

## SPECIAL MOLECULAR REVIEW

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# Mechanisms of C-myc oncogenic activity in head and neck squamous cell carcinoma

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## Summary

*Laryngeal squamous cell carcinoma (LSCC) demonstrates increased rates due to pathogenetic factors including tobacco, chronic alcohol consumption and also viral-mediated deregulation. During carcinogenetic process, laryngeal epithelia accumulate gross chromosome and specific gene aberrations. Oncogenes' overactivation is a crucial genetic event in malignant and pre-malignant neoplastic epithelia. Among oncogenes, C-myc (gene locus: 8q24.12-q24.13) acts as a strong transcription factor, implicated in the control of*

*cell differentiation and apoptosis. Upregulation of the gene - due to increased copy numbers (amplification) - seems to be correlated with aggressive biological behaviour in LSCCs. In the current special molecular article we explored the role of C-myc deregulation in LSCC.*

**Key words:** c-myc, oncogene, signaling pathway, larynx, carcinoma

## Introduction

Laryngeal squamous cell carcinoma (LSCC) is the prominent histopathological entity among head and neck squamous cell carcinomas (HNSC-Cs). It demonstrates increased rates due to pathogenetic factors including tobacco, chronic alcohol consumption and also viral-mediated deregulation [1]. Concerning the last one, persistent human papilloma virus (HPV) infection is responsible for malignant transformation of the corresponding laryngeal epithelia [2]. During laryngeal carcinogenetic process, a variety of genomic imbalances is involved in hyperplastic and dysplastic laryngeal

epithelia as early or progressive genetic events, respectively. Gross chromosome instability (CI-polysomy/aneuploidy) and specific gene alterations (amplification, deletion, point mutations or epigenetic: aberrant promoter methylation) are implicated in the development and progression of LSCC. Among the genes that are involved in LSCC development, overactivated proto-oncogenes in signaling transduction pathways play a significant role due to modified nuclear micro-environment [3]. In the current special molecular article we explored the role of C-myc deregulation in LSCC.

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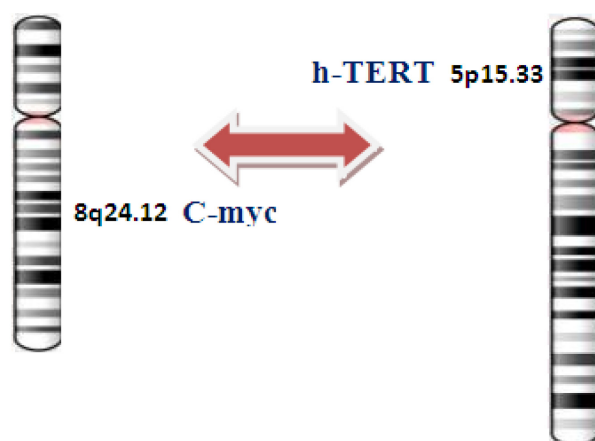
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## Introducing the C-myc gene and protein

C-myc proto-oncogene - the human cellular homologue of the v-myc oncogene of avian myelocytomatosis retrovirus MC29 - which is located on chromosome 8 (8q24.12-q24.13) - is found to act as a strong transcription factor, implicated in the control of cell differentiation and apoptosis [4]. Induction of this transcription factor promotes cell proliferation and transformation by activating growth-promoting genes, including the ornithine decarboxylase (ODC1) and CDC25A genes and also the E2F1, E2F2 and E2F3 genes [5]. The c-myc protein acts as a nuclear phosphoprotein that regulates cell cycle progression, apoptosis and cellular transformation. It activates transcription as part of a heteromeric complex with MAX protein. C-myc is also involved in direct human telomerase activation by inducing expression of its catalytic subunit, h-TERT (Figure 1) [6]. h-TERT is a target of C-myc activity and some pathways linking cell proliferation and chromosome integrity in normal and neoplastic cells have already been confirmed [7]. C-myc amplification is observed frequently in solid malignancies of different histogenetic origin [8-10]. Additionally, gross structural chromosomal aberrations affect C-myc gene function in viral-mediated neoplasia such as Burkitt lymphoma/ B lymphoblastic leukemia translocations t(8;14), t(8;22) or t(2;8) [11].

## C-myc in LSCC

Gene numerical imbalances, and especially increased copy number due to amplification, is a frequent deregulation mechanism in proto-oncogenes' overactivation, leading also to protein overexpression [12, 13]. Molecular studies focused on this genetic abnormality analyzed a variety of them in HNSCCs. One of them concluded that C-myc gene amplification combined or not with cyclin D1 (CCND1), MED1, MTDH, ZNF703 and PRDM14 in long and short arm of chromosome 8 are involved in the pathogenesis of HNSCCs and especially in LSCC [14]. Additionally, another study group analyzing C-myc gene expression by implementing polymerase chain reaction technique detected a significant proportion of amplified HNSCC cases [15]. They also reported that some early dysplastic epithelia harbored this genetic mechanism and that gene amplification was strongly correlated with an aggressive phenotype and advanced disease. Besides the association of C-myc with h-TERT -as previously described-, the oncogene's overexpression combined with mutated p53 aberrant protein expression seems to affect also negatively the bio-



**Figure 1.** Ideogram showing the interaction between C-myc (chromosome 8) and human telomerase reverse transcriptase (h-TERT) (chromosome 5).

logical behavior of HNSCC patients due to shorter survival rates. A study group evaluated the double p53/C-myc immunoreactivity showing that is correlated with worse disease-free survival status of the examined patients [16]. Another gene that seems to form a signaling pathway with C-myc is Notch 1. A study group investigating the role of Notch 1 in the development and progression of LSCC showed that C-myc overexpression indirectly increased Snail and vimentin activity combined with decreased levels of E-cadherin in HSC3 cells [17]. In fact, C-myc elevated oncogenic activity provided an upregulation of epithelial-mesenchymal transition (EMT). Also in this study the researchers explored the role of a novel anti-C myc inhibitor (DAPT). It reduced simultaneously nuclear co-expression of Notch and c-Myc proteins leading to a repressed cell proliferation status. Similarly, another gene that represents a target for the c-myc activation is the CT120. Its protein product is involved in Raf/MEK/ERK and PI3K/Akt signaling pathway activation. A study group co-analyzing both genes concluded that a significant fraction of the examined HNSCCs demonstrated simultaneous upregulation [18]. Concerning patients' resistance to targeted chemotherapeutic agents and the role of C-myc overactivation, clinico-molecular studies showed specific genetic signatures. In one of them, the gene combined with other altered ones, including BCL-2, BCL-XL, and cyclin D1 upon activation of MAPK signaling seems to play a crucial role in the resistance to monoclonal anti-growth factors receptors agents, such as cetuximab combined or not with RAS mutations [19]. Interestingly, inhibition of Wnt/ $\beta$ -catenin-mediated transcriptional activation by Chibby - a tumor suppressor gene- in LSCC seems to be correlated with aberrant expression of oncogenes including C-myc and Cyclin D1.

A molecular study showed that Chibby expression was low in LSCC compared to normal epithelia, associated also to C-myc overexpression [20]. Furthermore, overexpression of Chibby was correlated to cyclin D1  $\beta$ -catenin reduced activity.

In conclusion, C-myc overactivation is a frequently detected and crucial genetic event in LSCC and combined with other oncogenes upregulation and suppressor genes downregulation affect the biological behavior of the malignancy in patients

with specific genetic signatures. Development of novel agents that reduce the corresponding oncoprotein levels inhibiting its activity should be a very promising approach for applying targeted therapeutic strategies in selected groups of patients.

### Conflict of interests

The authors declare no conflict of interests.

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