The Genes in Pancreatic Carcinoma

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Pancreatic ductal carcinoma is still a devastating disease with increasing incidence. Since a breakthrough in therapy is pending, the vast majority of patients die within a year after diagnosis [1]. Therefore, major attention is drawn to the pathogenesis of pancreatic ductal carcinoma and factors involved such as genetic or environmental. Understanding the carcinogenesis of this tumor may lead to clinically applicable strategies as in colorectal carcinoma (CRC). The development of CRC from colorectal polyps, known as the adenoma-carcinoma sequence [2], instigated research interest in this area in pancreatic ductal adenocarcinoma. Inevitably, such research will have to begin with an analysis of genetic alterations in those who already developed pancreatic carcinoma, preferably hereditary.

Thanks to the Lemoine group which has contributed substantially to this area during decades [3–5] that a concise and up-to-date picture of the current level of knowledge of genetic alterations can be presented in this issue of Pancreatology. Efthimiou and coworkers [6] describe the cancer susceptibility genes that are altered in pancreatic carcinoma. Most of them are related to pivotal regulatory circuits such as the cell cycle. To date, this is for the most part phenomenology. However, this can be used as a molecular marker in individuals at risk, at least concerning the germline mutations. In case of a suspected familial pancreatic carcinoma or manifestation at early age, a search for these germline mutations is mandatory. Since there are more cases of pancreatic carcinoma than patients with inborn genetic alterations, there must be other genetic and environmental factors. The acquisition of somatic mutations in the ductal pancreatic epithelial cells eventually giving rise to the carcinoma is another well-investigated area. Again, many genetic alterations have been described [7]. The ones which are detected most frequently are mutations in the k-ras oncogene and p53 tumor suppressor gene. There is experimental evidence that mutations in these genes can drive an epithelial cell to build tumors [8, 9]. Furthermore, chronic pancreatitis, a condition leading to pancreatic carcinoma [10] was also shown to harbor ras and p53 mutations [11]. From all this experimental evidence from the genetics of hereditary and sporadic pancreatic carcinoma, a step-by-step model of pancreatic ductal carcinoma pathogenesis was proposed summarizing the putative sequence of molecular events in analogy to CRC [12]. This intriguing model makes heavy use of the recently acknowledged early lesions in the pancreas, i.e. pancreatic intraepithelial neoplasia (PanIN) [13]. Although these PanINs are almost impossible to diagnose in a patient without surgery or generous biopsy [14], they clearly mark a transitional lesion for the pancreatic duct epithelial cell on its way to full malignancy. We must utilize all this knowledge for large-scale prospective studies to follow-up what is now called molecular epidemiology.
References