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Influencing neuroplasticity in stroke treatment with advanced biomaterials-based approaches

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ABSTRACT

Since the early 1990s, we have known that the adult brain is not static and has the capacity to repair itself. The delivery of various therapeutic factors and cells have resulted in some exciting pre-clinical and clinical outcomes in stroke models by targeting post-injury plasticity to enhance recovery. Developing a deeper understanding of the pathways that modulate plasticity will enable us to optimize delivery strategies for therapeutics and achieve more robust effects. Biomaterials are a key tool for the optimization of these potential treatments, owing to their biocompatibility and tunability. In this review, we identify factors and targets that impact plastic processes known to contribute to recovery, discuss the role of biomaterials in enhancing the efficacy of treatment strategies, and suggest combinatorial approaches based on the stage of injury progression.

Contents

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1. Introduction

Increases in metabolic risk factors such as obesity and diabetes mellitus, in conjunction with the ageing population, have made stroke the second most common cause of death and the third leading cause of adult disability worldwide [1]. To add insult to injury, advancements in stroke treatment are severely lacking. Tissue plasminogen activator (tPA) remains the sole clinically-used therapeutic for patients presenting with ischemic stroke. Since the first use of tPA for stroke treatment in 1996 [2], the only significant standard of care improvement has been to widen the timeframe for administration of this drug via endovascular thrombectomy (ET) in large-vessel occlusions [3]. ET has dramatically increased the population eligible to receive tPA and limits the extent of the damage, but it does not address the chronic aspects of the illness. Rehabilitation therapy remains the gold standard for management of memory loss and functional deficits that affect stroke patients, yet it only restores partial function in most cases [4].

The inherent plasticity of the brain could be the key to pushing past this stagnation in stroke therapy innovation. By developing strategies that support and augment natural reparative mechanisms, we can take advantage of the existing architecture of the brain to achieve more robust long-term changes. Biomaterials have been fundamental to these strategies, owing to their versatility and tunability. These biocompatible, and often biodegradable, materials typically serve as the vehicles for sustained therapeutic factor release and cell delivery [5,6].

2. Defining neuroplasticity

Neuroplasticity is a broad term that encompasses any changes in nervous system structure, function or connections made in response to external or internal stimuli [7]. In order to affect neuroplasticity in a beneficial way, it is important to recognize that these changes happen on several different levels, often simultaneously. At the highest level, global plasticity is a rewiring of entire neural systems and can result from major traumatic injury. When large regions of tissue are compromised, compensatory mechanisms recruit the remaining tissue to take on functions that would otherwise be lost. This has been observed both in animal models [8] and in humans [9,10]. There is evidence of both ipsilesional [11] and contralesional [12] tissues taking on this functionality, though it remains unclear precisely what determines the redistribution to one hemisphere over the other [13]. There is also an ongoing debate surrounding which of these two scenarios is preferred when developing intervention strategies, or whether the goal should be to restore more bilateral balance between the hemispheres [14–16].

At the cellular level, most plasticity studies have focused on morphological changes in neurons in response to injury or disease [17]: the number and shape of dendritic spines [18], dendrite and axon arborization, axon initial segment (AIS) length and position, and axon bouton number. Recent studies have examined the changes that occur in other cell types of the brain as well. Astroglia, for example, possess perisynaptic astrocytic processes (PAPs) that envelop excitatory synapses to an extent that is dependent on a variety of different factors, such as the frequency of synapse use [19]. Increased synaptic activity increases Ca^{2+} transients in the PAPs and results in greater synapse coverage and longevity [20].

Synaptic plasticity refers to the strengthening or weakening of synapses through the expression of neurotransmitters. These changes, like the PAP synapse coverage, are also activity-dependent. With the recurring use of certain connections, long-term potentiation (LTP) is initiated, strengthening these synapses to make information transfer more efficient for processes that are frequently used. This concept, originally introduced in 1973 by Bliss and Lomo [21], has helped to explain why repetitive use and coordination of neural pathways is crucial to memory formation and skill development. Early studies by Levy and Steward furthered this understanding, showing that LTP has cooperative and associative properties. A strong input will induce cooperative LTP by recruiting many excitatory synapses to fire together. Associative LTP occurs when simultaneous activation of two separate inputs, one strong and one weak, induces LTP in the weak input that would not experience LTP on its own [22], as is the case in Pavlovian fear conditioning [23]. Though *N*-methyl-D-aspartate (NMDA) receptor-dependent LTP in hippocampal CA1 neurons has been the most heavily investigated form, LTP takes on different characteristics depending on the area of the brain in which it is observed [24]. Advances in optogenetics are shedding light on the mechanisms that contribute to long-term memory formation and have enabled the deactivation and reactivation of associative memories in a mouse model [25].

Confining the definition of neuroplasticity to alterations in existing neural and glial cells oversimplifies this phenomenon by neglecting to acknowledge other contributing factors. Neurogenesis, angiogenesis, and changes in the extracellular matrix (ECM) occur in conjunction with alterations to existing neural and glial cells. Adult neural stem cells, located in the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus, can be stimulated to rejuvenate neural circuitry or mitigate the effects of injury [26,27]. With increased or decreased usage of particular regions of the brain, demands for oxygen and nutrients fluctuate, dictating the required degree of vascularization and initiating angiogenesis [18,28]. The ECM must accommodate and support all of these architectural changes, and so will be catabolized and restructured accordingly [29]. As a multi-faceted and complex phenomenon, neuroplasticity offers many opportunities for therapeutic intervention.

3. Clinical strategies for stroke treatment

Stroke is generally broken down into two main types: hemorrhagic and ischemic. Hemorrhagic stroke is caused by blood vessels rupturing and is often fatal. The loss of blood supply combined with increased intracranial pressure and infiltration of inflammatory cytokines and matrix metalloproteinases typically results in severe and rapid tissue damage [30]. In ischemic stroke, a blockage such as a blood clot obstructs blood flow to one or more areas, interrupting the supply of oxygen and nutrients. The ischemic injury forms over a longer period of time than the hemorrhagic, and can be diminished if the blockage is transient. Due to the severity and usual fatal outcome of hemorrhagic stroke, most regenerative strategies are aimed at treating ischemic stroke [31].

With the exception of tissue plasminogen activator (tPa) administration or endovascular thrombectomy (ET) [32] in the acute phase of injury, no other therapeutic strategies have come close to augmenting stroke recovery in the same way as rehabilitation therapy. While ET or tPA have helped many stroke patients, both significantly increase risk of hemorrhage by disrupting the cerebrovascular physiology [33,34]. tPA transforms plasminogen into the proteolytic enzyme plasmin when both are bound to fibrin, a major component of blood clots. This complex acts to dissolve the clot, thereby restoring blood flow to affected areas of the brain tissue [2]. ET, a mechanical strategy for removing the thromboembolus from the blood vessel, can be used alone or in

conjunction with fibrinolytic treatment. A number of ET devices have been developed and tested in clinical trials in recent years, and while they increase the effective window of tPA, they also greatly increase the rates of asymptomatic hemorrhagic transformation [34].

At present, the gold standard of ischemic stroke treatment is rehabilitation therapy, which draws on the capacity of the brain for endogenous neuroplasticity. Extensive research in rodent models has demonstrated that major cortical remapping can be achieved through rehabilitation training following injury to the motor cortex. Nishibe et al. explored the temporal aspect of this reorganization in a rat endothelin-1 (ET-1) model using intracortical microstimulation in perilesional regions. Several kinematic measures were assessed, revealing a rapid improvement in rehabilitation-trained (rehab) animals that was sustained past the training period. While the animals' performance in behavioural tasks plateaued [35], reorganization of the forelimb representation area of the brain tissue continued and was more substantial in rehab animals than controls at 38 days post-injury. This has spurred additional studies into the underlying mechanism of rehab therapy and the consequent neuroplasticity.

4. Endogenous response to stroke injury

We highlight key events that are relevant to plasticity-based recovery and direct readers to excellent reviews of the processes that are initiated by stroke injury [36,37]. By examining the endogenous factors that the brain naturally releases at different stages of injury, we can inform our design of plasticity-enhancing strategies to support healing processes.

4.1. Injury progression

Following ischemic stroke injury, oxygen and nutrient supply to the brain tissue is interrupted, causing neurons and glial cells in the affected regions to undergo apoptosis within minutes. The damage increases as immune cells infiltrate, and waves of neuronal excitotoxicity propagate. The brain responds rapidly to this sudden assault by containing the damage, protecting surviving cells, and re-routing the circuitry to compensate for necrotic tissue. The lesion typically reaches its maximum size by 6 h post-injury [38], but in the following hours to days, cell death and necrosis continue to spread into the region surrounding the lesion core, termed the penumbra. This penumbra is one of the main targets of neuroprotective strategies, as the tissue here is damaged, but potentially salvageable.

Once the injury has stabilized, the brain shifts to repairing and reorganizing the penumbral tissue. The loss of neurons in the ischemic core triggers an increase in neural progenitors in the subventricular zone (SVZ) that gives rise to neuroblasts. In rodents, the neuroblasts normally migrate from the SVZ, along the rostral migratory stream (RMS) to the olfactory bulb. After injury, their path is altered as they are recruited to the area surrounding the infarct [39]. Angiogenesis and neurogenesis are initiated and act synergistically, with blood vessels providing directional cues to neural progenitor cells and acting as a scaffold for these cells as they migrate to the region of injury [36]. In addition, microvascular endothelial cells secrete growth factors and cytokines that support neurogenesis [40,41]. While these factors help to create a more favourable environment for post-stroke plasticity, the regenerative capacity of the neural progenitors is minimal due to the limited number of progenitors produced after the injury, and the low survival of new neurons. For example, Arvidsson et al. demonstrated that in adult rats, <1% of the lost neurons were replaced by progenitors from the SVZ [42]. Weeks to months after the initial injury, the chronic phase is characterized by decreased plasticity at every level [43,44]. Recognizing how the ischemic environment fluctuates over time is crucial to developing appropriate interventions.

4.2. Reactive astrocytes and the glial scar

Glutamate, the main excitatory neurotransmitter, enables the rapid transmission of signals between neurons in the healthy brain [45]. It exerts its function primarily through the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA ionotropic receptors that operate in synchrony; AMPA receptors are specialized for fast excitation, acting as gates for sodium and potassium cations, and NMDA receptors are calcium-permeable when activated by glutamate. Binding of glutamate to AMPA receptors causes depolarization of the membrane, enabling calcium influx through NMDA receptors. Subsequently, AMPA receptor expression and trafficking to the cell membrane is increased. This feed-forward mechanism is crucial for LTP to occur [46], but becomes a problem in the acute stroke microenvironment that is flooded with excess glutamate, which is released when neurons undergo apoptosis. In this scenario, the positive feedback loop perpetuates the hyperexcitability of the peri-infarct tissue as neurons fire rapidly, and without order, in response to this excitatory molecule [47,48]. To break the cycle, reactive astrocytes are recruited to the injury site, where they release gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter that acts against glutamate to quench the excitotoxicity in the lesioned tissue. In an uninjured brain, GABA has two main functions: (1) phasic (synaptic) signaling, where GABA is released by presynaptic boutons in response to interneuron action potentials, which then inhibit depolarization of the postsynaptic neuron transiently; and (2) tonic (extrasynaptic) signaling, where GABA maintains the overall neuron membrane potential and capacity to fire. Clarkson et al. reported that increased tonic GABA currents persisted for more than one month following stroke in mice, with the peri-infarct tissue exhibiting hypoexcitability. While beneficial in the acute phase, the peri-infarct tissue will have a diminished capacity for plasticity (and therefore recovery) if hypoexcitability persists chronically [49].

Reactive astrocytes and pericytes deposit chondroitin sulfate proteoglycans (CSPGs), which contribute to the formation of the glial scar [50]. The glial scar has been shown to inhibit axonal growth after injury in the brain, spinal cord and retina [51,52]. By degrading the CSPGs, one of the main chemical barriers to regeneration is diminished, enhancing recovery in central nervous system (CNS) injury [53]. However, not all CSPGs are inhibitory and may support some aspects of regeneration. The glial scar is a crucial part of CNS injury response, and manipulating the relative levels of different CSPGs may be more effective for regeneration than eliminating them completely [54,55]. CSPGs are an integral part of the normal CNS extracellular matrix [53], forming perineuronal nets with other ECM proteins during brain and spinal cord development to support and stabilize circuits [56]. Thus, the role of CSPGs in injury is complex and one that is being actively investigated.

4.3. Brain-derived neurotrophic factor

Gene expression in the peri-infarct tissue following stroke resembles that of early brain development in terms of neuronal growth, axonal sprouting, synaptogenesis and dendritic spine proliferation [57,58]. A brain in either the developing or acutely injured state lacks perineuronal nets and thus has the ability to create new connections. A homodimer with a molecular weight of 27 kDa, brain-derived neurotrophic factor (BDNF) is an endogenously produced protein that has been identified as a principal agent of plasticity in both the developing and adult brain [59,60]. In normal circumstances, BDNF is widely expressed throughout the parenchyma by neurons and ependymal cells and its expression is immediately upregulated following stroke (4 h) [61]. BDNF is first expressed in a pro-form (pBDNF) that binds the p75 receptor and triggers neuronal apoptosis [62]. It is only with enzymatic cleavage of pBDNF to the mature form (BDNF) that it is able to bind to tyrosine receptor kinase B (TrkB) and initiate intracellular signaling cascades that support survival, neuronal differentiation and plasticity. The largely opposing roles of these two forms underline the importance of the

relative amounts of each in the brain, and warrant the investigation of the factors that affect this ratio. Age may be one of the most significant mediators, with multiple groups demonstrating that with age, the brain naturally shifts this ratio to favour the pro-form of the protein [63,64]. Particularly interesting in the context of stroke is that the cleavage of pBDNF to BDNF is dependent on the presence of extracellular tPA, as shown by Farrell et al. [65]. In their mechanistic study, tPA homozygous null ($tPA^{-/-}$) mutant mice exhibited severely restricted late-phase LTP in hippocampal slices that could be rescued with application of mature BDNF.

The modulation of plasticity by mature BDNF occurs through three main intracellular signaling cascades that operate in tandem (Fig. 1). Binding of BDNF to TrkB causes dimerization and autophosphorylation of tyrosine residues on the receptor and initiates the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K) and phospholipase Cγ (PLCγ) pathways. The MAPK pathway regulates protein synthesis-dependent plasticity through activation of cAMP response element binding (CREB) transcription factor and eukaryotic initiation factor 4E (eIF4E). PI3K influences cell survival and protein translation via activation of Akt and the mammalian target of rapamycin (mTOR), while also regulating the transport of synaptic proteins to maintain synaptic plasticity. With the activation of PLCγ, calcium is both released from intracellular stores as well as pumped from the extracellular space into the cell via plasma membrane channels [66]. This increase in intracellular Ca^{2+} lowers the threshold for neuronal depolarization and allows increased amplitude and frequency of excitatory post-synaptic currents [67]. The PLCγ pathway in particular demonstrates why BDNF is key to LTP, and explains its involvement in rehabilitation therapy. Recent studies linking exercise with the upregulation of BDNF [68,69], combined with evidence that blocking BDNF expression negates the beneficial effects of rehabilitation [70], demonstrate the synergism of these physical and chemical elements of recovery.

4.4. Additional endogenous plasticity modulators

In addition to BDNF, a host of other endogenous plasticity modulators are generated following stroke. Among these are erythropoietin (EPO), vascular endothelial growth factor A (VEGF-A), and insulin-like growth factor (IGF-1) [71]. EPO is predominantly responsible for erythropoiesis, but also plays an important role in protecting and regenerating the brain following ischemic injury. Subsequently, neurons and astrocytes increase their production of EPO from basal levels, and other cell types also contribute to EPO production at various stages of injury progression [72]. This factor stabilizes mitochondrial membranes in neurons, limits the formation of reactive oxygen species and reduces inflammatory cytokine production and neutrophil infiltration [73]. Moreover, EPO encourages angiogenesis, neurogenesis, and white matter protection/regeneration. Involvement in both protective and regenerative pathways makes EPO a powerful contributor to endogenous plasticity processes. Plastic processes require oxygen and nutrients to be delivered by the vasculature, thus the brain increases expression of VEGF-A in an attempt to circumvent the blockage [74]. With ischemic injury, reperfusion of the peri-infarct tissue is critical and faster reperfusion results in greater recovery [75]. With an immediate increase in VEGF expression following injury, reperfusion is enhanced and lesion volume is diminished [76]. IGF-1 is another key contributor to neuroprotection following injury. Similar to BDNF, IGF-1 activates the PI3K-Akt and MEK-ERK pathways and inhibits apoptosis,

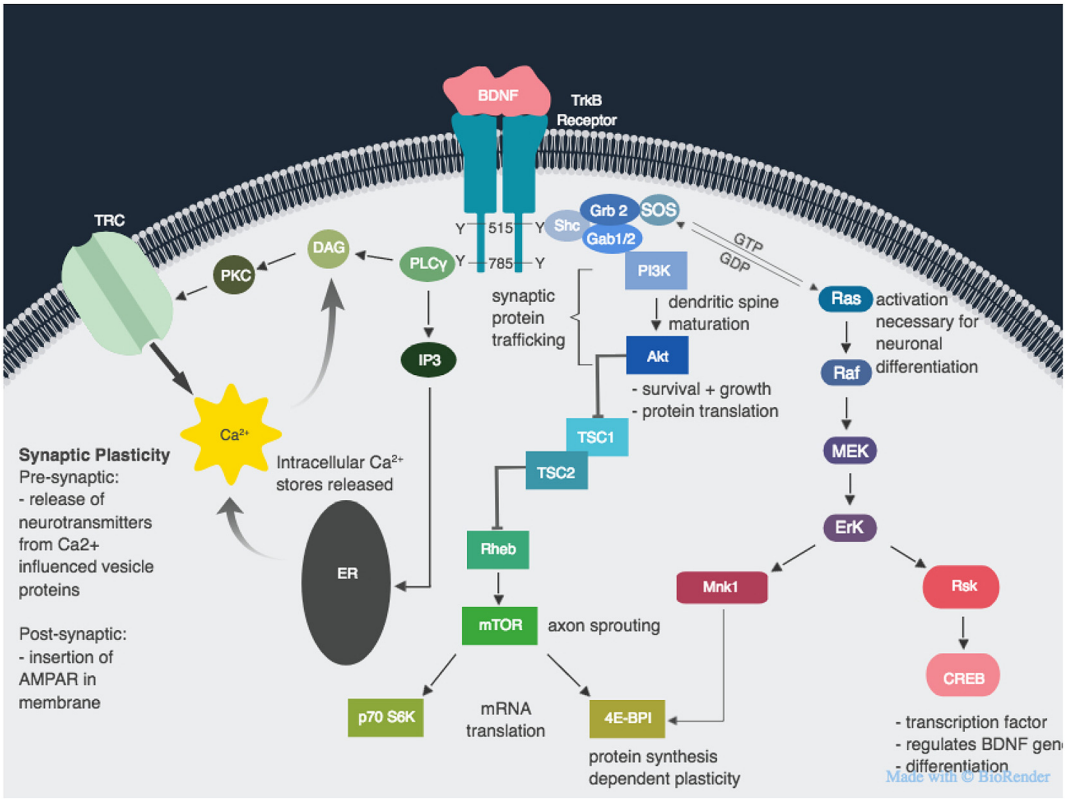

Fig. 1. Cascades initiated by BDNF that influence plasticity. Phosphorylation of tyrosine residue 785 on TrkB recruits PLCγ to the receptor, and activates the enzyme with tyrosine phosphorylation. PLCγ hydrolyses phosphatidylinositol 4,5-biphosphate to give a diacylglycerol (DAG), which activates protein kinase C (PKC). This also activates inositol triphosphate (IP3) that releases Ca^{2+} from intracellular stores and acts with DAG to activate TRC channels, causing an influx of Ca^{2+}. Phosphorylation of tyrosine residue 515 on TrkB mediates the interaction with Src homology 2-containing protein (Shc). Shc recruitment to the Trk receptor is followed by activation of the phosphatidylinositol 3-kinase (PI3K) pathway, which shuttles Akt (protein kinase B) to the plasma membrane. Akt then downregulates tuberous sclerosis complex (TSC1) that complexes with TSC2, inactivating Rheb and allowing activation of mTOR, permitting mRNA translation. The Shc/Trk receptor interaction also causes phosphorylation of an adaptor protein, leading to activation of Ras/Erk signaling pathway through recruitment of Grb2 and SOS. A phosphorylation cascade with kinases Raf, Mek, Erk, and Rsk ultimately phosphorylates cAMP response element binding protein, a transcription factor that regulates the expression of BDNF. Reproduced with permission [66].

thereby aiding neuronal survival in the excitotoxic environment [77]. Even with the brain's endogenous production of these plasticity modulators, spontaneous recovery is rarely seen in stroke patients, emphasizing the need for therapeutic intervention. Understanding the different niche functions of these molecules and how they work in synergy endogenously can help identify combinations of exogenous therapeutic factors to support and strengthen naturally occurring plasticity. Table 1 provides a summary of these additional exogenous plasticity modulators.

5. Exogenous plasticity modulators

Exogenous factors, including both biomolecules and cells, are delivered to the brain to supplement the endogenous factors already present and promote tissue repair and recovery. In this section, we review these exogenous factors with a focus on plasticity and summarize their effects and intended targets in Table 2.

5.1. Exogenous biomolecules

Of the endogenously produced plasticity modulators we have discussed, BDNF exhibits the greatest potential as an exogenously delivered factor. Owing to its size and short half-life in vivo, the largest obstacles to BDNF delivery are overcoming the BBB and maintaining effective concentrations in the parenchyma. Most investigators have shown that BDNF does not cross the BBB [78,79], making systemic delivery largely ineffective and potentially causing undesirable side effects [80–83]. Intraventricular infusion enables local BDNF delivery to the brain with reported benefits to tissue [84,85], but the invasive nature of these procedures combined with the need for multiple injections or implants pose a risk of infection and are not ideal for clinical translation. Some recent, less invasive biomaterial-based strategies for delivering BDNF will be discussed in greater detail in the following sections.

Alternatively, instead of delivering the protein itself, BDNF-mediated pathways can be triggered. For example, Clarkson et al. systemically delivered the BDNF-inducing ampakine, CX1837, resulting in BDNF expression in the peri-infarct cortex and behavioural recovery [46]. Interestingly AMPA receptor activation was beneficial when achieved one week after injury, turning its delivery from harmful to beneficial by delaying administration by 5 days from the time of stroke injury. The temporal aspect of the effect is noteworthy, and underlines the importance of determining the most appropriate timing for exogenous factor delivery. Niacin (nicotinic acid, vitamin B3) has also been shown to modulate neuroplasticity by upregulating BDNF expression. Cui et al. showed that when Niaspan, a prolonged release formulation of niacin, was orally administered 24 h after injury and daily for two weeks in a rodent model, there was improved synaptic plasticity, axon growth and greater angiogenesis [86]. These exogenous BDNF strategies are promising in pre-clinical stroke models, but have yet to be transferred to the clinic.

Another endogenously produced factor, EPO has shown some promise with exogenous delivery. Chau et al. treated rodent models with the trophic factor EPO with observed neuroprotective effects [87]; however, Ehrenreich et al. demonstrated unfavourable effects, including patient death, with intravenous delivery of EPO [88]. The poor outcome of this clinical study was associated with the high dose of EPO administered over a relatively short time frame of 6 to 48 h. As with BDNF, biomaterials can be used to address these delivery issues and tailor the administration of EPO appropriately.

To date, serotonergic and dopaminergic drugs have demonstrated the most potential clinically. Serotonin, a neurotransmitter that controls cognitive processes such as memory consolidation, is closely tied to plasticity. In animal studies, selective serotonin reuptake inhibitor (SSRI) drugs have been shown to increase neurogenesis and expression of neurotrophic factors, particularly BDNF [89,90]. Subsequent human studies have highlighted the role of these SSRI drugs in improving motor and non-motor functions after stroke via plastic mechanisms [91,92]. Dopamine, another neurotransmitter, is well known for governing reward-based behaviour and has also been implicated in the modulation of LTP [93]. The latter function is still not entirely understood, though we are learning that dopamine may elicit heterogeneous LTP effects that are dependent on the target of action [94]. This location dependency may explain the contradictory results obtained in studies that delivered L-Dopa to stroke patients. Scheidtmann et al. showed that in a randomized study in patients within six months of stroke, a combination of L-Dopa and physical therapy resulted in improved motor recovery as compared to the placebo when L-Dopa was delivered daily for 3 weeks [95]. Other studies that used a single dose of L-Dopa combined with physical therapy in stroke patients showed inconsistent results in motor function recovery [7,96]. The inconsistent results of these two studies suggest that repeated delivery of L-Dopa might be required to achieve functional recovery. Amphetamine, a psychomotor stimulant that modulates levels of neurotransmitters such as dopamine and serotonin, has also been extensively studied in the context of stroke with mixed results. Several clinical studies have used different treatments of amphetamine combined with physiotherapy to evaluate recovery though, according to a meta-analysis by Martinsson et al., there is no definitive indication for the routine use of amphetamine. Further studies with larger study groups may be needed to investigate this effect [97].

The excitotoxicity generated by an ischemic event presents another opportunity for exogenous drug intervention. Increased extracellular glutamate from apoptotic neurons leads to overstimulation of the glutamate receptor, NMDA, which in turn causes the release of additional glutamate and creates an environment that inhibits neuronal growth and plasticity [45]. NMDA agonists, such as Memantine and Flupirtine, prevent the activation of NMDA receptors, thus breaking the excitotoxicity cycle. Memantine was shown by Wang et al. to enhance neurological recovery and plasticity after stroke by improving motor coordination and spatial memory in a mouse model [98] and Flupirtine demonstrated a similar effect in mice, as reported by Jaeger et al. [99]. The sigma-1 receptor has also been targeted for excitotoxicity because it regulates calcium signaling and is involved in membrane trafficking, neurotransmisson and cell survival [100]. A study in rodents by Rushcher et al. demonstrated that the sigma-1 receptor was upregulated after stroke in astrocytes in peri-infarct tissue. Two days after

Table 1
Summary of additional endogenous plasticity modulators.

Factor	Stroke-associated mechanism of action	Target cell type	Refs
Erythropoeitin (EPO)	• Stabilizes mitochondrial membrane • Limits formation of reactive oxygen species • Has an anti-inflammatory effect • Promotes angiogenesis, neurogenesis, white matter protection/regeneration	Neurons, astrocytes, endothelial cells	[73]
Vascular Endothelial Growth Factor (VEGF)	• Induces angiogenesis • Enhances reperfusion • Decreases lesion volume	Neurons, astrocytes	[74,76]
Insulin-like growth factor (IGF-1)	• Inhibits apoptosis and supports neuronal survival • Stimulates neurogenesis, neuronal myelination and angiogenesis	Neurons, astrocytes	[77]

Table 2
Summary of exogenous plasticity-modulating biomolecules.

Factor	Stroke-associated mechanism of action	Target cell type	Refs
Serotonergic drugs	• Reduce neural inflammation • Increase neurogenesis • Enhance neurotrophin activity	Neurons, astrocytes	[89]–[92]
Dopaminergic drugs	• Regulate expression of growth factors such as FGF-2, BDNF, GDNF	Neurons, astrocytes	[93]–[95]
NMDA receptor antagonists	• Reduce astrogliosis • Promote capillary formation • Increase growth factors such as BDNF, GDNF, VEGF	Neurons, astrocytes	[45]
Sigma-1 receptor agonist	• Stimulates neurite outgrowth • Modulates membrane raft dynamics	Neurons, astrocytes	[100,101]
Niacin- associated compounds	• Improve synaptic plasticity, axon growth • Promote angiogenesis	Neurons	[86]
Chondroitinase ABC (ChABC)	• Improves neuronal differentiation and plasticity	Neurons, astrocytes and oligodendrocytes	[104]
Anti-Nogo A	• Enables axonal and dendritic remodelling • Increases dendritic spine density	Neurons, oligodendrocytes	[105]–[107]
Brain derived neurotrophic factor (BDNF)	• Stimulates neurogenesis • Supports survival and neuronal differentiation	Neurons, ependymal cells, astrocytes, microglia	[84,85]

injury, rats were subcutaneously injected with a sigma-1 receptor agonist and this treatment was continued for several weeks, which resulted in enhanced functional recovery, even after the treatment was discontinued [101].

Inhibitory cues are abundant in the lesion environment, especially in chronic stroke. The glial scar, composed mostly of CSPGs, inhibits axonal migration and neurorepair [102,103], and can be overcome by digestion of the glycosaminoglycan (GAG) side chains by the exogenous factor chondroitinase ABC (chABC). Hill et al., who administered chABC a week after stroke injury, demonstrated this in a rodent model [104]. With this intervention, they reported reduction in the thickness of the glial scar and improved motor recovery at 10 and 14 days post-injury [104]. As with CSPGs, the Nogo-A protein restricts the outgrowth of neurites, thereby stabilizing neural networks that are required for memory formation and skill learning [105]. Following injury, Nogo-A is seen as a hindrance to recovery as it blocks plastic processes that could allow rewiring of circuits and compensation for lost tissue. Delivery of anti-Nogo A blocks the function of Nogo-A and allows axonal and dendritic remodelling, while also increasing dendritic spine density [106]. Interestingly, Lindau et al. demonstrated that this effect was more prominent in the contralesional sensorimotor cortex following stroke when they delivered the antibody locally for two weeks following injury. The observed tissue effects were accompanied by enhanced behavioural recovery [107].

5.2. Transplantation of exogenous cells

While the endogenous neural stem cells contribute to repair and replacement after stroke injury, the inherent proliferative potential of these cells is insufficient to replace those lost [108]. Transplantation of exogenous neural precursor cells can both replace and regenerate lost tissue by stimulating endogenous recovery through processes such as angiogenesis, immunomodulation, and neurogenesis [109]. The cells transplanted can differ in source, rate of differentiation, and factor secretion, thus providing many mechanisms to influence plasticity pathways [109].

Cell survival and integration are key challenges in cell transplantation in the central nervous system and are further complicated by the hostile microenvironment after stroke injury. The recovery of lost function is enhanced when transplanted cells integrate into the host neural circuitry; however, it remains unclear whether transplanted stem cells promote tissue repair by replacing lost cells or by secreting factors that stimulate endogenous repair. Priming stem cell-derived populations towards a cortical neuronal phenotype has been beneficial for integration purposes, with the transplanted cells receiving a similar pattern of synaptic inputs to endogenous neurons [110] and contributing to improved motor function in a rodent model [111]. Shen et al. investigated the mechanism by which transplanted cells improved recovery in a rat model of stroke and demonstrated that cell transplantation increased the expression of synaptophysin in endogenous neurons in the area surrounding the injury [112], suggesting modulation of synaptic plasticity. Many other studies have shown evidence of functional recovery and neuroplasticity after cell transplantation in stroke injury models. Daadi et al. demonstrated that NSCs transplanted in the striatum of stroke-injured rats migrated to the lesion site and helped recovery by improving forelimb movement [113]. The recovery was attributed to the homogenous cell composition that facilitated engraftment. Furthermore, Hicks et al. reported that cortical lesion-transplanted human neural progenitor cells (NPCs) differentiated into neurons and induced motor function recovery in a rat model of stroke [114]. These studies demonstrate the promise of transplanting neuronal progenitor cells that integrate into the host tissue and thereby enhance synaptic plasticity.

Exogenous cell sources can also modulate the brain tissue microenvironment after injury by producing trophic factors that contribute to tissue recovery and plasticity in the stroke-injured brain. Lee et al. transplanted genetically-modified NSCs over-expressing VEGF, which stimulated angiogenesis surrounding the infarct, improved cell survival, and resulted in functional recovery in mice [115]. Cells have been engineered to express several different plasticity-modulating factors: glial cell-derived neurotrophic factor (GDNF), BDNF, and neurotrophin-3 (NT3) and ciliary neurotrophic factor (CNTF) [116,117]. Kurozumi et al. showed how BDNF and GDNF, when released from transplanted cells such as MSCs, improved functional recovery and reduced lesion volume as demonstrated at 7 and 14 days after injury. However, this positive outcome was not observed in the case of CNTF and NT-3 delivery in rats when assessed at the same time points after stroke injury. Further, Llado et al. demonstrated that NSCs engineered to express GDNF exhibited an increased effect on motor neuron survival compared to non-engineered controls, one week after transplantation. This strategy of transplanting cells that have been engineered to secrete specific factors has been pursued with multiple cells and factors: GDNF-secreting fibroblasts promoted axonal growth [118]; BDNF-secreting human bone marrow-derived MSCs demonstrated enhanced neurogenesis [119]; and NT-3-expressing NSCs exhibited improved survival, proliferation and neuronal differentiation of neurites [120]. Overall, pre-clinical studies have shown that cell delivery can complement and enhance endogenous repair processes, and that transplanting cells that secrete trophic factors that contribute to plasticity post-stroke [121].

ReNeuron, a UK-based stem cell research company, is leading the translation of cell transplantation strategies for human use. They obtained positive results in a phase IIa clinical trial where they demonstrated safety and efficacy of transplanted human neural stem cells for

patients living with disabilities post-stroke. The cells were administered intracranially via stereotaxic surgery adjacent to the area with the stroke injury. Three of the 21 patients enrolled in the study demonstrated functional recovery at three, six or twelve months after treatment and 15 out of 21 patients exhibited clinically relevant improvement on at least one efficacy measure [122]. This positive outcome led the FDA to grant regulatory approval for the randomized, placebo-controlled Phase IIb clinical study to begin in the US in 2018. Notwithstanding these exciting clinical data, several unresolved questions remain - what is the best cell type? When is the optimal time for transplantation? What is the optimal delivery vehicle? Cells can be delivered days, weeks and months after injury [123], and may fare better after the immune response has subsided. Further research is needed to establish the appropriate therapeutic window for cell delivery. The tumorigenic potential of transplanted cells remains a risk; however, innovations in cell characterization and cell cloaking should overcome this issue. Moreover, to date there are no clinical cases of tumorigenesis with the use of well-characterized cells.

6. Biomaterials for plasticity modulation

The plasticity-modulating potential that exogenous drugs and cells possess can only be fully realized if they are effectively delivered. Recent advances in biomaterials technology have generated novel tools that have heightened the efficacy of these exogenous agents by providing a greater degree of control over delivery parameters. For many of the drug-based therapeutic strategies, sustained concentrations are desired without high doses associated with bolus delivery, multiple injections, or invasive surgeries associated with implants. Moreover, crossing the BBB requires innovative strategies beyond traditional intravenous, intramuscular or intraperitoneal injections. For cell delivery, survival is the first and foremost design consideration, dictating foundational biomaterial characteristics. Although not as common, biomaterials themselves have also been used in the absence of drugs and cells, to direct and enhance plastic processes.

6.1. Biomaterials for exogenous factor delivery

The BBB is the largest obstacle to exogenous factor delivery to the CNS. Systemic delivery strategies typically use intravenous, oral, or olfactory administration, and thus are well suited to clinical translation, but generally do not achieve therapeutic concentrations of exogenous agents in the brain [124–126]. Local delivery targets the injured tissue, reducing the delivered dose and minimizing unwanted side effects commonly seen with systemic delivery. This efficiency comes at a cost though, as local delivery strategies tend to be significantly more invasive, requiring catheters, minipumps, or syringes to inject therapeutics directly into the brain parenchyma or ventricles [124]. Damage to healthy tissue is unavoidable in this scenario, and implants required for multiple doses pose greater risk of infection. Injectable biomaterials reconcile the advantages of the two routes of administration by making minimally invasive, local delivery strategies possible.

6.1.1. Systemic delivery using nanoparticle biomaterial formulations

The use of polymeric nanoparticles has been somewhat successful for systemic delivery to the CNS as they have increased the longevity of the therapeutics in the blood. The wide array of fabrication techniques and materials that can be used to create nanoparticles has made this possible, as the design parameters have been manipulated to achieve a specific size, morphology, surface charge, chemical composition, hydrophobicity, and topographical features, thereby tailoring the particles to their application. Though many types of nanoparticles exist, we will focus our discussion on liposomal and polymeric configurations, as these are the most widely used in CNS delivery. A summary of nanoparticle formulations is shown in Table 3.

Conventional liposomes, phospholipid bilayers enclosing an aqueous core, are efficient at encapsulating both hydrophobic and hydrophilic compounds in their lipid bilayers and aqueous core, respectively [136], yet liposomes are quickly cleared by the reticuloendothelial system (RES), and thus have much shorter half-lives compared to other nanoparticles. Still, nanoliposomes have been effective carriers for drug delivery to the CNS in some cases. For example, citicoline, which has been shown to improve functional recovery and plasticity after experimental stroke [137,138], was able to reach much higher levels in the brain when delivered intravenously in nanoliposomes compared to free drug [127,128]. Similar to nanoliposomes, nanoassemblies that are formed by conjugation of adenosine to the lipid squalene, allow prolonged circulation of the nucleoside, providing neuroprotection in mouse model of stroke and improved neurological severity scores [129]. Functionalization of nanoliposomes, with compounds like PEG and glutathione, have reduced their high clearance rate and allowed better longevity in the blood [139]. Site-specific ligands also offer a means of improving BBB crossing through receptor-mediated transport (Fig. 2). Zhao et al. showed that PEGylated liposomes conjugated with transferrin effectively target the BBB and deliver a VEGF plasmid, which increases vascular density and improves neurological recovery in a model of stroke injury [130]. Additionally, manipulating the charge of the liposome can affect BBB targeting. Campos-Martorell et al. delivered Simvastatin, known to upregulate BDNF and VEGF expression, intravenously in charged and neutral liposomes. They observed that positively charged liposomes did not significantly accumulate in the infarct while neutral and negatively charged particles increased the transportation of Simvastatin to the brain [131]. Though these studies demonstrate our ability to modify liposomal formulations to address certain challenges, they are not the ideal candidate for CNS delivery due to their instability and limited tunability.

Polymeric nanoparticles have also been used for systemic delivery to the CNS. These formulations can be easily functionalized and offer the advantage of being more stable than nanoliposomes while still being biocompatible/degradable. During the fabrication process, compounds of interest can be adsorbed to, encapsulated by, or chemically bonded to the particles, giving this biomaterial strategy another degree of tunability. Of the natural polymers used to create nanoparticles (chitosan, alginate, gelatin, and collagen), chitosan has shown great potential. A recent investigation by Yemisci et al. loaded chitosan nanoparticles with basic fibroblast growth factor (bFGF) and a small peptide inhibitor of caspase-3 for systemic delivery to the stroke-injured mouse brain [132]. By conjugating antibodies to the transferrin-1 receptor to the surface of these particles, they achieved BBB permeability and elicited a neuroprotective effect with their therapeutics. Though some additional caution is required when delivering synthetic materials to avoid overaccumulation in the kidneys, liver, and spleen [140], they can also be effective carriers when used appropriately. Synthetic polymers, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic co-glycolic acid) (PLGA), poly(ethylene glycol) (PEG), and poly(n-butyl cyanoacrylate) (PBCA), can be easily fabricated as nanoparticles with specific release profiles that can also protect molecules from degradation or elimination and improve their solubility. For example, Saucier-Sawyer et al. formed nanoparticles using a block copolymer of PLA and hyperbranched poly(glycerol), and modified the surface of the particles with adenosine (PLA-HPG-Ad). These particles, administered intravenously, were modestly effective at penetrating the BBB to deliver the chemotherapeutic agent, camptothecin. In addition to overcoming the BBB, the nanoparticles released camptothecin in a sustained manner, dictated by the degradation rate of the particles, that lasted several days [133]. Harnessing electrostatics between protein and polymers, Harris et al. formulated BDNF-loaded PEG-PGA block-copolymer nanoparticles that spontaneously formed upon mixing the components in water [78]. They delivered these particles intravenously and achieved enhanced bioavailability of BDNF in the brain, and improved neuroprotection and memory in stroke-injured mice. Previous studies have

Table 3
Summary of nanoparticle-based delivery vehicles.

Type	Material(s)	Therapeutic delivered	Features	Reference
Liposome	Dipalmitoylphosphatidylcholine (DPPC), Dipalmitoylphosphatidylserine (DPPS), Ganglioside GM1	CDP Choline	Extended bioavailability of therapeutic	[127,128]
	Squalene	Adenosine	Adenosine conjugated to squalene, extending bioavailibility	[129]
	1-Palmitoyl-2-oleoyl-*sn*-glycerol-3-phosphocholine (POPC), Didodecyl dimethyl ammonium bromide (DDAB), Polyethylene glycol distearoylphosphosphatidylethanolamine (PEG2000-DSPE), Maleimide-derivatized PEG2000-DSPE (Mal-PEG2000-DSP)	VEGF plasmid	PEGylated liposome to extend liposome stability Conjugated with transferrin to facilitate BBB targeting	[130]
	1,2-Didodecanoyl-*sn*-glycero-3-phosphocholine (DLPC), Cholesteryl–polyethylene glycol 600 sebacate (CHOL–PEG), 1,2-dioleoyl-*sn*-glycero-3-phosphoric acid monosodium salt (DOPA−), Cholesteryl 3β-N-(dimethylaminoethyl) carbamate hydrochloride (CHOL+), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE)	Simvastatin	Charged liposomes to better target the BBB	[131]
Polymeric	Chitosan	bFGF, z-DEVD-FMK (Cas 3 inhibitor)	PEGylated to extend stability Functionalized with antibodies to the transferrin receptor to facilitate BBB targeting	[132]
	PLGA	camptothecin	PEGylated to extend stability Functionalized with custom peptides for increased BBB targeting	[133]
	PLA	camptothecin	Coated with polyglycerol to extend stability Functionalized with custom peptides for increased BBB targeting	[133]
	Polyethylene glycol - poly(L-glutamate) diblock copolymer	BDNF	Extended bioavailability of protein	[78]
	Gelatin	Osteopontin	Extended bioavailability of protein	[134]
	Gelatin	IGF, HGF	Extended bioavailability of protein	[135]

Table 4
Summary of biomaterial scaffolds for drug and cell delivery.

Scaffold type	Material(s)	Therapeutic delivered	Features	Reference
Hyaluronan based	Hyaluronan and methylcellulose	CsA	Injectable, in situ gelation	[6]
		EPO	Injectable, in situ gelation	[157]
		BDNF, SDF-1α, NT-3	Proteins electrostatically adsorbed to PLGA nanoparticles mixed in hydrogel	[160]
		bFGF	bFGF was expressed as a fusion protein with SH3 SH3 binding peptides were conjugated to methylcellulose chains to bind bFGF-SH3	[162]
		EGF and EPO	EGF encapsulated within PLGA nanoparticles EPO encapsulated in double layer PLGA-poly(sebatic acid) nanoparticles Nanoparticles mixed in hydrogel	[170]
		Cortical neuroepithelial cells	Shear thinning properties can reduce shear stress on cells during implantation, improving survival	[5]
		NSCs	Pro-survival through CD44 and hyaluronan	[173]
	Acryl hydrazide hyaluronic acid crosslinked with an MMP degradable peptide	NSCs	Different proteins were functionalized to the hyaluronan chains to promote differentiation of encapsulated NSCs to either neurons or astrocytes	[171]
	Hyaluronan, Heparin, Collagen	NPCs	Injectable, in situ gelation	[153]
	Hyaluronan crosslinked with acrylamide	NPCs	The hydrogel was formed into microgel beads with a microfluidic device to create a microporous hydrogel	[153]
	Thiolated hyaluronan hydrogel with thiolated denatured collagen, with hyaluronan chains crosslinked with polyethylene-glycol-diacrylate	BDNF	Polymerizes in situ to achieve similar viscoelastic properties to the brain	[157]
	Hyaluronan	Nogo-66 pAb	Polyclonal antibody functionalized onto hyaluronan chains	[169]
Other	Collagen	NPC-like MSCs and bFGF	bFGF encapsulated in gelatin microspheres and mixed in hydrogel	[160]
	Poly(ε-caprolactone)		Electrospun nanofibrous scaffold to enable neurite infiltration into scaffold	[155]
	Poly(lactic acid) and linear polyethylene glycol triblock copolymer	BDNF and GDNF	Proteins encapsulated in PLGA nanoparticles and mixed in hydrogel	[159]
	Polydimethylsiloxane–tetraethoxysilane	VEGF	VEGF adsorbed to the scaffold surface	[170]
	Thiolated methylcellulose crosslinked with poly(ethylene glycol)-bismaleimide	ChABC and cortical neuroepithelial cells	ChABC expressed as a fusion protein with SH3 SH3 binding peptides were conjugated to methylcellulose chains to bind chABC-SH3	[166]
Peptide-based	$RADA_{16}$-IKVAV peptide motif	NSCs	Self-assembly in situ, promotes neural differentiation of encapsulated NSCs	[147]
	DDIKVAV peptide motif	NSCs	Promotes neural differentiation of encapsulated NSCs	[111]

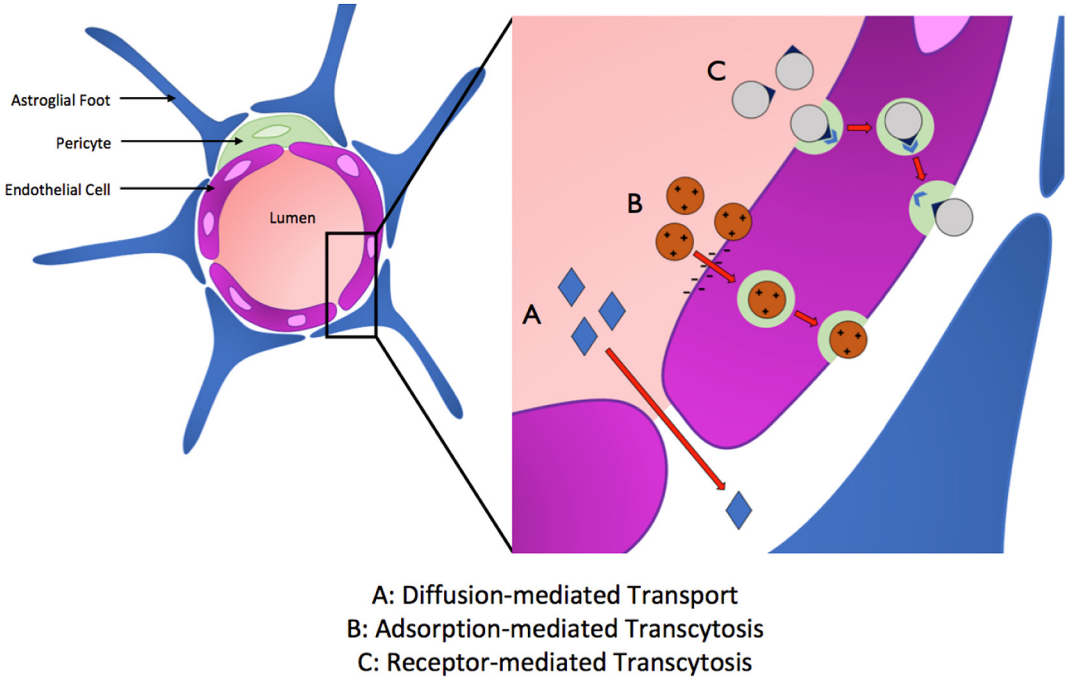

Fig. 2. Cross section of a blood vessel in the brain and the blood brain barrier's structure to demonstrate the various mechanisms that nanoparticles can cross the BBB: A) Diffusion-mediated transport where nanoparticles penetrate the BBB's tight junctions through a diffusion gradient. This transport limited for many compounds, but is improved somewhat by BBB disruption seen after ischemia. B) Adsorptive-mediated transcytosis where cationic nanoparticles can interact with the anionic membranes of the BBB's endothelial cells, triggering vesicle formation and subsequent BBB penetration. C) Receptor-mediated transport where targeting ligands to receptors on the BBB (transferrin receptor, insulin receptor, low density lipoprotein receptor) can be conjugated to nanoparticles to improve targeting and delivery.

shown that these polyion complexes accumulate in brain vasculature surrounding the lesion [141].

6.1.2. Local delivery of biomaterial particles

Even with additional targeting ligands and functionalization, the main limitation of nanoparticles for systemic delivery is the off-target effects that can result from the high drug loadings required to reach a therapeutic dose in the parenchyma [142]. Local delivery of nano- and microparticles, injected into the lesion site, peri-lesional tissue or intraventricularly, side-step this issue, placing the therapeutic directly at or near the site of interest. Osteopontin, a key mediator in bone formation, has also been shown to be upregulated after stroke, acting as an anti-inflammatory and chemoattractant compound [143]. It was delivered locally to the ischemic rat brain encapsulated in gelatin microspheres, where the release profile was significantly extended compared to free drug, resulting in lower neurological deficits and long-term neuroprotection [134]. Nakaguchi et al. also utilized local delivery of gelatin microspheres, delivering either insulin-like growth factor 1 (IGF-1) or hepatocyte growth factor (HGF), to the stroke injured mouse brain, improving neurogenesis and regeneration after stroke compared to free drug alone [135].

6.2. Scaffolds

Implantable scaffolds, like hydrogels or sponges, have also been studied in stroke treatment. Scaffolds are ideally biodegradable or bioresorbable, obviating the need for removal and limiting chronic inflammation [144]. Due to the intimate contact with brain tissue in local delivery, the host response must be tightly regulated. Scaffolds used in soft tissues are typically comprised of hydrogels due to their high water content, which contributes to their biocompatibility. Scaffolds can also be functionalized with anti-inflammatory monomers or peptides to limit the immune response. For example, a superoxide dismutase (SOD) mimetic metalloporphyrin macromer can reduce reactive oxygen species (ROS) damage in response to implanted biomaterials [145]. Certain materials can also prevent the formation of the glial scar and repress reactive astrogliosis, as was shown with a functionalized self-assembling peptide scaffold [146]. In addition to the immunogenicity of the biomaterial, other considerations are stiffness and swelling, as the brain is one of the softest organs in the body [147], and increases in intracranial pressure are a major cause of secondary damage after the initial stroke injury [148]. Implantable scaffolds can be synthesized with a multitude of biocompatible materials, like hyaluronan, methylcellulose, collagen, and agarose. The choice of material for these scaffolds can impact stroke repair. For example, high molecular weight hyaluronan is anti-inflammatory in the CNS [149,150], and collagen enables cell attachment and migration [151,152]. Their physical properties can be easily tuned to mimic the brain's physical properties, such as stiffness and morphology, while their chemical properties can be modified with binding peptides and trophic factors. Specifically, ECM mimetic hydrogels with specific microstructures, functional proteins, and topographical cues can be designed to drive proliferation, differentiation, and maturation of transplanted neural cells to promote tissue repair after cerebral ischemia. Nih et al. showed that microporous HA gels, functionalized with the RGD peptide and two factor XIIIa substrates, improved migration of NSCs in the infarct and also reduced inflammatory response and glial scar formation [153]. This cellular infiltration was also seen with electrospun poly(ε-caprolactone) implanted in the adult rat brain, which enabled neurite infiltration and extension [154]. The stiffness and rheological properties of the material are important parameters to optimize in 3D culture systems, especially if the system will eventually be translated to in vivo use. Stiffness influences cell phenotype in vitro: moderately stiff (100–1000 Pa) gels are associated with neuronal cells, while stiffer (1000–10,000 Pa) gels are associated with astrocytes. Additionally, if the gel is too stiff (>100,000 Pa) or too soft (<10 Pa), neural stem cell survival may be limited [155]. Biomaterial scaffolds can be used to deliver drugs to enhance endogenous plasticity-induced remodelling, serve as the vehicle for cell

transplantation to improve their survival, and sometimes enhance recovery with the physical properties of the material itself, as elucidated below.

6.2.1. Scaffolds as delivery vehicles

In addition to their mechanical properties, scaffolds can be combined with drugs or cells to further enhance their therapeutic effect. For drug delivery applications, scaffolds can be designed to achieve sustained release of encapsulated therapeutics to affect the plastic processes of endogenous repair like axonal sprouting, synaptogenesis, and angiogenesis. For example, a hydrogel composed of hyaluronan was used by Cook et al. to deliver BDNF locally over three weeks by injection directly into the infarct. This treatment improved motor recovery of stroke-injured mice at nine weeks post-injury through increased neuronal survival and axonal sprouting [156]. Similarly, Wang et al. were able to deliver EPO in a hydrogel composed of hyaluronan and methylcellulose (HAMC) in order to increase neurogenesis and brain remodelling (Fig. 3) [6,157]. Release rate can be controlled by encapsulating proteins in nanoparticles or microparticles prior to their dispersion within the gel to extend release and improve the longevity of the treatment [6], [155–157]. This was shown by Lampe et al., where each of BDNF and GDNF were encapsulated within PLGA particles that were dispersed in a PEG hydrogel, and released over 56 and 28 days, respectively [158]. Proteins can also be immobilized onto scaffolds or nanoparticles to control their release rate. For example, positively-charged therapeutic proteins were adsorbed onto negatively-charged PLGA particle surfaces, resulting in linear protein release over a period of 28 days in vitro [160].

Another method to control release from scaffolds is through affinity binding, such as with heparin and heparin-binding proteins or through specific design, such as that of fusion proteins with Src homology 3 (SH3) and SH3 binding peptides [161,162]. Willerth et al. exhibited one such application of affinity-based binding, where a phage display library was screened for peptide sequences that bound to NGF. When the optimized peptide was bound to a fibrin matrix, release was extended over 5 days [163]. Heparin based binding has also been utilized by, for example, Taylor et al. who demonstrated that heparin could be immobilized onto a fibrin gel with a linker peptide containing Factor XIIIa. The heparin sequestered NT-3 and controlled its release over a period of 9 days in vivo, increasing neural fiber density after spinal cord injury [164]. As shown by Pakulska et al., a crosslinked methylcellulose hydrogel, functionalized with SH3 binding peptides with either weak or strong affinity to SH3, was used to modulate the protein release rate of SH3 fusion proteins, such as ChABC-SH3, where release was extended in vitro [165] and in vivo in a rat model of spinal cord injury [166].

A recent study by Clarkson et al. demonstrated that these local delivery systems can also be used in conjunction with systemic delivery to significantly improve treatment. Previous work showed that the ampakine CX1837 promoted functional recovery after stroke, which was mediated by BDNF [46]; however this effect was markedly reduced in older animals, possibly due to age-related deficits of BDNF. By administering CX1837 intravenously alongside local delivery of BDNF in a hyaluronan/heparan sulfate proteoglycan hydrogel, they observed improved motor recovery in the aged mice compared to CX1837 treatment alone, highlighting critical signaling pathways that must be stimulated synchronously to elicit optimal repair [167]. Instead of using scaffolds to release biologics, others have used scaffolds functionalized with trophic factors to promote repair, or antibodies to sequester harmful or overly abundant molecules from the stroke microenvironment. For example, Ma et al. immobilized a polyclonal antibody to the Nogo-66 receptor onto a HA hydrogel to decrease Nogo-A's inhibitory effects to neurite outgrowth, which enabled axonal growth into the gel, although functional recovery was not significant compared to the vehicle control [168]. Zhang et al. adsorbed VEGF onto a TEOS-PDMS scaffold for local implantation, which enabled increased proliferation of both endothelial cells and astrocytes, as well as infiltration into the scaffold compared to vehicle only controls [169].

6.3. Biomaterials for cell delivery

Cell survival is a big challenge in transplantation and is negatively impacted by the delivery procedure and the hostile environment of the stroke injured brain, thereby limiting therapeutic potential [164–166]. Biomaterials can promote cell survival, differentiation, and maturation by modulating the hostile host microenvironment and providing trophic factors and/or topographical cues (Fig. 4) [5,166]. With specifically designed biomaterials, cells can be preferentially differentiated to a specific phenotype. For example, Cheng et al. demonstrated that by encapsulating neural stem cells in a self-assembling peptide scaffold, the survival and proliferation of the cells was enhanced and astrocyte differentiation was reduced in a traumatic brain injury model [146]. In this study, the hydrogel scaffold filled the injury cavity and improved cell integration. Moshayedi et al. controlled differentiation of neural stem cells by systematically modifying an HA-based hydrogel, whereby fibronectin and laminin promoted neuronal differentiation while bone morphogenic protein-4 and BDNF promoted astrocyte differentiation in vivo [171]. Somaa et al. used a peptide-based scaffold of laminin epitopes to improve both neuronal differentiation of embryonic stem cells (ESCs) and integration into the host circuitry [111]. The stroke-injured rats that received this combined cell/scaffold treatment showed improved neurological recovery compared to cell- and scaffold-only

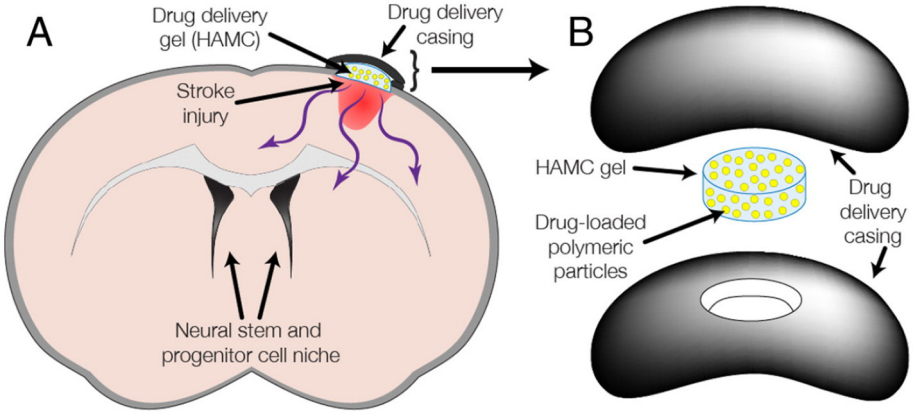

Fig. 3. Sustained local delivery to the brain can be achieved using drug-loaded polymeric particles suspended in hyaluronan/methylcellulose (HAMC) hydrogel. (A) Coronal view of stroke injured brain with drug delivery system shows that HAMC is injected directly onto the cortex. (B) Drug delivery system in expanded view shows that HAMC is held in place by both gelation and a casing comprised of polycarbonate discs. Adapted from work by Wang et al. and Tuladhar et al. [170,6].

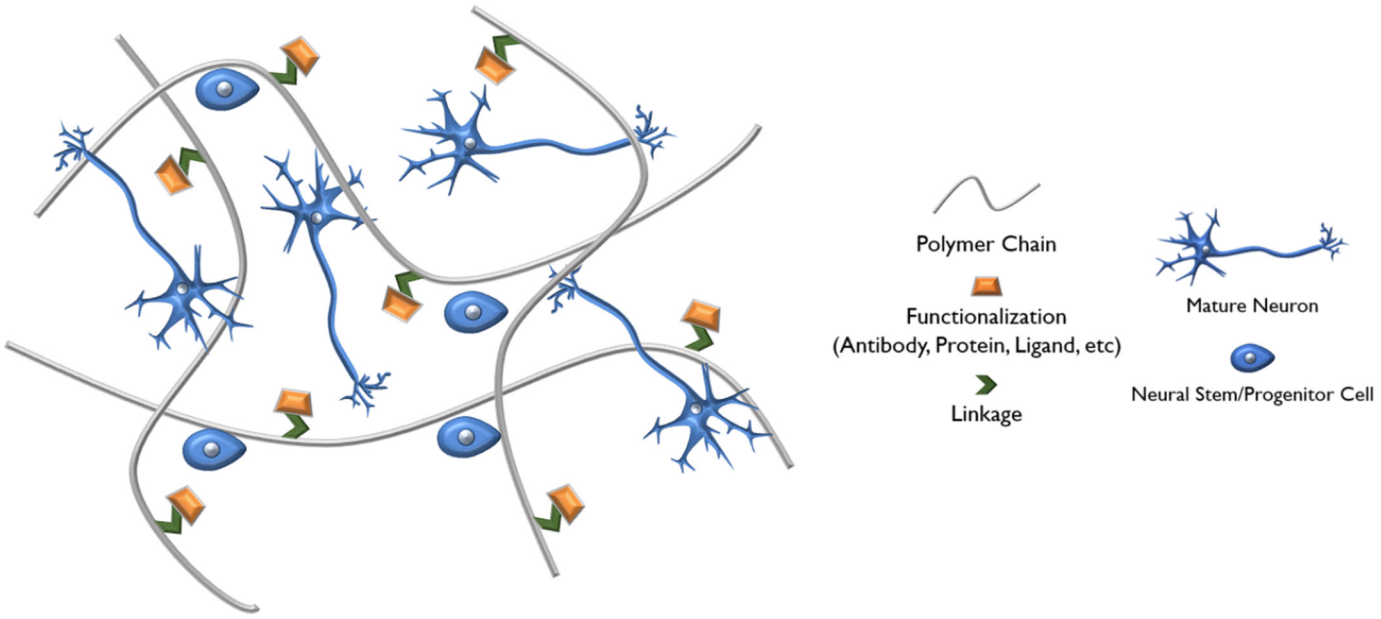

Fig. 4. Polymer scaffold for local transplantation of neural stem and progenitor cells to replace lost tissue after stroke. Polymer chains can be functionalized with many compounds (fibronectin or laminin, neurotrophins and other trophic factors, chemoattractants, peptides) to control the proliferation of the cells contained within, drive preferential differentiation into neurons, enable neurite outgrowth and synaptogenesis, and improve overall functional integration (Table 4).

controls over 9 months of analysis. Trophic factors can also be combined with transplanted cells to improve cellular integration. Matsuse et al. demonstrated this with the delivery of NPC-like cells differentiated from MSCs (Dezawa et al. [172]) in a collagen sponge containing bFGF-releasing gelatin microspheres. Improved cell survival and proliferation, as well as angiogenesis induced by bFGF, was observed [159]. Ballios et al. also demonstrated a pro-survival effect in neural stem cells, where a hyaluronan/methylcellulose based hydrogel improved transplant survival through the CD44 cell surface receptor of hyaluronan [173]. In addition to physical cues and available trophic support, cell survival can also be influenced by the delivery procedure. Cells experience significant shear stress when injected through fine-gauge needles, which can be lessened with the use of shear-thinning hydrogels, improving the survival rate post-transplantation [5].

Natural hydrogels, such as Matrigel, which is derived from a mouse sarcoma and composed primarily of laminin-1 and collagen IV, have been shown to promote cell viability in vivo, though the xenobiotic origin of this particular gel leads to batch to batch variability and makes it inappropriate for clinical translation [174]. Other common naturally-derived materials used to develop more well-defined ECM-based hydrogels include HA, fibrin, and collagen. HA-based biomaterials enabled better iPSC-derived progenitor cell distribution and increased expression in culture of Doublecortin (DCX), a marker for neuronal precursors [175]. ESC-derived NSCs delivered with collagen 1 gel in combination with laminin contributed to better cell survival in comparison to the untreated group in a mouse model of traumatic brain injury [176]. Further, iPSC-NPCs transplanted via a fibrin glue reduced infarct volume and enhanced functional recovery in an adult stroke rat model [177].

7. Outlook and future directions

There have been encouraging results with the delivery of individual therapeutics in models of stroke; however, to achieve greater functional and tissue repair, combination strategies must be pursued. For example, sequential release of biomolecules that target repair modalities, such as synaptic plasticity or neurogenesis, at specific times may provide better outcomes. Limiting the extent of the damage and reducing the inflammatory response would result in a smaller lesion, thereby preserving more tissue and requiring less rewiring and regeneration. Targeting the glial scar and plasticity-inhibiting molecules while re-activating plastic pathways and providing exogenous cells could extend the therapeutic window.

Although there has been substantial evidence demonstrating the potential of BDNF as a therapeutic agent for stroke, combining the delivery of this factor with, for example, ChABC to degrade the glial scar may enhance its plastic action. With advanced biomaterials to locally deliver protein therapeutics and cells, a multi-faceted strategy is possible and promising for tissue and functional repair. Stimuli-responsive materials for nanoparticle and scaffold formulations could also build on current strategies by allowing the dynamic cues from the stroke lesion environment to dictate the timing of factor delivery. For example, the presence of reactive oxygen species could be used as a trigger for therapeutic release. Ultimately, it will likely be necessary to combine biomaterials-based therapeutic delivery strategies with rehabilitation therapy to achieve the desired changes in long-term patient outcomes. Experience-based synaptic growth and pruning are essential for producing meaningful connections, and thus essential for functional recovery.

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