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Role of Tumor Suppressor P53 Family in Glucose Metabolism in Association with Diabetes

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Abstract

Subsequent manuscripts have shown that p53, a 391 amino acid protein, was associated with tumour suppression by inducing cell cycle arrest, senescence, or programmed cell death, and mainly focused on oncology. But recent studies are proclaiming that the p53 family of genes is also associated with regulating the balance of the glucose uptake via the many glucose transporters by directly repressing the expression of the GLUT1 & GLUT4, use of glycolysis and oxidative phosphorylation. The p53 regulates phenotypes of diabetes as it is interjecting in many points in regulating the pancreatic function and apoptosis, dysregulation of the beta cells, and developing insulin resistance. In the context of pancreatic beta cells, which are functioning for insulin secretion, it is regulated by the p53 by multiple signalling pathways. Endoplasmic stress results in the accumulation of the p53 that interacts with PARK2 (parkin), leading to insulin deficiency. Additionally, several proteins (N-terminal truncated isoforms of p53, factor TCFL2, the microRNA miR 200) regulate the p53 pathway, which can also regulate its ability to mediate pancreatic beta cell death. While in glucose haemostasis, wild-type p53 negatively and mutant p53 positively regulate glucose transporters and glucose importers. P21/CDKNIA plays an important role in developing insulin resistance as the p53-mediated senescence of adipose tissue marks it. Also, excessive O-GLcynated p53 inhibits the insulin signalling pathway from acting on the liver, generating insulin resistance. Here, we present a literature review on the role of p53 in metabolism, diabetes, pancreatic function, glucose homeostasis, and insulin resistance.

Interestingly, mutations in the p53 gene were shown to occur at different phases of the multistep process of malignant transformation.

Keywords: P53 Family; Gluconeogenesis; Glycolysis; Oxidative Phosphorylation; Tumor Suppression

Abbreviations: TP53: Induced Glycolysis and Apoptosis Regulator; TCA: Tricarboxylic Acid; ATP: Adenosine Triphosphate; NADH: Nicotinamide Adenine Dinucleotide; GLUT 4: Glucose Transporter 4; IRS-1: Insulin Receptor Substrate 1; HK2: Hexokinase 2.

Introduction

A key process that supplies energy for cellular functions, glucose metabolism is strictly controlled to preserve metabolic homeostasis. Although p53's function as a tumor suppressor has been thoroughly researched, new data point to p53's critical role in controlling glucose metabolism. p53, which has previously been known to have a role in DNA repair, cell cycle regulation, and apoptosis, is currently being studied for its effects on metabolic pathways like glycolysis, oxidative phosphorylation, and gluconeogenesis.

Due to its implications for both cancer biology and metabolic diseases, p53's multidimensional role in glucose metabolism is of great interest. Cancer cells frequently display increased glycolytic activity, or the Warburg effect, which is characterized by dysregulation of glucose metabolism. By limiting the supply of energy substrates and encouraging cell death under metabolic stress, p53's capacity to inhibit glycolysis and enhance oxidative phosphorylation adds to its tumor suppressor activity.

The protein p53, also referred to as the "guardian of the genome," is essential for controlling how the cell cycle progresses, how DNA is repaired, and how apoptosis occurs (programmed cell death). Even while p53 is primarily recognised for its function in the prevention of cancer, recent findings point to its possible participation in a number of metabolic processes, including glucose metabolism.

Additionally, p53 has an impact that goes beyond the Warburg effect. Today, it is understood that p53 controls several processes related to glucose metabolism, including glucose absorption, utilisation, and storage. P53 controls glucose homeostasis in healthy cells by modifying the expression of essential enzymes and transporters involved in these procedures.

Furthermore, the impact of p53 goes beyond the Warburg effect. It is now understood that p53 controls a number of processes involved in the metabolism of glucose, including glucose absorption, utilization, and storage. P53 regulates glucose homeostasis in healthy cells by altering the expression of crucial enzymes and transporters involved in these procedures.

Understanding the complex molecular pathways by which p53 controls glucose metabolism is essential for elucidating its myriad functions as well as for considering new treatment approaches. The management of metabolic diseases including diabetes and obesity as well as the therapy of cancer may both benefit from targeting p53-mediated glucose metabolism.

The goal of this review is to give a summary of what is currently known about the role of p53 in glucose metabolism. We'll go over the regulatory processes by which p53 affects oxidative phosphorylation, glycolysis, and other aspects of glucose metabolism. This study aims to advance our knowledge of the larger implications of p53 biology and its potential as a therapeutic target in metabolic illnesses by providing light on the relationship between p53 and glucose homeostasis.

Depending on the environment and cellular circumstances, p53's modulation of glucose metabolism can have both tumor-suppressive and tumor-promoting effects. Although p53's job in preserving genomic stability and preventing tumor growth is well known, its involvement in glucose metabolism adds an additional level of complexity to its roles in the growth of cancer. The following are some ways that p53's control over glucose metabolism may affect cancer:

1. Repression of important glycolytic enzymes and transporters, including GLUT1, GLUT4, HK2, and PFK1, can cause p53 to suppress glycolysis in healthy cells. The supply of energy substrates for cancer cells, which frequently largely rely on glycolysis for energy production, may be constrained by this change from glycolysis to oxidative phosphorylation. As a result, by limiting the energy source available to cancer cells, p53's inhibition of glycolysis can serve as a tumor-suppressive strategy.
2. **Switching to oxidative phosphorylation:** p53 can promote oxidative phosphorylation, a more efficient form of energy production that occurs in mitochondria. By increasing the expression of enzymes involved in oxidative phosphorylation and enhancing Change to oxidative phosphorylation: P53 can encourage oxidative phosphorylation, which is a more effective method of generating energy in mitochondria. P53 can switch glucose metabolism to this route by boosting mitochondrial biogenesis and upregulating the expression of oxidative phosphorylation-related enzymes. As a result of this change, the mitochondria may produce more reactive oxygen species (ROS), which when produced in excess can cause DNA damage and advance the development of cancer. However, apoptosis can also be induced and function as a tumor-suppressing mechanism in response to low amounts of ROS. Mitochondrial biogenesis, p53 can redirect glucose metabolism towards this pathway. This shift can lead to increased production of reactive oxygen species (ROS) within the mitochondria, which, in excessive amounts, can induce DNA damage and promote cancer development. However, moderate levels of ROS can also trigger apoptosis and act as a tumor-

suppressive mechanism.

3. **Modulation of the Warburg effect:** The Warburg effect, where glucose is preferentially digested through glycolysis even in the presence of oxygen, is frequently seen in cancer cells. As previously established, p53 can control the Warburg effect by inhibiting the production of glycolytic enzymes and encouraging oxidative phosphorylation. P53 can reduce the metabolic advantage of cancer cells and slow their proliferation by suppressing the Warburg effect.
4. **Cellular stress response:** In response to a variety of cellular stressors, such as DNA damage, hypoxia, and food deprivation, p53 is activated. In order to maintain energy production while glucose is scarce, p53 can activate autophagy, a cellular recycling process. While autophagy can initially serve as a defense mechanism against the onset of cancer, persistent autophagic activity may encourage tumor growth by supplying repurposed components for cancer cell survival.
5. **Regulation of insulin signalling:** A key component of glucose metabolism is insulin signalling, which p53 can affect. Insulin signalling can be suppressed by p53's ability to connect directly with insulin receptor substrate 1 (IRS1), which results in less efficient absorption and utilisation of glucose.
6. **Modulation of AMP-activated protein kinase (AMPK) pathway:** AMPK is a cellular energy sensor that regulates modification of the AMP-activated protein kinase (AMPK) pathway: AMPK is an energy sensor in cells that controls the metabolism of glucose and lipids. By boosting the production of AMPK subunits, p53 can activate AMPK. AMPK activation promotes glucose uptake and metabolism, facilitating energy balance in cells. Glucose and lipid metabolism. p53 can activate AMPK by increasing the expression of AMPKα subunits. AMPK activation promotes glucose uptake and metabolism, facilitating energy balance in cells.

It is crucial to remember that the context in which p53 regulation of glucose metabolism in cancer occurs affects its effects significantly, as might the particular genetic and environmental factors regulating p53 activity. Additionally, the p53 gene frequently develops mutations in cancer cells or is dysregulated, which results in abnormal glucose metabolism and different reactions to metabolic stress.

Overall, p53 controls several different aspects of glucose metabolism in cancer. While p53 can inhibit tumor growth by restricting glycolysis and encouraging oxidative phosphorylation, it can also affect other cellular processes that may play a dual function in the emergence of cancer.

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- **Mechanisms of P53 Family in Glucose Metabolism**

The Warburg effect is the finding that, in contrast to healthy cells, cancer cells have abnormal glucose metabolism. Otto Warburg, a well-known German biochemist, published the first description of it in the 1920s. The Warburg effect is a propensity for cancer cells to preferentially use glycolysis (the breakdown of glucose) rather than oxidative phosphorylation for energy production, even in the presence of oxygen (a more efficient process occurring in the mitochondria).

During typical cellular metabolism, a sequence of enzyme processes in the cytoplasm transform glucose into pyruvate. The tricarboxylic acid (TCA) cycle continues to metabolise pyruvate once it enters the mitochondria, which results in the production of adenosine triphosphate (ATP) via oxidative phosphorylation. With this method, each glucose molecule yields a significant amount of ATP.

However, even under aerobic settings, cancer cells show a greater reliance on glycolysis, which generates lactate from pyruvate. The "Warburg effect" or aerobic glycolysis is the term used to describe this phenomenon. Although glycolysis produces less ATP per glucose molecule than oxidative phosphorylation, it has a number of benefits for cancer cells that divide quickly, including:

1. **Rapid ATP production:** Glycolysis produces ATP faster than oxidative phosphorylation, allowing cancer cells to meet the high energy demands required for cell proliferation.
2. **Biosynthesis:** Cancer cells require a substantial amount of building blocks (e.g., Rapid ATP generation enables cancer cells to meet the high energy needs necessary for cell proliferation. Glycolysis produces ATP more quickly than oxidative phosphorylation.
3. **Biosynthesis:** To produce the macromolecules needed for cell growth and division, cancer cells need a lot of building blocks (such as nucleotides, amino acids, and lipids). Precursor molecules produced by glycolysis can be directed in the direction of various metabolic pathways. Nucleotides, amino acids, lipids) for the synthesis of macromolecules necessary for cell growth and division. Glycolysis generates precursor molecules that can be diverted toward these biosynthetic pathways.
4. **Equivalents in reduction:** The glycolytic pathway produces reduced nicotinamide adenine dinucleotide (NADH), which can aid in other cellular functions and preserve redox equilibrium.

It is crucial to completely comprehend the intricate molecular processes that underlie the Warburg effect. Its regulation is influenced by a number of variables, including oncogene activation, tumour suppressor loss, and changes to

signalling pathways including the PI3K-Akt-mTOR pathway. These modifications encourage cancer cells to rewire their metabolism to prioritise glycolysis over oxidative phosphorylation.

The development of cancer therapies and cancer research will be significantly impacted by understanding the Warburg effect. A promising method to selectively destroy cancer cells while preserving healthy cells is to target the metabolic changes linked to the Warburg effect. There are several treatment strategies being researched that try to interfere with cancer cell metabolism [1].

The transcription factors in the p53 family, which also includes p63 and p73, are essential for controlling biological functions such cell cycle control, apoptosis, DNA repair, and metabolism. Recent research has brought attention to the newly discovered involvement of the p53 family members in glucose metabolism, notably in relation to cancer. The following are some important studies and sources regarding the participation of the p53 family in glucose metabolism.

The two primary processes involved in cellular energy metabolism, glycolysis and oxidative phosphorylation, are controlled by the well-known tumour suppressor protein p53. Here are some important discoveries about how p53 controls glycolysis and oxidative phosphorylation:

p53 Regulation of Glycolysis and Oxidative Phosphorylation

Regulation of glycolysis by p53

- The expression of several glycolytic genes is directly suppressed by p53, which has been shown in numerous investigations to block glycolysis [1-3]. For instance, it has been demonstrated that p53 transcriptionally suppresses the expression of the important glycolytic enzymes hexokinase 2 (HK2) and phosphofructokinase, as well as the glucose transporters GLUT1 and GLUT4 (PFK-1) [2].
- In some circumstances, p53 can also encourage glycolysis by increasing the expression of particular glycolytic enzymes [4]. For instance, it has been discovered that p53 increases the expression of the glycolytic inhibitor TIGAR (TP53-induced glycolysis and apoptosis regulator), which can inhibit glycolysis by diverting the glycolytic intermediate fructose-6-phosphate to the pentose phosphate pathway [5].

Regulation of oxidative phosphorylation by p53

- **p53 promotes oxidative phosphorylation:** Several studies have shown that p53 can enhance oxidative phosphorylation by regulating mitochondrial metabolism [6].
- p53 has been found to promote the transcription of genes involved in oxidative phosphorylation and mitochondrial biogenesis, such as cytochrome c oxidase subunit IV (COX IV) and NADH dehydrogenase (NDH) [7].
- The oxidative phosphorylation process is inhibited by p53, however in some circumstances; p53 can also repress the process [8]. For instance, it has been observed that p53 inhibits the expression of TFAM, which is necessary for mitochondrial DNA replication and oxidative phosphorylation [9].

- **p63 and p73 roles in metabolic reprogramming:** p63 and p73, two members of the p53 family of transcription factors, have also been implicated in metabolic reprogramming, including the regulation of glucose metabolism [10]. Here are some key findings regarding the roles of p63 and p73 in metabolic reprogramming:
- **p63 and p73 regulation of glycolysis**
  The isoforms p63 and p73 can control glycolysis: There are isoforms of p63 and p73 with transcriptional activity that can affect glycolysis. For instance, it has been demonstrated that the TAp63 isoform inhibits the production of glucose transporters (GLUT1, GLUT3) and glycolytic enzymes, hence suppressing glycolysis (HK2, PFK-1). Similar to this, TAp73 isoforms can inhibit glycolysis by suppressing the expression of genes involved in glycolysis [11-13].
- **p63 and p73 modulation of TIGAR:** Both p63 and p73 isoforms can regulate glycolysis indirectly by modulating the expression of TP53-induced glycolysis and apoptosis regulator (TIGAR), which diverts glucose-6-phosphate away from glycolysis and into the pentose phosphate pathway. TIGAR promotes pentose phosphate pathway flux and NADPH production, increasing antioxidant capacity and potentially reducing glycolysis [10,12].
- **p63 and p73 involvement in mitochondrial metabolism:** Some isoforms of p63 and p73 have been identified to support oxidative phosphorylation and mitochondrial metabolism. P63 and p73 regulate mitochondrial respiration [19]. By encouraging the transcription of genes involved in oxidative phosphorylation, such as cytochrome c oxidase subunit IV (COX IV) and NADH dehydrogenase, for example, the TAp63 and TAp73 isoforms can improve mitochondrial respiration (NDH) [12].

The isoforms of TAp63 and TAp73 have been linked to the control of mitochondrial biogenesis by p63 and p73 [10]. They can promote mitochondrial biogenesis by promoting the expression of genes related to mitochondrial DNA replication and maintenance, such as TFAM and other genes [11].

p53 Family Members and the Warburg Effect

The Warburg effect, a typical metabolic reprogramming seen in cancer cells, has been linked to the p53 family members, specifically p53, p63, and p73. The following are some important discoveries on the contribution of the p53 family to the Warburg effect:

- **p53 and the Warburg effect:** Both oxidative phosphorylation and glycolysis are processes that p53 regulates; it has been discovered that p53 does so. Under normal circumstances, the transcription of genes involved in mitochondrial metabolism is stimulated by p53, which in turn promotes oxidative phosphorylation [6]. However, p53 mutant or functionally deficient cancer cells Both oxidative phosphorylation and glycolysis are processes that p53 regulates; it has been discovered that p53 does so.

Under normal circumstances, the transcription of genes involved in mitochondrial metabolism is stimulated by p53, which in turn promotes oxidative phosphorylation. The Warburg effect, however, is supported by cancer cells with mutant p53 or p53 function loss, which can result in increased glycolysis and decreased oxidative phosphorylation [8].

The expression of different metabolic enzymes involved in glycolysis and oxidative phosphorylation can be modulated by p53, which controls the activity of these enzymes [9]. It can activate the expression of oxidative phosphorylation-related genes including cytochrome c oxidase subunit IV (COX IV) and NADH dehydrogenase while suppressing the expression of glycolytic enzymes like hexokinase 2 (HK2) and phosphofructokinase (PFK-1) (NDH) [4].

- **p63 and p73 and the Warburg effect:** TAp63 and TAp73 isoforms can prevent glycolysis by suppressing the expression of genes involved in it, such as those for glucose transporters (GLUT1, GLUT3) and glycolytic enzymes (HK2, PFK-1). In some circumstances, this control may serve to mitigate the Warburg effect [10,11].
- **p63 and p73 isoforms promote oxidative phosphorylation:** By promoting the transcription of genes involved in mitochondrial metabolism and oxidative phosphorylation, such as COX IV and NDH, TAp63 and TAp73 isoforms can improve oxidative phosphorylation. The Warburg effect's glycolytic phenotype can be balanced by this modulation [19]. By promoting the transcription of genes involved in mitochondrial metabolism and oxidative phosphorylation, such as COX IV and NDH, TAp63 and TAp73 isoforms can improve oxidative phosphorylation. The Warburg effect's glycolytic phenotype can be balanced by this modulation [12].

p53 Family Members and Metabolic Reprogramming in Cancer

The p53 family members, including p53, p63, and p73, are involved in metabolic reprogramming in cancer cells. Here are some key findings regarding the roles of p53 family members in metabolic reprogramming in cancer:

- **p53 and metabolic reprogramming in cancer:** p53 regulates glucose metabolism: In cancer cells, p53 can modulate glucose metabolism by suppressing glycolysis and promoting oxidative phosphorylation. Wild-type p53 has been shown to repress the expression of glycolytic enzymes, including glucose transporters (GLUT1, GLUT4), hexokinase 2 (HK2), and phosphofructokinase (PFK-1). Moreover, p53 can enhance oxidative phosphorylation by activating the transcription of genes involved in mitochondrial metabolism [8].
- **p53 regulates other metabolic pathways:** In addition to glucose metabolism, p53 can impact other metabolic pathways. For instance, it can regulate lipid metabolism by modulating the expression of genes involved in fatty acid oxidation and synthesis. Moreover, p53 has been implicated in the regulation of amino acid metabolism, nucleotide metabolism, and the tricarboxylic acid (TCA) cycle [14].
- **p63 and p73 in metabolic reprogramming in cancer:** p63 and p73 isoforms regulate glycolysis: In cancer cells, certain isoforms of p63 and p73, such as TAp63 and TAp73, can inhibit glycolysis by suppressing the expression of glycolytic enzymes and glucose transporters. This regulation can impact the metabolic phenotype and contribute to metabolic reprogramming in cancer [12].

TAp63 and TAp73 isoforms can increase oxidative phosphorylation by upregulating the expression of genes involved in mitochondrial metabolism and oxidative phosphorylation. p63 and p73 regulate oxidative phosphorylation. Through oxidative phosphorylation, this regulation can support energy production by balancing glycolysis. TAp63 and TAp73 isoforms can increase oxidative phosphorylation by upregulating the expression of genes involved in mitochondrial metabolism and oxidative phosphorylation. p63 and p73 regulate oxidative phosphorylation. Through oxidative phosphorylation, this regulation can support energy production by balancing glycolysis. TAp63 and TAp73 isoforms can increase oxidative phosphorylation by upregulating the expression of genes involved in mitochondrial metabolism and oxidative phosphorylation. p63 and p73 regulate oxidative phosphorylation. Through oxidative phosphorylation, this regulation can support energy production by balancing glycolysis. TAp63 and TAp73 isoforms can increase

oxidative phosphorylation by upregulating the expression of genes involved in mitochondrial metabolism and oxidative phosphorylation. p63 and p73 regulate oxidative phosphorylation. Through oxidative phosphorylation, this regulation can support energy production by balancing glycolysis in cancer cells [11].

Isoform-specific p73 knockout mice reveal a novel role for delta Np73 in the DNA damage response pathway.

- **p63 and p73 affect other metabolic pathways:** p63 and p73 isoforms have been linked to controlling lipid metabolism, nucleotide metabolism, and amino acid metabolism in cancer cells, in addition to glycolysis and oxidative phosphorylation [10].

These studies highlight the involvement of p53 family members in metabolic reprogramming in cancer, emphasizing their roles in regulating glucose metabolism, oxidative phosphorylation, and other metabolic pathways to support energy demands, highlighting their roles in regulating metabolic pathways in various cellular contexts, including cancer.

Conclusion

The p53 tumour suppressor protein, primarily known for its role in preventing cancer development, has also been implicated in the regulation of metabolism, including its association with diabetes. Here are some key findings regarding the role of p53 in metabolism and diabetes:

- **Regulation of glucose metabolism**

p53 influences glucose homeostasis: p53 has been shown to impact glucose metabolism by regulating insulin sensitivity, glucose uptake, and glucose utilization in various tissues. In response to cellular stress, p53 can promote insulin resistance by inhibiting insulin signalling pathways and suppressing the expression of insulin receptor substrate 1 (IRS-1) and glucose transporter 4 (GLUT4), thereby reducing glucose uptake [15].

The regulation of AMPK β1, TSC2, and PTEN expression by p53: Stress, cell and tissue specificity, and the role of these gene products in modulating the IGF-1-AKT-mTOR pathways [1].

p53 and glucose metabolism-related genes: p53 can modulate the expression of genes involved in glucose metabolism [9]. It can repress the transcription of key glycolytic enzymes, including hexokinase 2 (HK2) and phosphofructokinase (PFK-1), leading to decreased glycolysis. Furthermore, p53 can enhance the expression of TP53-induced glycolysis and apoptosis regulator (TIGAR), which diverts glucose-6-phosphate away from glycolysis and into the pentose phosphate pathway [6].

- **Implications in diabetes**

p53 and insulin resistance: Dysregulated p53 activity has been associated with insulin resistance, a hallmark of type 2 diabetes. Increased p53 levels can lead to impaired insulin signalling and reduced glucose uptake in insulin-sensitive tissues, contributing to insulin resistance [15].

The regulation of AMPK β1, TSC2, and PTEN expression by p53: Stress, cell and tissue specificity, and the role of these gene products in modulating the IGF-1-AKT-mTOR pathways [18].

p53 inhibitors preserve dopamine neurons and motor function in experimental Parkinson's disease [19].

p53 and pancreatic beta-cell function: p53 has also been implicated in the regulation of pancreatic beta-cell function and survival. (Placeholder1) Dysregulated p53 activity in beta-cells can contribute to beta-cell dysfunction and apoptosis, which are observed in type 2 diabetes and may impact insulin secretion and glucose homeostasis [16,17].

- **Declaration of Conflicts of Interests**

Authors declare no conflict of interests.

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