Transcriptional control of inflammation as an innate immune sensor of metabolic stress in diabetes

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Abstract

In type-2 diabetes, sterile inflammation efferent from innate immunity is causal in the onset of insulin resistance and progression of complications and comorbidities. However, the precise metabolic stressors and their processing by innate immune cells remain elusive. Our aim is to determine which metabolic factors are immunogenic and to decipher the cellular metabolic pathways that integrate such signals and lead to an Inflammatory activation. We recently demonstrated that the type-1 interferon response underlies diabetogenic, genetic deletion of its mediator, interferon regulatory factor (Irf)-5, rescues mice from insulin resistance and steatohepatitis. Unexpectedly, the Irf5-deficient transcriptome in macrophages was characterized by up-regulation of pathways governing cellular lipid metabolism. In this capacity, we propose that Irf5 and its dependent transcripts, act as metabolic sensors, relaying glucolipotoxicity and mediating adaptive cellular metabolism for effective inflammatory activation. To address this we have carried out in-depth analysis of the macrophage cellular energetic and metabolic environment in response to metabolic stressors under Irf5-competence and Irf5-deficiency. We observed that indeed Irf5 and its inflammatory targets are responsive to specific metabolic stimuli. In a human study we analyzed Irf5 expression in circulating innate immune cells to determine the prognostic value of innate immunityâ??s sensitivity to metabolic cues. We observed that Irf5 expression is responsive in circulating cells from type-2 diabetic patients and is associated with specific serological parameters relating to dyslipidemia. Interestingly, Irf5 in monocyte and dendritic cell subtypes is specifically regulated in the presence of vascular and hepatic complications of long-standing diabetes. These data suggest that initiation of the type-1 interferon response is extremely sensitive to metabolic status and may be predictive of disease progression or susceptibility to diabetic complications. Further studies will delineate the pathways linking metabolic cues to activation of Irf5, developing novel immunotherapeutic targets in diabetes.

The metabolic syndrome is defined by the presence of metabolic abnormalities such as obesity, dyslipidemia, insulin resistance, and subsequent hyperinsulinemia in an individual (1). Dyslipidemia, the main characteristic of metabolic syndrome, is defined by decreased serum levels of high-density lipoproteins (HDLs) but increased levels of cholesterol, free fatty acids (FFAs), triglycerides (TG), VLDL, small dense LDL (sdLDL), and oxidized LDL (ox-LDL) (Table 1) (2). Individuals with the metabolic syndrome are much more likely to develop type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVDs), and fatty liver disease (2–4). T2DM, the most common form of diabetes (~90%), is characterized by a systemic inflammatory disease accompanied by insulin resistance (IR) or decreased metabolic response to insulin in several tissues, including the adipose tissue, liver, and skeletal muscle, as well as by reduced insulin synthesis by pancreatic beta cells (4, 5).

Studies on immunometabolism have indicated that the metabolic states and immunological processes are inherently interconnected (6). In this scenario, metabolites derived from the host or microbiota regulate immunological responses during health and disease (6). Accordingly, in obese individuals, expanded adipose tissue at different locations, by initiating and perpetuating the inflammation, induces a chronic low-level inflammatory state that promotes IR (4). Every organ system in human body can be affected by diabetes, but the extent of organ involvement depends largely on the severity and duration of the disease (Figure 1 and Table 1). During the progression of diabetes, hyperglycemia promotes mitochondrial dysfunction and induces the formation of reactive oxygen species (ROS) that cause oxidative stress in several tissues such as blood vessels and pancreatic beta cells (7–9). Accumulating damage to the mitochondria, as well as several macromolecules, including proteins, lipids, and nucleic acids by ROS promotes the process of aging (10). As a result, pancreatic β cells that require functional mitochondria to maintain insulin synthesis fail to generate high enough levels of insulin (11, 12). In the absence of compensatory mechanisms, stress-responsive intracellular signaling molecules are activated and cellular damage occurs. Elevated intracellular levels of ROS and subsequent oxidative stress play an important role in the pro-atherosclerotic consequences of diabetes and the development vascular complications (9, 13). Moreover, the

non-enzymatic covalent attachment of glucose and its toxic derivatives [e.g., glyoxal, methylglyoxal (MGO), and 3-deoxyglucosone] to the biological macromolecules such as nucleic acids, lipids, and proteins leads to the formation of advanced glycation end products (AGEs) (14, 15). Accumulated AGEs block the insulin signaling pathway and promote inflammation (16, 17). In addition, the attachment of AGEs to their receptors [e.g., CD36, galectin-3, scavenger receptors types I (SR-A1), and II (SR-A2)] on the surfaces of immune cells in the circulation and tissues activates the expression of pro-inflammatory cytokines and increases free radical generation (18). Furthermore, due to the chronic exposure of cells to high glucose levels in untreated T2DM patients, glucose toxicity might occur in several organs. This will eventually lead to nephropathy, cardiomyopathy, neuropathy, and retinopathy.

Biography

Fawaz Alzaid is a Research Associate of the French National Institute of Health and Medical Research (INSERM). His recent research highlights include first author publications in Nature Medicine and JCI Insight deciphering mechanisms of tissue inflammation in diabetes.