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PERSPECTIVE

Hyperglycemia-Induced Immune System Disorders in Diabetes Mellitus and the Concept of Hyperglycemic Memory of Innate Immune Cells: A Perspective

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Abstract: A wealth of information suggests that hyperglycemia plays a paramount role in diabetes-related chronic complications. Notably, in Type 2 Diabetes Mellitus (T2DM), a persistent condition of hyperglycemia and altered insulin signaling seems to account for a status of chronic low-grade inflammation. This systemic inflammatory condition, in turn, depends on the profound impairment of the immune machinery, especially in some corporeal districts such as the adipose tissue, pancreatic islets, endothelia, and circulating leukocytes. Interestingly, poor glycemic control has been associated with cardiac autoimmunity in patients with Type 1 Diabetes (T1DM), and cardiac autoantibody positivity is associated with an increased risk of Cardiovascular Diseases (CVD) decades later. This condition also suggests a role for autoimmune mechanisms in CVD development in patients with T1DM, possibly through inflammatory pathways. Evidence has been provided for an elevated release of cytokines, such as interleukin (IL)-1 beta and IL-6, as well as chemokines (C-C motif Ligand 2 and IL-8). Of note, these mediators are responsible for abnormal leukocyte trafficking into many tissues, contributing to insulin resistance, reduced insulin secretion, and vascular complications. In fact, hyperglycemia in individuals with diabetes mellitus is associated with higher circulating E-selectin, soluble Cell Adhesion Molecule (sCAM)-1, and vascular CAM-1 compared to normoglycemic healthy volunteers. Therefore, patients with diabetes mellitus exhibit an exaggerated adhesion of leukocytes to endothelia, and this phenomenon is related to hyperglycemia. The increased production of advanced glycosylation end products or AGEs activates a further cascade of noxious events with a massive generation of Reactive Oxygen Radicals (ROS) and enhanced expression of CAMs.

Keywords: Diabetes mellitus, hyperglycemia, hyperglycemic memory, epigenetics, inflammation, trained immunity.

IMMUNE SYSTEM DISORDERS IN DIABETES MELLITUS

In a recent review, Pezhman and associates highlighted the significant disorders of innate and adaptive immunity in the course of T2DM [4]. With special reference to innate immunity, macrophages have been an object of intensive study [1-8]. Wouters and associates [9] reported that high numbers of circulating monocytes correlated with CD11c+ macrophages in human visceral adipose tissue, and this condition was associated with insulin resistance. At the same time, in patients with T2DM, an increased number of circulating neutrophils may further activate inflammatory *via* secretion of macrophages in the context of adipose tissue elastase [10]. Also, in High-Fat Diet (HFD)-induced obese mice, evidence has been provided that neutrophil elastase could account for insulin resistance, hence suggesting a traditional role of this innate mechanism in the pathophysiology of insulin resistance and diabetes mellitus [11].

Dendritic Cells (DCs) are antigen-presenting cells, which polarize Tlymphocyte responses towards specific antigens. In the course of T2DM, numbers of DCs have been shown to increase either in the circulation [12] or the adipose tissue, especially plasmacytoid DCs [13], thus suggesting their involvement in the process of low-grade inflammation. In HFD obese mice, the abundance of CD11c+ DCs in adipose tissue led to the secretion of IL-6 and IL-23 with induction of the inflammatory T cell subset and T helper (h) 17 cells [14]. The same mechanism of DCs-induced polarization of Th17 cells may also likely occur in patients with T2DM.

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Adaptive immune response modifications are implicated in the pathogenesis of T2DM [15]. Remarkably, T regulatory (Treg) cell numbers, Treg-to-Th17, and Treg-to-Th1 ratios were reduced in the peripheral blood of T2DM patients, thus indicating a prevalence of a proinflammatory pattern in this disease [16, 17]. Experimentally, by increasing the quantity of Treg cells in murine adipose tissue, the release of IL-10 by these cells could improve the altered metabolic parameters [18]. Taken together, these data indicate that Treg cells infiltrating the adipose tissue in T2DM patients may represent a strategic target for suppressing inflammation and ameliorate insulin function. In this context, it has been reported that B cells also contribute to the polarization of Th17 cells since depletion of CD19+ cells in patients with T2DM prevented Th17 cell proliferation [19]. Of note, Th17 cell induction may also be triggered by the secretion of IL-21 as a product of T cells in diabetes and obesity [20].

Persistent hyperglycemia is correlated to the future development of diabetes-related chronic complications. This condition is fostered by chronic inflammatory complaints and may persist even after the achievement of better glucose control, the so-called "metabolic memory" [1, 21]. Mitochondria generate more ROS than expected when hyperglycemia occurs. This mechanism fosters mitochondrial DNA mutations, which further contribute to mitochondrial dysfunction. The hyperglycemia-induced changes modify the human epigenome in a very stable way, even in the absence of a remarkable hyperglycemic status [22]. Oxidative stress, chronic inflammation, non-enzymatic glycation of proteins, and epigenetic changes lead to defective protein folding in the endoplasmic reticulum with consequent alteration of protein function. It is to note that early treatment of diabetes has proven to be of great benefit since even transient hyperglycemia may lead to pathological effects and complications later on [23].

Thiem and associates investigated the mechanisms responsible for the association between hyperglycemic memory and inflammation [24]. Accordingly, hyperglycemia may induce non-specific immune memory (trained immunity) in mice. By definition, trained immunity is based on the protection mediated by the innate immune response, following exposure to a second pathogen, as in the case of a primary challenge with beta-glucan [25]. In particular, macrophages are involved in the pathogenesis of diabetes-related complications, with hyperglycemia promoting monocyte recruitment and plaque infiltration in arteries [26]. Then, activated macrophages undergo a shift from oxidative phosphorylation to aerobic glycolysis to gain energy and generate metabolites, such as fumarate or succinate [21]. The above-cited metabolites regulate histone methylation and acetylation or may act as cofactors for histone and methyl DNA transferases and demethylases, as well as histone acetyltransferases and deacetylases, thus, leading to epigenetic changes. Three recent papers have supported the hypothesis of trained immunity. Christ *et al*. reported that animals fed a hypercaloric western diet underwent hypercholesterolemia and systemic inflammation [27]. When mice turned to a low-calorie diet, Bone Marrow Progenitor Cells (BMPCs) still exhibited a proinflammatory profile. Keating and associates found that oxidized Low-Density Lipoproteins (LDL) contributed to trained immunity via upregulation of glycolytic metabolism [28]. Following exposure of oxidized LDL-treated cells to 3-(3 Pyridinil)-1- (4-Pyridinil)-2-propen-1-one, an inhibitor of the glycolytic enzyme PFKFB3, trained immunity was abrogated in healthy donor monocytes. In a model of *Candida albicans* infection in mice lacking T and B cell functions, previous administration of a small dose of microbial ligand was protective against a subsequent lethal dose of *Candida albicans* [29]. In this model, monocytes exerted trained immunity in virtue of unspecific memory mechanism. In their seminal paper, Thiem and associates demonstrated for the first time that hyperglycemia was able to induce trained immunity in mice [24]. In BMPCs, hyperglycemia, as an external stimulus, accounted for modifications of hemopoietic stem cells with a generation of inflammatory monocytes, which ultimately led to cardiovascular complications, as also sustained by Chavakis and associates [30]. Furthermore, in human monocytes, increased secretion of Tumor Necrosis Factor (TNF) alpha was observed after *ex vivo* challenge with lipopolysaccharides. In the presence of hyperglycemia, a further increase in genes involved in glycolysis occurred with the generation of end products, such as lactate. In turn, lactate correlated with increased TNF-alpha production as an expression of trained immunity [31]. The above results by Thiem and associates are related to epigenetic changes induced by hyperglycemia [24]. They found that glycolysis and Mixed-Lineage Leukemia (MLL), family of methyltransferase enzymes, were overexpressed in CD14+ monocytes from patients with Type 1 Diabetes (T1D). Then, treatment with the MLL inhibitor, menin-MLL, abrogated the process of trained immunity. However, further studies are needed to understand better the role of MLL enzymes on the chromatin of trained cells.

CONCLUSION

In conclusion, hyperglycemic memory mediated by innate immune cells seems to be the common denominator for the development of atherosclerosis and possibly cardiovascular complications in both T1DM and T2DM [24]. Hyperglycemic memory partly depends on the MLL gene family, and in this direction, future studies may offer new diagnostic and therapeutic tools in diabetes.

LIST OF ABBREVIATIONS

BMPCs	=	Bone-Marrow Progenitor Cells
CAMs	=	Cell Adhesion Molecules
DCs	=	Dendritic Cells
HFD	=	High Fat Diet
IL	=	Interleukin
MLL	=	Mixed Lineage Leukemia
Th	=	T helper

Treg	=	T regulatory
T1DM	=	Type 1 Diabetes Mellitus
T2DM	=	Type 2 Diabetes Mellitus

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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