CD44 and OTP are strong prognostic markers for pulmonary carcinoids.

Abstract:

Pulmonary carcinoids are well-differentiated neuroendocrine tumors showing usually a favorable prognosis. However, there is a risk for late recurrence and/or distant metastasis. Because histologic classification in typical and atypical carcinoids is difficult and its reliability to predict disease outcome varies, we evaluated three genes as potential prognostic markers, that is, orthopedia homeobox (OTP), CD44, and rearranged during transfection (RET). These genes were analyzed in 56 frozen carcinoids by quantitative real-time PCR (qRT-PCR). RET was further studied by methylation and mutation analysis. Immunohistochemistry for CD44 and OTP protein expression was conducted on 292 carcinoids. Low mRNA expression levels of CD44 (P = 1.8e(-5)) and OTP (P = 0.00054), and high levels of RET (P = 0.025), were strongly associated with a low 20-year survival of carcinoid patients. High RET expression was not related to promoter hypomethylation or gene mutations. A direct link between gene expression and protein levels was confirmed for CD44 and OTP but not for RET. Within all carcinoids as well as atypical carcinoids, absence of CD44 protein was significantly associated with low 20-year survival (P = 0.00014 and 0.00013, respectively). The absence of nuclear OTP followed by complete loss of
expression was also significantly associated with unfavorable disease outcome in all carcinoids (P = 5.2(-6)). Multivariate analyses revealed that age at diagnosis, histopathology, stage, and cytoplasmic OTP immunoreactivity were independent predictors of prognosis. Our study indicates that CD44 and OTP are strong indicators of poor outcome. We therefore argue for implementation of these markers in routine diagnostics in addition to histopathology to improve subclassification of pulmonary carcinoids into prognostically relevant categories.