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INPLASY

The Dual Role of mTOR in Multiple Sclerosis Pathophysiology: A Protocol for a Systematic Review.

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 May 2024 and was last updated on 1 June 2026.

INTRODUCTION

Review question / Objective The broad research question of this review is: "How is mTOR involved in the pathophysiology of Multiple Sclerosis?"

This broad research question is subdivided into multiple subquestions based on the main processes through which the mechanistic target of rapamycin (mTOR) affects Multiple Sclerosis (MS) pathology.

Sub-research questions:
In which manner does mTOR contribute to neuroinflammation in MS?
To what extent does mTOR influence the mechanism of action of T cells in MS?
How does mTOR influence growth factors that contribute to MS pathophysiology?
How is mTOR related to neurodegeneration in MS?
How is mTOR involved in oligodendrocyte development and myelination in MS?
How is mTOR involved in gliosis in MS?
How is mTOR involved in autophagy in MS?
How is mTOR involved in oxidative stress in MS?

Rationale The mTOR complex is a kinase that plays a key role in regulating important processes including cell proliferation, protein synthesis, autophagy, and transcription. Therefore, modulation of mTOR has been researched in relation to several different pathologies including Multiple Sclerosis (Vakrakou et al. 2022). However, a comprehensive evaluation of the influence of mTOR in MS, utilizing a combination of in vitro, in vivo, and clinical data, has yet to be conducted in existing literature. The utilization of in vitro, in vivo, and clinical studies allows the assessment of the consistency and translatability of the results. Both InPlasy and Prospero were searched for registered reviews about similar topics but none were found. Additionally, Google Scholar, PubMed, and Scopus were searched for systematic reviews with the same research question, and here also none were found.

Condition being studied This systematic review studies MS, a chronic autoimmune disorder affecting neuronal myelin sheaths (Vakrakou et al. 2022). This includes in vitro and in vivo models for

MS and studies performed in patients with either Relapsing-Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), or Primary Progressive MS (PPMS).

METHODS

Search strategy In this systematic review, the databases PubMed and Scopus are used to retrieve papers. The following search strategy was performed:

1. Data base: scopus
Search strategy: (synonyms of mTOR) AND (synonyms of MS) AND (synonyms of topic)
Fields searched: All search terms in article title, abstract or keywords
Limits: 2014 - 2025, document type: article

2. Data base: scopus
Search strategy: (synonyms of mTOR) AND (synonyms of MS) AND (synonyms of topic) AND (synonyms related to mTOR complex)
Fields searched: Synonyms of mTOR in all fields, all other search terms in article title, abstract or keywords
Limits: 2014 - 2025, document type: article

3. Data base PubMed:
Search strategy: (synonyms of mTOR) AND (synonyms of MS) AND (synonyms of topic)
Fields searched: All search terms in article title or abstract
Limits: 2014 - 2025, exclude reviews, systematic reviews and meta-analyses

4. Data base PubMed:
Search strategy: (synonyms of mTOR) AND (synonyms of MS) AND (synonyms of topic) AND synonyms related to mTOR complex)
Fields searched:
Synonyms of mTOR in all fields, all other search terms in article title or abstract
Limits: 2014 - 2025, exclude reviews, systematic reviews and meta-analyses

The following synonyms have been implemented:

Synonyms of mTOR: mTOR OR "Rapamycin target protein" OR "Mammalian Target of Rapamycin" OR MTORC1 OR MTORC2 OR FRAP OR FRAP1

Synonyms of MS: "Multiple sclerosis" OR "Sclerosis Multiplex" OR "Multiple cerebral sclerosis" OR "Multiple cerebro-spinal sclerosis" OR "Disseminated sclerosis" OR "Encephalomyelitis disseminata"

Synonyms of topic:
Autophagy: Autophagy OR Autophagosome OR Autophagic OR "Autophagic processes" OR Autolysis OR Autophagocytosis OR Self-degradation OR "Intracellular recycling"
Axonal and synaptic loss: "Axonal atrophy" OR axonopathy OR "axonal retraction" OR "axonal degeneration" OR "axonal toxicity" or "neurite retraction" OR "synaptic loss" OR synaptopathy OR "neurite retraction" OR "synaptic retraction" OR "synaptic degeneration" OR synaptotoxicity
BBB integrity: "BBB integrity" OR "blood brain barrier integrity" OR "BBB breakdown" OR "blood brain barrier breakdown" OR "BBB disruption" OR "blood brain barrier disruption" OR "pericyte dysfunction" OR "pericyte impairment" OR "BBB impairment" OR "blood brain barrier impairment"
B cells: "B cell" OR "B lymphocyte" OR "bone marrow derived lymphocyte" OR "B lymphocyte" OR "B-lymphoid cell" OR "B-lymphoblast" OR "B-lymphocytic cell" OR "CD19+ cell" OR "CD20+ cell" OR "CD22+ cell" OR "CD79a+ cell" OR "CD79b+ cell" OR "Breg" OR "B-leukocute" OR "B-immunocyte" OR "B-precursor cell"
Cell senescence: "Cell senescence" OR "replicative senescence" OR "cell cycle arrest" OR "growth arrest" OR "cellular aging"
Gliosis: Gliosis OR astrogliosis OR "reactive astrocytes" OR "reactive gliosis" OR "astrocyte activation" OR "glial scar formation" OR microgliosis OR "neuroglial activation"
Glucose metabolism: "Glucose metabolism" OR "Glucose homeostatis" OR "Glucose oxidation" OR "Glucose update" OR "Gluconeogenesis" OR "Carbohydrate metabolism" OR "Energy metabolism"
Growth factors: "Growth factor" OR "trophic factors" OR "neurothropic factors" OR "cytokines" OR "proliferation factors" OR "growth agent" OR "mitogen"
Iron accumulation: "Iron accumulation" OR "iron overload" OR "iron deposition" OR "iron build-up" OR "increased iron levels" OR "hemosiderosis" OR "ferroptosis" OR "NBIA" OR "neurodegeneration with brain iron accumulation"
Lipid synthesis: "Lipid synthesis" OR "Lipogenesis" OR "Lipid generation" OR "Fatty acid synthesis" OR "Triglyceride synthesis" OR "Cholesterol synthesis" OR "Lipid biosynthesis" OR "Lipid metabolism"
Mitochondrial dysfunction and oxidative stress: "Mitochondrial dysfunction" OR "mitochondrial biogenesis" OR "mitochondrial metabolism" OR "mitochondrial failure" OR "oxidative stress" OR "oxidative phosphorylation" OR "ROS production" OR "oxidative damage"
Myelination: Myelination OR Remyelination OR "Myelin repair" OR "Myelin regeneration" OR

"Myelin restoration" OR "Myelin sheath recovery" OR Demyelination
Neurodegeneration: "Neurodegeneration" OR "neuronal loss" OR "Neuronal Atrophy" OR "Neural atrophy" OR "Neuronal death" OR "neural death"OR "neural degeneration" OR "nerve degeneration" OR "neurological degeneration" OR "neural deterioration" OR "nerve deterioration" OR "neurological deterioration" OR "neural decay" OR "nerve cell degeneration"
Neuroinflammation: Neuroinflammation OR "Pro-inflammatory response" OR "Neuroimmune response" OR "Immunological response" OR Inflammation OR Neuroinflammatory OR Inflammatory OR "Perivenular inflammation" OR ''neuroimmunological response''
Oligodendrocytes: ''Oligodendrocyte'' OR "Oligodendroglia" OR "Oligodendroglia cell" OR "Oligodendroglial cell" OR "Oligodendroglia precursor" OR "Oligodendroglial precursor" OR "OPC" OR "OPCs" OR "neurogliacyte" OR "oligodendria"
T cells: "T cell" OR "T Lymphocyte" OR "Thymocyte" OR "T-lymphoid cell" OR "T-lymphoblast" OR "T-lymphocytic cell" OR "CD4+" OR "CD8+" OR "Regulatory T-cell" OR "T-regulatory cell" OR "Treg" OR "T-memory cell" OR "T-effector cell" OR "cytotoxic T-cell" OR "T-cytotoxic cell" OR "T helper cell" OR "T-helper lymphocyte" OR "T-suppressor cell" OR "T-killer cell"OR "T-immune cell" OR "T-immunocyte" OR "T-lymphs" OR "T-leukocyte" OR "T-lymphoid lineage" OR "T-cell Precursor" OR "T-lymphoid precursor" OR "T-lymphoblastoid cell" OR "T-lymphocytic precursor" OR "T-precursor cell" OR "T-lymphoblastic cell" OR "T-lymphoid progenitor" OR "T-lineage cell" OR "T-immunocompetent cell" OR "T-immunoreactive cell" OR "T-immunoprotective cell"

Synonyms related to mTOR complex: Rapamycin OR Sirolimus OR Rapamune OR AY22989 OR "AY 22989" OR Rapa OR FKBP38 OR FKBP38r OR mLST8 OR GBL OR LST8 OR POP3 OR WAT1 OR GbetaL OR PRAS40 OR CG10109 OR CG46146 OR Dmel/CG46146 OR dPRAS40 OR Deptor OR DEP.6 OR DEPDC6 OR hDEPTOR OR Raptor OR XPLN OR "Protor 2" OR "Protor 1" OR Rictor OR PIA OR AVO3 OR hAVO3 OR mSIN1 OR MIP1 OR SIN1 OR JC310 or SIN1b or SIN1g OR Deptor OR DEP6 OR DEPDC6 OR hDEPTOR OR FKBP12 OR Rheb OR Tuberin OR TSC1 OR TSC2 OR "tuberous sclerosis complex"

Participant or population In this systematic review, cellular models of MS, animal models of MS, and studies on patients with RRMS and SPMS will be included. Both the cellular and animal models have to be validated models to mimic MS pathology. Studies with patients diagnosed with Primary Progressive MS are excluded, due to the different nature of disease progression in this subtype of MS (Procaccini et al. 2015). There are no exclusion criteria concerning age or gender.

Intervention This systematic review does not study one specific intervention but includes all papers that research the role of mTOR in relation to neuroinflammation (including autophagy and T cells), growth factors, neurodegeneration, oligodendrocyte development, and myelination in in vivo and in vitro MS models and patients with MS.

Comparator Not applicable.

Study designs to be included In this systematic review, the following study designs published between 2014-2024 will be included: randomized controlled trials, observational study designs (cohort studies, case-control studies, cross-sectional studies), in vivo studies, and in vitro studies. These types of study designs will be included to get a full perspective on the topic. This review aims to provide a broad summary of relevant literature and compare the results between the different hierarchies of studies.

Eligibility criteria Studies to be included have to fit within the following eligibility criteria. The PICOS eligibility criteria are as follows:

Population: Patients with RRMS, Patients with SPMS, Patients with PPMS, validated in vivo MS models, and validated in vitro MS models.
Intervention: There is no specific intervention being studied. Studies looking at the influence of an intervention on mTOR expression and the pathology of MS will be included.
Comparison: There is no direct comparison between studied interventions.
Outcome: The main outcome used is the influence of mTOR on the pathophysiology of MS. This can be further defined as the influence of mTOR on neuroinflammation, myelination and mTOR-related autophagy through search terms related to autophagy, axonal and synaptic loss, blood-brain barrier (BBB) integrity, B cells, cell senescence, gliosis, glucose metabolism, growth factors, iron accumulation, lipid synthesis, mitochondrial dysfunction and oxidative stress, myelination, neurodegeneration, neuroinflammation, oligodendrocytes, and T cells.
Study designs: Randomized controlled trials, observational study designs (cohort studies, case-

control studies, cross-sectional studies), in vivo studies, and in vitro studies.

Additional inclusion and exclusion criteria outside of PICOS:
The PICOS eligibility criteria as described are applied for all papers, however, for the sub-research questions specific inclusion and exclusion criteria are defined as outlined in the section below.
A validated MS model is defined as a validated in vitro MS model and/or in vivo MS model and/or patient with RRMS and/or patient with SPMS and/or patient with PPMS

Research question: In which manner does mTOR contribute to neuroinflammation in MS?
Inclusion criteria:
Relates mTOR directly/indirectly to pro/anti-inflammatory factors that play a key role in a validated MS model
Exclusion criteria:
Does not directly/indirectly investigate the role of mTOR-mediated inflammatory factors in a validated MS model
Does not directly/indirectly link the role of pro/anti-inflammatory factors to mTOR in a validated MS model

Research question: What is the role of mTOR-mediated autophagy in MS pathophysiology?
Inclusion criteria:
A direct/indirect link between mTOR and autophagy in a validated MS model
A direct/indirect link between autophagy and subsequent mTOR modulation in a validated MS model
Exclusion criteria:
Does not relate mTOR-mediated autophagy to a validated MS model
No direct/indirect link between autophagy and at least one intermediate in the mTOR pathway

Research question: To what extent does mTOR influence the mechanism of action of T cells in MS?
Inclusion criteria:
Directly/indirectly describes the association of at least one type of T cell to mTOR in a validated MS model
Investigates proliferation markers of T cells in response to mTOR modulation in a validated MS model
Exclusion criteria:
Only investigates the association of innate immune cells to mTOR in a validated MS model
Does not directly/indirectly measure proliferation markers of T cells in response to mTOR modulation in a validated MS model
Only investigates the association of B cells to mTOR in a validated MS model

Research question: How does mTOR influence growth factors that contribute to MS pathophysiology?
Inclusion criteria:
Relates one or more growth factors directly/indirectly to both mTOR and a validated MS model
Describes disturbance of one or more growth factors directly/indirectly to both mTOR and a validated MS model
Exclusion criteria:
Does not directly/indirectly indicate the relationship between one or more growth factors and mTOR
Does not directly/indirectly indicate the relationship between one or more growth factors and a validated MS model

Research question: How is mTOR related to neurodegeneration in MS?
Inclusion criteria:
Relates mTOR directly to one or more neuronal/glial/astrocyte/synaptic/myelin degeneration pathways that play a key role in a validated MS model
Exclusion criteria:
Does not relate degeneration markers to mTOR in at least one cell type relevant to the pathology of MS, in a validated MS model.

Research question: How is mTOR involved in oligodendrocyte development and myelination in MS?
Inclusion criteria:
Study investigates the role of the mTOR pathway in at least 1 stage of the oligodendrocyte growth cycle
Investigates a direct/indirect link between mTOR and remyelination in at a validated MS model
Exclusion criteria:
Does not involve the mTOR pathway in the oligodendrocyte cell cycle

Research question: How is mTOR involved in oxidative stress in MS?
Inclusion criteria:
Study investigates the role of the mTOR pathway and oxidative stress in a validated MS model.
Exclusion criteria:
Does not involve the mTOR pathway and oxidative stress

Research question: How is mTOR involved in gliosis in MS?

Inclusion criteria:
Study investigates the role of the mTOR pathway gliosis in a validated MS model.
Exclusion criteria:
Does not involve the mTOR pathway and gliosis

Information sources Within this systematic review, the databases Scopus and PubMed will be used to retrieve papers. No additional databases or data sources will be used.

Main outcome(s) Within this review, the effect of mTOR on MS pathology will be assessed regarding neuroinflammation, myelination, and mTOR-related processes, using the search terms autophagy, axonal and synaptic loss, blood-brain barrier (BBB) integrity, B cells, cell senescence, gliosis, glucose metabolism, growth factors, iron accumulation, lipid synthesis, mitochondrial dysfunction and oxidative stress, myelination, neurodegeneration, neuroinflammation, oligodendrocytes, and T cells. Topics will be excluded if not enough paper fitting the inclusion criteria are available.

A validated MS model is defined as a validated in vitro MS model and/or in vivo MS model and/or patient with RRMS and/or patient with SPMS and/or patients with PPMS

Therefore the main outcomes are:
The effect of mTOR on neuroinflammation in validated MS models, this outcome can be measured through different methodologies as long as the techniques and outcomes are scientifically validated.
The effect of mTOR on autophagy in validated MS models, this outcome can be measured through different methodologies as long as the techniques and outcomes are scientifically validated.
The effect of mTOR on T-cell levels and behavior in validated MS models, this outcome can be measured through different methodologies as long as the techniques and outcomes are scientifically validated.
The effect of mTOR on growth factors in validated MS models, this outcome can be measured through different methodologies as long as the techniques and outcomes are scientifically validated.
The effect of mTOR on neurodegeneration in validated MS models, this outcome can be measured through different methodologies as long as the techniques and outcomes are scientifically validated.
The effect of mTOR on the myelination of neuronal sheaths and the development of oligodendrocytes in validated MS models, this outcome can be measured through different methodologies as long as the techniques and outcomes are scientifically validated.
The effect of mTOR on oxidative stress in validated MS models, this outcome can be measured through different methodologies as long as the techniques and outcomes are scientifically validated.
The effect of mTOR on gliosis in validated MS models, this outcome can be measured through different methodologies as long as the techniques and outcomes are scientifically validated.

Additional outcome(s) Not applicable.

Data management The data search using the search terms mentioned in item 11 is assessed by two reviewers independently and the number of papers extracted is compared to avoid mistakes in the searching stage. The exact search terms used and amount of papers extracted per search query are saved in EndNote and documented in an Excel sheet which will be handed in at the publication stage, to allow reproducibility of the results. Moreover, the screening of the abstracts against the eligibility criteria is also performed by two reviewers independently and compared. In case of disagreement concerning the inclusion or exclusion of a study, this will be discussed with all three writers and discussed until a consensus is reached. Additionally, the data extraction will also be documented in Excel and will be checked by two assessors independently. Throughout the whole screening process, a PRISMA flow chart will be updated to track the number of included and excluded articles, along with their respective reasons for exclusion.

Quality assessment / Risk of bias analysis The risk of bias in the selected studies will be performed using specific bias assessments tailored for the type of study design used. The risk of bias for the in vitro studies will be performed using the Quality Assessment Tool for In Vitro Studies (QUIN) (Vidhi et al. 2022). The risk of bias for the in vivo studies will be performed using the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) and the risk of bias for the included clinical studies will be assessed using the Quality Assessment Tool for Quantitative Studies (QATS) (Armijo-Olivo et al. 2012, Hooijmans et al. 2014). The risk of bias and quality assessment of the papers will be performed independently by two reviewers and compared.

Strategy of data synthesis The data extracted from the studies will be extracted in Excel and the outcomes used will be compared and summarized per subquestion. This review will not include a meta-analysis and therefore no statistical techniques will be used.

Subgroup analysis Not Applicable.

Sensitivity analysis Not Applicable.

Language restriction This systematic review will be written in English and all included papers must be written or translated into English as well.

Country(ies) involved The Netherlands.

Other relevant information The authors Floor Koks, Femke Reubens, and Hymke van der Zee contributed equally to this work. The author Assistant Professor Jacco J. Briedé provided feedback and guidance throughout the writing process.

Keywords Neurodegeneration, neuroinflammation, myelination, PI3K/AKT signalling, rapamycin.

Dissemination plans The paper is expected to be published upon completion.

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