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REVIEW

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Metabolic reprogramming of macrophages in the context of type 2 diabetes

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Abstract

Type 2 diabetes (T2D) is associated with insulin resistance and progressive dysfunction of β-pancreatic cells, leading to persistent hyperglycemia. Macrophages play a crucial role in this context, influencing both the development and progression of insulin resistance. These innate immune cells respond to inflammatory stimuli and reprogram their metabolism, directly impacting the pathophysiology of T2D. Macrophages are highly plastic and can adopt either pro-inflammatory or pro-resolutive phenotypic profiles. In T2D, pro-inflammatory macrophages, which rely on glycolysis, exacerbate insulin resistance through increased production of pro-inflammatory cytokines and nitric oxide. In contrast, pro-resolutive macrophages, which prioritize fatty acid metabolism, have different effects on glucose homeostasis. Metaflammation, a chronic low-grade inflammation, is induced by pro-inflammatory macrophages and significantly contributes to the progression of T2D, creating an environment conducive to metabolic dysfunction. This review aims to clarify the contribution of macrophages to the progression of T2D by detailing how their inflammatory responses and metabolic reprogramming influence insulin resistance and the disease's pathophysiology. The review seeks to deepen the understanding of the biochemical and metabolic mechanisms involved, offering broader insights into the impact on the quality of life for millions of patients worldwide.

Keywords Immunometabolism, T2D, Macrophage, Epigenetic modifications

Introduction

Type 2 diabetes (T2D) is a chronic condition characterized by insulin resistance and the progressive dysfunction of pancreatic β-cells, leading to persistent hyperglycemia. In this context, macrophages, key cells of the innate immune system, play a fundamental role in responding to inflammatory stimuli and contributing to metabolic stress in pancreatic tissues [9]. The interaction between elevated circulating glucose levels and the secretion of pro-inflammatory cytokines, such as IL-1β, induces an inflammatory response that exacerbates pancreatic islet dysfunction and promotes the polarization of macrophages toward a pro-inflammatory profile [51].

Insulin resistance, a central factor in the development of T2D, is intensified by the activation of inflammatory pathways in macrophages, such as the JNK and IKKβ pathways. These pathways activate serine/threonine enzymes that phosphorylate IRS-1, impairing insulin signaling [31]. Additionally, these pathways

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stimulate nuclear factor-κB (NF-κB), which increases the production of pro-inflammatory cytokines and nitric oxide (NO), elements that not only perpetuate inflammation but also aggravate insulin resistance [32, 40].

Under normal conditions, pro-regenerative macrophages predominantly rely on fatty acid metabolism and arginase-1 to maintain tissue homeostasis, reducing NO production [4]. However, the altered metabolic environment of T2D shifts macrophages to a pro-inflammatory phenotype, characterized by an increased reliance on glycolysis and NO synthesis via iNOS, fueling an inflammatory cycle that intensifies metabolic dysfunction [6, 45].

Metabolic variables related to insulin resistance, which contribute to the worsening of metaflammation, have been characterized using various methodological models, such as the use of mice, specifically in a lipodystrophic diabetic mouse model [53]. Additionally, in functional in vitro angiogenesis assays, the consequences of hyperglycemia were evaluated by simulating diabetic conditions [57]. In vivo models, especially in rodents, are widely used to analyze molecular, mechanistic, and phenotypic changes in transgenerational metabolic and cardiovascular programming. These models offer considerable advantages, such as short gestational periods and more offspring, allowing for the analysis of complex transgenerational mechanisms [8]. Therefore, these models enable a detailed analysis of underlying mechanisms, ensuring a more applied understanding of the consequences that T2D can have on immunometabolic interactions.

Thus, the objective of this article is to gather and analyze crucial information from the literature on the metabolic reprogramming of macrophages in the context of T2D, focusing on the main regulatory pathways that modulate macrophage polarization. Additionally, this review aims to discuss the impact that the diabetic context has on the innate immune system, specifically on macrophages, promoting a subclinical and persistent inflammatory alteration that directly affects the quality of life of millions of individuals. The review is organized into four main sections, exploring the impact of hyperglycemia on biochemical, metabolic, phenotypic, and epigenetic aspects, with the goal of expanding knowledge on the immunometabolic aspect of T2D.

The role of macrophages in T2D

Tissue-resident macrophages are long-lived cells derived from embryonic precursor cells, maintained through local proliferation [5]. These macrophages retain past immunological memories through trained immunity, which can alter their identity and impact acquired dysfunction over the years [5]. The inflammatory responses of macrophages are facilitated by changes in their cellular metabolism, where cells producing inflammatory mediators are induced to glycolysis, while inflammation is balanced by the stimulation of tissue repair [37]. Single-cell RNA sequencing studies have demonstrated that classifying macrophages as "M1" or "M2" does not adequately reflect the high heterogeneity present in tissues in vivo [36]. Instead of distinct populations, M1 and M2 signatures do not necessarily exclude each other and often coexist, depending on the balance between activating and inhibitory signals and the tissue environment [25]. For this reason, this review focused on highlighting predominantly pro- or anti-inflammatory phenotypes.

In Type 2 Diabetes (T2D), macrophages are reprogrammed to facilitate and exacerbate the inflammatory response when continuously exposed to pro-inflammatory stimuli and metabolic changes in tissues and organs, leading to metaflammation [26, 37]. This condition is characterized by chronic low-grade inflammation, which can result in various complications and comorbidities. The exacerbated inflammation is evidenced by markers, such as elevated levels of C-reactive protein (CRP), increased expression of pro-inflammatory cytokines, and a higher white blood cell count, notably a 20% increase in the monocyte population compared to the global population, which can be readily recruited to tissues under inflammatory conditions [5]. Although other immune cells participate in metaflammation in T2D, macrophages are the primary effector cells leading to reduced insulin sensitivity [36].

A study conducted by Valtierra-Alvarado and colleagues demonstrated that obese and diabetic patients exhibit a reduction in classical monocytes, which are associated with antimicrobial function, while there is an increase in monocytes that predominantly perform antigen processing and presentation. This suggests a close relationship between the reduction of classical monocytes in poorly controlled T2D and the susceptibility to multiple infections as a comorbidity of the disease. However, the same study showed that inadequate glycemic control negatively affects the expression of HLA-DR, a surface marker of antigen-presenting cells (APCs), such as macrophages and monocytes, as well as CD86, a co-stimulatory molecule. HLA-DR is responsible for presenting peptides to T lymphocytes, which interact with CD86 to promote T-cell activation and differentiation. This suggests that antigen presentation is also impaired in T2D, leading the patient to an immunosuppressed state [44].

In addition to playing a crucial role as APCs, macrophages are essential in glycemic control by contributing to insulin secretion by β-cells [55]. However, in T2D, macrophages are reprogrammed to impair this process

and are the main contributors to inflammation in pancreatic islets [55]. Studies in mice have demonstrated that the inhibitory effect of macrophages on glucose-stimulated insulin secretion (GSIS) depends on direct contact with β-cells through open cytoplasmic channels, through which a greater number of intact insulin secretory vesicles pass from β-cells to macrophages. Other factors also contribute to the reduction of GSIS and the increase in β-cell dysfunction [55]. The decrease in GSIS precedes an adaptive expansion of β-cells in the pre-diabetic phase, mediated by the interaction of platelet-derived growth factor (PDGF), produced by macrophages, with its receptor (PDGFR) on β-cells [55] (Fig. 1). This occurs, because hyperglycemia increases as insulin resistance worsens, until prolonged insulin production, glucolipotoxicity, oxidative stress, inflammation, and β-cell dedifferentiation result in functional decline and apoptosis [5] (Fig. 1; Table 1).

Patients with T2D exhibit elevated levels of CD68+ macrophages in the islets, primarily due to the local proliferation of resident macrophages, stimulated by high levels of glucose and free fatty acids (FFAs) [5, 47, 55]. Some of these signals are secreted by the stressed β-cells themselves, contributing to the infiltration and activation of more macrophages through the release of chemokines and ATP [55] (Fig. 3). ATP-stimulated macrophages increase the secretion of pro-inflammatory cytokines, such as IL-1β, TNF-α, and INF-γ, inducing the activation of pro-apoptotic proteins, endoplasmic reticulum stress, and a consequent reduction in GSIS, in addition to activating the NF-Kβ pathway, which acts to reduce the expression of cell differentiation genes and insulin secretion in β-cells [55] (Fig. 3; Table 1).

The prolonged activation of the NF-Kβ pathway in adipocytes stressed by pro-inflammatory macrophages is also responsible for increasing the expression of non-canonical kinases, which attenuate β-adrenergic signaling in adipose tissue by participating in the phosphorylation of catecholamines, reducing energy expenditure and consequently increasing the accumulation of FFAs [35]. Additionally, adipose tissue macrophages (ATMs) have a greater capacity to degrade catecholamines in T2D, resulting in a reduced response to thermal stress, once again contributing to lower energy expenditure [22] (Table 1).

Like pancreatic islets, white adipose tissue (WAT) undergoes a significant increase in the number of macrophages in T2D, which can reach up to 40% more than in a healthy individual [5]. In diabetic individuals, ATMs adopt a metabolic activation state (MMe), characterized by a pro-inflammatory phenotype along with increased lysosomal activity and survival, aiming to phagocytize necrotic adipocytes, which elevates lipolysis and FFA levels [37, 44]. The accumulation of triglycerides in T2D increases the volume and number of adipocytes, such that the capillary network, orchestrated by macrophages, cannot keep pace, leading to hypoxia and adipose tissue stress [26]. This stimulates inflammation, lipotoxicity,

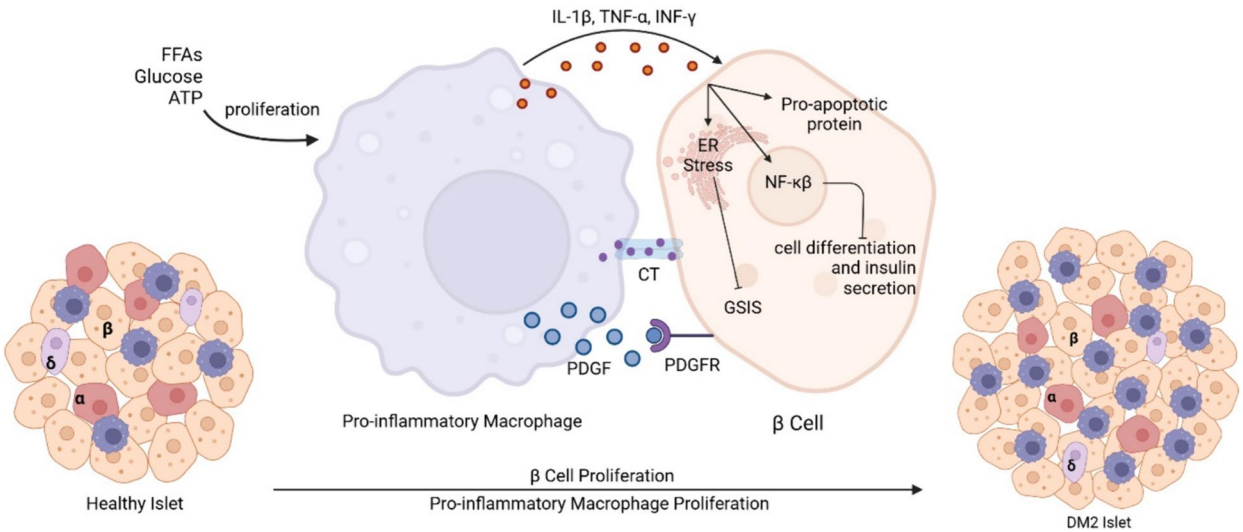

Fig. 1 Schematic representation of the proliferation of pro-inflammatory macrophages and β-cells in the diabetic pancreatic islet and the signaling mechanisms and interactions between pro-inflammatory macrophages and β-cells. Excess free fatty acids, glucose, and ATP stimulate macrophage proliferation, which in turn, by secreting pro-inflammatory cytokines, induces endoplasmic reticulum (ER) stress, production of pro-apoptotic proteins, and activation of the NF-Kβ pathway, which inhibits cell differentiation genes and insulin secretion. Additionally, interactions via the cytoplasmic channel (CT) affecting glucose-dependent insulin secretion and the PDGF-PDGFR signaling, stimulating β-cell proliferation in the islet are represented

Table 1 Role of macrophages in type 2 diabetes (T2D) by tissue

Tissue	Role of pro-inflammatory macrophages	Sources of proliferation and infiltration of pro-inflammatory macrophages	Activated pathway
Pancreas	Inhibition in glucose-stimulated insulin secretion, inflammation, increase in the number and dysfunction of β cells, leading to apoptosis	Stimulating factors from high levels of glucose and FFAs, chemokines released by β cells, and pro-inflammatory cytokines from activated macrophages	Reduction in expression of cell differentiation genes and insulin secretion in β cells
WAT	Decrease in response to heat stress, inflammation, increase in FFA accumulation, high phagocytosis of necrotic adipocytes	High levels of FFAs and necrotic adipocytes due to hypoxia	Elevation in expression of non-canonical kinases in adipocytes
Liver	Inflammation, insulin resistance, and exacerbation of non-alcoholic steatohepatitis	Excess FFAs from adipose tissue and diet, products related to gut microbiota, cytokines, and ROS from hepatocytes affected by non-alcoholic steatohepatitis	Development of non-alcoholic steatohepatitis
Intestine	Feedback of endotoxemia, inflammation, insulin resistance	High levels of LPS from *E. coli*, high-fat diet, and release of chemokines by intestinal epithelial cells	Affects intestinal permeability and promotes insulin resistance

and, eventually, macrophage infiltration, which forms crown-like structures around damaged adipocytes [26].

The excess of FFAs derived from adipose tissue and diet in T2D contributes to the pro-inflammatory activation of hepatic macrophages, known as Kupffer cells (KCs), leading to increased pro-inflammatory cytokines and the activation of the hepatic NF-Kβ pathway, contributing to the development of non-alcoholic steatohepatitis (NASH), a pathology commonly associated with T2D [5, 47]. Hepatocytes affected in NASH further activate KCs and recruit more monocytes to the liver, increasing levels of cytokines, and reactive oxygen species (ROS), which cyclically exacerbate NASH and insulin resistance [47] (Table 1).

Studies have also shown that levels of *Escherichia coli*, a significant source of lipopolysaccharides (LPS), are higher in patients with T2D [47]. LPS is recognized by Toll-like receptors on macrophages, leading again to the activation of the NF-Kβ pathway, which is widely associated with intestinal integrity and permeability, as well as insulin resistance [47]. Due to increased intestinal permeability in T2D, microbial products leak through the portal circulation, exacerbating inflammation and insulin resistance in the liver [47]. Moreover, a high-fat diet induces intestinal epithelial cells to produce monocyte chemotactic proteins, exacerbating chronic inflammation in the intestinal lamina propria and perpetuating endotoxemia [47] (Table 1).

Biochemical alterations within macrophages in T2D

The metabolic status of macrophages plays crucial roles in the development of immune responses. The population of pro-inflammatory macrophages is highly dependent on the glycolytic pathway, while the population of pro-resolutive ones utilizes the fatty acid oxidation pathway [21]. In the context of T2D, characterized by chronic hyperglycemia, driven mainly by insulin resistance, there is a high rate of glucose auto-oxidation, resulting in the synthesis and accumulation of reactive oxygen and nitrogen species in the body [27]. Additionally, the excessive available glucose is converted into fatty acids and stored as lipids, particularly triacylglycerols intracellularly [28].

Adipocyte hypertrophy, hypoxia, and increased cell death due to lipid accumulation contribute to the secretion of pro-inflammatory molecules, such as TNFα, IL-1β, IL-6, and IL-8 [42], which promote the recruitment of monocytes that tend to differentiate into pro-inflammatory macrophages [20]. These pro-inflammatory stimuli, in turn, activate JNK and IKKβ pathways, promoting insulin resistance by phosphorylating serine residues on IRS-1 and by transcriptional activation of nuclear factor-κB (NF-κB), respectively [40].

Phosphorylation sites of the JNK pathway include Ser312—in humans, and in mice, the site is called Ser307—as the primary site for protection by restriction of the phosphotyrosine-binding domain [1] and Ser302, which has also been shown to mediate the disruption of IRS-1 signaling. It is also important to highlight the importance of phosphorylation of other additional sites for this disruption to occur [49].

Once activated, serine/threonine enzymes act on NF-κB transcription, which, upon interaction with the cell nucleus, stimulates the production of cytokines, pro-inflammatory mediators, and iNOS, responsible for NO production. NO, upon interaction with the insulin receptor, leads to insulin signaling resistance [32], therefore contribution to the worsening of the clinical condition. Activation of MAP-kinase signaling pathways promotes ET-1 secretion, activates cation pumps, and increases the expression of VCAM-1 and E-selectin [39]. These molecules enhance monocyte adhesion to endothelial cells, where they differentiate into macrophages and produce inflammatory molecules, further promoting local inflammation [40].

Metabolism in the context of T2D

The regulation of different metabolic profiles in macrophages has profound implications for the immune response, being closely linked to the development of diabetic and inflammatory conditions [13]. As evidenced in the previous section, in homeostatic situations, macrophages meet their energy demands predominantly through oxidative phosphorylation (OXPHOS) [3]. During this state, glucose is absorbed by specific receptors present on the cell membrane of macrophages, such as GLUT, and directed toward glycolysis, generating pyruvate through pyruvate dehydrogenase (PDH), which is then internalized into the mitochondria and utilized in the tricarboxylic acid (TCA) cycle (Fig. 2) [3, 12, 11]. This efficient process produces ATP through OXPHOS, taking advantage of the presence of oxygen.

On the other hand, the microenvironment presented in T2D directs the macrophage profile toward a pro-inflammatory profile. These changes in macrophage metabolism under glucose excess exhibit similarities to the Warburg effect [3, 32, 48]. The Warburg effect, a phenomenon first observed in 1924 by Otto H. Warburg when studying malignant tumors, describes the increase in glucose uptake by cells and its conversion into lactate even in the presence of oxygen, an environment in which oxidative phosphorylation would be the most efficient, proposed as an adaptation mechanism to support the cell's biosynthetic needs, characterizing the term aerobic glycolysis [46]. This deviation contributes some advantages to the cell, promoting the excess production of

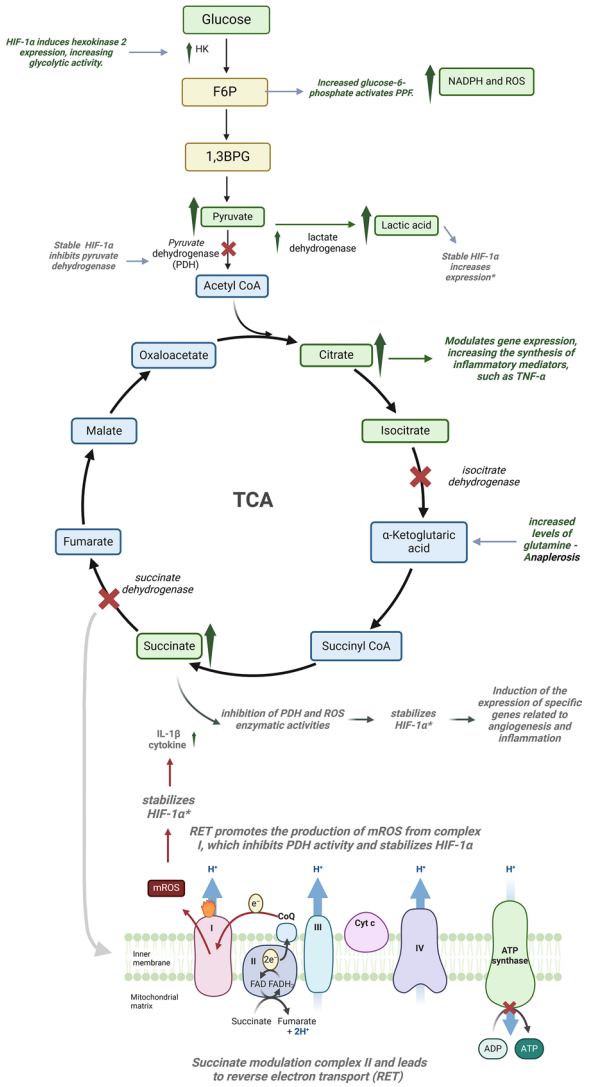

Fig. 2 Disruption of the citric acid (TCA) cycle to citrate and succinate causes significant modulations in the glycolytic pathway. The increase in hexokinase (HK) promotes the increase in fructose-6-phosphate (F6P), which activates the pentose phosphate pathway (PPF), resulting in the production of NADPH and reactive oxygen species (ROS). The action of HIF-1α inhibits pyruvate dehydrogenase, favoring the conversion of pyruvate into lactate by lactate dehydrogenase. The increase in succinate, due to the anaplerotic activity of glutamine, affects the electron transport chain, particularly complex II, inducing reverse electron transport (RET) and generating more ROS, which increases the expression of IL-1β, a cytokine pro-inflammatory

carbon sources, which are subsequently used to generate other macromolecules, such as nucleotides, lipids, and proteins [24, 54]. In addition, it also allows the generation of ATP, which when in the Warburg phenotype is less efficient compared to mitochondrial respiration, but is accelerated, since the rate of glucose metabolism through aerobic glycolysis allows the production of lactate 10–100 times faster than complete oxidation in the mitochondria [24, 54]. Studies and calculations indicate that cells with a higher rate but lower yield in ATP production may have a selective advantage when competing in microenvironments with shared and limited energy resources [24, 54]. The molecular mechanisms involved in the Warburg effect have not yet been clearly established, but studies suggest that the hypoxia-induced transcription factor (HIF) is important [19].

As in the Warburg effect, this pro-inflammatory metabolic profile in T2D is characterized by increased glucose uptake, resulting from the overexpression of glucose transporter 1 (GLUT1), which is characterized as the main glucose transporter in macrophages, increasing glucose uptake independently of insulin signaling via IRS-1 [12, 11, 30]. This process is mediated by the activation of HIF-1α, which is stabilized and induced by the combination of increased glycolysis and the release of pro-inflammatory cytokines resulting from metabolic stress [30]. HIF-1α also induces the expression of other genes that encode enzymes with glycolytic function, such as glucose-6-phosphate dehydrogenase and hexokinase (HK) [12, 11, 23]. This phenomenon is a less-efficient strategy for ATP production but is preferred by pro-inflammatory macrophages due to its speed, potentially contributing to the development of insulin resistance [12, 11, 48]. Additionally, the activity of mitochondria during metabolic reprogramming in the inflammatory state also undergoes crucial alterations, especially through dysregulation in the expression of key enzymes for the TCA cycle, such as citrate synthase (CS), α-ketoglutarate dehydrogenase (α-kGDH), isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), and malate dehydrogenase 2 (MDH) [15]. Therefore, the reprogramming of macrophages in inflammatory microenvironments allows a shift in the processing of energy substrates to obtain energy rapidly at the expense of lower ATP production [37].

In pro-inflammatory macrophages, the TCA cycle is interrupted at the level of isocitrate dehydrogenase (IDH) and succinate dehydrogenase (SDH), due to reduced expression of IDH and inhibition of SDH by itaconate, leading to the accumulation of citrate and succinate (Fig. 3). This allows for increased formation of acetyl-CoA, stimulating greater synthesis of fatty acids, prostaglandins, and histone acetylation, which modulates gene expression [37, 52]. Additionally, the accumulation of succinate allows for greater stabilization of transcription factors such as HIF-1α, which induces the expression of specific genes related to angiogenesis, cell proliferation, and inflammation (Ji et al. 2020). There is also a notable reduction in the expression of

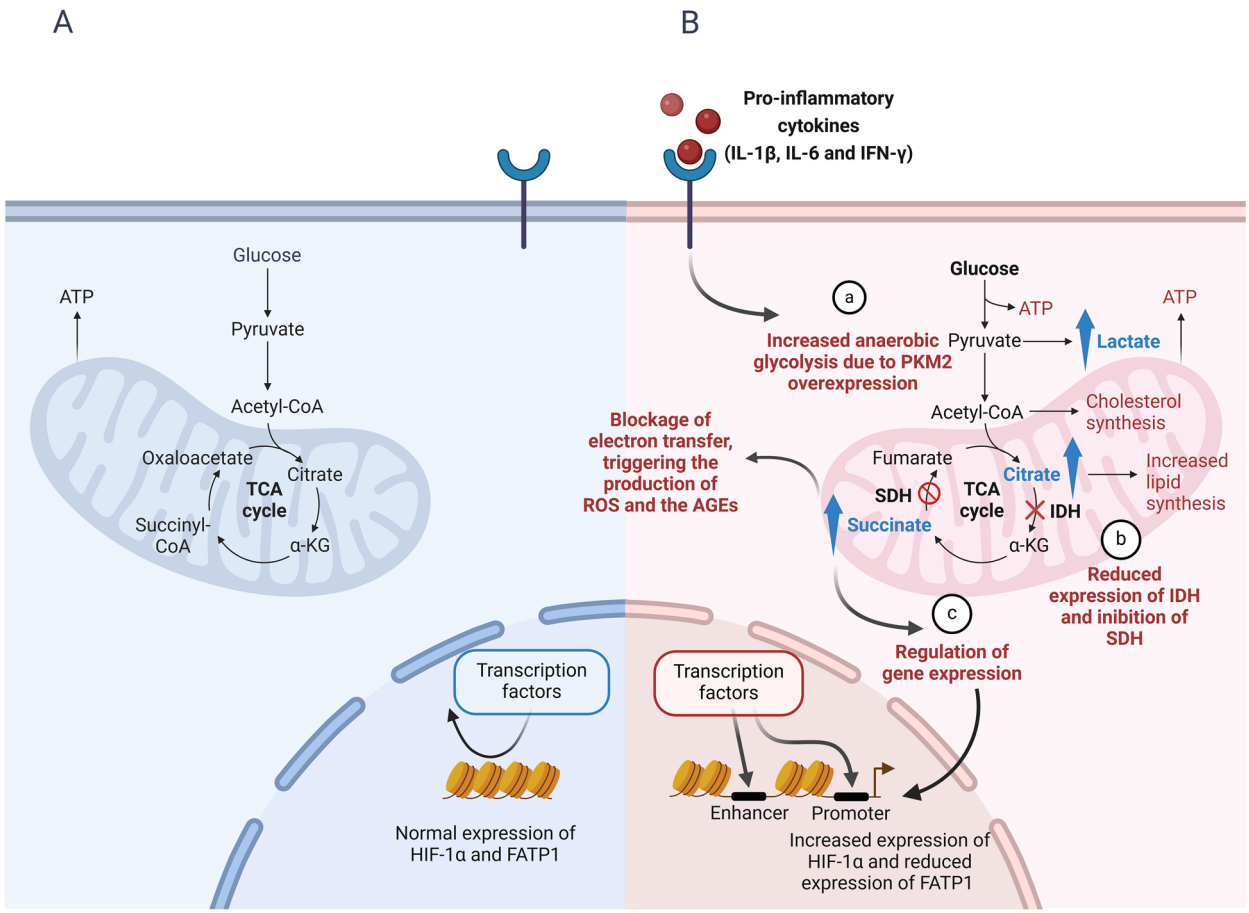

Fig. 3 Immunometabolic profile of pro-inflammatory macrophages under hyperglycemic conditions. Under hyperglycemic conditions, macrophages reorganize their metabolism, promoting a pro-inflammatory polarization. This condition results in lactate accumulation due to increased anaerobic glycolysis (a). Additionally, hyperglycemic conditions increase the levels of inflammatory cytokines, such as IL-β, which in turn stimulates the metabolic reprogramming of macrophages (a). Furthermore, an interruption in the TCA cycle is observed at two critical points: citrate and succinate, due to reduced expression of isocitrate dehydrogenase (IDH) and inhibition of succinate dehydrogenase (SDH) (b). This TCA cycle blockade contributes to the accumulation of corresponding metabolic intermediates and leads to increased production of inflammatory mediators, a pathway mediated by the activation of gene transcription factors that effectively regulate the expression of inflammatory genes (c). Blue arrows indicate the accumulation of the metabolic mediator. AGEs stand for advanced glycation end products. FATP1 stands for fatty acid transport protein 1

fatty acid transporter protein 1 (FATP1) [17], as there is a decrease in lipid intermediary metabolism under inflammatory conditions. In the T2D context, this contributes to the development of severe complications, such as impaired wound healing and compromised angiogenesis of vessels supplying large portions of the pelvic limbs [13].

This metabolic reorganization generates an increased flow of electron donors in the phosphorylation chain, reaching a critical threshold that blocks reverse electron transport (RET), triggering the production of superoxide and mitochondrial reactive oxygen species (mROS) [29]. This superoxide, in turn, triggers various pathogenic pathways, including the formation of advanced glycation end products (AGEs) and activation of protein kinase C (PKC) [13]. The metabolic remodeling not only contributes to the production of glycolytic intermediates but also impacts the functioning of oxidative phosphorylation (OXPHOS), resulting in increased production of ROS, especially at complexes I and III of the phosphorylation chain (Fig. 2). These mROS are considered unregulated byproducts of oxidative respiration, highlighting the dynamic importance of ROS production in macrophage mitochondria [50]. The accumulation of mROS can also lead to the degeneration of pancreatic β-cells, contributing to the development of diabetic complications [33].

Epigenetic modifications induced by metabolic reprograming in macrophage activity in T2D

The importance of genetic and epigenetic modifications in regulating macrophage activation is demonstrated in several studies [10, 34]. Main epigenetic modifications in T2D context rely on 1. Histone acetyl/methylation; 2. DNA methylation, and 3. micro-RNAs (miRNA) (Table 2). Regarding histone modifications, lysine residues receive acetyl or methyl groups that are capable of altering gene expression [2]. Positive markers such as di- or trimethylation on H3K4, H3K36, and H3K79 characterize an active transcriptional state, while an inactive transcriptional state is manifested through increased methylation on H3K9me2/me3 and H3K27me3 [14]. On the other hand, DNA methylation mainly implies gene silencing. The modification is localized in CpG islands, regulated by DNA methyltransferases, and usually catalyzed by 10–11 translocation (TET) proteins associated with active chromatin [38].

Both histone and DNA epigenetic modification have been associated with hyperglycemia and hyperlipidemia, characteristic of T2D. For example, important molecules in hyperlipidemia such as the advanced glycation end products (AGEs) interact with NF-κβ transcription factors, contributing to pro-inflammatory state [16]. In transient hyperglycemia models in vivo studies using animal model, there is an increase in H3K4 trimethylation at the NF-κβ p65 subunit promoter, leading to enhanced NF-κβ target gene metabolism characteristic of the T2D pathogenesis [41].

Finally, miRNAs contribute substantially to T2D by altering glucose and lipid metabolism especially in macrophages resident in adipose tissues; as contributors to these cell processes, there are miR-210, miR-375, and miR-223. First, miR-210, found in exosomes from macrophages exposed to a high glucose environment, negatively impacts the uptake of this monosaccharide and mitochondrial activity [43]. In detail, the presence of miR-210 impairs the expression of the alpha 4 subcomplex of NADH ubiquinone oxidoreductase (NDUFA4) in 3T3-L1 adipocytes, through direct binding to the mRNA sequences of this gene [43].

Also, miR-375 is associated with macrophage polarization: when silenced, it significantly attenuates pro-inflammatory macrophages by reducing the mRNA expression of prototypic genes associated with pro-inflammatory polarized macrophages, such as TNF-α, iNOS, Cox-2, and IL-6 [34].

On the other hand, miR-223 participates in the activation of adipose-resident macrophages together with transcription factor PPARγ. The metabolic abnormalities associated with obesity and insulin resistance were described as dependent on the PPARγ binding to Peroxisome Proliferator-Activated Response Elements (PPREs) in the promoter region of mir-223, which functions in lipid metabolism leading to an anti-inflammatory status of macrophages [56].

Therefore, these epigenetic alterations not only sustain an inflammatory response but also drive the metabolic reprogramming of macrophages, enhancing their glycolytic activity and altering their function. This interplay is crucial for maintaining the chronic inflammation in T2D and highlights potential therapeutic targets to modulate macrophage activity and reduce inflammation-related complications.

Concluding remarks

Understanding the metabolic reprogramming of macrophages in Type 2 Diabetes (T2D) is crucial for unraveling the complex biochemical, metabolic, functional, and genetic factors that drive the disease. The interaction between macrophages and the altered metabolic environment in T2D results in significant changes in macrophage function, often shifting their polarization toward

Table 2 Mechanisms mediating macrophage activation in hyperglycemic and hyperlipidemic environments

Regulatory mechanisms	Affected targets	Effects	References
Methylation in hyperglycemic environment	H3K4, p65 subunit promoter	Activation of pro-inflammatory macrophages	Jin et al. [16] and Brasacchio et al. [7]
INF-1 signaling and H3K9me3 modification in hyperglycemic environment	Setdb2	Amplification of inflammatory response	Kimball et al. [18]
Methylation in hyperlipidemic environment	(PPAR)γ1	Activation of pro-inflammatory macrophages	Yang et al. [53]
Reduction in expression of receptors associated with high-fat diets	A2AR and A3R	Exacerbated activation of the NF-κβ pathway associated with inflammation	Fakhoury et al. [10]
miR-210	NDUFA4	Glucose uptake and mitochondrial complex IV activity	Tian et al. [43]
miR-375	TNF-α, iNOS, Cox-2 and IL-6	Macrophage polarization	Qiu et al. [34]
PPARγ/miR-223	Peroxisome proliferator response elements (PPREs)	Control of macrophage activation in adipose tissue	Ying et al. [56]

pro-inflammatory profiles. This shift contributes to the chronic, low-grade inflammation characteristic of T2D.

Metabolic imbalances such as hyperglycemia and hyperlipidemia induce epigenetic modifications that exacerbate macrophage activation and the production of pro-inflammatory mediators, further advancing disease progression. Insights into these mechanisms not only deepen our understanding of T2D pathophysiology but also reveal potential therapeutic targets. Addressing both metabolic reprogramming and genetic modifications in macrophages offers promising strategies for developing effective treatments and managing T2D more effectively.

The relevance of these findings extends to clinical and therapeutic applications, emphasizing the need for targeted interventions that can modulate macrophage activity and ameliorate the inflammatory aspects of T2D. This approach could lead to more personalized and effective treatment strategies, ultimately improving patient outcomes.

Author contributions

L.W.J, L.B., A.G.S, T.S.U, G.L.P wrote the text of the main manuscript and L.W.J, L.B., T.S.U, G.L.P. prepared figures 1 to 3. T.S.B.B., A.G.P., R.B.L, J.D.L., A.P.C., M.R.D. and T.T.B. reviewed all the text. M.R.D. and T.T.B. conceptualized and guided the writing of the text. All authors have reviewed the manuscript.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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