

Epstein Barr Virus and Upper Aerodigestive Tract Lymphomagenesis

Rita Shaknovich M.D./Ph.D.

Montefiore Medical Center, Bronx, NY

List of References:

1. Harris NL, Swerdlow SH, Frizzera G, Knowles DM. Post-transplant lymphoproliferative disorders. Lyon: IARC press; 2001.
2. Rickinson A, Kieff E. Epstein-Barr virus. In: Fields BN, Knipe PM, Howley PM, et al., editors. Fields Virology. Philadelphia: Lippincott-Raven; 1996. p. 2397-447.
3. Capello D, Cerri M, Muti G, Berra E, Oreste P, Deambrogi C, et al. Molecular histogenesis of posttransplantation lymphoproliferative disorders. *Blood*. 2003;102:3775-85.
4. Knowles DM, Cesarman E, Chadburn A, Frizzera G, Chen J, Rose EA, et al. Correlative morphologic and molecular genetic analysis demonstrates three distinct categories of posttransplantation lymphoproliferative disorders. *Blood*. 1995;85:552-65.
5. Kuppers R. B cells under influence: transformation of B cells by Epstein-Barr virus. *Nat Rev Immunol*. 2003;3:801-12.
6. Thorley-Lawson DA. Epstein-Barr virus: exploiting the immune system. *Nat Rev Immunol*. 2001;1:75-82.
7. Kilger E, Kieser A, Baumann M, Hammerschmidt W. Epstein-Barr virus-mediated B-cell proliferation is dependent upon latent membrane protein 1, which simulates an activated CD40 receptor. *Embo J*. 1998;17:1700-9.
8. Gires O, Zimber-Strobl U, Gonnella R, Ueffing M, Marschall G, Zeidler R, et al. Latent membrane protein 1 of Epstein-Barr virus mimics a constitutively active receptor molecule. *Embo J*. 1997;16:6131-40.
9. Babcock GJ, Hochberg D, Thorley-Lawson AD. The expression pattern of Epstein-Barr virus latent genes in vivo is dependent upon the differentiation stage of the infected B cell. *Immunity*. 2000;13:497-506.
10. Babcock GJ, Thorley-Lawson DA. Tonsillar memory B cells, latently infected with Epstein-Barr virus, express the restricted pattern of latent genes previously found only in Epstein-Barr virus-associated tumors. *Proc Natl Acad Sci U S A*. 2000;97:12250-5.
11. Thorley-Lawson DA, Babcock GJ. A model for persistent infection with Epstein-Barr virus: the stealth virus of human B cells. *Life Sci*. 1999;65:1433-53.
12. Laichalk LL, Thorley-Lawson DA. Terminal differentiation into plasma cells initiates the replicative cycle of Epstein-Barr virus in vivo. *J Virol*. 2005;79:1296-307.
13. Laichalk LL, Hochberg D, Babcock GJ, Freeman RB, Thorley-Lawson DA. The dispersal of mucosal memory B cells: evidence from persistent EBV infection. *Immunity*. 2002;16:745-54.
14. Timms JM, Bell A, Flavell JR, Murray PG, Rickinson AB, Traverse-Glehen A, et al. Target cells of Epstein-Barr-virus (EBV)-positive post-transplant lymphoproliferative disease: similarities to EBV-positive Hodgkin's lymphoma. *Lancet*. 2003;361:217-23.
15. Brauning A, Spieker T, Mottok A, Baur AS, Kuppers R, Hansmann ML. Epstein-Barr virus (EBV)-positive lymphoproliferations in post-transplant patients show

immunoglobulin V gene mutation patterns suggesting interference of EBV with normal B cell differentiation processes. *Eur J Immunol.* 2003;33:1593-602.

16. Chadburn A, Chen JM, Hsu DT, Frizzera G, Cesarman E, Garrett TJ, et al. The morphologic and molecular genetic categories of posttransplantation lymphoproliferative disorders are clinically relevant. *Cancer.* 1998;82:1978-87.

17. Shaknovich R, Celestine A, Yang L, Cattoretti G. Novel relational database for tissue microarray analysis. *Arch Pathol Lab Med.* 2003;127:492-4.

18. Cattoretti G, Angelin-Duclos C, Shaknovich R, Zhou H, Wang D, Alobeid B. PRDM1/ BLIMP1 is expressed in human B-lymphocytes committed to plasma cell lineage. *J Pathol.* 2005.

19. Sioutos N, Bagg A, Michaud GY, Irving SG, Hartmann DP, Siragy H, et al. Polymerase chain reaction versus Southern blot hybridization. Detection of immunoglobulin heavy-chain gene rearrangements. *Diagn Mol Pathol.* 1995;4:8-13.

20. Kempkes B, Pawlita M, Zimmer-Strobl U, Eissner G, Laux G, Bornkamm GW. Epstein-Barr virus nuclear antigen 2-estrogen receptor fusion proteins transactivate viral and cellular genes and interact with RBP-J kappa in a conditional fashion. *Virology.* 1995;214:675-9.

21. Basso K, Klein U, Niu H, Stolovitzky GA, Tu Y, Califano A, et al. Tracking CD40 Signaling during Germinal Center Development. *Blood.* 2004.

22. Cahir-McFarland ED, Carter K, Rosenwald A, Giltneane JM, Henrickson SE, Staudt LM, et al. Role of NF-kappaB in Cell Survival and Transcription of Latent Membrane Protein 1-Expressing or Epstein-Barr Virus Latency III-Infected Cells. *J Virol.* 2004;78:4108-19.

23. Kieff E. Epstein-Barr Virus and its replication. In: Fields BN, Knipe PM, Howley PM, et al, editors. *Fields Virology.* Philadelphia: Lippincott-Raven; 1996. p. 2343-96.

24. Niedobitek G, Agathangelou A, Herbst H, Whitehead L, Wright DH, Young LS. Epstein-Barr virus (EBV) infection in infectious mononucleosis: virus latency, replication and phenotype of EBV-infected cells. *J Pathol.* 1997;182:151-9.

25. Kieser A, Kilger E, Gires O, Ueffing M, Kolch W, Hammerschmidt W. Epstein-Barr virus latent membrane protein-1 triggers AP-1 activity via the c-Jun N-terminal kinase cascade. *Embo J.* 1997;16:6478-85.

26. Barth TF, Martin-Subero JI, Joos S, Menz CK, Hasel C, Mechttersheimer G, et al. Gains of 2p involving the REL locus correlate with nuclear c-Rel protein accumulation in neoplastic cells of classical Hodgkin lymphoma. *Blood.* 2003;101:3681-6.

27. Savage KJ, Monti S, Kutok JL, Cattoretti G, Neuberg D, De Leval L, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. *Blood.* 2003;102:3871-9.

28. Pokrovskaja K, Ehlin-Henriksson B, Kiss C, Challa A, Gordon J, Gogolak P, et al. CD40 ligation downregulates EBNA-2 and LMP-1 expression in EBV-transformed lymphoblastoid cell lines. *Int J Cancer.* 2002;99:705-12.

29. Adler B, Schaadt E, Kempkes B, Zimmer-Strobl U, Baier B, Bornkamm GW. Control of Epstein-Barr virus reactivation by activated CD40 and viral latent membrane protein 1. *Proc Natl Acad Sci U S A.* 2002;99:437-42.

30. Mathas S, Hinz M, Anagnostopoulos I, Krappmann D, Lietz A, Jundt F, et al. Aberrantly expressed c-Jun and JunB are a hallmark of Hodgkin lymphoma cells, stimulate proliferation and synergize with NF-kappa B. *Embo J*. 2002;21:4104-13.
31. Gregory CD, Rowe M, Rickinson AB. Different Epstein-Barr virus-B cell interactions in phenotypically distinct clones of a Burkitt's lymphoma cell line. *J Gen Virol*. 1990;71 (Pt 7):1481-95.
32. Kurth J, Spieker T, Wustrow J, Strickler GJ, Hansmann LM, Rajewsky K, et al. EBV-infected B cells in infectious mononucleosis: viral strategies for spreading in the B cell compartment and establishing latency. *Immunity*. 2000;13:485-95.
33. Pelengaris S, Khan M, Evan G. c-myc: more than just a matter of life and death. *Nat Rev Cancer*. 2002;2:764-76.
34. Grumont RJ, Strasser A, Gerondakis S. B cell growth is controlled by phosphatidylinositol 3-kinase-dependent induction of Rel/NF-kappaB regulated c-myc transcription. *Mol Cell*. 2002;10:1283-94.
- Jaffe ES. Lymphoid lesions of the head and neck: a model of lymphocyte homing and lymphomagenesis. *Mod Pathol*. 2002;15(3):255-63. Review.
35. Thorley-Lawson DA, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. *N Engl J Med*. 2004 Mar 25;350(13):1328-37. Review.
36. Shakhovich R, Basso K, Bhagat G, Mansukhani M, Hatzivassiliou G, VVV Murty, Buettner M, Niedobitek G, Alobeid B, Cattoretti G. Identification of rare Epstein-Barr virus infected memory B cells and plasma cells in non-monomorphic post-transplant lymphoproliferative disorders and the signature of viral signaling. *Haematologica*. 2006 Oct;91(10):1313-20.

Epstein Barr Virus and Upper Aerodigestive Tract Lymphomagenesis.

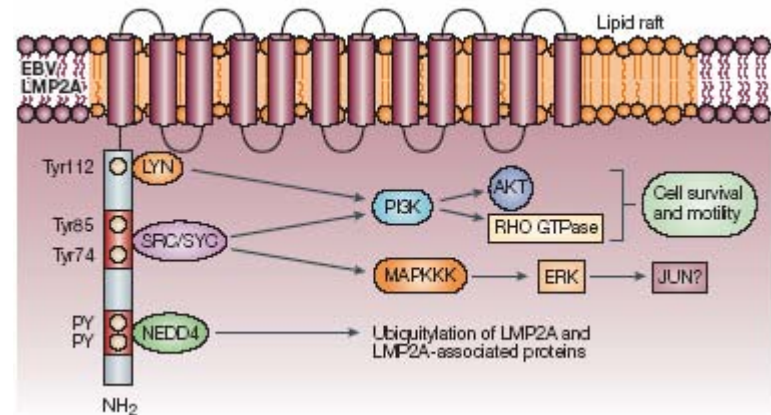
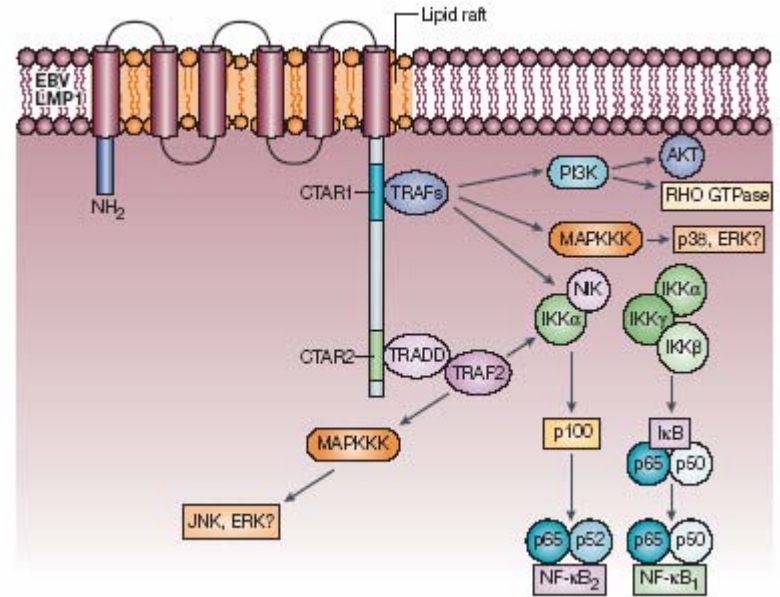
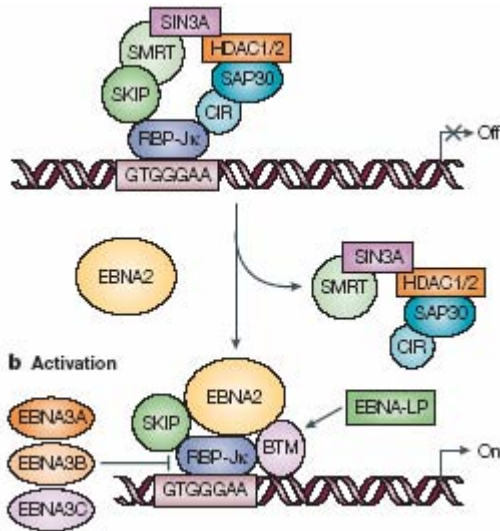
Rita Shaknovich, M.D./Ph.D.

Assistant Professor

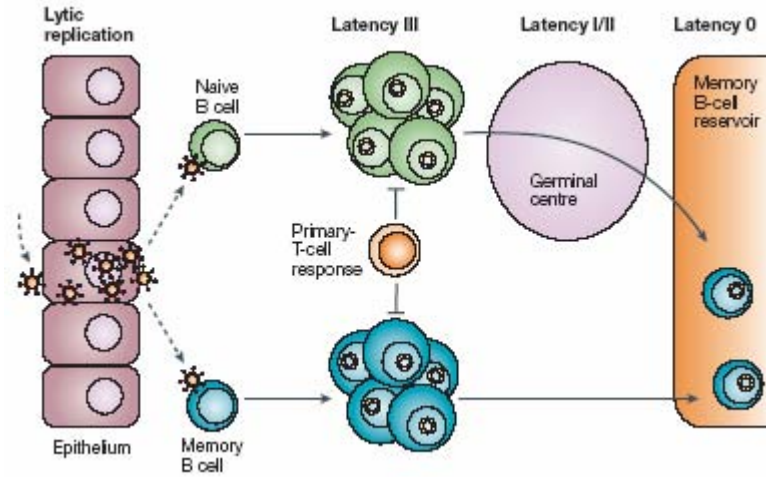
Albert Einstein College of Medicine

Montefiore Medical Center

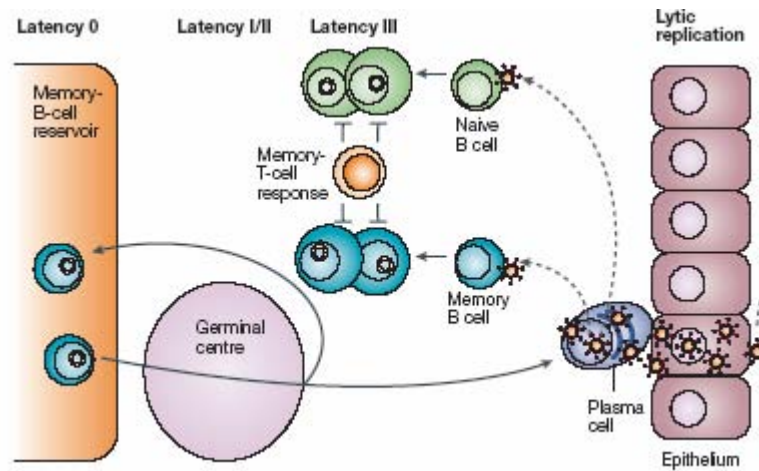
Biology of viral infection



Primary Infection

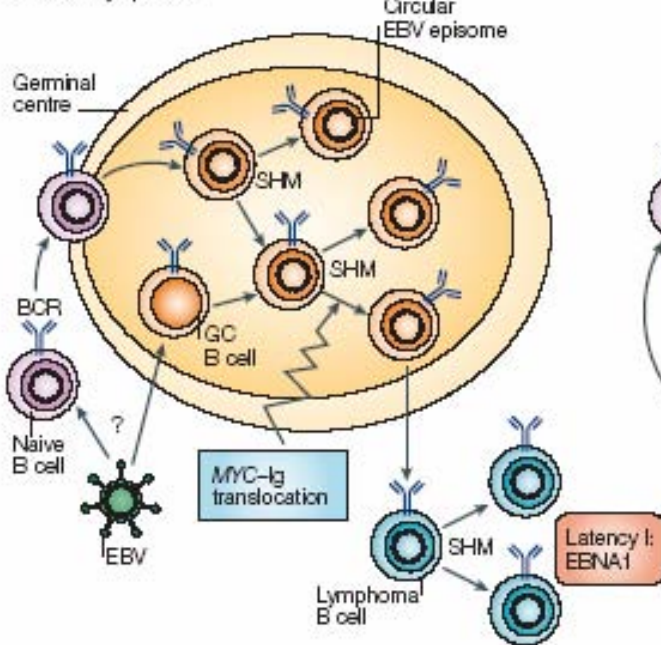


Persistent Infection

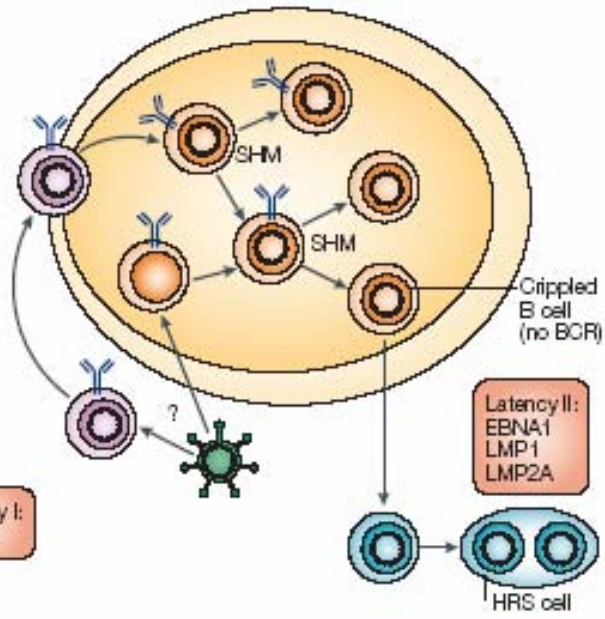


Lymphoma	% EBV +	EBV latency	Immuno-phenotype	V gene mutations	Cell of origin
Burkitt Lymphoma	95-100% (endemic) 20-30% (sporadic)	I	CD20+ CD79a+BCL6+ CD10+ CD77+ slg+	Mutated V genes Ongoing SHM	Centroblast
C Hodgkin Lymphoma	40% (West) 90% (Central America)	II	Loss of B cell Phenotype slg-	Mutated V genes Ongoing SHM	Pre-qpoptotic GC B cell
Post-transplant LPD	80% (diminishes with time)	III (mixture of latencies)	CD20+ CD79a+ BCL6- CD10+/- slg+/-	Mostly mutated V genes, mixed SHM	Variable stages of B cells
AILT	40-90%	0 (EBER+)	CD3+ CD4+ CD8- CD10+	TCR rerarranged	Infected B cell and expansion of helperT cells
NK/T, nasal	most	EBER+	cyCD3, CD56+	No TCR rerarrangement	NK/T cells
AIDS-associated B-cell lymphoma	30-50% BL	I	CD79a+BCL6+ CD10+ CD77+ slg+	Mutated V genes Ongoing SHM	GC
	100% PEL	I	CD20- CD138+	Mutated V genes	Post-GC cells
	90% DLBCL-IB	III	CD20+ CD138+/-	Mutated V genes, no ongoing SHM	GC or post-GC
LYG	most	EBER+	CD20+ CD79a+		Post GC B cell

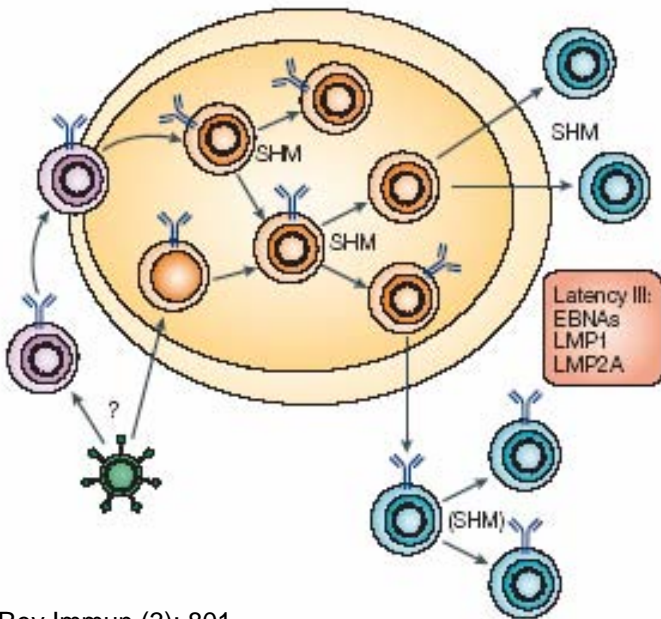
a Burkitt lymphoma



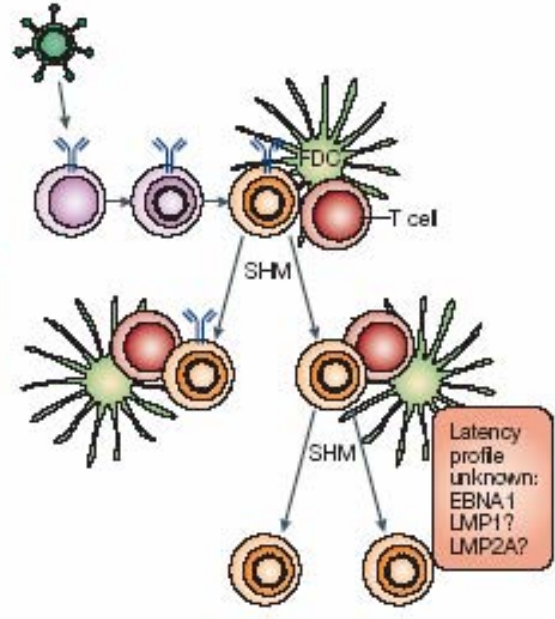
b Hodgkin lymphoma



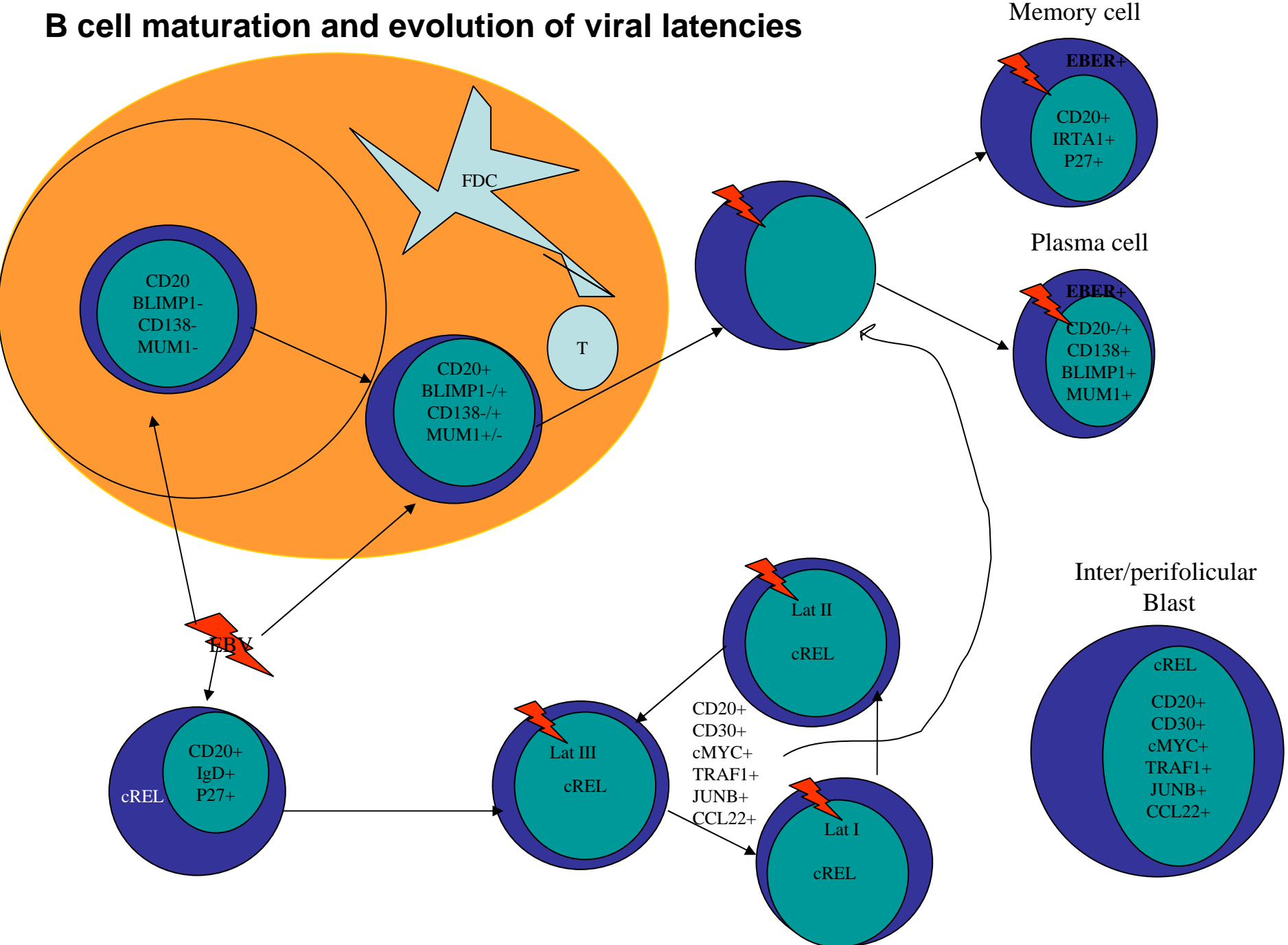
c Post-transplant lymphomas

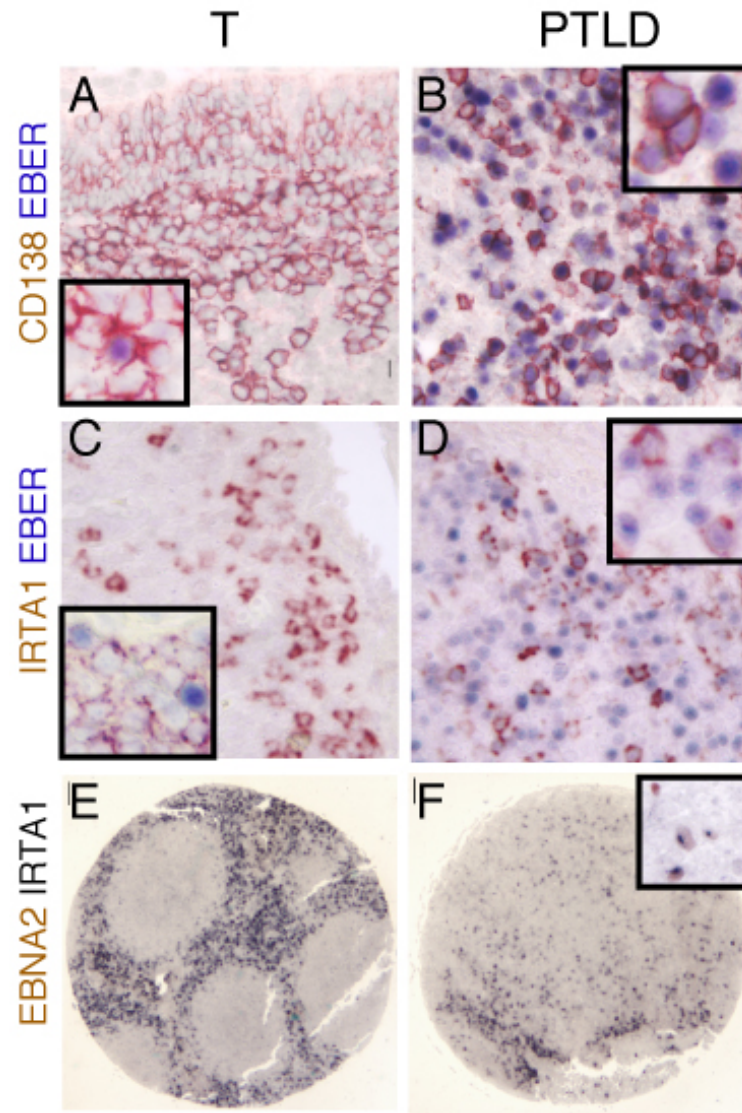


d EBV-infected B cells in ALLD



B cell maturation and evolution of viral latencies





Terminally differentiated EBV-infected plasma cells and memory B cells in Reactive tonsils (T) and in PTLD (Shaknovich et al Haematologica (2006) 91(10):1313)