Nerve growth factors elevated in pancreatic cancer model

June 19 2012

Severe pain is a major symptom of pancreatic cancer. The results of a new study show that four different factors involved in the growth and maintenance of nerves are elevated in a mouse model of pancreatic cancer. This is a step forward in understanding the relationship between the development of pain and the progression of pancreatic cancer.

"When other researchers have looked at samples of pancreatic cancer, they have described perineural tumor invasion in as many as 90 to 100 percent of cases," said Rachelle E. Stopczynski, a M.D./Ph.D. student at the University of Pittsburgh in Pa. "We used a mouse model of pancreatic cancer to look at what drives these interactions, and to investigate what role tumor-nerve interactions play in cancer progression ."

She presented these findings at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference.

Stopczynski and colleagues measured the levels of neurotrophic factors, which are proteins in charge of the growth and maintenance of nerve cells, in the pancreata of mice with a condition modeling pancreatic cancer and healthy controls aged between 16 and 30 weeks. They also measured the density and distribution of nerve fibers in the pancreas and observed levels of physical activity.

Expression levels of four neurotrophic factors were higher in the pancreata of mice with pancreatic cancer. Nerve bundles were also

observed to be larger and the overall physical activity undertaken by the mice with pancreatic cancer was reduced.

This adds important information to our understanding of pancreatic cancer, especially since not all cancers invade peripheral nerves as pancreatic tumor cells do, and not all cancers cause the same level of visceral pain, according to Stopczynski.

"A tumor invading a nerve is going to damage that nerve, causing pain. The nerve can also shield the tumor cells from chemotherapeutic drugs, while at the same time serving as a pathway for tumor cells to spread to other organs. Therefore, these interactions could be responsible for different aspects of cancer progression as well as the development of pain," she said.

More information:

Abstract

Neuroplastic changes and pain-related behavior in a transgenic mouse model of pancreatic ductal adenocarcinoma (PDAC). Rachelle E. Stopczynski1, Kathryn M. Albers1, Klaus Bielefeldt1, Ronald A. DePinho2, Haoqiang Ying2, Brian M. Davis1. 1University of Pittsburgh, Pittsburgh, PA, 2University of Texas MD Anderson Cancer Center, Houston, TX.

Pancreatic ductal adenocarcinoma (PDAC) is associated with significant morbidity and mortality. Morbidity in PDAC is partly due to the severe pain reported by patients with the disease. Tumor-nerve interactions including intrapancreatic perineural invasion, neurogenic inflammation, and neuritis are key features of pancreatic malignancies and are thought to play an important role in pancreatic cancer-related pain. Furthermore, neurotrophic factors such as nerve growth factor (NGF), glial cell line-

derived neurotrophic factor (GDNF), GDNF family member artemin (Artn), and brain-derived neurotrophic factor (BDNF) have been implicated in the development of PDAC-related pain. These neurotrophic factors have been shown to produce hypersensitivity in sensory afferents and may drive the neuropathology underlying PDAC pain. Thus, we hypothesized that neurotrophic factors would be increased in the pancreas of PDAC mice as tumors develop, leading to altered pancreatic innervation and changes in pain-related behavior.

Experiments were performed with transgenic mice that have pancreas-specific expression of a mutated Kras oncogene and heterozygous deletion of the p53 tumor suppressor gene (p48-Cre; LSL-KRASG12D; p53lox/+). PDAC mice demonstrated a varied disease time course but generally developed multifocal pancreatic cancer by week 16 as evidenced by nodular-appearing pancreata. Obstruction of the biliary tree, tumor involvement throughout the mesentery, and metastases to the liver were also observed in some PDAC mice at more advanced stages of disease (> 25 weeks). Sex- and age-matched littermate transgenic controls were used for all experiments. Pancreas RNA was isolated from PDAC mice and controls at 16-30 weeks of age and levels of neurotrophic factor and neurotrophic factor receptor mRNA expression was measured using PCR and qRT-PCR. Indeed, expression of NGF, the NGF receptor TrkA, Artn, GDNF, the GDNF receptor GFRα1, BDNF, and the BDNF receptor TrkB were all increased in the pancreas of PDAC mice compared to controls. Immunohistochemical studies were performed to examine the density and distribution of nerve fibers in the pancreas of PDAC mice. Large nerve bundles that stained intensely with the pan-neuronal marker PGP 9.5, tyrosine hydroxylase (TH; NGF-responsive sympathetic fibers), calcitonin gene-related peptide (CGRP; sensory fibers), and growth-associated protein 43 (GAP-43; nerve sprouting) were observed in the pancreas of PDAC mice but not controls. Open-field, exploratory behavior was monitored in PDAC mice between 16-30 weeks of age. Specifically, animals were placed in

Plexiglas boxes and their activity in both the horizontal plane and vertical plane was measured photoelectrically for a period of 15 minutes. PDAC mice spent less time moving horizontally and vertically, had a reduced number of reaching movements into the vertical plane, traveled less distance in the vertical plane, and made fewer movements in the vertical plane.

These data indicate that significant changes in pancreatic innervation and neurotrophic factor expression occur in a transgenic mouse model of pancreatic cancer and these changes correlate with pain-related decreases in ambulatory and reaching activity. Thus, this animal model will enable us to systematically study the impact of neuroplastic changes in the PDAC microenvironment on the development of pancreatic cancer-related pain.

Provided by American Association for Cancer Research