Global approach in Candida manifestations

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NUTRINED

Professional Disclosures

- Educational Board BSEM
  British Society Environment Medicine
- Past Board of directors 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

Candida Infection

Fungal infection can be caused by several candida spp.

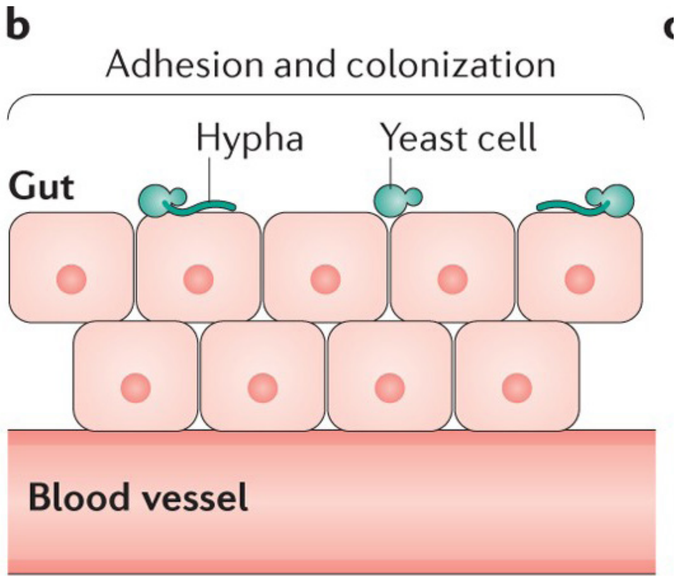
Candida alb., most common
(= the most prevalent Candida spp. Causing disease, number 2 in Europe and the States is C. glabrata)

Prevalence varies depending on geographical location

Spectrum of disease ranges from ordinary symptoms in local mucosal infections to fulminant sepsis with associated mortality

Candida is a yeast, but also a fungus

Aspergillus is a mold, but also a fungus



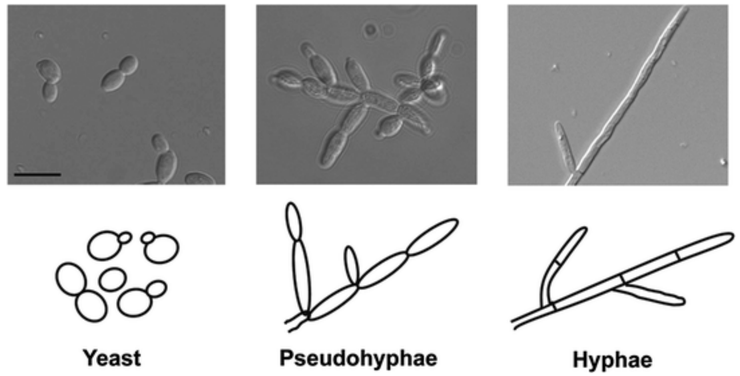
Candida spp. are commensal organisms

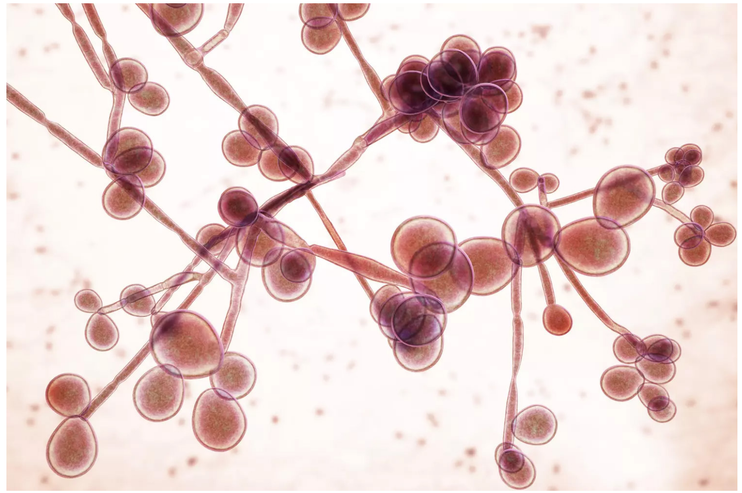
they colonize asymptomatically in many areas of the body, particularly the gastrointestinal tract and the genital area.

Under normal conditions the fungus is not causing harm or disease

This is the result of a proper equilibrium between host defense mechanisms and fungal biological properties

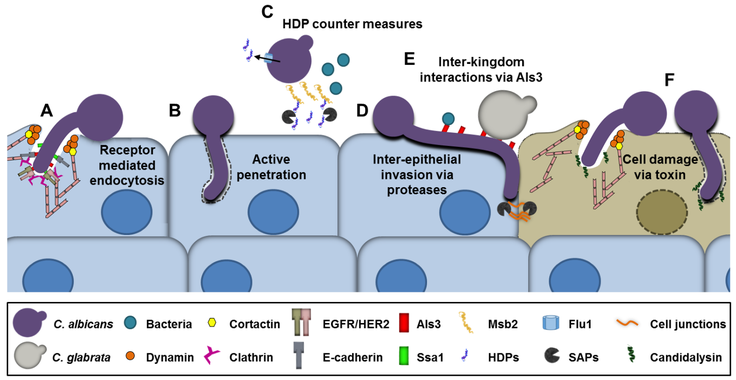
Grubb, Sarah EW, et al. "Candida albicans-endothelial cell interactions: a key step in the pathogenesis of systemic candidiasis." Infection and immunity 76.10 (2008): 4370-4377.

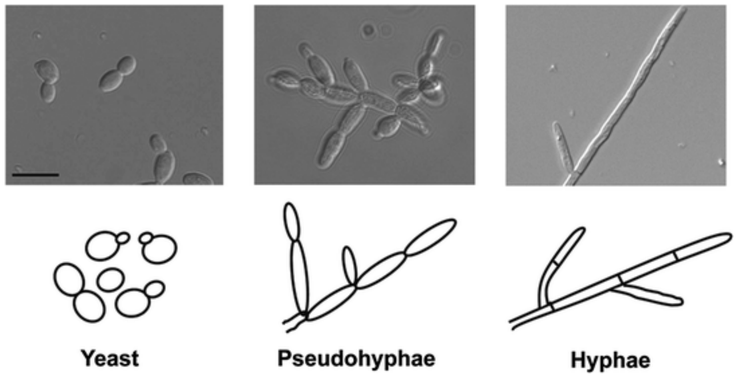


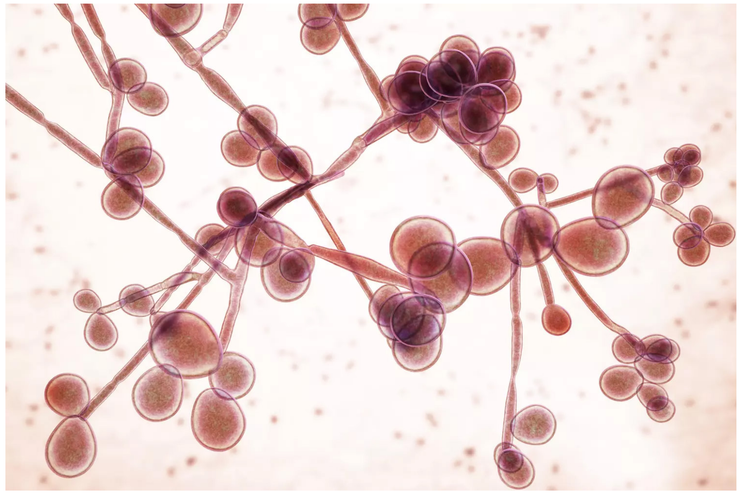


To infect host tissue, the unicellular form of candida is switching to a more invasive multicellular form

Candida can escape from our immune response: Phagocytized candida can pierce through immune cells and escape gaining access to all organ tissue throughout the body







Candida is using specialized proteins during the switch to virulent form

Adhesin allows adhesion
Invasin protein allows penetration

2 different ways have been described :

- Active penetration – with hyphae and simultaneous release of degrading enzymes
- Induced endocytosis

Adhesin & Invasin are both also involved in Biofilm formation

Felk, Angelika, et al. “Candida albicans hyphal formation and the expression of the Efg1-regulated proteinases Sap4 to Sap6 are required for the invasion of parenchymal organs.” Infection and immunity 70.7 (2002): 3689-3700.

Gabrielli, Elena, et al. “In vivo induction of neutrophil chemotaxis by secretory aspartyl proteinases of Candida albicans.” Virulence 7.7 (2016): 819-825.

Gow, Neil AR, et al. “Candida albicans morphogenesis and host defence: discriminating invasion from colonization.” Nature reviews microbiology 10.2 (2012): 112-122.

Netea, Mihai G., et al. “Immune defence against Candida fungal infections.” Nature Reviews Immunology 15.10 (2015): 630-642.

Netea, Mihai G., et al. “Immune sensing of Candida albicans requires cooperative recognition of mannans and glucans by lectin and Toll-like receptors.” The Journal of clinical investigation 116.6 (2006): 1642-1650.

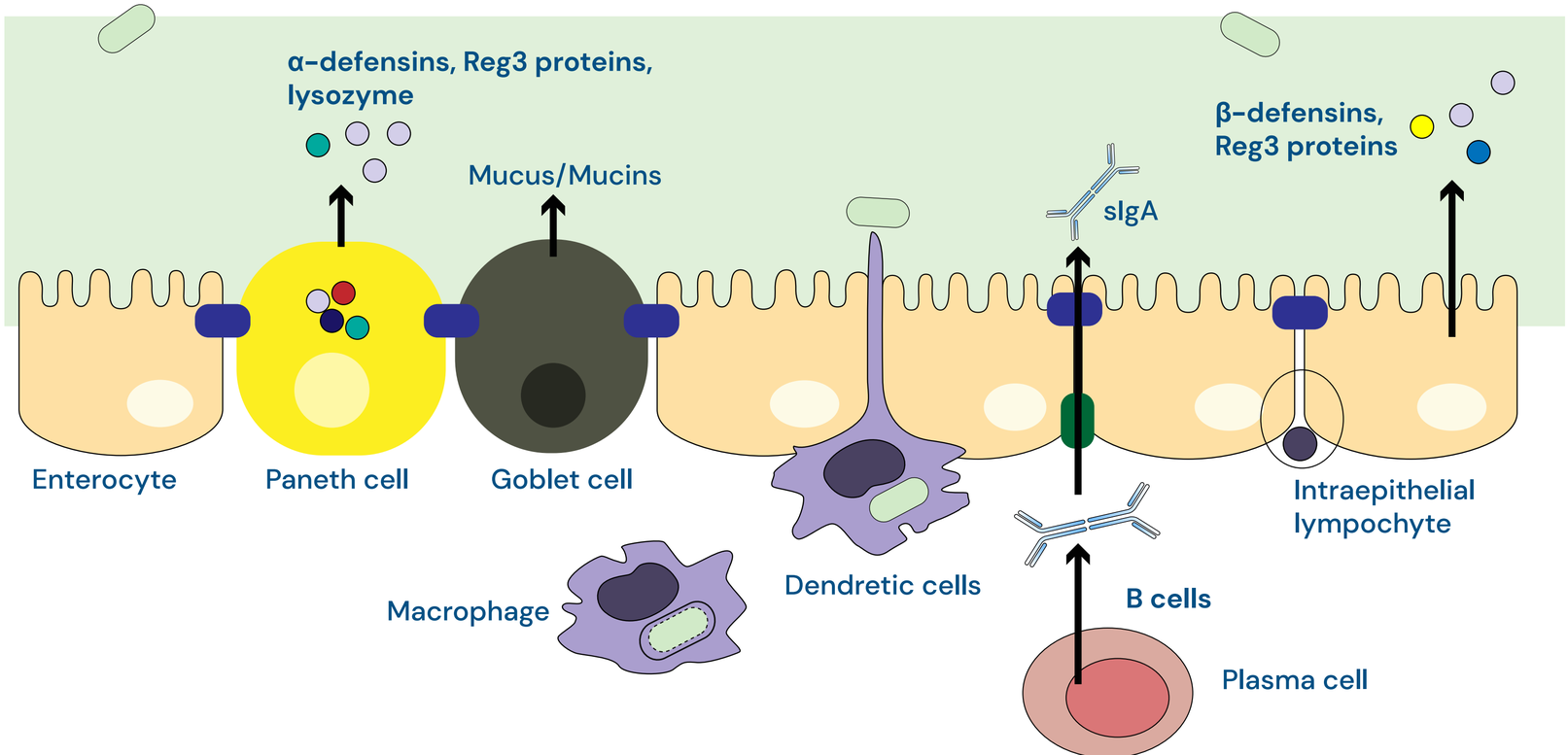
Marakalala, Mohlopheni J., et al. “Differential adaptation of Candida albicans in vivo modulates immune recognition by dectin-1.” PLoS pathogens 9.4 (2013): e1003315.

Wheeler, Robert T., et al. “Dynamic, morphotype-specific Candida albicans β-glucan exposure during infection and drug treatment.” PLoS pathogens 4.12 (2008): e1000227.

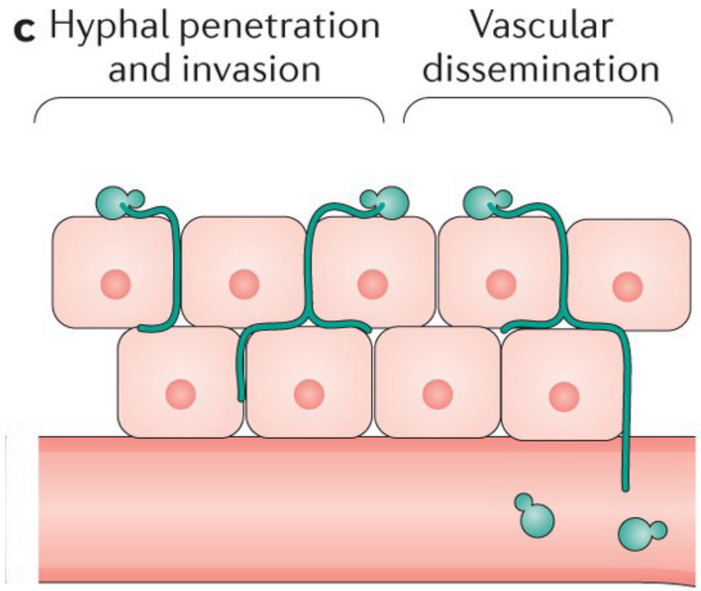
The Candida-induced epithelial damage is less severe in the intestinal lining than in oral cells.

The intestinal surface is better protected:

- A layer of mucus
- The secretion of s IgA's
- The production of anti-microbial molecules, such as defensins



Specific circumstances in which Candida alb. Transitions to a virulent form?



1. **perturbation of mucosal microbiota caused by long-term use or repeated use of broad spectrum antibiotics**
   Commensal gut microbiota species induce the release of anti-Candida spp. protective factors from the mucosa

   Antibiotics alter our microbiome and the release of protective factors
   = Candida spp.

   ↓

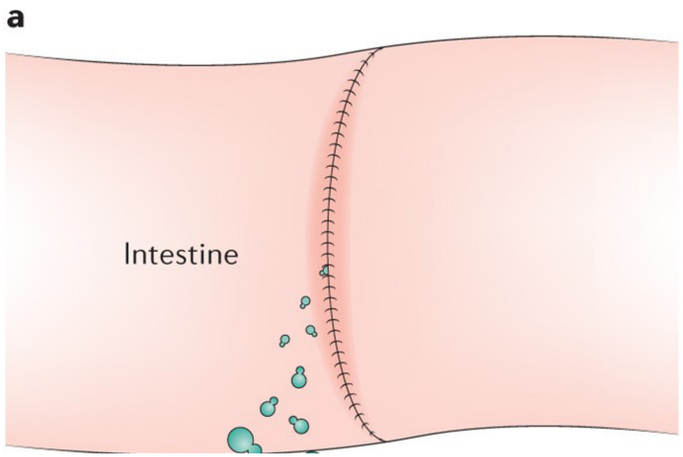
   Colonize, Penetrate, Invade

Kullberg, B. J. & Arendrup, M. C. Invasive candidiasis. N. Engl. J. Med. 373, 1445–1456 (2015).

Gow, N. A., van de Veerdonk, F. L., Brown, A. J. & Netea, M. G. Candida albicans morphogenesis and host defence: discriminating invasion from colonization. Nat. Rev. Microbiol. 10 112–122 (2011).

Netea, M. G., Joosten, L. A., van der Meer, J. W., Kullberg, B. J. & van de Veerdonk, F. L. Immune defence against Candida fungal infections. Nat. Rev. Immunol. 15, 630–642 (2015).

Fan, D. et al. Activation of HIF-1alpha and IL-37 by commensal bacteria inhibits Candida albicans colonization. Nat. Med. 21, 808–814 (2015).

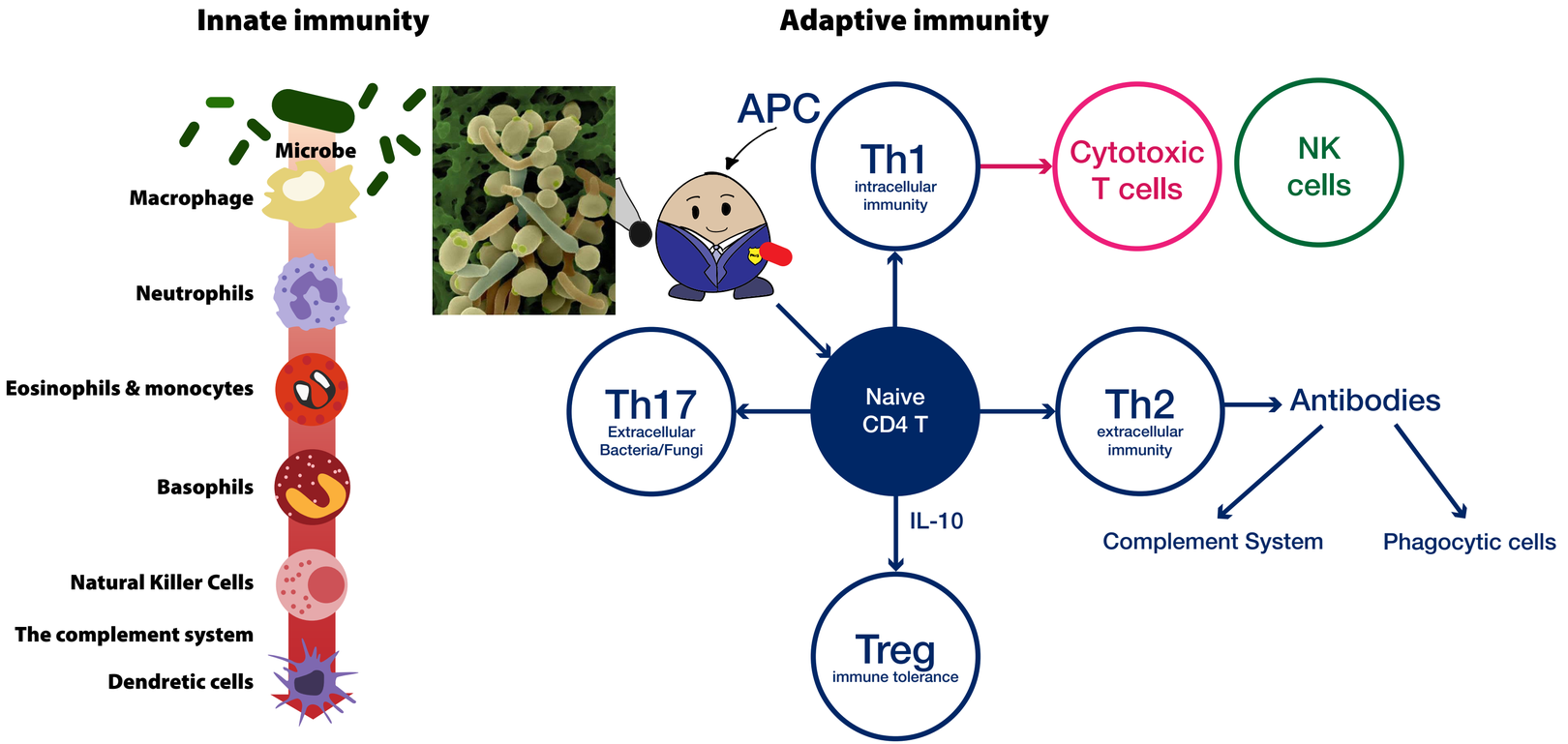


2. **Breach of the gastro-intestinal or cutaneous barriers**
   Mucositis induced by chemotherapy
   (mucosa of the GI tube are inflamed by cytotoxic chemotherapy)
   Gastro-intestinal surgery or perforation
   Central -venous catheters

   Variations in the local environment
   Shifts in PH or nutritional content

3. **Immunosuppression or poor immune response**
   Aging, cancer development, autoimmune disorders, stress
   Neutropenia , induced by chemotherapy
   Corticosteroid therapy’s impact on our innate immune defense

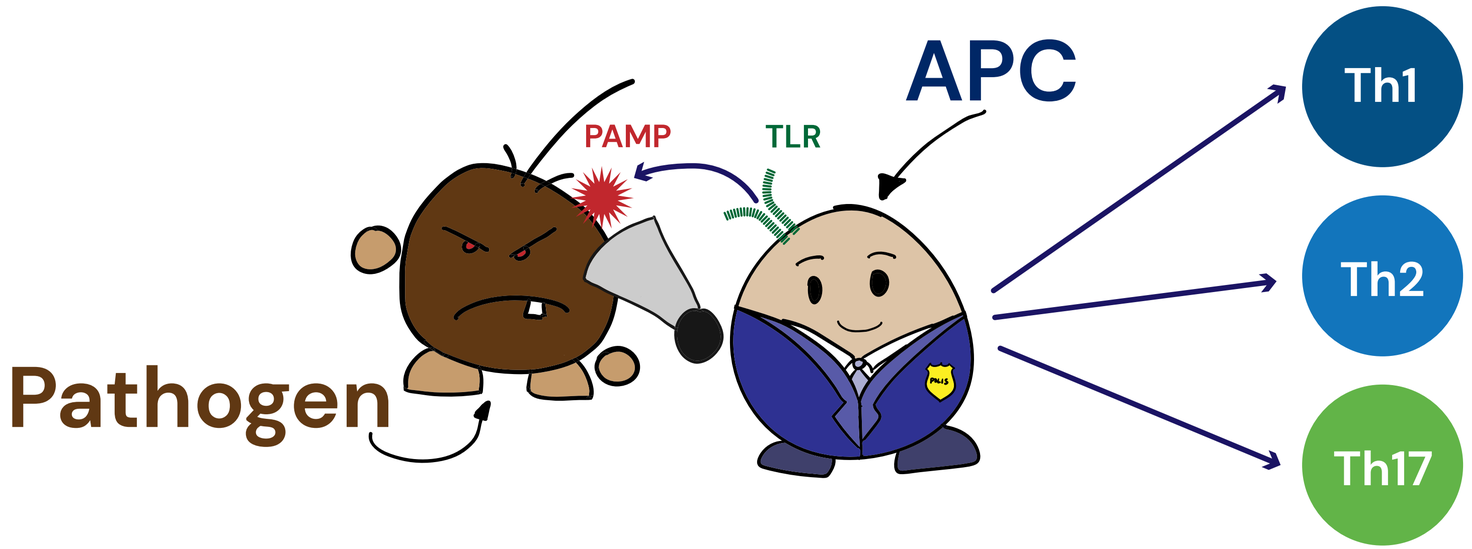
Understanding of fungal immunity



The innate immune system recognizes fungal pathogens

We develop a subsequent pathogen-specific adaptive immune response

Recognition elements for fungi = pattern recognition receptors



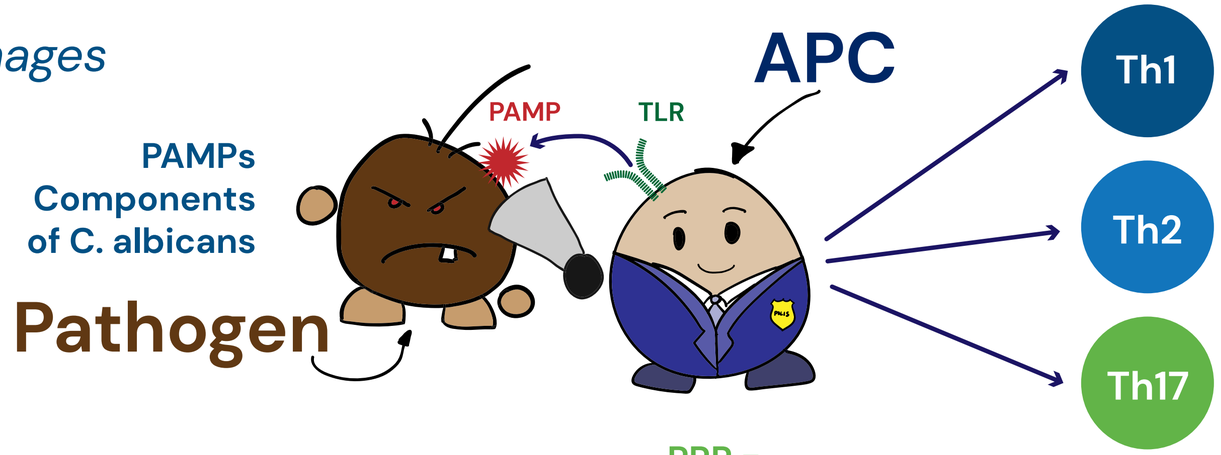
Recognition elements for fungi = pattern recognition receptors

Candida has a number of PAMPS

When PRR react on PAMPS, Candida starts to fight – producing proteins like adhesin & invasion

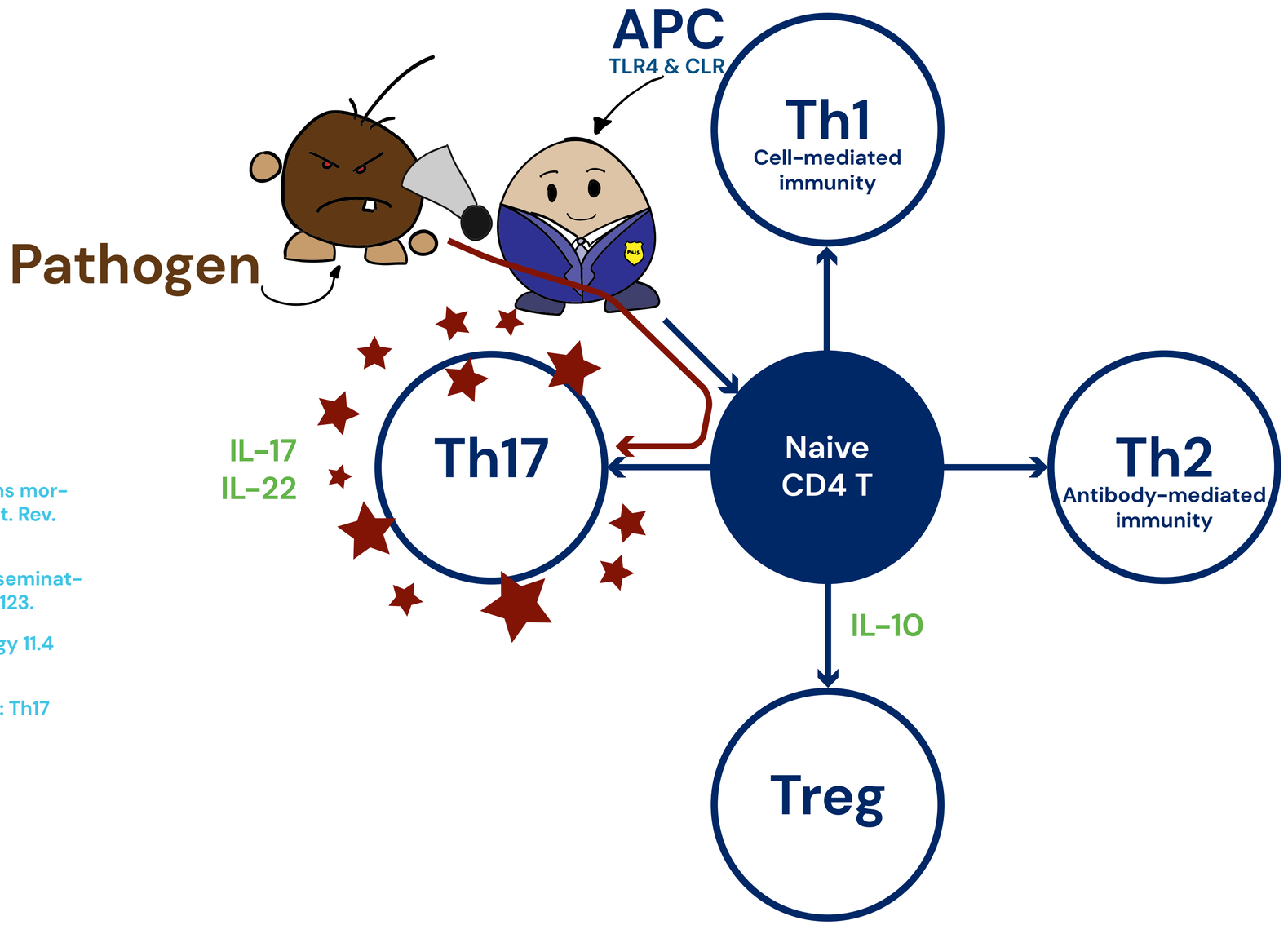
After detection by PRR, different mediators like NFKB are released
= signaling mechanism – they ask for more immune cells to fight Candida
= we set up an inflammation
The inflammation can become chronic if your macrophages are dysfunctional or if you can't convert monocytes into macrophages
+ more neutrophils are recruited
= chronic inflammation

It's problematic when this gets in a chronic loop



PRR =
Toll-like receptors (TLR)
C-type lectin receptors (CLR)

Cytokines promote the differentiation of CD4+ into the Th17 lineage



Gow, N. A., van de Veerdonk, F. L., Brown, A. J. & Netea, M. G. Candida albicans morphogenesis and host defence: discriminating invasion from colonization. Nat. Rev. Microbiol. 10 112–122 (2011).

Netea, Mihai G., et al. "Role of TLR1 and TLR6 in the host defense against disseminated candidiasis." FEMS Immunology & Medical Microbiology 52.1 (2008): 118-123.

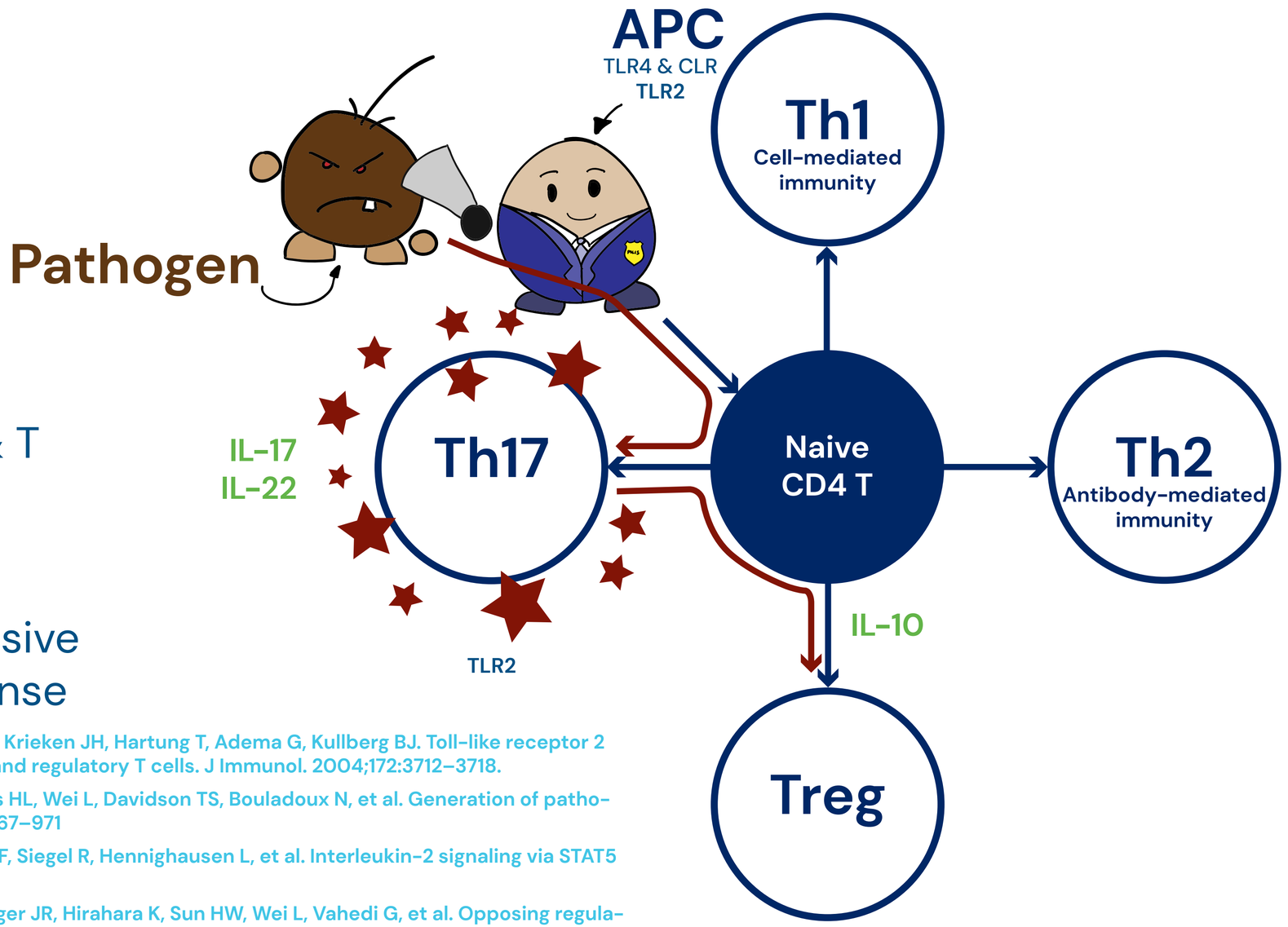
Romani, Luigina. "Immunity to fungal infections." Nature Reviews Immunology 11.4 (2011): 275-288.

Conti, Heather R., and Sarah L. Gaffen. "Host responses to Candida albicans: Th17 cells and mucosal candidiasis." Microbes and Infection 12.7 (2010): 518-527.

TLR2 has been shown to suppress inflammatory responses to Candida via production of IL-10 and enhanced T reg activity

Thus in addition to Th17 cells, we develop a T reg response we see an interplay between Th17 & T regs

Both required for effective host response to Candida without excessive inflammation or autoimmune response



Netea MG, Sutmuller R, Hermann C, Van der Graaf CA, Van der Meer JW, van Krieken JH, Hartung T, Adema G, Kullberg BJ. Toll-like receptor 2 suppresses immunity against Candida albicans through induction of IL-10 and regulatory T cells. J Immunol. 2004;172:3712–3718.

Ghoreschi K, Laurence A, Yang XP, Tato CM, McGeachy MJ, Konkel JE, Ramos HL, Wei L, Davidson TS, Bouladoux N, et al. Generation of pathogenic T(H)17 cells in the absence of TGF-beta signalling. Nature. 2010;467:967–971

Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, Blank RB, Meylan F, Siegel R, Hennighausen L, et al. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity. 2007;26:371–381

Yang XP, Ghoreschi K, Steward-Tharp SM, Rodriguez-Canales J, Zhu J, Grainger JR, Hirahara K, Sun HW, Wei L, Vahedi G, et al. Opposing regulation of the locus encoding IL-17 through direct, reciprocal actions of STAT3 and STAT5. Nat Immunol. 2011;12:247–254

Pandiyan P, Conti HR, Zheng L, Peterson AC, Mathern DR, Hernandez-Santos N, Edgerton M, Gaffen SL, Lenardo MJ. CD4(+)CD25(+)Foxp3(+) regulatory T cells promote Th17 cells in vitro and enhance host resistance in mouse Candida albicans Th17 cell infection model. Immunity. 2011;34:422–434

Life before Th17?

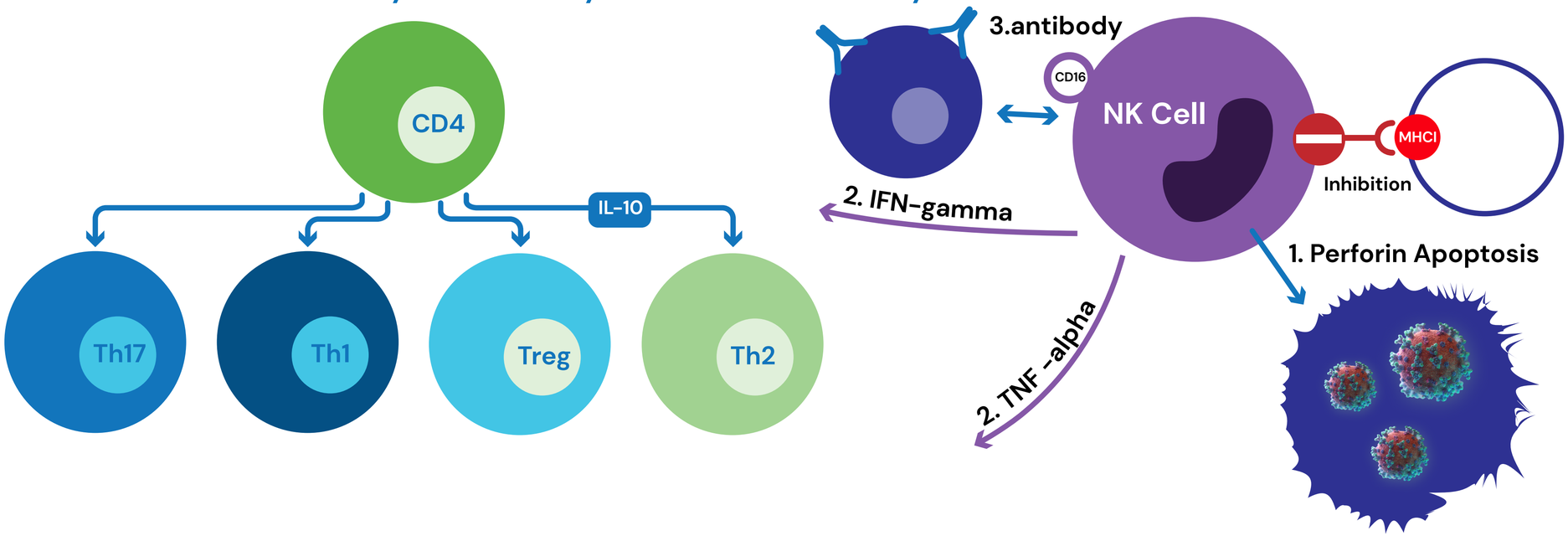
Th17 + T regs + Cell mediated immunity (Th1-NK cells)?

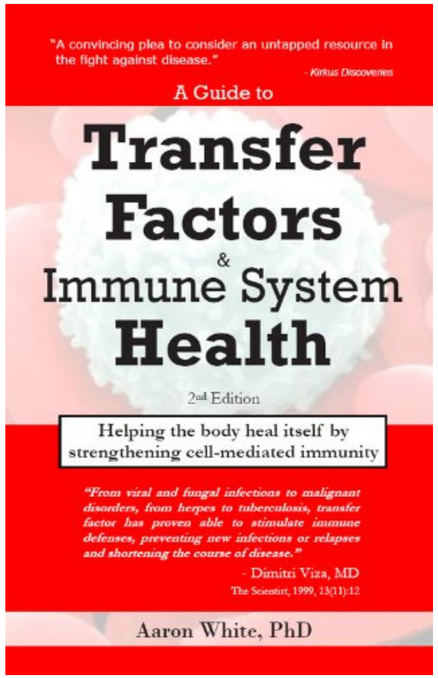
1. The importance of the Cell mediated immunity during the interplay Th17-T regs was dramatically illustrated during the AIDS pandemic

   HIV+ individuals were clearly more susceptible to many opportunistic fungal pathogens, including oral trush caused by C. Albicans

Activation

1. Degradation of the membranes of cells that have been infected by intracellular germs
   = lysis, using enzymes mainly perforin
2. Indirect elimination of target cells through production of inflammatory cytokines such as IFN-gamma & TNF-alpha
3. NK Cells express CD16 on their surface
   CD16 detects antibody-coated target cells which leads to cytotoxicity of the antibody-coated cells





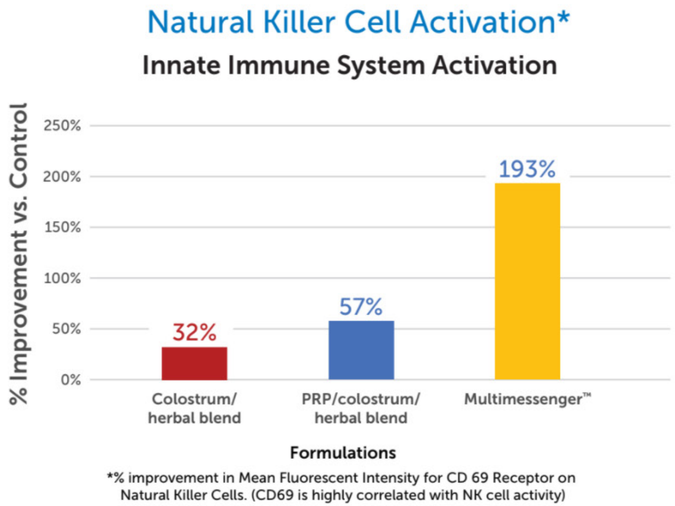
The activation of Natural Killer Cells through Transfer Factors is based on a direct interaction between Transfer Factors & activating receptors on the surface of NK cells

Conclusion and clinical features

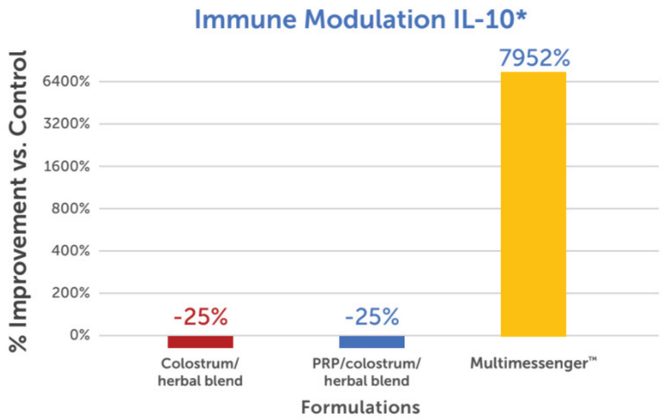
Transfer Factors (Multimessenger ®)

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

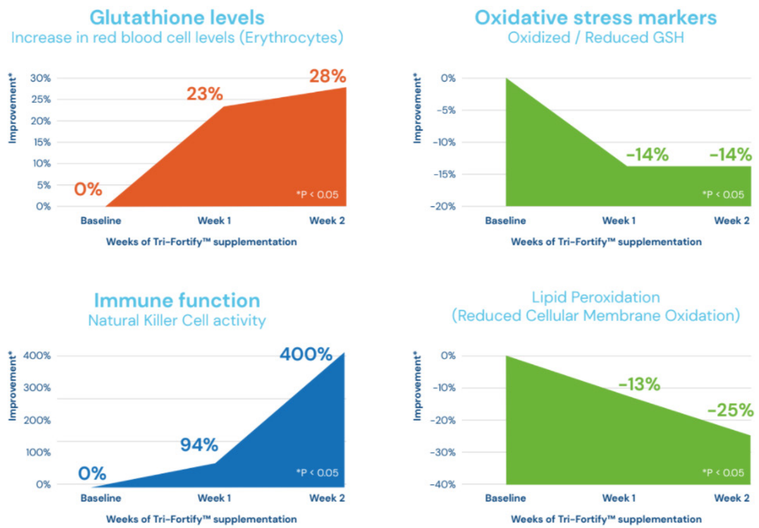
Multimessenger 1 x 3 caps just before breakfast in prevention
Multimessenger 2 x 3 caps just before meals during infection



*% 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)



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.

Liposomal Glutathione (TriFortify ®)

efficiently elevates intracellular levels of GSH and increases natural killer cell activity by reducing the adverse effects of oxidative stress on Natural Killer Cells

Trifortify 1 teaspoon separated from food in prevention
Trifortify 1 teaspoon several times per day during infection

How important are NK cells in the general picture?

1. NK cell depletion in immunocompetent mice did not increase susceptibility to C.albicans
2. NK cells depletion are essential if mice are immune suppressed, have defective T/B Lymphocyte immunity

Quintin, Jessica, et al. "Differential role of NK cells against Candida albicans infection in immunocompetent or immunocompromised mice." European journal of immunology 44.8 (2014): 2405-2414.

Th17 / Tregs + Th1/NK cells

Directives for performant immune modulation in fungal protection

Directives for development of vaccines against C .albicans

Proof of concept:
New researched drugs in treatment of autoimmune diseases, like rheumatoid arthritis and psoriasis, are antibodies targeting IL-17 expression.
As a side effect we see inevitably higher risk for
C. albicans infections

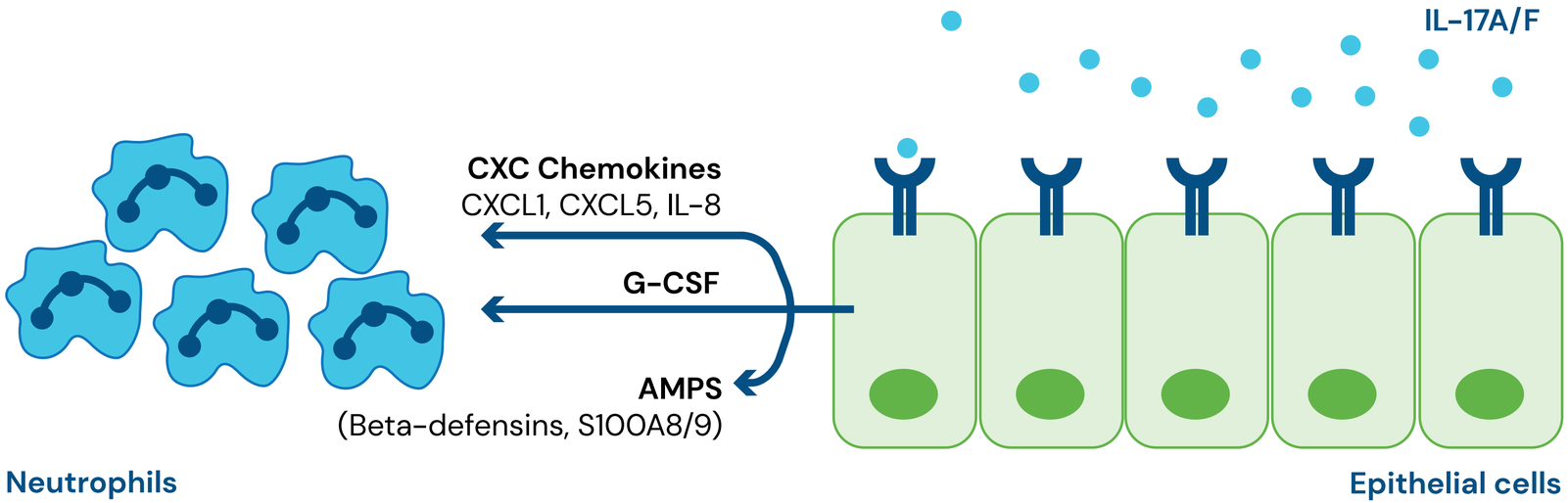
Lin, Lin, et al. "Th1-Th17 cells mediate protective adaptive immunity against Staphylococcus aureus and Candida albicans infection in mice." PLoS pathogens 5.12 (2009): e1000703

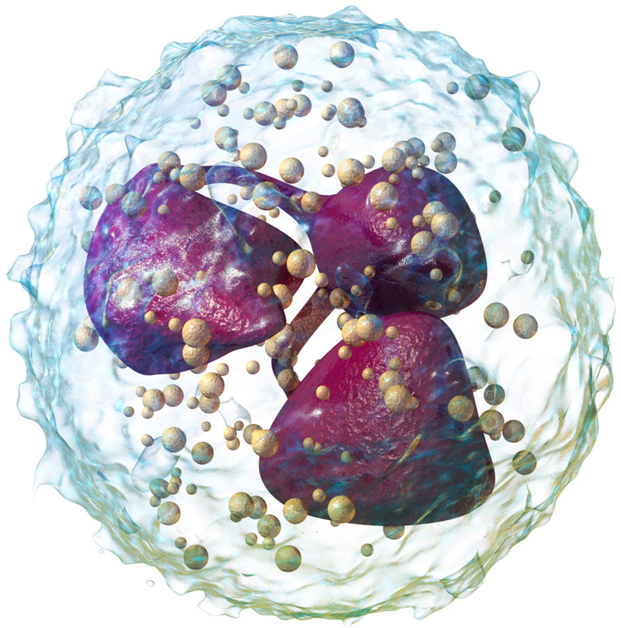
Strangfeld, Anja, and Joachim Listing. "Bacterial and opportunistic infections during anti-TNF therapy." Best Practice & Research Clinical Rheumatology 20.6 (2006): 1181-1195.

Farah, C. S., et al. "Distinct roles for interleukin□12p40 and tumour necrosis factor in resistance to oral candidiasis defined by gene□target-ing." Oral microbiology and immunology 21.4 (2006): 252-255.

Helping hands?

IL-17A & IL-17F, produced by TH17 cell , act on epithelial cells to induce the expression of neutrophil attracting chemokines





Neutrophils are professional killers and instructors of the immune system

- Neutrophils are the most abundant white blood cells in circulation
- Neutrophils are among the first responders to migrate toward the site of inflammation, chemotaxis

Neutrophils use different methods to eliminate germs?

1. **Phagocytosis**
2. **Degranulation**
   Neutrophils also release granules with antimicrobial properties: defensins, lysozyme, alkaline phosphatase, lactoferrin, collagenase, elastase and cathepsin, MPO (myeloperoxidase or NADPH oxidase)
3. **neutrophil extracellular traps (NETs)**
   A web of fibers is released to trap and kill microbes

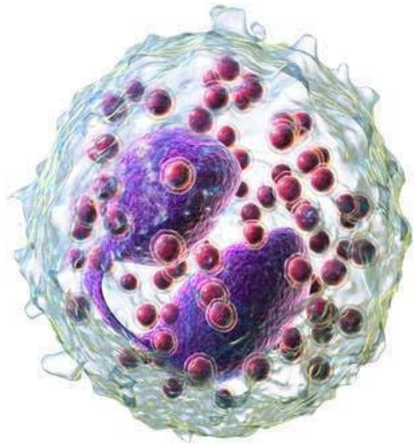
Lanza, Francesco. “Clinical manifestation of myeloperoxidase deficiency.” Journal of molecular medicine 76.10 (1998): 676-681.

Low neutrophil counts are termed Neutropenia

- Side effect of medication , most prominently chemotherapy
- Vit B12 deficiency
- Hyperglycemia

= Circumstances where we regularyly see fungal overgrowth...

Amulic, Borko, et al. “Neutrophil function: from mechanisms to disease.” Annual review of immunology 30 (2012): 459-489.



Eosinophils in fungal disease ?

Eosinophils, along with basophils and mast cells, are important mediators of allergic responses and asthma pathogenesis and are associated with disease severity.
They also fight helminth (worm) colonization and may be slightly elevated in the presence of certain parasites

Eosinophils are granulocytes, residing in tissue

The immunological mechanisms underlying direct effector interactions between fungi and eosinophils are still not fully known but we know that Dectin-1 receptors, recognizing fungal Beta-glucans, are expressed in human eosinophils

**Besides their roles as major pathogens,
fungi represent a source of major allergens**

Brown, Gordon D. "Dectin-1: a signalling non-TLR pattern-recognition receptor." Nature Reviews Immunology 6.1 (2006): 33-43.

Hardison, Sarah E., and Gordon D. Brown. "C-type lectin receptors orchestrate antifungal immunity." Nature immunology 13.9 (2012): 817-822.

Candida overgrowth & autoimmunity:

IL-17 will try to destroy the invading Candida
But IL-17 is a downregulator of T reg cells
= The link between Th17 & autoimmunity

Vojdani, A., et al. “Immunological cross reactivity between Candida albicans and human tissue.” Journal of clinical & laboratory immunology 48.1 (1996): 1-15.

Next to

This demonstration of immunological cross reactivity between Candida and human tissues show **a possible role between Candida Albicans and the development of autoimmune diseases**

Comorbidity or contributing factor?

Poor immunity
comorbidities like autoimmunity

↓

Candida albicans overgrowth

Candida albicans overgrowth

↓

Autoimmunity

Gürsoy, Semra, et al. "Autoimmunity and intestinal colonization by Candida albicans in patients with type 1 diabetes at the time of the diagnosis." Korean journal of pediatrics 61.7 (2018): 217.

Examination and culture of fresh stool samples in patients with Diabetes Type 1 show high prevalence of Candida albicans

Concerns?

- **We need rapid molecular diagnostics**
  (to intervene rapidly and possibly reduce mortality)

  Many clinicians still rely on physical examination or routine fungal cultures - low sensitivity or on empirical evidence (e.g.: sepsis in previously operated patient)

- **multidrug resistance in some species**, C. glabrata & C. auris
  (C. auris emerged as a major pathogen in some parts of the world)

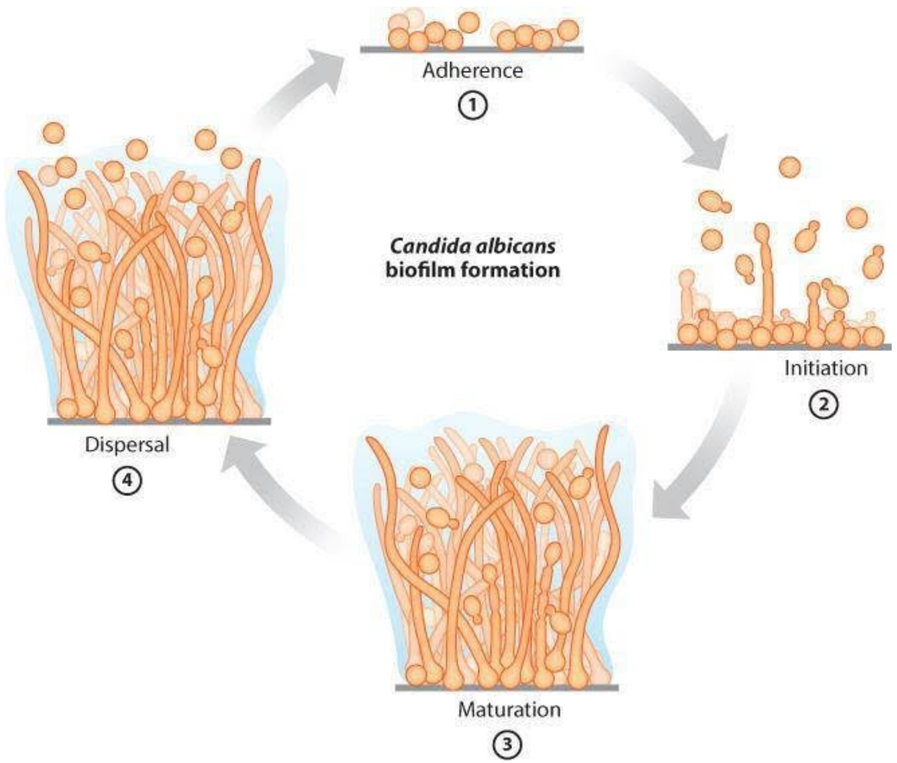
  Resistance to first-line antifungals like fluconazole or echinocandins in C. albicans are being recognized increasingly (often results of high usage in hospitals)

Anderson, James B. "Evolution of antifungal-drug resistance: mechanisms and pathogen fitness." Nature Reviews Microbiology 3.7 (2005): 547-556.

Bonhomme, Julie, and Christophe d'Enfert. "Candida albicans biofilms: building a heterogeneous, drug-tolerant environment." Current opinion in microbiology 16.4 (2013): 398-403.

Jabra-Rizk, Mary Ann, William A. Falkler, and Timothy F. Meiller. "Fungal biofilms and drug resistance." Emerging infectious diseases 10.1 (2004): 14.

- **Biofilm formation**
  the medical impact of C. albicans depends on its ability to thrive as a biofilm, a closely packed community of cells.
    - Biofilms form on implanted medical devices including catheters, pacemakers, dentures
    - Biofilms form on mucosal surfaces before they further invade



The 4 stages of biofilm formation in C. albicans

1. Adherence to a surface (and to each other)
2. Proliferation
3. Growth of hyphae
   The entire biofilm is encased in an extracellular matrix
4. Dispersal of yeast-form cells to form new sites (they are spread in the original round yeast form)

Multispecies Biofilms with C. albicans

We have learned from studies that **C. albicans and bacteria / other pathogen can interact with each other by secretion of signaling molecules** that influence the behavior of one species toward the other.

C. albicans interacts with several bacteria found in the gut,
like Enterococcus and Escherichia species

C. albicans forms **dual-species biofilms** with Streptococcus mutans, commonly isolated from denture stomatitis,
periodontitis or dental caries

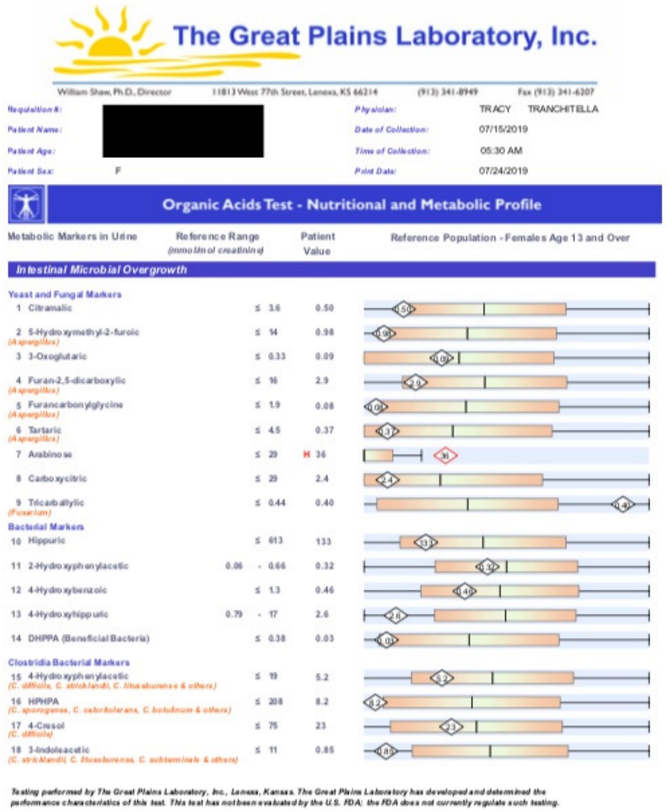
Bamford, Caroline V., et al. “Streptococcus gordonii modulates Candida albicans biofilm formation through intergeneric communication.” Infection and immunity 77.9 (2009): 3696-3704.

Jack, Alison A., et al. “Streptococcus gordonii comCDE (competence) operon modulates biofilm formation with Candida albicans.” Microbiology 161.Pt 2 (2015): 411.

Jarosz, Lucja M., et al. “Streptococcus mutans competence-stimulating peptide inhibits Candida albicans hypha formation.” Eukaryotic cell 8.11 (2009): 1658-1664.

Adam, Berit, George S. Baillie, and L. Julia Douglas. “Mixed species biofilms of Candida albicans and Staphylococcus epidermidis.” Journal of medical microbiology 51.4 (2002): 344-349.

Nobile, Clarissa J., and Alexander D. Johnson. “Candida albicans biofilms and human disease.” Annual review of microbiology 69 (2015): 71-92.



The Great Plains Laboratory, Inc.

William Shaw, Ph.D., Director 11813 West 77th Street, Lenexa, KS 66214 (913) 341-8949 Fax (913) 341-6207

Requisition #:
Patient Name: [redacted]
Patient Age:
Patient Sex: F
Physician: TRACY TRANCHITELLA
Date of Collection: 07/15/2019
Time of Collection: 05:30 AM
Print Date: 07/24/2019

Organic Acids Test - Nutritional and Metabolic Profile

Metabolic Markers in Urine	Reference Range (mmol/mol creatinine)	Patient Value	Reference Population - Females Age 13 and Over
Intestinal Microbial Overgrowth			
Yeast and Fungal Markers			
1 Citramalic	≤ 3.6	0.50	
2 5-Hydroxymethyl-2-furoic (*Aspergillus*)	≤ 14	0.98	
3 3-Oxoglutaric	≤ 0.33	0.09	
4 Furan-2,5-dicarboxylic (*Aspergillus*)	≤ 16	2.9	
5 Furancarbonylglycine (*Aspergillus*)	≤ 1.9	0.08	
6 Tartaric (*Aspergillus*)	≤ 4.5	0.37	
7 Arabinose	≤ 29	H 36	
8 Carboxycitric	≤ 29	2.4	
9 Tricarballylic (*Fusarium*)	≤ 0.44	0.40	
Bacterial Markers			
10 Hippuric	≤ 613	133	
11 2-Hydroxyphenylacetic	0.06 - 0.66	0.32	
12 4-Hydroxybenzoic	≤ 1.3	0.46	
13 4-Hydroxyhippuric	0.79 - 17	2.6	
14 DHPPA (Beneficial Bacteria)	≤ 0.38	0.03	
Clostridia Bacterial Markers			
15 4-Hydroxyphenylacetic (*C. difficile, C. sticklandii, C. litsuboumse & others*)	≤ 19	5.2	
16 HPHPA (*C. sporogenes, C. saccharolyticum, C botulinum & others*)	≤ 208	8.2	
17 4-Cresol (*C. difficile*)	≤ 75	23	
18 3-Indoleacetic (*C. sticklandii, C. thiosulfatireducens, C. subterminale & others*)	≤ 11	0.85	

Testing performed by The Great Plains Laboratory, Inc., Lenexa, Kansas. The Great Plains Laboratory has developed and determined the performance characteristics of this test. This test has not been evaluated by the U.S. FDA; the FDA does not currently regulate such testing.

Modern diagnostical methods detect Fungal Toxins

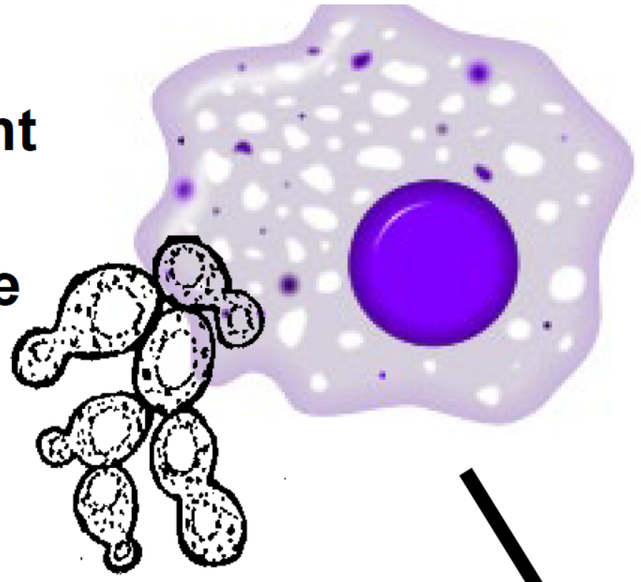
1. **Arabinose**
   is an indicator of invasive Candida reflective of systemic infection

2. **OAT Organic Acid Test**

Hyaluronic acid
Intercellular cement

hyaluronidase

Candida



Human macrophage

Kills Candida

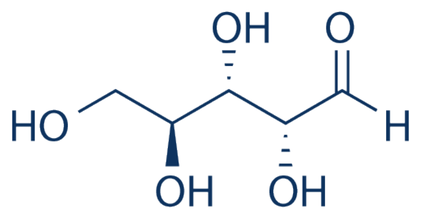
-acetyl
lucosamine,
lucuronic acid

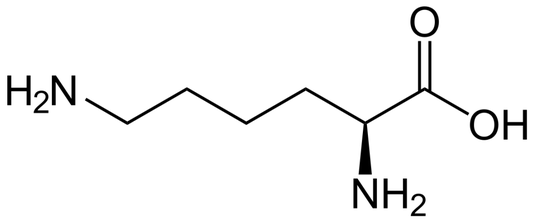
Myeloperoxidase-WBC enzyme
response to Candida infection

ClO^-

Arabinose,
Tartaric acid

Hypochlorite ion - *powerful oxidizing agent-tissue damage*
Active ingredient of Clorox®





Arabinose is a very toxic metabolite

The aldehyde is a very reactive group, can bind with the amino acid Lysine

Lysine

Some Nutrients help blocking the binding of the aldehyde group to lysine:

- Biotin
- Vit B6
- R- Alpha-Lipoic Acid

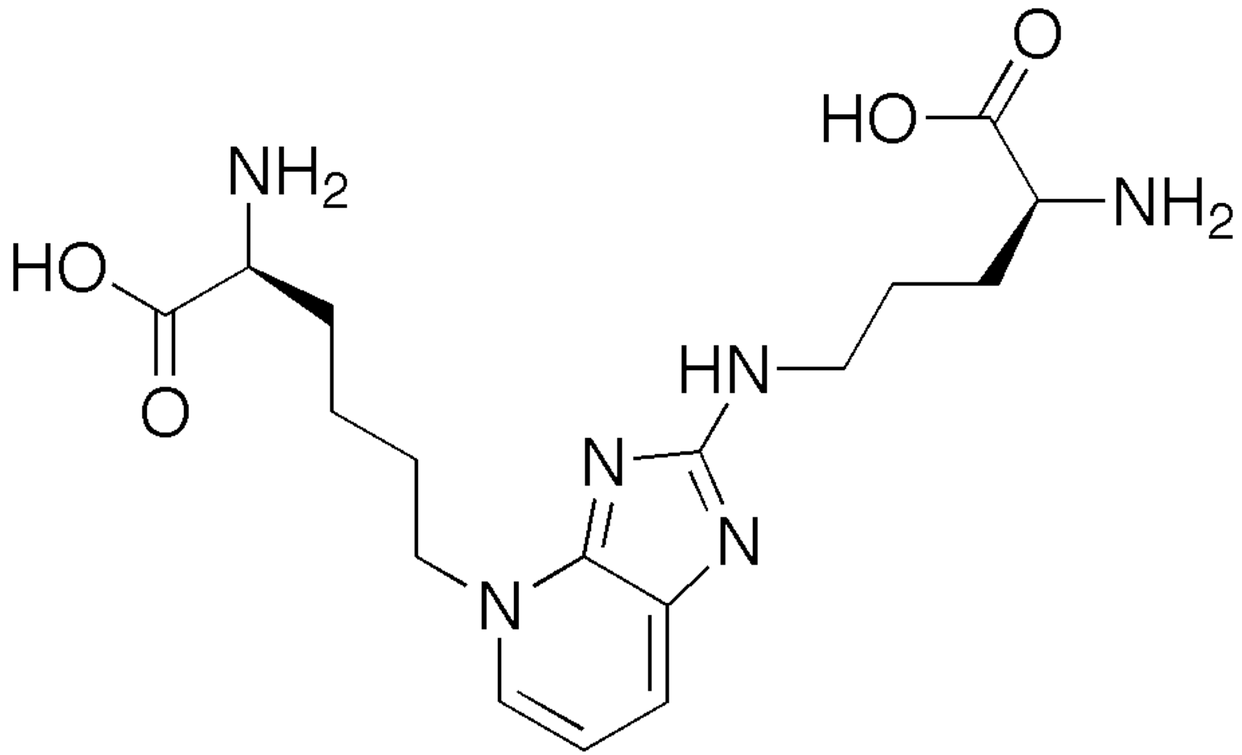
We need specific nutrients to break down aldehydes: Glutathione (bio-available)

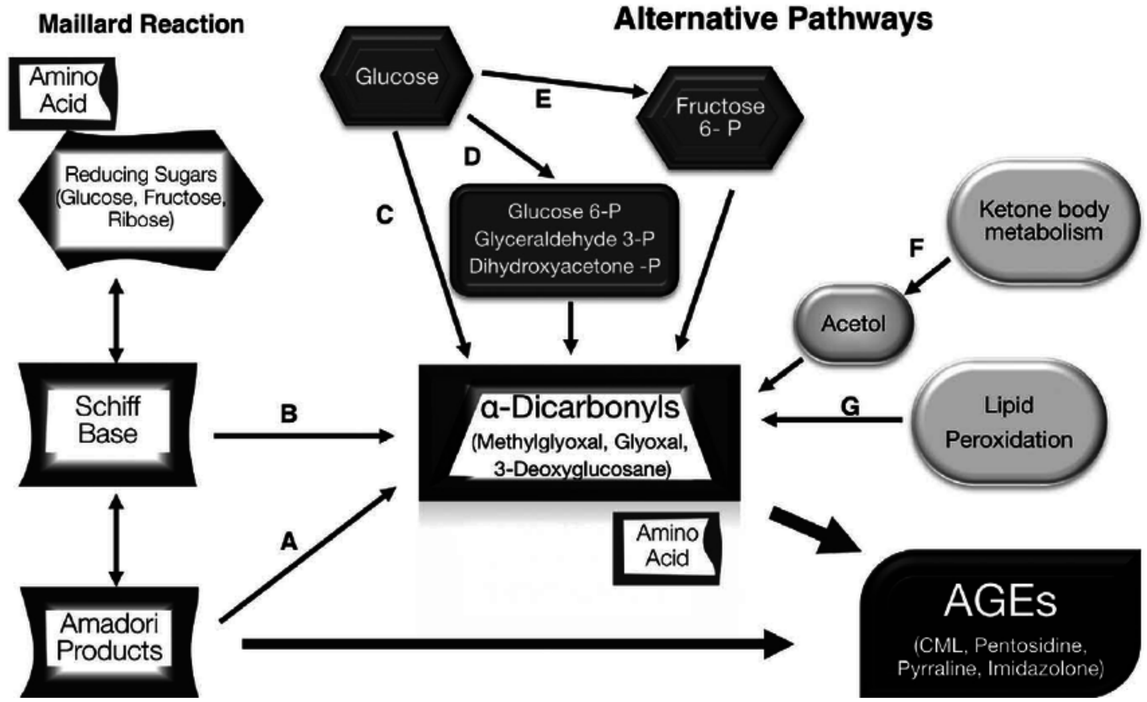
Jurnak, Frances. “The pivotal role of aldehyde toxicity in autism spectrum disorder: the therapeutic potential of micronutrient supplementation.” Nutrition and metabolic insights 8.Suppl 1 (2015): 57.

Pentosidine

Arabinose can complex with the amino acid Lysine
which then interacts with the amino acid Arginine to form the toxic byproduct called Pentosidine

Arabinose-Lysine complex + Arginine = Pentosidine





Different pathways for advanced glycation end products formation in vivo: (A) nonoxidative Amadori product cleavage, (B) Namiki pathway, (C) Wolff pathway, glucose autoxidation, (D) glycolytic pathway, (E) polyol pathway, (F) ketone body and threonine metabolism, (G) lipid peroxidation

Pentosidine falls under the category of Advanced Glycation End Products (AGE's)

AGE's are proteins, amino acids & lipids that become altered when exposed to sugars

source: Kurt Woeller, DO Great Plains, The Link between Invasive Candida & Various health issues

Pentosidine

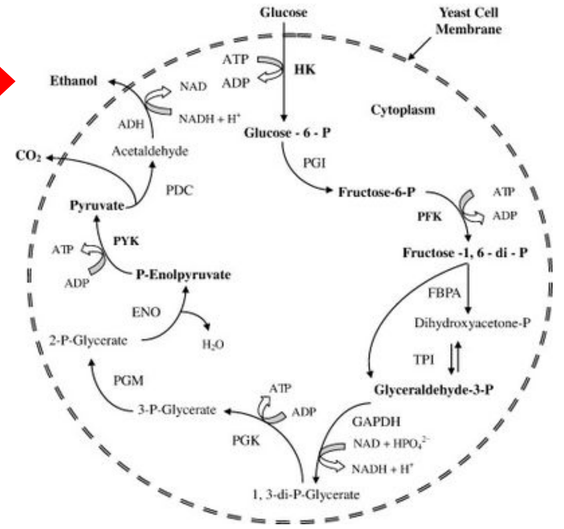
- Decreases enzyme activity
- Decreases flexibility of proteins in collagen and muscle tissue
- Damages myelin
- Induces kidney problems & cardiovascular issues

Fungal Toxicity

Candida converts glucose in alcohol, via acetaldehyde

Yeast can ferment carbohydrates into acetaldehyde & alcohol

Alcohol ⟶



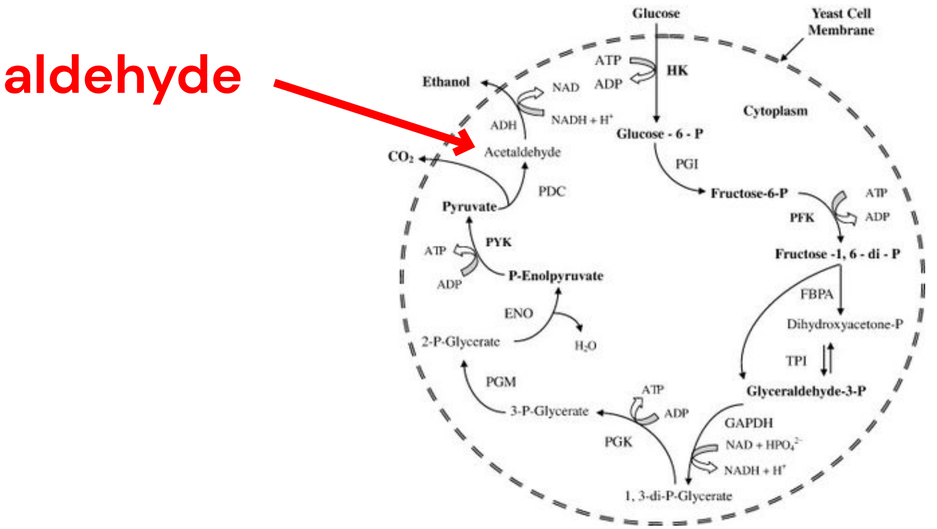
Drunk without consuming alcohol?

The Auto-Brewery Syndrome

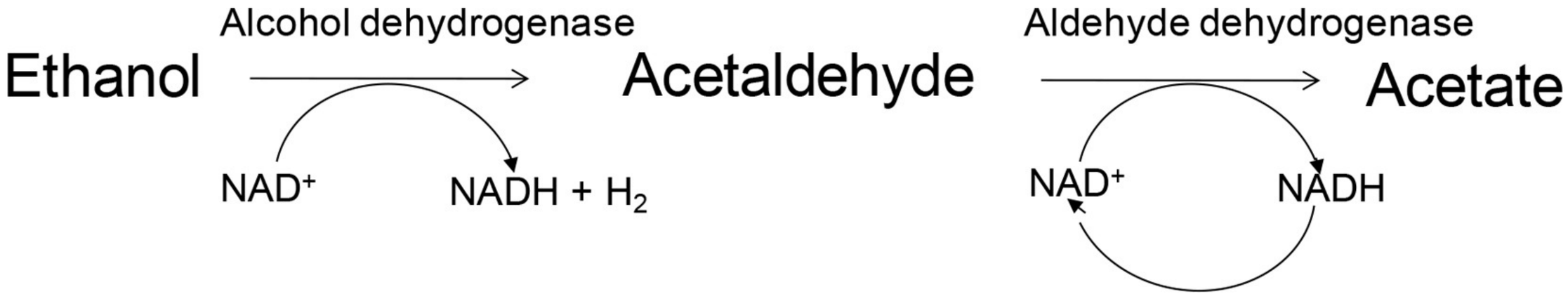
But Acetaldehyde can also be produced,

Plants, yeast and bacteria can ferment glucose into Acetaldehyde

Acetaldehyde



We see the same symptoms of acetaldehyde toxicity in alcohol overconsumption



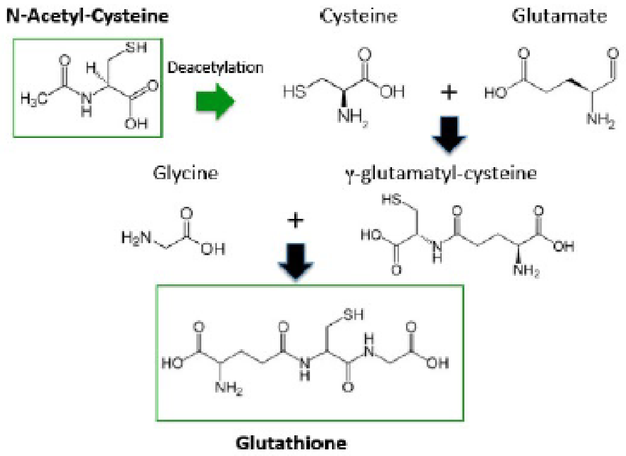
Accumulation of acetaldehyde manifests as

- Facial flushing
- Nausea
- Rapid heart beat

Symptoms we see in hangover, overconsumption of alcohol – but possibly also in Candida overgrowth

Acetaldehyde depletes Glutathione

Acetaldehyde binds gamma -Glutamyl Cysteine and prevents the binding to Glycine
= it blocks the formation of Glutathione



Acetaldehyde detoxification:

Liposomal Glutathione (Trifortify 1 teaspoon/day)

NAD+ precursors (CogniFuel NAD+/PQQ 3x1/day)

Vit B complex in active form (Cofactor B Complex 1/day)

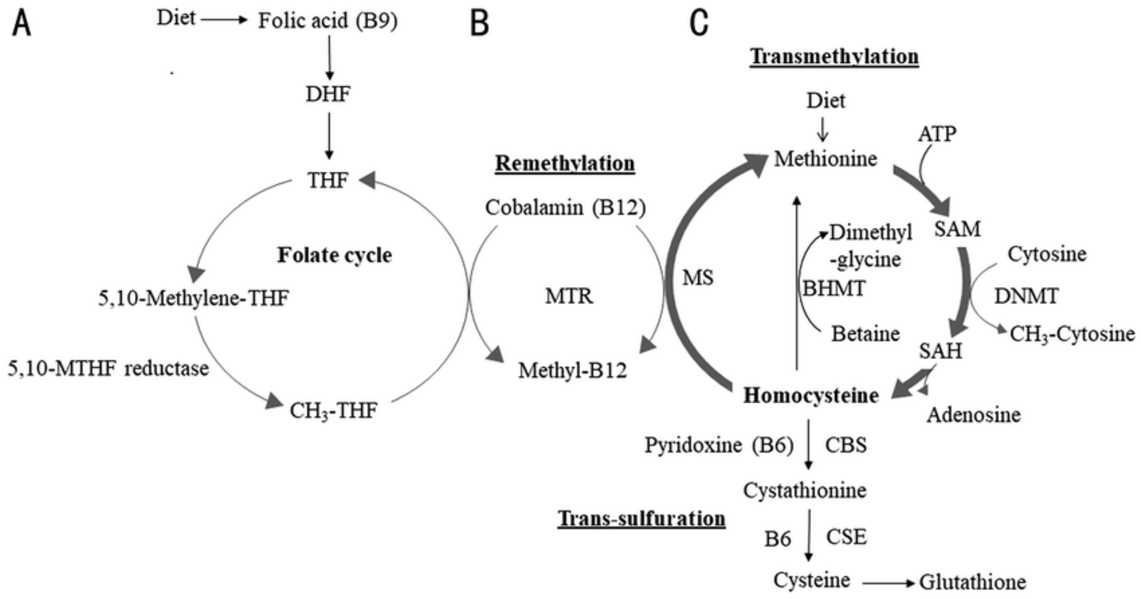
Molybdenum (Physician's Daily 1/day)

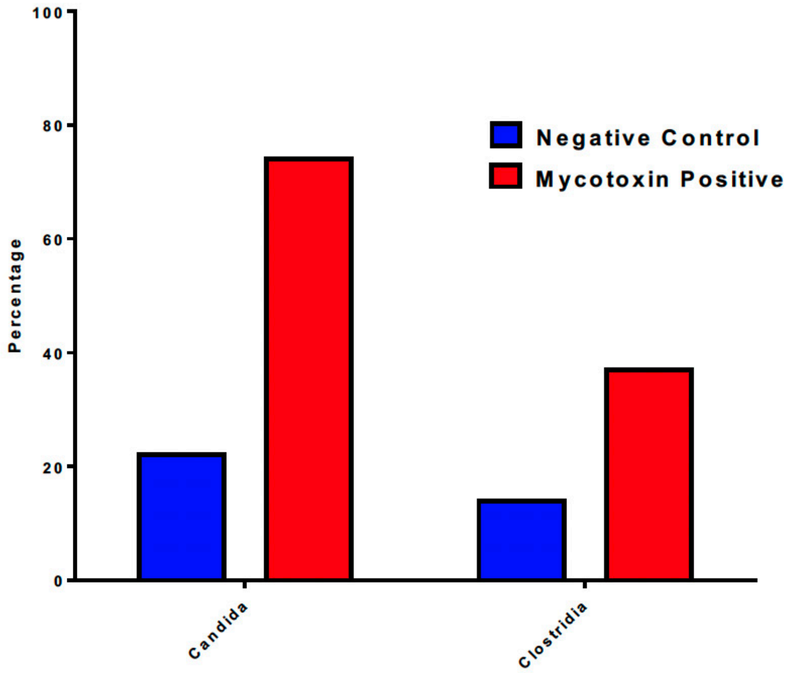
OAT & regular Labs show B2 deficiencies

Anni H, Pristatsky P, Israel Y. Binding of acetaldehyde to a glutathione metabo- lite: mass spectrometric characterization of an acetalde- hyde-cysteinylglycine conjugate. Alcohol Clin Exp Res. 2003;10:1613-1621.

Accumulation of Acetaldehyde inhibits MS (Methionine Synthetase) in the Methylation pathway

Kenyon, Susan H., Anna Nicolaou, and William A. Gibbons. "The effect of ethanol and its metabolites upon methionine synthase activity in vitro." Alcohol 15.4 (1998): 305-309.





More OAT markers in Candida overgrowth

- Oxolate metabolites (oxalic)

Oxalic elevated in Candida infections, Aspergillus, Clostridium overgrowth or dietary origin

Candida – Clostridium?

Candida disrupts microbiome and causes advantage for Clostridium

Oxalates

Drive pain & inflammation!

oxalate acid?

Metabolite produced by Candida
Oxalic acid often referred as oxalates (the conjugate)

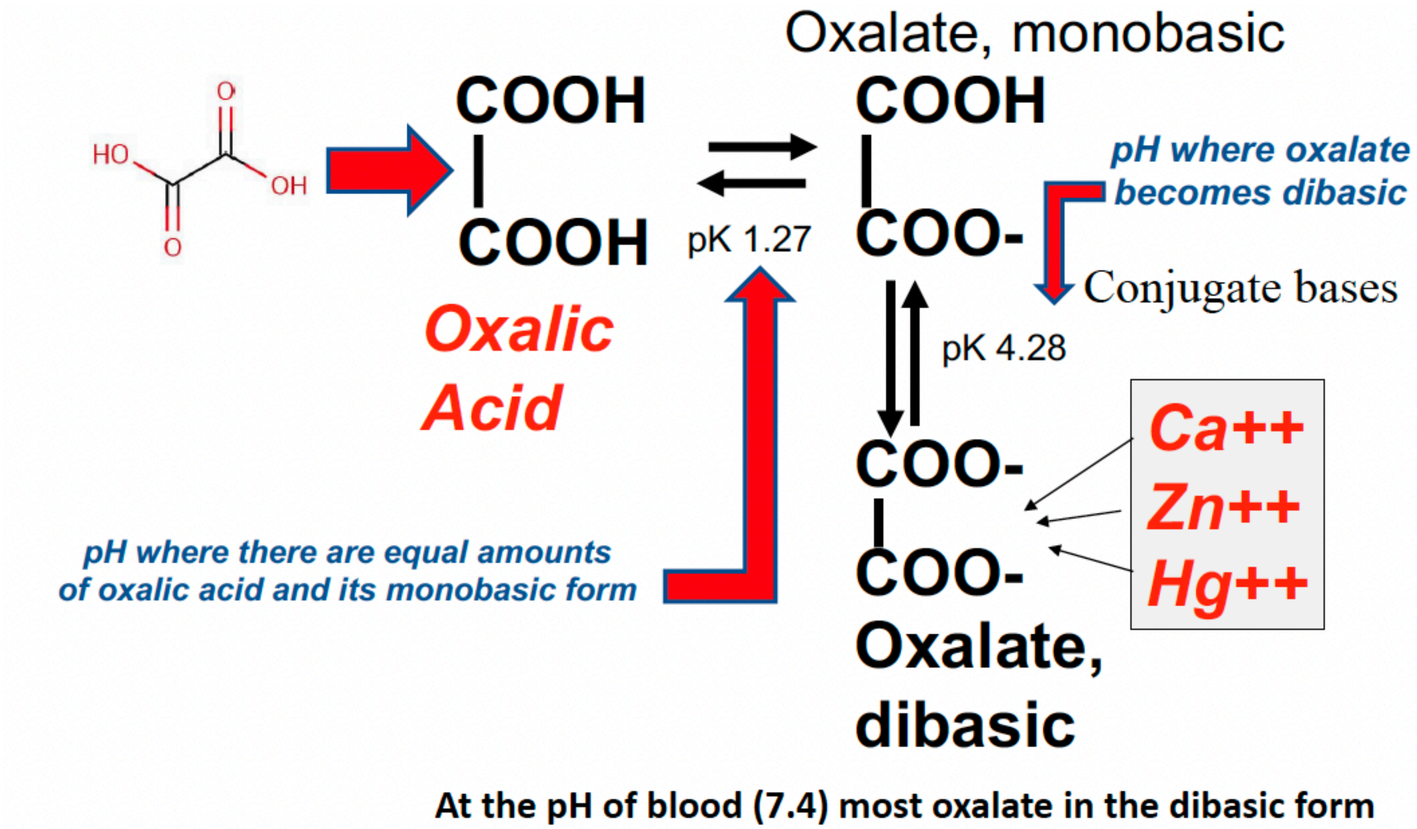
source: Kurt Woeller, DO Great Plains, The Link between Invasive Candida & Various health issues

Candida produces oxalates

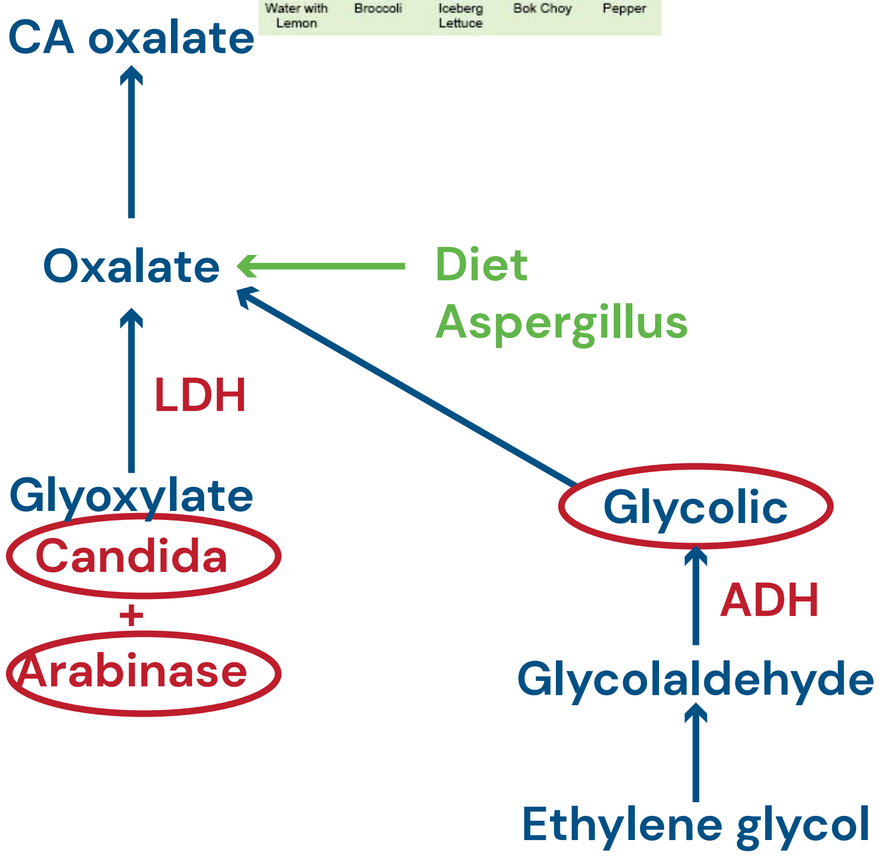
Conjugates can be formed with minerals like Calcium
The insoluble conjugates will be deposited like crystals in different tissues, like

- **Bone**
- **Brain**
- **Kidneys** (main damage to kidneys + kidney stones)
  The majority of the kidney stones are Calcium Oxalate
  It is the oxalate level in the blood which tends to drive calcium (or other mineral/metal) oxalate crystal formation in tissues.
- **Nerve tissue**
- **Thyroid gland**
- **Deposition of crystals in lungs in Aspergillus or Candida infections**

The interconversions of the Oxolates



At the pH of blood (7.4) most oxalate in the dibasic form

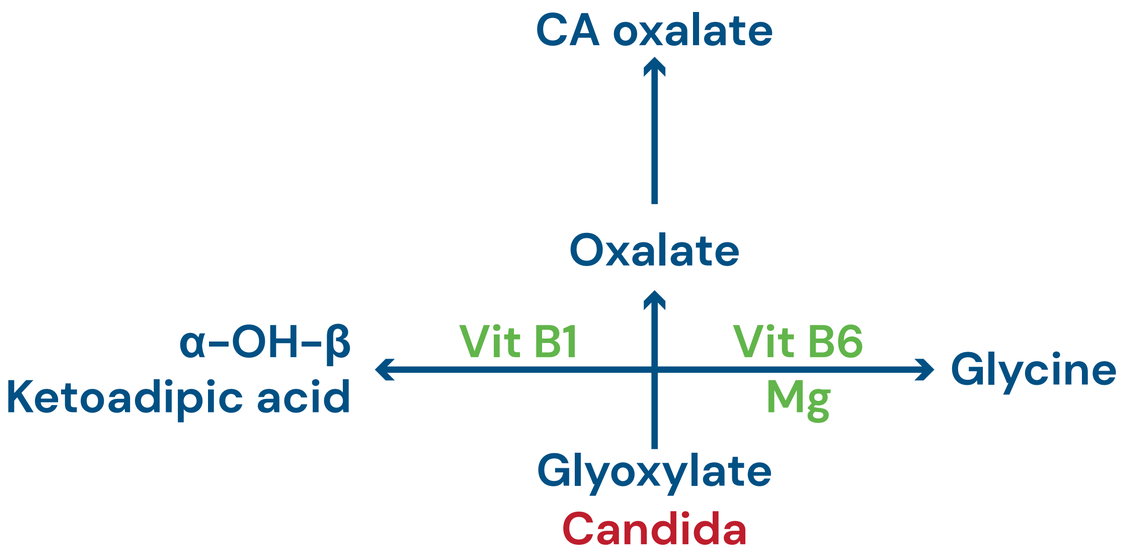


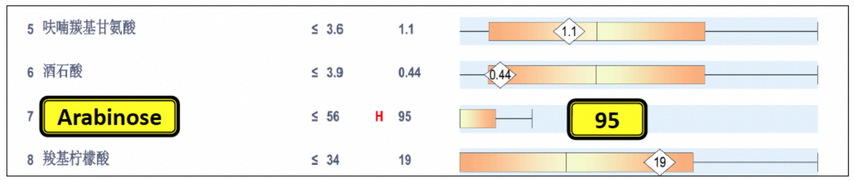
Other sources of oxalates:

1. **Diet**
   - Follow a low oxalate diet , while you are addressing the underlying cause
   - Cooking vegetables will reduce oxalate levels with 50%
2. **Aspergillus and Mold /Mycotoxins**
   If you can't entirely eliminate with adapting diet, often underlying Yeast or Mold infections contribute

More sources of oxalates:

3. **Fat malabsorption**
   Unabsorbed free fatty acids can bind to Calcium in the gut.
   More oxalates are absorbed systemically.
4. **Monsanto's Glyphosate**
   Oxalates were added to Roundup to enhance the herbicidal effectiveness
5. **Foods containg PEG (Polyethylene glycol)**
   in sports drinks, laxatives
   + PEG is main ingredient in antifreeze
6. **Genetics, enzyme dysfunction**





Nutritional deficiencies in Vit B1, Vit B6 & Magnesium can contribute

Supplemental use of bio-active Magnesium & Co-activated Vit B complexes is advised

Cofactor B Complex 1/day

Magnesium Malate 2x2/day

Lyon, E. S., et al. "Calcium oxalate lithiasis produced by pyridoxine deficiency and inhibition with high magnesium diets." Investigative
Urology 4.2 (1966): 133-142.dehyde-cysteinylglycine conjugate. Alcohol Clin Exp Res. 2003;10:1613-1621.

References

Finkielstein, V., Goldfarb, D., (2006). Strategies for preventing calcium oxalate stones. Canadian Medical Association Journal , 174 (100). Published online doi: 10.1503/cmaj.051517

Herb, Nutrient, and Drug Interactions. (1st edition). (2008). St. Louis, MO, Mosby, Elsevier

Liebman, M., Costa, G. (2000). Effects of calcium and magnesium on urinary oxalate excretion after oxalate loads. Journal of Urology, 163(5): 1565-1659.

Matkovic, V., Heaney, R.P., (1992). Calcium balance during human growth: evidence for threshold behavior. The American Society for Clinical Nutrition, 55(5): 992-996.

Pennistion, K., Nakada, S. (2009). Effect of Dietary Changes on Urinary Oxalate Excretion and Calcium Oxalate Supersaturation in Patients With Hyperoxaluric Stone Formation. Urology, 73(3):484-489.

Physicians Desk Reference for Nutritional Supplements. (2nd edition). (2008). Montvale, NJ: Thomson PDR

Rushton, HG., Spector, M. (1982). Effects of magnesium deficiency on intratublar calcium formation and crystalluria in hyperoxaluric rats. Journal of Urology, 127(3): 598-604.

Poore, R.E., Hurst, C.H., Assimos, D.G., Holmes, R.P. (1997). Pathways of hepatic oxalate synthesis and their regulation. Cell Physiology. 272(1), C289-C294

Shaw, W. (2009). Autism: Beyond the Basics. Self Published, USA.

Weaver, C. (1994). Age related calcium requirements due to changes in absorption and utilization. Journal of Nutrition, 124(8): 1418S-1425S.

Consider oxalates if patients have unexplained symptoms:

- Poor sleep
- Fibromyalgia
- Vulvar pain
- Joint pains
- Incontinence
- Kidney stones
- Fatigue

Treatment

- **Treat the underlying infection**
  Candida, Aspergiullus, Mold
- **Adapt diets & avoid foods high in oxalates**
- **Hydrate**
- **Vitamin B supplements in bio-active form**
  Cofactor B Complex 1/day during breakfast
- **Magnesium & Calcium supplements**
  Magnesium malate 2 x 1 - 2 /day
- **Epsom Salt? Glucosamine Sulphate?**
  Oxalates and sulphates use the same transporters
  Use Sulphate like Glucosamine sulphate
  (or Epsom Salt baths)

Candida overgrowth and the overlap with neuroinflammation & Autism?

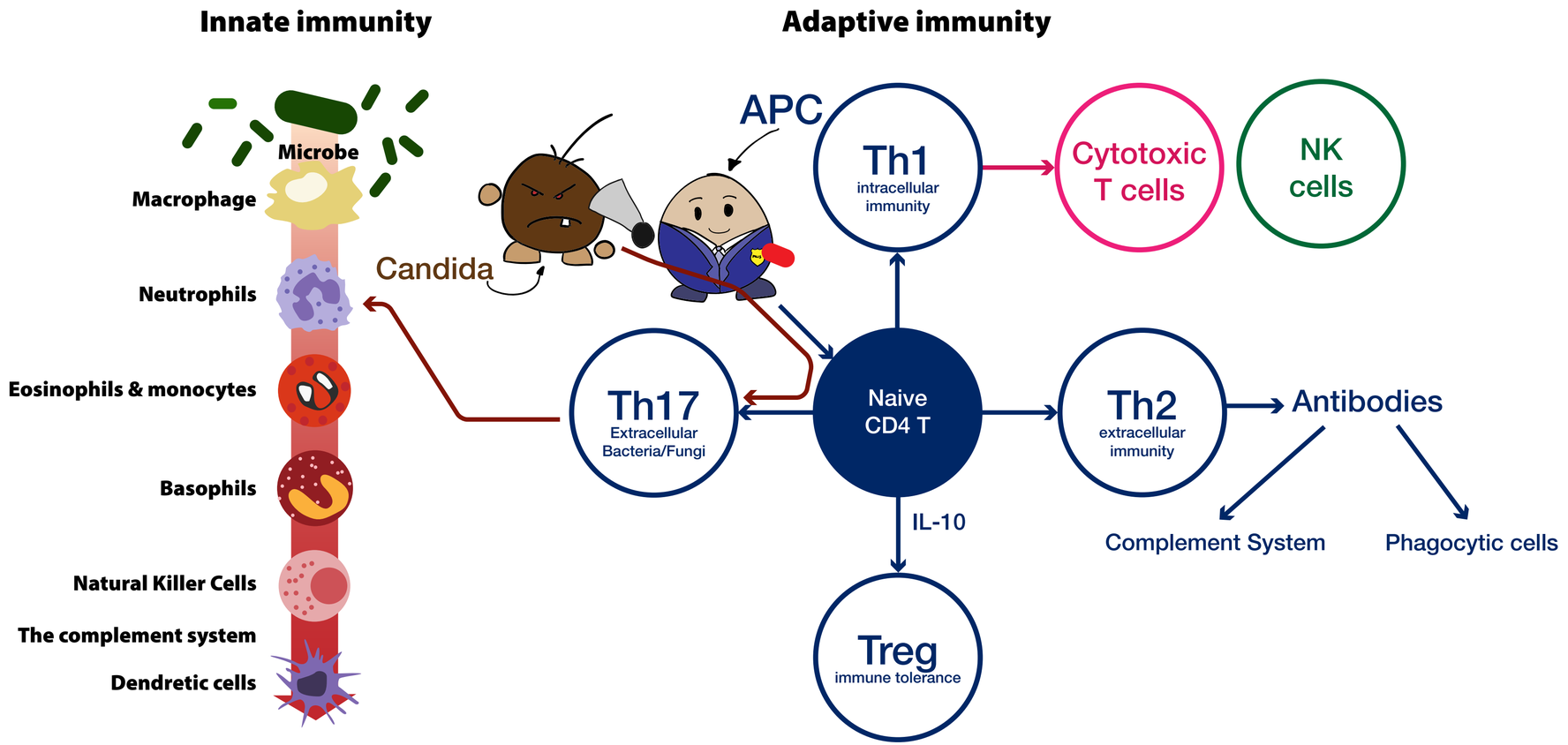
Some of the strange behaviors we have seen in ASD have been caused or exacerbated by Candida problems

- Sugar and carbohydrates cravings intensified
- Anxiety and emotional instability
- Silly, giddy, inappropriate laughter, almost acting drunk
- Gastrointestinal Candidiasis commonly contributes to digestive symptoms in autism
- Gastrointestinal Candidiasis can contribute to the accumulation of various toxic compounds such as Arabinose
  Arabinose is known to alter neural function

Sell, David R., and Vincent M. Monnier. “Structure elucidation of a senescence cross-link from human extracellular matrix: implication of pentoses in the aging process.” Journal of Biological Chemistry 264.36 (1989): 21597-21602.

A general and successful treatment approach includes

1. Immune support
2. Intestinal support
3. Eradication of the pathogen and its structures developed to escape to our immune strategies



1. Immune Support

Transfer Factors, general composition, Multimessenger
1 x 3 caps just before breakfast

NK cell activity ↑, IL-10/Treg ↑

Butyrate Coated, Butyflam Coated
3x2 caps/day 20 minutes before meals

IL-10/Treg ↑

to support Treg and prevent excessive inflammation or autoimmune dysfunction

Liposomal Glutathione, Trifortify
1 teaspoon/day

To promote Neutrophil activity ↑

To lower Oxidative stress ↓

To create more NK Cell activity ↑

To empower detoxification of fungal toxins

To compensate the loss of glutathione caused by accumulation of acetaldehyde

NK-cells affected by ROS lost the adherence to target cells in both in vitro and in vivo

ROS may change the surface of NK-cells, resulting in an inability of adhesion to target cells

Susceptibility of Natural Killer (NK) Cells to Reactive Oxygen Species (ROS) and Their Restoration by the Mimics of Superoxide Dismutase (SOD)

Kunie Nakamura[1] and Ken-ichi Matsunaga[2]
[1]Molecular Biology Laboratory, Department of Biochemistry, Kitasato University School of Medicine, Kanagawa, Japan; [2]Biomedical Research Laboratories, Kureha Chemical Industry, Co. Ltd., Tokyo, Japan.

Natural killer (NK) cells are susceptible to reactive oxygen species (ROS), and lose the activity by the effects of ROS. Cancer bearing hosts usually suffer from oxidative stress (OS), and the NK-activity decreases to a significantly lower level than normal controls. Superoxide dismutase (SOD)-mimicking substances, such as protein-bound polysaccharide of Coriolus versicolor (Fr) QUEL (PSK) and iron-chelating chlorin e6-Na (FeCNa), can restore the NK-activity of cancer bearing hosts, when collaborating with catalase. Incorporation of ^{3}H-thymidine by ROS-treated NK-cells is not affected, indicating that these cells are still active in the nucleic acid metabolism. Intraperitoneal administration of anti-Asialo GM1 antibody extinguished the NK-activity. NK-cells affected by ROS lost the adherence to target cancer cells in both in vitro and in vivo. ROS may change the surface charge of NK-cells to anionic, resulting in an inability of adhesion to target cancer cells which usually show the negative surface charge.

NEW RESEARCH ON LIPOSOMAL GLUTATHIONE

Clinical research presented at the 2015 ILADS medical conference demonstrated red blood cell absorption, increased natural killer cell function & reduced oxidative stress.

This study, conducted at Penn State University, measured the efficacy of Researched Nutritionals' Tri-Fortify™ liposomal glutathione. The product is formulated to promote healthy intracellular glutathione levels and natural killer cell function.

Healthy patients with glutathione levels at the low end of the normal range were included in the study. The patients were divided into two groups, one taking one serving (450mg) per day and the other taking two servings (900mg) per day. Both groups performed fairly close to one another so the results shown below are the combined impact, with a p-value of <0.05.

BACKGROUND

Glutathione is a tri-peptide, composed of the three amino acids: L-glutamic acid, L-cysteine and L-glycine. Healthy glutathione level plays a significant role in promoting normal:

- Detoxification
- Immune Response
- Antioxidant Action

Glutathione is required to maintain the normal function of the liver and to protect DNA, proteins & mitochondria against oxidative stress, while supporting NK cell function & lymphocyte (white blood cell) proliferation.

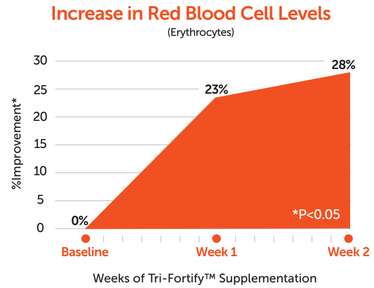
Researchers and clinicians view red blood cell absorption as essential for the body to achieve the benefits of exogenous glutathione supplementation.

RESEARCH RESULTS

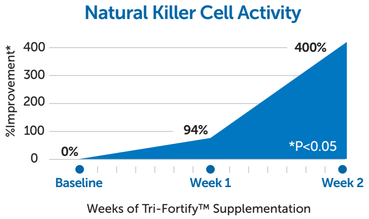
After two weeks of daily oral liposomal glutathione supplementation:

- Red blood cell levels (erythrocytes) increased 28% over the baseline.
- Natural Killer Cell function increased by 400% over the baseline.
- Oxidative stress, (as measured by lipid peroxidation) decreased by 25%

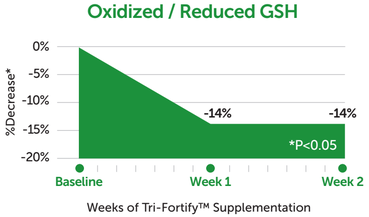
GLUTATHIONE LEVELS

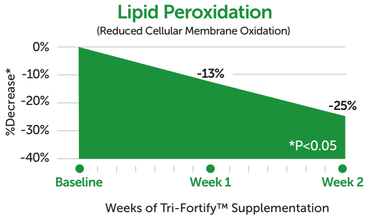


IMMUNE FUNCTION



OXIDATIVE STRESS MARKERS





Published study shows Liposomal Glutathione (Trifortify) is increasing Natural Killer Cell Activity by reducing oxidative stress

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.

Daily dose = 1 teaspoon/day

Bamford, Caroline V., et al. "Streptococcus gordonii modulates Candida albicans biofilm formation Elferink, Jan GR, and Ben M. De Koster. "Glutathione-induced enhancement of neutrophil l ocomotion." Immunobiology 184.1 (1991): 25-36.

Transfer Factors

Khan A., Hansen B., Hill N.O., Loeb E. Transfer factor is the treatment of herpes simplex types 1 and 2. Dermatologica 163, 177-85.

Comparative study of transfer factor and acyclovir in the treatment of herpes zoster. Int J Immunopharmacol. 1998 Oct;20(10):521-35.

Review: Pizza, E. (1998). Transfer Factors reduced both frequency and duration of outbreaks in patients + Only TF increased the number of T-cells.

Rita, R., Ellithorpea, B., Settineria, R., & Ellithorpeb, T. Nutrient supplement enhances natural killer cell function in women with chronic fatigue syndrome and fibromyalgia: preliminary report. 2015 November. Townsendletter.

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.

Debby Hamilton. Immune Modulation: Research Summary Transfer Factor vs. Colostrum vs. Proline-Rich Peptides. 2019. – on request

Butyrate

Aldo Roda, Patrizia Simoni. A new oral formulation for the release of sodium butyrate in the ileo-cecal region and colon World J Gastroenterol 2007 February 21; 13(7): 1079-1084

Hu Liu, Ji Wang, Ting He, Sage Becker, Guolong Zhang, Defa Li, Xi Ma. Butyrate: A Double-Edged Sword for Health? Adv Nutr. 2018 Jan 1, 9 (1), 21-29

A Di Sabatino, R Morera, R Ciccocioppo, P Cazzola, S Gotti, F P Tinozzi, S Tinozzi, G R Corazza. Oral Butyrate for Mildly to Moderately Active Crohn's Disease. Aliment Pharmacol Ther. 2005 Nov 1, 22 (9), 789-94 .

Smith DJ, et al. In vitro dissolution and in vivo absorption of calcium [1-(14)c]butyrate in free or protected forms. J Agric Food Chem 2012.

S J Lewis, K W Heaton. Increasing Butyrate Concentration in the Distal Colon by Accelerating Intestinal Transit. Gut. Aug 1997, 41 (2), 245-51 .

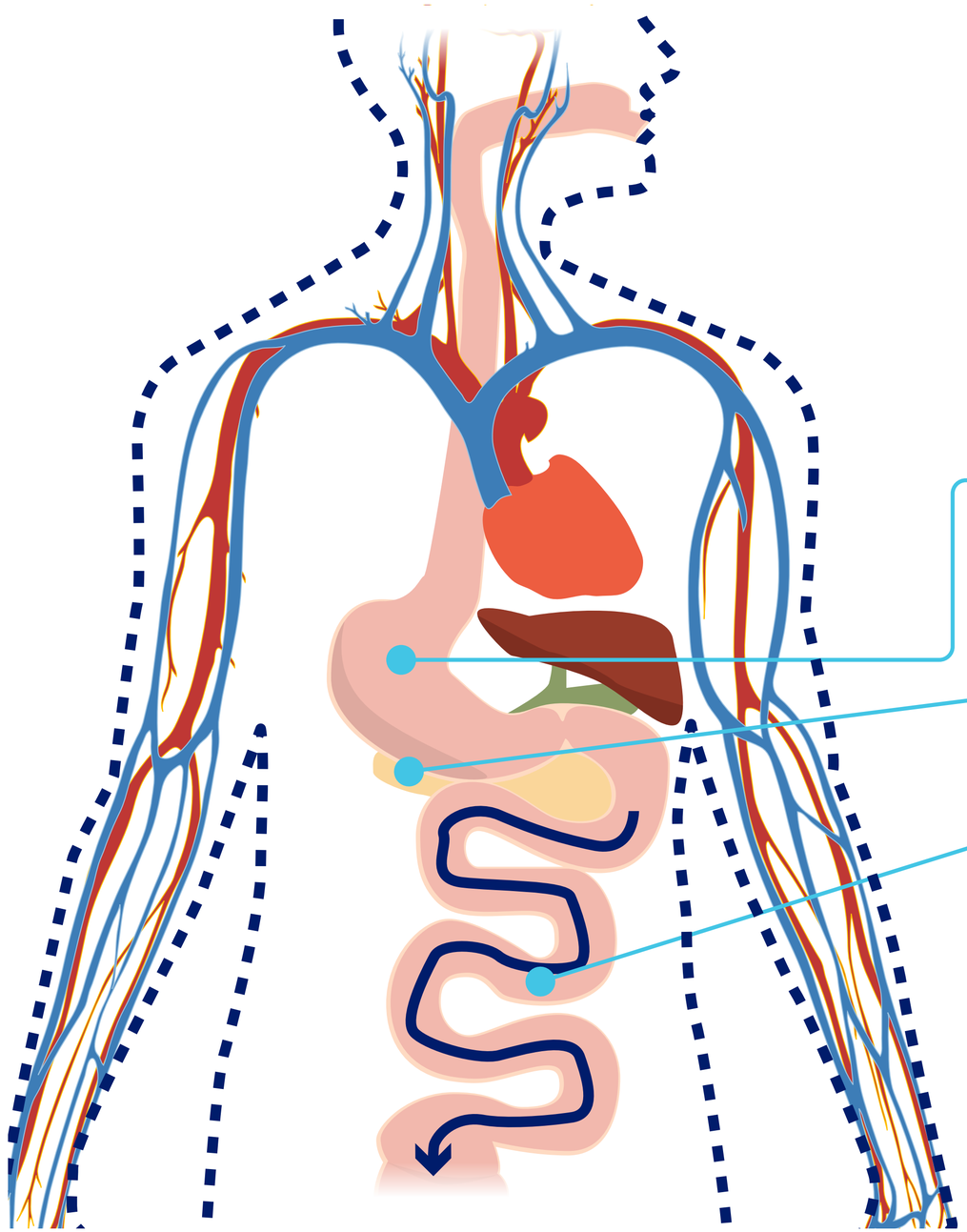
Ferreira TM, et al. Oral supplementation of butyrate reduces mucositis and intestinal permeability associated with 5-Fluorouracil administration. Lipids 2012.

Stilling RM, et al. The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? Neurochem Int 2016 - Review.

Chen X, et al. Sodium butyrate regulates Th17/Treg cell balance to ameliorate uveitis via the Nrf2/HO-1 pathway. Biochem Pharmacol 2017.

En-De Hu, Da-Zhi Chen, Jin-Lu Wu et al. Autoimmune Hepatitis Through Regulation of Immune Regulatory Cells and Intestinal Barrier. Cell Immunol , 328, 24-32.Jun 2018 High Fiber Dietary and Sodium Butyrate Attenuate Experimental

Cleophas, Maartje CP, et al. Effects of oral butyrate supplementation on inflammatory potential of circulating peripheral blood mononuclear cells in healthy and obese males. Scientific reports 9.1 (2019): 1-10.



2. Intestinal support

Overwhelming evidence suggests that the gastrointestinal tract is the main source of Candida albicans infections

Gastric Acid + pepsine, Guttae Pepsine, 3x5 drops/day at the start of each, gradually build up until 3x20drops

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

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

(including gluten modifying enzymes)

Targeted released Glutamine & cofactors

Heal the mucosal lining and tight juction optimazing (pH 6-7)

Permplus Coated 3x2 20minutes before meals

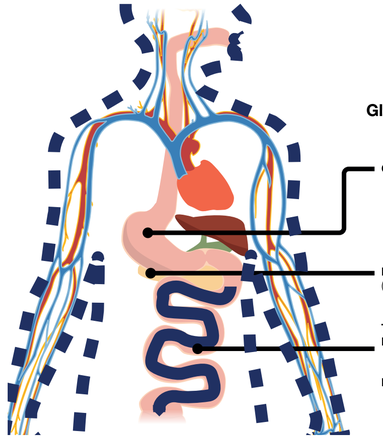
- ↓inflammation
- Improve the synthesis of s IgA by the intestinal lymphocytes

Butyrate coated

Butyflam Coated 3x2 20minutes before meals

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

GUT PROTOCOL



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 5,3 ml Glycerol 10 ml Hydrochloric acid HCl 37% 2,7 ml Pepsine 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
daily dose (based on 3 vegecaps)	**Digestive enzyme blend:** Amylase 5000 DU, Protease 4.5 24.500HUT, Gluco-amylase 16 AGU, 4 Protease 6.0 7500 HUT, Lipase 3000 FIP, Cellulase 7500 CU, Alpha-galactosidase 125 GalU, Pectinase 12 endo-PGU, Protease 3.0 10 SAPU, Phytase 5 FTU, Xylanase 100 XU, Hemicellulase 75 HCU. 150 mg **Hemicellulase (1500 U)** 75 mg **Phytase (7500 U)** 75 mg **Biocore DPP IV:** Protease (Aspergillus oryzae 18000 HUT / 300 DPP-IV, Aspergillus meleus 5.1 AP) 60 mg **Lactase (3900 U)** 60 mg

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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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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

Kim, Kyung-Yup, et al. “Acid suppression therapy as a risk factor for Candida esophagitis.” Digestive diseases and sciences 58.5 (2013): 1282-1286.

PPI-induced elimination of gastric acid is a major mechanism leading to more oro-pharyngeal and intestinal Candida colonization

Sherrington, Sarah L., et al. “Adaptation of Candida albicans to environmental pH induces cell wall remodelling and enhances innate immune recognition.” PLoS pathogens 13.5 (2017): e1006403.

Glutamine targeted released, Permplus Coated
3x2 tabs/day 20 minutes before meals

Bai, Xiao-Dong, Xian-Hua Liu, and Qing-Ying Tong. “Intestinal colonization with Candida albicans and mucosal immunity.” World Journal of Gastroenterology: WJG 10.14 (2004): 2124.

Studies observed the relationship between intestinal colonization with Candida albicans and mucosal secretory IgA, sIgA’s

The decreasing number of Candida albicans in intestine is related to the increased level of sIgA’s

Butyrate Coated, Butyflam Coated
3x2 caps/day 20 minutes before meals

Renewing epithelial intestinal lining ↑

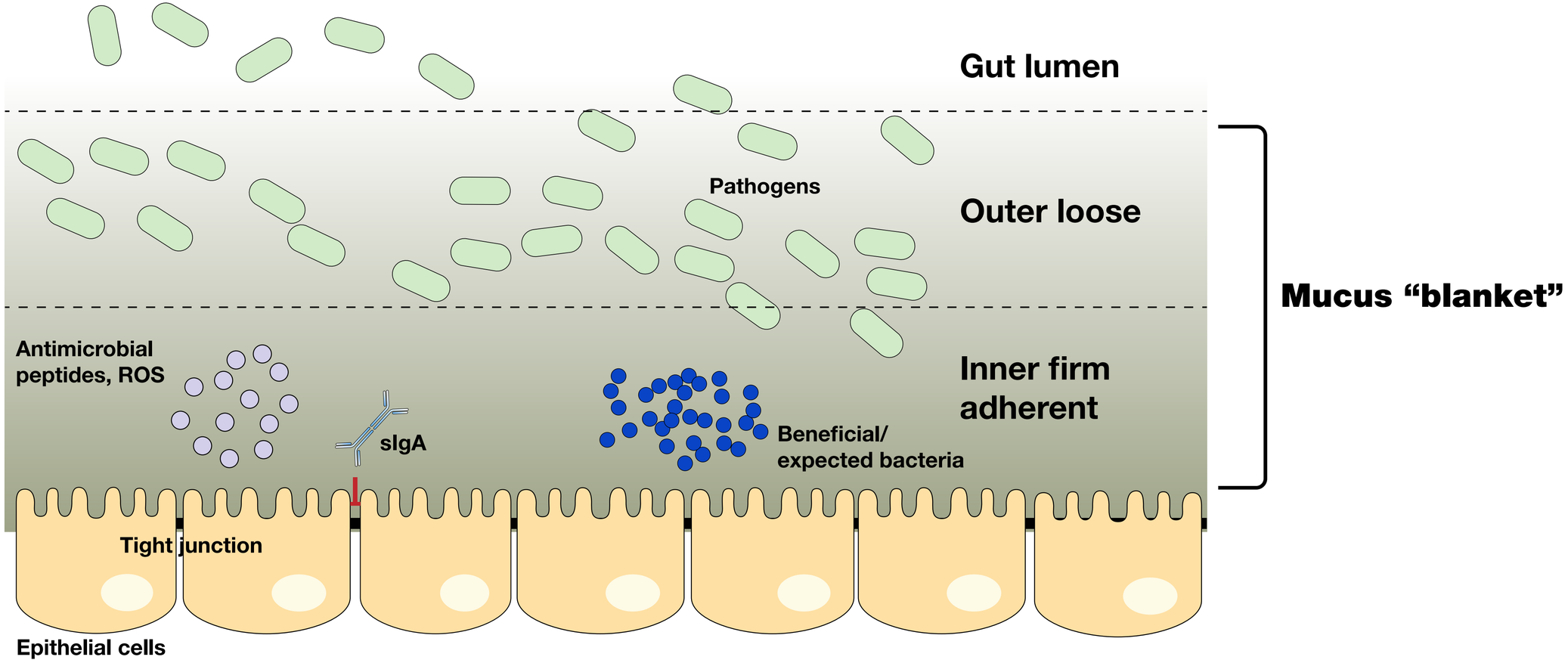
Mucus ↑

Neutrophil Chemotaxis ↑

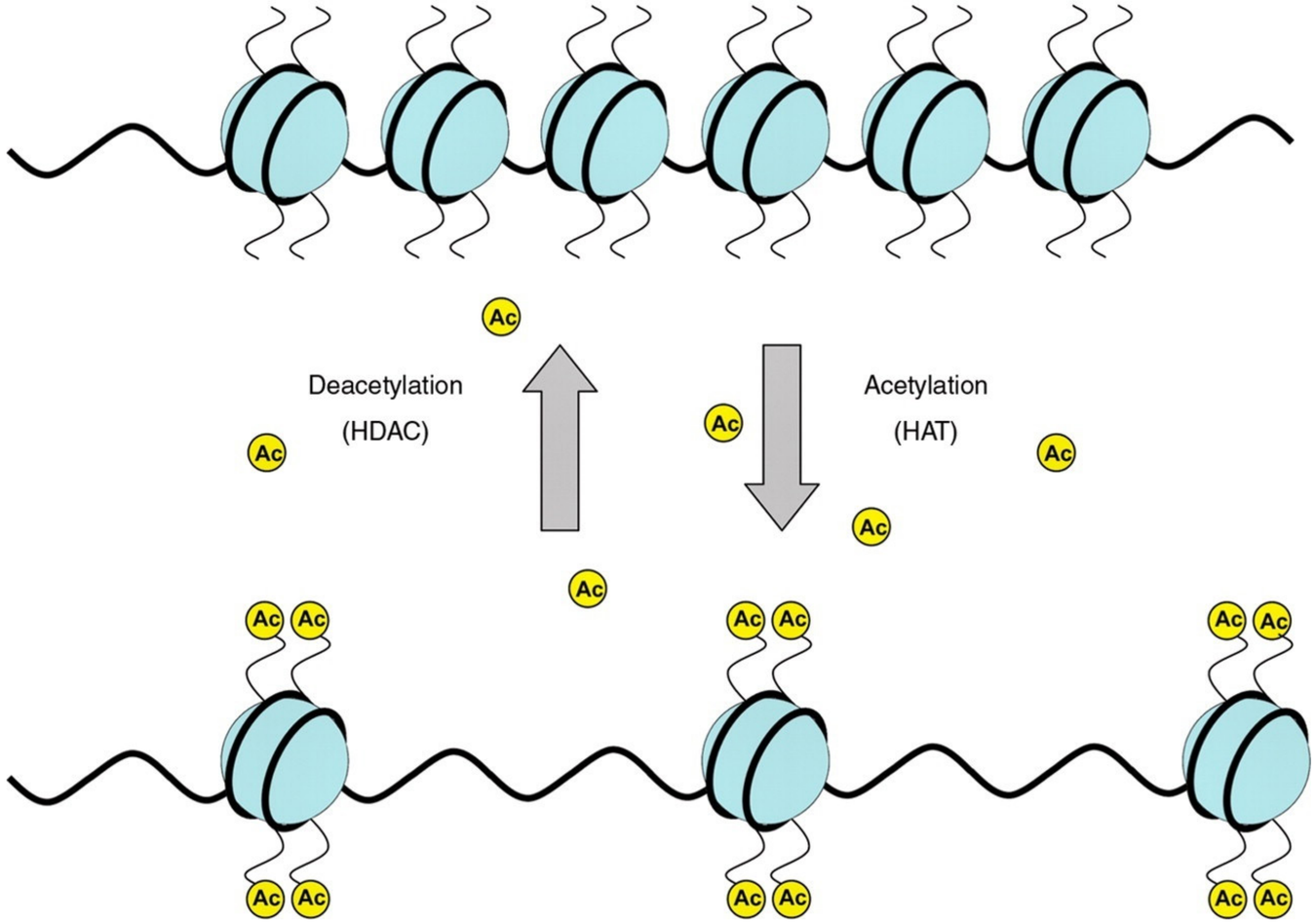
sIgA's ↑

From host prebiotic

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



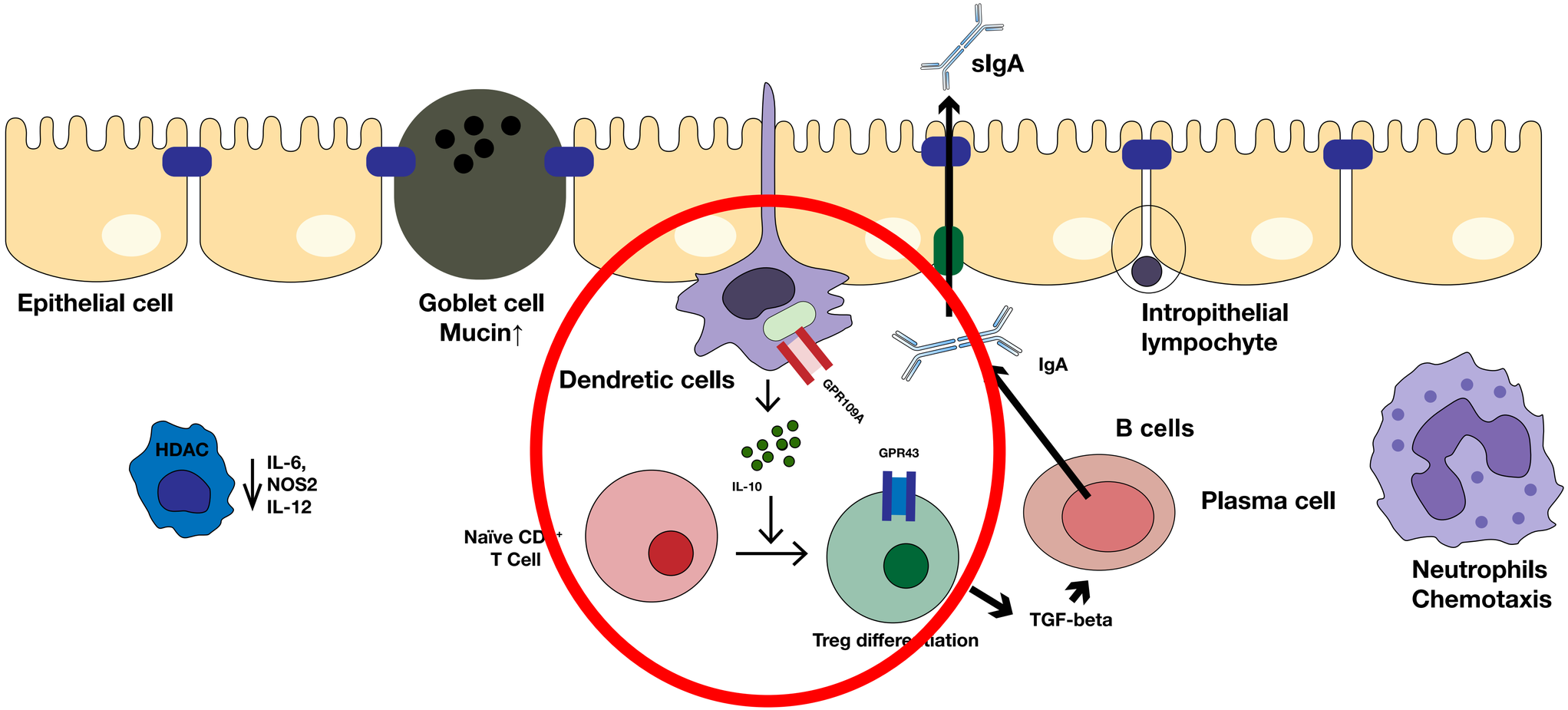
Immune modulation / anti inflammation on local level:
Butyrate inhibits HDAC (histone deacetylase)
– this modification is changing the gene expression

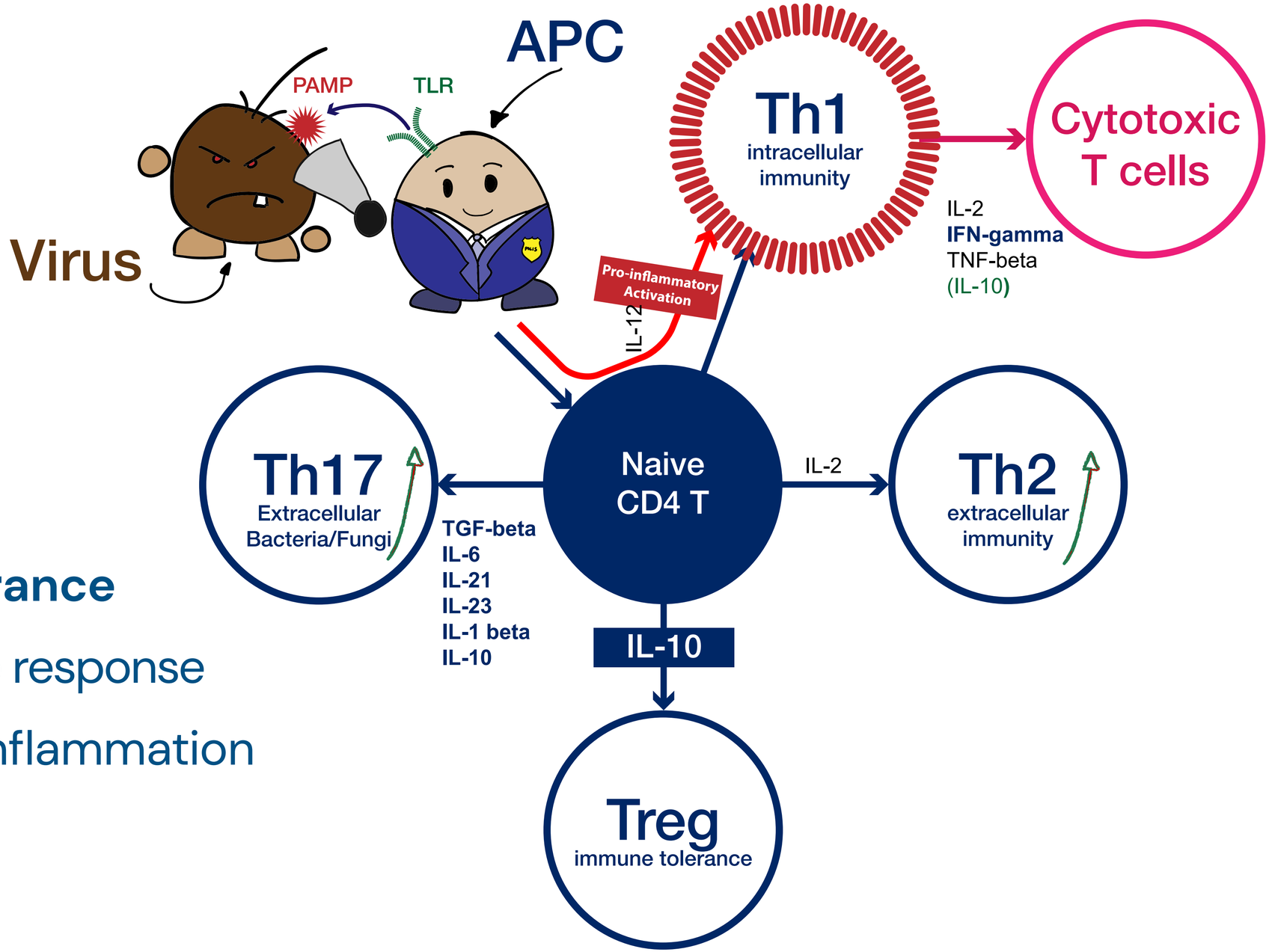


Gene expression is modified in Dendritic Cells

IL-6 is suppressed = more IL-10

More differentiation to T regs





T reg & IL–10 = self tolerance

- ↓ Risk for autoimmune response
- ↓ Risk for excessive inflammation

3. Eradication of the pathogen and its structures developed to escape to our immune strategies

Current antifungal drugs have only two specific targets

Ergosterol biosynthesis

1,3-Beta-D-glucan synthesis

What are Azoles?

Azoles are synthetic antifungals with broad-spectrum fungistatic activity against yeasts and fungi, including candidal species. By blocking fungal cytochrome P450-dependent enzymes, azoles disrupt the synthesis of ergosterol, which is the principal sterol in fungal cell membranes. The two subclasses of azoles are imidazoles (eg, clotrimazole, miconazole, econazole, ketoconazole) and triazoles (eg, fluconazole, itraconazole).

What are Echinocandins?

Echinocandins are a class of antifungal drugs that target the fungal cell wall.
They are lipopeptide molecules that noncompetitively inhibit (1,3) beta-d-glucan synthase enzyme.
This enzyme forms glucan, a major component of the fungal cell wall therefore by inhibiting its synthesis fungal cell walls are damaged.

cell walls are damaged

Caspofungin, Micafungin, Anidulafungin

Natural research-based antifungal remedies

Artemisinin

Artemisin Solo

2x2 caps/day 30 minutes before meals
5 days in a row / interruption during the weekend

Khatoon, N., et al. “Mode of action and anti-Candida activity of Artemisia annua mediated-synthesized silver nanoparticles.” Journal de mycologie medicale 29.3 (2019): 201-209.

Das, Sourav, et al. “Cytotoxic action of artemisinin and scopoletin on planktonic forms and on biofilms of Candida species.” Molecules 25.3 (2020): 476.

De Cremer, Kaat, et al. “Artemisinins, new miconazole potentiators resulting in increased activity against Candida albicans biofilms.” Antimicrobial agents and chemotherapy 59.1 (2015): 421-426.

Lactoferrin

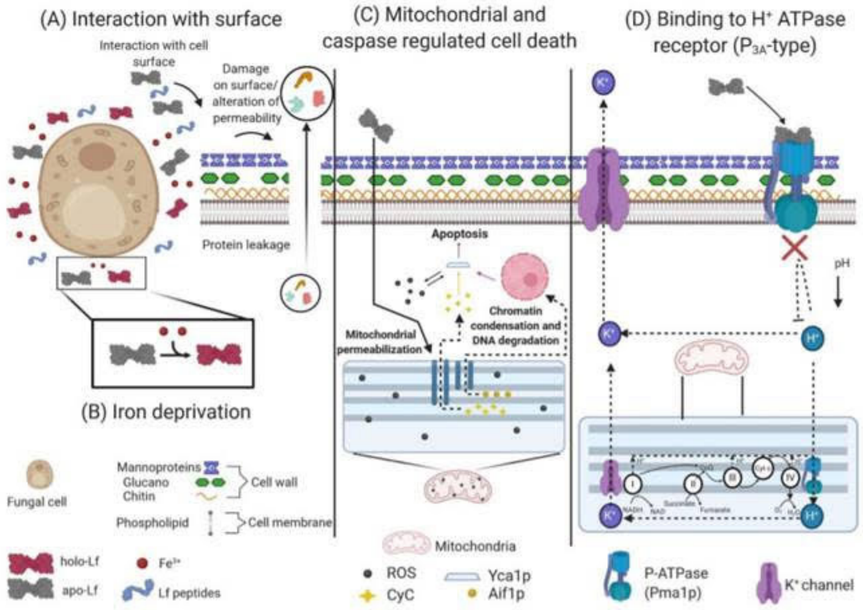
Lactoferrin is a glycoprotein with anti-infectious properties

Lactoferrin is one of the transferrin proteins that transfer iron to the cells and control the level of free iron in the blood and external secretions

Human LF & Bovine LF : the amino acid sequence overlap for 70%
The concentration is much higher in human milk than in Bovine mil

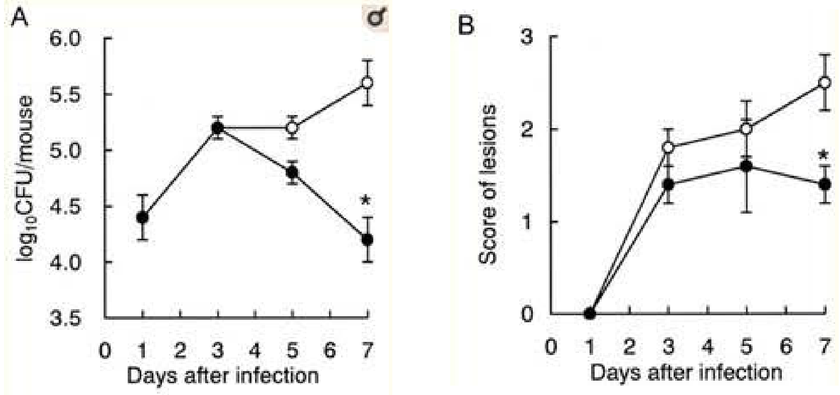
Synthesized by the mammary gland , abundant in colostrum
Also present in exocrine secretions like salvia & tears + present on mucosal surfaces to contribute in our innate immune response

After digestion partly degraded by pepsin in into Lactoferricins



Antifungal activity

1. Lactoferrin and lactoferricin B cause an alteration in cell surface permeability of the fungus.
2. Lactoferrin binds Iron, necessary for fungal growth
3. Mitochondrial and caspase-regulated cell death
4. Binding to H+-ATPase receptor (P3A-type)



Oral Lactoferrin Treatment of Oral Candidiasis in Mice

bLF administration 1 day before infection

End of the study: day 7 after inoculation

Acid resistant: DR capsules

The rate of partial conversion in Lactoferricin depends on moment of intake

Intake during meal = Lactoferrin + Lactoferricin
Intake separated from meals = Lactoferrin

In Bacterial infections: Lactoferrin and lactoferricin B are both active ingredients in antibacterial action.
Use: 2 x 2 DR caps / day during meals

In Viral infections: Lactoferrin, and not lactoferricin B, is the required active ingredient in antiviral action.
Use: 3 x2 DR caps 1 hour before or 2hours after meals

In fungal infections: Lactoferrin and lactoferricin B are both required for antifungal activity
Use: 2x2 DR caps / day during meals

new

The multifunctional role of Lactoferrin

Lactoferrin is a multifunctional glycoprotein existing in all human bodily fluids. **Ferrin** refers to its ability to bind free iron ions.

Lactoferrin acid resistant contains 100 mg Lactoferrin per capsule, a pure and specific whey protein of bovine origin.

The use of acid resistant capsules ensures stability and targeted activity.

indication	Antiviral activity Antibacterial activity (including Helicobacter pylori) Antifungal activity (including Candida albicans)
dosage	3 x 2 caps per day
packaging	84 acid resistant capsules per container
composition (amount per 6 caps)	Lactoferrin - 600 mg

Lactoferrin is **casein-free**. During the manufacturing process, Lactoferrin is washed of **lactose** to a content of **less than 0,1%.** People who may have a sensitivity to lactose should not react to this low level of lactose.

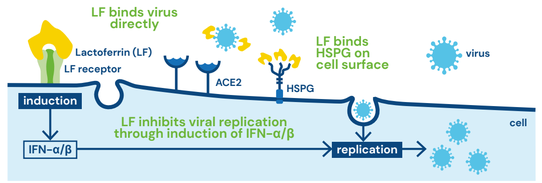
Antiviral

Mechanism:

The antiviral effect of LF lies mainly in the early phase of the infection. Lactoferrin prevents the infection of host cells by viruses, but also inhibits the growth of viruses after the host cells have been invaded.

Lactoferrin participates in the innate part of our immune defense, increasing NK-cell activity and TH1 cytokines. Lactoferrin partners very efficiently with Transfer Factors (Multimessenger: NK cell activity + IL-10).

Predetermined antiviral mechanism on 3 levels:



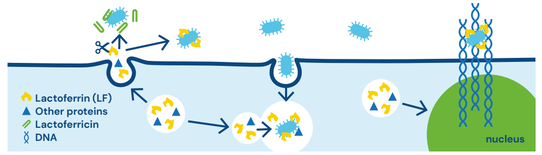
Recommended daily dosage in viral threats
Lactoferrin acid resistant 100mg
- Preventive measures: 3 x 1 capsule/day separated from meal
- Curative treatment: 3 x 2 capsules/day separated from meal

Antibacterial

Mechanism:

The 3 epitopes for Lactoferrin's antibacterial activity:
- Lactoferrin binds iron, required for the growth of bacteria
- Lactoferrin binds membrane proteins to disrupt permeability
- Competition for binding site(s)

Helicobacter pylori:
- Detaching the bacterium from the gastric epithelium
- Exerting a direct anti-bacterial effect



Recommended daily dosage in bacterial threats
Lactoferrin acid resistant 100mg
- Preventive measures: 3 x 1 capsule/day during meal
- Curative treatment: 3 x 2 capsules/day during meal

Antifungal

Mechanism:

- Lactoferrin binds directly to the fungal cell surface, leading to cell membrane damage and leakage
- Lactoferrin sequesters iron resulting in a fungistatic effect and inhibition of fungal growth

Candida: synergistic fungistatic effects of Lactoferrin in combination with antifungal drugs.

Recommended daily dosage in fungal threats
Lactoferrin acid resistant 100mg
- Preventive measures: 3 x 1 capsule/day during meal
- Curative treatment: 3 x 2 capsules/day during meal

Lactoferrin is included in different specific anti-infectious treatment plans, see page 4.

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Hendrix, Abernethy, Sloane, Misuraca, &. Moore. "Lactoferrin as a Natural Immune Modulator." Bone, vol. 23, no. 1, 2013.

Kuipers ME, de Vries HG, Eikelboom MC, Meijer DK, Swart PJ. Synergistic fungistatic effects of lactoferrin in combination with antifungal drugs against clinical Candida isolates. Antimicrob Agents Chemother. 1999;43(11):2635-2641.

Kanwar JR, Roy K, Patel Y, et al. Multifunctional iron bound lactoferrin and nanomedicinal approaches to enhance its bioactive functions. Molecules. 2015;20(6):9703-9731. Published 2015 May 26.

Komatsu, Akino, et al. "Effects of Bovine Lactoferrin to Oral Candida Albicans and Candida Glabrata Isolates Recovered from the Saliva in Elderly People." Odontology, vol. 103, no. 1, 2013, pp. 50–55.

Kuipers, M. E., et al. "Synergistic Fungistatic Effects of Lactoferrin in Combination with Antifungal Drugs against Clinical Candida Isolates." Antimicrobial Agents and Chemotherapy, vol. 43, no. 11, 1999, pp. 2635–41

Nikawa H, Samaranayake LP, Tenovuo J, Pang KM, Hamada T. The fungicidal effect of human lactoferrin on Candida albicans and Candida krusei. Arch Oral Biol. 1993;38(12):1057-1063.

Takakura N, Wakabayashi H, Ishibashi H, et al. Oral lactoferrin treatment of experimental oral candidiasis in mice. Antimicrob Agents Chemother. 2003;47(8):2619-2623. doi:10.1128/AAC.47.8.2619-2623.2003

Zarzosa-Moreno D, Avalos-Gómez C, Ramírez-Texcalco LS, et al. Lactoferrin and Its Derived Peptides: An Alternative for Combating Virulence Mechanisms Developed by Pathogens. Molecules. 2020;25(24):5763. Published 2020 Dec 8.

Microbinate®

indication	Microbinate is designed to promote the body's healthy response to microbial challenges, internally and externally. Indicated in intestinal infections like SIBO next to general Gut Protocol.
dosage	2 x 1 caps per day during the first week then 2 x 2 caps per day. For optimal results take away from food.
packaging	120 vegecaps per container
composition (amount per 2 vegecaps)	Monolaurin – Inosine 310 mg Oregano extract 300 mg Olive leaf extract 250 mg Allicin 200 mg CurcuWIN™ (Turmeric extract molecular dispersion technology) 100 mg

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Elim-A-Cand™

indication	Eradication of Candida infection
dosage	Starting dose for adults: 2 x 5 drops/day in water away from food. Gradually increase dose every 2 days up to 2 x 40 drops/day. Patients are advised to take a 3-day break every 4-8 weeks.
packaging	120 ml per bottle

composition (amount per 40 drops)	
Cinnamon (Cinnamomum Verum)	4 parts
Clove (Syzgium Aromaticum)	4 parts
Marshmallow Root (Althaea Officinalis)	4 parts
Pau D' Arco (Tabebuia Impetiginosa)	2 parts
Slippery Elm (Ulmus Rubra)	2 parts
Berberine	1 parts
Stillingia sylvatica	0.5 parts

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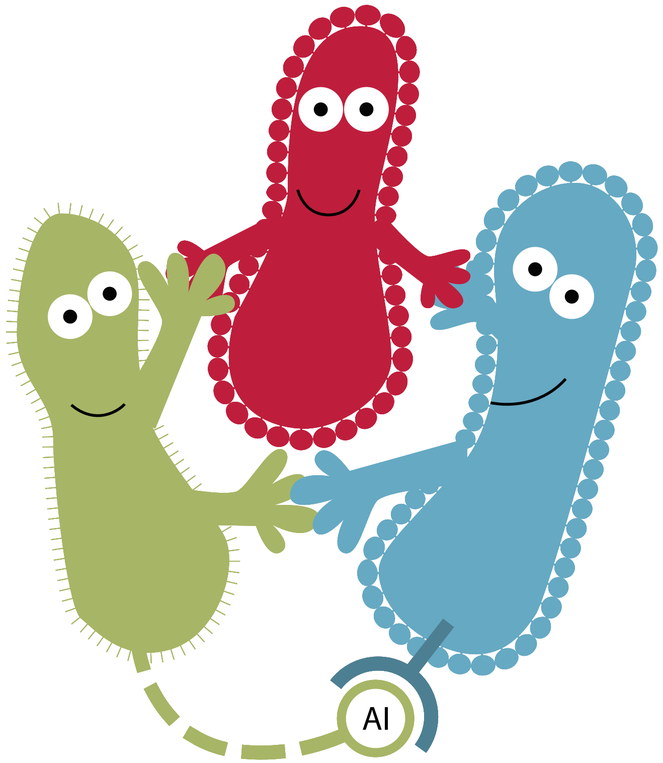
Fungal biofilms are largely resistant to current antifungal drugs, high antifungal doses together with removal of the colonized medical device are generally required

= removal of some devices is costly and could be dangerous

= high doses of antifungals can cause complications, critically ill patients don't tolerate

More research and better understanding of the molecular mechanisms underlying biofilm formation and maintenance could lead to development of new antifungals that specifically target biofilms



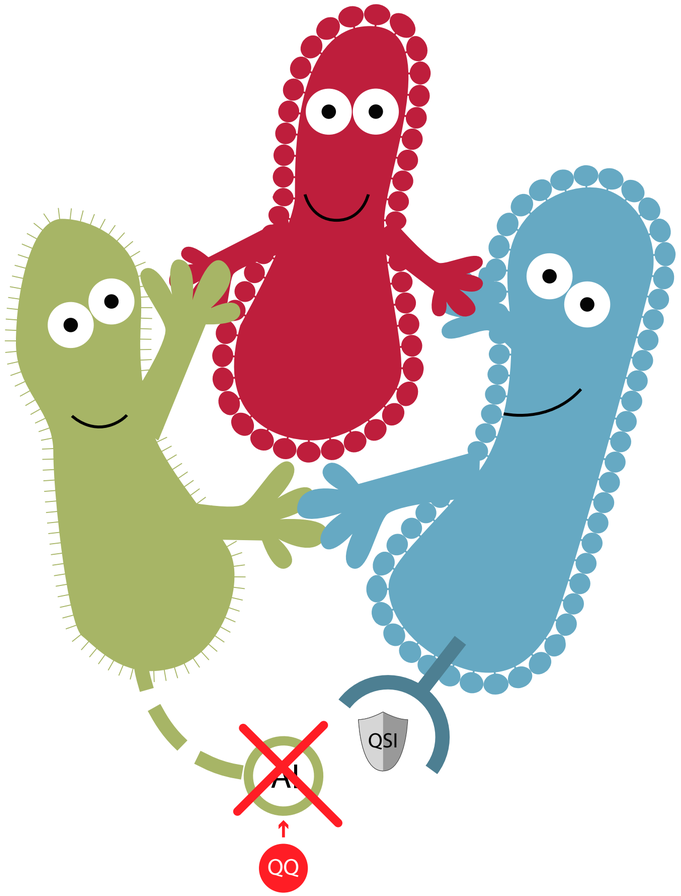
How do we address biofilms?

We address the molecular communication systems the germs, forming the biofilm community, are using to synchronize the expression of ge-nes

These genes regulate:

- Virulence factors
- Synthesis of biofilm

Communication
= Exchange of chemical mediators called autoinducers (AI's)
= Quorum sensing (QS) is a collective adaptation
& coordination of behavior



We interfere using:

Quorum Sensing inhibitors (QSIs) to block the action of the Autoinducers (AI's)

Quorum Quenching Enzymes (QQ) to degrade the Autoinducers

Recent studies have showed that these strategies are promising routes to decrease bacterial pathogenicity and break down biofilms

Study-based Molecules inhibiting QS

- **Azithromycin**

  Nalca Y., Jänsch L., Bredenbruch F., Geffers R., Buer J., Häussler S. (2006). Quorum-sensing antagonistic activities of azithromycin in Pseudomonas aeruginosa PAO1: a global approach. Antimicrob. Agents Chemother. 50, 1 680–1688. 10.1128/AAC.50.5.1680-1688.2006

But … In the current context of antibiotic resistance, novel therapeutic approaches have been introduced to inhibit QS:

- **Cranberry**

  Rajkumari, Jobina, et al. “Attenuation of quorum sensing controlled virulence factors and biofilm formation in Pseudomonas aeruginosa by pentacyclic triterpenes, betulin and betulinic acid.”
  Microbial pathogenesis 118 (2018): 48-60.

  Feldman, Mark, et al. “Interference of cranberry constituents in cell–cell signaling system of Vibrio harveyi.” Current microbiology 59.4 (2009): 469-474.

- **Rosemary**

  de Oliveira, Jonatas Rafael, et al. “Biological activities of Rosmarinus officinalis L. (rosemary) extract as analyzed in microorganisms and cells.” Experimental Biology and Medicine 242.6 (2017): 625-634.

  De Oliveira, Jonatas Rafael, Samira Esteves Afonso Camargo, and Luciane Dias De Oliveira. “Rosmarinus officinalis L.(rosemary) as therapeutic and prophylactic agent.” Journal of biomedical science 26.1 (2019): 5.

- **Berberine**

  Xie, Yufei, Xiaosong Liu, and Peiru Zhou. “In vitro Antifungal Effects of Berberine Against Candida spp. In Planktonic and Biofilm Conditions.” Drug Design, Development and Therapy 14 (2020): 87.

- **Peppermint oil**

  Budzynska, Aleksandra, et al. “Antibiofilm activity of selected plant essential oils and their major components.” Pol J Microbiol 60.1 (2011): 35-41.

+ Quorum Quenching enzymes

Fetzner, Susanne. “Quorum quenching enzymes.”
Journal of biotechnology 201 (2015): 2-14.

Deng, Yinyue, et al. “Cis-2-dodecenoic acid receptor RpfR links quorum-sensing signal perception with regulation of virulence through cyclic dimeric guanosine monophosphate turnover.”
Proceedings of the National Academy of Sciences 109.38 (2012): 15479-15484.

Weiland-Bräuer, Nancy, et al. “Highly effective inhibition of biofilm formation by the first metagenome-derived AI-2 quenching enzyme.”
Frontiers in microbiology 7 (2016): 1098.

BioDisrupt™

indication	Breakdown of bacterial and fungal biofilms. Induced hypercoagulation.
dosage	2 x 2 caps per day 1 hour before or 2 hours after food.
packaging	120 vegecaps per container

composition (amount per 4 vegecaps)	
N-Acetyl cysteine	600 mg
Cranberry (Vaccinium macrocarpon)	480 mg
Berberine (Berberis vulgaris)	300 mg
Rosemary (Rosmarinus officinalis)	250 mg
Peppermint oil (Mentha piperita)	180 mg
Lysozyme (from egg white)	60 mg
Serratiopeptidase	35.2 mg
Beta glucanase	17.2 mg
Lipase	12.6 mg
Protease	6.2 mg
Cellulase	1500 µg
Hemicellulase	400 µg

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BioDisrupt® Clinical Research Executive Summary

(Research has been submitted for peer- review)

Objectives

The objective of this study was to investigate the efficacy of BioDisrupt® to positively impact established biofilm communities.

Primary Outcomes Measured

Disruption of biofilm mass & biofilm metabolic activity on established biofilms of the following microbial species:

- Candida albicans
- Staphylococcus aureus
- Staphylococcus simulans

Study Design

This in vitro study was conducted in a research lab that grew the biofilms and then treated them with BioDisrupt®.

BioDisrupt® Anti-Biofilm Highlights

- Candida albicans
  - Disrupted & reduced biofilm mass & metabolic activity within 24 hours
  - Biofilm mass vs untreated control: -65%
  - Biofilm metabolic activity vs untreated control: -77%
- Staph aureus
  - Rapidly disrupted biofilm mass & metabolic activity
  - Biofilm mass vs untreated control: -72%
  - Biofilm metabolic activity vs untreated control: -44%
- Staph simulans
  - Rapidly disrupted biofilm mass & metabolic activity
  - Biofilm mass vs untreated control: -43%
  - Biofilm metabolic activity vs untreated control: -36%

Researchers' Conclusions

BioDisrupt®, a multi-mechanisms of action supplement, is "efficacious at disrupting established biofilms." "The bioavailability of the active herbal and enzyme components of [BioDisrupt] makes it likely that consumption of [BioDisrupt] may affect established biofilm in tissues."

The bioavailability of the active herbal and enzyme components of BioDisrupt® include:

- **EnzymeDisrupt™** blend contains enzymes to break down the biofilm structural matrix made of proteins, carbohydrates, and fats
- **HerbDisrupt™** blend contains herbs to provide anti-microbial, anti-adhesion, and anti-quorum sensing properties

Additional options.

- **Oral liposomal Glutathion (Trifortify)**

  Klare, William, et al. “Glutathione-disrupted biofilms of clinical Pseudomonas aeruginosa strains exhibit an enhanced antibiotic effect and a novel biofilm transcriptome.” Antimicrobial agents and chemotherapy 60.8 (2016): 4539-4551.

The incidence of fungal infections has become a worldwide health issue

Most important comorbidities are population aging, cancer development, autoimmune disorders, immune suppressive therapies and defects in our immune defense systems

Cases of invasive fungal disease are rising as the at-risk population continues to expand.

- Immune suppression
- Increased chemical use leading to more medication resistance
- Climate changes

The WHO published a report FPPL (First Priority Pathogens list)
https://www.who.int/publications/i/item/9789240060241

Aims:

- Direct and drive research efforts
- Monitor antifungal development
- Promote knowledge
- Inform politicians to implement measures to address antifungal resistance

Pathogens have been listed in categories

Critical (most dangerous) priority group

- Cryptococcus neoformans
- Candida auris
- Aspergillus fumigatus
- Candida albicans

The supportive therapies play a crucial role and determine the success of the treatment of this opportunistic infection

Candida

Immune support	**Multimessenger** 90 caps Dose: 1 x 3 caps per day, just before breakfast **Tri-Fortify Watermelon or Orange** 236 ml Dose: 1 teaspoon/day, separated from meals **Butyflam coated** 180 coated caps Dose: 3 x 2 caps per day, 20 min before meals
Intestinal support	**Guttae Pepsini** 30 ml Dose: 3 x 10 - 20 drops at the start of the meal and with a small amount of water (swallow immediately) **Gluten DPP IV Complex** 90 vcaps Dose: 3 x 1 caps per day, at the beginning of the meal **Perm Plus Coated tablets** 90 coated tablets Dose: first month: 3 x 2 tablets per day Then: 3 x 1 tablet per day, 20 minutes before the meal **Butyflam coated** 180 coated caps Dose: 3 x 2 caps per day, 20 min before meals
Eradication of the pathogen and its structures developed to escape to our immune strategies	**Artemisinin SOLO** 90 vcaps Dose: 2 x 2 caps per day, 30 minutes before meals - 5 days in a row & interruption during the weekend **Lactoferrin acid resistant 100mg** 84 acid resistant caps Dose: 3 x 2 caps per day during meals **Elim-A-Cand** 120 ml Dose: start dose adults days 1-3: 3-5 drops in 30-85ml water in morning and evening days 4 and beyond: Increase 3-5 drops every other day, in both morning and evening, to 2 times 40 drops per day **Microbinate** (2 – 4 months) 120 vcaps Dose: first week: 2 x 1 caps per day then: 2 x 2 caps per day
Biofilm disruption	**BioDisrupt** 120 vcaps Dose: 2 x 2 caps per day, separated from meals

Candida

Reduction of Fungal Toxicity	**Co-Factor B Complex** 30 tablets Dose: 1 tablet per day during breakfast **Tri-Fortify Watermelon or Orange** 236 ml Dose: 1 teaspoon/day, separated from meals **Physician's Daily** 60 vcaps Dose: 1 caps per day with food

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Tri-Fortify

Bamford, Caroline V., et al. "Streptococcus gordonii modulates Candida albicans biofilm formation Elferink, Jan GR, and Ben M. De Koster. "Glutathione-induced enhancement of neutrophil locomotion." Immunobiology 184.1 (1991): 25-36.

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Multimessenger

Comparative study of transfer factor and acyclovir in the treatment of herpes zoster. Int J Immunopharmacol. 1998 Oct;20(10):521-35.

Debby Hamilton. Immune Modulation: Research Summary Transfer Factor vs. Colostrum vs. Proline-Rich Peptides. 2019. – on request

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Khan A., Hansen B., Hill N.O., Loeb E. Transfer factor is the treatment of herpes simplex types 1 and 2. Dermatologica 163, 177-85.

Review: Pizza, E. (1998). Transfer Factors reduced both frequency and duration of outbreaks in patients + Only TF increased the number of T-cells.

Rita, R., Ellithorpea, B., Settineria, R., & Ellithorpeb, T. Nutrient supplement enhances natural killer cell function in women with chronic fatigue syndrome and fibromyalgia: preliminary report. 2015 November. Townsendletter.

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.

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