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REVIEW ARTICLE

Pancreatic Macrophages and their Diabetogenic Effects: Highlight on Several Metabolic Scenarios and Dietary Approach

Giuseppe Lisco[1], Vito Angelo Giagulli[1], Giovanni De Pergola[2], Edoardo Guastamacchia[1], Emilio Jirillo[1,*], Vincenzo Triggiani[1]

[1]Interdisciplinary Department of Medicine-Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases, School of Medicine, University of Bari "Aldo Moro", Policlinico, Piazza Giulio Cesare 11, 70124, Bari, Italy; [2]Unit of Research Methodology and Data Sciences for Population Health, National Institute of Gastroenterology "Saverio de Bellis", Research Hospital, Castellana Grotte, 70013 Bari, Italy

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Abstract: ***Background*****:** Evidence shows that a low-grade inflammation sustains type 2 diabetes (T2D). Pancreatic macrophages release cytokines and chemokines that play a fundamental role in the pathophysiology of islet damage and destruction of beta-cells.

Methods**:** The authors discuss the main mechanism by which resident (pancreatic) and circulating macrophages regulate beta-cell development and survival in several scenarios, including T2D, type 1 diabetes mellitus, obesity, and insulin resistance. Data are mostly related to in vitro and animal studies.

Results**:** Lastly, an overview of the role of the Mediterranean diet components (*i.e.*, polyphenols, polyunsaturated fatty acids, prebiotics, probiotics, and vitamins) will be illustrated as potential agents for reducing inflammation and oxidative stress in patients with T2D when used along with antihyperglycemic treatments.

Keywords: Diabetes mellitus, islets, macrophages, obesity, nutrition, Pancreatic macrophages

1. INTRODUCTION

Macrophages belong to the innate immune system and protect the host *via* phagocytosis and killing of pathogens, also acting as "Antigen Presenting Cells" (APCs) for triggering the T lymphocyte-mediated adaptive immunity [1, 2]. At the same time, macrophages contribute to organ development, disease progression, and tissue restoration. In a recent review [3], emphasis has been placed on macrophage properties to participate in the development of endocrine glands, maintain their homeostasis, respond to different types of injury, and, eventually, resolve inflammation. In this direction, op/op mice lacking colony-stimulating factor-1 (CSF-1), a differentiating factor for macrophages, do not produce macrophages [4]. These mice showed abnormalities in their endocrine gland morphology and function, supporting the role of macrophages in the morphogenesis and functioning of the endocrine system [5].

Herein, the authors focus on the multiple roles played by macrophages in the context of endocrine pancreas development and function. Islet resident macrophages (yolk sac origin) and circulating monocyte-derived macrophages play a fundamental role in islet morphogenesis [6, 7]. Peri-islet macrophages express the surface marker F4/80, regulating islet homeostasis and glucose-induced insulin secretion. These cells can acquire an M1 phenotype profile involved in the pathogenesis of type 2 diabetes mellitus (T2D). In addition, the modulation of pancreatic macrophage activity by food intake may be a target for dietary intervention. An appropriate nutritional approach in patients with T2D may reduce systemic inflammation and oxidative stress putatively acting on pancreatic macrophages.

2. PANCREATIC DEVELOPMENT

Pancreatic organogenesis undergoes three transitional stages (mouse model) (Fig. **1**). The proliferation of progenitor cells characterizes the primary transition during e9.0-e12.5 [8]. During this early stage of development, glucagon-producing cells start to develop, and the "master regulator" pancreatic homeobox 1, Pdx1, is responsible for pancreatic tubulogenesis and E-cadherin expression [9]. The transcription factor Ptf1a leads to the expansion of multipotent progenitor cells and the formation of acinar cells [10]. Furthermore, Sox9 regulates progenitor cells, contributing to the expression of the

*Address correspondence to this author at Department of Medicine-Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases, University of Bari "Aldo Moro", School of Medicine, Policlinico, Piazza Giulio Cesare 11, 70124, Bari, Italy; E-mail: emilio.jirillo@uniba.it

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neurogenin Ngn3, which mediates the differentiation of endocrine cells [11, 12].

The secondary transition includes the development of hormone-producing endocrine cells and amylase-producing acinar cells, mediated by Ngn3 [13].

The tertiary transition occurs from e16.5 through e19 and is featured by the clustering of Langerhans islets and acinar cells expansion [14]. The beta-cell formation is regulated by different molecules. Cdc42 mediates tubulogenesis, linking actin dynamics to beta-cell delamination and differentiation [15]. In this respect, Snail2/Slug, promoting epithelial to mesenchymal transition, plays an essential role in beta-cell delamination and migration [16, 17]. Similar functions are also performed by the transcription of co-repressor Grg3/Tle3 and EphB3 for beta cell development to occur [18, 19]. Parallelly, the pancreatic epithelium develops from e11.5 onwards, contributing to acinar or bipotent endocrine/duct structures [20].

In this framework, the HIPPO pathway is worthwhile to be mentioned. It consists of a kinase cascade that regulates proliferation, differentiation, survival, and organ size of the heart, lung, brain, liver, and pancreas. Phosphorylated MST1/2 kinases (p-Mst1/2) have been detected in the acinar and ductal areas of the developing murine pancreas and at higher levels in the islets [21]. In Mst1/2 KO mice, a branched ductal network formation failure has been found with leakage of digestive enzymes and subsequent autodigestion [21]. It has also been reported that loss of Mst1/2 causes de-differentiation of acinar cells and leukocyte invasion before cell death and pancreatitis [22].

In the early stage of embryonic development, multipotent progenitor cells differentiate into endocrine (mostly alpha cells), tubular and acinar cells (primary transition). During the secondary transition, endocrine-secreting and acinar cells differentiate and give rise to primordial tubular-acinar structure and islets. During the tertiary transition, beta cells differentiate, pancreatic islets evolve, and the exocrine pancreas develops.

3. MACROPHAGE MIGRATION TO THE PANCREAS

In general terms, one can distinguish three different populations of pancreatic macrophages: 1) yolk sac-derived resident macrophages; 2) fetal liver-derived resident macrophages; 3) bone-marrow-derived infiltrating macrophages [23-25]. Tissue-resident pancreatic and infiltrating macrophages originate from three distinct stages of hematopoiesis in the developmental period and adulthood (Table **1**) [26-29].

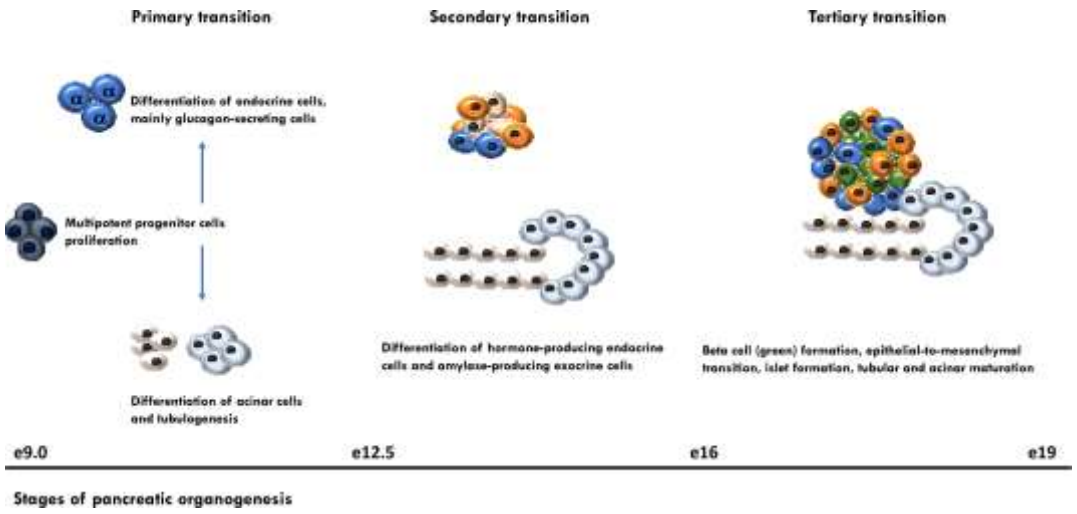

Fig. (1). Simplified representation of the characteristic steps of pancreatic organogenesis (data from *in vitro* and animal studies) [8-12]. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Table 1. Three different waves of HSCs are described in the course of embryogenesis (data from *in vitro* and animal studies).

Hematopoietic Wave	Time	Side	Kind of Progenitor Cells	Bi-omarkers
First	e7.0 – e8.0	Posterior plate mesoderm, blood islands of the extra-embryonic yolk sac	Primitive erythroblasts and megakaryocytes, macrophages	CSF-1R
Second	e8.25 – 10.5	Hemogenic endothelium in the yolk sac and subsequent migration into the fetal liver	Erythromyeloid precursors (immature hemopoietic stem cells) –> give origin to monocytes	c-Myb
Third	e10.5	Aorta, gonads, and mesonephros regions	Fetal hemopoietic stem cells –> give rise to adult hemopoietic stem cells (liver and bone marrow)	c-Myb

The first step corresponds to primitive hematopoiesis, originating from the extraembryonic yolk sac (yolk sac progenitors) that will differentiate into primitive macrophages, erythroblasts, and megakaryocytes [26].

The second wave is represented by erythromyeloid precursors, which differentiate into yolk sac macrophages and migrate to the fetal liver, ultimately differentiating into monocytes [27, 28].

The third wave contemplates the emergence of immature hematopoietic stem cells (HSCs) from the aorta-gonad-mesonephros, which migrate either to the fetal liver or to fetal bone-marrow, thus, generating adult HSCs [29]. Murine studies have revealed that pancreatic macrophages derive from the yolk sac [30]. They are located in close contact with insulin and beta cells, involved in islet morphogenesis [31]. Phenotypes of pancreatic macrophages depend on their location. The F4/80low CD11c+ subset has been detected within islets, while the F4/80hi CD11c- subset preferentially accumulates in the peripheral islet area [32].

4. INTERACTION BETWEEN MACROPHAGES AND PANCREATIC BETA-CELLS IN ISLET FORMATION

The involvement of macrophages in the development of islets is supported by a drastic reduction of beta-cell number in the osteopetrosis murine model op/op, which does not possess macrophages [33]. These mice lack CSF-1 and generate a restricted number of macrophages [31]. By contrast, alpha-cells in the op/op mice are preserved, thus, suggesting that macrophages are required for developing glucagon-secreting cells [34].

The exact mechanisms which lead to beta-cell differentiation by macrophages need to be better elucidated. In this respect, evidence has been provided that fetal M2 macrophages allow embryonic pancreatic epithelial cells to migrate, promoting endocrine differentiation from PDX1+ pancreatic progenitors [35]. Moreover, when embryonic pancreatic explants were treated with CSF-1, the number of insulin-secreting cells increased considerably [31].

Studying the mechanisms of beta-cell regeneration induced by the connective tissue growth factor (CTGF/CCN2), it was found that this molecule also acts *via* the expansion of islet macrophages [36]. Macrophage death induced by clodronate impaired the beta-cell regenerating effects by CTGF/CCN2. Other factors produced by islet macrophages are implicated in beta cell regeneration, including the insulin-like growth factor-1, epidermal growth factor, and transforming growth factor (TGF) 1-beta [37].

Over recent past years, emphasis has been placed on purinergic receptors placed on the cell surface of islet macrophages (Fig. **2**). These receptors play as sensors of ATP levels within islets [38]. Beta-cells release insulin and ATP in response to serum glucose concentration [39]. When stimulated by ATP, purinergic receptors induce calcium release in macrophages with consequent modifications in gene expression, increased motility, and retention of insulin-containing vesicles released by beta cells [40].

Furthermore, there is evidence that human islet macrophages are located close to blood vessels and secrete Interleukin (IL)-10 and metalloproteinase (MMP)-9, which contribute to islet homeostasis [41].

Conclusively, islet macrophages control the composition of the insular milieu, sensing beta-cell secretions and keeping tissue homeostasis.

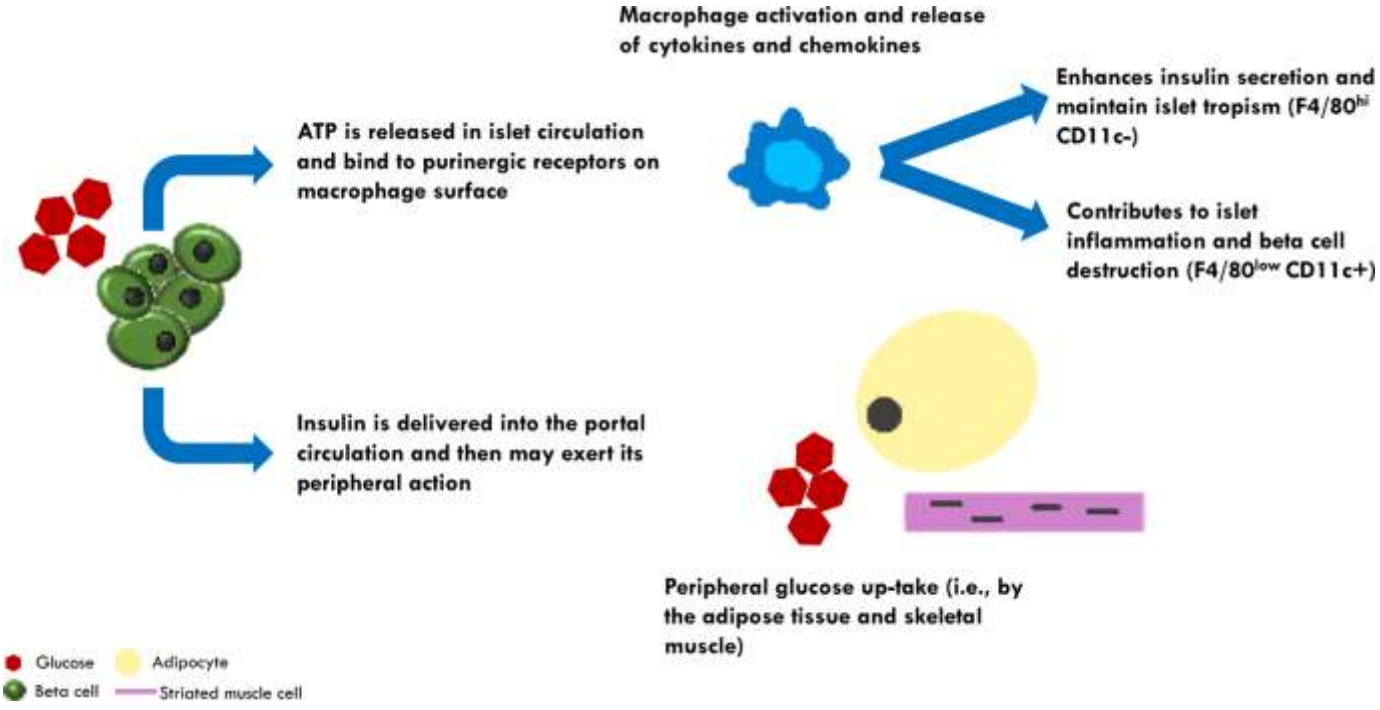

Fig. (2). Simplified illustration of the function of purinergic receptors located on the insular macrophage cell surfa0ce [38, 39, 40, 41]. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

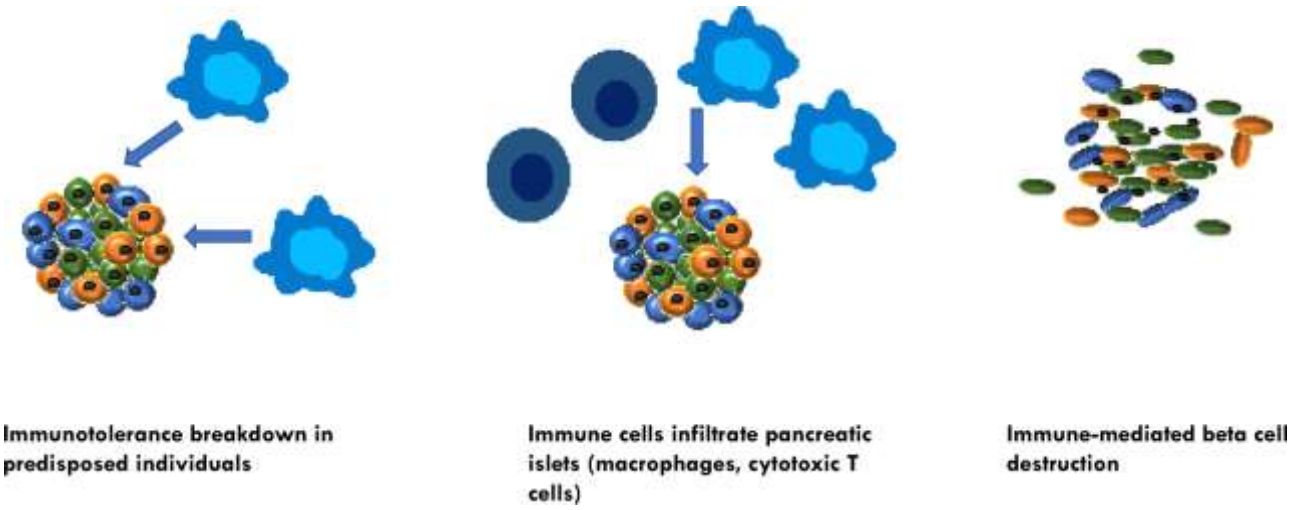

Fig. (3). Simplified representation of the leading mechanisms of insulitis in T1D. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Insulin and Adenosine Triphosphate (ATP) is co-secreted from beta cells in response to a glucose load. ATP enters the islet microcirculation and binds to purinergic receptors expressed on the resident macrophage cell membrane. After the binding, ATP stimulates an intracytoplasmic increase in calcium concentration, thus enhancing macrophage activation. Islet macrophages release several cytokines, such as IL-1beta, that stimulate (in acute but not chronic) insulin secretion from beta cells. However, overstimulation of insulin secretion and beta-cell activity (*e.g*., obesity, insulin resistance) increases the number of resident macrophages and facilitates a pro-inflammatory microenvironment, contributing to beta-cell apoptosis and decreasing insulin release.

5. FUNCTIONS OF TISSUE RESIDENT MACROPHAGES

In addition to their ability to act as APCs, tissue-resident macrophages exert other functions, such as clearance of cellular debris and apoptotic cells [42]. As resident cells adapt to the milieu they harbor, acquiring novel functions.

Local macrophages regulate lipid, energy metabolism, and insulin sensitivity [43]. For example, macrophages acquire a distinct transcriptome in the gastrointestinal tract according to their exposure to short-chain fatty acids (SCFAs), bile salts, and microbiota composition [44].

Classically, macrophages are divided into two main phenotypes: M1 macrophages which exert pro-inflammatory activities, and M2 macrophages, which are rather anti-inflammatory [1]. Tissue-resident macrophages are M2 cells receiving pro-survival and self-renewal signals from environmental factors such as CSF-1, glucocorticoids, and specific I Ls, including IL-4 and IL-13 [45].

For completion, M1 macrophages respond to various stimuli, including Interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha [46]. M1 and M2 macrophages produce different sets of cytokines when activated. M1 cells secrete pro-inflammatory mediators (*e.g*., TNF-alpha, IL-1, IL-6, IL-8, and IL-12) while M2 cells release a classical anti-inflammatory product, namely IL-10 [47]. IL-10 dampens the expression of IFN-gamma in T helper-1 cells and neutralizes the production of other pro-inflammatory cytokines.

Another interaction mechanism between macrophages and environmental cells resides in their aptitude to release extracellular vesicles. Vesicles can export proteins, metabolites, and nucleic acids to nearby cells or even at a distance, thus potentially playing a pathogenic role in chronic diseases [48].

6. TISSUE RESIDENT MACROPHAGES AND PATHOGENESIS OF TYPE 1 DIABETES (T1D)

The common cause of T1D is insulitis with loss of insulin-secreting beta-cells [49, 50]. Experimental evidence supports the pathogenic role of macrophages in murine models of T1D since their depletion with silicon dioxide administration or induced by monoclonal antibody treatment prevents insulitis [51, 52]. Interestingly, in mice and humans with T1D, prediabetic islets produce chemokines, which attract macrophages [53-55]. In response to this wave of chemokines, pro-inflammatory blood monocytes may also infiltrate the islets at the initial stages of disease (Fig. **3**).

In human T1D, post-mortem analysis of inflamed islets has confirmed the presence of macrophages in the early and late phases of insulitis [56]. Upon penetration into islets, macrophages exert detrimental functions, either releasing pro-inflammatory cytokines or overcoming insulin-containing vesicles delivered by beta cells [57-59].

Furthermore, as APCs, macrophages recruit T cytotoxic cells, which, in turn, participate in beta-cell destruction. The fundamental role of macrophages in beta-cell killing has been demonstrated in the NOD.scid mouse model, where depletion of macrophages with clodronate abrogated the outcome of T1D [60]. Noteworthy, NOD.scid mice are deprived of T and B cells, and autoimmune diabetes can be induced by inoculation of activated T cells. In synthesis, T1D pathogenesis seems to result from a combined action of circulating monocyte-derived macrophages, resident macrophages, and T cytotoxic cells, which contribute to beta-cell destruction. In this

last regard, a depletion of islet macrophages in NOD mice through monoclonal antibodies directed against CSF-1 receptor avoided T-cell infiltration and diabetes onset.

Bulk RNA sequencing of islet macrophages from NOD mice revealed that, during the progression of insulitis, an up-regulation of gene downstream of Interferon (IFN) gamma signaling and IL-2/STAT5 and IL-6/STAT3 pathways occurred [61]. In the same experiment set, five subpopulations of macrophages were detected: two with stable transcriptomic signatures, the other two with pro-inflammatory activity, and one displaying anti-inflammatory capacity.

Evidence has been provided that islet inflammatory response may depend on Pathogen-Associated Molecular Patterns and Damage-Associated Molecular Patterns, which bind to TLR on beta-cells and activate NF-Kappa B and STAT-1 pathways [62, 63]. Parallelly, TLR-2/-6 and TLR-4-activated macrophages suppress beta-cell insulin gene expression *via* the release of IL-1-beta and IL-6 [64].

Insular macrophages directly damage beta cells *via* the release of pro-inflammatory cytokines or engulfment of vesicles delivered by beta cells. Indirectly, macrophages activate cytotoxic T cells, which destroy beta cells.

7. OBESITY AND INDUCTION OF T2D

Nowadays, obesity represents a pandemic [65]. Obese individuals are at higher risk of developing insulin resistance and T2D. Obesity leads to a low-grade chronic inflammation with adipocytes as significant players. These cells recognize insulin secreted by beta-cells and respond by storing triglycerides and glycogen [66]. Then, adipocytes release leptin, reducing food intake and increasing lipolysis and thermogenesis. This virtuous cycle is interrupted by overnutrition, which accumulates pro-inflammatory macrophages and gives rise to insulin resistance (IR) and hyperglycemia [67]. In particular, obese murine macrophages release exosomes, whose injection into lean mice accounts for glucose intolerance, IR, and higher glucose-stimulated insulin secretion [68].

In supporting the association between overnutrition and T2D, saturated fatty acids (*i.e*., palmitate) can bind to TLR-4 on both beta-cells and islet macrophage cell surfaces and consequently trigger the release of pro-inflammatory cytokines and chemokines. Such a chain of events accounts for islet inflammation, beta-cell dysfunction, and further infiltration of macrophages into islets [69, 70]. In this framework, as recently reviewed by Liang *et al*. [71], different lipids (*e.g*., oxidized low-density lipoproteins, cholesterol crystals, saturated fatty acids, and sphingolipids) can activate the NLRP3 inflammasome on macrophages *via* mitochondrial stress and generation of reactive oxygen species (ROS).

From a pathogenic viewpoint, IR represents a fundamental event in the inflammatory process in the course of T2D. Since the reduced insulin response at tissue levels leads to an extra insulin production by beta-cells, islets undergo more significant oxidative stress and are prone to apoptosis and necrosis [72]. Upon insulitis, increasing waves of pro-inflammatory cytokines (*e.g*., TNF-alpha and IL-6) hamper insulin receptor tyrosine kinase to proceed downstream insulin signaling, eventually exacerbating IR [73].

Overnutrition-induced hyperinsulinemia is intended to compensate for systemic hyperglycemia, but, at the same time, it down-regulates the expression of the purinergic receptor genes IL-10 and MMP-9 that are implicated in anti-inflammation and tissue repair, respectively. Increased beta-cell death generates a switch of macrophages towards a reparative profile, as also observed after streptozotocin administration alone or in combination with a high-fat diet (HFD) [37].

Pancreatic stromal macrophages seem to play a pathogenic role in T2D too. KrasG12D mice fed with HFD gain weight, have hyperinsulinemia and hyperleptinemia, and exhibit a high release of pro-inflammatory cytokines [74]. An expansion of pancreatic stromal macrophages has been detected in these mice with polarization towards the M1 phenotype upon binding of lipopolysaccharides or endotoxins to TLR-4 [75]. In this context, the synergistic effect of lipopolysaccharides and leptin in the attraction of blood monocytes to the pancreas and hypersecretion of cytokines should be mentioned [76].

8. A DIETARY APPROACH FOR T2D

It is known that hypercaloric diets rich in saturated fatty acids, as in the western diet, profoundly affect lipid metabolism, leading to the activation of the inflammatory pathway and inhibition of insulin receptor signaling [77]. On the other hand, consumption of whole-grain foods and vegetables, as in the case of the Mediterranean diet, improves insulin resistance and may prevent T2D outcomes [78-81].

Some components of the Mediterranean diet will be illustrated for their capacity to prevent or attenuate inflammation and oxidative stress that characterize obesity and T2D [82].

9. POLYPHENOLS

Polyphenols (flavonoid and non-flavonoid compounds) are contained mainly in fruits, vegetables, cereals, red wine, and extra virgin olive oil [83]. Regularly consuming polyphenols through diet leads to beneficial effects given their anti-inflammatory and anti-oxidant capabilities (Table **2**). Notably, they inhibit the NF-kappa B pathway with reduced pro-inflammatory cytokine release, induce human T regulatory (Treg) cells with the production of IL-10, and decrease ROS generation by human neutrophils and monocytes [84, 85].

With particular reference to ROS, beta-cells, having low glutathione peroxidase levels, are susceptible to oxidative stress, and excessive oxidative stress is implicated in beta-cell injury and destruction [86]. In addition, endogenous regeneration of beta-cells is usually scarce, and the regeneration of preexisting beta-cells seems to decline over time.

Consumption of a polyphenols-enriched diet lowered the risk of developing T2D by 14% in one study [87]. According to the EPIC-INTERACT study, intake of flavanols reduced the risk of T2D in European populations [88]. Apple and pear are rich in flavanols, and regular consumption of these fruits reduces the risk of T2D [89].

A series of papers have reported a lower risk of T2D and improvement in IR in consumers of caffeinated beverages [90]. Similarly, intake of anthocyanidin and flavones improved IR and inflammation in women [91].

In vitro studies have also confirmed the beneficial effects of polyphenols on T2D development. Using white adipocyte 3T3-L1 cells, (-)-epicatechin reduced Mitogen-Activated Protein Kinase, NF-kappa B, and Activator Protein-1 pathway activation by TNF-alpha implicated in inflammation and insulin sensitivity [92].

INS-1 cells were derived from rat pancreatic beta-cells when stressed; they were protected by quercetin, increasing glucose-induced insulin secretion *via* activation of ERK 1/2 [93]. Furthermore, quercetin could preserve beta-cell mass and function in fructose-induced hyperinsulinemia, regulating the activation of pancreatic Protein Kinase B (Akt)/Forkhead Box Protein O1 [94].

Epicatechin has also been shown to enhance insulin secretion in INS-1 cells treated with saturated fatty acids or under oxidative stress [95, 96]. In the same cells, anthocyanins increased insulin secretion in the presence of glucose and protected autophagic cell death mediated by H_2O_2 [97].

In conclusion, only (-)-epicatechin and (-)-epicatechin-rich foods and anthocyanins are very effective in reducing IR. Abrogation or mitigation of IR could reduce inflammation in the islet milieu, even though modulation of resident and infiltrating macrophage's activity.

Table 2. Summary of the leading mechanisms by which polyphenols may reduce the inflammatory milieu within pancreatic islets in T2D.

Inhibition of NF-kappa B with reduced release of pro-inflammatory cytokines
Induction of Treg cells with a release of the anti-inflammatory cytokine IL-10
Decreased release of ROS by human neutrophils and monocytes
Abrogation or mitigation of IR

10. POLYUNSATURATED FATTY ACIDS (PUFAS)

Omega-3 is a family of PUFAs and includes longer n-3 fatty acids, such as eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) [98]. In animal studies and human trials, PUFA administration has been demonstrated to exert anti-inflammatory activity, especially by inhibiting the arachidonic acid and the NF-kappa B pathways and triggering the anti-inflammatory response *via* G-protein coupled receptor (GPCR) [99,100].

According to a meta-analysis conducted by Lin *et al*. [101], N-3 PUFAs supplementation in T2D patients reduced inflammation markers such as C-reactive Protein (CRP). In the other two studies, EPA and DHA reduced TNF-alpha concentrations while improving IR [102]. However, in another report, EPA and DHA failed to reduce TNF-alpha levels [103].

The consumption of fish oil enriched in EPA and DHA has been shown to decrease the risk of T2D and improve insulin sensitivity *via* inhibition of adipocyte-mediated inflammation [104].

11. PREBIOTICS/PROBIOTICS

There is evidence that alteration of gut microbiota is associated with the development of T2D [105]. Both prebiotics and probiotics may normalize the gut microbiota and represent suitable nutritional solutions for the management of T2D (Table **3**) [106]. Inulin-based fructose oligomers or galactic oligosaccharides represent the major prebiotics. Prebiotics provide the host health benefits, including protection against pathogens, regulating satiety, improving mineral absorption, bowel function, and immune modulation [107].

Lactobacilli and Bifidobacteria contribute to the intestinal microbial balance or improve the properties of indigenous microflora [108]. Following ingestion, probiotics exert several functions by modulating the immune response, protecting the intestinal barrier permeability, reducing bacterial translocation, and interacting with resident microbiota to improve intestinal performance [109].

As far as the mechanisms of action of prebiotics are concerned, they mainly act by increasing the generation of SCFAs such as acetate, butyrate, and propionate [110,111]. SCFAs are transported to the colonic epithelium and are in close contact with mucosal immune cells *via* monocarboxylate transporters 1 and 4 and GPRCs [112].

Butyrate inhibits histone deacetylase with the regulation of JAK2/STAT3 and vascular endothelial growth factor pathways and seems to exert beneficial effects on inflammatory bowel disease and cancer [113,114]. As recently reviewed by Jana *et al*. [115], gut microbiota may be involved in the pathogenesis of T2D. Fusobacterium, Ruminococcus, and Blautia are defined as diabetogenic bacteria, while Bacteroides, Akkermansia, Roseburia, and Faecalibacterium may decrease the risk of T2D [116]. In this direction, rice husk-derived xylooligosaccharides (XOS) display antihyperglycemic effects on a T2D rat model [117]. In this specific instance, XOS decreased the expression of glucose transporter type 4 to the plasma membrane. In patients with prediabetes, both XOS and mannooligosaccharides (MOS) increased the population of intestinal bacteria, such as Blautia, Akkermansia, and Bifidobacterium, thus, reducing systemic inflammation, IR, and high glucose uptake, while attenuating endotoxemia [118].

Furthermore, MOS up-regulated the expression of the leptin-associated protein while down-regulating the negative regulators of the insulin signaling pathway [119]. Several studies have confirmed that patients with diabetes mellitus harbor a so-called "diabetic microbiota", characterized by a loss of butyrate-producing bacteria with an abundance of opportunistic microorganisms [120, 121].

Experimentally, the administration of probiotics to HFD mice has provided a wealth of information on the effects of probiotics on metabolic and inflammatory biomarkers. For instance, Lactobacillus (L.) casei supplementation improved high-fructose-induced altered glucose tolerance in hyperinsulinemic rats [122]. Administration of L. reuteri in HFD obese rats decreased inflammation and insulin resistance-related gene expression [123]. L. casei administration decreased insulin resistance, TNF-alpha and IL-6 concentrations, and increased numbers of Lactobacillus and Bifidobacterium in T2D mice [124]. L. rhamnosus supplementation ameliorated

IR in HFD obese mice, reducing inflammatory parameters and oxidative stress [125, 126].

With particular reference to clinical trials in T2D patients, the effects of supplementation of a mixture of probiotic strains and the so-called "ecologic barrier" have been reported. This mixture is composed of Bifidobacterium Bifidum (B.) W23, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, L. lactis W29, and Lactococcus lactis W58 [127]. While short-term administration (12 weeks) did not reduce levels of endotoxins in T2D patients, a prolonged supplementation was very effective in decreasing endotoxins, triglycerides, and total cholesterol to high-density lipoprotein ratio TNF-alpha, IL-6, CRP, resistin, while elevating adiponectin concentration [128].

This last probiotic regimen ameliorated the health status of T2D patients in relation to cardiometabolic and inflammatory control. Supplementation of a mixture of *L. acidophilus, L. plantarum, L. paracasei, L. delbrueckji subsp, Bulgaricus, B. breve, B. longum, B. infantis*, and *S. thermophilus* could reduce IL-6, CRP, and TNF-alpha levels in patients with gestational diabetes mellitus [129]. Other studies denied the beneficial effects of probiotics on the health status of T2D, as reported by Linsday *et al*. [130]. In a more recent meta-analysis of randomized clinical trials [131], further evidence has been reported of a supplementary therapeutic effect with probiotics in T2D patients with improved lipid profile and metabolic control.

Table 3. Summary of prebiotics and probiotics contribution in experimental models and patients with T2D.

Prebiotics	Probiotics
Increase in SCFAs (acetate, butyrate and propionate)	Modulate the intestinal immune response, improve intestinal permeability and reduce bacterial translocation, interfere with the resident microbiota
Inhibit histone deacetylase and regulate the JAK2/STAT3 pathway	Reduce IR and inflammatory biomarkers in HFD mice
Normalize gut microbiota in prediabetic individuals, reducing IR and attenuating endotoxemia	Reduce inflammatory biomarkers, insulin and endotoxin levels while increasing circulating adiponectin

12. VITAMINS

The role of vitamin D in preventing T2D has been investigated because of the association of low serum levels of the 25-hydroxylated metabolite with the risk of diabetes in European and Chinese adults [132]. Other studies have revealed a high inflammatory status, IR, and beta-cell dysfunction in individuals with low serum vitamin D concentration [133,134]. On these bases, supplementation of vitamin D in adults prevented T2D development and ameliorated beta-cell function [135]. More recently, an interesting investigation did not confirm the aforementioned results in prediabetes after a 24-month supplementation of cholecalciferol [136].

Interestingly, there is evidence that vitamin D binds to vitamin D receptors on intestinal dendritic cells that activate Treg cells with the release of IL-10 and induction of the anti-inflammatory pathway [137]. A recent meta-analysis [138] of 10 studies with 34,882 participants strongly suggested a significant association between vitamin D levels and T2D even if its supplementation did not prevent the future development of T2D.

CONCLUSION AND FUTURE PERSPECTIVES

T2D is a metabolic disorder characterized by hyperglycemia, IR, and oxidative stress. Conventional anti-hyperglycemic medications are involved in glucose and lipid metabolism, insulin secretion, and signaling [139]. However, the inflammatory status maintained by intra-insular and peri-insular macrophages has been less investigated by interventional studies. Components of the Mediterranean diet, *i.e*., polyphenols, PUFAs, prebiotics, probiotics, and vitamin D, can reduce inflammation and oxidative stress in T2D and modify gut microbiota composition.

Therefore, along with antidiabetic drugs, food components may be beneficial in T2D. In this respect, personalized medicine to identify the nutritional needs of T2D individuals is to be encouraged.

LIST OF ABBREVIATIONS

APCs = Antigen Presenting Cells
CRP = C-Reactive Protein
CSF-1 = Colony Stimulating Factor-1
CTGF = Connective Tissue Growth Factor
DHA = Docosahexaenoic Acid
EPA = Eicosapentaenoic Acid
DPA = Decosapentaenoic Acid
GPCR = G Protein Coupled Receptor
HFD = High Fat Diet
HSCs = Hematopoietic Stem Cells
IFN = Interferon
IL = Interleukin
IR = Insulin Resistance
MOS = Mannooligosaccharides
PUFAs = Polyunsaturated Fatty Acids
ROS = Reactive Oxygen Species
SCFAs = Short-Chain Fatty Acids
T1D = Type 1 Diabetes
T2D = Type 2 Diabetes
TGF = Transforming Growth Factor
TLR = Toll Like Receptor
TNF = Tumor Necrosis Factor
TREG = T Regulatory
XOS = Xylooligosaccharides

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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