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THE BLOOD-BRAIN BARRIER IS HIGHLY SPECIALIZED TO PROTECT THE BRAIN

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ABSTRACT

The blood-brain barrier (BBB) is semipermeable and is composed of cells that, under physiological conditions, prevent the passage of toxic substances and microorganisms into the brain. The BBB only allows passage of small molecules such as oxygen, glucose, and certain amino acids necessary for the physiological functioning of the brain. Glucose passes between endothelial cells via glucose transporter (GLUT) 1, a transporter protein that is expressed by both endothelia and astrocytes. This transport function occurs through passive diffusion and without the consumption of ATP. Various microorganisms, including viruses, bacteria, fungi, and parasites, can infect the brain by bypassing the BBB using specific strategies. Abnormal functioning of the BBB is a characteristic feature of neurodegenerative diseases, where it occurs consequentially following brain pathology and contributes to the progression of neurodegeneration.

KEYWORDS: *Blood-brain barrier, brain, central nervous system, microorganism, glucose transporter, GLUT1*

INTRODUCTION

The blood-brain barrier (BBB) is highly specialized in selectively preventing the passage of harmful substances into the central nervous system (CNS). The BBB is semipermeable and composed of vascular endothelial cells that prevent toxins, microorganisms, and other toxic compounds from entering the brain. The BBB is a lipophilic and dynamic barrier critical for maintaining homeostasis in the CNS microenvironment (1). The BBB is highly specialized for selectively preventing the exchange of neurotoxic molecules and regulating molecular trafficking (2). It supplies the brain with nutrients, key substrates for DNA and RNA synthesis, and regulatory molecules, and removes metabolic waste products into the blood (3).

BBB dysfunction often occurs in neurodegenerative diseases, such as Alzheimer's disease (AD), where it is often observed early (4). The loss of pericytes in the BBB, along with reduced levels of glucose transporter (GLUT), leads to metabolic stress in the brain.

The endothelial cells of the cerebral capillaries are joined by tight junctions, including claudins and occludins that prevent the passage of harmful molecules, whose function is to protect the brain from substances circulating in the peripheral blood (5).

DISCUSSION

The BBB protects the brain from fluctuations in blood composition, while allowing the entry of nutrients and gases necessary for neuronal function (6). Additionally, the BBB allows the passage of substances such as oxygen, glucose, and

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certain amino acids that are necessary for the physiological functioning of the brain (7). Furthermore, it allows the passage of GLUT1, amino acids, and ions via specific transporters (8).

Glucose, the brain's main energy source, cannot circulate freely across the membrane, so it is transported by the protein GLUT1, the main transporter expressed in endothelial cells of the BBB and by astrocytes (Fig.1). This function occurs independently of insulin and without the consumption of ATP, as it occurs through passive diffusion (9). The BBB ensures a continuous physiological supply of glucose to neurons, which depend almost exclusively on ATP production. Low levels of GLUT1, as occurs in the genetic disorder GLUT1 deficiency syndrome, causes childhood epilepsy, developmental delay, and movement disorders (10). Treatment with a ketogenic diet allows ketone bodies to bypass the need for glucose (11).

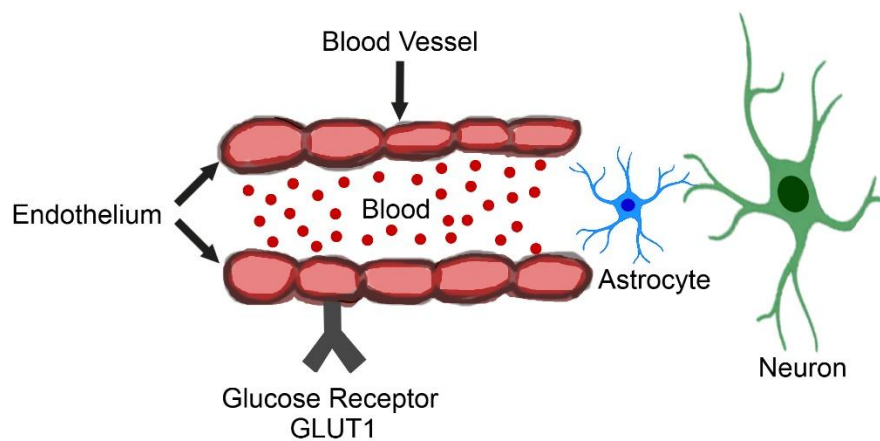


Fig. 1. Glucose binds the glucose receptor GLUT1, the main transporter expressed in endothelial cells, to circulate across the blood-brain barrier (BBB), to affect astrocytes and neurons.

The BBB maintains cerebral homeostasis by affecting ionic balance and neurotransmitter levels (12). The BBB is able to block toxins, pathogens, harmful drugs, and other insults, thus protecting the brain (13). Basement membranes are layers rich in collagen and fibronectin that surround the blood vessels (14). This layer provides important structural support to epithelia, acting as an anchor and physical barrier between epithelial cells and the underlying connective tissue (15). Pericytes are cells present in the BBB that support vascularization, helping maintain the integrity of the barrier itself (16). They regulate the proliferation of endothelial cells, participate in angiogenesis, and help to maintain the structural integrity of the BBB, which would otherwise become too permeable (16).

The formation of new blood vessels is called angiogenesis, which usually nourishes tumors, but it is also a critical process for brain development and health. An intact and effective BBB prevents harmful substances from passing from peripheral blood to the brain. This protection is also ensured by phagocytosis, which eliminates debris and dead cells (17). The endothelial cells that make up the BBB form the cerebral capillaries characterized by tight junctions, while astrocytes, which are glial cells, surround the blood vessels, helping regulate BBB function (2).

The BBB transports small lipophilic molecules into the brain, such as oxygen, carbon dioxide, and some drugs, as well as glucose via GLUT1, amino acids, and ions. It also restricts the passage of large hydrophilic molecules, such as most pathogenic microorganisms, toxins, and cells (18). The BBB protects neurons from harmful external influences and maintains cerebral homeostasis, such as ion balance and neurotransmitter levels, by limiting inflammation (19). The BBB can be disrupted by trauma, infection, neuroinflammation, ischemia, or diseases such as multiple sclerosis, AD, and stroke, which can cause neuroinflammation, edema, and neuronal damage (20).

Some microorganisms have developed strategies to cross the BBB and infect the brain, causing meningitis, encephalitis, and other CNS infections (21). Transcellular microorganisms, such as *Listeria monocytogenes*, *Escherichia coli*, *Streptococcus pneumoniae*, and others, directly cross endothelial cells (22). Paracellular microorganisms, such as *Neisseria meningitidis*, which can release endotoxins that increase permeability, alter tight junctions to pass the endothelial cell barrier (23). In some cases, the BBB is bypassed by the passage of infected immune cells, as occurs with HIV and *Mycobacterium tuberculosis* (24). Other viruses that can cross the BBB include herpes simplex virus, rhabdoviruses, arboviruses (e.g., West Nile virus), and SARS-CoV-2 (in some cases) (25). Fungi such as *Cryptococcus*

neoformans, protozoa such as *Naegleria fowleri*, and *Toxoplasma gondii* can also cross the BBB and damage brain tissue (26).

CONCLUSIONS

The BBB is highly specialized in protecting the CNS by selectively controlling what is able to enter it, and by maintaining homeostasis to create a stable and safe environment. This selectivity is expressed with respect to glucose, the brain's primary energy source on which neurons depend. Glucose does not passively cross the BBB but is transported via the GLUT1 transporter. The BBB maintains a constant supply of glucose even when peripheral blood glucose levels fluctuate. Neurons are protected by the BBB, which ensures their proper health and function.

Conflict of interest

The author declares that they have no conflict of interest.

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CELLULAR AND VASCULAR MECHANISMS IN NEURODEGENERATION

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ABSTRACT

Neurodegeneration is a brain disorder characterized by the death of neurons. It occurs in many brain diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD). The causes of neurodegeneration are poorly understood and still under study. However, it is known that excessive production of reactive oxygen species (ROS) can damage DNA, as well as some proteins, lipids, and other cellular structures. Mitochondria regulate programmed cell death, or apoptosis, but when they are damaged in neurodegeneration, they reduce ATP levels and increase ROS levels. This affects neurons, which are particularly vulnerable to mitochondrial dysfunction. In neurodegenerative diseases, damaged mitochondria accumulate, leading to apoptosis.

KEYWORDS: *Neurodegeneration, mechanisms, neurodegenerative diseases, amyloid beta, α -synuclein, reactive oxygen species*

INTRODUCTION

Neurodegeneration is characterized by the loss of neurons that can occur in many brain diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD), when abnormal proteins accumulate (1,2). For example, in AD, amyloid beta ($A\beta$) accumulates; while in PD, α -synuclein aggregates, or Lewy bodies, form (1-3). Abnormal protein aggregates are toxic to neurons and interfere with their function. The causes of these protein abnormalities are diverse and often unclear.

It is known that excessive production of reactive oxygen species (ROS) can damage DNA, proteins, lipids, and other vital cell structures (4). Neurons are particularly affected by ROS because they consume large amounts of oxygen and have little antioxidant capacity. Energy-producing mitochondria can undergo mutations and contribute to neurodegeneration.

DNA damage and repair defects can be harmful to the life of the neuron (5). Mitochondrial damage reduces ATP and increases ROS levels, altering the mitochondrial membrane potential, releasing cytochrome C, and activating apoptosis (6). Mitochondria produce ATP through oxidative phosphorylation and control intracellular calcium levels (7). They also regulate programmed cell death or apoptosis, and the balance between oxidation and reduction reactions within a cell (8). Being high-energy, post-mitotic cells, neurons are particularly vulnerable to mitochondrial dysfunction. Decreased ATP production compromises synaptic function and neuronal signaling (9) (Fig.1).

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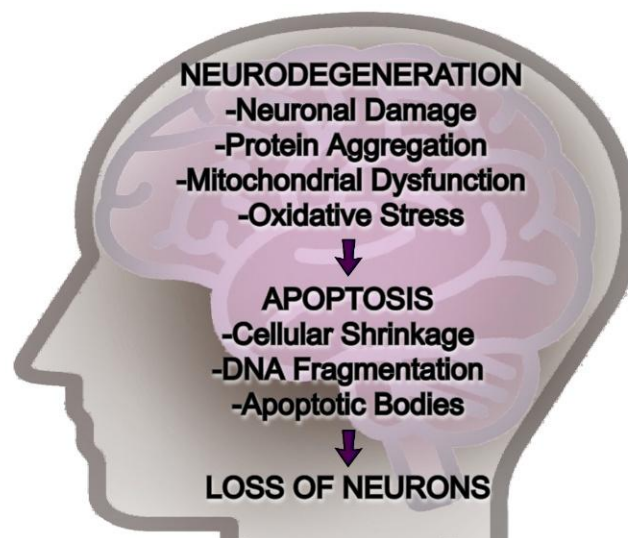


Fig. 1. Neurodegeneration is characterized by neuronal damage, protein aggregation, mitochondrial dysfunction, and oxidative stress that cause apoptosis and the loss of neurons.

Neurodegeneration is characterized by apoptosis, ferroptosis, pyroptosis, and necroptosis (10). These changes begin at the synaptic level, before neuronal death occurs. Neurodegeneration leads to impaired neurotransmitter formation, with the onset of numerous neurological and psychiatric disorders, depending on the type of neurotransmitter involved (1) (Table I).

Table I. The characteristics of neurodegeneration.

Loss of neuronal structure and function	Motor deficits
Death of brain tissue	Cognitive impairment
Oxidative stress	Mitochondrial dysfunction
Protein aggregation	

DISCUSSION

CNS diseases can be neurodegenerative, vascular, inflammatory, and neoplastic, affecting cerebral blood vessels, the BBB, neurons, and glial cells. Neurodegeneration involves the progressive loss of neuronal structure and function due to protein misfolding, inflammation, and oxidative stress. Neurodegeneration is closely linked to the vascular system, resulting in reduced blood flow, small infarcts, and BBB damage. Pathological proteins such as A β deposit in the vessels, causing cerebral angiopathy with inflammation that alters the endothelium and vascular dementia. Risk factors include hypertension, hypercholesterolemia, and diabetes.

In PD, when cellular autophagy fails, damaged mitochondria accumulate, leading to apoptosis through the release of cytochrome C (11). Oxidative stress also leads to the accumulation of α -synuclein (12). In AD, mitochondria interact with the A β protein, altering oxidative phosphorylation (11). Early mitochondrial damage often occurs in the preclinical stages. In amyotrophic lateral sclerosis (ALS), mutations in SOD1, TDP-43, and FUS result in increased oxidative stress and mitochondrial dysfunction (13). Therapeutic implications for neurodegenerative disorders include mitochondrial antioxidants, such as CoQ10, modulators of mitochondrial dynamics, and gene therapies to correct PINK1/Parkin mutations (14).

Excessive glutamate release causes hyperactivation of NMDA/AMPA receptors, leading to the influx of calcium ions and cell damage (15). The activation of lytic enzymes such as calpains and caspases is also harmful to neurons (16). Calpain activation in neurons is a very important process, both physiologically and pathologically (17). Calpain is a family of proteases, enzymes that degrade proteins and are activated by calcium. The main isoforms in the brain are calpain-1, which is activated by low Ca $^{2+}$ concentrations (18); and calpain-2, which is activated by higher Ca $^{2+}$ concentrations. When cerebral ischemia or any trauma occurs, calpain is hyperactivated, causing the degradation of structural proteins, breakdown of the blood-brain barrier (BBB), mitochondrial damage, and disruption of synaptic signaling (19).

Caspases are a family of proteolytic enzymes (20) that can be activated in neurons, where they play a key role in apoptosis, a process essential for eliminating excess neurons and refining synaptic connections. Caspase-3 is often implicated in pathological conditions such as ischemia, oxidative stress, stroke, and traumatic brain injury (21). The

phenomenon of altered neuronal survival involves the reduction of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), the increase of pro-apoptotic signals such as Bcl-2-associated X protein (BAX), and the reduction of anti-apoptotic signals such as Bcl-2 (22).

BDNF is a neurotrophic factor essential for the survival, development, synaptic plasticity, and function of neurons. It belongs to the neurotrophin family, which also includes nerve growth factor (NGF), NT-3, and NT-4/5 (23). BDNF promotes the survival of neurons during development and prevents apoptosis, increases the effectiveness of existing synapses, and stimulates the formation of new synapses and new neurons, especially in the hippocampus (24).

BAX is a pro-apoptotic protein belonging to the Bcl-2 family and plays a crucial role in regulating apoptosis (25). Under conditions of hypoxia, oxidative stress, and other cellular insults, BAX is activated and translocates from the cytosol to the mitochondrion, where it promotes the release of cytochrome C (26). This activates the mitochondrial apoptosis pathway, leading to the activation of caspases that degrade the cell and cause neuronal death. Bcl-2 regulates apoptosis and plays a fundamental role in neuronal survival both during nervous system development and in pathological conditions. In neurons, Bcl-2 inhibits apoptosis by blocking the release of cytochrome C from mitochondria, thus preventing the activation of the caspase cascade (27).

Chronic inflammation, with the activation of microglia, caspases, and pro-inflammatory cytokines such as TNF and IL-1 β , are detrimental to neuronal survival (28).

There is no specific therapy for neurodegeneration; however, drugs and other methods are used to slow the progression of the disease, manage symptoms, and improve quality of life. Some medications may be helpful, such as those that inhibit cholinesterase, the N-methyl-D-aspartate (NMDA) antagonist, and monoclonal antibodies against A β in AD (29).

Cholinesterase inhibitors

Cholinesterase inhibitors (anticholinesterases) are responsible for the degradation of acetylcholine (ACh) in the sympathetic nervous system and act on the enzyme acetylcholinesterase, reducing its effect (30). Acetylcholinesterase breaks down ACh into choline and acetate. The inhibitors bind to the enzyme's active site, preventing hydrolysis, increasing the amount and duration of action of ACh at cholinergic synapses, and improving neurodegeneration (31). Increased ACh in synapses causes prolonged stimulation of muscarinic and nicotinic cholinergic receptors (32). At the cellular level in the CNS, there is an increase in cholinergic transmission and an improvement in sympathetic function, memory, and learning. At the peripheral nervous system level, there is both sympathetic and parasympathetic stimulation in the autonomic ganglia, while at the neuromuscular junction, there is prolonged depolarization (33).

N-methyl-D-aspartate (NMDA) antagonist

NMDA receptor antagonist drugs inhibit the activity of ionotropic glutamate receptors, playing a fundamental role in excitatory synaptic transmission, neuronal plasticity, and learning and memory processes (34). The NMDA receptor is an ion channel activated by glutamate, but activation requires a co-agonist such as glycine or D-serine, as well as the removal of the blockade by Mg²⁺ ions. These antagonists can act at different levels and can be classified as competitive, noncompetitive, glycine-site antagonists, and allosteric negative modulators (35). Competitive antagonists bind to the glutamate binding site, preventing its activation; noncompetitive antagonists bind to an allosteric site or within the channel and block ion flow even if glutamate is bound; glycine-site agonists inhibit the binding of glycine to its co-agonist site on the NMDA receptor; while allosteric negative modulators act by altering the receptor's conformation, reducing its activity (36).

Monoclonal antibodies against amyloid-beta (A β)

Monoclonal antibodies against A β are one of the most widely studied therapeutic strategies for the treatment of AD (37). Monoclonal antibodies are designed to specifically recognize and bind to the A β protein, responsible for the formation of senile plaques that characterize AD. These antibodies bind to different forms of A β that consist of soluble monomers (A β 1-40, A β 1-42), toxic oligomers, and insoluble fibrils. Monoclonal antibodies neutralize the toxic soluble forms of A β , particularly the oligomers, which are thought to be the most damaging to synaptic function (38). After binding to the plaque, the antibody promotes its removal through phagocytosis by microglia and complement activation. Microglia recognize antibodies bound to A β via Fc γ receptors, inducing phagocytosis of the plaques (39). However, during phagocytosis, immune cells produce pro-inflammatory cytokines (IL-1 and TNF) that contribute to neuronal neurodegeneration.

CONCLUSIONS

Neurodegeneration is characterized by neuronal loss and damage to DNA, proteins, and lipids. In AD, it is caused by the accumulation of the protein beta-amyloid (A β), and in PD, it results in the formation of aggregates of α -synuclein. These diseases result in mitochondrial damage and impaired ATP production, leading to neuronal damage. Impaired neuronal survival results in a reduction of BDNF, an increase in pro-apoptotic signals such as BAX, and a reduction in anti-apoptotic signals such as Bcl-2. The onset of conic inflammation leads to the activation of microglia, caspases, and pro-inflammatory cytokines. To date, specific therapy for neurodegeneration is lacking. Monoclonal antibody therapy has been shown to neutralize various forms of A β in AD; however, therapies related to neurodegeneration often produce inflammation and are ineffective. Further studies are needed to develop satisfactory therapies.

Conflict of interest

The author declares that they have no conflict of interest.

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ADVANCES FOR AMYOTROPHIC LATERAL SCLEROSIS: DOES IPL344 SLOW THE PROGRESSION?

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KEYWORDS: *Amyotrophic lateral sclerosis, neurodegenerative disease, IPL344, therapy, neuron*

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects motor neurons, nerve cells in the brain and spinal cord, resulting in muscle weakness, atrophy, paralysis, and death of the patient (1). ALS is characterized by a progressive loss of upper motor neurons in the brain and lower motor neurons in the spinal cord and brainstem. Epidemiological data suggest that approximately 10% of ALS cases are familial, while 90% are sporadic. ALS is characterized by complex molecular and biological mechanisms and further studies are required to understand the impairment of voluntary muscles, neuronal death, and neurodegeneration (2).

DISCUSSION

The genes involved in ALS are superoxide dismutase 1 (SOD1) which, once mutated, can cause protein folding and aggregation, and oxidative stress (3). The mutation of the *C9orf72* gene is responsible for the expansion of the GGGGCC repeat and causes toxic RNA foci and disruption of nucleocytoplasmic transport (4). Some proteins such as TARDBP and Fused in Sarcoma (FUS) can bind RNA and form pathological cytoplasmic aggregates in neurons. TARDBP, which encodes the protein TDP-43, and FUS are RNA-binding proteins critical for the regulation of gene expression and are implicated in several neurodegenerative diseases (5). All of these proteins mentioned can alter cellular and neuronal pathophysiology leading to ALS. There is currently no cure for this disease, however some recent experimental data give us hope.

Recently, an interesting molecule has shown efficacy for ALS therapy. When administered intravenously daily for up to three years, IPL344 has shown safety and tolerability in a clinical study (6). IPL344 is a biologically active peptide designed to activate the PI3K-Akt signaling pathway and plays a crucial role in promoting cell survival and inhibiting apoptosis. The study reported a significant slowing of disease progression, compared to controls, with a 64% reduction in the rate of decline of ALS. In addition, patients experienced improved lung function and weight gain (6).

In ALS, the Akt signaling pathway is often downregulated, an effect that contributes to the degeneration of neurons. The PI3K-Akt biochemical pathway is observed in many cellular processes such as metabolism, proliferation, and survival. Activation of IPL344 leads to inhibition of motor neuron apoptosis and reduction of inflammation, which are relevant in ALS. Therefore, stimulating the Akt signaling pathway with IPL344 could have the potential to improve neuronal survival and slow disease progression.

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CONCLUSIONS

One of the experimental therapies currently being studied for ALS is the use of IPL344. This drug has shown encouraging results regarding the possibility of slowing disease progression. IPL344 is an experimentally used peptide that activates the Akt (Protein Kinase B) signaling pathway. Akt promotes cell survival by acting against apoptosis, reduces oxidative stress, and improves energy metabolism. In ALS, the PI3K–Akt pathway is often underactive, making motor neurons more vulnerable. Some preliminary data using IPL344 show a slowing of the decline in muscle function.

Conflict of interest

The author declares that they have no conflict of interest.

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IRAK ACTIVATES TLR AND IL-1R IN MICROGLIA AND MEDIATES NEUROINFLAMMATION

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ABSTRACT

Interleukin-1 receptor-associated kinase (IRAK) belongs to a family of intracellular kinases that mediate the innate immune response after antigen binds to Toll-like receptors (TLRs) and the interleukin-1 receptor (IL-1R). IRAKs 1, 2, 3, and 4 recognize pathogen-associated molecular patterns (PAMPs). In neuroinflammation, IRAK1 and IRAK4 mediate microglial activation, which has been noted in neurological disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). IRAK is involved in both immune and inflammatory processes when inflammatory cytokines are dysregulated, and the activating antigens can be diverse. IRAK4 and IRAK1 promote inflammation, while IRAK3 has a regulatory/inhibitory role and limits the excessive inflammatory response in microglia. IRAK inhibitors, especially IRAK4, are being studied as potential therapeutic agents to reduce neuroinflammation.

KEYWORDS: *Interleukin-1 receptor-associated kinase, intracellular kinase, Toll-like receptor, neuroimmunology, neuroinflammation, neurodegenerative disorder*

INTRODUCTION

Interleukin-1 Receptor-Associated Kinase (IRAK) is a family of intracellular kinases that play an important role in immune signaling after activation of Toll-like receptors (TLRs) and the interleukin-1 receptor (IL-1R) (1). IRAK is crucial for the activation of innate immune cells and the inflammatory response (2). IRAK comprises four proteins: IRAK1, 2, 3, and 4 (3). In the cellular activation cascade and following the response of TLRs and IL-1R, which recognize pathogen-associated molecular patterns (PAMPs), IRAK exerts biological transcriptional activity after recruiting the crucial adaptor myeloid differentiation primary response 88 (MyD88) (4). MyD88 recruits IRAK4, which in turn phosphorylates and activates IRAK1 and/or IRAK2 (5). IRAK4 and IRAK1 play an important role in the antibacterial response, but also in antiviral responses, albeit indirectly (6). The immune response to viruses is largely mediated by TLR3, which recognizes double-stranded RNA, TLR7/8, which recognize single-stranded RNA, and TLR9, which recognizes viral DNA (7).

DISCUSSION

The IRAK family of kinases plays an important role in the field of neuroimmunology and neuroinflammation (8). In innate immunity, the IRAK family consists of four main members: IRAK1, IRAK2, IRAK3 (IRAK-M), and IRAK4, involved in immune receptor signaling (9). In the central nervous system (CNS), IRAK is not directly linked to the pathophysiology of neurons but plays a key role in the inflammatory response mediated by microglia and the

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inflammatory modulation exerted by astrocytes (10). Activation of the IL-1 receptor (IL-1R) or TLR activates the inflammatory pathway initiated by MyD88, leading to the activation of IRAK and NF- κ B/MAPK, with the production of inflammatory cytokines such as IL-1 β , TNF, and IL-6 (11, 12). Thus, IRAK activation in the CNS leads to neuroinflammation, as occurs in Alzheimer's Disease (AD) and Parkinson's Disease (PD), multiple sclerosis (MS), stroke, and ischemic injury (13).

IRAK1 and IRAK4 mediate microglial activation in the neuroinflammation seen in AD; while in PD, IRAK3 is involved and plays a role in the loss of negative regulation of inflammation (14). Furthermore, IRAK1 and IRAK4 are important in acute myeloid leukemia, where they participate in the survival of leukemic cells (15). The inflammatory response may manifest with low-grade fever, but it may also be absent and show no increase in white blood cell count or inflammatory markers (16). This immunodeficiency can lead to increased vulnerability to bacterial infections, while IRAK1 overactivity can cause autoimmune disease (17).

Currently, drugs that inhibit IRAK4 are being studied for the inhibition of inflammation and cancer. IRAK4 deficiency leads to recurrent infections with pyogenic bacteria, particularly *Streptococcus pneumoniae* and *Staphylococcus aureus*, but other types of bacteria may also be involved (18). Viruses activate the immune system via TLR7 and TLR9 leading to stimulation of myeloid differentiation primary response 88 (MyD88) and NF- κ B with activation of innate immune cells, natural killer (NK) cells, and macrophages (19).

IRAK1 and IRAK4 play an important role in many inflammatory diseases, including autoimmune diseases and cancer (20). Autoimmune diseases involving IRAK1 are diverse and include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjogren's syndrome, and those involving IRAK4 include Crohn's disease, MS, and RA (21,22). IRAK3 is also involved in allergic diseases and bronchial asthma (23). IRAK1 and IRAK4 are implicated in B-cell lymphoma, where a MyD88 mutation activates NF- κ B (24). IRAK1 is important in ovarian and breast cancer, where it promotes invasiveness and drug resistance, and IRAK4 is associated with tumor inflammation and disease progression of pancreatic cancer (25,26).

Mutations in IRAK can cause immunodeficiency, especially those affecting the innate immune response. IRAK4 mutations are known to lead to primary immunodeficiency, an autosomal recessive genetic deficiency that causes a defect in the TLR/IL-1R pathway, inhibiting the production of IL-1 β and TNF (27). IRAK4 genetic mutations cause a primary immunodeficiency disorder characterized by recurrent bacterial infections, a reduced inflammatory response, and dysfunction of the innate immune response, effects that are less severe in the IRAK1 mutation (28). IRAK4 inhibitors are in the preclinical phase for diseases such as SLE, RA, lymphomas, and leukemia (29).

IRAK, and in particular, IRAK4 and IRAK1, are important in the immune response to microorganisms recognized by TLRs and IL-1R. After TLR and/or IL-1R activation, IRAK4 and IRAK1 are recruited via MyD88, initiating the inflammatory cascade. Activation of the MyD88 pathway, IRAK, and TRAF6 occurs through IRAK4, which activates IRAK1/2 and phosphorylation. IRAK1 binds to TRAF6 and activates TAK1, which in turn activates IKK and MAPK, reactions that lead to the production of cytokines such as IL-1, TNF, IL-6, and interferon (IFN), and the elimination of viruses, bacteria, or fungi.

CONCLUSIONS

In conclusion, IRAK, an intracellular kinase, mediates the innate immune response by binding to TLRs and IL-1R in CNS microglia. Activation begins with the involvement of MyD88, leading to the activation of IRAK and NF- κ B/MAPK with the production of inflammatory cytokines, while IRAK3 has a regulatory/inhibitory role. Activation of NF- κ B/MAPK by IRAK leads to neuroinflammation, which occurs in neurological diseases such as AD, PD, MS, and Crohn's disease. Inhibition of inflammatory IRAK offers new therapeutic hope for neuroinflammatory diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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PD-1 AND ANTI-PD-1 ANTIBODIES DURING INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

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ABSTRACT

Programmed cell death type 1 (PD-1) is a receptor expressed on activated T lymphocytes that is capable of limiting excessive immune system activation. When PD-1 binds to its ligands PD-L1 and PD-L2, T lymphocyte inhibition occurs. Inhibition of the T cell receptor (TCR) reduces cell proliferation, cytokine production, inflammation, and cytotoxicity toward abnormal cells. PD-1 regulates the immune response in many pathological conditions, such as tumors, infections, autoimmune phenomena, and brain diseases. PD-1 plays an important role in diseases of the central nervous system (CNS) by regulating the immune response and preventing it from overreacting. PD-1 inhibits the excessive activation of microglia, preventing inflammatory processes. In many diseases, including brain tumors, anti-PD-1 monoclonal antibodies block the PD-1 signal and restore inhibition of CD8⁺ cells that act against tumor cells. However, the use of these antibodies must be done with caution, as they can cause immunosuppression and trigger diseases where T cells play a crucial role.

KEYWORDS: *PD-1, anti-PD-1, antibody, infection, central nervous system, T cell*

INTRODUCTION

Programmed cell death-1 (PD-1) (*gene PDCD1*) is an inhibitory receptor expressed on activated T cells capable of limiting excessive immune system activation, which is important in autoimmune diseases and inflammation (1). PD-1 binds to its ligands PD-L1 and PD-L2 and prevents cellular and tissue damage caused by hyperactivated T-cell immunity (2).

PD-1 inhibits Toll-like receptors (TLRs), the receptors that recognize the pathogen, initiate the immune response, and prepare the environment for T-cell activation (3). The T cell receptor (TCR) initiates the activity of the cell and its inhibition by PD-1 reduces cell proliferation, cytokine production, and cytotoxicity (4). During infections, PD-1 is induced, which helps control pathogen-induced inflammation. The presence of microorganisms elevates PD-1 expression in T cells, while after elimination of the pathogen, PD-1 levels tend to decline and inflammation decreases (5). PD-1 prevents an excessive immune response, protecting tissues (6). If antigenic stimulation persists, PD-1 levels remain elevated.

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DISCUSSION

When T cells become incapable of functioning, the production of cytokines, such as interferon-gamma (IFN- γ), interleukin (IL)-2, and tumor necrosis factor (TNF), and the cytotoxic capacity toward foreign antigens decrease, resulting in a less effective immune system (7). Pathogens then gain the upper hand, and the infection becomes chronic (2). Anti-PD-1 antibodies block the PD-1/PD-L1 interaction and thus reactivate T cells and the production of cytokines that mediate the immune response (8).

Inhibiting PD-1 can lead to chronic inflammation (hyperinflammation), triggering a cytokine storm with organ and tissue damage (9) (Fig.1). Anti-PD-1 antibodies reactivate T cells, thereby enhancing the immune response against infections. However, inhibition can lead to an exaggerated inflammatory reaction, resulting in tissue damage and dysregulation of the immune response.

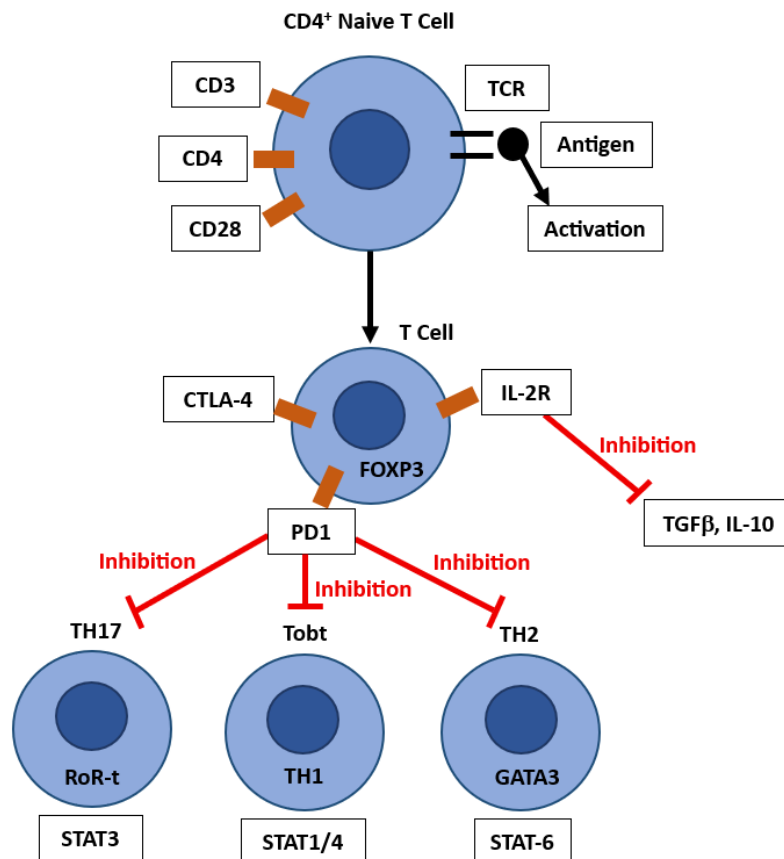


Fig. 1. PD-1 is a T-cell immune checkpoint receptor when it binds to its ligands PD-L1 or PD-L2. Inhibition occurs primarily on TH1, TH2, and TH17 cells, resulting in inhibition of STAT3, STAT1/4, and STAT6.

When T cells experience functional exhaustion after chronic antigenic stimulation, they express inhibitory immune checkpoints such as PD-1, T-cell immunoglobulin mucin-3 (TIM-3), lymphocyte-activation gene 3 (LAG-3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT) (10). These inhibitory reactions, which act as an immune brake, can occur primarily in chronic infections and tumors (11). In early T cell exhaustion, PD-1 is elevated, while in intermediate exhaustion, PD-1 + TIM-3 or TIGIT, and in terminal exhaustion, PD-1 + TIM-3 + LAG-3 + TIGIT, the levels are higher (12). These co-expressed molecules can synergistically increase immune inhibition, and blocking just one of these molecules is not sufficient to inhibit their effect.

Co-expression synergistically increases inhibition, and blocking a single checkpoint is not always sufficient to achieve a physiological effect. PD-1 transmits the PD-L1/PD-L2 signal, inhibits phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT), TCR signalling, and cellular metabolism (13). TIM-3 binds galectin-9 and ICAM-1, inducing apoptosis or functional suppression of T cells (14) (Fig.2). LAG-3 binds MHC-II, reducing TCR signalling. TIGIT binds CD155 (DNAM-1), a potent inhibitor of natural killer (NK) cells and CD8⁺ T cells (15).

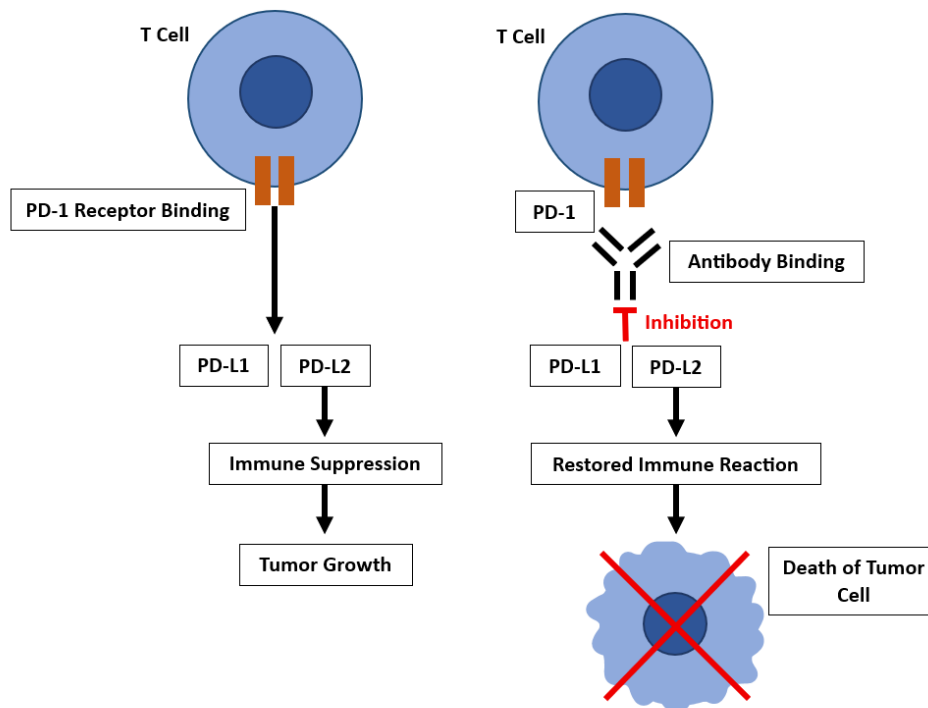


Fig. 2. The PD-1 receptor binds to the ligands PD-L1 and PD-L2 to exert its immunosuppressive effect. This effect leads to potential tumor growth. If PD-1 is blocked by a monoclonal antibody, it cannot bind to the ligands PD-L1 and PD-L2, restoring the immune effect by killing the tumor cell.

PD-1 and the central nervous system

PD-1 plays an important role in infections of the central nervous system (CNS), which activate T cells and generate inflammation (16).

PD-1 is an inhibitory receptor expressed primarily on CD4⁺ and CD8⁺ T cells, NK cells, and B cells (17). Endothelial cells, myeloid cells, astrocytes, and microglia express the ligand PD-L1 (CD274), while PD-L2 (CD273) is expressed primarily by dendritic cells and macrophages (18). PD-1 intervenes in the innate immune response by reducing TCR through phosphorylation, inhibits the generation of IFN- γ , TNF, and IL-2, and limits the proliferation of cytotoxic T cells, an important effect in limiting immune damage in autoimmune diseases (19).

PD-1 also plays a role in viral, bacterial, and parasitic cerebral infections. PD-1 is upregulated in T cells infiltrating the CNS, where it is expressed by activated microglia, endothelial cells comprising the blood-brain barrier (BBB), and astrocytes (20). PD-1 is a protective brake that can prevent certain brain diseases such as immune-mediated encephalitis by protecting neurons and synapses (21). It acts by limiting pathogen clearance and maintaining immune balance in the CNS. Inhibition of PD-1 leads to BBB permeability with increased infiltration of cytotoxic CD8⁺ cells, IFN- γ , TNF, and granzymes, and neuronal damage with demyelination. Activation of PD-1 leads to control of effector T cells, reduced neurotoxicity, and persistence of the pathogen (22).

In CNS infections, anti-PD-1 antibodies such as nivolumab and pembrolizumab block the inhibitory signal, demonstrating that PD-1 is an effective biological brake (23).

PD-1 affects the reactivation of dysfunctional T cells, enhances the proliferation of cytotoxic CD8⁺ cells, and increases the production of pro-inflammatory cytokines. However, in experimental models, the major risks associated with PD-1 treatment are fulminant encephalitis, cerebral edema, and worsening clinical status (24). Furthermore, PD-1 blockade increases mortality due to systemic pathological damage, amplifies T cell–microglia crosstalk, and promotes an M1-type inflammatory state linked to microglial activation (25). In these cases, pro-inflammatory cytokines, nitrous oxide (NO), and reactive oxygen species (ROS) are increased, with damage to neuronal survival, synapses, and myelin (26). Therefore, PD-1 in the CNS is not only a negative checkpoint but is also an important regulator of the neuroimmune system, protecting brain tissue from immune damage by limiting the abnormal effect of T cells. PD-1 inhibition can be beneficial in autoimmune diseases, but also harmful if the immune system is blocked and rendered unresponsive to pathogens.

CONCLUSIONS

Anti-PD-1 drugs are monoclonal antibodies, such as pembrolizumab and nivolumab, that inhibit the PD-1 receptor. These antibodies bind to PD-1, preventing its reaction with its ligands L1 and L2 and reactivating T cell function. This reaction restores the T cell's immune response, especially against tumors. Anti-PD-1 monoclonal antibodies are new pharmacological agents used in cancer immunotherapy where T cell reactivation is important. Conversely, the use of PD-1 may be useful in suppressing the T cell immune response in autoimmune diseases where T cells overrespond. PD-1 and its antibody, anti-PD-1, are crucial not only in oncology but also in the study of the CNS.

PD-1 regulates the brain's immune system, preventing autoimmune hyperreaction, protecting brain tissue and neurons, and reducing inflammation. Anti-PD-1 monoclonal antibodies are useful for fighting tumors and brain metastases, where PD-1 inhibits the immune response. For example, melanoma and non-small-cell lung cancer are implicated in brain metastases. Although they do not cross the BBB, these drugs activate peripheral T cells, which then migrate into brain tissue. However, the use of these antibodies can excessively reactivate T cells, resulting in autoimmune reactions.

Conflict of interest

The authors declare that they have no conflict of interest.

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NEW INSIGHTS IN ALZHEIMER'S DISEASE: THE USE OF STEM CELLS

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease that affects the central nervous system (CNS), causing deterioration of neurons and gradual loss of memory, cognition, and language. AD is caused not only by abnormal protein amyloid-beta ($A\beta$), but also by tau protein and brain inflammation, which plays a key role in cognitive decline. Microglia of the innate immune system contribute to disease progression. Early diagnosis, unhealthy lifestyle, and poor metabolism and vascular health can influence the risk of developing the disease. Treating AD with new humanised monoclonal antibodies reduces $A\beta$ plaques in the brain and modestly slows cognitive decline, especially in the initial phase of treatment, but it is not a definitive cure. Furthermore, the procedure can cause side effects such as edema and/or cerebral microhaemorrhages. Early treatment of AD has been shown to improve the therapeutic effect.

KEYWORDS: *Alzheimer's disease, neurodegenerative disorder, pathology, therapy, stem cell*

INTRODUCTION

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder that causes dementia and cognitive impairment (1). To date, much research has been conducted on AD, but no one has yet been able to understand what really drives the disease. However, with targeted therapeutic interventions, AD can now be partially controlled (2).

AD is characterized by protein alterations, synaptic dysfunction, neuroinflammation, and neuronal death (3). The pathogenesis is still not fully understood, yet ongoing clinical trials are creating new therapeutic hope (4). Research has been searching for effective treatments for AD since many years. Recently, the U.S. Food and Drug Administration (FDA) has approved several drugs for the treatment of this disease, which are aimed not only at alleviating symptoms but also to address AD biologically (5). This has allowed significant progress to be made in tackling the disease, but much work remains to be done.

Pathological studies conducted on the brains of deceased AD patients have shown the formation of aggregates and plaques of amyloid-beta ($A\beta$) proteins in the spaces between neurons (6). Neurofibrillary tangles (NFTs) of tau proteins also accumulate in nerve cells (7). Studies report that $A\beta$ accumulates early and NFTs form when nerve cell damage is ongoing, but symptoms have not yet appeared (8). These altered proteins lead to neurodegeneration because they no longer allow cross-talk between nerve cells.

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DISCUSSION

In the physiological pathway, amyloid precursor protein (APP) is normally cleaved by enzymes such as α -secretase, resulting in the failure of A β production (9). In the pathological pathway, A β produces peptides such as A β 40 and the aggregating A β 42. A β 42 can form soluble oligomers that are highly toxic to synapses that aggregate into lakes, reducing extracellular fluid (10). Synaptic toxicity results in a reduction of NMDA and AMPA receptors, impaired long-term potentiation, and an increase in intracellular Ca²⁺ (11). These reactions lead to microglia activation, the production of pro-inflammatory cytokines, and neuroinflammation (12).

Tau protein destabilizes microtubules in neurons, and hyperphosphorylation of Tau involves the kinases GSK3 β and CDK5 (13,14). This protein loses affinity for microtubules and forms intracellular NFTs (15). Cellular effects include microtubule instability, impaired axonal transport, mitochondrial dysfunction, and apoptotic cell death (16). Tau pathology includes neuroinflammation involving microglia and astrocytes (17).

A β activates Toll-like receptors (TLRs) and TREM2 of microglia, with the production of pro-inflammatory cytokines, such as IL-1 β and tumor necrosis factor (TNF), and reactive oxygen species (ROS) (18). This creates a chronic inflammatory state with progressive neuronal damage, mitochondrial dysfunction, and oxidative stress with reduced ATP production, increased ROS, and damage to membrane lipids, mitochondrial DNA, and synaptic proteins (19). Cerebral damage may present with rapidly occurring synaptic changes, loss of dendritic spines, reduction of excitatory synapses, alterations in glutamate metabolism, cholinergic deficit with degeneration of basal nucleus neurons, cognitive decline due to synaptic loss, and subsequent neuronal death (20).

In order to understand disease risk, DNA studies of genetic variants have indicated that immune and inflammatory processes may play a significant role in this disease (21). However, poor diet, smoking, diabetes, physical inactivity, and vascular disease have also been found to be risk factors (22). Genetic factors that increase the production of A β 42 may involve mutations in APP, PSEN1, and PSEN2 (23). The most common sporadic form and primary genetic risk factor is the APOE ϵ 4 allele, which reduces A β clearance, increases inflammation, and promotes A β deposition (24). Cortico-hippocampal neurodegeneration with cognitive symptoms is linked to Tau protein, which primarily affects the hippocampus, entorhinal cortex, and temporoparietal cortex (25).

New drugs such as donanemab, aducanumab and lecanemab aim to bind to A β proteins and then eliminate them, resulting in improved cognitive function (26). Current research into AD treatment has produced drugs that improve the disease, including dementia, but do not alter the course of neurodegeneration, although reducing A β slows the process. In recent years, monoclonal antibodies targeting A β , such as donanemab, aducanumab, and lecanemab, have been approved by FDA (2). The humanised monoclonal antibody aducanumab binds with high affinity to the neurotoxic soluble protofibrils of A β . After a year and a half of treatment, improvement in patients' clinical decline has been observed compared to untreated patients. Additionally, donanemab, an antibody that targets the deposited altered A β protein, resulted in improved cognitive performance after approximately 6 months of treatment, although further studies are needed to confirm these results (27). The accumulation of A β and tau proteins in AD is nonspecific, as these proteins can also accumulate in other diseases affecting the central nervous system (CNS) (5).

AD Patients also have accumulations of other proteins in the brain, such as α -synuclein, which can appear before A β plaques and cause vascular damage (28). Since other factors, for example, vascular and immune factors, contribute to the development of the disease, A β -reducing treatments are only part of the therapy (29). There is often a gap of decades between the accumulation of A β and cognitive decline (30). Recent studies have shown that many elderly individuals (>75 years old) who tested positive for A β on spinal fluid tests performed with positron emission tomography (PET) or computed tomography (CT) scans remained cognitively healthy (31). This may indicate that A β is not the sole cause of AD (32).

Stem cells are highly plastic cells capable of transforming into various specialized cell types. They may differentiate into new neurons and replace damaged or dead neurons in AD (33). Stem cells can also intervene in inflammatory processes, reducing their severity and promoting synapses (34,35). The cell types used are mesenchymal stem cells from bone marrow or adipose tissue, and adult induced pluripotent stem cells reprogrammed to behave like embryonic stem cells. The use of these cells in AD has shown improvements in memory and a reduction in A β plaques (35,36) (Fig.1). In animal models, injection using embryonic stem cells from cell cultures has been seen to replace damaged neurons in Alzheimer's disease (AD), favoring synapses, improving memory, and reducing cerebral inflammation (37).

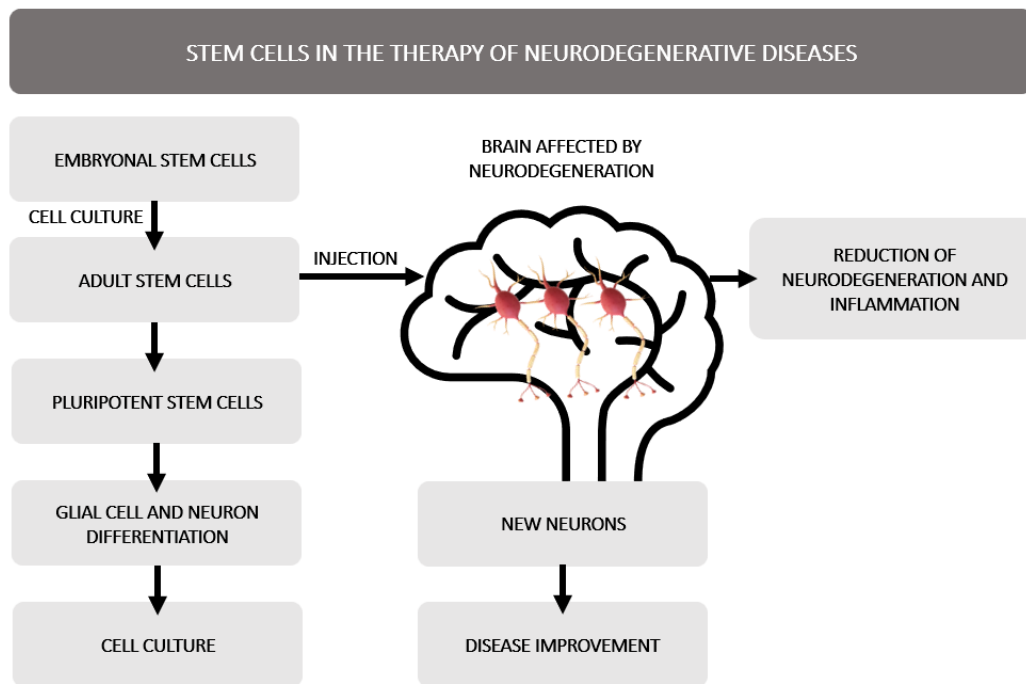


Fig. 1. Cell cultures of embryonal stem cells injected in damaged brain tissue produce new neurons and lead to improvement of the disease and also reduce neurodegeneration and inflammation.

CONCLUSIONS

Recent studies on AD are shedding light on this complex neurodegenerative disorder. Today, attention has shifted beyond the focus on A β and NFTs, and new research reveals a much more complex picture involving the immune and inflammatory systems, vascular and metabolic abnormalities, and genetic factors. Diagnostic methods, advanced neuroimaging techniques, and early diagnosis have proven to be strategies that are opening up innovative new avenues that can reduce protein metabolism and regulate the immune system. The knowledge gained to date about this disease has proven insufficient, and therefore, many molecular and clinical challenges remain to be addressed in AD.

Conflict of interest

The authors declare that they have no conflict of interest.

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