Original Research Article

Elucidation and prediction of molecular mechanisms and associated pathways of the prostaglandin-endoperoxide synthase-2 as a common key gene for diabetes and cachexia: Bioinformatics strategies

Abstract

Cachexia and diabetes both feature severe weight loss as a phenotype, and both diseases share several gene and protein abnormalities. This study investigates the PTGS2 gene as a common key gene for diabetes and cachexia. A variety of biological databases and enrichment approaches were used to explore this gene. Probable genes and substances that could be used to address disease symptoms were identified using STICH, a protein-protein, and protein-drug interactions. It was also established that PTGS2 is strongly linked to the pharmacology of the ibuprofen route of action. These findings and annotations will aid in further research into the therapeutic option of targeting the PTGS2 gene in the treatment of both disorders.

Keywords: Pathways, Molecular mechanisms, PTGS2 gene, bioinformatics

Introduction

Diabetes is a well-known chronic disease that affects the ability of the human body to convert glucose into energy [1]. [2]. In addition to causing blindness and kidney failure, diabetes is a leading cause of heart attacks, strokes, and lower-limb amputations, among other deadly diseases [3]. In low- and middle-income countries, the prevalence of HIV has increased at a faster rate than in high-income countries. The global population is being afflicted by this chronic condition on a daily basis, as Diabetes prevalence increased from 108 million in 1980 to 422 million in

2014. Diabetes was the ninth biggest cause of mortality in 2019, accounting for an estimated 1.5 million fatalities. Diet, physical exercise, medication, and frequent screening and treatment for complications can all help to control diabetes and postpone or prevent its repercussions [4].

Type 1, type 2, and gestational diabetes are the three primary categories of diabetes. Type 2 diabetes (T2DM) is a condition in which the body's ability to control and consume glucose as a fuel is impaired [5]. Too much sugar circulates in the circulation because of this chronic disease [6]. High blood sugar levels can eventually cause problems with the circulatory, neurological, and immunological systems [7]. T2DM has many critical consequences for the heart, blood vessels, nerves, eyes, kidneys, and other vital organs. Additionally, the same factors that raise one's risk of diabetes also increase one's chance of developing other serious chronic diseases [8].

Cachexia is a wasting condition characterized by considerable weight loss, muscular atrophy, and often body fat loss [9]. Physical weakness and disability can result from the loss of skeletal muscle. It affects persons with severe illnesses such as cancer, HIV/AIDS, COPD, renal impairment, multiple sclerosis, and cardiomyopathy. Cachexia can be classified into three categories, 1) **Precachexia** is defined as a weight loss of up to 5% of body weight while suffering from a recognized sickness or condition. It's characterized by a reduction of appetite, inflammation, and metabolic abnormalities. 2) **Cachexia** is defined as a loss of more than 5% of body weight in less than a year when the person is not seeking to reduce weight and has a recognized sickness or ailment. Loss of muscular strength, reduced appetite, weariness, and inflammation are among the other characteristics. 3) **Refractory cachexia,** which affects cancer patients. It is characterized by weight loss, muscle loss, loss of function, and a failure to react to cancer therapy.

There are some similarities between cachexia and T2DM. For example, diabetic neuropathic cachexia is a well-studied consequence of uncontrolled T2DM that is mostly seen in elderly men with a few cases recorded in women [10]. Strenuous DM management, neuropathic pain medicines, including antidepressants, and intensive dietary and physical therapy are the mainstays of treatment. In this study, we used several bioinformatics approaches to identify common genes involved in both cachexia and T2DM, and we investigated the molecular mechanisms and associated pathways of one of them, the PTGS2 gene, in order to gain a better understanding of its involvement in various pathways and interactions with other proteins and chemicals. Prostaglandin-endoperoxide synthase (PTGS), commonly known as cyclooxygenase, is a critical enzyme in prostaglandin synthesis because it functions as both a dioxygenase and a peroxidase. PTGS is composed of two isozymes: constitutive PTGS1 and inducible PTGS2, which differ in their expression regulation and tissue distribution. This gene is responsible for encoding the inducible isozyme. It is regulated by specific stimulatory events, implying that it is involved in the manufacture of prostanoid metabolites involved in inflammation and mitogenesis. In this study, we will look at the common key genes in T2DM and cachexia, as well as the potential therapeutic option of using *in silico* state-of-the-art techniques to target the PTGS2 gene in the treatment of both disorders.

Methodology

Common gene identification

The VennViewer tool, which creates a Venn diagram to compare associated data sets chemicals, diseases, or genes, was used to identify common genes involved in both cachexia and T2DM. This tool can be found in the 'Comparative Toxicogenomics Database (CTD),' a web-based database (http://ctdbase.org/).

Protein-protein and protein-drug interaction analysis

The STITCH database (http://stitch.embl.de/) was used to examine protein-protein and protein-drug interactions. It is a database of known and projected chemical and protein interactions. The interactions arise from computer prediction, knowledge transfer across species, and interactions gathered from other (primary) databases, and they comprise both direct (physical) and indirect (functional) correlations.

Pathway analysis

A pathway associated with PTGS2 was explored 'MetaCyc Metabolic Pathway Database' (https://metacyc.org/), a curated collection of metabolic pathways that have been experimentally characterized across all domains of life. MetaCyc comprises pathways involved in both primary and secondary metabolism, as well as the metabolites, processes, enzymes, and genes linked with them.

Results

The goal of this study was to see if there was a link between T2DM and cachexia at the gene level. We employed bioinformatics resources to discover the common gene(s) that are directly involved in the clinical manifestation of both T2DM and cachexia, as muscle loss/weight loss is a common hallmark of both disorders.

The VennViewer tool inbuilt in the CTD web-based database was used to identify the common gene **(table 1 and figure 1).** PTGS2 was identified as the common gene involved directly in both diseases.

Table1: list of genes involved in cachexia and T2DM

Cachexia_all	DiabetesMellitus_all
CD27	A

CDH6	ADIPOQ
CXCL8	ADRB1
GDF15	ALPK1
GHRL	AOC3
IGF1	ATP6
IL6	CAT
PTGS2	CP
PTHLH	CPT1A
TNF	CYBB
TNFRSF1A	FN1
ZFP36	INS
	INS2
	IRS1
	KIF1A
	KIF5B
	LEPR
	MAP3K5
	MT2A
	NCF1
	NR1I2
	NR1I3
	POMC
	PON1
	PPARG
	PTGS2
	RAC1
	SIRT1
	SOD1
	THBS2
	ZFP57

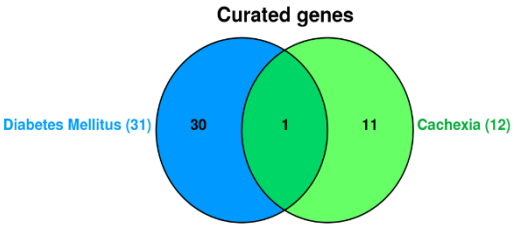

Figure 1: Venn diagram of curated genes of cachexia and T2DM

Several analyses, including protein-protein and protein-drug interaction analysis, pathway analysis, and prediction of possible inhibitors/drugs, were undertaken to discover more about the identified common gene, PTGS2. PPARG is the nearest gene/protein, and numerous chemicals, such as celecoxib, diclofenac, arachidonic acid, indomethacin, and others, are possible medications that interact with this target gene in diverse mechanisms of action, according to the STICH database (**Figure 2 and 3**). The predicted functional partner genes and chemicals of PTGS2 show that these interacting genes and chemicals are interacting with different action types e.g. activation, inhibition, binding, phenotype, catalysis, post-translational modifications, reaction, and expression (**figure 3**).

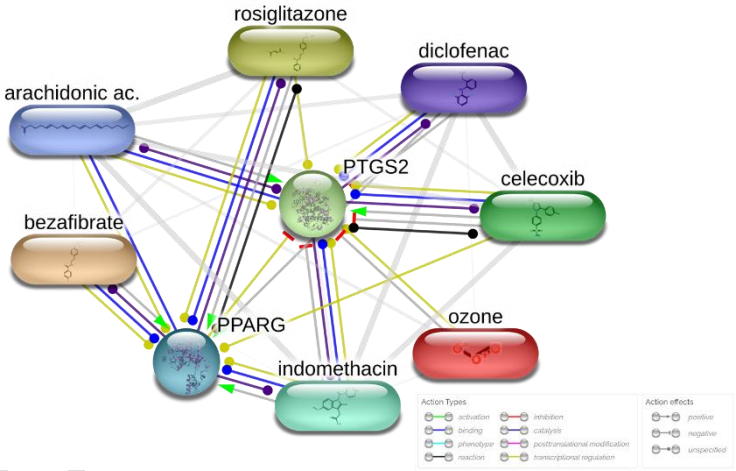

Figure 2: Protein-protein and protein-drug interaction analysis

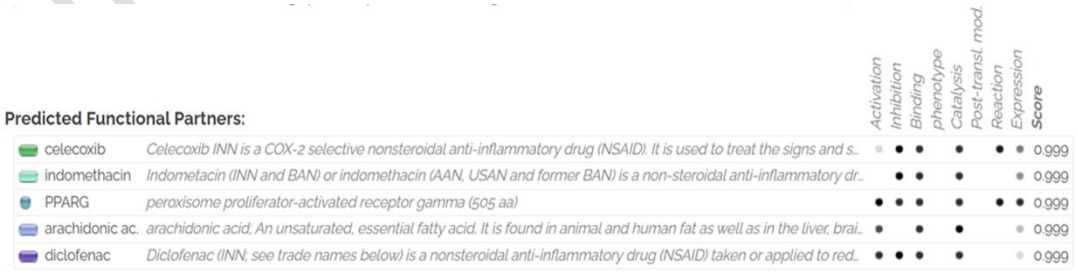

Figure 3: Predicted functional partner genes and chemicals of PTGS2

The 'Open Targets Platform,' a comprehensive platform that facilitates systematic discovery and prioritizing of prospective therapeutic drug targets, was used to run several other relevant analyses to investigate the PTGS2 gene, such as diseases or phenotypes relationship with PTGS2. It resulted in 1491 diseases or phenotypes associated with PTGS2 (**Figure 4).**

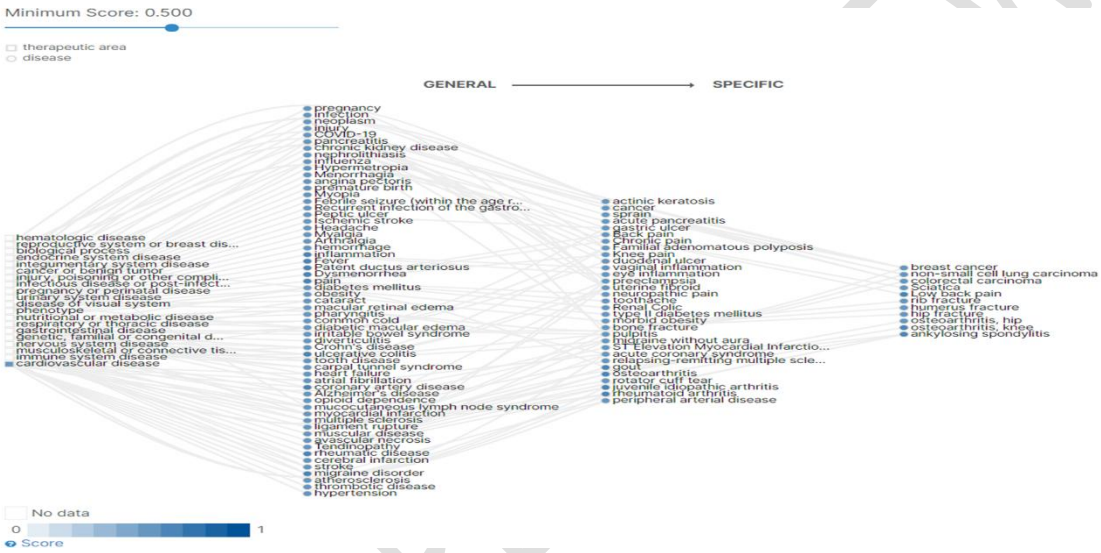

Figure 4: graphical representation of diseases or phenotypes associated with PTGS2

It was also discovered that PTGS2 plays a key role in the 'Ibuprofen Pathway [11].' The pharmacodynamics of the ibuprofen pathway clearly demonstrates the relevance of the PTGS2 gene [12]. Ibuprofen is a non-steroidal anti-inflammatory medicine (NSAID) that has long been used for analgesic, anti-inflammatory, and antipyretic purposes. Ibuprofen works by inhibiting the cyclooxygenase enzymes COX-1 and COX-2 in a non-selective and reversible manner (coded for by PTGS1 and PTGS2, respectively) (**Figure 5**).

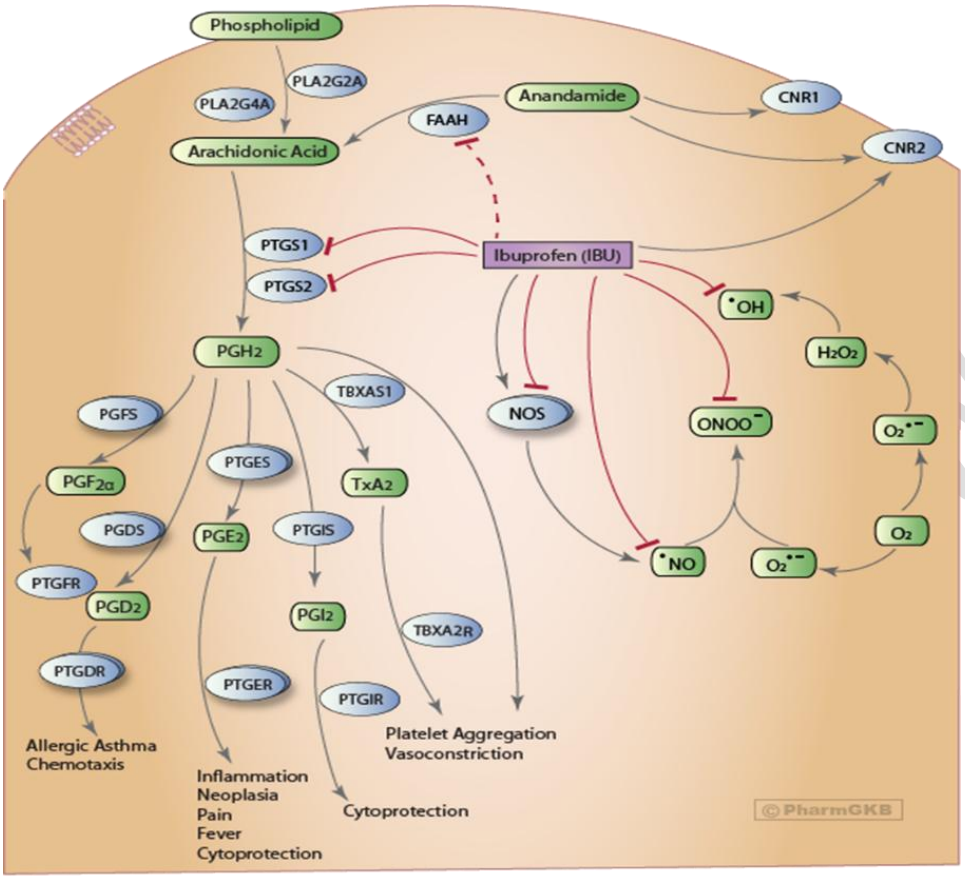

Figure 5: role of PTGS (1 and 2) gene in Ibuprofen Pathway.

Further, the signaling network was constructed using the SIGNOR web server (https://signor.uniroma2.it), the SIGnaling Network Open Resource organizes and stores signaling material presented in the scientific literature in an organized fashion (**Figure 6**).

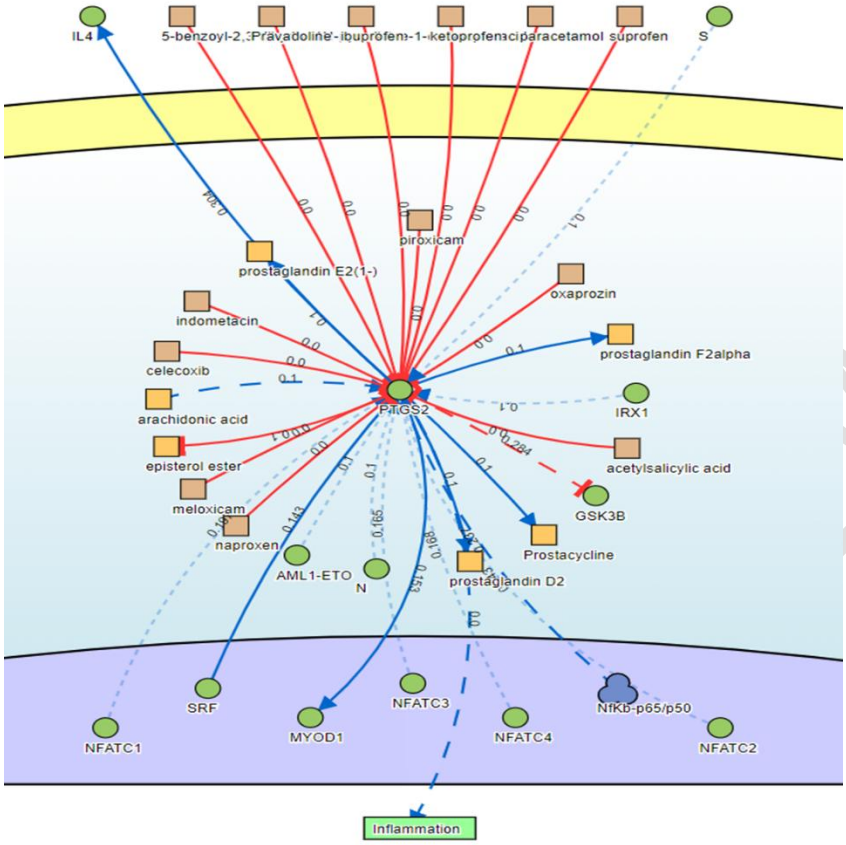

Figure 6: signaling pathway of PTGS2 analyzed by SIGNOR

The 3D structure of PTGS2 is available in protein databank (PDB). We illustrated the monomeric unit of this protein in 3D format **(Figure 7).** There are several potential inhibitors identified targeting this gene/protein active site previously and many are of FDA-approved drugs (**Figure 8**).

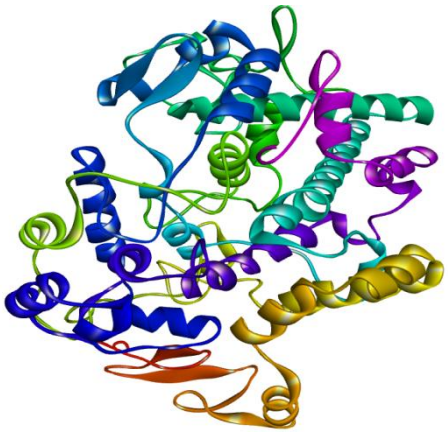

Figure 7: 3D structure of PTGS2

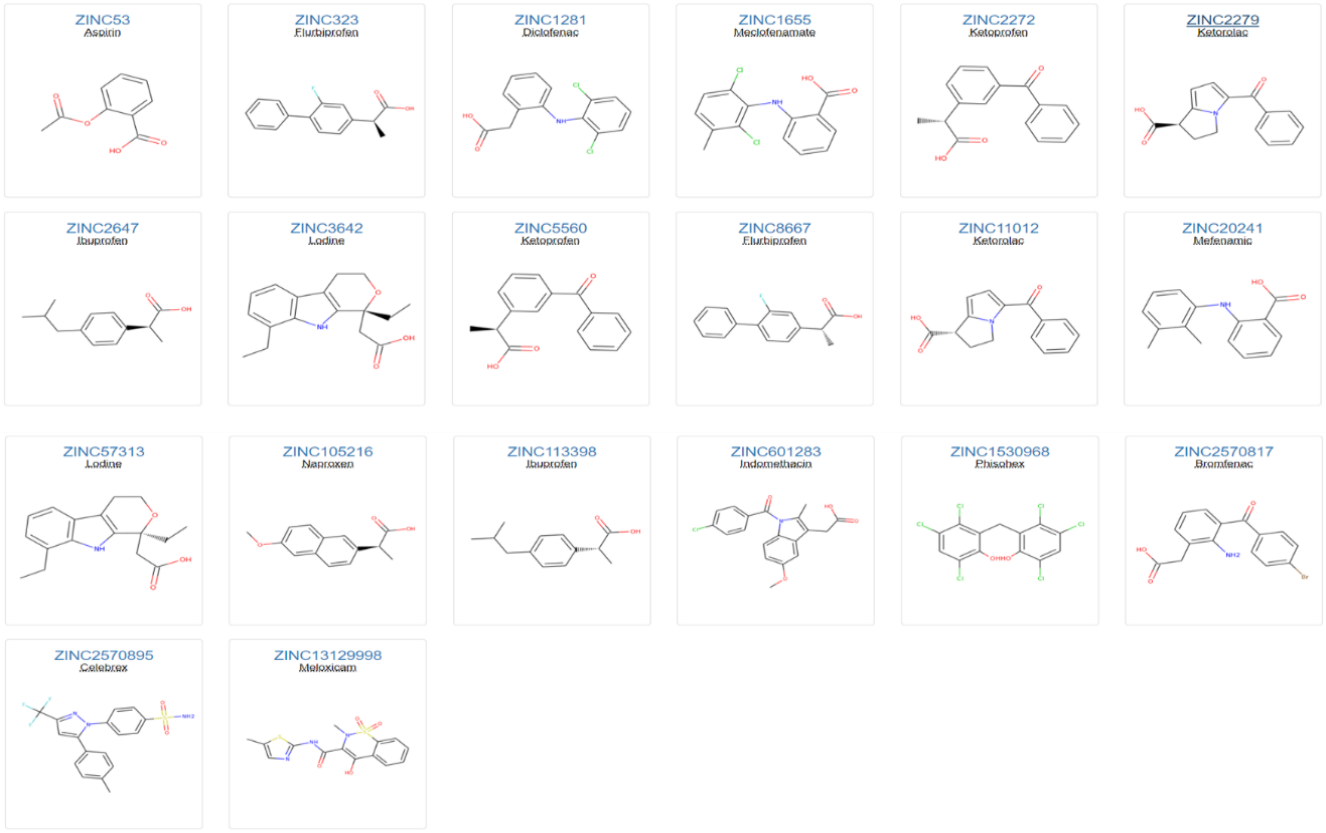

Figure 8: Predicted FDA approved drugs against PTGS2

Discussion

Cancer cachexia is a multifactorial disorder with many of the same symptoms as T2DM. While muscle wasting is a defining feature of cachexia, epidemiological evidence also suggests that T2DM patients experience increased age-related muscle loss. Both disorders have substantial weight loss as a phenotype, as well as various gene and protein abnormalities in common. This study explore the common key gene, PTGS2 using bioinformatics databases and tool.

The VennViewer tool revealed PTGS2 as the common gene involved directly in both disorders (table 1 and figure 1). In both groups, just one of these genes was discovered as common (PTGS2). Furthermore, protein-protein and protein-drug interaction analysis, pathway analysis, and prediction of potential inhibitors/drugs revealed that PPARG is the closest gene, and a variety of chemicals, including celecoxib, diclofenac, arachidonic acid, indomethacin, and others, are possible medications that interact with this target gene in various mechanisms of action.

Because these two disorders have been thoroughly studied by researchers, several medications have already been recognized, with several FDA-approved therapies specifically targeting PTGS2. Figure 8 shows the list of predicted FDA approved drugs against PTGS2. We anticipate that the findings of this study will aid researchers in the discovery of more promising treatments for a common target of cachexia and diabetes.

Conclusions

This study investigates the PTGS2 gene as a shared critical gene for diabetes and cachexia. This gene was investigated using a variety of biological databases and enrichment methods. Protein-protein and protein-drug interactions were used to identify prospective genes and compounds that could be used to treat disease symptoms. These findings will be beneficial in addressing the therapeutic management of both disorders.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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