10.5005/jp-journals-10024-2028

EDITORIAL

Etiologic Association between Epstein–Barr Virus and Oral Squamous Cell Carcinoma: A Brief Evidence-based Discussion

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How to cite this article: Majumdar B, Sarode SC, Sarode GS, Patil S. Etiologic Association between Epstein–Barr Virus and Oral Squamous Cell Carcinoma: A Brief Evidence-based Discussion. J Contemp Dent Pract 2017;18(4):261-264.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Epstein–Barr virus (EBV), also known as human herpes virus–4, belongs to the γ-subfamily of herpes viruses.[1] Nearly 90 to 95% of the world's adult population is an asymptomatic carrier of EBV.[1-3] After initial exposure, this virus coexists within the host cells throughout the individual's life.[2] However, majority of the infected individuals rarely demonstrate any serious sequelae. Nonetheless, in a small population, the virus is implicated in development of malignancies, depending upon the geographic and immunologic variations.[1] The oncogenic potential of EBV in relation to human cancers has been validated by the International Agency for Research on Cancer and it has been labeled as a group I carcinogen.[2]

The virus primarily affects the oropharyngeal region, subsequent to which it is known to persist in the immune cells, the epithelial cells of the oropharynx, and perhaps also the salivary glands and urogenital tract. The B cells serve as reservoirs of the latent viral genome, whereas the epithelial cells most likely contribute as a site for viral replication and amplification.[2] All the malignancies associated with EBV encompass the virus's latent cycle, which are of types I, II, and III. Mainly, four types of latent gene expressions have been noted, namely EBV nuclear antigens (EBNA), EBV-encoded RNAs (EBERs), latent membrane proteins (LMP), and Bam H1A right frame (BARF).[1]

Now, we attempt discoursing on its role in epithelial carcinomas, especially oral squamous cell carcinoma (OSCC). Among the epithelial origin neoplasms, EBV has been strongly associated with nasopharyngeal carcinoma. In addition, its role has been implicated in gastric, breast, liver, and oral carcinomas.[2,3] Nasopharyngeal carcinoma is associated with type II latency pattern of EBV, in which the viral genes expressed include EBNA-1, EBERs, LMP-1, LMP-2, and BARF0. The products of the above-mentioned genes primarily aid in immortalization of cells and replication of the viral genome.[1] Hence, to substantiate an etiologic association between the EBV and OSCC, these genes and their protein products ought to be demonstrated consistently and exclusively in the OSCC tumor cells/cell lines *per se*, rather than other types of sample, where latent viral DNA may also be present, resulting in false-positive data. Table 1[4-25] summarizes the various relevant original researches in relation to EBV and OSCC, assimilated from the PubMed search.

Analyzing the above data, only 8 out of 22 studies showed significant association of EBV with OSCC. The values of EBV positive cases showed a wide variation, ranging from 0 to 100%, among the various populations studied. Studies from Taiwan and Japan exhibited the highest figure of EBV-positive cases. A decrease or lack of

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Table 1: Occurrence of EBV in OSCC

Sl. no.	*Author, year*	*Population/Location*	*Sample size (OSCC)*	*Sample type*	*Target*	*EBV + cases*	*Statistical significance/prognosis*
1	Bagán et al 2016[4]	Spain	12	Saliva	EBV DNA (LMP-1 region)	7 (58.3%)	No
2	Polz-Gruszka et al 2015[5]	Poland (South-east)	92	Tumor tissue	EBV DNA	24 (26.1%)	No
3	Deng et al 2014[6]	Japan	37	Tumor tissue	EBNA-3C	22 (59.5%)	No
					del-LMP-1	22 (59.5%)	
				Tumor cells	EBER	0	
4	Nasher et al 2014[7]	Yemen	60	Tumor tissue	EBV DNA	44 (73.3%)	No
5	Acharya et al 2014[8]	Thailand (North-east)	91	Exfoliated cells	EBV DNA (BNLF-1 region)	41 (45.05%)	Yes
				Cells from tumor		26/80 (32.5%)	
6	Saravani et al 2014[9]	Iran	45	Tumor tissue	EBV DNA	8 (16.7%)	No
7	Jalouli et al 2012[10]	Norway, UK, Sweden, USA, Sri Lanka, India, Yemen, Sudan	155	Tumor tissue	EBV DNA (EBNA-1 region)	85 (55%)	Yes (industrialized countries)
8	Nola-Fuchs et al 2012[11]	Zagreb, Croatia	24	Exfoliated cells	EBV DNA	11 (45.8 %)	No
					EBNA	0	
9	Jalouli et al 2010[12]	Sudan	217	Tumor tissue	EBV DNA (EBNA-1 region)	69 (31.7)	Yes (w.r.t. toombak users with OSCC)
10	Jalouli et al 2010[13]	India (North)	62	Tumor tissue	EBV DNA (EBNA-1 region)	18 (29%)	No
11	Kis et al 2009[14]	Hungary (East)	65	Tumor tissue	BamH1-W fragment	48 (73.8%)	Yes
					LMP-1 (IHC)	0	–
12	Yen et al 2009[15]	Taiwan	57	Tumor tissue	EBV chip (71 spots) both latent and lytic viral genes were observed	47 (82.5%)	Yes
13	Anwar et al 2005[16]	Pakistan	56	Tumor tissue	EBER	0	No
14	Goldenberg et al 2004[17]	North American	113	Tumor tissue	EBV DNA (BamHI-W and EBNA-1 regions)	24 (Overt 2, Trace 22)	No
15	Higa et al 2003[18]	Japan (Okinawa)	177	Tumor tissue	EBNA-2 LMP-1 BamHI-W1-I1	128 (72%)	Good prognosis (compared with mainland OSCC cases)
16	Sand et al 2002[19]	Sweden	29	Tumor tissue	EBV DNA	11 (37.9%)	Yes
17	Tsuhako et al 2000[20]	Okinawa, Japan	60	Tumor tissue	EBV DNA, EBER-1 (in-situ PCR), Bam HI-W (NISH)	46 (76.6%), 12, 9	No
		Sapporo, Japan	42			16 (38.1%), 4, 4	
18	Kobayashi et al 1999[21]	Japan	46	Tumor tissue	EBV DNA (Bam HI-W region)	7 (15.2%)	Possibility of a good prognosis
					EBER-1 (ISH method)	0/7	
					LMP-1 (IHC)	6/7	
19	Cruz et al 1997[22]	The Netherlands	36	Tumor tissue	BamHI-W	36 (100%)	No
					BNLF-1	18 (50%)	
				Tumor cell line	EBV DNA	0	
20	van Heerden et al 1995[23]	South African	90	Tumor tissue	EBV DNA (BAM H1 W-fragment)	22 (24.4%)	No
21	van Rensburg et al 1995[24]	African	105	Tumor tissue	EBV DNA (BAM H1 W-fragment)	27	No
22	Horiuchi et al 1995[25]	Japan	36	Tumor tissue	EBV DNA (PCR)	19 (52.8%)	No
					BAM H1 W-fragment (ISH)	10/19	
					EBER1 (ISH)	101/9	
					LMP-1 (IHC)	0	

EBV gene expression specifically in tumor cells by *in situ* polymerase chain reaction (PCR) or *in situ* hybridization methods was noted, with the exception of the study by Acharya et al.[8] Lastly, in majority of the studies, chosen samples were tumor tissue specimens, which may contain considerable number of infiltrating immune cells or oral secretions, affecting the PCR results. In addition, the immune-compromised status of the cancer patients also might lead to an increased shedding of the EBV.

The pathogenesis of EBV in development of OSCC is unclear. The insignificant results of EBV DNA in OSCC with respect to control groups could be explained by the "hit and run theory," according to which the viral DNA only acts as an initiator and wanes with the malignant transformation of cells.[9] This hypothesis may be substantiated by the negative expression of LMP-1 viral protein in many cases. The LMP-1 is thought to be essential for transformation of cells and unnecessary in already-transformed cells. Other possible explanations, as previously suggested by Horiuchi et al,[25] include that viral DNA only exists as a passenger in the malignant cells or the malignant cells are vulnerable targets and get easily infected.

CONCLUSION

The role of EBV in pathogenesis of OSCC as a major etiological agent seems to be unlikely from the present available data. Studies with large number of patients, appropriate sample selection, strict inclusion criteria, and precise method of detection are critical for conclusive results.

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