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Evidence supporting a mechanistic role of sirtuins in mood and metabolic disorders

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ABSTRACT

Sirtuins are NAD^+-dependent histone deacetylases that play essential roles in cell survival, energy metabolism, inflammation, and aging; therefore, sirtuins are potential therapeutic targets in the treatment of type 2 diabetes, cancer, inflammatory and metabolic disorders, and neurodegenerative diseases.

Available evidence provides the basis for hypothesizing that sirtuins 1, 2, and 3 (SIRT1, SIRT2, and SIRT3) may have a mechanistic role subserving mood disorders (i.e. downregulation) and associated co-morbidity (e.g. metabolic disorders). Specifically, the domains of general cognitive processes, as well as cognitive emotional processing may be particularly relevant to sirtuin physiology.

Given the role of sirtuins in the perpetuation of circadian rhythmicity, and evidence of dysfunctional circadian cycling in mood disorders, sirtuins may be an underlying etiological factor that links circadian rhythm functionality with mood disorders.

Caloric restriction, and caloric restriction mimetics (e.g. resveratrol) are all capable of upregulating sirtuin isoforms implicated in stress response syndromes. Repurposing existing treatments and/or discovery of novel agents capable of modulating sirtuin physiology may represent genuinely novel approaches for trans-diagnostic domains affected in mood disorders and other brain-based illnesses.

1. Introduction

Mammalian sirtuins are nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases, which subserve cell survival, energy regulation, metabolism, inflammation, and aging. In addition to deacetylating several protein substrates, sirtuins possess other enzymatic activities, including adenosine diphosphate (ADP) ribosylation, demalonylation, desuccinylation, depropionylation, and debutyrylation (Fig. 1). There are seven sirtuins (SIRT1–7). In human cells, SIRT3, SIRT4, and SIRT5 are localized to the mitochondria, SIRT1, SIRT6, and SIRT7 are primarily localized to the nucleus, and SIRT1 and SIRT2 are localized to the cytosol.

The *SIR2* gene (Silent Information Regulator) was discovered in the late 1990s to moderate lifespan in the budding yeast (*Saccharomyces cerevisiae)* and the roundworm (*Caenorhabditis elegans*). Deletions of *SIR2* reduced cellular lifespan, whereas an increase in *SIR2* gene copies lengthened cellular lifespan (Imai et al., 2000). One method used to activate *SIR2* was through caloric restriction, which slowed the aging process and extended the lifespan of both yeasts and roundworms. Resveratrol, a polyphenol commonly found in red wine, was discovered to mimic caloric restriction by activating sirtuins, increasing cell survival, and prolonging lifespan across multiple species (Wood et al., 2004). For example, resveratrol protected mice against the adverse metabolic effects of high-fat diet (HFD) (e.g. dysregulation of insulin, glucose; development of diabetes mellitus [DM], hypertension [HTN], fatty liver disease) and increased overall lifespan (Baur et al., 2006). These successful experiments provide promise for the use of sirtuins in the protection, modification, and treatment of diseases such as cancer

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Sirtuin	Type of Biochemical Reactions
SIRT1	Deacetylase
SIRT2	Deacetylase,ADP-ribosyltransferase, Demyristoylase
SIRT3	Deacetylase, Decrotonylase
SIRT4	ADP-ribosyltransferase, Deacetylase, Lipoamidase.
SIRT5	Deacetylase, Desuccinylase, Deglutarylase, Demalonylase
SIRT6	Deacetylase, ADP-ribosyltransferase, Demyristoylase
SIRT7	Deacetylase

Fig. 1. Biochemical reactions of sirtuins (SIRTs).

and neurodegenerative diseases. The foregoing observations provide the basis for hypothesizing that members of the sirtuin family are considered potential targets for preventing and curing age-related diseases, such as type 2 diabetes, cancer, inflammatory disorders, neurodegenerative diseases, and psychiatric illnesses.

While research on the specific roles of sirtuins in mood disorders (MDs) is nascent, several promising studies have delineated the associations between sirtuin function and MDs. In particular, sirtuin genes have been significantly associated with depression in various populations. Previous studies have identified correlations between select single-nucleotide polymorphisms and major depressive disorder (MDD) diagnosis. In a study conducted within a Japanese population (n = 450 MDD patients and n = 766 controls), a significant correlation was drawn between the presence of a single-nucleotide polymorphism (SNP) in the *SIRT1* gene and major depressive disorder (MDD) diagnosis (Kishi et al., 2010). Similarly, a more recent study conducted on a larger sample consisting of women with MDD (n = 5303 cases of MDD, n = 5337 controls) concluded that MDD was significantly associated with SNPs located near the *SIRT1* locus (CONVERGE consortium, 2015). Furthermore, the above study demonstrated that patients with the most severe forms of MDD had identifiable genetic markers within the *SIRT1* locus (CONVERGE consortium, 2015). A separate study reported significant downregulation of *SIRT1* expression in the peripheral blood of MDD subjects compared to healthy controls, suggestive of the role of dysregulation of *SIRT1* expression in MDD (Luo and Zhang, 2016). Animal models have further linked depression-like behaviors to the dysregulation of *SIRT1* signaling (Luo and Zhang, 2016). These findings have been replicated in human studies, wherein select polymorphisms within the *SIRT1* gene have been shown to play roles in depressive symptoms and suicidal behaviors in patients with bipolar disorder (Nivoli et al., 2016). Taken together, convergent evidence indicates that a genetic association exists between *SIRT1* expression and MDs, thereby implicating a putative pathoetiological, and potentially therapeutic role for sirtuins in MDs.

SIRT1 signaling has additionally been associated with the regulation of anxiety- and depression-like behaviors in the nucleus accumbens and the hippocampus. Abe-Higuchi et al. investigated whether SIRT1 function was associated with chronic stress-elicited depression-like behaviors in mouse models using SIRT1 activators and inhibitors (Abe-Higuchi et al., 2016). Pharmacologic and genetic inhibition of hippocampal SIRT1 function led to an increase in depression-like behaviors, while SIRT1 activation blocked the development of these depression-related phenotypes. Conversely, SIRT1 signaling in the nucleus accumbens elicits the opposite effects. One study by Kim et al. illustrated that pharmacologic and genetic activation of SIRT1 in the nucleus accumbens increased depression- and anxiety-like behaviors, while inhibiting SIRT1 resulted in decreased depression and anxiety-like behaviors (Kim et al., 2016). SIRT1 thus may play an essential role in regulating mood-related disorders and may serve as a potential therapeutic target in the treatment of MDs. However, the manner in which the differential effects of SIRT1 activation and inhibition affect depression- and anxiety-like behaviors in different brain regions must be taken into account.

In this review, we will discuss the disparate roles of SIRT1 and SIRT3 in mood and metabolic disorders. Sirtuins have been proven to be directly, and indirectly, involved in MDs through the regulation of insulin signaling, mitochondrial function, oxidative stress, circadian rhythms, and learning and memory (Fig. 2). The overarching aim of this paper is to provide a basis for hypothesizing that sirtuins are mechanistically relevant to trans-diagnostic domains of psychopathology implicated in mood and other brain-based disorders (e.g. cognition).

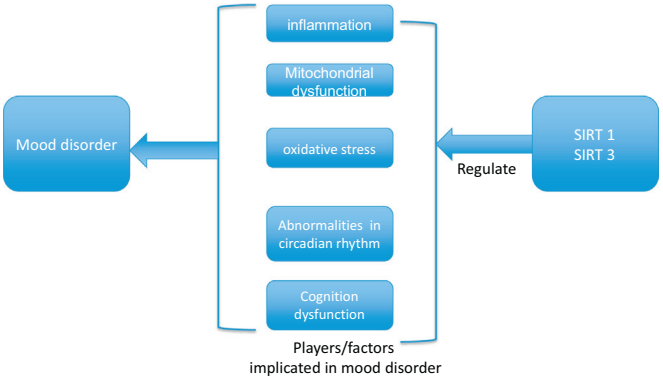

Fig. 2. Regulation of sirtuin 1 and sirtuin 3 player/factors implicated in mood disorders.

2. Sirtuins and metabolic disorders

2.1. Insulin and glucose regulation

Existing data provide evidence for the role of sirtuins 1 and 3 in the promotion of insulin secretion and the enhancement of its function (Kitamura et al., 2005; Sun et al., 2007; Zhang, 2007; Li et al., 2011; Zhang et al., 2016). Moreover, SIRT1 has additionally been implicated in the regulation of inflammatory responses (Luo and Zhang, 2016). Accumulating evidence provides the basis for an association between chronic, low-grade inflammation and resulting insulin resistance, thereby raising interest in the possibility of sirtuins as a protective agent. Within adipose tissue, SIRT1 is believed to function as a positive regulator of insulin through the prevention of pro-inflammatory responses. This concept was explored in a study conducted by Yoshizaki et al. (2009), wherein the knockdown of *SIRT1* in 3T3-L1 adipocytes was evidenced to inhibit insulin-stimulated glucose uptake and insulin signaling. The knockdown of *SIRT1* also resulted in increased expression levels of pro-inflammatory markers (e.g., tumor necrosis factor [TNF], interleukin 6 [IL-6], IL-1, and cyclooxygenase-2) and hyperacetylated nuclear factor kappa B (NFκB). Conversely, the SIRT1 activator, SRT1720, was demonstrated to decrease pro-inflammatory gene expression by deacetylating NFκB in 3T3-L1 adipocytes. SIRT1 activators enhance insulin action (glucose uptake and insulin signaling) in transduced cells and reduce TNF-α and NFκB acetylation (Luo and Zhang, 2016). These results are indicative of the role of SIRT1 as both an anti-inflammatory molecule and an enhancer of insulin sensitivity and action (Yoshizaki et al., 2009).

The pathogenesis of inflammatory diseases is understood to be mediated by immune cells such as macrophages and monocytes (Nivoli et al., 2016), and progresses in association with high blood glucose (Nivoli et al., 2016). The potential of SIRT1 to inhibit the release of pro-inflammatory cytokines, and the effect of high blood glucose on SIRT1 expression levels has been previously investigated (Nivoli et al., 2016). High levels of glucose were evidenced to lead to a reduction in the levels of SIRT1, accompanied by an increase in the levels of IL-1β and TNF-α in RAW264.7 macrophages, progressing the immune response. Moreover, the levels of the aforementioned inflammatory markers were further increased when the cells were treated with EX527, a SIRT inhibitor. Conversely, through SIRT activation, SRT1720 inhibited the