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When the Microbiome Meets Cancer Immunotherapy

BY EMESE ZSIROS, MD, PHD, FACOG

The human body is a large reservoir of microbial cells, such as bacteria, fungi, and viruses, that live with a symbiotic and commensal community with our body. The human body houses over 100 trillion (10^14) microbes, with over 3.3 million unique microbial genes—which means these microbes outnumber our own body cells by at least 10 times.

Most of these microbes live in the human gastrointestinal tract—particularly in the colon, which provides optimal growth conditions. *Firmicutes* and *Bacteroidetes* are the two dominating bacterial divisions in the gut, comprising more than 1,000 bacterial species. The human microbiome plays an essential role in food digestion and nutrient absorption, homeostasis of the epithelial

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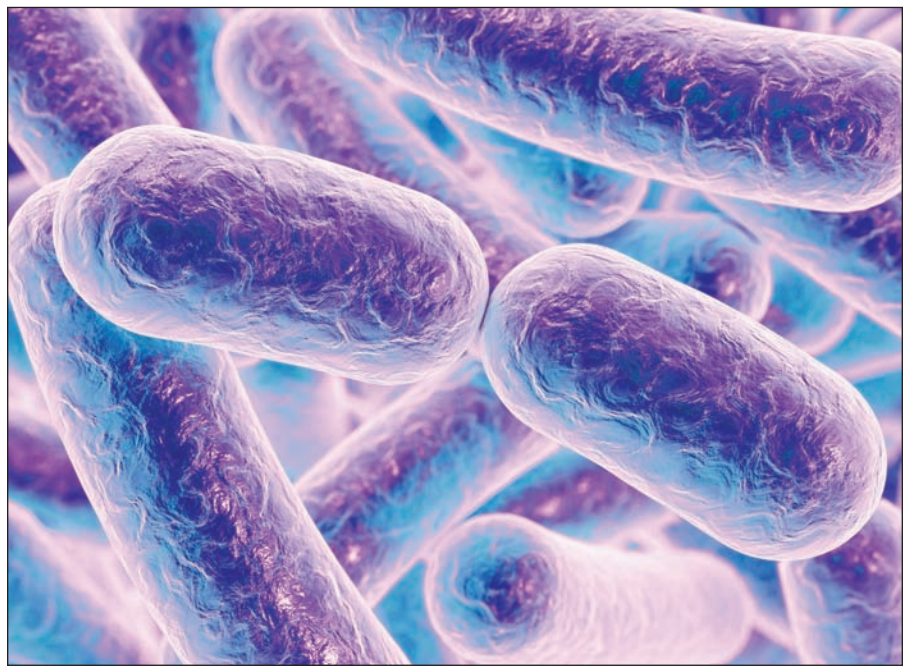

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Pancreatic Cancer-Induced Diabetes: A Call To Action

BY RICHARD FRANK, MD

"Will I be cured? Could it have been caught earlier?" These are perhaps the two most pressing questions all newly-diagnosed cancer patients ask. When it comes to pancreatic cancer, although we soften our answers with qualifying paragraphs, the answers invariably come down to "no and no." Fortunately, the response to the second question may be undergoing a sea change, with the potential to influence the first.

CME Article

Approximately 50 percent of individuals diagnosed with pancreatic cancer have diabetes mellitus, usually type 2. In over 75 percent of those cases, the diabetes was diagnosed within the preceding 24 months, suggesting new-onset diabetes mellitus (NoDM) may be a signpost for an earlier pancreatic cancer. This association

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Antibiotic Reduces Infection Risk in Young Leukemia Patients

St. Jude Children's Research Hospital researchers in Memphis, Tenn., have identified an antibiotic that significantly reduced the odds of infections in children starting treatment for acute lymphoblastic leukemia (ALL) without an apparent increase in antibiotic resistance (*Clin Infect Dis* 2017; https://doi.org/10.1093/cid/cix644).

The study was the largest yet focused on the safety and efficacy of proactive antibiotic therapy to prevent infections in pediatric ALL patients during induction therapy. These early weeks of chemotherapy often lead to neutropenia that leaves patients at risk for life-threatening infections that can delay cancer treatment. Nationwide, up to 4 percent of young ALL patients die from treatment-related infections.

"This research provides the first major evidence supporting targeted use of antibacterial prophylaxis for at-risk pediatric ALL patients, particularly use of the broad-spectrum antibiotic levofloxacin," said lead author Joshua Wolf, MD, Assistant Member of the St. Jude Department of Infectious Diseases. The findings have been incorporated into Total Therapy XVII, the current St. Jude clinical trial for children and adolescents newly-diagnosed with ALL.

Researchers reported that preventive therapy with levofloxacin or other antibiotics reduced the odds of infection, including fevers and bloodstream infections, by 70 percent or more in ALL patients with neutropenia during induction therapy. Levofloxacin also reduced patients' odds of antibiotic-associated infection with *Clostridium difficile* by 95 percent or more. Hospital-acquired

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PERIODICALS

Pancreatic Cancer-Induced Diabetes: A Call To Action

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is the subject of intensive research and the focus of a new prospective clinical trial.

Cause or Consequence?

Pancreatic cancer and diabetes are locked in a complicated dance, both pathogenetically and temporally. In the setting of a new pancreatic cancer diagnosis, the timing and course of the diabetes can be divided into three main categories:

1. long-standing diabetes: present for at least 3 years;
2. new-onset diabetes: variably defined as less than 1-3 years;
3. rapidly-deteriorating diabetes: sudden worsening of chronic, stable diabetes.

Each situation begs the question, "Which came first, diabetes or pancreatic cancer?" Aside from the fact that both diseases occur in the same organ, there is not a priori reason that one should directly impact the other. It has been appreciated for decades that long-standing diabetes is a risk factor for pancreatic cancer (RR 1.5-2), along with obesity, smoking, chronic pancreatitis, and others. In this situation, an environment of chronic hyperinsulinemia and inflammation is thought to promote or cause pancreatic cancer (*Diabetes* 2017;66:1103-1110). A dose-response meta-analysis found that, across the range of prediabetes and diabetes, every 10 mg/dL increase in fasting blood glucose increases the risk of pancreatic cancer by 14 percent (*BMJ* 2015;350:g7371). Additionally, the association of worsening glycemic control with pancreatic cancer in long-term diabetics is being increasingly appreciated (2017 European Cancer Congress, Abstract 540).

Focus on New-Onset Diabetes

One of my patients, whom I met a year ago, was a vigorous, 52–year-old non-smoking male with no family history of cancer. He was enjoying fulfilling work and a loving family when he developed persistent indigestion. After several months, pain and jaundice led to a diagnosis of borderline-resectable pancreatic cancer. Just as I was thinking how tragic his situation was, he said, "Oh, and by the way, I developed diabetes 10 months ago." My jaw dropped, having become a recent student of this field. My thoughts immediately veered off to "Would his cancer have been easily resectable back then? Would an earlier diagnosis have made a difference?"

A meta-analysis of 88 independent cohort and case-control studies examined the association between diabetes and pancreatic cancer. While the overall RR was 1.97 (95% CI 1.78-2.18), it was 6.7 at less than 1 year compared with 1.4 at 10 years (*Ann Surg Onc* 2014;21:2453-2462). In a study from the Mayo Clinic of 2,122 individuals with NoDM, age 50 and older in Olmstead County, Minn., 18 (0.8%) were diagnosed with pancreatic cancer within 3 years. Overall, NoDM conferred a 7.9-fold increased risk of pancreatic cancer (*Pancreas* 2015;44:693-712).

In NoDM, the diabetes is thought to be the consequence of an underlying, subclinical pancreatic cancer (although usually diagnosed as type 2, this type of "pancreatogenic" diabetes is classified as type 3c). How does a developing cancer cause insulin resistance and diabetes mellitus? Accumulating research supports a novel mechanism of metabolic crosstalk, wherein pancreatic cancer cells release extracellular vesicles (exosomes) into the bloodstream, carrying a payload of gene-altering microRNA molecules. The impact of pancreatic cancer exosomes on target tissues is protean, from islet B-cell dysfunction to insulin resistance in skeletal muscle, ultimately contributing to the sarcopenia and cachexia that is universal in late stages of the disease (*Scientific Reports* 2017;7:5384). Importantly, both circulating exosomes and their miRNA content are being investigated as possible biomarkers of early stage pancreatic cancer.

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Novel Approaches to Early Detection

The early detection of several malignancies has proven effective in reducing cancer mortality rates. Since survival of pancreatic cancer is directly related to tumor size and stage, it is estimated that early detection could improve long-term survival by 30-40 percent (*Nat Rev Gastroenerol Hepatol* 2016;13:74-75). Both endoscopic ultrasound (EUS) and MRI/MRCP have found the most success in recent pancreatic cancer screening studies of those at the highest genetic risk (*JAMA Surgery* 2015;150:512-5188,9, *J Clin Oncol* 2016;34:2010-2019). The ongoing Cancer of the Pancreas Screening Study 5 (CAPS5, NCT02000089) utilizes both modalities to screen this high-risk population. Hereditary cases, however, account for less than 10 percent of all pancreatic cancer cases. Thus, we are left with the conundrum of whom to screen for the other 90 percent of cases in the general population.

Screening Patients With NoDM

Many experts have called for a "2-sieve approach" to screening for sporadic pancreatic cancer, with NoDM as the first sieve and a serum biomarker or other form of enrichment as the second sieve (*Pancreas* 2016;45:1073-1079). The resultant at-risk population would then undergo periodic MRI or EUS. Given the rapid rise and descent of the risk of pancreatic cancer in NoDM, testing would only need to be done for 3 years. A current limitation of this approach is a reliable second sieve does not exist. This should not prevent us from designing clinical trials around this paradigm.

The Western Connecticut Health Network has initiated a pancreatic cancer screening trial in individuals over 50 years of age with NoDM, defined as being diagnosed within the past 12 months, according to standard American Diabetes Association criteria (HbA1C ≥ 6.5%). Those with prediabetes would require an increase in HbA1C of 1.5 percent over their prior value. Other inclusion/exclusion criteria are listed on ClinicalTrials.gov (identifier NCT03250078).

Eligible participants will be evaluated by an APRN, undergo a brief psychological survey, and have serum taken for a biobank every 6 months. They will undergo contrast-enhanced MRI/MRCP at entry and annually for 3 years. All costs will be covered by the study, which is presently supported by philanthropy. The enrollment target is 800. The main goals are to prospectively determine the incidence of pancreatic cancer or precursor lesions in those with NoDM and to develop a biobank of sera in the years leading up to the diagnosis that may be used for biomarker development.

Acknowledging the need to enroll many more individuals with NoDM than our one network can accomplish, we hope to partner with other medical centers in our state and ultimately combine our data with those from across the U.S. who are undertaking similar studies. As the Chinese philosopher Lao-Tzu wrote, "The journey of a thousand miles begins with a single step." OT

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Learning Objective for This Month's CME Activity: After participating in this CME activity, readers should be able to describe current information about research on whether new-onset diabetes mellitus may be an indicator of pancreatic cancer.