Chapter 21
EBV in T-/NK-Cell Tumorigenesis

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Abstract Epstein–Barr virus (EBV), which is associated with B-cell proliferative disorders, also transforms T- or natural killer (NK)-lineage cells and has been connected with various T- or NK (T/NK)-cell malignancies, such as extranodal NK/T-cell lymphoma-nasal type and aggressive NK-cell leukemia. Chronic active EBV (CAEBV) disease, which occurs most often in children and young adults in East Asia, is an EBV-associated T-/NK-cell lymphoproliferative disease. Patients with CAEBV often progress to overt lymphoma or leukemia over a long-term clinical course. EBV's transforming capacity in B cells is well characterized, but the molecular pathogenesis of clonal expansion caused by EBV in T/NK cells has not yet been clarified. In the primary infection, EBV infects B cells and epithelial cells and may also infect some T/NK cells. In some individuals, because of poor presentation by specific human leukocyte antigens or the genetic background, EBV-infected T/NK cells evade host immunity and survive. Occasionally, with the help of viral oncogenes, EBV-associated T/NK lymphoproliferative diseases, such as CAEBV, may develop. The subsequent accumulation of genetic mutations and/or epigenetic modifications in driver genes, such as DDX3X and TP53, may lead to overt lymphoma and leukemia. Activation-induced cytidine deaminase and the APOBEC3 family, driven by EBV infection, may induce chromosomal recombination and somatic mutations.

Keywords AID · CAEBV · Chronic active EBV disease · DDX3X · ENKL · Extranodal NK/T-cell lymphoma-nasal type · EBV-T/NK LPD · Lymphomagenesis · Lymphoproliferative disease

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21.1 Introduction

Epstein–Barr virus (EBV) infects only human beings, so its host range is very limited. Host-cell ranges are also narrow, primarily because of receptor tropism. EBV preferentially infects B cells and is associated with various B-cell-origin diseases (Longnecker et al. 2013; Grywalska and Rolinski 2015), such as infectious mononucleosis, Burkitt lymphoma, and posttransplant lymphoproliferative disorders (Table 21.1). EBV also infects epithelial cells and has been linked to several epithelial-cell-origin diseases, including nasopharyngeal carcinoma and gastric cancer (Table 21.1). However, EBV can infect non-B lymphocytes, such as T-cells and natural killer (NK) cells, and its association with T- and NK (T/NK)-cell-origin diseases has been demonstrated (Cohen et al. 2009).

Table 21.1 EBV-associated diseases (non-T/NK cells)

Disease entity	Association to EBV (%)	Infected cells	Latency type	Population at high risk
Infectious mononucleosis	100	B	III	Adolescents
Burkitt lymphoma, endemic	100	B	I	Equatorial Africa, New Guinea
Burkitt lymphoma, sporadic	30	B	I	
Hodgkin lymphoma, mixed cellularity	60–80	B	II	
Hodgkin lymphoma, nodular sclerosis	20–40	B	II	
Lymphomatoid granulomatosis	100	B	II	Western countries
EBV+ diffuse large B-cell lymphoma of elderly	100	B	III?	
Posttransplant lymphoproliferative disorders	>90	B	III	Recipients with heart, lung, or intestine transplantation
Lymphoma associated with HIV infection	40	B	I-III	
Primary effusion lymphoma[a]	70–80	B	III	HIV-infected individuals
Plasmablastic lymphoma	70	Plasma blasts	I?	HIV-infected individuals
Hairy leukoplakia	100	Epithelial cells	Lytic infection	HIV-infected individuals
Nasopharyngeal carcinoma	100	Epithelial cells	II	Southern China
Gastric cancer	9	Epithelial cells	I	

HIV human immunodeficiency virus

[a]Universally associated with human herpesvirus 8

EBV, which was originally isolated from Burkitt lymphoma in 1964 (Epstein et al. 1964), has been studied extensively in the context of B-cell lymphomagenesis for more than 50 years. Because EBV-associated T-/NK-cell tumors are rare and the generation and handling of EBV-positive T/NK cells are more difficult than B or epithelial cells, the precise mechanism of T-/NK-cell tumorigenesis has not yet been clarified. In this chapter, I will summarize the pathogenesis of EBV-associated T-/NK-cell neoplasms. In particular, oncogenicity in EBV-associated T-/NK-cell lymphoma will be the focus.

21.2 A Historical Perspective on T-/NK-Cell Tumorigenesis

An association between EBV, Burkitt lymphoma, and nasopharyngeal carcinoma was demonstrated soon after the first isolation of EBV (Epstein et al. 1964; Zur Hausen et al. 1970). However, a linkage to T-/NK-cell tumors was observed for the first time in the late 1980s. In 1988, Jones et al. reported T-cell lymphomas containing EBV DNA (Jones et al. 1988), nearly 25 years after the discovery of EBV (Table 21.2). This delay was partly due to the rarity of T-/NK-cell tumors, but the main reason was that there had been no reliable way to detect EBV-infected cells. The development of EBV-encoded small RNA (EBER) in situ hybridization boosted the discovery of a variety of EBV-associated diseases (Weiss et al. 1989). In 1989, the first case of EBV-associated NK-cell lymphoproliferative disease was reported (Kawa-Ha et al. 1989). Since then, linkages between previously known T-/NK-cell tumors and EBV have been found (Table 21.2) (Kikuta et al. 1988; Harabuchi et al. 1990; Hart et al. 1992; Kawaguchi et al. 1993; Ishihara et al. 1997; Iwatsuki et al. 1999).

In the 1990s, several EBV-positive T-/NK-cell lines were established. Most of them were derived from patient specimens (Imai et al. 1996; Tsuchiyama et al. 1998; Tsuge et al. 1999; Zhang et al. 2003), but some were established by in vitro infection of EBV-negative cell lines (Table 21.2) (Paterson et al. 1995; Fujiwara and Ono 1995; Isobe et al. 2004). These cell lines have helped greatly in studying the pathogenesis of EBV in T-/NK-cell tumors, combined with the development of mouse xenograft models (Imadome et al. 2011; Fujiwara et al. 2014).

In the twenty-first century, novel techniques, such as DNA microarrays, array comparative genomic hybridization, and "next-generation" sequencing, have been applied to genome-wide association studies and whole-genome/exome sequencing. With these techniques, the tumorigenesis of EBV-associated T-/NK-cell tumors is now being clarified to some extent (Iqbal et al. 2009; Karube et al. 2011; Jiang et al. 2015; Li et al. 2016), although the precise mechanism(s) remain unresolved (Table 21.2).

Table 21.2 Discoveries and events associated with T-/NK-cell tumorigenesis and EBV

Year	Investigators	Discovery and event	Reference
1988	Jones et al.	Linkage to T-cell lymphoma	Jones et al. (1988)
1988	Kikuta et al.	T-cell infection in chronic active EBV disease	Kikuta et al. (1988)
1989	Kawa-Ha et al.	Linkage to NK-cell lymphoproliferative disease	Kawa-Ha et al. (1989)
1990	Harabuchi et al.	Linkage to extranodal NK/T-cell lymphoma	Harabuchi et al. (1990)
1992	Hart et al.	Linkage to aggressive NK-cell leukemia	Hart et al. (1992)
1993	Kawaguchi et al.	T-cell infection in EBV-associated hemophagocytic lymphohistiocytosis	Kawaguchi et al. (1993)
1995	Paterson et al.	In vitro infection of T-cell line	Paterson et al. (1995)
1995	Fujiwara et al.	Establishment of T-cell lines by in vitro infection of HTLV-1-positive T-cell line	Fujiwara and Ono (1995)
1996	Imai et al.	Establishment of T-cell lines from clinical specimens	Imai et al. (1996)
1997	Ishihara et al.	Linkage to severe mosquito bite allergy	Ishihara et al. (1997)
1998	Tsuchiyama et al.	Establishment of an NK-cell line	Tsuchiyama et al. (1998)
1999	Iwatsuki et al.	Linkage to hydroa vacciniforme	Iwatsuki et al. (1999)
2004	Isobe et al.	Establishment of an NK-cell line by in vitro infection to an NK-cell leukemia line	Isobe et al. (2004)
2009	Iqbal et al.	Mutational analysis by array comparative genomic hybridization in NK-cell malignancies	Iqbal et al. (2009)
2011	Imadome et al.	Mouse xenograft model of chronic active EBV disease	Imadome et al. (2011)
2015	Jiang et al.	Whole exome sequencing in extranodal NK/T-cell lymphoma	Jiang et al. (2015)
2016	Li et al.	Genome-wide association study in extranodal NK/T-cell lymphoma	Li et al. (2016)

21.3 EBV-Associated T-/NK-Cell Tumors

There are various EBV-associated T-/NK-cell tumors, from lymphoproliferative disease to overt leukemia/lymphoma (Table 21.3). Although some have names suggesting seemingly benign diseases (e.g., mosquito bite allergy), all are basically neoplasms where EBV-infected T/NK cells proliferate with clonality and infiltrate organs.

In the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues, the following diseases are listed as mature T-cell and NK-cell neoplasms associated with EBV: aggressive NK-cell leukemia, extranodal NK/T-cell lymphoma-nasal type (ENKL), systemic EBV-positive T-cell lymphoproliferative disease of childhood, hydroa vacciniforme-like lymphoma, and EBV[+] peripheral T-cell lymphoma, not otherwise specified (Chan et al. 2008a, b; Quintanilla-Martinez

Table 21.3 EBV-associated T- or NK-cell lymphoproliferative diseases/lymphoma

Disease entity	Association with EBV (%)	Infected cells	Latency type	Population at high risk
Angioimmunoblastic T-cell lymphoma	>90	B[a]	II	
Aggressive NK-cell leukemia	>90	NK	II	Asians
Extranodal NK/T-cell lymphoma, nasal type	100	NK, T	II	East Asians
Peripheral T-cell lymphoma, not otherwise specified	30	T	II	
Chronic active EBV disease of T/NK type	100	T, NK (B)	II	East Asians
Severe mosquito bite allergy	100	NK (T)	II	East Asians
EBV-associated hemophagocytic lymphohistiocytosis	100	CD8+ T, NK	II	
Systemic EBV+ T-cell lymphoma of childhood	100	T	II	East Asians
Hydroa vacciniforme-like lymphoproliferative disorder	100	$\gamma\delta$T, NK	II	Asians, Native Americans

[a]Neoplastic T-cells are EBV-negative

et al. 2008; Pileri et al. 2008). Except for peripheral T-cell lymphoma, EBV is associated strongly with each disease (Table 21.3). In the 2016 revision of the WHO classification, EBV+ T-cell lymphoproliferative disease of childhood and hydroa vacciniforme-like lymphoma have been renamed EBV+ T-cell lymphoma of childhood and hydroa vacciniforme-like lymphoproliferative disorder, respectively (Swerdlow et al. 2016; Quintanilla-Martinez et al. 2017). Chronic active EBV disease (CAEBV) of the T-/NK-cell type and severe mosquito bite allergy are also described in the text of the classification under the umbrella term of EBV-associated T-/NK-cell lymphoproliferative disorders (EBV-T/NK LPD) in the pediatric age group (Quintanilla-Martinez et al. 2017). Because the etiology of each disease is not yet fully understood, the classification and terminology are incomplete and need further improvement.

ENKL, which is also called nasal NK-/T-cell lymphoma, is a predominantly extranodal lymphoma, characterized by vascular damage, necrosis, and a cytotoxic phenotype (Elenitoba-Johnson et al. 1998; Chan et al. 2008b). The upper aerodigestive tract, including the nasal cavity and paranasal sinuses, is most commonly involved. This disease often progresses, with extensive midfacial destructive lesions (previously called lethal midline granuloma), and sometimes disseminates to other sites, including the skin and gastrointestinal tract. As it has a poor response to chemotherapy, the prognosis of ENKL is poor (Chan et al. 2008b). EBV is invariantly associated with this lymphoma, so an etiological link with EBV infection has generally been assumed. ENKL is more prevalent in East Asians and Native Americans in Mexico, Central America, and South America. The most typical immunophenotype of ENKL is CD2+, CD3−, and CD56+, indicating NK cells.

CAEBV is a potentially life-threatening illness of children and young adults, characterized by the clonal proliferation of EBV-infected lymphocytes (Okano et al. 2005; Cohen et al. 2009; Kimura et al. 2012). The T-/NK-cell type of this disease has a strong racial predisposition, with most cases occurring in East Asians and some cases in Native American populations in the Western Hemisphere (Cohen et al. 2011; Quintanilla-Martinez et al. 2017); this distribution is analogous to that of ENKL. Typically, patients with CAEBV develop fever, hepatosplenomegaly, and lymphadenopathy; other common symptoms are thrombocytopenia, anemia, skin rash, diarrhea, and uveitis (Kimura et al. 2003). Patients often have abnormal liver function tests and an abnormal EBV serology, with high antiviral capsid antigen IgG antibodies (Straus et al. 1985). This disease is refractory to antiviral agents and conventional chemotherapies and thus has a poor prognosis. Stem-cell transplantation alone is a curative treatment for the disease, although the incidence of transplantation-related complications is high (Gotoh et al. 2008; Kawa et al. 2011).

21.4 Etiological Factors in the Development of T-/NK-Cell Tumors

Although EBV is ubiquitous, it remains unclear why the virus causes T-/NK-cell tumors in only some individuals (Kimura 2006). Some of them have risk factors, many of which are geographical (Table 21.3). This contrasts with B-cell diseases, where immunodeficiency is the main risk factor (Table 21.1). There are several hypotheses to account for the regional or racial deviation.

First, the genetic background may be related to the development of T-/NK-cell tumors. A positive association with human leukocyte antigen (HLA) A26 and a negative association with B52 were observed in EBV-T/NK LPD (Ito et al. 2013b). Interestingly, both the A26 and B52 alleles are frequently seen in East Asia and Mexico, where the prevalence of EBV-T/NK LPD is high. There are at least two possible explanations for these associations. One is that HLA-A26 does not effectively present epitopes from EBV latent antigens. Another is that genetic traits related to lymphomagenesis, which are codominantly expressed with HLA-A26, play important roles. Associations with HLA loci have been reported in other EBV-associated malignancies that show geographically distinct distributions. HLA-A02:07, which is common among Chinese people but not among Caucasians, is associated with nasopharyngeal carcinoma (Hildesheim et al. 2002). However, HLA-A1 is associated with an increased risk of developing EBV+ Hodgkin lymphoma (Niens et al. 2007).

Second, specific EBV strains or variants that can efficiently infect T/NK cells or can evade innate or acquired immunity may have a higher tendency to develop T-/NK-cell tumors. For example, nasopharyngeal carcinoma has a geographic bias to East Asia. Associations between nasopharyngeal carcinoma and specific strains or variants of EBV have been extensively studied, although definitive conclusions

have not been reached (Neves et al. 2017). There are anecdotal papers on defective EBV or specific variants among T-/NK-cell tumors (Alfieri and Joncas 1987; Itakura et al. 1996). However, so far, no direct evidence has demonstrated a relationship with specific strain variants or mutants (Shibata et al. 2006; Kimura 2006). Recently, Coleman et al. showed that type 2 EBV can more efficiently infect T-cells than type 1 EBV (Coleman et al. 2015), although type 2 is not common in East Asia, where T-/NK-cell tumors are more common. Indeed, all of the established EBV⁺ T-/NK-cell lines involve type 1 EBV (unpublished data).

Finally, environmental factors may be associated with the progression or development of T-/NK-cell tumors. In Burkitt lymphoma, which is endemic in central Africa, co-infections with malaria or plant exposure (*Euphorbia tirucalli*) may enhance the tumorigenesis of EBV (Osato et al. 1987; Longnecker et al. 2013). The consumption of salted fish is believed to be a risk factor for nasopharyngeal carcinoma (Louie et al. 1977). On the other hand, case-control studies have shown that exposure to pesticides and chemical solvents could cause ENKL (Xu et al. 2007; Aozasa et al. 2008). Agricultural pesticide use is associated with chromosomal translocation in non-Hodgkin lymphoma (Xu et al. 2007). Similar environmental and lifestyle factors may be associated with the development of ENKL.

21.5 Infection of T or NK Cells

In primary infection, EBV in saliva infects naïve B cells, directly or indirectly via epithelial cells, and EBV-infected B cells become transformed and proliferate (Cohen 2000; Thorley-Lawson and Gross 2004). EBV attaches to B cells through binding gp350/220 to CD21, which is the receptor for the C3d component of complement, and gH/gL/gp42 to HLA class II molecules (Hutt-Fletcher 2007; Longnecker et al. 2013). Both CD21 and HLA class II are expressed on the surface of B cells, so B cells are natural hosts of EBV. During primary infection, epithelial cells of Waldeyer's ring also become infected with EBV (Borza and Hutt-Fletcher 2002). EBV attaches to epithelial cells through the binding of BMRF2 to integrins (α1, α3, α5, and αv integrins) and gH/gL to αvβ6 and αvβ8 integrins (Tugizov et al. 2003; Longnecker et al. 2013).

Although it is limited, there is some evidence that EBV infects T/NK cells in the primary infection. EBER-positive T/NK cells are seen in both tonsils and peripheral blood from patients with acute infectious mononucleosis (Anagnostopoulos et al. 1995; Hudnall et al. 2005; Kasahara et al. 2001). However, the mechanism by which EBV attaches and enters T/NK cells remains unknown. Basically, T/NK cells express neither CD21 nor HLA class II. T/NK cells express some integrins, and their expression is increased when stimulated. Thus, integrins may function as the receptors in T/NK cells as well as in epithelial cells. It is also possible that EBV may attach to T-cells via CD21, which is expressed in premature T-cells and common lymphoid progenitors (Fischer et al. 1991). It has been shown that EBV can infect premature T-cells and common lymphoid progenitors (Panzer-Grumayer et al.

1993; Ichigi et al. 1993; Paterson et al. 1995; Fischer et al. 1999). Interestingly, there have been several reports that show dual infections in both T-cell and NK-cell lineages in patients with CAEBV (Endo et al. 2004; Ohga et al. 2011; Sugimoto et al. 2014), supporting the hypothesis that EBV may infect common progenitor cells. Regarding cell phenotypes, EBV-infected T-cells are variable: CD4+ T, CD8+ T, CD4+ CD8+ T, CD4− CD8− T, and γδ T-cells have been reported (Kimura et al. 2012).

Another possibility is that EBV may infect from EBV-infected B cells or epithelial cells to T/NK cells by cell-to-cell infection. It has been reported that NK cells activated by EBV-infected B cells acquire CD21 molecules by synaptic transfer, and these ectopic receptors allow EBV binding to NK cells (Tabiasco et al. 2003). Such cell-to-cell infection through an immunological synapse has been observed in HTLV-1 infection between T-cells (Van Prooyen et al. 2010). EBV-infected T/NK cells usually express cytotoxic molecules, such as perforin, granzyme, and T-cell intracytoplasmic antigen (TIA)-1 (Ohshima et al. 1997b, 1999; Quintanilla-Martinez et al. 2000), indicating that they have a killer cell phenotype. Indeed, NK cells, CD8+ T-cells, and γδ T-cells, which are typical EBV-infected cell types seen in EBV-associated T-/NK-cell tumors, are basically killer cells. These results suggest that T/NK cells that attempt to kill EBV-infected B or epithelial cells may become infected with EBV through close contact through an immunological synapse (Kimura et al. 2013).

21.6   EBV Gene Expression in T-/NK-Cell Tumors

Based on the pattern in normal B cells, EBV latency programs are classified as 0, I, II, or III (Longnecker et al. 2013). Similar to Hodgkin lymphoma and nasopharyngeal carcinoma, EBV-infected T/NK cells belong to latency type II, where only three viral proteins, EBNA1, LMP1, and LMP2A, are expressed (Chen et al. 1993; Kimura et al. 2005; Ito et al. 2013a). Noncoding RNAs, such as EBERs and BARTs, are also expressed in this latency type. In latency type II, immunodominant antigens, EBNA2 and EBNA3s, are not expressed. Thus, EBV-infected T/NK cells do not express major antigens against cytotoxic T lymphocytes and thus have an advantage in evading host immunity.

In CAEBV, which also belongs to type II latency, the frequency of LMP1 expression is variable among patients (Iwata et al. 2010; Kanemitsu et al. 2012). It seems that EBV latent gene expression in T/NK cells is heterogeneous, including variant transcripts (Yoshioka et al. 2001; Fox et al. 2010). LMP1 expression has a favorable impact on clinical outcomes in extranodal NK/T-cell lymphoma (Kanemitsu et al. 2012; Yamaguchi et al. 2014). This would seem to contradict the notion that LMP-1 is a potent oncoprotein that promotes proliferation and inhibit apoptosis. More recently, mutual exclusivity among tumors with somatic NF-κB pathway aberrations and LMP1 overexpression has been reported in nasopharyngeal carcinoma, suggesting that NF-κB activation is selected for by both somatic and viral events (Li

et al. 2017). Loss of EBV was reported in a patient with cutaneous ENKL (Teo and Tan 2011). In vitro disappearance of EBV has been reported in EBV-infected B-cell lines (Shimizu et al. 1994). These results support the idea that subclones of originally EBV-positive lymphoma cells may have evolved alternative, virus-independent mechanisms to sustain oncogenic signaling pathways (Gru et al. 2015).

21.7 Tumorigenesis

Tumorigenesis in EBV-associated lymphoma/leukemia is a multistage process. There are two potential models of the multistage process. One is that EBV infects T/NK cells, followed by host-gene mutations and/or epigenetic modifications (Fig. 21.1a). In this model, the EBV-infected cells proliferate and evade apoptosis with the help of viral oncogenes. In the long run, mutations/modifications accumulate, leading to the development of overt lymphoma/leukemia. EBV-T/NK LPD may be an intermediate phase in this process (Fig. 21.1a). CAEBV, which is a representative EBV-T/NK LPD, usually develops in children or adolescents. Onset at an early age matches the infection's first mode. Another model is that
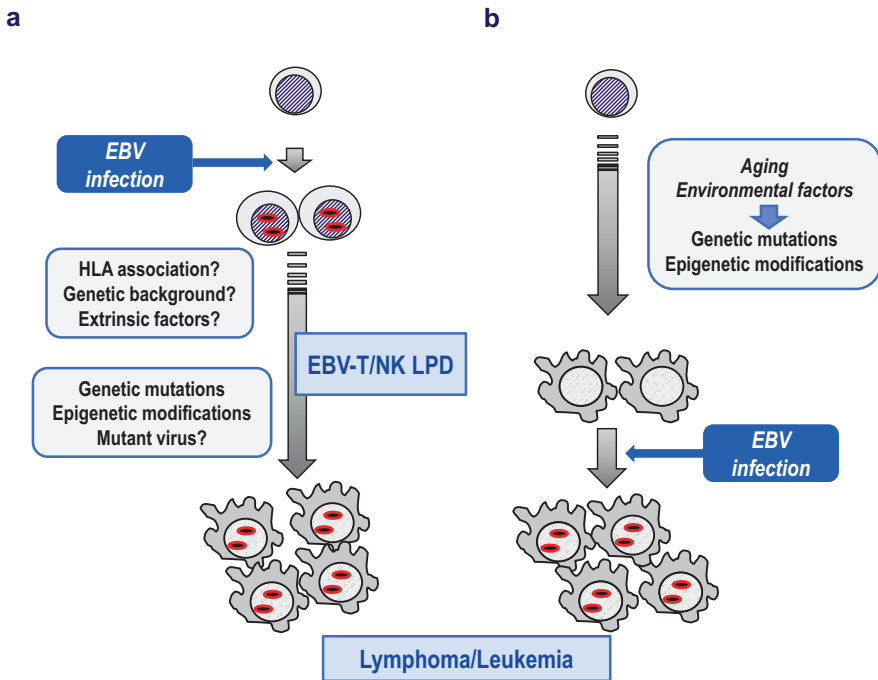

Fig. 21.1 Multistage models of tumorigenesis in EBV-associated T-/NK-cell lymphoma or leukemia (**a**) infection-genetic alteration sequence (**b**) genetic alteration-infection sequence

EBV infects cells where mutations/modifications have already accumulated (Fig. 21.1b). This second model corresponds to ENKL, which develops in older people (Chan et al. 2008b). Aging and long-term exposure to environmental factors could induce genetic mutations in T/NK cells of the nasal cavity. A bimodal age distribution has been noted in patients with ENKL: adolescents and the elderly (Takahashi et al. 2011). Patients with different peaks may have different processes of lymphomagenesis.

In the process of lymphomagenesis, mutations in host cell genes are necessary. What causes such genetic changes? Activation-induced cytidine deaminase (AID), which belongs to the APOBEC3 protein family, is one candidate. AID is expressed in germinal center B cells and induces somatic hypermutations and class switch recombination (Honjo et al. 2004). This enzyme is necessary for the chromosomal breaks in *c-myc* and its translocations (Robbiani et al. 2008). EBV-oncoprotein LMP-1 increases genomic instability through upregulation of AID in B-cell lymphomas (He et al. 2003; Kim et al. 2013). More recently, it has been shown that viral tegument protein BNRF1 can induce centrosome amplification and chromosomal instability, thereby conferring a risk of the development of tumors (Shumilov et al. 2017). By contrast, APOBEC3 cytidine deaminases can target and edit the EBV genome (Suspene et al. 2011). Thus, EBV infection per se may play an important role in *c-myc* translocation and lymphomagenesis of Burkitt lymphoma and other B-cell lymphomas. In AID transgenic mice, B-cell lymphoma develops (Okazaki et al. 2003). Interestingly, not only B-cell but also T-cell lymphoma develops in these mice. Furthermore, AID is expressed in HTLV-1^{+} cell lines and HTLV-1^{+} T-cells in peripheral blood (Ishikawa et al. 2011; Nakamura et al. 2011b). AID expression is high not only in EBV-positive T-/NK-cell lines but also in EBV-infected NK cells from patients with EBV-T/NK LPD (Nakamura et al. 2011a). In patients with ENKL, cytogenetic abnormalities are seen on the sixth chromosome (Ohshima et al. 1997a), although currently it is unclear whether this is a primary or progression-associated event (Chan et al. 2008b).

The next question is which are the key genes for development into T-/NK-cell lymphoma. Recent genetic studies have revealed that some of the driver gene mutations are related to the development of ENKL. Using a CGH array, PRDM1, HACE1, and FOXO3 were identified as driver gene candidates (Iqbal et al. 2009; Huang et al. 2010; Karube et al. 2011). More recently, JAK3 mutations were identified by exome sequencing (Koo et al. 2012), although the frequency is apparently not as high as first reported (Kimura et al. 2014; Guo et al. 2014). By whole exome sequencing, Jiang et al. reported that these driver gene mutations, such as DDX3X, TP53, and STAT3, were found at higher frequencies in Chinese patients with ENKL (Jiang et al. 2015) (Fig. 21.2). However, BCOR1 was the leading mutated gene in Japanese patients, followed by TP53 and DDX3X (Dobashi et al. 2016). DDX3X; DEAD-box helicase 3, X-linked, is an ATP-dependent RNA helicase and plays roles in transcriptional regulation, pre-mRNA splicing, and mRNA export. Its mutations are seen frequently not only in ENKL but also in Burkitt lymphoma (Schmitz et al. 2012). Although DDX3X mutations are also seen in EBV-unrelated
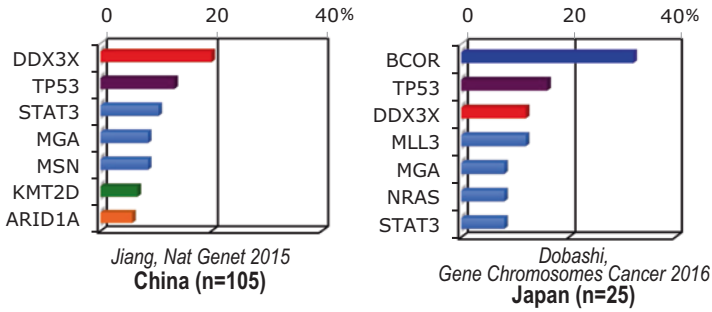
Fig. 21.2 Frequency of driver gene mutations in extranodal NK/T-cell lymphoma-nasal type (ENKL)

diseases, such as medulloblastoma (Pugh et al. 2012), its mutation may be associated with the development of EBV-associated tumors.

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