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PANCREAS NEWS

Pancreatic Ductal Carcinoma: From the Bench to the Bedside

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About 90% of all pancreatic cancers are ductal adenocarcinomas with an overall 5-year survival rate of less than 5%. The explanation as to why most pancreatic cancers arise from ductal cells has only come to light in the past few years. Most knowledge has been found at the molecular level which shows an increasing number of genetic and epigenetic alterations, in particular, on growth factors and related pathways. Furthermore, basic researchers have identified molecular alterations which render cancer cells capable of invading the perineurium and the retroperitoneal space, thus, explaining the high rate of local recurrence and the severe pain syndrome. A complete overview on the translational research, transferring advances from basic research to clinical studies for the benefit of pancreatic cancer patients has recently been published by Kleeff *et al*. [1] and we hope that the readers have appreciated this review because it has made the world of the translational research easier for physicians.

Regarding the morphological level of pancreatic cancer, an interesting paper has come from Japanese researchers [2]. In this paper, the authors endeavored to analyze the early stages and the progressive invasion of pancreatic ductal adenocarcinomas. They studied 82 cases of resected invasive pancreatic ductal adenocarcinoma and the non-invasive cancer parts of the resected specimens. According to the pancreatic intraepithelial neoplasia (PanIN) classification, they considered non-invasive cancer parts equivalent to PanIN-3; the non-invasive cancer parts in the invasive area and non-invasive intraductal spread area were histologically examined. Non-invasive intraductal spread means a diffuse PanIN-3 change which extends continuously outward from the invasive area. In cases with non-invasive intraductal spread, the length of the non-invasive intraductal spread was measured. They histologically categorized the non-invasive cancer parts into the three following types: flat, low papillary and mixed, consisting of flat and low papillary types. The frequencies of the three types were 18.3% for the flat lesions, 34.1%, for the low papillary type and 47.6% for the mixed type. Cases with non-invasive intraductal spread of 2 mm or more were found in 56.1% of all the patients, and the frequencies of flat, mixed and low papillary types were 13.3%, 59.0%, and 75.0%, respectively. The maximal non-invasive intraductal spread lengths were 10, 40, and 80 mm with averages of 1.5, 5.7, and 12.5 mm in the flat, mixed, and low papillary types, respectively. The cases with the low papillary component revealed positive non-invasive intraductal spread and longer non-invasive intraductal spread lengths more frequently than those without the component. The survival rates of the flat, mixed, and low papillary types were similar and the prognosis was better in cases of less advanced stages. What are the conclusions of this study? It is possible to recognize three types of lesions in the non-invasive cancer parts of invasive pancreatic ductal adenocarcinomas: flat, low papillary, and mixed. The low papillary type had a greater tendency to spread intraductally

than the flat type and seems to change to invasive cancer after or while spreading intraductally to some extent, whereas the flat type seemed to invade with little intraductal spread.

Another aspect of the importance of ductal cells on the development of carcinoma comes from the study of Adachi *et al*. [3]. The occurrence of intraductal papillary mucinous carcinoma has been reported in the main or large pancreatic ducts of patients with pancreaticobiliary maljunction. About 16 cases of pancreas carcinoma have been reported in patients with pancreaticobiliary maljunction [4 ,5 ,6 ,7, 8, 9, 10, 11, 12, 13, 14, 15], and about one-third of these tumors were intraductal papillary mucinous carcinomas. Because intraductal papillary mucinous carcinoma accounts for only about 3% of all pancreatic carcinomas, there seems to be a relationship between intraductal papillary mucinous carcinoma and pancreaticobiliary maljunction, and bile-reflux into the pancreatic ducts may be a risk factor for the development of intraductal papillary mucinous carcinoma. To test this hypothesis, the authors investigated the significance of bile-reflux into the pancreatic ducts in pancreatic carcinogenesis in hamsters, focusing on the development of carcinoma in the main pancreatic duct. The Syrian golden hamster was used because the anatomical structure of its pancreaticobiliary ductal system, the bile acid composition, and pancreatic juice components in this species are similar to those of humans. The authors showed that bile-reflux into the pancreatic ducts is a significant factor predisposing to the development of intraductal papillary mucinous carcinoma of the pancreas due to the acceleration of epithelial cell kinetics of the main pancreatic duct. The results of this study seem to be important and, of course, need to be evaluated in human by means of epidemiological and clinical studies.

Keywords Carcinoma, Pancreatic Ductal; Laboratory Animal Science; Pancreatic Neoplasms; Research

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