Sirtuin 1 in Male Germ Cells

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Reproduction is the way to immortality for an individual, and it is essential to the continuation of the species. Sirtuins are involved in cellular homeostasis, energy metabolism, apoptosis, age-related problems, and sexual reproduction. Sirtuin 1 (SIRT1) belongs to the sirtuin family of deacetylases, and it is a nicotinamide adenine dinucleotide (NAD)-dependent deacetylase. It removes the acetyl group from a variety of substrates. SIRT1 regulates endocrine/metabolic, reproductive, and placental development by deacetylating histone, different transcription factors, and signal transduction molecules in a variety of cellular processes. It also plays a very important role in the synthesis and secretion of sex hormones via regulating the hypothalamus-pituitary-gonadal (HPG) axis. Moreover, SIRT1 participates in several key stages of spermatogenesis and sperm maturation.

Keywords: sirtuins ; SIRT1 ; Germ Cells

1. Mechanism Underlying Sirtuin 1 (SIRT1)-Related Germ Cell Death

A huge number of investigations have been undertaken in the search for molecular pathways by which Sirtuin 1 (SIRT1) deficiency results in spermatogenic aberration. A significant decrease in spermatogenic cells was found in earlier stages when crossed a Sirt1$^{-/-}$ with an Oct4-GFP transgenic strain [1], and the Sirt1-deficient testes showed increased apoptosis in male germ cells and other testicular cells [1]. Male germ cell death in Sirt1$^{-/-}$ mice was related to a higher p53 activity, as testicular apoptosis is dependent on acetylation mediated-p53 activity[2][3][4][5]. Moreover, Sirt1$^{-/-}$ mice had their genomic integrity distorted characterized by DNA damages [6][7]. A histological examination of the testis of Sirt1$^{-/-}$ mice signified its role in late meiotic stages and spermiogenesis characterized by a higher expression of γH2AX and lower expression of the late-meiotic and post-meiotic genes including Polk, Prm1, and Prm2. Since the Gene Ontology (GO) has shown several genes involved in spermatogenesis are differentially expressed in the testis of Sirt1$^{-/-}$ mice, SIRT1 deficiency might influence fertility by regulating the transcription of several spermatogenic genes [1]. In addition, Sirt1$^{-/-}$ mice had an aberrant expression of sumoylation-related genes, according to a microarray investigation of global testicular gene expression [1]. SIRT1-mediated deacetylation can impact sumoylation [8][9] that regulates numerous cellular physiological activities [10]. And sumoylation has been linked to many functions in testis and spermatogenesis, including germ cell proliferation, heterochromatin remodeling, and change in nuclear morphology [11][12][13][14][15][16].

Moreover, SIRT1 along with SIRT3 and peroxisome proliferator-activated receptor γ coactivator 1 alpha (PGC1α) activate antioxidant defense systems, hence abnormal spermatogenesis in Sirt1$^{-/-}$ mice might be due to oxidative stress. Upon SIRT1-mediated deacetylation and activation, PGC1α stimulates the transcription of the Sirt3 gene [17], which is also expressed in mammalian testicular tissue [18]. The relationship between SIRT1/PGC1α/SIRT3 dysregulation and reactive oxygen species (ROS)/antioxidant defense system was investigated in a pre-diabetic rat model [19]. Reduced SIRT3 levels were observed to enhance glycolysis in the rat testis, suggesting the involvement of sirtuins in the regulation of testis metabolism [19][20], which is consistent with the previous findings where reduced SIRT1 or SIRT3 expression was found to be associated with higher glycolytic activity in numerous tissues [21]. Since glucose metabolism and lactate synthesis are necessary for optimal spermatogenesis[22][23], excessive glycolytic activity may lead to mitochondrial ROS overproduction [20]. Moreover, loss of SIRT1 or SIRT3 causes a malfunctioning electron transport chain, and a reduction in the activity of antioxidant defenses [24]. Because sperm membranes contain a large proportion of polyunsaturated fatty acids (PUFA), they are extremely vulnerable to oxidative stress [25]. The fluidity and fusogenicity are required for acrosomal processes and sperm–oolemma interactions are controlled by PUFAs. They are also, unfortunately, highly susceptible to lipid peroxidation[26][27][28]. SIRT1 suppression and germ cell apoptosis might be regulated by oxidative stress as ROS can affect mitochondrial apoptotic pathways in several aspects [29]. Consistent with the above findings, long-term Bisphenol A (BPA) exposure decreases SIRT1 activity while increasing p53 acetylation, ROS, and DNA damage, thus affecting the late meiotic and post-meiotic spermatogenic stages [30].

2. SIRT1 in Acrosome Biogenesis

To study the germ cell-specific functional role of SIRT1, $Sirt^{F/F}$ mice were crossed with Stra8-iCre or Prm1-Cre mice to obtain germ cell-specific Sirt1-KO mice that lack exon 4 in pre-meiotic or post-meiotic germ cells, respectively. They found that germ cell-specific Sirt1-KO causes several abnormalities including a reduction in the number of sperms, histone modifications, protamine transition, chromatin remodeling, and abnormal sperms, collectively leading to male reproductive senescence [6][31]. Researchers also generated germ cell-specific Sirt1 knockout mice by crossing $Sirt^{F/F}$ mice with Tnap-Cre, which produced subfertile males when mated with wild-type females. Researchers found significantly decreased sperm counts and abnormal spermatozoa with reduced sperm motility in these mice. Moreover, the immunofluorescence staining of their acrosomes with sperm protein 56 (sp56) revealed deformed, fragmented mislocalized acrosomes. Further investigation showed that the autophagic molecular marker microtubule-associated protein light chain 3 (LC3) was accumulated in the nucleus, which influences proacrosomal granule fusion to the nuclear membrane to form an acrosomic vesicle. Furthermore, SIRT1 performs the deacetylation of LC3, which subsequently moves to the cytoplasm where autophagy-related gene 7 (ATG7) activates it, thus promoting autophagy-mediated acrosome biogenesis[32]. In support of the above discovery, the levels of seminal SIRT1 in oligoasthenoteratozoospermic men were found to be notably decreased, and those suffering from varicocele have even lower SIRT1 levels, further supporting its role in acrosome biogenesis [33].

3. SIRT1-Mediated Protamine Replacement

During spermiogenesis, the histone-based nucleosomes must be removed and replaced by protamines that span most of the genome. Male mice were infertile when protamines were lost or when the testis-specific version of histone 2B was mutated because all of them affect histone removal [34][35]. Histone removal is triggered by nucleosome post-translational modifications. The testis-specific bromodomain protein BRDT binds to nucleosomes due to acetylation of histone H4 on sites K5 (H4K5) and K8 (H4K8) [36]. Transition protein 2 (TP2) and protamines (PRM) were unable to appropriately localize within the nuclei of elongating and condensing spermatids in the absence of BRDT-H4 interaction, resulting in aberrant chromatin condensation and finally infertility [37]. Recently, Bell et al. reported a chromatin condensation defect in Sirt1-deficient elongating and elongated spermatids, where TP2 failed to localize in the nucleus, and there was reduced acetylation of H4K5, H4K8, and H4K12 [6]. Similarly, abnormal histone to protamine transition and chromatin remodeling defects were observed in germ cell-specific Sirt1-knockout mice [6]; this defect makes sperm DNA more vulnerable to apoptotic/oxidative damage [38]. SIRT1 might also work in coordination with SIRT6 for chromatin regulation, as there was a downregulation and in turn poor sperm protamination in an obese mice model [39]. Collectively, SIRT1 might balance other factors to enhance H4 acetylation and the histone-to-protamine transition.

4. SIRT1 Functions in the Hypothalamic-Pituitary-Gonadal (HPG) Axis

The HPG axis plays a significant role in regulating reproductive functions, life cycle, and sexual dimorphism. SIRT1 is a key player in regulating the activities of the HPG (hypothalamus-pituitary–gonadal) axis and neuroendocrine systems[40]. Sirt1 is expressed in neurons as well, particularly those that control the hypothalamus' metabolic activity [40]. There exists a diffused network of GnRH neurons called pulse-generator in the hypothalamus; it is responsible for the releasing of GnRH. Gonads synthesize estrogen and testosterone under the influence of LH and FSH secreted under the stimulation of pulsatile secretion of GnRH[41][42]. Sirt1-knockout results in decreased hypothalamic gonadotropin-releasing hormone (GnRH) expression, and consequently lower serum LH and FSH levels and aberrant spermatogenesis, suggesting the significance of SIRT1 in regulating the HPG axis[7]. Furthermore, miR-132/212-mediated action of GnRH involved a posttranscriptional decrease in Sirt1. Subsequently, SIRT1-dependent FOXO1 deacetylation was decreased, limiting FOXO1-mediated inhibition of Fshβ transcription. This decrease in the FOXO1 deacetylation resulted in upregulation of Fshβ in rat primary pituitary cells and LβT2 cell line [43], further supporting the significance of SIRT1 in the HPG axis.

The function of SIRT1 has also been discovered in the hypothalamic Kiss1 neurons, where it inhibits Kiss1 activity [44]. Hence, SIRT1 controls puberty by regulating the puberty-stimulating gene, Kiss1 [44]. In line with it, Sirt1-deficient mice exhibited central hypogonadism due to aberrant migration of GnRH neurons to the hypothalamus, suggesting that SIRT1 may play an important role in the regulation of the reproductive axis [45]. In addition, hypogonadotropic hypogonadism has been found in $Sirt1^{-/-}$ mice due to failure of GnRH neural migration. SIRT1's catalytic domain promotes GN11 (mouse neuronal cell line) migration via deacetylating cortactin [45]. SIRT1 is found in the steroidogenic factor 1 (SF1) neuron of the ventromedial hypothalamic nucleus (VMH) and the pro-opiomelanocortin (POMC) and agouti-related protein (AgRP) neurons of the arcuate nucleus (ARH) [46][47][48]. Due to aberrant sympathetic activity, energy imbalance was seen in POMC neuron-specific $Sirt1^{-/-}$ mice [47]. Likewise, insulin resistance in skeletal muscles was observed in Sirt1-deficient SF1 neurons, while Sirt1-overexpression resulted in induced obesity and insulin resistance [46]. Moreover, overexpression

of Sirt1 prevented age-related weight gain in POMC or AgRP neurons. However, energy expenditure due to sympathetic activity was increased in the former one while food intake was reduced in the latter one, suggesting the existence of a hypothalamic nuclei-specific regulation [48]. Moreover, there was a higher level of SIRT1 in dorsomedial (DMH) and lateral hypothalamic nuclei (LHN) upon limiting the food provision [49]. Overexpression of Sirt1 in the brain cells of mice resulted in a longer life span characterized by the overactivity of DMH and LHN via elevated levels of orexin type 2 receptor (Ox2r) [49], suggesting a tissue-specific role of SIRT1 in regulating and maintaining hunger, use of energy, metabolic activities, and longevity.

Sirt1-knockdown results in low testosterone biosynthesis as it affects the Leydig cell maturation and reduces the steroidogenic acute regulatory protein (StAR) level [7]. A group has recently reported that Sirt1-deficiency in the Leydig cells interferes with the cholesterol uptake due to compromised autophagy, and consequently results in a decreased testosterone biosynthesis in mice [50]. A steroidogenic cell-specific Sirt1-knockout mouse line was generated via mating $Sirt1^{F/F}$ mice with SF1-Cre strain. Researchers found a significant decrease in testosterone levels and mating efficiency in $Sirt1^{-/-}$ mice. However, rresearchers found no differences in the testis size upon Sirt1-deletion. Furthermore, the mating efficiency instead of spermatogenesis was compromised in these mice[32][50]. Finally, upon SIRT1-mediated deacetylation, LC3 moves from the nucleus to the cytoplasm and helps autophagosome formation, which degrades the NHERF2 (a negative regulator of cholesterol uptake receptor, scavenger receptor class B type I (SR-BI)). Consequently, it maintains the SR-BI level to uptake cholesterol, thus fueling the process of steroidogenesis. However, in $Sirt1^{-/-}$ mice, LC3 remains in the nucleus, inhibiting NHERF2 clearance, thus stopping SR-BI expression and cholesterol uptake, finally resulting in reduced testosterone biosynthesis.

Proinflammatory cytokines also have an important role in steroidogenesis [51]. SIRT1 has significant anti-inflammatory effects in the presence of cytokines [52]. Sirt1 gene and protein levels in TNF-α-treated TM3 cells were found to be considerably lower, as were testicular Sirt1 mRNA levels in high-fat-induced obese mice. A huge increase in the cytokines and decrease in the genes expression of several steroidogenic enzymes were observed in Sirt1-deficient TM3 cells. This boom in cytokine levels halts the transactivation of SF1. In contrast, Sirt1-overexpression enhances SF1-activity and consequently the steroidogenic enzymes and testosterone biosynthesis [52].

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