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Milano, Best Western Hotel Madison

29 maggio 2026

La trasformazione dei linfociti B da parte del virus di Epstein-Barr

Luisa Lorenzi

Università degli Studi di Brescia - ASST Spedali Civili di Brescia

Disclosures of Luisa Lorenzi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sandoz	x						

Università di Brescia

ANATOMIA PATOLOGICA

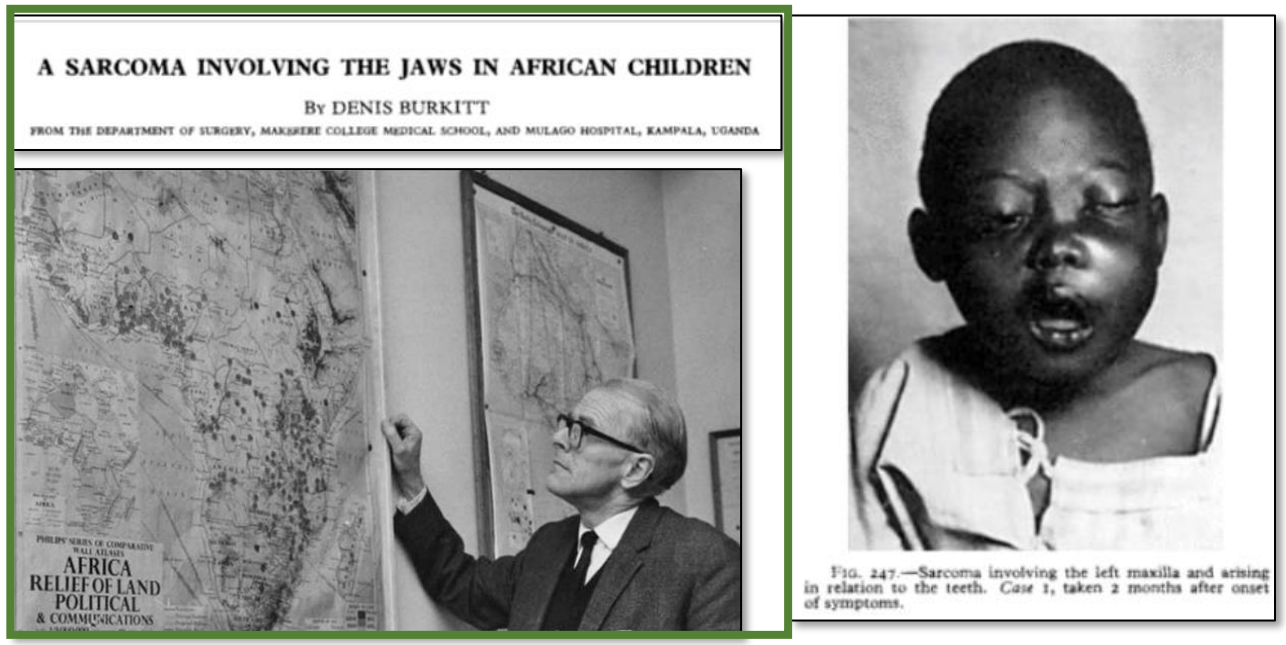
Regione Lombardia
ASST Spedali Civili

La trasformazione dei linfociti B da parte del virus di Epstein-Barr

AGENDA

- Epstein-Barr virus, the first oncovirus
- Infection, latency and reactivation
- Lymphomagenesis
- EBV-positive lymphomas (main subtypes)
- Conclusion

Epstein-Barr virus, the first oncovirus



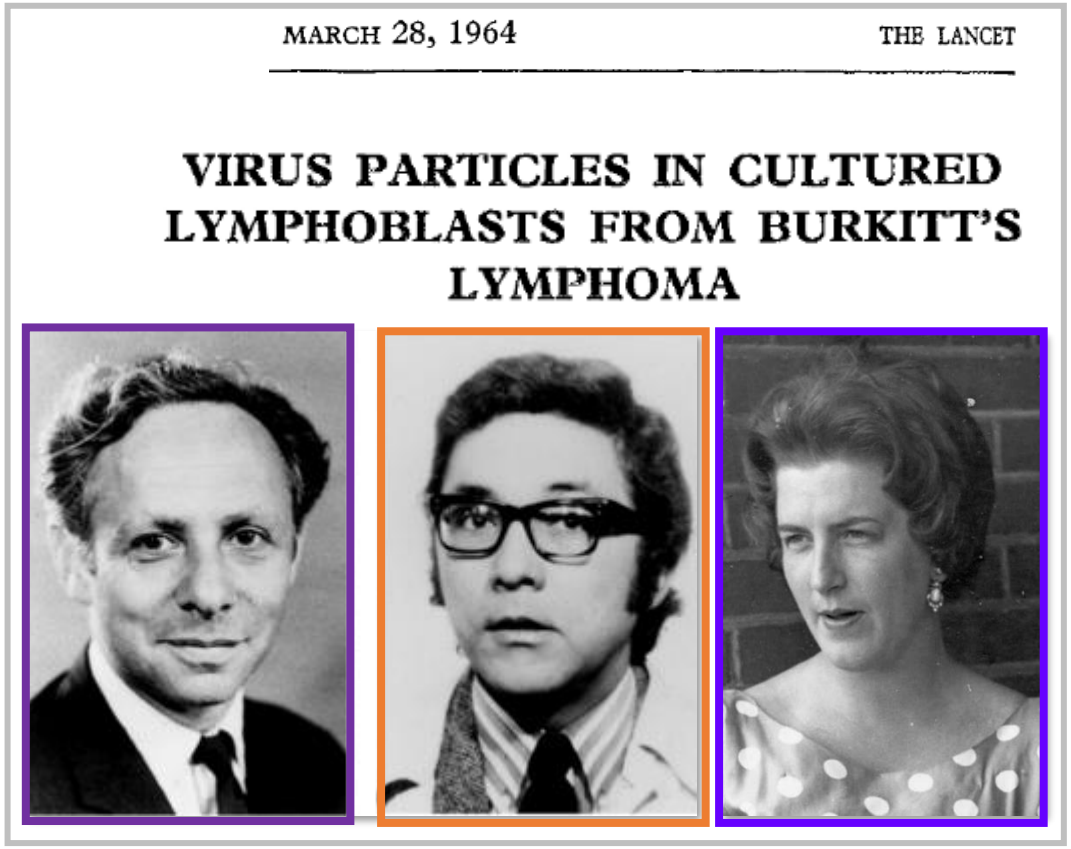
A SARCOMA INVOLVING THE JAWS IN AFRICAN CHILDREN

By DENIS BURKITT

FROM THE DEPARTMENT OF SURGERY, MAKERERE COLLEGE MEDICAL SCHOOL, AND MULAGO HOSPITAL, KAMPALA, UGANDA

FIG. 247.—Sarcoma involving the left maxilla and arising in relation to the teeth. *Case* 1, taken 2 months after onset of symptoms.

British Journal of Surgery, 1958



MARCH 28, 1964 THE LANCET

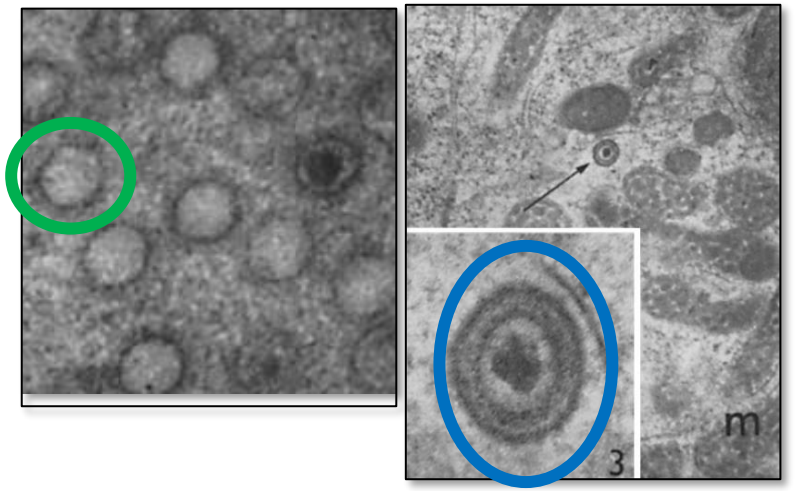
VIRUS PARTICLES IN CULTURED LYMPHOBLASTS FROM BURKITT'S LYMPHOMA

1958: surgeon **Denis Burkitt** describes 38 cases of «sarcoma» of the jaws observed in 7 years in Mulago Hospital-Uganda

1961: Burkitt and pathologist **Antony Epstein** meet in a conference in London

1963: two vital cell cultures (EB1 and EB2) are finally established from tumor samples form Uganda in Epstein's lab by **Yvonne Barr**

1964: viral particles are identified in lymphoblasts under the Electron Microscope by Epstein and **Bert Achong**, in two forms **«mature» and «immature»**



Journal of Experimental Medicine, 1965

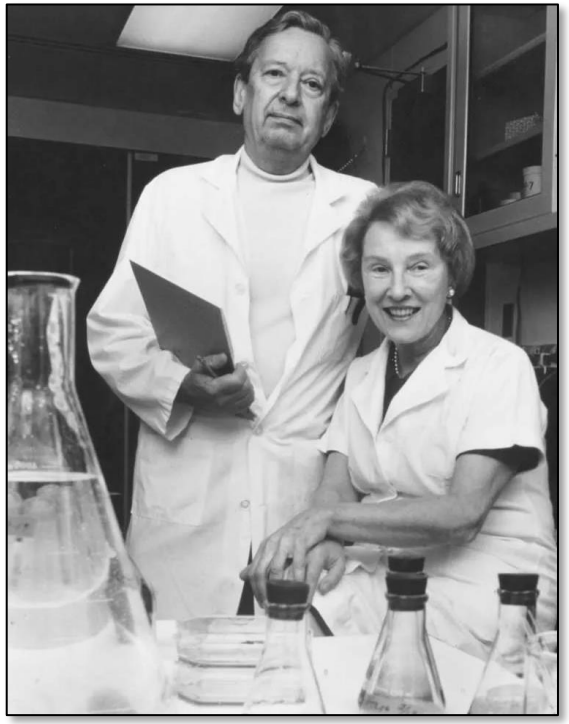
1965: in collaboration with Children's Hospital Philadelphia, EBV serological markers are developed by **Gertrude and Werner Henle**

JOURNAL OF BACTERIOLOGY, July, 1966
Copyright © 1966 American Society for Microbiology
Vol. 92, No. 1
Printed in U.S.A.

Indirect Immunofluorescence Tests with Sera from African Children and Cultured Burkitt Lymphoma Cells

JAY A. LEVY[1] AND GERTRUDE HENLE
Virus Laboratories, Children's Hospital of Philadelphia, and School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Received for publication 8 April 1966



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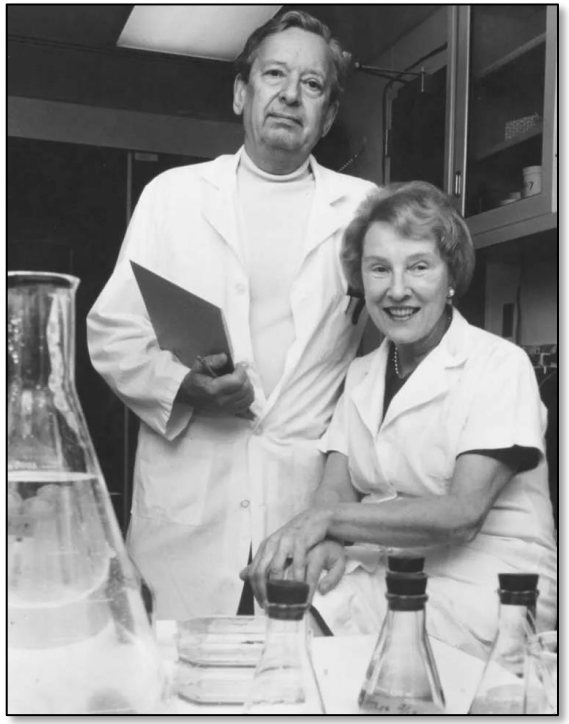

TABLE 2. *Comparison of results of immunofluorescence tests obtained with sera from African and American children*

Sera from	No. of sera tested	No. of positive reactions	Per cent
Burkitt lymphoma patients	30	30	100
Normal African children	140	76	54
American pediatric patients[a]	80	30	35

[a] Includes sera from children with leukemias, other malignancies, and various metabolic and infectious diseases.

Proc Natl Acad Sci U S A. 1968 Jan;59(1):94-101. doi: 10.1073/pnas.59.1.94.

Relation of Burkitt's tumor-associated herpes-ytpe virus to infectious mononucleosis

G Henle, W Henle, V Diehl

Int J Cancer. 1971 Nov 15;8(3):443-50. doi: 10.1002/ijc.2910080312.

The establishment of lymphoblastoid lines from adult and fetal human lymphoid tissue and its dependence on EBV

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1991: clonality of Tandem Repeats regions of EBV in Burkitt Lymphomas (sporadinc and endemic) and in AIDS-NHL
→ **evidences in support for EBV oncogenic role**

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Copyright © 1966 American Society for Microbiology Printed in U.S.A.

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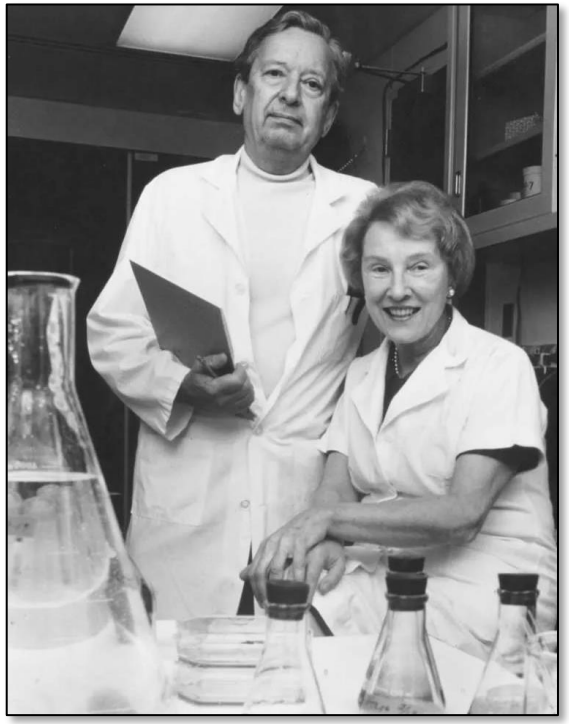

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Epstein-Barr Virus Infection Precedes Clonal Expansion in Burkitt's and Acquired Immunodeficiency Syndrome-Associated Lymphoma

By Antonino Neri, Francisco Barriga, Giorgio Inghirami, Daniel M. Knowles, Janet Neequaye, Ian T. Magrath, and Riccardo Dalla-Favera

Int J Cancer. 1971 Nov 15;8(3):443-50. doi: 10.1002/ijc.2910080312.

The establishment of lymphoblastoid lines from adult and fetal human lymphoid tissue and its dependence on EBV

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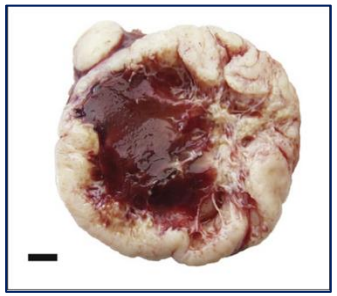
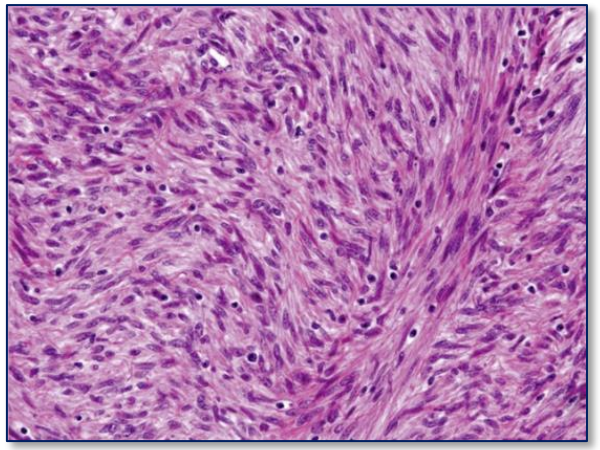
More recently….

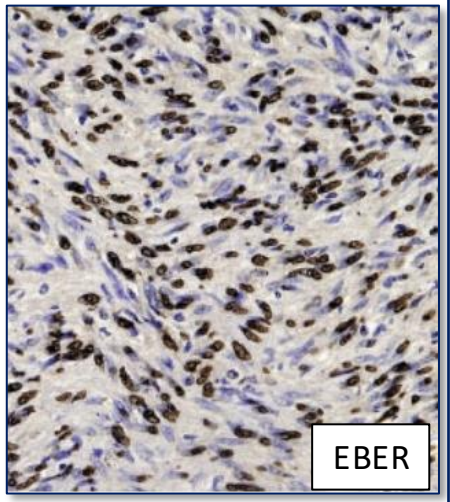
EBV was identified in a plethora of neoplastic diseases:

- Hodgkin lymphomas
- T and B non Hodgkin lymphomas
- post-transplant lymphoproliferative diseases
- **gastric adenocarcinoma**
- breast cancer
- haepatocarcinoma
- **smooth muscle tumors**
- follicular dendritic cell sarcoma
- *others*



Petrilli G et al., 2014 IJSP





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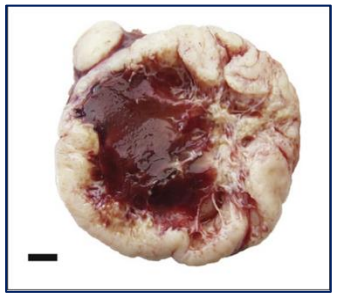

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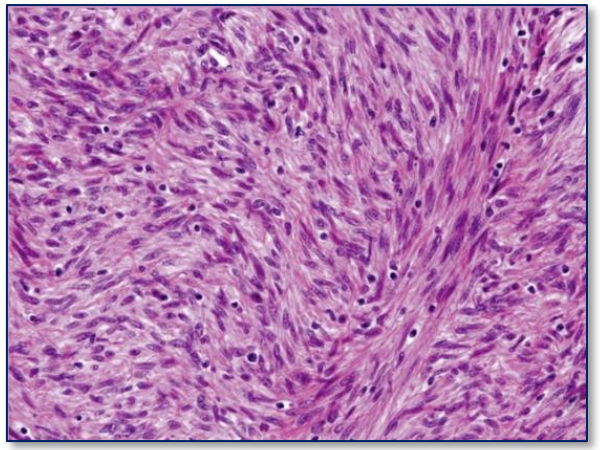
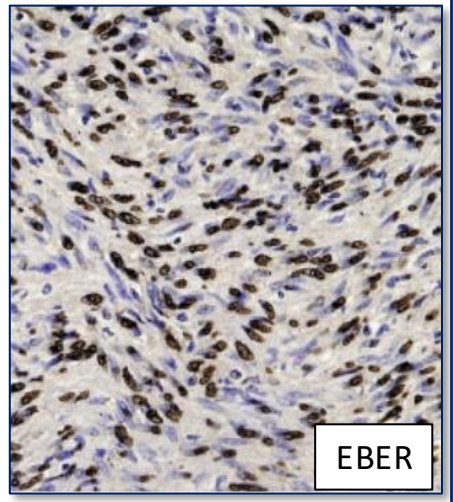




2022: Epidemiological and biological evidences of EBV in Multiple sclerosis

MULTIPLE SCLEROSIS

Science 2022

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1]†, Marianna Cortese[1]†, Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[6], Stephen J. Elledge[6], David W. Niebuhr[9], Ann I. Scher[9], Kassandra L. Munger[1]‡, Alberto Ascherio[1,10,11]*‡

Results of Harvard study

- Cohort of > 10 million active-duty military personnel from 1993 to 2013
- Using serum samples from DoD Serum Repository
- Identified 955 adults diagnosed with MS during service
- Risk of MS increased 32-fold after infection with EBV
- Serum levels of neurofilament light chain increased only after EBV infection

Article

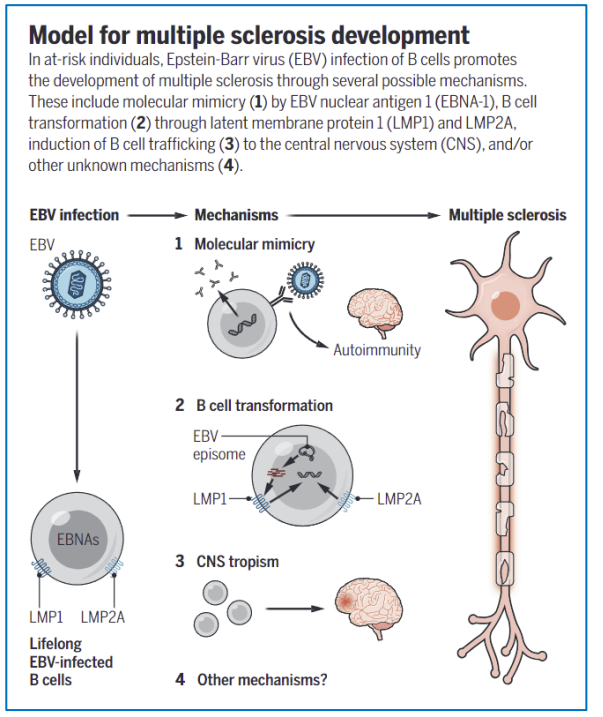
Nature 2022

Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM

https://doi.org/10.1038/s41586-022-04432-7
Received: 6 August 2021
Accepted: 14 January 2022
Published online: 24 January 2022
Check for updates

Tobias V. Lanz[1,2,3,4], R. Camille Brewer[1,4], Peggy P. Ho[5], Jae-Seung Moon[1,4], Kevin M. Jude[6], Daniel Fernandez[7], Ricardo A. Fernandes[6], Alejandro M. Gomez[1,4], Gabriel-Stefan Nadj[1,4], Christopher M. Bartley[8], Ryan D. Schubert[9], Isobel A. Hawes[9], Sara E. Vazquez[10], Manasi Iyer[11], J. Bradley Zuchero[11], Bianca Teegen[12], Jeffrey E. Dunn[13], Christopher B. Lock[13], Lucas B. Kipp[13], Victoria C. Cotham[14,15], Beatrix M. Ueberheide[14,15], Blake T. Aftab[16], Mark S. Anderson[17], Joseph L. DeRisi[10,18], Michael R. Wilson[9], Rachael J. M. Bashford-Rogers[19], Michael Platten[2,3,20], K. Christopher Garcia[6], Lawrence Steinman[5] & William H. Robinson[1,4]

- **32-fold increased risk for MS after EBV infection**
- **Molecular mimicry of EBNA1 with GlialCAM mielin protein provides the mechanism**

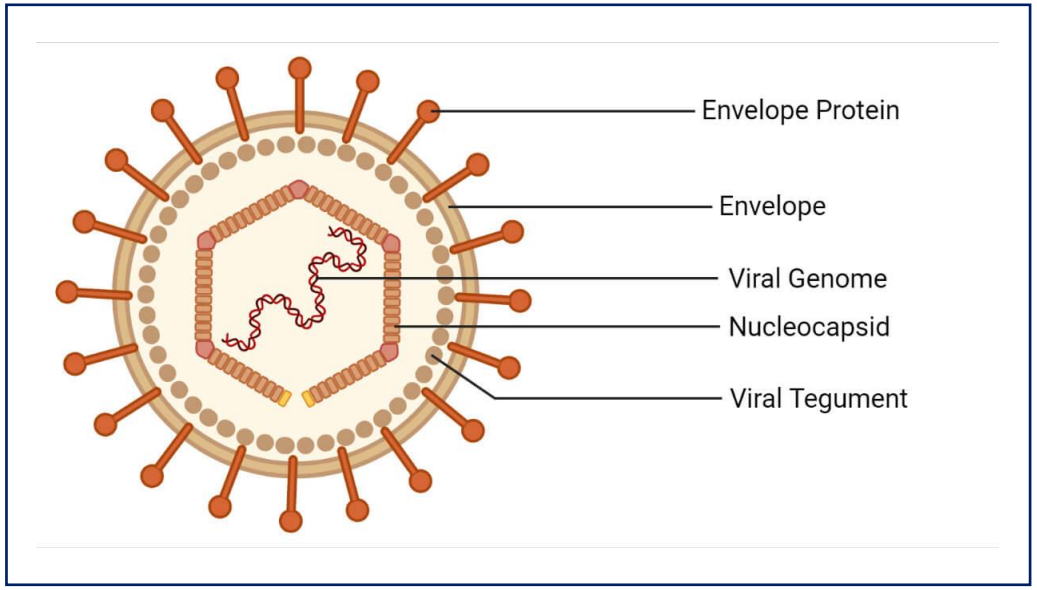


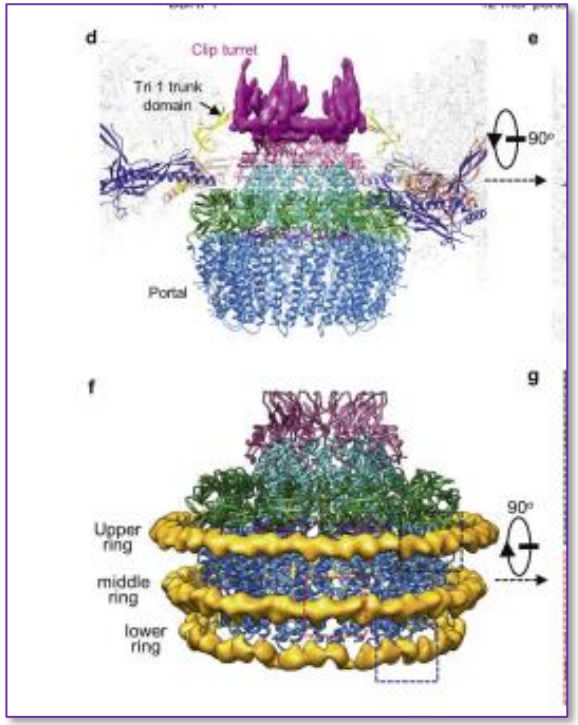
Epstein Barr Virus

Order: Herpesvirales
Family: Orthoherpesviridae
Genus: Lymphocriptovirus
Species: Human gammaherpesvirus 4

Haerpesviridae	
alfa-	HSV-1 HSV-2 VZV (HHV-3)
beta-	CMV (HHV-5) HHV-6 HHV-7
gamma-	**EBV (HHV-4)** **HHV-8**

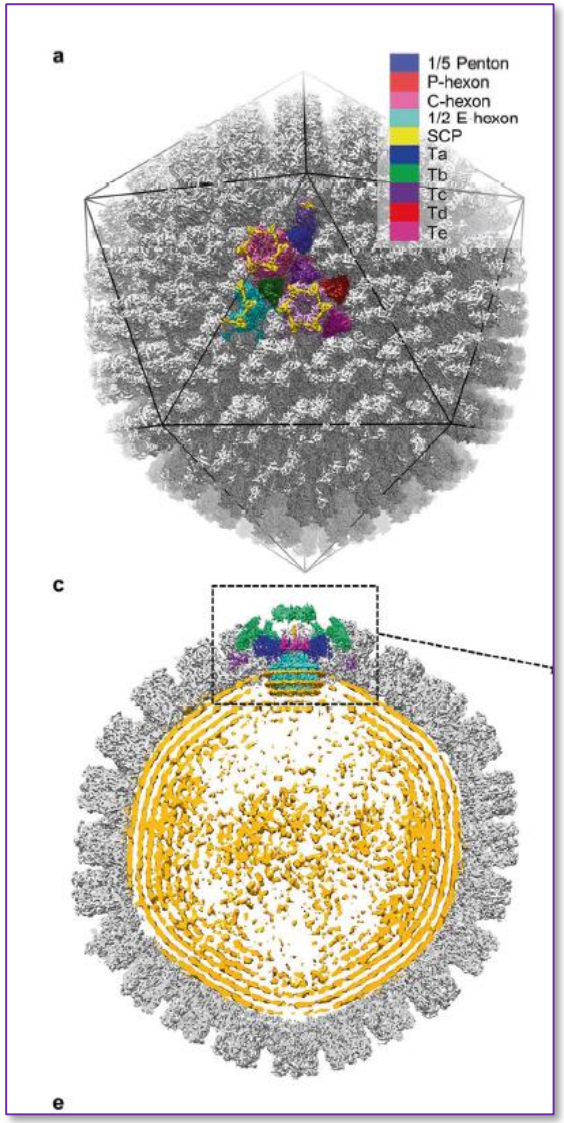
B





Li et al Cell Research 2020

Cryogenic electron microscopy of the tegumented capsid of EBV



Genome:

DNA double helix (172.000 bp) coding for **85 genes**.

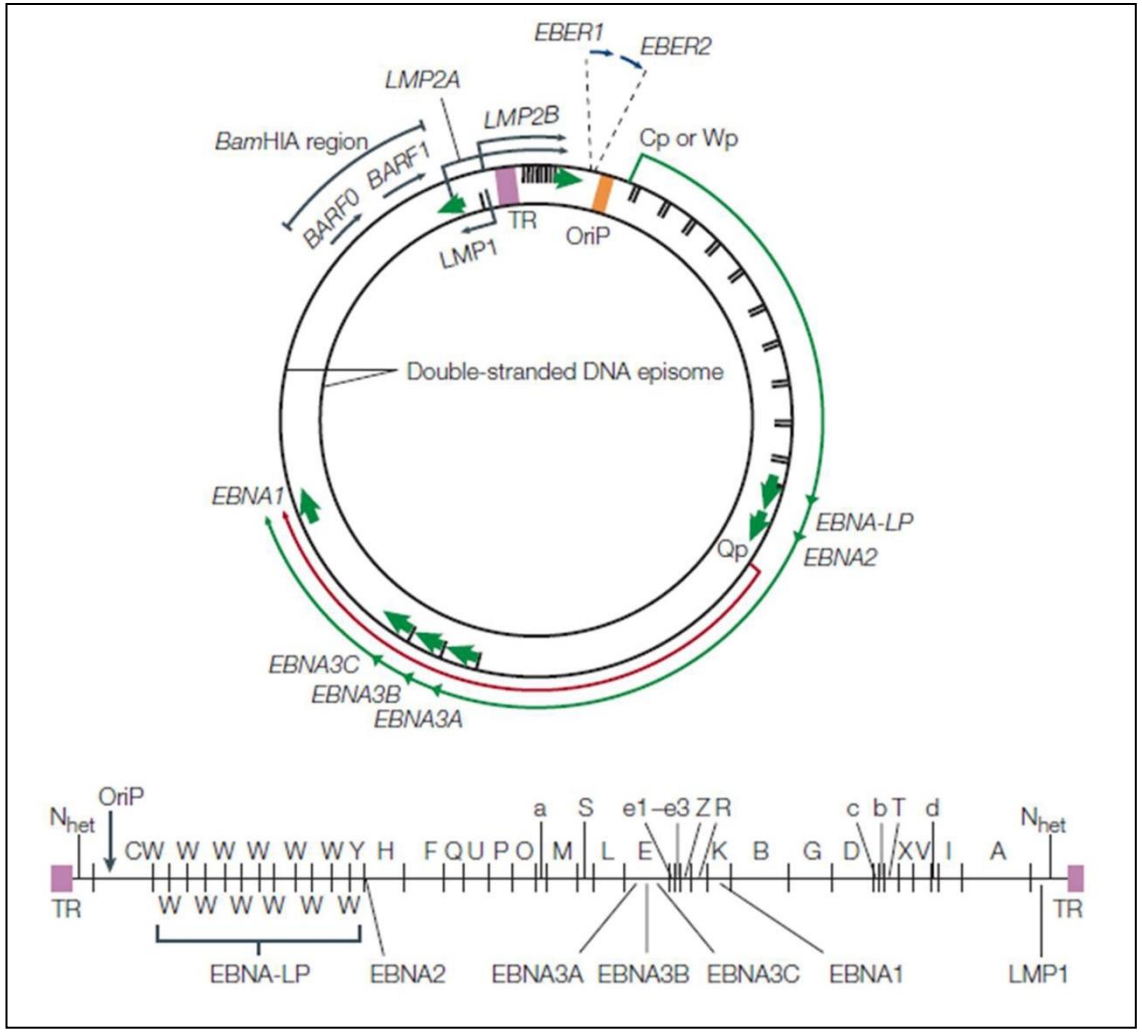
- **Linear DNA**: in the host cell nucleus in ***lytic phase***
- **Circular/episomial DNA**: in ***latency phase***, bond to host chromatin by EBNA1

Tandem repeats are cleaved in the episomial to linear conversion; a homogeneous TR length indicates **EBV clonality**.

Two different subtypes/*isolates* differing by polymorphisms on genes incoding for nuclear latency antigens *EBNA2, EBNA-LP ed EBNA3.*

- **Type 1:** prevalent, higher transforming capacities
- **Type 2**: less common, with reduced transforming capacities

→ *Coupled inflection, with both isolates, is described*



Epstein Barr Virus

Prevalence: >90% individuals worldwide

Transmission: oral (>>); blood; sexual; breast feeding; organ transplant

Infection symptoms:

- Infancy → asymptomatic
- Adolescence/young adults →(35-50%) infective mononucleosis

Associated with diseases in immunocompetent ed immunocompromised subjects

110.000 cancers/year are EBV-related worldwide

Global burden of cancers attributable to infections in 2008: a review and synthetic analysis

Catherine de Martel, MD • Jacques Ferlay, ME • Silvia Franceschi, MD • Jérôme Vignat, MSc • Freddie Bray, PhD •

	Less developed regions	More developed regions	World
Hepatitis B and C viruses	520 000 (32·0%)	80 000 (19·4%)	600 000 (29·5%)
Human papillomavirus	490 000 (30·2%)	120 000 (29·2%)	610 000 (30·0%)
Helicobacter pylori	470 000 (28·9%)	190 000 (46·2%)	660 000 (32·5%)
Epstein-Barr virus	96 000 (5·9%)	16 000 (3·9%)	110 000 (5·4%)
Human herpes virus type 8	39 000 (2·4%)	4100 (1·0%)	43 000 (2·1%)
Human T-cell lymphotropic virus type 1	660 (0·0%)	1500 (0·4%)	2100 (0·1%)
Opisthorchis viverrini and *Clonorchis sinensis*	2000 (0·1%)	0 (0·0%)	2000 (0·1%)
Schistosoma haematobium	6000 (0·4%)	0 (0·0%)	6000 (0·3%)
Total	1 600 000 (100·0%)	410 000 (100·0%)	2 000 000 (100·0%)

de Martel et al. 2012 Lancet Oncol

Infection, latency and reactivation

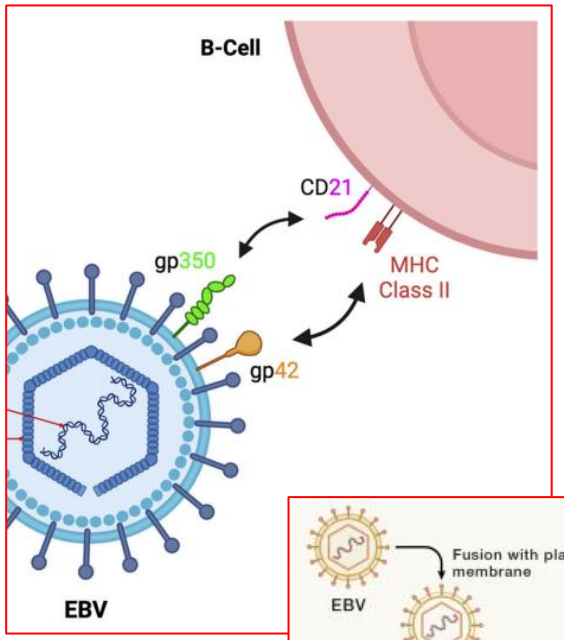
Primary infection

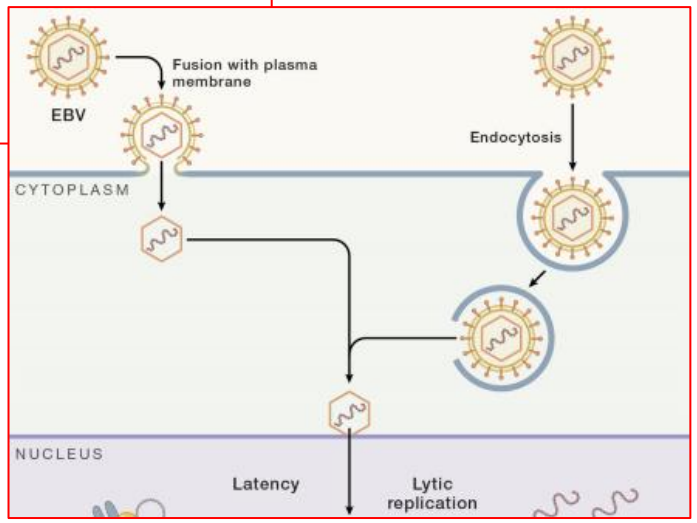
- Adhesion of EBV to epithelial cells and B-cell lymphocytes is mediated by specific interactions between viral glycoproteins and cell receptors

Viral protein	Cell type	Receptor on host cell
gp350/220	B, T	CD21(CR2); CD35 (CR1)
gp42	B	HLA class II
gH, gp85	epithelium	Integrin αvβ5, αvβ6, αvβ8
gL, gp25	B, epithelium	Chaperon for IgH

- The virus from the oral cavity/saliva penetrates the epithelium by endocytosis or fusion between envelope and cell membrane

Ross AM et al. Life 2023
Damania B et al. Cell 2022
Yu and Robertson Viruses 2023





Nature 2025, Li et al.

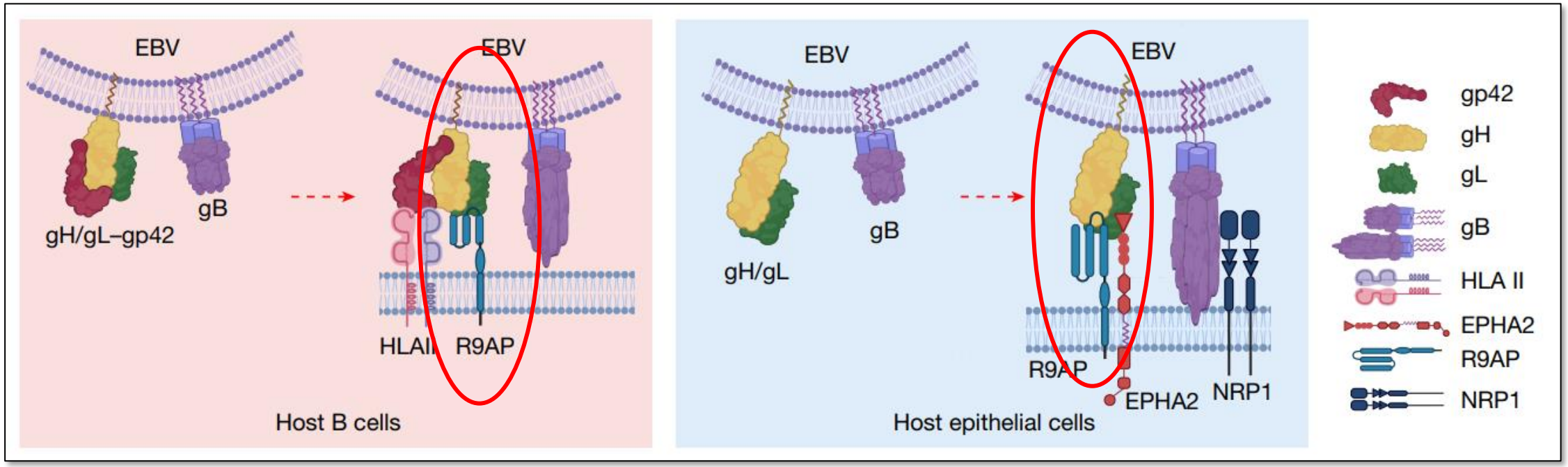
Article

R9AP is a common receptor for EBV infection in epithelial cells and B cells

https://doi.org/10.1038/s41586-025-09166-w
Received: 22 November 2020
Accepted: 15 May 2025
Published online: 18 June 2025

Yan Li[1,2,10], Hua Zhang[3,10], Cong Sun[1,10], Xiao-Dong Dong[1,10], Chu Xie[1], Yuan-Tao Liu[1], Ruo-Bin Lin[1], Xiang-Wei Kong[1], Zhu-Long Hu[1], Xiao-Yan Ma[1], Dan-Ling Dai[1], Qian-Ying Zhu[1], Yu-Chun Li[3], Ying Li[3], Shang-Xin Liu[1], Li Yuan[1], Peng-Hui Zhou[1], Song Gao[1], Ya-Ping Tang[4], Jin-Ying Yang[4], Ping Han[5], Andrew T. McGuire[6], Bo Zhao[7], Jin-Xin Bei[1], Erle Robertson[8], Yi-Xin Zeng[1], Qian Zhong[1]✉ & Mu-Sheng Zeng[1,9]✉

*Thus, our results provide a model in which **R9AP** has a critical role in EBV fusion with both B and epithelial cells.* ***This model may assist efforts to develop anti-EBV agents and vaccines that target the gH/gL–R9AP interaction***



Infection, latency and reactivation

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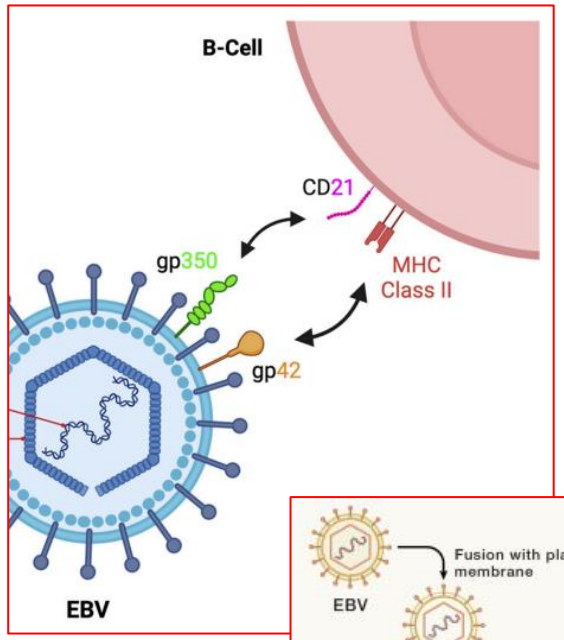
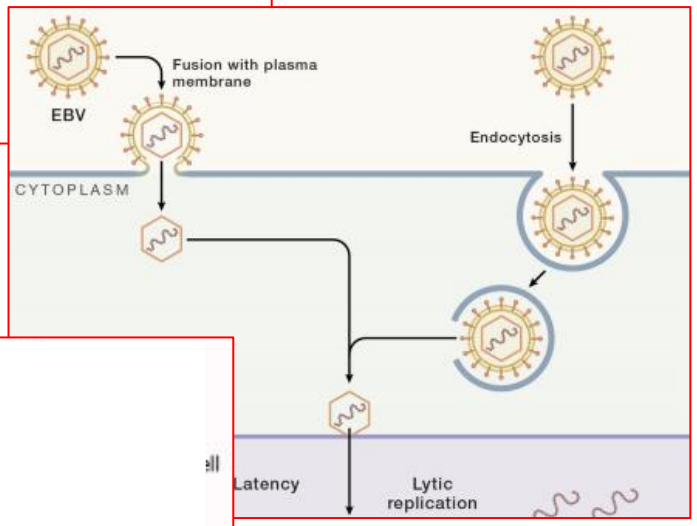
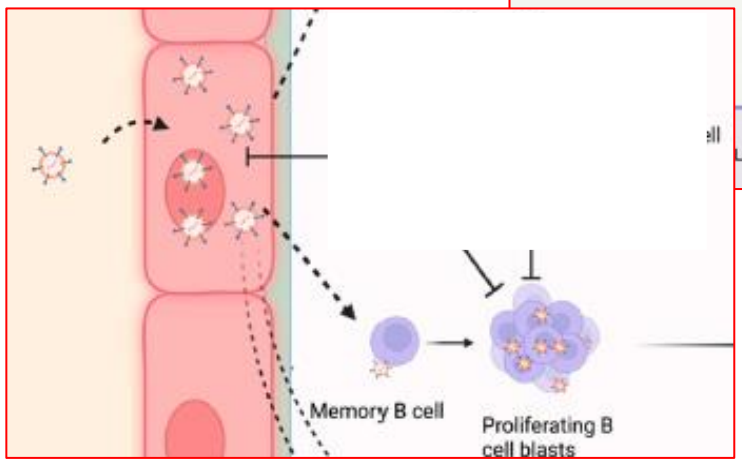






- The virus from the oral cavity/saliva penetrates the epithelium by endocytosis or fusion between envelope and cell membrane

- EBV induces **lytic phase** infection in infected cells with production of numerous virions free by host cell lysis (>epithelium)

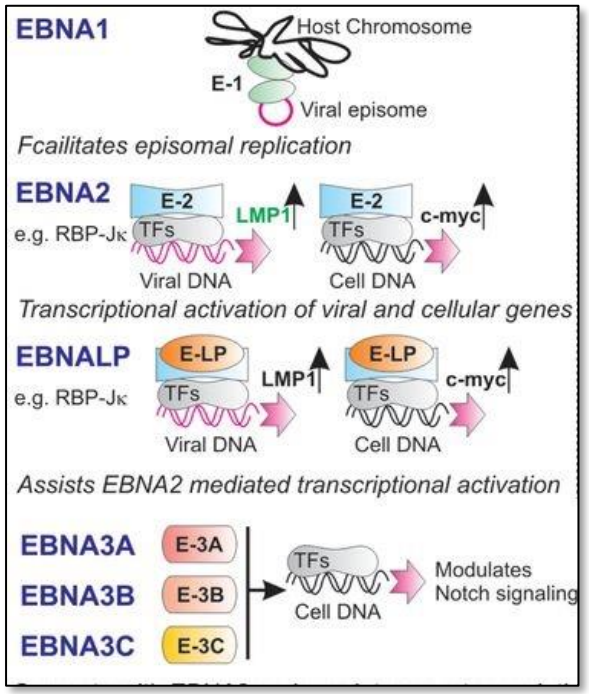
- alternatively it induces…

Infection, latency and reactivation

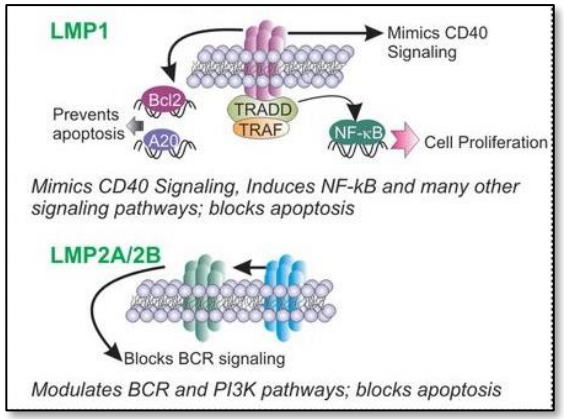
Latency III (*growth program*)

- Viral transcriptional program immediatly induced in naive or memory B lymphocytes
- ***In vitro* it sustains proliferation and immortalization**

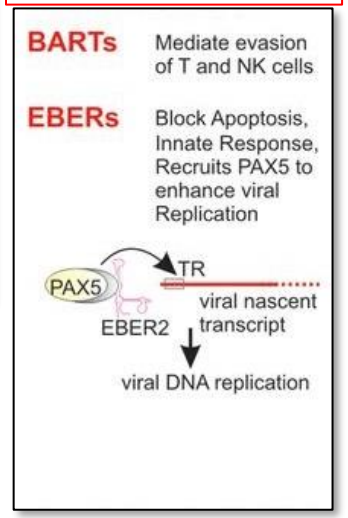
6 Nuclear Antigens (EBNAs)

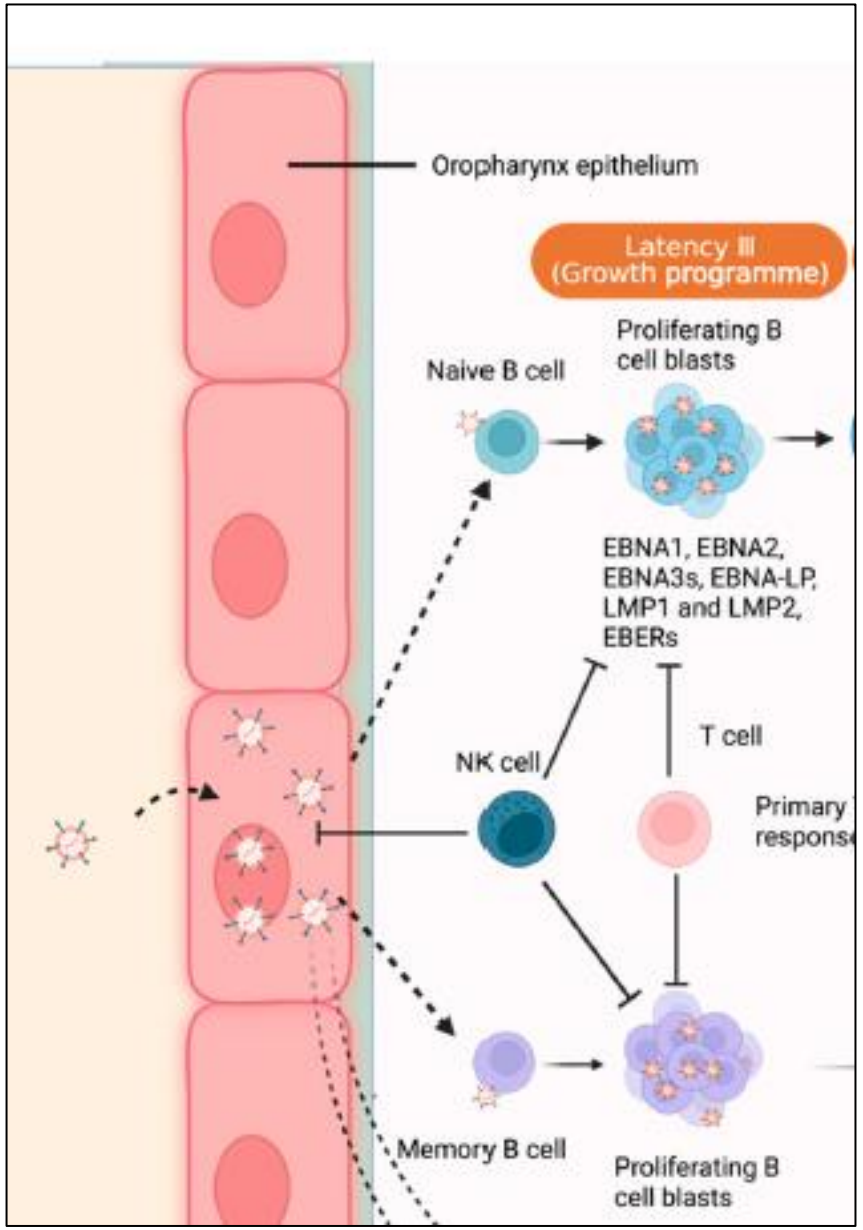


3 Membrane Antigens (LMPs)



Non coding RNA Including miRNA





Hui Yu and Erle S. Robertson. Viruses 2023

Infection, latency and reactivation

Latency III (*growth program*)

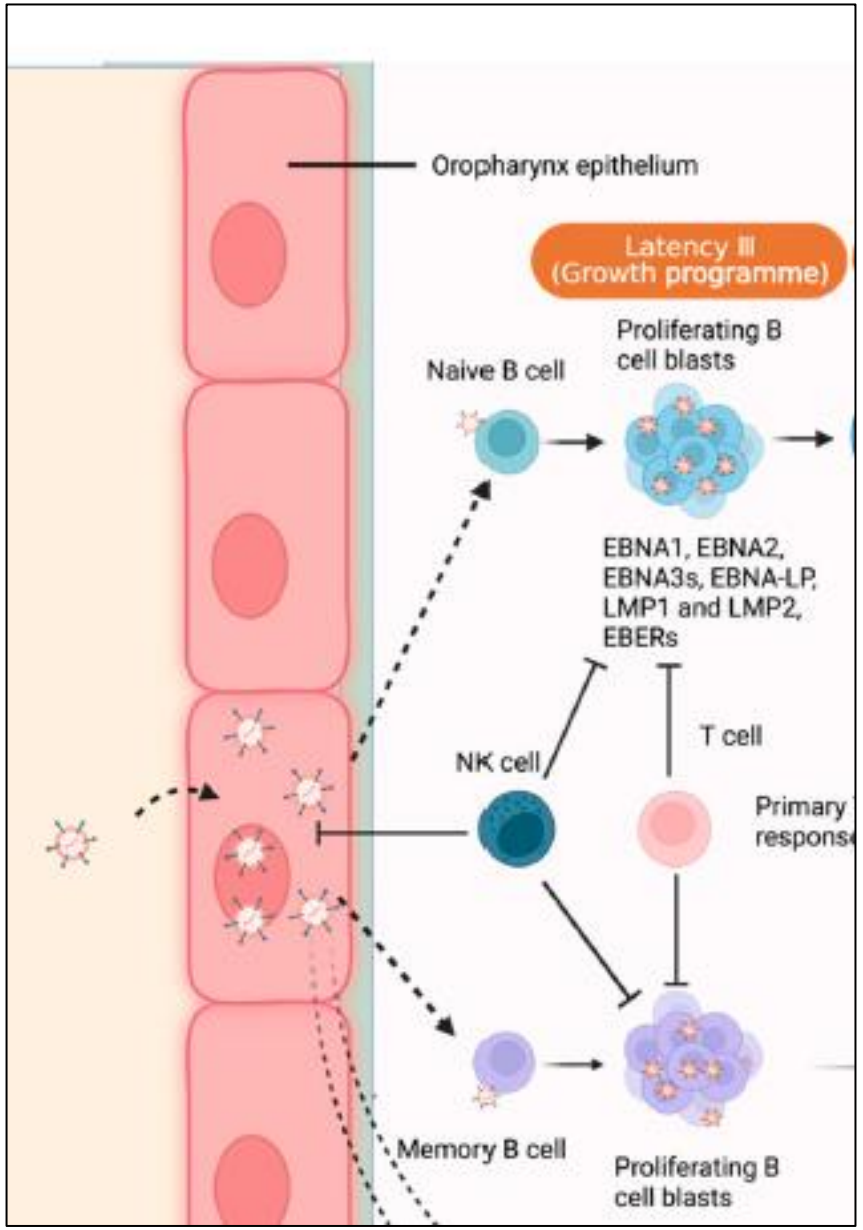
- Viral transcriptional program immediatly induced in naive or memory B lymphocytes
- ***In vitro* sustain proliferation and immortalization**

6 Nuclear Antigens (EBNAs)
EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C, EBNA-LP

3 Membrane Antigens (LMPs)
LMP1, LMP2A, LMP2B

Non coding RNA
EBER1, EBER2, BARTs, BHRF1

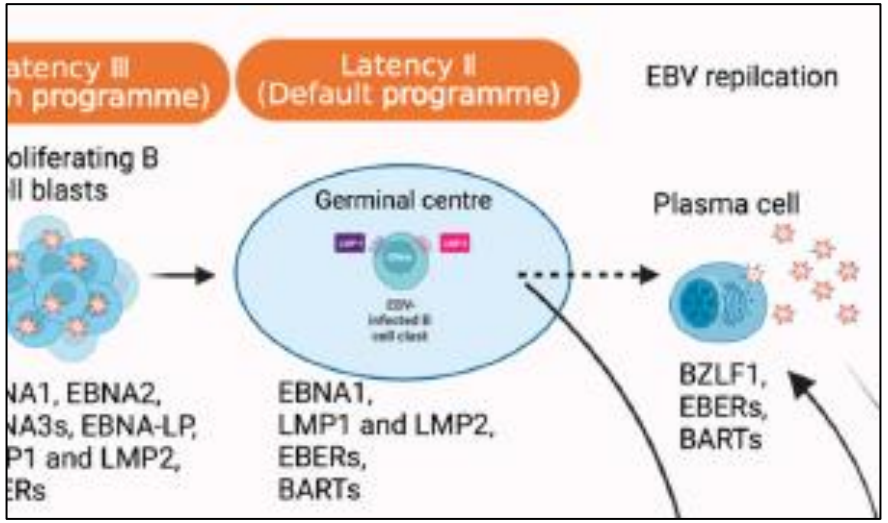
- In immunocompetent host **Lat III is transient** and rarely detected
- **Highly immunogenic** >>cytotoxic T and NK cells



Hui Yu and Erle S. Robertson. Viruses 2023

Infection, latency and reactivation

Latency II (default *program*)

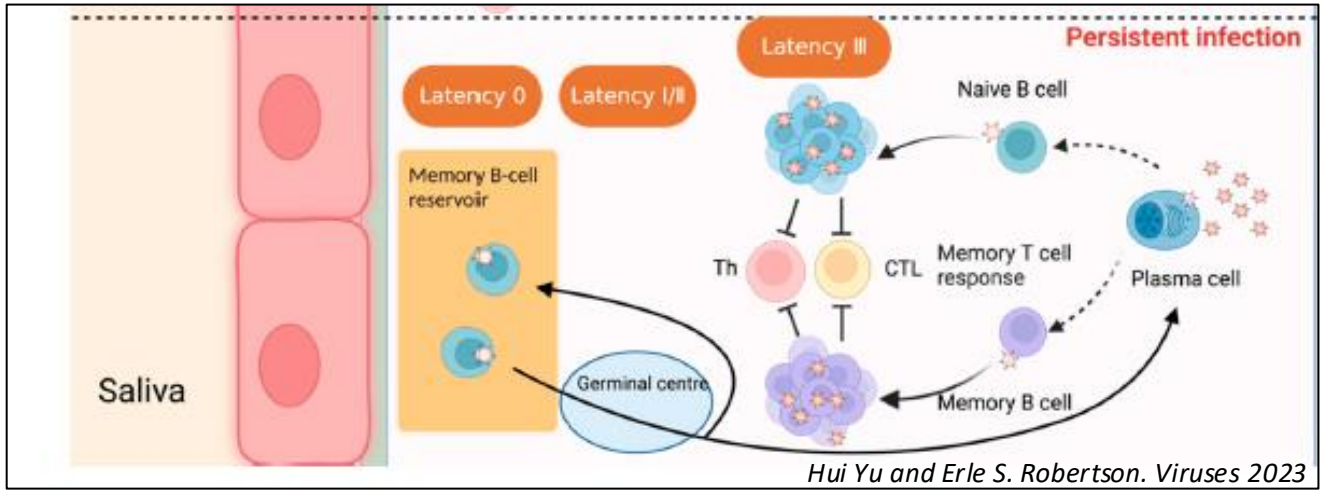


- In immunocompetent subjects only infected cells undergoing a change in transcriptional program survive immunological response

1 Nuclear Antigens	2 Membrane Antigens	Non coding RNA
EBNA1	LMP1, LMP2A	EBER1, EBER2, BARTs, BHRF1

- Naive B cell enter the Germinal center reaction and become memory cells and eventually selected become plasma cells.

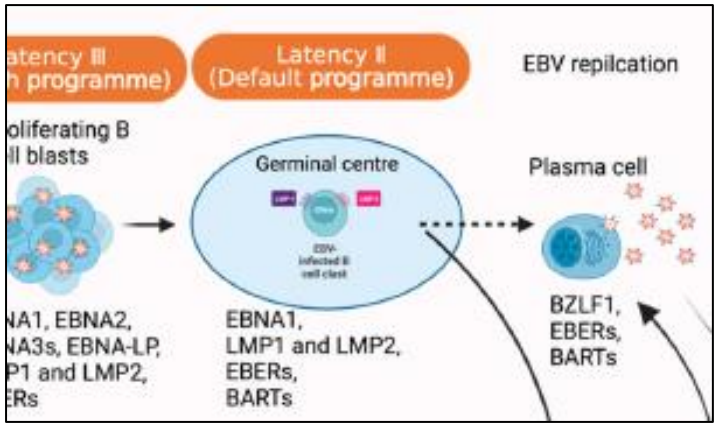
- In persistent infection the germinal center promotes induction of the lytic phase and sustains infection



Hui Yu and Erle S. Robertson. Viruses 2023

Infection, latency and reactivation

Latency I/0 (*program*)



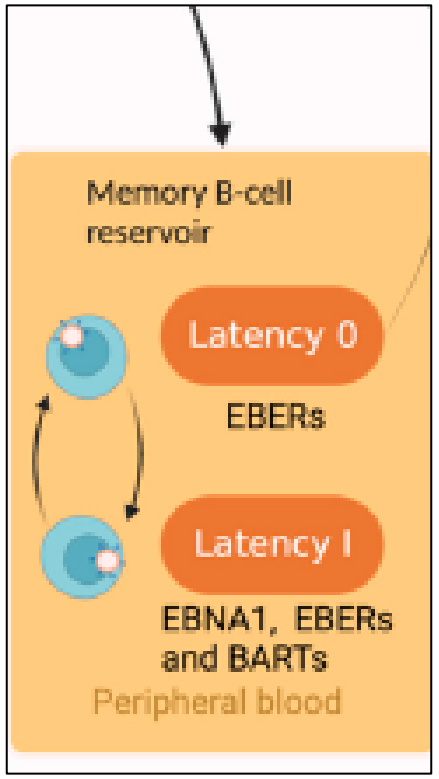
- B lymphocytes enter the reservoir of memory B cells

Lat I

1 Nuclear Antigens	**Non coding RNA**
EBNA1	EBER1, EBER2, BARTs, BHRF1

Lat 0

Non coding RNA
EBER1, EBER2, BARTs, BHRF1

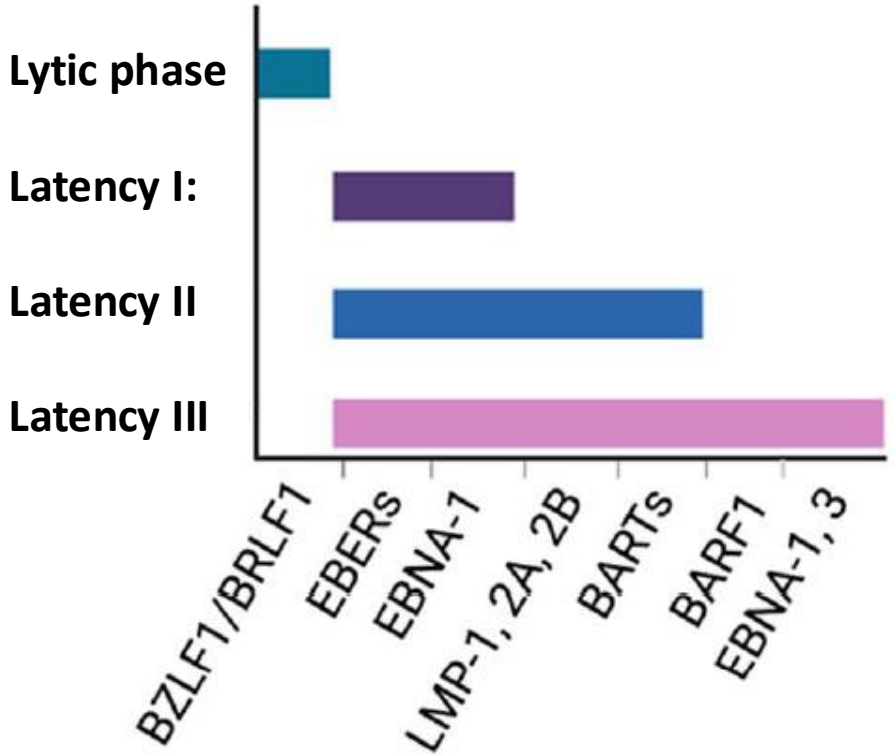


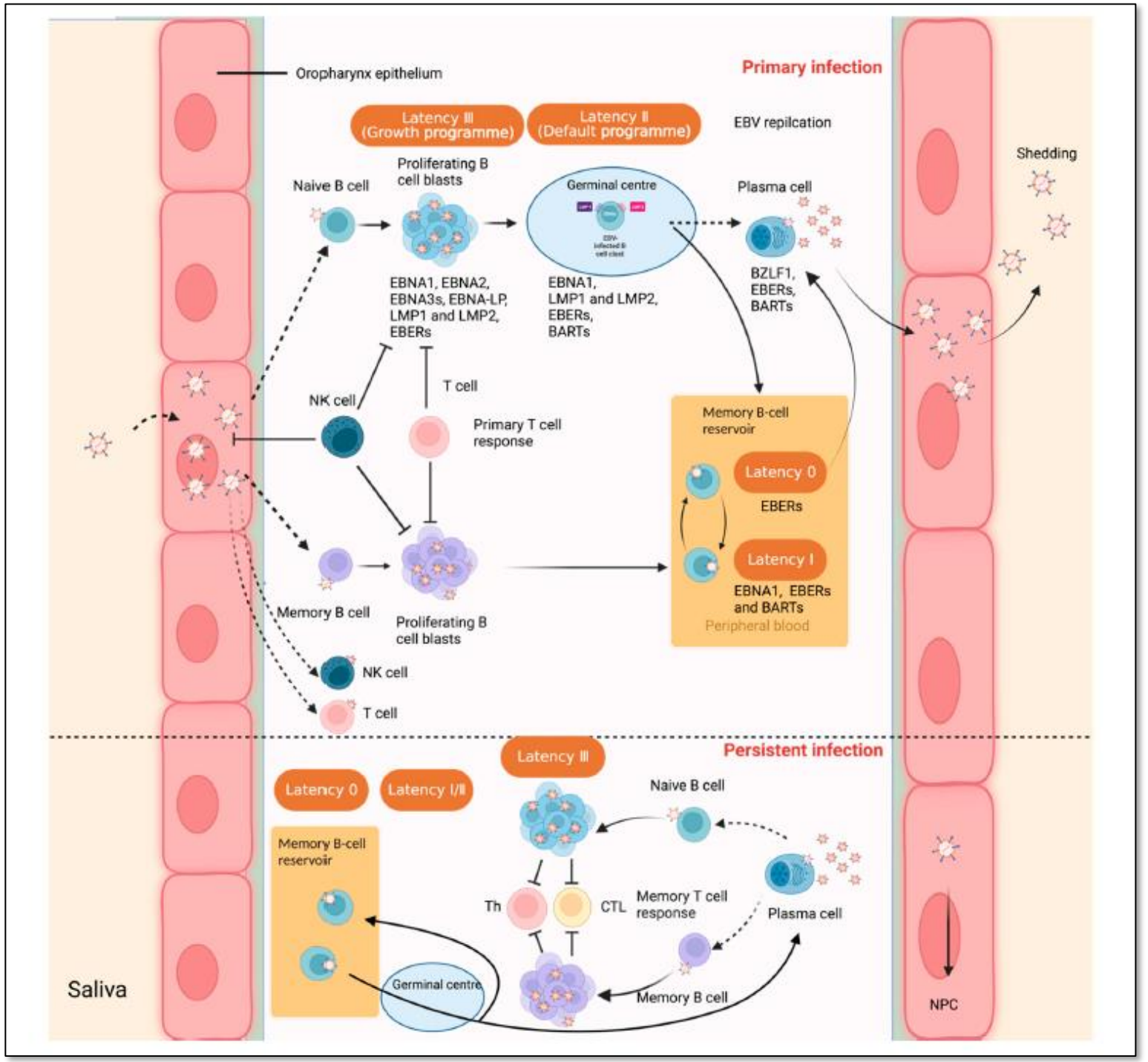
- **<u>Do not induce transformation</u>**

Hui Yu and Erle S. Robertson. Viruses 2023

Infection, latency and reactivation

EBV induces in the host cell specific transcriptional programs associated wih specific viral proteins expression



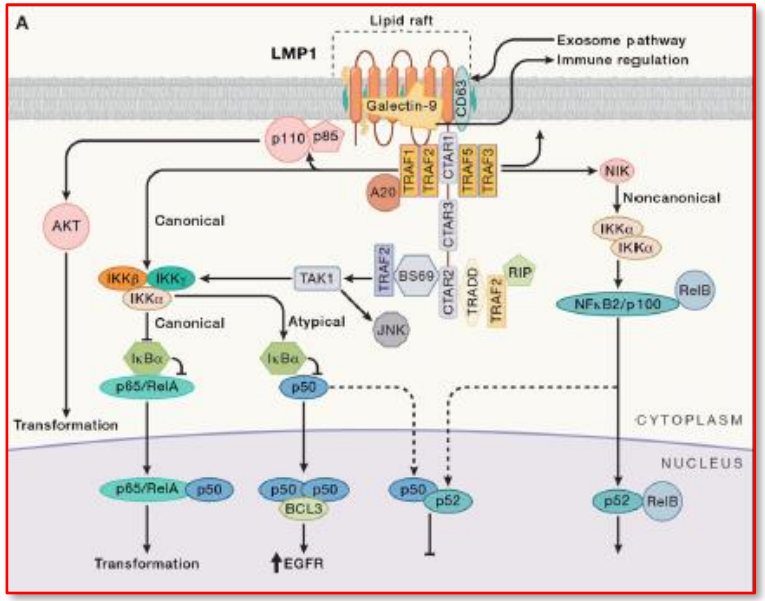


→ Viral latency proteins mediate lymphomagenesis

- **Inhibit apoptosis** (**LMP1**, EBNA1, BART)
- **Impair oncosoppressor genes** (**LMP1**, EBNA3, BART)

→ **Induce proliferation and neoplastic transformation**

LMP1 ≈ CD40



Damania B et al. Cell 2022
Chakravorty S et al Frontiers in Immunology 2022
Hui Yu and Erle S. Robertson. Viruses 2023
Ford M et al. Current Current Hematologic Malignancy Reports 2023

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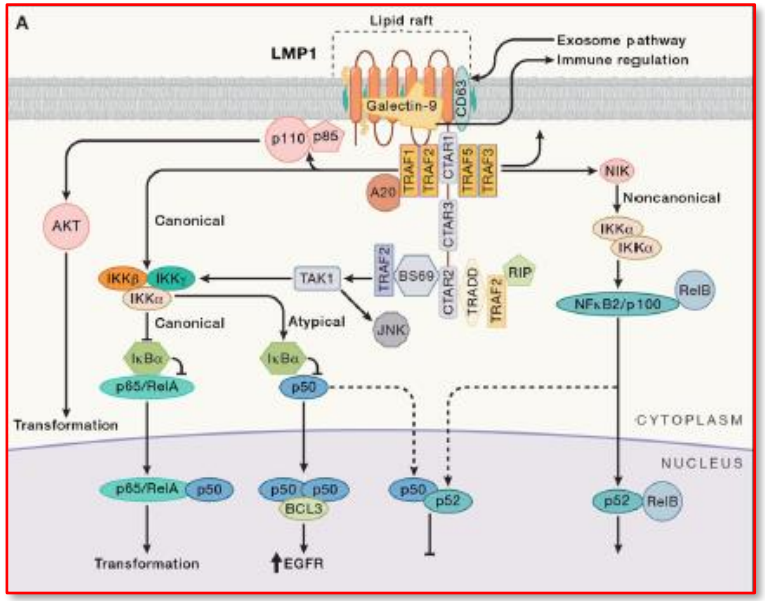
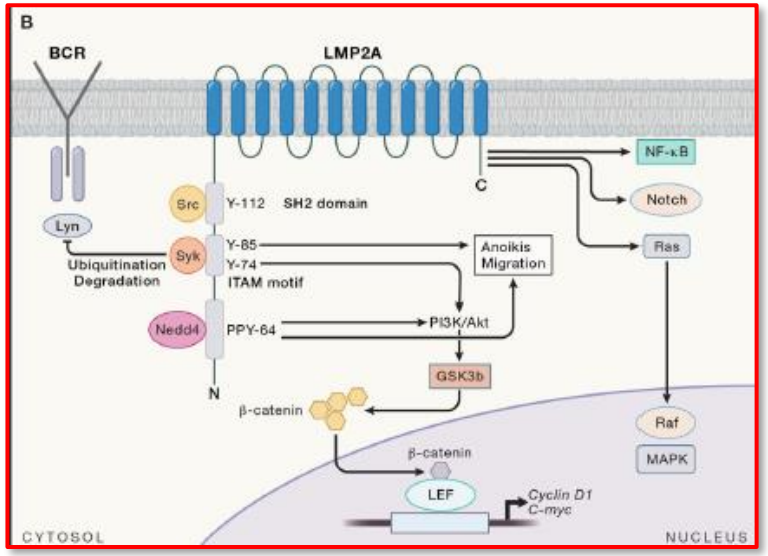
- Favour **angiogenesis** (**LMP1**)
- Promote **metastasis** (**LMP1/2A**)
- Induce **genomic instability** (EBNAs, **LMP1**, BALF, BNRF, BGLF)
- Alter **methabolic pathways** (**LMPs**)

LMP1 ≈ CD40



LMP2A ≈ BCR



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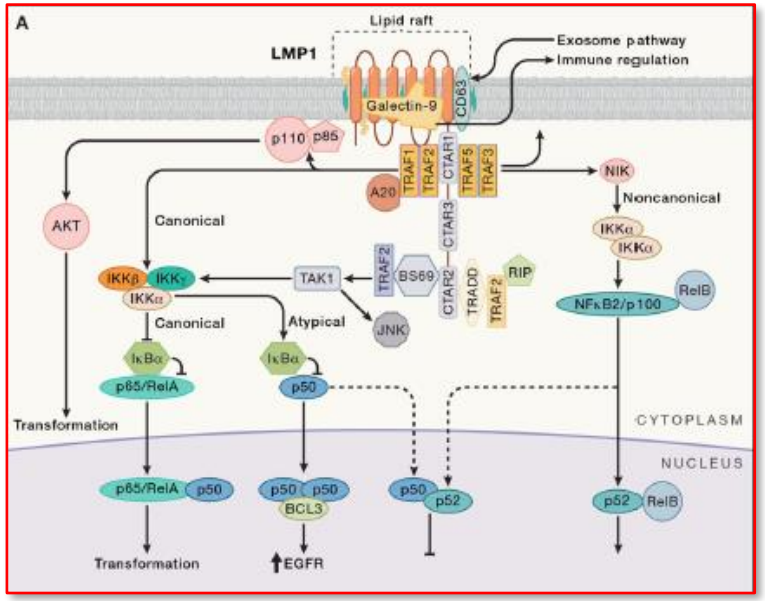

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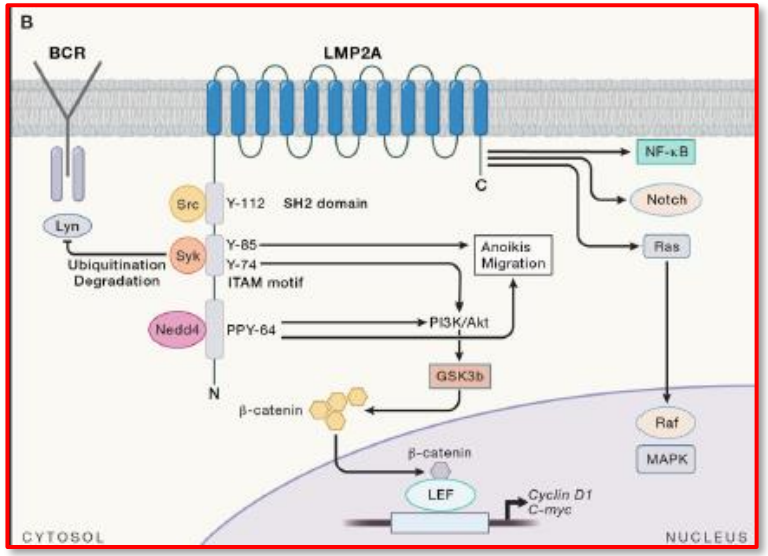

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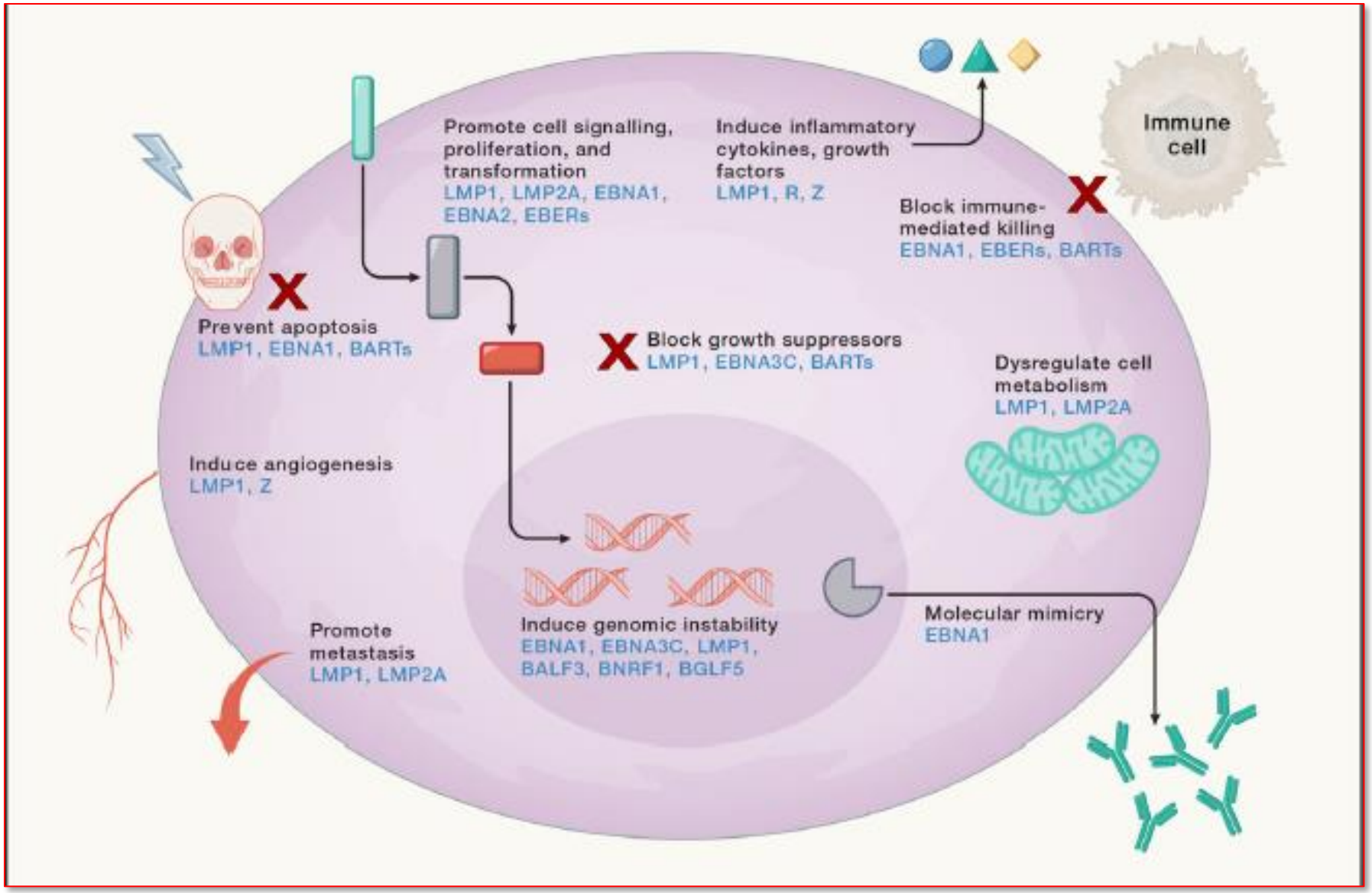
- Promote **metastasis** (**LMP1/2A**)
- Induce **genomic instability** (EBNAs, **LMP1**, BALF, BNRF, BGLF)
- Alter **methabolic pathways** (**LMPs**)

- Inhibit immune **risponse innate and adaptive** (EBNA1, EBER, BART)
- Induce inflammatory cytokine secretion (**LMP1**)
- **EBNA1** induces **molecular mimicry**

Damania B et al. Cell 2022
Chakravorty S et al Frontiers in Immunology 2022
Hui Yu and Erle S. Robertson. Viruses 2023
Ford M et al. Current Current Hematologic Malignancy Reports 2023

→ Viral latency proteins mediate lymphomagenesis on host cell directly



→ EBV+ lymphomas are associated with low genomic complexity

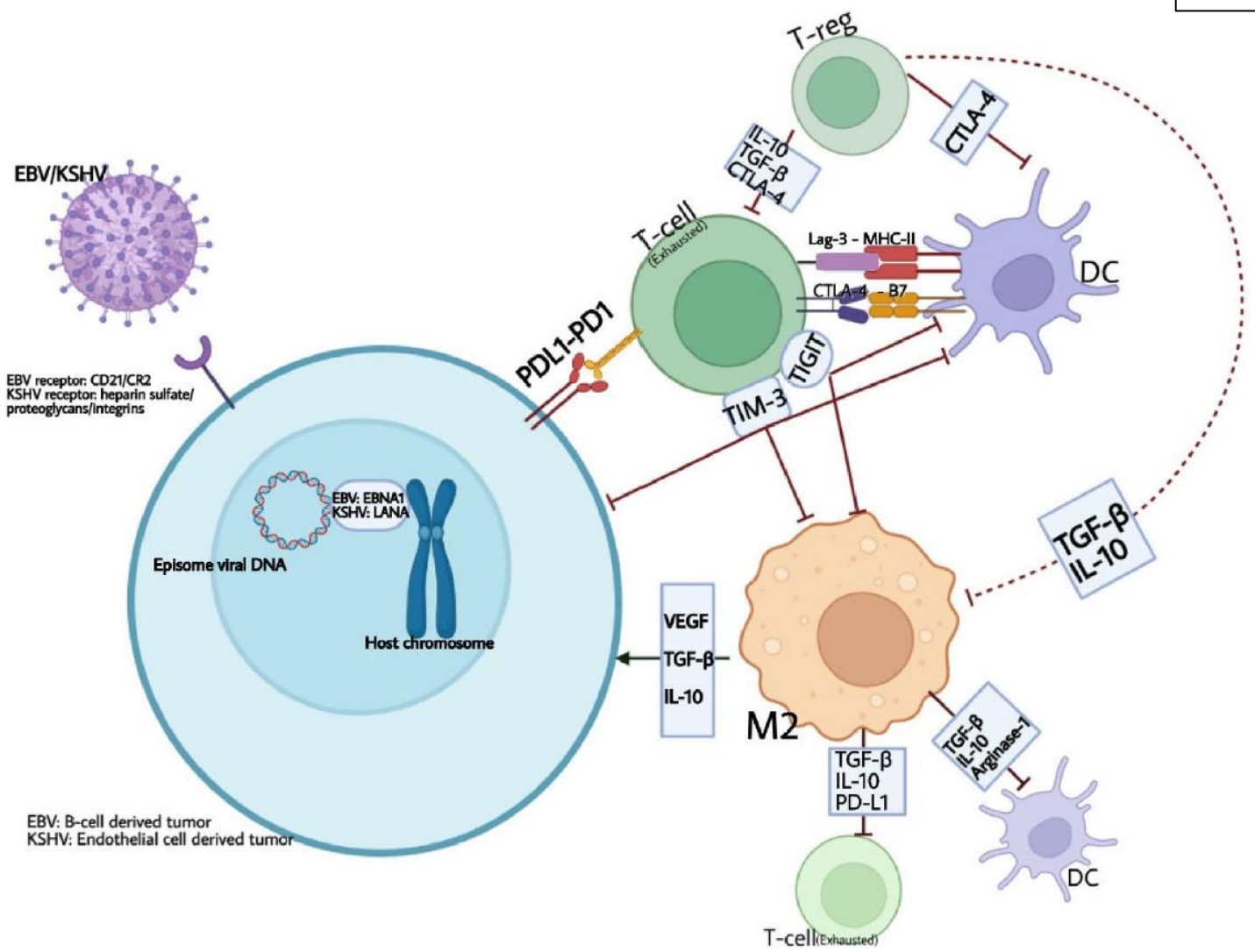
EBV influences the life cycle of host cells and shapes the tissue microenvironment to immuno escape

REVIEW

Medical Virology 2026

Immune Reprogramming by EBV and KSHV in the Tumour Microenvironment: From Mechanisms of Immune Escape to Immunotherapy

Yang Yu[1] | Taihu Wan[2]



upregulation of inhibitory pathways and increased expression of immune checkpoint molecules (PDL1)

Are lymphomas latency program specific?

Lymphomas are latency program specific

EBV-ASSOCIATED DISEASE	LATENCY TYPE	EBV VIRAL GENE EXPRESSION
Healthy individuals	0	EBERs, BARTs
Burkitt lymphoma (BL)	I	EBERs, BARTs, EBNA1
Gastric carcinoma	I or II	EBERs, BARTs, EBNA1
Hodgkin lymphoma (HL)	II	EBERs, BARTs, EBNA1, LMP1, LMP2
NK/T cell lymphoma (NKTL)	II	EBERs, BARTs, EBNA1, LMP1, LMP2
Nasopharyngeal carcinoma (NPC)	II	EBERs, BARTs, EBNA1, LMP1, LMP2
Diffused large B cell lymphoma (DLBCL)	II or III	EBERs, BARTs, EBNA1, EBNA2, EBNA3A,B,C, EBNA-LP, BHRF1 miRNAs
HIV-associated lymphomas	III	EBERs, BARTs, EBNA1, LMP1, LMP2, EBNA2, EBNA-3A,B,C, EBNA-LP, BHRF1 miRNAs
Post-transplant lymphoproliferative disease (PTLD)	III	EBERs, BARTs, EBNA1, LMP1, LMP2, EBNA2, EBNA3A,B,C, EBNA-LP, BHRF1 miRNAs

Damania B et al. Cell 2022

TYPE Review
PUBLISHED 24 March 2026
DOI 10.3389/fimmu.2026.1742214

Hit-and-run hypothesis: revisiting the impact of EBV in malignancies

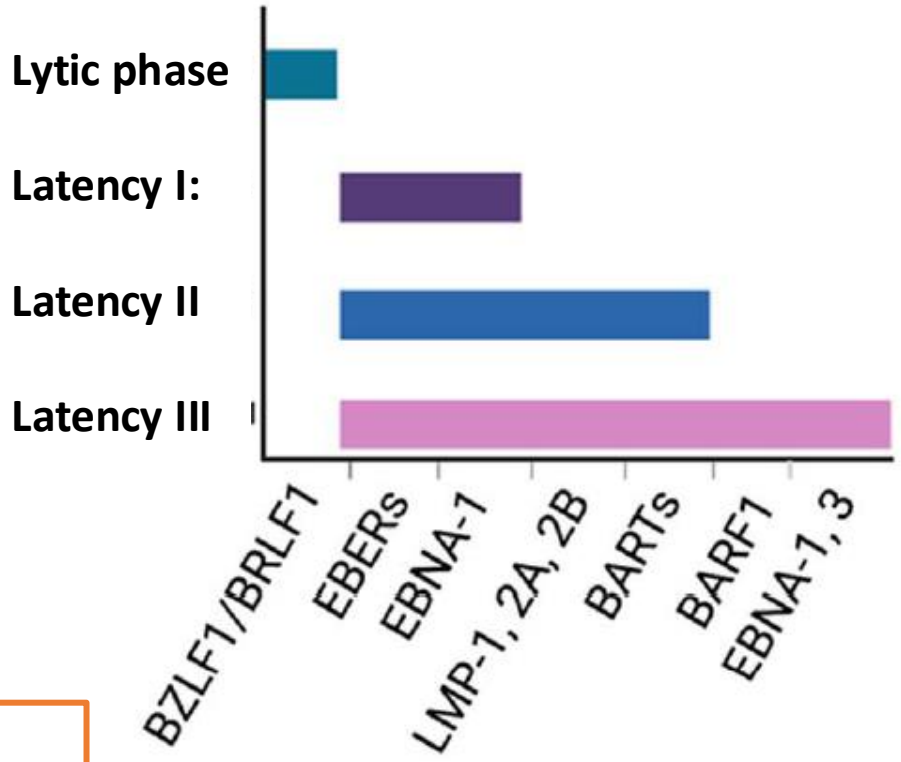
Tamara Mangiaterra[1], Paola Chabay[1], Cristiana Bellan[2], Stefano Lazzi[2], Noel Onyango[3], Pankaj Trivedi[4*], Paul Mur
Lucia Mundo[5,7†] and Eleni Anastasiadou[7†]

Latency	Antigens	EBV-associated diseases	Percentage of EBV incidence
0	EBERs	None	
I	EBERs miR-BARTs EBNA1	BL	95% (endemic)
			15-20% (sporadic)
		PEL (HIV-associated)	80%
		Plasmablastic lymphoma (HIV-associated)	60%
II	EBERs miR-BARTs EBNA1 LMP1 LMP2A LMP2B	cHL	50% - 100%
		EBV+ DLBCL	70-80%
		Lymphomatoid granulomatosis	100%
		Angioimmunoblastic T-cell lymphoma	85% - 95% large B-immunoblasts
		NK/T-cell lymphoma (nasal type)	100%
		Aggressive NK-cell leukemia	90%
		NPC	100%
		GC	10%
III	EBERs miR-BARTs miR-BHRF1 EBNA1 EBNA2 EBNA3A EBNA3B EBNA3C EBNA-LP LMP1 LMP2A LMP2B	PTLD	34% - 100%
		Primary CNS lymphoma (HIV-associated)	100%
		NK/T- cell lymphoma	100%
		DLCBL asssociated with chronic inflammation	80%
		EBV+ DLBCL	20-30%

Lymphomas are latency program specific

Lymphomas associated with Latency 0/I
- Linfoma di Burkitt

Lymphomas associated with Latency II:
- Classic Hodgkin lymphoma
- Extranodal NK/T cell lymphoma
- EBV-large B cell lymphomas



Lymphomas associated with Latency III:
- **Immunodeficiency associated lymphomas**
- Post-transplant lymphoproliferative disorders
- EBV-large B cell lymphomas (some EBV+ DLBCL; FA and FO-LBCL).

Are lymphomas latency program specific?

..not exactly….

Latency programs are influenced by Interdependent, transient phenomena:

- **Epigenetic mechanisms**
- **Viral reactivation processes**
- **Immunological context**

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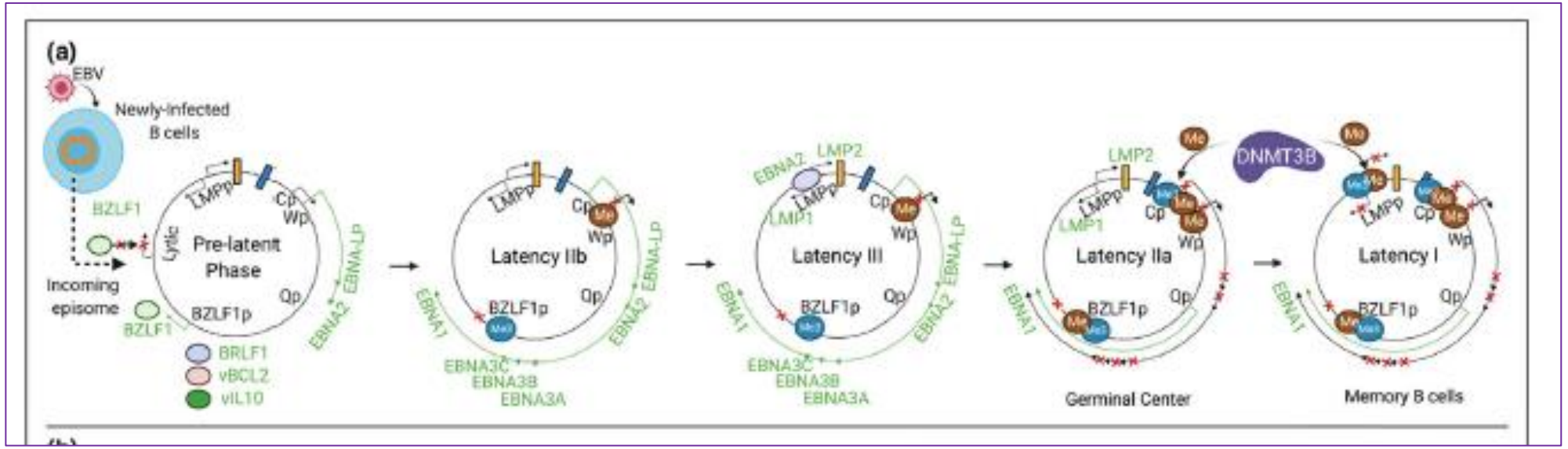
Published in final edited form as:
Curr Opin Virol. 2022 February ; 52: 78–88. doi:10.1016/j.coviro.2021.11.013.

Epigenetic control of the Epstein-Barr lifecycle

Rui Guo[1,2,3], **Benjamin E Gewurz**[1,2,3,4]



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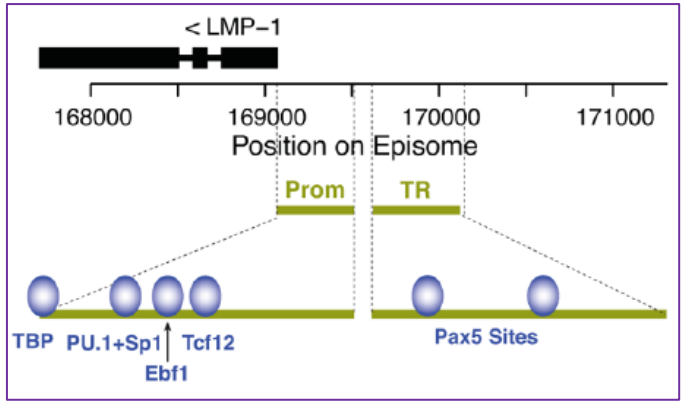
Cell Host Microbe. 2012 August 16; 12(2): 233–245. doi:10.1016/j.chom.2012.06.008.

An Atlas of the Epstein-Barr Virus Transcriptome and Epigenome Reveals Host-Virus Regulatory Interactions

Aaron Arvey[1], Italo Tempera[2], Kevin Tsai[2], Horng-Shen Chen[2], Nadezhda Tikhmyanova[2], Michael Klichinsky[2], Christina Leslie[1,*], and Paul M. Lieberman[2,*]



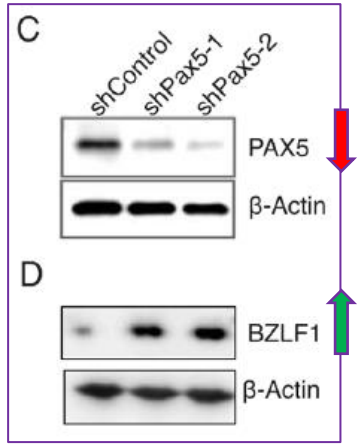
In EBV infected **B-cell transcriptional factors** are clustered in specific regions that **modulate viral proteins expression**

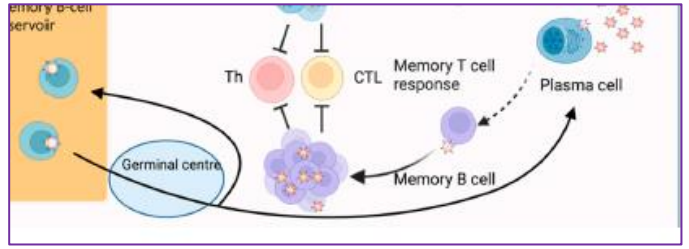
Physiological downregulation of **PAX5** during GC reaction induces:

upregulation of LMP1 e LMP2 e BZLF1

downregulation of EBNA1 and EBNA 2

→ GC reaction may induce lytic phase and virus reactivation





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Lytic phase

- expression of >80 viral proteins
- DNA linearization and cleavage of «terminal repeats»
- DNA replication and structural proteins syntesis

  → viral capsides released

Immediate/Early lytic phase TF
BZLF1, BRLF1

↓

IL6, VEGF, IL8 → B-cell proliferation
IL10, TGF-beta → immune-suppression

Lytic phase markers can be found in EBV+ lymphomas indicating virus reactivation during the neoplastic process

Plasmablastic transformation of a pre-existing plasmacytoma: a possible role for reactivation of Epstein Barr virus infection

Maria R. Ambrosio, Giulia De Falco, Alessandro Gozzetti, Bruno J. Rocca, Teresa Amato, Vasileios Mourmouras, Sara Gazaneo,

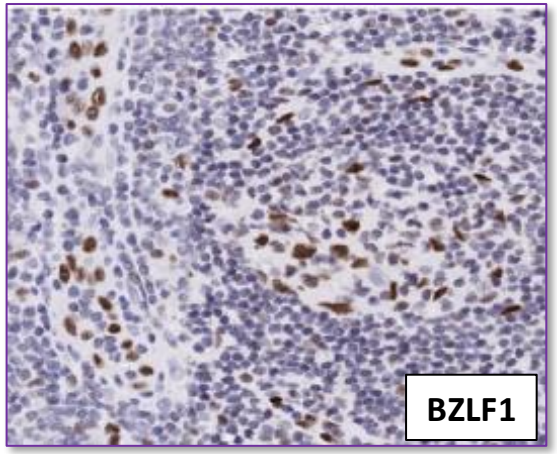
Histopathology

Histopathology 2022, **79**, 1099–1107. DOI: 10.1111/his.14551

SHORT REPORT

Epstein–Barr virus reactivation influences clonal evolution in human herpesvirus-8-related lymphoproliferative disorders

Massimo Granai,[1,2] Mattia Facchetti,[3] Virginia Mancini,[1] Jacqueline Goedhals,[4]



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Latency programs are influenced by Interdependent, transient phenomena:

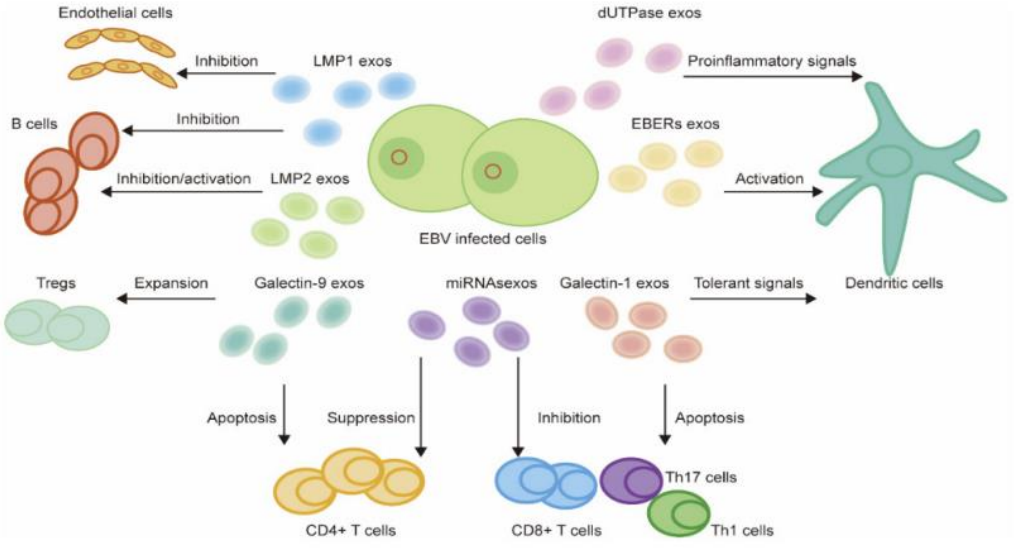
- Epigenetic mechanisms
- Viral reactivation processes
- Immunological context

viruses MDPI

Review

Immunosuppressive Tumor Microenvironment and Immunotherapy of Epstein–Barr Virus-Associated Malignancies

Xueyi Zheng [1], Yuhua Huang [1], Kai Li [2], Rongzhen Luo [1], Muyan Cai [1,*] and Jingping Yun [1,*]



Cellular components	Molecular componets
Effective CD8+T cells ↓ Exhausted CD8+T cells ↑ Tregs ↑ M2 TAMs ↑ CAFs ↑ MDSCs ↑ LAMP3+ DCs ↑ NK cells ↓ Endothelial cells ↑	Pro-inflammatory factors: IFN-γ, IP10, IL-1β, TNF-α ↑ Immunosuppressive factors: IL-4, IL-6, IL-8, IL-10, IL-13 ↑ Galectin-1 ↑ Immune checkpoints: PD-1, PD-L1, PD-L2, CTLA-4 ↑

- **Immunocompetence influences Latency programs**
- **Latency products induce more or less immunosuppressive tumor microenvironment**

Are lymphomas latency program specific?

..not exactly….

Latency programs are influenced by Interdependent, transient phenomena:

- **Epigenetic mechanisms**
- **Viral reactivation processes**
- **Immunological context**

EBV-Associated Malignancies	EBV Positive Rate	Latency Pattern	Immune Markers		Immunotherapy
			Immune Cells	Immune Molecules	
PTLD	100%	Latency III	Memory/helper T cells Decreased cytotoxic T cells	IFN-γ, IL-6, IL-10, IL-13	Adoptive T cell therapy
Classical HL	50%	Latency II	Tregs Exhausted CD8+ T cells	PD-L1, TNFR, Th2 cytokines and chemokines, IL-10, galectin-1, TGF-β	PD-1 inhibitors T cell therapy
Epidemic BL	100%	Latency I	M2 TAMs	IL-2, IL-6, IL-10	NA
DLBCL	10%	Latency II or III	M2 TAMs Exhausted CD8+ T cells	IL-10, PD-1, PD-L1, PD-L2, LAG3, TIM3	Chimeric antigen receptor T cell therapy
Extranodal NK/T cell lymphomas	100%	Latency II	Activated T cells and macrophages	IL-2, IL-10, CD27, TNF-α, PD-L1	PD-1 inhibitors
Undifferentiated NPC	100%	Latency I/II	Exhausted CD8+ T cells LAMP3+ DCs	PD-L1, PD-L2, CTLA-4, IDO1, HLA-G	PD-1 inhibitors Therapeutic EBV vaccines
GC	10%	Latency I or I/II	CD8+ T cells Tregs TAMs	PD-L1, IDO1	PD-1 inhibitors
ICC	6.6%	Latency I	CD8+ T cells M1 TAMs CD20+ B cells	PD-L1	NA
SMT	<1%	Latency III	T cells	NA	NA

Note: PTLD, Post-transplant lymphoproliferative disease; HL, Hodgkin lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B cell lymphoma; GC, gastric carcinoma; NPC, nasopharyngeal carcinoma; ICC, intrahepatic cholangiocarcinoma; SMT, smooth muscle tumor; NA, not applicable.

Immunomodulating Therapies…

Lymphomas are not necessarly latency program specific but can support the hypothesis of Immune-impaired background

Lymphomas associated with Latency 0/I
- Linfoma di Burkitt

Lymphomas associated with Latency II:
- Classic Hodgkin lymphoma
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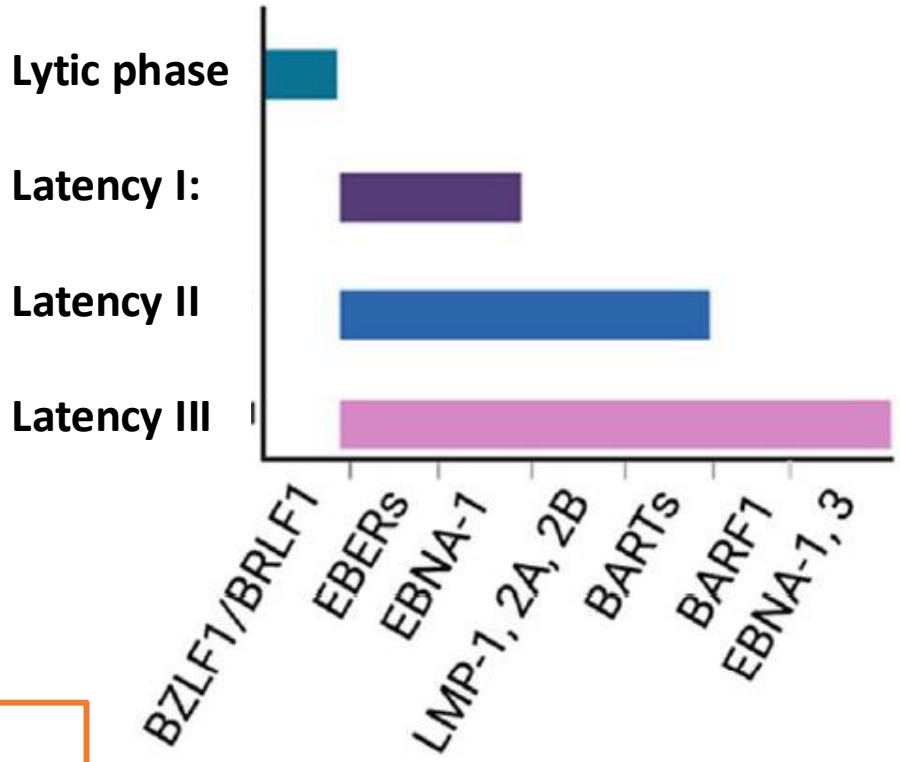
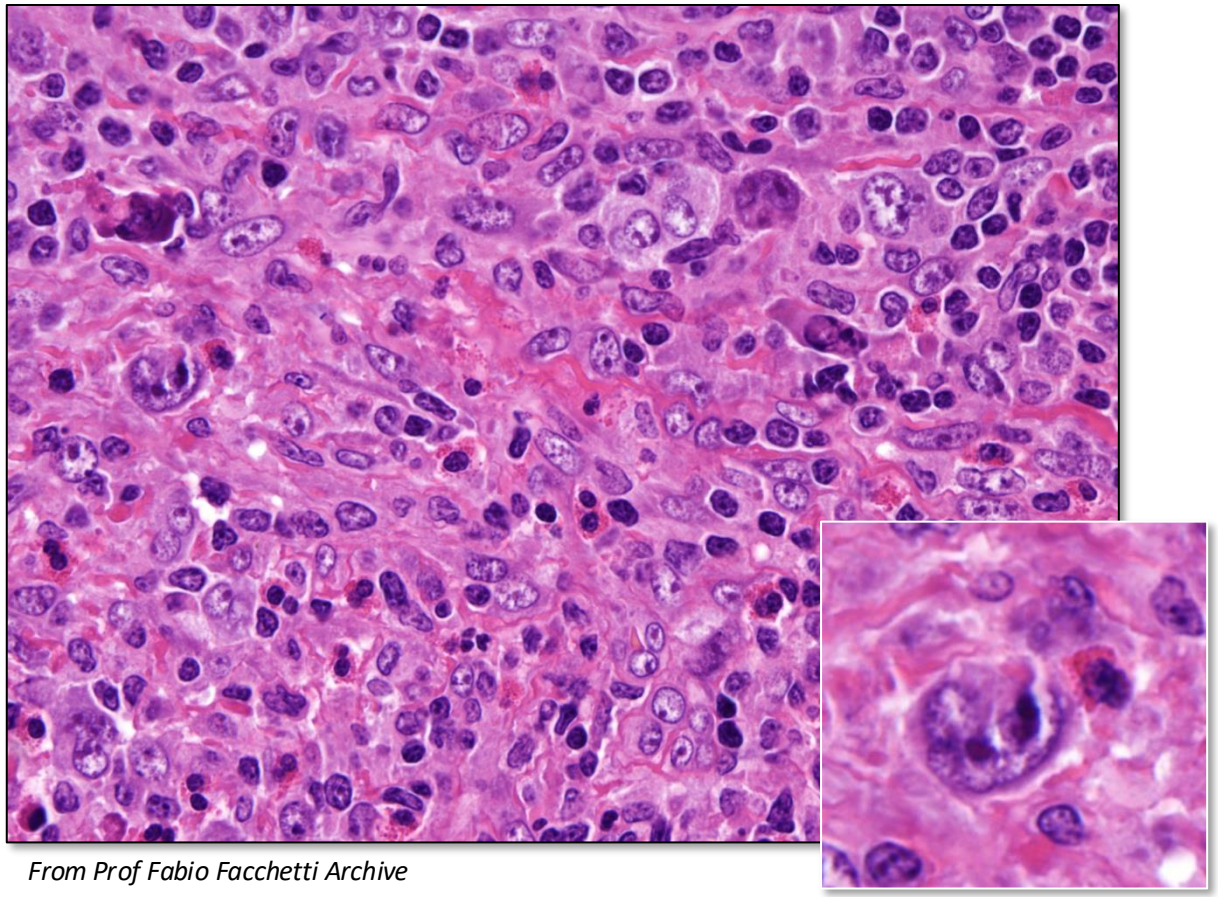


EBV-positive lymphomas (main subtypes)

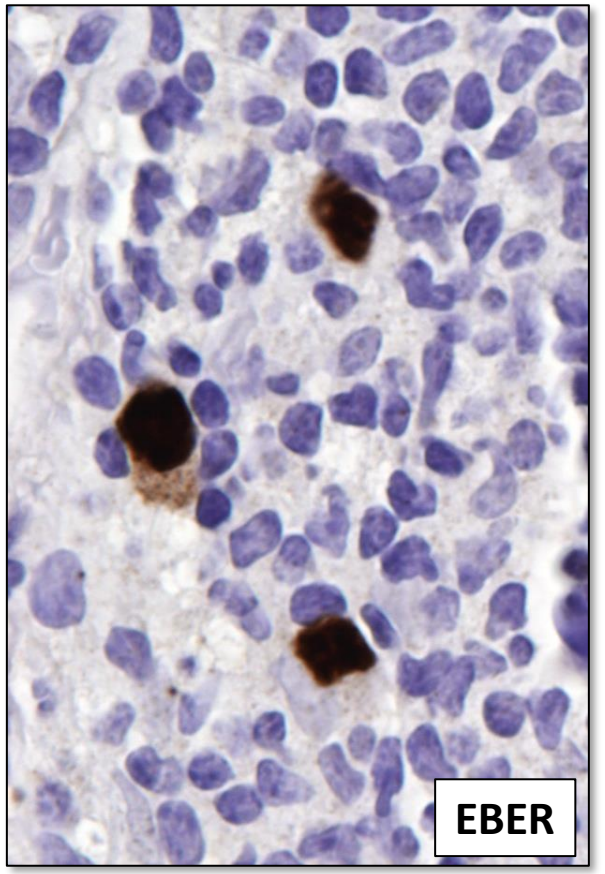
Classic Hodgkin Lymphoma

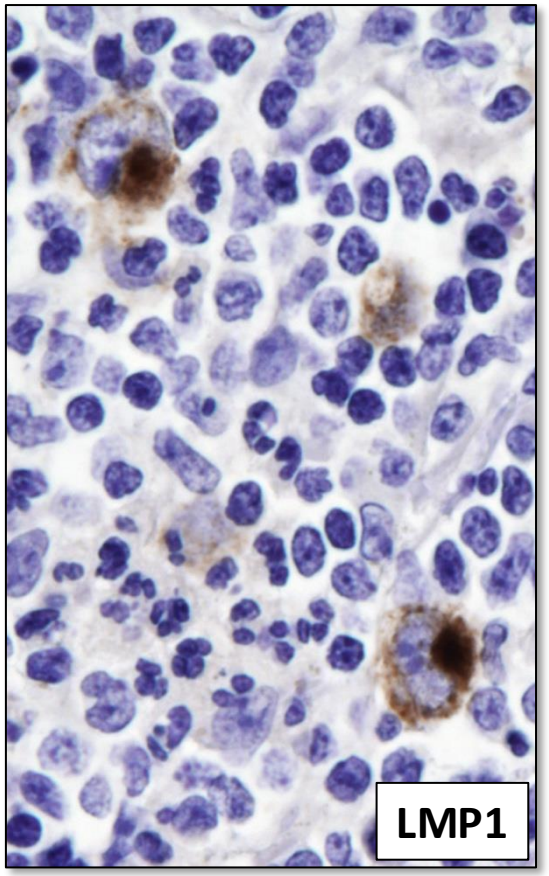
EBV infection is common in the **mixed cellularity** and **lymphocyte depleted** variants

Lat II: EBNA1, **LMP1**, LMP2, BARTs, **EBERs**.



From Prof Fabio Facchetti Archive





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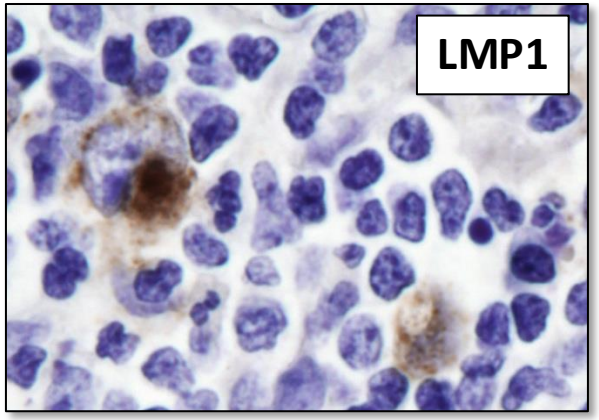
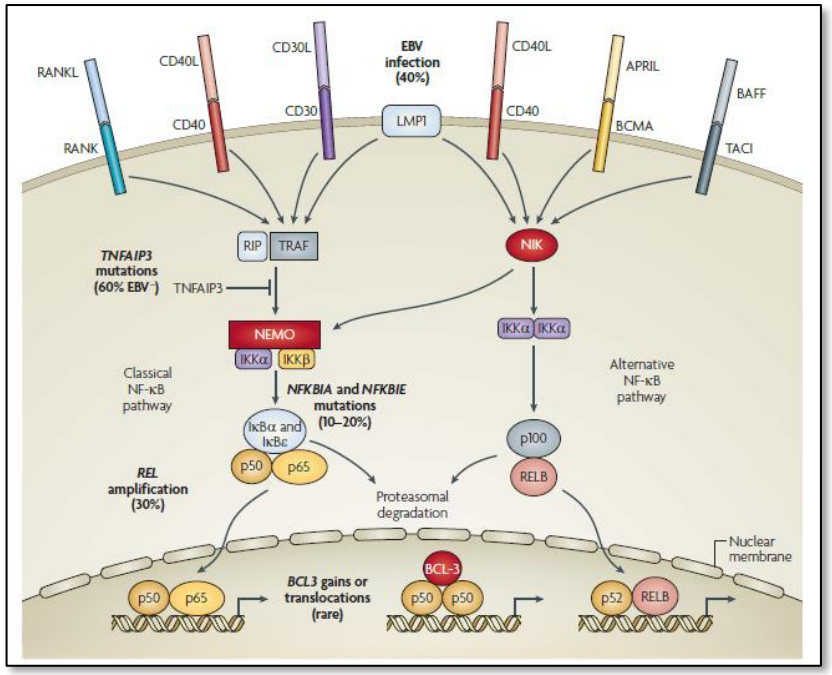
LMP1 sustain oncogenesis via activation of NF-kB pathway
LMP-1 e LMP-2 protect Hodgkin-Reed-Sternberg cells from apoptosis





Kuppers R Nat Rev Cancer 2009
Chetaille B et al Blood 2009

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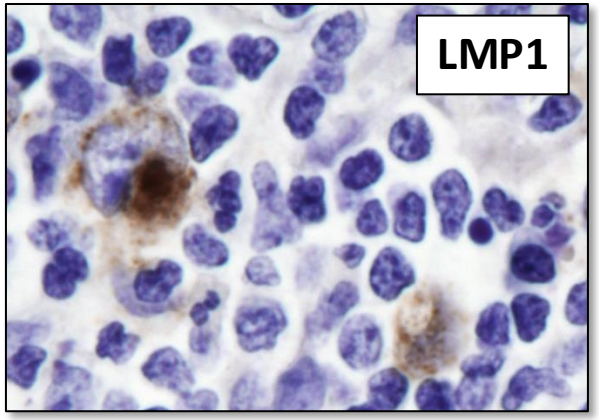
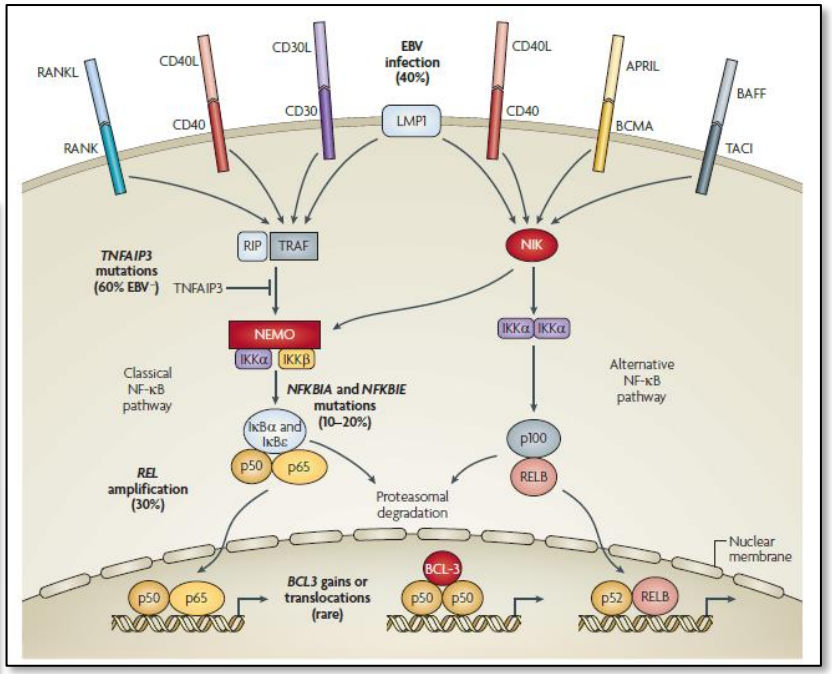
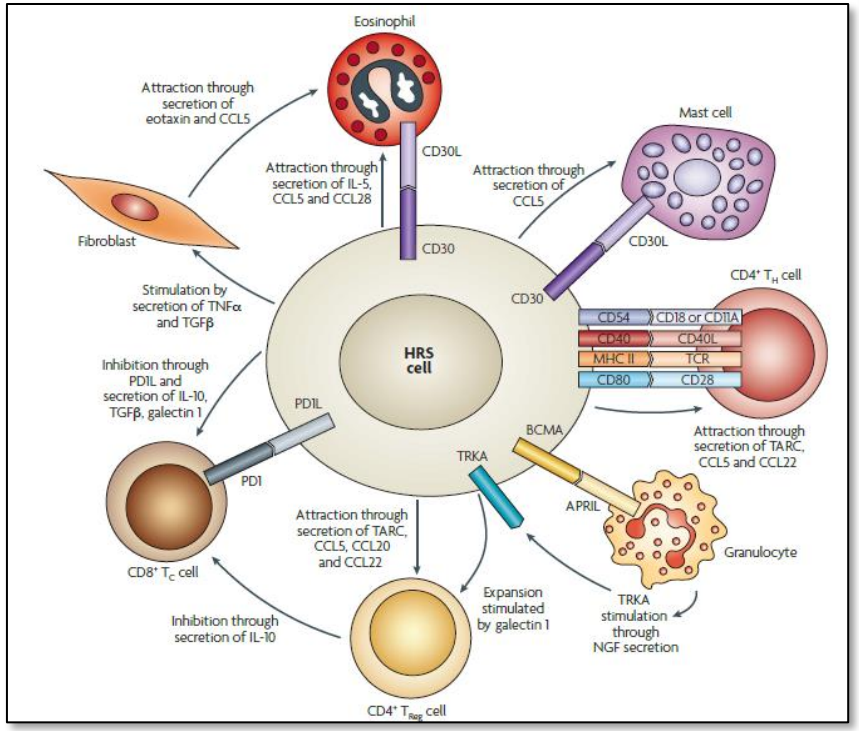




Microenvironment:

Gene expression studies have shown that in **EBV+ cHL:**

- high expression of antiviral response related genes (> interferon-dependent)
- increase in Th1 signatures (unefficient)



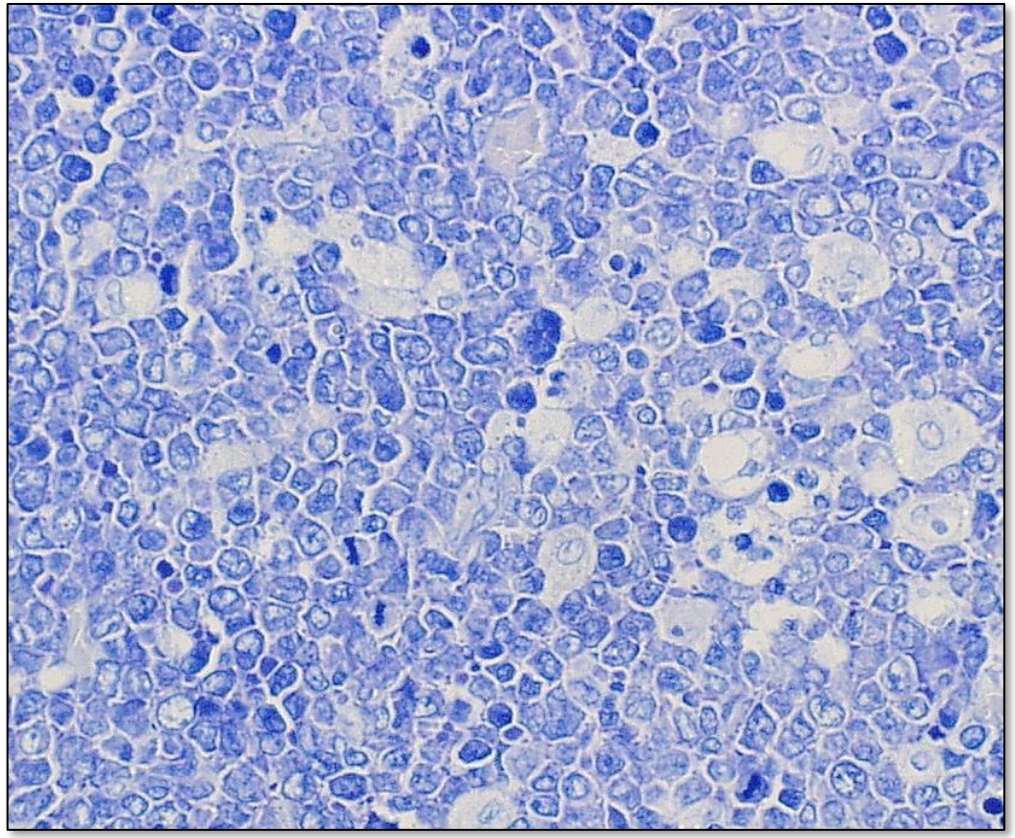
Kuppers R Nat Rev Cancer 2009
Chetaille B et al Blood 2009

EBV-positive lymphomas (main subtypes)

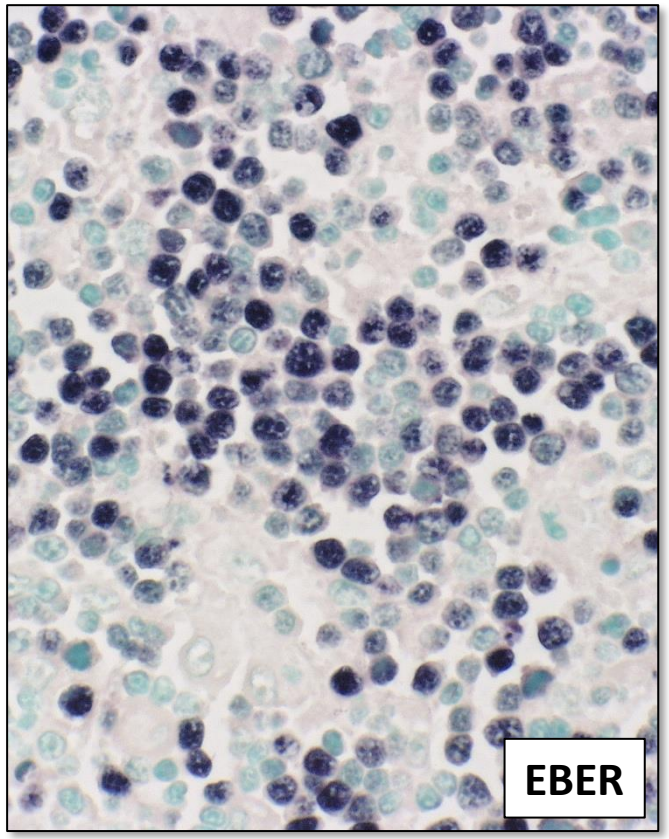
Burkitt Lymphoma

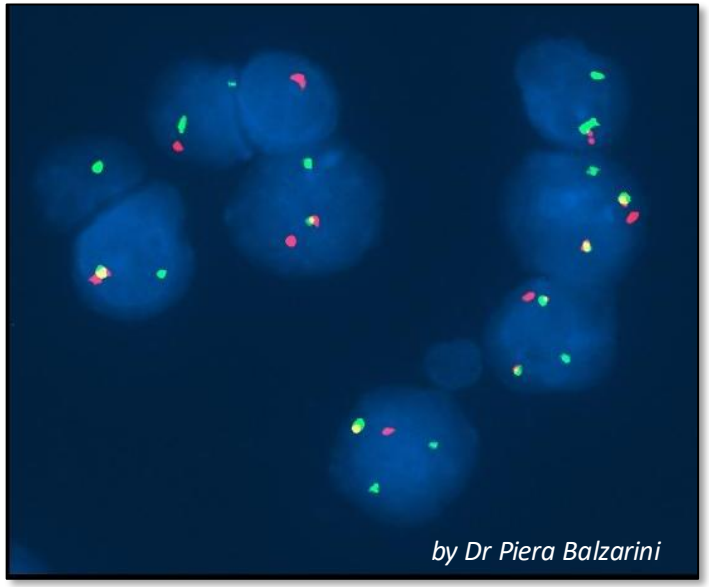
EBV-positive: 100% endemic; 20-30% sporadic

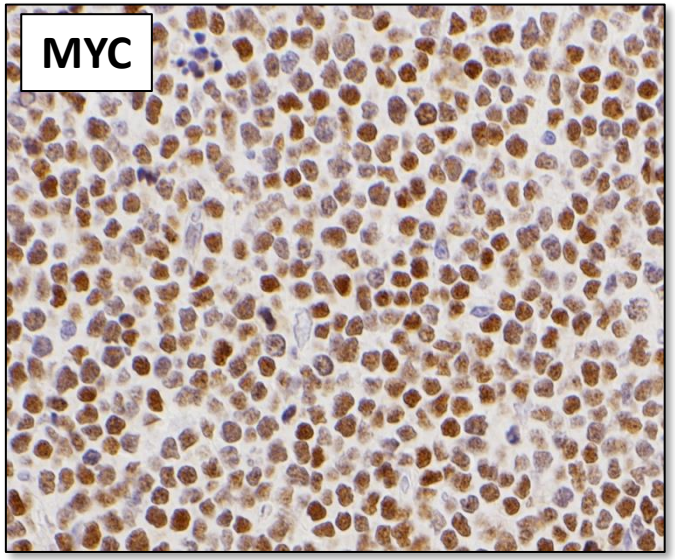
Latency I: EBNA1, BARTs, EBERs.



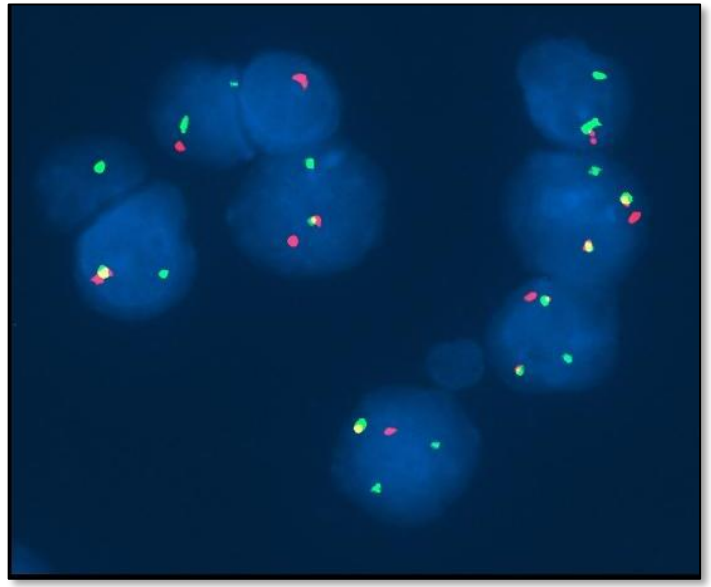
From Prof Fabio Facchetti Archive







EBV-positive lymphomas (main subtypes)



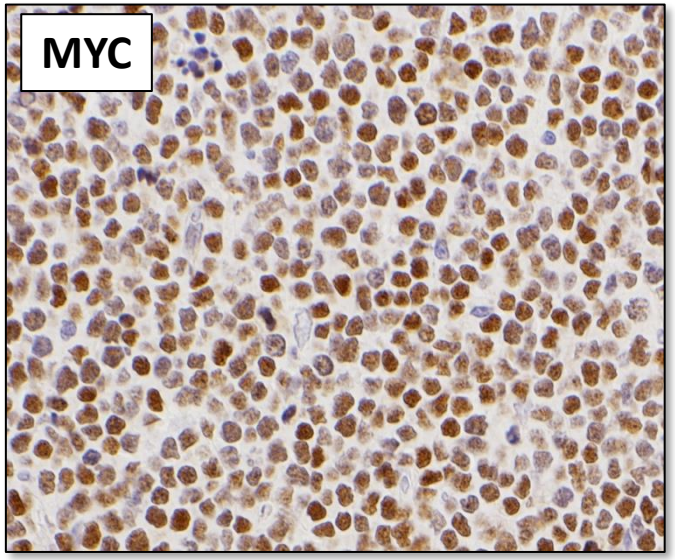
Burkitt Lymphoma

EBV-positive: 100% endemic; 20-30% sporadic

Latency I: EBNA1, BARTs, EBERs.

EBNA1 retain EBV episome during cell division but, alone, cannot induce transformation

EBV induces alterations of cell homeostasis by epigenetic modifications
→inhibit apoptosis e senescence
→ survival of MYC::IGH rearranged cells



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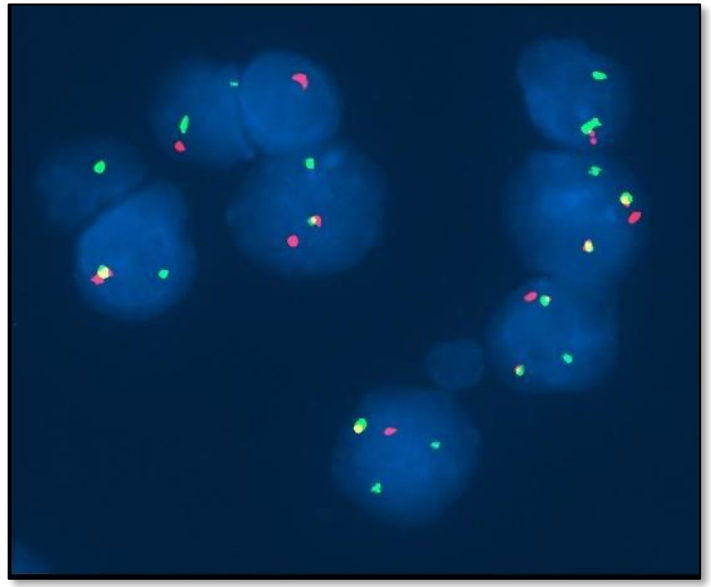

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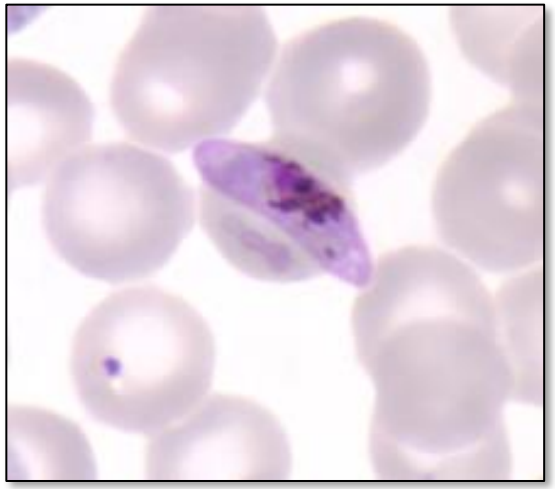
EBNA1 retain EBV episome during cell division but, alone, cannot induce transformation

EBV induces alterations of cell homeostasis by epigenetic modifications
→inhibit apoptosis e senescence.
→ survival of MYC::IGH rearranged cells

Endemic BL

Multiple infections by mixed sugroups of Plasmodium Falciparum:
-->chronic B-cell stimulation
→altered T-cell response
→ induce AICDA/AID activity
→MYC::IGH rearrangement



Endemic BL (≠ BL sporadic) shows antigen mediated BCR activation and somatic hypermutation of IGH gene

Amato T et al. Am J Clin Pathol 2006

EBV-positive lymphomas (main subtypes)

Aggressive B-cell lymphomas

WHO 2016	WHO 2022 5th	ICC 2022	EBV+	Lat
EBV-positive DLBCL, NOS	**EBV-positive DLBCL**	**EBV-positive DLBCL, NOS**	**100%**	**II/III**
Lymphomatoid granulomatosis	**Lymphomatoid granulomatosis**	**Lymphomatoid granulomatosis**	**100%**	**III**
Primary Effusion Lymphoma	**Primary Effusion Lymphoma**	**Primary Effusion Lymphoma**	**≈ 100%**	**I**
Plasmablastic lymphoma	**Plasmablastic lymphoma**	**Plasmablastic lymphoma**	**70-80%**	**I/II**
DLBCL associated with chronic inflammation (^)	**DLBCL associated with chronic inflammation**	**DLBCL associated with chronic inflammation**	**100%**	**III**
(included in ^)	**Fibrin-associated LBCL**	**Fibrin-associated DLBCL**	**100%**	**III**
(absent)	**Fluid overload-associated LBCL**	(HHV8 and EBV-negative PEL)	**WHO 13-30%**	**?**

Modified from Ross AM et al. Life 2023

Rarely EBV+: Primary CNS/Testis-DLBCL; Primary Mediastinal LBCL; HHV8+ DLBCL; High Grade DLBCL

EBV-positive lymphomas (main subtypes)

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Modified from Ross AM et al. Life 2023

Rarely EBV+: Primary CNS/Testis-DLBCL; Primary Mediastinal LBCL; HHV8+ DLBCL; High Grade DLBCL

EBV-positive lymphomas (main subtypes)

EBV-positive DLBCL, NOS

Immunocompetent patients

5-15% of all DLBCL, NOS

Latency II: EBNA1, LMP1, LMP2, BARTs, EBERs
Latency III: EBNA1, EBNA2, LMP1, LMP2, BARTs, EBERs
Latency I?

WHO 2008 *"of the elderly" (provisional)*
WHO 2016 *"NOS" (provisional)*
ICC 2022: ***EBV+ DLBCL, NOS*** *(80% cells EBV+)*
WHO 2022*:* ***EBV+DLBCL*** *(most cells EBV+)*

Frontzek F et al Leukemia 2023
Ross AM et al Life 2023

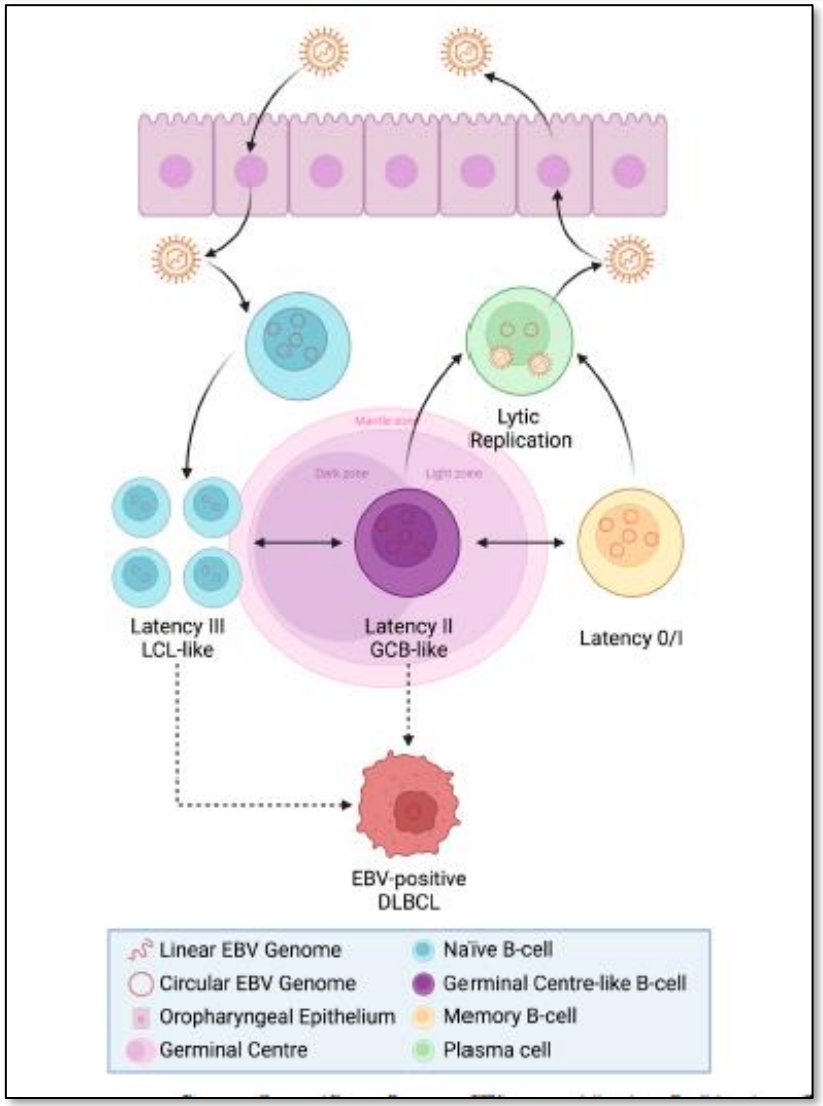
life

MDPI

Review

Epstein–Barr Virus and the Pathogenesis of Diffuse Large B-Cell Lymphoma

Aisling M. Ross [1,2], Ciara I. Leahy [1,2], Fiona Neylon [1,2], Jana Steigerova [3], Patrik Flodr [3,4], Martina Navratilova [3,4], Helena Urbankova [5], Katerina Vrzalikova [6], Lucia Mundo [1,7], Stefano Lazzi [7], Lorenzo Leoncini [7], Matthew Pugh [6,*] and Paul G. Murray [1,3,*]



EBV-positive lymphomas (main subtypes)

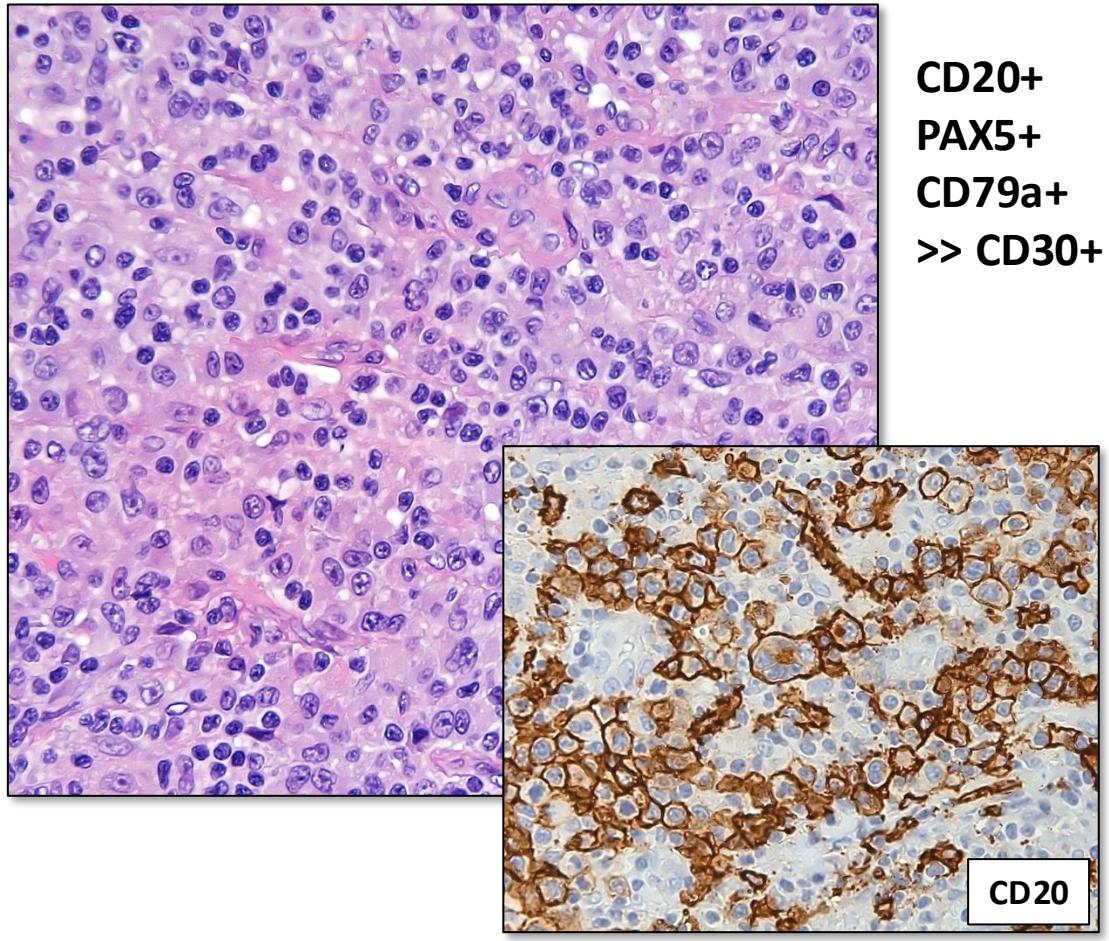
EBV-positive DLBCL, NOS

Immunocompetent patients

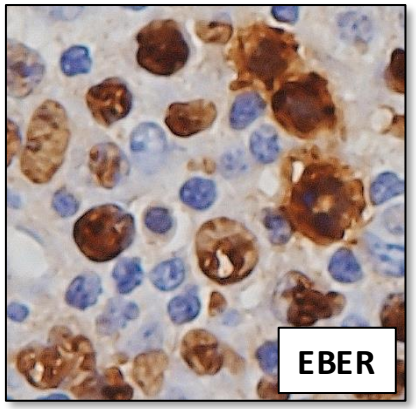
5-15% of all DLBCL, NOS

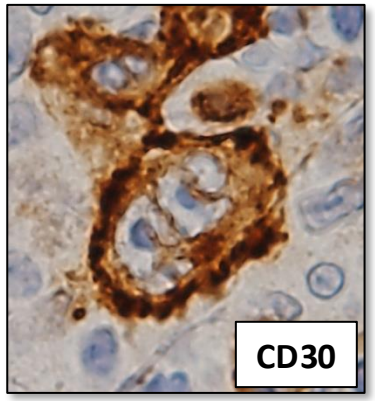
Latency II: EBNA1, LMP1, LMP2, BARTs, EBERs
Latency III: EBNA1, EBNA2, LMP1, LMP2, BARTs, EBERs
Latency I?

- In young patients the T, histiocyte rich-like variant is common and displays a better prognosis
- In adults and elderly 2 morfological variants recognized without prognostic impact: Mon- and poly-morphous



CD20+
PAX5+
CD79a+
>> CD30+





Frontzek F et al Leukemia 2023
Ross AM et al Life 2023

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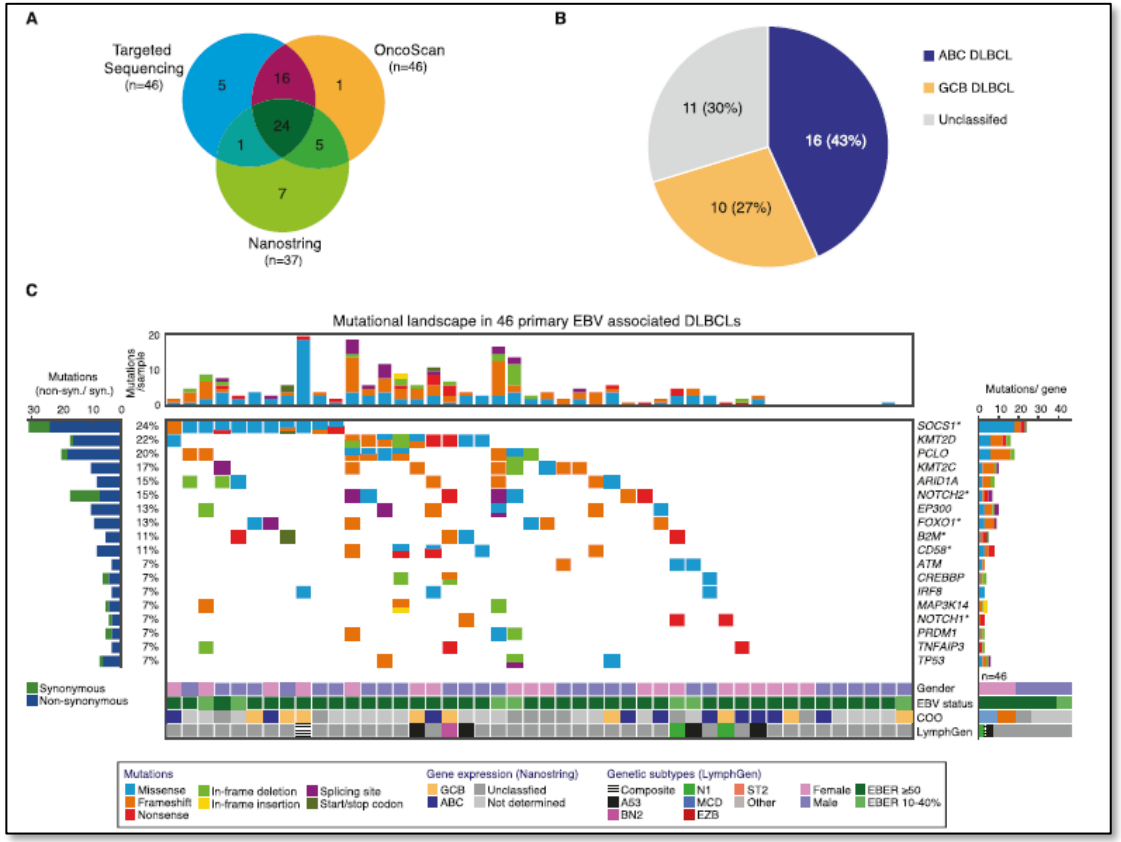
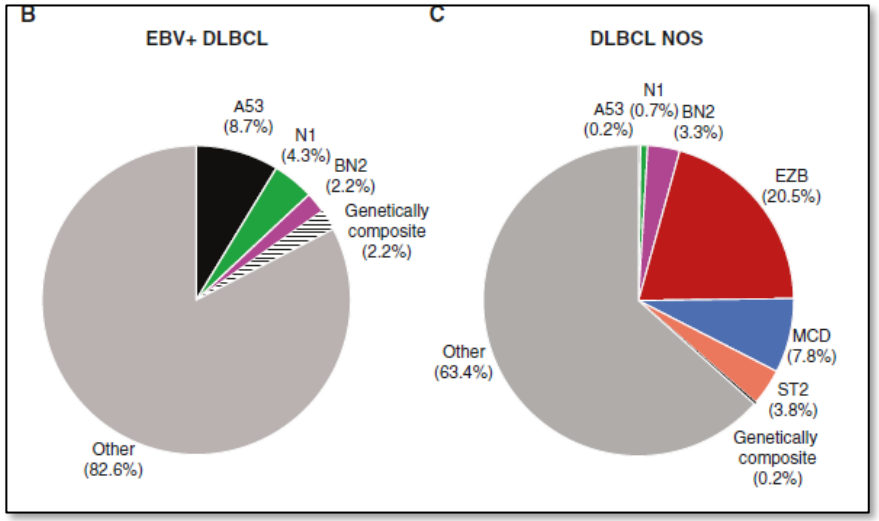
Latency I?

ABC>>GCB
(LMP1 → ↓BCL6 ↑MUM1/IRF4)

LymphGen classifier 2.0: >>"unclassifiable"
Recurrent mutations: *JAK-STAT and NOTCH*
Frequent 9p24.1 (PD-L1) amplification

Frontzek F et al Leukemia 2023
Ross AM et al Life 2023





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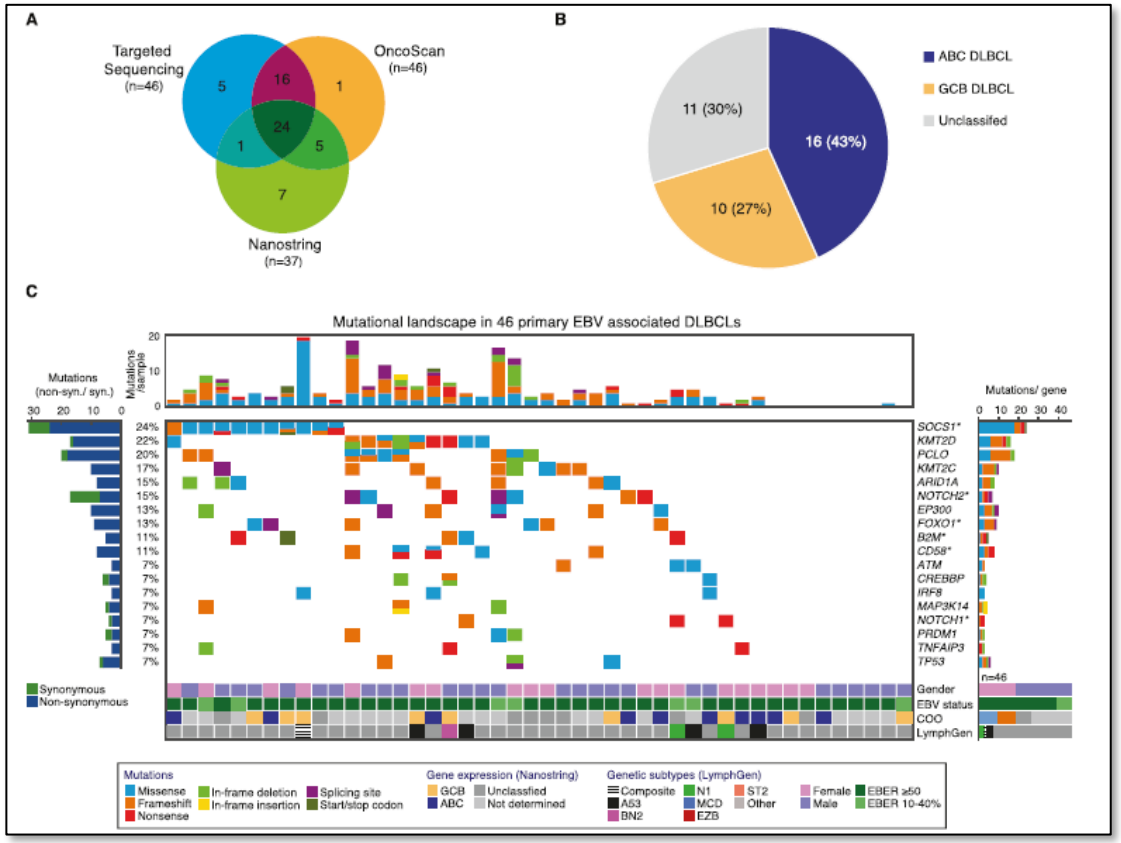


EBV+ DLBCL show a low mutational burden

Since EBV genes contribute to cellular transformation, lymphoma shows less dependency on genetic events

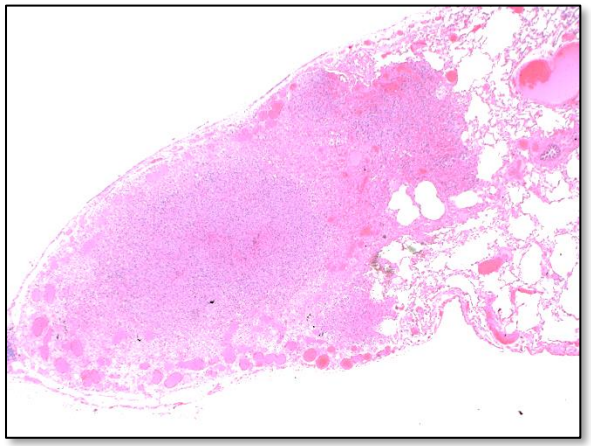
Frontzek F et al Leukemia 2023
Ross AM et al Life 2023
Gebauer N et al Blood Cancer 2021

EBV-positive lymphomas (main subtypes)

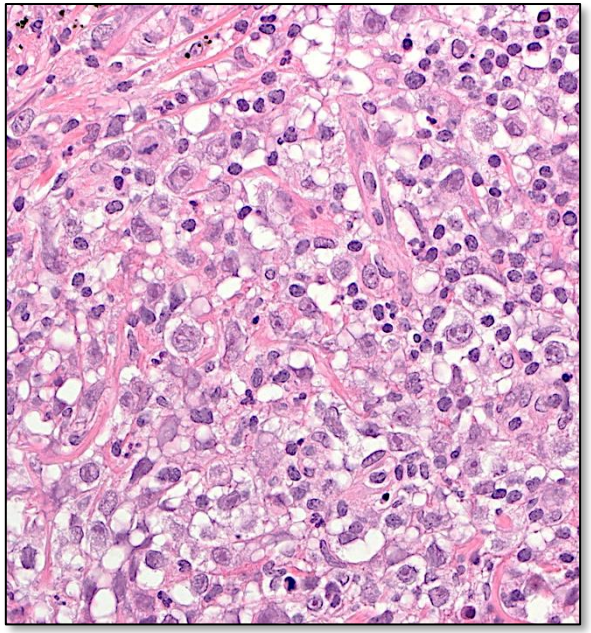
Aggressive B-cell lymphomas

WHO 2016	WHO 2022 5th	ICC 2022	EBV+	Lat
Lymphomatoid granulomatosis	**Lymphomatoid granulomatosis**	**Lymphomatoid granulomatosis**	**100%**	**III**

- Angiocentric and angiodistructive (with necrosis)
- Lung 100%; SNC, GI, cute, rene
- Immunocompetent subject
- Demonstrated altered cytotoxic T CD8+ response

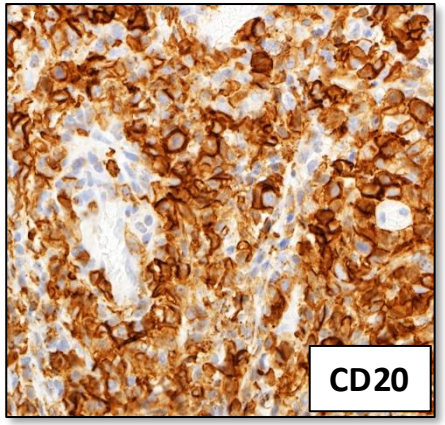


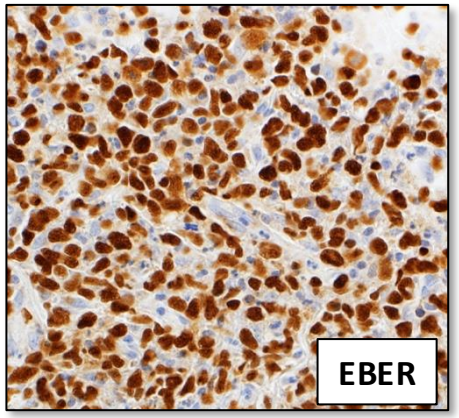
From Prof Fabio Facchetti Archive

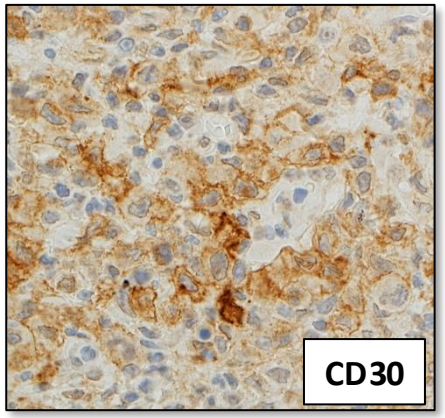


Large cells density/ atypia/necrosis

LyG grade 1
LyG grade 2
LyG grade 3 = EBV+DLBCL



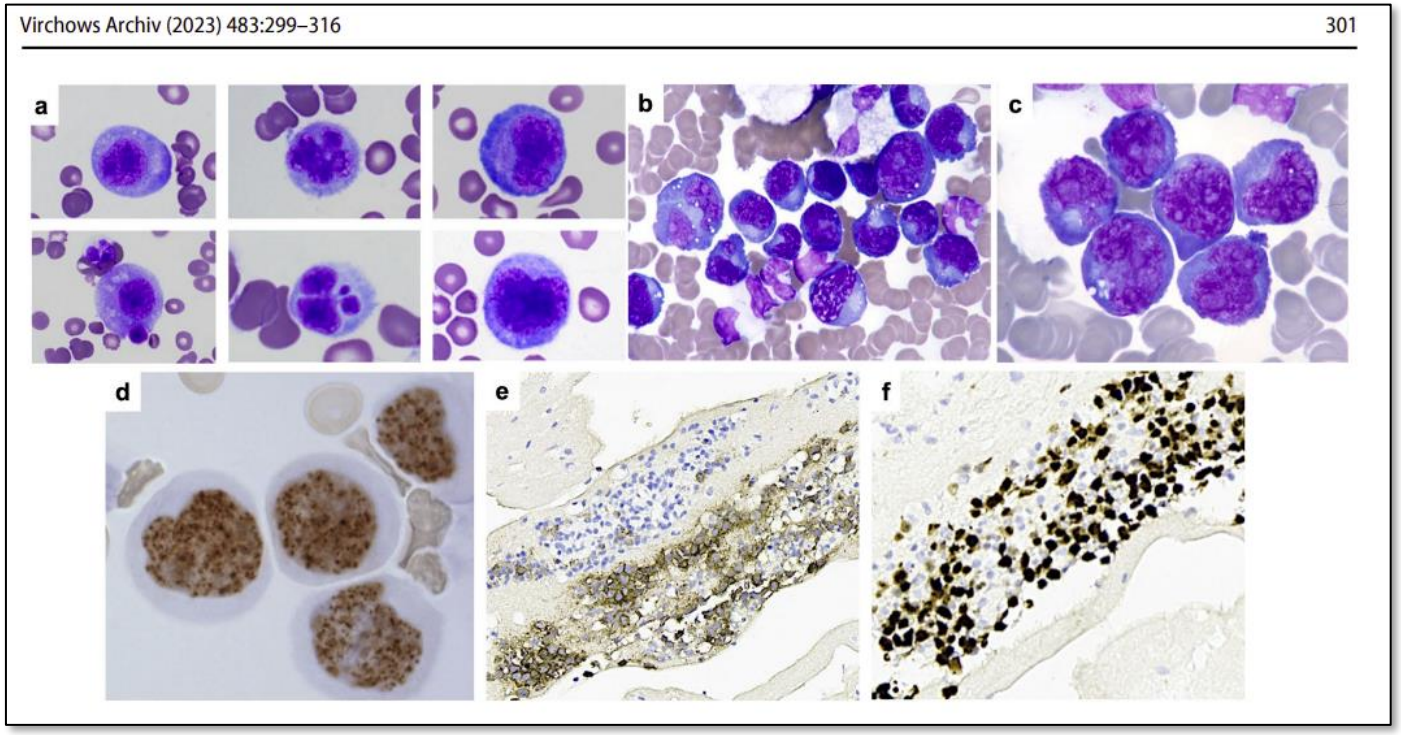




EBV-positive lymphomas (main subtypes)

Aggressive B-cell lymphomas

WHO 2016	WHO 2022 5th	ICC 2022	EBV+	Lat
Primary Effusion Lymphoma	Primary Effusion Lymphoma	Primary Effusion Lymphoma	≈ 100%	I



- **Cavitary and extracavitary**
- **HHV8+**
- Plasmablastic morphology

- **Defective B-cell phenotype & plasma diff**

  +: CD38, CD138, EMA, MUM1
  -: PAX5, CD19, CD20, CD79a

  aberrant T-cell markers
  CD3, CD5…

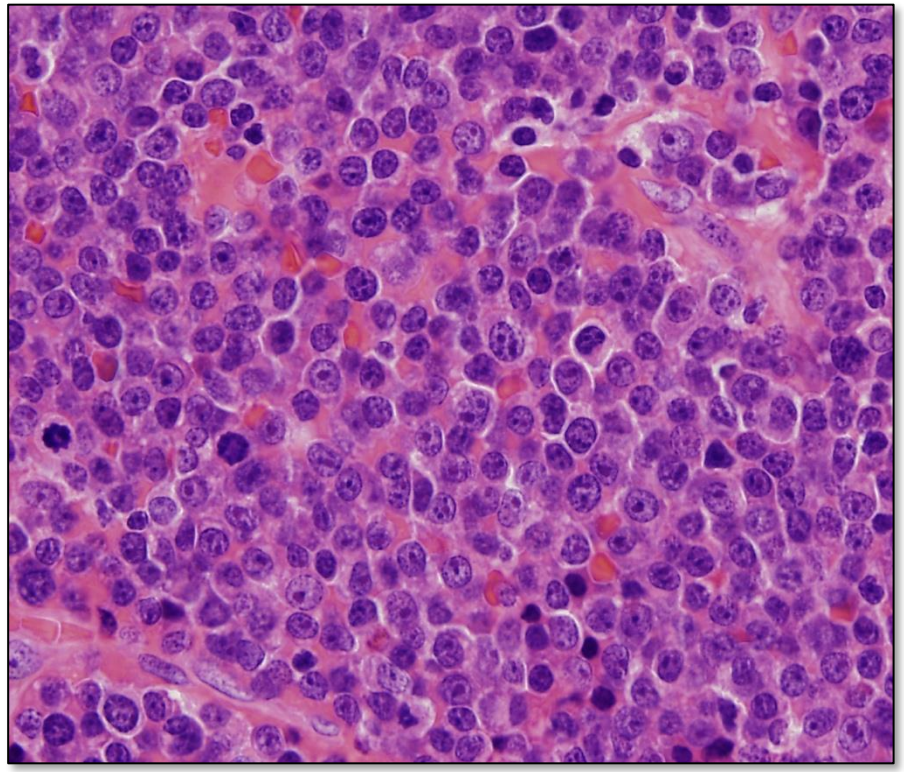
- **Gene expression profile ≈ Plasmablastic Lymphoma**

Di Napoli A et al Virkows Archiv 2023

EBV-positive lymphomas (main subtypes)

Aggressive B-cell lymphomas

WHO 2016	WHO 2022 5th	ICC 2022	EBV+	Lat
Plasmablastic lymphoma	**Plasmablastic lymphoma**	**Plasmablastic lymphoma**	**70-80%**	**I/II**



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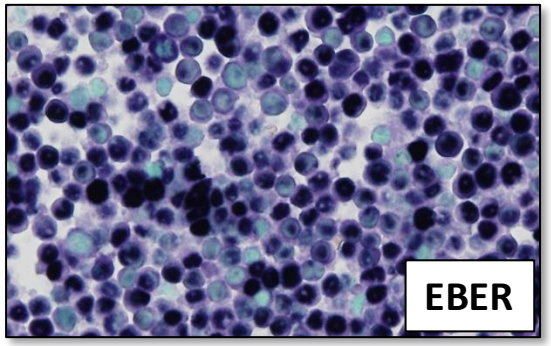

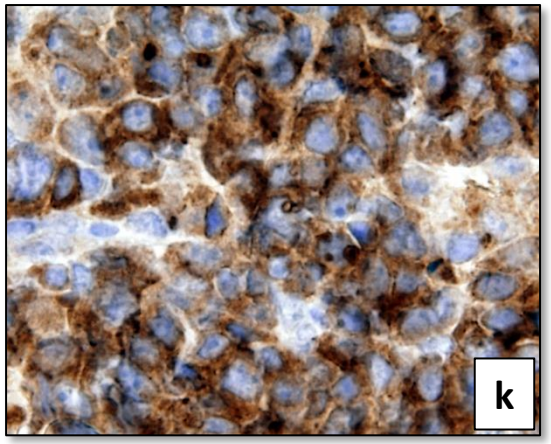

- **Associated with immune disregulation or deficit**
- >> **extranodal** (oral cavity, GI, skin)
- CD20- PAX5-
- CD138/CD38+/- MUM1+
- MYC+++
- **>MYC::IGH**
- Descritto **programma di EBV latenza non canonico**: Lat II + litico abortivo *(Ambrosio MR et al 2017)*
- **≠ mutational landscape**
  - EBV+ PBL (JAK-STAT) and
  - EBV- PBL (TP53; CARD11;MYC)

EBV-positive lymphomas (main subtypes)

Aggressive B-cell lymphomas

WHO 2016	WHO 2022 5th	ICC 2022	EBV+	Lat
DLBCL associated with chronic inflammation (^)	**DLBCL associated with chronic inflammation**	**DLBCL associated with chronic inflammation**	**100%**	**III**
(included in ^)	**Fibrin-associated LBCL**	**Fibrin-associated DLBCL**	**100%**	**III**
(absent)	**Fluid overload-associated LBCL**	(HHV8 and EBV-negative PEL)	**WHO 13-30%**	**?**

Modificato da Ross AM et al. Life 2023

EBV-positive lymphomas (main subtypes)

Aggressive B-cell lymphomas

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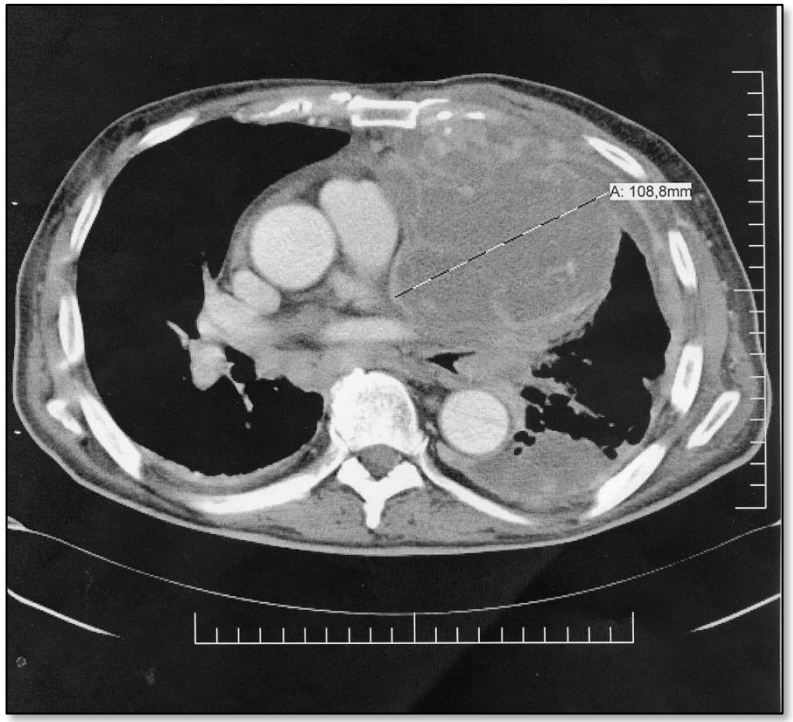
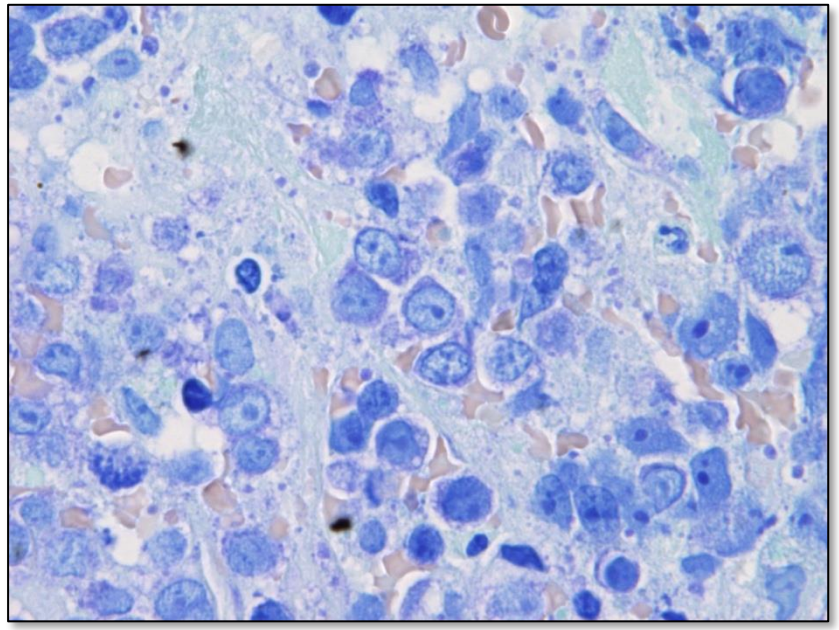
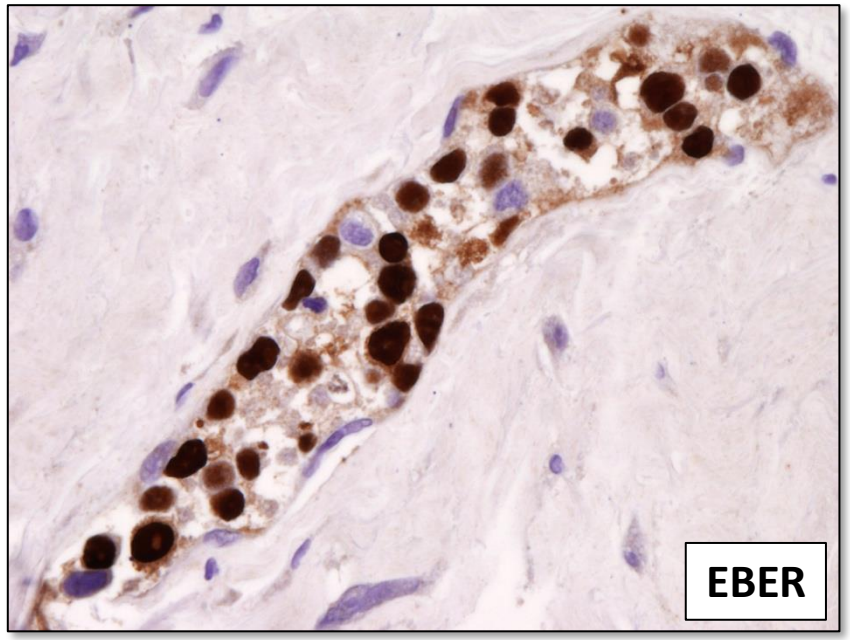
DLBCL associated with chronic inflammation (^)	DLBCL associated with chronic inflammation	DLBCL associated with chronic inflammation	100%	III

Pyothorax associated lymphoma (PAL)



From Prof Fabio Facchetti's archive

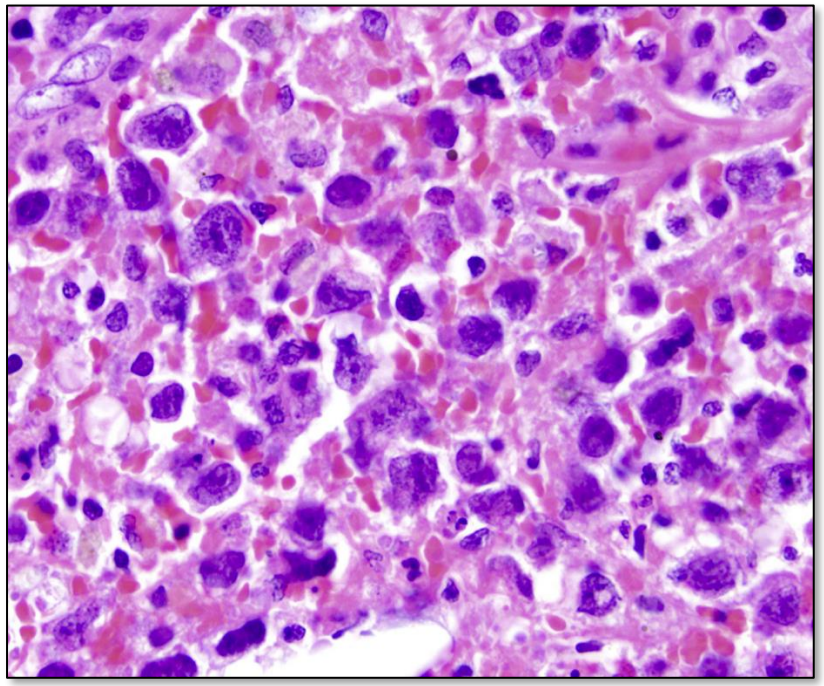




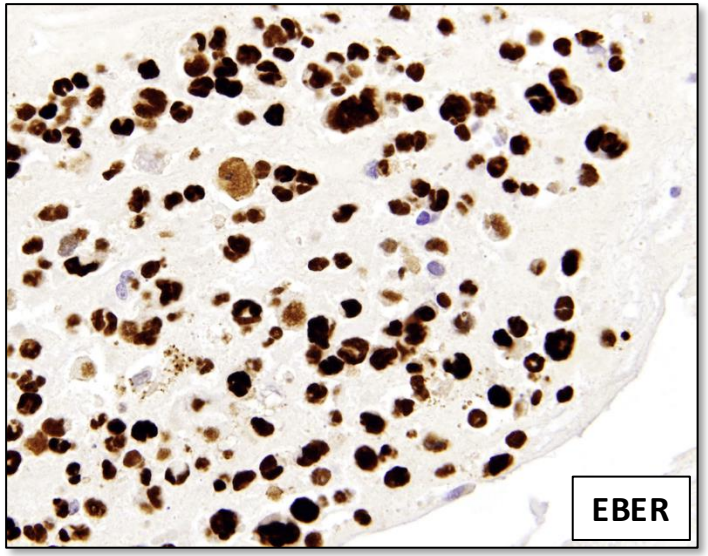
EBV-positive lymphomas (main subtypes)

Aggressive B-cell lymphomas

WHO 2016	WHO 2022 5th	ICC 2022	EBV+	Lat
(included in ^)	Fibrin-associated LBCL	Fibrin-associated DLBCL	100%	III



Fibrin associated (FA)



In sites of chronic fibrin deposition:

- cardiac atrial mixoma/thrombus
- breast implant (≠ BIA-ALCL)
- endovascular grafts
- cysts (adrenal, kidney, etc)
- …

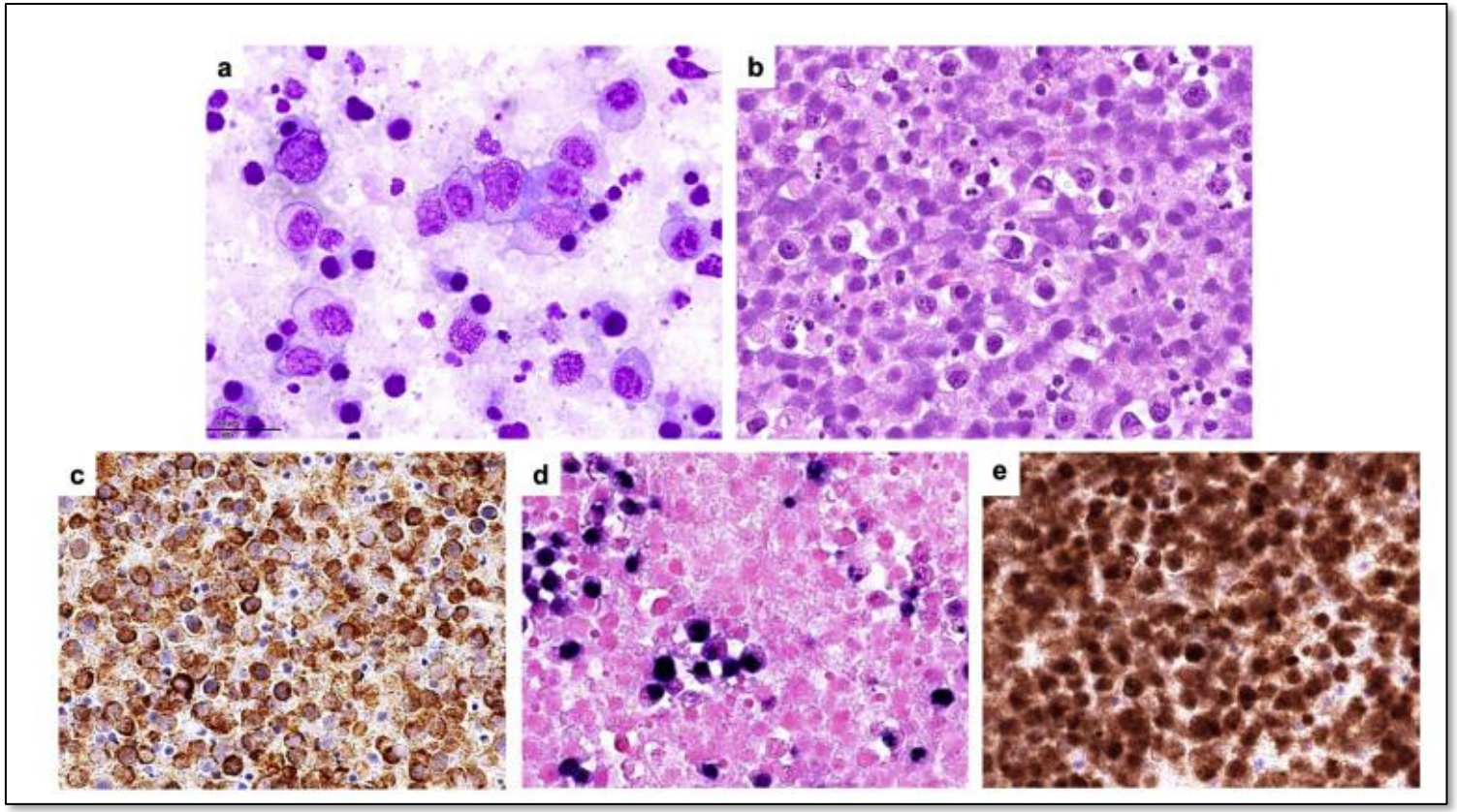
«Local immune-escape»
Sustaining EBV Lat III program

WHO 5th ed. 2022

EBV-positive lymphomas (main subtypes)

Aggressive B-cell lymphomas

WHO 2016	WHO 2022 5th	ICC 2022	EBV+	Lat
(absent)	**Fluid overload-associated LBCL**	(HHV8 and EBV-negative PEL)	**WHO 13-30%**	**?**



Di Napoli A et al Virkows Archiv 2023

Fluid Overload (FO)

- **Chronic effusions (pleural, ascites)**
- >>Asia
- **HHV8 negative!**
- may be associated with con HCV or HBV
- **B-cell phenotype with ABC profile.**

… and more may come

EBV
«Hit and Run hypothesis»

Modern Pathology (2020) 33:2407–2421
https://doi.org/10.1038/s41379-020-0575-3

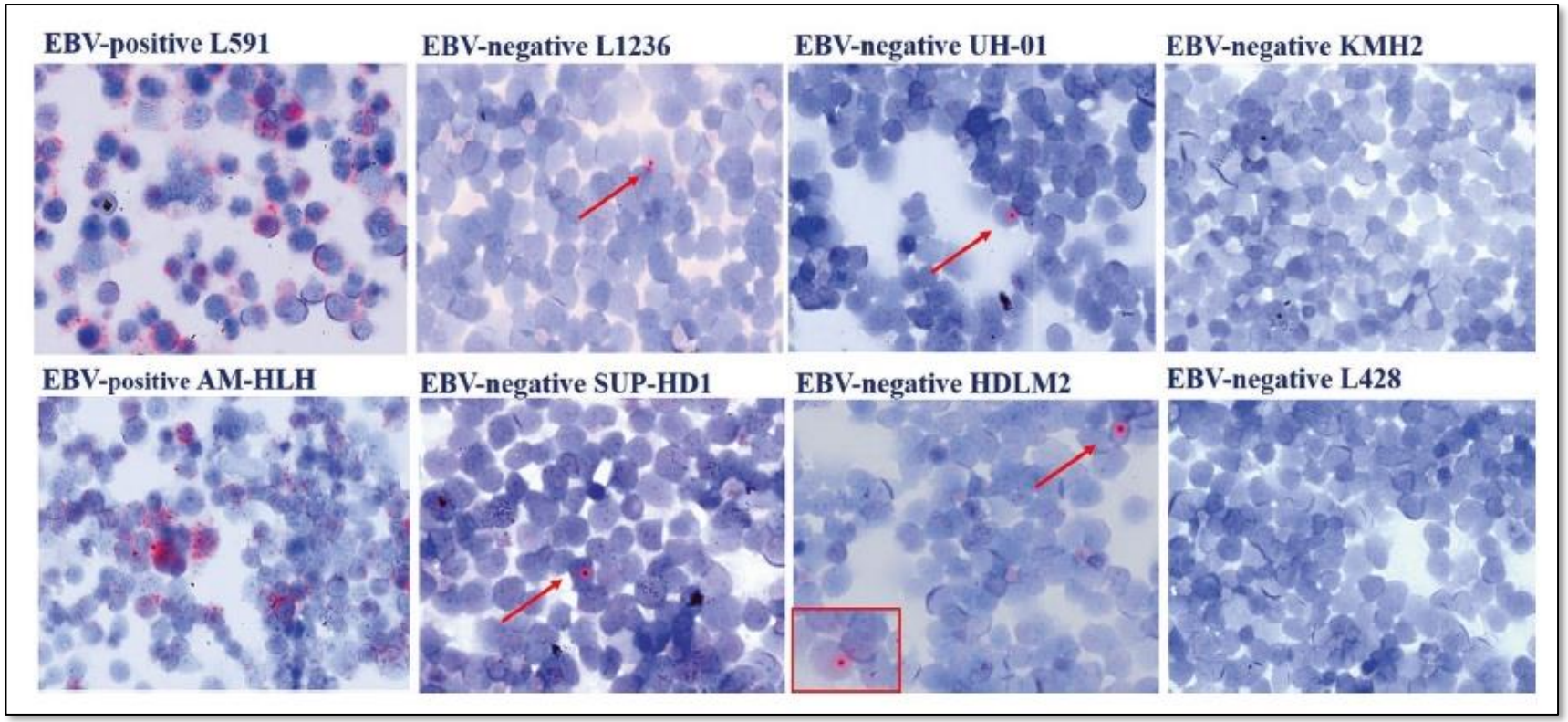
USCAP

ARTICLE

Frequent traces of EBV infection in Hodgkin and non-Hodgkin lymphomas classified as EBV-negative by routine methods: expanding the landscape of EBV-related lymphomas

Lucia Mundo[1] · Leonardo Del Porro[1] · Massimo Granai[1] · Maria Chiara Siciliano[1] · Virginia Mancini[1] ·

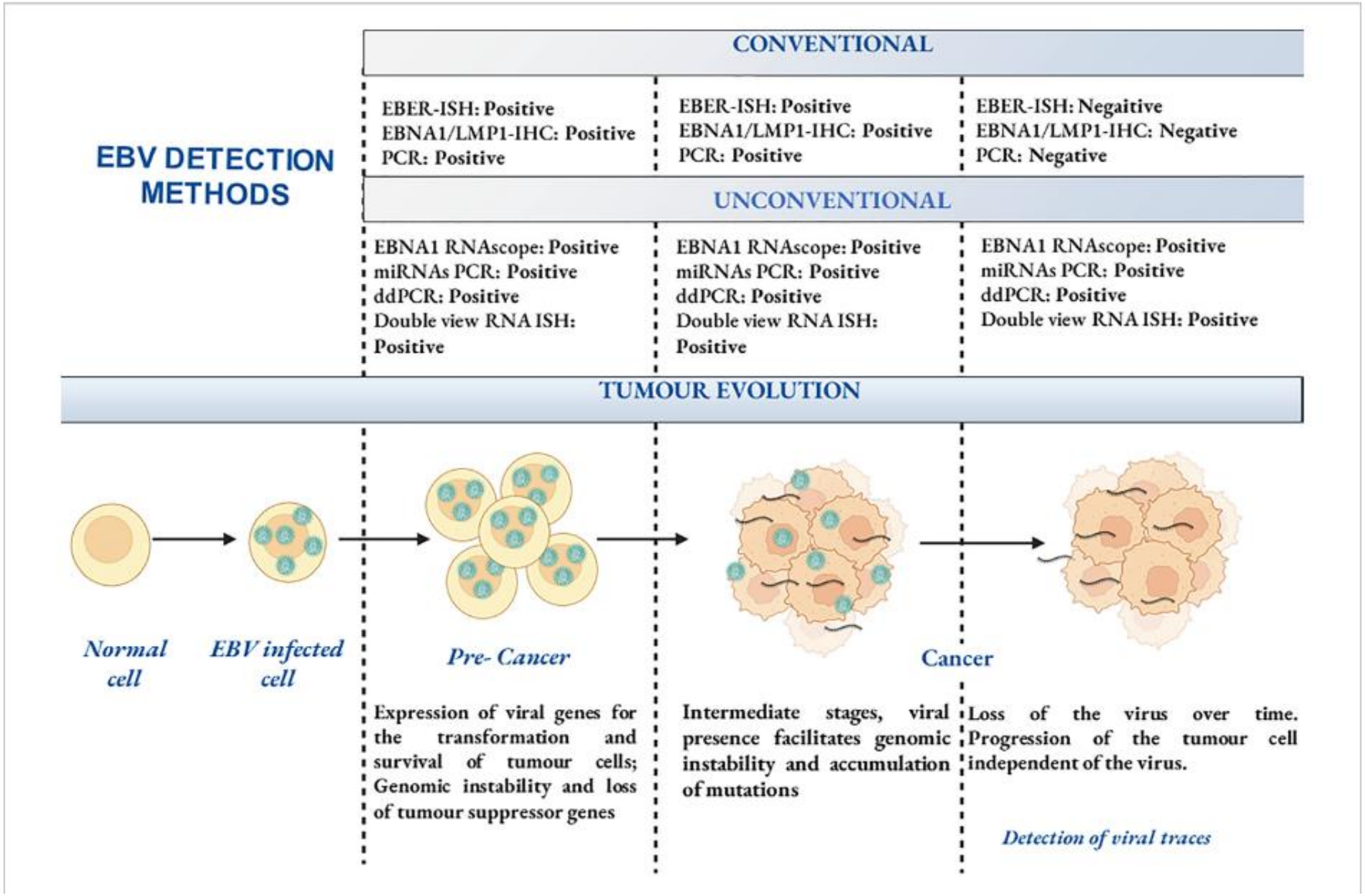
Highly sensitive RNAscope tecnology can identify viral transcript in EBER-negative lymphoma cells



Mangiaterra et al. Frontiers in Immunology 2026

Hit-and-run hypothesis: revisiting the impact of EBV in malignancies

"The "hit-and-run" hypothesis proposes that the oncogenic effects initiated by a virus are later sustained by stable genetic or epigenetic alterations within the host cells, rendering the virus itself no longer essential for tumour maintenance"



Mangiaterra et al. Frontiers in Immunology 2026

Hit-and-run hypothesis: revisiting the impact of EBV in malignancies

TABLE 3 Studies analysing viral traces using non-conventional methods.

Study group	Lymphoma types	Non-conventional methods	% of EBV-trace positive cases among EBV-negative samples by conventional methods
Mundo L. et al (61),	Burkitt lymphoma	miRNAs expression profile	100%
Mundo L. et al (56),	Burkitt lymphoma	qPCR/ddPCR/RNAscope	67%
	Classic Hodgkin lymphoma	qPCR/ddPCR/RNAscope	50%
	Diffuse large B-cell lymphoma (DLBCL)	qPCR/ddPCR/RNAscope	37%
Siciliano M.C. et al (63),	Gastric adenocarcinoma (ADK)	ddPCR/RNAscope	31%/15%
	Gastric cancer with lymphoid stroma (GCLS)	ddPCR/RNAscope	86%/43%
Mangiaterra T. et al (51),	DLBCL	Double viewRNA ISH	26%

Characteristics of cancer types, non-conventional detection techniques employed, and the percentage of cases showing the expression of viral traces among those classified as negative by conventional methods.

EXPERT REVIEW OF HEMATOLOGY
https://doi.org/10.1080/17474086.2026.2655963

REVIEW

The molecular pathogenesis of Epstein–Barr virus-associated B-cell lymphoproliferative disorders: a scoping review

Johanna Vets[a], Xenia Haest[a] and Thomas Tousseyn[a,b]

April 2026

Dissecting EBV pathogenesis without the immune context risks flattering a three dimensional biological problem into a two-dimensional proxy

Article highlights

- EBV latent genes substitute for driver mutations in EBV-negative LPDs, resulting in a distinct molecular profile between EBV-positive lymphomas and their EBV-negative counterpart lymphoma.
- Understanding differences in pathogenesis, the molecular background and the role of EBV as an oncogenic virus in these entities might contribute to diagnostic and therapeutic strategies.
- The role of 9p24.1 amplification, causing PD-L1 overexpression, seems to be different between immunocompetent and immune compromised patients. EBV can also induce PD-L1 upregulation.
- Immune suppression versus immune escape by PD-L1 overexpression is one of the most important differences between the various EBV-positive LPDs.
- NF-kB signaling, JAK-STAT signaling and NOTCH signaling Are the most affected signaling pathways being affected and might be important targets in EBV-positive DLBCL therapy.
- More genetic data are necessary to define the border between entities that are malignant, and entities on the border of malignancy, needing less intensive therapy.

Conclusions

- **EBV mediates B lymphomagenesis by**
  - direct effect of viral proteins on host cell survival and proliferation
  - Indirect effect on microenvironment inducing «immune evasion»
  - Inducing transformation «hit» and «run away» (?)

- **Definition of EBV Latency program** in EBV+ B-cell lymphoproliferations can
  - support lymphoma diagnosis
  - identify «likely to be» (local or systemic?) immunedeficiency related diseases

- **Old and new pathological markers can be of support**
  - EBV-detection and latency program definition
  - PDL1 expression
  - Genetic profiling of EBV+ LPD (NGS – OGM - Methilation profile
  - **mutidisciplinary interaction is desirable**