EDITORIAL

Early Detection of Pancreatic Cancer: Sweet Predictions Speak Volumes

See "Fasting blood glucose levels provide estimate of duration and progression of pancreatic cancer before diagnosis," by Sharma A, Smyrk TC, Levy MJ, et al, on page 000.

Pancreatic cancer offers few sweet promises. As one of the most lethal human cancers,[1,2] surgery is the only chance for cure. Unfortunately, only about 15% of tumors are resectable at diagnosis owing to either locally advanced disease or metastases. The diagnosis of pancreatic cancer is made difficult by the lack of specific symptoms, late presentation, and lack of reliable tests for early diagnosis. Currently, high-risk groups are restricted to either families with genetic syndromes[1] or patients with pancreatic cysts.[3] but this is a small subset of patients with pancreatic cancer (Figure 1). Most patients diagnosed with sporadic pancreatic cancer have risk factors found frequently in the general population, including age, smoking, and diabetes.[4] Accordingly, there is an unmet need for robust clinical risk factors in subpopulations that are at risk for pancreatic cancer. Such risk factors would allow for tailored screening and for an earlier diagnosis when surgical resection is feasible and cure may still be possible (Figure 1*A*).

In this issue *Gastroenterology*, Sharma et al[5] demonstrated a lag time of 2 to 3 years between increases in fasting blood glucose (FBG) and an eventual diagnosis of pancreatic cancer. Consequently, increased FBG could be explored as a cue to earlier diagnosis of pancreatic cancer. However, some considerations need to be born in mind. The difference in FBG between pancreatic cancer and controls started at tumor volumes of >1 mL, when a median tumor diameter was 18 mm (range, 15-20 mm), with the signal becoming stronger at volumes of >2.0 mL (diameter, 22 mm; range, 20-25 mm).[5] Notably, these volumes are at the high end of what is considered as "early" pancreatic cancer (<20 mm; pT1 stage). Also, the signal became stronger in tumors located in the body and tail, known to harbor a different biology[6] with poorer outcomes. Larger volumes were also related to higher rates of node metastases, poor differentiation, and a shorter survival.[5] Thus, one may ask, does the detection of glucose intolerance provide a strong enough signal to allow for earlier diagnosis, when cure is still possible? Also, if glucose intolerance is an early cue signal, what are the mechanisms that lead to its development?

Although several studies have investigated hyperglycemia as a *cause* to cancer (ie, long-term diabetes/hyperglycemia is a risk for the development of pancreatic cancer), the current study adds to hyperglycemias as an *effect* of cancer (ie, having pancreas cancer causes hyperglycemia to develop). The latter observation has been explained as a paraneoplastic syndrome.[7] A mechanism induced by pancreatic cancer cells is the release of exosomes delivering adrenomedullin to β-cells, leading to β-cell dysfunction and death, and consequently to hyperglycemia.[8,9] One may suggest that other biomarker signals related to the metabolic may be explored for even earlier diagnosis when the FBG signal may still be weak.

Pancreatic cancer cells undergo extensive metabolic reprogramming[10] owing to the nutrient-poor and hypoxic environment in the desmoplastic and cell-deprived tumor environment. The metabolic reprogramming occurs at several levels[11] and includes increased autophagy[12] and macropinocytosis.[13] Changes in metabolism is driven by cell-autonomous pathways mediated by, among others, the oncogene KRAS. The unique physiology of the tumor microenvironment is driven by a close tumor–stromal interaction, a strong desmoplastic development, and several cross-linked interactions between cancer cells and noncancer cells, such as fibroblasts, pancreatic stellate cells, and immune cells.[10] KRAS further induces abnormal mitochondrial metabolism and enhance glycolysis, with alterations in glutamine and lipid metabolism.[14] As extrinsic factors, the acidic and oxygen/nutrient-deprived microenvironment also induces cancer cells to reprogram their metabolic pathway and exploit the ability of cancer-associated fibroblasts and immunocytes to communicate, thereby adapting to metabolic stress.[14] Secreted products of these cells may be used as biomarkers. For example, thrombospondin-2 that is secreted by pancreatic stellate cells to promote invasion, demonstrated an earlier diagnosis of pancreatic cancer when measured together with CA19-9.[15]

Thus, measuring FBG may only reflect the metabolic tip of the iceberg and mirrors signals of underlying metabolic processes that were initiated from the very early steps of pancreas cancer progression (Figure 1*B*). However, it could represent a cue for deductive exploration of early events that may be captured in the circulation. Notably, glucose-based energy consumption driven by the oncogene KRAS starts very early in pancreatic cancer development (Figure 1*B*) and is associated with epigenetic reprogramming during tumor progression, development of aggressive tumor behavior, tumor–stroma interaction, and increased metastatic potential.[16,17]

Indeed, further investigation into the mechanisms preceding hyperglycemia may be necessary to capture the steps that lead to changes in the metabolism of pancreatic

EDI 5.5.0 DTD ■ YGAST61963_proof ■ 5 July 2018 ■ 1:34 pm ■ ce

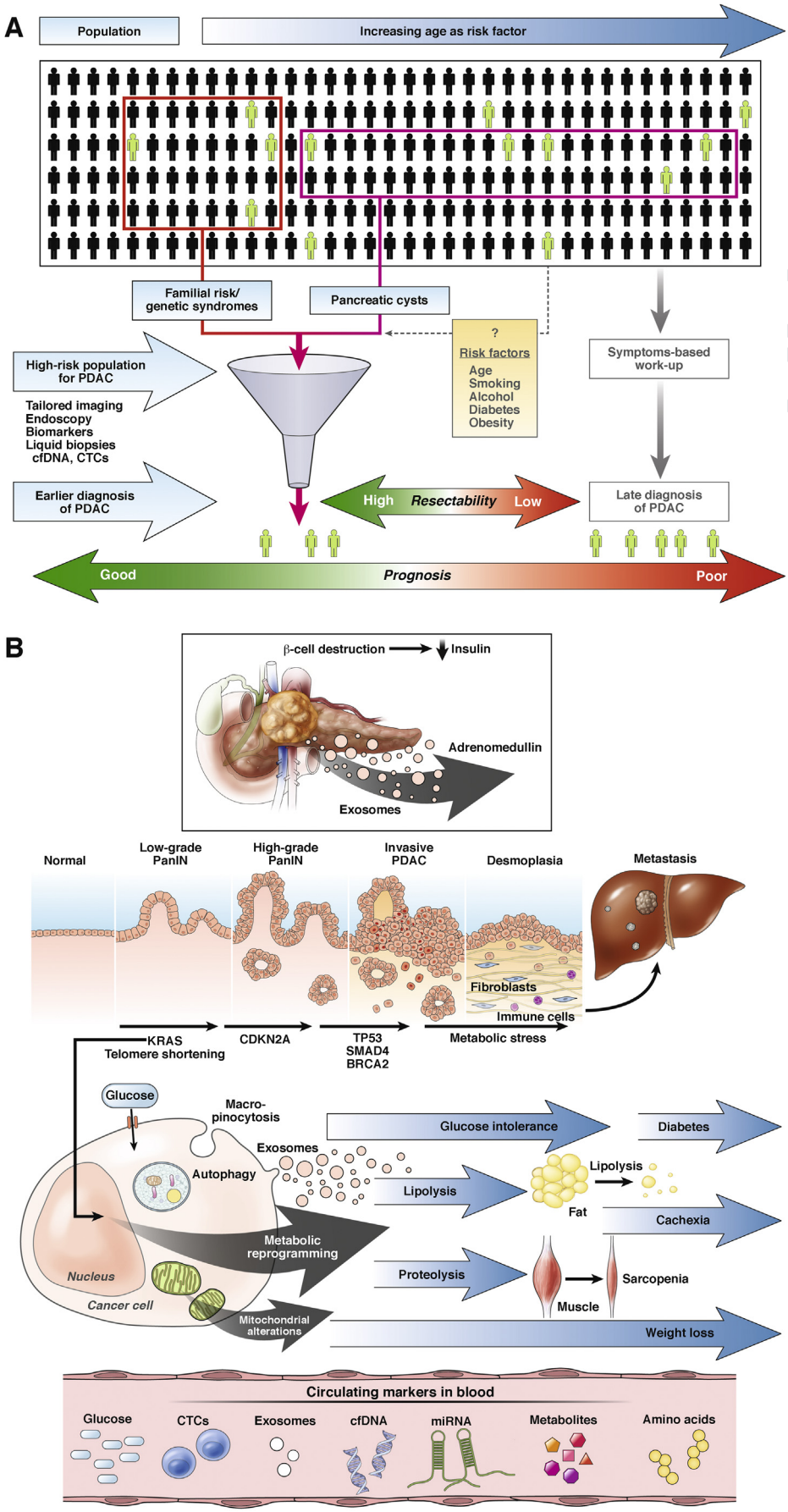

Figure 1. Early diagnosis of pancreatic cancer through metabolic changes. (*A*) Population-based screening of pancreatic cancer is made difficult by its relative low incidence. Risk populations are currently restricted to hereditary genetic syndromes and pancreatic cysts. Risk of pancreatic cancer increases with age, but otherwise the known risk factors are nonspecific (*yellow box*) and there is an unmet need for better risk features. An overall goal is to increase resectability by earlier diagnosis and thus prognosis. This goal can be facilitated by identification of novel high-risk groups that would be suitable targets for tailored surveillance. (*B*) Pancreatic cancer progresses through morphologic changes (PanIN) that eventually progresses to invasive PDAC. Known genetic alterations occur with each step in the progression. Other alterations associated with stepwise progression may be less well-described. PDAC is further characterized by a strong desmoplastic reaction and an intricate crosstalk between cancer-cells and the surrounding fibroblasts and immune cells in the stroma that fosters progression, epithelial–mesenchymal transition, and eventually metastasis. Pancreatic cancer cells are further characterized by a KRAS-driven extensive metabolic reprogramming. This eventually leads to the clinical phenotype of weight loss, diabetes, sarcopenia, and cachexia often seen in patients with pancreatic cancer. Increases in fasting blood glucose, possibly induced by mechanisms such as adrenomedullin-mediated beta-cell destruction may serve as an early cue to pancreatic cancer. Assuming that these molecular processes may occur earlier in carcinogenesis and, thus, may potentially be excreted in the circulating blood (*bottom*), the identification of such sensitive markers may eventually help to facilitate earlier diagnosis of pancreatic cancer at a curable stage. CTCs, circulating tumor cells; cfDNA, cell-free DNA; miRNA, microRNA; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic adenocarcinoma.

EDI 5.5.0 DTD ■ YGAST61963_proof ■ 5 July 2018 ■ 1:34 pm ■ ce