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Review Article

Stroke Pathogenesis: Unravelling the Complex Interplay of Autophagy, Oxidative Stress, and Inflammation

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Abstract

Stroke has caused far more deaths and disabilities than any other health problem, necessitating a comprehensive understanding of its pathophysiology that is crucial to developing effective therapeutic strategies. This review paper examines the complex relationship between stroke, autophagy, oxidative stress and inflammation highlighting their involvement in neuronal injury and therapy. The role that autophagy plays in stroke can be seen in different lights as it can either protect cells by removing damaged organelles or cause cell death when certain conditions prevail. Stroke pathogenesis is determined by major pathways, such as mTOR, NF-κB, and HIF-1, as well as their relationship to ischemic and pro-inflammatory responses. Oxidative stress in stoke, primarily caused by an imbalance in reactive oxygen species (ROS), is a major factor in neuronal damage caused by mitochondrial dysfunction and lipid peroxidation. The significance of antioxidant therapy is an increase in stroke management with oxidative stress as the mediator of cell death. Activation of microglial cells and release of cytokines resulting in inflammatory upsurge increase tissue damage after stroke. Inflammatory response combined with overactive autophagy/oxidative stress may heighten the severity of cerebrovascular disease; thus, neuroprotection can be significantly achieved through maintaining brain antioxidant and anti-inflammatory activities while responding to injury. Obstacles including translation gaps and individual variations in treatment response necessitate more research to clarify the signaling pathways' roles and identify new therapeutic targets.

Keywords: *Ischemia; Stroke; Autophagy; Inflammation; Oxidative Stress; Neurodegeneration*

Introduction

Stroke is one of the deadliest and most difficult health conditions that can occur, and ranks as one of the major causes of disability and mortality across the globe. According to the World Stroke Organization (WSO), stroke accounts for 6.5 million deaths globally and 2 million deaths each year, making it the leading cause of death globally [1,2]. According to the 2022 Global Stroke Factsheet, the lifetime risk of having a stroke has risen by 50% in the past 17 years, with an estimated 1 in 4 people expected to experience a stroke in their lifetime [2]. Between 1990 and 2019, there was a rise of 70% in the global incidence of stroke, 43% in the number of stroke-related deaths, 102% in the frequency of stroke, and 143% in Disability Adjusted Life Years (DALY) [1,2]. It is worrisome that lower- and lower-middle-income countries account for the majority of the world's stroke burden (86% of stroke-related deaths and 89% of DALYs). This disproportionate burden experienced by lower and lower-middle-income lower-middle income countries has posed an unprecedented problem to families with less resources [2]. Statistics suggest that the likelihood of long-term disabilities after stroke is above 50%, and a noticeable percentage of stroke survivors are exposed to motor deficits, cognitive impairments, and language disorders [1]. The figures above unequivocally point to the dire need for a more in-depth investigation of the molecular etiology of stroke-triggered brain damage and the development of more efficacious prophylactic and therapeutic methods. The etiology of stroke is complex and comprises the ischemic and haemorrhagic variants. In the majority of stroke cases (87% to be precise), an ischemia stroke, which is caused by an obstruction in a cerebral blood vessel, accounts for the majority of stroke cases [3].

The interruption of blood flow compromises the main physiological processes of cerebral cells, and leads to an increase of calcium overload, inflammatory responses, oxidative stress, alteration of the blood–brain barrier (BBB) permeability, and excitotoxity [4]. The inflammatory response and oxidative stress are among the earliest events that characterize the cascade of cerebral ischemic injury.

The process of ischemia gets haywire within minutes of the vessel occlusion and results in a chain of events that sooner or later becomes irreversible leading to tissue damage and death of brain cells. Ischemia is a medical condition caused by a temporary loss of blood flow to the tissues. When the blood supply is restored, referred to as "reperfusion", this condition exacerbates tissue damage through mechanisms including oxidative stress, inflammation, and excitotoxicity [5,6]. Haemorrhagic stroke, the less frequent, begets more complications than ischemic stroke because of the sudden tearing of blood vessels inside the brain which then fills the cerebral hemisphere with blood or the subarachnoid space on the inner side [7].

One of the most critical research focuses is to understand the roles of autophagy, oxidative stress, and inflammation in stroke pathophysiology. Autophagy, a crucial cellular process involved in maintaining cellular homeostasis, has been identified as an important factor promoting neuronal injury following a stroke [8]. As indicated in studies, stimulation of autophagy can present with both neuroprotective and harmful effects in different contexts, and at different times of the autophagy responses [9]. Oxidative stress is one of the most common ischemic injuries due to the increase in ROS (reactive oxygen species) or antioxidant imbalances. With the production of ROS involving superoxide radicals and hydrogen peroxide, the effect of lipid peroxidation, protein oxidation, and DNA damage is the culmination and addition of cellular injury which may lead to cell death [10]. Similarly, immune response, which is influenced by the activation of microglia and the presence of inflammatory cells, also contributes greatly to the pathophysiology of stroke by releasing pro-inflammatory cytokines and chemokines. Even though inflammation can help with neurovascular repair and support recovery as well causing secondary brain injury and stroke worsening, chronic or unbalanced it can promote the development or prolong the process [11]. The complex interplay of autophagy, oxidative stress, and inflammation provides a network of molecular communication that forms the base of potentially devastating stroke-induced brain injury.

This review aims to unfold the multifaceted roles of autophagy, oxidative stress, and inflammation during the progress of stroke pathophysiology, followed by piecing together the pieces of these preclinical studies and clinical observations. This review also aims to understand the involvement of autophagy in Ischemic stroke both in preclinical studies and clinical observation. Elucidating the molecular

pathways that underpin those processes drives us to identify novel potential therapeutic targets and techniques that can ultimately enhance treatment outcomes and lessen the latter's burden.

Literature Review

Role of autophagy in ischemic stroke

The interruption of blood flow compromises the main physiological processes of cerebral cells, and leads to an increase of calcium overload, inflammatory responses, oxidative stress, alteration of the blood–brain barrier (BBB) permeability, and excitotoxity. The increase of inflammation and oxidative stress, following IS, can induce the development of the autophagic process which, in turn, may exert both protective and detrimental effects, depending on the type of stress and on its duration, and on the type of cells involved.

Autophagy is activated in response to IS in all brain cells present in the damaged area such as neurons, glial cells, and microvascular cells [12]. It has been reported that autophagy plays a dual role in neuronal and vascular cells. A moderate level of autophagy protects neurons and restores cerebral function by reducing the inflammatory process and oxidative stress, whereas excessive autophagy induces neuronal cell death and exacerbates brain damage [13,14]. A dysregulation of autophagy may contribute to worsening brain damage [8,15,16]. Autophagy is an intracellular mechanism by which cells remove damaged or senescent cytoplasmic components. Autophagy helps to maintain cellular homeostasis by eliminating dysfunctional organelles, misfolded proteins as well as other cellular debris [17], it also maintains cellular integrity, and ultimately leading to cell survival when nutrients and oxygen become less available.

In models of IS autophagy is mostly regulated by the mechanistic target of rapamycin (mTOR) complex I (mTORC1) and by AMPK (Adenosine monophosphate-activated protein kinase (Figure 1), which interact with multiple signaling including the Phosphoinositide-3-kinase (PI3K)/Protein Kinase B (Akt), Mitogen-activated protein kinase (MAPK), NF-κB, Tumor protein p53, and B-cell lymphoma 2 (Bcl2) pathways [18]. In the specific, mTOR is an atypical serine/threonine kinase and the core component of two separate protein complexes named mTORC1 and mTOR complex 2 (mTORC2).

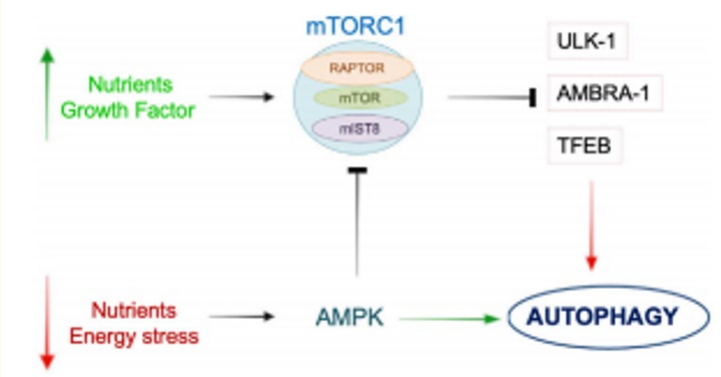

Figure 1: *Schematic overview of the main pathways involved in the regulation of autophagy [4].*

According to the bioavailability of nutrients, growth factors, energy and oxygen, mTORC1 promotes anabolic processes and inhibits catabolic mechanisms, such as autophagy [19]. The PI3K/Akt mediates mTOR activation through the inhibition of tuberous sclerosis complexes (TSC-1/2). Extracellular signal-regulated kinase (ERK), a member of MAPK family, regulates autophagy in IS through the inhibition of mTORC1 [20].

The AMPK pathway receives both activator and inhibitory inputs from stress sensors [21]. In the brain, AMPK activity increases following an ischemic insult, due to the reduction of the adenosine triphosphate (ATP)/adenosine monophosphate (AMP) ratio, to stimulate protective autophagy by inhibition of mTORC1 [22]. Moreover, mTOR inhibition by AMPK occurs through the activation of TSC-1/2 [23]. mTORC1 also inhibits autophagy by phosphorylating the transcription-factor-EB (TFEB), a positive regulator of autophagy and transcriptional regulator of genes involved both in autophagosome formation and lysosomal biogenesis. However, TFEB modulation in models of IS not dependent by mTORC1 activation [9].

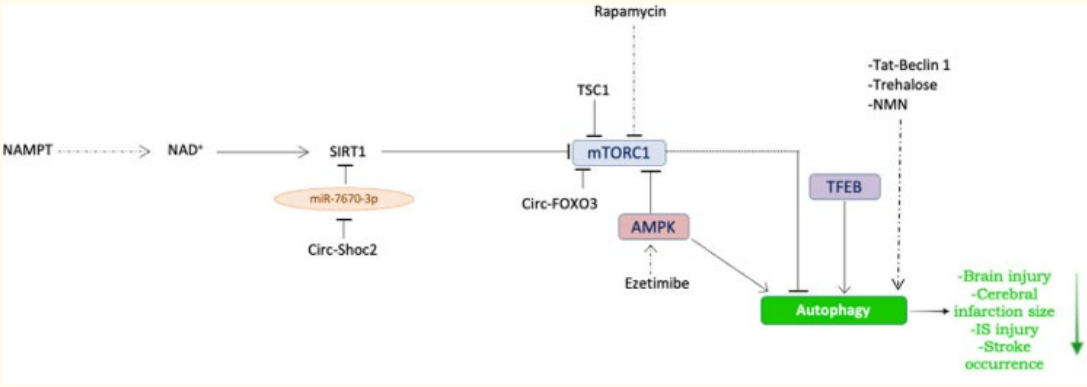

Figure 2: *The protective role of autophagy in preclinical models of stroke [4].*

Protective effect of autophagy in animal models of IS

In a rat model of MCAO, Wang., *et al*. demonstrated that overexpression of nicotinamide phosphoribosyl transferase (NAMPT), the rate-limiting enzyme in NAD+ biosynthesis, decreased the size of cerebral infarction via autophagy activation in an early stage of ischemia (2h) and not after 8 and 24h following ischemia [18]. NAMPT increases NAD+ levels, which in turn contributes to activate Sirtuin-1 (SIRT1). Once activated, SIRT1 induces autophagy via inhibition of mTORC1. Of interest, another study further demonstrated that NAMPT is released in exosomes by astrocytes undergoing acute ischemia. Once released, NAMPT can activate autophagy in neurons, therefore improving the neurofunctional recovery [24].

In rats subjected to permanent MCAO, autophagy is upregulated in the early phase of ischemia [9], along with an increased activity of TFEB, especially in neurons of the cortex. At later stages after ischemia, nuclear translocation of TFEB decreases, resulting in the accumulation of autophagosomes and autophagy substrates, with a consequent exacerbation of the ischemic injury. The decreased activity of TFEB in the later phases of ischemia was not dependent by mTORC1 activation, which is a TFEB inhibitor. TFEB overexpression in neurons reduces ischemic damage. These results suggest that TFEB plays a pivotal role in the MCAO-mediated dysfunction of autophagy-lysosomal pathway. Carloni., *et al*. showed that activation of autophagy by rapamycin, a mTORC1 inhibitor, was able to reduce the necrotic death of hippocampal and cortical neurons and to decrease brain injury in a neonatal mouse model of hypoxic-ischemic brain damage [25]. In a separate study, rapamycin reduced the infarct volume and improved neurological functions in rats undergoing focal MCAO [26]. Of interest, mTOR was reported to be activated in the ischemic penumbra whereas it was inhibited in the ischemic core following MCAO. The autophagy activation by ezetimibe also led to reduction of neuronal apoptosis [27]. Another study demonstrated that cerebral ischemia increased TSC1 activity in cultures of rat hippocampal CA3 neurons with a consequent activation of autophagy, along with the improvement of cell survival. Upregulation of TSC1 protected CA3 neurons toward ischemia also in rats undergoing global forebrain ischemi (a more severe type of IS) [28]. The latter was mediated by the inhibition of mTORC1 activity.

Another pathway that contributes to autophagy modulation during IS mediated by Beclin-1/B-Cell Leukemia/Lymphoma 2 (Bcl-2) (Figure 3). Beclin one is an important protein involved in the initial phase of autophagosome formation. Beclin-1 expression increases in neurons in response to ischemia [4]. In addition, Beclin-1 interacts with the antiapoptotic protein Bcl-2 to form a Beclin-1/Bcl-2 complex which inhibits autophagy. In a rat model of cerebral ischemia followed by reperfusion, remote ischemic conditioning induces Bcl-2 dissociation from Beclin 1, leading to the enhancement of autophagy and a consequent reduction of brain injury [29]. However, other reports demonstrated that ischemia/reperfusion induces autophagy via endoplasmic reticulum stress (ER) induced inhibition of Bcl-2 [30].

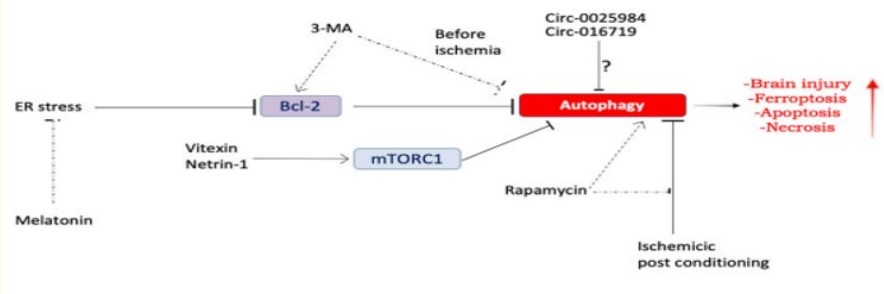

Figure 3: *The detrimental role of autophagy in preclinical models of stroke [4].*

The detrimental effect of autophagy in animal models of IS

Excessive levels of autophagy in models of MCAO promote cell death mechanisms, such as apoptosis, necrosis and ferroptosis. Autophagy is also activated by endoplasmic reticulum stress (ER stress), which in turn contributes to inhibition of the anti-apoptotic factor Bcl-2 [30]. Because of Bcl-2 inhibition, a detrimental autophagy is activated since Bcl-2 inhibits autophagy by interacting with Beclin-1 [31]. In addition, the reduced levels of Bcl-2 may also explain the increase of apoptosis, since the pro-apoptotic Bax is not inhibited by Bcl-2 [32].

Different studies suggest that autophagy plays a detrimental role in a few models of IS, leading to neuronal damage [33,34]. Autophagy is selectively activated in the damaged hippocampal area from 1 to 48h of reperfusion after 20-min global ischemia, with a peak at 12h; in this context, autophagy inhibition by 3-MA, administered before ischemia, prevented the neuronal injury (Figure 3).

Targeting circ-RNAs may also reduce detrimental autophagy. In this regard, circ_0025984 overexpression reduced cerebral injury in mice undergoing MCAO, along with autophagy inhibition [35]. In line with this evidence, circ_016719 expression increased in the brain of mice undergoing MCAO. Moreover, circ_016719 knockdown *in vitro* reduced apoptosis in neurons undergoing oxygen/deprivation along with the reduction of autophagy. Vitexin, a flavone C-glycoside found in several medical and other plants, reduced brain infarction in the MCAO rat model by suppression of the ischemia-induced autophagy through a mechanism that restored mTOR level and at the same time repressed Ulk1, Beclin1 and the rate of LC3Ⅱ/LC3Ⅰ [36]. Consistently, melatonin administration before induction of cerebral ischemia in an I/R mouse model was able to exert protective effects toward brain damage through inhibition of autophagy.

Autophagy as therapeutic target in IS

Restoration of autophagy in models of IS in most cases exerts beneficial effects and reduces brain injury. To date, several strategies have been developed to enhance autophagy with pharmacological agents. Natural compounds able to activate autophagy are promising tools, with limited side effects [37,38]. Among natural activators of autophagy, the disaccharide trehalose improves vascular function and

reduces stroke occurrence in the SHRSP [39]. Spermidine, a natural polyamine, reduces platelet aggregation in patients at high risk [38]. To the best of our knowledge, no clinical trials tested the effects of these compounds as an adjuvant therapy to improve stroke recovery or to protect patients at high risk. Synthetic compounds able to activate autophagy have also been developed. In this regard, the Tat-Beclin one is a synthetic peptide able to induce autophagy without targeting other pathways [40]. Tat-Beclin one was shown to reduce stroke occurrence in the SHRSP and to exert cardiac protective effects [41,42]. Also autophagy is a critical process in maintaining cellular homeostasis and can influence tumor survival [37]. CRISPR-Cas can be used to edit genes regulating autophagy, providing insights into how tumors adapt to stress and evade treatments [43,44]. By understanding the interplay between autophagy and immune responses, researchers can develop strategies that enhance the effectiveness of immunotherapies, potentially leading to better patient outcomes [43]. CRISPR-Cas gene editing holds significant promise in neuro-oncogenomics by enabling precise modulation of key signaling pathways and immune responses [43]. CRISPR-Cas enables the development of tailored treatments based on the specific genetic makeup of an individual's tumor. This precision approach can lead to more effective and less toxic therapies. Through its application in targeting Wnt/Frizzled-Toll-like receptors (TLRs) and autophagy, CRISPR-Cas can enhance the efficacy of immunotherapeutic strategies, paving the way for more effective and personalized treatment options for patients with brain tumors [43].

Overview of oxidative stress response in stroke

Oxidative stress refers to the imbalance between the production of reactive oxygen species (ROS) in tissues and antioxidant defense, in favour of the former leading to deleterious effects [45,46]. In organisms including humans, ROS are produced during normal metabolic and immune system function [47]. Fortunately, endogenous antioxidants such as; catalase, superoxide dismutase, and glutathione among others, keep ROS at physiologically normal levels by converting free radicals into more stable and less harmful molecules. Although, an overwhelming increase in the concentration of ROS beyond the capacity of these antioxidants alters the deoxyribose nucleic acid (DNA), proteins, lipids and carbohydrate components of tissues [48-50]. Oxidative stress is a silent participant in chronic progressive pathology and degenerative disorders (Figure 4). Progressive research has shown that it is implicated in pathologies including cancer, atherosclerosis, cardiovascular disorders, and, remains a fundamental mechanism of cellular damage following cerebral ischemia [51]. Studies have shown that the brain is more vulnerable to ROS than other organ in the biological system due to low neuronal antioxidant activity, high level of perioxidasable lipids, a high supply of iron and excessive oxygen consumption under pathological conditions [52]. During an ischemic stroke, the oxidative destruction of lipid is more damaging to cells than protein oxidation. ROS attacks polyunsaturated fatty acids in the neurons resulting in a formation of lipid radicals such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) which are known to be neurotoxic. This is because they both have the ability to induce apoptosis in neurons thereby exacerbating the damage caused by the initial ischemic event. ROS leads to deoxyribose nucleic acid (DNA) mutations and DNA structural alterations as a result of breaking DNA double strands [50,53].

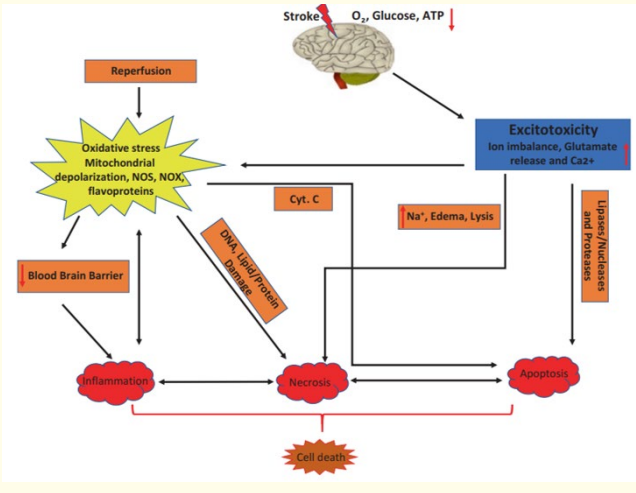

Figure 4: *Inflammation, oxidative stress, and cerebral stroke: basic principles [54].*

Ischemic stroke greatly contributes to the dysfunction of the blood-brain barrier (BBB) which plays a vital role in maintaining the brains microenvironment. ROS can initiate the breakdown of tight junctions in the BBB which can ultimately lead to increased permeability and potential cerebral edema further complicating the ischemic injury. This way, neurotoxins can penetrate the brain tissue aggravating neuronal damage. This cycle of process is usually followed by activation of apoptosis, necrosis and autophagy pathway by oxidative stress [55]. Oxidative stress plays a critical role in the pathophysiology of ischemic infarction resulting in the development of the ischemia infarction cascade. Both oxidative stress and inflammation have significant synergistic effects on cerebral ischaemia/reperfusion injury (CIRI). The CIRI causes oxidative phosphorylation uncoupling which increases ROS production and lipid peroxidation.

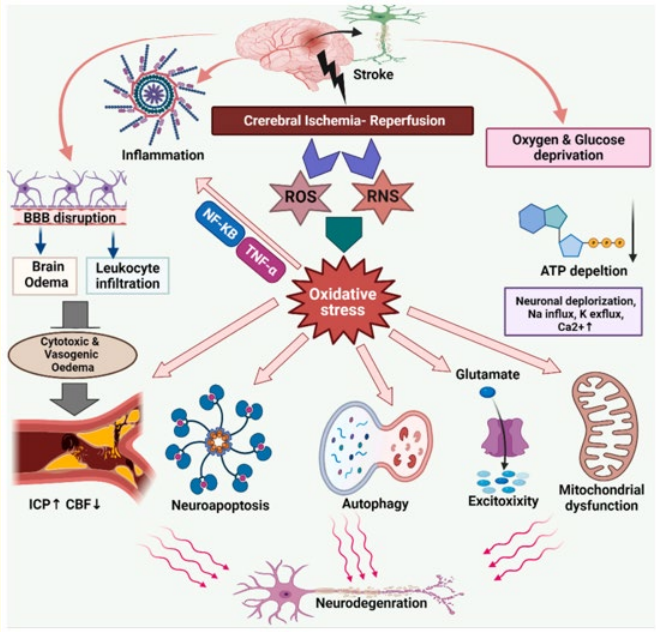

Figure 5: *Oxidative stress mediated molecular mechanisms contributing to ischaemic insult [56].*

Excessive Ros causes a chain reaction with the biological molecules in the environment affecting neuronal function leading to neuronal death and functional impairment which can lead to additional damage and dysfunction after blood flow is restored. Excitotoxicity and necrotic neuronal and non-neuronal deaths occur within minutes of the ischemic core, where blood flow is most severely restricted [57]. Increased production of ROS interferes with cellular signalling pathways and disrupts mitochondrial function, leading to energy deficits in neurons. The dysfunction leads to impairment in the ability of brain cells to recover from ischemic damage [50].

Overview of the inflammatory response in stroke

Initial ischemic event leads to oxidative stress and excitotoxicity which causes activation of microglia and astrocytes resulting in secretion of cytokines, MMP, and GFAP [58]. These proinflammatory factors lead to upregulation of cell adhesion molecules such as ICAM-1 and selectins on endothelial cells causing inflow of blood-derived inflammatory cells such as neutrophils, macrophages, and lymphocytes to the ischemic area (Figure 6). In addition, danger-associated molecular patterns (DAMPs) are released by dying neurons that in turn activate microglia and peripheral immune cells (neutrophil, macrophage, and lymphocyte) resulting in the production of proinflammatory factors causing further activation of microglia and astrocyte [58]. These pathological events lead to neuronal death and further increase damage to the ischemic brain.

The inflammatory reaction in stroke is very complicated, as it is a series of interactions between immune cells, like cytokines, chemokines, and signaling pathways. Stroke-induced inflammation is a complex process encompassing numerous cellular and molecular players where microglial activation is a major actor. Microglia are the immune elements that exist naturally in the central nervous system and they become active after the ischemic injury is performed. This activates an immune response chain, [59]. Activated microglia brain cells express IL-1β, TNF-α, and IL-6 which influence neuroinflammation and cell damage [60], also IL-6 increases the amplitudes of T-type voltage-gated calcium channels (VGCCs) in neurons, contributing to cellular stress and damage [61].

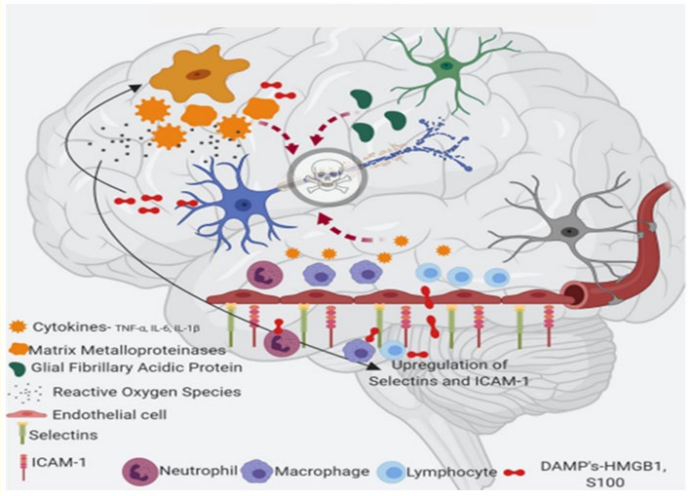

Figure 6: *Inflammatory response in ischemic stroke [60].*

Cytokine release is one of the inflammation characteristics in the brain after a stroke. Hence, these signaling molecules, including the ones produced by immune cells, endothelial cells, and neurons act as conductors to orchestrate the invasion of immune cells, the opening of the blood-brain barrier, and neuronal damage [11]. The disruption of cytokine signal regulation, with a marked imbalance between proinflammatory and anti-inflammatory cytokines, might be responsible for worsened neuronal damage and contribute to secondary brain trauma after a stroke.

Leukocyte infiltration into the brain parenchymal tissue is yet another major component of stroke-induced inflammation. Cells that participate in a reaction after blood circulation is restored, depriving brain tissue of oxygen contain neutrophils, monocytes, and lymphocytes [62]. Leukocytes, through the mechanism of ROS and proteinase release, cytokine production, and radical molecule formation, aggravate the inflammatory response and cause prolonged neuronal damage.

Inflammation and autophagy in ischemia/reperfusion brain injury

An initial ischemic event, such as a stroke, triggers a cascade of events that lead to neuronal damage and exacerbate the initial injury. The lack of blood flow causes oxygen and nutrient deprivation, resulting in oxidative stress and excitotoxicity, which damage neurons and release danger signals. These signals activate microglia and astrocytes, the brain's resident immune cells, initiating an inflammatory response [58]. Activated microglia and astrocytes release proinflammatory factors, including cytokines (IL-1β, TNF-α, IL-6), MMPs, and GFAP [59,60]. These factors disrupt the blood-brain barrier by upregulating cell adhesion molecules on endothelial cells, specifically selectins and ICAM-1 [11]. This upregulation promotes the adhesion and infiltration of blood-derived inflammatory cells, such as neutrophils, macrophages, and lymphocytes, into the ischemic area [63].

The influx of these cells further contributes to inflammation through the production of ROS, proteinase release, and cytokine production [65]. The increased expression of selectins and ICAM-1 on endothelial cells facilitates the rolling and firm adhesion of these inflammatory cells, respectively, leading to their migration across the blood-brain barrier [11]. Adding to the complexity, dying neurons release danger-associated molecular patterns (DAMPs), which activate both microglia and peripheral immune cells [58], creating a positive feedback loop that amplifies the inflammatory response. This vicious cycle of inflammation leads to neuronal death and exacerbates the initial ischemic damage. While the inflammatory response is detrimental, the ischemic event also triggers a protective mechanism: autophagy. The metabolic crisis caused by ischemia activates the 5'-AMP-activated protein kinase (AMPK) pathway, which serves as a cellular energy sensor [63], and inhibits the mammalian target of rapamycin (mTOR) pathway [64], both promoting autophagy. Autophagy helps clear damaged components, reducing inflammation and promoting cell survival [65]. However, under prolonged ischemic conditions, excessive autophagy can lead to cell death [66]. Further complicating this interplay, inflammatory pathways, such as the mitogen-activated protein kinase (MAPK) pathway, can inhibit ULK1 activity through direct phosphorylation, thereby reducing autophagic flux and exacerbating inflammation [63]. This creates a negative feedback loop where inflammation further impairs autophagy, leading to increased neuronal injury [63].

Microglia, the central players in the inflammatory response, can adopt different phenotypes: M1 (pro-inflammatory) and M2 (anti-inflammatory) [67]. Autophagy in microglia can suppress the activation of the NLRP3 inflammasome, a key mediator of neuroinflammation, by degrading its components, thus mitigating the inflammatory response [65]. Conversely, when autophagy is inhibited, inflammasome activation can lead to increased production of pro-inflammatory cytokines, further contributing to neuronal damage [65]. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway also plays a critical role in this interplay. Autophagy can regulate NF-κB activity, influencing the expression of inflammatory cytokines and the phenotypic transformation of microglia [68]. This regulation is crucial for tissue recovery following ischemic events [68].

Clinical studies have demonstrated that markers of autophagy, such as LC3-II and Beclin-1, are significantly upregulated following ischemic events, indicating increased autophagic activity [69]. For instance, a clinical trial involving patients with acute ischemic stroke showed that elevated levels of these markers correlated with better neurological outcomes, suggesting a protective role of autophagy [70]. Additionally, clinical trials are investigating the efficacy of pharmacological agents that modulate autophagy, such as resveratrol, which has shown neuroprotective effects by enhancing autophagy and reducing inflammation in preclinical models [71].

Preclinical studies using rodent models have shown that inhibiting autophagy can alleviate ischemic injury by reducing the activation of inflammasomes, which are critical mediators of the inflammatory response [16]. For example, research demonstrated that pharmacological inhibition of autophagy reduced neuronal death and improved functional recovery in models of ischemic stroke [72] Furthermore, computational studies have identified key regulatory proteins and microRNAs that modulate the autophagy-inflammation axis, providing potential targets for therapeutic intervention [70]. Recent studies have explored potential therapeutic interventions targeting these pathways. Compounds such as resveratrol have shown promise in modulating the autophagy-inflammation axis, providing neuroprotective effects by enhancing autophagy and reducing inflammatory responses [72]. By targeting the AMPK/mTOR signaling pathways, these therapies aim to restore the balance between autophagy and inflammation, promoting neuronal survival and recovery.

Overall, the inflammatory response to stroke is a complex and multifaceted process involving numerous cell types, signaling molecules, and pathways. Microglia are key players in this process, influencing both the initiation and progression of inflammation. Autophagy, while initially protective, can become detrimental under prolonged ischemia, further highlighting the intricate interplay between these mechanisms. Understanding these complex interactions is essential for developing therapeutic strategies to target inflammation and protect neurons after ischemic stroke.

Role of inflammation in exacerbating tissue damage and promoting neuroinflammation

Inflammation has two sides in the stroke pathophysiology that often give more or less advantageous effects. Acute inflammation which has its role in the recruitment of immune cells and repair of tissues, is required, while excessive or chronic inflammation causes neurotoxicity and neurodegeneration [73]. Activation of inflammatory pathways such as NF-κB pathway and inflammasome, which lead to the overproduction of pro-inflammatory mediators and tissue damage, is also been reported by several studies [58].

Neuroinflammation occurs due to the long-term activation of glial cells that in turn lead to the release of inflammatory substances that are linked to neuronal dysfunction and synaptic loss (Figure 7). Chronic Inflammation in the hippocampus and other memory-related regions may contribute to post-stroke cognitive impairment, and age-related dementia following a stroke [74,75]. While persistent microglial activation in remote brain areas suggests inflammation could impair neuroplasticity and recovery of function [76].

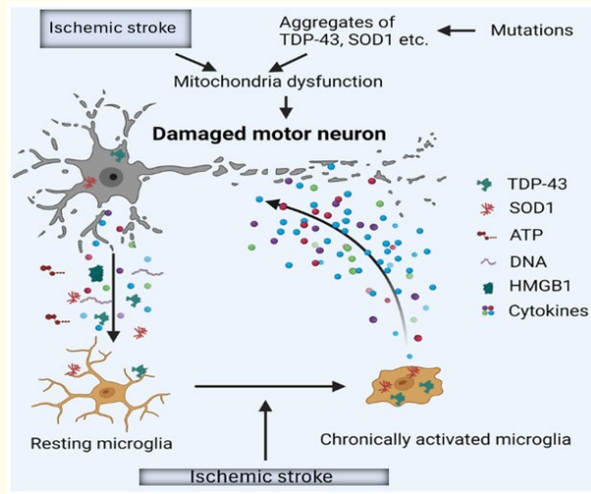

Figure 7: *Role of inflammation in stroke. Created with biorender.com.*

Cross-talk between inflammation and autophagy/oxidative stress pathways in stroke pathology

Communication between inflammation and other cellular pathways, like autophagy and oxidative stress, is very central to the mechanisms of stroke pathology. These inflammatory mediators can regulate autophagy, like TNF-α and IL-1β, and cause cell life or death in response to ischemic injury [77]. On the other hand, autophagy that may be dysregulated may affect cytokine secretion, the function of immune cells, and cellular homeostasis [78].

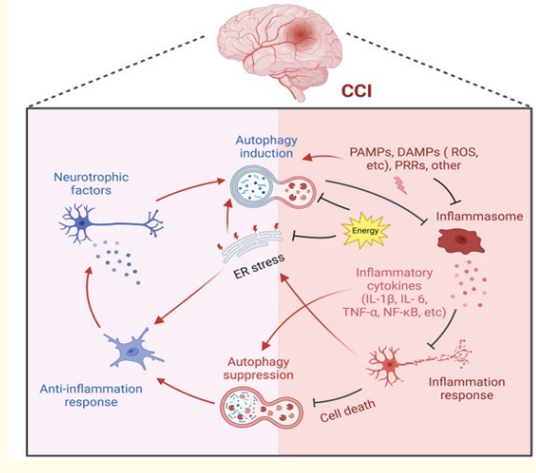

Figure 8: *Relationship between inflammation, autophagy and oxidative stress in stroke pathology. Created in Biorender. com.*

Oxidative stress, which entails the situation when free radicals are produced more than they are scavenged, is concurrent to inflammation in stroke. Reactive oxygen species (ROS) formation by ischemia activates inflammatory pathways and stimulates neuroinflammation, thus neuronal injury [10]. While cytokines that provoke inflammation can in turn induce Reactive Oxygen Spices (ROS) in different cells, and thus, a vicious cycle of oxidative damage and inflammation continues in stroke pathology. Knowledge of the complicated interactions between inflammation, autophagy, and oxidative stress pathways is the key factor for developing a targeted therapy based on cellular homeostasis restoration, treatment of inflammatory response, and providing neuroprotection in stroke.

Interactions between autophagy, oxidative stress, and inflammation

Mechanisms by which autophagy modulates oxidative stress and inflammation in stroke

Autophagy not only modulates oxidative stress and inflammation in stroke but also influences neuronal survival and tissue recovery. In addition to removing damaged mitochondria, autophagy uses (mitophagy) as one of the mechanisms to control oxidative stress. Mitochondria are the primary source of ROS, and dysfunctional mitochondria result in oxidative stress during stroke [78]. Selective removal of damaged mitochondria through autophagy is a great contributor to keeping a balance of redox energy in the cell and fighting against oxidative damage.

Also, autophagy can play a role in inflammation by controlling the degradation of the inflammasome and pro-inflammatory cytokine synthesis. Cytokines are a family of proteins composed of different subunits, including among others, interleukin-1β (IL-1β) and interleukin-18 (IL-18). The role of these particular cytokines is to initiate and regulate the inflammasome reactions in the body. Autophagy, by the degradation of the component inflammasome and cytokines, prevents too much inflammatory response and spares the neuroinflammation in stroke [80]. Furthermore, autophagy can influence the function and polarization of the immune cells involved in recovery mechanisms which is important for the balance between pro and anti-inflammatory responses. Both autophagy and macrophage phagocytic removal of protein aggregates and dysfunctional organelles in the immune cells ensure the proper functioning of these cells and prevent hyperinflammation in the brain [78]. These mechanisms taken together demonstrate the neuroprotective role of autophagy by removing oxidative stress and inflammation during stroke.

Feedback loops and regulatory networks linking autophagy, oxidative stress, and inflammation

Interactions between autophagy, oxidative stress, and inflammation create a complex network of cellular responses to ischemic injury forming intricate feedback loops and regulatory networks. An example of feedback regulation is the regulation of autophagy by oxidative stress and inflammation. ROS, generated in oxidative stress, can therefore both act as activators of autophagic pathways and cause cellular damage as part of the cellular defense system [81]. However, autophagy has a protective role to play in countering oxidative stress by clearing out the damaged organelles and proteins, thus systematically decreasing oxidation.

Inflammation, with special reference to neuroinflammation, is self-regulated and induced by autophagy. These inflammatory molecules and autophagy are induced by inflammasome activation which is a way of mounting an immune response to clear cellular debris and lower the inflammatory signaling [82]. However, excessive inflammation inhibits autophagy and causes damage, indicating a delicate balance between these two processes in the pathophysiology of stroke.

The regulatory networks comprising autophagy, oxidative stress, and inflammation entail cardinal signaling pathways like the mTOR pathway, the NF-κB pathway, and the Nrf2-Keap1 pathway [79,19,80]. The mTOR pathway, a main regulator of autophagy, responds to oxidative stress and inflammatory messages by adjusting the level of autophagy [82,84]. NF-κB, a transcription factor associated with inflammation already, can govern autophagy-related gene expression and influence autophagic flow when living with the inflammatory

stimulus [19,85]. Besides, the Nrf2-Keap1 pathway for antioxidant defense also interferes with both autophagy and inflammation, which coordinate the defenses against oxidative stress and inflammation in stroke [86].

Importance of balancing these processes for neuronal survival and recovery

Balancing autophagy, oxidative stress, and inflammation is critical for promoting neuronal survival and recovery following stroke. Excessive autophagy can lead to excessive protein degradation and cell death, while impaired autophagy can result in the accumulation of damaged organelles and proteins, exacerbating oxidative stress and inflammation [87]. Therefore, maintaining optimal autophagic activity is essential for cellular homeostasis and neuroprotection in stroke.

Similarly, oxidative stress and inflammation must be strictly regulated to prevent neurotoxicity and promote neurorepair. Excessive ROS production and inflammatory cytokine release can amplify neuronal damage and hinder recovery processes [88]. Strategies aimed at modulating autophagy, oxidative stress, and inflammation in a coordinated manner, such as pharmacological interventions targeting key signaling pathways or lifestyle interventions promoting antioxidant defense and anti-inflammatory responses, hold promise for improving stroke outcomes and enhancing neuronal resilience.

Clinical implications and therapeutic strategies

From preclinical findings to potential therapeutic avenues in stroke management

The translation of the pre-clinical studies related to autophagy, oxidative stress, and inflammation to the potential treatment options in stroke management opens up a whole new horizon of better prognosis for patients. In preclinical studies, the many complex mechanisms involved in stroke pathology have been revealed as well as their interaction with other processes, shedding light on the possibility to develop targeted medicines.

The possibility of developing the treatment line may be centered around stimulating autophagy to produce neuroprotection and tissue regeneration. The preclinical studies have identified pharmacological agents like rapamycin and caloric restriction as well as lifestyle interventions that induce autophagic activity as potential neuroprotective strategies for preventing the devastating effects of stroke [4,89,90]. This technique endeavors to enhance autophagic flux, minimize neuronal damage, and help in the return of function after stroke.

Additionally, the exploitation of anti-inflammatory pathways is eligible in the stroke treatment strategy, as it has been described [91]. Antioxidant therapies, including natural compounds like resveratrol and synthetic antioxidants like edaravone, have shown neuroprotective effects in preclinical studies, by reducing glutamate and thus inhibiting free radical formation, while at the same time improving cellular tolerance to ischemic injury [92-94]. These methods are aimed at deactivating ROS which trigger neuronal damage to alleviate these effects and elevate the endogenous compounds of stroke patients [94].

Anti-inflammatory agents, such as minocycline and omega-3 fatty acids, have demonstrated neuroprotective effects by attenuating neuroinflammation, reducing immune cell infiltration, and promoting tissue repair in preclinical studies [95,96]. These interventions aim to dampen excessive inflammatory responses and restore immune homeostasis in the ischemic brain.

Current clinical trials/therapeutic approaches targeting autophagy, oxidative stress, or inflammation in stroke patients

Various clinical trials and treatment approaches are now ongoing in an attempt to target autophagy, oxidative stress, and inflammation in stroke patients. These trials were designed to activate the transition of preclinical data to clinical treatments in patients which may lead to improved clinical outcomes and better recovery. Regarding the modulation of autophagy, clinical trials are aimed at studying the security and efficiency of autophagy inducers like rapamycin analog and metformin for stroke patients [97,98]. These trials aim to reveal

the neuroprotective effects of engaging autophagy function and to assess the application of autophagy-targeting therapies in real clinical conditions.

In terms of oxidative stress management, clinical trials are assessing the efficacy of antioxidant therapies in stroke patients [99,100]. The antioxidant agent, edaravone was explored in clinical trials to see its capability to lessen damage caused by oxidation and improve functional outcomes in patients who suffered ischemic stroke [101,102]. Which purpose is to check whether antioxidants are neuroprotective and how they are most effective in stroke management.

Relevant to inflammation regulation, clinical trials are assessing anti-inflammatory investigations of stroke patients. Agents that go for targets such as cytokines inhibitors, immune cell activity, and neuroinflammation cascades, such as minocycline, and monoclonal antibodies, are the focus of evaluating their efficacy in the treatment of stroke patients [102,103]. The goals of these trials are to find new anti-inflammatory therapies and adjust the use of available therapies in clinical settings.

Challenges and opportunities in developing targeted therapies based on these mechanisms

The development of new therapies that are based on autophagy, oxidative stress, and inflammation methods, produces a potential avenue for the care of stroke patients. However, that does not mean that there are no challenges to be overcome. Creation of therapeutics that effectively target the interactions between these pathways while minimizing cross-reactivities is a complex task that requires complete knowledge of their precise regulation and context-dependent roles in stroke pathogenesis. Secondly, there is the challenge of setting up reliable *in vivo* models that accurately mimic human stroke physiology and therapeutic reactions. Although clinical application of successes of preclinical trials still requires rigorous testing performed not only in the animal models but also in the predictive marker validation in human patients. In addition, personalized treatment options that considers the type of stroke, the patient's degree of severity, comorbidities, and genetic factors are also necessary. Such precision medicine methods that integrate clinical, imaging and molecular data, have prospects for suitable treatments and enhancing treatment responses in stroke management. Even though these barriers exist, the stroke treatment strategies based on autophagy, antioxidative stress, and anti-inflammatory mechanisms will constitute a paradigm shift in stroke management helping to establish neuroprotection, tissue repair, and functional recovery in stroke patients.

Conclusion and Future Perspectives

Looking ahead, three main themes need to be prioritized in future studies that will help to enrich our knowledge about stroke pathology and lead to better treatment methods. One of the most fundamental problems lies in the lack of information which is going to contribute to the further understanding of the autophagy, oxidation, and inflammation link in stroke. While considerable progress has been achieved in elucidating the molecular basis of the autophagy mechanism in stroke pathophysiology, questions on the specific roles of certain autophagy proteins at different stages of stroke, the temporal modulation of autophagy at different phases of stroke, and the integrated interactions between autophagy and inflammatory signalling networks remain to be solved. Understanding the complex interactions between autophagy, oxidative stress, and inflammation is paramount for developing personalized and targeted approaches in stroke care. By elucidating the signaling pathways, feedback loops, and regulatory networks that govern these processes, researchers can pave the way for precision medicine strategies tailored to individual patient profiles and stroke subtypes. Ultimately, this comprehensive understanding will not only lead to the development of more effective neuroprotective therapies but also contribute to improved patient outcomes, reduced disability, and enhanced quality of life for stroke survivors. To prevent the activation of dangerous forms of autophagy, it may be helpful to have a deeper understanding of the molecular mechanisms underlying autophagy and associated signal transduction pathways. The final step is to identify circulating autophagy biomarkers that can predict the prognosis and predisposition to stroke, as well as genetic techniques that target variations in autophagy genes. These approaches will help translate data from preclinical studies to the human disease. By focusing on these various facets, we could eventually be able to create therapeutic approaches that target autophagy to cure IS in humans.

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