Metaplasia in the gut

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MetaplasiaC and hyperplasiaC Changes of pancreatic epithelium affect almost exclusively cells of the duct system. The major types of such changes are squamous metaplasia, mucinous cell hyperplasia (including pyloric gland and goblet cell metaplasia), ductal papilla hyperplasia and adenomatoid hyperplasia. They occur in normal, disease-free pancreatic parenchyma as well as in association with carcinomas and chronic pancreatitis. All types, preferentially those of the mucinous cell type, harbor K-ras mutations at codon 12, the rate varying from about 6% in the normal pancreas to 50% in tumor-associated tissue. However, since there is evidence that these lesions are evenly distributed in the normal pancreas and since they do not show a preponderance in the head region, the preferential site of ductal adenocarcinomas, their role as a tumor precursor should perhaps be reconsidered. Only lesions with dysplasia harbor additional mutations, such as those of the p53 gene or the p16 gene and only these can be regarded as true tumor precursors. Compared with other organs, the role of metaplasia and hyperplasia of the ductal epithelium in the tumorigenesis of pancreatic cancer has not yet been defined and a sequence of stepwise mutations has yet to be discovered.

General remarks

More than 90% of metaplastic and hyperplastic changes occur in the ductal system. For acinar cells, only focal acinar transformation has been described. This has also been termed acinar adenomatous hyperplasia or acinar cell dysplasia, although this alteration is not related to any neoplastic changes of the pancreas and has been reported in various frequencies (1). The duct epithelium is assumed to be the site of origin of ductal pancreatic adenocarcinomas. Therefore, interest has focused on epithelial changes that might represent tumor precursor lesions. According to the World Health Organization (WHO) (2), four major types are distinguished: mucinous cell hyperplasia, papillary cell hyperplasia, adenomatoid hyperplasia and squamous metaplasia. Only the latter lesion is of nonmucinous cell type, and is preferentially observed in association with mechanical disturbances of the duct system due to prolonged stenting (2, 3) or with certain types of chemotherapy (4). It does not appear to be related to the development of pancreatic carcinomas. All of the other lesions are of mucinous cell type. Interest has focused on these lesions and studies have been undertaken to determine their distribution in the organ and possible genetic mutations, such as the K-ras or p53 mutations, which are the most common mutations in manifest carcinoma.

Duct lesions in normal pancreatic tissue

The distribution and frequencies of the different duct lesions in the normal pancreas could give a clue as to which lesions and sites are high-risk for the development of carcinomas. The large studies by Sommers (5), Cubilla and Fitzgerald (6), Kozuka et al. (7), Mukada and Yamada (8) and Kkppel et al. (9) have indicated that metaplastic and hyperplastic duct changes occur most frequently in the head of the pancreas, the preferential site of carcinomas. However, in these investigations often only one histological slide was evaluated per organ; hence the conclusions must be interpreted with caution. Systematic investigations of sections from the head, corpus and tail by Stamm (10) and by our group (submitted for publication) have revealed that duct changes are evenly distributed throughout the entire pancreas and do not share the same distribution as carcinomas. Nevertheless, they increase beyond the age of 40 (5-7). They can even harbor a K-ras mutation at codon 12, as Tada et al. (11) and our group have shown. Lesions that harbor the K-ras mutation do not, however, preferentially occur in the head of the pancreas. Therefore, other mutational events involving in particular the lesions in the head region seem to be necessary for tumor progression.

Duct lesions in the tumor-associated pancreas

In many organs, precursor lesions have been identified in the vicinity of the established tumor and they provide information on the development of the carcinomas. For the pancreas, several studies on carcinomas (6, 7, 9) have indicated that mucinous cell hyperplasia is the most frequent type of lesion in these organs, followed by papillary hyperplasia, adenomatoid hyperplasia and squamous metaplasia. Molecular analyses have revealed high frequencies of...
the K-ras mutation especially in the mucinous cell type (12), although no spatial relationship between the carcinomas and K-ras mutation positive lesions could be established (3). Of special interest are duct lesions that show dysplastic changes, as they appear to be the most likely tumor precursors. Molecular approaches have revealed that they harbor K-ras mutations at codon 12 in a range from 55-75% (12, 13). In addition, Moskaluk et al. detected mutations of the p16 (MTS1) gene, which is also frequently found in manifest carcinomas (13). A model of tumor progression comparable to that for colorectal cancer has been suggested by Brat et al. (14) with emphasis on the degree of cellular atypia. However, it has been pointed out that it is especially difficult to distinguish papillary ductal hyperplasia with severe dysplasia from intraductal extensions of the primary carcinoma.

Lesions associated with chronic pancreatitis
Chronic pancreatitis is considered a risk factor for the development of pancreatic ductal adenocarcinoma (15-18). So far, two histological studies have searched for possible precursor lesions in this disease (9, 19). It was found that nonpapillary epithelial hypertrophy (mucous cell type) was the most frequent (68%), followed by papillary hyperplasia and squamous metaplasia (both 11%). Severe dysplasia or ductal carcinoma in situ lesions were not observed. In contrast, in a study of 70 resection specimens from patients with chronic pancreatitis, severe dysplasia was reported in 8.6% of the cases and advanced fibrosis associated with dysplasia in 65% (20). The authors even concluded that surgical removal of these lesions should be recommended. Tabata et al. (21) and Møller et al. (22) also reported severe dysplasia in chronic pancreatitis, although this is not convincingly demonstrated by their illustrations. Because of the clinical importance and the major consequences for the patients, a general and reproducible definition and classification of the degree of cellular atypia and dysplasia are needed. An example of this is provided by the WHO classification (2). Moreover, such duct lesions need to be better characterized so that true high-risk lesions can be evaluated.

References