REVIEW

Viruses In The Etiology of Oral Carcinogenesis: Examination of Evidence

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ABSTRACT:

Viruses are small infectious agents that can replicate only inside living cells of an organism. They are linked approximately to 20% of all malignancies. They have been the key instruments in the revolution of cancer biology. Although viewed originally as unusual agents that caused cancer in animals, but were of no particular relevance to humans, viruses have turned out to be the rosette stone for unlocking the mysteries of cell growth control. They have revealed the functional foundations of genetic basis of cancer and have provided a conceptual framework, applicable not only to cancer induced by viruses but to all neoplasia. The RNA and DNA tumour viruses have made functional contributions to two major areas of cancer research over the last two decades: First as tools for the discovery of cell signalling and growth control pathways and, second, as appreciated causative agents of human neoplasia.

Key words: viruses,oral carcinogenesis,etiology.

INTRODUCTION

Cancer of the oral cavity is the sixth most common malignancy in developed countries, representing almost 3% of malignant tumours, and more than 95% of them are squamous cell carcinomas. Tobacco and alcohol use are the major risk factors for most cancers of the head and neck including oral cancer. About 15-20% of patients develop oral carcinoma in the absence of exposure to well known risk factors or without any obvious predisposing genetic defect strongly suggests that other risk factors, such as the presence of infectious agents can be involved in oral carcinogenesis.[1] In view of the changes in oncogenes and tumour suppressors in oral carcinogenesis, and the role of carcinogens such as tobacco and alcohol, it is reasonable to question

whether viruses play any role. In malignant neoplasia of other squamous epithelia, viruses have been implicated and it is conceivable that viruses might contribute aetiologically in at least some cases of oral carcinoma.

WHAT IS IT THAT IMPARTS A VIRUS ITS ONCOGENIC POTENTIAL?

The first basic requirement for oncogenicity is that the virus be capable of a dynamic interaction with the cell in which the cell not only survives but multiplies and, a persistence of viral influence in that dividing cell.

A tumour virus must be capable of modifying normal mechanisms responsible for control of cell replication.

Since the nucleic acid of all viruses is the source of the code that determines their characteristics, the nucleic acids of tumour viruses should be examined for unique characteristics that might be correlated with oncogenic properties. It has been suggested that the percentage of guanine plus cytosine (G+C) might be significant in determining the oncogenic potential of a given virus. The hypothesis was that G+C content of any oncogenic DNA virus might have to be of approximately the same order as that of mammalian cell DNA, which is 43%.

However, the overall base composition of nucleic acid is only a crude characterization, since it gives no evidence of the spatial arrangement of the bases in the functioning molecule[2]

RELATIONSHIP OF VIRUS TO TRANSFORMED CELL[2]

In case of RNA viruses, the evidence is direct since virus continues to be produced and released. Even with the DNA viruses, all the present evidence points to the persistence of the viral genome in the transformed cell.

The evidence for persistence of viral genetic material in cells transformed by DNA viruses is summarized:

1. Infectious DNA extractable. Rabbit papilloma (Ito)
2. Viral DNA hybridization with tumour cell DNA. Polyoma (Alexrod)
3. Tumor cell RNA hybridization with viral DNA. Polyoma, SV40 (Benjamin)
4. Infectious virus release.SV40 (Gerber)
5. Viral marker rescue. Polyoma (Ting)
6. Viral structural antigen in tumour cell. Adenovirus (Huebner)
7. Virus specific antigens in tumour cells. Polyoma, SV40, Adenovirus (Habel), (Huebner)

CELL FACTORS INVOLVED IN TRANSFORMATION OF A VIRUS

1. Attachment, penetration and uncoating of virus particle.
2. Association of viral genome with cell genome, base sequence homology implicated.
3. Physiologic state of cell, need for cell division, increased DNA target suggested.
4. Karyologic state of cell, chromosome imperfections.

TENETS OF VIRAL CARCINOGENESIS[3]

1. Viruses can cause cancer in animals and humans.
2. Tumour viruses frequently establish persistent infections in natural hosts.
3. Host factors are important determinants of virus-induced tumorigenesis.
4. Viruses are seldom complete carcinogens.
5. Virus infections are more common than virus-related tumour formation.
6. Long latent periods usually elapse between initial virus infection and tumour appearance.
7. Viral strains may differ in oncogenic potential.
8. Viruses may be either direct- or indirect acting carcinogenic agents.
9. Oncogenic viruses modulate growth control pathways in cells.
10. Animal models may reveal mechanisms of viral carcinogenesis.
11. Viral markers are usually present in tumour cells.

12. One virus may be associated with more than one type of tumour.

TUMOUR VIRUSES ARE INFECTIOUS AGENTS

The infectious nature of viruses distinguishes them from all other cancer-causing agents. The recognized tumour viruses tend to establish long-term persistent infections in humans as compared with self-limited infections typical of most common viral diseases.[3]

HUMAN CANCER VIRUSES: HOW DO THEY ACT?

Different mechanisms of transformation of cell are involved in case of direct and indirect acting viruses. Direct acting viruses possess viral oncogenes whereas indirect acting viruses do not possess any oncogene and lack any transforming potential usually. However, no single mechanism is implicated in causation of viral carcinogenesis and many diverse mechanisms are believed to play a role. Even direct acting viruses are not complete carcinogens and are supposed to be initiating or promoting factors which act in synergism with additional changes to transform the normal regulatory pathways in a cell leading to malignancy.

Direct acting viruses such as papilloma virus and polyoma virus encode proteins that act on tumour suppressor proteins such as p53 and Rb which cause their inactivation and lead to cell transformation. The E5 protein of bovine papilloma virus coupled with platelet derived growth factor-β causes the activation of latter and results in a sustained mitogenic signal.[4] However, if this takes place in human epithelial cells is yet to be ascertained. The viral proteins E5, E6 and E7 are involved in malignant transformation in Papilloma virus. EBV elaborates a protein LMP1 which associates with Tumour Necrosis Factor Receptor-Activated Factors (TRAFs) resulting in proliferation. Besides, EBV- encoded nuclear antigens (EBNAs) are important for a cell to be immortalized. Among the EBNAs, EBNA1 has been shown to be oncogenic.[5]

Tumour viruses such as HBV and HTLV-1 act by indirect mechanism of induction of tumour. HBV encodes HBV transactivator protein, the X protein, which is implicated in pathogenesis of hepatocellular carcinoma. This activates the Ras-Raf mitogen activated kinase signalling cascade by either activating the genes related to cellular proliferation or impairing the DNA repair mechanism, due to which, mutations are propagated.[6,7,8] HTLV1 is the only virus known to have a role in human carcinogenesis. Tax, a viral protein, is known to exert deleterious effects on the repair of damaged DNA.[9,10] A more indirect role for HIV in carcinogenesis has been suggested.[11] Immunosuppressed individuals are more prone to developing certain cancers such as EBV-positive lymphomas, HHV-8 and HPV positive tumours. However, much is to be elucidated about the role of retroviruses in human cancers.

PROBLEMS IN ESTABLISHING A VIRAL AETIOLOGY IN HUMAN CARCINOGENESIS

Evans and Mueller[12] and zur Hausen[13] stated the following difficulties that question the role of viruses in causation of cancer.

1. Virus, being ubiquitous in humans, but cancer does not always occur.
2. A long time period between disease onset and appearance of tumour is observed.
3. Time of initial occurrence of tumour may be not known.
4. The host factors which determine an individual being more prone to developing cancer vary.
5. Different virus species differ in their oncogenic potential.
6. Cofactors are needed for virus induced carcinogenesis.
7. Besides viruses, physical and chemical carcinogens may also be involved in causation.
8. Different geographic areas and individuals show different causative factors in causation of same tumour.
9. Detection techniques for viruses such as assays may not provide needed information.
10. The existence of animal model may be doubtful.

Certain criteria were proposed by Sir Austin Bradford Hill[14, 15] to confirm disease causation and infectious and/or non-infectious environmental factors in establishment of disease. These were as follows:

1. How often are viruses found in the tumour?
2. Is the association between disease and virus seen repeatedly among different people living in different areas?
3. Is the virus specific to a tumour or not?
4. Does the virus infection occur before the development of tumour?
5. Does the virus load correlate with dose and response relationship?
6. Is it possible biologically that the virus causes the production of tumour?
7. Does the virus and tumour association correlate with the history and biology of disease process?
8. Does experimental data suggest the association of virus with tumour?

CONCLUSION

When considering a virus as a possible etiologic agent in carcinogenesis, the classical Henle-Koch postulates are not met and even the most recent guidelines pose a problem in arriving at a diagnosis.[16,17] However, data on role of viruses as possible carcinogenic agents has been proposed based on viral biology. Based on this, there is not much doubt regarding viruses targeting cellular pathways by the proteins encoded by them leading to malignant transformation of a cell. Considering the multistep model for viral carcinogenesis a plausible role played by viruses in causation of tumours may be supported.[18] However, more research is needed to elucidate the mechanisms that suggest role of viruses as cancer causing agents.

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