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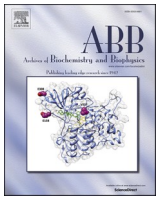

Biochemical and molecular determinants of the subclinical inflammatory mechanisms in Rett syndrome☆

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ABSTRACT

To date, Rett syndrome (RTT), a genetic disorder mainly caused by mutations in the X-linked *MECP2* gene, is increasingly considered a broad-spectrum pathology, instead of just a neurodevelopmental disease, due to the multitude of peripheral co-morbidities and the compromised metabolic pathways, affecting the patients. The altered molecular processes include an impaired mitochondrial function, a perturbed redox homeostasis, a chronic subclinical inflammation and an improper cholesterol metabolism.

The persistent subclinical inflammatory condition was first defined ten years ago, as a previously unrecognized feature of RTT, playing a role in the pathology progress and modulation of phenotypical severity. In light of this, the present work aims at reviewing the current knowledge on the chronic inflammatory status and the altered immune/inflammatory functions in RTT, as well as investigating the emerging mechanisms underlying this condition with a special focus on the latest findings about inflammasome system, autoimmunity responses and intestinal micro- and mycobiota. On these bases, although further research is needed, future therapeutic strategies able to re-establish an adequate immune/inflammatory response could represent potential approaches for RTT patients.

1. Introduction

In recent years, Rett syndrome (RTT; OMIM 312750), a genetic disorder mostly due to *de-novo* loss-of-function mutations in the X-linked methyl-CpG-binding protein 2 gene (*MECP2*), has been increasingly defined as a broad-spectrum pathology with multifaceted clinical appearance, rather than just a neurodevelopmental disease [1–3]. RTT has a prevalence rate of 7.1 out of every 100,000 females, and an incidence rate of 1 case per 10,000–15,000 female live births worldwide, without substantial regional or ethnic variability [4,5]. After a period of normal development (6–18 months of life), RTT patients typically undergo a rapid deterioration of the learned psychomotor skills, leading to severe intellectual disability, repetitive hand movements, seizures, motor abnormalities, irregular breathing, absent or very limited speech, cardiac problems, ataxia, autistic-like features, in parallel with a plethora of peripheral co-morbidities [6]. Indeed, although neurological signs are prominent, RTT affects also non-neurological organs and tissues (*i.e.*, gastrointestinal tract, respiratory, skeletal, endocrine, cardiovascular and urinary systems), evolving throughout the patients' life span [7].

Most literature papers are focused on the functions of MeCP2 in the central nervous system (CNS), an ubiquitous epigenetic reader and multifunctional protein, involved in regulating transcriptional activity, microRNA processing, chromatin compaction, and RNA splicing; however, the different manifestations identified in both RTT subjects and *Mecp2*-mutant animal models elucidate the importance of MeCP2 role in peripheral tissues [3]. In particular, Ross and colleagues, by using a knock-out (KO) mouse model in which *Mecp2* is silenced exclusively in peripheral tissues, were able to demonstrate that, although most signs are from neural origin, several RTT symptoms (*e.g.*, exercise fatigue, hypo-activity, and bone abnormalities) occur independently of defects in the nervous system [8].

In addition to the above illustrated organs and tissues affected in RTT, at molecular level, the patients exhibit compromised metabolic processes and signalling pathways, which comprise a perturbed lipid metabolism, an impaired redox homeostasis, dysfunctional mitochondrial bioenergetics and altered mitochondrial quality control, and a persistent subclinical inflammatory condition [9–13]. The cross-talk

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among all these abnormalities may explain the complexity and the broad-spectrum nature of this pathology.

In 2014, RTT was first associated with a subclinical inflammatory state, characterized by different immune dysregulations (see section 3) as a consequence of a likely impaired regulatory system of inflammatory processes. This deregulated control of inflammatory responses was defined as an unrecognized characteristic of RTT, closely related to oxidative stress (in a vicious circle termed 'OxInflammation'), and able to probably affect the development of the disorder [11].

In light of this and the progress made over the last ten years, the present review will summarize the current knowledge on the chronic subclinical inflammatory status and the altered immune/inflammatory responses in RTT, with a special focus on the emerging players involved in this complex picture. Furthermore, this work aimed at stimulating researchers to deepen the topic of aberrant inflammatory pathways in light of their involvement in RTT pathogenesis/progression, as well as in finding new therapeutic approaches for the patients.

2. Inflammation-related clinical signs in Rett syndrome: a brief overview

The spectrum of RTT clinical signs is broad and the onset of the different co-morbidities occurs at various stages of the syndrome [2].

RTT co-morbidities often include gastrointestinal (GI) problems, breathing disturbances, orthopaedic, endocrine, urinary and cardiac issues, which in combination make the management of RTT individuals extremely problematic [1]. Importantly, part of these peripheral dysfunctions has a common denominator, represented by a prominent inflammatory status [1–3].

Breathing abnormalities, like hyperventilation, breath-holding, apneas, respiratory arrhythmia, and spontaneous Valsalva manoeuvres are the most prevalent co-morbidities in RTT patients, starting before the age of 4 [14,15]. It is known that several neuronal mechanisms are likely to play a role in RTT breathing phenotype, principally deriving from severe autonomic and brainstem dysfunctions [16]. However, De Felice and colleagues, by using a high-resolution computed tomography (HRCT) on RTT patients, described 'ground glass opacities' (*i.e.*, radiological signs of alveolar inflammation), micronodules (*i.e.*, inflammatory infiltrates in the smaller airways), and thickening of bronchiolar walls (*i.e.*, a radiological sign of inflammatory infiltrate in the terminal bronchioles), thus suggesting an unrecognized inflammatory lung disease in RTT subjects [17]. In addition, non-specific lymphocytic bronchiolitis associated with lymphocytic vasculitis were found in about 50 % of *Mecp2*-null mice [18], together with other macroscopic and histological abnormalities particularly at the anterior right pulmonary lobes, and the presence of infiltrating cells (*i.e.*, lymphocytes, monocytes, eosinophils, and segmented neutrophils) in both the bronchoalveolar lavage fluid (BALF) and the epithelial layer of the alveoli [16]. Noteworthy, swallowing disturbances and oropharyngeal dysfunction typical of RTT subjects can result in aspiration, which in turn can lead to increased respiratory infections and lung inflammation [19]. Hence, these data strongly support the hypothesis that RTT breathing phenotype can be considered as the result of not only neurological dysfunctions, but also previously unrecognized inflammatory processes/abnormal immune responses.

Gastrointestinal and nutritional troubles are also frequently reported in RTT patients. Chewing and swallowing dysfunctions (as already mentioned above), gastroparesis, gastroesophageal reflux, gas bloating, and constipation can complicate the clinical phenotype of this pathology and predispose RTT girls to nutritional deficits and growth failure [20]. A study by Millar-Büchner and colleagues [21] reported GI dysmotility in *Mecp2*-null mice, characterized by a large increase in transit time, as compared to wild-type (WT) animals. While, from a morphological point of view, the intestine of *Mecp2*-null mice showed a significant reduction of the colon and crypt length, together with severe changes in colon epithelium and abnormal localization of key membrane proteins involved in electrolytes absorption. These alterations are also characteristic of animal models of colitis and inflammatory bowel disease, as well as high-fat diet mice presenting dyslipidemia [21,22]. This latter is known to be a metabolic impairment of both RTT patients and *Mecp2*-null animal models [12,23].

RTT individuals can also experience abdominal pain often due to gallbladder disease [20,24]. In particular, dysmotility of the gallbladder and/or obstruction of the cystic duct in conjunction with gallstones formation have been described in RTT patients [25], resulting in bile stasis and subsequent inflammation of the gallbladder, which can be further aggravated by starvation and dehydration. Moreover, recurrent obstruction together with inflammatory processes can progressively scar the gallbladder of girls and women with RTT, leading to additional gallbladder loss of function and worsening of biliary dyskinesia [25].

Then, besides the recurrent infections at respiratory system, frequent infections at urinary tract and kidney stones are also reported in RTT girls, therefore other sources of pro-inflammatory responses in the syndrome [26,27].

Taken together, the combination of all these clinical aspects presenting an overt inflammatory component causes significant pain to RTT girls. Thus, a better understanding and management of these multisystem inflammatory processes are needed to provide better care for patients.

3. Subclinical inflammation in Rett syndrome

A subclinical inflammation can be defined as a status of low-grade inflammation that is imperceptible to the 'naked eye', thus not leading to noticeable signs typical of acute inflammation, such as redness, swelling, or pain [28,29]. A subclinical inflammation is characterized by an alteration of several inflammatory markers and/or immune system response, that can be detected through biochemical and molecular analyses. Due to the lack of clear symptoms or clinical signs of inflammation, a subclinical inflammatory state may often become a chronic process, contributing to the pathogenesis and progression of several neurological and non-neurological pathologies (*i.e.*, neurodegenerative and neurodevelopmental disorders, atherosclerosis and cardiovascular diseases, obesity, and type 2 diabetes) [30]. In addition to the aforementioned hallmarks of acute inflammation, a chronic subclinical inflammatory condition can differ from the former in terms of duration, site, absence of an ongoing acute infection or injury, intensity of the cellular response, types of involved mediators (*i.e.*, long-term increase of reactive oxygen species (ROS), cytokines, and hydrolytic enzymes vs vasoactive amines and eicosanoids), as well as outcome [31].

Over the past ten years, immune system dysfunctions and persistent subclinical inflammation have been characterized as contributing factors of RTT broad-spectrum manifestations [9,11,32,33].

Indeed, some of RTT clinical features may have developed/progressed due to immune cell dysregulation and pro-inflammatory signals within the brain and throughout the peripheral tissues [34,35].

3.1. Altered inflammatory markers in patients and ex-vivo human models: an update

The first paper reporting a chronic subclinical inflammatory condition in RTT was published by Cortelazzo and colleagues [11]. The authors, by using a 2-DE/MALDI-TOF approach to perform a plasma proteome analysis, identified an up-regulation of several positive acute phase response (APR) proteins (*e.g.,* serum amyloid A-1 protein (SAA1), alpha-1 anti-trypsin (A1AT) and complement factor B (CFAB)), as well as the down-regulation of some negative APR proteins (*e.g.,* albumin and Retinol binding protein 4 (RET4)) in samples obtained from RTT girls at an early stage of the disease [11]. Then, an altered cytokine profile was also reported in RTT [36,37]. Indeed, T helper Type 2 (Th2)-cytokine response was increased (in particular the levels of interleukin (IL)-4, IL-5, IL-6, IL-9, IL-13 and IL-33 were higher than controls), while most of

the T helper Type 1 (Th1)-related cytokines were either lower or unchanged in plasma of RTT subjects. This Th2-shifted balance on one hand may be due to a possible compensatory effect of immune response related to a defective Th1 differentiation, on the other hand may trigger an autoimmune response (this aspect will be deepened in section 4.2) [36,38]. For example, IL-9, produced by mast cells and many T cell subsets besides Th2, such as Th-9, Th-17, and Treg cells, is able to induce the secretion of several pro-inflammatory cytokines, contributing to allergies, inflammation and autoimmune diseases [39]. IL-9 has been also related to cardiovascular and inflammatory lung diseases [40], whose compartments are involved in typical manifestations of RTT.

Moreover, RTT peripheral blood mononuclear cells (PBMCs) presented ultrastructural abnormalities, characterized by retracted and irregular nuclei, decreased nucleus/cytoplasm ratio, enlarged mitochondria, with membranous electrondense deposits and loss of cristae [37]. These cells also showed increased levels of arachidonate 15-lipoxygenase (ALOX15) mRNA, an enzyme implicated in the oxidation of polyunsaturated fatty acids including linoleic acid and generation of bioactive lipid metabolites such as 13-hydroxyoctadecadienoic acid (13-HODEs), whose levels were found augmented in RTT serum [41].

Recently, as a possible and alternative indicator of immune dysregulation in RTT, also salivary cytokines were investigated [42]. Consistently with the findings obtained in serum samples, higher levels of IL-1β, IL-6, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF) were noticed in saliva from RTT subjects, as compared to the controls [42].

3.2. Altered inflammatory markers in animal models: an update

Cortelazzo and co-workers showed for the first time that the persistent unresolved inflammation was present also in plasma of a symptomatic *Mecp2*-308 female mouse model [43], paving the way to further studies on the molecular cascade of events that leads to RTT phenotype.

Indeed, the use of animal models allows to investigate the inflammatory response both in pre-symptomatic and symptomatic stages of the disease. For example, a transcriptomic study on microglia isolated from *Mecp2*-deficient female mice revealed a deregulated expression of genes associated with innate immunity and cellular stress response already at pre-phenotypic stage, suggesting an early potential role of microglia in the later onset of neurological symptoms [44], which was consistent with other papers showing the importance of an aberrant activation of microglia (the primary brain-resident macrophages) in the onset and progression of RTT [45–48].

Several findings on *in vivo* and *ex-vivo* animal models also evidenced a role for astrocytes in RTT pathogenesis. In particular, *Mecp2*-mutant astrocytes, as well as their conditioned medium, can induce pathological alterations on neuronal development and overall maturation, and reduce dendritic outgrowth [49–51]. Coherently, the rescue of *Mecp2* expression exclusively in astrocytes ameliorated RTT manifestations, by leading to synaptic improvements [52]. A recent and elegant paper studied the cross-talk between *Mecp2*-KO astrocytes and WT neurons in a co-culture system, since RTT is characterized by a mosaic of cells, with part of them expressing either the WT or mutant *MECP2* allele [53]. The authors reported that mutant astrocytes can secrete molecules (like pro-inflammatory cytokines) able to affect synaptogenesis in WT neurons. Specifically, an augment of IL-6 levels, produced by these KO glial cells, was found in the co-culture medium; whereas, the blockade of this cytokine, by an anti-IL-6 antibody in cell culture medium, rescued the number of pre-synaptic dendritic terminals in WT neurons, induced by KO astrocytes. Intriguingly, this IL-6 over-production by *Mecp2*-lacking astrocytes occurs only in the co-culture system with WT neurons and is not present when KO astrocytes are cultured alone [53], suggesting that IL-6 plays a role as a synaptotoxic molecule in RTT.

Lastly, even meninges (characterized by a wide pool of immune cells taking part in CNS immune surveillance) from symptomatic *Mecp2*-deficient male mice exhibited a dysregulated activity of both innate and adaptive immune response [54], thus revealing new players in neuro-immune interactions in RTT.

4. Emerging potential mechanisms related to subclinical inflammation in Rett syndrome

Understanding the contributing factors to the subclinical inflammatory state in RTT is crucial for both elucidating the mechanisms underlying the complex picture of persistent inflammation and identifying potential therapeutic targets for symptomatic interventions. The following sections will focus on the latest evidence about inflammasome system, autoimmune responses, as well as gut microbiota and mycobiota in RTT.

4.1. Dysregulation of inflammasome response

The innate immune system is able to identify infections and alterations in cellular homeostasis in order to initiate responses to eliminate pathogens and repair tissue damages. One of the major players involved in these processes is the inflammasomes system, a group of intracellular multimeric protein complexes, characterized by the activation of inflammatory caspases (caspase-1, -4, -5, and -11), which are then responsible for the cleavage of multiple substrates including the pro-inflammatory cytokines IL-1β and IL-18 [55]. The inflammasomes can also initiate an inflammatory form of cell death defined as 'pyroptosis', where the N-terminal fragment of gasdermin D, cleaved by the afore-mentioned caspases, can form pores into the plasma membrane, thus acting as the trigger molecule of pyroptosis. Multiple distinct inflammasome complexes has been identified so far, however the best-characterized is the NLRP3 system, which was first linked with hereditary autoimmune diseases, termed cryopyrin-associated periodic syndromes [55,56]. It consists in its canonical form of the sensor protein 'NOD-, LRR- and pyrin domain-containing protein 3' (NLRP3), the adaptor protein 'apoptosis-associated speck-like protein containing a caspase activation and recruitment domain' (ASC), and the effector protein pro-caspase-1 [57]. NLRP3 activation generally occurs via a two-step model. The priming step (signal 1) is characterized by both the up-regulation of *NLPR3*, *IL-1b* and *IL-18* gene products (upon the activation of different receptors, like TLRs, TNFR, and IL1R, by pathogen- or damage-associated molecular patterns (PAMPs and DMAPs, respectively) and the subsequent NF-κB p65 nuclear translocation), and post-translational modifications of NLRP3, such as phosphorylation, ubiquitination, and SUMOylation, leading to the licensing of the sensor protein already present in the cells [58]. During the activation step (signal 2), triggered by a multitude of signals (PAMPs/DAMPs, potassium efflux, calcium mobilization, lysosomal damage, excessive ROS production and mitochondrial dysfunctions), the assembly of the NLRP3 inflammasome machinery occurs, followed by the auto-catalytic cleavage of pro-caspase-1 into its active forms p20 and p10, and the pro-inflammatory response, described above [57]. A prolonged and abnormal inflammasome response can participate in the onset/progression of chronic inflammatory conditions associated with pathologies, like autoimmune, metabolic, and infectious diseases, cancer, as well as neurodegenerative and neurodevelopmental disorders [59–65].

In this regard, an *ex-vivo* cellular model of RTT (*i.e.*, fibroblasts) exhibited a challenged NLRP3 inflammasome system, as compared to cells derived from control subjects, consisting of enhanced levels of nuclear NF-κB p65 (RelA), *IL-1b* mRNA, and ASC protein, as well as NLRP3:ASC interaction. RTT fibroblasts were also unable to induce a further response to LPS + ATP treatment, two well-known triggers of NLRP3 inflammasome response [66]. A trend of altered NLRP3 inflammasome machinery was detected also in primary PBMCs, a more immunocompetent cell model. Particularly, RTT patients-derived PBMCs showed augmented NF-κB p65 nuclear translocation and related up-stream pathway (*i.e.*, Toll-like receptor 4, and IRAK1), *IL*-18

mRNA levels, and NLRP3, ASC, and caspase-1 p20 protein amounts, together with the increased co-localization of the sensor and adaptor proteins in basal condition, as compared to PBMCs from control subjects [67].

The investigations of the role played by *MECP2* loss in these dysregulations revealed that it seems to account for several, although not all, pro-inflammatory and inflammasome-linked responses. Indeed, *MECP2* silencing in PBMCs and monocytic THP-1 cell line promoted an augmented expression of *IL-6*, *IL-3*, *TNF-a*, *ASC* and *IL*-18 mRNA, in parallel with enhanced NF-κB p65 signalling [67,68]. About the adaptor protein, its promoter region is known to be subjected to methylation [69] and notably, ASC was reported to be sensitive to MeCP2 activity [70]. Therefore, a possible decrease of MeCP2 transcriptional repression activity due to protein mutations could help to explain ASC over-expression in *MECP2*-knock down THP-1 cells and RTT lymphomonocytes. The major hypotheses for the aforementioned alterations of NLRP3 inflammasome activation in RTT models could be represented by the persistent impairment of redox homeostasis (in terms of augmented levels of hydrogen peroxide, superoxide anion, total ROS, and 4-hydroxynonenal protein adducts both in human/mouse primary cells and systemic compartment, in parallel with a reduction of the main antioxidant defence systems) [13,67,71–73] and mitochondrial dysfunctions (like a deregulated energetic profile and mitochondrial quality control system, characterized by an almost complete absence of Parkin and an impaired Pink1/Parkin-mediated mitophagy; an atypical structure of lymphomonocyte mitochondria; an altered gene expression of factors related to oxidative phosphorylation) [10,13,74,75]. Increasing evidence elucidated the broad roles played by mitochondria in innate immune responses against pathogens, like their functioning as signal transduction platforms, providing energy and metabolites for inflammation, and generating ROS as modulators of immune response. On the other hand, mitochondrial-DAMPs (mtDAMPs), such as excessive ROS production, cardiolipin/mtDNA release, and/or mitochondrial damage, may drive hyperactivation of innate immunity in absence of microorganisms' infection (*i.e.*, sterile inflammation), and play a key role upstream of NLRP3 inflammasome activation [76]. However, a mechanistic connection between the aberrant NLRP3 inflammasome response and ROS over-production/mitochondrial dysfunctions in RTT, with a specific focus on which ROS/mitochondrial elements are mainly implicated, has still to be elucidated.

NF-κB signalling cascade was also investigated in previously published papers by our group and others [35,68,77,78]. A proteomic analysis on RTT primary fibroblasts revealed that most of the RTT unique proteins, out of 2000 identified proteins, were enriched in immune function and inflammatory responses, showing also a positive regulation of NF-κB activity [35]. A deregulation of this transcription factor and its downstream protein interleukin-1 receptor-associated kinase 1 (IRAK1) was described to contribute to the decrease of dendritic complexity in cortices and purified cortical callosal projection neurons derived from *Mecp2*-null mice [78]. In addition, the inhibition of RelA pathway by direct (*i.e.*, knock-out mouse and cellular models) and indirect (*e.g.*, vitamin D supplementation; glycogen synthase kinase-3b (Gsk3b) inhibition; IRAK1 inhibition through Pacritinib; induction of NRF2 nuclear translocation, by dimethyl fumarate) mechanisms resulted in rescuing neuronal dendritic arborization, alleviating the clinical symptoms and improving lifespan of *Mecp2*-null mice, reducing several inflammatory cytokines in *Mecp2*-KO cerebellum, and up-regulating brain-derived neurotrophic factor (BDNF) expression in *Mecp2*-silenced microglial cells [78–81]. Hence, the roles played by NF-κB pathway seem to be crucial for RTT neuro- and peripheral inflammation, as well as overall pathogenesis.

Besides the augmented expression of TLR4 onto cell membranes of RTT PBMCs (likely due increase ROS generation and IL-18 systemic levels) [82,83], the expression of another receptor upstream of NLRP3 inflammasome trigger was found to be deregulated. P2X7 receptor (P2X7R) is a ligand-gated non-selective channel, activated by extracellular ATP and largely expressed in immune cells of myeloid lineage. Garré *et al.* demonstrated that *Mecp2* loss induced an accumulation of monocytes and macrophages expressing P2X7R specifically in the border of mouse cerebral cortex. In addition, P2X7R knock out in *Mecp2*$^{308/Y}$ mice diminished cortical inflammation and dendritic spine loss, and ameliorated social behavioural deficits. Interestingly, both the transplantation of *P2x7r*$^{-/-}$ peripheral leukocytes into WT mice and the pharmacological blocking of P2X7R (by using Brilliant Blue G molecule) principally in peripheral tissues has been showed to partially recapitulate the beneficial effects of total P2X7R knock out [84]. Hence, these findings elucidate the contribution of non-microglial cells and P2X7 receptor to CNS deficits in RTT.

About the inflammasome-related inflammatory molecules, our group found high levels of IL-18 and IL-1β cytokines, together with 'ASC specks' (which are the catalytically active oligomeric form of the adaptor, able to be internalized by bystander cells, escape from endosomes and propagate inflammasome activation in the recipient cells) in the systemic compartment of RTT patients [66,67]. Intriguingly, plasma IL-18 levels were augmented mostly in the first stages of the syndrome, where the most severe modifications, in terms of clinical manifestations onset and deterioration, commonly arise [67]. The enhanced systemic levels of IL-1β in RTT girls were positively correlated with the severity of MeCP2 mutations, whereas the augmented salivary levels of this cytokine showed a strong association with clinical severity scores of the enrolled patients [42,67]. Noteworthy, Tomasoni and colleagues reported that this cytokine plays a role also on neuronal plasticity, by following a U-shaped dose–response curve, where excessive or very low levels of IL-1β can be deleterious to neuronal functions [85], thus suggesting that further cognitive deteriorations may derive from the hyperactivation of the IL-1 signalling pathway and related enhanced inflammation.

Taken together, despite further *in vitro* and pre-clinical insights implying the use of NLRP3 inflammasome inhibitors are still needed, data on inflammasome-related dysregulations (Table 1) seem to indicate an involvement of this machinery in subclinical inflammatory condition, as well as pathogenesis and progression of RTT.

4.2. Presence of autoimmunity-related responses

An abnormal response of the adaptive immune system towards self-antigen recognition (which is the definition of autoimmunity) leads to multiple clinical manifestations, which are often debilitating and significantly affect patients quality of life [86]. Hence, subclinical inflammation and the presence of an autoimmune condition seem to be distinct concepts. Nevertheless, they can overlap in certain circumstances: indeed, as recently reviewed by Xiang *et al.* [87], chronic inflammation may contribute to the development of autoimmune diseases by promoting immune dysregulation and tissue damages. For example, the cytokine IL-1β can affect both innate and adaptive immune responses: on one hand, as already mentioned in the section 'Dysregulation of inflammasome response', an excess of this pro-inflammatory cytokine can cause innate immune abnormalities and contribute to persistent subclinical inflammation, whereas on the other hand, IL-1β may induce an augmented proliferation of lymphoid T and B cells, potentially enhancing the adaptive immunity. If this cascade of events is excessive or dysregulated, it may result in the onset of autoimmune disorders [87].

In this context, a possible role played by autoimmunity in RTT was first hypothesized about twenty years ago, where two different research groups found increased levels of brain-directed autoantibodies (AAB) against the neurotrophin nerve growth factor (NGF), as well as AAB against folate receptor (FR) in serum of RTT patients [88,89]. In particular, the levels of anti-NGF AAB were not dependent on the stage of the disease, whereas interestingly they were negatively correlated with the severity of the pathology (*i.e.*, girls with a more severe RTT phenotype exhibited lower levels of anti-NGF AAB). About this latter,

Table 1
Deregulated NLRP3 inflammasome components and responses in Rett syndrome subjects and human/animal-derived models.

	Sample type/experimental model	Ref
Dysregulated priming step/upstream pathways of NLRP3 inflammasome in RTT cells/tissue		
↑ nuclear NF-κB p65 levels and signalling	Human primary fibroblasts Human primary PBMCs *MECP2*-silenced PBMCs *MECP2*-silenced THP-1 cells	[35,66–68,78–81]
↑ TLR4 protein levels	Human primary PBMCs	[67]
↑ IRAK1 protein levels	Human primary PBMCs Cortex and neurons from *Mecp2*-null mice *MECP2*-silenced human microglial and neural stem cells	[67,78,81]
↑ P2X7 receptor	Cerebral cortex from *Mecp2*-null mice	[84]
↑ *IL-1b* mRNA	Human primary fibroblasts	[66]
↑ *IL*-18 mRNA	Human primary PBMCs *MECP2*-silenced THP-1 cells	[67]
↑ *ASC* mRNA	*MECP2*-silenced THP-1 cells	[67]
= *NLRP3* mRNA	Human primary PBMCs	[67]
Aberrant activation of NLRP3 inflammasome system in RTT cells		
↑ NLRP3 protein levels	Human primary fibroblasts Human primary PBMCs	[66,67]
↑ ASC protein levels	Human primary fibroblasts Human primary PBMCs *MECP2*-silenced THP-1 cells	[66,67]
↑ NLRP3:ASC co-localization	Human primary fibroblast Human primary PBMCs	[66,67]
↓ pro-CASP1 protein levels	Human primary fibroblasts	[66]
↑ CASP1 p20 protein levels	Human primary PBMCs	[67]
↑ $GSDMD^{N\text{-}term}/GSDMD^{FL}$ ratio	Human primary PBMCs	[67]
Systemic/peripheral inflammasome-dependent alterations in RTT		
↑ levels of ASC monomers and oligomers	Serum of RTT patients	[66]
↑ IL-1β levels	Plasma/saliva of RTT patients	[42,67]
↑ IL-18 levels	Serum/Plasma of RTT patients	[66,67]

Legend: RTT, Rett syndrome; MeCP2, methyl-CpG binding protein 2; NLRP3, nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; NF-κB, nuclear factor kappa B; PBMCs, peripheral blood mononuclear cells; TLR4, Toll-like receptor 4; IRAK1, interleukin 1 receptor associated kinase 1; *IL-1b*/IL-1β, interleukin-1β; IL-18, interleukin-18; ASC, apoptosis-associated speck-like protein containing a CARD domain; CASP1, caspase-1; $GSDMD^{N\text{-}term}$, N-terminus of gasdermin D; $GSDMD^{FL}$, full length-gasdermin D.

the authors speculated that in these RTT patients, a more active binding of anti-NGF AAB into immune complexes may occur, thus likely resulting in a serious autoimmune damage of brain structures. The reduction of NGF (mainly due to AAB reaction) may significantly impair the CNS development and preservation of nerve cells [88]. The other work reported low concentrations of 5-methyltetrahydrofolate (5MTHF) in the cerebrospinal fluid of RTT patients from North-Western Europe, that could be explained by the presence of serum anti-FR AAB (found in 24 % of the RTT examined population) [89]. Systemic anti-FR AAB can be also associated with the infantile-onset cerebral folate deficiency (CFD) syndrome, whose hallmarks may partially overlap with those of RTT (*e.g.*, irritability, sleep disturbances, psychomotor retardation).

In 2014, Papini and colleagues [90] found that RTT individuals presented high levels of IgM AAB against N-glycopeptide epitopes, as measured by an antibody recognition method based on a validated mimetic antigenic probe, termed CSF114(Glc), that has an N-glucosylation on its moiety [91], thus suggesting an alteration of protein N-glycosylation rate and a chronic activation of autoimmunity processes in the syndrome. The relevance of a deregulated N-glycosylation pattern in RTT pathogenesis was confirmed by a study on *Mecp2*-null mice, showing a reduced N-glycosylation of the N-linked brain nucleotide pyrophosphatase-5 (a protein involved in neuronal cell communication) in both pre-symptomatic and symptomatic mice. Importantly these N-glycosylation modifications were rescued by *Mecp2* reactivation [92].

Other literature papers described a connection between MeCP2 and autoimmunity or autoimmune disorders, like rheumatoid arthritis, systemic lupus erythematosus, and primary Sjögren's syndrome [38,93–97]. MeCP2 also exhibited a role in maintaining stable the expression of Foxp3, by binding the conserved non-coding sequence 2 region of the *foxp3* locus, and so the immunosuppressive activity of natural $CD4^+$ $CD25^+$ regulatory T cells (Tregs) during inflammatory processes. Foxp3, indeed, is a master regulator of Treg gene expression pattern, being responsible for immune homeostasis, peripheral tolerance, and prevention of autoimmunity [98]. Mice with Treg-specific *Mecp2* gene deletion showed diminished Foxp3 levels over time, resulting in increased IL-17 and interferon γ (IFN-γ) generation, colon leukocyte infiltration and tissue damages, as well as inability to prevent autoimmunity [98]. More recently, in order to better characterize the autoimmune response and concurrent neuroinflammatory condition, Zalosnik and co-workers used $Mecp2^{308/y}$ male mice, treated with myelin oligodendrocyte glycoprotein peptide ($MOG_{35–55}$), as a model of experimental autoimmune encephalomyelitis (EAE). As compared to WT-EAE mice, $Mecp2^{308/y}$ animals exhibited a persistent inflammatory response in CNS, with infiltration of immune cells and enhanced mRNA expression levels of *Tnf-a*, *Ifn-g*, and *Il-1b* in the spinal cord [99].

Taken together, despite not all studies were able to demonstrate the presence of AAB in RTT [100], these findings (summarized in Table 2) show that MeCP2 deficiency and RTT are associated with an increased vulnerability to develop autoimmune responses.

Table 2
Autoimmunity-related alterations in Rett syndrome individuals and animal models.

	Sample type/experimental model	Ref
Autoimmunity-related observations in RTT		
↑ levels of AAB against the neurotrophin NGF	Serum of RTT patients	[88]
↑ levels of AAB against folate receptor (found in 24 % of the RTT population)	Serum of RTT patients	[89]
↑ levels of IgM AAB against N-glycopeptide epitopes → leading to alteration of protein N-glycosylation rate	Plasma of RTT patients; *Mecp2*-null mice	[90,92]
= levels of AAB against thyroglobulin, thyroid peroxidase, and thyroid-stimulating hormone receptor	Serum of RTT patients	[100]
MeCP2 roles in autoimmune-related pathways/pathologies		
Mecp2 lack ↓ Foxp3 levels → ↑ IL-17 and IFN-γ levels, colon leukocyte infiltration, and failure in protecting against autoimmunity	Treg-specific *Mecp2*-deficient mice	[98]
Mecp2 deficiency ↑ autoreactive responses and susceptibility to develop EAE, ↑ immune cells infiltration and mRNA expression of *Tnf-a*, *Ifn-g*, and *Il-1b* in the spinal cord	$Mecp2^{308/y}$ male mice, treated with myelin oligodendrocyte glycoprotein peptide ($MOG_{35–55}$)	[99]
MECP2 gene polymorphism is associated to SLE, RA and Sjögren's syndrome	–	[93–97]

Legend: RTT, Rett syndrome; MeCP2, methyl-CpG binding protein 2; AAB, autoantibodies; NGF, nerve growth factor; Foxp3, Forkhead box P3; Treg, regulatory T cells; IL-17, interleukin 17; IFN-γ/*Ifn-g*, interferon γ; EAE, experimental autoimmune encephalomyelitis; *Tnf-a*, tumor necrosis factor-α; *Il-1b*, interleukin-1β; MOG, myelin oligodendrocyte glycoprotein; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

4.3. Alterations in gut microbiota

As already mentioned in section 2 'Inflammation-related clinical signs in Rett syndrome: a brief overview', GI dysfunctions accompany RTT subjects throughout their entire life [1]. The phenomenon of gut dysmotility noticed in RTT individuals may possibly arise from impairments in the enteric nervous system (ENS) due to MeCP2 lack [101]. Nonetheless, the causes of all GI dysfunctions are still not well clarified, and in recent years, the role played by gut microbiota in this scenario is attracting growing attention. Indeed, as known, gut microbiota is crucial in the integrity and functionality of the GI tract, in the maintenance of immune homeostasis and energy metabolism. In particular, modifications of commensal bacterial composition can lead to a chronic inflammation, which involves hyperactivation of T-helper 1 and 17 cell immune responses [102], thus also inducing subjects to be more prone to fungal infections [103]. Dysbiosis of gut microbiota is associated with a multitude of health conditions, including gastrointestinal pathologies, such as irritable bowel syndrome [104], and complex neurodegenerative and neurodevelopmental disorders, like autism spectrum disorders (ASD) [105–108]. Thus, the microbiota–gut–brain axis is becoming a central target to reduce or mitigate progression of these neurological diseases [109,110]. In light of this, several research studies have been conducted in both patients and animal models of RTT [111–116].

A work by Strati and colleagues (2016) reported increased values of faecal calprotectin and erythrocyte sedimentation rate (ESR) in RTT subjects, which were correlated to serum IgA titre, indicating an intestinal sub-inflammatory status [112]. A state of intestinal inflammation is also related to loss of intestinal barrier functionality in RTT, as reported above [21]. Elevated levels of IgA antibodies against gluten, gliadin, and casein in RTT subjects, suggestive of an increased gut permeability and protein uptake due to a damaged bowel epithelium, were first observed in 2006 [117]. RTT patients also exhibited a reduction in bacterial gut microbiota richness and diversity, as compared to healthy individuals, together with modified faecal short-chain fatty acid (SCFA) profiles, which are part of microbial metabolome, produced as fermentation byproducts from dietary components not properly absorbed/digested in the small intestine, and are important players for both colon health and neuronal physiology [112,118].

A following work by Borghi *et al.* [113] was partially in agreement with these findings; however, the authors detected enhanced levels of branched-chain fatty acids (BCFAs), like iso-butyrate and iso-valerate, and unchanged levels of SCFAs. The decrease in *Firmicutes* and the increase in *Bacteroidetes* in RTT microbial population is suggestive of a pro-inflammatory status of the gut microbiota [113]. Then, the reported microbiota dysbiosis was correlated to pubertal status (*i.e.*, bacterial diversity and richness decreased from pre- to post-puberty in RTT patients) and disease severity (*i.e.*, subjects with higher clinical severity score exhibited a reduced microbial diversity) [113,114]. These initial studies indicate that alterations in the gut microbiota and metabolome may underlie the intestinal dysfunctions typical of RTT patients.

However, to answer the question whether these changes of RTT subjects' microbiota are a consequence of their altered feeding behaviour/diet or important contributors to developmental regression, the researchers used animal models, since they allow the exclusion of the diet variable, and the manipulation of the microbiota [115,116]. *Mecp2*$^{ZFN/+}$ female rats showed modifications in the diversity, but not number, of the gut microbial populations, as compared to WT rats, starting at postnatal day (PND) 49 (after the appearance of the first social abnormalities, while before the peak of motor and metabolic symptoms), and persisting until PND196. Whereas no changes in SCFAs were reported between the RTT and control animals [115]. Another paper compared faecal microbiota and metabolome of male and female *Mecp2e1*-mutant mice, demonstrating that alterations of metabolites (SCFAs, like butyrate, isovalerate, and propionate) in the female model were evident before the onset of neuromotor signs (at 5 weeks of age), and highly correlated with lipid brain deficiencies, suggesting that a reduced lipid absorption in the GI tract may negatively influence brain lipid content in RTT. Intriguingly, these results were not noticed in male animals [116]. Furthermore, the alterations of gut microbial population and the inflammatory profile of female *Mecp2e1*-mutant mice were more reliable with those of RTT patients, than male mice [116]. Hence, these pre-clinical evidence support the hypothesis of the possible role of host-microbiota interactions in RTT inflammatory status and overall pathogenesis.

In parallel with the gut bacterial population dysbiosis, fungal opportunistic infections or impairments of mycobiota can often occur and are generally attributed to a defective host immunity. In this regard, studies on the gut mycobiota in RTT reported a distinct genotypic profile of *Candida parapsilosis* in girls with the disorder, as compared to control subjects, with the capacity to be more resistant to azole antifungals [112,119]. Moreover, PBMCs exposed to heat-killed RTT *C. parapsilosis* isolates showed a higher production of IL-1β and IL-10, suggesting an augmented fungal tolerance towards this strain, and the capacity of RTT *C. parapsilosis* to persist within the host, being likely involved in chronic inflammatory responses [119].

Taken together, dysbiotic intestinal microbiota and mycobiota contribute to RTT subclinical inflammation at gut, systemic and brain levels, being likely able to worsen several traits of the disorder (Fig. 1). Studies on the transplantation of faecal microbes from control donors to RTT models would be crucial to deepen the role of these gut microbial alterations in RTT pathogenesis and to individuate new therapeutic targets.

5. Anti-inflammatory therapies for Rett syndrome

Numerous possible treatments for RTT have been developed over the last few decades, thanks to research advances. Three broad categories encompass therapeutic options for RTT: 1) pharmacological compounds targeting downstream MeCP2 pathways, 2) symptom management, and 3) genetic approaches [120]. In regard to the second group, several anti-inflammatory options (with a direct or indirect action) are being evaluated both in pre-clinical studies and clinical trials.

Trofinetide is the first US FDA-approved treatment for RTT, and consists of the N-terminal tripeptide product of the cleavage of insulin-like growth factor 1 (IGF-1) in the brain. This molecule is able to improve synaptic functions and structure, decrease the effects of pro-inflammatory cytokines in the brain, augment antioxidant response and IGF-1 concentration in CNS, thus resulting in improvements of locomotor function, breathing, and lifespan of *Mecp2*-null mice [121–124]. Another compound in phase I/II clinical trial seems to show anti-inflammatory properties: although the results are still unavailable, NTI164, composed by cannabidiolic acid (CBDA) and other rarer cannabinoids, has been proposed as a powerful neuro-anti-inflammatory modulator, likely able to reduce various inflammatory cytokines, and improve neuronal health.

Different pre-clinical studies on animal models focused on the validation of new therapeutic targets and alternatives for RTT neuroinflammation. One of the first paper by Derecki and colleagues, showed that WT *Mecp2*-expressing microglia obtained through the transplantation of WT bone marrow in male *Mecp2*-null mice could reverse several signs of the pathology, including normalization of breathing patterns and decreased apneas, as well as increased lifespan, locomotor activity and body weight [125]. On this basis other authors investigated possible therapeutic approaches targeting microglia/glia. For example, the treatment of 6-month-old female *Mecp2*-heterozygous (Het) mice with N-acetyl cysteine conjugated to dendrimer (D-NAC) was able to significantly reduce microglial pro-inflammatory cytokine generation (*e.g.*, IL-1β and TNF-α) and improve the phenotype, like fear memory, epileptiform activity burden, mobility, and REM, as compared to saline-treated group [126]. Another molecule termed leriglitazone, a peroxisome proliferator-activated receptor (PPAR) γ agonist, was administered to *Mecp2*-Het mice (75 mg/kg/day orally delivered with

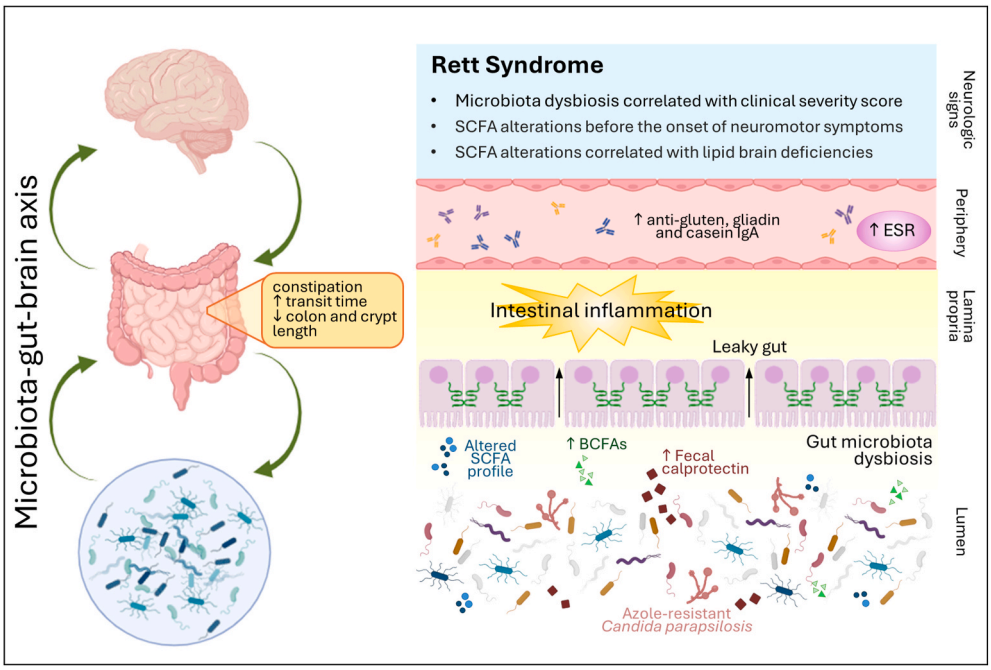

Fig. 1. Schematic representation of gut micro/mycobiota alterations in Rett syndrome, as evidenced from human and animal studies.
Dysbiotic gut microbiota, impaired fermentation by-product profile, together with increased intestinal permeability and dysmotility can contribute to the subclinical inflammation observed in Rett syndrome, at gut, systemic and brain levels. The affected microbiota-gut-brain axis seem to be involved in worsening several traits of the disorder.
SCFA, short-chain fatty acid; BCFA, branched-chain fatty acids; ESR, erythrocyte sedimentation rate.

the food from weaning until sacrifice at 7 months of age) in order to study the modulation of mitochondrial performance and the effect on neuroinflammation [127]. Leriglitazone, besides ameliorating the bioenergetic profile and the mice exploratory activity, exhibited an anti-inflammatory effect in cortices of RTT mice, by NF-κB modulation and subsequent reduction of IL-1α, IL-6, IL-10, IL-23, IFN-β, IL-17A, and TNF-α, as well as the decrease of Iba-1 and GFAP levels (markers of activated microglia and astrocytes, respectively), thus proposing this compound as a potential treatment for RTT clinical studies [127].

Lastly, as already discussed, a dysbiotic gut microbiota may be a potential contributor to RTT manifestations and chronic subclinical inflammation, so a likely target for new therapies. In addition to treating gastrointestinal problems, strategies aimed at re-establishing a healthy gut microbiota, through supplementation with pre- or probiotic, may be a non-pharmacological approach also for the behavioural and neurophysiological abnormalities observed in RTT. In a randomized pilot study, the probiotic *L. plantarum* PS128 (or placebo) was administered for 16 weeks to RTT patients, and it seemed to enhance overall cognitive developmental level, and improve dystonia, as compared to the placebo group, hence paving the way for future research exploring the potential of probiotics as a complementary therapy for RTT individuals [128].

6. Conclusions and future directions

In conclusion, this review has shown the latest works on new emerging players in the subclinical inflammatory state characterizing RTT, which was first reported ten years ago. From the current available knowledge on the altered pro-inflammatory cytokine profile, as well as the recent findings on inflammasome dysregulation, presence of autoimmunity-related responses and modifications of intestinal microbiota, it is clear that RTT clinical manifestations are strictly related to this persistent low-grade inflammatory state, which in turn contribute to the pathogenesis of this disorder. These alterations are only in part dependent on *MECP2* gene loss-of-function mutations. Therefore, future challenges for the treatment of RTT symptoms could be represented by the development of new therapeutic strategies able to restore an adequate immune/inflammatory response.

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Declaration of competing interest

The author declares that she has no conflicts of interest.

Data availability

Data will be made available on request.

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References

[1] E. Borloz, L. Villard, J.-C. Roux, Rett syndrome: think outside the (skull) box, Fac Rev 10 (2021) 59, insights.
[2] W.A. Gold, R. Krishnarajy, C. Ellaway, J. Christodoulou, Rett syndrome: a genetic update and clinical review focusing on comorbidities, ACS Chem. Neurosci. 9 (2018) 167–176, https://doi.org/10.1021/acschemneuro.7b00346.
[3] J. Wang, Y. Xiao, C. Liu, Y. Huang, R.B. Petersen, L. Zheng, K. Huang, Emerging physiological and pathological roles of MeCP2 in non-neurological systems, Arch. Biochem. Biophys. 700 (2021) 108768, https://doi.org/10.1016/j.abb.2021.108768.
[4] C.L. Laurvick, N. de Klerk, C. Bower, J. Christodoulou, D. Ravine, C. Ellaway, S. Williamson, H. Leonard, Rett syndrome in Australia: a review of the

epidemiology, J. Pediatr. 148 (2006) 347–352, https://doi.org/10.1016/j.jpeds.2005.10.037.
[5] U. Petriti, D.C. Dudman, E. Scosyrev, S. Lopez-Leon, Global prevalence of Rett syndrome: systematic review and meta-analysis, Syst. Rev. 12 (2023) 5, https://doi.org/10.1186/s13643-023-02169-6.
[6] M. Chahrour, H.Y. Zoghbi, The story of Rett syndrome: from clinic to neurobiology, Neuron 56 (2007) 422–437, https://doi.org/10.1016/j.neuron.2007.10.001.
[7] C. Fu, D. Armstrong, E. Marsh, D. Lieberman, K. Motil, R. Witt, S. Standridge, J. Lane, T. Dinkel, M. Jones, K. Hale, B. Suter, D. Glaze, J. Neul, A. Percy, T. Benke, Multisystem comorbidities in classic Rett syndrome: a scoping review, BMJ Paediatr Open 4 (2020), https://doi.org/10.1136/bmjpo-2020-000731.
[8] P.D. Ross, J. Guy, J. Selfridge, B. Kamal, N. Bahey, K.E. Tanner, T.H. Gillingwater, R.A. Jones, C.M. Loughrey, C.S. McCarroll, M.E.S. Bailey, A. Bird, S. Cobb, Exclusive expression of MeCP2 in the nervous system distinguishes between brain and peripheral Rett syndrome-like phenotypes, Hum. Mol. Genet. 25 (2016) 4389–4404, https://doi.org/10.1093/hmg/ddw269.
[9] A. Pecorelli, C. Cervellati, J. Hayek, G. Valacchi, OxInflammation in rett syndrome, Int. J. Biochem. Cell Biol. 81 (2016) 246–253, https://doi.org/10.1016/j.biocel.2016.07.015.
[10] I. Crivellari, A. Pecorelli, V. Cordone, S. Marchi, P. Pinton, J. Hayek, C. Cervellati, G. Valacchi, Impaired mitochondrial quality control in Rett Syndrome, Arch. Biochem. Biophys. 700 (2021) 108790, https://doi.org/10.1016/j.abb.2021.108790.
[11] A. Cortelazzo, C. De Felice, R. Guerranti, C. Signorini, S. Leoncini, A. Pecorelli, G. Zollo, C. Landi, G. Valacchi, L. Ciccoli, L. Bini, J. Hayek, Subclinical inflammatory status in Rett syndrome, Mediators Inflamm 2014 (2014) 480980, https://doi.org/10.1155/2014/480980.
[12] M. Segatto, L. Trapani, I. Di Tunno, C. Sticozzi, G. Valacchi, J. Hayek, V. Pallottini, Cholesterol metabolism is altered in Rett syndrome: a study on plasma and primary cultured fibroblasts derived from patients, PLoS One 9 (2014) e104834, https://doi.org/10.1371/journal.pone.0104834.
[13] C. Cervellati, C. Sticozzi, A. Romani, G. Belmonte, D. De Rasmo, A. Signorile, F. Cervellati, C. Milanese, P.G. Mastroberardino, A. Pecorelli, V. Savelli, H. J. Forman, J. Hayek, G. Valacchi, Impaired enzymatic defensive activity, mitochondrial dysfunction and proteasome activation are involved in RTT cell oxidative damage, Biochim. Biophys. Acta 1852 (2015) 2066–2074, https://doi.org/10.1016/j.bbadis.2015.07.014.
[14] A.M. Kerr, A review of the respiratory disorder in the Rett syndrome, Brain Dev. 14 (Suppl) (1992) S43–S45.
[15] D.M. Katz, M. Dutschmann, J.-M. Ramirez, G. Hilaire, Breathing disorders in rett syndrome: Progressive Neurochemical dysfunction in the respiratory network after birth, Respir. Physiol. Neurobiol. 168 (2009) 101–108, https://doi.org/10.1016/j.resp.2009.04.017.
[16] H. Kida, T. Takahashi, Y. Nakamura, T. Kinoshita, M. Hara, M. Okamoto, S. Okayama, K. Nakamura, K.-I. Kosai, T. Taniwaki, Y. Yamashita, T. Matsuishi, Pathogenesis of Lethal aspiration Pneumonia in mecp2-null mouse model for rett syndrome, Sci. Rep. 7 (2017) 12032, https://doi.org/10.1038/s41598-017-12293-8.
[17] C. De Felice, G. Guazzi, M. Rossi, L. Ciccoli, C. Signorini, S. Leoncini, G. Tonni, G. Latini, G. Valacchi, J. Hayek, Unrecognized lung disease in classic rett syndrome: a physiologic and high-resolution ct imaging study, Chest 138 (2010) 386–392, https://doi.org/10.1378/chest.09-3021.
[18] C. De Felice, M. Rossi, S. Leoncini, G. Chisci, C. Signorini, G. Lonetti, L. Vannuccini, D. Spina, A. Ginori, I. Iacona, A. Cortelazzo, A. Pecorelli, G. Valacchi, L. Ciccoli, T. Pizzorusso, J. Hayek, Inflammatory lung disease in rett syndrome, Mediat. Inflamm. 2014 (2014) e560120, https://doi.org/10.1155/2014/560120.
[19] J.-M. Ramirez, M. Karlen-Amarante, J.-D.J. Wang, N.E. Bush, M.S. Carroll, D. E. Weese-Mayer, A. Huff, The pathophysiology of rett syndrome with a focus on breathing dysfunctions, Physiology 35 (2020) 375–390, https://doi.org/10.1152/physiol.00008.2020.
[20] K.J. Motil, E. Caeg, J.O. Barrish, S. Geerts, J.B. Lane, A.K. Percy, F. Annese, L. McNair, S.A. Skinner, H.-S. Lee, J.L. Neul, D.G. Glaze, Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome, J. Pediatr. Gastroenterol. Nutr. 55 (2012) 292–298, https://doi.org/10.1097/MPG.0b013e31824b6159.
[21] P. Millar-Büchner, A.R. Philp, N. Gutierrez, S. Villanueva, B. Kerr, C.A. Flores, Severe changes in colon epithelium in the Mecp2-null mouse model of Rett syndrome, Mol Cell Pediatr 3 (2016) 37, https://doi.org/10.1186/s40348-016-0065-3.
[22] C.H.L. Dinh, Y. Yu, A. Szabo, Q. Zhang, P. Zhang, X.-F. Huang, Bardoxolone methyl prevents high-fat diet-induced colon inflammation in mice, J. Histochem. Cytochem. 64 (2016) 237–255, https://doi.org/10.1369/0022155416631803.
[23] C.M. Buchovecky, S.D. Turley, H.M. Brown, S.M. Kyle, J.G. McDonald, B. Liu, A. A. Pieper, W. Huang, D.M. Katz, D.W. Russell, J. Shendure, M.J. Justice, A suppressor screen in Mecp2 mutant mice implicates cholesterol metabolism in Rett syndrome, Nat. Genet. 45 (2013) 1013–1020, https://doi.org/10.1038/ng.2714.
[24] M. Freilinger, M. Böhm, I. Lanator, K. Vergesslich-Rothschild, W.-D. Huber, A. Anderson, K. Wong, G. Baikie, M. Ravikumara, J. Downs, H. Leonard, Prevalence, clinical investigation, and management of gallbladder disease in Rett syndrome, Dev. Med. Child Neurol. 56 (2014) 756–762, https://doi.org/10.1111/dmcn.12358.
[25] K.J. Motil, J.B. Lane, J.O. Barrish, F. Annese, S. Geerts, L. McNair, S.A. Skinner, J. L. Neul, D.G. Glaze, A.K. Percy, Biliary tract disease in girls and young women with rett syndrome, J. Pediatr. Gastroenterol. Nutr. 68 (2019) 799–805, https://doi.org/10.1097/MPG.0000000000002273.
[26] C.S. Ward, T.-W. Huang, J.A. Herrera, R.C. Samaco, M.R. Pitcher, A. Herron, S. A. Skinner, W.E. Kaufmann, D.G. Glaze, A.K. Percy, J.L. Neul, Loss of MeCP2 causes urological dysfunction and contributes to death by kidney failure in mouse models of rett syndrome, PLoS One 11 (2016) e0165550, https://doi.org/10.1371/journal.pone.0165550.
[27] J. Wang, M. Xiong, Y. Fan, C. Liu, Q. Wang, D. Yang, Y. Yuan, Y. Huang, S. Wang, Y. Zhang, S. Niu, J. Yue, H. Su, C. Zhang, H. Chen, L. Zheng, K. Huang, Mecp2 protects kidney from ischemia-reperfusion injury through transcriptional repressing IL-6/STAT3 signaling, Theranostics 12 (2022) 3896–3910, https://doi.org/10.7150/thno.72515.
[28] T.S. Tang, T. Bieber, H.C. Williams, Are the concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis clinically useful? J. Allergy Clin. Immunol. 133 (2014) 1615–1625.e1, https://doi.org/10.1016/j.jaci.2013.12.1079.
[29] R. Pahwa, A. Goyal, I. Jialal, Chronic Inflammation, in: StatPearls, StatPearls Publishing, Treasure Island (FL), 2024. http://www.ncbi.nlm.nih.gov/books/NBK493173/. (Accessed 12 March 2024).
[30] D. Monti, R. Ostan, V. Borelli, G. Castellani, C. Franceschi, Inflammaging and human longevity in the omics era, Mech. Ageing Dev. 165 (2017) 129–138, https://doi.org/10.1016/j.mad.2016.12.008.
[31] L. Chen, H. Deng, H. Cui, J. Fang, Z. Zuo, J. Deng, Y. Li, X. Wang, L. Zhao, Inflammatory responses and inflammation-associated diseases in organs, Oncotarget 9 (2018) 7204, https://doi.org/10.18632/oncotarget.23208.
[32] J.C. Cronk, N.C. Derecki, V. Litvak, J. Kipnis, Unexpected cellular players in Rett syndrome pathology, Neurobiol. Dis. 92 (2016) 64–71, https://doi.org/10.1016/j.nbd.2015.05.005.
[33] N.C. Derecki, E. Privman, J. Kipnis, Rett syndrome and other autism spectrum disorders—brain diseases of immune malfunction? Mol Psychiatry 15 (2010) 355–363, https://doi.org/10.1038/mp.2010.21.
[34] A.K. Percy, Progress in Rett Syndrome: from discovery to clinical trials, Wien Med. Wochenschr. 166 (2016) 325–332, https://doi.org/10.1007/s10354-016-0491-9.
[35] V. Cicaloni, A. Pecorelli, V. Cordone, L. Tinti, M. Rossi, J. Hayek, L. Salvini, C. Tinti, G. Valacchi, A proteomics approach to further highlight the altered inflammatory condition in Rett syndrome, Arch. Biochem. Biophys. 696 (2020) 108660, https://doi.org/10.1016/j.abb.2020.108660.
[36] S. Leoncini, C. De Felice, C. Signorini, G. Zollo, A. Cortelazzo, T. Durand, J.-M. Galano, R. Guerranti, M. Rossi, L. Ciccoli, J. Hayek, Cytokine dysregulation in MECP2- and CDKL5-related Rett syndrome: relationships with aberrant redox homeostasis, inflammation, and ω-3 PUFAs, Oxid. Med. Cell. Longev. 2015 (2015) 421624, https://doi.org/10.1155/2015/421624.
[37] A. Pecorelli, F. Cervellati, G. Belmonte, G. Montagner, P. Waldon, J. Hayek, R. Gambari, G. Valacchi, Cytokines profile and peripheral blood mononuclear cells morphology in Rett and autistic patients, Cytokine 77 (2016) 180–188, https://doi.org/10.1016/j.cyto.2015.10.002.
[38] C. De Felice, S. Leoncini, C. Signorini, A. Cortelazzo, P. Rovero, T. Durand, L. Ciccoli, A.M. Papini, J. Hayek, Rett syndrome: an autoimmune disease? Autoimmun. Rev. 15 (2016) 411–416, https://doi.org/10.1016/j.autrev.2016.01.011.
[39] Y. Deng, Z. Wang, C. Chang, L. Lu, C.S. Lau, Q. Lu, Th9 cells and IL-9 in autoimmune disorders: pathogenesis and therapeutic potentials, Hum. Immunol. 78 (2017) 120–128, https://doi.org/10.1016/j.humimm.2016.12.010.
[40] J. Heiss, K. Grün, L. Tempel, M. Matasci, A. Schrepper, M. Schwarzer, R. Bauer, M. Förster, A. Berndt, C. Jung, P.C. Schulze, D. Neri, M. Franz, Targeted Interleukin-9 delivery in pulmonary hypertension: comparison of immunocytokine formats and effector cell study, Eur. J. Clin. Invest. 53 (2023) e13907, https://doi.org/10.1111/eci.13907.
[41] A. Pecorelli, C. Cervellati, V. Cordone, F. Amicarelli, J. Hayek, G. Valacchi, 13-HODE, 9-HODE and ALOX15 as potential players in Rett syndrome OxInflammation, Free Radic. Biol. Med. 134 (2019) 598–603, https://doi.org/10.1016/j.freeradbiomed.2019.02.007.
[42] B.J. Byiers, A.M. Merbler, C.C. Barney, K.A. Frenn, A. Panoskaltsis-Mortari, M. J. Ehrhardt, T.J. Feyma, A.A. Beisang, F. Symons, Evidence of altered salivary cytokine concentrations in Rett syndrome and associations with clinical severity, Brain, Behavior, & Immunity - Health 1 (2020) 100008, https://doi.org/10.1016/j.bbih.2019.100008.
[43] A. Cortelazzo, C. De Felice, B. De Filippis, L. Ricceri, G. Laviola, S. Leoncini, C. Signorini, M. Pescaglini, R. Guerranti, A.M. Timperio, L. Zolla, L. Ciccoli, J. Hayek, Persistent unresolved inflammation in the mecp2-308 female mutated mouse model of rett syndrome, Mediators Inflamm 2017 (2017) 9467819, https://doi.org/10.1155/2017/9467819.
[44] D. Zhao, R. Mokhtari, E. Pedrosa, R. Birnbaum, D. Zheng, H.M. Lachman, Transcriptome analysis of microglia in a mouse model of Rett syndrome: differential expression of genes associated with microglia/macrophage activation and cellular stress, Mol. Autism. 8 (2017) 17, https://doi.org/10.1186/s13229-017-0134-z.
[45] J.C. Cronk, N.C. Derecki, E. Ji, Y. Xu, A.E. Lampano, I. Smirnov, W. Baker, G. T. Norris, I. Marin, N. Coddington, Y. Wolf, S.D. Turner, A. Aderem, A. L. Klibanov, T.H. Harris, S. Jung, V. Litvak, J. Kipnis, Methyl-CpG binding protein 2 regulates microglia and macrophage gene expression in response to inflammatory stimuli, Immunity 42 (2015) 679–691, https://doi.org/10.1016/j.immuni.2015.03.013.

[46] D.P. Schafer, B. Stevens, Brains, blood, and guts: MeCP2 regulates microglia, monocytes, and peripheral macrophages, Immunity 42 (2015) 600–602, https://doi.org/10.1016/j.immuni.2015.04.002.
[47] D.P. Schafer, C.T. Heller, G. Gunner, M. Heller, C. Gordon, T. Hammond, Y. Wolf, S. Jung, B. Stevens, Microglia contribute to circuit defects in Mecp2 null mice independent of microglia-specific loss of Mecp2 expression, Elife 5 (2016) e15224, https://doi.org/10.7554/eLife.15224.
[48] Z. Cao, X. Min, X. Xie, M. Huang, Y. Liu, W. Sun, G. Xu, M. He, K. He, Y. Li, J. Yuan, RIPK1 activation in Mecp2-deficient microglia promotes inflammation and glutamate release in RTT, Proc Natl Acad Sci U S A 121 (2024) e2320383121, https://doi.org/10.1073/pnas.2320383121.
[49] N.L. Pacheco, M.R. Heaven, L.M. Holt, D.K. Crossman, K.J. Boggio, S.A. Shaffer, D.L. Flint, M.L. Olsen, RNA sequencing and proteomics approaches reveal novel deficits in the cortex of Mecp2-deficient mice, a model for Rett syndrome, Mol. Autism. 8 (2017) 56, https://doi.org/10.1186/s13229-017-0174-4.
[50] J. Sun, S. Osenberg, A. Irwin, L.-H. Ma, N. Lee, Y. Xiang, F. Li, Y.-W. Wan, I.-H. Park, M. Maletic-Savatic, N. Ballas, Mutations in the transcriptional regulator MeCP2 severely impact key cellular and molecular signatures of human astrocytes during maturation, Cell Rep. 42 (2023) 111942, https://doi.org/10.1016/j.celrep.2022.111942.
[51] Y. Ehinger, V. Matagne, V. Cunin, E. Borloz, M. Seve, S. Bourgoin-Voillard, A. Borges-Correia, L. Villard, J.-C. Roux, Analysis of astroglial secretomic profile in the mecp2-deficient male mouse model of rett syndrome, Int. J. Mol. Sci. 22 (2021) 4316, https://doi.org/10.3390/ijms22094316.
[52] D.T. Lioy, S.K. Garg, C.E. Monaghan, J. Raber, K.D. Foust, B.K. Kaspar, P. G. Hirrlinger, F. Kirchhoff, J.M. Bissonnette, N. Ballas, G. Mandel, A role for glia in the progression of Rett's syndrome, Nature 475 (2011) 497–500, https://doi.org/10.1038/nature10214.
[53] E. Albizzati, M. Breccia, E. Florio, C. Cabasino, F.M. Postogna, R. Grassi, E. Boda, C. Battaglia, C. De Palma, C. De Quattro, D. Pozzi, N. Landsberger, A. Frasca, Mecp2 knock-out astrocytes affect synaptogenesis by interleukin 6 dependent mechanisms, iScience 27 (2024) 109296, https://doi.org/10.1016/j.isci.2024.109296.
[54] H. Li, M. Hu, Z. Huang, Y. Wang, Y. Xu, J. Deng, M. Zhu, W. Feng, X. Xu, A single-cell atlas reveals the heterogeneity of meningeal immunity in a mouse model of Methyl CpG binding protein 2 deficiency, Front. Immunol. 13 (2022) 1056447, https://doi.org/10.3389/fimmu.2022.1056447.
[55] D.E. Place, T.-D. Kanneganti, Recent advances in inflammasome biology, Curr. Opin. Immunol. 50 (2018) 32–38, https://doi.org/10.1016/j.coi.2017.10.011.
[56] H.M. Hoffman, J.L. Mueller, D.H. Broide, A.A. Wanderer, R.D. Kolodner, Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome, Nat. Genet. 29 (2001) 301–305, https://doi.org/10.1038/ng756.
[57] D. Liu, X. Zeng, X. Li, C. Cui, R. Hou, Z. Guo, J.L. Mehta, X. Wang, Advances in the molecular mechanisms of NLRP3 inflammasome activators and inactivators, Biochem. Pharmacol. 175 (2020) 113863, https://doi.org/10.1016/j.bcp.2020.113863.
[58] Y. Qin, W. Zhao, Posttranslational modifications of NLRP3 and their regulatory roles in inflammasome activation, Eur. J. Immunol. 53 (2023) 2350382, https://doi.org/10.1002/eji.202350382.
[59] C. Li, H. Lin, H. He, M. Ma, W. Jiang, R. Zhou, Inhibition of the NLRP3 inflammasome activation by manoalide ameliorates experimental autoimmune encephalomyelitis pathogenesis, Front. Cell Dev. Biol. 10 (2022), https://doi.org/10.3389/fcell.2022.822236.
[60] M. Saresella, F. Piancone, I. Marventano, M. Zoppis, A. Hernis, M. Zanette, D. Trabattoni, M. Chiappedi, A. Ghezzo, M.P. Canevini, F. la Rosa, S. Esposito, M. Clerici, Multiple inflammasome complexes are activated in autistic spectrum disorders, Brain Behav. Immun. 57 (2016) 125–133, https://doi.org/10.1016/j.bbi.2016.03.009.
[61] M. Saresella, F. La Rosa, F. Piancone, M. Zoppis, I. Marventano, E. Calabrese, V. Rainone, R. Nemni, R. Mancuso, M. Clerici, The NLRP3 and NLRP1 inflammasomes are activated in Alzheimer's disease, Mol. Neurodegener. 11 (2016) 23, https://doi.org/10.1186/s13024-016-0088-1.
[62] M. Moossavi, N. Parsamanesh, A. Bahrami, S.L. Atkin, A. Sahebkar, Role of the NLRP3 inflammasome in cancer, Mol. Cancer 17 (2018) 158, https://doi.org/10.1186/s12943-018-0900-3.
[63] A. Sharma, J.S.Y. Choi, N. Stefanovic, A. Al-Sharea, D.S. Simpson, N. Mukhamedova, K. Jandeleit-Dahm, A.J. Murphy, D. Sviridov, J.E. Vince, R. H. Ritchie, J.B. de Haan, Specific NLRP3 inhibition protects against diabetes-associated atherosclerosis, Diabetes 70 (2020) 772–787, https://doi.org/10.2337/db20-0357.
[64] S.K. Banerjee, A. Chatterjee, S. Gupta, A. Nagar, Activation and regulation of NLRP3 by sterile and infectious insults, Front. Immunol. 13 (2022), https://doi.org/10.3389/fimmu.2022.896353.
[65] A. Vallese, V. Cordone, A. Pecorelli, G. Valacchi, Ox-inflammasome involvement in neuroinflammation, Free Radic. Biol. Med. 207 (2023) 161–177, https://doi.org/10.1016/j.freeradbiomed.2023.07.010.
[66] A. Pecorelli, V. Cordone, N. Messano, C. Zhang, S. Falone, F. Amicarelli, J. Hayek, G. Valacchi, Altered inflammasome machinery as a key player in the perpetuation of Rett syndrome OxInflammation, Redox Biol. 28 (2020) 101334, https://doi.org/10.1016/j.redox.2019.101334.
[67] V. Cordone, F. Ferrara, A. Pecorelli, A. Guiotto, A. Vitale, F. Amicarelli, C. Cervellati, J. Hayek, G. Valacchi, The constitutive activation of TLR4-IRAK1-NFκB axis is involved in the early NLRP3 inflammasome response in peripheral blood mononuclear cells of Rett syndrome patients, Free Radic. Biol. Med. 181 (2022) 1–13, https://doi.org/10.1016/j.freeradbiomed.2022.01.017.
[68] C.M. O'Driscoll, M.P. Lima, W.E. Kaufmann, J.P. Bressler, Methyl CpG binding protein 2 deficiency enhances expression of inflammatory cytokines by sustaining NF-κB signaling in myeloid derived cells, J. Neuroimmunol. 283 (2015) 23–29, https://doi.org/10.1016/j.jneuroim.2015.04.005.
[69] R.L. Collard, N.S. Harya, F.A. Monzon, C.E. Maier, D.S. O'Keefe, Methylation of the ASC gene promoter is associated with aggressive prostate cancer, Prostate 66 (2006) 687–695, https://doi.org/10.1002/pros.20371.
[70] R. Webb, J.D. Wren, M. Jeffries, J.A. Kelly, K.M. Kaufman, Y. Tang, M.B. Frank, J. Merrill, R.P. Kimberly, J.C. Edberg, R. Ramsey-Goldman, M. Petri, J. D. Reveille, G.S. Alarcón, L.M. Vilá, M.E. Alarcón-Riquelme, J.A. James, T. J. Vyse, K.L. Moser, P.M. Gaffney, G.S. Gilkeson, J.B. Harley, A.H. Sawalha, Variants within MECP2, a key transcription regulator, are associated with increased susceptibility to lupus and differential gene expression in patients with systemic lupus erythematosus, Arthritis Rheum. 60 (2009) 1076–1084, https://doi.org/10.1002/art.24360.
[71] K. Can, C. Menzfeld, L. Rinne, P. Rehling, S. Kügler, G. Golubiani, J. Dudek, M. Müller, Neuronal redox-imbalance in rett syndrome affects mitochondria as well as cytosol, and is accompanied by intensified mitochondrial O2 consumption and ROS release, Front. Physiol. 10 (2019). https://www.frontiersin.org/articles/10.3389/fphys.2019.00479. (Accessed 7 April 2023).
[72] K. Festerling, K. Can, S. Kügler, M. Müller, Overshooting subcellular redox-responses in rett-mouse Hippocampus during neurotransmitter stimulation, Cells 9 (2020) E2539, https://doi.org/10.3390/cells9122539.
[73] A. Pecorelli, L. Ciccoli, C. Signorini, S. Leoncini, A. Giardini, M. D'Esposito, S. Filosa, J. Hayek, C. De Felice, G. Valacchi, Increased levels of 4HNE-protein plasma adducts in Rett syndrome, Clin. Biochem. 44 (2011) 368–371, https://doi.org/10.1016/j.clinbiochem.2011.01.007.
[74] N. Shulyakova, A.C. Andreazza, L.R. Mills, J.H. Eubanks, Mitochondrial dysfunction in the pathogenesis of Rett syndrome: implications for mitochondria-targeted therapies, Front. Cell. Neurosci. 11 (2017) 58, https://doi.org/10.3389/fncel.2017.00058.
[75] M. Müller, K. Can, Aberrant redox homoeostasis and mitochondrial dysfunction in Rett syndrome, Biochem. Soc. Trans. 42 (2014) 959–964, https://doi.org/10.1042/BST20140071.
[76] S.E. Weinberg, L.A. Sena, N.S. Chandel, Mitochondria in the regulation of innate and adaptive immunity, Immunity 42 (2015) 406–417, https://doi.org/10.1016/j.immuni.2015.02.002.
[77] D. Colak, H. Al-Dhalaan, M. Nester, A. Albakheet, B. Al-Younes, Z. Al-Hassnan, M. Al-Dosari, A. Chedrawi, M. Al-Owain, N. Abudheim, L. Al-Alwan, A. Al-Odaib, P. Ozand, M.S. Inan, N. Kaya, Genomic and transcriptomic analyses distinguish classic Rett and Rett-like syndrome and reveals shared altered pathways, Genomics 97 (2011) 19–28, https://doi.org/10.1016/j.ygeno.2010.09.004.
[78] N. Kishi, J.L. MacDonald, J. Ye, B.J. Molyneaux, E. Azim, J.D. Macklis, Reduction of aberrant NF-κB signalling ameliorates Rett syndrome phenotypes in Mecp2-null mice, Nat. Commun. 7 (2016) 10520, https://doi.org/10.1038/ncomms10520.
[79] M.C. Ribeiro, S.M. Moore, N. Kishi, J.D. Macklis, J.L. MacDonald, Vitamin D supplementation rescues aberrant NF-κB pathway activation and partially ameliorates rett syndrome phenotypes in Mecp2 mutant mice, eNeuro, ENEURO 7 (2020) 167, https://doi.org/10.1523/ENEURO.0167-20.2020, 20.2020.
[80] O.C. Jorge-Torres, K. Szczesna, L. Roa, C. Casal, L. Gonzalez-Somermeyer, M. Soler, C.D. Velasco, P. Martínez-San Segundo, P. Petazzi, M.A. Sáez, R. Delgado-Morales, S. Fourcade, A. Pujol, D. Huertas, A. Llobet, S. Guil, M. Esteller, Inhibition of Gsk3b reduces Nfkb1 signaling and rescues synaptic activity to improve the rett syndrome phenotype in mecp2-knockout mice, Cell Rep. 23 (2018) 1665–1677, https://doi.org/10.1016/j.celrep.2018.04.010.
[81] I. Unterman, I. Bloch, S. Cazacu, G. Kazimirsky, B. Ben-Zeev, B.P. Berman, C. Brodie, Y. Tabach, Expanding the MECP2 network using comparative genomics reveals potential therapeutic targets for Rett syndrome, Elife 10 (2021) e67085, https://doi.org/10.7554/eLife.67085.
[82] L.A. Dias-Melicio, R.K. Fernandes, D.R. Rodrigues, M.A. Golim, A.M.V.C. Soares, Interleukin-18 increases TLR4 and mannose receptor expression and modulates cytokine production in human monocytes, Mediators Inflamm 2015 (2015) 236839, https://doi.org/10.1155/2015/236839.
[83] P.S. Tawadros, K.A. Powers, M. Ailenberg, S.E. Birch, J.C. Marshall, K. Szaszi, A. Kapus, O.D. Rotstein, Oxidative stress increases surface toll-like receptor 4 expression in murine macrophages via ceramide generation, Shock 44 (2015) 157–165, https://doi.org/10.1097/SHK.0000000000000392.
[84] J.M. Garré, H.M. Silva, J.J. Lafaille, G. Yang, P2X7 receptor inhibition ameliorates dendritic spine pathology and social behavioral deficits in Rett syndrome mice, Nat. Commun. 11 (2020) 1784, https://doi.org/10.1038/s41467-020-15590-5.
[85] R. Tomasoni, R. Morini, J.P. Lopez-Atalaya, I. Corradini, A. Canzi, M. Rasile, C. Mantovani, D. Pozzi, C. Garlanda, A. Mantovani, E. Menna, A. Barco, M. Matteoli, Lack of IL-1R8 in neurons causes hyperactivation of IL-1 receptor pathway and induces MECP2-dependent synaptic defects, Elife 6 (n.d.) e21735. https://doi.org/10.7554/eLife.21735.
[86] S. Kurup, A. Pozun, Biochemistry, Autoimmunity, in: StatPearls, StatPearls Publishing, Treasure Island (FL), 2024. http://www.ncbi.nlm.nih.gov/books/NBK576418/. (Accessed 27 March 2024).
[87] Y. Xiang, M. Zhang, D. Jiang, Q. Su, J. Shi, The role of inflammation in autoimmune disease: a therapeutic target, Front. Immunol. 14 (2023), https://doi.org/10.3389/fimmu.2023.1267091.
[88] T.P. Klushnik, V.V. Gratchev, P.V. Belichenko, Brain-directed autoantibodies levels in the serum of Rett syndrome patients, Brain and Development 23 (2001) S113–S117, https://doi.org/10.1016/S0387-7604(01)00353-9.

[89] V.T. Ramaekers, J.M. Sequeira, R. Artuch, N. Blau, T. Temudo, A. Ormazabal, M. Pineda, A. Aracil, F. Roelens, F. Laccone, E.V. Quadros, Folate receptor autoantibodies and spinal fluid 5-methyltetrahydrofolate deficiency in rett syndrome, Neuropediatrics 38 (2007) 179–183, https://doi.org/10.1055/s-2007-991148.

[90] A.M. Papini, F. Nuti, F. Real-Fernandez, G. Rossi, C. Tiberi, G. Sabatino, S. Pandey, S. Leoncini, C. Signorini, A. Pecorelli, R. Guerranti, S. Lavielle, L. Ciccoli, P. Rovero, C. De Felice, J. Hayek, Immune dysfunction in rett syndrome patients revealed by high levels of serum anti-N(glc) IgM antibody fraction, Journal of Immunology Research 2014 (2014) e260973, https://doi.org/10.1155/2014/260973.

[91] F. Real Fernández, M. Di Pisa, G. Rossi, N. Auberger, O. Lequin, M. Larregola, A. Benchohra, C. Mansuy, G. Chassaing, F. Lolli, J. Hayek, S. Lavielle, P. Rovero, J.-M. Mallet, A.M. Papini, Antibody Recognition in multiple sclerosis and rett syndrome using a collection of linear and cyclic N-glucosylated antigenic probes, Peptide Science 104 (2015) 560–576, https://doi.org/10.1002/bip.22677.

[92] A. Cortelazzo, C. De Felice, R. Guerranti, C. Signorini, S. Leoncini, A. Pecorelli, F. Scalabrì, M. Madonna, S. Filosa, C. Della Giovampaola, A. Capone, T. Durand, C. Mirasole, L. Zolla, G. Valacchi, L. Ciccoli, J. Guy, M. D'Esposito, J. Hayek, Abnormal N-glycosylation pattern for brain nucleotide pyrophosphatase-5 (NPP-5) in Mecp2-mutant murine models of Rett syndrome, Neurosci. Res. 105 (2016) 28–34, https://doi.org/10.1016/j.neures.2015.10.002.

[93] F.D. Carmona, M.C. Cénit, L.-M. Diaz-Gallo, J.C.A. Broen, C.P. Simeón, P. E. Carreira, J.-L. Callejas-Rubio, V. Fonollosa, F.J. López-Longo, M.A. González-Gay, N. Hunzelmann, G. Riemekasten, T. Witte, A. Kreuter, J.H.W. Distler, R. Madhok, P. Shiels, J.M. van Laar, A.J. Schuerwegh, M.C. Vonk, A.E. Voskuyl, C. Fonseca, C.P. Denton, A. Herrick, J. Worthington, F.C. Arnett, F.K. Tan, S. Assassi, T.R.D.J. Radstake, M.D. Mayes, J. Martín, S.S. Group, New insight on the Xq28 association with systemic sclerosis, Ann. Rheum. Dis. 72 (2013) 2032–2038, https://doi.org/10.1136/annrheumdis-2012-202742.

[94] J. Miralvès, E. Magdeleine, L. Kaddoum, H. Brun, S. Peries, E. Joly, High levels of MeCP2 depress MHC class I expression in neuronal cells, PLoS One 2 (2007) e1354, https://doi.org/10.1371/journal.pone.0001354.

[95] S.I. Tayel, N.M. Muharram, D.S. Fotoh, H.S. Elbarbary, H.I. Abd-Elhafiz, E.A. El-Masry, A.E. Taha, S.E. Soliman, Prognostic impact of genetic variants of MECP2 and TIRAP on clinical outcomes of systemic lupus erythematosus with and without nephritis, Biomolecules 11 (2021) 1378, https://doi.org/10.3390/biom11091378.

[96] B.L. Cobb, Y. Fei, R. Jonsson, A.I. Bolstad, J.G. Brun, M. Rischmueller, S.E. Lester, T. Witte, G. Illei, M. Brennan, S. Bowman, K.L. Moser, J.B. Harley, A.H. Sawalha, Genetic association between methyl-CpG binding protein 2 (MECP2) and primary Sjogren's syndrome, Ann. Rheum. Dis. 69 (2010) 1731–1732, https://doi.org/10.1136/ard.2009.122903.

[97] Z.-H. Sun, Y.-H. Liu, J. Liu, D.-D. Xu, X.-F. Li, X.-M. Meng, T.-T. Ma, C. Huang, J. Li, MeCP2 regulates PTCH1 expression through DNA methylation in rheumatoid arthritis, Inflammation 40 (2017) 1497–1508, https://doi.org/10.1007/s10753-017-0591-8.

[98] C. Li, S. Jiang, S.-Q. Liu, E. Lykken, L. Zhao, J. Sevilla, B. Zhu, Q.-J. Li, MeCP2 enforces Foxp3 expression to promote regulatory T cells' resilience to inflammation, Proc. Natl. Acad. Sci. USA 111 (2014) E2807–E2816, https://doi.org/10.1073/pnas.1401505111.

[99] M.I. Zalosnik, M.C. Fabio, M.L. Bertoldi, C.N. Castañares, A.L. Degano, MeCP2 deficiency exacerbates the neuroinflammatory setting and autoreactive response during an autoimmune challenge, Sci. Rep. 11 (2021) 10997, https://doi.org/10.1038/s41598-021-90517-8.

[100] S. Stagi, L. Cavalli, L. Congiu, M.F. Scusa, A. Ferlini, S. Bigoni, A. Benincasa, B. Rossi, G. Pini, Thyroid function in Rett syndrome, Horm. Res. Paediatr. 83 (2015) 118–125, https://doi.org/10.1159/000370066.

[101] G. Wahba, S.C. Schock, E. Claridge, M. Bettolli, D. Grynspan, P. Humphreys, W. A. Staines, MeCP2 in the enteric nervous system, Neuro Gastroenterol. Motil. 27 (2015) 1156–1161, https://doi.org/10.1111/nmo.12605.

[102] D. Zheng, T. Liwinski, E. Elinav, Interaction between microbiota and immunity in health and disease, Cell Res. 30 (2020) 492–506, https://doi.org/10.1038/s41422-020-0332-7.

[103] J. Yang, H. Yang, Y. Li, The triple interactions between gut microbiota, mycobiota and host immunity, Crit. Rev. Food Sci. Nutr. 63 (2023) 11604–11624, https://doi.org/10.1080/10408398.2022.2094888.

[104] J. Tap, M. Derrien, H. Törnblom, R. Brazeilles, S. Cools-Portier, J. Doré, S. Störsrud, B. Le Nevé, L. Öhman, M. Simrén, Identification of an intestinal microbiota signature associated with severity of irritable bowel syndrome, Gastroenterology 152 (2017) 111–123.e8, https://doi.org/10.1053/j.gastro.2016.09.049.

[105] Q. Li, J.-M. Zhou, The microbiota-gut-brain axis and its potential therapeutic role in autism spectrum disorder, Neuroscience 324 (2016) 131–139, https://doi.org/10.1016/j.neuroscience.2016.03.013.

[106] S. Grabrucker, M. Marizzoni, E. Silajdžić, N. Lopizzo, E. Mombelli, S. Nicolas, S. Dohm-Hansen, C. Scassellati, D.V. Moretti, M. Rosa, K. Hoffmann, J.F. Cryan, O.F. O'Leary, J.A. English, A. Lavelle, C. O'Neill, S. Thuret, A. Cattaneo, Y. M. Nolan, Microbiota from Alzheimer's patients induce deficits in cognition and hippocampal neurogenesis, Brain 146 (2023) 4916–4934, https://doi.org/10.1093/brain/awad303.

[107] Z. Li, H. Liang, Y. Hu, L. Lu, C. Zheng, Y. Fan, B. Wu, T. Zou, X. Luo, X. Zhang, Y. Zeng, Z. Liu, Z. Zhou, Z. Yue, Y. Ren, Z. Li, Q. Su, P. Xu, Gut bacterial profiles in Parkinson's disease: a systematic review, CNS Neurosci. Ther. 29 (2022) 140–157, https://doi.org/10.1111/cns.13990.

[108] J. Wu, Q. Hu, X. Rao, H. Zhao, H. Tang, Y. Wang, Gut microbiome and metabolic profiles of mouse model for MeCP2 duplication syndrome, Brain Res. Bull. 206 (2024) 110862, https://doi.org/10.1016/j.brainresbull.2023.110862.

[109] J.S. Loh, W.Q. Mak, L.K.S. Tan, C.X. Ng, H.H. Chan, S.H. Yeow, J.B. Foo, Y.S. Ong, C.W. How, K.Y. Khaw, Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases, Sig Transduct Target Ther 9 (2024) 1–53, https://doi.org/10.1038/s41392-024-01743-1.

[110] M.A. Taniya, H.-J. Chung, A. Al Mamun, S. Alam, M.A. Aziz, N.U. Emon, M. M. Islam, S.-T. shool Hong, B.R. Podder, A. Ara Mimi, S. Aktar Suchi, J. Xiao, Role of gut microbiome in autism spectrum disorder and its therapeutic regulation, Front. Cell. Infect. Microbiol. 12 (2022), https://doi.org/10.3389/fcimb.2022.915701.

[111] E. Borghi, A. Vignoli, Rett syndrome and other neurodevelopmental disorders share common changes in gut microbial community: a descriptive review, Int. J. Mol. Sci. 20 (2019), https://doi.org/10.3390/ijms20174160.

[112] F. Strati, D. Cavalieri, D. Albanese, C. De Felice, C. Donati, J. Hayek, O. Jousson, S. Leoncini, M. Pindo, D. Renzi, L. Rizzetto, I. Stefanini, A. Calabrò, C. De Filippo, Altered gut microbiota in Rett syndrome, Microbiome 4 (2016) 41, https://doi.org/10.1186/s40168-016-0185-y.

[113] E. Borghi, F. Borgo, M. Severgnini, M.N. Savini, M.C. Casiraghi, A. Vignoli, Rett syndrome: a focus on gut microbiota, Int. J. Mol. Sci. 18 (2017) 344, https://doi.org/10.3390/ijms18020344.

[114] S. Thapa, A. Venkatachalam, N. Khan, M. Naqvi, M. Balderas, J.K. Runge, A. Haag, K.M. Hoch, D.G. Glaze, R.A. Luna, K.J. Motil, Assessment of the gut bacterial microbiome and metabolome of girls and women with Rett Syndrome, PLoS One 16 (2021) e0251231, https://doi.org/10.1371/journal.pone.0251231.

[115] A. Gallucci, K.C. Patterson, A.R. Weit, W.J. Van Der Pol, L.G. Dubois, A.K. Percy, C.D. Morrow, S.L. Campbell, M.L. Olsen, Microbial community changes in a female rat model of Rett syndrome, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 109 (2021) 110259, https://doi.org/10.1016/j.pnpbp.2021.110259.

[116] K. Neier, T.E. Grant, R.L. Palmer, D. Chappell, S.M. Hakam, K.M. Yasui, M. Rolston, M.L. Settles, S.S. Hunter, A. Madany, P. Ashwood, B. Durbin-Johnson, J.M. LaSalle, D.H. Yasui, Sex disparate gut microbiome and metabolome perturbations precede disease progression in a mouse model of Rett syndrome, Commun. Biol. 4 (2021) 1–16, https://doi.org/10.1038/s42003-021-02915-3.

[117] K.L. Reichelt, O. Skjeldal, IgA antibodies in Rett syndrome, Autism 10 (2006) 189–197, https://doi.org/10.1177/1362361306062024.

[118] Y.P. Silva, A. Bernardi, R.L. Frozza, The role of short-chain fatty acids from gut microbiota in gut-brain communication, Front. Endocrinol. 11 (2020), https://doi.org/10.3389/fendo.2020.00025.

[119] F. Strati, A. Calabrò, C. Donati, C. De Felice, J. Hayek, O. Jousson, S. Leoncini, D. Renzi, L. Rizzetto, C. De Filippo, D. Cavalieri, Intestinal Candida parapsilosis isolates from Rett syndrome subjects bear potential virulent traits and capacity to persist within the host, BMC Gastroenterol. 18 (2018) 57, https://doi.org/10.1186/s12876-018-0785-z.

[120] A.J. Sandweiss, V.L. Brandt, H.Y. Zoghbi, Advances in understanding of Rett syndrome and *MECP2* duplication syndrome: prospects for future therapies, Lancet Neurol. 19 (2020) 689–698, https://doi.org/10.1016/S1474-4422(20)30217-9.

[121] D.G. Glaze, J.L. Neul, W.E. Kaufmann, E. Berry-Kravis, S. Condon, G. Stoms, S. Oosterholt, O. Della Pasqua, L. Glass, N.E. Jones, A.K. Percy, Rett 002 Study Group, Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome, Neurology 92 (2019) e1912–e1925, https://doi.org/10.1212/WNL.0000000000007316.

[122] S.A. Hudu, F. Elmigdadi, A.A. Qtaitat, M. Almehmadi, A.A. Alsaiari, M. Allahyani, A. Aljuaid, M. Salih, A. Alghamdi, M.A. AlrofaidiAbida, M. Imran, Trofinetide for rett syndrome: highlights on the development and related inventions of the first USFDA-approved treatment for rare pediatric unmet medical need, J. Clin. Med. 12 (2023) 5114, https://doi.org/10.3390/jcm12155114.

[123] H.H. Wei, X.-C.M. Lu, D.A. Shear, A. Waghray, C. Yao, F.C. Tortella, J.R. Dave, NNZ-2566 treatment inhibits neuroinflammation and pro-inflammatory cytokine expression induced by experimental penetrating ballistic-like brain injury in rats, J. Neuroinflammation 6 (2009) 19, https://doi.org/10.1186/1742-2094-6-19.

[124] D. Tropea, E. Giacometti, N.R. Wilson, C. Beard, C. McCurry, D.D. Fu, R. Flannery, R. Jaenisch, M. Sur, Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice, Proc. Natl. Acad. Sci. USA 106 (2009) 2029–2034, https://doi.org/10.1073/pnas.0812394106.

[125] N.C. Derecki, J.C. Cronk, Z. Lu, E. Xu, S.B.G. Abbott, P.G. Guyenet, J. Kipnis, Wild-type microglia arrest pathology in a mouse model of Rett syndrome, Nature 484 (2012) 105–109, https://doi.org/10.1038/nature10907.

[126] E.S. Khoury, R.V. Patel, C. O'Ferrall, A. Fowler, N. Sah, A. Sharma, S. Gupta, S. Scafidi, J.S. Kurtz, S.J. Olmstead, S.R. Kudchadkar, R.M. Kannan, M.E. Blue, S. Kannan, Dendrimer nanotherapy targeting of glial dysfunction improves inflammation and neurobehavioral phenotype in adult female Mecp2-heterozygous mouse model of Rett syndrome, Journal of Neurochemistry n/a (n. d.). https://doi.org/10.1111/jnc.15960.

[127] U. Musokhranova, C. Grau, C. Vergara, L. Rodríguez-Pascau, C. Xiol, A.A. Castells, S. Alcántara, P. Rodríguez-Pombo, P. Pizcueta, M. Martinell, A. García-Cazorla, A. Oyarzábal, Mitochondrial modulation with leriglitazone as a potential treatment for Rett syndrome, J. Transl. Med. 21 (2023) 756, https://doi.org/10.1186/s12967-023-04622-5.

[128] L.C. Wong, C.-J. Hsu, Y.-T. Wu, H.-F. Chu, J.-H. Lin, H.-P. Wang, S.-C. Hu, Y.-C. Tsai, W.-C. Tsai, W.-T. Lee, Investigating the impact of probiotic on neurological outcomes in Rett syndrome: a randomized, double-blind, and placebo-controlled pilot study, Autism (2024) 13623613231225899, https://doi.org/10.1177/13623613231225899.