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Better Biomarkers for Pancreatic Diseases

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Physicians struggle to evaluate the human pancreas – an organ tucked in the retroperitoneal space behind the stomach and intestines where it is inaccessible to physical examination. Pancreatic disorders remain difficult to detect at early stages and have complex and highly variable clinical courses.

The major nonmalignant chronic diseases of the exocrine pancreas can be broadly divided into 4 categories. Infectious pancreatitis occurs but is uncommon, and traumatic injury can trigger pancreatitis, but accounts for a minority of cases. Monogenetic Mendelian disorders of the pancreas include cystic fibrosis, hereditary pancreatitis, and familial pancreatitis are well known, but together these account for a fraction of the burden of disease. The majority of exocrine pancreatic diseases fall into the fourth category. They include multiple, progressive, complex disorders that appear randomly in some individuals, presenting as recurrent acute pancreatitis, chronic pancreatitis, or pancreatic neoplasms. Pancreatic neoplasms typically occur independent of clinically evident inflammation and detection occurs at late stages because their development is also unexpected. Thus, complex disorders represent the majority of pancreatic disease, their unexpected occurrence, unpredictable clinical course and paucity of effective targeted treatment makes clinical evaluation and management challenging.

What are complex disorders?

Complex disorders are best understood when considered in contrast to the simple disorders that became the foundation and conceptual paradigm of all western medicine. Modern Western Medicine evolved from the 19th century Germ Theory of Disease. This new theory, which replaced the ancient humoral theory of disease, was built on the technological advances of the compound microscope allowing bacteria to be visualized and experimental evidence linked to epidemiologic studies, culture techniques, sterilization, etc. The germ theory predicted that complex disorders arise from invasion of the host by a single pathogenic microbe that is both necessary and sufficient to cause disease. The line of research and evidences supporting the germ theory followed Koch's postulates, with hypothesis generation and the statistical method of null hypothesis significance testing.

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While this approach was amazingly effective for identifying the cause of infectious diseases and a few other disorders, the Germ Theory failed to explain pancreatic diseases (1).

Most complex disorders are acquired diseases believed to arise from gene x environment interactions, gene x gene interactions, etc. These disorders include syndromes like chronic pancreatitis where multiple etiologies have the same pathology, the same pathology has multiple outcomes, and the treatment effect is unpredictable. Understanding complex disorders requires focusing on disease mechanisms rather than symptoms or associations. It relies on modeling and simulation rather than syndrome sub-classification. But resolving complex disorders into its component parts and modeling the predicted effect of variants in a specific subject is necessary to provide guidance for individuals rather than for populations. Improving the health of sequential individuals will improve the health of the population in ways that herd medicine cannot. These new approaches require new technologies and clarity on the relationship between the multiple parts of the underlying systems.

Disease models for complex disorders

A model is a simplified version of a thing that allows certain characteristics to be evaluated under different conditions so that the nature of the thing can be understood. For complex disorders such as chronic pancreatitis an understanding of the disease in an individual patient requires the development of a disease model that allows the component parts to be represented and evaluated in relationship to each other. The model should describe the observation that some individuals with acute pancreatitis progress to recurrent acute pancreatitis, that a subset of this groups continues to progress to chronic pancreatitis, with only a subset of these individuals developing fibrosis, pancreatic exocrine insufficiency, diabetes mellitus, chronic pain syndromes and/or metaplasia, in a defined order but at different rates.

While having a disease model is important, a model alone does not help the physician manage a patient with symptoms of pancreatic disease. For the individual patient to be managed using a precision medicine approach the physician needs to know something about the mechanism of disease, and to have tools to measure pathogenic disease activity, the state of the pancreas and pathologic processes at a point in time, and to track disease activity levels before and after a therapy has been initiated. The things that are used to measure variations in disease state and activity at specific points in time are biomarkers.

Biomarkers

A biological marker or biomarker is a characteristic that is objectively measured and evaluated as an indicator of a normal process, a pathogenic progress, or a pharmacologic response to a therapeutic intervention (2). In disorders with a dynamic and progressive clinical course, specific biomarkers must be identified that correspond to a component of a system that has been modeled, and they must be measured repeatedly to determine changes in disease state and to calculate disease trajectory.

As an example of the use of indicators in a complex, dynamic situation, consider an airplane with autopilot. A skilled pilot sits in the cockpit drinking coffee and relaxing most of the time. They are desperately needed, however, when one of the systems malfunctions, such as the altimeter. In this case the human pilot must focus on a specific component of the complex system that is malfunctioning and obtain information about the altitude of the airplane using various indicators of the airplane status such as visually scanning the horizon, calling a radar stations to get estimates of the airplanes height from the ground, and other measures to calculate trajectory. The pilot continually makes adjustments to the altitude based on this information to make sure that the airplane stays on track to avoid obstacles and eventually makes a safe landing. The pilot does not need to be concerned about the other parts of the aircraft and autopilot that are functioning normally. In the same way a physician must recognize when a component of the normal pancreas autopilot is not functioning properly. They must then identify biomarkers that are tracked over time as indicators of where the patient's pancreas is heading so that disease can be averted and the patient remains healthy. Just as an airplane needs multiple instruments to obtain information on the status of the aircraft at each point in time, multiple biomarkers are needed to monitor the status of a complex biological system. The conference reported in this issue of *Pancreas* describes a process of defining the processes that go wrong, the indicators that the physicians need, and the approaches that scientists have in their toolbox to help guide the physician in detection, management and prevention of major pancreas-related disasters (3).

Risk Factors

In contrast to a biomarker, a risk factor is “any attribute, characteristic, or exposure of an individual that increases the likelihood of developing a disease or injury.” (World Health Organization http://www.who.int/topics/risk_factors/en/). While a risk factor provides information as to the most probable mechanism of disease, a risk factor does not diagnose a disease, measure disease activity, or disease progression. Many risk factors such as genetic variance cannot be changed and therefore the objective of a physician caring for a patient with the risk of a complex disorder is to guide them through life to minimize their chance of developing that disorder.

Approaches to Pancreatitis and Pancreatic Cancer

Recurrent acute pancreatitis, chronic pancreatitis and pancreatic cancer are complex disorders that evolve through various states over time. Pathogenic germline genetic variants appear to be important in complex pancreatic diseases and represent risk factors that generally remain unchanged throughout life. If the pancreatic condition is not congenital, then the undesirable effects of the variants become manifest only with pancreatic stress or injury, altered responses to injury or variants in the repair process. Since the body has duplicate genetic haplotypes, physiologic reserve, and backup systems for the major systems, multiple genetic variants (inherited or acquired) are typically necessary to cause system dysfunction or failure as seen in end stage complex disorders. The effects of these multiple pathways interactions are why a statistical approach that assesses one variant at a time (null hypothesis significance testing as prescribed by the germ theory of disease) fails. However, integration of genetic information into a disease model allows normal and

abnormal functions to be predicted, the likely pathologic mechanism to be identified and provides guidance as to the systems that the physician should monitor more closely.

Complex Disease Models

To organize the steps involved in development of recurrent acute pancreatitis, chronic pancreatitis and pancreatic cancer, to study the component parts and to understand the transition between risk factors and disease activity we developed the sentinel acute pancreatitis event (SAPE) model of pancreatic disease (Figure 1) (4, 5). This model accounts for the observation that many individuals may have multiple susceptibility risk factors but are phenotypically normal through much of their life. Initiation of the inflammatory process requires pancreatic injury to occur at some time point resulting in an episode of acute pancreatitis (clinically evident or subclinical). Under normal circumstances acute pancreatitis is self limited, and there is complete resolution of inflammation with possible regeneration of some parenchyma and return of normal function. However, in a subset of patients the presence of modifying risk factors and additional pancreatic injury or stress leads to either recurrent acute pancreatitis. Of these patients, a subset appear to be at further risk of pathologic fibrosis (see (6)), loss of acinar cells, loss of islet of cells, neuropathology with various pain syndromes and initiation of processes leading to metaplasia and/or development of pancreatic cancer (7). Similar models have been developed for PDAC (8). At each step there may be different risk factors that alter susceptibility to pathology and progression to the next step. But to understand the state of the pancreas at any point in time, and to calculate the trajectory of disease and the response to therapy requires the use of biomarkers.

What is needed for management of patients with complex genetic disorders is the model, the risk factors predicting pathologic responses and the biomarkers that indicate the status of specific features at a point in time. The components of such an approach are being developed by independent groups of physicians and investigators in different institutions, in different disciplines and with different concepts of health and disease. Strategic meetings of members of these diverse groups is required to advance the holistic goals of precision medicine for complex disorders. Specifically, physicians must describe the clinical questions and problems, general agreement is needed for a minimal disease model, epidemiologists, geneticists and models are needed to identify the different important disease processes, and this information must be communicated to scientists who can transform knowledge of biology, physics and molecular tags into the biomarkers that are needed to manage patients.

In summary it is obvious that complex disorders can be very complex (e.g. RAP, CP, PDAC). Multiple mechanisms and pathways that potentially disrupt normal pancreatic function or response to stress or injury contribute to complex pancreatic diseases. Models are critical for organizing complex and dynamic data sets. Risk factors provide clues to mechanisms and biomarkers must be developed as better indicators of disease activity at a specific point in time. Key biomarkers must be measured repeatedly over time to assess disease progression and treatment effect. The physician's focus therefore should be on early detection of pathologic activities, with treatment targeted at preventing disease progression so that the patient never reaches pathologic endpoints.

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Figure 1. SAPE Model of Chronic Pancreatitis

A, Patients may spend years with multiple susceptibility risk factors (left) but remain asymptomatic. B, A stochastic injury to the pancreas is believed to initiate AP, which typical last a few days. This is critical to activating the immune system at multiple levels. The resolution phase is affected by multiple variables (yellow diamond) as genetic and environmental risk factors or modifiers that may alter the healing process, leading to progression of pathology depending on the cell type and system. C, Pathologic variants to the biology of the stellate cell leads to fibrosis, acinar cell loss leads to PEI, islet loss lead to DM, altered neural mechanisms leads to pain syndromes, and altered DNA repair leads to metaplasia and cancer. From Whitcomb⁵.