Total Pancreatectomy and Islet Autotransplantation for Chronic Pancreatitis

Pancreatitis causes excruciating abdominal pain that may severely impair quality of life. Patients commonly become addicted to the narcotics prescribed to treat the chronic pain and undergo repeat surgeries to remove parts of the pancreas causing the pain. These surgeries, as well as the general course of the disease, decrease the quantity and efficiency of the insulin-producing islets in the pancreas, contributing to insulin dependence and diabetes. Massachusetts General Hospital’s Pancreas/Islet Transplant Program now offers an innovative procedure aimed at addressing this challenge for patients in New England.

A DUAL PROCEDURE
Traditionally, the rationale for surgically treating chronic pancreatitis has been twofold: to relieve pain while preserving as much pancreatic function as possible in order to prevent diabetes. When other efforts to relieve a patient’s pain fail, physicians may recommend a total pancreatectomy (TP). TP appears to achieve the first pain relief goal while undermining the second goal of preventing the onset of diabetes. An innovative dual procedure follows TP with islet autotransplantation (IAT), intended to restore islet cell function and reduce the risk of diabetes. Together, the treatment is called total pancreatectomy/islet autotransplantation (TP-IAT). Minimally invasive islet transplantation is generally preferable to a pancreas organ transplant, and autotransplantation of islets is more effective at maintaining insulin levels than islet allotransplantation from cadavers—and it does not require lifelong immunosuppression, since the islets are not foreign. TP-IAT is intended to achieve both the goal of relieving pain and the...

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Patients reported decreased narcotic use and pain after undergoing TP-IAT.

and islet transplant surgeon James F. Markmann, MD, PhD, Chief of Surgery, Massachusetts General Hospital.

Regional service, which is overseen by Chief of Surgery Keith Lillemoe, MD, now offers the TP-IAT procedure as a Pancreas/Islet Transplant Program at Massachusetts General Hospital. The combined TP-IAT procedure was pioneered at the University of Minnesota in 1991. Eighty-five percent of patients experienced pain improvement and 59 percent had ceased narcotic use. After three years, about a third were insulin independent, a third required medication or insulin to control blood sugar levels and a third were diabetic.

A myotrophic lateral sclerosis (ALS) degrades motor neurons, causing muscle atrophy, paralysis and death, usually within five years of diagnosis. It has no cure and the only FDA-approved drug, riluzole (Rilutek), only slightly delays progression by reducing damage to motor neurons. Until the 1990s, researchers generally thought the disease was untreatable, and pharmaceutical companies were not invested in drug development for ALS. To stimulate more interest in studying the disease and in developing treatments, Massachusetts General Hospital researcher Merit Cudkowicz, MD, co-founded in 1995 a network group, now known as the Northeast ALS Consortium (NEALS), that comprises multidisciplinary and multi-institutional clinical networks, patient advocacy groups and funding agencies. The consortium’s efforts have resulted in a proliferation of basic and translational ALS research. They have also spurred the initiation of clinical trials testing investigational therapeutic agents and helped improve patient care, quality of life and longevity.

Strides in Understanding and Treating ALS

Several biological pathways, as shown above, play a role in ALS pathogenesis. Glutamate-mediated excitotoxicity is a potential underlying disease mechanism. For patients with familial ALS with a known mutation, antisense oligonucleotide infusion and administration of siRNA molecules are associated with reduced concentrations of mutant mRNA and protein and slowed disease progression in animal ALS models. Protein misfolding and accumulation can be neurotoxic and drugs that increase heat shock protein expression and block misfolded proteins from entering the ER may delay disease progression. Increasing intracellular calcium levels can also be neurotoxic. Several investigational treatment strategies are being pursued, including immunization strategies.

Genetic DISCOVERIES in ALS

In 1993, a Massachusetts General Hospital team led by Robert Brown, MD, discovered the first genetic mutation in ALS, a gene called superoxide dismutase (SOD1). The mutation causes a toxic gain of function independent of the enzyme’s normal activity. SOD1 accounts for 13 percent of familial ALS and 2 percent of all ALS patients.

ALK5 inhibitors and Growth factor replacement strategies

Novel Therapeutic Targets in ALS

ALS disease pathogenesis remains unclear, but a range of targets are being investigated.

(continued on page 4)

Patient Selection

There are a number of criteria for selecting patients for TP-IAT. Typically, the patient’s quality of life has diminished because of severe abdominal pain attributed to the pancreas for at least six months. Also, the patient has a constant need for narcotics despite exhausting all other surgical, medical and non-procedure-based options.

The patient must not resume any prior medication or insulin to control blood sugar levels and a third were diabetic.

Studying the disease and in developing treatments, Massachusetts General Hospital researcher Merit Cudkowicz, MD, co-founded in 1995 a network group, now known as the Northeast ALS Consortium (NEALS), that comprises multidisciplinary and multi-institutional clinical networks, patient advocacy groups and funding agencies. The consortium’s efforts have resulted in a proliferation of basic and translational ALS research. They have also spurred the initiation of clinical trials testing investigational therapeutic agents and helped improve patient care, quality of life and longevity.

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(continued on page 4)
SIRT6 Deficiency: A Driving Force in Cancer Progression

mong the characteristics that cells acquire to initiate and sustain a tumor is their ability to adapt metabolically by switching from cellular respiration to aerobic glycolysis. New research at Massachusetts General Hospital, led by Raul Mostoslavsky, MD, PhD, demonstrates that the SIRT6 enzyme functions as a tumor suppressor by blocking this metabolic switch to glycolysis. Moreover, SIRT6 deficiency is an early event in tumorigenesis and a driving force in cancer progression, independent of oncogenic activation. The research was reported in the Dec. 7, 2012 issue of Cell.1

THE CANCER METABOLISM HYPOTHESIS

Research on cancer cell metabolism began in the 1920s, when German physician Otto Warburg showed that cancer cells switch from metabolizing glucose via cellular respiration to aerobic glycolysis. During the last seven years, evidence has mounted to suggest that metabolic changes play a significant role in tumor development and maintenance. Specifically, aerobic glycolysis provides the intermediate metabolites to sustain cell duplication and growth in rapidly proliferating cells. The question remained whether the metabolic changes depend on the activity of oncogenes. Is the metabolic shift a consequence or a cause of tumorigenesis?

SIRT6, A METABOLIC SWITCH

Dr. Mostoslavsky sought to disentangle cause from effect by investigating sitrins, a family of protein deacetylases with roles in metabolism, as a multi-drug Phase II study and/or a clinical trial cHallenGes

Inhibition of glycolysis in SIRT6-deficient tumor cells can reverse tumorigenesis because the tumor cells have not acquired cancer-causing mutations. Working with mouse embryonic fibroblasts, he found that suppressing SIRT6 expression causes rapid proliferation and tumor formation without oncogene activation. Re-expression of SIRT6 reverses tumorigenesis and reduces glycolysis. Also, SIRT6 regulates cell proliferation by co-repressing the transcriptional activity of Myc, the global regulator of ribosome synthesis, which is required for protein synthesis. The researchers determined that ribosomal genes are up-regulated in SIRT6-deficient cells.

Another challenge for ALS trials is the limited number of ALS patients and the large number of promising therapeutics to be tested. But novel trial designs, such as a multi-drug Phase II study and/or a multistage adaptive design for dosing, could expedite the advancement of the most promising compound at the most effective dose to Phase III studies. As in oncology, ALS may require different agents—or a cocktail of drugs—for different patients, and also for different stages of disease.

CLINICAL TRIAL CHALLENGES

Two Phase III trials of ALS therapeutics—strategies that looked promising in Phase II studies have recently failed—unfortunately a common occurrence in neurological disorders. One drug, dexpramipexole, is designed to increase expression of the enzyme’s toxic gain of function. The researchers are analyzing the data to determine if a subset of participants responded favorably to the drug.

NEALS researchers are investigating stem cell transplant and anti-inflammatory strategies for treating ALS

Dr. Cudkowicz anticipates the advent of focused trials in different population cohorts of people with ALS subtypes, and improved targeted therapy development, as well as increasing team-based interactions among patients, physicians, drug companies, the FDA and funding groups. These developments show promise in improving patients’ quality of life and longevity.

SIRT6 deficiency caused increased glucose uptake by tumor cells and in multiple cell types, even under normoxia. This helped explain his 2006 finding in Cell that mice born with SIRT6 deficiency die of hypoglycemia as a result of up-regulated aerobic glycolysis. Those results led him to hypothesize that SIRT6 may function as a tumor suppressor and that its loss might initiate cancer.

Clinical trial challenges that need to be addressed include:

- The compound, which proved safe in this Phase I study, will be tested in a larger trial for additional safety, dose finding and efficacy.2
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3. Dr. Cudkowicz, who was involved in the Red Flag Campaign, aims to inform general practitioners of the early symptoms of ALS and encourage referral to a specialist, since earlier intervention might slow disease progression. A multi-drug Phase II trial program being piloted in Maine addresses the shortage of ALS specialists in many areas.

QUESTIONS ASKED ABOUT SIRT6

STUDIED WITH

CONCLUSION

Does SIRT6 deficiency promote cell proliferation and transformation?

Cell culture, SOD1 (null) / (immunodeficient) mice

SIRT6 may act as tumor suppressor.

What is the mechanism for tumor formation?

Cell culture, SOD1 mice

SIRT6-deficient cells do not activate cancer-initiating mutations.

Does SIRT6 deficiency promote tumor formation via activating commonly deregulated ERK and AKT oncogenic pathways?

Cell culture, SOD1 mice

Inhibition of glycolysis in SIRT6-deficient tumor cells can reverse tumorigenesis because the tumor cells have not acquired cancer-causing mutations.

Does inhibition of glycolysis abolish tumorigenic potential of SIRT6 KD cells?

Gene expression, human tissue samples

By interacting with ribosomal genes involved in protein synthesis and metabolic pathways, SIRT6 may contribute to cancer cell proliferation.

Does SIRT6 control cancer cell proliferation by controlling genes involved in protein synthesis?

Gene expression, human tissue samples

Low SIRT6 levels correlate with more aggressive colorectal cancers in patients.

Is SIRT6 down-regulated in human cancer?

Mouse model of colon cancer

Animal studies confirmed what was observed in cell cultures and in human cancer genome and tissue analyses.

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Does SIRT6 act as tumor suppressor in vivo?

The research was reported in the Dec. 7, 2012 issue of Cell,3 his group demonstrated that SIRT6 controls expression of glycolytic genes acting as a histone deacetylase.

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SIRT6 DEFICIENCY CAN INITIATE TUMORS

Working with mouse embryonic fibroblasts, he found that suppressing SIRT6 expression causes rapid proliferation and tumor formation without oncogene activation. Re-expression of SIRT6 reverses tumorigenesis and reduces glycolysis. Also, SIRT6 regulates cell proliferation by co-repressing the transcriptional activity of Myc, the global regulator of ribosome synthesis, which is required for protein synthesis. The researchers determined that ribosomal genes are up-regulated in SIRT6-deficient cells.

(continued on page 6)

(continued from page 3) The antisenso technique observes SOD1 gene expression, thus reducing the SOD1 enzyme’s toxic gain of function. NEALS researchers led a Phase I study with ISIS 333611 in patients with ALS from mutations in SOD1. The compound, which proved safe in this Phase I study, will be tested in a larger trial for additional safety, dose finding and efficacy. NEALS researchers are also working to identify new therapeutic strategies that can predict drug response and/or the progression of the disease, such as subtle changes in the motor cortex of ALS patients detected by brain imaging. Another, in collaboration with pharmaceutical companies, is to

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(continued on page 6)
SIRT6 as Tumor Promoter

SIRT6’s inhibition of aerobic glycolysis, anabolic glutamine metabolism and ribosome biogenesis promotes tumorigenesis and tumor growth. Therefore, as observed retrospectively in human tumor samples, it appears that the SIRT6 loss contributes to both tumor development and tumor progression in vivo.

Inhibiting the glycolytic enzyme PDK1 with either RNA interference or the chemical dichloracetate inhibited glycolysis and almost completely abolished tumor formation in the SIRT6 knockout mice, while showing minimal effects in the controls. Also, ribosomal gene expression was up-regulated in the SIRT6 knockout mice, as was glycolysis.

Thus, SIRT6-deficient tumors in mice had more proliferative capacity and were more aggressive than tumors with sufficient SIRT6 activity. But treating these mice with a glycolytic inhibitor shrunk the tumors, without the need to reactivate SIRT6.

FUTURE DIRECTIONS

With this research bolstering the hypothesis that glycolytic enzymes are important targets for cancer therapies, Dr. Mostoslavsky is investigating how general the SIRT6-deficiency-driven metabolic changes are in cancer, and which tumor types will be susceptible to glycolytic inhibition. “Many glycolytic inhibitors are in the drug development pipeline, and they will likely be part of a multipronged approach to cancer therapy,” he predicts. Meanwhile, he believes that measuring SIRT6 expression levels in patient tumors can serve as a valuable biomarker in cancer diagnosis and in predicting tumor progression and response to therapy—all part of the tool kit for personalized cancer medicine.

Intravascular Structural and Molecular Imaging of Atherosclerosis

The majority of the estimated 1 million myocardial infarctions (MIs) that occur each year in the United States arise from structurally mild coronary artery plaques that suddenly rupture and close the artery in previously asymptomatic patients, causing MI or stroke.

In 2011, a large Phase III trial, called Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT), looked at whether angiography and intracoronary imaging could detect these vulnerable plaques before they rupture, enabling early intervention. The trial demonstrated that standalone structural imaging is useful, but not clinically ready to predict which plaques are vulnerable to rupture and MI. To improve the ability to predict and prevent plaque rupture, investigators at Massachusetts General Hospital are developing a novel imaging technique intended to complement structural imaging with a new dimension of information about the plaque’s biological processes, using molecular imaging.

**COMBINING STRUCTURAL AND MOLECULAR IMAGING**

The intravascular angiography imaging technologies that are currently used in the clinical setting focus on the external physical structure of the plaques and vessels. But the characteristics that influence how plaques grow and whether they rupture are fundamentally rooted in molecular and, in particular, inflammatory processes. Structural imaging alone cannot detect these processes, so they cannot make the distinction between biologically vulnerable and stable plaques.

The technique under development at Mass General combines optical frequency domain imaging (OFDI) with fluorescent imaging using optical near-infrared fluorescence (NIRF) molecular imaging.1 In NIRF imaging, injectable NIR fluorescent probes label molecular structures that indicate plaque instability, including enzymes, fibrin, lipids, macrophages and inflammatory cytokines. Probes for both beams of light (OFDI and NIRF) are placed in the same catheter and focused on the same location in the coronary arteries at the same time. The combination provides simultaneous information about the structure and the molecular biology of a plaque.

**PRE-CLINICAL TESTING OF OFDI-NIRF**

Furouc Jaffer, MD, PhD, an interventional cardiologist with the Mass General Institute for Heart, Vascular and Stroke Care, is currently testing OFDI-NIRF in animal models, with plans to take this work into patients within the next two years. By working first in rabbits and now in swine, he is finding that OFDI-NIRF can capture information, including macrophage protease activity, that may be more predictive of plaque rupture. He is collaborating with Guillermo Tearney, MD, PhD, a pathologist and researcher in the Wellman Center for Photomedicine at Mass General, in an effort to bring intravascular optical imaging systems into human arteries.

**IMPLICATIONS FOR PATIENT MANAGEMENT**

The researchers expect that OFDI-NIRF, once translated to human subjects, will improve patient management by detecting vulnerable plaques in high-risk patients early enough to intervene. As the OFDI-NIRF method is invasive, requiring the injection of fluorescent contrast agents and intravascular imaging, it would not be used as a first-line screening or on patients who have already been diagnosed with a closed artery. However, the procedure may become justified for evaluating coronary plaques within high-risk patients, including those with unstable heart attacks or angina. About one-third of MIs each year occur in patients who had a previous MI. In addition, for the many patients who will receive intravascular OFDI structural imaging during cardiac catheterization, adding the NIRF molecular component will be a relatively safe and efficient procedure that could ultimately save lives.

Another application for OFDI-NIRF may be for diagnosing stent injury, in particular unhealed stents. The technique could identify both a newly implanted stent device and the type of tissue around it, and also identify the inflammatory activity at the same location.

**DRUG DEVELOPMENT**

OFDI-NIRF may also facilitate new drug development and testing for coronary artery disease, Dr. Tearney predicts. The technology could help in preclinical testing of a drug candidate by elucidating the molecular mechanism of action. OFDI-NIRF could simplify the clinical trial.

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**Two Imaging Systems, One Intra-Arterial Catheter**

One intra-arterial catheter, as shown below, allows simultaneous microstructural and molecular imaging. OFDI and NIRF systems are combined in a dual-modality rotary junction that rotates and pulls back the imaging probe contained in a transparent catheter sheath. The imaging probe features a double-clad fiber that transmits OFDI and NIRF light through separate channels and focuses the beams onto the sample.

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**Diagram:**

[Diagram showing OFDI-NIRF method and its applications in atherosclerosis research.]

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**References:**

process as well by serving as an intermediate biomarker that predicts outcome with good reliability. Because of the lack of an existing intermediate biomarker, trial investigators currently must follow large patient cohorts over many years to determine the appropriate outcome metric, making such trials expensive and difficult to conduct.

The combined structural and molecular imaging technique is broadly applicable to different organ systems and other diseases, including cancers of the colon, esophagus and lung. Uses will also likely expand as new imaging agents providing different types of contrast for specific cells and molecular activities are developed.

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