THE ROLE OF EPSTEIN-BARR VIRUS AS THE TRIGGER FOR MULTIPLE SCLEROSIS: hypotheses and emerging immunotherapies

Sabrina Diaz Mora
Microbiology Degree
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UAB Universitat Autònoma de Barcelona

INTRODUCTION

Multiple Sclerosis (MS) is a global disease with an increasing prevalence during the last years. Although it has been known since the mid-19th century, heterogeneity makes it a disease hard to understand. On the road to finding a possible cause for the onset of MS, many fingers pointed to **Epstein-Barr virus (EBV)**, a viral agent that infects more than 90% of the population.

OBJECTIVES & METHODOLOGY

- Describe the **immune mechanisms** during EBV infection and in MS patients.
- Explain the development of the **autoimmune response**.
- Analyse the **hypotheses** on why an EBV-infected patient may develop MS.
- Mention the existing **immunotherapies** and upcoming treatments.

KEYWORDS: multiple sclerosis, Epstein-Barr virus, autoimmunity, immunotherapies, immune response

EPSTEIN-BARR VIRUS

EBV establishes **lifelong** latent infections within B-cells, triggering latency transcription programs.

The immune response involves the expression of immediate early, early, and late-stage genes. Natural killer (NK) cells are the initial line of the **innate defense** and are abundant in EBV infections. The **adaptive immunity** is carried by $CD8^+$ T-cells, although bursts of $CD4^+$ T-cell reactivity can be detected.

Inability to control infection may lead to the development of EBV-related diseases, including **multiple sclerosis**.

MULTIPLE SCLEROSIS

MS is a **chronic autoimmune demyelinating disease** characterized by inflammatory lesions, axonal degeneration, gliosis and blood-brain barrier breakdown. It is consequence of environmental and genetic factors and is classified into four subtypes.

The **immune response** plays a huge part in its development, contributing to neuroinflammation, myelin damage, and white matter development.

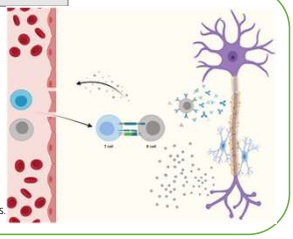

Figure 1: Pathogenesis of multiple sclerosis in the CNS. Created with BioRender.com

PROPOSED HYPOTHESES

1 MOLECULAR MIMICRY

A **cross-recognition event** (Figure 2) allows the activation of autoreactive cells because of structural similarity. 3%-4% of EBNA1 specific $CD4^+$ T-cells react against myelin-derived peptides.

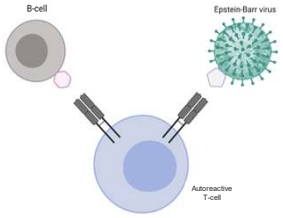

Figure 2: T-cell recognizing a B-cell epitope and an EBV epitope, triggering a cross recognition event. Created with BioRender.com

2 PENDER'S HYPOTHESIS

EBV-infected autoreactive B-cells proliferate and migrate to the brain where they produce autoantibodies. Cross-reactive $CD4^+$ T-cells arrive in the CNS, causing organ damage and autoimmune disease.

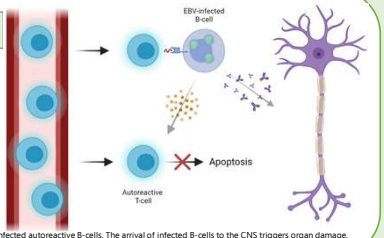

Figure 3: Depiction of Pender's hypothesis on infected autoreactive B-cells. The arrival of infected B-cells to the CNS triggers organ damage. Adapted from [4]. Created with BioRender.com

3 MISTAKEN SELF

αβ-Crystallin is a limited-expression protein in lymphocytes and oligodendrocytes. EBV infection triggers its expression, and the immune system mounts a response against it.

4 BYSTANDER DAMAGE

MS might be a consequence of the immune system trying to control EBV infection. The exaggerated response provokes the unveiling of **hidden autoantigens.**

5 INTERACTION WITH HERVs

Human endogenous retrovirus-W expression has been detected in **active lesions** as well as multiple sclerosis retrovirus titres. EBV infection predisposes to the presence of HERV-W.

IMMUNOTHERAPIES

Treatment is used to control inflammatory activity, prevent relapses, and avoid accumulation of disability. Non-symptomatic MS, Relapsing-remitting MS and Secondary progressive MS patients can be treated with **IFNβ**, a drug that inhibits infectivity, stimulates T-cell responses and diminishes the memory B-cell compartment. **Monoclonal antibodies** are also used in patients to decrease inflammation and block disease progression.

Therapies directed against EBV include:

1 B-cell depletion therapies

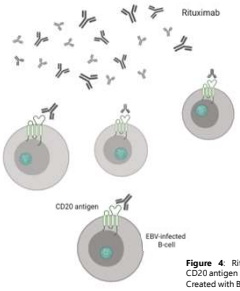

Figure 4: Rituximab antibodies attacking the CD20 antigen present in EBV-infected B-cells. Created with BioRender.com

2 Antiviral drugs

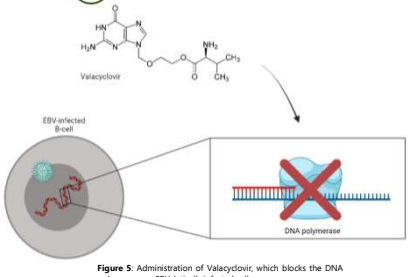

Figure 5: Administration of Valacyclovir, which blocks the DNA polymerase on EBV-lytically infected cells. Created with BioRender.com

3 Vaccination

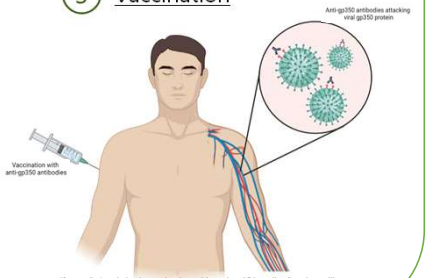

Figure 6: Prophylactic vaccination with anti-gp350 antibodies that will attack glycoprotein350 present on the membrane of EBV. Created with BioRender.com

CONCLUSIONS

- MS is a very heterogeneous disease whose causes are difficult to determine since many **environmental and genetic factors** are involved.
- EBV infection is a probable disease trigger, but no hypothesis has been confirmed. However, the most accepted one is **Pender's hypothesis on infected autoreactive B-cells**.
- The main immune event during EBV infection is the **$CD8^+$ T-cell response against lytic epitopes**.
- In MS patients, the immune response shows evidence of an **impaired attempt** to control viral infection.
- There is no ultimate cure for MS, but **B-cell depletion therapies** have proven successful.

How the path of research will evolve is mostly uncertain, but it is clear that causative agents must be deciphered to progress. Further research is needed in many fields surrounding MS, and it will not be until these fields are more known that a cure will be developed.

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