



Approaching to the Essence of Major Depressive Disorder

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Background of Major Depressive Disorder

Major Depressive Disorder (MDD) is a serious neuropsychic disease. It destroys person's family relationship and social connections seriously. Latest WHO investigation disclosed nearly 4.4% of the population worldwide (approximately 322 million people) were being affected by MDD extensively [1]. While in China, Dong M, et al. reported the occurrence rate of suicide attempt during hospitalization and after the onset of MDD were 17.3% (95% CI: 12.4-23.7%) and 42.1% (95% CI: 26.1-60.0%) respectively [2]. Another research made by Grupta S, et al. announced MDD in urban China might be under-diagnosed and untreated [3].

Gene-Related Antidepressant Studies

Currently MDD is often resistant to standard antidepressant treatment. Venlafaxine is norepinephrine reuptake inhibitor and widely used to cure MDD for many decades [4]. It presents lower rate of dizziness [5], more acceptability and tolerability [6], better efficacy [7]. Recently, 2018 Olgiati P, et al., compared treatment effect between Anti-Depressant (AD) naturalistic studies and Treatment-Resistant Depression (TRD, Venlafaxine). They pooled the publications from 2000 to 2017 and concluded that the nature of TRD is complicated and different with other subtype of MDD [8]. In the same year, Cipriani, A et al pooled 522 trials comprising 116477 participants, found that venlafaxine, amitriptyline, mirtazapine, escitalopram, paroxetine, agomelatine and vortioxetine presented better than placebo in efficacy and acceptability [9].

Accumulating clinical and basic gene-related researches, such as miRNAs, SNPs, Epigenetics, manifest an emerging focus on identifying the Differentially Expressed (DE) genes and associated antidepressant response in MDD. For examples, Taro Kishi demonstrated that rs10997875 in SIRT1 gene play a crucial role pathophysiology of MDD in Japanese population [10,11] and Shen X disclosed that the Tryptophan hydroxylase 2 gene have a sex-dependent-effect on MDD [12]. Moreover, Hu Y disclosed that the rs1549854 and rs1432441 polymorphisms of the MAP2K1 gene may be associated with MDD [13]. Our previous studies [14] employed the analysis of Differential Co-Expression (DCE) and Differential Regulation (DR) to compare the transcriptomic profiles of MDD patients, and validated the Venlafaxine having an obvious effect on the gene expression profile significantly.

System Biology Expand our Horizon on MDD

Early in 2010, de la Fuente A announced the disease-associated gene may be involved in the specific regulatory network. Therefore transcriptional profiles under the disease state may disclose the facts of interaction between gene and environment [15]. With the rapid developing of system biology, several novel approaches for uncovering the mechanism of MDD have emerged. For example in 2018, Akil H discussed the possibility and feasibility of multi-scale framework to disclose the relationship between disease-related gene expression to brain circuit, further by using of neuroimage technique to identify the candidate circuits and molecules [16].

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In 2016, Miyata S employed the transcriptomic biomarkers from blood in patients with late-onset MDD and testified the CIDE C (Cell Death-Inducing DFFA-Like Effector C) has the tremendous potential discriminant validity (specificity 87.5%, Sensitivity 91.3%) [17]. Moreover, in 2015, Malki K discovered some convergent genes participated in the pathogenesis of MDD in an integrative rat-human study. 8% of these genes were functionally linked with stress response signaling cascade, involving nuclear factor kappa-light-chain-enhancer of activated B (NF- κ B) cells, activator protein 1 (AP-1) and ERK/MAPK pathway, which has correlated with MDD's neuroplasticity and neurogenesis systematically [18].

Also, 2014 Powell TR validated the putative transcriptomic biomarker differentiates MDD significantly in the inflammatory cytokine pathway [19]. Several studies as to the dysmetabolism of MDD presented novel perspectives of MDD. In 2010, Oxenkrug GF emphasized that Tryptophan kynurenine pathway presents a significant gathering point of intercommunication between gene and environment in MDD [20,21]. 7 years later, Sorgdrager FJH revealed an imbalance between HPA axis function and tryptophan metabolism in recurrent of MDD [22]. Meanwhile, in 2016 Ali-Sisto T found that purine metabolism was dysregulated in patients with MDD [23].

Core Brain Circuit of MDD

Thanks to the discovery process for finding the precise target brain circuits that MDD affected, we got more precise knowledge on MDD. In 2013 Li K validated that β CaMKII as a robust regulator in lateral habenula mediating core symptoms of depression [24]. 5 years later, Yang Y et al. cross-validated that lateral habenula plays a crucial mediator function in the pathophysiology of depression [25]. They further block Ketamine bursting in the lateral habenula, which lead to rapid can relieve from depression [26]. In 2016, Lv Q blocked the N-methyl-D-aspartic acid receptors; local synaptic can inhibit the prolonged network of cortico-limbic-striatal circuit by using of monkey's model of MDD [27].

Summary

Dating back to 1834, Lamarck stated laws that the frequent use of organ can gradually strengthen, developing and enlargement. Otherwise, it will be progressively diminishing its functional capacity until it finally disappears [28]. These perspectives of evolution may be lighting the road of cure of MDD. For example, 2017 Kerling A demonstrated the exercise training may increase brain-derived neurotrophic factor BDNF, and it has beneficial effects in the treatment of MDD [29]. Accompanied by increasing mechanism understanding the essential neurobiology of MDD, the treatment guideline of MDD has been improved and modified annually [30]. The mechanism of MDD will be revealed gradually, more and more patients would benefit from these translational researches.

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