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Using Human Brain Organoids Model for Cerebral Malaria

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Abstract

In cerebral malaria patients, neurologic injuries are a significant cause of morbidity and mortality. However, there is a dearth of a comprehensive approach to this problem, so we propose an in vitro system for cellular approaches to human cerebral malaria research. Our primary objective was to develop a cellular system for the purpose of determining the molecular changes in human brain vasculature cells that are analogous to the blood–brain barrier (BBB) in cerebral malaria (CM). We identified specific gene expression profiles in Plasmodium falciparum-activated human brain microvascular endothelial cells (HBMEC) through transcriptomic analysis. In addition, we propose potential brand-new genes connected to parasitic activation.

Keywords: Neurologic injuries • Microvascular • Flaviviruses

Introduction

In order to gain a deeper comprehension of the physiological mechanisms that are responsible for CM, we investigated its effect on the brain following endothelial activation by *Plasmodium falciparum*. As a result, the effects of HBMEC- *P. falciparum*-activated secretomes on human brain organoids were examined. Our outcomes support the dependability of in vitro cell models created to copy CM in a few viewpoints. For the purpose of gaining a molecular understanding of the pathogenesis, brain injury and dysfunction, these systems can be of extreme importance when examining the parasitological and host factors that influence CM.

Literature Review

In 2021, there were 247 million reported cases of malaria and 619,000 reported deaths worldwide. Malaria is a parasitic infectious disease *P. falciparum* and *P. vivax* are the main Plasmodium species that cause human infections. Anaemia and fever are the most common clinical signs of malaria. The most severe form, cerebral malaria (CM), occurs when the parasite affects the integrity of the blood–brain barrier (BBB) and causes an inflammatory response, resulting in brain swelling. Neurological complications, cognitive impairments, epilepsy and behavioural issues are all possible outcomes of this. Endothelial cells, which cover the inner surface of blood vessels in the brain and regulate blood flow to prevent harmful substances from entering, make up the BBB, a specialized layer of various cell types [1].

Endothelial activation is associated with CM and is involved in the pathogenesis and progression of malaria because the endothelium serves as a barrier between the brain and the *P. falciparum*-infected red blood cells (iRBCs). Additionally, endothelial cells regulate haemostatic function and coagulation through adhesion molecules like intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), platelet endothelial cell Clinical complications and micro vascular obstruction are linked to the malaria parasite's adhesion receptors on the cell surface, which are involved in the parasite's sequestration mechanisms. EPCR, ICAM-1 and CD36, as well as the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) proteins of the parasites in the trophozoite and schizont stages, are also involved in the sequestration of iRBCs to endothelial cells [2].

Key factors, such as inflammation, vascular leakage and the singularity of *P. falciparum* variants, which are the mechanisms associated with CM, have been identified. Although the precise mechanisms underlying the interaction between human brain endothelial cells and the malarial parasite are not fully understood, these factors have been identified. Pro-inflammatory cytokines are released into the blood upon infection, triggering factors for coagulation and inflammation. Patients with malaria often have problems with the coagulation system because activated platelets and parasitized red blood cells cause the coagulation cascade to get bigger. The coagulation system is also connected to the innate immune response as a host defence mechanism and plays a crucial role in the sequestration of iRBCs in the cerebral vasculature, which can result in thrombosis of blood micro vessels. In patients with *P. falciparum* infection, altered plasma levels of biomarkers like thrombomodulin, thrombin and von Willebrand factor have been reported. In *P. falciparum* malaria, these coagulation–inflammatory mechanisms contribute to haemostatic dysfunction, which results in coma [3].

Discussion

Thioredoxin reductase (TrxR), which regulates oxidative damage and protects cells, is encoded by the TXNRD1 gene. In vascular endothelial cells, TrxR regulates NF-kappa B activity and the cellular inflammatory response. Additionally, the TXNRD1 gene regulates redox signalling and detoxifies reactive oxygen species (ROS), making it a potential contributor to epilepsy, which is frequently brought on by elevated oxidative stress in the brain. One of the enzymes, TrxR1, may reduce brain damage caused by seizures by preventing oxidative stress in the cortex and dopaminergic neurons. The transcriptomic results showed that the TXNRD1 gene was expressed less, which suggests that oxidative stress may not be properly controlled, which could result in less neuro protective effects. Seizures are a frequent symptom of severe malaria, which lends credence to the possibility that the TXNRD1 gene is involved in these symptoms [4].

When HBMEC are challenged by *P. falciparum* strains, the expression of heterogeneous receptors varies depending on the time of activation, as shown by our findings. The brain endothelial cell function and BBB permeability can be altered by malaria infection, which can cause toxic substances to build up in the brain and disrupt normal brain function. Seizures, confusion and other cognitive and behavioural changes can result from these occurrences, which can cause edema and disrupt the normal function of neurons. Immunofluorescence assays demonstrating normal, reproducible organoid development and maturation demonstrate that our human brain organoids were developed successfully. According to our findings, iPSCs differentiate into brain organoids that include neural tubes and regions with choroid plexus-like structures. Postmitotic projection neurons, which are necessary for normal brain development, contain TBR1, which is involved in the differentiation of neurons and is present in later stages of neuronal maturation. However, the absence of TBR1-positive cells in brain organoids was demonstrated by our findings.

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It is common to observe a gradual thickening of the TUBB3+ cell layer, particularly in the cortical plate, during the developmental stages of brain organoids, with immature neurons primarily concentrated in the outer region and fewer in the inner region. According to previous research, the TUBB3+ cell layer gradually thickens in the outer layer of organoids, which is consistent with our data's finding of positive cells for the protein. After 35 days of differentiation, brain organoids cortical plate (CP) expression of the neural tissue marker MAP2 is higher. In the BOMM condition, our immunofluorescence images demonstrated a clearer visual representation of the presence of MAP2 in a greater number of cells. NESTIN allows neural progenitors to differentiate from differentiated cells in the neural tube and is a well-known marker for neuronal progenitor cells in the adult brain. After 45 days of differentiation, brain organoids showed structures resembling cerebral ventricles and radial glia (RG) cells, which were identified by the NESTIN marker. As was to be expected, our data showed that there were cells that were positive for the NESTIN marker.

Expression of SOX2 in cells of the neural tube and proliferating CNS progenitors serves as a marker for neural stem cells. According to the literature, brain organoids contain human astrocytes that are functional. According to our findings, SOX-2-positive cells were present, albeit at a lower expression level. As previously mentioned, brain organoids that had matured for 100 days showed an increased level of positivity for GFAP, which is a marker for astrocytes in the central nervous system (CNS). When compared to the inner layer of the organoids, our findings revealed positive cells for GFAP. In cerebrum organoids, the spiral glia platform can be distinguished through the presence of the DCX marker, as portrayed in the writing. In all conditions, our data showed that cells were positive for DCX, with the expression of the marker being higher in the outer layer of the brain organoids.

Caspase-3, a cell death marker, has a higher profile because it is involved in the progression of brain injuries and neurodegenerative diseases. In addition, it is mentioned that CASP3+ cells significantly increased in microcephaly brain organoids. Our discoveries showed that all conditions had positive cells for CASP3 in cerebrum organoids for all circumstances, yet without a higher fixation. It has been established that the human brain's ciliary function is necessary for the development of the central nervous system. Motif-producing cilia are found in some brain cells, such as ependymal cells facing the ventricles and choroid plexus cells. Studies have also shown that ciliopathies are associated with neurodevelopmental disorders and issues in newborns, such as mental retardation and structural deficits.

As previously mentioned, cilium disassembly, which contributes to microcephaly, has been demonstrated in human brain organoids, which can replicate microcephaly. Together with our transcriptomic data, our findings in brain organoids indicated a pattern of altered structural organization, suggesting a slowed neurological development. Changes in the cilium's organization, extracellular organization and the microtubule bundle were also found in the transcriptomic results of the brain organoids. Our transcriptomics findings can shed new light on how activated BBB endothelial cells affect the brain at the biological, molecular and cellular levels. An important model for studying neurological disorders is a human brain organoid made from induced pluripotent stem cells (iPSCs). A human brain organoid is a replica of the foetal brain with structured brain regions like the cerebral cortex, hind/midbrain and hypothalamus made up of various cell types that can self-assemble into a complete brain. This makes it possible to investigate structural phenotypes as well as the cellular and molecular mechanisms underlying human brain development, neuronal disorders brought on by diseases and cognitive impairments. It has recently been demonstrated to be an effective instrument for comprehending the neuro pathogenesis of infectious parasitic diseases, such as cerebral malaria.

Using human endothelial cells, brain experimental models and malaria parasites, we developed a novel method to understand human CM and its impact on the nervous system in vitro. Our findings confirm that *P. falciparum* parasites can alter the transcriptome of endothelial cells by modulating human brain micro vascular endothelial activation and stimulating inflammatory mechanisms. Non-invasively, our findings contributed to a deeper comprehension of the CM-associated brain injury mechanisms. For non-invasively replicating clinical CM and investigating brain development, complexity and organization, these models are essential. To satisfy the requirement for a human in vitro framework to concentrate on CM, we have gathered an assortment of cell advances to reproduce this pathology in the lab.

The genetic background of the parasite *P. falciparum* and the time to activation of HBMEC secretomes generally affect how the parasite activates HBMEC. In addition, compared to an activation period of 24 hours, the *P. falciparum* 3D7 4 h condition induces the most significant transcriptomic changes, resulting in a greater up- and down-regulation of HBMEC. Additionally, the genes TXNRD1, PLEC and FLNB were down-regulated, while RNR2 and COX1 were up-regulated. The cyclooxygenase (COX) enzymes act as the catalysts for the arachidonic acid-based production of prostaglandins (PG). COX inhibitors have demonstrated a protective effect in CM models and there has been evidence that the brains of people with CM express COX-1 and COX-2 more frequently. The expanded presence of COX in CM cerebrums is additionally connected with more elevated levels of prostaglandins, for example, PGE2, which have been connected to fever and aggravation in human CM. When *P. falciparum* is activated in human brain micro vascular endothelial cells, this study demonstrated that COX1 is one of the genes that is expressed the most. This lays out a likely connection between intestinal sickness impact on COX-1 quality articulation and COX-2 and COX-3 qualities [5,6].

Conclusion

The cyclic vomiting syndrome disease and DNA synthesis and repair are both regulated by the RNR2 gene. Psychopathy is linked to the up regulation of mitochondrial (MT)-RNR2. In spite of the fact that as of recently no connection has been laid out among jungle fever and the RNR2 quality, our information highlight a fundamental effect of *P. falciparum* on the declaration of RNR2. The pathogenesis of CM, which resembles the BBB endothelium in CM, can now be better comprehended thanks to our findings. In addition, this study's data contributed to a deeper comprehension of the CM endothelial activation-induced injury mechanisms. Through non-invasive in vitro human endothelial and brain experimental models, we were able to gain a deeper understanding of the physiological processes that underpin CM.

In the context of CM, these models may be an important biological model for studying brain development, complexity and organization. We also talk about the use of brain organoids to learn more about the neurological problems that come with CM. From how different strains of *P. falciparum* affect human brain endothelial activation to how they affect brain organoids, we have established a translational study. In vitro CM research using human brain endothelial cells and human brain organoids as models can benefit from our findings and developments in human brain organoid technologies like vascularization and co-culture.

Acknowledgement

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Conflict of Interest

None.

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