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Epstein–Barr virus oncoprotein–driven B cell metabolism remodeling

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The γ-herpesvirus Epstein–Barr virus (EBV) persistently infects >95% of adults worldwide and contributes to 200,000 cancers annually [1]. EBV uses latency programs to convert metabolically quiescent B lymphocytes into blasts that enter germinal centers and differentiate into memory B cells, the reservoir for lifelong infection. Over the first 3 days of infection, EBV expresses the pre-proliferation program, where particularly high levels of Epstein–Barr nuclear antigen 2 (EBNA2) and its key host target MYC induce metabolism pathways needed for B cell remodeling and proliferation (**Fig 1**) [1–4]. Over this period, infected cells quadruple in volume in preparation for hyperproliferation [2,5], reminiscent of remodeling that fuels germinal center centroblasts [6]. The EBV latency IIb program, comprised of 6 EBNAs and noncoding RNA (ncRNA), then supports hyperproliferation between days 4 and 7 postinfection in cell culture (**Fig 1**). Subsequently, cells convert to lymphoblastoid physiology, where 6 EBNAs and 2 latent membrane proteins (LMPs) further remodel host metabolism [7,8]. If left unchecked by immune surveillance, latency III causes outgrowth of lymphoblastoid cell lines (LCLs) that model posttransplant lymphoproliferative diseases (PTLDs) and central nervous system lymphomas [1] (**Fig 1**). Here, we review key host metabolism pathways subverted by EBV oncoproteins, with a focus on B cell transformation.

Latent EBV induction of aerobic glycolysis

Within 4 days of infection, EBV highly induces glucose uptake and expression of all glycolysis enzymes at the mRNA and protein levels, in particular the first and rate-limiting enzyme hexokinase 2 [2,4,9]. Seahorse assays confirm that EBV increases glycolytic flux [4,9], which generates lower quantities of ATP than oxidative phosphorylation (OXPHOS), but provides key building blocks for anabolic metabolism. EBNA2, the only EBV oncoprotein required for newly infected B cell outgrowth over the first 8 days of in vitro infection [10], is required for glycolytic enzyme induction, likely together with MYC [4,10].

Prior to B cell proliferation, EBV down-regulates thioredoxin-interacting protein (TXNIP), a key negative regulator of the glucose transporter GLUT1 [4,9]. TXNIP is also down-regulated upon lytic reactivation [4,11,12]. GLUT1 plasma membrane abundance is further supported by LMP1, which mimics CD40 to activate NF-κB, MAPK, PI3K/AKT, and interferon regulatory factors [13–16]. Of these, canonical NF-κB and AKT are necessary for GLUT1 up-regulation [13–16]. LMP1 also promotes glycolysis through HIF1α, which it induces through MAPK signaling and by generation of reactive oxygen species [17–19]. LMP1-activated Poly(ADP-ribose) polymerase 1 (PARP1) coactivates HIF1α-dependent gene expression, including via the formation of a complex with PARylated HIF1α at target promoter regions. LMP1-driven
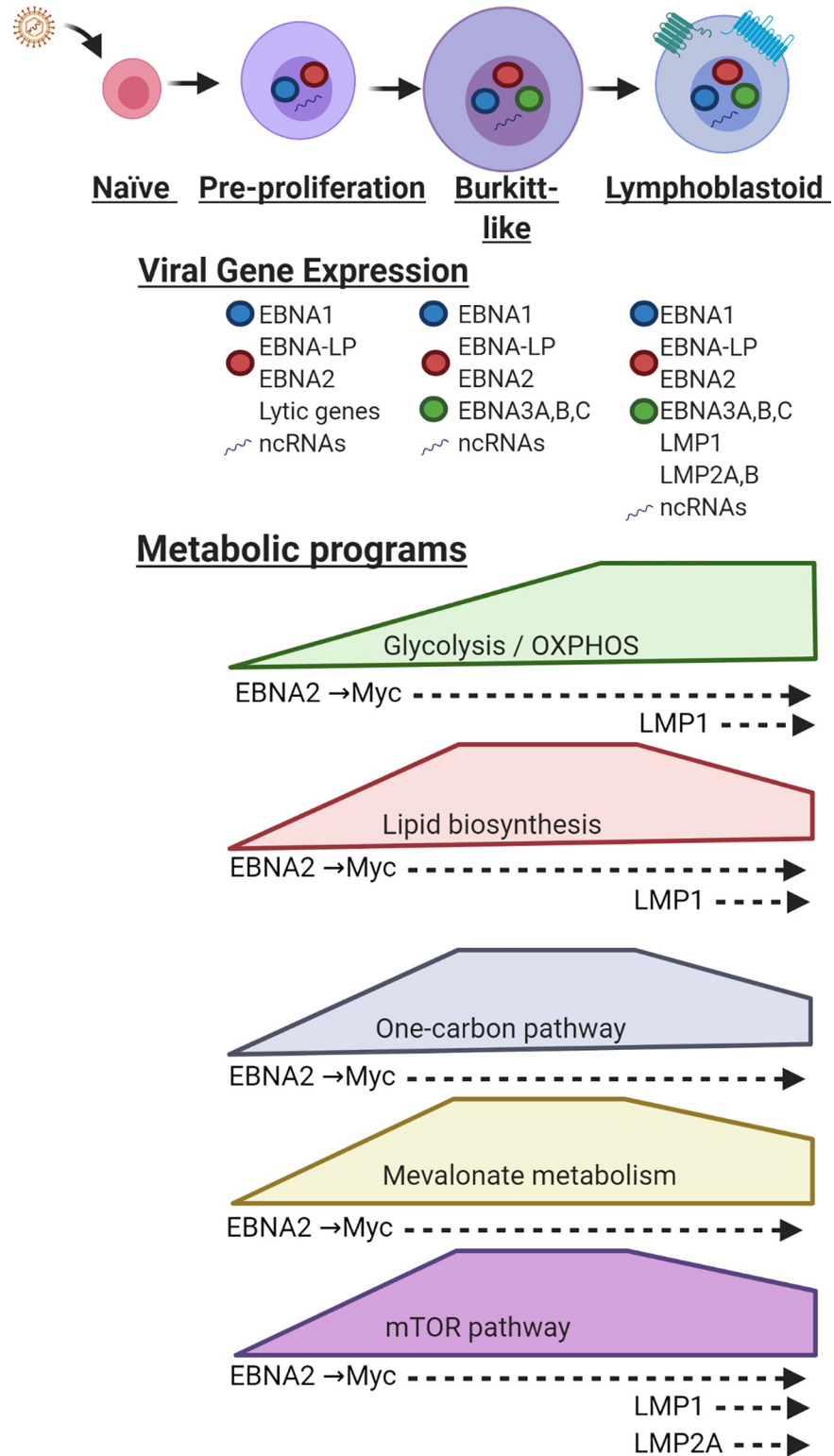
Fig 1. EBV latency oncoprotein–driven B cell metabolism remodeling. Schematic diagram demonstrating changes in key metabolic pathways during EBV-driven B cell transformation into LCLs. Relative cell size and pathway activation states are depicted. EBV factors associated with each phase of transformation are noted. Metabolic programs and EBV oncogenic factors that regulate them are displayed below. EBNA, Epstein–Barr nuclear antigen; EBV, Epstein–Barr virus; LCL, lymphoblastoid cell line; LMP, latent membrane protein; ncRNA, noncoding RNA; OXPHOS, oxidative phosphorylation.

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aerobic glycolysis is also observed in nasopharyngeal carcinoma tumor cells in culture [17–21]. Similarly, in latency III B cells, EBNA-LP and EBNA-3A further prevent HIF1α hydroxylation and degradation via association with prolyl hydroxylases 1 and 2, respectively [22].

Conversion of glucose to pyruvate produces NADH. To maintain redox balance and avoid reductive stress, NAD must be regenerated in cells with high glycolysis flux. This can occur by conversion of pyruvate to lactate or by OXPHOS, each of which oxidizes NADH to NAD, and each of which are important for EBV-mediated B cell transformation. To facilitate lactate release, EBNA2 and LMP1 induce expression of the monocarboxylate transporters MCT1 and MCT4, respectively [23].

EBNA2 and LMP1 induce oxidative phosphorylation

EBV strongly induces OXPHOS upon B cell infection [2,4,9], likely needed in addition to glycolysis to meet ATP demand. EBV-induced OXPHOS also likely serves to maintain cellular NAD/NADH redox balance, to support de novo pyrimidine synthesis at the level of the flavin-dependent enzyme dihydroorotate dehydrogenase (DHODH) and to regenerate ubiquinone/coenzyme Q for redox defense. OXPHOS genes are encoded by the host nuclear genome and therefore accessible to EBNAs and to LMP-activated host transcription factors. OXPHOS remodeling coincides with EBV-driven increases in oxygen consumption rates [4,9]. Underscoring the importance of EBV-driven OXPHOS, chemical inhibition of mitochondrial respiration impairs proliferation of newly EBV-infected primary human B cells [4,9]. Likewise, switching the media sugar source from glucose to galactose, which is metabolized by OXPHOS rather than by glycolysis, slows but does not prevent EBV-driven B cell outgrowth [4,9]. Furthermore, metabolic stress is a barrier to the outgrowth of EBV-infected B cells in vitro, where a population of EBV-infected cells growth arrest exhibit reduced OXPHOS and TCA activity. Anaplerotic supplementation of TCA intermediates restores proliferation in a subset of these arrested cells [9]. Autophagy also serves to manage metabolic stress in EBV-transformed cells [9,15,24].

EBV-driven purine and pyrimidine nucleotide metabolism

Nucleotide synthesis rates are low in resting B lymphocytes, which reside in a Go cell cycle state. Therefore, EBV must rapidly induce purine and pyrimidine biosynthesis for genome replication as well as ribosomal RNAs to support elevated translation rates in newly infected cells [2]. To meet purine and thymidylate demand, EBV induces the mitochondrial one-carbon (1C) pathway, which metabolizes serine into glycine and a carbon unit that can be used for downstream biochemical reactions [4] (**Fig 2**). Tracing studies demonstrate that 1C serine metabolism strongly contributes to purine and thymidylate pools in Burkitt-like hyperproliferation. Mechanistically, EBNA2 and MYC bind to the promoter of the host gene *MTHFD2* and up-regulate its expression to increase flux through the mitochondrial 1C pathway [4]. Nonetheless, limitations in purine pools induce replication stress and DNA damage, which can be reduced by nucleotide supplementation [9,25,26]. EBV also progressively induces the purine metabolism enzyme adenosine deaminase (ADA) in newly infected B cells in vitro [27]. Notably, ADA catalyzes the hydrolysis of adenosine to inosine and plays key roles in adenosine metabolism in germinal centers, where it serves to prevent the accumulation of deoxyadenosine triphosphate to toxic levels [28]. ADA levels progressively increase in EBV-infected cells, particularly as they convert to the lymphoblastoid phase [27]. Thus, EBV-induced ADA may serve to protect infected B cells as they transition through germinal center reactions and again in lymphoblastoid B cells, where ADA knockdown impairs proliferation in vitro [27]. Mechanistically, EBNA1 binds to an enhancer upstream of the *ADA* gene and is sufficient for ADA
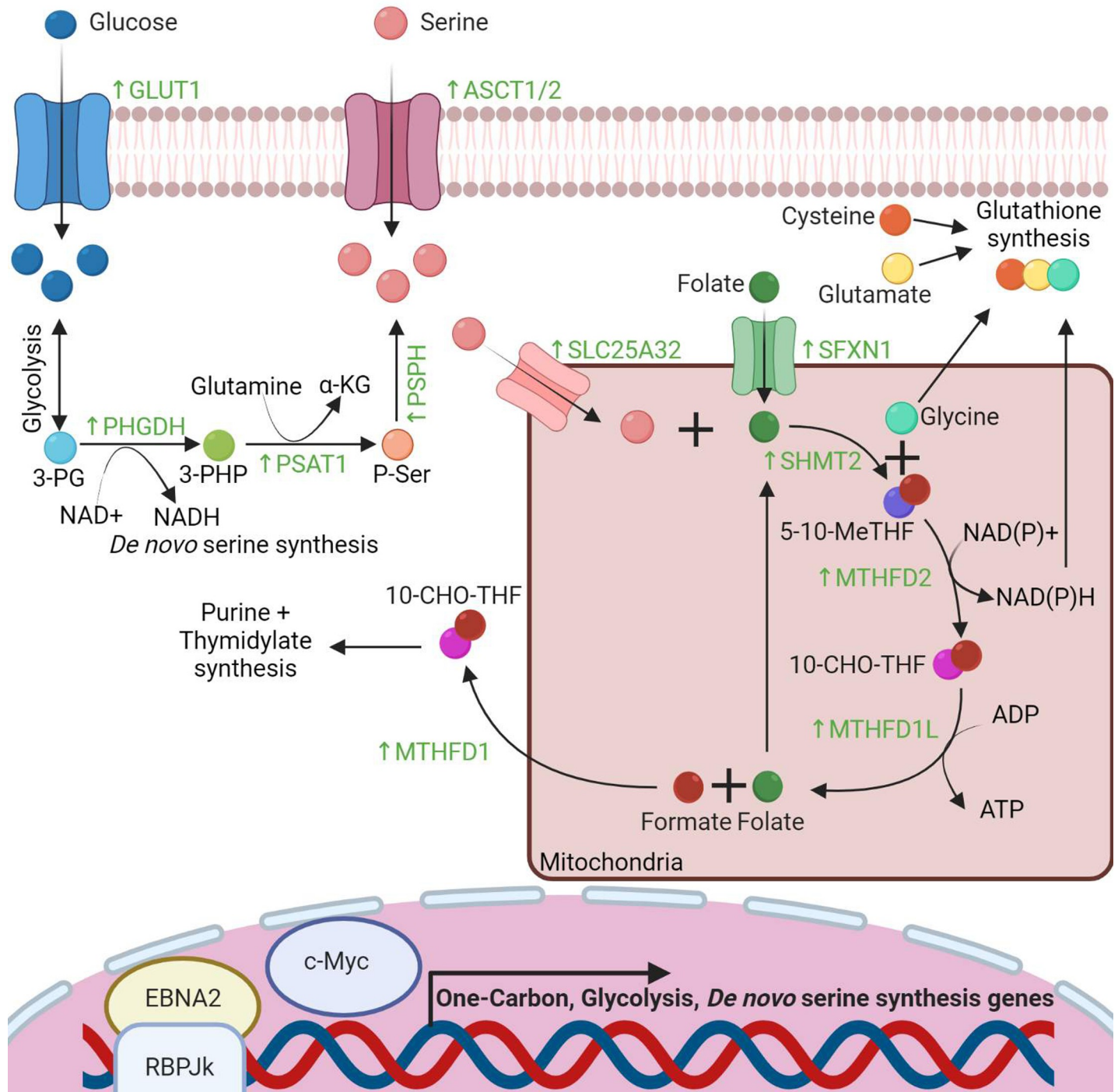
Fig 2. EBV-driven 1C pathway drives nucleotide and glutathione synthesis. EBNA2 and MYC induce the 1C, glycolysis, and de novo serine synthesis pathways in B cells. They also up-regulate plasma membrane abundance of the GLUT1 and ASCT1/2 transporters to increase glucose and serine import, respectively. Serine pools are further expanded by the de novo serine synthesis pathway, which metabolizes the glycolysis product 3-PG into serine and generate NADH and αKG byproducts. EBV also supports mitochondrial 1C metabolism via up-regulation of the SLC25A32 serine and SFXN1 folate transporters. Mitochondrial 1C metabolism converts serine into glycine, NADPH, and a serine-derived carbon unit (red ball), which is shuttled into the cytosol for use in purine and thymidylate biosynthesis. The carbon-loaded 1C folate carriers 5-10-meTHF and 10-CHO-THF are shown. 1C, one-carbon; 3-PG, 3-phosphoglycerate; 3-PHP, 3-phosphohydroxypyruvate; P-ser, 3-phosphoserine; 5-10-meTHF, 5-10-methylenetetrahydrofolate; 10-CHO-THF, 10-formyl THF; EBNA2, Epstein–Barr nuclear antigen 2; EBV, Epstein–Barr virus.

up-regulation in TERT-immortalized nasopharyngeal cells, but not in EBV-negative B cell lines, perhaps because of their higher basal ADA levels.

The pyrimidine cytidine nucleotide triphosphate (CTP) is critical for DNA, RNA, and phospholipid synthesis as well as for protein sialylation. To meet demand, EBNA2, MYC, and the LMP1-activated noncanonical NF-κB pathway highly up-regulate the rate-limiting enzyme cytidine 5′ triphosphate synthase 1 (CTPS1). EBV also up-regulates the isozyme CTPS2, which plays a partially redundant role with CTPS1 in EBV-transformed B cells. Interestingly, Burkitt and lymphoblastoid cells can utilize cytidine salvage metabolism, in which imported uridine or cytidine are converted to CTP [29]. This plasticity may underlie the clinical observation that EBV+ lymphomas frequently occur in patients with inborn hypomorphic CTPS1 mutations that severely impair T/NK cell immunity [30]. By contrast, inhibition of the enzyme DHODH, which supports de novo thymidylate and CTP biosynthesis, restrains EBV-transformed B cell proliferation and lytic replication in vitro and outgrowth of EBV+ lymphomas in humanized mice [31].

Latent EBV induction of amino acid metabolism

Plasma membrane proteomic analysis identified amino acid transporters as among the most highly EBV-induced host proteins upon primary human B cell infection [4]. These include the ASCT1/2 and LAT1 neutral amino acid transporters (**Fig 2**) and the xCT (also called SLC7A11) cystine/glutamate antiporter, which reach near maximal levels by day 4 post-EBV infection at the RNA and protein levels [2,4,32]. Transporter induction supports rapid amino acid influx, which likely serves to activate mTOR, to participate in redox defense, and to support myriad anabolic reactions [33,34]. At later time points, LMP1 and LMP2A further activate the PI3K/mTOR pathway, and LMP1 also promotes glutamine uptake in nasopharyngeal carcinoma (NPC) cells [35]. αKG is also produced by EBV-induced de novo serine synthesis (**Fig 2**) and has key roles in metabolic reactions, including in the TCA cycle and in EBV-induced TET2 DNA demethylase activity critical for latency III [35–37].

Latent EBV subversion of host lipid metabolism pathways

The mevalonate and fatty acid biosynthesis pathways are highly EBNA2 and MYC induced in newly infected primary human B cells [4,5]. These pathways use glucose-derived acetyl-CoA, together with NADPH reducing power, to produce sterols, isoprenoids, cholesterol, and fatty acids. The mevalonate pathway product geranylgeranyl pyrophosphate (GGPP) then plays a key cross talk role in support of LMP1 and LMP2A. Following EBNA3A/C-mediated up-regulation of the GTPase Rab13 expression [5,38], covalent GGPP modification licenses Rab13 to chaperone LMP1 and LMP2A to membrane signaling regions, thereby providing a metabolic link between multiple EBV latency III oncoproteins [5].

EBV also up-regulates the rate-limiting fatty acid synthesis enzymes acetyl-CoA carboxylase 1 (ACACA) and fatty acid synthase (FASN), which convert acetyl-CoA into palmitate for palmitoylation, triglyceride, and long-chain fatty acid pathways [5]. EBNA2, MYC, and sterol response element binding protein 2 (SREBP2) are each critical for ACACA and FASN induction. LMP1 further supports FASN up-regulation [39]. Similarly, LMP1 induces sterol response element binding protein 1 (SREBP1) in NPCs to up-regulate FASN and promote tumor progression, and LMP1 and FASN levels correlate in primary NPC samples [40]. Since CRISPR analysis indicates that SREBP2, rather than SREBP1, is an LCL dependency factor, EBV latency program and/or cell type may dictate which SREBP drives EBV-infected lipid metabolism. Upon lytic reactivation, the EBV immediate early gene RTA also up-regulates FASN, and FASN inhibition disrupts EBV lytic replication [41].

High rates of lipid biosynthesis raise the question of how EBV-infected cells are protected against ferroptosis, a programmed cell death pathway driven by iron-catalyzed lipid metabolism–generated reactive oxygen species. EBV-mediated metabolism reprograming likely supports redox defense, given that 1C supplies NADPH and glycine building blocks for antioxidant glutathione synthesis. Indeed, metabolic tracing studies demonstrate important 1C roles in support of glutathione biosynthesis and for the 1C enzyme MTHFD2 in supporting NADPH levels in newly infected B cells [4] (**Fig 2**).

Concluding remarks

Despite recent advances, key questions remain to be addressed about how EBV remodels host cell metabolism to support infected cell growth and survival, including in human cancers with characteristic latency programs. How EBV-driven metabolism pathways affects the microenvironment, and how this, in turn, might alter antiviral T and NK cell responses, is largely unstudied. It will also be of interest to define how EBV specifically alters infected B cell immunometabolism within germinal centers to cope with relative hypoxia and nutrient constraints in this specialized lymphoid microenvironment. We speculate that as infected cells transit through germinal centers and switch to the viral latency II program, comprised of EBNA1, LMP1, LMP2A, and ncRNAs (**Fig 1**), they increase their reliance on glycolysis and lactate secretion at the expense of OXPHOS to cope with hypoxia. How EBV latency II more broadly remodels B cell metabolism remains an open question, which has been limited by a paucity of latency II model systems. Newly developed tonsil organoid and humanized mouse models promise new insights into the metabolism of B cells in this germinal center latency II state [42]. With regard to latency I, little is presently known about whether EBV alters host cell metabolism in memory B cells to support this reservoir for lifelong infection. Although EBV + memory B cell models are needed, single-cell analyses of human tonsil samples may offer new insights into metabolism pathway states in EBV+ versus uninfected memory cells. With respect to EBV strains, little is presently known about how type I versus II EBV differentially alter infected B cell metabolism and how this contributes to observed differences in growth transformation and lytic gene expression. A key area will be to specifically define how EBNA2 polymorphisms, including one that contributes to superior type I growth transforming activity [43], affect flux through host metabolism pathways described above.

Enhanced understanding of EBV-driven metabolism network remodeling promises to lay the groundwork for new therapeutic approaches to EBV+ lymphomas. For instance, HMG-CoA reductase inhibitors (statins) block EBV-induced mevalonate metabolism and limit outgrowth of EBV-transformed B cells in culture [2,5], suggesting that it would be of interest to test these widely used medications in murine PTLD models. Similarly, given robust EBV-driven 1C pathway up-regulation, a next step will be to test 1C antagonists in xenograft and PTLD models in vivo. CRISPR analysis and small molecule studies suggest that the major metabolism regulator PI3K/AKT pathway is critical for lymphoblastoid B cell survival [44,45]. CRISPR screens also identified that Burkitt cells rely on the lysosomal iron reductase CYB561A3 to reduce transferrin-imported iron to bioavailable ferrous (Fe^{2+}) iron [46]. While effects on nontransformed cells remain to be defined, nearly 700 Cancer Dependency Map cell lines derived from a wide range of human tissues were not dependent on CYB561A3 for proliferation, suggesting that a therapeutic window may exist for CYB561A3 antagonists in Burkitt lymphoma treatment. LCLs instead use STEAP3 to reduce imported lysosomal iron [46], indicating that STEAP3 may be a druggable PTLD target. How EBV-driven metabolism remodeling controls the maintenance of restricted forms of EBV latency at the level of cross talk with DNA and histone methylation remains incompletely understood. It is plausible that

metabolism pathways can be exploited to derepress highly immunogenic latency III or lytic cycle antigens in order to sensitize EBV+ tumor cells to immunotherapy or lytic induction approaches, respectively. Finally, latent EBV infection can sensitize cells to synthetic lethal combinations that target multiple EBV oncometabolism pathways. For instance, blockade of EBV-induced MCT lactate exporters and electron transport chain complex I is highly toxic to LCLs [23].

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Schematic models for Figs 1 and 2 were made using BioRender.

References

1. Gewurz BE, Longnecker R, Cohen JL. Epstein-Barr Virus. In: Knipe DM, Howley PM, Damania BA, Cohen JI, editors. Fields Virology. 7th ed. Wolters Kluwer; 2021. p. 324–89.

2. Mrozek-Gorska P, Buschle A, Pich D, Schwarzmayr T, Fechtner R, Scialdone A, et al. Epstein-Barr virus reprograms human B lymphocytes immediately in the prelatent phase of infection. Proc Natl Acad Sci U S A. 2019; 116(32):16046–55. Epub 2019/07/26. https://doi.org/10.1073/pnas.1901314116 PMID: 31341086; PubMed Central PMCID: PMC6690029.

3. Price AM, Luftig MA. To be or not IIb: a multi-step process for Epstein-Barr virus latency establishment and consequences for B cell tumorigenesis. PLoS Pathog. 2015; 11(3):e1004656. Epub 2015/03/20. https://doi.org/10.1371/journal.ppat.1004656 PMID: 25790223; PubMed Central PMCID: PMC4366242.

4. Wang LW, Shen H, Nobre L, Ersing I, Paulo JA, Trudeau S, et al. Epstein-Barr-Virus-Induced One-Carbon Metabolism Drives B Cell Transformation. Cell Metab. 2019; 30(3):539–55 e11. Epub 2019/07/02. https://doi.org/10.1016/j.cmet.2019.06.003 PMID: 31257153; PubMed Central PMCID: PMC6720460.

5. Wang LW, Wang Z, Ersing I, Nobre L, Guo R, Jiang S, et al. Epstein-Barr virus subverts mevalonate and fatty acid pathways to promote infected B-cell proliferation and survival. PLoS Pathog. 2019; 15(9): e1008030. Epub 2019/09/14. https://doi.org/10.1371/journal.ppat.1008030 PMID: 31518366; PubMed Central PMCID: PMC6760809.

6. Finkin S, Hartweger H, Oliveira TY, Kara EE, Nussenzweig MC. Protein Amounts of the MYC Transcription Factor Determine Germinal Center B Cell Division Capacity. Immunity. 2019; 51(2):324–36 e5. Epub 2019/07/28. https://doi.org/10.1016/j.immuni.2019.06.013 PMID: 31350178; PubMed Central PMCID: PMC6703930.

7. Saha A, Robertson ES. Mechanisms of B-Cell Oncogenesis Induced by Epstein-Barr Virus. J Virol. 2019; 93(13). Epub 2019/04/12. https://doi.org/10.1128/JVI.00238-19 PMID: 30971472; PubMed Central PMCID: PMC6580952.

8. Farrell PJ. Epstein-Barr Virus and Cancer. Annu Rev Pathol. 2019; 14:29–53. Epub 2018/08/21. https://doi.org/10.1146/annurev-pathmechdis-012418-013023 PMID: 30125149.

9. McFadden K, Hafez AY, Kishton R, Messinger JE, Nikitin PA, Rathmell JC, et al. Metabolic stress is a barrier to Epstein-Barr virus-mediated B-cell immortalization. Proc Natl Acad Sci U S A. 2016; 113(6): E782–90. Epub 2016/01/24. https://doi.org/10.1073/pnas.1517141113 PMID: 26802124; PubMed Central PMCID: PMC4760815.

10. Pich D, Mrozek-Gorska P, Bouvet M, Sugimoto A, Akidil E, Grundhoff A, et al. First Days in the Life of Naive Human B Lymphocytes Infected with Epstein-Barr Virus. mBio. 2019; 10(5). Epub 2019/09/19. https://doi.org/10.1128/mBio.01723-19 PMID: 31530670; PubMed Central PMCID: PMC6751056.

11. Burton EM, Goldbach-Mansky R, Bhaduri-McIntosh S. A promiscuous inflammasome sparks replication of a common tumor virus. Proc Natl Acad Sci U S A. 2020; 117(3):1722–30. Epub 2020/01/11. https://doi.org/10.1073/pnas.1919133117 PMID: 31919284; PubMed Central PMCID: PMC6983388.

12. Ersing I, Nobre L, Wang LW, Soday L, Ma Y, Paulo JA, et al. A Temporal Proteomic Map of Epstein-Barr Virus Lytic Replication in B Cells. Cell Rep. 2017; 19(7):1479–93. Epub 2017/05/18. https://doi.org/10.1016/j.celrep.2017.04.062 PMID: 28514666; PubMed Central PMCID: PMC5446956.

13. Stunz LL, Bishop GA. Latent membrane protein 1 and the B lymphocyte-a complex relationship. Crit Rev Immunol. 2014; 34(3):177–98. Epub 2014/06/19. https://doi.org/10.1615/critrevimmunol.2014010041 PMID: 24941072.

14. Kieser A, Sterz KR. The Latent Membrane Protein 1 (LMP1). Curr Top Microbiol Immunol. 2015; 391:119–49. Epub 2015/10/03. https://doi.org/10.1007/978-3-319-22834-1_4 PMID: 26428373.

15. Sommermann TG, O'Neill K, Plas DR, Cahir-McFarland E. IKKbeta and NF-kappaB transcription govern lymphoma cell survival through AKT-induced plasma membrane trafficking of GLUT1. Cancer Res.

2011; 71(23):7291–300. Epub 2011/10/12. https://doi.org/10.1158/0008-5472.CAN-11-1715 PMID: 21987722; PubMed Central PMCID: PMC3228879.

16. Howley PM, Knipe DM, Whelan S. Fields Virology. 7th ed. Wolters Kluwer; 2021.

17. Wakisaka N, Kondo S, Yoshizaki T, Murono S, Furukawa M, Pagano JS. Epstein-Barr virus latent membrane protein 1 induces synthesis of hypoxia-inducible factor 1 alpha. Mol Cell Biol. 2004; 24(12):5223–34. Epub 2004/06/01. https://doi.org/10.1128/MCB.24.12.5223-5234.2004 PMID: 15169887; PubMed Central PMCID: PMC419879.

18. Zhang J, Jia L, Liu T, Yip YL, Tang WC, Lin W, et al. mTORC2-mediated PDHE1alpha nuclear translocation links EBV-LMP1 reprogrammed glucose metabolism to cancer metastasis in nasopharyngeal carcinoma. Oncogene. 2019; 38(24):4669–84. Epub 2019/02/13. https://doi.org/10.1038/s41388-019-0749-y PMID: 30745576; PubMed Central PMCID: PMC6756087.

19. Sung WW, Chen PR, Liao MH, Lee JW. Enhanced aerobic glycolysis of nasopharyngeal carcinoma cells by Epstein-Barr virus latent membrane protein 1. Exp Cell Res. 2017; 359(1):94–100. Epub 2017/08/23. https://doi.org/10.1016/j.yexcr.2017.08.005 PMID: 28827059.

20. Zhang J, Jia L, Lin W, Yip YL, Lo KW, Lau VMY, et al. Epstein-Barr Virus-Encoded Latent Membrane Protein 1 Upregulates Glucose Transporter 1 Transcription via the mTORC1/NF-kappaB Signaling Pathways. J Virol. 2017; 91(6). Epub 2017/01/06. https://doi.org/10.1128/JVI.02168-16 PMID: 28053105; PubMed Central PMCID: PMC5331802.

21. Hulse M, Caruso LB, Madzo J, Tan Y, Johnson S, Tempera I. Poly(ADP-ribose) polymerase 1 is necessary for coactivating hypoxia-inducible factor-1-dependent gene expression by Epstein-Barr virus latent membrane protein 1. PLoS Pathog. 2018; 14(11):e1007394. Epub 2018/11/06. https://doi.org/10.1371/journal.ppat.1007394 PMID: 30395643; PubMed Central PMCID: PMC6237423.

22. Darekar S, Georgiou K, Yurchenko M, Yenamandra SP, Chachami G, Simos G, et al. Epstein-Barr virus immortalization of human B-cells leads to stabilization of hypoxia-induced factor 1 alpha, congruent with the Warburg effect. PLoS ONE. 2012; 7(7):e42072. Epub 2012/08/01. https://doi.org/10.1371/journal.pone.0042072 PMID: 22848707; PubMed Central PMCID: PMC3407085.

23. Bonglack EN, Messinger JE, Cable JM, Ch'ng J, Parnell KM, Reinoso-Vizcaino NM, et al. Monocarboxylate transporter antagonism reveals metabolic vulnerabilities of viral-driven lymphomas. Proc Natl Acad Sci U S A. 2021; 118(25). Epub 2021/06/24. https://doi.org/10.1073/pnas.2022495118 PMID: 34161263; PubMed Central PMCID: PMC8237662.

24. Wang L, Howell MEA, Sparks-Wallace A, Hawkins C, Nicksic CA, Kohne C, et al. p62-mediated Selective autophagy endows virus-transformed cells with insusceptibility to DNA damage under oxidative stress. PLoS Pathog. 2019; 15(4):e1007541. Epub 2019/04/25. https://doi.org/10.1371/journal.ppat.1007541 PMID: 31017975; PubMed Central PMCID: PMC6502431.

25. Sugden B, Mark W. Clonal transformation of adult human leukocytes by Epstein-Barr virus. J Virol. 1977; 23(3):503–8. Epub 1977/09/01. https://doi.org/10.1128/JVI.23.3.503-508.1977 PubMed Central PMCID: PMC515860. PMID: 197258

26. Hafez AY, Messinger JE, McFadden K, Fenyofalvi G, Shepard CN, Lenzi GM, et al. Limited nucleotide pools restrict Epstein-Barr virus-mediated B-cell immortalization. Oncogenesis. 2017; 6(6):e349. Epub 2017/06/13. https://doi.org/10.1038/oncsis.2017.46 PMID: 28604764; PubMed Central PMCID: PMC5519195.

27. Lamontagne RJ, Soldan SS, Su C, Wiedmer A, Won KJ, Lu F, et al. A multi-omics approach to Epstein-Barr virus immortalization of B-cells reveals EBNA1 chromatin pioneering activities targeting nucleotide metabolism. PLoS Pathog. 2021; 17(1):e1009208. Epub 2021/01/27. https://doi.org/10.1371/journal.ppat.1009208 PMID: 33497421; PubMed Central PMCID: PMC7864721.

28. Aldrich MB, Chen W, Blackburn MR, Martinez-Valdez H, Datta SK, Kellems RE. Impaired germinal center maturation in adenosine deaminase deficiency. J Immunol. 2003; 171(10):5562–70. Epub 2003/11/11. https://doi.org/10.4049/jimmunol.171.10.5562 PMID: 14607964.

29. Liang JH, Wang C, Yiu SPT, Zhao B, Guo R, Gewurz BE. Epstein-Barr Virus Induced Cytidine Metabolism Roles in Transformed B-Cell Growth and Survival. mBio. 2021; 12(4):e0153021. Epub 2021/07/21. https://doi.org/10.1128/mBio.01530-21 PMID: 34281398; PubMed Central PMCID: PMC8406234.

30. Martin E, Palmic N, Sanquer S, Lenoir C, Hauck F, Mongellaz C, et al. CTP synthase 1 deficiency in humans reveals its central role in lymphocyte proliferation. Nature. 2014; 510(7504):288–92. Epub 2014/05/30. https://doi.org/10.1038/nature13386 PMID: 24870241; PubMed Central PMCID: PMC6485470.

31. Bilger A, Plowshay J, Ma S, Nawandar D, Barlow EA, Romero-Masters JC, et al. Leflunomide/teriflunomide inhibit Epstein-Barr virus (EBV)-induced lymphoproliferative disease and lytic viral replication. Oncotarget. 2017; 8(27):44266–80. Epub 2017/06/03. https://doi.org/10.18632/oncotarget.17863 PMID: 28574826; PubMed Central PMCID: PMC5546479.

32. Wang C, Li D, Zhang L, Jiang S, Liang J, Narita Y, et al. RNA Sequencing Analyses of Gene Expression during Epstein-Barr Virus Infection of Primary B Lymphocytes. J Virol. 2019; 93(13). Epub 2019/04/26. https://doi.org/10.1128/JVI.00226-19 PMID: 31019051; PubMed Central PMCID: PMC6580941.

33. Fish K, Sora RP, Schaller SJ, Longnecker R, Ikeda M. EBV latent membrane protein 2A orchestrates p27(kip1) degradation via Cks1 to accelerate MYC-driven lymphoma in mice. Blood. 2017; 130 (23):2516–26. Epub 2017/10/28. https://doi.org/10.1182/blood-2017-07-796821 PMID: 29074502; PubMed Central PMCID: PMC5721284.

34. Mainou BA, Everly DN Jr., Raab-Traub N. Epstein-Barr virus latent membrane protein 1 CTAR1 mediates rodent and human fibroblast transformation through activation of PI3K. Oncogene. 2005; 24 (46):6917–24. Epub 2005/07/12. https://doi.org/10.1038/sj.onc.1208846 PMID: 16007144.

35. Lo AK, Dawson CW, Young LS, Ko CW, Hau PM, Lo KW. Activation of the FGFR1 signalling pathway by the Epstein-Barr virus-encoded LMP1 promotes aerobic glycolysis and transformation of human nasopharyngeal epithelial cells. J Pathol. 2015; 237(2):238–48. Epub 2015/06/23. https://doi.org/10.1002/path.4575 PMID: 26096068.

36. Lu F, Wiedmer A, Martin KA, Wickramasinghe P, Kossenkov AV, Lieberman PM. Coordinate Regulation of TET2 and EBNA2 Controls the DNA Methylation State of Latent Epstein-Barr Virus. J Virol. 2017; 91(20). Epub 2017/08/11. https://doi.org/10.1128/JVI.00804-17 PMID: 28794029; PubMed Central PMCID: PMC5625499.

37. Dalton T, Doubrovina E, Pankov D, Reynolds R, Scholze H, Selvakumar A, et al. Epigenetic reprogramming sensitizes immunologically silent EBV+ lymphomas to virus-directed immunotherapy. Blood. 2020; 135(21):1870–81. Epub 2020/03/12. https://doi.org/10.1182/blood.2019004126 PMID: 32157281; PubMed Central PMCID: PMC7243148.

38. Hertle ML, Popp C, Petermann S, Maier S, Kremmer E, Lang R, et al. Differential gene expression patterns of EBV infected EBNA-3A positive and negative human B lymphocytes. PLoS Pathog. 2009; 5(7): e1000506. Epub 2009/07/07. https://doi.org/10.1371/journal.ppat.1000506 PMID: 19578441; PubMed Central PMCID: PMC2700271.

39. Hulse M, Johnson SM, Boyle S, Caruso LB, Tempera I. Epstein-Barr Virus-Encoded Latent Membrane Protein 1 and B-Cell Growth Transformation Induce Lipogenesis through Fatty Acid Synthase. J Virol. 2021; 95(4). Epub 2020/11/20. https://doi.org/10.1128/JVI.01857-20 PMID: 33208446; PubMed Central PMCID: PMC7851568.

40. Lo AK, Lung RW, Dawson CW, Young LS, Ko CW, Yeung WW, et al. Activation of sterol regulatory element-binding protein 1 (SREBP1)-mediated lipogenesis by the Epstein-Barr virus-encoded latent membrane protein 1 (LMP1) promotes cell proliferation and progression of nasopharyngeal carcinoma. J Pathol. 2018; 246(2):180–90. Epub 2018/07/04. https://doi.org/10.1002/path.5130 PMID: 29968360; PubMed Central PMCID: PMC6175466.

41. Li Y, Webster-Cyriaque J, Tomlinson CC, Yohe M, Kenney S. Fatty acid synthase expression is induced by the Epstein-Barr virus immediate-early protein BRLF1 and is required for lytic viral gene expression. J Virol. 2004; 78(8):4197–206. Epub 2004/03/30. https://doi.org/10.1128/jvi.78.8.4197-4206.2004 PMID: 15047835; PubMed Central PMCID: PMC374282.

42. Li C, Romero-Masters JC, Huebner S, Ohashi M, Hayes M, Bristol JA, et al. EBNA2-deleted Epstein-Barr virus (EBV) isolate, P3HR1, causes Hodgkin-like lymphomas and diffuse large B cell lymphomas with type II and Wp-restricted latency types in humanized mice. PLoS Pathog. 2020; 16(6):e1008590. Epub 2020/06/17. https://doi.org/10.1371/journal.ppat.1008590 PMID: 32542010; PubMed Central PMCID: PMC7316346.

43. Tzellos S, Correia PB, Karstegl CE, Cancian L, Cano-Flanagan J, McClellan MJ, et al. A single amino acid in EBNA-2 determines superior B lymphoblastoid cell line growth maintenance by Epstein-Barr virus type 1 EBNA-2. J Virol. 2014; 88(16):8743–53. Epub 2014/05/23. https://doi.org/10.1128/JVI.01000-14 PMID: 24850736; PubMed Central PMCID: PMC4136291.

44. Ma Y, Walsh MJ, Bernhardt K, Ashbaugh CW, Trudeau SJ, Ashbaugh IY, et al. CRISPR/Cas9 Screens Reveal Epstein-Barr Virus-Transformed B Cell Host Dependency Factors. Cell Host Microbe. 2017; 21 (5):580–91 e7. Epub 2017/05/12. https://doi.org/10.1016/j.chom.2017.04.005 PMID: 28494239.

45. Sang AX, McPherson MC, Ivison GT, Qu X, Rigdon J, Esquivel CO, et al. Dual blockade of the PI3K/ Akt/mTOR pathway inhibits posttransplant Epstein-Barr virus B cell lymphomas and promotes allograft survival. Am J Transplant. 2019; 19(5):1305–14. Epub 2018/12/15. https://doi.org/10.1111/ajt.15216 PMID: 30549430; PubMed Central PMCID: PMC6482059.

46. Wang Z, Guo R, Trudeau SJ, Wolinsky E, Ast T, Liang JH, et al. CYB561A3 is the Key Lysosomal Iron Reductase Required for Burkitt B-cell Growth and Survival. Blood. 2021. Epub 2021/07/08. https://doi.org/10.1182/blood.2021011079 PMID: 34232987.