1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease of the adult, characterized by degeneration of motor neurons in the spinal cord, brain stem and motor cortex. Despite the important efforts to find new therapies to ALS, including targeting the immune system, very limited options are available today. This highlights the need to better understand the processes implicated, especially in the progressive phase of the disease to slow down the course of motor neuron degeneration.

Although the cause of the disease is currently unknown, several hypotheses including oxidative stress, protein aggregation, mitochondrial dysfunction, glutamate excitotoxicity and neuro-immune reactions are believed to participate in the motor neuron degenerative process (Boillee et al.2006a). The majority of ALS cases are sporadic, but 10% are inherited (familial), however sporadic and familial ALS produces similar pathological hallmarks, including an immune response in the affected tissues.

The pathogenesis of amyotrophic lateral sclerosis (ALS) remains poorly understood, in part because of the highly complex and closely related intercellular interactions that occur throughout the pathological process. Therefore, despite the treatment options (Riluzole) to manage and slow the progression of ALS are very limited, and no effective treatment is available.

Cellular mechanisms of motor neurons and the axon contributes to the pathogenesis of ALS across multiple signaling pathways have been widely examined. However, accumulated evidence indicates that ALS is a non-cellular autonomic disease, influenced by sustained astrogliosis, with microglial activation and infiltration of immune cells derived from blood in the spinal cord, which may have critical functions during the course of the life cycle. evolution of the disease [14, 15].

More and more basic research but also clinical studies suggest that inflammatory activation of microglia may play an important role during the initiation and progression of the disease. Microglia are innate macrophages resident in the tissues of the central nervous system.
In healthy people, if the microglia are at rest it promotes an anti-inflammatory state and this induces the survival of neurons and prevents the proliferation of astroglia.
They are also capable of expressing pro-inflammatory mediators and reactive cellular varieties of oxygen when they are activated by inflammatory signals.

2. ALS pathogenesis hypothesis

A number of comprehensive reviews have been published on the contribution of the innate and adaptive immune system to the pathology of ALS.
In murine models and ALS patients, neuromuscular junction denervation and axonal retraction occur well before the loss of MN cell bodies in the spinal cord and before symptoms of neuromuscular deficiency become apparent [7, 9-12]. It is likely that initially still intact axons can generate compensatory collateral germination to maintain functional muscle activity, but later, when this compensatory mechanism fails and motor neuron degeneration progresses, there is irreversible muscle atrophy [13].

2.1. Physiology of motoneurons and muscular fibres

Motor neurons are the exit route from the central nervous system that precedes any motor act. The cellular bodies of motor neurons are located either in the brainstem or in the ventral horn of the gray matter of the spinal cord.

Each motor neuron has an axon that starts from the central nervous system to innervate the muscle

fibers of a muscle. The set consisting of a motor neuron and the muscle fibers it innervates is a motor unit.

The neuromuscular junction refers to the synaptic junction area of the motor nerve axon with a muscle fiber allowing neuromuscular transmission and muscle contraction.

However, a single motor neuron can control several muscle fibers in order to generate higher forces. In addition, motor neuron groups often work together to coordinate the contractions of a single muscle. All groups of motoneurons that serve the same muscle are considered to be a single entity. The number of muscle fibers connected to each entity can vary: the muscles of the thigh can gather up to a thousand fibers per entity, some groups of motor neurons controlling eye muscles can only group ten fibers.

When a motor neuron is activated, all the muscle fibers innervated by the motor neuron are stimulated and contracted. Activation of a motor neuron will result in a weak but distributed muscle contraction. The activation of several motor neurons will lead to the activation of more muscle fibers and therefore a stronger muscle contraction. Motor unit recruitment is a measure of the number of motor neurons and the number of muscle fibers activated in a particular muscle.
The higher the recruitment, the stronger the muscle contraction. Motor units are generally recruited in the order of the smallest to the largest motor neurons. This is known as "Henneman's principle".

The central nervous system has two distinct ways to control the force produced by a muscle through the recruitment of motor neurons: spatial recruitment and temporal recruitment.
* Space recruitment involves incorporating more motor neurons to produce greater strength.
* The temporal recruitment of motor neuron groups consists of a series of frequent contractions of the muscle, decreasing the interval between stimulations to produce a greater force with the same number of motoneurons.

In contact with the muscle fibers, the nerve branches out and ends with an anatomical structure contiguous to the muscle fibers: the neuromuscular junction.

2.2. Deregulation in the CNS

Step 1: Removal of the motor neuron from the neuromuscular junction

It has been suggested that the development of ALS symptoms is caused by the removal of the motor neuron from the neuromuscular junction, resulting in paralysis. It could be a mechanical injury, a genetic abnormality or an infection.
Let's start with the failure of the first neuromuscular junction: A motor neuron is no longer connected to a neuromuscular junction. This has two consequences:
* The motor neuron will release biochemical substances that tell the immune system (in this case glial cells) to kill it so that it no longer consumes resources and can be recycled.
* When the muscle fibers are no longer activated, they deteriorate in a few weeks, resulting in muscle atrophy. This loss of muscle mass generates a large amount of cellular debris that can activate the immune system, again to recycle resources.

When a nerve fiber is cut or crushed, the distal part of the lesion (ie the portion of the axon separated from the cell body containing the nucleus) will degenerate according to a process called Wallerian degeneration. Axons and their myelin sheaths are digested by macrophages and Schwann cells.

Step 2: Neurological recovery

However when axons and their myelin sheaths are digested, neurolemms (Schwann sheaths) of nerve fibers still persist in the form of tubes emptied of their contents. After 96 hours, the proximal end of the nerve fiber sends budding buds to these tubes. The buds are attracted to growth factors produced in the tubes by Schwann cells, provided that the separation distance is not too long. This is how the nerve fibers push back into the neural tubes and eventually reach the target muscle they reinnote.

Regeneration is effective in the peripheral nervous system, with almost complete recovery from lesions close to the distal nerve terminal. However, recovery is barely observed in the spinal cord. A crucial difference is that in the CNS, including the spinal cord, myelin sheaths are produced by oligodendrocytes and not by Schwann cells.
Peripheral neurologic recovery occurs in two forms: actual axonal regeneration and reinnervation of denervated muscle fibers by terminal collateral germination.

Axonal regeneration (peripheral nervous system)
True axon regeneration occurs at the site where the nerve has been injured and where axonal degeneration begins [2]. For axonal regeneration to occur, there must be an intact cell of the anterior horn, also called the motor neuron cell, and an intact channel for regeneration, the endoneurial tube.

When an axonal injury occurs, the distal axon at the site of the lesion undergoes Wallerian degeneration, while the proximal axonal component remains generally intact. The proximal axon forms a bud that begins to regenerate distally through the endoneural tube to the denervated muscle. This process occurs at a rate of 3-4 mm / day, so axonal regeneration depends on length [3, 4].

Neurological recovery also depends on healthy and viable muscle tissue. This is necessary for the release of the nerve growth factors of the denervated muscle. These factors act as a catalyst to stimulate regeneration of the axon. If the denervated muscle becomes fibrous, these factors may no longer be released. Muscle tissue must also remain viable and electrically active if a regenerating axon connects with a functional neuromuscular junction. The chronically denervated muscle will eventually become fibrous and electrically inactive. This usually occurs between 18 and 24 months.

Collateral germination (peripheral nervous system)
The second form of peripheral neurological recovery is terminal collateral germination. It is the reinnervation of denervated muscle fibers by small nerve cells from intact intact intact axons [5]. The most terminal part of these axons generates germs that grow to innervate denervated muscle fibers. This process occurs much earlier than actual axonal regeneration because the distances are much shorter. A motor unit is defined as the set of muscle fibers innervated by anterior horn cell and its axon. There is a limit to the amount of terminal collateral germs that only one motor unit can sustain. It has been estimated that a motor unit can reinforce the denervated muscle tissue until it innervates five times the amount of muscle tissue initially innervated [6, 7].

Giant Motor Units formation
If enough muscle tissue is denervated and re-controlled by the excrescences of the same motor unit, they can become big enough to become a "giant motor unit" (GMU) [0]. It usually takes a long time to reach their final size, often several years. They are classically observed in postpolio patients, in slow-onset hereditary conditions and in some very chronic axonal neuropathies.

A healthy person can also have a number of GMUs. It usually results from poor adaptation of muscle and neuronal growth during childhood, and/or minor injuries.

In the case of ALS, it is common for many GMUs to develop before the body runs out of motor neurons that are healthy enough to activate the denervated muscle fibers.
GMUs work surprisingly well for a while, which leads some scientists to say that by the time your symptoms are obvious, half of your neurons are already dead and you probably have ALS for years but you did not know it not.

Motoneuron supporting infrastructure:
In the nervous system, glial cells are the cells that form the environment of neurons. They maintain homeostasis, produce myelin and play a role in supporting and protecting nerve tissue by providing nutrients and oxygen, eliminating dead cells and fighting off pathogens.

An intriguing hypothesis suggests that the evolution of the adaptive immune system may have coincided with the development of the neural crest and the tissues derived from it (14, 15). Under these conditions, the adaptive immune system may be an evolutionary rejection of the vertebrate nervous system (14, 15). This notion is favored by several genomic studies indicating that signaling genes linked to the adaptive immune system were involved in ancestral way in the development and / or function of the nervous system [16, 17].

In this scenario, it is therefore hardly surprising to see how specialized immune cells - T cells, B cells and dendritic cells - have developed an immunological synapse that is structurally and functionally reminiscent of the neural synapse [18].

The molecules of the major class I histocompatibility complex are produced in the cytosol and are transferred to the endoplasmic reticulum (ER) through the antigen presentation transporter (TAP) (18). The MHCI is then transferred to a vesicle that fuses with the plasma membrane to extracellularly present the peptide fragment to CD8 + T cells. These cells recognize MHC by the CD8 receptor and the antigen peptide by the T cell receptor (TCR).

The composition of MHC-associated antigenic peptides varies from cell type to cell type and may be disrupted by intrinsic and extrinsic factors, including altered cellular metabolism and infection (42). This is not very surprising as those peptides result from the breaking of proteins in the cytosol that were marked for recycling. Those proteins were produced under the control of the cell’s nucleus essentially to satisfy the needs of the cell’s metabolism.

Once CD8 + T cells recognize peptides as non-self or neo-autoantigens, they activate PI and kill cells presenting directly via Fas or perforin pathways and / or indirectly by cytokine release. .

Genetic alterations in the MHC class I region have been associated with various neurological disorders, including spinocerebellar ataxia, Huntington's disease, Parkinson's disease, multiple sclerosis, narcolepsy, dyslexia, schizophrenia, and autism (44-47).
D'Antona found an increased heterogeneity in MHC isoforms in the elderly [19], [20]

In 2016, Brian Kaspar, at the Nationwide Children's Research Institute demonstrated that the explicit loss of Major Histocompatibility Complex I (MHCI) expression in the outer membrane of ALS motoneurons creates a vulnerability of neurons to astrocyte toxicity in ALS.

Glial cells find what they do not recognize as “self” cells and try to kill them, but what happens is that it is motor neurons that die.

Gliosis as the result of too many transformations
Indeed the gliosis has just settled. Gliosis is defined as the proliferation of glial cells that constitute the central nervous system support tissue. It is achieved by gradually occupying a damaged area in the central nervous system to form an astrocytic scar. In the nervous system, glial cells are the cells that form the environment of neurons. They maintain homeostasis, produce myelin and play a role in supporting and protecting nerve tissue by providing nutrients and oxygen, eliminating dead cells and fighting off pathogens.

Gliosis is a nonspecific reactive change in glial cells in response to central nervous system (CNS) lesions. In most cases, gliosis involves the proliferation or hypertrophy of several types of glial cells, including astrocytes, microglia and oligodendrocytes. In its most extreme form, proliferation associated with gliosis results in the formation of a glial scar.

The process of gliosis involves a series of cellular and molecular events over several days [1]. In

general, the first injury response is migration of local macrophages and microglia to the site of injury. This process, a form of gliosis known as microgliosis, begins within hours of initial CNS injury. [1] [2] Later, after 3 to 5 days, oligodendrocyte precursor cells are also recruited at the site and may contribute to remyelination [1]. The final component of gliosis is astrogliosis, the proliferation of surrounding astrocytes, which are the main constituents of the glial scar.

Loss of motoneuron in aging

With aging, due to neuropathic processes leading to motor denervation, loss of fast motor neurons (containing type IIA and IIX fibers) occurs [21], [22], which should result in a slower phenotype.

Wilkes et al. [23] reported that inhibition of insulin proteolysis in response to diet and activation of the Akt-protein kinase B signaling pathway is attenuated in older adults compared to young adults .

These results suggest that sarcopenia in humans is not only due to a blunted anabolic response (sensitivity and reduced reactivity) to the amino acid diet but also to a reduced sensitivity to the inhibitory effect of insulin on protein degradation.

Although intense and regular physical activity prevents or even reverses age-related muscle mass by causing hypertrophy of surviving muscle fibers, it is unlikely to reverse the loss of fiber numbers due to neuropathic processes.

Step 3: Neurological recovery failure spreads

We will therefore examine how ALS spreads from one neuron to another, almost as if it were an infectious process. It spreads because the activation of a repairing mechanism:
When an affected neuron withdraws from its neuromuscular junction, the denervated muscle fibers (or the neuromuscular junction itself) thus affected release biochemical signals that they are **available for a connection**,

If there is an adjacent motor neuron that is still healthy enough to detect an abandoned motor unit it will try to connect to it in addition to the muscle fibers which he already manages.
So this adjacent motor neuron extends its neurite to the end plate of the abandoned motor and thus activates the muscle fiber that the other neuron had abandoned.

Neurite is any extension of the cell body of a neuron. It can be an axon or a dendrite.
In the so-called neuritic growth stage, the neurites are the two excrescences starting from the cell body of the young neurons and which will differentiate later on to give, on the one hand, the axon and on the other, by branching, the dendrites.

Pretty soon (probably a few weeks) what was two groups of independent motoneurons is now a single giant driving unit. However, the patient is unaware that something is wrong. Indeed, healthy people have GMUs resulting from poor adaptation of muscle and neuronal growth during childhood, and / or minor injuries.

The neuron, which is now doing double work on muscle fibers, will also soon be doing double work in the spinal ganglia, as ganglion synapses reorganize to direct commands to the new neural circuit rather than the old circuit. activation of muscle fibers because it has now become a cul-de-sac.

Within a few weeks, the muscle fibers powered by this GMU atrophy. In the process of atrophy, they release biochemical signals ("cytokines") on the immune system, indicating that something is wrong.

The glial cells of the nervous system are seeing a kind of carnage at the level of motor neurons and believe that it is their duty to eliminate this problem. But the body has no way of replacing higher or lower motor neurons.

Glial cells try to kill an infectious agent, but what happens is the motor neurons that die.
By dying, they release caspases that alert the immune system. When a motor neuron begins to die, it triggers a neurodegenerative cascade that continues until there are more motor neurons. In fact they are activated by the inflammatory cytokines circulating in the system, each time a cell (neuron or muscle fiber) dies, it generates even more cytokines.

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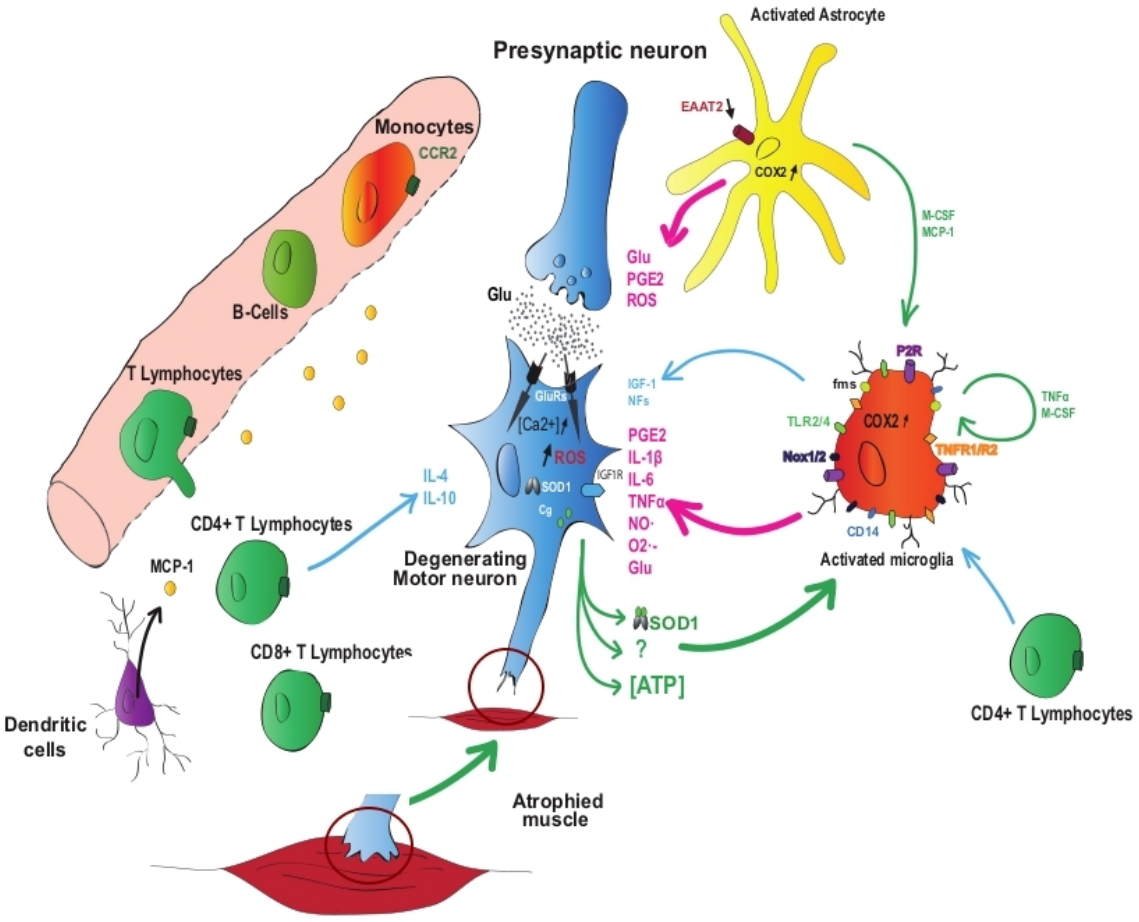
Mathematical model

In this study, we develop a **mathematical model** of the interactions between astrocytes and neurons during ALS disease course.
This model is available on Github:
https://github.com/Hjertesvikt/ALS_model

Of course, neither the present model nor any other theoretical model can decide between the controversial views put forward by various authors, since only unambiguous experiments can close the debate.
However, mathematical modeling can be a tool to give a coherent and quantitative framework for the discussion, to suggest possible physiological mechanisms and to help plan future experiments.



Amyotrophic Lateral Syndrome

SBML model of immune interactions
Figure adapted from Barbeito and al.

As inflammatory signals develop, microglia can become proinflammatory, leading to the proliferation of astroglia and the death of neurons. Neuronal debris and / or the proliferation of astroglia may in turn exacerbate the inflammatory phenotype of microglia. Knowledge of these

multiple positive and negative feedbacks between these different cells is therefore crucial, as these feedbacks significantly alter neuronal structure and function during the pathogenesis of ALS.

Which kind of Model?

Mathematical models can serve as powerful tools for understanding the molecular and cellular processes that control complex diseases. However, there have been few attempts to model the process of amyotrophic lateral sclerosis. Specifically, no systematic approach to modeling using has been reported to examine cross-referencing of the network between microglia, neurons and astroglia, and the corresponding pathological consequences in ALS.

Moreover, the modelizations using programs (Java / Python) are difficult to modify by people not involved in the design of the program and it becomes quickly obsolete simply because of the fast evolution of the languages, IDE and libraries.
Systems Biology Markup Language (SBML) is a widespread and tooling independent format that can be used for simulating, storing, and exchanging biological models. It allows for a detailed description of metabolic reactions and is able to connect the model's content to peer-reviewed databases

We propose in this evolving model, multiple pathways involving many cell varieties, as well as a formalization of intercellular signaling influences. The mechanism is based on the assumption of a constant risk of neuronal death, that is, a single event randomly triggers cell death, regardless of the status of any other neuron, at any time. The spatio-temporal influence of diffusion is neglected because local cellular events are assumed to occur on a slower time scale than the scattering of signals by chemotaxis. So, in this case, there is no initial event from which the disease develops, but it is very easy to modify this model to look for how a single event could be responsible for initiating the disease.

These metabolic and signaling pathways, link change in each cell population at any time to the values of all cell varieties occurring at that precise moment. For example, the rate of change in surviving neurons is related to the rate of change at resting astroglia, proliferation of astroglia, and pro-inflammatory microglia. At this stage of the modeling, we still use ad hoc biological pathway weights, but during the development of this model, we will gradually replace these arbitrary parameters with equations describing the underlying biology.

The evolution of the cell population in relation to the anti-inflammatory state of microglia is very complex. The evolution of neurons towards neuronal death is irreversible, whereas the evolutions of astroglia and microglia between the resting state, the anti-inflammatory state and the pro-inflammatory state of microglia are reversible.

Compared with other cell types, the proinflammatory population of microglia is highly sensitive to cell-mediated disturbances. Indirectly, this evolution of the population from microglia to the pro-inflammatory state influences the neuronal death which is very sensitive to the amounts of microglia in the anti-inflammatory state. This implies an important role for microglia during the progression of ALS.

Description of the model

The following features will be implemented:

- Immune cells of the central nervous system, including ***microglia*** and ***T cells***, affect the survival of motor neurons.
- In a healthy human, a ***pre-synaptic neuron*** releases ***glutamate*** (Glu), which binds to glutamate receptors (GluRs) on the corresponding ***post-synaptic motor neuron***, causing excitation by the influx of calcium.
- Extracellular glutamate is rapidly removed from the synaptic cleft (***Exocytosis***) by ***astrocytes*** through EAAT2 transporters.
- In a non-inflamed environment, the microglial cells remain in a state of rest or possibly "of vigilance", presumably ***releasing factors having a neurotrophic influence***.
- In the case of an ALS pathology, a ***decrease*** in the expression of the ***astrocyte glutamate EAAT2*** transporters leads to a prolonged excitation of the motoneurons and to participate in their ***degeneration*** (excitotoxic hypothesis).
- Activated microglial cells (pro inflammatory) and astrocytes produce toxic factors.
- Among the factors released by astrocytes, ***macrophage colony stimulating factor*** (M-CSF) and ***monocyte chemoattractant protein*** (MCP-1) are capable of activating microglial cells by increasing their ***proliferation*** (M-CSF) or their ***migration*** (MCP-1).
- Microglial cells are also subject to ***auto-activation*** by releasing tumor necrosis factor-α (TNFα) for which they express receptors 1 and 2 (TNFR 1/2) and M-CSF that act on the fms receptor.
- Activated (pro inflammatory) microglial cells will produce more reactive oxygen species (ROS) such as ***nitric oxide*** (NO) via NO synthase and ***superoxide*** (O2-) by activation of ***NADPH oxidases*** (Nox 1/2), but also ***pro-inflammatory cytokines 6 (IL-1β, IL-6)*** and ***prostaglandins*** (PGE2) by activation of ***cyclooxygenase 2 (COX2)***.
- ***Extracellular ATP***, probably from damaged motor neurons, binds to microglia purinergic P2 receptors, thereby contributing to microglial activation.
- Motor neurons can also participate in glial cell activation by ***releasing mutant SOD1*** co-secreted with chromogranin (Cg) that can bind to CD14 acting in concert with Toll-like receptors (TLR2 / 4).
- The adaptive immune system is also part of the degenerative response of motor neurons. T cells (***CD4+ and CD8+***) from the periphery of the spinal cord enter in it during (or even initiating) the inflammatory process of ALS.
- ***CD4+ lymphocytes*** appear to have a ***neuroprotective*** effect by directly releasing inflammatory factors such as interleukins 4 and 10 ***(IL-4, IL-10)*** or by acting on ***microglial cells to increase their neurotrophic function*** (production of insulin-like growth factor-1 (IGF-1)) .
- The role of infiltrating CD8+ T cells remains undetermined and B cells are not present in the spinal cord.

- Dendritic cells (antigen-presenting cells) secrete ***MCP-1***, which probably participates in the infiltration of peripheral immune cells.

- Overall, the inflammatory environment and increased oxidative stress contribute to the degeneration of motor neurons, resulting in muscle atrophy of ALS.

- ***Giant motor unit***

- The cell model includes the complete dopamine (DA) synthesis, metabolism, and transport introduced by Best et al.

- It models mitochondrial biogenesis and mitophagy, degradation processes of the lysosome and the proteasome, and reactions of the cell to reactive oxygen species (ROS).

- Additionally, the two genes HtrA2 and PINK1, both of which are involved in the mitochondrial stress response, are also integrated.

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