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> ONE MONTH, ONE PROTEIN <

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unconventional

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There are about 8 billion people living on our planet today. It's a lot. But consider the following: one human body harbours about 380 trillion viruses and 39 trillion bacteria – both on our skin and underneath it. That means there are thousands of times more organisms living off one of us than there are humans living off the whole Earth. So, as you stroll down a snow-clad path on a crisp and sunny winter's afternoon, thinking how wonderful it sometimes is to be alone, from a purely biological point of view you are not. Your body is literally teeming with organisms that use you as convenient terrain to reproduce, multiply and spread. The great majority of these organisms – viruses, bacteria and fungi – belong to what is called our microbiome. Over the years, we have formed some kind of understanding with our microbiome, and we all get on together fairly well on a give and take basis. As an illustration, the sum of viruses we carry, our virome, is thought to have an overall role in keeping our immune system alert. In this light, scientists recently discovered a novel immune strategy used by our brain cells to prevent the herpes virus from infecting them. The mechanism involves a protein known as TMEFF1.

Kamisakka Sekka (1866-1942)

woodcut, 1910

Herpes, or the herpes simplex virus (HSV), is a virus most of us have had close encounters with, more often than not in the form of cold sores. The Roman emperor Tiberius (42BC-37AD) is said to have banned kissing in the capital to stop the spread of such sores, suggesting that HSV has been travelling across the human population for at least 2,000 years. Thought to have originated in Africa, there is reason to believe herpes is the result of cross-species transmission from apes to humans. Surprisingly, it was only in the 1940s that scientists discovered that cold sores were the doings of a virus. Twenty years later, the first antiviral therapies were introduced, followed by others in the 1970s and the 1980s but to date, despite 30 years of research, no vaccine has been found.

There are two kinds of herpes: HSV-1 and HSV-2. HSV-1 affects 64% of the world's population under the age of 50. Usually caught during childhood, it is the main cause of oral herpes, or the common cold sore. HSV-2 is estimated to affect 13% of the world's population aged 15 to 49. It is the main cause of genital herpes and spreads by sexual contact. The maddening thing is our system never gets rid of HSV. The infection is kept at bay but once inside us the virus is there to stay. Following an initial infection in our epithelial cells, HSV gets into nerve cell roots and makes its way up to the sensory nerve ganglia. Here, the virus lies dormant until it is reactivated at a time impossible to predict, but usually when our immune system is not in top form.

HSV-1 is responsible for the rare occurrence of herpes simplex virus encephalitis (HSE) – the most common viral encephalitis in the Western world. HSE is life-threatening and affects about 2 people out of 100,000 individuals per year, especially children between the ages of 3 months and 6 years

old. Why is HSV-1 harmful to only un unlucky few? Why is the central nervous system of some individuals more vulnerable to HSV-1? Is there a genetic predisposition? Yes, there seems to be. Unlike other parts of the body, the central nervous system does not cope well with viral infection or a full-blown immune reaction. The blood-brain barrier is usually able to limit the damage as it filters the entry of cellular and molecular components – including those that are part of an immune reaction. However, the brain must also be able to fight off viruses that cross this barrier, naturally. This would then imply that it has different antiviral strategies for its own specific protection.

Recently, scientists discovered a protein which happens to be deficient on the surface of brain cortical cells in individuals prone to developing HSE. The protein is called *Transmembrane protein with EGF-like and two follistatin-like domains 1*, or TMEFF1, and is usually found predominantly on brain cells. Not only does TMEFF1turn out to be involved in countering HSV-1 infection, but it does not depend on classic antiviral immune response such as that triggered off by interferons for example. So TMEFF1 is an immune strategy specific to the central nervous system. How does its presence affect HSV-1?

Viruses only infect given cells. The flu virus, like the coronavirus, typically goes for cells in the respiratory tract, for instance, while the polio virus heads straight for brain cells involved in muscle movement. For this, viruses need to recognise specific targets – or receptors – on the surface of the cells they are going to attack. It turns out that HSV-1 specifically recognises the entry receptor Nectin-1 located on the surface of cortical brain cells. Once bound to it, the virus and the brain cell fuse thus initiating infection. Ultimately, HSV-1's DNA is injected into the brain cell nucleus and the host's replication machinery is hijacked to produce viral progeny. Now, if TMEFF1 is also present on the brain cell surface, researchers found out that HSV-1 is unable to bind to Nectin-1 and thus unable to infect the cell.

So what does it do? TMEFF1 acts as a restriction factor for HSV-1. A transmembrane protein, the N-terminus of TMEFF1 protrudes into the extracellular medium while its C-terminus dangles in the cell cytoplasm. The N-terminal portion interacts with Nectin-1 in such a way that HSV-1 is unable to bind to it – though, for the time being, no one knows exactly how this happens. Meanwhile, on the cytoplasmic side of the brain cell, the C-terminal portion of TMEFF1 interferes with other factors, namely NMHC-IIA and NMHC-IIB, which usually guarantee viral-cell fusion. Taken together, both actions ensure that HSV-1 has a hard time infecting brain cells.

It sounds straightforward, but viral entry always requires myriads of factors that need to cooperate for infection to be successful. In the same way, blocking viral infection also involves many factors. This said, besides the fact that TMEFF1 is something of a free-spirit and does not require activation by other immune factors, it certainly seems to have a pivotal role in stopping HSV-1 infection. It could also explain why people who are deficient for the restriction factor are more liable to suffer from HES. Did TMEFF1 evolve especially to preserve our brain from infection? Perhaps. With this in mind, producing the extracellular domain of TMEFF1 in soluble form could provide therapies to help fight off HSV-1 and perhaps even HSV-2 infections – both in the central nervous system and elsewhere.

Cross-references to UniProt

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