KIN SELECTION IN VIRUSES

Altruism in a virus

A recent study finds that viruses cooperate altruistically to overcome innate host immunity and that this can be explained in the same way we explain altruism between animals.

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In many organisms, the first line of defence against viruses is to quarantine the infected area. Mammalian cells achieve this by releasing interferons, which are signalling molecules that spread to neighbouring cells and place them on 'red alert', enhancing their antiviral defences. Many viruses fight back by blocking interferon signalling, keeping nearby cells susceptible to infection. Domingo-Calap and colleagues now show that in vesicular stomatitis virus (VSV), blocking interferon signalling is a form of altruistic cooperation that is favoured because it provides a benefit to the local population of viruses[1] (Fig. 1).

A behaviour or trait is altruistic when it is costly to perform and provides a benefit to others. Cost and benefit here are defined in terms of evolutionary fitness — the number of offspring produced. Explaining altruism is a fundamental problem for evolutionary biology. Given the Darwinian idea of 'survival of the fittest', how can we explain individuals carrying out a behaviour that reduces their own fitness, while increasing that of others?

Bill Hamilton's kin selection theory provides an explanation for altruism[2]. Hamilton showed that altruism could be favoured when it is directed towards relatives who share the gene for altruism. This theory is encapsulated in a pleasingly simple form by Hamilton's rule, which states that altruism is favoured when $rb - c > 0$; where c is the fitness cost to the altruist, b is the fitness benefit to the recipient of the altruism and r is the relatedness between these individuals[3]. Relatedness is a measure of genetic similarity (kinship) that essentially captures the likelihood that they would share a gene for altruism.

Altruism is usually discussed within the context of the animal world; for example, the sterile workers in social insect colonies, or helpers at the nest in cooperatively breeding birds such as long-tailed tits[4–6]. Domingo-Calap and colleagues show that altruism also occurs in viruses. To do this, they derived a version of Hamilton's rule that was appropriate to interferon blocking in VSV, and then estimated its parameters.

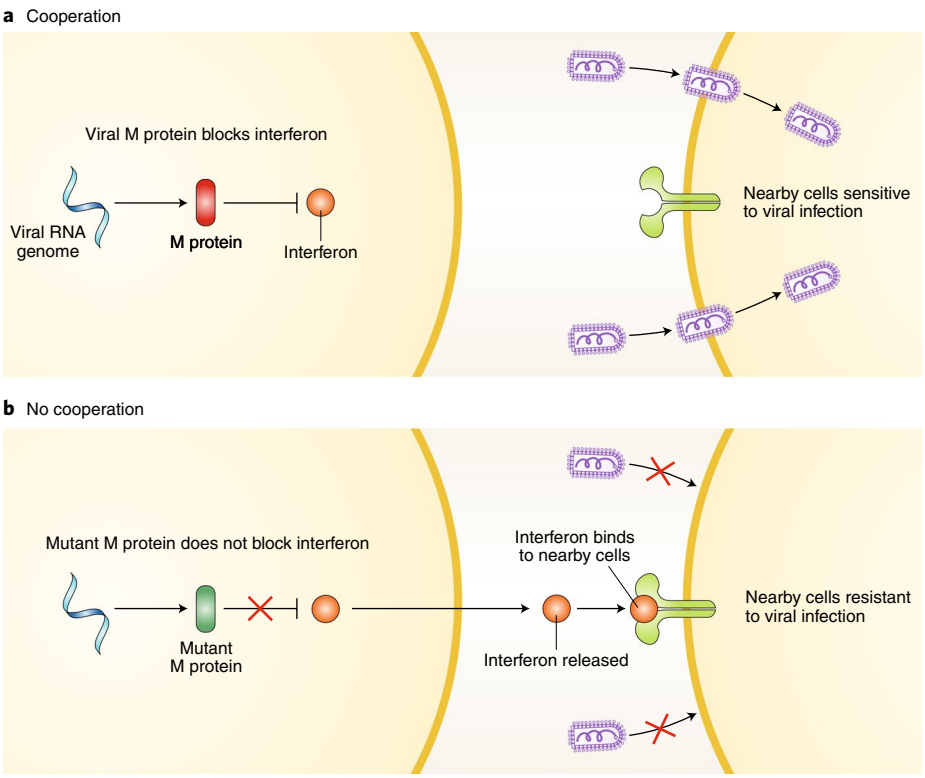

Fig. 1 | Blocking interferon release indicates altruistic cooperation in a virus. Following viral infection, mammalian cells release interferon, a signalling molecule that spreads to nearby cells and enhances antiviral defences. **a**, Wild-type VSV encodes a protein (the M protein) that blocks the release of interferon from infected cells. This provides a benefit to the local group of viruses because it keeps nearby cells susceptible to infection. **b**, In contrast, the non-cooperative Δ51 mutant of VSV encodes a different version of the M protein that does not block the release of interferon. This provides a growth advantage to Δ51, but it comes at a cost to the local group of viruses because nearby host cells activate their antiviral defences and become resistant to viral infection.

They did this through a series of elegant experiments using two mutants: a wild-type VSV strain that blocked interferon, and a genetically engineered mutant of VSV (Δ51) that differed from the wild type only in its inability to block interferon[7] (Fig. 1).

To isolate the cost of blocking interferon, the authors compared the growth rates of Δ51 and wild-type VSV when the host cells' interferon response was reduced. In these conditions, viruses would pay the cost of blocking interferon but not receive the benefit. They showed that Δ51 grew faster than wild-type VSV in the early stages of infections (before the cells' interferon response had kicked in). This showed that blocking interferon comes at a cost to an individual virus because it reduces the virus's growth rate. The authors used multiple lines of evidence to confirm this result, including competition assays over time and an additional experiment in which viruses were grown on cells that were not able to produce interferon.

Next, the authors determined the extent to which blocking interferon provided a shared benefit to local viruses. They did this by comparing the overall growth rates of pure wild-type and pure Δ51 infections, accounting for Δ51's faster inherent growth rate. Blocking interferon provided a group benefit, ultimately allowing wild-type VSV infections to reach more than 16 times higher viral densities than Δ51 infections.

Using values calculated 43 hours after the start of the infection, the authors obtained approximate estimates of $c = 0.4$ and $b = 1.6$. These can be used in Hamilton's rule to obtain $r \times 1.6 > 0.4$, giving $r = 0.25$ as the critical value of relatedness above which cooperation is favoured. This is not a very high level of relatedness — it roughly requires that benefits go to clone mates one-fourth of the time.

Domingo-Calap and colleagues did not directly measure relatedness, but they tested whether manipulating relatedness influenced the advantage of blocking interferon. Comparing across different relatedness treatments, they found that the wild type did better when relatedness was higher. Specifically, in a fully structured condition ($r = 1$), the wild type out-competed Δ51; in an intermediate condition, where the authors estimated that $r = 0.3$, the wild type won with a relatively small fitness advantage; and in a fully mixed condition ($r = 0$), Δ51 out-competed the wild type. The authors also performed in vivo work and showed that, in mixed infections, Δ51 out-competed wild-type VSV. A possible explanation for how cooperation could be maintained in natural infections is if infections often start with a small number of viral particles, keeping relatedness high and mixed infections relatively rare.

Overall, this study provides an elegant demonstration of how social interactions can be critical for the evolutionary success of viruses. In particular, it shows how cooperation can occur between viruses infecting different cells, as well as those infecting the same cell[8]. This raises a number of new questions about the social nature of viruses. Are other viral traits maintained by kin selection? Can we disrupt relatedness to select against cooperation for therapeutic purposes? Does cooperation break down in natural viral infections, and does this affect disease dynamics? Over the last 20 years, we have discovered that cooperation plays a fundamental role in the success and virulence of bacteria — are we about to experience a similar revolution in viruses[9]?

More broadly, this study shows how the idea of kin selection, though originally developed to explain altruism in animals, can also be applied to viruses[3]. Since its development, kin selection has been used to explain cooperation and conflict at all levels of biology, including animal behaviour, sterility in social insects, genes inside a genome, fruiting bodies in slime moulds and the production of virulence factors by bacteria[10]. It now seems that we can add viruses to this list. ❐

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Competing interests

The authors declare no competing interests.