Mold & Biotoxins

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CIRS

Chronic Inflammatory Response Syndrome, is a multi-system illness caused by fungi linging in the human body, making toxins, or has been acquired by exposure to the interior of water damaged buildings

Biological Elements

→ **Defective Antigen Presentation → Inflammation**

→ **Neural, cognitive and emotional dysfunction**

Correct Definitions

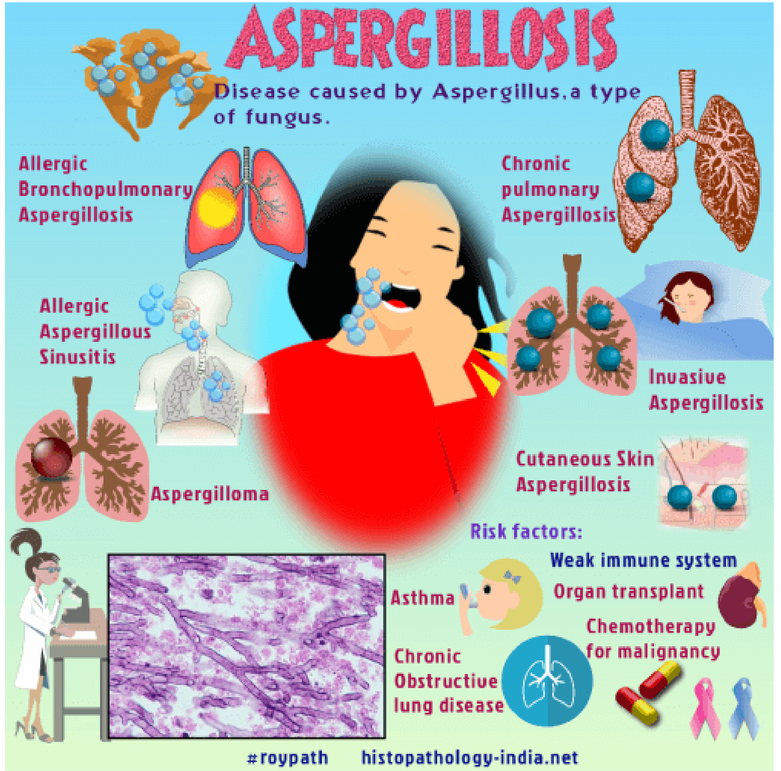
Fungi

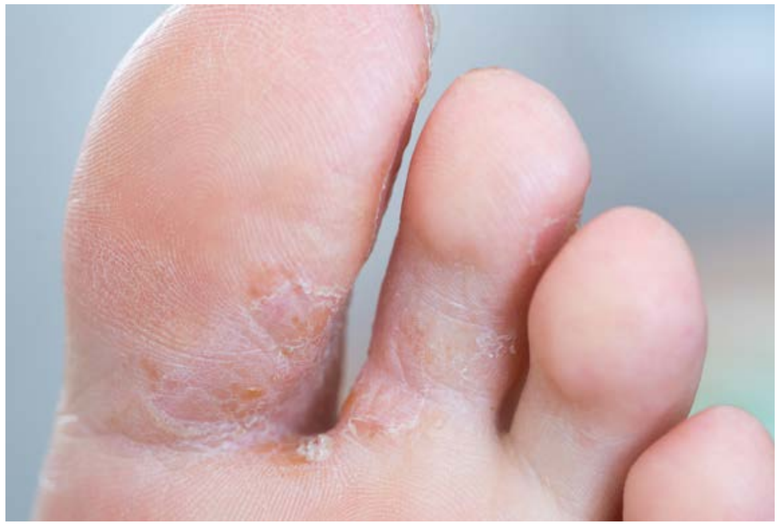
Mold versus Yeast

Mycotoxins

Fungi grow on animal hosts - can provoke diseases we know as mycosis:

Athlete’s foot
Invasive Aspergillosis





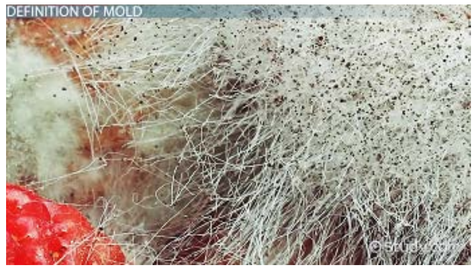
Two categories of Fungi:

1. **Primary Pathogens**
   Coccidioides immitis, Histoplasma capsulatum
   Affect healthy individuals with normal immune systems

2. **Opportunistic Pathogens cause** the majority of mycoses
   Candida albicans
   Affects immunocompromised hosts
   Some infections remain localized but could also progress to systemic infection

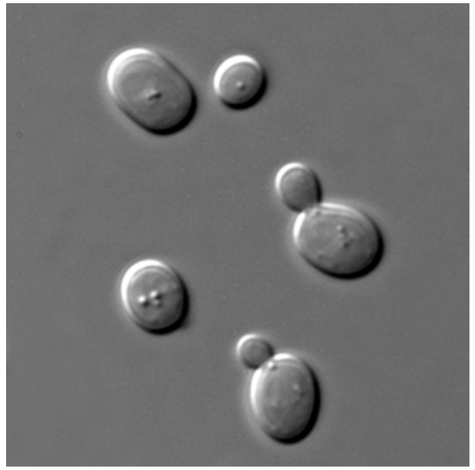
   ENTRY?
   Often through the pulmonary tract, sometimes through the skin

Mold versus Yeast



Mold is a type of fungus that grows in multicellular filaments, called Hyphae.

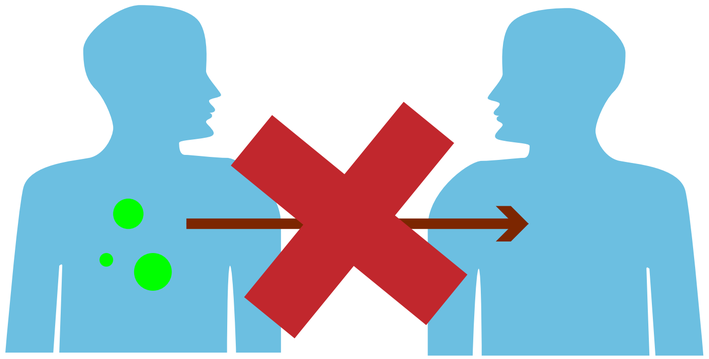
These tubular branches have multiple, genetically identical nuclei, yet from a single organism, known as a colony.



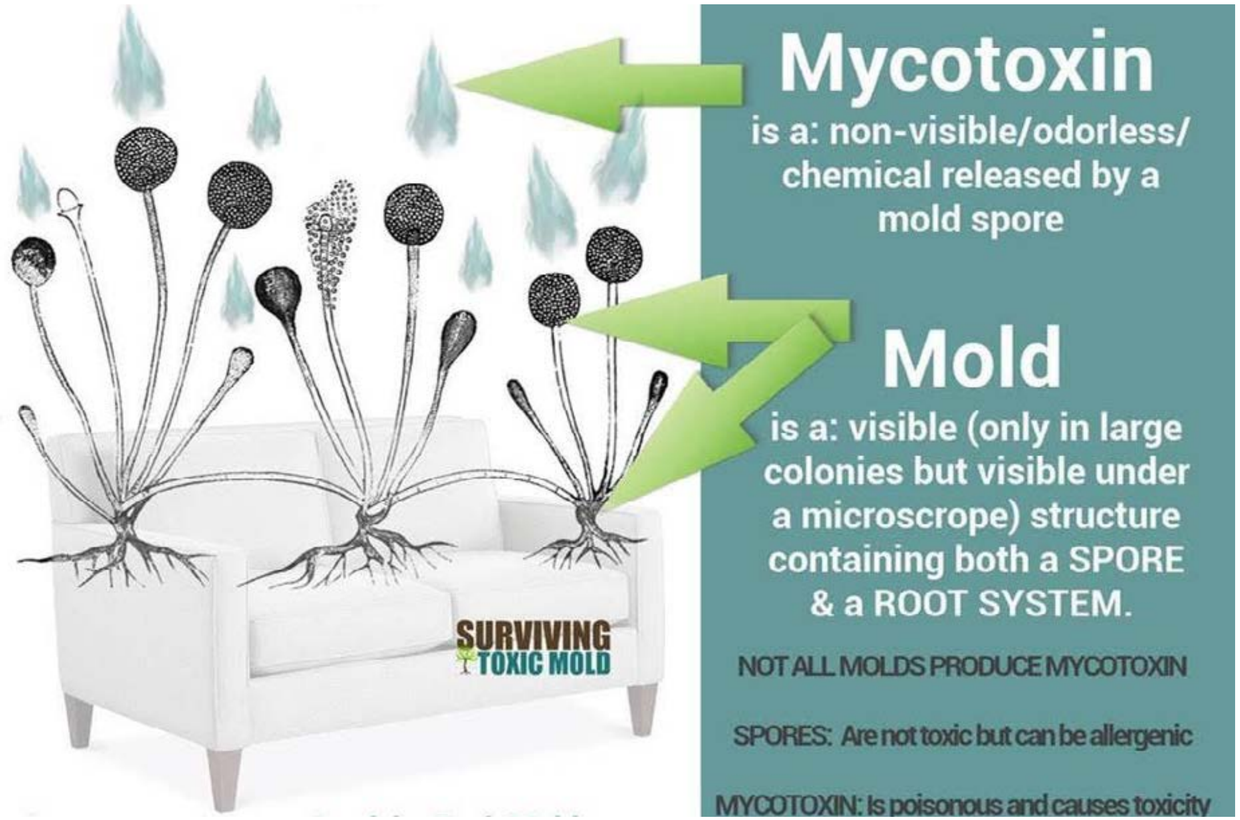
Yeast is a type of fungus that grows as a single cell

- Single celled fungus that grow by budding (splitting)
- Each new yeast cellbuds and the population grows quickly

Molds



- require moisture and organic material
- reproduce by producing large numbers of small spores
- secrete hydrolytic enzymes that degrade biopolymers
  = decomposition of organic material
- Mycoses or mycotoxicoses can
  not be transmitted from one person to another
- Mycoses are diseases from the developed world
- Mycotoxicoses are more common in the underdeveloped world
  = illness resulting from exposure to mycotoxins



Mycotoxins
are toxic mold metabolites, secondary metabolites

Mycotoxins are produced in response to oxidative stress
Pharmacological activity
Causing disease & death

Mold often results from water-damaged buildings

- Poor ventilation
- Faulty Structures
- Ground water intrusion...

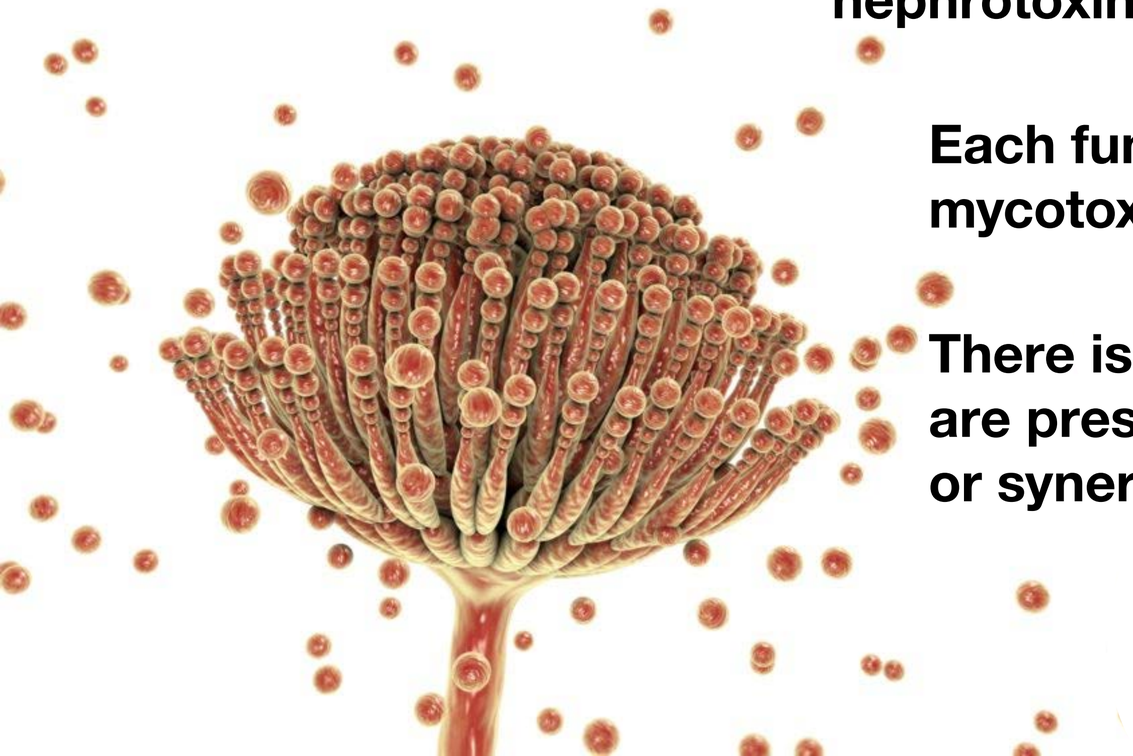
Various practices can be followed to mitigate mold issues in buildings:

Reduce moisture, properly functioning air conditioning, air filtration, removal of affected materials….

Overview of mycotoxins

It is a very heterogeneous assemblage, chemically spoken and toxigenically

Classification schemes are hard, sometimes **classified according to the organs they affect = mycotoxins classified as hepatotoxins, nephrotoxins, neurotoxins, immunotoxins etc...**



Each fungus and each strain can produce more than 1 mycotoxin

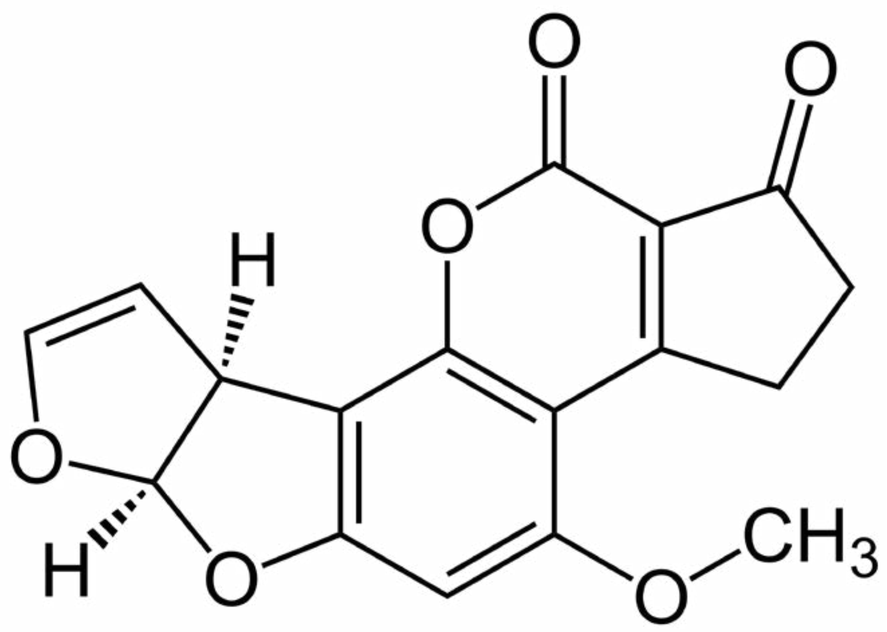
There is an high probability that many different mycotoxins are present – increasing the chances of interaction or synergy between mycotoxins

Aflatoxin = Aspergillus toxin
most commonly Aspergillus flavus (hepatotoxic, mutagenic, carcinogenic)

Difuranocoumarin derivates
Four major aflatoxins B1, B2, G1 and G2

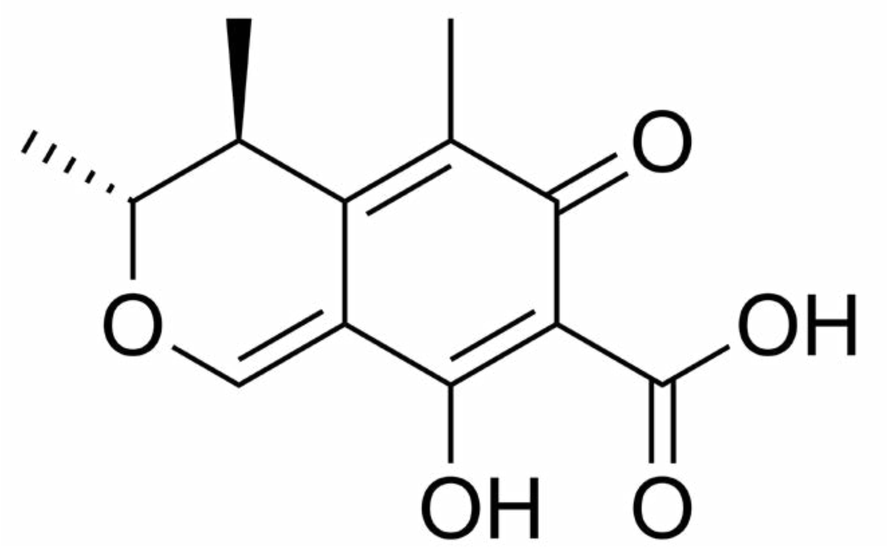
Aflatoxin B1 is the most potent natural carcinogen known

common contaminant in agriculture
Turkey X disease



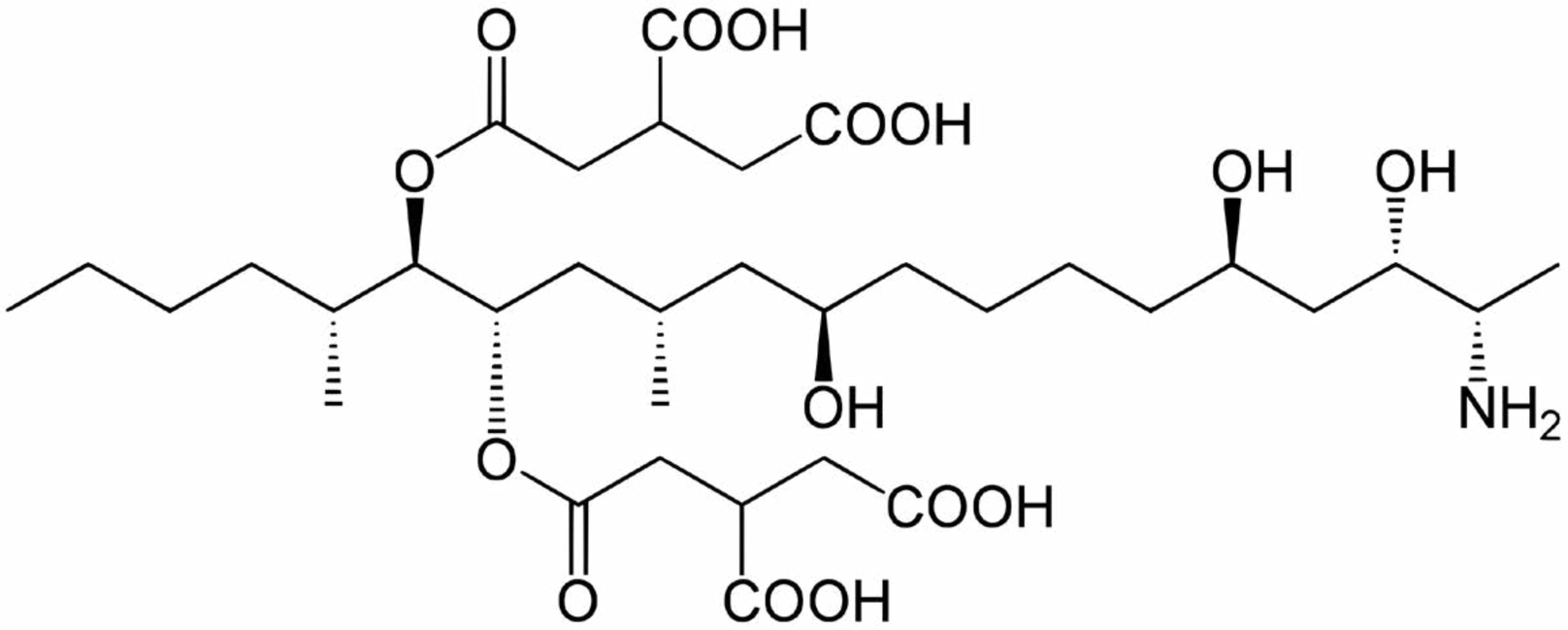
Citrinin = identified in different species of Penicillium, Aspergillus + also isolated from Monascus purpureus (red pigment)

Nephrotoxin



Fumonisins = produced by a number of Fusarium species: Fusarium verticillioides, Fusarium proliferatum as well as Alternaria alternate

Higher incidence of esophageal cancer, neural tube defects



Ochratoxin A = metabolite of Aspergillus ochraceus or Penicillium

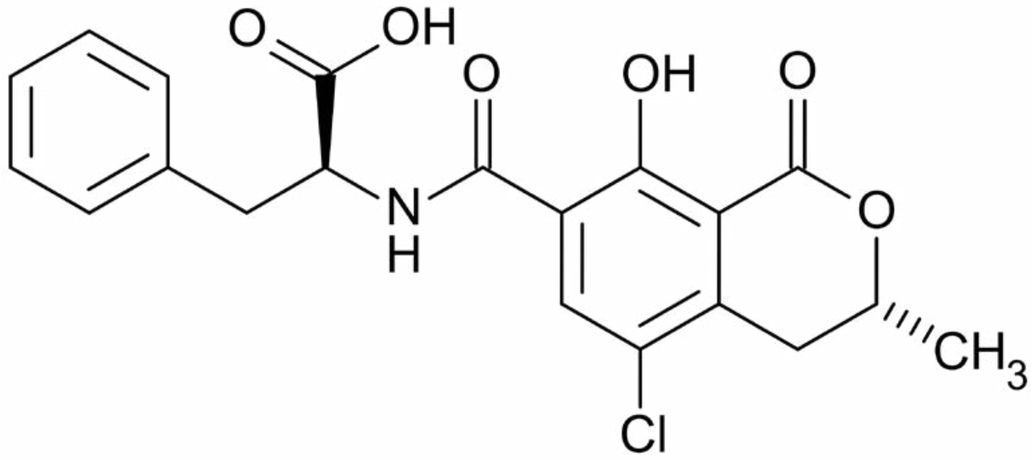
Nephrotoxin

Higher permeability through skin than other mycotoxins

In corn, oats, wheat, coffee beans and other plant products

Studies have detected Ochratoxin A in human blood and serum in many European Countries

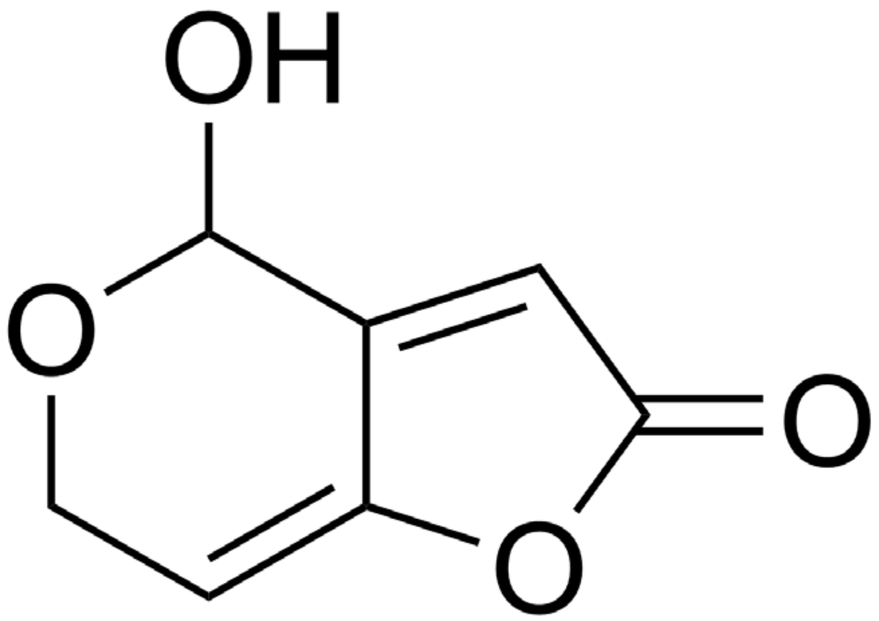
Members of the Ochratoxin family have been identified as metabolites of many different species of Aspergillus



Patulin = produced by many different molds including Penicillium patulum

Was first identified as an antibiotic, in the 50's it became apparent patulin was also toxic to humans and animals;

Patulin was reclassified as a mycotoxin.



Trichotecenes constitute a family of more than 60 sesquiterpenoid metabolites produced by a number of molds including Fusarium, Myrothecium, Stachybotrys Trichoderma and others

T2 and deoxynavenol appear to be the most potent

Commonly found as food contaminants

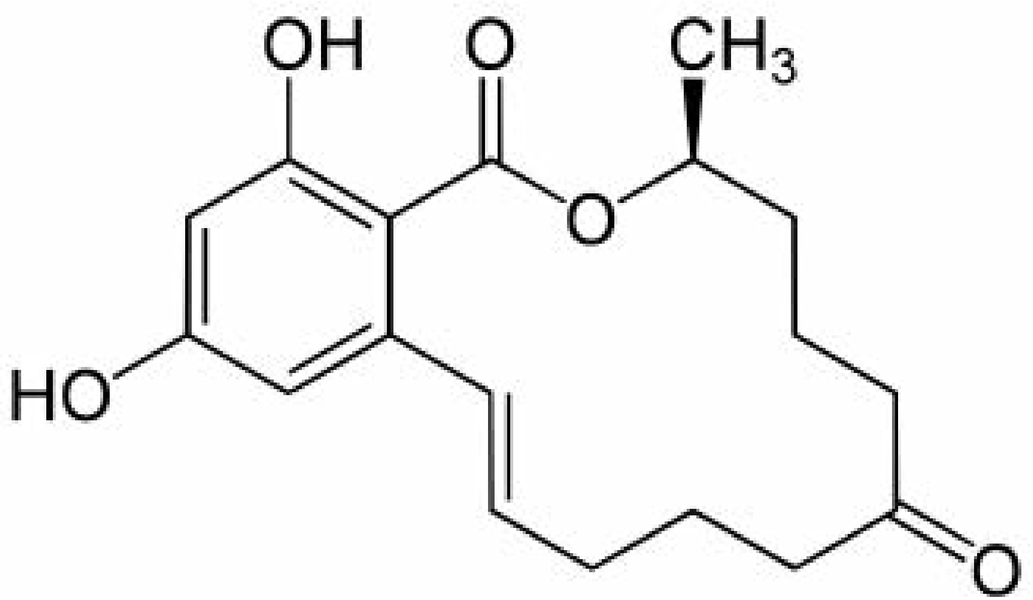
Powerful inhibitors of protein synthesis

Consumption can result in vomiting and hemorrhage

Zearalenone = Fusarium metabolite (F2)

potent estrogenic activity, also labelled as phyto-estrogen

regular contaminant of cereals

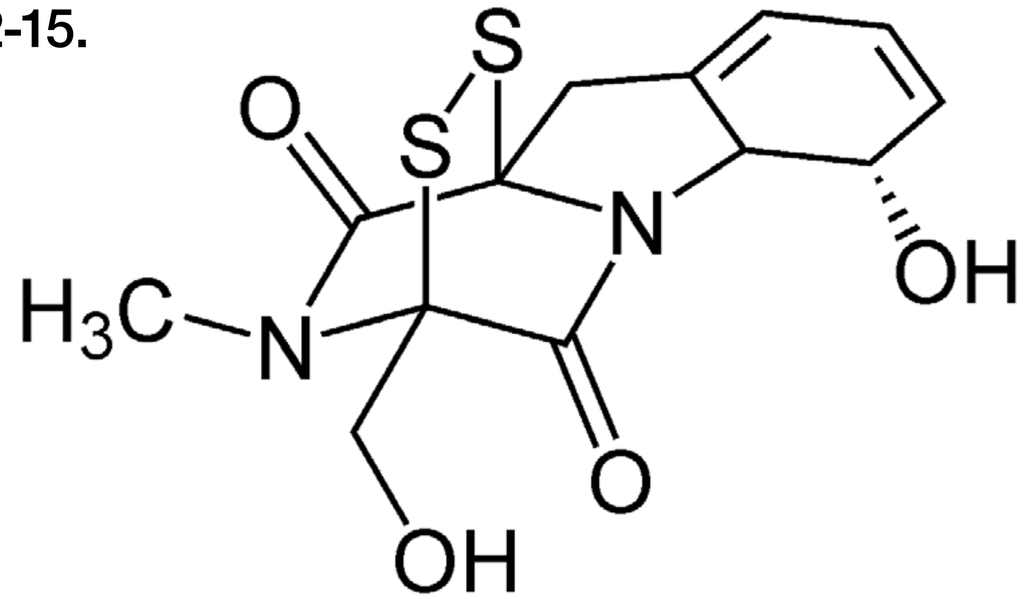


Gliotoxins = produced by Aspergillus fumigatus + Candida albicans

Inhibit T-cell activation & proliferation

Inhibit macrophage phagocytosise

Schlam, Daniel, et al.
“Gliotoxin suppresses macrophage immune function by subverting phosphatidylinositol 3, 4, 5-trisphosphate homeostasis.”
MBio 7.2 (2016): e02242-15.



Contamination results in Mycotoxicoses

- Eating contaminated food: optimum temperature for the biosynthesis of mycotoxins is 20-30°C
- Skin contact
- Inhalation: mycotoxins are not volatile but they get airborne on fungal spores and other particles of a size that is inhalable
- Mycotoxins are biological pollutants commonly found in human and animal diets

Overview

Mold spp	Mycotoxin	Urinary Testing
Aspergillus	Aflatoxin B (AF) Gliotoxin (GTX)	Aflatoxin MI (metabolite) GTX
Penicillium	Mycophenolic Acid (MPA)	MPA
Aspergillus Pencillium	Ochratoxin A (OTA) Sterigmatocystin(STG) Citrinin (CTN)	OTA STG CTN
Fusarium	Zearalenone (ZEA) Enniatin B Fumonisin(FB)	ZEA Enniatin B
Fusarium Stachybotrys	Trichothecenes: RoridinE VerrucarinA (VRA) T-2 and HT-2 toxins Deoxynavenol(DON)	RoridinE (VRA)
Chaetomium	ChaetoglobosinA (CHA)	CHA

+ Modified mycotoxins (Freire 2018)

Overview of toxic effects of Mycotoxins

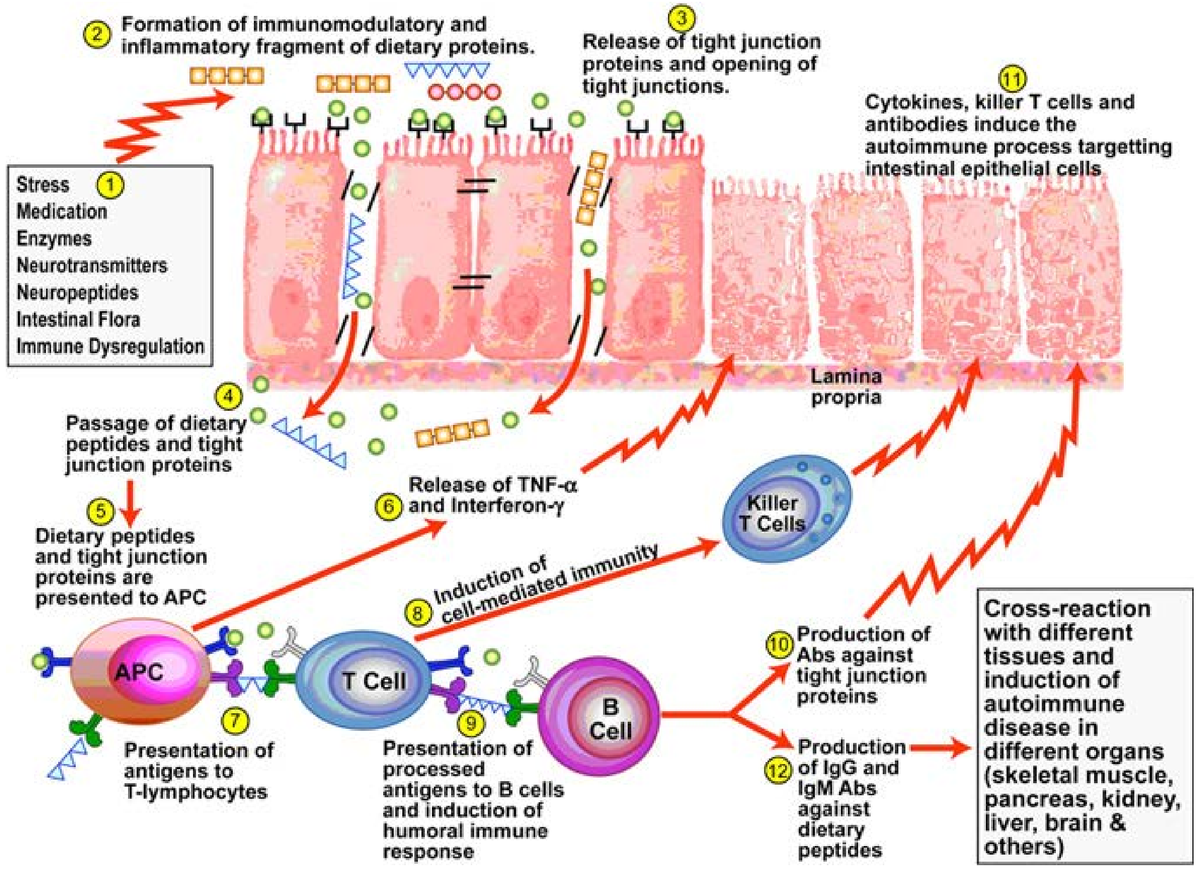
GI Toxicity

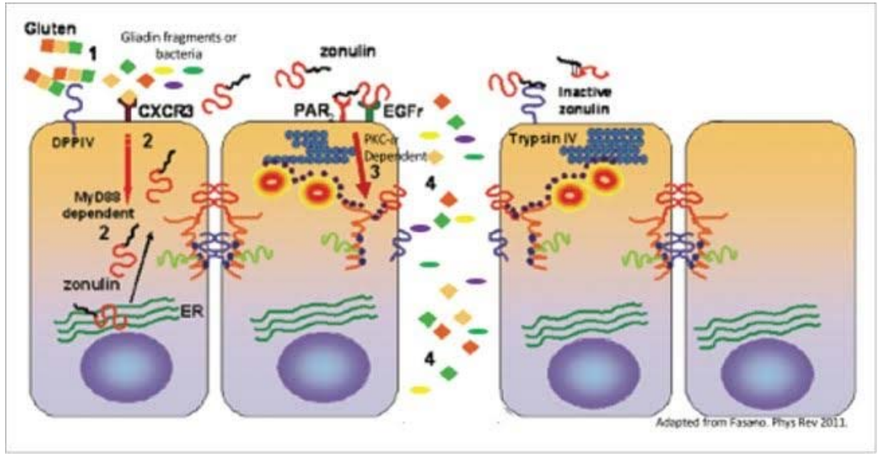
Often the GI tract is the first organ to be exposed to mycotoxins, it’s also the first tissue to suffer from the toxicity.

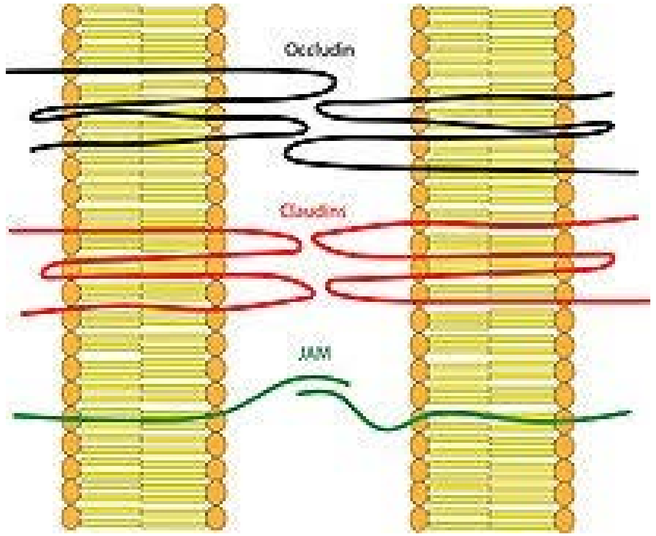
The epithelial barrier is a critical border preventing luminal material from entering the tissues.

Essential components of this barrier are the **tight junctions, the seals between the epithelial cells.**

Tight junctions restrict most microbes from penetrating







Different proteins control the plasticity of the tight junctions

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

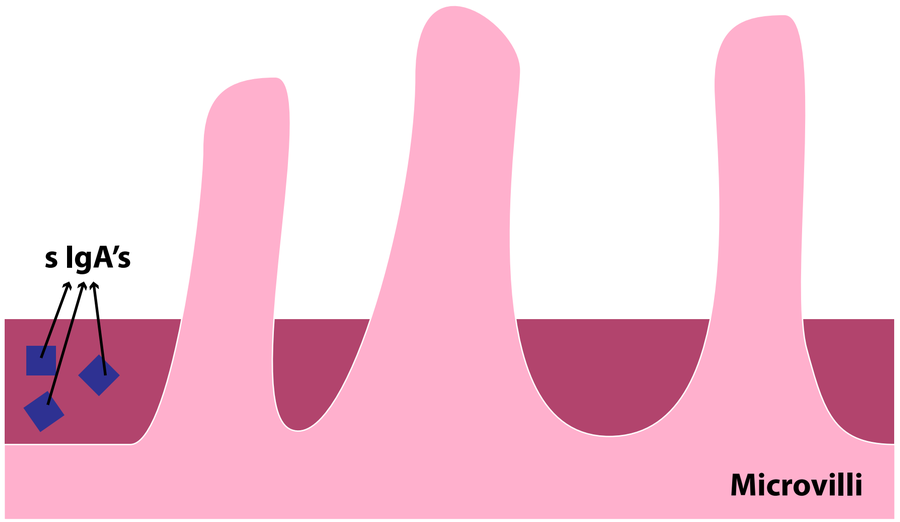
  Each strand is formed from a row of transmembrane proteins embedded in both plasma membranes

  Occludin and Adhesin are the main membrane proteins

GI Barrier dysfunction

Luo, Su, et al. **“In vitro and in vivo effects of a mycotoxin, deoxynivalenol, and a trace metal, cadmium, alone or in a mixture on the intestinal barrier.”** Environment international 132 (2019): 105082.

Deoxynavanol (DON) and Cadmium, individually and in combination, **increased paracellular permeability** in a dose dependent manner. Exposure was associated with a **decrease in occludin**



Ren, Zhihua, et al. **"Progress in Mycotoxins Affecting Intestinal Mucosal Barrier Function."** International journal of molecular sciences 20.11 (2019): 2777.

Mycotoxins downregulate adhesin & occludin
= more paracellular permeability

- oxidative damage and DNA damage induce apoptosis of intestinal epithelial cells
  + villous atrophy
- the mucin layer is disrupted
- Humoral immune lining of s IgA's is damaged

LPS

= The major part of the outer cell membrane of Gram-negative gut bacteria

Gram-negative Cell Wall

Lipid A of LPS acts as **endotoxin**; **O polysaccharides** are antigens for typing, e.g., *E. coli* O157:H7

Gram neg. bacteria are less sensitive to medications because outer membrane acts as additional barrier.

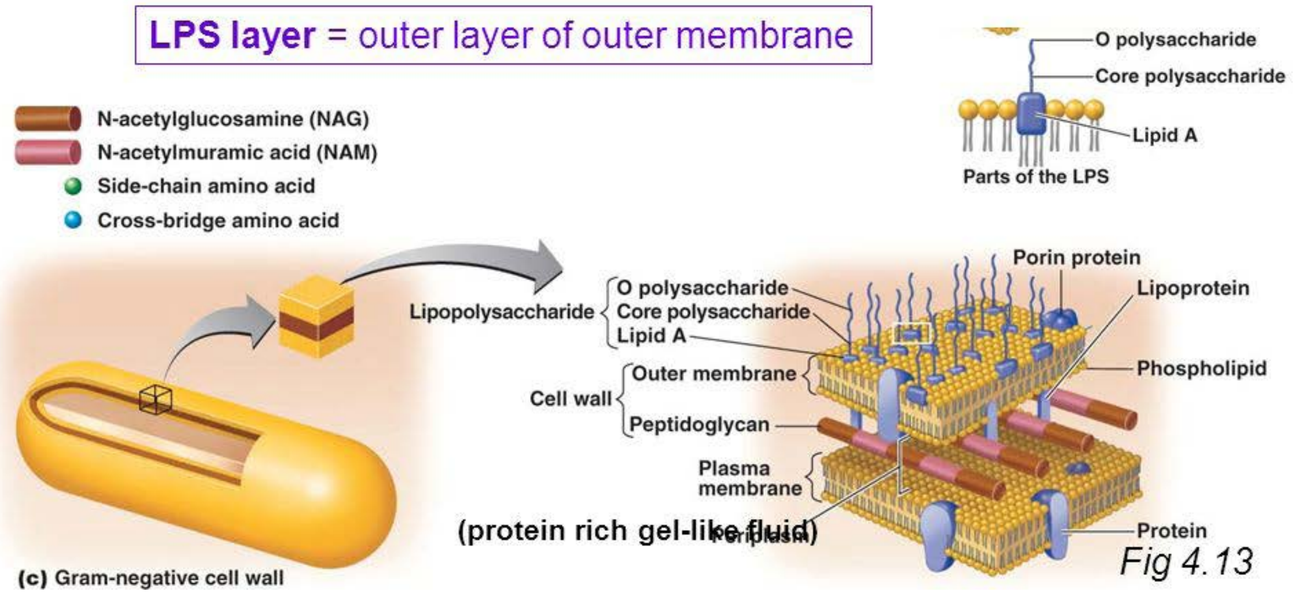
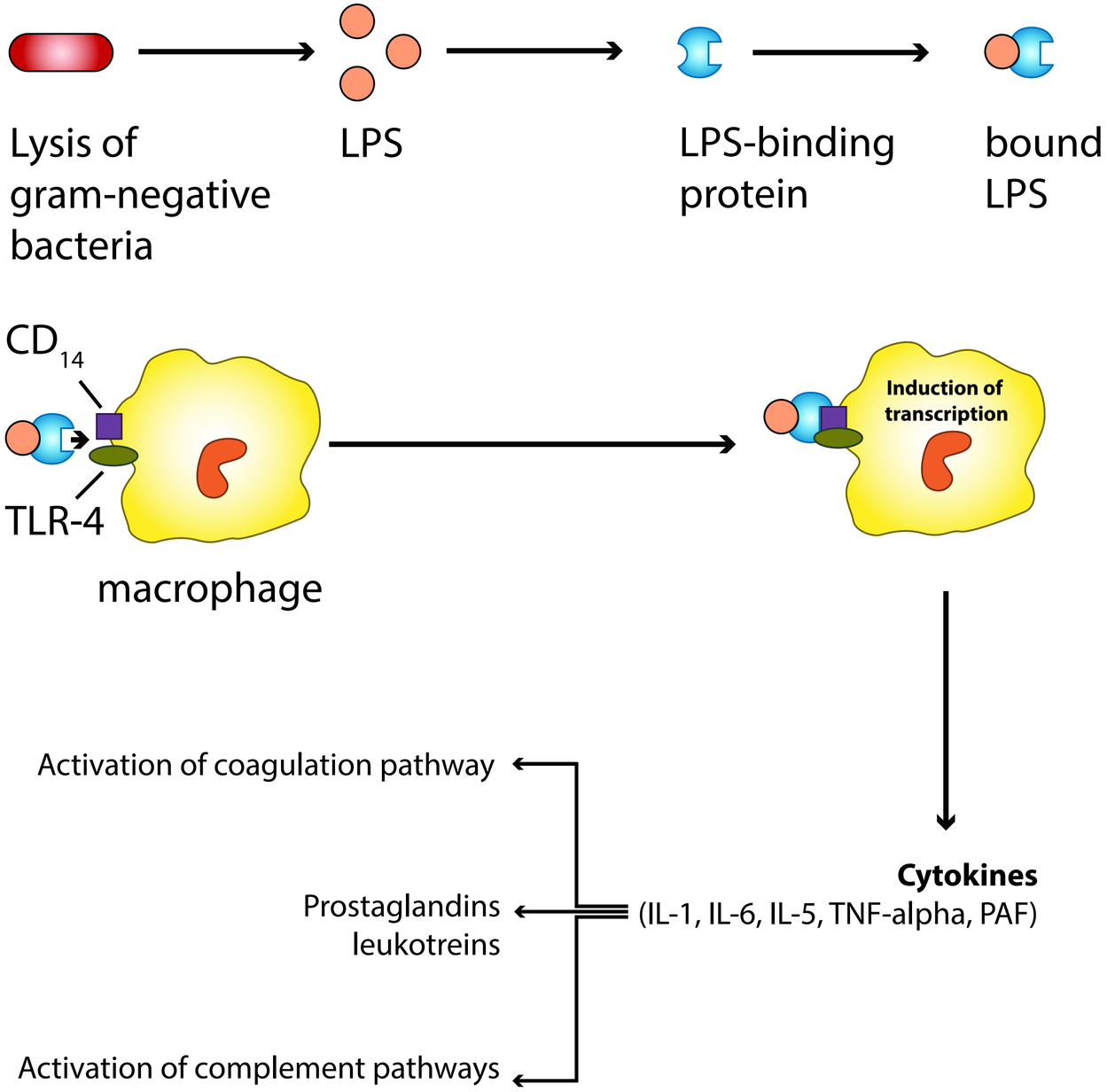
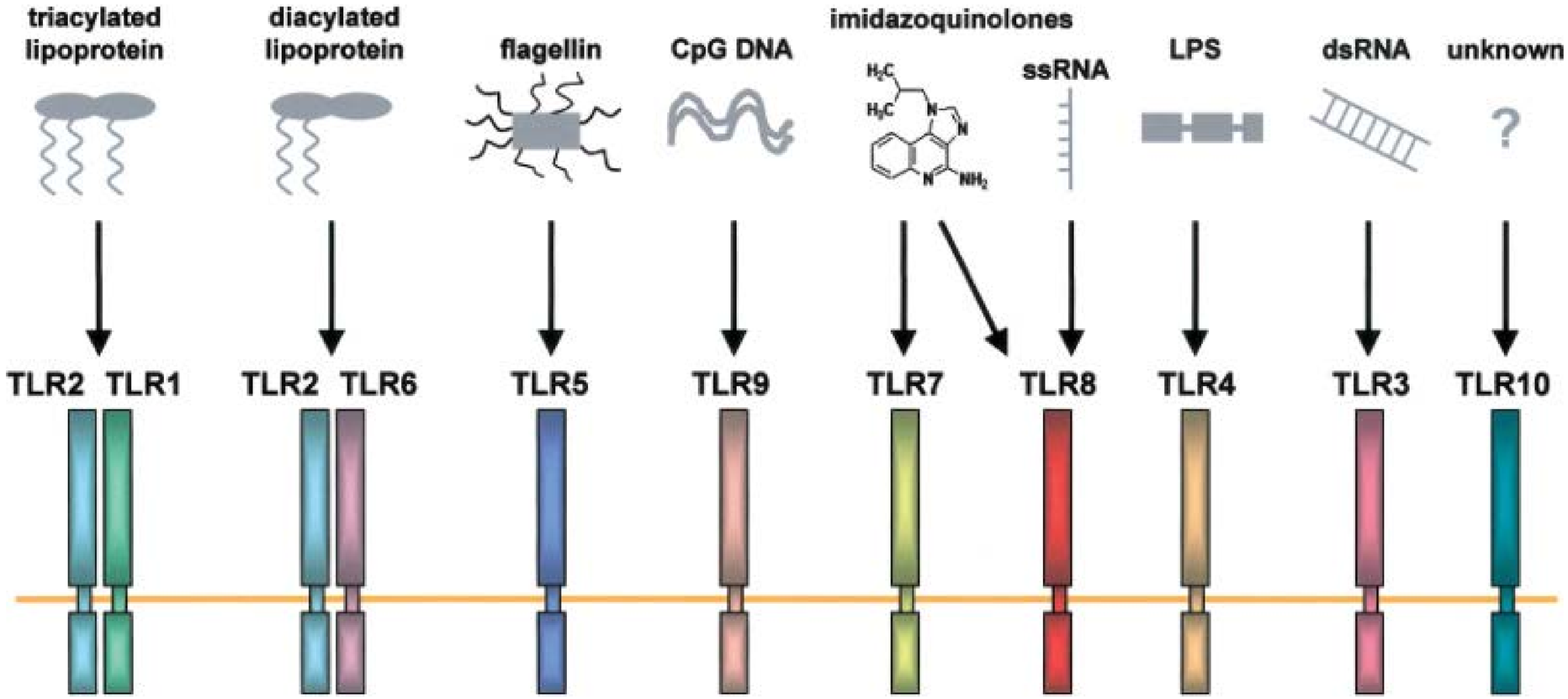


Fig 4.13


Lysis of gram-negative bacteria
LPS
LPS-binding protein
bound LPS
CD14
TLR-4
macrophage
Induction of transcription
Cytokines
(IL-1, IL-6, IL-5, TNF-alpha, PAF)
Activation of coagulation pathway
Prostaglandins leukotreins
Activation of complement pathways



TLR recognize specific microbial components derived from pathogens including bacteria, fungi, protozoa and viruses.

For recognition of Borrelia burgdorferi spirochetes : TLR1 & TLR 2
LPS are recognized by TL4 (some LPS are recognized by TLR2)
DNA viruses such as Herpes Simplex Virus (HSV) and CMV are recognized by TLR9

Modern life-style factors are causing increased intestinal barrier permeability.

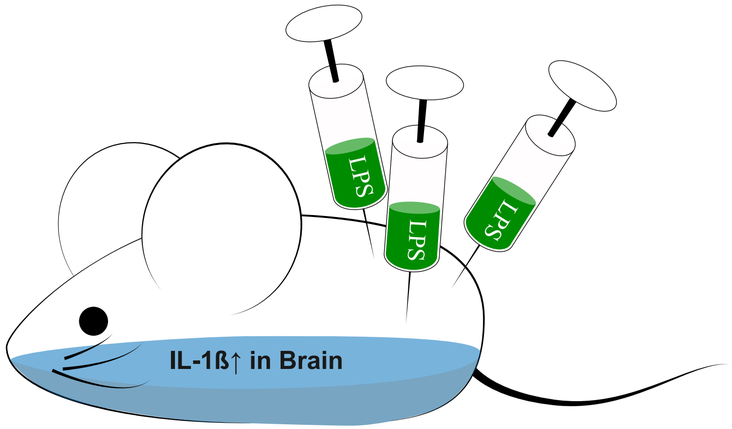
As a result we see more translocation of bacteria and toxins what is causing low-grade inflammation

This low-grade inflammation is one of the leading causes of work absence, disability and mortality.

+ we see a synergy between mycotoxins & modern life-style factors, both causing LPS-induced inflammation

Front. Immunol., 15 May 2015, **Stress induces endotoxemia and low-grade inflammation by increasing barrier permeability,** Karin de Punder and Leo Pruimboom

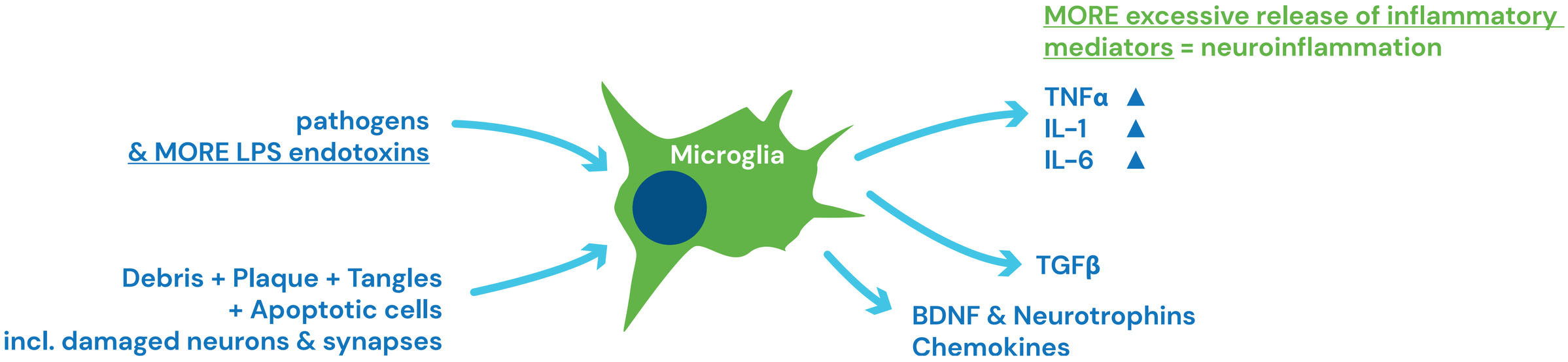
Toxicol Ind Health. 2009 Oct-Nov, **The biocontaminants and complexity of damp indoor spaces: more than what meets the eyes,** Thrasher JD, Crawley S.



Repeated exposure to systemic immune challenge increased brain IL-1β

LPS challenge on a regular basis

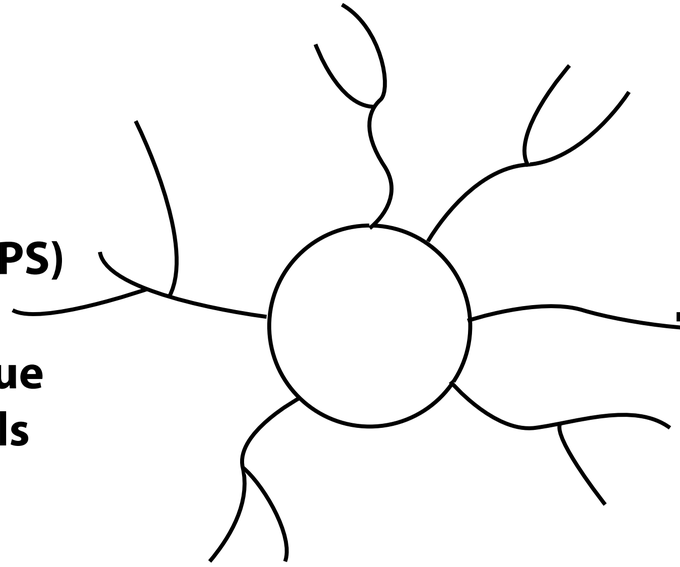
+ higher levels inflammatory mediators cause cognitive issues, behavior issues



Hoogland, Inge, et al. "Microglial activation after systemic stimulation with lipopolysaccharide and Escherichia coli." Frontiers in cellular neuroscience 12 (2018): 110.

UPDATE ON THE SITUATION IN SUSTAINED INFLAMMATION / PRIMING

Pathogens
Endotoxins (LPS)
Debris
Amyloid plaque
Apoptotic Cells



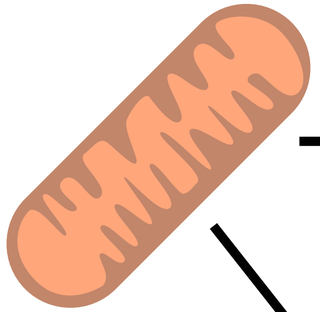
Microglia in surveillance

Pro-inflammatory mediators
Il-1β, TNFα, IL-6 IFN-γ, δ-LoxCOX-2

if release of inflammatory mediators is chronic & sustained

Neuro toxic factors
$ONOO^-$
ROS
NO
Glutamate

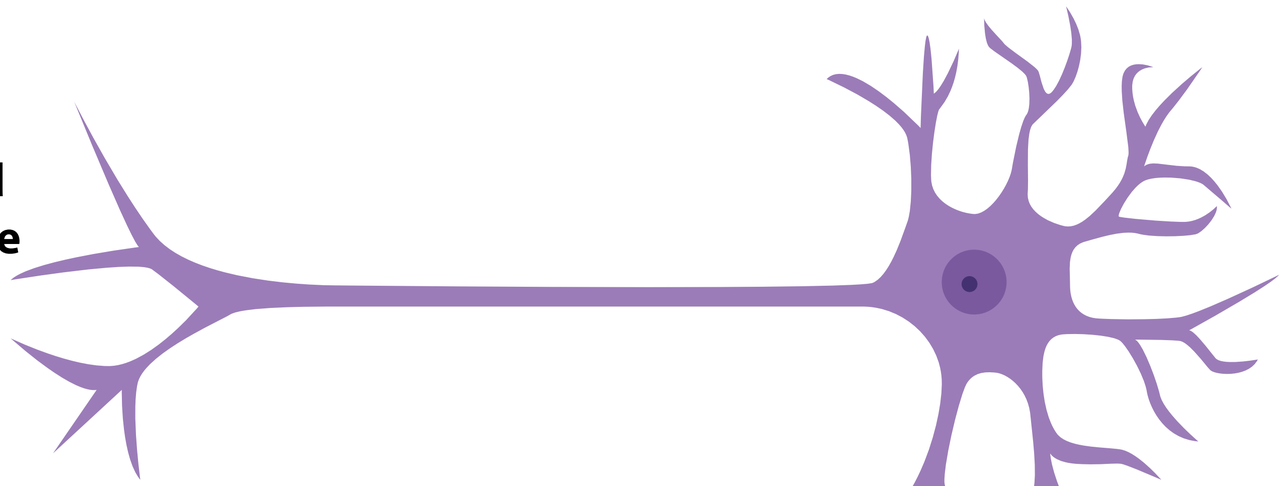
Neuronal damage & neurodegeneration



OH^-

O_2^-

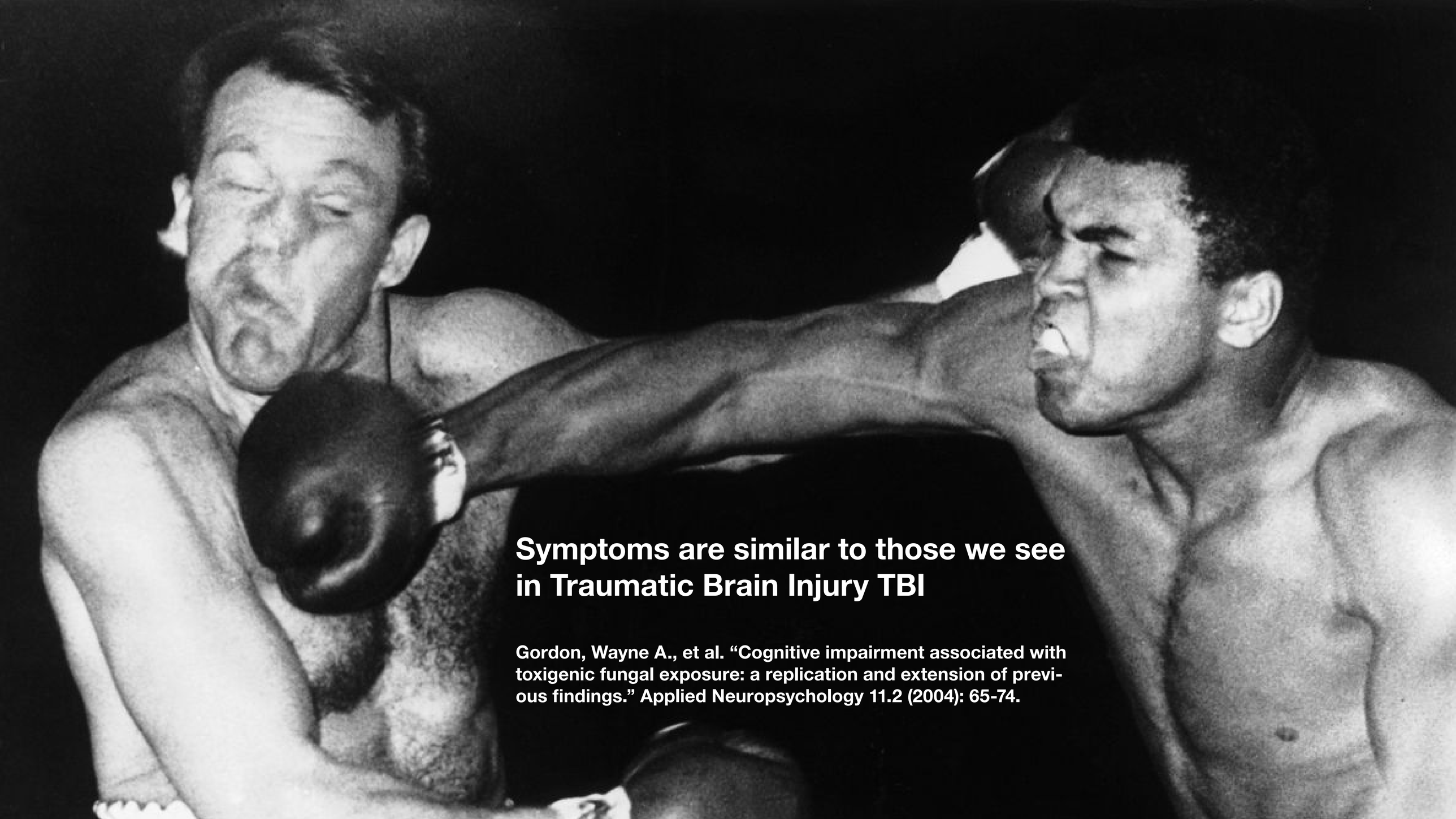
ATP synthesis blocked
Mitochondrial damage
Apoptosis induced



But Mycotoxins can also affect brain & nervous system directly

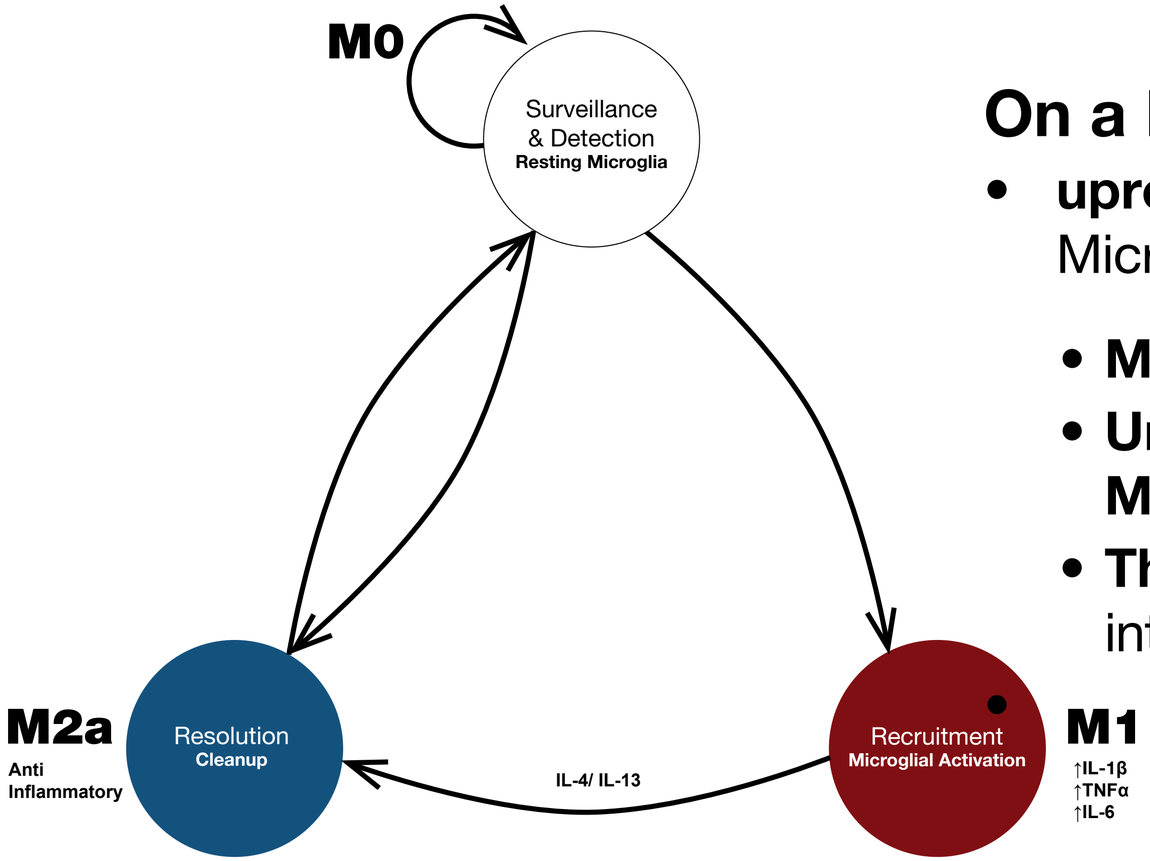
The brain is **highly vulnerable** to mold invasion due to its **high fat content and the lipophilic nature of mold**
Many mycotoxins easily cross BBB

- Demyelination
- Astrocyte disturbances
- Increased expression of pro-inflammatory cytokines
- Depletion of glutathione
- Reduced mitochondrial function and apoptosis of neurons



Symptoms are similar to those we see in Traumatic Brain Injury TBI

Gordon, Wayne A., et al. “Cognitive impairment associated with toxigenic fungal exposure: a replication and extension of previous findings.” Applied Neuropsychology 11.2 (2004): 65-74.



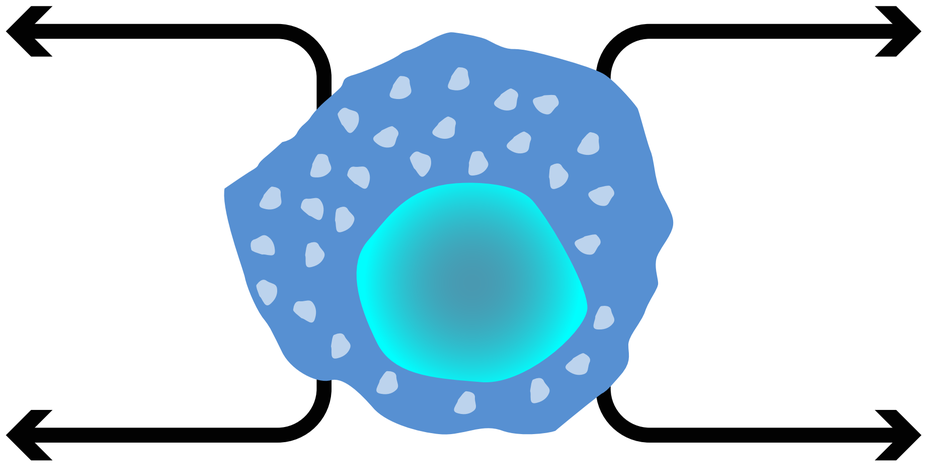
On a Microglial level

- **upregulation of M1 microglial phenotype**
  Microglia actually switch from 1 phenotype to another
  - **M0** = resting state, steady state
  - **Under Stress** Microglia are induced into **M1 phenotype**, releasing inflammatory cytokines
  - **The inflammation fades away** and microglia shift into **M2 neuroprotection**

On a Microglial level

- **More release of proinflammatory mediators in Mast cells**

Cytokines/ Chemokines
Transforming Growth Factor
Interleukins
Macrophage Inhibitory Factor
Tumor Necrosis Factor
Interferon Y



Growth Factors
Fibroblast Growth Factor
Vascuylar Endothelial Growth Factor
Nerve Growth Factor
Gonadotropin Releasing Hormone
Stem Cell Factor
Colony Stimulating Factor

Proteases
Chymase
Tryptase
Histamine
Carboxypeptidase

Leukotrienes
Leukotriene C4
Leukotriene B4
Prostaclandin D2
Prostaclandin E2

Ratnaseelan, Aarane M., Irene Tsilioni, and Theoharis C. Theoharides
“Effects of mycotoxins on neuropsychiatric symptoms and immune processes.” Clinical therapeutics 40.6 (2018): 903-917.

Individuals exposed to mycotoxins report an extensive range of symptoms

Malaise

Fatigue

Cognitive impairment

Emotional dysfunction

Inability to walk in a straight line with eyes closed

Short-term memory loss

Issues with reaction time

Depression

Different studies have focused on deficits in cognitive development, resulting from exposure to mold & mycotoxins both prenatally and during child-hood

Poland

277 infants exposed to mold in contaminated homes in the early postnatal period. We see **deficits in IQ** when exposu-re time was more than two years.

Spain

482 infants showed significant **decrease in cognitive sco-re** when persistent home dampness in children's bedroom

McCall, Robert B. "Childhood IQ's as predictors of adult educational and occupational status." Science 197.4302 (1977): 482-483.

Anyanwu, Ebere C., Andrew W. Campbell, and Aristo Vojdani. "Neurophysiological effects of chronic indoor environmental toxic mold exposure on children." The Scientific World Journal 3 (2003): 281-290.

Jedrychowski, Wieslaw, et al. "Cognitive function of 6-year old children exposed to mold-contaminated homes in early postnatal period. Prospective birth cohort study in Poland." Physiology & behavior 104.5 (2011): 989-995.

Casas, Lidia, et al. "Early life exposures to home dampness, pet ownership and farm animal contact and neuropsychological development in 4 year old children: A prospective birth cohort study." International journal of hygiene and environmental health 216.6 (2013): 690-697.

Recent studies have reported a significant association between exposure to mold and autism spectrum disorder (ASD)

A significant association between levels Ochratoxin A and children diagnosed with ASD

172 children with ASD have higher levels Aflatoxin M1, Ochratoxin A & Fumonisin B1 in serum , compared to healthy controls

Centers for Disease Control and Prevention. “CDC estimates 1 in 59 children has been identified with autism spectrum disorder.” (2018).

Geschwind, Daniel H., and Matthew W. State. “Gene hunting in autism spectrum disorder: on the path to precision medicine.” The Lancet Neurology 14.11 (2015): 1109-1120.

Willsey, A. Jeremy, and Matthew W. State. “Autism spectrum disorders: from genes to neurobiology.” Current opinion in neurobiology 30 (2015): 92-99.

De Santis, Barbara, et al. “Role of mycotoxins in the pathobiology of autism: A first evidence.” Nutritional neuroscience 22.2 (2019): 132-144.

Von Tobel, Jenny Sandström, et al. “Repeated exposure to Ochratoxin A generates a neuroinflammatory response, characterized by neurodegenerative M1 microglial phenotype.” Neurotoxicology 44 (2014): 61-70.

Treatment of impaired intestinal barrier induced by mycotoxins

What are treatment options?

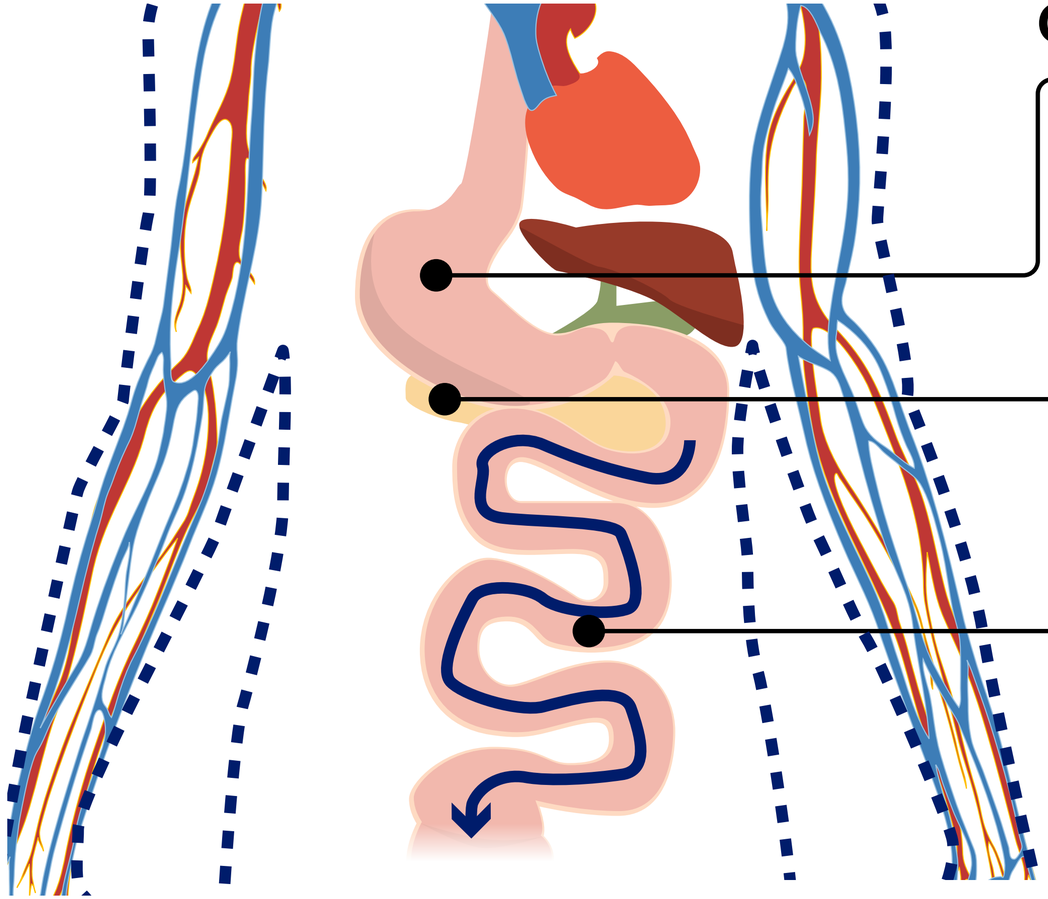
Rebuilding Gut and Intestinal permeability → Gut fixing protocol

- diluted chloric acid & pepsine **= rebuild PH**
- enzymes & DPP4 **= rebuild digestion**
- targeted glutamine **= rebuild sIgA barrier**

without increasing ammonia & glutamate

Shaik, Yasdani, et al. “Impact of polyphenols on mast cells with special emphasis on the effect of quercetin and luteolin.” Central-European journal of immunology 43.4 (2018): 476.

Angeloni, Cristina, and Silvana Hrelia. “Quercetin reduces inflammatory responses in LPS-stimulated cardiomyoblasts.” Oxidative medicine and cellular longevity 2012 (2012).



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: Take 3 x 10 - 20 drops per day at the start of each meal, swallow immediately.

Daily dose based on 30 drops 30 ml per bottle	
	Amount per 30 ml
Purified water	15,3 ml
Glycerol	10 ml
Hydrochloric acid HCl 37%	2,7 ml
Pepsine	2 ml

Gluten DPP4 Complex

Indication: DPP-IV proteolytic enzyme complex.
Intolerance for gluten and/or casein.
Indigestion, gas, bloating, constipation and diarrhea.

Dosage: Take 3 x 1 caps per day at the beginning of each meal.

Daily dose based on 3 vegecaps 90 vegecaps per container	
	Amount per 3 vegecaps
Protease IV	60 mg
Lactase	60 mg
Protease (zuur en neutraal)	70,35 mg
Amylase	30 mg
Maltodextrine	24,45 mg
Gluco-amylase	15 mg
Invertase	6 mg
Lipase	4,2 mg

Perm Plus Coated Tablets

Indication: Rebuilding intestinal permeability and immunity with targeted released molecules.

Dosage: The first month: take 3 x 2 tablets per day. Then take 3 x 1 tablet per day 20 min. before food.

Daily dose based on 3 tablets 90 tablets per container	
	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

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

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.

Treatment of inflammation induced by mycotoxins

Reducing the inflammation caused by LPS-translocation

LPS interacts with TLR4 receptors, NF-KB is induced and pro-inflammatory cytokines are released

- Curcumin, in its most bioavailable form, downregulates NF-KB and reduces inflammation
- Sulforaphane (from Cruciferous vegetables) significantly suppressed the LPS-induced COX-2 activation
- Resveratrol & Green Tea in a complementary way efficiently reduce LPS-induced inflammation

Chowdhury, Rupak, et al. “Curcumin attenuation of lipopolysaccharide induced cardiac hypertrophy in rodents.” ISRN inflammation 2013 (2013).

Woo, Kyung Jin, and Taeg Kyu Kwon. “Sulforaphane suppresses lipopolysaccharide-induced cyclooxygenase-2 (COX-2) expression through the modulation of multiple targets in COX-2 gene promoter.” International immunopharmacology 7.13 (2007): 1776-1783.

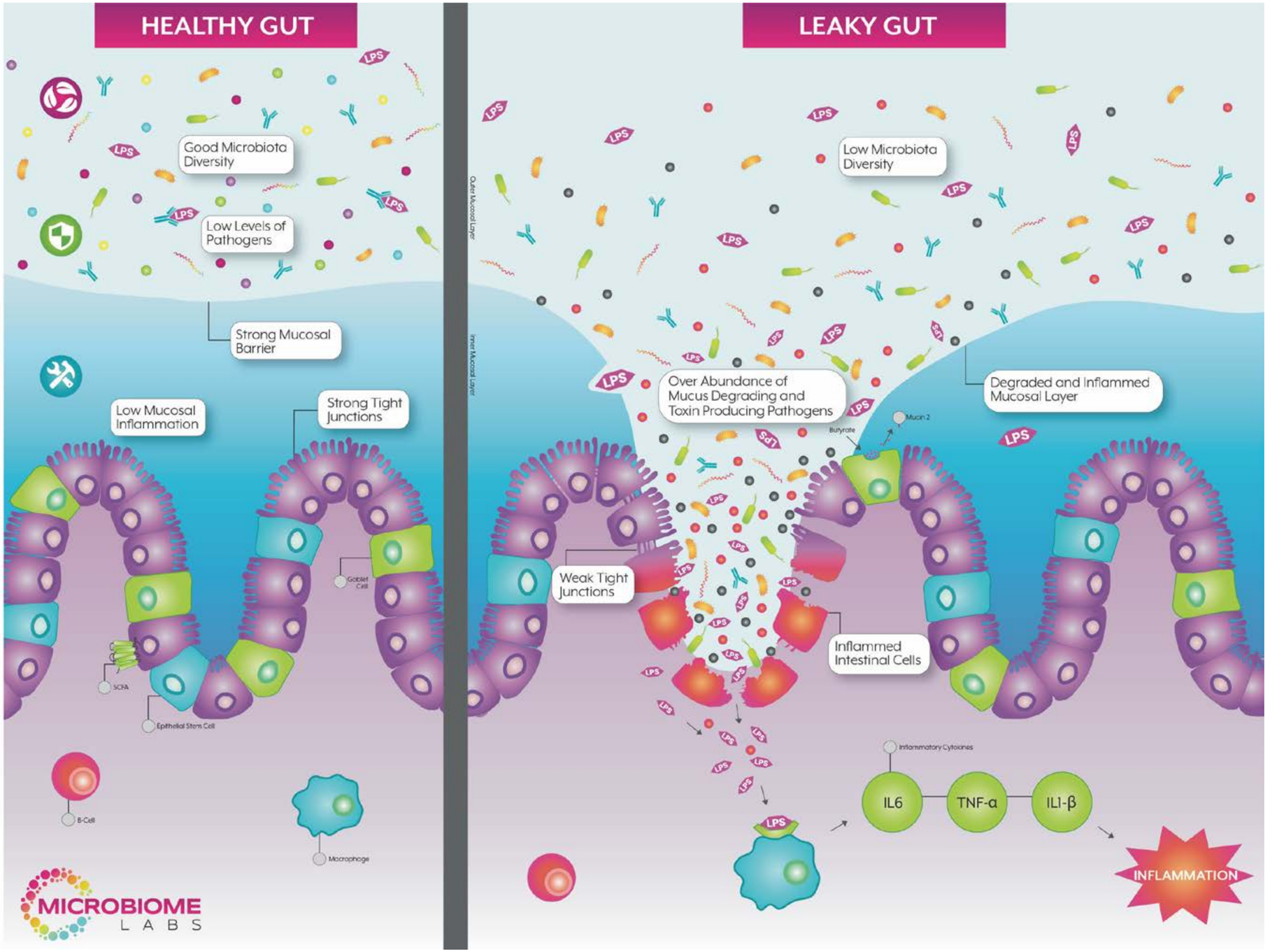
Birrell, Mark A., et al. “Resveratrol, an extract of red wine, inhibits lipopolysaccharide induced airway neutrophilia and inflammatory mediators through an NF-kB-independent mechanism.” The FASEB journal 19.7 (2005): 840-841.

+ The Spore solution

The use of soil-based probiotics to remote microbiome and reduce post-prandial raise in endotoxins

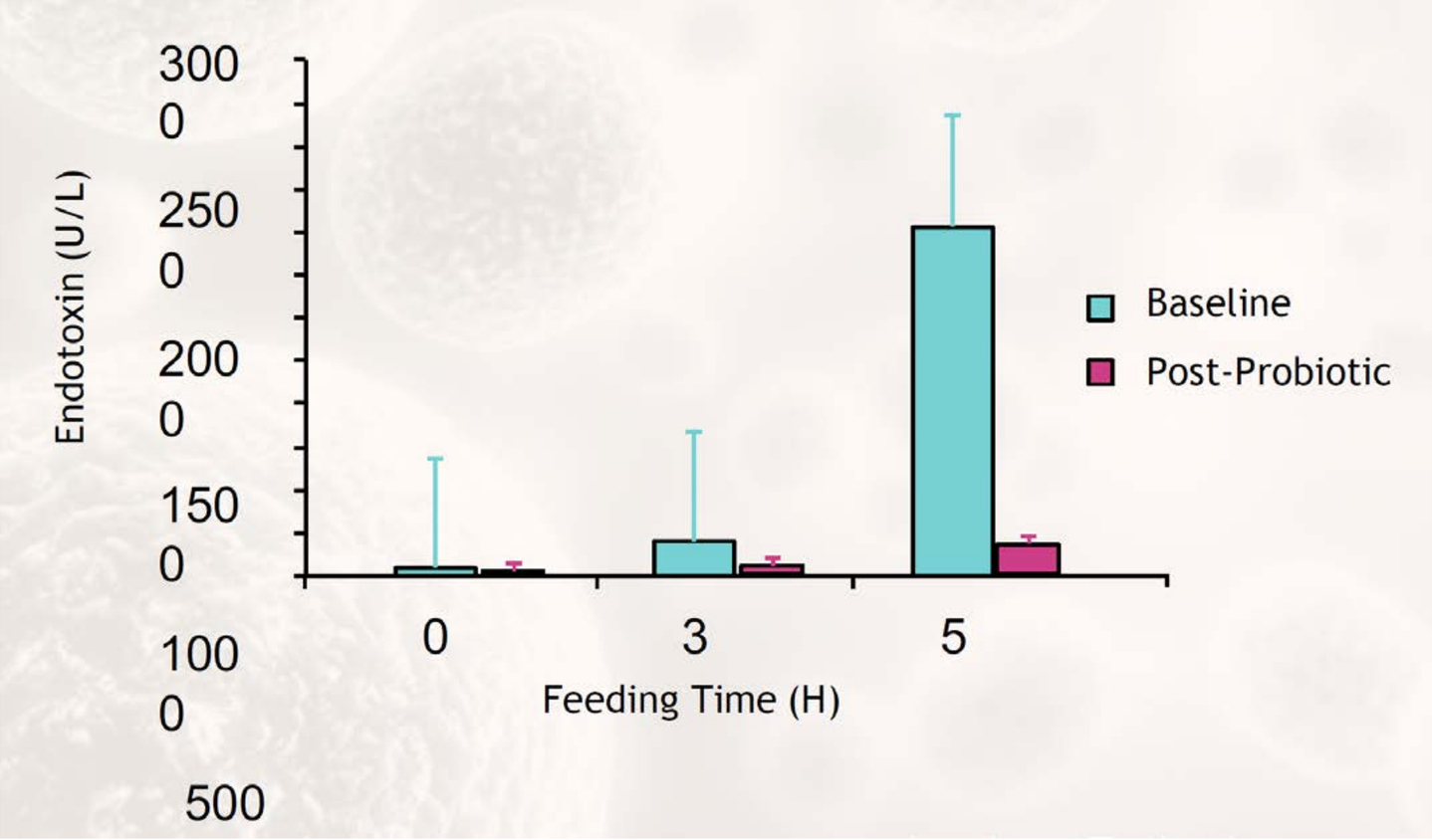
- Compositions with Bacillus subtilis & Bacillus coagulans show benefits

McFarlin, Brian K., et al. “Oral spore-based probiotic supplementation was associated with reduced incidence of post-prandial dietary endotoxin, triglycerides, and disease risk biomarkers.” World journal of gastrointestinal pathophysiology 8.3 (2017): 117.


HEALTHY GUT
LEAKY GUT
LPS
Good Microbiota Diversity
Low Levels of Pathogens
Strong Mucosal Barrier
Low Mucosal Inflammation
Strong Tight Junctions
Goblet Cell
SCFA
Epithelial Stem Cell
B-Cell
Macrophage
Outer Mucosal Layer
Inner Mucosal Layer
Low Microbiota Diversity
Over Abundance of Mucus Degrading and Toxin Producing Pathogens
Degraded and Inflammed Mucosal Layer
Mucin 2
Butyrate
Weak Tight Junctions
Inflammed Intestinal Cells
Inflammatory Cytokines
IL6
TNF-α
IL1-β
INFLAMMATION
MICROBIOME LABS

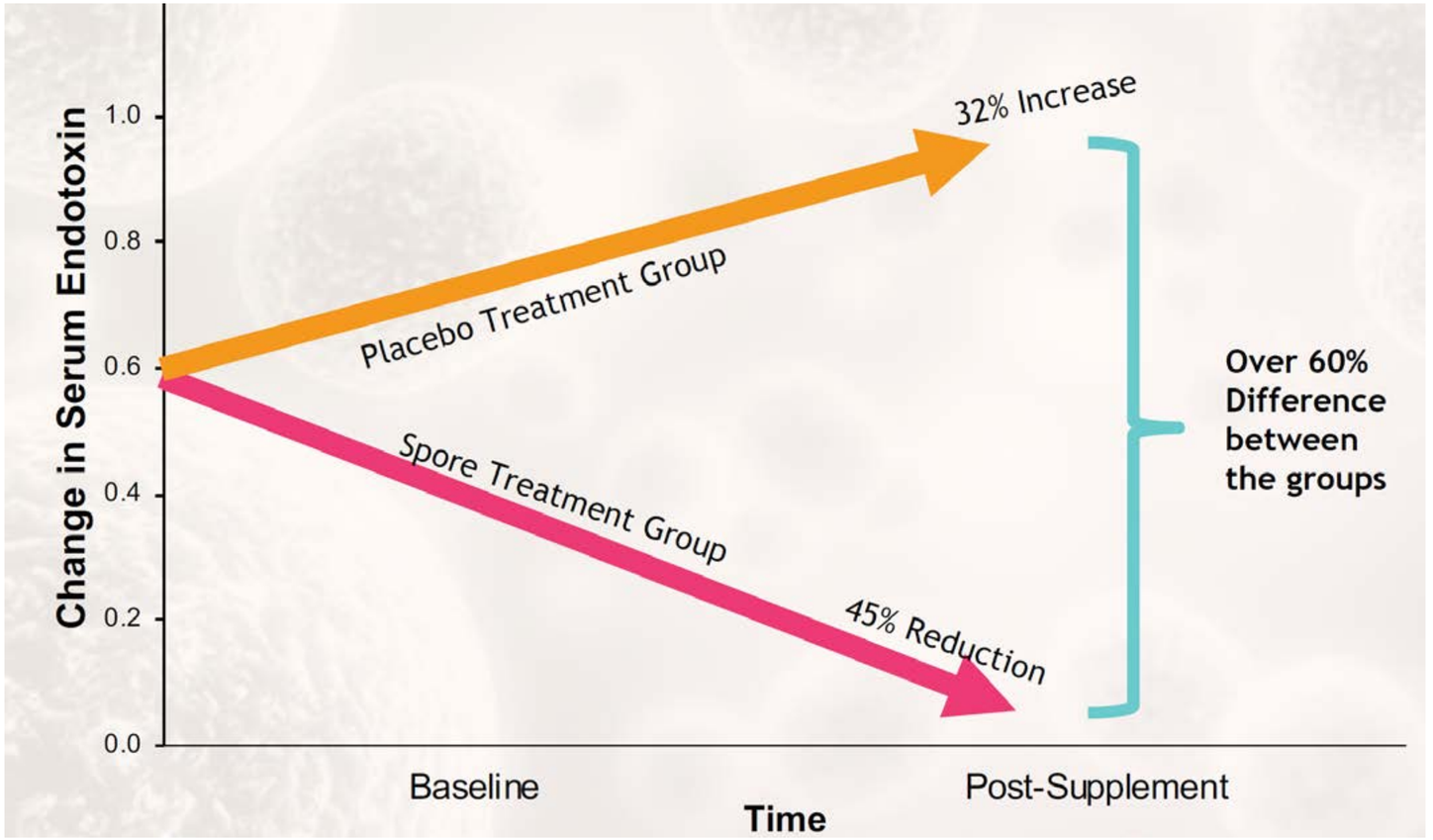
The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal: Pilot Study

Principal Investigator: Brian K. McFarlin, PhD, FACSM, FTOS
University of North Texas



The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal: An Expanded Pilot Study

Principal Investigator: Brian K. McFarlin, PhD, FACSM, FTOS
University of North Texas



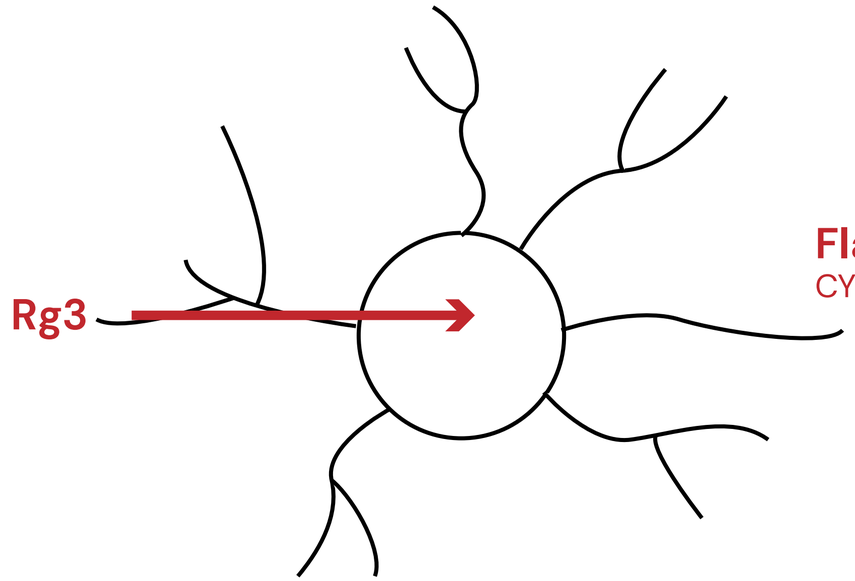
Gong, Yi, Hui Li, and Yan Li. “Effects of Bacillus subtilis on epithelial tight junctions of mice with inflammatory bowel disease.” Journal of Interferon & Cytokine Research 36.2 (2016): 75-85.

Samanya, Mongkol, and Koh-en Yamauchi. “Histological alterations of intestinal villi in chickens fed dried Bacillus subtilis var. natto.” Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology 133.1 (2002): 95-104.

Gu, Min Jeong, et al. “Bacillus subtilis protects porcine intestinal barrier from deoxynivalenol via improved zonula occludens-1 expression.” Asian-Australasian journal of animal sciences 27.4 (2014): 580.

Immunological inducers

Summary of studied treatment options = targeted molecules



Rg3

Flavonoids block
CYTOQUEL , AO Defense

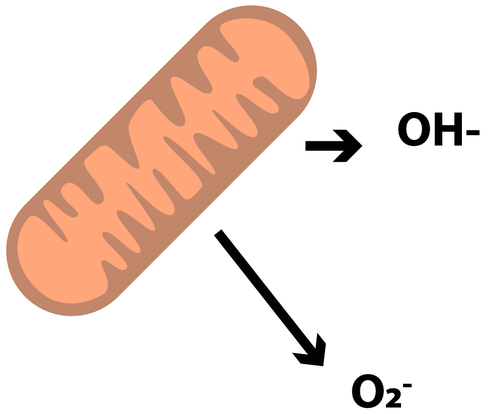
SCFA / butyrate coated

Pro-inflammatory mediators
Il-1β, TNFα, IL-6 IFN-γ, δ-LoxCOX-2

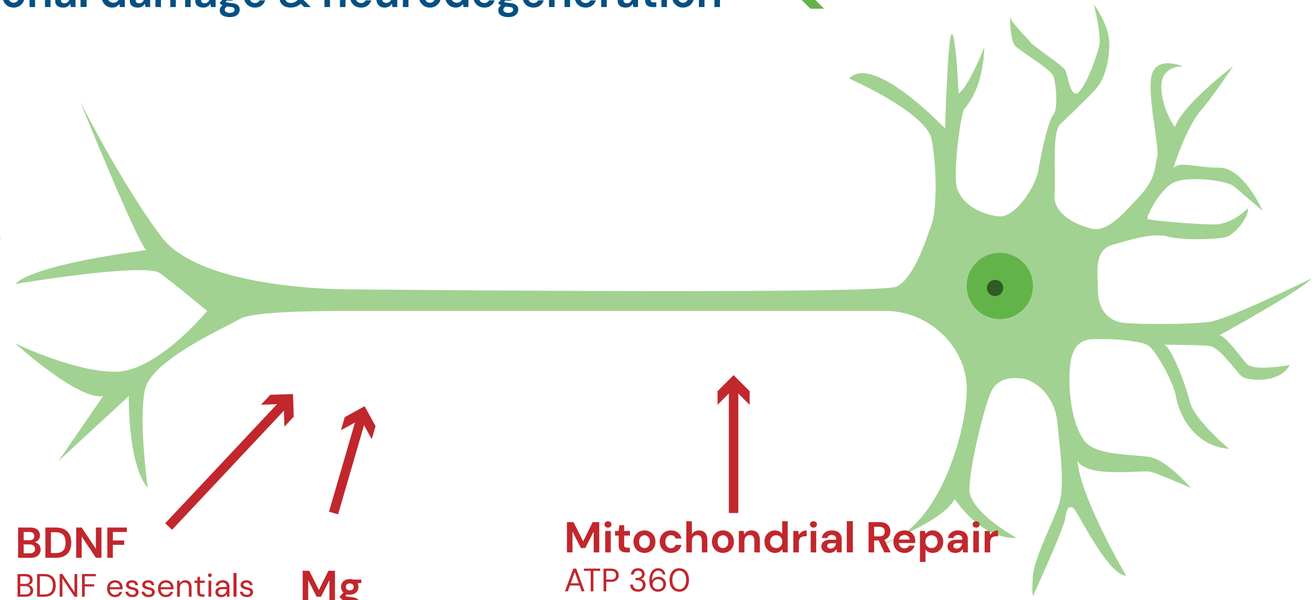
Neuro toxic factors
ONOO-
ROS
NO
Glutamate

Antioxidants
Trifortify, H20 absorb

Neuronal damage & neurodegeneration



ATP synthesis blocked
Mitochondrial damage
Apoptosis induced



BDNF
BDNF essentials

Mg
Magnesium C Complex

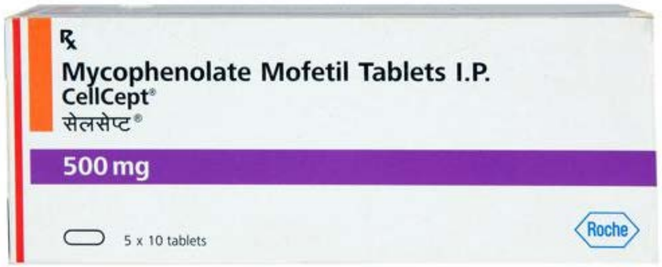
Mitochondrial Repair
ATP 360

Liew, Winnie-Pui-Pui, and Sabran Mohd-Redzwan. “Mycotoxin: its impact on gut health and microbiota.” Frontiers in cellular and infection microbiology 8 (2018): 60.

Ratnaseelan, Aarane M., Irene Tsilioni, and Theoharis C. Theoharides. “Effects of mycotoxins on neuropsychiatric symptoms and immune processes.” Clinical therapeutics 40.6 (2018): 903-917.

Von Tobel, Jenny Sandström, et al. “Repeated exposure to Ochratoxin A generates a neuroinflammatory response, characterized by neurodegenerative M1 microglial phenotype.” Neurotoxicology 44 (2014): 61-70.

Uetsuka, Koji. “Mechanisms of mycotoxin-induced neurotoxicity through oxidative stress-associated pathways.” International journal of molecular sciences 12.8 (2011): 5213-5237.



Overview of toxic effects of Mycotoxins

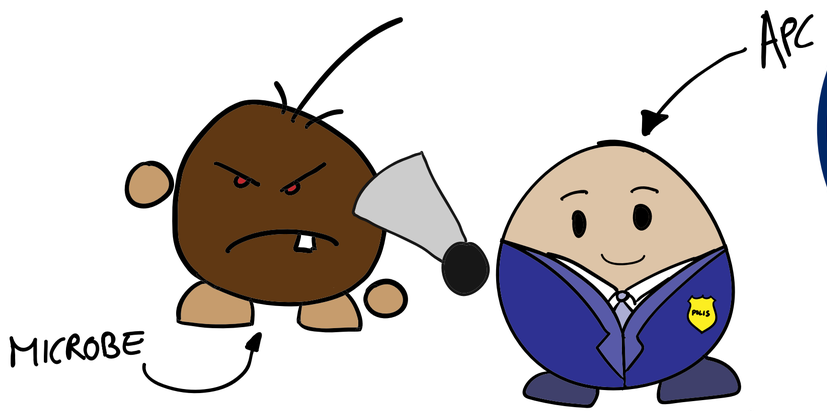
Immunotoxicity

Mycotoxins disrupt our immune response

Pathogen Specific immune response

Pathogen	Phagocytotic cells	Natural Killer cells	Complement activation	Example
Viruses	Yes	Yes	No	Influenza, mumps, measles, rhinovirus
Bacteria: intracellular	Yes*	Yes*	No	Listeria, Legionella, TB, Rickettsia
Bacteria: extracellular	Yes	No	Yes	Staph, Strep, Neisseria, Salmonella
Protozoa: intracellular	No	No	No	Plasmodium malaria, Leishmania donovani
Protozoa: extracellular	Yes	No	Yes	E. histolyticia, Giardia
Fungi	No	Yes	Yes	Candida, histoplasma, Cryptococcus

Doan T (2008).*Immunology*. Lippincott Williams & Wilkins. p.172.ISBN978-0-7817-9543-2.



Th1
intracellular immunity

Cytotoxic T cells

NK cells

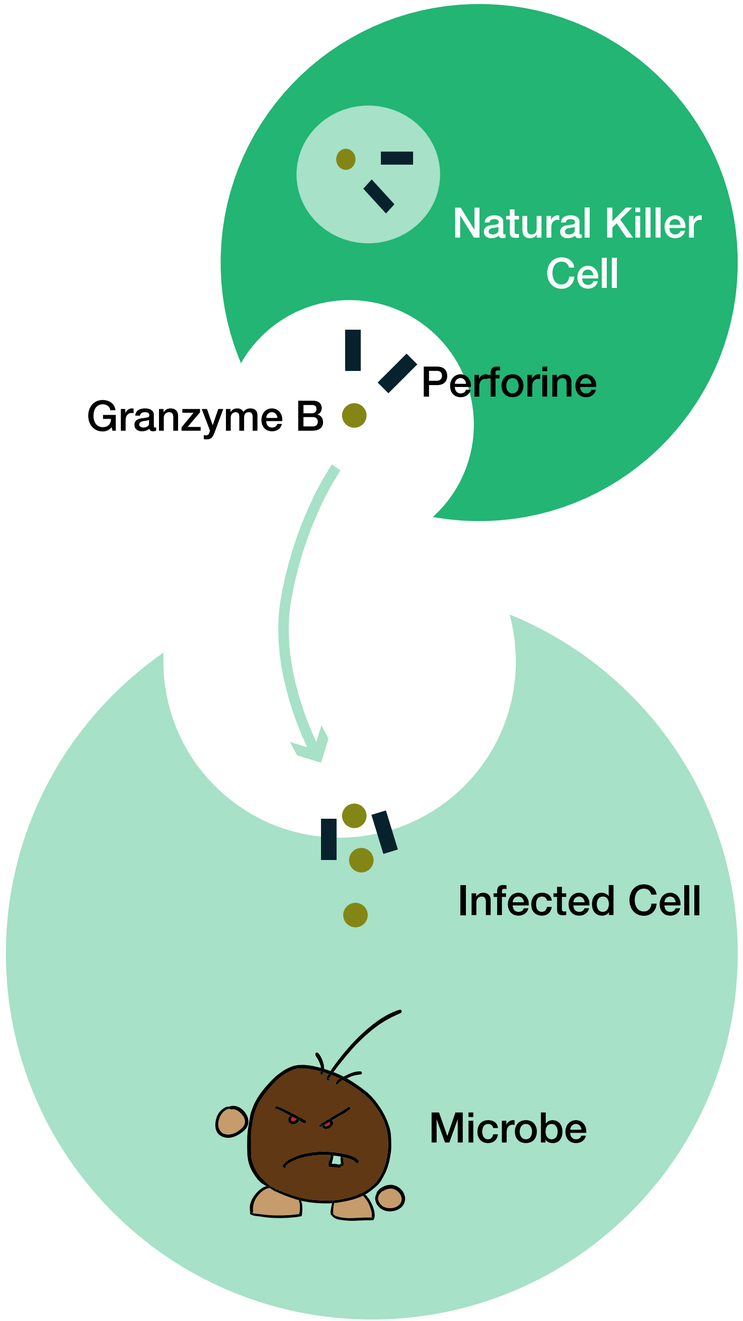
Th17
Extracellular Bacteria/Fungi

Naive CD4 T

Th2
extracellular immunity

Complement system

Treg
immune tolerance



The Adapative immune response: Part 1

T Cells & Natural Killer Cells

After effective activation NK cells release

- Perforine & proteases (granzyme)
- IFN-γ, TNF-α
  act on other immune cells to enhance our immune response

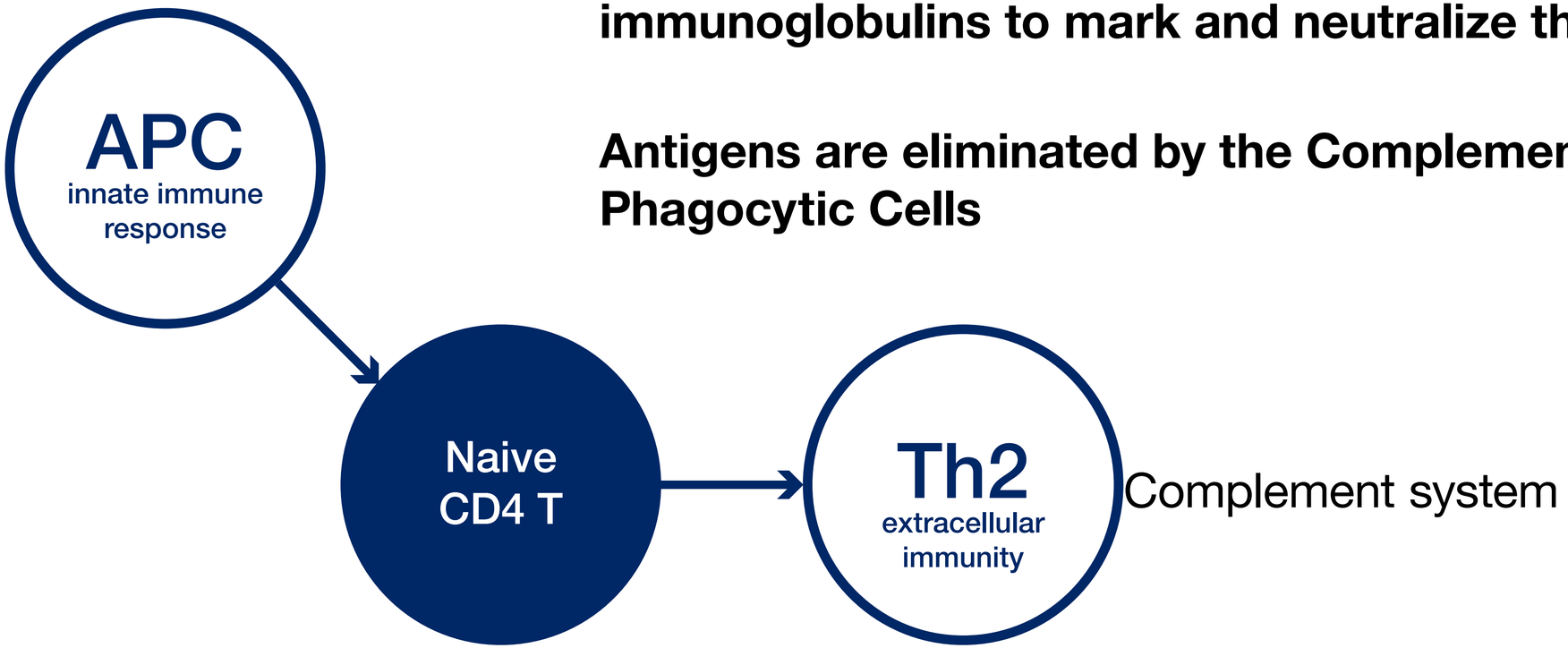
Paolini R, Bernardini G,Molfetta R.NKCells and interferons:Cytokine growth Factor Rev.2015 Apr;26(2):113-20.doi:10.1016/j.Cytog-fr.20014.11.003.Epub2014 Nov 13

The Adaptive immune response: Part 2

B-Cells

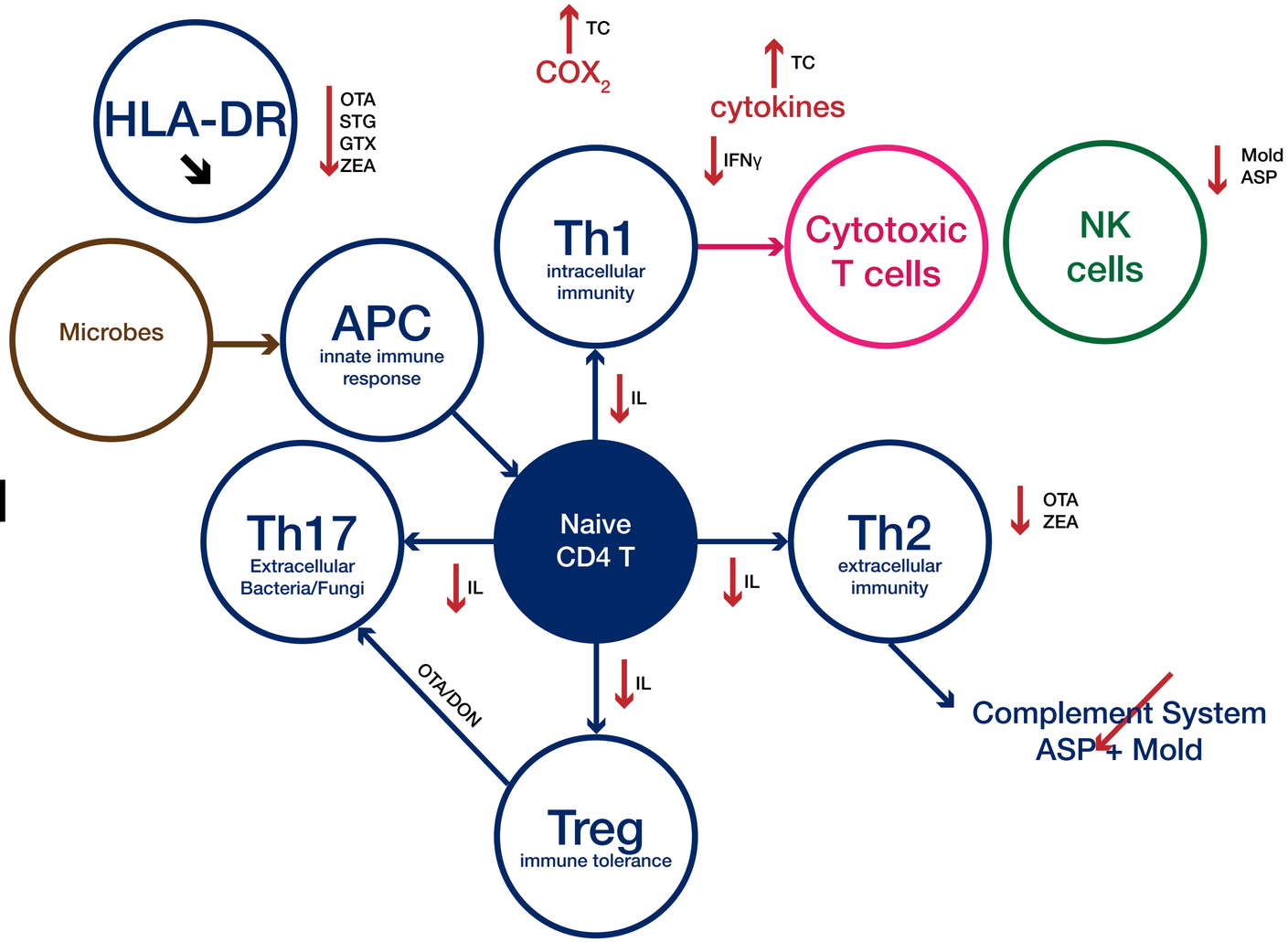
Immune cells communicate by releasing
Th2 cytokines activate B lymphocytes to produce immunoglobulins to mark and neutralize the antigens

Antigens are eliminated by the Complement System or by Phagocytic Cells



What is the impact of mycotoxins on our immune response?

+ Zearalenone (ZEA) & Deoxynavenol (DON) affect the Thymus gland
+ Overall reduction of numbers and functions of immune cells by mycotoxins



Al-AnatiL, PetzingerE. Immunotoxicactivity of ochratoxin A. Journal of Veterinary Pharmacology and Therapeutics. 2006;29(2):79-90. doi:10.1111/j.1365-2885.2006.00718.x

Campbell AW, Thrasher JD, Gray MR, VojdaniA. Mold and Mycotoxins: Effects on the Neurological and Immune Systems in Humans.Advances in Applied Microbiology. 2004:375-406. doi:10.1016/s0065-2164(04)55015-3.

ErmertD, Ram S, LaabeiM. The hijackers guide to escaping complement: Lessons learned from pathogens.Molecular Immunology. 2019;114:49-61. doi:10.1016/j.molimm.2019.07.018.

HuezaI, RaspantiniP, RaspantiniL, LatorreA, GórniakS. Zearalenone, an Estrogenic Mycotoxin, Is an ImmunotoxicCompound.Toxins. 2014;6(3):1080-1095. doi:10.3390/toxins6031080.

HymeryN, SibirilY, Parent-MassinD. In vitro effects of trichothecenes on human dendritic cells.Toxicology in Vitro. 2006;20(6):899-909. doi:10.1016/j.tiv.2006.01.015.

JahreisS, Kuhn S, MadajA-M, Bauer M, PolteT. Mold metabolites drive rheumatoid arthritis in mice via promotion of IFN-gamma-and IL-17-producing T cells.Food and Chemical Toxicology. 2017;109:405-413. doi:10.1016/j.fct.2017.09.027.

KankkunenP, RintahakaJ, Aalto A, et al. Trichothecene Mycotoxins Activate Inflammatory Response in Human Macrophages.The Journal of Immunology. 2009;182(10):6418-6425. doi:10.4049/jimmunol.0803309.

LehrnbecherT, Schmidt S. Why are natural killer cells important for defense against Aspergillus?Medical Mycology. 2019;57(Supplement_2). doi:10.1093/mmy/myy034.

Liew W-P-P, Mohd-RedzwanS. Mycotoxin: Its Impact on Gut Health and Microbiota.Frontiers in Cellular and Infection Microbiology. 2018;8. doi:10.3389/fcimb.2018.00060

PestkaJJ, Zhou H-R, Moon Y, Chung Y. Cellular and molecular mechanisms for immune modulation by deoxynivalenol and other trichothecenes: unraveling a paradox.Toxicology Letters. 2004;153(1):61-73. doi:10.1016/j.toxlet.2004.04.023.

SchützeN, Lehmann I, BönischU, Simon JC, PolteT. Exposure to Mycotoxins Increases the Allergic Immune Response in a Murine Asthma Model. American Journal of Respiratory and Critical Care Medicine. 2010;181(11):1188-1199. doi:10.1164/rccm.200909-1350oc.

Sherrington SL, KumwendaP, KousserC, Hall RA. Host Sensing by Pathogenic Fungi.Advances in Applied Microbiology. 2018:159-221. doi:10.1016/bs.aambs.2017.10.004.

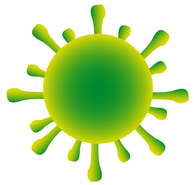
Smith M, McginnisMR. Mycotoxins and their effects on humans.Clinical Mycology. 2009:649-656. doi:10.1016/b978-1-4160-5680-5.00032-3.

VogIG, LesiakI, Jensen D, et al. Immune evasion by acquisition of complement inhibitors: The mouldAspergillus binds both factor H and C4b binding protein.Molecular Immunology. 2008;45(5):1485-1493. doi:10.1016/j.molimm.2007.08.011.

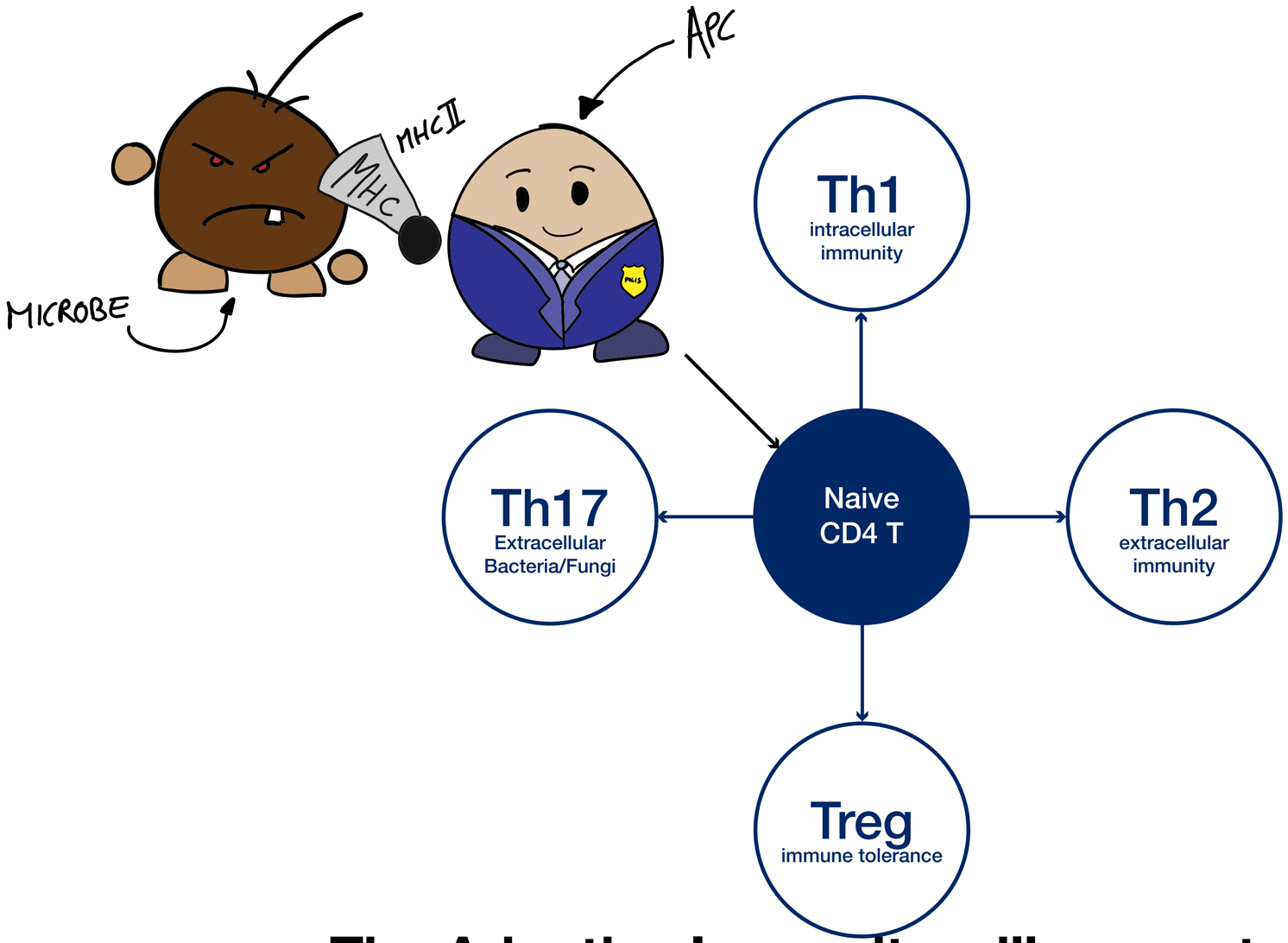
Wang H, Yadav JS. DNA damage, redox changes, and associated stress-inducible signaling events underlying the apoptosis and cytotoxicity in murine alveolar macrophage cell line MH-S by methanol-extracted Stachybotryschartarumtoxins.Toxicology and Applied Pharmacology. 2006;214(3):297-308. doi:10.1016/j.taap.2006.01.002

Biological Elements

→ Defective Antigen Presentation → Inflammation



INNATE IMMUNITY → ADAPTIVE IMMUNITY → Th_1 & Th_2



The Adaptive Immunity will generate a specific immune response

- MHC II interacts with CD4 receptors on naïve T helper Cells for further organization of the adaptive immunity

The HLA-DR Gene and Mold Sensitivity: Human Leukocyte Antigen

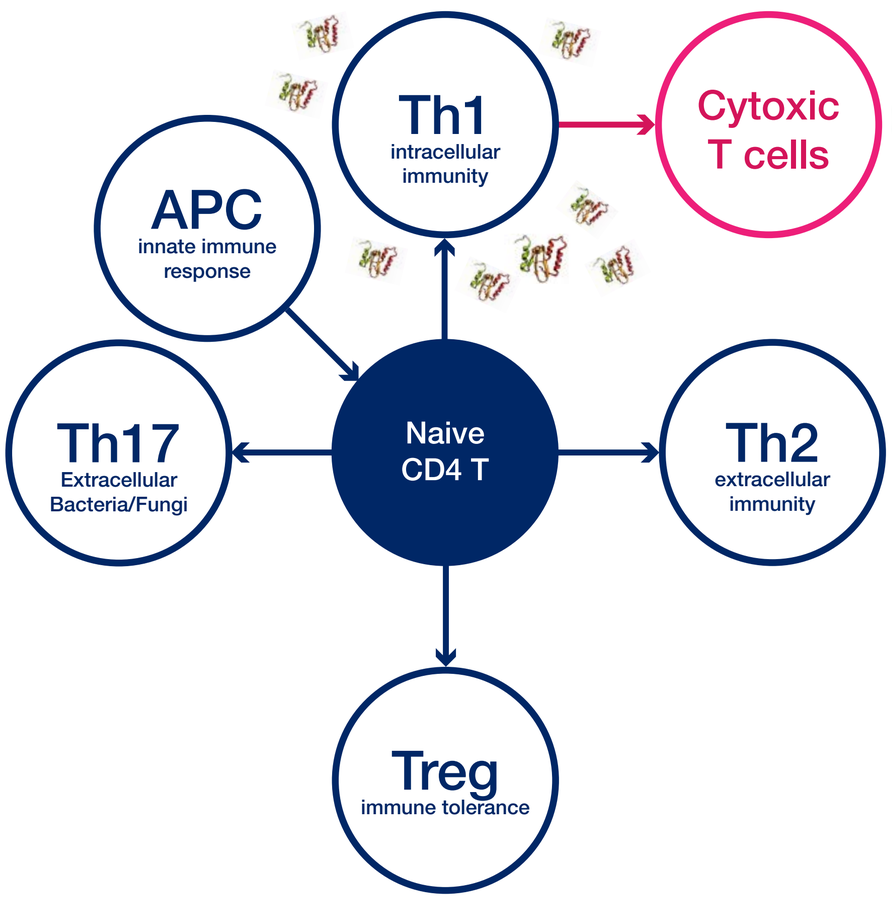
Genetic predisposition : HLA-DR (BQ) inhibits the immune system to react properly when mycotoxins are recognized

25% of the population carries the HLA-DR gene =

The innate immune system is overactive

The adaptive immune system can’t get organized

We develop a Chronic Inflammation = CIRS



Treatment Support immunity:

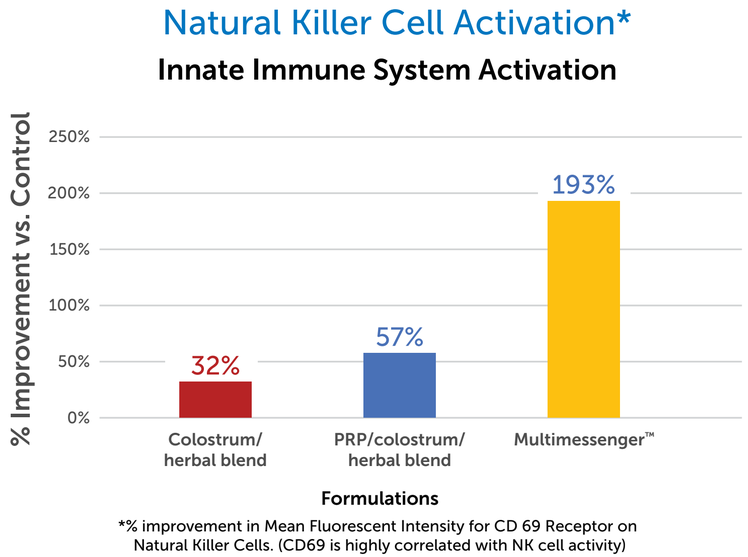
- **Transfer factors are like a cross between interleukins and antibodies**
  - General strengthening of communication between immune Cells = NK Cells increased activity
  - IL-10 goes up which is supportive for T reg (self-tolerance & Th1/Th2/Th17 – balance)

Transfer factors are like a cross between interleukins and antibodies

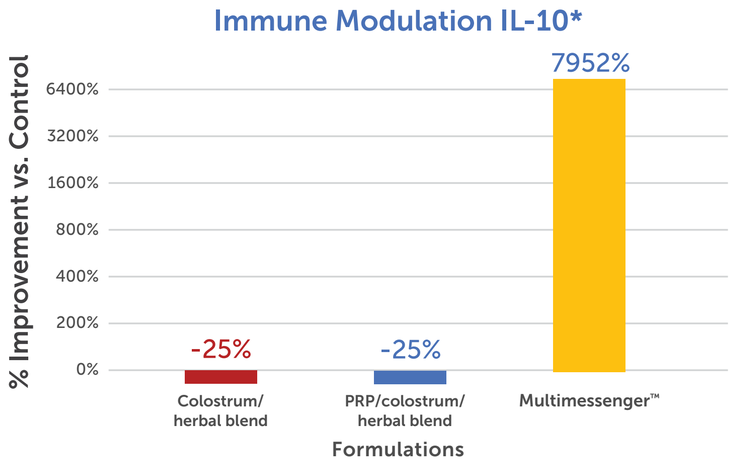
Carrying messages from immune cell to immune cell like interleukins

= 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)

Natural Killer Cell activity (Treg support)

- Multimessenger
    - 90 capsules
    - Dose: 3 capsules in the morning, right before breakfast

ADDITIONALLY: Specific transfer factors in mold invasion

- Transfer Factor Enviro
    - 60 capsules
    - Dose: 2 capsules before sleep

See Comparison table

Physician-Requested Transfer Factor Comparison Table

(not available to the public) *

	Multimessenger	Multimessenger *(mushroom-free)*	Transfer Factor Sensitive™	Transfer Factor L-Plus™	Messenger No. 1	Transfer Factor Enviro™
Natural Killer Cell - General Immune Support	X	X	X			
Bartonella				X		
Borrelia burgdorferi				X	X	
Babesia				X		
Ehrlichia				X		
EBV				X	X	
HHV6 B				X		
HHV6 A&B					X	
CMV	X	X	X	X	X	
Chlamydia pneumoniae				X	X	
Pneumocystic carinii					X	
Human TB					X	
Bovine TB					X	
Herpes 1					X	
Herpes 2					X	
Cryptosporosis					X	
Mycobacterium avian					X	
Hepatitis A,B,C					X	
Staphylcocci					X	

Staphylcocci					X	
Streptococci					X	
E. coli					X	
Parvo virus B19					X	
Varicella Zoster					X	
Candida (multiple strains)					X	X
MMR					X	
Mycoplasma – 14 strains					X	
Ureaplasma urealyticum					X	
Nanobacterium					X	
Human Papillomaviruses					X	
Penicillium						X
Epicoccum						X
Aspergillus fumigatus						X
Aspergillus niger						X
Aspergillus versicolor						X
Cladosporium						X
Fusarium						X
Geotrichum						X
Pithomyces						X
Ustilago						X

Global Treatment Approach

Response to exposure depends on

- Duration and severity of exposure
- Underlying health conditions and nutritional status including individual basic immune response
- Genetics

Mechanisms of illness include disrupted immune response, inflammation, oxidative stress, toxicity, infection and possibly allergy(IgE mediated)

Treatment needs to be multi-systemic:

Avoidance to further exposure, the most important component of the treatment plan

Treatment includes

- Immune support
- Intestinal support
- Novel approach inflammation/neuroinflammation
- Antioxidant support
- Sequestering Agents

Discussion: papers from German Literature showed that fungi could reside in nearly everyone's nose

INFECTION AND COLONIZATION: Local nasal treatment

Fungal growth in the nasal cavities can result from direct exposure to mold spores or could be the result of ongoing treatments with antibiotics and steroids

The manifestation of persistent nasal infection or rhinitis could actually mask a chronic fungal rhinitis

Mayo Clinic published a study where 96% of patients suffering from a chronic sinusitis had fungal growth

Types of mold identified were Aspergillus, Penicillium, Fusarium etc

E. Ponikau J, Frigas, T. Gaffey, and G. Roberts, "The diagnosis and incidence of allergic fungal sinusitis," Mayo Clinic Proceedings, vol. 74, no. 9, pp. 877–884, 1999

Discussion: papers from German Literature showed that fungi could reside in nearly everyone's nose

Treatment approach include avoidance of exposure to elevated spore counts + intranasal application of Amphotericin B

Studies report improvement in nasal obstruction in 75% of participants

J. U. Ponikau, D. A. Sherris, H. Kita, and E. B. Kern, "Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis," Journal of Allergy and Clinical Immunology, vol. 110, no. 6, pp. 862–866, 2002

Intranasal use of ketoconazole , fluconazole and Itraconazole are valuable alternatives but less documented in literature

ANTIOXIDANT SUPPORT:

Oxidative stress is a significant mechanism of illness in exposure to water-damaged buildings :

Mycotoxins, for example Aflatoxins, need to be detoxified in our systems by GST & Glutathione

Insufficient antioxidant capacity = intoxication

GST & Glutathione are defense mechanisms

J. Liu, Y. Wang, J. Cui et al., “Ochratoxin A induces oxidative DNA damage and G1 phase arrest in human peripheral blood mononuclear cells in vitro,” Toxicology Letters, vol. 211, no. 2, pp. 164–171, 2012.

Given the role of oxidative stress in illness from exposure to mold and mycotoxins, the use of Glutathione plays a large part in treatment:

- **Glutathione deficiency is seen in all patients exposed to water-damaged buildings**
  Aflatoxin B1 reduced intracellular levels of GSH
  L. Alpsoy, A. Yildirim, and G. Agar, “The antioxidant effects of vitamin A, C, and e on aflatoxin B1-induced oxidative stress in human lymphocytes,” Toxicology and Industrial Health, vol. 25, no. 2, pp. 121–127, 2009
- **Genetic predisposition with poor levels GST shows increased toxicity from Aflatoxin**
  C. A. Sun, L. Y. Wang, C. J. Chen et al., “Genetic polymorphisms of glutathione S-transferases M1 and T1 associated with susceptibility to aflatoxin-related hepatocarcinogenesis among chronic hepatitis B carriers: a nested case-control study in Taiwan,” Carcinogenesis, vol. 22, no. 8, pp. 1289–1294, 2001
- **Glutathione protects NK Cells and Mitochondria from oxidative damage**
- **Glutathione is necessary to maintain blood Brain Barrier**
- **Glutathione needs to be used next to binders**

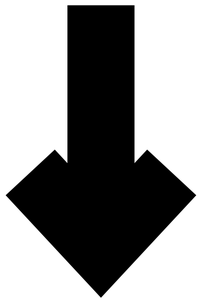
Sorrenti, Valeria, et al.
“Toxicity of ochratoxin a and its modulation by antioxidants: a review.”
Toxins 5.10 (2013): 1742-1766.

The role of oxidative stress in OTA toxicity and carcinogenicity :
Oxygen radicals are generated by OTA :

$O2^-$

OH^-

ROO^-



Uncoupling of oxidative phosphorylation

DNA damage

Lipid peroxidation

Cytotoxicity

OTA is efficiently absorbed from the gastrointestinal tract

**Biotransformation into several metabolites,
some being more toxic**

Review of different antioxidants capable to counteract OTA toxicity

- Glutathione
- EGCG: pretreatment for eight days protected cells
  from OTA – induced cell death

RESEARCH ALERT

Available only through healthcare professionals.

A Study on Liposomal Glutathione

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 participants with glutathione levels at the low end of the normal range were included in the study. The participants 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

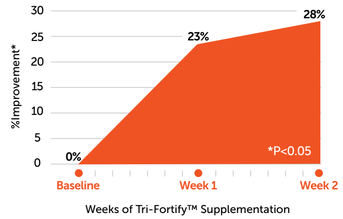
After two weeks of daily oral liposomal glutathione supplementation:

- 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

Increase in Red Blood Cell Levels

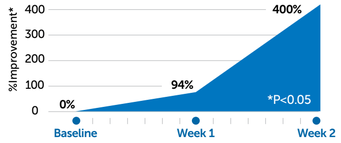
(Erythrocytes)



Weeks of Tri-Fortify™ Supplementation

IMMUNE FUNCTION

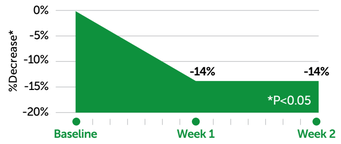
Natural Killer Cell Activity



Weeks of Tri-Fortify™ Supplementation

OXIDATIVE STRESS MARKERS

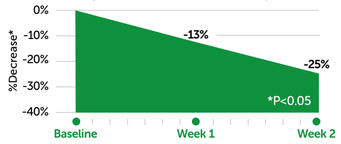
Oxidized / Reduced GSH



Weeks of Tri-Fortify™ Supplementation

Lipid Peroxidation

(Reduced Cellular Membrane Oxidation)



Weeks of Tri-Fortify™ Supplementation

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.

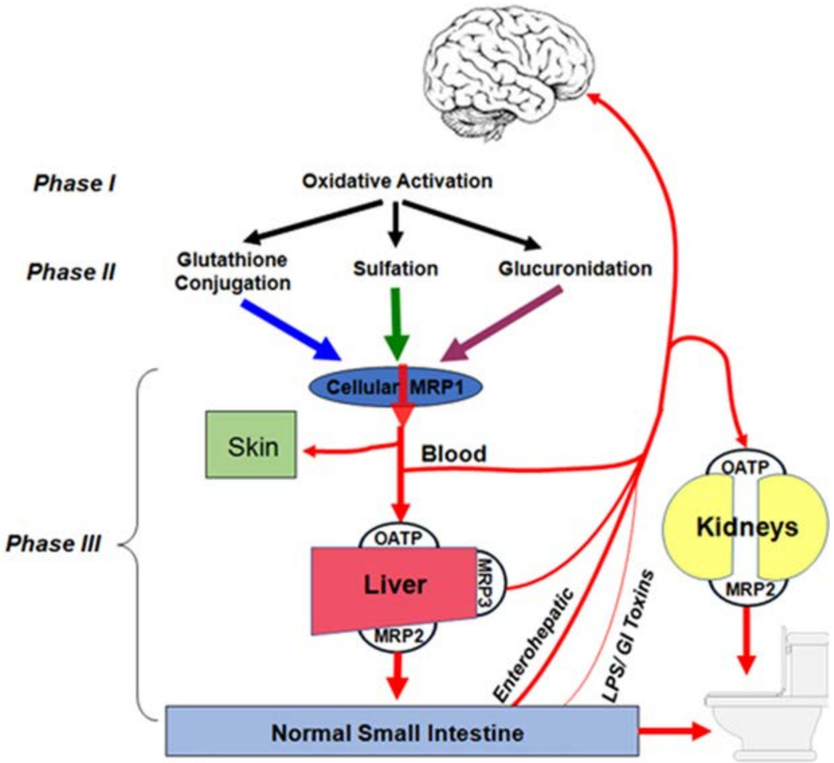
Toxins

Intake → **Exogenous origin** → **Removal**

Endogenous origin

Detoxifaction support

Antioxidant support



Detoxification in three phases

Phase 1 conversion of toxins

Reactions involve oxidation , reduction and hydrolysis via CYP450

Phase 2 conjugation into water-soluble forms

Glutathione conjugation, sulfation, glucuronidation

Phase 3 transport of the conjugates through membranes

MRP 1 exporting toxins to the circulation

OATP moves conjugates into hepatocytes or kidneys

MRP 2 moves conjugates into bile or renal proximal tubule lumen

MRP3 & MRP4 move conjugates and bile salts from hepatocytes into blood

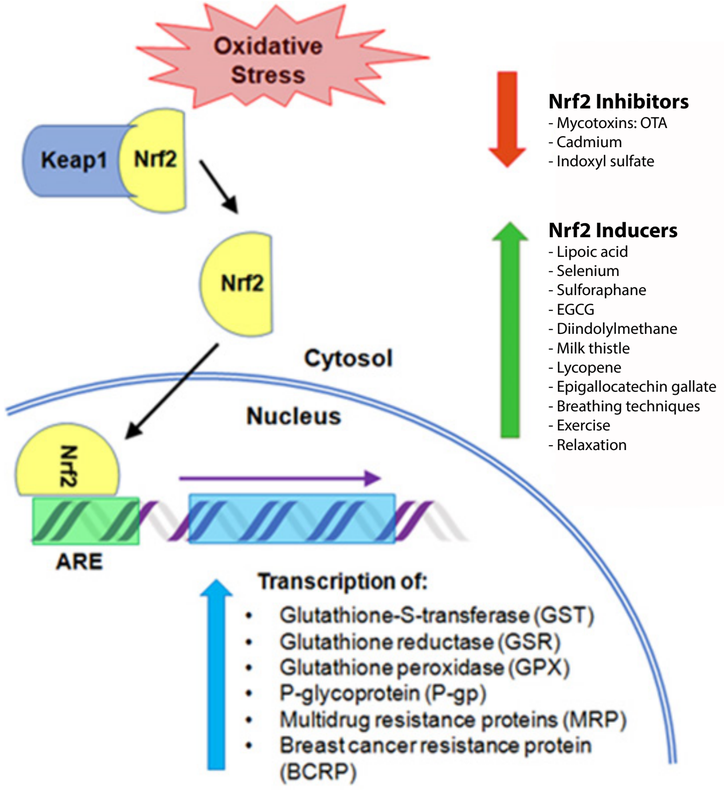
LPS – translocation and increased gut permeability downregulate Phase 3 enzymes

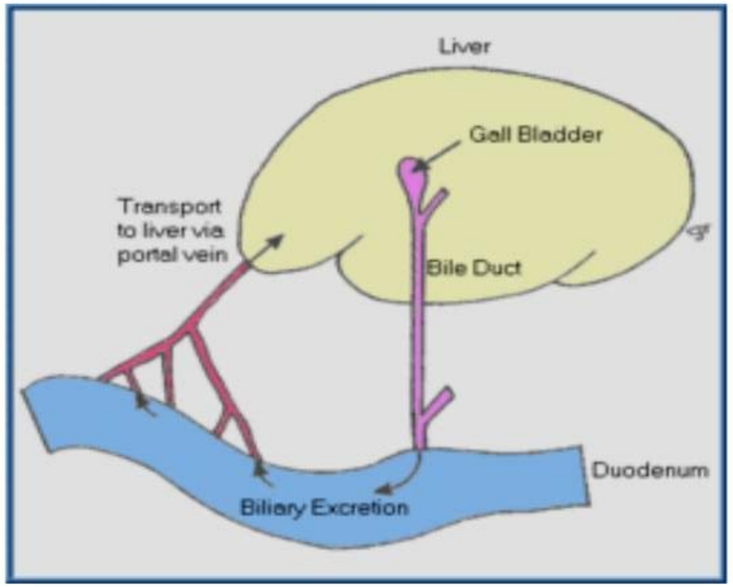
Rebuilding intestinal permeability is an essential part in detoxification support

The Cellular detoxification depends on Nrf2

Nrf2 responds to oxidative stress by translocation to the nucleus

Nrf2 activates genes coding for different detoxifying enzymes

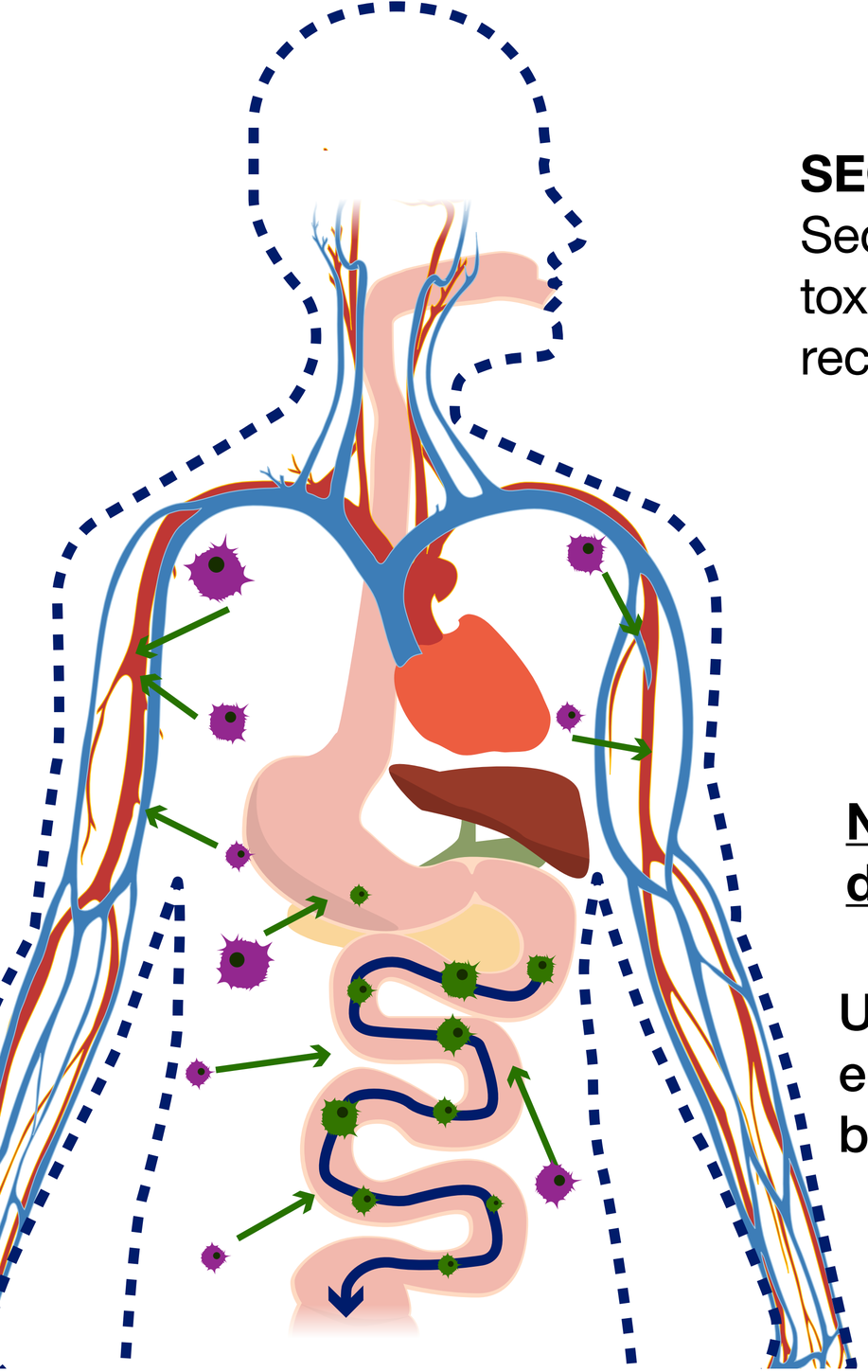




Enterohepatic recirculation

Bile salts and Cholesterol are secreted out of the liver and into the intestines = evacuation or reabsorption

Reabsorption = enterohepatic recirculation



SEQUESTERING AGENTS = BINDERS

Sequestering agents refer to nonabsorbable materials capable of binding toxins in the gastrointestinal tract, thus reducing enterohepatic recirculation and ultimately the body burden of toxins.

- **Side effects are limited to GI symptoms**
- **Malabsorption of medications and nutrients needs to be considered**
- **Usually not very specific**
- **Large surface area to volume ratio**

<u>Natural binders are often contaminated with toxins, dioxins & heavy metals – check origin & certificate of analysis !</u>

Usually not very specific: There is no universal binder that has an equal affinity for all toxins. A combination of binders is usually the best option

Activated Carbons (charcoal)
= amorphous form of carbon prepared from incomplete combustion of carbonaceous organic matter.

It is activated by an oxidizing gas flow at high temperature passed over its surface to make a fine network of pores, producing a material with large surface area and high affinity for various substances

High affinity for different mycotoxins, more specifically in
OA, DON, AFLATOXINS, TRICHOTECENS, FUMONISINS

Activated Charcoal is also very effective at binding and removing LPS endotoxins

Endotoxins largely contribute to blocked detoxification pathways

Typical dose = 1000-2000mg every 12 hours

F. Galvano, A. Pietri, T. Bertuzzi, A. Piva, L. Chies, and M. Galvano, “Activated carbons: in vitro affinity for Ochratoxin A and deoxynivalenol and relation of adsorption ability to physicochemical parameters,” Journal of Food Protection, vol. 61, no. 4, pp. 469–475, 1998

G. Avantaggiato, R. Havenaar, and A. Visconti, “Evaluation of the intestinal absorption of deoxynivalenol and nivalenol by an in vitro gastrointestinal model, and the binding efficacy of activated carbon and other adsorbent materials,” Food and Chemical Toxicology, vol. 42, no. 5, pp. 817–824, 2004

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Bentonite Clay

Absorbent aluminium phyllosilicate clay

Bentonite is polycationic, absorbing negatively charged toxins

Commonly used as a feed additive because it is effective, low cost and authorized + non-selective

Several studies showing good results in different mycotoxins:

Aflatoxins

In pigs, Bentonite Clay was added to aflatoxin- contaminated corn
= it partially restored liver function

Study shows Bentonite lowered immune-toxicity induced by AFB1 in chicken

Bentonite shows affinity for heavy metals such as Cadmium, Lead & Nickel

Trichotecenes, Zearalone, Fumonisin B1, Ochratoxin A, Gliotoxin

D. E. Diaz, W. M. Hagler, J. T. Blackwelder et al., “Aflatoxin Binders II: reduction of aflatoxin M1 in milk by sequestering agents of cows consuming aflatoxin in feed,” Mycopathologia, vol. 157, no. 2, pp. 233–241, 2004

P. Wang, E. Afriyie-Gyawu, Y. Tang et al., “NovaSil clay intervention in Ghanaians at high risk for aflatoxicosis: II. Reduction in biomarkers of aflatoxin exposure in blood and urine,” Food Additives and Contaminants Part A, vol. 25, no. 5, pp. 622–634, 2008.

Carson MS, Smith TK. (1983). Role of bentonite in prevention of T-2 toxicosis in rats. J Anim Sci, 57:1498–506

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Bhatti, Sheraz Ahmed, et al. “Protective role of bentonite against aflatoxin B1-and ochratoxin A-induced immunotoxicity in broilers.” Journal of immunotoxicology 14.1 (2017): 66-76.

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Abbès S, et al. Preventive role of phyllosilicate clay on the Immunological and Biochemical toxicity of zearalenone in Balb/c mice. Int Immunopharmacol. 2006 Aug;6(8):1251-8.

Practical applications with benonite & activated charcoal

Kong, Changsu, Seung Youp Shin, and Beob Gyun Kim.
“Evaluation of mycotoxin sequestering agents for aflatoxin and deoxynivalenol: an in vitro approach.” SpringerPlus 3.1 (2014): 346.

Study on swine feed shows Bentonite & Charcoal mixture binds AFB1 + DON but in a much lesser way

Mycotoxis are frequently found in feed

Bentonite and activated charcoal are frequently used in feed industry because of its economic feasibility and suitability for nutritional perspective

Various studies have been conducted in vitro, sometimes with method mimicking the gastrointestlnal system

Monge, María del Pilar, et al.
“Activated carbons as potentially useful non-nutritive additives to prevent the effect of fumonisin B1 on sodium bentonite activity against chronic aflatoxicosis.” Food Additives & Contaminants: Part A 33.6 (2016): 1043-1052.

Study on poultry feed : Aflatoxin B1 (AFB1) & Fumonisin B1 (FB1) are mycotoxins that often co-occur in feed.

Bentonite has a strong affinity for FB1

Activated Charcoal has a strong affinity for FB1

But : both mycotoxins are competitively adsorbed
= FB1 decreases the affinity for AFB1

Bhatti, Sheraz Ahmed, et al.
“Comparative efficacy of Bentonite clay, activated charcoal and Trichosporon mycotoxinivorans in regulating the feed-to-tissue transfer of mycotoxins.”
Journal of the Science of Food and Agriculture 98.3 (2018): 884-890.

Bird feed

Mixture of Bentonite Clay & Activated Charcoal was used and showed affinity for OTA & AFB1

Cholestyramine (CSM)

Cholestyramine is a bile acid sequestrant.

These molecules are positively charged non-digestible resins that bind to bile acids in the intestine to form an insoluble complex, which is excreted in the feces.

They are used mainly for the treatment of primary hypercholesterolemia possibly associated with mild hypertriglyceridemia.

Studies show efficiency in OTA exposure = CSM had higher affinity for **OTA** than bile salts + fecal excretion was enhanced

Cholestyramine needs to be without additives, aspartame or sugar

= Aspartame and its breakdown products cause hyperexcitability

= Artificial sweeteners change the gut microbiome

Constipation is a common side effect

2 to 4 x / day, max 4g, dissolved in water or juice

1 hour before or 2 hours after meal or medication

Go slow with the use of binders in hypersensitive patients

Start by 1 x 1 gram – 1 x 2 grams, slowly increase when tolerated

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Rycerz, Karol, and Jadwiga Elżbieta Jaworska-Adamu. “Effects of aspartame metabolites on astrocytes and neurons.” Folia Neuropathol 51.1 (2013): 10-7.

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Suh JH, et al. Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. Proc Natl Acad Sci U S A. 2004 Mar 9;101(10):3381-6.

Zhang C, et al. Selenium triggers Nrf2-mediated protection against cadmium-induced chicken hepatocyteautophagy and apoptosis. Toxicol In Vitro. 2017 Oct;44:349-356.

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Chlorella Glass Grown

Cultivated on glass with unsterilized tap water

Outdoor water culture is often contaminated
The heavy metal pollution in soils and aquatic environments is a serious ecological problem

Natural antioxidant
Bioactive compounds include carotenes, astaxanthin, lutein and fucoxanthin

studies show improved activity SOD, catalase, reduced glutathione + upregulation of primary antioxidant genes

Natural detoxifier

- Increased elimination of Mercury from tissues
- Increased elimination of phthalates, plasticizers and insecticides

Chlorella supplementation decreases dioxin and increases IgA concentrations in breast milk

Dioxins have been detected at high concentrations in breast milk and maternal blood samples from pregnant women in Japan

The study shows that Chlorella lowered dioxin levels, this may suggest that Chlorella supplementation reduces the transfers of dioxins through breast milk from mother to child. The same study showed increased levels IgA in breastmilk, which is beneficial for immunity

Nakano, Shiro, Hideo Takekoshi, and Masuo Nakano. “Chlorella (Chlorella pyrenoidosa) supplementation decreases dioxin and increases immunoglobulin a concentrations in breast milk.” Journal of medicinal food 10.1 (2007): 134-142.

Binder research document ISEAI suggests the use of glass grown Chlorella as a sequestering agent in Mold & biotoxins

- toxicity with Trichothecenes and Zearalenone
- commonly used in pregnancy

ISEAI = International Society of Environmental Acquired illnesses

Dosage

- It is best to take your chlorella dose 45-60 min. prior to your meal
- Chlorella is very complimentary with other detox agents and support agents
- Start slowly with 1 vegecaps/day and gradually build up the daily dose

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Nakano, Shiro, Hideo Takekoshi, and Masuo Nakano. “Chlorella (Chlorella pyrenoidosa) supplementation decreases dioxin and increases immunoglobulin a concentrations in breast milk.” Journal of medicinal food 10.1 (2007): 134-142.

Modified Citrus Pectine

Complex water soluble indigestible polysaccharide obtained from the peel and pulp of citrus fruits and modified by means of high PH & temperature treatment

Eliaz, Isaac, and Avraham Raz. “Pleiotropic Effects of Modified Citrus Pectin.” Nutrients 11.11 (2019): 2619.

Mycotoxins and their binders

Ochratoxin A

- Cholestyramine (first choice)
- Bentonite Clay / Activated charcoal
- Humic Acid
- Saccharomyces boulardii?

Aflatoxins

- Cholestyramine
- Bentonite Clay / Activated charcoal
- Chlorella
- Modified Citrus Pectine

Trichotecenes

- Cholestyramine
- Chlorella Glass Grown
- Modified Citrus Pectine
- Saccharomyces boulardii

Zearalanone

- Bentonite Clay (+ Humic Acid)
- Chlorella Glass Grown
- Modified Citrus Pectine
- Saccharomyces boulardii

Mycotoxins and their binders

Gliotoxin	Bentonite Clay Modified Citrus Pectine
Fumonisins	Cholestyramine
	Bentonite Clay Activated charcoal
Deoxynavenol	Cholestyramine Activated Charcoal

+ Choose the binders that target the most harmful of the toxins that you measured

+ Combine binders

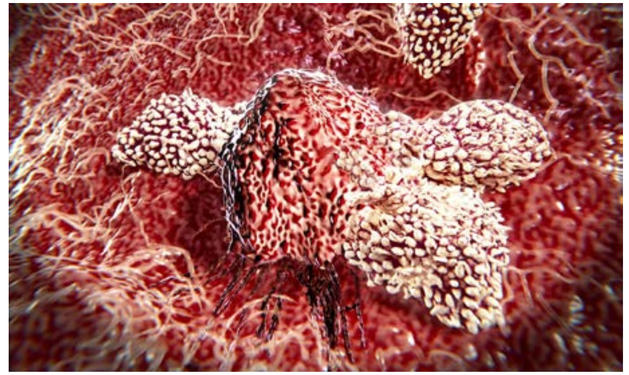
Where do we start?

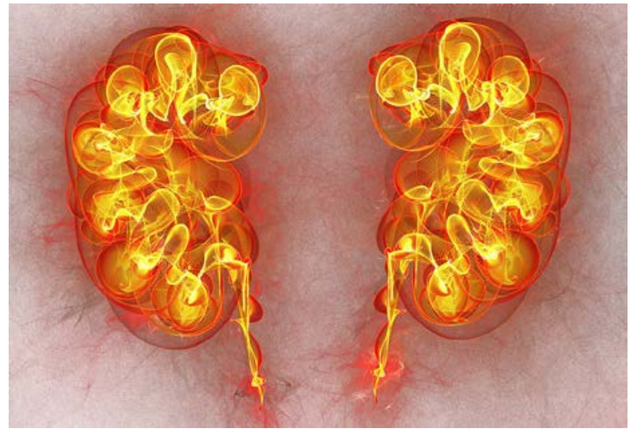
1. Remove patient from exposure
2. Gut repair + detoxification support (Phase 1+2+3, nrf2)
3. Use the correct binder for the toxin you have measured
   + liposomal Glutathione
4. Correct immunity and Inflammation
   +Use local anti-fungal nasal therapy if there is collonization

Ochratoxin A

Ochratoxin A is known to be

- Nephrotoxic
- Immunotoxic
- Carginogenic
- Neurotoxic





What are the mechanisms of toxicity?

- Dietary exposure to OTA
- inhalation of OTA = exposure to water-damaged buildings

Tissue distribution after exposure

Urinary & fecal excretory routes, elimination is slow and depends on

- Album- binding
- Enterohepatic recirculation
- various reasons : gender, genetics,…

Tissue distribution? Where do we measure ?

- After exposure the highest concentration is in kidneys, followed by liver & muscle tissue
- OTA is detected in blood , urine and breastmilk

+ in the umbilical cord and placental tissue of newborn whose mother had been exposed to OTA

Main focus in toxicity = kidney disease

Hope, Janette H., and Bradley E. Hope.
“A review of the diagnosis and treatment of Ochratoxin A inhalational exposure associated with human illness and kidney disease including focal segmental glomerulosclerosis.” Journal of environmental and public health 2012 (2012).

This paper reviews OTA ’s relationship to kidney disease with a focus on possible association with focal segmental glomerulosclerosis (FSGS)

FSGS is a devastating kidney disease

In early stage the kidneys are usually enlarged, while in the late stage of the illness, kidneys are typically shrunken.

FSGS is a common cause of kidney failure

There has been increasing recognition of causes (genetic, viral, drug toxicity, secondary to infections like HIV, Hepatatis, Parovirus, toxins like heroin…)

Treatments include

- salt and protein restriction
- diuretics for edema
- ACE inhibitors
- aldosterone antagonists
- immunosuppressants
- treatments for hyperlipidemia
  (which commonly occurs with the illness)

We saw two patients with an association between OTA exposure and development of FSGS

The paper explores further association between OTA & FSGS

Treatment possibilities

CSM is not absorbed systematically
= safe even for patients with advanced kidney disease

Charcoal : Charcoal is included in the military textbook recommendations for exposure to trichothecenes mycotoxins

Bentonite Clay was studied for its efficacy of mycotoxin binding in animals

Studies show that sauna increased sweat excretion

Antioxidants like Glutathione are helpful

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Personalized advise for practitioners

register as healthcare professional on academy@nutrined.nl

NEUROINFLAMMATION

FROM ADVANCED PROTOCOLS 2020

NUTRINED

Rebuilding gut in LPS-induced neuroinflammation

Guttae Pepsine
30 ml
Dose : 3 x 10 - 20 drops at the start of the meal and with a small amount of water (swallow immediately)

Gluten DPP4 Complex
90 vcaps
Dose : 3 x 1 capsule 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

Modulation of microglial release of inflammatory mediators

Rg3 nasal spray
30 ml
Dose: 2 x 2 sprays in each nostril

Reducing inflammation with anti-inflammatory molecules crossing the blood brain barrier

Cytoquel
90 caps
Dose: 3 x 1 capsule per day, during meals

Butyflam coated caps
180 coated caps
Dose: 3 x 1-2 coated caps per day, separated from meals

Antioxidants reducing neuronal inflammation and neuronal damage

Trifortify Watermelon
236 ml
Dose: 1 teaspoon (5ml) per day, separated from meals

H2 Absorb
60 tabs
Dose: 2 x 1 tab per day, in a glass of water

Modulation of mast cells and downregulation of inflammation

Histaquel
120 vcaps
Dose: 2 x 2 capsules per day, with or without food

Upregulation of BDNF gene expression

BDNF Essentials
120 vcaps
Dose: 2 x 2 capsules per day

Protecting and rebuilding mitochondria in neurons

ATP 360
90 vcaps
Dose: 3 capsules per day during meal

Magnesium L-threonate: reducing excessive calcium influx & excitotoxicity in neurons

Magnesium C-Complex
90 vcaps
Dose: 3 x 1 capsules per day

IF NECESSARY:
Lumbrokinase in case of cerebral ischemia

Boluoke
60 or 120 vcaps
Dose: 1 – 4 capsules, separated from meals

Neuropathic pain

PEA – certified 300mg vcaps
Dose: 1 – 4 capsules per day

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Researched Nutritionals
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MOLD AND BIOTOXINS

FROM ADVANCED PROTOCOLS 2020

NUTRINED

Fungi are a large group of pathogens with two subgroups: yeast are single cell organisms, molds are multicellular organisms. Molds reproduce by releasing spores. Some spores produce toxic mycotoxins.

Mold often grows in water damaged buildings. First step in treatment is removal from exposure (STEP 1). To remove the **mycotoxins** from the body, binders are used.

The toxic effects of mycotoxins include gastro-intestinal toxicity, inflammation, neuroinflammation and disruption of the immune response. Every treatment is an individualized interpretation on specific symptoms.

STEP 1: Removal from exposure

STEP 2: Treatment of impaired intestinal barried induced by mycotoxins: Gut protocol

Guttae Pepsine
30 ml
Dose : 3 x 10 - 20 drops at the start of the meal and with a small amount of water (swallow immediately)

Gluten DPP4 Complex
90 vcaps
Dose : 3 x 1 capsule 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

Corebiotic
The use of soil-based probiotics to remote microbiome and reduce post-prandial raise in endotoxins

60 vcaps
Dose : 1 x 2 capsules per day, at least 30 minutes before the meal, for minimum 2 months

STEP 3: Detoxification support & rebuilding Glutathione levels

Broccoraphanin 300mg
100 vegecaps
Dose : 1 caps per dag

Trifortify Watermelon or Orange
236 ml
Dose : 1 teaspoon/day, separated from meals

STEP 4: Immune support & reduce inflammation

Increasing NK Cell activity & Support to the Regulatory T Cells

Multimessenger
90 caps
Dose : 1x3 caps per day, just before breakfast

Specific activity targeting antigens

Transfer Factor Enviro
60 caps
Dose : 2 caps before sleep

Cytoquel
90 vcaps
Dose : 3x1 vcaps per day during or after meals

STEP 5:
Reducing mycotoxin load in the body with binders.
Binders are not systemically absorbed.
Constipation occurs but binders rarely cause more severe symptoms.

In a general way Binders should be taken separated from food , nutrition and drugs
Reducing mycotoxin load in the body with binders …etc
Combine binders based on general recommendations – see table

MYCOTOXINS AND THEIR BINDERS	
Ochratoxin A	**Cholestyramine (first choice)** **Activated charcoal – certified grade** **Bentonite clay – certified grade (combined with MetalPul)** **Humic Acid** **Saccharomyces boulardii**
Aflatoxins	**Cholestyramine without additives** **Bentonite clay – certified grade** **Activated charcoal – certified grade** **Chlorella glass grown** **Pectasol**
Trichotecenes	**Cholestyramine without additives** **Bentonite clay – certified grade** **Activated charcoal – certified grade** **Chlorella glass grown**
Zearalanone	**Bentonite clay (combined with MetalPul)** **Saccharomyces boulardii** **Pectasol**

	Cholestyramine without additives
Gliotoxin	**Bentonite clay – certified grade** **Pectasol**
Fumonisins	**Cholestyramine without additives** **Bentonite clay – certified grade** **Activated charcoal – certified grade**
Deoxynavenol	**Cholestyramine without additives** **Activated charcoal – certified grade**

Charcoal 400mg
200 vcaps
Dose : 1000-2000mg every 12hours

Bentonite Clay 500mg certified grade
200 vcaps
Dose : 500-100every 12hours

Cholestyramine CSM Pure without additives
200 vcaps
Dose : 2 to 4 x / day, max 4g, dissolved in water or juice
1 hour before or 2 hours after meal or medication

Go slow with the use of binders in hypersensitive patients
Start by 1 x 1 gram – 1 x 2 grams, slowly increase when tolerated

Chlorella Glass grown 250mg
200 vcaps
Dose : Start slowly with 1 vegecaps/day and gradually build up thedaily dose
45-60 minutes prior to food

MetalPul
90 capsules
Dose: adults: 1 x 2 - 3 capsules per day
bodyweight less than 45kg : 1 x 1 capsules per day

Pectasol
454 g powder
Dose: 1 - 3 scoops per day in water or juice

Further supportive measures depending on individual manifestations

Protocol Inflammation (page 13)
Protocol Neuroinflammation (page 17)
Protocol Oxidative stress (page 21)

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