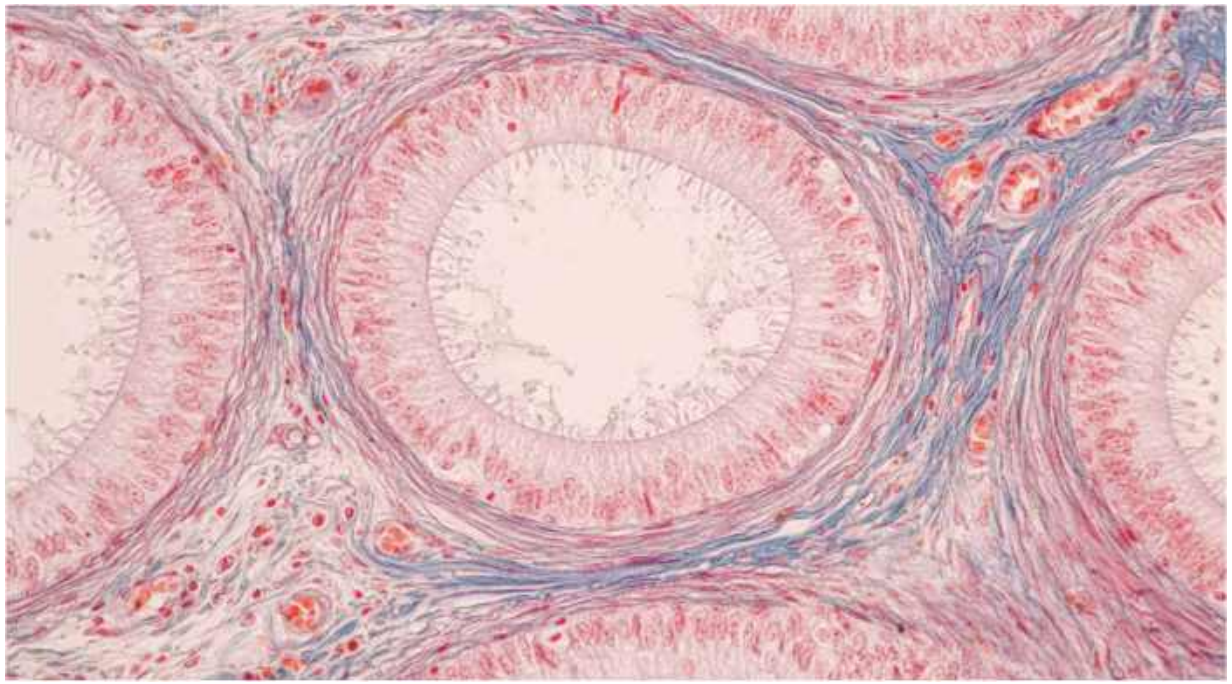
A4M | MEDICINE REDEFINED

MODULE II

PEPTIDE THERAPY CERTIFICATION

Peptides: Part II

One of Many Medicinal Signaling Therapies



Boston University
School of Medicine

Kathleen O'Neil M.D.

A4M Vegas 2025

Treat Wellness

treatwellness.boston

HARVARD MEDICAL SCHOOL

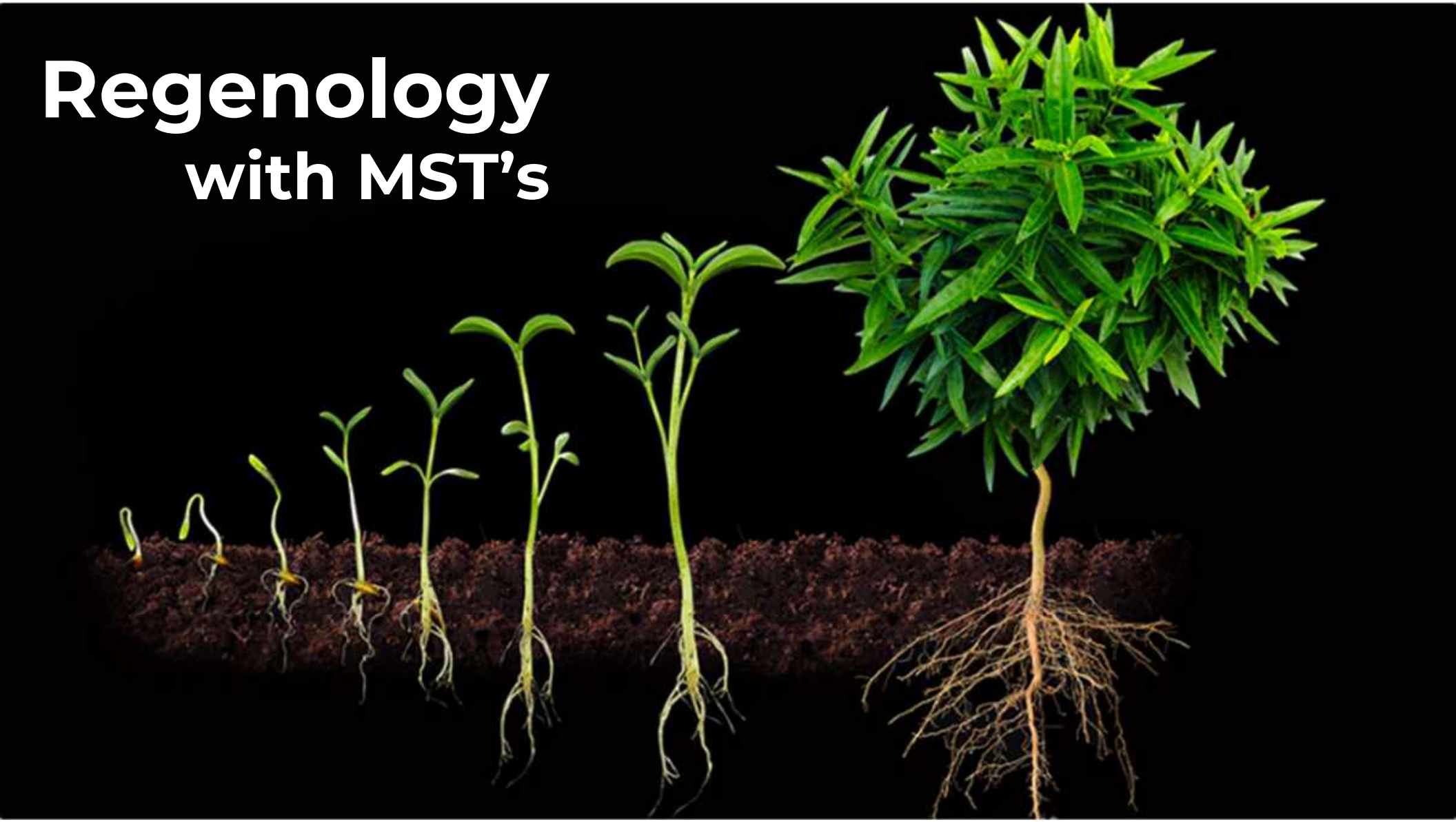
BRIGHAM AND WOMEN'S HOSPITAL

3 Pearls from A4M Sept 2025

1. *Fascia is an **ESSENTIAL** **bioactive** organ system*
2. ***Intrinsic & extrinsic** factors affect the **macro** and **micro** environments of the body*
3. *Injury is similar in **ALL** organ systems; **unresolved chronic low grade sterile inflammation** prevents repair process from occurring, and ultimately results in chronic age related dis-ease*

    —> ***inflammatory dx, autoimmune dx and / or cancer***

Regenology
with MST's



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Goals of Regenerative Medicine

address the patient's symptoms

Cellular Health
Mitochondrial Health

Immune dysregulation
Inflammation
Autoimmunity
Cancer

Genetics/Epigenetics
DDR

Detoxification
Methylation/PPAR Phenotypes

Redox: Oxidative Stress
Telomeres

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Regenology

Therapeutic Model

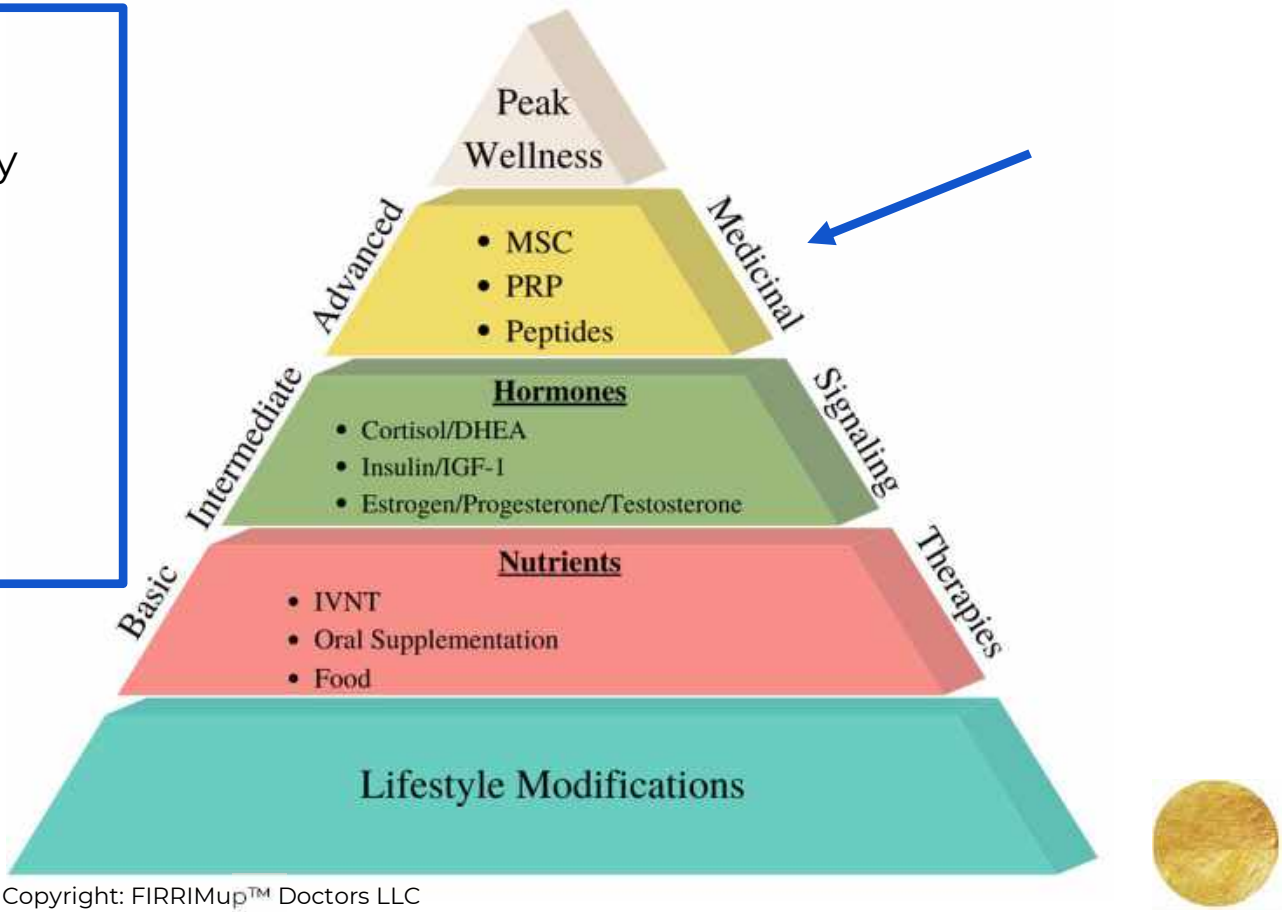
Key

MST = Medicinal Signaling Therapy

IVNT = Intravenous Nutritional Therapy

MSC = Medicinal Signaling Cells

PRP = Platelet Rich Plasma



Objectives

Review:

1. Fascia as an organ system

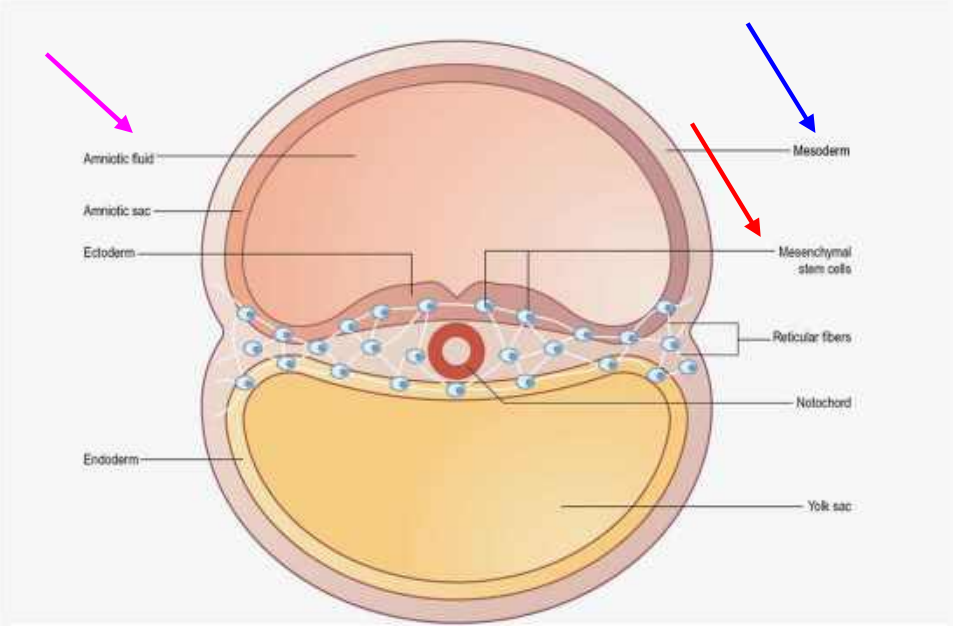
2. Fascia = ground zero in pain, injury & cellular/tissue healing

3. Medicinal Signaling Therapies (Nutrients, Hormones, Peptides, PRP, Exosomes, MSC's, energy modalities) for aberrant physiology

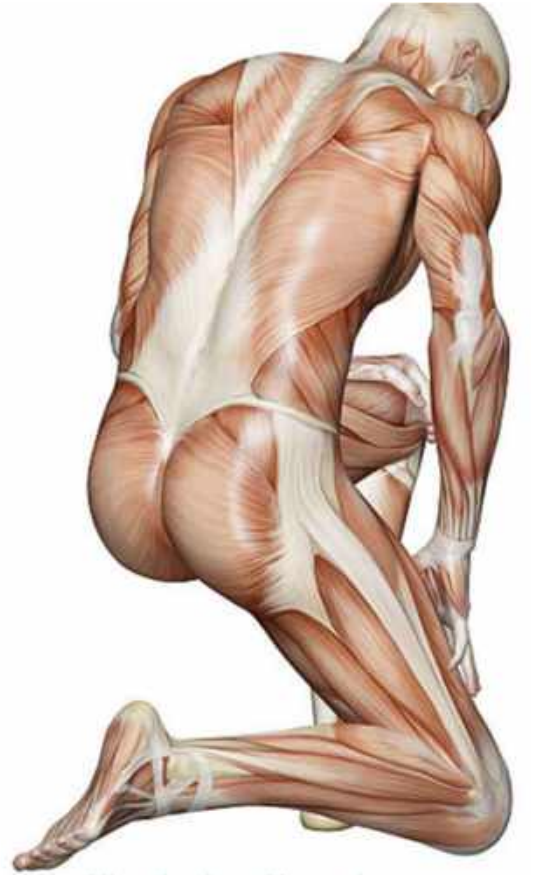
4. Demonstrative Case Studies for use of multi-modal therapies using the Regenology Therapeutic Model

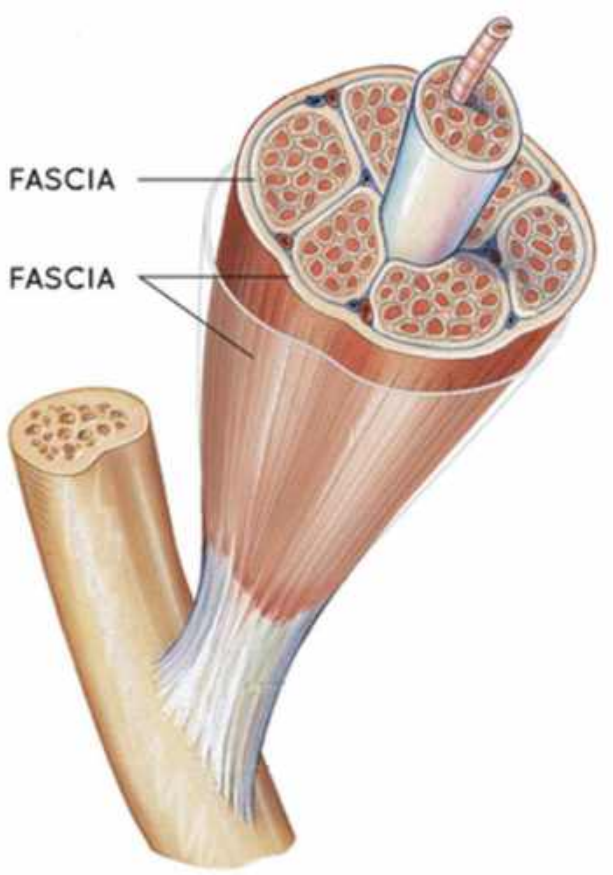
Fascia from MESODERM (Middle Layer)

- **Week 2-3 , one cell layer blastula**
- *Somites arise here for specialization*
- **Form smooth, cardiac, skeletal muscle; mesentery; bone; cartilage; RBC; WBC; dura mater; notochord; and microglia**
- *Mesoderm is folded and refolded by "gastrulation"*

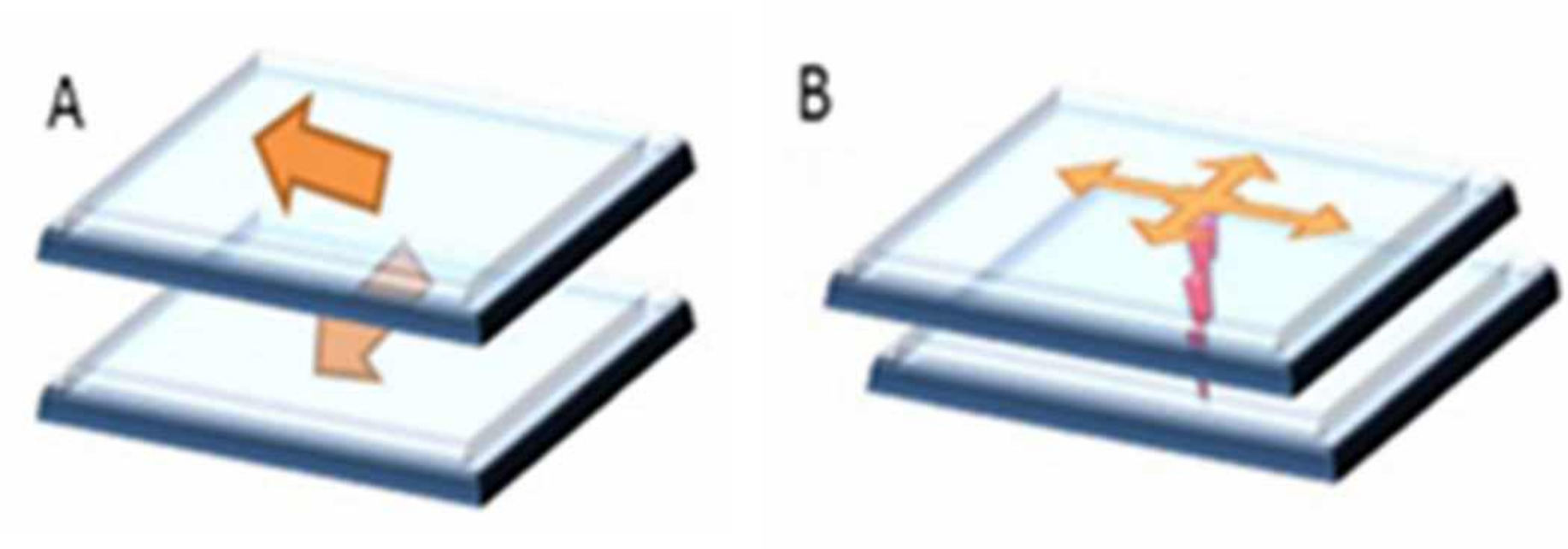


Macro → Micro





Three Dimensional Glide

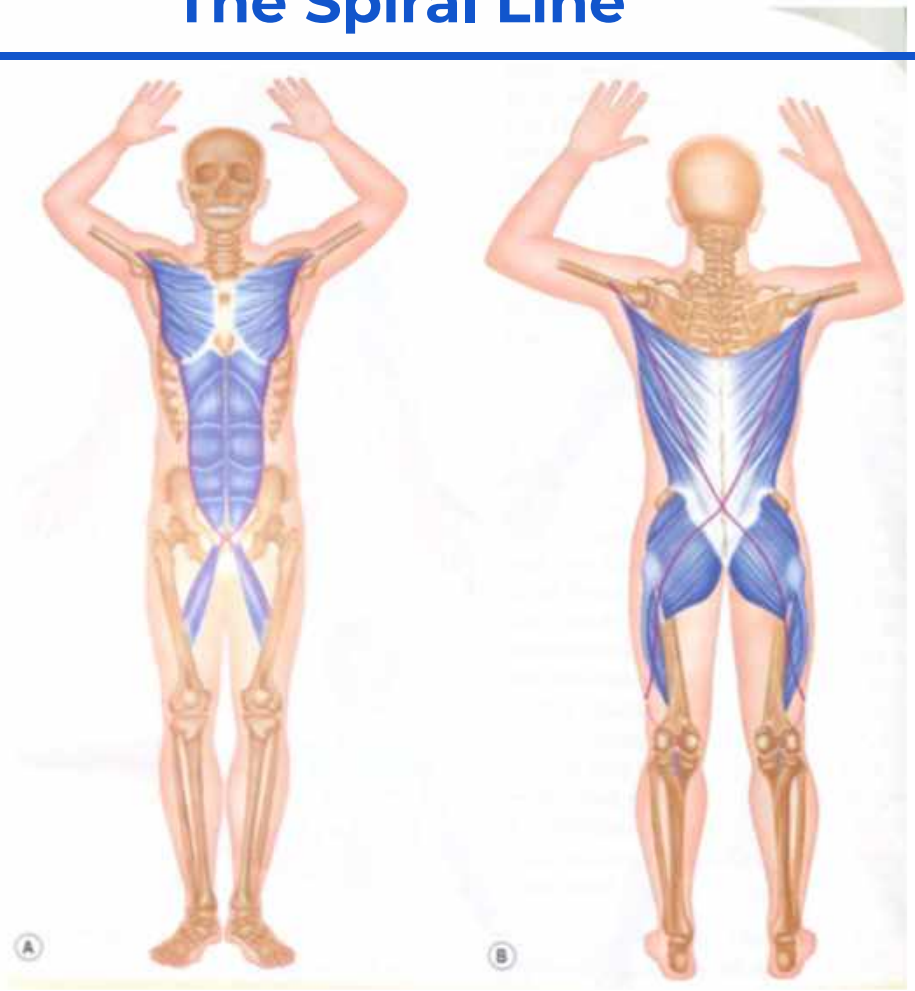


Pavan, Piero G., Antonio Stecco, Robert Stern, and Carla Stecco. "Painful connections: densification versus fibrosis of fascia." *Current pain and headache reports* 18, no. 8 (2014): 441. Adapted from: *Painful Connections: Densification Versus Fibrosis of Fascia. Piero G. Pavan et al*[7]

“YOU are the most elaborate piece of origami ever”
-David Lesondak

https://www.flickr.com/photos/69035340@N02/19849583512

The Spiral Line

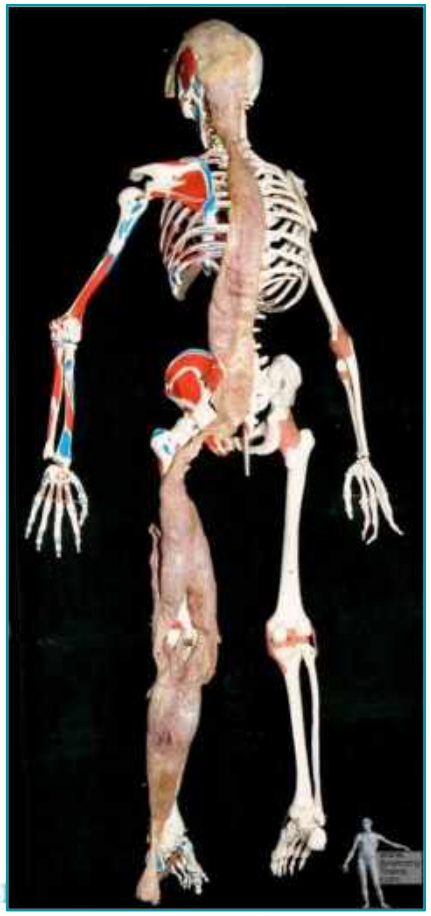


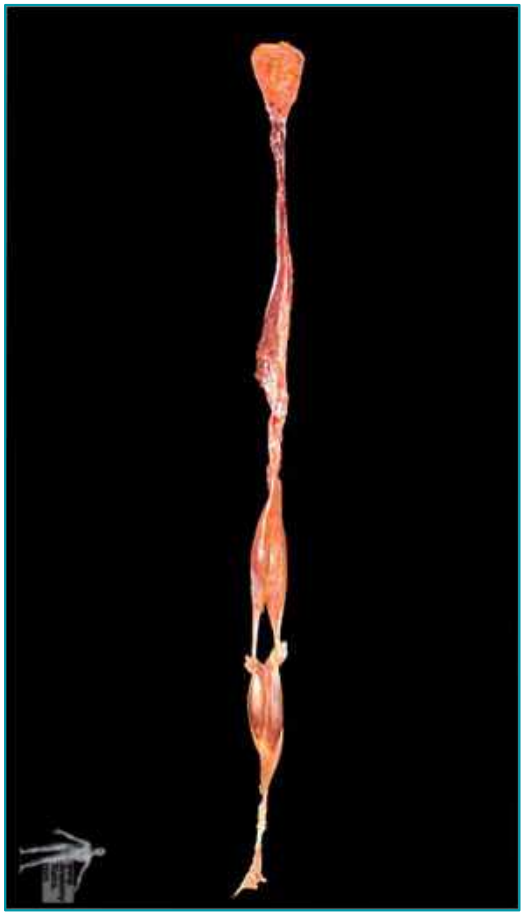
Used with permission from Thomas Myers, taken from Fascia: What it is and Why it Matters by David Lesondak, Handspring Publishing Ltd (2018).

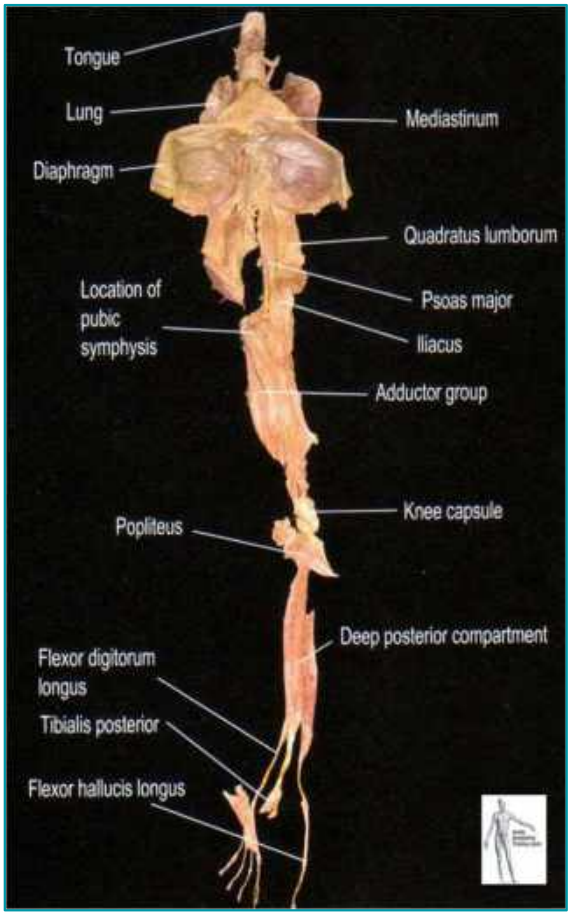
Fascia and Anatomy:

Classical vs. Fascial Anatomy

Used with permission from Thomas Myers, Anatomy Trains 4th edition by Thomas W. Myers







Fascia and Nerves

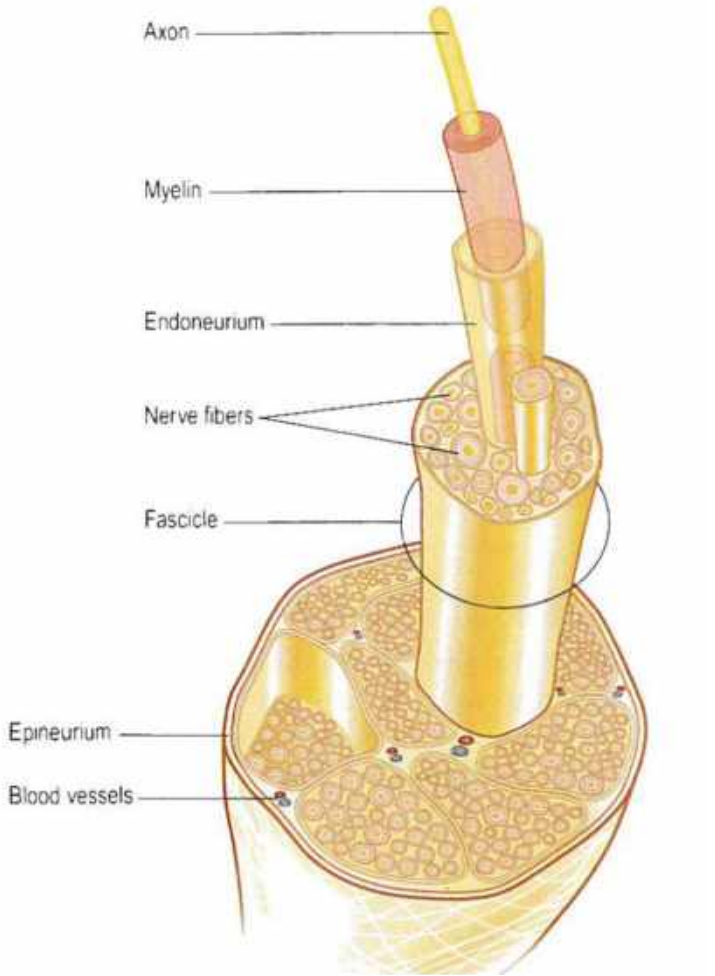


Figure 4.2
Cross-section of a typical spinal nerve. Note the similarities to the structure of the muscle (see Figure 3.11).

Used with permission from Thomas Myers, taken from Fascia: What it is and Why it Matters by David Lesondak, Handspring Publishing Ltd (2018).

Fascia and Nerves

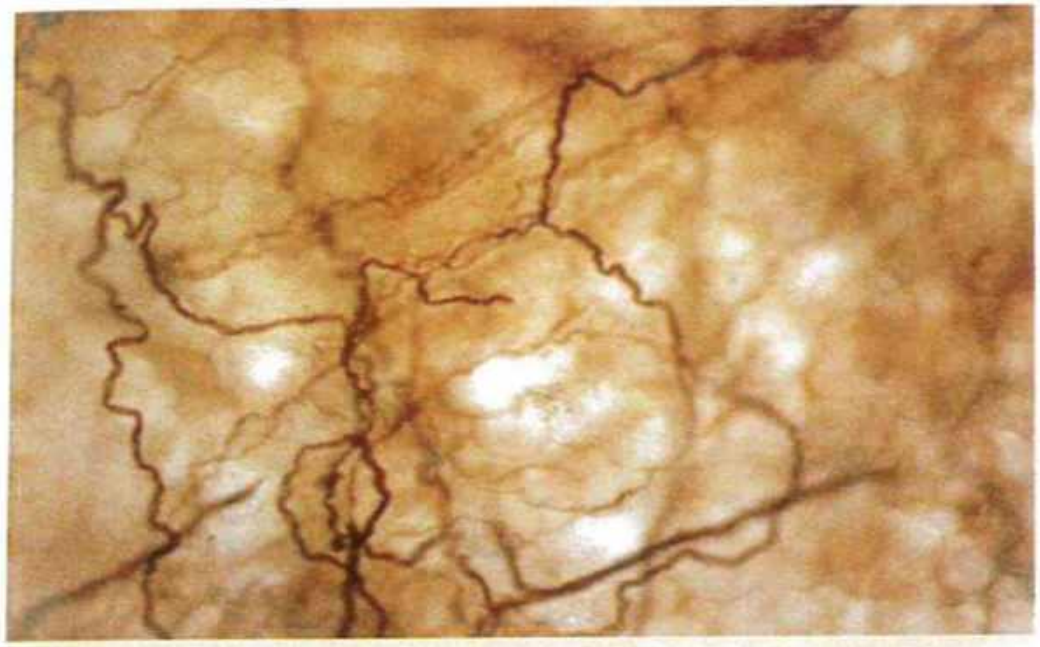


Figure 4.1
A dense network of nerve fibers in the thoracolumbar fascia of a rat. The surface area of the picture represents 0.5 mm (less than a tenth of an inch).
Reproduced with kind permission from Tesarz et al. 2011.

Used with permission from Thomas Myers, taken from Fascia: What it is and Why it Matters by David Lesondak, Handspring Publishing Ltd (2018).

Fascia and Nerves

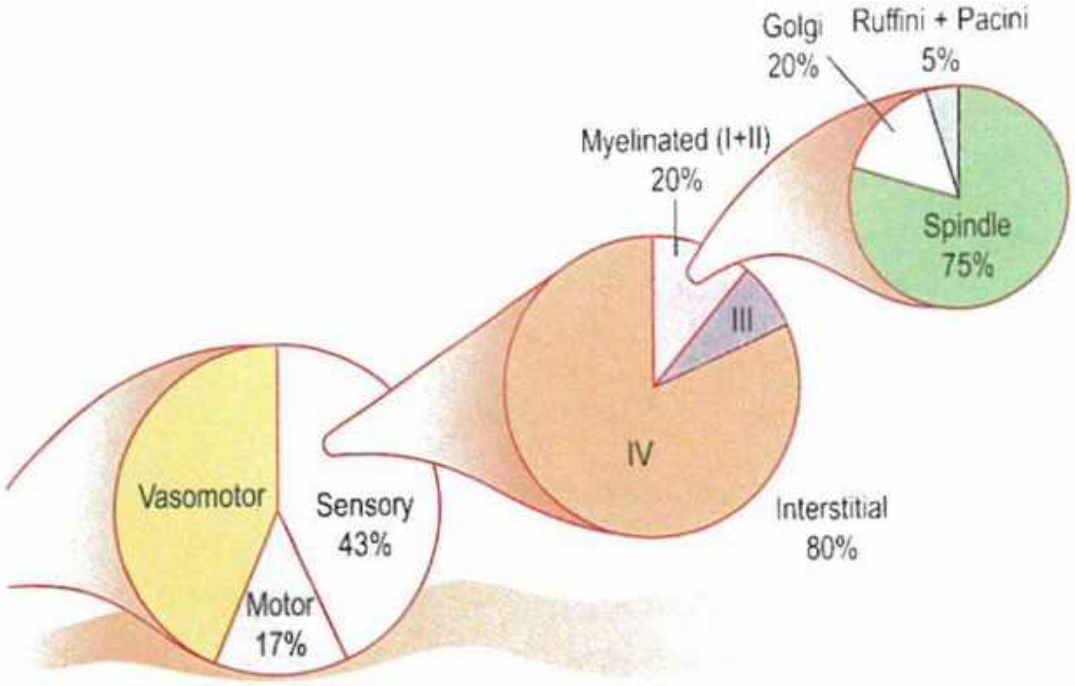


Figure 4.3
In the typical muscle nerve there are three times as many sensory nerves as there are motor nerves. Of those about 80 per cent of the sensory information comes from interstitial nerves.

Fascia and Nerves

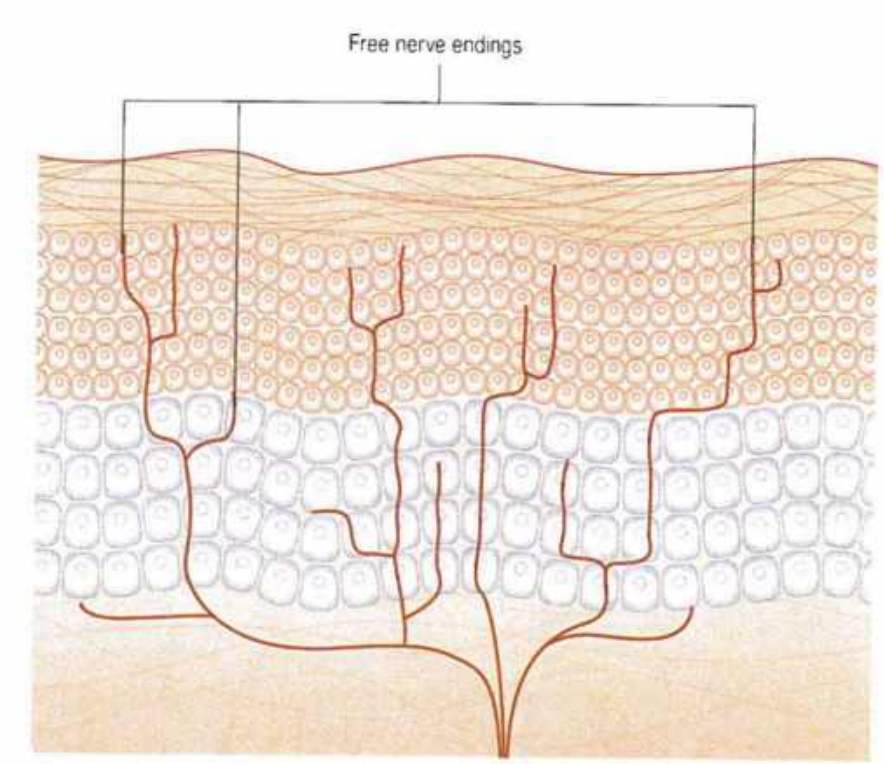


Figure 4.8
Interstitial or free nerve endings, which are responsible for 80 per cent of our sensory input.

Reproduced with permission from Handspring Publishing Ltd, taken from Fascia: what it is and why it matters by David Lesondak (2017)

Fascia:

An Essential Bioactive Organ System

Fascia: a new organ system

Fascia

- Like the Gut/*Microbiome*
- *Different types* of fascia in *different locations* with *specific functions*
- Primary cell is the FIBROBLAST: fibroblast *cell turnover q 2 months*
- Fascial web == a spider web (made of many fibroblasts

Fascial <u>WEB</u>

- A spider web (made of many fibroblasts)
- SPIDERWEB *turnover is 300-500 days*
- One signal depicted by a fibroblast occurs within a *12 minute window*
- Effect of signal can *last 3 days*: (no additional signal can occur)

Image Source: /www.lautrevoie-mfr.com/what-is-fascia

New cell:
FASCIACYTE-
releases
Hyaluronan-
GLIDE

- The fascial system is a three-dimensional continuum of various connective tissue that permeates the body.
- Injuries to the fascial system could have a potential role in the development and perpetuation of musculoskeletal disorders eg., LBP
- Understanding fascia adaptation to mechanical and biochemical conditions is important for injury prevention.
- The facial system or *"fascianet"* involves every level of the body from the microlevel (molecular and cellular response) to the macro-level (mechanical properties).

Fascial tissue research in sports medicine: from molecules to tissue adaptation, injury and diagnostics: consensus statement

PDF

Martina Zügel[1], Constantinos N Maganaris[2], Jan Wilke[3], Karin Jurkat-Rott[4], Werner Klingler[5], Scott C Wearing[6], Thomas Findley[7], Mary F Barbe[8], Jürgen Michael Steinacker[1], Andry Vleeming[9], Wilhelm Bloch[10], Robert Schleip[11], Paul William Hodges[12]

Author affiliations +

Abstract

The fascial system builds a three-dimensional continuum of soft, collagen-containing, loose and dense fibrous connective tissue that permeates the body and enables all body systems to operate in an integrated manner. Injuries to the fascial system cause a significant loss of performance in recreational exercise as well as high-performance sports, and could have a potential role in the development and perpetuation of musculoskeletal disorders, including lower back pain. Fascial tissues deserve more detailed attention in the field of sports medicine. A better understanding of their adaptation dynamics to mechanical loading as well as to biochemical conditions promises valuable improvements in terms of injury prevention, athletic performance and sports-related rehabilitation. This consensus statement reflects the state of knowledge regarding the role of fascial tissues in the discipline of sports medicine. It aims to (1) provide an overview of the contemporary state of knowledge regarding the fascial system from the *microlevel* (molecular and cellular responses) to the *macrolevel* (mechanical properties), (2) summarise the responses of the fascial system to altered loading (physical exercise), to injury and other physiological challenges including ageing, (3) outline the methods available to study the fascial system, and (4) highlight the contemporary view of interventions that target fascial tissue in sport and exercise medicine. Advancing this field will require a coordinated effort of researchers and clinicians combining mechanobiology, exercise physiology and improved assessment technologies.

Zügel M, *et al*. *Br J Sports Med* 2018;**52**:1497. doi:10.1136/bjsports-2018-099308

The Fascial System

Fascial System Component	Function
Fasciacytes	• form small clusters along the surface of each fascial sublayer, defining the boundary between the fibrous sublayer and the loose connective tissue (4) • regulation of the activity of fascial cells in HA production modulate gliding between adjacent fibrous fascial sublayers (4)
Fibroblasts	• secrete the joint lubricating molecule hyaluronan (4) found in connective tissue that is surrounded by the extracellular matrix it helps maintain (4) • generate collagen to provide structural integrity to the extracellular matrix through tissue remodeling (4)

The Fascial System

Collagen I	• produces the **thick fibers** with the most amount of tensile strength. • found in **ligaments, tendon, and bone**. • stronger than steel when compared gram per gram.
Collagen II	• peptide and component of joint cartilage. • responsible for **tensile strength** and **toughness** in the **cartilage**.
Collagen III	• **smaller, more web-like, elastic** and provides **weaker structural** support, and less tensile strength than Type I collagen.
Collagen IV	• found in **basement membrane** • bound to the **sides of type I fibrils** and may bind them together to form thicker collagen fibers.

Akey and O'Neil-Smith *Fascia Function and Medical Applications, CRC Press 2021*

The Fascial System

Fibrillin	glycoprotein that increases fascial elasticity (4)
Elastin	connective tissue molecule that gives the tissue its property of resilience, allowing it to extend and recoil with ease and form elastic fibers (5)

Akey and O'Neil-Smith Fascia Function and Medical Applications, CRC Press 2021

Objectives

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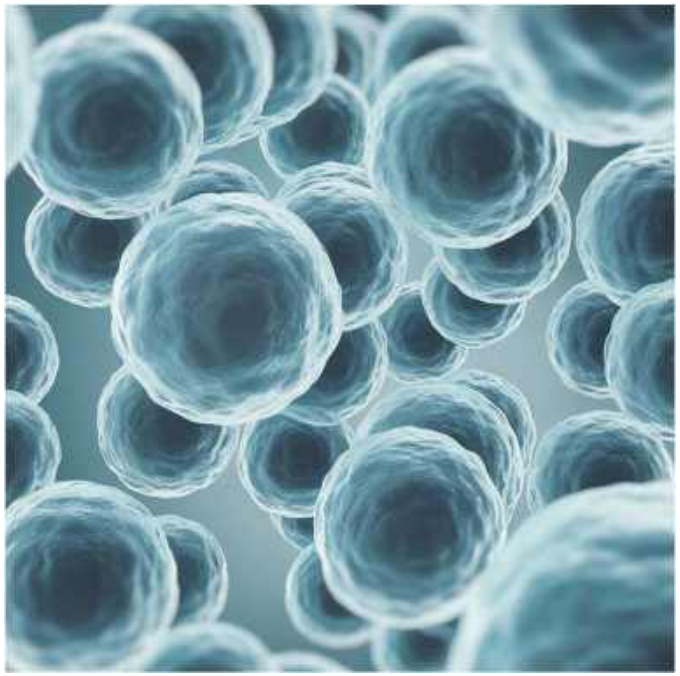
ECM: Governs Cellular Functions

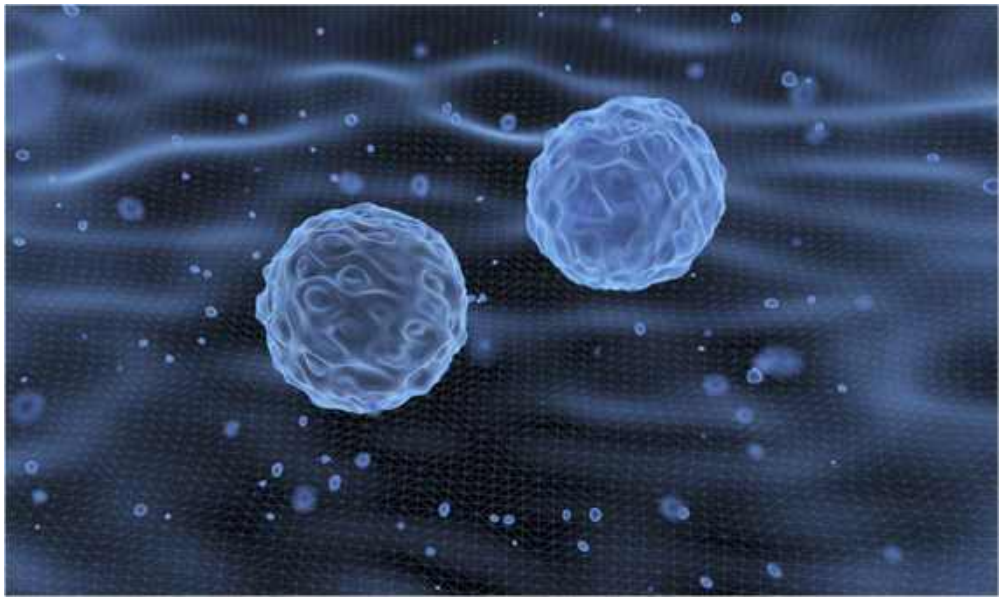
- Cocktail of **proteins, signalling molecules,** and **chemicals** that cells **exude** as they grow
- Cells use matrix to impart **strength & shape** to tissues like bone & brain
- ECM used to be dismissed as an inert garden trellis, now proven that ECM is **critical for cell behavior**



Nature 566, 563-565 (2019) *doi: 10.1038/d41586-019-00681-1*

ECM & Stem Cells

- ECM guides stem cells to **repair damaged tissues**, re-form **blood vessels** damaged by stroke & alter cellular responses to chemotherapy
- ECM serves as a reservoir of *signaling molecules* that serves as a *highway of communication* between cells
- (25 yrs ago, ECM was just thought to be simply structural)



Nature 566, 563-565 (2019) *doi: 10.1038/d41586-019-00681-1*

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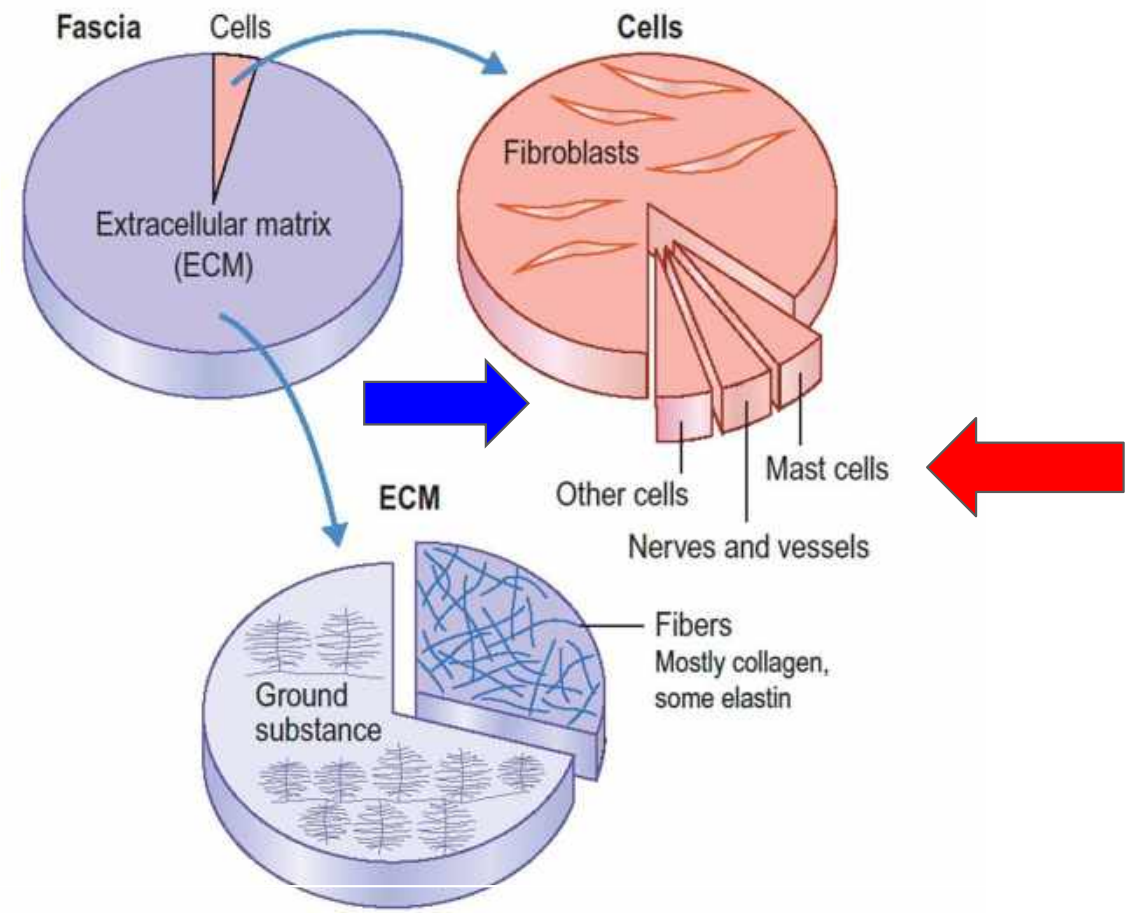
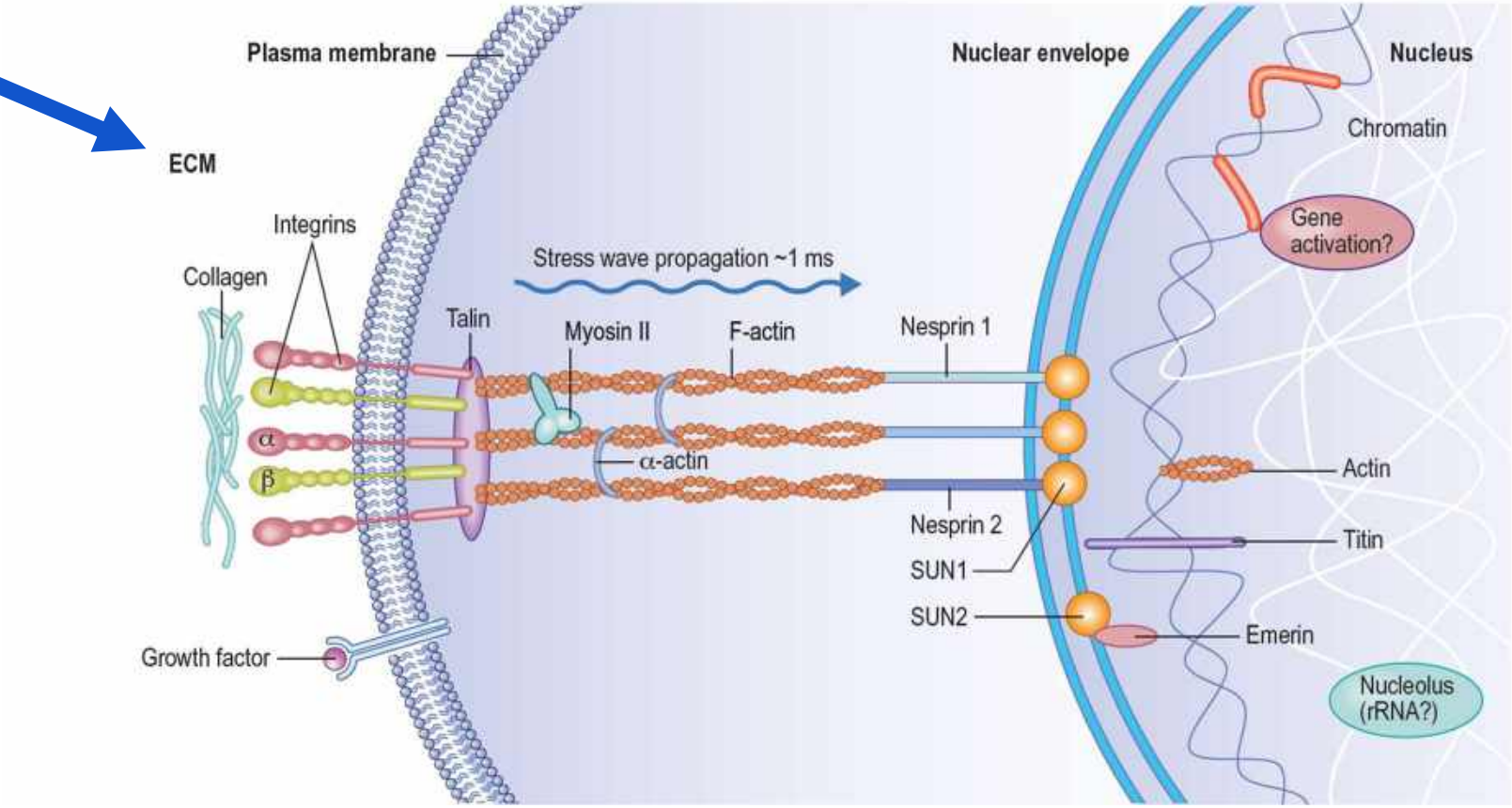


Reproduced with permission from Handspring Publishing Ltd, taken from Fascia: what it is and why it matters by David Lesondak (2017) Adapted from: Fascialnet.com

Terrain - Fascia - ECM



Reproduced with permission from Handspring Publishing Ltd, taken from Fascia: what it is and why it matters by David Lesondak (2017)"

FASCIAL ELASTICITY

dep on pH, temp, inflammation, hormones

https://nflspinzone.com/2015/08/10/tom-bradys-38-best-games/
https://time.com/4031023/tom-brady-shines-in-first-game-after-deflategate-ruling/
https://www.stack.com/a/heres-why-its-really-really-hard-to-sack-tom-brady

Factors affecting Fascia: form & fxn

- Mechanical force
- pH of tissue
- Immune dysregulation
- Inflammation
- Temperature
- Hormones, MST’s

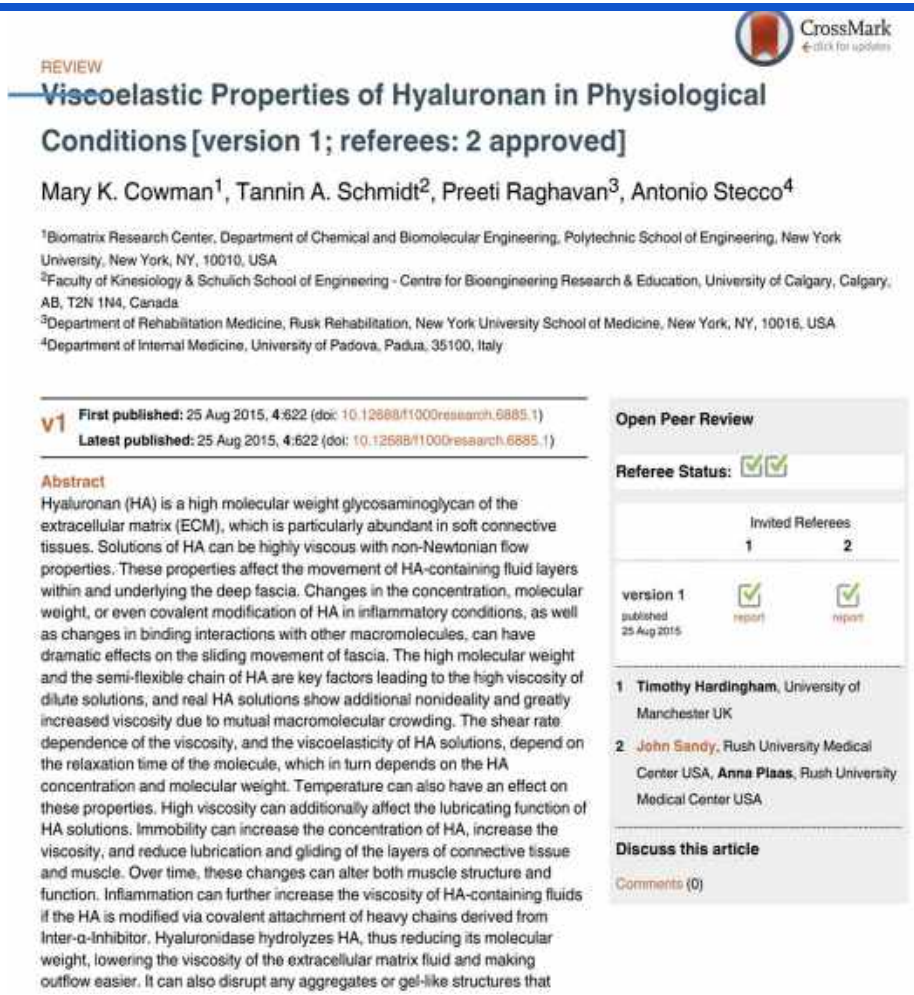
Fascia Needs to Move!

Fascia Likes Movement

- **High viscosity** impairs the lubricating function of hyaluronic acid (HA) solutions.
- **Immobility** increases HA concentration, which raises viscosity and reduces lubrication and gliding between layers of connective tissue and muscle.
- **Chronic changes** in viscosity and movement can alter both muscle structure and function over time.
- **Inflammation** can further elevate HA viscosity, compounding these effects and reducing tissue mobility.

Cowman MK, Schmidt TA, Raghavan P and Stecco A. Viscoelastic Properties of Hyaluronan in Physiological Conditions [version 1; peer review: 2 approved]. *F1000Research* 2015, **4**:622 (https://doi.org/10.12688/f1000research.6885.1)

Fascia and Temperature



REVIEW

Viscoelastic Properties of Hyaluronan in Physiological Conditions [version 1; referees: 2 approved]

Mary K. Cowman[1], Tannin A. Schmidt[2], Preeti Raghavan[3], Antonio Stecco[4]

[1]Biomatrix Research Center, Department of Chemical and Biomolecular Engineering, Polytechnic School of Engineering, New York University, New York, NY, 10010, USA
[2]Faculty of Kinesiology & Schulich School of Engineering - Centre for Bioengineering Research & Education, University of Calgary, Calgary, AB, T2N 1N4, Canada
[3]Department of Rehabilitation Medicine, Rusk Rehabilitation, New York University School of Medicine, New York, NY, 10016, USA
[4]Department of Internal Medicine, University of Padova, Padua, 35100, Italy

v1 **First published:** 25 Aug 2015, **4**:622 (doi: 10.12688/f1000research.6885.1)
Latest published: 25 Aug 2015, **4**:622 (doi: 10.12688/f1000research.6885.1)

Abstract

Hyaluronan (HA) is a high molecular weight glycosaminoglycan of the extracellular matrix (ECM), which is particularly abundant in soft connective tissues. Solutions of HA can be highly viscous with non-Newtonian flow properties. These properties affect the movement of HA-containing fluid layers within and underlying the deep fascia. Changes in the concentration, molecular weight, or even covalent modification of HA in inflammatory conditions, as well as changes in binding interactions with other macromolecules, can have dramatic effects on the sliding movement of fascia. The high molecular weight and the semi-flexible chain of HA are key factors leading to the high viscosity of dilute solutions, and real HA solutions show additional nonideality and greatly increased viscosity due to mutual macromolecular crowding. The shear rate dependence of the viscosity, and the viscoelasticity of HA solutions, depend on the relaxation time of the molecule, which in turn depends on the HA concentration and molecular weight. Temperature can also have an effect on these properties. High viscosity can additionally affect the lubricating function of HA solutions. Immobility can increase the concentration of HA, increase the viscosity, and reduce lubrication and gliding of the layers of connective tissue and muscle. Over time, these changes can alter both muscle structure and function. Inflammation can further increase the viscosity of HA-containing fluids if the HA is modified via covalent attachment of heavy chains derived from Inter-α-Inhibitor. Hyaluronidase hydrolyzes HA, thus reducing its molecular weight, lowering the viscosity of the extracellular matrix fluid and making outflow easier. It can also disrupt any aggregates or gel-like structures that

Open Peer Review

Referee Status: ✓ ✓

	Invited Referees 1	2
version 1 published 25 Aug 2015	✓ report	✓ report

1 **Timothy Hardingham**, University of Manchester UK

2 John Sandy, Rush University Medical Center USA, **Anna Plaas**, Rush University Medical Center USA

Discuss this article

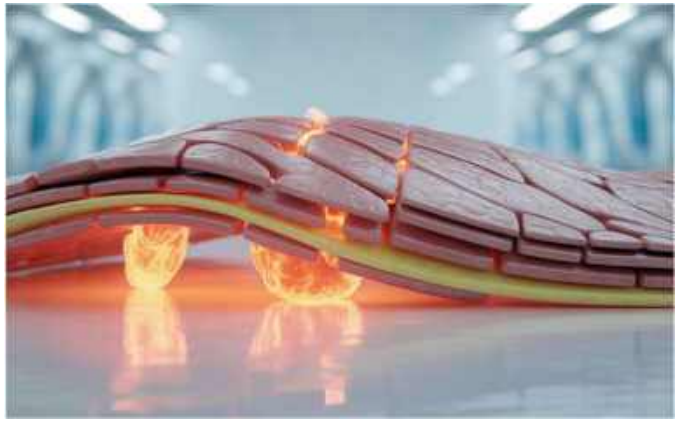
Comments (0)

Cowman MK, Schmidt TA, Raghavan P and Stecco A. Viscoelastic Properties of Hyaluronan in Physiological Conditions [version 1; peer review: 2 approved]. *F1000Research* 2015, **4**:622 (https://doi.org/10.12688/f1000research.6885.1)

Fascia likes Heat

Temperature has an effect on these viscoelastic properties.

HA viscosity and viscoelasticity depend on molecular relaxation time, which is influenced by HA concentration, molecular weight, and temperature.



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Fascia and Temperature

Comparative summary of *cold* plunge duration and *heat* therapy effects on fascia

Parameter	Cold plunge (≤10 min)	Cold plunge (>15 min or repeated)	Heat therapy (38–42°C, 15–20 min)
Acute effects	- Transient stiffness reduction - Pain relief - Improved mobility	- Increased stiffness - Reduced elasticity - Impaired healing	- Increased perfusion - Reduced stiffness - Improved mobility
Chronic effects	Minimal if infrequent	- Chronic stiffening - Fibrosis - Impaired healing	- Enhanced remodeling - Improved healing - Reduced stiffness
Clinical implications	Useful for acute relief	Risk of chronic stiffening and impaired healing	Beneficial for remodeling and healing

Fascia and Temperature

Clinical guidelines and recommendations

- **Cold plunge duration**: Limit immersions to 5–10 minutes to balance short-term relief with long-term fascial health.
- **Frequency**: Avoid frequent or prolonged cold exposure to prevent chronic stiffening and impaired healing.
- **Heat therapy**: Use heat therapy (38–42°C, 15–20 min) to promote fascial remodeling, healing, and reduce stiffness
- **Individual variability**: Consider age, sex, body composition, and health status when tailoring protocols.

Cold plunges provide **short-term relief** but risk chronic stiffening with prolonged or repeated use, whereas heat therapy supports **remodeling & healing** without this risk. Use cold briefly for acute relief & heat for remodeling, & avoid frequent or prolonged cold to preserve long-term fascial health.

1. Fascial tissue research in sports medicine: from molecules to tissue adaptation, injury and diagnostics: consensus statement. *British Journal of Sports Medicine*. (2018).
2. Postexercise cooling lowers skeletal muscle microvascular perfusion and blunts amino acid incorporation into muscle tissue in active young adults. *Medicine and Science in Sports and Exercise*. (2025).

Patient-specific factors influencing *cold and heat* therapy

Patient factor	Cold therapy considerations	Heat therapy considerations
Age	- Reduced circulation - Lower cold tolerance - Higher injury risk	Preferred for *chronic stiffness and poor perfusion*
Sex	- Greater cold sensitivity in women - Especially postmenopausal	*Preferred for women* *- Especially postmenopausal*
Body composition	- Higher adiposity reduces cold penetration - *Leaner patients respond more*	Effective across body types
Comorbidities	- *Avoid in Raynaud's* - Peripheral neuropathy - Cardiovascular disease	*Preferred in these conditions*
Thermal sensitivity	- Individualized dosing - Monitoring required	Individualized dosing - Monitoring required
Psychological factors	- Expectancy - Anxiety modulates outcomes	Address to improve adherence

What role does neuroplasticity play in individual responses to thermal therapies?

Neuroplasticity drives individual **variability in thermal therapy responses** through central sensitization, descending modulation, and BDNF-mediated plasticity.

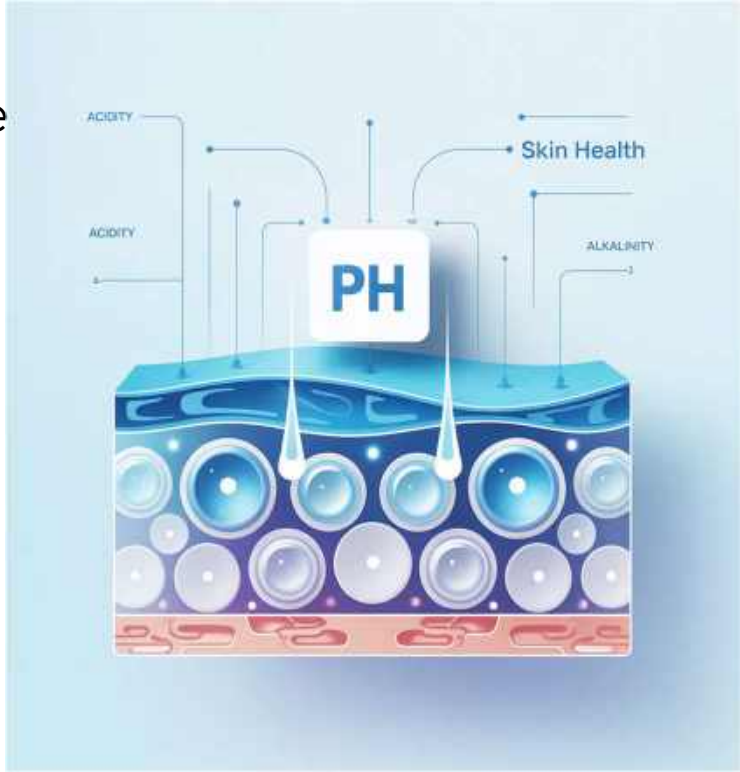
Heat therapy can reduce central sensitization and enhance descending inhibition, whereas

Cold herapymay transiently limit central sensitization via reduced neurotransmission.

Individual differences in BDNF, COMT, and serotonin pathways further shape thermal responses, supporting personalized therapy.

Fascia and pH

- Acid–base status is strongly linked with the **electrolyte balance** in the cells
- The whole body, including fascia, benefits when acid and ph levels are balanced



https://musculoskeletalkey.com/the-influence-of-ph-and-other-metabolic-factors-on-fascial-properties/

Relationship between Low pH in Intervertebral Discs and LBP

A Systematic Review (2012)

- **Low PH** stimulates **hyperstimulation of nerve roots & produces pain**
- Low PH changes **matrix metabolism**--> neuronal death
- Lactate **increases muscle tension**--> Low back pain (LBP)
- EXAMPLE:
  - Skin surgery: Local infiltration with lidocaine into the skin/fascia prior to surgery can sting; bicarbonate added to decrease pain (the 80% of peripheral nerves better with balanced/alkaline pH)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3542485/#:~:text=First%2C%20low%20pH%20caused%20by,death%20and%20low%20back%20pain

Muscle wasting & fascial stiffness in chronic metabolic acidosis

Chronic met acidosis promotes fascial fibrosis & stiffness via sev mechanisms:

- **Increased protein catabolism**: **Acidosis** activates the ubiquitin-proteasome system and caspase-3, increasing protein degradation and reducing muscle mass.
- **Impaired protein synthesis**: Acidosis suppresses protein synthesis via reduced insulin/IGF-1 signaling and altered amino acid transport.
- **Mitochondrial dysfunction**: Acidosis impairs mitochondrial energetics, reducing ATP and contributing to fatigue and weakness.
- **Insulin resistance**: Acidosis worsens insulin resistance, further impairing protein metabolism and muscle function.

Pathophysiological mechanisms leading to muscle loss in chronic kidney disease

Nature Reviews: Nephrology, 2022

Fascia and pH

Summary of chronic metabolic acidosis effects on muscle and fascial health

Pathophysiological mechanism	Clinical manifestation	Therapeutic intervention
Increased protein catabolism	Muscle wasting, reduced strength	Alkali therapy, exercise
Impaired protein synthesis	Reduced muscle mass, weakness	Alkali therapy, nutrition
Mitochondrial dysfunction	Fatigue, reduced endurance	Alkali therapy, exercise
TGF-β activation	Fascial fibrosis, stiffness	Anti-fibrotic agents, manual therapy
Collagen cross-linking	Increased fascial stiffness	Manual therapy, stretching

Pathophysiological mechanisms leading to muscle loss in chronic kidney disease Nature Reviews: Nephrology, 2022

Fascia and pH

Summary of therapeutic interventions

Intervention	Mechanism	Indication	Limitations
Manual therapy	Reduces stiffness	Fascial stiffness	Limited long-term data
Stretching/exercise	Improves compliance	Fascial stiffness	Requires adherence
Anti-fibrotic agents	Reduces fibrosis	Advanced fibrosis	Limited evidence
Plant-based diet	Reduces acid load	Mild acidosis	Dietary adherence

Alkali therapy plus **manual therapy and stretching** are the most effective interventions to reduce fascial stiffness in metabolic acidosis, with anti-fibrotic agents and dietary base-producing foods. Regular monitoring and patient education are essential to maintain **benefits.**

The continuum of acid stress. *Clinical Journal of the American Society of Nephrology*. (2021).

Plant based eating

Standard American Diet

Effects on the ECM/Fascia

- Activates the inflammasome
- Epigenetically, changes gene expression

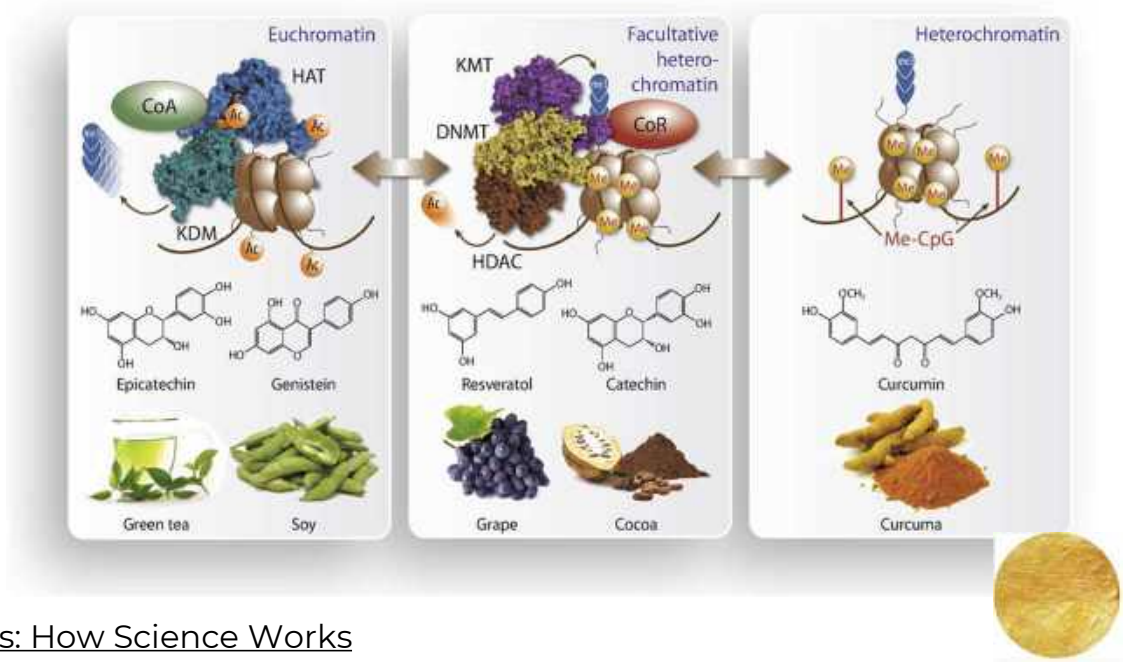


Image Source: Nutrigenomics: How Science Works

Omega 3 Fats For Fascia

"Eicosapentaenoic acid **(EPA)** is a key **anti-inflammatory**/anti-aggregatory polyunsaturated omega-3 fatty acid. Conversely, the omega-6 fatty acid, arachidonic acid (AA) is a precursor to **pro-inflammatory**/pro-aggregatory mediators (Nelson & Raskin, 2019)."

An OmegaCheck®, gives a ratio of arachidonic acid (AA) to EPA.

- Avg. AA:EPA ratio is 25
- **Ideal AA:EPA ratio is less than 3**

When fascia is inflamed, **omega 3** decreases inflammation.

Olive oil, an unsaturated fatty acid, has ability to reduce inflammation.

- Many people are low on **oleic acid**, which is found in olive oil

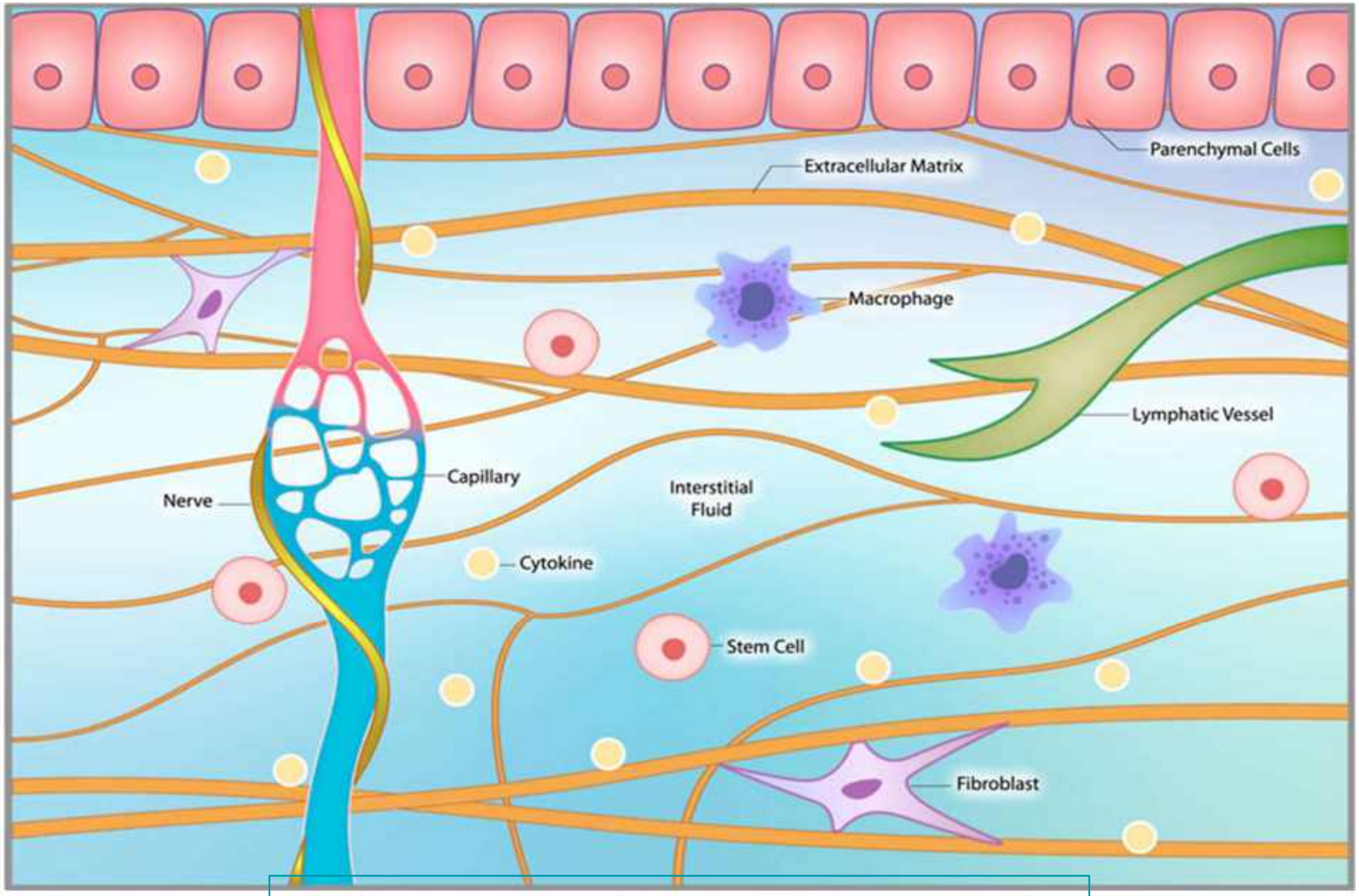
https://pubmed.ncbi.nlm.nih.gov/31063407/

https://pubmed.ncbi.nlm.nih.gov/23375840/

Immune cells in fascial tissue

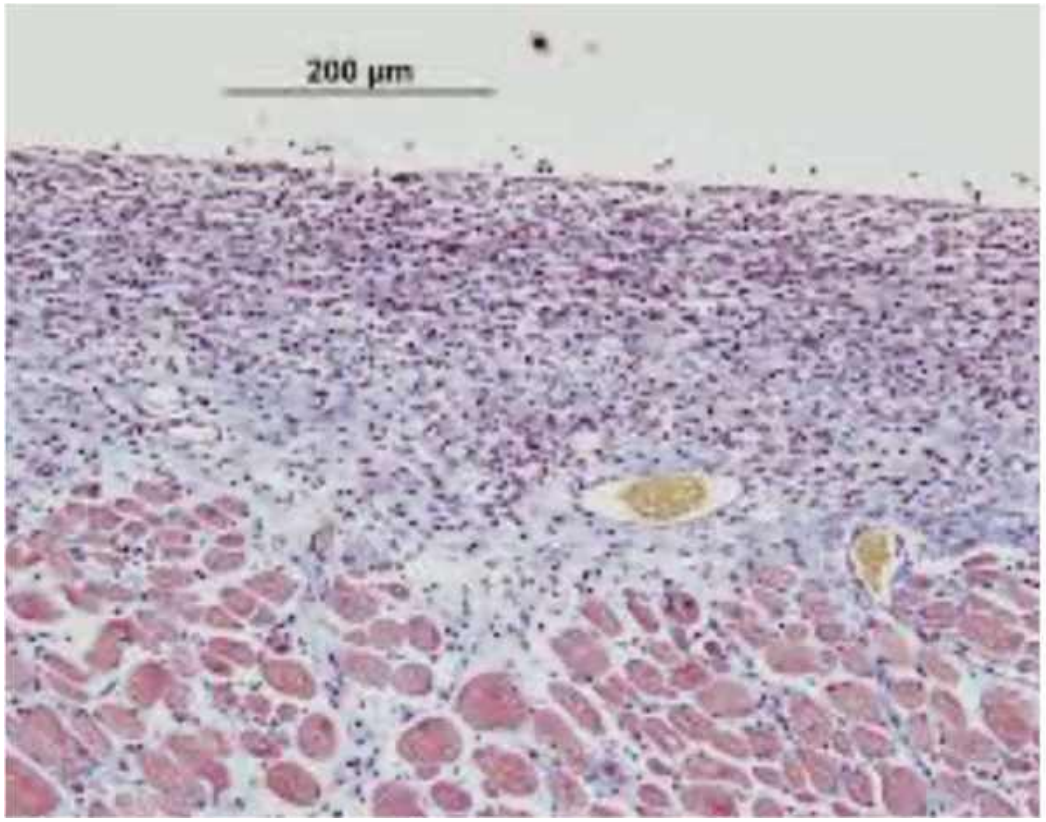
Fascial tissue harbors several immune cell types that contribute to homeostasis, inflammation, and repair.

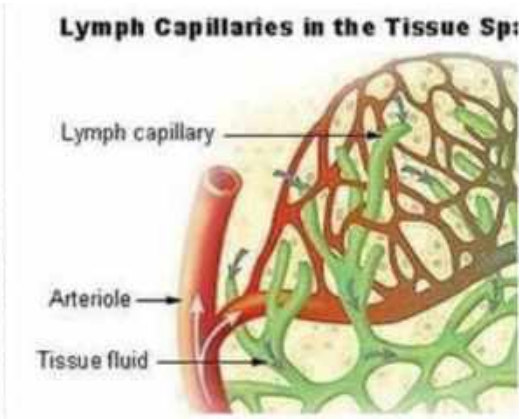
- **Macrophages:** Tissue-resident macrophages are key **innate immune** cells in fascia, sensing injury or infection and orchestrating ***early*** inflammatory responses. They release cytokines, chemokines, and proteases that recruit other immune cells and remodel the ECM.
- **Mast cells:** Mast cells are **abundant** in fascia and ***rapidly*** **respond** to injury or stress by releasing histamine, proteases, and cytokines. They amplify inflammation, increase vascular permeability, and recruit immune cells.
- **Fibroblasts:** Although considered structural cells, fibroblasts have **immunoregulatory** functions. They produce ECM components and can differentiate into myofibroblasts that **drive fibrosis** and tissue remodeling .
- **Lymphocytes: T and B lymphocytes** infiltrate fascia during inflammation or injury, contributing to adaptive immune responses and tissue repair.

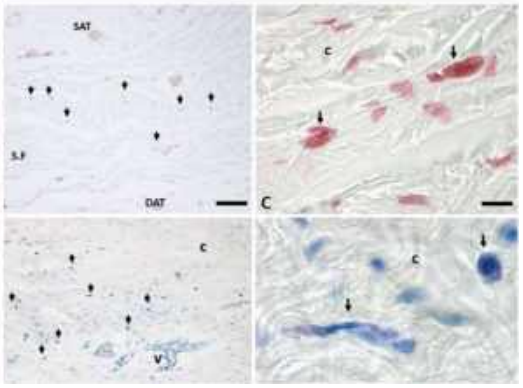


https://www.frontiersin.org/articles/10.3389/fphys.2022.904107/full

Immune cells in fascial tissue

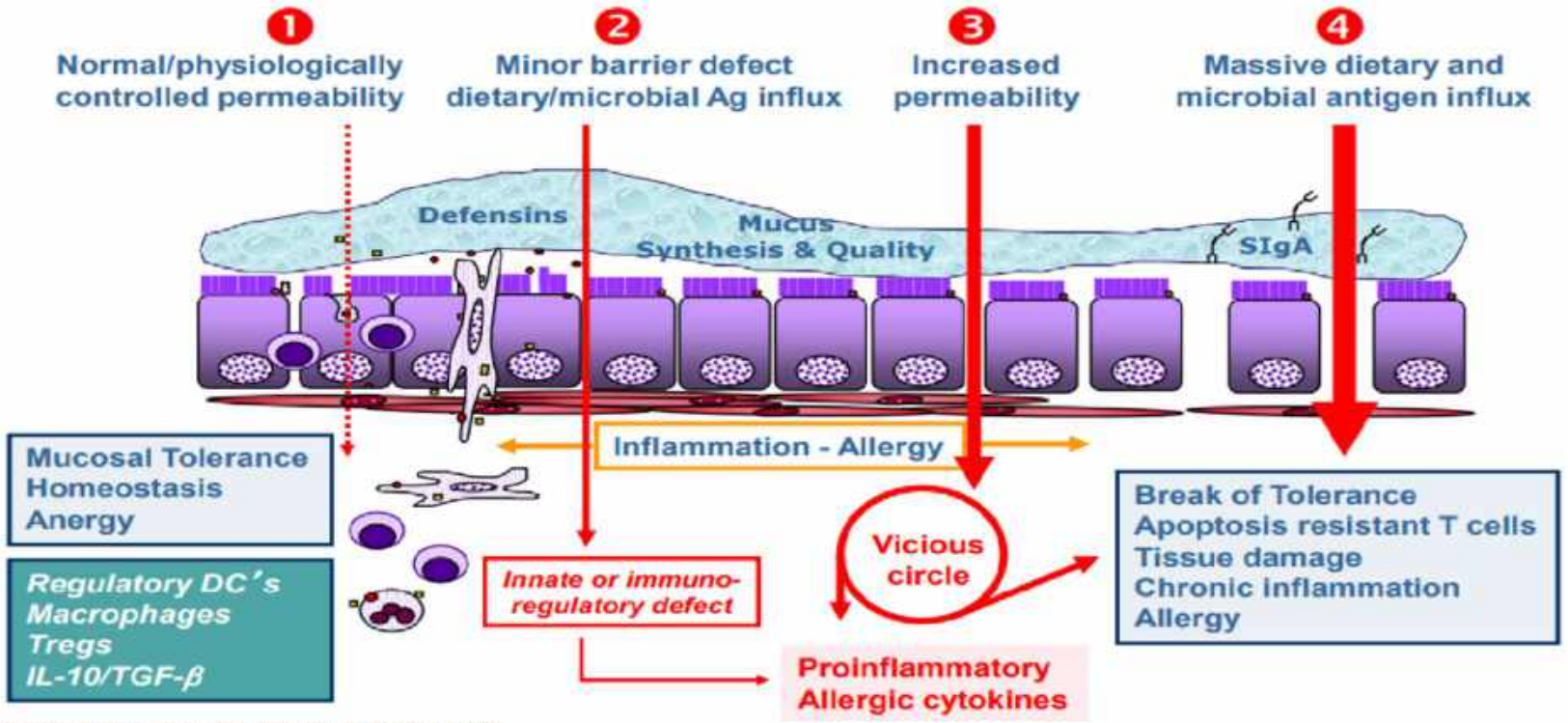




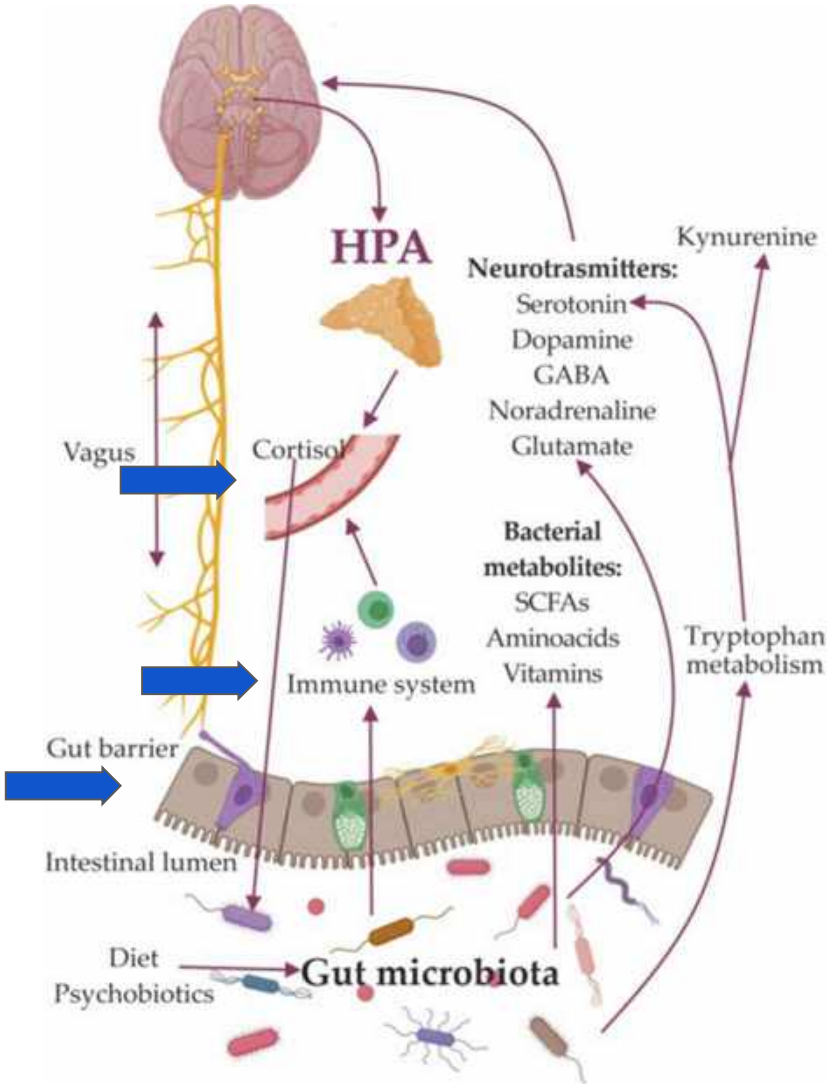


Loss of Mucosal Immune Homeostasis

Chronic Inflammation-Allergy



Adapted from P. Brandtzaeg, Beneficial Microbes 2010



Immune cells in fascial tissue

Interactions between immune cells and the ECM

Immune cells and the ECM engage in bidirectional interactions that regulate inflammation, repair, and fibrosis:

- **Immune cell-mediated ECM remodeling**: Macrophages and mast cells release proteases (e.g. MMPs) that degrade ECM components, facilitating immune cell migration and tissue remodeling.
- **ECM-guided immune cell behavior:** ECM components provide biochemical cues that guide immune cell adhesion, migration, and activation. For example, fibronectin and hyaluronic acid facilitate immune cell migration and activation.
- **Fibroblast-immune cell *crosstalk*:** Fibroblasts produce ECM components and cytokines that modulate immune cell behavior. Reciprocally, immune cells release cytokines (e.g. TGF-β, IL-1β) that activate fibroblasts and promote ECM production and fibrosis.

Fibroblasts as immune regulators in infection, inflammation and cancer

Nature Reviews: Immunology, 2021

Immune cells in fascial tissue

What are the implications of fibroblast differentiation on chronic pain management strategies

Fibroblast differentiation into *myofibroblasts* contributes to chronic pain through several mechanisms:

- **Increased** extracellular matrix **(ECM) stiffness: *Myofibroblasts*** produce excess collagen and ECM proteins, increasing tissue stiffness and *reducing compliance*, which *activates nociceptors* and causes pain.
- **Activation of nociceptors**: Stiffer ECM and myofibroblast-derived **factors** (e.g. ***TGF-β, IL-1β)*** sensitize nociceptors, lowering pain thresholds and causing **hyperalgesia**.
- **Sustained inflammation**: Myofibroblasts **secrete pro-inflammatory** cytokines and chemokines, **perpetuating** inflammation and **pain**.
- **Neuro-immune interactions**: ***Myofibroblasts*** **interact with sensory neurons**, amplifying nociceptive signaling and contributing to chronic pain.

1. Evidence-based clinical practice guidelines on regenerative medicine treatment for chronic pain: a consensus report from a multispecialty working group. *Journal of Pain Research*. (2024).

Immune cells in fascial tissue

Fibroblast differentiation into myofibroblasts is a **key driver of chronic pain** through ECM stiffness, nociceptor activation, and sustained inflammation.

Personalized medicine approaches

Consider **patient-specific factors** — such as genetic *polymorphisms*, *environmental exposures, and lifestyle* — to tailor interventions.

Genetic polymorphisms in TGF-β and ECM-related genes influence myofibroblast activity and pain sensitivity, supporting individualized therapy.

Environmental factors (e.g. mechanical stress, inflammation) modulate myofibroblast differentiation and pain, guiding targeted interventions.

Lifestyle factors (e.g. diet, exercise) influence myofibroblast activity and pain, supporting personalized management .

Inhibiting TGF-β signaling pathway for disease therapy: challenges and opportunities Cytokine, 2025

Immune cells in fascial tissue

Personalized medicine approaches

Manual therapy and exercise	Reduce ECM stiffness and improve tissue compliance, alleviating pain	Clinical studies show improvements in pain and function
Regenerative medicine (PRP, MSCs, MST's)	Modulate inflammation and ECM remodeling, promoting tissue repair and reducing pain	Growing clinical evidence supports analgesic and functional benefits

Evidence-based clinical practice guidelines on regenerative medicine treatment for chronic pain: a consensus report from a multispecialty working group Journal of Pain Research, 2024

How does the extracellular matrix composition influence myofibroblast function in different tissues?

ECM composition shapes **myofibroblast function** by providing **biochemical and mechanical cues** that regulate differentiation, contractility, and survival.

Collagen-rich, stiff matrices promote myofibroblast activation and persistence. Collagen **cross-linking** increases matrix stiffness, further enhancing myofibroblast activation and persistence

Fibronectin and hyaluronan support early migration and matrix assembly. **Hyaluronan** is a glycosaminoglycan that contributes to tissue hydration, lubrication, and cell migration

The ECM stores and releases growth factors and cytokines that regulate myofibroblast function.

TGF-β is a key profibrotic cytokine that promotes myofibroblast differentiation, contractility, and survival

Fibrosis: from mechanisms to medicines Nature, 2020

Matrix as an interstitial transport system Circulation Research, 2014

Clinical implications and therapeutic strategies

Understanding **ECM–myofibroblast interactions** has important clinical implications.

Targeting ECM stiffness and composition is a promising antifibrotic strategy.

Therapeutic approaches include:

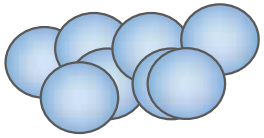
- **Anti-fibrotic agents**: Losartan, PRP/PRF and peptides/MSC's reduce ECM production and myofibroblast activation.
- **Mechanical modulation**: Controlled loading and soft substrates reduce myofibroblast activation and promote regeneration.
- **ECM-targeted therapies**: Targeting specific ECM components may modulate myofibroblast function..

Fibrosis: from mechanisms to medicines Nature, 2020

Extracellular matrix stiffness regulates microvascular stability by controlling endothelial paracrine signaling to determine pericyte fate Arteriosclerosis, Thrombosis, and Vascular Biology, 2023

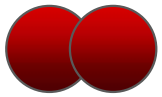
Salutary vs. Inflammatory Environment

Salutary Environment



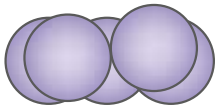
B-Cells

Robust secretion of
High-avidity antibodies



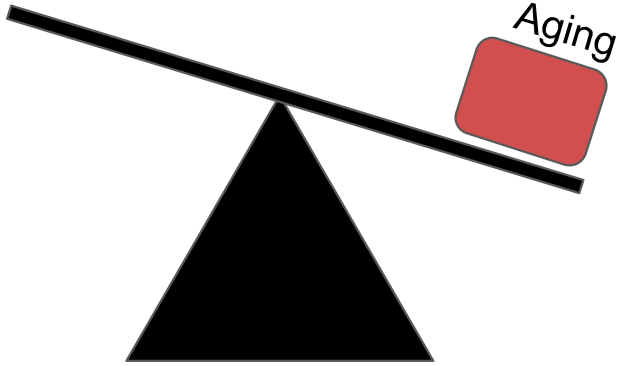
CD8+ CD28+ T Cells

Diverse repertoire
Robust response to antigens



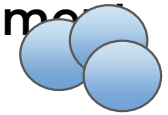
CD4+ T Cells

Diverse repertoire
Robust response to antigens



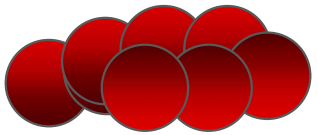
Strength of immune response

Inflammatory Environment



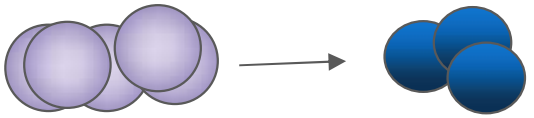
B-Cells

Reduced antibody avidity /
number of responding cells



CD8+ CD28+ T Cells

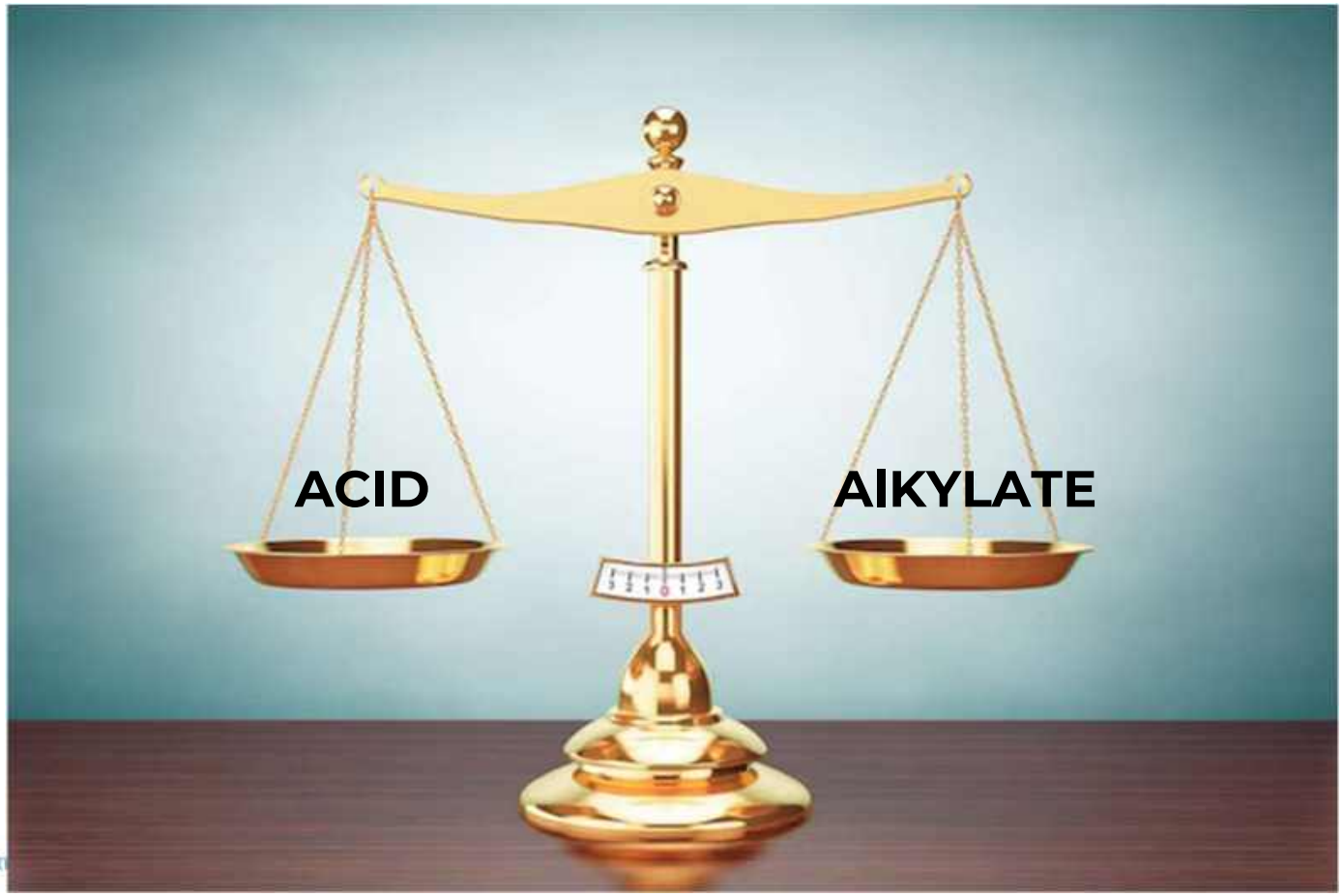
Expansion of CD8+ CD28- cells
Skewed repertoire



CD4+ T Cells

Increased differentiation into TH17 cells

Balance



Qi/Chi

Qi/Chi

The vital life force that animates all things and whose ***balance*** is crucial for health and well-being

Yin/Yang

Complimentary opposing forces that make up qi; not separate entities;

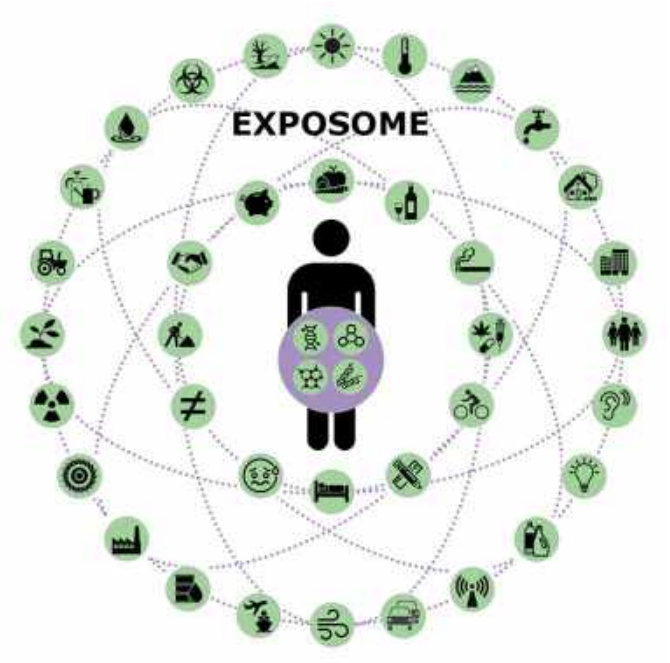
Interact and exist in relation to each other

Via interdependent, dynamic harmonious interplay

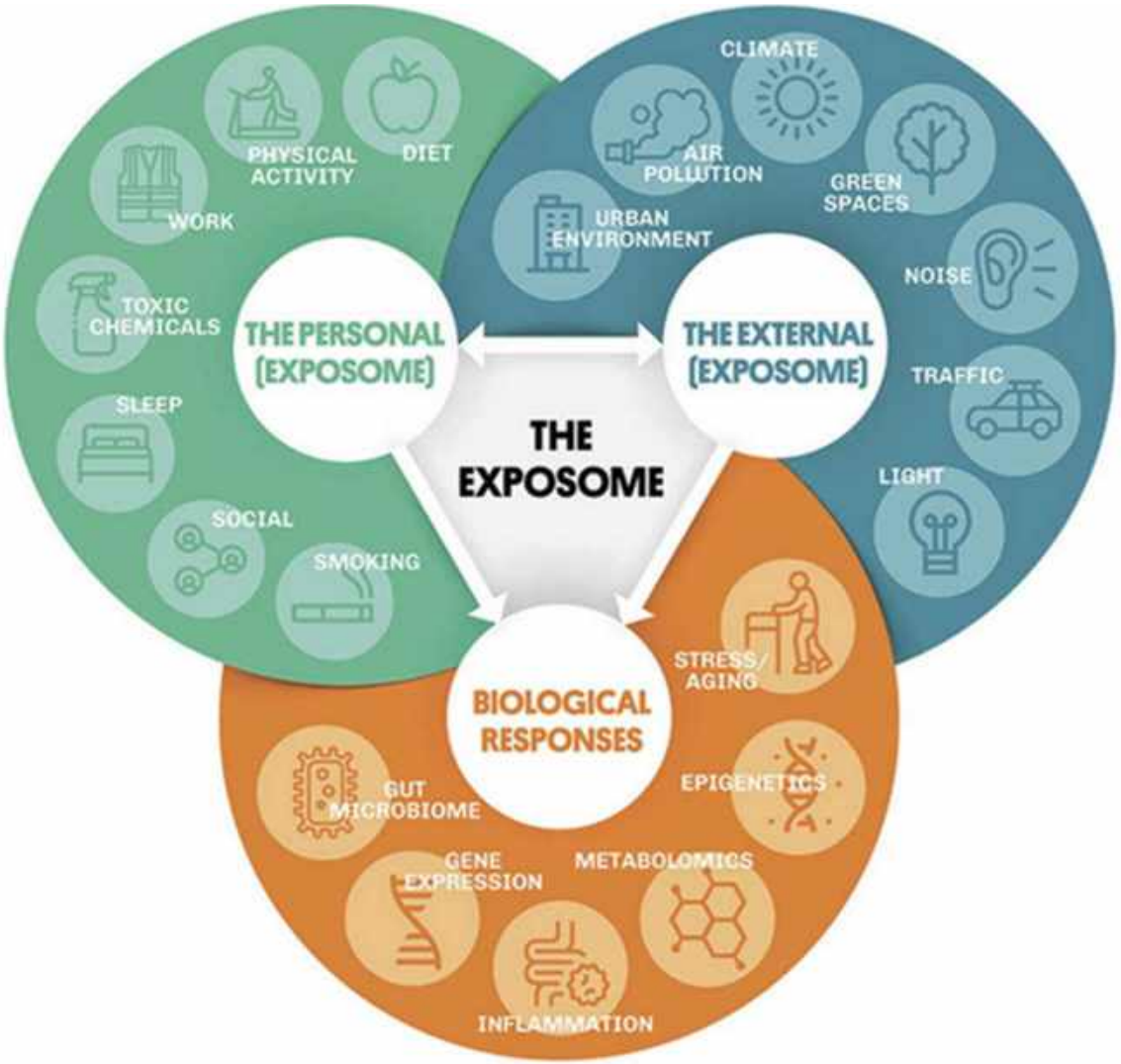
Yin represents the material form, and substance of things

Yang represents the function, movement and energy of things

Exposome + Fascia



Immune dysregulation,



The Exposome

- **Exposome** refers to the sum of all exposures an individual encounters throughout their life.

- According to the Centers for Disease Control and Prevention, “genetics has been found to account for only about 10% of diseases, and the remaining causes appear to be from environmental causes”.

- Factors affecting individual’s exposome: **genetics, lifestyle, occupation, living environment, and diet, etc**

(CDC, Exposome and Exposomics)

Environmental Stressors

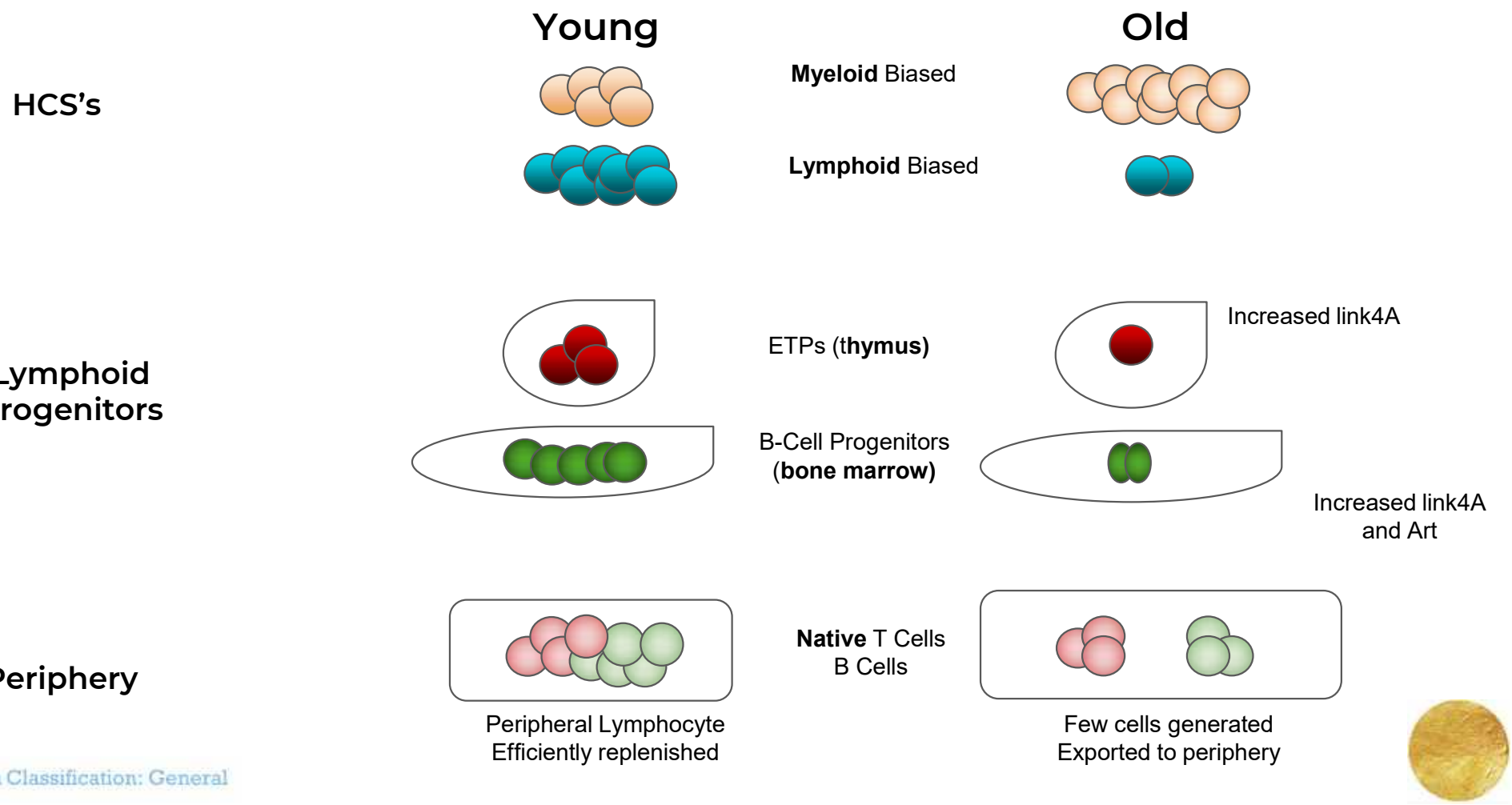
- The environment we live in exposes us to many **physical** and **chemical external factors** that affect our health.

- A research study by Jiang in 2019, called the ‘Dynamic Human Environment’
  - Fifteen different individuals from over 66 different geographical locations were studied for 890 days (2.5 yrs)
  - Researchers found that the participants were **exposed to thousands of environmental factors**, including chemical and microbial
  - The findings further reinforced exposome is highly **diverse** and **dynamic**; it is **dependent** on **location**, **lifestyles**, and different **seasonal times** of the year

Importance of lifestyle & the exposome

- The EXPOSOME: the cumulative influence of environmental, diet and lifestyle exposures can lead to differing "**immune identities**".
- The accumulation of immune cells that have had mutational injury and epigenetic changes as a result of lifestyle and environmental factors may increase the inflammatory state of the individual

Immunity: Bone Marrow + Thymus + Periphery



Exposome: Adjuvants

- Substances that enhance antigen-specific immune responses.

- Autoimmune/Inflammatory Syndrome Induced by Adjuvants **“ASIA”**
  - AKA Shoenfeld Syndrome
  - Three most common symptoms:
    - **Arthralgia**: commonly termed joint pain
    - **Myalgia**: muscle pain
    - **Chronic fatigue**: extreme long term fatigue
  - Most common ASIA is Undifferentiated Connective Tissue Disease (**UCTD**)

Introduction

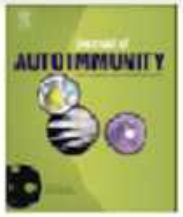
***Dr. Yehuda Shoenfeld**, whom many consider the father of modern day immunology, has said that autoimmune diseases are a "kaleidoscope". Like a kaleidoscope, when one part of the immune system is changed, it affects many of the other sequences of the immune system. Previously, the understanding of autoimmune and autoinflammatory disease was thought to be a mystery. Now, with this kaleidoscopic lens, our understanding of autoimmune and autoinflammatory diseases is advancing.*

ASIA Syndrome: 2010

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm



https://www.sciencedirect.com/science/article/pii/S155541552100547X

Review

'ASIA' – Autoimmune/inflammatory syndrome induced by adjuvants

Yehuda Shoenfeld [a,b,*], Nancy Agmon-Levin [a]

[a] The Zabludowicz Center for Autoimmune Diseases, Department of Medicine B' Sheba Medical Center, Tel-Hashomer, Israel
[b] Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Sackler Faculty of Medicine, Tel-Aviv University, Israel

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Silicone

ABSTRACT

The role of various environmental factors in the pathogenesis of immune mediated diseases is well established. Of which, factors entailing an immune adjuvant activity such as infectious agents, silicone, aluminium salts and others were associated with defined and non-defined immune mediated diseases both in animal models and in humans. In recent years, four conditions: siliconosis, the Gulf war syndrome (GWS), the macrophagic myofasciitis syndrome (MMF) and post-vaccination phenomena were linked with previous exposure to an adjuvant. Furthermore, these four diseases share a similar complex of signs and symptoms which further support a common denominator. Thus, we review herein the current data regarding the role of adjuvants in the pathogenesis of immune mediated diseases as well as the amassed data regarding each of these four conditions. Relating to the current knowledge we would like to suggest to include these comparable conditions under a common syndrome entitled **ASIA**, "Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants".

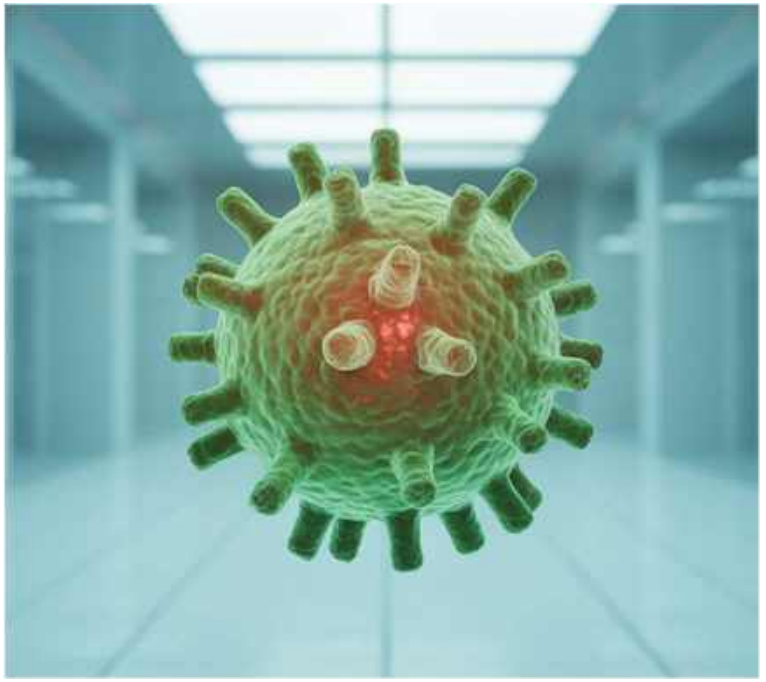
ASIA Syndrome

- **5 immune mediated conditions**: post vaccine phenomenon, macrophagic myofasciitis syndrome (MMF) , GWS, Siliconosis, SBS (sick building syndrome)
- All associated with **prior exposure** to various agents: **vaccines, silicone**
- Related to individual genetic predisposition : **HLA-DRB1, HLA-DRB4**
- Results from exposure to **external** or **endogenous adjuvants**
- Triggers clinical manifestations, autoimmune conditions

https://www.sciencedirect.com/science/article/pii/S155541552100547X

ASIA Syndrome

- **Post vaccination syndrome** and **MMF**- can be induced by adjuvants, such as **aluminum hydroxide**
- **GWS** – likely induced by adjuvants squalene, graphene
- **Siliocinosis** - likely induced by adjuvant silicone
- Sick building syndrome



Deployed who are ill	95% had antibodies to squalene
Undeployed but had same signs and symptoms of MMF	**100%** had antibodies to squalene

https://www.sciencedirect.com/science/article/pii/S155541552100547X

ME / CFS Definition

- ***Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*** will be a valuable resource to promote the prompt diagnosis of patients with this *complex, multisystem, and often devastating disorder* (IOM 2015)

- The IOM committee recommends a new name to replace **ME/CFS: systemic exertion intolerance disease (SEID)**. This name captures a central characteristic of the disease—the fact that exertion of any sort (physical, cognitive, or emotional)—can adversely affect multiple organ systems

"Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." *MECFS Clinicians Guide*, Institute of Medicine of The National Academies, https://nap.nationalacademies.org/resource/19012/MECFSclinicianguide.pdf.

Post Vaccine Syndrome/ ME / CFS/ Long Covid

As part of this ongoing inflammatory process common to individuals with LC and ME/CFS, mast cell activation and degranulation may occur, resulting in the initiation of pro-inflammatory cytokine cascades leading to hyperinflammation within the connective tissue of individuals with PASC and ME/CFS without hypermobility

Source: Ganesh R and Munipalli B (2024) Long COVID and hypermobility spectrum disorders have shared pathophysiology. *Frontiers in Neurology*. 15:1455498. doi: 10.3389/fneur.2024.1455498

PVS/ LC/ ME / CFS

Long COVID and hypermobility spectrum disorders have shared pathophysiology

Ravindra Ganesh[1†] and Bala Munipalli[2*†]

[1]Division of General Internal Medicine, Mayo Clinic, Rochester, MN, United States, [2]Division of General Internal Medicine, Mayo Clinic, Jacksonville, FL, United States

While the exact pathophysiology remains elusive, the major putative etiologies of both LC and ME/CFS include persistent viral remnants, persistent cell-mediated inflammation, endothelial dysfunction, and dysautonomia

hypermobility and other related conditions including fibromyalgia, POTS, ME/CFS, chronic pain conditions, joint pain, and myalgia is essential for individuals experiencing LC. Pharmacological treatments should be symptom-focused and geared to a patient's presentation. Paced exercise, massage, yoga, and meditation may also provide benefits.

Source: Ganesh R and Munipalli B (2024) Long COVID and hypermobility spectrum disorders have shared pathophysiology. *Frontiers in Neurology*. 15:1455498. doi: 10.3389/fneur.2024.1455498

ASIA Syndrome: 2017

Lupus (2017) 26, 675–681
journals.sagepub.com/home/lup

UPDATE

Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome) – An update

A Watad[1,2,3], M Quaresma[3], S Brown[2], JW Cohen Tervaert[4], I Rodríguez-Pint[5], R Cervera[5], C Perricone[6] and Y Shoenfeld[1,3,7]

[1]Department of Medicine B, Sheba Medical Center, Tel-Hashomer, Israel; [2]Sackler Faculty of Medicine, Tel-Aviv University, Israel; [3]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Israel; [4]Clinical and Experimental Immunology, Reinaert Clinic, The Netherlands; [5]Department of Autoimmune Diseases, Hospital Clinic, Spain; [6]Reumatologia, Dipartimento di Medicina Interna e Specialita Mediche, Sapienza Universita di Roma, Italy; and [7]Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Tel-Aviv University, Israel

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) has been widely described in many studies conducted thus far. The syndrome incorporates five immune-mediated conditions, all associated with previous exposure to various agents such as vaccines, silicone implants and several others. The emergence of ASIA syndrome is associated with individual genetic predisposition, for instance those carrying HLA-DRB1*01 or HLA-DRB4 and results from exposure to external or endogenous factors triggering autoimmunity. Such factors have been demonstrated as able to induce autoimmunity in both animal models and humans via a variety of proposed mechanisms. In recent years, physicians have become more aware of the existence of ASIA syndrome and the relationship between adjuvants exposure and autoimmunity and more cases are being reported. Accordingly, we have created a registry that includes at present more than 300 ASIA syndrome cases that have been reported by different physicians worldwide, describing various autoimmune conditions induced by diverse adjuvants.

In this review, we have summarized the updated literature on ASIA syndrome and the knowledge accumulated since 2013 in order to elucidate the association between the exposure to various adjuvant agents and its possible clinical manifestations. Furthermore, we especially referred to the relationship between ASIA syndrome and systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). *Lupus* (2017) **26**, 675–681.

ASIA Syndrome and Silicon

- Silicone implants : intraocular lenses, artificial heart valves, joints, breasts
- In genetically susceptible pts can act as an **immunologic adjuvant** to **enhance Ag-specific immune response**
- Enhanced production and activation of **T and B cells**, **high levels of IgG Ab, and TH1/TH17 cells** in the silicone capsule
- Induces **immunogenic response** via cross reaction w/GAGs, natural and silicone-containing molecules in connective tissues
- Effects are **local and distant** in lymph nodes, lung, liver & other **tissues**

https://www.sciencedirect.com/science/article/pii/S155541552100547X

Siliconosis

Current Progress in Breast Implant-Associated Anaplastic Large Cell Lymphoma

Yichen Wang‡, Qi Zhang‡, Yufang Tan, Wenchang Lv, Chongru Zhao, Mingchen Xiong, Kai Hou, Min Wu*, Yuping Ren*, Ning Zeng* and Yiping Wu*†

Department of Plastic and Cosmetic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is an uncommon type of T-cell lymphoma. Although with a low incidence, the epidemiological data raised the biosafety and health concerns of breast reconstruction and breast augmentation for BIA-ALCL. Emerging evidence confirms that genetic features, bacterial contamination, chronic inflammation, and textured breast implant are the relevant factors leading to the development of BIA-ALCL. Almost all reported cases with a medical history involve breast implants with a textured surface, which reflects the role of implant surface characteristics in BIA-ALCL. With this review, we expect to highlight the most significant features on etiology, pathogenesis, diagnosis, and therapy of BIA-ALCL, as well as we review the physical characteristics of breast implants and their potential pathogenic effect and hopefully provide a foundation for optimal choice of type of implant with minimal morbidity.

"Histologic examination of the skin nodules showed proliferation of lymphocytes with irregular shapes and polymorphic nuclei, indicating skin involvement as the first manifestation of BIA-ALCL. Notably, Bautista-Quach et al. reported the first case of bilateral BIA-ALCL after bilateral breast implantation in 2013 (10). "

"Besides, Laurent et al. investigated that BIA-ALCL was a unique clinical entity consisting of two histological subtypes depended on clinical characteristics: in situ BIA-ALCL, the effusion around the implant, anaplastic cell proliferation confined to the fibrous capsule; infiltrative BIA-ALCL, the palpable mass penetrating adjacent tissue and sometimes resembling Hodgkin lymphoma (7)."

Current Progress in Breast Implant-Associated Anaplastic Large Cell Lymphoma



Yichen Wang[‡], Qi Zhang[‡], Yufang Tan, Wenchang Lv, Chongru Zhao, Mingchen Xiong, Kai Hou, Min Wu[*], Yuping Ren[*], Ning Zeng[*] and Yiping Wu[*†]

Department of Plastic and Cosmetic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is an uncommon type of T-cell lymphoma. Although with a low incidence, the epidemiological data raised the biosafety and health concerns of breast reconstruction and breast augmentation for BIA-ALCL. Emerging evidence confirms that genetic features, bacterial contamination, chronic inflammation, and textured breast implant are the relevant factors leading to the development of BIA-ALCL. Almost all reported cases with a medical history involve breast implants with a textured surface, which reflects the role of implant surface characteristics in BIA-ALCL. With this review, we expect to highlight the most significant features on etiology, pathogenesis, diagnosis, and therapy of BIA-ALCL, as well as we review the physical characteristics of breast implants and their potential pathogenic effect and hopefully provide a foundation for optimal choice of type of implant with minimal morbidity.

https://www.frontiersin.org/articles/10.3389/fonc.2021.785887/full

ASIA Syndrome and Silicon

- Symptoms: **heterogeneous**

  aches, stiffness, pain, fatigue, headache, depression, dry eyes/mouth, hair loss, unexplained fever, impaired cognition, paresthesia

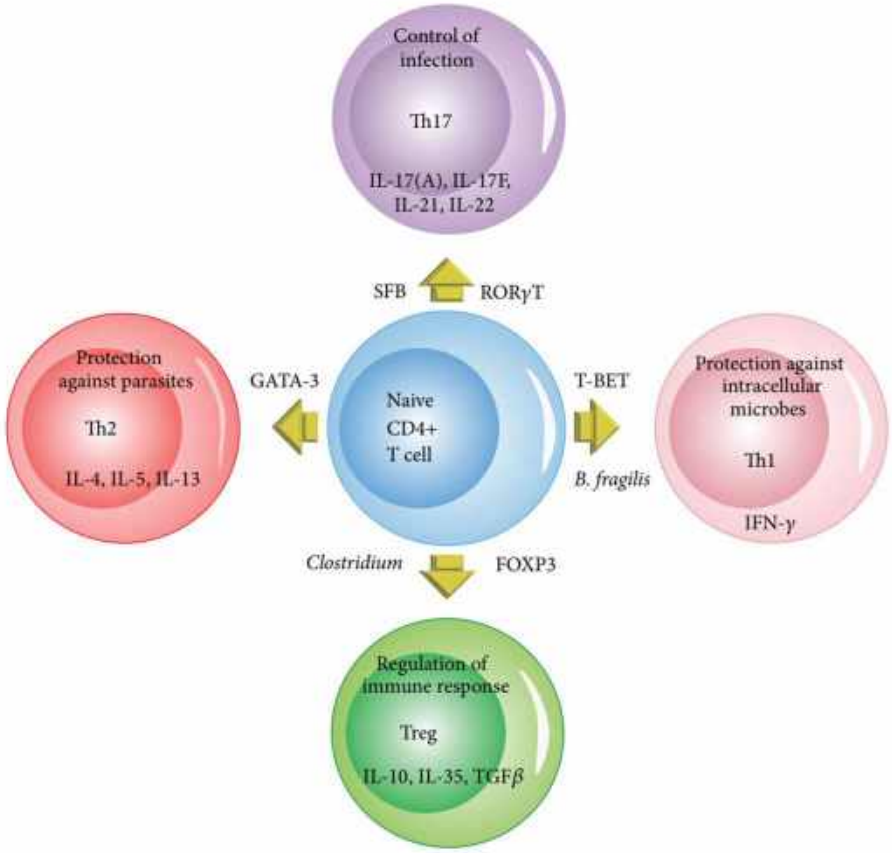
- Associated w/ a variety of **Connective Tissue Disorders**:

  UCTD, MCTD, Polymyositis, Raynauds, Scleroderma,

  Dermatomyositis

https://www.sciencedirect.com/science/article/pii/S155541552100547X

Autoimmunity: Imbalance of Treg/Th1 and Th17



Andrew W. Campbell. 2014. "Autoimmunity and the Gut." *Autoimmune Diseases* 2014: 152428-12. doi:10.1155/2014/152428. http://dx.doi.org/10.1155/2014/152428.

ASIA Syndrome: 2017

Clin Rheumatol (2018) 37:483–493
DOI 10.1007/s10067-017-3748-9

ORIGINAL ARTICLE

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry

Abdulla Watad[1,2] · Mariana Quaresma[1,3] · Nicola Luigi Bragazzi[4] · Ricard Cervera[5] · Jan Willem Cohen Tervaert[6] · Howard Amital[1,2] · Yehuda Shoenfeld[1,2,7]

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Abstract The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is a recently identified condition in which the exposure to an adjuvant leads to an aberrant autoimmune response. We aimed to summarize the results obtained from the ASIA syndrome registry up to December 2016, in a descriptive analysis of 300 cases of ASIA syndrome, with a focus on the adjuvants, the clinical manifestations, and the relationship with other autoimmune diseases. A Web-based registry, based on a multicenter international study, collected clinical and laboratory data in a form of a questionnaire applied to patients with ASIA syndrome. Experts in the disease validated all cases independently. A comparison study regarding type of adjuvants and differences in clinical and laboratory findings was performed. Three hundred patients were analyzed. The mean age at disease onset was 37 years, and the mean duration of time latency between adjuvant stimuli and development of autoimmune conditions was 16.8 months, ranging between 3 days to 5 years. Arthralgia, myalgia, and chronic fatigue were the most frequently reported symptoms. Eighty-nine percent of patients were also diagnosed with another defined rheumatic/autoimmune condition. The most frequent autoimmune disease related to ASIA syndrome was undifferentiated connective tissue disease (UCTD). ASIA syndrome is associated with a high incidence of UCTD and positive anti-nuclear antibodies (ANA) test. Clinical and laboratory features differ from the type of adjuvant used. These findings may contribute to an increased awareness of ASIA syndrome and help physicians to identify patients at a greater risk

Yehuda Shoenfeld
shoenfel@post.tau.ac.il

https://www.sciencedirect.com/science/article/pii/S155541552100547X

ASIA: Criteria for Diagnosis

Table 1 Proposed criteria for the diagnosis of "ASIA"

Major criteria

Exposure to an external stimulus (infection, vaccine, silicone, adjuvant) prior to clinical manifestations

The appearance of "typical" clinical manifestations

- Myalgia, myositis, or muscle weakness
- Arthralgia and/or arthritis
- Chronic fatigue, un-refreshing sleep, or sleep disturbances
- Neurological manifestations (especially associated with demyelination)
- Cognitive impairment, memory loss
- Pyrexia, dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor criteria

The appearance of autoantibodies or antibodies directed at the suspected adjuvant

Other clinical manifestations (i.e., irritable bowel syn.)

Specific HLA (i.e., HLA DRB1, HLA DQB1)

Evolvement of an autoimmune disease (i.e., multiple sclerosis, systemic sclerosis)

https://pubmed.ncbi.nlm.nih.gov/28741088/

ASIA: Clinical Findings

Table 2 Prevalence of relevant clinical findings in the ASIA registry cohort

Clinical findings	Frequency	Prevalence (%)
Arthralgia	184	61
Chronic fatigue	178	59
Myalgia	147	49
Sleep disturbances	112	37
Fever	101	34
General weakness	100	33
Arthritis	88	29
Neurological manifestations	78	26
Cognitive impairment	63	21
Sicca symptoms	55	18
Raynaud's phenomenon	48	16
Chronic rash	47	16
Lymphadenopathy	43	14
Photosensitivity	33	11
Mouth ulcers	18	6
Postural orthostatic tachycardia syndrome	13	4
Myositis	7	2

https://pubmed.ncbi.nlm.nih.gov/28741088/

ASIA: Defined Clinical Diagnoses

Table 3 Defined clinical diagnosis achieved in the ASIA registry cohort

Clinical diagnosis		Age	Gender	Vaccine adjuvant exposure	Foreign material adjuvant exposure
Vasculitis					
Giant cell arthritis/PMR	11	64–80 years, 72.3 ± 6.2	11 females, 1 male	Influenza vaccine	–
ANCA-associated vasculitis	2	53–54 years, 53.5 ± 0.7	2 females	HA (1), influenza vaccine (1)	–
Polyarteritis nodosa	1	32 years	Female	HBV vaccine	–
HS purpura	1	12 years	Female	HPV vaccine	–
Behçet's disease	1	18 years	Female	HPV vaccine	–
SLE and CTDs					
UCTD	78	15–82 years, 47.8 ± 15.8	71 females, 7 males	HBV vaccine (25), influenza vaccine (22), DTP vaccine (13), Td vaccine (12), smallpox vaccine (7), polio vaccine (5), DTP vaccine (3), HAV vaccine (3), HPV vaccine (3), pneumococcal vaccine (1), yellow fever vaccine (1), MMR vaccine (1), measles vaccine (1)	Metal implant (34), tooth amalgam (13), IUD (9), silicone (3), PAL and HA (1)
Systemic lupus erythematosus	18		16 females, 2 males	HBV vaccine (12), MMR vaccine (3), influenza vaccine (3), HPV vaccine (3), TD vaccine (2), DTP (1), DTD vaccine (1), HAV vaccine (1), oral typhoid vaccine (1), JE vaccine (1)	Mo (2), silicone (1)
Sjogren's syndrome	11	25–56 years, 39.9 ± 10.5	9 females, 2 males	HBV vaccine (6), HAV vaccine (1), oral typhoid vaccine (1), JE vaccine (1), MMR vaccine (1), influenza vaccine (1)	HA (3), PAC (2), PAL (1)
Rheumatoid arthritis	10	16–47 years, 29.7 ± 9.9	10 females	HBV vaccine (9), HPV vaccine (1)	–
Systemic sclerosis/morphea	5	31–55 years, 44.8 ± 11.4	5 females	HBV vaccine (2)	Silicone (2), PAC (1), metal implant (1), skin filler (1), IUD (1)
Juvenile rheumatoid arthritis	2	4–15 years, 9.5 ± 7.8	Female (1), male (1)	HBV vaccine (2)	–
Dermatomyositis	2	6 years	Female (1), male (1)	HBV vaccine (2)	–
Recurrent polychondrytis	1	39 years	Female	DTP vaccine	Silicone
APS	1	40 years	Female	HBV vaccine	–
MCTD	1	62 years	Female	HBV vaccine	–
Organ-specific					
Multiple sclerosis/optic neuritis/-neuromyelitis optica	20	15–55 years, 31.2 ± 8.9	18 females, 2 males	HBV vaccine (18), HPV vaccine (2)	–
Diabetes mellitus type 1	12	4–18 years, 11.0 ± 3.3	5 females, 7 males	HBV vaccine (10), HPV vaccine (2)	–
Guillain–Barré syndrome	8	11–66 years, 36.4 ± 24.2	6 females, 2 males	HBV vaccine (4), influenza vaccine (2), DTP vaccine (1), HAV vaccine (1), HPV vaccine (1)	–
Dysautononic neuropathy	7	12–20 years, 15.3 ± 3.2	7 females	HPV vaccine (7)	–
POTS	6	12–22 years, 16.8 ± 3.8	6 females	HPV vaccine (6)	–
Autoimmune liver diseases	5	11–39 years, 26.5 ± 9.2	5 females	HBV (5), MMR vaccine (1), influenza vaccine (1)	–
Inflammatory bowel disease	6	11–23 years, 13.8 ± 5.2	4 females, 2 males	HBV vaccine (5), influenza vaccine (1)	–

Clin Rheumatol (2018) 37:483–493

https://pubmed.ncbi.nlm.nih.gov/28741088/

ASIA: Defined Clinical Diagnoses

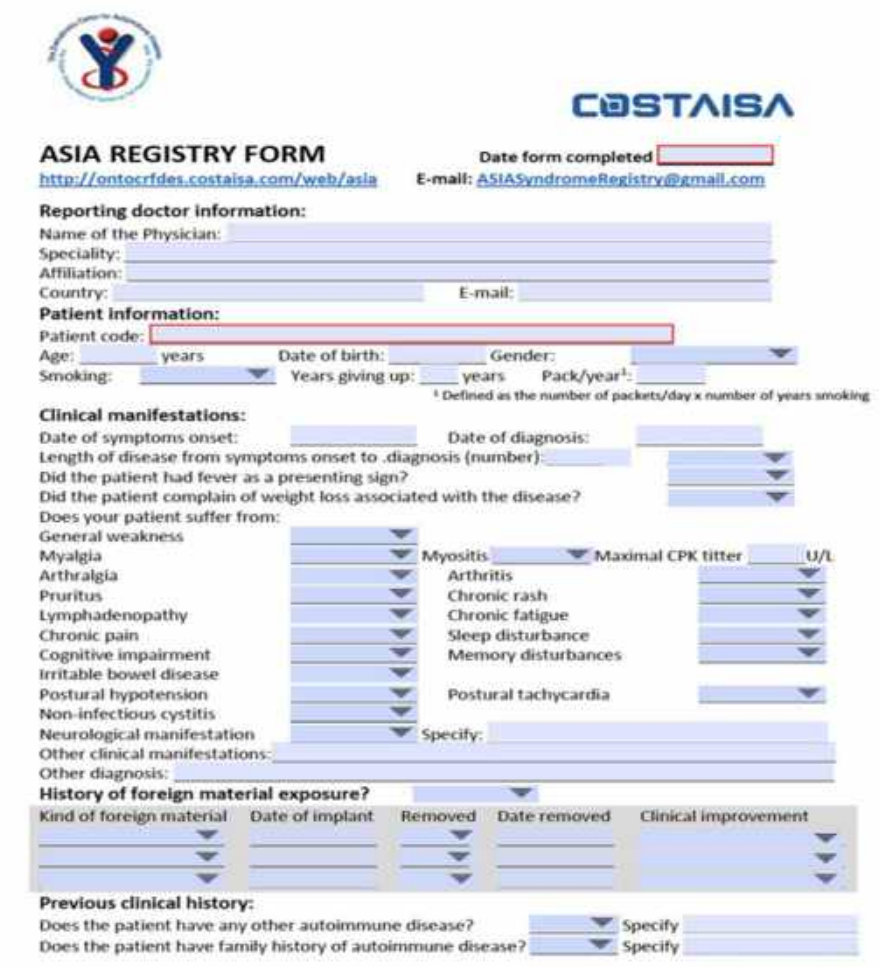
Table 3 (continued)

Clinical diagnosis		Age	Gender	Vaccine adjuvant exposure	Foreign material adjuvant exposure
Interstitial lung disease	2	59–65 years, 62.0 ± 4.2	1 female, 1 male	–	PAL (1), metal implant (1)
Transverse myelitis	4	14–67 years, 33.0 ± 23.7	3 females, 1 male	HAV vaccine (1), HBV vaccine (3), HPV vaccine (1), DPT vaccine (1), MCV4 vaccine (1)	–
Autoimmune encephalitis	2	17–37 years, 27.0 ± 14.1	2 males	HBV vaccine (2)	–
Hemolytic anemia	1	14 years	Male	HBV vaccine	–
Autoimmune thyroiditis	1	14 years	Female	HPV vaccine	–
Adrenal insufficiency	1	9 years	Female	HBV vaccine	–
Inflammatory polyradiculopathy	1	53 years	Male	Influenza vaccine	–
Primary biliary cirrhosis	1	56 years	Female	–	PAC and HA
CIDP	1	52 years	Female	HBV vaccine	–
Others autoimmune/rheumatic diseases					
Fibromyalgia	36	11–66 years, 28.0 ± 14.2	34 females, 2 males	HPV vaccine (16), HBV vaccine (14), HAV vaccine (1), influenza vaccine (1)	Silicone (6)
Chronic fatigue syndrome	11	12–54 years, 29.7 ± 17.9	7 females, 4 males	HBV vaccine (8), HPV vaccine (2), intranasal influenza vaccine (1), DTd vaccine (1), HAV vaccine (1), JE vaccine (1), oral typhoid vaccine (1)	Silicone (1)
Sarcoidosis (2 skin)	3	50–53 years, 51.5 ± 2.1	Females(2)	HBV vaccine (1)	PLA (1), HAM (1)
Macrophagic myofasciitis	1	13 years	Female	HPV vaccine	–
Ankylosing spondylitis	1	35 years	Female	HAV vaccine	–
Adult Still's disease	1	27 years	Female	–	Silicone

Mo mineral oil, *HA* hyaluronic acid, *PAL* polyalkylimide gel, *PAC* polyacrylamide gel, *SLE* systemic lupus erythematosus, *CTD* connective tissue disease, *MCTD* mixed connective tissue disease, *UCTD* undifferentiated connective tissue disease, *CIDP* chronic inflammatory demyelinating polyneuropathy, *POTS* postural orthostatic tachycardia syndrome, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HPV* human papilloma virus, *DTP* diphtheria/tetanus/pertussis, *MMR* mumps/mumps/rubella, *MCV4* meningococcal conjugate vaccine 4, *JE* Japanese encephalitis, *IUD* intrauterine device

https://pubmed.ncbi.nlm.nih.gov/28741088/

ASIA: Registry Form



COSTAISA

ASIA REGISTRY FORM

Date form completed

http://ontocrfdes.costaisa.com/web/asia E-mail: ASIASyndromeRegistry@gmail.com

Reporting doctor information:

Name of the Physician:
Speciality:
Affiliation:
Country: E-mail:

Patient information:

Patient code:
Age: years Date of birth: Gender:
Smoking: Years giving up: years Pack/year[1]:

[1] Defined as the number of packets/day x number of years smoking

Clinical manifestations:

Date of symptoms onset: Date of diagnosis:
Length of disease from symptoms onset to .diagnosis (number):
Did the patient had fever as a presenting sign?
Did the patient complain of weight loss associated with the disease?
Does your patient suffer from:

General weakness			
Myalgia		Myositis	Maximal CPK titter U/L
Arthralgia		Arthritis	
Pruritus		Chronic rash	
Lymphadenopathy		Chronic fatigue	
Chronic pain		Sleep disturbance	
Cognitive impairment		Memory disturbances	
Irritable bowel disease			
Postural hypotension		Postural tachycardia	
Non-infectious cystitis			
Neurological manifestation		Specify:	

Other clinical manifestations:
Other diagnosis:

History of foreign material exposure?

Kind of foreign material	Date of implant	Removed	Date removed	Clinical improvement

Previous clinical history:

Does the patient have any other autoimmune disease? Specify
Does the patient have family history of autoimmune disease? Specify

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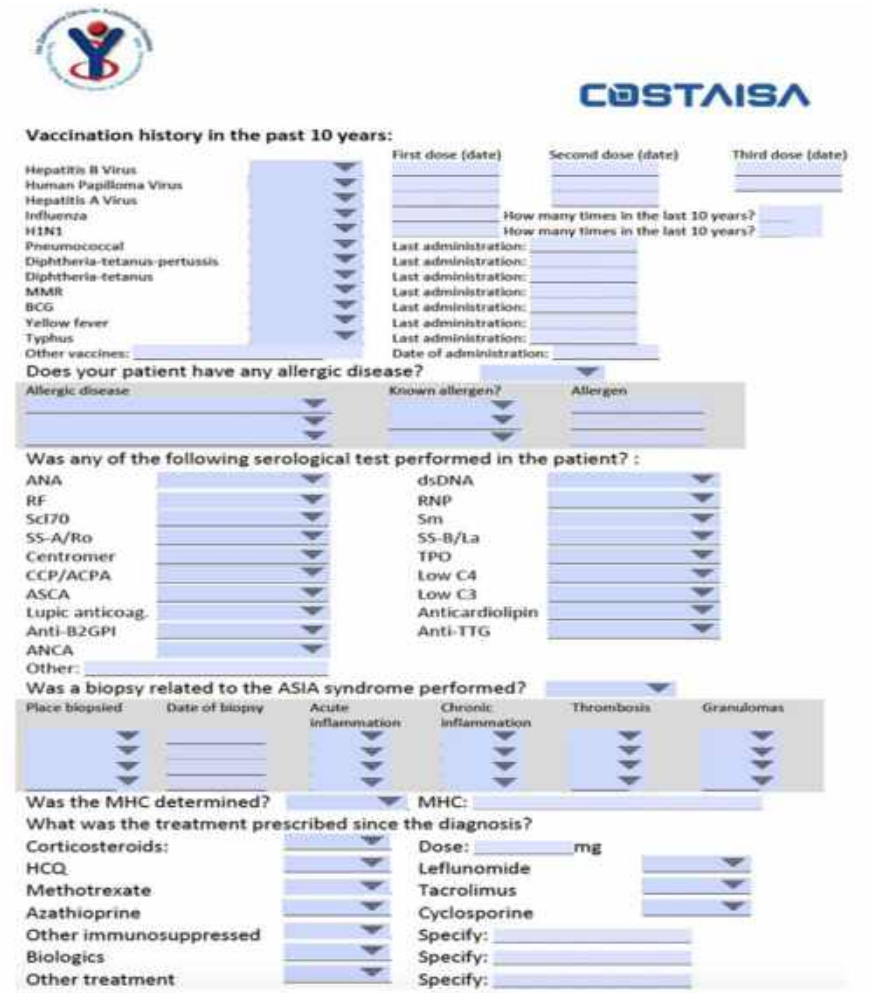
ASIA: Registry Form



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Vaccination history in the past 10 years:

		First dose (date)	Second dose (date)	Third dose (date)
Hepatitis B Virus				
Human Papilloma Virus				
Hepatitis A Virus				
Influenza			How many times in the last 10 years?	
H1N1			How many times in the last 10 years?	
Pneumococcal		Last administration:		
Diphtheria-tetanus-pertussis		Last administration:		
Diphtheria-tetanus		Last administration:		
MMR		Last administration:		
BCG		Last administration:		
Yellow fever		Last administration:		
Typhus		Last administration:		
Other vaccines:		Date of administration:		

Does your patient have any allergic disease?

Allergic disease	Known allergen?	Allergen

Was any of the following serological test performed in the patient? :

ANA		dsDNA	
RF		RNP	
Scl70		Sm	
SS-A/Ro		SS-B/La	
Centromer		TPO	
CCP/ACPA		Low C4	
ASCA		Low C3	
Lupic anticoag.		Anticardiolipin	
Anti-B2GPI		Anti-TTG	
ANCA			

Other:

Was a biopsy related to the ASIA syndrome performed?

Place biopsied	Date of biopsy	Acute inflammation	Chronic inflammation	Thrombosis	Granulomas

Was the MHC determined? MHC:

What was the treatment prescribed since the diagnosis?

Corticosteroids:		Dose: mg	
HCQ		Leflunomide	
Methotrexate		Tacrolimus	
Azathioprine		Cyclosporine	
Other immunosuppressed		Specify:	
Biologics		Specify:	
Other treatment		Specify:	

https://pubmed.ncbi.nlm.nih.gov/28741088/

ASIA Cases

https://pubmed.ncbi.nlm.nih.gov/28741088/

Hearing loss

Thoracic outlet syndrome

Frozen shoulder

Fascia:

Hormonal Medical Signaling Therapies

Objectives

Review:

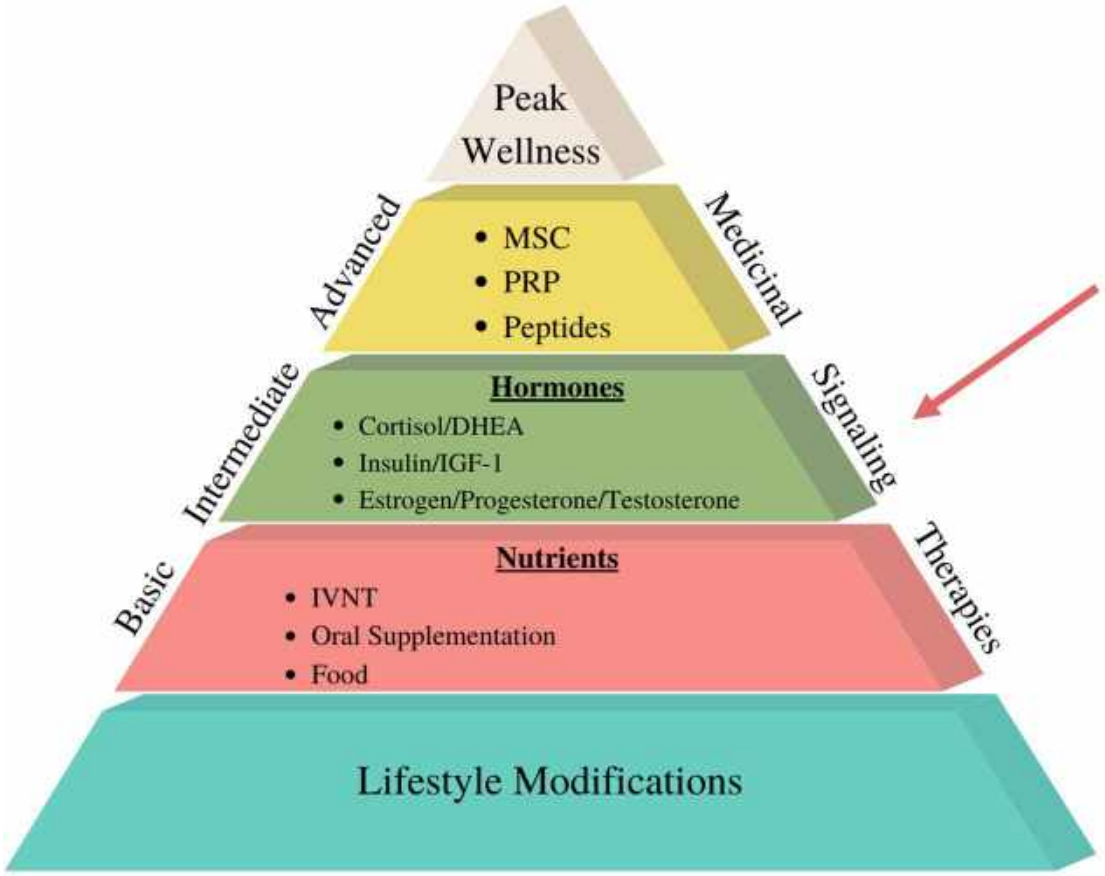
1. Fascia as an *organ* system

2. Fascia = ground zero in pain, injury & cellular/tissue healing

3. Medicinal Signaling Therapies (Nutrients, Hormones, Peptides, PRP, Exosomes, MSC's, ESWT/Equiscope) for aberrant physiology

4. Demonstrative Case Studies for use of multi-modal therapies using the Regenology Therapeutic Model

Fascia and Hormones



Conventional Biomarkers to “track”

“Nutrients” : Fatty acid balance, D3, B12, rbc folate, rbc Mg

Hormones: Insulin, glucose, fructosamine, IR, adiponectin, A1C, cortisol, DHEA, IGF-1, LH, FSH, total estrogen, estradiol, progesterone, total/free testosterone, DHT, SHBG

Inflammation/Oxidation: hsCRP, ESR, CBC w/diff, Ferritin, MPO, Fibrinogen,

Lp PLA2, Hcy, IL-6, IL-8, LDH, IgE, IgG etc, LFT’s, GGT, AA/EPA ratio

pH balance: glucose, CO2, Anion Gap, BUN, creatinine, eGFR, LDH

Immune system: CBC w/diff (PMN’s, Lymphs, Eos, Monos, Basos), D3, IgE, IgG

https://www.sciencedirect.com/science/article/pii/S155541552100547X

Speciality Biomarkers

Immune panels: Intestinal Permeability, Proteome reactivity and Autoimmunity etc

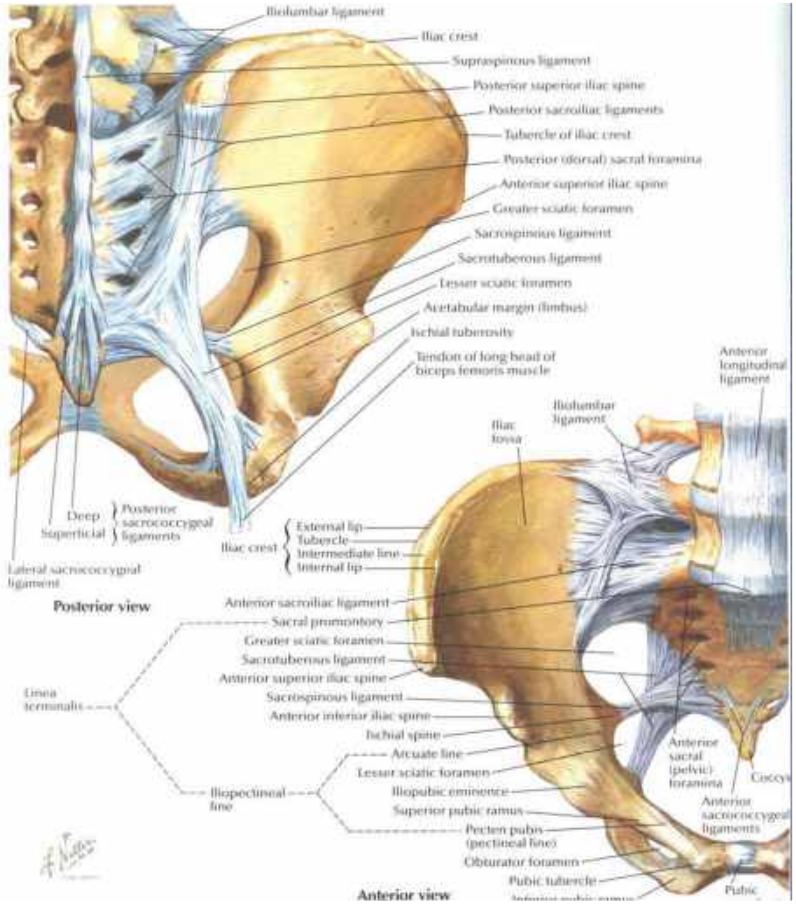
Stool testing: Microbiome, D I G

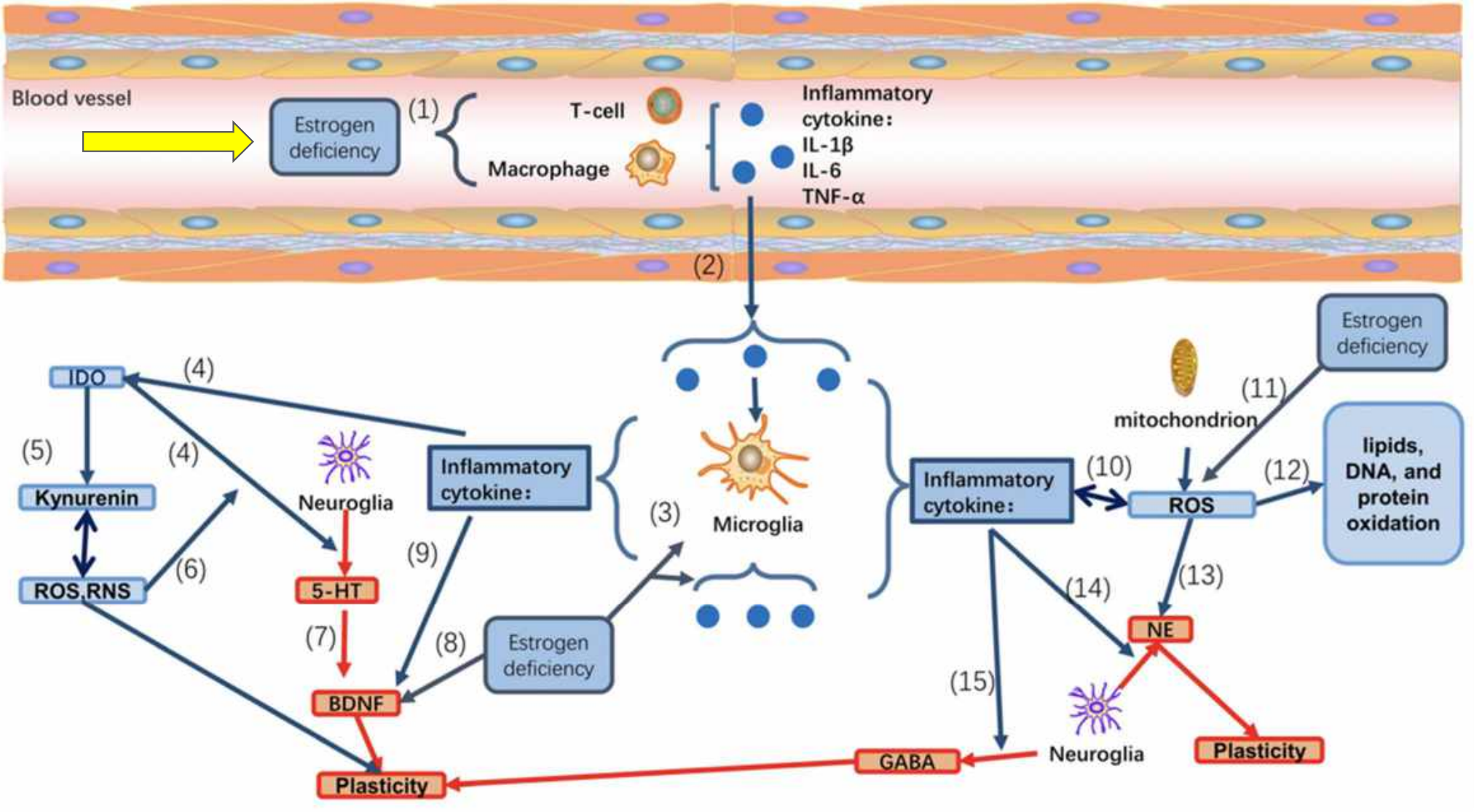
Boston Heart: Beta cell function and diabetes risk index

Toxin exposure/Detox capacity (GSH), Ox Stress, Fatty Acid Balance, Methylation Imbalance, Mitochondrial dysfunction, Ketones, Beta hydroxybutyric acid, beta HMG

https://www.sciencedirect.com/science/article/pii/S155541552100547X

Fascia and Hormones




Blood vessel
Estrogen deficiency
(1)
T-cell
Macrophage
Inflammatory cytokine:
IL-1β
IL-6
TNF-α
(2)
IDO
(4)
(5)
Kynurenin
ROS,RNS
(6)
Neuroglia
5-HT
(7)
BDNF
Inflammatory cytokine:
(9)
(8)
Estrogen deficiency
(3)
Microglia
Inflammatory cytokine:
(10)
mitochondrion
Estrogen deficiency
(11)
ROS
(12)
lipids, DNA, and protein oxidation
(13)
(14)
NE
(15)
Neuroglia
Plasticity
GABA
Plasticity

Hormones & Fascia in Women's Healt

Akey & O'Neil-Smith publication

- AIMSS
- ACL tears
- Myofascial pain syndrome
- POP
- SUI

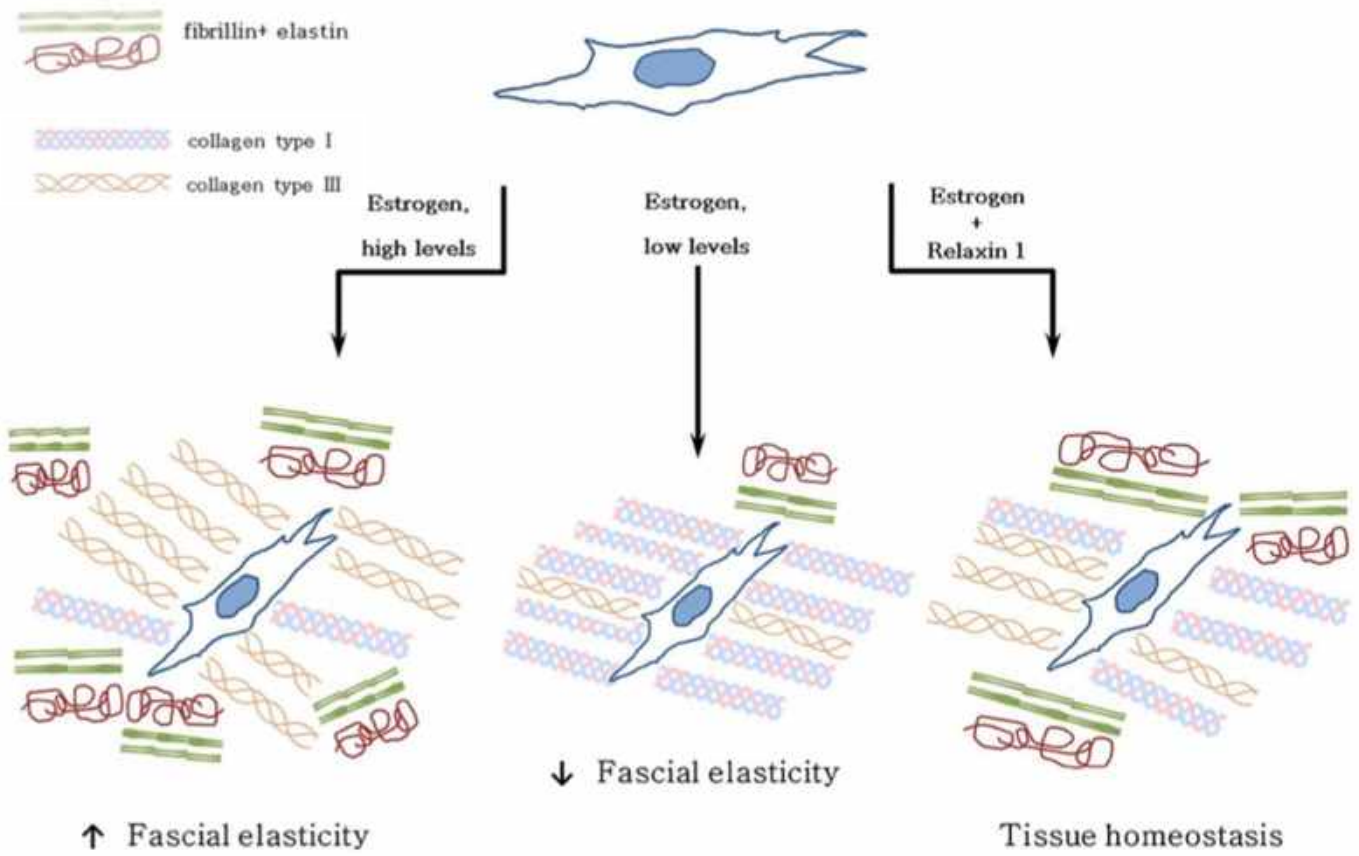


Fig 4. Fascia and ECM production according to hormone levels. Theoretical scheme of fascial cell response and extracellular matrix rearrangement at different hormone levels (estrogen and relaxin-1).

https://doi.org/10.1371/journal.pone.0223195.g004

Fedes & Stecco 2019

Hormonal Fascial Receptors

Tissue compartment	*ER*[a]	*PR*	*AR*
Vaginal smooth muscle cells	+++	+++	++
LA striated muscle fibers	0	++	+
LA muscle stromal cells	+	+	+
LA fascia	+++[b]	++[b]	+++[b]

[a]Semiquantitative grading (frequency of stained cells): +++, 60%–100%; ++, 20%–50%; +, 5%–10%; 0, none.

[b]Varies significantly among individual cases depending on age and hormonal status.

Estrogen, Progesterone, Androgen Receptor Expression in Levator Ani Muscle and Fascia. Pleas Copas, MD

TABLE 1
IMMUNOMODULATORY PROPERTIES OF SEX HORMONES

Hormone	Action	Examples
Estrogens	Immunostimulatory	Increased mixed-lymphocyte reaction Increased plaque-forming cells Increased CD4+ cells
	Immunosuppressive	Decreased bone marrow graft survival Prolonged graft survival Decreased phytohemagglutinin antigen and concanavalin A responses Decreased natural killer cell function Decreased cell-mediated immunity Suppressed neutrophil function
Progesterone	Immunosuppressive	Decreased phytohemagglutinin antigen and concanavalin A responses Decreased immunity during pregnancy Increased CD8+ cells
Androgens	Immunosuppressive	Lowered resistance to viral infections Decreased phytohemagglutinin antigen responses Decreased immunoglobulin A expression Decreased gammaglobulin synthesis Decreased graft rejection
Dehydroepiandrosterone	Immunomodulatory	Increased interleukin-2 Increased granulocyte-macrophage colony-stimulating factor (human) Decreased interleukin-4, interleukin-5, interleukin-6 (murine)

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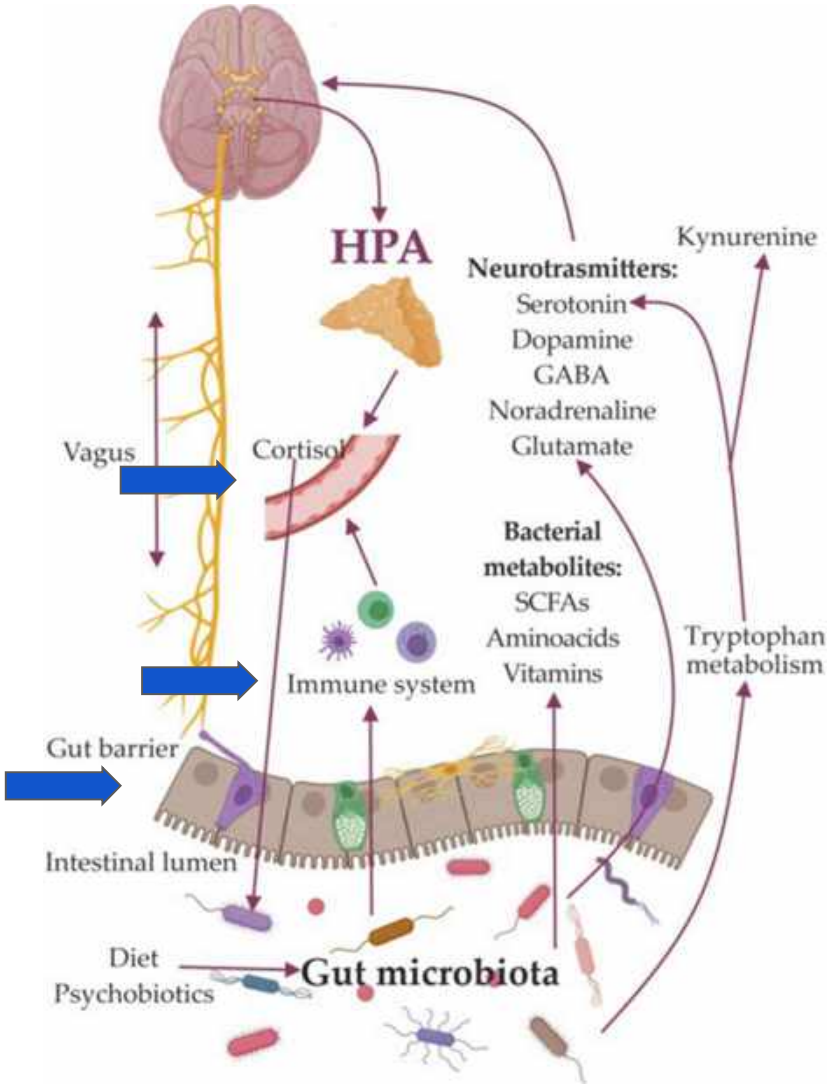
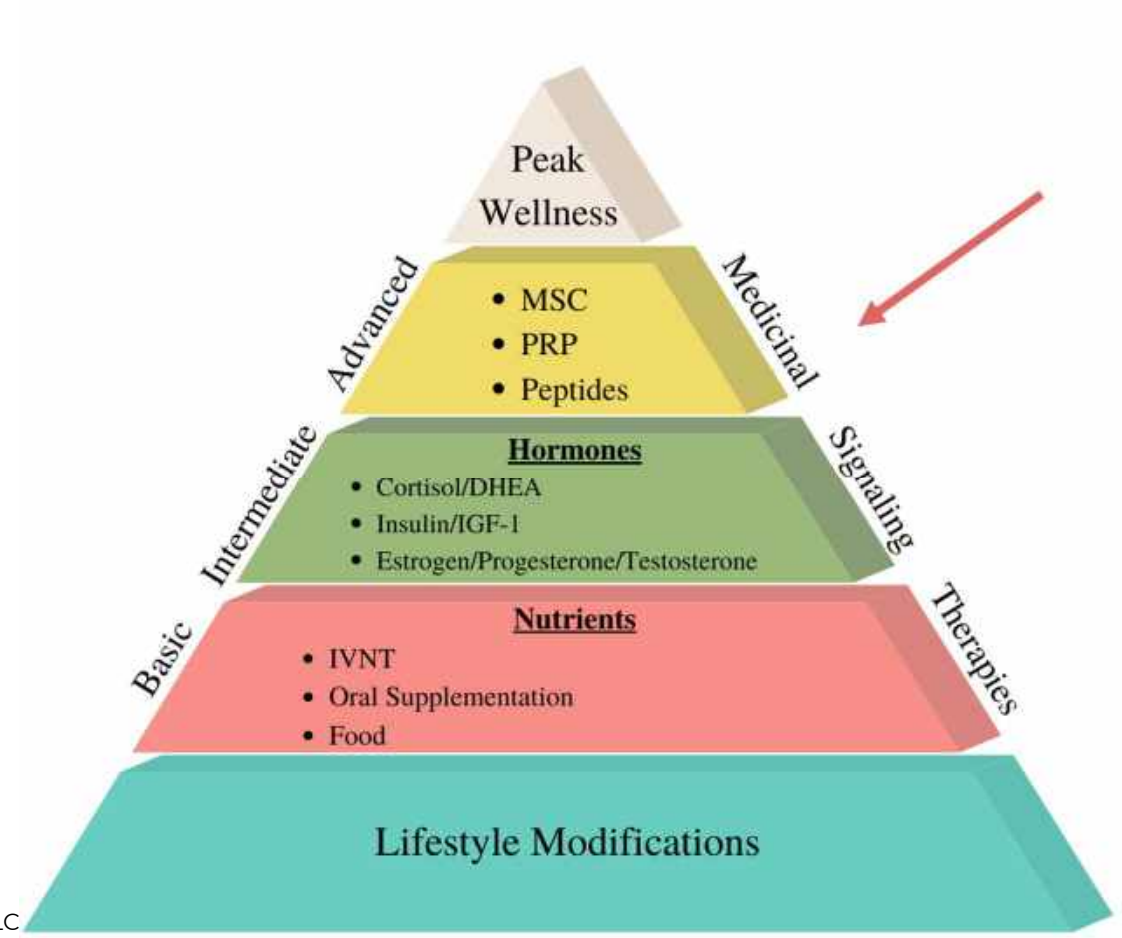


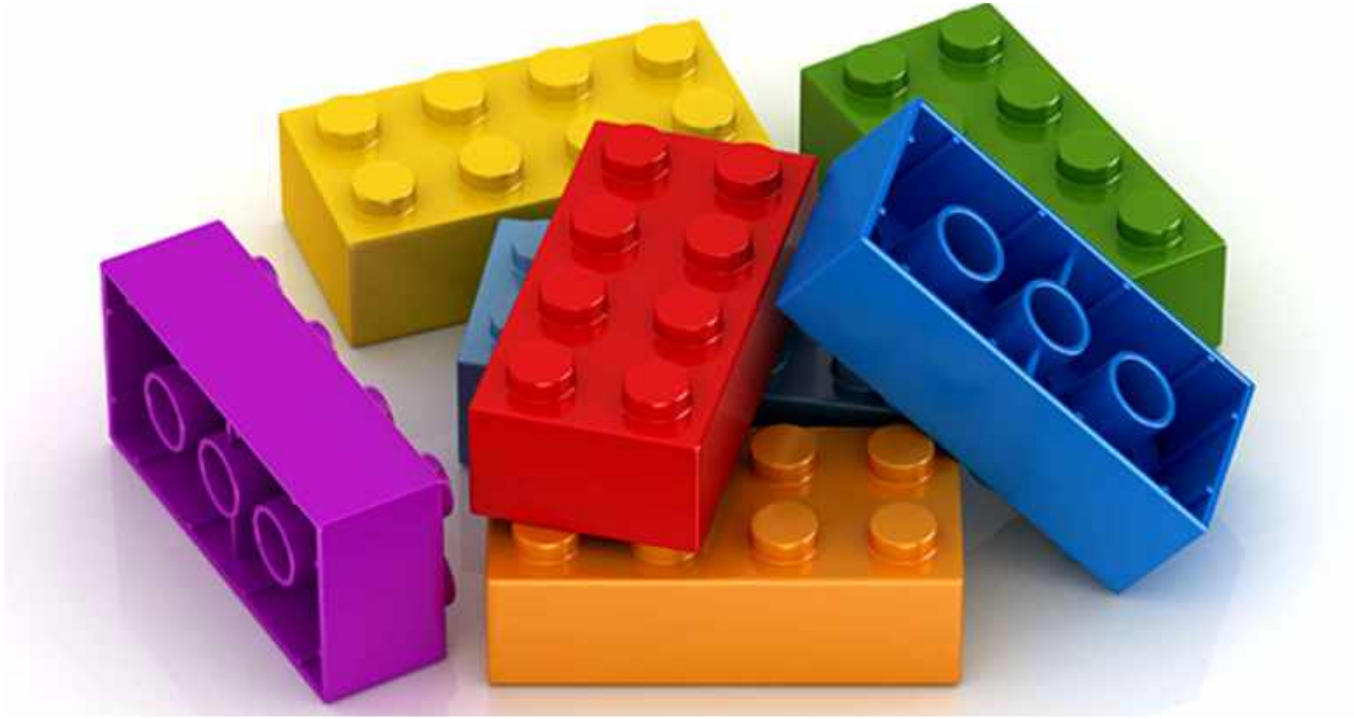
Fascia

Medical Signaling Therapies: Regenerative Potential of Small (smart) molecules

Advanced Signaling



From Part to Whole



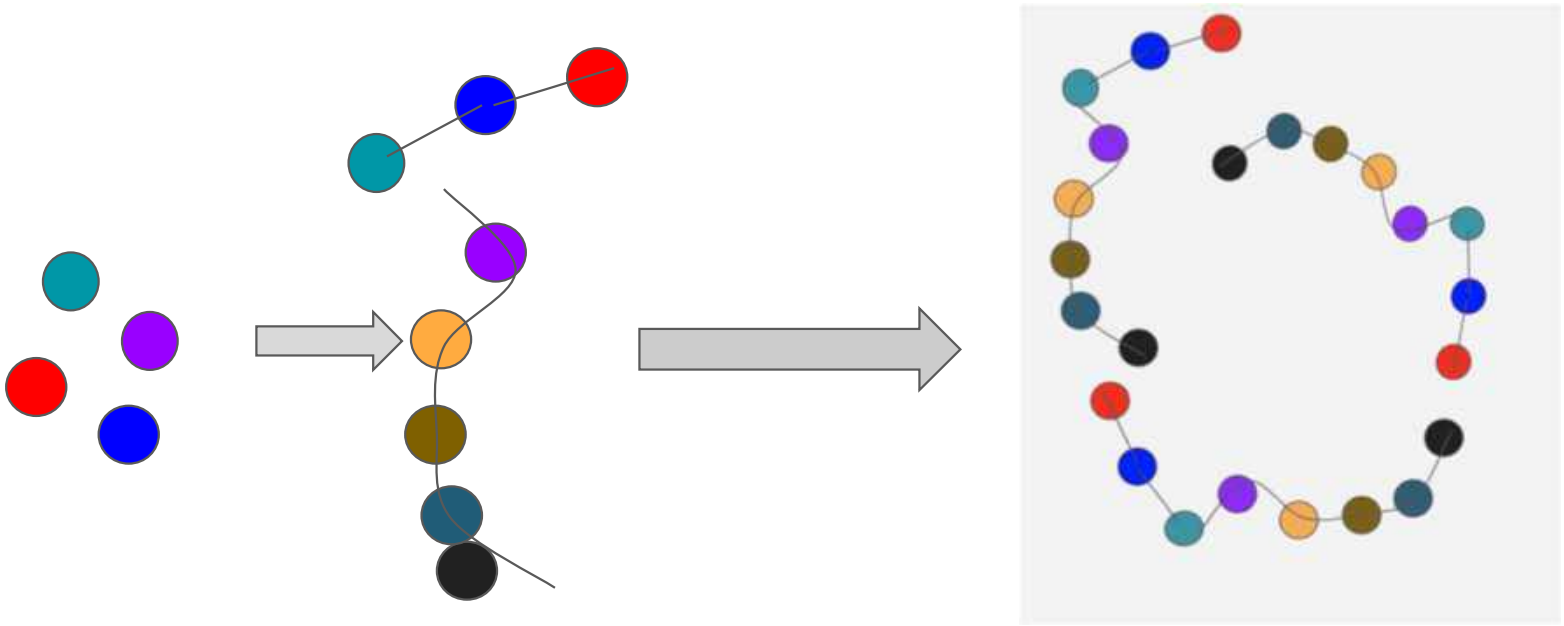
http://mentalfloss.com/article/92127/how-many-combinations-are-possible-using-6-lego-bricks

From Part to Whole

https://www.blendswap.com/blends/view/86309

http://www.mp3.xyz/awesome-winter-soldier-minifigure-collection-lego-marvel-super-heroes-xYluVeCVY7q.html

Peptides



Amino Acid

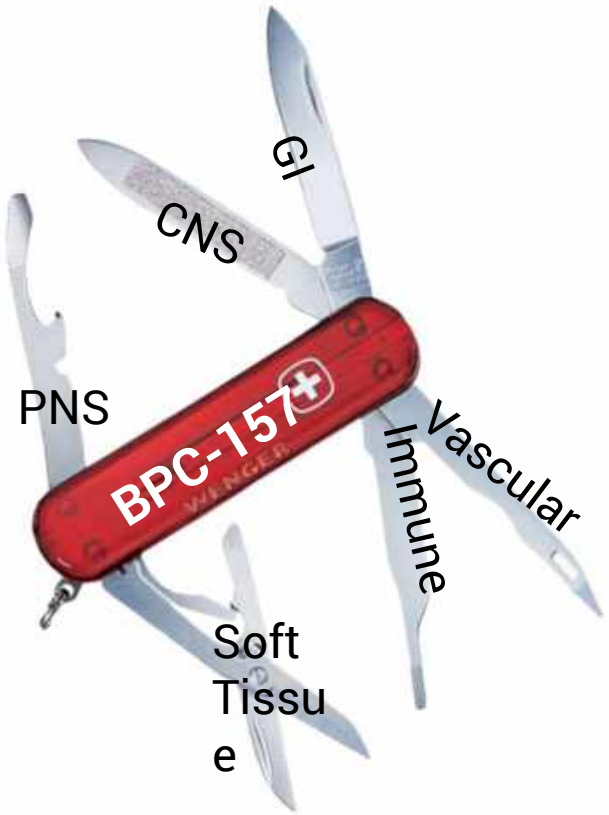
Peptide

Protein

Table 1
Thymosin proteins and their functions.

Name	Species	Role	References
PROTHYMOSIN α (ProTα)	mice, rat, human	chromatin remodeling, transcriptionally regulation, cell proliferation and survival	(Ueda et al., 2017; Samara et al., 2017; Samara et al., 2016; Ueda et al., 2012)
THYMOSIN-α1 (Tα – 1)	rat, mice, humans	immunoregulation	(You et al., 2006; Romani et al., 2004; King and Tuthill, 2016; Liu et al., 2016a; Romani et al., 2017; Garaci et al., 2007)
THYMOSIN-β4 (Tβ – 4)	mice, rats, humans, cattle, chimpazees	actin polymerization, angiogenesis, cell migration, collagen deposition, wound healing, fibrosis, neovasculogenesis, tissue repair and regeneration	(Chopp and Zhang, 2015; Kuzan, 2016; Goldstein and Kleinman, 2015)
THYMOSIN-β10 (Tβ – 10)	rat, mice, humans, cattle,	cytoskeleton organization and morphology, proliferation, motility, anti-inflammatory effects, insulin secretion	(Sribenja et al., 2009; Zhang et al., 2017b)
THYMOSIN-β15 (Tβ – 15)	rat, mice, human	motility, progression and metastatis of non-small cell lung cancer	(Banyard et al., 2007)

BPC - Swiss Army Knife of Peptides



BPC - Swiss Army Knife of Peptides

May promote muscle and tendon healing

May protect organs from toxins and damage

May reduce inflammation

May Benefit Inflammatory Bowel Disease (IBD)

May help in healing burns, cuts and broken bones

May protect the brain and nervous system

May help in healing stomach ulcers

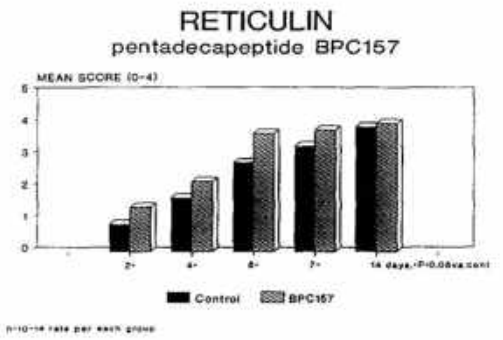
May help in reversing the damage of NSAIDs

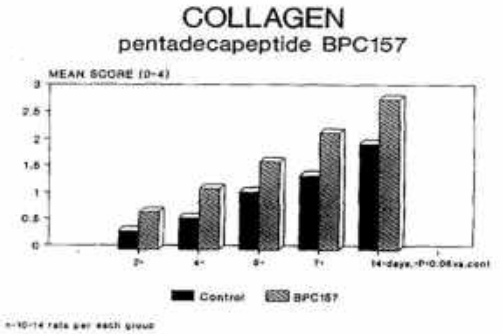
May help with pain

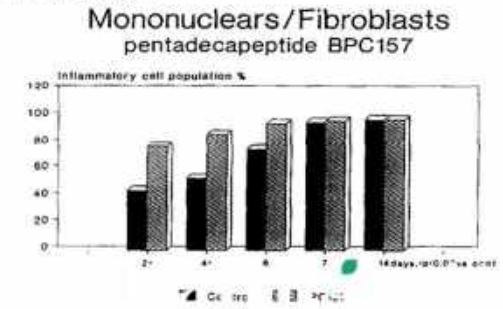
May help with balancing blood pressure

BPC 157 for Healing

- Healing processes == formation of granulation tissue, angiogenesis and production of collagen.
- In all experiments, significant differences between BPC 157-treated animals and controls were found, demonstrating involvement of BPC in the healing process.
- These effects were achieved by different routes of application, including oral subq, intragastric and local.







KPV

- A naturally occurring tripeptide: **Lysine - Proline - Valine** (KPV)
- A C-terminal peptide fragment of α-melanocyte stimulating hormone (α-MSH)
- A small molecule with broad **anti-inflammatory effect** & **antimicrobial action**
- In the **absence** of pro-inflammatory stimuli, **LPS/IL-1**, there is little to **no immunosuppressive potential of alpha MSH**
- Contributes to innate defense; **stabilizes mast cells**
- No stimulation of melanocytes

Luger, Thomas A, and Thomas Brzoska. “alpha-MSH related peptides: a new class of anti-inflammatory and immunomodulating drugs.” *Annals of the rheumatic diseases* vol. 66 Suppl 3,Suppl 3 (2007): iii52-5. doi:10.1136/ard.2007.079780

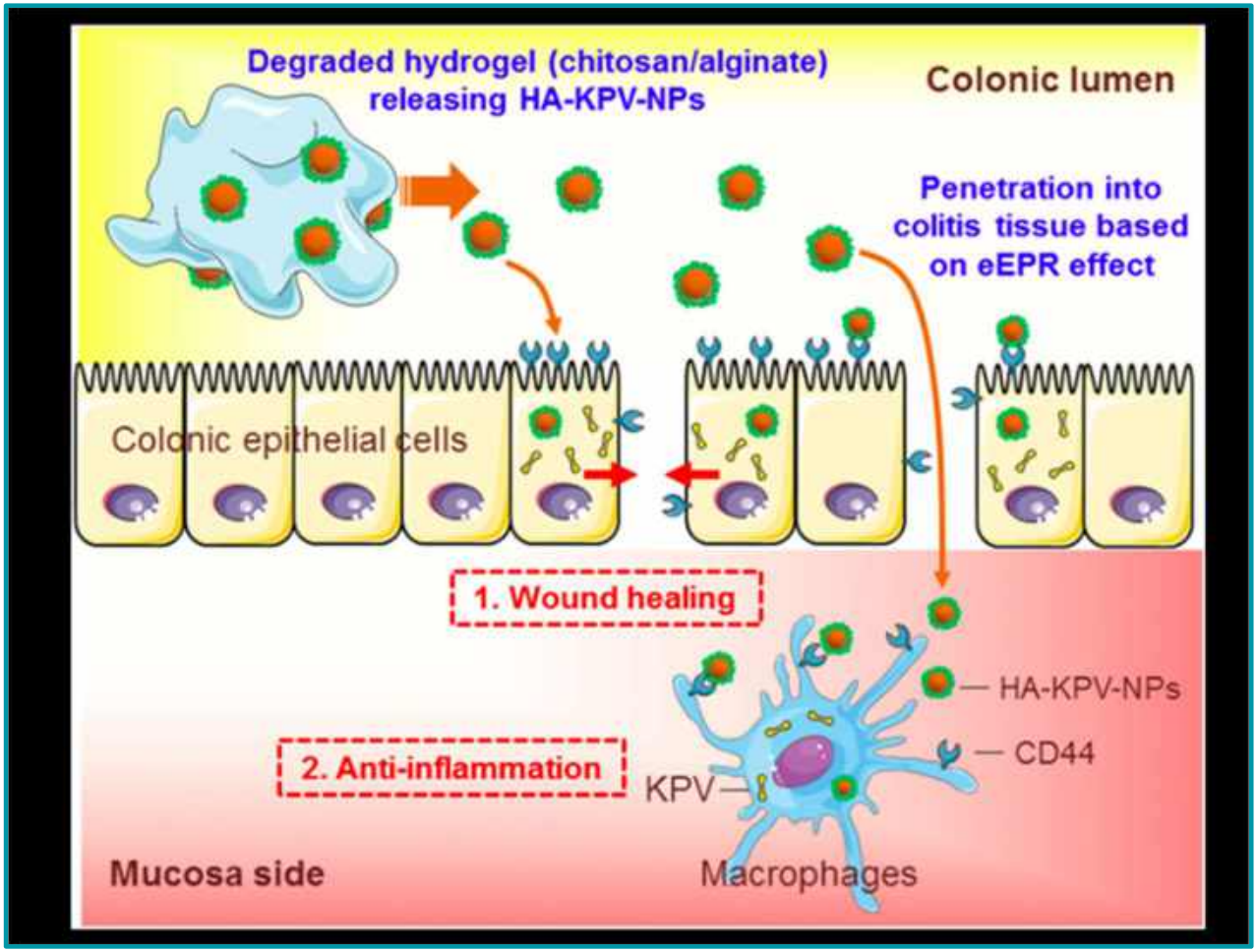


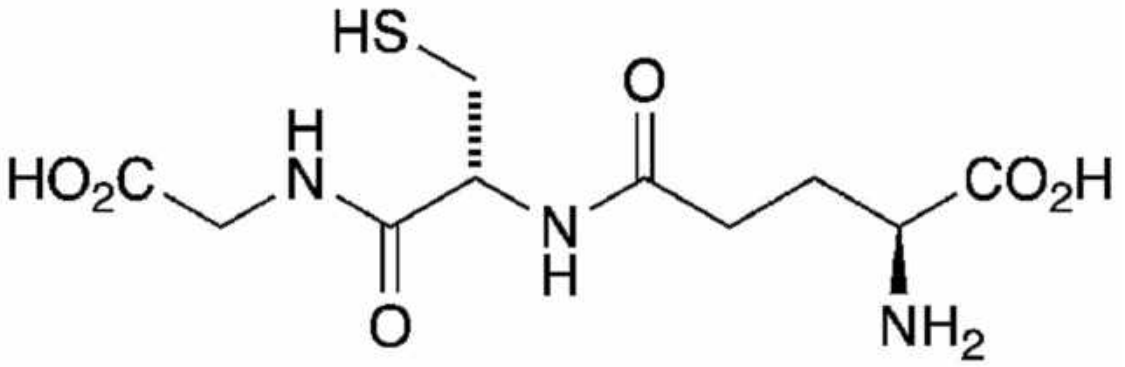
Fig. 8 The Therapeutic Effects of HA-KPV-NPs against UC Oral Administration of HA-KPV-NPs embedded by accelerating mucosa healing and alleviating inflammation.

doi:101016/j.ymthe.2016.11.020

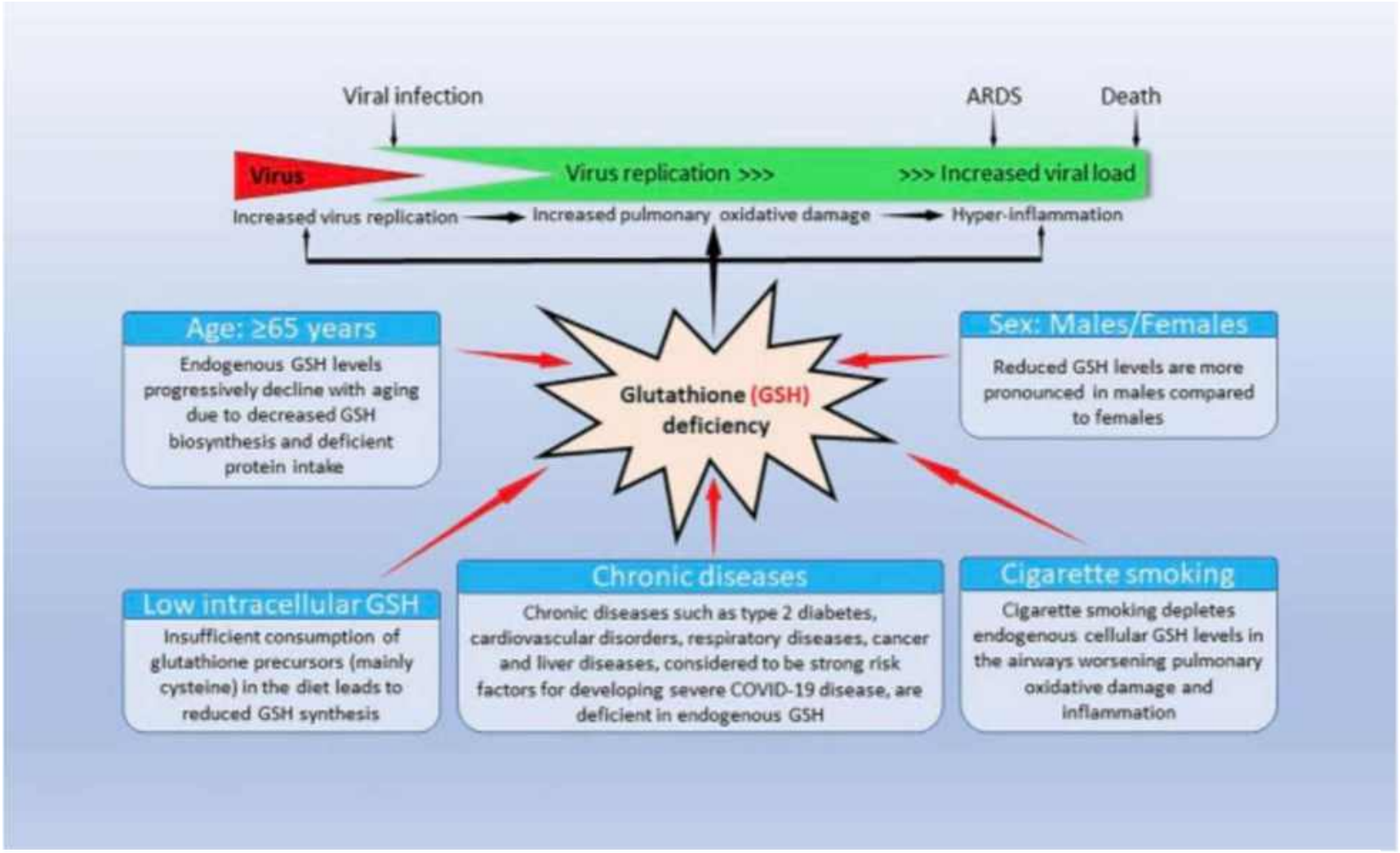
KPV: Therapeutic Uses

- **IBD, UC and Crohns Colitis**: mucosal healing
- **Colon cancer**
- **Inflammatory skin disorders**: Psoriasis, Nickel induced contact eczema
- **Wound healing**
- **Allergic asthma**
- Immune-mediated arthritis

Glutathione = Tripeptide



Glutathione (GSH) is a tripeptide, γ-L-glutamyl-L-cysteinylglycine, present in all mammalian tissues at 1–10 mM concentrations (highest concentration in liver) as the most abundant **non-protein** thiol that **defends against oxidative stress**.



Labarrere CA, Kassab GS. Glutathione deficiency in the pathogenesis of SARS-CoV-2 infection and its effects upon the host immune response in severe COVID-19 disease. Front Microbiol. 2022 Oct 6;13:979719. doi: 10.3389/fmicb.2022.979719. PMID: 36274722; PMCID: PMC9582773

Glutathione

Science News *from research organizations*

COVID-19 patients have severely increased levels of oxidative stress and oxidant damage, and glutathione deficiency, study finds

Date: January 3, 2022

Source: Baylor College of Medicine

Summary: Patients hospitalized with COVID-19 had significantly increased levels of oxidative stress and oxidant damage, and markedly reduced levels of glutathione, the most abundant physiological antioxidant, according to a new study.

Source: Baylor College of Medicine. "COVID-19 patients have severely increased levels of oxidative stress and oxidant damage, and glutathione deficiency, study finds." ScienceDaily. ScienceDaily, 3 January 2022. <www.sciencedaily.com/releases/2022/01/220103121754.htm>.

OXYTOCIN

Oxytocin “Nature’s Medicine”

Oxytocin, a **peptide hormone**, offers benefits across various *physiological and psychological* domains

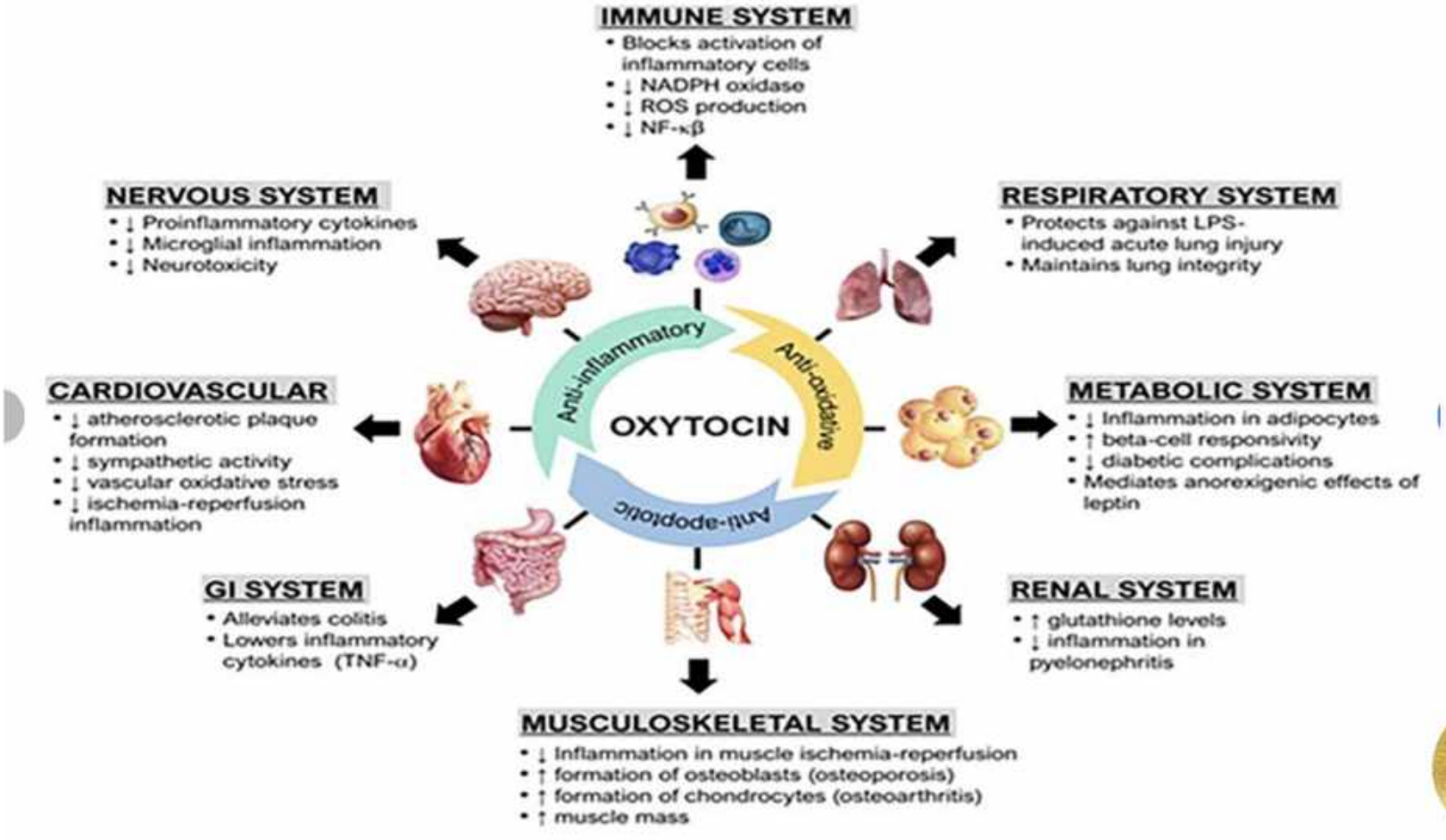
A simple nine–amino acid molecule has been called the “***best understood neuropeptide***”

Stress and Anxiety Reduction: Oxytocin acts as ***a stress-coping molecule***

Social Behavior and Bonding: It plays a crucial role in social behaviors, including pair bonding, ***trust***, and social decision-making

Pain Relief: Oxytocin has ***analgesic effects***, potentially relieving joint and muscle pain

Anti-inflammatory and Antioxidant Effects



Rx for **Improving Fascia:**

- **Lifestyle:**
  - Sleep, hydration, AI diet, fasting, movement, minimize foreign chemicals
- **Supplements:**
  - Omega 3 fish oils, phosphatidylcholine, quercetin, collagen & Vit C & Cu, glutathione , curcumin
- **Hormonal Balance:**
  - E, P, T, Cortisol, DHEA, Insulin, IGF-1
- **PRP/PRF/A2M**
- **Peptides:**
  - Thymosins, BPC-157, CJC/IPA, AOD
- **Acoustic Wave** ESWT, EMTT, Microcurrent/FSM
- **Other Medicinal Signaling Therapies :**
  - Acupuncture, needling, Structural Integration Therapy

Objectives

Review:

1. Fascia as an organ system

2. Fascia = ground zero in pain, injury & cellular/tissue healing

3. Medicinal Signaling Therapies (Nutrients, Hormones, Peptides, PRP, Exosomes, MSC's, multi-modalities) for aberrant physiology

4. Demonstrative Case Studies for use of multi-modal therapies using the Regenology Therapeutic Model

Peptides: Part II

One of Many Medicinal Signaling Therapies

Thank you!

??? Questions ???

Boston University School of Medicine

Kathleen O'Neil M.D.

A4M Vegas 2025

Treat Wellness

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BRIGHAM AND WOMEN'S HOSPITAL