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A UNIFIED PATHOPHYSIOLOGIC CONSTRUCT OF DIABETES AND ITS COMPLICATIONS, INCLUDING MALIGNANCIES, IN THE CONTEXT OF THE B-CELL CLASSIFICATION OF DIABETES: OPPORTUNITIES FOR DRUG DESIGN

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We have previously presented a proposal for a new, beta-cell centric classification of diabetes based on a consilience of genetic, metabolic, and clinical research that have accrued since the current classification was instituted. It recognizes that the beta-cell is THE core defect in all patients with diabetes. Differences in the genetics, insulin resistance, environment and inflammation/immune characteristics of the damage to the beta-cell in each individual will determine the phenotypic presentation of hyperglycemia and allow for a patient-centric, precision-medicine therapeutic approach, part of which we labeled 'the Egregious Eleven'. We now recognize the same pathophysiologic mechanisms that account for damage to the beta-cells that govern the susceptibility of the cells involved in the complications of diabetes to damage by the now well-defined abnormal metabolic environment that typifies beta-cell dysfunction. This abnormal metabolic environment is typified by oxidative stress which alters metabolic pathways a la Brownlee's Hypothesis model, alterations in gene expression, epigenetics, and inflammation. This unified pathophysiologic approach to the complications of diabetes in the context of the B-cell-classification of diabetes allows us to understand the varied risk of developing complications of diabetes with similar levels of glycemic control, how non-glycemic effects of some medications for diabetes result in marked complication risk modification and the value treating comorbidities of diabetes in effecting complication risk. We also believe that the same pathophysiologic mechanism that account for damage to the beta-cells and govern the susceptibility of the cells involved in the complications of diabetes are likely to explain the association of cancer to diabetes and obesity, and explains why diabetic medications may affect cancer risk and therapy. Opportunities for drug design and development abound.

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