Pancreatic Disorders & Therapy
ISSN: 2165-7092

Franco et al., Pancreat Disorders Ther 2012, 2:3
DOI: 10.4172/2165-7092.1000e119

Editorial Open Access

Deregulation of Developmental Genes in Pancreatic Malignancies

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The concept that neoplastic diseases are characterized by a deregulation of the genes that control, during embryogenesis, the correct development it has now been fully accepted by the scientific community. In fact, the common mechanisms between the two processes are very numerous, and for this reason at the end of eighties, the role of developmental genes in neoplastic transformation and progression has been investigated.

A pivotal role, in this context, is played by the homeobox-containing genes. These genes represent a wide family, subdivided in several classes, of transcription factors mostly involved with the determination of the developmental identity of animal body plan [1].

Their alteration in cancer has been widely described in the last twenty years, particularly for tumors of the gastrointestinal tract [2].

The homeobox genes control embryonic development of the pancreas, especially some genes of the subfamily PAX, such as PAX 4, involved in the differentiation of pancreatic beta cells [3]. But, the gene involved mainly in morphogenesis and functionality of the pancreas, is PDX-1, whose altered expression has been described abundantly in pancreas tumor evolution and progression [4,5]. Another homeobox gene described as a prognostic marker in this tumor is CDX-2, able to down regulate cyclin D1 by inhibiting pancreatic cancer cell proliferation [6]. Furthermore, in several studies it has been shown the pivotal role played by homeobox genes of class 1 (HOX genes in humans) in the pancreas development and carcinogenesis [7]. HOX B2 is expressed aberrantly in pancreatic cancer cells and is associated with a poor prognosis [8]. Moreover, downregulation of HOXD13 is strongly related to clinic outcome of patients with pancreatic tumors [9]. Finally, more recently, it was shown that HOXB7 is able to promote invasion and predict survival in pancreatic adenocarcinoma [10].

In future, the use of ever more advanced and reliable techniques, as gene arrays and tissue microarrays, will allow us to evaluate the simultaneous expression of these markers on large casuistries of pancreatic malignancies, permitting not only to establish their prognostic value, but also to stratify patients to establish new therapeutic strategies.

For many homeobox genes this possibility has already been made in other human cancers, while only one study was performed for targeting of PDX1 in pancreatic tumor cells [11].

However, more accurate functional studies are require for investigating the aberrant activity of these developmental-related genes, and for establishing personalized therapies for pancreatic tumors, as well as has happened for many other known biomarkers.

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Received September 25, 2012; **Accepted** September 26, 2012; **Published** September 29, 2012

Citation: Franco R, Cantile M, Botti G, Tatangelo F (2012) Deregulation of Developmental Genes in Pancreatic Malignancies. Pancreat Disorders Ther 2:e119. doi:10.4172/2165-7092.1000e119