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Review article

Sirtuins in Multiple Sclerosis: The crossroad of neurodegeneration, autoimmunity and metabolism

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ABSTRACT

Multiple Sclerosis (MS) is a challenging and disabling condition particularly in the secondary progressive (SP) phase of this disease. The available treatments cannot ameliorate or stop disease progression in this phase, and there is an urgent need to focus on effective therapies and the molecular pathways involved SPMS. Given the significant impact of neurodegeneration, autoimmunity and metabolic alterations in MS, focusing on the molecules that target these different pathways could help in finding new treatments. Sirtuins (SIRTs) are NAD^+ dependent epigenetic and metabolic regulators, which have critical roles in the physiology of central nervous system, immune system and metabolism. Based on these facts, SIRTs are crucial candidates of therapeutic targets in MS and collecting the information related to MS disease for each SIRT individually is noteworthy and highlights the lack of investigation in each part. In this review we summarized the role of different sirtuins as key regulator in neurodegeneration, autoimmunity and metabolism pathways. We also clarify the rationale behind selecting SIRTs as therapeutic targets in MS disease by collecting the researches showing alteration of these proteins in human samples of MS patients and animal model of MS, and also the improvement of modeled animals after SIRT-directed treatments.

1. Introduction

Multiple Sclerosis (MS), as an autoimmune inflammatory disorder of central nervous system (CNS), is a complex condition which is characterized by demyelination and axonal loss. It mostly appears in the early adult life of individuals, and has a great influence on the patients' life quality. Costs are noticeable and rise with progression of disease and disability (Brundin et al., 2017). MS is the major cause of disability in young adults (Kister et al., 2013; Orton et al., 2006), and its incidence in young women (between ages 20 and 40 years) is higher than men.

MS has complex etiology and its causes are still not fully understood, though various mechanisms have been suggested to be involved in pathology of MS progression. The disease shows both aspect of inflammation and neural degeneration (Compston and Coles, 2008); while the CNS lesions are driven by inflammatory processes, after several years of chronic inflammation, neurodegeneration and axonal damage cause disease progression (Lassmann et al., 2012). Furthermore, recent studies show that metabolic changes in either immune cells or the neurons/axons affect disease progression and the pathology (Tannahill et al., 2015).

Although, multiple biological approaches and assessing the different molecules have yielded important insights into MS pathology, the treatment are insufficient especially in SP form of the disease. The need for effective treatments has created an emergence for diagnostic biomarkers to show transition from relapsing-remitting (RR) to SP phase.

Mammalian sirtuins are nicotinamide adenine dinucleotide (NAD) dependent deacetylases which are widely conserved proteins from bacteria to humans. These proteins are known as lifespan regulators that inhibit genomic instability through chromatin modifications. There are seven homologs of sirtuins named SIRT1 to SIRT7 which possess various enzymatic activity and subcellular localization that affect their cellular functions. The major function of this family is related to protein acetylation state as a type of post-translational modifications. Members of sirtuin family are involved in several different molecular pathways including aging (Sack and Finkel, 2012), inflammation (Haigis and Sinclair, 2010), neurodegeneration (Donmez, 2012), metabolism (Houtkooper et al., 2012) and cancer (Brooks and Gu, 2009). Neurodegeneration, autoimmunity and altered metabolism are three different aspects of MS pathology. On the other hand, sirtuins have been reported

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as a key regulator in these pathways. Therefore reviewing the available information related to MS disease and the sirtuins seems helpful via creating a better understanding leading to future studies and shedding light on the lack of investigation in each part. In this review we have summarized the role of different sirtuins as key regulator in neurodegeneration, autoimmunity and metabolism pathways involved in MS pathology and progression. We have also discussed the diagnostic perspective and the possible therapeutic application of sirtuins in MS.

2. Sirtuins: SIRT1-SIRT7

About 20 years ago, Guarente and colleagues showed that Silent Information Regular 2 (SIR2) gene could affect the life span in budding yeast via repressing of genomic instability (Kaeberlein et al., 1999; Sinclair and Guarente, 1997). In most organisms such as the plants, bacteria and animals, SIR2-like genes, known as sirtuins have a crucial role in health and survival (Sinclair and Guarente, 2006). Several studies have focused on these roles and showed that sirtuins act at the molecular level as sensors for the amounts of energy, day light and stress. Additionally, they can respond to such signals and promote cell survival and health. Humans have seven sirtuin proteins (SIRT1-SIRT7) (Frye, 2000) that phylogenetically belong to the class III of histone deacetylase (HDAC) family (Gray and Ekstrom, 2001). Other classes of HDACs enzymes including I, II and IV, are zinc dependent, but in contrast SIRTs have been recognized as nicotinamide adenine dinucleotide (NAD^+) dependent enzymes. This feature characterizing SIRTs as a sensor of cellular energy status represented by NAD^+, hence the enzymes activity can generate some by-products as like as 1-O-acetyl-ADP-ribose (Chen et al., 2015; Imai et al., 2000; Tanner et al., 2000). Other type of enzymatic activities have been reported for each member of the sirtuins family. Overall, SIRT1, SIRT2, SIRT3 and SIRT7 are deacetylases (Bao et al., 2014; Barber et al., 2012; Chang and Guarente, 2014; Donmez and Outeiro, 2013). SIRT4 and SIRT6 has been reported to have deacetylase and ADP-ribosyltransferase functions. SIRT5 has been identified as a deacetylase, desuccinylase and demalonylase (Du et al., 2011; Nakamura et al., 2012) (Table 1). Besides, different cellular localization, target effectors and physiological function have been evaluated for these proteins (Table 1). SIRT1, SIRT6 and SIRT7 are nuclear enzymes, SIRT2 is localized in cytoplasm, while SIRT3, SIRT4 and SIRT5 are mitochondrial proteins. Based on several studies that assessed the effect of sirtuins family over the last two decades, these proteins have been implicated in the regulation of energy metabolism in a variety of tissues. Among the member of this family, SIRT1 has been detected in important metabolic centers of the brain, liver, pancreas, heart, muscle, and adipose tissue (Lavu et al., 2008; Ramadori et al., 2008; Yu and Auwerx, 2009). Also studies carried out with quantitative RT-PCR in different tissues show the highest expression of SIRT3 in kidney, brain, and heart, followed by liver and testes, with lower expression in lung, ovary, spleen, and thymus (Su et al., 2004; Wu et al., 2009).

In addition, sirtuins are acting as a mediator in many other biological functions including longevity, learning and memory, circadian rhythm, sleep, DNA repair, stress response, cell survival, telomere and chromatin regulation, cancer metabolism and autophagy (Haigis and Sinclair, 2010; Houtkooper et al., 2012; Min et al., 2013).

3. Involvement of sirtuins in physiological and pathological functions

3.1. Role of sirtuins in central nervous system

All sirtuins are detected in adult mammalian brains with various RNA and protein expression levels. While SIRT2 is widely expressed throughout the CNS, SIRT4 is only detected in minimal amounts (Sidorova-Darmos et al., 2014). Moreover, the sirtuins protein expression has a distinct distribution in different regions of the adult CNS that may indicate specific role of individual sirtuins in specific brain regions. The highest level of SIRT1 has been observed in the cortex, hippocampus, cerebellum and hypothalamus, and the lowest level in spinal cord and white matter (Ramadori et al., 2008; Sidorova-Darmos et al., 2014). SIRT2 is abundant in hippocampus, striatum, spinal cord, and brain stem, while elevated levels of SIRT5 are revealed in the cerebellum and brain stem (Sidorova-Darmos et al., 2014). Besides, this protein is highly expressed in the cortex of the human brain, especially in layer II (Glorioso et al., 2011).

On the other hand, these proteins have various level of expression in different cell types of CNS. For example SIRT1 is predominantly expressed in neurons (Hisahara et al., 2008; Ramadori et al., 2008; Sakamoto et al., 2004), while SIRT2 as a cytoplasmic protein has a high expression level in oligodendrocytes and plays a crucial role in myelin sheath formation and the interaction between myelin and axon (Li et al., 2007; Schwer et al., 2010). Oligodendrocytes express SIRT2 primarily and this protein is incorporated into the myelin sheath near paranodal loops (Li et al., 2007; Werner et al., 2007). SIRT2 expression promotes process formation and induces myelin gene expression during differentiation of oligodendrocytes in vitro (Ji et al., 2011). Loss of SIRT2 in the peripheral nervous system causes a delay in Schwann cell myelin formation (Beirowski et al., 2011), but its role in CNS myelination remains speculative.

As a matter of fact, sirtuins have been shown to have distinct roles in the higher-order brain functions including feeding behavior, endocrine regulation, physiological rhythms, and emotion (Fig. 1). These physiological functions have been particularly attributed to the hypothalamic sirtuins. Among all the family members, SIRT1 and SIRT2 are known as mediators in learning, memory and emotions (Donmez and Outeiro, 2013; Herskovits and Guarente, 2014). It seems that these proteins influence the physiological function through various neurological processes involving in dendritic arborization, synaptic plasticity, and adult neurogenesis. Deletion of SIRT1 could cause deficits in short- and long-term associative memory, and spatial learning (Michan et al., 2010). This alteration can occur in an ERK1/2-dependent manner (Abe-Higuchi et al., 2016; Michan et al., 2010). It is noteworthy that SIRT1 could increase presenilin (Torres et al., 2011) and brain-derived neurotrophic factor (BDNF) (Zocchi and Sassone-Corsi, 2012) expression, regulates p53 stability, and increases the induction of LTP (Lisachev et al., 2016). In addition, it induces the expression of CREB-binding protein-dependent genes (Gao et al., 2010) through the regulation of microRNAs (van Ham et al., 2008).

It has been reported that both SIRT1 and SIRT2 can mediate fate decisions of neural stem and/or progenitor cells into oligodendrocytes (Stein and Imai, 2014). SIRT2 seems to play a positive role in neuronal differentiation and it was reported that SIRT2 promotes neuronal differentiation of mesenchymal stem cells through its tubulin deacetylase activity and stimulation of the extracellular signal-regulated kinase (ERK)-cAMP response element-binding protein (CREB) signaling pathway (Jeong and Cho, 2017). SIRT1, SIRT2, and SIRT3 decrease microglia activation and inflammatory responses (Jiang et al., 2017; Li et al., 2015; Pais et al., 2013). Besides, SIRT6 could affect stem cell differentiation and modulated the expression of core pluripotent genes (Oct4, Sox2, and Nanog) by H3 deacetylation (Etchegaray et al., 2015).

These studies have demonstrated that sirtuins family members play an essential role in maintaining neural health and their alterations may be involved in several neurodegenerative disease pathogenesis including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS) and MS (Fujita and Yamashita, 2018; Szegő et al., 2018; Zhang et al., 2011).

3.2. Role of sirtuins in immune system

Sirtuins play a role in the control of immune responses and their effects on inflammation may be considered as a double-edged sword. These proteins appear to exert both pro- and anti-inflammatory roles

Table 1
Subcellular localization, enzymatic activity, gene target and function of sirtuins in CNS, immune system (IS), metabolism (Met.) and both metabolism and Immune response.

Name	Location	Enzymatic activity	Target molecules	Function	Reference(s)
SIRT1	Nucleus	Deacetylase	CNS:ERK1/2, presenilin, BDNF, P53 CREB binding protein	Learning, memory and emotions	(Abe-Higuchi et al., 2016; Donmez and Outeiro, 2013; Gao et al., 2010; Herskovits and Guarente, 2014; Lisachev et al., 2016; Michan et al., 2010; Zocchi and Sassone-Corsi, 2012)
			IS:NF- κβ, FOXO3, AP-1	Decrease microglia activation in the brain Reduce the mRNA level of COX-2	(Brunet et al., 2004; Jiang et al., 2017; Li et al., 2015; Motta et al., 2004; Pais et al., 2013; Rangarajan et al., 2015; Viswanathan et al., 2005; Yeung et al., 2004; Zhang et al., 2010)
			Met.: CRTC2, FOXO1, PGC-1α, HIF-1α, PGAM-1	Gluconeogenesis, glycolysis and insulin secretion	(Hallows et al., 2012; Houtkooper et al., 2012; Liu et al., 2008; Wang and Tong, 2009)
			SREBP-1 and 2, AMPK, PPARγ, SMRT	Lipid synthesis	(Frescas et al., 2005; Walker et al., 2010; Wang and Tong, 2009)
			IS & Met.: PGC-1α and 1β	Lipolysis switch toward fatty acid oxidation. Differentiation of activated CD8+ lymphocytes into memory cells	(Kelly et al., 2009; Rodgers et al., 2005)
SIRT2	Cytoplasm	Deacetylase	CNS: ERK, CREB	Learning, memory and emotions	(Donmez and Outeiro, 2013)
			α-Tubulin	Neuronal differentiation	(Jeong and Cho, 2017)
			IS: NF- κβ	Reduces several cytokines	(Pais et al., 2013)
			FOXO3	Decrease microglia activation in the brain	(Jiang et al., 2017; Li et al., 2015; Pais et al., 2013; Rangarajan et al., 2015)
			Met.: PEPCK-C	Gluconeogenesis	(Jiang et al., 2011; Wang and Tong, 2009)
			PPARγ	Inhibition of adipogenesis	
SIRT3	Mitochondria	Deacetylase	IS: NF- κβ, FOXO3	Decrease microglia activation in the brain	(Jiang et al., 2017; Li et al., 2015; Pais et al., 2013; Rangarajan et al., 2015)
			Met.: Subunits of the ETC and ATP synthase	Modulation of complex I proteins and mitochondrial translation	(Ahn et al., 2008; Cimen et al., 2010; Law et al., 2009; Yang et al., 2010)
			AceCS2, LCAD, IDH2, GDH	Influence the Krebs cycle	(Cimen et al., 2010; Hallows et al., 2006; Lombard et al., 2007; Schlicker et al., 2008; Schwer et al., 2009)
			IS & Met.:	Contribute in an immune response	(Finley et al., 2011; Hirschey et al., 2010)
SIRT4	Mitochondria	ADP-ribosyltransferase	Met.: GDH	Insulin secretion in pancreatic β cells	(Haigis et al., 2006)
		Deacetylase		Lipid metabolism	(Laurent et al., 2013)
				Krebs cycle	(Haigis et al., 2006)
SIRT5	Mitochondria	Deacetylase, Desuccinylase Demalonylase	Met.: CPSI	Urea cycle	(Nakagawa et al., 2009)
				Modulation of cytochrome C	(Huang et al., 2010)
SIRT6	Nucleus	ADP-ribosyltransferase Deacetylase	CNS: Oct4, Sox2, Nanog	Neural Stem cell differentiation	(Etchegaray et al., 2015)
			IS: NF- κβ	promoters of NF-κB target genes	(Kawahara et al., 2009)
			Met.:		
			AKt, IR, IRS	Lipid homeostasis	(Xiao et al., 2010)
			GLUT1, GLUT4	Glucose metabolism, down-regulates glycolysis	(Wu et al., 2015)
			SREBP, FOXO3, Srebp2	Cholesterol homeostasis	(Tao et al., 2013)
			IS & Met.: HIF-1α	Regulate the expression of different cytokines	(Fang et al., 2009; Greer et al., 2012; Kohler et al., 2012; Zhang et al., 2006)
SIRT7	Nucleus	Deacetylase	Met.:	Energy metabolism Hepatic lipid metabolism	(Ryu et al., 2014; Shin et al., 2013; Yoshizawa et al., 2014)

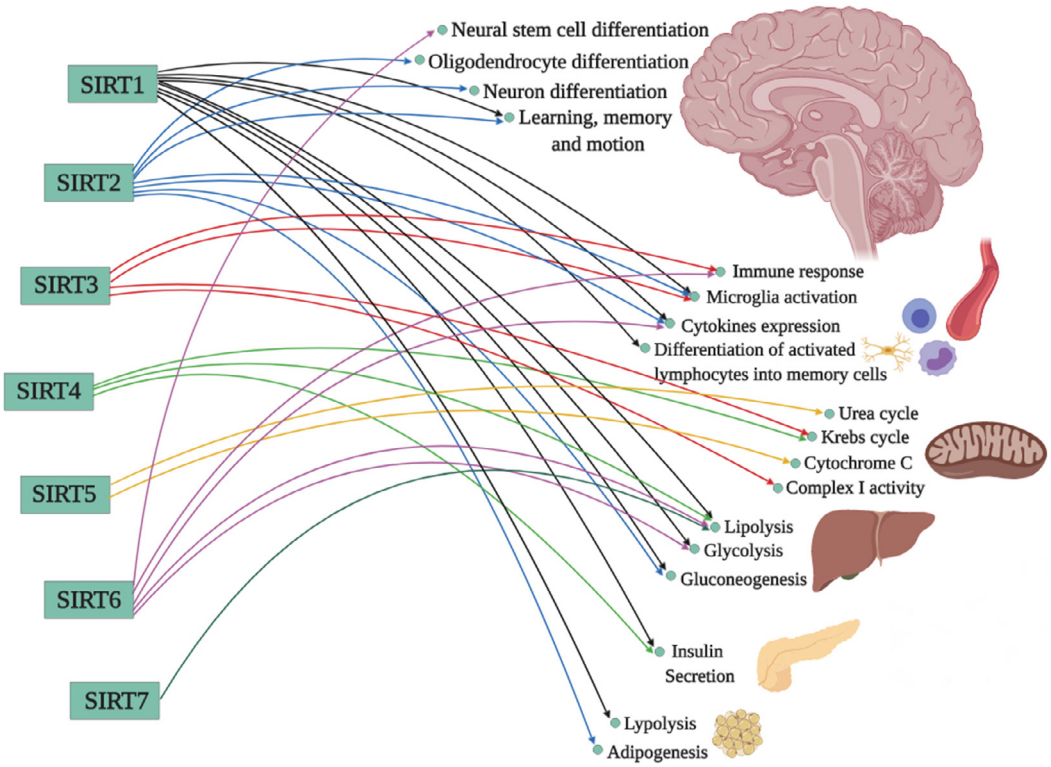

Fig. 1. Different roles of sirtuins in central nervous system, immune system, and metabolism.

(Fig. 1). Sirtuins regulate two major pathways, nuclear factor kappa β (NF-κβ) and AP-1, which are involved in the immune responses, both innate and adaptive ones.

One of the master regulators in immune responses and inflammation is NF-κβ (Hayden and Ghosh, 2012) which can be modulated by sirtuin proteins. Expression of pro-inflammatory genes, such as growth factors, chemokines, and cytokines occurs via activation of NF-κβ (Mattson and Meffert, 2006). In addition, a decrease in NF-κβ transcription activity happened by deacetylation of NF-κβ subunit p65, consequently, cytokines and anti-apoptotic genes products were reduced (Yeung et al., 2004). This molecule was revealed to be correlated with the synthesis of various cytokines, such as TNF-α, IL-1β, interleukin-6 (IL-6) and interleukin-8 (IL-8) (Maggio et al., 2015; Hoesel and Schmid, 2013). Physical interaction of SIRT1 with the RelA/p65 subunit of NF- κβ, causes a deacetylation of RelA/p65 at lysine 310 and results in transcription inhibition (Yeung et al., 2004). Furthermore, SIRT2 acts as a deacetylator of the p65 subunit of NF-κβ (Pais et al., 2013). Studies on cells obtained from SIRT2 knockout mice show hyper-acetylation of p65 and increased expression of NF-κβ-dependent genes induced by TNF. Deacetylation of p65 subunit of NF-κβ by SIRT2 resulted in reduced expression of IL-1β, IL-6, matrix metalloproteinase 9 (MMP-9), MMP-13 and monocyte chemo attractant protein 1 (MCP-1) (Lin et al., 2013; Rothgiesser et al., 2010). Moreover, SIRT6 has interaction with the RelA/p65 component of the NF-κB complex which recruits some promoters of NF-κB target genes (Kawahara et al., 2009).

It is noteworthy that sirtuins may also activate NF- κβ signaling by regulating FOXO proteins. FOXO3 can inhibit the TNFα-induced activation of NF- κβ, and modulate apoptosis (Peng, 2007). Deacetylation of FOXO proteins via SIRT1 is reported by several studies in different cell types and systems (Brunet et al., 2004; Motta et al., 2004; Viswanathan et al., 2005). Some other studies showed that SIRT1, SIRT2, and SIRT3 decrease microglia activation, as the innate immune cells of the brain, as well as the inflammatory responses. These responses have been attributed to the inhibition of NF- κβ signaling or FOXO3 activation (Jiang et al., 2017; Li et al., 2015; Pais et al., 2013; Rangarajan et al., 2015).

In addition to the NF- κβ pathway, evidence demonstrated the interaction between SIRT1 and AP-1 in macrophages (Zhang et al., 2010). In macrophages, SIRT1 overexpression could reduce the mRNA level of COX-2 as a target gene of AP-1 and reduce the production of prostaglandin E.

Although recent investigations have revealed that sirtuins are an important regulator of both innate and adaptive immune response (Kong et al., 2012; Szegő et al., 2018) and alteration in their functions are presumably related to autoimmune diseases, information regarding the mechanisms of their involvement in inflammatory signaling pathways and mechanisms are still insufficient.

3.3. Role of sirtuins in metabolic regulation

Several studies have demonstrated that sirtuins regulate the pathways involved in the control of metabolism and calorie restriction (Chang and Guarente, 2014; Guarente, 2000). As a supporting fact, various proteins which play critical roles in metabolism, such as acetyl coenzyme A synthetase 2 (AceCS2) and PGC-1α are deacylated by sirtuins (Hallows et al., 2006; Nemoto et al., 2005; Rodgers et al., 2005; Schwer et al., 2006).

SIRT1, as the most studied member of this family, mediates metabolic effects in various tissues and cell types including liver, heart, adipose tissue, CNS and the immune cells (Chang and Guarente, 2014; Kong et al., 2012). These proteins have pivotal actions in the maintenance of glucose and lipid homeostasis, control of insulin secretion and sensitivity, the promotion of fat mobilization and the control of oxidative stress (Fig. 1). As a regulator of glucose metabolism, SIRT1 affects several pathways including gluconeogenesis, glycolysis and insulin secretion through influencing several proteins as like as CREB-regulated transcription co-activator 2 (CRTC2) (Liu et al., 2008), FOXO1 and PGC-1α (Wang and Tong, 2009), hypoxia-inducible factor 1α (HIF-1α) (Houtkooper et al., 2012) and phosphoglycerate mutase-1(PGAM-1) (Hallows et al., 2012). It can modulate gluconeogenesis and

inhibit the process of glycolysis. On the other hand, SIRT1 is involved in the pathway of lipid synthesis by affecting sterol regulatory element-binding protein-1 (SREBP-1) and SREBP-2 proteins (Walker et al., 2010), AMP-activated protein kinase (AMPK) (Wang and Tong, 2009), lipolysis via PPARγ activity, silencing mediator for retinoid and thyroid hormone receptor (SMRT) (Frescas et al., 2005), and cholesterol transport.

Another member of the sirtuins family, SIRT2, mediates gluconeogenesis by affecting the activity of a rate-limiting enzyme in this process, phosphoenolpyruvate carboxykinase (PEPCK-C) (Jiang et al., 2011) and by blocking PPARγ can inhibit adipogenesis (Wang and Tong, 2009).

SIRT3, a major mitochondrial deacetylase, acts as a metabolic sensor responding to the alteration of energy status in the cells. This protein is responsible for epigenetic modulation of complex I proteins in the respiratory chain (Ahn et al., 2008; Cimen et al., 2010; Law et al., 2009), and regulation of mitochondrial translation (Yang et al., 2010).

SIRT3 can influence the Krebs cycle directly (Cimen et al., 2010; Schlicker et al., 2008) and indirectly (Hallows et al., 2006; Lombard et al., 2007; Schlicker et al., 2008; Schwer et al., 2009). It has different acetylation targets that all are involved in metabolic status of cells including AceCS2 (Schwer et al., 2006), long-chain acyl CoA dehydrogenase (LCAD) (Hirschey et al., 2010), isocitrate dehydrogenase 2 (IDH2) (Yu et al., 2012) and glutamate dehydrogenase (GDH) (Frescas et al., 2005).

It seems that SIRT4 is involved in insulin secretion in pancreatic β cells (Haigis et al., 2006) as well as lipid metabolism (Laurent et al., 2013) and in the transport of ATP. An indirect role in the Krebs cycle through GDH inhibition by ADP-ribosylation is also suggested (Haigis et al., 2006).

SIRT5 regulates the first and rate-limiting step (carbamoyl phosphate synthetase) of the urea cycle. Also, deacetylation activity of SIRT5 toward the mitochondrial protein, cytochrome C (Huang et al., 2010), plays a central role in oxidative metabolism and apoptosis initiation.

SIRT6 is reported to regulate lipid homeostasis and glucose metabolism. It was demonstrated that SIRT6 negatively regulates AKT, IR, insulin receptor substrate (IRS), glucose transporter-1 (GLUT1) and GLUT4 that result in the suppression of insulin/IGF-1 like signaling (Xiao et al., 2010). SIRT6 also inhibits the expression of several genes that are key modulators in glycolytic pathways and down-regulates glycolysis (Wu et al., 2015). In the cholesterol homeostasis pathway, SIRT6 can regulate the SREBP and FoxO3 and *Srebp2* genes promoter by deacetylation (Tao et al., 2013).

Recent studies have shown that the function of SIRT7 is associated with energy metabolism especially in hepatic cells lipid metabolism (Ryu et al., 2014; Shin et al., 2013; Yoshizawa et al., 2014).

3.4. Sirtuins as a link between metabolism and immune response

Considering the role of sirtuins in metabolic pathways, their activity is undoubtedly most prominent in immune cells. Changes in the metabolic status of these cells contributes in different facets of inflammation, including pro- or anti-inflammatory pathways (Fig. 1). The important role of cell metabolism in regulating an innate and adaptive immune response have been proven by several studies. These studies suggest a connection of inflammation with glycolysis and fatty acids that provide nutritional needs for immune cells in phase shifts after sensing the stress (Liu et al., 2012a). Before T cells activation, ATP is generated by tricarboxylic acid cycle and fatty acid β-oxidation in these cells (Michalek et al., 2011; Wang et al., 2011). Whereas after antigen stimulation, T cells markedly increase their glucose uptake and switch to a glycolytic mode. It can result in more intracellular ATP generation. Evidence have shown that pharmacological blockage of glycolysis reduces the differentiation of T cells into effector lymphocytes (Shi et al., 2011). Although the reason of this switch is still unclear, some studies suggested that it may be related to the capacity of glycolytic intermediates to fuel anabolic reactions in activated cells (Lunt and Vander Heiden, 2011). In addition, switching to fatty acid oxidation is required for several processes including $CD8^+$ memory T cells differentiation and the resolution/adaptation phase induction of an inflammatory response (Pearce, 2010). It is reported by some studies that SIRT1 and SIRT6 have the crucial role to link immune cell response to changes in metabolism (Liu et al., 2012b). Sirt6 has been shown to physically interact with HIF-1α which plays a crucial role in the immune cells by regulating the different pathways. It regulates the expression of different cytokines, such as IL-1β and IL-22 (Fang et al., 2009; Kohler et al., 2012; Zhang et al., 2006) and modulates T cells differentiation by targeting FOXO3 transcription factor (Greer et al., 2012). Moreover, SIRT1 mediates deacetylation which results in increased transcriptional activity of PGC-1α and PGC-1β (Kelly et al., 2009; Rodgers et al., 2005). It modulates switch toward fatty acid oxidation, as a determinative phase of inflammatory responses, and the differentiation of activated $CD8^+$ lymphocytes into memory cells (Lunt and Vander Heiden, 2011). Also mitochondrial SIRT3, as an important metabolism mediator, contributes to the immune response via recovering of oxidative metabolism during the resolution/memory phase (Finley et al., 2011; Hirschey et al., 2010).

4. Sirtuins in Multiple Sclerosis

Although a notable number of studies have focused on sirtuins functions in health and diseases, the relevance of sirtuins in MS is not clear. Most of the studies just indicated a possible role for SIRT1 while the role of other members of this family needs more consideration. We just summarize the available reports on sirtuins and MS related studies.

4.1. Sirtuin-1

Related to MS disease, SIRT1 is the most investigated member of this family in different animal models including experimental autoimmune encephalomyelitis (EAE), cuprizone fed animals, and in samples obtained from individuals suffering from MS (Table 2). EAE is one of the best available animal models for MS. There are some contradictory results about SIRT1 activation in this model; some studies have reported the protective function of SIRT1 in the EAE mice. Shindler and colleagues demonstrated that treating with SIRT1 activators, SRT501 and SRT647, reduced retinal ganglion cells death in optic neuritis following induction relapsing-remitting EAE. Besides, sirtinol as a SIRT1 inhibitor could block this neuroprotective effect (Shindler et al., 2007). In 2010, Shindler and colleagues continued their work and showed that SRT501 preserved the axons in the spinal cord (Shindler et al., 2010). In addition, genetically overexpression of SIRT1 in EAE mice had similar effects. Suppressed EAE symptoms compared to wild-type EAE mice have been shown in EAE induced by immunization with myelin oligodendrocyte glycoprotein (MOG) peptide in transgenic mice with neuron-specific overexpression of SIRT1 (Nimmagadda et al., 2013).

As neuroprotective agents, simultaneous overexpression of NRF2 or SIRT1 within RGCs could prevent impairment of visual function and induced RGCs survival in EAE mice (McDougald et al., 2018). Also, similar protective effects were reported in chronic EAE in C57BL/6 mice and in a virus-induced CNS demyelination model (Fonseca-Kelly et al., 2012; Khan et al., 2014).

On the other hand, other studies have reported opposite effects for SIRT1. SIRT1 expression was increased in GFAP-positive cells around the EAE lesions, and also the induction of mild activation of SIRT1 using resveratrol, caused suppression of neuronal progenitor cells (NPCs) proliferation and leading to their differentiation into astrocytes (Prozorovski et al., 2008). The elevated level in the generation of oligodendrocyte progenitor cells (OPCs) was also reported in NPC-specific knockout of SIRT1 in mice (Rafalski et al., 2013). Furthermore, several studies have shown that SIRT1 inhibition leads to improvement of

Table 2
The role of sirtuins in human pathologies or animal models of MS.

Name	Human/Mouse	Manipulation	Main findings	Reference(s)
SIRT1	EAE mouse	SRT501 and SRT647 (SIRT1 activators)	Reduction of retinal ganglion cell death in optic neuritis	(Shindler et al., 2007)
	EAE mouse	SRT501	Preservation of axonal density in the spinal cord	(Shindler et al., 2010)
	EAE mouse	Genetically SIRT1 overexpression	Suppression of EAE symptoms	(Nimmagadda et al., 2013)
	EAE mouse	Intravitreal overexpression of SIRT1	Neuroprotection of visual function and RGC survival	(McDougald et al., 2018)
	EAE mouse		Increase of SIRT1 expression in GFAP-positive cells around inflammatory lesions	(Prozorovski et al., 2008)
	C57BL/6 mice	Resveratrol (SIRT1 activator)	Suppression of proliferation in NPCs-differentiation toward astrocyte	(Prozorovski et al., 2008)
	C57BL/6 mice	Knockout of SIRT1	Elevated level in OPCs generation	(Rafalski et al., 2013)
	EAE mouse	Ex-527 (SIRT1 inhibitor)	Induction of remyelination, delay in paralysis onset, inhibition of pro-inflammatory Th17 cells and reduction of infiltration of immune cells into the spinal cord	(Lim et al., 2015)
	EAE mouse		Increase in level of transcription of SIRT1 in the CNS during chronic disease stages Upregulated level of SIRT1 in nuclei of NG2+ or PDGFRα+ OPCs in demyelinated brain lesions.	(Prozorovski et al., 2019)
		Ex527 (SIRT1 inhibitor)	Expansion of the endogenous pool of OPCs without affecting their differentiation	
	Human-MS		Decrease of SIRT1 expression in PBMCs in Relapse phase	(Ciriello et al., 2018; Hewes et al., 2017; Tegla et al., 2014)
	Human-MS		Increase of SIRT1 expression in acute and chronic lesion sites	(Tegla et al., 2014)
	Human-MS		Increase of SIRT1 level in plasma samples	(Pennisi et al., 2011)
SIRT2	Wistar rats	RNA knockdown of SIRT2	Increase of tubulin acetylation, MBP expression, and cell arbor complexity of OPCs	(Li et al., 2007)
	Human-MS		Presence of antibodies against SIRT2 in the CSF	(Lovato et al., 2008)
	EAE mouse		Decrease in the level of SIRT2	(Jastorff et al., 2009)
	EAE mouse		Increase in level of transcription of SIRT2 in the CNS during chronic disease stages	(Prozorovski et al., 2019)
	Human-MS		Decrease in level of several isoform of SIRT2 in MS lesions	(Jastorff et al., 2009)
SIRT3	Human-MS		Reduction in the level of SIRT3 expression in MS affected brain	(Rice et al., 2012)
SIRT4	Human-MS		Change in genetic variants	(Inkster et al., 2013)
SIRT5	Human-MS		Change in genetic variants	(Inkster et al., 2013)
SIRT6	EAE mouse		Increase in level of transcription of SIRT6 in the CNS during chronic disease stages	(Prozorovski et al., 2019)
SIRT7	EAE mouse	SIRT7 knockout	Decrease in cell differentiation and increase in cytokine production	(Burg et al., 2018)

clinical scores in EAE. Lim and colleagues reported that inactivation of SIRT1 induced remyelination and caused a delay in paralysis onset in chronic EAE model. In addition, production of pro-inflammatory T helper 17 (Th17) cells was inhibited in SIRT1 knockout mice and EAE clinical scores were ameliorated in a Th17 cell-mediated autoimmune disease. Pharmacological inhibition of SIRT1 could prove these data since using Ex-527 reduced infiltration of immune cells into the spinal cord and reduced EAE scores. SIRT1 can physically interact with transcription factor RAR-related orphan receptor ɣ-t (RORɣt) as a regulator in Th17 cells and induces Th17 cells differentiation through deacetylation of RORɣt (Lim et al., 2015). Prozorovski and colleagues in a recent study demonstrated that transcription of SIRT1, SIRT2 and SIRT6 is significantly increased in the CNS during chronic disease stages in EAE mice. Also, they showed upregulated levels of SIRT1 in nuclei of NG2+ or PDGFRα+ OPCs in demyelinated brain lesions. Their data using Ex527 suggest that SIRT1 inhibition may help to expand the endogenous pool of OPCs without affecting their differentiation (Prozorovski et al., 2019).

In addition to the studies that directly targeted SIRT1 and assessed the role of this protein in animal models of MS, there are numerous investigations that used disease protective agents and measured SIRT1 level. The effects of some of these protective drugs have been attributed to SIRT1 alterations. In this way, Singh and colleagues used lovastatin as an inhibitor of RhoA and AICAR as mediators for activation of AMPK and reported enhanced expression of the transcription of SIRT1 and attenuated EAE scores at the same time (Singh et al., 2018). Another report studied a cuprizone-induced demyelination model and reveal the neuroprotective effect of linagliptin on behavioral dysfunction in mice, and the modulatory role of AMPK/SIRT1 signaling pathway in this effect was demonstrated (Elbaz et al., 2018). Moreover, AMPK/SIRT1 signaling pathway could be targeted by NAD^+ inhibitor, methylene blue, and Adiponectin treatment, and resulted in the modulation of Th1/Th17 immune responses in EAE models (Wang et al., 2016b, a; Zhang et al., 2017).

Peripheral blood mononuclear cells (PBMCs) have been an important target for studies. Several studies demonstrated SIRT1 as a biomarker and reported that expression of this molecule in PBMCs obtained from MS patients in the relapse phase was decreased compared to healthy controls and patient with stable MS (Ciriello et al., 2018; Hewes et al., 2017; Tegla et al., 2014). Tegla and colleagues also showed the elevated expression of SIRT1 in acute and chronic lesion sites when compared to normal brain tissue. The expression of this protein is rarely detected in healthy brain samples. Besides, SIRT1 protein in MS plaques co-localize with CD4+ and CD8+ inflammatory cells, oligodendrocytes, and GFAP-positive astrocytes (Tegla et al., 2014). A study by Pennisi et al. in 2011 reported an increase in SIRT1 plasma levels in MS patients when compared with healthy plasma samples (Pennisi et al., 2011). One of the rational approaches for investigating the effect of candidate drugs on MS is their effectiveness on PBMCs inflammatory response, isolated from MS patients. Some of these experiments explained a link between the beneficial effect of the treatments and the modulation of SIRT1 expression (Emamgholipour et al., 2016).

Altogether, the review of the evidence shows the importance of SIRT1 in health and MS disease. This protein acts as a key regulator in normal brain function, immune system and metabolism. Some studies revealed the neuroprotective effects of this protein on MS animal models, whereas in other experiments neuroprotection were showed following SIRT1 inhibition. Besides, alteration of this protein in plasma samples, PBMC and lesion sites of MS patient confirm the role of SIRT1 in MS disease. So based on all these findings, SIRT1 may serve as a potential target for the treatment as well as a biomarker for MS.

4.2. Sirtuin-2

As mentioned in the aforementioned sections, SIRT2 plays an important role in oligodendrocyte differentiation, formation of myelin sheath, and the interaction of myelin and axons. SIRT2 protein exerts this effects by promoting both arborization and the expression of myelin-specific genes (Table 2). In 2007 Li et al. investigated an interfering RNA mediated knockdown of SIRT2 and showed increased tubulin acetylation, myelin basic protein expression, and cell arbor complexity of OPCs, whereas SIRT2 overexpression had the opposite effects, and counteracted the cell arborization. SIRT2 mutation caused a reduction in its deacetylase action and its effect on OPCs arborization (Li et al., 2007). Studying of human cerebrospinal fluid (CSF) in patients suffering from MS and healthy control individuals showed that antibodies against SIRT2 were present in the CSF of more than 44% of patients with MS but not in control CSF (Lovato et al., 2008). Another experiment in 2009 showed a diminished level of SIRT2 in EAE animals. In addition, they reported in post-mortem tissue that the level of several isoforms of SIRT2 in MS lesion was decreased when compared with normal appearing white matter (non-affected white matter) in MS patient and/or healthy controls (Jastorff et al., 2009). Some effective treatments on chronic EAE could enhance SIRT2 expression and other agents leading to ameliorating neurological function as determined by diminished clinical signs, protection of axonal integrity, induction of oligodendrocyte maturation and repopulation of neurons (Li et al., 2017).

4.3. Sirtuin-3, 4 and 5

Three sirtuins (SIRT3, SIRT4, and SIRT5) are known as mitochondrial sirtuins because they are located primarily within the mitochondria. Unlike SIRT1 and SIRT2, they have not been extensively studied in MS, but are thought to have important roles in energy production, cell signaling, and apoptosis (Verdin et al., 2010). Evidence is beginning to describe a role for mitochondrial sirtuins in protection against oxidative stress and excitotoxicity, although the mechanisms underlying these effects have not yet been clearly understood (Table 2) (Zhang et al., 2011).

In 2012, Rice et al. studied the role of mitochondrial sirtuins. They focused on these proteins as a new therapeutic target for repair and protection in MS. They performed immunohistochemistry studies on post-mortem human brain tissues that showed reduced levels of SIRT3 expression in MS affected brains compared to control samples (Rice et al., 2012). Furthermore, Inkster and colleagues carried out a neuroimaging study on the brains of MS patients (Inkster et al., 2013). They evaluated the predictive value of single nucleotide polymorphisms (SNPs) with several brain volumetric- and lesion-related measures in MS affected brains by advanced multivariate regression methods.

Their SIRT4 and SIRT5 findings were interestingly consistent with the literature showing that MS is associated with mitochondrial dysfunction (Inkster et al., 2013). SIRT4 contributed in the downregulation of GDH (Haigis et al., 2006), which reduced glutamate catabolism leading to increased glutamate levels. Several studies showed that MS has been linked with abnormal glutamate metabolism, excitotoxicity, and gene variants (Baranzini et al., 2010, 2009; Geurts et al., 2005, 2003; Matute et al., 2001). Besides, the absence of GDH expression in MS lesions was shown in postmortems, results were unlike the healthy control subjects (Werner et al., 2001). Inkster et al. demonstrated a relative link between mitochondrial-related gene variants in SIRT4 and SIRT5 and neurodegeneration in MS (Inkster et al., 2013).

4.4. Sirtuin-6

Although the key regulatory role of SIRT6 in the metabolism pathways and the link between changes in the metabolism and immune cell response has been proved, there is no sufficient evidence to show any alteration or stability in the levels of this protein in animal models of MS or in post mortem brain samples. Although a recent study assessed the transcription level of SIRT6 in EAE mouse and showed that it

is significantly increased in the CNS during the chronic disease stages (Prozorovski et al., 2019).

4.5. Sirtuin-7

A recent study by Burg and colleagues investigated the role of SIRT7 in EAE mice. They used SIRT7 knockout mice and EAE induction by myelin oligodendrocyte glycoprotein (MOG) peptide $_{35\text{-}55}$. Based on their results, SIRT7 could regulate cell differentiation and cytokine production especially by causing the reduction in the level of peripheral IFN and failure in the accumulation of regulatory T cells in the CNS of EAE in knockout mice. The effect was not strong enough to affect the clinical course of EAE. Besides they demonstrated that SIRT7 positively regulates the survival of adult-born neurons but did not impact the proliferation of hippocampal neurons. They concluded that SIRT7 could influence the immune and nervous system, but it was too weak to modulate the clinical scores in EAE mice as an animal model of MS (Burg et al., 2018).

5. Therapeutic potentials of sirtuins in MS

Current treatments for MS are mostly immunomodulation-based therapies that try to reduce inflammatory relapses (Arnold, 2005), but these do not prevent the progressive phase of neurodegeneration observed in MS patients. Sirtuins may be modulated by several activators and inhibitors that are natural or synthetic products (Table 3). Usually, activators can influence several targets besides SIRT1 and selective activators targeting the SIRT2-7 are very rare. On the other hand, most identified inhibitors for this family belongs to the SIRT1/2 isoform. Although none of the sirtuin modulators has received approval as a drug yet, some clinical trial using them are completed or recruiting for the treatment of cancer, diabetes and Huntington's disease (Bonkowski and Sinclair, 2016; Sussmuth et al., 2015).To date, the most studied sirtuins in the context of neurodegeneration and MS are SIRT1 and SIRT2. Additionally, as awareness grows for the roles that the mitochondrial sirtuins, SIRT3, SIRT4, and SIRT5 play in metabolic regulation and adaption their potential as therapeutic targets in MS become more promising. Increasing evidence suggests they may play different roles in neurodegeneration, autoimmunity, and metabolism with different protein targets, and provide different potentials for the development of therapeutic applications. Several experiments using drugs that target sirtuins and other HDACs show initial promise for treatment of the neurodegenerative and neurological part of MS (Aljada et al., 2010; Camelo et al., 2005; Chuang et al., 2009) and, therefore, these may be used as potential complementary therapeutic drugs with current immunotherapies (Shindler et al., 2010, 2007).

6. Conclusion

Evidence in recent years has clearly shown that the modulation of sirtuin activity may be a valuable therapeutic strategy to ameliorate or delay in the functional and pathological deficits associated with neurodegenerative diseases especially in MS disease. However, most of the focus of the researchers into sirtuin's role in neurodegeneration belong to SIRT1 and SIRT2. Insights into the metabolic roles of SIRT3–SIRT5 in the mitochondria, and SIRT6 role in metabolism and immune responses highlight their potential as therapeutic targets. SIRT7 is the least studied member of this family and the biological targets and possible roles of this protein are largely uninvestigated. As described in this review, sirtuins activity controls the multiple pathways in cells each one plays a crucial role in the pathology of MS in both phases of MS, RRMS and SPMS. Understanding the more detailed molecular mechanisms of sirtuins in regulating metabolism, immune response, neuroprotection and degeneration in MS, particularly in SP phase may contribute to the development of novel therapeutic target for MS.

Table 3
Sirtuins activators and inhibitors.

Name	Compound name	Related information	Use in clinical trials	Reference(s)
SIRT1	Piceatannol	Effects on SIRT3 and SIRT5; Natural activator		(Gertz et al., 2012; Howitz et al., 2003)
	Resveratrol	Effects on SIRT3 and SIRT5; Natural activator	Diabetes (Timmers et al., 2016) Cognitive function and mood (Evans et al., 2017) Alzheimer's disease (Turner et al., 2015)	(Gertz et al., 2012; Howitz et al., 2003)
	SRT1720	Synthetic activator		(Dai et al., 2010; Milne et al., 2007)
	SRT2104	Highly specific; Synthetic activator	Diabetes (Baksi et al., 2014)	(Hoffmann et al., 2013; Krueger et al., 2015)
	1,4-DHP derivative	In vitro and in vivo activator; Effect on SIRT2 and SIRT3		(Mai et al., 2009; Valente et al., 2016)
	Selisistat (Ex-527)	Effect on SIRT2 and SIRT3; Potent inhibitor	Huntington's disease (Sussmuth et al., 2015)	(Gertz et al., 2013; Napper et al., 2005)
	ELT-11c	Very potent inhibitor		(Disch et al., 2013)
SIRT2	ELT-11c	Very potent inhibitor		(Disch et al., 2013)
	AGK2	Widely used inhibitor		(Outeiro et al., 2007)
	3′-(3-fluoro-phenethyloxy)-2-anilinobenzamide	Effect on SIRT1; Potent inhibitor		(Suzuki et al., 2012)
	SirReal2	Effect on SIRT1, 3, 4, 5, 6; Potent inhibitor		(Rumpf et al., 2015)
	Compound 15e	Effect on SIRT1, 3; Potent inhibitor		(Sundriyal et al., 2017)
	UBCS0137	Effect on SIRT1, 3, 5; Potent inhibitor		(Moniot et al., 2017)
	Compound 28e	Effect on SIRT1 and SIRT3; Highly potent inhibitor		(Yang et al., 2017)
SIRT3	ELT-11c	Very potent inhibitor		(Disch et al., 2013)
	Compound 8	Effect on SIRT1 and SIRT2; Potent inhibitor		(Mahajan et al., 2014)
SIRT6	UBCS039	Effects on SIRT5; Synthetic activator		(You et al., 2017)

Declaration of Competing Interest

This is to declare that funding institutes had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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