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> ONE MONTH, ONE PROTEIN <

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side effects

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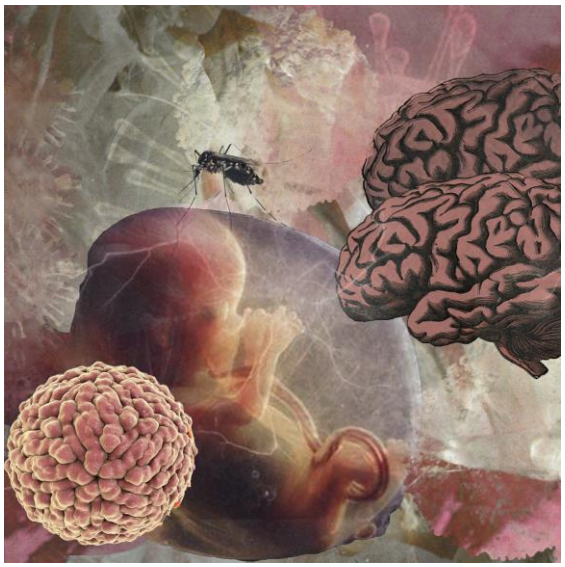
Nature tiptoes along a sturdy yet fragile tightrope. DNA is its backbone and provides a basis from which every single living species on this planet emerges and prospers. Time, however, tampers with everything. Silver turns black. Fruit rots. And DNA undergoes mutations. But mutations have their good side too; without them, there would not be such a diversity of species that has ended up colonising most of the planet. We know that evolution relies on chemical changes that slip into DNA – and so into proteins – because they can help a species adapt better to its surroundings. Some mutations turn out to be less beneficial for some, however, and can give rise to havoc. This is perhaps what has happened between the Zika virus (ZIKV) and humans. Everyone has heard of the ZIKV outbreak in South America that began in 2015, during which many babies were born with undersized heads and brains, and diminished cognitive skills. Some scientists suggest that a mutation in a protein located on the virus's shell, and known as prM, is responsible for this form of microcephaly in human foetuses.



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Zika virus (ZIKV) was first discovered in 1947 in Uganda, in the Zika Forest. At the time, researchers were carrying out studies on yellow fever virus, which is spread by mosquitoes. It was only in 1954, however, and in Nigeria that symptoms pertaining to human infection by ZIKV were described. The virus then travelled to Asia in the 1960s but remained under the radar until a few significant outbreaks of ZIKV were reported in Africa in 2007. It reached French Polynesia in 2013 where it was associated for the first time with another disease: Guillain-Barré syndrome, characterized by muscle weakness. It was also during this period that doctors discovered that ZIKV could be transmitted via blood, semen, saliva and urine. In 2014, the virus reached South America and it spread rapidly throughout most regions during the course of 2015. The first cases of foetal microcephaly associated with mothers who had been infected by ZIKV during the first term of their pregnancy were reported in 2016 in north-eastern Brazil, and it became cause for international concern.

Until 2016, ZIKV hadn't had any planetary attention because the symptoms caused by it were rarely severe. But congenital microcephaly was another cup of tea. Questions arose. Why is ZIKV suddenly involved in neuronal malformations? Why in South America, when there had been many outbreaks elsewhere? How are the foetuses infected? This said, in over 5'000 cases of microcephaly reported in Brazil, not all (37%) could be linked to ZIKV infection. But the problem also became a social one. Mothers had to stop working to care for babies whose cognitive and motor skills were hugely compromised. In some ways, this is reminiscent of the drug thalidomide that was given to many pregnant women in the early 1960s, and which impeded their babies' embryological development.

Researchers began by comparing the "ancestral" ZIKV genome with its contemporary counterpart. All genomes undergo mutations as they are passed from generation to generation, but it was a question of finding the mutation which made ZIKV turn to foetal cells involved in brain development. ZIKV belongs to the flaviviruses that are icosahedral in shape. Their shell – or envelope – is composed of envelope (E) and membrane (M) proteins embedded in a lipid membrane. Inside the envelope is an RNA genome, surrounded by capsid proteins. Researchers found that a serine to asparagine amino-acid mutation had occurred in the sequence of ZIKV's membrane protein prM, and it was this particular mutation that seemed to be at the heart of microcephaly in new-born infants.

What is going on at the molecular level? Most of what is currently known is based on knowledge acquired on other flaviviruses. In a nutshell, all viruses consist of a lipid envelope that surrounds the protein coat, which itself protects the virus's genetic material (DNA or RNA). Many viruses infect cells by recognising them, fusing to their membranes, slipping inside, inserting their genetic material into the cell's nucleus and using its machinery to replicate. New viruses are then formed and released from the host cell to infect other cells. In flaviviruses, the newly-formed envelopes are made up of an equal amount of precursor membrane (prM) proteins and envelope (E) proteins that are organised into heterohexamers. When the virus goes through the host cell's Golgi apparatus, a lowering of the pH changes the shape of the E proteins that shift from a trimeric state to a dimeric state, thus preparing them for fusion with the host cell's membrane. The prM proteins, however, are perched on top of the E proteins to form a sort of screen which prevents fusion. Fusion occurs once prM has been cleaved; only then can the mature virus exit the host cell.

So what happened with ZIKV? Why did it take a sudden interest in foetal neuronal cells? Before giving a tentative answer, it might be a good time to mention that ZIKV – like other viruses – is able to cross the blood-brain barrier. So its presence in the brain is not a scoop, but the effects it has on the foetal brain are. prM has a direct role in viral maturity, i.e. in the release of newly-formed viruses from the host cell. The mutation that has occurred in prM could have an effect on viral maturation, by creating a sort of imbalance in viral progeny which has a ricochet effect on neurovirulence. A second intriguing hypothesis is that the mutated prM has turned it into a receptor for neural cells. This would mean that virions are able to recognise and preferentially adhere to brain cells. It's a very attractive suggestion. ZIKV was first transmitted to humans in the 1950s, but if it wanted to stick around and adapt to humans in a stable manner, it would need to find a way to do so. The mutated form of prM could be a way for ZIKV to recognise human cells more effectively. Consequently, microcephaly in infants is an unfortunate side effect caused by ZIKV that has reached neuronal cells at a very early stage in brain development.

Vaccines are currently being developed but none are yet available, and ZIKV infection has dropped – thankfully – to such an extent that scientists are worried that they will not have time to proceed with clinical trials. Several countries are worried that they will have to face a sudden future outbreak, as there have been in the past, and not have the means to deal with it. As always, much remains to be understood. But it is fascinating to realise that though viruses are not provided with intelligence – as we define it – they are able to find ways of adapting from one species to another for their survival, as they are also able to outdo drugs that were designed to destroy them.

Cross-references to UniProt

Protein prM, *Zika virus* (ZIKV) : A0A024B7W1

References

1. Yuan L., Huang X.-Y., Liu Z.-Y., Zhang F., Zhu X.-L. *et al.*
   A single mutation in the prM protein of Zika virus contributes to fetal microcephaly
   Science 358:933-936(2017)
   PMID: 28971967

2. Weaver S.C., Costa F., Garcia-Blanco M.A., Ko A.I., Ribeiro G.S *et al.*
   Zika virus: History, emergence, biology, and prospects for control
   Antiviral Research 130:69-80 (2016)
   PMID: 26996139

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