CONSTRUCTION AND ANALYSIS OF THE PROTEIN INTERACTION NETWORK BETWEEN MYELOID AND LYMPHOID LEUKEMIA TYPES

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A thesis submitted in fulfilment of the
requirements for the award of the degree of
Doctor of Philosophy

Faculty of Science
Universiti Teknologi Malaysia

FEBRUARY 2022

DEDICATION

This thesis is dedicated to Mom. Thank you for always believing in me

ACKNOWLEDGEMENT

I wish to express my deepest appreciation to all those who helped me, in one way or another, to complete this project. First and foremost, I thank God almighty who provided me with strength, direction, and purpose throughout the project. Special thanks to my project supervisor Prof. Dr. Mohd. Shahir Shamsir bin Omar for all her patience, guidance, and support during the execution of this project. Through his expert guidance, I was able to overcome all the obstacles that I encountered in these enduring all the time of research and writing of this thesis. In fact, he always gave me immense hope every time I consulted with him over problems relating to my project. I wish to thank all the staff of Faculty of science for solving the administrative problems regarding of this research.

Sincere thanks to my dear husband "Ahmed Qasim" for his kindness and moral support during my study. Who encouraged me, and put his academic study on hold to achieve my dream and special thanks for his great assistance to me in the practical side and overcoming obstacles.

I would like to thank my family, especially Mom this thesis is dedicated to her, my brothers Mohammed, Abd- Allah, and My sisters Nawras, Nibras, Enaas, Manar, and Rafal for the continuous support they have given me throughout my study; I could not have done it without them. The last word goes for Leen, my baby girl, who has been the light of my life for the last two years and who has given me the extra strength and motivation to get things done.

ABSTRACT

Identifying the protein-protein interactions (PPI) is a key for understanding the underlying molecular mechanisms shared between different diseases. The PPI network and the interaction mechanism between human lymphoid and myeloid leukaemia are currently absent. Since both diseases shared many similar symptoms, an investigation into the interaction would be beneficial in identifying shared proteins and understanding their PPI, thus potentially revealing novel common drug treatments. Therefore, the main purpose of this study is to identify the PPI between human lymphoid and myeloid leukaemia. Bioinformatics and computational analysis, data mining, network development and protein interaction analysis were used to create a new lymphoid-amyloid PPI network. Further analysis using the Ingenuity Pathway Analysis (IPA) software was used to identify novel drug targets in the new PPI. The results revealed a new PPI that includes 76 proteins, of which 52 have yet to be studied and 24 proteins representing new physical interactions between lymphoid and myeloid leukaemia. Functional analysis of the new PPI network revealed that most of the proteins were involved in signal transduction, haemostasis, neutrophil degranulation, DNA repair, genetic transcription pathway and the immune system. Topological analysis of the new network identified the hubs and bottlenecks; P40763, IRF4, IL-6, P0t4637/ TP53, SMAD3, GSTM1, MTHFR, FASLG, BIRC3, PROM1, ITGB1, CYP2B6, CYP1A1and KMT2D as putative drug targets for future laboratory studies. The disease association analysis indicated that interaction defects in lymphoid–myeloid leukaemia is significantly associated with cancer, Type 2 diabetes and pulmonary disease. An assessment of the putative drug targets using the IPA software revealed that the drugs ocriplasmin (Jetrea©) for the treatment of symptomatic vitreomacular adhesion; bosutinib, dasatinib, ponatinib, and Src/multikinase inhibitors for the treatment of cancers; and siltuximab and tocilizumab for the treatment of multicentric Castleman disease (siltuximab), arthritis (tocilizumab), and chimeric antigen receptor (CAR) T-cell-induced cytokine-release syndrome (tocilizumab) were possible candidates for future efficacy testing for the treatment of leukaemia cases. In conclusion, the study has generated new insights regarding lymphoid–myeloid leukaemia interactions that are valuable for future proteomic studies.

ABSTRAK

Pengenalpastian interaksi protin-protin (IPP) adalah kunci untuk memahami mekanisme molekul yang dikongsi diantara penyakit-penyakit yang berbeza. Rangkaian IPP dan mekanisme interaksi antara penyakit leukemia limfoid dan myeloid masih belum dikenalpasti sehingga kini. Memandangkan kedua-dua penyakit ini berkongsi banyak simptom yang serupa, kajian interaksi ini akan memberi manfaat dalam mengenalpasti protin yang dikongsi dan seterusnya berpotensi untuk mengenalpasti rawatan baru. Justeru, tujuan utama kajian ini adalah untuk mengenal pasti IPP antara penyakit limfoid manusia dan leukemia mieloid. Analisis bioinformatik, perlombongan data, pembangunan rangkaian, dan analisis interaksi protein digunakan untuk mencipta rangkaian IPP limfoid-amiloid yang baharu. Analisis lanjut menggunakan perisian Ingenuity Pathway Analysis (IPA) telah dilakukan untuk mengenal pasti rawatan baru. Hasil kajian menunjukkan satu IPP baharu yang merangkumi 76 protin, yang mana 52 protin masih belum dikaji dan 24 protin mewakili interaksi fizikal baharu antara leukemia limfoid dan mieloid. Analisis fungsi rangkaian IPP baharu ini telah menunjukkan bahawa kebanyakan protin yang dikenaplasti terlibat di dalam transduksi isyarat, hemostasis, penyahgranulan neutrofil, pembaikan DNA, laluan transkripsi genetik dan sistem keimunan. Analisis topologi rangkaian baharu ini mengenal pasti hab dan cerutan baharu; P40763, IRF4, IL-6, P0t4637/ TP53, SMAD3, GSTM1, MTHFR, FASLG, BIRC3, PROM1, ITGB1, CYP2B6, CYP1A1 dan KMT2D dimana ia boleh bertindak sebagai sasaran rawatan untuk kajian makmal di masa hadapan. Analisis hubungkait penyakit menunjukkan bahawa kelemahan didalam interaksi leukemia limfoid-myeloid mempunyai kaitan signifikan dengan penyakit kanser, diabetes jenis 2 dan penyakit pulmonari. Penilaian rawatan bersasar menggunakan perisian IPA menunjukkan bahawa rawatan perubatan menggunakan Ocriplasmin (Jetrea©) untuk rawatan lekatan vitreomakular bergejala; bosutinib, dasatinib, ponatinib, dan perencat Src/kinase pelbagai untuk rawatan kanser; dan siltuximab dan tocilizumab untuk rawatan penyakit Castleman multisentrik (siltuximab), artritis (tocilizumab), dan reseptor antigen kimera (CAR) sindrom pelepasan sitokin yang disebabkan oleh sel T (tocilizumab) adalah cadangan rawatan yang boleh diuji keberkesanannya sebagai rawatan kes-kes leukemia. Kesimpulannya, kajian ini telah menghasilkan pengetahuan baharu berkenaan interaksi leukemia limfoid-myeloid yang berpotensi untuk kajian proteomik dimasa hadapan.

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LIST OF ABBREVIATIONS

PPI	–	Protein- Protein Interaction
NCI	–	National Cancer Institute
AML	–	Acute Myeloid Leukaemia
CML	–	Chronic Myelogenous Leukaemia
ALL	–	Acute Lymphocytic Leukaemia
CLL	–	Chronic Lymphocytic Leukaemia
MS	–	Mass Spectrometry
DNA	–	Deoxyribonucleic Acid
RNA	–	Ribonucleic Acid
Y2H	–	Yeast Two-Hybrid Method
TAP	–	Tandem Affinity Purification
GO	–	Gene Ontology
HPRD	–	Human Protein Reference Database
BioGRID	–	Biological General Repository For Interaction Datasets
UniProt	–	Universal Protein Resource
MINT	–	Molecular Interactions Database
SMART	–	Simple Modular Architecture Research Tool
GEO	–	Gene Expression Omnibus Database
GAD	–	Genetic Association Database
IPA	–	The Ingenuity Pathway Analysis
BC	–	Betweenness Centrality
BIND/BOND	–	Bimolecular Interaction Network Database
BioCyc	–	Biological Databases

PDB	–	Protein Data Bank
TAP-MS	–	Tandem Affinity Purification And Mass Spectrometry
dbLGL	–	Leukaemia Gene Literature Database
TSV	–	Tab-Separated Values
BIOPAX	–	Biological Pathway Exchange
CC	–	Closeness Centrality
CLU	–	Clusterin
cPath	–	Cancer Pathway Database
Cytoscape	–	An Open Source Platform For Complex Network Analysis And Visualisation
DAVID	–	Database For Annotation Visualization And Integrated Discovery
DIP	–	Database Of Interacting Proteins
DNA	–	Deoxyribonucleic Acid
FN	–	Fibronectin
GAD	–	Genetic Association Database Disease
GEO	–	Gene Expression Omnibus
Gephi	–	An Open Source Graph Visualization And Manipulation Software
GML	–	Geography Markup Language
HIF	–	Hypoxia-Inducible Factor
HPRD	–	Human Protein Reference Database
ID	–	Identifier
InterPro	–	Integrative Protein
IPA	–	Ingenuity Pathway Analysis
ITGA	–	Integrin
KEGG	–	Kyoto Encyclopaedia Of Genes And Genomes

Medusa	–	A Java Application For Visualizing And Manipulating Graphs Of Interaction
MI	–	Mint-Inspired
MINT	–	A Molecular Interaction Database
MIPS	–	Mammalian Protein-Protein Interaction Database
mRNA	–	Messenger Ribonucleic Acid
MS	–	Mass Spectrometry
NAViGaTOR	–	Network Analysis, Visualization And Graphing Toronto
NCBI	–	National Center For Biotechnology Information
OMIM	–	Online Mendelian Inheritance In Man
Pajek	–	Program For Analysis And Visualization Of Large Networks
PDF	–	Portable Document Format
Pfam	–	Protein Families
PIN	–	Protein Interaction Network
PPI	–	Protein-Protein Interaction
PSI-MI	–	Project Server Interface-Molecular Interactions
PubMed	–	National Library Of Medicine
RNA	–	Ribonucleic Acid
S. cerevisiae	–	Saccharomyces Cerevisiae
STRING	–	Search Tool For The Retrieval Of Interacting Genes
SVG	–	Scalable Vector Graphics
TAP	–	Tandem Affinity Purification
TIFF	–	Tagged Image File Format
UniProt	–	Universal Protein Knowledgebase
XML	–	Extensible Markup Language
Y2H	–	Yeast Two-Hybrid
	–	

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CHAPTER 1

INTRODUCTION

In the last two decades, the study of interrelated cellular processes and biological pathways has resulted in the discovery of novel disease-related genes or proteins; this effort has relied on the use of protein–protein interaction (PPI) networks [1, 2]. Even though PPI networks have been responsible for the discovery and understanding of many important molecular interactions that mediate interactions in diseases such as colorectal and breast cancer, those interactions in cancer of the blood, also known as leukaemia, are still not well understood. This is due to the complexity of and various restrictions in studying leukaemia processes using human gene interactions in vitro. In addition, the availability of information and data on such heterogeneous databases is still poor, and combined with the task of creating a precise and universal compilation of these databases, the effort is considered an immensely difficult task. As a result, creating a comprehensive proteome map for human cell types remains a long-term goal [3].

1.1 Background of the Study

Leukaemia is a cancer that infects the tissues, marrow, lymph nodes, and spleen, which are involved in the formation of new blood cells, and it is described as an uncontrolled proliferation of immature and abnormal blood cells. Two major classifications of leukaemia have been created according to the origin of the blood cells. On the one hand, cells that arise from myeloid descent – undeveloped blood cells that differentiate into monocytes or granulocytes – is referred to as myelogenous leukaemia. On the other hand, if leukaemia includes lymphocytes, it is classified as lymphocytic leukaemia. Under these two major classifications, the National Cancer Institute (NCI) has categorized four major groups of leukaemia.

First, acute myeloid leukaemia (AML) is considered the most common form of leukaemia. Second, chronic myelogenous leukaemia (CML) more commonly occurs in adults. Third, acute lymphocytic leukaemia (ALL) exists almost entirely in children, and fourth, chronic lymphocytic leukaemia (CLL) is the most common chronic adult leukaemia where the affected individual may be symptomless for years without needing medical treatment, thus generally affecting those older than 55 years old and rarely occurring in children [4]. One of the challenges is that conventional blood tests and bone marrow examinations are not sufficient to quickly diagnose, because it is not-specific and vague [5]. There is hence a need to investigate the biomarkers and molecular alterations in leukemogenesis [6]. Cancer is a complex disease, and the disease aetiology is not from the malfunction of single molecules but due to their collective behaviour in the network [7] Therefore, mapping the PPI of a disease in a network, which will identify key interactions and their respective biomarkers, has recently attracted much attention. This solution that potentially identifies protein interaction sub-networks would allow for early diagnosis, prognosis, and prediction efficiency of cancers treatments [8].

A PPI is a biological network that has been used to predict protein functions, identify essential genes or proteins, detect protein complexes, and discover network motifs [9, 10]. PPIs can interact in many ways, for example direct physical associations among proteins in complex and passing interactions that occur among members of particular protein pathways. The proteins involved in PPIs are engaged and interact spatially or temporally with other proteins in the process, and it works as a non-interacting member of the same pathway [11]. In addition, developments in computational and biochemical methods have contributed to the discovery and development of PPIs [12–14].

Different biochemical, cell biological, and genetics methods have been identified to map interatomic proteins for more than two decades [9]. For example, single-gene knockouts, RNA interference, proteomics approaches, and mass spectrometry (MS) have been used to distinguish PPIs between proteins [15, 16]. These traditional methods are less reliable and face various limitations, especially when compared to studies of dynamic PPIs, the complexity of the analysis membrane PPIs in

vivo as well as denaturing proteins, and the dynamics in the formation of protein complexes. Moreover, conventional methods are predominantly laboratory-based, requiring significantly more time, a larger workforce, and more funding. Therefore, to improve upon these limitations, research on efficient and low-cost computing methods can contribute to our understanding of PPIs beyond the current levels. Computational biology and big data have provided a path to comprehensively and synchronous analyse data to increase understanding of biological systems [17–20].

A computational methods can speedily and accurately recognize the genes and proteins that are fundamental in biological networks. The precision and effectiveness of computational methods have improved the building of networks that possess specific characteristics tailored to the nature of biological networks [21]. Many studies have shown that diseases and biological networks are closely related because diseases are often caused by errors occurring in biological networks, specifically in differentiating critical nodes. Therefore, studying biological networks and critical nodes may help to determine the key targets in treating diseases [20]. Recent discoveries in the interrelationships between disease-related genes and proteins as well as the subsequent studying of PPIs in humans has brought new insights into disease network biology [22].

1.2 Problem Statement

Diseases are the result of detrimental changes in molecular mechanisms, and the pathology of cancer is a typical example that is caused by the disruption of cellular performance. However, the complexity of such diseases and their mechanism of abnormalities involves myriad epigenetic and genetic changes that cause differing functions and expressions of proteins [23].

As conventional blood tests and bone marrow examinations are not sufficient to diagnose the symptoms of leukaemia early, biomarkers and their molecular interaction alterations in leukemogenesis present a potential candidate for novel leukaemia diagnosis [24]. While in vivo analysis is currently time-consuming and technically difficult without substantial costs, there is a need to understand the complex disease

mechanisms that explain the causality of the disease [25]. Previous studies on closely related diseases and their biological networks have successfully revealed errors in interaction nodes in their common biological networks [26] Therefore, studying the disease-associated genes and biological networks is important. To date, there are no clear nominee interaction proteins that have been attributed to the molecular interaction in leukaemia, as a comprehensive PPI network between myelogenous and lymphocytic leukaemia is yet to be mapped.

1.3 Research Objectives

The objectives of this study with regard to the two main types of leukaemia, namely, myelogenous and lymphocytic leukaemia, are as follows:

1. To prospect, identify, and map PPI networks for interaction between the two human leukaemia types.
2. To detect new PPIs connected with the interaction between human leukaemia types.
3. To predict the functional network for interaction between two types of leukaemia: myelogenous and lymphocytic leukaemia.
4. To identify putative drug targets in two types of leukaemia interaction networks.
5. To explore diseases associated with the interaction disorder of the leukaemia types.

1.4 Scope of Study

This study exclusively involves bioinformatics and computational analysis, which include data mining, network development, and protein interaction analysis. All the data were derived from dbLGL leukaemia gene literature database (http://soft.bioinfo-minzhao.org/lgl/). Classified to two groups (myelogenous and lymphocytic leukemia). Analytics software such as Cytoscape was used for

visualization and complex network analysis, and Cytoscape plug-ins were utilized to analyse the created network; these plug-ins include Allegro-Mcode, Bingo, CluGO, and CluGO Pedia. Furthermore, the diseases correlated with each leukaemia type's interaction disorder were found using DAVID software and the Genetic Association Database (GAD). The Ingenuity Pathway Analysis (IPA) software was employed to identify known drug targets in the two leukaemia types' interaction networks.

1.5 Significance of Study

The common molecular mechanisms underlying comorbidities remain vague, although they co-occur. Understanding the underlying disease mechanisms considering the interactions between molecular components is key to the identification of comorbid diseases. The coincidence of two or more diseases in the same individual consequently leads to the question regarding their underlying common etiological pathways [27]. The presence of a simultaneous occurrence of CLL and AML in the same patient is rare, and most of these cases occur as a secondary event in patients receiving chemotherapeutic agents for CLL [28–30]. Comorbid diseases occur in an individual for two reasons. First, the common diseases' genes are the common biological factors that cause comorbid diseases. Second, because they are co-regulated by high-level biological processes, these genes belong to the same cellular pathways. In addition to the numeral of direct PPIs between the causative proteins of two diseases believed to explain the hidden comorbidity patterns [31]. Therefore, it is important to build a broad PPI network to understand molecular disease mechanisms and the evolution of targeted treatments.

The research will result in an updated PPI map that depicts potential protein interactions, important biological activities, and disease-associated genes in major kinds of leukaemia interaction protein networks. It will also help future studies in biomarker identification and novel medication designs for leukemia diagnosis and therapy.

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LIST OF PUBLICATIONS

Indexed Journal (SCOPUS)

1. Hamad, O. N., Shamsir, M. S., Amran, S. I., & Abdalhasan, A. Q. (2021). Protein Network and Functional Analysis of Human Leukemia Type's Interaction. Annals of the Romanian .Society for Cell Biology, 25(6), 9756-9770

2. Hamad, O. N., Shamsir, M. S., Amran, S. I., & Abdalhasan, A. Q. (2021). Construction and analysis of the proteins interaction network for the four types of leukemia. International .Journal of Pharmaceutical Research, 13(2), 1129-1137

Non-Indexed Journal

1. Hamad, O., Amran, S., & Sabbah, A. (2018). Drug Discovery-Yesterday and Tomorrow: The Common Approaches in Drug Design and Cancer. Cell Cell. Life Sci. J , 3, 000119

2. Oras N.Hamad, Amran Sib, Bilal K. Sulaiman, Batool A li Shihab, Ahmed Qasim Abd A l-Hasan. (2018). Detection of The Optimum Conditions For The Amplification of Some Regions In The Multidrug Resistance Gene I n Acute Myeloid Leukemia Patients I n Iraq .IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 13.5 , 46-49