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Review Article

Exploring the Basic Molecular Pathways: Metformin as a Potential Treatment Option for Pancreatic Cancer

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Abstract

Background: Pancreatic cancer is one of the most aggressive and lethal malignancies, with limited treatment options and a poor prognosis. Recent research has highlighted the potential role of metformin, a widely used antidiabetic drug, in modulating cancer risk and progression. This review aims to explore the current evidence on the impact of metformin on pancreatic cancer outcomes and its potential mechanisms of action.

Materials and Methods: A comprehensive literature search was conducted using databases such as PubMed, Scopus, and Web of Science to identify studies investigating the relationship between metformin use and pancreatic cancer. Inclusion criteria encompassed clinical trials, cohort studies, and laboratory research published in the last two decades. Data extraction focused on patient outcomes, metformin dosage, study design, and proposed mechanisms of action.

Results: The review indicates that metformin use is associated with improved overall survival and reduced cancer incidence in patients with pancreatic cancer, particularly among those with concurrent diabetes. Mechanistic studies suggest that metformin exerts its anticancer effects through the inhibition of the mTOR pathway, reduction of insulin-like growth factors, and induction of autophagy. However, the results are heterogeneous, and several studies highlight the need for further clinical trials to establish causality and optimal therapeutic regimens.

Conclusion: While current evidence supports a potentially beneficial role of metformin in pancreatic cancer management, the findings are preliminary and require further validation through randomized controlled trials. The heterogeneity of the studies underscores the necessity for standardized protocols to assess the efficacy and safety of metformin as an adjunct therapy in pancreatic cancer treatment.

Keywords:

Metformin
Pancreatic Cancer
Molecular Pathways
Cancer Treatment
Cellular Energy
Metabolism

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1. INTRODUCTION

A Pancreatic cancer is a significant global health challenge, characterized by a notably high mortality rate. The diagnosis is frequently made at advanced stages, complicating treatment efforts and contributing to unfavorable survival outcomes. The intricate biology of pancreatic cancer, along with its resistance to traditional therapeutic modalities, emphasizes the pressing necessity for the development of innovative treatment strategies (1, 2). In recent years, metformin, a primary medication used in the management of type 2 diabetes, has garnered attention as a promising adjuvant therapy for pancreatic cancer. The initial recognition of metformin's anticancer potential arose from epidemiological studies, which revealed a decreased incidence of multiple cancer types among diabetic patients receiving this treatment. These findings have stimulated considerable interest within the scientific community, prompting extensive investigation into the therapeutic benefits and underlying mechanisms of metformin in the context of cancer treatment (3).

Numerous epidemiological studies have documented a diminished risk of developing pancreatic cancer among diabetic patients who have been administered metformin (4). These observations indicate that metformin may confer a protective effect against pancreatic cancer. Nevertheless, the precise biological mechanisms underlying this protective role remain insufficiently understood and warrant further elucidation (5). Additionally, several clinical investigations have indicated that pancreatic cancer patients who concurrently use metformin may experience enhanced survival rates. These studies present encouraging preliminary data supporting metformin's potential role as an adjunctive treatment in pancreatic cancer. Nevertheless, they underscore the necessity for further in-depth research to confirm these results and to better understand the underlying molecular mechanisms at play (6).

Nonetheless, the molecular mechanisms driving these effects remain incompletely characterized. It is well-established that metformin activates the AMP-activated protein kinase (AMPK) pathway and suppresses the mammalian target of rapamycin (mTOR) pathway, both of which are pivotal in regulating cellular metabolism and growth. However, the precise interplay between these pathways within the context of pancreatic cancer continues to be an area of active investigation (7). This review seeks to examine the current insights into the molecular pathways through which metformin may exert its anti-cancer effects in pancreatic cancer. We will critically assess the most recent studies investigating the impact of metformin on energy metabolism, cellular signaling, inflammation, cell cycle regulation, and transcription factors in pancreatic cancer cells. By exploring these mechanisms, the goal is to offer a thorough and nuanced understanding of metformin's potential role in the therapeutic management of pancreatic cancer (8). A deeper understanding of these mechanisms could offer valuable insights into the potential of metformin as an adjunctive therapy for pancreatic cancer and facilitate the design of more targeted and effective treatment strategies. As the intricate molecular landscape of pancreatic cancer continues to be elucidated, the significance of metformin within this context becomes progressively more evident. This review aspires to enhance the existing body of knowledge and encourage further exploration in this promising field (9).

2. METHODS

We conducted an extensive literature review utilizing the PubMed and Scopus databases, with the search covering publications up to August 2024. Our search strategy incorporated terms such as "Metformin," "Metformin treatment," "Metformin therapy," and "Metformin use," in combination with "Pancreatic cancer," "Pancreatic carcinoma," "Pancreatic neoplasm," "Pancreatic tumor," and "Pancreatic malignancy." Articles were included if they explored the molecular pathways affected by metformin in pancreatic cancer. Studies were excluded if they were duplicates, published in languages other than English, or lacked accessible full-texts. The article selection process was independently carried out by two reviewers (HD and SR), with an expert (DM) supervising to resolve any disagreements. Relevant data, including study design, methodology, and outcomes, were meticulously extracted.

2.1. Study Design

The findings from studies investigating the effects of metformin on pancreatic cancer exhibit significant variability. This is primarily attributed to variations in study design, sample sizes, participant selection criteria, confounding factors, and other methodological elements. Research on metformin as a treatment for pancreatic cancer faces several common challenges. Variations in study designs, small sample sizes, and inconsistent participant selection can lead to divergent results. Additionally, other concurrent medications and lifestyle factors can obscure the true impact of metformin. Methodological inconsistencies, the absence of long-term data, and the complexity of molecular pathways involved in pancreatic cancer further complicate the interpretation of results. Furthermore, laboratory findings do not always

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correlate with clinical outcomes, which introduces an additional layer of complexity. Publication bias and the use of different metformin formulations can also influence the results. These challenges underscore the need for more standardized and comprehensive studies to gain a clearer understanding of metformin's potential in the treatment of pancreatic cancer **(Table 1)**.

3. METFORMIN AND PANCREATIC CANCER: CLINICAL OBSERVATIONS

In a comprehensive and meticulously conducted review and meta-analysis spearheaded by Jian Hu and his esteemed colleagues, the intricate relationship between the administration of metformin and the associated risk of developing pancreatic cancer among individuals diagnosed with type 2 diabetes mellitus was thoroughly scrutinized and assessed. This extensive analysis encompassed an impressive dataset drawn from over two million participants, which were aggregated from a total of twenty-nine distinct studies, thereby providing a robust foundation for the scholarly inquiry. The findings derived from this rigorous investigation suggested that the utilization of metformin may correlate with a potentially diminished risk of the onset of pancreatic cancer in these patients when juxtaposed with individuals who did not engage in the use of this particular medication. Nevertheless, it is imperative to note that, in a comparative context, when metformin users were evaluated against patients who were either managing their condition solely through dietary interventions or those who were not receiving any form of treatment at all, it appeared that the individuals utilizing metformin might experience a heightened risk of developing pancreatic cancer. This duality in the results underscores the complexity of the interplay between pharmacological interventions and cancer risk, necessitating further exploration and longitudinal studies to unravel the underlying mechanisms at play. Ultimately, such findings evoke a critical dialogue regarding the safety and efficacy of metformin as a therapeutic agent in the management of type 2 diabetes, particularly in light of its potential implications for oncological health (15). An observational study examined the influence of metformin on patient survival and its potential association with distinct immune profiles in pancreatic ductal adenocarcinoma (PDAC) tumors. The findings revealed that patients who used metformin exhibited a longer median survival and a higher 5-year survival rate compared to those who did not use the drug. Additionally, metformin use was recognized as a favorable prognostic factor for overall survival in patients who underwent initial surgical treatment (16). According to a University of Texas MD Anderson Cancer Center research, patients using metformin had almost twice the 2-year survival rate, a significantly longer overall survival, and a lower chance of death. According to these results, metformin may improve the prognosis of pancreatic cancer patients (17). On the other hand, not every research supports metformin's preventive benefits. According to several studies, there is either not enough data or no discernible difference in the risk of cancer when using metformin. These conflicting results highlight the need for more thorough and rigorous study to definitively ascertain how metformin affects the risk and prognosis of pancreatic cancer.

4. MOLECULAR MECHANISMS OF METFORMIN

4.1. Metformin and Energy Reprogramming in Pancreatic Cancer

It is believed that metformin significantly affects the energy metabolism of cancer cells, which may prevent them from proliferating and growing. It is thought to have this impact via interfering with the respiratory chain of the mitochondria, which lowers the synthesis of ATP, the main source of energy for cells. This disturbance puts cancer cells under energy stress and may even stop their development by causing a metabolic shift towards glycolysis, a less effective energy-producing mechanism **(Table 2)** (18, 19).

Metformin's ability to change the energy metabolism of cancer cells, a critical mechanism for their survival and growth, is closely linked to its anti-cancer effects. Metformin may make it more difficult for cancer cells to survive and spread by interfering with this metabolic reprogramming (20).

In addition to these actions, metformin is believed to have other anti-cancer qualities. Its promise as a cancer therapy is further supported by the possibility that it might boost the body's immunological response against cancer cells. Furthermore, metformin may change the tumor microenvironment, making it less conducive to the growth and spread of cancer. These additional pathways demonstrate metformin's encouraging potential as a cancer treatment drug (21). Nevertheless, further investigation is required to comprehensively elucidate these mechanisms and establish the most effective application of metformin in cancer therapy (22, 23).

4.2. Metformin and ATP Production

Rapid AMPK activation often compensates for deficits in ATP generation, which depends on mitochondrial activity,

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in both healthy and malignant cells. This suggests that AMPK-mediated signaling plays a critical role in avoiding energy depletion when ATP production is impaired. This pattern is reliably seen in a variety of physiological circumstances (24-26). A transient decline in cellular energy, marked by a reduction in ATP levels and a simultaneous rise in AMP levels, along with the activation of AMPK through phosphorylation, triggers a shift in the cell's metabolism from an anabolic to a catabolic state (27, 28). Given the simultaneous observations that metformin both activates AMPK and causes cancer cells to undergo apoptosis, it has been hypothesized that metformin's anti-neoplastic effects might be largely explained by AMPK activation (29). Increased metabolic rates, which necessitate substantial ATP synthesis, are a hallmark of cancer cells. By blocking complex I of the mitochondrial respiratory chain, metformin interferes with this mechanism and lowers ATP generation. A series of cellular reactions intended to restore energy equilibrium are triggered by this imposed energy shortage (**Table 1**) (30).

4.3. Metformin and ROS Production

For host infections to be properly managed and resolved, phagocytes must produce and release reactive oxygen species (ROS) in a controlled manner (31). When molecular oxygen is reduced, tiny, very reactive molecules known as reactive oxygen species (ROS) are produced. These consist of hydrogen peroxide (H2O2), hypochlorous acid (HOCl), hydroxyl radical (OH°), and superoxide anion (O2−) (32). ROS are known to have functions in several biological and physiological processes in addition to their involvement in eliminating microorganisms. Actually, if there is an imbalance between the production and elimination of ROS, oxidative stress can lead to tissue damage (33, 34). Metformin exerts anti-inflammatory and antioxidant effects via changing the polarization of macrophages and AMPK-dependently regulating the production of ROS. By specifically inhibiting human M1 and M2 macrophage differentiation and reducing ROS generation through AMPK activation, it achieves these objectives (35, 36).

4.4. Metformin and the AMPK/mTORC1 Axis

The mechanistic target of rapamycin complex 1 (mTORC1) is crucial for regulating cell growth, proliferation, and metabolic functions. Research has shown that metformin, a widely used drug, interferes with two critical pathways required for the activation of mTORC1 (37). First, the activation of AMPK is driven by cellular energy stress and strain. AMPK (AMP-activated protein kinase) functions as a sensor of the cell's energy state. When energy levels are low, indicated by a high AMP/ATP ratio, AMPK becomes activated. Metformin is known to elevate the AMP/ATP ratio, thereby triggering AMPK activation. Upon activation, AMPK reduces the activity of RHEB (RAS homolog enriched in brain), a GTPase that directly stimulates mTORC1 (37, 38). Secondly, inhibition of amino acid signaling: Amino acids play a crucial role in cell signaling and metabolic regulation, influencing metabolic pathways, gene expression, and cell-to-cell communication. The phrase "suppression of amino acid signaling" refers to the downregulation or blockage of these pathways. This suppression can be initiated by various factors, including nutrient deprivation, cellular stress, or the action of specific drugs such as metformin (39). In relation to mTORC1 (mechanistic target of rapamycin complex 1) activation, the inhibition of amino acid signaling holds particular importance. mTORC1 acts as a key regulator of cell growth, proliferation, and metabolism, detecting the availability of amino acids within the cell and adjusting its activity in response (40). When amino acid signaling is inhibited, it leads to a reduction in the activity of lysosomal RAG GTPases, which are essential for the activation of mTORC1 at the lysosomal membrane. Consequently, the suppression of amino acid signaling can prevent the activation of mTORC1, thereby disrupting various cellular processes (41).

4.5. Metformin and Anti-inflammatory Effects in Pancreatic Cancer

Inflammation plays a critical role in the initiation and progression of pancreatic cancer (44). Metformin has been found to exhibit anti-inflammatory properties that may hold potential for combating pancreatic cancer. Specifically, it has been shown to decrease the production of inflammatory cytokines such as tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and IL-1β (45). These cytokines are recognized for promoting inflammation and may play a role in the progression of cancer (46).

Additionally, metformin inhibits the activity of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) and hypoxia-inducible factor-1-alpha (HIF-1α), both of which are key regulators of inflammation and cancer progression. By suppressing these factors, metformin may help slow the advancement of the disease (47, 48).

The effects of metformin go beyond its action on cancer cells and extend to the tumor microenvironment, which plays a crucial role in shaping cancer behavior. Metformin has been shown to boost anti-tumor immune responses,

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Table 1. clinical benefits of metformin in cancer therapy.

Authors	country	Year of Publishing	Number of Cases	Result	Reference
Jie Wen et al.	China	2022	5943	Metformin has shown potential positive effects on progression-free survival (PFS) in patients with cancers of the reproductive system.	(10)
Samy Suissa et al.	Canada	2014	87,600 (The Health Improvement Network (THIN) database)	Epidemiological, preclinical, and clinical studies provide strong support for the potential of metformin as a therapeutic agent in cancer treatment.	(11)
Wenhui Zhu et al.	China	2017	62	Metformin could potentially serve as an effective adjunctive treatment for patients with prostate cancer undergoing androgen deprivation therapy.	(12)
Jason A. Zell et al.	USA	2020	45	In obese individuals with a history of colorectal adenoma, a 12-week course of oral metformin did not lead to a decrease in the levels of rectal mucosa pS6 or Ki-67.	(13)
Casper W F van Eijck et al.	Netherlands	2024	148	The administration of metformin in patients who have undergone pancreatic cancer resection may induce alterations in their immune profiles, potentially improving survival outcomes. This effect may be attributed to a reduction in pro-tumoral M2 macrophages and an increase in dendritic cells that aid in tumor resolution, thereby fostering enhanced antitumor immune responses.	(14)

Table 2. Metformin and Energy Reprogramming in Pancreatic Cancer.

Cellular Response	Description	Reference
Metformin and ATP Production	Metformin is known to interfere with complex I of the electron transport chain (ETC) in the mitochondria, which lowers the synthesis of adenosine triphosphate (ATP) and raises AMP levels. Although metformin reduces ATP levels in cells, the exact kind of cell determines how this action is felt.	(42)
Metformin and ROS Production	Metformin has been shown to reduce the production of reactive oxygen species (ROS) in specific cell types, likely through the activation of AMPK. This reduction in ROS generation is believed to play a role in metformin's anti-inflammatory and antioxidant properties.	(43)
Metformin and the AMPK/mTORC1 Axis	Metformin exhibits a multifaceted interaction with the AMPK/mTORC1 pathway. It activates AMPK, which subsequently inhibits mTORC1, a key regulator of growth sensitive to nutrient levels. However, metformin also has the capacity to suppress mTORC1 through mechanisms that do not rely on AMPK activation.	(37)

potentially improving the prognosis for patients with pancreatic cancer (48, 49).

Specifically, metformin use may lower the abundance and activity of pro-tumoral M2 macrophages, which contribute to tumor growth and metastasis by inhibiting immune responses and promoting angiogenesis. In contrast, metformin has been found to enhance the recruitment and effectiveness of dendritic cells that help resolve tumors. These cells are essential for initiating and modulating the immune response against cancer cells (50, 51).

In addition to these effects, metformin has been found to exhibit further anti-cancer properties. For example, it is suggested that metformin may enhance the body's immune defense against cancer cells, further reinforcing its potential as a therapeutic agent in cancer treatment (52). Moreover, metformin may influence the tumor microenvironment, rendering it less conducive to cancer

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Table 3. Summary of Recent Studies about metformin Effects.

First author	Country	Study design	Key findings	Result	Reference
Casper W F van Eijck et al.2024	Netherlands	Observational study	Metformin boosts antitumor immunity and improves prognosis in upfront resected pancreatic cance	Users of upfront resected metformin had a greater 5-year OS rate of 19% compared to 5% and a higher median overall survival (OS) of 29 vs. 14 months.	(14)
Jian Hu et al.2023	China	Meta-analysis	Metformin use can reduce the risk of pancreatic cancer in patients with type 2 diabetes	Overall analysis revealed that using metformin might lower the incidence of pancreatic cancer in people with type 2 diabetes when compared to not taking it (OR = 0.82, 95% CI (0.69, 0.98).	(8)
Rukaia Sheneeb et al.2022	Libya	In vitro study	Metformin inhibits pancreatic cancer cells growth in a concentration and time-dependent manner	Metformin inhibits pancreatic cancer cell proliferation in a dose-and time-dependent manner. Additionally, it modifies gene expression, causing PanIN cells to have lower levels of TNFα and IKKβ whereas PDAC cells have higher levels of TNFα and lower levels of IKKβ.	(66)
Lauren O'Connor et al .2024	USA	Meta-analysis	Metformin may be associated with a decreased risk of many cancer types, but high heterogeneity and risk of publication bias limit confidence in these results	In case-control studies (RR=0.55, 95% CI=0.30 to 0.80) and cohort studies (RR=0.65, 95% CI=0.37 to 0.93), metformin usage was found to lower total cancer risk in 166 investigations. Additionally, it lowered the risk of hematologic (RR=0.87, 95% CI=0.75 to 0.99), urologic (RR=0.88, 95% CI=0.78 to 0.99), and gastrointestinal (RR=0.79, 95% CI=0.73 to 0.85) cancers. Significant publication bias was found, which is noteworthy (Egger P<.001).	(67)
Andreea Petrasca et al.2023	Ireland	in vivo study.	Changes may be brought about by metformin through the AMP-activated protein kinase (AMPK)–mammalian target of rapamycin (mTOR) pathway, which is connected to glycolysis and protein synthesis, and the NLR family pyrin domain containing 3 (NLRP3) inflammasome.	research elucidates metformin's workings in HS. Its anti-inflammatory properties endorse its therapeutic use in HS, and its impact on immunometabolism indicates metabolic targeting as a potential treatment for inflammatory conditions, including HS.	(68)

growth and metastasis. These additional mechanisms further emphasize the potential of metformin as a promising therapeutic agent in cancer treatment (53).

Nevertheless, further investigation is necessary to fully understand these mechanisms and establish the most effective use of metformin in cancer therapy. Consequently, ongoing and upcoming research is expected to offer additional insights into the potential advantages and applications of metformin in oncology.

4.6. Metformin and Cell Cycle Arrest in Pancreatic Cancer

Metformin has been demonstrated to impede cell proliferation by triggering cell cycle arrest in several cancer cell models. In particular, it has been observed to cause cell cycle arrest at the G0/G1 phase in various pancreatic cancer cell line models. Additionally, some studies have shown that metformin can induce both G0/G1 and G2/M phase arrest, effectively hindering cell growth (47).

The mechanism through which metformin induces cell cycle arrest is believed to involve the downregulation of cyclin D1, a critical regulator of the cell cycle. Furthermore, metformin has been found to upregulate the expression of the tumor suppressor p53, which plays a vital role in

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regulating the cell cycle and inhibiting cancer development (54).

4.7. Metformin and Transcription Factors in Pancreatic Cancer

Transcription factors are proteins that regulate the transcription of genetic material from DNA to messenger RNA. These factors are essential in modulating gene expression, which in turn governs numerous cellular processes such as cell growth and differentiation. In cancer, dysregulated activity of transcription factors can result in unchecked cell proliferation and tumor progression (55). Metformin has been shown to reduce the activity of several transcription factors, including those from the Specificity Protein (Sp) family, such as Sp1, Sp3, and Sp4. These transcription factors are crucial in regulating genes associated with cell growth, survival, and angiogenesis. By inhibiting the activity of these factors, metformin may effectively hinder the growth and proliferation of pancreatic cancer cells (56).

4.8. Mechanism of Action

The mechanism through which metformin downregulates transcription factors is believed to involve the inhibition of mitochondrial ATP production, which results in a reduction of adenosine triphosphate (ATP) levels and an increase in AMP levels. This elevation in AMP activates AMP-activated protein kinase (AMPK), which subsequently inhibits the mammalian target of rapamycin complex 1 (mTORC1). mTORC1 plays a critical role in regulating protein synthesis and cell growth, and its suppression can lead to the downregulation of various transcription factors **(Figure 1)** (56). In addition, the summary effect if metformin demonstrated in **Table 3**.

4.9. Metformin and Cancer Stem Cells

Numerous studies have documented the impact of metformin on the growth of various cell types (57). Additionally, it has been noted that metformin does not impact the survival of most cells at lower doses, suggesting that it is safe and exhibits minimal toxicity (58). However, the exact mechanisms by which metformin regulates the inhibition of cancer cells still require further exploration. Cancer stem cells are essential in driving tumor growth and its progression (59). Metformin demonstrates the ability to inhibit tumor growth, a property observed in both controlled laboratory environments (in vitro) and in living organisms (in vivo). This suggests that metformin's therapeutic potential may extend beyond its conventional role in managing diabetes, positioning it as a potential treatment for various forms of cancer (60). Additionally, studies have shown that Metformin can hinder tumor angiogenesis—the process through which new blood vessels are formed to support tumor growth—in a mouse model designed for pancreatic cancer research. This indicates that Metformin may help control the progression and metastasis of pancreatic cancer by disrupting the tumor's blood supply (61, 62).

4.10. Metformin and the Tumor Microenvironment

The diverse roles of tumor-infiltrating lymphocytes (TILs) can significantly influence the progression of various cancer types. In particular, a higher presence of cytotoxic CD8+ TILs, often referred to as CTCs, is commonly associated with improved overall survival outcomes (63).
Conversely, an increased presence of immunosuppressive CD4+ regulatory T cells (Tregs) in the tumor microenvironment (TME) is frequently associated with poorer prognosis. These Tregs have the ability to inhibit immune responses, thereby facilitating the tumor's escape from the body's immune surveillance (64).
In essence, this describes an immune-resistant tumor microenvironment (TME), where cancer cells manage to evade immune-induced apoptosis. This ability to bypass immune responses fosters the survival and growth of tumor cells, playing a critical role in cancer progression and presenting a significant challenge for therapeutic interventions (65).

4.11. Recent study about metformin

Type 2 diabetes (T2D) has been linked to an increased risk of certain malignancies, such as breast, colon, prostate, kidney, and pancreatic tumors, according to recent studies. The growth-promoting effects of persistent hyperinsulinemia, which arises from insulin resistance in type 2 diabetes, are primarily responsible for this elevated cancer risk. By boosting insulin-like growth factor (IGF) levels, steroid sex hormones, inflammatory processes, and adipokine homeostasis, hyperinsulinemia can indirectly contribute to carcinogenesis as well as directly through the insulin receptor. Furthermore, the link between T2D and cancer risk may be facilitated by persistently high plasma glucose levels **(Cellular and molecular mechanisms of metformin: an overview).**
Given this, extensive epidemiological research has examined the possible contribution of metformin, a medication frequently used to treat type 2 diabetes, to lowering the risk of cancer and cancer-related death. Metformin use was associated with a lower risk of cancer,

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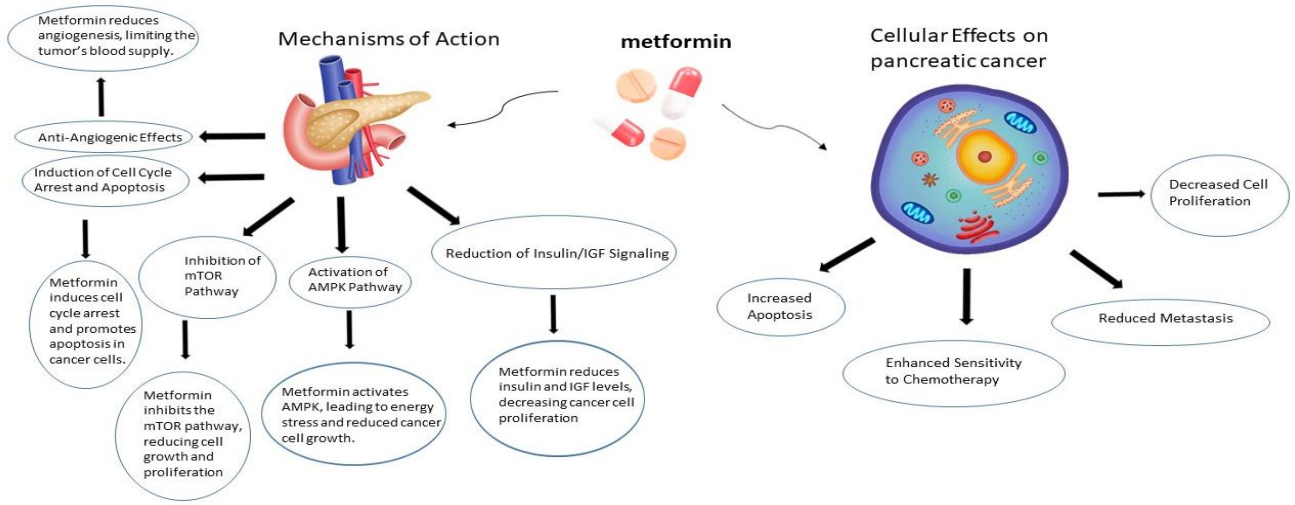

Figure 1. Molecular Mechanisms of Metformin.

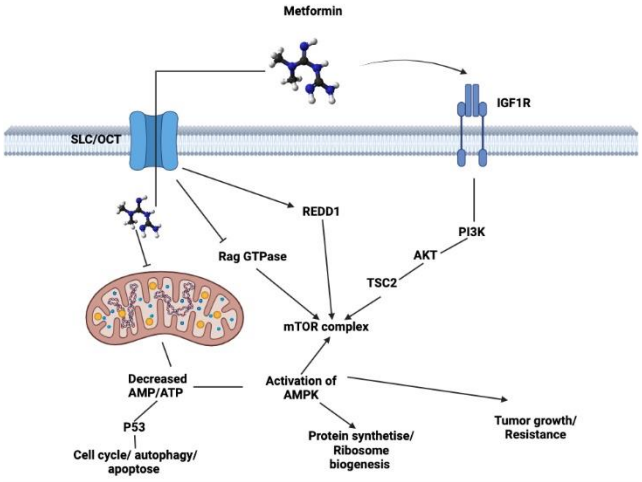

Figure 2. The molecular interactions and effects of metformin within cancerous cellular environments have garnered significant attention in recent years. Specifically, metformin exerts a direct inhibitory influence on complex I of the electron transport chain located within the mitochondria, which consequently leads to a noteworthy reduction in the ATP/AMP ratio while simultaneously facilitating the activation of AMP-Activated Protein Kinase (AMPK), as illustrated in Figure 2. The activation of AMPK plays a crucial role in inhibiting the mechanistic target of rapamycin (mTOR) and stimulating the tumor suppressor protein P53, which collectively influences a variety of subsequent cellular processes that are vital for maintaining cellular homeostasis and regulating growth. Moreover, metformin demonstrates an ability to inhibit mTOR through mechanisms that do not rely on AMPK, engaging instead with Rag GTPases and the regulated in development and DNA damage responses protein 1 (REDD1), thereby elucidating its multifaceted role in cellular signaling pathways. Additionally, the systemic effects of metformin contribute to a decrease in insulin availability, which indirectly modulates the proliferative signaling pathway involving phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT), further implicating metformin in the intricate regulation of cancer cell metabolism and growth. The terms used in this discourse include AMP, which stands for Adenosine Monophosphate; AMPK, referring to AMP-Activated Protein Kinase; ATP, denoting Adenosine Triphosphate; IGF, indicating Insulin-like Growth Factors; IGF-R, which represents Insulin-like Growth Factor Receptor; mTOR, known as the Mammalian Target of Rapamycin; OTC, denoting Organic Cation Transporter; PI3K, which stands for Phosphoinositide 3-kinase; REDD1, referring to Regulated in Development and DNA Damage Responses 1; SLC, which represents Solute Carrier Transporter; and TSC2, known as Tuberous Sclerosis Complex 2. This comprehensive understanding of metformin's molecular effects on cancer cells underscores its potential therapeutic implications, particularly in the realm of cancer treatment and metabolic regulation. Such insights are foundational for developing innovative strategies aimed at leveraging metformin's properties for improved clinical outcomes in oncology. The synthesis of these findings not only enhances our comprehension of cancer biology but also opens avenues for further research into the pharmacological applications of metformin in various malignancies. The visual representation created in BioRender offers an illustrative aid to encapsulate these intricate biological pathways and mechanisms, thereby enhancing the overall academic discourse surrounding the subject matter.

according to a pilot case-control research that included a cohort of 12,000 T2D patients. The incidence of cancer was shown to be dose-dependently related to the length of time that metformin exposure occurred. Similar results from observational and retrospective studies also point to a lower incidence of cancer mortality and neoplastic illnesses in T2D patients on metformin. In particular, taking metformin has been linked to a significant lower risk of developing some malignancies, including breast, prostate, and pancreatic cancer. These clinical observations are supported by in vitro and in vivo studies demonstrating the antiproliferative effects of metformin on various cancer cell lines (**A review for clinicians: Prostate cancer and the antineoplastic properties of metformin.**).

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The ability of metformin to raise insulin and blood glucose levels, which would lessen the tumor-promoting effects of hyperinsulinemia, is one tenable explanation for its anticancer properties, even if the exact mechanisms behind these actions are still not fully known. Reductions in circulation insulin levels have been associated with tumor development prevention in animal models of diet-induced hyperinsulinemia. Furthermore, one possible explanation for metformin's anticancer effectiveness is that it lowers IGF-1 levels, which are frequently increased in hyperinsulinemic situations. Studies demonstrating that calorie restriction dramatically lowers the incidence of cancer in mouse models by lowering insulin and IGF-1 levels provide more credence to this theory (**Targeting ageing and preventing organ degeneration with metformin.**).

Metformin appears to have direct antitumoral effects via activating the LKB1/AMPK pathway in addition to its effects on insulin and IGF-1. One important regulator of protein synthesis and cell division, mTORC1 signaling, is inhibited by AMPK activation. The antiproliferative impact of metformin is partially reversed in breast and ovarian cancer cell types by siRNA-mediated AMPK knockdown, highlighting the critical role that AMPK plays in mediating these effects. Further supporting its anticancer effects is the fact that metformin's activation of AMPK has been demonstrated to inhibit fatty acid production, which is frequently increased in cancer cells **(Inhibition of mTORC1 through ATF4-induced REDD1 and Sestrin2 expression by Metformin.) (Metformin inhibits growth of human non-small cell lung cancer cells via liver kinase B-1-independent activation of adenosine monophosphate-activated protein kinase.).**

Because metformin inhibits inflammatory responses through AMPK activation, it may potentially control inflammation, a critical component in the development of cancer. Furthermore, by decreasing levels of vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor-1 (PAI-1), two factors involved in the development of blood vessels in tumors, metformin has been shown to decrease neoplastic angiogenesis. These side effects suggest that metformin inhibits tumor development and metastasis through a multifaceted, intricate mechanism (**Targeting ageing and preventing organ degeneration with metformin.**).

The antineoplastic activity of metformin is not exclusively reliant on AMPK activation, despite its positive benefits. The adaptability of metformin's anticancer capabilities is demonstrated by the fact that it has been demonstrated to inhibit the oncoprotein HER2 in some situations, such as in breast cancer cells, through an AMPK-independent mechanism. Furthermore, metformin's promise as an anticancer drug is further supported by its capacity to cause cell cycle arrest and increase cell death through both caspase-dependent and caspase-independent pathways, such as activation of apoptosis-inducing factor (AIF) and poly(ADP-ribose) polymerase (PARP).

In conclusion, metformin is a viable option for cancer therapy due to its capacity to lower insulin levels, activate AMPK, and alter metabolic and inflammatory pathways, even if the precise mechanisms behind its anticancer benefits are still being studied. It is anticipated that additional study will clarify the entire range of its effects and offer more information about its possible clinical uses in cancer.

5. FUTURE PERSPECTIVE

The potential of metformin as an adjunct therapy for pancreatic cancer presents an exciting avenue for future research. As our understanding of the molecular mechanisms underlying metformin's anticancer effects deepens, several key areas warrant further investigation:

1. **Mechanistic Elucidation**: Future studies should aim to comprehensively delineate the molecular pathways influenced by metformin, particularly its interactions with the AMPK/mTOR axis, energy reprogramming, and immune modulation. Advanced techniques such as single-cell RNA sequencing and proteomics could provide granular insights into these mechanisms.
2. **Clinical Trials**: While epidemiological data and preliminary clinical studies suggest a protective role for metformin, large-scale, randomized controlled trials are essential to validate these findings. Future trials should focus on optimal dosing regimens, patient stratification based on genetic and metabolic profiles, and combination therapies with existing chemotherapeutics.
3. **Biomarker Development**: Identifying biomarkers predictive of response to metformin could enhance patient selection and treatment efficacy. Research into metabolomic and genetic markers associated with metformin sensitivity in pancreatic cancer could facilitate more personalized therapeutic approaches.
4. **Combination Strategies**: Exploring the synergistic effects of metformin with other anticancer agents, including immunotherapies and targeted therapies, could uncover novel combination strategies that enhance treatment outcomes. Preclinical models

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should be utilized to identify promising combinations before clinical translation.

5. **Long-term Outcomes and Safety**: Given the chronic nature of metformin use in diabetic populations, long-term studies are needed to assess the safety and potential adverse effects of prolonged metformin therapy in cancer patients. Monitoring for metabolic disturbances, gastrointestinal side effects, and other potential risks is crucial.

6. **Translational Research**: Bridging the gap between laboratory findings and clinical application remains a significant challenge. Future research should prioritize translational studies that validate preclinical findings in human subjects, ensuring that promising molecular insights are effectively translated into therapeutic innovations.

In conclusion, the exploration of metformin as a potential therapeutic agent in pancreatic cancer is at a promising but nascent stage. Continued multidisciplinary research efforts, integrating molecular biology, clinical oncology, and pharmacology, are essential to unlock the full therapeutic potential of metformin in this challenging malignancy.

6. CONCLUSION

In conclusion, metformin shows promise as a potential treatment for pancreatic cancer by activating the AMPK pathway, inhibiting the mTOR pathway, and modulating mitochondrial metabolism. These mechanisms reduce cancer cell proliferation and impact the tumor microenvironment. While these findings are promising for both molecular and clinical research, extensive further investigation is needed to fully validate metformin's efficacy and safety in treating pancreatic cancer. Continued research is essential to confirm these results and understand the long-term effects of metformin in cancer therapy.

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Conflicts of interest

The authors report there are no competing interests to declare

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