Understanding of “-omics” of Parkinson’s disease

Sha Zheng*, Xue Wen*, Jian Feng*, Fangfang Liu†, Greg Mirt† and Fan Xu‡

1Pharmacy School, Chengdu Medical College, Sichuan, China
2Department of Public Health, Chengdu medical college, Sichuan, China
3Art College, Southwest Minzu University, Sichuan, China
4Neuro Occupational Activity Centre Novo mesto, Slovenia

Abstract

Parkinson’s Disease (PD), as one neurodegenerative disease, reduce the life quality of our patients extensively. Since the identification and validation of role of alpha-synuclein in PD, several impactful hypotheses pointed out the direction of our research, while the bioinformatic studies initialized to focus on the generation, formation, transportation and aberrant clearance of alpha-synuclein. The pioneer studies of Braak provided a comprehensive classification between alpha-synuclein and the severity of PD. Currently our understanding of bioinformatic on PD are increasing sharply as well from genomic, proteomic and metabolomic. To our best knowledge, here we provide a comprehensive picture of this disease from genomic to metabolomic.

Introduction

Parkinson’s Disease (PD) is a serious neurodegenerative disease of the central nervous system. The prevalence of population over 65 years old arrived at 1.7% and the global incidence rate is 1.5% [1]. In 2016, there were 6.1 million people suffered from PD, including 2.9 million women and 3.2 million men. It caused 211,296 deaths [2], unfortunately incidence increased with age [3]. According to epidemiological statistics prediction, there will be more than 14 million patients of PD in 2040.

The treatment on PD requires robust financial support. Obviously, it is a huge economic burden not only for patients and his/her families, but also on the society. According to the global epidemiological statistics, the sum of direct and indirect costs of treatment on PD in Europe reached 7.7 billion Euros in 2010. While in United States, the total cost of medical and non-medical treatment for every PD patient has increased by a total of $22,800 [4]. As for China, the annual direct medical expenses for patients with PD per year in Shanghai, amount to 4,305 yuan, and the non-medical expenses are about 3,301 yuan [5].

Date back to 2003, Braak, et al. proposed the PD stage according to the specific pattern of α-syn diffusion, which describing the relationship between α-synuclein and disease severity [6]. These six stages clarified the severity of PD accordingly to deficit from sensory to sport zone in the brain. The key pathological traits of PD is the damage or deficit of dopaminergic neurons in the dense part of the substantia nigra. This can be leading to a decrease in the secretion of dopaminergic neurons [7]. The loss of dopaminergic neurons reaches 50%, and the corresponding clinical manifestations appears [8]. The clinical features are mainly static. Sport symptoms such as tremors, bradykinesia, muscle rigidity, and unstable posture are also associated with non-motor symptoms, including constipation, sensory disturbances, depression, autonomic disorders, and sleep disorders [9] (Figure 1). Non-motor symptoms of PD are earlier with exercise needle symptoms [10].

Accumulation of α-synuclein is the main cause of Parkinson’s disease [11], but recent studies have shown that dopamine metabolites can increase neuronal deformation, dopamine is oxidized to produce reactive sputum substances, hydrogen peroxide and other reactive oxygen species. These metabolites have an accelerating effect on PD [12].

The mainstream hypotheses on PD

Oxidative stress is a stress injury caused by intracellular oxidation and anti-oxidation imbalance [13]. Reactive oxygen species (ROS) is produced during oxidative stress, leading to mitochondrial disorders and ultimately neuronal death. Under physiological conditions, reactive oxygen is an important redox form that regulates various signaling pathways. It plays an important role in regulating different cellular metabolism, post-transcriptional modification, antioxidant defense mechanisms, and excessive reactive oxygen destroy cellular lipids. Studies disclosed that dopamine neurons in the brain damaged via the path of oxidative stress and mitochondrial dysfunction, due to the reduced dopamine secretion [14].

The accumulation of unfolded or misfolded proteins caused by glucose starvation, hypoxia, calcium homeostasis or oxidative stress is known as endoplasmic reticulum stress [15]. Folding false or unfolded proteins inhibit synaptic function and interfere with signal transduction pathways, these are key factors leading to ubiquitin proteasome system-mediated protein degradation dysfunction, thereby altering the normal physiological morphology of cells, disrupting protein homeostasis, triggering protein accumulation, and causing the neuron degeneration [11].

*Correspondence to: Fan Xu, Department of Public Health, Chengdu Medical College, Chengdu, Sichuan Province, China, Tel: +86 28 6273 9397; E-mail: xufan@cmc.edu.cn

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that the presence of pesticides in groundwater can cause Parkinson's concerns for the general public. The James Ka study in 2015 showed use of pesticides is very popular. Especially in rural areas, it caused food pollution, can be induced the onset of PD. Currently, the function performing. Several pollutants, such as water, air pollution validated that they associated with development of PD [18].

lead to autosomal recessive PD and/or Parkinson's disease, have been [23], VPS35 (encoding dakarin) [20], gene substantia nigra. The intestine, resulting in the production of lewy bodies in the intestine, and pro-inflammatory factors, while over-activated microglia also astrocytes and microglia releases harmful reactive oxygen species increase oxidative stress and cause neuronal cell deformation [17].

Activation of astrocytes and microglia releases harmful reactive oxygen species and pro-inflammatory factors, while over-activated microglia also increase oxidative stress and cause neuronal cell deformation [17]. Intestinal flora and its metabolites increase intestinal permeability and bacterial translocation, stimulate local and systemic inflammation of the intestine, resulting in the production of lewy bodies in the intestine, and the metabolic products (lipopolysaccharides, etc.) [18]. Ring blood-brain barrier, promoting inflammation and the damage of the substantia nigra.

Accompanied with our increased knowledge several interest gene SNCA (PARK1; encoding α-synuclein) [19], LRRK2 (PARK8; encoding dartakin) [20], VPS35 (encoding vacuolar protein sorting 35) [21], PINK1 (PARK6; PTEN-induced kinase 1) [22], DJ-1 (PARK7) [23], Parkin (PARK2) [22], ATP13A2 (PARK9) [24] and FBXO7 [25] lead to autosomal recessive PD and/or Parkinson’s disease, have been validated that they associated with development of PD [18].

Environment selection role is playing dominant role in gene function performing. Several pollutants, such as water, air pollution and food pollution, can be induced the onset of PD. Currently, the use of pesticides is very popular. Especially in rural areas, it caused concerns for the general public. The James Ka study in 2015 showed that the presence of pesticides in groundwater can cause Parkinson’s disease [26]. The pollutants in the air, including PM, ozone, diesel exhaust and fierce, can be leading to increased cytokine expression and oxidative stress in the brain. Activating microglia may affect the neurodegenerative pathway [27]. In 2017, Lee H, et al. reported that short-term exposure to air pollution may increase the risk of PD exacerbation [28]. Chen CY, et al. in 2017 established that long-term exposure to PM10 has a positive effect on subsequent PD development, and the presence of any combined disease increases the likelihood of PD [29].

Di, et al. so contributes as risk factor in the development of PD. In 2019, Anna Sauerbier, et al. reported a correlation existed between diet and Parkinson’s disease [30]. Andre Rodrigues Vasconcelos, et al. demonstrated that dietary energy restriction (DER) may induces activation of the transcription factor Nrf2, which activates the expression of phase 2 detoxification enzymes, thereby increasing neuronal resistance against oxidative stress and death, and reducing PD risk [31]. At the same time, X. Gao, et al. disclosed that the intake of some flavonoids may reduce the risk of PD. Oxidative stress has a negative impact on flavonoids such as apotosis and the formation of α-synuclein fibers. Also it inhibits the use of dopamine neurons [32].

Genomic understanding of PD

The pathology of PD is caused by the imbalance of alpha-synuclein generation and clearance [33]. In 1998, Polymeropoulos, et al. investigated the beta-synuclein gene was extremely high expressed in brain, this gene showed the inhabitation phospholipase D2 selectively [34]. In 2007, Gasser T, et al. studied the gene function of SNCA, causing the alpha-synuclein gene to develop sporadic PD [35]. Wade-Martins, et al. investigated the function of Leucine gene rich with repeat kinase 2 (LRRK2) in PD. The data disclosed this gene is involved in endosomal-autophagic pathway and the recruitment of specific membrane microdomains under the physiological human gene expression [36]. In 2010, Papapetropoulos S, et al. tested the function of RNA splicing gene SRRM2 (or SRm300), serine/arginine repetitive matrix 2. It is playing the crucial role in RNA splicing in PD [37]. In 2011, Das F, et al. discovered that oncogene DJ-1 prevents oxidative damage and apoptosis of dopaminergic neurons in animal models of Parkinson’s disease [38]. In 2012 Maraganore DM, et al. performed the first genome-wide association study (GWAS), identified a series of candidate gene including, C8orf4 participate in inflammation process. CACNB4 has a calcium channel function. TRPM3 inhibit AKT protein kinase and ITPK2 encode the ER function [39]. In 2014, Screeton RA, et al. reported upon mitochondrial damage such as PINK1s stabilized on the outer mitochondrial membrane where it phosphorylates ubiquitin, generates a signal for the recruitment and activation of Parkin [40].

Similar research interest, LRRK attracts numerous attentions as well. Saniz J found LRRK2-G2019S participated in Akt signaling, glucose metabolism and immunity in 2014 [41] and cell adhesion molecular, complement, coagulation cascade in 2016 [42]; Sealfon SC reported LRRK2-G2019S may increase kinase activity to antagonize specific microRNAs [43]. Moreover, the gene PARK5 also draws great research interest. Hoffman-Zacharska D, et al. found it predominantly involved in rearrangement processes in genomic region in 2015 [44]; while Alonso I, et al. validated its similar functions mediate the deletion of some flavonoids may reduce the risk of PD. Oxidative stress has a negative impact on flavonoids such as apotosis and the formation of α-synuclein fibers. Also it inhibits the use of dopamine neurons [32].
Proteomic understanding of PD

To our best knowledge, the imbalance between generation and clearance of alpha-synuclein is playing dominant role in PD [47]. The CSF is produced by the brain and participates in the internal circulation of the brain. Therefore, it is the best indicator to reflecting the structural characteristics of the pathophysiology of the brain [48]. The pathological marker of PD is the formation of Lewy bodies, while α-synuclein (α-syn) is the main component. Alpha-synuclein may resist damage through aggregation. So when the damage occurs, alpha-synuclein will be aggregate continuously, resulting in mitochondrial damage caused by oxidative stress, beyond the ability of the cell to withstand, and cannot clear abnormal proteins, thereby producing toxic effects on cells and accelerating cell deaths [49].

Studies also uncovered that the level of alpha-synuclein in CSF of patients with PD gradually decreases with the progression of the disease. Decrease in the total α-syn entering the systemic circulation after α-syn fibrosis in the brain tissue may result in total alpha CSF [50]. With respects to the function of alpha-synuclein, Nussbaum RL, et al. found that the alpha-synuclein may bind to the membrane of oligomers, lipid droplet and affected triglyceride metabolism [51]. In 2018, Yen SH demonstrated that it may participate in cell viability [52]. Maguire-Zeiss KA, et al. found that it was involved in oxidative stress and inflammation [53], while Lindquist S, et al. demonstrated that it inhibit the vesical transport [54].

Regarding to other researches interest proteins, Singh MP, et al. reported that the albumin precursor, serum albumin chain-A, PRR14 and serum transferrin N-terminal lobe can be reduce the neuronal dysfunction in 2009 [55]. Yang P, et al. summarized that apolipoprotein A-I is involve in lipid metabolism and deposition process of proteins in 2015 [56]. Burkhard PR, et al. disclosed that cytosolic non-specific dipeptidase 2 (CNDP2) participate in oxidative stress, protein aggregation and inflammation [57]. Robinson PA, et al. validated that protein Parkin participate in the regulating mitochondrial activity [58].

In 2018, Ketterman AJ validated that the human glutathione transferase omega 1 modulating stress response [59]. Arenas E, et al. reported that leucine-rich repeat kinase 2 accelerate the maturation of substantia nigra dopaminergic neurons [60]. While, Rubinsztein DC, et al. revealed that Leucine-rich repeat kinase 2, LRRK2, may impair the activity of ubiquitin proteasome pathway [61]. Harvey, et al. demonstrated that LRRK2 participate in protein translation and trafficking [62]. Mann M, et al. figured out that LRRK2 involve in vesicle transport [63].

Moreover, Cookson MR, et al. disclosed that the DJ-1 may protect the neurons against death [64]. Zhang Y, et al. reported that the mitochondrial heat shock protein 75 (MTHSP75), phosphoglycerate dehydrogenase (PHGDH), laminin binding protein (LBP), tyrosine 3/tryptophan 5-monooxygenase activation protein (14-3-3ε) and YWHAZ protein (14-3-3σ) are involved in mitochondrial dysfunction, serum synthesis, amyloid clearance, apoptosis process and neuroprotection [65] (Table 2).

Metabolism understanding of PD

Kaddurah-Daouk R, et al. disclosed that uric acid may reduce the antioxidative damage in 2009 [66]; Jones DP, et al. found that the polyamine regulate cell growth and its size value in 2013 [67]; Pamplona R, et al. reported that glutathione participate in buffering oxidative stress [68]; Kong L, et al. found that creatine may protect neurons from oxidative stress in 2014 [69]; Rango M, et al. reported in 2015 that HEP involved in oxidative phosphorylation, mitochondrial damage and lactic acid may reduce mitochondrial damage [70]; Powers R, et al. reported that sorbitol sugar can cause the mitochondrial dysfunction, oxidative stress. Pyruvate is involved in Tricarboxylic acid cycle. This is known since 2015 [71]; Liu H, et al. reported that serotonin participate in metabolic pathways including antioxidant activities and citrate cycle [72]. Cai H, et al. found that guanosine participate in neurodegeneration to prevent 1-methyl-4-phenylpyridinium (MPP⁺)-induced PC12 cell, and carnosine protect brains mainly through antioxidant, and antitiglycative properties in 2015 [73]. Gao H, et al. found that Glu, Gln, GABA inhibit neurotransmitter GABA and lactate may increase the lactate level in the striatum of 6-OHDA-induced PD rats in 2015 [74].

Madine J, et al. found that taurine may stabilise cell membranes because assisting in ion transport to antioxidant and increase cognitive

| Author                | Year  | Interested Gene | Function                                                                 |
|-----------------------|-------|-----------------|--------------------------------------------------------------------------|
| Polymereopoulos MH    | 1998  | beta-synuclein  | Inhibit phosphatase D2 selectively                                       |
| Gasser T              | 2007  | SNCA            | alpha-synuclein                                                         |
| Wade-Martins R        | 2009  | LRRK2-R1441C    | Abnormal autophagy balance, abnormal MVB formation                       |
| Papapetropoulos S     | 2010  | SRRM2           | mRNA expression, signal transduction                                    |
| Das F.                | 2011  | DJ-1            | Anti-apoptosis                                                          |
| Maragomare DM         | 2012  | C8orf4          | Inflammation                                                            |
| Screaton RA           | 2014  | PINK1           | Phospho-ubiquitin method on the outer membrane of mitochondria, recruitment and activation to generate signals |
| Sainz J               | 2014  | LRRK2-G2019S    | Akt signaling, glucose metabolism or immunity                           |
| Sealfon SC            | 2015  | LRRK2-G2019s    | Increases kinase activity to antagonize specific microRNAs             |
| Hoffman-Zacharska D   | 2015  | PARK2           | rearrangement processes                                                  |
| Orr-Utregger A        | 2015  | GBA             | Peripheral blood leukocyte-associated gene down-regulation              |
| Lou Z                 | 2015  | Parkin          | mitotic defects, genomic instability, tumorigenesis                     |
| Alonso I              | 2016  | PARK2           | rearrangement processes                                                  |
| Sainz J               | 2016  | LRRK2-G2019s    | Cell adhesion molecule, complement, coagulation cascade                 |
| Bosch E               | 2016  | PARK2           | Premature stop codon                                                    |
| Kim J                 | 2017  | GBA-GBAP1       | Pseudogene rearrangement, gene conversion                               |
|                       |       | LG2KGS          | gene expression in the intestinal cells.                                 |

Table 1. Genomic understanding of PD
function; Dimethylamine may produce NO which can induce oxidative/nitrative stress conditions and in turn damage mitochondrial complex I, complex II and mitochondrial aconitase [75]; Cai Z, et al. established that Tryptophan influent CNS inflammation and amino acid play a notable role in signal exchange between neurons [76] (Table 3.1).

Roy R, et al. found that branched-chain amino acids regulate the mitochondrial respiration and participate in the synthesis of neurotransmitters, while histidine helps in scavenging ROS [77]; Lambert JT, et al. found in 2019 that urate involved in antioxidant and reactive oxygen species (ROS) scavenger, meanwhile, adenosine play anti-inflammatory effects [78]; Eggers C, et al. found that mannose regulate the immune signal and mediate inflammatory response [79]; Le W, et al. found that cerebrospinal fluid metabolome involved in antioxidative stress responses and metabolic pathways of sphingolipid, glycerophospholipid and amino acid. Consistently, urate participate in against oxidative stress in 2019 [80]. Hattori N, et al. discovered that benzoate-related metabolites may altered in gut microbiota and caffeine and its metabolites affect the malabsorption [81]. Xu F, et al. reported that adenosine may attenuating oxidative stress, excitotoxicity and neuroinflammation, promoting sleep, improving cognitive function and exerting anti-depressive effects in 2019 [82] (Table 3.2).

Table 2. Proteins Discovered in PD

| Author               | Date  | Key protein                                                                 | Biological function (Annotation)                                                                 |
|----------------------|-------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Nussbaum RL          | 2005  | Alpha-synuclein                                                            | Preferentially binds to oligomers of the membrane, binds to lipid droplets and affects triglyceride metabolism |
| Singh MP             | 2009  | albumin precursor, serum albumin chain-A, PRR14 and serum transferrin N-terminal lobe | Neuronal dysfunction                                                                            |
| Fasano M             | 2014  | alpha-synuclein                                                            | reduces nuclear factor kappa B activation                                                           |
| Yang P               | 2015  | apolipoprotein A-I                                                        | lipid metabolism, deposition process of proteins                                                   |
| Burkhard PR          | 2016  | CNDP2                                                                      | oxidative stress, protein aggregation inflammation                                                  |
| Iseri P              | 2016  | E3-protein ubiquitin ligase                                                | cell metabolism                                                                                   |
| Robinson PA          | 2017  | Parkin                                                                     | regulating mitochondrial activity within cells                                                     |
| Mandell JW           | 2018  | caspases                                                                   | synapse loss                                                                                      |
| Kettermann AJ        | 2018  | Human glutathione transferase omega 1                                      | modulating stress response                                                                         |
| Arenas E             | 2018  | Leucine-rich repeat kinase 2                                               | Maturation of substantia nigra dopaminergic neurons                                                |
| Yen SH               | 2018  | alpha-synuclein                                                            | compromise cell viability                                                                           |
| Maguire-Zeiss KA     | 2018  | Alpha-synuclein                                                            | Oxidative stress, inflammation                                                                     |
| Rubinsztein DC       | 2018  | lrrk2                                                                       | impairs the activity of the ubiquitin-proteasome pathway,                                         |
| Lindquist S          | 2018  | Alpha-synuclein                                                            | Inhibition of vesicle transport                                                                     |
| Cookson MR           | 2018  | DJ-1                                                                       | Protected neurons against death                                                                   |
| Harvey K             | 2019  | lrrk2                                                                       | protein translation and trafficking                                                                |
| Zhang Y              | 2019  | (MTHSP75), (PHGDH), (LBP), (14-3-3epsilon) and YWHAZ protein(14-3-3zeta)   | mitochondrial dysfunction, serine synthesis, amyloidclearance, apoptosis process and neuroprotection |
| Mann M               | 2019  | lrrk2                                                                       | Vesicle transport                                                                                  |

Table 3. Metabolism of PD understanding from 2009-2017

| Author                | Date  | Metabolites                  | Pathway                                      |
|-----------------------|-------|------------------------------|----------------------------------------------|
| Kaddurah-Daouk R      | 2009  | uric acid                    | Antioxidative damage                         |
| Jones DP              | 2013  | Polyamine                    | Regulate cell growth and increase value       |
| Pamplona R            | 2014  | Glutathione                  | Buffering oxidative stress                   |
| Kong L                | 2014  | Creatine                     | Protect neurons from oxidative stress        |
| Rango M               | 2015  | HEP                          | Oxidative phosphorylation, mitochondrial damage |
| Powers R              | 2015  | Sorbitol sugar               | Mitochondrial dysfunction, oxidative stress  |
| Liu H                 | 2015  | Serotonin                    | Tricarboxylic acid cycle                     |
| Cai H                 | 2015  | Guanosine                    | metabolic pathways, antioxidant activities, citrate cycle                                    |
| Gao H                 | 2015  | Glu, Gln, GABA               | inhibitory neurotransmitter GABA              |
| Jolicoeur M           | 2017  | ATP                          | Energy metabolism, oxidative stress          |
| Madine J              | 2017  | Taurine                      | stabilise cell, membranes assisting in ion transport and is suggested to have antioxidant properties and to increase cognitive function |
| Cai Z                 | 2017  | Tryptophan                   | influence CNS inflammation                    |

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Philosophy on computational

Thanks to the knowledge of central dogma, it disclosed the basic life rules from replication, transcription, reverse transcription and translation of DNA. It maintains the general life process and responses the modification from inner and outer of body [83]. Several databases, such as GEO, GenBank etc., which collected the data from all over the world. This is not only an opportunity, but also a risk. Due to ununified samples and different design principles, the data we see may only one tip of iceberg.

Robust algorithm and powerful online platform

Due to numerous customized packaged developed and test in R, including sequencing [84], mapping [85], comparing [86], identifying [87], finding [25] and predicting [88]. More particular, the package named as "Bioconductor", so far there are 1714 packages. They can be classified into assay domain, biological question, annotation data, experiment data and workflow, which almost cover full aspects of bioinformatics. While many online platform developed to disclose the cellular pathway [89], including over-representation analysis tool, geneset enrichment analysis, network module-based pathway analysis. Furthermore, aim to get a comprehensive picture of changes, molecular network alteration became another emerging hot topic. For example, the network perturbation analysis, causal reasoning analysis, were developed as valuable complementary tools to conventional pathway analyses.

It is worth noting that no matter the robust code or powerful online platform, it is only handling the unique dataset. Because the experiment or trial on Parkinson’s patient was customized, including the inclusive and exclusive criteria, specific intervention, biological sampling, samples processing method. Any kind of different middle term may introduce the variation. It furtherly strength the difficult in data merge. Therefor the current data only reflect one perspective, not comprehensive and globe view of the object. The reason behind may explain as the below cartoon, every investigator may report one fact based on his/her dataset. But another challenge remains, that is how to merge the data orderly

Big data need big idea

An obvious tendency accompanied with the big data is that the mainstream data are overload with much noise, and the discovery of the truths that underly big data poses various challenges. Here are some challenges remaining, such as the sample uniformity in different bioinformatic databases including DNA, RNA and metabolism. The biggest challenge is heterogeneity, the bioinformatic data were generated by different methods from different biological samples at different periods. Therefore, it is obvious that the principle of current data merge is not suitable or reliable. Even though comprehensive data were being introduced more and more under the surroundings of big data era, however, the error fact or noise were also being introduced.

Big data needs big idea. Traditional data analysis explain the modifications under a certain period with specific purpose. As for the Parkinson’s Disease, the pathological changes occurred in time sequence. For example, with unknown etiologic reason, several toxins from environment such as rotenone, MPTP, paraquat, pesticide and heavy metal may induced the damage on structure of DNA, consequently, the balance between clearance and generation of alpha-synuclein was broken. The abnormal deposition of alpha-synuclein among neurons may reduce the depletion of dopamine. Consequently, the movement disorder may be presented from the early stage of PD, (Figure 2). Therefore, the concept of transomic is emerged. The integral data need to be drawn from different databases with unified samples, while the data flow needs to be merged or combined according to the time-series

Conclusion

Thanks to huge development of “-omic” studies, our understanding of PD grows rapidly as well. From the genomic perspective, to identifying and validating the key driver gene become a critical issue. Because more and more genes may be triggered and to modified the pattern of translation and transcription due to increased entropy, while it may be reported due to a single research. However, the general picture may missing. That is of importance to discover the key driver gene. While the treatment effect and adverse event of deep brain stimulation on PD receive great satisfactory from both patients and doctors. It has been serviced in front clinic for two decades. Numerous evidence validated the modification of electric field on micro-environment among neurons can be rearrangement of dopamine distribution. Therefore, to rearrange and generate the neuron transmitters may become the new strategy to against the Parkinson’s Disease. We place great expectations on these technologies to personalize treatment for patients with Parkinson’s Disease.

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Table 3.2. Metabolism of PD understanding from 2018-2019

| Author       | Date | Metabolites                  | Pathway                                                                 |
|--------------|------|------------------------------|------------------------------------------------------------------------|
| Roy R        | 2018 | branched-chain amino acids   | mitochondrial respiration, participate in the synthesis of neurotransmitters |
|              |      | histidine                   | an antioxidant, helps in scavenging ROS                                |
| Lamberts JT  | 2019 | Urate                       | antioxidant and reactive oxygen species (ROS) scavenger                 |
| Eggers C     | 2019 | fatty acids                 | fatty acid oxidation                                                   |
|              |      | mannose                     | immune signal, mediate inflammatory response                           |
| Le W         | 2019 | Cerebrospinal fluid metabolome | involved in antioxidative stress responses, and metabolic pathways of sphingolipid, glycerophospholipid and amino acid |
|              |      | Urate                       | against oxidative stress                                               |
| Hattori N    | 2019 | fatty acid                  | lipid metabolism                                                       |
|              |      | benzoate-related metabolites | alteration in gut microbiota                                           |
|              |      | caffeine and its metabolites | malabsorption                                                          |
| Xu F         | 2019 | Adenosine                   | attenuating oxidative stress, excitotoxicity and neuroinflammation, promoting sleep, improving cognitive function and exerting anti-depressive effects |
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Conflicts of interest

The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this manuscript.

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