



Unraveling the links between neurodegeneration and Epstein-Barr virus-mediated cell cycle dysregulation

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ABSTRACT

The Epstein-Barr virus is a well-known cell cycle modulator. To establish successful infection in the host, EBV alters the cell cycle at multiple steps via antigens such as EBNA, LMPs, and certain other EBV-encoded transcripts. Interestingly, several recent studies have indicated the possibility of EBV's neurotrophic potential. However, the effects and outcomes of EBV infection in the CNS are under-explored. Additionally, more and more epidemiological evidence implicates the cell-cycle dysregulation in neurodegeneration. Numerous hypotheses which describe the triggers that force post-mitotic neurons to re-enter the cell cycle are prevalent. Apart from the known genetic and epigenetic factors responsible, several reports have shown the association of microbial infections with neurodegenerative pathology. Although, studies implicating the herpesvirus family members in neurodegeneration exist, the involvement of Epstein-Barr virus (EBV), in particular, is under-evaluated. Interestingly, a few clinical studies have reported patients of AD or PD to be seropositive for EBV. Based on the findings mentioned above, in this review, we propose that EBV infection in neurons could drive it towards neurodegeneration through dysregulation of cell-cycle events and induction of apoptosis.

1. Introduction

Human Herpesvirus-4 (HHV-4) is also called Epstein-Barr virus (EBV) after its discoverers Anthony Epstein, Yvonne Barr, and Burt Achong (Epstein et al., 1964). It is a double-stranded DNA virus, and upon infection, it can either integrate into the host cell genome or exist in an episomal form (Reisinger et al., 2006). As a group-I carcinogen, it is associated with various lymphatic or epithelial malignancies such as Hodgkin's and Non-Hodgkin's (Burkitt's) lymphoma or nasopharyngeal carcinoma. It is linked to non-neoplastic diseases like infectious mononucleosis (IM) and lymphoproliferative disorders (Niedobitek et al., 2001). EBV is also reported to aggravate gastric cancer (Sonkar et al., 2020). A study reported that EBV infection could get laterally transferred from its natural host cells of B-cell lineage to the cells of epithelial origin (Shannon-Lowe et al., 2006). Interestingly, recent reports from various groups have suggested EBV's involvement in neurological manifestations such as multiple sclerosis and other neurodegenerative disorders, including Alzheimer's and Parkinson's disease (Biström et al., 2021; Carbone et al., 2014; Bu et al., 2015). Not much to surprise, some recent reports have also highlighted the importance of molecular

crosstalk between oncogenesis and neurodegeneration (Houck et al., 2019). Notably, most molecules shared among these phenomena are related to cell-cycle regulation (Seo and Park, 2020). Multiple studies have provided convincing evidence that cell-cycle dysregulation plays a critical role in the progression of neurodegenerative disorders (Yang and Gao, 2020; D. J. Bonda et al., 2010; Wang et al., 2009). Furthermore, EBV is well established to be capable of altering the host cell cycle. Various EBV antigens such as EBV nuclear antigen-1 (E1), E2, E3A, E3B, and E3C, EBV encoded small RNAs (EBERs), Bam-HI A rightward transcripts (BARTs), EBNA leader protein (E-LP) which is also known as E5, latent membrane proteins (LMP) -1, 2A, and 2B are involved in manipulating the host cell cycle (Yin et al., 2019). For example, the interaction of EBV latent genes with cellular oncogenes could promote G₁/S transition and halt apoptosis, leading to neoplastic transformation of the infected cells (Yin et al., 2019).

However, the neurovirulent and neuroinvasive capability of the virus is still debated; the genetic material of EBV and antiviral antibodies against the virus has been found in CSF samples of patients suffering from NDs (Carbone et al., 2014; Gate et al., 2020). A recent review beautifully shed light on the involvement of EBV in various NDs

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including AD, PD, MS, etc (Zhang et al., 2022). An earlier study done by Jha et al. has also established the neurotropic potential of EBV in primary neurons, Ntera2, and Sh-Sy5y cell lines (Jha et al., 2015). Additionally, our recent study has shown that EBV can infect and modulate glial cells (Tiwari et al., 2020; Jakhmola and Jha, 2021) in the brain, corroborating a previous finding by Menet et al., (1999). Also, we have observed that EBV can infect and alter the endothelial cells of the blood-brain barrier (Indari et al., 2021). These clues indicate the possibility of EBV being capable of establishing successful infection in neural cells: i.e., glial cells, and neurons. As stated earlier, EBV infection could cause deregulation of the cell cycle in the host cell. Therefore, in this review, we have tried to summarize the role of EBV infection in manipulating the host cell cycle and how dysregulation of these events in neurons could be involved in neurodegenerative disorders.

2. Understanding the role of EBV in the cell cycle and its regulation

The eukaryotic cell cycle is a highly regulated and coordinated process by which a cell gives rise to two daughter cells. A cell synthesizes various cellular components during this process, duplicates its genetic material, and eventually divides. A typical cell cycle consists of the interphase and the mitotic (M) phases. The interphase prepares for the upcoming division process. It can be further classified under three stages: gap-1 (G₁), synthesis (S), and gap-2 (G₂) phase [Fig. 1]. The gap phases function as a time interval allowing the cell to review its surroundings and prepare itself for upcoming cell cycle events. Although, under unfavorable conditions for division, a cell can enter a non-replicative state known as G₀, which occurs between the M-phase and the start of the next interphase. A cell in the G₀ phase neither divides nor prepares to divide. This G₀ state can be reversible (quiescent) or non-reversible (terminally differentiated). Certain cells of the body that are terminally differentiated, like neurons (Anda et al., 2016), and cardiac cells (Broughton and Sussman, 2019), remain in this inactive G₀ stage under physiological conditions.

The regulation of this well-tuned process is orchestrated mainly with the help of certain intracellular molecules, namely: cyclins (Cyc), cyclin-dependent kinases (CDKs), and CDK inhibitors (CKIs). The Cyclin/CDK

heterodimer drives a cell through various checkpoints by acting at specific points in the cycle, phosphorylating downstream proteins and modulating their activity (Satyanarayana and Kaldis, 2009) [Fig. 1].

Throughout the cell cycle, the activity of Cyclin/CDK complexes is controlled by timely production of the two proteins, phosphorylation/dephosphorylation of CDKs, controlled degradation of Cyclins, and binding of CKI proteins to specific complexes (Tarn and Lai, 2011; Suryadinata et al., 2010). The stage-specific expressions of cyclin/CDK complexes and respective CKIs are shown in [Table 1]

As an oncogenic virus, EBV has been reported to alter the host cell cycle at multiple steps. It can modulate protein-protein interactions, redistribute proteins, or encode homologs of cellular proteins (Fan et al., 2018). Previous studies have reported direct interaction between several EBV proteins and the host cell cycle proteins. The specific proteins of EBV acting at various stages of the cell cycle are discussed in the following section:

2.1. The G₁ phase

A cell begins the division process with the initiation of the G₁-phase, which calls for an external stimulus in the form of growth factors.

Table 1

The majorly involved Cyclins and Cyclin-dependent kinases (CDKs) at different cell cycle phases and respective checkpoints.

Cell cycle stage	Active Cyclins	Active CDKs	Active CKI	Checkpoint
G ₁ - phase (early)	Cyclin D1/2/3	CDK-4	Ink family (p15, p16, p18, and p19)	G ₁ checkpoint
G ₁ - phase (late)	Cyclin D1/2/3	CDK-6		
G ₁ /S- phase transition	Cyclin E	CDK-2	pRb	
S- phase	Cyclin A	CDK-2	Cip/Kip family (p21, p27, and p57)	G ₂ checkpoint
G ₂ /M- phase transition	Cyclin A	CDK-1		
M- phase	Cyclin B	CDK-1		Mitotic checkpoint

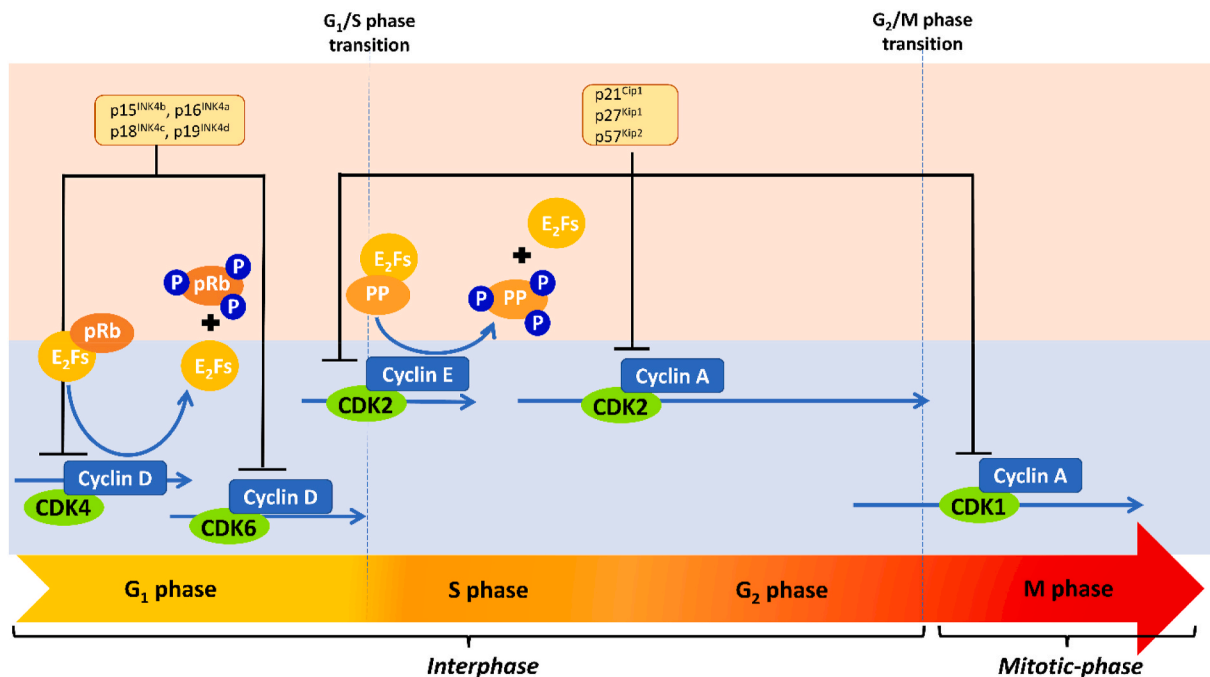


Fig. 1. Phases of the cell cycle. The cell cycle is mainly divided into the Interphase and Mitotic phase. Various heterodimers of cyclins and CDK complexes positively regulate the cell-cycle progression. On the other hand, the CKIs (CDK inhibitors) obstruct the cell-cycle progression if needed.

Continuous growth factor supply is required until the cell passes through the restriction point in G_1 (Pardee, 1974); after this, the process becomes growth factor-independent, and the cell is now committed to complete DNA replication and division. Unsurprisingly, this step becomes the first target for virus-mediated cell-cycle manipulation. Multiple studies involving EBV have shown that the virus infection could promote the expression of neurotropic growth factors such as brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) (Ng et al., 2012; Jakhmola and Jha, 2021) in the infected cells. Clinical reports evaluating EBV meningoencephalitis/meningitis have corroborated the claim, as an increase in neurotropic factors was observed in the patient's CSF samples (Chiaretti et al., 2014; Kozko et al., 2018).

Once a cell enters the G_1 -phase, it grows to its usual size and synthesizes mRNA and protein that will be used in the forthcoming stages of the cell cycle. As depicted in Table 1, progression through the G_1 -phase is under the regulation of CDK-4 and D type Cyclins (Cyclin D1/2/3). Various viruses, including EBV, modulate the expression and activity of cyclin/CDK complexes to gain control of the cellular machinery (Tavakolian et al., 2020). These intracellular pathogens have evolved impressive strategies to modulate the kinase activity of the Cyclin/CDK complex by interacting with the individual subunits of the heterodimer or altering the activity of CKIs. For instance, the EBV nuclear antigen-3C (E3C) interacts with the D-type cyclins D1 and D2 (Saha et al., 2011; Pei et al., 2018). E3C can form stable complexes with G_1 phase cyclins- D1 and D2/CDK-6 heterodimer [Fig. 2a] (Saha et al., 2011; Pei et al., 2018). By upregulating the expression of D-type cyclin, EBV can deregulate the activities of the G_1 phase.

Further, the latent membrane protein 1 (LMP-1) of EBV can also influence the activity of the Cyclin D/CDK-4 complex by interacting with and altering the activity of CKI, p16^{INK14a}. This interaction facilitates the progression of the cell cycle through the G_1 phase by releasing the Cyclin D/CDK-4 complexes from p16^{INK14a}-mediated inhibition of its kinase activity [Fig. 2b(i)] (Yang et al., 2000; Ohtani et al., 2003; Dawson et al., 2012). LMP-1 is reported to reduce the expression levels of p16^{INK14a} by blocking the transcriptional activity of various factors regulating its expressions, such as Ets2, bmi-1, JunB, 14-3-3 σ , and SNF5.

2.2. The G_1/S phase transition

Moving ahead in the cell cycle, the G_1/S phase transition is governed by the activity of the Cyclin E/ CDK-2 complex. Few studies have reported that EBV alters the kinase activity of the Cyclin E/ CDK-2 complex through the interaction of E3C with cyclin E [Fig. 2a]. However, the downstream effect of the association between E3C and cyclin E is not yet described (Knight et al., 2004). Several studies proclaimed that EBV employs LMP-1 to modulate the kinase activity of various cyclin/CDK complexes at the G_1/S phase transition. LMP-1 is reported to enhance cyclins' promoter activity in the late G_1 and G_1/S transition phase via the EGFR and STAT3 signaling pathways. Under the influence of LMP-1, the EGFR directly binds to cyclins- D1 and E, thereby accelerating the G_1/S phase transition (Tao et al., 2005; Xu et al., 2013) [Fig. 2a].

A checkpoint guards the G_1/S phase transition often referred to as "a point of no return." After passing this restriction point, the process becomes growth factor independent, and the cell is now committed to complete DNA replication and division. A member of the pocket protein family, pRb is one of the critical regulators of the G_1/S transition checkpoint (Y. J. Wang, et al., 2001). pRb acts as a guardian and lets the cell pass through the restriction point only under suitable growth conditions and if there is no DNA damage or metabolic disturbances. The regulation of pRb activity is mainly controlled by its timely phosphorylation (inactivation) and dephosphorylation (activation) at T373 and S608 by the G_1 phase Cyclin/ CDK complex (Cyclin D and CDK-4/6 complex) (Dowdy et al., 1993; Beijersbergen et al., 1995). This leads to its dissociation from a complex with transcription factor E2F (Bartek et al., 1996), and the subsequent release of E2F activates downstream

genes required for the progression of the cell cycle.

Previous reports have listed interactions of pRb with various nuclear antigens of EBV (Szekely et al., 1993; Saha and Robertson, 2013). One such study suggested the role of E3C in influencing cell cycle regulation via controlling the pRb activity (J. S. Knight et al., 2005). The study conducted by Knight et al. indicates that E3C mediates the phosphorylation of pRb by controlling the kinase activity of Cyclin D1/ CDK-4 complex [Fig. 2b(i)]. It was also revealed that besides regulating the phosphorylation status of pRb, E3C mediates its ubiquitination. The study further elaborated that E3C recruits the SCF^{Skp2}-E3 ubiquitin ligase complex to affect the stability of pRb in EBV-transformed cells. The conserved domain region of E3C from amino acids 140–149, which was responsible for regulating the SCF^{Skp2} complex, is also crucial for regulating pRb. It explicitly shows that E3C usurps SCF^{Skp2} in EBV-transformed cells to target and regulate the levels of pRb [Fig. 2b(ii)] (Maruo et al., 2006). Additionally, E3C is also reported to influence the regulation of pRb activity via aurora kinase B (AURKB) (Jha et al., 2013). The study done by Jha et al. demonstrates that the direct interaction of E3C with AURKB stabilizes the protein. This interaction reduces ubiquitination of AURKB, thus maintaining its phosphorylating activity towards pRb leading to cell proliferation [Fig. 2b(i)]. The following hyper-phosphorylated state of pRb would ultimately accelerate the G_1/S transition and cause the cell cycle to proceed unchecked.

Additionally, a study in virus-infected Akata cells has reported an interaction between EBV-immediate early lytic gene product BRLF-1 and the pRb (Zacny et al., 1998). BRLF-1 is speculated to interact with two regions of pRb, from amino acids 39–89 and 249–309. The interaction possibly occurs first at one site, followed by secondary interaction at the other. Although the BRLF1 does not directly interact with E2F bound to pRb, its binding region on pRb was observed to lie outside the pocket region. A correlation between the BRLF-1 binding and E2F displacement from the pRb was still observed. This indicates a potential role of BRLF-1 in regulating the cell cycle beyond relief of pRb-mediated E2F repression and thus cell cycle proliferation.

Furthermore, EBV is also known to target pRb via the binding of EBV nuclear antigen 5 (E5/EBNA-LP) during B-cell transformation (Szekely et al., 1993). E5 localizes with and binds to pRb without possessing an LXCXE motif. However, the pRb binding region of E5 was found to be on the N-terminal of the protein as a 66-amino acid long peptide, which is also the site for p53 binding. Therefore, the binding of E5 to pRb is competitively affected by p53. An in-vitro study revealed that the binding of p53 in a dose-dependent fashion could inhibit the formation of the E5-pRb complex, indicating that p53 competes with pRb for E5 binding. At the same time, the vice-versa cannot be feasible. Additionally, a study reported that E5 affects the pRb/p53 cascade by binding to its negative regulator, Mdm2 [Fig. 2b(ii)]. This binding of E5 with Mdm2 prevents Mdm2-mediated polyubiquitination of p53 and further degradation [Fig. 2b(ii)]. The formation of the E5- Mdm2-p53 trimolecular complex causes the cell to bypass G_1 arrest and proceed toward the S-phase of the cell cycle (Kashuba et al., 2011). The nuclear antigen E3C of EBV also directly interacts with p53 and attenuates the p53-mediated transcription of downstream genes and apoptosis. The interacting domain of p53 on E3C is mapped near the N-terminal at 130–190 amino acid residues (Yi et al., 2009).

An EBV protein Rta is known to transcriptionally upregulate the expression of 14-3-3 σ , which negatively regulates the cell cycle progression [Fig. 2b(ii)] (Dar et al., 2014; Gupta et al., 2020). Though 14-3-3 σ is under the control of p53, EBV-Rta could induce its expression in a p53-independent manner. Induction of 14-3-3 σ would cause the sequestration of CDK-1 and 2 in the cytoplasm. Coupled with the diminished activity of cyclin E/CDK-2, as mentioned in the earlier section, this is reported to finally lead the cell cycle to arrest at the G_1/S transition state in EBV infected cells [Fig. 2b(ii)] (Huang et al., 2012). Furthermore, EBV-Rta induces p21^{WAF1/CIP1} (CDKN1A) expression. By up-regulating the p21^{WAF1/CIP1} expression levels, EBV diminishes the activity of the Cyclin E/CDK-2 complex (Huang et al., 2012). The

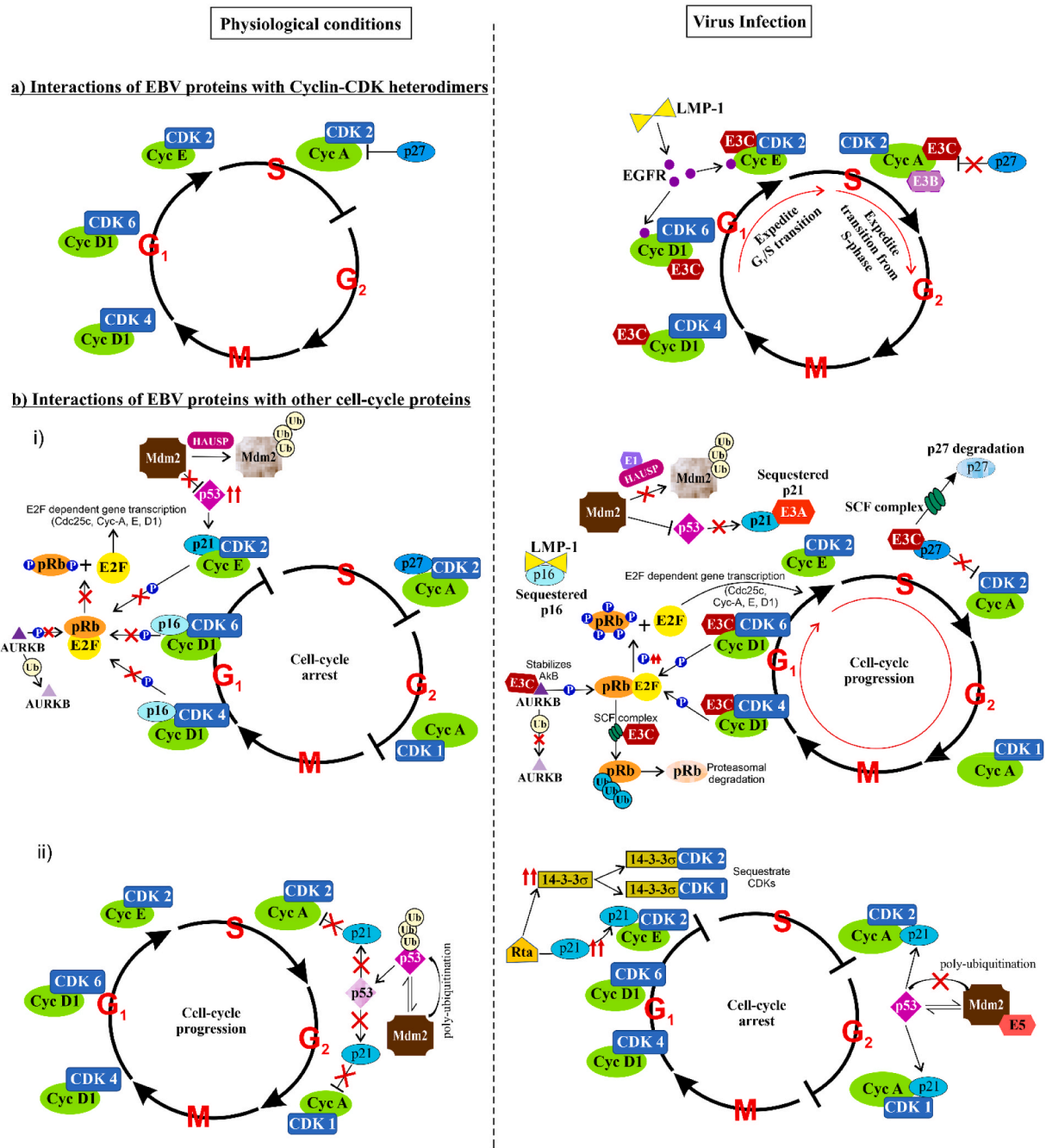


Fig. 2. Epstein-Barr virus utilizes different mechanisms to manipulate the cell cycle. Modulating protein-protein interactions of the host cell cycle proteins is one of the most favored strategies.

a) EBV can interact with positive cell cycle regulators to promote cell cycle progression. EBV antigen, E3C, interacts with various cyclins such as Cyc D1, E, and A to accelerate the cell cycle progression at respective steps. Further, another antigen, E3B, is also reported to interact with Cyc A and result in the expedition of S-phase transition. Another EBV antigen, LMP1, reportedly stimulates the expression of EGFR, that in turn acts as a mitogenic signal to promote G₁/S transition.

b) Alternatively, EBV can interact with negative cell cycle regulators to either hinder their activity and release cells from the arrest stage or halt cell cycle progression. **(i).** EBV antigen E1 interacts with HAUSP to obstruct the degradation of Mdm2, thereby allowing blockage of p53 from acting as a stimulator of p21. Another EBV antigen, E3A, also sequesters p21. Together, these molecules inhibit the cell cycle via p53 and p21; and aid in progression through G₁ to the S phase. Further, progression through the G₁ phase is reported to be expedited by E3C via interaction with various Cyclin/CDK complexes. E3C also regulates the pRb cascade by governing its degradation through the SCF complex or by interacting with and thereby stabilizing AURKB to promote pRb phosphorylation. The E3C is also reported to promote the degradation of p27 via the SCF complex, thereby releasing the Cyclin A/CDK-2 complex from inhibition, leading to the advancement of the cell cycle through the S phase. **(ii).** EBV antigen, Rta, is reported to upregulate the expression of p21 and thus facilitate inhibition of the Cyclin E/CDK-2 complex. Rta may also mediate sequestration of CDK1 and CDK2 by upregulating 14-3-3 σ, thereby obstructing G₁/S transition. Further, another EBV antigen, E5, is also known to modulate the cell cycle at the G₂ phase by inhibiting Mdm2-mediated poly-ubiquitination of p53, thus facilitating p53-mediated p21 activation resulting in blocking the activity of the respective cyclin/CDK complexes.

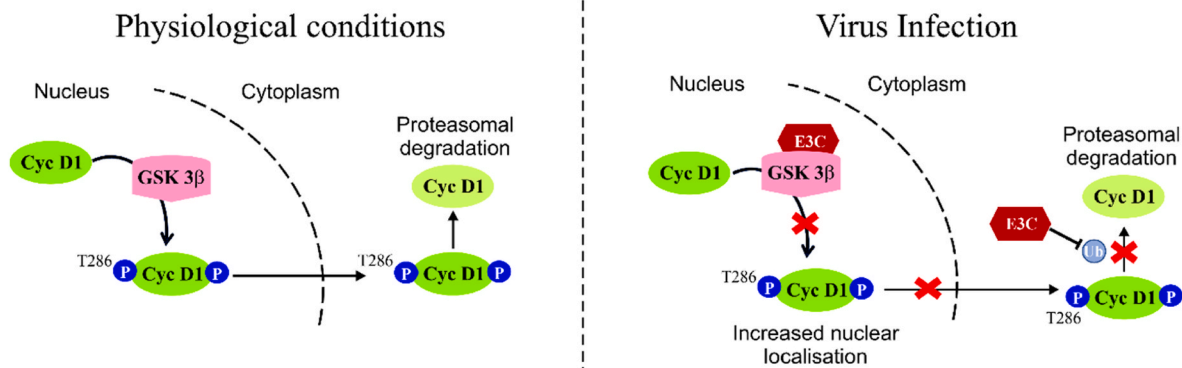
reduced kinase activity of the cyclin E/CDK-2 complex, along with certain other conditions, results in cell cycle arrest at the G₁/S transition phase and aids in viral reactivation. The binding of LMP-1 to p16^{INK14a} relieves the growth arrest at the G₁ phase, thus initiating G₁/S transition by targeting the downstream mediators of the pRb-p16^{INK14a} pathway.

Another effective strategy of viruses to hack the cellular machinery is protein redistribution. In order to control of the cell cycle, EBV mainly disturbs the localization and distribution of cyclins, p53 and survivin protein. During the G₁/S phase transition of the cell cycle, Cyclin D1 is primarily localized in the nuclear region [Fig. 3a] (Baldin et al., 1993). However, it is transported to the cytoplasm for ubiquitin-proteasome-mediated degradation upon GSK3β-mediated phosphorylation at T286 (Diehl et al., 1998). Remarkably, in a study by Saha et al., E3C was shown to play a dual role in blocking the poly-ubiquitination and GSK-3β mediated phosphorylation of Cyclin-D1, leading to its increased nuclear localization [Fig. 3a] (Pei

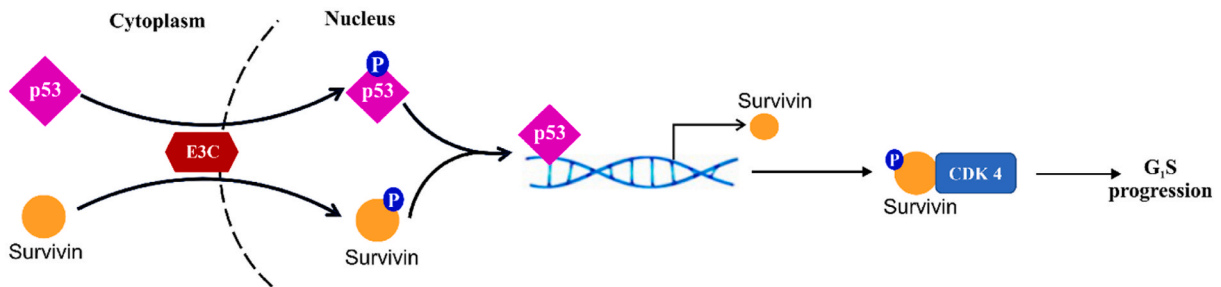
et al., 2018).

Another cellular protein whose localization is affected by EBV infection is p53. A study done by Gou et al. demonstrated that LMP-1 induces the nuclear localization of p53 and survivin [Fig. 3b] (Guo et al., 2012). It is reported to upregulate the expression and phosphorylation of these two proteins. Survivin also possesses a p53-binding element in its promoter region. Besides, it facilitates the cell cycle to progress from G₁ to S-phase by interacting with CDK-4 in the nucleus. Although p53 is predominantly reported as a tumor suppressor protein increasing evidence suggests its overexpression and accumulation be linked with nasopharyngeal carcinoma (NPC) (Saha et al., 2009; Banerjee et al., 2013; Pei et al., 2016). Under physiological and DNA damage conditions, the expression of LMP-1 is found to be associated with p53 expression in EBV transformed cells. p53 is essentially required to stimulate the expression of LMP-1 in response to DNA damage. Ectopic p53 stimulates endogenous LMP-1 expression, subsequently blocking

a) Cyclin D₁



b) Survivin and p53



c) MRPS18-2

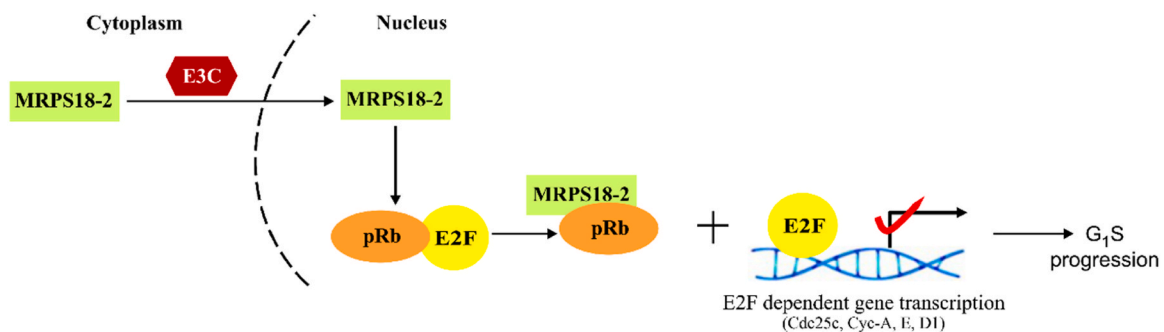


Fig. 3. EBV modulates the cellular protein distribution. EBV antigens could also redistribute the cellular proteins to facilitate the survival of the virus inside the host cell. (a) Cyclin D1- E3C mediates the nuclear localization of cyclin D1 by blocking GSK3β. (b) Survivin and p53- E3C aids in nuclear localization of survivin and p53. (c) MRPS18-2- E3C also enhances the nuclear localization of MRPS18-2 to facilitate the E2F-dependent gene transcription.

DNA damage-mediated apoptosis. Interferon regulatory factor 5 (IRF-5), a direct target of p53, is implicated in this process. In response to DNA damage-induced p53, IRF-5 increases the expression of LMP-1 by binding to and activating an LMP-1 promoter-reporter construct (Wang et al., 2017). Notably, IRF-5 is a well-known tumor suppressor gene that heightens apoptotic signaling in response to DNA damage. However, LMP-1 is predominantly considered a viral oncogene that blocks apoptosis. Therefore, it was evident that LMP-1 blocks apoptosis via modulating IRF-5 in EBV-infected cells to maintain latency (Hu and Barnes, 2009).

Apart from the proteins mentioned above, another cellular protein implicated in the cell cycle, MRPS18-2 (mitochondrial ribosomal protein S18-2), is also dislocated to the nucleus by E3C [Fig. 3c] (Kashuba et al., 2011). MRPS18-2 binds explicitly to both the hypo- and hyperphosphorylated forms of Rb protein. This binding occurs through a site in the small pocket of pRb, which is also involved in its interaction with E2F1. MRPS18-2 and E2F1 competitively interact with pRb, further elevating the free E2F1 level. The levels of nuclear MRPS18-2 protein are also affected by E3C. The EBV protein E3C binds to and raises the level of MRPS18-2, which may help in the progression of EBV-infected B cells into the S phase. These strategies would competitively inhibit pRb binding to E2F1 and lift the block to S-phase entry.

2.3. The S phase

The passage of a cell into the S phase initiates the synthesis of DNA, which generates two replicas of the genetic material. The progression of this cell cycle stage is under the governance of the Cyclin A/CDK-2 complex. The EBV nuclear antigen E3C is well known to interact with Cyclin/CDK complexes active at various cell cycle stages, including the one in the S-phase. As described in the previous section, E3C forms a stable complex with Cyclin A and promotes the Cyclin/CDK complex's kinase activity. Additionally, a study conducted by Knight and Robertson in 2004 demonstrated weak interactions between E3B and Cyclin A, owing to the conserved region in E3B that is similar to the Cyclin A binding site of E3C. However, the precise role of this binding is still unclear [Fig. 2a] (Knight et al., 2004).

The binding of E3C to Cyclin A decreases the association of p21^{WAF1/CIP1} with the Cyclin A/CDK-2 complex, thus rescuing it from p21^{WAF1/CIP1}-mediated inhibition, thereby aiding in cell cycle progression through the S phase (Knight and Robertson, 2004). Furthermore, the inhibitory activity of p21^{WAF1/CIP1} against the S phase Cyclin/CDK complex has been modulated by E3A of EBV (Tursiella et al., 2014). It contributes to apoptotic resistance in EBV-infected Burkitt's lymphoma cell lines through fine-tuning the expression of p21^{WAF1/CIP1}. The E3A-mediated repression of p21^{WAF1/CIP1} prevents the cell from succumbing to p53 and pRb-mediated cell cycle arrest and ensures continuous proliferation of the cell through the S phase [Fig. 2b(i)] (Tursiella et al., 2014).

Furthermore, an *in-vitro* study revealed that the N-terminal amino acids (130–159) of E3C are responsible for binding with Cyclin A and restricting the p27^{KIP1}-mediated inhibition of Cyclin A/CDK-2 kinase activity (Tursiella et al., 2014). At the same time, C-terminal domain amino acids (957–990) might be playing a role in stabilizing the elements of this complex [Fig. 2a] (Knight and Robertson, 2004; Saha et al., 2011). E3C might serve as a bridge between SCF^{Skp2} and p27^{KIP1}, resulting in the degradation of p27^{KIP1}, thereby relieving its inhibitory effect on the Cyclin A/CDK-2 complex (Jason S. Knight et al., 2005; Knight Jason et al., 2005). Thus, the enhanced activity of the Cyclin A/CDK-2 complex would cause the release of the cell from arrest at the S phase [Fig. 2b(i)] (Tursiella et al., 2014).

2.4. The G₂ phase and G₂/M phase transition

After the completion of DNA duplication in the S phase comes the G₂-phase, in which the cell growth continues along with protein synthesis as

the cell prepares for M-phase. The regulation of progress through the G₂ phase is controlled by Cyclin B and CDK-1 (cdc2). A study done by Mauser et al. has demonstrated that EBV can induce G₂/M block in HeLa cell lines and normal human fibroblasts by reducing the levels of Cyclin B1/CDK-1 [Fig. 2a] (Mauser et al., 2002). The EBV lytic protein Zta, also known as BZLF-1 (BamHI Z fragment leftward open reading frame 1), was demonstrated to decrease the transcript and protein expression levels of Cyclin B1, thus inducing cell cycle arrest at the G₂/M phase transition.

Before moving on to the M-phase, the cell must go through checkpoints at the G₂/M phase transition to ensure error-free and successful completion of DNA replication (Hartwell and Weinert, 1989). If DNA damage is identified, the cell undergoes growth arrest instead of repair without proceeding to the M-phase. Interestingly, E3C of EBV is demonstrated to disrupt this restriction by binding and inactivating the Chk2 (checkpoint kinase 2), the effector molecule of the ATM/ATR signaling pathway that regulates the G₂/M checkpoint. The binding of E3C to Chk2 induces phosphorylation of Cdc25c (cellular phosphatase) at Ser216, which leads to its sequestration in the cytoplasm by 14-3-3 σ thus permitting activation of Cyclin B/CDK-1 complex and bypassing of the G₂/M checkpoint [Fig. 2b(ii)] (Choudhuri et al., 2007).

Such contradictory reports suggest that blocking the cell cycle progression at certain stages would be advantageous under some circumstances, while promoting the progression would be more beneficial in some others. As described in the previous sections, a careful balance between the two processes is essential for establishing EBV infection, which is fine-tuned by various EBV proteins.

3. Evidence and implications of EBV-mediated cell cycle dysregulation in neurodegenerative disorders

The association between neurodegenerative pathology and different members of the *Herpesviridae* family has been consistently reported over the past two decades (Costa Sa et al. 2019a; Phuna and Madhavan, 2022 Mar 14). Although the role of EBV has been understated and frequently debated in this context (Carbone et al., 2014), the evidence does confirm the connection. The post-mortem human brain tissue and cerebrospinal fluid (CSF) samples of patients suffering from neurodegenerative disorders like multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), etc. have shown seropositivity for EBV and the presence of antibodies against EBV (Kleines et al., 2011). Interestingly, demographic studies done on elderly population that progressed to cognitive impairment from a healthy state showed elevated levels of anti-EBV antibodies (Shim et al., 2016). As described earlier, EBV is highly efficient in manipulating the cell cycle; and various pathophysiological conditions of the central nervous system (CNS), including chronic neurodegenerative disorders and acute damage, have been linked with abnormal cell cycle activation and progression (Wang et al., 2009; Woulfe et al., 2016). Therefore, in this review, we have focused on NDDs implicating virus-mediated cell cycle dysregulation as a possible mode of pathogenesis.

Unlike other cell types, neurons, once terminally differentiated, are supposed to have lost their proliferation capability. Most of the CNS neurons enter this post-mitotic quiescent state while going through embryonic development and remain in the "prolonged G₀ phase" in the adult nervous system (Frade and Ovejero-Benito, 2015a). These cells are unable to re-enter the cell cycle. However, surprisingly, various structures in a typical adult human brain express several genes that encode regulators of G₁/S transition (Kruman et al., 2004; Koeller et al., 2008; Lopes et al., 2009). These genes include cyclin D1, CDK-4, Rb proteins, E2Fs, and CKIs [Fig. 4]. In fact, most of these gene transcripts are translated to proteins in normal adult neurons. Traditionally, the presence of core cell cycle regulators in adult neurons is attributed to their functions in neuronal migration, maturation, and synaptic plasticity (Herrup and Yang, 2007). Nevertheless, these proteins could potentially force the cell to re-enter the cell cycle upon induction by various factors

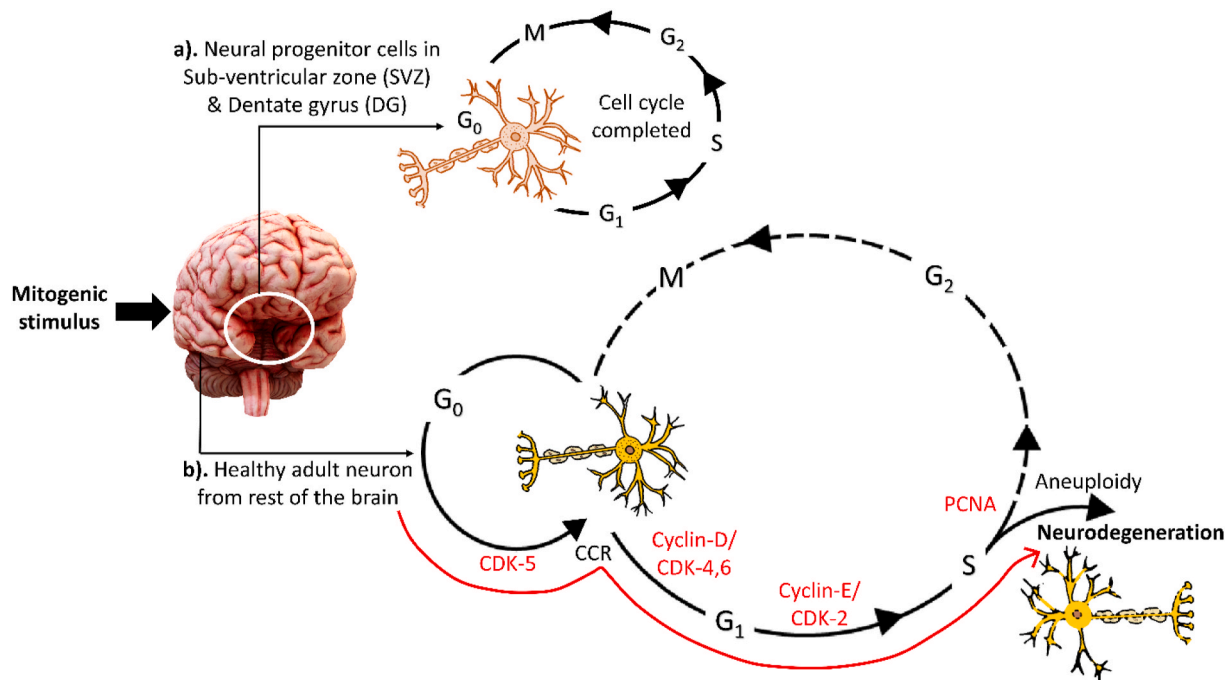


Fig. 4. Neuronal cell-cycle. Mitogenic signals received by neural progenitor cells in the subventricular zone (SVZ) and dentate gyrus (DG) give new cells. However, mitogenic stimulation could result in ectopic re-entry of the cells into the cell cycle, ultimately leading to neurodegeneration in the rest of the brain.

under certain conditions. Certain mitogenic stimuli including viral infections could induce the aberrant re-entry of neurons into the cell cycle, ultimately leading to cell death. Though, the association of cell cycle reentry with synaptic failure and neuronal death is well established by various studies, the functional connection between the two phenomena remains elusive (David J. Bonda et al., 2010; Barrio-Alonso et al., 2018a). When subjected to acute stress conditions such as lack of neurotrophic factors, DNA damage, oxidative stress, excitotoxicity, and sudden mitogenic stimuli, these cells would reactivate the cell cycle by aberrant expression of cell cycle proteins (Hernández-Ortega et al., 2011). Under such circumstances, neurons re-enter the cell cycle essentially to facilitate the recovery from damage caused by the insult. However, the regenerative capacity is limited to specialized neuronal progenitor cells located in the subventricular (SVZ) and subgranular zone of the dentate gyrus in the hippocampal region of the mammalian brain [Fig. 4a].

Nonetheless, if post-mitotic neurons are forced to re-enter the cell cycle, they die even before any sign of DNA synthesis appears (Herrup and Busser, 1995; Herrup, 2004; Marlier et al., 2020 May 31) [Fig. 4b]. This process, traditionally referred to as “abortive cell cycle re-entry,” is characterized by the increased activity of cyclin D-CDK4/6 and deregulation of E2F transcription factors, ultimately followed by cell death (Marlier et al., 2020 May 31). In this regard, E2F1 may act as a trigger of neuronal apoptosis. It has been reported to activate two pro-apoptotic signaling pathways in cerebellar granule cells and cortical neurons, namely, p53-independent activation of Bax/caspase-3 and the induction of the CDK1/FOXO1/Bad pathway (Schmidt-Kastner et al., 2000; Zhang et al., 2020). In addition, p130/E2F4, a repressive complex that maintains neurons’ post-mitotic state, is also deregulated. This dysregulation results in the induction of neuronal apoptosis through the upregulation of B-myb and C-myb (Liu and Greene, 2001). Overall, these observations indicate that different environmental conditions trigger various signaling pathways that can elicit cell cycle reactivation and cell death in specific neuronal phenotypes.

Aberrant induction of the cell cycle in glial cells causes them to activate and proliferate, leading to glial scar formation and the production of inflammatory factors. This microenvironment plays a crucial

role in developing neurodegenerative pathology (Woulfe et al., 2016; Caggiu et al., 2019). However, the forced re-entry of terminally differentiated neurons into the cell cycle leads them to death instead of proliferation (Hernández-Ortega et al., 2011; Frade and Ovejero-Benito, 2015a). Although in specific pathologies, various types of machinery are involved in distinct ways of neuronal demise. The abnormal cell cycle re-entry (CCR) of neurons leading to death may be a common pathway among different neurodegenerative conditions [Fig. 5]. Acute injury to CNS, such as stroke or trauma, is often accompanied by neuronal apoptosis and is usually associated with blockade of G₁/S transition (Wu et al., 2011). Whereas, in chronic circumstances such as neurodegenerative diseases like multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Alzheimer’s disease (AD), and Parkinson’s disease (PD), however, some of the neurons show S-phase markers (Bonda et al., 2009). In such neurons, successful completion of DNA synthesis is depicted by S-phase proteins such as phosphorylated Mcm2, and aneuploidy supports the notion (D. J. Bonda et al., 2010).

3.1. EBV-induced CCR in Alzheimer’s disease

AD is characterized by progressive and irreparable damage inflicted on the neurons, leading to cognitive impairment. According to WHO reports, it is the predominant cause of senile dementia globally, contributing 60–70% of the total cases (Carbone et al., 2014). Between 2020 and 2040, incidents of dementia associated with AD are speculated to increase by more than 300% in South-East Asian countries, including India (Rizzi et al., 2014; Ferri et al., 2005). Though a few key elements in the disease pathology are well-acknowledged, explicit molecular mechanisms leading to the disease pathogenesis are yet to be understood. While not the sole cause of neurodegeneration, amyloid- β (A β) plaques, and neurofibrillary tangles are hallmarks of AD and critical in the disease development [Fig. 5] (Braak et al., 1998; LaFerla and Oddo, 2005). Damage induced by oxidative stress is another crucial facet of neurodegeneration related to AD (Zhang et al., 2014; Kamat et al., 2016; Kang et al., 2017). Additionally, viral infections could be a risk factor for AD susceptibility (Carbone et al., 2014).

Over the past few years, an increasing number of reports have been

against brain infection (Eimer et al., 2018).

Recent studies have revealed a direct and indirect causal link between oxidative stress and cell cycle aberrations (Bresgen et al., 2003; Limoli and Giedzinski, 2003; Taniai et al., 2014). Specifically, a 'two-hit hypothesis' has been suggested to implicate oxidative stress and cell cycle malfunctioning conjointly, resulting in AD neurodegeneration (Zhu et al., 2007; Bonda et al., 2009). The disease pathogenesis, provoked by either of the two elements, advances as a combined process. Oxidative stress, as one factor, destructs neurons to evoke other factors involved in cell cycle dysfunction eventually or *vice-versa*. For instance, in sporadic AD (or late-onset), which is more prevalent, a steady-state of oxidative imbalance has been observed that predisposes the affected neurons to develop cell cycle malfunctions as a 'second hit.' Although neurons can counter the effect of acute oxidative stress, chronic large-scale accumulation of reactive oxygen species will require the cell to adapt and attain a state of oxidative imbalance. While the cell might survive with these adaptations for decades, eventual secondary abnormalities in the cell cycle ultimately result in its death. These two 'hits' finally launch the cell on a deteriorative course of oxidative stress, inflammation, A β aggregation, and mitotic dysfunction, followed by cell death, giving rise to the conditions responsible for disease pathology (Zhu et al., 2007). Based on the above-mentioned studies, it would not be farfetched to claim the association of EBV or HHV infection-mediated oxidative stress as a possible contributor to neurodegeneration in AD.

Besides, some crucial genes implicated in AD pathogenesis may be involved in abnormal CCR of neurons and subsequent neurodegeneration. In particular, three genes, the A β precursor protein (A β PP) gene, Presenilin 1 and 2 (PS-1/2) gene homologs, are linked with early-onset AD and have been reported to play a vital role in the cell cycle and its regulation (Porquet et al., 2015). A β PP, an integral transmembrane protein, undergoes proteolytic cleavage to produce A β peptide. The PS-1/2 genes are responsible for the proteolytic cleavage of A β PP and are hence involved in the regulation of the cell cycle as well as AD pathogenesis (De Strooper et al. 1998, 1999). *In-vitro*, both the protein and the resultant peptide have been shown to possess mitogenic activity (Greenberg et al., 1994).

Apart from their earlier mentioned interaction with A β PP, these homologous genes (PS-1/2) have also been associated with centrosomal assembly in the dividing cell, thus linking mitogenic alterations with neurodegeneration (Judge et al., 2011). For instance, deficiency of PS-1/2 in HeLa cells caused their accelerated transition from G₁ to S phase, while their overexpression resulted in G₁ phase arrest of the cell cycle (Janicki, 2000). Several studies with transgenic mice with A β PP, PS-1, and PS-2 mutations have also demonstrated that neurons exhibit CCR several months before amyloid deposition and full AD pathogenesis (D. J. Bonda et al., 2010). Also, the report suggests that these events occur in an anatomical pattern resembling the progression sequence of neuronal damage susceptibility observed in AD. Interestingly, though these mice show significant CCR as early as 6 months of age, their cognition and cellular functioning are maintained at a near-normal level for extended periods (Zhu et al., 2007). These mutant mice showed a phenotype of 'mitotic steady-state,' which ultimately evoked further abuse in the form of a 'second hit' of oxidative stress. Since the importance of PS-1/2 is well established in the onset of familial AD cases, the possibility of its role as a link between cell cycle aberration and neurodegeneration cannot be overlooked. Additionally, A β PP-binding protein 1 (A β PP-BP1), which binds to the carboxy-terminal domain of the A β PP, is a multifunctional adapter protein that is also implicated in the regulation of mitotic transition from S to M-phase (Chen et al., 2000). Therefore, a neuron overexpressing A β PP-BP1 would be pushed in S-phase, exhibiting DNA replication and expressing the corresponding cell cycle markers Cyclin B/cdc2, ultimately propelling the cell towards apoptosis. As these phenotypes are apparent in AD neurodegeneration, A β PP-BP1 could be partially responsible for CCR.

Further, multiple factors could be responsible for inducing vulnerable neurons into improper re-entry into the cell cycle. According to the

reports, mitogenic signaling induced by viral infections plays a pivotal role. Interestingly, EBV seropositivity has been demonstrated consistently over the decades in patients suffering from AD. However, the role of EBV in the disease remained debatable and underexplored. Several recent studies have provided convincing proof implicating EBV in the etiology of AD. A study done by Gate et al. showed that adaptive immune changes mediated by EBV were involved in AD pathogenesis (Kang and Liu, 2020). They reported the presence of CD8⁺ T effector memory CD45RA⁺ (TEMRA) cells specific for EBV as a part of adaptive immunity in AD patients.

Regardless of the cause, the outcomes of cell cycle dysfunction evident in AD are the same. The aberrant re-entry of already differentiated adult neurons into the cell cycle results in cellular malfunction and premature cell death, ultimately leading to neurodegeneration (Lee et al., 2009). As the cell cycle involves complex interactions of a wide variety of Cyclins and CDKs, which are crucial for cell proliferation and survival, any modulation of their expression, function, or control is likely to affect the cell negatively. Evidence suggests that the inability of neurons to complete the M-phase after the initial mitotic induction ultimately leads the cell to its death (Lombardi and Lasagni, 2016). Although many studies have reported neurons to complete or at least enter into the S-phase (indicated by DNA replication, chromosome maintenance protein expression, and binucleation events), some cells to be in the G₂ phase, and an entrance to M-phase, no study depicted completion of M-phase in the neurons (Currais et al., 2009b; Hardwick and Philpott, 2014; Frade and Ovejero-Benito, 2015b; Sharma et al., 2017; Walton et al., 2019). These neurons appear to experience a "mitotic catastrophe," a phenomenon indicating the inability of the cell to complete the cell cycle due to failure in its regulation. Unfortunately, as these neurons have already passed the mitotic point of no return (i.e., G₁-phase/S-phase), they ultimately succumb to death instead of proliferating.

Therefore, modulations in the cell cycle and its control system may play a crucial role in developing neurodegenerative pathology. Although the definite mechanisms resulting in such mitotic dysfunctions are not entirely understood, various factors seem to play, including oxidative damage, viral infections, etc. A complex and reciprocal relationship between these factors and CCR seems likely in AD. Altogether, these facts indicate that the neurodegenerative pathology in AD might result from cell-cycle modulation mediated by EBV.

3.2. EBV induced CCR in Parkinson's disease

PD is categorized as a progressive neurodegenerative disorder occurring either sporadically or due to hereditary mutations in genes such as parkin, a-synuclein, and ubiquitin C-terminal hydrolase L1 gene (Braak et al., 1998). The pathophysiology of PD is marked by the presence of proteinaceous aggregates known as Lewy bodies (LBs) and pigmentation in dopaminergic neurons of substantia nigra pars compacta (SNpc) [Fig. 4] (Antony et al., 2013). However, the mechanism of pathogenesis leading to neuronal death in PD is still unclear. Previous studies have advocated the role of environmental factors, such as viral infections, that conspire with a permissive genetic background to initiate the neurodegenerative pathology of PD (Jang et al., 2009; Wang et al., 2020). However, the precise identity of these viral infections remains elusive, and the definite mechanism underlying this association remains unclear to date. For instance, in many cases, a direct viral infection of nigral neurons has been demonstrated or implicated in disease pathology, whereas in others, virally induced autoimmune mechanisms are held responsible (Olsen et al., 2019; Pajares et al., 2020).

Specifically, the molecular mimicry exhibited by a repeat region in latent membrane protein 1 (LMP-1) encoded by EBV and the C-terminal region of alpha-synuclein corroborates the statement (Caggu et al., 2019). In genetically predisposed individuals, oligomerization of alpha-synuclein forming aggregates is believed to occur due to its

cross-reactivity with EBV LMP-1 antibodies. These antibodies target a critical repeat region of alpha-synuclein. However, it is believed that EBV infection is essential but not sufficient alone for the development of PD within the average human lifespan. Considerable studies indicate that environmental factors collaborate with the susceptible genetic background to initiate the PD pathology. Together, both factors contribute to disease onset and progression and critical modulation of its temporal profile. In the face of EBV-induced α -syn autoimmunity, the host genetics may govern the immune response (e.g., HLA-DR, LRRK2) against EBV proteins and α -syn aggregation kinetics. The host genes SNCA, PARKIN, DJ-1, and PINK-1, along with factors like oxidative stress respectively, dictate the aggregation propensity, oligomer or aggregate clearance ability of the cell, and its capacity to deal with the consequences of aggregated α -syn, etc. (Caggiu et al., 2019).

Interestingly, cell-cycle dysregulation has also been linked to the development of PD pathophysiology. Several studies with post-mortem tissues of PD patients have reported the presence of p35 and CDK-5 in LBs in the locus coeruleus, neocortex, and substantia nigra (He et al., 2020; Allnut et al., 2020). It suggests that CDK-5 is probably involved in LB formation. There is unquestionable evidence suggesting that proteinaceous aggregates of α -syn are key constituents of LBs that play a central role in PD pathogenesis (Takeda et al., 1998; Olanow and Brundin, 2013). Many studies demonstrated the co-localization of EBV with these protein aggregates (Woulfe et al., 2016). EBV signatures in α -syn aggregates have led scientists to hypothesize that PD is an EBV-induced autoimmune phenomenon. CDK-5 is known to play a crucial role in the cytoarchitecture of the CNS and is thereby indirectly linked to cell-cycle progression. Also, many studies have corroborated the implication of phase-related CDKs in PD neurodegeneration. Markedly, EBV has been repeatedly associated with modulation of Cyclin-CDK complexes, as described in previous sections. For instance, (the association of Cyclin E with EBV) Cyclin E, a CDK-2 activator, acts as a substrate of the parkin ubiquitin ligase complex, whose association is reported with familial forms of PD [Fig. 4] (Staropoli et al., 2003). Overexpression of parkin has been shown to rescue primary midbrain dopaminergic neurons from kainic acid (a neuro-excitotoxin)-induced death by reducing Cyclin E buildup in the cell. In the dopaminergic neurons of the substantia nigra of post-mortem PD brain tissue, ample cytoplasmic pRb, E2F-1, and PCNA immunostaining along with DNA duplication were also observed [Fig. 4] (Braak et al., 1998; Frade and Ovejero-Benito, 2015a).

Apart from human brain tissue samples, *in-vivo* and *in-vitro* models have been developed using neurotoxins like 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) and are used to study the disease pathophysiology (Schober, 2004). These models reproduce a subset of PD features and are majorly used to study the disease. In one such study done by Neystat et al. on 6-OHDA-treated rats, activation of CDK-5 and its concomitant increase along with p35 expression levels were detected in the nigral neurons. These nigral neurons were observed to be in the late morphological state of apoptosis (Neystat et al., 2001). Furthermore, another report suggested an increase in the expression of CDK-5 after MPTP administration. Dominant-negative CDK-5 or inhibition of CDK-5 activity by general CDK inhibitors have shown beneficial effects in curtailing disease progression (Binukumar et al., 2015). The data thus far available indicate an imperative role of CDK-5 as a mediator in the pathogenesis of PD.

Additionally, immunohistochemical examination of primary rat midbrain neuron cultures treated with MPTP also displayed unusual cell cycle protein expression in the G₁-M phase transition. The observed phenotype also corroborated with the data obtained from human studies. The dopaminergic neurons of rat SNpc displayed markers signifying entry of neurons in the S and G₂ phase after 6-OHDA administration (Schober, 2004). Strategies targeting the G₁ phase, such as flavopiridol-mediated inhibition of CDK-4 and E2F knockout, have shown neuroprotective effects against PD pathology in *in-vivo* and *in-vitro* studies (Verdaguer et al., 2005).

Altogether, these observations suggest that dopaminergic neurons post mitosis subvert the G₁/S checkpoint and re-enter the cell cycle in PD but get arrested at the M-phase. Perhaps, the miscarried cell cycle is the process that leads the neurons towards apoptosis and eventual neurodegeneration in PD.

4. Outlook: how is EBV supposedly driving neurons' cell cycle re-entry (CCR) and leading to degeneration?

Various studies have linked the neurodegenerative pathology of AD, PD, and other disorders with Herpesviral infections (De Chiara et al., 2012; Hogestyn et al., 2018; Costa Sa et al. 2019b). However, the precise mechanisms by which these viruses exert their deteriorative effect on the nervous system are still elusive. Although these viruses are well known to modulate cell cycle events [Fig. 6] for their benefit, as discussed above, and dysregulation of the cell cycle is reported to be an early event in neurodegeneration; no such study exists linking them to the two. This review has discussed some poorly understood, intensely debated, and underexplored avenues of virus-mediated neurodegeneration. Additionally, we propose a possible mechanism of EBV-mediated cell cycle dysregulation in causing neurodegeneration.

Various factors that might act as a trigger are reported to initiate the cell cycle in terminally differentiated neurons. A trending hypothesis states the implication of viral infections in the etiology of neurodegeneration via modulating the cell cycle. First, EBV has been shown to associate with neurodegenerative diseases. Second, EBV, a well-known oncogenic virus, is reported to manipulate the cell cycle at various stages of protein-protein interaction, protein redistribution, or molecular mimicry, as mentioned above in detail. Interestingly, these steps are also crucial in developing neurodegenerative pathology. For instance, pRb, a protein responsible for guarding the G₁ to S transition, is known to be modulated by EBV and is also associated with PD pathology. Moreover, in addition to the direct interaction of EBV with the effector molecules, it might be acting by creating favorable conditions for cell cycle progression. EBV could also instigate cell cycle progression via ectopic and untimely accumulation of various CDKs and other modulators. These facts suggest a strong association between neurodegeneration and EBV-mediated cell-cycle dysregulation. Further studies in this direction could provide a tangible causative link between the two and help us establish the precise role of EBV in aggravating neurodegenerative pathology.

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Data availability

Data sharing does not apply to this article as no data set was generated during the current study.

CRediT authorship contribution statement

Deeksha Tiwari: conceived the manuscript under the guidance of, Writing – original draft, review & editing, All authors have read and approved the final manuscript. **Nitish Mittal:** The final draft was prepared with the help of, Writing – review & editing, All authors have read and approved the final manuscript. **Hem Chandra Jha:** conceived the manuscript under the guidance of, Writing – review & editing, All authors have read and approved the final manuscript.

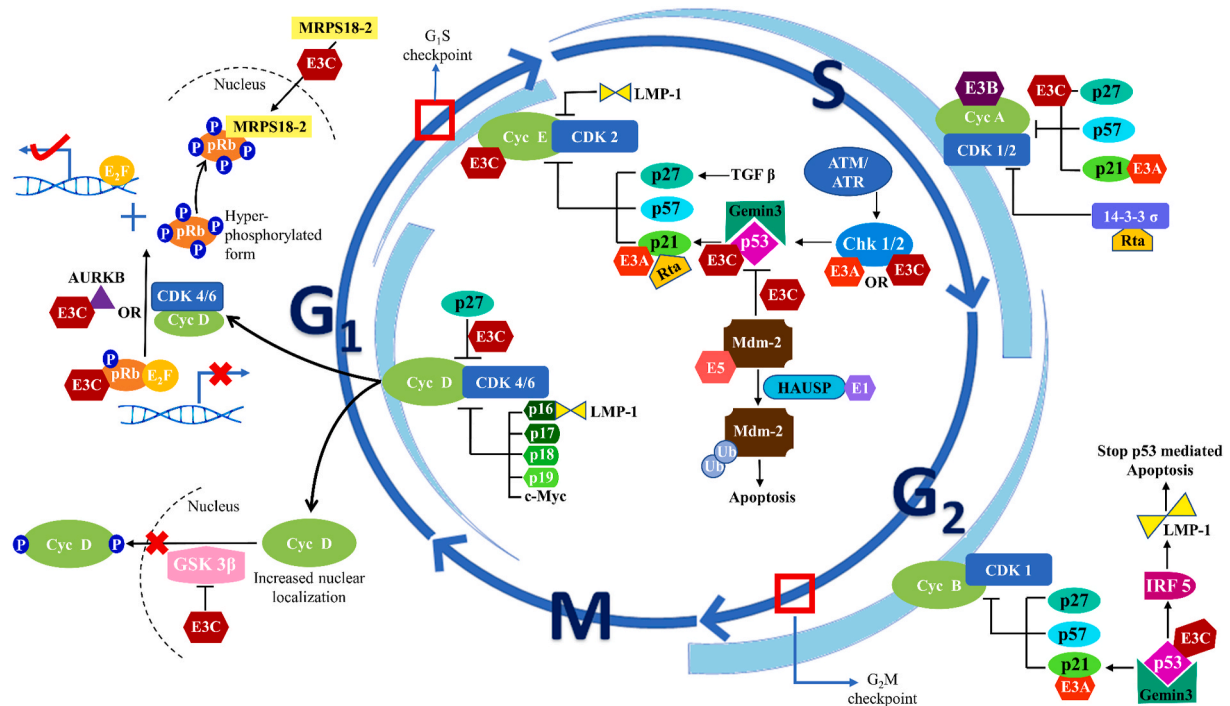


Fig. 6. Epstein-Barr virus antigens deregulate the cell cycle. Epstein-Barr virus (EBV) associated nuclear antigens (EBNA) – 1, 2, 3A, 3B, 3C, 5 (LP), LMPs, and Rta modulate the cell cycle at various stages. In brief, at the early G1 stage of the cell cycle, E3C and LMP-1 hinder the activity of p27 and p16, respectively, to block their inhibitory effect on the Cyclin D/CDK-4/6 complex. E3C also inhibits the cytoplasmic translocation of GSK-3 β to prevent Cyclin D phosphorylation. In addition, E3C modulates the E2F-mediated transcription by interacting with pRb and AURKB; E3C also mediates the nuclear translocation of mitochondrial protein MRPS18-2 to facilitate its binding with pRb and thereby regulating the level of free E2F. During the late G1 phase, the formation of the Cyclin E/CDK-2 complex is affected by the binding of LMP-1 and E3C. Further, the p21^{WAF1/CIP1} mediated inhibition of the Cyclin E/CDK-2 complex is obstructed by the binding of E3A and Rta antigens of EBV. Interaction of E3C with other host molecules such as p53 or Chk1/2 also affects cell cycle progression from G1 to the S phase. Along with E3, other EBV antigens such as E5 and E1 also modulate the Mdm-2-mediated apoptosis pathway in the late G1 phase of the cell cycle. E5 is reported to directly interact with Mdm-2, while E1 binds with HAUSP to promote ubiquitination of the Mdm-2 molecule, leading to its degradation and thereby modulating the host cell cycle. Progressing to the S phase of the cell cycle, EBV antigen E3B is reported to directly bind Cyclin A, while E3C and E3A curb the inhibitory effect of p27 and p21^{WAF1/CIP1} respectively towards Cyclin A/CDK-1/2 complex. Rta binding to 14-3-3 σ enhances its expression and thereby sequesters the activity of the Cyclin A/CDK-1/2 complex. During the G2 phase of the cell cycle, E3A binding to p21^{WAF1/CIP1} obstructs its blocking activity towards the Cyclin A/CDK-1 complex. Furthermore, the binding of E3C to the p53-gemin3 complex leads to IRF-5-mediated upregulation of LMP-1 expression that causes p53-mediated apoptosis to stop.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Peer Review Overview and Supplementary data

A Peer Review Overview and (sometimes) Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.crneur.2022.100046>

References

- Abe, T., Tohgi, H., Isobe, C., Murata, T., Sato, C., 2002. Remarkable increase in the concentration of 8-hydroxyguanosine in cerebrospinal fluid from patients with Alzheimer's disease. *J. Neurosci. Res.* 70 (3), 447–450. <https://doi.org/10.1002/jnr.10349>, 2020 Oct 12. <http://doi.wiley.com/10.1002/jnr.10349>.
- Allnutt, A.B., Waters, A.K., Kesari, S., Yenugonda, V.M., 2020. Physiological and pathological roles of Cdk5: potential directions for therapeutic targeting in neurodegenerative disease. *ACS Chem. Neurosci.* 11 (9), 1218–1230. <https://doi.org/10.1021/acschemneuro.0c00096>, 2020 Oct 12]. <https://pubs.acs.org/doi/10.1021/acschemneuro.0c00096>.

- Anda, F.C. de, Madabhushi, R., Rei, D., Meng, J., Gräff, J., Durak, O., Meletis, K., Richter, M., Schwanke, B., Mungenast, A., et al., 2016. Cortical neurons gradually attain a post-mitotic state. *Cell Res.* 26 (9), 1033–1047. <https://doi.org/10.1038/cr.2016.76>, 2020 Oct 9]. <http://www.nature.com/articles/cr201676>.
- Antony, P.M.A., Diederich, N.J., Krüger, R., Balling, R., 2013. The hallmarks of Parkinson's disease. *FEBS J.* 280 (23), 5981–5993. <https://doi.org/10.1111/febs.12335>, 2020 Oct 12. <http://doi.wiley.com/10.1111/febs.12335>.
- Arendt, T., 2012. Cell cycle activation and aneuploid neurons in Alzheimer's disease. *Mol. Neurobiol.* 46 (1), 125–135. <https://doi.org/10.1007/s12035-012-8262-0>, 2020 Oct 12]. <http://link.springer.com/10.1007/s12035-012-8262-0>.
- Aulia, S., Tang, B.L., 2006. Cdh1-APC/C, cyclin B-Cdc2, and Alzheimer's disease pathology. *Biochem. Biophys. Res. Commun.* 339 (1), 1–6. <https://doi.org/10.1016/j.bbrc.2005.10.059>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0006291X05023260>.
- Baldin, V., Lukas, J., Marcote, M.J., Pagano, M., Draetta, G., 1993. Cyclin D1 is a nuclear protein required for cell cycle progression in G1. *Genes Dev.* 7 (5), 812–821. <https://doi.org/10.1101/gad.7.5.812>, 2020 Oct 12]. <http://www.genesdev.org/cgi/doi/10.1101/gad.7.5.812>.
- Banerjee, S., Lu, J., Cai, Q., Saha, A., Jha, H.C., Dzung, R.K., Robertson, E.S., 2013. The EBV latent antigen 3C inhibits apoptosis through targeted regulation of interferon regulatory factors 4 and 8. *Raaf-traub N. PLoS Pathog.* 9 (5), e1003314 <https://doi.org/10.1371/journal.ppat.1003314>, 2020 Oct 9]. <https://dx.plos.org/10.1371/journal.ppat.1003314>.
- Barrio-Alonso, E., Hernández-Vivanco, A., Walton, C.C., Perea, G., Frade, J.M., 2018a. Cell cycle reentry triggers hyperploidy and synaptic dysfunction followed by delayed cell death in differentiated cortical neurons. *Sci. Rep.* 8 (1), 14316 <https://doi.org/10.1038/s41598-018-32708-4>, 2022 Apr 6]. <http://www.nature.com/articles/s41598-018-32708-4>.
- Barrio-Alonso, E., Hernández-Vivanco, A., Walton, C.C., Perea, G., Frade, J.M., 2018b. Cell cycle reentry triggers hyperploidy and synaptic dysfunction followed by delayed cell death in differentiated cortical neurons. *Sci. Rep.* 8 (1), 14316 <https://doi.org/10.1038/s41598-018-32708-4>, 2020 Oct 9]. <http://www.nature.com/articles/s41598-018-32708-4>.

- Bartek, J., Bartkova, J., Lukas, J., 1996. The retinoblastoma protein pathway and the restriction point. *Curr. Opin. Cell Biol.* 8 (6), 805–814. [https://doi.org/10.1016/S0955-0674\(96\)80081-0](https://doi.org/10.1016/S0955-0674(96)80081-0), 2020 Oct 9]. <https://linkinghub.elsevier.com/retrieve/pii/S0955067496800810>.
- Beijersbergen, R.L., Carlee, L., Kerkhoven, R.M., Bernards, R., 1995. Regulation of the retinoblastoma protein-related p107 by G1 cyclin complexes. *Genes Dev.* 9 (11), 1340–1353. <https://doi.org/10.1101/gad.9.11.1340>, 2020 Oct 11]. <http://www.genesdev.org/cgi/doi/10.1101/gad.9.11.1340>.
- Binukumar, Bk, Shukla, V., Amin, N.D., Grant, P., Bhaskar, M., Skuntz, S., Steiner, J., Pant, H.C., 2015. Peptide TFP5/TP5 derived from Cdk5 activator P35 provides neuroprotection in the MPTP model of Parkinson's disease. *Forsch. P. Mol. Biol. Cell* 26 (24), 4478–4491. <https://doi.org/10.1091/mbc.E15-06-0415>, 020 Oct 12]. <https://www.molbiolcell.org/doi/10.1091/mbc.E15-06-0415>.
- Biström, M., Jons, D., Engdahl, E., Gustafsson, R., Huang, J., Brenner, N., Butt, J., Alonso-Magdalena, L., Gunnarsson, M., Vrethem, M., et al., 2021. Epstein-Barr virus infection after adolescence and human herpesvirus 6A as risk factors for multiple sclerosis. *Eur. J. Neurol.* 28 (2), 579–586. <https://doi.org/10.1111/ene.14597>, 2021 Mar 26]. <https://onlinelibrary.wiley.com/doi/10.1111/ene.14597>.
- Bonda David, J., Hyun-pil, Lee, Kudo, W., Zhu, X., Smith, M.A., Lee, Hyoung-gon, 2010. Pathological implications of cell cycle re-entry in Alzheimer disease. *Exp. Rev. Mol. Med.* 12, e19. <https://doi.org/10.1017/S146239941000150X>, 2022 Apr 6]. <https://www.cambridge.org/core/product/identifier/S146239941000150X/type/journal-article>.
- Bonda, D.J., Evans, T.A., Santocanale, C., Llosá, J.C., Viña, J., Bajic, V.P., Castellani, R.J., Siedlak, S.L., Perry, G., Smith, M.A., et al., 2009. Evidence for the progression through S-phase in the ectopic cell cycle re-entry of neurons in Alzheimer disease. *Aging* 1 (4), 382–388. <https://doi.org/10.18632/aging.100044>, 2020 Oct 12]. <https://www.aging-us.com/lookup/doi/10.18632/aging.100044>.
- Bonda, D.J., Bajic, V.P., Spremo-Potparevic, B., Casadesu, G., Zhu, X., Smith, M.A., Lee, H.-G., 2010. Review: cell cycle aberrations and neurodegeneration. *Neuropathol. Appl. Neurobiol.* 36 (2), 157–163. <https://doi.org/10.1111/j.1365-2990.2010.01064.x>, 2020 Oct 9]. <http://doi.wiley.com/10.1111/j.1365-2990.2010.01064.x>.
- Braak, H., Vos, RAI de, Jansen, E.N.H., Bratzke, H., Braak, E., 1998. Chapter 20 Neuropathological hallmarks of Alzheimer's and Parkinson's diseases. In: *Progress in Brain Research*, 117. Elsevier, pp. 267–285, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0079612308640212>.
- Bresgen, N., Karlhuber, G., Krizbai, I., Bauer, H., Bauer, H.C., Eckl, P.M., 2003. Oxidative stress in cultured cerebral endothelial cells induces chromosomal aberrations, micronuclei, and apoptosis. *J. Neurosci. Res.* 72 (3), 327–333. <https://doi.org/10.1002/jnr.10582>, 2020 Oct 12]. <http://doi.wiley.com/10.1002/jnr.10582>.
- Broughton, K.M., Sussman, M.A., 2019. Adult cardiomyocyte cell cycle detour: off-ramp to quiescent destinations. *Trends Endocrinol. Metabol.* 30 (8), 557–567. <https://doi.org/10.1016/j.tem.2019.05.006>, 2020 Oct 9]. <https://linkinghub.elsevier.com/retrieve/pii/S1043276019301055>.
- Bu, X.-L., Wang, X., Xiang, Y., Shen, L.-L., Wang, Q.-H., Liu, Y.-H., Jiao, S.-S., Wang, Y.-R., Cao, H.-Y., Yi, X., et al., 2015. The association between infectious burden and Parkinson's disease: a case-control study. *Park. Relat. Disord.* 21 (8), 877–881. <https://doi.org/10.1016/j.parkrel.2015.05.015>, 2022 Mar 30]. <https://linkinghub.elsevier.com/retrieve/pii/S1353802015002333>.
- Caggiu, E., Arru, G., Hosseini, S., Niegowska, M., Sechi, G., Zarbo, I.R., Sechi, L.A., 2019. Inflammation, infectious triggers, and Parkinson's disease. *Front. Neurol.* 10, 122. <https://doi.org/10.3389/fneur.2019.00122>, 2020 Oct 12]. <https://www.frontiersin.org/article/10.3389/fneur.2019.00122/full>.
- Carbone, I., Lazzarotto, T., Ianni, M., Porcellini, E., Forti, P., Masliah, E., Gabrielli, L., Licastro, F., 2014. Herpes virus in Alzheimer's disease: relation to progression of the disease. *Neurobiol. Aging* 35 (1), 122–129. <https://doi.org/10.1016/j.neurobiolaging.2013.06.024>, 2020 Oct 9]. <https://linkinghub.elsevier.com/retrieve/pii/S0197458013002856>.
- Cheignon, C., Tomas, M., Bonnefont-Rousselot, D., Faller, P., Hureau, C., Collin, F., 2018. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. *Redox Biol.* 14, 450–464. <https://doi.org/10.1016/j.redox.2017.10.014>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S2213231717307267>.
- Chen, Y., McPhie, D.L., Hirschberg, J., Neve, R.L., 2000. The amyloid precursor protein-binding protein APP-BP1 drives the cell cycle through the S-M checkpoint and causes apoptosis in neurons. *J. Biol. Chem.* 275 (12), 8929–8935. <https://doi.org/10.1074/jbc.275.12.8929>, 2020 Oct 12]. <http://www.jbc.org/lookup/doi/10.1074/jbc.275.12.8929>.
- Chiaretti, A., Capozzi, D., Mariotti, P., Valentini, P., Manni, L., Buonsenso, D., Fantacci, C., Ferrara, P., 2014. Increased levels of neurotrophins in the cerebrospinal fluid of children with Epstein-Barr virus meningoencephalitis. *Int. J. Infect. Dis.* 20, 52–57. <https://doi.org/10.1016/j.ijid.2013.11.006>, 2022 Apr 6]. <https://linkinghub.elsevier.com/retrieve/pii/S1201971213003597>.
- Choudhuri, T., Verma, S.C., Lan, K., Murakami, M., Robertson, E.S., 2007. The ATM/ATR signaling effector Chk2 is targeted by Epstein-Barr Virus Nuclear Antigen 3C to release the G₂/M cell cycle block. *J. Virol.* 81 (12), 6718–6730. <https://doi.org/10.1128/JVI.00053-07>.
- Costa, Sa AC, Madsen, H., Brown, J.R., 2019a. Shared molecular signatures across neurodegenerative diseases and herpes virus infections highlights potential mechanisms for maladaptive innate immune responses. *Sci. Rep.* 9 (1), 8795. <https://doi.org/10.1038/s41598-019-45129-8>, 2022 Apr 8]. <http://www.nature.com/articles/s41598-019-45129-8>.
- Costa, Sa AC, Madsen, H., Brown, J.R., 2019b. Shared molecular signatures across neurodegenerative diseases and herpes virus infections highlights potential mechanisms for maladaptive innate immune responses. *Sci. Rep.* 9 (1), 8795. <https://doi.org/10.1038/s41598-019-45129-8>, 2020 Oct 12]. <http://www.nature.com/articles/s41598-019-45129-8>.
- Currais, A., Hortobágyi, T., Soriano, S., 2009a. The neuronal cell cycle as a mechanism of pathogenesis in Alzheimer's disease. *Aging* 1 (4), 363–371. <https://doi.org/10.18632/aging.100045>, 2020 Oct 12]. <https://www.aging-us.com/lookup/doi/10.18632/aging.100045>.
- Currais, A., Hortobágyi, T., Soriano, S., 2009b. The neuronal cell cycle as a mechanism of pathogenesis in Alzheimer's disease. *Aging* 1 (4), 363–371. <https://doi.org/10.18632/aging.100045>, 2021 May 1]. <https://www.aging-us.com/lookup/doi/10.18632/aging.100045>.
- Dar, A., Wu, D., Lee, N., Shibata, E., Dutta, A., 2014. 14-3-3 proteins play a role in the cell cycle by shielding Cdt2 from ubiquitin-mediated degradation. *Mol. Cell Biol.* 34 (21), 4049–4061. <https://doi.org/10.1128/MCB.00838-14>, 2021 Mar 26]. <http://mc.asm.org/cgi/doi/10.1128/MCB.00838-14>.
- Dawson, C.W., Port, R.J., Young, L.S., 2012. The role of the EBV-encoded latent membrane proteins LMP1 and LMP2 in the pathogenesis of nasopharyngeal carcinoma (NPC). *Semin. Cancer Biol.* 22 (2), 144–153. <https://doi.org/10.1016/j.semcancer.2012.01.004>, 2020 Oct 11]. <https://linkinghub.elsevier.com/retrieve/pii/S1044579X12000065>.
- De Chiara, G., Marocci, M.E., Sgarbanti, R., Civitelli, L., Ripoli, C., Piacentini, R., Garaci, E., Grassi, C., Palamara, A.T., 2012. Infectious agents and neurodegeneration. *Mol. Neurobiol.* 46 (3), 614–638. <https://doi.org/10.1007/s12035-012-8320-7>, 2021 May 1]. <http://link.springer.com/10.1007/s12035-012-8320-7>.
- De Strooper, B., Saftig, P., Craessaerts, K., Vanderstichele, H., Guhde, G., Annaert, W., Von Figura, K., Van Leuven, F., 1998. Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein. *Nature* 391 (6665), 387–390. <https://doi.org/10.1038/34910>, 2020 Oct 12]. <http://www.nature.com/articles/34910>.
- De Strooper, B., Annaert, W., Cupers, P., Saftig, P., Craessaerts, K., Mumm, J.S., Schroeter, E.H., Schrijvers, V., Wolfe, M.S., Ray, W.J., et al., 1999. A presenilin-1-dependent γ-secretase-like protease mediates release of Notch intracellular domain. *Nature* 398 (6727), 518–522. <https://doi.org/10.1038/19083>, 2020 Oct 12]. <http://www.nature.com/articles/19083>.
- Diehl, J.A., Cheng, M., Roussel, M.F., Sherr, C.J., 1998. Glycogen synthase kinase-3beta regulates cyclin D1 proteolysis and subcellular localization. *Genes Dev.* 12 (22), 3499–3511. <https://doi.org/10.1101/gad.12.22.3499>, 2020 Oct 12]. <http://www.genesdev.org/cgi/doi/10.1101/gad.12.22.3499>.
- Dowdy, S.F., Hinds, P.W., Louie, K., Reed, S.I., Arnold, A., Weinberg, R.A., 1993. Physical interaction of the retinoblastoma protein with human D cyclins. *Cell* 73 (3), 499–511. [https://doi.org/10.1016/0092-8674\(93\)90137-F](https://doi.org/10.1016/0092-8674(93)90137-F), 2020 Oct 11]. <https://linkinghub.elsevier.com/retrieve/pii/009286749390137F>.
- Eimer, W.A., Vijaya Kumar, D.K., Navalpur Shanmugam, N.K., Rodriguez, A.S., Mitchell, T., Washicosky, K.J., György, B., Breakfield, X.O., Tanzi, R.E., Moir, R.D., 2018. Alzheimer's disease-associated β-amyloid is rapidly seeded by Herpesviridae to protect against brain infection. *e3 Neuron* 99 (1), 56–63. <https://doi.org/10.1016/j.neuron.2018.06.030>, 2022 Apr 8]. <https://linkinghub.elsevier.com/retrieve/pii/S0896627318305269>.
- Epstein, M.A., Achong, B.G., Barr, Y.M., 1964. Virus particles in cultured lymphoblasts from BURKITT'S lymphoma. *Lancet* 283 (7335), 702–703. [https://doi.org/10.1016/S0140-6736\(64\)91524-7](https://doi.org/10.1016/S0140-6736(64)91524-7), 2022 May 25]. <https://linkinghub.elsevier.com/retrieve/pii/S0140673664915247>.
- Fan, Y., Sanyal, S., Bruzzone, R., 2018. Breaking bad: how viruses subvert the cell cycle. *Front. Cell. Infect. Microbiol.* 8, 396. <https://doi.org/10.3389/fcimb.2018.00396>, 2020 Oct 9]. <https://www.frontiersin.org/article/10.3389/fcimb.2018.00396/full>.
- Ferri, C.P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., Hall, K., Hasegawa, K., Hendrie, H., Huang, Y., et al., 2005. Global prevalence of dementia: a Delphi consensus study. *Lancet* 366 (9503), 2112–2117. [https://doi.org/10.1016/S0140-6736\(05\)67889-0](https://doi.org/10.1016/S0140-6736(05)67889-0), 2022 May 29]. <https://linkinghub.elsevier.com/retrieve/pii/S0140673605678890>.
- Frade, J.M., Ovejero-Benito, M.C., 2015a. Neuronal cell cycle: the neuron itself and its circumstances. *Cell Cycle* 14 (5), 712–720. <https://doi.org/10.1080/15384101.2015.1004937>, 2020 Oct 9]. <https://www.tandfonline.com/doi/full/10.1080/15384101.2015.1004937>.
- Frade, J.M., Ovejero-Benito, M.C., 2015b. Neuronal cell cycle: the neuron itself and its circumstances. *Cell Cycle* 14 (5), 712–720. <https://doi.org/10.1080/15384101.2015.1004937>, 2021 May 1]. <https://www.tandfonline.com/doi/full/10.1080/15384101.2015.1004937>.
- Gate, D., Saligrama, N., Leventhal, O., Yang, A.C., Unger, M.S., Middeldorp, J., Chen, K., Lehallier, B., Channappa, D., De Los Santos, M.B., et al., 2020. Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease. *Nature* 577 (7790), 399–404. <https://doi.org/10.1038/s41586-019-1895-7>, 2021 Apr 24]. <http://www.nature.com/articles/s41586-019-1895-7>.
- Greenberg, S.M., Koo, E.H., Selkoe, D.J., Qiu, W.Q., Kosik, K.S., 1994. Secreted beta-amyloid precursor protein stimulates mitogen-activated protein kinase and enhances tau phosphorylation. *Proc. Natl. Acad. Sci. USA* 91 (15), 7104–7108. <https://doi.org/10.1073/pnas.91.15.7104>, 2020 Oct 12]. <http://www.pnas.org/cgi/doi/10.1073/pnas.91.15.7104>.
- Guo, L., Tang, M., Yang, L., Xiao, L., Bode, A.M., Li, L., Dong, Z., Cao, Y., 2012. Epstein-Barr virus oncoprotein LMP1 mediates survivin upregulation by p53 contributing to G1/S cell cycle progression in nasopharyngeal carcinoma. *Int. J. Mol. Med.* 29 (4), 574–580. <https://doi.org/10.3892/ijmm.2012.889>, 2022 Apr 5]. <https://www.spandidos-publications.com/10.3892/ijmm.2012.889>.
- Gupta, S., Ylä-Anttila, P., Sandalova, T., Achour, A., Masucci, M.G., 2020. Interaction with 14-3-3 correlates with inactivation of the RIG-I signalosome by herpesvirus ubiquitin deconjugases. *Front. Immunol.* 11, 437. <https://doi.org/10.3389/fimm.2020.00437>.

- immu.2020.00437, 2021 Mar 26]. <https://www.frontiersin.org/article/10.3389/fimmu.2020.00437/full>.
- Hardwick, L.J.A., Philpott, A., 2014. Nervous decision-making: to divide or differentiate. *Trends Genet.* 30 (6), 254–261. <https://doi.org/10.1016/j.tig.2014.04.001>, 2021 May 1]. <https://linkinghub.elsevier.com/retrieve/pii/S0168952514000559>.
- Hartwell, L., Weinert, T., 1989. Checkpoints: controls that ensure the order of cell cycle events. *Science* 246 (4930), 629–634. <https://doi.org/10.1126/science.2683079>, 2020 Oct 9]. <https://www.sciencemag.org/lookup/doi/10.1126/science.2683079>.
- He, F., Qi, G., Zhang, Qian, Cai, H., Li, T., Li, M., Zhang, Qiaofeng, Chen, J., Ming, J., Tian, B., et al., 2020. Quantitative phosphoproteomic analysis in alpha-synuclein transgenic mice reveals the involvement of aberrant p25/cdk5 signaling in early-stage Parkinson's disease. *Cell. Mol. Neurobiol.* 40 (6), 897–909. <https://doi.org/10.1007/s10571-019-00780-7>, 2020 Oct 12]. <http://link.springer.com/10.1007/s10571-019-00780-7>.
- Heine, V.M., Maslam, S., Joëls, M., Lucassen, P.J., 2004. Increased P27KIP1 protein expression in the dentate gyrus of chronically stressed rats indicates G1 arrest involvement. *Neuroscience* 129 (3), 593–601. <https://doi.org/10.1016/j.neuroscience.2004.07.048>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S030645220400658X>.
- Hernández-Ortega, K., Quiroz-Baez, R., Arias, C., 2011. Cell cycle reactivation in mature neurons: a link with brain plasticity, neuronal injury and neurodegenerative diseases? *Neurosci. Bull.* 27 (3), 185–196. <https://doi.org/10.1007/s12264-011-1002-z>, 2020 Oct 12]. <http://link.springer.com/10.1007/s12264-011-1002-z>.
- Herrup, K., 2004. Divide and die: cell cycle events as triggers of nerve cell death. *J. Neurosci.* 24 (42), 9232–9239. <https://doi.org/10.1523/JNEUROSCI.3347-04.2004>, 2020 Oct 9]. <http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.3347-04.2004>.
- Herrup, K., Buser, J.C., 1995. The induction of multiple cell cycle events precedes target-related neuronal death. *Dev Camb Engl* 121 (8), 2385–2395.
- Herrup, K., Yang, Y., 2007. Cell cycle regulation in the postmitotic neuron: oxymoron or new biology? *Nat. Rev. Neurosci.* 8 (5), 368–378. <https://doi.org/10.1038/nrn2124>, 2020 Oct 9]. <http://www.nature.com/articles/nrn2124>.
- Hogestyn, J., Mock, D., Mayer-Proschel, M., 2018. Contributions of neurotropic human herpesviruses herpes simplex virus 1 and human herpesvirus 6 to neurodegenerative disease pathology. *Neural. Regen. Res.* 13 (2), 211. <https://doi.org/10.4103/1673-5374.226380>, 2021 May 1]. <http://www.nrronline.org/text.asp?2018/13/2/211/226380>.
- Houck, A.L., Seddighi, S., Driver, J.A., 2019. At the crossroads between neurodegeneration and cancer: a review of overlapping biology and its implications. *Curr. Aging Sci.* 11 (2), 77–89. <https://doi.org/10.2174/1874609811666180223154436>, 2020 Oct 9]. <http://www.eurekaselect.com/160074/article>.
- Hu, G., Barnes, B.J., 2009. IRF-5 is a mediator of the death receptor-induced apoptotic signaling pathway. *J. Biol. Chem.* 284 (5), 2767–2777. <https://doi.org/10.1074/jbc.M804744200>, 2021 May 3]. <https://linkinghub.elsevier.com/retrieve/pii/S0021925819818409>.
- Huang, S.-Y., Hsieh, M.-J., Chen, C.-Y., Chen, Y.-J., Chen, J.-Y., Chen, M.-R., Tsai, C.-H., Lin, S.-F., Hsu, T.-Y., 2012. Epstein-Barr virus Rta-mediated transactivation of p21 and 14-3-3 σ arrests cells at the G1/S transition by reducing cyclin E/CDK2 activity. *J. Gen. Virol.* 93 (1), 139–149. <https://doi.org/10.1099/vir.0.034405-0>, 2020 Oct 9]. <https://www.microbiologyresearch.org/content/journal/jgv/10.1099/vir.0.034405-0>.
- Indari, O., Chandramohanadas, R., Jha, H.C., 2021. Epstein-Barr virus infection modulates blood-brain barrier cells and its co-infection with *Plasmodium falciparum* induces RBC adhesion. *ftaa080 Pathog. Dis.* 79 (1). <https://doi.org/10.1093/fempdp/ftaa080> [accessed 2021 Mar 26]. <https://academic.oup.com/fempdp/article/doi/10.1093/fempdp/ftaa080/6405510>.
- Jakhmola, S., Jha, H.C., 2021. Glial cell response to Epstein-Barr Virus infection: a plausible contribution to virus-associated inflammatory reactions in the brain. *Virology* 559, 182–195. <https://doi.org/10.1016/j.virol.2021.04.005>, 2021 Jun 30]. <https://linkinghub.elsevier.com/retrieve/pii/S0042682221000969>.
- Jang, H., Boltz, D.A., Webster, R.G., Smeyne, R.J., 2009. Viral parkinsonism. *Biochim Biophys Acta BBA - Mol. Basis Dis.* 1792 (7), 714–721. <https://doi.org/10.1016/j.bbadis.2008.08.001>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0925443908001567>.
- Janicki, S., 2000. Familial Alzheimer's disease presenilin-1 mutants potentiate cell cycle arrest. *Neurobiol. Aging* 21 (6), 829–836. [https://doi.org/10.1016/S0197-4580\(00\)00222-0](https://doi.org/10.1016/S0197-4580(00)00222-0), 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S019745800002220>.
- Jha, H.C., Lu, J., Saha, A., Cai, Q., Banerjee, S., Prasad, M.A.J., Robertson, E.S., 2013. EBNA3C-Mediated regulation of aurora kinase B contributes to Epstein-Barr virus-induced B-cell proliferation through modulation of the activities of the retinoblastoma protein and apoptotic caspases. *J. Virol.* 87 (22), 12121–12138. <https://doi.org/10.1128/JVI.02379-13>, 2020 Oct 12]. <https://jvi.asm.org/content/87/22/12121>.
- Jha, H.C., Mehta, D., Lu, J., El-Naccache, D., Shukla, S.K., Kovacsics, C., Kolson, D., Robertson, E.S., 2015. Gammaherpesvirus infection of human neuronal cells. In: Nemerow, G. (Ed.), *mBio* 6 (6). <https://doi.org/10.1128/mBio.01844-15>, 2021 Dec 30]. <https://journals.asm.org/doi/10.1128/mBio.01844-15>.
- Judge, M., Hornbeck, L., Potter, H., Padmanabhan, J., 2011. Mitosis-specific phosphorylation of amyloid precursor protein at Threonine 668 leads to its altered processing and association with centrosomes. *Mol. Neurodegener.* 6 (1), 80. <https://doi.org/10.1186/1750-1326-6-80>, 2020 Oct 12]. <http://moleculareurodegeneracion.biomedcentral.com/articles/10.1186/1750-1326-6-80>.
- Kamat, P.K., Kalani, A., Rai, S., Swarnkar, S., Tota, S., Nath, C., Tyagi, N., 2016. Mechanism of oxidative stress and synaptic dysfunction in the pathogenesis of Alzheimer's disease: understanding the therapeutics strategies. *Mol. Neurobiol.* 53 (1), 648–661. <https://doi.org/10.1007/s12035-014-9053-6>, 2021 Mar 26]. <http://link.springer.com/10.1007/s12035-014-9053-6>.
- Kang, J.-S., Liu, P.-P., 2020. Human herpesvirus 4 and adaptive immunity in Alzheimer's disease. *Signal Transduct. Targeted Ther.* 5 (1), 48. <https://doi.org/10.1038/s41392-020-0125-y>, 2020 Oct 9]. <http://www.nature.com/articles/s41392-020-0125-y>.
- Kang, S.-W., Kim, S.J., Kim, M.-S., 2017. Oxidative stress with tau hyperphosphorylation in memory impaired 1,2-diacetylbenzene-treated mice. *Toxicol. Lett.* 279, 53–59. <https://doi.org/10.1016/j.toxlet.2017.07.892>, 2021 Mar 26]. <https://linkinghub.elsevier.com/retrieve/pii/S0378427417311384>.
- Kashuba, E., Yurchenko, M., Yenamandra, S.P., Snopok, B., Szekely, L., Bercovich, B., Ciechanover, A., Klein, G., 2011. Epstein-Barr virus-encoded EBNA-5 forms trimolecular protein complexes with MDM2 and p53 and inhibits the transactivating function of p53. *Int. J. Cancer* 128 (4), 817–825. <https://doi.org/10.1002/ijc.25414>, 2020 Oct 11]. <https://doi.wiley.com/10.1002/ijc.25414>.
- Klein, J.A., Ackerman, S.L., 2003. Oxidative stress, cell cycle, and neurodegeneration. *J. Clin. Invest.* 111 (6), 785–793. <https://doi.org/10.1172/JCI200318182>, 2021 Mar 26]. <http://www.jci.org/articles/view/18182>.
- Kleines, M., Schiefer, J., Stienen, A., Blaum, M., Ritter, K., Häusler, M., 2011. Expanding the spectrum of neurological disease associated with Epstein-Barr virus activity. *Eur. J. Clin. Microbiol. Infect. Dis.* 30 (12), 1561–1569. <https://doi.org/10.1007/s10096-011-1261-7>, 2020 Oct 12]. <http://link.springer.com/10.1007/s10096-011-1261-7>.
- Knight, J.S., Robertson, E.S., 2004. Epstein-Barr virus nuclear antigen 3C regulates cyclin A/p27 complexes and enhances cyclin A-dependent kinase activity. *J. Virol.* 78 (4), 1981–1991. <https://doi.org/10.1128/JVI.78.4.1981-1991.2004>, 2020 Oct 11]. <https://jvi.asm.org/content/78/4/1981>.
- Knight, J.S., Sharma, N., Kalman, D.E., Robertson, E.S., 2004. A cyclin-binding motif within the amino-terminal homology domain of EBNA3C binds cyclin A and modulates cyclin A-dependent kinase activity in Epstein-Barr virus-infected cells. *J. Virol.* 78 (23), 12857–12867. <https://doi.org/10.1128/JVI.78.23.12857-12867.2004>, 2020 Oct 11]. <https://jvi.asm.org/content/78/23/12857>.
- Knight, J.S., Sharma, N., Robertson, E.S., 2005. Epstein-Barr virus latent antigen 3C can mediate the degradation of the retinoblastoma protein through an SCF cellular ubiquitin ligase. *Proc. Natl. Acad. Sci. USA* 102 (51), 18562–18566. <https://doi.org/10.1073/pnas.0503886102>, 2020 Oct 12]. <http://www.pnas.org/cgi/doi/10.1073/pnas.0503886102>.
- Knight Jason, S., Sharma, N., Robertson, E.S., 2005. SCF β complex targeted by Epstein-Barr virus essential nuclear antigen. *Mol. Cell Biol.* 25 (5), 1749–1763. <https://doi.org/10.1128/MCB.25.5.1749-1763.2005>, 2021 Mar 26]. <https://mcb.asm.org/content/25/5/1749>.
- Koeller, H.B., Ross, M.E., Glickstein, S.B., 2008. Cyclin D1 in excitatory neurons of the adult brain enhances kainate-induced neurotoxicity. *Neurobiol. Dis.* 31 (2), 230–241. <https://doi.org/10.1016/j.nbd.2008.04.010>, 2020 Oct 9]. <https://linkinghub.elsevier.com/retrieve/pii/S0969996108000867>.
- Kozko, V.M., Sokhan, A.V., Yal, Burma, 2018. ДІАГНОСТИЧНЕ ЗНАЧЕННЯ НЕЙРОСПЕЦИФІЧНИХ МАРКЕРІВ NSE, S-100, GFAP, МВР І BDNF У ЦЕРЕБРОСПІНАЛЬНІЙ РІДИНІ ХВОРОБИ НА ВІРУСНИЙ МЕНІНГІТ. Інфекційні Хвороби (2) <https://doi.org/10.11603/1681-2727.2018.2.9025>, 2022 Apr 6]. <https://ojs.tdmu.edu.ua/index.php/inf-patol/article/view/9025>.
- Kruman II, Wersto, R.P., Cardozo-Pelaez, F., Smilenov, L., Chan, S.L., Chrest, F.J., Emokpa, R., Gorospe, M., Mattson, M.P., 2004. Cell cycle activation linked to neuronal cell death initiated by DNA damage. *Neuron* 41 (4), 549–561. [https://doi.org/10.1016/S0896-6273\(04\)00117-0](https://doi.org/10.1016/S0896-6273(04)00117-0), 2020 Oct 9]. <https://linkinghub.elsevier.com/retrieve/pii/S0896627304000170>.
- Lacoste, S., Wiechec, E., dos Santos Silva, A.G., Guffei, A., Williams, G., Lowbeer, M., Benedek, K., Henriksson, M., Klein, G., Mai, S., 2010. Chromosomal rearrangements after ex vivo Epstein-Barr virus (EBV) infection of human B cells. *Oncogene* 29 (4), 503–515. <https://doi.org/10.1038/ncr.2009.359>, 2022 Apr 8]. <https://www.nature.com/articles/ncr2009359>.
- LaFerla, F.M., Oddo, S., 2005. Alzheimer's disease: β , tau and synaptic dysfunction. *Trends Mol. Med.* 11 (4), 170–176. <https://doi.org/10.1016/j.molmed.2005.02.009>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S1471491405000511>.
- Lee, H., Zhu, X., Nunomura, A., Perry, G., Smith, M., 2006. Amyloid beta: the alternate hypothesis. *Curr. Alzheimer Res.* 3 (1), 75–80. <https://doi.org/10.2174/156720506775697124>, 2020 Oct 12]. <http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1567-2050&volume=3&issue=1&page=75>.
- Lee, C.-P., Chen, J.-Y., Wang, J.-T., Kimura, K., Takemoto, A., Lu, C.-C., Chen, M.-R., 2007. Epstein-Barr virus BGLF4 kinase induces premature chromosome condensation through activation of condensin and topoisomerase II. *J. Virol.* 81 (10), 5166–5180. <https://doi.org/10.1128/JVI.00120-07>, 2022 Apr 8]. <https://journals.asm.org/doi/10.1128/JVI.00120-07>.
- Lee, H., Casadesu, G., Zhu, X., Castellani, R.J., McShea, A., Perry, G., Petersen, R.B., Bajic, V., Smith, M.A., 2009. Cell cycle re-entry mediated neurodegeneration and its treatment role in the pathogenesis of Alzheimer's disease. *Neurochem. Int.* 54 (2), 84–88. <https://doi.org/10.1016/j.neuint.2008.10.013>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0197186808002039>.
- Limoli, C.L., Giedzinski, E., 2003. Induction of chromosomal instability by chronic oxidative stress. *Neoplasia* 5 (4), 339–346. [https://doi.org/10.1016/S1476-5586\(03\)80027-1](https://doi.org/10.1016/S1476-5586(03)80027-1), 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S1476558603800271>.
- Liu, D.X., Greene, L.A., 2001. Regulation of neuronal survival and death by E2F-dependent gene repression and depression. *Neuron* 32 (3), 425–438. [https://doi.org/10.1016/S0896-6273\(01\)00495-0](https://doi.org/10.1016/S0896-6273(01)00495-0), 2020 Oct 9]. <https://linkinghub.elsevier.com/retrieve/pii/S0896627301004950>.

- Lombardi, D., Lasagni, L., 2016. Cell-cycle alterations in post-mitotic cells and cell death by mitotic catastrophe. In: Najman, S. (Ed.), *Cell Biology - New Insights*. InTech, 2020 Oct 12. <http://www.intechopen.com/books/cell-biology-new-insights/cell-cycle-alterations-in-post-mitotic-cells-and-cell-death-by-mitotic-catastrophe>.
- Lopes, J.P., Oliveira, C.R., Agostinho, P., 2009. Cdk5 acts as a mediator of neuronal cell cycle re-entry triggered by amyloid- β and prion peptides. *Cell Cycle* 8 (1), 97–104. <https://doi.org/10.4161/cc.8.1.7506>, 2020 Oct 9]. <http://www.tandfonline.com/doi/abs/10.4161/cc.8.1.7506>.
- Marlier, Q., D'aes, T., Verteneuil, S., Vandenbosch, R., Malgrange, B., 2020 May 31. Core cell cycle machinery is crucially involved in both life and death of post-mitotic neurons. *Cell. Mol. Life Sci.* <https://doi.org/10.1007/s00018-020-03548-1>, 2020 Oct 9]. <http://link.springer.com/10.1007/s00018-020-03548-1>.
- Maruo, S., Wu, Y., Ishikawa, S., Kanda, T., Iwakiri, D., Takada, K., 2006. Epstein-Barr virus nuclear protein EBNA3C is required for cell cycle progression and growth maintenance of lymphoblastoid cells. *Proc. Natl. Acad. Sci. USA* 103 (51), 19500–19505. <https://doi.org/10.1073/pnas.0604919104>, 2020 Oct 12]. <http://www.pnas.org/cgi/doi/10.1073/pnas.0604919104>.
- Mausier, Amy, Holley-Guthrie, E., Simpson, D., Kaufmann, W., Kenney, S., 2002. The Epstein-Barr virus immediate-early protein BZLF1 induces both a G₂ and a mitotic block. *J. Virol.* 76 (19), 10030–10037. <https://doi.org/10.1128/JVI.76.19.10030-10037.2002>.
- McShea, A., Harris, P.L., Webster, K.R., Wahl, A.F., Smith, M.A., 1997. Abnormal expression of the cell cycle regulators P16 and CDK4 in Alzheimer's disease. *Am. J. Pathol.* 150 (6), 1933–1939.
- Menet, A., Speth, C., Larcher, C., Proding, W.M., Schwendinger, M.G., Chan, P., Jäger, M., Schwarzmann, F., Recheis, H., Fontaine, M., et al., 1999. Epstein-barr virus infection of human astrocyte cell lines. *J. Virol.* 73 (9), 7722–7733. <https://doi.org/10.1128/JVI.73.9.7722-7733.1999>, 2022 Apr 6]. <https://journals.asm.org/doi/10.1128/JVI.73.9.7722-7733.1999>.
- Nagy, Z., Esiri, M.M., Cato, A.-M., Smith, A.D., 1997. Cell cycle markers in the hippocampus in Alzheimer's disease. *Acta Neuropathol.* 94 (1), 6–15. <https://doi.org/10.1007/s004010050665>, 2020 Oct 12]. <http://link.springer.com/10.1007/s004010050665>.
- Neystat, M., Rzhetskaya, M., Oo, T.F., Kholodilov, N., Yarygina, O., Wilson, A., El-Khodori, B.F., Burke, R.E., 2001. Expression of cyclin-dependent kinase 5 and its activator p35 in models of induced apoptotic death in neurons of the substantia nigra in vivo: cdk5 and p35 in SN neuron apoptosis in vivo. *J. Neurochem.* 77 (6), 1611–1625. <https://doi.org/10.1046/j.1471-4159.2001.00376.x>, 2020 Oct 12]. <http://doi.wiley.com/10.1046/j.1471-4159.2001.00376.x>.
- Ng, Y.-K., Wong, E.Y.L., Lau, C.P.Y., Chan, J.P.L., Wong, S.C.C., Chan, A.S.-K., Kwan, M. P.C., Tsao, S.-W., Tsang, C.-M., Lai, P.B.S., et al., 2012. K252a induces anoikis-sensitization with suppression of cellular migration in Epstein-Barr virus (EBV)—associated nasopharyngeal carcinoma cells. *Invest. N. Drugs* 30 (1), 48–58. <https://doi.org/10.1007/s10637-010-9513-4>, 2022 Apr 6]. <http://link.springer.com/10.1007/s10637-010-9513-4>.
- Niedobitek, G., Meru, N., Delecluse, H.J., 2001. Epstein-Barr virus infection and human malignancies. *Int. J. Exp. Pathol.* 82 (3), 149–170. <https://doi.org/10.1046/j.1365-2613.2001.iep0082-0149-x>.
- Ohtani, N., Brennan, P., Gaubatz, S., Sanji, E., Hertzog, P., Wolvetang, E., Ghysdael, J., Rowe, M., Hara, E., 2003. Epstein-Barr virus LMP1 blocks p16INK4a-RB pathway by promoting nuclear export of E2F4/5. *J. Cell Biol.* 162 (2), 173–183. <https://doi.org/10.1083/jcb.200302085>, 2020 Oct 11]. <https://rupress.org/jcb/article/162/2/173/33557/Epstein-Barr-virus-LMP1-blocks-p16INK4aRB-pathway>.
- Olanow, C.W., Brundin, P., 2013. Parkinson's disease and alpha synuclein: is Parkinson's disease a prion-like disorder? PD, alpha synuclein, and prion disorders. *Mov. Disord.* 28 (1), 31–40. <https://doi.org/10.1002/mds.25373>, 2020 Oct 12]. <http://doi.wiley.com/10.1002/mds.25373>.
- Olsen, L.K., Cairns, A.G., Ådén, J., Moriarty, N., Cabre, S., Alamilla, V.R., Almqvist, F., Dowd, E., McKernan, D.P., 2019. Viral mimetic priming enhances α -synuclein-induced degeneration: implications for Parkinson's disease. *Brain Behav. Immun.* 80, 525–535. <https://doi.org/10.1016/j.bbi.2019.04.036>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S088915118307682>.
- Pajares, M., Rojo A, I., Manda, G., Boscá, L., Cuadrado, A., 2020. Inflammation in Parkinson's disease: mechanisms and therapeutic implications. *Cells* 9 (7), 1687. <https://doi.org/10.3390/cells9071687>, 2020 Oct 12]. <https://www.mdpi.com/2073-4409/9/7/1687>.
- Pardee, A.B., 1974. A restriction point for control of normal animal cell proliferation. *Proc. Natl. Acad. Sci. USA* 71 (4), 1286–1290. <https://doi.org/10.1073/pnas.71.4.1286>, 2020 Oct 9]. <http://www.pnas.org/cgi/doi/10.1073/pnas.71.4.1286>.
- Pei, Y., Banerjee, S., Sun, Z., Jha, H.C., Saha, A., Robertson, E.S., 2016. EBV nuclear antigen 3C mediates regulation of E2F6 to inhibit E2F1 transcription and promote cell proliferation. *Flemington EK. PLoS Pathog.* 12 (8), e1005844. <https://doi.org/10.1371/journal.ppat.1005844>, 2020 Oct 12]. <https://dx.plos.org/10.1371/journal.ppat.1005844>.
- Pei, Y., Singh, R.K., Shukla, S.K., Lang, F., Zhang, S., Robertson, E.S., 2018. Epstein-barr virus nuclear antigen 3C facilitates cell proliferation by regulating cyclin D2. *Longnecker RM. e00663-18, jvi/92/18/e00663-18.atom J. Virol.* 92 (18). <https://doi.org/10.1128/JVI.00663-18>, 2020 Oct 9]. <https://jvi.asm.org/content/92/18/e00663-18>.
- Phuna, Z.X., Madhavan, P., 2022 Mar 14. A reappraisal on amyloid cascade hypothesis: the role of chronic infection in Alzheimer's disease. *Int. J. Neurosci.* 1–19. <https://doi.org/10.1080/00207454.2022.2045290>, 2022 Apr 8]. <https://www.tandfonline.com/doi/full/10.1080/00207454.2022.2045290>.
- Porquet, D., Andrés-Benito, P., Griñán-Ferré, C., Camins, A., Ferrer, I., Canudas, A.M., Del Valle, J., Pallás, M., 2015. Amyloid and tau pathology of familial Alzheimer's disease APP/PS1 mouse model in a senescence phenotype background (SAMP8). *AGE* 37 (1), 12. <https://doi.org/10.1007/s11357-015-9747-3>, 2020 Oct 12]. <http://link.springer.com/10.1007/s11357-015-9747-3>.
- Reisinger, J., Rumpfer, S., Lion, T., Ambros, P.F., 2006. Visualization of episomal and integrated Epstein-Barr virus DNA by fiber fluorescence in situ hybridization. *Int. J. Cancer* 118 (7), 1603–1608. <https://doi.org/10.1002/ijc.21498>, 2021 May 1. <http://doi.wiley.com/10.1002/ijc.21498>.
- Rizzi, L., Rosset, I., Roriz-Cruz, M., 2014. Global epidemiology of dementia: Alzheimer's and vascular types. *BioMed Res. Int.* 1–8. <https://doi.org/10.1155/2014/908915>, 2022 May 29]. <http://www.hindawi.com/journals/bmri/2014/908915/>.
- Roberts, M.L., Cooper, N.R., 1998. Activation of a ras-MAPK-dependent pathway by Epstein-Barr virus latent membrane protein 1 is essential for cellular transformation. *Virology* 240 (1), 93–99. <https://doi.org/10.1006/viro.1997.8901>, 2022 Apr 8]. <http://linkinghub.elsevier.com/retrieve/pii/S0042682297989017>.
- Saha, A., Robertson, E.S., 2013. Impact of EBV essential nuclear protein EBNA-3C on B-cell proliferation and apoptosis. *Future Microbiol.* 8 (3), 323–352. <https://doi.org/10.2217/fmb.12.147>, 2020 Oct 9]. <https://www.futuremedicine.com/doi/10.2217/fmb.12.147>.
- Saha, A., Murakami, M., Kumar, P., Bajaj, B., Sims, K., Robertson, E.S., 2009. Epstein-barr virus nuclear antigen 3C augments mdm2-mediated p53 ubiquitination and degradation by deubiquitinating Mdm2. *J. Virol.* 83 (9), 4652–4669. <https://doi.org/10.1128/JVI.02408-08>, 2020 Oct 12]. <https://jvi.asm.org/content/83/9/4652>.
- Saha, A., Halder, S., Upadhyay, S.K., Lu, J., Kumar, P., Murakami, M., Cai, Q., Robertson, E.S., 2011. Epstein-barr virus nuclear antigen 3C facilitates G1-S transition by stabilizing and enhancing the function of cyclin D1. *Damania B. PLoS Pathog.* 7 (2), e1001275. <https://doi.org/10.1371/journal.ppat.1001275>, 2020 Oct 11]. <https://dx.plos.org/10.1371/journal.ppat.1001275>.
- Satyanarayana, A., Kaldis, P., 2009. Mammalian cell-cycle regulation: several Cdk, numerous cyclins and diverse compensatory mechanisms. *Oncogene* 28 (33), 2925–2939. <https://doi.org/10.1038/ncr.2009.170>, 2020 Oct 9]. <http://www.nature.com/articles/ncr2009170>.
- Scheff, S.W., Ansari, M.A., Mufson, E.J., 2016. Oxidative stress and hippocampal synaptic protein levels in elderly cognitively intact individuals with Alzheimer's disease pathology. *Neurobiol. Aging* 42, 1–12. <https://doi.org/10.1016/j.neurobiolaging.2016.02.030>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0197458016001962>.
- Schmidt-Kastner, R., Truettner, J., Zhao, W., Belayev, L., Krieger, C., Busto, R., Ginsberg, M.D., 2000. Differential changes of bax, caspase-3 and p21 mRNA expression after transient focal brain ischemia in the rat. *Mol. Brain Res.* 79 (1–2), 88–101. [https://doi.org/10.1016/S0169-328X\(00\)0104-2](https://doi.org/10.1016/S0169-328X(00)0104-2), 2020 Oct 9]. <https://linkinghub.elsevier.com/retrieve/pii/S0169328X000001042>.
- Schober, A., 2004. Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP. *Cell Tissue Res.* 318 (1), 215–224. <https://doi.org/10.1007/s00441-004-0938-y>, 2020 Oct 12]. <http://link.springer.com/10.1007/s00441-004-0938-y>.
- Seo, J., Park, M., 2020. Molecular crosstalk between cancer and neurodegenerative diseases. *Cell. Mol. Life Sci.* 77 (14), 2659–2680. <https://doi.org/10.1007/s00018-019-03428-3>, 2020 Oct 9]. <http://link.springer.com/10.1007/s00018-019-03428-3>.
- Shannon-Lowe, C.D., Neuhierl, B., Baldwin, G., Rickinson, A.B., Delecluse, H.-J., 2006. Resting B cells as a transfer vehicle for Epstein-Barr virus infection of epithelial cells. *Proc. Natl. Acad. Sci. USA* 103 (18), 7065–7070. <https://doi.org/10.1073/pnas.0510512103>, 2022 Apr 7]. <https://pnas.org/doi/full/10.1073/pnas.0510512103>.
- Sharma, R., Kumar, D., Jha, N.K., Jha, S.K., Ambasta, R.K., Kumar, P., 2017. Re-expression of cell cycle markers in aged neurons and muscles: whether cells should divide or die? *Biochim. Biophys. Acta BBA - Mol. Basis Dis.* 1863 (1), 324–336. <https://doi.org/10.1016/j.bbadis.2016.09.010>, 2021 May 1]. <https://linkinghub.elsevier.com/retrieve/pii/S0925443916302289>.
- Shim, S.-M., Cheon, H.-S., Jo, C., Koh, Y.H., Song, J., Jeon, J.-P., 2016. Elevated Epstein-barr virus antibody level is associated with cognitive decline in the Korean elderly. *J. Alzheimers Dis.* 55 (1), 293–301. <https://doi.org/10.3233/JAD-160563>, 2022 Mar 25]. <https://www.medra.org/aliasResolver?alias=iospress&doi=10.3233/JAD-160563>.
- Shumilov, A., Tsai, M.-H., Schlosser, Y.T., Kratz, A.-S., Bernhardt, K., Fink, S., Mizani, T., Lin, X., Jauch, A., Mautner, J., et al., 2017. Epstein-Barr virus particles induce centrosome amplification and chromosomal instability. *Nat. Commun.* 8 (1), 14257. <https://doi.org/10.1038/ncomms14257>, 2022 Apr 8]. <http://www.nature.com/articles/ncomms14257>.
- Smith, M.A., Rottkamp, C.A., Nunomura, A., Raina, A.K., Perry, G., 2000. Oxidative stress in Alzheimer's disease. *Biochim Biophys Acta BBA - Mol. Basis Dis.* 1502 (1), 139–144. [https://doi.org/10.1016/S0925-4439\(00\)00040-5](https://doi.org/10.1016/S0925-4439(00)00040-5), 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0925443900000405>.
- Sonkar, C., Verma, T., Chatterji, D., Jain, A.K., Jha, H.C., 2020. Status of kinases in Epstein-Barr virus and Helicobacter pylori Coinfection in gastric Cancer cells. *BMC Cancer* 20 (1), 925. <https://doi.org/10.1186/s12885-020-07377-0>, 2021 Mar 26]. <https://bmccancer.biomedcentral.com/articles/10.1186/s12885-020-07377-0>.
- Spremo-Potparević, B., Živković, L., Djelić, N., Plečaš-Solarović, B., Smith, M.A., Bajić, V., 2008. Premature centromere division of the X chromosome in neurons in Alzheimer's disease. *J. Neurochem.* 106 (5), 2218–2223. <https://doi.org/10.1111/j.1471-4159.2008.05555.x>, 2020 Oct 12]. <http://doi.wiley.com/10.1111/j.1471-4159.2008.05555.x>.
- Staropoli, J.F., McDermott, C., Martinat, C., Schulman, B., Demireva, E., Abielovitch, A., 2003. Parkin is a component of an SCF-like ubiquitin ligase complex and protects postmitotic neurons from kainate excitotoxicity. *Neuron* 37 (5), 735–749. [https://doi.org/10.1016/S0896-6273\(03\)00084-9](https://doi.org/10.1016/S0896-6273(03)00084-9), 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0896627303000849>.

- Suryadinata, R., Sadowski, M., Sarcevic, B., 2010. Control of cell cycle progression by phosphorylation of cyclin-dependent kinase (CDK) substrates. *Biosci. Rep.* 30 (4), 243–255. <https://doi.org/10.1042/BSR20090171>, 2020 Oct 10]. <https://portlandpress.com/bioscirep/article/30/4/243/55834/Control-of-cell-cycle-progression-by>
- Szekely, L., Selivanova, G., Magnusson, K.P., Klein, G., Wiman, K.G., 1993. EBNA-5, an Epstein-Barr virus-encoded nuclear antigen, binds to the retinoblastoma and p53 proteins. *Proc. Natl. Acad. Sci. USA* 90 (12), 5455–5459. <https://doi.org/10.1073/pnas.90.12.5455>, 2020 Oct 11]. <http://www.pnas.org/cgi/doi/10.1073/pnas.90.12.5455>.
- Takeda, A., Mallory, M., Sundsmo, M., Honer, W., Hansen, L., Masliah, E., 1998. Abnormal accumulation of NACP/alpha-synuclein in neurodegenerative disorders. *Am. J. Pathol.* 152 (2), 367–372.
- Tan, M., Wang, S., Song, J., Jia, J., 2012. Combination of p53(ser15) and p21/p21 (thr145) in peripheral blood lymphocytes as potential Alzheimer's disease biomarkers. *Neurosci. Lett.* 516 (2), 226–231. <https://doi.org/10.1016/j.neulet.2012.03.093>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0304394012004910>.
- Taniai, E., Yafune, A., Nakajima, M., Hayashi, S.-M., Nakane, F., Itahashi, M., Shibutani, M., 2014. Ochratoxin A induces karyomegaly and cell cycle aberrations in renal tubular cells without relation to induction of oxidative stress responses in rats. *Toxicol. Lett.* 224 (1), 64–72. <https://doi.org/10.1016/j.toxlet.2013.10.001>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S037842741301343X>.
- Tao, Y., Song, X., Deng, X., Xie, D., Lee, L.M., Liu, Y., Li, W., Li, L., Deng, L., Wu, Q., et al., 2005. Nuclear accumulation of epidermal growth factor receptor and acceleration of G1/S stage by Epstein-Barr-encoded oncoprotein latent membrane protein 1. *Exp. Cell Res.* 303 (2), 240–251. <https://doi.org/10.1016/j.yexcr.2004.09.030>, 2020 Oct 11]. <https://linkinghub.elsevier.com/retrieve/pii/S0014482704005725>.
- Tarn, W.-Y., Lai, M.-C., 2011. Translational control of cyclins. *Cell Div.* 6 (1), 5. <https://doi.org/10.1186/1747-1028-6-5>, 2020 Oct 9]. <http://celldiv.biomedcentral.com/articles/10.1186/1747-1028-6-5>.
- Tavakolian, S., Goudarzi, H., Faghiloo, E., 2020. Cyclin-dependent kinases and CDK inhibitors in virus-associated cancers. *Infect. Agents Cancer* 15 (1), 27. <https://doi.org/10.1186/s13027-020-00295-7>, 2022 Apr 5]. <https://infectedagentscancer.biomedcentral.com/articles/10.1186/s13027-020-00295-7>.
- Thakur, A., Siedlak, S.L., James, S.L., Bonda, D.J., Rao, A., Webber, K.M., Camins, A., Pallás, M., Casadesu, G., Lee, H.-G., et al., 2008. Retinoblastoma protein phosphorylation at multiple sites is associated with neurofibrillary pathology in Alzheimer disease. *Int. J. Clin. Exp. Pathol.* 1 (2), 134–146.
- Thathiah, A., De Strooper, B., 2011. The role of G protein-coupled receptors in the pathology of Alzheimer's disease. *Nat. Rev. Neurosci.* 12 (2), 73–87. <https://doi.org/10.1038/nrn2977>, 2020 Oct 12]. <http://www.nature.com/articles/nrn2977>.
- Tiwari, D., Jakhmola, S., Pathak, D.K., Kumar, R., Jha, H.C., 2020. Temporal *in vitro* Raman spectroscopy for monitoring replication kinetics of Epstein-Barr virus infection in glial cells. *ACS Omega* 5 (45), 29547–29560. <https://doi.org/10.1021/acsomega.0c04525>, 2021 Jun 30]. <https://pubs.acs.org/doi/10.1021/acsomega.0c04525>.
- Tursiella, M.L., Bowman, E.R., Wanzeck, K.C., Throm, R.E., Liao, J., Zhu, J., Sample, C. E., 2014. Epstein-Barr virus nuclear antigen 3A promotes cellular proliferation by repression of the cyclin-dependent kinase inhibitor p21WAF1/CIP1. *Flemington EK. PLoS Pathog.* 10 (10), e1004415 <https://doi.org/10.1371/journal.ppat.1004415>, 2020 Oct 9]. <https://dx.plos.org/10.1371/journal.ppat.1004415>.
- Uddin, MdS., Kabir, MdT., 2019. Oxidative stress in Alzheimer's disease: molecular hallmarks of underlying vulnerability. In: Ashraf, G.M., Alexiou, A. (Eds.), *Biological, Diagnostic and Therapeutic Advances in Alzheimer's Disease*. Springer Singapore, Singapore, pp. 91–115, 2020 Oct 12]. http://link.springer.com/10.1007/978-981-13-9636-6_5.
- Ueberham, U., 2003. Cyclin C expression is involved in the pathogenesis of Alzheimer's disease. *Neurobiol. Aging* 24 (3), 427–435. [https://doi.org/10.1016/S0197-4580\(02\)00132-X](https://doi.org/10.1016/S0197-4580(02)00132-X), 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S019745800200132X>.
- Ueberham, U., Arendt, T., 2005. The expression of cell cycle proteins in neurons and its relevance for Alzheimers disease. *Curr. Drug Targets - CNS Neurol. Disord.* 4 (3), 293–306. <https://doi.org/10.2174/1568007054038175>, 2020 Oct 12]. <http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1568-007X&volume=4&issue=3&page=293>.
- van Leeuwen, L.A.G., Hoozemans, J.J.M., 2015. Physiological and pathophysiological functions of cell cycle proteins in post-mitotic neurons: implications for Alzheimer's disease. *Acta Neuropathol.* 129 (4), 511–525. <https://doi.org/10.1007/s00401-015-1382-7>, 2020 Oct 12]. <http://link.springer.com/10.1007/s00401-015-1382-7>.
- Verdaguer, E., Jordà, E.G., Alvira, D., Jiménez, A., Canudas, A.M., Folch, J., Rimbau, V., Pallás, M., Camins, A., 2005. Inhibition of multiple pathways accounts for the antiapoptotic effects of flavopiridol on potassium withdrawal-induced apoptosis in neurons. *071-084 J. Mol. Neurosci.* 26 (1). <https://doi.org/10.1385/JMN:26:1:071>, 2020 Oct 12]. <http://link.springer.com/10.1385/JMN:26:1:071>.
- Walton, C.C., Zhang, W., Patiño-Parrado, I., Barrio-Alonso, E., Garrido, J.-J., Frade, J.M., 2019. Primary neurons can enter M-phase. *Sci. Rep.* 9 (1), 4594. <https://doi.org/10.1038/s41598-019-40462-4>, 2021 May 11]. <http://www.nature.com/articles/s41598-019-40462-4>.
- Wang, Y.J., Naderi, Soheil, Tung-Ti, J., 2001. Role of retinoblastoma tumor suppressor protein in DNA damage response. *Acta Oncol.* 40 (6), 689–695. <https://doi.org/10.1080/02841860152619098>, 2020 Oct 11]. <http://www.tandfonline.com/doi/full/10.1080/02841860152619098>.
- Wang, W., Bu, B., Xie, M., Zhang, M., Yu, Z., Tao, D., 2009. Neural cell cycle dysregulation and central nervous system diseases. *Prog. Neurobiol.* 89 (1), 1–17. <https://doi.org/10.1016/j.pneurobio.2009.01.007>, 2020 Oct 9]. <https://linkinghub.elsevier.com/retrieve/pii/S0301008209000203>.
- Wang, Q., Lingel, A., Geiser, V., Kwapnoski, Z., Zhang, L., 2017. Tumor suppressor p53 stimulates the expression of Epstein-Barr virus latent membrane protein 1, 20: e00312-e00317. In: Longnecker, R.M. (Ed.), *J Virol*, 91, pp. e00312–e00317. <https://doi.org/10.1128/JVI.00312-17>, 2020 Oct 12]. <https://JVI.asm.org/lookup/doi/10.1128/JVI.00312-17>.
- Wang, H., Liu, X., Tan, C., Zhou, W., Jiang, J., Peng, W., Zhou, X., Mo, L., Chen, L., 2020. Bacterial, viral, and fungal infection-related risk of Parkinson's disease: meta-analysis of cohort and case-control studies. *Brain Behav.* 10 (3) <https://doi.org/10.1002/brb3.1549>, 2020 Oct 12]. <https://onlinelibrary.wiley.com/doi/abs/10.1002/brb3.1549>.
- Woulfe, J., Gray, M.T., Ganesh, M.S., Middeldorp, J.M., 2016. Human serum antibodies against EBV latent membrane protein 1 cross-react with alpha-synuclein. *Neurol - Neuroimmunol. Neuroinflammation.* 3 (4), e239. <https://doi.org/10.1212/NXI.000000000000239>, 2020 Oct 12]. <http://nn.neurology.org/lookup/doi/10.1212/NXI.000000000000239>.
- Wright, J.W., Harding, J.W., 2010. The brain RAS and Alzheimer's disease. *Exp. Neurol.* 223 (2), 326–333. <https://doi.org/10.1016/j.expneurol.2009.09.012>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0014488609003860>.
- Wu, J., Stoica, B.A., Faden, A.L., 2011. Cell cycle activation and spinal cord injury. *Neurotherapeutics* 8 (2), 221–228. <https://doi.org/10.1007/s13311-011-0028-2>, 2020 Oct 12]. <http://link.springer.com/10.1007/s13311-011-0028-2>.
- Xu, Y., Shi, Y., Yuan, Q., Liu, X., Yan, B., Chen, L., Tao, Y., Cao, Y., 2013. Epstein-Barr Virus encoded LMP1 regulates cyclin D1 promoter activity by nuclear EGFR and STAT3 in CNE1 cells. *J. Exp. Clin. Cancer Res.* 32 (1), 90. <https://doi.org/10.1186/1756-9966-32-90>, 2020 Oct 11]. <http://jccr.biomedcentral.com/articles/10.1186/1756-9966-32-90>.
- Yang, Y., Gao, F., 2020. Clinical characteristics of primary and reactivated Epstein-Barr virus infection in children. *J. Med. Virol.* 92 (12), 3709–3716. <https://doi.org/10.1002/jmv.26202>, 2022 Feb 25]. <https://onlinelibrary.wiley.com/doi/10.1002/jmv.26202>.
- Yang, X., He, Z., Xin, B., Cao, L., 2000. LMP1 of Epstein-Barr virus suppresses cellular senescence associated with the inhibition of p16INK4a expression. *Oncogene* 19 (16), 2002–2013. <https://doi.org/10.1038/sj.onc.1203515>, 2020 Oct 11]. <http://www.nature.com/articles/1203515>.
- Yang, Y., Mufson, E.J., Herrup, K., 2003. Neuronal cell death is preceded by cell cycle events at all stages of Alzheimer's disease. *J. Neurosci.* 23 (7), 2557–2563. <https://doi.org/10.1523/JNEUROSCI.23-07-02557.2003>, 2020 Oct 12]. <http://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.23-07-02557.2003>.
- Yi, F., Saha, A., Murakami, M., Kumar, P., Knight, J.S., Cai, Q., Choudhuri, T., Robertson, E.S., 2009. Epstein-Barr virus nuclear antigen 3C targets p53 and modulates its transcriptional and apoptotic activities. *Virology* 388 (2), 236–247. <https://doi.org/10.1016/j.virol.2009.03.027>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0042682209002062>.
- Yin, H., Qu, J., Peng, Q., Gan, R., 2019. Molecular mechanisms of EBV-driven cell cycle progression and oncogenesis. *Med. Microbiol. Immunol.* 208 (5), 573–583. <https://doi.org/10.1007/s00430-018-0570-1>, 2020 Oct 9]. <http://link.springer.com/10.1007/s00430-018-0570-1>.
- Zacny, V.L., Wilson, J., Pagano, J.S., 1998. The Epstein-Barr virus immediate-early gene product, BRLF1, interacts with the retinoblastoma protein during the viral lytic cycle. *J. Virol.* 72 (10), 8043–8051. <https://doi.org/10.1128/JVI.72.10.8043-8051.1998>.
- Zhang, X., Wu, M., Lu, F., Luo, N., He, Z.-P., Yang, H., 2014. Involvement of alpha7 nAChR signaling cascade in epigallocatechin gallate suppression of beta-amyloid-induced apoptotic cortical neuronal insults. *Mol. Neurobiol.* 49 (1), 66–77. <https://doi.org/10.1007/s12035-013-8491-x>, 2021 Mar 26]. <http://link.springer.com/10.1007/s12035-013-8491-x>.
- Zhang, Y., Song, X., Herrup, K., 2020. Context-dependent functions of E2F1: cell cycle, cell death, and DNA damage repair in cortical neurons. *Mol. Neurobiol.* 57 (5), 2377–2390. <https://doi.org/10.1007/s12035-020-01887-5>, 2020 Oct 9]. <http://link.springer.com/10.1007/s12035-020-01887-5>.
- Zhang, N., Zuo, Y., Jiang, L., Peng, Y., Huang, X., Zuo, L., 2022. Epstein-Barr virus and neurological diseases. *Front. Mol. Biosci.* 8, 816098 <https://doi.org/10.3389/fmolb.2021.816098>, 2022 Mar 30]. <https://www.frontiersin.org/articles/10.3389/fmolb.2021.816098/full>.
- Zhu, X., Raina, A.K., Smith, M.A., 1999. Cell cycle events in neurons. *Am. J. Pathol.* 155 (2), 327–329. [https://doi.org/10.1016/S0002-9440\(10\)65127-9](https://doi.org/10.1016/S0002-9440(10)65127-9), 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0002944010651279>.
- Zhu, X., Castellani, R.J., Takeda, A., Nunomura, A., Atwood, C.S., Perry, G., Smith, M.A., 2001. Differential activation of neuronal ERK, JNK/SAPK and p38 in Alzheimer disease: the 'two hit' hypothesis. *Mech. Ageing Dev.* 123 (1), 39–46. [https://doi.org/10.1016/S0047-6374\(01\)00342-6](https://doi.org/10.1016/S0047-6374(01)00342-6), 2021 Mar 26]. <https://linkinghub.elsevier.com/retrieve/pii/S0047637401003426>.
- Zhu, X., Lee, H., Perry, G., Smith, M.A., 2007. Alzheimer disease, the two-hit hypothesis: an update. *Biochim Biophys Acta BBA - Mol. Basis Dis.* 1772 (4), 494–502. <https://doi.org/10.1016/j.bbadis.2006.10.014>, 2020 Oct 12]. <https://linkinghub.elsevier.com/retrieve/pii/S0925443906002304>.