gastrointestinal tumours, non-colorectal

COX-2 STATUS MODULATES THE ACTIVATION OF HEDGEHOG PATHWAY AND CONSEQUENTLY THE EXPRESSION OF STEM CELL MARKERS IN PATIENTS WITH PANCREATIC DUCTAL ADENOCARCINOMA

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Aim: Inflammation is a key driver in the development of pancreatic ductal adenocarcinoma (PDAC). Cyclooxygenase-2 (COX-2) and Interleukin (IL)-6 are key modulators of inflammation and act as a potential link between chronic pancreatitis and subsequent carcinogenesis. In this study, we analyzed the association between COX-2 and IL-6 status and the expression of Hedgehog signaling pathway and stem cell markers and their relationship with the clinico-pathological features and prognosis of PDAC patients.

Methods: The expressions of COX-2 and IL-6 were examined using immunohistochemistry in 79 resection specimens of PDAC. The expression of the Hedgehog components SHH, IHH, DHH, SMO, PTCH1, PTCH2, and stem cell markers CD24, CD44, OCT3/4 and PROM1 were analyzed by qRT-PCR. The correlation among gene expression levels was performed by the Pearson product moment correlation method. Survival analysis was conducted via Kaplan-Meier product-limit method.

Results: 49 patients (62%) had COX-2+ tumors, while 37 patients (47%) had IL-6+ tumors. SHH (p = 0.001), IHH (p = 0.011) and SMO (p = 0.040) were significantly more expressed in patients COX-2+. In addition, IHH was significantly more expressed in patients with IL-6+ tumors (p = 0.040). CD44 expression was associated with DHH (rho = 0.742), IHH (rho = 0.826) and SMO (rho = 0.899). PROM1 expression was associated with DHH (rho = 0.772), IHH (rho = 0.847) and SMO (rho = 0.915). T stage was higher in patients with COX-2+ (p = 0.020), whereas no associations were found between COX-2 and node involvement (p = 0.071) or grading (p = 0.237) as well as between IL-6 expression and the clinico-pathological characteristics of these patients. No significant differences in terms of survival were found based on COX-2 or IL-6 status.

Conclusions: Taken together, our data suggest for a model in which COX-2 expression modulates the activation of the Hedgehog pathway and, subsequently, the expression of stemness markers. These data may lead to a better characterization of patients to include in clinical trials in order to develop future therapeutic strategies.

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