



An Osteopathic Approach to the Immune System

AOMA Fall Conference 2023

James F. Keane, DO MEd

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Osteopathic Approach to the Immune System

- Disclosures – No Disclosures to Make



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Osteopathic Approach to the Immune System

- Goals:
 - Review Osteopathic Philosophy to provide both:
 - A metacognitive process that can be applied to the Immune System
 - An inductive framework with which to organize and arrange existing knowledge related to the Immune System
 - Highlighting the Lymphatic System (gross anatomy) and antibodies (molecular biology)
- Review current research related to tissue stiffness and immune function, and implications for understanding of somatic dysfunction and the mechanism of action of OMT.



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Osteopathic Approach to the Immune System

Functions of the Immune System Depend on the Structure of the Immune System:

1. Defend against invading pathogens (bacteria, viruses, parasites, etc.).
2. Immune surveillance (identify and destroy abnormal cells, i.e., cancer)
3. Remove "worn-out" cells and damaged tissues
4. Prepare the process of wound healing and tissue repair.

The Immune System, like all other homeostatic systems in the body, maintains the body's aggregated state

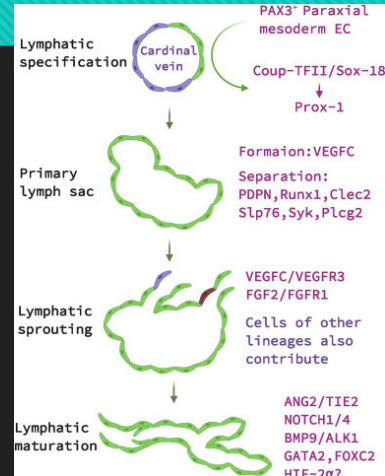


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Lymphatic System: Embryogenesis and Growth

LIFE AND HEALTH

- Life expresses a force on environmental matter to aggregate an organism (and lymphatic vessels)
- Health is the result of normal aggregated structure.
- Lymphangiogenesis: the process of new lymphatic vessel formation from existing ones.
- Lymphatic maturation is characterized by valve formation, mural cell recruitment, and basement membrane deposition of the collecting vessels, and involves angiopoietin/TIE pathways.
- Osteopathically speaking, lymphangiogenesis is the aggregation of inert matter to form lymphatic vessels.
- The structure of the lymphatic vessels that is formed of aggregated atoms relates to the function of the lymphatic system.

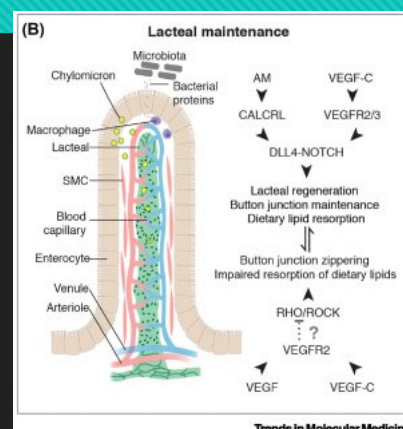


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Lymphatic System: Structural Maintenance

LIFE AND HEALTH

- The lymphatic system structure must be constantly maintained (or remodeled) due to cell turnover and tissue loss.
- Current areas of study include:
 - Regulation of (lymphatic endothelial cell) LEC junction integrity
 - Regulation of button junctions
 - Junction remodeling
 - Regulation of LEC quiescence and proliferation



Trends in Molecular Medicine



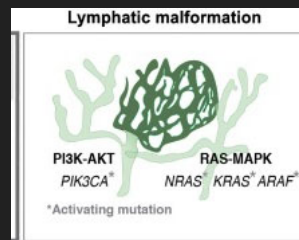
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Lymphatic System: Loss of Structure, Loss of Function

MORBIDITY

- Morbidity is due to a loss of aggregated structure resulting in a loss of function.
- Disruptions in lymphangiogenesis and other embryologic homeostatic processes involved in the formation of the lymphatic system result in an abnormally structured and dysfunctional lymphatic system. (Indirect Morbidity)
- One example is Meige disease: an idiopathic form of lymphedema thought to have a genetic cause.

<https://medlineplus.gov/genetics/condition/meige-disease/#causes>



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Lymphatic System Morbidity: Loss of Structure and Function

MORBIDITY

- Another example of morbidity in the lymphatic system is the loss of structure resulting from radiation therapy or lymph node dissection (Direct Morbidity).



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Lymphatic System: Restoring Structure and Function

HEALING

- Healing is the result of restoring normal structure.
- Mechanotransduction: The ability of a cell to sense, integrate, and convert mechanical stimuli into biochemical signals that result in intracellular changes, such as ion concentrations, activation of signaling pathways, and transcriptional regulation.
 - Dobner S, Amadi DC, and Lee RT. Chapter 14- Cardiovascular Mechanotransduction. Muscle, Fundamental biology and mechanisms of disease, Elsevier, v1, 2012. <https://doi.org/10.1016/B978-0-12-381113-1.00014-8>
- In Osteopathic terms, mechanotransduction describes changes in homeostatic function due to OMT that result in aggregated structural changes within the body (i.e., healing).

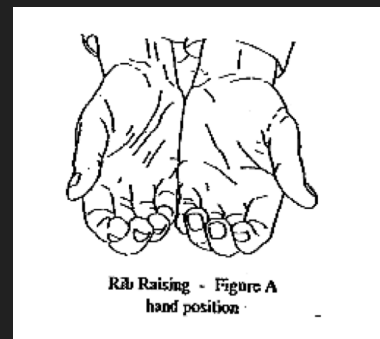


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Lymphatic System: Restoring Structure and Function

HEALING

- The mechanotransduction triggered by OMT:
 - Directly restores the structure of lymphatic vessels and moves fluid (i.e., kneading, lymphatic pump, diaphragm treatment), or
 - Indirectly changes homeostatic processes that form and maintain the aggregated structure of lymphatic vessels to affect their structure/function (i.e., rib raising, OA release)



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Osteopathic Consideration of Antibodies: Matter in Motion

ANTIBODIES

- Human antibodies or immunoglobins are Y-shaped proteins with two identical light chains (LC's), and two identical heavy chains (HC's) that are linked with disulfide bonds and bridges.
- Antibodies are synthesized by B-cells in billions of different structural forms
- Each B-cell produces a single species of antibody, each with a unique antigen binding site.
- Antibodies stick to, or opsonize, antibodies thus targeting the immune system
- Antibody function includes neutralization of infectivity, phagocytosis, antibody-dependent cellular cytotoxicity, and complement-mediated lysis of pathogens or of infected cells.



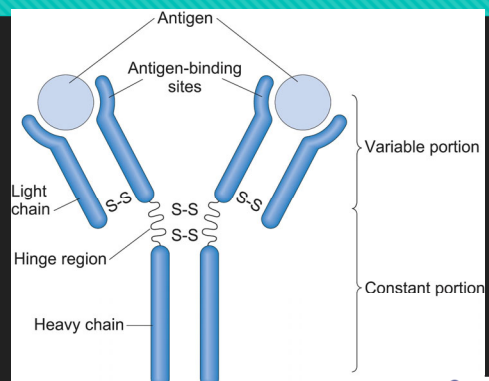
Dr. Still Examining the Structure of an Antibody



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Osteopathic Consideration of Antibodies: Structure and Function

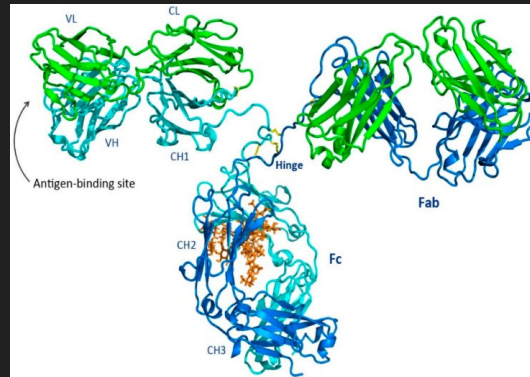
- Human antibody HC's can be one of five isotypes (IgA, IgD, IgE, IgG, and IgM)
- Human LC's have two domains: a variable domain and a constant domain.
- Antigen binding site in an aggregation of matter into a unique molecular structure with a specific function (i.e., to bind to a specific antibody)
- Other variable structures are found as well (i.e., IgA and IgM have additional J-chains that allow for formation of dimers and pentamers).



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Osteopathic Consideration of Antibodies: Structure and Function

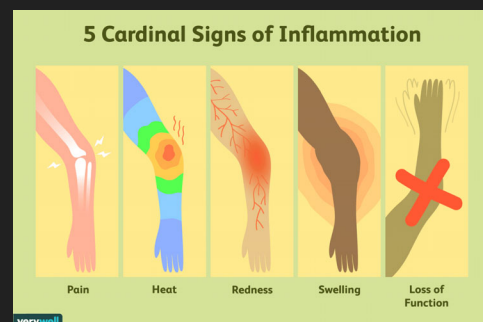
- Antibodies have three functional components that target specific antigens depending entirely on their aggregated structure
 - Two Fragment antigen binding domains (Fabs), and
 - The Fragment crystallizable (Fc)



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Tissue Mechanotransduction: Osteopathic Considerations

- Mechanotransduction: The process by which cells convert mechanical clues from their environment into biochemical signals, cellular pathway and changes to other functions.
- Simply speaking, tissue "stiffness" causes mechanotransduction in the immune system.
- Tissue inflammation signs are associated with biophysical cues that regulate immune response:
 - Tumor (rigidity)
 - Calor (warmth)
 - Rubor (redness)
 - Dolour (pain)



<https://www.verywellhealth.com/signs-of-inflammation-4583>



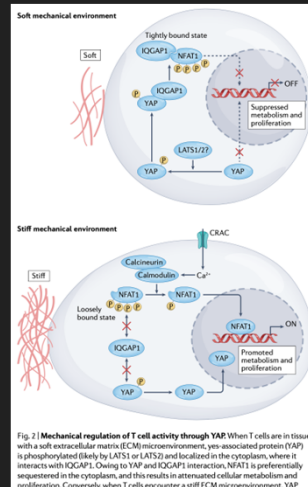
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Tissue Mechanotransduction: Osteopathic Considerations

Tissues can be:

- "stiff" (atherosclerosis, lung fibrosis, and peri-tumoral environment, etc.),
- or "soft" (abscess, necrotic core of tumors, etc.)
- or "normal" (healthy tissue)

These tissue environments provide mechanical stimuli to trigger widespread changes in immune function.



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Tissue Mechanotransduction: Osteopathic Considerations

- Therefore, somatic dysfunction causes immune changes and OMT that improves somatic dysfunction causes immune changes.
- Osteopaths have long known this; however, science has begun to provide more details.



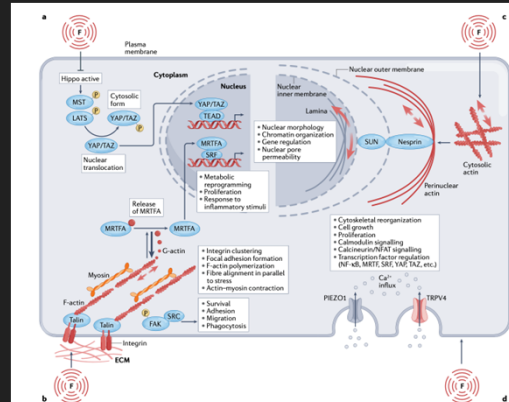
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Tissue Mechano-transduction: Osteopathic Considerations

Tissue mechano-transduction depends on molecules such as:

- adhesion molecules (i.e., integrins),
- ion channels (esp. TRPV4 and the PIEZO family of channels),
- cytoskeleton components (i.e., actin, myosin, nucleoskeleton and cytoskeleton (LINC) complex, and
- nesprin and SUN family proteins),

which lead to Ca^{2+} fluxes, cytoskeleton reorganization, and transcriptional regulation.

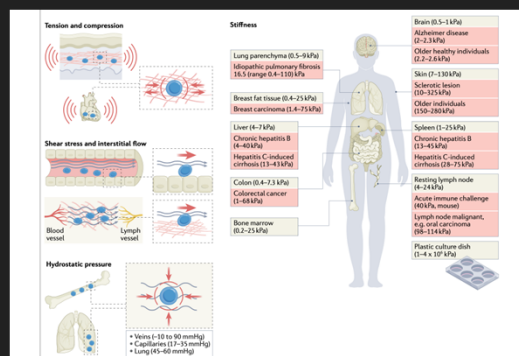


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Tissue Mechano-transduction: Osteopathic Considerations

The process of how tissue mechanical forces prompt immune responses is complex and follows multiple biochemical pathways:

- Toll-like receptors
- pro-inflammatory cytokine production
- histamine and active transforming growth factor-Beta 1 (TGFβ1)
- the Hippo pathway involving the phosphorylation of kinases
- the MRTFA-SRF pathway, and more

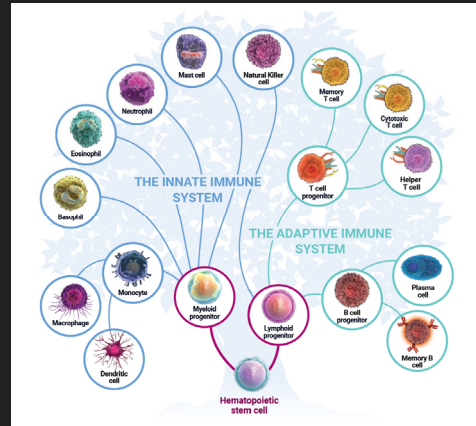


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Tissue Mechano-transduction: Osteopathic Considerations

- These immune responses involve activity of B-cells, dendritic cells, antigen presenting cells, neutrophils, T-cells, helper T-cells, mast cells, natural killer cells, and macrophages.

<https://lab-a-porter.com/2019/12/cells-of-the-immune-system/> →



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Tissue Mechano-transduction: Osteopathic Considerations

- Fibrotic and ageing tissue become "stiffer" and promote inflammation and possibly autoimmunity.
- These concepts influence the consideration of all aspects of the immune system, including:
 - Wound healing and fibrosis: mechanosensing may drive immune cell-dependent responses in aberrant healing, i.e., scarring or fibrosis
 - Cancer: Tumor development and tissue stiffness co-progress, and lead to an environment that can forestall immune response, altering the migration of T-cells. Metastasizing tumor cells can be soft or stiff depending on the environment through which they migrate. Stiff to crawl along basement membranes, or soft to crawl through small pores in the abnormal extracellular membrane around tumors.



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- An illustration showing three children in various states of motion. On the left, a boy is crawling on all fours, wearing an orange shirt and green shorts, with the word 'crawl' written above him. In the center, a boy is walking upright, wearing a yellow shirt and blue shorts, with the word 'walk' written below him. On the right, a boy is running, wearing a red and white tank top and blue shorts, with the word 'run' written above him.



Osteopathic Approach to the Immune System

	LIFE	HEALTH	MORBIDITY	HEALING
Classic Osteopathic Philosophy (AT Still Quotes)	"Life Is Matter in Motion"	"When all parts of the human body are in line we have health..."	"...when they are not the effect is disease..."	"... when the parts are readjusted disease gives place to health."
Metacognitive/ Inductive Reasoning Prompts	<input type="checkbox"/> What processes were involved in the embryologic formation of the immune system: immune related organs (thymus, bone marrow), cells (WBC's, natural killer, antigen presenting, T-cells, T-helper, B-cells), and molecules (antibodies, interleukins, histamine, etc)?	<input type="checkbox"/> How does the normal structure of the components of the immune system relate to their function?	<input type="checkbox"/> How can the normal structure and function of the immune system be disrupted, and what clinical signs and symptoms and diagnostic information are associated?	<input type="checkbox"/> How can the normal structure and function of the immune system be restored?



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Osteopathic Approach to the Immune System

SUMMARY

- Classic Osteopathic Philosophy can be applied to all components of the body, including the immune system
- The structure of any part of the immune system relates to its function, whether the lymphatic system or antibodies.
- Tissue stiffness or softness influences immune system function, i.e., somatic dysfunction like T3 ERSr causes immune system dysregulation
- OMT that normalizes tissue tensions has an immunomodulatory affect



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Osteopathic Approach to the Immune System

Reference

Du, H., Bartleson, J.M., Butenko, S. *et al.* Tuning immunity through tissue mechanotransduction. *Nat Rev Immunol* **23**, 174–188 (2023). <https://doi.org/10.1038/s41577-022-00761-w>

And as indicated on individual slides



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Osteopathic Approach to the Immune System

Thank You!!!



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