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Review

Genetic etiology of oral cancer

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ABSTRACT

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. It accounts for 2.5% of all new cancer cases and 1.9% of all cancer deaths annually. More than 90% of oral cancers (occurring in the mouth, lip, and tongue) are oral squamous cell carcinoma. The incidence rate of oral cancer varies widely throughout the world, with an evident prevalence in South Asian countries. This high incidence occurs in correlation with oral cancer-associated behaviors such as alcohol, tobacco use. Researchers have reported that these behaviors lead to genetic variations in tumor suppressor genes (*APC*, *p53*), proto-oncogenes (*Myc*), oncogene (*Ras*) and genes controlling normal cellular processes (*EIF3E*, *GSTM1*). Processes such as segregation of chromosomes, genomic copy number, loss of heterozygosity, telomere stabilities, regulations of cell-cycle checkpoints, DNA damage repairs and defects in notch signaling pathways are involved in causing oral cancer. In order to develop preventive and therapeutic options, it is necessary to comprehend the basic molecular mechanisms forcing oral tumorigenesis. This review examines, in detail, the mechanisms of genetic alteration which are considered to be responsible for the initiation of oral cancer.

Introduction

Carcinogenesis is an intricate multi-step process initiated by abnormal oncogenic signals in different signaling pathways [1]. Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide and characterized by a biologically highly diverse group of tumors [2]. HNSCC is the most common malignancy with an estimated 274,289 new cases and 127,459 deaths globally in 2002 and has approximately 2.5% of all new cases of cancers and 1.9% of all cancers deaths rates yearly [3]. In 2009, HNSCC was reported as the eighth most common cancer, with 650,000 new cases being reported each year worldwide [4] and its incidence is higher in Melanesian and South Asian countries [5]. More than 90% of HNSCCs occur in the mucosal surfaces, oropharynx and larynx [6] and oral squamous cell carcinoma (OSCC) accounts for more than 90% of oral cancers [7]. Oral cancer, which occur in the mouth, lip and tongue, causes significant morbidity and mortality [8], especially in low socioeconomic status groups [9]. Oral cancer is the cause of two third of all cancers related deaths in the developing world out of which one third happens in Indian subcontinent [10].

Head and Neck cancer affects more males than females and it is known to affect approximately 21% males and 11% females in Karachi, Pakistan [11]. Two thirds of all oral cancer cases are diagnosed only after being advanced locally [6]. Incidence rates of oral cancer vary widely throughout the world because of adapting oral cancer-associated behaviors including alcohol consumption, tobacco smoking, betel quid chewing [12–14] and using smokeless tobacco [15]. Oral smokeless tobacco in moist form, naswar, is available in Afghanistan, Iran, Pakistan and South Africa. It is used by placing or putting a pinch of the substance below the tongue, lips or in the cheek and then sucked [16]. It contains nicotine, nitrosamines and other noncombustible carcinogens [17]. In South Asia, more than 250 million people use smokeless tobacco [18]. Smokeless tobacco is the main risk factor related to high prevalence of oral cancer in these regions. It is estimated that South Asia makes up over 90% of the global smokeless tobacco use burden [15].

Oral cancer is highly prevalent in India, Pakistan, Brazil, France, Afghanistan, Bangladesh, Sri Lanka, Bhutan, Nepal, Iran and Maldives, ranking first or second with respect to different types of cancer occurrence in these countries [15,19]. Oral cancer occurrence is high in developing countries and is the most common cancer in India [20]. Pakistan holds the 10th position in the worldwide ranking of oral cancer [21]. In Pakistan, occurrence of null genotypes of

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GSTM1 and/or *GSTT1* along with variant alleles of *CYP1A1* might be the risk alleles for oral cancer susceptibility in Pashtun population addicted to tobacco, especially naswar [22]. Similarly, 28 and 33% mutations in H- and K-ras genes were observed in oral tumor specimens of Eastern Indians [23]. Two thirds of the global incidence of oral cancers are reported in low and middle income countries, with half of those cases in South Asia. One fifth of all oral cancer cases and one fourth of all oral cancer deaths occur in India [24]. This ethnic bias is due to the aforementioned prevalence of tobacco use in South Asian countries. However, an additional 10% of the oral cancers in South Asian countries have been linked to preexisting cases of leukoplakia and erythroplakia; in contrast, tobacco (either in the form of smoking or chewing) and alcohol consumption are regarded as the main risk factors of oral cancers in Western countries [25,26]. Oral erythroplakia and leukoplakia have high rate of malignant transformation and are believed to be the most common oral mucosal diseases [27]. Apart from tobacco and alcohol consumption, the occurrence of HNSCC also varies from developing countries to the Western world due to other various factors like age, site of disease, etiology and molecular biology [28]. Tobacco quid chewing increases the risk of oral cancers by six fold [29]. Oral cancer has been observed as a multifactorial disease in which environmental, genetic [5] and epigenetics factors [30] are involved in its etiology. The human papillomavirus (HPV) infection is also considered as a factor involved in oropharyngeal cancer [31]. It is suggested that *p53* polymorphism (Arg72Pro) increases susceptibility of oral cancer in the presence of HPV infection [32]. The external carcinogenic factors cause cancer by inducing DNA damage [33] and inactivating the tumor suppressor genes (TSGs) [34]. Genetic changes arise in oral cancer either by dominant or recessive changes. In dominant changes, mostly proto-oncogenes and certain TSGs while in recessive changes, growth-inhibitory pathway genes or common TSGs are affected by gain and loss of function, respectively [1]. A specific type of variation in genes controlling DNA repair, immortalization, apoptosis, proliferation, invasion, growth factor receptors, transcription factors, angiogenesis, signal transducers manifest the difference between cancerous and normal epithelium cells of the upper aerodigestive tract [2]. These variations in genes are caused by different types of abnormalities in normal genetic processes [35]. In addition to genetics, epigenetic alterations such as DNA methylation, histone modifications and RNA mediated silencing (miRNA) of genes have also been reported to be involved in oral cancer [36].

In order to develop preventive and therapeutic options, it is necessary to comprehend the basic molecular mechanisms forcing oral tumorigenesis. Therefore, this review explains the mechanisms of genetic alteration which are considered to be responsible for initiation of oral cancer.

Symptoms

Oral symptoms such as mucositis, dry mouth (xerostomia) and dysphagia generally appear during and after cancer treatments [37]. Mucositis is a pharyngeal esophago-gastrointestinal inflammation with physiological changes such as red, burn-like sores or ulcerations in the mouth and occurs in more than 40% of the patients who are under chemotherapy or irradiation [38]. The most commonly known symptom in oral cancer patients is xerostomia, in which there is reduction in salivary gland flow resulting in oral fungal infection, swallowing problems, and altered taste [39,40].

Genetics

Genetic alterations are carcinogenic and considered to be good candidates for the therapeutic interventions of cancer [41]. The occurrence of genetic alterations in oral carcinogenesis is currently being discovered [42]. The understanding of the genetic origin of oral cancer has grown significantly as it is accepted extensively that solid tumors are genetically not stable. It is mostly known that accumulation of genetic variations in proto-oncogenes and TSGs led to OSCC through a several-step process [43]. Identifying the genetic factors involved in oral carcinogenesis will provide basis for understanding and potential for preventing the spread of oral cancers worldwide [44]. In 2006, the Cancer Genome Atlas (TCGA) project started with the collection of more than 10,000 samples from 20 different types of tumors. Multiple high-throughput techniques were applied to investigate genomic variations which led to the development of two important observations: (1) tumors with the same origin vary considerably with respect to their genomic variations and (2) similar patterns of genomic variations are shown by tumors with different origins [45]. These types of findings make cancer treatment challenging. Thus, the researcher traces genetic instability or changes in numbers and structure of chromosomes by considering them an important feature of oncogenesis. Genetic instability is acquired in tumor cells due to defects in segregation of chromosomes [46], copy number alterations [5], loss of heterozygosity [47], telomere stabilities, regulation of cell-cycle checkpoints and DNA damage repairs [35].

Chromosome segregation

Chromosomal instability (CIN) is a characteristic of cancer cells with defects in segregations of chromosomes causing altered chromosome numbers in cells [46]. Solid tumors show mal-oriented attachment of chromosome to microtubule causing defects in chromosome segregation and aneuploidy. This mal-orientation is corrected by two microtubule-depolymerizing kinesin, Kif2b and MCAK, which stimulate microtubule dynamics at kinetochores and restore the stability of chromosomes in cells [48]. The association of CIN has been determined in lung cancer, malignant astrocytic tumor, and lymphoma. Chromosomes 3, 10, 11, and 17 frequently show tetrasomy and trisomy, but most commonly disomy in lung cancers [49]. In malignant astrocytic tumor DNA, aneuploidy revealed underlying CIN [50]; an increased risk of death of lymphoma patients are related to 17p13.1 and 11q22 chromosomal abnormalities [51]. The most sensitive, efficient, and promising method, a cytogenetic technique called fluorescence in situ hybridization (FISH), uses fluorescent DNA probes to localize chromosomal positions with highly complementary sequences with the help of fluorescent microscopes [52]. FISH was used to analyze fine-needle aspiration (FNA) biopsy specimens for the evaluation of CIN in OSCCs. This method confirmed that CIN score could be beneficial in predicting reappearance and poor prognosis in patients with OSCCs. CIN in chromosomes 7, 9 and 11 was shown by 11.7% patients with OSCC and is directly linked with reduced disease-free survival [53].

In 2016, chromosomal instability caused by chromosomal segregation defects (CSDs) was determined in OSCC cell lines such as cancer stem cells (CSCs), CSCs (SOX2+) and non-CSCs (SOX2−). CSDs were found to be higher in non-CSCs (SOX2−) in comparison to CSCs (SOX2+). Similarly, CSDs were also higher in symmetrical CSC (SOX2+) when compared to asymmetrical CSC (SOX2+/SOX2−) mitotic pairs. These findings suggest that chromosomal instability caused by CSDs can resist the treatment of CSCs in OSCC [54].

On investigating anaphase bridges, chromosomes lagging in metaphase and anaphase, multipolar spindle formation in metaphase in cell lines of OSCC, it was concluded that these cells have inherited ability to move toward segregation defects [55]. In 2000, CSDs were investigated in cultured OSCC through the combination of immunohistochemistry with cytogenetic analysis where