diabetology

MDPI

Review

The Interplay Between Reactive Oxygen Species, Glucose Metabolism and NF-kB in the Pathogenesis of Type 2 Diabetes

Hossein Mirmiranpour [1] and Catherine Arden [2,*]

[1] Endocrinology and Metabolism Research Centre (EMRC), School of Medicine, Tehran University of Medical Sciences, Tehran 1416753955, Iran
[2] Biosciences Institute, Newcastle University, Newcastle NE2 4HH, UK
* Correspondence: catherine.arden@newcastle.ac.uk

Abstract

Reactive oxygen species (ROS) are an essential component for the maintenance of cellular function. However, if produced in excess, ROS can drive cellular dysfunction and compromise cell viability. Indeed, uncontrolled ROS production plays a pivotal role in the pathogenesis of type 2 diabetes (T2D), contributing to the loss of β-cell function and the impairment in insulin signalling, as well as driving the development of diabetic complications, which can severely compromise quality of life. T2D is characterised by persistent hyperglycaemia, which is a leading contributor to ROS overproduction in this disease state. This enhanced, almost uncontrolled, increase in glucose metabolism upregulates several ROS-producing pathways, including the hexosamine pathway, protein kinase C, NADPH oxidase and the mitochondrial electron transport chain. There is accumulating evidence to suggest that in a bid to preserve redox homeostasis, ROS acts to suppress glucose metabolism by inactivating several enzymes involved in the regulation of glycolytic flux, including glucokinase, glyceraldehyde 3-phosphate dehydrogenase, phosphofructokinase-1 and pyruvate kinase. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a multi-faceted transcription factor, with a central role in ROS signalling and redox homeostasis. Whilst NF-κB mediates the transcriptional regulation of many pro-oxidants, NF-κB activity is also regulated by the oxidative status, with ROS having both inhibitory and stimulatory roles in these signalling pathways. Interestingly, NF-κB is also involved in controlling the delicate balance between glycolytic flux and mitochondrial respiration. This review will summarise the interplay linking hyperglycaemia with ROS formation, emphasising the role of glucose metabolism in the process, and the crosstalk of these pathways with NF-κB.

Keywords: diabetes; reactive oxygen species; glucose metabolism; glycolysis; NF-κB

Academic Editor: Bogdan Timar

Received: 12 January 2026
Revised: 6 February 2026
Accepted: 24 February 2026
Published: 4 March 2026

1. Introduction

Reactive oxygen species (ROS) are integral to normal cellular physiology, yet their overproduction can disrupt homeostasis and impair cell viability. In type 2 diabetes (T2D), excessive ROS generation has emerged as a central driver of disease progression, contributing to β cell dysfunction, impaired insulin signalling, and the development of long-term complications. Persistent hyperglycaemia, a hallmark of T2D, plays a major role in this process by accelerating glucose metabolism and activating multiple ROS-producing pathways, including the hexosamine pathway, protein kinase C, NADPH oxidase, and the mitochondrial electron transport chain. Increasing evidence suggests that ROS also act as metabolic

regulators, suppressing glycolytic flux through the oxidative inactivation of key enzymes such as glucokinase, glyceraldehyde 3 phosphate dehydrogenase, phosphofructokinase 1, and pyruvate kinase.

Nuclear factor kappa light chain enhancer of activated B cells (NF κB) sits at the intersection of these processes, functioning both as a mediator of pro-oxidant gene expression and as a redox-sensitive transcription factor whose activity is shaped by ROS levels. Beyond its canonical inflammatory roles, NF κB also influences the balance between glycolysis and mitochondrial respiration, positioning it as a key integrator of metabolic and oxidative signals.

This review examines the mechanistic links between hyperglycaemia, ROS formation, and metabolic regulation in T2D, with a particular focus on how glucose-driven oxidative stress intersects with NF κB signalling.

2. Reactive Oxygen Species and Their Role in Human Physiology

ROS are generated during natural aerobic metabolism and include a wide group of highly reactive oxygen-derived molecules [1]. This encompasses molecules that are free radicals and thus contain an unpaired electron in their outer orbit, which includes superoxide ($O2^{-}$), hydroxyl radicals (OH^{-}) and hydroperoxyl (O_2H), amongst others. ROS also encompass non-radical molecules, including hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$). These free and non-radicals are highly reactive, easily reacting with other molecules within cells, a process that drives many cellular processes. Indeed, ROS play a pivotal role in redox homeostasis, which balances oxidising and reducing reactions within cells leading to downstream signalling transduction events. This system regulates numerous essential physiological activities, including the immune response, cellular signalling, antimicrobial agent activation, longevity regulation, reproductive systems and metabolic homeostasis [2–5], as well as acting on many cellular pathways, including cellular differentiation, proteasomal function and autophagy [2,3]. Redox homeostasis is a balance between ROS production and scavenging activities facilitated by endogenous antioxidants [6]. The antioxidant system is cell type-dependent and involves enzymatic antioxidants such as glutathione peroxidases (GPx), thioredoxin (Trx), superoxide dismutase (SOD) and catalase (CAT) as well as non-enzymatic antioxidants including glutathione (GSH), metal-binding proteins (MBPSs) and uric acid (UA). These antioxidants act to neutralise excess ROS to prevent the development of oxidative stress and resulting cellular damage [4,7,8]. Different tissues sit at different redox points, reflecting their metabolic rate, oxygen exposure, antioxidant defences and signalling needs [9].

3. Increased ROS Production in T2D Due to Hyperglycaemia

3.1. Increased ROS Production in T2D

T2D, an epidemic and metabolic disease, is driven by insulin resistance and a relative insufficiency in insulin release. There has been much research aimed at identifying the molecular factors driving the pathophysiology of T2D. This has identified excess non-esterified fatty acids and chronic hyperglycaemia, also termed lipo- and glucotoxicity, respectively, as key mediators driving cellular dysfunction. The cellular pathways disrupted include mitochondria, endoplasmic reticulum, autophagy, amyloid deposition and inflammation, which together result in cellular dysfunction, impacting metabolic homeostasis [10]. Oxidative stress is another key mediator in driving cellular dysfunction in T2D, which results due to chronic accumulation of ROS [11]. The role for ROS production in mediating T2D pathogenesis is complex since low levels of ROS production are required for glucose homeostatic mechanisms. For example, ROS are essential for appropriate glucose-stimulated insulin secretion (GSIS) from pancreatic β-cells since elimination of cellular

ROS is associated with an impaired GSIS response [12]. Similarly, ROS play an essential role in myogenesis, adipogenesis, differentiation of both myocytes and adipocytes, as well as enhancing insulin sensitivity [13]. However, prolonged ROS accumulation impacts negatively on the function of numerous cell types involved in the pathogenesis of T2D and its associated complications, including the pancreatic islets, liver, adipose, muscle, brain, retina and kidney [14]. This process contributes to decreased insulin secretion by β-cells, insulin resistance of peripheral tissues and exacerbation of diabetes complications [11], including fatty liver, nephropathy, retinopathy, diabetic ulcer, neuropathy and cardiomyopathy (Table 1). The tissue-specific redox characteristics impact on the cell function and also on pathophysiological processes. For example, the liver operates at a high basal oxidative load due to numerous ongoing metabolic processes, and as such, demonstrates a strong antioxidant capacity. Meanwhile, skeletal muscle displays low levels of basal ROS production, with sharp increases due to muscle contraction, and antioxidant defences are moderate. Redox imbalance plays an important role in insulin resistance in T2D in both tissues [9]. Pancreatic β-cells are particularly sensitive to enhancement of ROS production, in part due to their low levels of antioxidant defences compared to other cell types [15]. Prolonged exposure of β-cells to excess ROS leads to the development of oxidative stress, which is associated with decreased GSIS, decreased proliferation, cell dedifferentiation and increased cell death [15]. Other cell types involved in glucose homeostasis are also negatively impacted by prolonged exposure to ROS, including liver, muscle and adipose tissue, which leads to their cellular dysfunction and contributes to the pathogenesis of T2D (Table 1). Furthermore, increased oxidative stress is also associated with the development of many diabetic complications commonly evident in individuals with T2D. Diabetic nephropathy is thought to be driven by the chronic accumulation of ROS, which leads to cellular apoptosis and kidney dysfunction [16]. Similarly, studies in diabetic retinopathy show that excessive production of ROS locally damages the cells of the microvessel wall, leading to microvascular cell apoptosis and disruption of the blood supply to the retina [17]. The lack of thermal and mechanical sensation evident in diabetic peripheral neuropathy is accompanied by an increase in ROS levels in the somatic cells of the sensory nerves and in the cells at the end of the axon of the peripheral nerves [18]. In addition, an increase in ROS production is considered an important factor in the development of diabetic cardiomyopathy, with a clear association between ROS production and monoamine oxidase in the pathogenesis of cardiomyopathy [19]. Cancer cells are also affected by enhanced ROS accumulation, which has been proposed as a potential causative effect driving the increased incidence of cancer in individuals with T2D [20].

Table 1. Beneficial and detrimental effect of ROS production on function/survival of different cell types.

	Effect of ROS	
Tissue/Cell Type	**Beneficial**	**Detrimental (in T2D)**
Pancreatic β-cell	Stimulates glucose-stimulated insulin secretion (GSIS) [21]	Decreased glucose-stimulated insulin secretion (GSIS) Decreased proliferation Increased cell death [22]
Liver	Hepatocyte survival [23]	Hepatocyte dysfunction Decreased glucose production [24]
Adipose	Essential for adipogenesis [25]	Restricted adipocyte differentiation [26]
Muscle	Normal force production [27]	Reduced force generation and increased muscle atrophy [28]
Brain	Necessary for synaptic plasticity and cognitive function [29]	Impaired synaptic plasticity and memory function [29]

Table 1. *Cont.*

	Effect of ROS	
Tissue/Cell Type	**Beneficial**	**Detrimental (in T2D)**
Retina	Required for physiological signalling and protective mechanisms in retina [30]	Retinal damage [31]
Vessels	Essential for maintaining normal vessel functions [32]	Proliferation and migration of vascular smooth muscle cells [32]
Kidney	Required for normal kidney cell function [33]	Abnormal kidney function and chronic kidney disease progression [33]
Heart	Essential of cardiomyocyte homeostasis including cell proliferation, differentiation, and excitation–contraction coupling [34]	Disruption of myocardial calcium handling, arrhythmia, inducing hypertrophic signalling, apoptosis, and necrosis [35]

3.2. ROS Generation from Enhanced Glycolysis

Chronic hyperglycaemia is the major driver increasing ROS production via enhanced flux through metabolic pathways. Glycolysis is the major metabolic pathway for carbohydrate breakdown, converting glucose to pyruvate. As well as producing adenosine triphosphate (ATP), which is required by the cell for function and survival, glycolysis also produces many metabolic intermediates that serve as building blocks for other metabolic pathways. This includes pyruvate, which can be shuttled into the mitochondria for further metabolism via the tricarboxylic acid cycle (TCA), and oxidative phosphorylation, which greatly increases ATP production [36]. Glycolysis also produces metabolites that can directed into other metabolic pathways such as glycogenesis, gluconeogenesis and lipogenesis, depending on the cell type. Fluxes through these metabolic pathways are themselves heavily influenced by metabolic intermediates as well as via hormonal control [37]. There are several pathways directly stimulated by enhanced glycolysis that are related to the overproduction of ROS in response to chronic hyperglycaemia during diabetes (Figure 1), as summarised under the following subheadings.

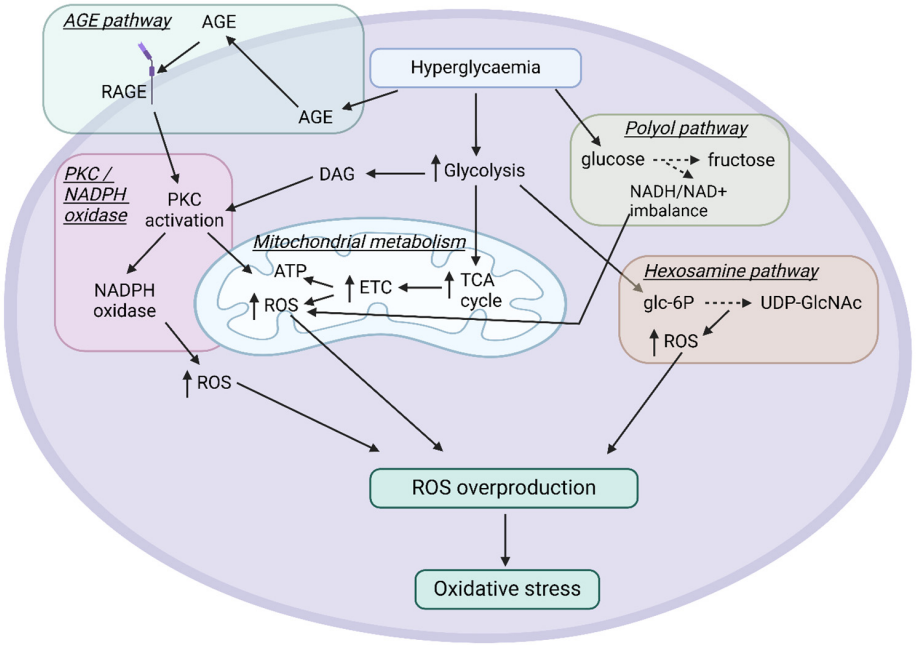

Figure 1. Pathways involved in the upregulation of reactive oxygen species production in response to chronic hyperglycaemia. Exposure of cells to chronically elevated glucose concentrations leads to an increase in glucose metabolism. This contributes to the production of reactive oxygen species via the

following pathways: (i) Mitochondrial electron transport chain (ETC): increased flux through glycolysis and mitochondrial metabolism enhances the production of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). These nucleotides enter the ETC chain, which functions to produce high amounts of Adenosine Triphosphate (ATP) but also increased Reactive Oxygen Species (ROS); (ii) hexosamine pathway: increased conversion of fructose-6-phosphate to uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc) leads to increased N- or O-linked glycosylation of proteins. Enhanced flux through this pathway increases ROS production; (iii) protein kinase C (PKC) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase: increased production of 1,2-diacylglycerol (DAG) leads to the direct activation of PKC. PKC induces ROS production by directly stimulating mitochondrial ROS production and also by activating NADPH oxidase (NOX), which is a critical source of ROS; (iv) polyol pathway: activation of the polyol pathway converts glucose to fructose, reactions that utilise NADPH and generate NADH, leading to an imbalance in $NADH/NAD^+$ redox homeostasis. This creates an oversupply of electron donors to the mitochondrial ETC, increasing ROS production; (v) advanced glycation end-product (AGE) formation: Glucose and glycolytic intermediates play a critical role in AGE formation. AGEs can initiate cellular damage via a number of mechanisms including the production of ROS via AGE receptor (AGE-R) binding to molecules such as RAGE and AGE-R1, 2 and 3, which leads to the activation of PKC and downstream accumulation of ROS. Image was created using Biorender.

3.2.1. Mitochondrial Electron Transport Chain (ETC)

In mammals, the mitochondrial ETC is a major source of ROS production. Following the formation of pyruvate by glycolysis, pyruvate can be further metabolised by the TCA cycle, which produces reducing equivalents in the form of NADH and $FADH_2$. These nucleotides are utilised by the ETC chain to produce high amounts of ATP. The ETC consists of complexes I-IV and two electron transporters, ubiquinone and cytochrome c. In order to produce ATP by complex V (ATP synthase), the proton gradient in the mitochondrial inner membrane aids the movement of electrons from complex I to complex V [38,39]. NADH:quinone oxidoreductase, along with NADH reduction, plays a key role in maintaining the proton electrochemical gradient in mitochondrial membranes. This enzyme is an antioxidant protein that, with the help of NADH, as an electron donor, reduces reactive quinone metabolites and produces NAD^+. NADH by ubiquinone (Q) helps the synthesis of NAD^+ and ubiquinol (QH2) and causes the transfer of four protons from the negative side to the positive side of the membrane. $FADH_2$ is also involved in this with the transfer of electrons from NADH and $FADH_2$ to oxygen via the electron transfer chain (ETC) and generation of the proton gradient driving ATP production [40,41]. During electron transport in the ETC, some electrons are transferred to O_2, resulting in the generation of ROS. Sites in complex I, complex II and site complex III produce reactive species in the form of superoxide anions ($O2^-$), amongst others [42]. In the situation of chronic hyperglycaemia, increased flux through glycolysis and mitochondrial metabolism results in the production of excess ROS, which is associated with mitochondrial respiration failure [43]. This failure further exacerbates ROS production and drives greater mitochondrial dysfunction [44].

3.2.2. Hexosamine Pathway

Under basal conditions, about 5% of glucose metabolised inside the cell enters the hexosamine pathway. During this process, the glutamine fructose-6-phosphate aminotransferase isoform 1 (GFAT1) enzyme catalyses the conversion of fructose-6-phosphate (a glycolytic intermediate), glutamine, acetyl coenzyme A and nucleotides to produce uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc), which is used for N- or O-link glycosylation of proteins [45,46]. These post-translational modifications regulate key cellular responses, including the stress response, the immune response, cell growth and viability, as well as acting as a nutrient sensor. Importantly, flux through the hexosamine pathway is

also further stimulated by ROS, notably superoxide, and the pathway is also a source of ROS itself. Studies in pancreatic β-cells show that activation of this pathway leads to β-cell dysfunction via enhanced ROS production, whilst studies in endothelial cells showed a similar effect [45,47,48].

3.2.3. Protein Kinase C and NADPH Oxidase

Protein kinase C (PKC) is a serine/threonine tyrosine kinase involved in cell division, proliferation, and survival [49]. Glyceraldehyde-3-phosphate (G3P), a metabolic intermediate of the glycolysis pathway, can be converted to 1,2-diacylglycerol (DAG), which leads to the direct activation of PKC. PKC induces ROS production by directly stimulating mitochondrial ROS production through binding to cytochrome c to act as a ROS-generating system [50]. PKC can also induce ROS production by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), which is a critical source of ROS and a mediator for redox signalling [51]. NOX resides in a dissociated form in its resting state, but upon activation, NOX produces ROS through the reduction of oxygen and simultaneous oxidation of NADPH, resulting in the formation of O_2^-, which can be further converted to other ROS, including H_2O_2. Seven isoforms of NOX have been identified in humans: NOX1-5, and dual oxidase (DUOX)1–2 [52]. Chronic hyperglycaemia activates NOX isoforms, in part via the activation of PKC, leading to increased ROS production [53]. Enhanced ROS production via NOX activity has been reported to be associated with microvascular diabetic comorbidities, including diabetic retinopathy and diabetic kidney disease, as well as β-cell dysfunction [54].

3.2.4. Polyol Pathway

Enhanced glucose metabolism resulting from hyperglycaemia can lead to activation of the polyol pathway, also designated the sorbitol pathway [55–57]. Here, glucose is converted to sorbitol, which is then converted to fructose, reactions that utilise NADPH and generate NADH, respectively [58]. Upregulation of this pathway can lead to an imbalance in $NADH/NAD^+$ redox homeostasis, the consequence being an oversupply of electron donors to the mitochondrial ETC. This increases complex I activity, leading to increased superoxide production and ROS imbalance. Indeed, the role of this pathway in T2D is significant, with 30% of glucose thought to flux through the polyol pathway during extreme hyperglycaemia in the ocular lens [59]. The resulting ROS production and redox imbalance lead to oxidative damage to DNA, lipids and proteins and aggravate the complications of diabetes [60].

3.2.5. AGE Formation

Advanced glycation end-products (AGEs) are formed via a spontaneous reaction involving nucleophilic addition between free amino groups of a protein or nucleic acid with the carbonyl group of a reducing sugar. The resulting Schiff bases can undergo transformation into Amadori products to produce AGEs [61]. The primary initiating event for this process is intracellular hyperglycaemia. Glucose and glycolytic intermediates, including glyceraldehyde 3-phosphate and dihydroxyacetone, play a critical role in AGE formation, leading to the generation of numerous AGE products, including carboxymethyl-lysine (CML), pentosidine, and methylglyoxal-lysine dimer (MOLD). AGEs can initiate cellular damage via a number of mechanisms, including the production of ROS via AGE receptor (RAGE, AGE-R) binding to molecules such as RAGE and AGE-R1, 2 and 3, which leads to the activation of PKC and downstream accumulation of ROS [62]. The role of AGE as an accelerator of oxidative stress contributes to the development of T2D and its associated complications [63].

It is necessary to mention that there are other reactions in glucose metabolism that can also produce ROS, to varying degrees. They include pyruvate dehydrogenase [64], aconitase [65], 2-oxoglutarate dehydrogenase [66], Sn-glycerol-3-phosphate dehydrogenase [67], dihydroorotate dehydrogenase [67] and p66shc/cytochrome-c [50], but, in the interests of space, these pathways are not discussed in any greater detail in this review. Furthermore, lipid-derived oxidative pathways also contribute to metabolic dysfunction in T2D, particularly given the important role that excess lipid plays in the pathogenesis of T2D [68]. However, in the interests of space and to maintain conceptual coherence, this review focuses specifically on glucose-induced ROS generation and hyperglycaemia-driven oxidative pathways.

The pathways discussed in detail above demonstrate that hyperglycaemia does not simply elevate ROS as an isolated event; rather, it initiates a coordinated network of metabolic and redox disturbances that reinforce one another over time. Multiple glucose-driven pathways converge to amplify oxidative stress, creating a self-sustaining cycle of metabolic disruption. Within this framework, ROS production in T2D functions both as a downstream consequence of hyperglycaemia and as an active contributor to further metabolic deterioration. This bidirectional relationship progressively compromises beta cell integrity and establishes the biochemical conditions that underlie beta cell failure and the development of diabetic complications.

4. Mechanisms to Preserve Redox Homeostasis

Given the impact of enhanced glucose metabolism on ROS production, it is not surprising that several compensatory mechanisms exist to prevent damage via these pathways and protect cells from oxidative stress.

4.1. Redox Homeostasis

Maintenance of redox homeostasis is essential to ensure the retention of cellular function. Redox homeostasis is dependent on a balance between electrophiles and nucleophiles [69,70]. Cells use several biochemical pathways to establish redox homeostasis. In this regard, glutathione tripeptide (GSH) and its oxidized form (GSSG) have an important role as redox couple buffers [71]. Other antioxidant enzymes, including SOD, peroxisomal CAT, GPx, Trx, glutaredoxin (Grx) and glutathione peroxidases, all play an important role in creating a redox balance, protecting cells against exogenous and endogenous toxins [72–74]. Expression of genes related to redox homeostasis is regulated by the nuclear factor erythroid 2-related factor 2/Kelch-like ECH-associated protein 1 (Nrf2/Keap1) pathway [75]. Nrf2 binds to the promoter region of several genes via the antioxidant response element (ARE) to initiate the transcription of various cytoprotective enzymes, including antioxidants as well as enzymes involved in the pentose phosphate pathway and subsequently NADPH production. Furthermore, many of the genes induced by Nrf2 activation encode enzymes that catalyse additional reactions that produce NADPH, including glucose-6-phosphate dehydrogenase (G6PDH), 6-phosphogluconate dehydrogenase (PGD), isocitrate dehydrogenase (IDH1) and malic enzyme (ME1). This further stimulates the cellular reducing power to establish a redox balance [76]. Some dietary compounds that aid the control of blood glucose homeostasis activate Nrf2. Most of these compounds are of plant origin, such as curcumin, sulforaphane, resveratrol and vitamin D [77].

4.2. Downregulation of Glycolytic Enzyme Activity by ROS/Hyperglycaemia

An imbalance in the cellular redox balance towards oxidative stress can impact the activity of enzymes involved in both glycolysis and the TCA cycle [78]. Several glycolytic enzymes are inhibited by accumulating levels of ROS. This includes key enzymes such as

glucokinase (GCK), phosphofructokinase-1 (PFK1), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), and pyruvate kinase (PK). It is assumed that this resulting inhibition of glycolytic flux has a positive impact on redox homeostasis by increasing flux via the pentose phosphate pathway, which increases NADPH production, improving the antioxidant activity within the cell [78]. However, it should be noted that the decrease in the activity of glycolysis enzymes can also lead to disruption of cellular antioxidant defences [79,80], and glycolysis suppression has also been shown to be associated with increased ROS accumulation [81]. Clearly, the relationship between suppression of glycolytic activity and the redox status is complex.

4.2.1. Glucokinase

Glucokinase (GCK), also termed hexokinase IV, is a key regulator of blood glucose homeostasis. It is one of four isoenzymes of the hexokinase enzyme, which phosphorylates glucose to glucose 6-phosphate, the first step in glycolysis. GCK differs from hexokinases I-III in its specialised kinetics, showing the low affinity of glucose (S0.5 ~ 7–8 mM glucose), sigmoidal kinetics with respect to glucose (Hill coefficient ~ 1.7–1.8) and lack of product inhibition [82]. These kinetics confer sensitivity to changes around the physiological glucose concentration, consistent with its role in regulating blood glucose homeostasis. GCK is expressed in tissues with key roles in blood glucose regulation, including parenchymal hepatocytes, glucose-sensing islet endocrine cells (pancreatic β and α-cells), L and K-cells in the gut, as well as specialised neurons in the brain. The activity of GCK is regulated at both the transcriptional and post-transcriptional levels. Transcriptional control is dictated by the promoter, which differs between the liver (downstream promoter) and endocrine cells (upstream promoter) [82]. Whilst there is no evidence for ROS impacting transcriptional regulation, both promoters are regulated by elevated intracellular glucose concentrations [83,84]. Insulin-induced upregulation of liver GCK transcription is inhibited by high glucose concentrations [85], whilst chronic hyperglycaemia inhibits expression of β-cell GCK [86]. GCK activity is also regulated post-translationally. In the liver, GCK binds to its inhibitory protein, GCKR, which inhibits GCK activity and translocates the complex to the nucleus. GCK-GCKR binding is dependent on carbohydrate metabolism, with fructose 6-phosphate and fructose 1-phosphate promoting and inhibiting binding, respectively [83]. GCK is also activated by binding to the bifunctional enzyme 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase (PFKFB), which occurs more readily at high glucose concentrations [87,88]. The nutritional status also determines the binding of GCK to the BCL2-associated agonist of cell death (BAD), via phosphorylation of BAD at Ser155, which in turn activates GCK [89]. There is also evidence suggesting that oxidative stress could also impact GCK activity. Several naturally occurring mutations in the human *GCK* gene showed increased susceptibility to protein instability induced by increasing oxidative stress within a β-cell model [90]. Given that the GCK protein contains 13-reduced cysteine residues that are essential for its activity, modulation of enzyme activity by the cellular oxidative status may play an important regulatory role.

4.2.2. Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH)

The conversion of glyceraldehyde 3-phosphate to 1,3-bisphosphoglycerate, the sixth step in glycolysis, is catalysed by GAPDH, through a reaction that involves the conversion of NAD^+ to NADH [91]. Whilst the glycolytic function of GAPDH is localised to the cytosol, there are also distinct pools of GAPDH located within the mitochondria, nucleus and membranes, where GAPDH functions in vesicle biogenesis, cell signalling and DNA replication, amongst other functions [92]. Whilst there are limited details of GAPDH regulating the redox status in insulin-releasing or sensitive tissues, studies in cancer cell

models report evidence for a GAPDH redox switch. The diverse functions of GAPDH are dependent on post-translational modifications, including oxidation of cysteine residues. The cysteine residue located in the active-cite of GAPDH (Cys152) has been shown to be reversibly S-thiolated by H_2O_2. This leads to enzyme inactivation and aggregation of GAPDH, limiting metabolic capacity, and thus leading to decreased ETC function and decreased ATP production [93]. The H_2O_2 reactivity of Cys152 is higher than other protein thiols, leading to the designation of oxidation at Cys152 of GAPDH as a redox switch. Recent studies in cancer cell models lacking this GAPDH redox switch show it to be essential for the activation of the pentose phosphate pathway, NADPH regeneration, and accordingly, maintenance of oxidative homeostasis [94]. Mouse models of the Cys152-defective redox switch display altered energy metabolism, with evidence for decreased fatty acid synthesis and increased fatty acid uptake and β-oxidation. GAPDH activity is also regulated by nutrient availability. Under glucose-deprived conditions, GAPDH is methylated by coactivator-associated arginine methyltransferase 1 (CARM1), leading to the inhibition of GAPDH activity [94].

4.2.3. Phosphofructokinase-1 (PFK1)

PFK1 catalyses the transfer of a phosphoryl group from ATP to fructose 6-phosphate, leading to the formation of fructose 1,6-bisphosphate and ADP [95]. Fructose 6-phosphate can also be converted to fructose 2,6-bisphosphate ($F26P_2$) by the bifunctional enzyme 6-phosphofructo 2-kinase/fructose 2,6-bisphosphatase (PFKFB), and notably, $F26P_2$ is the most potent allosteric activator of PFK1, facilitating glycolytic flux in the liver [96]. There are four isoforms of PFKFB encoded by genes *PFKFB1-4*. There is increasing evidence that PFKFB3 activity may be regulated by the ROS status, impacting on $F26P_2$ levels in cancer cells. The expression of PFKFB3 is regulated by ROS production in a cell-based model of acute myeloid leukaemia, with enhanced ROS production leading to increased PFKFB3 expression, which was required for ROS-mediated proliferation [97]. $F26P_2$ levels can also be controlled in cancer cells by TP53-induced glycolysis and apoptosis regulator (TIGAR), which shows high homology with the bisphosphatase domain of PFKFB and acts to degrade $F26P_2$. Thus, changes in TIGAR expression can regulate glycolytic flux in cancer cells. Increased ROS triggers activation of the tumour suppressor gene, *p53*, which acts to increase TIGAR expression and its activation [98,99]. This lowers $F26P_2$, leading to decreased activation of PFK-1 and decreased flux through glycolysis, in turn leading to lower levels of downstream ROS production. Consequently, glycolytic metabolites will be diverted to alternative metabolic fates, including the pentose phosphate pathway, leading to increased production of NADPH, which acts to preserve the redox status [98].

4.2.4. Pyruvate Kinase (PK)

PK catalyses the conversion of phosphoenolpyruvate and ADP to pyruvate and ATP, the final step in glycolysis. There are four isoforms of PK, two derived from the *PKLR* gene (PKL, PKR) and two from the *PKM* gene (PKM1, PKM2). The majority of research linking PK and oxidative stress stems from knowledge around PKM2 in cancer cell models [100]. H_2O_2, diamide and hypoxia oxidises Cys358 of PMK2 lead to decreased levels of the active tetramer, decreasing PK activity [101]. Mutation of Cys358 to prevent oxidation preserved the activity of PKM2 under oxidative stress. It is presumed that oxidation of PKM2 is a protective mechanism to prevent further ROS production, since PKM2 inhibition decreased glycolytic flux and increased the pentose phosphate pathway, leading to increased NADPH production and maintenance of the redox balance [101–103].

4.3. Regulation of Glucose Metabolism via Protein Oxidation

Recent data has uncovered an additional mechanism for the regulation of glycolytic flux by ROS/oxidative stress. The glucose-induced increase in ROS production in pancreatic β-cells was shown to induce oxidation of cysteine residues in the majority of glycolytic enzymes, as well as most of the TCA cycle enzymes and members of the mitochondrial respiratory chain. Interestingly, thiol oxidation was associated with a higher incidence of other post-translational modification in the vicinity of the oxidised cysteine residue, including ubiquitination, phosphorylation and acetylation. It is predicted that these modifications are critical for flux through glycolysis, coupling with mitochondrial metabolism and insulin secretion, and thus play an integral role in β-cell homeostasis [104]. Further work is required to understand the significant impact of these post-translational modifications.

The compensatory responses outlined above illustrate that cells actively adjust both their antioxidant defences and metabolic fluxes in the face of rising oxidative stress. These adaptations underscore that the cellular redox status in T2D is not a passive reflection of ROS exposure but a regulated, multilayered process. Redox homeostasis emerges from the coordinated interplay of metabolic reprogramming, post-translational enzyme modification, and transcriptional control, all of which act to preserve the cellular function under chronic metabolic strain. As the disease progresses, however, these protective mechanisms become insufficient, ultimately contributing to the loss of cellular resilience characteristic of advanced T2D.

5. Role of Nuclear Factor-κB (NF-κB)

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a multifaceted transcription factor that plays a central role in redox homeostasis. The relationship between NF-κB and redox signalling is complex, with ROS having both inhibitory and stimulatory roles over NF-κB signalling and NF-κB having both pro- and antioxidant roles [105,106]. Investigating the relationship between NF-κB and ROS is necessary to understand the effect of ROS on glycolysis and glucose metabolism, as well as the perception of the relevant transcriptional control by NF-κB.

5.1. Function of NF-κB in Relation to ROS and Its Transcriptional Activity

As its role is as a transcription factor, NF-κB plays a key role in regulating many cellular pathways, including cell survival, proliferation and differentiation [107–109]. This impacts many cellular systems, including the innate immune response, inflammation and organ development. NF-κB consists of five structurally related proteins, including the NF-κB subfamily, with p50 and p52, and the reticuloendotheliosis protein (REL) subfamily, with RelA, RelB and c-Rel, which form various homo- or hetero-dimers. The interplay between varying combinations of these subunits drives signalling through the canonical signalling pathway, which mediates inflammatory responses, and the non-canonical pathway, which is more classically involved in cell differentiation and maturation. The subcellular location and activity of these complexes are regulated by binding to numerous inhibitory proteins, the most well characterised being Inhibitor of κB (IκB). Once activated, the NF-κB complexes regulate gene transcription by binding to gene targets via a specific DNA element known as a κB enhancer [107–109].

The heterodimers comprising the NF-κB complex can be directly modified by oxidation, which has a varying impact on NF-κB signalling. This includes oxidation of a cysteine residue (Cys62) within p50, leading to decreased DNA binding, whilst oxidation-mediated phosphorylation of Ser-276 on RelA stimulates binding to some target DNA sequences [110]. Furthermore, the redox active protein thioredoxin can also block the degradation of the inhibitory protein IκB, relieving the inhibition of NF-κB activity, and

thus allowing increased binding to gene targets [111]. In addition, the activity of I-kB is also regulated by LC8 in an oxidation-dependent manner. Oxidation of LC8 causes its dissociation from IκB, leading to subsequent activation of NF-κB signalling [105]. Kinases upstream of the NF-κB pathway are also regulated by redox signalling. H_2O_2 induced the PI3K/PTEN/Akt pathway, leading to NF-κB modulation via its impact on inhibitor of κB kinase (IKK) activity [112]. Interestingly, H_2O_2 also prevented the tumour necrosis factor-α (TNFα)-mediated stimulation of IKK activity, which prevented IκB degradation [112].

5.2. NF-κB-Dependent Regulation of Glycolysis

NF-κB is involved in the regulation of numerous metabolic pathways, including coordinating the balance between glycolysis and mitochondrial respiration via regulation of the 'Warburg' effect, a known phenomenon whereby cancer cells increase glucose uptake and preferentially metabolise glucose anaerobically, leading to increased lactate production rather than downstream aerobic mitochondrial metabolism, and thus limiting ROS production [113]. The importance of NF-κB in this important cancer-progressing process was highlighted by the finding that knockdown of RelA prevented the p53-induced increase in anaerobic glucose metabolism [114]. In addition, hyperactivity of NF-κB has been shown to impact the activity of enzymes in glycolysis, resulting in an imbalance in glycolytic flux [115], thus confirming an impact on this pathway. Importantly, NF-κB has been shown to play a critical role in downregulating the expression of key glucose transporters (GLUT1/2) and also GCK in pancreatic β-cells in response to IL-1β exposure, which leads to impaired β-cell function [116–118]. Meanwhile, activation of NF-κB in the liver decreases glycolytic flux and alters glycolytic gene expression [119,120].

Further studies using cancer models have identified RelA as an intrinsic checkpoint that favours metabolism via mitochondrial oxidative phosphorylation by restricting aerobic glycolysis [121]. This conflicting data is perhaps partially explained by signalling via the non-canonical and canonical pathways, which promotes oxidative metabolism [122] or favours anaerobic glucose metabolism [123], respectively. Although evidence for direct associations between NF-κB and glycolytic genes is currently limited in all cell models, several mediators of NF-κB signalling have been identified to regulate glycolytic enzyme expression/activity. NF-κB-inducing kinase (NIK), a mediator of the non-canonical NF-κB pathway, has been identified as an essential regulator of energy metabolism in T-cells by preventing the autophagic degradation of hexokinase II [124]. Interestingly, NIK was able to stabilise hexokinase II protein by driving the production of NADPH, promoting the activity of G6PDH, and leading to lowered ROS production. Other glycolytic enzymes are also modulated by NF-κB and its modulators. In colorectal cancer cells, inflammatory mediators occurring secondarily to enhanced NF-κB signalling upregulated the expression of Snail, a transcriptional regulator, which in turn upregulated hexokinase 3 expression [125]. Furthermore, the upstream regulator of NF-κB activity, IKKβ, which is a component of the IKK complex, has been shown to bind and phosphorylate PFKFB3, leading to inhibition of PFKFB3 activity and decreased glycolysis.

NF-κB can also act on flux through glycolysis by altering signalling through hormonal mediators of blood glucose homeostasis. Some of these effects are beneficial, such as the enhancement of glucose-stimulated insulin secretion in the pancreatic β-cells, which appears to be important for appropriate insulin responsiveness [126]. However, some responses are pathogenic, including NF-κB-mediated inflammation, which decreases insulin sensitivity of peripheral tissues and is thought to contribute to the pathogenesis of T2D [127]. This is highlighted by forced expression of constitutively active IKKβ to increase NF-κB activity, which led to inflammation and insulin resistance [127]. Insulin plays a key role in regulating the translocation of certain glucose transporters to the plasma membrane to permit

glucose entry; enhancing the expression of liver glucokinase; and activating liver PFKFB1 kinase activity to increase $F26P_2$ levels. Insulin resistance, induced in part via NF-κB, will negatively impact these pathways [128].

5.3. NF-κB, ROS and Glycolysis in Diabetes

Signalling through NF-κB has been shown to impact the pathogenesis of T2D via the upregulation of pro-inflammatory pathways. However, its role is complex, showing both tissue-specific effects as well as dependence on the stage of disease progression [129]. During the early stages of diabetes, moderate ROS production and controlled NF-κB activation are cytoprotective and offer cell-specific protective effects, such as anti-apoptotic signalling and tissue repair, depending on the cell type (Table 2). However, as T2D progresses, NF-κB signalling is chronically activated, and this mechanism is strongly implicated in driving insulin resistance, β-cell failure and the development of diabetic complications (Table 2).

Table 2. NF-κB activation in type 2 diabetes: Adaptive vs. detrimental roles in different cell types.

	Effect of NF-κB Activity	
Tissue/Cell Type	**Early/Adaptive NF-κB (Acute)**	**Late/Pathological NF-κB (Chronic)**
Pancreatic β-cell	Anti-apoptotic, adaptive stress response [130]	Cytokine production, dedifferentiation, apoptosis, impaired glucose-stimulated insulin secretion (GSIS) [116–118].
Liver	Metabolic adaptation [131]	Insulin resistance, chronic inflammation, fibrosis [119,120]
Skeletal muscle	Tissue repair, innate immune response [132]	Insulin resistance [132,133]
Adipose tissue	Remodelling, innate immune response [134]	Insulin resistance, lipid deposition [128]
Vasculature	Immune surveillance, endothelial adaptation [135]	Endothelial dysfunction, vascular complications [136,137]
Kidney	Tissue repair, innate immune response [138]	Podocyte injury, fibrosis, albuminuria [139]
Heart	Anti-apoptotic, tissue adaptation [140]	Inflammation, fibrosis, impaired contractile function [141]
Retina	Immune surveillance [142]	Leukostasis, neovascularisation [143]
Brain	Innate immune response, synaptic plasticity [144]	Insulin resistance, neuroinflammation [145]

Focusing on insulin resistance, mice with heterozygous deletion of IKKβ were protected from both diet-induced and genetic obesity [128], whilst liver-specific expression of constitutively active (CA) IKKβ caused systemic insulin resistance and glucose intolerance [131]. These studies highlight the essential role for NF-κB signalling in the inflammatory response involved in insulin resistance, which is involved in the pathogenesis of T2D. Furthermore, NF-κB signalling also impacts on β-cell function/survival in T2D pathogenesis. β cell-specific overexpression of NIK results in spontaneous diabetes in male mice at a young age (≥10 weeks of age), which is likely due to insulin deficiency, β-cell death, and insulitis [146]. However, it should be noted that follow-up studies involving β-cell-specific knockout of NIK showed that NIK silencing had no impact on the incidence of diabetes in mice fed either chow or a high-fat diet and had no effect on glucose metabolism [147], warranting future investigations in this area.

Considering that NF-κB is regulated by ROS signalling, it is unsurprising that NF-κB is upregulated by conditions associated with high rates of glucose metabolism. Activation of NF-kβ is associated with the high level of AGEs, their receptors (RAGEs) and ROS [148,149], with the AGE–RAGE pathway directly increasing ROS via NF-κB production, leading to cellular impairment by directly damaging cellular components like proteins, lipids and DNA. On the other hand, research has also shown that in hyperglycaemic conditions, it is the increase in ROS production that leads to NF-κB-induced inflammation and eventual

cellular damage [150]. NF-κB also plays a role in regulating glycolysis in diabetic nephropathy. In this regard, NF-kB regulates the activity of HIF-1α a, which increases glycolytic metabolism via activation of hexokinase-1 (HK1) activity [151].

5.4. The Interaction Between NF-κB and ROS

The correlation between the NF-κB signalling pathway and ROS has always been a matter of debate and has been accompanied by various and sometimes contradictory scientific findings. In one study, chronic upregulation of ROS production, induced via alterations in gene expression, reduced inflammatory cytokines and decreased NF-κB in macrophages [152]. On the other hand, other studies have inferred a direct correlation between ROS levels and NF-κB activity, where a decrease in both acute and chronic ROS production was associated with a decrease in NF-κB activity [153–156]. Furthermore, 24 h exposure to anti-inflammatory compounds reduced ROS production and also prevented the activation of the NF-κB pathway in microglial cells [157]. Some of these compounds regulate inflammation by inhibiting cytokines that are associated with activation of the NF-κB signalling pathway [158], including in skeletal muscle [159], although some inflammatory-modulating compounds altered NF-κB activation without impacting ROS levels in fibroblasts [160]. Clearly, ROS regulate NF-κB in a highly context-, duration- and cell type-specific manner. When focusing on tissue involved in the pathogenesis of T2D, chronically upregulated ROS production was associated with activation of NF-κB activity, and downstream inhibition of GSIS in pancreatic β-cells [161]. Similarly, chronic exposure to pro-inflammatory cytokines increased ROS production and NF-κB activation and impaired β-cell function [162]. Studies in liver, adipose and skeletal muscle show similar patterns, where chronic exposure to increased ROS production is associated with NF-κB activation, leading to detrimental changes in gene expression, inflammation, fibrosis and tissue degeneration [163–165].

There is also a direct relationship of NF-κB with the Nrf2/Keap1 pathway, which regulates redox homeostasis. Activation of Nrf2 in both pancreatic β-cells and the liver increases the expression of numerous antioxidants, leading to lowered IKKβ activation and decreased NF-κB signalling [166,167]. In other cell types, Keap1 also induces NF-κB degradation by interacting with IKKβ, which subsequently regulates NF-κB activity [168,169]. Mutations in KEAP-1 are associated with increased TNFα activity, a key activator of NF-κB activity, in lung cancer cells, where mutant forms of Keap-1 interact more strongly with the TNFα receptor [170], leading to increased TNFα-mediated signalling and increased NF-κB activity. Meanwhile, other studies suggest that the interaction between NF-κB and Keap-1 decreases NF-κB expression [171].

5.5. Impact of Glycolytic Enzyme Activity on NF-κB Activity

The impact of glycolytic enzyme activity on NF-κB, and vice versa, manifests in different ways. Based on research on osteoblasts treated with porphyromonas gingivalis lipopolysaccharide, enhanced glycolysis, via hexokinase 2, increases the expression of NF-κB ligand receptor activator [172]. Also, elevated expression of GAPDH promoted NF-κB activity [173], whilst enolase also activated the NF-κB pathway, causing cell proliferation and invasion, a potential target in breast cancer treatment [174]. Phosphoglycerate mutase also modulates macrophage activation and is associated with the positive regulation of nuclear factor-kappa light chain enhancer of activated p50 [175]. Evidence linking glycolytic enzyme activity with NF-κB in tissues associated with T2D pathogenesis is limited. However, changes in PFKFB3 expression in the liver, adipose tissue and kidney are associated with activation of NF-κB [176–178]. As the role of NF-κB in cell metabolism becomes more apparent, the importance of this cell signalling pathway in

the pathogenesis of T2D becomes a more prominent research question. Further work is required to explore the impact of NF-κB on biochemical parameters and phenomena in both physiological and pathological conditions, such as the expression of glycolytic genes of hexokinase 2 and other enzymes of glycolysis, energy metabolism, autophagy, cytokines and hormonal mediators of blood glucose homeostasis like insulin.

6. Redox-Targeted Strategies for the Treatment of T2D

Owing to the central role of redox imbalance in the pathogenesis of T2D and the development of its complications, it was assumed that enhancement of antioxidant activity would improve glycaemic control and reduce the development of complications in diabetes. However, despite apparent success in cell-based and rodent model systems, clinical studies have failed to show any meaningful benefit of antioxidant supplements [179]. Large, randomised control trials of oral vitamin C and E supplements were unable to prevent the onset of T2D, and similarly, had minimal effect on glycaemic control or on the development of diabetic complications [179–182]. Similar trials utilising the antioxidant N-acetylcysteine (NAC) also had minimal effect on glycaemic control, although these studies did report some protection from the development of diabetic complications [183]. This disconnect has shifted the field away from non-specific ROS scavenging toward more pathway-focused redox modulation [179].

Selectively targeting ROS production by targeting specific ROS production pathways has gained traction in recent years for the treatment of diabetic complications, with selective NOX inhibition showing protection in preclinical animal models of nephropathy and vascular dysfunction [184,185]. However, early clinical evaluation of NOX inhibitors in metabolic disease has so far not yielded clear, practice-changing benefits [186]. A key issue is likely to be redox redundancy: mitochondrial ROS, xanthine oxidase, and advanced glycation pathways can compensate when one source is blocked. In addition, NOX-derived ROS participates in physiological signalling, including GSIS and insulin action, making chronic systemic inhibition unfeasible [187]. However, a new generation of selective NOX inhibitors shows higher isoform selectivity with good safety profiles and demonstrates strong anti-inflammatory effects in some cell systems [186]. Clinical trials exploring such inhibitors are ongoing for diabetic kidney disease and vascular complications.

Targeting NF κB itself is a potential therapeutic approach for the treatment of type 2 diabetes and its complications, particularly given its critical role in inflammation, nutrient stress and insulin signalling [161–165]. However, NF-κB signalling is multi-faceted, with key roles in immunity, tissue repair and stress response. Therefore, system inhibition is a difficult balance to achieve. Inhibition of IKKβ activity using salsalate to dampen NF-κB activation improved glycaemia in individuals with T2D but also increased circulating lipids and induced mild hypoglycaemia [188]. Similarly, targeting upstream IL-1β signalling via antibody therapy had no impact on glycaemia in T2D [189].

An alternative strategy is to modulate metabolism upstream of ROS generation rather than scavenge ROS directly. Metformin, for example, acts to inhibit complex I in the mitochondrial ETC in the liver, leading to activation of AMPK, which enhances insulin sensitivity and decreases hepatic glucose production [190]. As a byproduct of complex I inhibition, metformin exerts context-dependent antioxidant effects by limiting mitochondrial ROS and improving the redox balance [190]. However, it should be noted that its clinical success is primarily attributed to metabolic rather than antioxidant actions. Other approaches to modulate metabolism include the utilisation of dietary compounds such as polyphenols (e.g., resveratrol and curcumin) that act as cellular antioxidants, notably by scavenging ROS and increasing antioxidant enzyme expression via Nrf2 activation [191].

Clinical studies report a decrease in biomarkers of oxidative stress but only modest and heterogeneous effects on glycaemic control in T2D [192,193].

Although each of the approaches described above have shown mechanistic promise for treating T2D and its complications, their clinical impact has been largely limited by safety concerns, metabolic compensation and lack of tissue specificity. Targeting the redox balance remains an attractive approach, but it is essential that future therapies are designed to modulate redox signalling in a targeted and context-dependent manner without disrupting essential physiological functions.

7. Discussion

Molecular studies exploring the underlying pathogenesis of T2D have identified important roles for ROS and NF-κB signalling in this process, although these are often context-specific and also sometimes contradictory. Under physiological conditions, ROS function as a metabolic signal, modulating pathways such as glycolysis and contributing to normal insulin secretion and insulin sensitivity [12,13]. However, these effects occur within a narrow concentration range, which is highly dependent on the type of cells and their redox balance. In some tissues, even modest deviations can shift ROS from signalling molecules to drivers of cellular stress, a situation evident in many tissue types in T2D [14]. Currently, the threshold at which ROS shifts from critical signalling components to mediators of cellular injury remains poorly defined. This ambiguity complicates attempts to distinguish adaptive redox signalling from early pathological stress.

The relationship between ROS and NF-κB is similarly nuanced. ROS can either activate or suppress NF-κB depending on the cellular redox state, the specific ROS involved, and the tissue type [116–118,130–145]. Although NF-κB has been implicated in metabolic reprogramming [3], the mechanistic basis for this remains incompletely understood, and many proposed links rely on correlative rather than causal evidence. The extent to which NF-κB directly regulates glycolytic enzymes versus exerting indirect effects through inflammatory or stress response pathways remains an active area of debate.

In T2D, chronic hyperglycaemia disrupts the delicate balance between physiological and pathological redox signalling [14]. Excess glucose alters glycolytic flux, impairs β-cell function, reduces insulin secretion, promotes insulin resistance and drives the development of numerous diabetic complications [14–20]. The functional status of NF-κB and ROS shifts from a physiological state to a pathological state, with T2D being associated with increased ROS production, as well as upregulation of NF-κB activity, both contributing to inflammation, mitochondrial dysfunction, and impaired metabolic flexibility [107]. Yet it remains uncertain whether these changes are primary drivers of disease progression or secondary responses to metabolic stress.

The interplay between ROS and NF-κB in dysregulated glucose metabolism is dynamic and bidirectional (Figure 2). Each influences the other, but both also affect multiple nodes within glycolysis and broader metabolic networks. Mapping these interactions highlights the degree to which redox signalling and inflammatory transcriptional control are intertwined but also exposes significant gaps in our understanding. For example, while hyperglycaemia-induced ROS can modulate glycolytic enzymes [78], the extent to which NF-κB directly shapes glycolytic flux remains unresolved. Similarly, although both pathways influence β-cell survival, insulin signalling, mitochondrial electron transport, and ATP production, the causal hierarchy among these processes is still debated [3]. Furthermore, NF-κB-dependent metabolic changes extend beyond classical inflammatory pathways. Some studies suggest that NF-κB can influence lactate production and glycolytic bias, echoing features of the Warburg effect observed in proliferative or stressed cells [113–115]. However, whether a true "Warburg-like" phenotype exists in T2D remains

controversial, and current evidence is insufficient to determine whether these metabolic shifts are adaptive, maladaptive, or merely symptoms of broader cellular stress.

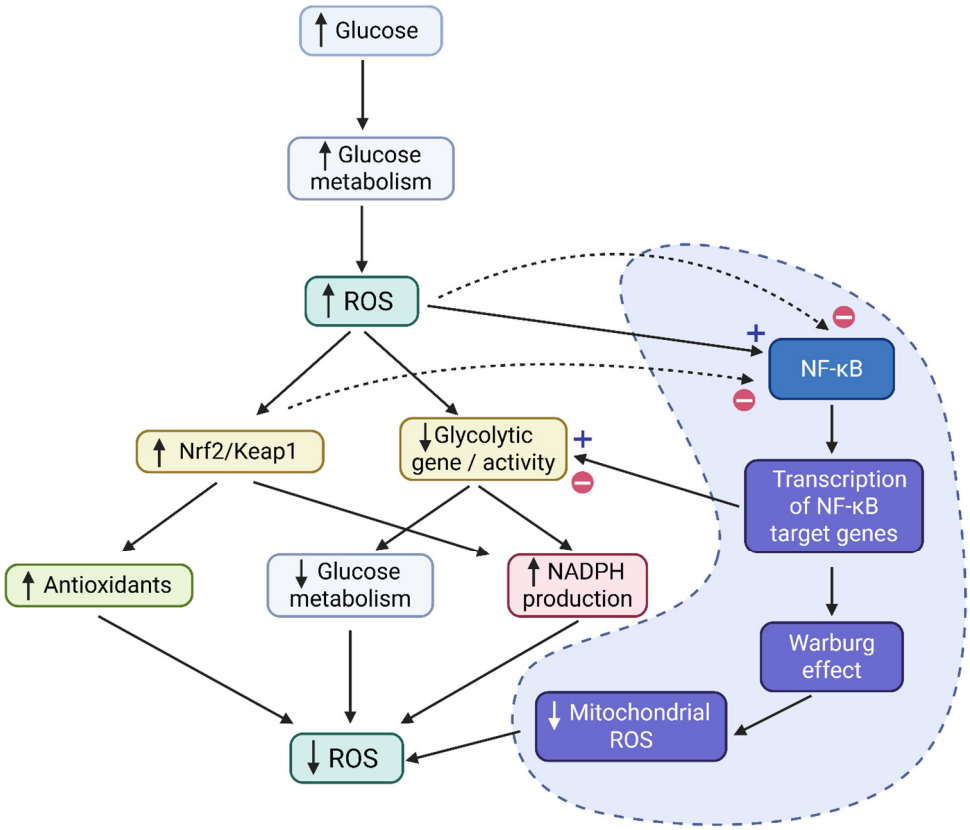

Figure 2. Compensatory downregulation of ROS production in response to increased glucose metabolism: Potential role for NF-κB signalling. Exposure of cells to chronically elevated glucose concentrations lead to an increase in glucose metabolism, which in turn increases ROS production via mechanisms identified in Figure 1. To maintain cellular homeostasis, several mechanisms are upregulated to decrease ROS production: (i) activation of the Nrf2/Keap1 pathway leading to increased transcription of antioxidant enzymes and enzymes involved in the pentose phosphate pathway to increased NADPH production; (ii) decreased expression or inhibition of activity of key enzymes involved in glycolysis, including glucokinase, GAPDH, PFK1 and PK. This leads to decreased glucose metabolism via glycolysis, whilst also increasing flux into the pentose phosphate pathway, which increases production of NADPH. Together, these actions lead to a decrease in ROS production. NF-κB also acts to regulate ROS production. There is evidence that increased ROS production stimulates NF-κB activity, leading to increased transcription of target genes (although it should be noted that increased ROS production has also been shown to inhibit NF-κB activity). One of the actions of increased NF-κB target transcription is the Warburg effect, which preferentially increases anaerobic glycolysis via the conversion of pyruvate to lactate, which limits mitochondrial metabolism of pyruvate, leading to decreased mitochondrial ROS production. In addition, NF-κB has been shown to alter glycolytic enzyme activity to modulate glucose metabolism, although whether this reflects a decrease or increase in flux is dependent of the cell type/cellular conditions. (+) refers to stimulation of the pathway; (−) refers to inhibition of the pathway. Image was created using Biorender.

8. Conclusions

A comprehensive understanding of T2D pathogenesis requires detailed investigation of the interplay between ROS and NF-κB signalling, particularly in the context of glucose metabolism. Growing evidence shows that these pathways interact bidirectionally to influence metabolic function, suggesting they may contribute directly to disease progression.

Further work is needed to define the underlying biochemical mechanisms and to clarify how this crosstalk drives metabolic dysfunction in T2D.

Author Contributions: The review was conceptualized by H.M.; writing—original draft by H.M.; writing—review and editing by C.A. All authors have read and agreed to the published version of the manuscript.

Funding: Work by C.A. funded by a project grant from the European Foundation for the Study of Diabetes/Lilly European Diabetes Research Programme.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AGEs	Advanced G2.
ARE	Antioxidant response element
ATP	Adenosine triphosphate
BAD	BCL2-associated agonist of cell death
BCL2	B-cell lymphoma 2
CARM1	Coactivator-associated arginine methyltransferase 1
CAT	Catalase
DAG	1,2-diacylglycerol
DUOX	Dual oxidase
ETC	Electron transport chain
$FADH_2$	Flavin adenine dinucleotide
$F26P_2$	Fructose 2,6-Bisphosphate
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GCK	Glucokinase
GCKR	Glucokinase regulatory protein
GFAT1	Glutamine fructose-6-phosphate aminotransferase isoform 1
G6PDH	Glucose 6-phosphate dehydrogenase
G3P	Glyceraldehyde 3-phosphate
GSH	Glutathione
GSIS	Glucose-stimulated insulin secretion
GPx	Glutathione peroxidases
Grx	Glutaredoxin
H_2O_2	Hydrogen peroxide
HIF-1α	Hypoxia-inducible factor 1-alpha
HK	Hexokinase
IDH1	Isocitrate dehydrogenase 1
IκB	Inhibitor of κB
IKK	Inhibitor of κB kinase
IKKβ	Inhibitory κB kinase beta
Keap1	Kelch-like ECH-associated protein 1
O_2^-	Superoxide
OH^-	Hydroxyl radicals
O_2H	Hydroperoxyl
MBPs	Metal-binding proteins
ME1	Malic enzyme
NADH	Nicotinamide adenine dinucleotide

NADPH	Nicotinamide adenine dinucleotide phosphate
NIK	NF-kappa-B-inducing kinase
Nrf2	Nuclear factor erythroid 2-related factor 2
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOX	NADPH oxidase
PGD	6-phosphogluconate dehydrogenase
PFK1	Phosphofructokinase-1
PFKFB	6-Phosphofructo-2-kinase/fructose 2,6-bisphosphatase
PI3K	Phosphoinositide 3-kinase
PKC	Protein kinase C
PK	Pyruvate kinase
PTEN	Phosphatase and TENsin homolog
REL	Reticuloendotheliosis protein
RAGE	Receptor for advanced glycation end-products
ROS	Reactive oxygen species
SOD	Superoxide dismutase
T2D	Type 2 diabetes
TCA	Tricarboxylic acid
TIGAR	TP53-induced glycolysis and apoptosis regulator
TNFα	Tumour necrosis factor-alpha
Trx	Thioredoxin
UA	Uric acid
UDP-GlcNAc	Uridine diphosphate-N-acetylglucosamine

References

1. Das, A.; Roychoudhury, S. Reactive Oxygen Species in the Reproductive System: Sources and Physiological Roles. *Adv. Exp. Med. Biol.* **2022**, *1358*, 9–40. [CrossRef]
2. Yang, B.; Chen, Y.; Shi, J. Reactive Oxygen Species (ROS)-Based Nanomedicine. *Chem. Rev.* **2019**, *119*, 4881–4985. [CrossRef]
3. Forrester, S.J.; Kikuchi, D.S.; Hernandes, M.S.; Xu, Q.; Griendling, K.K. Reactive Oxygen Species in Metabolic and Inflammatory Signaling. *Circ. Res.* **2018**, *122*, 877–902. [CrossRef]
4. Brieger, K.; Schiavone, S.; Miller, F.J., Jr.; Krause, K.H. Reactive oxygen species: From health to disease. *Swiss Med. Wkly.* **2012**, *142*, w13659. [CrossRef] [PubMed]
5. Lam, P.L.; Wong, R.S.; Lam, K.H.; Hung, L.K.; Wong, M.M.; Yung, L.H.; Ho, Y.W.; Wong, W.Y.; Hau, D.K.; Gambari, R.; et al. The role of reactive oxygen species in the biological activity of antimicrobial agents: An updated mini review. *Chem. Biol. Interact.* **2020**, *320*, 109023. [CrossRef]
6. Mittler, R.; Zandalinas, S.I.; Fichman, Y.; Van Breusegem, F. Reactive oxygen species signalling in plant stress responses. *Nat. Rev. Mol. Cell Biol.* **2022**, *23*, 663–679. [CrossRef]
7. Redza-Dutordoir, M.; Averill-Bates, D.A. Activation of apoptosis signalling pathways by reactive oxygen species. *Biochim. Biophys. Acta (BBA)—Mol. Cell Res.* **2016**, *1863*, 2977–2992. [CrossRef]
8. Lennicke, C.; Cochemé, H.M. Redox metabolism: ROS as specific molecular regulators of cell signaling and function. *Mol. Cell* **2021**, *81*, 3691–3707. [CrossRef]
9. Corkey, B.E.; Deeney, J.T. The Redox Communication Network as a Regulator of Metabolism. *Front. Physiol.* **2020**, *11*, 567796. [CrossRef] [PubMed]
10. Lytrivi, M.; Castell, A.L.; Poitout, V.; Cnop, M. Recent Insights Into Mechanisms of β-Cell Lipo- and Glucolipotoxicity in Type 2 Diabetes. *J. Mol. Biol.* **2020**, *432*, 1514–1534. [CrossRef]
11. Caturano, A.; D'Angelo, M.; Mormone, A.; Russo, V.; Mollica, M.P.; Salvatore, T.; Galiero, R.; Rinaldi, L.; Vetrano, E.; Marfella, R.; et al. Oxidative Stress in Type 2 Diabetes: Impacts from Pathogenesis to Lifestyle Modifications. *Curr. Issues Mol. Biol.* **2023**, *45*, 6651–6666. [CrossRef]
12. Leloup, C.; Tourrel-Cuzin, C.; Magnan, C.; Karaca, M.; Castel, J.; Carneiro, L.; Colombani, A.L.; Ktorza, A.; Casteilla, L.; Pénicaud, L. Mitochondrial reactive oxygen species are obligatory signals for glucose-induced insulin secretion. *Diabetes* **2009**, *58*, 673–681. [CrossRef]
13. Loh, K.; Deng, H.; Fukushima, A.; Cai, X.; Boivin, B.; Galic, S.; Bruce, C.; Shields, B.J.; Skiba, B.; Ooms, L.M.; et al. Reactive oxygen species enhance insulin sensitivity. *Cell Metab.* **2009**, *10*, 260–272. [CrossRef] [PubMed]

14. Abdal Dayem, A.; Hossain, M.K.; Lee, S.B.; Kim, K.; Saha, S.K.; Yang, G.M.; Choi, H.Y.; Cho, S.G. The Role of Reactive Oxygen Species (ROS) in the Biological Activities of Metallic Nanoparticles. *Int. J. Mol. Sci.* **2017**, *18*, 120. [CrossRef] [PubMed]
15. Leenders, F.; Groen, N.; de Graaf, N.; Engelse, M.A.; Rabelink, T.J.; de Koning, E.J.P.; Carlotti, F. Oxidative Stress Leads to β-Cell Dysfunction Through Loss of β-Cell Identity. *Front. Immunol.* **2021**, *12*, 690379. [CrossRef]
16. Wang, X.W.; Tian, R.M.; Yang, Y.Q.; Lu, Z.Y.; Han, X.D.; Liu, X.S.; Mao, W.; Xu, P.; Xu, H.T.; Liu, B. Triptriolide antagonizes triptolide-induced nephrocyte apoptosis via inhibiting oxidative stress in vitro and in vivo. *Biomed. Pharmacother.* **2019**, *118*, 109232. [CrossRef]
17. Wu, M.Y.; Yiang, G.T.; Lai, T.T.; Li, C.J. The Oxidative Stress and Mitochondrial Dysfunction during the Pathogenesis of Diabetic Retinopathy. *Oxidative Med. Cell. Longev.* **2018**, *2018*, 3420187. [CrossRef]
18. Mandel, N.; Büttner, M.; Poschet, G.; Kuner, R.; Agarwal, N. SUMOylation Modulates Reactive Oxygen Species (ROS) Levels and Acts as a Protective Mechanism in the Type 2 Model of Diabetic Peripheral Neuropathy. *Cells* **2023**, *12*, 2511. [CrossRef]
19. Li, T.; Wang, N.; Yi, D.; Xiao, Y.; Li, X.; Shao, B.; Wu, Z.; Bai, J.; Shi, X.; Wu, C.; et al. ROS-mediated ferroptosis and pyroptosis in cardiomyocytes: An update. *Life Sci.* **2025**, *370*, 123565. [CrossRef] [PubMed]
20. Cheung, E.C.; Vousden, K.H. The role of ROS in tumour development and progression. *Nat. Rev. Cancer* **2022**, *22*, 280–297. [CrossRef]
21. Pi, J.; Zhang, Q.; Fu, J.; Woods, C.G.; Hou, Y.; Corkey, B.E.; Collins, S.; Andersen, M.E. ROS signaling, oxidative stress and Nrf2 in pancreatic beta-cell function. *Toxicol. Appl. Pharmacol.* **2010**, *244*, 77–83. [CrossRef]
22. Dinić, S.; Arambašić Jovanović, J.; Uskoković, A.; Mihailović, M.; Grdović, N.; Tolić, A.; Rajić, J.; Đorđević, M.; Vidaković, M. Oxidative stress-mediated beta cell death and dysfunction as a target for diabetes management. *Front. Endocrinol.* **2022**, *13*, 1006376. [CrossRef]
23. Miller, I.P.; Pavlović, I.; Poljšak, B.; Šuput, D.; Milisav, I. Beneficial Role of ROS in Cell Survival: Moderate Increases in H_2O_2 Production Induced by Hepatocyte Isolation Mediate Stress Adaptation and Enhanced Survival. *Antioxidants* **2019**, *8*, 434. [CrossRef]
24. Liu, J.; Li, D.; Zhang, T.; Tong, Q.; Ye, R.D.; Lin, L. SIRT3 protects hepatocytes from oxidative injury by enhancing ROS scavenging and mitochondrial integrity. *Cell Death Dis.* **2017**, *8*, e3158. [CrossRef]
25. De Villiers, D.; Potgieter, M.; Ambele, M.A.; Adam, L.; Durandt, C.; Pepper, M.S. The Role of Reactive Oxygen Species in Adipogenic Differentiation. *Stem Cells Biol. Eng.* **2018**, *1083*, 125–144. [CrossRef]
26. Masschelin, P.M.; Cox, A.R.; Chernis, N.; Hartig, S.M. The Impact of Oxidative Stress on Adipose Tissue Energy Balance. *Front. Physiol.* **2020**, *10*, 1638. [CrossRef]
27. Powers, S.K.; Ji, L.L.; Kavazis, A.N.; Jackson, M.J. Reactive oxygen species: Impact on skeletal muscle. *Compr. Physiol.* **2011**, *1*, 941–969. [CrossRef]
28. Steinbacher, P.; Eckl, P. Impact of oxidative stress on exercising skeletal muscle. *Biomolecules* **2015**, *5*, 356–377. [CrossRef]
29. Massaad, C.A.; Klann, E. Reactive oxygen species in the regulation of synaptic plasticity and memory. *Antioxid. Redox Signal.* **2011**, *14*, 2013–2054. [CrossRef] [PubMed]
30. Rohowetz, L.J.; Kraus, J.G.; Koulen, P. Reactive Oxygen Species-Mediated Damage of Retinal Neurons: Drug Development Targets for Therapies of Chronic Neurodegeneration of the Retina. *Int. J. Mol. Sci.* **2018**, *19*, 3362. [CrossRef] [PubMed]
31. Wang, J.; Li, M.; Geng, Z.; Khattak, S.; Ji, X.; Wu, D.; Dang, Y. Role of Oxidative Stress in Retinal Disease and the Early Intervention Strategies: A Review. *Oxidative Med. Cell. Longev.* **2022**, *2022*, 7836828. [CrossRef]
32. Chen, Q.; Wang, Q.; Zhu, J.; Xiao, Q.; Zhang, L. Reactive oxygen species: Key regulators in vascular health and diseases. *Br. J. Pharmacol.* **2018**, *175*, 1279–1292. [CrossRef]
33. Irazabal, M.V.; Torres, V.E. Reactive Oxygen Species and Redox Signaling in Chronic Kidney Disease. *Cells* **2020**, *9*, 1342. [CrossRef]
34. D'Oria, R.; Schipani, R.; Leonardini, A.; Natalicchio, A.; Perrini, S.; Cignarelli, A.; Laviola, L.; Giorgino, F. The Role of Oxidative Stress in Cardiac Disease: From Physiological Response to Injury Factor. *Oxidative Med. Cell. Longev.* **2020**, *2020*, 5732956. [CrossRef] [PubMed]
35. Münzel, T.; Camici, G.G.; Maack, C.; Bonetti, N.R.; Fuster, V.; Kovacic, J.C. Impact of Oxidative Stress on the Heart and Vasculature: Part 2 of a 3-Part Series. *J. Am. Coll. Cardiol.* **2017**, *70*, 212–229. [CrossRef] [PubMed]
36. Chen, S.; Zou, Y.; Song, C.; Cao, K.; Cai, K.; Wu, Y.; Zhang, Z.; Geng, D.; Sun, W.; Ouyang, N.; et al. The role of glycolytic metabolic pathways in cardiovascular disease and potential therapeutic approaches. *Basic Res. Cardiol.* **2023**, *118*, 48. [CrossRef]
37. Wu, C.; Khan, S.A.; Lange, A.J. Regulation of glycolysis-role of insulin. *Exp. Gerontol.* **2005**, *40*, 894–899. [CrossRef]
38. Zhao, R.Z.; Jiang, S.; Zhang, L.; Yu, Z.B. Mitochondrial electron transport chain, ROS generation and uncoupling (Review). *Int. J. Mol. Med.* **2019**, *44*, 3–15. [CrossRef]
39. Maldonado, E.N. VDAC-Tubulin, an Anti-Warburg Pro-Oxidant Switch. *Front. Oncol.* **2017**, *7*, 4. [CrossRef]
40. Haapanen, O.; Reidelbach, M.; Sharma, V. Coupling of quinone dynamics to proton pumping in respiratory complex I. *Biochim. Biophys. Acta Bioenerg.* **2020**, *1861*, 148287. [CrossRef]

41. Wikström, M.; Djurabekova, A.; Sharma, V. On the role of ubiquinone in the proton translocation mechanism of respiratory complex I. *FEBS Lett.* **2023**, *597*, 224–236. [CrossRef]
42. Ishii, T.; Miyazawa, M.; Onouchi, H.; Yasuda, K.; Hartman, P.S.; Ishii, N. Model animals for the study of oxidative stress from complex II. *Biochim. Biophys. Acta* **2013**, *1827*, 588–597. [CrossRef] [PubMed]
43. Bedi, M.; Ray, M.; Ghosh, A. Active mitochondrial respiration in cancer: A target for the drug. *Mol. Cell Biochem.* **2022**, *477*, 345–361. [CrossRef]
44. Heo, J.M.; Rutter, J. Ubiquitin-dependent mitochondrial protein degradation. *Int. J. Biochem. Cell Biol.* **2011**, *43*, 1422–1426. [CrossRef] [PubMed]
45. Paneque, A.; Fortus, H.; Zheng, J.; Werlen, G.; Jacinto, E. The Hexosamine Biosynthesis Pathway: Regulation and Function. *Genes* **2023**, *14*, 933. [CrossRef] [PubMed]
46. Wojcik, M.; Krawczyk, M.; Wojcik, P.; Cypryk, K.; Wozniak, L.A. Molecular Mechanisms Underlying Curcumin-Mediated Therapeutic Effects in Type 2 Diabetes and Cancer. *Oxidative Med. Cell. Longev.* **2018**, *2018*, 9698258. [CrossRef]
47. Kaneto, H.; Xu, G.; Song, K.H.; Suzuma, K.; Bonner-Weir, S.; Sharma, A.; Weir, G.C. Activation of the hexosamine pathway leads to deterioration of pancreatic beta-cell function through the induction of oxidative stress. *J. Biol. Chem.* **2001**, *276*, 31099–31104. [CrossRef] [PubMed]
48. Fernández-Rojas, B.; Gómez-Sierra, T.; Medina-Campos, O.N.; Hernández-Juárez, J.; Hernández-Cruz, P.A.; Gallegos-Velasco, I.B.; Pérez-Cervera, Y.; Pedraza-Chaverri, J. Antioxidant activity of glucosamine and its effects on ROS production, Nrf2, and O-GlcNAc expression in HMEC-1 cells. *Curr. Res. Toxicol.* **2023**, *5*, 100128. [CrossRef]
49. Martin-Liberal, J.; Cameron, A.J.; Claus, J.; Judson, I.R.; Parker, P.J.; Linch, M. Targeting protein kinase C in sarcoma. *Biochim. Biophys. Acta* **2014**, *1846*, 547–559. [CrossRef]
50. Giorgio, M.; Migliaccio, E.; Orsini, F.; Paolucci, D.; Moroni, M.; Contursi, C.; Pelliccia, G.; Luzi, L.; Minucci, S.; Marcaccio, M.; et al. Electron transfer between cytochrome c and p66Shc generates reactive oxygen species that trigger mitochondrial apoptosis. *Cell* **2005**, *122*, 221–233. [CrossRef]
51. Mao, S.; Huang, S. The signaling pathway of NADPH oxidase and its role in glomerular diseases. *J. Recept. Signal Transduct. Res.* **2014**, *34*, 6–11. [CrossRef] [PubMed]
52. Bedard, K.; Krause, K.H. The NOX family of ROS-generating NADPH oxidases: Physiology and pathophysiology. *Physiol. Rev.* **2007**, *87*, 245–313. [CrossRef]
53. Meza, C.A.; La Favor, J.D.; Kim, D.H.; Hickner, R.C. Endothelial Dysfunction: Is There a Hyperglycemia-Induced Imbalance of NOX and NOS? *Int. J. Mol. Sci.* **2019**, *20*, 3775. [CrossRef]
54. Laddha, A.P.; Kulkarni, Y.A. NADPH oxidase: A membrane-bound enzyme and its inhibitors in diabetic complications. *Eur. J. Pharmacol.* **2020**, *881*, 173206. [CrossRef]
55. Dunlop, M. Aldose reductase and the role of the polyol pathway in diabetic nephropathy. *Kidney Int.* **2000**, *77*, S3–S12. [CrossRef] [PubMed]
56. Lyons, T.J.; Jenkins, A.J. Glycation, oxidation, and lipoxidation in the development of the complications of diabetes: A carbonyl stress hypothesis. *Diabetes Rev.* **1997**, *5*, 365–391.
57. Wolff, S.P.; Dean, R.T. Glucose autoxidation and protein modification. The potential role of 'autoxidative glycosylation' in diabetes. *Biochem. J.* **1987**, *245*, 243–250. [CrossRef]
58. Yan, L.J. Redox imbalance stress in diabetes mellitus: Role of the polyol pathway. *Anim. Models Exp. Med.* **2018**, *1*, 7–13. [CrossRef]
59. González, R.G.; Barnett, P.; Aguayo, J.; Cheng, H.M.; Chylack, L.T., Jr. Direct measurement of polyol pathway activity in the ocular lens. *Diabetes* **1984**, *33*, 196–199. [CrossRef]
60. Garg, S.S.; Gupta, J. Polyol pathway and redox balance in diabetes. *Pharmacol. Res.* **2022**, *182*, 106326. [CrossRef] [PubMed]
61. Perrone, A.; Giovino, A.; Benny, J.; Martinelli, F. Advanced Glycation End Products (AGEs): Biochemistry, Signaling, Analytical Methods, and Epigenetic Effects. *Oxidative Med. Cell. Longev.* **2020**, *2020*, 3818196. [CrossRef] [PubMed]
62. Khalid, M.; Petroianu, G.; Adem, A. Advanced Glycation End Products and Diabetes Mellitus: Mechanisms and Perspectives. *Biomolecules* **2022**, *12*, 542. [CrossRef] [PubMed]
63. Chen, Y.; Meng, Z.; Li, Y.; Liu, S.; Hu, P.; Luo, E. Advanced glycation end products and reactive oxygen species: Uncovering the potential role of ferroptosis in diabetic complications. *Mol. Med.* **2024**, *30*, 141. [CrossRef]
64. Fisher-Wellman, K.H.; Gilliam, L.A.A.; Lin, C.T.; Cathey, B.L.; Lark, D.S.; Darrell Neufer, P. Mitochondrial glutathione depletion reveals a novel role for the pyruvate dehydrogenase complex as a key H_2O_2-emitting source under conditions of nutrient overload. *Free Radic. Biol. Med.* **2013**, *65*, 1201–1208. [CrossRef]
65. Gardner, P.R. Aconitase: Sensitive target and measure of superoxide. *Methods Enzymol.* **2002**, *349*, 9–23. [CrossRef] [PubMed]
66. Quinlan, C.L.; Goncalves, R.L.; Hey-Mogensen, M.; Yadava, N.; Bunik, V.I.; Brand, M.D. The 2-oxoacid dehydrogenase complexes in mitochondria can produce superoxide/hydrogen peroxide at much higher rates than complex I. *J. Biol. Chem.* **2014**, *289*, 8312–8325. [CrossRef] [PubMed]

67. Orr, A.L.; Quinlan, C.L.; Perevoshchikova, I.V.; Brand, M.D. A refined analysis of superoxide production by mitochondrial sn-glycerol 3-phosphate dehydrogenase. *J. Biol. Chem.* **2012**, *287*, 42921–42935. [CrossRef]
68. Vilas-Boas, E.A.; Almeida, D.C.; Roma, L.P.; Ortis, F.; Carpinelli, A.R. Lipotoxicity and β-Cell Failure in Type 2 Diabetes: Oxidative Stress Linked to NADPH Oxidase and ER Stress. *Cells* **2021**, *10*, 3328. [CrossRef]
69. Murphy, M.P. How mitochondria produce reactive oxygen species. *Biochem. J.* **2009**, *417*, 1–13. [CrossRef]
70. Le Gal, K.; Schmidt, E.E.; Sayin, V.I. Cellular Redox Homeostasis. *Antioxidants* **2021**, *10*, 1377. [CrossRef]
71. Ursini, F.; Maiorino, M.; Forman, H.J. Redox homeostasis: The Golden Mean of healthy living. *Redox Biol.* **2016**, *8*, 205–215. [CrossRef]
72. Brandes, N.; Schmitt, S.; Jakob, U. Thiol-based redox switches in eukaryotic proteins. *Antioxid. Redox Signal.* **2009**, *11*, 997–1014. [CrossRef] [PubMed]
73. Andreyev, A.Y.; Kushnareva, Y.E.; Starkov, A.A. Mitochondrial metabolism of reactive oxygen species. *Biochemistry* **2005**, *70*, 200–214. [CrossRef] [PubMed]
74. Thomas, J.P.; Maiorino, M.; Ursini, F.; Girotti, A.W. Protective action of phospholipid hydroperoxide glutathione peroxidase against membrane-damaging lipid peroxidation. In situ reduction of phospholipid and cholesterol hydroperoxides. *J. Biol. Chem.* **1990**, *265*, 454–461. [CrossRef]
75. Kanwugu, O.N.; Glukhareva, T.V. Activation of Nrf2 pathway as a protective mechanism against oxidative stress-induced diseases: Potential of astaxanthin. *Arch. Biochem. Biophys.* **2023**, *741*, 109601. [CrossRef] [PubMed]
76. Wang, C.; Li, C.; Peng, H.; Ye, Z.; Zhang, J.; Liu, X.; Lou, T. Activation of the Nrf2-ARE pathway attenuates hyperglycemia-mediated injuries in mouse podocytes. *Cell Physiol. Biochem.* **2014**, *34*, 891–902. [CrossRef]
77. Jiménez-Osorio, A.S.; González-Reyes, S.; Pedraza-Chaverri, J. Natural Nrf2 activators in diabetes. *Clin. Chim. Acta* **2015**, *448*, 182–192. [CrossRef]
78. Mullarky, E.; Cantley, L.C. Diverting Glycolysis to Combat Oxidative Stress. In *Innovative Medicine: Basic Research and Development*; Nakao, K., Minato, N., Uemoto, S., Eds.; Springer: Tokyo, Japan, 2015. [CrossRef]
79. Korga, A.; Ostrowska, M.; Iwan, M.; Herbet, M.; Dudka, J. Inhibition of glycolysis disrupts cellular antioxidant defense and sensitizes HepG2 cells to doxorubicin treatment. *FEBS Open Bio* **2019**, *9*, 959–972. [CrossRef]
80. Vatashchuk, M.V.; Hurza, V.V.; Stefanyshyn, N.; Bayliak, M.M.; Gospodaryov, D.V.; Garaschuk, O.; Lushchak, V.I. Impact of caloric restriction on oxidative stress and key glycolytic enzymes in the cerebral cortex, liver and kidney of old and middle-aged mice. *Neuropharmacology* **2024**, *247*, 109859. [CrossRef]
81. Shen, D.; Deng, Z.; Liu, W.; Zhou, F.; Fang, Y.; Shan, D.; Wang, G.; Qian, K.; Yu, M.; Zhang, Y.; et al. Melatonin inhibits bladder tumorigenesis by suppressing PPARγ/ENO1-mediated glycolysis. *Cell Death Dis.* **2023**, *14*, 246. [CrossRef]
82. Matschinsky, F.M.; Wilson, D.F. The Central Role of Glucokinase in Glucose Homeostasis: A Perspective 50 Years After Demonstrating the Presence of the Enzyme in Islets of Langerhans. *Front. Physiol.* **2019**, *10*, 148. [CrossRef]
83. Agius, L. Hormonal and Metabolite Regulation of Hepatic Glucokinase. *Annu. Rev. Nutr.* **2016**, *36*, 389–415. [CrossRef]
84. Moede, T.; Leibiger, B.; Vaca Sanchez, P.; Daré, E.; Köhler, M.; Muhandiramlage, T.P.; Leibiger, I.B.; Berggren, P.O. Glucokinase intrinsically regulates glucose sensing and glucagon secretion in pancreatic alpha cells. *Sci. Rep.* **2020**, *10*, 20145. [CrossRef] [PubMed]
85. Arden, C.; Petrie, J.L.; Tudhope, S.J.; Al-Oanzi, Z.; Claydon, A.J.; Beynon, R.J.; Towle, H.C.; Agius, L. Elevated glucose represses liver glucokinase and induces its regulatory protein to safeguard hepatic phosphate homeostasis. *Diabetes* **2011**, *60*, 3110–3120. [CrossRef]
86. Kim, W.H.; Lee, J.W.; Suh, Y.H.; Hong, S.H.; Choi, J.S.; Lim, J.H.; Song, J.H.; Gao, B.; Jung, M.H. Exposure to chronic high glucose induces beta-cell apoptosis through decreased interaction of glucokinase with mitochondria: Downregulation of glucokinase in pancreatic beta-cells. *Diabetes* **2005**, *54*, 2602–2611. [CrossRef] [PubMed]
87. Baltrusch, S.; Lenzen, S.; Okar, D.A.; Lange, A.J.; Tiedge, M. Characterization of glucokinase-binding protein epitopes by a phage-displayed peptide library. Identification of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase as a novel interaction partner. *J. Biol. Chem.* **2001**, *276*, 43915–43923. [CrossRef]
88. Cullen, K.S.; Al-Oanzi, Z.H.; O'Harte, F.P.; Agius, L.; Arden, C. Glucagon induces translocation of glucokinase from the cytoplasm to the nucleus of hepatocytes by transfer between 6-phosphofructo 2-kinase/fructose 2,6-bisphosphatase-2 and the glucokinase regulatory protein. *Biochim. Biophys. Acta* **2014**, *1843*, 1123–1134. [CrossRef]
89. Danial, N.N.; Gramm, C.F.; Scorrano, L.; Zhang, C.Y.; Krauss, S.; Ranger, A.M.; Datta, S.R.; Greenberg, M.E.; Licklider, L.J.; Lowell, B.B.; et al. BAD and glucokinase reside in a mitochondrial complex that integrates glycolysis and apoptosis. *Nature* **2003**, *424*, 952–956. [CrossRef]
90. Cullen, K.S.; Matschinsky, F.M.; Agius, L.; Arden, C. Susceptibility of glucokinase-MODY mutants to inactivation by oxidative stress in pancreatic β-cells. *Diabetes* **2011**, *60*, 3175–3185. [CrossRef]
91. El Kadmiri, N.; Slassi, I.; El Moutawakil, B.; Nadifi, S.; Tadevosyan, A.; Hachem, A.; Soukri, A. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and Alzheimer's disease. *Pathol. Biol.* **2014**, *62*, 333–336. [CrossRef]

92. Morigasaki, S.; Shimada, K.; Ikner, A.; Yanagida, M.; Shiozaki, K. Glycolytic enzyme GAPDH promotes peroxide stress signaling through multistep phosphorelay to a MAPK cascade. *Mol. Cell* **2008**, *30*, 108–113. [CrossRef] [PubMed]
93. Talwar, D.; Miller, C.G.; Grossmann, J.; Szyrwiel, L.; Schwecke, T.; Demichev, V.; Mikecin Drazic, A.M.; Mayakonda, A.; Lutsik, P.; Veith, C.; et al. The GAPDH redox switch safeguards reductive capacity and enables survival of stressed tumour cells. *Nat. Metab.* **2023**, *5*, 660–676. [CrossRef] [PubMed]
94. Zhong, X.Y.; Yuan, X.M.; Xu, Y.Y.; Yin, M.; Yan, W.W.; Zou, S.W.; Wei, L.M.; Lu, H.J.; Wang, Y.P.; Lei, Q.Y. CARM1 Methylates GAPDH to Regulate Glucose Metabolism and Is Suppressed in Liver Cancer. *Cell Rep.* **2018**, *24*, 3207–3223. [CrossRef]
95. Jenkins, C.M.; Yang, J.; Sims, H.F.; Gross, R.W. Reversible high affinity inhibition of phosphofructokinase-1 by acyl-CoA: A mechanism integrating glycolytic flux with lipid metabolism. *J. Biol. Chem.* **2011**, *286*, 11937–11950. [CrossRef] [PubMed]
96. Rider, M.H.; Bertrand, L.; Vertommen, D.; Michels, P.A.; Rousseau, G.G.; Hue, L. 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase: Head-to-head with a bifunctional enzyme that controls glycolysis. *Biochem. J.* **2004**, *381*, 561–579. [CrossRef]
97. Robinson, A.J.; Hopkins, G.L.; Rastogi, N.; Hodges, M.; Doyle, M.; Davies, S.; Hole, P.S.; Omidvar, N.; Darley, R.L.; Tonks, A. Reactive Oxygen Species Drive Proliferation in Acute Myeloid Leukemia via the Glycolytic Regulator PFKFB3. *Cancer Res.* **2020**, *80*, 937–949. [CrossRef]
98. Bensaad, K.; Tsuruta, A.; Selak, M.A.; Vidal, M.N.; Nakano, K.; Bartrons, R.; Gottlieb, E.; Vousden, K.H. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell* **2006**, *126*, 107–120. [CrossRef]
99. Yin, L.; Kosugi, M.; Kufe, D. Inhibition of the MUC1-C oncoprotein induces multiple myeloma cell death by down-regulating TIGAR expression and depleting NADPH. *Blood* **2012**, *119*, 810–816. [CrossRef]
100. Israelsen, W.J.; Vander Heiden, M.G. Pyruvate kinase: Function, regulation and role in cancer. *Semin. Cell Dev. Biol.* **2015**, *43*, 43–51. [CrossRef]
101. Irokawa, H.; Numasaki, S.; Kato, S.; Iwai, K.; Inose-Maruyama, A.; Ohdate, T.; Hwang, G.W.; Toyama, T.; Watanabe, T.; Kuge, S. Comprehensive analyses of the cysteine thiol oxidation of PKM2 reveal the effects of multiple oxidation on cellular oxidative stress response. *Biochem. J.* **2021**, *478*, 1453–1470. [CrossRef]
102. Anastasiou, D.; Poulogiannis, G.; Asara, J.M.; Boxer, M.B.; Jiang, J.K.; Shen, M.; Bellinger, G.; Sasaki, A.T.; Locasale, J.W.; Auld, D.S.; et al. Inhibition of pyruvate kinase M2 by reactive oxygen species contributes to cellular antioxidant responses. *Science* **2011**, *334*, 1278–1283. [CrossRef] [PubMed]
103. Anastasiou, D.; Yu, Y.; Israelsen, W.J.; Jiang, J.K.; Boxer, M.B.; Hong, B.S.; Tempel, W.; Dimov, S.; Shen, M.; Jha, A.; et al. Pyruvate kinase M2 activators promote tetramer formation and suppress tumorigenesis. *Nat. Chem. Biol.* **2012**, *8*, 839–847. [CrossRef]
104. Holendová, B.; Šalovská, B.; Benáková, Š.; Plecitá-Hlavatá, L. Beyond glucose: The crucial role of redox signaling in β-cell metabolic adaptation. *Metabolism* **2024**, *161*, 156027. [CrossRef]
105. Lingappan, K. NF-κB in Oxidative Stress. *Curr. Opin. Toxicol.* **2018**, *7*, 81–86. [CrossRef]
106. Pizzino, G.; Irrera, N.; Cucinotta, M.; Pallio, G.; Mannino, F.; Arcoraci, V.; Squadrito, F.; Altavilla, D.; Bitto, A. Oxidative Stress: Harms and Benefits for Human Health. *Oxidative Med. Cell. Longev.* **2017**, *2017*, 8416763. [CrossRef]
107. Guo, Q.; Jin, Y.; Chen, X.; Ye, X.; Shen, X.; Lin, M.; Zeng, C.; Zhou, T.; Zhang, J. NF-κB in biology and targeted therapy: New insights and translational implications. *Signal Transduct. Target. Ther.* **2024**, *9*, 53. [CrossRef]
108. Morgan, M.J.; Liu, Z.G. Crosstalk of reactive oxygen species and NF-κB signaling. *Cell Res.* **2011**, *21*, 103–115. [CrossRef]
109. Zhang, Q.; Lenardo, M.J.; Baltimore, D. 30 Years of NF-κB: A Blossoming of Relevance to Human Pathobiology. *Cell* **2017**, *168*, 37–57. [CrossRef]
110. Matthews, J.R.; Kaszubska, W.; Turcatti, G.; Wells, T.N.; Hay, R.T. Role of cysteine62 in DNA recognition by the P50 subunit of NF-kappa B. *Nucleic Acids Res.* **1993**, *21*, 1727–1734. [CrossRef] [PubMed]
111. Matthews, J.R.; Wakasugi, N.; Virelizier, J.L.; Yodoi, J.; Hay, R.T. Thioredoxin regulates the DNA binding activity of NF-kappa B by reduction of a disulphide bond involving cysteine 62. *Nucleic Acids Res.* **1992**, *20*, 3821–3830. [CrossRef] [PubMed]
112. Oliveira-Marques, V.; Marinho, H.S.; Cyrne, L.; Antunes, F. Role of hydrogen peroxide in NF-kappaB activation: From inducer to modulator. *Antioxid. Redox Signal.* **2009**, *11*, 2223–2243. [CrossRef]
113. Mao, H.; Zhao, X.; Sun, S.C. NF-κB in inflammation and cancer. *Cell Mol. Immunol.* **2025**, *22*, 811–839. [CrossRef] [PubMed]
114. Bai, D.; Ueno, L.; Vogt, P.K. Akt-mediated regulation of NFkappaB and the essentialness of NFkappaB for the oncogenicity of PI3K and Akt. *Int. J. Cancer* **2009**, *125*, 2863–2870. [CrossRef]
115. Xu, J.; Gao, C.; He, Y.; Fang, X.; Sun, D.; Peng, Z.; Xiao, H.; Sun, M.; Zhang, P.; Zhou, T.; et al. NLRC3 expression in macrophage impairs glycolysis and host immune defense by modulating the NF-κB-NFAT5 complex during septic immunosuppression. *Mol. Ther.* **2023**, *31*, 154–173. [CrossRef]
116. Cardozo, A.K.; Heimberg, H.; Heremans, Y.; Leeman, R.; Kutlu, B.; Kruhøffer, M.; Ørntoft, T.; Eizirik, D.L. A comprehensive analysis of cytokine-induced and nuclear factor-kappa B-dependent genes in primary rat pancreatic beta-cells. *J. Biol. Chem.* **2001**, *276*, 48879–48886. [CrossRef]
117. Eizirik, D.L.; Korbutt, G.S.; Hellerström, C. Prolonged exposure of human pancreatic islets to high glucose concentrations in vitro impairs the beta-cell function. *J. Clin. Investig.* **1992**, *90*, 1263–1268. [CrossRef]

118. Allagnat, F.; Fukaya, M.; Nogueira, T.C.; Delaroche, D.; Welsh, N.; Marselli, L.; Marchetti, P.; Haefliger, J.A.; Eizirik, D.L.; Cardozo, A.K. C/EBP homologous protein contributes to cytokine-induced pro-inflammatory responses and apoptosis in β-cells. *Cell Death Differ.* **2012**, *19*, 1836–1846. [CrossRef]
119. Arkan, M.C.; Hevener, A.L.; Greten, F.R.; Maeda, S.; Li, Z.W.; Long, J.M.; Wynshaw-Boris, A.; Poli, G.; Olefsky, J.; Karin, M. IKK-beta links inflammation to obesity-induced insulin resistance. *Nat. Med.* **2005**, *11*, 191–198. [CrossRef]
120. Ke, B.; Zhao, Z.; Ye, X.; Gao, Z.; Manganiello, V.; Wu, B.; Ye, J. Inactivation of NF-κB p65 (RelA) in Liver Improves Insulin Sensitivity and Inhibits cAMP/PKA Pathway. *Diabetes* **2015**, *64*, 3355–3362. [CrossRef] [PubMed]
121. Li, L.; Han, L.; Qu, Z. NF-κB RelA is a cell-intrinsic metabolic checkpoint restricting glycolysis. *Cell Biosci.* **2024**, *14*, 11. [CrossRef]
122. Bakkar, N.; Wang, J.; Ladner, K.J.; Wang, H.; Dahlman, J.M.; Carathers, M.; Acharyya, S.; Rudnicki, M.A.; Hollenbach, A.D.; Guttridge, D.C. IKK/NF-kappaB regulates skeletal myogenesis via a signaling switch to inhibit differentiation and promote mitochondrial biogenesis. *J. Cell Biol.* **2008**, *180*, 787–802. [CrossRef]
123. Londhe, P.; Yu, P.Y.; Ijiri, Y.; Ladner, K.J.; Fenger, J.M.; London, C.; Houghton, P.J.; Guttridge, D.C. Classical NF-κB Metabolically Reprograms Sarcoma Cells Through Regulation of Hexokinase 2. *Front. Oncol.* **2018**, *8*, 104. [CrossRef] [PubMed]
124. Gu, M.; Zhou, X.; Sohn, J.H.; Zhu, L.; Jie, Z.; Yang, J.Y.; Zheng, X.; Xie, X.; Yang, J.; Shi, Y.; et al. NF-κB-inducing kinase maintains T cell metabolic fitness in antitumor immunity. *Nat. Immunol.* **2021**, *22*, 193–204. Erratum in *Nat. Immunol.* **2021**, *22*, 530. https://doi.org/10.1038/s41590-021-00892-7. [CrossRef] [PubMed]
125. Wu, X.; Qian, S.; Zhang, J.; Feng, J.; Luo, K.; Sun, L.; Zhao, L.; Ran, Y.; Sun, L.; Wang, J.; et al. Lipopolysaccharide promotes metastasis via acceleration of glycolysis by the nuclear factor-κB/snail/hexokinase3 signaling axis in colorectal cancer. *Cancer Metab.* **2021**, *9*, 23. [CrossRef]
126. Reid, M.A.; Lowman, X.H.; Pan, M.; Tran, T.Q.; Warmoes, M.O.; Ishak Gabra, M.B.; Yang, Y.; Locasale, J.W.; Kong, M. IKKβ promotes metabolic adaptation to glutamine deprivation via phosphorylation and inhibition of PFKFB3. *Genes Dev.* **2016**, *30*, 1837–1851. [CrossRef]
127. Baker, R.G.; Hayden, M.S.; Ghosh, S. NF-κB, inflammation, and metabolic disease. *Cell Metab.* **2011**, *13*, 11–22. [CrossRef]
128. Yuan, M.; Konstantopoulos, N.; Lee, J.; Hansen, L.; Li, Z.W.; Karin, M.; Shoelson, S.E. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. *Science* **2001**, *293*, 1673–1677. [CrossRef]
129. Donath, M.Y.; Shoelson, S.E. Type 2 diabetes as an inflammatory disease. *Nat. Rev. Immunol.* **2011**, *11*, 98–107. [CrossRef]
130. Plaisance, V.; Rolland, J.F.; Gauthier, B.R.; Berthou, F.; Philippe, J.; Schuit, F.C.; Henquin, J.C.; Van de Casteele, M. Activation of NF-κB protects pancreatic β-cells against oxidative stress–induced apoptosis. *J. Biol. Chem.* **1997**, *272*, 30410–30418.
131. Cai, D.; Yuan, M.; Frantz, D.F.; Melendez, P.A.; Hansen, L.; Lee, J.; Shoelson, S.E. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat. Med.* **2005**, *11*, 183–190. [CrossRef]
132. Cai, D.; Frantz, J.D.; Tawa NEJr Melendez, P.A.; Oh, B.C.; Lidov, H.G.; Hasselgren, P.O.; Frontera, W.R.; Lee, J.; Glass, D.J.; Shoelson, S.E. IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. *Cell* **2004**, *119*, 285–298. [CrossRef] [PubMed]
133. De Alvaro, C.; Teruel, T.; Hernandez, R.; Lorenzo, M. Tumor necrosis factor alpha produces insulin resistance in skeletal muscle by activation of inhibitor kappaB kinase in a p38 MAPK-dependent manner. *J. Biol. Chem.* **2004**, *279*, 17070–17078. [CrossRef]
134. Suganami, T.; Nishida, J.; Ogawa, Y. A paracrine loop between adipocytes and macrophages aggravates inflammatory changes: Role of free fatty acids and tumor necrosis factor-α. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 2062–2068. [CrossRef]
135. Collins, T.; Read, M.A.; Neish, A.S.; Whitley, M.Z.; Thanos, D.; Maniatis, T. Transcriptional regulation of endothelial cell adhesion molecules: NF-κB and cytokine-induced expression of E-selectin, ICAM-1, and VCAM-1. *FASEB J.* **1995**, *9*, 899–909. [CrossRef]
136. Schiekofer, S.; Andrassy, M.; Chen, J.; Rudofsky, G.; Schneider, J.; Wendt, T.; Stefan, N.; Humpert, P.; Fritsche, A.; Stumvoll, M.; et al. Acute hyperglycemia causes intracellular formation of CML and activation of ras, p42/44 MAPK, and nuclear factor kappaB in PBMCs. *Diabetes* **2003**, *52*, 621–633. [CrossRef]
137. Schmidt, A.M.; Yan, S.D.; Wautier, J.L.; Stern, D. Activation of receptor for advanced glycation end products: A mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. *Circ. Res.* **1999**, *84*, 489–497. [CrossRef]
138. Sanz, A.B.; Sanchez-Niño, M.D.; Ramos, A.M.; Moreno, J.A.; Santamaria, B.; Ruiz-Ortega, M.; Egido, J.; Ortiz, A. NF-kappaB in renal inflammation. *J. Am. Soc. Nephrol.* **2010**, *21*, 1254–1262. [CrossRef]
139. Mezzano, S.; Aros, C.; Droguett, A.; Burgos, M.E.; Ardiles, L.; Flores, C.; Schneider, H.; Ruiz-Ortega, M.; Egido, J. NF-kappaB activation and overexpression of regulated genes in human diabetic nephropathy. *Nephrol. Dial. Transplant.* **2004**, *19*, 2505–2512. [CrossRef] [PubMed]
140. Li, Q.; Van Antwerp, D.; Mercurio, F.; Lee, K.F.; Verma, I.M. Severe heart failure in mice lacking the IκB kinase 2 gene. *Science* **1999**, *284*, 321–325. [CrossRef]
141. Frati, G.; Schirone, L.; Chimenti, I.; Yee, D.; Biondi-Zoccai, G.; Volpe, M.; Sciarretta, S. An overview of the inflammatory signalling mechanisms in the myocardium underlying the development of diabetic cardiomyopathy. *Cardiovasc. Res.* **2017**, *113*, 378–388. [CrossRef]
142. Rattner, A.; Nathans, J. Macrophage activation and acute inflammation in the retina following photoreceptor cell death. *J. Neurosci.* **2005**, *25*, 3663–3673.

143. Joussen, A.M.; Poulaki, V.; Le, M.L.; Koizumi, K.; Esser, C.; Janicki, H.; Schraermeyer, U.; Kociok, N.; Fauser, S.; Kirchhof, B.; et al. A central role for inflammation in the pathogenesis of diabetic retinopathy. *FASEB J.* **2004**, *18*, 1450–1452. [CrossRef] [PubMed]
144. Meffert, M.K.; Chang, J.M.; Wiltgen, B.J.; Fanselow, M.S.; Baltimore, D. NF-kappa B functions in synaptic signaling and behavior. *Nat. Neurosci.* **2003**, *6*, 1072–1078. Erratum in *Nat. Neurosci.* **2003**, *6*, 1329. [CrossRef]
145. Zhang, X.; Zhang, G.; Zhang, H.; Karin, M.; Bai, H.; Cai, D. Hypothalamic IKKβ/NF-κB and ER stress link overnutrition to energy imbalance and obesity. *Cell* **2008**, *135*, 61–73. [CrossRef]
146. Li, X.; Wu, Y.; Song, Y.; Ding, N.; Lu, M.; Jia, L.; Zhao, Y.; Liu, M.; Chen, Z. Activation of NF-κB-Inducing Kinase in Islet β Cells Causes β Cell Failure and Diabetes. *Mol. Ther.* **2020**, *28*, 2430–2441. [CrossRef]
147. Xiao, P.; Takiishi, T.; Violato, N.M.; Licata, G.; Dotta, F.; Sebastiani, G.; Marselli, L.; Singh, S.P.; Sze, M.; Van Loo, G.; et al. NF-κB-inducing kinase (NIK) is activated in pancreatic β-cells but does not contribute to the development of diabetes. *Cell Death Dis.* **2022**, *13*, 476. [CrossRef]
148. Cepas, V.; Collino, M.; Mayo, J.C.; Sainz, R.M. Redox Signaling and Advanced Glycation Endproducts (AGEs) in Diet-Related Diseases. *Antioxidants* **2020**, *9*, 142. [CrossRef]
149. Singh, A.; Kukreti, R.; Saso, L.; Kukreti, S. Mechanistic Insight into Oxidative Stress-Triggered Signaling Pathways and Type 2 Diabetes. *Molecules* **2022**, *27*, 950. [CrossRef]
150. Wei, M.; Li, Z.; Xiao, L.; Yang, Z. Effects of ROS-relative NF-κB signaling on high glucose-induced TLR4 and MCP-1 expression in podocyte injury. *Mol. Immunol.* **2015**, *68*, 261–271. [CrossRef]
151. Zeng, H.; Qi, X.; Xu, X.; Wu, Y. TAB1 regulates glycolysis and activation of macrophages in diabetic nephropathy. *Inflamm. Res.* **2020**, *69*, 1215–1234. [CrossRef] [PubMed]
152. Zhu, X.; Guo, Y.; Liu, Z.; Yang, J.; Tang, H.; Wang, Y. Itaconic acid exerts anti-inflammatory and antibacterial effects via promoting pentose phosphate pathway to produce ROS. *Sci. Rep.* **2021**, *11*, 18173. [CrossRef]
153. Saunders, J.A.; Rogers, L.C.; Klomsiri, C.; Poole, L.B.; Daniel, L.W. Reactive oxygen species mediate lysophosphatidic acid induced signaling in ovarian cancer cells. *Free Radic. Biol. Med.* **2010**, *49*, 2058–2067. [CrossRef]
154. Lee, T.Y.; Lee, K.C.; Chen, S.Y.; Chang, H.H. 6-Gingerol inhibits ROS and iNOS through the suppression of PKC-alpha and NF-kappaB pathways in lipopolysaccharide-stimulated mouse macrophages. *Biochem. Biophys. Res. Commun.* **2009**, *382*, 134–139. [CrossRef]
155. Feng, L.; Zhu, M.; Zhang, M.; Jia, X.; Cheng, X.; Ding, S.; Zhu, Q. Amelioration of compound 4,4′-diphenylmethane-bis(methyl)carbamate on high mobility group box1-mediated inflammation and oxidant stress responses in human umbilical vein endothelial cells via RAGE/ERK1/2/NF-κB pathway. *Int. Immunopharmacol.* **2013**, *15*, 206–216. [CrossRef] [PubMed]
156. Lesmana, R.; Felia Yusuf, I.; Goenawan, H.; Achadiyani, A.; Khairani, A.F.; Nur Fatimah, S.; Supratman, U. Low Dose of β-Carotene Regulates Inflammation, Reduces Caspase Signaling, and Correlates with Autophagy Activation in Cardiomyoblast Cell Lines. *Med. Sci. Monit. Basic. Res.* **2020**, *26*, e928648. [CrossRef]
157. Park, S.E.; Sapkota, K.; Kim, S.; Kim, H.; Kim, S.J. Kaempferol acts through mitogen-activated protein kinases and protein kinase B/AKT to elicit protection in a model of neuroinflammation in BV2 microglial cells. *Br. J. Pharmacol.* **2011**, *164*, 1008–1025. [CrossRef]
158. Wu, Y.; Cui, J.; Bao, X.; Chan, S.; Young, D.O.; Liu, D.; Shen, P. Triptolide attenuates oxidative stress, NF-kappaB activation and multiple cytokine gene expression in murine peritoneal macrophage. *Int. J. Mol. Med.* **2006**, *17*, 141–150.
159. Ikegami, Y.; Inukai, K.; Imai, K.; Sakamoto, Y.; Katagiri, H.; Kurihara, S.; Awata, T.; Katayama, S. Adiponectin upregulates ferritin heavy chain in skeletal muscle cells. *Diabetes* **2009**, *58*, 61–70. [CrossRef]
160. Du, J.; Wang, N.; Sun, H.; Zheng, L.; Qi, X. Cl-amidine attenuates lipopolysaccharide-induced inflammation in human gingival fibroblasts via the JNK/MAPK, NF-κB, and Nrf2 signalling pathways. *Hum. Cell.* **2023**, *36*, 223–233. [CrossRef] [PubMed]
161. Fan, H.Q.; He, W.; Xu, K.F.; Wang, Z.X.; Xu, X.Y.; Chen, H. FTO Inhibits Insulin Secretion and Promotes NF-κB Activation through Positively Regulating ROS Production in Pancreatic β cells. *PLoS ONE* **2015**, *10*, e0127705. [CrossRef] [PubMed]
162. Choudhury, S.; Ghosh, S.; Gupta, P.; Mukherjee, S.; Chattopadhyay, S. Inflammation-induced ROS generation causes pancreatic cell death through modulation of Nrf2/NF-κB and SAPK/JNK pathway. *Free Radic. Res.* **2015**, *49*, 1371–1383. [CrossRef]
163. Furukawa, S.; Fujita, T.; Shimabukuro, M.; Iwaki, M.; Yamada, Y.; Nakajima, Y.; Nakayama, O.; Makishima, M.; Matsuda, M.; Shimomura, I. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J. Clin. Investig.* **2004**, *114*, 1752–1761. [CrossRef]
164. Zhong, X.; Zhang, Z.; Shen, H.; Xiong, Y.; Shah, Y.M.; Liu, Y.; Fan, X.G.; Rui, L. Hepatic NF-κB-Inducing Kinase and Inhibitor of NF-κB Kinase Subunit α Promote Liver Oxidative Stress, Ferroptosis, and Liver Injury. *Hepatol. Commun.* **2021**, *5*, 1704–1720. [CrossRef]
165. Sriram, S.; Subramanian, S.; Sathiakumar, D.; Venkatesh, R.; Salerno, M.S.; McFarlane, C.D.; Kambadur, R.; Sharma, M. Modulation of reactive oxygen species in skeletal muscle by myostatin is mediated through NF-κB. *Aging Cell* **2011**, *10*, 931–948. [CrossRef]
166. Song, M.Y.; Kim, E.K.; Moon, W.S.; Park, J.W.; Kim, H.J.; So, H.S.; Park, R.; Kwon, K.B.; Park, B.H. Sulforaphane protects pancreatic β-cells against cytokine-induced damage by suppressing NF-κB signalling. *Biochem. Biophys. Res. Commun.* **2009**, *387*, 377–382.

167. Shen, G.; Xu, C.; Hu, R.; Jain, M.R.; Nair, S.; Lin, W.; Yang, C.S.; Chan, J.Y.; Kong, A.N. Modulation of nuclear factor E2–related factor 2 (Nrf2)–mediated antioxidant response by Keap1 knockdown and electrophiles: Differential effects on Nrf2 activation and cytoprotection. *Mol. Pharmacol.* **2005**, *68*, 699–708.
168. Edwards, M.R.; Basler, C.F. Marburg Virus VP24 Protein Relieves Suppression of the NF-κB Pathway Through Interaction with Kelch-like ECH-Associated Protein 1. *J. Infect. Dis.* **2015**, *212*, S154–S159. [CrossRef]
169. Sayed, A.M.; Hassanein, E.H.M.; Ali, F.E.M.; Omar, Z.M.M.; Rashwan, E.K.; Mohammedsaleh, Z.M.; Abd El-Ghafar, O.A.M. Regulation of Keap-1/Nrf2/AKT and iNOS/NF-κB/TLR4 signals by apocynin abrogated methotrexate-induced testicular toxicity: Mechanistic insights and computational pharmacological analysis. *Life Sci.* **2021**, *284*, 119911. [CrossRef]
170. Deen, A.J.; Adinolfi, S.; Härkönen, J.; Patinen, T.; Liu, X.; Laitinen, T.; Takabe, P.; Kainulainen, K.; Pasonen-Seppänen, S.; Gawriyski, L.M.; et al. Oncogenic KEAP1 mutations activate TRAF2-NFκB signaling to prevent apoptosis in lung cancer cells. *Redox Biol.* **2024**, *69*, 103031. [CrossRef] [PubMed]
171. Dolgacheva, L.P.; Berezhnov, A.V.; Fedotova, E.I.; Zinchenko, V.P.; Abramov, A.Y. Role of DJ-1 in the mechanism of pathogenesis of Parkinson's disease. *J. Bioenerg. Biomembr.* **2019**, *51*, 175–188. [CrossRef] [PubMed]
172. Yu, Y.; Jiang, L.; Li, J.; Lei, L.; Li, H. Hexokinase 2-mediated glycolysis promotes receptor activator of NF-κB ligand expression in Porphyromonas gingivalis lipopolysaccharide-treated osteoblasts. *J. Periodontol.* **2022**, *93*, 1036–1047. [CrossRef] [PubMed]
173. Chiche, J.; Pommier, S.; Beneteau, M.; Mondragón, L.; Meynet, O.; Zunino, B.; Mouchotte, A.; Verhoeyen, E.; Guyot, M.; Pagès, G.; et al. GAPDH enhances the aggressiveness and the vascularization of non-Hodgkin's B lymphomas via NF-κB-dependent induction of HIF-1α. *Leukemia* **2015**, *29*, 1163–1176. [CrossRef]
174. Bu, Y.; Hao, J.; He, J.; Li, X.; Liu, Y.; Ma, L. Tumor-promoting properties of enolase-phosphatase 1 in breast cancer via activating the NF-κB signaling pathway. *Mol. Biol. Rep.* **2023**, *50*, 993–1004. [CrossRef] [PubMed]
175. Singh, M.K.; Jamal, F.; Dubey, A.K.; Shivam, P.; Kumari, S.; Pushpanjali Ahmed, G.; Dikhit, M.R.; Narayan, S.; Das, V.N.R.; Pandey, K.; et al. Co-factor-independent phosphoglycerate mutase of Leishmania donovani modulates macrophage signalling and promotes T-cell repertoires bearing epitopes for both MHC-I and MHC-II. *Parasitology* **2018**, *145*, 292–306. [CrossRef]
176. Batori, M.; Varga, Z.; Kovács, T.; Szabó, A.J.; Fekete, A. Nrf2 as a therapeutic target in metabolic and inflammatory diseases: Mechanisms and translational perspectives. *Antioxidants* **2024**, *13*, 45.
177. Gao, B.; Bataller, R. Alcoholic liver disease: Pathogenesis and new therapeutic targets. *Hepatology* **2009**, *50*, 307–328. [CrossRef]
178. Song, M.; Zhang, J.; Li, X.; Chen, L.; Wang, Y.; Liu, Y.; Sun, Y.; Wang, X. Nrf2 activation protects against β-cell dysfunction and apoptosis by suppressing oxidative stress and inflammatory signalling. *Cell Death Dis.* **2022**, *13*, 210.
179. Argaev-Frenkel, L.; Rosenzweig, T. Redox Balance in Type 2 Diabetes: Therapeutic Potential and the Challenge of Antioxidant-Based Therapy. *Antioxidants* **2023**, *12*, 994. [CrossRef]
180. Song, Y.; Cook, N.R.; Albert, C.M.; Van Denburgh, M.; Manson, J.E. Effects of vitamins C and E and beta-carotene on the risk of type 2 diabetes in women. *Diabetes Care* **2009**, *32*, 909–914.
181. Ashor, A.W.; Werner, A.D.; Lara, J.; Willis, N.D.; Mathers, J.C.; Siervo, M. Effects of vitamin C supplementation on glycaemic control: A systematic review and meta-analysis of randomised controlled trials. *Eur. J. Clin. Nutr.* **2017**, *71*, 1371–1380. [CrossRef]
182. Xu, R.; Zhang, S.; Tao, A.; Chen, G.; Zhang, M. Influence of vitamin E supplementation on glycaemic control: A meta-analysis of randomised controlled trials. *PLoS ONE* **2014**, *9*, e95008. [CrossRef]
183. Martina, V.; Masha, A.; Gigliardi, V.R.; Brocato, L.; Manzato, E.; Berchio, A.; Massarenti, P.; Settanni, F.; Della Casa, L.; Bergamini, S.; et al. Long-term N-acetylcysteine and L-arginine administration reduces endothelial activation and systolic blood pressure in hypertensive patients with type 2 diabetes. *Diabetes Care* **2008**, *31*, 940–944. [CrossRef]
184. Jha, J.C.; Banal, C.; Okabe, J.; Gray, S.P.; Hettige, T.; Chow, B.S.M.; Thallas-Bonke, V.; De Vos, L.; Holterman, C.E.; Coughlan, M.T.; et al. NADPH Oxidase Nox5 Accelerates Renal Injury in Diabetic Nephropathy. *Diabetes* **2017**, *66*, 2691–2703. [CrossRef]
185. Schröder, K.; Zhang, M.; Benkhoff, S.; Mieth, A.; Pliquett, R.; Kosowski, J.; Kruse, C.; Luedike, P.; Michaelis, U.R.; Weissmann, N.; et al. Nox4 is a protective reactive oxygen species generating vascular NADPH oxidase. *Circ. Res.* **2012**, *110*, 1217–1225. [CrossRef]
186. Dustin, C.M.; Cifuentes-Pagano, E.; Pagano, P.J. Isoform-Selective Nox Inhibitors: Advances and Future Perspectives. In *NADPH Oxidases Revisited: From Function to Structure*; Pick, E., Ed.; Springer: Cham, Switzerland, 2023.
187. Elbatreek, M.H.; Mucke, H.; Schmidt, H.H.H.W. NOX Inhibitors: From Bench to Naxibs to Bedside. *Handb. Exp. Pharmacol.* **2021**, *264*, 145–168.
188. Goldfine, A.B.; Fonseca, V.; Jablonski, K.A.; Pyle, L.; Staten, M.A.; Shoelson, S.E.; TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) Study Team. The effects of salsalate on glycemic control in patients with type 2 diabetes: A randomized trial. *Ann. Intern. Med.* **2010**, *152*, 346–357. [CrossRef] [PubMed]
189. Ridker, P.M.; Everett, B.M.; Thuren, T.; MacFadyen, J.G.; Chang, W.H.; Ballantyne, C.; Fonseca, F.; Nicolau, J.; Koenig, W.; Anker, S.D.; et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N. Engl. J. Med.* **2017**, *377*, 1119–1131. [CrossRef]
190. Rena, G.; Hardie, D.G.; Pearson, E.R. The mechanisms of action of metformin. *Diabetologia* **2017**, *60*, 1577–1585. [CrossRef]

191. Barik, S.K.; Sengupta, S.; Arya, R.; Kumar, S.; Kim, J.J.; Chaurasia, R. Dietary Polyphenols as Potential Therapeutic Agents in Type 2 Diabetes Management: Advances and Opportunities. *Adv. Nutr.* **2025**, *16*, 100346. [CrossRef] [PubMed]
192. Hausenblas, H.A.; Schoulda, J.A.; Smoliga, J.M. Resveratrol treatment as an adjunct to pharmacological management in type 2 diabetes mellitus—systematic review and meta-analysis. *Mol. Nutr. Food Res.* **2015**, *59*, 147–159. [CrossRef]
193. Panahi, Y.; Khalili, N.; Sahebi, E.; Namazi, S.; Reiner, Ž.; Majeed, M.; Sahebkar, A. Curcuminoids modify lipid profile in type 2 diabetes mellitus: A randomized controlled trial. *Complement. Ther. Med.* **2017**, *33*, 1–5. [CrossRef] [PubMed]