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ORIGINAL ARTICLE

Simultaneous deregulation of p16 and cyclin D1 genes in pancreatic ductal adenocarcinoma: a combined immunohistochemistry and image analysis study based on tissue microarrays

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Summary

Purpose: *Deregulation of cell cycle control molecules, such as cyclins and their inhibitors, is a crucial event in the carcinogenetic process. Our aim was to identify potential correlations between p16 and cyclin D1 expression in pancreatic ductal adenocarcinoma (PDAC) that affect the biological behavior of this neoplasm.*

Materials and methods: *Using tissue microarray (TMA) technology, 50 paraffin-embedded tissue samples of histologically confirmed primary PDACs were cored twice and re-embedded to the final recipient block. Immunohistochemistry (IHC) was performed using monoclonal anti-p16 and anti-cyclin D1 antibodies. Protein expression levels were determined by performing computerized image analysis (CIA; estimation of Nuclear Labeling Index-NLI). SPSS (chi square test and interrater Cohen's kappa) was used for statistical analysis.*

Results: *Cyclin D1 overexpression was observed in 24/50 (48%) of the examined carcinomas, whereas p16 loss or reduced expression was detected in 40/50 (80%) cases. Statistical significance was noted when correlating grade to cyclin D1 (p=0.038), stage to p16 (p=0.012) and also to cyclin D1 (p=0.011). Interestingly, combined protein alterations (p16 loss and cyclin D1 overexpression) were observed in 23/50 (46%) cases associated with advanced stage (p=0.019). Overall combined expression of the two molecules demonstrated a significantly low value (kappa=0.012; 95% confidence interval-CI: 0.010-0.014).*

Conclusion: *A significant proportion of PDACs is characterized by simultaneous protein alterations regarding p16 and cyclin D1 genes. This mechanism of genetic deregulation in cell cycle potentially explains in part the aggressive phenotype of this neoplasm.*

Key words: cyclin D1, image analysis, immunohistochemistry, p16, pancreatic ductal adenocarcinoma, tissue microarrays

Introduction

PDAC represents a highly aggressive and chemoresistant type of cancer with a very poor prognosis [1]. According to extensive cytogenetic analyses, a significant number of oncogenes and tumor suppressor genes is associated with the carcinogenetic process of the neoplasm, including k-ras and p53 mutations, c-myc and HER2/neu amplification and also DPC4 deletion/mutation [2-4]. Furthermore, deregulation regarding molecules involved in cell cycle control leads to imbalances of proliferation/apoptosis status and combined to telomerase overexpression is responsible for "immortalization" of the neoplastic cells [5-7].

Activation of cyclins stimulates the progression of cell proliferation via interactions with specific catalytic cyclin-dependent kinases (cdks) [8]. Cyclins D

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