



HIF-1 α in the Crosstalk Between Reactive Oxygen Species and Autophagy Process: A Review in Multiple Sclerosis

Rezvan Asgari¹ · Reza Yarani² · Pantea Mohammadi¹ · Mohammad Sajad Emami Aleagha³

Received: 8 February 2021 / Accepted: 27 May 2021 / Published online: 5 June 2021
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2021

Abstract

Cellular stress can lead to the production of reactive oxygen species (ROS) while autophagy, as a catabolic pathway, protects the cells against stress. Autophagy in its turn plays a pivotal role in the pathophysiology of multiple sclerosis (MS). In the current review, we first summarized the contribution of ROS and autophagy to MS pathogenesis. Then probable crosstalk between these two pathways through HIF-1 α for the first time has been proposed with the hope of employing a better understanding of MS pathophysiology and probable therapeutic approaches.

Keywords Multiple sclerosis · ROS · Autophagy · HIF-1 α

Introduction

Multiple Sclerosis (MS) is an autoimmune inflammatory disease that affects the central nervous system (CNS) and leads to demyelination, neurodegeneration, and axonal loss in young adults (Andhavarapu et al. 2019). The underlying factors that affect the etiology and pathogenesis of MS remain largely unknown, however, the role of some factors like oxidative stress (OS) and autophagy which are involved in cell damage, degradation, and recycling of cellular components have been highlighted extensively (Gilgun-Sherki et al. 2004; Liang and Le 2015; Aleagha et al. 2015; Ahmadi et al. 2016; Karami et al. 2017). OS mainly occurs with the overproduction of reactive oxygen species (ROS) and disturbs the normal function of the immune system and could be a risk factor for the development and progression of autoimmune diseases (Gilgun-Sherki et al. 2001, 2004).

Autophagy, as a lysosome-dependent degradation procedure, plays a critical role in maintaining the homeostasis of neurons (Ravikumar et al. 2010). Defects in the autophagy process can lead to neuroinflammation and neuronal cell death which results in hypoxia and inducing numerous transcription factors (TFs) such as hypoxia-inducible factor-1 α (HIF-1 α), nuclear factor- κ B (NF- κ B), cAMP response-element binding protein (CREB), kruppel-like factor 4 (Klf4), interferon regulatory factor-8 (IRF8), nuclear receptor 4a1 (Nr4a1) (Zou and Crews 2006; Kaushik et al. 2010; Yoshida et al. 2014; Shaked et al. 2015; Liang and Le 2015; Movafagh et al. 2015). HIF-1 α is a key factor that regulates the transcription of the genes involved in several vital processes including autophagy and mitochondrial production of ROS. HIF-1 α can affect autophagy by various pathways including regulating the interaction of Bcl-2 and Beclin1 which leads to the formation of the Bcl-2/Beclin1 complex, the effect on LC3 levels via ATG5 and maintaining the levels of Beclin1 protein (Bohensky et al. 2007; Williams et al. 2010). Based on a review of the literature, HIF-1 α has a paradoxical role through gene activation. So this factor can protect or kill the affected cells (Merelli et al. 2018). The present review focuses on the roles of autophagy and ROS and their possible crosstalk in MS pathophysiology through HIF-1 α .

✉ Mohammad Sajad Emami Aleagha
Mohammadsajad.aleagha@kums.ac.ir

¹ Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

² Translational Type 1 Diabetes Biology, Department of Clinical Research, Steno Diabetes Center Copenhagen, Copenhagen, Denmark

³ Medical Technology Research Center (MTRC), Kermanshah University of Medical Sciences, Kermanshah, Iran

ROS and Pathogenesis of MS

Cells produce controlled amounts of ROS to regulate their physiological activity. The regulated levels of ROS act as secondary messengers in various signaling pathways and help in maintaining cell homeostasis (Sauer et al. 2001; He et al. 2017). However, high levels of ROS cause the oxidation of some critical macromolecules such as nucleic acids, proteins, and lipids, which in this way can disturb the normal function of cells and be a risk factor in the development of various diseases. In fact, ROS leads to cellular injury by overwhelming the capacity of antioxidants (Van Horssen et al. 2011). In the nervous system, ROS are produced in different ways, and inflammation, inflammation-induced hypoxia, and mitochondrial dysfunction raise the level of ROS in this system (Beal 1996; Fiorini et al. 2013). Concomitantly, it has been reported that patients with relapsing–remitting MS (RRMS) show elevated levels of oxidized proteins in the CNS compared to healthy individuals (Di Dalmazi et al. 2016). Increased levels of ROS in the brain and spinal cord cause deterioration of oligodendrocytes and axons which ultimately result in active demyelination and neural cell death (Gilgun-Sherki et al. 2001; Ohl et al. 2016). Moreover, the respiratory burst (rapid release of ROS) in activated mononuclear cells (e.g., microglial cells) generates a large amount of ROS in patients with MS which especially makes remarkable damages in mitochondrial DNA and up-regulates the expression of genes that contribute to the OS (Fischer et al. 2012).

ROS are involved in the dysregulation of the blood–brain barrier (BBB) that leads to rapid disease progression because of the enhanced infiltration of monocytes and inflammation (Ortiz et al. 2013). Accordingly, these results show that ROS is also implicated in the early stages of MS disease when the myelin sheath is still undamaged and the microglial cells and lymphocytes infiltration have occurred (Fischer et al. 2012; Ortiz et al. 2013). Moreover, it has been found that high levels of ROS can promote T-cell activity through the arachidonic acid cascade, or injury to myelin or BBB (Haider et al. 2011).

Another example providing evidence for the contribution of OS to MS pathogenesis is the involvement of mesenchymal stem cells in attenuation of MS progression via decreasing the OS and enhancement of antioxidant factors (Shiri et al. 2020). Taken together, high levels of ROS might damage important cells of the nervous and immune systems and ultimately result in ROS-induced lesions and cell death in the CNS during various stages of MS.

Autophagy

Mechanisms of Autophagy

Autophagy is a highly conserved cellular recycling process that is promoted under cellular stress to increase the survival of the cells (Dikic and Elazar 2018). There are three main types of autophagy, which are mechanistically different from each other: macro-autophagy, chaperone-mediated autophagy (CMA), and micro-autophagy (Fig. 1) (Parzych and Klionsky 2014). Macro-autophagy is a breakdown system that associates with the formation of autophagosomes, whilst micro-autophagy is the direct engulfment of a part of the cytoplasm by the lysosomes. These two types of autophagy degrade the organelles, proteins, and lipids non-selectively. In contrast, CMA is a selective (specific) pathway that leads to protein degradation with the help of the KFERQ peptide motif and a cytosolic chaperone called Hsc70. This type of autophagy fails to participate in the

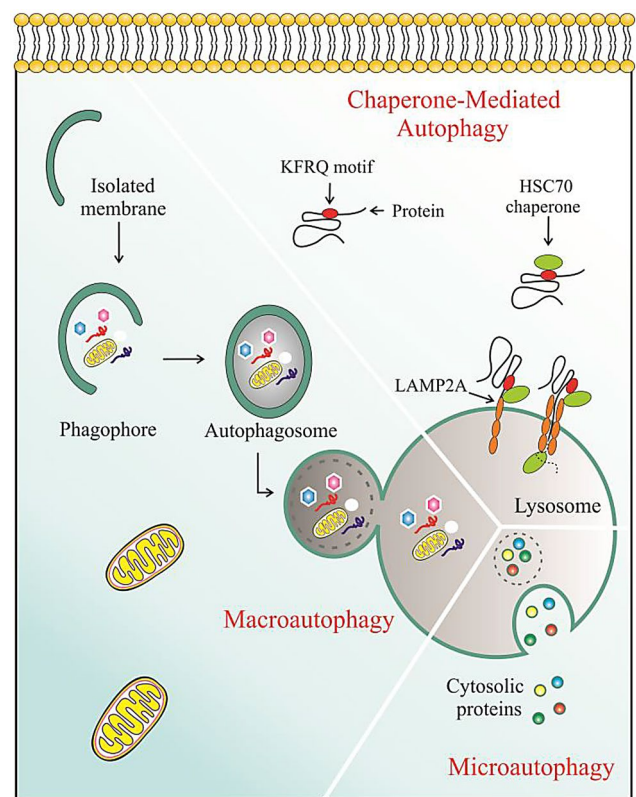


Fig. 1 The main pathways of autophagy: Macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA), which are mechanistically different from each other. Macroautophagy acts by the formation of autophagosomes, while microautophagy is the direct confinement of a part of the cytoplasm content by the lysosomes. These two types of autophagy are non-selective pathways. The CMA is a selective pathway that degrades the proteins by the KFERQ peptide motif dependent on the cytosolic chaperone called Hsc70

degradation of organelles and lipids (Parzych and Klionsky 2014). Macro-autophagy is the most prevalent pathway of autophagy that often referred to as “autophagy” and is distinguished from micro-autophagy and CMA. Autophagy is initiated by various signals that originate from different stress conditions, including hypoxia, starvation, protein aggregation, OS, and endoplasmic reticulum (ER) stress (Dikic and Elazar 2018). When autophagy is started, membrane budding and extension occur and results in the creation of phagophores. Then, double-membrane vesicles, namely autophagosomes, are formed that deliver their contents to the lysosome for degradation and recycling (Parzych and Klionsky 2014). In this stage, the autophagosome outer membrane fuses to the membrane of the lysosome and makes the autolysosome (Yang and Klionsky 2009). In the acidic lumen of the lysosome, the inner membrane of the autophagosome and its contents are degraded by lysosomal hydrolases. Finally, the resulting components of degradation are transferred into the cytoplasm via permeases of the lysosomal membrane and used in different biosynthetic pathways (Yorimitsu and Klionsky 2005).

Autophagy and the Pathogenesis of MS

Autophagy is involved in the homeostasis of the nervous system. Neurons are differentiated cells, which due to their post-mitotic nature and great polarization may be especially sensitive to the accumulation of aggregated or defective compounds, and their survival depends on the process of autophagy. Therefore, the important role of autophagy in the nervous system is mainly related to maintaining the natural balance between the formation and degradation of cellular compounds (Ciechanover 2005; Rubinsztein 2006). Under the physiologic conditions, autophagy is neuroprotective, however, physiopathological increased or decreased activity of autophagy, in turn, can relate to neurodegenerative disorders. Thus, autophagy has a dual role in the nervous system. In literature, autophagy is referred to as a double-edged sword. For example, it has been revealed that autophagy is involved in the homeostasis of amyloid- β (A β) under the physiological conditions, and in Alzheimer’s disease (degradation vs. production, respectively) (Tung et al. 2012).

Previous investigations proposed that deficient autophagy is related to neuronal damage in a mouse model of MS (Feng et al. 2017). Another study has shown that the autophagy up-regulation in mice model through inhibitors of mTOR, like Rapamycin, protects the cells from neurodegeneration (Ravikumar et al. 2004). In this regard, it has been shown that Rapamycin, as an autophagy inducer, promotes myelination and increased survival of the neurons (Meikle et al. 2008). In addition, autophagy participates in immune system functions through eliminating cellular pathogens, increasing the

antigen-presentation to CD4⁺ T-cells, and regulating inflammation (Liang and Le 2015). Autophagy also contributes to the proliferation, maturation, and differentiation of lymphocytes via participation in positive and negative selection in the thymus (Yang et al. 2015). It has been reported that the autophagy process is activated in the peripheral blood mononuclear cells (PBMCs) during the acute phase of the disease and alleviated after therapy (Zheng et al. 2014). Moreover, microglial cells, as resident macrophages in the CNS, control intrinsic and extrinsic pathogens and the phagocytosis of the cell debris during demyelination through autophagy-related genes (ATGs). Thus, defective autophagy in microglial cells may inhibit the remyelination of neurons and potentiates continuous neuroinflammation (Sanjuan et al. 2007).

Overexpression of the ATGs including *ATG2B*, *ATG4C*, *ATG5*, *ATG11*, *Bcl2*, *ULK1*, *ULK2*, *ATG-9A*, and *ATG16L2* in the T cells, demyelinated lesions and blood samples of MS patients have been reported (Igci et al. 2016; Plaza-Zabala et al. 2017; Andhavarapu et al. 2019). The ATG5 plays an important role in the survival of T-cells and involves the proliferation and differentiation of CD4/8⁺ T-cells and B-cells. Moreover, the ATG5 is significantly increased within the T-cells of MS plaques. The serum levels of ATG5 and Parkin, as biomarkers of autophagic and mitophagic pathways, respectively, are significantly increased in the cerebrospinal fluid (CSF) of patients with MS (Castellazzi et al. 2019). Astrocytes could also be affected by defects in the autophagy pathway (Lee et al. 2009; Wang and Xu 2020). Moreover, in dendritic cells, Atg7 contributes to the activation of T cells, as the *Atg7* gene deficient in these cells is accompanied by fewer T-cells presentation in the model of EAE (Plaza-Zabala et al., 2017). Thus, these pieces of evidence indicate that the excess autophagy process contributes to MS pathogenesis. In this regard, demyelination of MS may be potentiated through the extended survival of autoreactive T-cells which these mechanisms can be promoted by autophagy.

On the other hand, mitophagy, as selective autophagy of mitochondria, prevents the excessive generation of ROS and exerts a protective role against MS-induced neurodegeneration (Chen et al. 2008; Shefa et al. 2019). This results in the lower release of toxic molecules including ROS from mitochondria.

Mutual Relationship Between ROS and Autophagy

There are two main sources of ROS: mitochondria that produce ROS as a byproduct of cellular respiration, and the NADPH oxidase complex that actively generates superoxide at the membrane of the neutrophils (Scherz-Shouval and Elazar 2011). ROS and autophagy act in a negative regulatory feedback loop (Azad et al. 2009). It has been shown

that mitochondria are involved in autophagy regulation through ROS production (Scherz-Shouval and Elazar 2007; Azad et al. 2009). ROS, as cell signaling molecules, can potentiate the formation of autophagosomes and autophagic degradation. In fact, mitochondria can be involved in the formation of autophagosomes by providing the membrane sources for the biogenesis of autophagosomes. In contrast, autophagy also can decrease oxidative damage and levels of ROS by the elimination of damaged organelles and protein aggregates and the pathways including mitophagy, CMA, and P62 delivery (Chen et al. 2009; Ureshino et al. 2014; Li et al. 2015).

ROS and autophagy act in a negative regulatory feedback loop. In this line, various molecular pathways regulate the interactions between ROS and the process of autophagy. These regulatory mechanisms often contain transcriptional and post-transcriptional regulations, which occur in the nucleus and cytoplasm. In response to excess production of ROS, the HIF-1 transcription factor, p53, FOXO3, and NRF2 are activated, and then induce the transcription of BNIP3/NIX, TIGAR/DRAM, LC3/BNIP3, and p62, respectively (Scherz-Shouval and Elazar 2011). Moreover, PKR-like ER kinase (PERK), an ER stress sensor, is stimulated by ROS which its downstream effectors promote the expression of genes involved in the autophagy pathway. Under hypoxia conditions, the unfolded protein response (UPR) as a HIF-independent pathway is involved in autophagy. This pathway is activated via ER stress sensors of inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6) and PERK, and responds to ER stress (Wouters and Koritzinsky 2008). In fact, hypoxia leads to the activation of PERK and then induces the transcription of LC3 and ATG5 by the activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP) transcription factors, which the cell capacity for maintaining autophagy in prolonged hypoxia is enhanced (Rouschop et al. 2010). Moreover, in the cytoplasm, ROS can be involved in the organization of autophagic membranes through the regulation of Atg4 activity (Li et al. 2015).

Hypoxia and HIF-1 α in the Pathogenesis of MS

Hypoxia is a state where cells and tissues of the body fail to receive enough oxygen. Hypoxia may exert undesirable effects on the different tissues including the brain. The brain requires a continuous oxygen supply for the maintenance of its normal function. Therefore, prompt detection and response to hypoxic conditions can be very essential. Moreover, the brain is known as an important energy consumer which intense and protracted oxygen deprivation can associate with brain injury through the induction of

neurodegeneration and cell death (Merelli et al. 2018). Under deep hypoxia, the cells from CNS, especially oligodendrocytes, are severely and even lethally at risk, and resulting in demyelination. It has been found that hypoxia is present in patients with MS which leads to the creation of neurological deficits including oligodendrocyte loss and demyelination (Lassmann 2003; Desai et al. 2016; Martinez Sosa and Smith 2017). Moreover, the lesions in the brain of patients with MS tend to form in regions that are sensitive to hypoxia (Martinez Sosa and Smith 2017).

HIF is an important transcription factor, which enables adaptive response to hypoxic state in physiological and pathological conditions through activating a large number of genes responsible for oxygen delivery, and other processes. The HIF-1 is a heterodimer composed of two subunits: alpha and beta. The alpha subunit is an inducible and oxygen-sensitive subunit while the beta subunit shows a constitutive expression (Movafagh et al. 2015). Therefore, reactions to the hypoxic states are mainly dependent on HIF-1 α . The HIF-1 α is a key factor in activating the transcription of genes involved in various aspects of cellular processes such as autophagy, inflammation, metabolism, proliferation, and cell death. In addition, this factor regulates the mitochondrial production of ROS, and it plays an important role in innate and adaptive immunity (Movafagh et al. 2015). In myeloid cells, HIF-1 α is required for glycolytic capacity regulation. Lack of the *HIF-1 α* gene may also cause the defect in the aggregation of the myeloid cells, invasiveness, and killing of the bacterial pathogens (Cramer et al. 2003). Moreover, HIF-1 α enhances neutrophil survival by triggering the NF- κ B-related neutrophilic inflammation and inhibition of apoptosis (Walmsley et al. 2005).

Generally, in the nervous system, the function of HIF-1 α can be detrimental via inducing the disruption of BBB or be protective by enhancement of oligodendrocytes and neurons survival (Argaw et al. 2006; Baranova et al. 2007; Vangeison et al. 2008; Weidemann et al. 2009). Regarding the type of the cell in which HIF-1 α is expressed, negative or positive impacts on inflammatory demyelination can be predictable. So, the HIF-1 α might either have protective impacts on the survival of nerve cells and oligodendrocytes or may intensify the neural damage through enhancement of BBB opening and inflammatory infiltration (Guan et al. 2017).

Interestingly, it has been reported that HIF-1 α is upregulated in pre-demyelinating lesions, without observable changes in the white matter of patients with MS (Graumann et al. 2003; Zeis et al. 2008). It has been shown that at the peak of the disease, the expression of HIF-1 α is induced in microglia/macrophages, and astrocytes in the spinal cord of experimental autoimmune encephalomyelitis (EAE) mice (Le Moan et al. 2015). In the early lesions of MS, the high level of HIF-1 α at mRNA and protein levels makes evidence for the role of this protein in the pathogenesis of

the disease (Uurlink 2013). Early hypoxic alterations occurring at pre-demyelinating plaques are linked to lymphocytes' perivascular accumulation, activation of microglial, disruption of BBB, and mild axonal damage (Marik et al. 2007). HIF-1 α overexpression results in exacerbation of vascular permeability and inflammatory responses, whilst the HIF-1 α ablation reduces the inflammation (Peyssonnaud et al. 2007; Thiel et al. 2007; Weidemann et al. 2009). Inside the active white matter lesions (WMLs), the expression of HIF-1 α is generally minimal or absent (Aboul-Enein et al. 2003; Marik et al. 2007), whereas in oligodendrocytes, especially in the lesions with distal dying-back oligodendroglialopathy, it has a high level of expression (Lassmann 2003).

On the other hand, hypoxia is known to be one of the causes of the inducing process of autophagy (Bellot et al. 2009; Schaaf et al. 2013). Based on the intensity and duration of oxygen deprivation, hypoxia promotes various pathways of autophagy. For example, chronic and moderate hypoxia promotes HIF-1 α and PKC δ -JNK1-dependent pathways for autophagy induction (Semenza 2000; Mazure and Pouyssegur 2010). In contrast, the intense and rapid oscillation of oxygen triggers autophagy through HIF-1 α independent procedures such as the mTOR-mediated pathway and UPR (Papandreou et al. 2008). Totally, accumulating data indicates that autophagy impairment also occurs in MS and may contribute to neurodegeneration.

Crosstalk Between ROS and Autophagy During MS Pathogenesis

We mentioned several pieces of evidence that support the mutual crosstalk between ROS and autophagy. Here, we proposed a probable link between autophagy and ROS by HIF-1 in MS disease. ROS that is produced under OS conditions can damage the vascular endothelium and decrease the ability of vascular smooth muscles for relaxation and vasodilation. This mechanism might be one of the factors leading to decreased cerebral blood flow and hypoxia in MS (Yang and Dunn 2019). On the other hand, cerebrovascular dysfunction leads to hypo-perfusion and promotes the transient hypoxic condition in the vulnerable regions of the CNS. This phenomenon causes the disruption of BBB and leak of serum proteins such as fibronectin and fibrinogen which eventually leads to the activation of the microglial cells. Afterward, cytotoxic factors such as ROS and NO are released by activated microglial cells that trigger the damage to the oligodendrocytes which in turn, results in cellular death and demyelination (Halder and Milner 2021).

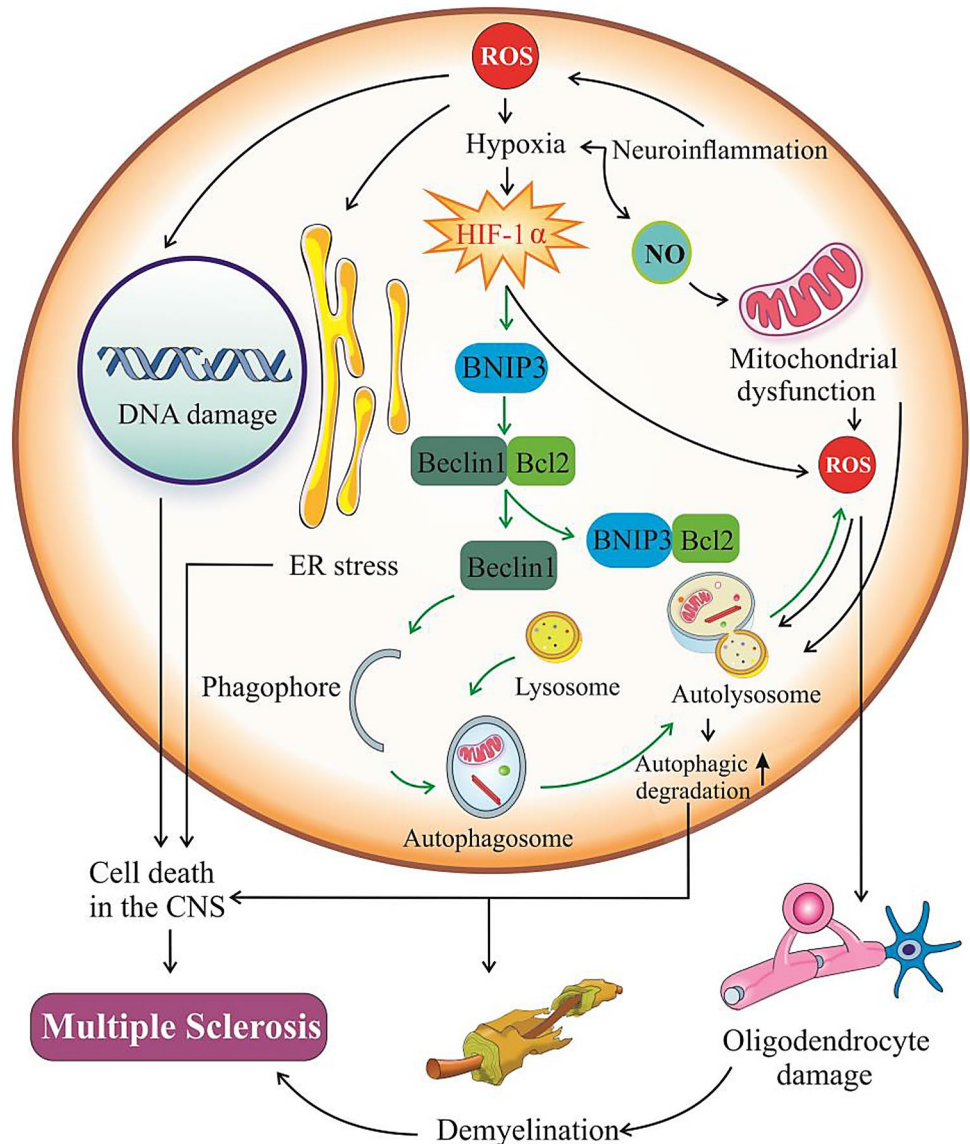
Under hypoxic conditions, HIF-1 α also reduces the level of ROS by various mechanisms. These include induction of lactate dehydrogenase A and pyruvate dehydrogenase kinase 1, improvement of efficiency of complex IV via switching of

cytochrome c oxidase subunit COX4-1 to COX4-2, the direct regulation of mitochondrial performance through its nuclear-independent activities, shunting the pyruvate away from the mitochondria and the conversion of pyruvate to lactate, induction of microRNA-210 that is able to block the Fe/S clusters assembly needed for oxidative phosphorylation, induction of the BNIP3 and triggering the autophagy (Tormos and Chandel 2010; Li et al. 2019).

In connection with autophagy, HIF-1 induces the *BNIP3* gene expression which competes with Beclin-1 for binding to the BCL2, the inhibitory binding partner of Beclin-1. Then autophagy is induced by releasing Beclin-1 from BCL2 (Semenza 2011). Thus, HIF-1 α -mediated BNIP3 expression has a key role in hypoxia-induced mitophagy (Zhang et al. 2008). The mitochondrial autophagy, as the metabolic adaptive response, promotes cell survival in protracted hypoxic conditions that is essential to prevent ROS production and cell death (Zhang et al. 2008; Dhuria et al. 2010). In mitochondria, HIF regulates mitochondrial oxidative stress and respiration and vice versa. Of note, mitochondria are known as the major oxygen consumers in the cell. So, mitochondria and HIF are intimately linked in order to regulate each other and respond properly to hypoxic conditions (Tormos and Chandel 2010). In general, HIF-1 α may play a dual role as "protective" or "harmful" during the pathogenesis of neurodegenerative diseases which is dependent on the severity of hypoxia and environmental conditions (Merelli et al. 2018).

Although determining the exact relationship of ROS, hypoxia, and autophagy in MS requires supportive clinical evidence, based on available data, it seems that HIF-1 α can make crosstalk between these processes during the pathogenesis of MS. So that ROS probably exacerbates the situation of hypoxia. Afterward, by activating the HIF-1 α under hypoxic conditions, various pathways including autophagy are induced. The enhancement of autophagic degradation can damage nerve cells and leads to demyelination or cell death in the CNS and contributes to MS progression. Generally, hyperactivity or hypoactivity of autophagy is undesirable for the normal function of neurons and these cells need a regulated amount of autophagy to maintain cell survival under different stress conditions. Thereby, it is possible to infer a "ROS—hypoxia—autophagy pathway" in MS pathogenesis (Fig. 2). According to available data, the factors and signaling pathways, which link autophagy and ROS, can be of great importance in MS combinatorial treatment. However, more investigations are required to find whether the crosstalk between autophagy and ROS can be more efficient in MS therapy.

Fig. 2 The crosstalk between ROS and autophagy by HIF-1 α in the pathogenesis of multiple sclerosis. Cellular stresses lead to increased ROS levels. ROS can intensify the situation of hypoxia. Then, under hypoxic condition, HIF-1 α is activated, which induces the various pathways including autophagy. The enhancement of autophagic degradation can result in neuronal cell damage and demyelination. In the figure, green arrows show the protective pathways, while black arrows show the neurodegenerative pathways



Conclusion

ROS production in the brain and autophagy dysregulation can damage cells of the nervous system and are associated with various stages of MS. In this review, for the first time, we suggested crosstalk between ROS and autophagy in MS pathogenesis by HIF-1 α . Accordingly, targeting ROS—hypoxia—autophagy cycle may lead to more efficient results in combinatorial treatments of MS.

Author Contributions RA and MSEA designed the structure of the manuscript. RA, MSEA, RY, and PM drafted the manuscript. RA, MSEA, RY, and PM finalized the paper. All authors approved the final version of the manuscript.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Informed Consent No informed consent is needed.

References

- Aboul-Enein F, Rauschka H, Kornek B, Stadelmann C, Steffler A, Brück W, Lucchinetti C, Schmidbauer M, Jellinger K, Lassmann H (2003) Preferential loss of myelin-associated glycoprotein reflects hypoxia-like white matter damage in stroke and inflammatory brain diseases. *J Neuropathol Exp Neurol* 62:25–33
- Ahmadi M, Aleagha MS, Harirchian MH, Yarani R, Tavakoli F, Siroos B (2016) Multiple sclerosis influences on the augmentation of serum Klotho concentration. *J Neurol Sci* 362:69–72

- Aleagha MS, Siroos B, Ahmadi M, Balood M, Palangi A, Haghghi AN, Harirchian MH (2015) Decreased concentration of Klotho in the cerebrospinal fluid of patients with relapsing–remitting multiple sclerosis. *J Neuroimmunol* 281:5–8
- Andhavarapu S, Mubariz F, Arvas M, Bever Jr C, Makar TK (2019) Interplay between ER stress and autophagy: a possible mechanism in multiple sclerosis pathology. *Exp Mol Pathol* 108:183–190
- Argaw AT, Zhang Y, Snyder BJ, Zhao ML, Kopp N, Lee SC, Raine CS, Brosnan CF, John GR (2006) IL-1 β regulates blood–brain barrier permeability via reactivation of the hypoxia–angiogenesis program. *J Immunol* 177:5574–5584
- Azad MB, Chen Y, Gibson SB (2009) Regulation of autophagy by reactive oxygen species (ROS): implications for cancer progression and treatment. *Antioxid Redox Signal* 11(4):777–790
- Baranova O, Miranda LF, Pichiule P, Dragatsis I, Johnson RS, Chavez JC (2007) Neuron-specific inactivation of the hypoxia inducible factor 1 alpha increases brain injury in a mouse model of transient focal cerebral ischemia. *J Neurosci* 27:6320–6332
- Beal M (1996) Aging, energy, and oxidative stress in neurodegenerative diseases. *Restor Neurol Neurosci* 3:180–181
- Bellot G, Garcia-Medina R, Gounon P, Chiche J, Roux D, Pouyssegur J, Mazure NM (2009) Hypoxia-induced autophagy is mediated through HIF-induction of BNIP3 and BNIP3L via their BH3-domains. *Mol Cell Biol* 29:2570–2581
- Bohensky J, Shapiro IM, Leshinsky S, Terkhorn SP, Adams CS, Srinivas V (2007) HIF-1 regulation of chondrocyte apoptosis: induction of the autophagic pathway. *Autophagy* 3:207–214
- Castellazzi M, Patergnani S, Donadio M, Giorgi C, Bonora M, Fainardi E, Casetta I, Granieri E, Pugliatti M, Pinton P (2019) Correlation between auto/mitophagic processes and magnetic resonance imaging activity in multiple sclerosis patients. *J Neuroinflamm* 16(1):1–8
- Chen Y, McMillan-Ward E, Kong J, Israels SJ, Gibson SB (2008) Oxidative stress induces autophagic cell death independent of apoptosis in transformed and cancer cells. *Cell Death Differ* 15(1):171–182
- Chen Y, Azad MB, Gibson SB (2009) Superoxide is the major reactive oxygen species regulating autophagy. *Cell Death Differ* 16(7):1040–1052
- Ciechanover A (2005) Proteolysis: from the lysosome to ubiquitin and the proteasome. *Nat Rev Mol Cell Biol* 6:79–87
- Cramer T, Yamanishi Y, Clausen BE, Förster I, Pawlinski R, Mackman N, Haase VH, Jaenisch R, Corr M, Nizet V, Firestein GS (2003) HIF-1 α is essential for myeloid cell-mediated inflammation. *Cell* 112:645–657
- Desai RA, Davies AL, Tachrount M, Kasti M, Laulund F, Golay X, Smith KJ (2016) Cause and prevention of demyelination in a model multiple sclerosis lesion. *Ann Neurol* 79(4):591–604
- Dhuria SV, Hanson LR, Frey WH (2010) II Intranasal delivery to the central nervous system: mechanisms and experimental considerations. *J Pharm Sci* 99(4):1654–1673
- Di Dalmazi G, Hirshberg J, Lyle D, Freij JB, Caturegli P (2016) Reactive oxygen species in organ-specific autoimmunity. *Autoimmun Highlights* 7(1):1–1
- Dikic I, Elazar Z (2018) Mechanism and medical implications of mammalian autophagy. *Nat Rev Mol Cell Biol* 19(6):349–364
- Feng X, Hou H, Zou Y, Guo L (2017) Defective autophagy is associated with neuronal injury in a mouse model of multiple sclerosis. *Bosn J Basic Med Sci* 17(2):95
- Fiorini A, Koudriavtseva T, Bucaj E, Coccia R, Foppoli C, Giorgi A, Schininà ME, Di Domenico F, De Marco F, Perluigi M (2013) Involvement of oxidative stress in occurrence of relapses in multiple sclerosis: the spectrum of oxidatively modified serum proteins detected by proteomics and redox proteomics analysis. *PLoS ONE* 8(6):e65184
- Fischer MT, Sharma R, Lim JL, Haider L, Frischer JM, Drexhage J, Mahad D, Bradl M, van Horssen J, Lassmann H (2012) NADPH oxidase expression in active multiple sclerosis lesions in relation to oxidative tissue damage and mitochondrial injury. *Brain* 135(3):886–899
- Gilgun-Sherki Y, Melamed E, Offen D (2001) Oxidative stress induced-neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier. *Neuropharmacology* 40(8):959–975
- Gilgun-Sherki Y, Melamed E, Offen D (2004) The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. *J Neurol* 251(3):261–268
- Graumann U, Reynolds R, Steck AJ, Schaeren-Wiemers N (2003) Molecular changes in normal appearing white matter in multiple sclerosis are characteristic of neuroprotective mechanisms against hypoxic insult. *Brain Pathol* 13:554–573
- Guan SY, Leng RX, Tao JH, Li XP, Ye DQ, Olsen N, Zheng SG, Pan HF (2017) Hypoxia-inducible factor-1 α : a promising therapeutic target for autoimmune diseases. *Expert Opin Ther Targets* 21(7):715–723
- Haider L, Fischer MT, Frischer JM, Bauer J, Höftberger R, Botond G, Esterbauer H, Binder CJ, Witztum JL, Lassmann H (2011) Oxidative damage in multiple sclerosis lesions. *Brain* 134(7):1914–1924
- Halder SK, Milner R (2021) Hypoxia in multiple sclerosis; is it the chicken or the egg? *Brain* 144(2):402–410
- He L, He T, Farrar S, Ji L, Liu T, Ma X (2017) Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. *Cell Physiol Biochem* 44(2):532–553
- Igci M, Baysan M, Yigiter R, Ulasli M, Geyik S, Bayraktar R, Bozgeyik I, Bozgeyik E, Bayram A, Cakmak EA (2016) Gene expression profiles of autophagy-related genes in multiple sclerosis. *Gene* 588(1):38–46
- Karami M, Mehrabi F, Allameh A, Kakhki MP, Amiri M, Aleagha MS (2017) Klotho gene expression decreases in peripheral blood mononuclear cells (PBMCs) of patients with relapsing–remitting multiple sclerosis. *J Neurol Sci* 381:305–307
- Kaushik DK, Gupta M, Das S, Basu A (2010) Krüppel-like factor 4, a novel transcription factor regulates microglial activation and subsequent neuroinflammation. *J Neuroinflamm* 7(1):1–20
- Lassmann H (2003) Hypoxia-like tissue injury as a component of multiple sclerosis lesions. *J Neurol Sci* 206(2):187–191
- Le Moan N, Baeten KM, Rafalski VA, Ryu JK, Coronado PE, Bedard C, Syme C, Davalos D, Akassoglou K (2015) Hypoxia inducible factor-1 in astrocytes and/or myeloid cells is not required for the development of autoimmune demyelinating disease. *eNeuro* 2
- Lee SJ, Cho KS, Koh JY (2009) Oxidative injury triggers autophagy in astrocytes: the role of endogenous zinc. *Glia* 57(12):1351–1361
- Li L, Tan J, Miao Y, Lei P, Zhang Q (2015) ROS and autophagy: interactions and molecular regulatory mechanisms. *Cell Mol Neurobiol* 35(5):615–621
- Li HS, Zhou YN, Li L, Li SF, Long D, Chen XL, Zhang JB, Feng L, Li YP (2019) HIF-1 α protects against oxidative stress by directly targeting mitochondria. *Redox Biol* 25:101109
- Liang P, Le W (2015) Role of autophagy in the pathogenesis of multiple sclerosis. *Neurosci Bull* 31(4):435–444
- Marik C, Felts PA, Bauer J, Lassmann H, Smith KJ (2007) Lesion genesis in a subset of patients with multiple sclerosis: a role for innate immunity? *Brain* 130:2800–2815
- Martinez Sosa S, Smith KJ (2017) Understanding a role for hypoxia in lesion formation and location in the deep and periventricular white matter in small vessel disease and multiple sclerosis. *Clin Sci* 131(20):2503–2524
- Mazure NM, Pouyssegur J (2010) Hypoxia-induced autophagy: cell death or cell survival? *Curr Opin Cell Biol* 22(2):177–180
- Meikle L, Pollizzi K, Egnor A, Kramvis I, Lane H, Sahin M, Kwiatkowski DJ (2008) Response of a neuronal model of tuberous sclerosis to mammalian target of rapamycin (mTOR) inhibitors:

- effects on mTORC1 and Akt signaling lead to improved survival and function. *J Neurosci* 28(21):5422–5432
- Merelli A, Rodríguez JC, Folch J, Regueiro MR, Camins A, Lazarowski A (2018) Understanding the role of hypoxia inducible factor during neurodegeneration for new therapeutics opportunities. *Curr Neuropharmacol* 16(10):1484–1498
- Movafagh S, Crook S, Vo K (2015) Regulation of hypoxia-inducible factor-1 α by reactive oxygen species: new developments in an old debate. *J Cell Biochem* 116(5):696–703
- Ohl K, Tenbrock K, Kipp M (2016) Oxidative stress in multiple sclerosis: central and peripheral mode of action. *Exp Neurol* 277:58–67
- Ortiz GG, Pacheco-Moises FP, Bitzer-Quintero OK, Ramírez-Anguiano AC, Flores-Alvarado LJ, Ramírez-Ramírez V, Macias-Islas MA, Torres-Sanchez ED (2013) Immunology and oxidative stress in multiple sclerosis: clinical and basic approach. *Clin Dev Immunol*. <https://doi.org/10.1155/2013/708659>
- Papandreou I, Lim AL, Laderoute K, Denko NC (2008) Hypoxia signals autophagy in tumor cells via AMPK activity, independent of HIF-1, BNIP3, and BNIP3L. *Cell Death Differ* 15:1572–1581
- Parzych KR, Klionsky DJ (2014) An overview of autophagy: morphology, mechanism, and regulation. *Antioxid Redox Signal* 20(3):460–473
- Peyssonaux C, Cejudo-Martin P, Doedens A, Zinkernagel AS, Johnson RS, Nizet V (2007) Cutting edge: essential role of hypoxia inducible factor-1 α in development of lipopolysaccharide-induced sepsis. *J Immunol* 178:7516–7519
- Plaza-Zabala A, Sierra-Torre V, Sierra A (2017) Autophagy and microglia: novel partners in neurodegeneration and aging. *Int J Mol Sci* 18(3):598
- Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scarpavilli F, Easton DF, Duden R, O’Kane CJ, Rubinsztein DC (2004) Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat Genet* 36(6):585–595
- Ravikumar B, Sarkar S, Davies JE, Futter M, Garcia-Arencibia M, Green-Thompson ZW, Jimenez-Sanchez M, Korolchuk VI, Lichtenberg M, Luo S, Massey DC (2010) Regulation of mammalian autophagy in physiology and pathophysiology. *Physiol Rev* 90(4):1383–1435
- Rouschop KM, Van Den Beucken T, Dubois L, Niessen H, Bussink J, Savelkoul K, Keulers T, Mujcic H, Landuyt W, Voncken JW, Lambin P (2010) The unfolded protein response protects human tumor cells during hypoxia through regulation of the autophagy genes MAP1LC3B and ATG5. *J Clin Invest* 120:127–141
- Rubinsztein DC (2006) The roles of intracellular protein-degradation pathways in neurodegeneration. *Nature* 443:780–786
- Sanjuan MA, Dillon CP, Tait SW, Moshiah S, Dorsey F, Connell S, Komatsu M, Tanaka K, Cleveland JL, Withoff S, Green DR (2007) Toll-like receptor signalling in macrophages links the autophagy pathway to phagocytosis. *Nature* 450(7173):1253–1257
- Sauer H, Wartenberg M, Hescheler J (2001) Reactive oxygen species as intracellular messengers during cell growth and differentiation. *Cell Physiol Biochem* 11(4):173–186
- Schaaf MB, Cojocari D, Keulers TG, Jutten B, Starmans MH, de Jong MC, Begg AC, Savelkoul KG, Bussink J, Vooijs M, Wouters BG (2013) The autophagy associated gene, ULK1, promotes tolerance to chronic and acute hypoxia. *Radiother Oncol* 108:529–534
- Scherz-Shouval R, Elazar Z (2007) ROS, mitochondria and the regulation of autophagy. *Trends Cell Biol* 17(9):422–427
- Scherz-Shouval R, Elazar Z (2011) Regulation of autophagy by ROS: physiology and pathology. *Trends Biochem Sci* 36(1):30–38
- Semenza GL (2000) HIF-1 and human disease: one highly involved factor. *Genes Dev* 14:1983–1991
- Semenza GL (2011) Hypoxia-inducible factor 1: regulator of mitochondrial metabolism and mediator of ischemic preconditioning. *Biochim Biophys Acta Mol Cell Res* 1813(7):1263–1268
- Shaked I, Hanna RN, Shaked H, Chodaczek G, Nowyhed HN, Tweet G, Tacke R, Basat AB, Mikulski Z, Togher S, Miller J (2015) Transcription factor Nr4a1 couples sympathetic and inflammatory cues in CNS-recruited macrophages to limit neuroinflammation. *Nat Immunol* 16(12):1228–1234
- Shefa U, Jeong NY, Song IO, Chung HJ, Kim D, Jung J, Huh Y (2019) Mitophagy links oxidative stress conditions and neurodegenerative diseases. *Neural Regen Res* 14(5):749
- Shiri E, Pasbakhsh P, Borhani-Haghighi M, Alizadeh Z, Nekoonam S, Mojaverrostami S, Mahabadi VP, Mehdi A, Zibara K, Kashani IR (2020) Mesenchymal stem cells ameliorate cuprizone-induced demyelination by targeting oxidative stress and mitochondrial dysfunction. *Cell Mol Neurobiol* 27:1–5
- Thiel M, Caldwell CC, Kreth S, Kuboki S, Chen P, Smith P, Ohta A, Lentsch AB, Lukashev D, Sitkovsky MV (2007) Targeted deletion of HIF-1 α gene in T cells prevents their inhibition in hypoxic inflamed tissues and improves septic mice survival. *PLoS ONE* 2:e853
- Tormos KV, Chandel NS (2010) Inter-connection between mitochondria and HIFs. *J Cell Mol Med* 14(4):795–804
- Tung YT, Wang BJ, Hu MK, Hsu WM, Lee H, Huang WP, Liao YF (2012) Autophagy: a double-edged sword in Alzheimer’s disease. *J Biosci* 37(1):157–165
- Ureshino RP, Rocha KK, Lopes GS, Bincoletto C, Smaili SS (2014) Calcium signaling alterations, oxidative stress, and autophagy in aging. *Antioxid Redox Signal* 21(1):123–137
- Uurlink BHJ (2013) The evidence for Hypoperfusion as a factor in multiplesclerosis lesion development. *Mult Scler Int* 2013:6
- Van Horssen J, Witte ME, Schreibelt G, de Vries HE (2011) Radical changes in multiple sclerosis pathogenesis. *Biochem Biophys Acta* 1812(2):141–150
- Vangeison G, Carr D, Federoff HJ, Rempe DA (2008) The good, the bad, and the cell type-specific roles of hypoxia inducible factor-1 α in neurons and astrocytes. *J Neurosci* 28:1988–1993
- Walmsley SR, Print C, Farahi N (2005) Hypoxia-induced neutrophil survival is mediated by HIF-1 α -dependent NF- κ B activity. *J Exp Med* 201:105–115
- Wang JL, Xu CJ (2020) Astrocytes autophagy in aging and neurodegenerative disorders. *Biomed Pharmacother* 122:109691
- Weidemann A, Kerdiles YM, Knaup KX, Rafie CA, Boutin AT, Stockmann C, Takeda N, Scadeng M, Shih AY, Haase VH, Simon MC (2009) The glial cell response is an essential component of hypoxia-induced erythropoiesis in mice. *J Clin Invest* 119:3373–3383
- Williams H, Johnson JL, Jackson CL, White SJ, George SJ (2010) MMP-7 mediates cleavage of N-cadherin and promotes smooth muscle cell apoptosis. *Cardiovasc Res* 87:137–146
- Wouters BG, Koritzinsky M (2008) Hypoxia signalling through mTOR and the unfolded protein response in cancer. *Nat Rev Cancer* 8:851–864
- Yang R, Dunn JF (2019) Multiple sclerosis disease progression: contributions from a hypoxia–inflammation cycle. *Mult Scler J* 25(13):1715–1718
- Yang Z, Klionsky DJ (2009) An overview of the molecular mechanism of autophagy. *Curr Top Microbiol Immunol* 335:1–32
- Yang Z, Goronzy JJ, Weyand CM (2015) Autophagy in autoimmune disease. *J Mol Med* 93(7):707–717
- Yorimitsu T, Klionsky DJ (2005) Autophagy: molecular machinery for self-eating. *Cell Death Differ* 12(2):1542–1552
- Yoshida Y, Yoshimi R, Yoshii H, Kim D, Dey A, Xiong H, Munasinghe J, Yazawa I, O’Donovan MJ, Maximova OA, Sharma S (2014) The transcription factor IRF8 activates integrin-mediated TGF- β signaling and promotes neuroinflammation. *Immunity* 40(2):187–198
- Zeis T, Graumann U, Reynolds R, Schaeren-Wiemers N (2008) Normal-appearing white matter in multiple sclerosis is in a

- subtle balance between inflammation and neuroprotection. *Brain* 131:288–303
- Zhang H, Bosch-Marce M, Shimoda LA, Tan YS, Baek JH, Wesley JB, Gonzalez FJ, Semenza GL (2008) Mitochondrial autophagy is an HIF-1-dependent adaptive metabolic response to hypoxia. *J Biol Chem* 283(16):10892–10903
- Zheng L, Xue Q, Ni J, Guo S, Dong W (2014) Levels of Beclin 1 and LC3 in peripheral blood mononuclear cells of patients with multiple sclerosis and neuromyelitisoptica and its significance. *Zhonghuayixuezhazhi* 94(39):3052–3055
- Zou J, Crews F (2006) CREB and NF- κ B transcription factors regulate sensitivity to excitotoxic and oxidative stress induced neuronal cell death. *Cell Mol Neurobiol* 26(4):383–403

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.