Review article

The interplay between Epstein-Bar virus (EBV) with the p53 and its homologs during EBV associated malignancies

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ABSTRACT

p53, p63, and p73, the members of the p53 family of proteins, are structurally similar proteins that play central roles regulating cell cycle and apoptotic cell death. Alternative splicing at the carboxyl terminus and the utilization of different promoters further categorizes these proteins as having different isoforms for each. Among such isoforms, TA and ΔN versions of each protein serve as the pro and the anti-apoptotic proteins, respectively. Changes in the expression patterns of these isoforms are noted in many human cancers. Proteins of certain human herpesviruses, like Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV), interact with p53 family members and alter their expressions in many malignancies. Upon infections in the B cells and epithelial cells, EBV expresses different lytic or latent proteins during viral replication and latency respectively to preserve viral copy number, chromosomal integrity and viral persistence inside the host. In this review, we have surveyed and summarised the interactions of EBV gene products, known so far, with the p53 family proteins. The interactions between P53 and EBV oncoproteins are observed in stomach cancer, non-Hodgkin's lymphoma (NHL) of the head and neck, Nasopharyngeal Cancer (NPC), Gastric carcinoma (GC) and Burkitt's lymphoma (BL). EBV latent protein EBNA1, EBNA3C, LMP-1, and lytic proteins BZLF-1 can alter p53 expressions in many cancer cell lines. Interactions of p63 with EBNA-1, 2, 5, LMP-2A and BARF-1 have also been investigated in several cancers. Similarly, associations of p73 isoform with EBV latent proteins EBNA3C and LMP-1 have been reported. Methylation and single nucleotide polymorphisms in p53 have also been found to be correlated with EBV infection. Therefore, interactions and altered expression strategies of the isoforms of p53 family proteins in EBV associated cancers propose an important field for further molecular research.

1. Introduction

Initiation of any malignancy involves a series of mutations in the progenitor cell induced by external and internal stress stimuli, leading to the uncontrolled cell division, clonal proliferation, and invasion. p53, a human tumor suppressor protein, plays a crucial role in cell cycle control and apoptosis (Pflaum et al., 2014; Sullivan et al., 2017). It is also involved in transcription independent cellular signaling, including cell death via mitochondria or through the cytosol mediated pathway (Speidel, 2010; Sullivan et al., 2017; Vaseva and Moll, 2009). Two other recently discovered proteins p63 and p73, which belongs to the P53 family, share a high degree of homology with p53 and aroused from the triplication of a common inherited gene (Murray-Zmijewski et al., 2006).

N-terminal transactivation domain (TAD), DNA-binding domain (DBD) and the C-terminal oligomerization domain (OD) are the three common structural domains of p53, p63, and p73 recognized so far (Candi et al., 2014; Sullivan et al., 2017). p63 is involved in the limb, skin and craniofacial development, whereas p73 is known to facilitate neurogenesis (Yang et al., 1999; Yang et al., 2000). Several studies have shown that dysfunction in any of the p53 family proteins plays a key role in the progression of tumorigenesis.

Certain Human Herpesviruses (HHVs), like Herpes simplex virus (HSV) and Kaposi sarcoma-associated Herpesvirus (KSHV), interact with proteins of p53 family (Mohanty et al., 2015; Friborg et al., 1999; Maruzuru et al., 2013; Orosz et al., 2010; Santag et al., 2012). EBV (HHV-4) is an oncogenic virus of the Gamma herpesvirus family and was identified

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Table 1
Function of the lytic genes of EBV or their products.

Lytic Gene product		Utility	Reference
Immediate Early	BZLF 1 (ZEBRA, Z, EB 1 and Zta)	• Transcription regulator. • Induce DNA damage response.	(Baumann et al., 1998; Yang et al., 2015)
	BRLF 1 (R, Rta)	• Transcription factor. • Latency to lytic activator.	(Chang and Liu, 2000; Chen et al., 2009; Swenson et al., 2001)
Early	BMRF 1	• Act as a transactivator. • Participate in the viral replication.	(Holley-Guthrie et al., 2005; Neuhierl and Delecluse, 2006; Zhang et al., 1997)
	BRRF1	• Transactivator. • Induce lytic infection.	(Hagemeier et al., 2011; Hong et al., 2004; Yoshida et al., 2017)
	BALF5, BALF2, BBLF4, BSLF1, BBLF2/3,	• Participates in viral replication	(Narita et al., 2015; Tsurumi et al., 1996; Yokoyama et al., 1999)
	BXLF1, BORF2	• Involve in deoxynucleotide metabolism	(Holton and Gentry, 1996; Johannsen et al., 2004)
	BARF 1	• Act as viral oncogene. • Mitogenic growth Factor. • Immune modulator.	(Hoebe et al., 2013)
	SM	• Regulate RNA transport and stability	(Ruvolo et al., 2001)
	BHRF 1	• Inhibit cellular apoptosis and immune evasion.	(Kawanishi et al., 2002; Zuo et al., 2017)
	BGLF 4	• Have Viral Kinase activity. • Induce premature chromosome condensation. • Facilitate virion production	(Lee et al., 2007, 2008)
	BGLF 5	• Has exonuclease activity. • Contribute to the immune evasion.	(Feederle et al., 2009a; Feederle et al., 2009b; Rowe et al., 2007)
Late	BcLF1, BFRF3, BLRF2, and BdRF1	• Encode capsid proteins	(Reischl et al., 1996; van Grunsven et al., 1993)
	BLLF1 and BXLF2	• Encode major and envelope glycoproteins	(Heineman et al., 1988; Janz et al., 2000)

Table 2
Role of EBV latent genes or their products.

Latency gene product	Utility	Reference
EBNA1	• Genome replication, • Viral persistence, • Transcription • Suppress spontaneous lytic reactivation.	(Reisman et al., 1985; Sivachandran et al., 2012; Sugden et al., 1985; Yates et al., 1984; Yates et al., 1985)
EBNA2	• Helps in B cell transformation • Act as a transactivator	(Cohen et al., 1989)
EBNA3A	• Interact with RBPJ protein. • Interfere with polycomb group-mediated epigenetic silencing. • Interact with cellular apoptotic and cell cycle regulatory proteins.	(Bazot et al., 2014; Harth-Hertle et al., 2013; Maruo et al., 2011; Paschos et al., 2009)
EBNA3B	• *In Vitro* cell transformation, up-regulate chemokines,	(White et al., 2012)
EBNA3C	• Co-activates ENBA2, • Interact with cell cycle regulation, apoptosis and tumor suppressor proteins	(Lin et al., 2002; Piovan et al., 2005; Saha et al, 2011a, 2011b; Saha and Robertson, 2011)
EBNA5	• Helps in B cell transformation, • Act as a transcriptional activator	(Harada and Kieff, 1997; Mannick et al., 1991)
LMP1	• Mimic CD40 signaling, • Act as an oncogene.	(F Hu et al., 1993; Izumi et al., 1997; Mancao et al., 2005; Mosialos et al., 1995; Wang et al., 1985)
LMP2A	• Mimics BCR signalling. • Helps in B cell transformation, and growth *in vivo* and *in vitro*. • Interact with cell cycle regulation and apoptosis, suppression epithelial cell differentiation and promote epithelial cell motility.	(Allen et al., 2005; Bieging et al., 2009; Fish et al., 2014; Fukuda and Kawaguchi, 2014; Mancao and Hammerschmidt, 2007; Morrison and Raab-Traub, 2005; Swanson-Mungerson et al., 2010)
LMP2B	• Interferes with LMP2B function. • Increases lytic activation.	(Rechsteiner et al., 2008; Rovedo and Longnecker, 2007)
EBERs	• Induce growth in both *in vitro* and *in vivo*, • Modulate the innate immune response. • Modulate protein translation.	(Fok et al., 2006; Houmani et al., 2009; Iwakiri et al., 2009; Komano et al., 1999; Samanta et al., 2006)
BHRF1	• Binds with the apoptotic protein. • Modulate the immune response. • Progressive growth and *in vitro* transformation • Promote cell cycle progression.	(Feederle et al., 2011; Seto et al., 2010; Xia et al., 2008)
BART	• Interact with the apoptotic proteins and promote apoptosis,	(Choi et al., 2013; Haneklaus et al., 2012)

as the first human virus linked to malignancies among immunocompetent people in developing countries. EBV initially infects the oropharyngeal epithelial cell, followed by the establishment of the latency in B cells, epithelial cells and natural killer/T cells (Kang and Kieff, 2015). During latency, it can cause many human cancers, including Nasopharyngeal Carcinoma, Burkitt's lymphoma, Hodgkin's and non-Hodgkin's lymphomas (Thompson and Kurzrock, 2004) etc. This review has focused on the altered expression patterns of the p53 family proteins due to the involvement of EBV genes or their products during malignancies.

2. Main text

2.1. p53, p63, and p73 isoforms

Three promoter regions (two reside in exon 1 and one in intron 4) are identified in p53. Δ133p53 isoform is generated from the truncation of the amino-terminal region of intron 4 (Bourdon et al., 2005). Alternative splicing of exon 2 and alternative translational initiation of ATG40 in the TAD domain have created the Δ40p53 isoform (Murray-Zmijewski et al., 2006). Another isoform Δ160p53 has been generated from the start of translation at ATG160, which lacks the first 159 residues at intron 4 (Marcel et al., 2010). There are another three known isoforms of p53 (Full-length p53, p53β, andp53γ) which are produced from the alternative splicing of intron 9 (Murray-Zmijewski et al., 2006). To date, twelve p53 isoforms have been reported (Aoubala et al., 2010; Surget et al., 2014).

p63 and p73 proteins have both structural and functional similarities with the p53 protein. Due to alternative splicing of the carboxyl-terminal and utilization of different promoters, p53 family members are expressed in various isomeric forms. Transcription from P1 promoter has created

TA isoform (i.e., TAp63 and TAp73); whereas the N-terminal truncated region or ΔN isoform (i.e., ΔNp63 and ΔNp73), which lacks TA domain, is generated from the P2 promoter (Moll and Slade, 2004; Soares and Zhou, 2018; Wei et al., 2012). It is evident that ΔN isoform acts as a critical negative inhibitor of TA isoform which further elaborates the functions of ΔN and TA isoforms as an anti-apoptotic factor and a pro-apoptotic factor respectively (Melino et al., 2003). Alternative splicing in the carboxyl-terminal region of the transcript has additionally produced variants of p63 and p73. Three such splice variants for p63 (α, β and γ) and nine for p73 (α, β, γ, δ, ε, θ, ζ, η, and η1) have been described to express TA or ΔN isomeric forms (Moll and Slade, 2004; Soares and Zhou, 2018; Wei et al., 2012). p63 and p73 is distinctively contained a motif, known as the sterile alpha motif (SAM), in the C-terminal region responsible for protein-protein interactions (Vikhreva et al., 2018; Wei et al., 2012).

2.2. EBV infection and gene expression

Inside the nucleus, the EBV genome either circularizes (episomal state) and undergoes latency, or it remains linear and goes through the lytic cycle (Tao et al., 2006). Different studies have demonstrated that the latency and lytic cycle in B cells and epithelial cells occur in somewhat different ways. In most cases, the lytic phase occurs after reactivation from latency in B cells followed by replication by viral DNA polymerase; in epithelial cells, this event often occurs after viral entry, followed by host DNA polymerase mediated replication (Odumade et al., 2011; Ragoczy et al., 1998). Following reactivation from latency, three types of temporal lytic genes are expressed, namely immediate early (IE), early, and late genes. Products of IE genes mainly encode transcriptional activators that act as a switch between lytic cycle and latency and enhance the expression of early genes. Early genes are responsible for replication and metabolism of the virus and for blocking of antigen processing. Finally, the late gene products play structural roles such as formation of viral capsid (VCA), and immune evasion of viruses. The functions of the EBV lytic genes are summarized in Table 1.

The latent genes of EBV and their roles are summarized in Table 2. During latency, EBNA-1, 2, 3A, 3B, 3C, LP or EBNA-5 (nuclear antigen) and LMP-1, 2A, 2B (membrane proteins) are expressed (Young and Murray, 2003). Besides latent proteins, expression of BART (Bam H1 A upright transcript) from Bam H1 A region of the viral genome and EBERs (EBV-encoded RNAs 1and 2) have been noticed in several malignancies (Iwakiri, 2014). The establishment of three distinct types of latent infection (Latency III, II, I), depending on viral gene expressions, have been demonstrated in infected B cells, particularly in memory cells. Latency III (EBNA-1, 2,3A, 3B, 3C, LP, LMP1and 2A/2B) is highly immunogenic and activates native B cells (Blast transformation); Latency II (EBNA1 and LMP1) is involved in B cell differentiation and Latency I (EBNA1) is essential for B cell proliferation (Young and Murray, 2003). It has been observed that latency II genes are expressed only in the epithelial cells (Shannon-Lowe et al., 2009).

2.3. Interaction of EBV with p53 isoform

The relationship between EBV infection and p53 expression is reported in idiopathic pulmonary fibrosis, gastric adenoma, gastric carcinoma, non-Hodgkin's lymphoma (NHL) of the head and neck, Nasopharyngeal Cancer, Burkitt's lymphoma and Gastric carcinoma (Lok et al., 2001). Moreover, the concentration of p53 is reported to determine cell cycle arrest and apoptosis in EBV infected B cells (Chen et al., 1998). Deletion of the residues 130–159 of EBNA3C open reading frame (ORF) is reported to have altered p53 expression compared to the wild type EBV, when the human PBMCs have been infected with EBNA3C construct (Shukla et al., 2016). Luciferase-based reporter assay has shown that the N-terminal domain of residue 130–190 of EBNA3C repressed the transcriptional activity of p53 by inhibiting DNA binding activity of p53 (Yi et al., 2009). Likewise, a direct association between EBNA3C and

Table 3
Interaction of the P53 isoforms with EBV.

p53 family	Interaction with the EBV genes or oncoproteins	EBV transformed cells/malignant tissue used
p53	EBNA3C repress the transcriptional activity of p53 through130-190 region or by direct interaction with Gemim3	B cell lymphoma cell
	USP7 lowers the p53 level through the binding with EBNA1,	Osteosarcoma cell
	LMP-1 inhibits the transcription activation of p53 through the interaction of NF-κB pathway, stimulate A20 expression and inhibit p53, interact with IRF5.	Large cell lung carcinoma and Osteogenic sarcoma, Non-small-cell lung cells
	C terminal region of BZLF-1 binds with the p53 and alter its expression	Lymphoid and T-lymphoblastoid cell
p63	ΔNp63α interact with BARF1 and transactivate many folds.	Gastric Carcinoma cell
	LMP-2A increases and stabilized the expression of ΔNp63α via the modulation of itch.	human keratinocyte cell
	EBNA5 has a direct interaction with the p63 in EBV positive Burkitt's lymphoma cell.	Burkitt's lymphoma cell
	EBNA2 interact with p63 through 310 to 336 amino acid sequence.	B cell lymphoma cell
	EBNA1 interact with the p63, but the mechanism of their interaction is still unknown.	Breast cancer tissue
p73	EBNA3C directly interfere with the p73 in the nucleus and stabilized ΔNp73.	B-cell
	LMP-1 binds with p73 through the displacement of polycomb 2 complex component EZH2 and epigenetic changes via activation of JNK-1	B cell
	Aberrant methylation in the exon 1 and SNPs in the p73 are associated with the EBV interaction.	Gastric Carcinoma and chronic lymphocytic leukemia

Gemim3 is observed, which stimulates the complex formation of p53 with gemim3, and thus inhibits the DNA binding activity of p53 in both B cell lymphoma and EBV transformed lymphoblastoid cells (Cai et al., 2011). Ubiquitin-specific-processing protease 7 (USP7) has a functional role in cell proliferation and apoptotic regulation through the interaction of p53 and Mdm2. USP7 is shown to interact with EBNA1 with a better affinity than p53 with the conserve DPGEGPS peptide in the osteosarcoma cell line (Saridakis et al., 2005). In Nasopharyngeal carcinoma, overexpression of LMP1 is reported and accumulated with p53 with an unknown mechanism. It has been noticed that LMP1 inhibits p53 mediated apoptosis through the activation of A20 (Shao et al., 2004, Liu et al., 2004). Transfection of LMP1 recombinant construct in human large cell lung carcinoma (with p53 deleted gene) and human osteogenic sarcoma cell line have established that the carboxyl-terminus activating regions of LMP1, CTAR1 or CTAR2 (related the region responsible for NF-κB activation) inhibit the transactivation of p53 through the influencing N-terminal transactivation domain. At the same time, p53-mediated DNA repair and transcription was repressed through the NF-κB pathway (Liu et al., 2004). LMP1 also blocked the p53 mediated apoptosis through the stimulation of the A20 gene expression in the non-small-cell lung cancer where temperature sensitive (ts) p53 and LMP1were stably expressed (Fries et al., 1996). DNA damage is shown to influence the ectopic p53 expression, which stimulated the endogenous expression of LMP1 in EBV transformed cell through the interaction with interferon regulatory factor 5 (IRF5) at the LMP1 promoter. Moreover ectopic IRF5 can increase the expression of endogenous LMP1 and blocked the p53 mediated apoptosis (Wang et al., 2017). EBV immediate-early protein BZLF1 (Z) is found to be interacting with the p53 through its C-terminus region and inhibits the p53 dependent

transactivation in lymphoid cell, but overexpression of p53 restores its function (Zhang et al., 1994). Transfection of BZLF1 in HeLa cells was shown to enhance the p53 expression through the p53-DNA binding acceleration which eventually leads to the lytic gene replication (Sato et al., 2010). Transiently transfected p53 and p53 reporter genes in Jurkat T-lymphoblastoid cells expressing BZLF1 ORF encoded ZEBRA protein is shown to interact with p53 in vitro and alters the transcription of p53, thus enhanced the p53 dependent apoptosis in B lymphocytes and epithelial cells (Dreyfus et al., 2000). Complex formation between W repeats of 66 amino acid long peptides of EBNA5 (EBNA-LP) and p53 are also noted but how they affect the progression of malignancies is a bit unclear (Szekely et al., 1993). Table 3 lists the association of EBV with the expressions of p53 proteins.

2.4. Interaction of EBV with p63 isoform

BARF1 promoter contains multiple binding sites for p53 family proteins. Chromatin Immune Precipitation (ChIP) analysis has demonstrated that ΔNp63α binds to the immediate proximity of BARF1 promoter in NPC and Gastric carcinoma (GC). Co-transfection of various BARF1 promoter-reporter construct with the individual p53 family member in epithelial cell have revealed the p63 mediated transactivation of BARF1 with many folds (Hoebe et al., 2018). A physical association of LMP2A with ΔNp63α is observed in human keratinocyte, which has increased the expression and stabilization of ΔNp63α in cytoplasm and the nuclear membrane. This association is linked to the calcium-induced impairment of cellular differentiation with the involvement of PY and ITAM motifs. Co-immunoprecipitation studies have confirmed the LMP2A induced ΔNp63α expression through the modulation of Itch over ΔNp63α (Fotheringham et al., 2010). Another Co-immunoprecipitation study has explained the direct interaction between EBNA 5 and p63 in NPC and EBV positive Burkitt's lymphoma which may contribute to the stability of p63, but the mechanism is still unknown (Guo et al., 2006). To find out the relationship between EBV latent infection and the expression of p53 and p63 in breast cancer, immunohistochemistry study was performed in 85 formalin-fixed paraffin-embedded breast cancer using anti-EBNA-1, anti-p63, and anti-p53 antibodies. A significant correlation of EBNA-1 with p63 (p < 0.001) was found, but no significant association with p53 was detected (p = 0.10) (Ribeiro-Silva et al., 2004). The interaction of p63 with EBNA2 is reported in B cell lymphoma. P63 specifically recognizes and binds to the amino acid sequence of 310–336 in EBNA2. Mutation of the codon GTG > TCT in GTGGGA motif leads to the loss of recognition. The most common motif has been found among these 27 amino acid sequences to EBNA2 of both type1 and type2 EBV is GPPWWPP. Mutation of WW to SS or FF ablates the interaction of p63 which suggests that the hydrophobic and aromatic property of WW is essential for the interaction (Yalamanchili et al., 1994). Alterations of p63 expressions with the involvement of EBV are listed in Table 3.

2.5. Interaction of EBV with p73 isoform

The overview of the interaction between p73 and EBV in different malignancies is enumerated in Table 3. Immunoprecipitation and co-immunoprecipitation experiments have confirmed the formation of stable complexes between EBNA3C and p73 in the nucleus. Moreover, EBNA3C have down-regulated the p73 protein expression by stabilizing the ΔNp73 and inhibited doxorubicin-induced apoptosis in p53-null cell lines (Saos-2 and HCT p53 double mutant) (Sahu et al., 2014). The upregulation of ΔNp73 by LMP1 is reported in primary B cell infected recombinant EBV. Chip experiments have displayed the activation of ΔNp73 through the recruitment of p73 with the displacement of the polycomb 2 complex component EZH2 and epigenetic changes via activation of c-Jun NH2-terminal kinase 1 (JNK-1). LMP-1 mutant lacking the JNK-1 activating domain (CTAR2) did not influence the ΔNp73α expression levels (Accardi et al., 2013). DNA methylation in the CpG island of p73 was observed in EBV associated gastric carcinoma. The

immunohistochemical assay has showed the loss of p73 expression in the EBV-associated GC compared to EBV negative GC. Methylation specific PCR reaction has detected the aberrant methylation patterns in p73 exon 1 in EBV associated gastric carcinoma (Tetsuo et al., 2007). It is observed that single nucleotide polymorphisms (SNPs) in p73 gene are important for the interaction with EBV in chronic lymphocytic leukemia. In the dominant model, two SNPs of p73 (rs3765701 and rs1885859) were shown to alter the association between aberrant EBV and chronic lymphocytic leukemia. A higher OR (odds ratio) was found in aberrant EBV positive patients with carriers of the wild-type homozygous genotypes compared to the EBV negative patients (Casabonne et al., 2011).

3. Conclusions

Despite the structural and functional similarities among p53, P63 and p73, there are many functional differences among them in relation to cell cycle regulation and malignancies. P53 regulates numerous gene expressions associated with G2/M and G1 cell cycle checkpoint regulation, DNA damage recognition and repair, apoptosis and cell death regulation (Levine and Oren, 2009). The roles of different p53 isoforms are depicted in many cancers. Elevated expression of Δ133p53 is reported in breast cancer, renal cell carcinoma, colon tumor but not in squamous carcinoma of the head and neck, suggesting a tissue-specific expression of this isoform (Boldrup et al., 2007; Bourdon et al., 2005; Fujita et al., 2009; Song et al., 2009). Like Δ133p53, overexpression of Δ40p53 is reported in human melanoma cell lines (Avery-Kiejda et al., 2008). Other isoforms like p53β and p53γ, have been found to be associated with the prognoses of several cancers. Association of p53β is reported with renal cell carcinoma and in ovarian cancer (Hofstetter et al., 2010; Song et al., 2009). Reduced expressions of p53β and p53γ have been detected in breast cancer (Bourdon et al., 2005). Logical functions of p53β and p53γ isoforms are still unclear.

The predominant expression of TAp63 is observed in the oocyte and epidermis. The absence of TAp63 in knock-out mice forms ulcers, hair defects, and decreased wound healing capacity (Suh et al., 2007). TAp63 also causes G1 cell cycle arrest by interacting with the p21 and p57/Kip2 (Guo et al., 2009b). p63 is found to interact with Bax and apoptotic death receptor in the intrinsic and extrinsic pathways, and increase apoptosis (Gressner et al., 2005). A significant expression of the ΔNp63 isoform in most epithelial cells has been described and is observed to have oncogenic potential. The Higher expression of p63, specifically ΔNp63 isoform, is associated with the prognosis of Nasopharyngeal Carcinoma (NPC), Head and Neck squamous cell carcinoma (HNSCC), Breast cancer, Lung and ovarian cancers with poor survival (Compérat et al., 2007; Crook et al., 2000; Dang et al., 2015; Marchini et al., 2008; Massion et al., 2003; Yamaguchi et al., 2000). ΔNp63α is observed to induce tumor-initiating stem-like proliferation by cooperating with Ras via interaction with the chromatin remodeling protein Lsh (Keyes et al., 2011). ΔNp63α also interact functionally with the transcription factor GLI2 in the hedgehog signaling pathway and induce tumorigenesis in osteosarcoma (Ram Kumar et al., 2014). Conversely, ΔNp63 has showed an opposite effect on metastasis. It has been suggested that the loss of ΔNp63 expression, p63 mediated repression of TGFβ-dependent cell migration, and ΔNp63α mediated regulation are involved in many cancer metastases (Barbieri et al., 2006; Hu et al., 2017; Koga et al., 2003). Contrariwise, TAp63 expression is associated with the induction of senescence and the inhibition of cell proliferation (Guo et al., 2009a; Wang et al., 2005). Absence or downregulation of that isoform can induce oncogenesis and metastasis, as studied in several cancers (Guo et al., 2004; Guo et al., 2009a; Lo Iacono et al., 2011; Park et al., 2000).

p73 has various utilities in cell cycle regulation, neuronal differentiation, and regulation of tumorigenesis. Like p53, it is involved in the regulation of different cell cycle checkpoint like the G1, G2/M and S phase through the interaction of several cell cycle controlling proteins (Balint et al., 2002; Innocente and Lee, 2005; Scian et al., 2007). p73 has been reported to transactivate the p75 neurotrophin receptor (have
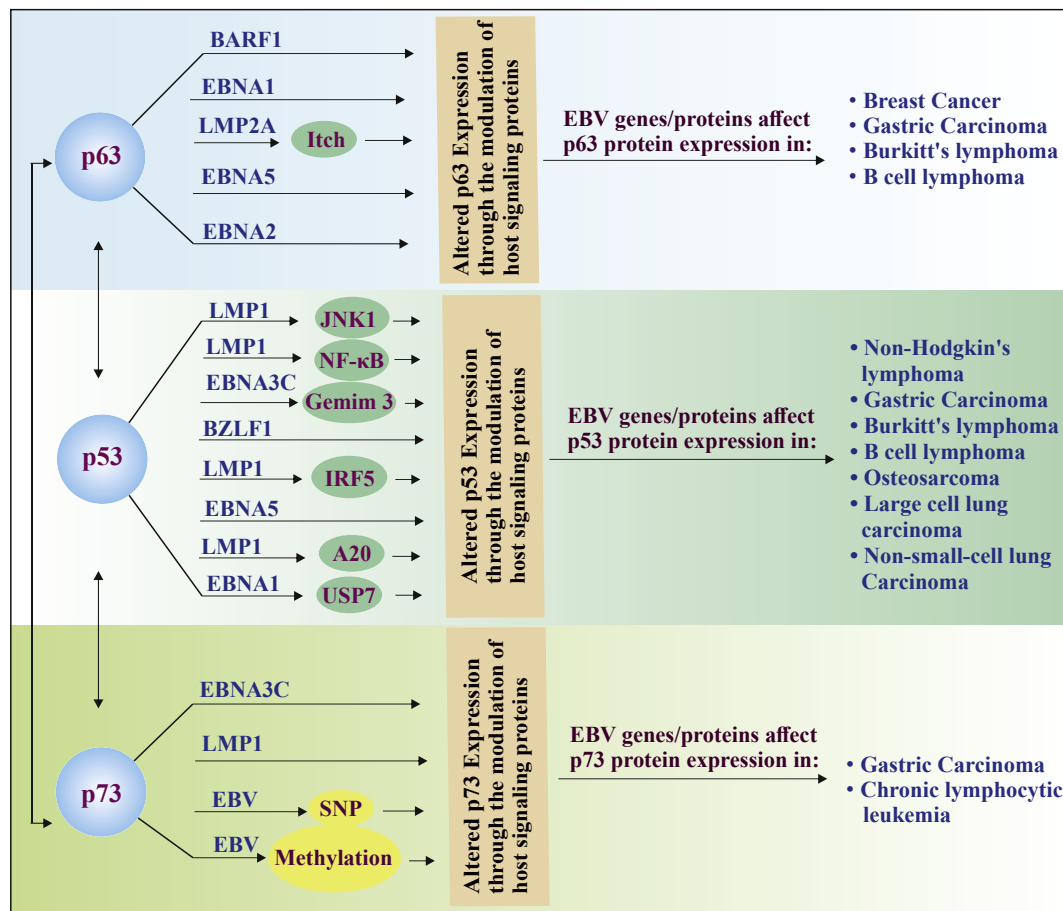
Fig. 1. The figure has illustrated the inter-P53 family interaction and the association of the p53 family proteins with the EBV genes or their product during lytic and latency phase in several EBV associated cancer.

crucial functions in neurogenesis) and participate in the neuronal differentiation (Niklison-Chirou et al., 2013). The upregulation of Tp73 is found to be associated with the risk of breast, ovarian, hepatocellular, vulvar cancers and melanoma (Concin et al., 2004; Domínguez et al., 2006; O'Nions et al., 2001; Stiewe et al., 2004; Tve et al., 2004; Vikhanskaya et al., 2000; Zaika et al., 1999). Similarly, the expression of Np73 is reported with the projection of cervical cancer, gastric, esophageal, lung and colon and other cancers (Becker et al., 2006; Liu et al., 2006; Lööf et al., 2012; Uramoto et al., 2004; Vilgelm et al., 2010a,b). The expressions of p73α and p73β isoforms are predominant in normal colon and breast tissues, but different splice variants like p73γ, p73δ, p73φ, and p73ε are identified in colon and breast cancer (Vilgelm et al., 2010a,b; Zaika et al., 1999). Likewise, p73ε is reported to be expressed in Leukemic cell but is absent in mature myeloid cells (Tschan et al., 2000).

In this article, we have conceded the interaction of human herpesviruses 4 (EBV) genes or their products with the p53 family members in diverse EBV associated malignancies (Fig. 1) and highlighted the target sites of the EBV genes/proteins for future research. Furthermore, these viral-host protein interactions provide intimation for further molecular research of targeted antiviral therapy. EBV is an etiological factor for the development of NPC. A strong interaction has been reported between p63 and EBNA-5, which generally induce the expression of p63. p63 also interacts with EBNA-2, which transactivates LMP-1 and consequently induces cell proliferation and inhibits apoptosis. But it is yet to be deciphered whether p63 may have imposed any impact on LMP-1 after communicating with EBNA-2. Also, the detection of the association between p53 family members and EBV has been investigated in several cancers like carcinoma, leukemia, sarcoma, lymphoma; but the

mechanisms of interactions or the expression patterns of those concerned proteins are yet to be deciphered. Despite the molecular mechanism or expression patterns, it is confirmed that the infection and expression of EBV genes are tissue specific. During infection, latency II associated genes have been found to be expressed in the epithelial cells instead of B cells (Shannon-Lowe et al., 2009). Similarly, the expression of BZLF1 variants is appeared to be cell-specific. In the same NPC patient, one variant of BZLF1 is associated with the epithelial cell and another variant with lymphocytes (Sacaze et al., 2001). This information generates curiosity about the tissue-specific interaction and expression of p53 family proteins in EBV associated cancers.

Moreover, the interactions among p53 family members and their isoforms have been investigated in the onset of tumorigenesis. Alteration of the TAp73 expression by ΔNp63 is reported in breast cancer (Rocco et al., 2006). Collecting data propose that the isoforms of p53, p63 and p73 interact and alter each other's expressions in the regulation of cell cycle, DNA damage, cellular stress defense and in carcinogenesis (Chen et al., 2001; Johnson et al., 2007; Wang et al., 2007; Wang and El-Deiry, 2006). Mutations in different regions of p53 have also been shown to interfere with the activation of TAp63 and TAp73 (Di Como et al., 1999; Gaiddon et al., 2001; Strano et al., 2002). It is still contradictory whether the alteration of the expression of one of the p53 family protein by EBV regulates the other protein of the same family in the same array or by any different manner. Much elaborate research is required to find out more specific mechanisms for the EBV induced regulation of p53/p63/p73 in EBV associated malignancies in particular tissues. The overall review of literature has paved a path for future studies of high importance in the virus-host interactions for oncogenic onset and in the field of molecular

or clinical research to investigate the viral gene specific inhibitors.

Declarations

Author contribution statement

Koustav Chatterjee, Tathagata Choudhuri: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Piyanki Das, Nabanita Roy Chattopadhyay, Sudipa Mal: Analyzed and interpreted the data.

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