Minireview

Progression Model for Pancreatic Cancer[1]

Ralph H. Hruban,[2] Michael Goggins, Jennifer Parsons, and Scott E. Kern

Departments of Pathology [R. H. H., M. G., J. P., S. E. K.], Oncology [R. H. H., M. G., S. E. K.], and Gastroenterology [M. G.], The Johns Hopkins Medical Institutions, Baltimore, Maryland 21287

It has been >10 years since Vogelstein and colleagues (1, 2) proposed a progression model for colorectal neoplasia in which they hypothesized that the progression from normal colonic epithelium, to small adenomatous polyps, to infiltrating adenocarcinoma is associated with the activation of oncogenes and the inactivation of tumor suppressor genes. Mutations in the *APC* gene initiate the adenomatous process, resulting in the clonal growth of a single cell (3–5). Over the years, additional mutations can occur in these adenomas, resulting in waves of clonal expansion and competition among persistent subclones, increasing severity of dysplasia, and eventually in the development of an invasive adenocarcinoma (1, 2, 6, 7). This genetic progression model not only has formed the basis of our understanding of the mechanisms underlying the development of colorectal neoplasia, but it also has important implications for chemoprevention, for the development of genetic screening tests for the presymptomatic diagnosis of colorectal carcinomas, and for the development of prognostic genetic markers (8–10).

Pancreatic cancer is the fourth leading cause of cancer death in both men and women; yet, at the time the progression model was proposed for colorectal neoplasms, remarkably little was known about pancreatic cancer. For example, in 1988, the only significant genetic alteration that had been identified in pancreatic cancer was mutation of the K-*ras* oncogene (11). The last 10 years has seen, however, an explosion in our understanding of pancreatic cancer, and pancreatic cancer is now one of the better characterized neoplasms at the genetic level. We believe that there is now sufficient pathological, clinical, and genetic evidence for us to develop a rational progression model for pancreatic cancer.

The first clue that there may be a distinctive precursor lesion to infiltrating adenocarcinoma of the pancreas came from careful morphological studies (12). In 1976, Cubilla and Fitzgerald (13) reported a seminal paper in which they identified histologically distinct proliferative lesions in the pancreatic ducts and ductules adjacent to infiltrating adenocarcinomas of the pancreas. They called these duct lesions "hyperplasias" and showed that they were more common in pancreata with cancer than they were in pancreata without cancer. Kozuka *et al.* (14) reported similar findings shortly thereafter, and more recently, Furukawa *et al.* (15), using three-dimensional mapping techniques, have demonstrated a stepwise progression from mild dysplasia to severe dysplasia in these pancreatic duct lesions (14–16). These observations were, however, static, and it was not universally agreed upon whether these pancreatic duct lesions represented the intraductal extension of an invasive cancer or a true precursor to invasive cancer (17).

Clinical studies were needed to establish the temporal relationship between pancreatic duct lesions and invasive carcinoma. These studies proved to be more difficult then one might hope because, unlike the colon, skin, breast, cervix, and prostate, the pancreas is not readily accessible to biopsy. Nonetheless, Brat *et al.* (18) have reported three patients who developed infiltrating ductal pancreatic adenocarcinoma 17 months to 10 years after the histological identification of atypical papillary duct lesions in their pancreata. Similarly, Brockie *et al.* (19) reported two patients with atypical papillary duct lesions who developed invasive pancreatic ductal carcinomas years later. Although there have only been a handful of such cases reported, they provide strong support that duct lesions in the pancreas can progress to invasive cancer (20).

Molecular genetic analyses have provided the third and most convincing line of evidence that pancreatic duct lesions are the precursors to infiltrating adenocarcinomas of the pancreas. Almost all of the genetic alterations that have been identified in infiltrating ductal adenocarcinomas of the pancreas have also been identified in these duct lesions, and remarkably, the prevalence of these genetic alterations increases as the degree of cytological and architectural atypia in the duct lesions increases (Fig. 1; Refs. 21–27).

Pancreatic duct lesions with minimal cytological and architectural atypia have been shown to harbor activating point mutations in the K-*ras* oncogene and to overexpress the HER-2/*neu* gene product (17, 21, 24, 28–31). For example, Day *et al.* (21) reported that HER-2/*neu* is only rarely overexpressed in histologically normal pancreatic ductal epithelium, but it is overexpressed in almost all duct lesions with significant cytological and architectural atypia. Similarly, ~45% of papillary pancreatic duct lesions without atypia harbor K-*ras* gene mutations, and the prevalence of these mutations in K-*ras* increases with increasing degrees of atypia in the duct lesions (reviewed in Ref. 22). These alterations in K-*ras* and Her-2/*neu* are believed to be "early" genetic events in the development of pancreatic neoplasia because they occur in pancreatic duct lesions with minimal atypia.

Inactivation of the *p16* tumor suppressor gene appears to occur slightly later. For example, the *p16* tumor suppressor gene is located on chromosome 9p, and Yamano *et al.* (32) have shown loss of heterozygosity at 9p in ~13% of histologically low-grade pancreatic duct lesions, whereas 90% of the histologically high-grade duct lesions that they examined had loss of heterozygosity of this chromosome arm. Similarly, Moskaluk *et*

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[1] Supported by NIH Grant P50-CA 62924.
[2] To whom requests for reprints should be addressed, at The Johns Hopkins Hospital, Meyer 7-181, 600 North Wolfe Street, Baltimore, MD 21287. Phone: (410) 955-9132; Fax: (410) 955-0115; E-mail: rhruban@jhmi.edu.

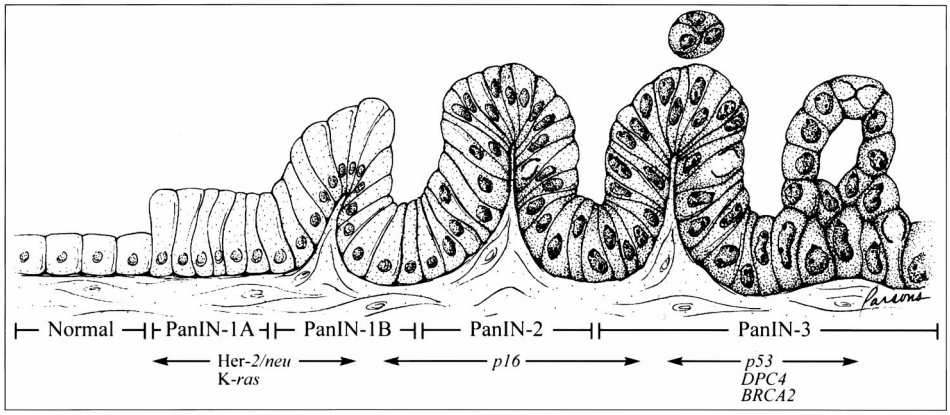

Fig. 1 Progression model for pancreatic cancer. Normal duct epithelium progresses to infiltrating cancer (*left* to *right*) through a series of histologically defined precursors (PanINs). The overexpression of HER-2/*neu* and point mutations in the K-*ras* gene occur early, inactivation of the *p16* gene at an intermediate stage, and the inactivation of *p53*, *DPC4*, and *BRCA2* occur relatively late.

al. (24) microdissected a series of duct lesions and demonstrated biallelic inactivation of the *p16* gene in three of nine duct lesions. Wilentz *et al.* (23) extended these observations by immunohistochemically labeling over 125 pancreatic duct lesions for the *p16* gene product. They not only confirmed that *p16* is frequently inactivated, but they also correlated the loss of *p16* gene expression with the severity cytological and architectural atypia in the duct lesions (23). Nine (30%) of 30 flat, 4 (27%) of 15 papillary, 37 (55%) of 67 papillary with atypia, and 10 (71%) of 14 carcinomas *in situ* duct lesions showed loss of p16 expression (23). The differences in p16 expression between the flat and papillary lesions and between the nonatypical and atypical duct lesions were statistically significant. Thus, loss of p16 expression occurs most frequently, but not exclusively, in higher-grade duct lesions.

Loss of the *p53*, *DPC4*, and *BRCA2* tumor suppressor genes appears to occur late in the development of pancreatic neoplasia. Loss of heterozygosity at chromosome 17p (the location of the *p53* gene) and at 18q (the location of the *DPC4* gene), loss of *DPC4* gene expression, abnormalities of *p53* gene expression, and biallelic inactivation of the *BRCA2* tumor suppressor gene have all also been reported in pancreatic duct lesions (22, 26, 27, 32, 33). However, in contrast to K-*ras*, HER-2/*neu*, and *p16*, these gene abnormalities appear to occur almost exclusively in duct lesions with significant cytological and architectural atypia (carcinoma *in situ*; reviewed in Refs. 22 and 34).

The timing of DNA methylation, of telomerase activation, and of a number of low frequency genetic alterations, such as inactivation of the *MKK4*, *STK11*, *ALK5*, and *TGFBR2* tumor suppressor genes, remains to be defined (35–38).

These pathological, clinical, and molecular observations can now form the foundation for a progression model for pancreatic cancer. Just as there is a progression in the colorectum from normal colonic epithelium, to adenoma, to infiltrating carcinoma, so too is there a progression in the pancreas from normal ductal epithelium, to duct lesions, to invasive ductal adenocarcinoma (20). This progression is associated with multiple genetic alterations including activating point mutations in the K-*ras* gene, the overexpression of HER-2/*neu*, and the inactivation of the *p16*, *p53*, *DPC4*, and occasionally *BRCA2* tumor suppressor genes. Although *APC* appears to be the "gatekeeper" gene in the development of colonic neoplasia, a gatekeeper gene for the initiation of pancreatic neoplasia has not been identified (3).

This model has a number of important implications:

(*a*) If we define a neoplasm as a clonal cell population that has highly patterned alterations in cancer-causing genes, then pancreatic duct lesions are true neoplasms. The nomenclature should reflect the neoplastic nature of these lesions, and indeed, the terminology PanIN[3] was proposed by the National Cancer Institute- sponsored Pancreatic Think Tank held in Park City, Utah in September 1999.[4]

(*b*) This progression model suggests that molecular genetic based screening tests can be developed to detect early pancreatic neoplasms before they have spread beyond the gland (39, 40). For example, mutant K-*ras* genes can be detected in samples of duodenal fluid and stool from patients with pancreatic cancer, and Berthélemy *et al.* (41) have demonstrated that these genetic alterations may be present in samples of pancreatic secretions more than a year before a neoplasm is clinically apparent in the pancreas (28, 41–44).

(*c*) This progression model suggests that these early pancreatic duct lesions in the pancreas might also be reasonable targets for chemoprevention (45, 46). For example, the progression model for colorectal carcinoma has formed the basis for chemoprevention trials in patients with familial adenomatous polyposis (10). Similarly, patients with an inherited susceptibility to pancreatic cancer may also be a reasonable group to study the benefit of chemoprevention of pancreatic cancer (37, 47–52).

What doesn't this model suggest? This model doesn't imply that all PanINs progress to infiltrating carcinomas. Indeed, low-grade PanINs probably only rarely, if ever, progress, akin to aberrant crypt foci in the colon (53). Additional studies are needed to determine whether specific morphological findings or genetic abnormalities can predict which PanINs have a

[3] The abbreviation used is: PanIN, pancreatic intraepithelial neoplasia.
[4] Internet address: http://pathology.jhu.edu/pancreas_panin.

significant risk of progressing. The model also does not rule out other pathways for the development of infiltrating ductal adenocarcinomas. For example, it is possible that carcinomas with DNA replication errors progress through an alternate pathway (54). Additional studies are needed to examine such possibilities.

In summary, infiltrating carcinomas of the pancreas appear to arise from histologically well-defined precursor lesions in the small ducts and ductules of the pancreas. These lesions, called PanINs, harbor a number of well-characterized genetic alterations. A better understanding of the genetic progression in the pancreas will form the basis for future early detection and chemoprevention studies.

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