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Exploring Novel Therapeutics for Acute Ischemic Stroke

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Abstract: Stroke remains one of the leading causes of morbidity and mortality worldwide, with ischemic stroke accounting for nearly 80–85% of all cases. It occurs due to obstruction of cerebral blood flow by thrombus or embolus, leading to irreversible neuronal death in the ischemic core and salvageable but vulnerable tissue in the penumbra. Despite the established role of intravenous recombinant tissue plasminogen activator (rtPA) as the only FDA-approved pharmacological therapy, its limited therapeutic window and modest efficacy highlight the urgent need for more effective interventions. Advances in neuroprotective strategies, stem cell therapy, and gene therapy have shown potential by targeting excitotoxicity, oxidative stress, apoptosis, and neuroinflammation, though translation from preclinical studies to clinical success remains challenging. Mechanical thrombectomy has transformed acute ischemic stroke management, offered rapid reperfusion and improved functional outcomes, particularly in large vessel occlusions. Next-generation thrombectomy devices—including refined stent retrievers (e.g., Embotrap, Tigertriever, NeVa), aspiration systems (e.g., Penumbra ACE, React Catheter), and hybrid approaches (e.g., Solumbra technique, balloon guide catheters such as FlowGate^2 and Walrus)—have achieved recanalization rates exceeding 90% in clinical trials. Emerging technologies, including laser-based clot fragmentation, ultrasound-assisted thrombectomy, micro-net mesh systems, and robotics-assisted interventions, are under active investigation to expand treatment options, improve safety, and extend access, especially in remote settings. The growing emphasis on multimodal approaches integrating pharmacological, regenerative, and mechanical strategies reflects a paradigm shift in stroke care. Future directions will focus on optimizing device design, enhancing neuroprotective adjuncts, and personalizing therapies to reduce disability and global stroke burden.
Keywords: Acute ischemic stroke; Stem cell therapy; Gene therapy; Mechanical thrombectomy; Next-generation devices; Neuroregeneration; Recanalization.

I. INTRODUCTION

Cerebral infarction or stroke is a life-threatening event that can involve both breathing and heart function. It may result in serious neurological sequelae. (1) When the blood supply to part of the brain is interrupted or reduced, a stroke is a life-threatening emergency. This break disrupts the flow of blood to the brain, leaving brain tissue without needed oxygen and nourishment. (2) As a result, brain cells can begin to die in a matter of minutes. Stroke is one of the leading causes of death worldwide, especially in the developed countries. It's also undermining the economy. (3) Strokes can be broadly classified into three main types: ischemic stroke, haemorrhagic stroke, and transient ischemic attack (TIA). (4) Thromboembolism as a cause of either cerebral ischemia or in situ thrombosis is responsible for 80%− 85% of all brain ischemia, whereas hypertensive haemorrhage and vessel wall abnormality account for 15%−20% of all haemorrhaged. Reperfusion can rescue saved penumbral tissue, and rapid recanalization is the most powerful factor for the prediction of good clinical outcome in ischemic stroke. (5) Early intravenous recombinant tissue plasminogen activator (rt-PA) therapy in ischemic stroke increases the likelihood of recanalization and independent living according to disability and handicap scales. (6) Acute ischaemic stroke (AIS) which is considered as the most common subtype, is developed by an obstruction of the cerebral arteries due to thrombus or embolus formation. (7) Current management of acute ischemic stroke relies mostly on antiplatelet therapy (e.g. aspirin), the administration of recombinant tissue plasminogen activator (rtPA) intravenously, and complex arterial recanalization methods. rtPA is the only pharmacological agent among these options approved by the Food and Drug Administration (FDA) in the USA for the treatment of acute ischemic stroke. It encourages the dissolution of fibrin clots and helps with thrombolysis. However, therapeutic results remain suboptimal. Others have reported lower success rates, with successful functional independence in approximately 35% of patients. (8) We have learned new lessons from the fact that, despite recent breakthroughs in drug development, implementation of the positive outcome of a large number of animal studies to successful clinical trials has remained major translational challenges.

Although positive results in preclinical studies have been realized, many neuroprotective agents have demonstrated little efficacy in the human trial population. This situation has led researchers to explore new strategies. They are combining these drugs with other agents to improve their effectiveness. Neuroprotection remains a key focus in pharmacological research. Researchers are working on ways to reduce neuronal damage after a stroke. (9) Right after a stroke, a series of harmful processes happens. These include cerebral edema, deafferentation, and neuroinflammation around the ischemic core. While some early neurological recovery can be due to the natural resolution of swelling and inflammation, this improvement is often temporary and limited. Surgical intervention may be needed in some cases, but it can be costly and carries significant risks, limiting its wider use in clinics. Moreover, without effective treatment options, rehabilitation alone is typically not enough to completely restore neurological function. This highlights the need to develop new treatment strategies that address the underlying causes of brain injury while supporting long-term recovery. (10)

A. *Types Of Ischemic Stroke*

Thrombotic Stroke, caused by a blood clot forming in an artery that supplies the brain, often results from atherosclerosis. Embolic Stroke, caused by an embolus, usually from the heart in atrial fibrillation, travels to and blocks a brain artery. Lacunar Stroke, a small vessel blockage often due to hypertension, affects deep brain structures. (11)

B. *Etiology*

Stroke is a complex disorder with different causes and conditions. Understanding the cause is important for accurately diagnosing the patient's symptoms and distinguishing them from other issues that might show similar signs. (12)

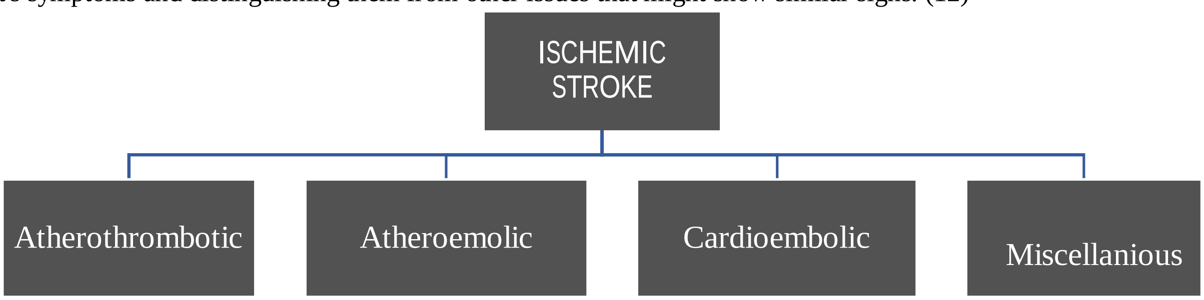

Figure 1. various type of ischemic stroke

Atherothrombotic stroke often occurs in patients with other health issues like high blood pressure, diabetes, and abnormal cholesterol levels. High blood pressure increases the risk of stroke by causing damage to the blood vessels and changing the way the smooth muscles in the blood vessels work. Diabetes affects the risk through both large and small blood vessel problems. (13) Atheroembolic stroke occurs when fatty plaques form in the ascending aorta or in the arteries of the neck and brain, often where the endothelial cells are damaged and reactive. During actions like the Valsalva maneuver, weak thrombi can break apart, sending embolic material upstream to block blood flow in the brain's vessels. When these plaques break open, they can release jelly-like cholesterol crystals, which can cause serious blockages in the brain's arteries. This condition is usually seen in patients who have high levels of low-density lipoproteins (LDL) and low levels of high-density lipoproteins (HDL). (14) Cardioembolic stroke happens when a blood clot or other material forms in the heart. This material travels through the bloodstream and blocks an artery in the brain. It makes up about 15 to 30 percent of all ischemic strokes and has a high risk of happening again along with a high chance of death. The most common causes include atrial fibrillation, left ventricular dysfunction, heart valve diseases, prosthetic heart valves, and recent heart attacks. Atrial fibrillation, especially, causes blood to pool in the heart’s atria, making it easier for clots to form and travel to the brain. (15) Miscellaneous stroke, or a stroke from another known cause, refers to ischemic strokes that result from rare or less common mechanisms. These do not belong to the main categories of atherothrombotic, cardioembolic, or lacunar stroke. These strokes come from unusual vascular, blood-related, or systemic conditions. Examples include non-atherosclerotic vasculopathies such as arterial dissection and vasculitis, blood disorders like sickle cell disease and thrombophilia, infectious or inflammatory diseases such as endocarditis, syphilis, and HIV-related vasculopathy, and genetic or metabolic syndromes like CADASIL and MELAS. Iatrogenic causes, like radiation injury or drug-induced vasospasm, also apply. The clinical presentation can vary, and treatment is specific to the cause, focusing on managing the underlying condition. (16)

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II. EPIDEMIOLOGY AND BURDEN ON GLOBAL AND REGIONAL AND PREVALENCE

A. Global Burden of Acute Ischemic Stroke

In 2021, around 69.9 million people were living with ischemic stroke worldwide. The age-standardized prevalence rate was 819.5 per 100,000. Each year, there were about 7.8 million new cases of acute ischemic stroke, leading to an age-standardized incidence rate of 92 per 100,000. Nearly 3.6 million deaths happened due to ischemic stroke yearly, with an age-standardized death rate of 44 per 100,000. The total disability burden, represented in disability-adjusted life years (DALYs), exceeded 70 million years lost. This corresponded to an age-standardized DALY rate of 837 per 100,000. Although the total numbers of stroke cases, deaths, and DALYs have risen since 1990, mainly due to population growth and aging, the age-standardized rates have generally gone down worldwide. This indicates progress in prevention and care. (17)

B. Key modifiable risk factors contributing to stroke-related DALYs include

High systolic blood pressure: about 57%. Ambient contributors include high fasting glucose, a high sodium diet, kidney dysfunction, and low physical activity. Air pollution accounts for about 17%. Smoking contributes around 14%, and high LDL cholesterol is about 13%. Combined, these factors make up more than 80% of the global stroke burden. This highlights the chances for prevention. (18)

C. Regional Variations

The burden of AIS varies significantly across regions according to socio-demographic index (SDI):

REGIONAL\SDI LEVEL	KEY OBSEVATIONS
High-middle SDI	Highest ASPR, ASIR, ASDR, and DALYs rates
Middle SDI	Notable increases in incidence and burden
High SDI	Lower rates and decreasing trends as of 2021

Table 1. Sociodemographic index of regional burden

D. Areas with Particularly High Burden

Prevalence (ASPR): Southern Sub-Saharan Africa has more than 1,100 cases per 100,000 people. Western Sub-Saharan Africa and East Asia also have high rates. Incidence (ASIR): Eastern Europe has about 143 cases per 100,000 people, East Asia has around 135, and Central Asia has approximately 133. Death and DALY Rates (ASDR & age-standardized DALYs): The highest rates are found in Eastern Europe, Central Asia, North Africa, and the Middle East. (19)

E. Recent Trends and Forecasts

Between 1990 and 2019, East Asia saw the biggest rise in ASIR. Countries like Egypt and China also had marked increases in AIS incidence. Southern and Eastern Sub-Saharan Africa and Southeast Asia recorded the largest jumps in ASDR and DALY. Although age-standardized rates showed downward trends, the actual burden of ischemic stroke grew slightly between 2019 and 2021. This increase may have resulted from disruptions caused by the COVID-19 pandemic. Predictions for the future indicate continued growth in the stroke burden, especially among people aged 45 and older, unless preventive measures are strengthened. One forecast estimates a 50% rise in global stroke deaths by 2050. This increase will likely stem from aging populations and a higher prevalence of risk factors, particularly in low- and middle-income countries. (20)

F. Summary

Absolute burden: AIS affects about 70 million people around the world. There are 7.8 million new cases and 3.6 million deaths each year. Risk factors: More than 80% of the stroke burden comes from modifiable risks like high blood pressure, pollution, and lifestyle choices. Regional disparities: Low- to middle-income regions, such as Sub-Saharan Africa, Eastern Europe, and Asia, face the highest burden. Outlook: Although age-standardized rates are going down, the total burden is increasing because of aging, population growth, and a rising number of cases in adults over 45. (21)

III. PATHOPHYSIOLOGY

The causes of stroke are still not fully understood. Not everyone with common cerebrovascular risk factors has a stroke. Some strokes happen in people without clear risk factors. More research shows that neuroinflammation may play a role in both the early and later stages of stroke. Neuroinflammation affects tissue damage, healing, recovery, and the rise of complications after a stroke. This process involves different types of cells, including microglia, astrocytes, endothelial cells, and traveling white blood cells. It also includes the release of cytokines, chemokines (like CXCL8, CCL2, CCL3), and adhesion molecules. (22) Furthermore, epidemiological data suggest a role for genetic susceptibility in both common stroke types and Mendelian disorders linked to cerebrovascular disease. Stroke is widely seen as a disorder that results from the interaction of genetic, environmental, and lifestyle factors, along with complex cellular and molecular signalling pathways. This complexity has made it particularly challenging to develop effective therapies. In recent years, there have been significant advances in acute-phase interventions, especially with improved thrombolytic strategies and the development of mechanical thrombectomy, either alone or in combination. However, most patients remain ineligible due to limited treatment windows and strict selection criteria. To better understand the biological mechanisms involved and to support the creation of new or more personalized therapies, researchers have established a range of experimental animal models and in vitro cellular models of ischemic stroke. (23) Vessel blockages from atherosclerotic plaque, thrombus, or embolus reduce blood flow to the brain.

Based on mechanism different pathway for pathogenesis first one thrombus formation this is caused by rupture of vascular endothelial tissue initiating coagulating cascade. Pathogenesis of embolism from the deep vein thrombus and other in different vessel walls rupture and travel into brain arteries and block vessel core of blood vessel or penumbra. This leads to an ischemic core, where neurons quickly die from energy failure, which includes ATP depletion, ion pump dysfunction, excitotoxicity, and calcium overload. Surrounding this core is the ischemic penumbra, a recoverable area where cells are not functioning well but could survive with quick treatment. The ischemic core is the central region with very low blood flow, where neurons experience rapid and irreversible death due to energy failure, ion pump dysfunction, excitotoxicity, and calcium overload. The ischemic penumbra is the area around it with partial blood flow, where cells are not functioning properly but may be saved if blood flow is restored quickly. Secondary factors, including oxidative stress, mitochondrial dysfunction, neuroinflammation, apoptosis, and disruption of the blood-brain barrier, further damage neurons and increase the size of the affected area. (24)

A. Ischemic Core

The ischemic core is the central area of the infarct, where cerebral blood flow drops below 10 to 15 mL/100 g/min, compared to the normal range of about 50 to 60 mL/100 g/min. This serious lack of blood flow leads to several issues: ATP depletion causes Na^+/K^+-ATPase pumps to fail. Ionic imbalance results in the buildup of intracellular Na^+ and Ca^{2+}, leading to water influx and cytotoxic edema. Glutamate excitotoxicity occurs when excessive glutamate release activates NMDA/AMPA receptors, which causes calcium overload and the formation of free radicals. Necrosis happens, leading to rapid and irreversible death of neuronal and glial cells within minutes. The ischemic core is therefore seen as irreversible tissue damage, creating a permanent infarct. (25)

B. Ischemic Penumbra

Surrounding the core is the ischemic penumbra, where blood flow drops to 20 to 25 mL/100 g/min. Neurons in this area are electrically silent but still structurally intact. This is because partial oxygen and glucose supply allows for some ATP production. Ion gradients are maintained to a limited degree, which helps prevent immediate cell death. However, the penumbra is very sensitive to secondary injury. Oxidative stress occurs when excess free radicals damage membranes and mitochondria. Inflammation happens due to microglia activation, leukocyte infiltration, and cytokine release, which enlarge the injury. Apoptosis leads to programmed cell death in penumbral neurons, contributing to delayed infarct growth. Breakdown of the blood–brain barrier worsens tissue damage by promoting vasogenic edema (26)

C. Dynamic Relationship

Over time, without intervention, the penumbra gradually turns into core infarct. This change increases the area of permanent brain damage.

The size and duration of the penumbra depend on collateral circulation. Well-developed collaterals can keep the penumbra viable for several hours. In contrast, poor collaterals result in quick infarct progression. (27)

IV. NOVEL THERAPEUTICS

Antiplatelets in Stroke: Antiplatelet drugs lower platelet clumping and stop clot formation in cerebral arteries. This helps reduce the chance of repeated ischemic stroke. Antiplatelets play a key role in preventing ischemic stroke from happening again. Newer strategies now focus on using two short-term therapies and new $P2Y_{12}$ inhibitors to find a balance between effectiveness and the risk of bleeding. (28)

A. $P2Y_{12}$ Receptor Inhibitors (Novel Generation)

1) Ticagrelor: Reversible, direct-acting $P2Y_{12}$ inhibitor (doesn't need liver activation like clopidogrel). Use in stroke: minor ischemic stroke or high-risk TIA (dual therapy with aspirin for 30 days, Thales trials). This is an option when clopidogrel resistance is suspected. (29)
2) Prasugrel: Strong $P2Y_{12}$ blocker. It is not commonly used in stroke because it carries a higher risk of bleeding in cerebrovascular disease. (30)

B. Thromboxane (TXA_2) Inhibitors

Aspirin: Should be given within 24 to 48 hours after a stroke begins, provided that brain imaging shows no signs of bleeding. If the patient has had IV thrombolysis (rt-PA), wait 24 hours to give aspirin. Only administer it after a repeat CT or MRI confirms there is no bleeding. (31)

C. Dual Antiplatelet Strategies (Short-term Novel Use in Stroke)

Aspirin + Ticagrelor leads to minor stroke or TIA for up to 30 days. Aspirin + Clopidogrel leads to minor stroke or TIA for up to 21 days. This short-term dual therapy is a new approach compared to the old practice of lifelong monotherapy. (32)

1) Neuroprotective agents: Neuroprotective agents are drugs or treatments designed to protect the structure and function of neurons during or after an ischemic stroke. After recanalization area of blood vessels neuroprotective agents are used for the purpose of protection of neurons in the penumbra and core region. They reduce neuronal injury caused by excitotoxicity, oxidative stress, inflammation, calcium overload, and apoptosis. Excitotoxicity due to overactivation of n-methyl D-aspartate leads to overload of calcium in the neuronal cells which cause trigger nitric oxide production and free radical then necrosis occurs. Neuroprotective agents help limit brain damage and improves recovery outcomes. (33)
2) Anti-excitotoxic & ion-channel modulators. NMDA receptor pathway disruptors include PSD-95 protein inhibitors, such as nerinetide and NA-1, as well as GluN2B-selective antagonists like ifenprodil derivatives. During stroke neuronal tissue under stress that trigger release too much of glutamate excess glutamate activate NMDA receptor excess calcium and synthesis of hydroxy free radicals and peroxynitrite, superoxides synthesis block. Acid-sensing ion channel blockers, specifically ASIC1a, consist of amiloride and peptide derivatives, including PcTx1 analogues. TRP channel inhibitors are represented by TRPM2 and TRPM7 blockers, which are tool compounds in early translation. Sodium and calcium channel modulators feature selective Nav1.x and Cav inhibitors that are next-generation and can penetrate the brain. (34)
3) Metabolic Rescue Mitochondrial stabilizers. Mito-targeted antioxidants include MitoQ and elamipretide. In short term study shows that mitoAOXs well tolerated and in the management of glycaemic control and cardiovascular health. (35) NAD^+ boosting and sirtuin activators include nicotinamide riboside and nicotinamide mononucleotide, as well as SIRT1 agonists. (36) PARP inhibitors, such as veliparib and Olaparib, have gained interest for repurposing. (37) SARM1 pathway inhibitors are experimental blockers for axon degeneration. (38) Mito-dynamics modulators: Drp1 inhibitors. (39)
4) Redox/oxidative-stress modulators. Free-radical scavengers of hydroxy radical and peroxynitrite include edaravone and uric acid as natural antioxidant which is approved in some countries and has varying uses for stroke. Uric acid is an additional concept. (40) Nrf2/ARE pathway activators: dimethyl fumarate, sulforaphane analogues, bardoxolone-like agents. (41) NOX (NADPH oxidase) inhibitors: GKT137831 (NOX1/4), apocynin (prototype). These all are supporting during oxidative stress. (42)
5) Anti-inflammatory & immunomodulatory agents. Cytokine axis: IL-1 receptor antagonist (anakinra), selective TNF pathway modulators. (43) Microglia-targeted approaches include CSF1R modulators and minocycline, which is repurposed and has multiple effects. (44) Sphingosine-1-phosphate modulators: fingolimod, Siponimod. These affect lymphocyte movement and the blood-brain barrier. (45)

D. Blood–brain barrier (BBB) & neurovascular unit protectors

Activated protein C variants: 3K3A-APC (cytoprotective, anti-apoptotic, endothelial stabilizing). (46) MMP inhibitors / gelatinase-selective: doxycycline (broad), SB-3CT (47). Adenosine receptor modulators: A1/A2A agents with BBB and anti-inflammatory actions. (48) Stem cell therapy: Stem cell therapy for stroke is an emerging regenerative treatment approach that uses stem cells to repair and replace damaged brain tissue, enhance neurogenesis, and promote functional recovery after ischemic injury. By restoring blood supply, reducing inflammation, and stimulating neural repair mechanisms, stem cells offer potential beyond conventional therapies, aiming to improve long-term recovery in stroke patients. First, transplanted stem cells can differentiate into neuronal and glial lineages, replacing dead or damaged brain cells. Second, they exert paracrine effects by secreting growth factors and cytokines that promote angiogenesis (new blood vessel formation), neurogenesis (new neuron formation), and synaptic plasticity, thereby enhancing brain repair. Third, they modulate the immune response by reducing harmful neuroinflammation, limiting secondary injury after stroke. (49)

E. Based on Cell Source

Embryonic Stem Cells (ESCs)

Derived from early embryos (inner cell mass of pluripotent blastocysts). Pluripotent, capable of differentiating into neurons, glial cells, or endothelial cells. Ethical issues and risk of tumor formation limit their clinical use. Embryonic pluripotent stem cell is obtained from the embryo and used for the effectiveness in the brain tissue like neurons and glia supporting cells. (50)

Adult Stem Cells

Bone Marrow–Derived Stem Cells (BMSCs): Contain mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs). Mesenchymal Stem Cells (MSCs): Obtained from bone marrow, adipose tissue, or umbilical cord. Show strong immunomodulatory and neuroprotective effects. Neural Stem/Progenitor Cells (NSCs): Found in the subventricular zone and hippocampus; can differentiate into neurons, astrocytes, and oligodendrocytes. (51)

Perinatal Stem Cells

Derived from umbilical cord blood, Wharton's jelly, or placenta. Readily available, immunologically tolerant, and ethically less controversial. (52)

Induced Pluripotent Stem Cells (iPSCs)

Adult somatic cells reprogrammed into pluripotent stem cells. Can differentiate into neuronal lineages, providing personalized cell therapy. Concerns: risk of genetic instability and tumorigenesis. (53)

F. Based on Differentiation Potential

Totipotent Cells – Give rise to all cell types including placenta (not used in therapy). Pluripotent Cells – ESCs, induced pluripotent stem cells (can form any cell type of the body). Multipotent Cells – MSCs, NSCs (restricted to certain lineages like neural or mesenchymal). Unipotent Cells – Restricted to a single cell type (least common in stroke therapy). (54)

Gene therapy: Gene therapy for stroke is an experimental treatment approach that involves delivering specific genes or genetic material into brain cells to repair damaged tissue. In gene therapy the main aim is to promote three functions; promote neuroprotection, enhance neuroprotection and neural regeneration by modulating the expression of therapeutic proteins such as growth factors, anti-apoptotic molecules, or anti-inflammatory agents, gene therapy aims to improve functional recovery and provide long-term benefits beyond conventional pharmacological treatments (55)

G. Based on Approach

- In Vivo Gene Therapy: Genetic material is directly delivered into the patient's brain or systemic circulation. Example: injection of viral vectors carrying genes for neurotrophic factors into the ischemic region. Delivery nucleic acid specific product so cell in brain express silence and gene edit. In vivo gene therapy our goal is time sensitive so reduce immediate neuronal death and limit secondary injury, promote early neurogenesis and angiogenesis. For neurogenesis following neurotrophic factors BDNF, GDNF, NGF (Brain derived neurotrophic factors, Glia cell derived neurotrophic factor, Nerve growth factor). Bind to GFR alpha 1 receptor activation of p13k- survival signalling and ERK cell proliferation. For angiogenesis VEGF (Vascular Endothelial Growth Factor). Release From the hypoxic injured tissue. Bind to VEGFR1 AND VEGFR2.
- Ex Vivo Gene Therapy: Patient's or donor cells are genetically modified outside the body, then transplanted back. Example: stem cells engineered to express vascular endothelial growth factor (VEGF) and then transplanted to enhance angiogenesis. (56)

H. Based on Delivery Vector

Viral Vectors (high efficiency, but risk of immune reaction)

Adenoviruses: High transduction efficiency, transient expression. Specific gene introduced by virus directly inject into body. But chances of immune reaction and cause secondary inflammation event. Adeno-associated Viruses (AAVs): Long-term expression, lower immunogenicity, widely used in CNS disorders. Lentiviruses/Retroviruses: Integrate into host genome for stable expression, useful for ex vivo therapy. Herpes Simplex Virus (HSV) vectors: Neurotropic, ideal for neuronal gene delivery.

Non-Viral Vectors (safer, but lower efficiency) Liposomes/Nanoparticles: Encapsulate DNA or RNA for targeted delivery. Polymeric Carriers: Biodegradable polymers (e.g., PEI, PLGA). Physical Methods: Electroporation, ultrasound, gene gun, or direct injection of naked DNA/RNA. (57)

I. Based on Therapeutic Strategy

Gene Addition (Replacement Therapy): Introducing genes that produce protective proteins (e.g., BDNF, VEGF). Gene Silencing (Antisense/siRNA/miRNA): Suppressing harmful genes such as pro-apoptotic or inflammatory mediators. Gene Editing (CRISPR/Cas9, TALENs, ZFNs): Direct modification of stroke-related genetic pathways. (58)

J. Based on Therapeutic Targets in Stroke

Neuroprotection: Genes encoding anti-apoptotic proteins (e.g., Bcl-2, HSP70). Angiogenesis & Neurogenesis: VEGF, FGF, GDNF, and BDNF genes to promote vascular and neuronal growth. Anti-inflammatory Genes: IL-10, TGF-β to suppress damaging immune responses. Oxidative Stress Resistance: Genes encoding antioxidant enzymes (e.g., superoxide dismutase, catalase). Synaptic Plasticity & Repair: Genes enhancing neurotransmitter regulation or axonal regeneration. (59)

V. CONCLUSION

Acute ischemic stroke continues to be a major cause of death and disability around the globe, highlighting the pressing need for new strategies that focus on both immediate care and long-term recovery. While intravenous thrombolysis with rtPA and mechanical thrombectomy are currently the primary treatments for restoring blood flow, their limited treatment windows and associated risks often leave many patients without effective options. This situation emphasizes the importance of creating additional strategies that not only restore blood circulation but also protect and mend brain tissue. New neuroprotective drugs have shown promising potential in reducing excitotoxicity, oxidative damage, and inflammation, which are critical processes that lead to neuronal injury in the ischemic penumbra. At the same time, advancements in stem cell and gene therapy are paving the way for new and exciting opportunities to encourage neurogenesis, angiogenesis, and functional brain repair, although challenges related to safety, delivery methods, and clinical application still need to be tackled. The emergence of next-generation mechanical thrombectomy technologies, including laser- and ultrasound-assisted systems, has also enhanced revascularization outcomes and expanded the treatment window. As we look to the future, the most exciting possibility involves integrating pharmacological, cellular, and mechanical treatments into a personalized, multimodal approach, supported by biomarkers and cutting-edge neuroimaging to guide therapy. Making this vision a reality will require close teamwork between scientists and clinicians to transform laboratory innovations into practical treatments that can reduce disability, enhance recovery, and ultimately lessen the global impact of ischemic stroke.

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