Casual Friday Presents

Autoimmune Mechanisms Pt 4 (dysbiosis)

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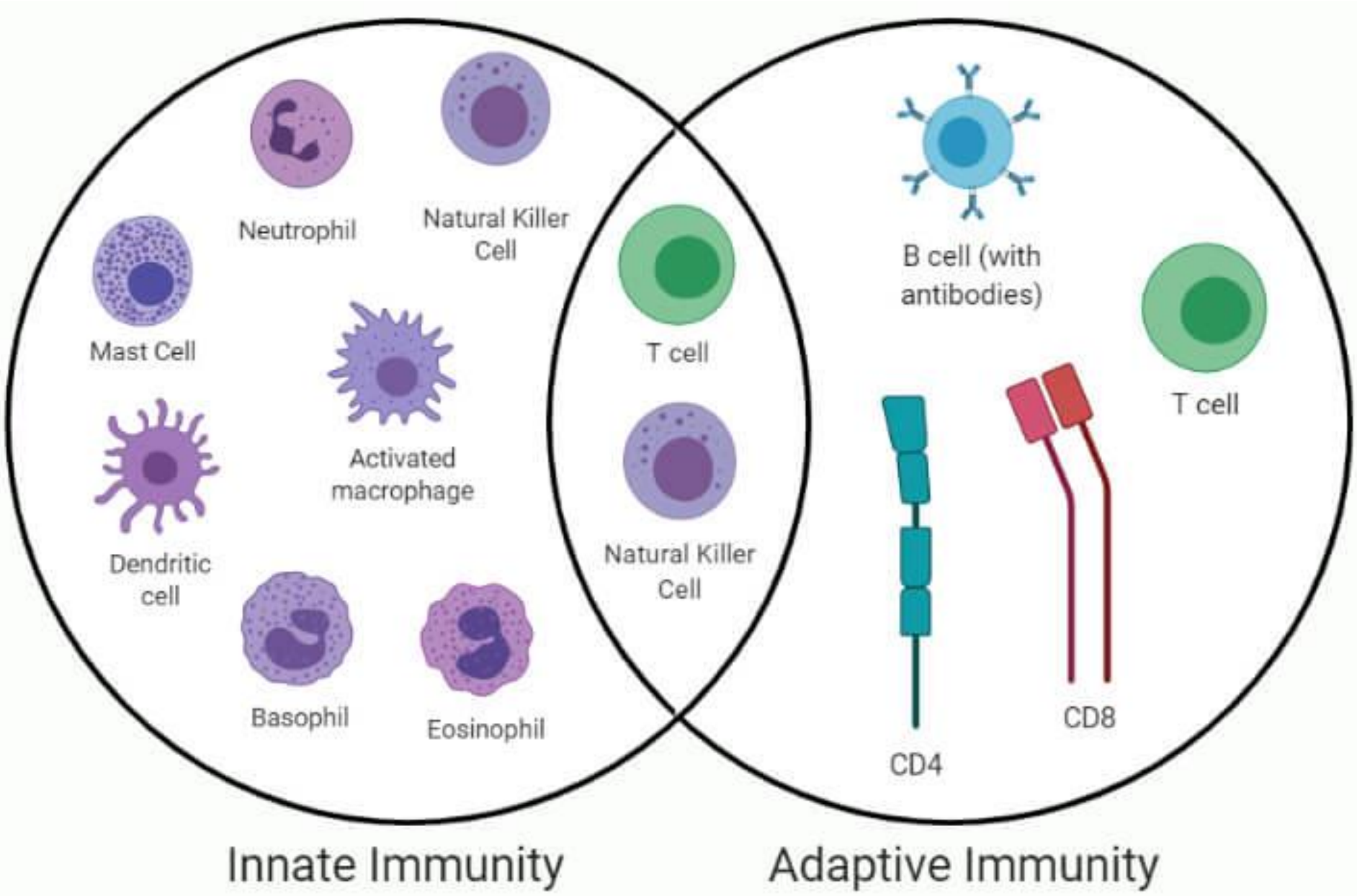
Neutrophil
Natural Killer Cell
Mast Cell
Activated macrophage
Dendritic cell
Basophil
Eosinophil
T cell
Natural Killer Cell
B cell (with antibodies)
T cell
CD4
CD8
Innate Immunity
Adaptive Immunity

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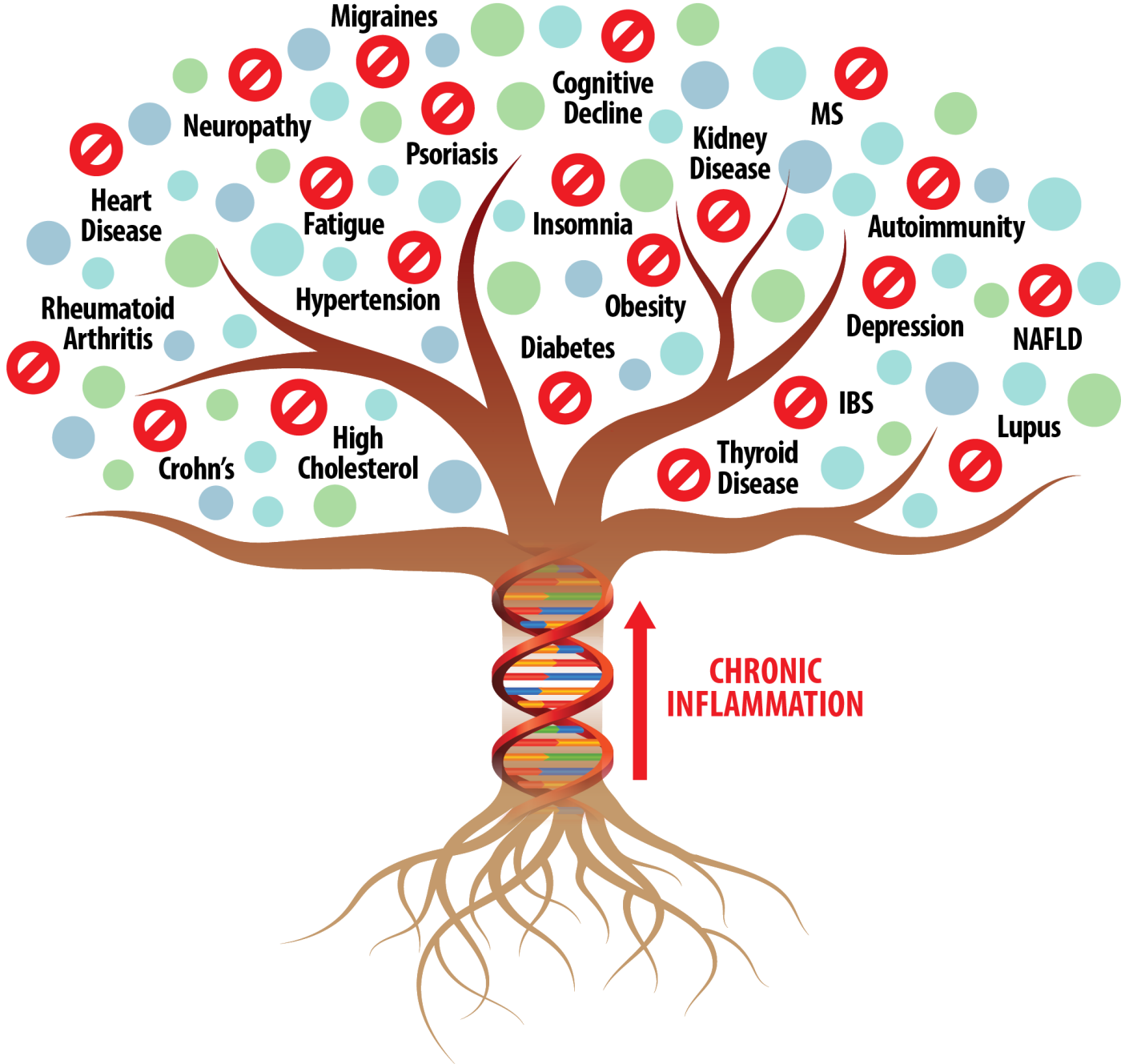
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Crohn's
High Cholesterol
Lupus
Thyroid Disease
CHRONIC INFLAMMATION

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Molecular mimicry in autoimmunity and vaccinations

Miri Blank, Eitan Israeli, Smadar Gertel, Howard Amital, and Yehuda Shoenfeld.

The healthy immune system is tolerant to the molecules which are the building bricks of our body. Braking the self tolerance due to clonal escape, DNA rearrangement epigenetic and environmental factors, all in concert with genetic predisposition, may lead to an autoimmunity termed “The mosaic of autoimmunity” (2). This kaleidoscope of autoimmunity may lead to a variety of autoimmune diseases or to autoimmune (autoinflammatory) syndrome induced by adjuvant (ASIA) (3). One of the mechanisms involved in induction of an autoimmune response is molecular mimicry.

During the last few decades, molecular mimicry was demonstrated between self and non-self molecules that lead to an autoimmune response (4-26). As a prelude, a shared sequence/structure between a non-self microbial/viral infection or a drug and host antigen entails a particular inflammatory state in order to induce an autoimmune state. The severity of the inflammation is influenced by the strength of the infection or perturbation of the immune system. Studies in animal models support the view that a specified infection determines the inflammatory state. To establish the autoimmune nature of the inflammation, it is important to show that it persists in the absence of the inciting microbe. Although the microbe may have been cleared long before disease manifestations appeared, a common infecting agent, may provoke a disease only in combination with genetic or environmental elements, or it may just prime/stimulate the immune system, being a second virus or a nonspecific adjuvant as a second “hit.“ Viruses, microbes, and parasites may brake peripheral self-tolerance and induce and maintain autoimmunity via several overlapping mechanisms such as epitope spreading, bystander activation, viral persistence, or post-translational modifications of self and altered proteins (3-10). The shared epitopes between the pathogens and autoantigen may induce or trigger chronic inflammation, which is mandatory for establishing all the above listed mechanisms that contribute to an autoimmune response by unveiling “hidden” self-epitopes, cross-reactive peptide presentation, determinant spreading, upregulation of Major Histocompatability Complex (MHC), adhesion, co-stimulatory molecules on antigen presenting cells, upregulation of cellular and extracellular processing, apoptosis, infection of professional Antigen Presenting Cells (APCs), autoantibody production subversion of T cell responses and the immunological homunculus networks (1-11). Excluding shared epitopes between a pathogen and self molecules, structural mimicry can be exemplified also between drugs and self molecules. Molecular mimicry can be an inducer of an autoimmune response or a protector of an autoimmune scenario.

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Review

Interaction between food antigens and the immune system: Association with autoimmune disorders

Aristo Vojdani [a b], Lydia R. Gushgari [c], Elroy Vojdani [d]

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Highlights

- Dietary components and their effects on the gut microbiome are major players in autoimmune disease but are often overlooked
- Failure of the oral tolerance mechanism can cause the immune system to react to the very food the body needs for sustenance
- Many foods share sequence homology with human tissues; this molecular mimicry can induce or exacerbate autoimmune diseases
- Factors that contribute to post-translational protein modification may play a role in the induction of autoimmune disease

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Review > Climacteric. 2009 Oct;12(5):378-86. doi: 10.1080/13697130903025449.

The effects of hormone replacement therapy on autoimmune disease: rheumatoid arthritis and systemic lupus erythematosus

C R Holroyd [1], C J Edwards

Autoimmune diseases are generally more common in women than men; however, there is no simple explanation for this. Sex hormones, especially estrogen (but also prolactin and testosterone), play important roles in these diseases. Estrogens are generally considered to enhance autoimmunity and have multiple effects on the immune system through various cell types and molecular pathways. There is much evidence supporting the role of estrogen in the pathogenesis of systemic lupus erythematosus (SLE): the disease occurs much more frequently in women, especially during the years of child-bearing potential, and commonly flares during pregnancy. The relationship between estrogen and the development of SLE is complex, however. Exogenous estrogens have been historically avoided in women with SLE due to the widely held view that they could activate disease and their use remains controversial. Current evidence from prospective trials suggests that there may be a small increased risk of mild/moderate flares in women with SLE taking hormone replacement therapy (HRT), but the risk of major flare does not appear to be increased. In rheumatoid arthritis, HRT does not appear to be associated with an increased risk of disease flare and may actually improve disease activity. In all individuals with autoimmune disease, the risk of venous thrombosis associated with oral HRT is an important factor that should also be considered.

Linacre Q. 2017 Aug 18;84(3):275–295. doi: 10.1080/00243639.2017.1360065

Hormonal contraception and the development of autoimmunity: A review of t

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Sex steroids have several potent effects on the body. Sex steroid receptors can be found in almost every cell in the body, including those of the adaptive and innate immune systems. Sex steroids are strongly implicated in the development and modulation of the immune system (Schuurs and Verheul 1990; Mann et al. 1994). Estrogens have been demonstrated to enhance cellular proliferation and antibody secretion (Cutolo et al. 2010) while progestins clearly have immunomodulatory effects on the immune system, especially on T cells and T cell subsets (Tan, Peeva, and Zandman-Goddard 2015). Hormonal contraceptives also suppress pituitary gonadotropins, which have a number of additional immunomodulatory effects (Athreya, Rettig, and Williams 1998). Gonadotropin releasing hormone (GnRH) and its receptor are expressed in immune cell subsets and GnRH plays a role in programming the immune system (Tanriverdi et al. 2003). In addition, several autoimmune diseases have a marked sex predominance, with females much more susceptible to diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), autoimmune thyroid disease, and multiple sclerosis, while males are more susceptible to ankylosing spondylitis and reactive arthritis. Thus, while a specific mechanism linking hormonal contraceptives to autoimmune disease pathogenesis has not been elucidated, it is reasonable to speculate that the administration of hormonal contraceptives, either combined estrogen-progestin contraceptives or progestin-only contraceptives, would modulate the immune system and may affect the predisposition of hormonal-contraceptive users to autoimmune diseases.

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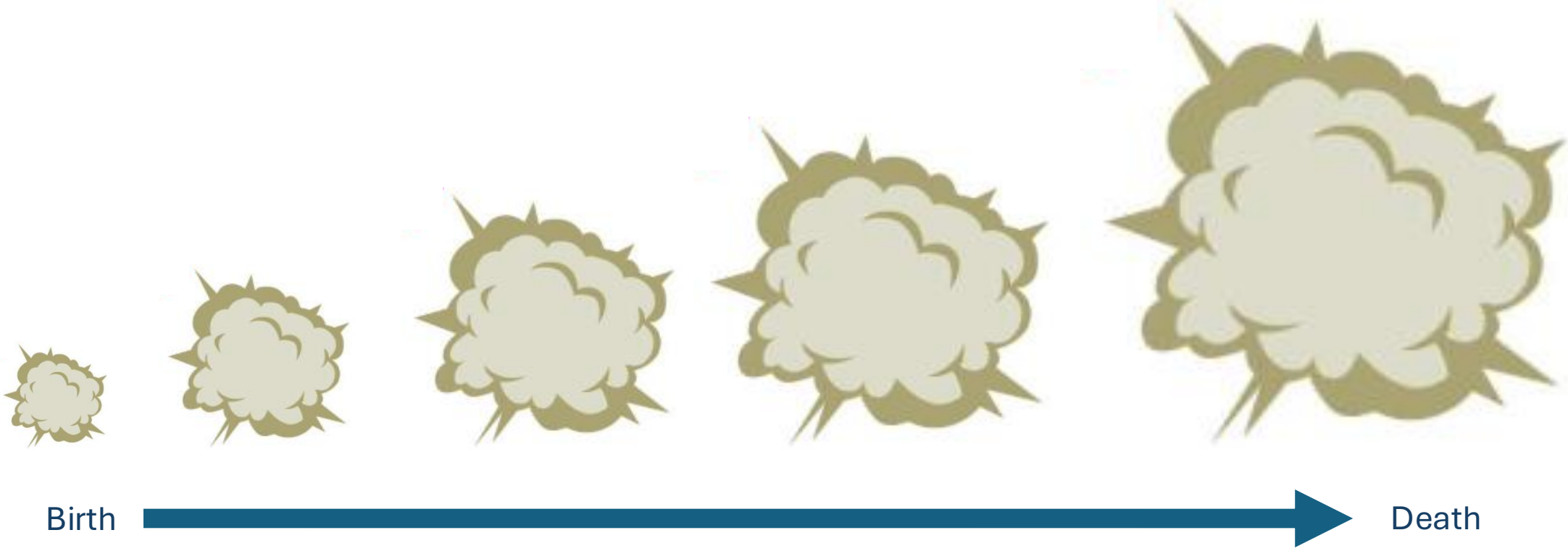
The Antigenic Cloud



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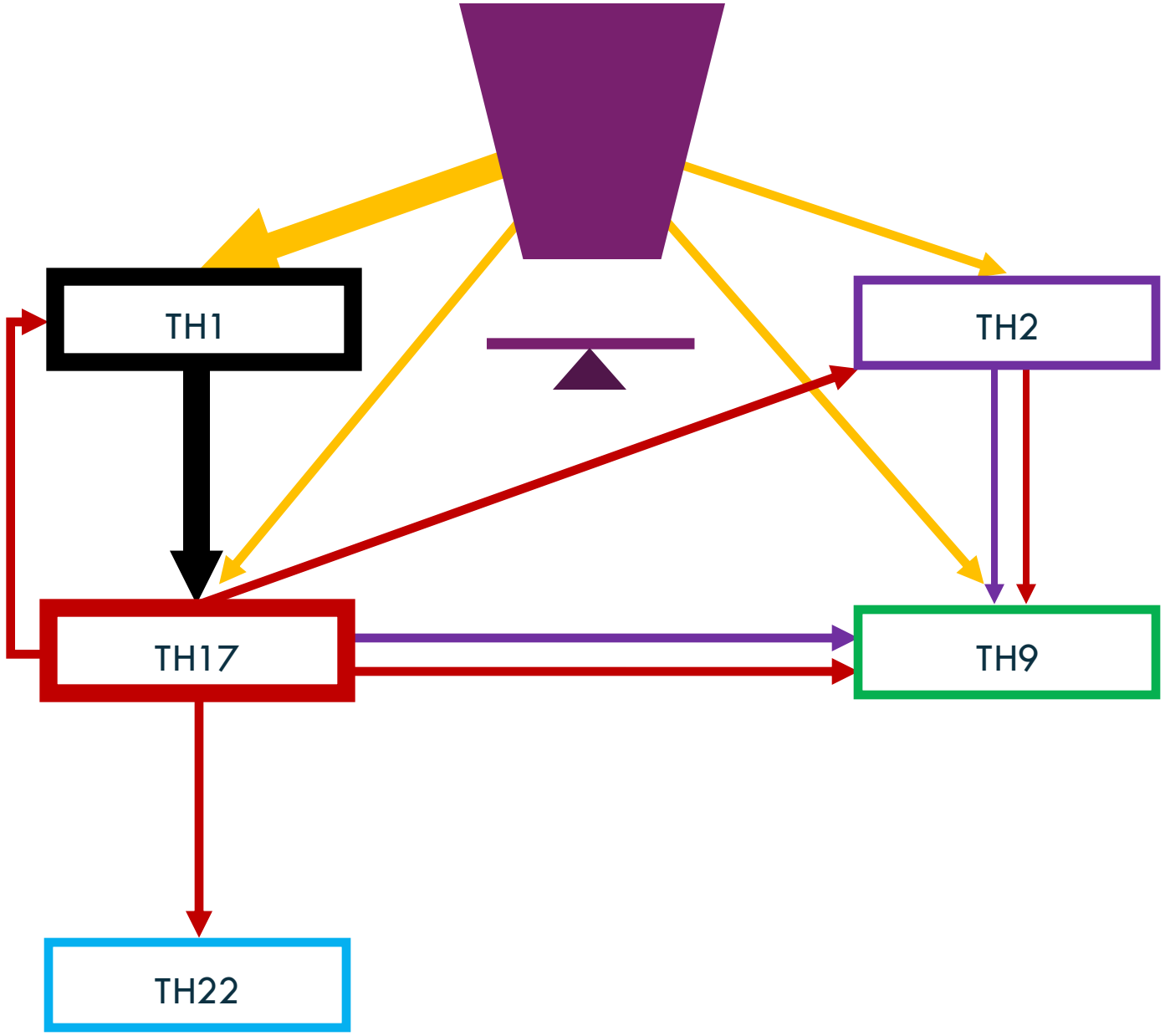
TH1
TH2
TH17
TH9
TH22
(Dermatologic)

EMBO Mol Med. 2025 Jun 17;17(7):1501–1518. doi: 10.1038/s44321-025-00262-y

Interplay between fungal infections and autoimmunity: mechanisms and therapeutic perspectives

Devon T DiPalma [1], Miranda K Lumbreras [1], Mari L Shinohara [1,2,3,4,✉]

Fungi are ubiquitous microorganisms with significant roles in human health and disease. Although traditionally studied for their pathogenic capabilities, fungi are increasingly recognized for their involvement in autoimmune diseases. Fungal pathogens have evolved mechanisms to invade human tissues, evade immune responses, and persist within the host. Concurrently, these pathogens and the broader mycobiome—the fungal component of the microbiome—exert profound immunomodulatory effects that can predispose susceptible individuals to autoimmunity.

Emerging evidence links fungal pathogens to autoimmune diseases, suggesting possible mechanisms such as dysbiosis, molecular mimicry, and immune dysregulation. This review explores the complex interplay between fungal infections and autoimmunity, focusing on how immune responses to fungi contribute to disease progression and how antifungal treatments might influence these interactions. Advancing our understanding of fungal–host immune dynamics is crucial for developing targeted therapies and improving outcomes for patients with fungal infections and autoimmune diseases.

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Fungal species associated with autoimmune and inflammatory diseases.

Fungal genus/species	Autoimmune disease	Inflammatory disease	Proposed roles	References
Candida albicans	MS, RA, T1D	CD, UC	Th17 stimulation; gut dysbiosis; translocation; immune priming	Sokol et al, 2017; Benito-Leon and Laurence, 2017; Benito-León et al, 2010; Yadav et al, 2022; Gursoy et al, 2018; Honkanen et al, 2020; Lee et al, 2022; Li et al, 2014
Candida tropicalis		CD	Gut enrichment; interkingdom interactions	Hoarau et al, 2016
Candida krusei	MS		Enhancing Th1/Th17 responses	Fraga-Silva et al, 2022

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Candida galabrata	MS; SLE	CD	Enhancing Th1/Th17 responses;	Liguori et al, 2016; Fraga-Silva et al, 2022; Yang et al, 2023
Saccharomyces cerevisiae	T1D, SLE, MS, RA	CD	Target of ASCA antibodies; loss of tolerance	Main et al, 1988; Sendid et al 2024; Sokol et al, 2017
Aspergillus spp.	MS	CD, ABPA	Th2/Th17 stimulator; hypersensitivity	Li et al, 2014; Shah et al, 2021;Chauhan et al, 2000
Cryptococcus neoformans	MS	CD	CNS tolerance disruption, Immunomodulatory therapies	Li et al, 2014; Scotto et al, 2021; Nasir et al, 2023

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C. albicans is a common opportunistic fungal pathogen but also thrives as a commensal organism in mucosal tissues (Gow et al, 2011; Talapko et al, 2021). Given its presence in the gut mycobiota, research linked *C. albicans* to autoimmune diseases such as multiple sclerosis (MS) (Benito-Leon and Laurence, 2017; Benito-León et al, 2010; Yadav et al, 2022), type-1 diabetes (T1D) (Gursoy et al, 2018; Honkanen et al, 2020), and rheumatoid arthritis (RA) (Lee et al, 2022). Other *Candida* species, such as *C. glabrata* and *C. krusei*, have also been implicated in autoimmunity (Fraga-Silva et al, 2022). Their association with autoimmune disorders may stem from their prevalence in the human body and high infection rate, especially in females (Denning et al, 2018).

The *Cryptococcus* genus includes two major species that infect humans: *C. neoformans* (including recently subcategorized *C. deneoformans*) and *C. gattii*. *C. neoformans* primarily infects immunocompromised individuals, whereas *C. gattii* can infect healthy individuals (Kwon-Chung et al, 2014; Li and Mody, 2010). These encapsulated fungi pose a serious threat to patients with T-cell deficiencies, such as AIDS patients, where cryptococcal infection often progresses to meningoencephalitis (Brizendine et al, 2013). *Cryptococcus* infection has also been linked to MS immunomodulatory therapies, which will be discussed in the section “Studies highlighting autoimmune diseases and fungal infections”.

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Among the *Aspergillus* species, *A. fumigatus* is a major human fungal pathogen. This saprophytic fungus generates airborne conidia, which can cause pulmonary infection in immunocompromised individuals. Studies have connected *Aspergillus* species with autoimmune diseases, such as MS (Shah et al, 2021) and Systemic Lupus Erythematosus (SLE) (Yang et al, 2023), in addition to the immune-mediated, but not autoimmune, Crohn's disease (CD) (Li et al, 2014).

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Interplay between fungal infections and autoimmunity: mechanisms and therapeutic perspectives

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Neutrophils are recruited early in infections, clear fungi through phagocytosis, generate reactive oxygen species (ROS), produce antifungal molecules, and increase production of proinflammatory molecules, as well as neutrophil extracellular traps (NETs) formation (Desai and Lionakis, 2018; Urban and Backman, 2020). Neutropenia increases susceptibility to invasive fungal infections (IFIs) (Herbrecht et al, 2000). Recent studies indicated that subpopulations of neutrophils with suggested distinct functions emerged during fungal infection (Deerhake et al, 2021b).

Macrophages can be tissue-resident or monocyte-derived. Tissue-resident macrophages are generally long-lived and act as immune sentinels (Kanayama et al, 2015; Xu and Shinohara, 2017; Xu-Vanpala et al, 2020). Monocyte-derived macrophages are crucial to clear fungal infections (Kanayama et al, 2015; Ngo et al, 2014), but they can also act as fungal reservoirs (Gilbert et al, 2014; Heung, 2020). Unresolved inflammatory responses by macrophages may contribute to autoimmunity.

Dendritic cells (DCs), the main APCs, link innate and adaptive immunity. They initiate antifungal Th1 and Th17 responses, as well as control the proliferation of regulatory T cells (Tregs) (Yamazaki et al, 2003). Although DCs activate T cells against fungi, they may also initiate autoimmunity by presenting autoantigens (Saferding and Bluml, 2020).

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The adaptive immune system also plays a critical role in fungal defense, as evidenced by increased susceptibility in immunocompromised patients (Brown et al, 2012; Wuthrich et al, 2012). The involvement of $CD4^+$ T cells is well-studied in antifungal immunity and antifungal vaccine development, with growing research on $CD8^+$ T-cell contributions. Th17 responses maintain epithelial barriers and recruit neutrophils, whereas Th1 responses sustain IFNγ production (Hernandez-Santos and Gaffen, 2012). Th1 and Th17 are protective, but Th2 responses can be detrimental to fungal infections (Wuthrich et al, 2012). Th1 and Th17 cell responses also contribute to autoimmune diseases such as MS and RA. In contrast, Tregs negatively control and balance immune responses, though a study suggested Tregs could promote Th17 differentiation and enhance host resistance in a candidiasis model (Pandiyan et al, 2011). Increased Th17/Treg ratios are linked to autoimmune diseases (Lee, 2018), highlighting the need for balanced Th cell responses. $CD8^+$ T cells have been less studied, but studies have suggested their protective role in general, particularly in histoplasmosis (Deepe, 1994; Nanjappa et al, 2012a; Nanjappa et al, 2012b).

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B cells contribute to antifungal immunity via antibody production, cytokine production, and antigen presentation. They generate antibodies against fungal polysaccharides, such as β-glucans and glucuronoxylomannan (GXM) in *C. neoformans* (Casadevall and Pirofski, 2012). Antibodies exert fungicidal effects through methods of killing, opsonization, complement activation, and antibody-dependent cellular toxicity (ADCC) with evidence from *C. albicans*, *C. neoformans*, and *Histoplasma capsulatum* (Han et al, 2001; Nabavi and Murphy, 1986; Shi et al, 2008). However, excessive B-cell activity, ectopic germinal centers, proinflammatory cytokine production, and autoantibody production can promote autoimmunity. It is possible that memory B cells trigger autoimmunity if fungal antigens cross-react with self-epitopes.

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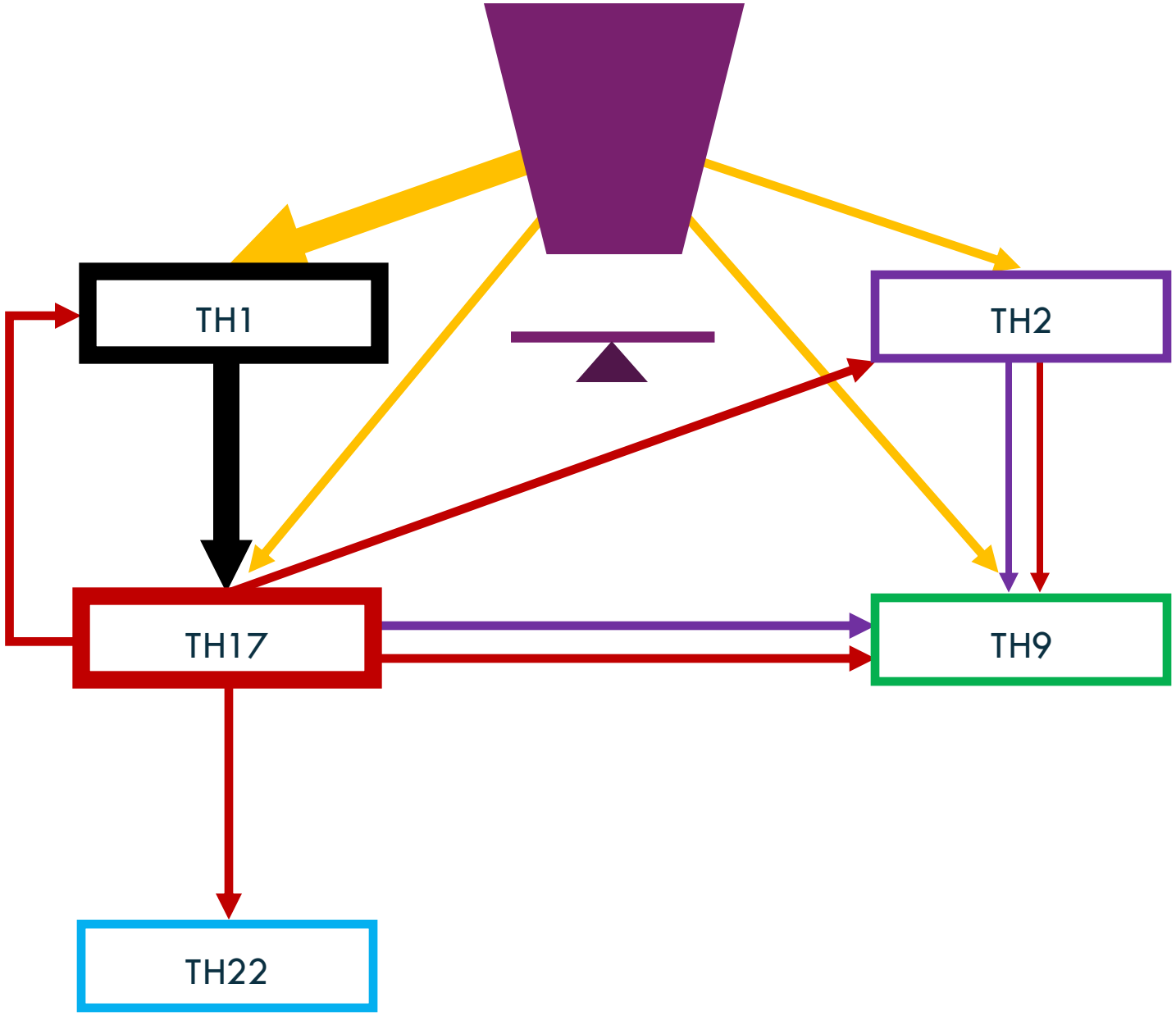
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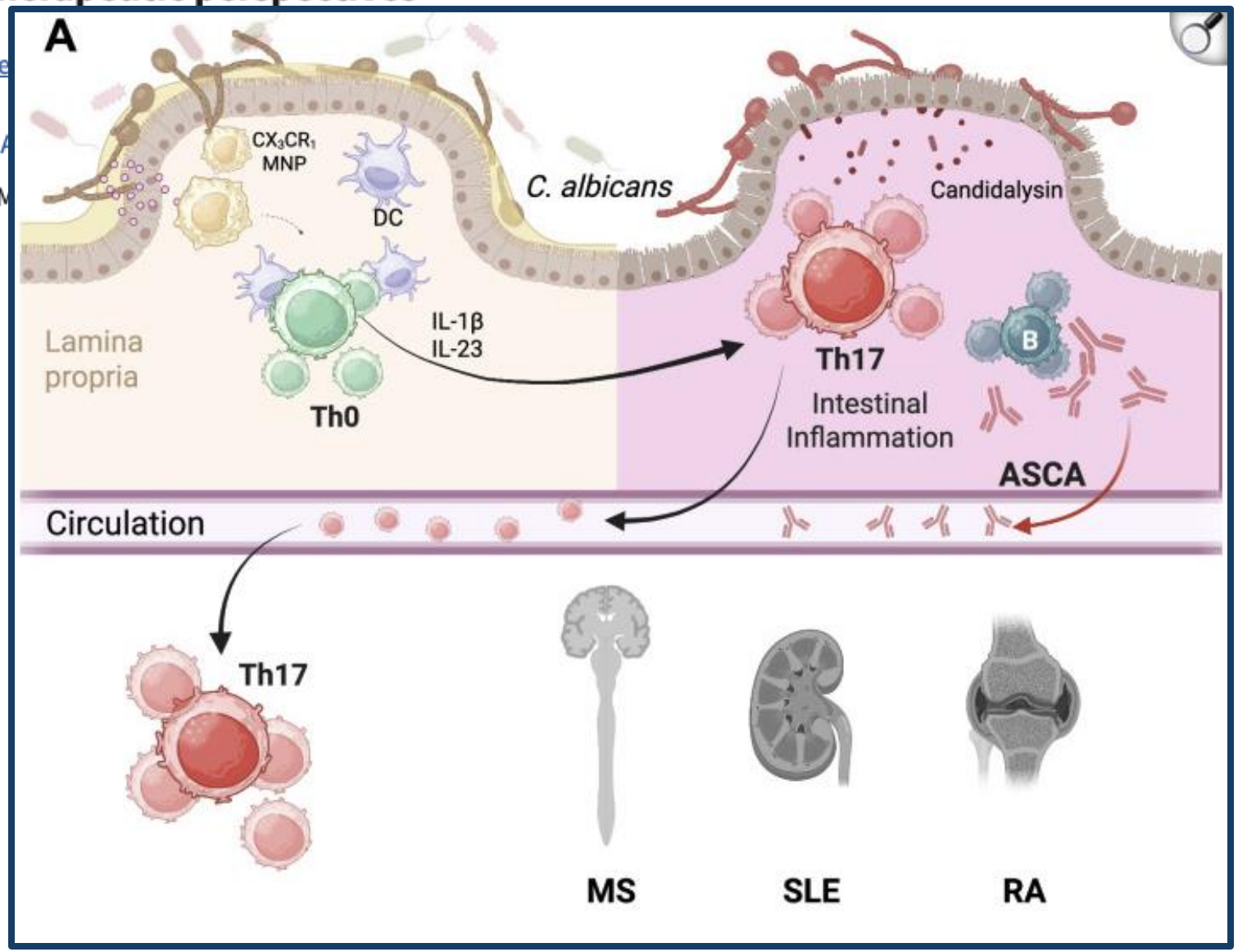

* Persistent presentation drives TH17 polarity.

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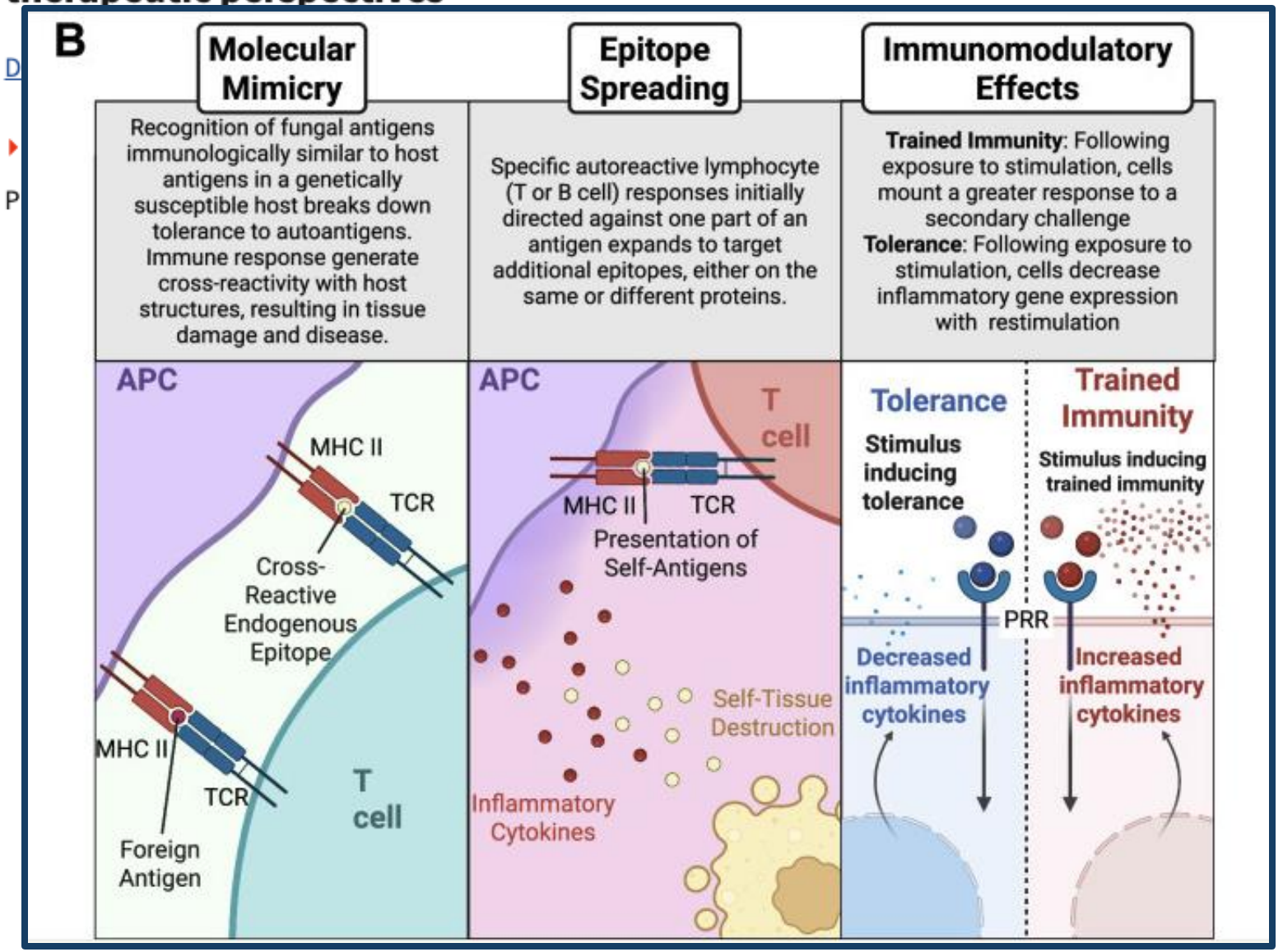

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68 yo female:

TEST	RESULT			
Array 10 - Food Immune Reactivity Screen **	**IN RANGE (Normal)**	**EQUIVOCAL***	**OUT OF RANGE**	**REFERENCE** (ELISA Index)
DAIRY and EGGS, Modified				
Egg White, cooked	0.59			0.0-0.9
Egg Yolk, cooked	0.54			0.0-1.0
Goat's Milk			3.37	0.0-2.2
Soft Cheese + Hard Cheese			3.26	0.1-1.7
Yogurt			1.57	0.0-1.5
GRAINS, Raw and Modified				
Rice, white + brown, cooked			1.50	0.1-1.3
Rice Cake	1.02			0.2-1.8
Rice Protein		0.68		0.1-0.8
Rice Endochitinase	0.39			0.1-0.8
Wild Rice, cooked	0.75			0.2-1.1
Wheat + Alpha-Gliadins			2.66	0.2-1.9
BEANS and LEGUMES, Modified				
Black Bean, cooked	0.54			0.1-1.0
Bean Agglutinins	0.64			0.2-1.5
Dark Chocolate + Cocoa	0.51			0.2-0.9
Fava Bean, cooked			1.22	0.0-1.1
Garbanzo Bean, cooked	1.11			0.2-1.8
Kidney Bean, cooked			>3.10	0.0-0.8
Lentil, cooked			2.77	0.1-1.5
Lentil Lectin	1.00			0.5-1.5
Lima Bean, cooked			2.76	0.2-1.5
Pinto Bean, cooked	1.47			0.4-2.4
Soybean Agglutinin	0.57			0.0-1.1
Soybean Oleosin + Aquaporin			4.18	0.0-0.9
Soy Sauce, gluten-free	1.66			0.1-2.3

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TEST	RESULT			
Array 11 Chemical Immune Reactivity Screen	**IN RANGE (Normal)**	**EQUIVOCAL***	**OUT OF RANGE**	**REFERENCE** (ELISA Index)
Aflatoxins IgG+IgA	1.70			0.9-3.2
Aflatoxins IgM			>2.40	0.4-2.3
Formaldehyde and Glutaraldehyde IgG+IgA			2.62	0.6-2.4
Formaldehyde and Glutaraldehyde IgM	0.99			0.4-2.7
Isocyanate IgG+IgA	0.39			0.2-1.5
Isocyanate IgM			2.43	0.2-2.1
Trimellitic and Phthalic Anhydrides IgG+IgA	0.98			0.3-1.5
Trimellitic and Phthalic Anhydrides IgM	0.66			0.0-3.1
Benzene Ring Compounds IgG+IgA	0.85			0.4-1.6
Benzene Ring Compounds IgM	1.03			0.3-2.1
BPA Binding Protein IgG+IgA	0.80			0.4-1.5
BPA Binding Protein IgM	<0.30			0.2-1.2
Bisphenol A IgG+IgA	1.08			0.1-1.8
Bisphenol A IgM	0.43			0.1-2.0
Tetrabromobisphenol A IgG+IgA	0.68			0.3-1.4
Tetrabromobisphenol A IgM	0.78			0.0-2.5
Tetrachloroethylene IgG+IgA	0.87			0.1-1.5
Tetrachloroethylene IgM		1.63		0.1-2.1
Parabens IgG+IgA	0.65			0.2-1.5
Parabens IgM	0.65			0.0-1.2
Mercury Compounds IgG+IgA	0.47			0.2-1.3
Mercury Compounds IgM	0.49			0.1-2.2
Mixed Heavy Metals IgG+IgA	0.99			0.2-1.8
Mixed Heavy Metals IgM	0.71			0.0-2.1

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TEST	RESULT			
Array 12 - Pathogen-Associated Immune Reactivity Screen **	**IN RANGE (Normal)**	**EQUIVOCAL***	**OUT OF RANGE**	**REFERENCE** (ELISA Index)
Porphyromonas gingivalis	0.82			0.4-1.4
Streptococcus mutans	<0.70			0.4-1.9
Helicobacter pylori	<0.70			0.5-1.9
Campylobacter jejuni	0.46			0.5-2.4
Yersinia enterocolitica	0.75			0.2-1.8
Clostridium difficile	0.23			0.2-1.3
Candida albicans			2.55	0.2-1.8
Rotavirus	0.75			0.0-3.0
Entamoeba histolytica	0.61			0.2-1.9
Giardia lamblia	0.66			0.2-1.6
Cryptosporidium	1.01			0.4-2.6
Blastocystis hominis	0.53			0.1-1.6
Human + Chlamydia HSP-60	0.99			1.0-2.6
Chlamydias	<0.50			0.0-1.8
Streptozymes	0.91			0.0-2.6
Streptococcal M Protein			2.94	0.1-1.4
Mycoplasmas	0.84			0.2-1.8
Acinetobacter	1.11			0.3-2.2
Klebsiella	0.94			0.0-1.3
Mycobacterium avium	1.08			0.2-1.5
Aspergillus		0.93		0.2-1.1
Penicillium	1.43			0.0-1.9
Stachybotrys chartarum	1.86			0.4-2.7
Citrullinated EBV	0.79			0.3-1.1
CYP450, mimic Hepatitis C Peptide		1.40		0.1-1.7
Cytomegalovirus	1.00			0.2-1.2
Human Herpesvirus-6	0.62			0.2-1.4
Borrelia burgdorferi		0.99		0.2-1.0
Babesia + Ehrlichia + Bartonella		0.77		0.1-0.9

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Pathophysiology. 2022 Aug 25;29(3):486–494. doi: 10.3390/pathophysiology29030039

Molecular Mimicry between SARS-CoV-2 and Human Endocrinocytes: A Prerequisite of Post-COVID-19 Endocrine Autoimmunity?

Leonid P Churilov [1,2,*], Muslimbek G Normatov [1,*], Vladimir J Utekhin [1,3,*]

Editor: Jonathan Steven Alexander

Molecular mimicry between human and microbial/viral/parasite peptides is common and has long been associated with the etiology of autoimmune disorders provoked by exogenous pathogens. A growing body of evidence accumulated in recent years suggests a strong correlation between SARS-CoV-2 infection and autoimmunity. The article analyzes the immunogenic potential of the peptides shared between the SARS-CoV-2 spike glycoprotein (S-protein) and antigens of human endocrinocytes involved in most common autoimmune endocrinopathies. A total of 14 pentapeptides shared by the SARS-CoV-2 S-protein, thyroid, pituitary, adrenal cortex autoantigens and beta-cells of the islets of Langerhans were identified, all of them belong to the immunoreactive epitopes of SARS-CoV-2. The discussion of the findings relates the results to the clinical correlates of COVID-19-associated autoimmune endocrinopathies. The most common of these illnesses is an autoimmune thyroid disease, so the majority of shared pentapeptides belong to the marker autoantigens of this disease. The most important in pathogenesis of severe COVID-19, according to the authors, may be autoimmunity against adrenals because their adequate response prevents