Genomic instability in Oral Cancer: An update and Review
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Abstract
Studies have established that human cancers are principally genetic diseases, that is, they arise as consequence of the accumulation of a set of mutational events that enable a specific clone of tumor cells to develop. The precise number of genetic changes required for the events that remains unresolved in the pathogenesis of cancer range from few to several. This review includes the nature of genomic instability in oral cancer which includes microsatellite instability, chromosomal instability and DNA methylation and how these factors may be the paramount agents for the decision of therapeutic approach in oral cancer.

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Genomic DNA in normal or tumor cells, is continuously encountered by a large variety of agents that damage DNA. To ensure the integrity of the genome and viability of cells, the DNA lesions that are formed as a result of this damage are normally repaired. This is done by an elaborate network of genome surveillance mechanisms and DNA repair pathways. These pathways include non-homologous end joining (NHEJ), homologous recombination (HR), base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and translation synthesis. Briefly, the NHEJ pathway rapidly repairs double-strand breaks (DSBs).(4) The HR pathway is also involved in the repair of DSBs, but in addition processes inter strand crosslinks and other DNA lesions that disrupt the DNA replication fork. The BER pathway utilizes DNA glycosylases to remove modified or incorrect bases and NER eliminates a wide variety of DNA lesions, including UV-induced photoproducts and chemical adducts.(5) MMR is involved in the repair of DNA lesions such as base–base or insertion/deletion mismatches that occur during DNA replication or upon DNA damage.(6) Finally, TLS is an error-prone repair pathway that uses low-fidelity polymerases to bypass modified bases that stall replication fork. Besides all these mechanisms, genomic integrity is also maintained by the cellular machinery that controls chromosome segregation prior to cell division. This process ensures that the correct complement of chromosomes is passed from parental to daughter cells. When these pathways fail, for example when genes that control DNA repair are themselves mutated the level of genomic instability rises. This instability may take the form of DNA changes that are only apparent at the nucleotide level or those changes that are characterized as gross chromosomal rearrangements, where whole chromosomes or fractions of chromosomes are either lost or gained. Given that both of these types of changes modify the function of the genome, they likely foster tumor genesis by allowing tumor cells to acquire new characteristics associated with growth and metastasis.(7, 8) the three types of genetic instability in oral cancer, a) Microsatellite instability, b) Chromosomal instability and c) DNA Methylation.

Genetic instability is a determinant of propensity to single and multiple malignancies. Two of the most common and well characterized forms of this instability are microsatellite instability (MSI) and chromosome instability (CIN). (9) Microsatellite instability is characterized by changes in short DNA repeat sequences. Microsatellite occur in normal DNA and consist of short tandem repeated sequences that are found to be scattered throughout the genome. MSI is characterized by an abnormal shortening or lengthening of these repeat sequences and is observed in all solid tumors including colorectal,
endometrial and ovarian cancers. Field et al investigated that MSI is a detectable phenomenon in HNSCC.(10) They analyzed genomic instability on ten chromosomes using 34 microsatellite markers, and 25 of the SCCHN were examined with at least ten microsatellite markers. In this study they have not considered one microsatellite alteration to be diagnostic of MI, because it may be argued that some of the alterations observed in these highly unstable sequences could be simply due to their high background mutation rates.(11) Thus, the clinical correlations were based on microsatellite instability being observed in two or more markers and 28% (7/25) of the SCCHN were found to fall into this group. The results indicated that this genotype alteration is most likely an important mechanism in the development of SCCHN. No correlation was found between MI and previously untreated and previously treated tumors, histological differentiation, positive nodes at pathology, TNM staging or survival. An association was found between high incidence of MI and the early stage (T1NO) of this disease; however the results were not statistically significant.(11) But significant retrospective studies have been done which has suggested that MSI phenotype as a molecular marker can provide valuable prognostic and predictive information.(12)

Chromosomal instability (CIN) phenotype is characterized by gross chromosomal abnormalities, such as aneuploidy and loss of heterozygosity (LOH). CIN is the most prevalent form of genomic instability. Constitutional chromosomal instability can result in a variety of syndromes which are characterized by growth abnormalities, haematopoietic defects, mutagen sensitivity and also cancer predisposition. These syndromes include ataxia–telangiectasia, Nijmegen breakage syndrome, Bloom's syndrome and Fanconi anaemia.(5) The CIN phenotype has also been associated with a poorer prognosis in many cancers. CIN is thought to promote tumorigenesis through the accumulation of mutations in tumor suppressor genes and oncogenes. A prerequisite for the induction of CIN is partial inactivation of the normal DNA damage response, along with mitotic checkpoint functions. Mutations in genes encoding mitotic checkpoint proteins have been suggested as the cause of a CIN phenotype in a subset of various head and neck squamous cell carcinomas. Additionally, abnormal centrosome number and function via amplification of the centrosome-associated serine threonine kinase Aurora kinase A has been implicated as a mechanism for CIN.(5) Studies in colorectal cancer cells have suggested that this neoplasm arises primarily from defective kinetochore–spindle attachments that evade detection by the spindle checkpoint and persist into anaphase. Whether the CIN phenotype occurs as a consequence of other events, or whether abnormalities in CIN pathways drive the development of CIN, has been widely debated. First, CIN may occur as a consequence of an unstable tumor genome, driven by mutations in critical oncogenes and tumour suppressors. Alternatively, CIN may result from the clonal selection of a chance abnormal chromosomal missegregation event, which in turn drives further aneuploidy. Finally, CIN may result from mutations in chromosomal stability genes.(9, 13)

Besides CIN and MI, changes in DNA methylation can greatly influence genetic instability. Hypermethylation of gene promoter islands can alter expression of genes required for maintaining chromosomal stability or minimizing mutagenesis. Recent studies have demonstrated that microRNAs (miRNAs), which are small, noncoding RNAs, play important roles in carcinogenesis with oncogene or tumor suppressor gene activity. In addition, we have learned that some miRNAs are aberrantly methylated and silenced, causing tumorigenesis. Chronic inflammation alters DNA methylation and expression of cancer-associated genes in OSCC. This was established in an in vitro model of interleukin (IL)-6 mediating chronic inflammation in OSCC cell lines. The authors here measured the ability of IL-6 to induce global hypermethylation of long interspersed nuclear element-1 (LINE-1) sequences, as well as CpG methylation changes. The results indicated that IL-6-induced inflammation promotes tumorigenesis in the oral cavity by altering global LINE-1 hypomethylation. In addition, concurrent hypermethylation of multiple tumor suppressor genes by IL-6 suggests that epigenetic gene silencing may be an important consequence of chronic inflammation in the oral cavity.(14)

A central challenge to improve efficacy is to target specific therapies to genetically distinct tumor types. The potential of molecularly directed therapy, based on targeting the underlying genetic defects, is that it may cause highly selective killing of tumor cells while sparing normal cells, resulting in both increased efficacy and reduced toxicity. Synthetic lethality has been proposed as a means of doing this, by identifying genes whose losses are selectively lethal with loss-of-function mutations in cancer susceptibility genes, such as those involved in genomic stability.(6)

A critical link is thus proved to exist between DNA mutation and chromosomal rearrangements.
which suggest that genomic instability and cancer development are closely associated. This genomic instability can manifest itself at all the levels whether small changes at the nucleotide level or as gross chromosomal alterations. The reason for studying the genomic instabilities is to classify the tumors not only by tumor site but also by the type of genetic instability. Targeting the tumors based on the underlying genetic defect may not only allow the identification of novel therapeutics to be used for the wide range of tumors but also in optimizing the existing treatment regimens.

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