Effects of Cytokines on Blood Brain Barrier in Neuropsychiatric Systemic Lupus Erythematosus

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Introduction

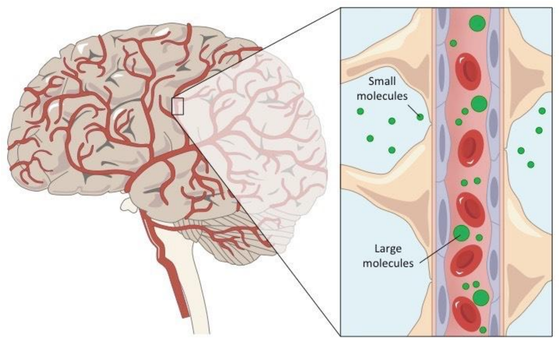

Figure 1. Arrangement and structure of the blood brain barrier (BBB) (1)

Currently, serum albumin is the gold-standard marker for serum leakage in people with neuropsychiatric systemic lupus erythematosus (NPSLE), however attempting to extract cerebrospinal fluid (CSF) is a highly invasive procedure and is not done in patients during regular check-ups. (2) Therefore, it is difficult to diagnose NPSLE early on in its development.

There are certain cytokines that contribute to the disruption to the blood brain barrier, such as interleukin-2 (IL-2) and interleukin-17 (IL-17). This research attempted to investigate the effect of these cytokines in the BBB. Previous literature implicates that these cytokines contribute to the disruption of the BBB in diseases like Alzheimer's.

Materials and Methods

- 12 mm Transwells™
- BMVEC
- Human astrocytes
- Attachment factor
- ACM factor □ AGM factor
- Cytokines

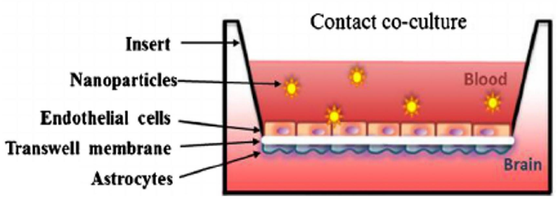

Figure 2. Diagram of Transwells' ™ cell set-up (3)

12 mm Transwells™ with pore sizes of 0.4 µm were developed using attachment factors and AGM medium. The cultures were always incubated at a temperature of 37 °C. They were produced as contact co-cultures and contained cells from two different species (human astrocytes and bovine microvascular endothelial cells (BMVEC)). Cytokines were added to the Transwells from the top, and media was changed every 3 days. The experiment required regular monitoring of cell growth and conditions. Permeability of blood brain barrier was measured using a transepithelial electrical resistance (TEER) machine.

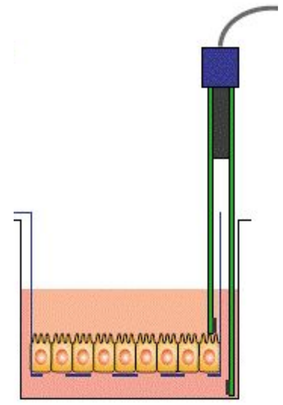

Figure 3. Diagram of TEER probe in wells (4)

Results and Discussion

TEER results can be calculated by multiplying the surface area of the transwell in cm^2 with the net resistance of the cells, which is the resistance measured minus the resistance of a blank Transwell covered by cell culture media.) (5)

The TEER machine results primarily show that IL-17 at a concentration of 10 ng/mL causes a decrease in permeability. The results seem to not replicate trends observed in experiments from previously established literature and research as IL-17 should have caused higher levels of destruction of the BBB cells.

A major limitation of this research was that the BBB cultures consisted of a combination of human and bovine cells. In order to more accurately simulate the environment of NPSLE, using a fully human model *in vitro,* and then *in vivo*, might shed more light on the mechanism. It is also likely that the AGM media used contained high amounts of protective serum, which protected the BBB from damage by the cytokines. In order to produce more accurate results, future experiments could use basal media, so there are no growth factors involved that come from external or uncontrolled stimuli.

Areas of Further Research

Further research in validating markers using in vitro cultures before putting together a manuscript can help to attempt to identify whether and how neurotrophic factors can be introduced to simulated BBB breaches, or in times of cytokine flares in serum. Neurotrophins could act as anti-cytokine therapy, encourage reparations of any damage done to the BBB and could shed light on the mechanism of NPSLE, by investigating how cytokines and neurotrophic factors interact with each other within a simulated BBB, and investigating methods of repairing disrupted barriers.

Conclusion

Despite NPSLE being so common, there is very little understanding of the molecular basis of a disease so prevalent. The research conducted attempted to find a molecular signature of BBB breaches and CSF leakage in the CNS by investigating cytokines like IL-2 and IL-17. The results were inconclusive because they seemed to be controversial in reference to previous literature research that has been done. Follow-up studies are necessary. The premise of this research will also allow scientists to investigate cognitive impairment and help gain a better understanding of how one would measure cognitive decline.

References

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