Programmed Cell Death 4: A New Target for Antidepressant Research

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1. Abstract

Depression is a widespread and serious global mental illness. Approximately 322 million people worldwide suffer from depression, which accounts for 4.4% of the total population. Currently, antidepressants are the preferred treatment for depression. However, clinical antidepressants such as selective 5-hydroxytryptamine reuptake inhibitors (SSRIs), and norepinephrine reuptake inhibitors (SNRIs) are commonly associated with serious side effects. As a result, it is crucial to explore new therapeutic targets for the treatment of depression. Our results indicate that Programmed Cell Death 4 (PDCD4) is an effective antidepressant target, which holds important implications in the development of antidepressant drugs.

2. Clinical treatment strategies and bottlenecks in anti-depressant

The “monoamine theory” of depression suggests that the dysfunction of monoamine transmission and the decreased sensitivity of 5-HT receptor are important pathological bases for the development of depression. Hence, antidepressants that improve monoamine transmission or increasing sensitivity of 5-HT receptor, such as selective 5-hydroxytryptamine reuptake inhibitors (SSRIs), and norepinephrine reuptake inhibitors (SNRIs) have been developed, and they are now a mainstay of depression treatment. However, clinical data shows that SNRIs and SSRIs only cure 30% of patients, and they are also accompanied by serious side effects, such as headache, nausea, and an increase in blood pressure [1]. Although psychotherapy has been shown to be effective, its antidepressant effects must be cumulative over time, and it has no significant effect on the treatment of acute and major depression disorders. Modified electroconvulsive therapy (MECT) has a 70% to 90% cure rate for depression, but is primarily used for suicidal patients with major depression, moreover, this physical therapy is associated with memory loss, fear and hallucinations. Subanesthetic drug administration (Ketamine) significantly reduces suicidal ideation in depressed patients in a short period of time and has a rapid and long-lasting antidepressant effect [2,3]. However, ketamine’s use in clinical settings...
has been restricted due to its hallucinogenic and addictive effects. Therefore, clarifying the pathogenesis of depression will provide a theoretical basis for precise treatment. In depression, synaptic plasticity impairment is one of the major pathological manifestations, and BDNF plays a critical role in synaptic plasticity restoration [4,5]. Interestingly, all of these depression treatment strategies were able to significantly upregulate BDNF expression in depressed patients, and the latest studies have confirmed that the anti-depressive effect of above treatments are depend on BDNF-TrkB response [6]. Consequently, clarifying the molecular mechanism of BDNF in depression regulation will provide insights into the development of novel antidepressant drugs.

3. PDCD4 promotes depression-like behavior via inhibiting BDNF translation

PDCD4 gene was discovered as a tumor suppressor [7], and most of the research has been conducted on tumor metabolism and development [8]. In the last 20 years, our group focused on the relevance and regulatory mechanisms of PDCD4 in various diseases [9]. Recently, we found that PDCD4 is involved in chronic restraint stress-induced depression-like behavior [10].

Studies have shown that PDCD4 regulates mRNA translation by inhibiting activity of eIF4A, a translation initiation factor. The eIF4A as an ATP hydrolase and an RNA helicase is the only regulator with catalytic activity within the translation initiation complex and is involved in initiation of protein translation. By binding with eIF4A, PDCD4 realizes the switch function of protein synthesis [11]. Moreover, for PDCD4 regulating mRNA translation with substrate selection characteristics, we have identified that PDCD4 selectively inhibits translation of BDNF mRNA with IIc-5’-UTR. Therefore, we think that PDCD4 is an effective antidepressant target for the specific modification of BDNF expression [10].

4. Modulating PDCD4 expression for antidepressant purposes

4.1 Injection of PDCD4 shRNA locally in the brain

Previously, we found significant upregulation of PDCD4 mRNA expression in the hippocampus of depressed patients and mice. Therefore, we proposed the hypothesis that “silencing PDCD4 expression at the transcriptional level could alleviates depression”. PDCD4-interfering lentivirus was injected into the hippocampus of mice to silence the expression of PDCD4. We found that silencing PDCD4 expression in hippocampal significantly resisted CRS-induced anxiety-like and depression-like behaviors [10].

4.2 Brain-targeted siPdcd4 delivery is enabled by modifying RVG peptides

The development of new drugs is facilitated by small nucleic acid drugs such as siRNA. Therefore, we screened for PDCD4-specific small interfering RNA (siPdcd4) and performed brain-targeted modification of siPdcd4 by the rabies virus peptide RVG-9dR (RVG/siPdcd4). The results In vivo showed that intravenous administration of RVG/siPdcd4 alleviated CRS-induced depression-like behavior by upregulating BDNF and repairing synaptic plasticity [12].

4.3 Design of peptides interfering the interaction of PDCD4 with eIF4A

We identified a peptide that specifically interfered the interaction of PDCD4 and eIF4A. In the cultured neuronal cells, the PDCD4-interfering peptide significantly reversed the inhibitory effect of PDCD4 overexpression on BDNF and increased endogenous BDNF expression. Further, the targeted injections of PDCD4-interfering peptides into the hippocampal region of mice effectively resisted depress-like behavior [10].

5. Issues remains to be explored

In addition to tumor-related studies [13], our group has made the original discovery that PDCD4 plays an important role in inflammation models. We found that

(1) PDCD4 negatively regulates the IL-10 expression and then promotes hyperlipidemia-induced atherosclerosis [14].

(2) PDCD4 promotes high-fat diet-induced obesity and insulin resistance by negatively regulating hepatic X receptor (LXR-α) expression [15].

(3) PDCD4 negatively regulates IL-6/STAT3 to inhibit DSS-induced acute colitis [16].

(4) PDCD4 blocks the autophagy-lysosomal pathway by inhibiting the formation of the ATG5/ATG12 complex [17] and by inhibiting translation of TFEB [18], key transcriptor for autophagy-lysosomal pathway. However, the role of PDCD4 in other neurodegenerative disorders (Parkinson’s disease, Alzheimer’s disease) besides depression is not well understood.

6. Discussion

No clear conclusions have been drawn about the triggering mechanisms of depression. Our findings suggest that impairment of the PDCD4 degradation pathway due to
sustained stressful stimuli (chronic stress) may be responsible for depression. Neurotrophic factors are the main mediators in the repair function of the nervous system and involved in a variety of physiological functions, including cell differentiation, learning memory, and emotion regulation. There is reason to believe that PDCD4 is involved in the development and progression of many neurodegenerative and neuroinflammatory diseases through the regulation of other members of the neurotrophic factor family [19].

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8. Conflict of Interest
The authors declare that they have no conflict of interest.

9. References