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REVIEW PAPER

Research Advances of Germinal Matrix Hemorrhage: An Update Review

Jinqi Luo[1] · Yujie Luo[1] · Hanhai Zeng[2] · Cesar Reis[3] · Sheng Chen[1,4]

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Abstract

Germinal matrix hemorrhage (GMH) refers to bleeding that derives from the subependymal (or periventricular) germinal region of the premature brain. GMH can induce severe and irreversible damage attributing to the vulnerable structure of germinal matrix and deleterious circumstances. Molecular mechanisms remain obscure so far. In this review, we summarized the newest preclinical discoveries recent years about GMH to distill a deeper understanding of the neuropathology, and then discuss the potential diagnostic or therapeutic targets among these pathways. GMH studies mostly in recent 5 years were sorted out and the authors generalized the newest discoveries and ideas into four parts of this essay. Intrinsic fragile structure of preterm germinal matrix is the fundamental cause leading to GMH. Many molecules have been found effective in the pathophysiological courses. Some of these molecules like minocycline are suggested active to reduce the damage in animal GMH model. However, researchers are still trying to find efficient diagnostic methods and remedies that are available in preterm infants to rehabilitate or cure the sequent injury. Merits have been obtained in the last several years on molecular pathways of GMH, but more work is required to further unravel the whole pathophysiology.

Keywords Germinal matrix hemorrhage · Preterm infant · Neuropathology

Introduction

Germinal matrix hemorrhage (GMH) occurs in the subependymal (or periventricular) germinal region of the premature brain (Fig. 1), and sometimes develops into intraventricular hemorrhage (IVH). It is very common in preterm infants, the incidence of which is usually disproportionate to the gestational age of premature (Hefti et al. 2016; Supramaniam et al. 2013). About 20–30% infants born with very low weight (birth weight < 1500 g) or gestational age < 28 weeks suffer GM-IVH (Coen 2013; Haines et al. 2013; de Bijl-Marcus et al. 2017). Occurrence of GM-IVH is highly related to the gestational age and birth weight, and it is in the first 4 days that GM-IVH typically occurs in immature infants (Itsiakos et al. 2016; Okazaki et al. 2013). Intrauterine demise is frequent in fetus with GMH (Sanapo et al. 2017). The mortality of infants with GM-IVH has dropped thanks to the development of diagnostic techniques and intensive care in recent decade, but it still induces severe and permanent damage on premature brain, leading to hydrocephalus, cerebral palsy, seizures, hemiplegia, learning disabilities, and so on (Haines et al. 2013; Vesoulis and Mathur 2017; Sheehan et al. 2017; Movsas et al. 2013; Hefti et al. 2016; Payne et al. 2013). Recent discoveries even indicate the decreased development of cerebellum, and the developmental retardation of preterm neonates is proportional to the grade of GM-IVH (Lee et al. 2016).

Researchers notice the tendency of getting injured during 22–36 weeks of gestation when the developing course start maximizing, accounting for a lot of neonatal neural disorders that develop in this specific gestation stage (Huang and Vasung 2014; Zhan et al. 2013). Attributing to the vulnerable structure, germinal matrix is highly exposed to insults

✉ Sheng Chen
saintchan@zju.edu.cn

1 Department of Neurosurgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, No. 88 Jiefang Rd, Hangzhou 310009, Zhejiang, China

2 Department of Neurological Surgery, The Children's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

3 Department of Physiology and Pharmacology, Loma Linda University, Loma Linda, CA, USA

4 Department of Neurosurgery, Taizhou Hospital, Wenzhou Medical University, Linhai, Zhejiang, China

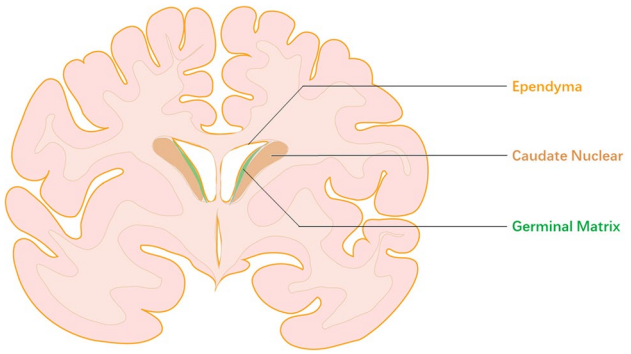

Fig. 1 The periventricular anatomy. The germinal matrix is a thin layer of gray matter (in green color) which locates just beneath the ependyma, which is full of matrix cells and immature vasculature

such as hypoxia, hypocarbia, systemic or partial circulatory dysfunction, and electrolyte disturbances (Baburamani et al. 2012; Waitz et al. 2016). Moreover, maternal disorders, fetal disorders, and poisons during perinatology, such as maternal infection, drugs abuse, smoking, inherent diseases, lead to a higher risk that premature fetal suffer GM-IVH (Xiaoyu 2015).

Even if rescued from fatality, premature infants who suffered GM-IVH could inevitably have neural disabilities because these early injuries damage the functional area as well as interrupt normal maturation of nervous system (Panigrahy et al. 2012; Hinojosa-Rodriguez et al. 2017). Given the special condition of neonates, it is much of difficulty to precisely identify GM-IVH from limited clinical features, and thus paramount attention is laid on diagnostic technics, especially radiology and ultrasonography. Based on various clinical backgrounds and conditions of individual infants born immature, pediatrists grade these infants into 4 levels according to the extent of periventricular hemorrhage (Fig. 2). CT provides us a rapid acknowledgement of severe lesions. MRI provides much more details to quantify and grade the hemorrhage as well as confirm the lesion of ventricles and brain parenchyma, such as hydrocephalus and leukomalacia. Even transcranial ultrasonography (TUS) shows unsatisfactory sensitivity of diagnosing low-grade GMH in a few cases, it is increasingly efficient and convenient to detect intracranial lesions (Parodi et al. 2015) (Fig. 3). Color Doppler ultrasonography enjoys the advantages of sensitivity when it comes to congenital vascular disease (Vesoulis and Mathur 2017). Automated assessment of electroencephalography (EEG) developed by Iyer and the teammates is probable to detect GMH bedsides earlier and more sensible to some extent (Iyer et al. 2015).

Nowadays survival of premature infant has increased a lot attributing to developing neonatal intensive therapeutic methods, but preterm-associated sequelae persist and become chronic problems to these little patients. Because of the difficulty in identically simulating the course of GM-IVH by proper animal model, what we understand so far is still unsatisfactory despite the long-term hard work of predecessors. More efficient diagnosis and therapies are needed to cure these patients.

Based on cellular experiments, there are several theories and pathways where some confirmed molecules work and will possibly become the therapeutic targets. In this paper, we attempt to review pathological and molecular developments of GM-IVH so far and introduce some newest discoveries about the mechanisms and have a prospect of potential treatments.

Pathological Anatomy: Fragilities of Germinal Matrix

Due to the fragility of brain tissue and immature respiratory function, preterm infants are highly exposed to brain injury caused by premature delivery even if they do not suffer GM-IVH (Gao et al. 2015). What is more, germinal matrix is a highly cellular and highly vascularized structure beneath ependymal (or periventricular) germinal region in the brain where cells migrate out during brain development. The proliferation and differentiation of neurons with specific

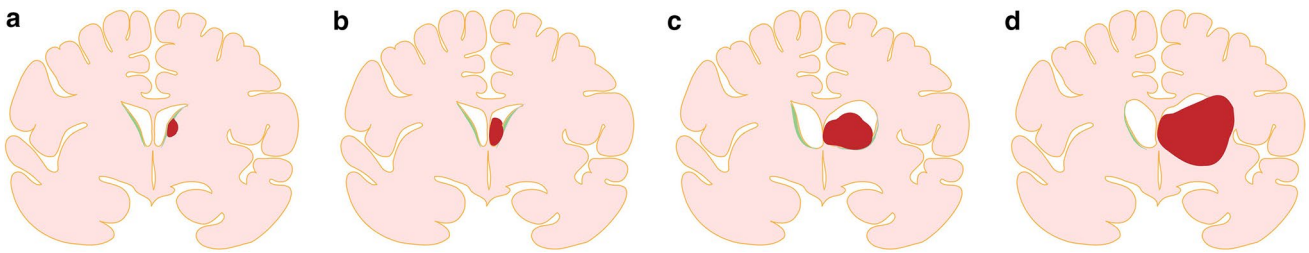

Fig. 2 Series of GM-IVH of different grades. **a** Grade I: the hematoma is limited inside the germinal matrix, or sometimes occurs within caudate nuclei. **b** Grade II: the bleeding bursts into ipsilateral ventricle with smooth CSF flowing course. **c** Grade III: hemorrhage of Grade II plus hydrocephalus. **d** Grade IV: hematoma breaks into parenchyma and causes intraparenchymal hemorrhage with or without intraventricular hemorrhage

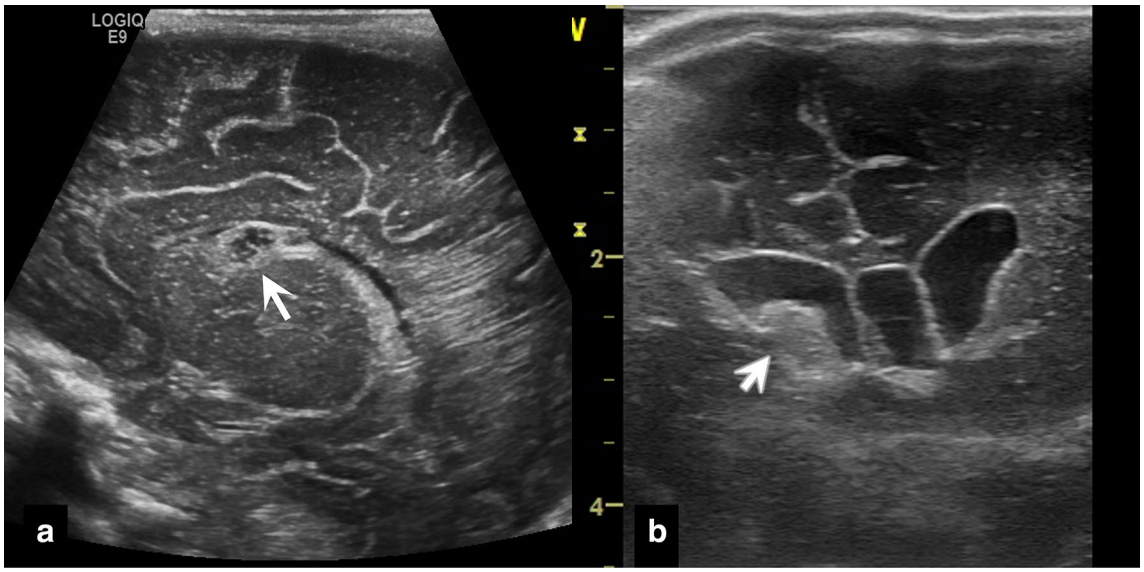

Fig. 3 **a** A delayed ultrasonic image of a GMH case, grade I. A low-density cystic mass can be seen beneath the ependyma of this premature, and the ventricle remains intact. **b** A transcranial ultrasonography image taken 17 days after birth of a twin infant on gestation age of 29 + 3 weeks, with a concomitant preterm pneumorrhagia. The high-density lesion pointed by arrow shows the hematoma disrupting into lateral ventricle with significant ventriculomegaly

functional potentials in the fetal rely on the specific parts of germinal vasculature (Ma et al. 2017). The histological structure is much more of vulnerability and complexity, to which researchers have been seeking the keys for decades.

Structural fragility of the germinal matrix is fundamentally what leads it to GM-IVH. Primarily, the parenchyma of basal lamina is relatively soft and fragile because of deficient fibronectin and collagen (Ballabh 2014). Secondly, intracranial vasculature of preterm neonates has the same innate immaturity as the vessels in other organs, which means that the vessels walls with endothelia much weaker than adult are more prone to rupture. Decreased expression of glial fibrillary acidic protein (GFAP) in the germinal matrix is very likely to decrease the strength of the cytoskeletal structure, and expose the delicate vasculature of germinal matrix into higher rupture risk (Lekic et al. 2015b). The structural variants of subependymal veins are also confirmed to bring about the brittleness of germinal matrix, as well as the inclination of thrombosis (Tortora et al. 2017; Raybaud et al. 2013). Besides, the highly vascularization adds to the fragility of germinal matrix as well, especially when the fetal encounters hypoxia (Lekic et al. 2015b). Furthermore, the premature vasculature lacks the auto-adaptability to modulate the lumen under fluctuant hemodynamics (Ma et al. 2017; Andreone et al. 2015; Lekic et al. 2015b). As a result, once encountered either external or internal environmental changes that lead to rapid fluctuation of blood pressure, these immature infants are in great danger of GM vascular rupture (Baburamani et al. 2012; Ballabh 2014).

Recently the disorder of hemodynamics also has been indicated to impede the normal coagulation course when vasculature gets injured, encouraging the occurrence of GM-IVH (Kuperman et al. 2013). Platelets dysfunction probably participates deeply into the pathogenesis (Coen 2013; Mitsiakos et al. 2016). Besides, based on specially immature vasculature of germinal matrix, preterm neonates bear much higher risk of thrombosis, if faced with platelet dysfunction simultaneously (Itsiakos et al. 2016; Brew et al. 2014). In addition, maternal condition affects immature fetal as well. The blood becomes hypercoagulable when the mother gets pregnant. Microthrombus originated from mother or placenta can possibly pass through placental barrier of highly porosity. What is more, a parent giving birth to premature baby is usually suffering some other antenatal disorders that have adverse impacts on the fetal. As a result, neonates may probably have been injured when it was still in womb.

Right after the germinal matrix bleeds, this periventricular lamina basalis gets injured because of structural fracture, mechanical compression and intracranial hypertension. Brain swelling immediately aggravates out of interstitial and cytotoxic edema (Michinaga and Koyama 2015). Secondary compressive ischemia, partially resulted from vasospasm and edema, occurs in peripheral nervous tissue as cerebral blood flow plunges. Some severe germinal hematoma with immense volume may lead to herniation, or break through ependymal layer, namely IVH. During these serial processes, destruction of neurons and axons will inevitably take place due to mechanical mass

effect, hypoxia, ischemia and cytotoxicity. Even if the preterm neonates get rid of fatality, they are still subjected to many sequelae caused by GM-IVH.

Even though GM-IVH bears much resemblance to the adult intracranial hemorrhage, it holds some typical characters relevant to neurological growth. There appears to be a considerable proportion of leukomalacia following the survival in GM-IVH, and cortical maturation will inevitably get retarded (Okazaki et al. 2013; O'Dell et al. 2015). Even the infant cerebellar development gets impaired because of GM-IVH (Lee et al. 2016). Nonetheless, since there is still no animal model that is perfectly congruent with the real pathogenesis, our knowledge remains far from the whole mechanism of GM-IVH, even though we have known pretty much of the histopathological defection of neonatal brain.

Neuropathological Mechanism

Researchers have been looking for the mechanisms and molecular pathways that lead to injury of GM-IVH. However, what we achieved so far is not satisfied, which appears to be complicated and interweaving (Fig. 4). Overall, there are some major individual or serial molecules that occupy the core status. The authors try to introduce the prevalent theories of preterm GM-IVH with some new discoveries as follows.

Blood Components and Metabolites

Researchers have long confirmed the important role of blood components in intracranial hemorrhagic diseases, especially the hemoglobin metabolite, iron compounds,

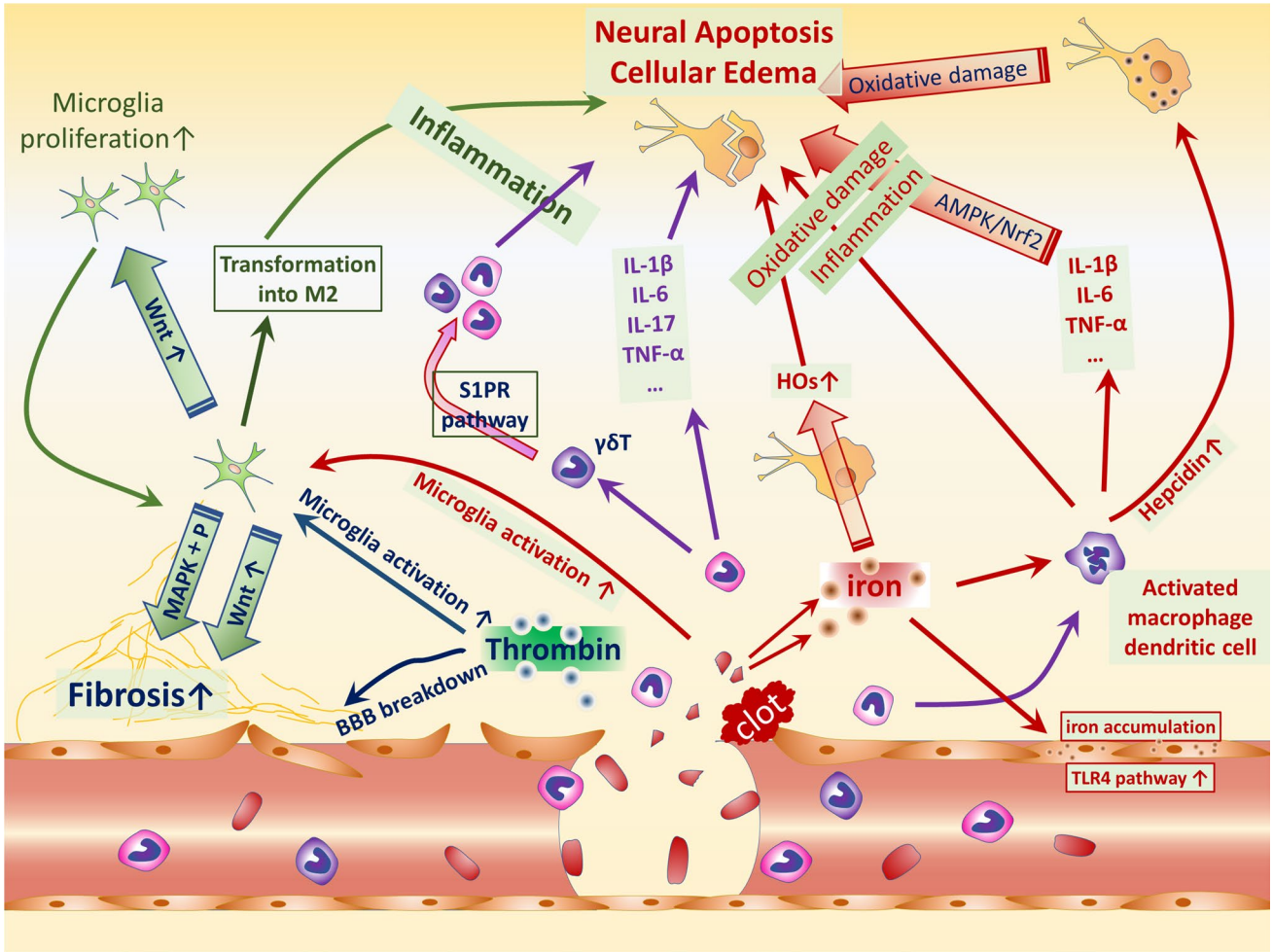

Fig. 4 The complicated mechanisms of how GM-IVH injures the premature infant brain. The solid arrows and texts without a box illustrate the mainly extracellular mechanisms and molecules involved in the damaging course of GMH; the hollow arrows and texts inside boxes shows those mainly intracellular mechanisms and molecules involved. HOs: heme-oxygenases; S1PR: sphingosine-1-phosphate receptor; TLR: toll-like receptor; AMPK/Nrf2: adenosine monophosphate-activated protein kinase/nuclear factor erythroid 2-related factor 2.

and thrombin (Strahle et al. 2014; Lekic et al. 2015a; Gao et al. 2014; Garton et al. 2016). Heme-oxygenase (HO) expressions are significantly increased in brain parenchyma by exogenous hemoglobin or protoporphyrin injection (Strahle et al. 2014). Iron imposes adverse impact on apoplexy infants mainly through encouraging fibrosis and sequent adhesion of arachnoid potentially aggravates brain edema (Guo et al. 2015; Klebe et al. 2014). Wnt signaling pathway is a well-known active target for cancer therapy (Tai et al. 2015), and researchers have testified that it is activated in fibrosis of many organs varying from skeleton to kidney (Cisternas et al. 2014). Meng's and Kaur's findings particularly highlight the relationship between iron and Wnt1/Wnt3a gene expression pathway. Iron suppresses renewal of neurons and enhances fibrotic process and gliocyte's proliferation by stimulus to Wnt pathway, and further leads to post-hemorrhagic sequelae such as hydrocephalus (Meng et al. 2015; Kaur et al. 2013). Another research also implicates the active role of Wnt pathway in regulating the myelination of neonatal white matter, and the construction of synapses is disrupted through irregulating Wnt signaling (Back 2017). On another aspect, hepcidin, which inhibits the intracellular iron efflux of endotheliocytes, was described in adult animals as the effective molecule on cognitive impairment through Toll-like receptor 4 (TLR4)/MyD88 signaling pathway, which is the potential target of preterm-related injury (Xiong et al. 2016). Discoveries relevant to this process also indicate the effective role of iron on inflammatory factor (like interleukin-6), and oxidative stress after intracranial hemorrhage (Hu et al. 2016; Xiong et al. 2016; Vela 2018). It is intriguing of iron to be multifunctional on various interactive signaling pathways, which needs further study.

Thrombin is a well-proven agent to construct hydrocephalus animal model. The disruptive effect of thrombin to the blood brain barrier (BBB) has been described in GMH by Tao and the teammates (Tao et al. 2015). Apart from that, thrombin induces the phosphorylation of mitogen-activated protein kinase (MAPK) leading to disruption of tight-junction protein which is another key to break down BBB (Li et al. 2015). Lekic also led a research that unveiled the activation of proteinase-activated-receptors (PAR) signaling pathway resulted by thrombin, and cyclooxygenase (COX)-2 is promising to be the effective treatment for GM-IVH neonates (Lekic et al. 2015a; Cheng et al. 2014).

Given the researches based on animals and cells so far, we still need more evidence to explain the definite relationship among blood cell metabolites, molecular mechanisms, and secondary neurologic deficits of preterm neonates with GM-IVH.

Microglia and Inflammation

Inflammation has long been believed as one of the paramount mechanisms of hemorrhagic stroke, and microglia deeply participate in the inflammatory response in the signal transmitting course of GMH (Blaho et al. 2015; Shigemoto-Mogami et al. 2014; Supramaniam et al. 2013). Microglia have two differentiated states. One is a pro-inflammatory classically activated state (M1), and the other is an immune-dampening and tissue-regenerative alternatively activated state (M2)(Klebe et al. 2015). Microglia get activated and infiltrate into the subventricular zone including germinal matrix (Shigemoto-Mogami et al. 2014). This phenomenon becomes evident when hemorrhage happens in germinal matrix (Tang et al. 2015). A variety of inflammatory cytokines were decreased when the activated microglia are suppressed, verifying the inflammatory activity of microglia (Shigemoto-Mogami et al. 2014; Zhang et al. 2018; Wan et al. 2016). Peroxisome proliferator-activated receptor gamma (PPARγ) induces the microglia of GMH brain to transform into M2 state, contributing to attenuation of hemorrhagic brain inflammatory response (Flores et al. 2016). In addition, there exists CD36 expression in microgliocyte activated with PPARγ, which helps improve the long-term neurofunctional development after GMH (Flores et al. 2016).

Over a decade before, researchers have already confirmed the efficiency of celecoxib (an anti-inflammation) on premature animal model, reducing the risk of neonatal brain hemorrhage by proliferation of germinal matrix endotheliocytes. However, after the hemorrhage occurs, endothelial proliferation seems to be beneficial to the neurologic deficits by vascular endothelial growth factor (VEGF) treatment (Dzietko et al. 2013). VEGF and the downstream mediators are believed to be of great participation in the inflammatory courses, and anti-inflammatory drugs such as celecoxib turn out effective in attenuate the severity of GM-IVH (Yang et al. 2013; Phillips et al. 2013). Recently, Zhang et al. (2018) substantiated that GMH-induced inflammatory response by promoting ChemR23/CAMKK2/AMPK/Nrf2 pathway. In addition, aminomethyl phosphonic acid (AMPA) receptor pathway are believed active in preventing injured neurons from restoration, maturation, and regeneration through various inflammatory cytokines, and leading to apoptosis of neurons as well (Dohare et al. 2016). Several animal experiments, respectively, indicated MAPK family pathway is also involved, and cannabinoid receptor 2 (CB2R) is a functional target that ameliorates injury induced by GM-IVH (Tang et al. 2015, 2017; Tao et al. 2015; Li et al. 2015). Besides, they also found traces on oxidation stress during pathogenic progress of GM-IVH just as some other scientists did (Esiaba et al. 2016). According to this hypothesis, some researchers try to treat intracranial hemorrhage in adult by antioxidants like Resveratrol and

hydrogen (Duan et al. 2016; Bonsack et al. 2017; Eckermann et al. 2012), which may be helpful in preterm GM-IVH. In conclusion, inflammation response is of great complexity interweaving with other molecular mechanisms, but it is still a promising breakthrough seeking effective therapies for GM-IVH.

Lymphocytes and Immunity

Regardless of the age, lymphocytes infiltrate into the lesion when the brain suffers an attack. There are many researchers devoting to finding out the deeper relationship among immunity, lymphocytes, and apoplectic neuropathology, including hemorrhagic and ischemic stroke in neonates (Doyle et al. 2015; Nazmi et al. 2018). Albertsson and the colleagues noticed a special type of immune response held by $CD4^+$ T-helper (Th) cell in a mice model of hypoxia-ischemic stroke, some of which result in GM-IVH (Albertsson et al. 2014). As the first subset of T lymphocytes to emerge during ontogeny, γδT cells are confirmed to specifically take part in the injury of developing brain other than mature one. In both sepsis and ischemic brain injury, it is indicated that γδT cells induce the long-term neurologic deficit resulted by demyelination of and gliosis (Albertsson et al. 2018; Zhang et al. 2017). Besides, this kind of autoimmune response also found interweaving with broad-spectrum inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin-17 (IL-17). Not only does the immune system affect the expression of inflammatory cytokines, but the elevated cytokines such as Sphingosine-1-phosphate (S1P) also affect the proliferation and differentiation of lymphocytes (Albertsson et al. 2014). Inflammatory cytokines can also become the potential targets to develop immune modulators (Tsai and Han 2016). Several adult-related studies indicated that S1P and S1P receptor (S1PR) pathway take an active part in this course. Molecules as its antagonists can reduce the neuroinflammation by arresting lymphocyte egress from secondary lymphoid tissues in the central nervous system, and at the same time regulate macrophages dendritic cell functions (Tsai and Han 2016; Blaho et al. 2015). Immune system of fetus and preterm neonate is immature, so the immune response is possibly characteristic in comparison with adults. Altogether, more evidences are needed to define the effects of different types of lymphocytes and cytokines involved in the GM-IVH course.

Treatments and Preventions

The outcome of premature GM-IVH turns out quite pessimistic. In the acute stage of GM-IVH, intracranial hypertension is often what leads the afflicted infants to fatality. To decrease the intracranial pressure with dehydrator and corticosteroid is the essential part of treatment. Nevertheless, because of the fragile vasculature of germinal matrix, dehydration with mannitol is a double-edged sword that decompresses the cranial cavity as well as imperils the infant to higher risk of re-bleeding and renal failure. Surgical operation, mainly inclusive of trephination drainage and external ventricular drainage, is the last choice to save the life yet with awful prognosis. In the chronic stage out of danger, treatments aim at reducing the secondary injury caused by hemorrhage, attenuating the sequelae and facilitating the recovery of neural functions. Infant disabilities of sucking, swallowing, and coughing arise after GM-IVH, so their survival and quality of life can be deeply derogated (Laptook 2013). Consequently, this kind of complications should be carefully controlled by elaborative nursing in case of sudden accidents like choking.

In terms of medical treatments, many drugs seem to be influential to either vivo or vitro animal models. Oestradiol show the effects on ameliorating the neurologic outcomes by increasing the expression of neurotrophic factor (Firozan et al. 2014). Based on the theories introduced in Iron chelators such as minocycline, deferoxamine has a favorable reaction in vitro and animal experiments as well (Guo et al. 2015; Meng et al. 2015). Just in 2018, melatonin was reported protective in secondary brain injury induced by hemorrhage. It is variously effective in impacting apoptosis, oxidative stress, inflammation, DNA damage, brain edema, and BBB damage, and reducing mitochondrial membrane permeability transition pore opening (Wang et al. 2018). Simvastatin was found with potential impacts on upregulating CD36 expression, which probably promotes the absorption of intraventricular hemorrhage (Chen et al. 2017). Researchers also found the positive role of glibenclamide in reducing the expression of MMPs and thereby protect brain from further injury (Jiang et al. 2017). Even though researches showed positive effects in preclinical modes, how they work and whether they are curative in apoplectic patients are still unknown. Some other drugs targeted at pathways including PPAR, TGF-β, and CB2R also impress scientists very well (Tang et al. 2015; Flores et al. 2016; Tsai and Han 2016). But some of the mechanisms of how these medications wore are still controversial, so what authors mentioned need to confirm their curative effects by more evidences.

In the recent decade, stem cell dominates the treatment research of restoration after brain injury. Treatments are mainly characterized by types of stem cells and transplantation methods (Phillips et al. 2013). Mesenchymal stem cells deriving from placenta and umbilical cord planted intraventricularly take effect in reducing the hydrocephalus, and the reporters confirmed their assumption on anti-inflammatory effects according to the regulation of inflammation-involved cytokines (Ahn et al. 2013; Ding et al. 2017). Neural progenitor cells (NPCs) can be more beneficial to neuron

regeneration for the functions of releasing neurotrophic factors, and differentiated types of cells are capable of performing corresponding functions (Bae et al. 2016). Besides, there are some traces that induced pluripotent stem (iPS) cells, which also have the likened value of treating the brain deficit, but it is an incomplete technics that need improving, especially the inclination of tumorigenesis (Li et al. 2014). Despite all the problems that stem cell scientists encounter today, stem cells therapy is one of the most promising approaches to GM-IVH.

Compared with post-hemorrhagic treatment, prediction and prevention seem to be more effective, but our knowledge on it goes hardly further than pathophysiology for decades. Since there are plenty of reports implying the risk factor of GM-IVH, the risk can be reduced by measures like controlling the maternal diseases and intensive care for newborn premature (Waitz et al. 2016). In the past some, pediatrists tried to reduce risk of GM-IVH by altering the head position in the hope of improving the hemodynamics and oxygen supply, but insufficient evidence has proven the feasibility so far (de Bijl-Marcus et al. 2017).

Ment and coworkers reported that methylenetetrahydrofolate reductase (MTHFR) variants may make neonates more vulnerable when encountering hypoxia (Ment et al. 2014). Szpecht and associates reported several intriguing discoveries about the impact of genotypes on GM-IVH. Infants with genotype GT eNOS 894G > T or MTHFR 1298A > C polymorphism suffer a higher risk of IVH born before 28^{+6} weeks of gestation (Szpecht et al. 2017b, a). These discoveries strongly demonstrate the definite genetic effect on the occurrence of GM-IVH, which holds a promising future of genetic diagnosis and prevention to GM-IVH.

Conclusion

GM-IVH in preterm infants is a disastrous disease with considerable fatality and morbidity, which is highly relevant to gestational age, maternal conditions, and delivering situations. Special vulnerability of germinal matrix pathologically leads to higher risk of GM-IVH. Pediatrists and scientists have been deeply looking for the keys to lowering the risk, reducing the mortality and attenuating the sequelae. Given the limited acknowledge of GM-IVH, there are only several methods we can choose to deal with it, while the advanced treatments such as neurotrophic drugs, iron chelators, NSAIDs, and stem cells therapy are still in research. But researchers are still in hope of bigger breakthroughs in this issue to promote the survival of GM-IVH.

Author Contributions SC was the principal investigator. JL and YL wrote the paper and made the original figures. HZ revised the figures. CR handled the language and made some comments.

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Compliance with Ethical Standards

Conflict of interest The authors declare there is no conflict of interest.

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