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Understanding the role of immune receptors to uncover their inherent potential as therapeutic targets in Ischemic stroke

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Abstract

An ischemic stroke occurs when the blood supply to cerebral region is obstructed, resulting in severe neuroinflammation and neuronal damage. Ischemic stroke is one of the leading causes of death and permanent disability worldwide. The receptors expressed on the surface of immune cells play a critical role in pathogenesis and recovery during and after cerebral ischemia. Important receptors of the innate and adaptive immune system like Pattern Recognition receptors, T cell Receptors and others for various ligands released by damaged brain cells initiate neuroinflammation, orchestrate inflammatory cascades and channelize diverse molecular pathways, thereby influencing neuroprotection and post stroke recovery. This review highlights important roles of these immune receptors in cerebral ischemia, focusing on their involvement in recognizing molecular patterns associated with cellular damage, modulating neuroinflammation and influencing the equilibrium between inflammatory tissue damage and recovery. Additionally, the review also focusses on various strategies by which these receptors can be targeted for the development of novel stroke therapeutics. Since there is a scarcity of treatments available in the market for stroke patients, understanding the multifaceted role of these receptors may help in developing novel and potential stroke therapeutics.

Keywords: Cerebral ischemia, Pattern Recognition Receptors (PRRs), Neuroinflammation, Immune receptors, Stroke Therapeutics

Introduction

Stroke is a critical biomedical condition resulting in interruption of blood supply, preventing it from receiving necessary oxygen and nutrients. It is one of the leading causes of death, disability and cognitive impairment worldwide[1,2] and it remains the second leading cause of death.[3] The mortality rate of stroke increased from 38.8 per 100,000 in 2020 to 41.1 per 100,000 in 2021[4] and in India, 1.8 million people are affected by stroke every year.[5] The financial burden of stroke treatment and post-stroke care is massive and is expected to rise to 184.1 billion USD in the year 2030, according to the American Stroke Association.[6] Unfortunately, due to restricted medical access, high cost and very limited capacity of regeneration within the Central Nervous System (CNS), there is no such effective treatment for stroke other than reperfusion therapy till date. Early detection and treatment are crucial as the number of stroke cases is rising at an alarming rate.[7]

1.1. Neuroinflammation in Ischemic Stroke:

Ischemic stroke is caused by a deficiency of oxygen, lipids and glucose in the brain due to an arterial embolism, resulting in the production of oxidative stress, excitotoxicity and neuroinflammation.[8–10] Damage to neuronal cells due to this deficiency causes excessive release of glutamate that activates N-methyl D-aspartic Acid (NMDA) receptors and leads to a Ca2+ influx into the cells, causing cell death.[11] These damaged neurons and astrocytes then release Reactive Oxygen Species (ROS) that deplete glutathione, thereby inducing a more rapid tissue injury and death. Neuroinflammation results in the activation of the immune system in response to ischemic insult and involves various immune cells, immune receptors, and molecular mediators causing increased infarct size leading to worse neurological outcomes.[12] The Stroke Roundtable Consortium proposed to designate the first 24 hours as the hyperacute phase, the first 7 days as the acute

phase, the first 3 months as the early sub-acute phase, the months 4–6 as the late sub-acute phase, and from 6 months onwards as the chronic phase.[13]

1.2. Role of the Immune System in stroke:

The innate immune system acts as the first line of defence in response to tissue injury. Upon disruption of blood flow to the brain, tissue of the affected area becomes hypoxic and dies, resulting in the release of certain molecules called Damage Associated Molecular Patterns (DAMPs). It also activates resident microglial cells that are responsible for immune surveillance in the brain[14] that polarize into the pro-inflammatory phenotypes and bind the DAMPS via PRRs. One such PRR are Toll-like Receptors (TLRs) that release many pro-inflammatory cytokines. This activation further recruits other innate immune cells such as neutrophils, monocytes, dendritic cells, lymphocytes and macrophages. Activation of the innate immune cascade also activates the adaptive immune system. This adaptive immune response retains immunological memory and plays a potent role in the recovery phase of stroke.[15,16] Since many therapeutic interventions primarily emphasises on these receptors as potential targets, a comprehensive study of the immune receptors involved in the pathogenesis and recovery of ischemic stroke is crucial.

Immune Receptors

A cell surface receptor binds to ligands such as hormones and neurotransmitters, induce a conformational change, relaying the signal to the target cell, that elucidates an appropriate response. Among many receptors found on the surface of numerous cell types in the human body, the immune receptors expressed on the immune cells are most characterized till date due to their potential role in immunity-related diseases and therefore, are highly targeted for use in Stroke therapeutics.[17]

2.1. Types of Immune Receptors:

Receptors of the innate immune system generally orchestrate an inflammatory response whereas those of the adaptive immune system are involved in anti-inflammation, antigen presentation and memory. Innate immune cells such as microglia, astrocytes, monocytes, etc., possess various receptors that recognize neuronal damage induced DAMPs such as Adenosine Triphosphate (ATP), High Mobility Group Box Protein – 1 (HMGB1) and Heat Shock proteins. Apart from these, there are other components of the immune system such as complements and Fc receptors binding to Immunoglobulins that play a significant role in the progression of Ischemic stroke.[18,19]

The receptors of immune system are classified into following types:

2.1.1. Receptors of the innate immune system:

Among the receptors of the innate immune system some of the most important ones are Pattern Recognition Receptors (PRRs), Phagocytic receptors and Chemotactic receptors.

2.1.1.1. Pattern Recognition Receptors:

Various Heat Shock Proteins (HSPs) (HSP60 and 70) and fibronectin released by neurons post stroke acts as DAMPs and activate the innate immune system via various PRRs thereby inducing an intense proinflammatory response.[16] PRRs are divided into the following five types: TLRs, NLRs, RLRs, CLRs and ALRs. They are not only found in the plasma membrane but also in the intracellular component's membrane and the cytoplasm.[14] **Fig.1** shows the role of crucial PRRs in Ischemic stroke and their ligands.

Some of the important PRRs and their role are as follows:

A. Toll Like Receptors (TLRs):

TLRs are a group of evolutionarily conserved transmembrane receptor proteins. Previously, TLRs were known to recognize microbial pathogens via Pathogen Associated Molecular Patterns (PAMPs). Different types of TLRs include TLR1, TLR2, TLR4, TLR5 and TLR6. That are expressed on the plasma membrane and TLR3, TLR7, TLR8 and TLR9 that are expressed on endosomes.[20] They are also found in brain cells including microglia, neural stem cells, neurons, oligodendrocytes and astrocytes. Upon binding to adaptor molecules, TLRs activate two different pathways, i.e., the Myeloid differentiation primary response 88 (MyD88)-dependent pathway and the TIR domain-containing adaptor inducing interferon-β (TRIF)-dependent pathway.[21–23] Activation of TLRs following an Ischemic insult also activates various downstream signalling pathways which may be destructive or neuroprotective depending on the timing, localization and intensity of receptor activation.

TLR2 and TLR4 are the main receptors that are activated post ischemic insult. In a study involving 110 stroke patients, the levels of TLR2 and TLR4 were analysed at 24 hours, 72 hours and 7 days. Their increased expression was associated with increased levels of IL-1β, IL-6, TNF-α and VCAM-1.[24] It was found that TLR2 was the most significantly upregulated TLR among all TLRs and is involved in exacerbating the brain damage post ischemia. TLR2 suppression improved neuronal recovery and reduced infarct size.[25,26]

Zhou et al showed that a neuroprotectant called Tetrahedral Framework Nucleic Acids (tFNAs) protected neurons from apoptosis after oxygen and glucose deprivation (OGD) in *in vitro* and reduced the infarct volume from 33.9% to 2.7% in Middle Carotid Artery Occlusion (MCAO) rat models through the TLR2/Myd88/NFkb pathway.[27] Similarly, binding of High Mobility Group Box 1 (HMGB1) to TLR4 causes the infiltration of immune cells via increased Blood Brain Barrier (BBB) permeability. After the injection of neutralizing anti-HMGB1 antibodies, microglia activation and BBB permeability were reduced.[28] Polyphenols have also been found to suppress inflammatory response and promote neuronal recovery through the TLR4 pathway.[29]

Recently, TLR preconditioning has been associated with reduced ischemia injury. In an MCAO model, reduction in ischemic injury was found to have occurred partially through TLR4.[30] In similar studies, a low dose of various TLR ligands had reduced infarct size prior to stroke.[31-35] Interestingly, Interferon Regulatory Factors (IRF3 and IRF7) were found to be mediated through TLR4 and TLR9 preconditioning.[36] Moreover, Lipopolysaccharide (LPS) preconditioning also induced high levels of interferon (IFN-β) in the brain through TLR4.[37]

A group of researchers preconditioned mesenchymal stem cells with lithium and isolated the extracellular vesicles (Li-EVs). Upon injecting these into MCAO mice, a downregulation of TLR4 was observed with increased Micro RNA (miR-1906) (a modulator of TLR4) and decreased Nitric Oxide (NO) synthase and Nuclear Factor kappa (Nf-kb) activity, reducing cerebral inflammation.[38] Therefore, pre-conditioning shifts the brain's response from an inflammatory to a neuro protective state, paving the way to target neuro protective proteins as therapeutics.

Various DAMPs of TLRs:

Some of the most important ligands that are associated with TLRs are as follows.

• ATP:

Following ischemia, Adenosine Triphosphate (ATP) is released uncontrollably in the interstitial space through cell damage. Upon their release, ATP molecules activate Purinergic Receptors (P2X or P2Y). Of the seven members of the P2X family, P2X1, P2X4 and P2X7 are functional in Ischemia and are highly expressed on microglial cells.[39] P2X1 is expressed on both platelets and neutrophils, thereby promoting platelet aggregation and neutrophil chemotaxis to the site of ischemic insult[40,41] P2X4 shows sustained activation on brain immune cells that contributes to ischemic injury and are also expressed on T cells leading to T cell activation and chemotaxis.[42,43] Many P2X4 agonists have been developed that has shown to reduce brain damage after stroke providing a therapeutic approach and it has also been found to be highly expressed in female mice proving there may be sex difference in its expression.[44]

The P2Y family of receptors are activated by Adenosine Diphosphate (ADP) and ATP. P2Y12 and P2Y13 are the most abundantly expressed in microglial cells. Binding of ADP to these receptors reduce cyclic Adenosine Monophosphate (cAMP) via inhibition of adenylate cyclase thereby activating microglia. They also activate P2Y1 receptors expressed on astrocytes.[45] P2Y2 and P2Y11receptors that induce monocyte and neutrophil migration.[46,47]

Ectonucleotidases are membrane proteins that are catalytic in nature and hydrolyse high levels of ATP in the inflammatory and ischemic environment into AMP, that acts as an immunosuppressant.[48] Cluster Differentiation proteins (CD38, CD39, CD73) and Ectonucleotide Pyrophosphatase/Phosphodiesterase-1 (ENPP1) plays a significant role in the pathophysiology of stroke. CD38 expression is highest on astrocytes and endothelial cells. Nicotinamide Adenine Dinucleotide (NAD) have strong anti-inflammatory and neuroprotective properties in stroke and has also been found to increase with aging; hence, there might be a link between aging and stroke that is relevant to CD38 expression, making it a potential target for stroke therapeutics.[49] CD39 is highly expressed on microglial cells and endothelial cells.[50] It was found to inhibit platelet recruitment and aggregation at the site of ischemic insult.[51] CD73 is highly expressed on B, T cells, macrophages and neutrophils whereas ENPP1 is expressed on microglia.[50] There are contradicting results regarding the role of CD73 in Ischemic stroke since their expression is absent on endothelial cells in mice and most of the studies are conducted on different experimental models of mice.[52] Within 20 minutes of stroke onset, most of the adenosine produced from ATP is mediated by CD73. Treg cells co-express both CD38 and CD73 and therefore, the adenosine produced by their co-ordinated activity promote their own immunosuppressive state.[53] CD73 also regulates Helper 17 (Th17) responses.[54]

During ischemia, adenosine is continuously secreted into the extracellular space. When the mitochondria consume ATP, it is converted to AMP. This AMP can't be reconverted to ATP due to lack of glucose and oxygen. Thus, ATP levels decrease leading to an accumulation of adenosine that is formed from AMP.[55] Four main receptors for adenosine differ in their affinity and location: A_1, A_{2A}, A_{2B} and A_3. These are G-protein coupled receptors and signals mainly through Phospholipase C (PLC), calcium and Mitogen-Activated Protein Kinase (MAP) pathways.[56] In normal physiological conditions, adenosine activates high-affinity receptors A_1 and A_{2A} while during ischemia, they activate the low-affinity receptors A_{2B} and A_3.[57] A_1 receptor expression is evenly distributed across neurons in all areas of the brain whereas A_{2A} expression is the highest in endothelial cells, astrocytes and lymphocytes. A_{2B} expression is highest in CNS and A_3 is found in microglia and hippocampal neurons. Once, A_1R is activated, it inhibits glutamate synaptic transmission, which is important for the recovery of circuits in hippocampus upon reoxygenation while A_{2A} signalling leads to an increase in glutamate excitotoxicity, thereby both receptors exhibit counteracting effects.[58] A_{2A} also mediates their effects on microglia converting their shape to amoeboid and regulate their phagocytic properties. A_{2B} is found to have a dual role where it influences mast cells to release pro-inflammatory cytokines and influences dendritic cells and macrophages towards an anti-inflammatory state. A_3 Receptor activation during Ischemia is mainly found to have a damaging effect on cells and tissues.[59] P2 receptor inhibitors are being considered as therapeutic targets. In a study where Pyridoxalphosphate-6-azophenyl-2′,4′-disulphonic acid (PPADS) was injected 15 minutes prior to the surgery for up to 7 days and functional improvements were assessed after 28th day revealed a reduced infarct volume and recovery of motor impairments.[60]

• Heat Shock proteins (HSPs):

Heat Shock Proteins are molecular chaperones, participating in protein–protein interactions especially in the folding, assembly and translocation of intracellular proteins. Under stressful conditions, the intracellular concentration of HSPs increases. The role of HSPs in haemorrhagic stroke has already been studied in detail.[61] HSP70 is the most studied HSP protein in neuroprotection and is robustly produced during ischemia. Palanisami et al suggested that HSPs may be used as anti-stroke therapeutic molecules.[62] HSP70 promotes cell survival by suppressing the production of inflammatory cytokines. In one study, intranasal injection of recombinant HSP70 in mouse, significantly reduced the infract volume in PFC.[63] A Single Nucleotide Polymorphism (SNP) rs11682567 in HSP60 gene was associated with an increased risk of ischemic stroke.[64] HSP90 was also found to attenuate ischemia by acting through the complements C3 and C5a and Nf-κβsignalling.[65]

• High Mobility Group Box Protein1 (HMGB1):

HMGB1 binds to TLR2 and 4 and acts through Myd88 dependent pathway leading to the formation of monocyte-platelet complex, thereby promoting thrombosis. Initially, non-acetylated forms of HMGB1 are released following infarction where it reaches its peak concentration within 24 hours. A continuous release of immune cells prompts the release of acetylated forms of HMGB1 that reaches peak concentration in about 6 days post stroke.[66] In a study involving 132 patients, the HMGB1 levels were measured, and its increased expression was found to be directly related to poor stroke prognosis.[67] Similarly, a total of 154 Acute Ischemic Stroke (AIS) patients were followed up monthly for 43 months to measure the levels of HMGB1 until the subsequent stroke recurrence which revealed that elevated levels of HMGB1 was a predictive indicator of AIS recurrence.[68] It was also found to be elevated in post-stroke depression patients.[69] In contrast, 1066 acute stroke patients were analysed for The Receptor for Advanced Glycation End Products (RAGE) and HMGB1 polymorphisms and found no association between HMGB1 levels and ischemic stroke risk.[70]

HMGB1 mediates its mechanistic action by binding to TLR2, TLR4 and RAGE influencing BBB disruption and haemorrhagic transformation. It also promotes Metalloproteinase protein (MMP9) activation, oligodendrocyte migration and neurovascular remodelling by binding to these receptors. HMGB1 also mediates its effects through the activation of NLRP3, cytochrome c oxidase subunit 2, NOS, IL-1β and promotes neuronal cell death.[71] In a study, GA-boronated ester-conjugated diethylaminomethyl-dextran polymer-drug conjugate nanoparticles (an inhibitor of HMGB1) were used in stroke-affected mice to evaluate their efficacy in stroke recovery. Administration of the nano particles showed significant reduction in infract volume, upregulation of neurogenesis and polarisation of microglia to M2 phenotype.[72]

• Hyaluronan:

Hyaluronan binds to TLR4, and its activation is mediated through HA receptors CD44 and the Receptor for Hyaluronan-Mediated Motility (RHAMM). It is a crucial component of the extracellular matrix and plays an essential role in angiogenesis, promoting neuronal survival and micro vessel formation.[73] CD44 and RHAMM are expressed on various cell types in the brain. CD44 is present in microglia after an ischemic stroke with its expression upregulated post-stroke in the infarct area, thereby enhancing inflammatory effects.[74] RHAMM is expressed in a subset of neurons and oligodendrocytes, mediating its function intracellularly and acting as a receptor influencing cell migration and growth.[75] Following ischemia, RHAMM is found to be expressed on astrocytes in the periinfarct area.[76]

A study discovered that the expression of CD44 and Tumour Necrosis Factor (TNF)-stimulated gene/protein 6 (TSG-6) is elevated in infiltrating mononuclear cells. TSG-6 appears to play a significant role in tissue remodelling following a stroke. In mice post-MCAO, CD44 was shown to be present in stem cells and microglia, contributing to the brain repair process by inhibiting IL-1β production and decreasing infarct size by over 50%.[77] Likewise, RHAMM was expressed in neuroblast stem cells in the mouse subventricular zone (SVZ) and the rostral migratory stream (RMS), suggesting Hyaluronan-mediated migration of stem cells in these regions.[78] After ischemia, its expression increased in the peri-infarct neurons and micro vessels of stroke patients. This enhanced expression is associated with increased calmodulin signalling, promoting angiogenesis and mitosis.[79] Hyaluronan exists in High-Molecular-Weight (HMW) and Low-Molecular-Weight (LMW) forms. HMW HA binds to CD44 and blocks TLR4 activation on microglia that are induced by the binding of LMW HA. Thus, HMW HA is found to be neuroprotective in ischemic stroke.[80]

B. Nod like receptors (NLRs):

The inflammasome is a multi-protein complex involved in sensing DAMPs and PAMPs, the activation of which leads to the production of IL-1β and IL-18. There are four subtypes of the NLR family based on their amino-terminal domain: NLR1, NLRB, NLRP and NLRC. Except NLRP1, NLRP3, NLRP12, other NLR protein complexes are involved in the recognition of pathogenic ligands.[81] The pro-inflammatory cytokine IL-1β has a profound deleterious effect on brain damage during stroke. NLRP3 is also seen to be increased in mouse cortical neural cells in *in vitro* and *in vivo* models of ischemic stroke.[82] Recently, NLRP2 has been found to be expressed in the astrocytes of the CNS and is elevated in Ischemic Stroke. In a study involving 60 AIS patients and 30 control groups, the serum levels of NLRP3 and its downstream signalling mediators like IL-18, IL-1β and TNF-α were increased at 24 hours. Also, the levels remained higher in the poor prognosis group as compared to the healthy group.[83]

Bruton's Tyrosine Kinase (BTK) is involved in the phosphorylation of ASC and redistribution of macrophages influencing NLRP3 inflammasome activation and IL-1β production. Therefore, inhibition of BTK can lead to an impaired activation of NLRP3.[84] Moreover, BTK was found to perform as a platform protein for ASC and NLRP3 where BTK is initially activated by DAMP binding, and it interacts with ASC; Nigerecin (a NLP3 activator) induces the recruitment of NLRP3 to this BTK–ASC complex. Administration of Ibrutinibis is known to suppress the NLRP3 activation and signalling pathway. Thioredoxin-interacting protein (TXNIP) is a crucial regulator of oxidative stress, cellular injury and a glucose sensor.[85] To investigate its role in stroke and diabetes, mice were induced with hyperglycaemia and embolic MCAo (eMCAo) was performed after which molecular parameters were investigated. The expression of TXNIP and NLRP3 were found to be upregulated in Hyperglycaemic mice compared to normal mice suggesting their role in BBB permeability and neuronal damage. On treatment with tPA, the NLRP3 activation was slightly reduced.[86]

Therapeutically, the anti-inflammatory activity of Ligustroflavone, a compound derived from Ligustrum lucidum, was assessed in a MCAO model of mice by measuring the levels of NLRP1 and its inflammatory cytokines. It was found that the compound inhibited NLRP1 activity.[87] In another study, the miRNA miR-9a-5p was found to attenuate Ischemic stroke through NLRP1 whereas overexpression of miR-9a-5p decreased the NLRP1 expression in MCAO rats and OGD cells.[88]

C. C-Type Lectin Receptors (CLRs):

C-Type Lectin Receptors are dysregulated during excessive tissue injury that leads to development of inflammatory diseases.[89] There are many CLR subtypes out of which only MINCLE is found to be involved in the pathogenesis of stroke, whereas DC NK lectin group receptor-1 (DNGR1) promotes disease progression in atherosclerosis.[90] MINCLE is found to induce an inflammatory response, reperfusion in experimental ischemic stroke and is found in Ischemic brains.[91,92] Its ligand Secreted Aspartyl Proteinases (SAP10) and its downstream signalling molecule Spleen Tyrosine Kinase (Syk) are all upregulated in Ischemia.

D. RIG like Receptors (RLRs):

Retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) are key sensors of virus infection, mediating the transcriptional induction of type I interferons and other genes that collectively establish an antiviral host response.[96] Recently, it has been found that RLRs are elevated in the cortex of Alzheimer's patients and contribute to the inflammatory response post spinal cord injury.[97] Frank et al., alone analyzed Retinoic Acid Inducible Gene -1 (RIG-1) and IFN-α in the hippocampus of MCAo rats and found that both show an increase in astrocytes, indicating their significant role in innate immune response. It has been shown that RLR and IFN signalling possess anti-inflammatory effects.[98]

E. Absent in Melanoma like Receptors (ALRs):

AIM2 inflammasome, a multiprotein complex, plays a crucial role in the inflammatory response and contributes to brain injury by triggering cell pyroptosis and increasing blood-brain barrier permeability by forming AIM-2 inflammasome.[99] The role of ALR in other diseases such as Alzheimer's[100] and cancer have been

studied previously, but their role in ischemic stroke has only been studied recently. AIM2 protein has been found in the blood clots of patients who had acute stroke and underwent thrombectomy.[101] The AIM-2 inflammasome and its downstream signalling molecules are increased in neuronal cell lines such as astrocytes, microglia, and human Neuroblastoma.[102] Therapeutically, three AIM-2 inhibitors that were found to confer neuroprotection in Ischemic stroke are cGMP-AMP synthase (cGAS) antagonist A151, miR-485 and the selective inhibitor of histone deacetylase 3 (HDAC3).[103-105]

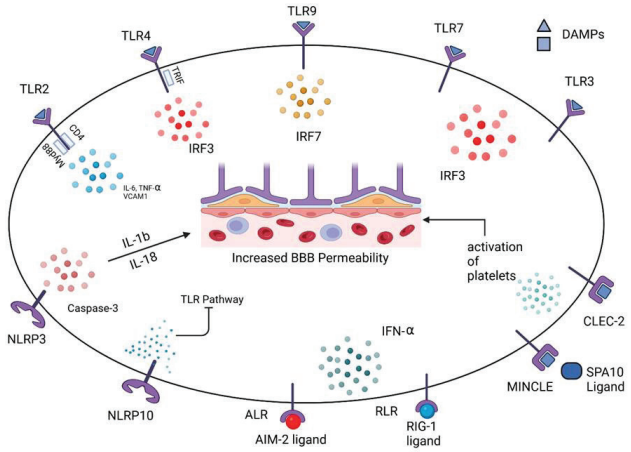

Fig.1: Role of Innate immune receptors in Ischemic stroke. DAMPs upon binding to TLR2 and TLR4, activate the Myd88 and TRIF-dependent pathways respectively and produce increased levels of IL-6, TNF-α, VCAM-1 and IRF-3. TLR7, TLR3 and TLR9 secrete IRF3 and IRF7. CLEC-2 is involved in the activation of platelets, thereby increasing BBB permeability. Mincle activates Syk signalling pathway that is also contributing to BBB breakdown. Activation of RLR and ALR induces the production of IFNα. NLRP10 suppresses the activation of TLR pathway and NLRP3 secretes IL-1β and IL-18, increasing BBB permeability. These inflammatory mediators collectively exacerbate brain damage during Ischemic stroke.

2.1.1.2. Phagocytic Receptors:

Neutrophils, Monocytes and Dendritic cells are phagocytic cells that engulf damaged cells in the phagosome and initiate lysis via lysosomes. This process takes place through a variety of receptors on the surface of phagocytic cells and are classified based on the ligands they recognize. These include different PRRs (Mannose Receptor and Dectin-1), Scavenger receptors, TAM Receptors, CD47-Signal Regulated Protein Alpha (SIRPα) System and the Macrophage Receptor with Collagenase Structure (MARCO). Macrophages are derived from free monocytes and upon recognition of DAMPs, they differentiate into the MI or M2 phenotype depending on the type of cytokines.[106]

A. Mannose receptor:

The Mannose receptor (MR) also known as CD206 and belongs to the family of C – Type Lectin family of Receptors. They are especially expressed on the surface of immature dendritic cells, endothelial cells, and macrophages. The main function of the MRs is the recognition and internalization of specific endogenous and exogenous ligands. The MR has been found in the serum samples of hospitalized patients suffering from various inflammatory diseases.[107] It is also found that MRs are expressed in high levels post-stroke in microglia and are very significant since these receptors are known to clear cell debris and DAMPs helping in post stroke recovery.[108]

B. Dectin -1:

Dectin-1 expression increases on day 3 post Ischemic stroke. Dectin-1 and Syk antagonist treatment once led to a decrease in the levels of these molecules. Moreover, it is also found to be responsible for the activation of NLRP3 inflammasome.[109] Ye et al suggested that Dectin-1/Syksignalling overexpression enhances neuroinflammation by microglial polarization in stroke and may have a deleterious effect on brain tissue.[110] In an MCAo model of mice, Jasminoidin (JA) and Ursodeoxycholic Acid (UA) synergistically conferred neuroprotection by inhibiting the Dectin-1 induced NF-kB activation.[111]

C. Scavenger Receptors:

These are a subcategory of PRRs found on phagocytic cells such as microglia, macrophages and dendritic cells. Previously, they were thought to internalize oxidized Low-Density Lipoproteins (LDL) but were later found to recognize a variety of exogenous and endogenous ligands including DAMPs.[112] They are of different classes from A to J and are also found in the cytosol post proteolytic cleavage.[113] They play an important role in atherosclerosis and might play critical role in stroke. CD36, a type B receptor (SCARB-B), is the most studied in Ischemic stroke. It is found to be involved in phagocytosis of monocytes and modulation of immune cell recruitment in Ischemic stroke.[114-116]

Liu et al. found that the inhibition of the TLR4 signalling pathway by the phthalide derivative CD21 reduced tPA-induced Haemorrhagic Transformation (HT) through Macrophage Scavenger Receptor 1 (MSR1) mediated DAMP clearance.[117] In an MSR1-deficient mouse induced with cerebral ischemia, MSR1 was overexpressed, thereby increasing white matter degeneration and behavioural defects through PI3/Akt pathway, indicating their importance in phagocytosis post-stroke.[118] To investigate the role of another scavenger receptor CD36 in the infiltration of myeloid cells in the Choroid Plexus post stroke, MCAo was carried out in neonatal mice. It was found that CD36 mediates neutrophil and monocyte recruitment and changes in gene expression in the Choroid Plexus (CP) Ipsilateral to the MCAO.[119] Also. Scavenger Receptor A (SRA) was found to pivot macrophages to M1 phenotype in an MCAo animal model[120] and its importance in ischemic stroke has been investigated by Xu et al., where MCAo was performed after knockout of SRA mice. They found that SRA plays a critical role in pivoting macrophages to M2 phenotype too.[116]

D. Macrophage Receptor with Collagenous Structure (MARCO) Receptor:

Macrophage Receptor with Collagenous Structure (MARCO) are found to internalize DAMPs post tissue injury in stroke. They are found in increased levels in the mouse cortex after MCAo, indicating their role in clearing debris and in differentiating monocytes to dendritic cells.[121]

E. Triggering Receptor expressed on Myeloid Cells 2 (TREM 2):

Triggering Receptor Expressed on Myeloid Cells – 2 (TREM-2) is found on microglial cells and they phagocytose damaged brain cells. TREM2 mediates its action by reducing the transcription of pro-inflammatory cytokines, chemokines and their receptors, thereby activating microglia and promoting clearance of debris.[122] TREM-2 knockout mice showed reduced phagocytosis of injured neurons and worsened neurological recovery. It is also suggested that nucleic acids maybe a ligand for TREM-2 post ischemia in

in vitro cultures of neurons by TREM2-Fc.[123] Similarly, Kurisu et al. found that in microglial TREM2 knockout mice, myeloid cell activation and phagocyte number were reduced, suggesting their importance in post-stroke recovery and that TREM2 on microglia played a more important role in recovery than those present on macrophages.[124]

F. Mer Tyrosine Kinase Receptors (MerTK):

Mer Tyrosine Kinase Receptor (MerTK) is found on astrocytes and microglia in the brain. It is known to phagocytose neurons, and its inhibition was found to prevent neuronal recovery and promote neuronal death.[125] Further, in a MerTK MCAo model of knockout mice, MerTK inhibited synapse engulfment and improved neurological recovery post stroke in astrocytes or microglia by increasing synaptic density.[126]

G. Tyro3, Axl and MerTK Receptors:

Tyro3, Axl, and MerTK constitute the TAM family of receptor tyrosine kinase that are activated by their ligands Growth Arrest Specific 6 (GAS6) and Protein S 1 (PROS1), found on phagocytes. Protein S (PS) is an anticoagulant whose mutations are linked with thrombosis[127] and is known to activate the TAM receptor in neurons. Zhu et al. found that PS inhibits BBB breakdown in hypoxic/ischemic brain in the BBB model of human brain endothelial cells and is mediated by Tyro-3 after which PS activates SIP1.[128]

H. CD47- Signal Regulated Protein Alpha (SIRPα) System:

SIRPα is a transmembrane protein that is found on neurons, macrophages and dendritic cells. In a SIRPα knockout mice followed by MCAo, it was found that there was reduced infarct size, neuronal injury, oxidative stress and improved neurological outcome which maybe mediated through upregulation of phospho-Akt, Nuclear factor erythroid-derived 2-like 2 (Nrf2) and heme oxygenase -1, indicating the first study to investigate the importance of SIRPα in ischemic stroke.[129]

I. Protein S(PS) Receptor:

The PS receptor constitutes 5-10% of the lipid bilayer. Its function involves activation of signalling pathways, neurotransmission, synapse formation and apoptosis, improving cognitive function and inhibiting neuroinflammation.[130] These receptors are decreased below the control level in the ischemic brain due to enormous cell death and degradation of the membrane component.[131] Its role as a therapeutic target in ischemia has been extensively discussed.[132] CD300a, a type of PS Receptor found on brain myeloid cells was found to inhibit the DNAX activating protein of 12 kDa (DAP12) signalling pathway, thereby enhancing phagocytosis of apoptotic myeloid cells 1 hour after MCAo. Hence, there was decreased production of DAMPs in the penumbra region.[133]

2.1.1.3. Chemotactic Receptors:

Chemokines are small, secreted proteins that act through chemotactic receptors to stimulate the migration of immune cells to the site of tissue injury There are two types of chemokine receptors: Conventional (cCKRs) and Atypical (aCKRs). There are 23 cCKRs and five major aCKR receptors: ACKR1/DARC (Duffy Antigen Receptor for Chemokines), ACKR2/D6, ACKR3/CXCR7, ACKR4/CCRL1 (CC-Chemokine Receptors like 1) and ACKR5/CCRL2.[134] The crucial role of potent phagocytic and chemotactic receptors in Ischemic stroke is given in Fig.2.Recently, CCR5 expression is found to be increased in post stroke neurons, and its inhibition improved post stroke recovery and cognitive memory. It is also suggested that CCR5 deficiency contributes to BBB damage and increased inflammation post stroke via Tred dependent pathway.[135] Chen et al. administered Maraviroc, an FDA approved anti-viral drug for HIV in the MCAo model of mice and found that it conferred Neuroprotection through CCR5 by reducing infarct sizes, decreasing cytokine production, inhibiting the MAPK and NF-κβ pathway.[136] Maraviroc also improved motor recovery in stroke.[137] Another study suggests that loss of function of CCR5, is compensated by CCR2 and CCR3.[138]

CXCL12 via its receptor CXCR4 is involved in the recruitment of immature immune cells to the Ischemia penumbra and induces recovery.[139] Similarly, to identify the role of CXCR7 in ischemic stroke, Endotherin-1 was induced in the ipsilateral motor cortex and striatum to induce ischemia in mice. Further, in six Ischemic stroke patients, Cerebral cortical infarcts were isolated and investigated for the expression of Stromal-derived factor – 1 (SDF-1/CXCL12) and its receptors CXCR4 and CXCR7. There was an increased expression of CXCR7 in humans and not CXCR4 in the penumbra, suggesting that CXCR7 maybe the primary receptor for SDF-1 in humans but not in mice.[140] Tarazzo et al. analysed the role of Fractalkine and its receptor CX3CR1 in transient MCAo model of mice and found that the receptor concentration increased at 24 hours and 48 hours, and overexpressed at 7 days in activated microglial cells post ischemia, indicating that their signalling pathway is important for the infiltration of microglia into the infarcted tissue.[141] In contrast, Denes et al. also analysed the expression of CX3CR1 in knock out mice and found that infarct sizes were reduced to about 56% after MCAo compared to the wild type.[142]

CCL2 and its receptor CCR2 are involved in the monocyte recruitment and leukocyte infiltration.[143] To prove Oliver B et al. induced Focal cerebral ischemia in CCR2 knockout mice and found that BBB permeability and edema formation were reduced compared to wild-type mice. Monocyte and neutrophil infiltration were also reduced by 7 and 4-fold respectively, thereby indicating the importance of CCR2.[144] Similarly, in MCP-1 and CCR2 deficient - GFP labelled transgenic mice, there was a complete inhibition of neutrophils and macrophages infiltration, 4 days and 7 days post ischemia.[145] CCR2 and CX3CR1 role in neuroprotection was also confirmed by Giulia et al., in a ferric chloride induced middle cerebral artery thrombus model.[146]

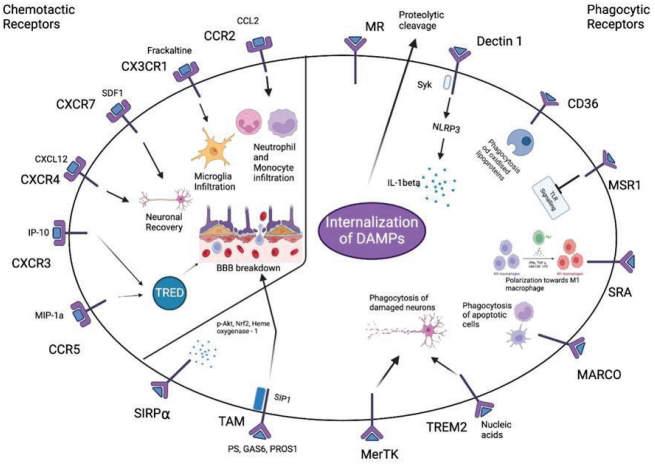

Fig.2: Role of Phagocytic and Chemotactic Receptors in Ischemic Stroke. The important chemokines playing an active role in Ischemic stroke such as MIP-1α, IP-10, CXCL12, SDF-1, Fractalkine and CCL2 bind to their respective receptors CCR5, CCR3, CXCR4, CXCR7, CX3CR1, CCR2. CCR5 and CCR3 and activate the Tred and MAPK/Nfkb pathway to initiate BBB breakdown. CXCR4 and CXCR7 are involved in the stroke recovery process. CX3CR1 activation

induces infiltration of microglia to the infarct. CCR2 recruits monocytes and neutrophils. Phagocytic receptors internalize the DAMPs and induce proteolytic cleavage. Dectin-1 initiate Sky signalling and activate NLRP3 inflammasomes, exacerbating brain damage. CD36, MARCO and TREM-2 phagocytose Oxidized lipoproteins, apoptotic cells and damaged neurons respectively. SRA activation polarizes macrophages to the M1/M2 phenotype. MerTK and TAM receptors activate SIP1 and initiate BBB breakdown. SIRPα induces neuroprotection by activating antioxidant enzymes.

2.1.2. Receptors of the Adaptive Immune response:

The adaptive immune response involves activating two cell types: B cells and T cells. There are two types of T cells: CD4+ and CD8+ T cells. CD4+ cells differentiate into Th1, Th2 to produce proinflammatory effects and Th17, or Tregs to produce anti-inflammatory effects. CD8+ cells release perforin and granzyme that helps in killing of cancer cells and other virus Infected cells through cytotoxicity. These cells are activated by binding of extracellular ligands to specific membrane receptors called B cell (BCR) and T cell Receptors (TCR). The adaptive immune response is activated within 24 hours post injury during ischemic stroke.[147]

A. T cell Receptors (TCRs):

The activation of T cells is induced by the binding of specific ligands such as Class II MHC molecules to its receptor (TCR). Multiple signalling pathways are activated once T cells are engaged.[148,149] T cells also possess co-stimulatory or co-inhibitory molecules which either amplify or inhibit the immune response respectively.[150,151] Different studies have evaluated the TCR gene repertoire in Haemorrhagic stroke.[152] In Ischemic stroke, the TCR of Treg cells were more diversely expressed in the brain than in Splenic cells.[153] T cell activation after Ischemic stroke can be antigen-independent since HMGB1 and other TLR ligands can also induce a T cell response 24 hours post stroke.[154] However, they can be antigen dependent as well where neuronal and myelin antigens are found to induce CD69+ T cell activation in AIS patients.[155]

Since T-cell Receptors are potent in the activation and mechanism of action of T cells, Zong et al. conducted TCR sequencing in the peripheral blood of 25 AIS patients and 10 controls. They found that both immunosuppression and enhanced T cell responses were active in the AIS patients.[156] Similarly, in another study, the TCRβ and CDR3 region of the TCR gene was sequenced in patients with subarachnoid haemorrhage in addition to Delayed Cerebral Ischemia (DCI) (severe and non-severe), which suggests that the increased expression of these genes may serve as a biomarker in severe DCI patients.[157] Considering the function of TCRs in ischemic stroke, immunomodulatory drugs that block the stimulatory effects of TCR while improving the anti-inflammatory effects need to be further explored. But immunosuppression also leads to poor prognosis in stroke. Many FDA approved drugs have potential to balance the pro-inflammatory and anti-inflammatory responses but showed adverse reactions in other diseases.[150] Therefore, therapeutic interventions aiming at TCR and its signalling pathway should be developed with careful consideration of the dosage, time, and location with decreased side effects in ischemic Stroke.

B. B cell Receptors (BCR)s:

Although the role of B cells has been widely discussed by Wu et al.,[158] the crucial role of B Cell Receptors in ischemic stroke is yet to be investigated.

2.1.3. Receptors common to both innate and adaptive immune systems:

A. Complement Receptors:

The complement system is a crucial part of the innate immune system that has been previously thought to be involved only in host defence and tissue homeostasis.[159] There are more than 50 different types of membrane proteins associated with the complement system and therefore it is found to play a critical role in other physiological functions such as synapse pruning, tissue regeneration, clearance of immune complexes and angiogenesis.[160] Several complement system components were found in the post-stroke ischemic brain [161,162] and inhibition of the complement components were observed to reduce the ischemic damage.[163]

Among the different complement components, C3a mediates an immune response by binding to its receptor C3aR. A detailed review on the role of C3aR in ischemic stroke has already been discussed.[164] C3a, a 21-amino acid neuropeptide derived from the VGF precursor protein (TLQP-21) are specific ligands for C3aR. The C3a Receptor is expressed on many central nervous system cells and involves different functions such as neuronal differentiation, cytokine expression and synaptic modulation. Hence, their role during the ischemic stroke recovery phase depends on the type of cells they are expressed on and the duration of the response.[165] C3aR signalling has been shown to improve recovery by inducing neural plasticity and synaptogenesis; therefore, several C3aR antagonists have been developed to enhance long-term stroke recovery. In a mouse MCAo model of Ischemic stroke, C5aR antagonists improved neurological outcome 24 hours after Ischemic injury by causing a significant reduction in the size of the infarct volume suggesting that modulating the C5aR activity differentially regulates neuronal damage.[166]

B. Fc receptors:

Immunoglobulins have a Fragment Antigen Binding (Fab) region that binds to an antigen and A Fragment Crystallizable (Fc) region that binds to different FcRs. These receptors bind isotypes of immunoglobulins including IgG, IgM, IgE, IgD and IgA. Specific FcR exists for each antibody sub-class, with FcαR binding to IgA, FcγR binding to IgG, FcδR binding to IgD, FcεR binding to IgE, and FcμR binding to IgM.[167] Most studies involving the Fc receptors focus on the FcγR's role in Ischemic stroke. Komine-Kobiyashi et al used FcγR knockout mice and induced MCAO, where the receptor deficient mice showed reduced infarct sizes 72 hours post stroke. They also proved the importance of the FcγR in progression of neuronal damage and proliferation of microglial cells.[168] Therapeutically, Intravenous Immunoglobulin (IVIG) is an immunomodulator approved for treatment of various other neurological diseases and prevents neuronal death in stroke.[169]

C. Cytokine Receptors:

Inflammatory cytokines are glycoproteins released by brain cells such as microglia, glial cells, endothelial cells and neurons. An increase in the production of pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines is correlated with worse clinical outcomes and large infarct sizes.[170,171] Understanding the timing of release of these cytokines determines their utility as therapeutic agents.[172] Fig.3 depicts the function of TCRs, receptors of the Complement, Fc system and various cytokine receptors in Ischemic stroke.TNF-α binds to leukocytes via TNFR1 and TNFR2.Hansan et al. evaluated the plasma levels of these receptors in 33 patients with AIS and 10 healthy controls and found that their

levels were increased with stroke severity but had no correlation with outcomes. A decreased population of non-classical monocytes and neutrophils expressing TNFR1 and an increased population of neutrophils expressing TNFR2, was seen, implicating the importance of the peripheral immune response in mediating the acute phase of stroke.[173] Similarly, in another study, blood samples were drawn from 34 patients at the time of admission (<8hrs) and at 72 hours post-stroke. They found that the plasma levels of TNFR1 and TNFR2 were increased at 8 hours, whereas there was no significant change in TNFR1 and TNFR2 at 72 hours, suggesting that add-on therapy targeting these receptors can be developed as a therapeutic target.[174]

In one study, Bone Marrow cells expressing high levels of ILR1 antagonists were induced in MCAO mice, where it was found that ILR1a increased the expression of TNF, IL-10 and IL-4 while decreasing the expression of IL-12p70, IL-1β and TLR2. Hence, correlating with improved stroke outcomes, the study described the mechanism by which Bone Marrow cells promote neuroprotection.[175] Similarly, in another study Involving 844 stroke1 patients and 668 Controls, genetic variation analysis was done in IL1Ra and found that three SNPs (rs380092) were associated with IL1Ra supporting their role in Ischemic Stroke.[176] IL-6 binds to IL-6R and recruits Glycoprotein (gp130) further activating the PI3K/Akt, MAPK and the Janus Kinase (Jak)/Signal Transducer and Activator of Transcription (STAT) molecules, increasing the risk of Ischemic stroke. Blocking IL-6 signalling has been found to reduce the risk of stroke.[177,178] Like, IL-1R, three SNPs were found to be associated with genetic polymorphisms in IL-6R.[179] Finally, the binding of IL-10 to its receptor (IL-10R) initiates the anti-inflammatory response in stroke. The mRNA levels of IL-10R are increased on astrocytes in the ischemic penumbra and one study found that IL-10 signalling downregulates IL-17A production on Th17 cells in the Ischemic brain.[180]

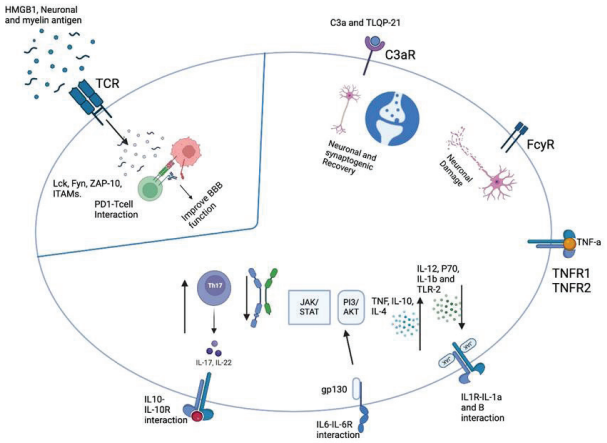

Fig.3. Role of TCRs, Complements and Cytokine receptors in Ischemic stroke: On binding of DAMPs such as HMGB1, neuronal and myelin antigens to diverse TCRs, T cells activate an inflammatory response that may induce neuroinflammation in the early phase and neuroprotection in the late phase by activating the Lck, Fyn, ZAP-10 and ITAMs, thereby improving BBB function. The complement receptor C3aR is involved in neuronal and synaptogenic recovery whereas the FcγR Immunoglobulin receptor induces neuronal damage. TNFR1 activates monocyte and neutrophil infiltration. IL-1R increases TNF, IL-10 and IL-4 while decreasing IL-12p70, IL-1β and TLR2. IL-6R along with its co-receptor gp130 activates the JAK/STAT and PI3K/Akt pathway to induce brain damage. Activation of IL-10R decreases the production of Th17 cells while increasing IL-17A levels, which subsequently reduces neuronal damage and induces neuroprotection.

2.2 Temporal dynamics of immune receptors during the different phases of stroke:

While the production of various inflammatory mediators and role of immune cells in different phases of ischemic stroke are well established. Recently, it has been discovered that temporal dynamics of receptors activation and deactivation plays critical role in stroke patients. TLR2 expression declined at Day 14 in a photothrombotic mouse model called TLR2sm-fluc-GFP mice.[181] Inflammasome expression increased at 3-5 days post stroke and declined at day 7.[182] Atsuchi et al. studied the transcriptome profile of the DAMP-related genes in an experimental stroke model at different time points ranging from day 1 to day 28 and found that expression of DAMPs increases at the acute and sub-acute phase of stroke. Some of the up-regulated genes of immune receptors in these two phases are TLR 2, 4, 6, 7, 8 and 13, Clec7a, MSR1, CD57, Trem2. Ccr, Cxcr, Clec4d and Clec4e peaked at Day 1-14 while C3ar1, Clec7a, Trem2, Msr1, NLRP3, CD36 peaked after day 3-14. The phagocytotic transcriptome profile indicates an increase in phagocytosis at the sub-acute phase from 3 days to 2 months post-stroke.[183] TLR expression was continuously up-regulated through all stages of stroke with a peak concentration from 3 days to 1-month post-stroke.[184] CCR5 and CXCR4 expression was increased at days 3 to 11 days post stroke in CD11 positive cells, astrocytes and neurons.[185] TNF Receptors are up regulated from 4 to 6 hours till up to 5 days post-stroke.[184] The first randomized, double-blind, placebo-controlled trial using I.V. injected recombinant human (rh)IL-1Ra in acute stroke patients (given within the first 6 h of stroke onset) showed a reduction in neutrophil count, plasma CRP, and IL-6 compared to the placebo with minimal to no disability three months after stroke. IL-R receptor expression is known to increase 3 days post-stroke.[186] Inhibition of C3aR receptor in the acute phase and facilitation in the later phase induces functional recovery in stroke.[187] Hence, more studies related to the temporal expression of the most relevant immune receptors involved in stroke are necessary to evaluate a therapeutic window for these receptors for translational stroke research.

Therapeutic interventions targeting the immune receptors:

So far, tissue Plasminogen Activator (tPA) administration and endovascular thrombectomy are the only approved treatments for ischemic stroke.[188] The limitation for this therapy is the time

Table 1: Summary of clinical studies and research papers denote the various antagonists developed targeting their respective receptors for Ischemic stroke.

S. No.	Model	Compound	Receptor	Therapeutic Outcomes	Reference
1	Human	ApTOLL	TLR4	Low NIHSS (NIH Stroke Scale) score at 72 hours (-10%), smaller final infarct volume (1%) and lowered disability at 90 days post-stroke. (1.76 – 5.00)	[192]

2	Mice MCAO	Pam2/3CSK4, 1a, 1b	TLR1/2 and TLR2/6	Reduced brain infarct size (1.9 ± 0.5% vs 9.4 ± 2.2%) Reduced acute mortality (4.3% vs 24.2%), Preserved neurological function (8.22 ± 0.64 vs 3.91 ± 0.57), Attenuated brain edema (84.61 ± 0.08% vs 85.29 ± 0.09%). Preserved BBB function as evidenced by decreased leakage of serum albumin (0.528 ± 0.026 vs 0.771 ± 0.059) and Evans Blue (9.23 ± 0.72 μg/mg vs 12.56 ± 0.65 μg/mg) into brain tissue.	[193]
3	MCAO in C57BL/6	TAK-242	TLR4	Reduced brain infarct size (12.5%) compared to untreated mice (21.3%; #Po0.05). Improved neurologic function (6.73) compared with untreated mice (4.38; #Po0.05).	[194]
4	MCAO in Rats	ApTLR#4F and ApTLR#4FT	TLR4	49% reduction in infarct size. Improved neurological outcome at 2-and 7-days post-stroke.	[195]
5	Preconditioning followed by MCAO in Rats	DPCPX (8-cyclopentyl-1,3-dipropylxanthine)	Adenosine A1 Receptor	Ischemic Preconditioning. Reduction in the cortical and subcortical infarct volume following 120 minute MCAO.	[196]
6	MCAO Rats	Pyridoxalphosphate-6-azophenyl-2`,4`-disulphonic acid (PPADS)	P2 Receptor	Infarct volume reduced upto day 7 whereas functional recovery was sustained till Day 28.	[60]
7	tMCAO Mice	Inhibitory oligodeoxynucleotide (iCpG-ODN)	TLR9	Decreased infarct size in a dose-dependent manner. Suppression of NFkb, IRF7, IL-1β, TNF-α, and IFN-β and	[197,198]
8	Rat MCAO Model	Luteolin	TLR5 and TLR4	Reduction in infarct volume at 24-72 hrs. Reduced Brain edema: around 86% in 72 hours	[199]
9	Mice Photothrombosis and OGD	A14	CCR5	Infarct volume reduced 7 days post-stroke, significant reduction in BBB permeability	[200]
10	Adult SD Rats and C57BL/6 mice.	CX549	CXCR4	Inhibition of CXCL12 – mediated chemotaxis, significantly improved behavioural function, reduced brain infarction, and suppresses the expression of inflammatory markers.	[201]
11	Adult CD1 Mice	AMD3100	CXCR4	Brain edema–induced change of water content, IgG protein leakage, Evans blue extravasation, occludin, and ZO-1 expression in ipsilateral hemisphere were alleviated by acute treatment of AMD3100 3 days post MCAO.	[202,203]
12	Mice MCAO	Maraviroc	CXCR4	Anti-inflammatory and anti-apoptotic.	[204–206]
13	tMCAO mice	SB290157	C3aR	Reduced infarct volume at 48 hours and improved neurological and functional recovery. Suppression of T cell infiltration.	[207]
14	MCAO Mice	JR14a	C3aR	Reduced, infarct volume, BBB permeability and neural impairment. Suppression of TNF-α and IL-6.	[208]
15	OGD on cortical neurons	DF3016A	C5aR	Restorage of intracellular calcium levels.	[209]
16	C57BL6 mice	Intravenous Immunoglobulin (IVIG)	FcR	Polarization of Microglia towards the M2 Phenotype.	[210]

window which includes <4 hours for tPA and <24 hours for thrombectomy. More studies are focused on stem cell therapy and microRNA-based post stroke treatment.[189,190] Unfortunately, most of these therapies failed during clinical trials due to inability of target specific delivery, avoidance of degradation and pluripotency of stem cells. Hence the development of therapeutics with minimal side effects and targeted time- and dose-dependent delivery is pivotal in modern stroke therapeutics.[191] Tables 1 and 2 summarize the antagonists and inhibitors developed against the various immune receptors, the model organism used, and its effects in Ischemic stroke.

Table 2: Summary of the different inhibitors developed targeting their respective receptors or their associated signalling molecules/mediators in Ischemic stroke.

S. No.	Model	Inhibitor	Receptor	Effects	References
1	Adult SD Rats	Baicalin	TLR2 and TLR4	Reduced infarct size and volume and Suppression of TLR2/4 signalling.	[211]
2	Mice MCAO	Salvianolic acid B	CD36	Sal B significantly improved neurological deficits, reduced infarct size, attenuated cerebral edema and GFAP, Iba1, IL-1β, IL-6, TNF-α and Cleaved-caspase 3 production was reduced.	[212–214]
3	Mice MCAO	Curcumin	NLRP3	Curcumin ameliorated white matter (WM) lesions and brain tissue loss 21 days post-stroke and improved sensorimotor function 3, 10, and 21 days after stroke. Decreased pyroptosis-related proteins.	[215,216]
4	Rat MCAO	Phthalide derivative CD21	MSR1	PRX1 clearance and TLR4 inhibition.	[117]
5	Adult CD1 mice	apoE-mimetic peptide COG1410 (TREM-2 agonist)	TREM-2	Improvement in both short-term and long-term neurological functions, reduced brain edema, inhibited microglia/macrophage activation and neutrophil infiltration.	[217,218]
6	C57BL/6 Mice	UNC2025	MerTK	Decreased platelet activation and protected animals from pulmonary embolism and arterial thrombosis without increased bleeding times. Anti-thrombolytic activity.	[219]
7	MCAO Mice	Proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i)	CD44	Significantly improved neurological deficits and reduced the volume of cerebral infarction. Activation of GPNMB/CD44 pathway.	[220]
8	22 Human patients with acute stroke	Fingolimod	Sphingosine – 1 – phosphate receptor	Patients with acute and anterior cerebral circulation occlusion stroke, oral fingolimod within 72 h of disease onset was safe, limited secondary tissue injury from baseline to 7 d, decreased microvascular permeability, attenuated neurological deficits and promoted recovery.	[221]

Conclusion

Although the function of each receptor is known, their effect on the neuroinflammation mechanism of ischemic stroke depends on the time, duration, and extent of neurological damage, co-morbidities, age, gender, environmental influence and other unknown factors. For example, the levels of IL-6R vary in the acute phase, chronic phase and recovery phase of stroke. Moreover, females are more prone to Stroke and poor outcomes occur during their old age as compared to males. Patients with high blood pressure and diabetes possess an increased risk of stroke than those with no such co-morbidities. Epigenetic modulators have been known to change gene expressions in ischemic stroke, thereby influencing stroke outcomes. The immune mechanism of stroke depends on these factors and therefore, more studies are required to uncover the function of these receptors concerning the aforementioned factors to understand the overall mechanism of Ischemic stroke. There are other unexplored receptors of the immune system that warrant extensive research to uncover their function in Ischemic stroke. Furthermore, there are other receptors on other cells apart from the immune system that crosstalk with these immune receptors, which may influence the treatment and outcome that is beyond the scope of our review. Even after decades of research, stroke is still classified as the third leading cause of death globally. A comprehensive study of immune receptors at different time points with the inclusion of epigenetic mechanisms and other co-morbidities in a sex-specific manner may be the key to identifying potential therapeutic targets.

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Author contributions

S.V. and S.C. planned and conceptualised the review. S.V. and S.G. were involved in data collection, writing and editing of the original draft of the manuscript. S.C. arranged the fund acquisition, overall supervision and editing of the manuscript. All the authors have read and reviewed the manuscript.

Conflict of interest

The authors have declared no conflict of interest in the project.

Other Declarations

(A) Since our study is based on the publicly available literature reported by other researchers including clinical reports, 'Clinical trial number: not applicable.'

(B) Consent to Publish declaration: not applicable.

(C) Our study is not based on the clinical trials. The study was based on the available literatures to public including clinical trial reports. Hence, Consent to Participate declaration: not applicable.

(D) Our article is neither based on any experiments involving animals nor human clinical trials. This is purely based on the available literature in public domain. Therefore, ethics declaration is not applicable.

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