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Commentary

A sirtuin 6 activator in the pipeline: New perspectives in depressive disorder treatment

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Abstract

Major Depressive Disorder (MDD) is among the most prevalent mental illnesses worldwide. Its symptoms include persistent feelings of sadness, loss of interest in previously enjoyed activities, and a lack of motivation for daily tasks. While FDA-approved medications are available, they often come with side effects, especially those targeting monoamine neurotransmitters like SSRIs and SNRIs. Thus, there is a need for innovative medications with different mechanisms of action. Sp-624, a derivative of griseofulvin, is currently undergoing clinical trials for MDD treatment. It acts as a sirtuin 6 (SIRT6) activator, offering a novel approach to treating this disorder. This article discusses the biochemical aspects related to the mechanism of action of sp-624, provides a brief overview of related patents, and highlights ongoing clinical trials involving this substance.

Abbreviations

ADPr: ADP-ribose; Akt-GSK3: Protein Kinase B-glycogen Synthase Kinase 3; CRMP2: Collapsin Response Mediator Protein 2; CUS: Chronic Unpredictable Stress; FDA: Food and Drug Administration; GBD: Global Burden of Disease; MADRS: Montgomery-Asberg Depression Rating Scale; MAOIs: Monoamine Oxidase Inhibitors; MDD: Major Depressive Disorder; NAADPr: 2-*N*-acetyl-ADP-ribose; NAD^+: Nicotinamide Adenine Dinucleotide; NMDA: *N*-methyl-D-aspartate; SIRT6: Sirtuin 6; SNRIs: Serotonin/Norepinephrine Reuptake Inhibitors; SSRIs: Selective Serotonin Reuptake Inhibitors; TCAs: Tricyclic Antidepressants; TMS: Transcranial Magnetic Stimulation

Commentary

A mental disorder is characterized by a significant disturbance in an individual's cognition, emotional regulation, or behavior. Among the various classifications outlined in the Diagnostic and Statistical Manual of Mental Disorders, Major Depressive Disorder (MDD) stands out as one of the most prevalent. According to the World Health Organization, in 2023, approximately 280 million people experienced depression worldwide [1]. Its clinical features include depressed mood, lack of pleasure, and motivation in everyday activities. Moreover, high rates of physical comorbidity are also associated with individuals with MDD, such as cardiovascular diseases, obesity, and type 2 diabetes mellitus [2]. Another aspect related to these individuals is the increase in negative outcomes related to education, employment [3] and personal relationships [4].

The current understanding of the etiology of MDD remains incomplete and cannot be fully explained by a single established biological or environmental pathway. It appears to be caused by a combined effect of genetic, environmental (such as poverty, negative life events, and abuse), psychological (such as cognitive patterns), and biological factors (such

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as inflammatory pathways) [5]. Particularly, an event that contributed to the increase of these effects was the COVID-19 pandemic. In 2020 the Global Burden of Disease (GBD) estimated that this pandemic caused a 27.6% increase in cases of MDD worldwide [6].

The recommended and commonly used treatments for MDD usually entail pharmacological therapy, and the substances available on the market act by increasing certain neurotransmitters such as serotonin and norepinephrine in the synapse to modulate mood and behavior. The main classes of antidepressants include Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs), Atypical Antidepressants, Serotonin Modulators, Tricyclic Antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOIs), and N-methyl-D-aspartate (NMDA) Antagonists [7]. In individuals with severe and/or treatment-resistant MDD, other biological therapies, like electroconvulsive therapy, may also be offered. Several newly developed and emerging interventions are being evaluated in clinical trials or have been introduced into clinical practice, including biological interventions such as transcranial magnetic stimulation (TMS), ketamine, or psychedelics [5].

Despite the availability of drugs that have received Food and Drug Administration (FDA) approval, it is common for these substances to exhibit side effects, particularly those that target various monoamine neurotransmitters, such as SSRIs and SNRIs [7]. In this context, the need for the development of new medications featuring innovative mechanisms of action persists as a critical component in the treatment of MDD. Hence, we comment on the chemical and pharmacological aspects of sp-624, a derivative of griseofulvin currently undergoing clinical trials. It is recognized as an activator of sirtuin 6 (SIRT6), which represents a promising new pharmacological target for MDD.

SIRT6: A new target for MDD treatment

SIRT6 is a member of the sirtuin family, a class of signaling proteins involved in metabolic regulation that utilize nicotinamide adenine dinucleotide (NAD^+) as a cofactor [8]. Human sirtuins are composed of seven members, named SIRT1 to SIRT7. They regulate many cellular physiological processes, including metabolism, autophagy, differentiation, and development, and exhibit diversity and complexity in their cellular localization patterns and targets [9]. Particularly, SIRT6 is prominently expressed in the brain and acts as a critical regulator of metabolic homeostasis, overseeing DNA repair and genome maintenance, in addition to playing a pivotal role in glucose and lipid metabolism [10,11]. Among its diverse catalytic activities are ADP-ribosyl transferase, deacetylase, and deacylase [12,13]. In this way, considering the complex array of biological functions of SIRT6 within the human body, targeting SIRT6 with small molecules has emerged as a promising strategy for addressing a range of diseases, such as diabetes, obesity, cancer, and neurodegeneration [14].

Regarding SIRT6 as a potential target for depression treatment, different studies have been reported in the literature. In a pioneering study, Abe and coworkers analyzed alterations in the mRNA expression of SIRT isoforms (SIRT1–7) in peripheral white blood cells of patients with MDD or bipolar disorder (BPD) [15]. It was observed that there were significant reductions in SIRT1, 2, and 6 mRNA levels in individuals with MDD and BPD during depressive episodes, in contrast to healthy controls. Furthermore, the mRNA expression of these genes in MDD and BPD patients in a remissive state was comparable to that of healthy controls. In this way, the authors demonstrated that alteration in SIRT1, 2, and 6 expressions potentially contributes to the pathogenesis or pathophysiology of mood disorders. In another study, Li and co-workers identified phencynonate hydrochloride as a modulator of Chronic Unpredictable Mild Stress (CUMS)-induced depressive-like phenotypes via activation of the SIRT6 signaling pathway [16]. Their investigation revealed that phencynonate hydrochloride significantly up-regulates SIRT6 expression in the prefrontal cortex via increasing NAD^+/NADH ratio. Therefore, the authors propose that the activation of the SIRT6 signaling is required for preventing depressive phenotypes. However, the results are still controversial. Mao and co-workers analyzed mRNA and protein expression profiles of the sirtuin family (SIRT1-7) in the hippocampus of rats subjected to a CUMS model of depression [17]. It was demonstrated that upregulation of SIRT6 in the hippocampus could potentially induce depression-like behavior by inhibiting the protein kinase B-glycogen synthase kinase 3 (Akt-GSK3) signaling pathway. Interestingly, they observed a selective increase in expression only for SIRT6. Similarly, Li and co-workers demonstrated that the knockdown of hippocampal SIRT6 alleviated depression-like behaviors induced by Chronic Unpredictable Stress (CUS) in mice [18]. They verified that the knockdown of SIRT6 significantly increased AKT phosphorylation activity while reducing collapsin response mediator protein 2 (CRMP2) phosphorylation activity. Subsequently, they utilized ferulic acid as an inhibitor of SIRT6, demonstrating that the inhibition process activated the AKT/CRMP2 pathway *in vitro*. So, it was observed that inhibition of SIRT6 exerts an antidepressant-like effect on CUS-induced depressive models. In a recent study, Hu and co-workers constructed a strain of mice deficient in astrocytic SIRT6. The researchers subjected these mice to CUMS to assess their response to depression and anxiety [19]. Interestingly, in both the tail suspension test and forced swimming test, no depression-like phenotype induced by CUMS was observed. Moreover, the knockout of SIRT6 in astrocytes alleviated the anxiety levels induced by CUMS, as evidenced by the results of the light and dark box test, open field test, and elevated plus maze test. Subsequently, the authors demonstrated that re-expression of SIRT6 in astrocytes reversed the anti-depression and anti-anxiety effects observed in the mice. Therefore, they concluded that astrocytic SIRT6 knockout mice exhibited anxiety and depression resistance, supporting the notion that SIRT6 knockout induces anti-depression and anti-anxiety effects.

Despite the controversies related to the model used for studies with SIRT6, there is a consensus that modulating this protein is a relevant strategy for developing new therapies against MDD. As mentioned, sp-624 acts as an activator of this enzyme, and interesting results have been observed in both preclinical and clinical trials.

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Sp-624: Patent analysis, chemical features and clinical trials

Sp-624 is protected by five WO patents. Patents WO 2021/202822 Al, WO 2024/026443 Al, and WO2024/059705 Al assigned to Sirtsei Pharmaceuticals, Inc are composition and method patents describing use of target molecule and several derivatives in age-related diseases [20], improving memory and cognition [21] and treating depression in females [22].

Patent WO 2024/026443 Al [23] describes pre-clinical tests of the target molecule. *Ex vivo* electrophysiology in Sprague Dawley rat hippocampal slices indicated that the compound acted presynaptically to increase the frequency of miniature excitatory post-synaptic potentials in the hippocampus, enhanced short-term plasticity, and tended to increase short-lasting long-term potentiation, thus indicating it facilitates neurotransmitter release in the hippocampus. Also, object recognition tests (which evaluate visual learning and memory) indicated the target molecule improved the scopolamine-induced cognitive impairment and ameliorated cognitive deficits involved in NMDA receptor hypofunction. Finally sp-624 increased long-term potentiation as compared to controls indicating that the compound may positively affect cognition.

As mentioned previously, upregulation of SIRT6 in the hippocampus inhibits the Akt-GSK3 signaling pathway and GSK3 tends to up-regulation. Recently, Amici and coworkers investigated the synaptic role of phosphatidylinositol 4 kinase type IIα (PI4KIIα), a neuronal GSK-3β substrate, in organotypic rat hippocampal slices. They verified that GSK-3β phosphorylation of PI4KIIα stabilizes a pool of synaptic NMDA receptors in a subunit-dependent manner and perturbation of this GSK-3β regulation of PI4KIIα may be associated with impaired NMDA receptor function at synapses [24]. Therefore, the restoration of NMDA hypofunction by sp-624 could be linked to its ability to activate SIRT6.

The other two patents WO 2017/170623 Al and WO 2019/065928 Al assigned to Daiichi Sankyo Company, Limited describe several compounds derivatives of griseofulvin and pharmaceutically acceptable salts and preparations thereof as anti-inflammatory [25] or prevent/treat a central inflammatory disease [26].

Regarding the clinical trials of sp-624, a prior study was conducted in 2022. The study was structured as a double-blind, multicenter, randomized, placebo-controlled trial with 319 participants enrolled. Participants were randomly assigned to receive either sp-624 or a placebo once daily (20 mg/day) for a period of 4 weeks. The primary endpoint was centered around changes in the Montgomery-Asberg Depression Rating Scale (MADRS) score, serving as a measure of sp-624's efficacy compared to the placebo. The findings revealed a statistically significant difference in efficacy between the active compound and the placebo, with particularly notable effects observed among female participants [27]. Notably, by week 3, the MADRS scores demonstrated significant improvement, and sp-624 was well-tolerated without the need for dose reduction. The results indicated that the group receiving sp-624 showed improvements in concentration/decision making, retardation (slowness of thought and speech, impaired ability to concentrate, decreased motor activity), and concentration difficulties (representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration, rated according to intensity, frequency, and degree of incapacity produced) [28]. At the conclusion of the treatment, female patients showed a reduction of 3.9 points on the MADRS score compared to the placebo. Besides this, 25% of female patients receiving sp-624 achieved reemission (MADRS score ≤ 10), and 38% of them achieved clinical response, which is a reduction greater or equal a 50% on MADRS from baseline. Although some side effects such as headaches and nausea were reported, they occurred more frequently in participants receiving the placebo than those taking sp-624 [28]. One potential explanation for these results is the higher levels of SIRT6 observed in females compared to males, as demonstrated in a study conducted by Zhao and colleagues [29].

The company Arrivo BioVentures has recently initiated a new phase 2 clinical trial study, projecting the participation of 456 individuals to assess the compound's efficacy and safety in treating adults with MDD. This study is a similar double-blind, multi-center, randomized, placebo-controlled trial, but now, involving the administration of two capsules (20 mg/day) of sp-624 or a placebo. Initially, the study aims to detect changes from baseline in the MADRS total score to week 4. In addition to the primary endpoint, seven secondary outcome measures will be analyzed to determine the drug's effectiveness [30]. The study is expected to be concluded in July 2025 if it provides good results. A new mechanism drug will be closer to proving its effectiveness.

In summary, this commentary discloses the development, mechanism of action, patent analysis, pre-clinical and clinical trials of sp-624, and a new promise for the treatment of Major Depressive Disorder by the new mechanism of action of sirtuin 6 activation.

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