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A lipidomic concept in infectious diseases

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ABSTRACT

Infectious diseases resemble a great threat to the human health according to World Health Organization where about 17% of all deaths (≈9.2 million deaths) in 2013 recorded are related to infectious diseases. The pathogenic microorganisms such as bacteria, viruses, fungi and parasites are the principle causes of infectious diseases. Ebola, AIDS, dengue, hepatitis, malaria, tuberculosis and schistosomiasis are among 216 infectious diseases found where the immunity represents the first line defense in infection. Lipidomic includes examination of different biological lipids in the biological cell. The lipidomic research covers all aspects of individual lipid molecule including its structure, function, connection with other cell constituents such as protein, lipid, and metabolite in both health and disease conditions. Details of cell biology obtained from different pathogens (viruses, bacteria, and parasites) provide a great data on molecular structure of host-pathogen relation and consequently on infection process. The lipids here play a very important role in many processes involved in host-pathogen relations. The role of lipid in host-pathogen link includes many processes in (1) structural host constituents, (2) host recognition, (3) intracellular transferring, and (4) energy and resource homeostasis during pathogen duplication. There are many lipid phosphatases, kinases, and lipases molecules that greatly involved in these processes and controlling pathogen expression and infection progress. The cell lipid metabolism depends on an adequate energy stores that push the infection to be accelerated and disease symptoms to be appeared. Consequently, future lipidomics studies are the basic for detecting the lipid role in host-pathogen relations which help in therapy advances and biomarkers development.

1. Introduction

Lipidomics was first detected by Han and Gross [1], through including the defined chemical properties in individual lipid molecules with a specific mass spectrometry technique. Lipidomics is identified as a study of different pathways of each individual cellular lipid inside specific biological systems [2–4]. The lipidomic research covers qualification and quantification of individual lipid molecules and their connections with other cell constituents such as proteins, lipids and metabolites. The lipidomic research includes different individual lipid structure, function and interaction with the changes that happened during pathophysiology of the cell biological system under investigation. The research concerning lipidomic technique comprises information dealing with lipid content and structure changes after invading of a cell through the change in cell physiological or pathological conditions. The data collected from these researches enable scientists to observe changes reported in the cell function. Consequently, lipidomic researches play a vital role in identification the biochemical mechanism condition of lipid-related disease progressions through categorizing the changes found in lipid metabolism and transfer inside the biological system. The lipidomic can combine with metabolomic to display anti-hyperlipidemic effect of grape seed extract where biliary acid, dicarboxylic fatty acid, and metabolites of cholesterol, purine, and eicosanoid were determined by mass spectrometry, multivariate analysis, mass spectrometry-mass spectrometry scan and mass database techniques [5]. Moreover, the lipidomic profiling and metabolomic profiling communicate together through using

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high performance liquid chromatography together with quadrupole mass spectrometry to examine different pathways of each individual amino acid metabolism and lipid metabolism [6].

The lipidomic research can be shown in a full and sharp picture through application of lipid metabolites and pathways plan as recommended by LIPID MAPS Consortium [7], and the fundamentals points are taken from the European Lipidomics Initiative program [8]. The lipidomic study is an innovative field that has been determined by the novel technologies used and these new applications include mass spectrometry, nuclear magnetic resonance technique, fluorescence spectroscopy, dual polarization interferometry and computational applications. The lipidomic study includes the identification of the lipid role in many metabolic diseases such as atherosclerosis, diabetes and obesity. The lipid research is a basic technique for the metabolomic study where lipidomic gave a full details data for different lipid occurred inside the biological system. The electrospray ionization tandem mass spectrometry is a new technique used in lipidomic research that provides quantitative data and is accurately adaptable to high analysis result [9]. A mass spectrometry technique is another new application used showed in details the alterations reported in each individual addition to proteomic study which focuses in detail on different protein structure and function changes to complete the pyramide shape which gives us all information about pathophysiological conditions metabolic pathways changes. Figure 1 reveals the general figure to explain the associations between lipidome to another one studies such as genome, transcriptome, proteome and metabolome techniques [11]. The lipids in another function adjust protein function changes and gene transcription induction and these conditions are responsible for pathophysiological state. In the infection case, the formation of biological system lipids needs more work to be understood while lipids formation decreased according to disappearance of many genes that incorporated in the process of lipid formation where the lipidomic study provides a great information about the lipid role in infection diseases and the lipid role in pathological condition-related to infection [2,3]. The lipidomic research investigates each individual lipid such as choline ether and ethanolamine lipids as well as seminolipids which are important for cell membrane function. For example, sperm (O-acyl)-ω-hydroxy-fatty acids are important for sperm quality, and function and seminal plasma phosphatidylethanolamines are very important lipids for sperm function [12].

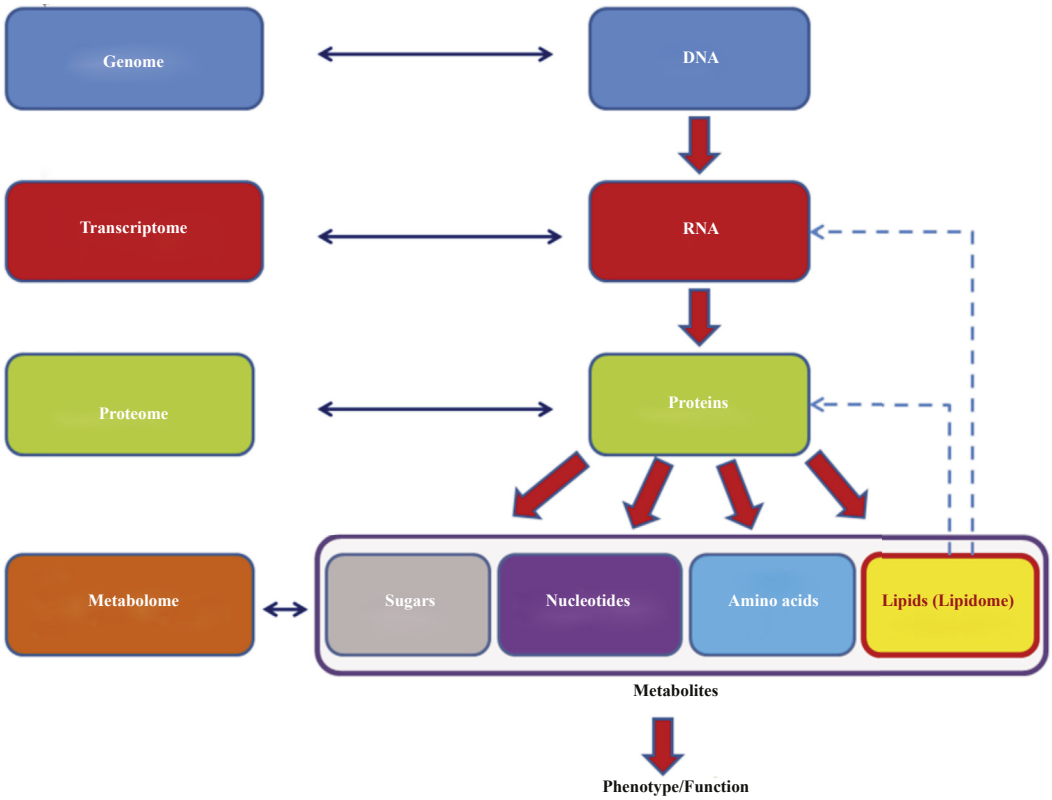

Figure 1. General schema showing the relationships of the lipidome to the genome, transcriptome, proteome and metabolome. Lipids as part of metabolomics. Lipids also regulate protein function and gene transcription as part of a dynamic interaction [11].

lipid profile in mice induced by endometriosis where the authors recognized many modified and structurally-changed lipids such as phosphatidylethanolamines, phosphatidylcholines, triglycerides and sphingomyelins [10].

To understand the metabolic pathways in a full consideration, the lipidomic research must communicate with genomic study which includes gene array application and genetic map in

Infectious diseases resemble a great threat to the human health according to World Health Organization. About 17% of all deaths (≈9.2 million deaths) in 2013 recorded are related to infectious diseases [13]. The pathogenic microorganisms such as bacteria, viruses, fungi and parasites are the principle causes of infectious diseases. Ebola, AIDS, dengue, hepatitis, malaria, tuberculosis and schistosomiasis are among 216

infectious diseases found [14]. Infectious factors comprise viruses, bacteria and parasites. The immunity represents the first line defense against infection to be happened. The inflammation is the fast reaction occurred in humans when infection occurred [15]. The Ebola virus caused 39.5% (11 315 death) of the total human death, while in developed countries, Ebola virus is also found in 7 infectious rare cases as follow: 4 cases in United States, 1 case in Spain, 1 case in United Kingdom and 1 case in Italy; on the contrary, from 3 January 2016, no more infected Ebola virus case is occurred [16]. Table 1 exhibits the worldwide human deaths in 1990, 2005 and 2015 [17]. It is clear from the data in this table that the top 5 diseases responsible for human deaths in 1990 are (1) lower respiratory infections, (2) neonatal preterm birth complications, (3) diarrheal diseases, (4) ischaemic heart disease, and (5) cerebrovascular disease while the top 5 diseases responsible for human deaths in 2005 are (1) ischaemic heart disease, (2) lower respiratory infections, (3) cerebrovascular disease, (4) HIV/AIDS, and (5) neonatal preterm birth complications. Moreover, the top 5 diseases responsible for human deaths in 2015 are (1) ischaemic heart disease, (2) cerebrovascular disease, (3) lower respiratory infections, (4) neonatal preterm birth complications, and (5) diarrheal diseases. Lipidomics research provides vision into an important role of different lipid in healthy and pathophysiological cases, in addition lipidomic study helps to develop a biomarker which used for protective and treatment purposes in infectious diseases [18]. There is a common procedures backbone that relates to infections cases [19], and these procedures involve several successive steps as follow: infection factor, infectious tank, human invading by specific infectious factor, controlling of human genetic codes and copying of infectious new generations, and finally infectious factor leaves human biological system and transfer into new human subject. Scientists, pharmacists and physicians are concern to realize the whole figure of infectious disease infection into human to be used the data to prevent the infection in infections places [20]. Several biochemical check-ups are very important to detect infection symptoms such as different metabolic compounds and many end-product enzymes emerges from this specific infectious factor. The lipidomic research provides us with a complete map of specific lipid inside the cell of the biological system and this study developed nowadays to focus on structure, chemical, biochemical and function of individual lipid in technology and medicine fields. There are new technical instruments which are being fast growing to face the huge and complicated lipids molecules needed for many biochemical researches. These new techniques used in lipidomic study is greatly related to new development and advancement in biochemical and analytical new instruments such as mass spectrometry and chromatography instruments used to identify and quantify a huge numbers of lipids inside the cell of biological system [21]. A comparative study of lipidomic to proteomic and metabolomic showed that lipidomic study focused on the important role of specific lipid in different biochemical cycles inside the biological system where any abnormal metabolism process of each individual lipid molecule reflected directly to pathological human condition and disease occurred such as infectious disease and many other respiratory, metabolic, cardiac and brain diseases, therefore, lipidomic research helps medical field to discover a new disease biomarkers and following the metabolic and biochemical pathways of lipid involved [22].

Table 1
Worldwide mortality causes due to infectious disease for 1990, 2005 and 2015 [17].

No.	Mortality causes 1990	Mortality causes 2005	Mortality causes 2015
1	Lower respiratory infections	Ischaemic heart disease	Ischaemic heart disease
2	Neonatal preterm birth complications	Lower respiratory infections	Cerebrovascular disease
3	Diarrheal diseases	Cerebrovascular disease	Lower respiratory infections
4	Ischaemic heart disease	HIV/AIDS	Neonatal preterm birth complications
5	Cerebrovascular disease	Neonatal preterm birth complications	Diarrheal diseases
6	Neonatal encephalopathy	Diarrheal diseases	Neonatal encephalopathy
7	Malaria	Malaria	HIV/AIDS
8	Measles	Neonatal encephalopathy	Road injuries
9	Congenital anomalies	Road injuries	Malaria
10	Road injuries	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease
11	Tuberculosis	Congenital anomalies	Congenital anomalies
12	Chronic obstructive pulmonary disease	Tuberculosis	Tuberculosis
13	Drowning	Self-harm	Lung cancer
14	Protein-energy malnutrition	Lung cancer	Self-harm
15	Meningitis	Neonatal sepsis	Diabetes
16	Self-harm	Meningitis	Neonatal sepsis
17	Other neonatal disorders	Measles	Chronic kidney disease
18	Neonatal sepsis	Diabetes	Meningitis
19	Tetanus	Drowning	Interpersonal violence
20	Lung cancer	Protein-energy malnutrition	Liver cancer
21	Interpersonal violence	Chronic kidney disease	Other neonatal disorders
22	Intestinal infectious diseases	Other neonatal disorders	Protein-energy malnutrition
23	Stomach cancer	Interpersonal violence	Drowning
24	Sexually transmitted diseases	Liver cancer	Stomach cancer
25	Chronic kidney disease	Stomach cancer	Alzheimer's disease
26	Asthma	Intestinal infectious diseases	Hypertensive heart disease
27	Diabetes	Hypertensive heart disease	Colorectal cancer
28	Liver cancer	Colorectal cancer	Falls
29	HIV/AIDS	Falls	Breast cancer
30	Whooping cough	Alzheimer's disease	Intestinal infectious diseases

This review should perform to encourage a thought process on the important role of lipid key trigger of virus, bacteria and parasites during interaction of specific pathogen with the human host cell inside the biological system.

2. Pathogen replication cycles: A lipidomic view

The links between pathogen (virus, bacteria or parasite) infection into human host cells depend on lipid structure and function. The links formed between pathogen and human host generate many processes such as controlling of human host cells, destruction of host cell membrane, settling down of the specific pathogen at the specific host place. All these infectious processes are controlling by lipid enzymes such as phosphatases, lipid kinases and lipases, although the relation between lipid metabolism in both pathogen and host is unclear until now.

2.1. Viruses

The molecular investigation during pathogen invading and entry into host cell, replication of host cell genome, transferring of host cell and production of pathogen next generations can be showed by microscope technique. The fluorescence microscope is the best one which can be identified different stages of viral infection as well as observe the relation between host and pathogen. Also, high resolution conventional microscope can be overcome any technical limits found and can provide full detail on infection process and controlling of human virus infection process. Moreover, high progress in electron microscope technique is very important to study virus morphogen through observing ultrastructure detail of infection process. Furthermore, imaging microscopes have a large step in the new technology to study virus pathogens and provide an early detection of viral infection as well as development of new treatments in the specific virus infection [23]. On the other hand, the process of human cell replication during human infection process depends on several host function which changed in different types according to time and place of infection. The mathematical model of virus infection process is very important to realize how pathogens controlled during virus life cycle; so the communication of both mathematical model and experimental observations provide a quantitative information for this specific various infection process which gives new quantitative technique needed in infection process and the information push the medical treatments and applications of this specific virus in a great step such as human hepatitis C virus (HCV) and immunodeficiency virus-1 [24]. On the other side, the virus contained large DNA that induces infectious diseases in wild and captive cold blood vertebrate through the whole world is called ranaviruses (iridoviridae). The experimental investigation showed identically between ranaviruses (iridoviridae) and poxviruses in many files such as virus biology, general procedures of virus replication, host-virus relations, and infection process evolution steps especially *in vivo*. Many strategies have been applied and developed several years to prepare specific recombinant for called ranaviruses (iridoviridae) through two main steps: (1) express fluorescent reporter genes and (2) deficient for specific viral gene [25]. Furthermore, Perales *et al*. [26] detected an active mechanistic recombinant obtained from evolutionary recombinant and this recombinant clarified by episodes in the field and through evolution of the experiment. In episode in the field, a recombinant explores a new viral pathogen and has been fitted to some viruses if the original (mother) viruses found a suitable environmental factor where virus mutation has been occurred. In the experiment, a recombinant controls genome segments found in foot and mouth of the host biological system and produces host unsegmented genome. Consequently, virus clonal is standard mode of evolution process for virus because a recombinant is insignificant or minor, so the principle factors for virus replication do not depend on the exchange of genetic material or production of recombinant genomes. Moreover, the mechanism through which the arbovirus replicates and spreads could be controlled during infection process is called RNA interference (RNAi) in arthropod vectors. There are many explanations needed to be clear in infection process, although several mechanisms and substances are produced during antiviral pathways in arthropods. In the infection invading, study related to RNAi showed numerous pathways and constituents are included where the term RNAi mentioned to controlling process of gene expression by RNAi. The term RNAi mentioned to stopping cell endogenous genes by induction of external double-stranded RNA have the same arrangement of genes orders of the stopping genes. A study on RNAi reveals that this gene consists of three processes of gene regulation that controlled by small RNAs; and these processes are: microRNA, small interfering RNA (siRNA), and Piwi-interacting RNA pathways. The exogenous siRNA pathway is described recently as immunity response of orthopods to virus infection process. There are important roles of both microRNA and Piwi-interacting RNA pathways in arbovirus-vector relations. The arboviruses should avoid antiviral response of vector's RNAi to keep the virus gene expression process although the mechanism by which this virus can keep this process is not clear until now. Consequently, RNAi resembles an important process for arthropod gene expression in an effective and adequate genomics research and in the development of arbovirus resistant processes [27]. The strand RNA virus that expresses in the host cytoplasm has many difficulties especially in keeping biological functions and processes needed for gene expression. The majority of these viruses have a simple genetic structure which related to host cell proteins that bind with virus RNA and convert host proteins to help and support the infection process of this virus by gene expression process and produce numerous RNA copies of this virus. During the process of virus infection, a lot of nuclear proteins are transferred into the cytoplasm and kept arrested in the cytoplasm by this virus. Human viruses control many proteins in the cytoplasm [28].

2.2. Bacteria

In the infection process, bacteria cause host cell death from outside or inside place which lead to protect or destruct of the host biological system. The information collected showed that inside bacteria which induce immunity host programmed cell death stimulate associate type I interferon (IFN) signaling and lead to virulence. A lot of genetic pathways occurred and led to host cell death which depend on IFN gene control. These processes produce virulence although the processes of bacterial pathogens produced by IFN are not clear until now. There is not any interferon expressed genes found in cell death processes due to pathogens. Infection process of bacteria induced by inside pathogens and type I IFN signaling genes could be produced

outside bacterial gene expression instead of host cell protection process. These pathogens could be in phagocytosis state, but the life cycles of their cells are completely different where these cells stimulate factors of virulence and initiate different immunity stimulation pathways processes. All these differentiation caused many production of type I IFN gene expression processes although these differentiations do not effect on the pathological properties of bacteria on the host cell; each pathogen produces apoptosis or programmed cell death of the immunity host cells which are effected by stimulation of type I IFN gene response [29]. On the other hand, the diversity of prokaryotic, planktonic, and eukaryotic phytoplankton bacteria have a vital role in controlling marine foods, earth's climate and biogeochemical cycles. Phytoplankton plays a vital role in marine ecosystems so its die defined movement and providence of photosynthetic organic matter, biogeochemistry of compelling upper ocean. The program of bacterial cell death and its related genes expression pathways are controlled by many nutrient stimulators and activated by invading pathogens which play an important role in defining the cell state of diversity in modern ocean. The diversity of cell death program determined the success route of phytoplankton genetic diversity in the sea. The recent studies using biochemical, hereditary, and physiological applications to obtain new, effective and applicable tools to estimate the factors that control this procedure [30]. Moreover, the experimental infection process is very significant for suitable relations of pathogens and their hosts as an example of red flour beetle *Tribolium castaneum* (*T. castaneum*) and spore forming bacterial insect pathogen *Bacillus thuringiensis* (*B. thuringiensis*) where both have not used until now as a better experimental example to observe host-pathogen relations. The infection process through oral route was applied to infect insects of *T. castaneum* type with bacteria of coleopteran specific *B. thuringiensis* bv. *tenebrionis* type where the results obtain showed that the death of the pathogen larva relied on concentration of dietary spore as well as exposure time to the bacterial spore. Also, the host genetic effect on the infection process increased infectious spores recovery numbers. This consequently increased bacterial gene expression inside the host biological system. As an example, *B. thuringiensis* bv. *tenebrionis* induces infectious process cycles in *T. castaneum* in the environment. The transfer of plasmids of *B. thuringiensis* bv. *tenebrionis* bacteria into the biological system of the host occurred and was defined by genetic methods and these processes were successful in infecting *T. castaneum* insect model; so the factors that control the plasmids transfer are very effective for the infection to be occurred and the availability of more novel genetic strains to be obtained which gave an ideal example for an accurate and effective method of pathological factors that affect oral infection process [31]. The environmental surrounding temperature has a great impact in infection process as in the case of *Escherichia coli* (*E. coli*) O157:H7 symbol which used as a symbol system. The mathematical symbol used has been greatly developed to be susceptible-infectious-susceptible symbol of infection in host groups incorporated with metapopulation symbol of *E. coli* O157:H7 to form a new system which enables for growth of bacteria to be effected by surrounding temperature. The effective role of environmental surrounding temperature on infection process mechanisms for pathogens can be concluded that environmental temperature has an effective impact on pathogens growing in the environment especially outside surfaces, water mangers and leads to bacterial growing dominant of host growing infection process. According to the above mentioned symbol, transfer of *E. coli* O157:H7 bacteria to cattle is increased in contaminated drinking water and this transfer of bacteria to cattle is high in warmer months if this contaminated water to cattle is increased. This is because high environment temperature increases bacteria expression especially with slower rate of water replacement leading to higher bacterial infection process and this result can give us a clarification about seasonal differences of *E. coli* O157:H7 predominant in cattle and drinking water contaminated with bacteria should be filtered to control infection process [32].

2.3. Parasites

The protozoa parasites developed many advanced techniques to invade and transfer to host groups. For example, the causative mediators of malaria such as *Plasmodium* spp. and its related haemosporidian parasites consist of eukaryotic pathogens that greatly attach humans and mammalian erythrocytes that caused disorder development of sexual organs and gametogenesis and led to increased deaths of the infected host. The bats from the tropical zone of Africa eating insects species of haemosporidian genus *Nycteria* were included in this study. These *Nycteria* parasites showed differences in their activities to infect these two species of bats from chiropteran suborders. These two suborders are rhinolophid and nycterid bat hosts from different area of sub-Saharan area of Africa, however the molecular investigations of these two suborders reported differences in these two parasites according to the two host genera. So, these parasites names subtracted from (1) ancient genetic aberration and (2) host moving of the two parasites. In one of these two parasites, cytochrome b genes could not be expressed while cytochrome oxidase I sequences revealed high growing rates which supposed that mitochondrial genes of these parasites could be lost or changed in its shape [33]. Furthermore, the mitochondria play an important and essential role in metabolism and antiviral pathways processes such as its role in the production of adenosine triphosphate. The virus represents intracellular parasite that needs viral growing and energy supplementation needed for viral generation and expression from the host. Some viruses make adaptation to increase the numbers of infected cells where viruses directed cell metabolism for viruses growing and generations. The relation between viruses and mitochondria is affected by many factors such as viral duplication speed and cellular enzymes and metabolites of the host where viruses depended on. There are three principle mitochondrial metabolic pathways: (1) β-oxidation, (2) the tricarboxylic cycle, and (3) oxidative phosphorylation. These three processes explain the antiviral treatment with either antimetabolites or prometabolites and explore the relation of viruses metabolism of the host mitochondria [34]. Moreover, parasites that initiated malaria to be grown inside the host erythrocytes are free in the cytoplasm of the host and induced sexual impairment expression cycles, and accordingly these parasites are caused unstable and changed levels of both K^+ and Na^+ ions which are very important for infectious process invading of human pathogen *Plasmodium falciparum*. The change in Na^+ and K^+ ions as well as sucrose level in the host cells increased parasites growth and expression rates higher as in the same case of physiological state. In this condition, eliminating Na^+ ion from inside to outside through these

parasites increased the erythrocytes ion outside and stopped any recovery process of this ion. Consequently, Na^+, K^+ and Cl^- ions were in lower concentrations than parasites needed, but parasite growth was not affected by this lower concentration until 148 mmol/L K^+ ion where parasites started to affect which supposed that low outside K^+ ion is not needed for infectious invading process. In the same time, emerging of merozoite and infectious process need lower threshold ions levels which supposed that electrostatic connections between macromolecules at infectious stages and these findings gave an explanation in electrostatic signaling through host cell membrane and showed a principle difference between host and parasite ions needed [35]. In addition, viruses that resemble inside parasites depend on host cells for their expression. During host cells infection process, RNA of invading viruses controlled and directed host cell machines and programs into viral production through protein–lipid, protein–protein, and protein-RNA relations. The molecular relations between host production and invading viruses are constant process during life cycles of the virus and this process defines the relation between virus and host as well as pathogenic products of the invading virus and controlled next viral generations. This process gave an explanation on normal cell function and helped to identify an accurate and effective antiviral drug development process [36]. Furthermore, in the millennia, the invading pathogens attach their host biological system and must have the ability to mimic and disrupt many singling pathways of the host cells. So, the research of host-pathogen relations gave us more information about the biological processes of these invading parasites and also delivered information about principle cell biology processes in both host cell and biological system organism. The host-pathogen relations gave us focus on pathogens expression forces that re-constructed the biological differences. The pathogens such as viruses, bacteria, and parasites induce tyrosine kinase-mediated and Rho guanosine triphosphatase-mediated signaling pathways of their hosts to accept effective invading, expression and leaving in their infectious pathways cycles [37]. Additionally, the most well-known protozoan parasite of humans is *Toxoplasma gondii* (*T. gondii*); this parasite infection process could be produced by many diseases that caused life dangerous due to constant and frequent invasion of the host, parasite expression processes and host cell death. Unfortunately, invading mechanism of *T. gondii* into Phylum Apicomplexa (including *Plasmodium* spp.) that induced malaria is very infrequent because of problem in studying genes that is principle to invading process into the host cell organism. To solve this problem, a high technique and resolution microscope information is advanced and used to figure about 12 160 molecules with different structure for the inhibition of *T. gondii* infectious process and the results were 24 inhibitors identified for infection process. A more data analysis revealed that these different inhibitor molecules initiate different ways of infection methods such as sliding motility, secretion of the host cell, and addition of an exclusive tubulin-based structure in the parasite front part which is called the conoid. About six molecules were responsible for infectious process, sliding motility, and secretion of microneme where these molecules determined showed difficulty in controlling sliding motility, and secretion of microneme and these molecules consisted a suitable way for separating the infectious mechanisms of *T. gondii* and their related parasites so the techniques used in these small molecules gave a suitable way to explain problems in host-pathogen relation and support the development of drug [38]. Furthermore, the host immune cells that have a vital role in the discovery and excluding of pathogens organisms are macrophages where macrophages have a lot of receptor in their membrane surface that can differentiate between structure of both host and pathogen. Macrophages can detect foreign organisms and phagocytosis which lead to completely death of these microorganisms by lysosomal enzymes, nitrogen intermediates, toxic reactive oxygen species, and nutritional lack systems. The protozoa parasites such as *Trypanosoma cruzi*, *T. gondii*, and *Leishmania* spp. attack host macrophages and utilize them for parasites growth, expression and conservation of parasites life cycles. The expression of protozoan parasites of the genus *Leishmania* is different in its expression inside the host where it is restricted to a single cell macrophage. The connection between macrophages and invading parasites could be used as an experimental model of *Leishmania* spp. [39]. The parasites *Schistosoma mansoni* are greatly related to hepatocellular toxicity, apoptosis and carcinoma where these parasites accelerate hepatic dysplastic changes in the presence of other risk carcinogenic factors making cancer appear early and with a more aggressive nature, compared to the same risk in absence of these parasites both in human and animals models [40–42]. Finally, the parasites *Schistosoma mansoni* induce oxidative stress and apoptosis in host vital organs such as kidney [43], and decrease lipid profile in *Schistosoma* snails to induce oxidative stress, apoptosis and hypolipidemic activity during the infection process [44].

3. The role of lipids during host-pathogen interactions

The lipidomic and metabolomic techniques communicate with phenotype tests to determine the host response time to invading *Mycobacterium tuberculosis* (*M. tuberculosis*) at the physiological attitudes of NaCl levels. The first phase of this method is accurate, fast, successive and reversible case associated with metabolism change in core and amino acid. In the second phase, *M. tuberculosis* replied with a constant phase of plasma membrane and outside membrane composition. Consequently, the phenotype presence at the physiological attitudes of NaCl levels is occurred due to changes in plasma and outside membrane lipid model not related to changes in metabolism of core. So, the physiological state that caused antibacterial activity is connected with changes in cell envelope and explains that the metabolic changes and stop of bacterial growth is not the principle case of phenotype appearance showed in *M. tuberculosis* found in physiological levels of NaCl [45]. Furthermore, the comparing of RNA sequencing showed that 2 651 expressed genes in macrophages of murine [bone marrow derived macrophages (BMDMs)] that infected with *M. tuberculosis* (R179T *M. tuberculosis*) *vs*. macrophages of murine (BMDMs) infected with R179NT *M. tuberculosis*. There are a lot of genes expression that found in macrophages of murine (BMDMs) receptor relation with *M. tuberculosis* (*Mrc1*, *Ifngr1*, *Tlr9*, *Fpr1* and *Itgax*) and pro-inflammatory cytokines/chemokines (*Il6*, *Il1b*, *Tnf*, *Ccl5* and *Cxcl14*) were chosen to be analyzed through qPCR. BMDMs infected with R179NT initiate vigorous inflammatory responses. In the same time, R179NT *M. tuberculosis* causes a transcription of *Fpr1*, a receptor which detects bacterial formyl peptides and induces a lot of immune responses. The host components *Cxcl14*, with an unknown role

in *M. tuberculosis* infection, and *Tlr9*, an emerging role player, are only initiated by infection with R179NT *M. tuberculosis* [46]. The bacteria introduce alterations in epigenetic shape in epithelial cell of oral cavity controlled by alterations in histone. *In vivo* dysbiosis caused alterations in epigenetic shape such as histone acetylation and DNA methyltransferase 1 downregulation. Also, lipopolysaccharides applied to epithelial cell of oral cavity *in vitro* caused histone alterations, initiation of transcriptional coactivators such as p300/CBP, and nuclear factor-κB increasing. The initiation of Toll-like receptors 1, 2, and 4 and the nucleotide-binding oligomerization domain protein 1 caused histone acetylation in epithelial cells of the oral cavity. So, alterations in epigenetic shape play an important role in the initiation and development of periodontitis (chronic infectious disease driven by dysbiosis) [47]. On the other hand, the microbiome in the host gut is incorporated in the appearance and the progression of human cardiovascular disease and this microbiome involved in the relation between host-microbe which controlled the immunity and metabolic processes. The microbiome plays a vital role in the changes of body mass guide and lipid profile in the blood, differences in age, sex and genetics of the host. Consequently, the microbiome initiates many biological processes such as body mass guide, high density lipoproteins and triglycerides [48]. Moreover, the analysis of blood and organ detected approximately 400 different metabolites including a lot of lipids keys that incorporated in inflammatory process inhibited by *Bacillus anthracis*. The changes in metabolites were identified quickly on Day 1 of infection before the infection disease extended or the bacterial infection moved to the host organs. The researches that include pharmacological decreasing of phospholipases of the host explain the role of these lipids keys enzymes and lipid mediators in host existence in anthrax disease where *Bacillus anthracis* changes the physiology of the host. So, metabolite technique is a tool to detect and investigate a new relations that appeared in host-pathogen relations [49]. Furthermore, HCV occurred inside the biological system of the host communicates with very-low-density lipoprotein molecules. The virus extended from one cell to another through apolipoproteins E (ApoE) in the host cell not ApoE in the virus cell. On the contrary, ApoE reduced in both donor and invading cells did not affect the transfer from cell to another. Consequently, ApoE contributed in infectious process of the viruses which supposed different controlling in infection process from cell to another as well as cell free of HCV infection one [50]. On the other side, mitochondrial detergent-resistant membrane molecules is a mitochondrial lipid host that plays a vital role for enrolling indicating molecules that incorporated in host response to infection such as quick immunity and apoptosis where viruses initiate functional mitochondria cycles for viral existence and expression process [51].

3.1. Cell and chemical biology in lipidomics

The intercellular key mediator which helps to communicate inside the host cells is called extracellular vesicles (EVs), which is secreted and taken by different cell of the central nervous system (CNS). The lipidomic technique in CNS vessels is helping to detect the above mentioned EV-lipids such as sphingomyelins, lysophosphatidylethanolamine, lysophosphatidylcholines, and phosphatidylserines as well as discover new lipids molecules that do not discover before in human host EVs. About 80% of the total microparticles were exosomes and their diameters were from 100 nm to 300 nm by using flow cytometry of protein organic solvent precipitation-CNS-EVs technique [52]. In addition, gallic acid-L-leucine conjugate molecules botched in phagocytosis activity increase the host macrophage while leukotriene B4 12-hydroxydehydrogenase molecules are still inactive through the controlling of siRNA. Also, the mediators of pain, fever, and inflammation are eicosanoids where the mediators control host cells expression in acute and chronic state of the disease. The lipidomic technique explored that human platelets activated thrombin to produce new eicosanoid molecules to initiate and increase expression of neutrophil integrin (Mac-1) of the human after the exposure to formylmethionylleucylphenylalanine. The lipid molecules are in nanograms and produced by the platelets that produced from cell arachidonate in the physiological stimulation process with the aspirin inhibition *in vitro* and *in vivo* that stimulates cyclooxygenase-1 [53]. Moreover, the lipidomic research has been advanced by mass spectrometry method. This technique helps to determine of lipid molecules isomers C=C location obtained from cell lipid mixtures through using the reaction of Paternò-Büchi connected with suitable mass spectrometry to determine the different lipid molecules. About 50% of the lipids in the form of C=C location isomers isolated from 96 fatty acid glycerophospholipids in the brain tissues, and about 50% of these lipids occurred as mixtures of C=C location isomers. This technique is a good and accurate method to determine and quantify the fatty acids and glycerophospholipid in normal and carcinogenic tissues [54]. Furthermore, the regulatory cell process that initiates in different cells and pathways processes is called apoptosis. Apoptosis process in mitochondria is initiated by increasing permeability of mitochondrial membrane by Bcl-2 proteins where stimulation of caspase and cell death occurred. The role of lipids and their metabolism in this apoptosis process is very important. The apoptotic BAK and BAX proteins in embryonic fibroblasts of mice were absent in lipidome where d18:2-Cers were increased in epithelial cells of mice kidney that missed BAK and BAX [55]. The genetic disorder disease that caused lower limb weakness and temporary disability is called hereditary spastic paraplegia (HSP). The mutations in serine hydrolase DDHD2 is the principle of HSP. In DDHD2 mutation, phospholipase activity is the principle cause of this disease, but the cell biochemical and function processes remain unclear until now. The lipidomic research was used mass spectrometry to reveal that DDHD2 control brain triacylglycerols which exhibit increase in the CNS only not in the peripheral tissues in HSP where large lipid molecules increased in brain tissues and moved into inside of the neuron and these conditions lead consequently into motor injuries. These results reveal that CNS has a specialized pathway for triacylglycerols; therefore, in HSP disease large lipid molecules increased in the neurin and HSP symptoms appeared [56]. Moreover, Cai *et al.* estimated a new method to allow an accurate and quick detection of six major phospholipids (PLs) groups [57]. This method was done through acid accelerating hydrogen/deuterium mutual change process which include labeled and unlabeled PLs. The structure of PLs is different in both virus and host cells where in most mammalian cell membranes phosphatidylcholine is the major lipid molecules while in virus phosphatidylethanolamine molecule is the principle

lipid molecules. The structure of PLs is completely different and these are important in the infection process of the virus, and these differences in glycerophospholipids offer an explanation for the determination of virus infection specific process [58].

3.2. Lipid profiling

The cholesterol synthesis, uptake and exclusion processes include lipid united, and proteins molecules are also involved. Stimulation of aldo-keto reductase family 1 expression process, member C1, and C3 increased metabolism of sterol and lipid peroxidation related to reactive oxygen species is also increased. The fatty acid metabolism freed and directed into lipid pathways that caused lipotoxicity. The decreased histones levels equal to increased protein synthesis process and DNA oxidative stress may also occur [59]. Furthermore, phospholipases have a significant role in the phospholipids maintenance of the cell membrance where the loss of three major phospholipases B in *Saccharomyces cerevisiae* has not any affects on the membrane phospholipids hydrolysis which indicates that other phospholipases and lipids are included to maintain the membrane integrity. There are 13 proteins found in *Saccharomyces cerevisiae* which is responsible for constant serine hydrolase. The phosphatidylserine lipase such as Atg15p formed through ATG15 expression process in autophage process [60]. Additionally, the fasting plasma glucose, total cholesterol, triglyceride, high density lipoprotein, and low density lipoprotein levels are more higher in females than males and these related to matches and variances between both male and female in cynomolgus monkeys where age associated with glucose and lipoprotein metabolisms in physiological state. The map drawn to describe glucose and lipoprotein levels provides good information about prediabetic state, so cynomolgus monkey is a good example for prediabetes and diabetes states and for discovering new treatment of diabetes [61]. Moreover, the lipogenesis mechanisms need genes expression or mutation for phospholipid, fatty acid, and triglyceride synthesis. The sterol regulatory element binding protein-1 (SREBP-1) is a transcription factor which inspires in genes expression mechanisms according to many metabolites found in the infection process. The SREBPs were controlled by cholesterol in the membrane where phosphatidylcholine in decreasing concentrations led to SBP-1/SREBP-1 maturation in host models. Therefore, the changes in ratio of cell lipids may reflect on ARF1 to increase SBP-1/SREBP-1 activity [62]. When genes expression in the metabolism of lipid was changed, it led into lipidotoxic effect on the muscles of immunosuppressive therapy. The immunosuppressive therapy has anti-inflammatory effect communicating with genes harmful effects that occurred in muscle tissue control and lipid metabolism and resulted in harmful effect on muscle performance therapy and consequently led to constant muscle impairment patients of dermatomyositis and polymyositis [63]. Furthermore, lipids especially PLs are the control key in the membrane. PLs control storage of energy inside the cell, expression of the cell, and communication of cell and their neighbor cells. All these cellular processes are very important in cell transformation and tumor progress. There are many PLs found in tumor cells and tissues. There are two techniques used in proteomic and are also used in lipidomic study in tumor research, and these two techniques are matrix-assisted laser desorption/ionization and mass spectrometric soft-ionization electrospray ionization (ESI). The PLs states in cells, tissues, and biological system gave indication on the whole organism condition and the existence of tumor or not [64]. Finally, the data obtained exhibit that lipidome in the liver tissues show change in high-cholesterol diet; so high-cholesterol diet or high-cholesterol diet associated with inflammation is greatly related with nonalcoholic fatty liver disease levels but not to inflammation alone using the nanoflow ultrahigh-pressure liquid chromatography-tandem mass spectrometry [65].

4. Conclusions

Many scientific windows have been opened in the lipid role of the host-pathogen relation specially modern lipidomic research field. The host-pathogen links are very complicated, energetic and include many successively and consequently steps of replication cycle. The role of lipid in host-pathogen link includes many functions in (1) structural host constituents, (2) host recognition, (3) intracellular transferring, and (4) energy and resource homeostasis during pathogen duplication. Proteomics, genomics and metabolomics are integrated with lipidomics to give us better view about the role of lipids in complicated lipid signing process during host-pathogen relation which helps us for using in biomarkers and therapy advances.

Conflict of interest statement

I declare that I have no conflict of interest.

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