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Review

What real influence does the proto-oncogene c-myc have in OSCC behavior?

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ABSTRACT

The influence of c-myc in the carcinogenic process has been previously described although in the specific case of oral tumors it has been poorly tested. Myc proteins are a family of proto-oncogenes involved in the cell proliferation regulation, differentiation and apoptosis. The goal of this paper is to describe the functions of c-myc and its role as oncogene, assessing its expression by immunohistochemistry and genetic amplification studies, and studying its relationship with tumoral clinical and pathological variables, and describing genetic and molecular interactions in OSCC.

Introduction

An oral squamous cell carcinoma (OSCC) is a solid tumor characterized by multiple multistep genetic alterations that lead to genomic instability and disordered cell growth due to oncogene overexpression, subexpression of tumor suppressor genes and other genetic and epigenetic alterations.[1–4] The two most studied oncogenes (dominant) in human solid tumors are HER-2/neu and C-Myc; while p53 is the tumor suppressor gene is involved in almost all human malignancies.[5] The idea is to use some of these genes as early markers for OSCC diagnosis, to discriminate between malignant and normal cells, given bad prognosis of this sort of tumors.[6,7]

Myc genes are a family of proto-oncogenes comprised by several members (L-myc, N-myc and c-myc). Myc proteins are members of the family of transcription factors, "basic/helix-loop-helix/leucine zipper" (HLH-LZ), implicated in cell proliferation regulation, differentiation and apoptosis.[8] They are found in normal cells and encode proteins of the nucleus of the cell that bind to DNA, facilitating transcription and regulating the activity of other cells involved in cell division (Fig. 1). Contrary to what has been classically thought, it seems that c-myc is also implied in the control of apoptotic phenomena, possibly leading to tumor regression depending on cell types, cell interactions, extracellular matrix and neighboring cells.[3,9,10]

The c-myc gene is located at chromosome 8q21 and it consists of three exons that are believed to regulate about 15% of the expression of all the genes, through the union of Enhancer Box sequences (E-boxes) and the recruitment of histone acetylase (HATs). C-myc protein is a HLH-LZ phosphoprotein, acting as a transcription factor.[11] Ectopic c-myc expression is sufficient to induce cell-cycle progression and it has been related to bad tumoral prognosis.[12–15] Therefore, c-myc functions are far from the traditionally recognized functions of a proto-oncogene, acting on: cell-cycle progression, cell growth and differentiation, apoptosis, metabolism cell metabolism and adhesion, in addition to promoting self-renovation of tumor stem cells (Fig. 2).[16–19]

The mutated version of c-myc acts as an oncogene and has been found in numerous cancers generating a persistent expression of

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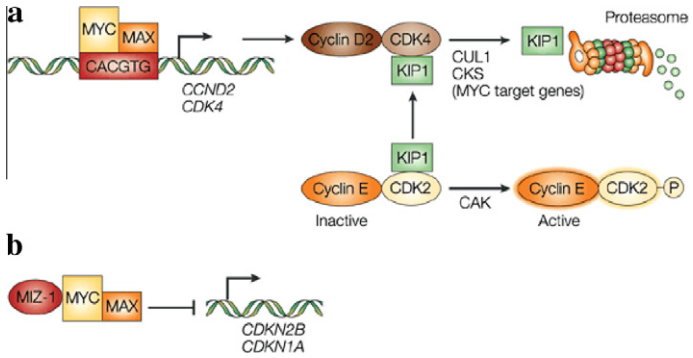

Fig. 1 C-myc promotes G1-S progression through gene activation and repression. (a) MYC–MAX heterodimers activate target genes *CCND2* (which encodes cyclin D2) and cyclindependent kinase 4 (*CDK4*), which leads to the sequestration of CDK inhibitor KIP1 (also known as p27) in cyclin-D2–CDK4 complexes. Subsequent degradation of KIP1 involves two further MYC target genes, *CUL1* and *CKS*. In so doing, KIP1 is not available to bind to and inhibit cyclin- E–CDK2 complexes, thereby allowing cyclin-E–CDK2 to be phosphorylated by cyclin-activating kinase (CAK). (b) MYC–MAX heterodimers repress CDK inhibitors, INK4B (also known as p15) and WAF1 (also known as p21), which are involved in cell-cycle arrest. By interacting with transcription factors MIZ1 (and/or SP1), MYC–MAX prevents the transactivation of *CDKN2B* (which encodes INK4B) and *CDKN1A* (which encodes WAF1).

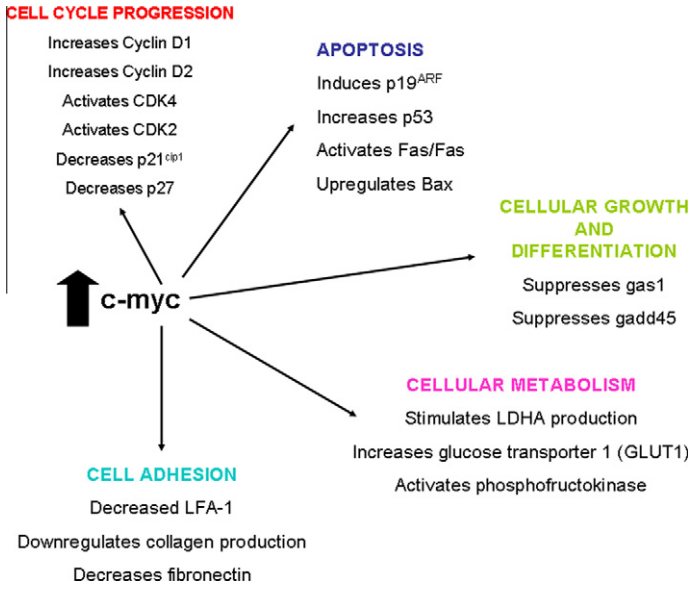

Fig. 2 Table summarizing the effects of c-myc upregulation.

the same, leading to deregulation of the expression of many genes, some of which are involved in cell proliferation resulting in oncogenesis. T(8:14) is a classical translocation involved in Burkitt lymphoma.[20–23]

The influence of c-myc in the carcinogenic process, in general, has been previously described, and, in the specific case of oral tumors, Goessel et al.[24] have developed a cellular model of oral-esophageal carcinogenesis, in which cyclin D1 overexpression and inactivation of p53 leads to the immortalization of keratinocytes, additionally overexpression of ectopic epidermal growth factor receptor (EGFR) and c-myc, and the resulting malignant reactivation of telomerase induced by EGFR, are sufficient for a malignant transformation of oral epithelial cells. Thus demonstrating the importance of the overexpression of this gene in OSCC, which is in agreement with other works by Foster et al.[25]

Chromosome aberrations are known to impact the initiation and progression of OSCC but the individual genes involved in the pathology of these tumors is poorly described. The goal of this paper is to describe the functions of c-myc and its role in oncogene expression, analyzing its expression by immunohistochemistry and perform gene amplification studies, observing its relationship with the clinical and pathological variables of tumors and to describe the genetic and molecular interactions with OSCC.

C-myc expression in OSCC and its relationship with clinical and pathological parameters

C-myc immunostaining in OSCC shows three different patterns; nuclear, granular cytoplasmic perinuclear and diffuse cytoplasmic.[26–28] A characteristic feature of nuclear tinting is that chromatin in mitotic phase is frequently observed.[26] Several studies have analyzed c-myc expression in this type of tumors and have reported different results (Table 1).[5,21,28–35]

Shah et al.,[5] found a significantly higher expression in T3/T4 tumors in comparison with T1/T2 tumors, whereas c-myc was correlated with tumor staging and lymphatic permeation. Additionally, c-myc showed positive correlation with Stat3 (a protein capable of acting in the cell nucleus as an activator of transcription and oncogenic effect) and both, together, with p53 and Bcl-2 (key protein in regulating the intrinsic pathway of apoptosis). It was also positively related with the loss of expression of Rb. Rodrigo et al.,[36] found no relationship between c-myc overexpression and tumor prognosis, as Hayry et al.[34]

Baral et al.,[28] found that tumors with positive p53 and c-myc, were in advanced stages of the disease (poorly differentiated, stage III), while OSCCs in early stages did not show positive immonoreactivity for p53 and c-myc. They also found that the largest amount