REDOX EXPERIMENTAL MEDICINE

V Cordone and others | 2022:1 | R26–R39

REVIEW

Sirtuins as potential therapeutic targets for mitigating OxInflammation in typical Rett syndrome: plausible mechanisms and evidence

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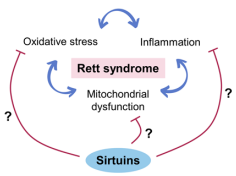
Graphical abstract



Key Words

- RTT syndrome
- MeCP2
- OxInflammation
- SIRT
- resveratrol

Abstract

Rett syndrome (RTT), a monogenic neurodevelopmental disorder mainly affecting female, is caused by mutations in X-linked *MECP2* gene, an ubiquitous epigenetic regulator. In addition to neurological issues, RTT patients show a variety of multisystem manifestations and impairment of different signalling and metabolic pathways, including compromised mitochondrial function, altered redox homeostasis, improper cholesterol metabolism and subclinical inflammation. The sirtuin family (SIRTs), comprising seven members, catalyses the NAD^+-dependent deacetylation, ADP-ribosylation and deacylation of a wide range of targets and works as sensors of cellular energetic status. In addition, SIRTs can modulate activities and gene expression of proteins involved in cellular stress responses related to oxidative stress, mitochondrial dysfunctions and inflammation, in both physiological and pathological conditions. Given some shared molecular aspects, herein, we revised the current scientific literature and hypothesized the possible relationship of SIRTs signalling involvement in RTT pathogenesis and OxInflammation. Although further research is needed, uncovering the possible involvement of SIRTs in RTT could reveal new potential pharmacological targets for the disorder. In light of this, SIRT-enhancing compounds could likely represent a new option to be tested as co-adjuvant alternatives to the current therapies.

Redox Experimental Medicine (2022) **2022**, R26–R39

https://rem.bioscientifica.com
https://doi.org/10.1530/REM-22-0004

Introduction

Rett syndrome (RTT) is a genetically defined neurodevelopmental pathology, primarily caused by mutations in the methyl-CpG-binding protein 2 (*MECP2*). Patients affected by RTT suffer from both neurologic (i.e. microcephaly, intellectual disability, seizures, absent or very limited speech) and non-neurologic manifestations (i.e. breathing, gastrointestinal and cardiac problems and recurrent infections), which make this syndrome a broad-spectrum pathology (Gold *et al.* 2018). In addition, at molecular level, RTT is characterized by an alteration of several metabolic traits, such as redox homeostasis, mitochondrial bioenergetics, cholesterol metabolism and inflammatory responses (Sticozzi *et al.* 2013, Segatto *et al.* 2014, Pecorelli *et al.* 2016*a*, Shulyakova *et al.* 2017).

Sirtuins (SIRTs) are a family of evolutionarily conserved enzymes, whose deacetylating function is mainly dependent on NAD^+/NADH ratio. Therefore, these enzymes may serve as sensors of cellular energetic condition (Imai *et al.* 2000). Not only this, SIRTs play critical roles in the regulation of cellular homeostasis, in particular oxidative stress, inflammation, metabolism and senescence (Vachharajani *et al.* 2016, Singh *et al.* 2018, Lee *et al.* 2019). Different studies reported that activation of SIRTs may be helpful in metabolic diseases such as obesity and type 2 diabetes, as well as in ageing and neurological disorders (Rahman & Islam 2011).

Given some shared molecular aspects, herein, we attempted to summarize current knowledge on SIRTs in RTT. Our work aimed at stimulating researchers to deepen the role of SIRTs in this complex syndrome, in light of the likely involvement of these deacetylases in RTT and the potential beneficial effect of SIRT activators as possible co-adjuvants of the current therapies.

Rett syndrome

Rett syndrome (OMIM #312750) is a complex neurodevelopmental disorder, which mainly affects the female gender with an incidence rate ranging from 1:10,000 to 1:15,000 live births. Although considered a rare disease, RTT is the second most common cause of severe intellectual disability in females after Down syndrome (Neul *et al.* 2010).

After a period of normal development (6–18 months of life), RTT patients typically experience stagnation and rapid deterioration of the acquired psychomotor skills, leading to a distinctive clinical phenotype, characterized by severe intellectual disability, microcephaly, repetitive hand movements, seizures, absent or very limited speech, irregular breathing, cardiac abnormalities, ataxia and autistic features (Chahrour & Zoghbi 2007).

RTT was first described by Doctor Andreas Rett in 1966 (Rett 1966); however, only in 1999, Zoghbi's group could identify the genetic source of the disease (95% of the cases), uncovering mutations in the X-linked *MECP2* gene in RTT patients (Amir *et al.* 1999). The majority of RTT mutations occur in *MECP2* exons 3 and 4, which consist of 4 key functional domains in the translated protein: a methyl-binding domain, a transcriptional repressor domain, an NCoR-interaction domain and a C-terminal domain, important for MeCP2 DNA-binding ability (Kyle *et al.* 2018). According to recent prediction algorithms, based on a FAIRification (Findable, Accessible, Interoperable, and Reusable) workflow, to date, more than 800 unique confirmed RTT-causing mutations in *MECP2* have been identified (Ehrhart *et al.* 2021). However, eight missense and nonsense 'hotspot' mutations (R106W, R133C, T158M, R306C, R168X, R255X, R270X and R294X) are responsible for approximately 78% of total cases of RTT, and C-terminal deletions and large deletions are responsible for another 8% and 5%, respectively (Christodoulou *et al.* 2003). The type and location of the mutations are known to modulate clinical severity, hence, contributing to the high phenotypic variability observed in the disorder (Cuddapah *et al.* 2014).

MeCP2 is a nuclear protein, ubiquitously expressed throughout all human tissues and thanks even to its intrinsically disordered (ID) nature, MeCP2 plays multifunctional roles: it is implicated in the transcriptional regulation of numerous genes (by both activating and repressing transcription), chromatin organization, microRNA processing and RNA splicing (Ip *et al.* 2018).

In the CNS, MeCP2 is expressed at low levels prenatally but rises progressively during synaptogenesis and neuronal maturation with a maximum in mature, post-migratory neurons, suggesting a role for MeCP2 in sustaining neuronal activity, maturation and plasticity (Bedogni *et al.* 2016).

As already mentioned, the symptomatic hallmarks of RTT are mainly neurological and are associated with reduced brain volume, abnormally small neuronal body size and densely packed neurons, presenting decreased dendritic complexity and spine density particularly in cerebral cortex, thalamus, substantia nigra, basal ganglia, amygdala, cerebellum and hippocampus (Armstrong *et al.* 1995, Carter *et al.* 2008).

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However, in the last few years, a multifaceted clinical appearance with variety of co-morbidities involving other tissues and organs have been identified in RTT patients, including sleep disturbances, periodic breathing disorder, electrocardiograms with prolonged cardiac QT interval, osteopenia, endocrine alterations, gastrointestinal problems, dysphagia, recurrent infections (especially at gallbladder, urinary and respiratory tract) or unexplained augment of fever (Borloz *et al.* 2021, Wang *et al.* 2021). In addition, from a molecular point of view, RTT patients exhibit deregulations of signalling and metabolic pathways, such as abnormal mitochondrial bioenergetics, unbalanced redox homeostasis, perturbed lipid metabolism and compromised immune-inflammatory responses (Segatto *et al.* 2014, Filosa *et al.* 2015, Shulyakova *et al.* 2017, Pecorelli *et al.* 2020*a*). This topic will be better deepened in the next section ('Oxidative stress and inflammation ('OxInflammation') in Rett syndrome pathogenesis).

Taken together, the combination of all these alterations can help to explain the complex nature of RTT, which is now increasingly considered a broad-spectrum pathology with multisystem disturbances (Borloz *et al.* 2021).

Oxidative stress and subclinical inflammation ('OxInflammation') in Rett syndrome pathogenesis

Despite advances in understanding the role of MeCP2, it is still unclear how the mutation of a single protein leads to all the manifestations mentioned in the previous section. Patients with RTT even present an impairment of signalling and metabolic pathways, like dysfunctional mitochondria, compromised redox homeostasis and chronic subclinical inflammatory status, which act in a vicious loop termed 'OxInflammation' (Pecorelli *et al.* 2016*a*).

In particular, several papers reported increased levels of 4-hydroxynonenal protein adducts (4-HNE-PAs) and non-protein-bound iron (NPBI) in the systemic compartment of RTT subjects (De Felice *et al.* 2009, Pecorelli *et al.* 2011). Fibroblasts and peripheral blood mononuclear cells (PBMCs) derived from RTT patients showed increased levels of hydrogen peroxide (H_2O_2), mitochondrial reactive oxygen species (ROS) and 4-HNE-PAs (Cervellati *et al.* 2015, Cordone *et al.* 2022), in parallel with an alteration of the main antioxidant enzymes (i.e. glutathione reductase, thioredoxin reductase and glutathione peroxidase) and higher levels of oxidized glutathione (Signorini *et al.* 2014, Cervellati *et al.* 2015), as compared to cells isolated from control subjects.

In addition, RTT patients showed a dysregulation of acute phase response proteins, augmented levels of the bioactive lipid metabolite 13-hydroxyoctadecadienoic acid (13-HODE) and a perturbed cytokine profile, characterized by high serum levels of interleukin (IL)-3, IL-8, IL-9, IL-13 and IL-15 and a Th2-shifted balance (Cortelazzo *et al.* 2014, Leoncini *et al.* 2015, Pecorelli *et al.* 2016*b*, 2019). Other studies on both primary fibroblasts and PBMCs evidenced a deregulated NLRP3 inflammasome response (Pecorelli *et al.* 2020*b*, Cordone *et al.* 2022), an intracellular multi-protein complex assembled in response to different stimuli (both pathogens and sterile stressors, like ROS, cardiolipin and mitochondrial dysfunction) and characterized by the activation of inflammatory caspase 1, able to activate the pro-inflammatory cytokines IL-1β and IL-18 or cleave gasdermin D, leading to a pro-inflammatory form of cell death, known as pyroptosis (Broz & Dixit 2016). Macrophage populations, including microglia, are even deregulated in *Mecp2*-null mice (Cronk *et al.* 2015). Intriguingly, brains of pre-phenotypic and phenotypic RTT mice (*Mecp2* knock-out and *Mecp2*^{308}) exhibit signs of oxidative stress and related damages, together with an impaired expression of genes associated with innate immunity already before the appearance of the typical symptoms (De Felice *et al.* 2014, Bebensee *et al.* 2017, Zhao *et al.* 2017, Adebayo *et al.* 2020, Cortelazzo *et al.* 2020). As corroborating findings, systemic levels of IL-18, 4-HNE and F2-dihomo-isoprostanes were enhanced mostly in the early stages of the disease (De Felice *et al.* 2011, Pecorelli *et al.* 2011, Cordone *et al.* 2022), suggesting that the vicious circle of OxInflammation can take part in both RTT pathogenesis and progression (Valacchi *et al.* 2018).

Sirtuins as defensive mechanisms

SIRTs are a family of conserved enzymes, initially classified as histone deacetylases (HDACs), that are able to deacetylate a variety of target proteins besides histones (Imai *et al.* 2000). In a lesser extent, they also catalyse mono-ADP ribosylation of protein acceptors and deacylation, by hydrolysing lysines modified with longer acyl chains (Zhao *et al.* 2004, Feldman *et al.* 2013). Unlike the zinc-related class I, II and IV HDACs, SIRTs use NAD^+ as a co-factor to exert their activity. Considering the importance of the fine-regulated balance of NAD^+/NADH ratio, SIRTs may serve even as sensors of the cellular energy status (Imai & Guarente 2016).

In mammals, seven paralogs have been identified (SIRT1–7). The seven mammalian SIRTs vary in sequence (especially, the terminal aminoacidic structure, which

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is responsible for the different subcellular localizations; however, they possess a conserved catalytic core), enzyme activity, substrate specificity and cell functions, like metabolism, genome maintenance and stress responses. Although new *in vivo* specificities and targets are reported every day, in Table 1 are summarized the main functions and effects of SIRTs in human cells.

SIRTs with different subcellular localizations can influence the spatial control of protein post-translational modifications (PTMs). SIRT3–5 are mitochondrial proteins (mtSIRTs) that are thought to have a key role in coordinating essential aspects of mitochondrial function (Di Emidio *et al.* 2021). Whereas, SIRT1, the most studied human isoform, is able to shuttle between nucleus and cytoplasm and regulate other essential physiological processes, linked to chronic inflammatory pathologies and metabolic dysfunctions such as obesity, diabetes, ageing and ageing-related disorders and cancer (Rahman & Islam 2011).

Sirtuins role in redox homeostasis and mitochondrial function

Evidence from scientific literature shows that almost all the known mammalian sirtuins may be directly or indirectly associated with oxidative stress and antioxidant cell defence (Singh *et al.* 2018). For example, the action of SIRT1 is mainly mediated by redox-linked transcription factors, like FOXOs and p53. Forkhead box (FOXO) proteins are responsible for the regulation of stress resistance, energy metabolism, cell cycle and cell death (Du & Zheng 2021). Several studies reported that SIRT1 and SIRT2 are able to deacetylate FOXO proteins, thus inducing their nuclear translocation, enhancing their DNA-binding ability and activating the transcription of different FOXO-dependent antioxidant genes in mitochondria (i.e. peroxiredoxins 3 and 5 and superoxide dismutase (SOD) 2), peroxisomes (i.e. catalase) and plasma (i.e. ceruloplasmin and selenoprotein P), as well as other stress resistance genes, including β-catenin and growth arrest and DNA damage-inducible 45 (Gadd45) (Brunet *et al.* 2004, Wang *et al.* 2007, 2017, Hughes *et al.* 2011, Nakagawa & Guarente 2011, Krafczyk & Klotz 2022). Interestingly, knocking down FOXO1 leads to a decrease of SIRT1 expression in HEK293 and vascular smooth muscle cells, suggesting a positive feedback loop for SIRT1 activity (Xiong *et al.* 2011).

SIRT1 can also prevent the formation of ROS by inhibiting nuclear factor-κB (NF-κB) translocation into the nucleus and reducing the gene expression of *GP91*^{PHOX} and *P22*^{PHOX}, which are part of NADPH oxidase enzyme (Salminen *et al.* 2013, Zarzuelo *et al.* 2013, Zhu *et al.* 2014). The control of ROS production by SIRT1 can be even due to its effect on mitochondrial electron transport chain (ETC); indeed, the activation of SIRT1, by SRT1720, restored the expression of some ETC proteins, like ATPβ, NDUFB8 and cytochrome c oxidase subunit I (COX I) in an intracerebral haemorrhage (ICH) mouse model (Zhou *et al.* 2017).

As known, mitochondria is the main site of ROS production and also the hub of various metabolic pathways such as oxidative phosphorylation (OXPHOS), β-oxidation of fatty acids, tricarboxylic acid cycle and urea cycle (Di Emidio *et al.* 2021). Peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α), a master regulator of mitochondrial biogenesis and oxidative metabolism, represents one of the key targets of SIRT1 involvement in mitochondrial function (Gurd 2011, Guo *et al.* 2014). Indeed, SIRT1 can regulate the acetylation state and activity level of PGC-1α, which can rapidly translocate into the nucleus and co-activate the nuclear respiratory factors (NRFs), nuclear receptor peroxisome proliferator-activated receptor, estrogen-related receptor and mitochondrial transcription factor A (TFAM) to control the expression of key genes for respiration, metabolism of glucose and lipids, mtDNA transcription and mtDNA replication machineries (Rodgers *et al.* 2005, Ventura-Clapier *et al.* 2008).

About mitochondrial functions, a particular attention should be paid to mtSIRTs. SIRT3, in particular, has been demonstrated to promote mitochondrial respiration and OXPHOS, by its deacetylating action on all ETC complexes, which can facilitate the electron flow and ATP production (Finley *et al.* 2011, Wu *et al.* 2013, Rahman *et al.* 2014, van de Ven *et al.* 2017). SIRT3 is able to directly deacetylate and activate SOD2, the primary scavenger of superoxide anion (Tao *et al.* 2010). Recently, it has been shown that SIRT3 plays a role in the regulation of mitochondrial quality control and in preventing the accumulation of damaged mitochondria. SIRT3 may indeed activate the mitochondrial unfolded protein response (mtUPR), thus inducing alterations in mitochondrial fission, fusion and mitophagy (Meng *et al.* 2019). In particular, SIRT3 is able to activate the Lon protease P1 by deacetylation, leading to the degradation of mitochondrial oxidized proteins (Gibellini *et al.* 2014). The complex mechanism of cellular control of the redox milieu is even regulated by SIRT5. Lin *et al.* (2013) found that the increased SOD1 activity in reducing superoxide anions was due to SIRT5-dependent desuccinylation of Lys123 (Lin *et al.* 2013).

Taken together, sirtuins, especially SIRT1 and mtSIRTs, increasingly represent a fascinating research topic in

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Table 1 Summary of the main functions and effects of SIRTs in human cells.

SIRT isoform	Catalytic activity	Subcellular localization	Target proteins	Cellular functions
SIRT1	Deacetylase	Nucleus Cytoplasm	p53, H3K9, H1K26, H4K16, PGC1α, SREBP-1c, PPARγ NF-κB, AKT, FOXOs, HIF-1α, TFAM, AceCS1, APE1, and PARP-1	↓ Inflammation ↓ Oxidative stress ↓↑ Gluconeogenesis ↓ Lipogenesis ↑ Lipolysis
SIRT2	Deacetylase Demyristoylase	Cytoplasm	PEPCK, α-tubulin, H4K16, and FOXO3a, NLRP3	↑ Gluconeogenesis Control of mitotic exit
SIRT3	Deacetylase	Mitochondria	LCAD, HMGCS2, SOD2, IDH2, PDC, AceCS2, OGG1, OPA1, LONP1, FOXO3a/PINK1/PARKIN	↓ Lipid accumulation ↑ Fatty acid oxidation ↑ Ketone body production ↑ Mitogenesis ↑ Mitophagy ↑ mtUPR ↑ Glutamine catabolism ↓ Oxidative stress
SIRT4	ADP-ribosyltransferase Lipoamidase	Mitochondria	GDH, PDC, MCD, OPA1	↓ Insulin secretion ↓ Fatty acid oxidation ↓ Mitogenesis ↓ Mitophagy ↓ Glutammine catabolism
SIRT5	Desuccinylase Demalonylase Deglutarylase	Mitochondria	CPS1, IDH2, SOD1	↑ Urea cycle ↑ Ketogenesis ↓ Oxidative stress
SIRT6	Deacetylase Depalmitoylase Demyristoylase ADP-ribosyltransferase	Nucleus Cytoplasmic reticulum	H3K9, H3K56, TNFα, PARP-1, GCN5, and HIF-1α	↓ Glucose uptake ↑ Inflammation ↑ DNA reparation
SIRT7	Deacetylase ADP-ribosyltransferase	Nucleolus	PAF53, H3K18, OSX	↑ RNA polymerase I transcription ↑ Bone formation

AceCS, acetyl-CoA synthetase; AKT, protein kinase B; APE1, apurinic/apyrimidinic endonuclease 1; CPS1, carbamoyl-phosphate synthase 1; FOXOs, forkhead box proteins; GCN5, histone acetyltransferase; GDH, glutamate dehydrogenase; HIF-1α, hypoxia-inducible factor 1 alpha; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; IDH2, isocitrate dehydrogenase 2; LCAD, long-chain acyl-CoA dehydrogenase; LONP1, LON protease; MCD, malonyl-CoA decarboxylase; mtUPR, mitochondrial unfolded protein response; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; OGG1, 8-oxoguanine-DNA glycosylase 1; OPA1, GTPase optic atrophy 1 protein; OSX, SP7/Osterix; PAF53, RNA polymerase associated factor; PARP-1, poly(ADP-ribose) polymerase 1; PDC, pyruvate dehydrogenase complex; PEPCK, phosphoenolpyruvate carboxykinase; PGC1α, peroxisome proliferator-activated receptor gamma co-activator 1 alpha; PINK1, PTEN-induced kinase 1; PPARα, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; SOD, superoxide dismutase; SREBP-1c, sterol regulatory element binding protein c; TFAM, mitochondrial transcription factor A; TNFα, tumor necrotic factor alpha; UCP-2, uncoupling protein 2.

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both physiological and pathological conditions, given the strict link between them and redox homeostasis and mitochondrial metabolism/function.

Sirtuins role in inflammatory pathways

A number of works elucidated the role of SIRTs, in particular SIRT1, in mediating different stress responses, including inflammation, heat shock and hypoxic stress (Vachharajani *et al.* 2016). SIRT1 can reduce inflammation through its effect on nuclear factor-κB (NF-κB); indeed, SIRT1 is able to interact and deacetylate the p65 subunit/RelA at Lys310 residue, thus inhibiting NF-κB activity (Yeung *et al.* 2004). Treatment with resveratrol, one of the most studied SIRT1 agonists, inhibited NF-κB and ROS build-up in tumor necrosis factor (TNF)-α-stimulated HUVEC cells (Pan *et al.* 2016). On the other hand, NF-κB signalling may in turn suppress SIRT1 activity through the expression of miR-34a, interferon (IFN)-γ and ROS, thus determining a negative feedback regulation of SIRT1 and stimulating the NF-κB-related inflammatory response typical of chronic, metabolic and age-linked diseases (Kauppinen *et al.* 2013). During acute inflammation, several steps aimed at eliminating the cause of tissue injury and restoring the immune homeostasis. Innate immune cells express different types of receptors, including toll-like receptors (TLRs) able to sense and bind pathogen-associated molecular patterns (PAMPs). Once activated by PAMPs, TLRs rapidly trigger the expression and transcriptional activation of hypoxia inducible factor 1 subunit alpha (HIF-1α), which can switch mitochondrial OXPHOS towards aerobic glycolysis and enhance glucose levels to support the expression of pro-inflammatory genes, like *IL-12*, *IL-1A* and *TNF-A* (Koo & Garg 2019). The switching from a pro-inflammatory to an immuno-regulatory or anti-inflammatory state requires a transcriptional change, regulated by SIRT1-related deacetylation of NF-κB and histones (i.e. H1K26, H3K9, H3K14 and H4K16) and the enrolment of new methyltransferases (Liu & McCall 2013). In addition, SIRT1 may participate in counteracting acute inflammatory responses by mediating PGC-1α activation and promoting fatty acid oxidation as mitochondrial energy source, hence inducing a metabolic switch (Liu & McCall 2013, Koo & Garg 2019). A state of chronic inflammation is caused by persistent low-level *stimuli* that can be both pathogenic and non-pathogenic. A downregulation of SIRT1 activity is reported in a variety of diseases with an important chronic inflammatory component, including obesity, chronic obstructive pulmonary disease, Alzheimer's and Parkinson's disease, atherosclerosis and ageing (Rahman *et al.* 2012, Chun 2015, Kitada *et al.* 2016, Gomes *et al.* 2018, Pardo & Boriek 2020, Fernando & Wijayasinghe 2021). Besides the reduced shut down of NF-κB-dependent gene expression of pro-inflammatory molecules, the mechanisms linking SIRT1 decline to chronic inflammation are not fully understood. However, enhancing NAD^+ levels or activating SIRT1 could likely decrease chronic inflammation and help establish metabolic homeostasis (De Sá Coutinho *et al.* 2018).

Growing evidence suggests a role for SIRT1 in the inflammatory responses in CNS (Jiao & Gong 2020). It has been shown that the SIRT1 activator resveratrol reduced the secretion of IL-6 and TNF-α in microglial BV2 cells upon lipopolysaccharides (LPS) challenge, while the inhibition of SIRT1 through sirtinol and EX-527 induced, respectively, the release of inflammatory factors in the same cells, and the upregulation of gene expression levels of *TNF-A* and *IL-1B* and ROS generation in astrocytes, after LPS stimulation (Ye *et al.* 2013, Cheng *et al.* 2014).

In the last 4 years, a growing body of literature indicates a new potential regulatory mechanism of SIRT1 on NLRP3 inflammasome response in the neuroinflammation involved in several pathologies. In specific, it has been suggested that SIRT1 activators could inhibit the inflammatory cytokine production of IL-1β, IL-18 and TNF-α via the inhibition of NLRP3 inflammasome response (He *et al.* 2017, Zou *et al.* 2018, Han *et al.* 2020, Shaheen *et al.* 2021, Xia *et al.* 2021, Zheng *et al.* 2021). Besides SIRT1, also SIRT3 seems to be linked to neuroinflammation and NLRP3 inflammasome; indeed, a comprehensive acetylome analysis revealed that SIRT3 deficiency can lead to microgliosis, brain mitochondrial dysfunction, increased caspase-1 cleavage and *IL-1B* gene expression levels, thus suggesting a role of this mtSIRT in late-life cognitive decline (Tyagi *et al.* 2018).

Taken together, SIRTs are important for their action in response to various inflammation-related stress and to organize the survival signals trying to counteract these stressors.

Sirtuins in neurological diseases

As recently reviewed, SIRTs are crucial, at different molecular levels, for the regulation of neuronal cell death and the pathology of neurodegenerative diseases, like Alzheimer's and Parkinson's diseases, multiple sclerosis and amyotrophic lateral sclerosis (Manjula *et al.* 2020, Bhatt & Tiwari 2022, Leite *et al.* 2022). Several studies revealed that SIRT1 and 3 expression is reduced in the brain of patients with Alzheimer's disease (Lutz *et al.* 2014, Yin *et al.* 2018).

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In particular, besides the role of SIRTs in mitochondrial dysfunction, oxidative stress and neuroinflammation (mainly through the involvement in NF-κB signalling and inflammasome pathways), SIRTs can regulate the processing of amyloid precursor protein (APP) by promoting the formation of non-amyloidogenic soluble APPα and the deacetylation of tau protein resulting in an attenuation of its accumulation and toxicity (Manjula *et al.* 2020).

Moreover, of note, an efficient control of NAD^+/NADH ratio is necessary for the proper functioning of mitochondrial bioenergetic processes and for SIRTs enzymatic activity. For example, NAD^+ hydrolases such as sterile alpha and TIR motif containing 1 (SARM1) can modulate SIRTs activation and contribute to axonal degeneration and NAD^+ depletion (Gerdts *et al.* 2015).

Several studies reported an impaired energy metabolism and a reduced NAD^+/NADH ratio even in patients affected by the neurodevelopmental and neuropsychiatric disorders, such as autism, schizophrenia and bipolar disorder (Boccuto *et al.* 2013, Kim *et al.* 2017, Jeong *et al.* 2020).

Possible role of sirtuins in Rett syndrome

Despite SIRTs action influencing several cellular metabolic and OxInflammatory aspects, involved in RTT pathogenesis, to date, only a few literature papers investigated the possible link between this class of enzymes in the disease.

Zocchi and Sassone-Corsi (2012) first demonstrated that SIRT1 is able to deacetylate MeCP2 at Lys464, in both *in vitro* and *in vivo* assays. In particular, the treatment with SIRT1-inhibitor EX-527 significantly augmented the acetylated state of MeCP2 in HEK-293 cells, uncovering the specificity of interaction between MeCP2 and SIRT1 but not the other members of the SIRTs family. Moreover, MeCP2 recruitment on the brain-derived neurotrophic factor (BDNF) promoter was higher in $SIRT1^{\Delta ex4}$ (lacking the catalytic domain) mice, resulting in a decrease of BDNF protein and mRNA levels. These data suggest that SIRT1-dependent action on MeCP2 allows its release from the BDNF promoter, thus leading to increased BDNF transcription (Zocchi & Sassone-Corsi 2012). Accordingly, resveratrol has been found to induce an increase of BDNF in developing mice exposed to sevoflurane (an anaesthetic toxic during neonatal exposure), corroborating the role of SIRT1 as a crucial player in synaptic plasticity and cognitive performance (Tang *et al.* 2020).

In addition, a recent work has showed a reduction of miR-199a in mouse *Mecp2*-KO neurons and neural stem cells (NSCs), which seems relevant to RTT pathophysiology due to its positive regulation of mammalian target of rapamycin (mTOR) signalling. miR-199a is able to inhibit *Pde4d*, *Sirt1* and *Hif-1α* downstream of MeCP2 (Tsujimura *et al.* 2015).

SIRT1 is even implied in regulating the expression of the neuron-specific K^+/Cl^- cotransporter 2 (KCC2), which has been found to be reduced in human RTT neurons and in RTT mouse models (Tang *et al.* 2016). KCC2 plays a pivotal role in the maintenance of excitatory/inhibitory (E/I) balance, determining the polarity and efficacy of GABA inhibition, thus, it is a regulator of excitatory synapse development and dendritic spine morphogenesis (Li *et al.* 2007). Tang *et al.* (2019), by using a high-throughput drug screening platform, identified the activators of SIRT1 as KCC2 expression-enhancing compounds. They further demonstrated that resveratrol could effectively increase KCC2 expression in *MECP2*-null RTT human neurons (isogenic to the wild-type cells, derived from embryonic stem cells), hence, confirming the therapeutic benefit of SIRT1 activator on a number of brain diseases and likely on RTT (Tang *et al.* 2019).

The acetylation state of microtubules plays key functions in increasing the fast axonal transport of BDNF and mitochondria and in recruitment and binding of kinesin-1 and dynein to the microtubules (Sferra *et al.* 2020). It was found that AGK2, a SIRT2-specific inhibitor, can enhance the α-tubulin acetylation and the subsequent activation of NLRP3 inflammasome complex in macrophages (Misawa *et al.* 2013). Specifically, SIRT2, by its deacetylating action on α-tubulin, can induce microtubule destabilization, thus preventing the approximation of mitochondria (presenting the adaptor protein ASC) towards the perinuclear area and endoplasmic reticulum, where NLRP3 is localized, and also avoiding the association of NLRP3 with mitochondrial products, such as oxidized mtDNA and cardiolipin (Misawa *et al.* 2013, Traba & Sack 2017). The acetylation state of α-tubulin seems to be altered in primary cultures of fibroblasts derived from two male RTT patients (Gold *et al.* 2015).

Moreover, He *et al.* (2020) revealed that NLRP3 is post-translationally modified by acetylation in macrophages, facilitating the activation of the inflammasome system, and is directly deacetylated by SIRT2. Hence, SIRT2 and NLRP3 deacetylation could be modulated to prevent ageing-associated and chronic inflammatory conditions (He *et al.* 2020). Besides SIRT2, SIRT1 is also implicated in regulating the activation of the NLRP3 inflammasome. Indeed, resveratrol is reported to both inhibit the accumulation of acetylated α-tubulin and activate AMP-activated protein

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kinase (AMPK), resulting in the induction of autophagy, which is involved in the switch-off of NLRP3 response (Chang *et al.* 2015, Misawa *et al.* 2015).

In this regard, we recently demonstrated that the assembly of NLRP3 machinery was increased in both RTT fibroblasts and PBMCs already at basal condition (Pecorelli *et al.* 2020*b*, Cordone *et al.* 2022). We could hypothesize that an impairment of SIRT1 or SIRT2 may be involved, together with high ROS levels and mitochondrial dysfunction, in the aberrant response of the inflammasome complex occurring in RTT, thus likely contributing to the inflammatory status typical of the pathology.

In addition, as previously mentioned, two of the main SIRT1 targets are NF-κB and PGC-1α, with the resulting suppression of p65 binding to promoter regions of several pro-inflammatory genes, and the activation of PGC-1α downstream signalling, respectively. Several papers reported augmented NF-κB nuclear translocation and pro-inflammatory signalling in both *in vitro* and *in vivo* models of RTT (Kishi *et al.* 2016, Pecorelli *et al.* 2020*b*, Cordone *et al.* 2022). A downregulation of PGC-1α and NRF1, but not TFAM, was found in primary dermal fibroblasts of RTT patients (Cervellati *et al.* 2015). The same authors also demonstrated that RTT cells presented a reduced activity of both SOD1 and SOD2. As reported above, SOD1 and SOD2 PTMs and enhanced enzymatic activity are dependent directly on SIRT5 and SIRT3, respectively, and indirectly on SIRT1/FOXOs axis. Although they are just hypothesis, not yet mechanistically demonstrated in Rett syndrome, we could hypothesize that the OxInflammatory status occurring in RTT can likely be linked to an alteration of SIRTs functionality (Fig. 1).

Sirtuins in autism spectrum disorders

Finally, considering that RTT has been classified as part of the autism spectrum disorders (ASD) up to May 2013, due to its autistic-like symptomatology, the possible involvement of sirtuins in ASD is summarized in the following section.

ASD has a high prevalence rate in children, influences neurodevelopment, and leads to social and communication impairments. ASD is considered as a complex disease, being determined by both genetic and environmental components (Bai *et al.* 2019). A study by Bu *et al.* (2017) evaluated the function of SIRT1/PGC-1α axis in the oxidative stress condition of ASD. They found that both gene and protein expression levels of SIRT1 and PGC-1α were reduced in lymphoblastoid cell lines (LCLs) derived from ASD patients. While the over-expression of PGC-1α, through plasmid cell transfection, inhibited ROS production and LCL apoptosis, suggesting that the improvement of PGC-1α activity could decrease the oxidative injury in ASD LCLs, thus making this transcription co-activator a likely target for future treatments (Bu *et al.* 2017).

Despite some controversial findings (Bennuri *et al.* 2019, Smedler *et al.* 2021), the effect of resveratrol has been assessed in several ASD mouse models, exhibiting increased anti-oxidative (i.e. decreased lipid peroxidation levels) and anti-inflammatory (i.e. reduced levels of IL-6, IFN-γ, TNF-α and pJAK1; ameliorated dysregulation of Th1, Th2 and Th17) responses in treated animals (Bakheet *et al.* 2017, Bhandari & Kuhad 2017, Ahmad *et al.* 2018). Recently, Hendouei *et al.* (2020) tested resveratrol in an early-stage clinical trial: specifically, the molecule was used as a co-adjuvant of risperidone therapy (a drug able to rebalance dopamine and serotonin to improve mood, thinking and behaviour) in a double-blind, randomized clinical trial. Although the authors have not observed significant differences between the two groups (resveratrol + risperidone and placebo + risperidone) in ameliorating irritability and other ASD-associated symptoms such as social and communication skills, the patients treated with resveratrol showed decreased signs of hyperactivity, as compared to risperidone alone (Hendouei *et al.* 2020).

Despite the promising results of SIRTs activators, the molecular mechanisms and the role played by these deacetylases in the development and treatment of ASD need further investigations.

Conclusions

Extensive research within the past decades revealed that SIRTs family is implied in metabolic diseases, ageing and neurological disorders. At a molecular level, a positive modulation of SIRTs can be neuroprotective and counteract conditions of altered redox homeostasis and chronic, low-grade inflammation, which are common denominators of these pathologies and even RTT. For example, resveratrol, SRT1720 and SRT2104, some common SIRT1 activators, were found to have a broad-spectrum antioxidant and anti-inflammatory effects, as well as to reduce levels of protein carbonylation and formation of 4-HNE-PAs in pre-clinical studies of different diseases (Mercken *et al.* 2014, De Sá Coutinho *et al.* 2018). In addition, resveratrol treatment was able to modulate neuroinflammation and slow down functional and cognitive decline of subjects with mild-moderate Alzheimer's disease (Moussa *et al.* 2017). Thanks

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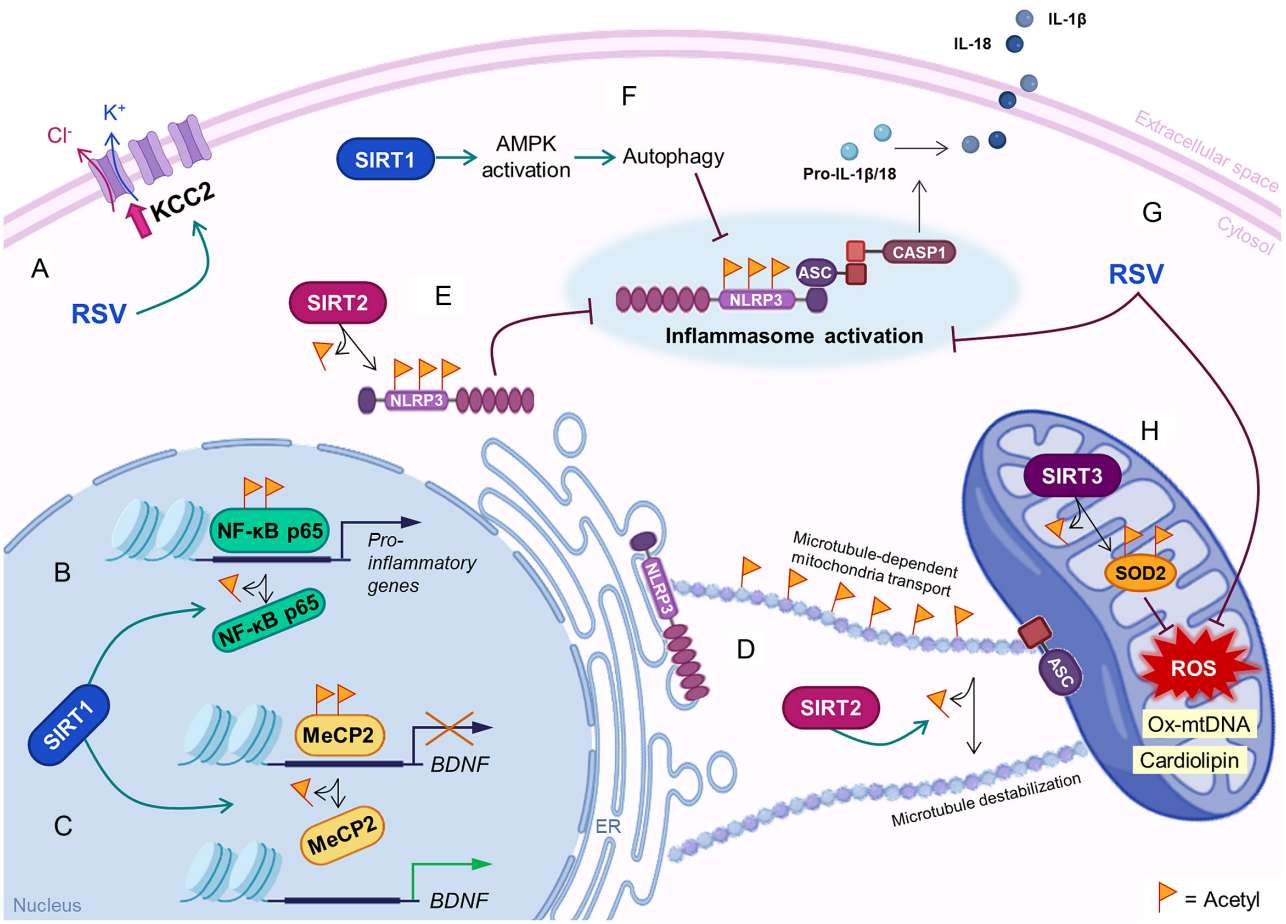

Figure 1
Possible roles of SIRTs in pathogenesis and OxInflammatory status typical of Rett syndrome. (A) Resveratrol can induce an increase of K^+/Cl^- cotransporter 2 (KCC2) expression, an important regulator of excitatory synapse development and dendritic spine morphogenesis, whose expression is reduced in RTT; (B) an enhancement of SIRT1 could inhibit the aberrant NF-κB p65 signalling observed in RTT, by its deacetylating action; (C) SIRT1 can promote a transcriptional de-repression of *BDNF*, by deacetylating MeCP2 and inducing its release from *BDNF* promoter region; (D and E) a positive modulation of SIRT2 on one hand could deacetylate microtubules, avoiding the approximation of mitochondria (presenting ASC) towards the perinuclear area and endoplasmic reticulum (presenting NLRP3), on the other hand could directly deacetylate NLRP3, preventing the constitutive inflammasome activation reported in RTT; (F and G) SIRT1 activators could inhibit the activation of inflammasome complex of RTT cells, by several indirect mechanisms, like reducing ROS or stimulating the AMPK-dependent autophagy; (H) an increased activity of SIRT3 could reduce mitochondrial ROS levels, by inducing the deacetylation of SOD2, and increasing its activity, which is impaired in several RTT cellular models.

to its safety and tolerability up to 5 g/day in healthy individuals (Patel *et al.* 2011), the natural compound resveratrol may represent a promising candidate for further testing in clinical trials of neurodegenerative disorders and, maybe, for starting *in vitro* and pre-clinical studies in RTT.

Honokiol, a poly-phenolic molecule and SIRT3 activator, even showed neuroprotective properties, enhanced antioxidant activity and mitochondrial function, through activating mitophagy and mtUPR in animal models of Alzheimer's and Parkinson's diseases (Chen *et al.* 2018, Li *et al.* 2018, Hou *et al.* 2022), which makes this compound another likely candidate to be investigated in trying to counteract mitochondrial alterations typical of RTT.

Taken together, although further research is needed, our hypotheses suggest that an alteration of SIRTs could take part in the OxInflammation typical of RTT, and both natural and chemical SIRT-enhancing compounds could represent a new option to be tested as co-adjuvant alternative to the current therapies.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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https://doi.org/10.1530/REM-22-0004

Funding
This study did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author contribution statement
V C and G V conceived the study. V C wrote the paper with support of A P. G V contributed to the final version of the manuscript.

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Received 31 May 2022
Accepted 6 June 2022