Abstract

Cancer is a condition characterized by the uncontrolled growth and spreading of certain cells within the body. The formation of malignant tumors necessitates a substantial amount of energy to sustain the abnormal rate of cell division. This process leads to a significant alteration in the primary metabolic pathway, transitioning from mitochondrial respiration to aerobic glycolysis, particularly in cancers associated with diabetes. This shift creates an opportunity for less invasive treatment options that can limit cancer growth by targeting specific transporters and enzymes crucial for energy production. This article focuses on the biological functions of Fasentin and Metformin, exploring their effectiveness in constraining cancer development. The discussion delves into their roles in regulating metabolism and highlights how these drugs can be instrumental in impeding the progression of cancer.
1. Introduction

Since its initial discovery, cancer has been one of the most formidable diseases. Though its early-stage symptoms are less virulent and the rate of recovery can be as high as 90%, advanced stages are faced with a high mortality rate. During intermediate and advanced stages, common treatments are invasive and seek to eradicate all cancer cells -- though recurrence is possible. If the cancer progresses to advanced stages, however, the mortality rate will quickly rise to 70% over the span of five years.¹

There are various causes and risk factors for different types of cancer, but chronic diseases², high body mass index, (BMI) and unhealthy lifestyles appear as general components in all types. Diabetes mellitus, one of the most common chronic diseases, has proved to be positively correlated with the progression of cancer. Diabetes Mellitus refers to a group of diseases that affect how the body uses blood glucose with regulations by Insulin, adiponectin, leptin, and glucose transporter groups (GLUTs) that manipulates the metabolic flux of metabolites between bloodstream and peripheral tissues with energy needs. Type I Diabetes will disable the pancreas from producing insulin and type II Diabetes is characterized by insulin resistance, which heavily impairs the patient's ability to utilize insulin for the regulation of sugar. Insulin is a hormone secreted by the pancreas and is used extensively for the metabolism of glucose and adipose tissue after food intake, especially for the synthesis of glycogen. Glucose is the major energy source and upon the damage of insulin's function, the homeostasis for glucose and glycogen is broken. Insulin also serves as a negative feedback signal for glycogenolysis, which transforms stored glycogen to free glucose. Moreover, more insulin circulating in the bloodstream will inhibit the synthesis of various proteins in different tissues, interfering with normal physiological functions throughout the body, especially in the digestive system. In discussion of diabetes and the risk of faster cancer progression, diabetes provides extra energy supply to the uncontrolled dividing cancer cells, filling the gap with an abnormally high consumption of energy. Heavily depending on the intake of energy, the shifted metabolic mechanism is a novel interest for the treatment of diabetes-related cancer. The complex energy transfer process including the
use of insulin, glucose transporter, and the change-of-function of many metabolism-related cells in mitochondria are hypothesized as new aims with a non-invasive treatment: treatment with no need of physical insertion of instruments into the patient’s body. In this article, the relationship among the chain of obesity, diabetes mellitus, and cancer development researched by different articles regarding to distinct diabetes-associated cancer types is reviewed, the potential metabolic reprogramming pathways of glucose uptake and digestion by cancer cells are studied, and the mechanisms of inhibitory functions on process of reprogramming by Fasentin, Panitumumab, and Metformin are possessed for the possibility as drug treatments of diabetes-associated cancer.

2. Obesity and its Correlation to Diabetes Development
Obesity is considered a common risk factor for many diseases. Regarding the accumulation of excess adipose tissue, a Body Mass Index (BMI) of over 30 kg/m² is utilized as an indicator. Obesity leads to metabolic disturbance, the severe impairments of the ability to regulate the synthesis of adipocytokines and the conversion between glucose and glycogen. Researchers have revealed that common metabolic disturbances like dyslipidemia and hyperinsulinemia are the causal factors of cancer development.

Many adipose cytokines are critical regulators for the maintenance of homeostasis between glucose and energy supply with some of them impacting a range of metabolic pathways to other organs. Two of the most intensively studied adipocytokines are adiponectin and leptin. While both are heavily impacted by the change in adiposity, the change in concentration and distribution of adipose tissue impacts the body’s response to metabolites. Adiponectin is secreted by adipose tissue into the bloodstream, with a function of mediating glucose metabolism and fatty acid oxidation process. Study conducted by Reneau, James et al reveals that the linkage between the accumulation of adipose tissue and secretion of adiponectin shows a negative correlation. Therefore, the increased adiposity inhibits the production of adiponectin, disabling its function to regulate gluconeogenesis. Leptin, another cytokine secreted by adipose tissue, has an opposite effect to adiponectin. Acting on the central nervous system, namely the hypothalamus, leptin serves to decrease the sense of hunger while inducing
the activity of beta pancreatic cells that produce insulin. It is shown that leptin production is positively correlated with the increased adiposity, with a positive feedback loop involving increased circulating insulin and the resulting increase of adipose tissue. Both researched adipokines promote the risk of getting diabetes.

Furthermore, insulin also plays a critical role in the hydrolyzation of fatty acid, which serves to increase the rate of glucose uptake and fatty acid synthesis, as well as decrease the rate of fatty acid decomposition. The tumor, upon receiving beneficial signals from the adipose tissue, also feeds back with inhibitory signals on the decomposition of fats. Therefore, a positive feedback loop is observed among obesity-high blood insulin-tumor development, as shown here in figure 1.

![Figure 1. The positive feedback of adipose tissue accumulation and cancer development.](image)

For summary, the abnormally high BMI level indicates the obesity level of an individual, resulting in the fluctuation of production for critical metabolic regulators, which leads to the increasing level of insulin circulating in the body and subsequently, will cause Type II Diabetes Mellitus by inducing insulin resistance. Over time, the disturbance of homeostasis can generate enough energy to promote the growth of cancer, particularly in organs with high concentrations of adipose tissue.

3. **Type II Diabetes Mellitus (T2DM) and its Correlation to Cancer Progression**
The compilation of the mentioned negative impacts from the previous section will lead to the development of T2DM. Establishment of insulin resistance (IR) by tissues will be disabled to respond normally to the hormone insulin or downregulate insulin receptors in response to hyperinsulinemia\(^\text{10}\). The detailed development of IR remains unclear, but the hypothesis is that decrease in insulin sensitivity with adjustments in the PI3K/Akt/mTOR signaling pathway\(^\text{11}\).

Hyperinsulinemia boosts the advancement of cancer by providing access to excess glucose from the bloodstream\(^\text{12}\). Normal functioning cells, upon receiving glucose, will degrade it for energy with the assistance of oxygen in the process of glycolysis, Citric Acid Cycle, and Oxidative Phosphorylation, producing approximately 34 ATP per glucose used\(^\text{13}\). However, during the pre-malignant expansion stage of tumor, the development of peripheral Tumor Microenvironment (TME) will separate the interior of tumor cells farther away from the local bloodstream\(^\text{14}\), which is the carrier of oxygen-rich hemoglobin. The result of this isolation is the leveled average partial pressure of oxygen in TME around 5 mmHg, which is only 12.5% in average of the venous oxygen pressure\(^\text{15}\). This shift of oxygen level disallows cancer tissue to utilize oxygen for the mitochondrial respiration process and instead, it switches its dependence for energy to the Warburg Effect, the metabolic reprogramming effect done by tumor cells to rely on the energy provided by aerobic glycolysis. This is only effective when there is an excessive supply of glucose and an anaerobic environment, for the production of energy is only 4 ATP per glucose consumed, rather inefficient compared to the normal process\(^\text{16}\). Therefore, the T2DM with its influence on tissues incapable of utilizing glucose efficiently, the extra circulating glucose in the bloodstream will be recruited and made use of by the tumor complex\(^\text{17}\).

On the other hand, T2DM also provides conveniences for the progression of cancer by the hyper-expressed insulin. Insulin serves as a mitogen in the human body\(^\text{18}\). With high levels of insulin expressed, cells are excited by the signal from mitogens to proceed with more mitosis. Besides insulin, Insulin-like Growth Factor 1 (IGF1) also serves as an important mitogen. However, IGF1 is not induced by the increased level of blood glucose, but the excess circulating insulin serves to compete with IGF for the constant amount of IGF Binding
Protein 3 (IGFBP3). As IGF1 is a mitogen as well, the imbalance between IGF1-IGFBP3 ratio leads to excess proliferation of cancer cells. On top of that, IGFBP3 is considered a negative regulator of cancer as a low-penetrance tumor suppressor gene.19

4. The Role of Glucose Transporter (GLUT) and Treatment with Fasentin and Panitumumab

The two mentioned changes negatively impact the in vivo microbiological environment for all cancer types, because energy is a common restriction for the development of all tumors. This has led the discussion to the molecular metabolic pathway of energy generation, especially the relationship of blood glucose and insulin level, as well as the mechanism of how glucose enters into tissues.

In order for the intake of glucose to peripheral tissues from the bloodstream for further mitochondrial oxidation and ATP production, mammalian cells have developed a family of glucose transporter proteins for the transportation of sugar through the plasma membrane.20 The abnormal blood glucose level within the T2DM patients will induce a stronger expression of GLUT families, especially in the energy-demanding tissue like adipose tissue and breast cells, the emphasis of our paper. There are 3 classes of GLUT, and the responsible group here is class I GLUT, which contains GLUT1-4 and GLUT14.21 Different GLUT types are responsible for the intake by different tissues, and our emphasis will be on GLUT4, the one that controls uptake of glucose by skeletal muscle, cardiac muscle, and most importantly for cancer development, adipose tissue.22

The expression of GLUT4 is heavily regulated by the level of presenting insulin. Stored in intracellular vesicles, GLUT4 is released vesicular fusion once insulin binds with the insulin receptors expressed on the plasma membrane.23 Increased GLUT4 availability to glucose in the bloodstream causes more glucose uptake by fat. This is thought to be the effort against the development of Insulin Resistance, although it also promotes the creation of a positive feedback loop for fat accumulation and development of diabetes.22 This has led
the research interest to a potential drug that restricts metabolic efficiency of cancer cells by inhibiting the process of glucose intake.

There are two potential targets in regard to this possible map. First, the insulin receptors are Receptor Tyrosine Kinase (RTK), which requires the process of dimerization and phosphorylation to the transduction of the chemical substances from ligands to intracellular electric signals\textsuperscript{24}. This is not unique because many signal regulation pathways utilize RTK as well, and they can also be seen as targets. Therefore, a potential therapy is to block or terminate the phosphorylation process of RTKs with pharmaceutical interventions. There are already drugs developed for cancer treatments via this pathway, namely the Panitumumab\textsuperscript{25}. Panitumumab is an agent serving to restrict progression of colorectal cancer on epithelial level\textsuperscript{26}. Epithelial cancer is a critical cancer type that is affected by T2DM, for the transformation of normal epithelial to cancerous cells requires enormous amounts of energy consumption. Panitumumab inhibits the function of Epithelial-Growth Factor Receptor (EGFR), which after cancerous lesion, starts the process of uncontrolled replication\textsuperscript{27}. Panitumumab, by binding to the extracellular receptor of EGFR and outcompeting the essential nutrients for cell proliferation, effectively inhibits the progression. Recently, clinical trials were made with Panitumumab on its pharmaceutical effect on cancer types other than colorectal cancer. Records show that it can also repress the development of head cancer and neck cancer\textsuperscript{28}.

Secondly, the drug can also target the intake of glucose by the direct blockage of GLUT4. Fasentin serves 2 functions for the suppression of tumor establishment. Firstly, Fasentin is a direct inhibitor of GLUT4. By outcompeting the glucose on binding affinity represented by a higher IC50 value\textsuperscript{29}, Fasentin effectively reduces the glucose uptake by cancer-surrounding tissue and therefore, an inhibitory effort is made to reduce energy production. Secondly, Fasentin presence serves as a stimulatory signal for the activation of Fas-directed apoptosis process of cancer\textsuperscript{30}. Therefore, intake of Fasentin can both directly, by inducing cancer cell death by apoptosis and indirectly, by restricting the amount of glucose inflow.
5. Treatment Incorporating Monocarboxylate Transporter 4 and Cannabinoid Receptor 2

The distorted glucose in cancer cells results in the upregulation of glycolysis in cancer cells. This induces a high amount of lactate production, and consequently, its accumulation in these cells. Blocking upregulation of aerobic glycolysis has been ineffective, such as using 2-DG as an anti-cancer agent. Mere inhibition of glycolysis is insufficient for the eradication of cancer cells due to the reason that cancer cells have the potential to adapt their metabolism to their environmental conditions. Upon glycolytic suppression in multiple types of tumor cells, intracellular energy metabolism is reprogrammed in an autophagy-dependent manner to ensure cellular survival.

Rather, a possible treatment method for these cancer cells is aggravation into a hyper-glycemic condition, followed by blocking products from TCA cycle, resulting in high amounts of lactate production. This lactate export is then blocked, causing intracellular acidification and consequently cell death. The high amount of lactate can cause a strong acidification process, in which most of the normal cell functions are inhibited, including division. The high amount of lactate can cause a strong acidification process, in which most of the normal cell functions are inhibited, including division. In addition, lactate released from tumor cells through Monocarboxylate Transporter 4 (MCT4) is enough to stimulate angiogenesis and tumor growth. Increased lactic acid can in turn enhance glycolysis in cancer cells, causing a vicious cycle. However, this high lactate content causes normal cell functions to be inhibited, including the process of replication and division.

Using this manner, a treatment of poisoning the cancer cells is feasible by inducing over-production of lactate to decrease pH level. However, research shows that a highly acidic environment surrounding the tumor is responsible for the development of chemotherapy resistance. Thus, two needs that must be met are to increase lactate formation and block the lactate from exiting the cancer cell.

A potential pathway of this treatment is the utilization of Monocarboxylate Transporter 4 (MCT4) along with the cannabinoid receptor 2 (CB2).
Monocarboxylate transporter 4 (MCT4) is highly expressed in metastatic tumors and at inflammatory sites, referentially in glycolytic muscle fibers and facilitating the lactate efflux. MCT4 is responsible for the bidirectional transport of lactate across the plasma membrane. The CB2 receptor modulates immune cell functions. Cannabinoid receptors (CB1 and CB2)—G-protein coupled receptors, inhibit adenylate cyclase activity in response to psychoactive cannabinoids. The activation of CB2 receptors does not appear to produce psychotropic effects, and therefore, it may also be helpful in treating diseases that have a neuroinflammatory or neurodegenerative component, such as multiple sclerosis.

MAPKs are enzymes involved in a wide variety of important signaling cascades in many cellular responses—cell proliferation, migration, transformation, and cell death. MAPK activation by a nonselective CB2 receptor agonist (D9-THC) was found to have a proapoptotic effect in the Jurkat human leukemia cell line (Herrera et al., 2005) and cytotoxicity in J774-1 macrophages; In the same cells, there was also a c-Jun N-terminal kinase–mediated cytoprotective effect mediated by Δ9-THC activation of CB2 receptors, displaying the same CB2 receptor ligand can activate multiple MAPKs, each with different outcomes.

The activation of CB2 receptors by natural or synthetic ligands favors a range of receptor conformations that can variably affect different signaling pathways as the following procedure— inhibition of adenylyl cyclase, decreased cAMP (production, and less activation of cAMP-dependent protein kinase (PKA), inhibiting A-type potassium channels as well as specific gene expression. This is followed by activation of Akt/protein kinase B—stimulating cell survival, migration, and growth. Proceeding activation of the mitogen-activated protein kinase (MAPK) cascade favors cell survival and modulates gene expression. In addition, there is inhibition of specific calcium channels and enhanced opening of G protein–gated inwardly rectifying potassium (GIRK) channels. Lastly, stimulation of de novo synthesis of ceramide and inhibition of the MAPK cascade promotes apoptosis. Recruitment of β-arrestin to the activated CB2 receptor results in desensitization and/or internalization of the receptor and potential activation of arrestin-specific signaling. Decreased PKA activity increases Raf-1 to stimulate the MAPK cascade, positively regulating the
expression of many genes and indicating activation of a pathway by CB2 receptor agonists. Functional selectivity of CB2 receptor agonists must be considered during the therapeutic development of CB2 agonists, which increases the possibilities for developing drugs targeting CB2 receptors.

By forcing glycolysis with metformin and a NF-kB inhibitor lowers the pH of a cell, our treatment has a minor effect on normal cells and most effective in cancer patients with any hyperglycemic stages, including. As an example, NK-kB inhibition causes increased lactate secretion from breast cancer cell line MCF-7. The effect of this metabolic reprogramming strategy was observed by checking oxygen consumption and extracellular acidification rates. This resulted in reduced OCR and blocked ECAR, essentially leading to an accumulation of lactate. Fluorescent BCFL-AM was used as a probe for detecting pHi. Therefore, the reprogramming did not decrease viability in (normal) MCF-12A cells. It did, however, affect MCF-7, T47D, and MDA-MB-231 (breast cancer cells), demonstrating significantly inhibited migration and invasion ability. Consequently, in high glucose cancer cells, a higher glycolysis rate is present, allowing the reprogramming strategy to further promote the process and raise intracellular lactate, permitting cancer cells to poison themselves. Essentially, there is limited cytotoxic effect on non-subject cells, reducing the chance of untargeted damage.

CB-2 might bind to a pocket of MCT4 composed of Ser156, Phe243, Tyr332, Gln339 and Glu363. The combination of Metformin and CB-2 exerts a deleterious effect on breast cancer cell viability and exhibits synergistic antitumor effects. Results of the combination treatment showed a 63% inhibition of cell viability in MDA-MB-231 breast cancer cells. In addition, moderate effect on cell viability was observed in normal MCF-10A human mammary epithelial cells. Disrupting MCT4 function leads to an accumulation of intracellular lactate and a decrease in intracellular pH which may rapidly damage a cell thereby inducing necrosis, apoptosis or growth arrest. Metformin increases glycolysis thereby increasing the buildup of intracellular lactate, thereby accelerating the effects of the MCT4 inhibitor. This can be used to treat high glycolytic rate/MCT4-expressing malignancies. Another possible combination is the MCT4 inhibitor CB-2 and a GLS1 inhibitor CB-839 to reengineer cancer metabolism. This combination solves
the problem of increasing ammonia production to neutralize lactate via restricting the metabolic flexibility of these cancer cells.

6. Metformin to Target Cancer Cells’ Glucose Metabolism and mTOR Pathway

The collection of genetic alterations in cancer cells causes interference with the regular cellular signaling pathways, this then leads to cell growth for cancer. Despite the different current treatment plans that are offered, many recoveries fail due to the drug resistance and its adverse side effects. Though in recent studies, metabolic reprogramming has served as a possible cancer therapy. With this, we want to identify the glucose metabolism of cancer cells to alter so it causes glucose-lowering agents like metformin to be a possible treatment in cancer cells.

One change we can see in cancer metabolism is known as the Warburg effect. The metabolic adaptation shifts their energy production from oxidative phosphorylation in the process of aerobic glycolysis. Metformin is a commonly prescribed drug used for type 2 diabetes, which also displays anticancer properties in inhibiting mitochondrial complex I,41,42 activating AMPK, a regulator for energy metabolism, and reducing insulin and insulin-like growth factor 1 (IGF-1), which performs anti-tumor functions. In addition, Metformin has shown ability to inhibit the mTOR pathway, which is involved in the protein synthesis and cell growth process. There are two types of forms of mTOR: complex 1 (mTORC1) used in growth factors, glucose, and helps with protein synthesis; and complex 2 (mTORC1) used for regulating cell survival and metabolism43.

Metformin inhibits mTORC1 which then activates AMPK and phosphorylates the TSC2 protein, the negative regulator of mTOC1. This inhibition can occur both dependent and independent of AMP-activated protein kinase (AMPK) activation, leading to the decrease in protein synthesis and cell growth. Metformin is able to inhibit mTORC1 independently when AMPK is activated as it is binding to the complex.43 This dual mechanism causes a positive treatment for the host, since metformin has multiple strategies to repress pathways critical for cancer cell growth.
Recent studies with mice given metformin after being exposed to carcinogen show a reduction of lung tumor burden by up to 53%. However, only modest effects presented as mTOR was inhibited in lung tumors. The researchers then inject mice with metformin to assess whether this method would improve mTOR inhibition. The result shows that plasma levels of metformin were higher after injection than oral administration. On the other hand, Metformin also activates AMPK and inhibits mTOR in liver tissue, but it only inhibits phosphorylation process of IGF-IR/IR, Akt, ERK, and mTOR in lung tissue. This suggests that Metformin indirectly inhibited mTOR in lung tissue by decreasing activation of IGF-1R/IR and Akt upstream of mTOR. A follow-up study showed that intraperitoneal administration of metformin decreased tumor burden by 72%, which correlates with decreased cellular proliferation and marked inhibition of mTOR in tumors, as shown in figure 2.

![Graph showing plasma levels of metformin](image)

**Figure 2.** As the intake of Metformin treatment inhibits plasma IGF-1 level in all tissues. As mentioned, the Metformin inhibition also has specificity in lung and liver tissue.

Metformin swords decrease with the phosphorylation of IGF-1 and the insulin receptors in lung tissues. The drug is known for reducing the levels of hormones presentation in patients. With oral administration of Metformin, study shows a decrease of 1 or 5 mg/ml of circulating IGF-1 by approximately 20% and the insulin by 20% and 35%. 

![Image of Western Blots showing phosphorylation](image)
There was an injection of metformin intraperitoneally to assess its inhibitory effect on mTOR pathway. However, the intraperitoneal injection did not decrease the IGF-I levels significantly. Instead, the levels of IGF-1 inside the mice shows a significant reduction from the wild type comparison group. This can indicate that stress in daily injection can alter the masked inhibitory effect of metformin in circulating the levels of IGF-1. This supports the hypothesis that metformin can be used in mTOR pathways with cancer patients, since it will decrease the levels of circulating IGF-1 (insulin) in preventing the NNK-induced lung tumorigenesis\textsuperscript{45}.

In addition to its ability to inhibit the mTOR pathway, Metformin triggers a decrease in cap-dependent translation. A study utilizes MCF-7 cells, Metformin treatment and led to a maximal inhibition of 40\% in cap-dependent translation\textsuperscript{45}. The polysome profile analysis shows how the metformin treatment of MCF-7 cells leads to a shift of mRNAs from heavy to light polysomes and how concomitant increased 80s ribosomes\textsuperscript{46}. This suggests that metformin can be a treat and cause significant impact on the translation of specific mRNAs and leads to alteration of protein expression in cancer cells. The change in polysome profiles towards lighter polysomes indicates a reduction in the translation efficiency of specific mRNAs. This can help with further implication for cancer cells that rely on increased protein synthesis for their survival and proliferation\textsuperscript{47}. The increase of 80s ribosomes indicates that Metformin treatment may also affect the biogenesis of ribosomes, which is essential for protein synthesis. This decreases the rate of protein synthesis within cancer hosts, which can then be added to the growing body of evidence supporting the potential of Metformin as a therapeutic agent for cancer.

In MCF-7 breast cancer cells, Metformin has been shown to inhibit translation initiation by activating SMP-activated protein kinase (AMPK) through its upstream kinase, liver kinase b1 (LKB1)\textsuperscript{48}. This results in the inhibition of the mammalian target of mTORC1. Although in contrast, in MDA-MB-231 breast cancer cells, didn’t express LKB1 mRNA, metformin had no effect on its protein synthesis, confirming the requirement of LKB1 for inhibition of translation by metformin in MCR-7 breast cancer cells\textsuperscript{49}. This confirms the requirement of LKB1 for inhibition of translation by metformin in MCF-7
breast cancer cells. It is an important biomarker for predicting the response to metformin treatment.

7. Conclusion
As discussed, the development of diabetes is a result of imbalance between glucose metabolism and anabolism. This distorted metabolic system can be caused by abnormally increased glucose intake and the subsequent development of insulin resistance, causing T2DM. Furthermore, the establishment of T2DM, along with an anaerobic environment that is beneficial for the cancer progression, will reshape the metabolic dependence of tumor from mitochondrial respiration to aerobic glycolysis. Extensive supply of glucose can be advantageous for cancers with high energy demand to fulfill its need of rapid division and proliferation. Therefore, a new target for non-invasive cancer treatment emerges. By limiting the energy influx to tumor tissue with either direct blockage on membrane receptors or indirect pathways that induce specific cell killing, three of the potential candidates are available for consideration, which are Panitumumab, Fasentin, and Metformin. Even though all the mentioned treatments are proven to be effective to some extent, assistance from corresponding drugs and therapies is highly recommended since some of the directed pathways are not exclusive to cancer, which leaves potential risk of affecting normal cell functioning. Moreover, many of the mentioned pathways are distinct from each other, which gives the possibility of combinational use, similar to a cocktail therapy for HIV patients\textsuperscript{50}. 
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