We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

5,300
Open access books available

131,000
International authors and editors

160M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS

BOOK CITATION INDEX

INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Role of the Epstein-Barr Virus ZEBRA Protein and HPV in the Carcinogenesis of Nasopharyngeal Carcinoma

Moumad Khalid[1,4], Laantri Nadia[1], Attaleb Mohammed[2],
Dardari R'kia[1], Benider Abdellatif[3], Benchakroun Nadia[3],
Ennaji Mustapha[4] and Khyatti Meriem[1]
[1]Laboratory of Oncovirology, Institut Pasteur du Maroc, Casablanca,
[2]Biology and Medical Research Unit, Centre National de l'Energie,
des Sciences et Techniques Nucléaires (CNESTEN), Rabat,
[3]Service de Radiothérapie, Centre d'Oncologie IBN Rochd, Casablanca,
[4]Laboratoire de Biologie Moléculaire, Institut Pasteur du Maroc, Casablanca
Morocco

1. Introduction

Approximately 15% of all cancers worldwide appear to be associated with viral infections, and several human DNA viruses are now accepted as causative factors of specific malignancies. Human papillomaviruses (HPVs) cause cervical and anogenital cancers (zur Hausen 1999) and is now associated with oral cancers (Gillison & Shah 2001), but, the natural history of oncogenic HPV infections in the oral cavity is poorly understood. Epstein-Barr virus (EBV) causes infectious mononucleosis and is closely associated with Burkitt's lymphoma, nasopharyngeal carcinoma (NPC), and Hodgkin's disease (Raab-Traub 1996).

NPC is a malignant tumour that originates within the post nasal space (Pathmanathan et al. 1995). The etiologic factors of endemic NPC include environmental risk factors, genetic susceptibility and viral infection (Yu 1991). Evidence of EBV DNA in almost all NPC cells that were studied supports the association of NPC with EBV, while, HPV has been detected in a variety of head and neck tumours including NPC. Current data suggest that approximately 15–20% of head and neck squamous cell carcinomas (HNSCC) are linked to HPV infection. To date, different degrees of associations between HPV and NPC have been described, yet no conclusive data have been obtained. Given the particular characteristics of NPC in the Moroccan population in terms of incidence, age distribution and the predominance of specific EBV strains, and HPV genotype we describe in this chapter the role of the Epstein-Barr virus ZEBRA protein and HPV in the carcinogenesis of NPC.

1.1 Nasopharyngeal carcinoma

NPC is a malignancy of the head and neck region that arises in the epithelium surface of the posterior nasopharynx, and shows a peculiar geographic and ethnic distribution. The

highest incidence rates of NPC are found among the southern Chinese population and in isolated northern populations such as Eskimos and Greenlanders (30 to 80 cases per 100,000 per year) (Parkin & Muir 1992). Intermediate incidence (8 to 12 cases per 100,000 per year) was reported in the Mediterranean basin, especially among the Arabic populations of North Africa (7-10% of all cancers among men), where NPC is also the commonest tumour of the ear, nose and throat region (Benider et al. 1995). The aetiology of NPC seems to be multifactorial with evidence that genetic susceptibility, environmental factors and viral infection with EBV reactivation and HPV infection are involved together or separately, simultaneously or consecutively (Hildesheim & Levine 1993).

The increased risk of NPC in North African population was associated with the consumption of rancid butter and rancid sheep fat. In fact, higher level of N-nitrosamines in rancid fat has not been demonstrated, which suggests some other disease causing chemicals in this population. A possible compound is butyric acid, which is also named n-Butanoic Acid. The glyceride form of butyric acid makes up 3 to 4% of butter, and is released into free butyric acid by hydrolysis when it becomes rancid (Feng et al. 2007). Butyric acid is known to be able to activate EBV in the B-lymphoid cells into lyric cycle (Takimoto et al. 1984), and therefore, could be related to NPC. In addition, Marijuana smoking was associated significantly to high NPC risk independently of cigarette smoking which suggests dissimilar carcinogenic mechanisms between cannabis and tobacco.

Genetic traits play a significant role in the development of NPC. Specific human leukocyte antigen (HLA) haplotypes have been reported to be associated with high risk for NPC, namely HLA-B13 in Tunisians, HLA-A3, B5 and B15 in Algerians and HLA-B18 allele in Moroccans population. In contrast, HLA-Aw33, -B14 and A9 were associated to low risk of NPC in Tunisians, Algerians and Moroccans, respectively.

Retrospectives and prospectives epidemiologic studies have indicated that assocaition between EBV, an ubiquitous human herpesvirus, and the development of different malignancies, such as Burkitt's lymphoma, 40%–50% of Hodgkin's disease, B-cell lymphoma in immunocompromised individuals, and NPC (Rickinson 2002). Undifferentiated NPC is one of the most striking examples of human malignancies that have been found strongly associated with the EBV, and interest in HPV as a cofactor in NPC occurrences has emerged over the last few years (Punwaney et al. 1999).

2. EBV life cycle in brief

During primary infection, EBV initially undergoes a brief replication in the epithelial cells of the oropharynx and salivary glands (Young & Rickinson 2004). The virus subsequently infects trafficking B-cells where the virus establishes a lifelong persistence and proceeds periodic spontaneous reactivation, resulting in lytic replication, infectious virus production and transmission (Cohen 2000). Upon reactivation, EBV can productively infect oropharyngeal epithelium, leading to infectious virus production and transmission (Jenkins, Binne & Farrell 2000). In latent infection, EBV genomic DNA exists as an episome, replicating only once during S phase and partitioning accurately into daughter cells during the mitotic phase. In lytic state, the EBV genomic DNA is linear. The initiation of lytic replication process greatly depends on the expression of two EBV immediate-early (IE)

genes, BZLF1 and BRLF1, whose protein products (Zta and Rta) function as transcriptional transactivators and induce the lytic cascade of viral gene expression (Flemington & Speck 1990). Interestingly, a variety of important proteins encoded by EBV show the homology of sequences and functions to diverse human cellular proteins. Furthermore, the EBV proteins can modulate the expressions of a large number of cellular proteins.

2.1 ZEBRA on the scene

In cancer cells, EBV is also present in a latent state. During latency, EBV is effectively hidden from the immune system but if viral replication is initiated and lytic replication ensues, the cells express EBV genes that are more readily recognized by the immune system. The lytic DNA replication of EBV requires many viral proteins, including ZEBRA, polymerase, polymerase processivity factor, single-stranded DNA binding protein, primase, helicase and primase-associated factor. Among them ZEBRA (also called BZLF1, EB1 and Zta) is a lytic switch transactivator for expression of many early lytic genes and plays a critical role in both viral gene transcription and viral replication (Fixman, Hayward & Hayward 1995). Of all the viral transactivators, ZEBRA is unique in initiation of the ordered cascade of EBV gene expression, resulting in the expression of an estimated over 100 viral replication associated genes including those encoding early antigens, viral capsid antigens and membrane antigens (Baer et al. 1984). Many target genes of ZEBRA, such as BZLF1, BRLF1 and BMLF1 encoding the transactivators, BHRF1 and BHLF1 encoding the viral homologues of Bcl-2 (Marshall et al. 1999), and BMRF1 encoding EBV DNA polymerase accessory protein (Zhang et al. 1997), have been identified in the EBV genome. Through binding to cis-acting AP-1 or ZEBRA responsive elements (ZREs) in lytic cycle promoters ZEBRA activates the transcription of the target genes (Lieberman et al. 1990). Recently, some cellular genes modulated by ZEBRA have also been revealed. The products of these cellular genes are fundamentally linked to the viral life cycle, virus-host interactions, hosT-cell environment, cell cycle progression and immunomodulation.

2.2 ZEBRA structure

ZEBRA or Zta is a member of the family of bZIP transcription factors (Sinclair 2003); it contains adjacent DNA contact (approximately amino acids 175 to 195) and multimerization domains (approximately amino acids 196 to 245) (figure 1) (Sinclair 2006) and can interact directly with specific DNA sequence elements, i.e., ZREs as a multimer . By analogy with other members of the bZIP family, the multimerization interface of ZEBRA has been predicted to fold through a coiled-coil structure (Sinclair & Farrell 1992). Biophysical evidence that this prediction holds true was recently provided (Hicks et al. 2001).

The DNA binding region and dimerization region partly conform to the well-characterized bZIP (basic/leucine zipper) domain that is found in a family of cellular transcription factors such as fos/jun, C/EBPa and GCN4. Interestingly, ZEBRA recognizes a wider range of DNA binding sites than other bZIP members. bZIP proteins are homo- or heterodimers that contain highly basic DNA binding regions adjacent to regions of a-helix that fold together as coiled coils (Sinclair 2006); the interaction with DNA is dependent on dimer formation (Busch & Sassone-Corsi 1990).
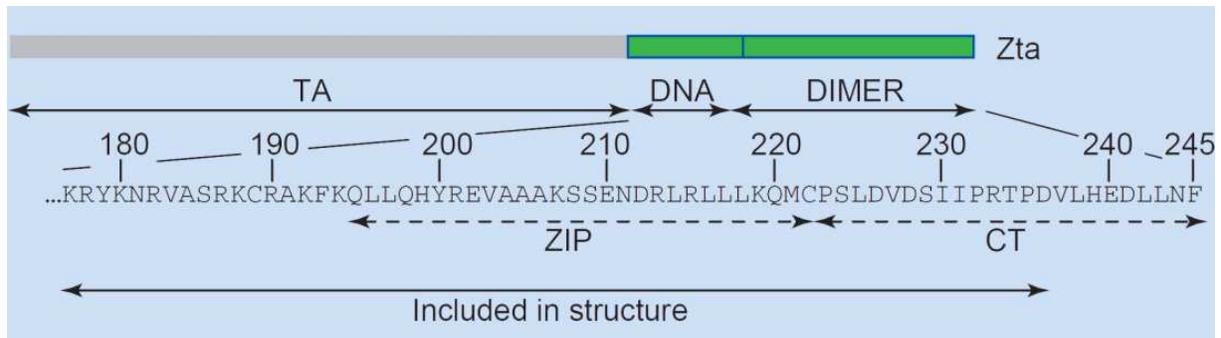
Fig. 1. Schematic representation of the functional regions of ZEBRA and its structure. The transactivation (TA) domain is shown in grey and the DNA contact region and the dimerization region are shown in green and blue. The amino acid sequence of the DNA binding and dimerization domain is expanded below. The location of the region with homology to leucine zippers (ZIP) and the additional region required for dimerization function (CT) are indicated below the sequence

2.3 Role of ZEBRA during viral replication

During the lytic phase of the EBV life cycle, the activation of viral DNA synthesis is related to ZEBRA efficient recognition of a large (~1 kb) complex intergenic region that serves as the origin of replication. This region, known as oriLyt, consists of essential and auxiliary segments (Hammerschmidt & Sugden 1988).The two essential components of oriLyt, the upstream and downstream elements, together constitute the minimal origin of DNA replication (Rennekamp, Wang & Lieberman 2010). The auxiliary component serves as an enhancer element that augments DNA replication (Cox, Leahy & Hardwick 1990). ZEBRA recognizes the origin of lytic DNA replication (oriLyt) by interacting with seven ZEBRA-binding sites (Schepers, Pich & Hammerschmidt 1993). Mutation of all seven binding motifs in the background of a recombinant virus drastically reduces production of infectious virus particles (Feederle & Delecluse 2004).These ZEBRA binding elements are located in two noncontiguous regions of oriLyt. Four elements are present in the upstream core region of oriLyt and overlap with the promoter of the BHLF1 open reading frame and three additional ZEBRA binding elements located mainly in the enhancer region are dispensable for viral replication (Schepers, Pich & Hammerschmidt 1996).

The current model for the role of ZEBRA in lytic DNA replication suggests that the protein serves as a physical link between oriLyt and core components of the replication machinery. The six core replication factors encoded by EBV are the DNA polymerase (BALF5); the polymerase processivity factor (BMRF1); the helicase (BBLF4); the primase (BSLF1); the primase associated factor (BBLF2/3), and the single-stranded DNA binding protein (BALF2) (El-Guindy, Heston & Miller 2010). The function of tethering replication proteins to oriLyt is not limited to ZEBRA; the transactivation domains of Sp1 and ZBP89 interact with BMRF1 and BALF5 and target them to the downstream region of oriLyt (Baumann et al. 1999). Similarly, ZBRK1, a cellular DNA binding zinc finger protein, serves as a contact point for BBLF2/3 on oriLyt (Liao et al. 2005).

2.4 Cellular genes induction

The EBV lytic transactivator ZEBRA not only initiates expression cascade of viral lytic genes but also induces some cellular genes involved in immune regulation (Cayrol & Flemington 1995; Chen, C., Li & Guo 2009). ZEBRA can turn on gene expression through binding to and activation of the target promoters. Notably, a previous study shows that ZEBRA induces transcription of human interleukin 10 (IL-10) in B cells (Mahot et al. 2003).

Table 2 lists a number of genes whose expression is perturbed by ZEBRA. In each case, the regulation occurs in the absence of other viral genes. Regulation at the RNA level implies that ZEBRA may act as transcription factors on the cellular promoters by direct binding or via their associations with other transcription factors. However, the mechanisms of regulation of the cellular genes have not been assessed further as yet. Several of these genes have also been shown to be regulated at the protein level, suggesting relevance. Of special note is the identification of a series of cell cycle regulatory genes such as p21CIP1, p53, CDC25A and E2F1.

RNA changes	Proteins changes
TGFβ inh3 (Cayrol & Flemington 1995)	C/EBPα (Wu et al. 2003)
TGFβ (Cayrol & Flemington 1995)	p21 (Cayrol & Flemington 1996)
α1 collagen (Cayrol & Flemington 1995)	p53 (Wu et al. 2003)
TKT tyrosine kinase (Lu, J. et al. 2000)	p27 (Cayrol & Flemington 1996)
MMP1 (Lu, J. et al. 2000)	E2F1 (MauserHolley-Guthrie, et al. 2002)
IFN-γ receptor (Morrison et al. 2001)	Stem–loop binding protein (MauserHolley-Guthrie, et al. 2002)
E2F1 (MauserHolley-Guthrie, et al. 2002)	CDC25 (MauserHolley-Guthrie, et al. 2002)
Stem–loop binding protein (MauserHolley-Guthrie, et al. 2002)	Cyclin E (MauserHolley-Guthrie, et al. 2002)
CDC25A (MauserHolley-Guthrie, et al. 2002)	
Cyclin E (MauserHolley-Guthrie, et al. 2002)	
C/EBPα (Wu et al. 2003)	
p21 (Wu et al. 2003)	

Table 1. Cell genes regulated by ZEBRA

In NPC, ZEBRA was found to be a potent inducer of IL-8, increasing IL-8 at both protein and RNA levels and activating the IL-8 promoter suggesting that the EBV lytic infection may contribute to the inflammation-like microenvironment of NPC by the upregulation of chemokines (Hsu et al. 2008).

During EBV reactivation in NPC cells, the lytic protein ZEBRA not only induces GM-CSF expression but also upregulates COX-2 that increases production of PGE2 (Dolcetti et al. 2010; Kared et al. 2008). The secreted GM-CSF and PGE2 may cooperatively promote IL-10 production from monocytes (Lee et al. 2011). Thus, through the Zta-induced immunomodulators, EBV lytic infection in NPC cells may drive nearby monocytes into IL-10 producing cells, facilitating local immunosuppression.

By initiating or enhancing leukocyte infiltration, the lytic-cycle-induced chemokines may contribute to an inflammation-like microenvironment, where the interaction between immune infiltrates and tumour cells is crucial for NPC development (Sbih-Lammali et al. 1999). The contribution possibly occurs not only in the developed NPC tumours but also at the precancer stage where an inflammation like microenvironment predisposes precancerous cells to tumour formation (Lu, H., Ouyang & Huang 2006), which may account for how EBV reactivation serves as a risk factor before the onset of NPC (Chien et al. 2001).

2.5 Prognostic value of ZEBRA

Antibodies against ZEBRA are produced during primary EBV infection, and thus, the detection of ZEBRA-specific antibodies may allow an early diagnosis of EBV infections. In 1991, Joab and al were able to detect IgG anti-ZEBRA antibodies (IgG/ZEBRA) in 87% of NPC patients. These antibodies were absent in control sera (Joab et al. 1991). In a more recent study, IgG-ZEBRA antibodies have been shown to represent a sensitive marker for the diagnosis of NPC in children than IgA-VCA and IgA-EA antibodies, which have been recognized as specific markers for this tumour. This study also indicates that Zp125, identified as the most immunogenic epitope of the activation domain of ZEBRA protein, showed a high degree of immunoreactivity with sera from children, young adult and older adult patients with NPC (Dardari et al. 2008). The analysis of antibody patterns in patients with NPC indicates that IgG-ZEBRA had better prognostic value than IgA-EA and IgA-VCA. Stable low IgG-ZEBRA antibody titer, or a striking decline in IgG-ZEBRA antibodies, was observed in children during treatment (Gutierrez et al. 2001; Schaade, Kleines & Hausler 2001). Of note, children showing low IgG-ZEBRA titers were also negative for IgAVCA and IgA-EA; the latter have been identified as being produced following frequent reactivation of latent EBV, repeated EBV infection, or both (Gutierrez et al. 2001; Yip et al. 1994).

Epigenetic dysregulation plays significant role in oncogenesis. Methylation changes in both global and targeted genes have been attributed to EBV+ lymphomas and carcinomas (Niller, Wolf & Minarovits 2009). These studies suggest the contribution of EBV genome in the epigenetic dysregulation of genes involved in tumorigenesis. Systemic analyses of epigenetic alterations under the expression of specific viral gene that may help to specify the contribution of EBV genome. Although results from the Ying-Fan Chen (Chen, Y. F. et al. 2011) suggest that the expression of major viral lytic protein Zta has no effect on changing DNA methylation in the host genome, the comprehensive methods established by him provide a useful platform to investigate genomic methylation changes upon various conditions. These results from these studies will lead to a better understanding of the EBV pathogenesis and may facilitate the development of new therapies.

3. Human Papilloma Virus

The papilloma viruses and its viral nature were first seen in human warts in 1907, and the first papilloma virus was isolated from a rabbit that was identified by Richard Shoppe in the year 1983. Even it was an early start for the detection of human papilloma viruses; this topic remained closed till 1970's. Studies related with papilloma viruses were allowed to move

forth only when cervical cancer's proximity with HPV was proved and with its increasing significance in the field of molecular virology (Levinson, 2008).

HPVs are small non enveloped virus containing double stranded DNA as their genetic material and are about 55 nm in size. HPV are strictly epitheliotropic viruses infecting skin or mucosal surfaces, and displaying a very high selectivity for the specific epithelium infected [7,8], and are one of the most common viruses which are transmitted sexually and are found in both men and women. Its ratio is much higher in western countries as compared to other regions of the world. The genome is a circular molecule of double-stranded DNA 8000 base pairs or so. Ten open reading frames (POL) are grouped in a region L (early) coding non-structural protein and an L (late) region encoding the capsid proteins. The non-coding region (NCR of 850 bp for HPV 16) is located between the POL L1 and E6/E7. It contains the promoters of early genes, regulatory sequences (original site) and transcription (cis sequence).

According to their ability to transform epithelial cells, HPV genotypes are divided into low-risk and high-risk types. Low-risk types are associated with benign lesions such as warts, while infections with high-risk types progress to malignant lesions (Munoz et al. 2003). More than 100 different HPV genotypes have been described, but only 30 genotypes identified in the female genital tract are associated with epithelial neoplasms ranging from benign common warts to malignant carcinoma of the uterine cervix (McGlennen 2000). It is widely reported that in addition to HPV 16 and 18, which are frequently found in association with cervical cancer (CC), HPVs 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82, while other three as probable high-risk types (types 26, 53, and 66) are also considered as carcinogenic (Munoz et al. 2003).

3.1 HPV and head and neck cancer

Approximately 15% of malignant diseases are caused by infectious agents. HPV can be frequently found in oral carcinomas, especially tonsillar cancer. A group of HPV-infected tumours shows clear signs for a virally induced transformation process: high-risk HPVs can be detected in all tumour cells, the viral oncogenes E6 and E7 are constantly expressed and lead to upregulation of cellular p16(INK4a), a cyclin-dependent kinase inhibitor. The patients frequently lack typical risk factors associated with head and neck cancers such as drinking and smoking. An association of herpes viruses with head and neck cancer has been for long time suspected and there is good evidence there, but only for a relationship of EBV nasopharyngeal carcinoma. HPV aetiology is now accepted for up to 20% of head and neck cancer. However, the relationship between carcinogenesis and HPV infection is not as clear as with cervical cancer. HPV is not detectable in many head and neck cancers, and it is frequently detected in normal oral mucosa, which is why HPV infections were in head and neck cancer is often regarded only as an accompanying infection. Initial investigations into a causal role for HPV in the aetiology of head and neck lesions relied upon electron microscopy (EM) or immunohistochemical staining. Human papillomavirus virions could be identified by EM from specimens of papillomas (Frithiof & Wersall 1967), fibromas (Gross et al. 1982), verruca, condyloma acuminatav (Shaffer, Reimann & Gysland 1980; Syrjanen, K. J. & Surjanen 1981), focal epithelial hyperplasia, and oral nodular leukoplakias (Jenson et al. 1982). Immunohistochemical staining has revealed the presence of HPV capsid antigens in HPV-infected cells (Loning et al. 1984). Capsid antigen, however, has rarely been

detected in high-grade neoplasias or invasive cancer, probably because such tissue contains limited numbers of highly differentiated squamous cell epithelial cells. Consequently, the majority of head and neck lesions that contained HPV structural antigens were either benign or precancerous. Inconsistencies in antigen detection also resulted from sampling error, variable expression or lack of HPV capsid antigens, destruction of antigens during cellular processing or long term storage, or lack of sensitivity to a particular assay (Koutsky, Galloway & Holmes 1988; Syrjanen, S. M. 1990). From published studies, the overall antigen positivity in noncancerous head and neck lesions was about 34.4% (Adler-Storthz et al. 1986; Syrjanen, K., Syrjanen & Pyrhonen 1982). Whereas light microscopy, EM, and immunohistochemistry have resulted in inconsistent or irreproducible findings, the use of DNA hybridization has revolutionized the detection of HPV DNA types in benign and malignant lesions.

New data from case–control studies suggest that HPV is an independent risk factor for oral and oropharyngeal squamous-cell carcinomas (Rosenquist et al. 2005; Schwartz et al. 1998). Moreover, a systematic review showed an overall prevalence of HPV infection of 25.9% in specimens obtained from 5046 patients with head and neck squamous-cell carcinoma that had been analyzed in 60 separate studies (Kreimer et al. 2005). Using PCR detection from 26 countries which included 5046 cases of squamous cell cancers; 2642 oral cancers, 969 oropharyngeal cancers and 1435 laryngeal cancers. HPV prevalence was 35.6% in oropharyngeal cancers, 23.5% in oral cancers and 24.0% in laryngeal cancers. Overall prevalence of HPV in HNSCC was estimated at 26%. HPV 16 was by far the commonest subtype in all types of HPV+ cancers; 86.7% of oropharyngeal, 68.2% of oral and 69.2% of laryngeal cancers. HPV 18 was next most common but found in only 1% of oropharyngeal, 8.0% of oral and 3.9% of laryngeal cancers. A more recent meta-analysis by Termine et al 2008 (Termine et al. 2008), estimated that from studies utilising only FFPE samples, the pooled prevalence of HPV detected in these HNSCC (defined as SCCs originating in the oral, pharyngeal and laryngeal cavities only) was 34.5% (Goon et al. 2009).

3.2 HPV and NPC

NPC is one of the most striking examples of human malignancies that have been found strongly associated with the EBV, and interest in HPV as a cofactor in NPC occurrences has emerged over the last few years (Lin 2009). EBV has been detected in a large proportion of patients with WHO-II/III NPC, but a significant subset of patients with WHO-I NPC are EBV negative (Hording et al. 1994; Rassekh et al. 1998; Tsai et al. 1998). High-risk HPV may contribute to the development of NPC, given HPV's acknowledged role in the pathogenesis of oropharyngeal carcinomas.

Furthermore, it has been suggested that normal human oral epithelial cells, especially nasopharyngeal cells, could be very susceptible to persistent HPV and EBV co-infections and that EBV and high-risk HPV co-infections may play an important role in the initiation of a neoplastic transformation of human oral epithelial cells (Al Moustafa et al. 2009). To date, different degrees of associations between HPV and NPC have been described, yet no conclusive data have been obtained.

Coinfection by HPV and EBV has not been well documented and the significance of the presence of both viruses in nasopharyngeal cells has not been determined. In a recent study,

coinfection with both viruses was observed in 34% of patients in Morocco. Tung et al. showed that among 88 fresh NPC specimens from Chinese population, coexistence of EBV and HPV DNA was observed in 42% of samples (Tung et al. 1999).

These results are in agreement with other studies reporting the same prevalence of HPV DNA in NPC cases. In fact, using the same consensus primers, HPV DNA was detected in 31 of 103 NPC samples (30%). Moreover, Krishna et al. have shown that HPV DNA was detected in 38.8% of 36 southern Indian NPC cases (Krishna et al. 2004). Tung et al. in Eighty-eight fresh tissue samples of NPC showed that HPV DNA was detected in 51% of the specimens (Tung et al. 1999).

With regard to HPV genotypes, HPV31 was the most frequent genotype in Moroccan NPC patients (20.8 %). The same genotype was also frequently found in tonsils and nasopharyngeal cells in western Mexico NPC cases (Lopez-Lizarraga et al. 2000). The second prevalent HPV type detected in Moroccan NPC biopsies is HPV59 (16,7%). Of interest, HPV-16 and -18, which are the most virulent genotypes associated with CC in Moroccan woman (35% to 45 %) (Khair et al. 2009), were detected in very few NPC cases (8.3 %), and similar data were reported in an Iranian study (Mirzamani et al. 2006). However, a recent study suggests that WHO-I NPC may be associated with oncogenic HPV. Oncogenic HPV was detected by in situ hybridization in half of the WHO-I NPCs but only 5% of the WHO-II/III NPCs. In addition in a HPV genotyping cohort study, oncogenic HPVs were detected equally in WHO-II/III NPCs (31%, 13/42) and nasopharyngeal controls (35%, 14/40). Tumour high-risk HPV status did not correlate with the prognosis of patients with NPC. In the high-risk HPV in situ hybridisation cohort, 14 (88%) of the 16 oncogenic HPV-positive WHO-II/III NPCs showed a unique cytoplasmic/perinuclear staining pattern, which is distinct from the typical dot/punctate nuclear staining pattern indicating HPV genome integration. In addition, oncogenic HPVs were not always retained in NPC cells during the process of metastasis (Lo et al. 2010). Therefore, considering the fact that oncogenic HPV has not been consistently detected in NPC specimens from different endemic regions, it is likely that HPV infection may not be essential in the carcinogenesis of EBV-associated WHO-II/III NPCs in areas endemic for NPC.

3.3 Insights into the molecular mechanisms of HPV carcinogenesis

These inconsistent results are likely to reflect a difference in life cycles of the different HPV subtypes in different mucosal locations, with an associated difference in mucosal immune responses. The high risk subtypes of HPV involved in cervical carcinogenesis have been defined (Munoz et al. 2003). We speculate the HPV subtypes associated with NPC are broadly similar (but not identical) (figure 2) with those seen in cervical carcinoma. Briefly, through wounds or abrasions, the papillomaviruses infect basal epithelial cells, which are the only actively dividing cells in the epithelial layer. The viral DNA is maintained in the nuclei of infected basal epithelial cells as a low-copy-number plasmid (Stubenrauch & Laimins 1999). Squamous epithelial cells normally undergo differentiation as they move from the basement membrane towards the surface epithelium, and HPV-DNA replicates to a high copy number only in terminally differentiated cells near the epithelial surface (Stubenrauch & Laimins 1999). Similarly, the late viral genes, which encode the L1 and L2 proteins that constitute the virus particle, are expressed only in the highly differentiated cells, where infectious progeny virus is produced and released. Three critical steps can be

discriminated in this model (figure 2): the conversion of a single mutated stem cell in a patch into a group of stem cells without proper growth control (field); the eventual transforming event, which turns a field into an overt carcinoma showing invasive growth and metastasis; and the development of metastasis. Both aneuploidy and the accumulation of cancer-associated genetic changes in fields are linked to the risk of malignant progression.

It has been shown that these subtypes (particularly 16) are able to transform and immortalise cells in vitro. These effects are predominantly due to the E6 and E7 oncogenes, which bind and enhance degradation of p53 and Rb tumour suppressor genes respectively. There is evidence that immortalisation of oral keratinocytes and epithelial cells occur quite readily (Park et al. 1991).

HPV integration usually leads to disruption and/or deletion of HPV E1 or E2 open reading frame (ORF), which are important for viral replication and transcription. E2 functions also as a repressor of E6 and E7 and disruption of E2 activity allows increased E6 and E7 expression, thus maintaining the immortalised phenotype (zur Hausen 2009). Integration of HPV 16 DNA also correlates with a selective growth advantage and may allow the cancerous cell to outgrow its rivals; this may be an important step in the pathway of oncogenesis (Jeon, Allen-Hoffmann & Lambert 1995). However, despite the dominance of the integrated HPV genome in terms of cervical carcinogenesis, 15-30% of cervical cancer contains HPV only in the episomal form (Watts et al. 2002). In some of these cases, investigators have found deletions in the YY1-binding sites of the LCR (long control region) of HPV 16 episomal DNA which may allow elevated activity of the E6/ E7 promoter (Dong et al. 1994). It is clear that the actual molecular pathway to cervical carcinogenesis is far from homogeneous. The situation in head and neck cancers is less than clear but heterogeneity and the existence of multiple pathways to carcinogenesis is highly likely. Koskinen et al (2003) reported that in their series of head and neck cancers, 61% were HPV DNA positive. HPV 16 was the dominant subtype, and found in 84% of HPV+ cancers. Tonsillar carcinomas have been reported to have the highest prevalence rate of HPV DNA contained within cancerous cells (51%) of all the forms of head and neck cancers (Syrjanen, S. 2004). Mellin et al 2002 reported that all 11 cases of HPV+ tonsillar carcinomas in their series contained HPV DNA in episomal form (Mellin et al. 2002). Another study in 1992 reported two HPV 16+ tonsillar carcinomas which contained episomal HPV DNA, and two HPV 33+ tonsillar carcinomas in which one was integrated and the other had mixed forms (Snijders et al. 1992). It is unclear why tonsillar carcinomas appear to have a higher predominance of episomal HPV DNA than other types of head and neck cancer. It is likely though, that these various observations suggest a high heterogeneity and variation in the oncogenic pathways among these tumours.

3.4 Similarities between HPV and ZEBRA

HPV and EBV co-infections have not been well documented and the significance of the presence of both viruses in nasopharyngeal cells has not been determined. It has been shown that ZEBRA, an EBV immediate early protein expressed during lytic replication that activates early EBV genes, binds to p53 (Quinlivan et al. 1993). The physical interaction of the ZEBRA and p53 protein prevents p53 from activating p53-responsive promoters (MauserSaito, et al. 2002). Similarly, HPV has been found to interact with p53, suggesting that this interaction promotes cell growth and thereby enhance viral replication (Levine

1990). Targeting p53 may be a common requirement for the replication of many types of DNA viruses (Prayitno 2006). In addition, B cells transfected with EBV latent membrane protein lost the regulatory effects of the retinoblastoma (RB) protein, and the HPV E7 transcript has been shown to immunoprecipitate the RB protein (Giovannelli et al. 2002). Thus, the functional loss of the RB protein might be one event common to both the HPV and EBV carcinogenic pathways.
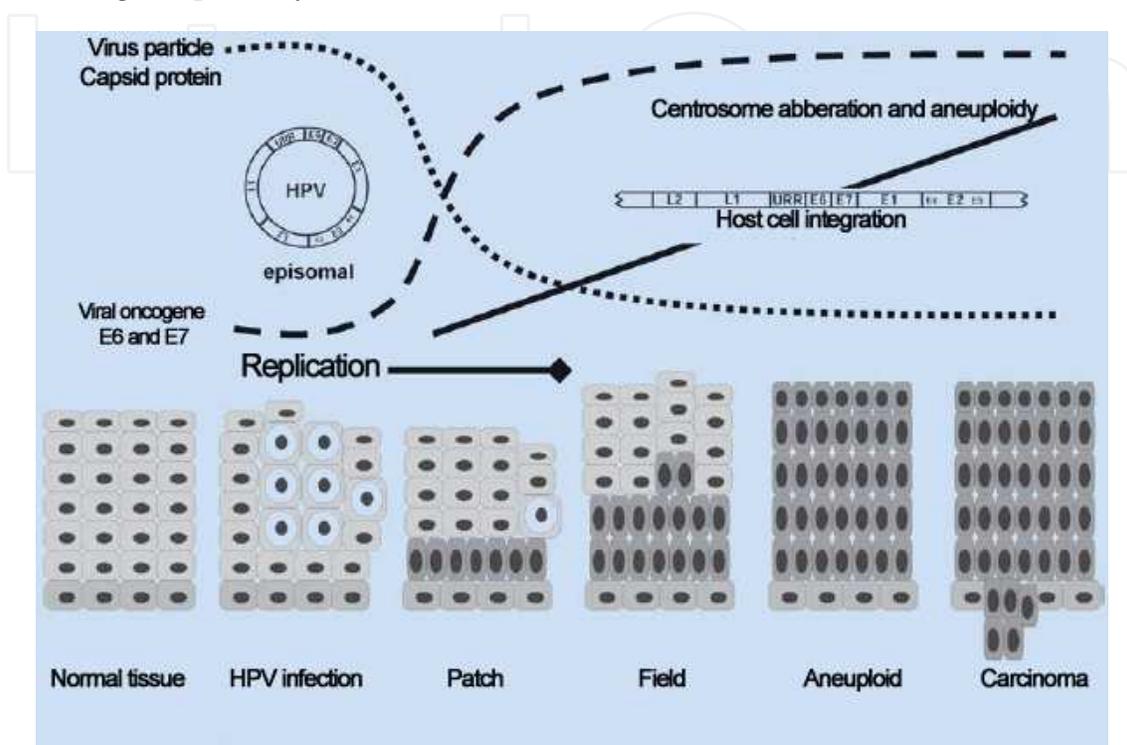

Fig. 2. A hypothetical model of HPV-associated NPC development. Most information has been deciphered from oral carcinogenesis; there are fewer data on the other subsites of NPC. Light cells: Normal epithelium. Cells with a white ring: Koilocytes, as a result of an active viral replication. Dark cells: Dysplastic epithelium with increased chromosomal instability reflected by increasing aneuploidy of the cells and leading to progression to high grade dysplasia and invasive carcinoma.

4. Conclusion

EBV is associated with the development of both B-cell and epithelial cell malignancies. The capacity of EBV to transform B lymphocytes has been well documented. EBV latent proteins are known to contribute to cellular transformation. Several lines of evidence demonstrated that reactivation of the latent viral genome in EBV associated cancers can cause cancer cell death. However, the underlying molecular mechanisms are unclear. Although ZEBRA plays an important role in immunomodulation, its capacity to reprogram the hosT-cell cycle control machinery is also notified in some tumour cell lines. Therefore, gene delivery techniques might be a novel therapeutic strategy for treating EBV positive malignancies especially NPC, via the induction of lytic viral transcription in certain tumour cells.

HPV-associated nasopharyngeal carcinoma represents a distinct clinical and biological entity with many unresolved issues that will be studied in future translational, clinical

research. We need to further investigate. It is possible that HPV-associated nasopharyngeal carcinoma arises by a different mechanism from that involved in the pathogenesis of HPV-associated cervical carcinoma. Still that the association between some NPC and HPV infection appears to be not firmly established, and the question that arises is whether there is any need for screening for NPC HPV infection in high-risk groups. Moreover, we need to examine how to treat HPV-positive intraepithelial neoplastic lesions, which are cancer precursor lesions, in the head and neck region. Should HPV-associated nasopharyngeal carcinoma be treated in the same way that their HPV-negative counterpart? And finally, it is worth considering the possibility that some NPC might be prevented by HPV vaccination.

5. References

Adler-Storthz, K., Newland, J. R., Tessin, B. A., Yeudall, W. A. & Shillitoe, E. J. 1986, 'Human papillomavirus type 2 DNA in oral verrucous carcinoma', J Oral Pathol, vol. 15, no. 9, pp. 472-5.

Al Moustafa, A. E., Chen, D., Ghabreau, L. & Akil, N. 2009, 'Association between human papillomavirus and Epstein-Barr virus infections in human oral carcinogenesis', Med Hypotheses, vol. 73, no. 2, pp. 184-6.

Baer, R., Bankier, A. T., Biggin, M. D., Deininger, P. L., Farrell, P. J., Gibson, T. J., Hatfull, G., Hudson, G. S., Satchwell, S. C., Seguin, C. & et al. 1984, 'DNA sequence and expression of the B95-8 Epstein-Barr virus genome', Nature, vol. 310, no. 5974, pp. 207-11.

Baumann, M., Feederle, R., Kremmer, E. & Hammerschmidt, W. 1999, 'Cellular transcription factors recruit viral replication proteins to activate the Epstein-Barr virus origin of lytic DNA replication, oriLyt', EMBO J, vol. 18, no. 21, pp. 6095-105.

Benider, A., Sahraoui, S., Acharki, A., Samlali, R. & Kahlain, A. 1995, '[Carcinomas of the nasopharynx in children. Analysis of 50 cases]', Bull Cancer, vol. 82, no. 2, pp. 155-61.

Busch, S. J. & Sassone-Corsi, P. 1990, 'Dimers, leucine zippers and DNA-binding domains', Trends Genet, vol. 6, no. 2, pp. 36-40.

Cayrol, C. & Flemington, E. 1996, 'G0/G1 growth arrest mediated by a region encompassing the basic leucine zipper (bZIP) domain of the Epstein-Barr virus transactivator Zta', J Biol Chem, vol. 271, no. 50, pp. 31799-802.

Cayrol, C. & Flemington, E. K. 1995, 'Identification of cellular target genes of the Epstein-Barr virus transactivator Zta: activation of transforming growth factor beta igh3 (TGF-beta igh3) and TGF-beta 1', J Virol, vol. 69, no. 7, pp. 4206-12.

Chen, C., Li, D. & Guo, N. 2009, 'Regulation of cellular and viral protein expression by the Epstein-Barr virus transcriptional regulator Zta: implications for therapy of EBV associated tumors', Cancer Biol Ther, vol. 8, no. 11, pp. 987-95.

Chen, Y. F., Tung, C. L., Chang, Y., Hsiao, W. C., Su, L. J. & Sun, H. S. 2011, 'Analysis of global methylation using a Zta-expressing nasopharyngeal carcinoma cell line', Genomics, vol. 97, no. 4, pp. 205-13.

Chien, Y. C., Chen, J. Y., Liu, M. Y., Yang, H. I., Hsu, M. M., Chen, C. J. & Yang, C. S. 2001, 'Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men', N Engl J Med, vol. 345, no. 26, pp. 1877-82.

Cohen, J. I. 2000, 'Epstein-Barr virus infection', N Engl J Med, vol. 343, no. 7, pp. 481-92.

Cox, M. A., Leahy, J. & Hardwick, J. M. 1990, 'An enhancer within the divergent promoter of Epstein-Barr virus responds synergistically to the R and Z transactivators', J Virol, vol. 64, no. 1, pp. 313-21.

Dardari, R., Menezes, J., Drouet, E., Joab, I., Benider, A., Bakkali, H., Kanouni, L., Jouhadi, H., Benjaafar, N., El Gueddari, B., Hassar, M. & Khyatti, M. 2008, 'Analyses of the prognostic significance of the Epstein-Barr virus transactivator ZEBRA protein and diagnostic value of its two synthetic peptides in nasopharyngeal carcinoma', J Clin Virol, vol. 41, no. 2, pp. 96-103.

Dolcetti, L., Peranzoni, E., Ugel, S., Marigo, I., Fernandez Gomez, A., Mesa, C., Geilich, M., Winkels, G., Traggiai, E., Casati, A., Grassi, F. & Bronte, V. 2010, 'Hierarchy of immunosuppressive strength among myeloid-derived suppressor cell subsets is determined by GM-CSF', Eur J Immunol, vol. 40, no. 1, pp. 22-35.

Dong, X. P., Stubenrauch, F., Beyer-Finkler, E. & Pfister, H. 1994, 'Prevalence of deletions of YY1-binding sites in episomal HPV 16 DNA from cervical cancers', Int J Cancer, vol. 58, no. 6, pp. 803-8.

El-Guindy, A., Heston, L. & Miller, G. 2010, 'A subset of replication proteins enhances origin recognition and lytic replication by the Epstein-Barr virus ZEBRA protein', PLoS Pathog, vol. 6, no. 8.

Feederle, R. & Delecluse, H. J. 2004, 'Low level of lytic replication in a recombinant Epstein-Barr virus carrying an origin of replication devoid of BZLF1-binding sites', J Virol, vol. 78, no. 21, pp. 12082-4.

Feng, B. J., Jalbout, M., Ayoub, W. B., Khyatti, M., Dahmoul, S., Ayad, M., Maachi, F., Bedadra, W., Abdoun, M., Mesli, S., Hamdi-Cherif, M., Boualga, K., Bouaouina, N., Chouchane, L., Benider, A., Ben Ayed, F., Goldgar, D. & Corbex, M. 2007, 'Dietary risk factors for nasopharyngeal carcinoma in Maghrebian countries', Int J Cancer, vol. 121, no. 7, pp. 1550-5.

Fixman, E. D., Hayward, G. S. & Hayward, S. D. 1995, 'Replication of Epstein-Barr virus oriLyt: lack of a dedicated virally encoded origin-binding protein and dependence on Zta in cotransfection assays', J Virol, vol. 69, no. 5, pp. 2998-3006.

Flemington, E. & Speck, S. H. 1990, 'Autoregulation of Epstein-Barr virus putative lytic switch gene BZLF1', J Virol, vol. 64, no. 3, pp. 1227-32.

Frithiof, L. & Wersall, J. 1967, 'Virus-like particles in papillomas of the human oral cavity', Arch Gesamte Virusforsch, vol. 21, no. 1, pp. 31-44.

Gillison, M. L. & Shah, K. V. 2001, 'Human papillomavirus-associated head and neck squamous cell carcinoma: mounting evidence for an etiologic role for human papillomavirus in a subset of head and neck cancers', Curr Opin Oncol, vol. 13, no. 3, pp. 183-8.

Giovannelli, L., Campisi, G., Lama, A., Giambalvo, O., Osborn, J., Margiotta, V. & Ammatuna, P. 2002, 'Human papillomavirus DNA in oral mucosal lesions', J Infect Dis, vol. 185, no. 6, pp. 833-6.

Goon, P. K., Stanley, M. A., Ebmeyer, J., Steinstrasser, L., Upile, T., Jerjes, W., Bernal-Sprekelsen, M., Gorner, M. & Sudhoff, H. H. 2009, 'HPV & head and neck cancer: a descriptive update', Head Neck Oncol, vol. 1, p. 36.

Gross, G., Pfister, H., Hagedorn, M. & Gissmann, L. 1982, 'Correlation between human papillomavirus (HPV) type and histology of warts', J Invest Dermatol, vol. 78, no. 2, pp. 160-4.

Gutierrez, J., Rodriguez, M., Soto, M. J., Suarez, S., Morales, P., Piedrola, G. & Maroto, M. C. 2001, 'An evaluation of a polyantigenic ELISA to detect Epstein-Barr virus reactivation', Microbios, vol. 106, no. 413, pp. 49-54.

Hammerschmidt, W. & Sugden, B. 1988, 'Identification and characterization of oriLyt, a lytic origin of DNA replication of Epstein-Barr virus', Cell, vol. 55, no. 3, pp. 427-33.

Hicks, M. R., Balesaria, S., Medina-Palazon, C., Pandya, M. J., Woolfson, D. N. & Sinclair, A. J. 2001, 'Biophysical analysis of natural variants of the multimerization region of Epstein-Barr virus lytic-switch protein BZLF1', J Virol, vol. 75, no. 11, pp. 5381-4.

Hildesheim, A. & Levine, P. H. 1993, 'Etiology of nasopharyngeal carcinoma: a review', Epidemiol Rev, vol. 15, no. 2, pp. 466-85.

Hording, U., Nielsen, H. W., Daugaard, S. & Albeck, H. 1994, 'Human papillomavirus types 11 and 16 detected in nasopharyngeal carcinomas by the polymerase chain reaction', Laryngoscope, vol. 104, no. 1 Pt 1, pp. 99-102.

Hsu, M., Wu, S. Y., Chang, S. S., Su, I. J., Tsai, C. H., Lai, S. J., Shiau, A. L., Takada, K. & Chang, Y. 2008, 'Epstein-Barr virus lytic transactivator Zta enhances chemotactic activity through induction of interleukin-8 in nasopharyngeal carcinoma cells', J Virol, vol. 82, no. 7, pp. 3679-88.

Jenkins, P. J., Binne, U. K. & Farrell, P. J. 2000, 'Histone acetylation and reactivation of Epstein-Barr virus from latency', J Virol, vol. 74, no. 2, pp. 710-20.

Jenson, A. B., Lancaster, W. D., Hartmann, D. P. & Shaffer, E. L., Jr. 1982, 'Frequency and distribution of papillomavirus structural antigens in verrucae, multiple papillomas, and condylomata of the oral cavity', Am J Pathol, vol. 107, no. 2, pp. 212-8.

Jeon, S., Allen-Hoffmann, B. L. & Lambert, P. F. 1995, 'Integration of human papillomavirus type 16 into the human genome correlates with a selective growth advantage of cells', J Virol, vol. 69, no. 5, pp. 2989-97.

Joab, I., Nicolas, J. C., Schwaab, G., de-The, G., Clausse, B., Perricaudet, M. & Zeng, Y. 1991, 'Detection of anti-Epstein-Barr-virus transactivator (ZEBRA) antibodies in sera from patients with nasopharyngeal carcinoma', Int J Cancer, vol. 48, no. 5, pp. 647-9.

Kared, H., Leforban, B., Montandon, R., Renand, A., Layseca Espinosa, E., Chatenoud, L., Rosenstein, Y., Schneider, E., Dy, M. & Zavala, F. 2008, 'Role of GM-CSF in tolerance induction by mobilized hematopoietic progenitors', Blood, vol. 112, no. 6, pp. 2575-8.

Khair, M. M., Mzibri, M. E., Mhand, R. A., Benider, A., Benchekroun, N., Fahime, E. M., Benchekroun, M. N. & Ennaji, M. M. 2009, 'Molecular detection and genotyping of human papillomavirus in cervical carcinoma biopsies in an area of high incidence of cancer from Moroccan women', J Med Virol, vol. 81, no. 4, pp. 678-84.

Koutsky, L. A., Galloway, D. A. & Holmes, K. K. 1988, 'Epidemiology of genital human papillomavirus infection', Epidemiol Rev, vol. 10, pp. 122-63.

Kreimer, A. R., Clifford, G. M., Boyle, P. & Franceschi, S. 2005, 'Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review', Cancer Epidemiol Biomarkers Prev, vol. 14, no. 2, pp. 467-75.

Krishna, S. M., James, S., Kattoor, J. & Balaram, P. 2004, 'Human papilloma virus infection in Indian nasopharyngeal carcinomas in relation to the histology of tumour', Indian J Pathol Microbiol, vol. 47, no. 2, pp. 181-5.

Lee, C. H., Yeh, T. H., Lai, H. C., Wu, S. Y., Su, I. J., Takada, K. & Chang, Y. 2011, 'Epstein-Barr virus Zta-induced immunomodulators from nasopharyngeal carcinoma cells upregulate interleukin-10 production from monocytes', J Virol, vol. 85, no. 14, pp. 7333-42.

Levine, A. J. 1990, 'The p53 protein and its interactions with the oncogene products of the small DNA tumor viruses', Virology, vol. 177, no. 2, pp. 419-26.

Liao, G., Huang, J., Fixman, E. D. & Hayward, S. D. 2005, 'The Epstein-Barr virus replication protein BBLF2/3 provides an origin-tethering function through interaction with the zinc finger DNA binding protein ZBRK1 and the KAP-1 corepressor', J Virol, vol. 79, no. 1, pp. 245-56.

Lieberman, P. M., Hardwick, J. M., Sample, J., Hayward, G. S. & Hayward, S. D. 1990, 'The zta transactivator involved in induction of lytic cycle gene expression in Epstein-Barr virus-infected lymphocytes binds to both AP-1 and ZRE sites in target promoter and enhancer regions', J Virol, vol. 64, no. 3, pp. 1143-55.

Lin, C. T. 2009, 'Relationship between Epstein-Barr virus infection and nasopharyngeal carcinoma pathogenesis', Ai Zheng, vol. 28, no. 8, pp. 791-804.

Lo, E. J., Bell, D., Woo, J. S., Li, G., Hanna, E. Y., El-Naggar, A. K. & Sturgis, E. M. 2010, 'Human papillomavirus and WHO type I nasopharyngeal carcinoma', Laryngoscope, vol. 120, no. 10, pp. 1990-7.

Loning, T., Reichart, P., Staquet, M. J., Becker, J. & Thivolet, J. 1984, 'Occurrence of papillomavirus structural antigens in oral papillomas and leukoplakias', J Oral Pathol, vol. 13, no. 2, pp. 155-65.

Lopez-Lizarraga, E., Sanchez-Corona, J., Montoya-Fuentes, H., Bravo-Cuellar, A., Campollo-Rivas, O., Lopez-Demerutis, E., Morgan-Villela, G., Arcaute-Velazquez, F., Monreal-Martinez, J. A. & Troyo, R. 2000, 'Human papillomavirus in tonsillar and nasopharyngeal carcinoma: isolation of HPV subtype 31', Ear Nose Throat J, vol. 79, no. 12, pp. 942-4.

Lu, H., Ouyang, W. & Huang, C. 2006, 'Inflammation, a key event in cancer development', Mol Cancer Res, vol. 4, no. 4, pp. 221-33.

Lu, J., Chen, S. Y., Chua, H. H., Liu, Y. S., Huang, Y. T., Chang, Y., Chen, J. Y., Sheen, T. S. & Tsai, C. H. 2000, 'Upregulation of tyrosine kinase TKT by the Epstein-Barr virus transactivator Zta', J Virol, vol. 74, no. 16, pp. 7391-9.

Mahot, S., Sergeant, A., Drouet, E. & Gruffat, H. 2003, 'A novel function for the Epstein-Barr virus transcription factor EB1/Zta: induction of transcription of the hIL-10 gene', J Gen Virol, vol. 84, no. Pt 4, pp. 965-74.

Marshall, W. L., Yim, C., Gustafson, E., Graf, T., Sage, D. R., Hanify, K., Williams, L., Fingeroth, J. & Finberg, R. W. 1999, 'Epstein-Barr virus encodes a novel homolog of the bcl-2 oncogene that inhibits apoptosis and associates with Bax and Bak', J Virol, vol. 73, no. 6, pp. 5181-5.

Mauser, A., Holley-Guthrie, E., Zanation, A., Yarborough, W., Kaufmann, W., Klingelhutz, A., Seaman, W. T. & Kenney, S. 2002, 'The Epstein-Barr virus immediate-early protein BZLF1 induces expression of E2F-1 and other proteins involved in cell cycle progression in primary keratinocytes and gastric carcinoma cells', J Virol, vol. 76, no. 24, pp. 12543-52.

Mauser, A., Saito, S., Appella, E., Anderson, C. W., Seaman, W. T. & Kenney, S. 2002, 'The Epstein-Barr virus immediate-early protein BZLF1 regulates p53 function through multiple mechanisms', J Virol, vol. 76, no. 24, pp. 12503-12.

McGlennen, R. C. 2000, 'Human papillomavirus oncogenesis', Clin Lab Med, vol. 20, no. 2, pp. 383-406.

Mellin, H., Dahlgren, L., Munck-Wikland, E., Lindholm, J., Rabbani, H., Kalantari, M. & Dalianis, T. 2002, 'Human papillomavirus type 16 is episomal and a high viral load may be correlated to better prognosis in tonsillar cancer', Int J Cancer, vol. 102, no. 2, pp. 152-8.

Mirzamani, N., Salehian, P., Farhadi, M. & Tehran, E. A. 2006, 'Detection of EBV and HPV in nasopharyngeal carcinoma by in situ hybridization', Exp Mol Pathol, vol. 81, no. 3, pp. 231-4.

Morrison, T. E., Mauser, A., Wong, A., Ting, J. P. & Kenney, S. C. 2001, 'Inhibition of IFN-gamma signaling by an Epstein-Barr virus immediate-early protein', Immunity, vol. 15, no. 5, pp. 787-99.

Munoz, N., Bosch, F. X., de Sanjose, S., Herrero, R., Castellsague, X., Shah, K. V., Snijders, P. J. & Meijer, C. J. 2003, 'Epidemiologic classification of human papillomavirus types associated with cervical cancer', N Engl J Med, vol. 348, no. 6, pp. 518-27.

Niller, H. H., Wolf, H. & Minarovits, J. 2009, 'Epigenetic dysregulation of the host cell genome in Epstein-Barr virus-associated neoplasia', Semin Cancer Biol, vol. 19, no. 3, pp. 158-64.

Park, N. H., Min, B. M., Li, S. L., Huang, M. Z., Cherick, H. M. & Doniger, J. 1991, 'Immortalization of normal human oral keratinocytes with type 16 human papillomavirus', Carcinogenesis, vol. 12, no. 9, pp. 1627-31.

Parkin, D. M. & Muir, C. S. 1992, 'Cancer Incidence in Five Continents. Comparability and quality of data', IARC Sci Publ, no. 120, pp. 45-173.

Pathmanathan, R., Prasad, U., Chandrika, G., Sadler, R., Flynn, K. & Raab-Traub, N. 1995, 'Undifferentiated, nonkeratinizing, and squamous cell carcinoma of the nasopharynx. Variants of Epstein-Barr virus-infected neoplasia', Am J Pathol, vol. 146, no. 6, pp. 1355-67.

Prayitno, A. 2006, 'Cervical cancer with human papilloma virus and Epstein Barr virus positive', J Carcinog, vol. 5, p. 13.

Punwaney, R., Brandwein, M. S., Zhang, D. Y., Urken, M. L., Cheng, R., Park, C. S., Li, H. B. & Li, X. 1999, 'Human papillomavirus may be common within nasopharyngeal carcinoma of Caucasian Americans: investigation of Epstein-Barr virus and human papillomavirus in eastern and western nasopharyngeal carcinoma using ligation-dependent polymerase chain reaction', Head Neck, vol. 21, no. 1, pp. 21-9.

Quinlivan, E. B., Holley-Guthrie, E. A., Norris, M., Gutsch, D., Bachenheimer, S. L. & Kenney, S. C. 1993, 'Direct BRLF1 binding is required for cooperative BZLF1/BRLF1 activation of the Epstein-Barr virus early promoter, BMRF1', Nucleic Acids Res, vol. 21, no. 14, pp. 1999-2007.

Raab-Traub, N. 1996, 'Pathogenesis of Epstein-Barr virus and its associated malignancies', Seminars in Virology, vol. 7, no. 5, pp. 315-23.

Rassekh, C. H., Rady, P. L., Arany, I., Tyring, S. K., Knudsen, S., Calhoun, K. H., Seikaly, H. & Bailey, B. J. 1998, 'Combined Epstein-Barr virus and human papillomavirus infection in nasopharyngeal carcinoma', Laryngoscope, vol. 108, no. 3, pp. 362-7.

Rennekamp, A. J., Wang, P. & Lieberman, P. M. 2010, 'Evidence for DNA hairpin recognition by Zta at the Epstein-Barr virus origin of lytic replication', J Virol, vol. 84, no. 14, pp. 7073-82.

Rickinson, A. 2002, 'Epstein-Barr virus', Virus Res, vol. 82, no. 1-2, pp. 109-13.

Rosenquist, K., Wennerberg, J., Schildt, E. B., Bladstrom, A., Goran Hansson, B. & Andersson, G. 2005, 'Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden', Acta Otolaryngol, vol. 125, no. 12, pp. 1327-36.

Sbih-Lammali, F., Clausse, B., Ardila-Osorio, H., Guerry, R., Talbot, M., Havouis, S., Ferradini, L., Bosq, J., Tursz, T. & Busson, P. 1999, 'Control of apoptosis in Epstein Barr virus-positive nasopharyngeal carcinoma cells: opposite effects of CD95 and CD40 stimulation', Cancer Res, vol. 59, no. 4, pp. 924-30.

Schaade, L., Kleines, M. & Hausler, M. 2001, 'Application of virus-specific immunoglobulin M (IgM), IgG, and IgA antibody detection with a polyantigenic enzyme-linked immunosorbent assay for diagnosis of Epstein-Barr virus infections in childhood', J Clin Microbiol, vol. 39, no. 11, pp. 3902-5.

Schepers, A., Pich, D. & Hammerschmidt, W. 1993, 'A transcription factor with homology to the AP-1 family links RNA transcription and DNA replication in the lytic cycle of Epstein-Barr virus', EMBO J, vol. 12, no. 10, pp. 3921-9.

---- 1996, 'Activation of oriLyt, the lytic origin of DNA replication of Epstein-Barr virus, by BZLF1', Virology, vol. 220, no. 2, pp. 367-76.

Schwartz, S. M., Daling, J. R., Doody, D. R., Wipf, G. C., Carter, J. J., Madeleine, M. M., Mao, E. J., Fitzgibbons, E. D., Huang, S., Beckmann, A. M., McDougall, J. K. & Galloway, D. A. 1998, 'Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection', J Natl Cancer Inst, vol. 90, no. 21, pp. 1626-36.

Shaffer, E. L., Jr., Reimann, B. E. & Gysland, W. B. 1980, 'Oral condyloma acuminatum. A case report with light microscopic and ultrastructural features', J Oral Pathol, vol. 9, no. 3, pp. 163-73.

Sinclair, A. J. 2003, 'bZIP proteins of human gammaherpesviruses', Journal of General Virology, vol. 84, no. 8, pp. 1941-9.

---- 2006, 'Unexpected structure of Epstein-Barr virus lytic cycle activator Zta', Trends Microbiol, vol. 14, no. 7, pp. 289-91.

Sinclair, A. J. & Farrell, P. J. 1992, 'Epstein-Barr virus transcription factors', Cell Growth Differ, vol. 3, no. 8, pp. 557-63.

Snijders, P. J., Meijer, C. J., van den Brule, A. J., Schrijnemakers, H. F., Snow, G. B. & Walboomers, J. M. 1992, 'Human papillomavirus (HPV) type 16 and 33 E6/E7 region transcripts in tonsillar carcinomas can originate from integrated and episomal HPV DNA', J Gen Virol, vol. 73 (Pt 8), pp. 2059-66.

Stubenrauch, F. & Laimins, L. A. 1999, 'Human papillomavirus life cycle: active and latent phases', Semin Cancer Biol, vol. 9, no. 6, pp. 379-86.

Syrjanen, K., Syrjanen, S. & Pyrhonen, S. 1982, 'Human papilloma virus (HPV) antigens in lesions of laryngeal squamous cell carcinomas', ORL J Otorhinolaryngol Relat Spec, vol. 44, no. 6, pp. 323-34.

Syrjanen, K. J. & Surjanen, S. M. 1981, 'Histological evidence for the presence of condylomatous epithelial lesions in association with laryngeal squamous cell carcinoma', ORL J Otorhinolaryngol Relat Spec, vol. 43, no. 4, pp. 181-94.

Syrjanen, S. 2004, 'HPV infections and tonsillar carcinoma', J Clin Pathol, vol. 57, no. 5, pp. 449-55.

Syrjanen, S. M. 1990, 'Basic concepts and practical applications of recombinant DNA techniques in detection of human papillomavirus (HPV) infection. Review article', APMIS, vol. 98, no. 2, pp. 95-110.

Takimoto, T., Ishiguro, H., Umeda, R., Ogura, H. & Hatano, M. 1984, 'Effects of chemical inducers on the Epstein-Barr virus cycle in epithelial/nasopharyngeal carcinoma hybrid cell line', ORL J Otorhinolaryngol Relat Spec, vol. 46, no. 4, pp. 192-4.

Termine, N., Panzarella, V., Falaschini, S., Russo, A., Matranga, D., Lo Muzio, L. & Campisi, G. 2008, 'HPV in oral squamous cell carcinoma vs head and neck squamous cell carcinoma biopsies: a meta-analysis (1988-2007)', Ann Oncol, vol. 19, no. 10, pp. 1681-90.

Tsai, S. T., Jin, Y. T., Mann, R. B. & Ambinder, R. F. 1998, 'Epstein-Barr virus detection in nasopharyngeal tissues of patients with suspected nasopharyngeal carcinoma', Cancer, vol. 82, no. 8, pp. 1449-53.

Tung, Y. C., Lin, K. H., Chu, P. Y., Hsu, C. C. & Kuo, W. R. 1999, 'Detection of human papilloma virus and Epstein-Barr virus DNA in nasopharyngeal carcinoma by polymerase chain reaction', Kaohsiung J Med Sci, vol. 15, no. 5, pp. 256-62.

Watts, K. J., Thompson, C. H., Cossart, Y. E. & Rose, B. R. 2002, 'Sequence variation and physical state of human papillomavirus type 16 cervical cancer isolates from Australia and New Caledonia', Int J Cancer, vol. 97, no. 6, pp. 868-74.

Wu, F. Y., Chen, H., Wang, S. E., ApRhys, C. M., Liao, G., Fujimuro, M., Farrell, C. J., Huang, J., Hayward, S. D. & Hayward, G. S. 2003, 'CCAAT/enhancer binding protein alpha interacts with ZTA and mediates ZTA-induced p21(CIP-1) accumulation and G(1) cell cycle arrest during the Epstein-Barr virus lytic cycle', J Virol, vol. 77, no. 2, pp. 1481-500.

Yip, T. T., Ngan, R. K., Lau, W. H., Poon, Y. F., Joab, I., Cochet, C. & Cheng, A. K. 1994, 'A possible prognostic role of immunoglobulin-G antibody against recombinant Epstein-Barr virus BZLF-1 transactivator protein ZEBRA in patients with nasopharyngeal carcinoma', Cancer, vol. 74, no. 9, pp. 2414-24.

Young, L. S. & Rickinson, A. B. 2004, 'Epstein-Barr virus: 40 years on', Nat Rev Cancer, vol. 4, no. 10, pp. 757-68.

Yu, M. C. 1991, 'Nasopharyngeal carcinoma: epidemiology and dietary factors', IARC Sci Publ, no. 105, pp. 39-47.

Zhang, Q., Holley-Guthrie, E., Ge, J. Q., Dorsky, D. & Kenney, S. 1997, 'The Epstein-Barr virus (EBV) DNA polymerase accessory protein, BMRF1, activates the essential downstream component of the EBV oriLyt', Virology, vol. 230, no. 1, pp. 22-34.

zur Hausen, H. 1999, 'Papillomaviruses in human cancers', Proc Assoc Am Physicians, vol. 111, no. 6, pp. 581-7.
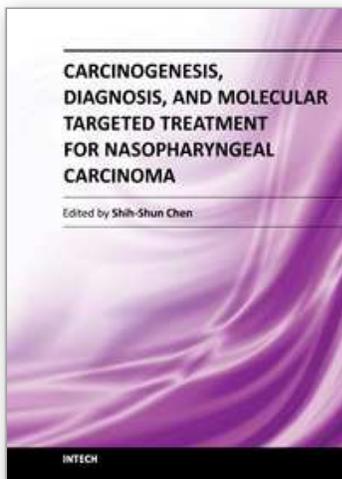
Carcinogenesis, Diagnosis, and Molecular Targeted Treatment for Nasopharyngeal Carcinoma
Edited by Dr. Shih-Shun Chen

This book is a comprehensive treatise of the potential risk factors associated with NPC development, the tools employed in the diagnosis and detection of NPC, the concepts behind NPC patients who develop neuro-endocrine abnormalities and ear-related complications after radiotherapy and chemotherapy, the molecular mechanisms leading to NPC carcinogenesis, and the potential therapeutic molecular targets for NPC.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Moumad Khalid, Laantri Nadia, Attaleb Mohammed, Dardari R'kia, Benider Abdellatif, Benchakroun Nadia, Ennaji Mustapha and Khyatti Meriem (2012). Role of the Epstein-Barr Virus ZEBRA Protein and HPV in the Carcinogenesis of Nasopharyngeal Carcinoma, Carcinogenesis, Diagnosis, and Molecular Targeted Treatment for Nasopharyngeal Carcinoma, Dr. Shih-Shun Chen (Ed.), ISBN: 978-953-307-867-0, InTech, Available from: http://www.intechopen.com/books/carcinogenesis-diagnosis-and-molecular-targeted-treatment-for-nasopharyngeal-carcinoma/role-of-the-epstein-barr-virus-zebra-protein-and-hpv-in-the-carcinogenesis-and-diagnostic-of-nasopha

INTECH
open science | open minds