Application of nanomaterials in the treatment of intracerebral hemorrhage

Xiangyu Zhang[1,2], Suliman Khan[1,2], Ruixue Wei[1,2], Yan Zhang[1,2], Yang Liu[1,2], Voon Wee Yong[3] and Mengzhou Xue[1,2] (iD)

Abstract

Intracerebral hemorrhage (ICH) is a non-traumatic hemorrhage caused by the rupture of blood vessels in the brain parenchyma, with an acute mortality rate of 30%–40%. Currently, available treatment options that include surgery are not promising, and new approaches are urgently needed. Nanotechnology offers new prospects in ICH because of its unique benefits. In this review, we summarize the applications of various nanomaterials in ICH. Nanomaterials not only enhance the therapeutic effects of drugs as delivery carriers but also contribute to several facets after ICH such as repressing detrimental neuroinflammation, resisting oxidative stress, reducing cell death, and improving functional deficits.

Keywords

Intracerebral hemorrhage, nanomaterials, nanomicelle, hydrogel

Introduction

Intracerebral hemorrhage (ICH) is caused by the spontaneous rupture of blood vessels in the brain, thereby leading to primary and secondary brain injury. Primary brain injury is a mass effect induced by hematoma formation and increased pressure on adjacent brain tissues. A series of metabolic reactions generated in response to the primary brain injury, such as hemolysis and thrombin activation, then lead to secondary brain injury.[1] Neuroinflammation and oxidative stress are involved in secondary brain injury after ICH,[2–4] and the extensive literature on these pathogenic mechanisms uncover new insights to counter the pathologic sequelae of ICH. At present, surgical or traditional treatments are still the main options,[5,6] broad pre-clinical studies have been completed,[7–9] and numerous researches are pouring in,[10–12] however, there is no widely recognized and effective method to ameliorate secondary brain injury[13] and improve the prognosis of ICH.[14] For example, applying hyperosmolar agents and external ventricular drain placement to cope with the decreased alertness caused by mass effect of ICH may be appropriate.[15,16] Recent clinical trial which used tissue plasminogen activator to resolve hemorrhagic products turned out to be unsatisfactory in prognosis.[17] Numerous clinical trials targeting correcting elevated blood pressure and reversing coagulopathy are still ongoing.[18–21]

In the past few decades, nanotechnology has emerged as an important class in medical research, where it impacts molecular imaging, drug delivery, cancer therapy, and other aspects.[22,23] Nanomedicine has attracted much attention as a safe and effective strategy because some materials possess special properties such as good biocompatibility, biodegradability, and low toxicity when they are modified into the nanoscale. Due to the multi-ligand valency, engineered nanomaterials offer other advantages such as long circulation time, crossing biological barriers, and enhanced targeting properties.[24] The different advantages of

[1]Department of Cerebrovascular Diseases, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China
[2]Academy of Medical Science, Zhengzhou University, Zhengzhou, Henan, China
[3]Hotchkiss Brain Institute and Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada

Corresponding authors:
Voon Wee Yong, Hotchkiss Brain Institute and Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada.
Email: vyong@ucalgary.ca

Mengzhou Xue, Department of Cerebrovascular Diseases, The Second Affiliated Hospital of Zhengzhou University, 2 Jingba Road, Zhengzhou, Henan 450001, China.
Email: xuemengzhou@zzu.edu.cn

nanomaterials are highly dependent on their features which vary broadly from shape, size, and composition, to the surface charge, hydrophilicity, conductivity, and rigidity.[25,26]

Nanomaterials, mainly nanoparticles (NPs), have the potential to be applied in preclinical studies and clinical trials. They have exerted advantages in the studies of several neurological diseases such as Parkinson's disease, Alzheimer's disease, and ischemic stroke.[27–29] Although access to the brain is often restricted for many drugs due to blood-brain barrier (BBB) and its selective transport of drugs,[30] nanomedicines improve the bioavailability, pharmacokinetics, blood circulation time and biological distribution of drugs into the central nervous system (CNS), and achieve the purpose of micro, high efficiency, stability and targeting compared to free drugs.[31,32] The rapid development of nanotechnology has made it possible to consider its prospects to improve the therapeutic efficacy of drugs in ICH.

Roles of nanomaterials in ICH treatment

Neuroprotection still represents a major therapeutic goal in ICH in order to prevent the progression of ICH-triggered damage in the brain parenchyma.[33] Unfortunately, most protective therapeutic approaches in animal research have been disappointing when they were translated into clinical trials, mainly because of the side effects of the drugs, low BBB permeability, or narrow therapeutic window.[34–36] The application of traditional medicines is often restricted by poor distribution and low selectivity. These problems may be solved by using nanotechnology,[37] which can conquer the main obstacles that hinder the implementation of neuroprotective approaches by transporting neurotherapeutic agents to the brain.[38] Multiple types of nanomaterials have been tested for delivering a variety of substances.[38,39] Nanomaterials have been regarded as suitable carriers for overcoming pharmacokinetic limitations associated with conventional drug formulations. Nanotechnology has been mentioned as an emerging therapeutic strategy targeting ICH.[40] In this review, we summarize some nanomaterials which appear to exert influence on brain injury mechanisms of ICH including inhibiting brain cell death, resisting oxidative damage (Table 1), repressing neuroinflammation, and promoting brain tissue repair and functional recovery (Table 2), eventually improving neurological impairment and prognosis of ICH.

Nanomaterials can improve the capacity of drugs to inhibit neuronal cell death

Drugs combined with nanomaterials can significantly reduce iron accumulation and ferroptosis. The blood components from hematoma after ICH including hemoglobin, heme, and free iron, have neurotoxic effects.[41,42] However, the iron chelating agent deferoxamine (DEF) is dose-limited in human ICH trials due to its drawbacks of poor cellular absorption, toxicity, and short shelf life. A broad action antioxidant, poly (ethylene glycol)-conjugated hydrophilic carbon clusters (PEG-HCCs), was incapable of ameliorating the dual toxic effects of heme and iron and decreasing the susceptibility to ferroptosis.[43] The DEF-HCC-PEG, a synthesized, catalytic, multifunctional, and rapidly internalized carbon nanomaterial formed by PEG-HCC, covalently bonds to DEF.[43] The synthesized DEF-HCC-PEG was significantly more effective than PEG-HCCs, free DEF treatment alone, or combined but worked as a single drug, in reducing heme and iron-mediated toxicity, inhibiting neuronal aging and ferroptosis in culture. This combination strategy effectively protected neurons from the toxicity of ICH hemolysis (Figure 1). Using nanomaterials can greatly enhance the effect and decrease the dosage of drugs, and the optimal proportion of DEF and PEG-HCCs should be considered.

Another iron chelator, minocycline, has been used to reduce ICH-induced brain edema, neuronal death, and neurological deficits.[44,45] However, there were some adverse issues in clinical trials.[46] Keratose hydrogel, a kind of hydrogel formed from keratose, could delay hemoglobin-induced iron accumulation in rat primary neuronal culture owing to its adsorptive capacity, while minocycline hydrochloride-loaded keratose hydrogel displayed a stronger and more thorough cytoprotective effect than blank hydrogel (Figure 1). In vivo, the minocycline hydrochloride-loaded keratose hydrogel effectively reduced ICH postoperative iron accumulation and edema, and improved functional recovery and survival rate in rats compared to the systemic administration of minocycline.[14]

Resveratrol, a widely used non-flavonoid polyphenol compound,[47] has neuroprotective roles in ICH.[48–51] However, its poor oral bioavailability and difficulty in crossing physiological barriers[52,53] limit its clinical application. NPs, as a commonly used drug delivery matrix material with good biocompatibility, can transport across physiological barriers and improve resveratrol accumulation in plasma and brain. Resveratrol-NPs safely and effectively attenuated the progression of ICH-induced brain injury by inhibiting ferroptosis[54] (Figure 1). In this condition, it can be considered to combine other agents which target necrosis or necroptosis, with nanomaterials, to investigate if they can effectively ameliorate the death of neurons post-ICH.

Using nanomaterials can remarkably reduce the neuronal cells apoptosis. Polybutylcyanoacrylate NPs have shown potential as an appropriate non-viral system for gene delivery,[55,56] and they are also efficacious vectors for delivering large molecules to the injured brain.[57] A delivery system comprising polybutylcyanoacrylate NPs of plasmid neurotrophin-3 containing hormone response element (HRE) with a cytomegalovirus (CMV) promoter was used to treat

Table 1. The strategies in targeted delivery of nanomedicines to inhibit cell death and resist oxidative stress after ICH.

Action	Nanomedicine and intervention strategy	Traits	Achievements	References
Inhibit cell death	Deferoxamine-HCC-PEG		Prevents heme and iron-mediated toxicity; reduces neuronal aging and ferroptosis	Dharmalingam et al.[43]
	Minocycline-loaded keratose hydrogel	Good biocompatibility, porous property; promising for bone regeneration and nerve repair	Reduces ICH postoperative iron accumulation, edema; improves functional recovery and survival rate in rats	Luo et al.[14]
	Resveratrol-NPs	Have good biocompatibility; can cross physiological barriers; improve drug accumulation within the plasma and brain	Attenuate the progression of ICH-induced brain injury by inhibiting ferroptosis	Mo et al.[54]
	Polybutylcyanocr-ylate NPs		Protect neurons against apoptosis	Chung et al.[58]
	Exosomes		Attenuate ferroptosis and neurologic injury; reduce neuronal apoptosis and inflammation	Yi and Tang,[62] Duan et al.[63]
Resist oxidative stress	Curcumin-nanoemulsions Quercetin-nanoemulsions	Low toxicity; control the release of selenium; ensure favorable effects and reduce potential toxicity	Increase total antioxidant capacity; modulate antioxidant responses; reduce the size of the hematoma; recover locomotor activity	Marques et al.[75] Galho et al.[76]
	Selenium-SiO2		Protects cells from ROS toxicity; alleviates brain edema; reduces BBB damage	Yang et al.[80]
	PEG-CeNPs		Reduces ROS level; improves the anatomical integrity of myelinated fibers; ameliorates white matter injury	Zheng et al.[83]
	RNPs	Extremely stable in vivo conditions; possess long blood circulation lifetimes	Minimize oxidative damage; decrease brain edema; decrease neurologic deficit	Krishna et al.[90]

BBB: blood-brain barrier; HCC: hydrophilic carbon cluster; NPs: nanoparticles; PEG: poly (ethylene glycol); RNPs: Redox polymer self-assembled nanoparticles; ROS: reactive oxygen species;.

ICH rats.[58] The results showed that polybutylcyanoacr-ylate NPs could raise the delivery of cmv-neurotrophin-3-HRE across the BBB in vivo, therefore increasing the expression of neurotrophin-3, and protecting neurons against apoptosis after ICH in vivo (Figure 1).

Exosomes are nanosized 30–100 nm diameter membranous vesicles released from diverse cell types, and they transfer biomolecules from one site to another. They are thought to play important functions in various biological pathways including cell-to-cell communication, tumor progression, and cellular waste disposal.[59] A large collection of recent research papers has revealed that exosomes released from various stem cells can improve multiple diseases,[60,61] including ICH. For example, exosomes derived from miR-19b-3p-overexpressing adipose-derived stem cells attenuated ICH-induced ferroptosis and neuronal injury.[62] MiR-146a-5p-enriched exosomes released from bone marrow mesenchymal stem cells elicited neuroprotection and functional improvement after ICH by reducing neuronal apoptosis and neuroinflammation asso-ciated with the suppression of microglial pro-inflammatory polarization[63] (Figure 1).

Nanomaterials can improve the ability of drugs to resist oxidative stress

Curcumin has been described to prevent or delay the onset of ischemic stroke and multiple CNS diseases.[64–70] Quercetin is known for its antioxidant activity and anti-inflammatory properties.[71,72] However, they both have low bioavailability in their natural states.[73,74] Nanoemulsions (NEs) are surfactant stabilized heterogeneous systems and their oil droplet sizes make them potential systems for improving drug delivery.[65] Studies have compared the possible therapeutic effect of these two free drugs versus their drug-loaded NEs in an ICH rat model.[75,76] The results showed that the formulations of curcumin-NEs and quercetin-NEs increased total antioxidant capacity in ICH than them alone. Both drug-loaded NEs reduced the size of the hematoma, recovered locomotor activity, and

Table 2. Strategies in targeted delivery of nanomedicines to repress inflammation and promote tissue repair and functional recovery after ICH.

Phase of cascade	Nanomedicine and intervention strategy	Traits	Achievements	References
Repress inflammation	Rosuvastatin nanomicelles	Good biocompatibility and nontoxicity	Inhibit the expression of downstream inflammatory factors; modulate the polarization of microglia/macrophages	Zi et al.[97]
	Gelatin hydrogel	Excellent biodegradability, biocompatibility, and target activity	Attenuate postoperative neurological deficits; reduce neuron loss; repress inflammation	Xu et al.[104]
Promote tissue repair and functional recovery	Gelatin-EGF-loaded hydrogel	Suitable for minimally invasive implantation	Fills irregularly shaped cavities; attracts cells for migration; improves recovery	Lim et al.[111]
	RADA16mix		Reduces acute brain injury; decreases inflammatory response; promotes functional recovery and nerve fiber growth	Zhang et al.[118]
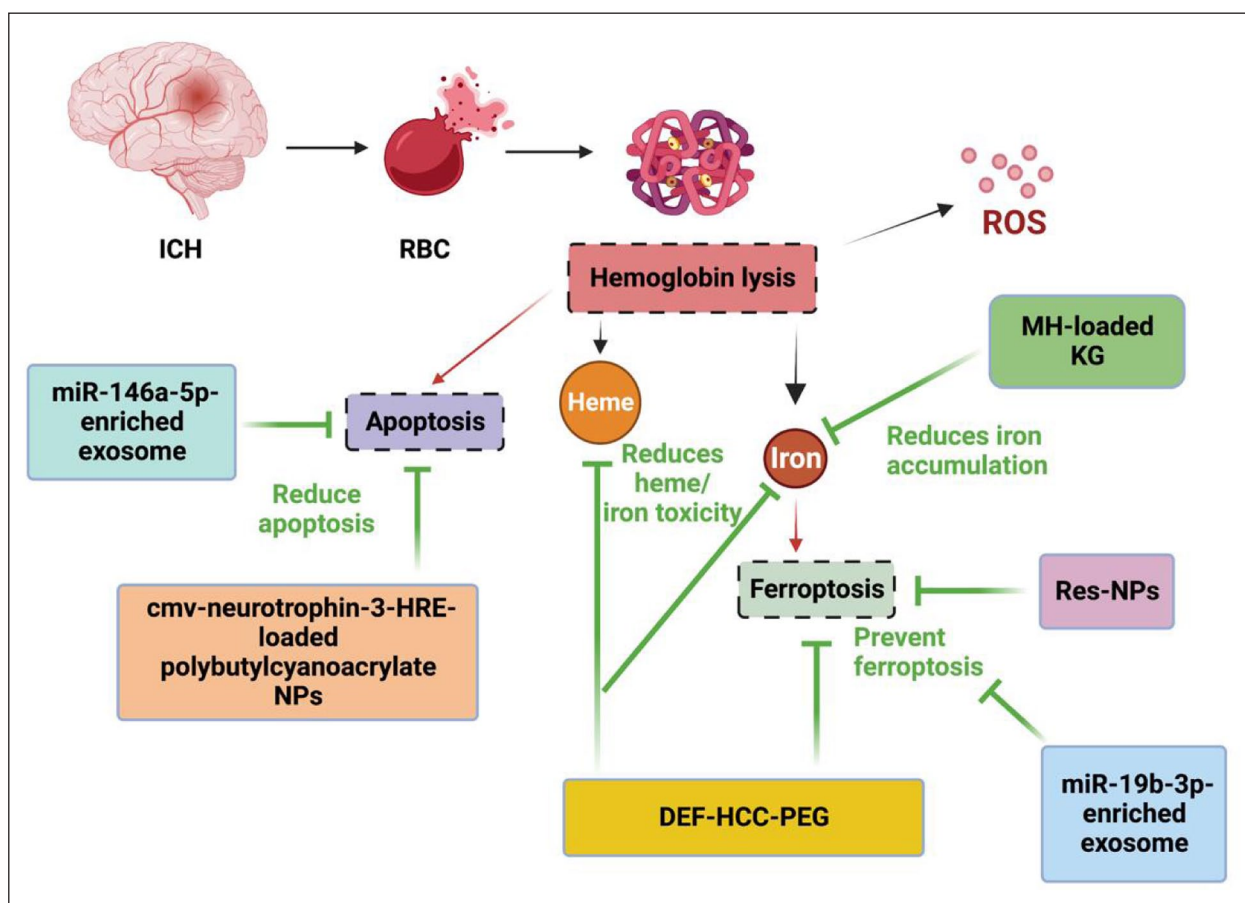
Figure 1. Model illustrating the effects of nanomedicine on the ferroptosis and apoptosis after ICH. Deferoxamine-HCC-PEG is a complex of the iron chelator deferoxamine and antioxidant PEG-HCC, which can effectively reduce heme/iron toxicity, and prevent senescence and ferroptosis. Minocycline-loaded keratose hydrogel can reduce iron accumulation, resveratrol-NPs and miR-19b-3p-enriched exosome can inhibit ferroptosis. miR-146a-5p-enriched exosome and cmv-neurotrophin-3-HRE-loaded polybutylcyanoacrylate NPs can reduce apoptosis following ICH.
cmv: cytomegalovirus; DEF: deferoxamine; HCC: hydrophilic carbon cluster; HRE: hormone response element; KG: keratose hydrogel; MH: minocycline hydrochloride; NPs: nanoparticles; PEG: poly (ethylene glycol); RBC: red blood cell; ROS: reactive oxygen species.

attenuated weight loss caused by ICH, without obvious toxic effects.[71]

Selenium is a cofactor of glutathione peroxidase and thioredoxin reductase, which are antioxidant enzymes that resist oxidative stress and maintain redox balance.[77] However, the use of selenium is restricted by the narrow gap between its beneficial and harmful effects.[78] The porous selenium-SiO_2 nanocomposites with an average diameter of about 55 nm[79] could control the release of selenium, ensure favorable effects and reduce potential toxicity.[80] After intraperitoneal injection into ICH mice, the activity of glutathione peroxidase was increased, while the level of malonaldehyde was significantly decreased. By protecting cells from reactive oxygen species (ROS) toxicity, alleviating brain edema and reducing BBB damage, the porous selenium-SiO_2 nanocomposites improved neurological functions of ICH mice.

Ceria NPs (CeNPs) are known to possess potent-free radical scavenging activity.[81,82] One study found that PEG-CeNP, which was formed by CeNPs with a PEG coating, strongly reduced ROS levels in the brain tissue. It also modulated ROS-induced microglial polarization and astrocyte alteration improved the anatomical integrity of myelinated fibers and ameliorated white matter injury after ICH.[83]

The nitroxide radical compound 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO) is one of the strongest antioxidants that catalytically scavenge ROS.[84,85] Under in vivo conditions, however, these low molecular weight nitroxide compounds have several problems, including nonspecific dispersion in normal tissues, preferential renal clearance and rapid reduction to the corresponding hydroxylamine form. Redox polymer self-assembled NPs (nitroxide radical-containing NPs [RNPs]) with diameters of approximately 40 nm were developed to solve these issues.[86] By contrast, RNPs are extremely stable in vivo and possess long blood circulation lifetimes.[87,88] Nitroxide radicals in RNPs have catalytic ROS scavenging activity including for superoxide and hydroxyl radicals,[89] which is superior to that of superoxide dismutase (SOD).[90] Systemic RNP treatment at an early stage after ICH decreased levels of superoxide anion radicals and minimized ICH-induced oxidative damage to other molecules in addition to DNA. RNPs also decreased acute ICH-induced brain edema and neurologic deficit, probably by decreasing the hemorrhagic area.

Nanomaterials can improve the capacity of drugs to repress neuroinflammation

Statins are considered as neuroprotective agents that can reduce microglia activation and differentiation in many CNS diseases including ICH.[91–93] Rosuvastatin is a synthetic, highly effective second-generation statin with poor water-solubility and low oral bioavailability.

Polymeric nanomicelles as self-assembled copolymers are good candidates for poorly water-soluble or hydrophobic drugs.[94–96] Rosuvastatin nanomicelles were prepared by cosolvent evaporation method using Poly (ethylene glycol)-poly (ε-caprolactone) (PEG-PCL) nanomicelles as nanocarrier[97] because of their good biocompatibility and nontoxicity.[98–100] The rosuvastatin nanomicelles employed in the treatment after ICH inhibited the expression of downstream inflammatory factors such as tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β), and promoted the polarization of microglia/macrophages toward a regulatory phenotype, effectively repressing neuroinflammation.[97]

Injectable hydrogels are particularly suitable for ischemic and hemorrhagic stroke owing to their advantages of minimally invasive implantation.[101,102] Hydrogels themselves can bind to specific cell-surface receptors of endogenous brain cells, inducing a variety of repair and anti-inflammatory cellular pathways. Gelatin is derived from denatured and partially degraded collagen. It has excellent biodegradability and biocompatibility, as well as adhesion to cells and lack of antigenicity, and can retain the cell adhesion motif of RGD.[103] There is an injectable hydrogel formed by Thiolated gelatin reacting with polyethylene glycol diacrylate. The in vivo experiment showed that the gelatin hydrogels interacted with different host cells, making it possible to attenuate postoperative neurological deficits, reduce neuronal loss, and repress the activation of astrocytes and microglia/macrophages. In addition, hydrogel injection reduced the release of inflammatory cytokines, IL-1β and TNF-α[104] (Figure 2).

Using nanomaterials can significantly promote brain tissue repair and functional recovery

Rebuilding the damaged CNS is a momentous goal for studies in neuroscience. Typical scaffolds are unsuitable in the damaged brain owing to massive manipulation of overlying tissues during implantation.[105,106] Moreover, the advances of exogenous stem cells are still limited by some practical and ethical hurdles.[107–110] In this light, injectable hydrogels are promising because they allow for a minimally invasive method that can eventually be compatible with current stereotactic procedures, as mentioned earlier.[101,102] An injectable gelatin hydrogel containing epidermal growth factor (gelatin-EGF) as a therapy for ICH was evaluated.[111] This result indicated that growth factor-containing biomaterials could be safely introduced into an ICH cavity to rebuild tissue and potentially improve recovery in ICH rats. On this basis, the best time to inject the biomaterial and how long it will take to take effect after ICH still need exploration. Diverse recovery pathway and factors are involved in CNS recovery,[112] and given the good practices in brain ischemia, such as injectable hydrogels containing brain-derived neurotrophic factor was
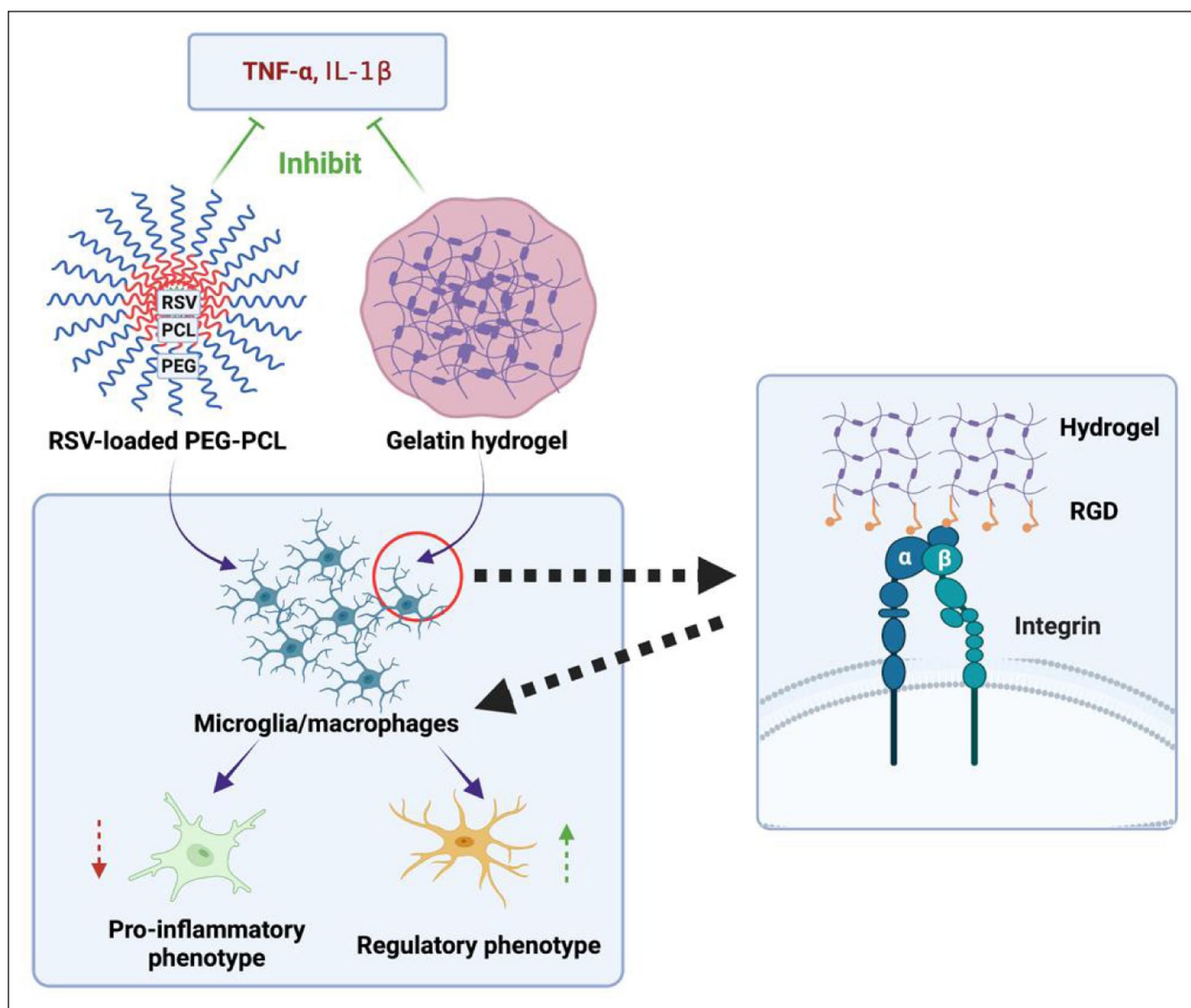
Figure 2. Schematic presentation of the effect of the injectable gelatin hydrogel and rosuvastatin nanomicelles on neuroinflammation after ICH. The implanted hydrogels bind to integrins on microglia/macrophages via cell adhesion RGD peptide, and then promote the regulatory phenotype polarization of the microglia/macrophages. Rosuvastatin-loaded PEG-PCL can also promote regulatory polarization.
PEG-PCL: Poly (ethylene glycol)-poly (ε-caprolactone); RGD: Arg-Gly-Asp.

deposited into the cavity to promote repair and recovery,[113–115] nanomaterials containing different growth factors or neuroprotective agents could be further studied.

A traditional self-assembly peptide nanofibrous (SAPNS) called RADA16-I, is frequently used in tissue engineering.[116] In an ICH model that incorporated stereotactic minimally invasive hematoma aspiration to provide space for local delivery of nanomaterials,[116] SAPNS served as a biocompatible material in the hemorrhagic brain cavity. It replaced the hematoma, reduced acute brain injury and brain cavity formation, and improved sensorimotor functional recovery.[117] With this ICH model, it has been found that RADA16-I could reduce acute brain injury and decrease the inflammatory response. In addition, a modified synthesized neutral SAPNS, which structure is RADA16-RGD (Arg-Gly-Asp), could overcome

the disadvantages of RADA16-I, including poor biocompatibility caused by its acidity, very fine functional recovery and even no nerve fibers to ICH mice.[117] Another self-assembly peptide nanofibrous scaffold, RADA16mix, reduced acute brain injury, decreased inflammatory response, and promoted functional recovery and nerve fiber growth.[118]

Potential applications of nanomaterials

The volume of hematoma is one of the most important predictors of functional outcome in ICH patients.[119] However, the clinical trials of hemostatic measures have turned out to be unsatisfactory. For example, intravenous administration of an activated recombinant factor VII did not improve

functional outcomes after ICH,[120] and platelet transfusion was detrimental in patients taking antiplatelet therapy before ICH.[121] Compared to cell-derived microparticles, such as thrombosomes and synthocytes, which are ineffective at reducing bleeding and increase the risk of adverse immunoreaction,[122] nano-engineered agents have efficiently improved hemostasis with fewer side effects.[123] These are promising to improve the progress of ICH. Various topical NPs have been developed,[124,125] but only a few have been tested in ICH. In this case, polymeric NPs are applied to stabilize the structure of some clot's components such as platelets or fibrin, and reduce bleeding time. Synthetic platelets, made of a poly (lactic-coglycolic acid)-poly-L-lysine block copolymer core with PEG arms terminated with RGD functionalities,[126] bind to activated platelets and favor platelet aggregation, thus reducing bleeding time in arterial injury models. Further optimized NPs, which is closer to endogenous platelets owing to deformability characteristics,[127] could better accumulate at the wound site and improve the hemostatic functions of natural platelets. A similar approach, intravenous administration of a hemostatic polymer (PolySTAT), enhanced fibrin crosslinking and prevented clot degradation because of multiple binding sites for fibrin, and therefore improving survival by reducing blood loss in the trauma model.[128] The efficacy of these treatments for limiting bleeding in ICH remains to be confirmed.[129]

In recent years, stem cell therapy has been a promising method for ICH treatment, aiming to replace the damaged neurons and therefore improve the functional recovery and prognosis post-ICH.[130] A magnetic resonance imaging (MRI)-visible PAsp (DMA)-Lys-(CA)2 polymer-based nanoscale polymeric micelle, has been used to deliver small interfering RNA/antisense oligonucleotides (siRNA/ASO) against Pnky long noncoding RNA (lncRNA) into neural stem cells. This multifunctional nanomedicine can direct stem cell differentiation in vivo and in vitro, as well as track the stem cells after transplantation in vivo in ischemic stroke.[131] If MRI-visible nanomaterials could be applied in ICH, it will be more targeted and more controllable for nanomaterials to play their roles and deliver therapeutic agents. Apart from delivering therapeutic genes into stem cells to regulate neuronal differentiation as vehicles, nanomaterials can exert their effects on stem cells in several ways as well. Nanomaterials can protect stem cells from a series of pathological processes such as inflammation,[132] and deliver growth-related factors to provide microenvironments for stem cells to survive and proliferate then form new tissue in the brain.[89,133] Furthermore, nano-sized exosomes released by stem cells can reduce neuronal death and improve neurological function on their own.[62,63] It is promising to develop nanomaterials-based stem cell therapies for ICH.

Based on the benefits of good biocompatibility, good targeting, and well-controlled drug release,[134] nanomaterials not only hold great prospects in treating primary and secondary injuries, but also in improving the neurological recovery after ICH. Meanwhile, many crossing strategies have combined nanotechnology with multiple substances such as cell-penetrating peptides, receptor, shuttle peptide, and cells to transport the therapeutic drugs through the BBB for improved precision of drug delivery, prolonged half-life, great stability, and increased drug loads.[135] In this condition, it is worthwhile to consider which nanomaterial to choose, whether nanomaterials need to be modified, and how to combine nanomaterials and agents when applied to ICH. More importantly, attention needs to be paid to whether the application of nanomaterials improves prognosis.

The concerns of nanomaterials

Toxicological analyses are essential before formulations or drugs are applying in clinical studies. The good news is that according to the pre-clinical experiments in ICH models, nanomaterials have not been found to cause renal or hepatic toxicity.[54,75] However, despite the many advantages and advances of nanotechnology to improve neuroprotection, potential side effects and the complex metabolic processes of nanomaterials may limit their applications in clinical practice. For example, NPs based on pure copper, silver, or aluminum, can impair endothelial cell function and increase BBB permeability in rodents.[136] These processes are regarded as adverse in ICH,[137] although they might promote drugs into the brain. Furthermore, NPs are more easily identified as pathogens by the host than small molecules, resulting in rapid clearance and response of the complement system.[138] In addition to immune reactions that could be triggered by contact with blood components, nanomedicines may damage organelles such as mitochondria, endoplasmic reticulum or lysosome of macrophages, leading to the release of excessive ROS and pro-inflammatory mediators.[139] Since the nucleus is also exposed, DNA may be damaged, so extensive monitoring for genotoxicity is required. All these reasons should be noted in the application of ICH treatment, therefore, further in-depth assessment of the risks associated with the use of nanomaterials is necessary.

Summary

ICH is an intractable disorder. The emergence of nanotechnology provides a promising option for treating ICH. Compared to free drugs, nanomaterials improve the capacity of agents to cross the BBB, prolong the half-life of drugs, reduce adverse effects, and enhance drug stability. Citations within this review highlight that nanomaterials can exert protective role after ICH. However, current intervention approaches based on nanomedicine are far from being clinical applications. Moreover, we should consider their side effects. The toxicity of nanomaterials should be thoroughly investigated before they are applied to patient treatment. Fortunately, the toxicity of nanomaterials has

received increasing attention, and more measures have been developed in the field of nanomedicine[140–142] to support their eventual clinical translation. Furthermore, the application of nanomaterials should be based on clear drug targets and pathways.

Based on a series of conservative treatments, our attention has been turned to some innovative therapeutics targeting ICH. Among all, nanotechnology is undoubtedly a very efficient and effective method. More and more novel and useful nanomaterials are being developed to treat ICH and this has brought hope in improving the prognosis of this often-fatal form of stroke.

Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

ORCID iD

Mengzhou Xue [iD] https://orcid.org/0000-0002-4427-7285

References

1. Hua Y, Keep RF, Hoff JT, et al. Brain injury after intracerebral hemorrhage: the role of thrombin and iron. *Stroke* 2007; 38: 759–762.
2. Zhang Y, Khan S, Liu Y, et al. Modes of brain cell death following intracerebral hemorrhage. *Front Cell Neurosci* 2022; 16: 799753.
3. Bai Q, Xue M and Yong VW. Microglia and macrophage phenotypes in intracerebral haemorrhage injury: therapeutic opportunities. *Brain* 2020; 143: 1297–1314.
4. Liu Y, Bai Q, Yong VW, et al. EMMPRIN promotes the expression of MMP-9 and exacerbates neurological dysfunction in a mouse model of intracerebral hemorrhage. *Neurochem Res* 2022; 47: 2383–2395.
5. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet* 2005; 365: 387–397.
6. Chen L, Chen T, Mao G, et al. Clinical neurorestorative therapeutic guideline for brainstem hemorrhage (2020 China version). *J Neurorestoratology* 2020; 8: 232–240.
7. Zhang Y, Zhang X, Yong VW, et al. Vildagliptin improves neurological function by inhibiting apoptosis and ferroptosis following intracerebral hemorrhage in mice. *Neurosci Lett* 2022; 776: 136579.
8. Liu Y, Li Z, Khan S, et al. Neuroprotection of minocycline by inhibition of extracellular matrix metalloproteinase inducer expression following intracerebral hemorrhage in mice. *Neurosci Lett* 2021; 764: 136297.
9. Li Z, Liu Y, Wei R, et al. The combination of deferoxamine and minocycline strengthens neuroprotective effect on acute intracerebral hemorrhage in rats. *Neurol Res* 2021; 43: 854–864.
10. Liu Y, Wang F, Li Z, et al. Neuroprotective effects of chlorogenic acid in a mouse model of intracerebral hemorrhage associated with reduced extracellular matrix metalloproteinase inducer. *Biomolecules* 2022; 12: 1020.
11. Wang F, Zhang X, Liu Y, et al. Neuroprotection by ozanimod following intracerebral hemorrhage in mice. *Front Mol Neurosci* 2022; 15: 927150.
12. Zhang X, Zhang Y, Wang F, et al. Necrosulfonamide alleviates acute brain injury of intracerebral hemorrhage via inhibiting inflammation and necroptosis. *Front Mol Neurosci* 2022; 15: 916249.
13. Bai Q, Sheng Z, Liu Y, et al. Intracerebral haemorrhage: from clinical settings to animal models. *Stroke Vasc Neurol* 2020; 5: 388–395.
14. Luo T, Guo T, Yang Q, et al. In situ hydrogels enhancing postoperative functional recovery by reducing iron overload after intracerebral haemorrhage. *Int J Pharm* 2017; 534:179–189.
15. Hemphill Jc, 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015; 46: 2032–2060.
16. Wagner I, Hauer EM, Staykov D, et al. Effects of continuous hypertonic saline infusion on perihemorrhagic edema evolution. *Stroke* 2011; 42: 1540–1545.
17. Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet* 2017; 389: 603–611.
18. Schrag M and Kirshner H. Management of intracerebral hemorrhage: JACC focus seminar. *J Am Coll Cardiol* 2020; 75: 1819–1831.
19. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *New Engl J Med* 2013; 368: 2355–2365.
20. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *New Engl J Med* 2016; 375: 1033–1043.
21. Rehmani R, Han A, Hassan J, et al. Role of prothrombin complex concentrate (PCC) in acute intracerebral hemorrhage with positive CTA spot sign: an institutional experience at a regional and state designated stroke center. *Emerg Radiol* 2017; 24: 241–247.
22. Shi J, Kantoff PW, Wooster R, et al. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer* 2017; 17: 20–37.
23. Lammers T, Aime S, Hennink WE, et al. Theranostic nanomedicine. *Account Chem Res* 2011; 44: 1029–1038.

24. Zhang W, Wang W, Yu DX, et al. Application of nanodiagnostics and nanotherapy to CNS diseases. *Nanomed* 2018; 13: 2341–2371.

25. Farokhzad OC and Langer R. Impact of nanotechnology on drug delivery. *ACS Nano* 2009; 3: 16–20.

26. Mishra D, Hubenak JR and Mathur AB. Nanoparticle systems as tools to improve drug delivery and therapeutic efficacy. *J Biomed Mater Res A* 2013; 101: 3646–3660.

27. Lu X, Zhang Y, Wang L, et al. Development of L-carnosine functionalized iron oxide nanoparticles loaded with dexamethasone for simultaneous therapeutic potential of blood brain barrier crossing and ischemic stroke treatment. *Drug Deliv* 2021; 28: 380–389.

28. Liu R, Yang J, Liu L, et al. An "Amyloid-β Cleaner" for the treatment of Alzheimer's disease by normalizing microglial dysfunction. *Adv Sci* 2020; 7: 1901555.

29. Kim D, Yoo JM, Hwang H, et al. Graphene quantum dots prevent α-synucleinopathy in Parkinson's disease. *Nat Nanotechnol* 2018; 13: 812–818.

30. Kaushik A, Jayant RD, Bhardwaj V, et al. Personalized nanomedicine for CNS diseases. *Drug Discov Today* 2018; 23: 1007–1015.

31. Blanco E, Shen H and Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat Biotechnol* 2015; 33: 941–951.

32. Weissleder R, Kelly K, Sun EY, et al. Cell-specific targeting of nanoparticles by multivalent attachment of small molecules. *Nat Biotechnol* 2005; 23: 1418–1423.

33. Lo EH. A new penumbra: transitioning from injury into repair after stroke. *Nat Med* 2008; 14: 497–500.

34. Braeuninger S and Kleinschnitz C. Rodent models of focal cerebral ischemia: procedural pitfalls and translational problems. *Exp Transl Stroke Med* 2009; 1: 8.

35. Paul S and Candelario-Jalil E. Emerging neuroprotective strategies for the treatment of ischemic stroke: an overview of clinical and preclinical studies. *Exp Neurol* 2021; 335: 113518.

36. Sacchetti ML. Is it time to definitely abandon neuroprotection in acute ischemic stroke? *Stroke* 2008; 39: 1659–1660.

37. Wei R, Xu Y and Xue M. Hollow iron oxide nanomaterials: synthesis, functionalization, and biomedical applications. *J Mater Chem B* 2021; 9: 1965–1979.

38. Ramos-Cabrer P and Campos F. Liposomes and nanotechnology in drug development: focus on neurological targets. *Int J Nanomed* 2013; 8: 951–960. 2013.

39. Da Silva-Candal A, Argibay B, Iglesias-Rey R, et al. Vectorized nanodelivery systems for ischemic stroke: a concept and a need. *J Nanobiotechnol* 2017; 15: 30.

40. Li Z, Khan S, Liu Y, et al. Therapeutic strategies for intracerebral hemorrhage. *Front Neurol* 2022; 13: 1032343.

41. Xi G, Keep RF and Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. *Lancet Neurol* 2006; 5: 53–63.

42. Cao JY and Dixon SJ. Mechanisms of ferroptosis. *Cell Mol Life Sci* 2016; 73: 2195–2209.

43. Dharmalingam P, Talakatta G, Mitra J, et al. Pervasive genomic damage in experimental intracerebral hemorrhage: Therapeutic Potential of a mechanistic-based carbon nanoparticle. *ACS Nano* 2020; 14: 2827–2846.

44. Wu H, Wu T, Xu X, et al. Iron toxicity in mice with collagenase-induced intracerebral hemorrhage. *J Cereb Blood Flow Metab* 2011; 31: 1243–1250.

45. Zhao F, Hua Y, He Y, et al. Minocycline-induced attenuation of iron overload and brain injury after experimental intracerebral hemorrhage. *Stroke* 2011; 42: 3587–3593.

46. Garton T, Keep RF, Hua Y, et al. Brain iron overload following intracranial haemorrhage. *Stroke Vasc Neurol* 2016; 1: 172–184.

47. Hou Y, Wang K, Wan W, et al. Resveratrol provides neuroprotection by regulating the JAK2/STAT3/PI3K/AKT/mTOR pathway after stroke in rats. *Genes Dis* 2018; 5: 245–255.

48. Bonsack F, Alleyne Ch, Jr and Sukumari-Ramesh S. Resveratrol attenuates neurodegeneration and improves neurological outcomes after intracerebral hemorrhage in mice. *Front Cell Neurosci* 2017; 11: 228.

49. Cai JC, Liu W, Lu F, et al. Resveratrol attenuates neurological deficit and neuroinflammation following intracerebral hemorrhage. *Exp Ther Med* 2018; 15: 4131–4138.

50. Zhao R, Zhao K, Su H, et al. Resveratrol ameliorates brain injury via the TGF-β-mediated ERK signaling pathway in a rat model of cerebral hemorrhage. *Exp Ther Med* 2019; 18: 3397–3404.

51. Abd Aziz NAW, Iezhitsa I, Agarwal R, et al. Neuroprotection by trans-resveratrol against collagenase-induced neurological and neurobehavioural deficits in rats involves adenosine A1 receptors. *Neurol Res* 2020; 42: 189–208.

52. Bano S, Ahmed F, Khan F, et al. Enhancement of the cancer inhibitory effect of the bioactive food component resveratrol by nanoparticle based delivery. *Food Funct* 2020; 11: 3213–3226.

53. Duarte AC, Rosado T, Costa AR, et al. The bitter taste receptor TAS2R14 regulates resveratrol transport across the human blood-cerebrospinal fluid barrier. *Biochem Pharmacol* 2020; 177: 113953.

54. Mo Y, Duan L, Yang Y, et al. Nanoparticles improved resveratrol brain delivery and its therapeutic efficacy against intracerebral hemorrhage. *Nanoscale* 2021; 13: 3827–3840.

55. Duan J, Zhang Y, Chen W, et al. Cationic polybutyl cyanoacrylate nanoparticles for DNA delivery. *J Biomed Biotechnol* 2009; 2009: 149254.

56. Baier G, Musyanovych A, Landfester K, et al. DNA amplification via polymerase chain reaction inside miniemulsion droplets with subsequent poly(n-butylcyanoacrylate) shell formation and delivery of polymeric capsules into mammalian cells. *Macromol Biosci* 2011; 11: 1099–1109.

57. Lin Y, Pan Y, Shi Y, et al. Delivery of large molecules via poly(butyl cyanoacrylate) nanoparticles into the injured rat brain. *Nanotechnol* 2012; 23: 165101.

58. Chung CY, Yang JT and Kuo YC. Polybutylcyanoacrylate nanoparticles for delivering hormone response element-conjugated neurotrophin-3 to the brain of intracerebral hemorrhagic rats. *Biomaterials* 2013; 34: 9717–9727.

59. Gurunathan S, Kang MH, Jeyaraj M, et al. Review of the isolation, characterization, biological function, and multifarious therapeutic approaches of exosomes. *Cells* 2019; 8: 307.

60. Xiao Y, Geng F, Wang G, et al. Bone marrow-derived mesenchymal stem cells-derived exosomes prevent oligodendrocyte apoptosis through exosomal miR-134 by targeting caspase-8. *J Cell Biochem* 2019; 120: 2109–2118.

61. Wang Y, Zhao R, Liu D, et al. Exosomes derived from miR-214-Enriched bone marrow-derived mesenchymal stem cells regulate oxidative damage in cardiac stem cells by targeting CaMKII. *Oxid Med Cell Longev* 2018; 2018: 4971261.

62. Yi X and Tang X. Exosomes from miR-19b-3p-Modified ADSCs inhibit ferroptosis in intracerebral hemorrhage mice. *Front Cell Dev Biol* 2021; 9: 661317.

63. Duan S, Wang F, Cao J, et al. Exosomes derived from MicroRNA-146a-5p-Enriched bone marrow mesenchymal stem cells alleviate intracerebral hemorrhage by inhibiting neuronal apoptosis and microglial M1 polarization. *Drug Des Devel Ther* 2020; 14: 3143–3158.

64. Wu A, Noble EE, Tyagi E, et al. Curcumin boosts DHA in the brain: Implications for the prevention of anxiety disorders. *Biochim Biophys Acta* 2015; 1852: 951–961.

65. Wang XS, Zhang ZR, Zhang MM, et al. Neuroprotective properties of curcumin in toxin-base animal models of Parkinson's disease: a systematic experiment literatures review. *BMC Complement Altern Med* 2017; 17: 412.

66. Bielak-Zmijewska A, Grabowska W, Ciolko A, et al. The role of curcumin in the modulation of Ageing. *Int J Mol Sci* 2019; 20: eng1010927911422.

67. Lopresti AL and Drummond PD. Efficacy of curcumin, and a saffron/curcumin combination for the treatment of major depression: a randomised, double-blind, placebo-controlled study. *J Affect Disord* 2017; 207: 188–196.

68. Tang M and Taghibiglou C. The mechanisms of action of curcumin in Alzheimer's disease. *J Alzheimers Dis* 2017; 58: 1003–1016.

69. Qureshi M, Al-Suhaimi EA, Wahid F, et al. Therapeutic potential of curcumin for multiple sclerosis. *Neurol Sci* 2018; 39: 207–214.

70. Chongtham A and Agrawal N. Curcumin modulates cell death and is protective in Huntington's disease model. *Sci Rep* 2016; 6: 18736.

71. Hädrich G, Vaz GR, Maidana M, et al. Anti-inflammatory effect and toxicology analysis of oral delivery quercetin nanosized emulsion in rats. *Pharm Res* 2016; 33: 983–993.

72. Lee J-C, Kim J, Park J-K, et al. The antioxidant, rather than prooxidant, activities of quercetin on normal cells: quercetin protects mouse thymocytes from glucose oxidase-mediated apoptosis. *Exp Cell Res* 2003; 291: 386–397.

73. Ma Z, Wang N, He H, et al. Pharmaceutical strategies of improving oral systemic bioavailability of curcumin for clinical application. *J Control Release* 2019; 316: 359–380.

74. Yousef MI, Omar SA, El-Guendi MI, et al. Potential protective effects of quercetin and curcumin on paracetamol-induced histological changes, oxidative stress, impaired liver and kidney functions and haematotoxicity in rat. *Food Chem Toxicol* 2010; 48: 3246–3261.

75. Marques MS, Cordeiro MF, Marinho MAG, et al. Curcumin-loaded nanoemulsion improves haemorrhagic stroke recovery in wistar rats. *Brain Res* 2020; 1746: 147007.

76. Galho AR, Cordeiro MF, Ribeiro SA, et al. Protective role of free and quercetin-loaded nanoemulsion against damage induced by intracerebral haemorrhage in rats. *Nanotechnol* 2016; 27: 175101.

77. Zachara BA. Selenium and selenium-dependent antioxidants in chronic kidney disease. *Adv Clin Chem* 2015; 68: 131–151.

78. Zhai X, Zhang C, Zhao G, et al. Antioxidant capacities of the selenium nanoparticles stabilized by chitosan. *J Nanobiotechnol* 2017; 15: 4.

79. Liu X, Deng G, Wang Y, et al. A novel and facile synthesis of porous SiO2-coated ultrasmall Se particles as a drug delivery nanoplatform for efficient synergistic treatment of cancer cells. *Nanoscale* 2016; 8: 8536–8541.

80. Yang Y, Deng G, Wang P, et al. A selenium nanocomposite protects the mouse brain from oxidative injury following intracerebral hemorrhage. *Int J Nanomedicine* 2021; 16: 775–788.

81. Bao Q, Hu P, Xu Y, et al. Simultaneous Blood-brain barrier crossing and protection for stroke treatment based on edaravone-loaded ceria nanoparticles. *ACS Nano* 2018; 12: 6794–6805.

82. Jeong HG, Cha BG, Kang DW, et al. Ceria nanoparticles synthesized with aminocaproic acid for the treatment of subarachnoid hemorrhage. *Stroke* 2018; 49: 3030–3038.

83. Zheng J, Lu J, Mei S, et al. Ceria nanoparticles ameliorate white matter injury after intracerebral hemorrhage: microglia-astrocyte involvement in remyelination. *J Neuroinflammation* 2021; 18: 43.

84. Hahn SM, Lepinski DL, DeLuca AM, et al. Neurophysiological consequences of nitroxide antioxidants. *Can J Physiol Pharmacol* 1995; 73: 399–403.

85. Samuni A, Krishna CM, Riesz P, et al. A novel metal-free low molecular weight superoxide dismutase mimic. *J Biol Chem* 1988; 263: 17921–17924.

86. Chonpathompikunlert P, Fan C-H, Ozaki Y, et al. Redox nanoparticle treatment protects against neurological deficit in focused ultrasoundinduced intracerebral hemorrhage. *Nanomed* 2012; 7: 1029–1043.

87. Maeda H, Wu J, Sawa T, et al. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *J Control Release* 2000; 65: 271–284.

88. Maeda H, Fang J, Inutsuka T, et al. Vascular permeability enhancement in solid tumor: various factors, mechanisms involved and its implications. *Int Immunopharmacol* 2003; 3: 319–328.

89. Chonpathompikunlert P, Yoshitomi T, Han J, et al. Chemical nanotherapy: nitroxyl radical-containing nanoparticle protects neuroblastoma SH-SY5Y cells from aβ-induced oxidative stress. *Ther Deliv* 2011; 2: 585–597.

90. Krishna MC, Russo A, Mitchell JB, et al. Do nitroxide antioxidants act as scavengers of O2-. Or as SOD mimics? *J Biol Chem* 1996; 271: 26026–26031.

91. Youssef S, Stüve O, Patarroyo JC, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. *Nature* 2002; 420: 78–84.

92. Cheng SM, Lai JH, Yang SP, et al. Modulation of human T cells signaling transduction by lovastatin. *Int J Cardiol* 2010; 140: 24–33.

93. Bagheri H, Ghasemi F, Barreto GE, et al. The effects of statins on microglial cells to protect against neurodegenerative disorders: a mechanistic review. *Biofactors* 2020; 46: 309–325.

94. Ding J, Chen J, Gao L, et al. Engineered nanomedicines with enhanced tumor penetration. *Nano Today* 2019; 29: 19.

95. Feng X, Xu W, Li Z, et al. Immunomodulatory nanosystems. *Adv Sci* 2019; 6: 1900101.

96. Han S, Huang K, Gu Z, et al. Tumor immune microenvironment modulation-based drug delivery strategies for cancer immunotherapy. *Nanoscale* 2020; 12: 413–436.

97. Zi L, Zhou W, Xu J, et al. Rosuvastatin nanomicelles target neuroinflammation and improve neurological deficit in a mouse model of intracerebral hemorrhage. *Int J Nanomed* 2021; 16: 2933–2947.

98. Wu C, Xu Q, Chen X, et al. Delivery luteolin with folacin-modified nanoparticle for glioma therapy. *Int J Nanomed* 2019; 14: 7515–7531.

99. Wang Y, Xie J, Ai Z, et al. Nobiletin-loaded micelles reduce ovariectomy-induced bone loss by suppressing osteoclastogenesis. *Int J Nanomed* 2019; 14: 7839–7849.

100. Yang L, Zhang Z, Hou J, et al. Targeted delivery of ginsenoside compound K using TPGS/PEG-PCL mixed micelles for effective treatment of lung cancer. *Int J Nanomed* 2017; 12: 7653–7667.

101. Dimatteo R, Darling NJ and Segura T. In situ forming injectable hydrogels for drug delivery and wound repair. *Adv Drug Deliv Rev* 2018; 127: 167–184.

102. Wang C, Feng N, Chang F, et al. Injectable cholesterol-enhanced stereocomplex polylactide thermogel loading chondrocytes for optimized cartilage regeneration. *Adv Healthc Mater* 2019; 8: e1900312.

103. Echave MC, Saenz del Burgo L, Pedraz JL, et al. Gelatin as biomaterial for tissue engineering. *Curr Pharm Des* 2017; 23: 3567–3584.

104. Xu J, Duan Z, Qi X, et al. Injectable gelatin hydrogel suppresses inflammation and enhances functional recovery in a mouse model of intracerebral hemorrhage. *Front Bioeng Biotechnol* 2020; 8: 785.

105. Deguchi K, Tsuru K, Hayashi T, et al. Implantation of a new porous gelatin-siloxane hybrid into a brain lesion as a potential scaffold for tissue regeneration. *J Cereb Blood Flow Metab* 2006; 26: 1263–1273.

106. Elias PZ and Spector M. Treatment of penetrating brain injury in a rat model using collagen scaffolds incorporating soluble Nogo receptor. *J Tissue Eng Regen Med* 2015; 9: 137–150.

107. Lam J, Lowry WE, Carmichael ST, et al. Delivery of iPS-NPCs to the stroke cavity within a hyaluronic acid matrix promotes the differentiation of transplanted cells. *Adv Funct Mater* 2014; 24: 7053–7062.

108. Borlongan CV. Preliminary reports of stereotaxic stem cell transplants in chronic stroke patients. *Mol Ther* 2016; 24: 1710–1711.

109. Zhong J, Chan A, Morad L, et al. Hydrogel matrix to support stem cell survival after brain transplantation in stroke. *Neurorehabil Neural Repair* 2010; 24: 636–644.

110. Steinberg GK, Kondziolka D, Wechsler LR, et al. Clinical outcomes of transplanted modified bone marrow-derived mesenchymal stem cells in stroke: a Phase 1/2a study. *Stroke* 2016; 47: 1817–1824.

111. Lim TC, Mandeville E, Weng D, et al. Hydrogel-based therapy for Brain Repair after intracerebral hemorrhage. *Transl Stroke Res* 2020; 11: 412–417.

112. Kokaia Z, Martino G, Schwartz M, et al. Cross-talk between neural stem cells and immune cells: the key to better brain repair? *Nat Neurosci* 2012; 15: 1078–1087.

113. Nih LR, Carmichael ST and Segura T. Hydrogels for brain repair after stroke: an emerging treatment option. *Curr Opin Biotechnol* 2016; 40: 155–163.

114. Lim TC, Rokkappanavar S, Toh WS, et al. Chemotactic recruitment of adult neural progenitor cells into multifunctional hydrogels providing sustained SDF-1α release and compatible structural support. *FASEB J* 2013; 27: 1023–1033.

115. Cook DJ, Nguyen C, Chun HN, et al. Hydrogel-delivered brain-derived neurotrophic factor promotes tissue repair and recovery after stroke. *J Cereb Blood Flow Metab* 2017; 37: 1030–1045.

116. Sang Y-H, Liang Y-X, Liu LG, et al. Rat model of intracerebral hemorrhage permitting hematoma aspiration plus intralesional injection. *Exp Anim* 2013; 62: 63–69.

117. Hua Sang LY. A self-assembling nanomaterial reduces acute brain injury and enhances functional recovery in a rat model of hypertensive intracerebral hemorrhage. *J Nanomed Nanotech* 2015; 05: 611–620.

118. Zhang N, Luo Y, He L, et al. A self-assembly peptide nanofibrous scaffold reduces inflammatory response and promotes functional recovery in a mouse model of intracerebral hemorrhage. *Nanomed* 2016; 12: 1205–1217.

119. Broderick JP, Brott TG, Duldner JE, et al. Volume of intracerebral hemorrhage A powerful and Easy-to-Use predictor of 30-Day mortality. *Stroke* 1993; 24: 987–993.

120. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *New Engl J Med* 2008; 358: 2127–2137.

121. Baharoglu MI, Cordonnier C, Salman RA-S, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet* 2016; 387: 2605–2613.

122. Shoffstall AJ, Atkins KT, Groynom RE, et al. Intravenous hemostatic nanoparticles increase survival following blunt trauma injury. *Biomacromolecules* 2012; 13: 3850–3857.

123. Hangge P, Stone J, Albadawi H, et al. Hemostasis and nanotechnology. *Cardiovasc Diagn Ther* 2017; 7: S267–S275.

124. Luo Z, Wang S and Zhang S. Fabrication of self-assembling D-form peptide nanofiber scaffold d-EAK16 for rapid hemostasis. *Biomaterials* 2011; 32: 2013–2020.

125. Gu BK, Park SJ, Kim MS, et al. Fabrication of sonicated chitosan nanofiber mat with enlarged porosity for use as hemostatic materials. *Carbohydr Polym* 2013; 97: 65–73.

126. Bertram JP, Williams CA, Robinson R, et al. Intravenous hemostat: nanotechnology to halt bleeding. *Sci Transl Med* 2009; 1: 11ra22.

127. Anselmo AC, Modery-Pawlowski CL, Menegatti S, et al. Platelet-like nanoparticles: mimicking shape, flexibility, and surface biology of platelets to target vascular injuries. *ACS Nano* 2014; 8: 11243–11253.

128. Chan LW, Wang X, Wei H, et al. A synthetic fibrin cross-linking polymer for modulating clot properties and inducing hemostasis. *Sci Transl Med* 2015; 7: 277ra29.

129. Bonnard T, Gauberti M, Martinez de Lizarrondo S, et al. Recent advances in nanomedicine for ischemic and hemorrhagic stroke. *Stroke* 2019; 50: 1318–1324.

130. Wei L, Wei ZZ, Jiang MQ, et al. Stem cell transplantation therapy for multifaceted therapeutic benefits after stroke. *Prog Neurobiol* 2017; 157: 49–78.

131. Lin B, Lu L, Wang Y, et al. Nanomedicine directs neuronal differentiation of neural stem cells via silencing long noncoding RNA for stroke therapy. *Nano Lett* 2021; 21: 806–815.

132. Ahmad A, Fauzia E, Kumar M, et al. Gelatin-coated polycaprolactone nanoparticle-mediated naringenin delivery rescue human mesenchymal stem cells from oxygen glucose deprivation-induced inflammatory stress. *ACS Biomater Sci Eng* 2019; 5: 683–695.

133. Liu Z, Yuan X, Fernandes G, et al. The combination of nano-calcium sulfate/platelet rich plasma gel scaffold with BMP2 gene-modified mesenchymal stem cells promotes bone regeneration in rat critical-sized calvarial defects. *Stem Cell Res Ther* 2017; 8: 122.

134. Torres FG, Troncoso OP, Pisani A, et al. Natural polysaccharide nanomaterials: an overview of their immunological properties. *Int J Mol Sci* 2019; 20: 5092.

135. Zhang Y, Guo P, Ma Z, et al. Combination of cell-penetrating peptides with nanomaterials for the potential therapeutics of central nervous system disorders: a review. *J Nanobiotechnol* 2021; 19: 255.

136. Sharma HS, Hussain S, Schlager J, et al. Influence of nanoparticles on blood-brain barrier permeability and brain edema formation in rats. *Acta Neurochir Suppl* 2010; 106: 359–364.

137. Tschoe C, Bushnell CD, Duncan PW, et al. Neuro-inflammation after intracerebral hemorrhage and potential therapeutic targets. *J Stroke* 2020; 22: 29–46.

138. Pallardy MJ, Turbica I and Biola-Vidamment A. Why the immune system should Be concerned by nanomaterials? *Front Immunol* 2017; 8: 544.

139. Alexander A, Agrawal M, Uddin A, et al. Recent expansions of novel strategies towards the drug targeting into the brain. *Int J Nanomed* 2019; 14: 5895–5909.

140. Croissant JG, Fatieiev Y and Khashab NM. Degradability and clearance of silicon, organosilica, silsesquioxane, silica mixed oxide, and mesoporous silica nanoparticles. *Adv Mater (Deerfield Beach, Fla.)* 2017; 29: 1604634.

141. Bonnard T, Jayapadman A, Putri JA, et al. Low-Fouling and biodegradable protein-based particles for thrombus imaging. *ACS Nano* 2018; 12: 6988–6996.

142. Luk BT and Zhang L. Cell membrane-camouflaged nanoparticles for drug delivery. *J Control Release* 2015; 220: 600–607.