme/infectious disease, autoimmunity, environmental medicine, pain management, hormone regulation, metabolic/weight loss optimization, and neuropsychiatric conditions to name a few. Dr. Kunkle is skilled in low dose immunotherapy and low dose antigen therapy for treatment of allergies, is trained in hyperbaric oxygen therapies, botanical medicine including Chinese herbs, and intravenous/intramuscular nutrition. Dr. Kunkle is an active member of International Lyme and Associated Diseases Society (ILADS).

Dr. Jamie Kunkle ND has been practicing as a dual licensed Naturopathic Doctor and East Asian Medicine Practitioner (Acupuncturist) for 10 years. He currently holds a Naturopathic Doctor's license in California and will be pursuing acupuncture licensure in the future. He recently practiced primary care and infectious disease management in Brattleboro, Vermont where lyme disease and co-infections are endemic. Dr. Kunkle received a Bachelors of Science in Neuroscience from the University of Pittsburgh. He received his masters in acupuncture and traditional Chinese medicine and doctorate in Naturopathic Medicine at Bastyr University in Seattle, WA.

WHAT WE WILL COVER

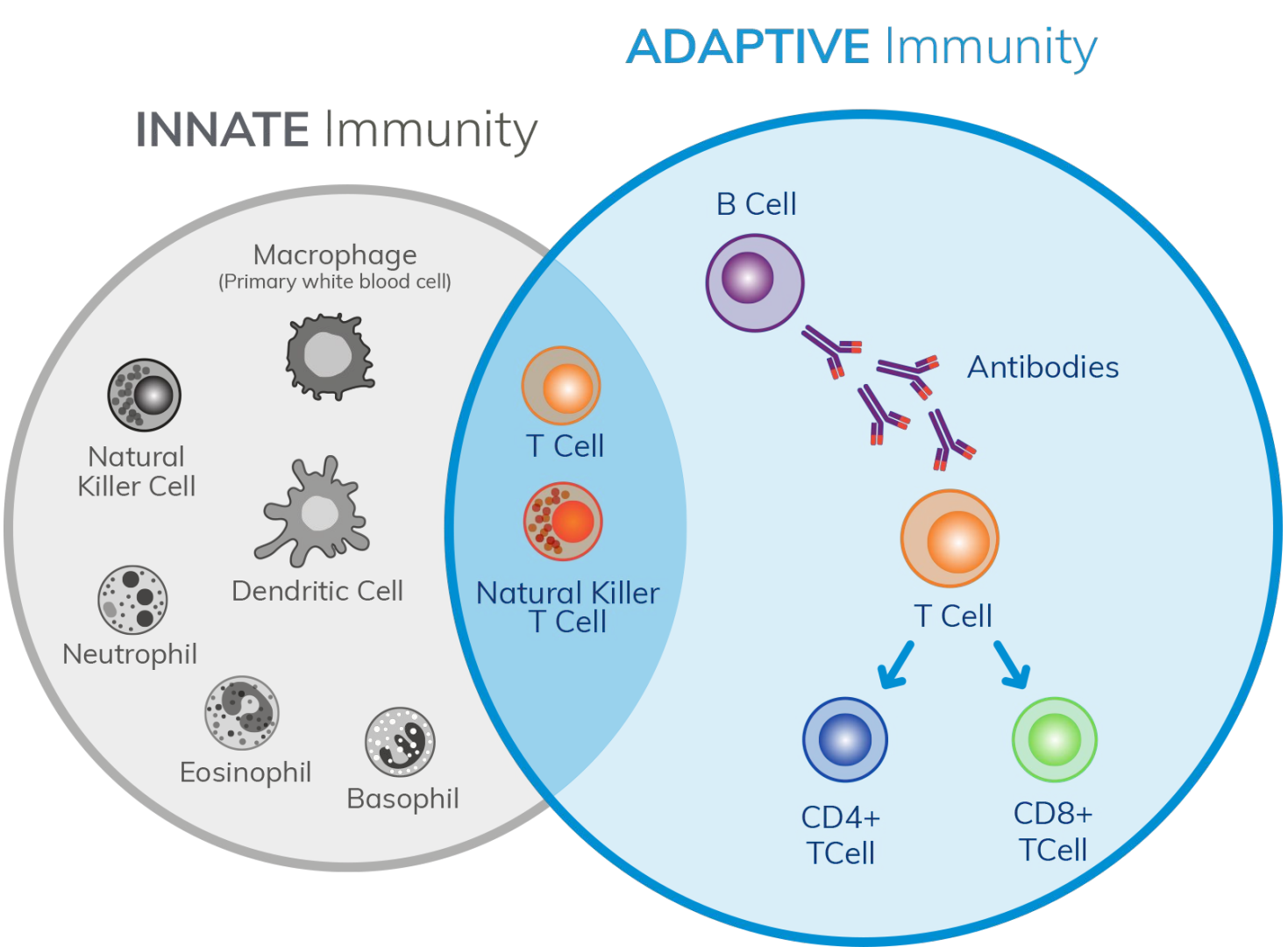
- What is immune tolerance and what are the two types?
- How might the immune system lose this tolerance?
- What are some possible mechanisms for how this may occur in Long COVID?
- How does this manifest clinically, what diagnoses are associated with a loss of immune tolerance?
- How we can support the body in restoring immune tolerance?
- What emerging therapies may be beneficial to reach these goals?

Defining Immune Tolerance

- Immune tolerance is defined as the normal (healthy) functioning state of the immune system in retaining homeostasis.
- When working correctly, the immune system responds to appropriate pathogens or toxins efficiently while avoiding or limiting adverse responses to self.
- Loss of immune tolerance can lead to autoimmune diseases, allergies, reactivation of infections and other multisystem inflammatory syndromes (i.e. CIRS)
- Too much immune tolerance pathway induction can lower our body's ability to fight pathogens effectively (too much of a good thing?)

What Happens Normally During an Infection Exposure?

- The first step is the signaling of antigen-presenting cells (APCs), which include B lymphocytes (B cells) to T lymphocytes (T cells)
- T cells then attack and destroy the foreign organisms
- The antigen-specific antibodies produced by the B cells remain to facilitate clearance of the foreign antigen
- If you are infected with the same antigen again, the immune system will recognize and attack it often using a combination above, preventing illness and often minimizing symptoms
- This is known as adaptive immunity


ADAPTIVE Immunity
INNATE Immunity
Macrophage
(Primary white blood cell)
Natural
Killer Cell
Dendritic Cell
Neutrophil
Eosinophil
Basophil
T Cell
Natural Killer
T Cell
B Cell
Antibodies
T Cell
CD4+
TCell
CD8+
TCell

Central Versus Peripheral Tolerance

- Central tolerance is primarily in lymphoid organs (places where immune cells originate like the thymus/T-cells and bone marrow for B-cells)
- Occurs during early immune cell development
- Peripheral tolerance is located in secondary lymphoid organs and peripheral tissues (lymph nodes, spleen and mucosal tissue)
- Occurs after immune cells have matured and entered circulation
- Central tolerance acts as the first checkpoint during immune cell development, eliminating MOST self-reactive (considered “defective” cells).
- Peripheral tolerance provides additional safeguards in the body’s tissues, suppressing or deleting any persisting self-reactive cells that escape the central process.

SARS-CoV-2 Infection

- COVID infection can induce immune intolerance through several mechanisms:
  - Severe infection is associated with immune dysregulation including lymphocytopenia (reduced lymphocytes) and T-cell exhaustion and can lead to disruption in immune tolerance
  - High cytokines (inflammation signals) may lead to impaired adaptive immunity
  - Persistent or overactivation of complement system (cross talk between innate and adaptive immune systems)
  - Abnormal activation of mast cell systems has been proposed as another mechanism in which normal immune tolerance is influenced adversely

COVID-19 MRNA Vaccination

- Induces immune tolerance through upregulation of IgG4 (antibodies that can reduce inflammation but are not effective at regulating active infections)
- Innate immune reprogramming: may reprogram existing innate immune responses increasing potential for infection reactivation or worsening chronic infections
- Impairs activation of CD4 and CD8 T-cells reducing normal antibody production and influencing adaptive immune tolerance (antibody production).
- Has a potential to activate mast cell systems
- Excessive or too frequent of boosting may create an immunosuppressive environment especially in folks with chronic immune disorders or chronic infections

Spike Protein and Immune Tolerance

- Spike protein is the only commonality between COVID infection and COVID MRNA vaccination
- The Spike Protein of SARS-CoV-2 functions to facilitate viral entry into host cells and is a major target of immune responses
- Spike protein may antagonize certain innate immune pathways by interacting with interferon regulatory factor 3 (IRF3) which can dampen the initial antiviral response
- Spike is recognized by pattern recognition receptors such as TLR2 on macrophages and epithelial cells triggering pro-inflammatory cytokine production of NF-Kappa-B

Spike Protein Toxicity

- Can bind to ACE2 receptors found in heart, blood vessels, lungs, kidneys, intestines and brain leading to inflammation, vascular dysfunction and organ damage
- This can trigger cytokine (inflammatory) response directly in these organs
- Spike protein can induce mitochondrial dysfunction, oxidative stress (redox shift) and celluar metabolic changes which may lead to long term tissue injury
- Coagulation dysfunction, microclot fibrinaloid formation may result
- Microbiome loss and disruption of gut barrier and blood brain barrier may influence GALT (gut immune system) and microglia (brain immune system)

Fibrin and Microclots

- Fibrin, a blood-clotting protein is formed in response to infection, heightened inflammatory signaling or direct mechanical injury
- Fibrin is beneficial if there is an outside injury (like a wound) so that bleeding may stop promptly (extrinsic pathway of clotting)
- Fibrin is less beneficial functionally when it occurs inside the vascular space (especially small capillaries—known as intrinsic pathway of clotting)
- Fibrinogen can polymerize into and anomalous form of fibrin that is amyloid in character.
- Build-up of amyloid has been previously studied in Alzheimer’s and other metabolic diseases

Amyloid, Fibrinaloids, Tau, Prions and Immune Tolerance

- Each of these plays a complex role in immune tolerance
- In some ways their presence modulates normal immune tolerance in T-regulatory cells, inhibiting CD4s, inhibiting cytokines, possibly even training system to identify biofilm elements
- Too much (and in the wrong configuration) can cause disruption
- Abnormal protein malformations (novel epitopes) may lead to loss of immune tolerance and ability for immune system to distinguish self from pathogen
- In some cases slight disruptions in the configuration of these proteins can lead to changes in immune response (for better or worse)

Microbiome and Immune Tolerance

- Bifidobacterium support normal immune regulation and tolerance in gut and gut associated lymphoid tissue (GALT)
- Spike may damage gut barrier and increase inflammation locally in epithelium
- Spike protein may directly damage bifidobacterium and possibly other microbiome balance
- This may lead to loss of immune tolerance in the gut
- Some autoimmune disorders (not just gut centered autoimmunity) may start in this region

Mast Cell Activation and Immune Intolerance

- Chronic mast cell activation correlates with elevated auto-antibody formation targeting vascular and neuronal tissues often making immune intolerance worse.
- Disrupts blood brain barrier (and gut barrier) worsening inflammation and antibody effect in central nervous system
- May worsen vascular inflammatory response leading to more fibrinaloid activity
- Generally correlated with increased autoimmunity risk (see pentad/septad model)

Treatment Strategies

- Antioxidants (Glutathione, curcumin, resveratrol, EGCG, luteolin, quercetin)
- Mast Cell stabilization (natural and drug treatments)
- Coagulation therapy (fibrinolytic enzymes like nattokinase, lumbrokinase)
- Low dose immunotherapy (LDI)

- Drug Treatments:
- Low dose naltrexone (reduced IL-6, TNF alpha), inhibits TLR4 mediated inflammation
- Anti-coagulants: aspirin, Plavix, Eliquis, heparin etc.
- HIGH DOSE IVIG
- Rituximab (Rituxan)
- IL-6 Inhibitors
- JAK/STAT inhibitors

CONCLUSION

- Imbalances in normal Immune tolerance is a complex issue but should be considered following any post viral or post immunologic syndrome
- Spike protein is the only common factor in COVID infection and Vaccination related illness, perhaps it could be an appropriate therapeutic target in working with immune tolerance issues
- There is a wide range of therapeutic options to meet the needs of the individual but like most complex illnesses and individualized approach is certainly required
- Defining where the dysfunction may be occurring in the immune system can better allow targeted therapies
- Palliative therapies have their place (putting out the fire is sometimes appropriate)