Evaluating the prognostic value of BubR1 and Mad2 mitotic checkpoint protein expression in oral squamous cell carcinoma

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The spindle assembly checkpoint (SAC) activity is compromised in several malignant tumors and has been implicated as a contributor to aneuploidy and carcinogenesis. This surveillance mechanism ensures the fidelity of the chromosome segregation in each cellular division, through the assembly of mitotic checkpoint complex (MCC). The MCC includes BubR1, Mad2 and Bub3 proteins, which inhibit Cdc20 and prevent the anaphase promoting complex/cyclosome (APC/C) activation. Hence, anaphase is delayed until all chromosomes have established a bipolar attachment with spindle microtubules and become aligned into the metaphase plate. Abnormal expression of SAC proteins has been already reported in several types of cancer and has been associated with a poor prognosis. However, little is known about the expression of these proteins in oral squamous cell carcinoma (OSCC).

Our aim was to study the BubR1 and Mad2 proteins expression in tissues of patients with OSCC; relate them to clinicopathological characteristics and evaluate their potential as prognostic biomarker. For that, paraffin tissue blocks of 65 patients (18 females and 47 males; median age of 61.57 years) diagnosed with primary OSCC, between the year 2000-2006, were obtained from the Pathology archive of Hospital de Santo António, Porto. The expression of BubR1 and Mad2 was analyzed by immunohistochemistry on paraffin sections. Chi-square test was used for comparing clinicopathological characteristics with protein expression (p<0.05). The overall survival and disease-free survival were studied using Kaplan-Meier method and Cox regression method (p<0.05).

Our results demonstrated increased levels of BubR1 (64.9±18.7) and Mad2 (54.9±22) expression in OSCC, compared to normal tissue (8.5±1.58) and (46.85±14.97), respectively. Regarding the intensity of protein labeling, we obtained significant results with size (p=0.040) and tumor stage (p=0.011), in the case of BubR1, and the mean patient age (p=0.016) with Mad2 protein intensity. In the univariable analysis, patients with higher labeling index (p=0.026) and tumors with high intense staining of BubR1 (p=0.001) showed lower survival rate. On the other hand, the multivariable analysis identified BubR1 labeling intensity as a factor for independent prognosis (p=0.030), suggesting this protein as a prognosis factor for the survival rate of OSCC patients.
Our work demonstrated and characterized for the first time, the expression of Mad2 in histological OSCC patient samples using immunohistochemistry. Increased levels of Mad2 expression were observed by cytoplasmatic and nuclear staining, with high intensity and peripheral distribution in OSCC. Nevertheless, this expression was not associated with patient prognosis. On the other hand, BubR1 expression, evaluated by the intensity of the labeling, is suggested as a potential molecular marker for prognosis in OSCC.

1. Kopps GJPL et al., PNAS 2004, 23:8699-8704