Type 2 Diabetes Mellitus
A Metabolic Autoinflammatory Disease

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KEYWORDS

• Beta-cell • Cytokines • Interleukin-1 • Insulin resistance • Islets • Low-grade inflammation • Macrophage • Pancreas

KEY POINTS

- Type 2 diabetes mellitus shares features with autoinflammatory disorders and is known for its recurrent inflammatory skin complications.
- Inhibitory treatments of aberrant inflammasome activation that dramatically cure the diverse rashes, erythemas, hives, pustoloses, and pyodermas of rare autoinflammatory disorders may have a place in the therapy for common disorders, such as type 2 diabetes mellitus, and thereby it is hoped also reduce its dermatologic complications.

THE SKIN AND THE PANCREATIC ISLETS AS AUTOINFLAMMATORY TARGETS: HOMAGE TO PAUL LANGERHANS

To the dermatologist the name of the German histopathologist Paul Langerhans (1847–1888) is as inseparably connected with the dendritic epidermal Langerhans cells as it is with the pancreatic islets of Langerhans to the diabetologist. Langerhans trained at the Friedrich Wilhelm Universität in Berlin with his main mentors Rudolf Virchow (1821–1902) and Julius Cohnheim (1839–1884). While applying the gold chloride staining developed by Julius Cohnheim to study cutaneous innervation in Virchow's laboratory at the Charité Institute of Pathology in Berlin, Langerhans discovered already as an undergraduate student in 1868 the dendritic cells in the epidermis, which he erroneously classified as neuronal cells because of their stellate appearance.[1] Only a year later in his doctorate thesis he described the pancreatic islets and suggested that they were small intrapancreatic lymph nodes.[2]

Tragically, at the age of 41 Paul Langerhans succumbed to the inflammatory consequences of disseminated tuberculosis that he contracted as a 27-year-old Chair of Pathology at the University of Freiburg. He died unknowingly of the functions of the cells that to date bear his name. It would no doubt have been gratifying to him to realize that the Langerhans cells of the skin belong to the innate immune system, and that the pancreatic islets of Langerhans constitute the endocrine pancreas. Most certainly he would have been amazed if he had lived to take part in the progress that in the last decade has united the two anatomically remote and apparently functionally disparate cell types he discovered: that both the Langerhans cell of the skin and the pancreatic β-cell of the islets of Langerhans strongly express the protein complex that is the subject of this special issue of *Dermatologic Clinics* and caused much of the symptomatology that haunted him the last 14 years of his life: the inflammasome.[3–5]

Conflicts of Interest: None.

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THE PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Before reviewing the growing evidence that type 2 diabetes mellitus (T2D) has an autoinflammatory origin, the following list summarizes inflammation in its metabolic context.

- T2D is the metabolic consequence of failure of the insulin-producing pancreatic β-cell to compensate for increased insulin needs.
- Most commonly, insulin resistance caused by obesity is the reason for increased insulin needs; puberty, pregnancy, and certain drugs are additional causes.
- Sedentary lifestyle and inappropriate quality and quantity of foods mediate inflammatory and neurohumoral alterations in appetite regulation, thermogenesis, satiety, and food choices believed to instigate a vicious cycle that contribute to obesity.
- The accumulation of fats, particularly in visceral depots, alters adipocyte differentiation and size that leads to alterations in adipose tissue blood flow, hypoxia, and shear stress activating the transcription, translation, and processing of proinflammatory cytokines and adipokines.
- Adipocytokines elicit a systemic low-grade inflammatory response characterized by discretely elevated C-reactive protein (CRP) driven in particular by circulating interleukin (IL)-1 and IL-6.
- Intrahepatic fat deposition contributes to local inflammation that may progress into nonalcoholic steatohepatitis and potentiate the systemic inflammatory response.
- Circulating proinflammatory cytokines may amplify insulin resistance by interfering directly with the insulin signaling cascade in liver, skeletal muscle, fat, and pancreatic β-cells and stimulate proinflammatory gene transcription in these tissues and in the hypothalamus, further contributing to neurohumoral dysregulation of metabolism; however, clinical proof-of-principle is lacking.
- The increased insulin need caused by insulin resistance is initially compensated by expansion of the functional β-cell mass and secretory hyperactivity leading to hyperinsulinemia.
- Insulin is a potent macrophage chemoattractant and compensatory hypersecretion may be a primary cause for increased recruitment of islet macrophages.
- With insulin, islet amyloid polypeptide (IAPP) and extracellular danger-associated molecular patterns (DAMPs), such as ATP, are secreted. IAPP and ATP are believed to activate the intraislet macrophage and β-cell inflammasomes leading to local secretion of IL-1, known for long to signal β-cell apoptosis.
- Once β-cell functional mass starts to decline, insulin secretory decompensation follows, leading to impaired glucose and lipid homeostasis and eventually overt T2D.
- Elevated extracellular glucose and lipids (glucolipotoxicity) in turn enhance insulin resistance and β-cell dysfunction, believed in part to involve inflammatory pathways and inflammasome activation in insulin-responsive and insulin-secreting cells. This accelerating process leads to the progressive metabolic deterioration of T2D.
- Blockade of IL-1 signaling improves glycemia and β-cell function, but not insulin resistance, in particular in patients genetically deficient in endogenous production of the naturally occurring IL-1 receptor antagonist. Thus, T2D shares properties with the genetic deficiency of IL-1Ra syndrome.
- T2D and Alzheimer's disease share genetic susceptibility genes, cooccur more frequently than expected, and in both diseases inflammasome activation by IAPP and β-amyloid has been implicated in β-cell and neuronal failure, respectively.

Thus, accumulating genetic, preclinical, and clinical evidence supports a primary role of inflammasome activation in T2D, justifying the inclusion of T2D to the group of autoinflammatory diseases. This appreciation may provide novel therapeutic options for the treatment of T2D.[6–9]

T2D AND THE DEFINITIONS OF AUTOINFLAMMATION

Autoinflammatory diseases are clinical disorders marked by abnormally increased sterile inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant genetic or epigenetic host predisposition.[10]

With the recognition that T2D is characterized by sterile low-grade systemic inflammation, discrete but significant inflammatory cell infiltrates in fat, liver, and islets of Langerhans and in most organs affected by the late diabetic complications (ie, the vascular wall, the glomerulus, and the retina), a polygenetic predisposition, and significant and dynamic epigenetic changes, such as gene methylation/demethylation induced by inactivity, metabolic, and inflammatory factors, it is