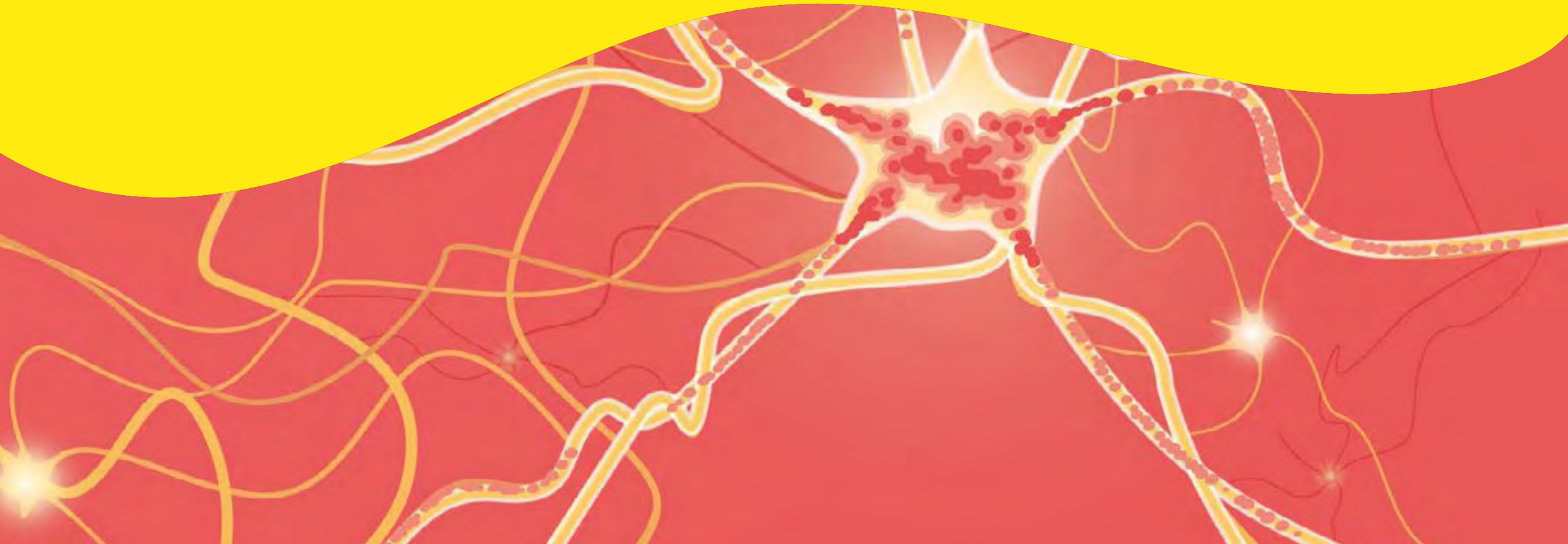
Neuroscience

Guide to neurodegenerative diseases and neuroinflammation pathways



INTRODUCTION
Purpose and Scope

Welcome to the Neurodegeneration and Neuroinflammation Booklet, a document that helps scientists and researchers appreciate and navigate the diversity of the molecular pathways associated with the development of neurodegenerative diseases. Neurodegenerative disorders encompass a range of progressive central nervous system (CNS) diseases that include Alzheimer's Disease, Parkinson's Disease, Amyotrophic Lateral Sclerosis, Frontotemporal Dementia and Lewy Body Dementia, among others. Over the last few years, indications as to the complex nature and multifactorial etiology of such diseases and their many pathways have emerged. We hope the visuals provided in this document will help shed light on and clarify otherwise complex mechanisms.

This document is organized around the progression of the pre-cited neurodegenerative disorders. The first section will detail the pathogenesis and related molecular pathways of the major CNS conditions. The second section will further depict the chronic neuroinflammation mechanisms that have been considered as prominent drivers of the onset of neurodegeneration.

The collection of molecular pathways presented in the document was prepared based on authentic and highly regarded articles and journals. Footnotes at the bottom of each page indicate the references used. All pathways have been curated for scientific knowledge and accuracy by Revvity's scientific team.

Although some of the molecular pathways which will be vital for our full understanding of neurodegenerative disorders still remain to be elucidated, we believe this review will provide its readers with the most up to date snapshot of current molecular pathophysiology. Your feedback about your experience with this document is important to us, and will help us continue to improve this resource.

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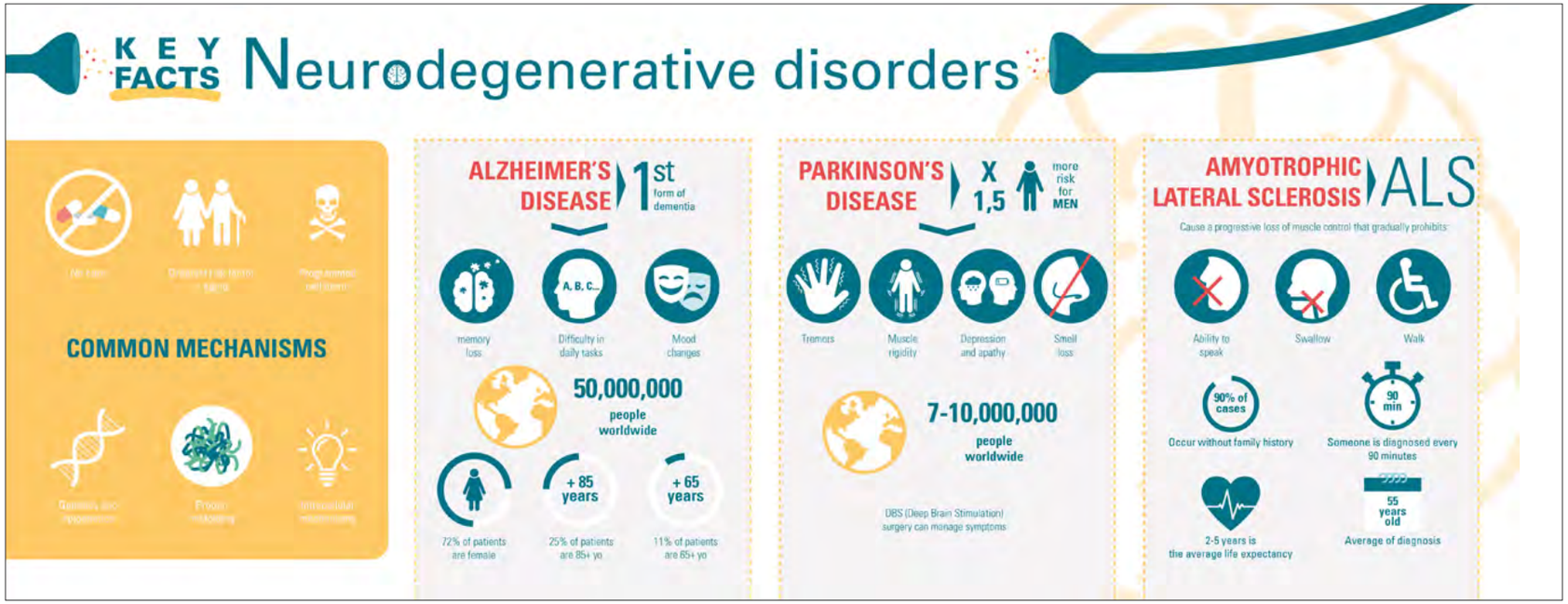
INTRODUCTION

Key facts: Neurodegenerative disorders



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PATHOGENESIS OF NEURODEGENERATIVE DISEASES

Alzheimer's disease

Alzheimer's Disease (AD) is the most prominent cause of dementia characterized by progressive cognitive deficits, memory impairment and behavioral abnormalities. 40 million people suffer from AD worldwide, and this community is expected to rise to over 150 million people by 2050.

The origin of AD has not been fully elucidated, but epidemiological studies have underlined a multifactorial etiology comprising a less prevalent autosomal-dominant pattern with mutations in amyloid precursor protein (APP), presenilin 1 or 2, and a sporadic form that affects 90% of patients with multiple genetic risk factors [1].

Despite different etiologies in AD, the distribution of Amyloid beta (Aβ) peptide accumulation throughout the brain is similar, affecting the medial frontal and the lateral temporal and parietal cortex [2].

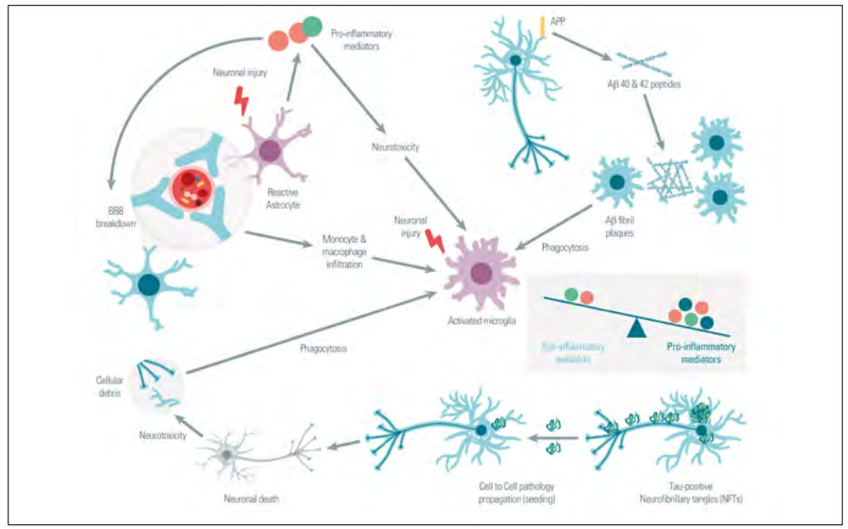
The brains of AD patients display a pathological accumulation of Amyloid beta peptides that will further aggregate to form Aβ fibril plaques and an intraneuronal accumulation of neurofibrillary tangles consisting of hyperphosphorylated aggregated microtubule-associated tau, representing the two major disease hallmarks.

Recent studies have suggested the existence of extracellular tau aggregates (seeds) that act as drivers of the pathology by traveling between neurons in a prion-like way, spreading the disorder across neuronal tissue and leading to neuronal cytotoxicity [3].

Recent epidemiological studies have suggested a key role for neuroinflammation as a pathological facilitator of AD progression through chronic glial activation (See page 21). Elevated titers of pro-inflammatory mediators have been found in cerebrospinal fluid (CSF) of AD patients.

Microglial cells have a role in monitoring the neuronal microenvironment in a healthy physiological state, removing cellular debris and amyloid beta aggregates, and maintaining brain homeostasis. In neuronal injury processes provoked by AD progression, activated microglia will secrete a variety of pro-inflammatory mediators leading to neurotoxicity [4].

Astrocytes regulate the maturation and maintenance of neuronal synapses in a healthy state, but turn into pro-inflammation contributors in diseased states and are implicated in blood brain barrier breakdown (BBB) (See page 32) [5].



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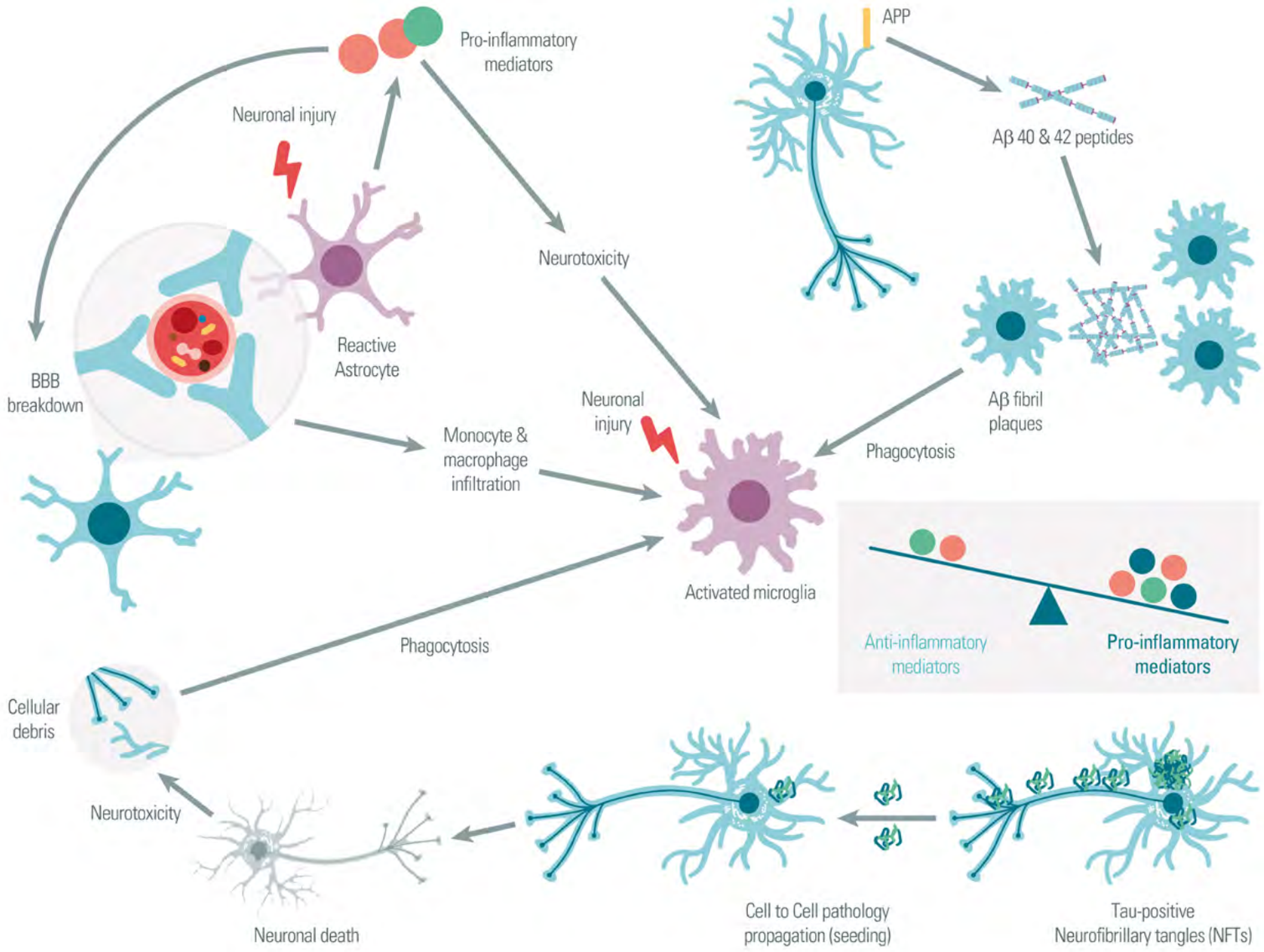

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PATHOGENESIS OF NEURODEGENERATIVE DISEASES

Molecular pathways in AD

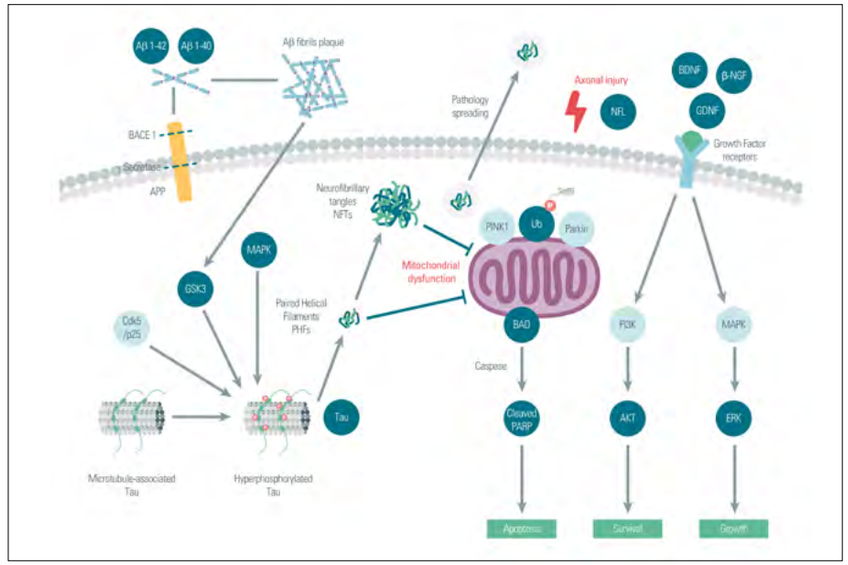
Microtubule-associated protein tau plays a key role in the neuronal pathogenesis of AD. Tau becomes hyperphosphorylated (goes from 2-3 phosphorylation sites to up to 85, for the longest Tau isoform) which causes it to detach from microtubules, misfold, and associate in Paired Helical Filaments (PHFs). These PHF structures can further condense and aggregate into neurofibrillary tangles (NFTs), which lead to cellular death upon critical accumulation. Tau aggregates or "seeds" may propagate pathology by spreading from cell to cell in a prion-like manner [1].

Among the many brain protein kinases that regulate tau, glycogen synthase kinase 3b (GSK 3b) is one of the most active Ser/Thr tau kinases. It has also been proven that p25-mediated Cdk5 kinase and MAPK activities regulate tau phosphorylation [2].

The pathological accumulation of Amyloid beta peptides, including Aβ38, Aβ40, and Aβ42, represent the second important hallmark of AD. These peptides are generated from the Amyloid Precursor Protein (APP) following the sequential cleavage by γ and β secretase (BACE) enzymes. Many Pharmaceutical and Biotech companies have considered the amyloid beta pathway as the main culprit in AD progression, and consequently have developed anti-Amyloid and BACE inhibitors though with a relatively low success rate so far. The exact pathogenesis molecular mechanism is not yet fully elucidated [3,4].

The positive contributions of BDNF (brain-derived neurotrophic factor) and similar neurotrophic factors have been associated with therapeutic benefits in AD treatment, since downregulations of neurotrophic signals are correlated with AD progression. Upregulation of BDNF may represent an effective therapeutic approach for neuroprotection [3,4].

Recent research studies have established the prominent role of defective mitophagy processes in the onset of AD. The exact mechanism underlying this dysregulation is still elusive, but the mitophagy-related proteins PINK1 and Parkin seem crucial in mitochondrial homeostasis, opening new hopes for the identification of innovative treatments [5].



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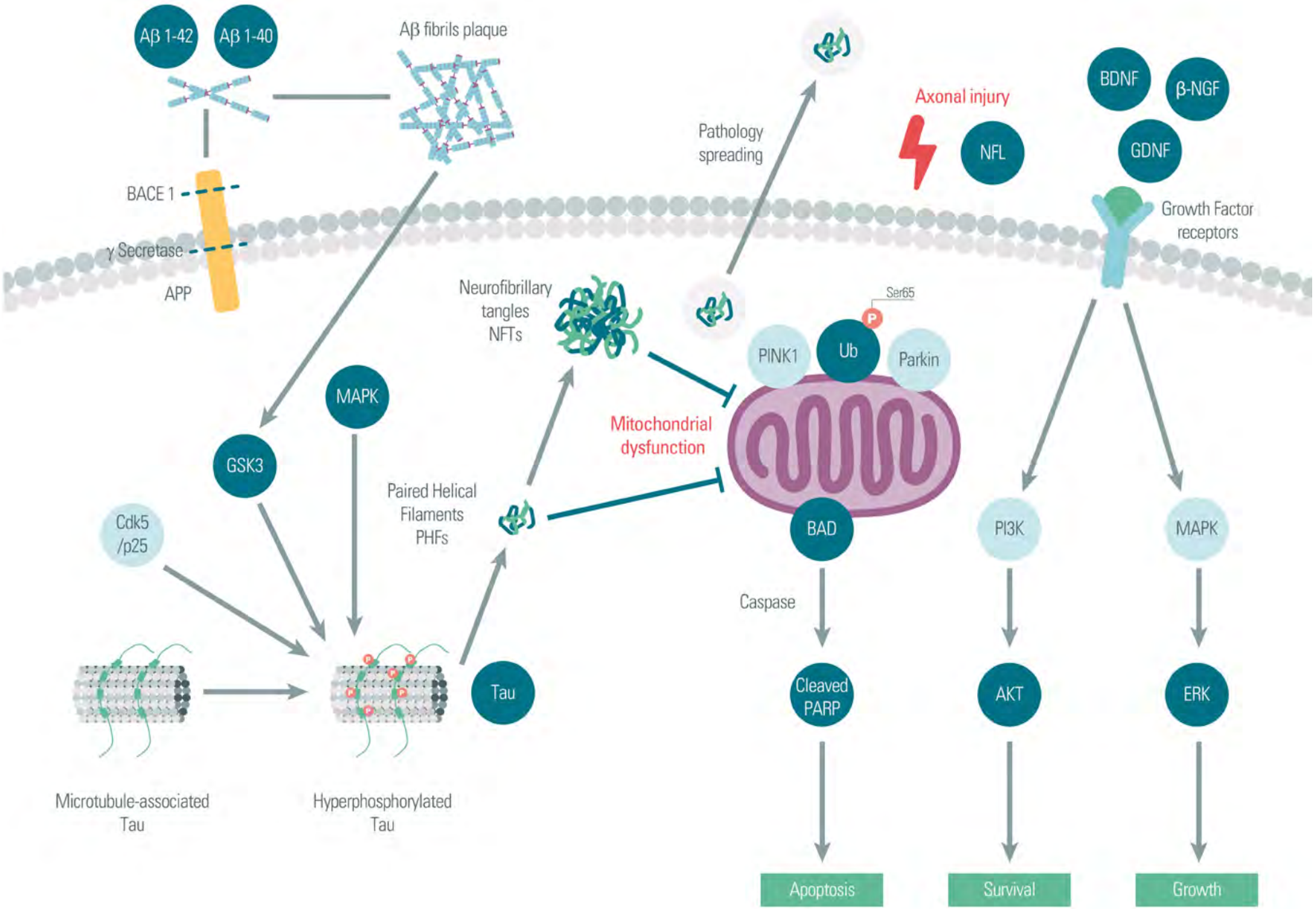

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PATHOGENESIS OF NEURODEGENERATIVE DISEASES

Parkinson's disease

Parkinson's Disease (PD) is the second most common neurodegenerative disorder after AD, and is characterized by tremors, bradykinesia, rigid muscles, and impaired posture and balance. In 2017, 7 million people suffered from PD worldwide. Epidemiological studies reveal that 1–3% of those older than 65 years and 4–5% of those aged over 85 years suffer from PD.

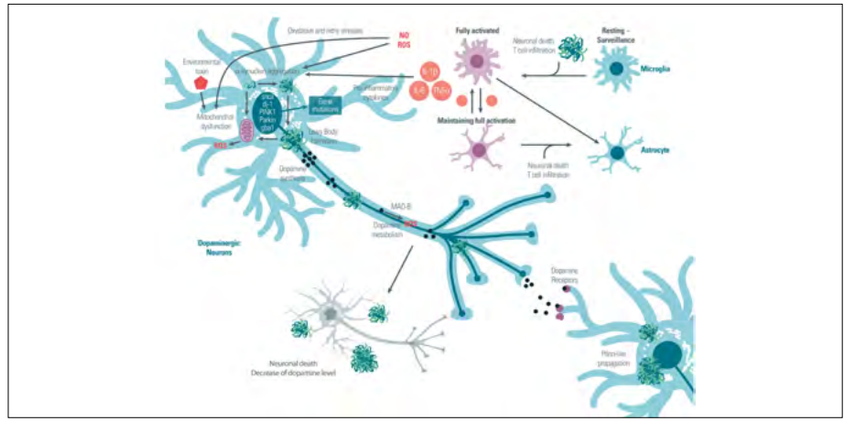
The hallmarks of PD are loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc), depletion of dopamine in Striatum, and Lewy body accumulation. As for numerous neurological disorders, the origin of PD has not been fully elucidated. However, its etiology reveals that environmental toxin exposure and genetic factors, such as mutation on α-synuclein (SNCA), Parkin, DJ-1, PINK1, and GBA1, can be linked to PD. However, aging remains the major risk factor [1].

PD patients display a pathological accumulation of α-synuclein in SNpc that will further adopt oligomeric forms and then fibrils due to oxidative stress, mutations, post-translational modifications, or Ubiquitin-Proteasome System or Autophagy System deficiencies. These fibrils will be associated with other aggregated proteins (such as Tau or Aβ) to form bigger structures called Lewy bodies [2].

As in the case for Tau in AD, α-synuclein in PD has been suggested to self-propagate and spread progressively between neurons in a prion-like manner. Other studies support "the prion-like hypothesis" that first refers to a host-to-graft transmission of the Lewy body pathology into the human brain. Thereafter, it has been proposed that α-synuclein propagation spreads from the gut to the brain via the vagal nerve. Mostly, this involves the endogenous expression of α-synuclein in enteric neurons, the probability that food contains α-synuclein, and the dysfunction of the microbiota [3,4].

Due to their involvement in dopamine metabolism, dopaminergic neurons are particularly sensitive to oxidative stress. Dopamine can be metabolized into DOPAC with the Monoamine Oxidase B (MAO-B) mitochondrial enzyme. This reaction also induces H2O2 and reactive oxygen species (ROS) generation which can favor a vicious circle of oxidative stress, mitochondrial dysfunction and protein aggregation. This may further be amplified by mutations, environmental toxins, and/or neuroinflammation.

Microglia and astrocytes are also involved in PD through neuroinflammation (See page 24 and See page 32). Neuronal injuries, extracellular Lewy bodies, and T cell brain infiltration owing to BBB breakdown activate microglia and astrocytes that in turn secrete many pro-inflammatory mediators, ROS, and nitric oxide (NO), leading to neurotoxicity [5,6].



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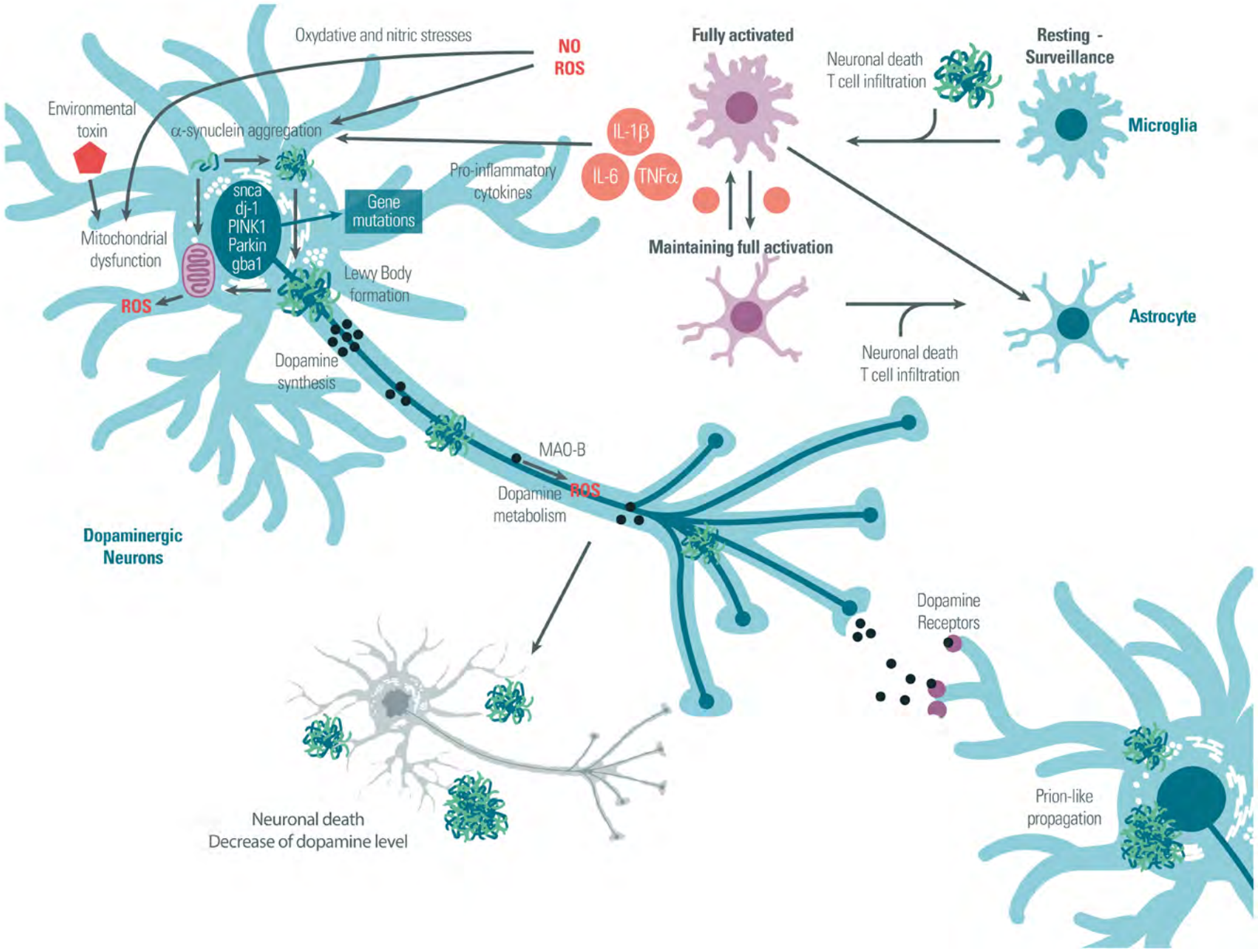

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PATHOGENESIS OF NEURODEGENERATIVE DISEASES

Molecular pathways in idiopathic PD

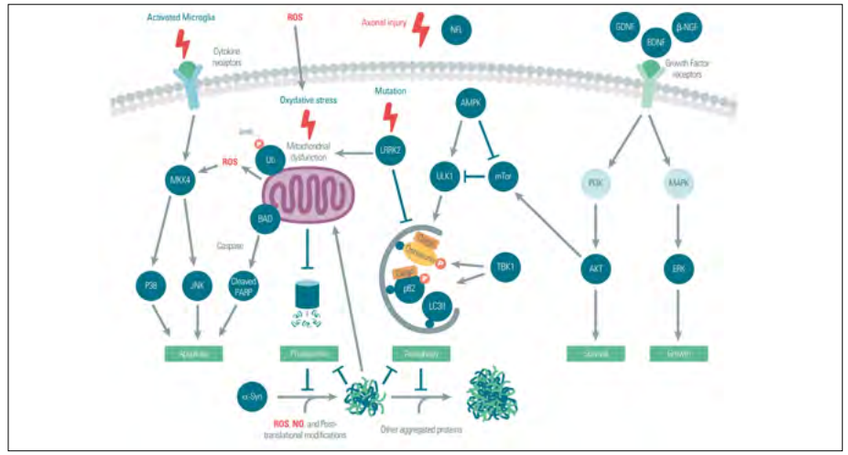
Alpha-synuclein is a key player in the pathogenesis of PD. Protein accumulation or overexpression, ROS, NO, and post-translational modifications will favor oligomeric and fibril forms of aggregated α-synuclein. These toxic oligomers induce mitochondrial dysfunction and Ubiquitin/Proteasome system and Autophagy-Lysosomal Pathway (ALP) inhibition, which raise the oligomerization of α-synuclein, ROS production, and Lewy body formation. Finally, this vicious circle of oxidative stress, mitochondrial dysfunction, and protein aggregation enhances the spread of Lewy bodies from cell to cell, and neuronal death [1].

Many studies have revealed that ALP, especially macroautophagy and chaperon-emediated autophagy, is the main pathway involved in the degradation of α-synuclein forms and damaged mitochondria in PD. The activated mammalian target of rapamycin (mTor) is the major inhibitor of autophagy by negative regulation of UNC-51-like kinase 1 (ULK1) activity, whereas AMP activated kinase (AMPK) inhibits mTor and activates ULK1 and autophagy. α-synuclein overexpression and oligomeric forms will impair ALP and the Ubiquitin/Proteasome system, thus enhancing α-synuclein accumulation [2,3].

Neuroinflammation and oxidative stress are induced by either activated microglia or astrocytes and infiltrated T cells, resulting in ROS production and IL-6, TNF-α, and IL-1β release. These inflammatory and stress stimuli activate the c-jun N-terminal kinase (JNK) and p38 pathways after activation of Mitogen-activated protein Kinase Kinases (MKK) such as MKK4. Eventually, this signaling pathway causes neurodegeneration and apoptosis [4].

Neurotrophic factors like BDNF (Brain-derived neurotrophic factor), GDNF (glial cell-derived neurotrophic factor), β-NGF (Beta-Nerve Growth Factor) or CDNF (cerebral dopamine neurotrophic factor) play an essential role in the survival, growth, proliferation, and regeneration of neurons. They are neuroprotective and neurorestorative. Notably, it has been shown in clinical and pre-clinical studies that BDNF is downregulated in dopaminergic areas. For all these reasons, neurotrophic factor approaches could be a promising therapy for PD and neurodegenerative diseases in general. So far there is no established treatment, although promising results are expected from current clinical trials [5].

Mutations on genes such as lrrk2, snca, gb1, parkin, PINK1, and dj-1, or environmental toxins like MPTP or rotenone, can enhance or constitutively induce mitochondrial dysfunction, ROS accumulation, Ubiquitin/Proteasome system and ALP impairment, and α-synuclein over-expression and aggregation in PD. These genetic factors enable us to have a better understanding of PD mechanisms.



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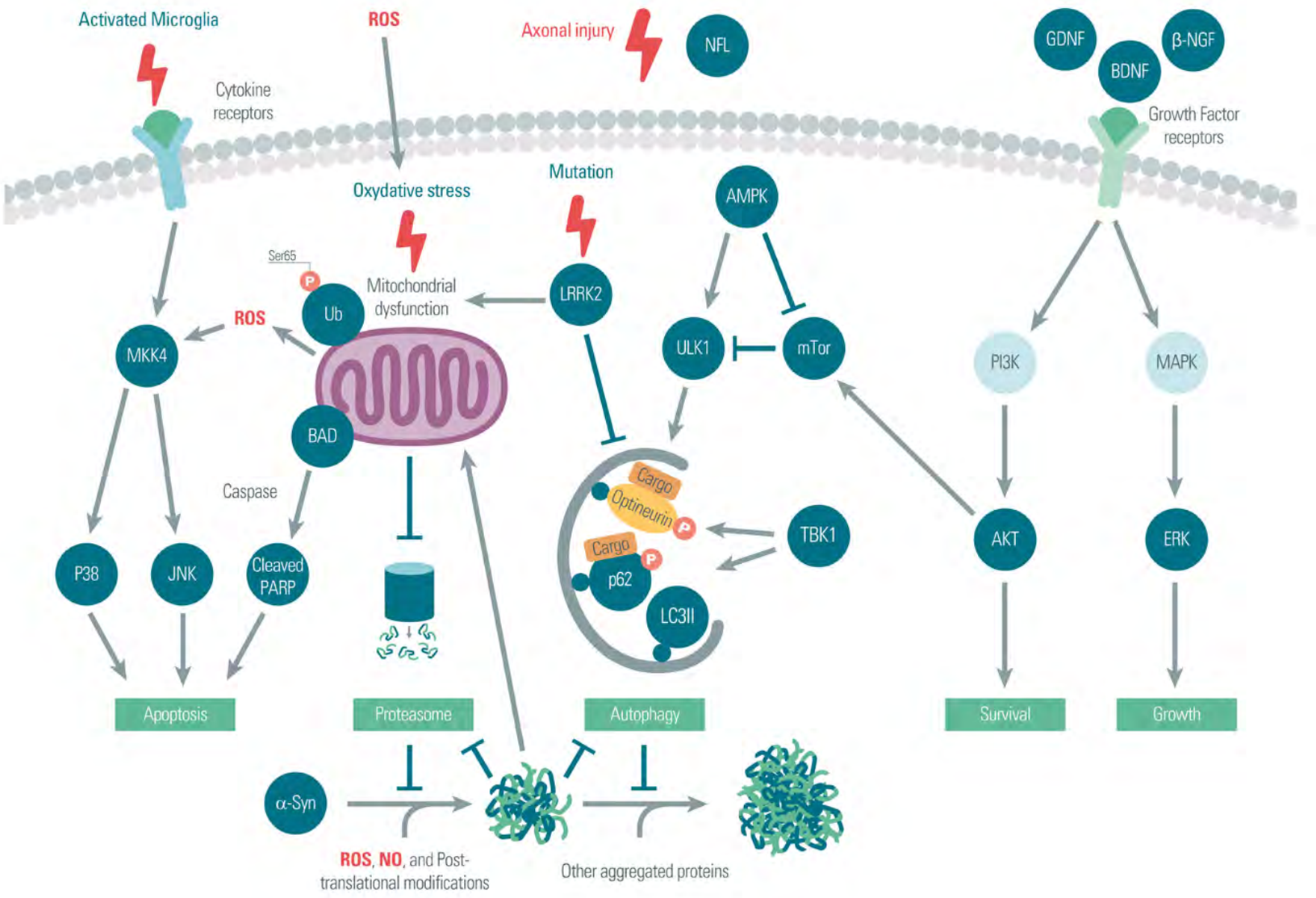

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PATHOGENESIS OF NEURODEGENERATIVE DISEASES

ALS and FTD

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects the motor system leading to a progressive muscle weakness, including that of the respiratory system. This results in a progressive loss and death of upper (cortical) and lower (spinal) motor neurons. Approximatively 10% of ALS patients have a familial form of the disease (genetic mutations), while the remaining 90% have a sporadic form.

Frontotemporal dementia (FTD) is a disease characterized by the degeneration of cortical neurons (frontal and temporal lobes) and basal ganglia, associated with a loss of cognitive functions as well as behavioral and personality changes.

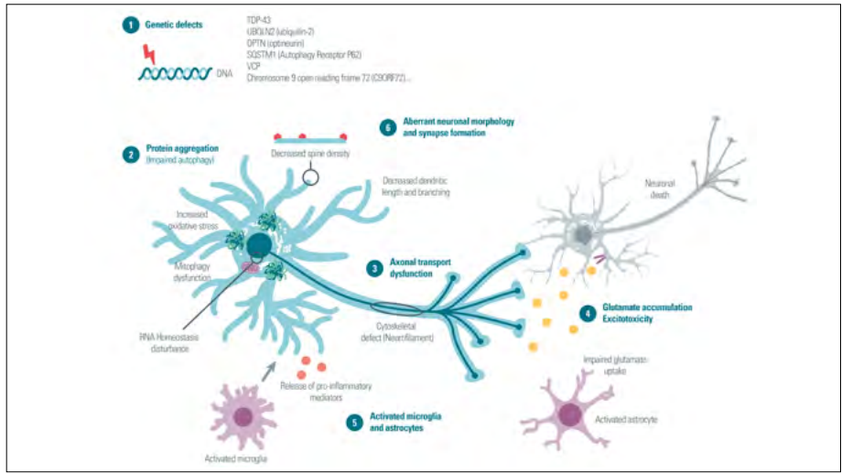
Up to 50% of patients with ALS develop frontotemporal dysfunction, while 15% of patients with FTD develop motor neuron dysfunction. Despite distinctly different symptoms, ALS and FTD share significant overlaps at the molecular level [1].

A combination of genetic and environmental factors causes ALS and FTD, and more than 20 genes have been identified as being involved in these diseases. Mutations of the genes (1) impact protein regulation, leading to ubiquitinated inclusions of bodies in cells (2) and cytoskeleton dynamics (3). More precisely, defective axonal transport is a characteristic of these diseases and leads to disorganization of cytoskeletal proteins and disruption of axonal transports. One of the most widely studied proteins is the Neurofilament Light Chain (NFL), described as a biomarker of axonal damage in ALS. Altered function or expression of different proteins that aggregate will impair autophagy and proteasome activation, disturb RNA homeostasis and mitophagy, and increase oxidative stress in the cell [2].

At the cellular level, these toxic changes in neurons induce an aberrant neuronal morphology which reduces dendritic arborization and spine density, and leads to a lack in synapse formation [3].

Excitotoxicity contributes to the degeneration of neurons in ALS but is less known in FTD. In ALS, a loss of glutamate transporter EAAT2 in astrocytes is correlated with an excessive glutamate concentration in the synaptic cleft (4), leading to neuronal death [3]. In addition, deficiency or downregulation in glutamic acid decarboxylase 67 (GAD67), which is the major enzyme converting glutamate into GABA, has been shown to play a critical role in the case of ALS, promoting excitotoxicity and likely to be related to a decrease in TDP-43 protein expression [4].

Then neuronal cell death induces neuroinflammation that activates astrocytes and microglia (See page 24 and See page 32) (5). In turn, the activation of glial cells leads to the release of more toxic factors (pro-inflammatory) [2].



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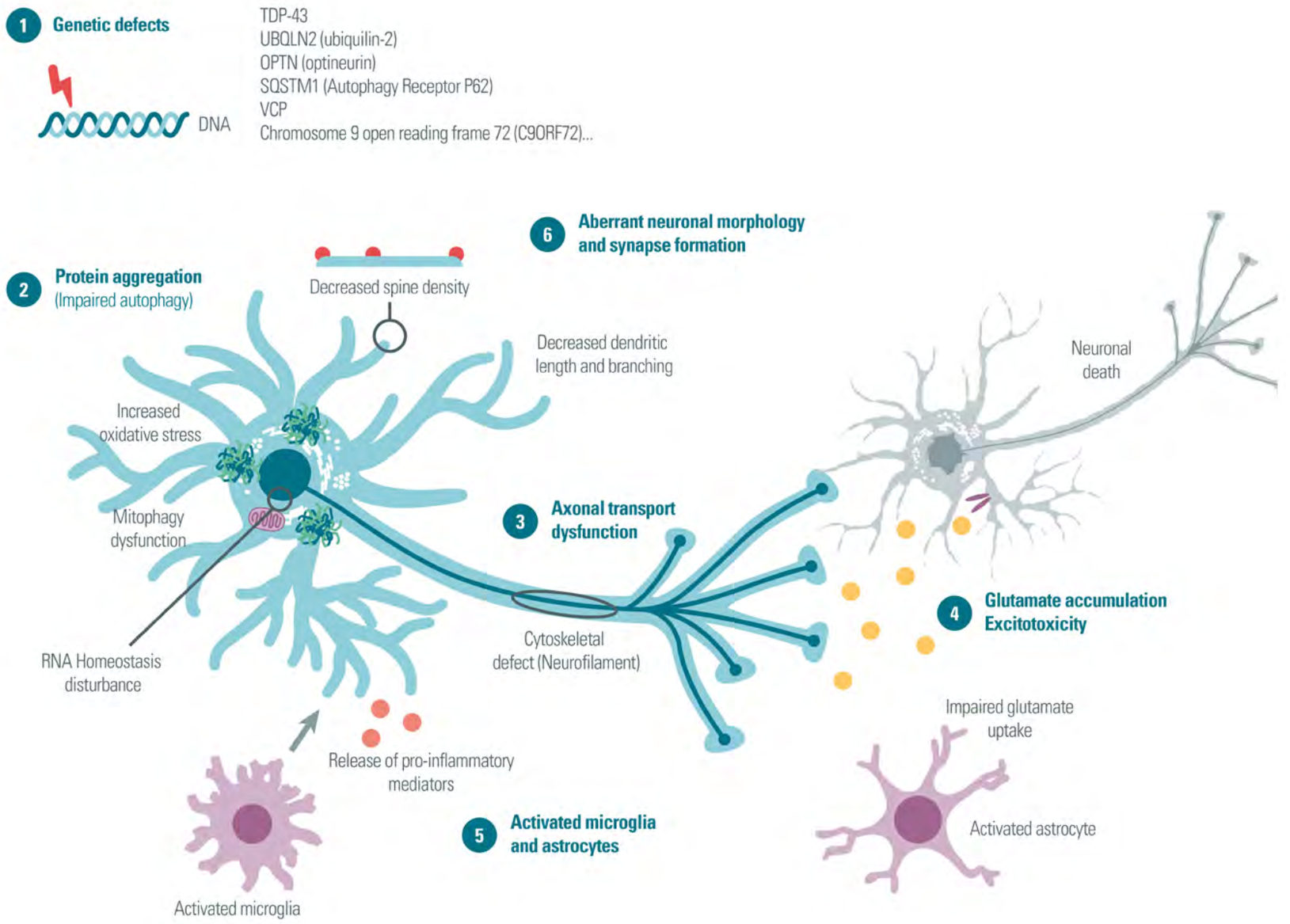

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PATHOGENESIS OF NEURODEGENERATIVE DISEASES

Molecular pathways in ALS and FTD

Similar molecular pathways occur in ALS and FTD. A subset of genes discovered to be involved in the pathologies encodes RNA-binding proteins, including TAR DNA binding protein 43 (TDP-43) and fused sarcoma (FUS). These proteins predominantly reside in the nucleus to regulate RNA splicing, but they can pass into the cytoplasm. In pathological conditions (often mutations), these proteins are mislocated and misfolded in excess and form aggregates of different sizes. Finally, cytoplasmic inclusions associate with phosphorylation and ubiquitination [1].

These aberrant forms become substrates of the ubiquitin proteasome system and autophagy, but impair these regulatory mechanisms due to mutations in other proteins or the sizes of aggregosomes [1,2].

More precisely, TANK-binding kinase-1 (TBK1) is a key protein in the regulation of autophagy by activating and phosphorylating cargo proteins like p62/SQSTM1 and optineurin. In addition, the C9orf72 complex mediated by ULK1 is also involved in the autophagy process as GDP/GTP exchange factor for Rab protein, which contributes to membrane formation of autophagosome. Therefore, mutations on TBK1 and/or C9orf72 are responsible for autophagy dysfunction and neurotoxicity of aggregated proteins.

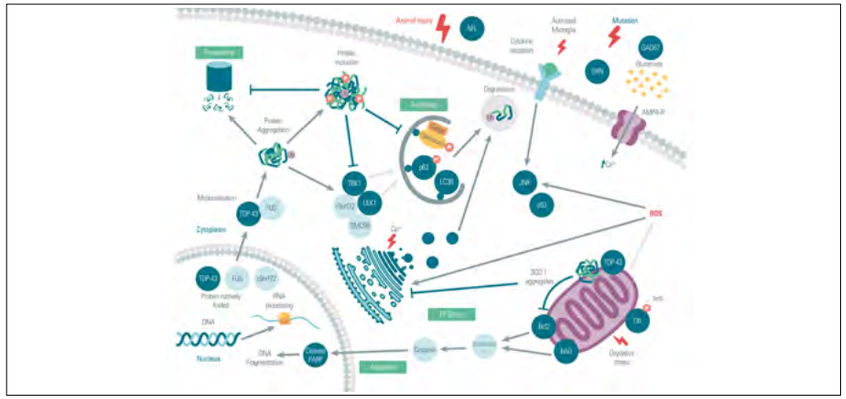
Cytosolic protein accumulation is a hallmark of ALS and FTD. It disrupts cellular physiological functions resulting in oxidative stress, mitochondrial dysfunction, and excitotoxicity.

Mitochondrial dysfunction results in defective mitochondrial transport, and increases the production of reactive oxygen species (ROS) leading to the activation of JNK/p38 pathways and the caspase pathway, thus inducing apoptosis. A mutant of Super Oxide Dismutase (SOD1), which is found as aggregates at the outer membrane of mitochondria, induces mitochondrial apoptotic signaling, inactivating the anti-apoptosis protein Bcl-2. Mutant TDP-43 can be localized to mitochondria and induces mitochondrial fragmentation, activation of the caspase pathway, or increases in ROS production [3].

Excitotoxicity induced by an excessive glutamate concentration in the synaptic cleft increases Ca2+ permeability via AMPA receptors. Intracellular calcium overload induces endoplasmic reticulum stress (ER stress) and a massive entry into the mitochondria, which cause neuronal death [4].

Progranulin (GRN) is secreted in numerous tissues, including the brain where it is involved in neuronal and microglial processes such as inflammation or neurite outgrowth. Loss-of-function mutations in GRN have been described to be a common cause of familial FTD. However, many biological functions of GRN and pathological mechanisms are still not completely understood [5].

Neuroinflammation induced by astrocytes and microglia activation releases pro-inflammatory cytokines [6].



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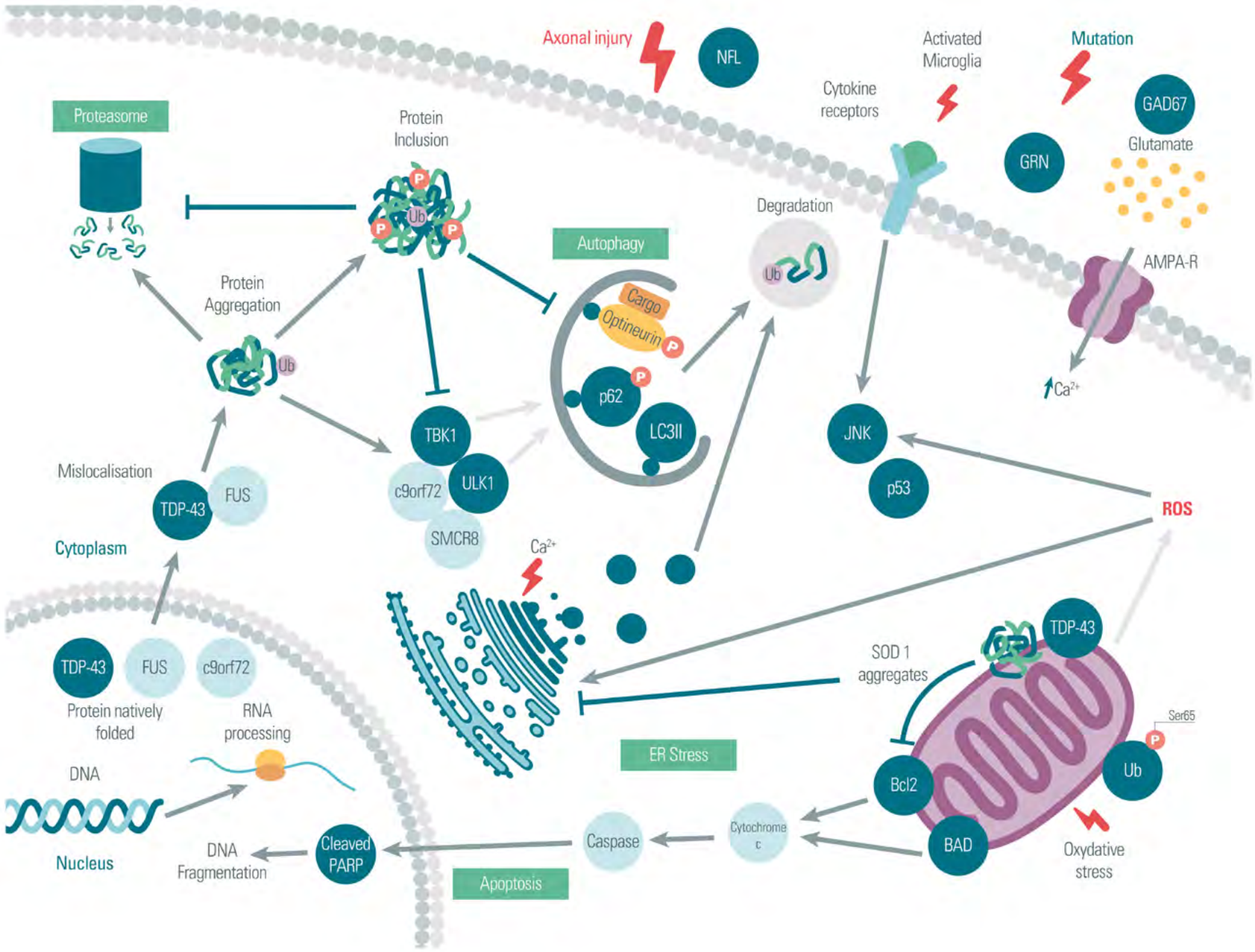

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GLIAL CELLS AND NEUROINFLAMMATION

Microglia homeostasis: A finely-tuned mechanism

Microglia are the resident immune cells of the brain and represent 10-15% of the glial cell population [1]. Microglia are thought to originate from the embryonic yolk sac, then migrate to the brain during early development. The number there stays stable during adulthood [2].

They are highly versatile cells: in a non-stimulated state (resting or surveillance state) microglia sense the environment with their long ramifications. Upon activation, they undergo morphological changes to an amoeboid shape.

In a resting state, microglia interact with neurons and astrocytes and secrete neuroprotective factors such as BDNF or GDNF. They also play a role in controlling excitotoxicity by the uptake and recycling of glutamate.

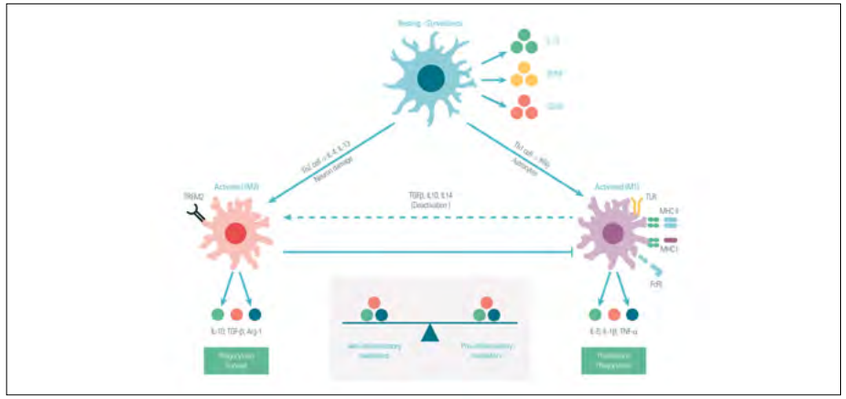
It is well established that in a healthy brain, microglia respond rapidly to immature or defective neurons, injury, and to damaged cells or pathogen invasion, which they phagocytose. However, the activation profile leads to either a pro- or anti-inflammatory response, thus promoting either neuroprotection or neuronal damage [3]. This dichotomy is further explained below.

The classical activation, M1 phenotype, results in the phagocytosis of molecules, pathogens... It can be triggered by LPS, IFNg, or reactive astrocytes that activate the production of pro-inflammatory cytokines IL-6, IL-1β, or tumor necrosis factor TNFα. Along with this, an increase in reactive oxygen species and nitric oxide has well been documented [3].

In a physiological context, the phagocytosis and inflammation are then regulated by the secretion of anti-inflammatory cytokines (IL-10 for example) to reach an equilibrium. Although triggered by IL-4 and IL-13 cytokines, the activation of the M2 phenotype is mainly illustrated through the binding of numerous ligands to the triggering receptor expressed on myeloid cells 2 (TREM2).

Activated M2 microglia produce anti-inflammatory cytokines like IL-10, and secrete Arginase and Chitinase, beneficial for tissue repair and wound healing. Therefore, a balance between pro- and anti-inflammatory molecules is reached which maintains homeostasis in the brain.

The two above-mentioned microglia phenotypes are a simplified view of the different activation profiles.



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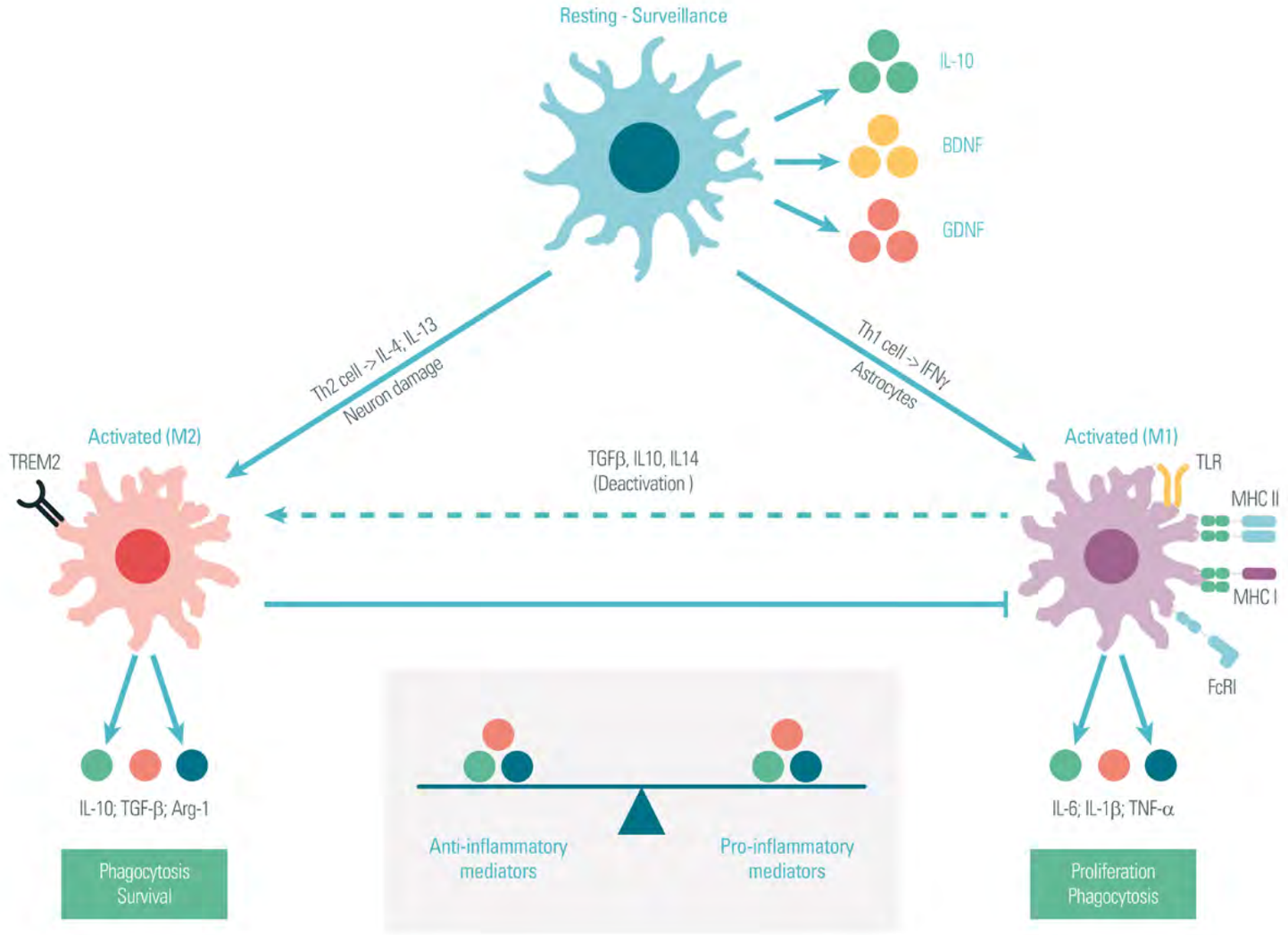

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GLIAL CELLS AND NEUROINFLAMMATION

Microglia dysregulation: Neuroinflammation and neurodegeneration

Microglia have been described to express cellular markers such as Iba1, CD45, CD68, CD11b, and TMEM119, and specific receptors such as P2Y12R, CX3CR1, and TREM2 which is often assimilated with the M2 phenotype. Like macrophages, they also express pathogen recognition receptors, integrins, TLR, and FcR. Microglia also express major histocompatibility complex I (MHCI) and II (MHCII) receptors. They are commonly thought to be expressed on M1 activated microglia. Activation of all these receptors results in the microglia immune response [1].

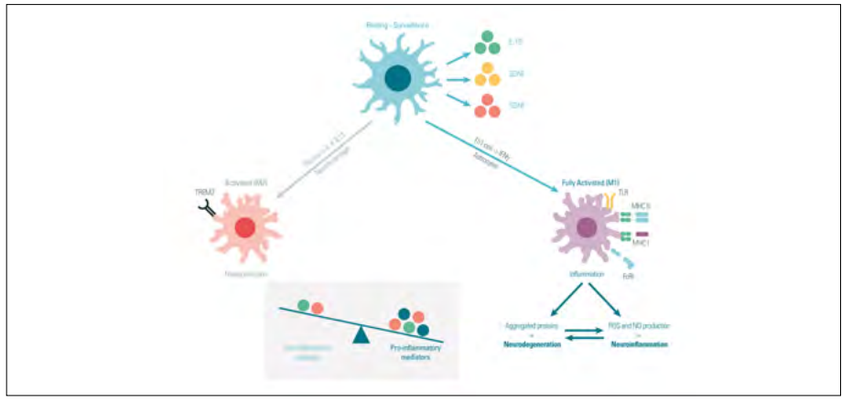
A sustained activation of microglia in an M1 phenotype is deleterious for microglia and glial cells. A continuous pro-inflammatory state increases inflammation, activating astrocytes and thus increasing ROS and NO production. In this vicious circle, neuroinflammation eventually leads to neurodegeneration with dysfunctional cells, neuronal death, and the aggregation of proteins as explained below.

In the case of PD, activated microglia phagocytose damaged neurons, inducing the secretion of a wide range of mediators whose ROS, NO, and IL-6 and play a role in astrogliosis. It further exacerbates inflammation and increases the phagocytosis of neuronal debris mediated by microglia cells. However, it is not known whether microglia prime neuroinflammation or whether inflammation prime microglia activation. Furthermore, aggregated alpha-synuclein accelerates this process by inducing IL-1β production via TLR signaling [2,3]. (See page 13).

Activated microglia are also involved in AD. As discussed previously, the hallmark of AD is the aggregation of Aβ and hyperphosphorylated Tau (See page 9). This aggregation activates microglia that in turn enhance pro-inflammatory cytokine and chemokine release, which further activates microglia [3]. Evidence suggests that microglia are part of the initiation but also of the amplification of neurodegeneration in AD patients. Moreover, microglia activation has been shown to be a key component of Tau hyperphosphorylation [4].

On the other hand, the deactivation of microglia into the M2 state is abrogated, thus sustaining the inflammation in CNS. TGF-β is an important cytokine that regulates microglia deactivation and favors their homeostatic state. It has been hypothesized that a modulation of TGF-β protein changes its signaling in AD and PD, triggering microglia dysfunction [5].

TREM2, a mediator of neuroprotection, has also been described to be a major player in neurodegenerative diseases. TREM2 undergoes a proteolytic cleavage by ADAM10 and ADAM17 proteins, releasing a soluble TREM2 (sTREM2). sTREM2 has been detected in human CSF, and its high level in patients with AD is modulated throughout the disease progression. Because the level of sTREM2 correlates with the level of neuronal injury, it is in the spotlight as a new biomarker for neurodegeneration [5,6].



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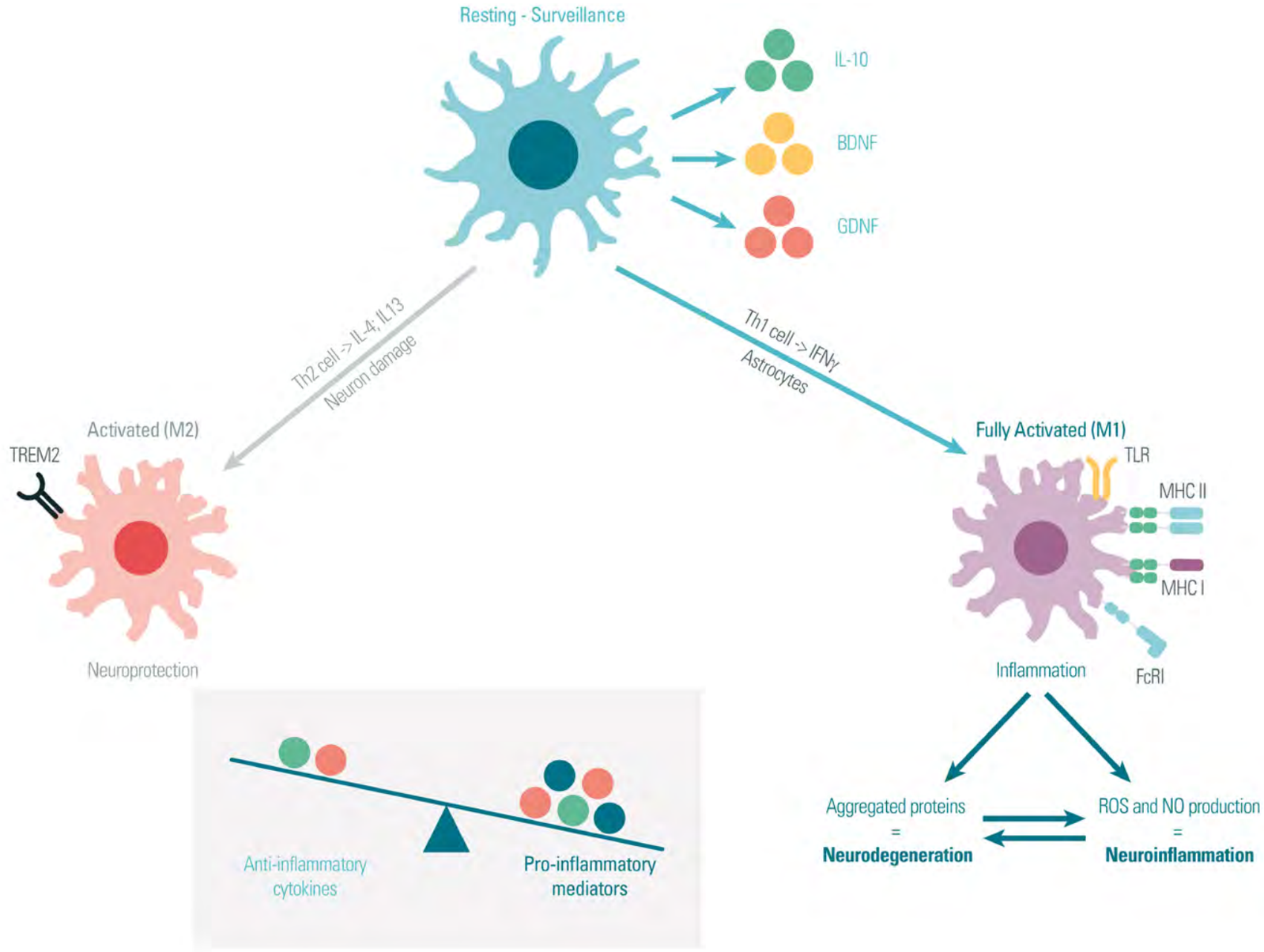

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GLIAL CELLS AND NEUROINFLAMMATION

Activation of TREM2 pathway: Physiologic vs pathologic

The triggering receptor expressed on myeloid cells 2 is a transmembrane glycoprotein. It is composed of an extracellular Ig-like domain, a transmembrane domain, and a short cytoplasmic tail [1].

TREM2 is a receptor that recognizes a variety of ligands. At first, neuronal debris only were thought to activate TREM2. However, anionic bacterial, mammalian ligands (phosphatidylethanolamine, phosphatidylserine or DNA, for example), and cellular proteins such as HSP60 have been shown to bind TREM2. Recently, apolipoprotein E and Aβ oligomers have also been described as efficiently binding TREM2 [2].

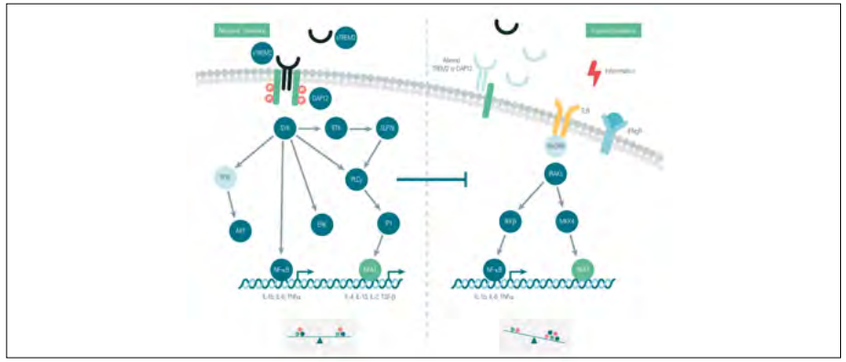
TREM2 requires the adaptor protein DAP12 for downstream signaling. Upon binding to TREM2, the ITAM domain of DAP12 is phosphorylated by a Src kinase. This allows the (auto)phosphorylation of SYK, which activates diverse molecules like BTK or PLCg to modulate calcium concentration. This in turn acts on the nuclear factor of activated T cells (NFAT) which mediates the secretion of anti-inflammatory cytokines. SYK also activates ERK and Akt phosphorylation, and the nuclear factor NF-κB signaling pathway. It leads to the secretion of pro-inflammatory cytokines. As a regulatory signal, SYK phosphorylation via the TREM2/DAP12 pathway negatively regulates the TLR signaling cascade. Therefore in a healthy adult brain, a balance of pro- versus anti-inflammation is reached with a beneficial impact on glial cells [3,4].

In contrast, TREM2/DAP12 signaling impairment has been documented as fostering neuroinflammation. In this case, the adaptor protein is improperly phosphorylated, which allows the TLR signaling pathway to be activated. This results in the release of pro-inflammatory cytokines via the up regulation of NFκB and the down regulation of NFAT [2,3,4].

The best characterized dysfunctional signaling has been shown for AD, with two main genetic risk factors identified: TREM2 and APOE. APOE4 is the greatest genetic risk factor for AD; one ε4 allele increases 3-fold the risk of AD, while two copies increase the risk 12-fold [5]. TREM2 is the second genetic risk factor for AD, with the R47H variant being the most significant. It increases the risk of AD by two to threefold [5].

APOE is a lipoprotein that carries lipids between cells. In the brain, APOE is expressed mainly by astrocytes and microglia cells. APOE4 expression impairs the clearance of Aβ plaques and exacerbates Tau pathology, albeit via unclear involved mechanisms [6].

Furthermore, cerebrospinal fluid sTREM2 levels have been found to be elevated for MS patients and at early stage of AD and ALS. Whether this is a protective response needs to be clarified [4].



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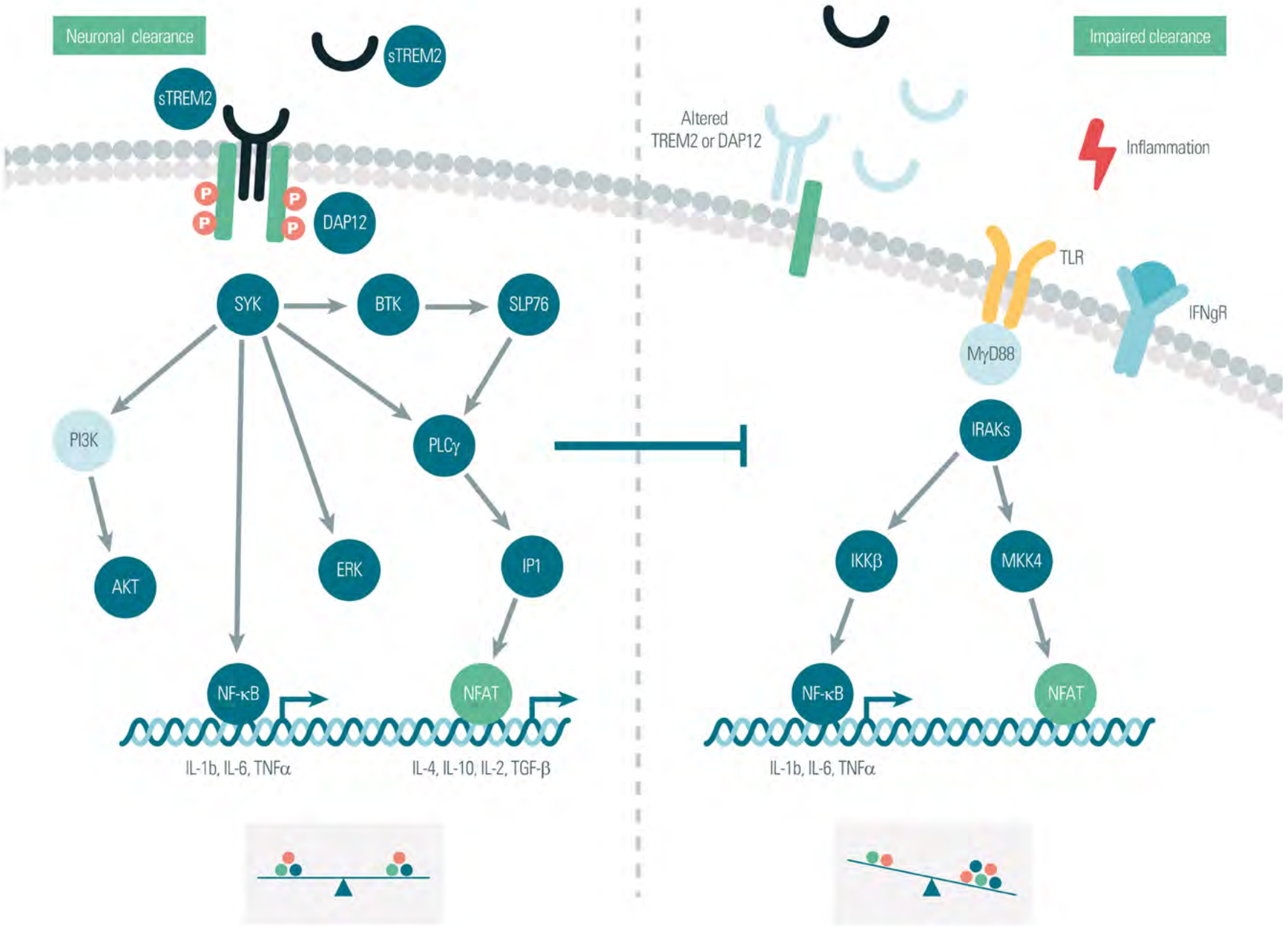

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Inflammasome pathway in microglial cells

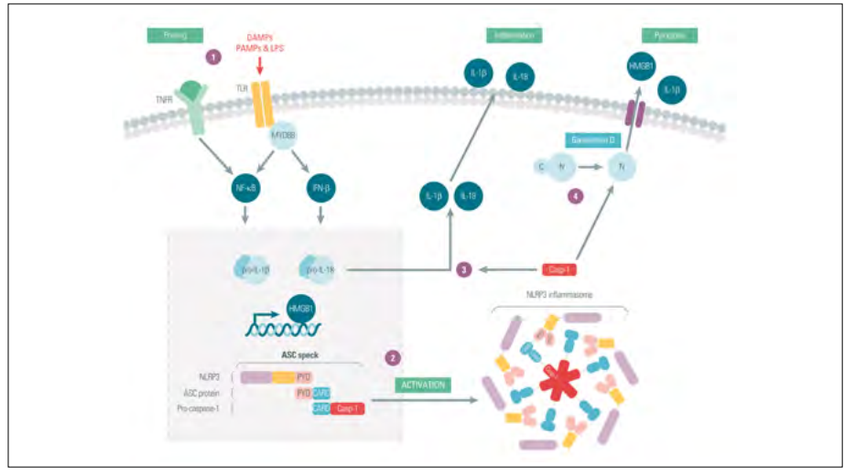
In line with neuroinflammation and neurodegeneration, inflammasomes are part of the inflammation processes that are involved in many CNS diseases.

These complexes are usually discribed as an assembly of identical ASC specks made up of an upstream sensor protein (NLRP1, 2, 3 , 6 or 7 and NLRC4 from the NLR receptor famil or AIM2) linked to a downstream effector pro-caspase-1 by an adpator protein ASC. This association is made possible by the matching PYD and CARD domains of ASC proteins and both partners respectively. Inflammasomes are named after their sensor proteins, hence inflammasome NLRP3, inflammasome AIM2, and others.

Assembly of the complex upon cellular stress activates a two-step mechanism. First, a priming signal (1) involves the activation of the NF-κB signaling pathway and the transcriptional up-regulation of NLRP3, pro-IL-b1, and pro-IL-18. Inflammasomes are activated by TNFR, ILR, or TLR4 that recognizes pathogen- or damage-associated molecular patterns (PAMPs/DAMPs), among others. Next, the activation signal (2) refers to a cellular stress that leads to the oligomerization and activation of the inflammasome. Thirdly, caspase-1 is activated and cleaves inactive pro-IL-1β and pro-IL-18 into active inflammatory IL-1β and IL-18 cytokines, thereby activating inflammation in microglia (3). Finally, caspase-1 (4) is also implicated in the cleavage of the C-terminal domain of Gasdermin D. The released N terminal domain is involved in pyroptosis, a cell death process that increases inflammation by releasing the cellular content into the extracellular environment [1,2,3].

The cleavage of Gasdermin and the activation of NLRP3 inflammasome result in cell death, called pyroptosis. During this process, high mobility group box 1 (HMGB1) is released into the extracellular environment together with IL-1β. Released HMGB1 is then recognized as a DAMP. In fact, depending on the redox state of the protein, it is either a chemotactic factor that signals through C-X-C chemokine receptor type 4 (CXCR4) or a pro-inflammatory modulator that activates TLR4 [4]. Furthermore, it has been shown that HMGB1 induces the priming of microglia.

Because of its role in microglia, NLRP3 inflammasome has been shown to be involved in CNS disorders. For example, α-synuclein has been reported to activate NLRP3 inflammasome in PD, while activation of NLRP3 in AD is responsible for a synaptic deficit, thus increasing neuroinflammation [5]. Although mainly described in microglia cells, NLRP3 activation also takes place in other glial cells.



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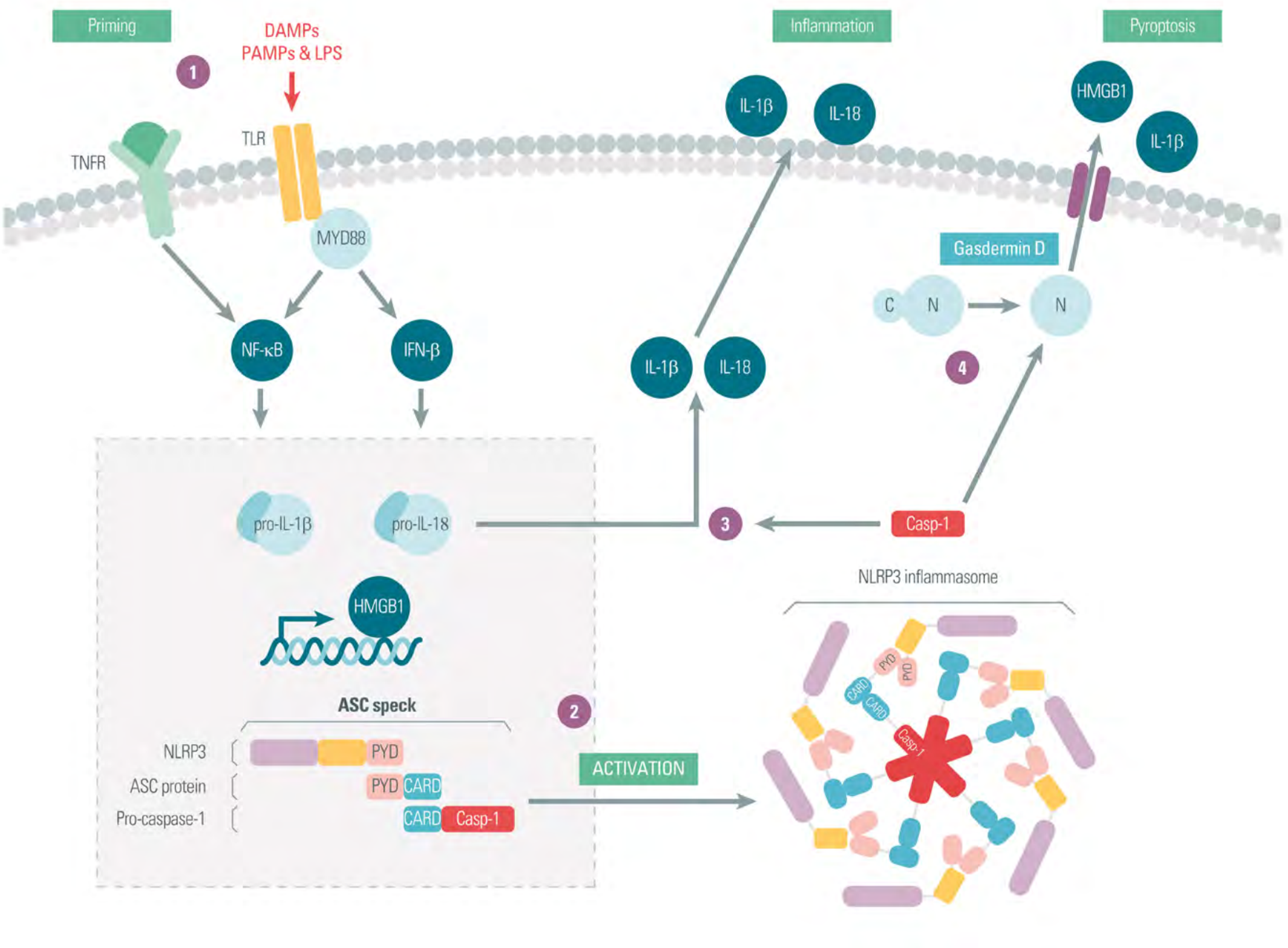

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GLIAL CELLS AND NEUROINFLAMMATION

Astrocytes: Roles and functions

Astrocytes are the most abundant glial cells in the mammalian brain (~30%). Astrocytes are distributed throughout the grey matter and are integral components of the CNS structure by regulating brain function and plasticity. They provide key functions like structural integrity of the blood-brain-barrier (BBB), metabolic support to neurons, synapse formation/maintenance/elimination, as well as recycling of ions and neurotransmitters (NTs). They constitutively express intermediate filament proteins such as GFAP, vimentin, nestin, and S100β that can be used for their identification. As neurons, astrocytes are very diverse and heterogeneous, having distinct properties depending on brain regions and development stages [1].

Pre- and post-synaptic membranes and one astrocyte contact compose the "tripartite synapse" where signaling pathways in the astrocyte modulate the synaptic response. Astrocytes are non-electrically excitable, but nevertheless they participate in activity by responding to NTs via metabotropic (i.e. mGluR) and ionotropic receptors, inducing Ca2+ elevation that leads to glutamate, ATP, or GABA release in the synaptic cleft. Moreover, astrocytes are also interconnected at gap junctions through connections that enable another level of regulation through the diffusion of nutrients, ions, and NTs [2].

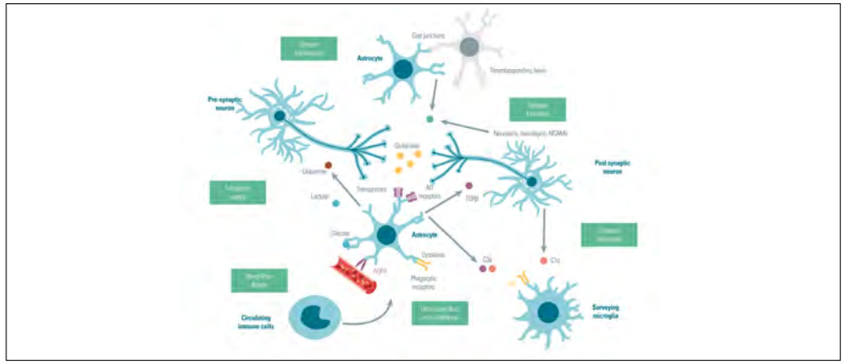
The metabolic support of astrocytes is essential for neurons, as they regulate glucose uptake from blood vessels and subsequent lactate release into neurons. Astrocytes are also instrumental in water homeostasis and ion buffering through the AQP4 water channel and the Kir4.1 potassium channel at the BBB [3].

Astrocytes express glutamate transporters (GLAST, GLT1) and GABA transporters (GAT3), enabling NT uptake and subsequent conversion into glutamine via the cytoplasmic Glutamine Synthase enzyme (GS). Glutamine is then secreted and uptaken by neurons for further NTs synthesis [4]. This tight regulation prevents glutamate accumulation that could lead to excitotoxicity, an excessive neuronal activation, and cell death.

Neurons and astrocytes secrete several synaptogenic molecules such as thrombospondins, hevin, neurexin, neuroligins, and NCAMs to support synapse formation. This is a dynamic process in which synapses are eliminated to ensure neuronal plasticity. Astrocytes mediate direct synapse engulfment through phagocytic MERTK and MEGF10 receptors [4], or by microglia recruitment via complement receptors (CR) either directly through C3a secretion or indirectly by TGF-β secretion that upregulates C1q in neurons [5].

Astrocytes also participate in the integrity and permeability of the BBB. This interface is composed of endothelial cells, pericytes, and astrocytic endfeet, the latter establishing a link between the endothelial blood flux and neurons. The regulation of BBB formation and maintenance avoids toxic substances and immune cell infiltration.

All these astrocytic central functions are beneficial, but can become unfavorable when responses are inappropriate or unbalanced in pathological conditions. Astrocytes are highly sensitive to the environment, and when they overreact in response to injuries they undergo numerous changes that can became deleterious, facilitating neuronal death, inflammation, and impeding repair mechanisms [6].



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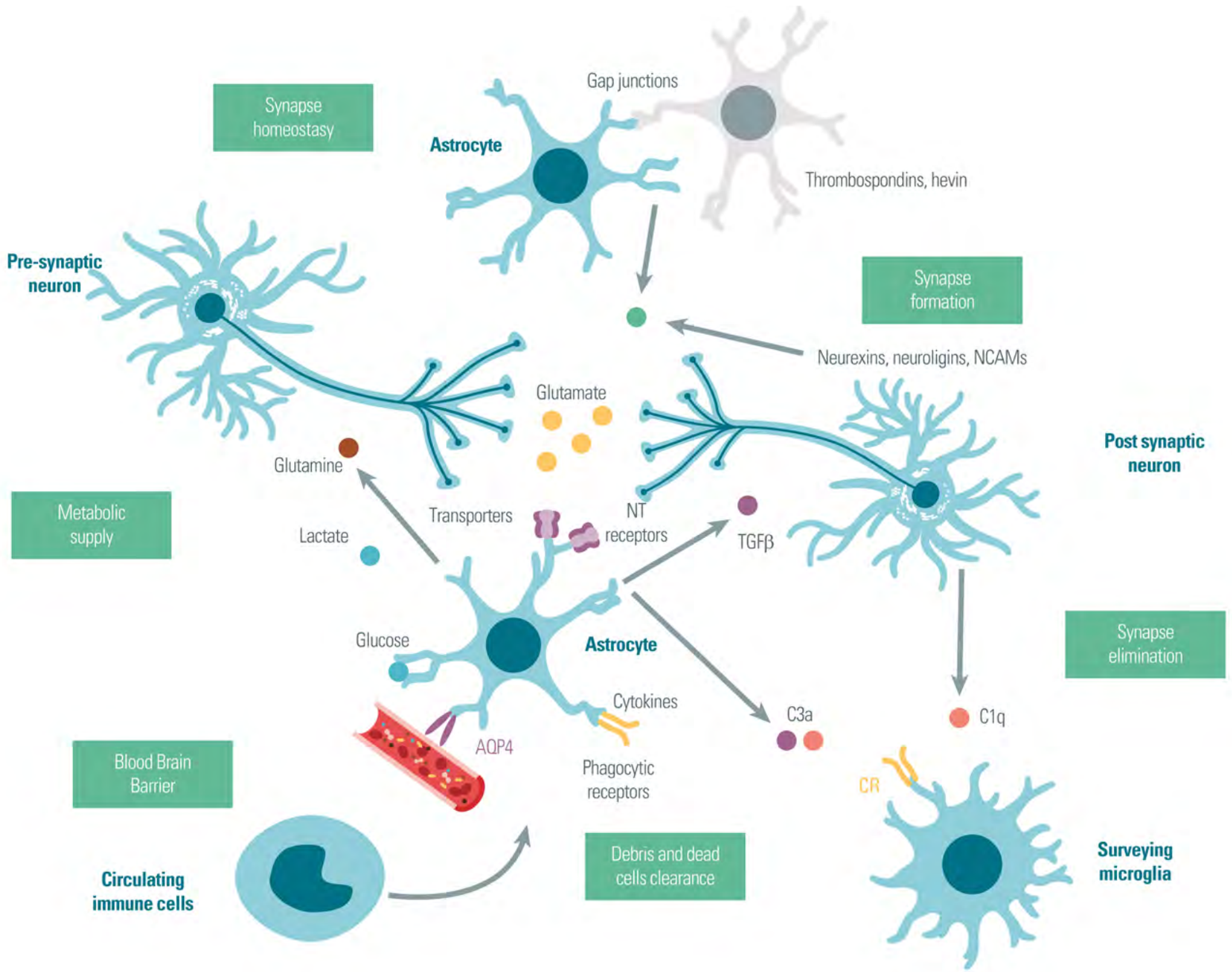

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GLIAL CELLS AND NEUROINFLAMMATION

Astrocyte reactivity

Astrocytes are very sensitive to their environment and respond quickly in response to CNS damage. Depending on the severity of the diseases, they become reactive and undergo molecular and cellular modifications. Activated signaling pathways lead to pro- or anti-inflammatory phenotypes, named A1 and A2 respectively, as a parallel to M1 and M2 phenotypes for microglia [1]. However, it is now recognized that more states may exist; as the astrocyte reactivity is context-specific and changes with the nature and severity of the damage [2].

Pro-inflammatory cytokines like IL-1β or TNF-α released from M1 activated microglia bind to astrocyte cytokine receptors, and activate downstream non-overlapping pathways that lead to transcriptional activation of NF-κB and C/EBPβ. NF-κB is activated by the canonical pathway through IKKβ whereas C/EBPβ is activated downstream from the MEK-ERK1/2 pathway [3].

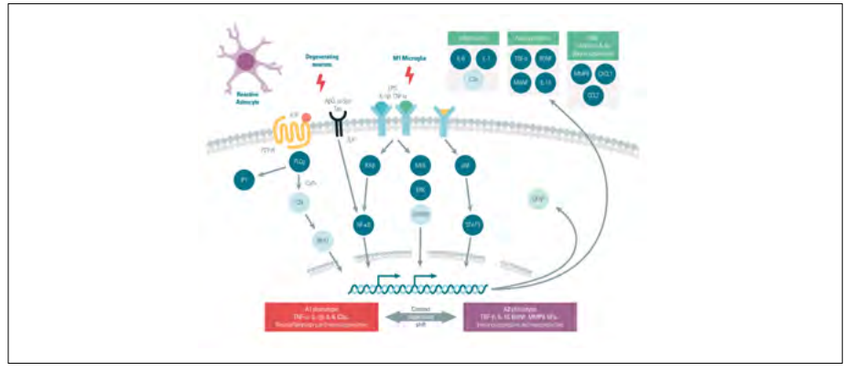
Toxic proteins such as amyloid oligomers, Tau, and α-synuclein aggregates, as well as other DAMPs like HMGB1, are known to activate pattern recognition receptors like TLRs (Toll-Like Receptors). These can further activate Myd88-dependent downstream pathways, leading to activation of NF-κB [4].

In response to some cytokines and growth factors, astrocytes activate the Jak/STAT3 pathway, which is supposed to be responsible for the upregulation and secretion of many neurotrophic and neuroprotective factors promoting neuron survival and synapse repair [1].

Purines (ATP) also activate purinergic P2Y metabotropic Gq coupled GPCRs, which activate the Calcineurin (CN)-NFAT pathway leading to the activation of NFAT target genes [5,6].

The diversity of triggers leading to astrocyte reactivity and the existence of complex interactions/cross-talks between signaling cascades that are disease- and contextspecific results in a spectrum of functional phenotypes, from the protective A2 to the neurotoxic A1 astrocyte [1,2].

Upon the integration of these signaling events, A1 astrocytes mainly upregulate pro-inflammatory and complement cascade genes such as TNF-α, IL-1β, IL-6, and C3, that are harmful and destructive to synapses. On the contrary, A2 astrocytes will upregulate immunosuppressive cytokines, neurotrophins, thrombospondins, MMPs, and growth factor genes such as TGF-β, IL-10, MMP9, and BDNF, to reduce inflammation while stimulating tissue repair [1,7].



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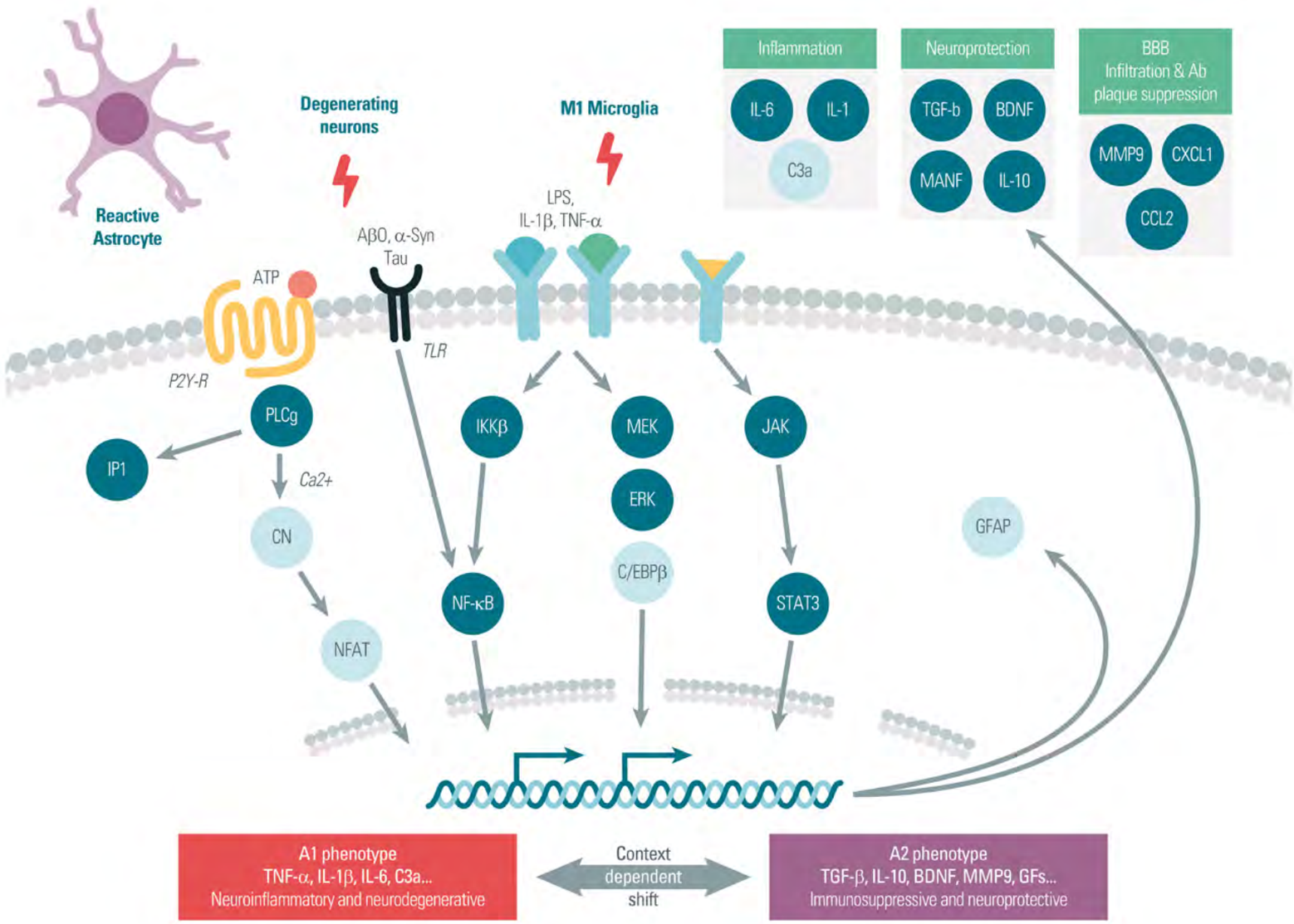

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Oligodendrocyte roles and functions

Oligodendrocytes are generated from oligodendrocyte precursor cells. They are round cells surrounded by long branching processes that wrap axons and protect them by creating the myelin sheath. They myelinate several axons at the same time, up to 60 according to Egdar et Sibille. Myelin is a membrane composed of 70% lipids and 30% proteins whose major components are the myelin basic protein (MBP), proteolipid protein (PLP), and 2',3'-cyclic nucleotide-3'-phosphodiesterase (CNP) [1].

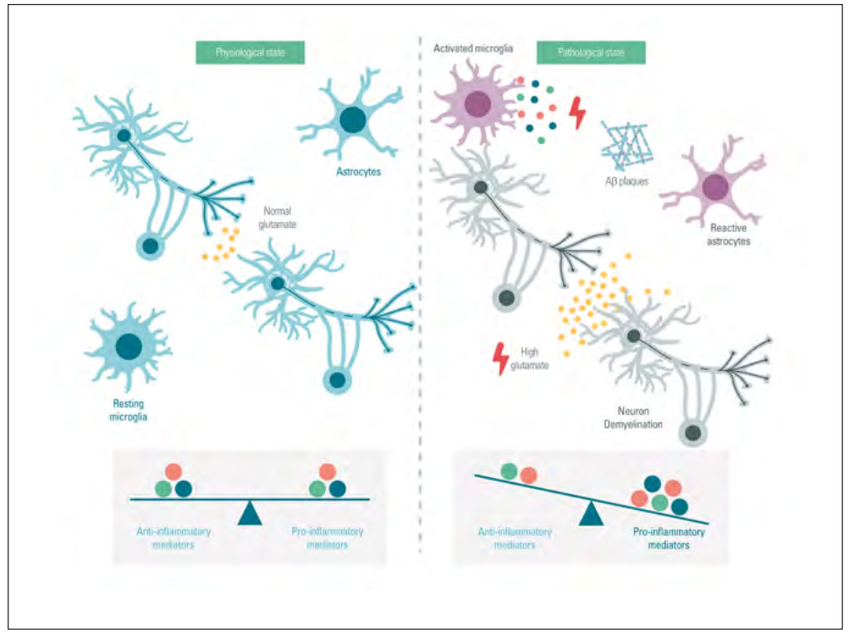
They have a critical role in neurotransmission, homeostasis and immune regulation. For instance, together with astrocytes, oligodendrocytes regulate the optimal speed of information from neuron to neuron and between glial cells through the regulation of the myelin sheath. Furthermore, they are sensitive to inflammatory cytokine dysregulation. TNF-α and IL-1β increase glutamate concentration, which triggers glutamate toxicity and promotes oligodendrocyte loss, and thus demyelination [2].

A growing body of evidence indicates that oligodendrocyte dysfunction is important in neurodegenerative diseases. They have been implicated in mood disorders and schizophrenia due to ROS production for the first disease and to the loss of oligodendrocytes for the latter [2].

In the case of Multiple Sclerosis (MS), oligodendrocytes fail to remyelinate axons. The consequences are a local demyelination and axonal loss. The disruption of oligodendrocytes has also been linked to AD. In the white matter of AD patients, it has been shown that MBP, PLP, and CNP (proteins constituting the myelin) were significantly decreased, probably following oligodendrocyte death. Additionally, Aβ itself has been suggested to be toxic for oligodendrocytes [3,4].

Aging is the greatest risk factor for neurodegeneration. With age, myelin erodes in an as-yet undefined process, which leads to neuronal death aggravating neuroinflammation and subsequently to neurodegeneration [4].

As the interdependency between glial cells becomes more defined, it will open new avenues for neurodegenerative therapies.



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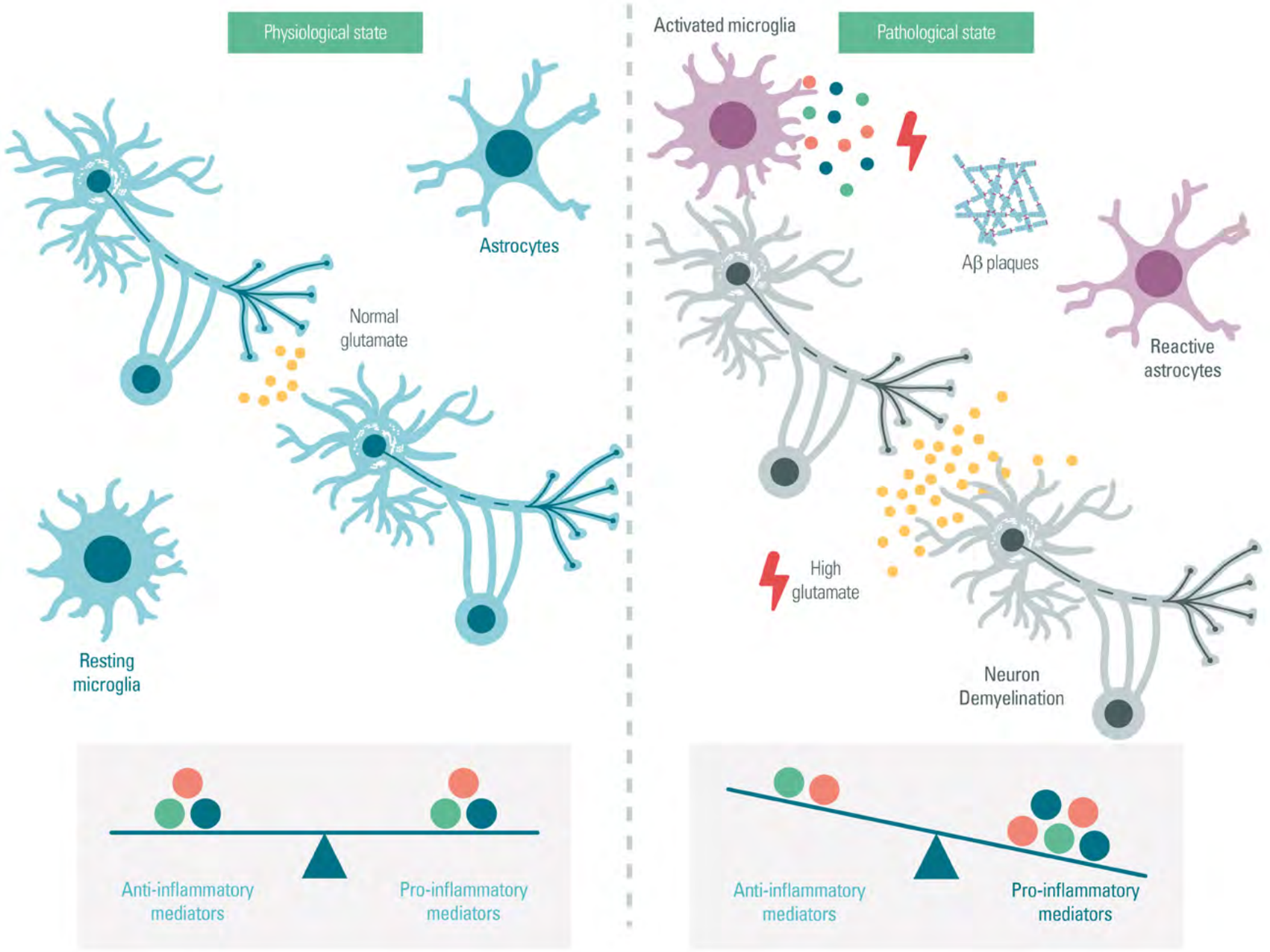

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Acronyms

Name	Definition
A1	Reactive Astrocyte phenotype 1
A2	Reactive Astrocyte phenotype 2
AD	Alzheimer's Disease
ADAM10	A Disintegrin And Metalloproteinase domain-containing protein 10
ADAM17	A Disintegrin And Metalloproteinase domain-containing protein 17
AKT	Protein Kinase B (PKB)
ALP	Autophagy-Lysosomal Pathways
ALS	Amyotrophic Lateral Sclerosis
AMPA-R	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AMPK	AMP-activated protein Kinase
APOE	Apolipoprotein E
APOE4	Apolipoprotein E allele 4
APP	Amyloid Precursor Protein
AQP4	AQuaPorin 4
Arg-1	Arginase 1
Asc	Apoptosis-associated speck-like protein
ATP	Adenosin TriPhosphate
Aβ / AβO	Amyloid beta / Amyloid beta Oligomer(s)
Aβ 40	Amyloid beta of 40 residues
Aβ 42	Amyloid beta of 42 residues
Aβ fibril plaques	Amyloid beta fibril plaques
BACE1	Beta-site APP Cleaving Enzyme 1 or β-secretase
BAD	Bcl-2-associated death promoter protein
BBB	Blood Brain Barrier
Bcl-2	B-cell lymphoma 2 protein
BDNF	Brain-Derived Neurotrophic Factor

Name	Definition
Btk	Bruton tyrosine kinase
C/EBPβ	CCAAT/Enhancer-Binding Protein beta
C1q	Complement component 1 q
C3a	Complement component 3 a
C9ORF72	Chromosome 9 Open Reading Frame 72
Ca2+	Calcium ions
cAMP	Cyclic Adenosine MonoPhosphate
Card	Caspase recruitment domain
Casp-1	Cysteine-dependent ASPArtate-directed proteaSE 1
CCL2	C-C motif Chemokine Ligand 2
CD11b	Cluster of Differentiation 11b
CD45	Cluster of Differentiation 45
CD68	Cluster of Differentiation 68
Cdk5	Cyclin-dependent kinase 5
CDNF	Cerebral Dopamine Neurotrophic Factor
CHOP	C/EBP Homologous Protein
C-jun	Trancription Factor
CN	Calcineurin
CNS	Central Nervous System
CR	Complement Receptor
CSF	CerebroSpinal Fluid
CXCL1	C-X-C motif chemokine Ligand 1
CXCR1	C-X-C chemokine receptor type 1
DAMP	Damage-Associated Molecular Patterns
DAP12	DNAX-activation protein 12 or TYROBP (TYRO protein tyrosine kinase-Binding Protein)
DJ-1	Parkinson disease protein 7

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Acronyms

Name	Definition
EAAT2	Excitatory Amino Acid Transporter 2
ERK	Extracellular signal-Regulated Kinase
FcR	Fc receptor
FTD	FrontoTemporal dementia
FUS	FUsed Sarcoma protein
GABA	gamma-AminoButyric Acid
GAT3	GABA Transporter 3
GBA1	Glucocerebrosidase 1
GDNF	Glial-Derived Neurotrophic Factor
GFAP	Glial Fibrillary Acidic Protein
GLAST	GLutamate ASpartate Transporter
GLT1	Glutamate Transporter 1
GPCR	G protein-coupled receptors
GRN	Progranulin
GSK3b	Glycogen Synthase Kinase 3b
HMGB1	High-Mobility Group Box 1
HSP60	Heat Shock Protein 60
Iba1	Ionized calcium Binding Adaptor molecule 1
IFNgR	Interferon gamma Receptor or IFNγR
IFN-α	Interferon alpha
IFN-β	Interferon beta
IFN-γ	Interferon gamma
IKKβ	IkappaB kinase beta or IKK2
IL-10	Interleukin 10
IL-13	Interleukin 13
IL-14	Interleukin 14
IL-18	Interleukin 18

Name	Definition
IL-1β	Interleukin 1 beta
IL-2	Interleukin 2
IL-4	Interleukin 4
IL-6	Interleukin 6
IP1	Inositol-phosphate
IRAKs	Interleukin-1 Receptor-Associated Kinase
ITAM	Immunoreceptor Tyrosine-based Activation Motif
JAK	Janus Kinase
JNK	c-Jun N-terminal kinase
Kir4.1	(ATP-sensitive) inward rectifier potassium channel
LC3II	Microtubule-associated proteins 1A/1B Light Chain 3B (LC3)-phosphatidylethanolamine conjugate
LPS	Lipopolysaccharide
LRRK2	Leucine-Rich Repeat Kinase 2
M1	Microglia M1 phenotype
M2	Microglia M2 phenotype
MANF	Mesencephalic Astrocyte-derived Neurotrophic Factor
MAO-B	MonoAmine Oxidase B
MAPK	Mitogen-Activated Protein Kinase or p38
MEGF10	Multiple EGF-like-domains 10 protein
MEK	MAPK Extracellular signal-regulated Kinase
MERTK	MER receptor Tyrosine Kinase
mGluR	metabotropic Glutamate Receptor
MHC I	Major Histocompatibility Complex I
MHC II	Major Histocompatibility Complex II
MKK	Mitogen-activated protein Kinase Kinase
MKK4	Mitogen-activated protein Kinase Kinase 4

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Acronyms

Name	Definition
MMPs	Matrix Metallo Proteins
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mTOR	mammalian Target Of Rapamycin
Myd88	Myeloid differentiation primary response 88 protein
NCAM	Neural Cell Adhesion Molecule
NFAT	Nuclear Factor of Activated T cells
NFKB	Nuclear Factor Kappa B
NFL	NeuroFilament Light chain
NFTs	NeuroFribrillary Tangles
NLRP3	NLR family pyrin domain containing 3
NO	Nitric Oxide
NT	Neurotransmitters
OPTN	Optineurin
p25	Proteolytically cleaved form of p35 that is a is a neuron-specific activator of Cdk5
P2Y12R	Chemoreceptor of the P2YR family
P2YR	Purinergic GPCR
p38 (MAPK)	P38 or Mitogen-Activated Protein Kinase
p53	tumor protein p53
p62	nucleoporin p62
PAMP	Pathogen-Associated Molecular Patterns
Parkin	E3 ubiquitin ligase
PARP	Poly (ADP-ribose) polymerase
PD	Parkinson's Disease
PHFs	Paired Helical Filaments
PI3K	Phosphoinositide 3-Kinase
PINK1	PTEN-induced putative kinase 1
PKC	Protein Kinase C

Name	Definition
PLC	PhosphoLipase C
PRR	Pattern Recognition Receptor
PYD	Pyrin Domain
ROS	Reactive Oxygen Species
SLP76	Lymphocyte Cytosolic Protein 2 or LCP2
SMCR8	Guanine nucleotide exchange protein
SNCA	alpha-synuclein
SOD1	Super Oxide Dismutase 1
SQSTM1	Sequestosome-1 protein
STAT3	Signal Transducer and Activator of Transcription 3
sTREM2	Soluble Triggering Receptor Expressed on Myeloid cells 2
SYK	Spleen tyrosine Kinase
TBK1	TANK Binding Kinase 1
TDP-43	TAR DNA binding Protein 43
TGF-b	Transforming Growth Factor beta
TLR	Toll Like Receptor
TLR4	Toll Like Receptor 4
TLR9	Toll Like Receptor 9
TMEM119	TransMEMbrane protein 119
TNFR	TNF Receptor
TNF-α	Tumor Necrosis Factor alpha
TREM2	Triggering Receptor Expressed on Myeloid cells 2
Trk B	Tropomyosin Receptor Kinase B
UBQLN2	Ubiquilin-2
ULK1	UNC-51-like kinase 1
VCP	Valosin-Containing Protein
α-Syn	alpha-synuclein or SNCA

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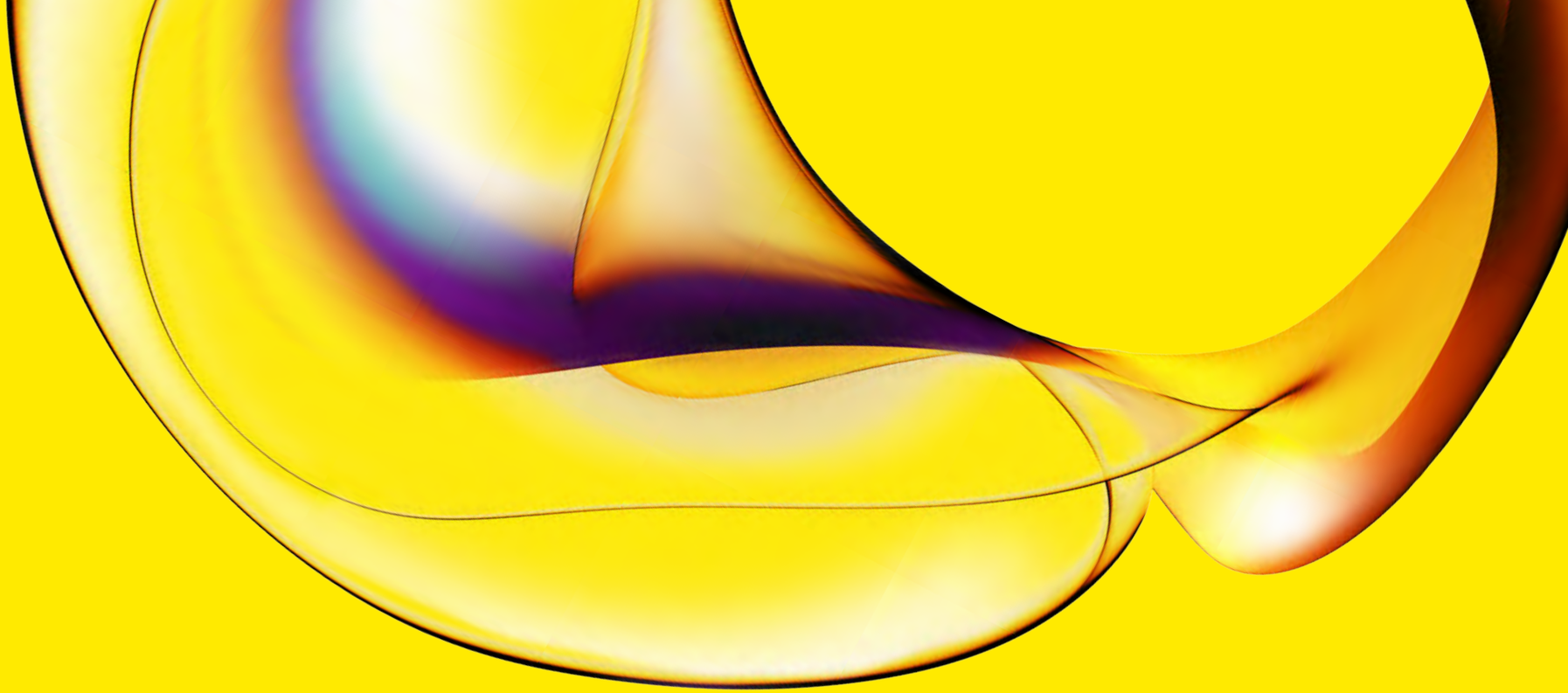

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