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Brief Communication

Conceptual model for progression of oral cancer - our perspective

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Abstract: Oral cancer was and still is an underestimated disease in terms of incidence and mortality rates. As a result, requires early detection and urgent prevention. This article describes a framework that covers the significant stages of conceptual development of oral cancer. Conceptual model is useful in understanding the pathogenesis and understand the disease processes. This article signifies information on various aspects of perspective risk and the role played by it. Article covers the following aspects: what are the perspective risks, what changes it causes to normal cell, what are the direct and indirect effects on normal cell, cellular changes seen with normal cell when affected with perspective risk, transformation of normal cell to oral potentially malignant disorders (OPMD) and changes seen during transformation into cancer. Understanding the conceptual model of oral cancer transformation will be a paradigm shift in future research in the field and early management of oral cancer, which will reduce the disease burden on the nation.

Keywords: Oral cancer, conceptual model, perspective risk, OPMD, dysplasia, malignancy, carcinogenesis, immune system

Introduction

Among oral cancers, Oral squamous cell carcinoma (OSCC) has been showing a low 5-year survival rate and poor prognosis. To have better survival and prognosis, causes and processes involved in process of carcinogenesis should be evaluated [1]. Oral cancer can be fatal if untreated, as it may not be noticed by the patient in early stages. In its early stages, oral cancer can frequently progress without producing pain or symptoms [2, 3]. Oral cancer can form directly or can form through transformation of oral potentially malignant disorders (OPMD). Potentially malignant oral cavity lesions are a diverse set of lesions that are linked to a varying risk of malignant development into invasive cancer. The most prevalent lesions include leukoplakia, lichen planus, oral lichenoid lesions, oral erythroplakia, oral submucous fibrosis, and proliferative verrucous leukoplakia [4]. These may or may not be associated with dysplasia of the epithelium [5]. Among several types of oral cancers, approximately 90% are squamous cell carcinomas. Cancer is a multifactorial disease [6-8]. Understanding the various factors and their influence in carcinogenesis is need of the hour to tackle the poor mortality & morbidity rate associated with it. Different molecular abnormalities have been described in early lesions linked with a possible malignant behaviour, and extrinsic and intrinsic risk factors and aetiologies are implicated in the development and malignant transformation of oral lesions [4]. There is a very important need of conceptual model of oral cancer in understanding its various aspects. The concept which are discussed here shows various factors/steps that will individually play a role in cancer formation [9, 10].

Discussion

The conceptual model which is discussed here is divided into two steps, one comprising of determinants (perceptive risks) and other is cellular changes in formation of cancer (**Figure 1**) [11]. It is this perceptive risk which initiates

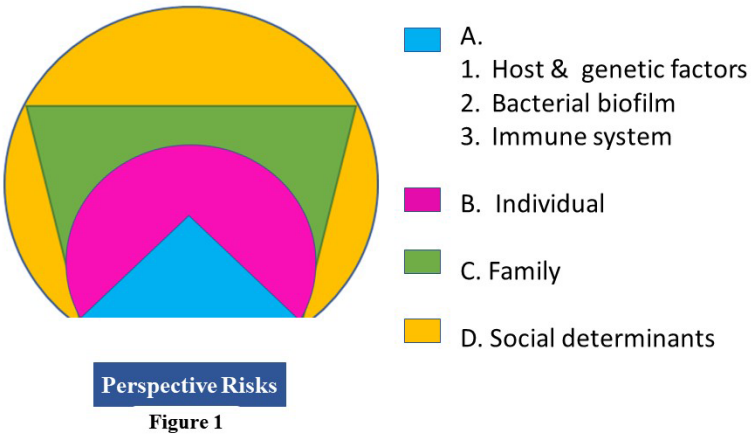

Figure 1. All the 4 factor, A, B, C, & D have equal role in contributing to the perspective risk.

the processes of cellular changes in normal cells which leads to formation of OPMD which leads to formation of oral cancer. It rarely happens that formation of the lesion like OPMD is bypassed and direct conversion of normal cell to cancerous cells are seen. During the processes of conversion from normal cell to cancerous or malignant cells follow pathway and certain processes which will be high lightened. Architectural, cytological and molecular alterations are one which bring changes from normal cells to malignant cells through the stage of OPMD most of the time. The alterations seen with perspective risk are detailed in the article.

The different aspects involved in carcinogenesis are host and genetic factor, immune system, bacterial biofilm to name a few [12, 13]. They form a group which influence major aspects of etiology of oral cancer [14]. Even though these factors play a major role, we cannot deny the effects played by individual, family, environment and social determinants [15]. As an individual, the person will be influenced by various factors like gender, personal habit of smoking, chewing tobacco, alcohol, drug abuse, oral hygiene, stress, along with any other co morbidities [16]. All of them play an equivalent role in bringing tissue changes. Similarly, health of family members, social/cultural relationship, behaviour and health status bear a direct influence on the changes which will be influenced by individual factor too [17]. The role played by each one of them has direct/indirect effect on oral cancer formation. Both of the above factors are also influenced by educational policies, availability health care facilities, health awareness, basic education, public policies, economical background of an individual as well as the society as a whole [14, 17]. Social inequalities may result in stressful situation which will affect the personality of the person. The above said factors may combine or add to the existing factors to make the person vulnerable to cancer.

The perspectives have direct influence on normal cells, the changes seen in normal cells are slow and constant towards potentially malignant disorders. The process of transformation from normal cell to OPMD (oral potential malignant disorder) to Oral cancer is interesting, as it is multimodal/multifactorial (**Figure 2**) [18, 19].

The abnormal cellular changes occurring in normal cell starts with cellular stress leading to immunological changes in the body, which further have an impact on tumour suppression, angiogenesis and metastasis leading to malignant cancerous cell [19].

Certain lesions of oral mucosa are denoted by the term 'Precancerous'/'Potentially' cancerous based on the following findings:

1. Research studies done over a long period of time have shown that, when clinically examined, areas of oral mucosa with alterations which were assessed as being potentially cancerous on initial examination, have undergone malignant transformation on subsequent follow-up.

2. Clinically visible alterations like red and white patches, are seen to co-exist at the margins of oral squamous cell carcinoma.

3. Few percent of these alterations may share cytological and architectural changes that are seen in epithelial malignancies without obvious invasion.

4. Certain genetic and molecular alterations which are evident in frank oral carcinomas are seen in these potentially cancerous lesions.

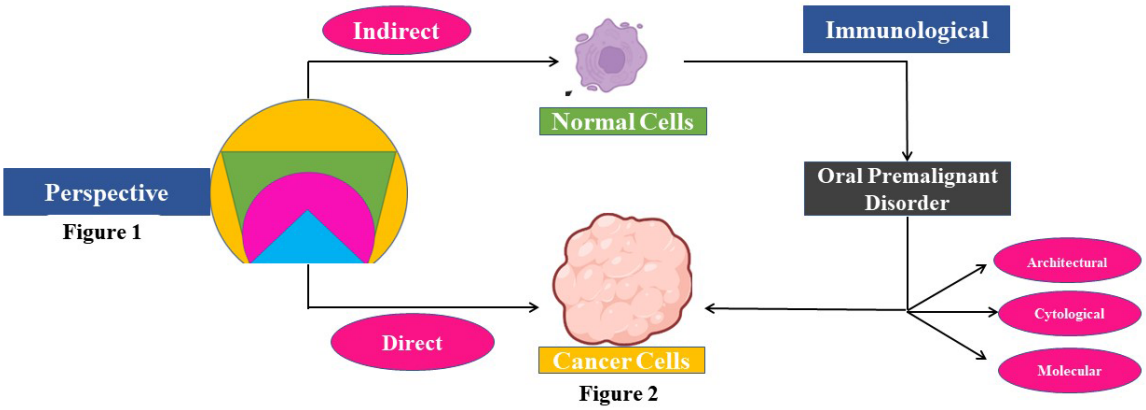

Figure 2. Flow chart depicting the path of transformation of normal cell to OPMD to Oral cancer and the role of perspective risks.

Table 1. Architectural and cytological changes are due to changes at the molecular levels in cells [23]

Architectural Changes	Cytological Changes
Irregular stratification	Abnormal variation in nuclear size
Loss of polarity of basal cells	Abnormal variation in nuclear shape
Bulbous rete ridges	Abnormal variation in cell size
Increased number of mitotic figures	Abnormal variation in cell shape
Abnormally superficial mitoses	Increased nuclear/cytoplasm ratio
Premature keratinization in a single cell	Atypical mitotic figures
Squamous eddies within rete ridges	Increased number and size of nucleoli
Loss of intracellular cohesion	Hyperchromasia

The following are some of the major OPMD seen in clinical practice. Eg: lichen planus, Oral Sub Mucous Fibrosis (OSMF), Erythroplakia, Leukoplakia, Lupus erythematosus, Lichenoid reaction, Carcinoma in situ [19, 20].

The normal cells change to pathological hyperplasia which is a common preneoplastic response to stimulus. Histopathologically, these cells have increased in number. But they resemble normal cells. These cells cease to proliferate if the stimuli are removed. Even then, this pathologic hyperplasia can provide a fertile ground for neoplastic formation [21].

Pathological hyperplasia is followed by three forms of oral epithelial dysplasia, i.e. mild, moderate & severe.

Alterations and mutations in the genetic content of oral epithelium are an integral part of "premalignancy" [22]. Molecular alterations have a crucial role in transformation of OPMD into cancer (**Table 1**) [23]. These are seen as cytological and architectural changes. Combining the cytological & architectural changes, the diagnosis & grading of oral epithelial dysplasia is done [24, 25].

Cytological Changes include Abnormal variation in nuclear size, Abnormal variation in nuclear shape, Abnormal variation in cell size, Abnormal variation in cell shape, Increased nuclear/cytoplasm ratio, Atypical mitotic figures, Increased number and size of nucleoli, Hyperchromatism.

Architectural changes represent the organizational changes seen in the epithelium. They show the changes seen in each cell to its surrounding cells [26]. Each of these changes, put together contribute in the process of carcinogenesis. Loss of polarity is one of the important steps in transformation of normal cells to abnormality leading towards carcinogenesis. Loss of polarity prevents the cells from interpreting the clues from their surroundings which are essential in controlling apoptosis, cellular metabolism, Loss of polarity proliferation [27]. Loss of cohesion is due to the breakdown of

Table 2. Epithelial and stromal alterations seen in the process of transformation from normal to OPMD to oral cancer [30-39]

Epithelial alterations	Stromal alteration	Changes at cellular level
• Tumour promoting genetic mutations • Epigenetic changes • Chromosomal instability • Loss of heterozygosity • Mitochondrial DNA alterations • DNA methylation	• Epigenetic changes • Mitochondrial DNA alterations • Tissue atrophy • Stromal senescence • CAF activation • Chronic inflammation	• Genetic and epigenetic clonal instability, alterations and evolutions • Aging/environmental insults • Hypoxia • Angiogenesis • Dysregulated metabolism • Alterations in Cell cycle, proliferation & apoptosis • Alterations in Signalling pathways • DNA damage • Stem cells

junctional complex either directly or indirectly [28]. Increased proliferation of basal and suprabasal cells in comparison of other cells leads to bulbous reteridges. Increases mitosis is due to dysregulation of cell cycle. Abnormal mitosis is due to failure of the apoptosis in-spite of abnormal cell division. Premature keratinization in a cell indicates rapid cell division in that particular cell which is abnormal and not in line with the cell division of adjacent cells.

This is followed by carcinoma-in-situ where in the whole thickness of epithelium shows architectural and cytological changes. Statistically, a high percentage of PMDs', severe grade of oral epithelial dysplasia and carcinoma-n-situ show progression to carcinoma which may lead to metastasis [29].

Carcinogenesis results from progressive accumulation of key molecular changes in specific sequence until the threshold is reached which results in triggering of the carcinogenesis process (**Table 2**). The factors in **Table 2** influence the cells and the changes are constant and slow leading to OPMD [30-39]. At the cellular level these changes are seen from normal cells to OPMD. Dysplasia shows clones of cells showing genetic and epigenetic changes which stabilises for a questionable duration after which there is sudden transformation leading to progress towards cancer [40].

Loss of heterozygosity, aneuploidy, changes in microRNA expression, epigenetic and genetic modifications [23] and a host of other changes contribute to carcinogenesis.

Changes in the p & q arm of chromosomes 3, 4, 8, 9, 11, 13, 17 are said to be responsible for the genetic progression from normal cells to carcinoma [41]. These involve complex multistep process which are both qualitative and quantitative. Activation & overexpression of TGF alpha & EGFR and inactivation of APC, P53 mutation of K-RAS, over expression of Myc, down regulation of E cadherin, bcl-2 are few which are involved in the progression of normal cells in the oral cavity to hyperplasia, dysplasia, carcinoma & metastasis [42-50].

The phase of normal cell transforming to OPMD is due to dysplastic changes, as mentioned earlier. The transformation of OPMD to cancer is influenced by cellular changes and molecular or genetic alterations.

Following are the cellular changes seen during the processes:

1. Cellular stress leading to changes in innate immunity.

2. Changes in innate immunity leading to inflammatory response. It activated T cells and macrophages leading to increase in cytokines, IL-6, TNF, IF α and increase in growth factor leading to tumour proliferation and tumour suppression

3. Tumour suppression, loss of apoptosis and lysis of cell

4. Tumour proliferation, cellular proliferation, angiogenesis, metastasis

5. Increase in aromatic hydrocarbon due to inflammatory response which binds to DNA leading to DNA adduct which will have miscoding of DNA.

6. Mutation of p^{53}, RAS, leading to loss or changes in normal growth pattern, causing of oral cancer.

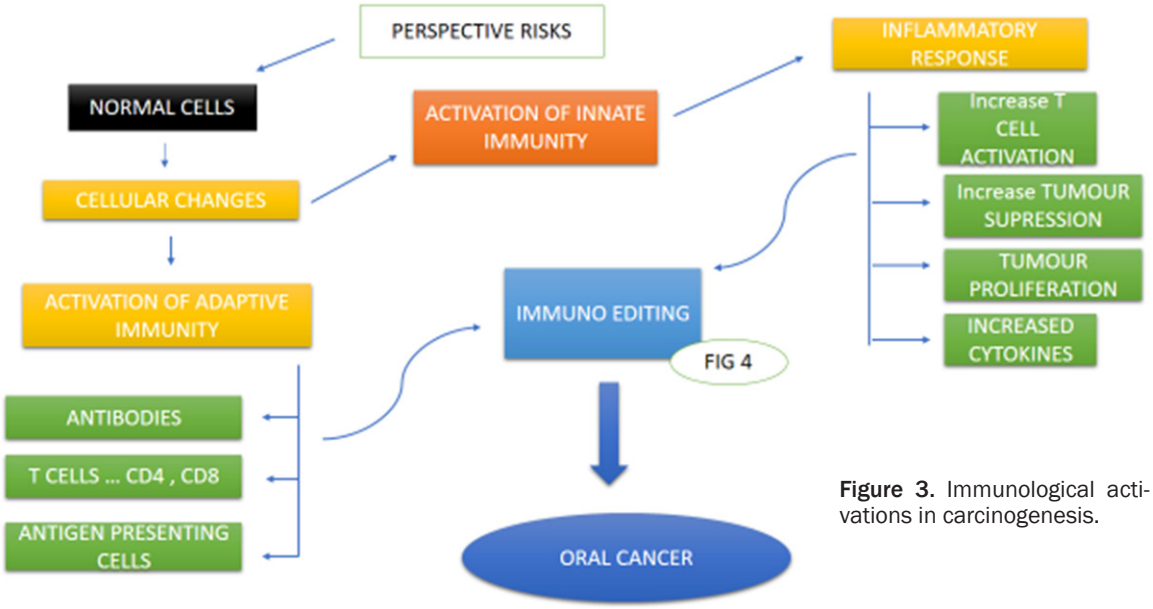

Figure 3. Immunological activations in carcinogenesis.

The progression from pathological hyperplasia to dysplasia and subsequent progression to squamous cell carcinoma echo the genetic alteration and aberrations that occur during carcinogenesis. This involves interruptions of various regulatory mechanisms that govern the cellular functions of the body [37, 39].

The role of immune system in the initiation and progression of oral cancer is undeniable. The presence of inflammatory immune cells in human tumors raises a fundamental oncology concern. Cancer cells adopt diverse methods that imitate peripheral immune tolerance to resist tumoricidal action as the tumor progresses from neoplastic tissue to clinically detectable tumors.

At various stages of tumorigenesis, cancer-associated inflammation contributes to genomic instability, induction of cancer cell proliferation, epigenetic modification, enhancement of cancer anti-apoptotic pathways, stimulation of angiogenesis, and, ultimately, cancer dissemination [51]. Inflammatory immune cells have recently been discovered to be significantly involved in cancer-related inflammation, according to many researches. Understanding how immune cells influence tumour fate at various stages of disease: early neoplastic transformation, clinically detected tumours, metastatic dissemination, and therapeutic intervention have been the focus of these researches. Tumor-associated inflammation is crucial to our current knowledge of cancer progression, and it is this inflammation that is recognised as a hallmark of cancer (**Figure 1**). Microbial infections, autoimmunity, and immunological dysregulation are all possible underlying causes. Elimination, equilibrium, and escape are the three fundamental steps of this multidimensional system, which contribute to cancer elimination, dormancy, and progression respectively. Surprisingly, capacity of cancer to evade or escape the immune response is now acknowledged as one of the most prominent cancer characteristics, providing the basic foundation.

Whether inflammation is a cause or a result, the tumor microenvironment (TME) is harmed, causing an immune inflammatory response, and histopathological investigations show that innate and adaptive immune cells are present in most human tumors, which are characterized as cancer progression features.

Innate immunity and cancer

Several components of innate immunity are activated during cancer pathogenesis in order to reduce cancer-mediated inflammation (**Figure 3**). Adaptive immune responses are also triggered as a result of this process, allowing more specialized immune systems to target the tumor. Changes in cancer cells will be correlated with changes in complementary surface protein, putting cancer cells at risk of complement-mediated death. While complement acti-

vation promotes processes that aid in cancer cell eradication, the presence of soluble and membrane-bound complement regulatory proteins (CRPs) that block various stages in the many complement signalling pathways protects cancer cells from complement-mediated damage. Cell surface marker MHC-1 is a protein whose expression is changed or diminished in cancer. NK cells will be activated if MHC levels are reduced. Tumor necrosis factor alpha (TNF-α)-dependent cytoplasmic granule release is one way by which NK-induced programmed cell death (apoptosis) might occur [52].

Neutrophils, which have been more commonly known to promote cancer progression, are another method by which innate immunity contributes to cancer pathogenesis. Proteases found in neutrophil granules, such as neutrophil elastase, aids in cancer cell proliferation.

Proteases found in neutrophil granules, such as neutrophil elastase, promote cancer cell proliferation. Other proteases found in neutrophil granules aid in the cleavage of extracellular matrix proteins, allowing cancer to invade and spread. These neutrophils also have phagolysosomes, which contain enzymes such as NADPH oxidase, which oxidizes superoxide radicals and other reactive oxygen species (ROS). DNA damage and cell death will occur as a result of the ROS and superoxide.

Innate immunity is crucial in controlling cancer pathogenesis, but adaptive immunity is just as important in cancer biology. Adaptive immunity's effector actions result in tumour elimination or multiplication, depending on the environmental signals.

Adaptive immunity and cancer

Adaptive immunity, like innate immunity, is made up of various components that may either eliminate or promote the proliferation of cancer cells. By using the effector activities of antibodies, T cells, B cells, and antigen-presenting cells, this type of immune response is capable of targeting antigens unique to cancer cells. The core postulate behind the cancer immunity idea is that neoantigens, such as novel antigens generated as a result of tumorigenesis/oncogenesis, are phagocytized by antigen-presenting cells (APCs) or pinocytosed by dendritic cells for antigen processing. Exogenous peptides of tumour antigens are presented by MHC class II molecules, whereas endogenous peptides derived from cancer antigens are presented by MHC class I molecules. MHC class II and MHC class I molecules on the APC then deliver the processed tumor-associated antigens to the antigen-specific T cell receptor on CD4+ T cells or CD8+ T cells, respectively. MHC class II on APC activates CD4+ T cells, priming them for further antigenic peptide/MHC class II complex exposures, resulting in the formation of memory T cells [39, 46]. When T cells are stimulated, they create IL-2, which increases T cell proliferation. B cells operate on APCs, causing T cells to become activated, resulting in CD4T CELL activation (HELPER T CELLS). T cell anergy and immunological tolerance to cancer cell associated antigens occur from a lack of an effective costimulatory signal; adaptive immunity is shut off and cancer advances in this setting. The basic premise for immune surveillance and cancer immunoediting is the function of these innate and adaptive immune responses in oncogenesis [53].

Immunoediting

The cancer immunoediting process is divided into three stages: elimination, equilibrium, and escape. The immune cells' effector function in the elimination phase is to target and eliminate cancer. In the equilibrium phase, the immune system achieves a balance between cancer development and cancer elimination. If the cancer is left untreated, it will eventually overpower the immune system and spread to other organs (**Figure 4**).

Immunotherapy outcomes in all patients, particularly those with immunologically "cool" malignancies, could be improved by rational immuno-oncology combination methods that control these pathways and activate both innate and adaptive immunity.

Conclusion

The perspective conceptual model on oral cancer genesis is a journey with various aspects involved. It starts with various etiological factors involved which is the first part of the concept. Formation OPMD is slow and constant. Rapid changes seen in normal cell leads to direct presentation of oral cancer. It has to be

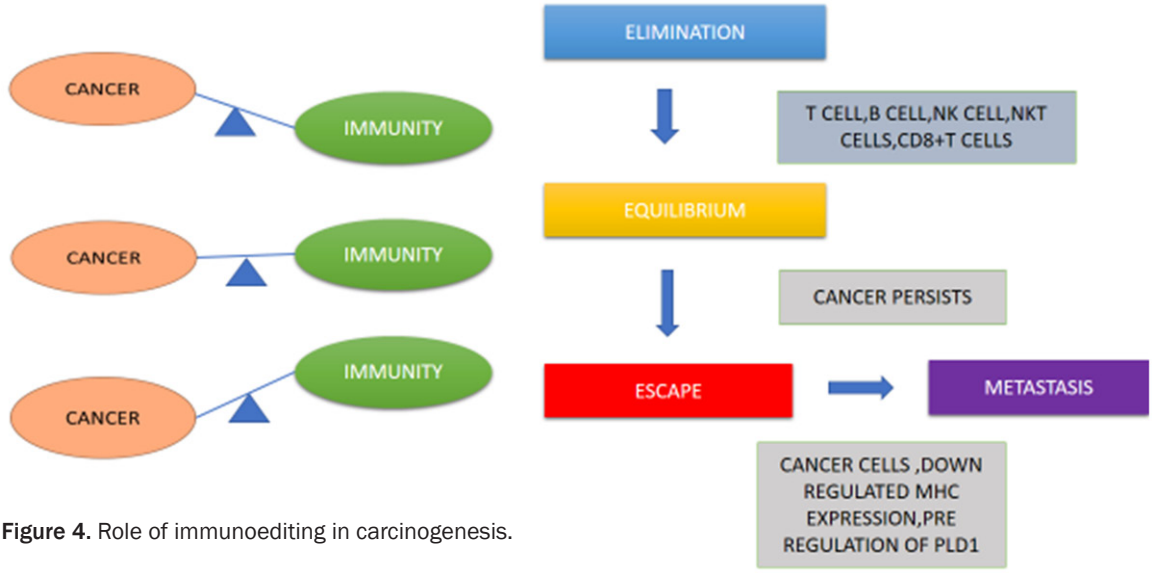

Figure 4. Role of immunoediting in carcinogenesis.

noted that all the factors are not essential for transformation and individual factor at various level will influence other factors. OPMD forms the INTERMIDIATE STAGE in oral cancer formation. OPMD can lead to cancer in due time under appropriate influences. Sometimes, the normal cell, due to constant insult directly transform into oral cancer. The conceptual model here, tries to bridge the various levels of influences in cancer formation from etiological factor to formation of OPMD and cancer formation.

Disclosure of conflict of interest

None.

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