Casual Friday Series

Functional Approaches and EBV

A Biogenetix Clinical Presentation

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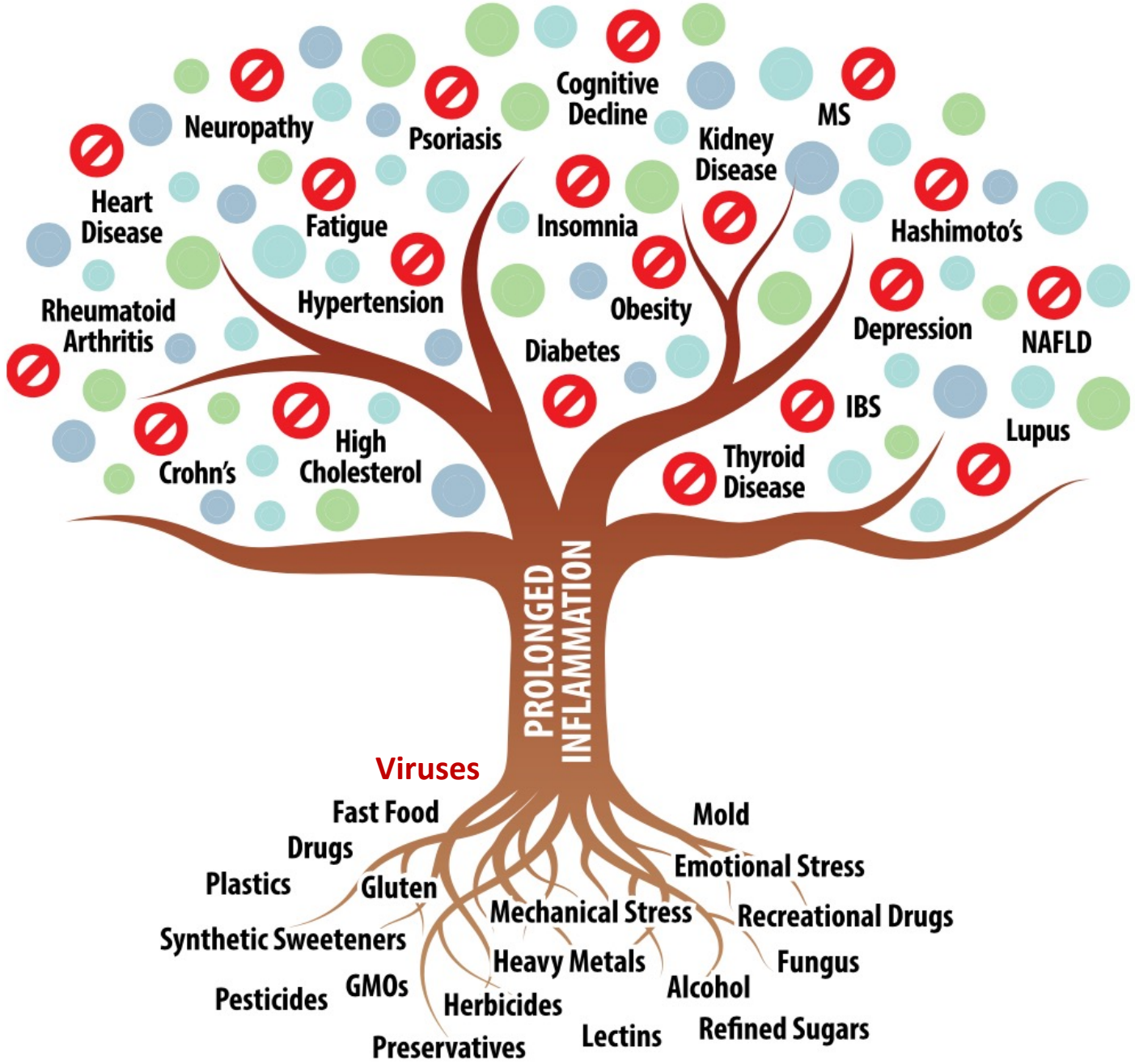
- *Information in this presentation is not intended, in itself, to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*


Neuropathy
Psoriasis
Cognitive Decline
MS
Heart Disease
Fatigue
Kidney Disease
Insomnia
Hashimoto's
Rheumatoid Arthritis
Hypertension
Obesity
Depression
NAFLD
Diabetes
IBS
Crohn's
High Cholesterol
Lupus
Thyroid Disease
PROLONGED INFLAMMATION
Viruses
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Lectins
Refined Sugars
Preservatives

Severe Epstein–Barr virus infection in primary immunodeficiency and the normal host

Austen J. J. Worth ✉, Charlotte J. Houldcroft, Claire Booth

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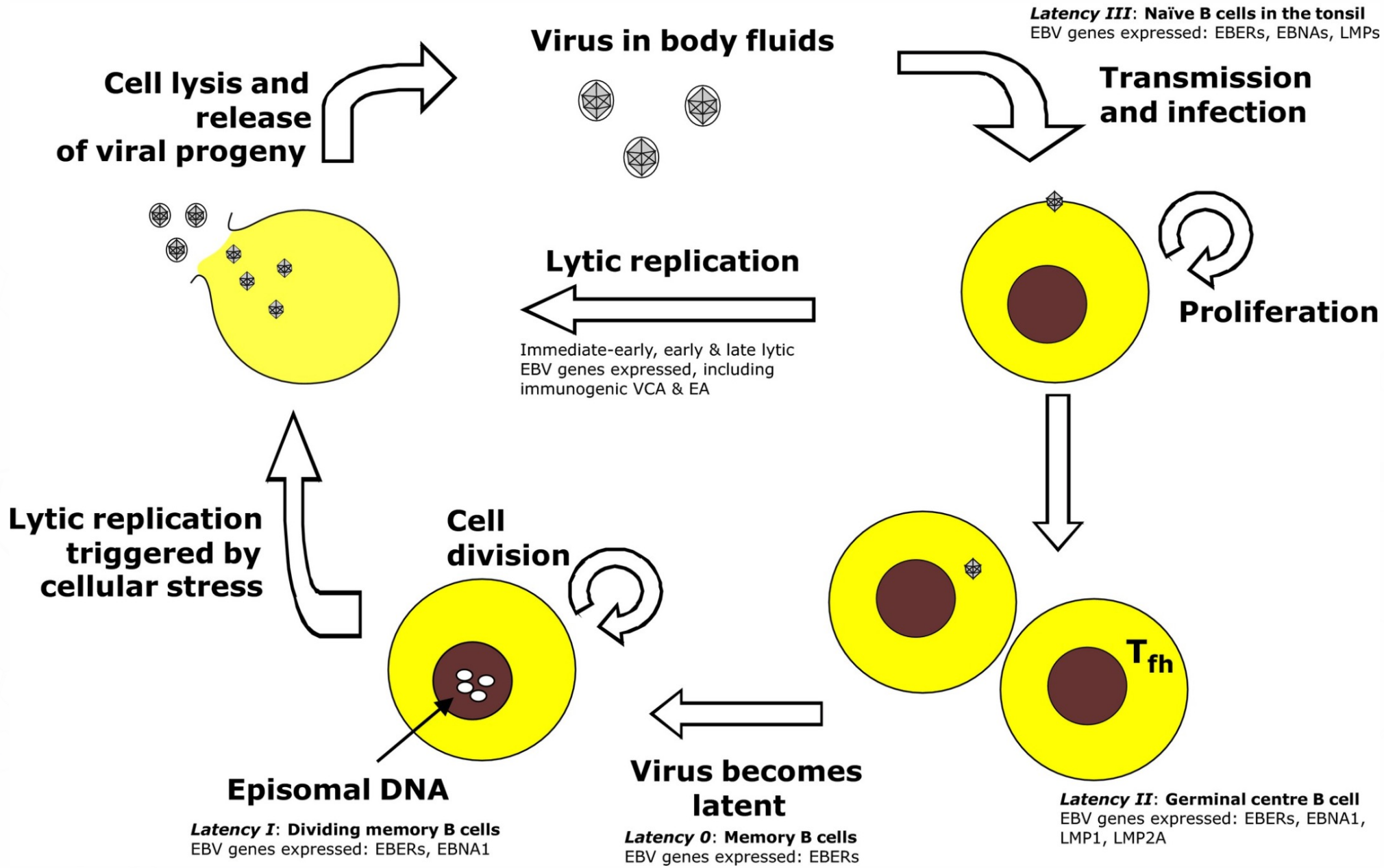
Epstein Barr virus (EBV) is a γ-herpesvirus characterised by restricted infectious specificity to humans, and latent infection in B lymphocytes. Primary infection with EBV typically occurs in childhood as a symptomless or mild infection, with early infection seen in a higher proportion of the population of low income, compared to high income countries (Cohen, 2000; Hjalgrim *et al*, 2007; Pariente *et al*, 2007) [e.g. 58·9% of Zambian infants aged 12 months are EBV seropositive (Minhas *et al*, 2010) compared to 7·1% in Swedish infants (Hesla *et al*, 2013)]. By age 30 years, > 95% of adults in Europe and North America are seropositive (Cohen, 2000; Pariente *et al*, 2007; Pembrey *et al*, 2013). Primary EBV infection in adolescence or adulthood leads to a 25–70% risk of developing a symptomatic EBV infection, known as infectious mononucleosis (IM) (Higgins *et al*, 2007; McAulay *et al*, 2007). This is characterised by pharyngitis, benign lymphoproliferation, fever and malaise; symptoms last up to 6 weeks duration in the majority of patients.

Following primary infection, EBV persists within resting memory B-cells (Miyashita *et al*, 1997) with low immunogenicity (Babcock *et al*, 2000), allowing a life-long infection to be established, which the immune system cannot clear.


Latency III: Naïve B cells in the tonsil
EBV genes expressed: EBERs, EBNAs, LMPs
Virus in body fluids
Transmission and infection
Cell lysis and release of viral progeny
Proliferation
Lytic replication
Immediate-early, early & late lytic EBV genes expressed, including immunogenic VCA & EA
Lytic replication triggered by cellular stress
Cell division
Tfh
Episomal DNA
Latency I: Dividing memory B cells
EBV genes expressed: EBERs, EBNA1
Virus becomes latent
Latency 0: Memory B cells
EBV genes expressed: EBERs
Latency II: Germinal centre B cell
EBV genes expressed: EBERs, EBNA1, LMP1, LMP2A

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The Epstein–Barr virus life cycle. Following initial infection (typically through saliva) the Epstein–Barr virus (EBV) establishes a biphasic life cycle within the host, allowing non-productive genome maintenance in situations of immune surveillance, termed the latent cycle, and reactivating to the productive, infectious lytic cycle when in situations of primary infection or immune suppression. EBV induces different stages of latency (in B cells of different differentiation states), with progressively less viral protein and RNA production as B cells become more differentiated/less activated. Individuals with chronic active EBV or other EBV genetic susceptibilities may be unable to mount an effective cytotoxic T lymphocyte or antibody response to lytically replicating EBV-positive cells, leading to high virus loads and constitutive immune activation. EA- Early

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The virus is shed at particularly high levels from 4 to 6 weeks after initial infection (Dunmire *et al*, 2015), reducing as the infected individual convalesces. Low-level shedding of EBV in saliva continues sporadically for life (Hadinoto *et al*, 2009), as cycles of lytic reactivation within B-cells and oropharyngeal epithelial cells are interrupted by immunological control, leading to a return to latent infection (Taylor *et al*, 2015).

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Although the majority of individuals infected with EBV have an asymptomatic or self-limiting clinical course, there is a broad range of pathological responses to infection, encompassing prolonged fever and lymphoproliferation (severe IM), haemophagocytic lymphohistiocytosis, autoimmunity and malignancy. These states arise from unregulated cytotoxic and inflammatory responses to EBV infected B-cells, impaired T-cell or NK-cell immune surveillance of EBV infected cells, EBV infection in aberrant (non-B) cells or as yet undefined mechanisms. Each of these pathological mechanisms can be in seen in immunodeficient patients (primary or secondary) or apparently normal hosts.

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In the normal setting, cytotoxic T lymphocytes (CTLs) and NK-cells, once in contact with a virally infected cell, respond by forming an immunological synapse with the target cell, followed by granule-mediated cytotoxicity. This not only clears the virally infected cells but regulates the inflammatory response by removing antigenic stimulus. Familial HLH results from impaired granule-dependent cytotoxicity, resulting in impaired target cell death, continued stimulation of cytotoxic cells and ongoing production of inflammatory cytokines. The clinical features of HLH are a consequence of the resultant uncontrolled macrophage activation and histiocytic transformation (Jordan *et al*, 2004).

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Standard of care treatment remains established, highly immunosuppressive, chemotherapeutic protocols (Henter *et al*, 2007). Alternative and salvage therapies, including the use of anti-thymocyte globulin (ATG) and monoclonal antibodies are reviewed elsewhere (Mahlaoui *et al*, 2007; Jordan *et al*, 2011). Supportive care, particularly to prevent and treat infection is critical, and in EBV-HLH, removal of the infectious trigger with multiple courses of Rituximab is essential (Chellapandian *et al*, 2013).

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Chronic Active EBV (CAEBV) was originally used to describe patients with chronic or recurrent IM (Straus, 1988). It is now defined as EBV-related illness lasting > 3 months, associated with systemic EBV positive lymphoproliferative disease (LPD) (with elevated EBV DNA/RNA in affected tissues), and high level EBV viraemia or increased anti-VCA IgG titre, in the absence of defined primary or secondary immunodeficiency (Okano *et al*, 2005; Cohen *et al*, 2011; Kimura *et al*, 2012) (see Table 2). CAEBV has been most commonly described in East Asia where the proliferating cells are usually T- or NK-cells (Kimura *et al*, 2012). This clinically heterozygous condition has overlap with two cutaneous syndromes – Hydroa Vacciniforme-like lymphoma (a recurrent vesiculopapular eruption usually caused by an EBV infected γδT-cell infiltration) and mosquito bite sensitivity associated with EBV positive lymphoproliferation (usually NK-cells) (Kimura *et al*, 2013) (see Fig 2). In Western countries, CAEBV is more rare, but usually associated with B-cell proliferation (Cohen *et al*, 2011). In all of these conditions the lymphocyte and EBV clonality may be monoclonal, oligoclonal or polyclonal (Kimura *et al*, 2012).

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Clinical manifestations of EBV infection. Although the vast majority of EBV infected individuals have an asymptomatic or self-limiting primary infection (infectious mononucleosis), rare individuals develop more severe clinical syndrome as a consequence of an impaired ability to control lytic or latent EBV infection, or the establishment of latent EBV infection in aberrant (non-B-cell) types. These complications can be immune dysregulatory, leading to lymphproliferation and a local or systemic hyperinflammatory state, or they can be malignant. Increasingly it appears that these pathologies are closely linked, with dysregulated inflammatory responses driving EBV-induced malignant proliferation. As a consequence, there is considerable overlap between many of the malignant and inflammatory EBV clinical syndromes. The relationship between these main syndromes is shown in the figure. Arrows represent clinical overlap or progression between individual clinical syndromes. EBV – Epstein–Barr virus, HLH – haemophagocytic lymphohistiocytosis, LPD – lymphoproliferative disease, NK cell – Natural Killer cell.

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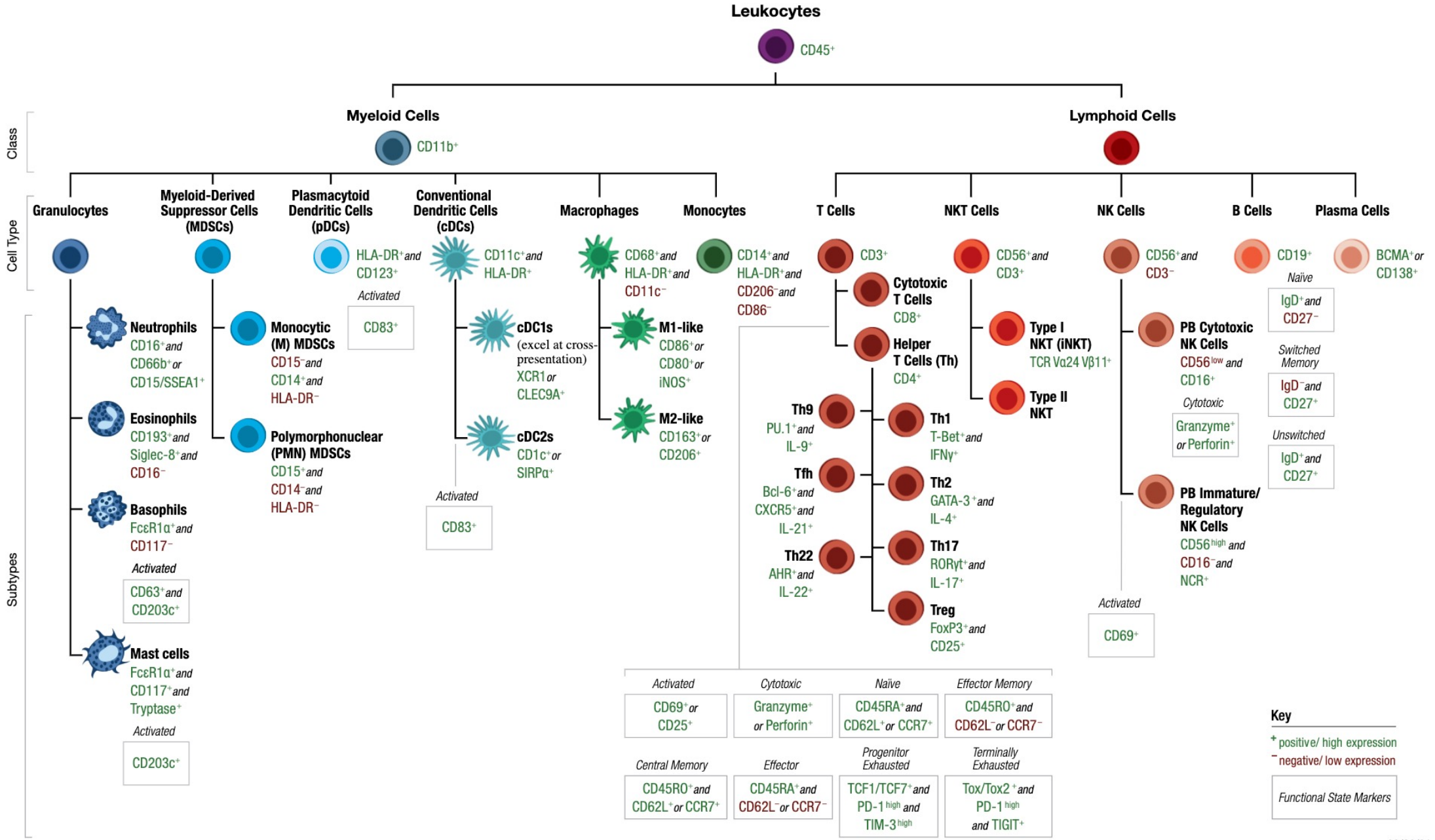
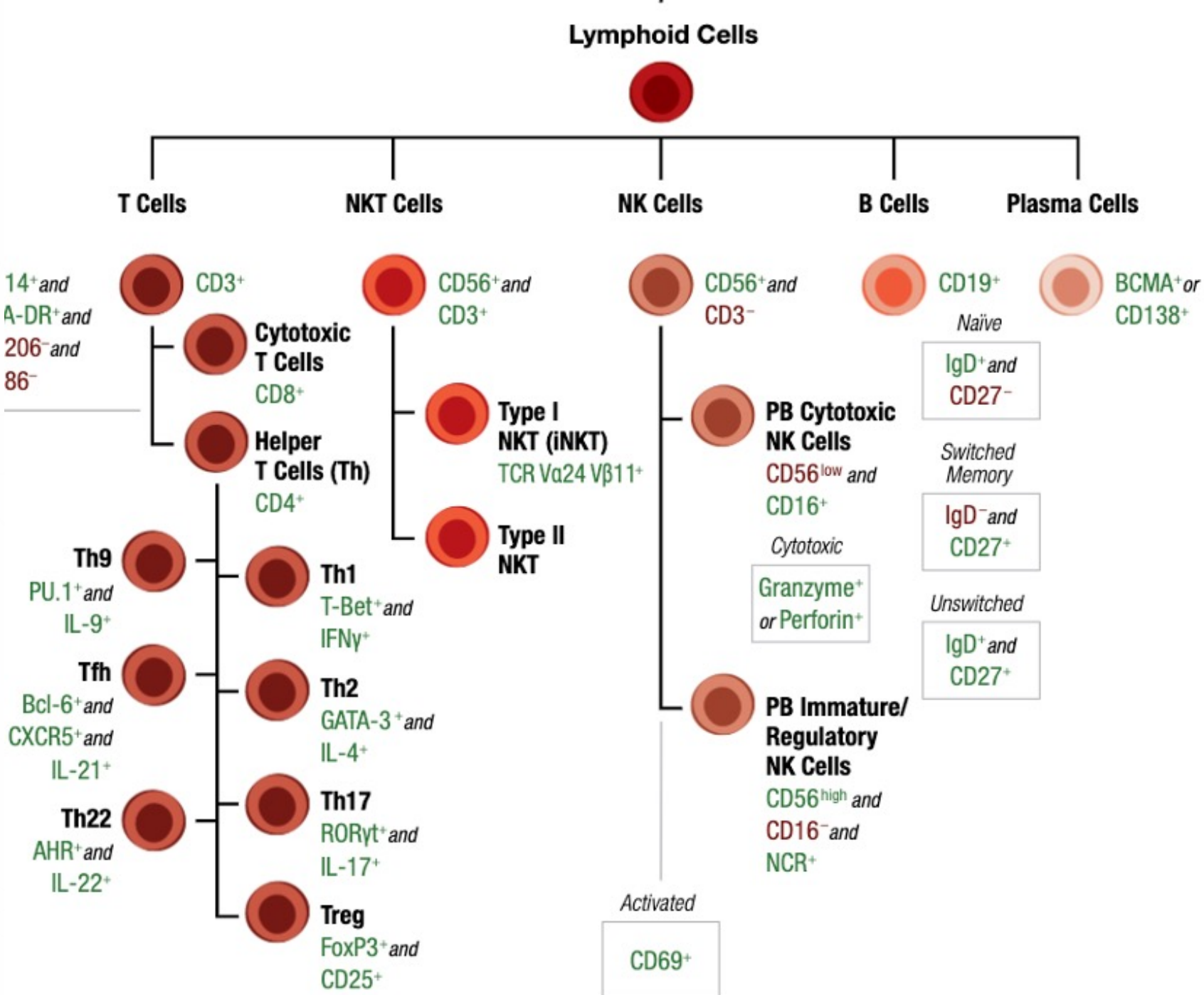
EBV has also been implicated in the pathophysiology of autoimmunity, best characterised by associations with multiple sclerosis and systemic lupus erythematosis (Thacker *et al*, 2006; Taylor *et al*, 2015)

Human Immune Cell Marker Guide



rev. 02/26/21

https://www.cellsignal.com/pathways/immune-cell-markers-human



https://www.cellsignal.com/pathways/immune-cell-markers-human

Non EBV DNA test:

VCA IgM	VCA IgG + EA IgG	EBNA IgG	Interpretation
-	-	-	Negative EBV status
+	-	-	Early primary infection [2]
+	+	-	Acute primary infection
-	+	+ [1]	Past infection
-	-	+	Isolated EBNA IgG [2]
-	+	-	Isolated VCA/EA IgG [2]
+	+	+	Indeterminate [2]

[1] In rare cases, anti-EBNA antibodies are not detected in patients with past infection status.

[2] To be confirmed on a new sample 1 to 2 weeks later or with another technique.

***Early Antigen Testing:
Additionally, Early Antigen D Ab results will quantify a value (where available).

Show 10 entries

Search: EBV

	Test Code	Test	Sales Amount	
+	557	Epstein-Barr Virus (EBV) Antibodies to Viral Capsid Antigen (VCA), IgG (096230) (096230)	**$16.00**	☆
+	558	Epstein-Barr Virus (EBV) Nuclear Antigen Antibodies, IgG (010272) (010272)	**$17.00**	☆
+	819	Epstein-Barr Virus (EBV) Antibodies to Early Antigen, IgG (096248)	**$16.00**	☆
+	1105	Epstein-Barr Virus (EBV) Antibodies to Viral Capsid Antigen (VCA), IgM (096735)	**$16.00**	☆
+	5128	EBV-VCA and EA, IgG Antibody Profile (096255) (096255)	**$34.00**	☆
+	5131	Epstein-Barr Virus (EBV), Quantitative, PCR (138230)	**$167.00**	☆
+	6619	Epstein-Barr Virus (EBV) Antibody Profile (240610)	**$52.00**	☆

Supplement Facts

Serving Size: 2 Capsule
Servings per Container: 45

	Amount per serving	% Daily Value
Calories	5	
Total Calories	<1 g	<1%
Dietary Fiber	<1 g	2%
Vitamin A (as beta carotene)	300 mcgRAE	33%
Vitamin C (as calcium ascorbate, magnesium ascorbate, ascorbic acid)	1000 mg	1111%
Vitamin D3 (as cholecalciferol)	25 mcg	125%
Vitamin E (as d-alpha tocopheryl succinate)	74 mg	493%
Vitamin B6 (as pyridoxal 5-phosphate)	10 mg	588%
Folate (as levomefolate calcium)	170mcgDFE	43%
Vitamin B12 (as methylcobalamin)	100 mcg	4166%
Calcium (as calcium ascorbate)	50 mg	4%
Iodine (as potassium iodide)	3 mg	2000%
Magnesium (as magnesium ascorbate)	25 mg	6%
Zinc (as zinc L-monomethionine)	25 mg	227%
Echinacea Purpura Extract	15 mg	**
Echinacea Angustifolia Extract	15 mg	**
Andrographis Extract	20 mg	**
Holy Basil Extract	15 mg	**
Astragalus Extract	20 mg	**
L-Lysine	25 mg	**
L-Ornithine	10 mg	**
L-Methionine	25 mg	**
Spanish Black Radish Extract	20 mg	**
Monolaurin	25 mg	**
Olive Leaf Extract	20 mg	**
Quercetin	10 mg	**
Beta Sitosterol	10 mg	**

Daily Value based on a 2,000 calorie diet

** Daily Value (DV) not established.

Ochratoxin A

Members of the ochratoxin A have been found as metabolites of many different species of Aspergillus and Penicillium. The level of Ochratoxin A production also influenced by the substrate on which the molds grow as well as the moisture level, temperature, and presence of competitive microflora interact to influence the level of toxin produced. Ochratoxin A has been found in barley, oats, rye, wheat, coffee beans, and other plant products, with barley having a particularly high likelihood of contamination. Ochratoxin has been detected in blood and other animal tissues and in milk, including human milk. Ochratoxin A is a nephrotoxin to all animal species studied to date and is most likely toxic to humans, who have the longest half-life for its elimination of any of the species. It is frequently found in pork intended for human consumption. Ochratoxin is believed to be responsible for a porcine nephropathy that has been studied intensively in the Scandinavian countries. The disease is endemic in Denmark, where rates of porcine nephropathy and ochratoxin contamination in pig feed are highly correlated. In addition to being a nephrotoxin, animal studies indicate that ochratoxin A is a liver toxin, an immune suppressant, a potent teratogen, and a carcinogen.[3]

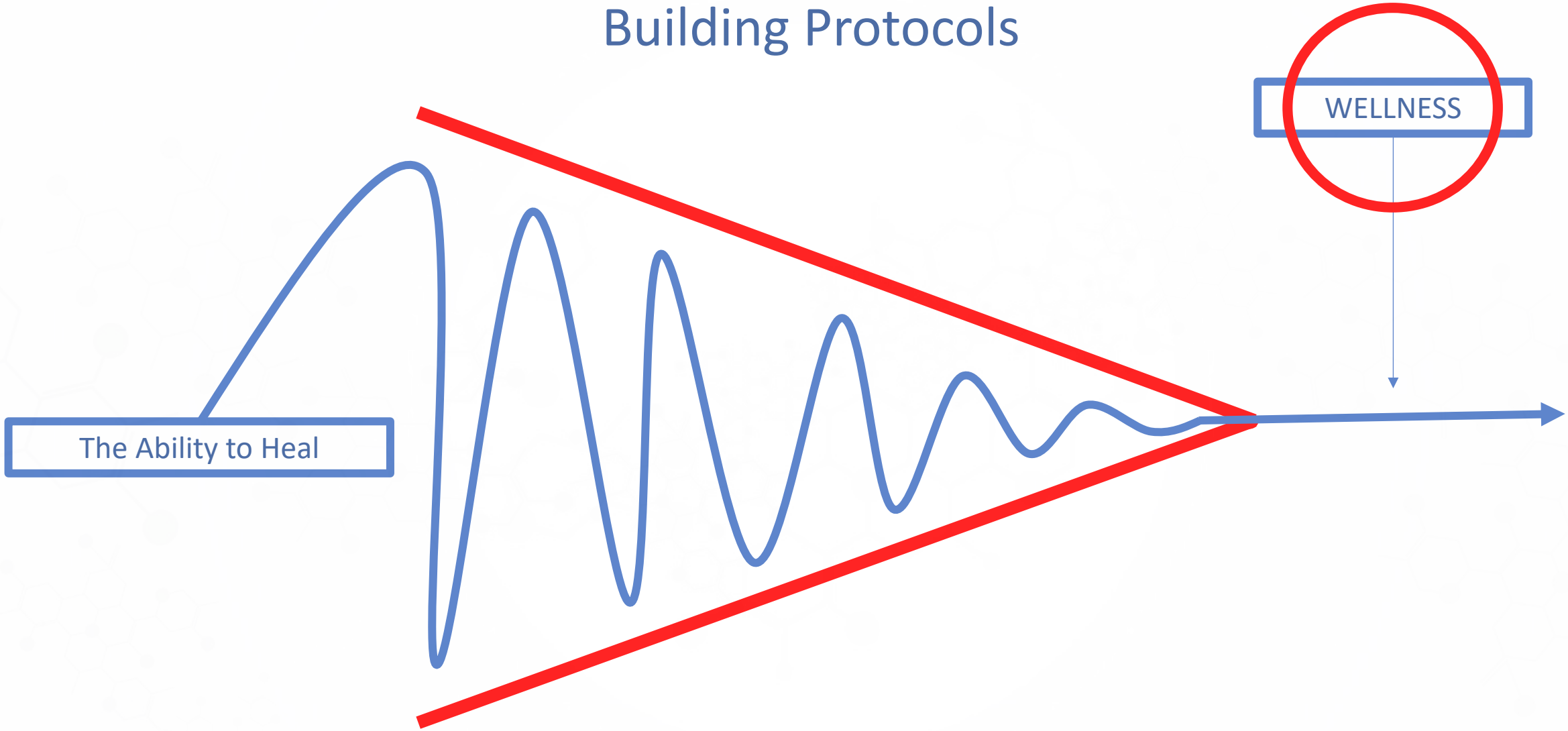
Fumonisins B1

Fusarium is one of the most prevalent fungi associated with contamination of corn and other agricultural products throughout the world. Many different fumonisins have so far been reported, and they have been grouped into four main categories (A, B, C, and P). The most abundant of the fumonisins is fumonisin B1 (FB1). They can also be found in moisture-damaged buildings, and, therefore, exposure of humans to Fusarium mycotoxins including FB1 may take place. FB1 bears a clear structural similarity to the cellular sphingolipids, and this similarity has been shown to disturb the metabolism of sphingolipids by inhibiting a key enzyme in sphingolipid biosynthesis. FB1 is neurotoxic, hepatotoxic, and nephrotoxic in animals, and it has been classified as a possible carcinogen to humans. The cellular mechanisms behind FB1-induced toxicity include the induction of oxidative stress, apoptosis, and cytotoxicity, as well as alterations in cytokine expression.[9]

Gliotoxin

Gliotoxin is mainly produced by Aspergillus and sometimes by Penicillium species. Gliotoxin can be produced by common indoor molds and enter the human body via inhalation of mycotoxin containing spores and particulates.[14] Gliotoxin produced by Aspergillus fumigatus could promote immunosuppression by inhibiting/interfering with the activation of transcription factors that are involved in T cell activation. In addition to targeting immune system, gliotoxins have adverse effects on kidney and liver too.

Building Protocols



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