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SPECIAL MOLECULAR REVIEW ARTICLE

Chromosomal instability in oral squamous cell carcinoma

Vasileios S. Papanikolaou[1], Efthymios Kyrodimos[1], Evangelos Tsiambas[2], Evangelos Giotakis[1], Amanta Psyrri[3], Vasileios Ragos[4], Aristeidis Chrysovergis[1]

[1]1st ENT Dept, Hippocration Hospital, University of Athens, Athens, Greece; [2]Dept of Pathology-Cytology, 401 GAH, Athens, Greece; [3]Oncology Unit, 2nd Dept of Internal Medicine, Propaideutic, Attikon University Hospital, National and Kapodistrian University of Athens, Greece; [4]Dept of Maxillofacial Surgery, Dept of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

Summary

Oral squamous cell carcinoma (OSCC) demonstrates an increasing rate due to high risk Human Papilloma Virus (HR-HPV) persistent infection, and also to chronic cigarette and alcohol consumption. Gross chromosomal alterations (polysomy, aneuploidy, intra-chromosome rearrangements) and specific gene aberrations such as amplifications, deletions, point mutations combined or not with epigenetic ones (promoter methylations and miRNA deregulations) are responsible for the progressive transformation of normal squamous cell epithelia to the corresponding malignant. Chromosomal instability (CI) -based on structural or numerical abnormalities- leads to specific abnormal karyotypes combined or not with functional suppressor gene inactivation and oncogene overactivation in solid malignancies, including OSCC. Extensive cytogenetic analyses have shown that gross alterations (gains/losses) in chromosomes 3, 4, 7, 8, 9, 11, 14, 17, 18, 19 and also 20 form different CI patterns in OSCC, which in conjunction with an aggressive phenotype (presence of lymph nodal metastasis) negatively affect the prognosis in the corresponding patients. In the majority of OSCC cases, loss of chromosomal bands are almost equally detected compared with gains regarding the chromosomes referred above. In the current special molecular paper we explored the role of CI in the progression and biological behavior of OSCCs.

Key words: *aneuploidy, carcinoma, chromosome, instability, oral*

Introduction

Cancer genome consists of all genetic alterations that modify the normal DNA/mRNA sequences triggering a cataract of molecular reactions inside and outside the nucleus micro-environment [1] Gross chromosomal and specific gene alterations are genetic aspects that are involved in its rise, progression and metastatic expansion [2]. Concerning solid tumors, a variety of gene functional and numerical imbalances in crucial molecular pathways such as cell cycle regulation, signaling transduction, apoptosis or angiogenesis have been identified and explained [3]. Cell malignant transformation is mediated by an aberrant gene expression, including predominantly oncogenes' upregulation combined with suppressor genes' downregulation that lead to cell cycle deregulation [4]. Point mutations, polymorphisms, abnormal gene copy number (amplification,deletion), or structural chromosomal rearrangements (translocations) and epigenetic modifications detectable by different molecular techniques provide critical information to oncologists for handling those patients in a rational therapeutic way regarding their isolated molecular landscape [5].

CI is referred to gross chromosome aberrations including abnormal numerical alterations

Correspondence to: Evangelos Tsiambas, MD, MSc, PhD. 17 Patriarchou Grigoriou E΄ Street, Ag. Paraskevi, 153 41 Athens, Greece. Fax: +30 210 6526259, E-mail: tsiambasecyto@yahoo.gr
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such as polysomy / aneuploidy (usually 3-5 chromosome copies per nucleus) and monosomy (loss of one chromosome) detectable by karyotyping technique and fluoresence *in situ* hybridization (FISH) analyses. Furthermore, structural changes and rearrangements (i.e. translocations) in specific or vast chromosome regions are identified by applying predominantly polymerase chain reaction (PCR) and FISH, especially comparative genomic hybridization (CGH) [6,7]. In the current paper, we focused on CI in OSCC which categorizes the corresponding patients based on specific molecular patterns.

Mechanisms of carcinogenesis in OSCC

OSCC is characterized by a broad spectrum of genomic imbalances, including gross chromosomal alterations, such as polysomy/aneuploidy and specific gene aberrations. Concerning the development of OCSSC, main factors are chronic tobacco, alcohol and also betel quid consumption combined or not with persistent viral infections, especially HR HPV related [8]. Oncogene amplifications, point mutations and suppressor gene deletions (loss of heterozygosity)/point mutations combined or not with epigenetic changes, including promoter methylations and miRNA deregulations are molecular alterations responsible for the progressive transformation of normal squamous epithelia to malignant ones [9]. Additionally, deregulation of specific genes that induce chromosome segregation or modify cytokinesis is a crucial genetic abnormality affecting the nuclear homeostasis [10]. Centromeric amplification combined with abnormal centriole orientation and multipolar mitotic spindles are serious topographical and structural events that affect normal chromosome functions. All of these genetic events in nucleic microenvironment are responsible for deregulating normal cell genome, by amplifying drastically the signal transduction to the nucleus, desynchronizing the cell cycle, partially the normal apoptotic procedure and in combination with other genetic events lead the cell to a neoplasmatic and finally to a malignant (cancerous) transformation [11].

CI in OSCC

Extensive cytogenetic analyses in OSCC - based on FISH, CGH and also array comparative genomic hybridization (aCGH) implementation - have detected structural and numerical aberrations in many chromosomes affecting the whole cell genome integrity and balance. Modern research pathology provides a fine cancerous tissue substrate such as laser-capture micro-dissection and tissue microarray cores. These histotechniques are focused on pure cancer cell subpopulation resection for molecular analyses providing genetic subclassifications of the corresponding patients [12]. Furthermore, pure OSCC cell lines (cell cultures) have been used for the same reasons. According to a multi-chromosome probes CGH analysis, a variety of gross aberrations in a chromosome spectrum was assessed. Structural abnormalities were detected in chromosomes 3, 4 , 5 ,7, 8, 9, 11, 14, 19 and 20 [13]. 3q, 5p, 7p/q, 8q, 9q, 11q, 14q, 19q, and 20q chromosome segments were found to be multi-copied (gains) combined or not with a specific band amplification (11q13), whereas chromosomal losses were identified at 3p, 4p, 8p, 11q, and l8q regions. Among them, the majority of lost bands harbor suppressor genes, whereas gains are referred most selectively to oncogenes.

Interestingly, chromosome 7 - which was the first fully analyzed metacentric chromosome, representing approximately 5.5% of the total DNA content in cells - demonstrated gains in both of its arms (p & q). Critical genes for signal transduction to the nucleus regulation are located on chromosome 7. Among them, epidermal growth factor receptor (EGFR-gene locus: 7p12, exons: 30), MET protooncogene, receptor tyrosine kinase (c MET-gene locus: 7q31, exons: 24), and also V-raf murine sarcoma viral oncogene homolog B1B-Raf protooncogene, serine/threonine kinase (BRAF- gene locus: 7q34, exons: 22) are frequently deregulated in solid malignancies including lung, colon, head & neck carcinomas [14,15]. Concerning the impact of 7p12 gains (EGFR gene amplification) in OSCC, another study showed that patients characterized by this specific molecular profile are eligible for targeted therapeutic regimens based on monoclonal antibodies [16]. Additionally to the previously referred genetic data regarding the broad spectrum of chromosome imbalances, a study group analyzed tissue with epithelial dysplasia as precursor lesions, OSCC and also their invasive components. They observed that disease progression is provided by accumulating structural and numerical aberrations in specific chromosomes, whereas others demonstrate regional losses [17]. Among them, gains detected in 3q, 5p, 7p, 8q, 11q, 20q and losses in 3p, 8p, 9p and 18q were the most common. They also compared the overall gain and loss status and concluded that losses are less frequent than gains but it appears that they might be the primary clonal events in rising OSCCs. Furthermore, CI in premalignant epithelial lesions like leukoplakia is under investigation due to its critical impact in the progression of disease. A study group analyzed tissue

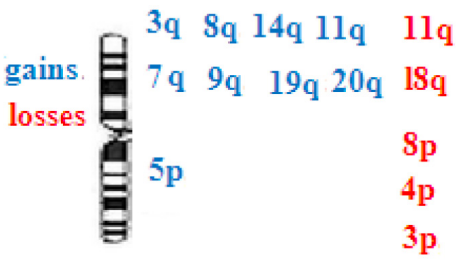

Figure 1. Schematic representation of CI regarding chromosomes 1, 3, 4, 5, 7, 8, 9, 11, 14, 18, 19, 20 in OSCC (p/q: chromosome arms, red: segment losses, blue: segment gains).

sections based on a combination of DNA image cytometry (ICM) and dual target FISH for chromosomes 1 and 7 [18]. The authors concluded that a 9% of the examined cases developed carcinoma *in situ* or OSCC. Based on these molecular data they proposed that CI detection seems a reliable method for risk assessment in oral premalignancies. Similarly, another study analyzed fine-needle aspiration (FNA) biopsied OSCCs using FISH for investigating the CI status and its prognostic significance in them [19]. They observed that severe CI regarding chromosomes 7, 9, and 11 in patients with OSCCs was correlated significantly with reduced disease-free survival and overall survival.

In conclusion, CI is a crucial genetic event in OSCC and also in its precursors as an initial neoplastic substrate. Chromosomes 1, 3, 4, 5, 7, 8, 9, 11, 14, 18, 19, 20 are predominantly implicated in the carcinogenetic process and also in an aggressive malignant phenotype (Figure 1). In conjunction to high or low grade CI, amplifications of specific gene loci such as 11q13(CCND1) that encode cyclin D1 cell cycle protein, are also critical genetic aberrations associated with poor prognosis and recurrence of the malignancy [20].

Conflict of interests

The authors declare no conflict of interests.

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