Casual Friday Presents

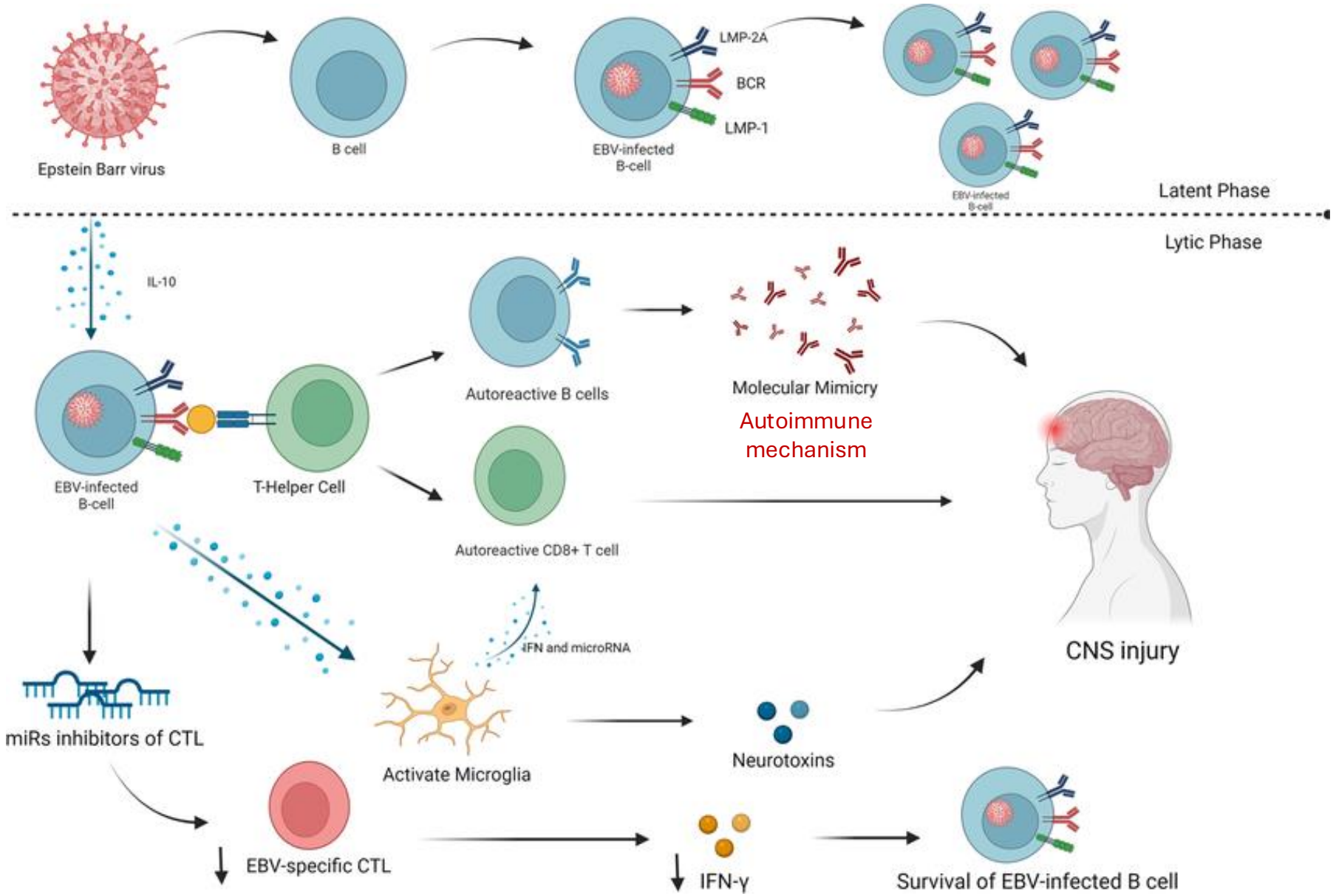
Epstein-Barr Virus Chronic and Reactivation III

FM Strategies: Physiology, Pathology, Interventions.

A BIOGENETIX CLINICAL PRESENTATION

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https://www.researchgate.net/publication/370980833/figure/fig2/AS:11431281160890175@1684895615926/The-mechanism-of-Epstein-Barr-Virus-induced-Nervous-System-damage-EBV-life-cycle-has-two.png

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Quick Notes from Last Week

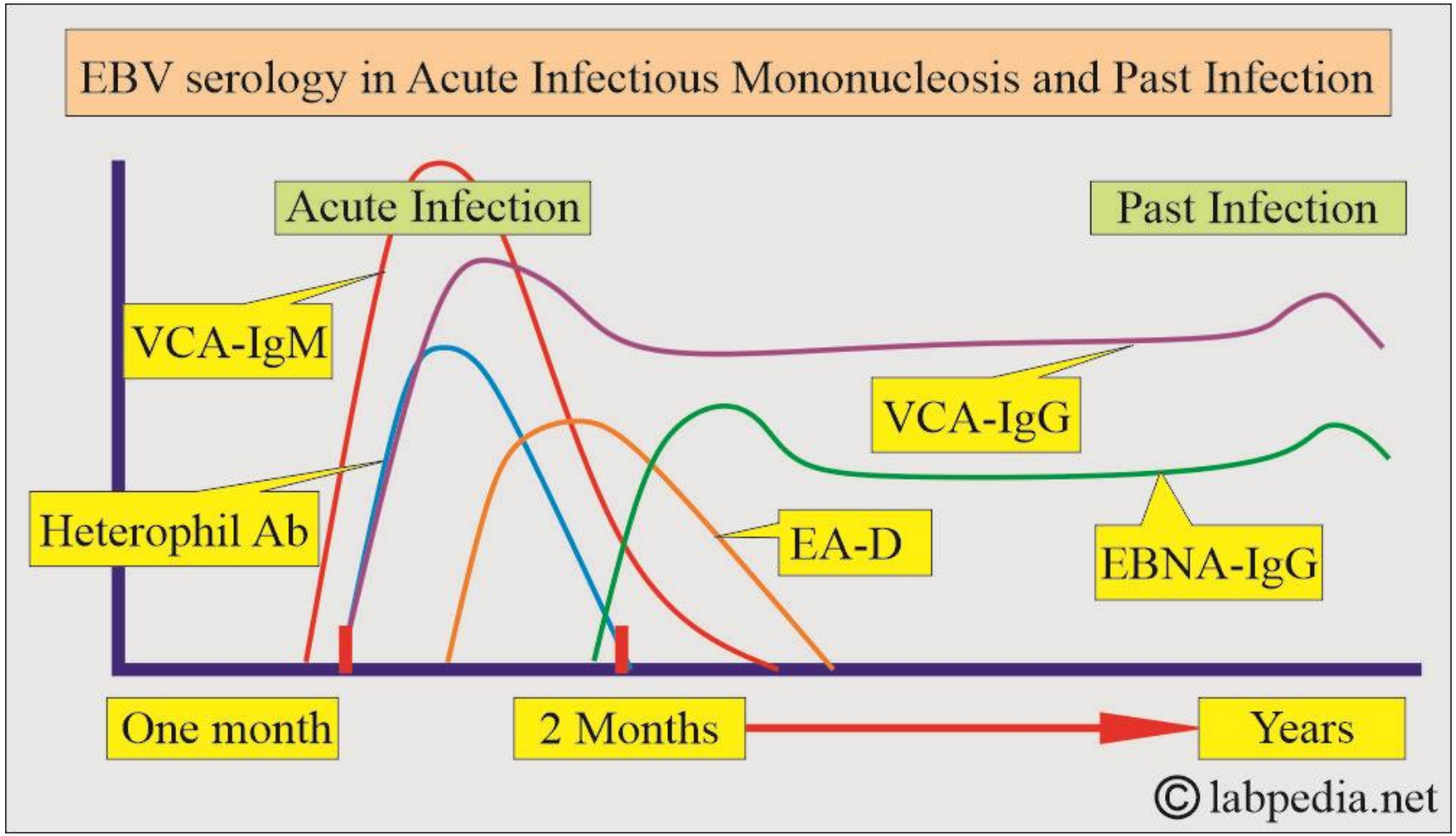
1. Apoptosis inhibition (EBNAs)
2. Cell growth accelerant (EBNAs)
3. Advanced cellular proliferation (LMPs)
4. “Camouflage” escape from CD4 T cell recognition. (LMPs)
5. Blinds host immune system for lifetime latency. (vIL-10)

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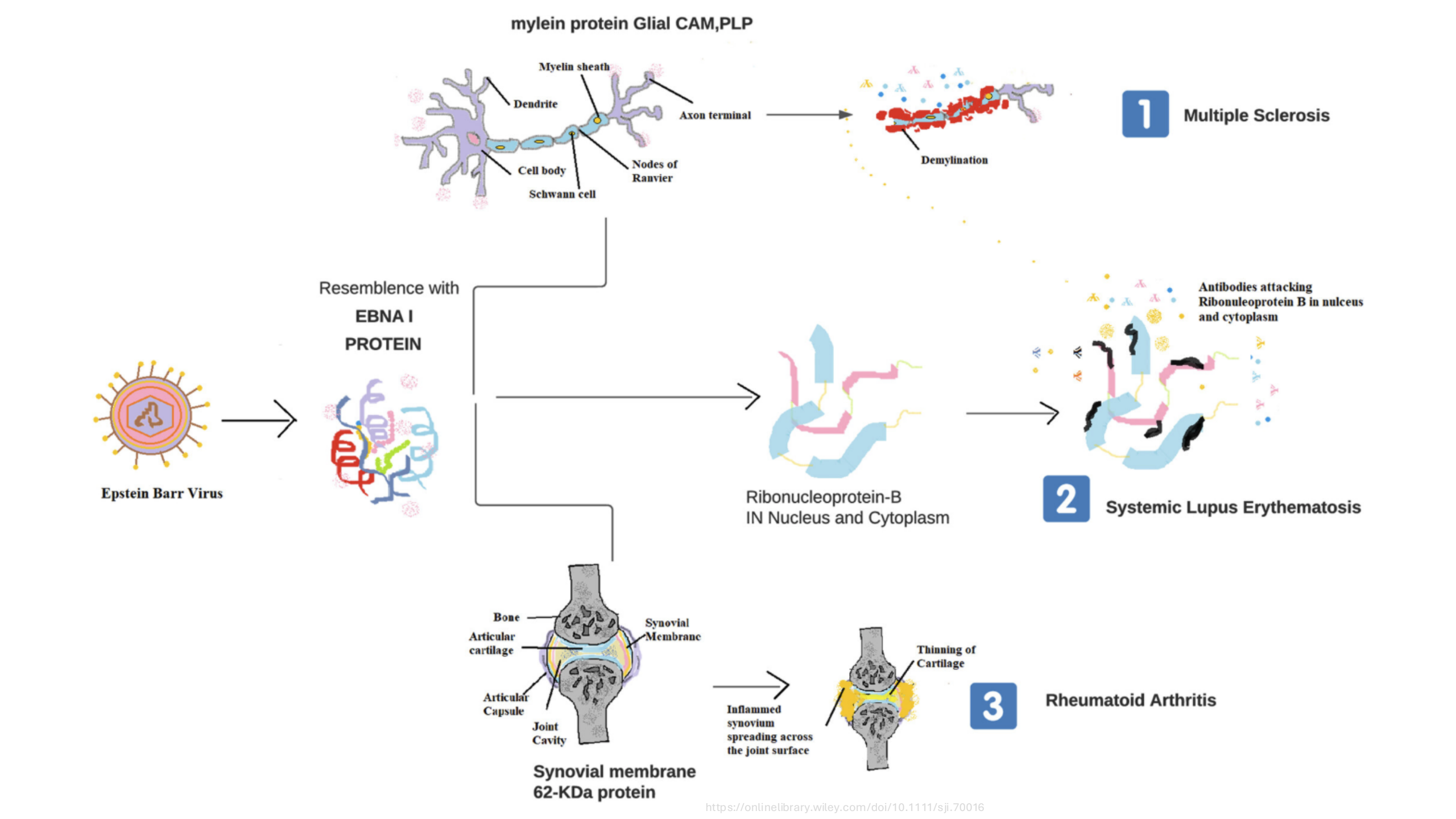
Standard Interpretation Table (Mayo, CDC)

VCA IgM	VCA IgG	EBNA IgG	EA-D IgG	Most Likely Interpretation	Next Step / Notes
–	–	–	–	Susceptible (no prior infection)	Retest if symptoms are very early
+	±	–	±	Primary / recent acute infection	Classic mono pattern; supportive care
–	+	+	–	Past infection	Expected in most adults; no action if asymptomatic
–	+	+	+	Possible reactivation or persistent EA antibodies	Correlate with symptoms; EA can stay positive for years in some healthy people; consider PCR if clinically indicated
–	+	–	±	Indeterminate	Recent infection (pre-EBNA) or remote infection in the ~5–10% who never produce detectable EBNA. Repeat in 2–4 weeks or consider avidity/PCR
+	+	+	±	Indeterminate	Late primary infection, possible reactivation, or false-positive IgM. Clinical correlation ± PCR or avidity

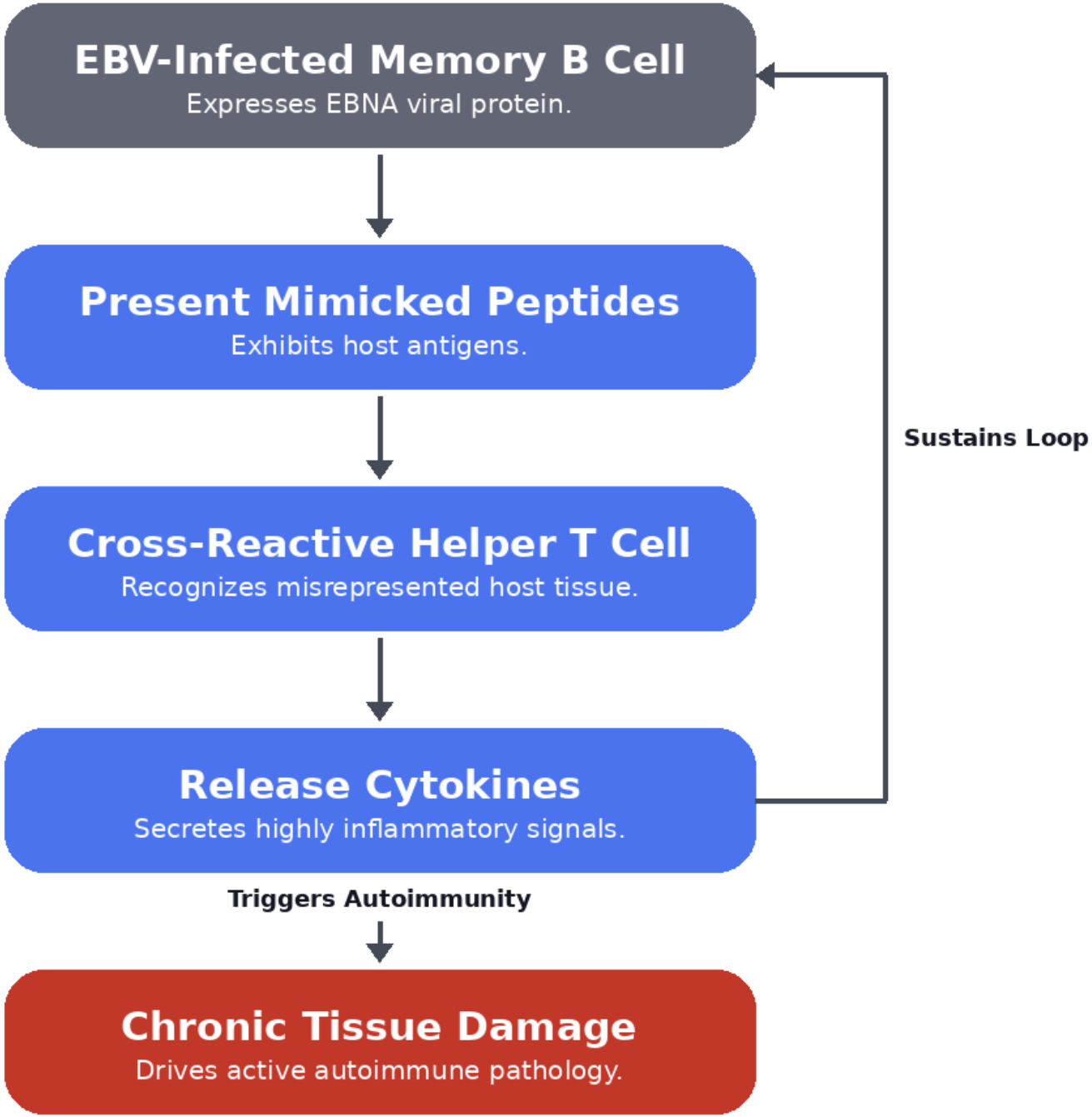
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EBV serology in Acute Infectious Mononucleosis and Past Infection
Acute Infection
Past Infection
VCA-IgM
VCA-IgG
Heterophil Ab
EA-D
EBNA-IgG
One month
2 Months
Years
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https://onlinelibrary.wiley.com/doi/10.1111/sji.70016


EBV-Infected Memory B Cell
Expresses EBNA viral protein.
Present Mimicked Peptides
Exhibits host antigens.
Cross-Reactive Helper T Cell
Recognizes misrepresented host tissue.
Release Cytokines
Secretes highly inflammatory signals.
Sustains Loop
Triggers Autoimmunity
Chronic Tissue Damage
Drives active autoimmune pathology.

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Viruses. 2024 Jan 15;16(1):124. doi: 10.3390/v16010124

Update of Natural Products and Their Derivatives Targeting Epstein–Barr Infection

Rosamaria Pennisi [1,*], Paola Trischitta [1,2], Marianna Costa [1,2], Assunta Venuti [3], Maria Pia Tamburello [1], Maria Teresa Sciortino [1,*]

Editors: Massimiliano Galdiero, Carla Zannella, Annalisa Chianese, Rosa Giugliano

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Epstein–Barr (EBV) is a human γ-herpesvirus that undergoes both a productive (lytic) cycle and a non-productive (latent) phase. The virus establishes enduring latent infection in B lymphocytes and productive infection in the oral mucosal epithelium. Like other herpesviruses, EBV expresses its genes in a coordinated pattern during acute infection. Unlike others, it replicates its DNA during latency to maintain the viral genome in an expanding pool of B lymphocytes, which are stimulated to divide upon infection. The reactivation from the latent state is associated with a productive gene expression pattern mediated by virus-encoded transcriptional activators BZLF-1 and BRLF-1. EBV is a highly transforming virus that contributes to the development of human lymphomas. Though viral vectors and mRNA platforms have been used to develop an EBV prophylactic vaccine, currently, there are no vaccines or antiviral drugs for the prophylaxis or treatment of EBV infection and EBV-

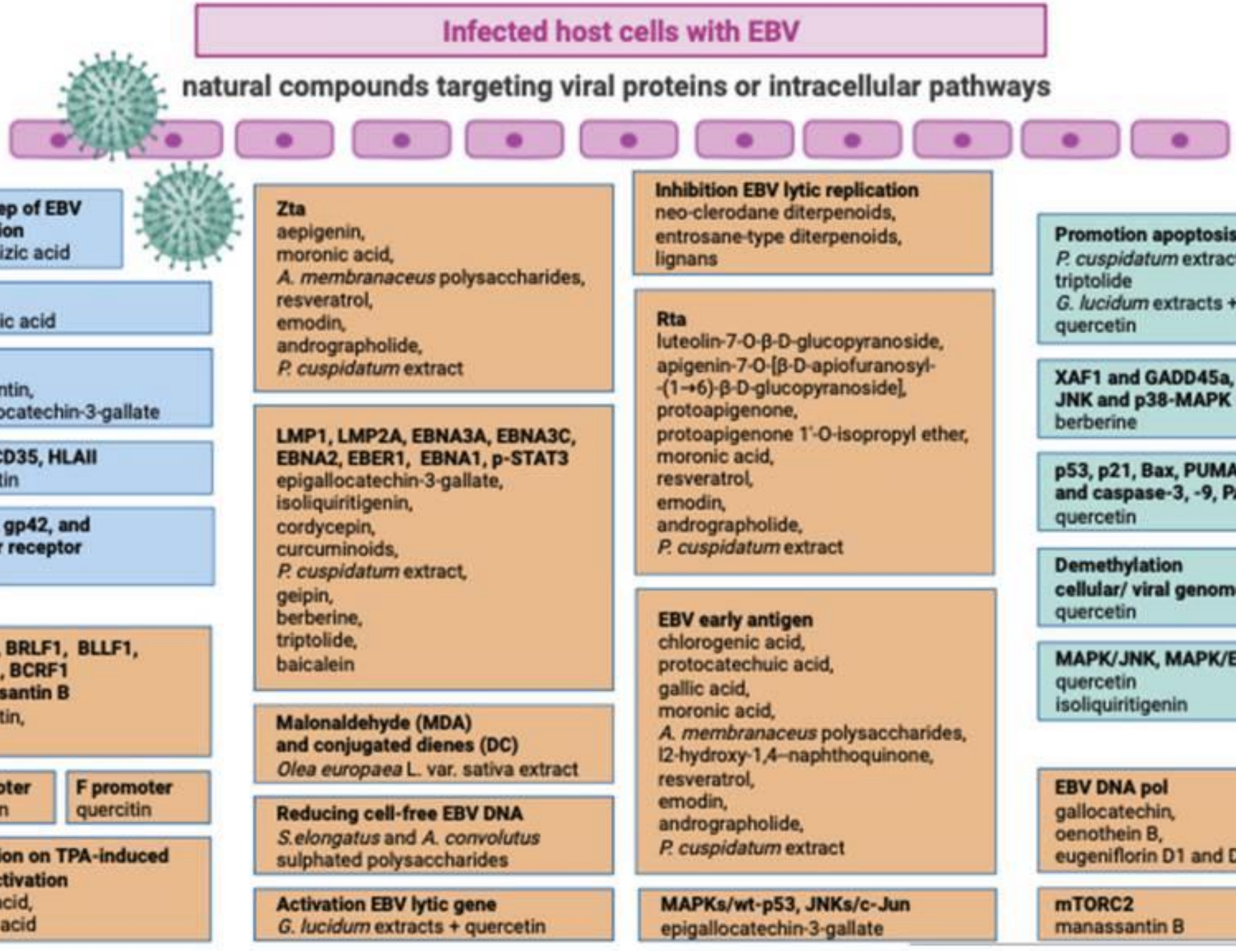
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The categorization of antiviral agents into virucides, chemotherapeutic agents, and immunomodulators is a common classification based on their mechanisms of action. Virucides are substances or agents that directly inactivate or destroy viruses. They act by disrupting the viral structure or interfering with essential viral functions. Otherwise, antiviral chemotherapeutic agents are drugs designed to target viral replication processes specifically. These drugs interfere with the virus's ability to replicate or spread within the host. Several antiviral drugs may target various stages of the viral life cycle, such as viral entry, genome replication, or virion release. Lastly, immunomodulators are substances that modulate or regulate the immune system's response to viral infections. They can enhance or suppress immune functions to achieve a balanced and effective antiviral response. Immunomodulators are often used to treat viral infections by either boosting the immune system's ability to fight the virus or preventing excessive immune responses that can lead to inflammation and tissue damage [73]. It is important to note that these categories are not mutually exclusive, and some antiviral agents may exhibit properties of more than one category. Several natural compounds have been studied for their potential antiviral properties. It is important to note that while these compounds may exhibit antiviral activity in in vitro studies, their effectiveness in treating viral infections in humans may differ. Here are some examples of

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Infected host cells with EBV
natural compounds targeting viral proteins or intracellular pathways
Early step of EBV replication
glycyrrhizic acid
gB
ginkgolic acid
gH
bruceantin,
epigallocatechin-3-gallate
CD21,CD35, HLAII
quercetin
gp350, gp42, and cellular receptor
geipin
BZLF1, BRLF1, BLLF1, BNRF1, BCRF1
manassantin B
quercetin,
geipin
Q promoter
baicalein
F promoter
quercitin
Inhibition on TPA-induced EBV activation
gallic acid,
ferulic acid
Zta
aepigenin,
moronic acid,
A. membranaceus polysaccharides,
resveratrol,
emodin,
andrographolide,
P. cuspidatum extract
LMP1, LMP2A, EBNA3A, EBNA3C, EBNA2, EBER1, EBNA1, p-STAT3
epigallocatechin-3-gallate,
isoliquiritigenin,
cordycepin,
curcuminoids,
P. cuspidatum extract,
geipin,
berberine,
triptolide,
baicalein
Malonaldehyde (MDA) and conjugated dienes (DC)
Olea europaea L. var. sativa extract
Reducing cell-free EBV DNA
S.elongatus and A. convolutus
sulphated polysaccharides
Activation EBV lytic gene
G. lucidum extracts + quercetin
Inhibition EBV lytic replication
neo-clerodane diterpenoids,
entrosane-type diterpenoids,
lignans
Rta
luteolin-7-O-β-D-glucopyranoside,
apigenin-7-O-[β-D-apiofuranosyl-
-(1→6)-β-D-glucopyranoside],
protoapigenone,
protoapigenone 1'-O-isopropyl ether,
moronic acid,
resveratrol,
emodin,
andrographolide,
P. cuspidatum extract
EBV early antigen
chlorogenic acid,
protocatechuic acid,
gallic acid,
moronic acid,
A. membranaceus polysaccharides,
l2-hydroxy-1,4–naphthoquinone,
resveratrol,
emodin,
andrographolide,
P. cuspidatum extract
MAPKs/wt-p53, JNKs/c-Jun
epigallocatechin-3-gallate
Promotion apoptosis
P. cuspidatum extract,
triptolide
G. lucidum extracts +
quercetin
XAF1 and GADD45a, JNK and p38-MAPK
berberine
p53, p21, Bax, PUMA, and caspase-3, -9, PARP
quercetin
Demethylation cellular/ viral genomes
quercetin
MAPK/JNK, MAPK/ERK
quercetin
isoliquiritigenin
EBV DNA pol
gallocatechin,
oenothein B,
eugeniflorin D1 and D2
mTORC2
manassantin B

EBV's Action

1. Apoptosis inhibition (EBNAs)
2. Cell growth accelerant (EBNAs)
3. Advanced cellular proliferation (LMPs)
4. "Camouflage" escape from CD4 T cell recognition. (LMPs)
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Table 1.

Natural products targeting EBV binding.

Plant	Substance	Class	Target	References
Licorice	Quercetin	Flavonoids	CD21, CD35 and HLAII EBV receptor	Lee, M. et al., 2015 [75]
Glycyrrhizae radix	Glycyrrhizic acid	Pentacyclic triterpenoid	Interference with early step of EBV replication	Lin, J.-C. 2003 [76]
Gardenia jasminoides	Genipin	Monoterpenoids	gp350 and gp42 attachment proteins, and cellular receptors	Liu, H. et al., 2013 Son, M. et al., 2015 [77,78]
-	Bruceantin	Secotriterpenoid	gH protein	Jakhmola, S. et al., 2022 [79]
Green tea	Epigallocatechin-3-gallate	Flavonoid	gH protein	Jakhmola, S. et al., 2022 [79]
Ginkgo biloba	Ginkgolic acid	Alkylphenol	gB protein	Borenstein, et al., 2020 [83]

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Table 2.

Natural compounds targeting EBV lytic infection.

Astragalus membranaceus	Polysaccharides		Rta and Zta EBV early antigen	Guo, Q. et al., 2014 [110]
Lawsonia inermis L.	2-hydroxy-1,4- -naphthoquinone	Quinones	EBV early antigen	Kapadia, G.J. et al., 2013 [111]
-	Resveratrol	Nonflavonoid polyphenol	Rta and Zta EBV early antigen	Yiu, C.-Y. et al., 2010, De Leo, A. 2012 [112,113]
-	Quercetin	Flavonoid	BZLF1, BRLF1, BLLF1 and F promoter	Lee, M. et al., 2015 Lee, M. et al., 2016 [75,114]
-	Isoliquiritigenin	Flavonoid	LMP1, LMP2, EBNA3A, EBNA1	Lee, M. et al., 2015 Lee, M. et al., 2016 [75,114]
Andrographis paniculata	Andrographolide	Terpenoid	Rta and Zta EBV early antigen	Lin, T.-P. et al., 2008 [115]
Polygonum cuspidatum	Resveratrol, Emodin	Nonflavonoid polyphenol,	Rta and Zta EBV early antigen	Yiu, C.-Y. et al., 2011, Yiu, C.-Y. et al., 2013 Yiu, C.-Y. et al., 2014 [116,117,118]
Cordyceps	Cordycepin	Trihydroxyanthraquinone	LMP2A, EBNA1	Ryu, E. et al., 2014 [119]

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Table 3.

Natural compounds targeting EBV latent proteins and intracellular pathways.

Plant	Substance	Class	EBV Target
-	Curcumin and curcuminoids	Curcuminoids/Polyphenols	EBNA1
Gardenia jasminoides	100 µM genipin	Monoterpenoids	BNRF1, BCRF1, BLLF1, BZLF1, LMP1, LMP2A, EBNA2, EBER1, EBNA3A, EBNA3C, EBNA1, BRLF1
Gardenia jasminoides	50 µM genipin	Monoterpenoids	BZLF1, LMP1, LMP2A, EBER1, EBNA2, EBNA3A, EBNA3C, EBNA1, BNRF1, BCRF1, BLLF1, BRLF1
Polygonum cuspidatum	Ethanolic extract	Alcohol	LMP1
Berberis vulgaris	Berberine	Protoberberine alkaloids	EBNA1, p-STAT3
Coptidis rhizome	Berberine	Protoberberine alkaloids	EBNA1, p-STAT3
Tripterygium wilfordii	Triptolide	Epoxide	LMP1, EBNA1
Ganoderma lucidum	*Ganoderma lucidum* extracts + quercetin	Agaricomycetes	Activation of EBV lytic gene
Scutellariae baicaleinsis	Baicalein	Flavonoid	EBNA1 Q-promoter
-	Quercetin	Flavonoid	-
-	Isoliquiritigenin	Flavonoid	-

Int J Mol Sci. 2023 Jan 15;24(2):1716. doi: 10.3390/ijms24021716

Topic for another day.

The Fight against the Carcinogenic Epstein-Barr Virus: Gut Microbiota, Natural Medicines, and Beyond

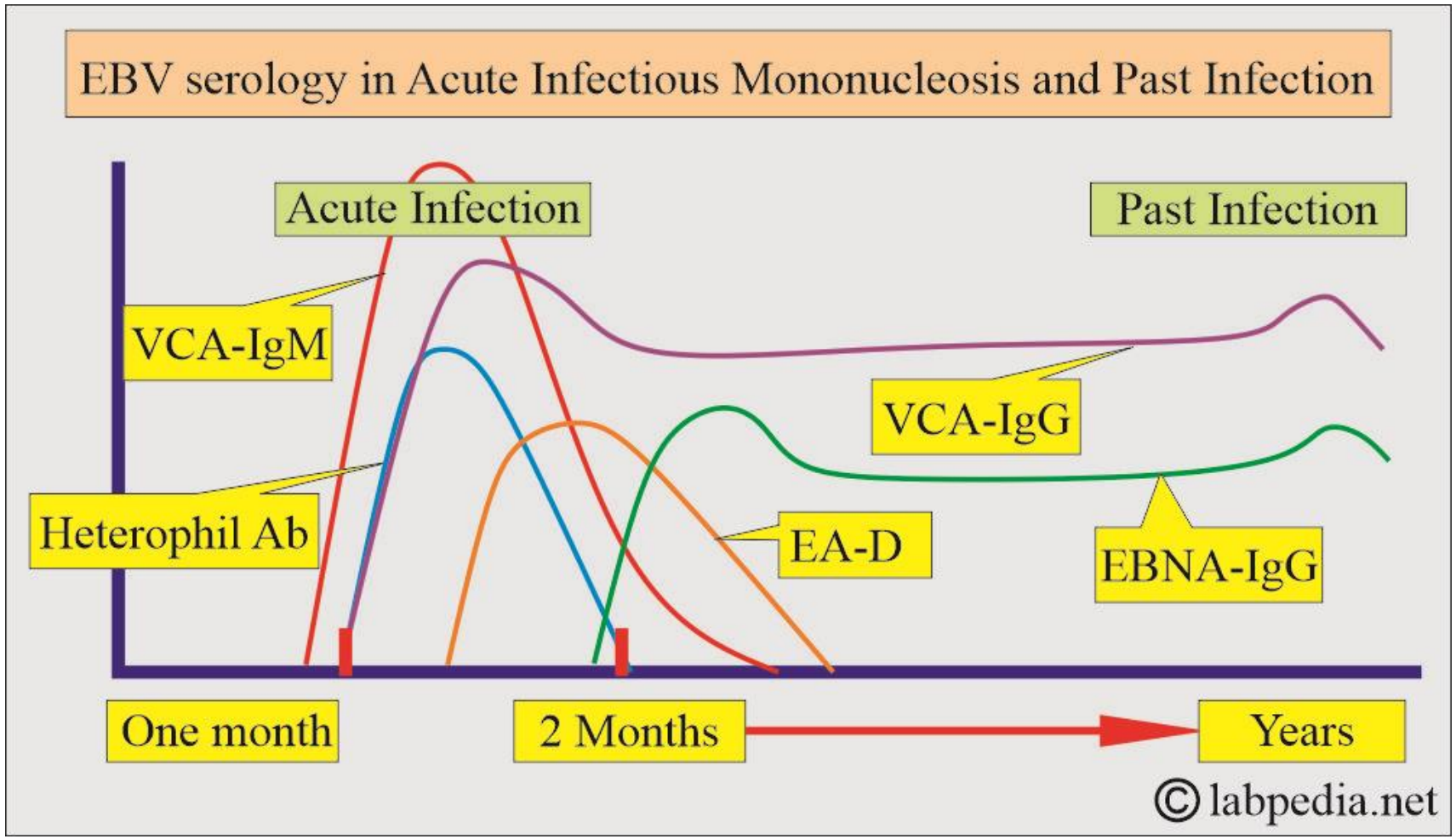
Radwa A Eladwy [1], Hang Thi Vu [2], Ravi Shah [1], Chun Guang Li [1], Dennis Chang [1], Deep Jyoti Bhuyan [1,*]

Editors: Kamalendra Singh, Christian Lorson

year. Currently, there are no vaccines or antiviral drugs for the prophylaxis or treatment of EBV infection. Recently, the gut microbiota has been investigated for its pivotal roles in pathogen protection and regulating metabolic, endocrine, and immune functions. Several studies have investigated the efficacy of antiviral agents, gut microbial metabolites, and natural products against EBV infection. In this review, we aim to summarise and analyse the reported molecular mechanistic and clinical studies on the activities of gut microbial metabolites and natural medicines against carcinogenic viruses, with a particular emphasis on EBV. Gut microbial metabolites such as short-chain fatty acids were reported to activate the EBV lytic cycle, while bacteriocins, produced by *Enterococcus durans* strains, have shown antiviral properties. Furthermore, several natural products and dietary bioactive compounds, such as curcumin, epigallocatechin gallate, resveratrol, moronic acid, and andrographolide, have shown antiviral activity against EBV. In this review, we proposed several exciting future directions for research on carcinogenic viruses.

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So…
What do we know for sure?
How do we support early vs reactivation vs latent stages?



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Sample Nutritional Support Across the Stages of EBV

Targeting viral entry, lytic replication, and latency

Early Stage

Viral entry / acute infection

Vitamin C

BioG-Max C with R-Lipoic Acid

Higher levels linked to lower acute EBV antibodies (VCA IgM).

Quercetin

QuercenX

Interferes with EBV receptor recognition (CD21, CD35, HLA II).

Licorice

Whole root with glycyrrhizic acid

Blocks an early step of EBV replication.

Lytic Stage

Active replication / reactivation

Vitamin C

BioG-Max C with R-Lipoic Acid

High-dose use linked to falling early antigen (EA IgG) levels.

Resveratrol

BioG-Max Resveratrol

Inhibits lytic proteins Rta, Zta, and EA-D.

Astragalus

ViraX Plus

Astragalus polysaccharide inhibits the EBV lytic cycle.

Licorice

Whole root with glycyrrhizic acid

Glycyrrhizic acid inhibits EBV replication in vitro.

Latent Stage

Dormant virus in memory B cells

Vitamin D

Liquid D 2000 or D3K2

Trials found lower EBNA-1 antibody levels with D3.

Quercetin

QuercenX

Reduces EBNA-1 expression in infected cells.

Berberine

Berberine X

Acts through an EBNA-1-dependent mechanism.

Gut Support Protocol

GI ResQ+ and UltraBiotix

Supports the microbiome and gut barrier to aid immune control.

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We Want to Hear from You!

Give us your Casual Friday feedback
with this short 5-question survey.

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