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Review

Exploring autophagy in treating SARS-CoV-2 spike protein-related pathology

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ABSTRACT

Fasting, a practice with historical roots in various cultures, has recently garnered significant interest in the field of medicine. In this article, we delve into the mechanisms underlying fasting-induced autophagy and its therapeutic applications for spike protein associated pathology. We explore the therapeutic potential of fasting on spike protein-related pathology and the role of interventions to upregulate autophagy, including compounds like spermidine, resveratrol, rapamycin, and metformin. In conclusion, fasting, coupled with an understanding of its nuances, holds promise as a therapeutic intervention for SARS-CoV-2 spike protein related diseases; with broad implications for human health. This review presents the therapeutic possibility of using autophagy to treat spike protein related diseases, and details the interventions to deploy this therapeutic modality.

1. Introduction

Fasting has been used by multiple different spiritual (Venegas-Borsellino et al., 2018; Fazel, 1998; Sanchetee et al., 2020; Cohen, 1998; Sanz-Biset and Cañigueral, 2011; Krakoff, 2017; Hoffman, 1995; Patterson et al., 2015) and medicinal traditions (Visioli et al., 2022), including ancient Greek medicine, traditional Chinese medicine, Ayurveda, Indigenous medicine of the Americas, shamanic medicine, the Islamic world (Table 1).

There are a great many indigenous cultures that practice some form of fasting or food deprivation. Additionally, fasting may help in various diseases, particularly metabolic disorders, cancers and neurodegenerative diseases (Hubert et al., 2022; Galan-Acosta et al., 2015; Kaushik and Cuervo, 2018).

While fasting is identified for its therapeutic effect in these other instances, there is a potential therapeutic course for fasting in removing SARS-CoV-2 spike protein, an associated factor (Swank et al., 2023) and possible aetiological agent (Theoharides, 2022) in long COVID. Fasting is a potent inducer of autophagy, and while the benefits of fasting have been known for centuries (Table 1), the mechanism of autophagy has only recently come under investigation (Takeshige et al., 1992), most notably being the subject of the 2016 Nobel Prize in Medicine and Physiology (Levine and Klionsky, 2017).

This article describes the therapeutic potential of autophagy in treating spike protein related ailments, including long COVID-19 and post-vaccination syndrome from COVID-19 vaccines encoding the spike protein. Induction of autophagy can be facilitated via several therapeutic avenues, which include fasting (Attinà et al., 2021), fasting mimetics (Kepp et al., 2020) and nutritional support (Attinà et al., 2021). Clinical use of autophagy is still limited, however, clinical trials are demonstrating positive results (Patikorn et al., 2021), and knowledge is disseminating from practitioners to the scientific field and vice-versa.

This review presents the pathophysiology of spike protein and its interference with the autophagic machinery of the body (Liang et al., 2023), and how autophagy can be used to clear its lingering damage, especially in mitochondria (Clough et al., 2021). We then explore the various ways to upregulate autophagy and mitophagy, as well to restore mitochondrial function through promotion of mitogenesis and improving mitochondrial efficiency.

2. Pathophysiology related to spike protein

Spike protein has pathological interactions with multiple organ systems, as described by several reviews (Cosentino and Marino, 2022; Parry et al., 2023; Lin, 2023; Bellavite et al., 2023). Several of the documented pathological impacts are described in Fig. 1 and Table 2

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(Cosentino and Marino, 2022).

Most prominently, the interactions between the spike protein and ACE2 are responsible for the entry of SARS-CoV-2 into the cells during acute Covid-19 infection (Jackson et al., 2022), and activation of the ACE2 receptors can also be involved in the pathogenesis of myocarditis (Bellavite et al., 2023). An alternate cell entry pathway exists via interactions of the spike protein with CD147 (Wang et al., 2020), a pathway also implicated in the pathogenesis of myocarditis and microvascular damage (Avolio et al., 2021).

Alongside the cardiovascular implications, excessive spike protein can result in metabolic abnormalities and a down-regulation of autophagy (Nguyen et al., 1916). Other interaction partners include the estrogen receptor ERα (Solis et al., 2022), which could possibly be an explanatory factor in the menstrual irregularities observed by Covid-19 vaccinated women (Nazir et al., 2022).

Additionally, interaction with the Toll-like receptors, particularly TLR4 (Zhao et al., 2021) and TLR2 (Khan et al., 2021), can be implicated in the release of proinflammatory cytokines and a subsequent down-regulation of immune capability (Khan et al., 2021; Alturaiki et al., 2022; Halajian et al., 2022; Shirato and Kizaki, 2021).

In silico studies have suggested the possibility of interactions between the spike protein and the tumor suppressor gene p53 (Singh and Bharara Singh, 2020). If this is a real effect that withstands scrutiny, then this interaction could potentially disrupt the tumor surveillance activity of p53 (Zong et al., 2021).

Some scientists additionally have brought attention to the possibility of the spike protein, or one of its peptides, misfolding and causing the formation of prion-like aggregates (Grobbelaar et al., 2021). There is potential for neurodegenerative illness if this is an actual mechanism (Zhao et al., 2022). Simultaneously, it is known that the spike protein

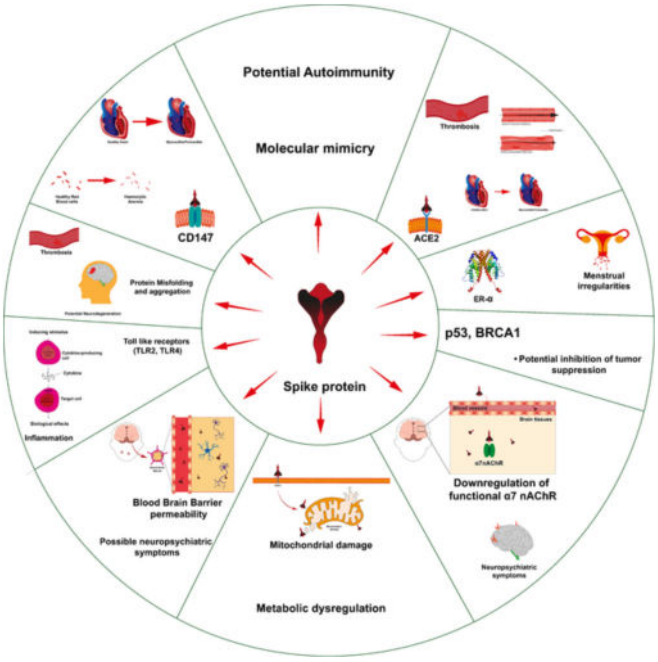

Fig. 1. Pathophysiology related to spike protein. Slices show potential mechanisms (inside) and subsequent pathophysiology (outside). These are also covered in Table 2.

Table 1
An overview of fasting in different spiritual and medical traditions, showing wide use across the Earth.

Spiritual tradition	World region	Fasting rituals
Islam	Middle East, Africa, Asia, and beyond	Ramadan: Observing a month-long fast from sunrise to sunset as a religious obligation (Krakoff, 2017).
Christianity	Europe, Americas, Africa, Asia, and beyond	Lent: Fasting for a period of 40 days leading up to Easter, often involving specific dietary restrictions (Krakoff, 2017).
Buddhism	East Asia, Southeast Asia, South Asia	Uposatha: Observing monthly fasting days to purify the mind and reaffirm spiritual commitments (Krakoff, 2017).
Hinduism	South Asia, Southeast Asia, Mauritius	Ekadashi: Fasting on the 11th day of each lunar fortnight, abstaining from grains and certain foods (Krakoff, 2017).
Judaism	Middle East, Europe, Americas, Africa, Asia	Yom Kippur: Observing a 24-h fast as a day of atonement and repentance (Krakoff, 2017).
Bahá'í Faith	Global	Nineteen-Day Fast: Fasting from sunrise to sunset during the last month of the Bahá'í calendar (Krakoff, 2017).
Jainism	India, East Africa	Ayambil: Observing a one-day fast by consuming only boiled water and specific foods (Sanchetee et al., 2020).
Native American	Americas	Vision Quest: Fasting and solitary retreat to seek spiritual guidance and connection with nature. Sun dance: Fasting and dancing, without water for multiple straight days (Cohen, 1998) Plant dietas: Preparation for ceremony (Sanz-Biset and Cañigueral, 2011)
Sufism	Middle East, South Asia, North Africa, Europe	Chilla: Engaging in extended periods of fasting and meditation for spiritual growth and purification (Hoffman, 1995).
Mormonism (Church of Latter Day Saints)	North America	Fasting one day each month (Krakoff, 2017)

Medical tradition	Region	Fasting rituals
Ayurveda	India, South Asia	Upavasa: Observing occasional fasting as a means to cleanse the body, balance doshas, and support digestion (Shripathi Adiga and Adiga, 2013).
Traditional Chinese medicine	China, East Asia	Engaging in intermittent or prolonged fasting to restore harmony and promote vitality (Wang et al., 2018).
Naturopathy	Europe, Global	Juice Fasting: Consuming only fresh fruit or vegetable juices for a specific duration to support detoxification and rejuvenation (Nair et al., 2015).
Siddha medicine	India	Ekadashi Fasting: Observing fasting on specific lunar days to eliminate toxins, promote purification, and enhance energy levels (Visioli et al., 2022).
Western medicine	Global	Preoperative Fasting: Temporarily refraining from food and drink before surgical procedures to minimize the risk of complications (Falconer et al., 2014).
Greek medicine	Ancient Greece, Mediterranean	Fasting was used in the treatment of epilepsy (Temkin, 1994).

Table 2
An overview of pathological mechanisms of spike protein.

Interacting protein	Interaction	Physiological impact
ACE-2	Binding of spike receptor binding domain (RBD) to ACE2 (Yang et al., 2020; Ozono et al., 2021)	Cell entry of SARS-CoV-2 (in the case of acute infection) (Jackson et al., 2022), thrombosis (Bellavite et al., 2023), myocarditis/ pericarditis (Bellavite et al., 2023), and vasculitis/ endotheliatis (Bellavite et al., 2023)
CD-147	Inhibition of CD-147 (Wang et al., 2020)	Myocarditis/pericarditits (Avolio et al., 2021), microvascular disease (Avolio et al., 2021), and haemolytic anemia (Al-kuraishy et al., 2022)
Toll like receptors	Binding/activation TLR4 (Zhao et al., 2021), activation of TLR2 (Khan et al., 2021)	Cytokine release and inflammation (Khan et al., 2021; Alturaiki et al., 2022; Halajian et al., 2022; Shirato and Kizaki, 2021)
High affinity estrogen receptor (ERα)	Binding/modulation to ERα (Solis et al., 2022)	Menstrual irregularities (Nazir et al., 2022)
P53 BP1, BRCA1	General interaction with spike S2 subunit observed in silico (Singh and Bharara Singh, 2020)	Potential inhibition of tumor suppression mechanisms (Zong et al., 2021)
Spike proteins or other potentially misfolding proteins	Prion like propagation of spike aggregates (Grobbelaar et al., 2021). Interaction with human prion protein and amyloid beta peptide (Larsson et al., 2023)	Potential neurodegeneration (Zhao et al., 2022), and blood microclots (Grobbelaar et al., 2021)
Functional α7 nicotinic acetylcholine receptor (α7nAChR)	A helical motif in the neck of spike protein downregulates cell surface α7nAChR (Tillman et al., 2023)	Neuropsychiatric symptoms (Changeux et al., 2020)
Blood brain barrier (BBB)	Degradation of barrier function (DeOre et al., 2021; Buzhdygan et al., 2020). Relative permeability of BBB to spike (Petrovszki et al., 2022; Rhea et al., 2021)	Possible contributor to neurologic manifestations (Mao et al., 2020)

can cross the blood-brain barrier (DeOre et al., 2021; Buzhdygan et al., 2020), which is a potential factor contributing to the high neurovirulence of SARS-CoV-2 (Bauer et al., 2022).

Other concerns include the potential for molecular mimicry between spike protein peptides and other human proteins (Devaux and Camoin-Jau, 2023) to induce autoimmune reactions (Nunez-Castilla et al., 2022). Another mechanism, downregulation of functional α7 nAChR (Tillman et al., 2023), can contribute to neuropsychiatric symptoms, which were observed in acute covid-19 (Changeux et al., 2020).

While it must be emphasized that long covid symptoms are not all due to spike protein, still the spike protein plays roles in many disease processes. While autophagy may mediate several disease mechanisms beyond those of the spike protein, the spike protein will remain the focus of this review.

Spike protein can increase levels of pyroptosis, an inflammatory process for destroying cells (Sun et al., 2022), and downregulates autophagy (Nguyen et al., 1916), though spike protein can upregulate autophagy and apoptosis in ACE2 expressing cells (Li et al., 1867). In the latter case of spike protein-induced autophagy and apoptosis, this is a highly inflammatory process (Li et al., 1867; Davidovich et al., 2014).

Spike protein S1 subunit, as well as the full trimer, can induce mitochondrial damage (Clough et al., 2021; Kim et al., 2021; Huynh et al., 2023), lowering to decreased mitochondrial energy production (Clough et al., 2021; Kim et al., 2021) and the accumulation of ROS (Clough et al., 2021). Under normal physiological conditions, damaged mitochondria are cleared via PINK1/Parkin mediated mitophagy (Pickrell and Youle, 2015; Tanaka, 2020; Jin et al., 2010), however, spike protein S1 subunit (S1) and Receptor binding domain (RBD) segments both inhibit mitophagy and increase mitochondrial ROS (Liang et al., 2023). Here, the impact on mitophagy differs between vaccination and infection; in SARS-CoV-2 infection, the ORF10 element upregulates mitophagy (Li et al., 2022), which may partially compensate for the inhibition of mitophagy by spike protein. In addition to damaging mitochondria (Clough et al., 2021; Kim et al., 2021; Huynh et al., 2023), and inhibiting turnover via mitophagy (Liang et al., 2023), energy production can also be affected by blood clots interfering with tissue oxygenation, which many COVID-19 patients experienced (Couzin-Frankel, 2020; Pujhari et al., 2021). Hypoxic conditions negatively impact mitochondrial energy production (Adzigbli et al., 2022; Solaini et al., 2010).

A wide variety of other harms are attributed to the spike protein (Halma et al., 2023a), including inflammation (Khan et al., 2021; Hsu et al., 2020; Forsyth et al., 1996), vascular damage (Lei et al., 2021; Choi et al., 2022; Bhargavan and Kanmogne, 2022), potential disruption of the blood-brain barrier (Buzhdygan et al., 2020), and the formation of aggregates (Nyström and Hammarström, 2022; Petrlova et al., 2022). Several autopsies from those deceased soon after vaccination show spike protein in cardiac (Gill et al., 2022; Schwab et al., 2023; Choi et al., 2021) and brain (Mörz, 2022) tissue. In some of these autopsies, lack of the nucleocapsid protein in these autopsies means SARS-CoV-2 infection as the cause of death is less likely (Gill et al., 2022; Mörz, 2022).

3. Autophagy mechanism

Autophagy in mammals proceeds through a series of steps, whereby abnormal proteins are marked for degradation, and an autophagosome forms around the cell contents marked for degradation. Then, a lysosome fuses to the autophagosome, and the cellular contents of the lysosome break down the contents of the autophagosome. This can be induced towards the degradation of specific cell components or towards the degradation of general cytoplasmic contents.

It was observed in the initial experiments by Ohsumi that yeast cells deficient in genes necessary for autophagy rapidly died under nutrient starvation, whereas control yeast cells survived (Tsukada and Ohsumi, 1993). This difference in robustness was later attributed to the accumulation of defective mitochondria in the autophagy deficient yeast cells (Suzuki et al., 2011). Several lines of evidence converge to the understanding that spike protein both impairs mitochondrial function (Kim et al., 2021; Huynh et al., 2023; Shang et al., 2021), as well as the process of mitophagy (Shang et al., 2021). Mitophagy is important for the maintenance of cellular energy production (Yang et al., 2019), and it is downregulated or completely inhibited in various cancers (Chourasia et al., 2015), neurodegenerative diseases (Pickrell and Youle, 2015; Park et al., 2020).

One of the pathological features of COVID-19 is the negative impact on kidney function. This may possibly be through the induction of reactive oxygen species by damaged mitochondria (Su et al., 2023), which may explain why those with pre-existing kidney disorders suffered far worse COVID-19 outcomes than other groups (Cheng et al., 2020; Bruchfeld, 2021).

Autophagy has two major roles in treating spike-protein related illness. As spike protein both damages mitochondria (Kim et al., 2021; Huynh et al., 2023; Shang et al., 2021) and also inhibits their clearance through mitophagy (Shang et al., 2021), it is important to clear out the damaged mitochondria and restore proper energy function. Additionally, the other role is the removal of the spike protein itself, whether as a protein or composing an aggregate, where the aggregate can be composed of possibly misfolded proteins.

3.1. Regulation of autophagy

Autophagy is regulated by a complex network of genes (Vargas et al., 2023; Yamamoto et al., 2023; Lei and Klionsky, 2023), and can broadly be divided into non-selective and selective autophagy, though both proceed through the formation of an autophagosome, fusion with a lysosome to form an autolysosome, and degradation of the contents (Fig. 2). Selective autophagy requires the process of ubiquitination before autophagy, where the targets are marked by ubiquitin chains, which stimulate the formation of an isolation membrane around the target contents. Targets are usually damaged organelles, misfolded proteins, or aggregates, which are sensed by the ubiquitin-proteasome system (Kriegenburg et al., 2012).

Misfolded proteins are sensed by a network of protein specific chaperones, which can refold misfolded proteins (Hartl et al., 2011). In cases where the protein is irreversibly misfolded, the chaperone can induce protein degradation via the proteasome (Arndt et al., 2007), or through the chaperone-mediated autophagy (CMA) pathway (Dice, 2007), presumed to be only present in mammals and birds (Lescat et al., 2020; Liao et al., 2021). The CMA pathway is stimulated by ketone bodies (Finn and Dice, 2005), which is a possible mechanism of its upregulation during fasting (Cuervo et al., 1995; Schneider et al., 2014). Dysregulation of CMA is observed in several disorders, and is a potential therapeutic moiety for several disorders, including age-related diseases and cancer (Hubert et al., 2022; Galan-Acosta et al., 2015; Kaushik and Cuervo, 2018).

Non-selective or bulk autophagy occurs under conditions of nutrient starvation (Hurley and Young, 2017; Montella-Manuel et al., 2021) and provides a source of nutrients for cells during periods of low or zero caloric intake (Bento et al., 2016). Unlike selective autophagy, it does not require ubiquitin tagging of autophagic targets (Vargas et al., 2023).

4. Autophagy of spike protein and aggregates

Removal of spike protein can be accomplished in part by autophagy (Halma et al., 2023b), which can be upregulated via various interventions (Fig. 3). Additionally, there are also some specific compounds that may be taken to hasten the removal of spike protein. Concerningly, spike protein bodies have been found in the autopsies of both people deceased of severe COVID-19 (Stein et al., 2022), as well as those deceased in temporal relation to receiving COVID-19 vaccines (Sessa et al., 2021).

Specifically, these compounds include nattokinase, which has been observed in vitro to degrade extracellular and membrane-bound spike protein (Tanikawa et al., 2022), and also prevents SARS-CoV-2 infection in vitro (Oba et al., 2021). In addition, for proteolytic agents to even have solvent access to proteins, it is necessary to break apart aggregates (Grune et al., 2004). Nattokinase, is a fibrinolytic compound derived from the fermentation of soy (Fujita et al., 1993; Sumi et al., 1987) which functions as a thrombolytic and fibrinolytic compound (Fujita et al., 1993; Chen et al., 2018; Jang et al., 2013; Pais et al., 2006; Kurosawa et al., 2015). It is likely that nattokinase breaks down spike protein incorporated in fibroid-amyloid clots (Hsu et al., 2009) as well as membrane bound spike protein and extracellular spike protein (Tanikawa et al., 2022). Nattokinase's ability to break down intracellular spike has not been tested, and little is known about its membrane permeability. However, computational prediction of membrane permeability for the nattokinase structure (PDB ID: 4DWW) (Yanagisawa et al., 2010) using the webserver BChemRF-CPPred (Frallicciardi et al., 2022) provides a permeability probability of 83 %, so it is possible that nattokinase can enter the cell to degrade intracellular spike protein.

Bulk autophagy has some use in degrading cellular components indiscriminately, however, selective autophagy is useful for degrading specific targets, in our cases mitochondria (mitophagy) and aggregates (aggrephagy). Selective autophagy marks targets (often with ubiquitin) prior to encapsulation in the autophagosome and degradation in the autolysosome (Vargas et al., 2023).

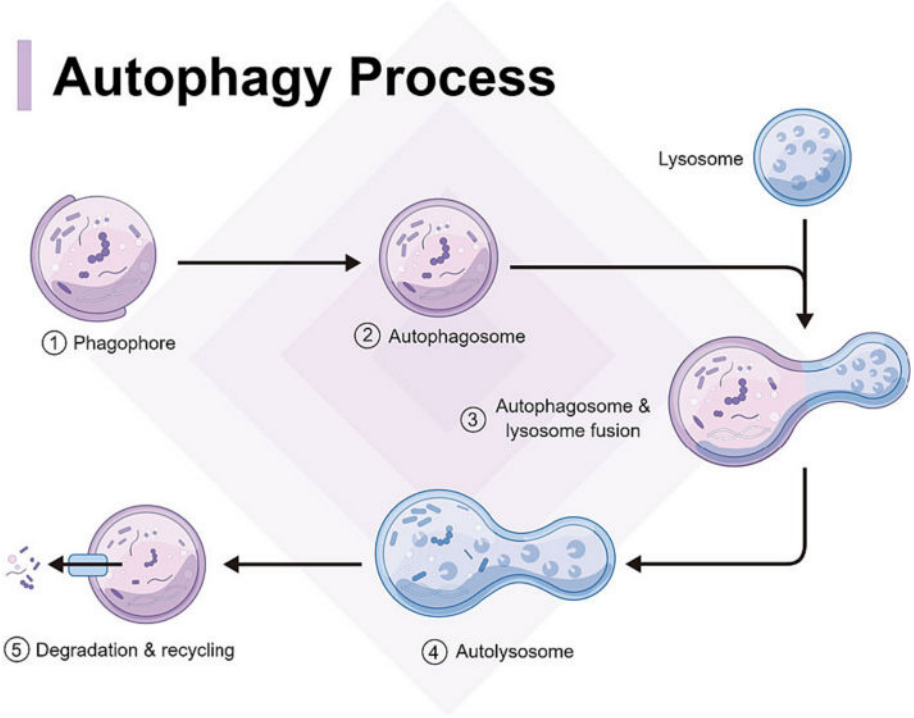

Fig. 2. The process of autophagy. Degradation requires encapsulation by the isolation membrane (process shown in (1)) and the formation of the autophagosome (2). Lysosomes, containing proteases fuse to the autophagosome (3), forming the autolysosome (4). Contents can then be degraded and recycled (5).
Reproduced from Cheng et al. (2022) under the terms of the Creative Commons Attribution License (CC BY).

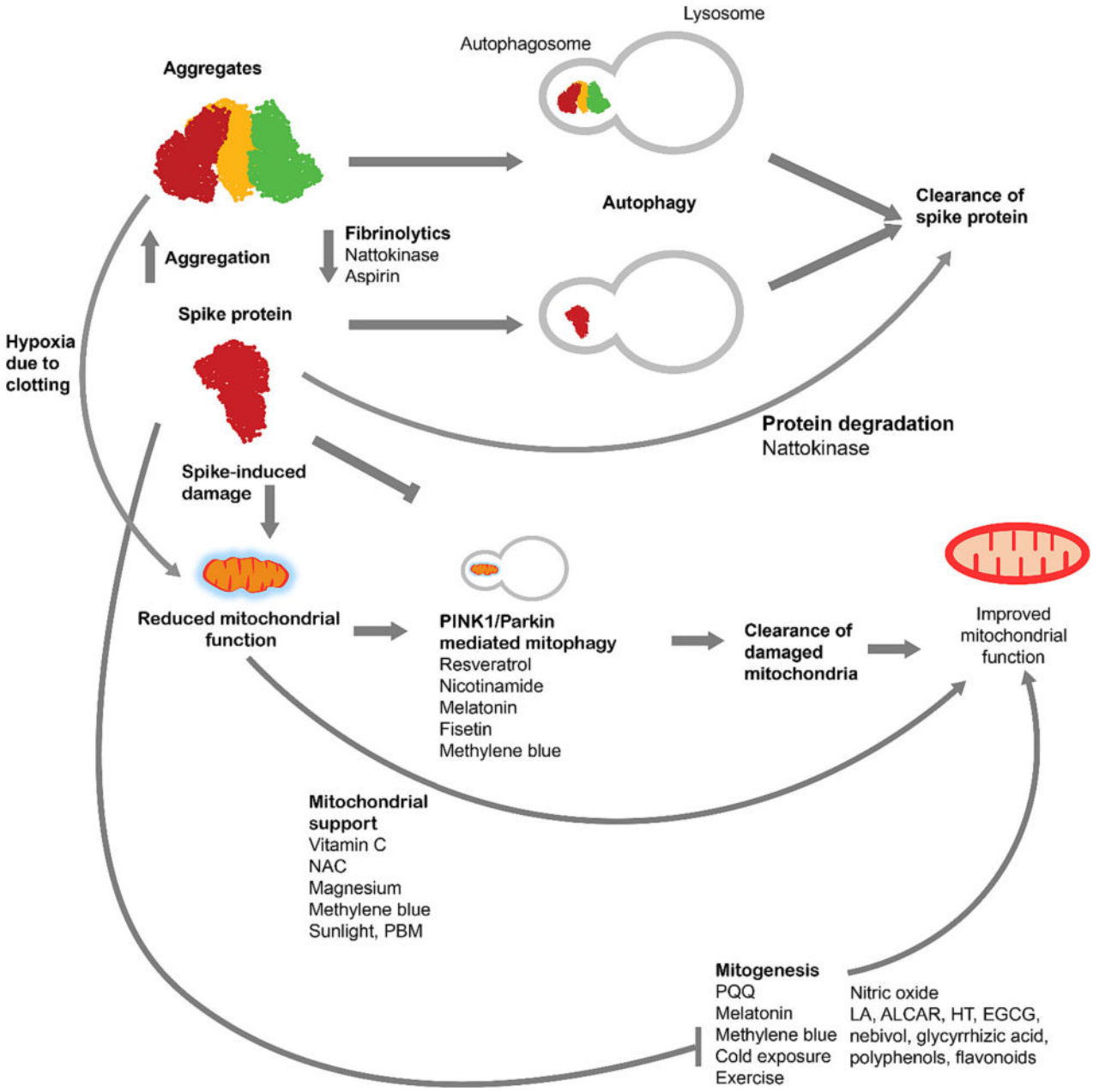

Fig. 3. Pathways involved in the pathogenesis of spike-protein induced damage and available therapeutic pathways.

5. Autophagy for treatment of spike protein-induced pathologies

There are multiple points at which autophagy can be influenced, as there are many genes and signaling mechanisms regulating autophagy. The factors which influence autophagy are broadly broken into two classes, lifestyle (fasting) and pharmacological.

In the context of acute Covid-19 infection, periodic fasting is associated with a lower severity of Covid-19 outcomes (Horne et al., 2022). Impaired fasting glucose and diabetes are also associated with lower anti-spike antibody titers after vaccination (Islam et al., 2022), which may be a proxy measurement associated with a poorer response to Covid-19 infection. Elevated blood glucose is also associated with slower clearance of SARS-CoV-2 omicron infection (Zhang et al., 2022). The worsening of infection outcomes with lowered metabolic parameters in cases of acute infection may support the efficacy of fasting for the treatment of long Covid.

In addition to proxy evidence, a case series of long Covid patients performing long-term fasting exists, showing improvements in thirteen out of fourteen patients (Grundler et al., 2023).

5.1. *Fasting and autophagy*

Time -restricted eating (TRE) and Intermittent fasting (IF) are effective methods to activate autophagy and mitophagy (Jamshed et al., 2019; Alirezaei et al., 2010; Godar et al., 2015; Martinez-Lopez et al., 2017). The mammalian target of rapamycin (mTOR) is a nutrient sensor and regulator of cell growth that is activated by glucose and protein (leucine) which switch on the pathway, inhibiting autophagy (Fernandes and Demetriades, 2021; Kim and Guan, 2019). Under low nutrient conditions, mTOR is deactivated, which enables autophagy (Yu et al., 2010).

Fasting, by definition, means abstaining from eating. TRE is a type of fasting where food intake is limited to a short window during the day (1

to 8 h), with only fluids such as water, tea, or coffee for the rest of the day (Regmi and Heilbronn, 2020). IF usually involves a longer period of fasting; the most common is alternative day fasting (24-h fasting, followed by a 24-h eating window) (Patterson et al., 2015). However, many people fast for several days (3–7 days, or up to 14 days) followed by slow refeeding (Longo and Mattson, 2014).

TRE and IF have many metabolic, cellular, and immunologic benefits (Mattson et al., 2017; Anton et al., 2018; Patterson and Sears, 2017). It is important to emphasize that TRE/IF are not synonymous with caloric restriction (CR), though people do tend to eat less ad libitum following a fasting regimen (Chowdhury et al., 2016). Additionally, eating nutrient-dense (Fuhrman et al., 2010) and high-protein (Oliveira et al., 2021) foods can decrease the sensation of hunger. More extended (1–2 days) fasting, can increase basal metabolic rate (BMR) (Zauner et al., 2000; Catenacci et al., 2016) and growth hormone (GH) levels (Thissen et al., 1994; Ho et al., 1988). Calorie-matched studies show a greater improvement in metabolic parameters (insulin sensitivity) in individuals adopting IF as opposed to CR (Harvie et al., 2011; Harvie et al., 2013).

TRE/IF has a profound effect on promoting immune system homeostasis (He et al., 2023). Fasting improves mitochondrial health (Lettieri-Barbato et al., 2018; Singh et al., 2021; Rojas-Morales et al., 2020; Real-Hohn et al., 2018) and protects hematopoietic stem cells from damage (Cheng et al., 2014). TRE/IF may be an effective therapy for the treatment of insulin resistance (Sutton et al., 2018), metabolic syndrome (Rajpal and Ismail-Beigi, 2020; Guo et al., 2021), and type II diabetes (Furmli et al., 2018; Albosta and Bakke, 2021). In addition, Intermittent fasting has additional benefit in prolonging health-span, alleviating the symptoms/curing many chronic diseases as well as preventing cardiovascular disease (Mattson and Wan, 2005), neurodegenerative diseases (Martin et al., 2006) (e.g. Alzheimer's Disease) and cancer (Clifton et al., 2021).

5.2. Compounds for increasing autophagy

Increasing the level of autophagy is important to increase the rate at which foreign proteins and aggregates can be cleared. This section describes pharmacological strategies to induce or upregulate autophagy.

5.2.1. Spermidine

Spermidine is produced endogenously from the precursor putrescine. It is a polyamine which can stimulate autophagy via inhibition of the acetyltransferase EP300 (Pietrocola et al., 2015). It can be consumed exogenously and is found in high concentrations in wheat germ and other vegetables (Ali et al., 2011; Madeo et al., 2020), though conflicting information exists on whether supplementation raises polyamine levels. Studies show that oral polyamine intake raises levels (Soda et al., 2009; Soda et al., 2021) supplementation does not appear to raise spermidine levels (Senekowitsch et al., 1852). However, spermidine supplementation shows improvement in cognitive function in animal models (Madeo et al., 2018). In human trials, spermidine improved memory performance in older adults at risk for dementia (Wirth et al., 2018) though this effect was not seen in a different study on older adults experiencing cognitive decline (Schwarz et al., 2022; Schwarz et al., 2018).

5.2.2. Caffeine

Multiple article have demonstrated a link between caffeine consumption and enhanced autophagy in in vivo studies (Ray, 2013; Pietrocola et al., 2014).

5.2.3. Resveratrol

Resveratrol is a plant phytochemical (non-flavonoid polyphenol) that is a potent inducer of autophagy (Ferraresi et al., 2017; Josifovska et al., 2020). In addition, resveratrol has anti-inflammatory (Meng et al., 2021) and antiviral (Pasquereau et al., 2021) (incl. SARS-CoV-2) properties and has beneficial effects on the microbiome (Chen et al., 2020). Resveratrol activates the fasting state (Chatam et al., 2022) and inhibits mTOR-related inhibition of autophagy (Park et al., 2016).

5.2.4. Curcumin

Curcumin, the active ingredient in turmeric, has antiviral activity against SARS-CoV-2. In addition, this spice has anti-inflammatory, immune-modulating properties, and potent anti-cancer activity (Hewlings and Kalman, 2017). Curcumin activates autophagy (Lee et al., 2011; Shakeri et al., 2019). Curcumin has low solubility in water and is poorly absorbed by the body (Anand et al., 2007); consequently, it is traditionally taken with full-fat milk and black pepper, the latter of which greatly enhances bioavailability (Shoba et al., 1998). Nano-curcumin preparations or formulations designed to enhance absorption are recommended (Anand et al., 2007).

5.2.5. Other compounds

There is some that evidence that Epigallocatechin gallate (EGCG) may increase autophagy (Ferrari et al., 2022; Zhou et al., 2014). The diabetes drug rapamycin is also a potent inducer of autophagy (Rubinsztein and Nixon, 2010; Rangaraju et al., 2010; Sarkar et al., 2009; Sotthibundhu et al., 2016). There are other compounds which may increase autophagy through various pathways, and some have supporting in vitro evidence. These were covered in a recent review (Lin et al., 2017).

5.2.6. Other non-pharmacological modalities

Fasted intense exercise can increase autophagy (Martin-Rincon et al., 2018; He et al., 2012; Vainshtein and Hood, 2016), as can acute heat stress (Summers and Valentine, 2020). One unconventional way of potentially boosting autophagy is via electrical stimulation (Moser et al., 2022; He-Ling et al., 2021; Lyamzaev et al., 2018).

6. Improving mitochondrial function

In addition to clearing damaged mitochondria, it may be of therapeutic benefit to improve the mitochondrial function of the other mitochondria. Ideally, we do not want these processes to interfere.

6.1. Mitophagy

Spike protein can damage mitochondria (Clough et al., 2021; Denaro et al., 2022), and is therefore important to both clear spike and restore the damaged mitochondria. Degradation of mitochondria via a selective form of autophagy, named mitophagy, is a fundamental mechanism conserved from yeast to humans that regulates mitochondrial quality and quantity control. Mitophagy is promoted via specific mitochondrial outer membrane receptors, or ubiquitin molecules conjugated to proteins on the mitochondrial surface (PINK1 and Parkin) leading to the formation of autophagosomes surrounding mitochondria. PINK1 is a protein that surveils for damaged mitochondria (Tanaka, 2020; Narendra et al., 2008). In healthy mitochondria, PINK1 is imported into the mitochondria, and then is subsequently cleaved by proteases (PARL and Oma1) on the inner mitochondrial membrane (Yamano and Youle, 2013). When mitochondria lose their membrane potential, PINK1 cannot reach the inner membrane (Jin et al., 2010) and accumulates in the outer mitochondrial membrane, where it begins to phosphorylate serine 65 on ubiquitin chains, which in turn activates Parkin (Kazlauskaite et al., 2014; Shiba-Fukushima et al., 2014; Koyano et al., 2014; Kane et al., 2014), and subsequently signals mitophagy (Heo et al., 2015).

Disrupted mitochondrial membrane potential is the signal which ultimately leads to mitophagy, and several pathological mechanisms work by downregulating mitophagy via increasing the membrane potential (Hu et al., 2016). There are several pharmacological pathways through which mitophagy can be induced (Georgakopoulos et al., 2017). Notably, this list includes the natural compounds resveratrol (Huang et al., 2015), fisetin (Schiavi et al., 2015), and nicotinamide (Jang et al.,

2012), which have been examined for their potential therapeutic impacts in acute- or long-COVID (Block and Kuo, 2022; Domi et al., 2022; Wissler Gerdes et al., 2022). Melatonin is another compound which can increase mitophagy (Kang et al., 2016; Chen et al., 2021; Coto-Montes et al., 2012).

6.2. Mitochondrial biogenesis

Clearing damaged mitochondria will leave a lack of energy production capacity in the cell if not replaced. Mitochondrial population is regulated through multiple processes, including mitochondrial fission (breaking apart to form more mitochondria), fusion (Bertholet et al., 2016) (two or more mitochondria fusing to reduce mitochondrial population), mitophagy (Hattori et al., 2014) and mitochondrial biogenesis (MB) (Jornayvaz and Shulman, 2010).

6.2.1. PQQ

Pyrroloquinoline quinone (PQQ) increases mitochondrial biogenesis via elevation of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), a biochemical marker for mitochondrial biogenesis (Hwang et al., 2020).

6.2.2. Cold exposure

Cold exposure increases the expression of PGC-1α in (soleus) muscle tissue (Chung et al., 2017). When combined with endurance exercise (mice swimming for 30 to 60 min), gene expression changes promoting mitochondrial biogenesis were highly upregulated (Chung et al., 2017).

6.2.3. Endurance exercise

Endurance exercise induces the increase in mitochondrial density of skeletal muscle (Booth et al., 2015; Coyle, 1999). For the purpose of this investigation into treatment of spike protein related pathology, the reintroduction of exercise needs to be tempered (Cattadori et al., 2022).

6.2.4. Nitric oxide

Additionally, one pathway which increases mitochondrial biogenesis is via the production of nitric oxide (NO) (Nisoli et al., 2003; Nisoli et al., 2003; Leary and Shoubridge, 2003), which can be upregulated during exercise (Shen et al., 1995; Roberts et al., 1999), ultraviolet A light (Hazell et al., 2022). Plant studies also observe an increase in NO production during cold stress (Puyaubert and Baudouin, 2014; Sánchez-Vicente and Lorenzo, 2021). NO can also be upregulated by ROS (Zhen et al., 2008), estrogen (Kauser and Rubanyi, 2008), statins (Laufs et al., 1998).

6.2.5. Melatonin

Melatonin is an important agent in upregulating mitochondrial biogenesis (Kang et al., 2016; Kato et al., 2015; Niu et al., 2020). A recent review identified it as a molecule of interest for treating long COVID (Cardinali et al., 2022).

6.2.6. Others

Other compounds have demonstrated potential in improving both mitochondrial biogenesis as well as mitochondrial function (Singh et al., 2021; Lewis Luján et al., 1985; Chodari et al., 2021).

Lipoic acid (LA) has demonstrated capability to increase mitochondrial biogenesis (Fernández-Galilea et al., 2015; Shen et al., 2011; Shen et al., 2008). Acetyl-L-Carnitine (ALCAR) also shows benefits when combined with LA (Shen et al., 2008), and other studies show ALCAR increases the expression of gene pathways in mitochondrial biogenesis (Nicassio et al., 2017; Pesce et al., 2012; Pesce et al., 2010). Hydroxytyrosol, a compound in extra-virgin olive oil may also stimulate mitochondrial biogenesis (Hao et al., 2010). The compound nebivolol, a beta blocker, also stimulates mitochondrial biogenesis (Huang et al., 2013). EGCG (Valenti et al., 2013; Lee et al., 2017; Ha et al., 2018), green tea polyphenols (Rehman et al., 2013), isoflavones (Rasbach and Schnellmann, 2008), quercetin (Henagan et al., 2014), mulberry (You et al., 2017; You et al., 2015), anthocyanins (Gomes et al., 2019), rutin (Su et al., 2014), curcumin (Hamidie et al., 2015), glycyrrhizic acid (licorice) (Rashedinia et al., 2019), cyanidin-3-glucoside (Mogalli et al., 2018), citrus tangeretin (Kou et al., 2018), isorhamnetin (Lee and Kim, 1853), nobiletin (Dusabimana et al., 2019), eriocitrin (citrus lemon compound) (Hiramitsu et al., 2014), sudachitin (a flavone found in citrus fruit) (Tsutsumi et al., 2014), Amla (Indian medicinal plant) (Yamamoto et al., 2016), and *Platycodon grandiflorum* extract (Kim et al., 2015) also may stimulate mitochondrial biogenesis (Chodari et al., 2021).

6.3. Improving mitochondrial function

In addition to removing damaged mitochondria and restoring tissue oxygenation via the removal of clotting bodies, it is important to increase mitochondrial energy production. Studies demonstrate deleterious impacts of the spike protein (Clough et al., 2021), SARS-CoV-2 (Ajaz et al., 2021) and the COVID-19 mRNA vaccines (Abramczyk et al., 2022) on mitochondrial parameters.

Mitochondrial dysfunction is a hallmark of long COVID (Nunn et al., 2022; Díaz-Resendiz et al., 2022a; Guntur et al., 2022; Prasada Kabekkodu et al., 2023), and multiple agents with a mitochondrial mode-of-action are currently being investigated therapeutically for long COVID (Halma et al., 2023b). Below, we include several factors known to improve mitochondrial function.

6.3.1. Vitamin C

Vitamin C has important anti-inflammatory (Mikirova et al., 2012), antioxidant (Kc et al., 2005), and immune-enhancing properties (Carr and Maggini, 2017). It is transported into the mitochondria and confers protection against oxidative injury (Kc et al., 2005), though little is known about its influence on mitochondria (Vineetha et al., 2021).

Oral Vitamin C helps promote the growth of protective bacterial populations in the microbiome (Otten et al., 2021). As gut dysbiosis is associated with long COVID (Giannos and Prokopidis, 2022; Ancona et al., 2023), supplemental vitamin C may confer benefit to those experiencing long COVID (Vollbracht and Kraft, 2021). Trials on the impact of L-Arginine combined with Vitamin C showed positive results for long-COVID (Izzo et al., 2022; Tosato et al., 2022).

6.3.2. N-acetyl cysteine

N-acetyl cysteine (NAC) is the precursor of hepatic glutathione (GSH) (Rushworth and Megson, 2014). NAC penetrates cells where it is deacetylated to yield L-cysteine thereby promoting GSH synthesis (Rushworth and Megson, 2014). GSH is an important intracellular antioxidant (Cnubben et al., 2001). In addition, NAC has anti-inflammatory and immune-modulating properties (Tenório et al., 2021). NAC is well absorbed by the intestine and supplementation with NAC is effective for increasing GSH levels (Atkuri et al., 2007). NAC acts as a protective factor for mitochondrial energy production (Aparicio-Trejo et al., 2019) and supplementation with glycine improves mitochondrial markers in older adults (Kumar et al., 2021).

6.3.3. Magnesium

Magnesium is an important mineral for health, as magnesium deficiencies are linked with many disease processes (Barbagallo et al., 2021), as well as more severe COVID-19 outcomes (Nouri-Majd et al., 2022). Magnesium plays important roles in maintaining mitochondrial membrane potential (Racay, 2008; Pilchova et al., 2017).

6.3.4. Methylene blue

Methylene blue (MB) induces mitophagy (Di et al., 2015) and has neuroprotective (Di et al., 2015; Tucker et al., 2018; Poteet et al., 2012) and antiviral properties (Chuang et al., 2022). It is capable of directly rerouting electrons in the mitochondrial electron transport chain to

promote mitochondrial activity (Tucker et al., 2018).

MB should be avoided during pregnancy (Kidd et al., 1996). Also, MB is a potent monoamine oxidase inhibitor that, in conjunction with an selective serotonin reuptake inhibitor, can potentiate serotonin syndrome, a life-threatening medical emergency (Gillman, 2011).

6.3.5. *Light therapy*

Modern humans currently spend the majority of their time indoors (Brasche and Bischof, 2005), approximately 93 % by one survey of medical students (Dörre, 1997). Early humans were exposed to sunlight daily, likely with profoundly important health benefits (Wang and Chen, 2020). A recent large prospective study demonstrated that avoiding sun exposure is a risk factor for all-cause mortality, demonstrating lower life expectancies (0.6 to 2.1 years) in those avoiding sun exposure when compared to the highest sun exposure group (Lindqvist et al., 2016). Apart from UV radiation stimulating vitamin D synthesis (Holick, 2018), red and near-infrared (NIR) radiation have a profound effect on human physiology (Walski et al., 2019), notably acting as a mitochondrial stimulant and increasing ATP production (Begum et al., 2015). Indeed, during the 1918 influenza pandemic, "open-air treatment of influenzae" appeared to be an effective treatment for seriously ill patients (Hobday and Cason, 2009).

The most well-studied mechanism of action of PBM centers around enhancing the activity of cytochrome *c* oxidase, which is unit four of the mitochondrial respiratory chain, responsible for the final reduction of oxygen to water (Tsai and Hamblin, 2017). In addition, one of the most reproducible effects of PBM is an overall reduction in inflammation (Shamloo et al., 2023). It has also been demonstrated that NIR light increases the expression of genes associated with mitochondrial biogenesis (Nguyen et al., 2014).

6.3.6. *Others*

Multiple other compounds have been identified which modulate mitochondrial function, including fucoidan, a brown marine algae, which improves mitochondrial membrane potential (Díaz-Resendiz et al., 2022b). Investigational compounds are covered in recent reviews (Vásquez-Reyes et al., 2021; Forbes-Hernández et al., 2014; Rai et al., 2015).

7. Conclusion

The spike protein, notably the S1 segment, is likely a pathogenetic factor leading to both long COVID and post-vaccination syndrome. Multiple intersecting and overlapping pathophysiologic processes contribute to the vast spectrum of pathology caused by spike-protein, including inflammation, clotting (fibrin-amyloid clots), autoantibodies, mitochondrial dysfunction, and endothelialitis. This is a novel pathology and requires the development of treatment protocols to meet this pressing need. Autophagy is a promising technique to remove foreign proteins and restore cellular function, as well as restoring cellular energy production. Some of the interventions discussed in this manuscript have been subject to study in the context of spike protein diseases (Halma et al., 2023b), we include a table of current clinical trials and evidence summaries for the interventions in this manuscript in the appendix (Supplementary Table 1) (McCreary et al., 2022; Mittra et al., 2020; Vahedian-Azimi et al., 2022; Pawar et al., 2021; Bettuzzi et al., 2021; Camell et al., 2021; Hu et al., 2022; Khalaji et al., 2023; Lan et al., 2022; Pattnaik et al., 2022; Barbara et al., 2022; Nopp et al., 2022; Romanet et al., 2023; Winchester et al., 2021; Zhong et al., 2022; Altay et al., 2021; Li et al., 2021; Negro et al., 2022; Cheema et al., 2023; Gomaa et al., 2022a; Banerjee et al., 2023; Gomaa et al., 2022b; Semmarath et al., 2022; Jaimes-Gualdrón et al., 2022; Dabholkar et al., 2021; Hamidi-Alamdari et al., 2021; Patidar et al., 2022; Alamdari et al., 2020; Mahale et al., 2021; Yella et al., 2022; Henry et al., 2020; Rawat et al., 2021; Hemilä and de Man, 2021; Assimakopoulos et al., 2021; Paraskevas et al., 2023; La Carrubba et al., 2023; Segev et al., 2016; Pulido Perez et al., 2022; Díez et al., 2023; Guerrero-Romero et al., 2022; Tian et al., 2022; Tan et al., 2020; Nejatifard et al., 2021; Vetrici et al., 2021).

Autophagy has a long and broad history in medicine as well as spiritual practice, its use in medicine, pending validation, is sure to increase, given its therapeutic potential. Modifiable lifestyle factors as well as pharmacological factors can upregulate autophagy. Further work is of course required in the development of spike-protein therapeutics, and their clinical validation, as well as extending the therapeutic use of fasting to other disorders. Autophagy has much potential in the future of medicine.

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Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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