

## SPECIAL MOLECULAR REVIEW

# mdm2 oncogene in laryngeal squamous cell carcinoma

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## Summary

Laryngeal squamous cell carcinoma (LSCC) demonstrates increasing rates worldwide due to viral-related (High Risk Human Papilloma Virus-HR HPV) persistent infection, cigarette and alcohol consumptions. Gross chromosomal alterations and specific gene aberrations-such as amplifications, deletions, point mutations-combined or not with epigenetic changes are responsible for the progressive transformation of normal squamous epithelia to their malignant phenotype. Among oncogenes that are implicated in the development and progression of LSCC, mouse double minute 2 homolog / murine double minute 2 (*mdm2*) seems to be an interesting marker for the biological behavior of the malignancy.

*Mdm2* is a proto-oncogene (gene locus: 12q14.3), encodes for a nuclear-localized E3 ubiquitin ligase, and acts as a major negative regulator in p53-*mdm2* auto-regulatory pathway. *Mdm2* directly binds to p53 and represses its transcriptional activity and promotes p53 proteasomal degradation. Aberrant *mdm2* overexpression is a frequent observation in breast carcinomas, whereas there are limited data regarding LSCC. In the current molecular review we explored the role and specific aspects of *mdm2* gene in LSCC.

**Key words:** gene, *mdm2*, larynx, carcinoma

## Introduction

Head and neck squamous cell carcinoma (HNSCC) is a super-family of pathological entities demonstrating increased rates worldwide [1]. As a sub-category of HNSCC, laryngeal SCC (LCSSC) 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 and progression of LCSSC, main factors are chronic tobacco and alcohol use 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 the rise and progression of LSCC, mouse double minute 2 homolog/murine double minute 2 (*mdm2*) gene deregulation seems to be an important genetic event affecting the biological behavior of the malignancy in subsets of patients [4].

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Overexpression of the marker has been identified in a significant series of analyzed LCSSC tissues, correlated significantly or not to specific clinico-pathological features of the examined patients [5,6]. Additionally, specific mdm2 polymorphisms and aberrant splicing are associated with susceptibility to LSCC in the corresponding carriers [7]. In the current study we analyzed the role of mdm2 gene/protein in normal intra-cellular functions exploring also its deregulation's impact in LSCCs.

### Introducing the mdm2 gene and protein

Murine double minute 2 (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 and promotes p53 proteasomal degradation. Aberrant p53/mdm2 over expression is a frequent observation in breast carcinomas [8]. Gene amplification is the major mechanism of mdm2 deregulation and overexpression in breast carcinoma correlated with aggressive phenotype [9]. In fact, wild type p53 is influenced by two main inhibitors: mdm2 and mdm4 (also called MDMx). The role of mdm4 is critical because it inhibits the transcriptional activity of p53 enhancing also the ability of mdm2 to target p53 for degradation [10]. Overexpression of these molecules is mediated mainly by gene amplification although there are differences in the frequency of this genetic mechanism among breast carcinomas [11]. Novel agents with a potential anticancer activity, such as violacein, seem to upregulate apoptotic genes, including p53 and markedly reduce mdm2 expression levels [12]. Concerning also mdm2 regulation, nuclear factor of activated T-cells 1 (NFAT1)- interacting with signal transducers and activators of transcription 5 (Stat 5)- induces its oncogenic function. Based on this observation, a study group showed that JapA molecule inhibits NFAT1-mediated mdm2 at transcriptional and post-translational levels [13,14]. Another important study [15] suggested that the cholesterol metabolite 27-hydroxycholesterol (27-OHC) regulates p53 activity and increases cell proliferation via mdm2 in breast cancer cells. This is a selective estrogen receptor modulator involved in ER-positive breast cancer progression by disrupting constitutive p53 signaling in an mdm2-dependent manner.

### mdm2 deregulation in LSCC

Extensive genomic analyses in LSCC have shown that mdm2 overactivation plays an important role in LSCC biological behavior. Furthermore, some studies suggest that the molecule should be evaluated as a potential biomarker in them [16]. A study group co-analyzing the expression patterns of p53, its upstream regulator mdm2, and also p21/WAF molecule concluded that p53 mainly and mdm2 aberrant expression could be used as markers for inferior and worse prognosis (overall survival), respectively [17]. Interestingly, specific genetic imbalances (gene polymorphisms) regarding mdm2 gene seem to be associated to increased risk for LSCC onset. A study group implemented a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) protocol for the detection of specific mdm2 polymorphisms (mdm2 rs769412 and mdm2 rs937283). They observed that both of the analyzed polymorphisms were correlated with high susceptibility to LSCC rise and progression especially in sub-groups of patients with a history of chronic alcohol consumption [18]. Similarly, another study group based on a combination of pyrosequencing and enzyme-linked immunosorbent assay (ELISA) analyzed the status of a specific single-nucleotide polymorphism (SNP) 309T/G SNP in the promoter region of mdm2 and measured mdm2 plasma levels, respectively [19]. They observed that the mdm2 SNP309 G allele acts as a significant LSCC and vocal leukoplakia inhibition genetic marker in the Chinese population, whereas GT type patients correlated with a lower plasma mdm2 level than the TT genotypes. In these patients, a low tumor stage and metastatic potential was also observed. Additionally, novel published genetic data - based on TaqMan probes or restriction fragment length assays in peripheral blood DNA- have shown that mdm2 rs2279744 SNP is strongly correlated to LSCC genetic susceptibility in Spanish population [20].

In conclusion, the previously referred molecular data show that overactivation of mdm2 gene is critical for LSCC rise and progression. mdm2 deregulation is involved in the early genomic instability of normal laryngeal epithelia (dysplastic lesions, leukoplakia).

### Conflict of interests

The authors declare no conflict of interests.

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