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INFECTION

Viruses hijack a long non-coding RNA

Manipulation of host-cell metabolism is an essential aspect of viral replication cycles. Viral co-option of a cellular long non-protein-coding RNA has now been found to be a key step in this process.

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Viruses are totally reliant on the metabolic products of the cells they infect. Indeed, there have been numerous reports of viruses actively modulating cellular metabolism to establish an optimal environment for replication[1]. Most such studies have found that these metabolic alterations are accomplished by viral targeting of protein–protein interactions, or targeting of host messenger RNAs by virally derived, non-protein-coding microRNAs. Could a class of host RNA known as long non-coding RNAs (lncRNAs) also be targeted to achieve a similar goal? Analysis of the roles of cellular and viral lncRNAs in infection has previously focused mainly on modulation of innate immune responses[2]. Now, writing in *Science*, Wang *et al.*[3] reveal a different mechanism by which the virus appropriates host-derived lncRNA: activation of a host-cell metabolic pathway required for viral replication.

Long non-coding RNAs (non-coding RNAs more than 200 nucleotides long) have roles in many aspects of cell biology[4,5]. In the nucleus, they are involved in transcriptional regulation and remodelling of chromosomes, and in the cytoplasm, they regulate microRNA function as well as the translation of mRNAs to generate proteins. But there are scores of lncRNAs whose functions have not been identified, so there are potentially many more roles to uncover.

To search for lncRNAs that might have a role in viral infection, Wang *et al.* performed a screen in which they inhibited the expression of a library of lncRNAs in cells and then determined the effects of inhibiting each molecule on the ability of vesicular stomatitis virus (VSV) to replicate in the cells. They identified a lncRNA that, when depleted, inhibited replication not only of VSV, but also of the unrelated viruses herpes simplex virus 1 and vaccinia virus, implying that this molecule plays a part in boosting the replication of a wide variety of virus species. Furthermore, this lncRNA — dubbed lncRNA-ACOD1 because its nearest known host gene is *ACOD1* — is actively upregulated by viral infection of wild-type cells.

To understand how depletion of lncRNA-ACOD1 inhibits virus replication, the authors first looked for a possible role in the regulation of innate immune responses. However, no clear effect was observed. They next analysed gene expression in cells deficient in lncRNA-ACOD1 and identified changes in the expression of many metabolic genes, suggesting that this lncRNA indirectly affects virus replication by modulating host metabolism.

Wang *et al.* then recovered lncRNA-ACOD1 from cells and analysed the proteins associated with it. This revealed that lncRNA-ACOD1 specifically bound to the host protein glutamic-oxaloacetic transaminase 2 (GOT2) — an enzyme involved in a variety of metabolic pathways, including the tricarboxylic acid (TCA) cycle, which generates energy, and the uptake of long-chain fatty acids, which can be used as metabolic fuel by cells. Subsequent mechanistic analyses showed that lncRNA-ACOD1 not only bound GOT2, but also strongly potentiated its enzymatic activity (Fig. 1). This activation was, in turn, crucial for the generation of metabolites required for viral replication.

Finally, the researchers deleted lncRNA-ACOD1 in mice. Here, lack of lncRNA-ACOD1 had the same inhibitory effect on viral replication. But surprisingly, given its new-found role in a key metabolic process, deletion of lncRNA-ACOD1 had no effect on the viability of the animals. Thus, the authors conclude that inhibition of lncRNA-ACOD1 function might be a way to specifically inhibit the replication and spread of a wide range of harmful human viruses.

Wang and colleagues' work adds to the list of known mechanisms by which lncRNAs can regulate crucial physiological processes. Much previous work has focused on the roles of mRNAs, even though they comprise only about 2% of the human genome. But some 80% of the genome is actively transcribed[6], resulting

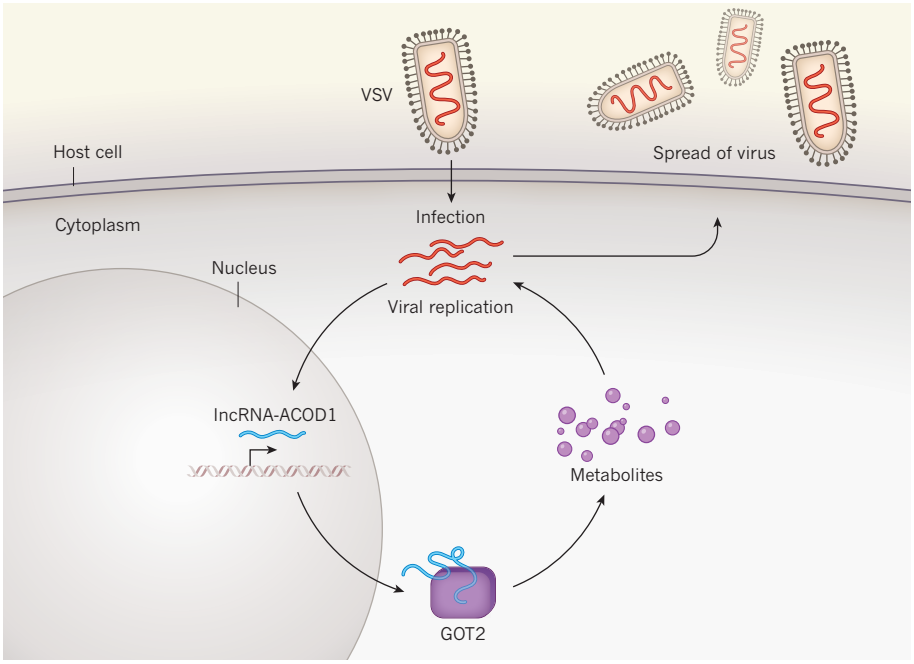

Figure 1 | Viral replication through modulation of host-cell metabolism. Vesicular stomatitis virus (VSV) deposits its genetic material in host cells for replication. Wang *et al.*[3] report that VSV triggers transcription of a long non-protein-coding RNA called lncRNA-ACOD1 in the host-cell nucleus. LncRNA-ACOD1 moves to the cytoplasm, where it binds to and promotes the activity of the metabolic enzyme glutamic-oxaloacetic transaminase 2 (GOT2). This enzyme produces metabolites that enable higher rates of viral replication. In this way, VSV hijacks the host cell's metabolism to promote its own spread.

in RNAs with no obvious coding potential, many of which may well have regulatory functions. Viruses have extremely limited genomic space relative to that of their hosts, and targeting a host-cell factor central to many metabolic processes, such as a key host lncRNA, would be an efficient way of adjusting the host-cell environment to suit their own needs. Clearly, further work that focuses on how viruses manipulate non-coding RNA function (and, in particular, the relatively under-studied lncRNAs) has the potential to greatly increase our understanding of how viruses take control of the cells they infect.

Despite the elegance of Wang and colleagues' story, questions remain about both lncRNA-ACOD1 and other viral metabolic targeting strategies. Prominent among these is understanding why decreasing GOT2 activity has such a marked effect on virus replication without detectably affecting host-cell viability. Wang *et al.* found that GOT2 depletion led to decreased levels of L-aspartate (an amino acid required for the biosynthesis of almost all proteins) and α-ketoglutarate (a key molecule in the TCA cycle, and hence central to energy production in the cell) — both of which are expected to have vital roles in host-cell metabolism. It is reasonable to expect that virus-infected cells, which produce thousands of viral progeny, would have higher energy requirements than uninfected cells. However, the finding that lncRNA-ACOD1 is largely dispensable for normal host-cell metabolism raises the question of why the molecule would be evolutionarily conserved when it is potentially so harmful to the host.

If it is indeed true that viral replication and normal host-cell physiology have major differences in terms of the metabolic intermediates and enzymes they require, then exciting possibilities for the development of broadly acting antiviral therapies clearly exist. More generally, the discovery that GOT2 is regulated by lncRNA-ACOD1 highlights not only the complexity underlying the regulation of key physiological processes by lncRNAs, but also the intimacy of the interactions that occur between viruses and their hosts. ■

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