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Neuroimmunology: The undeniable connection between the nervous and immune systems

August 9, 2019 Presented by Dr. Ward Jones

Goals for Today

Review the immune system in the traditional sense

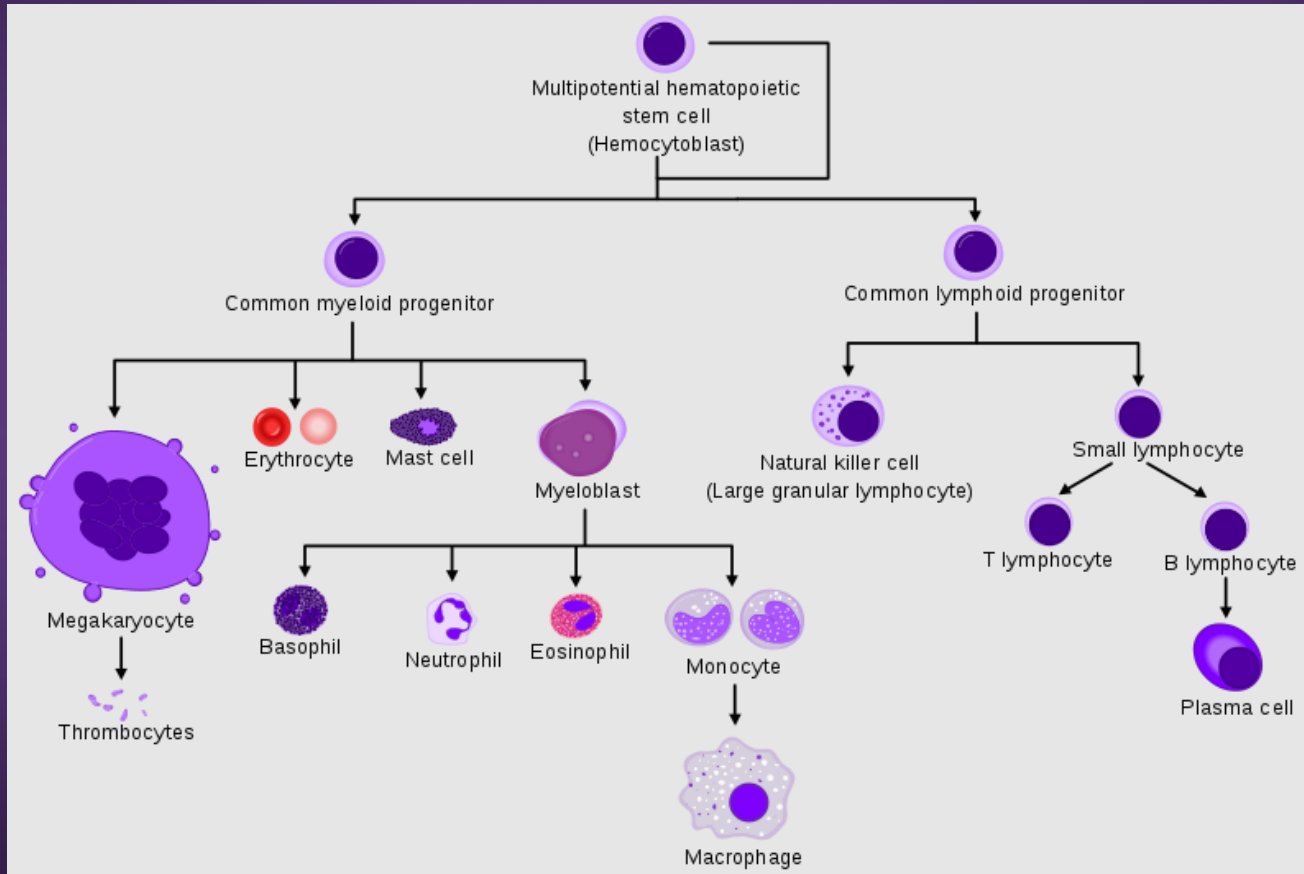
Define neuroimmunology

Explore recent developments describing the interaction between the immune system and nervous system

Immunology Review

- Innate system – Born with it!
 - Physical barriers – skin, mucosa, tears, saliva
 - Chemical barriers – complement, lysozyme, defensins
 - Cells – neutrophils, macrophages, natural killer cells
- Adaptive system – Developed over time!
 - B cells – antibody production
 - T cells – helper cells, killer cells, regulatory cells

Cells of the Immune System



Immunology Review – Innate System

Phagocytosis

Pattern Recognition
Receptors – PRRs

Pathogen Associated
Molecular Patterns – PAMPs

Damage Associated
Molecular Patterns – DAMPs

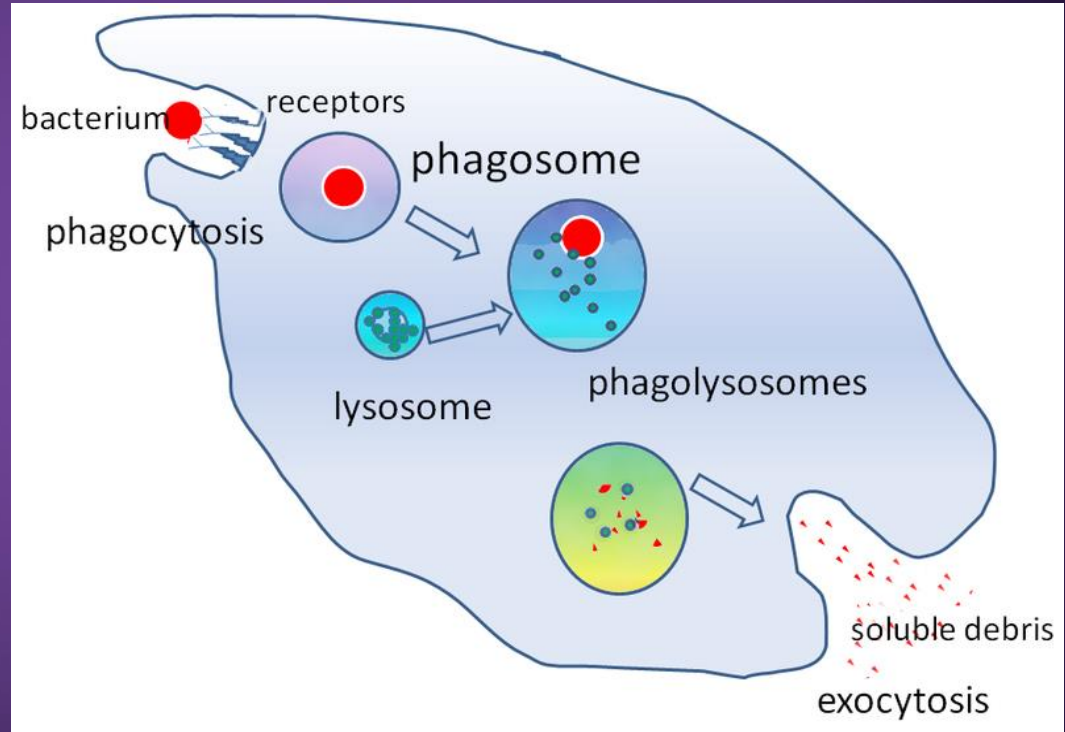
Immunology Review – Innate System

Phagocytosis

Phagocyte uses PRRs to bind PAMPs and DAMPs

Internalize target and destroy in phagolysosome

Classic example of innate mechanism



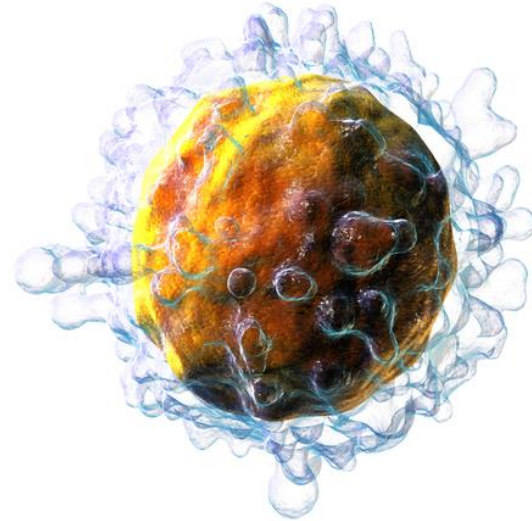
Immunology Review – Adaptive System

T cells

Helper T cells (CD4) – communicate with a variety of cells

Killer T cells (CD8) – deal with intracellular pathogens

Regulatory T cells – prevent autoimmunity and over active immune responses



Lymphocyte
T cell

https://commons.wikimedia.org/wiki/File:Blausen_0625_Lymphocyte_T_cell.png

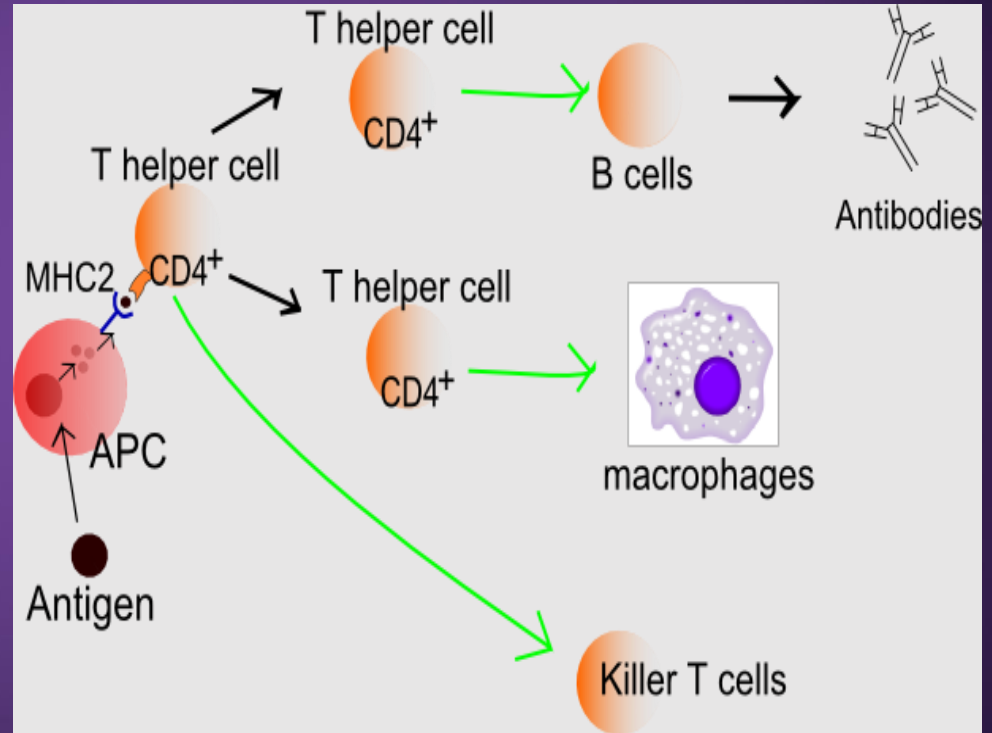
Immunology Review – Adaptive System

Helper T cells (CD4)

Activated by antigen presenting cell (APC)

Communicates with B cells, T cells and macrophages

How do they communicate?

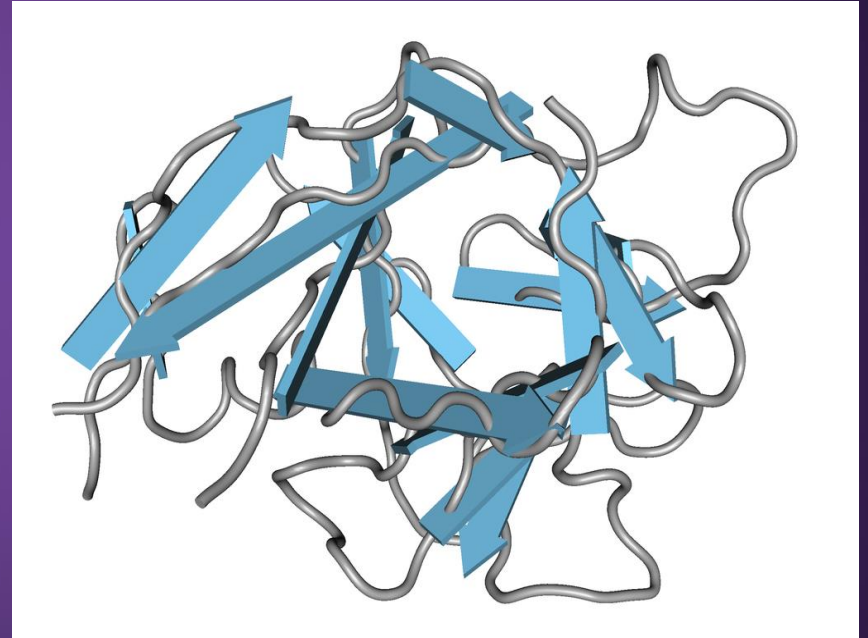


Immunology Review – Cell Communication

Small molecular weight proteins called cytokines

Tumor necrosis factor, interleukins, interferons

Cells other than WBCs can produce cytokines



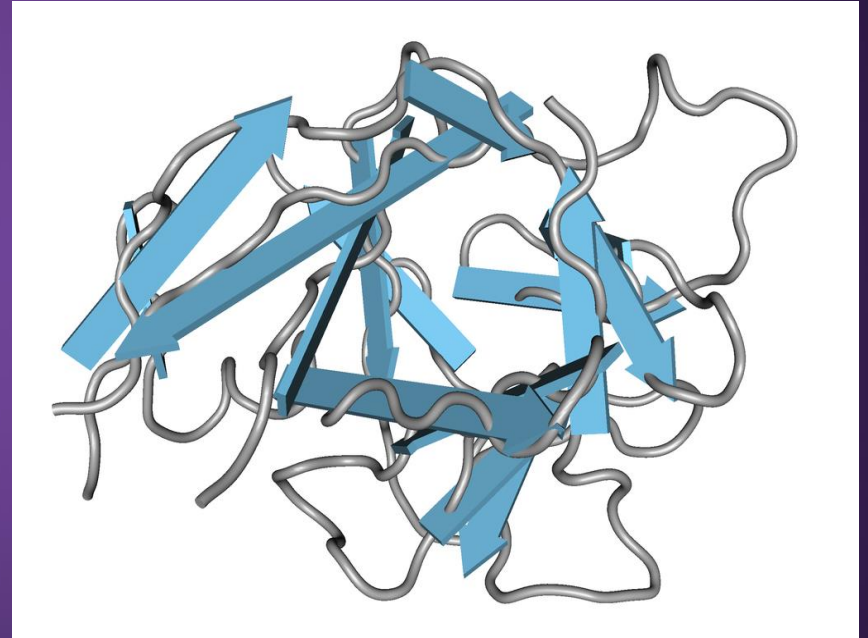
By Nevit Dilmen - Self created from PDB entry with Cn3D Data
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<https://commons.wikimedia.org/w/index.php?curid=1309576>

Immunology Review – Cytokine Confusion

Cytokines generally act locally,
for the most part

They do not work in isolation

Pleiotropy due to interactions



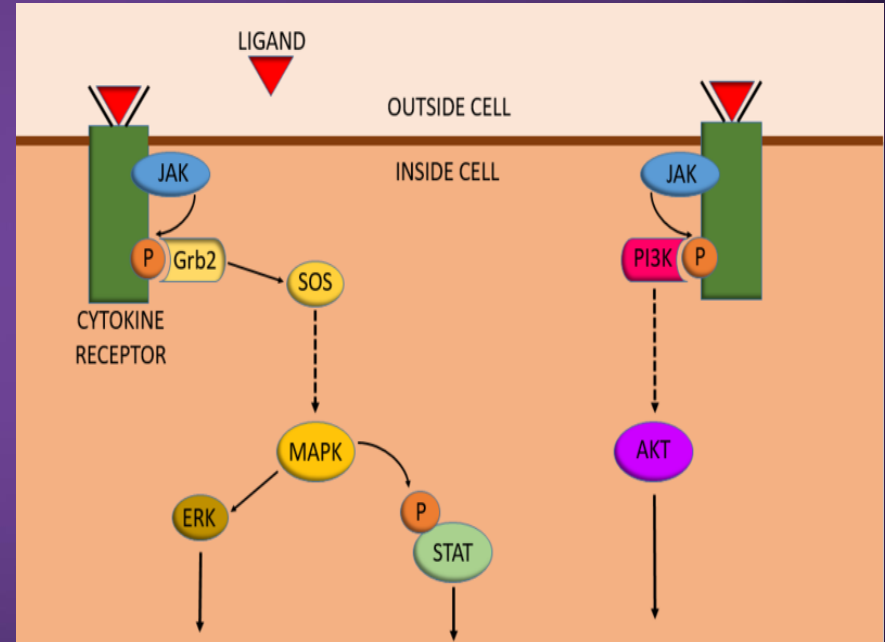
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Source: <https://www.ncbi.nlm.nih.gov/Structure/>, CC BY-SA 3.0,
<https://commons.wikimedia.org/w/index.php?curid=1309576>

Immunology Review – Cell Response

What happens when “ligands” bind receptors

Intracellular signaling pathways initiated

Results in change in cell “behavior”



https://commons.wikimedia.org/wiki/File:JAK-STAT_MAPK_PI3K_Crosstalk.png

Immunology Review – Immune Dysfunction

Cytokine production

Too much inflammation

Pain and loss of function

Rheumatoid arthritis

<https://newsnetwork.mayoclinic.org/discussion/mayo-clinic-research-sheds-light-on-why-some-rheumatoid-arthritis-patients-respond-poorly-to-biologics/>

Immunology Review – Treatments

Treat by targeting immune system cells

Treat by targeting specific cytokines

Humira (adalimumab) blocks tumor necrosis factor

<https://www.humira.com/citrate-free>

Neuroimmunology Defined

“Neuroimmunology encompasses fundamental and applied biology, immunology, chemistry, neurology, pathology, psychiatry and virology of the central nervous system (CNS). Scientists in the field study the interactions of the immune and nervous system during development, homeostasis and response to injuries with the major aim of developing approaches to treat or prevent neuroimmunological diseases.”

<https://www.ncbi.nlm.nih.gov/pubmed/30768789>

Neuroimmunology Questions

Can white blood cells respond to nervous system signals?

Can nerve cells respond to immune system signals?

Immune Cells and Nociceptors

WBCs release cytokines that activate nociceptors

Response by nociceptor receptors and ion channels

Action potential reaches brain and we experience pain

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5205568/>

Immune Cells and Nociceptors

Cytokines shown to mediate pain

Cytokines bind receptors and directly impact ion channels (IL-1 β , IL-6, IL-17, TNF)

Mediators lower threshold for pain by altering ion channels

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5205568/>

Immune Cells and Nociceptors

Other mediators produced by immune cells (NGF)

Immune response abates and pain subsides – nociceptors less “sensitive”

Potential treatments?

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5205568/>

Immune Cells and Nociceptors

Nociceptors produce neuropeptides that directly impact WBCs (and other tissues)

Calcitonin peptide, vasoactive peptide, substance P

Bind receptors on WBCs

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5205568/>

Immune Cells and Nociceptors

CGRP inhibits TNF and produces IL-10

VIP activates innate lymphocytes producing IL-5 and IL-13 causing degranulation of granulocytes

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5205568/>

Nerve Cell and Immune Cell Interactions

WBCs release mediators that influence neurons

Nerve cells release neuropeptides that influence WBCs

Pathogens and tissue injury impact nerves and WBCs

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5578398/>

More Questions!

“Do distinct innate and adaptive immune cell-types communicate with nociceptor neuron subsets as determined by their phenotypic or anatomical categorization?”

“Does pain blockade by current analgesic approaches (e.g. opioids) lead to defects in host-pathogen defense or immune-mediated disease outcomes?”

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5205568/>

Neuroimmune Modulation and Reflex

Afferent VN senses cytokines,
DAMPs and PAMPs

Nerve impulse to brain

Efferent VN activates splenic
nerve

Release NE in spleen

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4056170/>

Neuroimmune Modulation and Reflex

NE binds receptors on ChAT T cells

Release acetylcholine binds AChR on macrophages

Block release of TNF

Attenuate immune response

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4056170/>

Bioelectronic Control of TNF Release

Stimulate efferent VN with small device

Theoretically block TNF release

Tested on patients refractory to or intolerant of traditional treatments for RA

Reported reduced TNF and improved patient outcomes – inflammatory reflex

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4961187/>

The Antigen Restriction Reflex

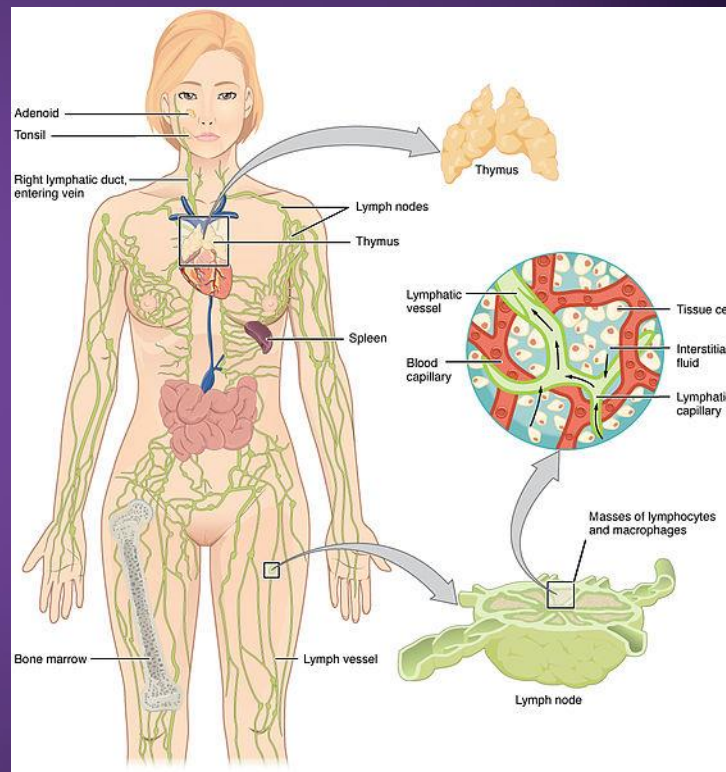
Lymphatic system

Lymph nodes, vessels and WBCs

Serves as surveillance system

Provides opportunity for antigen concentration and WBC activation

<https://bioelecmed.biomedcentral.com/articles/10.15424/bioelectronmed.2016.00001>



https://commons.wikimedia.org/wiki/File:2201_Anatomy_of_the_Lymphatic_System.jpg

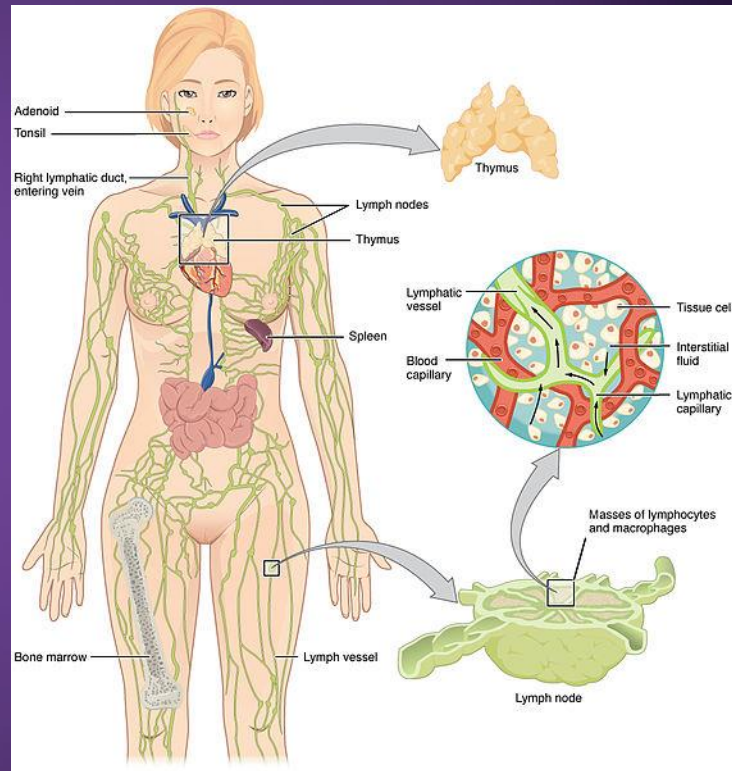
The Antigen Restriction Reflex

Specific antigen flows freely in lymph system in antigen naïve animals

Antigen flow in experienced animals is restricted or sequestered

Specific neurons responsible for restricted lymphatic flow

<https://bioelecmed.biomedcentral.com/articles/10.15424/bioelectronmed.2016.00001>



https://commons.wikimedia.org/wiki/File:2201_Anatomy_of_the_Lymphatic_System.jpg

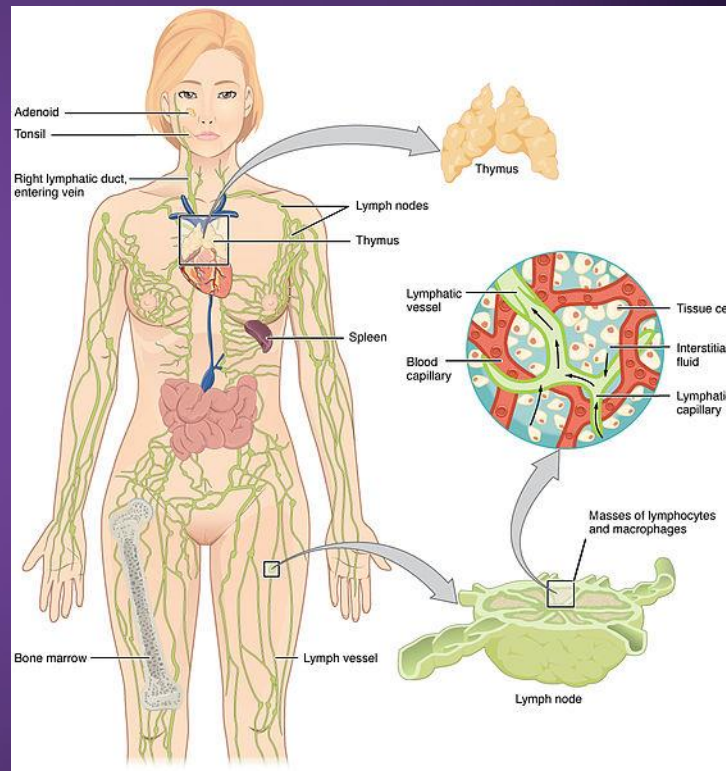
The Antigen Restriction Reflex

Blocking neurons relieves restricted flow in antigen experienced animals

Activating neurons in antigen naïve animals restricts flow

Could we control spread of pathogens through lymphatics?

<https://bioelecmed.biomedcentral.com/articles/10.15424/bioelectronmed.2016.00001>



https://commons.wikimedia.org/wiki/File:2201_Anatomy_of_the_Lymphatic_System.jpg

An Allergic Airway Reflex?

Specific nociceptors in the lung respond to stimuli such as capsaicin

Results in release of neuropeptides and WBC involvement

General “push” towards what we call a Th2 CD4 T cell response

Blocking these nociceptors reduces inflammation

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4506220/>

An Allergic Airway Reflex?

IL-5 release by inflammatory cells activates IL-5R on neurons

Neurons release VIP acting on ILC2 and CD4 cells by binding VIP receptors

Blocking specific sodium channels reduces response

Possible that these neurons “promote” type 2 response, IgE production and release of proinflammatory mediators

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4506220/>

An Allergic Airway Reflex?

Current treatments for these conditions include rapid bronchodilators and corticosteroids

Would it be possible to modulate nerve response to treat severe allergy longer term?

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4506220/>

An Allergic Airway Reflex?

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4506220/>

Do Inconsistencies Exist? Always!

The Claim

Cytokines bind receptors
on neurons and
influence pain

Do Inconsistencies Exist? Always!

IL-1 β involved in pain pathways

IL-1R expression results conflicting

Experimental procedures influence results

<https://www.ncbi.nlm.nih.gov/pubmed/29338939>

<https://www.ncbi.nlm.nih.gov/pubmed/29338939>

Do Inconsistencies Exist? Always!

In vivo vs in vitro studies

Contamination by other
cells

Experimental procedures
influence results

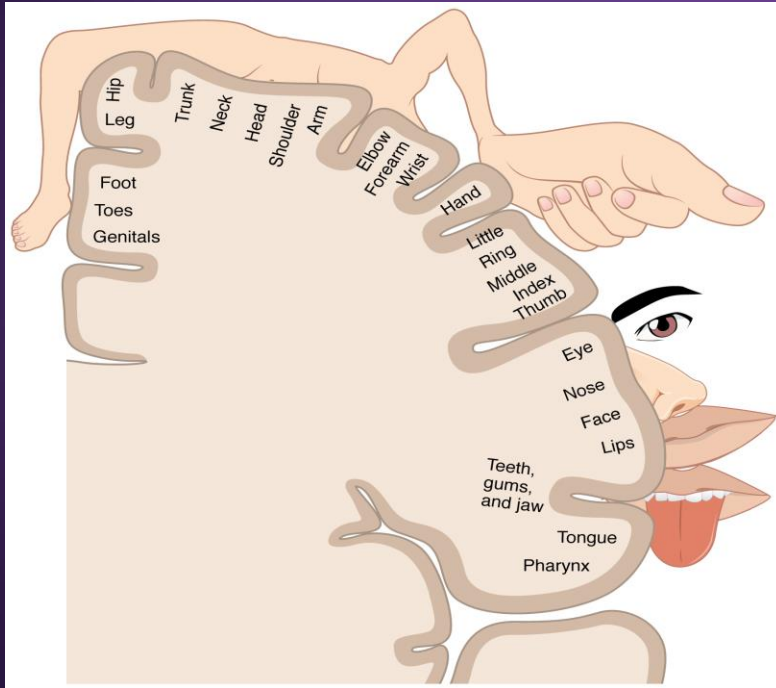
<https://www.ncbi.nlm.nih.gov/pubmed/29338939>

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Could It Be?

Immune Homunculus?

Sensory Homunculus



https://commons.wikimedia.org/wiki/File:1421_Sensory_Homunculus.jpg

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6057146/>

Did We Accomplish Our Goals Today?

Review the immune system in the traditional sense

Define neuroimmunology

Explore recent developments describing the interaction between the immune system and nervous system

What Is The Take Home Message?

No doubt the nervous system and immune system are communicating

Clearly defined molecular connections

When describing immune reactions we must consider the impact of the nervous system

Many unanswered questions!

Questions