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Interaction of Epstein-Barr virus (EBV) with human B-lymphocytes

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ABSTRACT

Epstein-Barr virus, EBV, and humans have a common history that reaches back to our primate ancestors. The virus co-evolved with man and has established a largely harmless and highly complex co-existence. It is carried as silent infection by almost all human adults. A serendipitous discovery established that it is the causative agent of infectious mononucleosis.

Still, EBV became known first in 1964, in a rare, geographically prevalent malignant lymphoma of B-cell origin, Burkitt lymphoma BL. Its association with a malignancy prompted intensive studies and its capacity to immortalize B-lymphocytes *in vitro* was soon demonstrated. Consequently EBV was classified therefore as a potentially tumorigenic virus. Despite of this property however, the virus carrier state itself does not lead to malignancies because the transformed cells are recognized by the immune response. Consequently the EBV induced proliferation of EBV carrying B-lymphocytes is manifested only under immunosuppressive conditions.

The expression of EBV encoded genes is regulated by the cell phenotype. The virus genome can be found in malignancies originating from cell types other than the B-lymphocyte. Even in the EBV infected B-cell, the direct transforming capacity is restricted to a defined window of differentiation. A complex interaction between virally encoded proteins and B-cell specific cellular proteins constitute the proliferation inducing program.

In this short review we touch upon aspects which are the subject of our present work.

We describe the mechanisms of some of the functional interactions between EBV encoded and cellular proteins that determine the phenotype of latently infected B-cells.

The growth promoting EBV encoded genes are not expressed in the virus carrying BL cells. Still, EBV seems to contribute to the etiology of this tumor by modifying events that influence cell survival and proliferation. We describe a possible growth promoting mechanism in the genesis of Burkitt lymphoma that depends on the presence of EBV.

1. Introduction

Epstein-Barr virus (EBV), a human gamma herpesvirus, was first seen in cell lines derived from Burkitt's lymphoma (BL), a B-cell derived childhood malignancy that is endemic in the rain forest regions of tropical Africa (for recent reviews see [1]). This confined occurrence was taken to suggest that the disease is induced by an insect transmitted virus. The assumption was substantiated by the finding that the virus can immortalize B-lymphocytes *in vitro* and turn them into lymphoblastoid cell lines (LCL) [2]. Three unexpected discoveries indicated, however, that the virus-tumor relation is more complex than it was first visualized: (1) almost all human adults are virus carriers; (2) the virus is the etiological agent of infectious mononucleosis; and (3) both EBV positive and negative BLs carry a chromosomal translocation juxtaposing one of the immunoglobulin genes to the *C-MYC* protooncogene. The constitutively activated C-MYC provides the cells with proliferative capacity whether EBV is or is not present. This was consistent with the fact that the proliferation driving viral program is not expressed in the BL cells.

Thus, the translocation would be sufficient and a role of the virus in the etiology of the tumor could be less important. Recent developments, to which we will return later, provided, however, new aspects and suggested a critical role of EBV in the development of BL.

EBV infection is acquired by young children under low, by adolescents under high socioeconomic conditions. Primary infection of children is usually symptomless. Infection during adolescence or later can cause infectious mononucleosis (IM) [3]. The clinical picture of IM is highly variable but even if it is severe and alarming, it always subsides in immunocompetent individuals. After the primary infection a low number of B-lymphocytes carry silent viral genomes and EBV specific cellular and humoral immunological

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memory is maintained. The immune response maintains the symptomless virus carrier state, by eliminating cells that express the virally encoded proliferation driving genes.

The proliferation of EBV carrying B-lymphocytes may become life threatening, on the other hand, in immunodefective individuals, e.g., in immunosuppressed transplant recipients, and manifest as lymphoproliferative disease, PTLD. EBV is thus a potentially dangerous virus, normally checked by an efficient immune response.

Several aspects of EBV induced B-cell transformation and the immunological recognition of the transformed cells are well understood. EBV driven immunoblasts express nine virally encoded proteins (EBNA-1–6 (alternative nomenclature EBNA-1, 2, 3A, 3B, LP, and 3C) and LMP-1, -2A, -2B). The virally encoded proteins and the phenotypic change imposed in transformed cells render the cells immunogenic, they are readily recognized by the immune system and are eliminated. On the other hand, the rare resting B-cells in which the virus persists in the healthy individuals do not express these proteins and they are not immunogenic.

The EBV genome can be present in certain non-B-cell derived malignancies as well, in most NK/T cell lymphomas, in low differentiated or anaplastic nasopharyngeal carcinomas, and approximately 10% of gastric carcinomas. A restricted set of EBV-encoded proteins is expressed in these malignancies and this does not drive cell proliferation; it contributes to the development of the tumor nevertheless by changing the cell phenotype, modifying their interaction with the stromal cells, and their sensitivity to growth promoting lymphokines. This is also the case of the EBV carrying Hodgkin's lymphomas that originate from B-lymphocytes with faulty differentiation. These cells are normally prone to apoptosis, but assumed to be rescued by EBV [4].

We confine our discussion to the interaction of EBV with the B-lymphocyte.

2. Transformation of B-lymphocytes

The EBV encoded genes expressed in the non-producing latent infection of B-lymphocytes were characterized in the *in vitro* generated LCLs. The viral genomes reside as episomes in these cells. In 1973, we have discovered that all EBV-carrying cells express a nuclear antigen that we termed EBV-encoded nuclear antigen, or EBNA [5]. Subsequent work by other groups showed that EBNA is a complex, consisting of six proteins. In addition to these, the proliferating phenotype expresses three cell membrane localized proteins, LMP-1, LMP-2A and -2B. Genetic analysis by Hammerschmidt and Kieff [6,7–11] showed that EBNA-2, -3, -5 and -6 and also LMP-1 [12] are essential for the immortalizing effect of the virus, EBNA-2 and LMP-1 being the main contributors.

Depending on the type of infected cells, the virus uses different expression programs. It is determined by the cell phenotype acting probably through its flora of transcription factors with exquisite specificity. Table 1 lists the EBV-encoded proteins expressed in B-lymphocytes in the symptomless virus carrier state, in IM and in various B-lymphocyte derived malignancies and cell lines. The full growth transformation program (also called latency type III) is only expressed in the B-blasts. In Fig. 1 the regulation of the EBV nuclear protein expression is illustrated. In latency I a single protein, EBNA-1, is transcribed from Qp. In latency III the six nuclear proteins (EBNA-1–6) are spliced from a long primary transcript initiated either from the W or from the C promoter. The membrane localized proteins LMP-1, -2A and -2B have their own promoter, and it is not depicted here.

3. The functions of EBV-encoded proteins

The B-cell activating and transforming strategy of EBV is still incomplete. The EBV-encoded proteins and their functions are presented in Fig. 2 and Table 2 provides the list of the cellular proteins which bind to the EBV-encoded nuclear antigens (EBNAs).

Table 1
Latency types in B-cells.

Latency type designation	Promoter used	Genes expressed	*In vivo*		*In vitro* derived cell lines
			Non-malignant	Malignancy	
0			Memory subset		
I	Qp	EBNA-1	Germinal center, IM	BL; pleural effusion lymphoma (PEL); PTLD	BL and PEL
II	Qp, LMP	EBNA-1, LMP-1, LMP-2A, LMP-2B	Germinal center, IM	Hodgkin lymphoma (HL); PTLD	None available
III	Cp, Wp, LMP	EBNA-1–6, LMP-1, LMP-2A, LMP-2B	IM	PTLD	LCL; BL

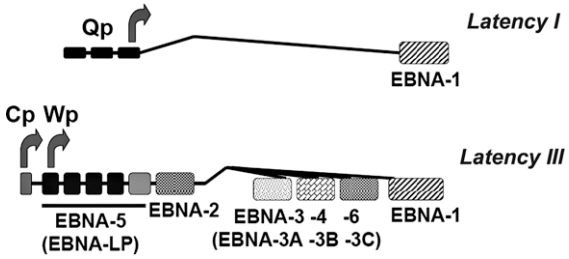

Fig. 1. EBV promoter usage for transcription of EBNAs.

3.1. EBNA-1

EBNA-1 is a DNA binding protein [13,14] that is essential for the persistence and replication of the viral genome [15] and the transactivation from the Cp viral promoter [16–18]. It binds to short sequences (dyad symmetry, DS) at the origin of latent replication, oriP.

EBNA-1 controls EBV genome partition during cell division. It does so through the binding to the EBP2 protein, associated with mitotic chromosomes [19–21]. It was proposed, however, that EBNA-1 contains the AT-hook domain and can therefore bind to the scaffold-associated metaphase chromosomes without help of EBP2 [22].

In certain conditions EBNA-1 may inhibit apoptosis [23,24].

EBNA-1 was implicated in the regulation of p53 through the binding to an ubiquitin-specific protease, HAUSP [25].

3.2. EBNA-2

Its transcriptional activation function depends on the short (27 aa) acidic domain. EBNA-2 does not bind to DNA directly. It is included in a complex with DNA-binding cellular transcription factors, such as SPI1 (also known as PU.1, NP_001074016) [33], and RBP-Jκ (also named CBF1, NP_005340) [32,35,65]. It acts on both viral (Cp, LMP-1 and LMP-2) and cellular (e.g., CD21, CD23, CD25 and C-FGR) promoters (see [66]). These interactions promote cell proliferation [67].

EBNA-2 expression requires the B-cell specific transcription factors, such as PAX5 (NP_057953) and OCT2 (also known as POU2F2, NP_002689) [68].

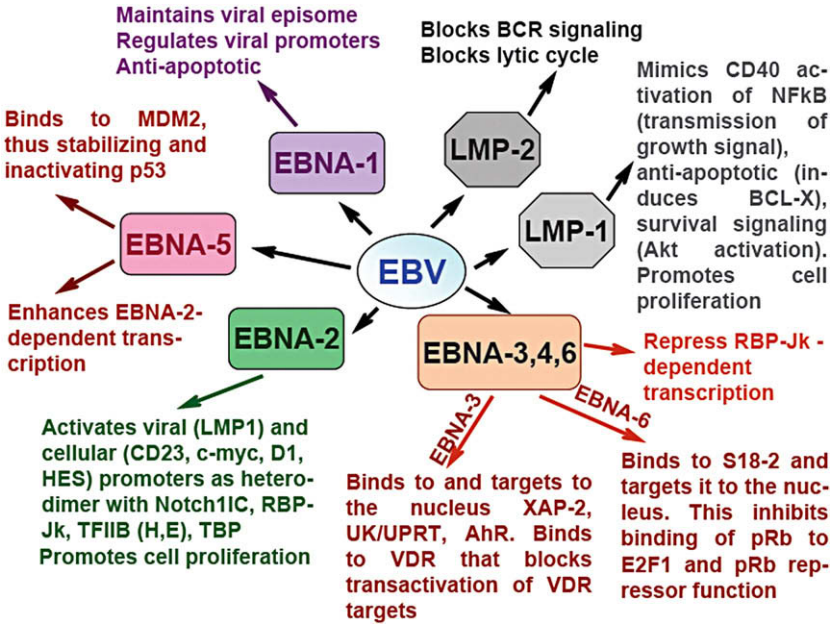

Fig. 2. Some of the functions of the EBV-encoded proteins expressed in latent infection of B-lymphocytes.

One of the important partners of EBNA-2 is RBP-Jκ that binds specifically to the consensus DNA sequence 5′-RTGGGAA-3 and is involved in the Notch signaling pathway [69]. It is the downstream target of the intracellular fragment cleaved from the Notch 1–4 proteins. *Notch* genes encode cell surface receptors that regulate development of several cell types. Mutations in *Notch* loci led to abnormalities from the notching of the wing in *Drosophila melanogaster* and are involved in the development of T-cell malignancy in humans. After ligand binding (Delta-like 1–3 and Jagged 1, 2 in humans) to the extracellular part of the Notch protein, which contains EGF-like repeats, the intracellular part is cleaved off and targeted to the nucleus, where it binds to RBP-Jκ. Possible targets are the genes of the Hairy/Enhancer of split (*HES*) family, cyclin D1 (*CCND1*, NM_053056) and p21 (*CDKN1A*, NM_000389). Notch signaling is involved in early T-cell development from the common lymphoid progenitors in the bone marrow and adult thymus [70].

Table 2
EBNA binding proteins.

EBNA	Cellular proteins
EBNA-1	Karyopherins alpha 1, 2 and 2, 3 beta [26–28]; importin-1 (NPI-1); RPA [29]; EBP2 [19]; NAP-1, SET, PP32, ORC, TAF-I, TAP/p32, USP7 (HAUSP), CK2, PRMT5 [25]; NM23-H1 [30]; BRD4 [31]
EBNA-2	RBP-J kappa [32]; SPI1 (PU.1) [33], SNF5 [34]; DP103 [35]; SMN [36]; SND1 (p100) [37]; P300/CBP, PCAF (K (lysine) acetyltransferase) [38]; NUR77 [39]
All members of EBNA-3 family	RBP-J kappa [40]; RPB-2N [41]; CHK2/CDS1 [42]
EBNA-3	XAP-2 [43]; TCP-1 [44]; AHR [45]; UK/UPRT [46]
EBNA-5	Hsp27; Hsp70 (Hsp72), Hsc70 (Hsp73) [47]; HAX-1 [48]; HA95 (the catalytic subunits of DNA-PK), α and β tubulins, prolyl-4-hydroxylase α-1 subunit [49]; p14ARF [50]; Fte-1/S3a [51]; HDAC4 [52]; SP100 [53], MDM2 (Kashuba, to be published)
EBNA-6	SPI1 (PU.1) [33]; CTBP [54]; HDAC1 [55]; mSIN3A, NCOR, HDAC1 [56]; acetyltransferase P300, prothymosin alpha [57]; DP103 [58]; SMN1 protein [59]; cyclin A [60]; E3 ubiquitin ligase, SCF complex [61]; NM23-H1 [62]; MRSPS18-2 [63]; MDM2 [64]

EBNA-2 might be involved in chromatin re-modeling that is mediated by binding to the SNF5 subunit of SWI/SNF chromatin re-modeling complex (NP_003064) [34], acetyltransferase P300/CBP (NP_001420) and its associated factor, PCAF (NP_003875) [38], and the helicase DP103 (NP_009135) [58].

3.3. EBNA-3 family proteins

EBNA-3, EBNA-4 and EBNA-6 (EBNA-3A, -3B and -3C according to the alternative nomenclature) are encoded by tandemly arranged genes and have similar genomic organization. They contain short intron sequences that may be retained in the mRNA [71].

All three EBNA-3 proteins associate with RBP-Jκ [40] through which they may be involved in transcriptional regulation. They are expressed exclusively in the B-blasts and bind to RBP-2N that is the major isoform of RBP-Jκ in B-lymphocytes [41]. Together with EBNA-2 they can be involved in transcription of the LMP-1 promoter [72,73].

The EBNA-3 proteins may also act in the G_2/M checkpoint control, as suggested by the binding of EBNA-3 to the checkpoint kinase chk2/cds1 (NP_001005735) [42].

We have found that EBNA-3 enhances the transcription of AhR responsive genes, at the basal level and when the receptor is activated by a ligand (e.g., TCDD) [45] due to the binding to aryl hydrocarbon receptor (AhR, NP_001612). EBNA-3 also binds to the XAP-2 regulatory subunit of AhR cytoplasmic complex [43], and induces its translocation from the cytoplasm to the nucleus. It is noteworthy, that XAP-2 is involved in the strategy of another DNA tumor virus, hepatitis B [74].

EBNA-3 is essential for LCL proliferation. When conditionally expressed from a 4-hydroxy-tamoxifen (HT) dependent promoter, withdrawal of HT led to growth arrest and cell death [75]. Tonsil derived B-cells, immortalized with EBNA-3 deficient virus, grow more slowly than cells transformed with wild type virus [76].

We have also found that EBNA-3 targets the enzyme UK/UPRT [46] and may be involved in the protein folding machinery [44].

EBNA-6 is the most extensively studied one among the EBNA-3 family. It associates with the co-repressors CTBP (NP_001319, binding protein to the C-terminal half of E1A) [54], mSin3A

(NP_001138829, homolog to the yeast SIN3), and nuclear receptor co-repressor NcoR (O75376) [56]. This may explain the ability of EBNA-6 to activate or repress transcription from the LMP-1 promoter.

EBNA-6 binds to histone deacetylases HDAC1 (NP_004955) [55] and HDAC2 (NP_001518) [56], acetyltransferase p300 and prothymosin alpha (NP_001092755) [57]. EBNA-6 was also shown to interact with the DEAD-box protein DP103 that has helicase activity [58] and the SMN1 protein (NP_000335.1, survival of motor neurons), a DP103 binding partner [59]. These interactions indicate that EBNA-6 plays a role in chromatin re-modeling.

EBNA-6 may play a role in cell cycle regulation. It was found to decrease the level of phosphorylated pRb and p27 (NP_004055) proteins in primary rat fibroblasts [77]. It was proposed that the SCF complex is involved in the EBNA-6 mediated degradation of pRb [78] and p27 as well [61]. However, in LCL EBNA-6 is not responsible for the degradation of pRb [79]. The fraction of lymphoblastoid cells in S and G_2/M phases were reduced within 1 week after the inactivation of EBNA-6. Thus, EBNA-6 interferes with components of the pRb–E2F pathway.

3.4. EBNA-5

EBNA-5 (EBNA-LP, leader protein) is expressed already 8–12 h in B-cells after EBV infection, in parallel with EBNA-2. The EBNA-5 and EBNA-2 message is spliced from the large transcript that also encodes other EBNAs. The size of EBNA-5 protein differs between LCLs, transformed by different EBV isolates, depending on the different number of W_1W_2 repeats. EBNA-5 potentiates EBNA-2-mediated transactivation [67,80–81], through binding to SP100 [82].

We have shown that EBNA-5 accumulates in PML bodies (also called ND10 bodies or PODs) together with heat shock protein, Hsp70 [83,84]. Upon heat shock or inhibition of the proteasome mediated protein degradation, EBNA-5 and Hsp70 move into the nucleoli [85]. At the same time the different components of the PML bodies and the 20S proteasomes also migrate into the nucleoli [86]. Recently it was shown that EBNA-5 binds to Sp100 and displaces Sp100 and HP1-alpha from the PML bodies [53].

We have found that p14ARF can induce growth arrest and cell death of cells with wild type, mutant, and even in the absence of p53. EBNA-5 binds to p14ARF and reduced p14ARF-induced cell death significantly. A minor fraction of the exogenous p14ARF targeted the nucleoli that contained no p53, HDM2 or EBNA-5, while the main portion of the p14ARF accumulated in extranucleolar foci where p53, HDM2, and EBNA-5 localized also. These inclusions also attracted most of the PML bodies, 20S proteasomes, and Hsp70 [50,87].

4. EBV interferes with cell-cycle control

Similar to other DNA tumor viruses, EBV impairs the two major tumor suppressor pathways, p53 and Rb.

4.1. p53 pathway

Primary EBV infection of B-lymphocytes induces high levels of p53 [88,89] and the LCLs maintain wild-type p53 during prolonged *in vitro* culture. In EBV positive cells induction of p53 does not lead to apoptosis. This raises the question of how EBV-transformed B-blasts and the derived lines can tolerate an increased level of p53 expression. We have shown that p14ARF, that is a p53-binding protein, binds EBNA-5 [50]. This raises the question of the relationship of EBNA-5 to the p53 antagonist MDM2. We have found that EBNA-5 binds to MDM2 and form trimolecular complexes with p53 (Kashuba, to be published). Unexpectedly, the binding of EBNA-5 to MDM2 was not accompanied by a decrease in p53 stability. Similarly to p14ARF, EBNA-5 inhibited p53 poly- but not monoubiquitination. Moreover, EBNA-5 inhibited p53 degradation *in vitro*. This is understandable, because only polyubiquitinated proteins are degraded on proteasomes. This would explain the high level of wild-type p53 in LCLs.

EBNA-5 binding to MDM2 influences the function of p53. We have previously found [89] that P21 that is a p53 target, is not expressed in LCLs, in contrast to mitogen-activated cells. *P21* and *VDR* were not induced in the EBV-infected cells, despite an increase in p53 under the treatment with mitomycin C. This may explain that in spite of high levels of p53 LCLs do not undergo apoptosis. Inhibition of *P21* expression was detected at the mRNA level. We also found that p53 in the trimolecular protein complex with MDM2 and EBNA-5 did not bind to the *P21* promoter (Fig. 3).

Thus, EBNA-5 stabilizes the levels of p53 in LCLs by binding to MDM2. The functional activity of p53 is blocked by the formation of trimolecular complexes between EBNA-5, MDM2 and p53.

4.2. pRb–E2F1 pathway

As we discussed earlier, EBNA-6 may be involved in the regulation of cell cycle entry. Our experiments revealed the mechanism of this regulation. We have shown that MRPS18-2 (S18-2), found by the yeast two-hybrid system with EBNA-6 as the bait [63], could also bind pRb [90]. A ternary complex of these three proteins was formed, where S18-2 served as a bridge between EBNA-6 and pRb. EBNA-6 binds to S18-2 and targets it to the nucleus. The binding of S18-2 to pRb is specific. It targets the small pocket of pRb, the site of the interaction with E2F1 [90]. This binding competes with the binding of E2F1 to pRb, thereby elevates the level of free E2F1. This may promote the entry of the EBV infected B-cell into the cell cycle (Fig. 4).

5. Burkitt's lymphoma (BL)

We return now to Burkitt lymphoma, the malignancy where EBV was first encountered.

As discussed before, the BL cells do not express the proliferation driving EBV program. They express only EBNA-1. Several findings suggest that this restricted virus program may counteract apoptosis. This could be sufficient to induce BL [1].

The chromosomal translocations that juxtapose one of the three immunoglobulin loci to the *C-MYC* protooncogene are the hallmark of BLs, whether or not they carry EBV.

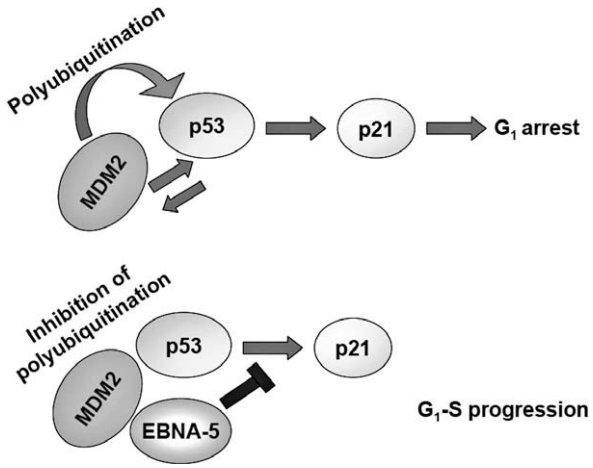

Fig. 3. EBNA-5 binding to MDM2 prevents p53 polyubiquitination and blocks its transactivating activity.

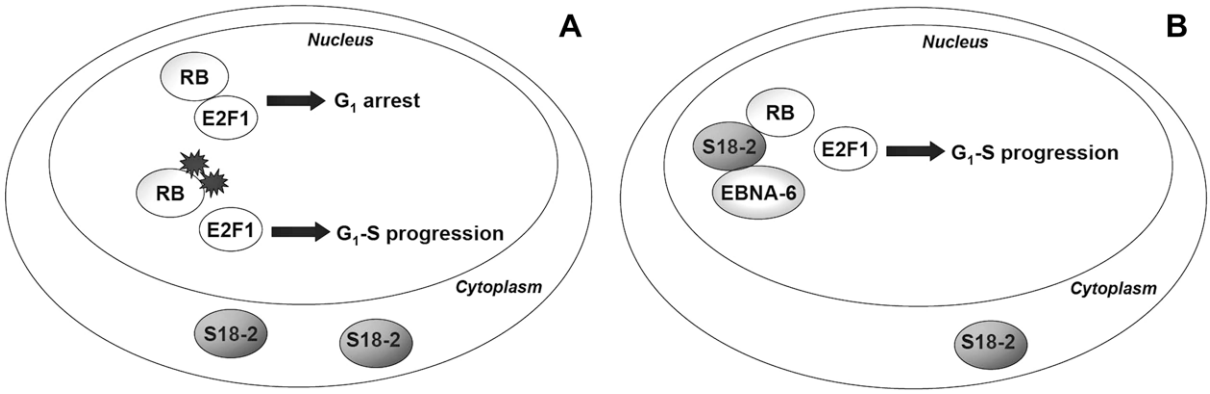

Fig. 4. Regulation of an S-phase by the Rb pathyway (A), involvement of EBNA-6 in G_1–S transition through the interaction with the pRb binding protein S18-2 (B).

These translocations are believed to occur as accidents of normal B-cell differentiation. They could be found in individuals without malignancy as well [91]. The *Ig/C-MYC* translocation leads to the constitutive activation of *C-MYC*. This may lead to cell proliferation. In most cases, however, this is not realized because *MYC* activation makes the cells prone to apoptosis [92].

Almost all endemic (but not the sporadic) BLs carry EBV and the viral genomes are never lost from the tumor, while they can be lost from established cell lines [93,24]. The presence of the viral genomes is therefore regarded as essential for the proliferation of the cells *in vivo*.

We have reported earlier that 7 of 9 EBV positive (only EBNA-1 expressing) type I BL lines expressed the SAP protein whereas none of 9 EBV negative BL lines tested were SAP positive [94]. This was the first described phenotypic difference between EBV positive and negative BLs.

The SAP protein was discovered in studies on the X-linked lymphoproliferative disease (XLP). It is a rare hereditary condition characterized by extreme sensitivity to EBV infection [95]. The molecular basis of the disease was identified as mutation of the *SAP* gene (*SH2D1A*) [96]. The protein was shown to regulate signal transduction pathways in lymphocytes [97].

We have found that the SAP protein is involved in apoptosis and it is a target of p53 [98]. The correlation between EBNA-1 and SAP has led us to suggest that the documented anti-apoptotic effect of EBNA-1 [99] counteracts the pro-apoptotic function of SAP in the EBV positive BLs. It has been suggested that the EBV negative and positive BLs originate from phenotypically different B-cells [100]. We can presume that these precursor differ in the expression of SAP.

The following scenario may be proposed: The development of BL is initiated by the Ig/myc translocation in a B-cell of a certain differentiation stage [99]. Constitutive activation of myc by the active Ig genes leads to apoptosis [92]. In the absence of SAP the apoptotic machinery is inactive and the cell can survive. Constitutive activation of *MYC* could then induce proliferation. In EBV infected SAP positive cells with the translocation, apoptosis might be counteracted by the anti-apoptotic effect of EBNA-1. The expression of EBNA-1 and SAP would thus determine the fate of the Ig/myc translocation carrying B-cells.

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References

[1] E. Klein, G. Klein (Ed.), Burkitt lymphoma, Semin. Cancer Biol. 19 (6) (2009).
[2] J.H. Pope, W. Scott, D.J. Moss, Human lymphoid cell transformation by Epstein-Barr virus, Nat. New Biol. 246 (1973) 140–141.
[3] G. Henle, W. Henle, V. Diehl, Relation of Burkitt's tumor-associated herpes-type virus to infectious mononucleosis, Proc. Natl. Acad. Sci. USA 59 (1968) 94–101.
[4] D. Siemer, J. Kurth, S. Lang, G. Lehnerdt, J. Stanelle, R. Kuppers, EBV transformation overrides gene expression patterns of B cell differentiation stages, Mol. Immunol. 45 (2008) 3133–3141.
[5] B.M. Reedman, G. Klein, Cellular localization of an Epstein-Barr virus (EBV)-associated complement-fixing antigen in producer and non-producer lymphoblastoid cell lines, Int. J. Cancer 11 (1973) 499–520.
[6] W. Hammerschmidt, B. Sugden, Genetic analysis of immortalizing functions of Epstein-Barr virus in human B lymphocytes, Nature 340 (1989) 393–397.
[7] J.I. Cohen, F. Wang, J. Mannick, E. Kieff, Epstein-Barr virus nuclear protein 2 is a key determinant of lymphocyte transformation, Proc. Natl. Acad. Sci. USA 86 (1989) 9558–9562.
[8] B. Tomkinson, E. Robertson, E. Kieff, Epstein-Barr virus nuclear proteins EBNA-3A and EBNA-3C are essential for B-lymphocyte growth transformation, J. Virol. 67 (1993) 2014–2025.
[9] B. Kempkes, D. Pich, R. Zeidler, B. Sugden, W. Hammerschmidt, Immortalization of human B lymphocytes by a plasmid containing 71 kilobase pairs of Epstein-Barr virus DNA, J. Virol. 69 (1995) 231–238.
[10] B. Kempkes, D. Spitkovsky, P. Jansen-Durr, J.W. Ellwart, E. Kremmer, H.J. Delecluse, C. Rottenberger, G.W. Bornkamm, W. Hammerschmidt, B-cell proliferation and induction of early G1-regulating proteins by Epstein-Barr virus mutants conditional for EBNA2, EMBO J. 14 (1995) 88–96.
[11] J.B. Mannick, J.I. Cohen, M. Birkenbach, A. Marchini, E. Kieff, The Epstein-Barr virus nuclear protein encoded by the leader of the EBNA RNAs is important in B-lymphocyte transformation, J. Virol. 65 (1991) 6826–6837.
[12] K.M. Kaye, K.M. Izumi, E. Kieff, Epstein-Barr virus latent membrane protein 1 is essential for B-lymphocyte growth transformation, Proc. Natl. Acad. Sci. USA 90 (1993) 9150–9154.
[13] D.R. Rawlins, G. Milman, S.D. Hayward, G.S. Hayward, Sequence-specific DNA binding of the Epstein-Barr virus nuclear antigen (EBNA-1) to clustered sites in the plasmid maintenance region, Cell 42 (1985) 859–868.
[14] C.H. Jones, S.D. Hayward, D.R. Rawlins, Interaction of the lymphocyte-derived Epstein-Barr virus nuclear antigen EBNA-1 with its DNA-binding sites, J. Virol. 63 (1989) 101–110.
[15] J. Yates, N. Warren, D. Reisman, B. Sugden, A cis-acting element from the Epstein-Barr viral genome that permits stable replication of recombinant plasmids in latently infected cells, Proc. Natl. Acad. Sci. USA 81 (1984) 3806–3810.
[16] D. Reisman, B. Sugden, Trans activation of an Epstein-Barr viral transcriptional enhancer by the Epstein-Barr viral nuclear antigen 1, Mol. Cell. Biol. 6 (1986) 3838–3846.
[17] G. Kennedy, B. Sugden, EBNA-1, a bifunctional transcriptional activator, Mol. Cell. Biol. 23 (2003) 6901–6908.
[18] M. Altmann, D. Pich, R. Ruiss, J. Wang, B. Sugden, W. Hammerschmidt, Transcriptional activation by EBV nuclear antigen 1 is essential for the expression of EBV's transforming genes, Proc. Natl. Acad. Sci. USA 103 (2006) 14188–14193.
[19] K. Shire, D.F. Ceccarelli, T.M. Avolio-Hunter, L. Frappier, EBP2, a human protein that interacts with sequences of the Epstein-Barr virus nuclear antigen 1 important for plasmid maintenance, J. Virol. 73 (1999) 2587–2595.
[20] H. Wu, P. Kapoor, L. Frappier, Separation of the DNA replication, segregation, and transcriptional activation functions of Epstein-Barr nuclear antigen 1, J. Virol. 76 (2002) 2480–2490.

[21] P. Kapoor, B.D. Lavoie, L. Frappier, EBP2 plays a key role in Epstein-Barr virus mitotic segregation and is regulated by aurora family kinases, Mol. Cell. Biol. 25 (2005) 4934–4945.
[22] J. Sears, M. Ujihara, S. Wong, C. Ott, J. Middeldorp, A. Aiyar, The amino terminus of Epstein-Barr Virus (EBV) nuclear antigen 1 contains AT hooks that facilitate the replication and partitioning of latent EBV genomes by tethering them to cellular chromosomes, J. Virol. 78 (2004) 11487–11505.
[23] J. Komano, M. Sugiura, K. Takada, Epstein-Barr virus contributes to the malignant phenotype and to apoptosis resistance in Burkitt's lymphoma cell line Akata, J. Virol. 72 (1998) 9150–9156.
[24] G. Kennedy, J. Komano, B. Sugden, Epstein-Barr virus provides a survival factor to Burkitt's lymphomas, Proc. Natl. Acad. Sci. USA 100 (2003) 14269–14274.
[25] M.N. Holowaty, M. Zeghouf, H. Wu, J. Tellam, V. Athanasopoulos, J. Greenblatt, L. Frappier, Protein profiling with Epstein-Barr nuclear antigen-1 reveals an interaction with the herpesvirus-associated ubiquitin-specific protease HAUSP/USP7, J. Biol. Chem. 278 (2003) 29987–29994.
[26] N. Fischer, E. Kremmer, G. Lautscham, N. Mueller-Lantzsch, F.A. Grasser, Epstein-Barr virus nuclear antigen 1 forms a complex with the nuclear transporter karyopherin alpha2, J. Biol. Chem. 272 (1997) 3999–4005.
[27] S. Ito, M. Ikeda, N. Kato, A. Matsumoto, Y. Ishikawa, S. Kumakubo, K. Yanagi, Epstein-Barr virus nuclear antigen-1 binds to nuclear transporter karyopherin alpha1/NPI-1 in addition to karyopherin alpha2/Rch1, Virology 266 (2000) 110–119.
[28] A.L. Kim, M. Maher, J.B. Hayman, J. Ozer, D. Zerby, J.L. Yates, P.M. Lieberman, An imperfect correlation between DNA replication activity of Epstein-Barr virus nuclear antigen 1 (EBNA1) and binding to the nuclear import receptor, Rch1/importin alpha, Virology 239 (1997) 340–351.
[29] D. Zhang, L. Frappier, E. Gibbs, J. Hurwitz, M. O'Donnell, Human RPA (hSSB) interacts with EBNA1, the latent origin binding protein of Epstein-Barr virus, Nucleic Acids Res. 26 (1998) 631–637.
[30] M. Murakami, K. Lan, C. Subramanian, E.S. Robertson, Epstein-Barr virus nuclear antigen 1 interacts with Nm23-H1 in lymphoblastoid cell lines and inhibits its ability to suppress cell migration, J. Virol. 79 (2005) 1559–1568.
[31] A. Lin, S. Wang, T. Nguyen, K. Shire, L. Frappier, The EBNA1 protein of Epstein-Barr virus functionally interacts with Brd4, J. Virol. 82 (2008) 12009–12019.
[32] T. Henkel, P.D. Ling, S.D. Hayward, M.G. Peterson, Mediation of Epstein-Barr virus EBNA2 transactivation by recombination signal-binding protein J kappa, Science 265 (1994) 92–95.
[33] E. Johannsen, E. Koh, G. Mosialos, X. Tong, E. Kieff, S.R. Grossman, Epstein-Barr virus nuclear protein 2 transactivation of the latent membrane protein 1 promoter is mediated by J kappa and PU.1, J. Virol. 69 (1995) 253–262.
[34] D.Y. Wu, G.V. Kalpana, S.P. Goff, W.H. Schubach, Epstein-Barr virus nuclear protein 2 (EBNA2) binds to a component of the human SNF–SWI complex, hSNF5/Ini1, J. Virol. 70 (1996) 6020–6028.
[35] S.R. Grossman, E. Johannsen, X. Tong, R. Yalamanchili, E. Kieff, The Epstein-Barr virus nuclear antigen 2 transactivator is directed to response elements by the J kappa recombination signal binding protein, Proc. Natl. Acad. Sci. USA 91 (1994) 7568–7572.
[36] S. Barth, M. Liss, M.D. Voss, T. Dobner, U. Fischer, G. Meister, F.A. Grasser, Epstein-Barr virus nuclear antigen 2 binds via its methylated arginine–glycine repeat to the survival motor neuron protein, J. Virol. 77 (2003) 5008–5013.
[37] X. Tong, R. Drapkin, R. Yalamanchili, G. Mosialos, E. Kieff, The Epstein-Barr virus nuclear protein 2 acidic domain forms a complex with a novel cellular coactivator that can interact with TFIIE, Mol. Cell. Biol. 15 (1995) 4735–4744.
[38] L. Wang, S.R. Grossman, E. Kieff, Epstein-Barr virus nuclear protein 2 interacts with p300, CBP, and PCAF histone acetyltransferases in activation of the LMP1 promoter, Proc. Natl. Acad. Sci. USA 97 (2000) 430–435.
[39] J.M. Lee, K.H. Lee, C.J. Farrell, P.D. Ling, B. Kempkes, J.H. Park, S.D. Hayward, EBNA2 is required for protection of latently Epstein-Barr virus-infected B cells against specific apoptotic stimuli, J. Virol. 78 (2004) 12694–12697.
[40] E.S. Robertson, S. Grossman, E. Johannsen, C. Miller, J. Lin, B. Tomkinson, E. Kieff, Epstein-Barr virus nuclear protein 3C modulates transcription through interaction with the sequence-specific DNA-binding protein J kappa, J. Virol. 69 (1995) 3108–3116.
[41] K.G. Krauer, N. Kienzle, D.B. Young, T.B. Sculley, Epstein-Barr nuclear antigen-3 and -4 interact with RBP-2N, a major isoform of RBP-J kappa in B lymphocytes, Virology 226 (1996) 346–353.
[42] K.G. Krauer, A. Burgess, M. Buck, J. Flanagan, T.B. Sculley, B. Gabrielli, The EBNA-3 gene family proteins disrupt the G2/M checkpoint, Oncogene 23 (2004) 1342–1353.
[43] E. Kashuba, V. Kashuba, K. Pokrovskaja, G. Klein, L. Szekely, Epstein-Barr virus encoded nuclear protein EBNA-3 binds XAP-2, a protein associated with hepatitis B virus X antigen, Oncogene 19 (2000) 1801–1806.
[44] E. Kashuba, K. Pokrovskaja, G. Klein, L. Szekely, Epstein-Barr virus-encoded nuclear protein EBNA-3 interacts with the epsilon-subunit of the T-complex protein 1 chaperonin complex, J. Hum. Virol. 2 (1999) 33–37.
[45] E.V. Kashuba, K. Gradin, M. Isaguliants, L. Szekely, L. Poellinger, G. Klein, A. Kazlauskas, Regulation of transactivation function of the aryl hydrocarbon receptor by the Epstein-Barr virus-encoded EBNA-3 protein, J. Biol. Chem. 281 (2006) 1215–1223.
[46] E. Kashuba, V. Kashuba, T. Sandalova, G. Klein, L. Szekely, Epstein-Barr virus encoded nuclear protein EBNA-3 binds a novel human uridine kinase/uracil phosphoribosyltransferase, BMC Cell Biol. 3 (2002) 23.
[47] J.B. Mannick, X. Tong, A. Hemnes, E. Kieff, The Epstein-Barr virus nuclear antigen leader protein associates with hsp72/hsc73, J. Virol. 69 (1995) 8169–8172.
[48] Y. Kawaguchi, K. Nakajima, M. Igarashi, T. Morita, M. Tanaka, M. Suzuki, A. Yokoyama, G. Matsuda, K. Kato, M. Kanamori, K. Hirai, Interaction of Epstein-Barr virus nuclear antigen leader protein (EBNA-LP) with HS1-associated protein X-1: implication of cytoplasmic function of EBNA-LP, J. Virol. 74 (2000) 10104–10111.
[49] I. Han, S. Harada, D. Weaver, Y. Xue, W. Lane, S. Orstavik, B. Skalhegg, E. Kieff, EBNA-LP associates with cellular proteins including DNA-PK and HA95, J. Virol. 75 (2001) 2475–2481.
[50] E. Kashuba, K. Mattsson, K. Pokrovskaja, C. Kiss, M. Protopopova, B. Ehlin-Henriksson, G. Klein, L. Szekely, EBV-encoded EBNA-5 associates with P14ARF in extranucleolar inclusions and prolongs the survival of P14ARF-expressing cells, Int. J. Cancer 105 (2003) 644–653.
[51] E. Kashuba, M. Yurchenko, K. Szirak, J. Stahl, G. Klein, L. Szekely, Epstein-Barr virus-encoded EBNA-5 binds to Epstein-Barr virus-induced Fte1/S3a protein, Exp. Cell Res. 303 (2005) 47–55.
[52] D. Portal, A. Rosendorff, E. Kieff, Epstein-Barr nuclear antigen leader protein coactivates transcription through interaction with histone deacetylase 4, Proc. Natl. Acad. Sci. USA 103 (2006) 19278–19283.
[53] C.W. Echendu, P.D. Ling, Regulation of Sp100A subnuclear localization and transcriptional function by EBNA-LP and interferon, J. Interferon Cytokine Res. 28 (2008) 667–678.
[54] R. Touitou, M. Hickabottom, G. Parker, T. Crook, M.J. Allday, Physical and functional interactions between the corepressor CtBP and the Epstein-Barr virus nuclear antigen EBNA3C, J. Virol. 75 (2001) 7749–7755.
[55] S.A. Radkov, R. Touitou, A. Brehm, M. Rowe, M. West, T. Kouzarides, M.J. Allday, Epstein-Barr virus nuclear antigen 3C interacts with histone deacetylase to repress transcription, J. Virol. 73 (1999) 5688–5697.
[56] J.S. Knight, K. Lan, C. Subramanian, E.S. Robertson, Epstein-Barr virus nuclear antigen 3C recruits histone deacetylase activity and associates with the corepressors mSin3A and NCoR in human B-cell lines, J. Virol. 77 (2003) 4261–4272.
[57] M.A. Cotter 2nd, E.S. Robertson, Modulation of histone acetyltransferase activity through interaction of epstein-barr nuclear antigen 3C with prothymosin alpha, Mol. Cell. Biol. 20 (2000) 5722–5735.
[58] A.T. Grundhoff, E. Kremmer, O. Tureci, A. Glieden, C. Gindorf, J. Atz, N. Mueller-Lantzsch, W.H. Schubach, F.A. Grasser, Characterization of DP103, a novel DEAD box protein that binds to the Epstein-Barr virus nuclear proteins EBNA2 and EBNA3C, J. Biol. Chem. 274 (1999) 19136–19144.
[59] K.G. Krauer, M. Buck, D.K. Belzer, J. Flanagan, G.M. Chojnowski, T.B. Sculley, The Epstein-Barr virus nuclear antigen-6 protein co-localizes with EBNA-3 and survival of motor neurons protein, Virology 318 (2004) 280–294.
[60] J.S. Knight, E.S. Robertson, Epstein-Barr virus nuclear antigen 3C regulates cyclin A/p27 complexes and enhances cyclin A-dependent kinase activity, J. Virol. 78 (2004) 1981–1991.
[61] J.S. Knight, N. Sharma, E.S. Robertson, SCFSkp2 complex targeted by Epstein-Barr virus essential nuclear antigen, Mol. Cell. Biol. 25 (2005) 1749–1763.
[62] C. Subramanian, M.A. Cotter 2nd, E.S. Robertson, Epstein-Barr virus nuclear protein EBNA-3C interacts with the human metastatic suppressor Nm23-H1: a molecular link to cancer metastasis, Nat. Med. 7 (2001) 350–355.
[63] E. Kashuba, M. Yurchenko, S.P. Yenamandra, B. Snopok, M. Isaguliants, L. Szekely, G. Klein, EBV-encoded EBNA-6 binds and targets MRS18-2 to the nucleus, resulting in the disruption of pRb–E2F1 complexes, Proc. Natl. Acad. Sci. USA 105 (2008) 5489–5494.
[64] A. Saha, M. Murakami, P. Kumar, B. Bajaj, K. Sims, E.S. Robertson, Epstein-Barr virus nuclear antigen 3C augments Mdm2-mediated p53 ubiquitination and degradation by deubiquitinating Mdm2, J. Virol. 83 (2009) 4652–4669.
[65] R. Yalamanchili, X. Tong, S. Grossman, E. Johannsen, G. Mosialos, E. Kieff, Genetic and biochemical evidence that EBNA 2 interaction with a 63-kDa cellular GTG-binding protein is essential for B lymphocyte growth transformation by EBV, Virology 204 (1994) 634–641.
[66] E. Kieff, A. Rikinson, Epstein-Barr virus and its replication, in: D.M. Knipe, B.N. Fields, P.M. Howley (Eds.), Fields Virology, Lippincott-Williams & Wilkins Publishers, Philadelphia, 2007, pp. 2603–2654.
[67] A.J. Sinclair, I. Palmero, G. Peters, P.J. Farrell, EBNA-2 and EBNA-LP cooperate to cause G0 to G1 transition during immortalization of resting human B lymphocytes by Epstein-Barr virus, EMBO J. 13 (1994) 3321–3328.
[68] L.L. Kis, D. Salamon, E.K. Persson, N. Nagy, F.A. Scheeren, H. Spits, G. Klein, E. Klein, IL-21 imposes a type II EBV gene expression on type III and type I B cells by the repression of C- and activation of LMP-1-promoter, Proc. Natl. Acad. Sci. USA 107 (2010) 872–877.
[69] E.S. Seto, H.J. Bellen, T.E. Lloyd, When cell biology meets development: endocytic regulation of signaling pathways, Genes Dev. 16 (2002) 1314–1336.
[70] D. Allman, J.A. Punt, D.J. Izon, J.C. Aster, W.S. Pear, An invitation to T and more: notch signaling in lymphopoiesis, Cell 109 (Suppl.) (2002) S1–S11.
[71] N. Kienzle, D.B. Young, D. Liaskou, M. Buck, S. Greco, T.B. Sculley, Intron retention may regulate expression of Epstein-Barr virus nuclear antigen 3 family genes, J. Virol. 73 (1999) 1195–1204.
[72] D. Marshall, C. Sample, Epstein-Barr virus nuclear antigen 3C is a transcriptional regulator, J. Virol. 69 (1995) 3624–3630.
[73] J. Lin, E. Johannsen, E. Robertson, E. Kieff, Epstein-Barr virus nuclear antigen 3C putative repression domain mediates coactivation of the LMP1 promoter with EBNA-2, J. Virol. 76 (2002) 232–242.

[74] N. Kuzhandaivelu, Y.S. Cong, C. Inouye, W.M. Yang, E. Seto, XAP2, a novel hepatitis B virus X-associated protein that inhibits X transactivation, Nucleic Acids Res. 24 (1996) 4741–4750.
[75] S. Maruo, E. Johannsen, D. Illanes, A. Cooper, E. Kieff, Epstein-Barr virus nuclear protein EBNA3A is critical for maintaining lymphoblastoid cell line growth, J. Virol. 77 (2003) 10437–10447.
[76] M.L. Hertle, C. Popp, S. Petermann, S. Maier, E. Kremmer, R. Lang, J. Mages, B. Kempkes, Differential gene expression patterns of EBV infected EBNA-3A positive and negative human B lymphocytes, PLoS Pathog. 5 (2009) e1000506.
[77] G.A. Parker, R. Touitou, M.J. Allday, Epstein-Barr virus EBNA3C can disrupt multiple cell cycle checkpoints and induce nuclear division divorced from cytokinesis, Oncogene 19 (2000) 700–709.
[78] J.S. Knight, N. Sharma, E.S. Robertson, 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 (2005) 18562–18566.
[79] S. Maruo, Y. Wu, S. Ishikawa, T. Kanda, D. Iwakiri, K. Takada, Epstein-Barr virus nuclear protein EBNA3C is required for cell cycle progression and growth maintenance of lymphoblastoid cells, Proc. Natl. Acad. Sci. USA 103 (2006) 19500–19505.
[80] S. Harada, E. Kieff, Epstein-Barr virus nuclear protein LP stimulates EBNA-2 acidic domain-mediated transcriptional activation, J. Virol. 71 (1997) 6611–6618.
[81] F. Nitsche, A. Bell, A. Rickinson, Epstein-Barr virus leader protein enhances EBNA-2-mediated transactivation of latent membrane protein 1 expression: a role for the W1W2 repeat domain, J. Virol. 71 (1997) 6619–6628.
[82] P.D. Ling, R.S. Peng, A. Nakajima, J.H. Yu, J. Tan, S.M. Moses, W.H. Yang, B. Zhao, E. Kieff, K.D. Bloch, D.B. Bloch, Mediation of Epstein-Barr virus EBNA-LP transcriptional coactivation by Sp100, EMBO J. 24 (2005) 3565–3575.
[83] L. Szekely, K. Pokrovskaja, W.Q. Jiang, H. de The, N. Ringertz, G. Klein, The Epstein-Barr virus-encoded nuclear antigen EBNA-5 accumulates in PML-containing bodies, J. Virol. 70 (1996) 2562–2568.
[84] L. Szekely, W.Q. Jiang, K. Pokrovskaja, K.G. Wiman, G. Klein, N. Ringertz, Reversible nucleolar translocation of Epstein-Barr virus-encoded EBNA-5 and hsp70 proteins after exposure to heat shock or cell density congestion, J. Gen. Virol. 76 (Pt. 10) (1995) 2423–2432.
[85] K. Pokrovskaja, K. Mattsson, E. Kashuba, G. Klein, L. Szekely, Proteasome inhibitor induces nucleolar translocation of Epstein-Barr virus-encoded EBNA-5, J. Gen. Virol. 82 (2001) 345–358.
[86] K. Mattsson, K. Pokrovskaja, C. Kiss, G. Klein, L. Szekely, Proteins associated with the promyelocytic leukemia gene product (PML)-containing nuclear body move to the nucleolus upon inhibition of proteasome-dependent protein degradation, Proc. Natl. Acad. Sci. USA 98 (2001) 1012–1017.
[87] E. Kashuba, K. Mattsson, G. Klein, L. Szekely, P14ARF induces the relocation of HDM2 and p53 to extranucleolar sites that are targeted by PML bodies and proteasomes, Mol. Cancer 2 (2003) 18.
[88] M.J. Allday, G.J. Inman, D.H. Crawford, P.J. Farrell, DNA damage in human B cells can induce apoptosis, proceeding from G1/S when p53 is transactivation competent and G2/M when it is transactivation defective, EMBO J. 14 (1995) 4994–5005.
[89] K. Pokrovskaja, I. Okan, E. Kashuba, M. Lowbeer, G. Klein, L. Szekely, Epstein-Barr virus infection and mitogen stimulation of normal B cells induces wild-type p53 without subsequent growth arrest or apoptosis, J. Gen. Virol. 80 (Pt. 4) (1999) 987–995.
[90] B. Snopok, M. Yurchenko, L. Szekely, G. Klein, E. Kashuba, SPR-based immunocapture approach to creating an interfacial sensing architecture: mapping of the MRS18-2 binding site on retinoblastoma protein, Anal. Bioanal. Chem. 386 (2006) 2063–2073.
[91] J.R. Muller, S. Janz, J.J. Goedert, M. Potter, C.S. Rabkin, Persistence of immunoglobulin heavy chain/c-myc recombination-positive lymphocyte clones in the blood of human immunodeficiency virus-infected homosexual men, Proc. Natl. Acad. Sci. USA 92 (1995) 6577–6581.
[92] G.I. Evan, A.H. Wyllie, C.S. Gilbert, T.D. Littlewood, H. Land, M. Brooks, C.M. Waters, L.Z. Penn, D.C. Hancock, Induction of apoptosis in fibroblasts by c-myc protein, Cell 69 (1992) 119–128.
[93] N. Shimizu, A. Tanabe-Tochikura, Y. Kuroiwa, K. Takada, Isolation of Epstein-Barr virus (EBV)-negative cell clones from the EBV-positive Burkitt's lymphoma (BL) line Akata: malignant phenotypes of BL cells are dependent on EBV, J. Virol. 68 (1994) 6069–6073.
[94] N. Nagy, A. Maeda, K. Bandobashi, L.L. Kis, J. Nishikawa, P. Trivedi, A. Faggioni, G. Klein, E. Klein, SH2D1A expression in Burkitt lymphoma cells is restricted to EBV positive group I lines and is downregulated in parallel with immunoblastic transformation, Int. J. Cancer 100 (2002) 433–440.
[95] D.T. Purtilo, C.K. Cassel, J.P. Yang, R. Harper, X-linked recessive progressive combined variable immunodeficiency (Duncan's disease), Lancet 1 (1975) 935–940.
[96] K.E. Nichols, D.P. Harkin, S. Levitz, M. Krainer, K.A. Kolquist, C. Genovese, A. Bernard, M. Ferguson, L. Zuo, E. Snyder, A.J. Buckler, C. Wise, J. Ashley, M. Lovett, M.B. Valentine, A.T. Look, W. Gerald, D.E. Housman, D.A. Haber, Inactivating mutations in an SH2 domain-encoding gene in X-linked lymphoproliferative syndrome, Proc. Natl. Acad. Sci. USA 95 (1998) 13765–13770.
[97] J. Sayos, C. Wu, M. Morra, N. Wang, X. Zhang, D. Allen, S. Van Schaik, L. Notarangelo, R. Geha, M.G. Roncarolo, H. Oettgen, J.E. De Vries, G. Aversa, C. Terhorst, The X-linked lymphoproliferative-disease gene product SAP regulates signals induced through the co-receptor SLAM, Nature 395 (1998) 462–469.
[98] N. Nagy, L. Matskova, L.L. Kis, U. Hellman, G. Klein, E. Klein, The proapoptotic function of SAP provides a clue to the clinical picture of X-linked lymphoproliferative disease, Proc. Natl. Acad. Sci. USA 106 (2009) 11966–11971.
[99] N. Nagy, G. Klein, E. Klein, To the genesis of Burkitt lymphoma: regulation of apoptosis by EBNA-1 and SAP may determine the fate of Ig-myc translocation carrying B lymphocytes, Semin. Cancer Biol. 19 (2009) 407–410.
[100] C. Bellan, S. Lazzi, M. Hummel, N. Palummo, M. de Santi, T. Amato, J. Nyagol, E. Sabattini, T. Lazure, S.A. Pileri, M. Raphael, H. Stein, P. Tosi, L. Leoncini, Immunoglobulin gene analysis reveals 2 distinct cells of origin for EBV-positive and EBV-negative Burkitt lymphomas, Blood 106 (2005) 1031–1036.