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Editorial

Histological Differentiation and Genetic Alterations during Tumor Progression of Pancreatic Ductal Adenocarcinomas

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In pancreatic ductal adenocarcinomas (PDACs), the step-wise progression model of genetic alterations is well known [1-3]. On the other hand, it has been reported that as the tumor size increases, dedifferentiation from a well-differentiated tumor grade to a moderately differentiated tumor grade occurs [4]. However, the significance of this histological differentiation during tumor progression and the genetic alterations related to the differentiation process are not clearly defined. Thus, in this editorial, we describe new findings concerning the differentiation process during PDAC progression based on our recent study and a review of the literature.

According to the Japan Pancreatic Cancer Registry Report 2007 [5], the frequency of well-differentiated, moderately, and poorly differentiated tumor grade in all resected PDACs, for which a description of differentiation was available, is approximately 28% (529/1868), 56% (1046/1868), and 16% (292/1868), respectively. We reported that the mean tumor size of PDACs during their development is >2 cm and that these tumors are commonly moderately or poorly differentiated [4], which suggest that the high incidence of moderately or poorly differentiated tumor grade is a characteristic feature of invasive PDACs.

With regard to the carcinogenesis of PDACs, the multiple progression model of pancreatic intraepithelial neoplasm (PanIN) is widely known [1-3]. However, the features of the transitional stage during the progression from high-grade PanINs to invasive PDACs are not well described [6]. In addition, histological features of early-stage invasive PDACs have not been sufficiently clarified [7]. Previously, we encountered 5 well-differentiated PDACs measuring ≤1 cm that appeared to be of very early stage with respect to tumor progression according to a study of the abnormal expression of molecular alterations associated with carcinogenesis [4]. The notable histopathological features observed in those PDAC lesions were mild architectural and cytological atypia in the tumor glands, no angiolymphatic invasion, and few cancer cells compared to large PDACs measuring ≥2 cm. These features suggest that well-differentiated PDACs measuring ≤1 cm might have less malignant potential than large PDACs. In fact, patients with PDACs measuring ≤1 cm exhibited good overall survival [4,7]. Thus, we believe that well-differentiated PDACs measuring ≤1 cm are early-stage invasive PDACs. Additionally, according to our data, 65% of 35 resected PDACs measuring ≥2 cm were moderately or poorly differentiated, whereas all 6 PDACs measuring ≤1 cm were well-differentiated. In summary, as tumor size increases, the incidence of moderately or poorly differentiated tumor grade increases and dedifferentiation progresses.

Groove PDACs (GPDACs), which mainly develop at the groove between the pancreatic head and the first or second portion of the duodenum, are a rare and specific tumor subclass of invasive PDACs of the pancreatic head (8,9). Although the histopathological features of GPDACs have been ill-defined, we encountered 6 cases of GPDACs and compared their features with those of conventional PDACs (cPDACs) of the pancreatic head. One of the specific features of GPDACs is the easy invasiveness of the duodenal wall. Moreover, GPDACs are more commonly well differentiated than cPDACs. According to the literature on histological differentiation [5,8,9], the incidence rates of well-differentiated GPDACs and cPDACs was almost similar to those in our study (56% vs. 28% and 80% vs. 22%, respectively). The high incidence of well-differentiated tumors seems to be a specific feature of GPDACs. Interestingly, patients with well-differentiated GPDACs exhibited considerably good overall survival in our study, although the mean size of GPDACs was similar to the mean size of cPDACs at the pancreatic head (2.7 cm vs. 2.8 cm). We could not explain why the incidence of well-differentiated tumors was higher in the GPDACs group, but the site of PDAC occurrence (the border or inner area of the pancreatic head) may determine tumor progressivity.

Representative PDAC-associated genetic alterations are MUC1, p16, p53, and Smad4. These genetic alterations can be classified into the following 3 categories based on the timing of their occurrence during tumor progression: early, intermediate, and late event types [7]. For example, it is known that the inactivation of p16 is an early event in the genetic progression of PDAC carcinogenesis [3,10], whereas the inactivation of p53 and Smad4 are late events [3,11,12]. On the other hand, MUC1 expression is commonly observed in normal pancreatic ducts and invasive PDACs. In the PanIN-1A and PanIN-1B lesions, the expression of MUC1 is decreased, but MUC1 is reexpressed with a considerably high frequency in PanIN-2 and PanIN-3 lesions [3,13]. The incidence of abnormal immune labeling for MUC1, p16, p53, and Smad4 in PDACs was reported to be 96%, 80–95%, 50–75%, and

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–55%, respectively [1,3,10,11]. Wilentz et al. reported that the better differentiated glandular component expressed Smad4, whereas the more poorly differentiated component did not [11]. Our previously reported study revealed that the frequency of abnormal Smad4 expression and the mean number of samples staining positive for the 4 abnormally expressed molecular markers described above were significantly lower in well-differentiated PDACs measuring ≤1 cm than in large PDACs measuring ≥2 cm [4]. Additionally, according to our study, the 14 well-differentiated PDACs exhibited a significantly lower frequency of Smad4 expression as well as fewer abnormally stained samples than the 18 moderately differentiated PDACs (both groups were adjusted to exhibit a similar tumor size). In summary, the progression of dedifferentiation that occurs with increasing tumor size is associated with increasing molecular abnormalities, particularly the abnormal expression of S mad 4.

The Japan Pancreatic society reported that the strongest prognostic factor for Union for International Cancer Control-stage IIA and IIB adenocarcinoma in the pancreatic head is histological grade, followed by tumor size, the extent of lymph node dissection, and postoperative chemotherapy [14]. Pongprasobchai et al. reported that tumor differentiation may be a better predictor of survival than tumor stage in resectable pancreatic cancer [15]. According to our data, patients with well-differentiated PDACs showed a significantly better overall survival than patients with moderately or poorly differentiated PDACs. Therefore, it is very important to elucidate the genetic alterations related to the dedifferentiation process.

In summary, tumor dedifferentiation has a significant influence on the prognosis of PDAC patients and abnormal expression of Smad4 may be associated with dedifferentiation. Study of the genetic alterations related to the dedifferentiation process might help us better understand the carcinogenesis and therapeutic strategies for PDACs.

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