Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 13, Issue 1, 2023, 27
https://doi.org/10.33263/BRIAC131.027

Human Health and COVID-19: Metabolome Approach

Khaled Mohamed Mohamed Koriem [1,*]

[1] Department of Medical Physiology, Medical Research and Clinical Studies Institute, National Research Centre, 33 El-Buhouth Street, Dokki, Cairo, 12622, Egypt;
* Correspondence: kkoriem@yahoo.com (K.M.M.K.);

Scopus Author ID 24477156100
Received: 30.10.2021; Accepted: 10.12.2021; Published: 23.01.2022

Abstract: Metabolome refers to small molecules inside the biological sample. This review focuses on human health and COVID-19 from a metabolome point of view. The metabolome includes endogenous and exogenous metabolites. Endogenous metabolites contain natural compounds such as nucleic acids, amino acids, vitamins, fatty acids, and sugars. Exogenous metabolites include food additives, environmental toxicants, drugs, and xenobiotics. Human health is a physical, mental, and social well-being state without any disease. Many factors influence human health, such as human lifestyle, background, social, and economic state. The human diet provides principal nutrients in food that sustenance human life. There are 7 main nutrients (fats, proteins, minerals, carbohydrates, fiber, vitamins, and water). Human exercise is body movement that improves or sustains human physical fitness and health. Human exercise supports human growth and recovers human strength. Human sleep is a natural regular state of mind and body. It is changed consciousness and declines both sensory and muscle activities. Human sleep maintains memory, mood, and biological function. The viral shape of the crown is the reason for its name. The World Health Organization report reveals that this virus occurred first in animals (1940) then occurred in humans (2003). The COVID-19 occurred in Wuhan state in China in December 2019.There are 4 types of coronavirus: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. The 4 known types of this virus (COVID-19, MERS, SARS-CoV, and SARS-CoV-2) are under the *Betacoronavirus* classification. In conclusion, the metabolome has an important role in human health and COVID-19.

Keywords: metabolome; human; health; diet; exercise; sleep; COVID-19.

1. Introduction

The metabolome is mentioned to small molecules inside the biological sample [1]. The metabolome includes endogenous metabolites such as natural compounds such as nucleic acids, amino acids, vitamins, fatty acids, sugars, antibiotics, etc. The metabolome also contains exogenous compounds such as food additives, environmental toxicants, drugs, and xenobiotics. So, metabolome includes both an endogenous metabolome and an exogenous metabolome. The endogenous metabolome is divided into primary and secondary metabolomes. The primary metabolite includes normal reproduction, growth, and development. The secondary metabolite includes antibiotics and pigments. The research of the metabolome is termed metabolomics [2,3]. The metabolome refers to metabolites and chromosomes. Metabolites are controlled by genes or act on genes. The metabolome was first appeared in 1998 [1,4]. The metabolome is the 4th generation following genome, proteome, and transcriptome. There is a connection between lipidome (a group of lipids), proteome, and metabolome [5-8]. The metabolome is a

connection between the genome and the environment. Nuclear magnetic resonance (NMR) and mass spectrometry (MS) are the famous techniques used in the metabolome. The human metabolome database (HMDB) is an open-access database of human metabolites with more than 40,000 identified inside the human body. The HMDB contains chemical, clinical, and biochemical data. The chemical data contain higher than 40,000 metabolite structures. The clinical data contains 10,000 metabolite-biofluid concentrations. The biochemical data contains 6000 protein structures and 5000 biochemical reactions.

Human health is a physical, mental, and social well-being state without any disease. This case is described as physiologic, anatomic, and psychological harmony; capability to do individual work and community responsibilities; capability to tolerate biological, social, physical, and psychological stress [9]. Human diet, exercise, and sleep are 3 factors that affect human health. A healthy diet is very important to preserve human health. This healthy diet contains plant- and animal-related foods that give human energy and keep the human body's system homeostasis. These nutrients build, support human bones, muscles, and tendons, and control human body processes. The human diet contains carbohydrates, proteins, vitamins, fats, and minerals important to maintaining human body processes. Physical exercise improves and preserves human health and well-being. It improves muscles and preserves the cardiovascular system. Sleep is important to sustain human health. Sleep is important to growth and progress in children. Insufficient sleep is correlated with chronic health diseases. Sleep is essential to human metabolism.

The viral shape of the crown is the reason for its name. The World Health Organization report reveals that this virus occurred first in animals (1940) then occurred in humans (2003). The COVID-19 occurred in Wuhan state in China in December 2019.There are 4 types of coronavirus: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. The 4 known types of this virus (COVID-19, MERS, SARS-CoV, and SARS-CoV-2) are under the *Betacoronavirus* classification. SARS-CoV, according to WHO report, appeared first in 2002, then MERS-CoV appeared ten years later before COVID-19 appeared in the Wuhan state of China at the end of 2019 [10]. Not all types of this virus are very dangerous. The majority of these viruses have mild cold symptoms. On the contrary, SARS-CoV, MERS-CoV, and COVID-19 have major indications [11]. The spike proteins of this virus are characteristic of 27 base pairs that may reach 34 base pairs. The virus invading the human body then directed the human cells to produce many copies of this virus, and finally, this virus transferred to another human to cause massive infection. The binding of the spike protein of this virus with human cells is the principal reason for all viral indications. *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* are coronavirus types. COVID-19, MERS, SARS-CoV, and SARS-CoV-2 are belong to *Betacoronavirus*.

This review focuses on human health and COVID-19 from a metabolome point of view.

2. Role of Metabolome in Human Health

Human health is an expression that refers to the level where the individual or the group is capable of recognizing objectives and fulfilling requirements. Human health is mentioned to sustain homeostasis, including emotional, mental, social, and intellectual health. Healthy People give more importance to health advancement and preventive styles. So, human health contains activities that prevent or cure health problems and support good health in humans. Many factors influence human health, such as lifestyle, background, social, and economic state.

The human health state and quality of life affect the circumstance in which human lives. Human health is sustained and developed via the efforts lifestyle varieties of each person, community, and society. Human milk is required for best growth because it fulfills a human kid's nutritional and biological requirements. There is a connection between breastfeeding and kid's health due to human milk's nutritional, functional ingredients (metabolites, e.g., amino acids, lipids, biogenic amines, and carbohydrates). These ingredients have many functions, such as the child's protection against infections and controlling the growth of the child's immature immunity [12]. The human diet controls the gut microbiome, and this effect has a great effect on competing for human diseases. The polyphenols from red wine and tea, as well as vitamin D, control beneficial bacteria. The dietary fibers such as galactooligosaccharides, inulin, arabinoxylans, and oligofructose stimulate beneficial bacteria and inhibit harmful ones. The type and amount of dietary proteins affect the gastrointestinal tract microbiota, while the type and amount of dietary fat control beneficial and harmful microbes in the gastrointestinal tract [13]. Human autophagy such as lipophagy, clockophagy, ferritinophagy, and chaperone-facilitated autophagy) discovers human homeostasis. Autophagy includes biological molecules such as lipids, DNA, protein, glycogen, RNA, and biological organs such as ribosomes, endoplasmic reticulum, mitochondria, lysosomes, and micronuclei [14]. The gastrointestinal microbiome is affected by the change in the human diet. In African countries, prolonged starvation and growth retardation are found. In the American community, obesity and type 2 diabetes are found and related to the gastrointestinal tract microbiome, and these effects depend on ethnicity, geography, race, and climate. In Asia, low and high-fat diets and low and high-carbohydrate diets affect microbiota performance. So, microbiota structure and gastrointestinal metabolic functions lead to microbiota change, leading to the loss of colonization and performance [15,16]. Metabolome and lipidome, proteome, and genome produce diagnostic agents for the non-alcoholic fatty liver disease associated with liver fibrosis, cirrhosis, hepatocellular carcinoma, and hepatic failure. This metabolome, lipidome, proteome, and genome occur at the cellular, tissue, and system levels [17]. Metabolome helps to understand the microbiota's role in autism syndromes. The gastrointestinal disturbances occur in autism due to gastrointestinal microbiota changes, which vary according to changes in diet, disease severity, demographics, gastrointestinal disturbances, and allergies [18]. Aging and age-associated diseases, e.g., cardiovascular complications, neurodegenerative disturbances, and cancer, are correlated with mitochondrial dysfunction, which is described by asymmetrical mitochondrial morphology, inadequate adenosine triphosphate (ATP) manufacture, increase of mitochondrial DNA (mtDNA) mutations, increased manufacture of mitochondrial reactive oxygen species (ROS) and oxidative damage to nucleic acids, lipids, and proteins [19]. Metabolome, transcriptome, and epigenome help understand the gastrointestinal tract microbiome in human chronic gastrointestinal disturbances [20]. The gastrointestinal tract microbiota connects with the host by metabolites produced from bacteria or bacterial metabolism in the diet or through alterations of host molecules, e.g., bile acids. So, microbial metabolites affect body homeostasis, immunity, energy metabolism, the mucosal structure of humans [21]. The metabolome is very important to investigate aging and its specific metabolic pathways to prolong human life. Metabolic change leads to decreased organismal fitness and increased weakness. The intake of various metabolites affects metabolic pathways to improve human health and extend human life. Metabolome enables researchers the development of effective strategies for human health and life extension [22]. Metabolome study distinguishes milk ingredients through their dietary program and mode of transport. It increases

immunoglobulin A (IgA) and declines the change of gastrointestinal tract microbiota similar to breast milk. Therefore, fermented milk increases the activity of the immune system [23]. Metabolome research gives more details about patients' symptoms' physiologic and pathophysiologic processes. These metabolomes are applied to study respiratory, autoimmunity, cardiovascular, endocrine, and infectious states. These researches help understand the microbial metabolism of circulating and excreted biomarkers such as trimethylamine N-oxide [24]. Metabolome and bioinformatics analyses give more details about human-related microbiota and sustain human homeostasis. The microbial bioactive compounds affect human physiological processes. This occurs through the relation between the nervous system and the gastrointestinal tract, i.e., the gut-brain axis. In this respect, the metabolome detects the quantify of microbial proteins and metabolites in the human body [25]. Metabolome technique through the application of magnetic resonance spectroscopy and nuclear magnetic resonance methods enables researchers to understand prostate cancer by focusing on definite metabolites that correlate with the progress of prostate cancer cells. This result enables researchers for the early detection, prognosis, diagnosis, and effective treatment of prostate cancer [26]. The metabolome approach reveals that type 2 diabetes in children is increased by maternal diabetes exposure and exposure to many mother factors such as maternal obesity and metabolic disease. So, maternal diabetes and maternal obesity, hyperlipidemia, and gestational diabetes affect the metabolic health of the children [27]. Metabolome analysis explores the increase of perfluoroalkyl substances correlated with liver fibrosis, lobular inflammation, and higher non-alcoholic fatty liver disease in children. Increased perfluoroalkyl substances levels changed the metabolite organization, such as higher plasma levels of tyrosine, aspartate, phosphoethanolamine, phenylalanine, and creatine, and decreased plasma level betaine [28]. Metabolomics analysis helps understand the human secretion of metabolites due to Probiotics (live bacteria) and prebiotics (dietary substrates) exposure, which change the gastrointestinal microbiota. These microbiotas possess a vital role in sustain of human health, as well as the progress of human disease [29]. Human diet, exercise, and sleep are 3 factors that influence human health as follows:

2.1. Role of the metabolome in the human diet.

The human diet provides principal nutrients in food that sustenance human life. The insufficient diet resembles prolonged problems and induces human disease. Malnutrition is correlated with human death, while good nutrition is correlated with human growth and health. There are 7 main nutrients: fats, proteins, minerals, carbohydrates, fiber, vitamins, and water. Diet contains large and small molecules. Large molecules are proteins, fats, and carbohydrates, while small molecules are vitamins and minerals. Metabolome analysis investigates the effect of treated meat oxidation on human health and aging progression. The physiochemical and food character of meat has great importance to human health. The meat protein oxidation changes the redox state and mechanism [30]. Human nutrition prevents diseases and consequently has a great influence on Public Health. Nutrigenomics and nutriproteomics resemble the integration of both nutritional, genomics, and proteomics [31]. The human diet protects from gastric ulcers and hyperlipidemia [32,33]. The metabolome method helps to understand the role of microorganisms in colorectal tumors. Many microbial species correlate with colorectal cancer and red/treated meat intake. Among these microbial species are; *Escherichia coli*, *Streptococcus bovis/gallolyticus*, *Fusobacterium nucleatum*, and *Bacteroides fragilis* in colorectal patients. These microbes connect to colon cells and causes angiogenesis

[34]. Metabolome explores the role of diet in healthy aging, e.g., the effect on the gastrointestinal tract microbiome. Metabolome reveals the mechanisms that recover brain health across human life [35]. There is a correlation between the human diet and cerebral function in Alzheimer`s disease. Metabolome analysis reveals variations in purine, tryptophan, tyrosine, and tocopherol pathways. Alpha-tocopherol declines symptoms of Alzheimer`s disease. Intake of Souvenaid recovers synaptic synthesis. Souvenaid increases brain neuronal connection. Intake of the B vitamins cobalamin, folate, and pyridoxine through a period of 1 year declines brain atrophy [36]. Intakes of polyphenols counteract the harmful effects of plastic materials. Plastic exposure causes inflammation, hepatotoxicity, neurodegenerative, metabolic diseases, nephrotoxicity, allergies, insulin resistance, and carcinogenesis. Polyphenols intake influences the enzymes of both the antioxidant system and elimination of xenobiotics and polyphenol's role on the level of reactive oxygen species [37]. The human diet with high cholesterol content led to liver steatosis, steatohepatitis, fibrosis, and hepatocellular carcinoma with insulin resistance. The high cholesterol in the diet causes changes in gastrointestinal bacterial metabolites such as an increase of taurocholic acid and a decrease of 3-indolepropionic acid. The high-fat diet increase liver lipids, inflammation, and hepatic multiplying [38]. Metabolome as genome reveals that microbiome controls neurological disturbances such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, autism disturbances. The change of microbial structure related to human diseases. These microbiomes are affected by human diet and exercise [39]. Metabolome analysis explores that structure change of gastrointestinal microbiota occurred due to increased level of *Bacteriodetes taxa* in type 1 diabetes. This autoimmune disease possesses insulin insufficiency due to damage of pancreatic β-cells. The change of gastrointestinal microbiota occurred due to many factors such as diet, birth mode, and antibiotic use [40]. The metabolome technique establishes the relation between human diet intake and the endogenous metabolic processes which lead to gastrointestinal microbiota change. Metabolome analysis explains to researchers that gastrointestinal microbiota change predicts the effects of a healthy diet on human health [41]. Metabolome analysis uses biofluids and tissues to determine the metabolic effects of xenobiotics. The metabolome is the most accurate and sensitive method applied to the cells and tissues. This technique explores the mechanisms involved and their connections with human age, diet, sex, and environment [42]. The reformed diet induces alteration in the metabolome analysis (involved 664 metabolites). The modified diet detects 30 metabolites at months 1 and 3. The reformed diet contains 25 lipids (10 odd-chain saturated fatty acids) is the highest lipids occurred. The reformed diet increases erythrocyte levels and hemoglobin, and anemia occurs [43]. The human diet has a vital role in tumors' beginning, advancement, and progression. Human disease leads to a decline in nutrient intake. This case leads to diet scarcities, and malnutrition occurs. The biogenic amines treat patients with neuroendocrine neoplasms, which helps treat patients with gastroenteropancreatic neuroendocrine neoplasms [44].

2.2. Role of the metabolome in human exercise.

Human exercise is body movement that improves or sustains human physical fitness and health. Human exercise supports human growth and recovers human strength. Exercise inhibits aging increases body muscles and blood circulation. Exercise improves athletic skills, bodyweight decrease, recovers human health. Human exercise performs in groups increases human health. The degree of exercise performed related to the goal, the type of exercise, and the age of the human. Human exercise is divided into 3 groups: aerobic exercise, anaerobic

exercise, and flexibility exercises. In general, human exercise is vital to sustain body fitness and maintain a healthy weight, regulate the gastrointestinal tract, increase and sustain healthy bone mass, muscle strength, and joint mobility, promote physiological health, decline surgical threats, and strengthen immunity. Metabolome, lipidome, and proteome reveal exercise immunology where immunity is dependent on acute and chronic exercise training. Moderate exercise increases immunity and health benefits. Exercise can influence gut microbiota with applications to human health and immunity. Exercise causes an increase in immunity by counteracting immunosenescence and many chronic diseases [45]. After exercise, the blood lactate levels are higher to be 130% than normal human lactate. But, muscle levels are slightly higher than the normal human muscle. Human exercise increases blood pH in the Lactate sample without any change in intramuscular pH. The fractional protein synthesis rate does not show any change after human exercise. So, blood lactate levels modify anabolic signaling in contracted human muscle, as well, the exercise effect on rested muscle and intramuscular lactate is necessary to explain its effect [46]. In athletes, the structure and function of the gastrointestinal microbiome are varied. This observation is due to the microbiomes of athletes in sports possessing high dynamic constituents. Metabolome analysis reveals that succinic acid, *cis*-aconitate, and lactate levels in urine and creatinine levels in feces differ between athletes and normal persons [47]. The training program impacts the plasma metabolome. The training program increases beginning of the Cori cycle. The training program increases lactate and pyruvate levels and anti-inflammatory interleukin (IL)-10 level. The increase of lactate and pyruvate levels increases IL-10 secretion and the pro-inflammatory secretion of IL-1β and IL-6 levels. So, human exercise increases the Cori cycle activity [48]. There are 186 lipids detected in 2 mg of a sample using lipidome analysis. The variation of these lipids is less than 5%. The triacylglycerols are higher lipids found in the adipose tissue. Also, long polyunsaturated triacylglycerols are higher in the thigh than their concentrations in the abdomen, breast, and lower back [49]. The metabolome is a suitable method to detect human metabolism by investigating the chemical composition of feces. There are 2326 metabolic components detected. These metabolites are carboxylic acids, fatty acids, amino acids, and phenolic compounds. Lipids are triacylglycerols, diacylglycerols, and ceramides. Metabolites are homogeneous or heterogeneous. The ceramides, diacylglycerols, phenolic compounds, and triacyl-glycerols are the main metabolites identified in the feces of healthy humans [50]. The metabolic syndrome is treated by human exercise. The metabolome is a good method to investigate the exercise remedy. Time plays a vital role in treating metabolic syndrome after exercise, where the greater change in metabolism occurs after exercise. The resistance exercise reveals a higher response. Human exercise possesses a vital role in serum metabolic biomarkers such as alanine, acetylcarnitine, amino acids, choline, and betaine [51]. The metabolic reflex to healthy physical exercise is good for antioxidant effect and for preventing and treating several diseases such as obesity, dyslipidemia, insulin resistance, and hypertension. Human exercise is good for the human metabolic state, and this result is evaluated by metabolome analysis in serum, urine, stool, or tissue samples. The human blood circulating metabolites are changed by human exercise, and this observation is evaluated by metabolome analysis [52]. In patients with psychiatric disturbances, Spa treatment refreshes the mood state. Spa treatment is responsible for human homeostasis. The increase of these steroids re-balances the immunoprotective adrenal androgens, neuroactive steroids, and mental activity [53]. A physical exercise is an important tool for lessening osteoarthritis. The protective effect of physical exercise in osteoarthritis is performed in pyridoxamine 5'-phosphate and pyridoxal 5'-

phosphate [54]. The metabolomic analysis shows that acetyl-lysine is related to oxygen uptake. Heart failure is related to less work and less oxygen uptake. The protein acetylation of gastric mitochondria is higher by 48% than normal. The protein acetylation includes the electron transport chain and the tricarboxylic acid cycle [55]. Human exercise induces irisin (new myokine) related to insulin obesity and resistance. The irisin level in human plasma is related to insulin resistance, glucose, and cholesterol plasma level in children. The type and period of human exercise are related to irisin secretion in healthy and unhealthy ones. Also, mother-infant relations and plasma irisin is occurred [56]. The metabolome collects and examines sweat after human exercise for metabolite and protein content. The observation shows protein degradation is found. Therefore, metabolome and proteome are good and accurate methods to examine sweat [57].

2.3. Role of the metabolome in human sleep.

Human sleep is a natural regular state of mind and body. It is changed consciousness and declines both sensory and muscle activities. It is discriminated from wakefulness by declining its capability to respond to stimuli. At the same time, human sleep is different from human coma. The dream is a famous sleep and looks like waking life. In human sleep, most of the body's systems are in an anabolic state, such as returning the nervous, skeletal, immunity, and muscular systems. Human sleep is an important state that maintains memory, mood, and biological function. It possesses a great role in human immune and endocrine systems. Human suffers from many sleep disturbances such as narcolepsy, insomnia, hypersomnia, sleep apnea, bruxism, sleepwalking, and circadian sleep disturbances. Table 1 reveals the sleep time needed for different human ages.

Table 1. The sleep time needed for different human ages.

Human age	Sleep hours
Newborns (0-3 months)	14 - 17 hours
Infants (4-11 months)	12 - 15 hours
Toddlers (1-2 years)	11 - 14 hours
Preschoolers (3-5 years)	10 - 13 hours
School-age children (6-13 years)	9 - 11 hours
Teenagers (14-17 years)	8 - 10 hours
Adults (18-64 years)	7 - 9 hours
Older adults (65 years and over)	7 - 8 hours

There is a difference in sleep period and bedtime, and less physical activity correlates with fewer metabolic components in adolescents. So, enough time for physical activity and systematic sleep time is vital for the human metabolic health of adolescents [58]. Metabolome analysis reveals the endocannabinoid system's role in sleep and obstructive sleep apnea. The changes in vascular tone, smoking, inflammation, metabolic balance, hypertension, physical activity, and heart attack are associated with the endocannabinoid system [59]. Obstructive sleep apnea is a common clinical state linked with cardiovascular disease and attack. Obstructive sleep apnea increases cardiovascular disease through stimulating hemodynamic, inflammatory, autonomic, and metabolic disturbances. Obstructive sleep apnea contains molecular pathways such as the role of metabolomics, proteomics, and microRNAs [60]. Metabolome helps to understand obstructive sleep apnea, a public disturbance that possesses obstacles to inhalation due to upper collapse in human sleep. The variation in inhalation of O_2 and CO_2 affects the gastrointestinal tract microbiota, leading to many cardiac and metabolic disturbances [61]. The metabolome is a suitable method to examine chronic obstructive sleep

apnea, accompanied by hypoxia and hypercapnia. This case is associated with cardiovascular disease, i.e., atherosclerosis using metabolome analysis in the stool. Chronic obstructive sleep apnea reveals microbial and metabolic changes [62]. Metabolome analysis investigates psychosocial stress effects on human sleep, human diet, and physical activity. Cortisol is the main factor in human sleep, physical training, and diet. The main effect of cortisol on psychosocial stress is the human brain, with cortisol's role on leptin, endocannabinoids, orexin insulin, neuropeptide Y, and gastrointestinal hormones [63]. The metabolome is an accurate and suitable method for examining idiopathic pulmonary fibrosis (a progressive and lethal disorder) associated with human sleep disturbances. Idiopathic pulmonary fibrosis induces disparate cellular and molecular disorders due to fibroblasts and inflammatory cells [64]. Metabolome analysis reveals that proline metabolism is changed in hepatocellular carcinoma. This increases the intake of proline and accumulation of hydroxyproline directly, leading to an increase in α-fetoprotein level. The hydroxyproline increases hypoxia in hepatocellular carcinoma. The hypoxia increases proline synthesis. The decline of proline synthesis increases the cytotoxicity of sorafenib *in vitro* and *in vivo*. Therefore, hypoxic increases proline metabolism and leads to the accumulation of hydroxyproline that increases hepatocellular carcinoma and sorafenib synthesis [65].

Metabolome plays the principal role in asthma associated with disturbances of human sleep, chronic airflow obstacle breath, and inflammation. The breath of statins evades metabolism through the liver and consequently possesses minor air with higher efficiency. Therefore, statin is a new inhaler in treating asthma [66]. The metabolome is a good analysis for chronic obstructive pulmonary disease, which is correlated with disturbances of human sleep. Chronic obstructive pulmonary disease is started from a viral infection in the lung. The infection occurs in both smokers and nonsmokers. The lung viromes and metabolic pathways are different between smokers and nonsmokers groups. The viral infection induces a higher arachidonic acid and interleukin-8 [67].

3. Role of Metabolome in Human COVID-19

Coronaviruses are huge group possesses RNA strand. MERS and SARS worldwide spread and cause dangerous symptoms to the human superior breathing region [68]. Metabolome analysis of feces reveals polyunsaturated fatty acids, sphingolipids, and the short-chain fatty acid increases in respiratory viral infection. Respiratory viral infection causes a change in gut microbiota. Respiratory viral infection causes weight loss due to a decrease in food consumption. The decrease of cytotoxic cells 8^+ ($CD8^+$) reverses the gut microbiota change. This decrease in $CD8^+$ induces cell apoptosis, increases food intake, and prevents weight loss [69]. The coronaviruses are induced acute respiratory infections. In 2019, a new coronavirus was appeared globally and caused pandemic diseases all over the world. Older people possess a higher threat of this new coronavirus infection. Cell therapy and regenerative medicine techniques are very important in treating many threatening diseases and for recovering patients with severe acute respiratory infections of this virus.

Consequently, the mesenchymal stem cells to decline inflammatory processes of acute respiratory infections induced by this new virus coronavirus are very important in the future treatment of this virus [70]. The coronavirus needs extreme lock-down detection for early diagnosis of the virus. The metabolome analysis is urgently applied for the early cellular response. This virus affects human metabolites, so it could detect new therapeutic factors. The

results investigate the response of interleukin 6 with keratan sulfate synthesis processes in viral infection. The inhibition of matrix metalloproteinase 9 stops the cytokine storm in severely infected patients [71]. The mitochondrial metabolomic result provides new signs of COVID-19 diagnosis. Human COVID-19 is a new beta-coronavirus that induces the global health crisis called the COVID-19 pandemic. The COVID-19 is correlated with mitochondrial dysfunction with COVID-19. There are many environmental chemicals, and endocrine-disrupting chemicals damage mitochondria and cause mitochondrial dysfunction. The genomic RNA of virus and structural proteins affect the normal function of the mitochondria/endoplasmic reticulum/Golgi tool.

Mitochondrial balance through mitophagy is a very important COVID-19 infection and protects mitochondria against COVID-19. The role of mitochondria during COVID-19 infection improves viral therapies and protects mitochondrial disease patients [72]. Metabolome analysis reveals that the immunoglobulin G antibody is very important for protection in external pathogens. Afucosylated Immunoglobulin G variations are applied in anti-tumor treatment antibodies. This increases cytokine storms and immune-associated pathologies. The COVID-19 patients possess high levels of fucosylated Immunoglobulin G antibodies against COVID-19, which increases pro-inflammatory cytokine secretion and acute phase reactions. Consequently, antibody glycosylation possesses a vital role in immunity to human COVID-19 [73]. The human COVID-19 pandemic affected more than 20 million people globally, with mortality exceeding 5 million patients. The factors affecting the mortality rate due to human COVID-19 are diabetes, hypertension, advanced age, and obesity. These factors disorder the lipidome, such as docosanoid lipid mediators and immunomodulatory eicosanoid. The dysregulation of lipid mediators controls the severity of human COVID-19. The moderate and severe type of human COVID-19 is defined by variations in polyunsaturated fatty acid, immune-regulatory, and pro-inflammatory lipid mediator levels.

Consequently, the immunity and-regulatory role of lipid mediators controls an immuno-lipidomic imbalance in severe human COVID-19 [74]. The metabolome approach helps scientists to understand the biological mechanisms in COVID-19 infection. Metabolome searches for treatment and diagnosis biomarkers and improves the metabolic disorder in this infection. The results were obtained to explore the role of the cytosine and tryptophan-nicotinamide paths in metabolome analysis. The role of the tryptophan-nicotinamide path correlated with inflammatory signals and microbiota, and this includes cytosine [75]. Metabolome study enables the researchers to understand the host immune reaction to COVID-19, the viral mode of transmission, and variations in biological paths in humans that enable viral survival. In human COVID-19, there are variations in the fatty acid and amino acid metabolism and immunity, hyperglycemic, and hypoxic sequelae [76].

4. Conclusion

Metabolome refers to small molecules inside the biological sample. The metabolome includes endogenous metabolome and exogenous metabolome. Human health is a physical, mental, and social well-being state without any disease. Human diet, exercise, and sleep are 3 factors that affect human health. Human disease is an abnormal case that negatively affects the structure and function of one organism of the whole human body. The viral shape of the crown is the reason for its name. The World Health Organization report reveals that this virus occurred first in animals (1940) then occurred in humans (2003). The COVID-19 occurred in Wuhan

state in China in December 2019. There are 4 types of coronavirus: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. The *Betacoronavirus* is the dangerous one. In conclusion, the metabolome plays an important role in human health and COVID-19 infection.

Funding

This research received no external funding.

Acknowledgments

This research has no acknowledgment.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Oliver, S.G.; Winson, M.K.; Kell, D.B.; Baganz, F. Systematic functional analysis of the yeast genome. *Trends Biotechnol* **1998**, *16*, 373-378, https://doi.org/10.1016/S0167-7799(98)01214-1.
2. Wishart, D.S. Current progress in computational metabolomics. *Brief Bioinform* **2007**, *8*, 279-93, https://doi.org/10.1093/bib/bbm030.
3. Nordström, A.; O'Maille, G.; Qin, C.; Siuzdak, G. Nonlinear data alignment for UPLC-MS and HPLC-MS based metabolomics: quantitative analysis of endogenous and exogenous metabolites in human serum. *Anal Chem* **2006**, *78*, 3289-3295, https://doi.org/10.1021/ac060245f.
4. Tweeddale, H.; Notley-McRobb, L.; Ferenci, T. Effect of slow growth on metabolism of Escherichia coli, as revealed by global metabolite pool (metabolome) analysis. *J Bacteriol* **1998**, *180*, 5109-5116.
5. Koriem, K.M.M. A lipidomic concept in infectious diseases. *Asian Pac J Trop Biomed* **2017**, *7*, 265-274, https://doi.org/10.1016/j.apjtb.2016.12.010.
6. Koriem, K.M.M. Protective effect of natural products and hormones in colon cancer using metabolome: A physiological overview. *Asian Pac J Trop Biomed* **2017**, *7*, 957-966, https://doi.org/10.1016/j.apjtb.2017.09.002.
7. Koriem, K.M.M. Proteomic approach in human health and disease: Preventive and cure studies. *Asian Pac J Trop Biomed* **2018**, *8*, 226-236, https://doi.org/10.4103/2221-1691.231285.
8. Koriem, K.M.M. Lipidome is lipids regulator in gastrointestinal tract and it is a life collar in COVID-19: A review. *World J Gastroenterol* **2021**, *27*, 37-54, https://doi.org/10.3748/wjg.v27.i1.37.
9. Yang, Y.; Peng, F.; Wang, R.; Yange, M.; Guan, K.; Jiang, T.; Xu, G.; Sun, J.; Chang, C. The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *J Autoimmun* **2020**, *109*, https://doi.org/10.1016/j.jaut.2020.102434.
10. Hasöksüz, M.; Kiliç, S.; Saraç, F. Coronaviruses and SARS-COV-2. *Turk J Med Sci* **2020**, *50*, 549-556, https://doi.org/10.3906/sag-2004-127.
11. Stokes, J.; Noren, J.; Shindell, S. Definition of terms and concepts applicable to clinical preventive medicine. *J Community Health* **1982**, *8*, 33-41, https://doi.org/10.1007/bf01324395.
12. Ojo-Okunola, A.; Cacciatore, S.; Nicol, M.P.; du Toit, E. The determinants of the human milk metabolome and its role in infant health. *Metabolites* **2020**, *10*, https://doi.org/10.3390/metabo10020077.
13. Yang, Q.; Liang, Q.; Balakrishnan, B.; Belobrajdic, D.P.; Feng, Q.J.; Zhang, W. Role of dietary nutrients in the modulation of gut microbiota: A narrative review. *Nutrients* **2020**, *12*, https://doi.org/10.3390/nu12020381.
14. Liu, J.; Kuang, F.; Kroemer, G.; Klionsky, D.J.; Kang, R.; Tang, D. Autophagy-dependent ferroptosis: Machinery and regulation. *Cell Chem Biol* **2020**, *27*, 420-435, https://doi.org/10.1016/j.chembiol.2020.02.005.
15. Wilson, A.S.; Koller, K.R.; Ramaboli, M.C.; Nesengani, L.T.; Ocvirk, S.; Chen, C.; Flanagan, C.A.; Sapp, F.R.; Merritt, Z.T.; Bhatti, F.; Thomas, T.K.; O'Keefe, S.J.D. Diet and the human gut microbiome: An international review. *Dig Dis Sci* **2020**, *65*, 723-740, https://doi.org/10.1007/s10620-020-06112-w.
16. Kachrimanidou, M.; Tsintarakis, E. Insights into the role of human gut microbiota in *Clostridioides difficile* infection. *Microorganisms* **2020**, *8*, https://doi.org/10.3390/microorganisms8020200.
17. Perakakis, N.; Stefanakis, K.; Mantzoros, C.S. The role of omics in the patho-physiology, diagnosis and treatment of non-alcoholic fatty liver disease. *Metabolism* **2020**, *111S*, https://doi.org/10.1016/j.metabol.2020.154320.

18. Lasheras, I.; Seral, P.; Latorre, E.; Barroso, E.; Gracia-García, P.; Santabárbara, J. Microbiota and gut-brain axis dysfunction in autism spectrum disorder: Evidence for functional gastrointestinal disorders. *Asian J Psychiatr* **2020**, *47*, https://doi.org/10.1016/j.ajp.2019.101874.
19. Chen, G.; Kroemer, G.; Kepp, O. Mitophagy: An emerging role in aging and age-associated diseases. *Front Cell Dev Biol* **2020**, *8*, https://doi.org/10.3389/fcell.2020.00200.
20. Mars, R.A.T.; Yang, Y.; Ward, T.; Houtti, M.; Priya, S.; Lekatz, H.R.; Tang, X.; Sun, Z.; Kalari, K.R.; Korem, T.; Bhattarai, Y.; Zheng, T.; Bar, N.; Frost, G.; Johnson, A.J.; van Treuren, W.; Han, S.; Ordog, T.; Grover, M.; Sonnenburg, J.; D'Amato, M.; Camilleri, M.; Elinav, E.; Segal, E.; Blekhman, R.; Farrugia, G.; Swann, J.R.; Knights, D.; Kashyap, P.C. Longitudinal multi-omics reveals subset-specific mechanisms underlying irritable bowel syndrome. *Cell* **2020**, *182*, 1460-1473, https://doi.org/10.1016/j.cell.2020.08.007.
21. Lavelle, A.; Sokol, H. Gut microbiota-derived metabolites as key actors in infla-mmatory bowel disease. *Nat Rev Gastroenterol Hepatol* **2020**, *17*, 223-237, https://doi.org/10.1038/s41575-019-0258-z.
22. Parkhitko, A.A.; Filine, E.; Mohr, S.E.; Moskalev, A.; Perrimon, N. Targeting metabolic pathways for extension of lifespan and healthspan across multiple species. *Ageing Res Rev* **2020**, *64*, https://doi.org/10.1016/j.arr.2020.101188.
23. Roggero, P.; Liotto, N.; Pozzi, C.; Braga, D.; Troisi, J.; Menis, C.; Giannì, M.L.; Berni Canani, R.; Paparo, L.; Nocerino, R.; Budelli, A.; Mosca, F.; Rescigno, M. Analysis of immune, microbiota and metabolome maturation in infants in a clinical trial of Lactobacillus paracasei CBA L74-fermented formula. *Nat Commun* **2020**, *11*, https://doi.org/10.1038/s41467-020-16582-1.
24. Diallo, A.F.; Lockwood, M.B.; Maki, K.A.; Franks, A.T.; Roy, A.; Jaime-Lara, R.; Joseph, P.V.; Henderson, W.A.; Chung, S.Y.; McGrath, J.; Green, S.J.; Fink, A.M. Metabolic profiling of blood and urine for exploring the functional role of the microbiota in human health. *Biol Res Nurs* **2020**, *22*, 449-457, https://doi.org/10.1177/1099800420941080.
25. Tilocca, B.; Pieroni, L.; Soggiu, A.; Britti, D.; Bonizzi, L.; Roncada, P.; Greco, V. Gut-Brain axis and neurodegeneration: State-of-the-art of meta-omics sciences for microbiota characterization. *Int J Mol Sci* **2020**, *21*, https://doi.org/10.3390/ijms21114045.
26. Gholizadeh, N.; Pundavela, J.; Nagarajan, R.; Dona, A.; Quadrelli, S.; Biswas, T.; Greer, P.B.; Ramadan, S. Nuclear magnetic resonance spectroscopy of human body fluids and in vivo magnetic resonance spectroscopy: Potential role in the diagnosis and management of prostate cancer. *Urol Oncol* **2020**, *38*, 150-173, https://doi.org/10.1016/j.urolonc.2019.10.019.
27. Rughani, A.; Friedman, J.E.; Tryggestad, J.B. Type 2 diabetes in youth: the role of early life exposures. *Curr Diab Rep* **2020**, *20*, https://doi.org/10.1007/s11892-020-01328-6.
28. Jin, R.; McConnell, R.; Catherine, C.; Xu, S.; Walker, D.I.; Stratakis, N.; Jones, D.P.; Miller, G.W.; Peng, C.; Conti, D.V.; Vos, M.B.; Chatzi, L. Perfluoroalkyl substances and severity of non-alcoholic fatty liver in Children: An untargeted metabolomics approach. *Environ Int* **2020**, *134*, https://doi.org/10.1016/j.envint.2019.105220.
29. O'Connell, T.M. The application of metabolomics to probiotic and prebiotic interventions in human clinical studies. *Metabolites* **2020**, *10*, https://doi.org/10.3390/metabo10030120.
30. Ahmad, M.I.; Ijaz, M.U.; Haq, I.U.; Li, C. The role of meat protein in generation of oxidative stress and pathophysiology of metabolic syndromes. *Food Sci Anim Resour* **2020**, *40*, 1-10, https://doi.org/10.5851/kosfa.2019.e96.
31. Sellami, M.; Bragazzi, N.L. Nutrigenomics and breast cancer: State-of-art, future perspectives and insights for prevention. *Nutrients* **2020**, *12*, https://doi.org/10.3390/nu12020512.
32. Koriem, K.M.M.; Gad, I.B.; Nasiry, Z.K. Protective effect of *Cupressus sempervirens* extract against indomethacin-induced gastric ulcer in rats. *Interdiscip Toxicol* **2015**, *8*, 25-34, https://doi.org/10.1515/intox-2015-0006.
33. Koriem, K.M.M. Antihyperlipidemic activity of the medicinal plants among Kadazan and Dusun communities in Sabah, Malaysia: A review. *Asian Pac J Trop Biomed* **2014**, *10*, 768-779, https://doi.org/10.12980/APJTB.4.2014C1144.
34. Abu-Ghazaleh, N.; Chua, W.J.; Gopalan, V. Intestinal microbiota and its association with colon cancer and red/processed meat consumption. *J Gastroenterol Hepatol* **2020,** *36*, 75-88, https://doi.org/10.1111/jgh.15042.
35. Flanagan, E.; Lamport, D.; Brennan, L.; Burnet, P.; Calabrese, V.; Cunnane, S.C.; de Wilde, M.C.; Dye, L.; Farrimond, J.A.; Emerson Lombardo, N.; Hartmann, T.; Hartung, T.; Kalliomäki, M.; Kuhnle, G.G.; La Fata, G.; Sala-Vila, A.; Samieri, C.; Smith, A.D.; Spencer, J.P.E.; Thuret, S.; Tuohy, K.; Turroni, S.; Vanden Berghe, W.; Verkuijl, M.; Verzijden, K.; Yannakoulia, M.; Geurts, L.; Vauzour, D. Nutrition and the ageing brain: Moving towards clinical applications. *Ageing Res Rev* **2020**, *62*, https://doi.org/10.1016/j.arr.2020.101079.
36. Albrahim, T. The potential role of nutritional components in improving brain function among patients with Alzheimers disease: a meta-analysis of RCT studies. *Neurosciences (Riyadh)* **2020**, *25*, 4-17, https://doi.org/10.17712/nsj.2020.1.20190037.
37. Żwierełło, W.; Maruszewska, A.; Skórka-Majewicz, M.; Goschorska, M.; Baranowska- Bosiacka, I.; Dec, K.; Styburski, D.; Nowakowska, A.; Gutowska, I. The influence of polyphenols on metabolic disorders

caused by compounds released from plastics - Review. *Chemosphere* **2020**, *240*, https://doi.org/10.1016/j.chemosphere.2019.124901.
38. Zhang, X.; Coker, O.O.; Chu, E.S.; Fu, K.; Lau, H.C.H.; Wang, Y.X.; Chan, A.W.H.; Wei, H.; Yang, X.; Sung, J.J.Y.; Yu, J. Dietary cholesterol drives fatty liver-associated liver cancer by modulating gut microbiota and metabolites. *Gut* **2020**, https://doi.org/10.1136/gutjnl-2019-319664.
39. Cryan, J.F.; O'Riordan, K.J.; Sandhu, K.; Peterson, V.; Dinan, T.G. The gut microbiome in neurological disorders. *Lancet Neurol* **2020**, *19*, 179-194, https://doi.org/10.1016/S1474-4422(19)30356-4.
40. Dedrick, S.; Sundaresh, B.; Huang, Q.; Brady, C.; Yoo, T.; Cronin, C.; Rudnicki, C.; Flood, M.; Momeni, B.; Ludvigsson, J.; Altindis, E. The role of gut microbiota and environmental factors in type 1 diabetes pathogenesis. *Front Endocrinol (Lausanne)* **2020**, *11*, https://doi.org/10.3389/fendo.2020.00078.
41. Landberg, R.; Hanhineva, K. Biomarkers of a healthy nordic diet-from dietary exposure biomarkers to microbiota signatures in the metabolome. *Nutrients* **2019**, *12*, https://doi.org/10.3390/nu12010027.
42. Griffin, J.L. Twenty years of metabonomics: so what has metabonomics done for toxicology? *Xenobiotica* **2020**, *50*, 110-114, https://doi.org/10.1080/00498254.2019.1697015.
43. Venn-Watson, S.; Baird, M.; Novick, B.; Parry, C.; Jensen, E.D. Modified fish diet shifted serum metabolome and alleviated chronic anemia in bottlenose dolphins (Tursiops truncatus): Potential role of odd-chain saturated fatty acids. *PLoS One* **2020**, *15*, https://doi.org/10.1371/journal.pone.0230769.
44. Pobłocki, J.; Jasińska, A.; Syrenicz, A, Andrysiak-Mamos, E.; Szczuko, M. The neuroendocrine neoplasms of the digestive tract: diagnosis, treatment and nutrition. *Nutrients* **2020**, *12*, https://doi.org/10.3390/nu12051437.
45. Nieman, D.C.; Pence, B.D. Exercise immunology: Future directions. *J Sport Health Sci* **2020**, *9*, 432-445, https://doi.org/10.1016/j.jshs.2019.12.003.
46. Liegnell, R.; Apró, W.; Danielsson, S.; Ekblom, B.; van Hall, G.; Holmberg, H.C.; Moberg, M. Elevated plasma lactate levels via exogenous lactate infusion do not alter resistance exercise-induced signaling or protein synthesis in human skeletal muscle. *Am J Physiol Endocrinol Metab* **2020**, *319*, E792-E804, https://doi.org/10.1152/ajpendo.00291.2020.
47. O'Donovan, C.M.; Madigan, S.M.; Garcia-Perez, I.; Rankin, A. O.; Sullivan, O.; Cotter, P.D. Distinct microbiome composition and metabolome exists across subgroups of elite Irish athletes. *J Sci Med Sport* **2020**, *23*, 63-68, https://doi.org/10.1016/j.jsams.2019.08.290.
48. Zwaag, J.; Ter Horst, R.; Blaženović, I.; Stoessel, D.; Ratter, J.; Worseck, J.M.; Schauer, N.; Stienstra, R.; Netea, M.G.; Jahn, D.; Pickkers, P.; Kox, M. Involvement of lactate and pyruvate in the anti-Inflammatory effects exerted by voluntary activation of the sympathetic nervous system. *Metabolites* **2020**, *10*, https://doi.org/10.3390/metabo10040148.
49. Al-Sari, N.; Suvitaival, T.; Mattila, I.; Ali, A.; Ahonen, L.; Trost, K.; Henriksen, T.F.; Pociot, F.; Dragsted, L.O.; Legido-Quigley, C. Lipidomics of human adipose tissue reveals diversity between body areas. *PLoS One* **2020**, *15*, https://doi.org/10.1371/journal.pone.0228521.
50. Trošt, K.; Ahonen, L.; Suvitaival, T.; Christiansen, N.; Nielsen, T.; Thiele, M.; Jacobsen, S.; Krag, A.; Rossing, P.; Hansen, T.; Dragsted, L.O.; Legido-Quigley, C. Describing the fecal metabolome in cryogenically collected samples from healthy participants. *Sci Rep* **2020**, *10*, https://doi.org/10.1038/s41598-020-57888-w.
51. Siopi, A.; Deda, O.; Manou, V.; Kosmidis, I.; Komninou, D.; Raikos, N.; Theodoridis, G.A.; Mougios, V. Comparison of the serum metabolic fingerprint of different exercise modes in men with and without metabolic syndrome. *Metabolites* **2019**, *9*, https://doi.org/10.3390/metabo9060116.
52. Herrero, P.; Rodríguez, M.Á.; Ras, M.R.; Del Pino, A.; Arola, L.; Canela, N. Metabolomics Analyses to investigate the role of diet and physical training. *Methods Mol Biol* **2019**, *1978*, 403-430, https://doi.org/10.1007/978-1-4939-9236-2_25.
53. Honců, P.; Hill, M.; Bičíková, M.; Jandová, D.; Velíková, M.; Kajzar, J.; Kolátorová, L.; Bešťák, J.; Máčová, L.; Kancheva, R.; Krejčí, M.; Novotný, J.; Stárka, Ľ. Activation of adrenal steroidogenesis and an improvement of mood balance in postmenopausal females after Spa treatment based on physical activity. *Int J Mol Sci* **2019**, *20*, https://doi.org/10.3390/ijms20153687.
54. Deiana, M.; Malerba, G.; Dalle Carbonare, L.; Cheri, S.; Patuzzo, C.; Tsenov, G.; Moron Dalla Tor, L.; Mori, A.; Saviola, G.; Zipeto, D.; Schena, F.; Mottes, M.; Valenti, M.T. Physical activity prevents cartilage degradation: A metabolomics study pinpoints the involvement of vitamin B6. *Cells* **2019**, *8*, https://doi.org/10.3390/cells8111374.
55. Tsuda, M.; Fukushima, A.; Matsumoto, J.; Takada, S.; Kakutani, N.; Nambu, H.; Yamanashi, K.; Furihata, T.; Yokota, T.; Okita, K.; Kinugawa, S.; Anzai, T. Protein acetylation in skeletal muscle mitochondria is involved in impaired fatty acid oxidation and exercise intolerance in heart failure. *J Cachexia Sarcopenia Muscle* **2018**, *9*, 844-859, https://doi.org/10.1002/jcsm.12322.
56. Elizondo-Montemayor, L.; Mendoza-Lara, G.; Gutierrez-DelBosque, G.; Peschard -Franco, M.; Nieblas, B.; Garcia-Rivas, G. Relationship of circulating irisin with body composition, physical activity, and cardiovascular and metabolic disorders in the [ediatric [opulation. *Int J Mol Sci* **2018**, *19*, https://doi.org/10.3390/ijms19123727.

57. Harshman, S.W.; Pitsch, R.L.; Smith, Z.K.; O'Connor, M.L.; Geier, B.A.; Qualley, A.V.; Schaeublin, N.M.; Fischer, M.V.; Eckerle, J.J.; Strang, A.J.; Martin, J.A. The proteomic and metabolomic characterization of exercise-induced sweat for human performance monitoring: A pilot investigation. *PLoS One* **2018**, *13*, https://doi.org/10.1371/journal.pone.0203133.
58. Rognvaldsdottir, V.; Brychta, R.J.; Hrafnkelsdottir, S.M.; Chen, K.Y.; Arngrimsson, S.A.; Johannsson, E.; Guðmundsdottir, S.L. Less physical activity and more varied and disrupted sleep is associated with a less favorable metabolic profile in adolescents. *PLoS One* **2020**, *15*, https://doi.org/10.1371/journal.pone.0229114.
59. Scharf, E.L.; Ebbert, J.O. Endocannabinoids and stroke prevention: Review of clinical studies. *Cannabis Cannabinoid Res* **2020**, *5*, 6-11, https://doi.org/10.1089/can.2018.0066.
60. Lebkuchen, A.; Freitas, L.S.; Cardozo, K.H.M.; Drager, L.F. Advances and challenges in pursuing biomarkers for obstructive sleep apnea: Implications for the cardiovascular risk. *Trends Cardiovasc Med* **2020**, *31*, 242-249, https://doi.org/10.1016/j.tcm.2020.04.003.
61. Tripathi, A.; Melnik, A.V.; Xue, J.; Poulsen, O.; Meehan, M.J.; Humphrey, G.; Jiang, L.; Ackermann, G.; McDonald, D.; Zhou, D.; Knight, R.; Dorrestein, P.C.; Haddad, G.G. Intermittent hypoxia and hypercapnia, a hallmark of obstructive sleep apnea, alters the gut microbiome and metabolome. *mSystems* **2018**, *3*, e00020-18, https://doi.org/10.1128/mSystems.00020-18.
62. Tripathi, A.; Xu, Z.Z.; Xue, J.; Poulsen, O.; Gonzalez, A.; Humphrey, G.; Meehan, M.J.; Melnik, A.V.; Ackermann, G.; Zhou, D.; Malhotra, A.; Haddad, G.G.; Dorrestein, P.C.; Knight, R. Intermittent hypoxia and hypercapnia reproducibly change the gut microbiome and metabolome across rodent model systems. *mSystems* **2019**, *4*, e00058-19, https://doi.org/10.1128/mSystems.00058-19.
63. Michels, N. Biological underpinnings from psychosocial stress towards appetite and obesity during youth: research implications towards metagenomics, epigenomics and metabolomics. *Nutr Res Rev* **2019**, *32*, 282-293, https://doi.org/10.1017/S0954422419000143.
64. Yu, G.; Ibarra, G.H.; Kaminski, N. Fibrosis: Lessons from OMICS analyses of the human lung. *Matrix Biol* **2018**, *68-69*, 422-434, https://doi.org/10.1016/j.matbio.2018.03.014.
65. Tang, L.; Zeng, J.; Geng, P.; Fang, C.; Wang, Y.; Sun, M.; Wang, C.; Wang, J.; Yin, P.; Hu, C.; Guo, L.; Yu, J.; Gao, P.; Li, E.; Zhuang, Z.; Xu, G.; Liu, Y. Global metabolic profiling identifies a pivotal role of proline and hydroxyproline metabolism in supporting hypoxic response in hepatocellular carcinoma. *Clin Cancer Res* **2018**, *24*, 474-485, https://doi.org/10.1158/1078-0432.CCR-17-1707.
66. Zeki, A.A.; Elbadawi-Sidhu, M. Innovations in asthma therapy: is there a role for inhaled statins?. *Expert Rev Respir Med* **2018**, *12*, 461-473, https://doi.org/10.1080/17476348.2018.1457437.
67. Gregory, A.C.; Sullivan, M.B.; Segal, L.N.; Keller, B.C. Smoking is associated with quantifiable differences in the human lung DNA virome and metabolome. *Respir Res* **2018**, *19*, https://doi.org/10.1186/s12931-018-0878-9.
68. Raoult, D.; Zumla, A.; Locatelli, F.; Ippolito, G.; Kroemer, G. Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. *Cell Stress* **2020**, *4*, 66-75, https://doi.org/10.15698/cst2020.04.216.
69. Groves, H.T.; Higham, S.L.; Moffatt, M.F.; Cox, M.J.; Tregoning, J.S. Respiratory viral infection alters the gut microbiota by inducing inappetence. *mBio* **2020**, *11*, e03236-19, https://doi.org/10.1128/mBio.03236-19.
70. Parhizkar Roudsari, P.; Alavi-Moghadam, S.; Payab, M.; Sayahpour, F.A.; Aghayan, H.R.; Goodarzi, P.; Mohamadi-Jahani, F.; Larijani, B.; Arjmand, B. Auxiliary role of mesenchymal stem cells as regenerative medicine soldiers to attenuate inflammatory processes of severe acute respiratory infections caused by COVID-19. *Cell Tissue Bank* **2020**, *21*, 405-425, https://doi.org/10.1007/s10561-020-09842-3.
71. Karakurt, H.U.; Pİr, P. Integration of transcriptomic profile of SARS-CoV-2 infected normal human bronchial epithelial cells with metabolic and protein-protein interaction networks. *Turk J Biol* **2020**, *44*, 168-177, https://doi.org/10.3906/biy-2005-115.
72. Yao, Y.; Lawrence, D.A. Susceptibility to COVID-19 in populations with health disparities: Posited involvement of mitochondrial disorder, socioeconomic stress, and pollutants. *J Biochem Mol Toxicol* **2021**, *35*, https://doi.org/10.1002/jbt.22626.
73. Larsen, M.D.; de Graaf, E.L.; Sonneveld, M.E.; Plomp, H.R.; Nouta, J.; Hoepel, W.; Chen, H.J.; Linty, F.; Visser, R.; Brinkhaus, M.; Šuštić, T.; de Taeye, S.W.; Bentlage, A.E.H.; Toivonen, S.; Koeleman, C.A.M.; Sainio, S.; Kootstra, N.A.; Brouwer, P.J.M.; Geyer, C.E.; Derksen, N.I.L.; Wolbink, G.; de Winther, M.; Sanders, R.W.; van Gils, M.J.; de Bruin, S.; Vlaar, A.P.J.; Amsterdam UMC COVID-19 biobank study group, Rispens, T.; den Dunnen, J.; Zaaijer, H.L.; Wuhrer, M.; Ellen van der Schoot, C.; Vidarsson, G. Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity. *Science* **2020,** *10*, https://doi.org/10.1126/science.abc8378.
74. Schwarz, B.; Sharma, L.; Roberts, L.; Peng, X.; Bermejo, S.; Leighton, I.; Casanovas-Massana, A.; Minasyan, M.; Farhadian, S,; Ko, A.I.; Yale IMPACT Team, Dela Cruz, C.S.; Bosio, C.M. Cutting edge: Severe SARS-CoV-2 infection in humans is defined by a shift in the serum lipidome, resulting in dysregulation of eicosanoid immune mediators. *J Immunol* **2021**, *206*, 329-334, https://doi.org/10.4049/jimmunol.2001025.
75. Blasco, H.; Bessy, C.; Plantier, L.; Lefevre, A.; Piver, E.; Bernard, L.; Marlet, J.; Stefic, K.; Benz-de Bretagne, I.; Cannet, P.; Lumbu, H.; Morel, T.; Boulard, P.; Andres, C.R.; Vourc'h, P.; Hérault, O.; Guillon, A.; Emond,

P. The specific metabolome profiling of patients infected by SARS-COV-2 supports the key role of tryptophan-nicotinamide pathway and cytosine metabolism. *Sci Rep* **2020**, *10*, https://doi.org/10.1038/s41598-020-73966-5.

76. Aggarwal, S.; Acharjee, A.; Mukherjee, A.; Baker, M.S.; Srivastava, S. Role of multiomics data to understand host-pathogen interactions in COVID-19 pathogenesis. *J Proteome Res* **2021**, *20*, 1107-1132, https://doi.org/10.1021/acs.jproteome.0c00771.