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Review

Genetic deletion of *Sirt1* results in a Kallmann syndrome phenotype in mice due to defective GnRH neuronal migration

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ABSTRACT

Sirt1 gene encodes an NAD^+-dependent histone deacetylase. Hypogonadotropic hypogonadism is associated with energy restriction or may be inherited as congenital hypogonadotropic hypogonadism (CHH). CHH associated with a loss in sense of smell (anosmia) is called Kallmann syndrome. Kallmann syndrome is also associated with mutations in a group of genes that impact FGF8 function. In the recent studies by Di Sante *et al.*, *Sirt1*$^{-/-}$ mice showed a hypogonadotropic hypogonadism due to failed gonadotropin-releasing hormone neuronal migration (GnRH). The Sirt1 catalytic function was required for GnRH neuronal migration via binding and deacetylating cortactin in an FGF8/FGFR1-dependent manner. The effect of Sirt1 on the hormonal status of *Sirt1*$^{-/-}$ mice, mediated via defective GnRH neuronal migration, links energy metabolism directly to the hypogonadal state. This review focuses on the biological function of Sirt1 in the brain and the mechanism by which Sirt1 promotes GnRH neuronal migration into the brain from the vomeronasal organ to the forebrain and how the failure of this migration leads to the development of Kallmann syndrome.

KEYWORDS: sirtuins, Sirt1, hypogonadotropic hypogonadism, GnRH neuronal migration

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INTRODUCTION

Nicotinamide adenine nucleotide (NAD^+)-dependent histone deacetylases (HDACs) belong to the sirtuin family, conserved from archaeobacteria to eukaryotes and are classified as class III HDACs [1]. Initially, sirtuins were classified as class III HDACs for their ability to deacetylate histones in *Saccharomyces Cerevisiae* (*S. Cerevisiae*) [2]. However, this definition appeared to be too narrow to describe all the sirtuin biological functions. For example, Sirtuin-1 (Sirt1) deacetylates a number of non-histone substrates and some other sirtuins not located in the nuclear compartment [3]. *Sirt1* is the mammalian ortholog of the *S. Cerevisiae*, *Caenorhabditis Elegans* (*C. Elegans*), and *Drosophila Melanogaster* (*D. Melanogaster) Sir2* gene [4] and is involved in a wide range of cellular functions; gene expression, metabolism, aging [5], proliferation, senescence and apoptosis [3]. McBurney *et al*. found that mice null for *Sirt1* (*Sirt1*$^{-/-}$) were smaller than wilde type mice (*Sirt*$^{+/+}$) at birth and most died in the early post natal period. Moreover, the majority of the sex organs are smaller in *Sirt1*$^{-/-}$ mice compared to *Sirt1*$^{+/+}$ mice. These data suggest that Sirt1 is essential for both normal embryogenesis and gametogenesis [6]. Hypogonadotropic hypogonadism (HH) is a pathology acquired through energy restriction or inherited as congenital hypogonadotropic hypogonadism (CHH). CHH can also be associated with anosmia (Kallmann Syndrome, KS) and is caused by mutations in genes that affect the

molecular signaling pathway by fibroblast growth factor 8 (FGF8). *Sirt1*$^{-/-}$ mice also show HH due to failed gonadotropin-releasing hormone (GnRH) neuronal migration and anosmia; thus *Sirt1*$^{-/-}$ mice represent many of the key features of KS [7, 8]. The current review details the biological functions of Sirt1 and primarily focuses on the Sirt1-dependent migration of GnRH neurons from the vomeronasl organ (VNO) to the forebrain (FB) and how the failure of this migration leads to development of HH.

1. Sirtuins

The gene encoding Sir2 (*Sir2*) was first identified in budding yeast. Sir2 was shown to regulate the replicative life span [1]. The Mammalian sirtuin family consists of seven members (Sirt1-7), which are characterized by different N- and C-terminal domains. However, they have a highly conserved central NAD^+-binding catalytic domain [1]. Sirtuins are heterogeneous with regard to their a) cellular localization; some sirtuins are constitutively localized to the nucleus (Sirt6 and 7) or mitochondria (Sirt3-5), whereas others sirtuins (Sirt1 and Sirt2) shuttle between the nucleus and cytoplasm [2, 3, 9], and b) cellular enzymatic activity. For example, SIRT4 possesses NAD^+-dependent mono-ADP-ribosyltransferase activity, whereas Sirt1 and Sirt6 perform both auto-ADP-ribosyltransferase and substrate specific deacetylase activities. A deacetylase activity for Sirt4 and Sirt7 has not been reported, but their activities likely require specific substrates [10]. Sirtuin deacetylation reactions begin with a removal of an acetyl group from proteins by transferring the acetyl group to NAD^+, generating two metabolites, nicotinamide (NAM) and the covalent ADP-ribose (ADPR) peptide-imidate intermediate. The intermediate is resolved to form O-acetyl-ADP-ribose (AADPR) and the deacetylated substrate is released [1].

2. Major Sirt1 biological functions

Sirt1 has been the most studied sirtuin. Sirt1 represses transcription through chromatin silencing by interacting with many trascription factors (TFs) and co-regulators. Upon recruitment, Sirt1 can deacetylate histone 3 at lysine 9 and 14 (H3K9 and H3K14, respectively), histone 4 at lysine 16 (H4K16) and histone 1 at lysine 26 (H1K26) [11]. Substrates for Sirt1 are acetylated lysine residues of hormone nuclear receptors, including the androgen receptor (AR) [12] and estrogen receptor (ERα) [13], and TFs as the peroxisome proliferator-activated receptor γ (PPARγ) [14, 15], the cell fate determination factor DACH1 [16], p53, MyoD, FOXO and $TAF_1$68 [3]. Sirt1 deacetylates and thereby regulates a variety of TFs and p300 is often a limiting co-factor in the activity of these TFs; therefore the finding that p300 was a substrate for Sirt1 likely has broad implications for transcriptional regulation by Sirt1 [17]. Sirt1 repression of androgen receptor (AR) activity by deacetylating its acetylated lysine motif is of particular importance to the current study [12]. The AR was the first transcription factor in which the acetylated lysine residues were shown to directly govern contact-independent growth. Furthermore, SIRT1 transduction of AR expressing prostate cancer cell lines blocked prostate cancer cellular proliferation and growth in mice [12]. Sirt1-dependent deacetylation repressed p53 function and promoted cell survival in response to stress signals and deacetylation of DACH1 selectively augmented p53 functions governing growth and apoptosis [18]. DACH1 restrains prostate cancer cellular growth and the expression of DACH1 is reduced in prostate cancer. p53 mutations arise in prostate cancer and most p53 mutations evade DACH1 binding [18], suggesting DACH1-p53 and the AR together may be important substrates for Sirt1 in the prostate.

2.1. Caloric restriction

It has been shown that a diet with reduced calories, also know as caloric restriction (CR), promotes life span extension in a wide range of organisms, including yeast, worms, flies and mice [19]. Activation of *Sirt1* has a beneficial role in life span extension. Rodents and humans under CR diets have reduced insulin and glucose levels. It has been demonstrated that Sirt1 affects downstream regulators of the insulin/IGF1 signaling pathway in worms and mice, decreasing adipogenesis [20]. CR has been shown to up-regulate Sirt1 expression in different tissues such as the brain, kidney, liver, white adipose and skeletal muscle. In addition, *Sirt1*-overexpressing mice are leaner and more glucose tolerant with reduced levels of blood cholesterol, adipokines and insulin than wild-type mice. In contrast, *Sirt1*$^{-/-}$ mice have a shorter life span compared to wild-type littermates and have developmental defects [1].

2.2. Metabolism

Because Sirt1 requires NAD^+ as a cofactor, it has been suggested that Sirt1 provides a link between cellular metabolism and redox equivalents. Alteration of NAD^+ levels affects a central substrate, PGC-1α. PGC-1α induces mitochondrial biogenesis and function. Sirt1 binds and deacetylates PGC-1α on multiple lysine sites. Deacetylation of PGC-1α increases gluconeogenesis gene expression and decreases glycolytic gene expression. The importance of Sirt1 in gluconeogenesis *in vivo* was tested using adenovirus to decrease the level of Sirt1 in adult mouse liver. Loss of hepatic Sirt1 improved glucose clearance and increased insulin sensitivity. Other studies that used liver-specific *Sirt1* knockout mice did not observe changes in insulin or glucose homeostasis [1].

2.3. Inflammation

In vitro and *in vivo* studies have shown a role for Sirt1 in the inflammatory response. Sirt1 directly associates with the RelA/p65 subunit of NF-κB and deacetylates K310 of RelA/p65, an important NF-κB transcriptional activation site. The inhibitory role of Sirt1 in inflammation suggests a possible therapeutic approach for Sirt1 agonists, in chronic inflammatory diseases such as diabetes and colitis [1].

2.4. Apoptosis

Sirt1 activity affects several biological processes that alter cellular response to genotoxic stress, detoxification of reactive oxygen species (ROS) and sensitivity to apoptosis. Sirt1 antagonizes p53-mediated apoptosis by deacetylating the carboxyl-terminus of p53, thereby decreasing its ability to induce apoptosis [13].

2.5. Sirt1 role in cancer

The role of Sirt1 in tumorigenesis is still controversial [21]. It has been suggested that Sirt1 could potentiate carcinogenesis, but other reports showed an anti-carcinogenic role. The first evidence of Sirt1 acting as an oncogene came from experiments showing that Sirt1 binds p53 and inhibits p53-mediated functions through deacetylation of p53 at its C-terminal lysine 382 residue [13, 22, 23]. Other studies showed that increased Sirt1 expression in human fibroblasts promotes cellular proliferation, reduces cellular senescence and increases the cellular life span through the promotion of retinoblastoma protein (Rb) phosphorylation [24]. However, a recent study shows evidences supporting the notion that Sirt1 can act as tumor suppressor inhibiting prostatic intraepithelial neoplasia (PIN) in mice [25]. In support of a tumor-suppressor role for Sirt1, it has been showed that Sirt1 has a crucial role in repairing broken DNA and maintaining genome stability [26-28].

2.6. Fat tissue

Sirt1 inhibits adipogenesis in white adipose tissue (WAT) [20]. WAT functions both to store fats and to serve as an endocrine organ by secreting hormones such as leptin and adiponectin, and inflammatory agents such as tumor necrosis factor alpha (TNFα) and resistin. For example, Sirt1 contributes to the production of adiponectin from WAT by enhancing the interaction between FOXO1 and C/EBP [1, 20].

2.7. Cellular migration

It has been shown that cortactin is a regulatory protein, coordinating the molecular components of the cellular protrusive apparatus and promoting cellular migration. In order to promote cellular migration, cortactin binds F-actin that coordinates the cytoskeletal network assembly. Cortactin function in promoting cellular migration depends on its acetylation status [29]. Zhang *et al.* showed that Sirt1 activates cortactin by deacetylating it both directly and indirectly, reducing its acetylation by p300 [30]. These results support the hypothesis that deacetylation of cortactin increases cell migration [31].

3. Sirt1 and brain

Sakamoto J. *et al.* [32] have detected Sirt1 mRNA expression levels at mouse embryonic day (E) 4.5. Sirt1 mRNA levels are still found in late embryogenesis (E18.5). In mouse embryos, Sirt1 is expressed in the heart, brain, spinal cord, and dorsal root ganglia. Moreover, Ramadori G. *et al.* have also found Sirt1 mRNA expression in adult brain mice, including but not limited to the hypothalamic arcuate, ventromedial, dorsomedial, and paraventricular nuclei and the area postrema and the nucleus of the solitary tract in the hindbrain [33]. This suggests that Sirt1 has multiple functions in both brain development and physiology.

Neuronal stem cells (neural progenitor cells, NPCs) can differentiate to astrocytes, neurons and oligodendrocytes. Astrocytes perform many different functions, including providing structural and nutrient support for neurons, secretion of signaling molecules, and uptake and metabolism of neurotransmitters. In response to brain injury, NPCs differentiate preferentially into astrocytes rather than neurons [34]. Mild oxidation or direct activation of Sirt1 suppressed proliferation of NPCs and directed their differentiation towards the astroglial lineage at the expense of the neuronal lineage, whereas reducing conditions had the opposite effect. *In vitro* and *in vivo* studies show that, under oxidative conditions, Sirt1 is up-regulated in NPCs and binds the transcription factor Hes1, inhibiting pro-neuronal Mash1 [35]. Sirt1 seems to regulate numerous survival strategies of metabolic tissues in response to stressful environments. The regulation of neural stem-cell differentiation in the brain may be one such adaptation [34].

Modulation of Sirt1 levels and/or activity has been shown to have beneficial effects in different models of Alzheimer Disease (AD), the most common and devastating age-related neurodegenerative disease [36]. CR was shown to reduce amyloid plaques, one of the typical pathological hallmarks of the disease, in the APPswe/PS1dE9 mouse model [37]. Activation of Sirt1 was dependent upon CR. In an *in vitro* model, Sirt1 protected against microglia-dependent amyloid-beta (Aβ) toxicity through inhibiting NF-κB signaling [38].

Parkinson Disease (PD) is an age-associated neurodegenerative disorder primarily known as a motor disorder due to loss of dopaminergic neurons from the substantia nigra in the brain. PD is also associated with the accumulation of protein inclusions known as Lewy bodies, that are mainly composed of misfolded α-synuclein [39], a protein whose function remains obscure. Recently, overexpression of Sirt1 in animal and cell models of PD was shown to suppress the formation of α-synuclein aggregates by activating molecular chaperones [40].

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by a gradual and progressive loss of neurons, predominantly in the cortex and striatum leading to impairment in muscle coordination, cognitive decline and dementia. In a *C. Elegans* model of HD, upregulation of Sirt1 or resveratrol treatment were shown to rescue neurons from injury induced by mutant huntingtin protein (HTT) [41]. Expansion of CAG-trinucleotide repeats in the IT-15 gene that encodes HTT, resulted in the production of an HTT protein containing extended polyglutamine repeats that caused the misfolding and aggregation of the protein [42].

Conservation of normal cognitive functions relies on the proper performance of the nervous system at the cellular and molecular level. SIRT1 deficiency and overexpression in mouse models affects learning and memory as well as synaptic plasticity. Michán S. *et al.* demonstrated that the absence of Sirt1 impaired cognitive abilities including immediate memory, classical conditioning, and spatial learning. In addition, Gao J. *et al.* found that the cognitive deficits in *Sirt1*$^{-/-}$ mice were associated with defects in synaptic plasticity without alterations in basal synaptic transmission or N-Methyl-D-aspartate (NMDA) receptor function [43, 44].

4. Kallmann syndrome

Development of the reproductive system is dependent on specific neurons located in the hypothalamus that secrete GnRH [45]. During embryogenesis, GnRH neurons originate in the VNO at E10.5 and migrate into the FB at E17.5 along the olfactory-vomeronasal nerves (VNNs) [46]. Alterations of this migratory process lead to disorders such as HH and other reproductive diseases characterized by the reduction or failure of sexual maturation and function. HH can be associated with a normal sense of smell (normosmic HH) or loss of smell (anosmia, KS) [45]. KS is also associated with mutation in specific genes including *KAL1*, *FGFR1*, *PROKR2*, *PROK2* and *TACR3*, *TAC3*, *KISS1R* and *KISS1* [7, 8]. The genes associated with Kallmann syndrome play a role in the development of certain areas of the brain before birth. Although some of their specific functions are unclear, these genes appear to be involved in the formation and movement (migration) of a group of neurons that are specialized in processing odors (olfactory neurons). GnRH controls the production of several other hormones that direct sexual development before birth and during puberty. These hormones are important for

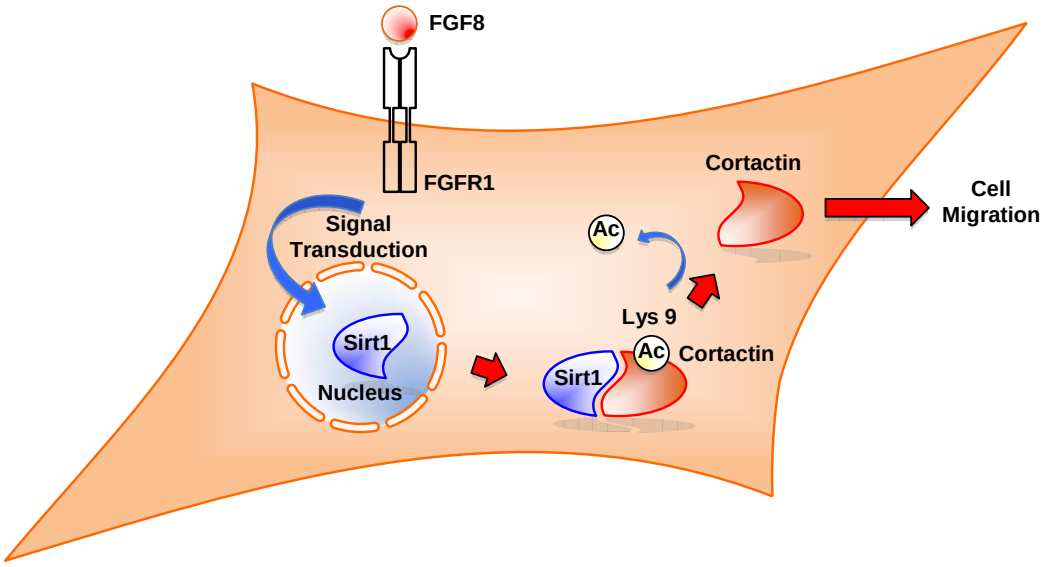

Figure 1. GnRH neuronal migration is promoted upon cortactin deacetylation by Sirt1. Sirt1 translocation into the cytoplasmic compartment is enhanced by an FGF8/FGFR1-mediated signal. Sirt1 binds and deacetylates cortactin thereby promoting cellular migration.

the normal function of the gonads (ovaries in women and testes in men).

5. Sirt1 promotes GnRH neuronal migration

Di Sante *et al*. discovered impaired GnRH neuronal migration occurs during the embryogenesis of *Sirt1*$^{-/-}$ mice [7]. Adult *Sirt1*$^{-/-}$ mice exhibit a failure to develop a complete and functional reproductive system in addition to loss of the sense of smell [6, 7]. This data suggests that *Sirt1* is essential for GnRH neuronal migration that is responsible for normal embryogenesis and for development of normal reproductive system in both sexes. Sirt1 was found to promote GN11 cellular migration *in vitro* through its catalytic action [7]. Di Sante *et al*. showed that Sirt1 induces GnRH cellular migration by deacetylating and activating cytoplasmic cortactin. Sirt1 translocation between the nuclear and cytoplasmic compartments was shown to be induced by the FGF8/FGFR1 signaling (Figure 1) [7]. In summary, the data suggest FGF8/FGR1 signaling axis determines both Sirt1 subcellular localization and Sirt-dependent cortactin deacetylation promoting migration of GnRH neurons from the VNO to the forebrain, ensuring normal brain development. The authors describe an impaired GnRH migration phenotype in *Sirt1*$^{-/-}$ mice, which leads to a failure of normal gametogenesis, leading to HH. Di Sante *et al*. highlights a novel *in vivo* neuronal function for Sirt1, linking Sirt1 to normal GnRH system development.

CONCLUSION

Sirtuin-1 (Sirt1) catalytic function induces GnRH neuronal migration through deacetylating cortactin in an FGF8/fibroblast growth factor receptor-1 dependent manner linking Sirt1 to normal brain and reproductive system development.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest associated with this manuscript.

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