

Review Article 

Biochemistry, Pathophysiological Perspective, and Therapeutic Advances in Diabetes, Obesity, and Pancreatic Cancer

P. Balaji¹, Ram Prasad P. L.², Patibandla Jahnvi³, Malarkodi Velraj⁴, Anuradha Averineni⁵, Shaik Mobeen⁶, Nithin Vidiyala⁷, A. Venkata Badarinath^{8,*}

¹Department of Pharmacology, School of Pharmaceutical Sciences, VELS Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai - 600117, India

²Department of respiratory Medicine, Vels Medical College and Hospital, Manjankaranai, Thiruvallur 601102, India

³Department of Pharmaceutics, KVSR Siddhartha College of pharmaceutical sciences, Vijayawada, Andhra Pradesh India

⁴Department of Pharmacognosy, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Old Pallavaram, Chennai 600117, India

⁵KL Business school, Koneru Lakshmaiah Education Foundation, Vaddeswaram, Guntur-522502, India

⁶KL college of Pharmacy, KLEF (Deemed to be University), Guntur, Andhra Pradesh, India

⁷Principal Scientist, Cerevel therapeutics, 222 Jacobs St. Suite 200, Boston, Massachusetts 02141, United States

⁸Department of Pharmaceutics, Santhiram College of Pharmacy, Autonomous, NAAC Accredited with A+, NH 40, Nerawada, Nandyal 518112, Nandyal District, Andhra Pradesh, India



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ABSTRACT

Diabetes, obesity, and pancreatic cancer are interconnected diseases that share overlapping biochemical and molecular pathways, presenting formidable challenges for global healthcare. This review examines their complex link through a biochemical lens, emphasizing shared pathophysiological mechanisms such as insulin resistance, chronic inflammation, oxidative stress, and dysregulated metabolic signaling. The bidirectional relationship between type 2 diabetes and pancreatic cancer has been explored, and obesity has been identified as a critical mediator influencing hormone secretion, adipokine balance, and energy metabolism. Key molecular pathways, including the PI3K/Akt/mTOR and JAK/STAT axes, as well as alterations in glucose and lipid metabolism, are discussed in terms of their roles in tumorigenesis and metabolic dysfunction. The review also evaluates current and emerging therapeutic strategies, including metabolic reprogramming, targeted therapies, immunotherapies, and surgical approaches, within the context of the biochemical alterations observed in these conditions. Advances in precision medicine, biomarker discovery, and personalized treatment approaches have been highlighted and supported by innovations in systems biology, gene editing, and artificial intelligence. A deeper biochemical understanding of the interactions between diabetes, obesity, and pancreatic cancer holds promise for identifying novel therapeutic targets and improving patient outcomes in this multifactorial disease landscape.

*Corresponding Author: A. Venkata Badarinath(avbadrinatha@gmail.com)



P. Balaji: He is a professor of Pharmacology at VISTAS, Chennai, with 18 years of academic and research experience. He holds his B.Pharm, M.Pharm, and Ph.D. from Annamalai University under the UGC-JRF MRP program. A university rank holder in both UG and PG, he has published over 65 research articles in reputed journals. In 2024, he was appointed as FAPP (National Coordinator) in the Molecular Pharmacology Division. Dr. Balaji is a dedicated mentor known for his academic excellence and research leadership.



Ram Prasad P. L.: He is currently working as an assistant professor in the Department of Respiratory medicine at Vels Medical College and Hospital. He has been invited as guest speaker & faculty in various national conferences. He is an active member of European respiratory society (ERS) and Indian Chest Society (ICS). His areas of interests include pulmonary infectious diseases and airway disorders.



Patibandla Jahnvi: She is an assistant professor at KVSRR Siddhartha College of Pharmaceutical Sciences, Vijayawada. She holds a Master's degree from JSS University, Mysore, and a Bachelor's from Sri Ramachandra University, Chennai. Currently, she is pursuing her PhD degree from Galgotias University, Uttar Pradesh. She has authored several national and international publications and holds patents. Her dedication to teaching and research makes her a valuable asset in pharmaceutical science.



Malarkodi Velraj: M.Pharm., Ph.D., Professor and Head, Department of Pharmacognosy, SPS, VISTAS, with 30 years of teaching and research experience. Published 65 numbers of research articles, 6 patents, 10 book chapters, 4 books, and many awards. Appointed as National Head for the App Natural Products Research Development Division from the year 2024.



Anuradha Averineni: She is an assistant professor at KL Business School, KLEF, Vaddeswaram, with over 22 years of teaching experience in Human Resources and Soft Skills. She earned her Ph.D. degree from Rayalaseema University in 2017 and has published a book on Industrial Relations. Her areas of interest include HRM, Organizational Behaviour, Stress Management, and Marketing. She has presented at numerous national and international conferences and published 30 articles in UGC CARE and Scopus-indexed journals.



Shaik Mobeen: M.Pharm., Ph.D., an associate professor, Department of Pharmaceutics, KL College of Pharmacy, Koneru Lakshmaiah Education Foundation (Deemed to be University), Guntur, with 15 years of teaching and research experience. Published 8 numbers of research articles, 2 patents, 2 book chapters, and 1 award.



Nithin Vidiyala: He is a seasoned pharmaceutical professional with over 15 years of experience in drug development. He has advanced multiple small and large molecule drug candidates from discovery to clinical trials. His expertise spans medicinal chemistry, biologics, and regulatory pathways. He is known for his innovative approach and effective cross-functional collaboration. Nithin remains dedicated to developing impactful therapies that enhance patient outcomes



A. Venkata Badarinath: He is a professor and Head of the Department of Pharmaceutics at Santhiram College of Pharmacy. He is the founder of the popular YouTube channel *Pharma Tricks for Exams* and its companion mobile app. With a passion for pharmaceutical education, he has created accessible learning resources for pharmacy students. His contributions have made a significant impact on exam preparation in the field of pharmaceutics. Dr. Badari Nath continues to inspire learners through his academic leadership and digital initiatives

Content

1. Introduction
2. Obesity and Diabetes Lead to PC
 - 2.1. Enhanced PC risk is associated to T1DM, T2DM, and T3cDM
 - 2.2. Risk factor of obesity and pancreatic cancer
3. Development of Obesity and Pancreatic Cancer
4. Genetic Associations among Diabetes, Chronic Pancreatitis, and Pancreatic Cancer
5. Obesity and Inflammation Associated with Pancreatitis in PDAC Formation
6. Biochemistry of Diabetes and Pancreatic Cancer
7. Diabetes and Pancreatic Cancer
 - 7.1. Pathophysiology of diabetes affected by pancreatic cancer
 - 7.2. Diagnosis of diabetes due to pancreatic ductal adenocarcinoma
8. Interaction of Obesity, Diabetes, and Pancreatic Ductal Adenocarcinoma
9. Processes by Which Obesity and Type 2 Diabetes Raise the Risk of Pancreatic Ductal Adenocarcinoma
10. Impact of Type 2 Diabetes and Obesity on the Pancreatic Microenvironment: Stellate Cells and Islets' Interaction
11. Chemoprevention of Pancreatic Cancer
12. Function of Diabetes Medications in Pancreatic Cancer
 - 12.1. Effect of metformin
 - 12.2. Thiazolidinediones, PC therapy, and PPAR- γ ligands
13. Early detection of Premalignant Cancers and their Therapy
14. Developments in the Field of Surgery
15. Conclusion and Future Perspectives

1. Introduction

Pancreatic cancer (PC) is a lethal disease with a bleak prognosis, ranking fourth among cancer-related deaths in the US. Being overweight and having diabetes, particularly type-2 diabetes (T2DM), are associated with a higher risk, causing public health concerns [1]. The pancreas is comprised of exocrine and endocrine cells. Endocrine cells release insulin, glucagon, and somatostatin, whereas exocrine cells secrete digestive enzymes. PC is a highly fatal cancer, with approximately 95% of cases originating from exocrine cells. Early diagnosis of PC is challenging because of the absence of symptoms and the deep retroperitoneal

location of the pancreas. The term used to refer to this type of cancer is pancreatic ductal adenocarcinoma (PDAC), which has a 5-year survival rate of approximately 7.2% in the US [2]. In recent years, there has been a substantial increase in the incidence of T2DM and obesity in Western countries. The relationship between obesity, T2DM, and PC is complex. By 2040, it is expected that the death rate from PC will have increased dramatically due to increased rates of obesity, diabetes, alcohol abuse, and an unhealthy lifestyle. Diabetes and obesity are factors that lead to the development of pancreatic tumors, with metabolism and the micro-environment influencing carcinogenesis. Modifiable lifestyle risk factors may reduce the population-level PC risk [3].

PC has emerged as the third most significant contributor to cancer-related fatalities, resulting in approximately 44,330 deaths out of an expected 55,440 new cases in 2018 [4].

The individual's probability of having PC over their lifetime is 1.6%, and it is projected to exceed that of colon cancer in terms of death by 2030 [5]. Prostate cancer is often detected at an advanced stage and is characterized by the spread of cancer cells to distant organs, such as the liver, lung, lymph nodes, and peritoneal cavity [6]. Regrettably, 85% of tumors cannot be surgically removed based on the way the disease is shown [7,8].

This leads to a bleak outlook and a significant likelihood of death in the absence of appropriate chemotherapy and radiotherapy. PDAC risk factors include advanced age (with a notable prevalence among the senior population), male sex (with a higher occurrence in men), genetic abnormalities, tobacco smoking (accounting for approximately 25% of all PC cases), obesity, chronic pancreatitis, and diabetes [9,10].

Obesity is an epidemic that has become a major global issue. It results from alterations in lifestyle (inactivity, high-fat/caloric diet, and high-sugar diet) and is linked to lifestyle factors, including alcohol and cigarette use. Furthermore, chromosomal defects cause syndromic obesity, whereas mutations in the leptin pathway lead to monogenic obesity [11]. Adipose tissue (AT) in the body stores triglycerides (TG) and is classified as brown or white. Brown AT, which is located in the cervical area, generates heat through thermogenesis. White AT stores excess fat in the subcutaneous and retroperitoneal cavities [12].

PC is a growing malignancy with a connection between obesity and diabetes. Diabetes may serve as both a potential indicator and a symptom, while being overweight is closely associated with an elevated PC risk. The symposium reviewed energy metabolism, diabetes, obesity, inflammation, immune system dysfunction, and therapeutic resistance [13].

This review emphasizes the need for a multidisciplinary approach to manage diabetes, obesity, and PC, incorporating

immunotherapies, targeted treatments, biomarker identification, personalized medicine, and innovative therapies.

2. Obesity and Diabetes Lead to PC

2.1. Enhanced PC risk is associated with T1DM, T2DM, and T3cDM

Diabetes mellitus (DM) and PC (**Figure 1**) are related, and recently, research has shown that approximately 85% of patients with PC also have diabetes [14].

Hyperglycemia is a metabolic disease known as DM. However, the three most prevalent DM subtypes differ significantly in terms of their metabolic and hormonal features [15]. Severe or complete exogenous insulin is necessary because of the lack of endogenous insulin synthesis and injection related to T1DM. Due to peripheral insulin resistance in the body, which is often associated with obesity, hyperglycemia and hyperinsulinemia coexist in T2DM. T3cDM is characterized by an extreme lack of all glucoregulatory hormones in the pancreas and is linked to malignant and benign exocrine pancreatic diseases, such as acute and chronic pancreatitis (CP), caused by many factors such as hemochromatosis, cystic fibrosis, surgical removal of the pancreas, pancreatic injuries, pancreatic tumors, fibrocalculous pancreatopathy, and absence of the pancreas [15,16].

Epidemiological research has shown that DM increases the risk of developing several types of cancers, including PC [17-19]. A recent meta-analysis of 35 cohort studies showed that patients with diabetes have a two-fold higher chance of developing PC [20]. A higher relative risk for the relationship between PC and DM was found to be (RR) (RR=1.94; 95% CI: 1.66-2.27), with strong proof of study heterogeneity (I²=93.6%).

Subset analysis demonstrated that the elevated risk (**Table 1**) of PC was unrelated to the research design, sex, geography, body mass index (BMI), and drinking or tobacco consumption patterns. Additionally, there was a negative correlation between PC risk and DM duration, with individuals diagnosed with DM within a year having the highest PC risk.

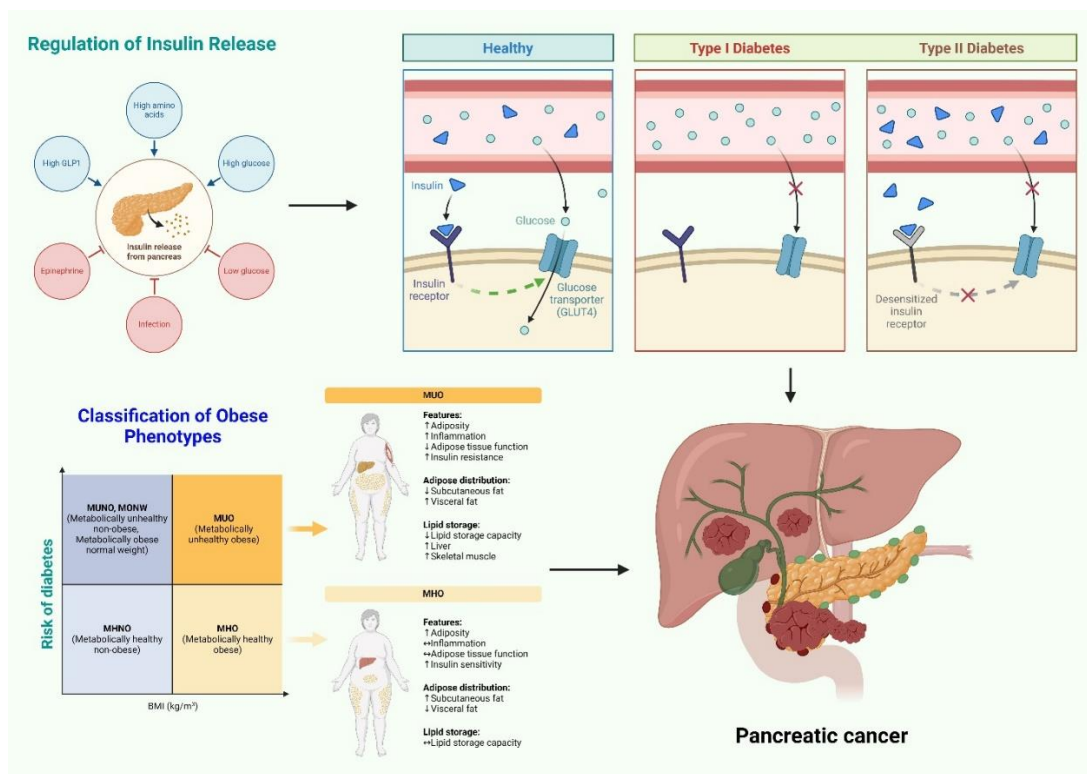


Figure 1. Diabetes and pancreatic cancer interaction

Table 1. Lists of probable etiological factors for pancreatic cancer, the quantity of recognized instrumental single-nucleotide polymorphisms (SNPs), phenotype distribution in the discovery sample, and the percentage of instrument-explained variance

Phenotype	Variance described, %	Mean ± SD	Units used	Number of single-nucleotide polymorphism	Ref.
High-density cholesterol	13.7	53.3 ± 15.5	mg/dL	70	[23]
Height	16.0	169.9 ± 6.9	Cm	567	[24]
Low-density cholesterol	14.6	133.6 ± 38	mg/dL	54	[23]
Body mass index	2.7	27.0 ± 4.6	kg/m ²	96	[25]
Fasting glucose	4.8	5.2 ± 0.8	mmol/L	37	[26]
Waist-to-hip ratio	1.4	1.1 ± 0.1	cm/cm	34	[27]
Fasting insulin	1.2	56.9 ± 44.4	pmol/L	17	[26]

These data suggest that many patients with diabetes had T3cDM or PC-induced diabetes, even though most epidemiological studies did not specify the type of DM. According to a meta-analysis of three recently released studies that compared 2192 PC patients and 5113 controls, there was a 1.8-fold higher incidence of PC in people with T2DM. However, a significant number of individuals who were labeled as having T2DM had T3cDM, which became apparent shortly before cancer was diagnosed [21]. Finally, a new cohort study comparing

211,695 controls to 110,919 individuals with DM offers significant evidence for the etiology of PC being caused by T2DM and hyperinsulinemia [22].

2.2. Risk factors of obesity and pancreatic cancer

In 2003, [18] studied Check using the American Cancer Society database to determine whether obesity affects cancer risk. Extreme overweight (BMI >40) was linked to a 50-60% higher mortality rate from malignancies of the

esophagus, rectum, colon, kidney, liver, pancreas, multiple myeloma, and non-Hodgkin lymphoma in their cohort of more than 900,000 people during 16 years. PC (RR 1.49 for men and 2.76 for women), colorectal cancer (RR 1.84 for men and 1.46 for women), and liver cancer (RR 4.52 for men and 1.68 for women) were the three cancers with the worst outcomes in men and women, respectively. Research on the link between obesity and PC is impacted by the elevated incidence of overweight in T2DM patients and the high proportion of undiagnosed T2DM. More than 80% of T2DM patients also have obesity. Recent epidemiological studies have shown that, independent of the presence of T2DM, a high BMI is associated with a higher risk of several ailments, such as cancers [28], and a separate PC risk factor has been established as having a high BMI [29-32].

Large prospective cohort studies with long follow-up periods have recently been conducted in the USA and revealed a correlation between PC risk and high BMI [33,34], demonstrating that being overweight and obese increases the chance of PC development and eventual mortality. Hyperinsulinemia, food, dietary factors, and further abnormalities of hormones have all been suggested as contributory factors among several potential processes at play. Exercise and calorie restriction have both been demonstrated to lower the risk of PC [29,30]. Studies on the results of bariatric surgery further support the lower risk of PC after weight loss. Comparing operated controls with identical BMI to non-operated controls, a 38% decrease in the Swedish Bariatric Surgery Trial revealed a decrease in cancer-related fatalities [35], and a study comparing 5746 highly obese controls to 1035 patients who underwent bariatric surgery revealed a significant decrease in the need for cancer-related medical treatment [36].

3. Development of Obesity and Pancreatic Cancer

Obesity and being overweight are known to increase the incidence of T2DM, hypertension, and cardiovascular diseases. Epidemiological

research has shown that high BMI puts individuals at a greater risk of acquiring a variety of prevalent cancers, including colorectal, endometrial, breast, pancreatic, and liver cancers [28,31,37-44].

Despite inconsistent or inconclusive results from early epidemiological studies, the majority of prospective epidemiological studies on the subject have found a connection between high BMI and a heightened risk of PC mortality or incidence, regardless of a history of DM [18,29,45-52].

Retrospective methodology, a small sample size, a biased research design, residual or uncontrolled variables including smoking history and gender, and insufficient statistical power, are thought to be some of the causes of the inconsistent early findings [32,52-55]. In 2003, a meta-analysis of six case-control studies, eight prospective studies, and 6391 PC cases was performed to investigate the relationship between high BMI and PC risk [56]. The results revealed a slightly positive connection (2% risk increase for every kg/m² increase in BMI). In 2007, a meta-analysis of 21 prospective trials with 3,495,981 participants and 8062 PC cases was conducted [57].

Ten of the 21 prospective studies originated in the US, nine in Europe, and two in Asia. A nested case-control prospective cohort study was the sole exception to this rule. Thirteen studies included adjustments for cigarette smoking-controlled DM. Because BMI was only divided into two groups (males with high BMI: N25.2 vs. 25.2 kg/m²; females with low BMI: N24.7 vs. 24.7 kg/m²), disregarded was a cohort study involving 63,000 subjects and 166 cases of PC [54] was disregarded. The calculated summary risk ratio (RR) for a 5 kg/m² augmentation in BMI for both genders was 1.12 (95% CI: 1.06-1.17). The aggregate RR did not vary significantly between men and women. As a result, scientists concluded that BMI and PC risk were positively correlated in both males and females. In general, a 12% greater risk of PC was linked to a 5 kg/m² rise in BMI. In another meta-analysis conducted in 2008, 221 datasets were used, containing 282,137 instances of cancer incidence [58].

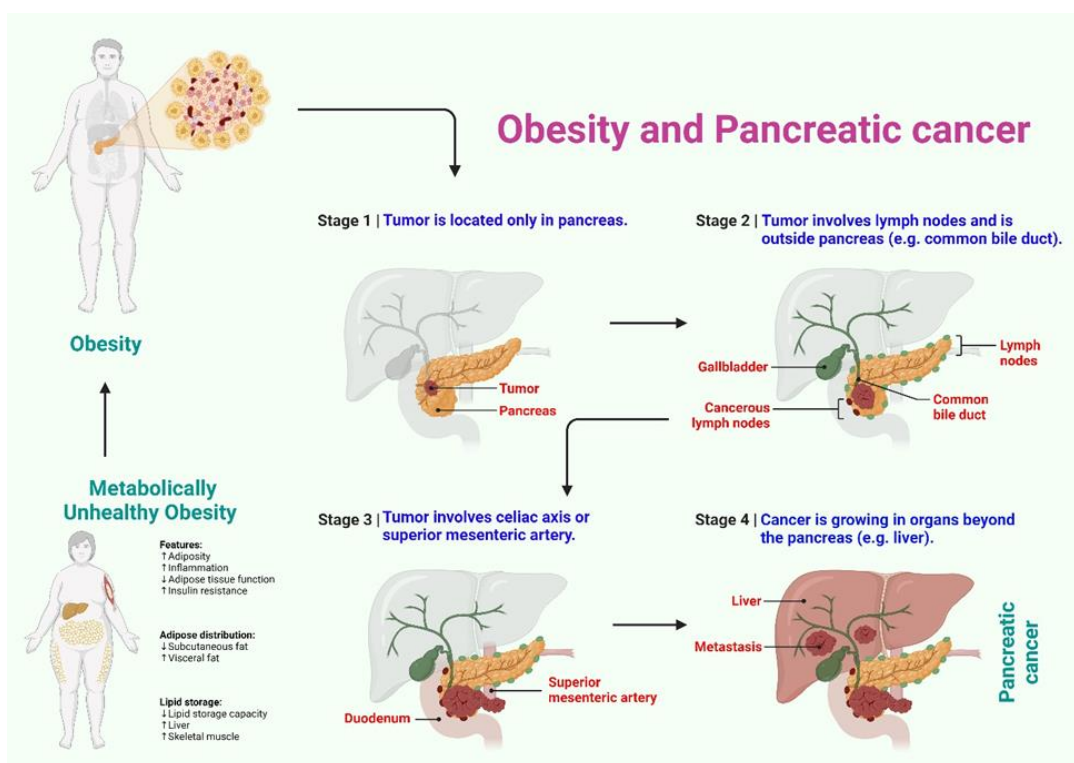


Figure 2. Development of obesity and pancreatic cancer and their stages

The overall sample size was 3,338,001 people who participated in the study on high BMI and risk of PC (2390 male PC cases and 2053 female PC cases). The data demonstrate a slight correlation between the prevalence of PC and high BMI, similar to the 2003 findings (RR, 1.12; CI, 1.02-1.22). A recent extensive prospective cohort study was undertaken in the United States as part of the Women's Health Initiative, involving 138,503 postmenopausal women. This study examined the connection between obesity, specifically central obesity, and PC over 7.7 years of follow-up on average. (n=251) [59]. Females in the top percentile of the waist-to-hip ratio had a 70% increased risk of PC compared to those in the bottom quintile. This implies that an increased risk of PC (Figure 2) is positively related to obesity, particularly central adiposity. A recent case-control study investigated the correlation between an individual's age at risk, high BMI, age at which PC first appears, and the overall prognosis. This study included 841 people with PCs and 754 healthy people [60].

4. Genetic Associations among Diabetes, Chronic Pancreatitis, and Pancreatic Cancer

However, it is the most common cause of T3cDM. or long-standing T2DM that links higher PDAC risk to genetic overlap and a broad range of genetic susceptibility among all three disorders. All three species exhibited genetic variability. Catalogues of genes have been found for each ailment using different study approaches and thorough analyses of case series and families. Because of the many approaches taken to discover genes, it is interesting to note that knowledge of these genes impacts susceptibility in distinct ways, each through a different mechanism. The following traits are shared by all three diseases: there are several signs of common genetic and/or environmental etiologies: 1) subgroups of patients expressing familial clustering or family history; 2) some patients' varying diagnostic ages are associated with familial risk; and 3) there is evidence of a genetic component in certain families. Additionally, epidemiological danger elements are present (for instance, diabetes [fat], alcoholism [CP],

and PDAC]) that might increase the risk by interacting with genetic risk factors. Several methods have been employed to identify susceptibility genes, including large investigations of genome-wide associations (GWAS), without bias, which look for a narrow list of candidate genes, case-control and cohort studies, related single-nucleotide polymorphisms (SNPs) that are frequently noncoding, case-control and cohort studies, and next-generation sequencing are all examples of family-based research. The required analytical techniques for bioinformatics have kept pace with time and have given statisticians the tools they need to analyze the collected data. With over 50 genes implicated, T2DM has a hereditary basis that is best characterized as polygenic [61]. Except in a very few subgroups, the inherited risk of T2DM is not explained by a single major gene. [62].

In contrast, several instances of CP and PDAC families have been well-documented, and GWAS investigations have shown numerous frequent SNPs with poor penetrance that are linked to higher risk, and many mutations in significant genes have been attributed to these mutations. T2DM has received the greatest research attention out of the three disorders, and far more money has been spent on learning about diabetes genetics, which is consistent with the disease's high prevalence and significant financial cost. However, genetic advancements have not yet resulted in ready-to-use therapeutic applications. Numerous studies have demonstrated that diabetes is a complicated, polygenic, and genetically varied disease. The candidate gene method was used to identify PPAR γ and KDNJ11, and association and GWAS methods were used to identify SLC20A8, CDKN2A, FTO, HDF1B, WFS1, and TCF7L2, among others, which are associated with a slightly increased likelihood of developing specific diseases. By adding more details, genetic research establishing subclinical or comparable symptoms as a diabetic basis, researchers have created novel approaches in the search for genes that cause diabetes [63].

Each genetic variation had a relatively small impact on the polygenic risk model that diabetes susceptibility follows. Contrary to popular belief, despite these endeavors, genetic

differences do not provide a considerably better risk assessment than traditional variables that increase risk, including age, sex, familial medical background, BMI, and clinical indicators [64].

Early work in identifying the genetic diversity underlying CP was made possible by family oriented approaches and understanding of the disease pathophysiology, which revealed CASR, CFTR, CTSC, SPINK1, and PRSS1 as susceptibility loci for the disorder [65].

Genetic variations between individuals account for a large portion of the variation in vulnerability to recurring pancreatitis, both in the acute and long-term. Whitcomb et al.'s extensive two-stage GWAS investigation [66] identified PRSS1-PRSS2 and X-linked CLDN2 as sites of susceptibility, with variations in how the latter gene might interact with alcohol consumption. Although alcohol has long been believed to be the main cause of pancreatitis, recent research has shown that a function for hereditary factors may also be possible. These factors include uncommon variations in PRSS1, CFTR, and SPINK1. Thus, several gene variations or the interactions of several genes that are epistatic, together with the stresses, are the main causes of recurrent acute and chronic pancreatitis in the majority of patients. Owing to the logistical difficulties involved in identifying and obtaining bio-specimens for research from patients with poor survival, the investigation of genetic susceptibility to PDAC has proven to be extremely difficult. PDAC has a genetic makeup that differs from those of diabetes and CP. The identified susceptibility genes include both common and uncommon mutations in genes associated with cancer syndromes. Genetic alterations in established syndrome-associated genes, such as CFTR, CDKN2A, BRCA1, and BRCA2, have been discovered using family based and case-control studies. Additional variants, including PALB2, have been identified using next-generation sequencing [67] and *ATM* [68].

More recently, it was discovered that patients with apparent sporadic PDAC also possess germline mutations in important genes [69]. This will likely alter the existing paradigm for risk assessment. SNPs in areas that contain genes for ABO, TERT, and CLPTM1L, among

many other genes, have been linked to pancreatic cancer through GWAS analyses of a significant number of control patients and sporadic cases. However, genetic information does not improve prediction in a broader population, as shown by GWAS SNP-based risk modeling [70].

5. Obesity and Inflammation are Associated with Pancreatitis in PDAC Formation

The risk of cancer, especially PC, is significantly increased by obesity [71]. In fact, the predicted spike in PC could be partly attributed to the overweight pandemic. Obesity may cause (pancreatic) cancer through a variety of processes such as insulin resistance, which results in hyperinsulinemia and inflammation [72].

In a genetically modified mouse model, non-steroidal anti-inflammatory medicines prevented pancreatic cancer from spreading, highlighting the significance of tissue inflammation in this condition [73]. It is believed that tissue inflammation caused by obesity fosters a favorable milieu for tumorigenesis and/or promotion. Recent research has shown that visceral adiposity has a substantial connection with metabolic disorders and gastrointestinal malignancies, including PC, in addition to assessments of general obesity, such as BMI [74].

In comparison to the peri-gonadal depot, the adipose tissue in the mesentery around the peri-pancreatic deposit of the pancreas has a significantly increased diet high in calories and fat, which causes an inflammatory reaction [75].

Understanding diet-induced obesity-specific responses in adipose tissue depots is crucial for understanding the link between body types and cancer risk, as a diet rich in calories and fats increases PC prevalence [76,77].

6. Biochemistry of Diabetes and Pancreatic Cancer

Research shows that 47% of patients with PDAC have diabetes compared to 7% of control participants, and only 14% have typical fasting blood sugar levels [14]. When the tumor is

often imaged with radiography, 74% of PDAC patients have diabetes diagnosed sooner than 24 months before having the condition [78]. Tumors usually cause new-onset diabetes in individuals and potentially serve as useful biomarkers for PDAC detection. Diabetes prevalence in PDAC is higher than that in other malignancies, with 68% of patients having diabetes, compared to 14.8-23.5% of prostate, lung, colon, and breast cancer patients and age-matched controls [79].

Additionally, while both PDAC and diabetic patients exhibit high levels of insulin resistance, most PDAC patients mention weight reduction as opposed to weight gain. Before PDAC is diagnosed, it exhibits clinical signs of poor glycemic control and weight loss that are unusual for T2DM. These signs should notify the doctor of the likelihood of diabetes linked to PDAC. The evidence that newly diagnosed diabetes is linked to PDAC may disappear after tumor removal, whenever the remaining pancreatic tissue contains adequate islets may be the most convincing factor. Due to the reduction in islet mass, T3cDM is known to be caused by pancreatic resection and is observed in approximately 50% of patients following proximal pancreatectomy. The removal of certain pancreatic tumors improves the condition of some patients with diabetes [80].

A study was conducted with 104 patients who underwent PDAC resection, of whom forty-one had diabetes at the time of surgery, and found that 57% of those who had recently developed diabetes saw an improvement in their condition postoperatively, while all of those who had long-standing diabetes continued to experience their condition after pancreatic resection [14]. These results show that PDAC-related new-onset diabetes is perhaps a paraneoplastic disease, in which one or more variables are brought about by the interference of cancer with insulin synthesis or activity. Several studies have focused on identifying the mechanism(s) and/or genetic and/or protein indicators of PDAC-induced diabetes. The gap junction protein connexin 26 has been noted to be significantly over-expressed in the islets of PDAC patients with diabetes [81], and Basso *et al.* identified an S-100A8 N-terminal peptide

generated from PDAC as a factor contributing to diabetes [82].

Huang *et al.* [83] found that Vanin-1, as well as matrix metalloproteinase 9, have been characterized as two elevated genes associated with new-onset diabetes in 27 PDAC patients, and many miRNA fragments have been proposed as potentially effective predictors [84].

Chari *et al.* [85] found that the lower insulin secretion and sensitivity observed in PDAC diabetes may be caused by adrenomedullin, a peptide present in exosomes generated from PDAC, according to a theory put forth by Mayo Clinic researchers. A multifunctional vasoactive peptide known as adrenomedullin has been linked to sepsis and inflammation and is overexpressed in PDAC [85].

7. Diabetes and Pancreatic Cancer

7.1. Pathophysiology of diabetes affected by pancreatic cancer

Growing evidence suggests that PDAC commonly results in DM [85]. Almost 85% of patients with PDAC have diabetes or hyperglycemia, which commonly occurs up two to three years before being diagnosed with cancer [85]. Furthermore, within one to three years of developing diabetes, persons with newly diagnosed diabetes had a 5- to 8-fold greater chance of having PDAC identified [85]. Ironically, this type of DM develops despite persistent, usually significant weight reduction, and frequently moves away once malignancy is removed [85,86]. One of the numerous theories explaining how PDAC results in DM is a paraneoplastic syndrome caused by one or more tumor-producing substances that result in insulin sensitivity and insufficient beta cell responsiveness to stimuli, which eventually results in beta cell failure [86].

This idea is supported by laboratory studies showing that the supernatant from cultivated PDAC cell lines decreases insulin production in addition to clinical and epidemiological findings. Similarly, PDAC exosomes prevent insulin release. These effects were linked to adrenomedullin in several studies [87,88].

Moreover, the fact that exosomopathy underlies PDAC-DM has been proposed [89,90].

If this finding is confirmed, it may be employed as a biomarker for early PDAC diagnosis in individuals who have just been diagnosed with diabetes. The difficulty in creating PDAC-DM animal models has been a barrier to advancement in this field. Understanding the cellular processes of PDAC-induced DM is predicted to result in the generation of a biomarker that may enable the early diagnosis of PDAC, given that hyperglycemia is one of the first, if not the earliest, harbingers of PDAC [91]. The early identification of PDAC in patients with newly developed DM and hyperglycemia may be achieved by distinguishing T2DM from diabetes caused by PC. Furthermore, the effects of compounds generated by the tumor, insulin secretory deficiencies, can also be brought on by activated PSCs, a problem with the secretion of incretin, or the suppressive impact of cytokines released by macrophages that the tumor attracted to the pancreas. In a model of PSC/beta cell co-culture, beta cell dysfunction and programmed cell death have been demonstrated [92].

In models of pancreatitis-induced pancreatogenic diabetes, interferon has also been shown to temporarily reduce the movement of the transcription factor pancreatic duodenal homeobox 1 into the cell nucleus [87]. The availability of hepatic IRs is regulated by islet peptide pancreatic polypeptide (PP), a crucial part of insulin control over glucose homeostasis [93]. Hepatic insulin resistance has been demonstrated to be reversible by PP deficiency [94] and recent research has shown a connection between PP deficiency and PDAC [95,96].

Insulin sensitivity of the B kinase subunit can be decreased with the help of inflammatory cytokines such as nuclear factor inhibitor [97] or the depletion of peptide IR availability mediators in the liver, such as PP [98]. PP and insulin are released when glucose-dependent insulinotropic polypeptide is a type of incretin [99]. PP and insulin release are induced by acting as an incretin, such as glucose-dependent insulinotropic polypeptide (GIP) [96].

7.2. Diagnosis of diabetes due to pancreatic ductal adenocarcinoma

Detecting PDAC-DM is challenging because of the limited number of individuals over 50 who will develop it within two–three years. Various strategies have been used to differentiate between T2DM and pancreaticogenic diabetes, with studies showing CA 19-9 levels can be elevated for up to 24 months [100].

Moreover, PDAC has reduced thrombospondin 1 levels [101]. The Liverpool ensemble discovers highly discriminating T3cDM proteins by mixing them with different markers. PANDIA conducted the UK's first bio-bank for PDAC identification. Lund University investigated a panel of circulating immunoregulatory indicators for cancer diagnosis [102].

This has been used in the investigation of PDAC biomarkers, where a panel of approximately 25 serum indicators has been recognized [103,104]. When compared to healthy participants, these markers showed a recognizable pattern in PDAC patients, especially those with autoimmune pancreatitis, CP, or other inflammatory conditions, disorders, or malignancies [105].

The multiplexed strategy addresses the drawbacks of a single protein marker by concentrating on a few important immunoregulatory molecules that are excessively generated in PDAC, and have shown good performance in later validation experiments, sensitivity, and specificity [106].

8. Interaction of Obesity, Diabetes, and Pancreatic Ductal Adenocarcinoma

Substantial research shows that overweight imparts a high cancer risk regardless of the existence of T2DM, although numerous epidemiologic studies have been hampered by the common coexistence of T2DM in overweight individuals. For instance, Jiao et al. found that [33] 2,454 people in a pooled cohort of almost 900,000 participants who underwent the study had PDAC. The T2DM presence had little impact on PDAC incidence, which increased by 19% in the 30-35 BMI group. Studies examining the role of metabolic changes brought about by obesity have

demonstrated that the dangers and high insulin levels brought about by obesity-related insulin resistance have a significant influence. Added by Stolzenberg-Solomon *et al.* [107], a survey of 29,133 Finnish people examining insulin and glucose levels as well as indicators of insulin resistance was conducted in male smokers who were followed for more than 20 years. PDAC favorably correlated with fasting blood sugar, insulin levels, and insulin resistance, as determined by the insulin resistance homeostatic model assessment. The highest quartile of individuals' insulin resistance, PDAC's risk ratio (RR) was 2.71 (95% CI: 1.19 to 6.18; P:1:4.006). Since insulin resistance affects practically all obese people, hyperinsulinemia is considered to play a causal role in the growth of PDAC tumors [108].

9. Processes by which Obesity and Type 2 Diabetes Raise the Risk of Pancreatic Ductal Adenocarcinoma

There are several crossings across and unique ways through which T2DM and obesity might encourage PDAC development. In T2DM patients and the great majority of obese people, hyperinsulinemia and elevated insulin-like growth factor-1 (IGF-1) levels are prevalent. Insulin resistance causes these conditions [71,72,109-114]. They exhibit potent growth-enhancing properties. The activities of insulin and/or IGF-1 are mediated via the binding of insulin, the insulin/IGF-1 receptor complex, IGF-1, and the subsequent activation of the PI3K signaling cascade [115].

Human pancreatic cancer cells express insulin/IGF-1 receptors [116]. Metformin, an anti-diabetes drug that minimizes circulating insulin/IGF-1 levels, may have anticancer properties, which emphasizes the significance of increased insulin/IGF-1 levels in PDAC development. According to recent preclinical and clinical research, metformin usage decreases the incidence of PDAC, slows cancer cell development, and increases patient survival, according to recent preclinical and clinical research [117-125].

The finding that metformin did not have a positive impact on individuals with advanced PDAC in several study trials [126-128] shows

that metformin may have a greater function in early intervention and primary/secondary prevention settings [129].

Obesity and T2DM are associated with increased levels of pro-inflammatory cytokines, adipokines, eicosanoids, and reactive oxygen species, and are chronic, systemic, low-grade inflammatory diseases [71,111-112]. This widespread and localized inflammatory environment may favor tumor initiation and promotion [130, 131]. Additionally, it is believed that the main mechanism by which chronic pancreatitis results in PDAC development is the inflammatory microenvironment [132-135].

It has been demonstrated that cancer can be prevented from developing or progressing by decreasing inflammation in the pancreas, lowering cyclooxygenase activity, taking aspirin, or directly inhibiting inflammatory cytokines [136-141]. Obesity has been linked to faster neoplasia, infiltrating immune cells, and enhanced pancreatic inflammation in mouse models [76-77,142]. Using calorie restriction as an obesity treatment lowered pancreatic inflammation and slowed the onset and development of PDAC [143,144]. Similar to T2DM, hyperglycemia has been linked to cancer risk and chronic inflammation [145], whereas in a diabetic animal model, suppression of inflammatory signaling pathways decreased PDAC development [146].

The complicated interplay linking inflammation, T2DM, and obesity is highlighted by a newly discovered interaction between the mammalian target of rapamycin complex 1, which is connected to T2DM and overweight-related insulin resistance, and the inflammatory prostaglandin signaling pathway [147].

Recent research suggests that by controlling the synthesis of insulin, adipokines, and inflammatory markers, the nexus is the nuclear receptor PPAR gamma, which is activated by peroxisome proliferators, the regularity of type 2 diabetes, and prostate cancer [148]. In certain laboratory and clinical studies, it has been demonstrated that n-3 polyunsaturated fatty acids (PUFAs) and fish oil consumption are linked to decreased rates of PDAC and slower tumor progression [148-153]; however, some studies found no positive benefits [154].

According to the Continuous Update Project's Pancreatic Cancer 2012 Report, although there was a weak link between total fat consumption and PDAC incidence, no conclusions could be drawn for PUFAs [155]. Consuming fish oil has been linked to reduced rates of cardiovascular disease, nonalcoholic fatty liver disease, insulin resistance, and obesity prevention [156-161]. By altering the synthesis of adipokines and cytokines and reducing proinflammatory immune cells, it has been shown that high levels of n-3 PUFAs support an anti-inflammatory environment [162-165].

PPAR is a peroxisome proliferator-activated receptor that is known to be liganded by n-3 PUFAs. Thus, this nuclear receptor plays a crucial role in regulating inflammatory response, metabolism, and cancer risk [166,167].

10. Chemoprevention of Pancreatic Cancer

Chemopreventive measures may be beneficial for people with premalignant lesions or those who are likely to develop pancreatic cancer [168]. Numerous organic and man-made *in vitro* and *in vivo*, substances have been proposed as pancreatic cancer chemopreventive agents. Section 4 claims that a high-fat diet has been shown to improve tumor development in animal models. by hyper-activating the carcinogenic KRAS gene [169].

Another study supported this idea by showing that aspirin is a sufficient anti-inflammatory medication to shield HFD animals from this danger [170]. Environmental factors, such as smoking, illness, and age, may influence cell competition; however, opinions on PDAC risk are divided. Statins lower cholesterol, but not aspirin, reducing the risk of PDAC [171].

Statins had a dose-dependent protective effect, which was more significant in individuals who were smokers, older, and obese. For instance, the combination of statins and aspirin did not reduce the risk to a greater extent than statins alone. Evidence that consuming statins, particularly atorvastatin, is connected to a 30% drop in the incidence of PDAC has been strengthened by a more complete meta-analysis study [172].

Metformin, a biguanide medication used for treating T2D, has been extensively studied for cancer, chemoprevention, and to reduce the risk and improve the prognosis of various cancers, including PDAC and pancreatic neuroendocrine tumors [173-175], supporting this as the initial course of action for any newly discovered T2D. In particular, metformin appears to phosphorylate 5' AMP-activated protein kinase (AMPK) and prevent activated PSCs from developing a desmoplastic protumoral response to exert its tumor-suppressing effects [176]. A recent study showed that metformin combined with intermittent fasting can inhibit tumor plasticity in mice, blocking tumor development by decreasing oxidative phosphorylation and glycolysis [177].

11. Function of Diabetes Medications in Pancreatic Cancer

11.1. Effect of Metformin

The most commonly used anti-diabetic medication in the world to treat T2DM is metformin, which falls under the category of oral hypoglycemic drugs known as biguanides. The main overall impact of metformin is to lower blood sugar levels by reducing glucose absorption in peripheral tissues, including skeletal muscle and adipose tissue, and hepatic gluconeogenesis [178].

Furthermore, it improves insulin sensitivity, thereby reducing insulinemia. Metformin is a fairly safe medicine with a minimal occurrence of lactic acidosis (b1/10,000), which is generally encountered in individuals with compromised kidney performance and is well-tolerated [179,180]. Many epidemiological studies have revealed that the use of metformin in adults increases the risk of diabetes has a preventive impact by lowering the frequency of various tumors and enhancing the prognosis of cancer patients [181-185].

The antitumor effect of metformin on site-specific tumors was inspired by its protective effects on the growth and spread of tumors. Specifically, metformin may lower the chance of developing malignancies, including PC and breast cancer, according to clinical research in

both diabetic and non-diabetic patients. Additionally, several randomized studies have proven its beneficial significance in the treatment of breast and colorectal cancers as adjuvant therapy and cancer prevention [186-189]. In women using metformin compared with placebo, metformin achieved a pathologic complete response rate of 24%, just 8% of those not taking metformin [190].

From 2004 to 2008, a new, sizable case-control clinical study comprising a study examining metformin was used to treat PC in 973 individuals, with 259 having diabetes and 863 controls, including 109 diabetic patients. was conducted [191].

Metformin-treated diabetes patients had a markedly reduced risk of PC compared to those who were not administered the treatment. Insulin treatment significantly increased the likelihood of PC in patients with diabetes compared with that in patients without insulin. Metformin treatment is linked to a lower risk of PC in individuals with diabetes, unlike insulin or other medicines, which have been linked to an elevated risk. Thus, metformin appears to have a preventive effect on the onset and spread of PC. Additionally, animal research has illustrated that metformin can stop the development of tumors in xenograft models [192-195].

Although the precise molecular processes underlying these discoveries are not fully known, several explanations have been proposed, and metformin's direct and indirect mechanisms are likely to contribute to its anti-tumor effects. The capacity of metformin to enhance insulin sensitivity and lower insulin levels has been demonstrated to block mTOR signaling, which stimulates AMP kinase (AMPK), preventing the growth of cancer cells [196,197]. When the AMP/ATP ratio increases, AMPK is activated. When AMPK is active, mTOR is phosphorylated, which inhibits the PI3K/Akt/mTOR signaling pathway. Normally, the pathways that respond to mitogenesis, mTOR, are activated by Ras/ERK, while PI3K/Akt are two pathways that indicate the presence of intracellular energy and nutrition, including amino acids.

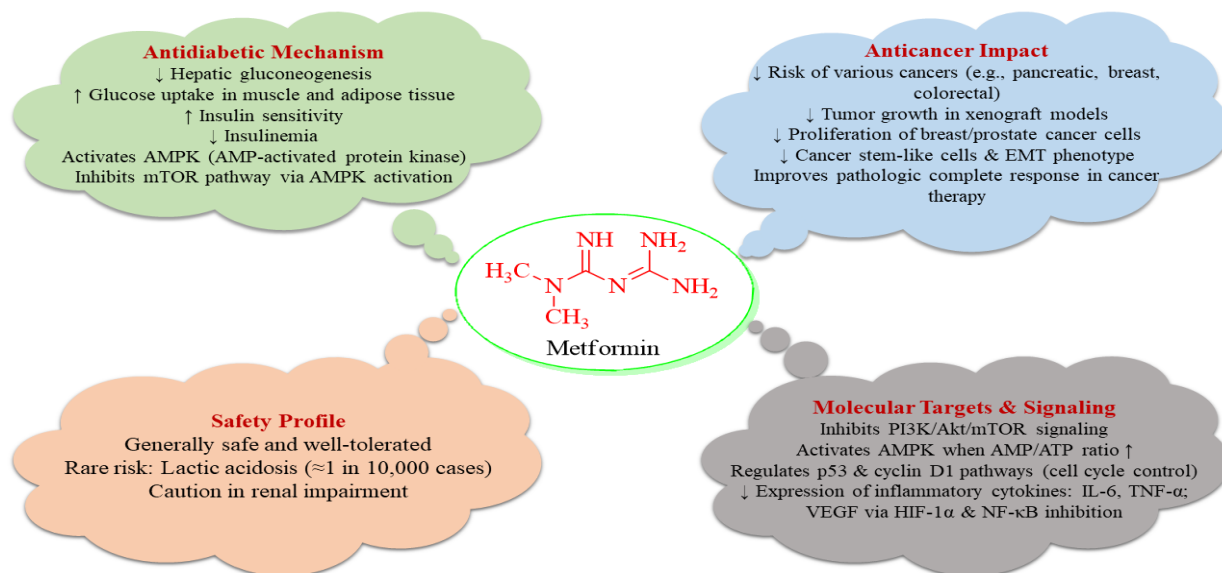


Figure 3. The Metformin biochemistry as an anticancer impact and effect on other signaling pathways

However, since metformin inhibits the mTOR pathway by activating AMPK, cell protein synthesis and growth are sharply reduced [186-188].

Furthermore, metformin can protect against breast and prostate cancer cells by increasing and enhancing the expression and phosphorylation of the p53 gene and the cyclin D1-mediated cell cycle [198-203].

Metformin is hypothesized to decrease the synthesis of inflammatory cytokines such as IL-6, TNF- α , and VEGF by inactivating HIF-1 α and NF- κ B [204-206]. Metformin inhibits the development of tumors by inactivating breast cancer stem-like cells, and the epithelial-mesenchymal transition (EMT) phenotype is thought to be the primary initiator of tumor recurrence and spread to other parts of the body [207,208]. According to the first animal investigation on the drug's impact on pancreatic tumors, metformin has been shown in studies to reduce the formation of cancerous pancreatic tumors in hamsters exposed to carcinogens while consuming a high-fat diet (**Figure 3**) [209].

11.2. Thiazolidinediones, PC therapy, and PPAR- γ ligands

PPAR- γ , or peroxisome proliferator-activated receptor- γ (PPAR), mostly situated in the

immune system and adipose tissue [182,210,211], is a transcription factor that responds to ligands that play a role in the control of inflammation as well as control of lipid and glucose balance [212]. PPAR- γ migrates to the nucleus after the ligand is bound, where its heterodimers with RXR, [182,213-214] start the transcription of genes containing a PPRE in their promoter regions (peroxisome proliferator response element) [215,216]. Obesity, T2DM, and carcinogenesis are only a few of the disease processes that have been linked to altered PPAR- γ regulation [182,217-219]. Thiazolidinediones (TZD), PPAR- γ agonists, have been successfully utilized to increase insulin sensitivity and lower insulin levels by increasing PPAR- γ . However, the chemical processes involved are not entirely understood. The United States FDA and Drug Administration formally sanctioned the use of pioglitazone and rosiglitazone, two synthetic TZD types PPAR- γ agonists (ligands), as anti-diabetic medications for managing T2DM. On the other hand, pioglitazone is a safer option. because of its ability to affect insulin signaling, TZD has been suggested as a promising anti-cancer medication [220,221]. Numerous Clinical trials have assessed the efficacy of TZD-class PPAR- γ agonists. Most investigations produced conflicting or ambiguous findings [185,222]. This is most

likely due to the short duration of the therapy, bias in the research design, lingering confounders, or targeting specific cells or tissues [221]. Recent clinical trials have revealed that administering PPAR- γ agonists to patients with DM may have preventative benefits for the malignancy growth. PPAR- γ agonists may therefore be helpful as adjuvant treatments in conjunction with standard chemotherapeutics [223-225]. In terms of the use of PPAR- γ ligands in patients with PC, there has not been a single clinical report. However, it has been discovered that Overexpression of PPAR- γ activation is related to advanced cancer stage and degree, as well as decreased patient longevity, indicating a probable role in PC development [226,227]. Although the biological function of PPAR- γ in the progression of PC remains unknown, the TZD family of PPAR- γ Ligands has demonstrated efficacy in *in vitro* and xenograft animal models [228-231]. One study using animals found that feeding 800 ppm pioglitazone to Syrian golden hamsters for twenty-two weeks was related to a reduced

occurrence and number of pancreatic tumors caused by carcinogens, implying that TZD may have a chemopreventive function in PC development [232]. The TZD family of PPAR- γ ligands has inhibitory effects on cancer initiation and development, encompassing both PPAR- γ -independent and PPAR- γ -dependent pathways. First, PPAR- γ ligands have been shown to improve insulin sensitivity and lower insulin levels by activating PPAR- γ , which suppresses the insulin/IGF-1R signaling pathways [228,229]. Second, PPAR- γ activation can suppress several different proteins, including leptin, uPA, MMPs, COX2, VEGF, PAI-1, and IL-6, IL-8 [231,233-242]. Through the activation of AMPK and the control of mitochondrial activity and ROS generation through PPAR- γ -independent pathways, PPAR- γ ligands can immediately decrease the inflammatory response [243]. Additionally, PPAR- γ ligands can stop proliferating brain cancer stem cells and trigger death (Figure 4) [244].

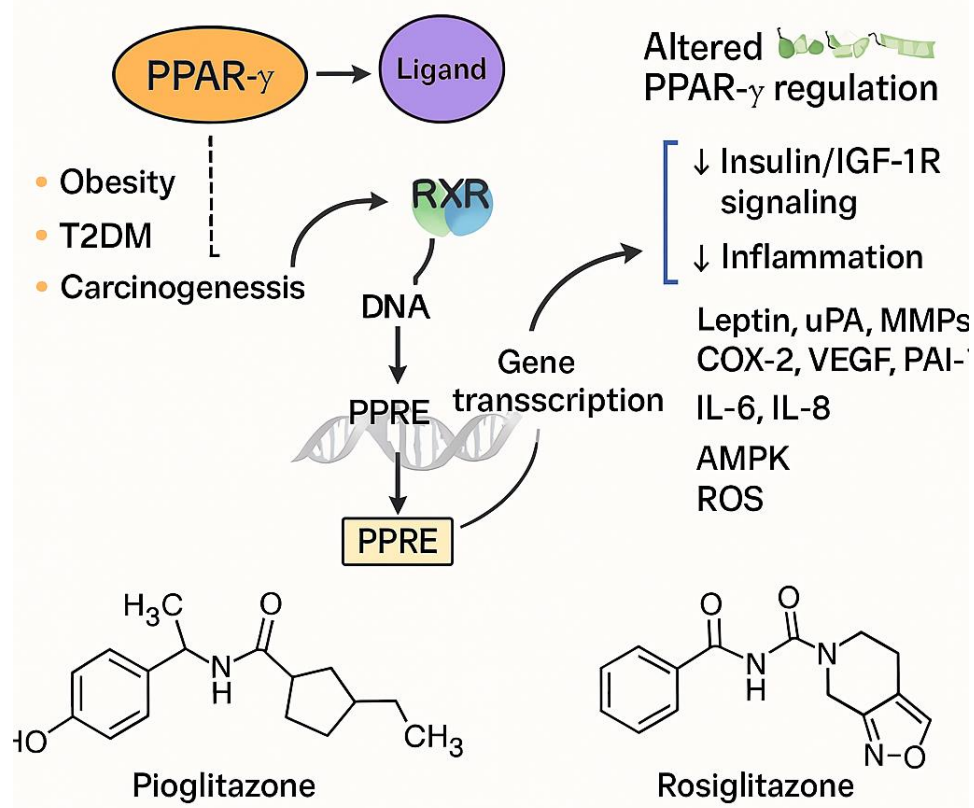


Figure 4. Biochemistry of Thiazolidinediones, PC therapy, and PPAR- γ ligands

12. Conclusion and Future Perspectives

Through modified metabolic pathways, metabolic disorders such as obesity and T2DM contribute to PC development. Identifying important participants in the PC development as a result of metabolic disorders may prove to be a useful tactic in the fight against cancers related to these metabolic disorders, specifically PC [245]. The complex interconnection among obesity, diabetes, and cancer of the pancreas necessitates a comprehensive approach to its management and treatment. Advanced treatment modalities, including precision medicine, novel therapeutic targets, and innovative technologies can improve patient outcomes and combat these health challenges. A holistic understanding of these interactions can lead to more effective prevention, diagnosis, and treatment. Recent molecular mechanisms underlying diabetes, obesity, and PC have led to the development of potential therapeutic strategies for managing pancreatic cancer in patients with diabetes and obesity. Recent studies have revealed that diabetes and obesity are linked to PC development due to some factors such as insulin resistance, inflammation, altered adipokine profiles, lipid metabolism, and dysfunctional pancreatic β -cells. Future research in this field should focus on precision medicine, metabolic targeting, immunotherapy, lifestyle interventions, early detection and screening, and multidisciplinary collaboration. Precision medicine can stratify patients based on risk profiles, genetic predisposition, and molecular characteristics, while metabolic targeting addresses metabolic susceptibilities associated with diabetes and obesity in PC cells. Immunotherapy can harness the immune system to target cancer cells, whereas lifestyle interventions promote diet, exercise, and weight management. Research on the interactions among diabetes, obesity, and PC interactions is progressing; however, further studies are needed to develop effective clinical strategies to improve outcomes and quality of life.

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Conflicts of Interest

The authors reported no potential conflict of interest.

Orcid

P. Balaji

<https://orcid.org/0000-0001-5317-1661>

Ram Prasad P. L.

<https://orcid.org/0000-0003-0556-0499>

Patibandla Jahnavi

<https://orcid.org/0009-0004-2501-7375>

Malarkodi Velraj

<https://orcid.org/0000-0001-5569-6840>

Anuradha Averineni

<https://orcid.org/000-0002-9035-6021>

Shaik Mobeen

<https://orcid.org/0000-0002-8644-7617>

Nithin Vidiyala

<https://orcid.org/0009-0005-3241-1669>

A. Venkata Badarinath

<https://orcid.org/0000-0003-4724-3416>

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