MEA Summary Review: Does a mystery factor in ME/CFS serum cause viral immunity at the cost of reduced energy metabolism?

By: Charlotte Stephens 5th May 2020

Introduction

There has been quite a bit of discussion over an interesting new study from a team of researchers at the University of California San Diego School of Medicine and 3 German Universities. The study, published in the journal 'ImmunoHorizons', is called:

Human Herpesvirus-6 Reactivation, Mitochondrial Fragmentation, and the Coordination of Antiviral and Metabolic Phenotypes in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Prof. Robert Naviaux and Dr Bhupesh Prusty, who led the research, found that mitochondria in some ME/CFS patients may have undergone a switch, possibly triggered by HHV-6 reactivation, resulting in the mitochondria having antiviral properties, at the high cost of drastically decreased energy production. This switch may be caused by an unidentified factor in patient serum that can be transferred to healthy cells.

San Diego University Health published an article about the study, including quotes from the authors.

Key Points

- The researchers hypothesised that HHV-6 infection may play a role in ME/CFS as they found that HHV-6 reactivation in cells induces mitochondrial dysfunction and lowered cellular energy production.
- They found that the decreased energy state in mitochondria can be induced in healthy cells by an unknown transferable factor secreted by HHV-6 reactivated cells.
- They looked into HHV-6 as a potential causative factor for ME/CFS but found very low copies of viral genome in the 25 ME/CFS patients tested, which was not enough to point to any direct role of active viral infection.
- Serum taken from ME/CFS patients and applied to healthy cells induced the same changes in the mitochondria and resultant antiviral properties in healthy cells as the unknown factor secreted from the HHV-6 reactivated cells.
- The ME/CFS cells had antiviral properties, at the high cost of mitochondrial dysfunction and lowered energy production.
- These serum experiments could be used to develop a diagnostic test and also be used to further study the mystery factor causing these changes.

Background

Prof. Robert Naviaux is co-senior author of the study, together with Dr Bhupesh Prusty, a molecular virologist at a University in Germany.

Prof. Naviaux is an expert in mitochondrial disease and metabolomics and has done much research into the metabolic features of ME/CFS.

He is most well-known for his 'cell danger response' or 'hibernation theory' in which he hypothesised that something keeps cells stuck in 'defence' mode after an infection or stressful event, resulting in a chronically low metabolic state with very low cellular energy production.

The ME Association is currently funding Dr. Karl Morten, at Oxford University, who is attempting to replicate this work and is studying mitochondria and metabolomics in ME/CFS cells.

Images of Dr. Naviaux and Bhupesh Prusty. Sources: naviauxlab.ucsd.edu

Mitochondria

Mitochondria are the 'powerhouse' of the cell – they are the location of energy production (in the form of ATP) within cells. However, they have also been shown to provide a role in immune defence.

Mitochondrial dysfunction has previously been demonstrated in ME/CFS, with less efficient energy production in cells resulting in a range of symptoms, but it is not known what might be causing this dysfunction.

The researchers in this study suspect that HHV-6 reactivation may be responsible for the mitochondrial dysfunction observed in ME/CFS.

HHV-6

HHV-6 (or Human herpesvirus) is present in 100% of the human population, with most people being infected by the age of 3. It is in the same family of viruses as Epstein Barr or EBV, that causes glandular fever, Cytomegalovirus, and chicken pox.

These viruses can insert themselves into DNA within cells and remain latent (inactive) for years, which causes no problems in most people, but they can become reactivated later in life.

Reactivation of HHV-6 has been implicated in a number of different diseases, including heart disease, Epilepsy, Hashimoto's Thyroiditis, Lupus, Sjogren's syndrome, Multiple Sclerosis and ME/CFS.

HHV-6 reactivation has long been suspected to play a role in ME/CFS, however it can be difficult to detect as, after the initial infection, the viral DNA does not circulate in the bloodstream so cannot be detected by standard blood tests.

The possible role of HHV-6 in ME/CFS is what has formed the rationale behind some researchers trying to treat ME/CFS with antiviral drugs (Montoya *et al.,* 2013). But there has been no definitive research establishing HHV-6 reactivation as a causal agent in ME/CFS.

Study breakdown

In an attempt to understand if there is any causative role of HHV-6 in ME/CFS, the researchers in this latest study looked at mitochondrial structure and function together with antiviral properties of cells with reactivated HHV-6 and compared them to healthy cells incubated with serum from ME/CFS patients.

Changes in mitochondria caused by HHV-6 reactivation

The researchers used a model to look at what happened to cells when they chemically induced HHV-6 reactivation.

They found that it caused mitochondrial fragmentation (a change in structure) and altered the expression of some proteins, including decreasing several mitochondrial proteins.

This led to **decreased cellular energy production** and decreased levels of ATP. This is known as a 'hypometabolic' (low energy metabolism) state.

Antiviral properties induced by HHV-6 reactivation

The changes in mitochondrial structure, along with decreased energy production, has been suggested to increase proinflammatory cell danger response (CDR) and play a role in cellular defence against pathogens.

To test this theory, the researchers took cells with or without reactivated HHV-6 and infected them with two different types of viruses: Influenza-A and HSV-1.

The results revealed that the cells with reactivated HHV-6 were **protected against viral infection.**

Transferable 'mystery factor' causing these changes

Next, the researchers took it a step further and put some of the supernatant (liquid surrounding the cells) from the cells with reactivated HHV-6 onto some healthy cells.

They observed the same changes in mitochondrial structure and an induced hypometabolic state.

These results show that there is an unknown transferable factor in the fluid, secreted from the HHV-6 reactivated cells, that can be transmitted to other cells and cause the changes that result in lowered energy production.

This led the researchers to speculate that HHV-6 may play a role in ME/CFS pathology.

Possible role of HHV-6 in the causation of ME/CFS

The researchers tested blood and hair samples from 25 ME/CFS patients and 10 controls for the presence of active HHV-6 infection.

They found no viral DNA in any of the ME/CFS hair samples and only 3 patients tested positive for HHV-6 DNA in their blood, which is not enough to point to any direct role of active viral infection in ME/CFS.

However, this could be due to latent (inactive) virus or that only a few cells have viral activation and so the 'viral load' is not high enough to be detected.

> "Lack of a strong HHV-6 and HHV-7 infection in ME/CFS patients in our study and several others has historically cast doubt on the involvement of these viruses in ME/CFS.
>
> "However, in this study, we show that incomplete HHV-6 reactivation, even in a small fraction of latently infected cells, causes reactivated cells to secrete an activity that can be transferred in serum and produces mitochondrial fragmentation and coordinates a powerful antiviral program in responding cells."

Transferable 'mystery factor' in ME/CFS serum

Next, the researchers applied serum (fluid from the blood) taken from ME/CFS patients and controls onto healthy cells and observed what happened to the mitochondria.

They found that the same changes in mitochondrial structure observed in the previous experiment occurred in the healthy cells that were incubated with ME/CFS serum, but not the ones incubated with control serum (see figure 1).

This suggests that changes in mitochondrial structure and metabolism are an important characteristic feature of ME/CFS and that it does not require direct viral infection in every cell because there is an unknown secreted factor causing these changes.

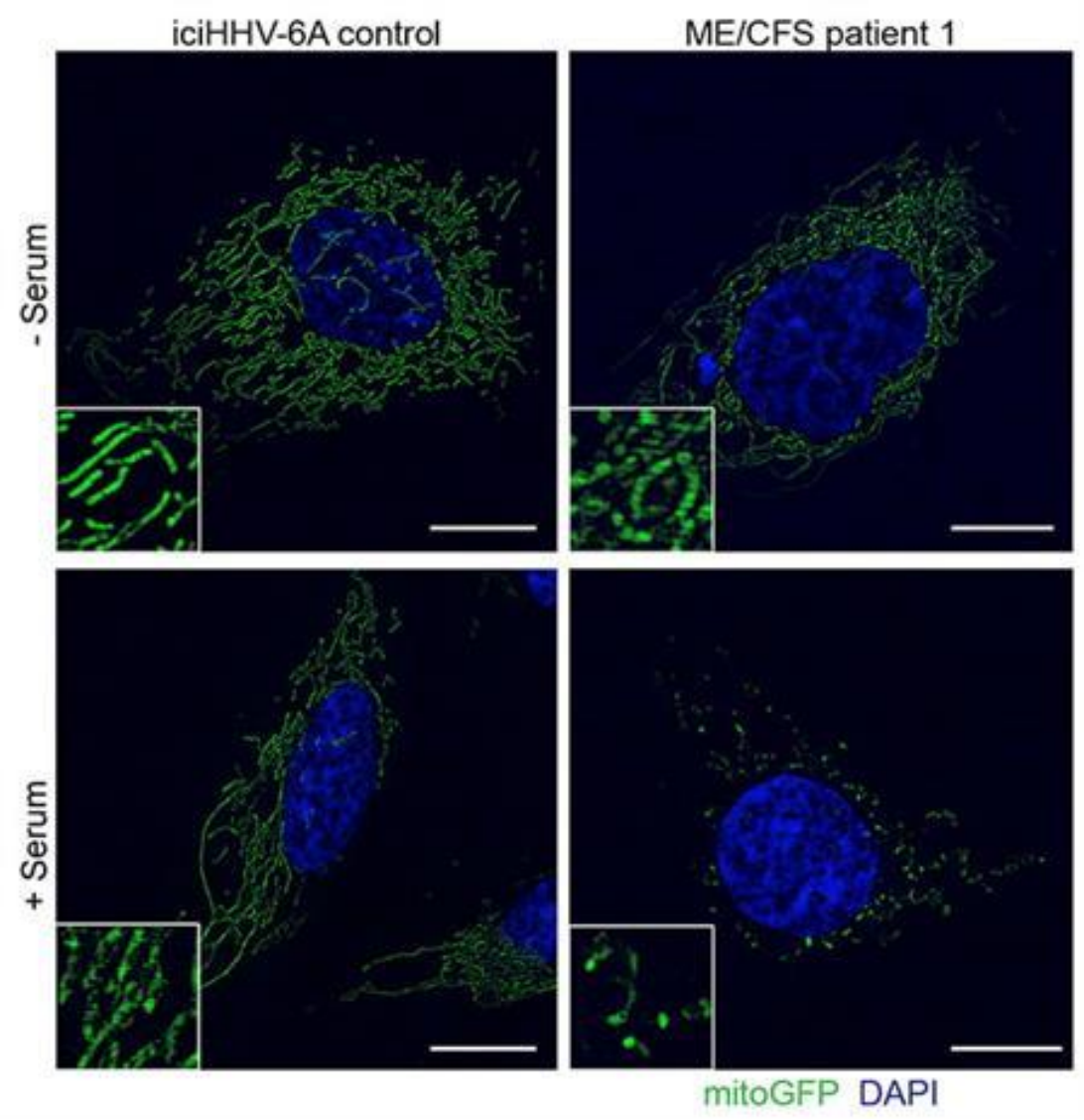

Figure 1. Mitochondrial structure in cultured cells before and after treatment with serum from either controls or ME/CFS patients. The green mitochondrial networks are normally filamentous (as seen in the top images). After treatment with healthy control serum, mitochondria remain the same (bottom left). After treatment with ME/CFS patient serum, mitochondria are fragmented (bottom right).

Antiviral properties induced by 'mystery factor' in ME/CFS serum

Finally, the researchers tested if the serum from the ME/CFS patients resulted in the same anti-viral protection as was seen from the factor from HHV-6 reactivated cells.

They found that the healthy cells incubated in ME/CFS serum **did have significant protection** against infection with influenza-A and HSV-1, whereas the control serum offered no protection against infection (see figure 2).

This could offer an explanation for why there is a subgroup of ME/CFS patients who report that they rarely get any colds or infections.

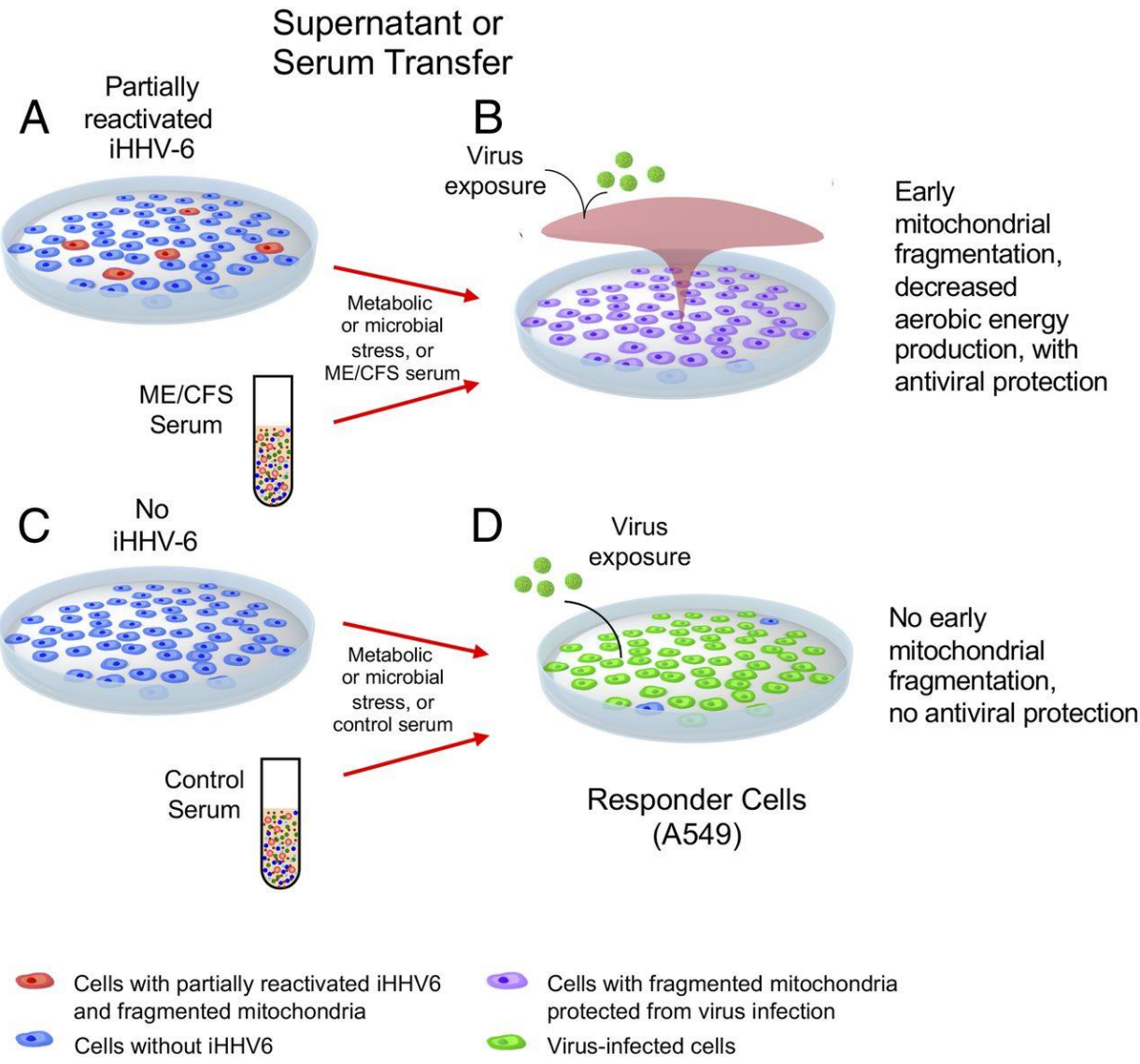

Figure 2. A visual overview of the study. Both reactivated HHV-6 cells and ME/CFS serum applied to healthy cells results in changes in mitochondrial structure, decreased energy production and antiviral protection. Whereas cells without reactivated HHV-6 and healthy control serum does not result in any of these changes when applied to healthy cells.

Summary of findings and what they mean

This study shows that there is a transferable factor in the serum of people with ME/CFS that results in a level of immunity against certain types of viruses, but at the cost of decreased mitochondrial function, resulting in low energy production.

It found that both HHV-6 reactivation and ME/CFS patient serum treatment induced changes in mitochondrial structure and state (into defence mode instead of energy production mode), caused a hypometabolic state (reduced energy production) and a strong proinflammatory state in the cell that protects against certain viruses. Furthermore, the unknown factor that causes these changes is transferable to healthy cells under lab conditions.

The transferable factor in the serum is yet to be identified and so further studies are needed in order to isolate the factor that is causing these cell changes. The authors offered some possible candidates; cytokines, autoantibodies, or broken mitochondrial DNA released by the fragmented mitochondria.

The effect that the ME/CFS serum had on healthy control cells was so significant and specific that it was able to distinguish ME/CFS patient's serum from controls with high accuracy. This could have implications for developing a diagnostic test.

> "Our mitochondrial reporter-based cell system will provide an opportunity to develop a diagnostic test for ME/CFS as well as provide a platform for further identification of potential factors that define ME/CFS pathophysiology."

The authors concluded:

"Our results show a serum-transferrable innate immune activity in ME/CFS patients that induces a state of low mitochondrial activity accompanied by changes in mitochondrial dynamics that might contribute to disease pathophysiology."

Researcher Comments

San Diego University Health published an article about the study, including quotes from the authors:

"These findings are important because they show for the first time that there is an **antiviral activity in the serum** of patients with ME/CFS that is tightly associated with an activity that fragments the mitochondrial network and **decreases cellular energy** (ATP) production," said Robert Naviaux.

"This provides an explanation for the common observation that ME/CFS patients often report a sharp decrease in the number of colds and other viral infections they experience

after they developed the disease. Our work also helps us understand the long-known, but poorly understood link of ME/CFS to past infections with Human Herpes Virus-6 (HHV-6) or HHV-7,"

"We found that exposure to new metabolic or environmental chemical stresses caused cells with an integrated copy of HHV-6 to secrete an activity that warned neighbouring cells of the threat.

"The secreted activity not only protected neighbouring and distant cells from new RNA and DNA virus infections, but also fragmented the mitochondrial network and lowered their intracellular ATP reserve capacity. Cells without an integrated copy of HHV-6 did not secrete the antiviral activity."

"Our results show that cellular bioenergetic fatigue and cellular defence are two sides to the same coin in ME/CFS. When energy is used for cellular defence, it is not available for normal cell functions like growth, repair, neuroendocrine and autonomic nervous system functions."

"This paper will be a paradigm shift in our understanding of potential infectious causes behind ME/CFS. Human herpesvirus 6 and HHV-7 have long been thought to play a role in this disease, but there was hardly any causative mechanism known before," said senior co-author Prusty.

"For the first time, we show that even a few HHV-6 infected or reactivated cells can drive a powerful metabolic and mitochondrial remodelling response that can push even the non-virus containing cells towards a hypometabolic (abnormally low metabolic) state.

"Hypometabolic cells are resistant to other viral infections and to many environmental stresses, but this comes at the cost of severe symptoms and suffering for patients with ME/CFS."

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