Casual Friday Presents

Building Resilient Kids

Immune Balance.

A BIOGENETIX CLINICAL PRESENTATION

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Building Resilient Kids

Nervous system regulation

Mitochondrial function

Immune balance

Nutrient sufficiency

Healthy attachment

Environmental inputs

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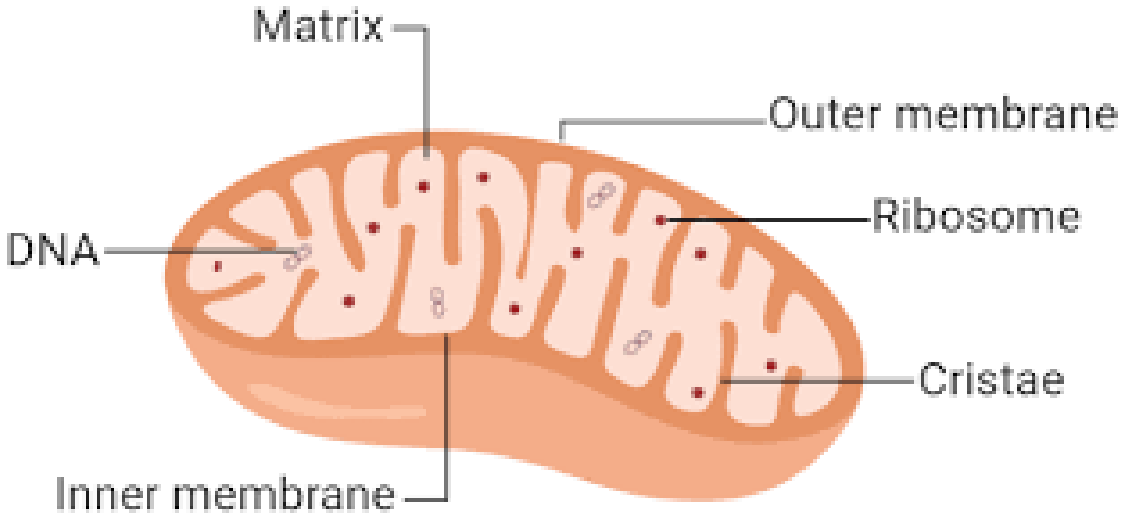
Mitochondria:
Environmental response organelles.

Continuously adapt to:

1. nutrient status
2. toxins
3. inflammation
4. stress hormones
5. circadian signals
6. movement
7. light exposure
8. infections



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Sleep Deprivation
Sleep is mitochondrial repair time.

During sleep:
1. oxidative cleanup occurs
2. brain's lymphatic clearance improves
3. mitochondrial repair increases

Sleep deprivation impairs:
1. ATP production
2. insulin sensitivity
3. emotional regulation

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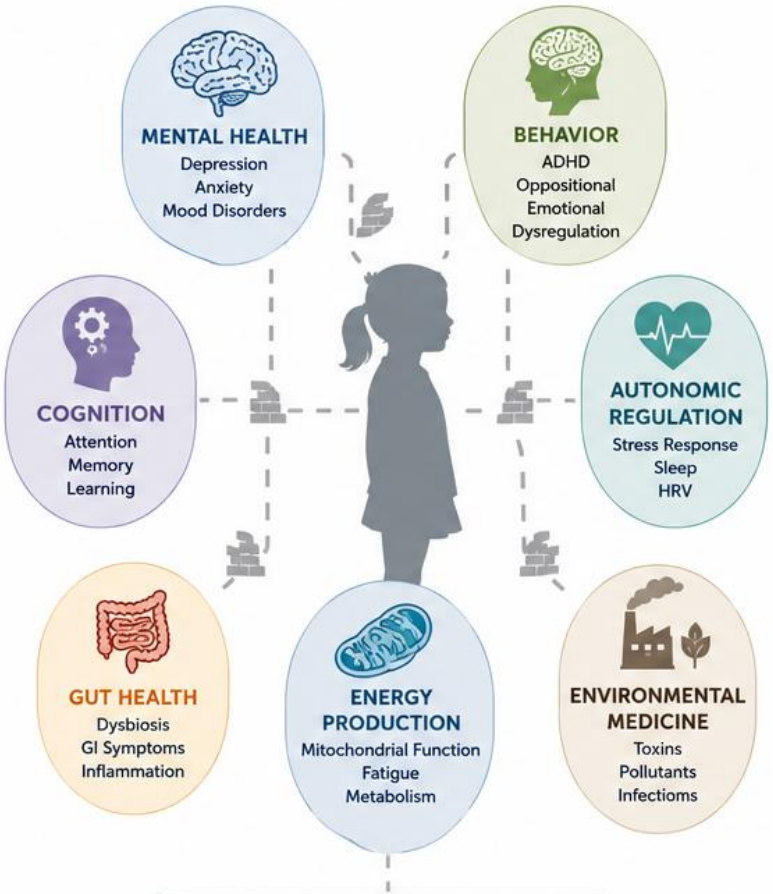
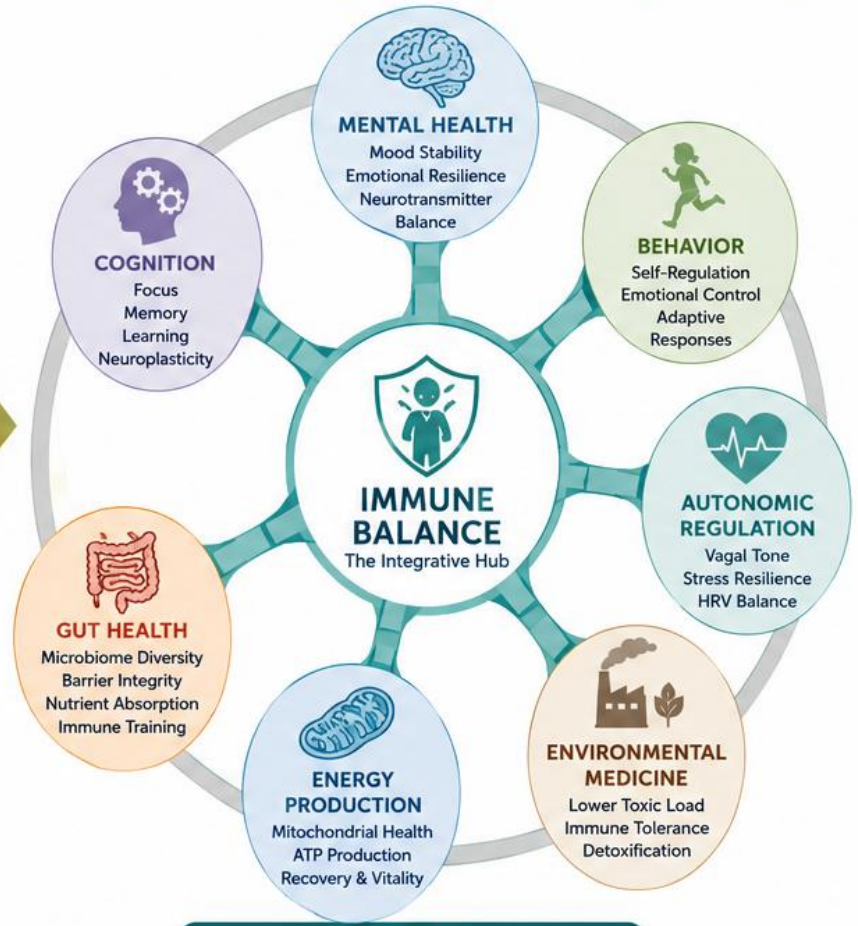
THE IMMUNE SYSTEM:
THE UNDERAPPRECIATED BRIDGE IN PEDIATRIC RESILIENCE

THE CONVENTIONAL MODEL
Systems Are Viewed in Isolation



OUTCOME
Fragmented Care, Missed Connections, Persistent Symptoms, Limited Resilience

THE FUNCTIONAL MEDICINE MODEL
The Immune System Bridges and Integrates All Systems

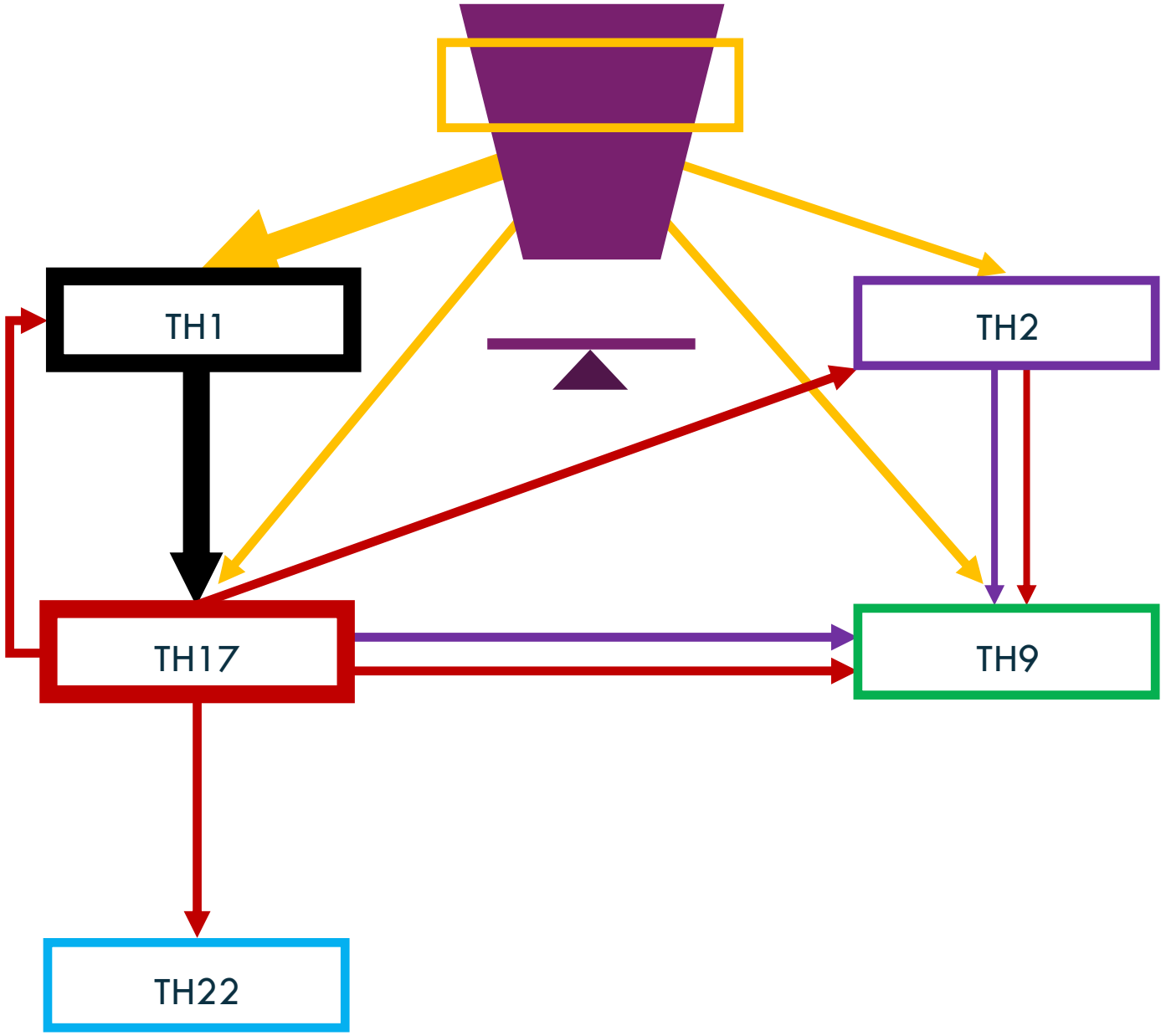


OUTCOME
Whole-Child Health, Systemic Resilience, Optimal Development, Lifelong Well-Being

HOW THE IMMUNE SYSTEM CONNECTS THE DOTS

- Communicates with the brain (cytokines, vagus nerve, microglia)
- Regulates inflammation and recovery
- Shapes the microbiome and gut barrier
- Influences neurotransmitters and mood
- Responds to environmental exposures
- Uses energy to defend, repair and adapt
- Teaches tolerance, calibrates threat, builds resilience

IMMUNE BALANCE IS NOT JUST ABOUT AVOIDING DISEASE— IT IS THE FOUNDATION OF RESILIENCE.



(Dermatologic)

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Nat Rev Neurosci. Author manuscript; available in PMC: 2010 Aug 10.

Published in final edited form as: Nat Rev Neurosci. 2008 Jan;9(1):46–56. doi: 10.1038/nrn2297

From inflammation to sickness and depression: when the immune system subjugates the brain

Robert Dantzer [*,‡], Jason C O'Connor [*], Gregory G Freund [*,‡], Rodney W Johnson [*], Keith W Kelley [*,‡]

Sickness is a normal response to infection, just as fear is normal in the face of a predator. It is characterized by endocrine, autonomic and behavioural changes and is triggered by soluble mediators that are produced at the site of infection by activated accessory immune cells. These mediators are known as pro-inflammatory cytokines, and include interleukin-1α and β (IL-1α and IL-1β), tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6). They coordinate the local and systemic inflammatory response to microbial pathogens. However, these peripherally produced cytokines also act on the brain to cause the aforementioned behavioural symptoms of sickness. Recently, it has been suggested that 'sickness behaviour'[2,3], a term used to describe the drastic changes in subjective experience and behaviour that occur in physically ill patients and animals, is an expression of a previously unrecognized motivational state. It is responsible for re-organizing perceptions and actions to enable ill individuals to cope better with an infection[4].

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The brain has long been considered an 'immune-privileged' organ but this immune status is far from absolute and varies with age and brain region[6]. Moreover, the brain contains immune cells, such as macrophages and dendritic cells, which are present in the choroid plexus and meninges. Brain parenchymal macrophages, known as microglial cells, are more quiescent in comparison with other tissue macrophages but can respond to inflammatory stimuli by producing pro-inflammatory cytokines and prostaglandins. In addition, both neuronal and non-neuronal brain cells express receptors for these mediators[7].

The brain monitors peripheral innate immune responses by several means that act in parallel (FIG. 1). One pathway involves afferent nerves: locally produced cytokines activate primary afferent nerves, such as the vagal nerves during abdominal and visceral infections[8,9] and the trigeminal nerves during oro-lingual infections[10]. In a second, humoral pathway, Toll-like receptors (TLRs) on macrophage-like cells residing in the circumventricular organs and the choroid plexus respond to circulating pathogen-associated molecular patterns by producing pro-inflammatory cytokines[11]. As the circumventricular organs lie outside the blood–brain barrier, these cytokines can enter the brain by volume diffusion[12]. A third pathway comprises cytokine transporters at the blood–brain barrier: pro-inflammatory cytokines overflowing in the systemic circulation can gain access to the brain through these saturable transport systems[13]. Finally, a fourth pathway involves IL-1 receptors that are located on perivascular macrophages and endothelial cells of brain venules[14,15]. Activation of these IL-1 receptors by circulating cytokines results in the local production of prostaglandin E2.

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Engagement of these immune-to-brain communication pathways ultimately leads to the production of pro-inflammatory cytokines by microglial cells. This process requires the convergent action of two events with different time courses: the activation of the rapid afferent neural pathway, and a slower propagation of the cytokine message within the brain. Activation of the neural pathway (FIG. 1) probably sensitizes target brain structures for the production and action of cytokines that propagate from the circumventricular organs and the choroid plexus into the brain[16]. This way the brain forms an 'image' of the peripheral innate immune response that is similar in its elementary molecular components to the response in the periphery. The main difference is that this brain image does not involve an invasion of immune cells into the parenchyma and is not distorted by tissue damage that occurs at the site of infection.

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The similarity between the symptoms of cytokine-induced sickness behaviour and depression is striking: in both cases there is a withdrawal from the physical and social environment that is accompanied by pain, malaise and decreased reactivity to reward (anhedonia). Moreover, some components of sickness behaviour, such as a decreased preference for sweet solutions and reduced social exploration, are improved by anti-depressant treatment[40]. In humans, major depressive disorders develop in roughly a third of patients who are treated with the recombinant human cytokines IL-2 and interferon-α (IFN-α)[41]. In agreement with these findings, major depressive disorders are more prevalent in patients afflicted with conditions that lead to chronic inflammation (such as cardiovascular diseases, type 2 diabetes and rheumatoid arthritis) than in the general population[5]. However, the similarity between sickness and depression is only partial; whereas sickness is an adaptive response to infection by pathogens and fully reversible once the pathogen has been cleared, this is not the case for depression. It is possible that depression represents a maladaptive version of cytokine-induced sickness, which could occur when activation of the innate immune response is exacerbated in intensity and/or duration, or that takes place in the context of an increased vulnerability to depression, for example, in individuals with hyperactive corticotrophin-releasing factor (CRH) neuronal circuits[42].

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From inflammation to sickness and depression: when the immune system subjugates the brain

In the clinic, symptoms of sickness (for example, fatigue, reduced appetite, sleep disorders, altered mood and cognition) are well known to have a negative impact on the quality of life of patients with chronic inflammatory disorders, but not much can be done to alleviate these symptoms. Controlled studies are necessary to validate the putative beneficial value of various nutriments and intervention (for example, physical exercise) on the symptoms of sickness. Such studies can now be carried out at the preclinical and clinical levels by not only evaluating clinically relevant end-points (for example, alleviation of fatigue or depressed mood) but also by taking into account intermediate mechanisms using biomarkers of inflammation. If confirmed in the clinic, the efficacy of compounds targeting IDO and inflammatory mediators for the alleviation of symptoms of depression will open new opportunities for drug development. However, as such compounds have the potential to compromise resistance to infection, targets in the brain should be preferred over peripheral ones.

Review Article | Published: 21 November 2012

The vagus nerve and the inflammatory reflex—linking immunity and metabolism

Valentin A. Pavlov & Kevin J. Tracey

Nature Reviews Endocrinology **8**, 743–754 (2012) | Cite this article

Abstract

The vagus nerve has an important role in regulation of metabolic homeostasis, and efferent vagus nerve-mediated cholinergic signalling controls immune function and proinflammatory responses via the inflammatory reflex. Dysregulation of metabolism and immune function in obesity are associated with chronic inflammation, a critical step in the pathogenesis of insulin resistance and type 2 diabetes mellitus. Cholinergic mechanisms within the inflammatory reflex have, in the past 2 years, been implicated in attenuating obesity-related inflammation and metabolic complications. This knowledge has led to the exploration of novel therapeutic approaches in the treatment of obesity-related disorders.

The Vagus nerve is a prominent battle ground.

The Vagus nerve doesn't merely regulate heart rate.

It regulates inflammation.

This is known as:
The Cholinergic Anti-inflammatory Reflex

Healthy vagal tone helps suppress excessive cytokine production.

Higher vagal tone =

- better regulation
- better resilience
- lower inflammation

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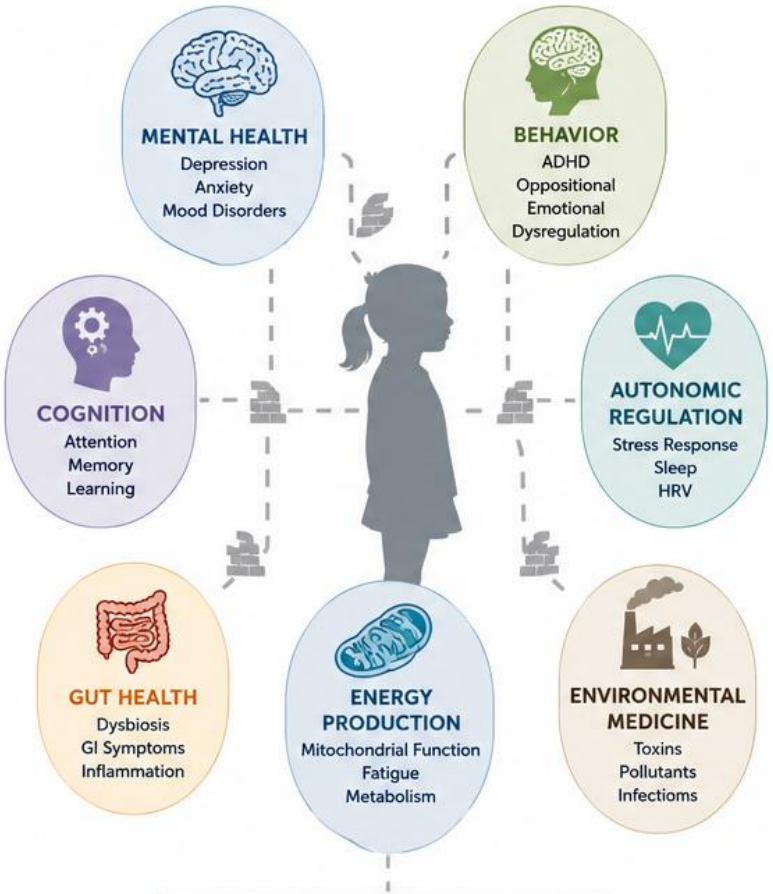

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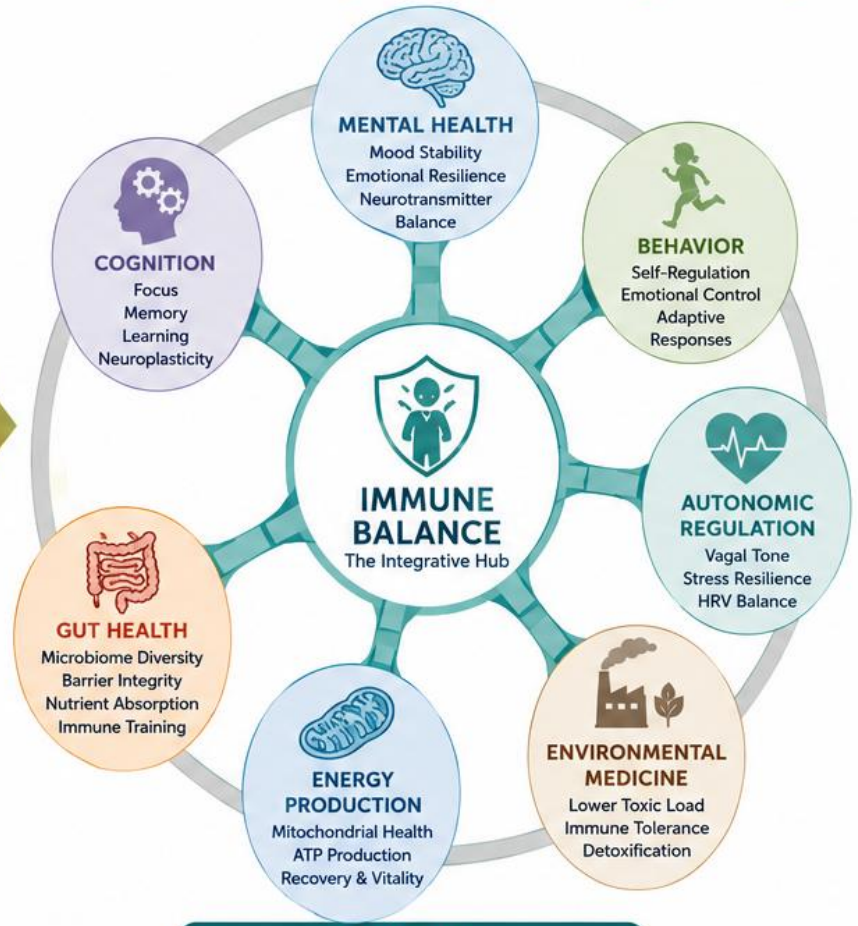

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IMMUNE BALANCE IS NOT JUST ABOUT AVOIDING DISEASE— IT IS THE FOUNDATION OF RESILIENCE.

Ideally, inflammation should:

1. Activate
2. Address threat
3. Resolve
4. Return to baseline

What happens when we have kids that fail step 4?

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Immune Resilience Players:

- microbial diversity
- healthy barriers (gut, skin, lungs)
- adequate nutrients
- restorative sleep
- healthy vagal tone
- movement
- inflammation resolution
- low toxic burden

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Standard approach:
Inflammation → immune problem

The FM approach:

- mitochondria
- autonomics
- neurodevelopment
- neurotransmitters
- behavior
- cognition

The immune system is one of the primary architects of resilience.

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Kids will not think their way into resilience. Their immune system, nervous system, microbiome, and mitochondria must be capable of supporting resilience biologically.

A kid whose immune system is chronically signaling danger will have a very difficult time convincing their brain their world is safe.

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NUTRITION & IMMUNE BALANCE

Key Nutrients That Regulate, Support & Strengthen the Immune System

VITAMIN D

- Innate immunity
- T-regulatory cells
- Inflammatory modulation

SUPPORTS
Immune tolerance & balanced responses

BEST FOOD SOURCES

Fatty fish, egg yolks, mushrooms, fortified foods

Sunlight is a key source

ZINC

- Barrier integrity
- Immune signaling

SUPPORTS
Mucosal barriers & immune defense

BEST FOOD SOURCES

Oysters, beef, chickpeas, pumpkin seeds, lentils, nuts

OMEGA-3s

- Inflammatory resolution
- Specialized pro-resolving mediators (SPMs)

SUPPORTS
Resolution of inflammation & immune balance

BEST FOOD SOURCES

Fatty fish, flaxseeds, chia seeds, walnuts, algae oil

MAGNESIUM

- Stress modulation
- Inflammatory control

SUPPORTS
Calm immune response & reduces overactivation

BEST FOOD SOURCES

Leafy greens, nuts, seeds, avocado, legumes, dark chocolate

PROTEIN

- Antibodies
- Immune cell production

SUPPORTS
Structural components of immune cells

BEST FOOD SOURCES

Lean meats, fish, eggs, dairy, beans, lentils, quinoa, tofu

A nutrient-dense diet provides the building blocks and regulators your immune system needs to detect threats, respond appropriately, and return to balance.

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We Want to Hear from You!

Give us your Casual Friday feedback
with this short 5-question survey.

biogenetix.com/survey