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Drug Target of Protein and Diabetic Nephropathy

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Abstract

In biomedical research, the discovery and validation of drug targets are essential, and numerous studies have been done to analyse drug target properties in order to better understand the fundamentals of their actions. However, the majority of them are based on either solid biological assumptions or the distinct chemical and physical characteristics of those targets. In this study, we evaluated three major approaches to understanding functional biomolecules based on the topological characteristics of pharmacological targets. The protein-protein interactions network shows no discernible distinctions between targets and common proteins, indicating the drug targets are neither the bridge proteins nor the dominating hub proteins. There are notable distinctions between known targets and other proteins based on some unique topological structures of the pharmacological targets. There are notable distinctions between the known targets and other proteins based on certain unique topological structures of the pharmacological targets. Additionally, based on their modularity, the pharmacological targets primarily belong to three types of communities. These topological characteristics can be used to better understand how the PPI network's drug targets function. In particular, it is a different approach to extract no targets or anticipate possible targets to test a new therapeutic target quickly and affordably. In this manner, the homologous set of a pharmacological target, which contains 102 possible target proteins, is predicted in the article.

People with diabetic nephropathy (DN) have a lower quality of life and a shorter life expectancy. Evidence suggests that interactions between activated protein kinase C (PKC), advanced glycation end products (AGEs), and angiotensin II worsen the course of DN. A number of drugs have been studied to see if they can reduce the progression of DN, including AGEs, PKC, renin-angiotensin-aldosterone system (RAAS), and angiotensin-converting enzyme (ACEI) inhibitors. It is unclear whether specific molecular targets of drugs cause an improvement in renal damage in DN. In this review, the prospective treatment targets are outlined based on hypothesised illness progression mechanisms.

Keywords: Hypothesized; Biomedical

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Introduction

From experimental plans to target selection and validation processes, drug target studies have been carried out in both dry and wet labs [1]. A system approach and a molecular approach are the two methods for finding targets. 2006 saw the cataloguing of 218 molecular targets for approved medicinal compounds by Imming and the proposal of 324 drug targets as a consensus for all types of authorised therapeutic medicines. In addition to discussing the network pharmacology of the pharmaceuticals in our dataset, Rask-Andersen examined patterns in the introduction of medications that affect previously untapped targets [2]. In order to link medications and proteins that have received US Food and Drug Administration approval, Yildirim

constructed a bipartite graph. Novel molecular targets for well-known medicines were predicted utilising chemical 2D structure similarity. He used phenotypic side-effect similarities to infer whether the two drugs had the same target. The main molecular targets of the drug are proteins (primarily enzymes, receptors and transport proteins) and nucleic acids (DNA and RNA) [3]. It is truly encouraging that developments in cell biology, molecular biology, and biochemistry research have produced a remarkable amount of knowledge about the function and molecular characterization of individual proteins [4]. However, a protein usually performs a typical function by regulating other molecules. In other words, he rarely acts alone. Therefore, in recent years, with the emergence of high-throughput technologies for omics data, such as Yeast 2 Hybrid Protein Interactions, research on protein-protein interactions (PPIs) has taken place with high frequency. Bultinck concludes that an increasing number of functional PPI modulators are reported and clinically evaluated [5]. PPIs provide us with additional information to understand the relationship between drug targets and other proteins from a systemic point of view.

Many researchers believe that topographic analysis of the complex network of protein interactions between cells could also open new avenues for target prediction. Based on the theory of graph modeling in computer science, protein networks are widely studied in the field of systems biology. Royer used power graph analysis to unambiguously represent repetitive network patterns [6]. From a systems point of view, gene regulatory networks and drug-targeting protein networks differ from their normal counterparts. At present, drug-target interactions have also been studied as an interaction network. Chautard described high-throughput methods used to identify new interactions and to build large datasets recording identified interactions. Yamanishi describes four classes of drug-target interaction networks and reveals significant correlations between drug structure similarity, target sequence similarity, and the topology of the target interaction network [7].The basic aim of these methods tries to take into account specific information about time or space. Thus, these systems biology approaches will lead to time-, space-sensitive, and synergistic treatments by considering multidimensional drug administration. Instead of concentrating on the topological characteristics of the targets, these investigations largely examined drug target interactions [8]. It is a reasonable method for figuring out the targets that the conventional medications affect. However, because most of them have some topological traits that are distinct from those of typical proteins, the targets' topological features can be used to forecast future targets. In order to create a comprehensive understanding of drug targets, we looked at the intermediaries, the source of the pharmacological stimulus, and unique topological properties in this research. We examined lists of the topological indices connected to the three conventional viewpoints above based on the PPI network. The findings reveal, rather surprise that a medication target's topology does not benefit [9].

Between 2000 and 2030, it is anticipated that the number of people living with diabetes would more than double. Urbanization and population ageing enhance the chance that the Asia-Pacific area will experience this global health issue. With a population of around 200 million, Indonesia ranks as the fourth most populous nation and has a large medical burden. The micro- and macrovascular consequences of diabetes will definitely advance as a result of this rise in diabetes prevalence worldwide. Hyperglycemia is a key contributor to the development of problems in diabetic individuals. The most frequent microvascular consequence of diabetes mellitus is diabetic nephropathy (DN). It contributes significantly to considerable morbidity and death in diabetic patients and is a leading cause of end-stage renal failure. During the previous 20 years, theories have explained how glucose encourages kidney injury. Interactions between harmful hemodynamic and metabolic variables lead to the development of DN. The interactions cause the release of growth factors and inflammatory mediators, as well as the activation of transcription factors and intracellular signalling pathways. Proteinuria, altered vascular permeability, and extracellular matrix (ECM) protein buildup were caused by these in turn. In the past, aggressive blood pressure and glucose management were the main goals of DN treatment. Currently, glucose-dependent pathways have come into prominence as a key tactic for slowing DN progression [10].By controlling the oxidative stress, inflammation, and lipid buildup that hyperglycemia-induced oxidative stress causes, several in vitro and in animal investigations have demonstrated DN amelioration.

Materials and Method

Proteins serve as biological tissues' primary catalysts, structural components, signalling messengers, and molecular machineries. Protein interactions are the building blocks of transcriptional regulatory networks and signal transduction pathways. As a result, it is crucial for coordinating the actions within a cell. Target proteins are useful biomolecules that biologically active substances interact with and regulate. Currently, the five most popular PPI databases (HPRD version R9), IntActBioGRID, MINT, and DIP serve as the primary sources of information on protein interactions. A total of 65,785 nonredundant interactions were present in the databases. The main data about drug targets was taken from the DrugBank database, where 1,604 proteins from the approved targets set are included. After that, PISCES was used to exclude any sequences with an identity of more than 20%, whether they were part of the pharmacological target or not. Using this approach, we discovered 3,834 common proteins and 517 therapeutic candidates. Single peptide cleavage, trans membrane helices, low complexity area, N- and O-glycosylation were all characteristics of the drug's protein. The biological activity of a protein is determined by the amino acid's chemical characteristics. In light of this, they can notify us of a protein's suitability as a therapeutic target protein.

Drug Target as Intermediary

Complex biological networks control the progression of diseases, which depend on numerous stages of genetic and environmental obstacles. Drug targets with high potential include disease-relevant intracellular PPI happening at specific cellular locations. They provide much targeted pharmacological disruption of specified cellular processes. In other words, the proteins that the drug seems to target are those via which the effects of the drug tend to travel across the PPI to stimulate other associated

proteins. In this study, we examined the degree and betweenness to examine the drug targets' intermediary role.

Drug Targets as Source

Drug effects are influenced by the intricate cell signalling transduction networks or the intricate profiles of drug potency and selectivity. Generally speaking, if a drug stimulates different targets, the in vivo effect on the signalling pathway should alter and the drug's effectiveness to suppress the activity will be varied. In other words, it is feasible that a drug target appears to be the source that receives the drug signal and transforms it into a different stimulus that normal proteins can respond to. If so, the easy-to-access sources for other proteins in PPI networks should be the therapeutic targets.

Hemodynamic Factors—Renin Angiotensin System (RAS)

In addition to systemic hypertension, particular intrarenal changes—which can take place in the presence of normal blood pressure—were a factor in the advancement of DN. Progressive glomerular damage was caused by intrarenal hemodynamic anomalies such as elevated intraglomerular pressure, elevated single nephron glomerular filtration rate, and preferred afferent versus efferent arteriolar vasodilation. RAS has recently been identified as a key mediator of renal damage. High glucose levels and mechanical stress can enhance the local production of angiotensin II (Ang II) in the kidneys, which results in a number of pathophysiological alterations linked to DN.

Long recognised as the clinical identifier of DN, albuminuria. As a no hemodynamic driver of disease progression in DN, it denoted glomerular damage. In order to stop the progression of DN, lowering proteinuria to less than 1 g/24 h has been added to the targets of glycemic management and decreased blood pressure goals.Olmesartan considerably reduced the level of proteinuria in diabetic circumstances, according to Haller's research. ARB therapy has been demonstrated to slow the course of DN by increasing glomerular permeability and so reducing the levels of urine protein excretion. According to experimental evidence, diabetes causes a shift in the expression of the slit-diaphragm protein nephrin as a result of RAS blockage. ACEI can maintain the level of nephrin mRNA expression, which is decreased in diabetes.

PKC Inhibitors

PKC is a group of homologous serine/threonine kinases that play a key role in the pathophysiology of complications of diabetes, including the production of ECM basement membrane, the release of growth factors, and albuminuria. PKC catalyses a variety of biochemical processes essential to cellular processes. Three isoforms of the PKC family can be distinguished: the classical (I, II, and III), new (I, III, and IV), and atypical (I, IV, and V). The stimulation of the diacylglycerol (DAG)-PKC pathway has been linked to renal damage in diabetes. De novo production from intermediates in the glycolytic process is the main source of DAG. In diabetes, there is an increase in the creation of DAG, which causes the PKC activity to rise. Under conditions of high glucose exposure, PKC activity was elevated in glomeruli and proximal tubule cells as well as mesangial cells.

Keap1-Nrf2 Signaling Pathway

An adaptive response to both internal and external cellular stressors is mediated by the transcription factor Nrf2. Nrf2 regulates a variety of signalling cascades for the detoxification of toxic chemicals and upholds cellular redox equilibrium. Under normal circumstances, Keap1 homodimer, Nrf2's inhibitor protein, sequesters Nrf2 in the cytosol where it is more easily ubiquitinated and degraded by the proteasome. This breakdown is slowed down when a cellular insult, such as chemical, oxidative, or electrophilic stress, or when Nrf2 activating substances are present. As a result, Nrf2 moves to the nucleus and attaches to the antioxidant response element. This in turn triggers the production of genes involved in cellular defence, including those for antioxidant enzymes. Then, antioxidant enzymes boosted the production of glutathione and promoted the synthesis of nicotinamide adenine dinucleotide phosphate (NADPH).

Results

More generally, coreness and eigenvector suggest that drug target proteins may not be the hub in the PPI network, but rather, they are able to transmit the transcription signal to other related proteins through some hub-like proteins and propagate the affection to them. One of the potential explanations is that, in the cancer network, for instance, just a portion of the interactions between the associated proteins may be functional in a particular circumstance. The first hub will therefore almost certainly transform into a typical protein. On the other hand, despite the possibility that the medication signal will be broadly disseminated through hubs in order to block the disease function, it is nearly certain that it will become a barrier for many crucial processes.

According to the outcome of the aforementioned studies, a variety of factors may contribute to the onset and progression of DN. The gold standard treatment to stop the progression of DN is still RAS disruption. Additionally, stringent blood glucose management, blood pressure regulation, and therapy of hyperlipidemia are essential components for maximising renal function in diabetes. A wide spectrum of problems linked to oxidative stress, inflammation, and fat buildup exist in addition to hemodynamic and metabolic abnormalities. These have surfaced in the emerging understanding of the pathophysiology of DN and the potential for DN therapy. We find out, it demonstrates how crucial and interconnected each molecular signalling route was to the emergence and spread of DN.

Discussion

We studied the topological properties of the drug targets with three plausible views from which a drug target is known, including the intermediaries that play a significant role in interactions of the drug targets network; the sources that convert drug stimulus into the desired therapeutic effects and spread to other proteins; and the proteins that have special topological and functional properties. Their topological indices led us to some unexpected

conclusions, which we discovered.

One finding was that although the medication interacts with a target protein to carry out its activity, known drug targets do not enjoy the privilege of the first two roles. In other words, it appears that the role of spreading pharmacological stimulation is not significant for the targets of the drugs. The drug targets, however, have unique topological features that set them apart from regular proteins. These unique topological structures may facilitate drug target response to pharmacological stimulation, according to our hypothesis. Actually, a few researches have supported the claim. For instance, Overington proposed that the majority of pharmaceuticals are dependent on a number of distinct PPI network motifs. Hopkins stated that in order to determine the best sites for protein-protein interactions, therapeutic targets must be mapped into integrated biological networks.

Here, we employ the modularity and coreness of naive Bayes to choose non-drug targets from the PT1 dataset, where each protein comprises of 39 chemical and physical properties. Assume that each protein in the dataset for the upcoming test is a pharmacological target with a 50% chance. Based on the probability determined by naïve Bayes, we chose proteins among the 1,180 proteins in PT1 as the nondrug target dataset. We trained the Weka support vector machine (SVM)-based drug target classifier utilising the drug target dataset (D) and nondrug target dataset. As a result of PT1, 102 proteins are anticipated to be potential therapeutic targets. By using 10-fold cross-validation, the classifier's accuracy is 82.01%. The positive and negative predictive values are 72.7% and 82.4%, respectively.

Conclusion

Protein-protein interactions, which have been extensively studied in numerous research investigations at the molecular level, offer a better way to understand biological activities through a holistic view. In this study, a systemic biological mechanism of drug target protein interactions was revealed by a contrastive analysis of the topology of PPI networks between drug target proteins and other proteins. We discovered that the five topological indices between drug target proteins and other proteins in the PPI network—degree, betweenness, eigenvector centrality, average distance, and cluster coefficient—are remarkably comparable. It suggests that recognised drug target proteins are not eligible to serve as an intermediary or source of pharmacological effects. It contrasts with some conventional viewpoints that implicitly regard a pharmacological target protein as the PPI's central node. The other three topological qualities, eccentricity, modularity, and coreness, each have unique properties for a therapeutic target protein. This suggests that a drug's target protein may be able to interact with hub proteins, which transmit their pharmacological stimulation to associated proteins. The function of the drug target proteins can be understood and potential therapeutic effects can be tested thanks to these topological properties. One application, for instance, is to determine the new medication target. Similar to the drug target dataset, which captures chemical and physical features; there are currently no nondrug target datasets available. The non-drug target proteins, however, can be gathered in accordance with these topological traits. End-stage renal disease is mostly brought on by DN, which is still a serious consequence of both type 1 and type 2diabetes. It is critical to develop new treatments for DN. The progression of DN is mediated by a number of signalling mechanisms. Further research into newly discovered substances or the creation of novel synthetic medications that are needed for multi-targeted therapy is likely to succeed in achieving the end aim, which might be the complete halting of the progression of DN.

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Conflict of Interest

The author has no known conflict of interest associated with this paper.

References

1 Aste Amezaga, Zhang, Lineberger, Arnold, Toner (2010) Characterization of Notch1 antibodies that inhibit signaling of both normal and mutated Notch1 receptors. PLoS One 5 76: 90-94.

2 Batlle, Wysocki, Soler, Ranganath (2012) Angiotensin-converting enzyme 2: enhancing the degradation of angiotensin II as a potential therapy for diabetic nephropathy. Kidney Int 81: 520-528.

3 Benedetti, Lavecchia, Locatelli, Brizi, Todeschini (2019) Alteration of thyroid hormone signaling triggers the diabetes-induced pathological growth, remodeling, and dedifferentiation of podocytes. JCI Insight 4: 130-249.

4 Benigni, Cassis, Conti, Perico, Corna (2019) Sirt3 deficiency shortens life span and impairs cardiac mitochondrial function rescued by Opa1 gene transfer. Antioxidants Redox Signal 31: 1255-1271.

5 Benigni, Gagliardini, Tomasoni, Abbate, Ruggenenti (2004) Selective impairment of gene expression and assembly of nephrin in human diabetic nephropathy. Kidney Int 65: 2193-2200.

6 Benigni, Perico, Macconi (2016) Mitochondrial dynamics is linked to longevity and protects from end-organ injury: the emerging role of sirtuin 3. Antioxidants Redox Signal 25: 185-199.

7 Bernstein, Shen, Gonzalez Villalobos, Billet, Okwan Duodu (2011) Different in vivo functions of the two catalytic domains of angiotensin-converting enzyme (ACE). Curr Opin Pharmacol 11: 105-111.

8 Bessho, Takiyama, Kitsunai, Takeda, Sakagami (2019) Hypoxia-inducible factor-1α is the therapeutic target of the SGLT2 inhibitor for diabetic nephropathy. Sci Rep 9: 147-154.

9 Bossi, Bernardi, De Nardo, Bramante, Candido (2016) Angiotensin 1-7 significantly reduces diabetes-induced leukocyte recruitment both in vivo and in vitro. Atherosclerosis 244: 121-130.

10 Brent, G A (2012) Mechanisms of thyroid hormone action. J Clin Invest 122: 3035-3043.