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To Stay Happy, Keep Your SIRT1 Active

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Depression is one of the most common psychiatric disorders and a major cause of disability that affects almost 350 million people worldwide. Common symptoms include depressed mood, persistent anxiety, loss of interest or pleasure in hobbies, feelings of hopelessness, suicidal thoughts, and reduced motivation. Antidepressant drugs often take weeks or even months to reach therapeutic levels and may result in exacerbated symptoms. The pathophysiological cause of depression has not been clearly identified; however, researchers are actively investigating the molecular pathways that contribute to major depressive disorder in human subjects and examining the basis of stress sensitivity and resilience in rodent subjects. One underlying mechanism may be epigenetic, involving the long-lasting regulation of gene expression via histone modification, DNA modification, and chromatin remodeling. Epigenetic enzymes have been linked to various pathophysiological conditions, including depression (1). Sirtuin 1 (SIRT1), a lysine deacetylase, has been extensively studied for its connection to depression, but the specific role of SIRT1 remains controversial. Deciphering the molecular pathways by which SIRT1 may lead to depressed behavior will provide valuable information from a therapeutic perspective.

In the article by Abe-Higuchi *et al.* in this issue of *Biological Psychiatry*, the authors identify SIRT1 in the dentate gyrus as a major regulator of depression-like behavior in mice (2). They report that increasing SIRT1 specifically in the dentate gyrus region of the dorsal hippocampus in chronically stressed animals reduces depression-like behaviors caused by chronic stress, whereas blocking SIRT1 activity leads to depression-like behavior. Importantly, treatment with SRT2104, a drug that activates SIRT1 function, rescued chronic stress-elicited dendritic spine loss in dentate gyrus granular neurons. Also, activation of SIRT1 in the hippocampus after chronic stress induced phosphorylation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2), which in turn can modulate depression-like behaviors (Figure 1). These findings have important implications for future treatment targets. However, some of these data contradict the present literature about SIRT1 function in major depressive disorder.

Libert *et al.* (3) found that brain-specific knockout of SIRT1, with exon 4 deleted in the nervous system, led to reduced depression-like behavior in mice. Likewise, Ferland and Schrader (4) reported increased hippocampal SIRT1 activity following chronic stress in rats. Abe-Higuchi *et al.* argue that the inconsistency in the data from these different groups could

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be caused by different genetic backgrounds of mice. Abe-Higuchi *et al.* used BALB/c mice, whereas Libert *et al.* used mixed genetic background mice back-crossed with C57BL/6 (3). It is possible that these different genetic backgrounds explain the different behavioral effects. A second possibility is the different regional and cellular specificity of the manipulations carried out in the two studies. Different stress protocols used between the studies could also lead to differences in SIRT1 expression. In addition, SIRT1 activity follows a circadian pattern in the brain, where it activates transcription of two important circadian regulators, *Bmal1* and *Clock* (5). Circadian rhythms have been linked to mood disorder. Brains from patients with major depressive disorder show dysregulation in the circadian pattern of gene expression in the hippocampus (6). Therefore, time of day could be an important factor for behavioral experiments, as could tissue collection, which could lead to discrepancies in data obtained from different groups. These will be important issues to address in future studies.

Typically, the ventral hippocampus is believed to be associated with anxiety and stress responses, whereas the dorsal hippocampus is more often associated with memory formation. Abe-Higuchi *et al.* suggest an interesting aspect of the role of the dorsal hippocampus in chronic stress-related behavioral responses: the dentate gyrus. Using a Golgi staining approach, the authors found that chronic stress induced neuronal atrophy and spine loss in dentate granule neurons. Similarly, SIRT inhibition by sirtinol also reduced dendritic length and spine loss in the dentate granule neurons, suggesting a critical role of SIRT1 in aberrant neuronal plasticity induced by chronic stress. Importantly, the authors' dendritic plasticity results fall in line with the previously published data that mice lacking SIRT1 catalytic activity specifically in the brain show reduced dendritic complexity and spine density (7,8). In depressed patients and in mouse models of depression, hippocampal atrophy is characterized by reduced dendritic arborization and spine density (9).

While others have shown that SIRT1 knockout mice have reduced ERK1/2 activity (8,10), here, the authors also identify ERK1/2 as a downstream target of SIRT1. They show that hippocampal infusion of sirtinol, a SIRT inhibitor, reduced phosphorylated ERK1/2, whereas infusion of SRT2104, a SIRT activator, blocks repeated restraint stress-induced phosphorylated ERK1/2 reduction in the dentate gyrus. Interestingly, overexpression of ERK2 in the dentate gyrus reduced anxiety- and depression-like behaviors, as evidenced from forced swim and novelty-suppressed feeding tests. Conversely, overexpression of a dominant-negative ERK2 leads to increased anxiety- and depression-like behaviors. Even though the molecular mechanism through which SIRT1 regulates ERK1/2 activity still needs to be thoroughly characterized, one possible mechanism could be through deacetylation of target proteins regulating ERK1/2 activation, such as insulin receptor substrate 2. Cytoplasmic SIRT1 deacetylates insulin receptor substrate 2, promoting activation of the Ras/ERK1/2 signaling cascade (10), and SIRT1 is predominantly localized in the cytoplasm of adult mouse brain.

Altered activity and expression of epigenetic enzymes are common in various pathological conditions, including cancer, psychiatric and neurodevelopmental disorders, and intellectual disability. Therefore, deciphering the epigenetic machinery related to depressive states is a promising approach to identify novel therapeutic targets for treatment of depression.

Targeting lysine deacetylases has already been a preferred approach for the treatment of cancers, with at least two lysine deacetylase inhibitors, vorinostat and romidepsin, currently in clinical trials. Therefore, manipulating SIRT1 activity by pharmacological intervention may be a feasible approach for depression therapy. In addition, SIRT1 deacetylase activity depends on nicotinamide adenine dinucleotide. Nicotinamide, an amide of vitamin B3, can be supplemented through diet. Therefore, epigenetic therapy supplemented with balanced diet could be a potential approach for treating patients with depression.

The present study uncovered some important and interesting aspects of the genetic and molecular pathways involved in chronic stress-induced depression-like behavior. The authors demonstrated the role of SIRT1 signaling in a particular brain area, the dentate gyrus, with behavioral, structural, and functional relevance. These data provide insight into possible future treatments for depression. The authors focused on modulation of SIRT1 function, especially in the hippocampus, but such effects also need to be explored in other brain regions, including the nucleus accumbens, amygdala and prefrontal cortex, and in other behavioral manifestations of depressive behavior in addition to those induced by chronic stress.

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Figure 1.

Chronic stress–elicited depression- and anxiety-like behavior can be reversed by modulating sirtuin 1 (SIRT1) function in dorsal dentate gyrus of the hippocampus. Chronic stress reduces levels of SIRT1 and phosphorylated forms of extracellular signal-regulated protein kinases 1 and 2 in the dentate gyrus of mouse hippocampus, leading to neuronal atrophy and dendritic spine loss in the dentate granule neurons. Pharmacological- or viral-based approaches to activate SIRT1 or extracellular signal-regulated protein kinase 2 function in the hippocampus of chronically stressed mice rescue such neuronal atrophy and spine loss,

leading to reduced depression-like behavior. ERK1/2, extracellular signal-regulated protein kinases 1 and 2.

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