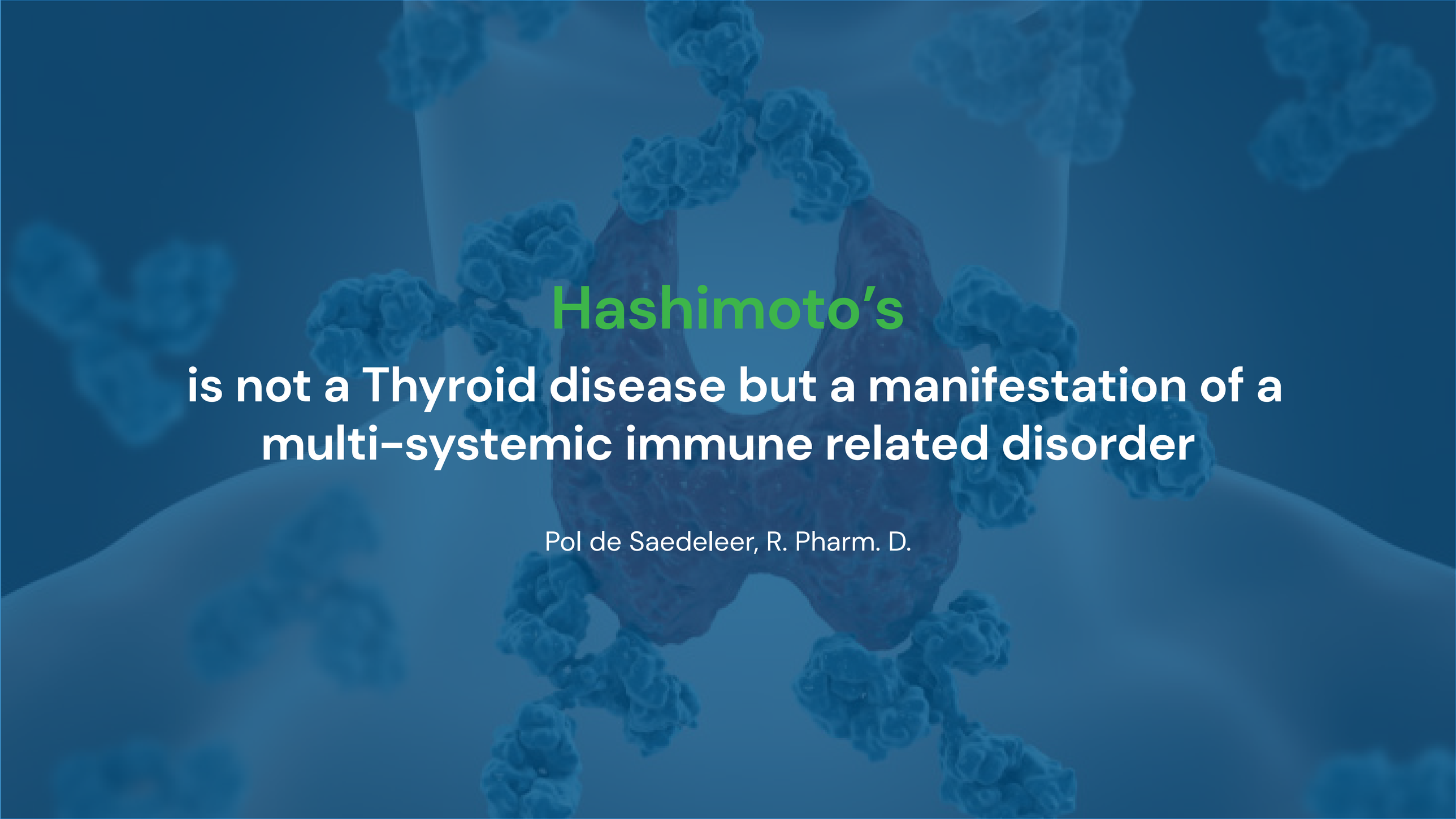


Hashimoto's

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

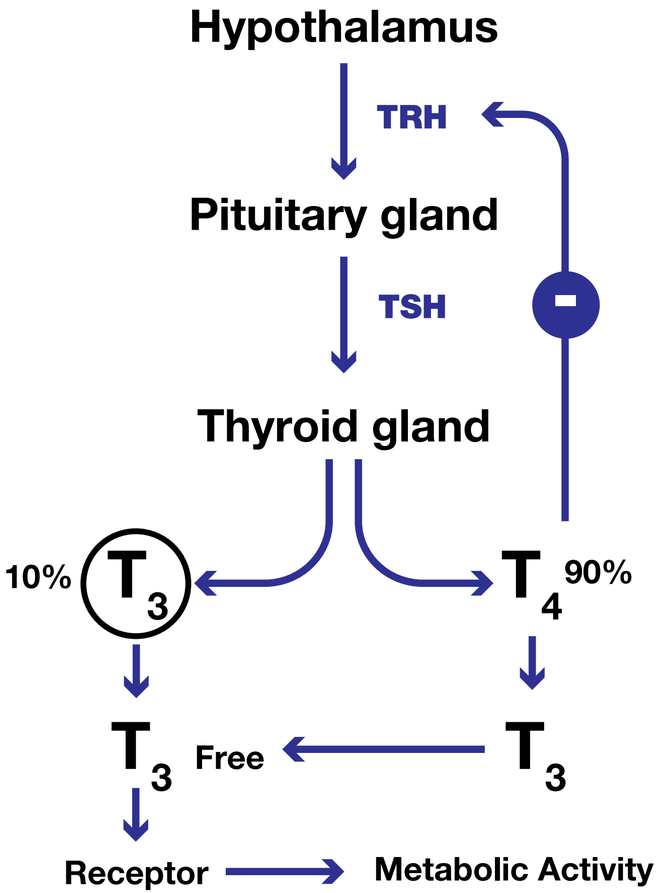
What are the most common clinical complaints with Hashimoto's?

- 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**

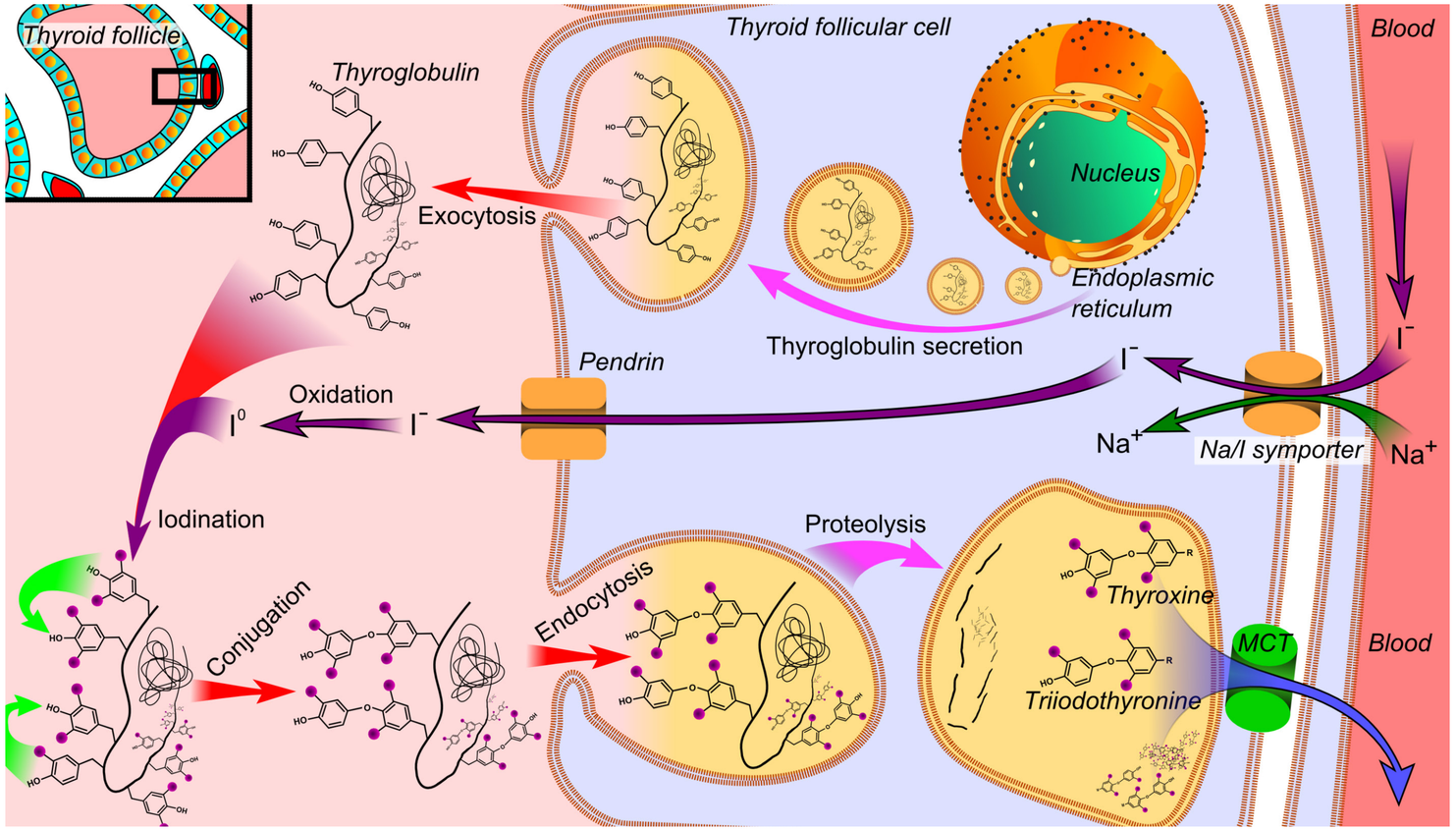
Thyroid hormones impact every cell in the body,
every cell in our body has receptors for thyroid hormones

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**

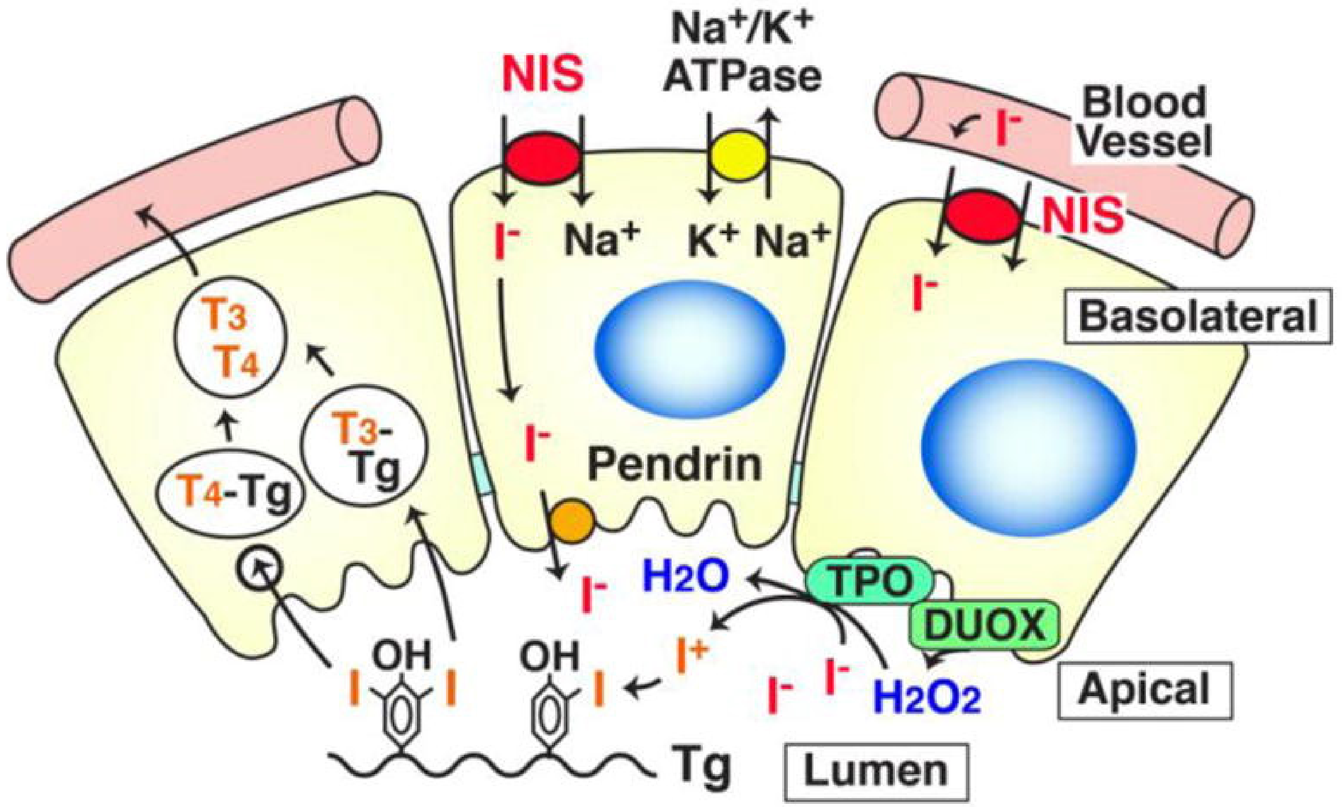
The **negative feedback loops depends on T4**, protein bound T4



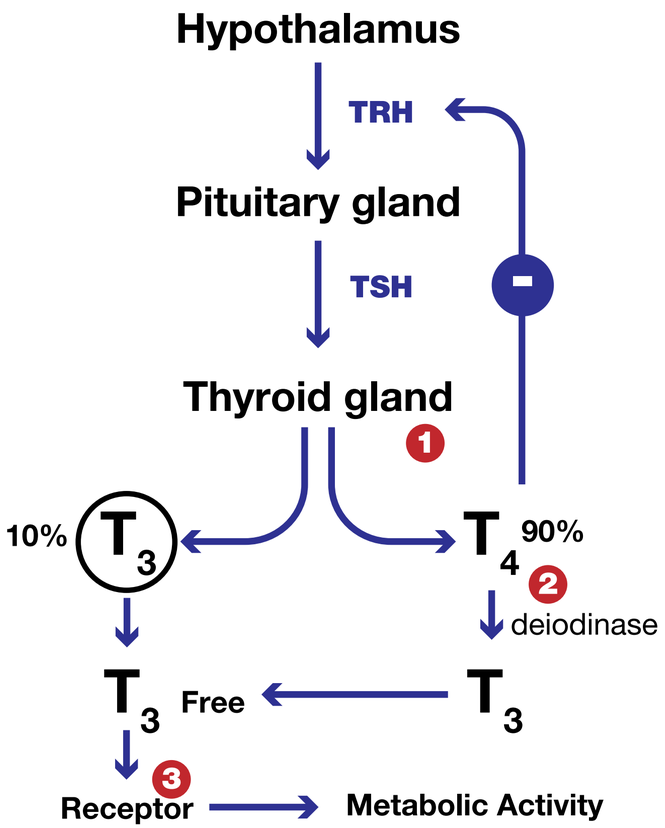
What is the specific role of TPO & Thyroglobulin

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?

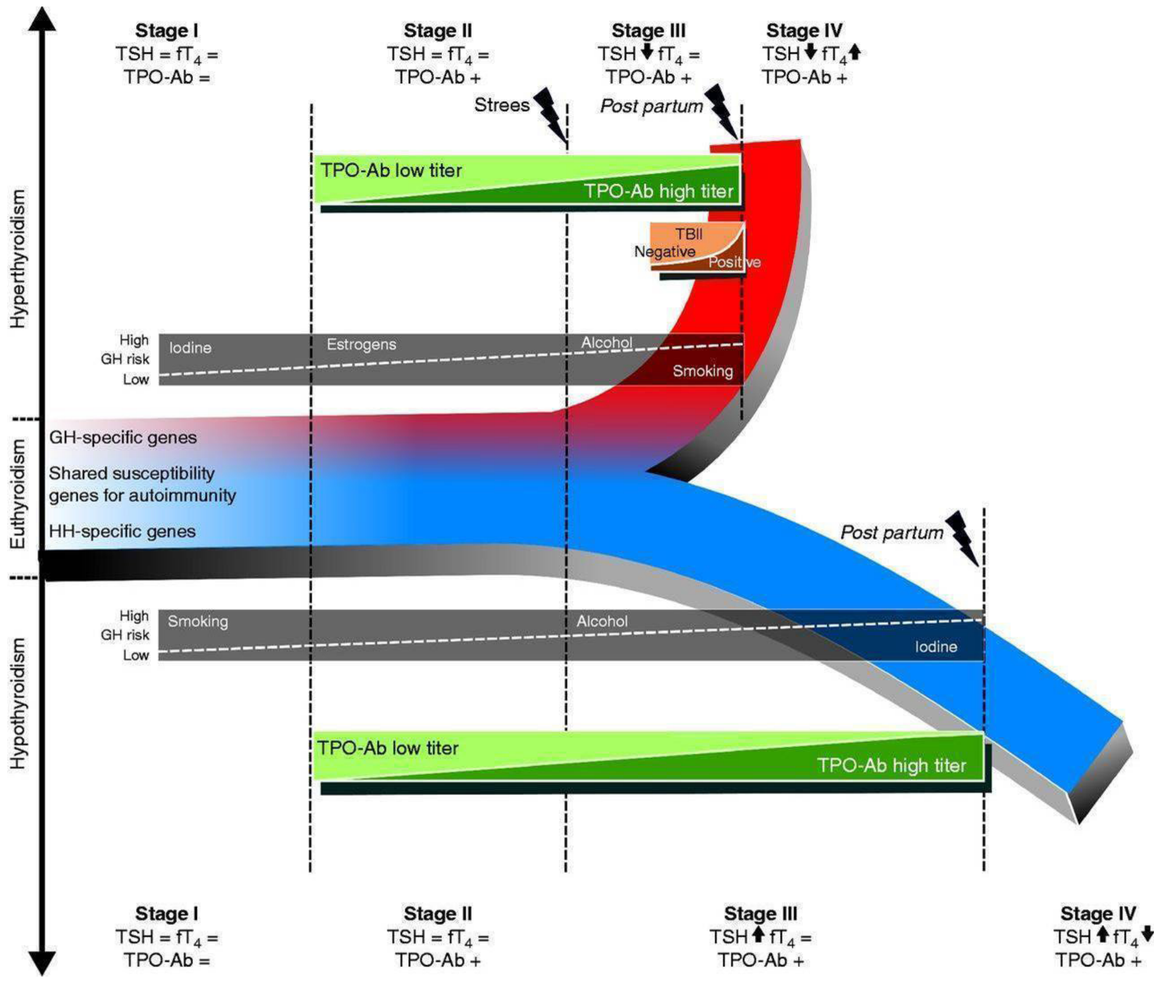
Hashimoto disrupts normal thyroid metabolism on site 1, 2 or 3

- **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

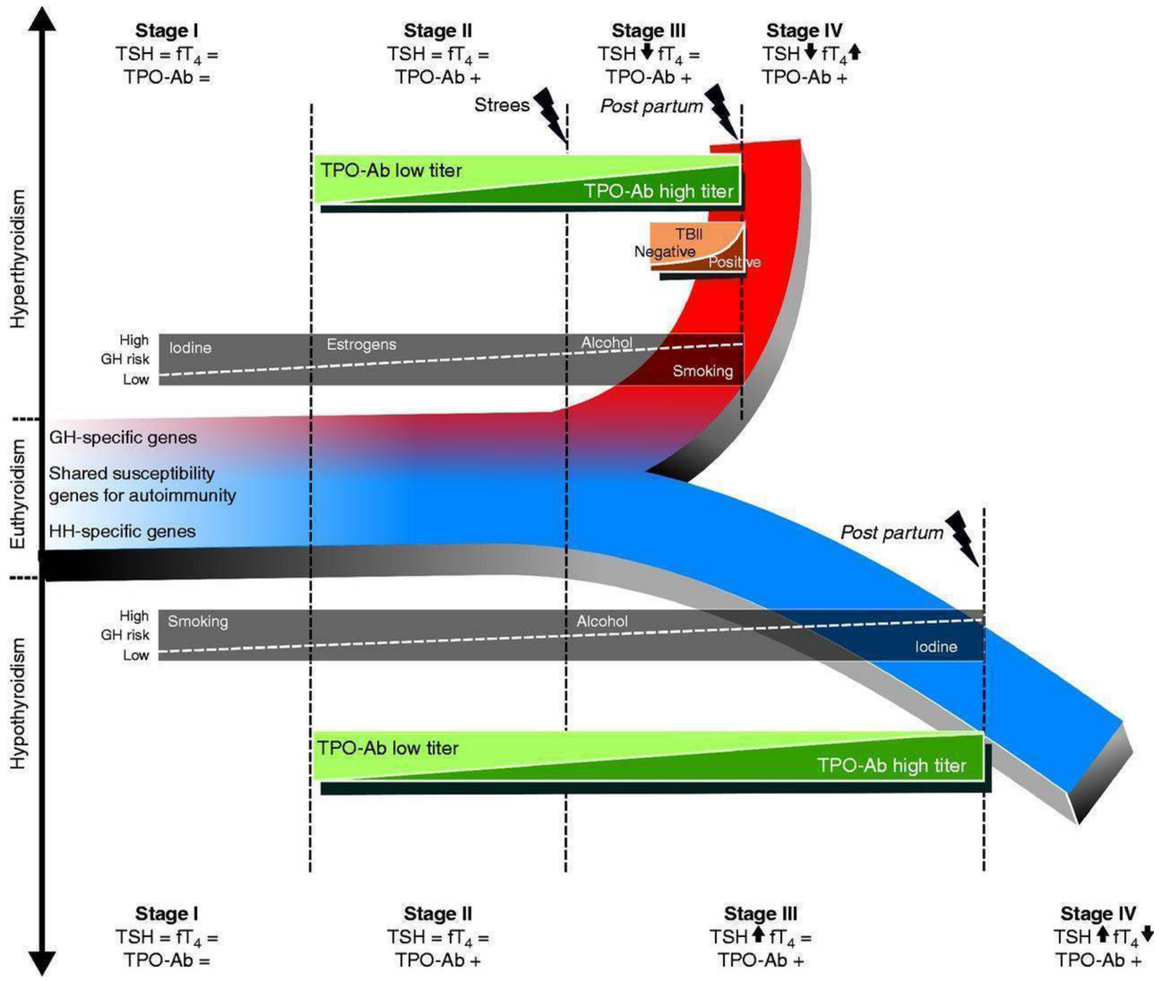
clinically euthyroid *= patients do not have elevated thyroid-stimulating hormone (TSH) levels. Pathogenesis is unknown but may include decreased peripheral conversion of T4 to T3, decreased clearance of rT3 generated from T4, and decreased binding of thyroid hormones to thyroxine-binding globulin (TBG).*

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% overall

But probably much higher:

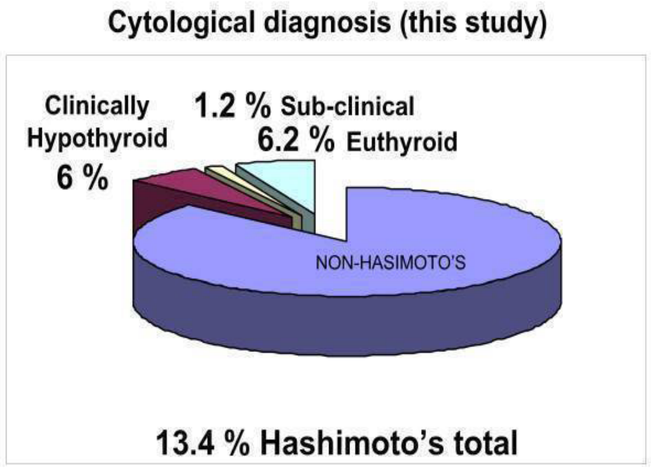
Risk in women 8x

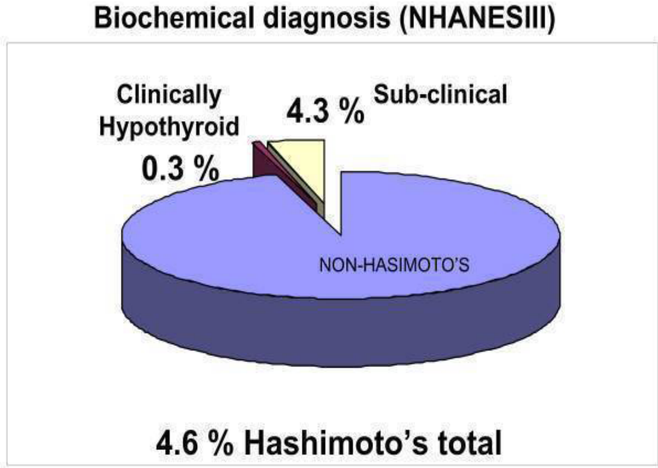
Diagnosis by measuring antibodies

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**

What do we expect in a classic model?
TSH goes up because your Thyroid gland is destroyed and stops producing T4 & T3

But fluctuations are common …

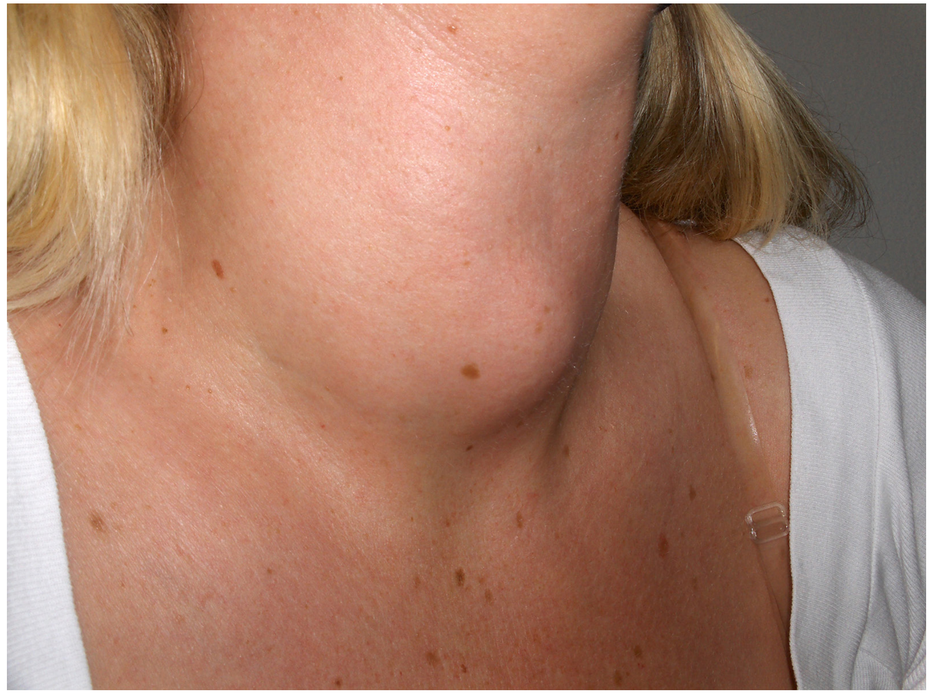
Thyroid Antibodies and Thyroid Autoimmunity

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

Conventional management of Hashimoto's

What is the conventional model of hypothyroidism diagnosis management?

If patients have overt thyroid symptoms, TSH is tested
If TSH is positive, they are diagnosed hypothyroid

Prescribed thyroid replacement therapy and monitored until
TSH is normal again (it's a negative loop)

They are asked to return every year and possibly the dosage of thyroid hormones will be increased (re-test every year)

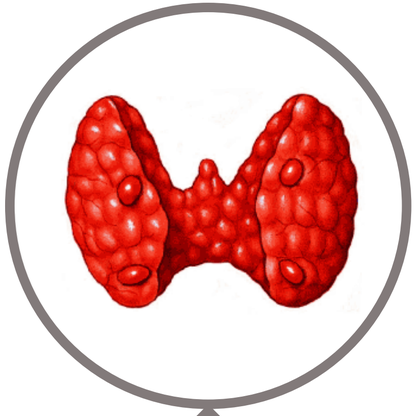
If TSH is negative?
In the early stage many Hashimoto's don't have enough Thyroid destruction, TSH is normal – TEST is negative

Treatment is than focused on management of underlying Hashimoto's symptoms without knowing the cause

- antidepressants
- anti-anxiety medication
- oral contraceptives
- etc

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

Insuline

- glycogen
- Muscle tissue
- Fat tissue

↑ Glucose

↓

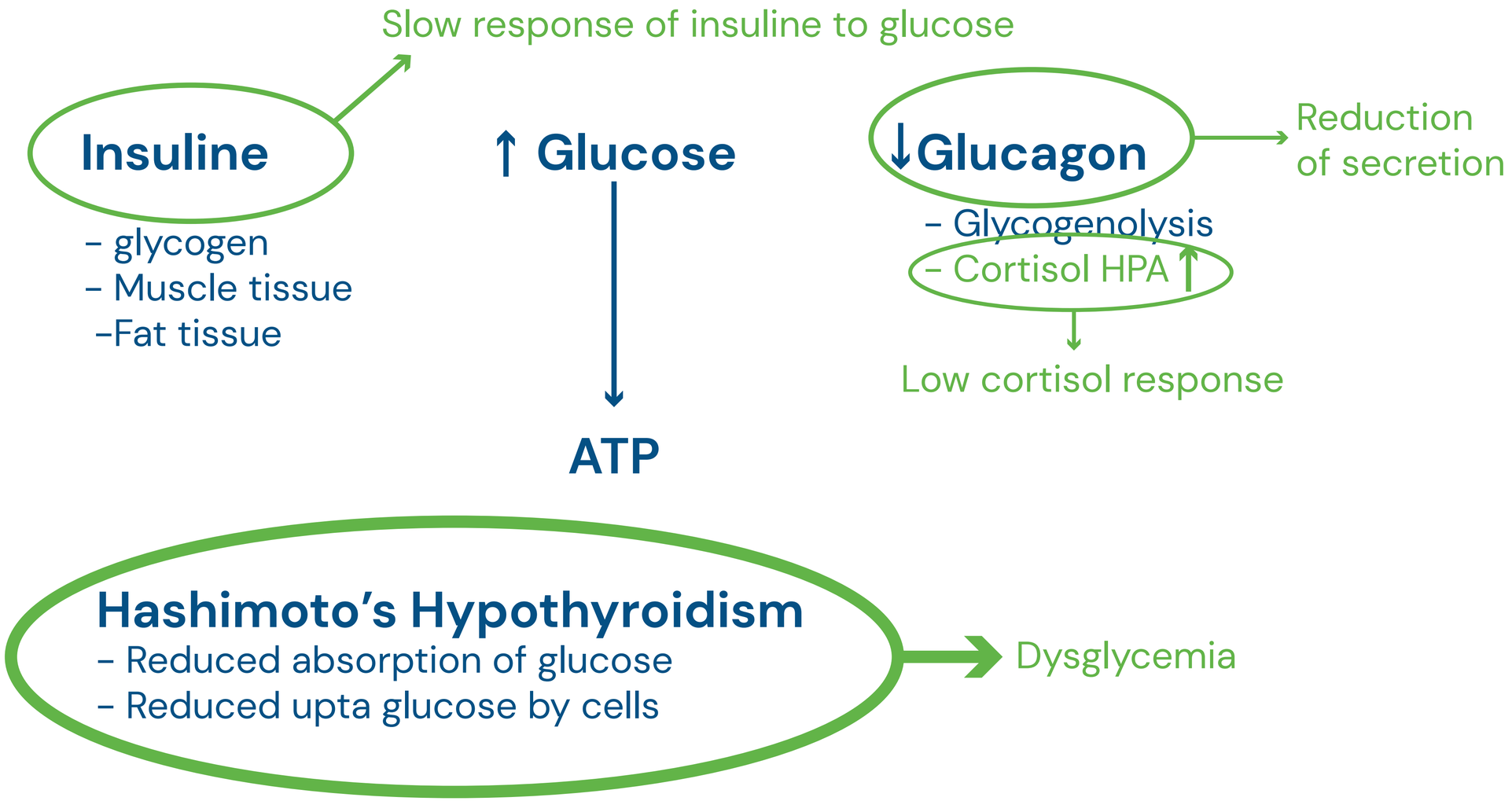
ATP

↓Glucagon

- Glycogenolysis
- Cortisol HPA ↑

Hashimoto’s Hypothyroidism

- Reduced absorption of glucose
- Reduced upta 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 upta 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

- **metformine**

Anti-diabetic therapy improve thyroid function

Metformine

Kalra S, Dhamija P, Unnikrishnan AG. Metformin and the thyroid: An unexplored therapeutic option. Thyroid Res Pract. 2012;9:75–7.

Berberine + Cinnulin

Berberine : different studies show effect on glucose and lipid metabolism

Significant decrease in

- Hemoglobin A1c
- Fasting blood glucose
- Postprandial blood glucose

Some studies are comparative studies between Berberine & Metformine

- 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

Berberine is a potent oral hypoglycemic agent with beneficial effects on lipid metabolism

Dose was limited to 250mg / capsule to avoid side effects like flatulence or diarrhea

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-α-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

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

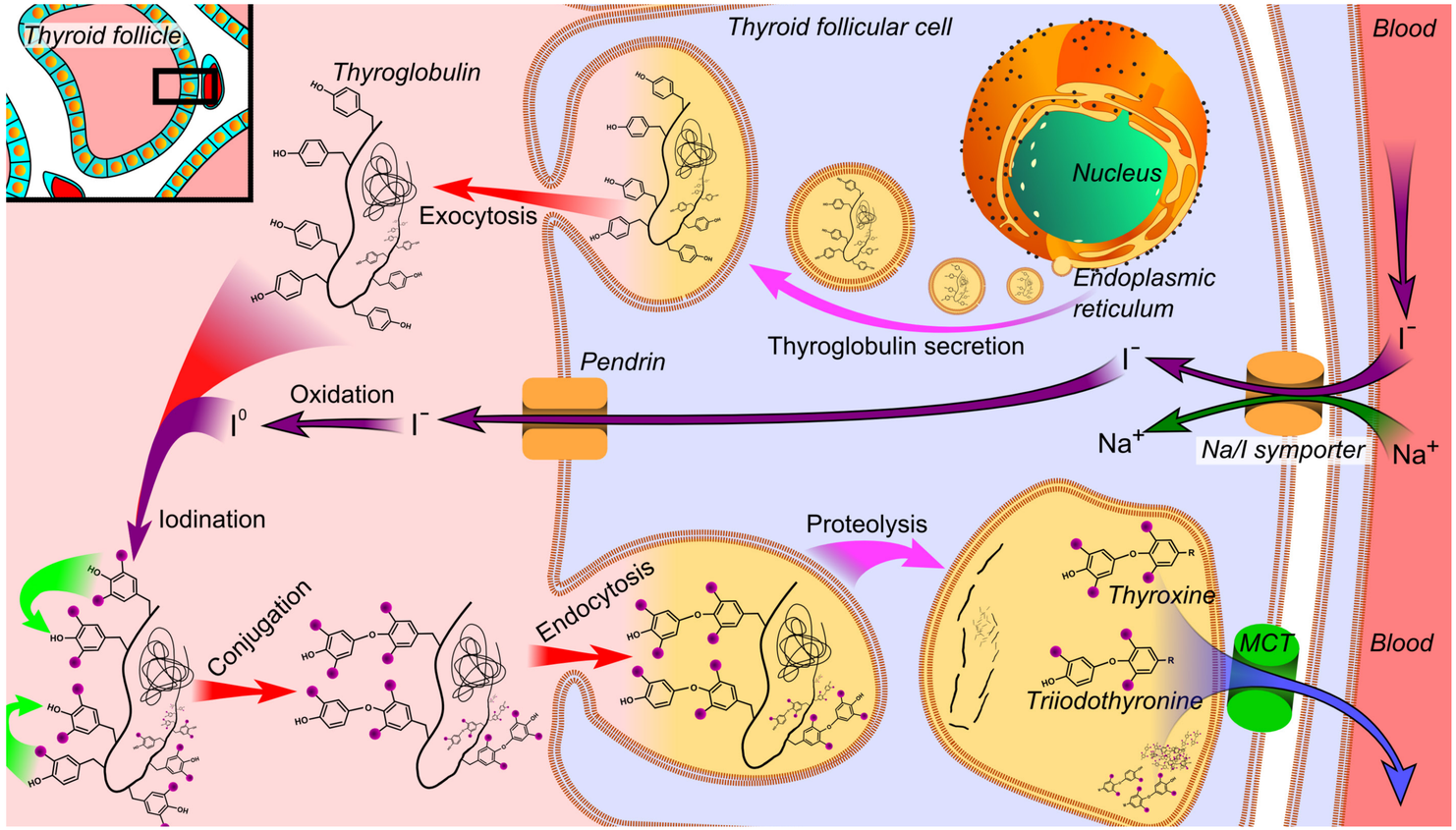
Effraimidis, Grigoris, and Wilmar M. Wiersinga. "Mechanisms in endocrinology: autoimmune thyroid disease: old and new players." European journal of endocrinology 170.6 (2014): R241-52.

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

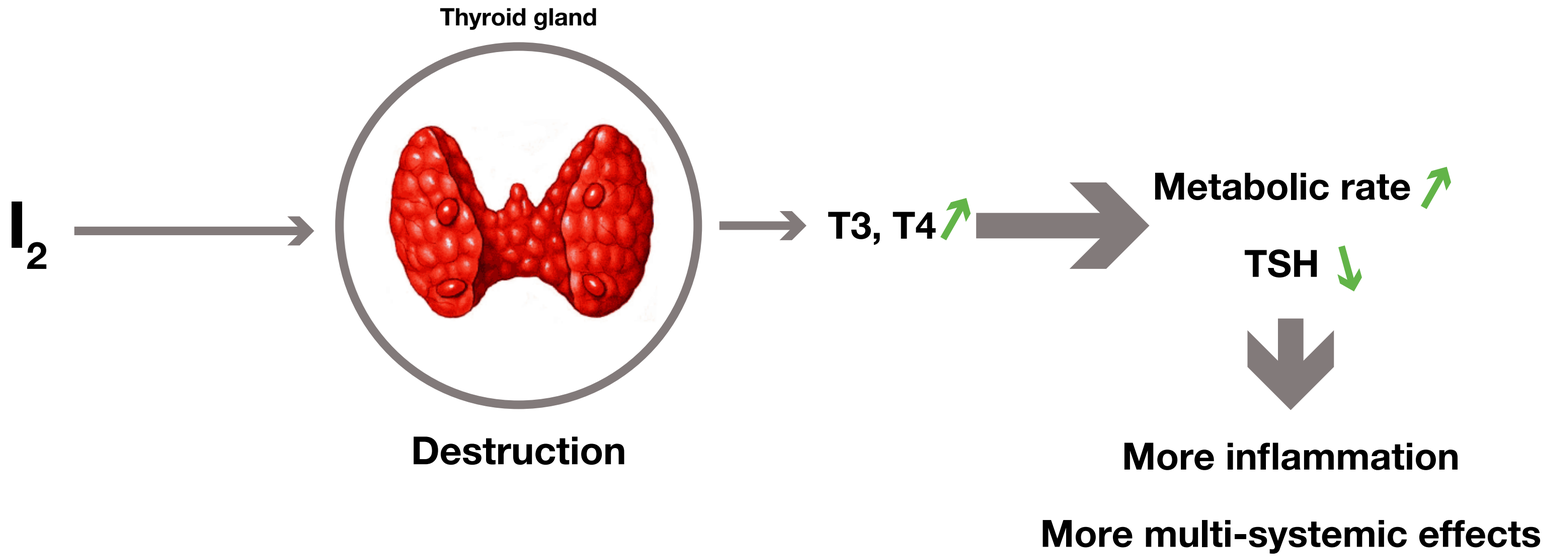


Iodide enters the Thyroid follicle via a Na+ / I- pump

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

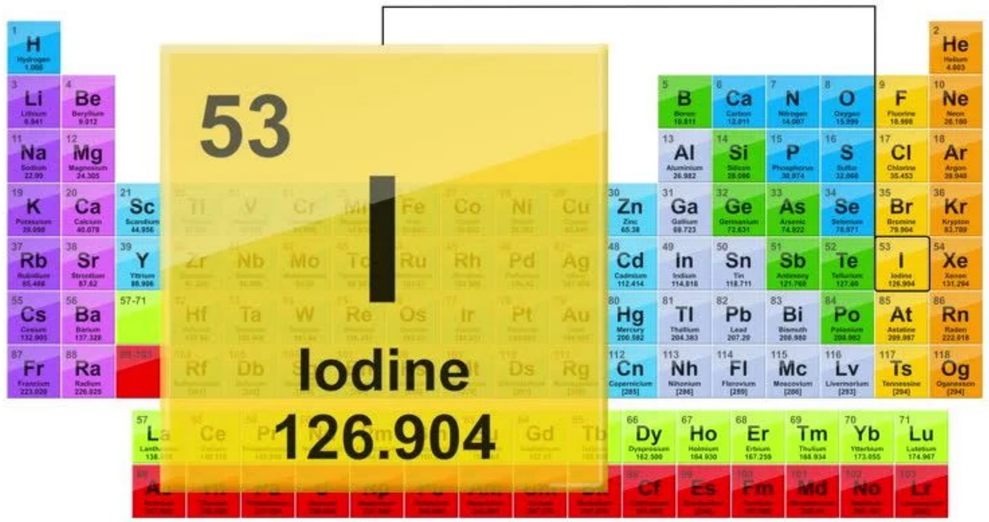
A randomized controlled trial was performed in healthy women and in women with underlying thyroid abnormalities due to subclinical Hashimoto's thyroiditis (diagnosed on the basis of antithyroid antibodies) were supplemented with 500 micrograms/day iodine (giving a total intake of approximately 750 micrograms/day)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

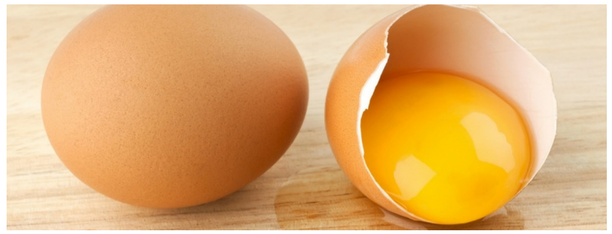
Only iodine restriction!

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

Sicherer, Scott H. **"Clinical implications of cross-reactive food allergens."** Journal of Allergy and Clinical Immunology 108.6 (2001): 881-890.

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).

Many hypothyroid and autoimmune thyroid patients experience reactions with specific foods.

Dietary proteins may play a potential immunoreactive role in autoimmune thyroid disease

Cross reactivity = TSH, 5-deiodinase, TPO, Tg, Thyroid Binding Globulins, T4, T3, dietary proteins

Basis = Molecular Mimicry

Raising Glutathione levels protects the Thyroid Gland against oxidative stress in Hashimoto’s

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.

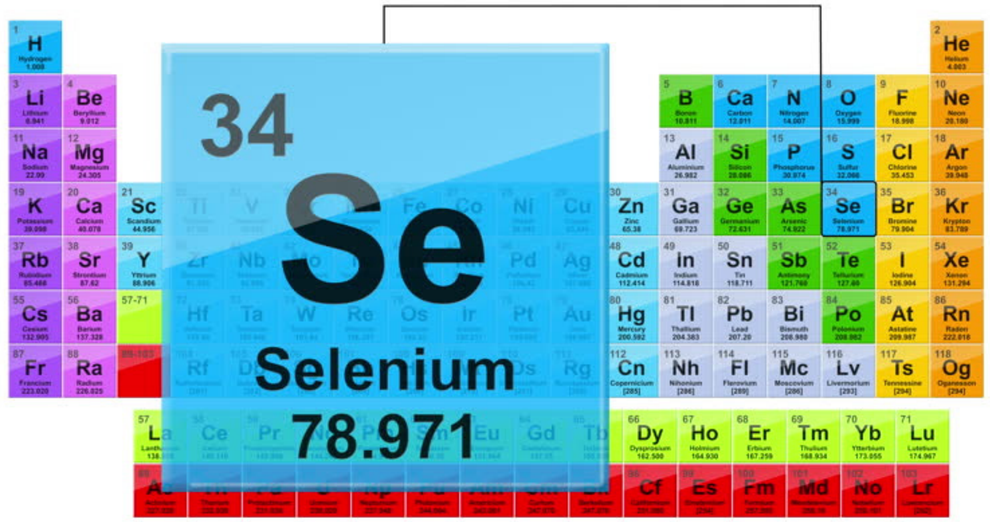
Fecal samples of Hashimoto’s and controls were compared

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.

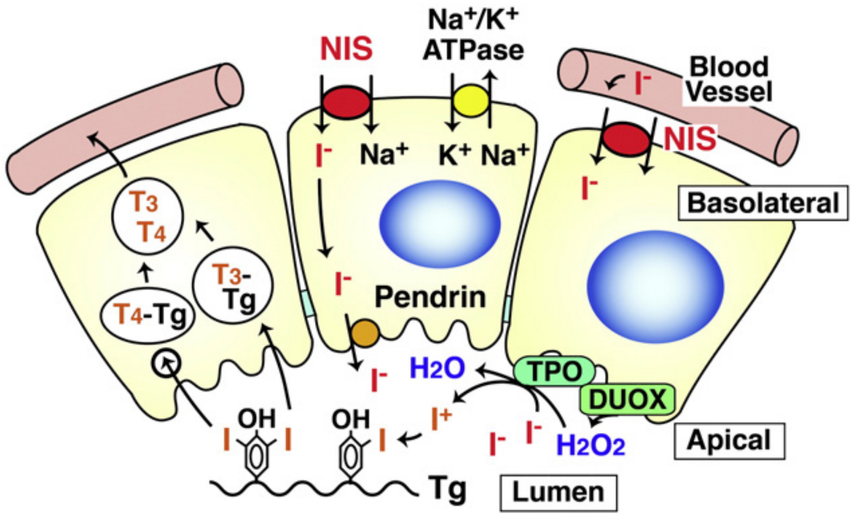
Summary of literature search shows TPO ab decreased in participants using T4 & participants not using T4

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-y & 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

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↑ 🤝 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.

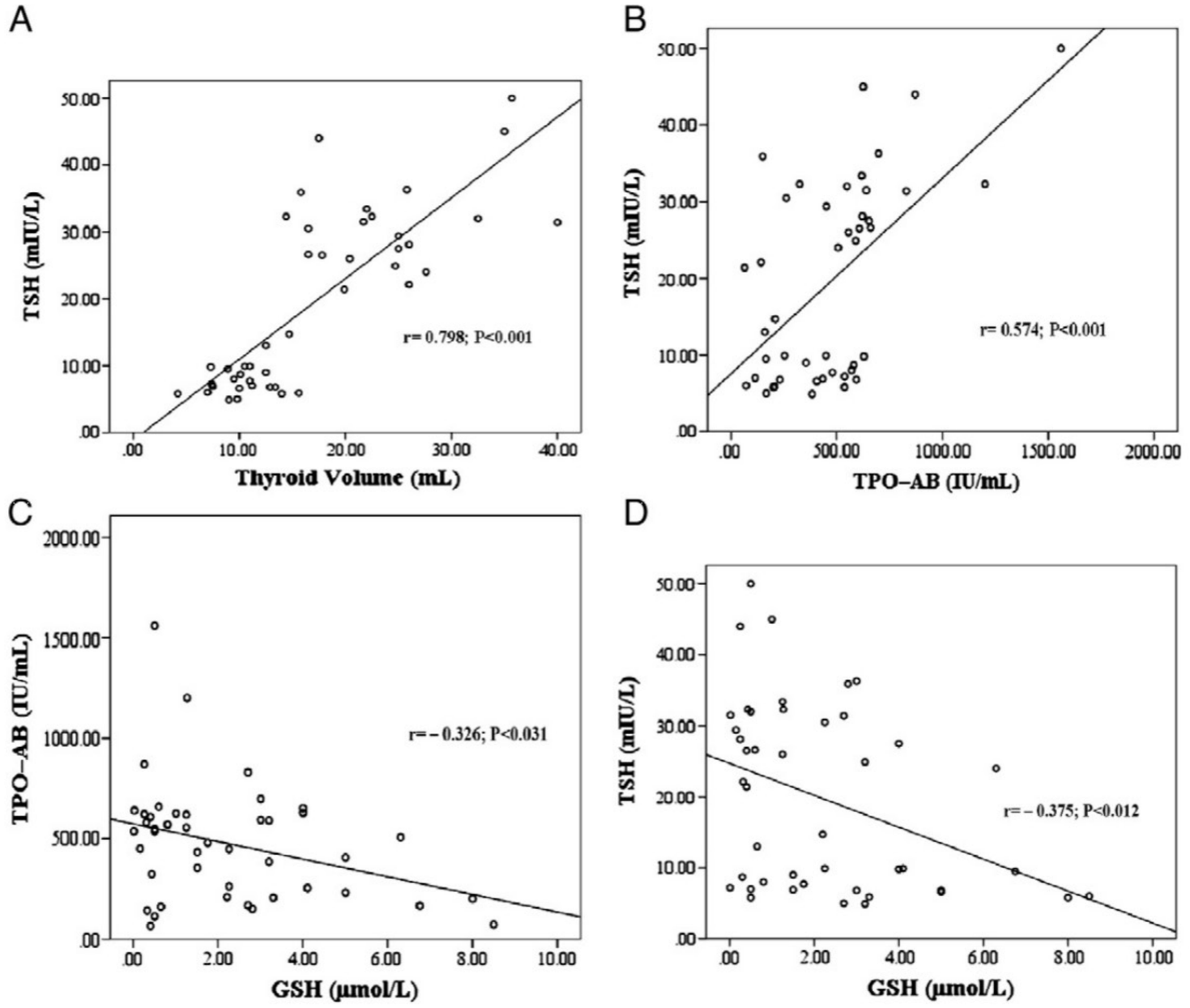


Fig. 2. Associations between markers of thyroid malfunction and/or oxidative stress in individuals with Hashimoto thyroiditis (n = 44). A: Thyroid volume (Tvol) and thyroid stimulating hormone (TSH) levels; B: Thyroid stimulating hormone (TSH) levels and anti-thyroperoxidase antibody (TPO-AB) titers;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

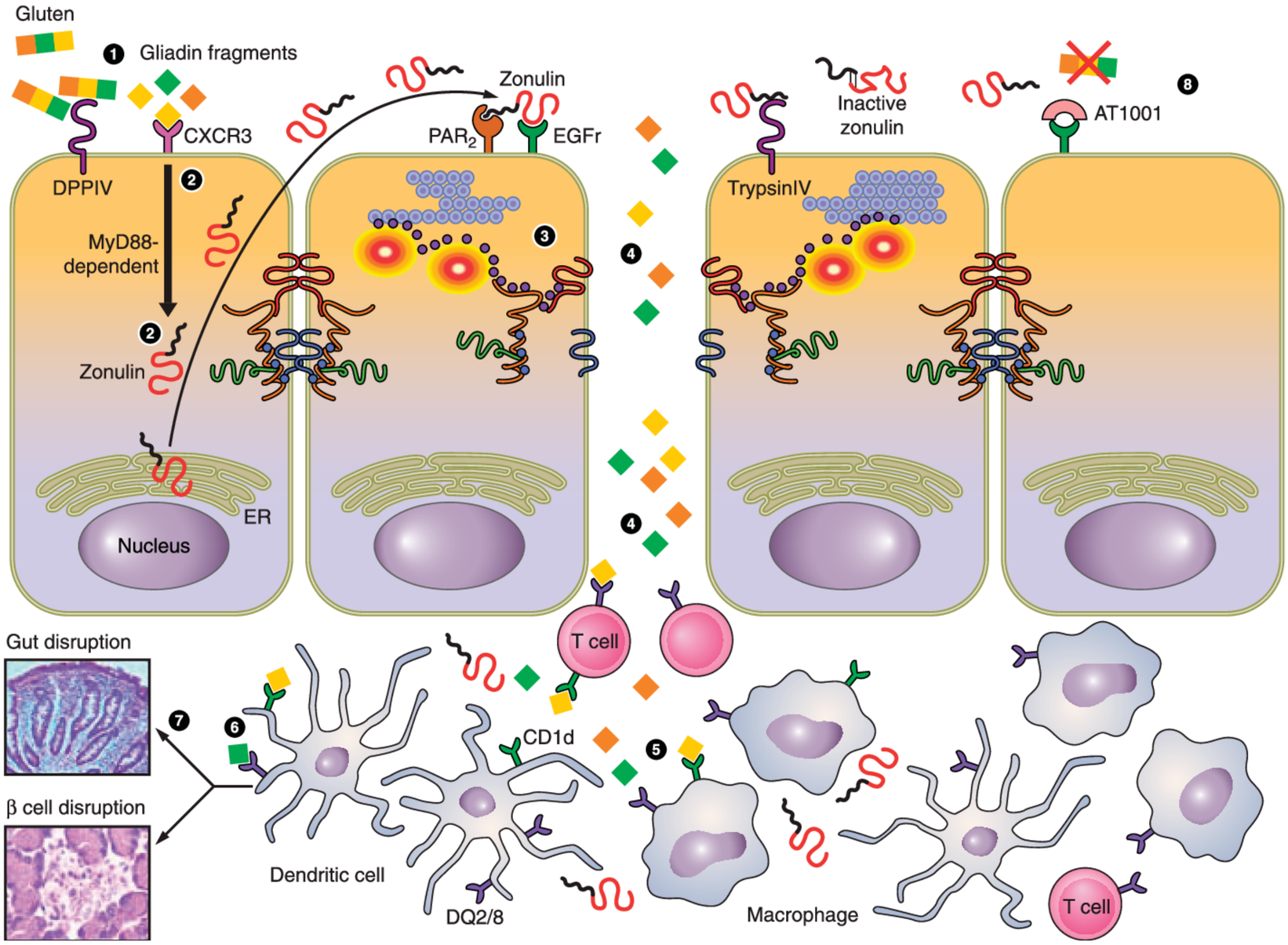
Study shows zonulin levels in 30 children and adolescents were consistently higher

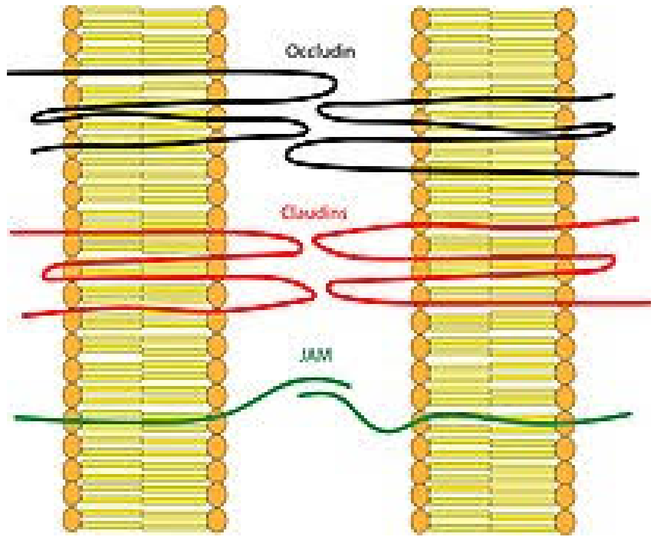
Smyth, Megan Ciara. "Intestinal permeability and autoimmune diseases." Bioscience Horizons: The International Journal of Student Research 10 (2017).

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.

Gliadin-induced Zonulin Release





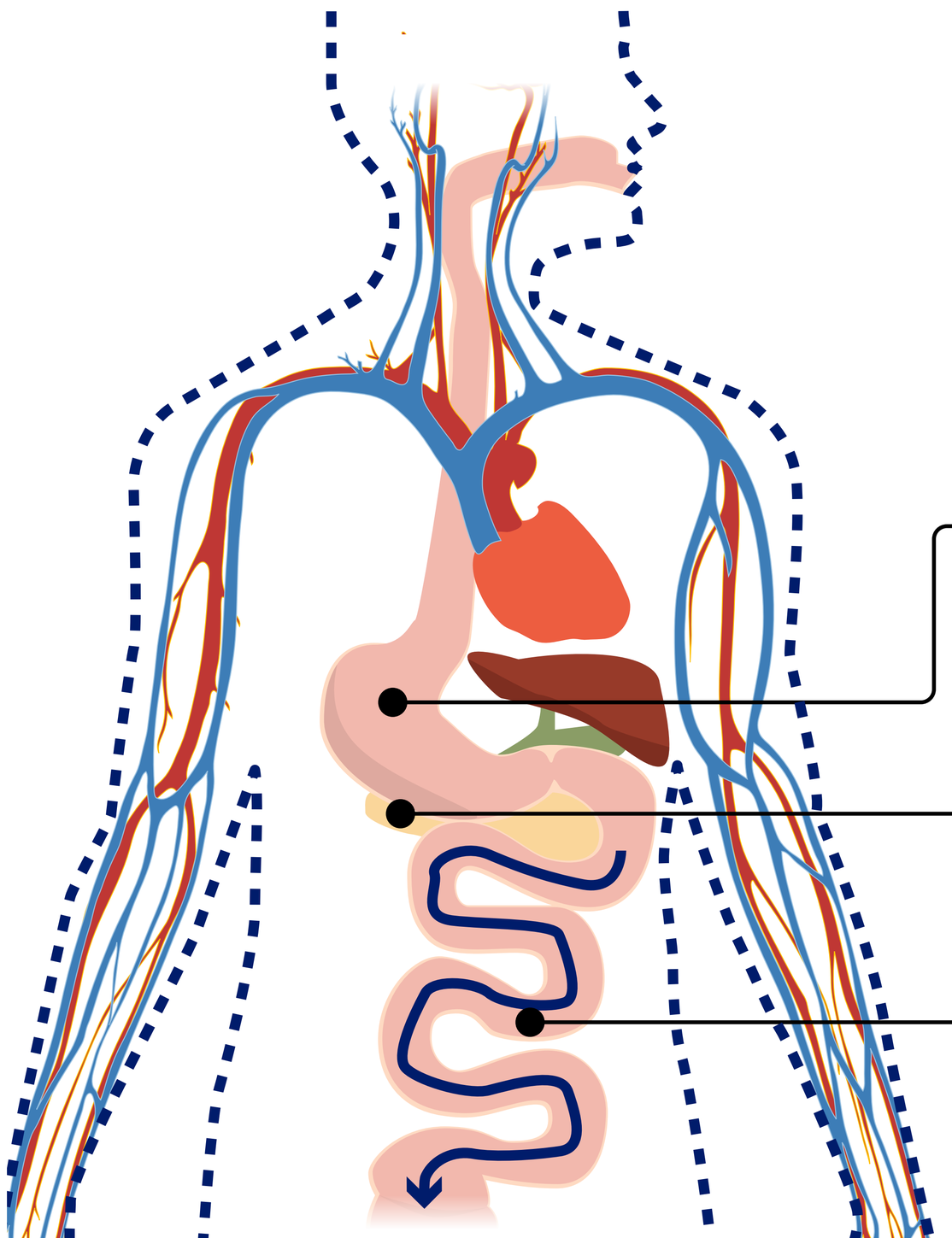
- Tight junctions are composed of a branching network of sealing strands

  Each strand is formed from a row of transmembrane proteins embedded in both plasma membranes

  Occludin and Adhesin are the main membrane proteins

- **Tight junctions regulate paracellular influx**
- **Zonulin upregulation**
  = decrease in tight junctions proteins

Sturgeon, Craig, and Alessio Fasano. "Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases." Tissue barriers 4.4 (2016): e1251384.



Supportive treatments in managements of Hashimoto's

- Intestinal support

Global intestinal is a multilevel support

Guttae Pepsini
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)

Gluten DPP4
Enzyme complex to optimize digestion
(including gluten modifying enzymes)

Permplus Coated
Heal the mucosal lining and tight juction optimazing (pH 6-7)
- ↓inflammation
- Improve the synthesis of s IgA by the intestinal lymphocytes

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.

DPP4?

König, Julia, et al. **““Randomized clinical trial: Effective gluten degradation by Aspergillus niger-derived enzyme in a complex meal setting.””** Scientific reports 7.1 (2017): 13100.

Gluten is a protein with a high content of proline residues (15%)

Normal enzymes in our GI tract can’t break down proline rich sides

This study shows the immunogenicity of Gluten was reduced using DPPIV enzymes

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

Please find our referenced version on the professional section of our website.
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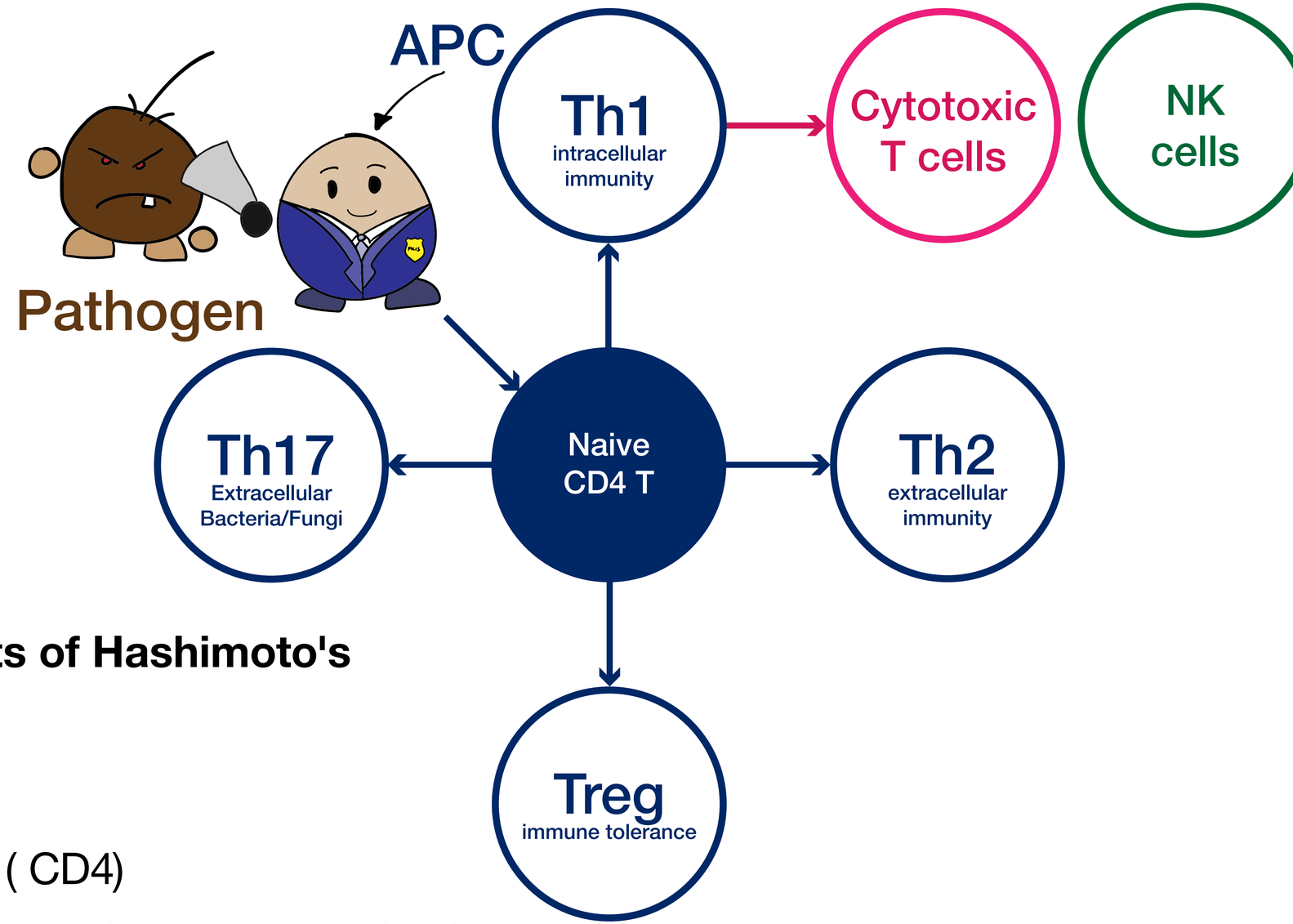


Supportive treatments in managements of Hashimoto's

- Intestinal support
- Immune support

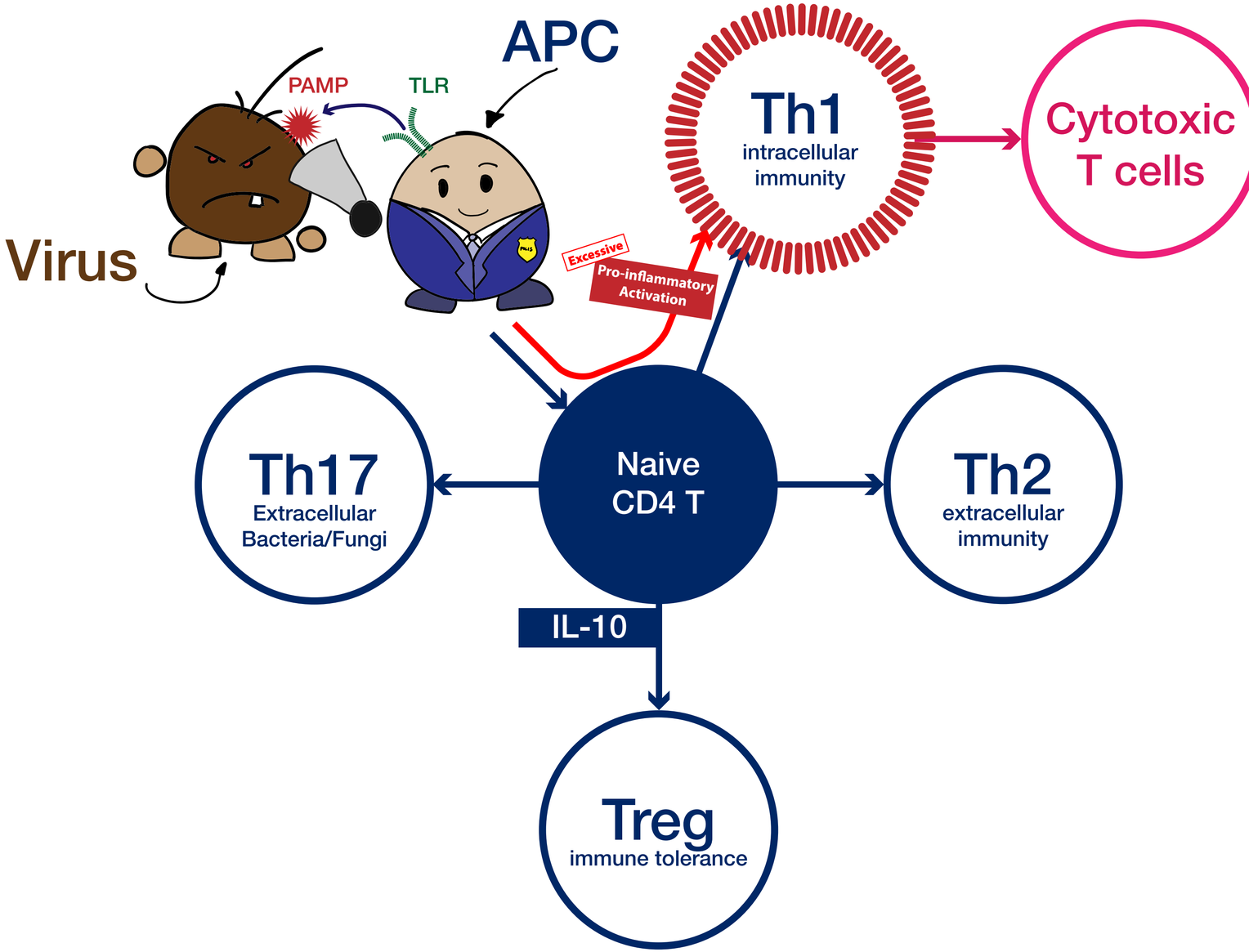
APC communicate with T helper Cells (CD4)

Specific Adaptive immune response depends on communication

Excessive activation =

Storm of cytokines

Autoimmunity

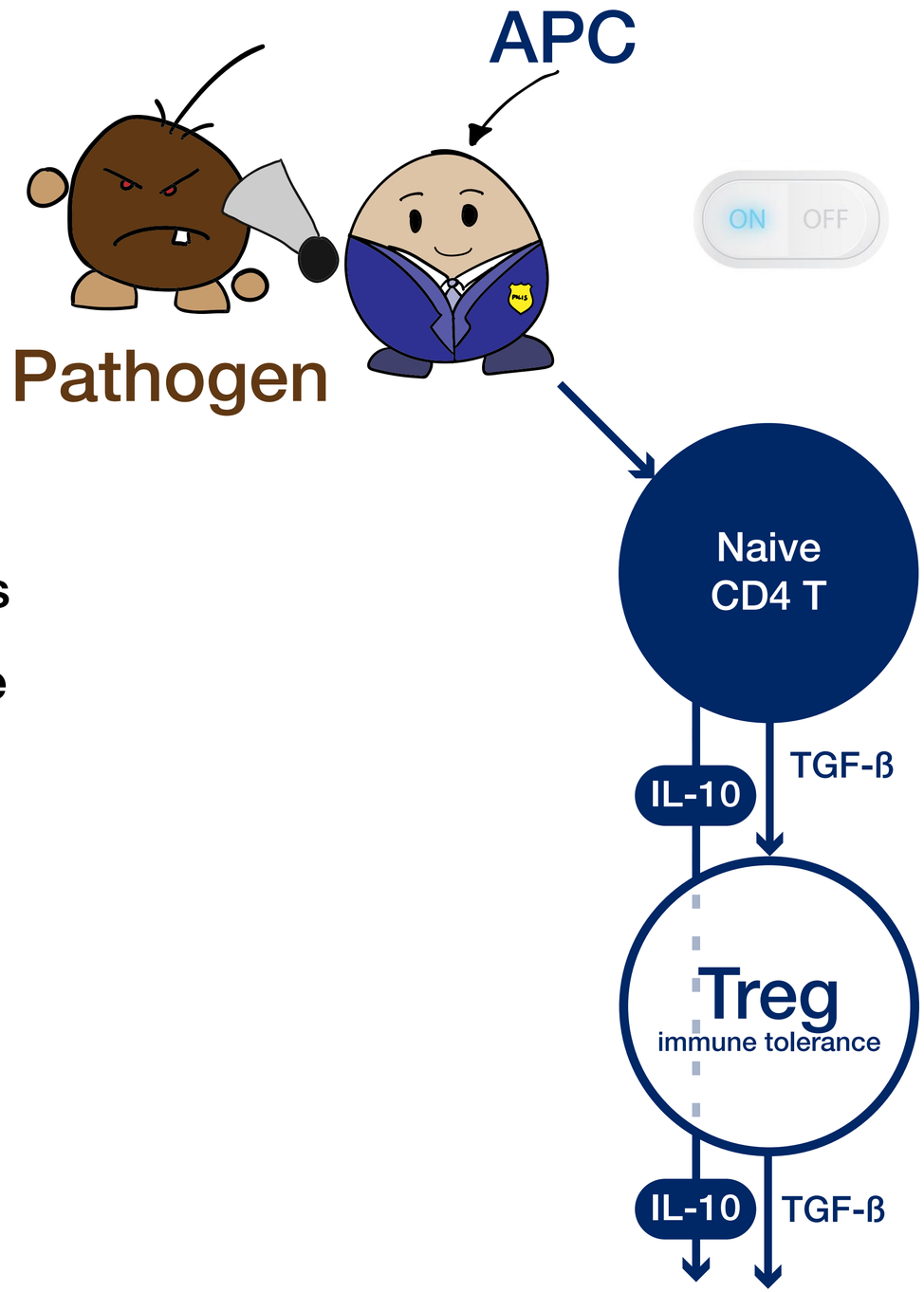


Regulatory T Cells (T reg's)

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
  Polymorphism on VDR is regular in HT = high doses are required!
- **Optimizing DHEA** - individual
- **Butyrate coated:** metabolite produced by fermentation through anaerobic colon bacteria
  Supplementation in coated form (Butyflam)
- **Transfer Factors: Multimessenger**
  Small proteins with RNA (nucleotide material)
  Made by activated T-helper cells or pure amino acid extracts of colostrum

NK Cell Activity↑ + IL-10↑

Mukhtar, Maryam, et al. "Vitamin D receptor gene polymorphism: an important predictor of arthritis development." BioMed research international 2019 (2019).

Clinical Applications

Research Alert

Studies on Multimessenger™

Available only through health care professionals.

IN VIVO & IN VITRO RESEARCH SUMMARY

Multiple clinical research studies have now been conducted on Multimessenger™.

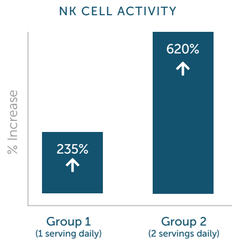
Study No. 1

The effects of Multimessenger™ on NK cell activity were assessed in two groups of participants. Both groups had no more than 110% of the bottom reference range for NK cell activity.

GROUP 1: Ten patients were given 1 serving daily
GROUP 2: Ten patients were given 2 servings daily

Results:

After 30 days both groups showed significant increases in NK cell activity. Group 1 showed an increase of 235% and Group 2 an increase of 620%.

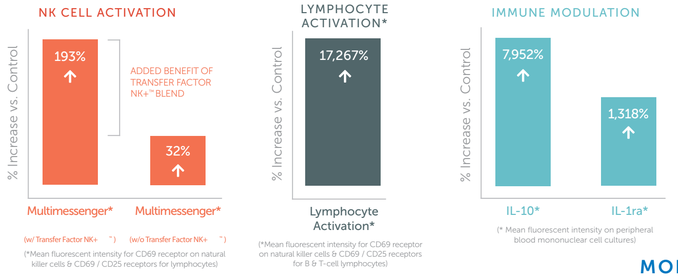


Study No. 2

The second study, designed to build upon the first, was an in vitro study, assessing the effects of Multimessenger™, using blood samples from healthy individuals. In addition to NK cell activation, the study also looked at lymphocyte activation and immune modulation. Each of these was tested against a control.

Results:

Multimessenger™ demonstrated a significant increase in NK cell function, cytokine response, and immune modulation.



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Physician-Requested Product Sheet

Multimessenger™

Natural Killer Cell Formula

90 caps per container	Amount per 3 caps*
Colostrum (dairy)	500 mg
West american Larch (Larix occidentalis)	333 mg
Inositol	200 mg
Beta Glucan	200 mg
Green tea (Camelia sinensis)	200 mg
Pomegranate tree (Punica granatum)	200 mg
Astragale (Astragalus membraneus)	70 mg
Stiitake (Lentinula edodes)	25 mg
Dancing mushroom = Maitake (Grifola frondosa)	25 mg
Zinc (as zinc citrate)	15 mg
Selenium (as L-Selenomthionine)	70 µg

* Daily dose based on 3 caps

Other Ingredients: Gelatin (capsule shell), vegetable stearate ,silica.
Contains: Ingredients derived from milk.
Manufactured without eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, soy, corn and gluten. Produced in a GMP facility that may process other ingredients containing these allergens.

Features & Benefits

Multimessenger™ provides an advanced comprehensive immune support formula, promoting healthy natural killer cells, macrophage, T-cells, and cell division. Product may be used as a daily-use supplement to promote and maintain healthy natural killer cell function as well as providing additional support to the immune system during acute health challenges.

Suggested Use

As a dietary supplement, take 3 capsules away from meals (one hour before eating or two hours after eating) or as directed by your health care professional.

Cautions

None Known.

Each Capsule Includes:

Features	Constituents/Actions	Benefits*
NK Maximizer Bioplex™	• Proprietary super blend of transfer factor, larch arabinogalactan, IP-6, shiitake and maitake mushrooms	• Promotes healthy NK cell levels & immune modulation • Engulfs foreign particles in blood stream and tissues • Promotes metal chelation to prevent buildup of minerals which may weaken immune system
Macrophage & T-Cell Pro Blend™	• Proprietary blend of TMG, beta glucan, and astragalus	• Activates white blood cells known as macrophages and neutrophils • Provides one of the immune system's first line of defense against foreign invaders • Removes cellular debris & speeds up recovery of damaged tissue • Promotes healthy T-cell function, cellular replication, and liver function
Healthy Cell GTP™	• Proprietary blend of potent green tea and pomegranate extracts	• Promotes healthy cell division • Supports body's malignant cell apoptosis response • Effective antioxidant properties
Zinc, Selenium	• Integrated blend of key immune nutrients	• Strengthens immune function • Promotes normal cell growth • Boosts antioxidant levels

MORE

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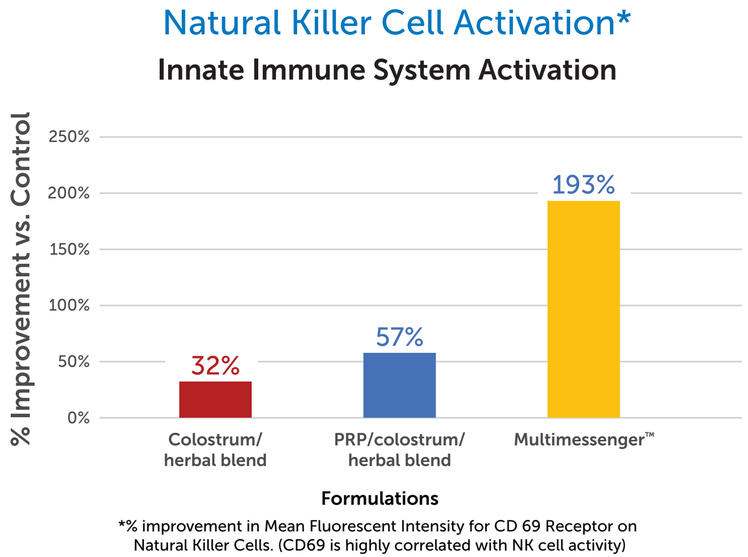
Researched Nutritionals® solutions for life

Transfer factors are like a cross between interleukins and antibodies

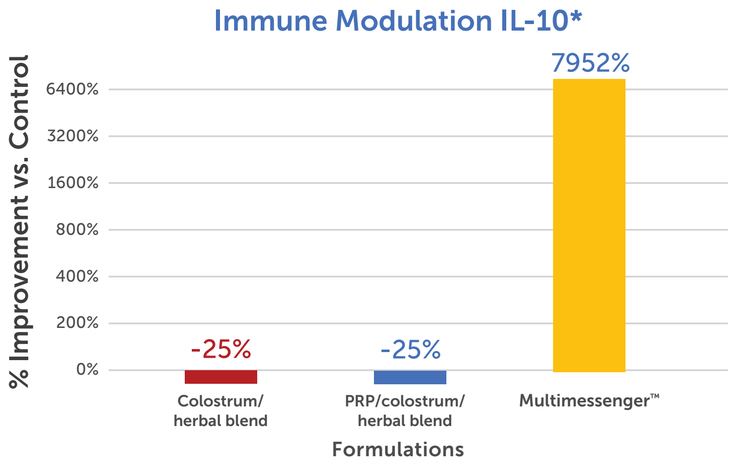
Carrying messages from immune cell to immune cell like interleukins

= General strengthening of Th1 & NK Cells

= rebuilding balance Th1/Th2/Th17 & downregulate autoimmunity

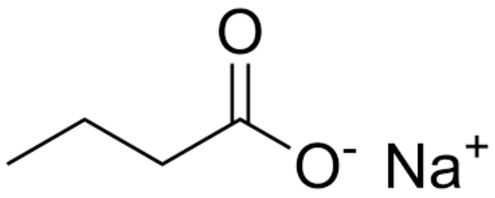


*% improvement in Mean Fluorescent Intensity for CD 69 Receptor on Natural Killer Cells. (CD69 is highly correlated with NK cell activity)



* % 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)



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

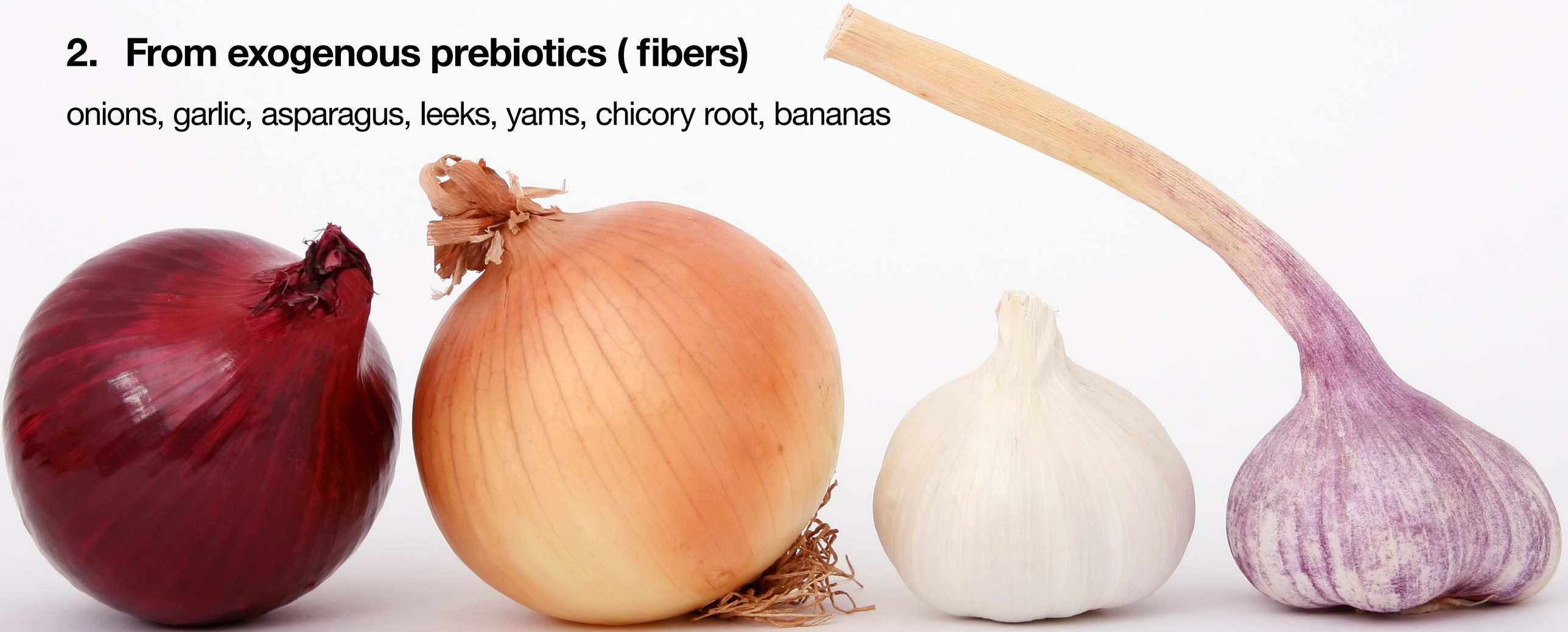
What bacteria produce butyrate?

- **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

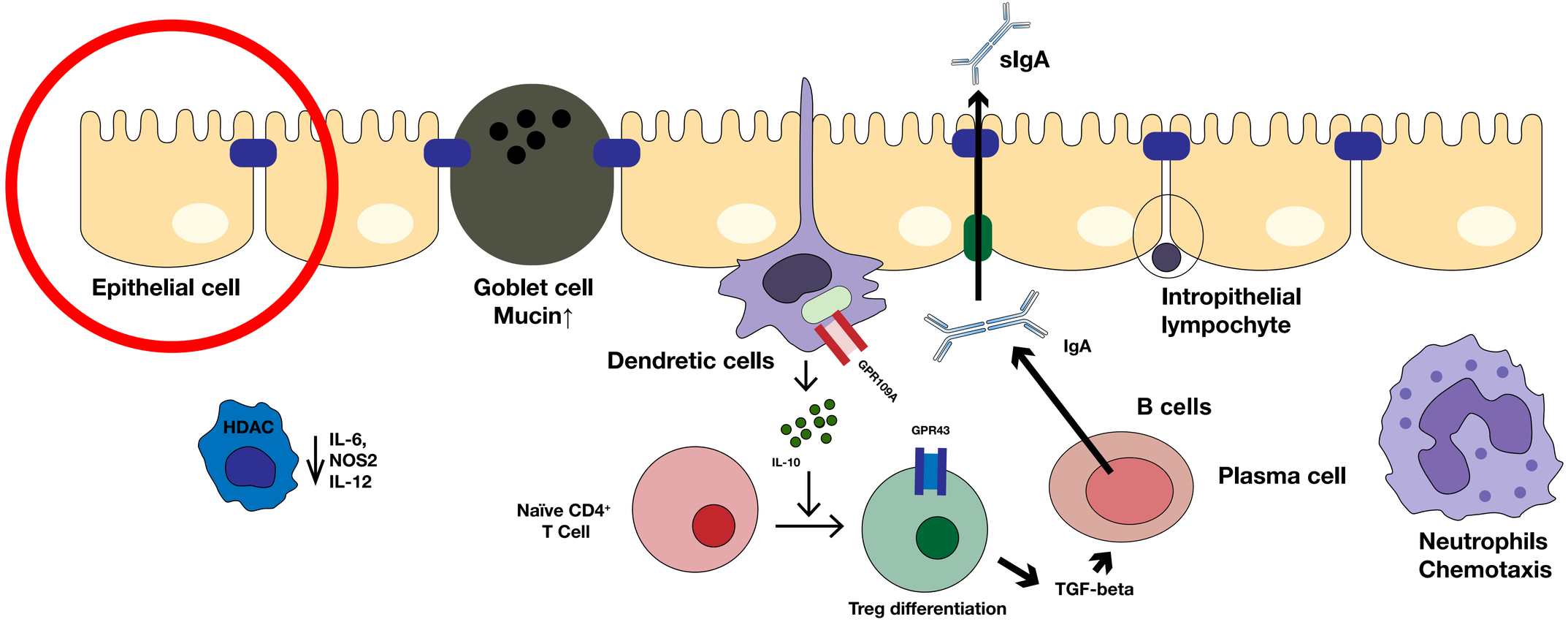


What is the role of butyrate and SCFA's?

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”

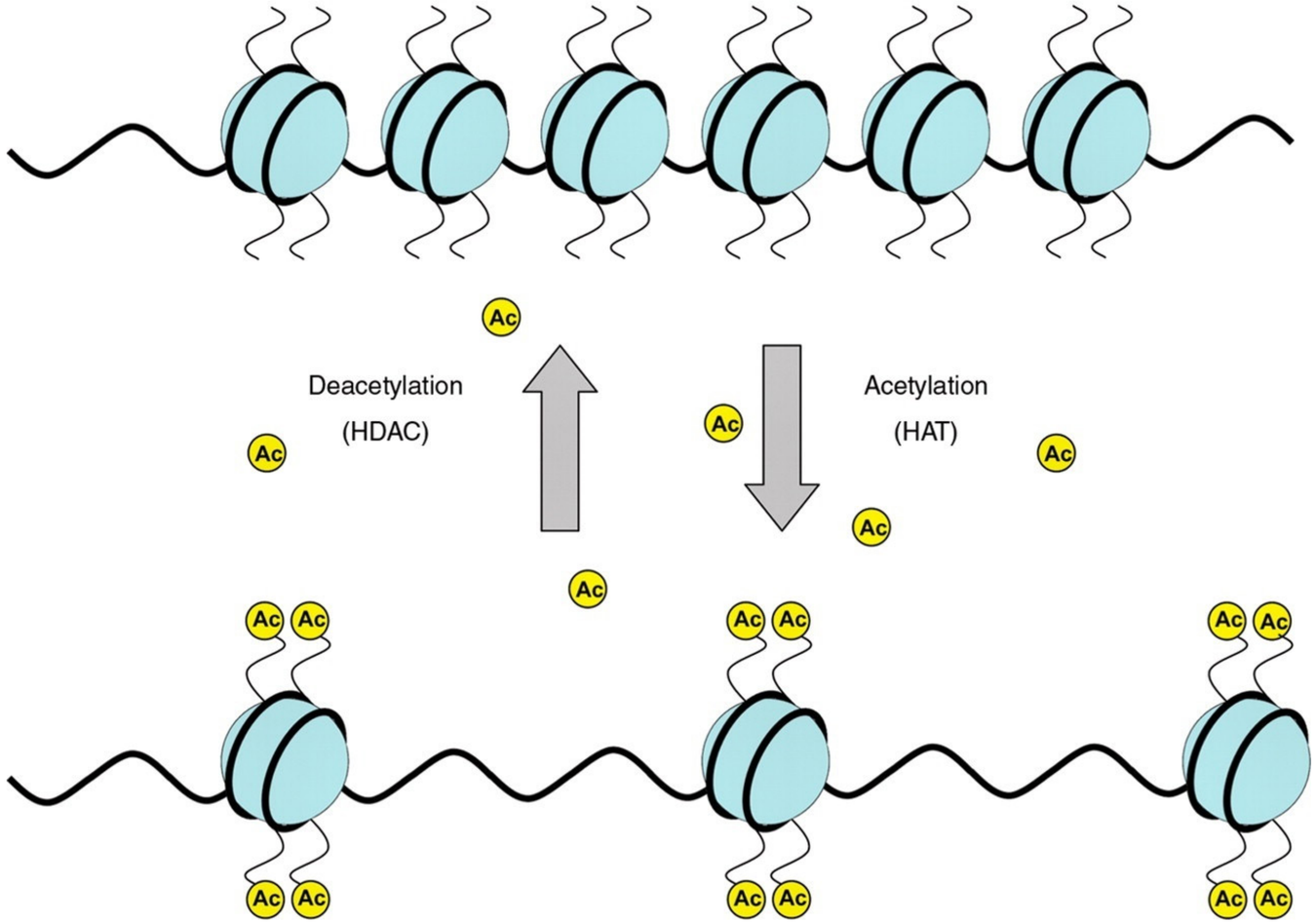
=Butyrate impacts epigenetics
= Butyrate modifies genetic material
→ impact on gene expression and transcription

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.

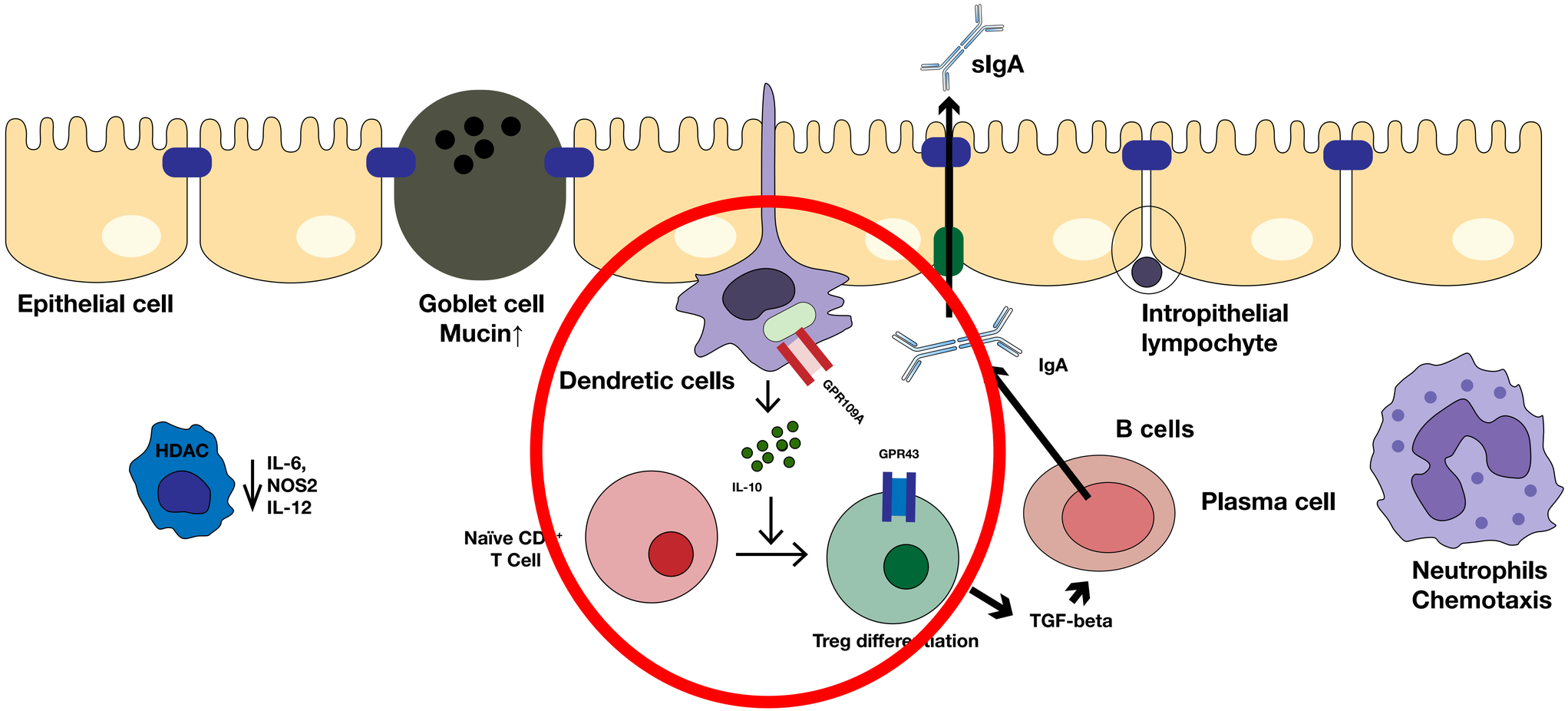
Immune modulation / anti inflammation on local level:
Butyrate inhibits HDAC (histone deacetylase) – this modification is changing the gene expression



Gene expression is modified in Dendritic Cells

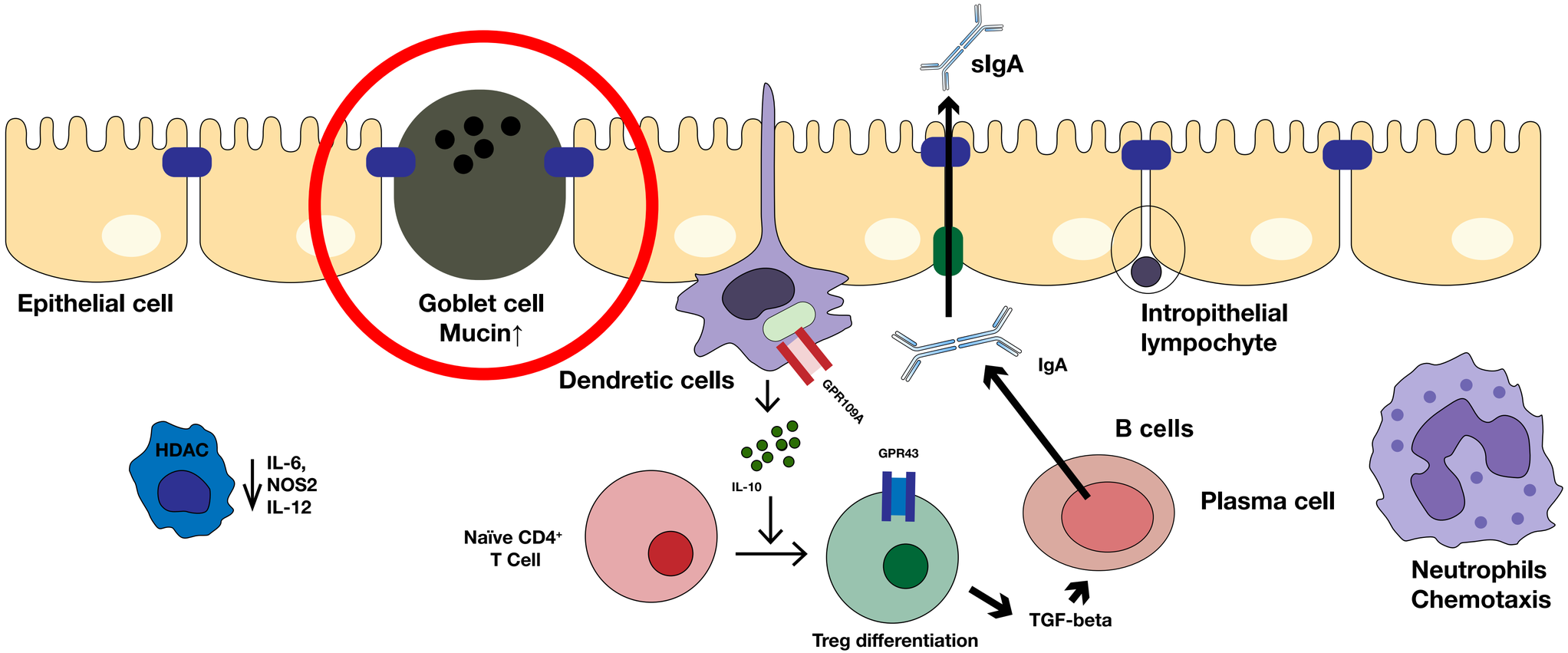
IL-6 is suppressed = more IL-10

More differentiation to T regs



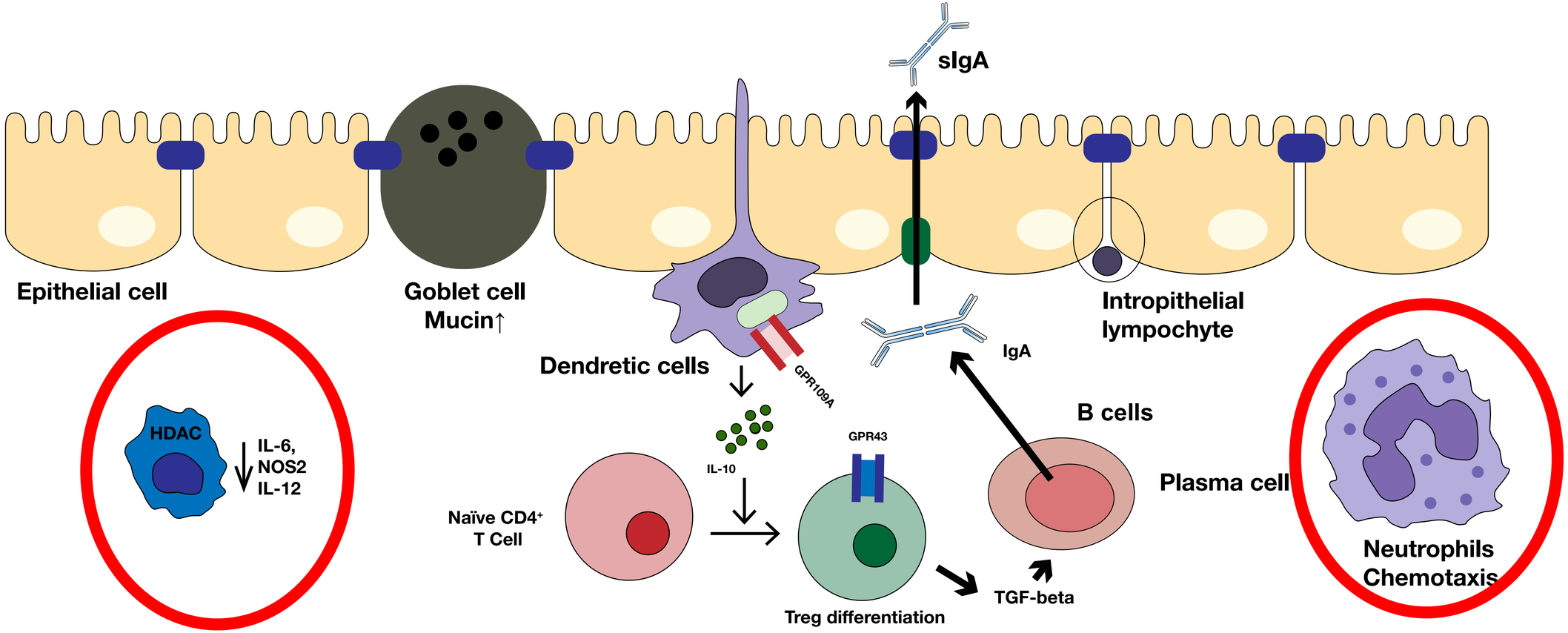
Differentiation of Goblet Cells and mucus formation

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

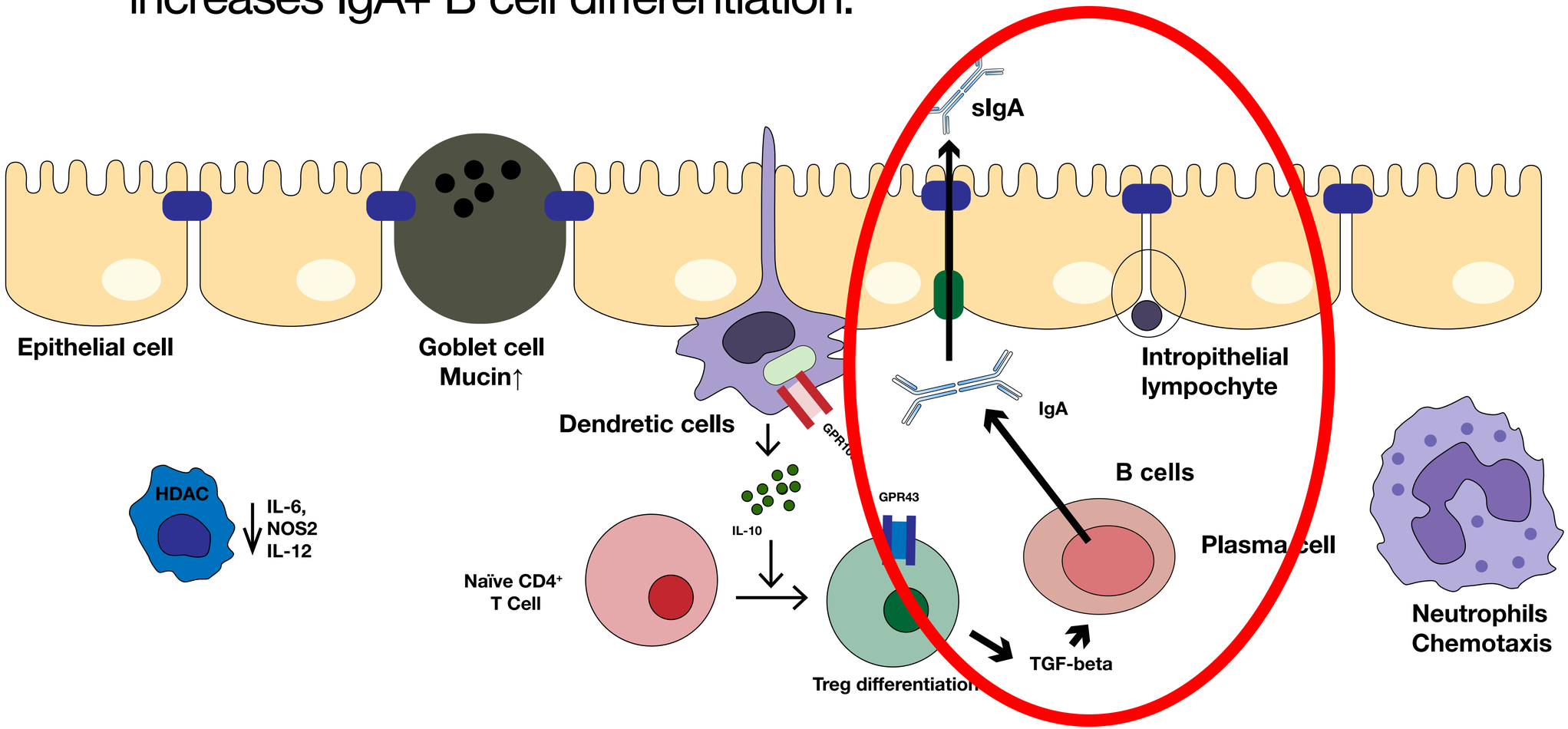
Butyrate affects neutrophil chemotaxis anti inflammation on local level



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

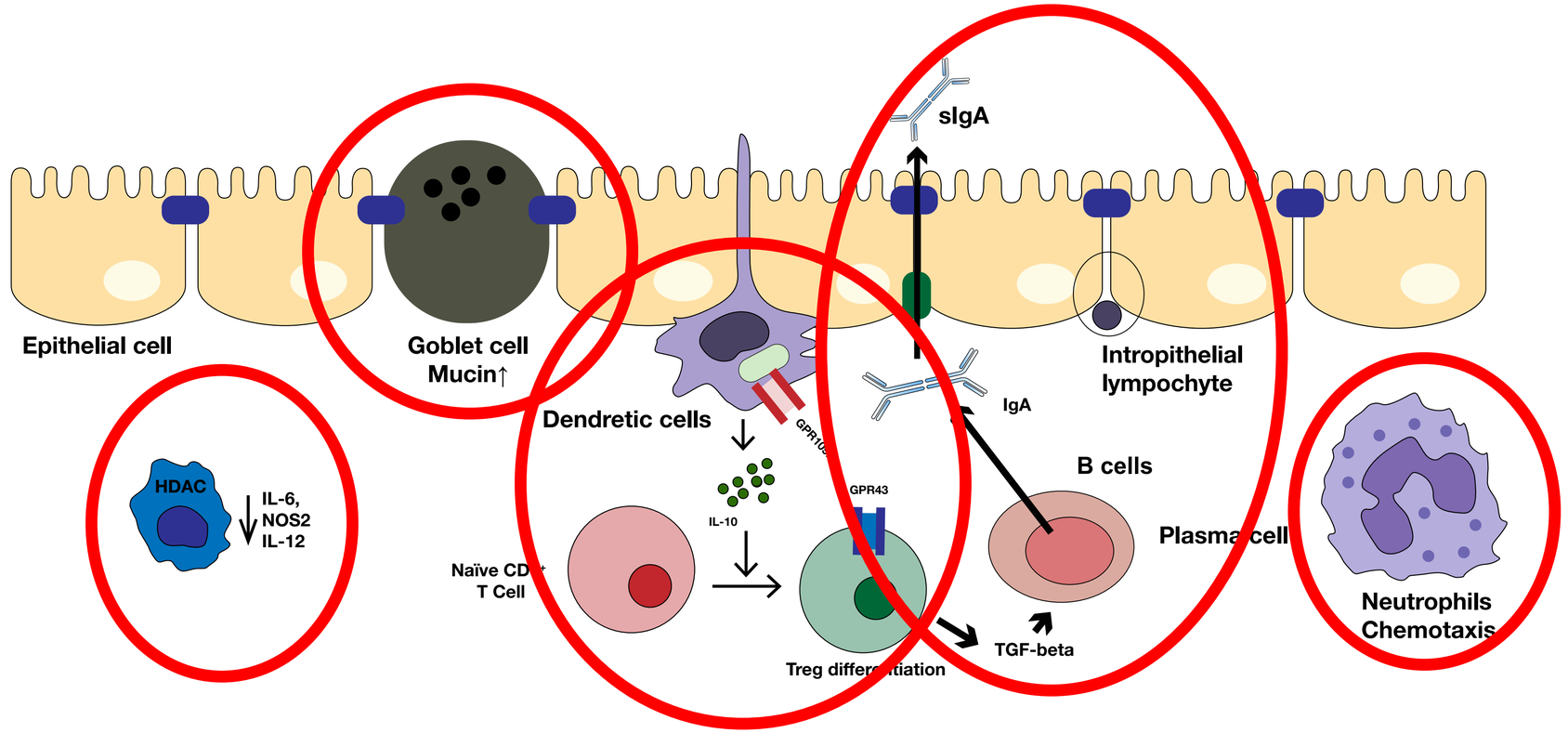
Impact on dendritic cells, more IL-10 & T regs

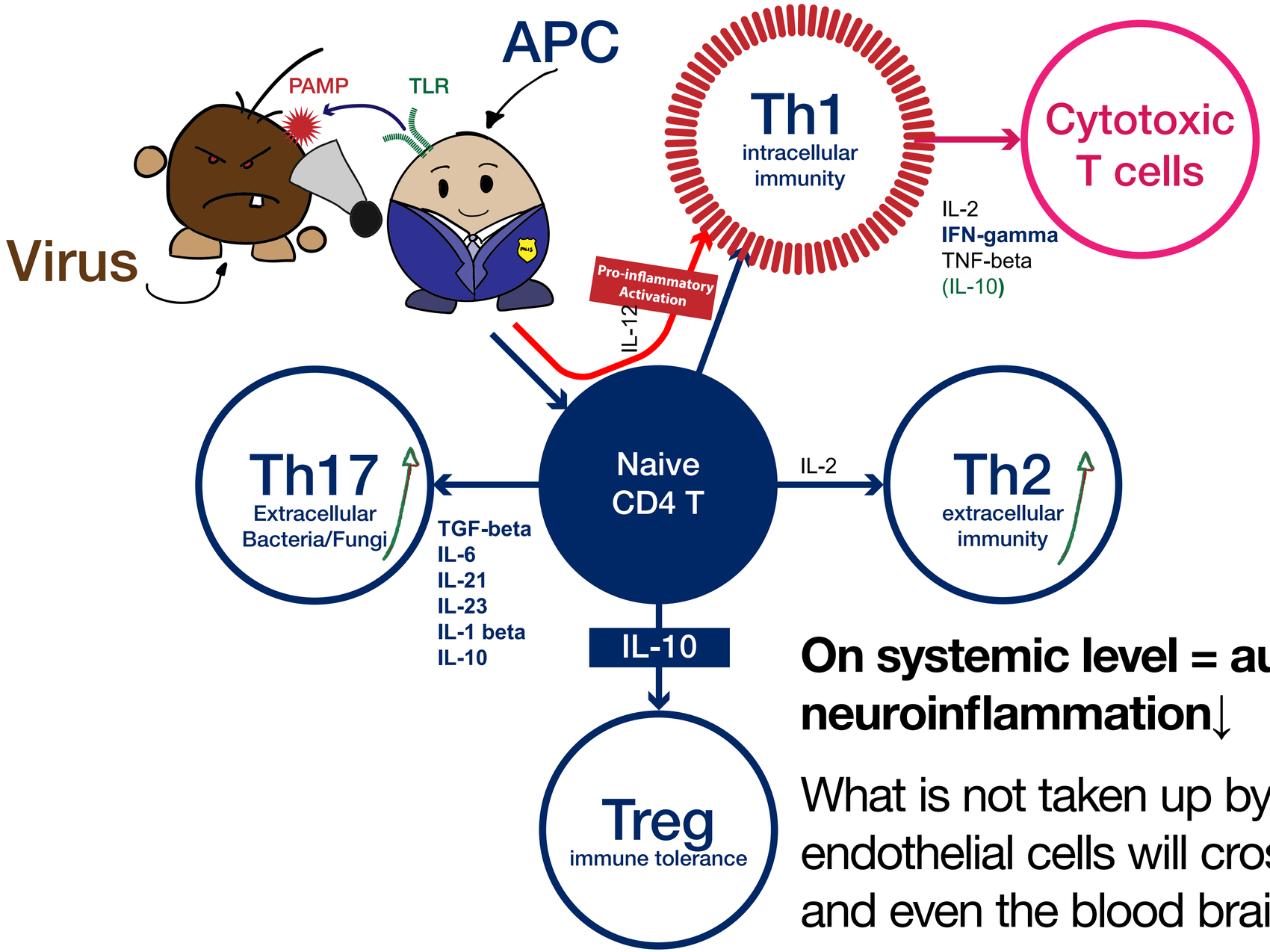
Goblet Cells release more mucins

Macrophages more tolerant towards commensal bacteria

Neutrophil chemotaxis

B cells synthesize more s IgA's





On systemic level = autoimmunity↓ & neuroinflammation↓

What is not taken up by enterocytes and endothelial cells will cross into systemic circulation and even the blood brain barrier

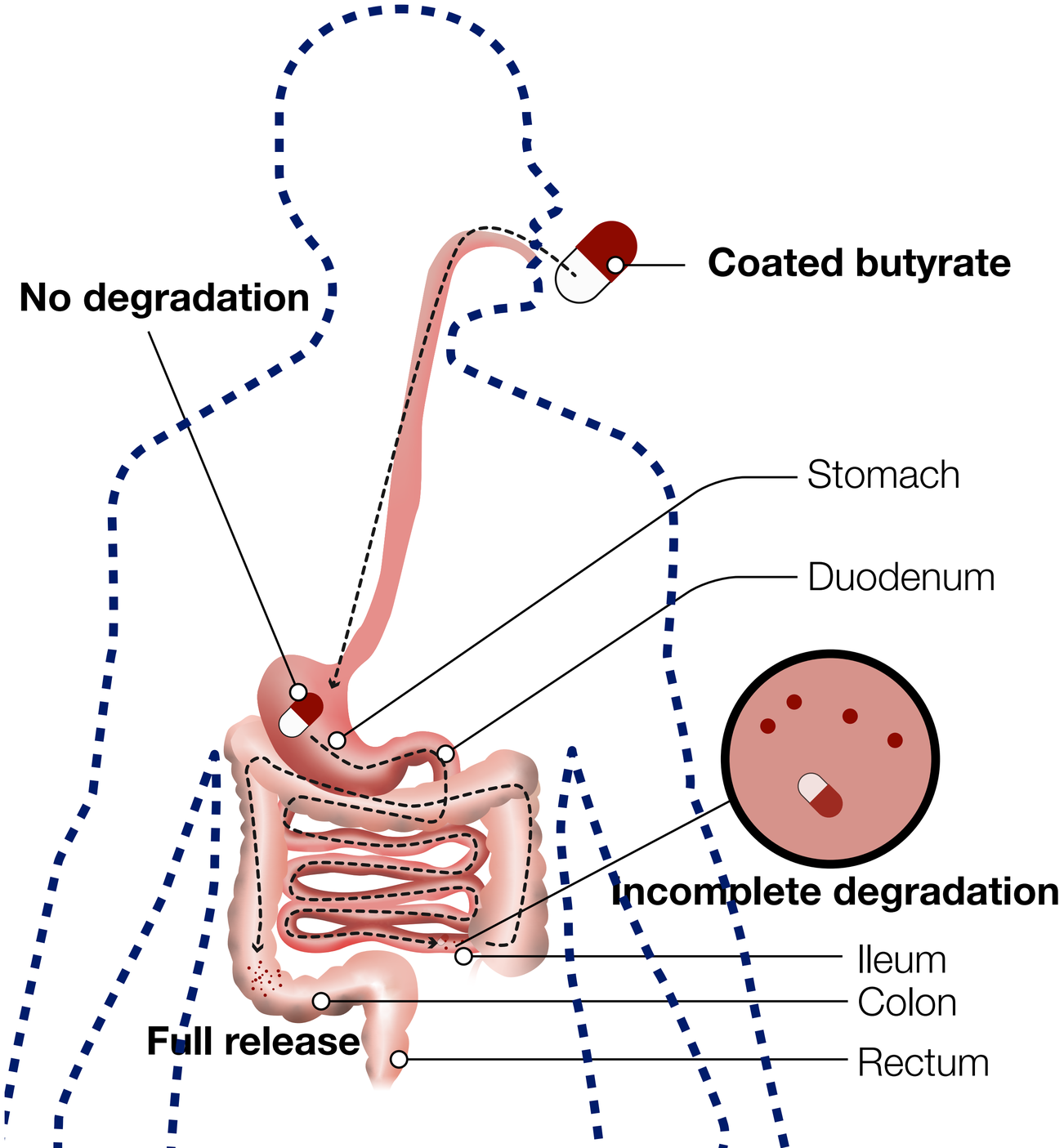
IL-10 favors the differentiation of naïve CD4 cells into T regs

Tregs dampen excessive manifestation of immunity / autoimmunity

Mice deficient in IL-10 showed manifestations of local autoimmune conditions and systemic autoimmunity

Butyrate coated contributes to supportive treatment in Hashimoto's on 2 levels

1. Maintenance intestinal barrier
2. Immune tolerance = **Butyrate calms autoimmunity**



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

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.

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

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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-13Rκ2–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 shortκchain 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.

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

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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- Selenium
- Myo-inositol
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Supportive treatments in management

- Intestinal Support
- Immune Support

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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	1st month 3x2 tabs/day 20minutes before meals 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