Assessment #2

Research Assessment #2

Annotated Bibliography Assessment

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Topic: Biomedical Engineering

Key: (1) Citation, (2) Introduction, (3) Aims & Research Methods, (4) Scope, (5) Usefulness, (6) Limitations, (7) Conclusion, (8) Reflection

Langevin, Christelle et al. “Rabies virus glycoprotein (RVG) is a trimeric ligand for the N-terminal cysteine-rich domain of the mammalian p75 neurotrophin receptor.” The Journal of biological chemistry, vol. 277,40 (2002): 37655-62. doi:10.1074/jbc.M201374200

(2) The rabies virus glycoprotein (RVG) is a surface protein that allows viruses to enter the host cells, and in this case, get in through the blood-brain barrier. The research has suggested that the protein interacts with the murine p75 neurotrophin receptor, which works with neurotrophin signaling. (3) The researchers investigated how the RVG protein binds to the receptor and how this interaction differs from traditional p75 binding. They specifically studied the structural features that allow RVG to bind to p75. The experimental methodologies used included assaying with mammalian and avian assays, competitiveness experiments with nerve growth factor (NGF), and mutational analysis of the p75 receptor domains. (4) The research focused on the RVG binding to mammalian versus avian receptors and testing all different metrics that show how well it binds. They specifically tested binding to Trk receptors, seeing whether RVG and NGF share binding sites, identifying which cysteine-rich domain (CRD) mediates RVG binding,

and testing the impact of a point mutation (Gln33→Glu) on binding affinity. (5) The findings identify CRD1 as a novel high-affinity binding site for RVG (distinct from neurotrophin binding domains), providing valuable insight into the mechanism. This knowledge helps me in my ISM project because it helps me about how viral glycoproteins exploit host receptors. Of course, this is an older study, so it doesn't have the same amount of up-to-date info, but it helps me a lot with context for the project I am building. (6) The study is limited by its reliance on in vitro binding assays; it does not directly demonstrate how RVG–p75 binding functions during live viral infection in vivo. The other main limitation is that it is an older study, which makes the information less credible. Still, as I also want to work in the same scope as they are, I felt that it could help me contextualize the situation. (7) The study shows that RVG strongly binds to a new site on the p75 receptor (called CRD1) using three copies of itself. A key amino acid, Gln33, is needed for this binding, which only happens in mammals and may explain why rabies mainly infects them. Other viruses, like herpes, also use CRD1, suggesting this site could be a common entry point for different viruses. (8) This research highlights how viruses adapt to exploit host receptors in unique ways, often repurposing domains not typically involved in ligand binding. The work encourages me to further explore receptor virus interactions as potential targets for therapeutic intervention, especially in the context of alzheimers where we can exploit these binding affinities to our advantage.

Yang, Fanli et al. “Structural Analysis of Rabies Virus Glycoprotein Reveals pH-Dependent Conformational Changes and Interactions with a Neutralizing Antibody.” Cell host & microbe vol. 27,3 (2020): 441-453.e7. doi:10.1016/j.chom.2019.12.012

(2) The rabies virus glycoprotein (RVG) changes shape based on environmental cues. The research in this field usually only shows the protein in a more summarized format, making it

hard to determine its full-length, functional conformation on intact viral particles. Understanding its shape changes, especially regarding different pH, is key to explaining how rabies infects host cells and how neutralizing antibodies block this process. (3)The study's objectives were to map the binding mechanism of a neutralizing antibody, determine the full-length structure of RVG, and demonstrate how it changes shape in response to acidic environments (523-11). The researchers captured RVG's structural states at neutral and acidic pH levels using cryo-electron microscopy (cryo-EM), allowing for near-atomic resolution. They performed antibody-mapping experiments to determine how 523-11 interacts with various glycoproteins. Additionally, they conducted studies analyzing different vesiculovirus glycoproteins and emphasized characteristics specific to the rabies virus. (4) In particular, the study examined domain rearrangements between prefusion and postfusion states, identified the flexible linkers and residues that function as molecular "switches" during these transitions, and captured the structural characteristics of RVG under conditions that resemble viral entry. The scope also included thoroughly mapping the recognized bipartite epitope-11. However, the study did not include in vivo models of viral infection or receptor interactions within living systems; instead, it was restricted to structural and biochemical analyses carried out in vitro. (5) The study offers important new information about how the rabies virus enters host cells. The results expand our knowledge of viral fusion proteins by demonstrating how RABV-G reversibly changes between structural states. By guiding the development of therapeutic antibodies and vaccines, the discovery of a bipartite antibody-binding epitope contributes translational value. The work offers a structural framework for researching how viral glycoproteins take advantage of noncanonical stability and reversibility mechanisms, which opens up possibilities for antiviral tactics against related viruses outside of rabies. (6) Despite its contributions, the study has limitations. The structural changes were

observed under controlled pH buffer conditions, which may not fully reflect the complexity of the endosomal environment inside host cells. The research did not directly look at RABV-G's interactions with its cellular receptors during live infection or examine the structural dynamics in living organisms. Furthermore, while antibody 523-11 was analyzed in detail, the study does not consider the possibly diverse mechanisms used by other neutralizing antibodies. These limitations indicate that further investigation is needed to understand the structural findings in the context of the entire viral lifecycle. (7) The study successfully captures the structure of full-length, trimeric RABV-G and reveals the reversible nature of its pH-driven conformational changes. It identifies flexible linkers as the molecular basis of structural transitions and highlights the critical role of bipartite antibody binding in neutralization. Together, these findings advance the understanding of rabies virus entry and structural features, such as the CRD-like viral docking spaces. This work deepens knowledge of rabies pathogenesis and provides structural insights relevant to my project. (8) This research demonstrates how viruses adapt at the molecular level to exploit host-cell mechanisms with remarkable precision. Unlike many viral fusion proteins, RVG combines structural stability and reversibility, underscoring rabies's unique strategies for successful infection. More broadly, the work illustrates the power of structural biology in virology: single shape change snapshots or residue-level changes can redefine our understanding of viral behavior. I can use this information to help manipulate the shape changes of the RVG protein so I can actually change how the protein attaches to the blood-brain barrier.

Liu, Hui et al. "Mechanisms of Blood-Brain Barrier Disruption in Herpes Simplex Encephalitis." Journal of Neuroimmune Pharmacology: The Society on NeuroImmune Pharmacology official journal vol. 14,2 (2019): 157-172. doi:10.1007/s11481-018-9821-6

(2) Herpes simplex encephalitis (HSE) is a severe neurological disorder most often caused by herpes simplex virus 1 (HSV-1), a neurotropic double-stranded DNA virus. The condition typically affects the temporal and frontal lobes or limbic system, leading to edema, hemorrhage, and necrosis in the brain parenchyma. Despite antiviral therapies, many patients suffer long-term complications such as dementia and epilepsy. Understanding how HSV-1 contributes to brain injury requires examining the blood-brain barrier (BBB), a selective interface composed of endothelial cells, tight junctions, astrocytes, pericytes, and basement membranes. Because the BBB regulates the movement of molecules and immune cells into the brain, its disruption is increasingly recognized as a central factor in HSE pathogenesis. (3) The study aimed to explore the link between HSV-1 infection, BBB breakdown, and the progression of HSE. Specifically, the research sought to describe how HSV-1 alters BBB integrity and how these changes contribute to inflammatory responses in the central nervous system. The methods involved reviewing structural and functional aspects of the BBB, analyzing evidence from studies documenting viral entry, cytokine trafficking, and immune cell infiltration, and synthesizing emerging data that connects BBB permeability with brain pathology in HSE. (4) The scope of this work includes a comprehensive discussion of HSV-1 biology, the normal function of the BBB, and the cascade of events following infection that compromise BBB integrity. It also examines the consequences of increased viral and immune-cell passage into the brain parenchyma, focusing on how such breaches amplify neuroinflammation and neuronal damage. Finally, the study highlights potential therapeutic targets and research avenues for mitigating BBB disruption during HSE. However, the analysis is restricted to existing research and does not incorporate new experimental findings or in vivo studies beyond what is available in the literature. (5) This work helps frame a viral infection and a disorder of barrier dysfunction. It

emphasizes the therapeutic potential of protecting or restoring barrier integrity by highlighting the BBB as a structural and functional regulator of brain homeostasis. Clinically, these insights could lead to novel strategies that go beyond antiviral treatment to prevent long-term complications such as epilepsy and cognitive decline. On a broader level, the study adds to a growing body of evidence linking viral infections to BBB dysfunction, which may inform research into other neurotropic pathogens and neurodegenerative conditions. (6) The study is limited by its reliance on secondary data and literature review. It cannot establish causal mechanisms between HSV-1 infection and BBB disruption in human patients, as much of the evidence comes from animal models or in vitro systems. Additionally, BBB breakdown in HSE is likely influenced by multiple overlapping mechanisms, including viral replication, immune response, and host genetic susceptibility, which remain incompletely understood. These limitations underscore the need for longitudinal and mechanistic studies that can directly track BBB integrity and function in the context of HSV-1 infection. (7) The study concludes that BBB disruption plays a central role in the pathogenesis of HSE. HSV-1 infection alters barrier integrity, enabling viruses, immune cells, and cytokines to enter the brain parenchyma, where they fuel neuroinflammation and tissue damage. This breach helps explain why patients often suffer long-term neurological consequences even after antiviral treatment. Protecting the BBB, therefore, emerges as a promising strategy for reducing brain injury in HSE, complementing current therapeutic approaches. (8) This research highlights the importance of viewing the BBB not as a static wall but as a dynamic interface that shapes neurological health. The findings also point toward a shift in therapeutic priorities—from focusing solely on eradicating the virus to addressing the host's structural defenses. This helps me develop a more thorough understanding of the blood-brain barrier as a whole, allowing me to develop more ways we can bypass the

barrier. Beforehand, I considered it an impermeable wall, but my study changed that assumption and grew my perspective.

Taskinen, E et al. “Herpes simplex virus encephalitis. Prolonged intrathecal IgG synthesis and cellular activity in the cerebrospinal fluid with transient blood-brain barrier impairment.” Journal of the neurological sciences vol. 63,3 (1984): 331-8. doi:10.1016/0022-510x(84)90156-4

(2) Herpes simplex virus encephalitis (HSVE) is a severe and acute infection; alterations in cerebrospinal fluid (CSF) composition and blood-brain barrier (BBB) function can continue for months to years, shaping long-term neurological outcomes. Understanding these changes, particularly immunoglobulin synthesis and cellular responses, offers essential insights into the immunopathology of HSVE. (3) This study aimed to investigate CSF protein and cellular alterations in HSVE, explicitly focusing on intrathecal immunoglobulin production, pleocytosis, and BBB impairment. Six patients (four confirmed, two presumptive HSVE) were studied over follow-up periods ranging from 17 to 855 days. Methods included nephelometric measurements of CSF and serum albumin and immunoglobulins to assess intrathecal synthesis and BBB integrity, along with Millipore filtration–cytocentrifuge techniques for cytological analysis of CSF cell populations. (4) The research focused on longitudinal monitoring of CSF changes in HSVE patients, particularly during the early acute phase (first two months) and extending into long-term follow-up (up to 28.5 months). Parameters examined included daily intrathecal IgG production, changes in IgA and IgM during early disease, variability in BBB impairment, and the persistence of pleocytosis and lymphoid activation. While limited to a small patient sample, the scope provided detailed temporal insight into CNS immunological activity during and after HSVE. (5) The findings highlight the intensity and persistence of CNS immunoactivation in

HSVE. The sustained intrathecal IgG synthesis—lasting over two years in one case—demonstrates how viral infection can lead to long-term, perhaps maladaptive, immune activity in the brain. Elevated IgA and IgM in early disease suggest a broader spectrum of humoral responses than previously appreciated. Identifying BBB impairment as most pronounced within the first two months provides a critical therapeutic window for interventions aimed at preserving barrier integrity and reducing secondary brain injury. (6) The study is constrained by its small sample size (six patients) and heterogeneous follow-up periods, which limit generalizability. While robust for protein and cell quantification, the methods do not directly address the mechanisms driving prolonged intrathecal IgG synthesis or lymphoid activation. Moreover, the observational design cannot establish causal links between immunoactivation, BBB impairment, and long-term neurological symptoms. Finally, the study predates more advanced molecular and imaging tools, meaning that specific mechanistic details remain speculative. (7) This work establishes that HSVE is associated with sustained immunological activity in the CNS, characterized by persistent intrathecal IgG synthesis, variable but transient BBB impairment, and long-lasting lymphoid activation. The intensity of these responses peaks during the first two months but can endure for up to 28.5 months, suggesting that HSVE triggers chronic immune dysregulation in the brain. These findings underscore the need for therapeutic approaches that target viral replication and address ongoing immune activity. (8) This study reflects the broader challenge of neurotropic viral infections: they often leave behind structural brain damage and long-term immune scars. The persistence of IgG synthesis and lymphoid activity illustrates how the CNS, despite being an immune-privileged site, can sustain chronic activation once breached. This highlights the importance of balancing antiviral therapy with immunomodulation to reduce secondary damage.

This study helped me understand how the HSV disease works and how people have treated it, but it doesn't connect directly to my project. I need to look at more similar articles that are more relevant to me.

Zhao, Yibin et al. “Factors influencing the blood-brain barrier permeability.” Brain research vol. 1788 (2022): 147937. doi:10.1016/j.brainres.2022.147937

(2) The blood-brain barrier (BBB) is a dynamic, multicellular structure that protects the brain from harmful substances while maintaining homeostasis. Comprising brain microvascular endothelial cells (BMECs), pericytes, astrocytes, neurons, microglia, and extracellular matrix, the BBB limits paracellular and transcellular transport. Tight junctions (TJs), adherens junctions (AJs), and transporters regulate permeability. The neurovascular unit (NVU) concept highlights the interaction of multiple cell types in maintaining BBB integrity. BBB permeability can be altered under pathological conditions by inflammation, chemical mediators, age, sex, temperature, microRNAs, and other non-physicochemical factors. (3) The aim is to review mechanistic insights into BBB maintenance and disruption and identify factors influencing BBB permeability. The researchers conducted a Narrative review of recent literature, including studies on endothelial cells, pericytes, astrocytes, neurons, microglia, junctional proteins, transporters, chemical mediators, and other physical/physiological factors. The authors summarized findings from in vivo, in vitro, and molecular studies to provide a comprehensive overview. (4) This review focuses on multiple aspects of BBB regulation, including cellular components such as endothelial cells, pericytes, and astrocytes, as well as molecular structures like tight junctions (claudins, occludin, tricellulin, junctional adhesion molecules) and adherens junctions (VE-cadherin). It also covers transporters, vesicular transcytosis, chemical mediators such as bradykinin, histamine, and cytokines, and physiological or environmental factors including age,

sex, temperature, exercise, and microRNAs. Mechanistic pathways affecting BBB integrity under both normal and pathological conditions are highlighted, illustrating the complex regulation of BBB permeability. (5) The review provides a detailed and up-to-date understanding of the factors influencing BBB permeability. It identifies potential therapeutic targets for improving drug delivery to the central nervous system and protecting the BBB under pathological conditions. The paper is valuable for researchers and clinicians seeking insights into the protective and disruptive mechanisms governing BBB function. (6) As a narrative review, the article does not provide quantitative analysis or meta-analytic data. Many mechanistic insights are derived from experimental models, which may not fully translate to human physiology. Additionally, emerging factors and novel molecular pathways affecting the BBB may not be comprehensively covered. (7) A complex interplay of cellular, molecular, and chemical factors controls BBB permeability. Tight junctions, adherens junctions, transporters, and NVU components are essential for maintaining BBB integrity, while chemical mediators and physiological conditions can compromise it. Understanding these mechanisms may inform therapeutic strategies to preserve BBB function or facilitate targeted drug delivery to the brain. (8) This review highlights the critical role of the NVU and the dynamic regulation of BBB permeability. The dual functions of astrocytes, the interplay of transporters, and the influence of chemical mediators illustrate the delicate balance between brain protection and substance exchange. I can use these as focuses for what part of the blood-brain barrier I want to access.