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SPECIAL MOLECULAR REVIEW ARTICLE

p53 mutations in oral cavity carcinoma

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Summary

Head and neck squamous cell carcinoma (HNSCC) includes a variety of SCCs derived from the anatomic regions of the oral and nasal cavity and also of the pharynx and larynx. Oral cavity SCC (OCSCC) demonstrates an increasing rate due to viral –related (High Risk Human Papilloma Virus-HR HPV) persistent infection, cigarette smoking and alcohol consumption. Gross chromosomal alterations (polysomy, aneuploidy) 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 epithelia to the corresponding malignant. In the majority of OCSCC cases, critical genes, such as p53 are found to be inactivated, leading to an overactivated cell cycle correlated to carcinogenetic process. P53 (gene location: 17p13.1) is a suppressor gene acting as a key regulator of the cell's genomic stability, function and homeostasis. P53 aberrant overexpression is frequently observed in OCSCC tissues as a result of point mutation or deletion. In the current special article we explored the role of the p53 gene deregulation - especially focused on its mutation status - in OCSCCs.

Key words: *carcinoma, gene, mutation, oral, p53*

Introduction

Head and neck squamous cell carcinoma (HNSCC) demonstrates increased rates worldwide [1]. As a sub-category of HNSCC, oral cavity SCC (OCSCC) is characterized by a broad spectrum of genomic imbalances, including gross chromosomal alterations, such as polysomy/aneuploidy and specific gene aberrations. Oncogene amplifications, point mutations and suppressor gene deletions and 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 [2]. Concerning the development of OCSSC, the main factors are chronic tobacco, alcohol and also betel quid consumption combined or not with persistent viral infections, especially High Risk Human Papilloma Virus-HR HPV related [3].

Among genetic aberrations that are involved in rise and progression of OCSCC, p53 gene deregulation seems to be a very important event correlating also with survival and indirectly with response rates to specific chemotherapy regimens [4]. Point mutations and deletions of the gene have

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been identified in a significant series of analyzed OCSSC tissues, interestingly not correlated significantly with smoking status of the patients [5,6]. Additionally, specific p53 codon polymorphisms appear to be involved in HPV-related cases indicating an interaction to OCSCC susceptibility [7]. In the current study we analyzed the crucial role of p53 gene/protein in normal intracellular functions, exploring also its deregulation's impact in oral cavity malignancies.

Introducing the p53 gene and protein

The p53 gene that encodes for the corresponding protein 53-kilodalton (kDa) protein (actually its molecular weight is aprox. 43.7 kDa) is located on chromosome 17 (cytogenetic band: 17p13.1, 11 exons). Concerning p53 protein variations, 15 isoforms have been identified. Crystallographic analysis of the protein has shown that it consists of 7 main domains for molecules binding [8]. Acidic N-terminus transcription-activation domain is responsible for activating transcription factors. The activation domain 2 (AD2) mediates strongly the apoptotic activity. Similarly, rich in proline domain enhances also the apoptotic activity due to MAPK induction. The central DNA-binding core domain (DBD) and the corresponding homo-oligomerization domain (OD) regulate the tetramerization of p53, a crucial biochemical event for its normal function. Finally, the C-terminal end regulates negatively the central DNA binding.

The molecule is classified as a tumor suppressor protein, but based on its multiple roles in cell homeostasis it represents a central genome regulator [9]. P53 nuclear phosphoprotein is implicated in activating DNA repair proteins when double-stranded DNA copies transfer abnormal genetic information. It also arrests cell growth and proliferation by holding the cell cycle at the G1/S regulation point on DNA damage recognition. The protein acts also as a strong apoptosis (programmed cell death) positive regulator, whereas it is involved in senescence response to short telomeres [10]. Interaction of p53 with other molecules includes MDM2 protein, p21(WAF1) which positively regulates cyclin-CDK complexes inhibiting their kinase activity and also RB1 activation based on, due to p14 protein, upregulation. Interestingly, MDM2, a proto-oncogene (12q14.3) encoding a nuclear-localized E3 ubiquitin ligase, acts as a major negative regulator in p53-MDM2 auto-regulatory pathway. MDM2 directly binds to p53 and represses its transcriptional activity promoting p53 proteasomal degradation [11]. Gene amplification is the major mechanism of MDM2 deregulation in many malignancies.

Mechanisms of p53 gene deregulation include mutations and epigenetic changes [12]. Approximately 50% of malignancies demonstrate mutant p53 leading to an aberrant protein overexpression. In fact, insertion/deletion polymorphisms, or simpler base substitutions occur frequently. Another epigenetic mechanism of p53/MDM2 auto-regulatory pathway deregulation is the aberrant alternative splicing of mRNA precursors. This genetic process leads to abnormal protein expression that promotes cell growth, local invasion, and metastasis by enhancing oncogenes and downregulating suppressor genes [13]. Furthermore, the role of post-transcriptional regulators - termed microRNAs - seems to be significant for regulating positively or not the p53/MDM2 depended pathway. In particular, positive feedback loops involving miR-192, miR-34a, and miR-29a have been already identified, especially in HPV-related cases [14].

P53 mutations in oral carcinoma

Extensive genomic analyses have shown that p53 mutations happen frequently in HNSCCs. Missense, stop-gain, splice site, frameshift deletions, and inframe deletions represent different types of p53 mutations that are implicated in the early stages during the carcinogenetic process of the corresponding epithelia. Focused on OSCCs, p53 has been found to be mutated in a high percentage of cases (approximately 70%) [15]. Missense and truncating mutations are associated with malignant cell proliferation, increased invasion, and resistance to chemotherapeutic regimens. All of these histological and biochemical factors contribute to a poor prognosis (decreased drug response rates-short survival span), especially in missense mutations carriers. A study group analyzed a significant number of OSCC tissues and concluded that p53 mutations are linked to reduced survival in these patients. They also suggested that detecting missense mutations and correlating them with specific clinicopathological parameters is an optimal tool for improving the prognostic stratification of OSCC cases [16]. Similarly, another study group applied a whole-exome sequencing of OSCC tissues based on a broad spectrum of genes including p53, FAT1, EPHA2, CDKN2A, NOTCH1, CASP8, HRAS, RASA1, PIK3CA, HUK, and ELAVL1. All of them are mutated in different proportions in this specific malignancy. They concluded that OSCC patients could be categorized in different molecular subgroups with specific genetic signatures [17]. In fact, p53 and CCND1 mutated genes should be interesting targets for implementing therapeutic strategies. There are phase I-III clinical trials especially impli-

cating tongue OSCC with these mutated genes that demonstrate a better prognosis to current targeted therapies. Another critical molecular observation is the combined p53 mutation/receptor tyrosine kinase amplification in these malignancies. A study group applying next-generation sequencing in OSCC tissues showed that p53, CDKN2A, PIK3CA mutations correlated with PIK3CA and AKT1 copy number amplification induced distant metastasis, leading also to significantly poorer prognosis in this group [18]. Concerning the relation between HPV-mediated carcinogenesis and p53 mutations in OSCC, a molecular co-analysis concluded that the combination of HPV-16 infectivity and p53 mutation was significantly related to poor prognosis in the corresponding examined cases [19]. Furthermore, the interaction between p53 specific codon polymorphisms and persistent HR-HPV infection in OSCC susceptibility is under investigation. Molecular analyses have shown that the HPV oncoprotein E6 overactivation may induce degradation of p53 function. Based on this, a study group analyzed p53 Arg72Pro polymorphism and found that it may partly contribute to the pathogenesis of oral cancer development as an increased risk factor [20]. Although the HPV influence in p53 gene mutations remains inconclusive, there is strong genetic evidence that modifies specific molecular pathways that are related with the protein.

In conclusion, chromosome 17 gross structural and numerical aberrations combined with p53 mutations are significant genetic events in the rise, progression and aggressive biological behavior (decreased response rates to chemo-targeted therapeutic regimens, increased metastatic volume, and short survival rates) in OSCC. The role of p53 mutations and specific intragenic polymorphisms is critical in these malignancies, supporting the idea of discriminating the patients on the basis of isolated p53-related genetic signatures.

Conflict of interests

The authors declare no conflict of interests.

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