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"THE EXPRESSION OF p53 AND c-Myc AT THE INVASIVE FRONT OF ORAL SQUAMOUS CELL CARCINOMA: AN IMMUNOHISTOCHEMICAL AND CLINICOPATHOLOGICAL STUDY"

By
Dr. PRAGATI RAI

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Dr. SWETHA ACHARYA

DEPARTMENT OF ORAL AND MAXILLOFACIAL PATHOLOGY & MICROBIOLOGY

S.D.M. COLLEGE OF DENTAL SCIENCES & HOSPITAL, DHARWAD

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ABSTRACT

Background and objective: The prognostic significance of the Invasive Tumor Front (ITF) in Oral Squamous Cell Carcinoma (OSCC) has presently been documented. Though ITF has been comprehensively studied in OSCC, only a few studies have analysed the expression of cell cycle regulatory proteins in this region. p53 and c-Myc have been shown to work together in the regulation of both cell proliferation and apoptosis, however when altered by mutational events, seem to be a key regulatory component of oncogenesis. At present limited information exist on the association of p53 and c-Myc expression at the ITF of OSCC. The purpose of this study was to assess the expression of p53 and c-Myc in OSCC and to analyze and compare this expression in the Whole Tumor (WT) and ITF. To evaluate the correlation between p53 and c-Myc expression in each region and also to study the association between p53 and c-Myc expression at the ITF with clinicopathologic features in OSCC patients.

Methods: A total of sixty cases of OSCC, which showed WT and ITF were evaluated for immunohistochemical (IHC) expression of p53 and c-Myc. Tumor cells with distinct brown nuclear staining were regarded as p53 positive. For c-Myc both nuclear and cytoplasmic immunostainings was considered positive. Tumor cells were independently counted at the ITF and in the WT. Quantitative labelling index (LI) was assessed for each region. The data was subjected to statistical analysis such as Wilcoxon test, Spearman rank correlation test and Chi-square test.

Results: Overexpression of p53 (LI>10%) was found in 38/60 (63.3%) of cases. p53 LI was higher at ITF than in the WT. Statistically significant difference were found between p53 LI at the ITF and in the WT ($p < 0.05$). Overexpression of c-Myc (LI>10%) was found in 54/60 (90%) of cases. c-Myc LI was higher at ITF than in the

WT. Statistically significant difference were found between c-Myc LI at ITF and at WT ($p<0.05$). Statistically significant positive correlation was detected between WT and ITF with respect to p53 LI and c-Myc LI.

c-Myc LI was higher than p53 LI in the WT and at the ITF. Statistically significant differences were found between c-Myc and p53 expression in the WT and at the ITF ($p<0.05$). Statistically significant positive correlation was detected between p53 and c-Myc expression in the WT and at the ITF ($p<0.05$)

p53 expression did not show a significant association with clinicopathologic parameters except for habits ($p<0.05$) and side of lesion ($p<0.05$). c-Myc expression did not show a significant association with any of clinicopathologic parameters ($p>0.05$)

Concordant p53 and c-Myc expression was observed in 36/60 (60%) of OSCC cases. p53 and c-Myc co-expression did not show a significant association with clinicopathologic parameters except for habits ($p>0.05$).

Conclusion: The study confirms the overexpression of p53 and c-Myc in OSCC thus emphasizing the fact that p53 and c-Myc genes are frequently deregulated in Head and Neck squamous cell carcinoma (HNSCC).

p53 LI was higher at ITF than in the WT which is indicative of noticeable accumulation of p53 positive cells at the IF of tumors. This study demonstrates a high incidence of expression of mutant p53 in OSCC at the ITF, underpinning genomic instability and increased cell proliferation due to loss of p53 function. Higher expression of p53 signifies actively proliferating malignant cells. Owing to the

presence of amplified and uninhibited cell proliferation at ITF, tumor cells may accumulate essential genetic alterations for invasion and metastasis.

c-Myc is associated with loss of differentiation and uncontrolled proliferation leading to greater expression of c-Myc in actively proliferating cells. A high level of c-Myc expression is known to accelerate the growth rate of the cells. ITF of OSCC is composed of tumor subpopulations with high proliferative activity and shows a lower degree of differentiation when compared to other parts of the tumor. This suggests the possibility of increased c-Myc expression at the ITF than in the WT in this investigation.

In general, the difference in the expression of cell cycle regulatory proteins at the ITF and in the WT may be attributable to the following reasons which are heterogeneity in tumor cell population, different molecular characteristics of tumor cells in ITF and center /superficial area, difference in cell proliferative activity in both the zones, disparity in stromal vascular characteristics, clonal evolution of tumor nests with similar proliferative behaviour and clonal / subclonal evolution of tumor nests with additional aberrations.

Concordant p53 and c-Myc overexpression may be indicative of aggressive tumors or anaplastic tumor zones which have gathered too many alterations/mutations in genes which control the cell cycle.

Key words: Oral Squamous Cell Carcinoma, Invasive Tumor Front, Whole Tumor, p53, c-Myc, Immunohistochemical expression