The blood-brain barrier's role in health and disease

Authors: Eline Geervliet, Suzie Grigorjan, Susan Roelofs

Function of the Blood-Brain Barrier

The blood-brain barrier (BBB), as the name states, is a highly selective and protective interface between the bloodstream and the brain. It consists of endothelial cells that line the brain's capillaries, forming tight junctions that restrict the passage of substances from the blood into the brain. This barrier serves several key functions [1]:

- Protection: Prevents toxins, pathogens, and harmful molecules from entering the brain.
- Homeostasis: Maintains a stable microenvironment necessary for neuronal function.
- Regulated transport: Selectively allows essential nutrients (e.g., glucose, amino acids) and removes waste products.
- Immune privilege: Limits the entry of immune cells to prevent excessive inflammation in the brain.

History of blood-brain barrier research

Humphrey Ridley was the first to demonstrate the restrictive characteristics of the cerebral blood vessels and thereby emphasizing the barrier function in 1695. Almost 200 years later, this research continued when the German scientist Paul Ehrlich discovered that intravenously injected dyes did not stain the brain. Later, his student Edwin Goldmann confirmed the existence of a barrier by doing the exact opposite and injecting a dye directly into the cerebrospinal fluid, which stained the brain but not the rest of the body. While by this time a lot of the BBB was investigated, it took another 70 years to develop the first in vitro BBB made of cell-lines, in 1980. This was quickly followed (1982) by the first transendothelial electrical resistance (TEER) measurements to validate the barrier function of these models and compare it to the TEER of in vivo BBBs [2].

Barrier function and dysfunction

The integrity of the BBB is critical for brain health. If the barrier is compromised, harmful substances can infiltrate the brain, leading to neurological damage. A compromised BBB is implicated in numerous neurological disorders, including [3]:

- Epilepsy: Epilepsy patients show a compromised barrier function during contrast-enhanced MRI.
- Amyotrophic lateral sclerosis (ALS): ALS patients express a mutant of a gene that is involved in barrier formation. While the disease caused the disrupted barrier, the barrier in turn exacerbates the disease progression.
- Multiple sclerosis (MS): During MS, the disrupted barrier enables the infiltration of pathogenic immune cells in the central nervous system (CNS), which leads to neurodegeneration.

In vitro models of the BBB

To study the BBB and develop new treatments, researchers use in vitro models that replicate the barrier's function. Common models include [4], [5]:

- Transwell-based models: Brain endothelial cells are cultured on porous membranes, allowing researchers to study permeability and transport mechanisms.
- Microfluidic models: These "organ-on-a-chip" systems mimic the BBB's dynamic environment, including blood flow and shear stress.
- Three-dimensional (3D) spheroid models: BBB spheroids better replicate the complex cell-cell interactions seen in vivo.

For all models either a monoculture or a co-culture can be used. While a monoculture is easier to work with and better reproducible, a co-culture better mimics the in vitro situation, by including cell-cell and cell-extracellular matrix (ECM) interactions. Three cell types commonly used are: endothelial cells (also used in monocultures), pericytes, and astrocytes. Endothelial cells form the primary barrier with tight junctions that regulate permeability. Pericytes, embedded in the ECM, support endothelial cell function and contribute to barrier stability. Astrocytes, a type of glial cells, play a crucial role in BBB maintenance by secreting signaling molecules that enhance tight junction integrity and overall barrier function.

Importance of barrier function measurements in in vitro models

For in vitro BBB models to be effective, researchers must assess their barrier integrity. Key measurement techniques include [6]:

- Transendothelial electrical resistance (TEER): Measures electrical resistance across the endothelial monolayer to evaluate tight junction integrity.
- Permeability assays: Use fluorescent or radioactive tracers to determine how well substances cross the BBB model.
- Immunostaining and imaging: Visualizes tight junction proteins and endothelial cell morphology.
- Gene and protein expression analysis: Confirms the presence of BBB-specific markers and transporters.

These measurements, mainly focusing on validating the barrier function of the in vitro models, ensure that these models accurately reflect the in vivo BBB, thereby improving drug screening and neurovascular research.

Conclusion

The blood-brain barrier is a vital structure that protects the brain while posing significant challenges for treating neurological diseases. Understanding its function, associated disorders, and advances in BBB modeling is crucial for developing effective therapies. Ongoing research into more sophisticated in vitro models and barrier function measurements continues to push the boundaries of neuroscience and biomedical innovation.

Join the conversation

How can advancing in vitro cell culture models of the blood-brain barrier transform the early stages of drug discovery, and what challenges or opportunities do you foresee in implementing these systems?

References

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