Genetic ‘editing’ could help treat PML

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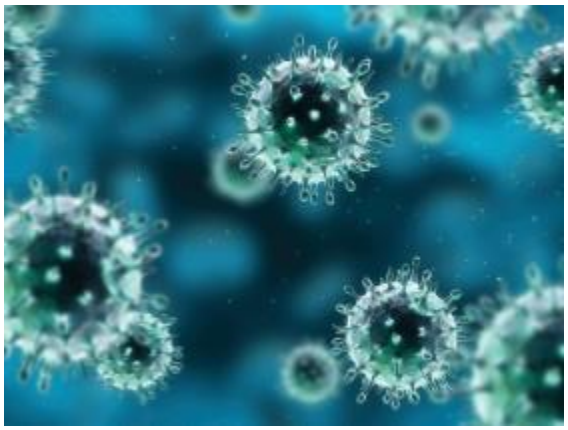

Progressive multifocal leukoencephalopathy (PML) is a potentially fatal brain infection that is caused by activation of the JC virus.

It has been found that a large number of the population carry the JC virus in an inactive state but it is only when reactivated by a weakened or suppressed immune system that it can cause PML to develop.

Immunomodulatory drugs such as natalizumab, and other medications used to treat MS, work by suppressing the immune system or preventing the immune system from entering the brain and therefore increase the risk of developing PML.

There is currently no effective treatment for PML so a group of scientists in the USA (Wollebo et al. *PLoS One*) have been investigating a new method called CRISPR/Cas9. CRISPR/Cas9 is a ‘gene editing’ technique that has already shown potential in the treatment of other viral diseases such as the HIV pro-virus and Hepatitis B, by disrupting the sequence of viral DNA to prevent it from replicating.
CRISPR is a short repeating segment of DNA that encodes the enzyme Cas9. Cas9 is an enzyme which cuts the DNA sequence. The enzyme can be guided using specific gene sequences to cut the DNA sequence of the virus at specific points.

One of the proteins in the JC virus called T-antigen (T-ag) has been found to be vital for the JC virus to replicate. Scientists have used the CRISPR/Cas9 system to mutate the gene encoding the T-ag protein in order to inhibit its production and therefore prevent viral replication.

Using hamster cells containing the JC virus they used Cas9 to cut and alter the genetic sequence of the T-Ag protein. The results showed that by inactivating the T-Ag protein expression, the ability of the cell to form clones was reduced, therefore inhibiting viral replication.

They also investigated the specificity of the Cas9 system to see if it had any unwanted effects on other genes. They identified the human genes most similar to the genetic code of the T-ag protein to see if these would be affected. It was found that these human “off-target” cells were not cut or mutated by the Cas9 enzyme.

This suggests that the CRISPR/Cas9 system is highly specific and will only affect the target gene of the virus.

One major benefit of this method is that it has the potential to not only inhibit the JC virus in people with PML but could also be used to eradicate the dormant virus; removing the risk of developing PML in the first place.

These findings suggest that with more research, the CRISPR/Cas9 technique has the potential to eliminate the JC virus making the use of immunosuppressive drugs safer for people with MS and other auto immune diseases.