The Polarization States of Microglia in TBI: A New Paradigm for Pharmacological Intervention

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Traumatic brain injury (TBI) is a serious medical and social problem worldwide. Because of the complex pathophysiological mechanisms of TBI, effective pharmacotherapy is still lacking. Thus, further elucidation of the pathophysiological mechanisms of TBI is warranted, and it could help to develop new targets of pharmacological intervention for TBI.

1. Introduction

Traumatic brain injury is a major health problem worldwide [1, 2]. The pathophysiological mechanisms of TBI are complex and unclear, and effective pharmacotherapies for TBI patients remain lacking. Thus, further elucidation of the pathophysiological mechanisms of TBI is warranted, and it could help to develop new targets of pharmacological intervention for TBI.

Neuroinflammation, which includes activation of local microglia and recruitment of other immune cells from the blood, as well as production of inflammatory cytokines, plays an important role in the pathophysiology of TBI [3]. On the one hand, neuroinflammation is detrimental and contributes to brain injury following TBI; on the other hand, neuroinflammation is necessary for the clearance of harmful substances, such as cell debris, after TBI [4]. Therefore, elucidation of the role and the underlying molecular mechanisms of neuroinflammation in TBI pathology is extremely vital for presenting potential new therapeutic targets for TBI.

The microglial cells are the resident macrophage cells of the brain [5], and they can activate rapidly in response to pathological changes in the central nervous system (CNS) [6, 7], for example, traumatic/ischemic brain injury or subarachnoid hemorrhage (SAH). In recent years, researchers have discovered two polarization states of microglial cells when they are activated, the M1 phenotype and the M2 phenotype [8–11], exactly like macrophages in nonneuronal tissues [12]. There is a large difference between the roles of the two phenotypes of activated microglial cells: the M1 phenotype is related to the release of several proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), while the M2 phenotype has been proved to be responsible for the release of anti-inflammatory cytokines, such as...
interleukin-10 (IL-10), and for neural regeneration processes, such as neurogenesis, angiogenesis, oligodendrogenesis, and remyelination [10]. Thus, how to alter the M1/M2 ratio to improve functional recovery after TBI has become a new pharmacological therapeutic direction in TBI. In this review, we aimed to summarize the current knowledge about the pathological significance of microglial M1/M2 polarization in the pathophysiology of TBI. In addition, we reviewed several drugs that have provided neuroprotective effects against brain injury following TBI by altering the polarization states of the microglia.

2. Microglial Phenotypes and Pathological Significance in TBI

In the parenchyma of the CNS, microglia constitute about 0.5% to 16.6% of all cells, especially in the white matter [13]. These microglial cells can remove cell debris and toxic substances, thus maintaining the homeostasis of the CNS. When insult occurs, the microglial cells activate rapidly, change their morphology into a motile “amoeboid” state, proliferate, and migrate into the damaged regions, and they release a variety of cytokines depending on the polarization states [14, 15]. Nowadays, there is a growing number of papers discussing the topic of phenotypes of microglia. The keyword “microglia phenotypes” return over 1,700 hits from PubMed in later 2016, and more than half of them were published in recent four years. Thus, exploring of the mechanisms for microglia/macrophage phenotype shift is becoming a meaningful topic.

Two distinct polarization states of the activated microglial cells have been discovered, the M1 phenotype and the M2 phenotype, depending on particular microenvironments [16]. The M1 phenotype microglia are induced by proinflammatory molecules, such as lipopolysaccharide (LPS) or interferon-gamma (IFN-γ). This phenotype closely matches the classical activation stage and secretes high levels of proinflammatory cytokines, such as IFN-γ, TNF-α, IL-1β, chemokines, and reactive oxygen species (ROS), which are essential for host defense [17]. They also secrete a low level of IL-10 [18]. The M2 phenotype microglia are subdivided into three subtypes: M2a, M2b, and M2c. Each of these subtypes has different trigger factors and phenotypic markers. The M2a subtype, which can be triggered by IL-4 and IL-13, is the first alternative activation stage of the microglia. It can act as an anti-inflammatory microglia subtype compared to M1 phenotype by competing for arginine, a nitrogen pool for the production of reactive nitrogen species during M1 phase [19]. The M2b subtype is a mixed activation state of microglia, it produces pro- and anti-inflammatory cytokines, such as TNF-α, IL-6, and IL-10, and it can be triggered by treating with LPS and IL-1β concurrently or with activated IgA complexes [19, 20]. The M2c subtype can be triggered by IL-10; it can shut down the immune response of the microglia [19], and it appears to play a role in tissue remodeling and matrix deposition [17] (Figure 1). The neuroprotective effects of M2 phenotype microglia have been well-studied, including the secretion of neurotrophic factors and anti-inflammatory cytokines and the clearance of cell debris through phagocytosis [10, 14]. Moreover, M2 microglia/macrophages have been found to play essential roles in driving oligodendrocyte differentiation toward the process of remyelination in the central nervous system, probably by contributing transforming growth factor-β (TGF-β) superfamily member activin-A to the remyelinating lesion environment [21].

Because different phenotypes of microglia appear and function in different phases, it is necessary to determine the time evolution of each subtype of microglial cells after TBI. However, this process has not yet been completely learned, and the experimental results have seemed different between in vitro and in vivo models. Several years ago in an in vitro experiment, researchers found that “acutely activated microglia” could reduce neural precursor cell survival and prevent neuronal differentiation, while “chronically activated microglia” could facilitate neural differentiation and cell survival [22]. Some experimental studies have supported that the “chronically activated microglia” seem to be M2 phenotype microglia and not M1. For example, there is an alteration in cytokine production. In a prolonged in vitro experiment, when exposed to LPS, the proinflammatory cytokines IL-1α/β, IL-6, and TNF-α secreted by microglia were strongly decreased, while the anti-inflammatory cytokine IL-10 and the immunomodulatory prostaglandin E2 (PGE2) increased greatly, indicating that the chronically activated M2 phenotype microglia might play a beneficial role in neuronal differentiation and cell survival [22]. In addition, in normal wound and spinal cord injury (SCI) healing, the M1 and M2a types seem to be the primary subtypes that start immediately after brain injury, and then they are gradually replaced by the M2b and M2c subtypes after 3 dpi (days after injury), indicating the start of the proliferation phase [23]. However, with in vivo TBI models, the findings have been different. Jin et al. [24] found that CD206 (+)/CD11b (+) M2 phenotype microglia were increased at 1 week after controlled cortical impact (CCI), whereas CD86 (+)/CD11b (+) M1 phenotype microglia were increased at 4 weeks. In a mouse model of TBI, transient M2 phenotype microglia were the initial phenotype of activated microglia in the acute stage of brain insult and peaked at 5 days after injury, but the M1 phenotype microglia remained elevated until at least 14 days [25]. Recently, another in vivo experiment demonstrated that the M2 phenotype microglia were upregulated transiently and then were replaced by M1 or a mixed transitional phenotype at 7 days after injury [26]. Actually, activated microglia could be observed in the injured cortex even 1 year after injury in a mouse CCI model, in association with lesion expansion and neurodegeneration [27]. The conflict of chronic microglial phenotypes between in vitro and in vivo models might be due to the complex signaling events surrounding microglial cells in vivo, and exploring the mechanisms underlying this phenomenon could help us to find new targets of pharmacological intervention in TBI. In humans, using the positron emission tomography (PET) ligand [11C(R)PK11195 (PK)], researchers demonstrated that increased microglial activation could persist for 17 years after TBI [28]. Another study of human brain samples after TBI found that the reactive microglia could exist for up to 18 years after trauma [29].
Although the phenotype of these microglia cells has not been clarified, these activated microglia indicate a chronic inflammatory response after brain injury.

In addition, it is important to know that this classification system only represents two major extreme types of activated microglia. Currently, this paradigm that simply divide the activated microglia into M1/M2 phenotypes has been challenged. Unlike the simple microenvironments in the in vitro experiments, the complex signaling events after tissue injury in vivo can lead the microglia/macrophage to a complex response or perhaps mixed phenotypes [30], which is consistent with previous studies focused on single-cell level. In mouse CCI model, microglia/macrophages could concurrently express both M1 and M2 phenotypic markers on the same cell in multiple time points [31]. This phenomenon has also been observed in other diseases such as multiple sclerosis [32] and cutaneous squamous cell carcinoma [33]. Also, the activated microglia population can change from an early “healthy” M2 phenotype into a “sick” M1 phenotype and exist for a very long time [24, 31, 34]. This point of view has changed our treatment concept of TBI and other brain insults in recent years. Therapies should no longer focus only on suppressing microglia/macrophenage activation, but they should pay greater attention to the ratio of M1/M2 phenotype of microglia to decrease the harmful effects of neuroinflammation [10, 14, 35].

### 3. Polarization States of Microglia in TBI: Potential Therapeutic Targets for Pharmacological Intervention

So far, many anti-inflammation drugs have been discovered to manage the neuroinflammation process after TBI. Although some of these drugs have shown neuroprotective effects in animal models, none have succeeded in clinical trials, perhaps due to the strict treatment time window and the heterogeneity of subtypes of TBI. Microglial cells are the target of many anti-inflammation strategies, and their phenotypes are of great significance in TBI treatment. As mentioned above, the dominant phenotype of activated microglia could shift from acutely activated M2 to chronically activated M1 after TBI [26]. This time dependent property of microglia activation indicates that M2 phenotype microglia may have more potential in clearing cell debris in the early stage of TBI, and M1 phenotype microglia may have relationship with chronic neuroinflammation [35]. So, anti-inflammation strategies that targeted whole microglia system might not be the best answer. An increasing number of studies trying to regulate the ratio of M1 and M2 phenotype microglia have already got promising effects after brain injury, which made the polarization states of microglia a new paradigm for pharmacological intervention. Strategies inhibiting the M1 phenotype and promoting the M2 phenotype of microglial
cells could alleviate cerebral cell damage and improve neurobiological function recovery in variety of brain injury animal models such as CCI [18, 36] and middle cerebral artery occlusion (MCAO) [37, 38]. These efforts pay more attention on later neurogenesis, which directly leads to better long-term prognosis. Thus, developing drugs that can modulate the immune system through altering the M1/M2 ratio is a promising pharmacological intervention in TBI treatment.

However, although the phenotypes and roles of microglia have been known for several years, many drugs with the effect of inhibiting microglial activation are still regarded as having the effect of anti-inflammation and many studies that have evaluated microglia activation only using pan-microglial markers such as Iba-1 or Cd11b [3]. In fact, total microglia activation inhibition cannot represent the anti-inflammation effect, and the therapeutic purpose is far more than anti-inflammation. In this section, we review several drugs that might provide neuroprotective effects after TBI by changing microglia polarization states, and we discuss the potential mechanisms underlying them. These mechanisms include enhanced Wnt/β-catenin signaling and JAK-STAT signaling, inhibition of TLR4-mediated signaling, and p38 MAPK-dependent PPARγ activation.

3.1. Minocycline. Minocycline is a second-generation tetracycline with a variety of nonantibiotic biological effects, such as neuroprotection in experimental models of TBI, ischemia, and neurodegenerative diseases [39]. The anti-inflammation effect is the most well-known advantage of the neuroprotective effects of minocycline. A series of studies have demonstrated that minocycline can inhibit microglial activation, using pan-microglial markers in TBI, SCI, SAH, and cerebral ischemia [40–45]. Although there is a large amount of data showing this anti-inflammatory effect is mostly mediated by microglia, the molecular targets still need to be discovered. One possible explanation is that minocycline may regulate microglial activation through inhibition of poly(ADP-ribose) polymerase (PARP), since minocycline contains an aromatic ring-linked carboxamide group just as other competitive PARP inhibitors [46], and PARP regulates the NF-κB driven transcription and microglia activation [47].

Despite the huge data of microglia inhibition effect, a few studies have demonstrated the function of minocycline in changing the M1/M2 ratios of microglial cells. Kobayashi and colleagues found that minocycline selectively inhibited M1 but not M2 microglia in a mouse amyotrophic lateral sclerosis (ALS) model and in primary cultured microglial cells [48]. Another study using minocycline-loaded nanoparticles in SCI drew a similar conclusion [49]. In a rat model of depression, chronic administration of minocycline decreased not only the expression of the pan-microglial marker CD11b but also the M1 proinflammatory cytokine IL-1β in sham spinal nerve ligation (SNL) animals. The expression of the M2 microglia marker MRC2 and of IL-10 and IL-1β was increased in the prefrontal cortex of olfactory bulbectomized-SNL rats, which indicated that chronic minocycline administration had an effect on altering M1/M2 microglia markers [50]. Recently, in a cerebral ischemia model, researchers discovered that treatment with minocycline could significantly decrease the levels of TNF-α and IL-1β and increase the levels of TGF-β, IL-10, and YMI [51]. These results indicated that minocycline might also have the alternate effect of microglia/macrophage activation in TBI, and further research must be undertaken to discover it.

3.2. Etanercept. Etanercept is a biologic TNF antagonist, and it has been proved to have anti-inflammatory effects by inhibiting brain TNF-α [15]. Considering its molecular weight, it is too large to pass the blood-brain barrier (BBB); therefore, it cannot reach therapeutic concentrations in the cerebrospinal fluid in theory [52]. However, experiments have confirmed that etanercept can penetrate into contused brain tissues for unknown reasons and can play a neuroprotective role in a series of diseases, such as TBI [53, 54], SCI [55, 56], and ischemic brain injury [57, 58]. The functions of etanercept in TBI are not only to inhibit microglial activation [15] but also to reduce early overexpression of TNF-α in microglia [54] and to stimulate the newly formed neurogenesis [53]. Thus, etanercept can attenuate the effects of M1 phenotype microglia and can have neural regeneration effects, like M2 phenotype microglia [18]. These experiments showed the potential effects of etanercept in altering the M1/M2 ratio and promoting neural regeneration. Furthermore, treatment with perispinal etanercept of chronic stroke and TBI patients could produce clinical improvement, even a decade later [59]. The therapeutic efficacy of etanercept in TBI is worth studying.

3.3. Statins. Statins, known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are well known for the effects of lowering serum cholesterol level and decreasing the risk of cardiovascular events [60]. Despite their cholesterol-lowering function, the anti-inflammatory effects of statins have gained recognition in recent years. Because of their pleiotropy, statins have been used in the management of ischemic stroke [61], neurodegenerative diseases [62, 63], and even chronic subdural hematoma [64]. In TBI management, simvastatin has the effects of attenuating microglia and astrocyte activation, decreasing proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [65], suppressing neuronal cell apoptosis [66], and inducing angiogenesis [67]. Although the microglia inhibition effects of statins have been proved, the mechanisms are still in exploration. In cultured microglia cells, rosuvastatin strongly inhibited microglia proliferation and adhesion and additionally increased the expression of several anti-inflammatory genes such as Ccl2 and Cxcl1, which were implicated in microglia recruitment [68]. Another in vivo study suggests that simvastatin can exert analgesic effects by attenuating spinal microglial activation through interruption of microglial RhoA translocation and p38 MAPK activation [69].

To our knowledge, there has been no direct evidence of statins altering the M1/M2 ratio of microglia, but some studies have suggested a positive answer. In an in vitro experiment, simvastatin could play an anti-inflammation role by enhancing the switching of the M1 macrophage phenotype to the M2 macrophage phenotype [70]. Atorvastatin also has shown similar effects in myocardial infarction [71] and
might promote circulating monocyte differentiation into M2 phenotype macrophages via p38 MAPK-dependent PPARγ activation [72]. The effects of statins on microglial activation and differentiation in TBI deserve further research.

3.4. Resveratrol. Resveratrol, a stilbene formed in many edible plants as a reaction to fungal infection, has been proved effective in cancer, heart diseases, and a series of nervous system disorders in vitro and in vivo [73,74], also including ischemic stroke [74,75], neurodegenerative diseases [76], TBI [74,77], and SAH [78]. There are many potential pathways for the neuroprotective effects of resveratrol, such as activation of the silent mating type information regulation 2 homolog 1 (SIR2T), AMP-activated kinase (AMPK), nuclear factor erythroid 2 (Nrf2) pathways [74], and inhibition of the NF-κB, ERK, and JNK/MAPK pathways [79,80]. The inhibition of the microglial activation of resveratrol occurs not only in TBI models [81] but also in other in vitro and in vivo models [82–84], possibly by activating an SOCS-1-mediated signaling pathway [85], and it might be associated with neurogenesis [86]. As a natural modulator of microglial activity, resveratrol has the ability to counteract the excessive response of activated M1 microglia [87]. In a BV2 microglia cell line of hypoxia injury model, resveratrol suppressed the mRNA expression of TNF-α and promoted the mRNA expression of IL-10 [88], suggesting its ability to change microglia phenotypes. Another experiment using LPS-stimulated microglia drew the same conclusion, and the JAK-STAT signaling pathway might be involved in this process [89]. Hence, the prospective value of resveratrol in TBI is worth being studied further.

3.5. MGluR5 Agonist and Positive Allosteric Modulator. In recent years, the metabotropic glutamate receptor 5 (mGluR5) selective agonist (RS)-2-chloro-5-hydroxyphenylglycine (CHPG) and the positive allosteric modulator (PAM) VU0360172 have attracted increasing attention in the treatment of various brain insults. Both CHPG and VU0360172 could significantly reduce the numbers of activated microglia and improve neurological function in a rat endovascular perforation model of SAH [90]. CHPG could limit neuroinflammation and improve functional recovery even a month later after TBI [91,92], and it significantly decreased the levels of proinflammatory cytokines and increased the expression of anti-inflammatory cytokines after SO2 treatment in BV2 microglial cells [93]. This anti-inflammatory effect might be mediated by G-protein signal transduction pathway, including activation of the phospholipase C-protein kinase C signal transduction system [94]. However, because of the weak potency and brain permeability of CHPG, researchers have found another more efficient mGluR5 PAM, VU0360172, and its ability to shift the M1/M2 microglial activation balance towards an M2 phenotype in vivo and in vitro has been shown [95]. An increasing number of studies have reported the protective effects of mGluR5 agonists and PAMs, making this young drug class a promising agent in TBI therapy.

3.6. Gp91ds-tat. Gp91ds-tat is a selective nicotinamide adenine dinucleotide phosphate oxidase (NOX-2) inhibitor. The neuroprotective effect of gp91ds-tat was first discovered in cerebrovascular dysregulation associated with increasing age [96,97]. A more recent study showed that gp91ds-tat could significantly improve functional recovery and reduce inflammation in an SCI model, accompanied by a reduction in M1 microglia phenotype markers [98]. It seems alterations in microglia polarization and NOX activity could influence each other [98–100]. In a mouse CCI model, gp91ds-tat significantly reduced neuron damage and edema [101], and delayed gp91ds-tat treatment (24 h post injury) could alter the M1/M2 balance to the anti-inflammatory M2 phenotype, reducing oxidative damage in neurons and cognitive function deficits [26,102]. Therefore, gp91ds-tat could have promising therapeutic effects in TBI treatment.

3.7. Rosiglitazone. As a peroxisome-proliferator-activated receptor- (PPAR-) γ agonist, rosiglitazone is not only an antidiabetic drug but also a neuroprotective agent, and it has shown various effects in treating brain ischemia [103], TBI [104], and SAH [105]. A study demonstrated rosiglitazone’s ability to attenuate microglia/macrophage activation and neuronal loss after TBI [104]. In mouse models of focal cerebral ischemia and progressive Parkinson’s disease, rosiglitazone showed the ability to promote microglial M2 polarization [103,106]. Another PPAR-γ agonist pioglitazone has also been reported to decrease the M1/M2 ratio in experimental Alzheimer’s disease [107], but the relationship between PPAR-γ agonists and microglia phenotype switching is still not clear. Since studies about rosiglitazone’s function in microglia have been very limited, the effects of rosiglitazone in TBI still require exploration.

3.8. Azithromycin. Many macrolide antibiotics might have neuroprotective effects. Among them, azithromycin is an extraordinary drug with the effect of reducing infarct volume, decreasing brain edema, and increasing neurological deficit scores in acute ischemic damage [108]. Additionally, azithromycin had the effect of altering the macrophage phenotype from proinflammatory M1 to alternatively activated M2 cells [109,110], probably by inhibition of TLR4-mediated signaling [111] or activation of activator protein-1 and impairment of lysosomal functions [112]. This effect was observed not only in chronic obstructive pulmonary disease [110] but also in ischemic brain injury [113] and spinal cord injury [114] at a dose of approximately 150 mg/kg. Whether it will be effective in altering microglia phenotypes in TBI treatment remains to be determined.

3.9. Alpha-7 Nicotinic Acetylcholine Receptor Agonists. TBI-induced deficits in alpha-7 nicotinic acetylcholine receptor (nAChR) expression were found to play a role in cognitive impairment as early as 2003 [115]. In recent years, nAChR has been receiving attention again. α-7 nAChR agonist, PNU-282987, could attenuate early brain injury in SAH rats [116] and could reduce peripheral inflammation and BBB disruption in TBI mice [117]. Another α-7 nAChR agonist, PHA568487, could attenuate neuroinflammation, oxidative stress, and brain injury in stroke and bone fracture.
mice, probably by decreasing the number of M1 phenotype microglia/macrophages and by increasing M2 phenotype microglia/macrophages [118, 119]. Future experiments are needed to determine whether such drugs also have the same effects in TBI.

3.10. Interleukin-1 Receptor Antagonist. Interleukin-1 receptor antagonist (IL1ra) is a competitive antagonist of the interleukin-1 type-1 receptor (IL-1R). Researchers identified the effects of IL1ra in improving recovery and delayed cytokine induction in ischemic brain injury and TBI a dozen years ago [120, 121]. Several experiments on IL-1β antibody in TBI have shown similar conclusions [122, 123]. In 2014, a phase II, randomized, controlled trial of recombinant human IL1ra in severe TBI reported promising data using this agent in the modification of neuroinflammatory response [124]. Recently, using Partial Least Squares Discriminant Analysis, researchers have found a “counterintuitive” effect of rhIL1ra on microglia, namely, that rhIL1ra treatment could increase microglial activation following severe TBI and could bias the microglial responses to the M1 phenotype but not the M2 phenotype following human TBI [125]. This result has caused us to rethink the theory of dividing cytokines into “pro-” and “anti-” inflammatory subtypes simplistically in brain insults such as TBI.

3.11. Cell Therapy. Cell therapy has been proved to be effective in many kinds of brain injury, including TBI [126]. Nowadays researchers have found that the neuroprotective mechanism of cell therapy is limited to not only neuronal replacement, but also immunomodulation. Mosher et al. showed that transplanted neural progenitor cells (NPCs) could secrete a variety of signaling proteins which have the capacity to modulate microglia functions and activity [127]. Liu et al. described that NPCs and microglia could be significantly affected by each other’s presence in an allogeneic coculture model, and NPCs might have the ability of regulating the phagocytic activity of microglia [128]. These results have led to several recent studies about cell therapy’s effect in mediating the microglial/macrophage phenotypes after TBI. For example, intravenous delivery of multipotent adult progenitor cells (MAPC) and intracerebral injection of human neural stem cells (NSCs) after experimental TBI can both demonstrate a decrease in M1/M2 ratio [129, 130]. Thus, modulation of M1/M2 ratio through cell therapy could be one of the therapeutic methods after TBI.

4. Conclusion

So far, there is still no management providing a strong benefit in TBI, so it is important to find therapeutic drugs with promising new mechanisms after brain damage. The neuroinflammation process, which could serve a dual function, is of great importance after TBI. Different phenotypes of activated microglial cells could play different roles in the neuroinflammation process, so finding new drugs that can alter the M1/M2 ratio of activated microglial cells could be a promising approach to decrease neuroinflammation damage and to improve outcomes. In this review, we summarized the current knowledge about the pathological significance of microglial M1/M2 polarization in the pathophysiology of TBI, and we listed several drugs with neuroprotective effects against TBI by altering the polarization states of microglial cells.

However, some limitations in the current research should be noticed. First, the methods for evaluating the effects of drugs on microglial cells must keep up with the pace; simply inhibiting the activation of microglial cells cannot replace anti-inflammation and neuroprotection. Second, the appearing time periods of the subtypes of microglial cells and the changes in the microenvironment surrounding these cells after TBI must be more deeply explored to discover the best therapeutic time window for the aforementioned drugs. Third, most of the current experiments in pharmacological intervention have focused on the phenomenon of microglial phenotype changes, while studies of mechanisms have been fewer. Future investigations should focus on the regulation mechanisms of microglial M1/M2 polarization and develop new targets of pharmacological intervention in TBI, thus providing new hope for TBI management.

Competing Interests

The authors have no conflict of interests to disclose.

Authors’ Contributions

Hangzhe Xu and Zhijiang Wang contributed equally to this work.

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