SHORT COMMUNICATION

Indigenous Causes of Human Papilloma Virus Negative Non-habit-associated Oral Squamous Cell Carcinoma: Perspectives and Prospects

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Oral squamous cell carcinoma (OSCC) is predominantly a habit-associated neoplasm caused mainly by tobacco and alcohol consumption habits. Other exogenous etiological factors such as poor oral hygiene, chronic irritation, candidiasis, and human papilloma virus (HPV) have also been involved in the pathogenesis of OSCC. Nonetheless, non-habit-associated oral squamous cell carcinoma (NHA-OSCC) is growing in incidence.[1] The NHA-OSCC population currently represents about 13–35% of the OSCC population.[2] NHA-OSCC has mostly been described in the literature as possibly associated with HPV. This is especially true with the oropharyngeal NHA-OSCC.[3] However, the nature of HPV negative NHA-OSCC has not been discussed widely in the literature and they represent true non-habit-associated neoplasms. The present paper makes an attempt to discuss the perspectives and various prospects associated with indigenous causative factors associated with HPV negative NHA-OSCC.

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Random (R) Mutations

Apart from the environmental and hereditary mutations, random (R) mutations have been proposed to be associated with the carcinogenesis process.[4] Some tissues are more prone to develop this process than the others. Researchers have suggested that most of the carcinogenesis process is because of 'bad luck' which is, R mutations occurring in normal, non-cancerous stem cells during replication of DNA.[4] When a stem cell is compelled to proliferate (particularly during development), there is always a possibility of a 'DNA replication mistake.' This initiating step in the adult stem cell likely halts the stem cell's final differentiation, allowing it to accumulate more mutations. Such stochastic effects which are associated with number of stem cell divisions are now being considered in many studies as a major cause of cancer development.[4]

These mutations occur throughout the natural DNA replication of cell division and associated with the quantum effects based on base pairing, polymerase mistakes, hydrolytic deamination of bases, and endogenous reactive species.[5] There can be a small insertion, deletion, or transition leading to carcinogenesis.[6] Due to random nature of such mutations, they are regarded as unpredictable and uncontrollable. Recent studies have identified R mutations as a crucial driving force for malignant transformation of a normal cell.[7] It is observed that R mutations are responsible for 66% of cancer mutations in contrast to the environmental (29%) and hereditary factors (5%).[7] Looking at these evidences, the R mutations can be considered as a cause for NHA-OSCC development.

One of the challenges for the researchers is the identification and interpretation of R mutations in the OSCC. This is mainly because of structurally and compositionally diversified locations in the oral cavity. The oral epithelium at each location possesses variable epithelial turnover rate and thus likely to cause variations in the R mutation rate. This could be one of reasons why certain locations are more common for OSCC development than others. These interesting propositions should be investigated in the future to better understand the NHA-OSCC.

Hereditary Cancer Syndromes

The second indigenous causative factor could be the presence of hereditary cancer syndromes. They are initiated by heritable genetic mutations that encode for the oncogenes and tumor suppressor genes.[8] Some of these syndromes specially associated with development of OSCC are xeroderma pigmentosum, ataxia telangiectasia, Bloom syndrome, Fanconi's anemia, and Li-Fraumeni syndrome.[9] In the recently proposed classification of oral potentially malignant disorders, these syndromes have been considered as potential entities.[10] Although these syndromes are mostly symptomatic in nature, the possibility of OSCC development in asymptomatic/undiagnosed cases is quite conceivable. Such cases could be attributed to the low-grade expression of mutated genes. OSCC development due to such asymptomatic cases could present as NHA-OSCC. In most of the cases, NHA-OSCC patient rarely undergoes genetic testing for the identification of such

mutations. Ruling out any underlying hereditary cancer syndrome in NHA-OSCC will help in better understanding of actual prevalence of true NHA-OSCC.

Depyrimidination and Depurination of DNA, Proofreading, and Mismatch Errors

Various endogenous processes can cause spontaneous depyrimidination and depurination of DNA, proofreading, and mismatch errors during DNA replication.[11] Endogenous mutagens such as 5-methylcytosine (5mC) undergo oxidative deamination at CpG dinucleotides to substitute cytosine (C) with thymine (T) base pairs.[11] Thymine, being a normal base, misses recognition by repair enzymes, thus leading to mutations. So, 5mCpG sites are prone to mutations and become an etiology for human genetic disorders. This transition (CpG to TpG) is also associated with the p53 gene.[11] The loss of normal functions of p53 is a well-established etiology for OSCC.[12] Such cytosine to thymine transitions often occur at CpG dinucleotide in p53, thus, establishing endogenous mutations to be a significant cause of NHA-OSCC.

DNA insults and DNA replication can be governed by the products of metabolism such as oxidative DNA damage due to oxygen-free radicals.[11] A deficiency in the mechanisms which protect cells from genetic accidents may equally be responsible for spontaneous mutations. These deficiencies can be in the form of low levels of anti-oxidants and enzymes, defective DNA excision repair, low levels of nucleophiles, which help in trapping DNA-reactive electrophiles. Defects in enzymes can exist which might lead to the conjugation of nucleophiles with DNA-damaging electrophiles.[11] Spontaneous mutations can also be provoked by suboptimal levels of substrates that are involved in DNA biomethylation.[13] Thus, genes, governing them, undergoing any polymorphism or germ-line mutation can eventually give rise to NHA-OSCC.

Since the surrounding environment is continuously switching during division, molecules are not evenly assigned to the daughter cell. As cells do not stay in contiguity with the same, remixing of the adjacent areas also accords to stochasticity. Regulatory mechanisms unroll to check the negative effects of molecular noise when the equilibrium is impaired.[14] The majority of gene expression noise emerges from stochasticity in mRNA production as the consequence of arbitrarily binding transcription factors and other transcriptional machinery to the DNA. Gene expression noise has two types: extrinsic and intrinsic noise. Intrinsic factor is regarded as a gene-dependent characteristic as it differs from gene to gene and from cell-to-cell interactions.[15] Various conclusion of isogenic heterogeneity represents phenotypic alteration and cellular differentiation. Few cellular procedures intensify or expand intrinsic noise in some sense, rather than completely supervising or terminating it.[16] Thus, we believe that such molecular noise might be partly contributing to the development of NHA-OSCC.

Epigenetic Alterations

Epigenetic mechanisms control the expression of genes and cellular processes which initiate carcinogenesis. Several modifications like promoter methylation of genes have a contributing factor in malignant transformation.[17] Epigenetic inactivation of tumor suppressor genes is also considered a factor for OSCC aggressiveness. Studies have indicated that epigenetic alterations lead to gene deregulation via hypermethylation, histone modification, and microRNAs.[17] This disturbs various biological functions such as cell cycle disruption, proliferation, apoptosis, migration, invasion, and DNA repair. Cell cycle genes like p14, p15, p16; apoptosis-related genes like DAPK; DNA repair genes like methyltransferase are usually affected by epigenetic alterations.[17] These genes are either silenced or deleted during the process and can be a significant contributing factor for NHA-OSCC.

Hormones

Hormonal imbalance has been involved in the carcinogenesis of many tumors (prostate, breast, and endometrial carcinomas), however, its role in OSCC development is controversial.[18] This could be ascribed to the effect of sex hormones on the mitotic activity as well as direct DNA damage. Regarding sex steroid receptors, ER*α* mRNA is found to be more expressed in the OSCC as compared to control tissues. The exact opposite results were obtained for androgen receptors.[19] High-levels of follicle-stimulating and luteinizing hormones, and prolactin and decreased ratio of testosterone/estradiol in patients with tongue cancer further strengthens the role of the hormones in OSCC.[20] It is quite conceivable to ascribe hormonal imbalance as a causative agent in NHA-OSCC. However, there are no studies on the hormonal status in NHA-OSCC and we recommend future studies on the same.

Therapeutic Potential

The continuous and monotonous association of carcinogens to OSCC has created a lacuna in identifying the other potential underlying factors of OSCC. The modifications and alterations going on at the genetic level have contributed significantly to creating a NHA-OSCC group. Thus, recognizing the different genetic factors is very crucial in developing therapeutic strategies.

Genetic screening for habit and NHA-OSCC should be effectively planned in routine practice. Improved tools combining genetic and epidemiological factors should be set to predict the risk of OSCC development. Such screening approaches need to be designed for identifying and tailoring the carcinogenesis process at an early stage. Personalized treatment for cancer patients should be strategized which will help to find the discrete genetic and epigenetic alterations responsible for carcinogenesis. Based on these genetic and epigenetic modifications, relevant biomarkers should be spotted to develop OSCC diagnostic procedure at an initial stage. Epigenetic changes are the early events at an early stage of OSCC and hence should become the predictive biomarkers. A procedure to quantify methylation, deamination at the genetic level may indicate an individual's response to the therapy.

Conclusion

In conclusion, we have discussed some of the indigenous attributes of carcinogenesis that can be led to the NHA-OSCCs. Despite the significant incidence rate, NHA-OSCC has not been thoroughly investigated in the literature. We recommend that all NHA-OSCCs should be screened for such indigenous causes to better understand the pathogenesis of this unique group. Moreover, there could be a contribution from the aforementioned endogenous factors in habit-associated OSCC and future studies need to take appropriate cognizance of the same.

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