

CONSTRUCTION AND ANALYSIS OF PROTEIN-PROTEIN INTERACTION  
NETWORK ASSOCIATED WITH HUMAN SPERM-EGG INTERACTION

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To my beloved family, especially my husband

“Alireza Valipour”

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## ABSTRACT

Complete elucidation of sperm-egg interaction at molecular level is one of the unresolved challenges in sexual reproduction studies, and the understanding the molecular mechanism is crucial in overcoming difficulties in infertility and unsuccessful *in-vitro* fertilization. Numerous molecular interactions in the form of protein-protein interactions mediate the sperm-egg membrane interaction process. Due to the various limitations of materials and difficulties in analyzing *vivo* membrane protein-protein interaction, many efforts have failed to comprehensively consider the interaction mechanism at molecular level which mediates sperm-egg membrane interaction. The main purpose of this study was to identify the possible protein interaction in human sperm-egg interaction using the protein-protein interaction network approach. Datasets from varying databases containing information on membrane-associated proteins in sperm-egg binding and fusion process have been utilized to construct human sperm-egg interaction network using Cytoscape Software. The analyzing network represented new interactions in binding and fusion of sperm to egg. CD151 and CD9 in human oocyte had interaction with CD49 in sperm, and CD49 and ITGA4 in sperm interacted with CD63 and CD81 respectively in the oocyte. These results showed that the different integrins in sperm may be involved in human sperm-egg interaction. It also revealed novel interactions between acrosomal proteins in sperm and membrane proteins in oocyte. The Fn1, PDIA6 and ARSA from acrosome content of sperm have been shown to interact with ITGA9, IGSF8 and BMPR2 in oocyte, respectively. Topological analysis of the sperm-egg interaction network identified ITGB1, FN1, EGFR, ITGA3, ITGAV, ITGB3 and COL1A1 as putative drug targets to future study on sperm-egg interaction disorder. Using functional analysis of the network by ClueGo and ClueGo Pedia (two Cytoscape Plugins), the major molecular functions in sperm-egg interaction protein network was identified. The Interleukin-4 receptor activity, receptor signaling protein tyrosine kinase activity, manganese ion transmembrane transport activity were identified as the major molecular function group in sperm-egg interaction protein network. The disease association analysis using Database for Annotation Visualization and Integrated Discovery (DAVID) analysis represented the associated diseases with sperm-egg interaction disorder and indicated that sperm-egg interaction defects possess significant association with diseases such as cardiovascular, hematological and breast cancer. The Ingenuity Pathway Analysis (IPA) of the putative drug targets showed that the drugs ocriplasmin (Jetrea®), gefitinib (Iressa®), erlotinib hydrochloride (Tarceva®), clingerite, cetuximab (Erbix®) and panitumumab (Vectibix®) are possible candidates for efficacy testing for the treatment of infertility cases. In conclusion, the result of this study has generated new knowledge regarding sperm-egg interaction that is for future proteomic studies.

## ABSTRAK

Merungkai interaksi sperma-telur di peringkat molekul adalah satu cabaran yang masih tidak dapat diselesaikan di dalam kajian pembiakan seksual, dan memahaminya adalah penting dalam mengatasi masalah kemandulan dan kegagalan persenyawaan *in-vitro*. Terdapat pelbagai interaksi molekul dalam bentuk interaksi protein-protein pengantara antara sperma dan telur. Oleh kerana pelbagai halangan dalam kaedah makmal dan kesulitan dalam menganalisis interaksi protein-protein secara kaedah *in-vivo*, banyak usaha telah gagal untuk mengkaji secara komprehensif mekanisme interaksi sperma dan telur di peringkat molekul. Tujuan utama kajian ini adalah untuk mengenal pasti interaksi yang mungkin wujud dalam interaksi sperma-telur manusia menggunakan pendekatan rangkaian interaksi protein-protein. Set data dari pelbagai pangkalan data yang mengandungi maklumat mengenai protein membran yang terkait dalam mengikat dan gabungan sperma-telur proses telah digunakan untuk membina rangkaian interaksi sperma-telur manusia. Analisa rangkaian menunjukkan protein CD151 dan CD9 dalam oosit manusia mempunyai interaksi dengan CD49 dalam sperma, dan CD49 dan ITGA4 dalam sperma berinteraksi dengan CD63 dan CD81 di dalam oosit. Hasil kajian ini menunjukkan bahawa berbagai jenis integrin yang berbeza dalam sperma dijangka terlibat dalam interaksi sperma-telur manusia. Ia juga mendedahkan interaksi antara protein novel akrosom dalam sperma dan membran protein di dalam oosit. Protein fn1, PDIA6 dan Arsa yang terkandung di dalam akrosom sperma telah dibuktikan mempunyai interaksi dengan ITGA9, IGSF8 dan BMPR2 di dalam oosit. Analisis topologi rangkaian interaksi sperma-telur telah mengenal pasti ITGB1, FN1, EGFR, ITGA3, ITGAV, ITGB3 dan COL1A1 telah dikenalpasti sebagai sasaran ubat (drug target) dan sesuai digunakan di dalam kajian masa depan terhadap penyakit berkaitan persenyawaan sperma-telur. Dengan menggunakan analisis fungsi rangkaian oleh ClueGo dan ClueGo Pedia (dua Cytoscape Plugins), fungsi utama molekul dalam sperma-telur rangkaian protein interaksi telah dikenal pasti. Reseptor Interleukin-4, penerima isyarat protein tyrosine kinase dan pengangkutan transmembran ion mangan telah dikenal pasti sebagai kumpulan fungsi molekul utama dalam rangkaian interaksi protein telur-sperma. Analisis penyakit persatuan menggunakan Database untuk Anotasi Visualisasi dan Integrated Discovery (DAVID) analisis mewakili penyakit yang berkaitan dengan sperma-telur gangguan interaksi dan menunjukkan bahawa interaksi kecacatan sperma-telur mempunyai hubungan yang signifikan dengan penyakit seperti kardiovaskular, hematologi dan kanser payudara. The Pathway Analysis Ingenuity (IPA) menasaskan beberapa ubat yang berpotensi seperti ociprasmin (Jetrea ©), gefitinib (Iressa ©), erlotinib hidroklorida (Tarceva ©), Clingitide ©, cetuximab (Erbix ©) dan panitumumab (Vectibix ©) dimana ia boleh menjadi calon-calon ujian keberkesanan yang untuk merawat kes-kes kemandulan. Kesimpulannya, hasil kajian ini telah menghasilkan pengetahuan baru mengenai interaksi sperma-telur dan bakal menyumbang kepada kajian proteomik di masa depan.

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## CHAPTER 1

### INTRODUCTION

#### 1.1 Background of Study

Sperm-egg interaction is a unique cell-cell connection process in sexual reproduction that involves two gametes recognize, bind and eventually fuse with each other (Wortzman *et al.*, 2006). The potential intermediaries of molecular process in sperm– oocyte fusion and binding have been studied over the past 20 years (Kaji and Kudo, 2004; Primakoff and Myles, 2002; Stein *et al.*, 2004). However, the molecular adhesions that intercede sperm– egg membrane interaction event is still poorly understood due to limitations in studying the process *in-vitro* and the analysis of membrane associated sperm-egg interactions in human (Brewis *et al.*, 2005).

Fertilization is the process in which sperm and egg recognize, bind and fuse with each other (Inoue *et al.*, 2005; Inoue *et al.*, 2010; Kaji and Kudo, 2004). During this process, many molecular interactions in the form of protein-protein interactions will mediate the sperm-egg binding process. The elucidation of sperm-egg interaction at the molecular level is one of the unresolved problems in sexual reproduction, and understanding the molecular mechanism is crucial in solving problems in infertility and in vitro fertilization failure (Evans, 2012).

Infertility is a current medical problem affecting 10–15% of reproduction-aged couples in the world (Hotaling *et al.*, 2011). The percentage of infertility is being higher in underdeveloped countries in which limited resources for diagnosis and treatment exist (Hamada *et al.*, 2011b).

Male factor problems, mainly defined by abnormal semen analysis, are the single most conventionally diagnosed reason of infertility. In vitro fertilization (IVF) is implemented for men with no sperm dysfunction. Nevertheless it is surprising that the complete fertilization fail is still prevalent event in the process of IVF. This suggests that the sperm dysfunction is not certain even with common semen analyzing while is a considerable cause of fertilization failure. This phenomenon is called unexplained male infertility and remains an unknown syndrome as researchers have limited information regarding the clinical nature of the sperm dysfunction (Brewis *et al.*, 2005; Hamada *et al.*, 2012). Recent studies have suggested that sperm deficiencies such as zona binding, the zona-induced AR (Acrosome Reaction) or oocyte plasma membrane fusion defects are significant causes of reduced fertilization and total fertilization fail in assisted reproductive technologies. Therefore the major cause of fertilization failure in conventional IVF of unexplained male infertile is due to abnormalities of sperm–oocyte interaction and penetration (Brewis *et al.*, 2005; Hamada *et al.*, 2012; Liu and Baker, 2000).

The proteins-protein interactions (PPI) can interact in various ways, ranging from direct physical relationships amongst proteins in a complex, to indirect interactions that happen amid components of specific protein pathways. These links between the proteins in a protein set can make a protein-protein interaction network (PIN) and all proteins which involved in PINs are spatially or temporally engaged to interact with other proteins within the process as well as functioning as an indirect interacting members of the same pathway (Brewis *et al.*, 2005; Strong and Eisenberg, 2007). Currently, the discovery of protein connections has been assisted by developments in both biochemical (Brown and Botstein, 1999; Ho *et al.*, 2002; Ito *et al.*, 2001; Uetz *et al.*, 2000) and computational methods (Janga and Moreno-Hagelsieb, 2004; Salgado *et al.*, 2000; Strong *et al.*, 2003), which have produced precious awareness into the fundamental building of protein interactions in cellular

networks (Jeong *et al.*, 2000; Marcotte *et al.*, 1999; Ravasz *et al.*, 2002; Rives and Galitski, 2003; Wuchty, 2002).

Until now, the original experimental methods, for instance, mass spectrometry and proteomics approaches have been used to identify protein-protein interaction between human sperm and egg (Evans, 2012). However, due to the complexity of the problems like difficulties in analyzing *in-vivo* membrane PPIs, denaturing proteins and possible disruption in the formation of protein complexes, many efforts have failed to comprehensively elucidate the fusion mechanism and the molecular interactions that facilitate sperm-egg membrane fusion, leaving the molecular mechanism during sperm-egg interaction still poorly understood (Brewis *et al.*, 2005; Evans, 2012; Kaji and Kudo, 2004).

Existing computational approaches, in addition to experimental methods, can assist our understanding of PPIs at various levels. The computational approaches may be utilised for comprehensive examination or perform a wide scale analysis across large datasets (Lu *et al.*, 2002; Salwinski and Eisenberg, 2003). This approach signifies the multifaceted association of proteins with PPI links, in a protein interaction network and would help to comprehend how signalling pathways linked with a disease are connected (Xu and Li, 2006). By using computational methods, it is possible to identify a comprehensive information about complex diseases not discernible in laboratory methods such as the putative disease target genes, putative drug targets, new prognostic biomarkers and understanding the mechanism of complex disease by network analysis (Devaux *et al.*, 2010; Flórez *et al.*, 2010; Yao *et al.*, 2010). Thus, computational approach denotes a novel technique for investigating the complex impacts of candidate genes that are connected to complex diseases, and is also worthwhile in recognizing important drug targets and genes in a disease and in complex biological systems (Hwang *et al.*, 2008; Kim and Kim, 2009).

## 1.2 Problem Statement

Sperm–oocyte interaction is one of the most remarkable events in fertilization process and its surrounding molecular events have been studied in various attempts over the last 20 years. Due to detection the molecules that immediate human membrane sperm-oocyte interaction, different techniques have been used and represented a low number of sperm and oocyte proteins which have a fusogenic role in sperm–egg interaction event (Evans, 2012).

Because of difficulties *in vitro* analyzing membrane protein-protein interactions and the limitation of technical materials, the molecular mechanisms involved in sperm–egg membrane adhesion are still poorly understood (Inoue *et al.*, 2010; Kaji and Kudo, 2004). Moreover, the focus of the wide majority of the previous studies was on utilizing animal models to understand subsequent related molecular mechanisms, but in order to understand the human infertility and fertilization mechanisms, the emphasis must be on the human model. The study on human model in this conception could be predominantly a difficult task because of the modicum of human oocytes or embryos (Ola *et al.*, 2001; Tournaye *et al.*, 2002). Elucidation of sperm-egg interaction at molecular level is one of the unresolved problems in sexual reproduction and the major cause of fertilization failure in conventional IVF and unexplained male infertile is due to defect in sperm–oocyte interaction and penetration (Brewis *et al.*, 2005; Hamada *et al.*, 2012).

Therefore understanding the molecular mechanism surrounding human sperm–egg interaction is crucial in solving problems in infertility and in vitro fertilization failure. To date, no clear candidate interaction proteins have identified and the molecular interaction events still poorly understood. There is a lack of a comprehensive protein-protein interaction network for human sperm-egg interaction and also a lack of a protein links network of human sperm-egg interaction process with other cellular pathways (Evans, 2012).

### **1.3 Objectives**

The main purpose of this study was to reveal possible protein interaction and associated molecular function during sperm-egg interaction using protein interaction network approach. The objectives of this research are:

1. To mine, identify and map protein-protein interaction network for human sperm-egg interaction
2. To find new protein-protein interaction associated with human sperm-egg interaction
3. To identify putative drug targets in sperm-egg interaction network
4. To predict the functional network for interaction between sperm and egg
5. To investigate associated diseases with the sperm-egg interaction disorder

### **1.4 Scope of study**

In this research, the focus was on the proteins that involved in human sperm-egg interaction. These proteins were mined from PubMed research articles, UniProt database and protein-protein interaction databases which store the physical and functional interactions. It has also included the predicted interactions from predicted database. The results were then mapped using Cytoscape software as a general platform for complex network analysis and visualization. The created network has been analyzed using Cytoscape plugins: Allegro-Mcode, Bingo, ClueGO and ClueGO Pedia. Then the diseases associated with sperm-egg interaction disorder would be discovered using DAVID software and GAD database. In order to find out known drug targets in sperm-egg interaction network, the analysis using IPA (Ingenuity Pathway Analysis) software have been carried out.



## 1.5 Significance of study

The elucidation of sperm-egg interaction at the molecular level is one of the main unresolved problems in sexual reproduction, and it is also crucial to understand the molecular mechanism in solving problems in infertility and failed IVF. Many molecular interactions in the form of protein-protein interactions (PPI's) mediate the sperm-egg membrane interaction process. But, due to the complexity of the problems such as difficulties in analyzing *vivo* membrane PPI's, many experimental efforts have failed to comprehensively elucidate the fusion mechanism and the molecular events that mediate sperm-egg membrane interaction (Brewis *et al.*, 2005; Evans, 2012; Hamada *et al.*, 2012; Kaji and Kudo, 2004).

In addition to experimental methods, computational methods can deal with PPIs at various levels. Computational approach for constructing protein interaction networks, utilizing genomic and protein sequence information contain a study of the absence or presence of genes in associated species, co-occurrence of sequence domains, gene fusion occurrences, conservation of gene neighborhood, interrelated mutations on protein surfaces, the resemblance of phylogenetic trees, co-expression and functional annotations (Salwinski and Eisenberg, 2003). Sometimes, combinations of these aspects are implemented to foresee novel interactions or to appraise the trustworthiness of PPIs measured experimentally (Brown and Jurisica, 2005; Jensen *et al.*, 2009).

Therefore, this study was carried out to promote a protein-protein interaction map that reveals the possible protein interaction, major molecular functions and disease association genes in sperm-egg interaction protein network. This study facilitates future research in biomarker detection and new drug designs for diagnosis and treatment of the infertile cases, who suffer from failures in assisted reproductive technology.

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