Juicy Genes
Molecular Analysis of Pancreatic Secretions

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Since endoscopy is available for decades now, it is long forgotten how this new method impressed by its ease and elegance. Endoscopic retrograde cholangiopancreatography (ERCP) allowed the first direct access to the pancreas in a patient not undergoing open abdominal surgery [1]. It was soon clear that cytological analysis of pancreatic juice could aid in the difficult differential diagnosis of chronic pancreatitis and pancreatic cancer, however, sensitivity and specificity were low. With the advent of readily available molecular biology techniques, namely PCR, the combination of endoscopy (ERCP) and molecular diagnosis serving the clinician seemed to be within reach [2]. Unfortunately, these high expectations could not be met. The most frequent genetic alterations in pancreatic carcinoma, mutations in the ras oncogene, could also be found in chronic pancreatitis [3, 4]. The material collected during ERCP is sparse and needs special care for preparation of DNA [5]. Since there is a pattern supporting the communication of ‘positive’ results after an initial ‘positive’ observation, this has lead to the application of mutation-enriched PCR techniques resulting in a plethora of reports with high frequencies of ras in pancreatic juice in chronic pancreatitis [6]. Method matters [7]. Nevertheless, the application of molecular biology as a diagnostic tool for pancreatic secretions is intriguing. As a consequence, other molecular markers such as the tumor suppressor gene p53 [8] have been tried with limited success in making the differential diagnosis [9]. While PCR analysis of ras point mutations is rather easy with one hot spot at codon 12/13, analysis of p53 point mutations is already more challenging presenting with a variety of hot spots dispersed through 6 exons. The analysis of the next most frequent genetic changes in pancreatic carcinoma, p16 and DPC4/SMAD4 [10, 11], is even more demanding since they represent deletions that are difficult to detect in a mixture of cells such as represented in a pancreatic juice sample. The paper by Costentin and coworkers in this issue of Pancreatology [12] analyses the frequency of these two genes in relation to ras mutations in a considerable number of patients with pancreatic diseases. Their finding of low ras mutations in chronic pancreatitis is consistent with the current knowledge. However, they find frequent changes in p16 and DPC4/SMAD4 in chronic pancreatitis. At first sight, this is disappointingly high. During the last years, in analogy to the adenoma-carcinoma sequence in colorectal cancer [13], a progression model for pancreatic neoplasias has been proposed [14]. There, the known but clinically inapparent pancreatic intraductal neoplasias (PanIN) [15] are taken into account. They bear both p16 and DPC4/SMAD4 alterations [16, 17]. Therefore, the data of Costentin and coworkers are consistent with this concept of pancreatic carcinogenesis,
even though this does not help us in establishing the clinical diagnosis of a pancreatic malignancy from pancreatic juice. Do mutations such as ras and p53 bear a meaning to pancreatic carcinogenesis? The roads to cancer can be rebuilt [18] with alteration or inactivation of ras, p53 and telomerase both in embryonic kidney cells [19] and in pancreatic duct cells [20], thus fulfilling the molecular variant of Koch’s postulates [21]. The light at the end of the tunnel in molecular diagnostics from pancreatic juice is not yet in sight. However, one glimpse adds to another.

References