Closer Look

NIDDK/NCI Workshop on Pancreatitis-Diabetes-Pancreatic Cancer

June 12-13, 2013: Bethesda, MD Day #1 - Draft

Executive Highlights

Hello from the NIH in Bethesda, Maryland, where we are digesting the learnings from Day #1 of the NIDDK workshop on diabetes, pancreatitis, and pancreatic cancer. As background, we previously discussed the high-level takeaways from today's presentations in our mid-day report, available at http://www.closeconcerns.com/knowledgebase/r/eeb7ef00. In this report, we bring you more detailed coverage of the individual talks; overall, we felt that today provided a valuable look at the science behind this issue and set the stage for the more clinically-oriented discussion that will take place tomorrow.

A highlight of this morning was an engaging presentation by Dr. Albert Lowenfels (New York Medical College, Valhalla, NY) on the association between chronic pancreatitis and pancreatic cancer. Focusing on epidemiological studies, he reviewed data suggesting that people with chronic pancreatitis have an increased risk of pancreatic cancer, though the magnitude of the relative risk varies by study. Diabetes also seems likely to be a risk factor for pancreatic cancer, as persuasively argued by Dr. Vinciane Rebours (Beaujon Hospital, Clichy, France).

The afternoon included an in-depth discussion of "type 3c" diabetes, described as diabetes that presents with pancreatitis. Dr. Nils Ewald (Justus-Liebig-University, Giessen, Germany) cited data from his study showing that in western populations, chronic pancreatitis-induced diabetes accounts for 7% of all diabetes cases. In the same session, Dr. Suresh Chari (Mayo Clinic, Rochester, MN) discussed mechanisms through which pancreatic cancer causes diabetes. He focused on the protein adrenomedullin, which influences both cancer development and hyperglycemia, and could thus mediate the effects of pancreatic cancer on the beta cell. As for clinical care in type 3c diabetes, Dr. Michael Rickels (University of Pennsylvania Perelman School of Medicine, Philadelphia, PA) presented the latest expert recommendations. He also looked forward to studies that could provide much-desired clinical data on how type 3c diabetes should be diagnosed and treated.

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Detailed Discussion and Commentary Session 1: Overview of the Problem

PANCREATIC CANCER: THE PROBLEM

Margaret Tempero, MD (University of California at San Francisco, San Francisco, CA)

Dr. Margaret Tempero reviewed current understandings of pancreatic cancer, the fourth leading cause of cancer death in the US. She reminded listeners that the five-year survival rate is only 6% but expressed optimism that survival can improve with wider use of new chemotherapeutic agents, as is being done in her center. She also believes that screening might be clinically valuable and cost-effective, if and when researchers develop a biomarker that can narrow down the at-risk population to 25% or less of the general population. (Dr. Tempero explained that unlike colonoscopies for colon cancer, imaging studies for pancreatic cancer would not be cost-effective for the general population, because pancreatic cancer is so much more rare.) As for screening efforts today, Dr. Tempero noted that some genetic subpopulations are already known to have extremely elevated risk, but few people fall into this category. Diabetes, pancreatitis, and the presence of pancreatic intraepithelial neoplasms (PanINs) are also risk factors, but the rates of cancer incidence are not as high, and the causal relationship is less clear. For example, one progression of cancer is known to involve PanIN-1 lesions, which can progress to PanIN-2 lesions, PanIN-3 lesions, and ultimately cancer. But PanIN-1s are extremely common among middle-aged adults, and the factors that lead some people's lesions to become cancerous are not well understood.

Questions and Answers

Q: You said that PanIN-2 and PanIN-3 are likely to lead to invasive disease. We know from autopsies that PanIN-1s are common in people over 50; your statement implies that there must be a low rate for PanIN-2s and -3s. Do you indeed see a low rate of these?

A: I don't think anyone would have any numbers. Is a pathologist presenting at this meeting? The association came out of studying the uninvolved pancreata of people who have had resections, and seeing the prevalence of PanINs in those uninvolved pancreata. That has been my understanding.

Q: Yes, but in those people it is mostly PanIN-3, correct?

A: I think that we see PanIN-2 as being on the way to PanIN-3.

Q: How do you envision using a biomarker test - before or after imaging studies?

A: I envision biomarkers' being used before imaging studies. I see biomarkers as a crude way to identify that someone's pancreas needs another look, which would lead to the hopefully minimally invasive procedure, which could then be justified economically. To make it cost-effective, we would need the biomarkers to identify 25% or less of the overall population.

Q: Right now we are being drowned by cystic pancreatic tumors. It costs a lot to follow these up. How important are these quantitatively to pancreatic cancer?

A: I think that others, more experienced than I, will be speaking about this.

Session 2: Chronic Pancreatitis as a Risk Factor for PDAC

EPIDEMIOLOGY OF PDAC RISK IN CP POPULATIONS

Albert Lowenfels, MD (New York Medical College, Valhalla, NY)

In a thoughtful and well-structured presentation, Dr. Albert Lowenfels discussed the link between chronic pancreatitis and pancreatic cancer, focusing on epidemiological data and potential research problems. In opening, he remarked that this workshop marks the first time that exocrine and endocrine specialists have come together to solve the issue of pancreatic cancer. In looking at the issue, he explained that since many inflammatory agents and conditions are known to cause cancer, a relationship between chronic pancreatitis (which is inflammatory) and pancreatic cancer is not surprising. Turning to epidemiological studies, he reviewed three sets of data that indicate that risk of pancreatic cancer is increased in patients with chronic pancreatitis (details below). However, interestingly, only a small proportion of patients with non-hereditary chronic pancreatitis will eventually develop pancreatitis cancer (roughly 5% will be diagnosed with cancer over 20 years).

- **Epidemiological studies have provided strong evidence that patients with chronic pancreatitis have an increased risk of pancreatic cancer.** Before reviewing the data, Dr. Lowenfels cautioned that since chronic pancreatitis is quite difficult to diagnose, study investigators cannot be sure that each participant had the condition. Dr. Lowenfels first reviewed pooled data from the Panc4 group suggesting that chronic pancreatitis is associated with a two-to- three-fold greater relative risk of pancreatic cancer (Duell et al., *Ann Oncol* 2012). A meta- analysis of five studies (two record-linkage studies and three cohort studies) confirmed this association and found a risk ratio of 7-8. Three additional cohort studies that looked at chronic pancreatitis and pancreatic cancer also found elevated risk ratios ranging from 11.8 (Ueda, 2013) to 16.5 (the International Study Group, 1993) to 26 (Malka 2002). Combining data from these three cohort studies yielded a risk ratio of 15.10 (95% CI: 11.02-20.67).
- **Dr. Lowenfels highlighted two issues that complicate the study of chronic pancreatitis and pancreatic cancer:** First, risk factors for chronic pancreatitis - and not the condition itself - could explain the increased risk for pancreatic cancer; Dr. Lowenfels noted that smoking and alcohol, both risk factors for chronic pancreatitis, are together associated with ~4- fold increased risk of pancreatic cancer, and thus may explain part of the relationship between chronic pancreatitis and cancer. Second, Dr. Lowenfels also cautioned that pancreatic cancer has a long incubation period and can cause symptoms of pancreatitis, indicating a potential for reverse causality. To resolve these two issues, researchers have turned to hereditary pancreatitis, a rare form that presents in people younger than 20 years - the early onset indicates a low chance that pancreatic cancer causes the disease. Furthermore, hereditary pancreatitis does not share the same risk factors as chronic pancreatitis, since those with the former rarely smoke or drink alcohol. Three studies show that the risk for pancreatic cancer in patients with hereditarypancreatitis is also quite high, suggesting that it is the pancreatitis itself - and not common risk factors or reverse causality - that explains the increased cancer risk.

Questions and Answers

Q: If only 4-5% of chronic pancreatitis patients go on to develop pancreatic cancer over 20 years, what's the difference between those 4% and the 95% of people who don't get it?

A: That's a wonderful question. Why do a very small percent of patients with chronic pancreatitis develop cancer and are they in any way different? I don't have a good answer and I'm not sure how we can go about doing that. If you look at the usual risk factors - smoking, alcohol, etc. - they don't seem to explain the difference. That's a challenging question - we should look for the answer.

Q: Very interesting data. I wonder if you've considered the potential role of K-ras activity. We now know that oncogenic K-ras is not constitutively on but that it needs to be stimulated from the outside. And risk factors for pancreatic cancer - such as smoking and dietary factors and of course inflammation - are all ras stimulants. And K-ras can generate its own inflammation. So regarding the connection between K-ras activity, inflammation, cancer and chronic pancreatitis- if you think about all the data, you'll see that there's a potential mechanistic explanation in K-ras.

A: Great, that's a wonderful comment. I don't have much to add, but in certain parts of the world, if you have something that looks suspicious in the pancreas, your doctors will do a needle biopsy and if they find K-ras, they will take out your pancreas because it's considered a hallmark for pancreatic cancer. The K-ras story is fascinating. It could be the link between inflammation, pancreatitis, and cancer.

Q: Would about the role of infection leading to pancreatitis?

A: We've missed a couple of big things with pancreatic cancer and one of them was the blood group story. We just missed that completely. We don't want to make the same mistake. There have been a few studies looking at infection and we now know that major common cancers are caused by infection. We never would have dreamed that stomach cancer and cervical cancer and head/neck cancer are caused by infection, so sure, I think it's a fruitful avenue to explore.

MECHANISMS OF CP-INDUCED PDAC

David Whitcomb, MD, PhD (University of Pittsburgh, Pittsburgh, PA)

In a clear and engaging lecture, Dr. David Whitcomb summarized the complex mechanisms of chronic-pancreatitis (CP)-induced pancreatic ductal adenocarcinoma (PDAC). He noted that chronic pancreatitis is a disease of one phenotype with many etiologies and that a variety of genetic- environmental interactions affect cancer risk. (He emphasized that the "usual suspects" of smoking and drinking are not the only relevant risk factors, and that - contrary to years of conventional wisdom - smoking is more of a risk factor than drinking.) Dr. Whitcomb focused especially on hereditary pancreatitis, an autosomal dominant disorder in which people are at high risk of acute pancreatitis, subsequent chronic pancreatitis roughly 10 years later, and eventual pancreatic cancer 30-plus years later. However, even in hereditary pancreatitis the situation is complex: among people predisposed to hereditary pancreatitis with "the worst genes possible," only 80% get acute pancreatitis, only half of these get chronic pancreatitis, and fewer than half of these get pancreatic cancer. In the transition from chronic pancreatitis to pancreatic cancer, the key process seems to be a feed-forward loop of activating mutations in KRAS and inflammation mediated by NF-kappa-B. This carcinogenic process can be exacerbated by germ-line mutations affecting DNA damage and repair.

ROLE OF STELLATE CELL ACTIVATION IN PDAC

Rosa Hwang, MD (The University of Texas MD Anderson Cancer Center, Houston, TX)

Dr. Rosa Hwang highlighted pancreatic stellate cells as a key player in the development of pancreatic cancer. She opened by citing Dr. Stephen Paget's long-standing "seed and soil" theory of cancer, which states that tumor cells (cancer "seeds") require a fertile microenvironment ("soil") to grow. This viewpoint is consistent with the finding that pancreatic adenocarcinomas are comprised mostly of cancer-promoting stroma (connective tissue), which supports the cancer cells. Dr. Hwang explained that under conditions of pancreatic cancer, stellate cells become activated (by factors such as TGFβ1, TNFα, IL1, IL6, and IL8) and transform to adopt a myofibroblast phenotype and contribute to the stroma. In a whirlwind review of experiments, Dr. Hwang expounded that these activated stellate cells interact with other elements of the tumor microenvironment to increase cancer cell activity (invasion, migration, progression etc.), to strengthen the tumor's resistance to chemotherapy, and to promote tumor metastasis (the spread of a cancer from one organ to another non-adjacent organ). Dr. Hwang noted that two unique factors secreted by stellate cells - shh and Dkk3 - could be attractive candidates for stroma-targeted therapy. In concluding, she highlighted that many questions remain regarding the role of stellate cells in pancreatic cancer, including their basic biology, their role in early tumor development, the factors they secret, and their interactions within the tumor microenvironment.

ROLE OF CCK IN PDAC DEVELOPMENT

Jill Smith, MD (Division of Digestive Diseases and Nutrition, NIDDK, Bethesda, MD)

Dr. Jill Smith proposed that cholecystokinin (CCK) could be "the forgotten peptide" in pancreatic cancer - a key mediator of risk as well as a promising target for prevention and treatment. Cholecystokinin is secreted by duodenal I cells in response to free fatty acids and amino acids in the gut. In animal models,

cholecystokinin stimulates the release of bile but also has several effects on the pancreas - including the release of digestive enzymes from the pancreatic acinar cells, insulin secretion by the islet cells, and collagen formation by the stellate cells. When animals are exposed to high levels of CCK (whether from exogenous dosing or from exposure to high-fat-diet-induced obesity), those animals have greater risk of pancreatitis and pancreatic cancer. Dr. Smith believes that the normal human pancreas has a similar distribution of CCK receptors (albeit a different type of receptor - CCK-B instead of CCK-A). She also noted that human cancer cells have been shown to over-express receptors to CCK (CCK-C receptors). Therefore she contends that CCK antagonists could be useful for cancer prevention and treatment. She also proposed that CCK-targeting therapies could be used to preferentially attack cancer cells without harming healthy cells. However - as Dr. Smith acknowledged - the translation from preclinical models to humans is not straightforward, and the exact role of CCK remains controversial. (For example, one questioner argued that CCK receptors are expressed in healthy human acinar cells at all.)

Questions and Answers

Q: The best evidence is that the human acinar cell has neither CCK-A nor CCK-B receptors. We published this years ago. Our work was called into question by one of the papers you presented, but it has since been duplicated by other groups. There are indeed CCK-B receptors in the human pancreas, but they tend to be on stellate cells and islet cells.

A: This issue is controversial; this is why I presented the work of others and not just my own. The studies I showed say the opposite of what you just said - that there are indeed CCK receptors on the human acinar cells. I think that we need to keep exploring. These receptors are definitely expressed in pancreatic cancer.

SUMMARY

Eric Duell, PhD, MS (L'Hospitalet de Llobregat, Barcelona, Spain)

Dr. Eric Duell raised a number of potential discussion points inspired by the morning's talks. Most epidemiologic studies of chronic pancreatitis seem to have drawbacks, because they use self-reported data and/or do not distinguish between acute and chronic pancreatitis (which have the same ICD-9 code). On the other hand, self-reported data may be more reliable than in other indications (since a particular kind of pain is so associated with pancreatitis), and chronic pancreatitis and acute pancreatitis may be just two parts of the same disease continuum. Dr. Duell closed with a series of as- yet-unanswered questions: what is the origin of the ductal cells in pancreatic ductal adenocarcinoma - might it be acinar cells? Will knowledge of the cancer cells' origins improve our screening and prevention efforts? Should patients with chronic pancreatitis who present with diabetes be carefully studied and screened? What types of screening would be clinically effective and cost-effective? (After all, Dr. Duell noted, a key goal for this workshop is to improve the identification of people at high risk for pancreatic cancer.)

Session 3: Diabetes as a Risk Factor for PDAC

EFFECT OF COMBINED CP AND DM RISKS ON PDAC DEVELOPMENT

Vinciane Rebours, MD, PhD (Beaujon Hospital, Clichy, France)

Discussing both epidemiology and pathophysiology, Dr. Vinciane Rebours shared her thoughts on how chronic pancreatitis and diabetes are related to pancreatic cancer. Some researchers have proposed that among people with chronic pancreatitis, diabetes is simply a surrogate marker of pancreatic inflammation rather than a carcinogenic factor in its own right. Dr. Rebours argued the contrary: that diabetes and pancreatitis synergistically increase the risk of pancreatic cancer. She cited a multivariate analysis of a retrospective British cohort study in which the adjusted hazard ratio of pancreatic cancer was 12 for people with both pancreatitis and type 2 diabetes, as opposed to an adjusted hazard ratio below 3 for either pancreatitis or type 2 diabetes alone (Brodovicz et al., Diabetes Obes Metab 2012). Dr. Rebours then explained mechanisms by which chronic pancreatitis and diabetes might jointly contribute to "the two key conditions for pancreatic cancer development." The first condition is increased activation and proliferation of the stellate cells, which could be encouraged by hyperglycemia and hyperinsulinemia in the pancreas. (Even if insulin levels are low systemically in pancreatitis-associated diabetes, they are high in the vicinity

of the islets, because fibrosis prevents insulin from diffusing normally.) The other condition of pancreatic cancer development is stress and hypoxia, which could be encouraged by inflammation and hyperglycemia.

Questions and Answers

Q: In the paper that described a 12-fold risk of pancreatic cancer in people with chronic pancreatitis and diabetes, did the authors exclude people whose diagnosis of cancer was made within one-to-two years of the diagnosis of CP?

A: Yes.

MECHANISMS OF DM-INDUCED PDAC

Michael Pollak, MD (McGill University, Montreal, Canada)

Dr. Michael Pollak's presentation highlighted the complex relationships between insulin, insulin resistance, diabetes, and pancreatic cancer. While describing how aspects of the metabolic syndrome could promote cancer, he observed: "it's the classic chicken and the egg problem - there are lots of associations, what's the driver?" The picture grows more complicated when one considers that pancreatic cancer can also occur in the absence of the metabolic syndrome. Dr. Pollak then briefly reviewed data showing that hormones such as adiponectin are related to cancer risk, though such findings are far from conclusive. Turning to metformin, Dr. Pollak noted that clinical data (which he cautioned is hypothesis-generating at best) suggests that metformin can be protective for pancreatic cancer. Mechanistically, metformin decreases ATP production (by acting on complex 1 in the mitochondrial respiratory chain), causing organs to favor pathways that conserve energy. The liver thus decreases the production of glucose, which cancer cells need to proliferate. Dr. Pollak also hypothesized that metformin could act directly on pancreatic cancer cells and decrease their energy supply, causing the cells to stop growing or to die if they continue to expend energy. He ended by commenting briefly on incretin therapies and pancreatic cancer, posing three possible perspectives: 1) incretin therapies encourage pancreatic cancer development; 2) incretin therapies are associated with pancreatic cancer because the need for second-line therapy (i.e., more progressive diabetes) is linked with cancer; or 3) the relationship is spurious and does not need an explanation. He was reluctant to accept any perspective.

ROLE OF PDX-1 IN PDAC DEVELOPMENT

F. Charles Brunicardi, MD (David Geffen School of Medicine at the University of California, Los Angeles, Santa Monica, CA)

Presenting a series of experiments in mice, Dr. F. Charles Brunicardi described a potential cancer treatment using RNA interference (RNAi) to knock down the gene pancreatic and duodenal homeobox 1 (PDX1). Dr. Brunicardi and his colleagues have found PDX1 to be overexpressed in each of the dozens of varieties of pancreatic cancer that they have studied, including pancreatic neuroendocrine tumors (PNETs) as well as pancreatic adenocarcinomas (PDACs). In mice transfected with human cancer cells, RNAi-based knockdown of PDX1 has been shown to significantly reduce tumor size and significantly improve cancer survival rates. (PDX1 is important in normal islet function as well, so knocking out PDX1 could lead to the destruction of healthy islets - however, at least in mice, the islets regenerate after transient PDX1 knockdown.) Dr. Brunicardi is working with the company Gradalis to develop intravenous bifunctional human shRNA-PDX1 nanoplexes (bi-shRNAPDX1 NP) as a therapy for pancreatic cancer; most of the mouse studies that he presented were of bi-shRNAPDX1 NP. He looked forward to pig studies in 2013 and, if all goes well, a phase 1 trial starting in 2014.

Questions and Answers

Q: The shRNA to PDX-1 was very specific for the human PDX-1, so you don't really know from those studies what would happen if you hit to the rodent if you knocked out rodent PDX-1. Did you try mouse PDX-1?

A: Yes. We first saw diabetes. But the islets appeared to regenerate between days 30 and 90. This is exciting - we could do further investigations to see why the islets are regenerating after PDX-1 knockdown.

SUMMARY

Craig Logsdon, PhD (The University of Texas MD Anderson Cancer Center, Houston, TX)

Dr. Craig Logsdon said that his head was spinning from the presentation of complex, conflicting data about diabetes as a risk factor for pancreatic cancer. He mentioned the chicken-and-egg problem and said that epidemiology research has still not untangled the causality of inflammation, diabetes, and cancer ("I couldn't see clearly what was going on"). Given the difficulty of gathering clinical data, he said that "we may wind up having to use animal models, like it or not" - despite the impossibility of direct extrapolation from animals to humans. He said that the problem of pancreatic cancer is important and becoming more so, especially with the rise of obesity. Unfortunately, he concluded, "we don't have the answers yet."

Session 4: Pancreatogenic (Type 3c) Diabetes

CLASSIFICATION AND PREVALENCE OF T3CDM IN CP AND PDAC

Nils Ewald, MD, PhD (Merck & Co., Rahway, NJ)

Dr. Nils Ewald remarked that giving a talk on type 3c diabetes is "rather tough" since the topic has "hardly any data." He first cited several findings that indicate that the exocrine and endocrine functions of the pancreas influence one another. First, the prevalence of diabetes is quite high among people with acute pancreatitis (32% within 3.5 years after the first episode), as well as those with chronic pancreatitis (40-70%). Second, diabetes patients exhibit several markers of exocrine pathology - e.g., a higher risk of acute pancreatitis, a smaller and lighter pancreas, ductal alterations, and a loss of acinar cells. Furthermore, indirect function tests show that exocrine pancreatic insufficiency is present in 51% of type 1 patients and 32% of type 2 patients. These data suggest that some cases of diabetes are caused by chronic pancreatitis, a form of diabetes classified as "type 3c." Dr. Ewald explained that the prevalence of type 3c diabetes is difficult to assess, and different studies have found varying prevalence rates. To investigate this issue, his group conducted a retrospective analysis of 1,900 patients who were diagnosed with diabetes at a German endocrinology center. The data showed a 9% prevalence rate for type 3c diabetes and found that 79% of the type 3c cases were caused by chronic pancreatitis (in contrast, only 8% of the cases were caused by pancreatic cancer). Together, these results indicate that in western populations, chronic pancreatitis-induced diabetes accounts for 7% of all diabetes cases.

DISCRIMINATION FROM T2DM AND MANAGEMENT OF T3CDM

Michael Rickels, MD, MS (University of Pennsylvania Perelman School of Medicine, Philadelphia, PA)

Dr. Michael Rickels shared expert opinions on the diagnosis and treatment of type 3c diabetes from two recent papers, both lead-authored by speakers during this session. Drs. Ewald and Bretzel (Eur J Intern Med 2013) proposed three major criteria for type 3c diabetes: pancreatic exocrine insufficiency (as assessed by fecal elastase or a direct function test), pathologic pancreatic imaging, and an absence of type 1 diabetes-associated antibodies. Another potentially important diagnostic measurement is the secretion of pancreatic polypeptide (PP). After a mixed-meal test, PP levels are normal or high in type 2 diabetes but low or absent in type 3c diabetes. As for therapy, Dr. Rickels said that longstanding type 3c diabetes almost always requires insulin therapy but that no clinical data are available on the best early- stage treatment strategy. According to recommendations from the Pancreasfest 2012 meeting (Rickels et al., Pancreatology 2013), insulin therapy is generally preferred, but metformin should be considered when insulin resistance is present, and non-incretin insulin secretagogues might be considered when patients do not tolerate metformin due to GI side effects. The authors recommend against the use of incretin therapies in type 3c diabetes, at least until those drugs' risks are better understood.

Questions and Answers

Q: Any comment from Dr. Ewald, since Dr. Rickels commented on your recommendations?

Dr. Nils Ewald: I think it's important to stress vitamin D again. Many people with chronic pancreatitis have a vitamin D deficiency. Aside from the bone issues, what about non-classical actions of vitamin D? Correlational

studies show that bad metabolic control is associated with vitamin D deficiency, and immunological studies suggest ill effects as well.

MECHANISM(S) OF PDAC-INDUCED T3CDM

Suresh Chari, MD (Mayo Clinic, Rochester, MN)

In a fast-paced presentation, Dr. Suresh Chari reviewed a cache of data on the relationship between pancreatic cancer and type 3c diabetes. He began by detailing several observations between the two diseases: 1) there is a high prevalence of new-onset diabetes among those with pancreatic cancer; 2) patients show an improvement in glucose tolerance and insulin resistance after pancreatic cancer resection; however, this amelioration occurs only for new-onset diabetes, not for long-standing diabetes; 3) patients with pancreatic cancer-induced diabetes actually experience weight loss prior to diabetes onset, an observation which Dr. Chari believes requires further study. Dr. Chari then discussed potential mechanisms for pancreatic cancer-induced diabetes, focusing on the protein adrenomedullin. Adrenomedullin is mildly overexpressed in pancreatic cancer and appears to be a required factor for cancer progression. Overexpression of adrenomedullin also leads to hyperglycemia in mice and the protein inhibits insulin release in vitro. These findings suggest that adrenomedullin could be a factor through which pancreatic cancer causes beta cell dysfunction. In ending his presentation, Dr. Chari noted that researchers have not yet identified a potential mechanism to explain the insulin resistance and weight loss observed with pancreatic cancer-induced type 3c diabetes.

THE ROLE OF PANCREATIC POLYPEPTIDE IN T3CDM

Dana Andersen, MD (NIDDK, Bethesda, Maryland)

Dr. Dana Andersen gave an excellent primer on pancreatic polypeptide, which he believes could be a key diagnostic and therapeutic tool in type 3c diabetes. Pancreatic polypeptide (PP) is an endocrine hormone that is normally secreted in response to mixed meals. Postprandial PP levels are elevated in type 2 diabetes. However, PP secretion is deficient in type 3c diabetes, especially in the late stages of type 3c diabetes. Thus, Dr. Andersen expressed his hope that primary care practitioners could distinguish type 2 and type 3c diabetes simply by testing blood PP concentrations 30 minutes after a mixed-meal test. (As we understand it, the blood test already exists, but Dr. Andersen acknowledged that clinical trials have not been conducted to confirm the validity of diagnosing type 3c diabetes in this way.) Deficiency of PP is associated with hepatic insulin resistance in both type 1 and type 3c diabetes.

Fortunately, PP-replacement therapy can reduce insulin requirements (Rabiee et al., J Diabetes Sci Technol 2011). Unfortunately, PP has a half-life of roughly seven minutes. Several groups are developing slow-release formulations or PP analogs, but to our knowledge therapies are still in the early stages of development.

Questions and Answers

Q: In type 3c diabetes, there is a bifurcation - insulin resistance in the liver and insulin sensitivity in the periphery. Does this explain the weight loss or go against weight loss, since weight loss is in periphery.

A: That is a good question; I haven't seen data on this.

Q: Is pancreatic polypeptide a good therapeutic candidate?

A: PP unfortunately is metabolized very rapidly - it has a half-life in the body of about 7 minutes, so it has to be given by some sort of continuous infusion. Many groups have been working on formulation or agonist of Y4, which is quite an avid receptor for PP. A group in Chicago has described a formulation of PP within lipid micelles. Other groups have tried to turn PP into an analog that lasts longer but has similar effects. These are all potential therapeutic approaches.

Q: Between the three of you in this session so far, you have persuaded me that type 3c exists, but Dr. Ewald persuaded me that I wouldn't be the one to diagnose it, since this seems so

complicated. Is it realistic that we can differentiate type 3c diabetes? Type 2 diabetes progresses through all the same stages of insulin, C-peptide, and glucagon levels as type 3c diabetes. Other than using a test of pancreatic polypeptide - which I assume would be cost-prohibitive at this point - is there a way to improve our clinical diagnosis?

A: I think the simplest, cheapest, easiest way to discriminate between type 2 and type 3c diabetes would be to give someone a bottle of Boost or Ensure, and then draw a blood sample afterwards. A clinician would do this test in someone who has been diagnosed with type 2 diabetes but who is not obese, or who has no family history - something just doesn't fit. If PP levels are less than 10, the diabetes is pancreatogenic; if over 200, it's type 2 diabetes. This is my hypothesis.

Q: Do we know what is happening in pancreas to cause the decrease in PP?

A: I am fascinated by the work of Dr. Rebours and Dr. Hwang. I want to know what the stellate cells are doing. I bet that they can inhibit PP release. As Dr. Chari says, it happens before a tumor is apparent on CT scan. This is a paracrine effect, not a physical effect of tumors. I would put my money on the stellate cells as the actor.

Q: How do you reconcile the different rates of fecal elastase deficiency and PP insufficiency in type 2 diabetes?

A: That is a good question; I am not sure what is happening there.

SUMMARY

Ake Andren-Sandberg, MD, PhD (Karolinska University Hospital, Stockholm, Sweden)

Dr. Ake Andren-Sandberg emphasized uncertainty in his summary of the session on type 3c diabetes. As many as half of patients with type 1 diabetes and one third of patients with type 2 diabetes may have decreased exocrine function, he noted. Given these blurred lines between different types of diabetes, he wondered aloud whether the type 3c "label" is clinically useful, or whether "ordinary doctors" can treat type 3c diabetes patients in the same way as type 1 and type 2 diabetes patients. He also noted that the guidelines on diagnosis and treatment of type 3c diabetes are not evidence-based and that the clinical community will need to conduct long-term studies to know whether these recommendations improve patient outcomes.

GENERAL OVERVIEW OF DAY #1

David Whitcomb, MD, PhD (University of Pittsburgh, Pittsburgh, PA)

Giving high-level summaries of the day's sessions in chronological order, Dr. David Whitcomb complimented Dr. Tempero for explaining pancreatic cancer and expressed excitement that "for the first time," therapeutic advances seem to be improving pancreatic-cancer survival. He said that "compelling evidence" suggests that chronic pancreatitis is a risk factor for pancreatic cancer, and he believes that diabetes looks like a risk factor for pancreatic cancer as well. Pancreatogenic (type 3c) diabetes has been hypothesized as the link between chronic pancreatitis, diabetes, and cancer. However, Dr. Whitcomb said that this hypothesized relationship has not been properly, systematically evaluated in clinical studies. Looking to the next day's sessions (and beyond), Dr. Whitcomb called for research on how best to approach patients who may be at risk for pancreatic cancer, and how to decide which treatments to use. We very much look forward to clinical discussions tomorrow.

-- by Nina Ran, Joseph Shivers, and Kelly Close