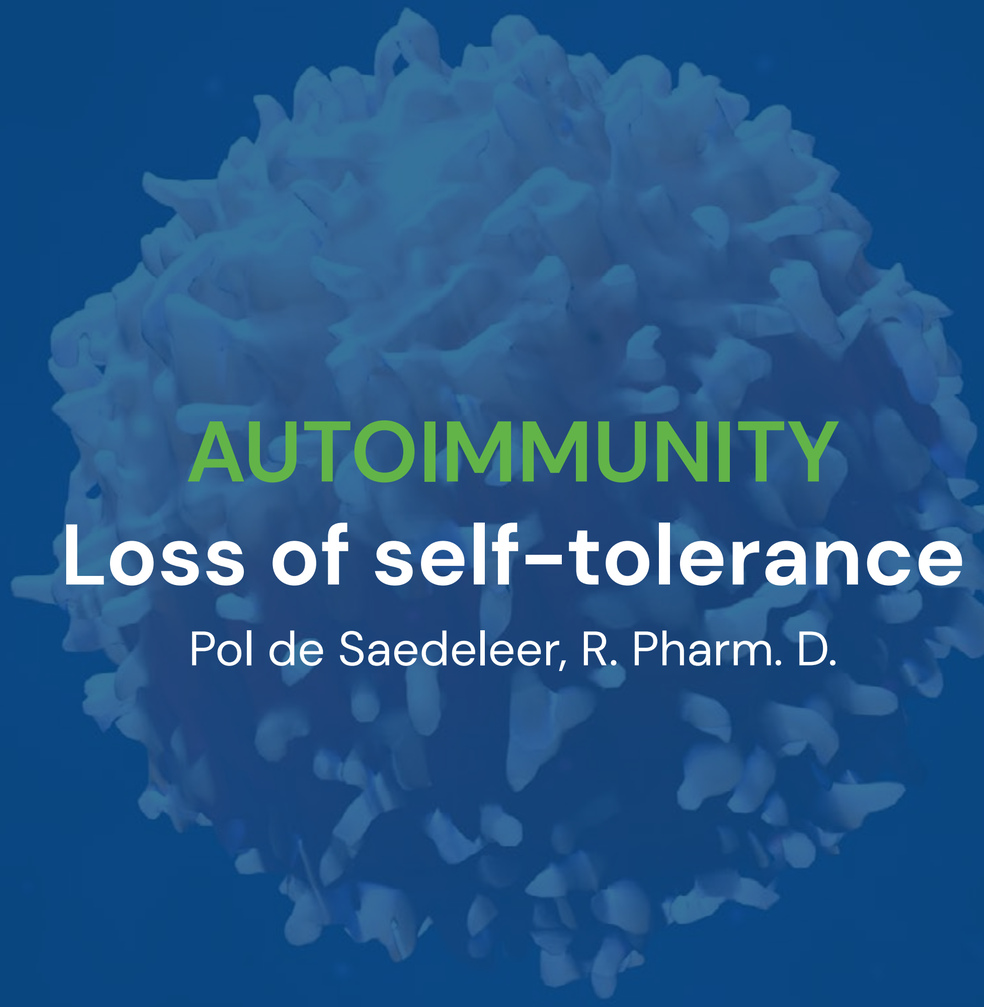


AUTOIMMUNITY

Loss of self-tolerance

Pol de Saedeleer, R. Pharm. D.

NUTRINED

Professional Disclosures

- Board director ILADEF
  ILADS medical association
- Scientific Consultancy for various Clinics and Laboratories
- Medical Director Nutrined/
  Researched Nutritionals

During our talks we respect the rule that statements need to be based on scientific references & scientific research

In order to make this clinical training as efficient as possible, the organizers have asked me to mention and name products and doses during the lectures

I hope this does not disturb you

Two types of autoimmune patients

1. not yet diagnosed
2. diagnosed and in need for guidance and treatment

We see three stages

Stage 1

Silent Autoimmunity
Antibodies elevated but no symptoms

Stage 2

Autoimmune Reactivity
Antibodies elevated and symptoms

Stage 3

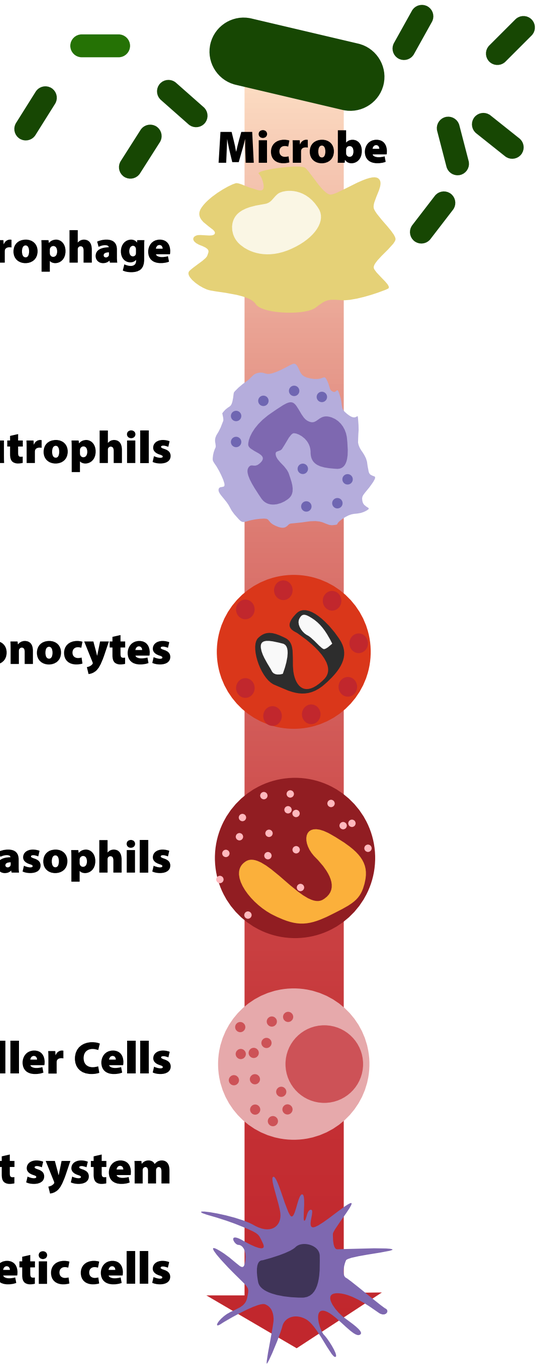
Destructive Autoimmunity
Antibodies, symptoms & tissue destruction

- **Complex disease, different in every single patient**
- **Clinical approach is different in every patient:**
  Diet, nutrition and lifestyle are an essential part
  Goal is to improve
- **What are the triggers?**

Review of basic immunity & autoimmunity

Microbe → Innate Immune System → Adaptive Immune System

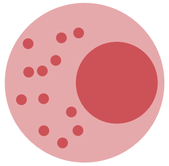
Autoimmune antibodies sabotage our immune response



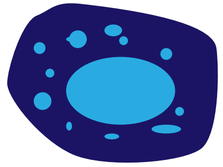
Innate Immunity

Macrophage

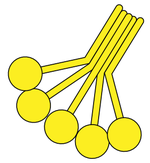

Dendritic Cell

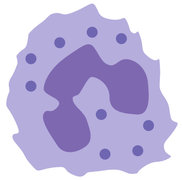

NK cell

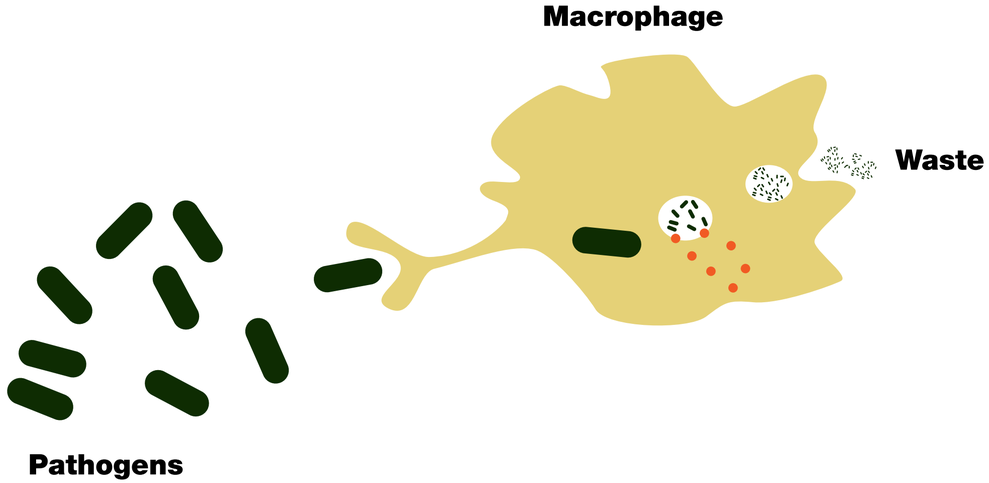

Basophil


Mast Cell


Eosinophil

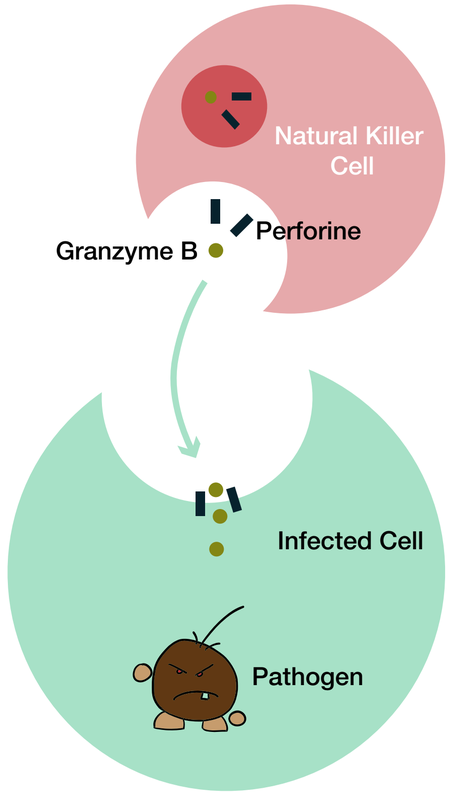

Complement protein


Neutrophil



Microbes are engulfed and eliminated

Chemokines & cytokines are released
= start of inflammation



Activation

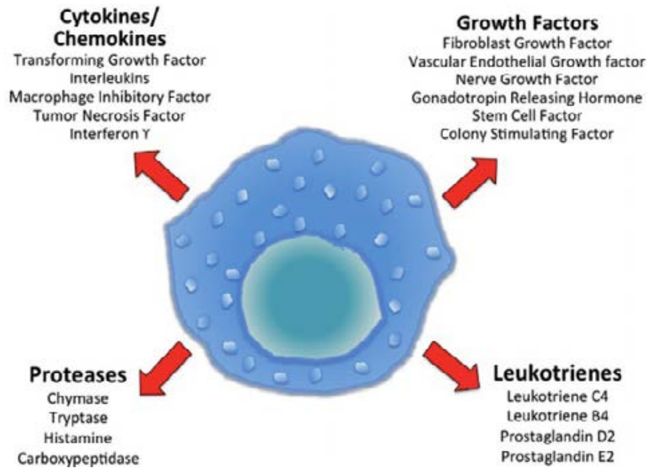
Attachment
+ pores are formed

Apoptosis

IFN gamma is secreted

Activity is susceptible
to oxidative stress

mast cells



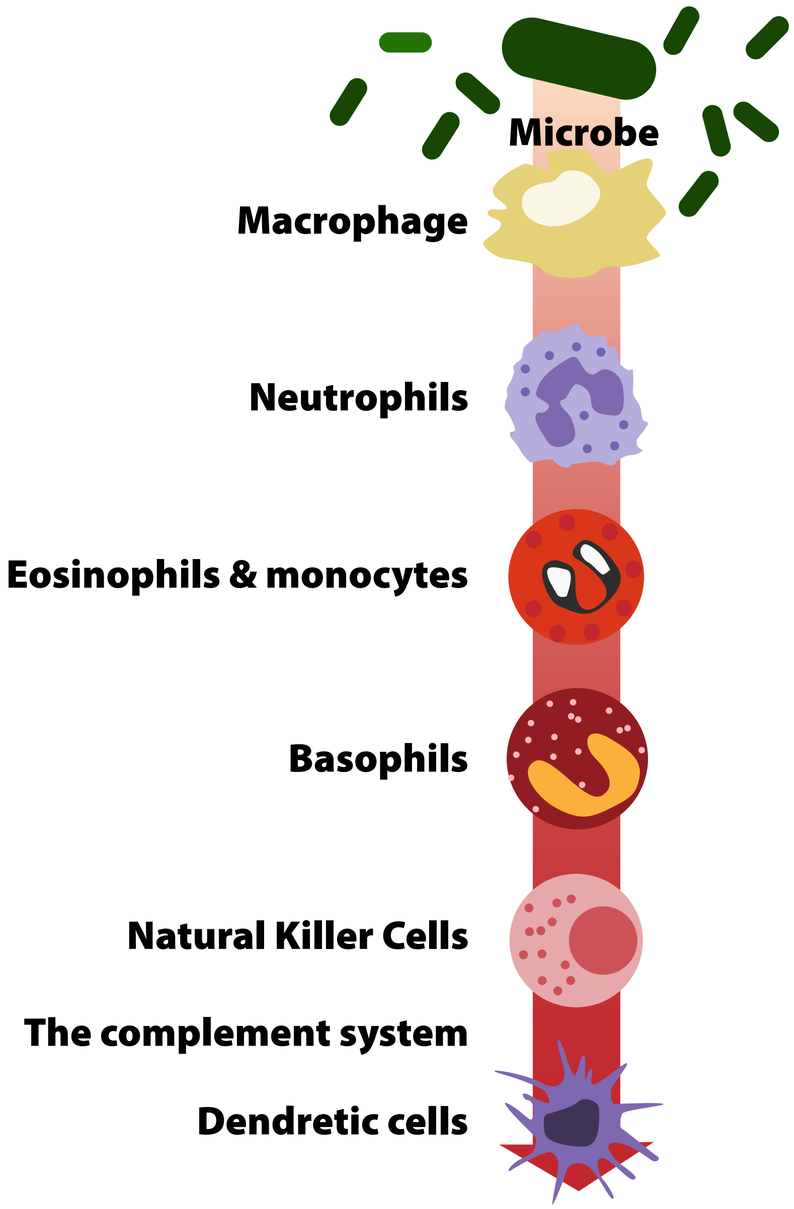
Located in the first line on mucus membranes, react rapidly - mucosa are loaded with mastcells!

IgE mediated in allergy

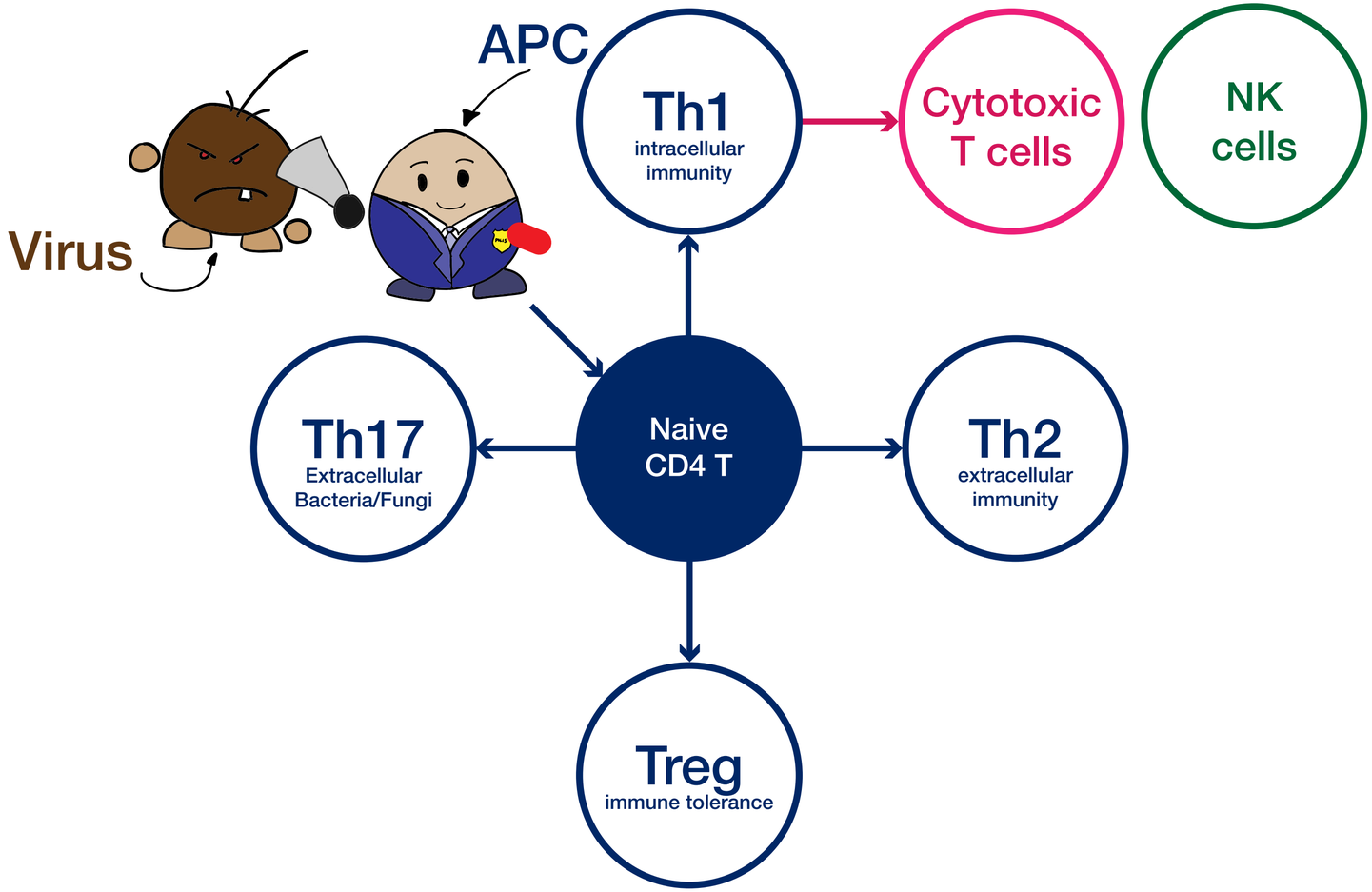
Mast cells are triggered by the environment and by parasites: many mediators, not only histamine

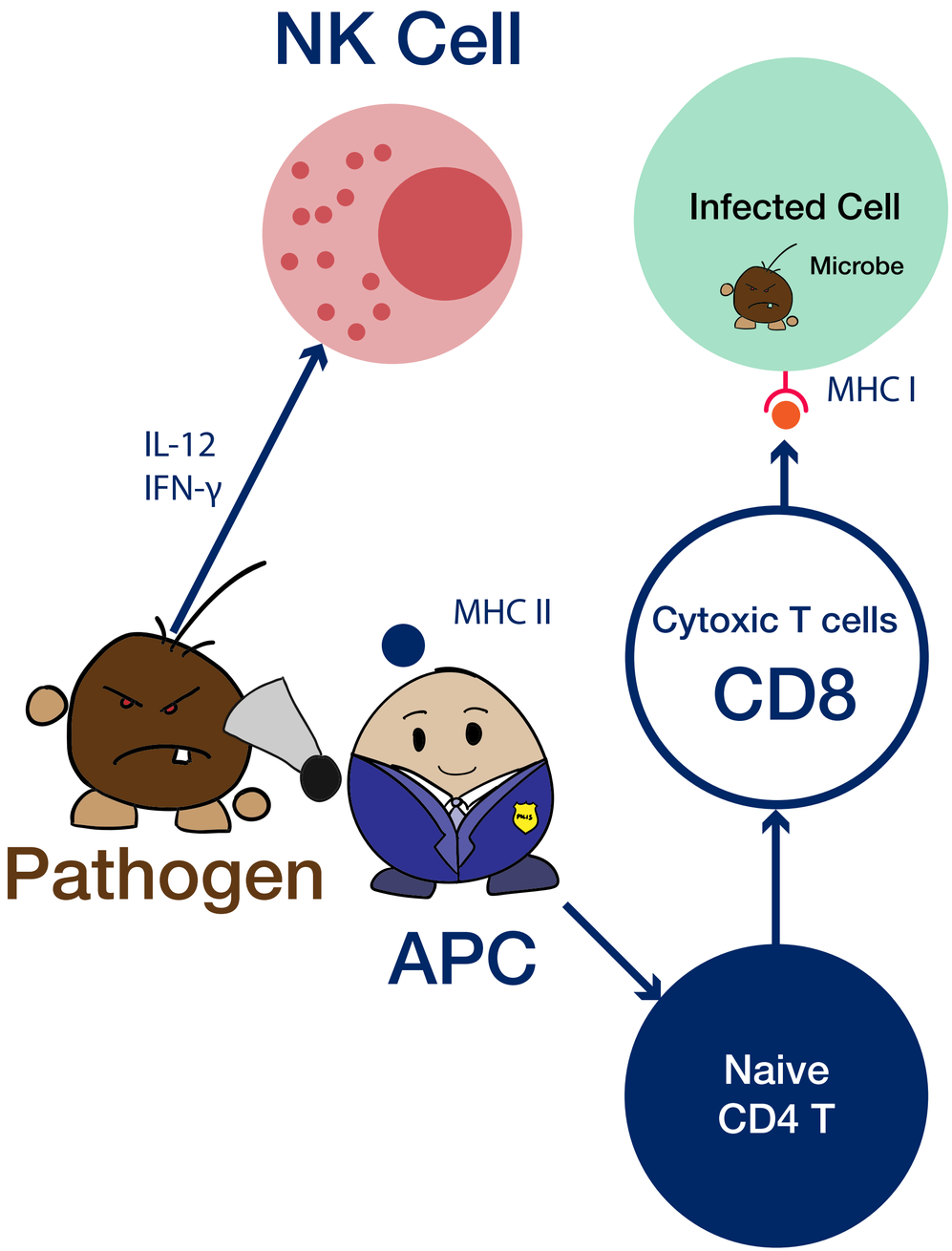
Mast cells trigger eosinophils

Innate Immunity



Adaptive Immunity



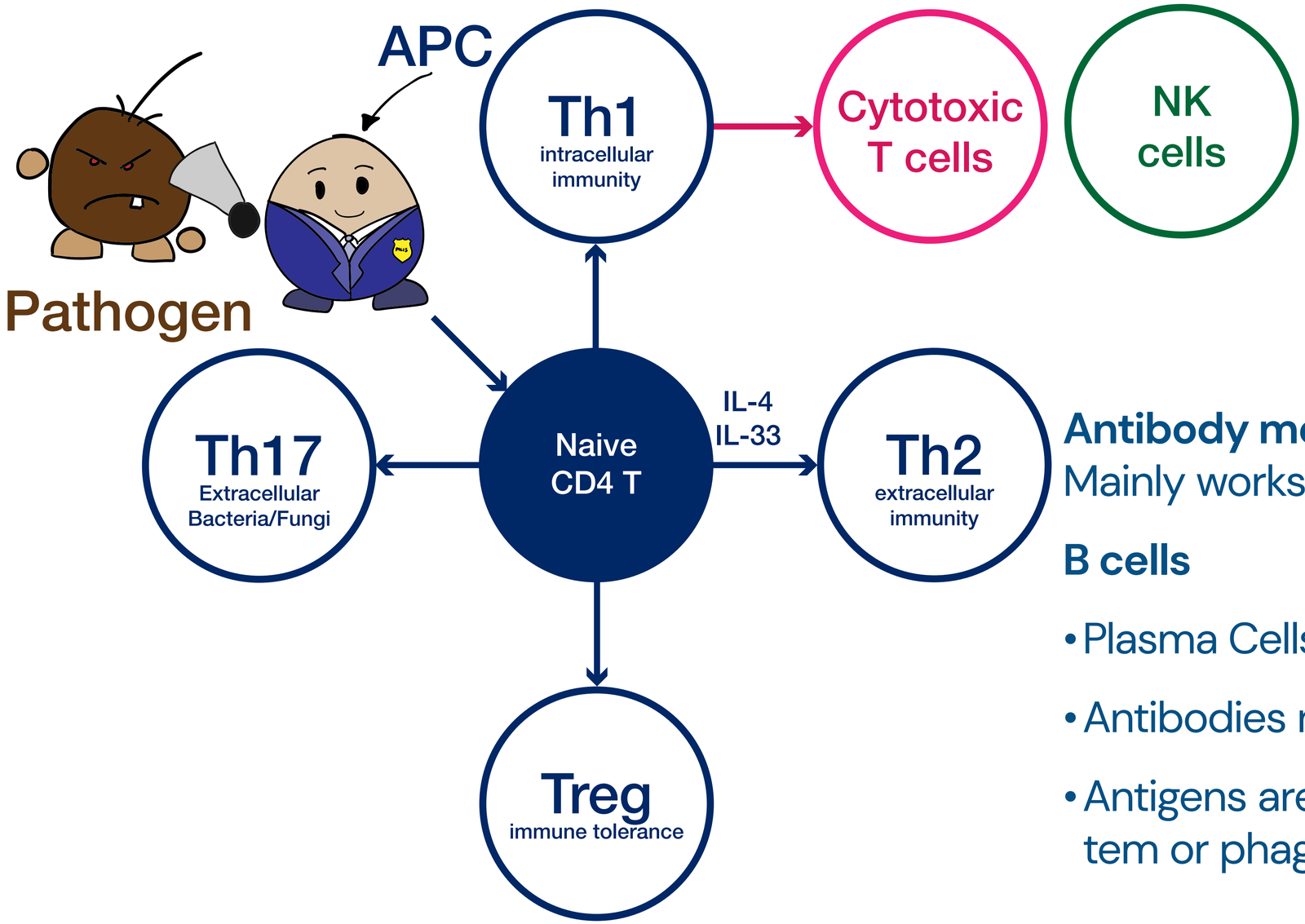


Cell Mediated Immunity

The immune response we manifest in intracellular infections

The role of NK Cells is similar to CD8 Cytoxic Cells

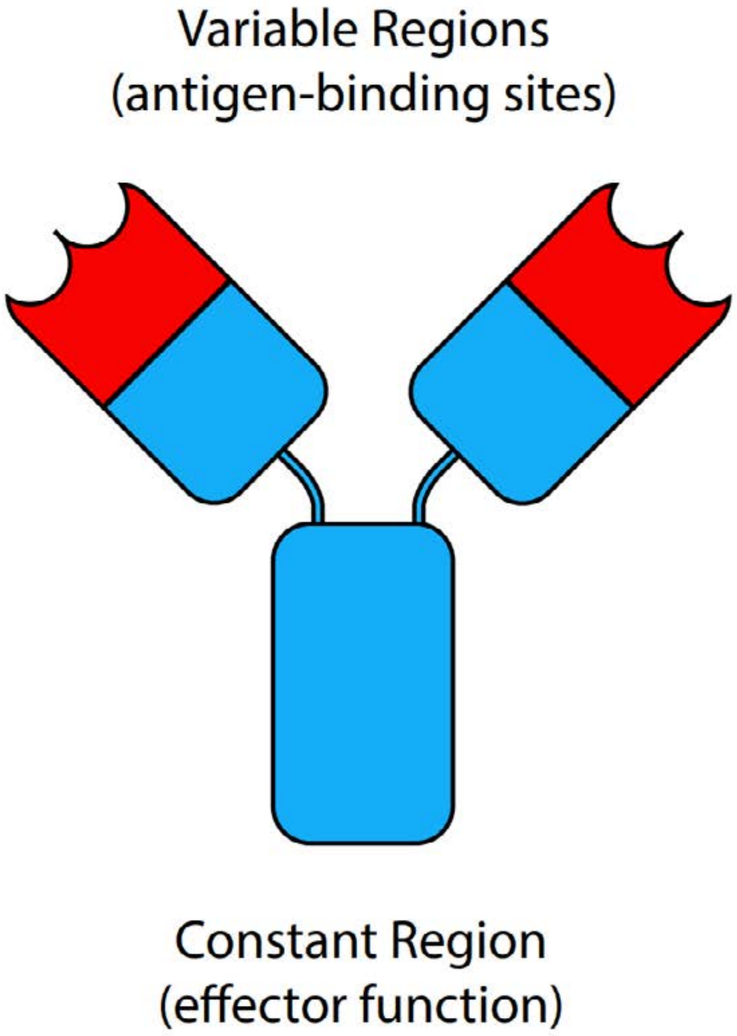
- MHC1 is expressed by all nucleated cell
- MHC2 complexes are only expressed by APC
  often used as a marker for microglial activity
- MHC1 enables antigen presentation to CD8
- MHC2 enables antigen presentation to CD4



Antibody mediated immunity Th2
Mainly works against extracellular pathogens

B cells

- Plasma Cells secrete antibodies
- Antibodies neutralize the antigen
- Antigens are eliminated by the Complement system or phagocytic cells from our innate immunity



Antibodies have no destructive properties

IgM, the first released antibodies ?
They have a structure that brings complement proteins together

Complement proteins respond in a sequential manner producing a cascade of reactions

IgG are efficient in attracting Natural Killer Cells
If IgG's are attached to a pathogen? NK Cells will detect

IgE are triggered by allergy, helminths or parasites

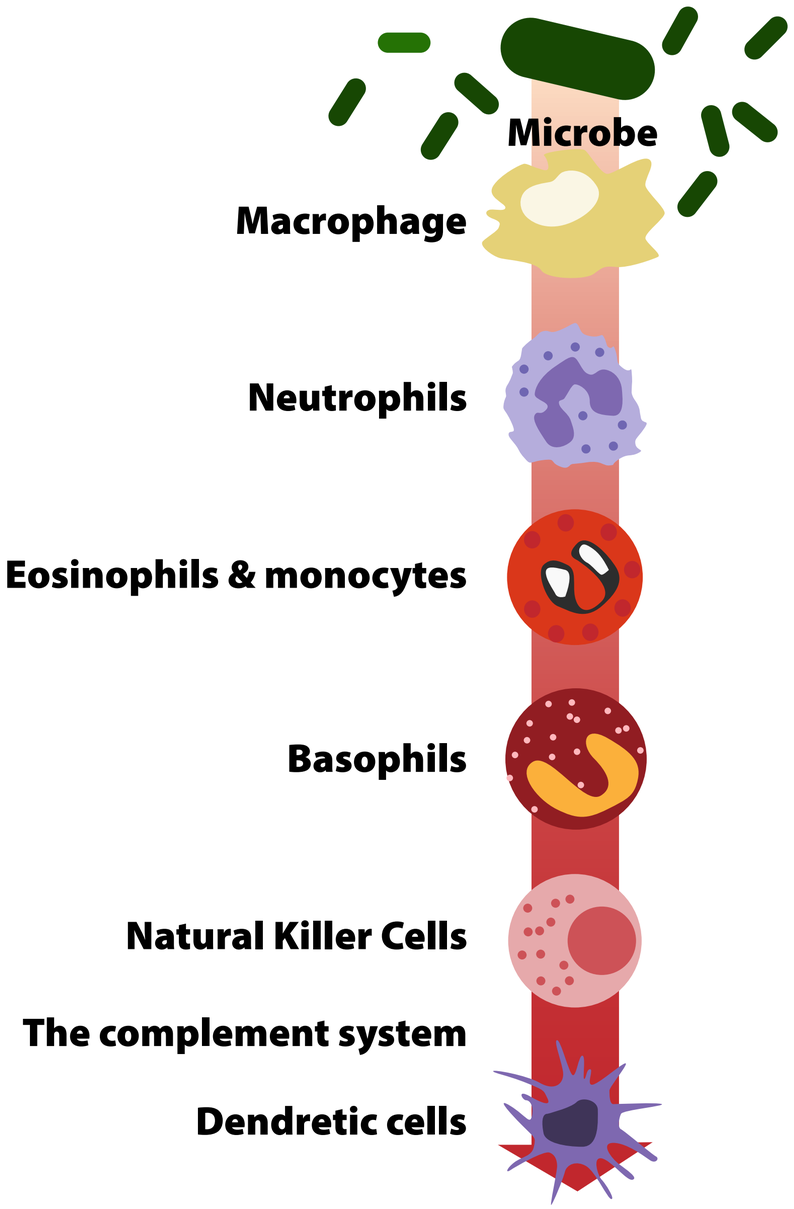
IgA = mucosal immunity , also stimulated by mast cells

Where can it go wrong in our immune response?

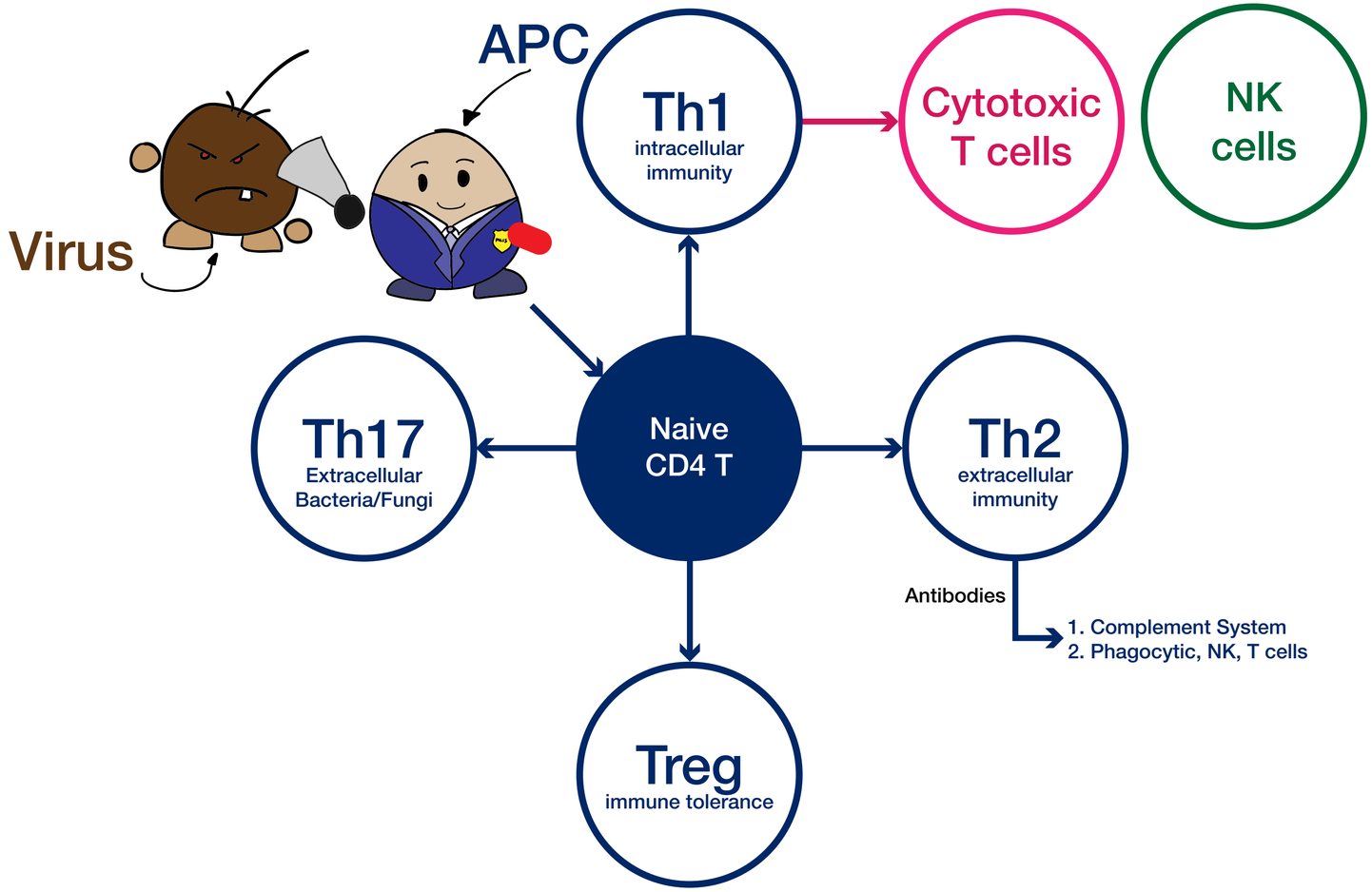
Complex disease , different in every patient?

Every patient suffering from an autoimmune disease is having a personalized combination of immune dysfunction patterns

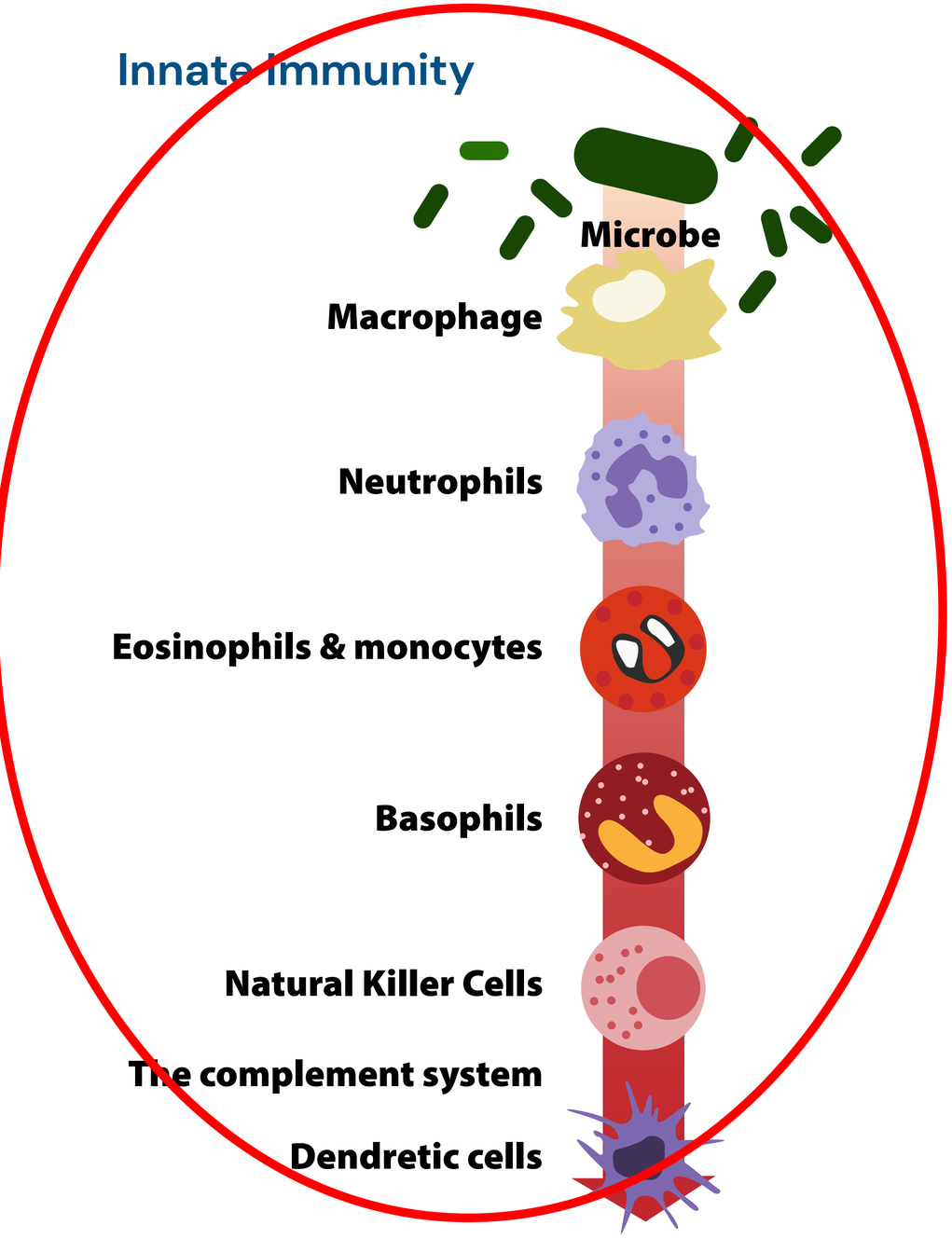
Innate Immunity



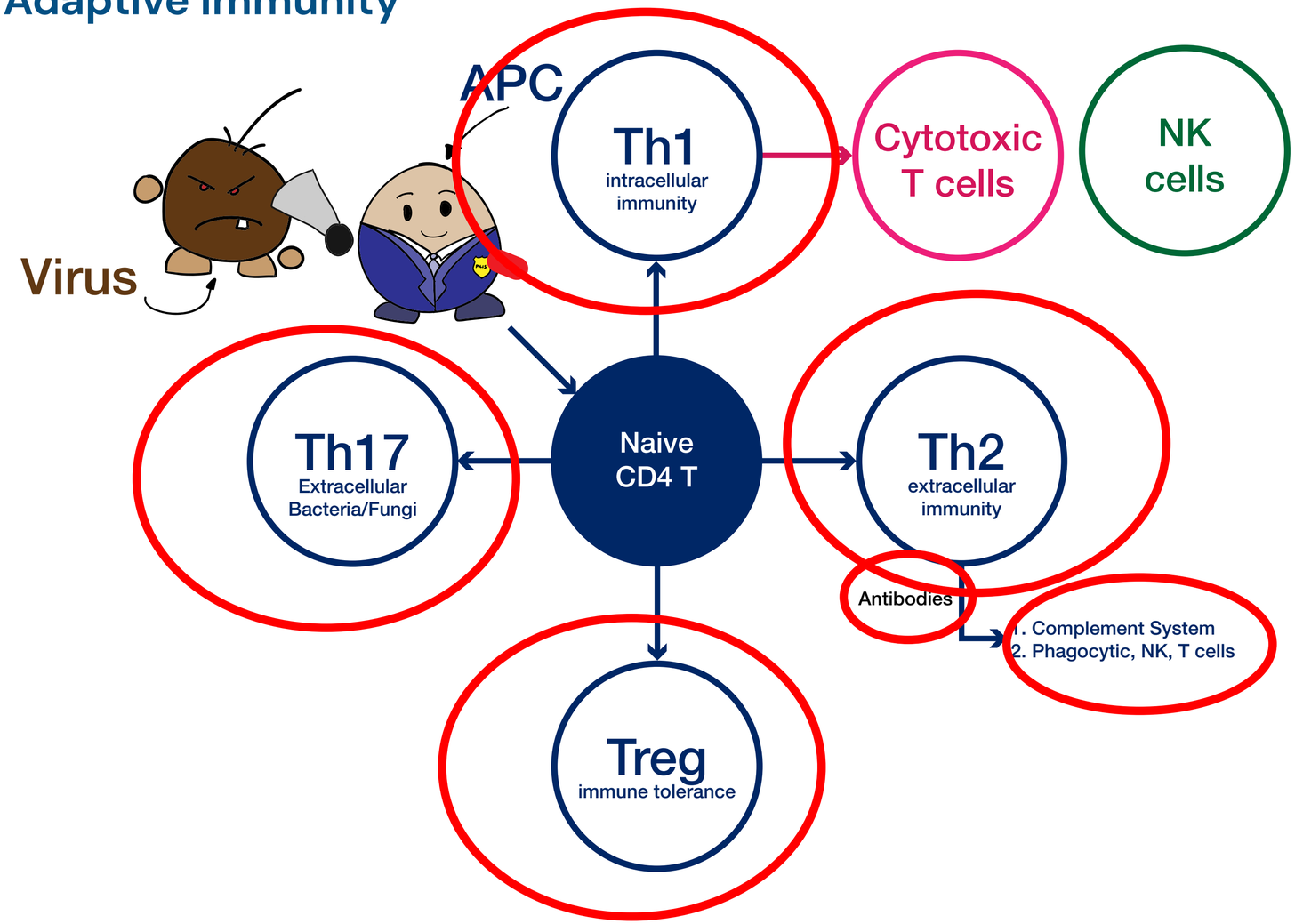
Adaptive Immunity



Innate Immunity



Adaptive Immunity



Multiple factors in autoimmunity

- Overactive phagocytic Cells
  monocytes, neutrophils, eosinophils, macrophages,
  dendritic cells, microglia
- Overactive NK Cells & T cells **Th1**
- Overactive Complement System
- Abnormal T cell differentiation leading to Th1, Th2, Th17 dysregulation
  = Immunity could be Th1,Th2 or Th17 dominance
  Or sometimes there is no dominance but this is basically because the Regulatory T Cells don’t work

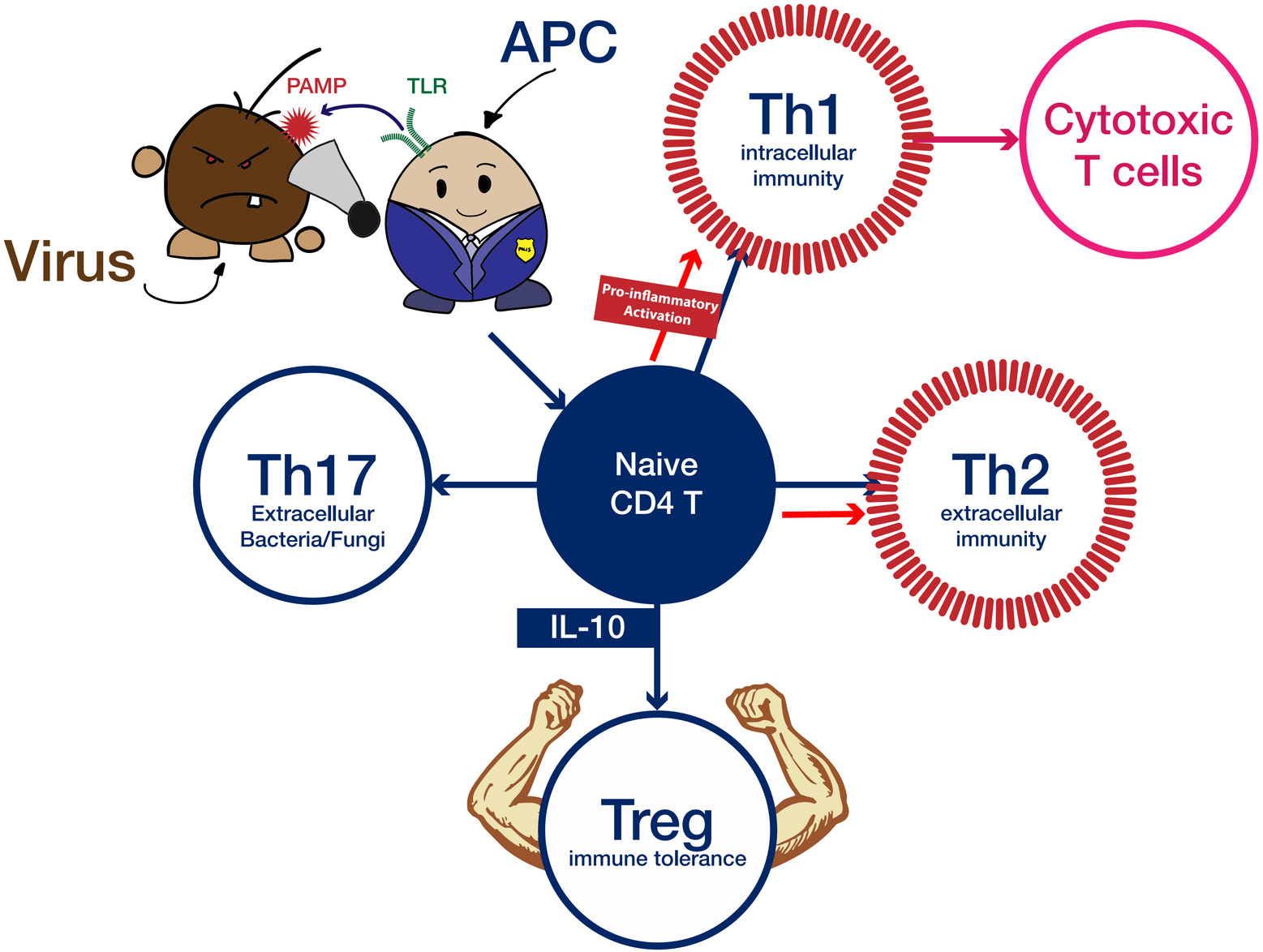
Multiple factors in autoimmunity

- Loss of tolerance = **poor Treg**
  In the adaptive part, T helper cells are activated:

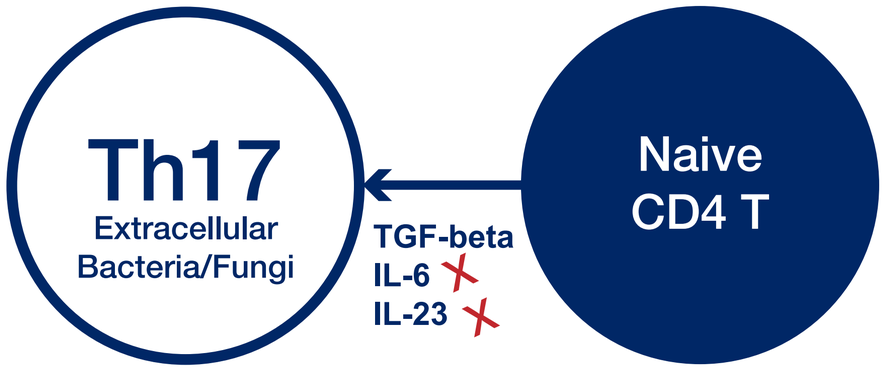
  → release cytokines and activate B Cells;

  → B Cells release antibodies

  → release cytokines to activate T Cells
  At some time this should stop = T reg / Suppressor T Cells


APC
PAMP
TLR
Virus
Th1
intracellular
immunity
Cytotoxic
T cells
Pro-inflammatory
Activation
Th17
Extracellular
Bacteria/Fungi
Naive
CD4 T
Th2
extracellular
immunity
IL-10
Treg
immune tolerance

The most characteristic in autoimmunity is Th17↑ & Treg ↓



- **Th17 cells play an important role in maintaining mucosal barriers and contributing to pathogen clearance at mucosal surfaces**
- The loss of Th17 cell populations at mucosal surfaces has been linked to chronic inflammation and microbial translocation.
- These regulatory Th17 cells are generated by TGF-beta + IL-6
- But if the CD4+ T cells polarized with IL-23 and IL-6 we generate a damaging Th17 response & we measure IL-17a & IL-17f

- **IL-17A & IL-17F are both pro-inflammatory cytokines responsible for development of inflammation & autoimmunity** (Tesmer et al 2008, Adami et al 2014)
- Mice with over expressed IL-23 develop inflammation and autoimmunity, IL-23 activates STAT3
- Cyclosporine , an immunosuppressive drug used in transplantation and treatment of autoimmune diseases is actually reducing the expression of IL-17 (Zhang et al 2008)

(Adami et al. 2014; Hot and Miossec 2011; Hu et al. 2011; Piper et al. 2014; Tesmer et al. 2008).

Other origins or contributing factors

- permeability / endotoxemia
- inflammation
- active infection

Permeability of the barriers and autoimmunity

Factors causing more permeability cause inflammation
& can induce or contribute to autoimmunity :

LPS ENDOTOXEMIA

Endotoxemia ?
LPS binds to Tol like receptors and automatically you activate autoimmunity

1. **Lung & nasopharynx**
   Air pollution - cigarette smoke - infections - chemicals
2. **Intestinal barrier**
   Dietary proteins - parasites - chemicals - dysbiosis - yeast
   Causing ENDOTOXEMIA / CHRONIC INFLAMMATION
3. **Blood Brain Barrier**
   Metals - organic chemicals cause BBB permeability,
   neuroinflammation and possibly autoimmunity

Immunity – Bloodwork – Infections

What is the contribution of infections?

- WBC are low immune compromised, immune system is exhausted
- WBC are high = active infection
- **What if IgA , IgM & IgG are very low?**
  Sometimes WBC are so low that there is hardly an immune response
  Or if patients with autoimmunity are taking corticosteroids to suppress immune response
- **If antibodies go down, it means you are in remission, which is good – unless the entire immune system's reaction is going down**

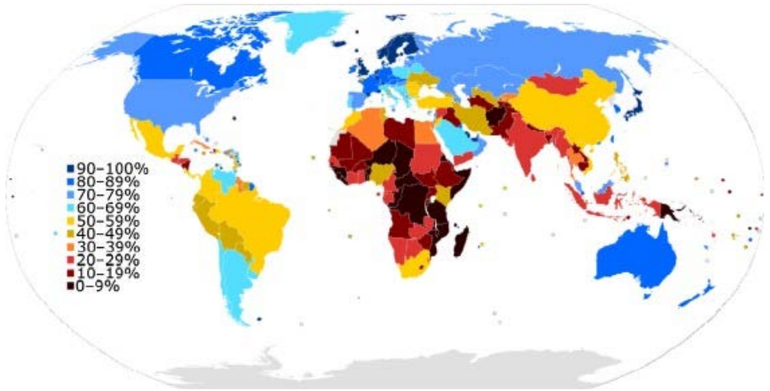
Pathogens, active infections? Two options

Can cause onset of autoimmunity
Can activate pre-existing autoimmune disease
Can cause Vaccine reactivity?

Pathogens

Protect against autoimmune development
Protect against autoimmune reactivity

Double edged Sword?



- **Countries with a lot of pathogens or parasites have less Lupus or MS**
  Inglese, Matilde. “Multiple sclerosis: new insights and trends.” American journal of neuroradiology 27.5 (2006): 954-957.
- **Some patients with RA get the flu & we see that the autoimmune symptoms dissapear?**
  J.Immunol 2005;174 : 7481-7486

Pathogens can protect against autoimmunity?

- **Helicobacter p can induce autoimmune diseases like Psoriasis, Vitiligo But the same Helicobacter p can protect against MS?**
- **Same with EBV**
  Curr Opin Rheumatoid 2018 , 30:000–000
- **Overview of pathogens and all the autoimmune diseases they could induce on Viruses 2019, 762; doc 10.3390/v 11080762**
- **NIH Research matters April 24, 2018**
  Epstein–Barr and autoimmune diseases :
  This paper describes how a viral protein called EBNA2 impacts expression of genes what augments the risk to develop autoimmune diseases like RA, Diabetes 1, MS

Parasites and autoimmunity

Immune reactivity (eosinophils)

Intestinal inflammatory response

- Dysbiosis
- Intestinal hyperpermeability & endotoxemia
- Microvilli injured
- Intestinal malabsorption
- Intestinal inflammatory markers (calprotectin, fecal eosinophils)

Helminth model in autoimmunity

Helminths being used to treat autoimmunity?

Wang, Meng, et al.
“Therapeutic potential of helminths in autoimmune diseases: helminth-derived immune-regulators and immune balance.”
Parasitology research 116.8 (2017): 2065-2074.

Zakeri, Amin, et al.
“Immunomodulation by helminths: intracellular pathways and extracellular vesicles.”
Frontiers in immunology 9 (2018): 2349.

Helminths are master in manipulating host immune responses.

Helminths target pattern recognition receptors (PRR’s) including toll-like receptors = helminths release mediators that manipulate the differentiation induced by dendritic cells

Helminths manipulate our Th1/Th2/Th17 expression

Blank, Miri, and Yehuda Shoenfeld.
“Helminth-Related Tuftsin-Phosphorylcholine Compound and its Interplay with Autoimmune Diseases.”
The Israel Medical Association Journal: IMAJ 21.3 (2019): 158-162.

This reviews focuses on a mediator released by helminths Tuftsin phosphoryl choline (TPC). In animal models it actually cured autoimmune diseases

Studies in rats where RA was first induced
TPC turned on T regs = Th1 , Th2 and Th17 don’t flair up the wrong way
It’s in clinical trial now , maybe a new drug in development...

BUT HELMINTH THERAPIES HAVE BEEN USED IN AUTOIMMUNITY

Dietary management

Dietary proteins & autoimmunity

Autoimmunity

= loss of tolerance

= food restrictions & dietary advise

Dietary advice in autoimmunity

Key concept about dietary protein immune reactivity

- Dietary proteins change their antigenicity depending on if they are cooked or raw
- Their antigenicity can change if they are combined with other foods during cooking
- Dietary proteins can cross-react with other food proteins
- Dietary proteins can cross react with body-tissue proteins

Food sensitivities?

- **Dietary proteins change their antigenicity if they are cooked raw**

Example :

- eggs cooked at different times,
  the protein structure changed – amino acid sequence is changed
- raw versus cooked shrimps or tuna or bacon
- Test, but accept limitations

Vojdani, Aristo. “Detection of IgE, IgG, IgA and IgM antibodies against raw and processed food antigens.” Nutrition & metabolism 6.1 (2009): 1-17.

How do we test?

- Antibody testing
- Elisa method
- Cyrex checks cooked & raw

Suppose the reactivity is high, example 40-50%, what will you do?
You can’t remove all the food proteins= work on oral tolerance

Start with paleo , no gluten – no dairy and a lot of diversity + work on immune tolerance and test again after a while to see if it has changed

If you have a panel of cross-reactivities, adapt

- **Dietary proteins change antigenicity when they are combined with other foods**
- **Dietary proteins can cross-react with other food proteins**
  if 2 food proteins share a similar sequence of amino acids, then antibodies made for 1 protein may bind to similar amino acid sequence of the other protein
  Fish : cross reaction between different fish species

- **Dietary proteins can cross-react with body-tissue proteins**
  Due to molecular mimicry!
  Antigen -binding mechanism
  If there is enough similarity , they will bind

Shanti, K. N, et al.
“Identification of tropomyosin as the major shrimp allergen and characterization of its IgE-binding epitopes.”
The Journal of Immunology 151.10 (1993): 5354-5363.

Blanchin, Stéphanie, et al.
“Anti-thyroperoxidase antibodies from patients with Hashimoto’s encephalopathy bind to cerebellar astrocytes.”
Journal of neuroimmunology 192.1-2 (2007): 13-20.

It’s not because it’s gluten free or paleo , that it’s safe

Kharrazian, Datis, Martha Herbert, and Aristo Vojdani.
“Immunological reactivity using monoclonal and polyclonal antibodies of autoimmune thyroid target sites with dietary proteins.”
Journal of thyroid research 2017 (2017).

High risk in autoimmunity

- Gluten
- Salt
- Food coloring agents
- Lack of HCl & digestive enzymes
- Food variability
- Sugar

3 major reasons why Gluten should be eliminated from your diet in autoimmunity

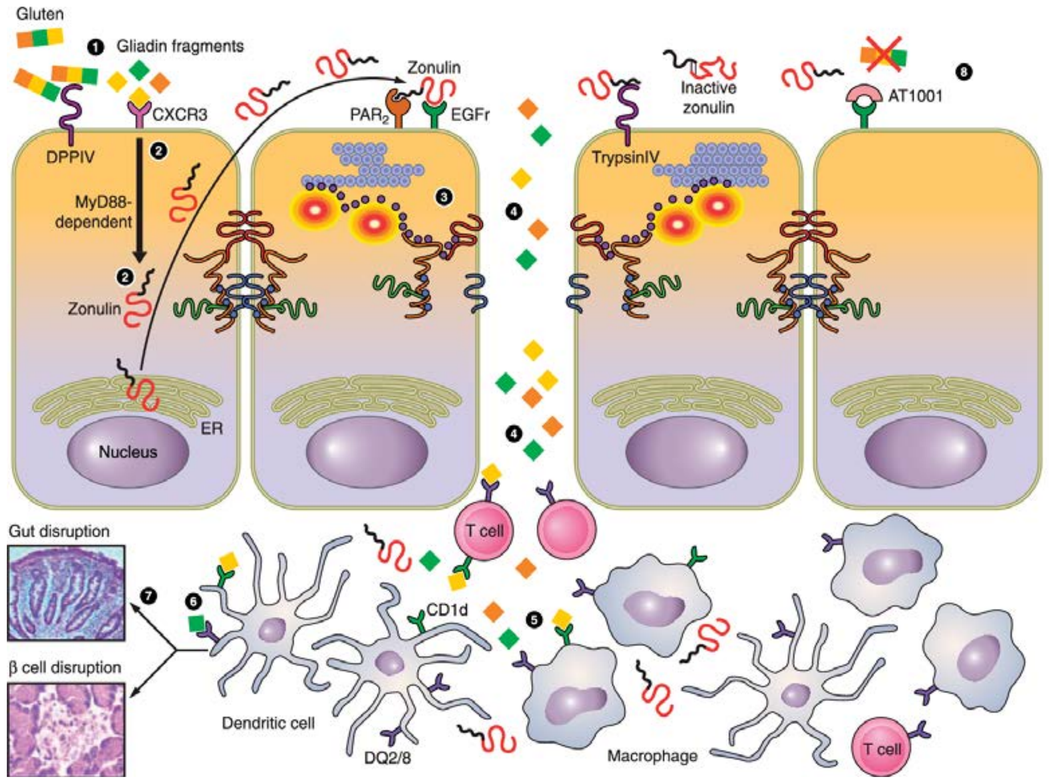
Why?

Gluten is bad in all inflammatory conditions

1° Gluten breaks down tight junctions

The gastro-intestinal barrier is a multi-layered and integrated system , an essential part of our immune system

Gliadin-induced Zonulin Release



3 major reasons why Gluten should be eliminated from your diet in autoimmunity

Why?

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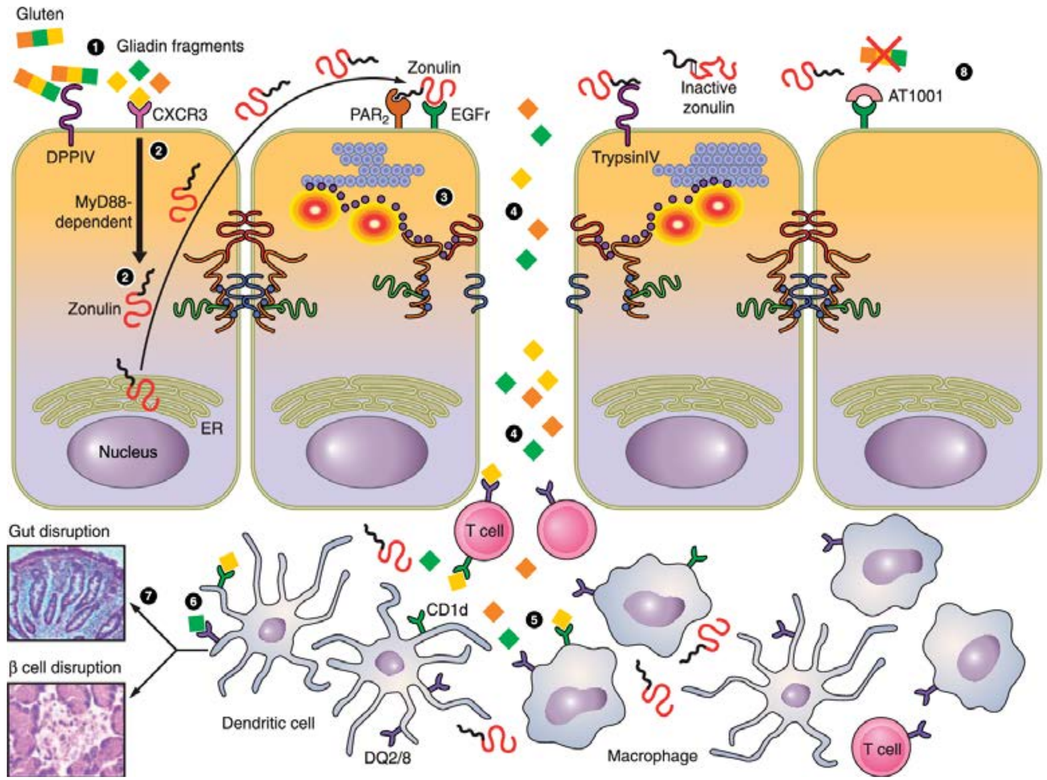
The gastro-intestinal barrier is a multi-layered and integrated system , an essential part of our immune system

Gliadin-induced Zonulin Release

Gluten DPP4 3x1 /day ate the start of each meal

DPP4 enzymes break down proline residues in gluten & reduce the damage to the tight junctions

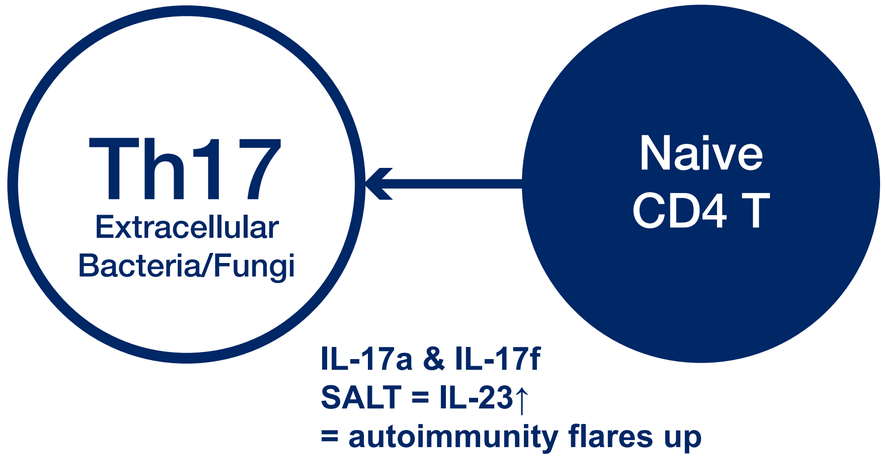


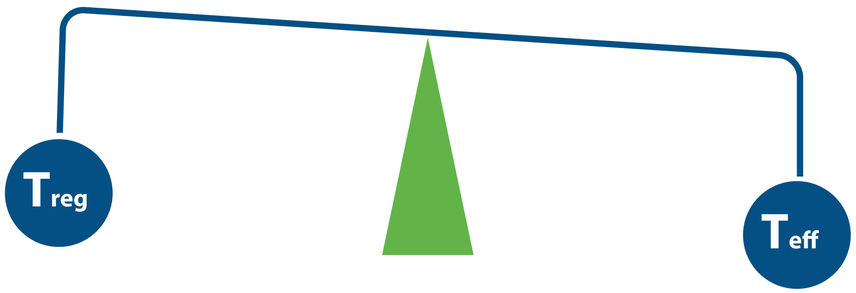
2. There is a lot of **molecular mimicry to gluten** because many tissue proteins have the same amino acid sequence as gluten

   Milk & dairy and many other grains have similar amino acid sequence as gluten = so often they need to eliminate all grains & milk in diet

3. **Cross – reactivity driven by gluten**
   Antibodies bind to much more than just the target tissue

   Celiac disease: genetic predisposition HLADQ2 & HLADQ8
   T Cells react against transglutaminase 2
   Cross-reactivity against transglutaminase 3 (skin)
   & transglutaminase 6 (cerebellum /ataxia)





Salt = NR2

Kleinewietfeld, Markus, et al.
"Sodium chloride drives autoimmune disease by the induction of pathogenic TH 17 cells." Nature 496.7446 (2013): 518–522.

Th17 adds fuel to the fire wherever the autoimmune disease is… !!!

More references show worsening arthritis with salt

Sigaux, Johanna, et al.
"Salt, inflammatory joint disease, and autoimmunity."
Joint Bone Spine 85.4 (2018): 411–416.

But also many other papers in MS, Lupus etc
Unless potassium is taken

Wen, Wen, et al. **"Potassium supplementation inhibits IL-17A production induced by salt loading in human T lymphocytes via p38/MAPK-SGK1 pathway."** Experimental and molecular pathology 100.3 (2016): 370–377.

Watch out for food coloring = NR3

food colors inhibit enzymes , there is no breaking down

Any reaction to food?

Load up with digestive enzymes and stomach acid

<u>Lack of HCl & digestive enzymes = NR4</u>

antibodies don’t bind to amino acids: if you have sufficient HCl , they break down the amino acid sequences

No HCl = the proteins are still targets for the antibodies

Guttae Pepsini

indication	Stomach acid deficiency Poor digestion Intestinal malabsorption Rebuilds intestinal pH	
dosage	3 x 10 - 20 drops per day at the start of each meal, dilute in water and swallow immediately.	
packaging	30 ml per bottle	
composition (amount per 30 drops)	Purified water Glycerol Hydrochloric acid HCl 37% Pepsine	5,3 ml 10 ml 2,7 ml 2 ml

Please find our referenced version on the professional section of our website.
All information is exclusively aimed at and released to an audience of health care professionals.

Food variability = NR5

= microbiome diversity

= lots of fibers

= good fermentation, SCFA's & Butyrate

Sugar = NR6

Blood sugar control and autoimmunity = spikes of sugar

stabilize blood sugars! Sugar activates the autoimmune response

Elevated glucose = direct activation of Toll like receptors = NKFB / Inflammation

Fluctuations in blood sugar aggravate the autoimmune response

Stabilisation of blood sugar levels

- **Improve insulin sensitivity**
  Insulin promotes uptake of carbohydrates in muscle tissue , liver and adipose tissue via GLUT-4 transporters
- **Promote fatty acid oxidation**
  Insulin resistance & low insulin sensitivity
  = poor fatty acid oxidation

  Lipid intermediates build up and slow down the electron trans-port chain with finally poor ATP Synthesis
- **Support mitochondrial activity**

Nutritional support

indication	Fluctuating blood sugar levels Dysglycemia Poor insulin sensitivity Elevated fasting blood glucose High glycated hemoglobin HbA1c Lipid metabolism (triglycerides & cholesterol)
dosage	3 x 1 caps per day during meals The daily dose can be increased gradually up to 3 x 2 caps per day during meals, depending on tolerance and results
packaging	180 vegecaps per container
composition (amount per 3 vegecaps)	Berberine 750 mg Cinnulin PF 255 mg

component 1: Berberine

Berberine 97% (Berberis aristata)

Significant decrease in

- Hemoglobin A1c
- Fasting blood glucose
- Postprandial blood glucose

Comparative studies between Berberine and Metformin:

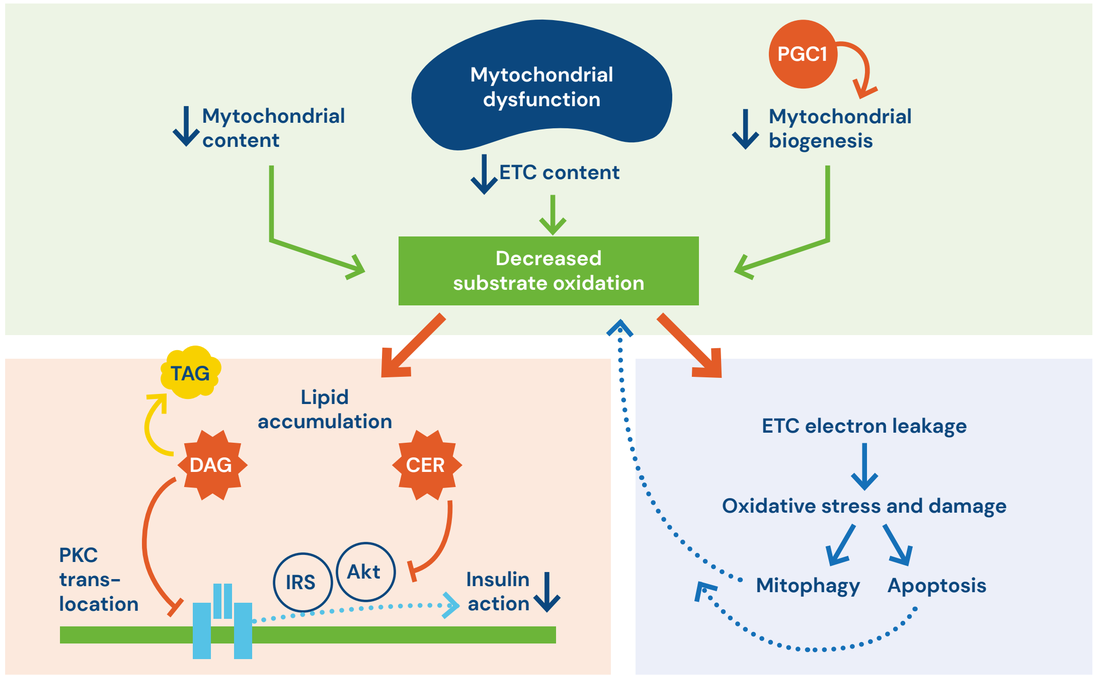
The hypoglycemic effect of berberine was similar to that of metformin. Their effects on lipid metabolism were different: Berberine decreased serum triglyceride and total cholesterol.

component 2: Cinnulin PF

Cinnulin PF is a unique proprietary, patented cinnamon extract, which is one of the few cinnamon extracts that has research to support its functions

Significant improvement in fasting blood sugar

- Increased insulin receptor sensitivity – reduced insulin resistance
- Glucose uptake and glycogen synthesis increased + positive outcome on systolic blood pressure, reduction of body fat



Impairments in mitochondrial biogenesis and electron transport chain are the markers of mitochondrial dysfunction.

→ Poor conversion of fatty acids causes **accumulation of lipid metabolites and downregulation of insulin sensitivity.**

→ Electron leakage in the electron transport chain causes **oxidative damage to mitochondria.**

Krebsplus
(Ac-Carnitine, Q10, Alpha-Lipoic Acid)
2x2/day fatty acid oxidation

CogniFuel
(NAD+ precursor Nicotonamide Riboside, PQQ)
3x1/day ATP synthesis & mitochondrial biogenesis

Lifestyle triggers

Sleep, exercise, stress

Sleep?
How many hours non-interrupted sleep/night? Is your sleep interrupted?
Do you have difficulties falling asleep?

Constantly waking up = poor regulation of the immune system

= KEY FACTOR!

Regular sleep is essential in controlling autoimmune diseases

Stress?

Sedentary lifestyle ? will worsen autoimmune patients

Consider :
Relaxation, meditation, nutritional support
(Glycine , GABA & Cofactors , Melatonine , Melisse & Theanine…)

General approach in treatment

Triggers :

- Lifestyle management
- Dietary management
- Pathogens/antigens management: virus, bacteria, lyme, mold, parasites

- Correct immune tolerance
- Manage intestinal and BBB

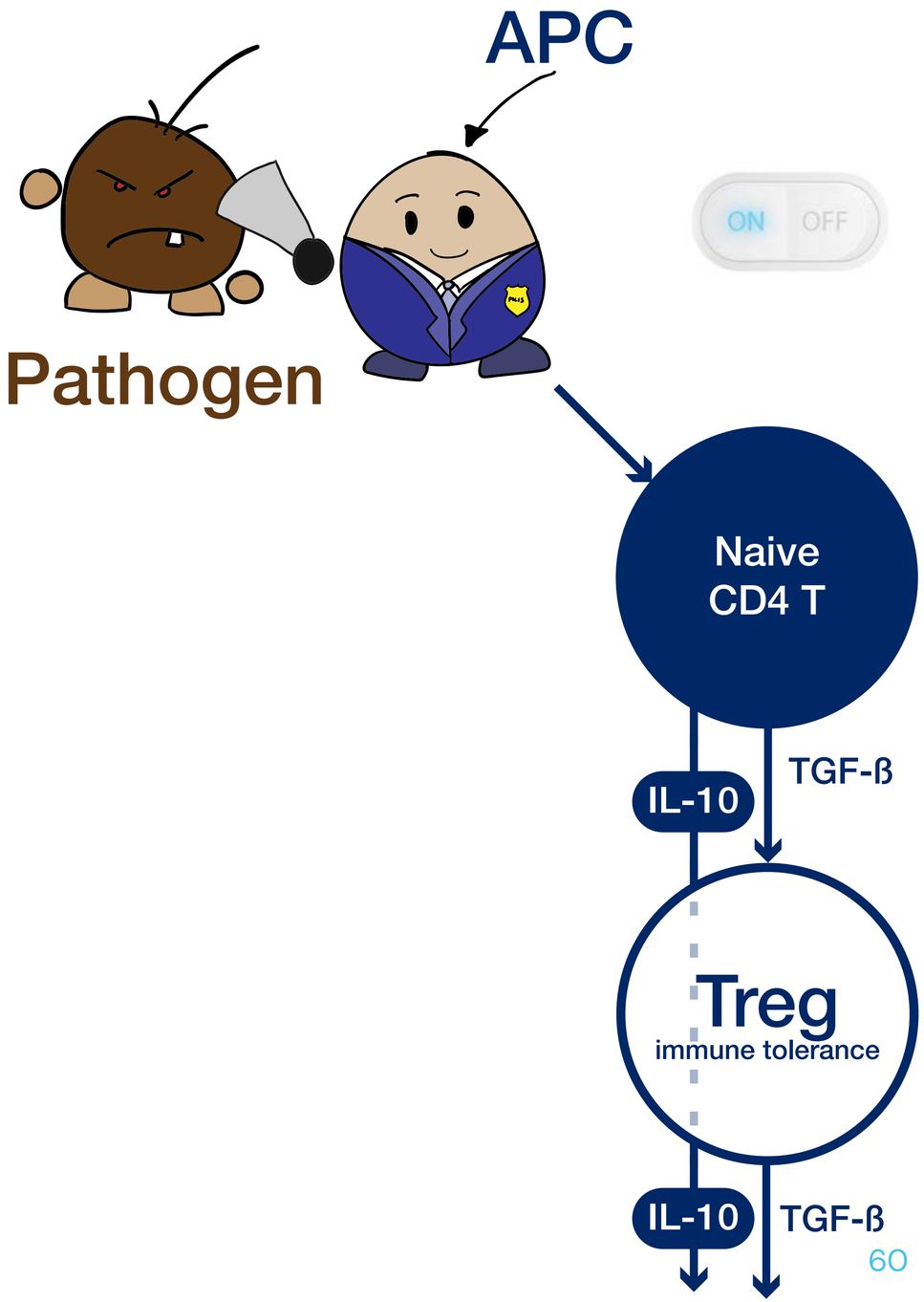
Correct immune tolerance

Regulatory T Cells (T reg's)

Decide about tolerance = also called suppressor T cells

Regulatory T Cells prevent excessive immune response

- Auto-immunity
- Excessive inflammation

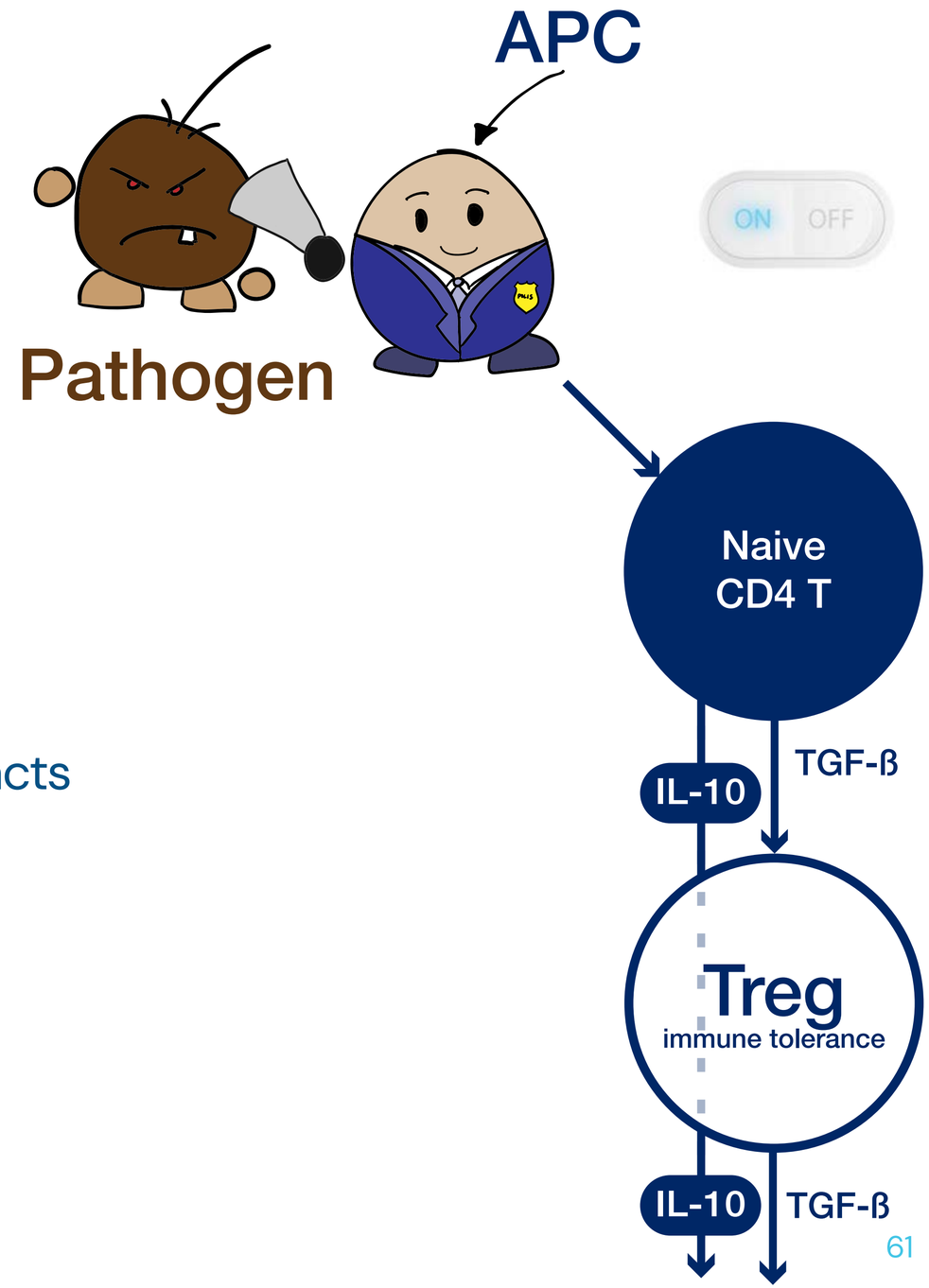


We improve tolerance if IL-10 goes up

- **Optimizing Vit D3** – individual
- **Butyrate coated:** metabolite produced by fermentation through anaerobic colon bacteria
  Supplementation in coated form (Butyflam)
- **Transfer Factors**
  Small proteins with RNA (nucleotide material)
  Made by activated T-helper cells or pure amino acid extracts of colostrum

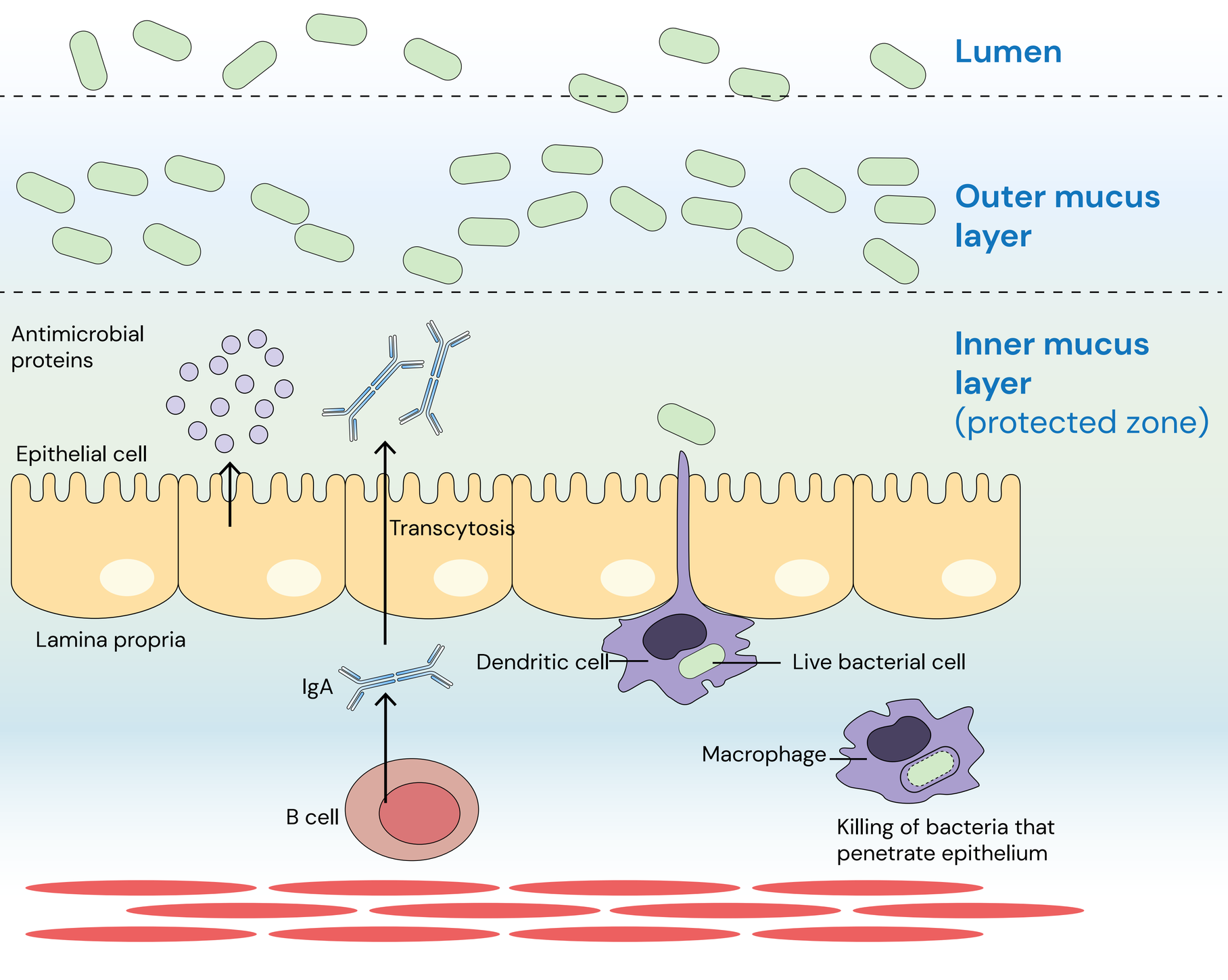
NK Cell Activity↑ + IL-10↑

- **Optimizing DHEA** - individual



How is butyrate formed?

- From host prebiotic, glycans in the mucus layer
- From exogenous prebiotics in diet (fibers)



Microbial barrier
commensal bacteria

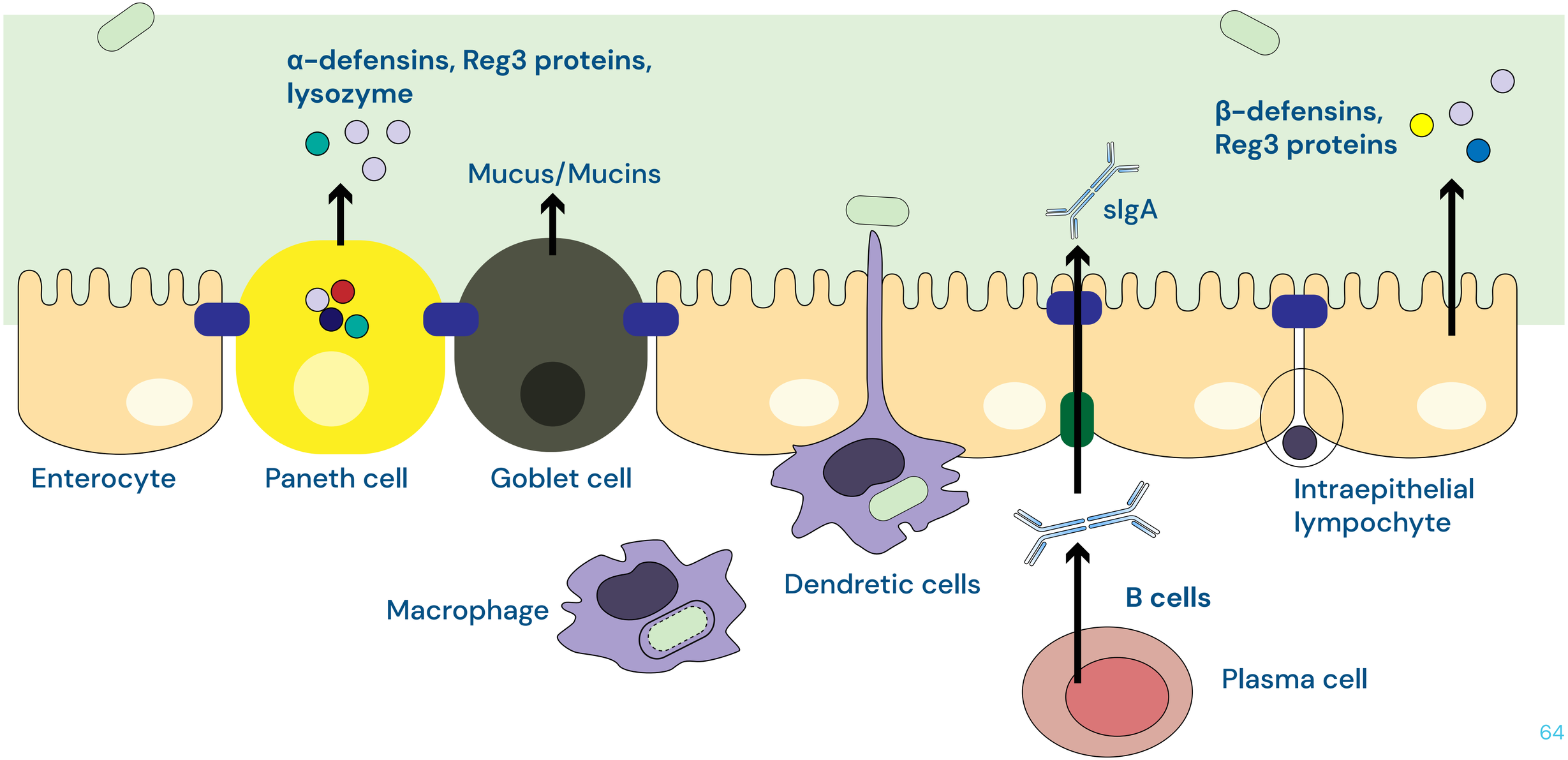
Chemical barrier
mucus layer

Physical barrier
the epithelium

Immunological barrier
immune cells
of the lamina propria

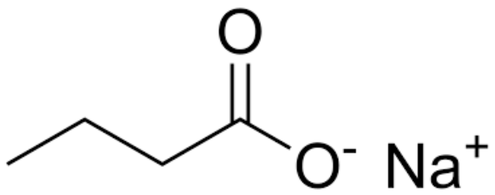
Muscle layers
smooth muscle intestinall wall

Mucus is a “slimy” material that coats many epithelial surfaces
It is composed chiefly of mucins
Goblet Cells secrete Mucins



Mucins are highly glycosylated proteins, polymers form a gel-like network

Mucins contain amino acids with high concentration serine & threonine, and that is where the glycans bind to form a water attracting network of glycoproteins



How is butyrate formed?

1. From host prebiotic

Mucin harvesting bacteria that release glycans
= mucin derived glycans are fermented by other bacteria
to form butyrate

What bacteria produce butyrate?

- **Clostridium spp.** have a key regulatory role
  = major butyrate producers – initiating that cross talk
- **Fecalibacterium prausnitzii**

- We have a decreased amount of Clostridium spp.in colorectal cancer and IBD versus controls
- The more fibers, vegetables and beans we eat, the more abundant Clostridium spp.are
- Vs. we also have 5 very pathogenic spp.like C difficile
  – THE MAJORITY OF CLOSTRIDIUM spp. ARE NOT BAD

2. From exogenous prebiotics (fibers)

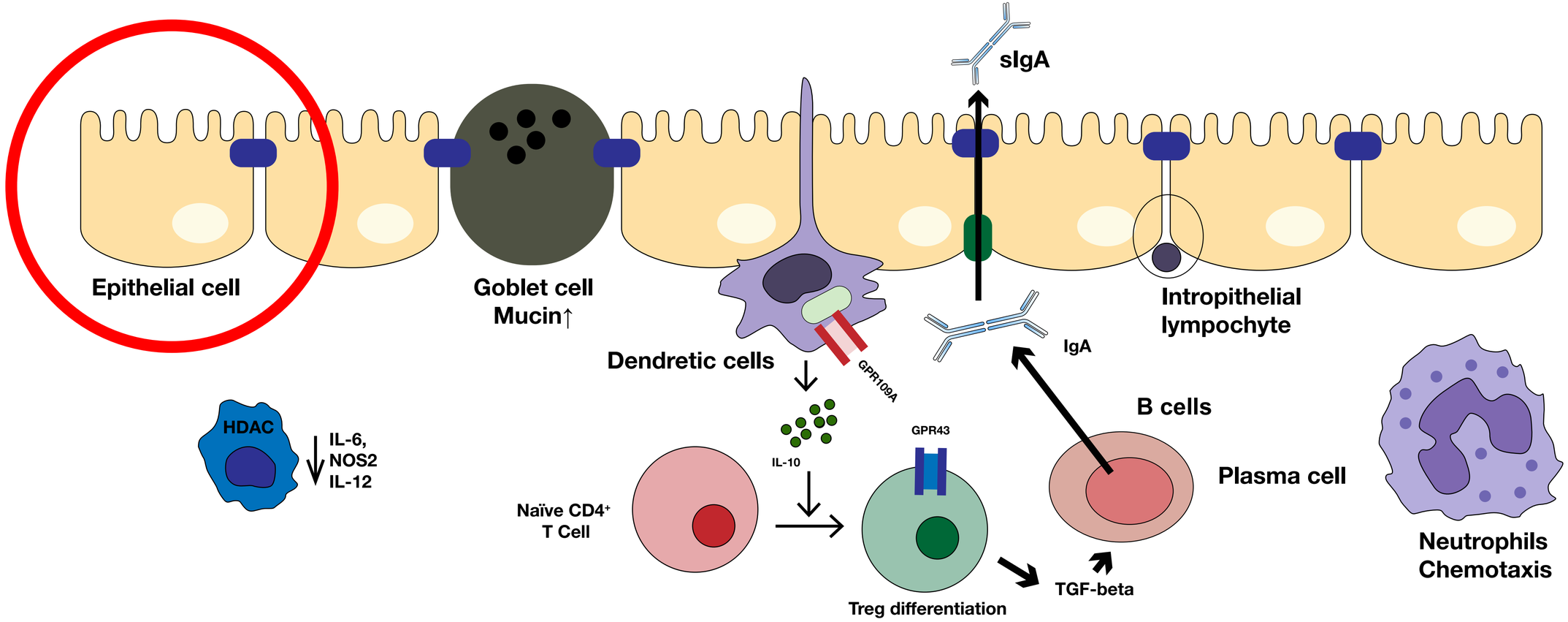
onions, garlic, asparagus, leeks, yams, chicory root, bananas

What is the role of butyrate and SCFA's?

Butyrate, acetate, propionate

Fuel to renew the intestinal epithelial cells (IEC)

IEC need to be renewed every 3–5 days



Microbial-host cross talk: “ the host listens to butyrate”

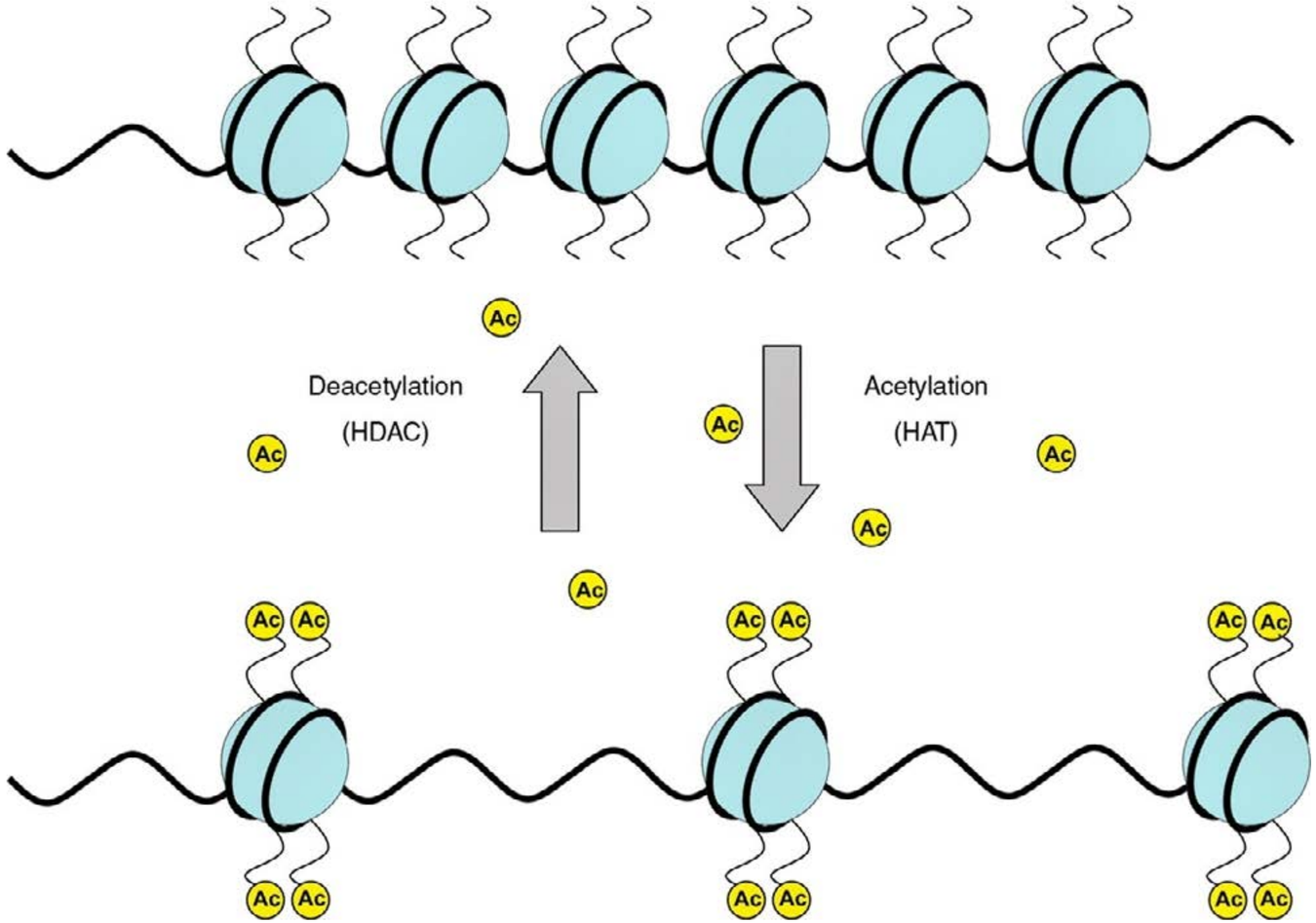
=Butyrate impacts epigenetics
= Butyrate modifies genetic material
→ impact on gene expression and transcription

Epigenetics most often involves changes that affect gene activity and expression

Such effects may result from external or environmental factors, or be part of normal development.

Examples of mechanisms that produce such changes are DNA methylation and histone modification, each of which alters how genes are expressed without altering the underlying DNA sequence.

Immune modulation / anti inflammation on local level:
Butyrate inhibits HDAC (histone deacetylase)
– this modification is changing the gene expression

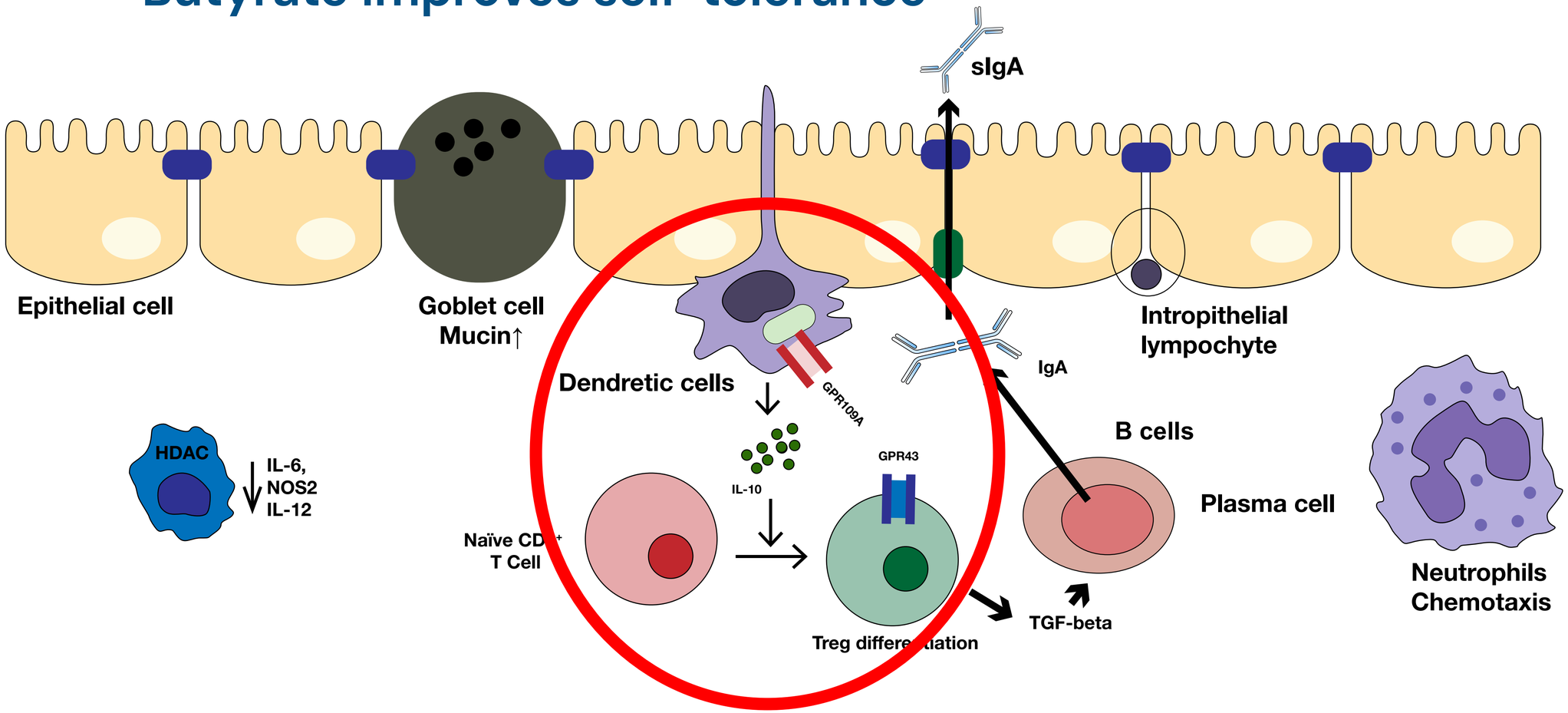


Gene expression is modified in Dendritic Cells

IL-6 is suppressed = more IL-10

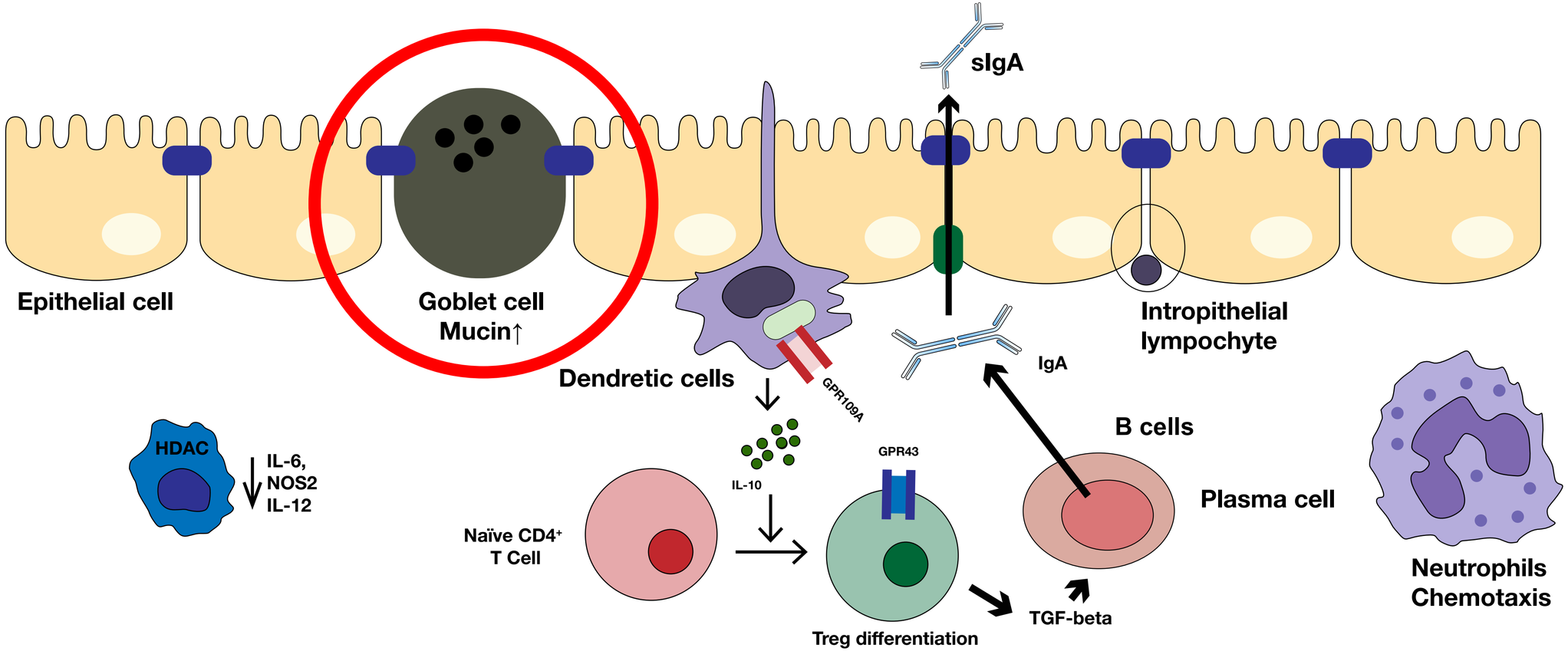
More differentiation to T regs

Butyrate improves self-tolerance



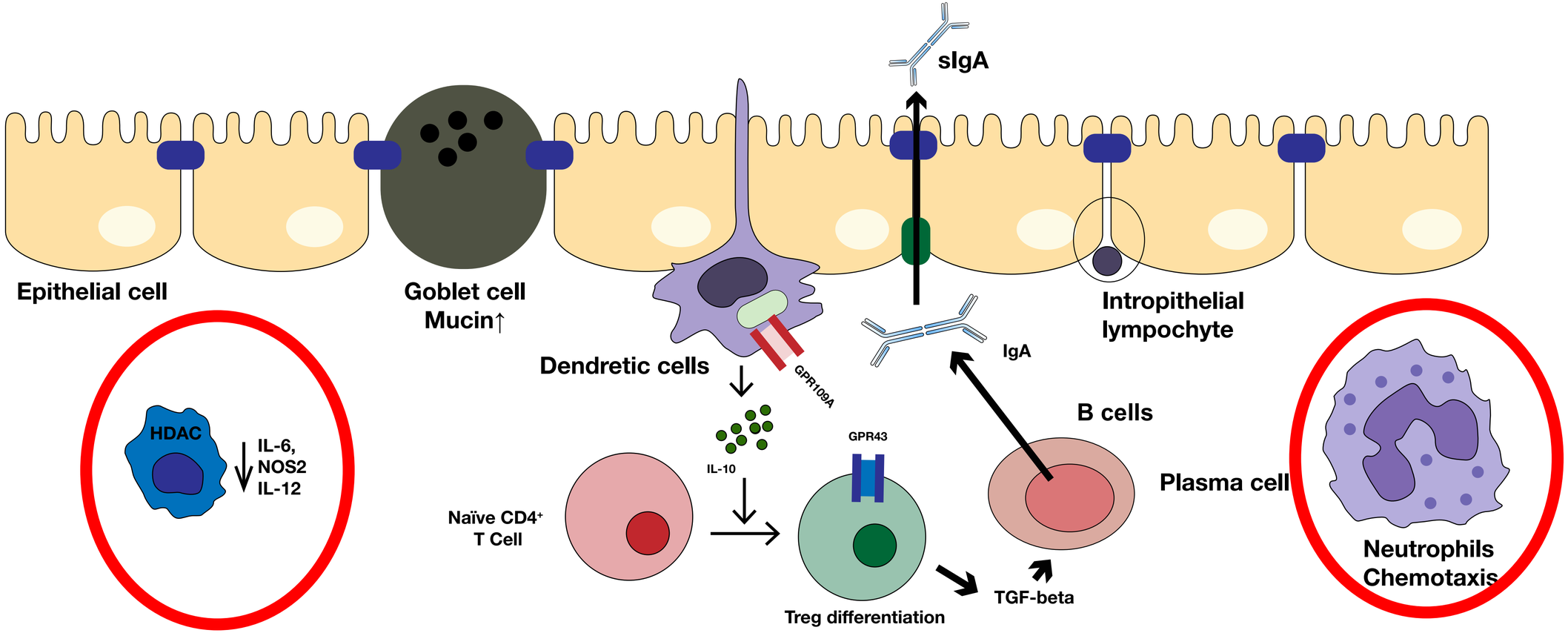
Differentiation of Goblet Cells and mucus formation

More mucin is a better immune defense against invading pathogens



Butyrate modulates the immune response in macrophages what makes macrophages more tolerant towards commensal bacteria

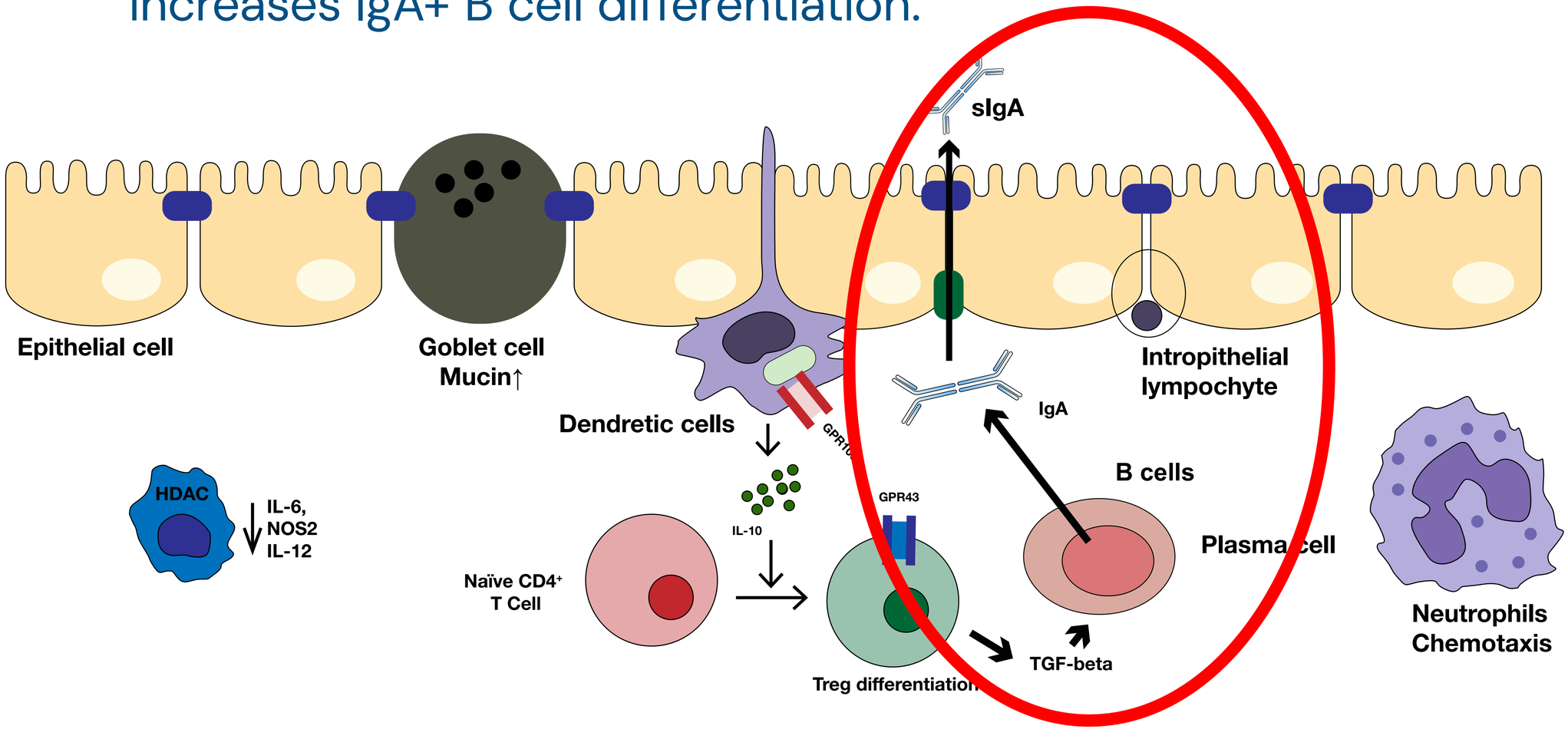
Butyrate affects neutrophil chemotaxis anti inflammation on local level



sIgA

TGF-beta produced by Treg cells drives naïve B cells to differentiate into IgA-producing cells.

IL-21 from Th17 cells accentuates the effect of TGFb and increases IgA+ B cell differentiation.



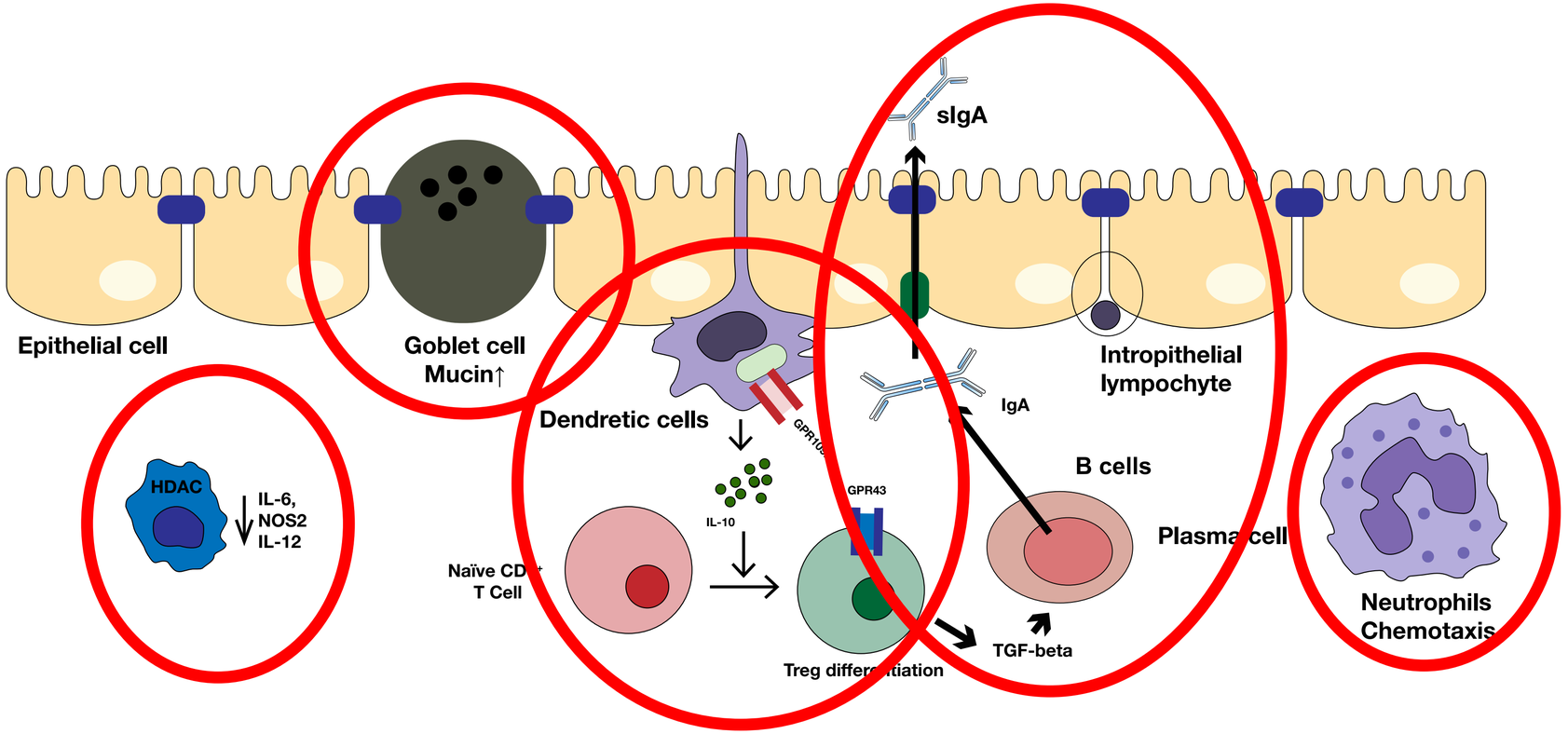
Fuel to renew epithelial cells

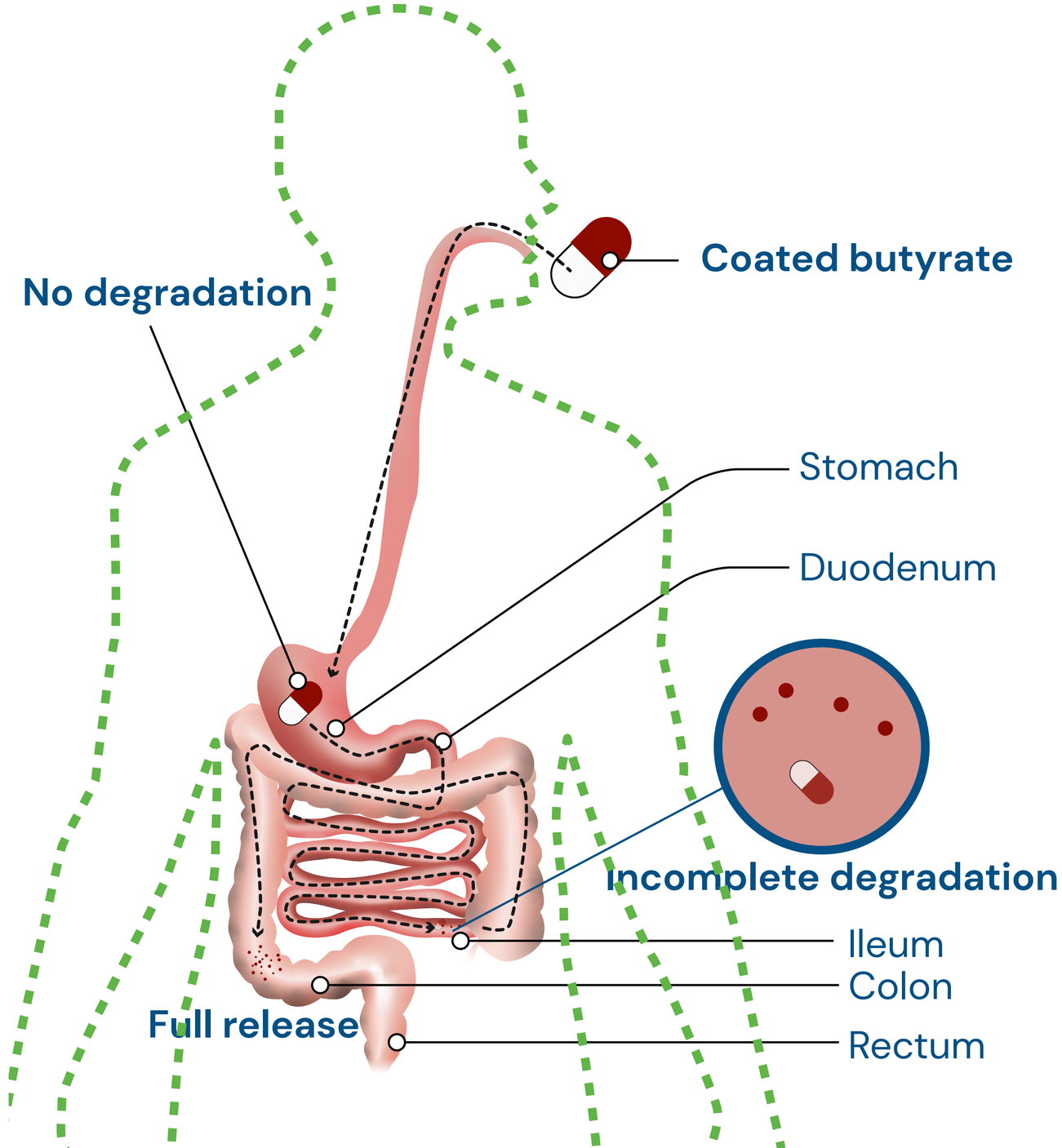
Impact on dendritic cells, more IL-10 & T regs

Goblet Cells release more mucins

Macrophages more tolerant towards commensal bacteria

Neutrophil chemotaxis





Supplemental Butyrate needs coating for overall activity on different levels

- To obtain both local and systemic effect
- To avoid a premature release and absorption of butyrate
- To ensure complete release of the active ingredient at a time comparable to the oro-ilear transit time

Butyflam Coated

Butyrate is a short-chain fatty acid produced by the intestinal bacteria through fermentation of non-digestible fibers. Butyflam Coated delivers bio-available levels of butyrate in our intestines to guarantee immune tolerance and avoid excessive inflammation or auto-immune reactions.

indication	Neuroinflammation Immune modulating (T reg + IL-10 anti-inflammation) Remodeling intestinal barrier function
dosage	3 x 2 caps per day, 20 minutes before meals
packaging	180 coated caps per container
composition (amount per 6 caps)	Butyrate - 3000 mg

Donohoe, Dallas R., et al. “Microbial regulation of glucose metabolism and cell-cycle progression in mammalian colonocytes.” PloS one 7.9 (2012).

Donohoe, Dallas R., et al. “The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon.” Cell metabolism 13.5 (2011): 517-526.

Sanderson, Ian R. “Short chain fatty acid regulation of signaling genes expressed by the intestinal epithelium.” The Journal of nutrition 134.9 (2004): 2450S-2454S.

Arpaia, Nicholas, et al. “Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation.” Nature 504.7480 (2013): 451-455.

Chang, Pamela V., et al. “The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition.” Proceedings of the National Academy of Sciences 111.6 (2014): 2247-2252.

Vinolo, Marco AR, et al. “Suppressive effect of short-chain fatty acids on production of proinflammatory mediators by neutrophils.” The Journal of nutritional biochemistry 22.9 (2011): 849-855.

Usami, Makoto, et al. “Butyrate and trichostatin A attenuate nuclear factor □B activation and tumor necrosis factor □ secretion and increase prostaglandin E2 secretion in human peripheral blood mononuclear cells.” Nutrition research 28.5 (2008): 321-328.

Kim, Ha-Jung, et al. “Clinical efficacy and mechanism of probiotics in allergic diseases.” Korean journal of pediatrics 56.9 (2013): 369.

Marchix, Justine, Gillian Goddard, and Michael A. Helmrath. “Host-gut microbiota crosstalk in intestinal adaptation.” Cellular and molecular gastroenterology and hepatology 6.2 (2018): 149-162.

Cao, Anthony T., et al. “Th17 cells upregulate polymeric Ig receptor and intestinal IgA and contribute to intestinal homeostasis.” The Journal of Immunology 189.9 (2012): 4666-4673.

Keubler, Lydia M., et al. “A multihit model: colitis lessons from the interleukin-10–deficient mouse.” Inflammatory bowel diseases 21.8 (2015): 1967-1975.

Wilson, Mark S., et al. “Colitis and intestinal inflammation in IL10-/- mice results from IL-13R□2–mediated attenuation of IL-13 activity.” Gastroenterology 140.1 (2011): 254-264.

Matt, Stephanie M., et al. “Butyrate and dietary soluble fiber improve neuroinflammation associated with aging in mice.” Frontiers in immunology 9 (2018): 1832.

Bourassa, Megan W., et al. “Butyrate, neuroepigenetics and the gut microbiome: can a high fiber diet improve brain health?.” Neuroscience letters 625 (2016): 56-63.

Huuskonen, Jari, et al. “Regulation of microglial inflammatory response by sodium butyrate and short□chain fatty acids.” British journal of pharmacology 141.5 (2004): 874-880.

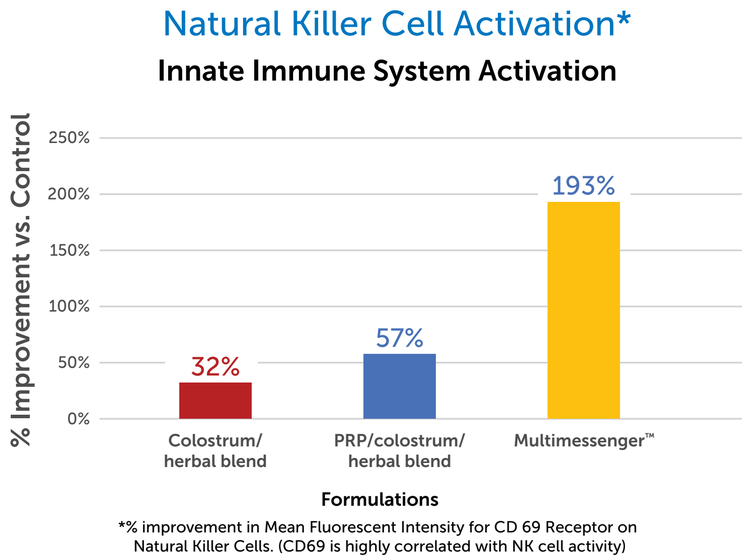
Roda, Aldo, et al. “A new oral formulation for the release of sodium butyrate in the ileo-cecal region and colon.” World Journal of Gastroenterology: WJG 13.7 (2007): 1079.

Transfer factors are like a cross between interleukins and antibodies

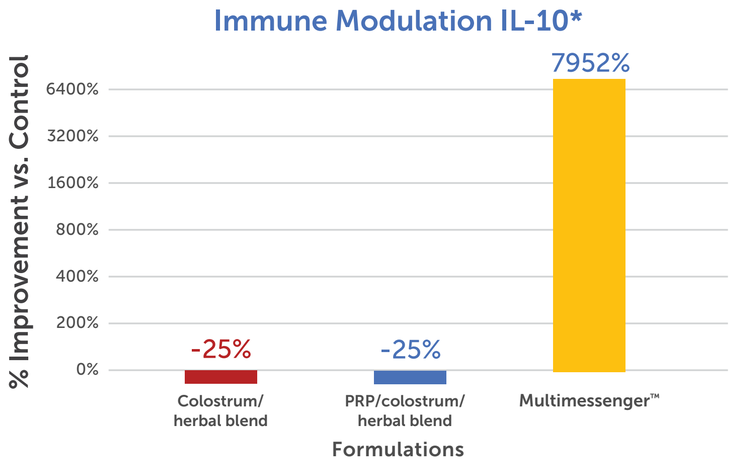
Carrying messages from immune cell to immune cell like interleukins

= General strengthening of Th1 & NK Cells

= rebuilding balance Th1/Th2/Th17 & downregulate autoimmunity



*% improvement in Mean Fluorescent Intensity for CD 69 Receptor on Natural Killer Cells. (CD69 is highly correlated with NK cell activity)



* % Improvement In Mean Fluorescent Intensity for IL-10 on Peripheral Blood Mononuclear Cell Cultures (PBMC)

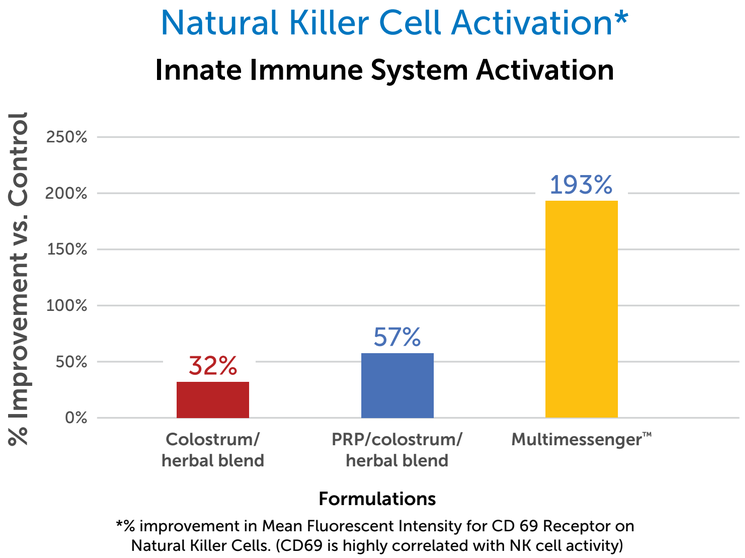
Binding to antigens on infected cells like antibodies (= specific Transfer Factors)

Conclusion and clinical features

Transfer Factors (Multimessenger ®)

bind on activating receptors on the surface of natural killer cells & empower our defense and recovery systems.

Multimessenger 1 x 3 caps just before breakfast in prevention
Multimessenger 2 x 3 caps just before meals during infection



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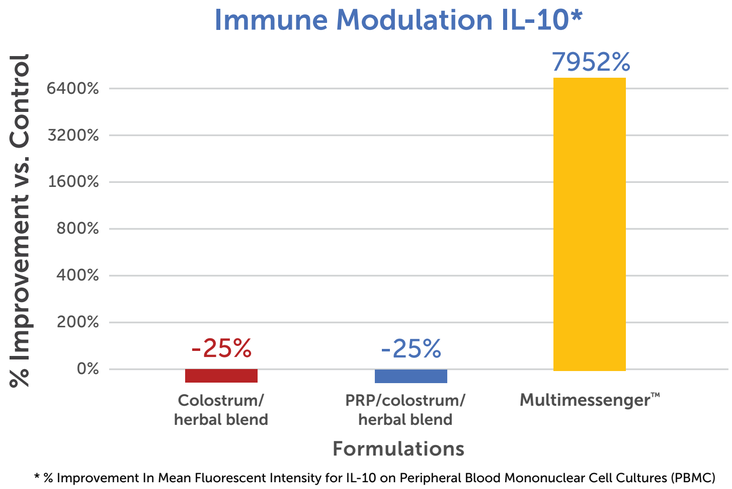
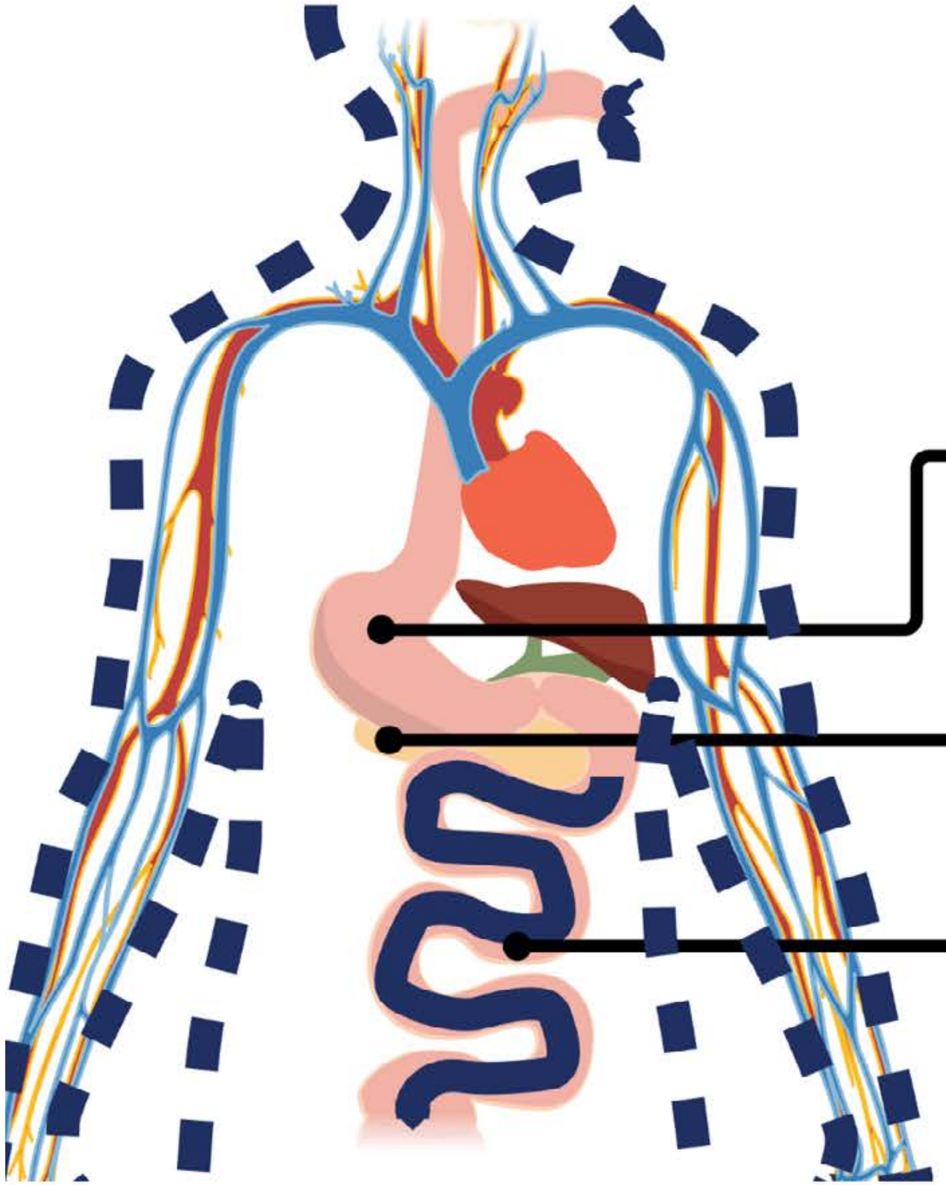


* % Improvement In Mean Fluorescent Intensity for IL-10 on Peripheral Blood Mononuclear Cell Cultures (PBMC)

Manage intestinal barrier



Global intestinal is a multilevel support

Optimize gastric acid level
- Prevents pathogenic overgrowth
- First line defense
- Essential for activation of the pancreas to secrete digestive enzyme
- polypeptides → amino acids (↓auto-immune reactivity)

Enzyme complex to optimize digestion
(including gluten modifying enzymes)

Targeted released Glutamine & cofactors
Heal the mucosal lining and tight juction optimazing (pH 6-7)
- ↓inflammation
- Improve the synthesis of s IgA by the intestinal lymphocytes

Butyrate coated
- Immune tolerance intestinal & systemic
- sIgA barrier
- Mucus barrier

Guttae Pepsini

indication	Stomach acid deficiency Poor digestion Intestinal malabsorption Rebuilds intestinal pH	
dosage	3 x 10 - 20 drops per day at the start of each meal, dilute in water and swallow immediately.	
packaging	30 ml per bottle	
composition (amount per 30 drops)	Purified water Glycerol Hydrochloric acid HCl 37% Pepsine	5,3 ml 10 ml 2,7 ml 2 ml

Please find our referenced version on the professional section of our website.
All information is exclusively aimed at and released to an audience of health care professionals.

Gluten DPP IV Complex

indication	DPP-IV proteolytic enzyme complex. Breaks down proline residues in Gluten and decreases the intestinal immune reaction Intolerance for gluten and/or casein. Indigestion, gas, bloating, constipation and diarrhea.	
dosage	3 x 1 caps per day at the beginning of each meal.	
packaging	90 vegecaps per container	
composition (amount per 3 vegecaps)	Protease IV Lactase Protease (zuur en neutraal) Amylase Maltodextrine Gluco-amylase Invertase Lipase	60 mg 60 mg 70,35 mg 30 mg 24,45 mg 15 mg 6 mg 4,2 mg

Please find our referenced version on the professional section of our website.
All information is exclusively aimed at and released to an audience of health care professionals.

Perm Plus Coated

indication	Rebuilding intestinal permeability and immunity with targeted released molecules.
dosage	The first month: 3 x 2 tablets per day. Then take 3 x 1 tablet per day 20 min. before food.
packaging	90 tablets per container

composition (amount per 3 tablets)	
L-Glutamine	975 mg
N-Acetyl-D - Glucosamine	375 mg
N-Acetylcystein	300 mg
Liquorice root powder (Glycyrrhiza Glabra L.)	255 mg
Gamma oryzanol	180 mg
L-Carnosine	60 mg
Zinc (as zinc bisglycinate and zinc methionin)	22,5 mg

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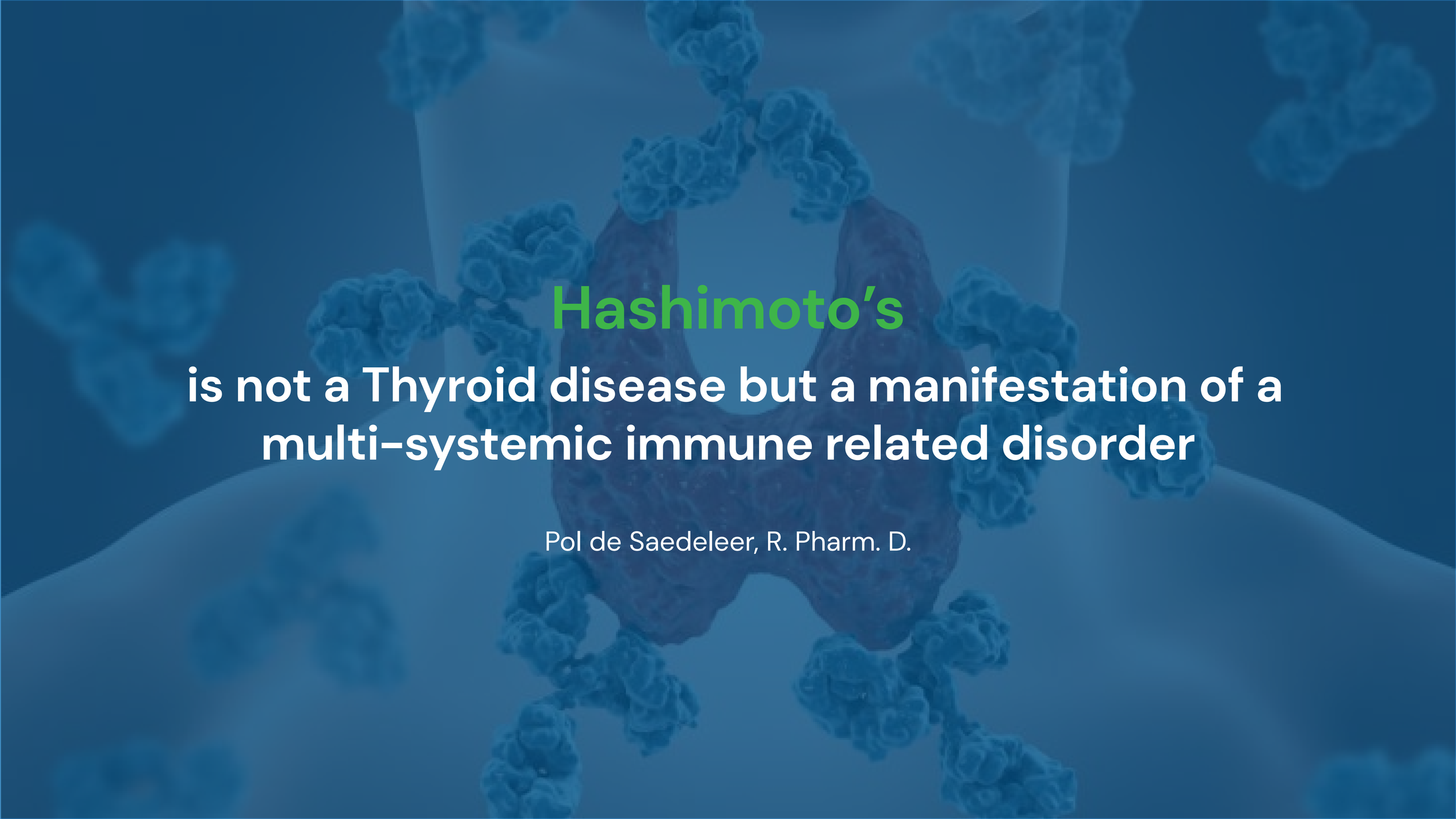
All information is exclusively aimed at and released to an audience of health care professionals.

Butyflam Coated

Butyrate is a short-chain fatty acid produced by the intestinal bacteria through fermentation of non-digestible fibers. Butyflam Coated delivers bio-available levels of butyrate in our intestines to guarantee immune tolerance and avoid excessive inflammation or auto-immune reactions.

indication	Neuroinflammation Immune modulating (T reg + IL-10 anti-inflammation) Remodeling intestinal barrier function
dosage	3 x 2 caps per day, 20 minutes before meals
packaging	180 coated caps per container
composition (amount per 6 caps)	Butyrate - 3000 mg



Hashimoto's

is not a Thyroid disease but a manifestation of a multi-systemic immune related disorder

Pol de Saedeleer, R. Pharm. D.

Most common auto-immune disease in the world

Important & overlooked

Hashimoto's should be ruled out in every chronic pathology

Majority of Hashimoto’s were diagnosed Hypothyroidism

Were your antibodies measured?

Antibodies direct a chronic inflammatory destructive response against thyroid follicular cells

When these cells are destroyed they have less ability to produce thyroid hormones over time

The majority of Hashimoto patients are women aged between 20 & 60 years old and only 10% show overt hypothyroidism

What are OVERT SYMPTOMS in hypothyroidism?

Dry hair

Loss of eyebrow hair

Puffy face

Enlarged thyroid

Slow heart beat

Arthritis

Cold intolerance

Depression

Dry skin

Fatigue

Poor memory

Menstrual disorders

Infertility

Muscle aches

Weight gain

Constipation

Brittle nails

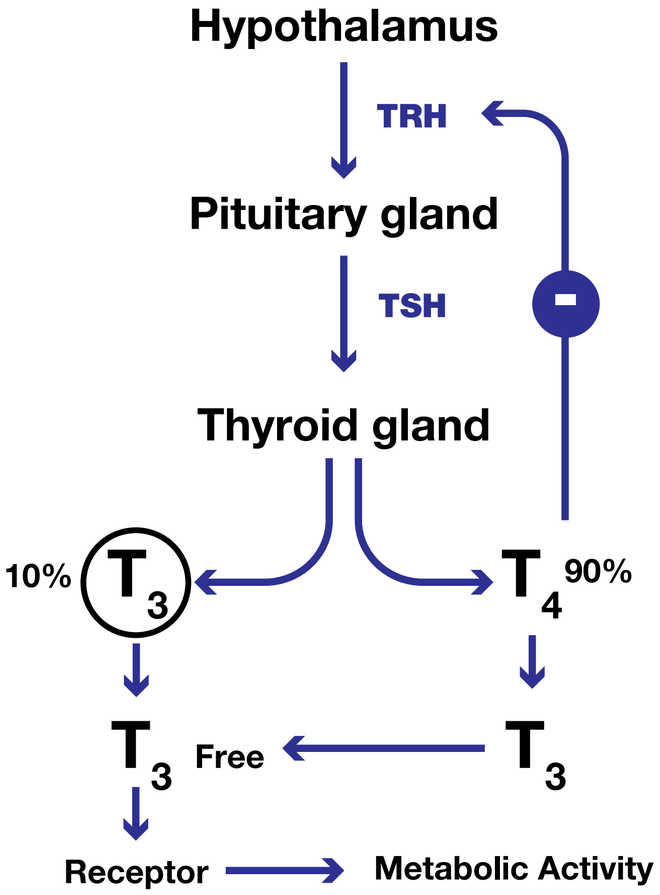
90% doesn’t show these symptoms in Hashimoto

What are the most common clinical complaints with Hashimoto's?

- General fatigue
- Depression and Brain function
- Chronic constipation & chronic gastrointestinal problems

Weight?

More than 50% of Hashimoto's have normal weight or could even be underweight + HT patients usually don't believe they are sick



Clinical Review of Thyroid Physiology

Regulation of Thyroid hormone synthesis

There is a need for **T4 & T3 synthesis to control metabolism**

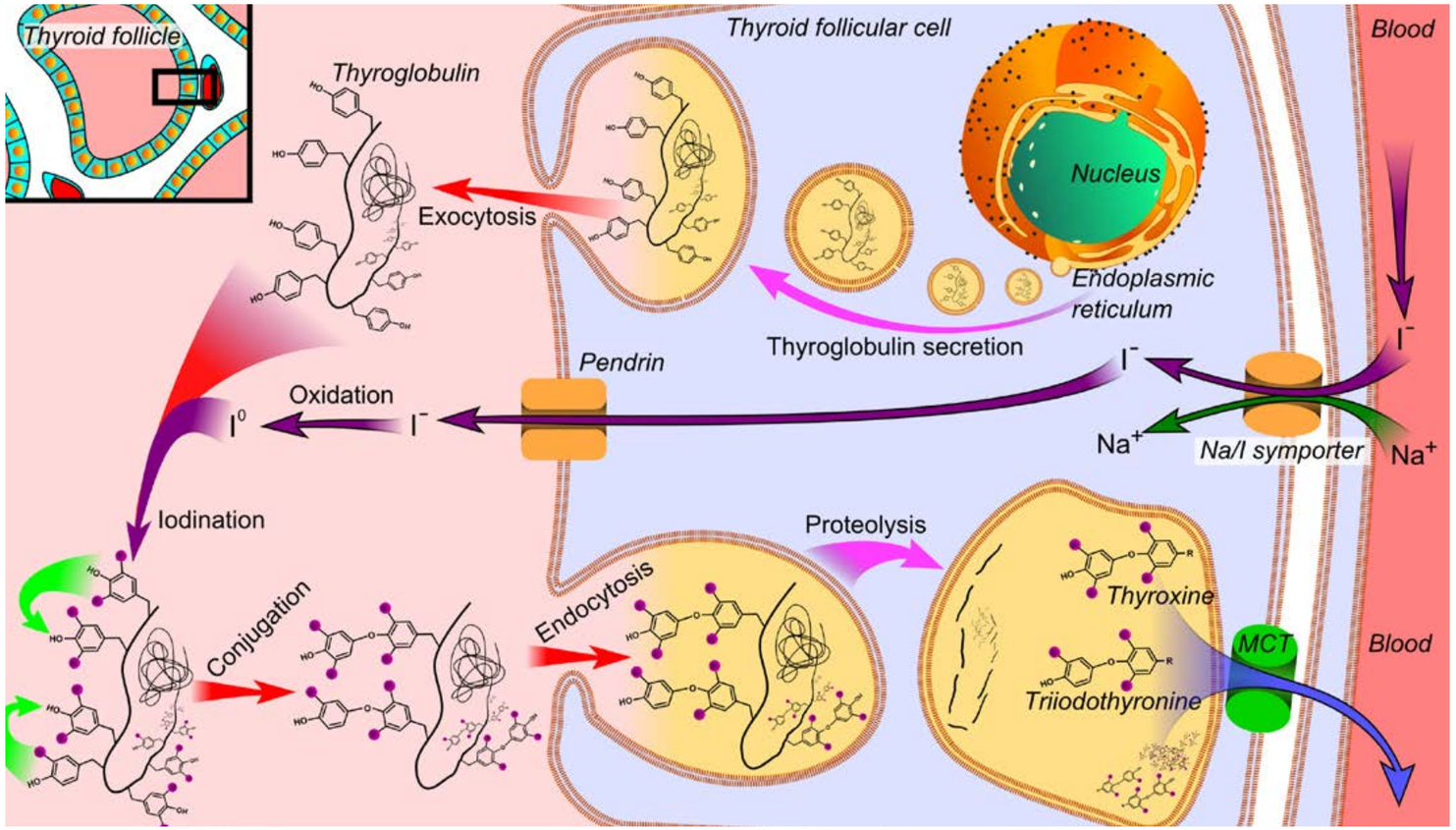
Thyroid hormones impact every cell in the body,
every cell in our body has receptors for thyroid hormones

T4 doesn't have much metabolic activity, it **need s to be converted to T3**

This **conversion** from T4 to T3 doesn't happen in the Thyroid gland, it happens **AFTER the thyroid gland**

At some point when there is sufficient thyroid hormone,
there is a **negative feedback** – which actually **suppresses TRH & TSH**

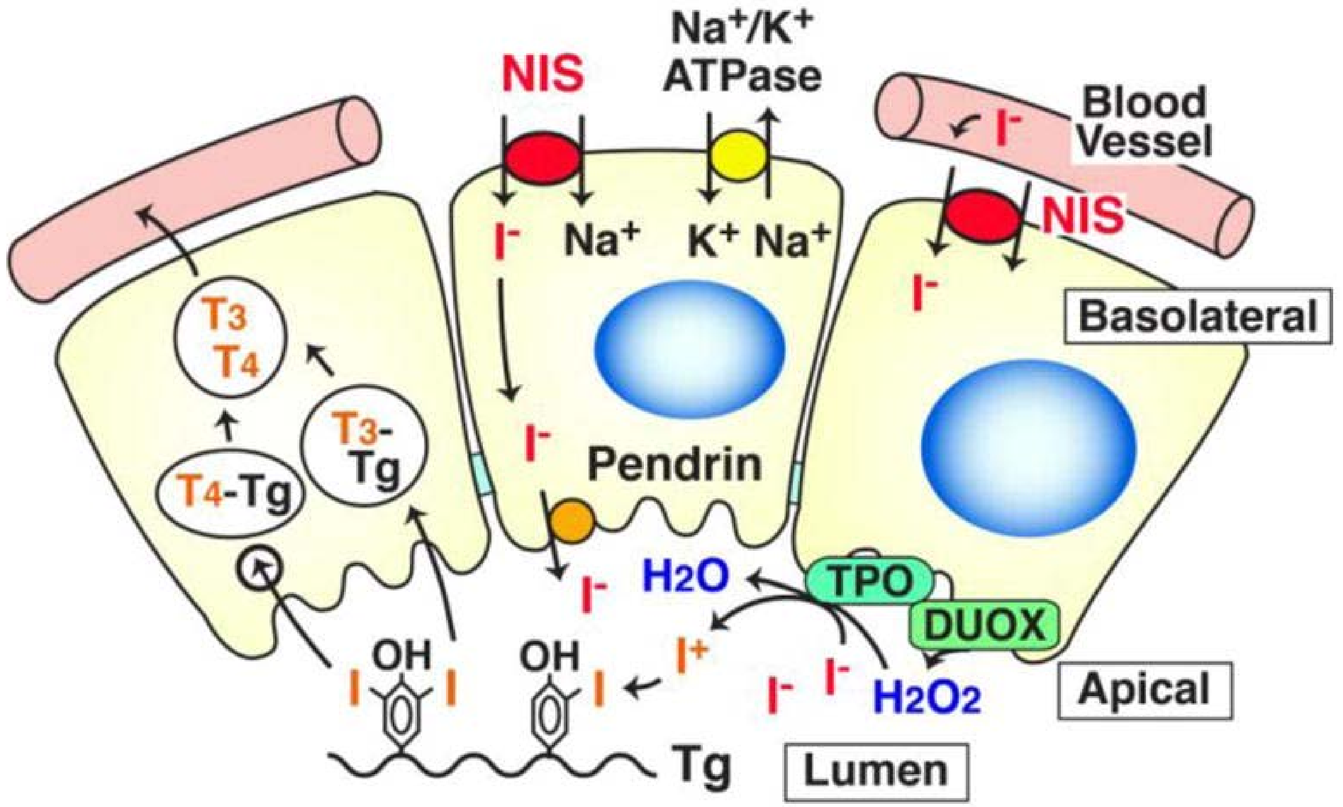
The **negative feedback loops depends on T4**, protein bound T4



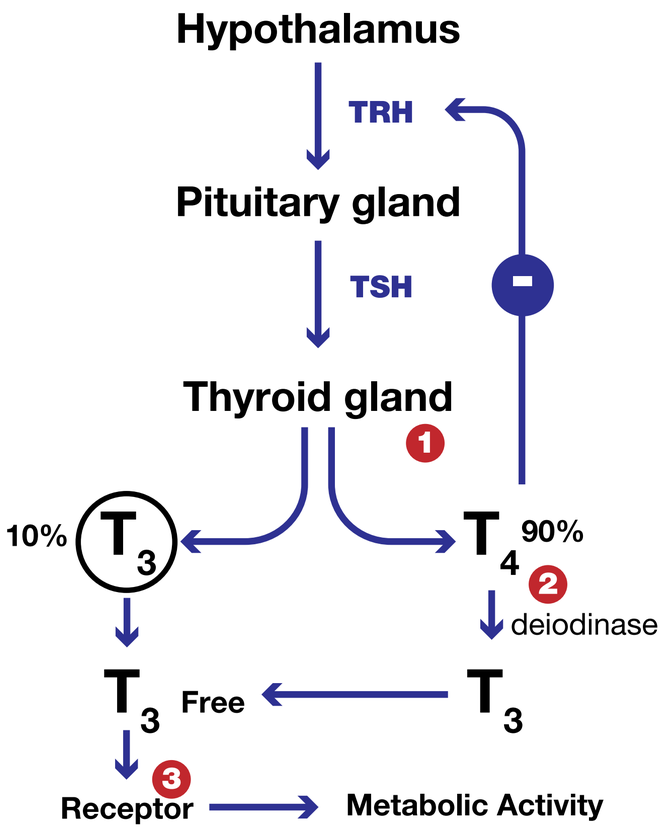
What is the specific role of TPO & Thyroglobulin

Thyroid peroxidase (TPO) oxidizes iodide ions to form iodine atoms for addition onto tyrosine residues on thyroglobulin for the production of Thyroid hormones

Thyroglobulins are produced by the follicular cells, are stored in the Thyroid glands and are the main precursors of Thyroid hormones



Kogai, Takahiko, and Gregory A. Brent. "The sodium iodide symporter (NIS): regulation and approaches to targeting for cancer therapeutics." Pharmacology & therapeutics 135.3 (2012): 355-370.



Thyroid peroxidase & Thyroglobulin are frequent epitopes of autoantibodies in autoimmune thyroid disease

How does Hashimoto's impact normal Thyroid physiology?

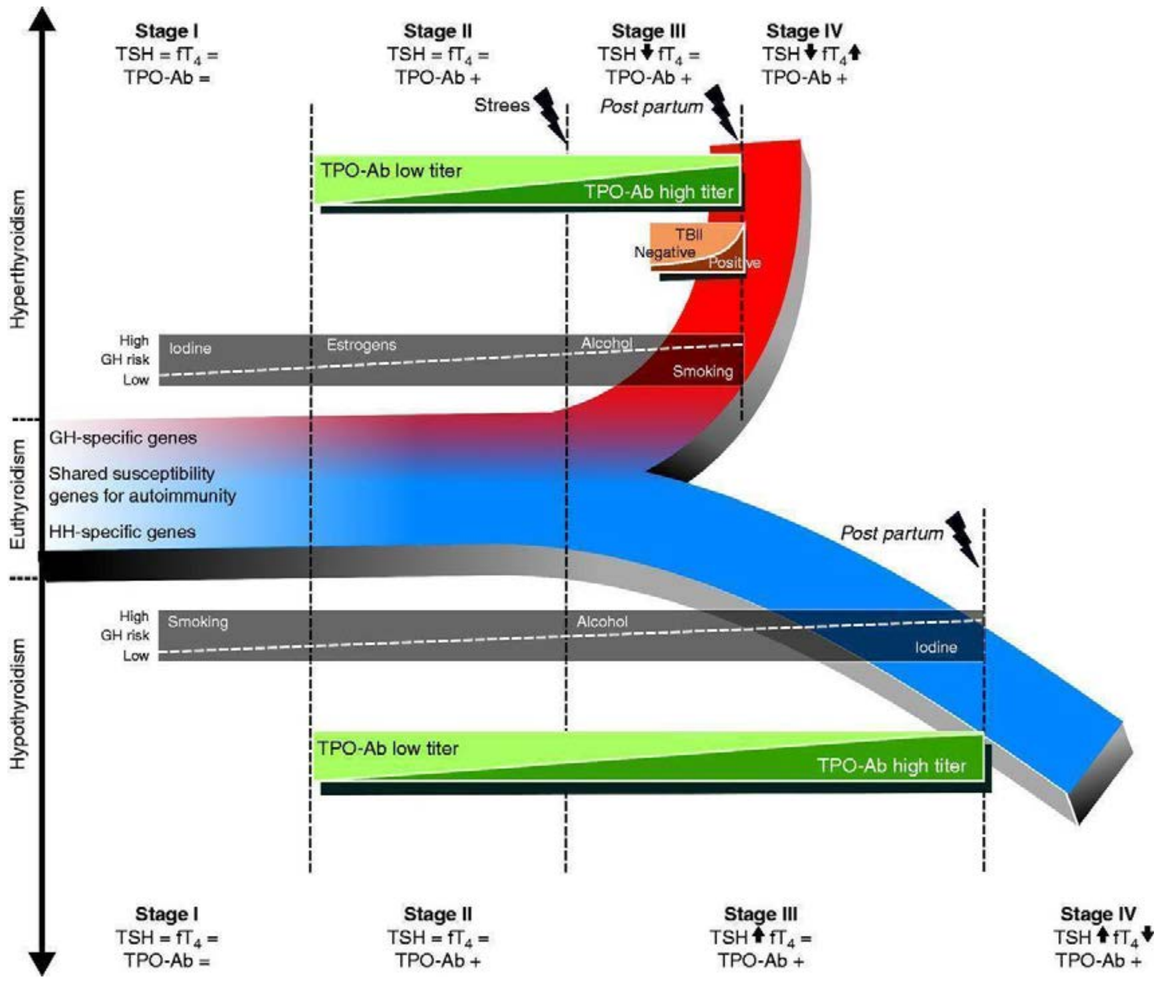
Hashimoto disrupts normal thyroid metabolism on site 1, 2 or 3

- 1 = autoimmune response against TPO and Tg
- 2 = inflammatory downregulation of 5-Deiodinase
- 3 = impaired receptor response

Evolution of the disease

With time euthyroid patients progress to hypothyroidism, thus the prevalence of hypothyroidism is higher in elderly patients

Effraimidis, Grigoris, and Wilmar M. Wiersinga. "Autoimmune thyroid disease: old and new players." Eur J Endocrinol 170.6 (2014): R241-R252.



In <u>stage 1</u>, the euthyroid stage
there are no clear symptoms

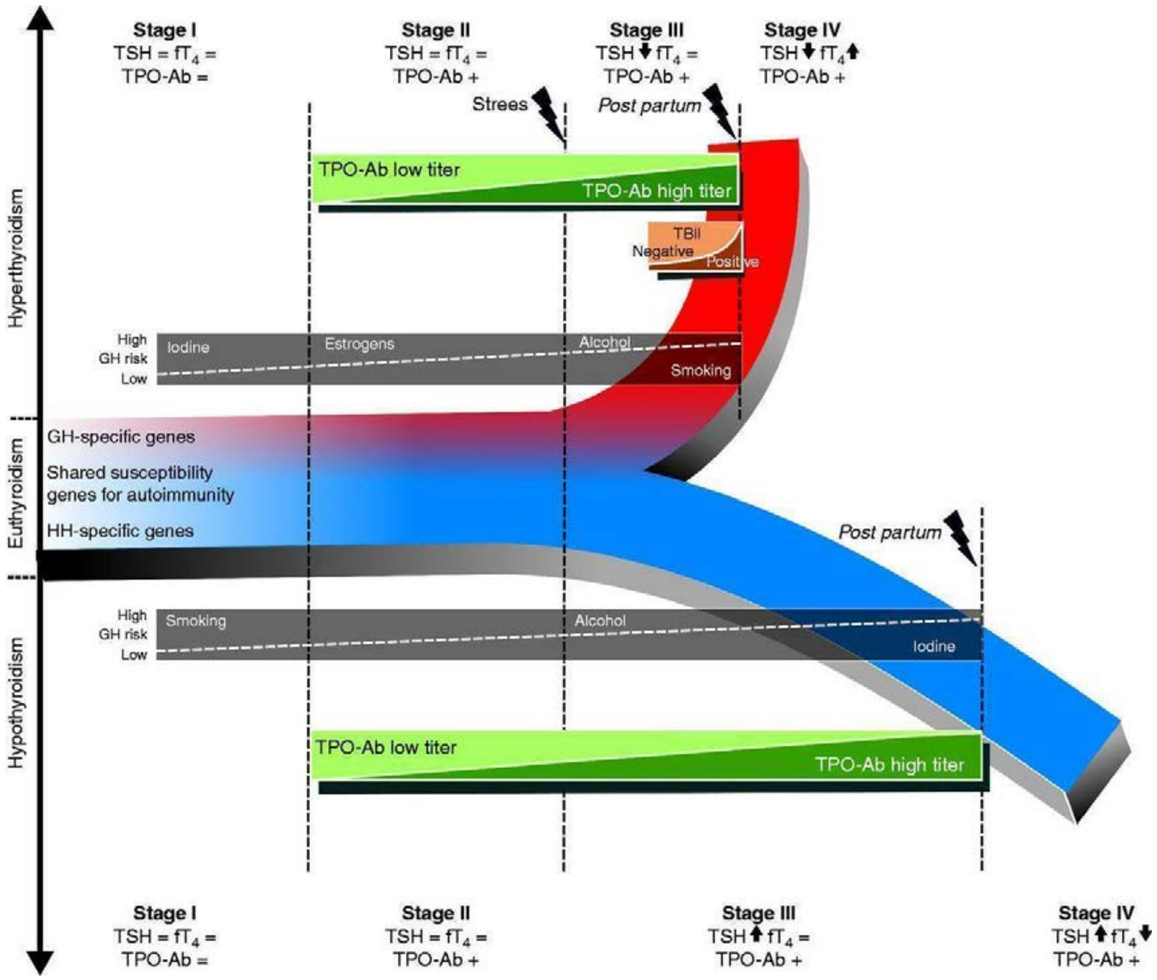
clinically euthyroid *= patients do not have elevated thyroid-stimulating hormone (TSH) levels. Pathogenesis is unknown but may include decreased peripheral conversion of T4 to T3, decreased clearance of rT3 generated from T4, and decreased binding of thyroid hormones to thyroxine-binding globulin (TBG).*

but they have genes, multifactorial susceptible genes

Graves – Hyperthyroid genes GH

Hashimoto – Hypothyroid genes HH

In this stage 1 no clear symptoms,
no clear clinical findings



Then we have some triggers like alcohol , infections etc

In <u>stage 2</u>, *In the seconds stage they start to have TPO antibodies. But TSH is still normal*

Progression
<u>stage 3</u>

TSH goes up

They reached the point where they don't make as much thyroid hormone

TPO antibodies are positive
+ often dependence on thyroid substitution

The Stages of autoimmunity

<u>Stage 1,</u> Silent autoimmunity
no clear symptoms

<u>Stage 2,</u> Autoimmune reactivity
Elevated TPO and / or thyroglobulin antibodies
They have symptoms
Normal TSH levels

<u>Stage 3,</u> Autoimmune disease
Elevated TPO and / or thyroglobulin antibodies
They have symptoms
Elevated TSH
Measurable tissue destruction

Hypothyroidism is stage 3, from a clinical standpoint

What is the incidence for Hashimoto?

Prevalence of Tg or TPO antibodies is between 10-14% over-all

But probably much higher:

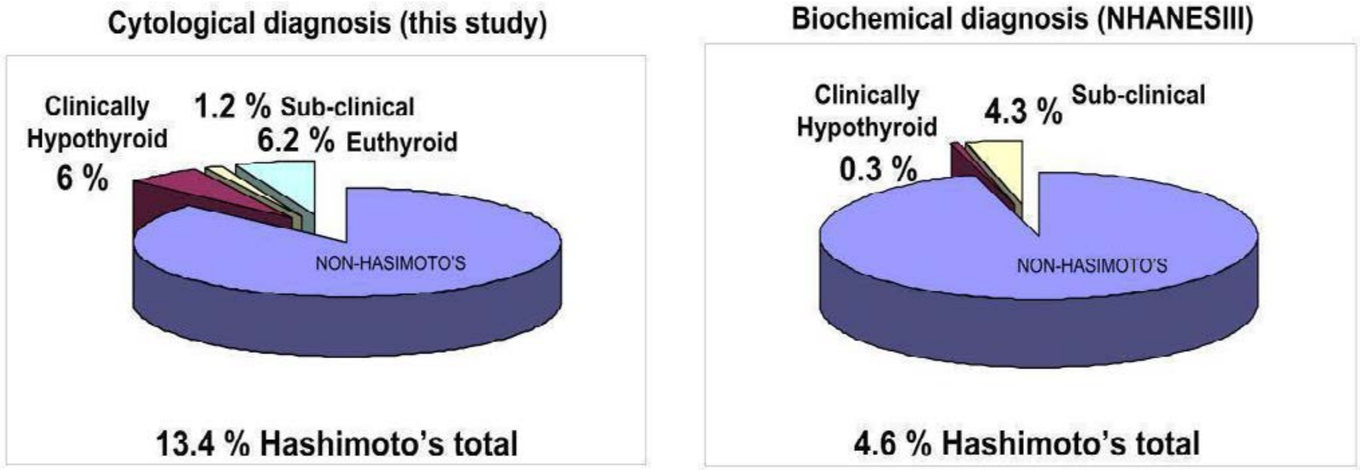
Risk in women 8x

Diagnosis by measuring antibodies

Ruf, J., et al. "Significance of thyroglobulin antibodies cross-reactive with thyroperoxidase (TGPO antibodies) in individual patients and immunized mice." Clinical & Experimental Immunology 92.1 (1993): 65-72.

Staii, Anca, et al.
“Hashimoto thyroiditis is more frequent than expected when diagnosed by cytology which uncovers a pre-clinical state.” Thyroid research 3.1 (2010): 1-7.

Frequency is much higher when diagnosed by cytology vs. biochemical diagnosis



Progressive decline in the age of presentation of Hashimoto thyroiditis

+ the rates continue to raise

+ in much younger age groups

The sooner you diagnose the better

Benvenga, Salvatore, Alessandro Antonelli, and Roberto Vita. “Thyroid nodules and thyroid autoimmunity in the context of environmental pollution.” Reviews in Endocrine and Metabolic Disorders 16.4 (2015): 319-340.

Interpretation of lab markers

Fluctuating TSH levels of Hashimoto's

Antibodies are much more stable
TPO antibodies are found in 95% of all Hashimoto's
Tg ab are found in 60-80% of all Hashimoto's

+ **studies also show your antibodies have been elevated for minimum 7 years before you see any symptoms**
  Early stages = silent
+ **Thyroid antibodies levels are not associated with the severity of the disease**
+ **Antibodies don't destroy the glands, they mark proteins and then our immune system destroys**

Thyroid Antibodies and Thyroid Autoimmunity

Grave's disease

TSH ab +
TPO ab +
Tg ab +

Hyperthyroidism

Thyroid storm = medical emergency

Hashimoto's
TSH ab –
TPO ab +
Tg ab +

Hyperthyroidism TSH low T3, T4 elevated

Hypothyroidism TSH elevated

Silent TSH normal

Clinical findings of Hyperactive response

- Palpitations
- Intolerance to heat
- Trembling, physiological tremor or eyelid tremor
- Eyes staring at you
- Anxiety
- Increased heart rate
- Insomnia
- Sweating for no reason
- Increased bowel motility
- Exaggerated deep tendon reflex
- **+ taking hormone replacement is very hard when the lab markers are unstable!**

Aren’t we treating Thyroid symptoms wrong?

- Treatment should probably not be focused so much on thyroid gland but on autoimmunity…
- What are the triggers?
- We need dietary advise, nutritional advise & lifestyle advise

What is the basic story of a Hashimoto patient?

What is the basic story of a Hashimoto patient?

Usually a female

Not feeling well, can't focus, can't concentrate

They have seen many Doctors, physical exam & lab tests but no diagnosis

They think they are getting old or maybe crazy?

Patient is often afraid to tell symptoms…

When finally the thyroid gland is destroyed they feel happy
– **finally a diagnosis! Someone figured out my condition**

They go on replacement and they feel better

But after a while the metabolism is going down again, even if the TSH is normal

The Doctor doesn't want to increase the dose…

The underling cause (= systemic inflammation) has not been managed

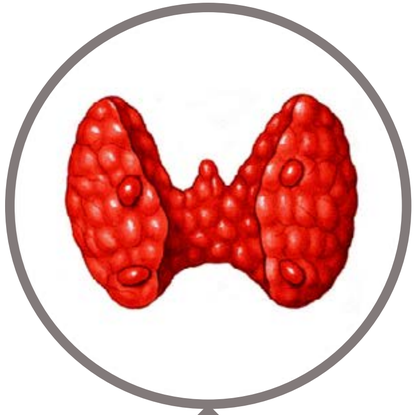
So usually they end up with taking Thyroid replacement and many other drugs and nutritionals to address the other symptoms

Some of them go for the perfect Thyroid hormone replacement therapy, what means they have T4/T3 replacement

They can be better for years but the causative factor is still not addressed

Basic Pathophysiology, Hashimoto's is a multisystemic disease

Thyroid gland



Cross reaction
Hepatitis C

Cross reaction
Gluten

Autoimmunity → + HLA DQ 2/8 susceptibility → Gluten
Celiac Disease

→ Cross reactivity between transglutaminase 2, transglutaminase 3 (skin), transglutaminase 6 (cerebellum)

→ Intestinal tight junction breakdown

→ Other autoimmune reactions
Brains, Joints, etc

Dysglycemia is very common in Hashimoto's

Insuline

- glycogen
- Muscle tissue
- Fat tissue

↑ Glucose

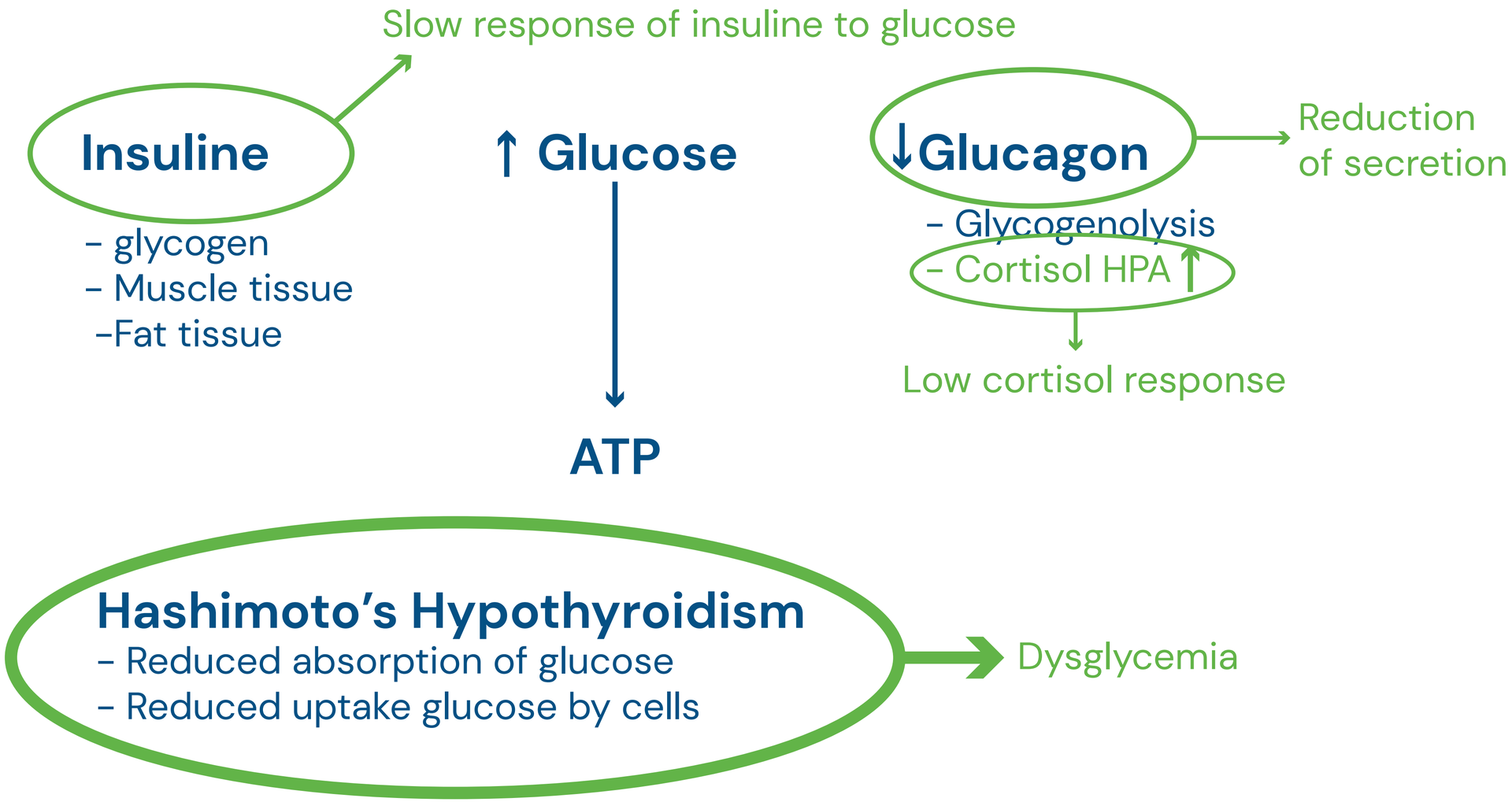
ATP

↓Glucagon

- Glycogenolysis
- Cortisol HPA ↑

Hashimoto’s Hypothyroidism

- Reduced absorption of glucose
- Reduced uptake glucose by cells


Slow response of insuline to glucose
Insuline
- glycogen
- Muscle tissue
-Fat tissue
↑ Glucose
ATP
↓Glucagon
Reduction of secretion
- Glycogenolysis
- Cortisol HPA ↑
Low cortisol response
Hashimoto's Hypothyroidism
- Reduced absorption of glucose
- Reduced uptake glucose by cells
Dysglycemia

Dysglycemia = regular dips in mood , energy and concentration

Hashimoto's and Diabetes Type 1 + Type 2 often coexist

Kalra S, Kalra B, Chatley G. Prevalence of hypothyroidism in pediatric type 1 diabetes mellitus in Haryana, Northern India. Thyroid Res Pract. 2012;9:12–4.

Demitrost L, Ranabir S. Thyroid dysfunction in type 2 diabetes mellitus: A retrospective study. Indian J Endocrinol Metab. 2012;16:S334–5

Anti-diabetic therapy improve thyroid function

- **Glycosense** = improving insulin sensitivity
- **Krebsplus** = improving fatty acid oxidation
- **CogniFuel** = supporting mitochondrial metabolism & mitochondrial biogenesis

Cinnulin : different studies show the effect on glucose metabolism

- Significant improvement in fasting blood sugar
- Increased insulin receptor sensitivity – reduced insulin resistance
- Glucose uptake and glycogen synthesis increased

+ positive outcome on systolic blood pressure, reduction of body fat

Yina, Jun, H. Xing, and J. Yeb. "Efficacy of berberine in patients with type 2 diabetes." Metabolism 57.5 (2008): 712-717.

Qin, B., M. M. Polansky, and R. A. Anderson. "Cinnamon extract regulates plasma levels of adipose-derived factors and expression of multiple genes related to carbohydrate metabolism and lipogenesis in adipose tissue of fructose-fed rats." Hormone and Metabolic Research 42.03 (2010): 187-193.

Wang, Jeff G., et al. "The effect of cinnamon extract on insulin resistance parameters in polycystic ovary syndrome: a pilot study." Fertility and sterility 88.1 (2007): 240-243.

Qin, B. O. L. I. N., et al. "Cinnamon extract attenuates TNF-□-induced intestinal lipoprotein ApoB48 overproduction by regulating inflammatory, insulin, and lipoprotein pathways in enterocytes." Hormone and Metabolic Research 41.07 (2009): 516-522.

Additional dietary recommendations

- low-to-moderate carbohydrate diet to prevent blood sugar fluctuations
- frequent small meals
- avoid nutrition with high glycemic index
- avoid caffeine and nicotine

Glycosense

indication	Fluctuating blood sugar levels Dysglycemia Poor insulin sensitivity Elevated fasting blood glucose High glycated hemoglobin HbA1c Lipid metabolism (triglycerides & cholesterol)	
dosage	3 x 1 caps per day during meals. The daily dose can be increased gradually up to 3 x 2 caps per day during meals, depending on tolerance & results	
packaging	180 vegecaps per container	
composition (amount per 3 vegecaps)	Berberine Cinnulin PF	750 mg 255 mg

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Krebsplus

indication	-Upregulation fatty acid oxidation. -Optimisation of mitochondrial enzyme affinity. -More energy for mental and physical activities.	
dosage	2 x 1 - 2 caps per day with or after food.	
packaging	60 vegecaps per container	
composition (amount per 2 vegecaps)	Acetyl-L-Carnitine HCl R-Alpha lipoic acid Coenzym Q10	1000 mg 200 mg 50 mg

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CogniFuel

indication	Prevention and treatment of various neurological disorders and neurodegenerative diseases Cognitive disorders Mitochondrial dysfunction and optimisation	
dosage	3 x 1 caps per day	
packaging	90 vegecaps per container	
composition (amount per 3 vegecaps)	Centella Asiatica Coffea (Whole Coffee Fruit Extract) Vit B3 (as Nicotinamide riboside) PQQ	1000 mg 200 mg 200 mg 20 mg

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Just using a Thyroid treatment will often not be enough...

There is a disruption in many systems

Triggers for Hashimoto's
Summary of literature search

Dietary triggers: gluten, Sodium, Iodine, Lectins, lack of dietary diversity, Glyphosate-rich foods, casein

Lifestyle triggers: insomnia, sedentary lifestyle, overtraining, smoking, alcohol

Chemical triggers: Bisphenol-A, pesticides, benzene, pollution, mercury

Infections (molecular mimicry): Helicobacter p, Toxoplasma Gondii, Yersinia E., Candida alb, Hepatitis C, EBV, Parvovirus, Borrelia b, CMV

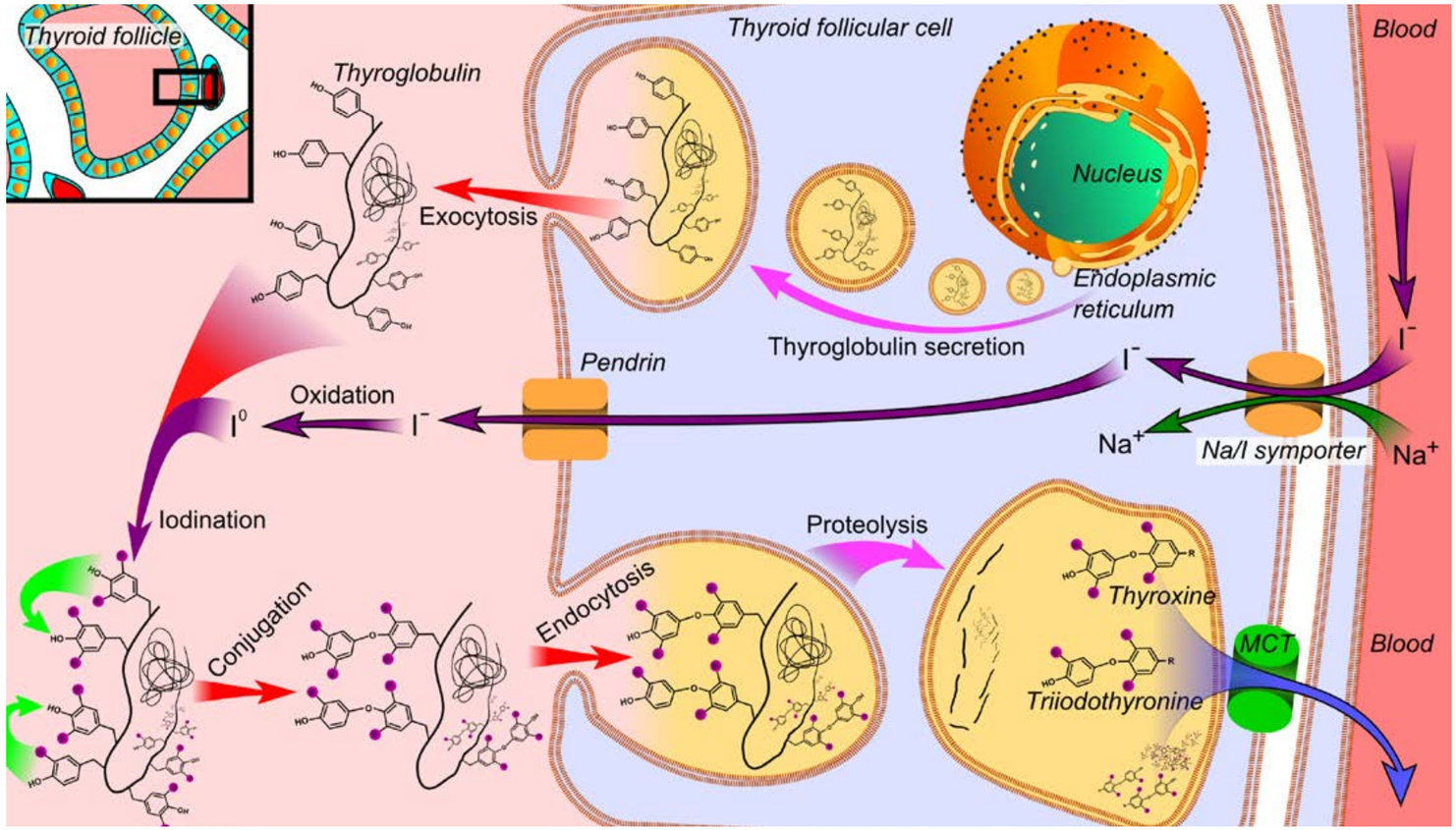
Effraimidis, Grigoris, and Wilmar M. Wiersinga. "Mechanisms in endocrinology: autoimmune thyroid disease: old and new players." European journal of endocrinology 170.6 (2014): R241-52.

Diet, nutritional and lifestyle interventions for Hashimoto’s

Dietary advice:

Do we need to consider Iodine restriction?

Hashimoto’s is not caused by a deficiency in Iodine

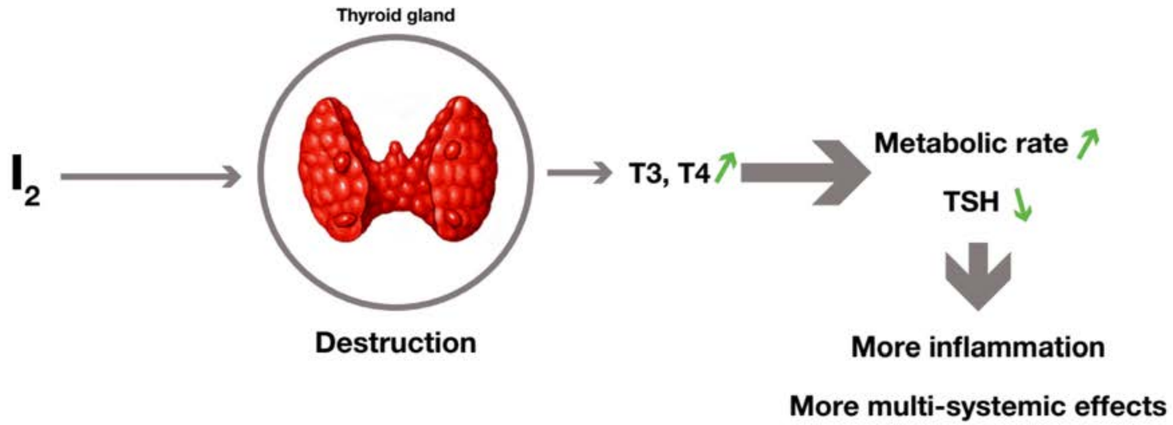


Iodide enters the Thyroid follicle via a Na+ / I- pump

Thyroid peroxidase (TPO) oxidizes iodide ions to form iodine atoms for addition onto tyrosine residues on thyroglobulin for the production of Thyroid hormones

Thyroid peroxidase & Thyroglobulin are a frequent epitopes of autoantibodies in autoimmune thyroid disease

Different scientific publications show that exogenous iodine promotes oxidative stress and destruction of Thyroid follicular cells



Sometimes patients feel better?

More destruction
= More Thyroid hormones are released into circulation
= better metabolic rate & TSH goes down

Overview of scientific research and publications

Zaletel, Katja, and Simona Gaberscek.
“Hashimoto’s thyroiditis: from genes to the disease.”
Current genomics 12.8 (2011): 576-588.

Study shows:

tissue samples of Hashimoto patients

iodine exposure

histological level?

Inflammatory markers elevated

Mechanism

Iodine → ROS → NFKB → IL-1 beta → pyroptotic cell death

Teng, Weiping, et al.
"Effect of iodine intake on thyroid diseases in China."
New England Journal of Medicine 354.26 (2006): 2783-2793.

Reinhardt, W., et al.
"Effect of small doses of iodine on thyroid function in patients with Hashimoto's thyroiditis residing in an area of mild iodine deficiency."

European journal of endocrinology 139.1 (1998): 23-28.

We see dietary or supplemental iodine is problematic

May cause a faster progression to hypothyroidism in patients with TPO antibodies

Gaberšček, Simona, and Katja Zaletel.
"Epidemiological trends of iodine-related thyroid disorders: an example from Slovenia." Archives of Industrial Hygiene and Toxicology 67.2 (2016): 93-98.

In 1999 Slovenia increased iodine content in kitchen salt from 10mg to 25mg of potassium iodide per kg of salt

We saw the incidence for Hashimoto's more than doubled after the increase in
iodine supply

Chow, C. C., et al. **"Effect of low dose iodide supplementation on thyroid function in potentially susceptible subjects: are dietary iodide levels in Britain acceptable?."** Clinical endocrinology 34.5 (1991): 413-416.

Design

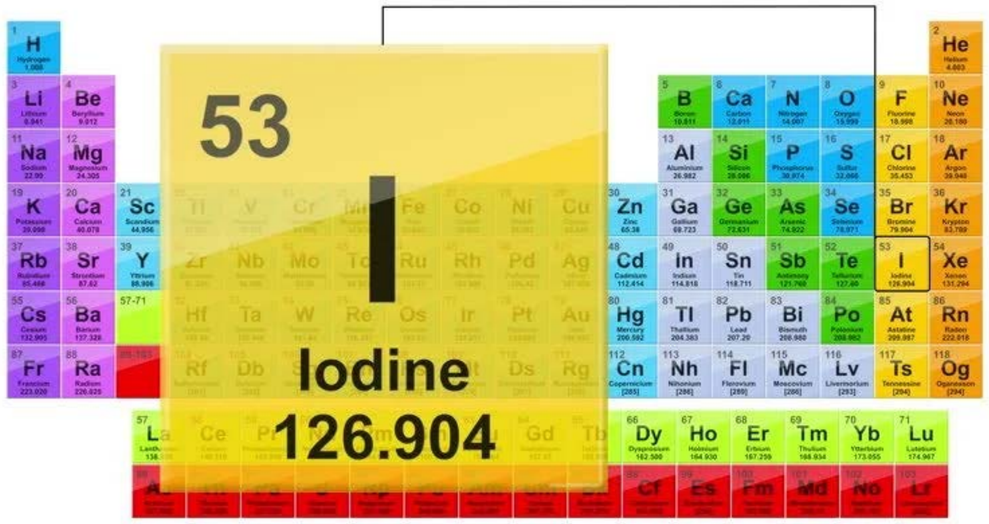
A randomized controlled trial was performed in healthy women and in women with underlying thyroid abnormalities due to subclinical Hashimoto's thyroiditis (diagnosed on the basis of antithyroid antibodies) were supplemented with 500 micrograms/day iodine (giving a total intake of approximately 750 micrograms/day) for 28 days versus placebo.

We saw free T4 decreased and TSH increased

Conclusion

dietary iodine intake of 750mcg or more may adversely affect thyroid function in patients with borderline hypothyroidism

Should we consider iodine restriction for Hashimoto's?
Scientific References clearly indicate we should...



Iodine occurs in many states...

LUGOL (I_2 + KI)

Should we restrict iodine for Hashimoto’s?

Yoon, Soo Jee, et al. **"The effect of iodine restriction on thyroid function in patients with hypothyroidism due to Hashimoto's thyroiditis."** Yonsei medical journal 44.2 (2003): 227-235.

Iodine restriction is less than 100mcg/day

Within a period of 3 months patients population with hypothyroidism due to Hashimoto’s **78.3% returned to normal thyroid function**

Only iodine restriction!

Joung, Ji Young, et al. **"Effect of iodine restriction on thyroid function in subclinical hypothyroid patients in an iodine-replete area: a long period observation in a large-scale cohort."** Thyroid 24.9 (2014): 1361-1368.

Subclinical hypothyroid patients

Decrease in serum TSH

Level TSH in serum correlates with urinary iodine concentration

Restriction of Iodine intake could be a primary treatment option in Hashimoto's

Food and drinks containing iodine

- Iodized salt
- Selery salt, garlic salt
- Seaweed (nori, kelp, wakame)
- Bakery products containing bread conditioners like calcium iodate & potassium iodate
- Milk products
- Egg yolks (as long as animals received enough Iodine!)
- Seafood (except fresh-water fish)
- Vitamins and minerals containing iodine

Further Complementary advice in treatment of Hashimoto’s

- Dietary advice
- Supplemental advice
- Lifestyle advice

Dietary advice

- Iodine restriction
- Elimination of Gluten

Krysiak, Robert, Witold Szkróbka, and Bogusław Okopień. "The effect of gluten-free diet on thyroid autoimmunity in drug-naive women with Hashimoto's thyroiditis: A pilot study." Experimental and Clinical Endocrinology & Diabetes 127.07 (2019): 417-422.

Participants all suffer from autoimmune thyroiditis

Participants were divided in 2 groups

First group remained to gluten-free diet for 6 months

Second group no dietary restrictions

Levels of TPO ab & Tg ab were reduced

25-OH-D3 was increased

Dietary advice

- Iodine restriction
- Elimination of Gluten
- Specific Dietary Cross-Reactivity with the Thyroid Axis
- Dietary fiber diversity = microbiome diversity

Zhao, Fuya, et al. **"Alterations of the gut microbiota in Hashimoto's thyroiditis patients."** Thyroid 28.2 (2018): 175-186.

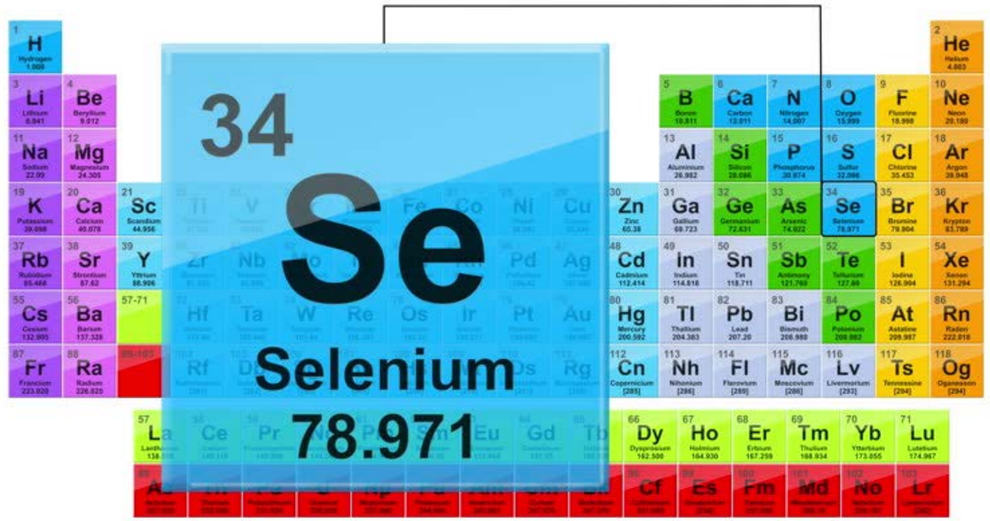
Fecal samples of Hashimoto’s and controls were compared

Gut microbiome in Hashimoto’s was altered

Heiman, Mark L., and Frank L. Greenway. **"A healthy gastrointestinal microbiome is dependent on dietary diversity."** Molecular metabolism 5.5 (2016): 317-320.

Supplemental advice in Hashimoto's

- Selenium
- Myo-inositol



Selenium is an essential micronutrient required for the synthesis of selenoproteins

It’s incorporated in Selenoproteins

Selenoproteins are enzymes

Selenoproteins expressed in Thyroid metabolism:

- Gpx Glutathion peroxidase protects the Thyroid gland against oxidative stress
- Iodothyronine deiodinase DIO type 1 , type 2 , type 3 are involved in the biosynthesis of Thyroid hormones
  (example type 1 is conversion T4 to T3)

Maintaining sufficient levels of Selenium prevents immune related Thyroid disorders

Santos, Liliana R., et al **"Selenium and selenoproteins in immune mediated thyroid disorders."** Diagnostics 8.4 (2018): 70.

It has been shown that during severe selenium deficiency, the lack of GPx activity may contribute to oxidative damage of the thyroid cell and initiation of thyroid damage and fibrosis

Contempre, Bernard, et al **"Effects of selenium deficiency on thyroid necrosis,**
fibrosis and proliferation: a possible role in myxoedematous cretinism."
European Journal of Endocrinology 133.1 (1995): 99-109.

TPO ab concentrations decreased up to 60% after 3 months treatment with 200mcg Selenium

Gärtner, Roland, et al. **"Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations."**
The Journal of Clinical Endocrinology & Metabolism 87.4 (2002): 1687-1691.

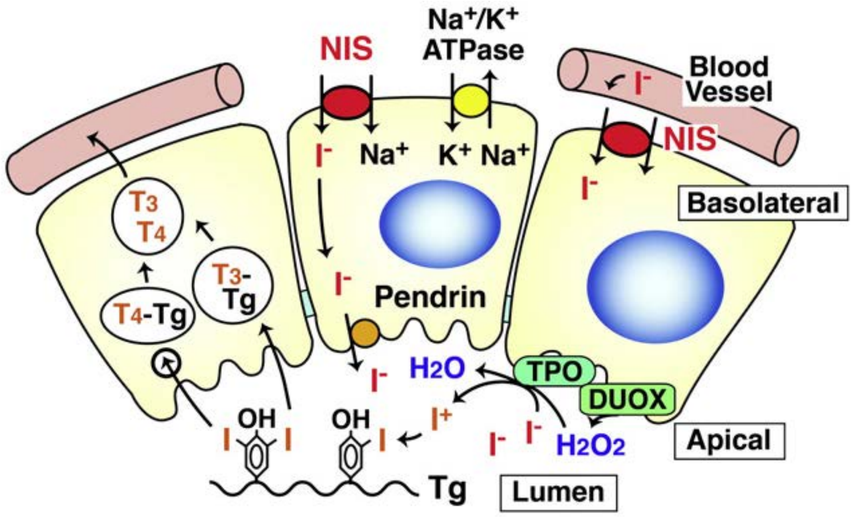
Summary of literature search shows TPO ab decreased in participants using T4 & participants not using T4

Wichman, Johanna, et al. **"Selenium Supplementation Significantly Reduces Thyroid Autoantibody Levels in Patients with Chronic Autoimmune Thyroiditis: A Systematic Review and Meta-Analysis"**
Thyroid 26.12 (2016): 1681-1692

Ferrari, Silvia Martina, et al. **"The protective effect of myo-inositol on human thyrocytes."** Reviews in Endocrine and Metabolic Disorders 19.4 (2018): 355-362.

After treatment with Myo-inositol, serum CXCL10 levels declined, confirming the immune-modulatory effect of Myo-Ins.

Thyroid cells were incubated with IFN-γ & TNF-alpha = CXCL-10↑



More publications show beneficial antioxidative properties of myo-inositol in combination with Selenium

Thyroid cells from Hashimoto's exposed to H2O2

Iodide is oxidized by TPO – meanwhile H2O2 is used

Normal physiology of the Thyroid Cells requires the generation of H2O2

But H2O2 is produced in large excess compared to the amounts of iodide attached to tyrosine residues.

Still H2O2 has a signaling role

At higher concentrations, overproduction or lack of degradation H2O2 is inducing oxidative stress and damage

This study shows myo-inositol & Selenium protect Thyroid cells from oxidative stress induced by H2O2 in vitro

Benvenga, S., et al. "Favorable effects of myo-inositol, selenomethionine or their combination on the hydrogen peroxide-induced oxidative stress of peripheral mononuclear cells from patients with Hashimoto's thyroiditis: preliminary in vitro studies." Eur Rev Med Pharmacol Sci 21.Suppl 2 (2017): 89-101.

Song, Yue, et al. "Roles of hydrogen peroxide in thyroid physiology and disease." The Journal of Clinical Endocrinology & Metabolism 92.10 (2007): 3764-3773.

Ferrari, S. M., et al. **"Myo-inositol and selenium reduce the risk of developing overt hypothyroidism in patients with autoimmune thyroiditis."** Eur Rev Med Pharmacol Sci 21.2 Suppl (2017): 36-42.

Patients were recently diagnosed with **Euthyroid Autoimmune Thyroiditis**

All were treated with **myo-inositol & selenomethionine**

Conclusion

TSH levels significantly decreased in contrast to initial values

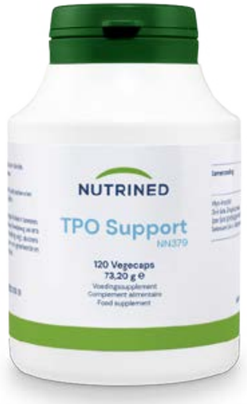
+ Levels TPO ab decreased

+ levels Tg ab decreased

+ CXCL10 levels also declined

Suggested treatment reduced the risk of a further progression to hypothyroidism in patients with autoimmune thyroiditis

TPO Support



indication	Supplemental advice in Hashimoto's to reduce the risk of a further progression	
dosage	1 caps in the morning and 1 caps in the evening	
packaging	120 vegecaps per container	
composition (amount per 2 vegecaps)	Myo-inositol Iron (as Iron bisglycinate) Zinc (as Zinc gluconate) Selenium (as Selenomethionine)	600 mg 30 mg 22.5 mg 84 µg

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Supplemental advice in Hashimoto's

- Selenium
- Myo-inositol
- Glutathione

Rostami, R., et al. "Enhanced oxidative stress in Hashimoto's thyroiditis: inter-relationships to biomarkers of thyroid function." Clinical biochemistry 46.4-5 (2013): 308-312.

GSH levels are reduced in Hashimoto's GSH↓

Correlation between TPO ab & GSH in Hashimoto's TPO ab↑ Handshak GSH↓

Poor GSH = less protection against oxidative stress & immune intolerance
GSH↓ Oxidative stress & immune intolerance↑

Conclusion

Optimization of GSH levels, introducing very bio-available forms like oral liposomal Glutathione, downregulate oxidative stress & and promote immune tolerance GSH↑ Oxidative stress↓ & immune tolerance↑

Sinha, Raghu, et al. "Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function." European journal of clinical nutrition 72.1 (2018): 105-111.

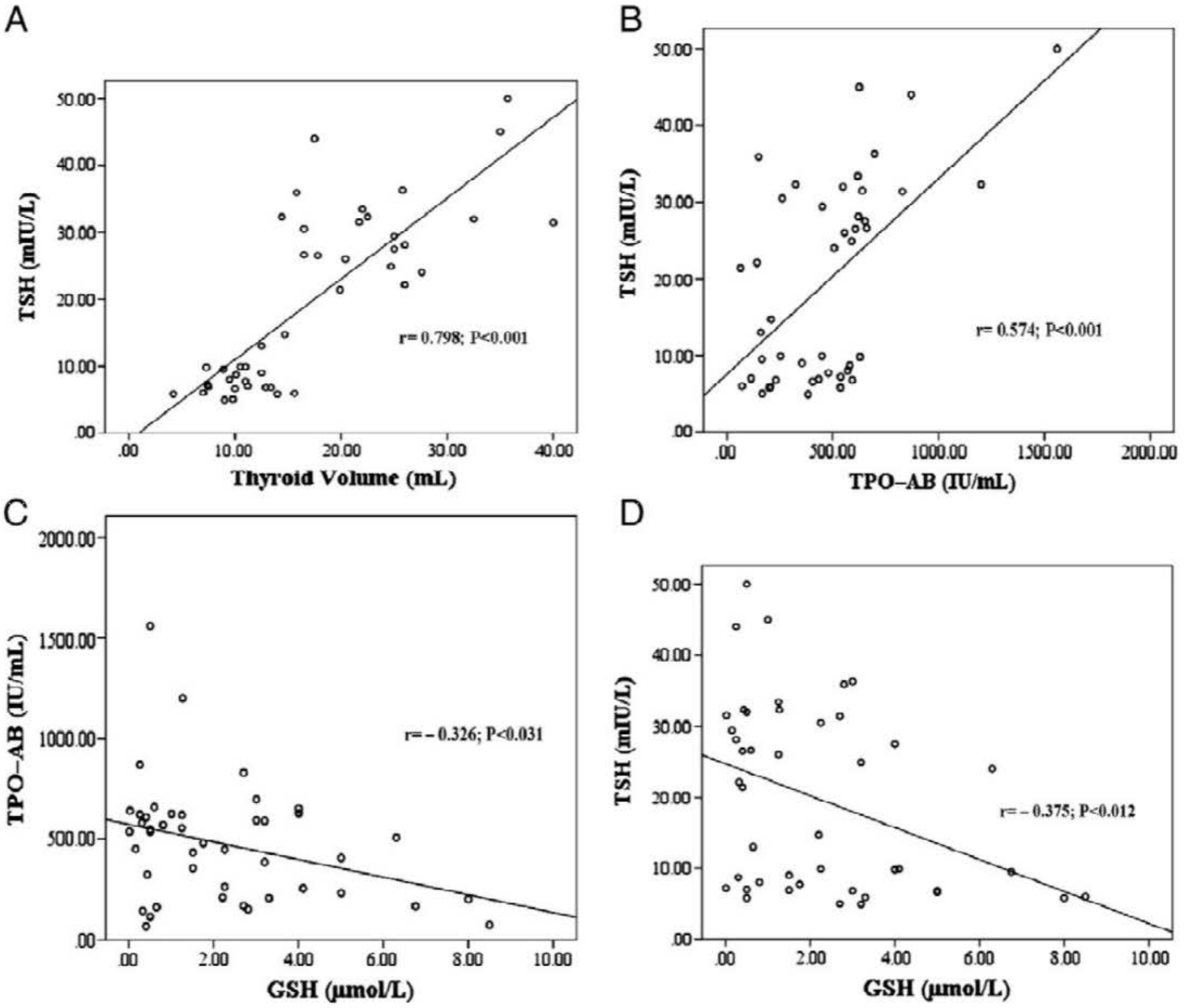

Fig. 2. Associations between markers of thyroid malfunction and/or oxidative stress in individuals with Hashimoto thyroiditis (n = 44). A: Thyroid volume (Tvol) and thyroid stimulating hormone (TSH) levels; B: Thyroid stimulating hormone (TSH) levels and anti-thyroperoxidase antibody (TPO-AB) titers; C: Glutathione (GSH) levels and anti-thyroperoxidase antibody (TPO-AB) titers; D: Glutathione (GSH) contents and thyroid stimulating hormone (TSH) levels.

Supportive treatments in managements of Hashimoto's

- Intestinal support

Küçükemre-Aydın, Banu, et al. "Children with Hashimoto's Thyroiditis Have Increased Intestinal Permeability: Results of a Pilot Study." Journal of clinical research in pediatric endocrinology (2020).

Increased intestinal permeability (IIP) precedes several autoimmune disorders. Although Hashimoto's thyroiditis (HT) is the most common autoimmune disorder, the role of IIP in its pathogenesis had received little attention

Study shows zonulin levels in 30 children and adolescents were consistently higher

A gluten- free diet benefits all patients with elevated serum-zonulin levels: IBS, Celiac and non-celiac Gluten sensitive, Autoimmune patients

Fasano, Alessio. “Intestinal permeability and its regulation by zonulin: diagnostic and therapeutic implications.” Clinical Gastroenterology and Hepatology 10.10 (2012): 1096-1100.

Tri-Fortify Watermelon® or Orange®

indication	Detoxification with glutathione in high bioavailable formulation, powerful antioxidant, Natural Killer Cell support	
dosage	1 teaspoon (1 pack) per day, away from food	
packaging	236 ml per tube or 20 packs per box	
composition (amount per 1 teaspoon)	Glutathione Liposomal Vitamin C	450 mg 50 mg

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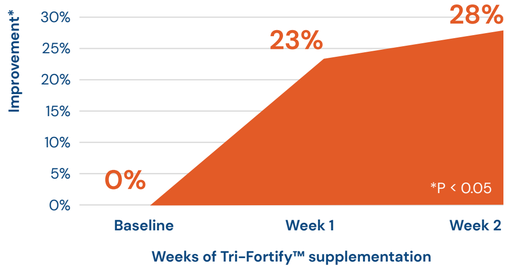
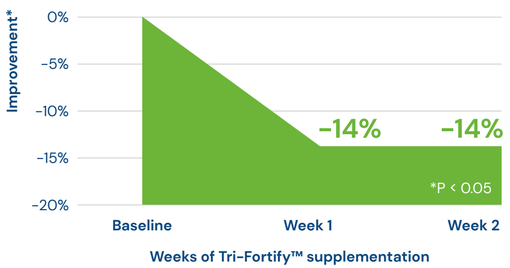
Glutathione levels

Increase in red blood cell levels (Erythrocytes)



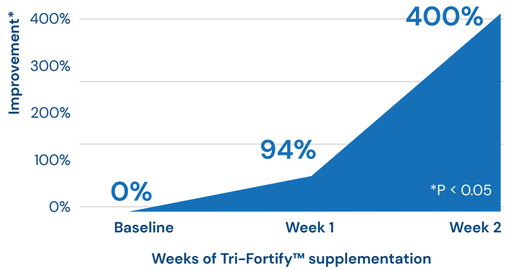
Oxidative stress markers

Oxidized / Reduced GSH

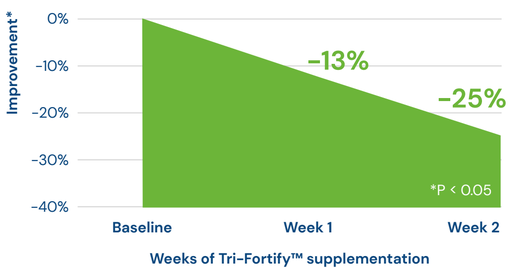


Immune function

Natural Killer Cell activity



Lipid Peroxidation (Reduced Cellular Membrane Oxidation)



Published research : Sinha, R., Sinha, I., Calcagnotto, A., Trushin, N. Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function. Eur J Clin Nutr. 2018 Jan;72(1):105-111.

Lifestyle advice in Hashimoto's

- Stress management

Markomanolaki, Zoe S., et al. **"Stress Management in Women with Hashimoto's thyroiditis: A Randomized Controlled Trial."** Journal of molecular biochemistry 8.1 (2019): 3.

60 participants , women with HT

Study measures the impact of an
8-weeks stress management intervention

We see a significant amelioration of lab markers, together with better scores in the questionnaire

Stress↓ = TPO ab ↓ & TG ab↓ & TSH normalization

Lifestyle advice in Hashimoto's

- Stress management
- Sleep improvement

Radomski, M. W., et al. **"Aerobic fitness and hormonal responses to prolonged sleep deprivation and sustained mental work."** Aviation, space, and environmental medicine (1992).

Study shows negative impact on Thyroid metabolism

Especially r T3 increased during sleep deprivation

Schmid, Sebastian M., et al. **"Partial sleep restriction modulates secretory activity of thyrotropic axis in healthy men."** Journal of Sleep Research 22.2 (2013): 166-169.

Alterations are manifest after 2 nights with sleep restriction to 4 hours

Lifestyle advice in Hashimoto's

- Stress management
- Sleep improvement
- Exercise

Werneck, Francisco Zacaron, et al. **"Exercise training improves quality of life in women with subclinical hypothyroidism: a randomized clinical trial."** Archives of endocrinology and metabolism 62.5 (2018): 530-536.

Women diagnosed with HT tend to score lower in quality of life

Physical exercise has been shown to compensate

Sports and exercise should be encouraged in HT

Considerations

Make sure you are not creating unrealistic expectations

The goal of a treatment is to control the disease and to keep the patient in remission, as long as possible, but there is no ultimate cure

There is no general protocol for Hashimoto's but guidelines make sense

Dietary advice:

- iodine restriction
- Elimination of Gluten & milk
- Specific Dietary Cross-Reactivity with the Thyroid Axis
- Anti-diabetic therapy to address abnormalities in blood sugar level

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Supportive treatments in management

- Intestinal Support
- Immune Support

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Lifestyle advice

- Stress management
- Sleep improvement
- Exercise

Treatment guidelines

TPO support	2x1/day
Trifortify watermelon or Orange	1 teaspoon/day
Guttae Pepsine	3x5-20 drops/day at the start of each meal
Gluten DPP4 Complex	3x1 caps/day at the start of each meal
Permplus Coated meals	1st month 3x2 tabs/day 20minutes before 2nd month and further 3x1tab/day
Glycosense	3x1-2 caps/day at the start of each meal
Butyflam	3x2 coated caps/day
Vit D3 individual	
Multimessenger	1x3 caps/day just before breakfast