October 23, 2020

Evolution & Behavior

Repurposing of retroviral genes: when foe becomes self

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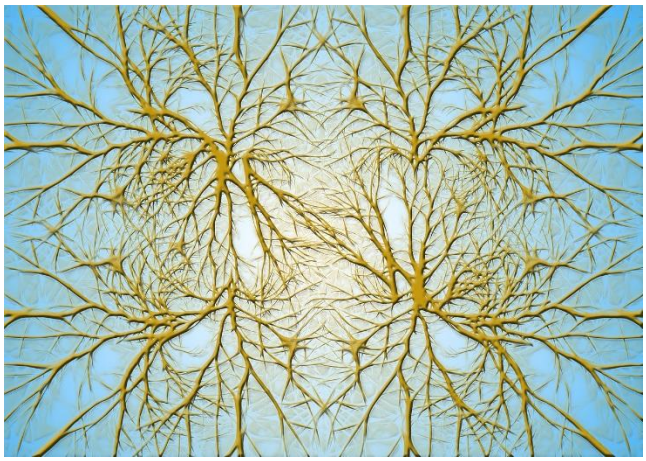
This Break was edited by Max Caine, Editor-in-chief - TheScienceBreaker

Throughout evolution, our genomes have been under attack by potentially harmful viruses. However, sometimes genes from the viral invaders have been captured and converted to provide a beneficial function for the host. A viral gene responsible for protecting retroviral RNA has been repurposed in both human and insect hosts to protect and transmit neurological mRNA signals.



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The genomes of all organisms are constantly under attack from a variety of sources, including the everyday effects of solar and ionising radiation together with chemical and oxidative insults. However, there are also more specific threats to our genomes like those that posed through invasion by viral pathogens. In particular, retroviruses like HIV that can insert their genetic material into the genome of their hosts. These attacks have continued over tens if not hundreds of millions of years. As a result, the human genome is littered with the remnants of past encounters with retroviruses. These invasive events have happened to such an extent that the DNA of so-called endogenous retroviruses, and the related retrotransposons, now makes up around 8% of all the DNA in the human genome. This is four-six times greater than that encoding the proteins of our cells. At first consideration, the colonisation of our genomes with these elements potentially acting as carcinogens or mutating our genes would appear to be alarming. However, harmful integrations will be lost rapidly during evolution, and occasionally integrations will have positive outcomes where viral genes are repurposed to perform beneficial roles for the host. This is the process of exaptation “where a gene acquires a function for which it was not originally adapted or selected”. In our study, we looked at how encounters with an ancient retrotransposon have twice resulted in exaptation of a viral gene called Gag to perform a new host function.

Our study originated because we wanted to discover more about a protein called ARC (its short name for "Activity-regulated cytoskeleton-associated protein") that is found throughout the animal kingdom. In humans, ARC is an important neurological protein associated with synaptic activity and essential for memory and learning. Deficiencies in ARC are found in patients with neurological

disorders, Alzheimer's disease and schizophrenia. In fruit flies, ARC is involved in regulating fly behaviour in response to nutrients. Intriguingly, it has been observed that ARC could form particles inside neurons that contained messenger RNA (mRNA) in a manner similar to a retrovirus packaging its RNA. Therefore, we wanted to analyse the structural properties of human and fly ARC to try and gain a better understanding of its function in cognition and memory consolidation. We first determined the 3-Dimensional structure of the ARC protein using X-rays to image the individual protein molecules packed into crystals. We were then able to search with this structure against all known 3D structures of proteins that are held in the Protein Data Bank (https://www.rcsb.org) to look for matches. The best matches were with retroviral Gag proteins. These are the proteins that assemble into protective cages that surround the genomes of retroviruses as they move from one cell to another during infection. Together with this structural similarity, we also found that the building blocks of ARC and retroviral Gag assembly were the same. Therefore, although the ARC genes of humans and flies arose independently, in each case they result from the capture of a Gag gene and repurposing of the original viral genome packaging function to now enable transfer of information across synapses in the brain. Determined efforts to further understand this function are in progress.

Notably, ARC does not appear to be the only example of exaptation of a retroviral gene. The function of the retroviral Env gene is to allow an infecting virus to attach and enter into a target cell by initiating membrane fusion between cell and virus. Membrane fusion is also essential for placenta formation in all vertebrates and is mediated by a protein called Syncitin. A variety of studies have revealed that Syncytin is derived from Env and that the original function to promote fusion of the viral and cellular membrane during virus entry has been repurposed for the fusion of trophoblast cells during placenta formation. Remarkably, it appears that different orders of mammals have exapted membrane-fusing function from different endogenous retroviruses at different times. It appears that nature likes to reuse mechanisms that work!

There are reasons to think that these functions of ARC and Syncytin may only represent the tip of the iceberg in uncovering positive roles for viral elements shaping human physiology. Viral proteins appear to be important factors in providing resistance to infection by other viruses. Viral DNA sequences may also coordinate and regulate mammalian genes. Therefore, much further research is necessary to discover the full extent that host exaptation of viral genes has played in human development.