Mini Review
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Focus on proteomics and bioinformatics in translational research and plant research of obesity and diabetes

Abstract

Obesity and diabetes are diseases that emerge as serious health problems to our day-to-day life. In both developed and developing countries the share of public health expenditures for diabetes and obesity increases rapidly. This results in an intense expansion of research in the area of the pathogenesis of these diseases. Translational research which defines studies where knowledge obtained in research laboratories is used to understand the molecular bases of these diseases and implement it for clinical applications is a major part of efforts to have knowledge of and potentially cure obesity and diabetes. Additionally, there is a significant number of studies researching on the potential use of plants and plant extracts to cure these two metabolic anomalies. In this context, concepts of plant biotechnology and medicinal plants began to gain a special importance in the area. The supply of a considerable number of information based on translational and plant research on the field of diabetes and obesity made it inevitable to make use of the advantages of proteomics and bioinformatics. We in our mini review focused on the studies regarding obesity and diabetes in a frame of translational research and plant research. We also highlighted the importance of proteomics and bioinformatics for the systematic dissection of accumulated data on the pathogenesis of these diseases.

Keywords: obesity, diabetes mellitus, translational research, medicinal plants, bioinformatics, proteomics

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Abbreviations: IL-1β, interleukin 1 beta; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor alpha; GLP-1, glucagon like peptide-1; PHASST-MS, smart sampling technique-mass spectrometry; Apo A-IV, lipid metabolism associated protein; TPM3, muscle function- related protein

Introduction

Obesity and diabetes are two diseases which cause a significant threat to the populations in developed countries like the United States[1,2] and started to cause significant health issues in developing countries like Turkey.[3,4] In both pathologies, the presence of an imbalance; the imbalance between food intake and energy expenditure and the imbalance in blood glucose homeostasis results in the development of obesity[5] and diabetes mellitus,[6] respectively.

It is well known today that, alterations on molecular level play a significant role in the pathogenesis of both metabolic diseases. Consistent with its complexity, molecular mechanisms associated with the pathogenesis of obesity and diabetes may be regulated on transcriptional,[7] translational and post-translational levels of gene regulation.[8] Cutting edge approaches developed as a result of recombinant DNA technology provided the opportunity to focus on investigations to unreveal these mechanisms that might be associated with the pathogenesis of obesity and/or diabetes. Translational research uses the information accumulated through this technology to apply it to clinical settings in order to potentially cure patients dealing with these diseases.[9] Recent studies brought out the use of plants and plant extracts as another significant resource towards gaining information about molecular bases of obesity and diabetes. This is evident by a significant number of reports identifying numerous plants and plant extracts as favourable alternatives to synthetic drugs.[10–13] Since ancient times, so called "medicinal plants" are considered as "natural medicines".[14]

A common ground where both translational and plant research meets regarding the investigations on obesity and diabetes is that both result in a buid up of a substantial amount of biological information. This accumulated information requires a thorough elucidation which brings bioinformatics as a handy tool into play. There is a broad consent regarding the use of tools like microarrays to monitor regulational changes at transcriptional and translational levels to uncover molecular bases of obesity and diabetes however microarrays would not be appropriate for use to investigate post-translational modifications. These modifications might be crucial for functionality of a protein.[15] Additionally although there is in general a good correlation between the levels of a single mRNA and its corresponding protein,[16] there also are mRNA protein correlations present that conflict with this observation.[17] Therefore, proteomics that covers the analyses of the data regarding the protein collection of an organism in distinct conditions in lifetime plays also a vital role within the frame of translational and plant research.

We in our mini review intended to give an overview about how translational research studies and the studies using plant extracts might serve to understand pathogenesis of obesity and diabetes. We also highlighted how proteomics and bioinformatics might serve as useful tools to process information collected as a consequence of these studies to understand molecular mechanisms underlying obesity and diabetes.

Discussion

Proteomics in translational research of obesity and diabetes

The number of diabetes and obesity cases are predicted to be increasing in explosing numbers. In both diseases there are a number of tissues that are specially of interest because of their role in the pathogenesis of them.[18] In the translational research part of our review we will shortly try to mention about the physiological processes that occur in these tissues to lead to disease states.

The pancreas,[19,20] liver,[21] skeletal muscle[22] and adipose tissue[23] are intimately associated with diabetes and/or obesity because of the role of these tissues in glucose homeostasis, insulin resistance, dyslipidemia and chronic mild inflammation.

Pancreas: Pancreas is one of the organs where intense studies are pursuit to investigate molecular mechanisms underlying diabetes since it is the source for hormone insulin. Pancreas and cells associated with this organ are also subject to proteomic studies for different perspectives. Molecular components of certain cells in pancreas may interact via different pathways with each other to get involved in pathogenesis of diabetes. Destruction and dysfunction of pancreatic beta cells are significant causes for appearance of Type 1 and Type II diabetes. Proinflammatory cytokines such as interleukin 1 beta (IL-1β), interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) are implicated of being mediators of pacreatic beta cell dysfunction. On the other hand glucagon like peptide-1 (GLP-1) is shown to protect pancreatic beta cells against cytokine induced dysfunction and disruption. Investigators used proteomic approches involving analyses of protein expression profiles of Langerhans islets of humans. In order to do so, they treated Langerhans islands with above mentioned cytokines in presence or absence of GLP-1 and elucidation of protein networks. As a result the role of GLP-1 in protecting pancreatic beta cells against cytokine mediated disruption and dysfunction is shown by making use of protein profiles and networks involved in this process.[24] Proteomic tools might also be useful to increase the yield of proteins obtained in comparison to traditional tools. Pancreatic islet cells were target of such a study where a group of investigators used secreted products of pancreatic islet cultures and did peptidomic profiling of them. They chose Peptide Hormone Acquisition through Smart Sampling Technique-Mass Spectrometry (PHASST-MS) platform for their studies. Using this approach they were able to conclude that despite they were able to identify fewer peptides in total, they had a greater representation of intact peptide hormones.[25]

Liver, skeletal muscle and adipose tissue: The main target tissues that insulin acts on in order to regulate blood stream glucose levels are liver[26–29] and skeletal muscle.[30–32] Adipose tissue which serves as a storage tissue and also acts as an active endocrine structure is mainly involved in whole body energy balance by regulating lipid metabolism.[33,34] The involvement of these tissues and the presence of some proteins that act on glucose homeostasis[35] on one side and lipid regulation on other side[36] in these tissues causes a cross-talk between diabetes and obesity.[31,32,37] It is known that there are detrimental effects of adipose tissue on the sensitivity of the whole body to the actions of insulin.[38] Depending on the need of cells for glucose, mechanisms stimulating glucose accumulation are enhanced[26] or if there is a need to use the stored glucose, such as the presence of a fasting state, an opposite mechanism is triggered that promotes glucose release in organs involved in glucose homeostasis.[39] The need for glucose in the cells results in an increase in the uptake of glucose by skeletal muscle cells[40] and adipose tissue.[41] Glycogen storage is increased through the synthesis of glycogen in liver and muscle cells and the prevention of the breakdown of glycogen. Fasting is characteristic with a state where glucose and insulin levels are low, so mechanisms keeping glucose in the blood stream need to be triggered.

Member of a group of nuclear receptor proteins, Peroxisome Proliferator Activated Receptor-γ (PPAR-γ) is identified as a protein that is playing a key role both in lipid metabolism and glucose homeostasis. This is a protein that is predominantly expressed in liver and functions to increase β-oxidation of fatty acids which links its use to the treatment of dyslipidemia. Using proteomic approaches, a certain number of PPAR-γ agonists are identified as targets for the treatment of dyslipidemia and hyperglycaemia.[42]

There are also a number of proteins that are located in skeletal muscle cells which are identified as being associated with insulin resistance. The deficiency in the enzymes which are a part of AMP-activated protein kinase signaling pathway in skeletal muscle cells are linked to cellular stress and alterations in skeletal muscle mitochondrial metabolism leading to type 2 diabetes. Proteomic studies using biopsies from diabetic and control subjects enabled to work on the members of different signaling pathways and the proteins of these pathways simultaneously.[43]

Adipose tissue is the center of investigation when the target is to asses the molecular mechanisms underlying obesity. Obesity is defined as a state of mild chronic inflammation.[44–46] The common observation in obesity is the increase in the number and cell size of adipocyte cells.[47,48] Therefore, proteins that are components of inflammatory system, inflammatory regulators like angiotensinogen and proteins specific and exclusive for adipocytes like adiponectin were found through proteomic studies to be components of a network contributing to the development of obesity.[49,50] Some proteins which showed altered expression patterns in obesity were also associated with diabetes.[51,52]

Proteomic studies to investigate the role of cellular and secreted proteins of adipocytes were analysed using different groups of subjects such as normoglycaemic and hyperglycemic patients or undifferentiated preadipocytes and fully diffrentiated adipocytes, to investigate mechanisms that might be associated with diabetes /and or obesity.[51,53]

Applications of bioinformatics and proteomics as tools in plant biotechnology for the use of plant extracts to potentially cure diabetes mellitus and/or obesity

Diabetes is a disease that has been managed with the use of some plants and plant extracts since ancient time way before studies on molecular medicine and research were as intense as today. These plants are considered as 'natural medicines'[14] and they also are known as medicinal plants. Table 1 illustrates which plants are mostly used and what their active constituents are to treat obesity.[54–57] Compelling amount of literature is already existing regarding the use of plants to treat diabetes[58–60] and many studies have confirmed the use of natural plants with hypoglycaemic effect to treat this metabolic disorder.[11,61] There are also a number of studies reporting the association of some plant extracts with different beneficial activity parameters such as antidiabetic effect, anticancer effect, antispadomic

effect.[58,62] It is estimated that more than 800 plants may possess potential antidiabetic activity.[12,58,59,63,64] These plant species belong to different families (Alliceae, Asteraceae, Bixaceae, Cucurbitaceae, Fabaceae, Ginkgoaceae, Leguminosae, Rosaceae, etc.).[11,63,64] Previous studies were not comprehensive to develop a database for diabetes. Currently there are a lot of databases available. InDiaMed, Phyto-Mellitus, Database on Antidiabetic Plants, DIAB can be given as examples to such databases.[65–68] These databases which can be accessed alphabetically using genus name serve to provide a platform for diabetes research. The aim is to form a platform to get the plants found quickly which are associated with diabetes and/or obesity. All databases are based primarily on data collection, design and their features and utility. Data are collected from various literature sources such as Pubmed, Science Direct, Mary Ann Liebert, Black Well Synergy, Ingenta connect, Scirus, Bentham Publishers, Wiley journals, Journals of phyto-medicine, Journal of Ethanopharmacology, Biomed Central, Springer link and also from folklore medicinal usage for all databases.[65–68] Researchers are trying to improve current methods for the treatment of diabetes. One of the ways is by molecular docking which predicts and analyses the interactions between protein receptors and ligands. This approach plays an important role in the rational design of drugs for diabetes. Protein ligand docking studies have been developed using Autodock 4.0 and Argus lab 4.0.1 software by various research groups.[10,69] Docking studies of green tea flavonids showed that epicatechin can act as an effective insulin receptor activator,[10] and also docking studies on *Peperromia pellucida* indicated that yohimbine contained maximum reductase inhibition activity. This result demonstrated yohimbine as the potent bioactive constituent for antidiabetic activity.[69] The molecule Scoraric acid D isolated from *Scoparia dulcis* L. was docked by using FlexX. Docking score of this molecule is comparable to that of two commercially available human alfa glucocidase inhibitors Miglitol and Voglibose.[70]

Table 1 Modified list of medicinal plants used to cure obesity by Aslan and Orhan.[54]

Name of Plant (Botanical nomenclature)	Type of action	Mechanism of action	The reported therapeutic indications	Active constituents
Allium sativum*[55]			Cancer High Colesterol, Diabetes	Allicin, Alliins, Ajoens, Oligosulfides
Amorphophallus konjac	Direct	Affecting Appetite	Obesity	Fiber
Ananas sativus	Indirect	Anti-Inflammatory	Cellulite, Hypertansion	Bromelian
Betula alba	Indirect	Diuretic	Hypertension. Cellulite, Effect On Protein Metabolism	Total Flavanoid
Camellia thea	Direct	Metabolism Stimuli	Obesity, Protein Metabolism, Cellulite	Cafein
Citrus aurantium	Direct	Metabolism Stimuli	Obesity	Synephrine
Citrus decumana	Direct	Metabolism Stimuli	Obesity, Cellulite	Total Concentrated Extract
Fucus vesiculosus	Direct	Metabolism Stimuli	Obesity, Cellulite	Iodine
Garciana cambogia	Direct	Affecting Appetite	Obesity, Major Effect On Lipid And Glucose Metabolism	Hydroxyacetic Acid
Gelidium amansii	Direct	Affecting Appetite	Obesity, Constipation	Agar Agar
Ginkgo biloba	Indirect	Capillary Protective	Dementia, Cognitive Decline, Mental Fatique,	Bioflavanoid
Gymnema sylvestre	Direct	Affecting Appetite	Obesity, Major Effect On Lipid And Glucose Metabolism	Gymnemic Acid
Hieracium pilosella	Indirect	Diuretic	Obesity, Hypertension	Hydroxycinnamic Acid (Chlorogenic Acid)
Hydrocotyle asiatica	Indirect	Capillary Protective	Cellulite, Hemorrhoids	Total Triterpen
Hypericum perforatum*[55–57]			Mild And Moderate Depression, Epilepsy, Obesity	Hyperforin,Hypericin, Flavanol Glycosides
Ortosiphon staminus	Indirect	Diuretic	Obesity, Edema	Potassium, Flavanol
Passiflora incarnata	Indirect	Neuro vegetative	Stress,Varicosity	Total Flavaoid
Panax ginseng*[55]			Fatigue And Stress, High Cholesterol, Diabetes, Gastrointestinal Disorders	Ginsenosides, Panaxans, Seqiterpenes

Tbale Continued....

Name of Plant (Botanical nomenclature)	Type of action	Mechanism of action	The reported therapeutic indications	Active constituents
Paullina sorbilis	Direct	Metabolism Stimuli	Obesity, Mental Fatigue	Cafein
Phaseolus vulgaris	Direct	Affecting Appetite	Obesity Major Effect On Lipid And Glucose Metabolism	Total Phytocomplex
Plantago ovata	Direct	Affecting Appetite	Obesity Major Effect On Lipid And Glucose Metabolism	Mucilage
Rheum officinale	Indirect	Cholaretic Cholagogue	Constipation	Total Concentrated Extract
Taraxacum officinale	Indirect	Diuretic	Cellulite, Major Effect On Lipid And Glucose Metabolism, Liver Disease	Sesquiterpene Lactones

Published proteomic data of plants is insufficient for diabetes. Studies by Karthik et al.,[71] are performed to examine the alterations in differential proteome in rat liver associated with diabetes in the absence or presence of *Cynodon dactylon* plant extract. They obtained three proteins that were up regulated in alloxan-induced diabetic rats; nucleophosmin, L-xylulose reductase and carbonic andhydrase by using 2D Electrophoresis and MALDI- TOF- MS. These detected proteins can help to understand molecular mechanism associated with diabetes. Four differentially expressed proteins from rat plasma have been identified by using 2D Electrophoresis and MALDI- TOF- MS in the same plant extract.[72] The authors classified them into three groups based on their function. Apo A-IV (lipid metabolism associated protein), HspB8 and preprohaptoglobin (both are antioxidant activity related protein) and TPM3 (muscle function- related protein) were normalized after administrations of *C. dactylon* leaf extract to rats. These proteins were up regulated in diabetic condition and the authors have reported the value of proteomic approach in identifying them also as potential markers for various types of diseases.[72] Proteins involved in regulating inflammatory pathways were obtained from the ethanolic extract of *Artemisia dracunculus* L. (PMI 5011) using differential proteomics data by Kheterpal et al.,[73] and Scherp et al.,[74] They have shown that this extract modulates proteins involved in regulating inflammatory pathways and regulate carbohydrate metabolism in human skeletal muscle culture, respectively.[73,74] *Panax ginseng* has been used to treat diabetes.[75] The previous studies with plants have been performed to obtain potential biomarkers for the pathogenesis of diabetes and following studies were carried out by Cho[76,77] & Cho et al.,[78,79] to analyse antidiabetic actions of ginsenoside Re. They reported that ginsenoside Re has a significant antidiabetic action by using SELDI-TOF-MS and bioinformatics technologies simultaneously.

Conclusion

The need to understand molecular mechanisms that might lead to the development of technologies to cure and improve obesity and/or diabetes puts the relatively new disciplines proteomics and bioinformatics at the center of attention. In addition to translational research, diabetes and obesity became also the interest of another field where a significant number of research studies are performed. Plant biotechnology also provides an immense amount of data. The use of medicinal plants especially opens alternative options to approach these diseases. This review also focused on the increasingly developed technological applications that are being used to support target confirmation in plant research for diabetes and obesity. There is a good potential that better approach options will be much easily accessible in the future. Thanks to proteomics and bioinformatics studies in plants!

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Conflict of interest

The author declares no conflict of interest.

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