Review Article

Immunology and Oral Cancer: A Review

Angel Aghera[1]*, Bhavin Dudhia[1], Siddharth Modi[1], Nidhi Senta[1], Tabish Mashhadi[1], Vishvajit Aghera[2]

[1]Department of Oral medicine and Radiology, Ahmedabad Dental College and Hospital, Ahmedabad, Gujarat, India.
[2]Clinical Researcher.

Abstract

The word "cancer" is an uncontrolled growth of cells and second, the ability to invade and damage normal tissues either locally or at distant sites in the body. This high morbidity rate can be attributed to many factors, including failure to respond to available chemotherapy, late presentation of the lesions, and the lack of suitable markers for early detection. The poor prognosis for head-and-neck squamous cell carcinoma (HNSCC) patients may be a reflection of the fact that while many of the risk factors involved in HNSCC pathogenesis, such as alcohol and tobacco, are well-recognized, by contrast very little is known about the molecular mechanisms responsible for this type of cancer. In addition to cellular changes, the body's normal defense mechanisms can play a key role in encouraging or combating carcinogenesis and tumor spread. Apart from traditional tools of treatment, immunotherapy has been used as a novel mode to treat oral cancer. Extensive persuasive health education is needed to be directed to control/reduce the tobacco habit, nutrition education, safe sexual practices, attention to personal and genital hygiene needs to be imported for increasing public awareness. Prophylactic vaccinations against HPV infection are useful strategies for the prevention of oral cancer. An aggressive interdisciplinary approach of education and enhanced oral cancer screening services is required to increase early detection of oral cancers and ultimately increase the 5-year survival rates of oral and pharyngeal cancer patients.

Keywords: Immunology, Immunotherapy, Oral cancer.

Introduction

The word "cancer" is an umbrella term that refers to about 200 diseases that share two common characteristics: first, an uncontrolled growth of cells and second, the ability to invade and damage normal tissues either locally or at distant sites in the body.[1]

This high morbidity rate can be attributed to many factors, including failure to respond to available chemotherapy, late presentation of the lesions, and the lack of suitable markers for early detection. The poor prognosis for head-and-neck squamous cell carcinoma (HNSCC) patients may be a reflection of the fact that while many of the risk factors involved in HNSCC pathogenesis, such as alcohol and tobacco, are well recognized, by contrast very little is known about the molecular mechanisms responsible for this type of cancer.[2]

Cellular changes, such as gain of function mutations of oncogenes and loss of function mutations in tumor suppressor genes (TSGs), can lead to relative cellular immortality, proliferation, and carcinogenesis. In addition to cellular changes, the body's normal defense mechanisms can play a key role in encouraging or combating carcinogenesis and tumor spread. Cells of the immune system can also inhibit tumor growth and progression through the recognition and rejection of malignant cells, a process referred to as immunosurveillance or immunoediting.[3,4]

In this respect, immunodeficiency can predispose an individual to the development of both spontaneous and virally induced cancers, and established tumors often generate immunosuppressive microenvironments that can block productive antitumor immunity. The plethora of cells, soluble factors and cytokines involved, tumor-associated macrophages (TAM) or myeloid-derived suppressive cells and their secreted cytokines interleukin (IL)-6, tumor necrosis factor, and IL-1 may be key in promoting the progress of tumor development. However, the cellular and molecular mechanisms that positively and negatively regulate the function and phenotype of TAM remain largely unknown. Elucidation

Access this article online

Website: www.jrad.co.in

DOI: https://doi.org/10.53064/jrad.2022.15.1.454

Address for correspondence: Dr. Angel Aghera, Ahmedabad Dental College and Hospital, Ahmedabad, Gujarat, India.
Email: angelagheramds@gmail.com

Received: Oct. 07, 2023; **Accepted:** Oct. 29, 2023; **Published:** Nov. 25, 2023

How to cite this article: Aghera A, Dudhia B, Modi S, Senta N, Mashhadi T, Aghera V. Immunology and Oral Cancer: A Review. J Res Adv Dent 2024;15(1):1-5.

of these mechanisms would have a significant impact on understanding the pathogenesis of inflammation-associated cancers and could aid progress in the development of more effective cancer therapies.[5]

Patients with primary (genetically determined) immunodeficiencies are predisposed to neoplasia, particularly of the lymphoreticular system, although carcinomas occur in some.[6]

An association between oral carcinoma and the histocompatibility human leukocyte antigen (HLA) antigen Hl-A8 has been demonstrated (Tarpley *et al*., 1975).[6] In other tumors, the onset of malignancy is associated with the loss of some cell surface HLA antigens and in this respect, it is interesting that microglobulin a small molecular weight component of HLA antigens is lost from the tumor cell surface (Sculiy, 1983a) and is increased in the serum of patients with oral carcinoma (Scully, 1981a).[7]

Other cellular antigens that may be lost in oral carcinoma include blood group antigens A and B.[6]

Serum markers of oral cancer such as microglobulin and carcinoembryonic antigen (CEA) are unfortunately insufficiently specific for use as indicators of tumor or metastases (Scully, 1981a).[7]

The presence of leukocytes within tumors, observed in the 19th century by Rudolf Virchow, provided the first indication of a possible link between inflammation and cancer. Yet, it is only during the last decade that clear evidence has been obtained that inflammation plays a critical role in tumorigenesis, and some of the underlying molecular mechanisms have been elucidated.[7,8]

Tumor Immunology

The focus of tumor immunology is mainly on to study the immunogenicity of tumor and the mechanism of immune response to tumor, to demonstrate the relationship between the status of immune system and the generation, development of tumor, and to explore the method of tumor diagnosis, therapy, and prevention.[9]

Tumor immunology has been marked historically by great expectations and bitter disappointments, but it is currently being viewed with increasing interest by clinical and basic scientists. From its inception as an area of investigation, two presumptions have driven the field: (1) Tumors express antigens which can elicit immune responses and (2) the immune responses specific for these tumor antigens can mediate a protective and/or therapeutic antitumor effect.[8]

Self-sufficiency to growth signals

Oncogenes, Proto-oncogene and Oncoproteins.

Genes that promote autonomous cell growth in cancer cells are called oncogenes and their normal cellular counterpart are called proto-oncogenes.[6]

Proto-oncogenes are physiological regulator of cell cycle while oncogenes are characterized by the ability to promote cell growth in the absence of normal mitogenic signals. Their products, i.e., oncoproteins also resemble normal products of proto-oncogenes with exception that they are devoid of the important regulatory element.[10]

There are five different steps which are regulated by proto-oncogenes under normal physiologic condition.

1. Binding of the growth factor to its specific receptor is generally located on the cell membrane
2. Transient and limited activation of growth factor receptor which in turn activates several signal transduction proteins on the inner leaflet of plasma membrane
3. Transmission of the transduced signal across the cytosol to the nucleus through second messengers or by signal transduction molecules that directly activate transcription
4. Induction and activation of nuclear regulatory factors that initiate DNA transcription
5. Entry and progression of the cell into cell cycle, ultimately resulting in cell division.[6]

Whenever mutations/changes occur, there is the formation of oncogenes. Oncogenes encode oncoproteins which have similar functions as their normal counterparts. But as they are constitutively expressed, they endow the cell with self-sufficiency in growth.[10]

Principles of the seed and soil hypothesis

1. Tumors are biologically heterogeneous and contain subpopulations of cells with different angiogenic, invasive, and metastatic properties[11]
2. Metastases are a selective process for cells that succeed in invasion, embolization, survival in the circulation, arrest in a distal capillary bed, extravasations into the distant organ, and survival and proliferation in the distant organ.[11]

The outcome of metastasis depends on multiple interactions ("cross-talk") between the metastatic subpopulation in the primary tumor and the host organ microenvironment.[11]

Molecular Biology of Oral Cancer

Carcinogenesis is a complex, multi-step process in which genetic events within signal transduction pathways governing normal cellular physiology are quantitatively or qualitatively altered.[12] The genetic basis of cancer is now well established. Under normal conditions, these tightly controlled excitatory and inhibitory pathways regulate oral keratinocyte biology. Basic cellular functions under these controls include cell division, differentiation, senescence, and adhesion.[13] These regulatory pathways are composed of extracellular ligands that bind to cell-surface receptors to generate intracellular signals sent through secondary messengers. These signals either directly alter cell function or stimulate the transcription of genes whose proteins effect changes.[13]

To understand the process of carcinogenesis, first regulation of normal cell cycle should be overviewed.[6]

The orderly progression of cells through various phases of cell cycle is orchestrated by cyclins and cyclin-dependent kinesis (CDKs) and by their inhibitors.[6,13]

CDKs drive the cell cycle by phosphorylating critical target proteins that are required for the progression of cells to the next phase of cell cycle. CDKs are expressed constitutively during cell cycle but in an inactive form. They are activated by phosphorylation after binding to family of proteins called cyclins.[6]

Unlike CDKs, cyclins are synthesized at specific stages and they activate CDKs. On activation of CDKs, the cyclin levels decline rapidly. More than 15 cyclins have been identified but cyclins D, E, A, and B are important.[6]

Transcription factors

Transcription factors, or proteins that regulate the expression of other genes, are also altered in oral cancer. Modulation of gene expression is an important outcome in the alteration of the intracellular pathways. The transcription factor *c-myc,* which helps regulate cell proliferation and differentiation, is frequently over expressed in oral cancers.[6,14]

However, oncogenes alone are not sufficient to cause oral cancer but appear to be initiators of the process. The critical event in the transformation of a premalignant cell to a malignant cell is the inactivation of cellular negative regulators, TSGs.[6]

TSGs

TSGs or anti-oncogenes have been documented to potent negative regulatory controls which are lost due to chromosomal alterations during tumor formation. Functional loss of multiple TSGs is believed to be the major event leading to the development of malignancy. Unlike oncogenes, which can effect a cellular change through mutation of only one of the two gene copies, TSGs are most often inactivated by point mutations, deletions, and rearrangements in both gene copies in a "two-hit" fashion. Therefore, the critical events for the malignant transformation of oral keratinocyte, i.e., the loss of function of TSGs are difficult to achieve.[14]

Many TSGs were initially identified in pediatric tumors that formed early in life because one mutated TSG had been inherited. However, identification of these genes lagged a decade behind the isolation of the first oncogenes, because, in cancer cells, TSGs are a negative phenotype, an event no longer present within the cell.[14]

Through mathematical models analyzing genetic pedigrees of pediatric tumor patients, Knudson predicted that the inactivation of both copies of TSGs occurs in a two-hit fashion (Knudson). Experimental evidence followed with the observation that normal: tumor hybrids demonstrated normal phenotypes, which suggested that normal cells contained suppressors of the tumor phenotype.[14]

To date, only three genes—p53, deleted in oral cancer-1 (doc-I), and thrombospondin 1 (TSP-1) have exhibited tumor suppressor activity in malignant oral keratinocytes.[14]

P53

The TSG p53 is known to be mutated in approximately 70% of adult solid tumors. Identification of members of its suppressor pathway, which themselves may be altered, may prove the importance of p53 to a higher percentage of cancers.[12]

In normal cell biology, p53 acts as a regulator of DNA synthesis. P53 also activates pathways leading to apoptosis. Mutation of p53 allows tumors to the genetic alterations that lead to other activated oncogenes or inactivated TSGs. The p53 gene appears to be mutated at the transition of superficial to invasive carcinoma. Alteration of the p53 gene occurs as point mutations and deletions.[12]

Doc-1

Oral TSG named "deleted in oral cancer-1." Mutation of this gene in oral keratinocytes leads to a reduction of expression and protein production. Re-expression of Doc-1 in malignant oral keratinocytes results in the reversion of many malignant phenotypes to normal, thus causing the doc-1 transfected oral cancer cell to look and act like its normal counterpart. The precise function of doc-1in normal oral keratinocyte biology is presently unclear.[14]

TSP-1

Morocco *et al*. have shown that the control of angiogenesis was lost during oral carcinogenesis. This loss of the regulation of the angiogenic phenotype in the malignant keratinocytes was correlated with a reduction of TSP1.[6,14]

Tumor antigens

Tumor antigen refers to all newly expressed antigens or over-expressed antigens during the generation and development of the tumor.

Base on their patterns of expression:

- Tumor-specific antigen (TSA)
- Tumor-associated antigens (TAA).[15]

TSA

Antigens that are only expressed on tumor cells but not on normal cells and having high specificity.[15,16]

TAA

Antigens are also expressed on normal cells, but high expressed on tumor cells without tumor specificity. e.g. CEA and alpha-fetoprotein.[15,16]

1. TSAs which induce rejection of tumor transplants in immunized hosts are termed tumor-specific transplantation antigens or tumor-associated transplantation antigens [Figure 1].

Normal cells

Require mitogenic growth signals to stimulate active proliferation (Signals transmitted to cell by transmembrane receptors that bind signaling molecules: diffusible growth factors, extracellular matrix components, cell–cell adhesion molecules).[6]

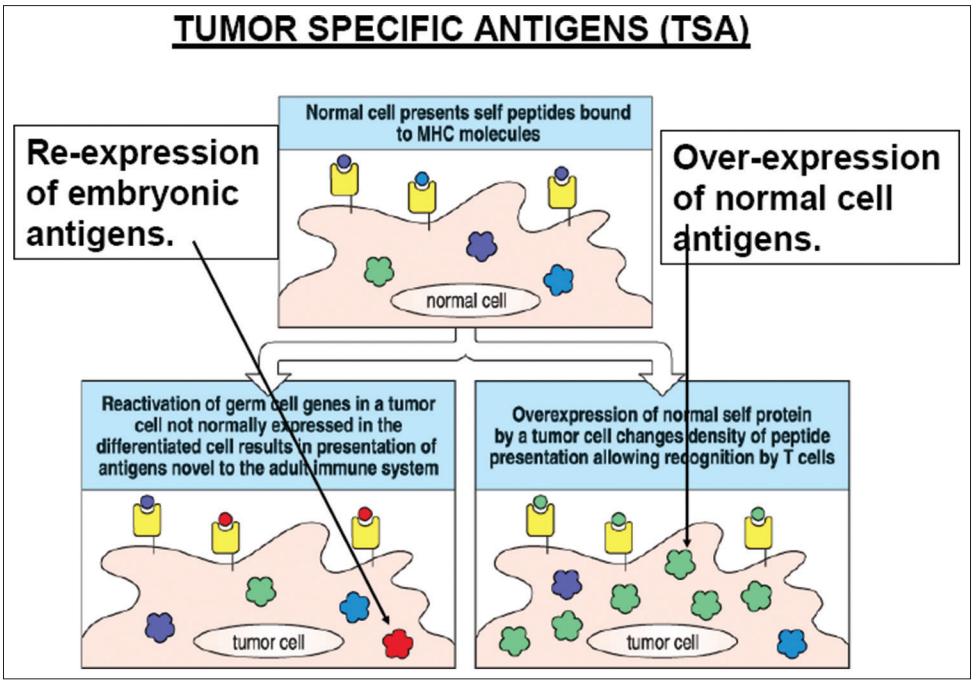

Figure 1: Mechanism of tumor-specific antigen recognition

Cancer cells

Acquire a reduced dependence on exogenous growth stimulation.

- Alteration of extracellular growth signals
- Alteration of transcellular transducers of the signals
- Alteration of intracellular mechanisms that translate the signals.

Thus, they generate their own growth signals and do not depend on stimulation from the environment which results in the disruption of important homeostatic mechanism for cell census.[6]

Tumor-derived soluble factors

Tumors evolve mechanisms to escape immune control by a process called immune editing, which provides a selective pressure in the tumor microenvironment that can lead to malignant progression. A variety of tumor-derived soluble factors contribute to the emergence of complex local and regional immunosuppressive networks.

Although deposited at the primary tumor site, these secreted factors can extend immunosuppressive effects into local lymph nodes and the spleen, thereby promoting invasion and metastasis.[17]

Vascular endothelial growth factor plays a key role in recruiting immature myeloid cells from the bone marrow to enrich the microenvironment as tumor-associated immature dendritic cell (iDCs) and macrophages.[18]

Immunological ignorance and tolerance in tumors

A tumor-specific immune response is regulated by tumor antigen levels and maturation stages of antigen-presenting cells such as dendritic cells (DCs). Many solid tumors, such as sarcomas and carcinomas, express TSAs that can serve as targets for immune effector T cells. Nevertheless, the overall immune surveillance against such tumors seems relatively inefficient.

Tumor cells are capable of inducing a protective cytotoxic T-cell response if transferred as a single-cell suspension. However, if they are transplanted as small tumor pieces, tumors readily grow because the tumor antigen level can be modulated in the tumor microenvironment.[19]

Thus, tumor cells are surrounded by non-tumor cells, including bone marrow-derived cells such as iDCs and non-bone-marrow-derived cells such as fibroblasts, endothelium, and extracellular matrix (ECM). The ECM binds tumor antigen, 120 and fibroblasts and endothelial cells compete with DCs for the antigen, 121 whereby many tumor antigens are down-regulated, thereby allowing tumor progression.[20]

Furthermore, these stromal cells increase interstitial fluid pressure in the tumor, resulting in escape from immune attack by effector cells.[21]

Conclusion

Apart from traditional tools of treatment, immunotherapy has been used as a novel mode to treat oral cancer. Both active and passive means of stimulating the non-specific and specific immune systems have been employed, in some cases with significant success. It includes active immunotherapy, wherein the host actively participates in mounting an immune response (vaccines) and passive immunotherapy which involves transfer

of preformed Abs, immune cells and other factors into the hosts.

Extensive persuasive health education is needed to be directed to control/reduce the tobacco habit, nutrition education, safe sexual practices, attention to personal and genital hygiene need to be imported for increasing public awareness. Prophylactic vaccinations against HPV infection are useful strategies for the prevention of oral cancer.[4,17]

An aggressive interdisciplinary approach of education and enhanced oral cancer screening services is required to increase early detection of oral cancers and ultimately increase the five-year survival rates of oral and pharyngeal cancer patients.

References

1. Dzivenu OK, O'Donnell-Tormey J. Cancer and the Immune System: The Vital Connection. New York: Cancer Research Institute; 2003.
2. Patel V, Leethanakul C, Gutkind JS. New approaches to the understanding of the molecular basis of oral cancer. Crit Rev Oral Biol Med 2001;12:55-63.
3. Bui JD, Schreiber RD. Cancer immunosurveillance, immunoediting and inflammation: Independent or interdependent processes? Curr Opin Immunol 2007;19:203-8.
4. Dunn GP, Ikeda H, Bruce AT, Koebel C, Uppaluri R, Bui J, *et al.* Interferon-gamma and cancer immunoediting. Immunol Res 2005;32:231-45.
5. Brostoff D, Male D, Roitt I. Immunology. 7th ed. Netherlands: Elsevier; 2006.
6. Tarpley JL, Chretien PB, Alexander JC, Hoye RC, Block JB, Ketcham AS. High dose methotrexate as a preoperative adjuvant in the treatment of epidermoid carcinoma of the head and neck: A feasibility study and clinical trial. American J Surgery. 1975;30:481-6.
7. Scully C. Immunology and oral cancer. Br J Oral Surg. 1983;21:136-46
8. Ord R, Blanchaert R. Tumor immunology, Section II. Oral cancer. Quintessence Int 2000;132:9-21.
9. Shillitoe EJ. The role of immunology in the diagnosis, prognosis and treatment planning of oral cancer. Proc R Soc Med 1976;69:747-9.
10. Hasina R, Lingen MW**.** Angiogenesis in oral cancer. J Dent Educ 2001;65:1282-90.
11. Langley RR, Fidler IJ**.** The seed and soil hypothesis revisited-the role of tumor-stroma interactions in metastasis to different organs. Int J Cancer 2011;128:2527-35.
12. Shah J, Johnson N, Batsakis G. Oral Cancer. 1st ed. United Kingdom: Taylor & Francis Group; 2003. p. 3-75.
13. Martinez JD. Molecular Biology of Cancer. Burger's Medicinal Chemistry and Drug Discovery. 6th ed., Ch. 1., Vol. 5. United States: John Wiley & Sons; 2003. p. 1-50.
14. Wong DT. Molecular biology of human oral cancer. Crit Rev Oral Biol Med 1996;7:319-28.
15. Mueller MM, Fusenig NE. Friends or foes - bipolar effects of the tumour stroma in cancer. Nat Rev Cancer 2004;4:839-49.
16. Schorey JS, Bhatnagar S. Exosome function: From tumor immunology to pathogen biology. Traffic 2008;9:871-81.
17. Boon T, van der Bruggen P. Human tumor antigens recognized by T lymphocytes. J Exp Med 1996;183:725-9.
18. Zancope E, Costa NL, Junqueira-Kipnis AP, Valadares MC, Silva TA, Leles CR, *et al.* Differential infiltration of CD8+ and NK cells in lip and oral cavity squamous cell carcinoma. J Oral Pathol Med 2010;39:162-7.
19. Raza SA, Clifford GM, Franceschi S. Worldwide variation in the relative importance of hepatitis B and hepatitis C viruses in hepatocellular carcinoma: A systematic review. Br J Cancer 2007;96:1127-34.
20. Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest 2007;117:1137-46.
21. Schreiber RD. Cancer vaccines 2004 opening address: The molecular and cellular basis of cancer immunosurveillance and immunoediting. Cancer Immun 2005;5:1.