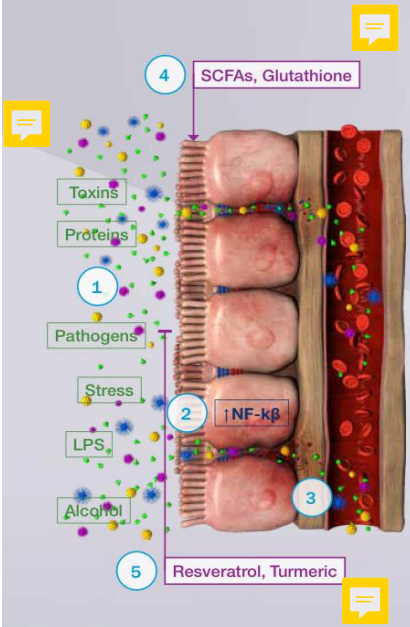
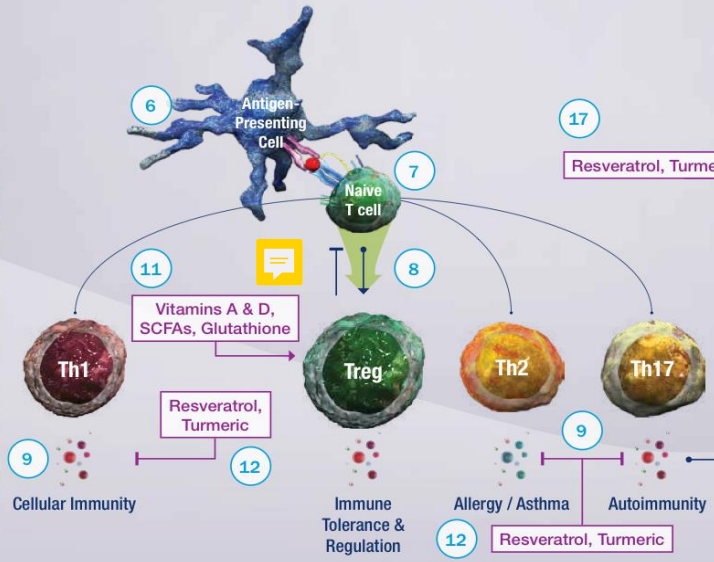
Intestinal Inflammation

Reduce inflammatory signaling and support barrier function



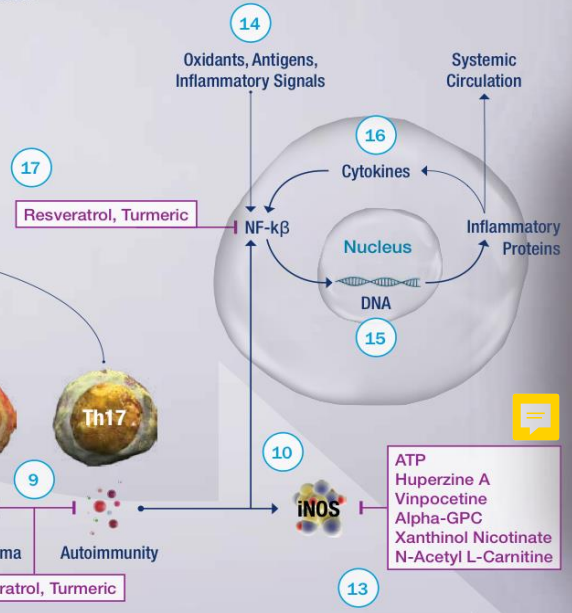
Immune Dysregulation

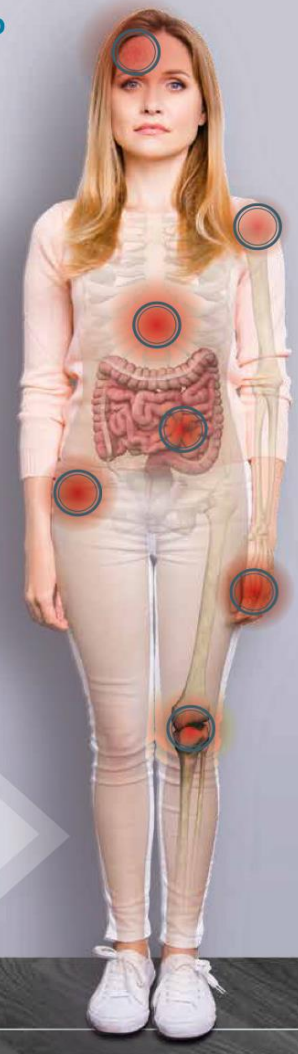
Support immune regulation by promoting T-regulatory (Treg) cell activity and reducing pro-inflammatory cytokine production



NF-κβ Self-Amplifying Loop

Dampen NF-κβ activity





Tissue Damage 18

The complexes and signals released through these three intertwined pathways: 1) intestinal inflammation and permeability, 2) immune dysregulation, and 3) sustained NF-κβ activity travel throughout the body via the bloodstream, lymphatic system, and portal circulation enabling them to cause localized tissue damage and pain.

INFLAMMATORY CYTOKINES
iNOS
ANTIGEN-IMMUNE COMPLEXES
MOLECULAR MIMICRY
LPS

Inflammation-Immune Signaling Infographic

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Intestinal Inflammation

1. Dietary and environmental triggers (proteins, stress, toxins, pathogens, etc) can increase intestinal inflammation through mucosal damage, barrier dysfunction, or mucosal immune activation.[1 2 3]
2. The resulting inflammatory cytokines activate nuclear factor kappa beta (NF-κβ), which increases the production of inflammatory proteins, contributes to disruption of intestinal tight junctions, and activates T cells.[4 5 6 7]
3. Lipopolysaccharides (LPS), pathogens, toxins, dietary proteins, etc that breach the intestinal barrier can be picked up by antigen-presenting cells or directly circulate to cause an immune reaction in other tissues.[2 8 9 10]
4. Short chain fatty acids (SCFAs) and glutathione support mucosal health and are important in tight junction synthesis.[11 12 13 14] SCFAs also have anti-inflammatory effects through interaction with G protein-coupled receptors (GPRs) and histone deacetylases (HDACs), which influence NF-κβ and T-cell proliferation, respectively.[15]
5. Turmeric/curcumin reduces inflammatory signaling in the gut and NF-κβ activation.[16 17 18] Resveratrol positively influences the microbiota and decreases oxidative stress to reduce intestinal inflammation.[19 20]

Immune Dysregulation

6. Continued exposure to triggers may result in a dysregulated immune system.[10]
7. Dysregulation can negatively affect both innate and adaptive immunity including naïve T-cell differentiation, such as upregulating humoral (Th2, Th17) and cellular (Th1) immunity and downregulating T-regulatory cells (Tregs).[21 22 23 24 25]
8. Tregs play an important role in modulating Th1-, Th2-, and Th17-mediated responses and maintaining immune tolerance and immune homeostasis.[26 27 28]
9. The persistently imbalanced activity of T-effector cells (Th1, Th2, and Th17) and their cytokines is associated with chronic illness related to inflammation, allergy, reduced oral tolerance, and autoimmunity.[29 30]
10. Proinflammatory cytokines, such as IL-17 (a product of Th17), are involved in the upregulation of inducible nitric oxide synthase (iNOS) expression.[31 32 33]
11. Certain nutrients, including vitamins A and D and SCFAs, support differentiation of naïve T cells to Tregs, the activity of Tregs, and anti-inflammatory IL-10 production.[34 35 36 37] Glutathione may support equilibrium between ROS and antioxidants in tissue microenvironments and intracellular compartments, thus allowing normal T-cell responses.[38]
12. Turmeric and resveratrol positively modulate inflammatory cytokines, such as those produced by dysregulated T cells.[39 40 41]
13. Nutrients, such as huperzine A, adenosine triphosphate (ATP), and acetyl L-carnitine, show some evidence to support the nitric oxide synthase (NOS) system by modulating levels of inducible, endothelial, and neuronal NOS.[42 43 44]

NF-κβ Amplifying Loop

14. Oxidants, antigens, and inflammatory signals and cytokines increase systemic NF-κβ activity.[45]
15. NF-κβ transcribes DNA to express an inflammatory state and synthesize inflammatory proteins.
16. *Even once triggers are removed,* NF-κβ can be chronically activated through its feed-forward, self-amplifying loop.[45]
17. Resveratrol and turmeric/curcumin dampen NF-κβ in a synergistic manner.[46 47 48]

Tissue Damage

18. The complexes and signals released through these three intertwined pathways: 1) intestinal inflammation, 2) immune dysregulation, and 3) sustained NF-κβ activity travel throughout the body via the bloodstream, lymphatic system, and portal circulation, enabling them to cause localized tissue damage.

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