Casual Friday Series

Epstein-Barr Virus as a Driver of Autoimmunity

A Biogenetix Clinical Presentation

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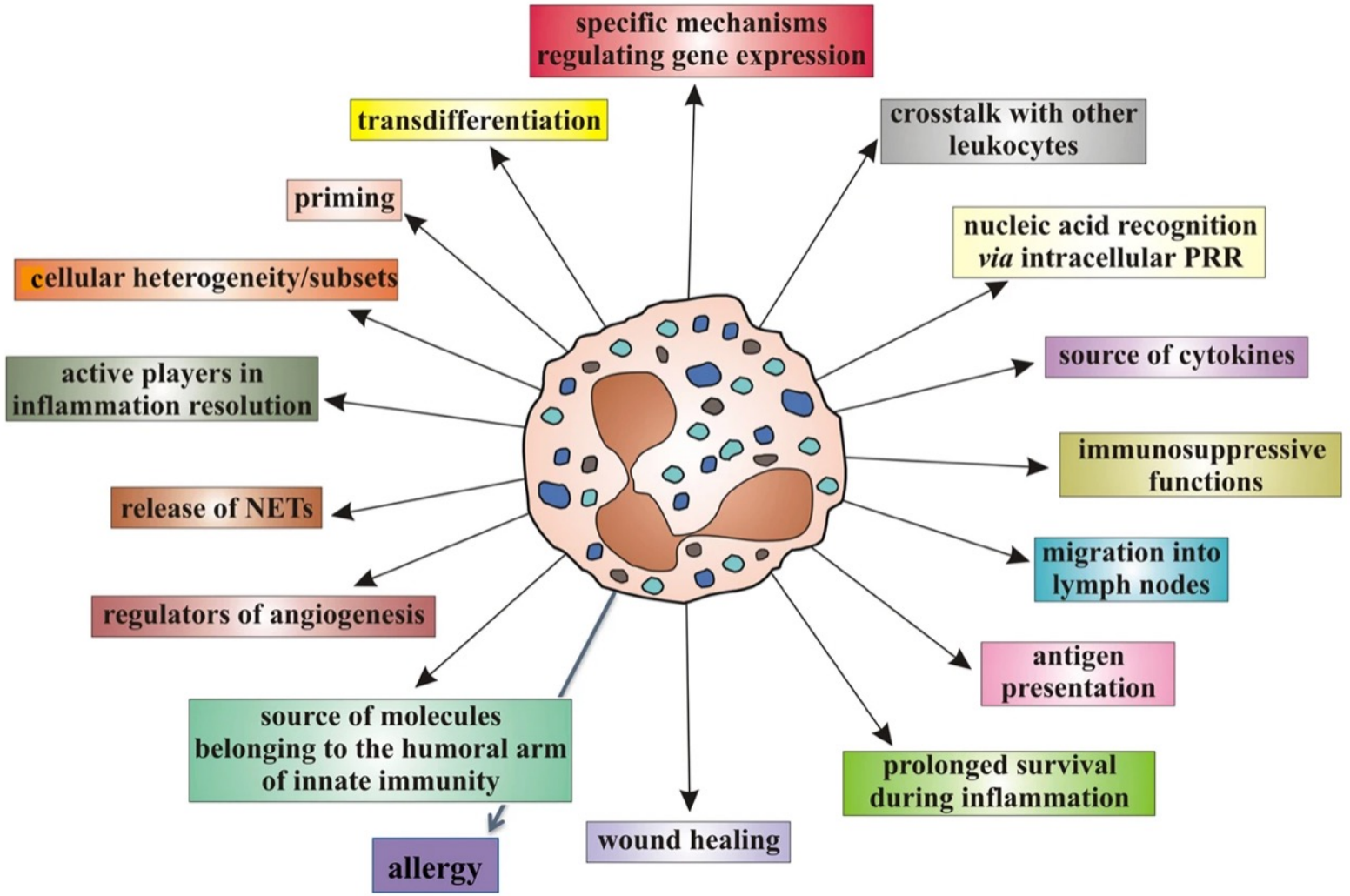
Biologic Activity of Neutrophils



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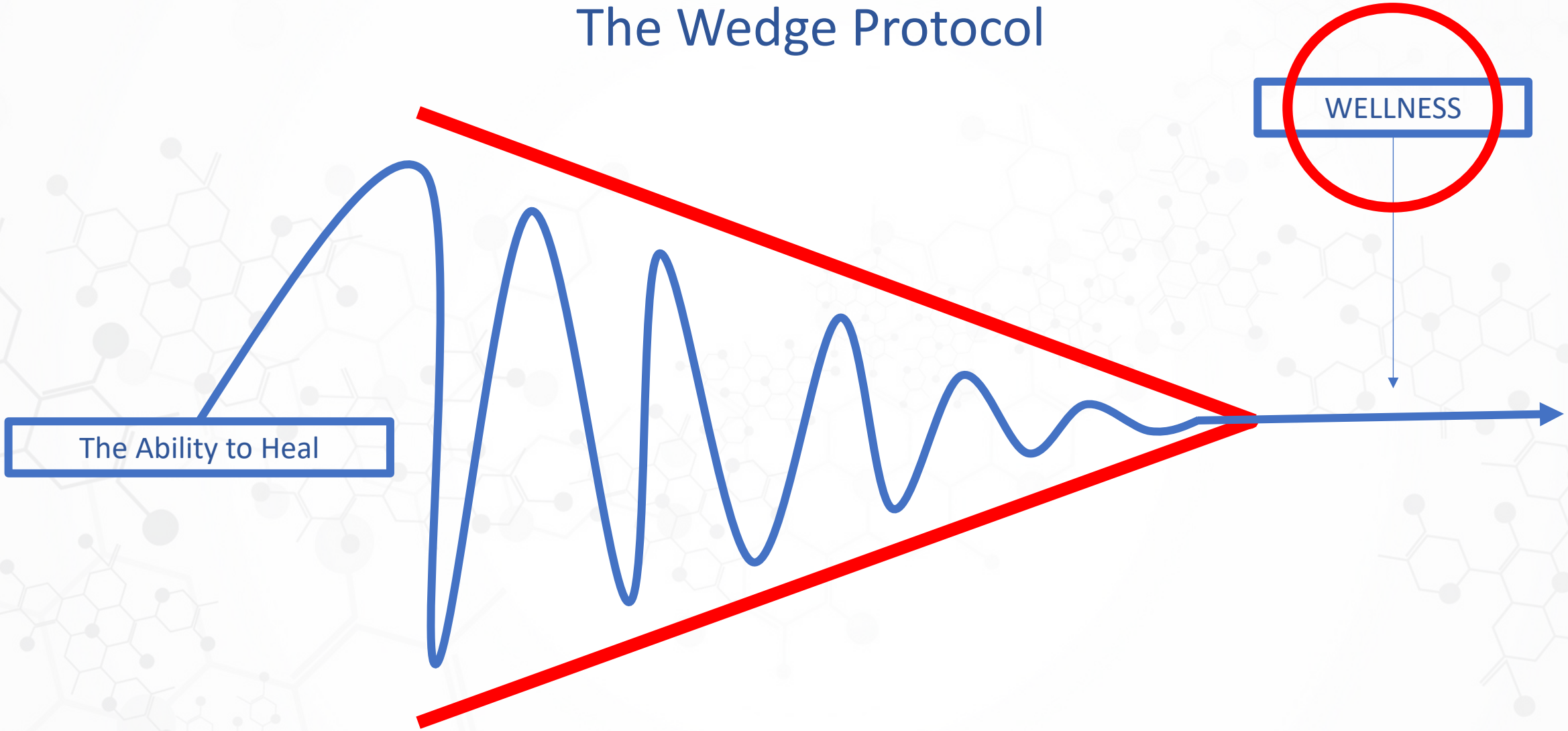
The Wedge Protocol



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Epstein Barr Virus

Epstein Barr virus (EBV) is a double-stranded DNA virus that infects B lymphocyte cells. It is in the herpesvirus family and was discovered in 1964.[1][2] It can cause a variety of diseases and is spread mainly from saliva containing virus-infected epithelial cells.[1][3] Close to 95% of adults throughout the world have been infected with EBV.[2] It is a causative agent of infectious mononucleosis. Treatment is generally supportive care.[1]

Symptoms of EBV infection can include

- fatigue
- fever
- inflamed throat
- swollen lymph nodes in the neck
- enlarged spleen
- swollen liver
- rash

The transmission of the Epstein Barr virus occurs in several ways, such as deep kissing or food-sharing. Increased levels of viral DNA are found in salivary secretions after the initial infection. Children can be infected after eating food that has already been chewed by an EBV infected individual.[3] The transmission has occurred through stem cell and organ transplantation, as well as blood transfusion.[1][3]

Epstein Barr virus has several associated complications. One dangerous complication is splenic rupture due to infectious mononucleosis. In one case study, splenic rupture occurred 6 days after symptoms of infection. It can be treated conservatively or surgically. Pain control and close monitoring are appropriate conservative management strategies reserved for hemodynamically stable patients. Another non-surgical management option is splenic artery embolization. The surgical option is splenectomy which requires post-operative immunizations, antibiotics, and close follow-up.[14]

Another complication of infectious mononucleosis from EBV is airway obstruction from tonsillar edema of the pharyngeal tissues. Treatment of airway obstruction includes steroids, tracheotomy, or intubation. Airway obstruction is a rare (1-3.5% of cases) but an important complication of infectious mononucleosis that occurs mostly in children.[2][15][16]

Acute acalculous cholecystitis is a complication that can be treated conservatively with pain medication and antiemetics.[17][18] In some cases, patients elected to have laparoscopic cholecystectomy due to unbearable abdominal pain.[18]

There are many other complications from Epstein Barr virus infection that can occur, such as myocarditis, encephalitis, hemophagocytic lymphohistiocytosis, pancreatitis, and autoimmune hemolytic anemia.[19][20][21][22] EBV has also been implicated in causing lymphomas and nasopharyngeal cancers.[1]

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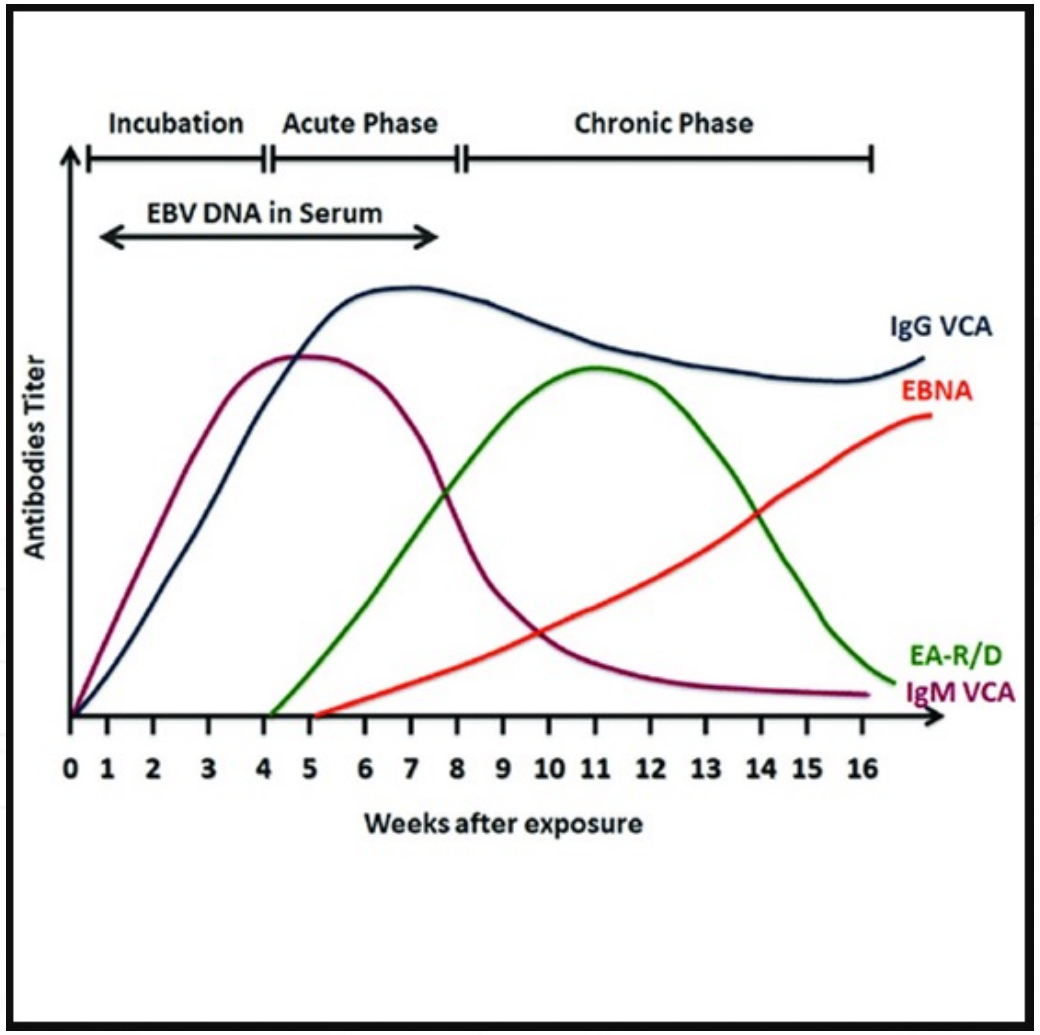
- Viral Capsid Antigen (VCA)
    1. Anti-VCA IgM appears early in EBV infection and usually disappears within four to six weeks.
    2. Anti-VCA IgG appears in the acute phase of EBV infection, peaks at two to four weeks after onset, declines slightly then persists for the rest of a person's life.

- Early antigen (EA)
  Anti-EA IgG appears in the acute phase of illness and generally falls to undetectable levels after three to six months. In many people, detection of antibody to EA is a sign of active infection. However, 20% of healthy people may have antibodies against EA for years.

- EBV nuclear antigen (EBNA)
  Antibody to EBNA, determined by the standard immunofluorescent test, is not seen in the acute phase of EBV infection but slowly appears two to four months after onset of symptoms and persists for the rest of a person's life. Other EBNA enzyme immunoassays may report false positive results.

- Monospot test
  The Monospot test is not recommended for general use. The antibodies detected by Monospot can be caused by conditions other than infectious mononucleosis. Moreover, studies have shown that the Monospot produces both false positive and false negative results. For example, the heterophile antibodies detected by Monospot are often not present in children with infectious mononucleosis. At best, the Monospot test may indicate that a person has a typical case of infectious mononucleosis but does not confirm the presence of EBV infection.



*High levels of anti-EA(D) are typical for late acute and convalescence phase of infectious mononucleosis, while anti-EA(R) is more frequent marker of EBV reactivation. In chronic reactivation and chronic active EBV infection antibody response against both the components can be found.

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https://www.ganeshdiagnostic.com/admin/public/assets/images/product/1672490047-EPSTEIN-BARR%20VIRUS%20ANTIBODY%20TO%20NUCLEAR%20ANTIGEN,%20IgG.webp

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EBV antibody tests are not usually needed to diagnose infectious mononucleosis. However, specific antibody tests may be needed to identify the cause of illness in people who do not have a typical case of infectious mononucleosis or have other illnesses that can be caused by EBV infection. Symptoms of infectious mononucleosis generally resolve within four weeks. If a person is ill for more than six months and does not have a laboratory-confirmed diagnosis of EBV infection, other causes of chronic illness or chronic fatigue syndrome should be considered.

The interpretation of EBV antibody tests requires familiarity with these tests and access to the patient's clinical information. Interpretation of EBV antibody tests and diagnosis of EBV infection is summarized as follows:

Susceptibility to infection

- People are considered susceptible to EBV infection if they do not have antibodies to the VCA.

Primary (new or recent) infection

- People are considered to have a primary EBV infection if they have anti-VCA IgM but do not have antibody to EBNA. Other results that strongly suggest a primary infection are a high or rising level of anti-VCA IgG and no antibody to EBNA after at least four weeks of illness. Resolution of the illness may occur before the diagnostic antibody levels appear. In rare cases, people with active EBV infections may not have detectable EBV-specic antibodies.

Past infection

- The presence of antibodies to both VCA and EBNA suggests past infection (from several months to years earlier). Since over 90% of adults have been infected with EBV, most adults will show antibodies to EBV from infection years earlier. High or elevated antibody levels may be present for years and are not diagnostic of recent infection.

Testing paired acute- and convalescent-phase serum samples is not useful to distinguish between recent and past EBV infections. In most cases, the antibody response occurs rapidly during primary EBV infection. The clinical ndings of infectious mononucleosis occur in conjunction with the appearance of IgG and IgM anti-VCA antibodies. However, the antibody pattern
is not stable before symptoms appear.

EBV Antibody Profile

EBV Ab VCA, IgM	<36.0		U/mL	0.0-35.9	01
			Negative	<36.0	
			Equivocal	36.0 - 43.9	
			Positive	>43.9	
EBV Ab VCA, IgG	**>600.0**	**High**	U/mL	0.0-17.9	01
			Negative	**<18.0**	
			Equivocal	**18.0 - 21.9**	
			Positive	**>21.9**	
EBV Nuclear Antigen Ab, IgG					
	>600.0	**High**	U/mL	0.0-17.9	01
			Negative	**<18.0**	
			Equivocal	**18.0 - 21.9**	
			Positive	**>21.9**	

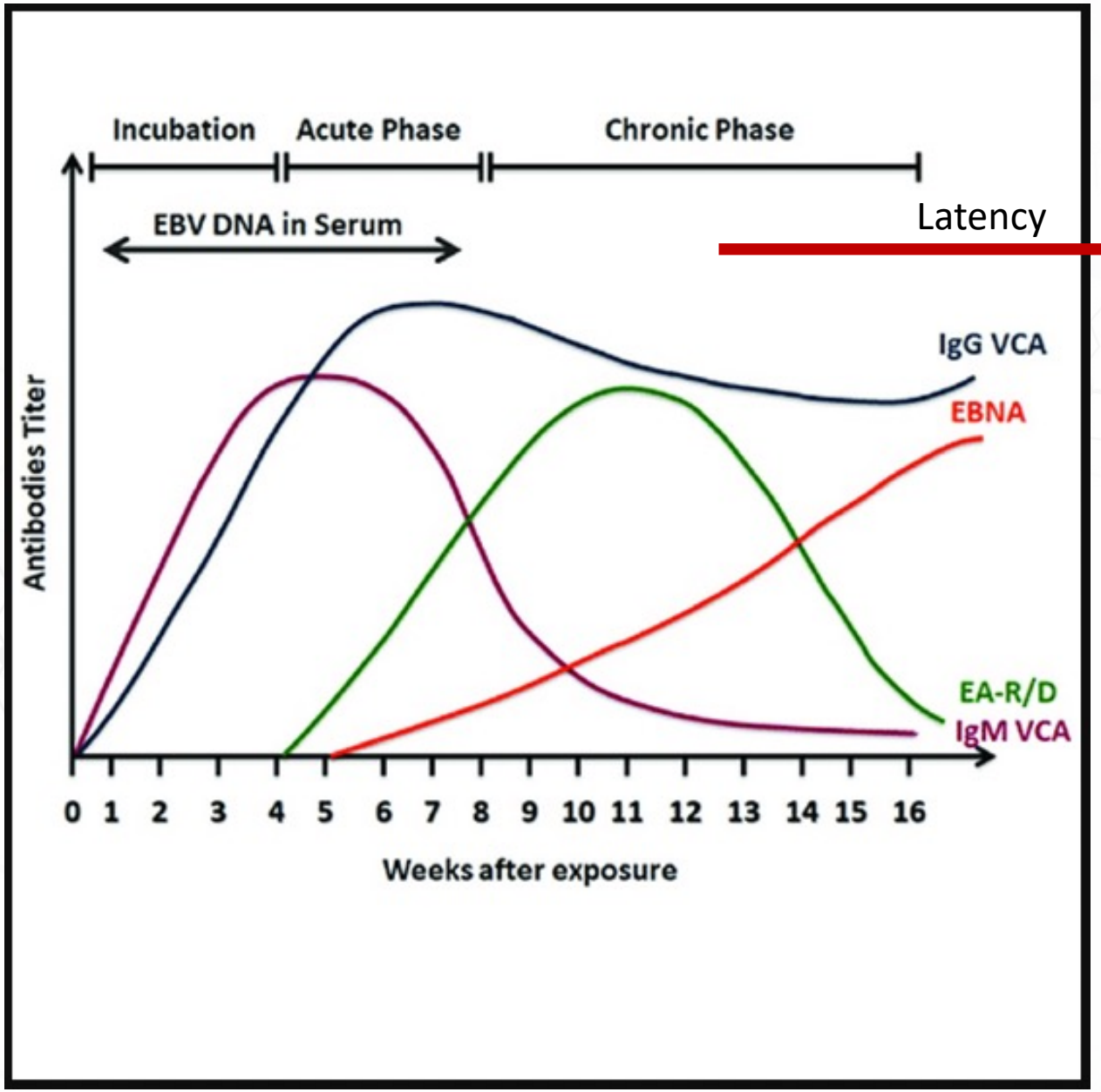
Interpretation: 01

EBV Interpretation Chart

Key: Antibody Present + Interpretation	Antibody Absent - VCA-IgM	VCA-IgG	EBNA-IgG
No previous infection/ Susceptible	-	-	-
Primary infection (new or recent)	+	+	-
Past Infection	+or-	+	+
See comment below*	+	-	-

*Results indicate infection with EBV at some time however cannot predict the timing of the infection since antibodies to EBNA usually develop after primary infection or, alternatively, approximately 5-10% of patients with EBV never develop antibodies to EBNA.

C-Reactive Protein, Cardiac	**17.29**	**High**	mg/L	0.00-3.00	01
			Relative Risk for Future Cardiovascular Event		
			Low	**<1.00**	
			Average	**1.00 - 3.00**	
			High	**>3.00**	



Latency

Reactivation

https://www.ganeshdiagnostic.com/admin/public/assets/images/product/1672490047-EPSTEIN-BARR%20VIRUS%20ANTIBODY%20TO%20NUCLEAR%20ANTIGEN,%20IgG.webp

Nat Genet. 2018 May;50(5):699-707. doi: 10.1038/s41588-018-0102-3. Epub 2018 Apr 16.

Transcription factors operate across disease loci, with EBNA2 implicated in autoimmunity

John B Harley [# 1 2 3 4 5], Xiaoting Chen [# 6], Mario Pujato [# 6], Daniel Miller [6], Avery Maddox [6], Carmy Forney [6], Albert F Magnusen [6], Arthur Lynch [6], Kashish Chetal [7], Masashi Yukawa [8], Artem Barski [9 8 10], Nathan Salomonis [9 7], Kenneth M Kaufman [6 11 9 12], Leah C Kottyan [13 14], Matthew T Weirauch [15 16 17 18]

Affiliations + expand

PMID: 29662164 PMCID: PMC6022759 DOI: 10.1038/s41588-018-0102-3

Explaining the genetics of many diseases is challenging because most associations localize to incompletely characterized regulatory regions. Using new computational methods, we show that transcription factors (TFs) occupy multiple loci associated with individual complex genetic disorders. Application to 213 phenotypes and 1,544 TF binding datasets identified 2,264 relationships between hundreds of TFs and 94 phenotypes, including androgen receptor in prostate cancer and GATA3 in breast cancer. Strikingly, nearly half of systemic lupus erythematosus risk loci are occupied by the Epstein-Barr virus EBNA2 protein and many coclustering human TFs, showing gene-environment interaction. Similar EBNA2-anchored associations exist in multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, juvenile idiopathic arthritis and celiac disease. Instances of allele-dependent DNA binding and downstream effects on gene expression at plausibly causal variants support genetic mechanisms dependent on EBNA2. Our results nominate mechanisms that operate across risk loci within disease phenotypes, suggesting new models for disease origins.

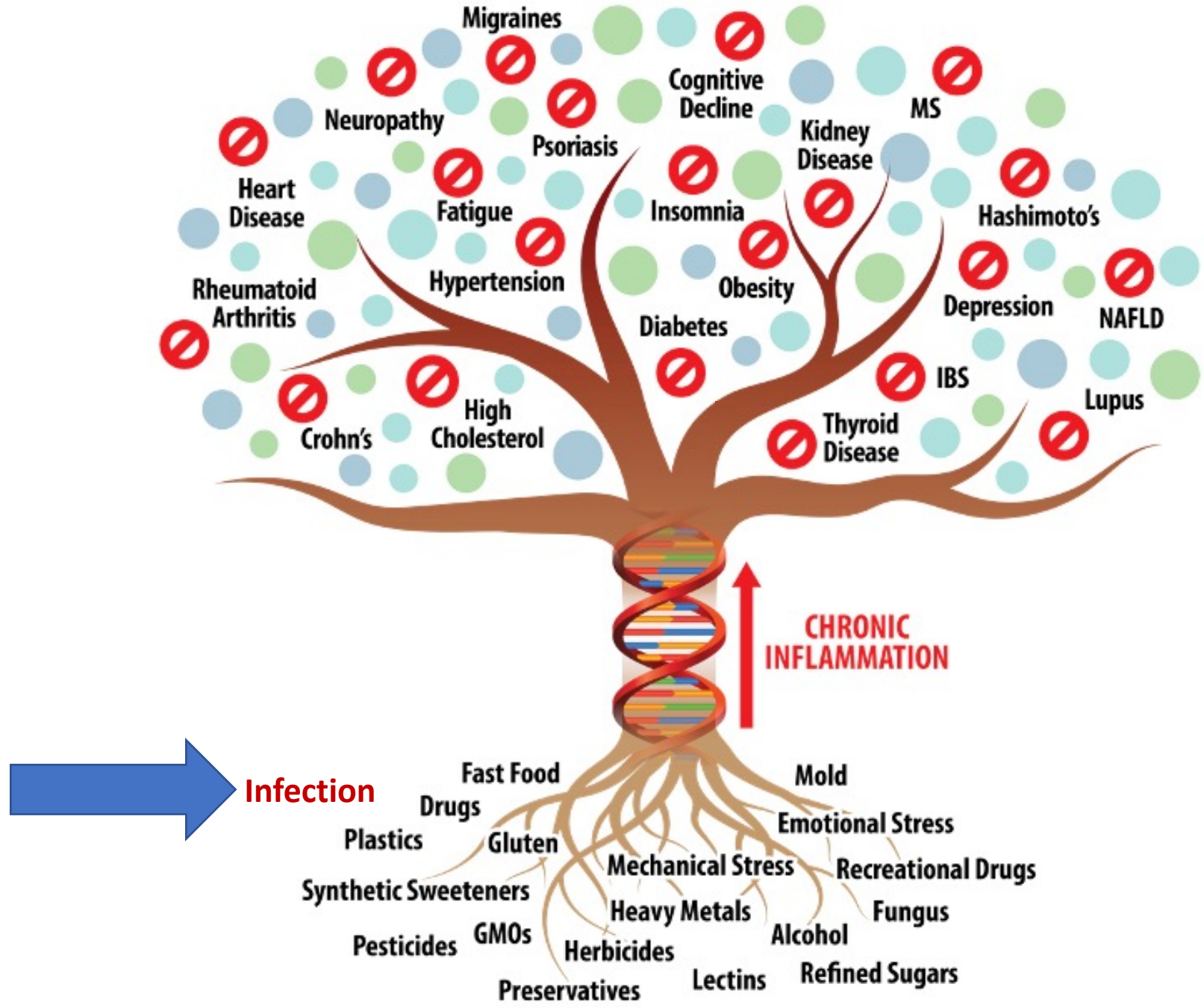
"Because EBV is most often encountered in early childhood, avoiding infection is practically impossible," said Daniel Rotrosen, M.D., director of the Division of Allergy, Immunology and Transplantation at NIAID. "However, now that we understand how EBV infection may contribute to autoimmune diseases in some people, researchers may be able to develop therapies that interrupt or reverse this process."

Researchers note that EBV infection is not the only factor that contributes to the development of the seven autoimmune conditions discussed in the paper. Many of the regulatory genes that contribute to lupus and other autoimmune disorders did not interact with EBNA2, and some individuals with activated regulatory genes associated with disease risk do not develop disease.

When EBV infects human immune cells, a protein produced by the virus — EBNA2 — recruits human proteins called transcription factors to bind to regions of both the EBV genome and the cell's own genome. Together, EBNA2 and the human transcription factors change the expression of neighboring viral genes.

In the current study, the researchers found that EBNA2 and its related transcription factors activate some of the human genes associated with the risk for lupus and several other autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, juvenile idiopathic arthritis and celiac disease.

"We were surprised to see that nearly half of the locations on the human genome known to contribute to lupus risk were also binding sites for EBNA2," said Dr. Harley. "These findings suggest that EBV infection in cells can actually drive the activation of these genes and contribute to an individual's risk of developing the disease."


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

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Epstein-Barr Virus and Systemic Autoimmune Diseases

Gunnar Houen [1,2,*] and Nicole Hartwig Trier [2,*]

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Table 2

Systemic autoimmune diseases (SADs) and their characteristics.

Disease	Genetics	Environmental factors
Mixed connective tissue disease (MCTD)	HLA-DRB1, multiple genes	VitD, smoking, EBV, sunburn, silica dust
Polymyositis – dermatomyositis (PM-DM)	HLA-DRB1, multiple genes	Smoking
Rheumatoid arthritis (RA)	HLA-DRB1, PTPN22, multiple genes	VitD, smoking, EBV
Sjögren's syndrome (SS)	HLA-DRB1, PTPN22, multiple genes	VitD, EBV, inverse correlation with smoking
Systemic lupus erythematosus (SLE)	HLA-DRB1, C', multiple genes	VitD, smoking, EBV, sunburn, silica dust
Systemic sclerosis (SSc)	HLA-DRB1, multiple genes	Silica dust, solvents

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CANCER RESEARCH UK

Together we will beat cancer

50 years of Epstein-Barr virus

Category: Science blog | March 26, 2014 | Emma Smith | Comments are closed | 7 minute read

This entry is part 3 of 5 in the series Cancer and Infections

https://news.cancerresearchuk.org/2014/03/26/50-years-of-epstein-barr-virus/#:~:text=In%20March%201964%20The%20Lancet,%2DBarr%20virus%20(EBV).

JOURNAL ARTICLE

Detection of Epstein-Barr Virus in Invasive Breast Cancers

Mathilde Bonnet, Jean-Marc Guinebretiere, Elisabeth Kremmer, Virginie Grunewald, Ellen Benhamou, Genevieve Contesso, Irene Joab

JNCI: Journal of the National Cancer Institute, Volume 91, Issue 16, 18 August 1999, Pages 1376–1381, https://doi.org/10.1093/jnci/91.16.1376

Publish

BACKGROUND: Epstein-Barr virus (EBV) may be a cofactor in the development of different malignancies, including several types of carcinomas. In this study, we investigated the presence of EBV in human breast cancers. METHODS: We used tissues from 100 consecutive primary invasive breast carcinomas, as well as 30 healthy tissues adjacent to a subset of the tumors. DNA was amplified by use of the polymerase chain reaction (PCR), with the primers covering three different regions of the EBV genome. Southern blot analysis was performed by use of a labeled EBV *Bam* HI W restriction fragment as the probe. Infected cells were identified by means of immunohistochemical staining, using monoclonal antibodies directed against the EBV nuclear protein EBNA-1. RESULTS: We were able to detect the EBV genome by PCR in 51% of the tumors, whereas, in 90% of the cases studied, the virus was not detected in healthy tissue adjacent to the tumor ($P < .001$). The presence of the EBV genome in breast tumors was confirmed by Southern blot analysis. The observed EBNA-1 expression was restricted to a fraction (5%-30%) of tumor epithelial cells. Moreover, no immunohistochemical staining was observed in tumors that were negative for EBV by PCR. EBV was detected more frequently in breast tumors that were hormone-receptor negative ($P = .01$) and those of high histologic grade ($P = .03$). EBV detection in primary tumors varied by nodal status ($P = .01$), largely because of the difference between subjects with more than three lymph nodes versus less than or equal to three lymph nodes involved (72% versus 44%). CONCLUSIONS: Our results demonstrated the presence of the EBV genome in a large subset of breast cancers. The virus was restricted to tumor cells and was more frequently associated with the most aggressive tumors. EBV may be a cofactor in the development of some breast cancers.

The Wedge Protocol