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Review Article

Inspecting Post-stroke Mechanisms and Treatment for Stroke Recovery

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Abstract : Followed by not only neurological detriment including motor disorders, but also decline in the quality of life, stroke is a well-known major factor of death, worldwide. Plenty of methods to enhance patient recovery and several post-stroke remedies are being explored until now. In this review, post-stroke inflammatory processes, including BBB breakdown and its effect, will be handled along with the work of microglia activation. Necroptosis, a type of cell death as a result of proinflammatory reaction, will also be addressed to specify its mechanism throughout the post-stroke procedure. This review displays those factors in the spotlight these days to deduce progressive post-stroke therapeutic approaches, as well as the other participants of the post-stroke inflammatory process such as the work of T cells. Meanwhile, there are some other approaches under investigation related to making out post-stroke recovery advancement. This review handles the utilization of iPSCs (induced pluripotent stem cells) as a promising access toward innovative post-stroke treatment. Furthermore, this review concludes by pointing out some targets that are under research to develop efficacious post-stroke treatment and highlights the directions where the future investigation for effective post-stroke therapeutic approaches have to head for.

Keywords : Stroke, BBB, Microglia, Inflammation, Necroptosis

INTRODUCTION

Stroke, notable for its mortality rate globally, turns out to be the second most common factor of worldwide death as well as the third leading factor of disability [1]. It also takes up approximately 12% of total death in South Korea [2].

Stroke is usually identified as ischemic or hemorrhagic. The loss of blood flow to our brain owing to occlusion in blood vessels causes ischemic stroke, while hemorrhagic stroke breaks out by the burst of a blood vessel in brain. About 87% of total cases are related to the former [3].

A lot of research show that post-ischemic inflammation is related to Blood-Brain Barrier (BBB) disruption [4], one of the main features in ischemic stroke process. With the outbreak of ischemic stroke, the tight junction breaks down, increasing both permeability of BBB and the transportation of molecules between the brain and the blood [5]. As a result, an unrestrained inflow of blood cells and substances leads

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to further inflammation reactions and worsens brain damage [6].

'Estimated annual percentage changes (EAPCs)' made projections on the tendency to the incidence of deaths caused by ischemic stroke between 2020 and 2030. The incidence by ischemic stroke was projected to rise in several countries, including all age groups during the mentioned period [7].

As the number of victims seems to increase regardless of age and the national background, it becomes imperative to develop and explore effective post-stroke treatments. As most consequences after the impairment of BBB brings inimical consequences to our health, we can consider BBB as one of the promising targets for stroke treatment [8].

Besides BBB disruption, there are a number of other factors and processes involved in the stroke outbreak mechanism, which gradually gain attention as the potential aspects for developing post-stroke recovery.

Neuroinflammation induced as a result of stroke outbreak is highly related to the activation of microglia. Microglia cells, which occupy a chief role in the process of inflammatory mechanisms by creating proinflammatory cytokines, are also known to be the major factor which leads and worsens brain injury.

One of the procedures of cell death by post-stroke occurrence can be explained with the word 'necroptosis'. It starts off with the release of the pro-inflammatory cytokines and finally makes the brain injury worser, by adversely affecting cell membranes.

The exploration towards the effect of those parts included in stroke mechanism mentioned above will be unfolded to discuss related therapeutic and future-oriented methods for the development of effective post-stroke treatments, including the overview of applying stem cells in the research of post-stroke treatment, as iPSCs are consistently receiving attention to be used for cell generation and further recovery.

BBB DISRUPTION IN ISCHEMIC STROKE

BBB is composed of neurovascular units, highly connected with endothelial cells, astrocytes, pericytes and tight junctions [9]. BBB is known as an extremely selective barrier whose role is separating the central nervous system (CNS) and the outlying blood circulation. BBB plays a crucial role in maintaining brain homeostasis by restricting influx of outer substances to the brain [9,10].

BBB disruption, identified by tight junction (TJs) breakdown with rise in permeability, is known as a pathological indicator of ischemic stroke [11]. After an ischemic stroke, the injured BBB with increased permeability allows the inflow of blood cells and other chemicals to invade into the brain parenchyma [8]. It leads to the collapse of the BBB homeostasis as a result of its malfunction in the end. The broken homeostasis and the function of BBB can lead to the worsening of brain injury, the eruption brain edema in particular.

Our brain is made up of up to 80% of water which is distributed into numerous brain cells and compartments. We can define the type of brain edema largely into two groups, following the traditional way. We call the persistent accumulation of intercellular water featuring the cell swelling without BBB damage 'cytotoxic', while the process that causes BBB disruption with the extracellular water accumulation is called 'vasogenic'. The brain edema is known to be cytotoxic at first and followed by vasogenic features due to the TJ breakdown in the BBB, but they are a kind of successive phenomenon rather than a strictly distinguishable one [12,13].

The cytotoxic phase, featuring the internal water building-up, is known to disturb the cerebral blood flow, resulting in the loss of oxygen and glucose within minutes. Vasogenic edema, which takes place with the loss of TJs in BBB, causes extracellular water accumulation, leading to the result of the swollen brain of increased cerebral pressure, which in turn creates the vicious cycle of ischemia worsening [12]. This is the reason why BBB breakdown and disrupted hemostasis cause severe brain injury in the name of cerebral edema.

The involvement of immune cells in stroke is also related to BBB dysfunction and brain injury [8]. A few hours after the outbreak of ischemic stroke, microglia cells get activated and release proinflammatory cytokines such as interleukin (IL)-1 or IL-6. These substances make immune cells accumulate in the infarct area and exaggerate inflammatory process, aggravating the injury as a result. There are also some factors that play protective roles for neuronal recovery such as regulatory T-cells (T-regs) [14].

MICROGLIA ACTIVATION

Microglia are tiny cells that make up approximately 10-15 percent of total cells in CNS. Microglia are activated in response to several stresses, thereby polarizing into two types: M1 and M2 phenotypes [15]. These two phenotypes

of microglia are antagonistic to one another. M1 microglia produce proinflammatory cytokines and cytotoxic factors, exacerbating neuronal injury, whereas M2 microglia promote anti-inflammatory response, inducing neurogenesis (Fig. 1) [16].

M1 MEDIATED INFLAMMATORY RESPONSE

Again, M1 microglia play a major role in proinflammatory response by producing proinflammatory cytokines that lead to further brain damage. While undergoing ischemia, activated NF-κB actuates the release of proinflammatory cytokines including IL-1β, IL-6, and tumor necrosis factor-α (TNF-α), leading to secondary brain injury [17].

M1 microglia-derived TNF-α is recognized as a factor that affects both endothelial necroptosis and BBB damage after ischemia, exacerbating injury with further neuroinflammation and brain edema [18]. IL-1β produced by M1 microglia impairs cognitive works by reducing the number of synapses of brain cortex and hippocampus [15]. Those interplays between M1 microglia and M1- generated proinflammatory cytokines identify that M1 microglia work is a major factor worsening brain infarction.

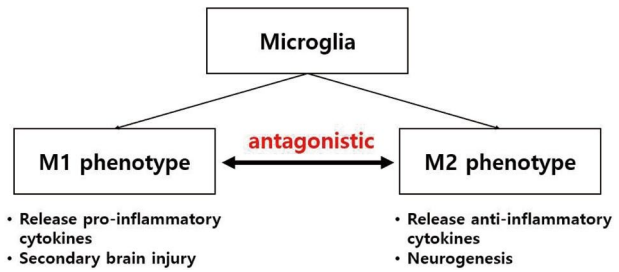

Fig. 1. This is a simple diagram to illustrate how two phenotypes of microglia differs after differentiation. M1 accelerates secondary brain injury by releasing pro-inflammatory cytokines whereas M2 induces neurogenesis with the release of anti-inflammatory substances. The differentiation and the action of each phenotype is characteristic as their roles are antagonistic to one another.

NECROPTOSIS IN ISCHEMIC STROKE

Necroptosis is a programmed and pro-inflammatory mechanism, a caspase-independent cell death which is triggered by TNF-α, TRAIL or Fas [19]. Necroptosis is related to the activation of receptor-interacting protein kinase (RIPK) 1, RIPK3, and mixed lineage kinase domain-like pseudo kinase (MLKL).

The activation of death receptors by the work of cytokines causes RIPK1 to be de-ubiquitylated with the de-ubiquitinating enzyme called Cylindromatosis (CYLD). The de-ubiquitylation of RIPK1 leads to the activation of RIPK3, which phosphorylates MLKL. RIPK1, RIPK3 and MLKL forms a complex called necrosome. Then, the activated

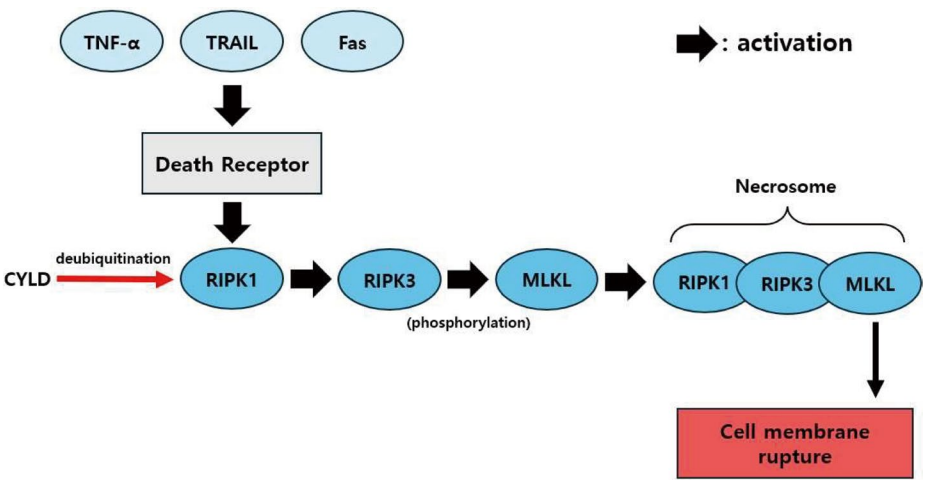

Fig. 2. This is a diagram illustrating the mechanism of necroptosis. With the activation of the death receptor by TNF-α, TRAIL and Fas, RIPK1 becomes deubiquitinated by the enzyme called CYLD. RIPK3 and MLKL also become activated in a row. Then, RIPK1, RIPK3 and MLKL create a complex named "necrosome". With the formation of necrosome, MLKL is activated and causes a rupture in the cell membrane. This process is called "Necroptosis".

MLKL moves forward to the cell membrane, inducing necroptosis by causing rupture of membrane and aggravating inflammation as a result [20].

As an ischemic stroke occurs, microglia get activated and release cytokines like TNF-α, TRAIL or Fas. This process recruits RIPK1, and causes the activation of RIPK3, MLKL in a chain as mentioned above, proving the cell death by necroptosis under the ischemic condition (Fig. 2) [21].

NECROPTOSIS AS A TARGET FOR POST-STROKE RECOVERY

The main factors taking part in the occurrence of necroptosis are RIPK1, RIPK3, MLKL and their complex, necrosome, as mentioned above. We can devise the method of utilizing inhibitors that correspond to the respective factors.

The already-known inhibitors for RIPK1 are Nec-1, 3, 4 and 5. They are believed to help the recovery of post-MCAO damage afflicted to neurons. GSK'843, GSK'872, two are regarded as the inhibitors of RIPK3. Besides, it is said that necro-sulfonamide could be used to inhibit the activation of MLKL [22]. However, it is the critical problem that we have not enough clinical results for their potency [21]. The additional research would be needed to prove its efficacy to alleviate the cell death owed to necroptosis.

T CELLS AS TARGETS FOR POST-STROKE RECOVERY

T lymphocytes are the main factors of neuroinflammation in ischemic strokes. There was research that had proven ischemic stroke patients showed an increase in Th17 but a decrease in T-reg cells [23]. According to its result, we could induce that imbalance between Th17 and T-reg cells is related to ischemic stroke. Therefore, understanding the roles of T lymphocytes in ischemic stroke becomes important to get novel therapeutic approaches to modulate immune responses and promote recovery.

A lot of research has proven that several cytokines such as IL-6, IL-21, and IL-23 have an impact on the differentiation of Th17 cells, which play a critical role in ischemic stroke exacerbation [24]. In other words, it means that we can alleviate ischemia through inhibiting the activation of Th17 cells by regulating the signaling of those cytokines.

Unlike Th17, T-regs are known to regulate immune responses and facilitate tissue recovery [23]. After a stroke outbreak, T-regs show neuroprotective work, regulating microglia activation by producing anti-inflammatory cytokines, curbing the effect of pro-inflammatory substances including IL-6 and TNF- α, facilitating BBB recovery as well [25].

IPSCS APPLICATION: UTILITY AND LIMITATIONS

No one can emphasize more about the importance of developing ischemic stroke recovery methods. As it becomes clear that neuronal cells undergo necroptosis throughout the ischemic process, a new approach is now under investigation, which is to transplant new cells into the injured sector. A number of stem cells, including Embryonic Stem Cells (ESCs), neural stem cells (NSCs), and mesenchymal stem cells (MSCs), have been studied for years. Recently, researchers have been focusing on induced pluripotent stem cells (iPSCs) for post-stroke recovery [26], as iPSCs have been regarded as one of the approaches to treat cerebrovascular disease effectively since the technology using them was first recognized [23].

iPSCs are a type of pluripotent stem cells originated from somatic cells. They remain their own genetic settings and can be generated with a relatively safer way, showing little immune rejection risks, thereby being able to replace cells damaged by injury or disease in a patient-specific manner without ethical issues [27]. The efficacy of applying iPSCs therapy has been tested in animal models to identify its therapeutic effect on neurological deficits caused by nerve cell damage in ischemic stroke, and it seems to be effective not only in reducing lesion volume by modulating inflammation and immune responses but also in promoting cell regeneration [28].

In addition to those advantages mentioned above, there are two main problems that arise when using iPSCs so that we have to exert effort to overcome. The first limitation is that we cannot ignore the differentiation potential gap among iPSCs, as they are generated from multiple donors of various genetic differences, and they can be cultured in all different methods [29]. And it is clear that such factors are bound to affect whenever we use iPSC-based models in further research. The other thing is concerned with the maturation of iPSCs-derived cell, as they tend to be immature both structu-

rally or functionally [30]. This indicates that we should come up with some methods to handle the maturation of iPSCs to have them to do with effective post-stroke recovery.

There are still several issues to be settled, we also check the efficacy of applying iPSCs in stroke treatment as mentioned above. As numerous research related to iPSCs as promising post-stroke therapy are continuously conducted with a positive outlook, we may anticipate iPSCs to yield meaningful results in the upcoming future.

CONCLUSION

With significant advances both in the scientific and medical fields, the mechanisms of IS are being defined better, looking forward to finding out more effective as well as more diverse methods for treatment. Both the negative impact that stroke brings to our life and the importance of defining the mechanism included in stroke are significant element to discuss.

Exploring the post-stroke mechanisms and associated potential post-stroke therapies, we first examined the inflammatory response taking place in the process of stroke onset, particulary focusing on BBB breakdown and following brain edema, as well as the induction of inflammation with microglia activation. It becomes certain that the result of BBB damage can have a crucial impact in worsening brain ischemia.

We also discussed the role of microglia activation as one of the factors that exacerbates brain ischemia. We could check the fact that the antagonistic feature of microglia, which differentiate into two types: M1 and M2. While M1 microglia have an influence on worsening the inflammatory response, M2 microglia are crucial for inducing the recovery process later.

In the aspect of the mechanism of necroptosis, a type of cell death induced by the inflammatory response during the stroke, understanding how ischemia leads to cell death by worsening symptoms can be helpful in hunting for the promising advancement in the field of post-storke therapy.

The reason we have to understand the mechanism of IS lies on finding out better and effective post-stroke therapies. Moreover, it is necessary to make our treatments go further, not staying on general treatments but developing personalized methods, as the sypmtoms and the severity of stroke vary among individual patients. It will be also vital to dig into deeper study to define post-stroke mechanism more precisely for the development of multi-faceted therapeutic methods. One such approach contains applying iPSCs to research for rehabiliation of injured brain after stroke, as iPSCs can differentiate into various cell types for multi-purposed usage and be far away from the controversies of ethical issues.

However, there are still some barriers we face and have to overcome at the same time, including two issues regarding the utilization of iPSCs as mentioned above. We could envisage that advanced future technologies would help us to resolve problems in concern. One of our top priority would be to find out the most effective methods that can maximize therapeutic impact for individual patients as well as eliminating adverse effects and related social problems including ethical problems. To carry out our goal into reality, we need to conduct cautious, path-finding research to identify still-unknown mechanisms accurately and develop innovative treatments free from any flaws and make them emerge in our upcoming future.

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