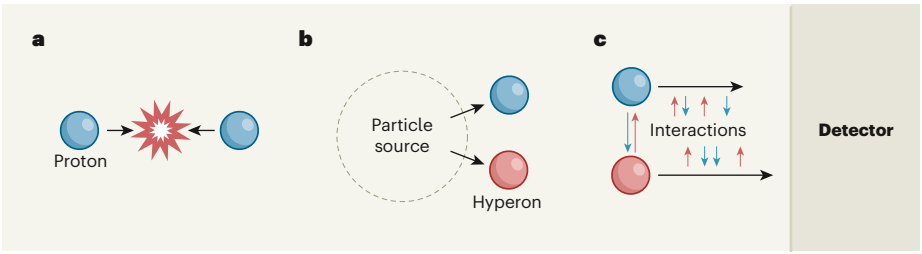

Figure 1 | Investigating the proton–hyperon interaction. a, The ALICE Collaboration[1] smashed together high-energy protons in CERN's Large Hadron Collider. **b**, The collisions generate a 'particle source' – a volume of space in which components of the colliding protons interact and become confined within new particles. These new particles are emitted from the source, and include protons that pair up with heavier particles known as hyperons. **c**, The paired-up protons and hyperons interact with each other in a way that alters the relative momentum of the system, which is then measured by a detector. These measurements are then used to determine the nuclear force between the proton–hyperon pair.

by a 'source' produced by the collision – a volume of space in which quarks and gluons that originally came from the protons interact and become confined within new hadrons. The source emits various types of hadron, including protons and hyperons, some of which form proton–hyperon pairs. Finally, the proton and hyperon in each of these pairs interact with each other in ways that alter the momentum of the paired system. This momentum is measured by a detector and used to determine the momentum correlations.

The momentum correlations reflect the size of the hadron source and the properties of the interaction between the produced proton–hyperon pairs. Such correlation analyses were originally used to determine the source size in collisions of heavy ions[6], but in the new work, they are instead used to investigate the interaction between the particles of interest. This approach to studying particle interactions was pioneered by the HADES Collaboration[7] at the GSI Helmholtz Centre for Heavy Ion Research in Darmstadt, Germany, and was further developed by the ALICE collaboration[8] at the LHC. The current work depends on the fact that the extremely high-energy proton–proton collisions carried out at the LHC produce a high abundance of hyperons from small-volume hadron sources. The authors used this method to measure the strong force between protons and Ω^- hyperons (which consist of three strange quarks) and between protons and Ξ hyperons (which consist of two strange quarks and one up or down quark).

The ALICE Collaboration's findings open up a new 'laboratory' for investigating other nucleon–hyperon interactions, including the little-explored interactions with hyperons that contain two or three strange quarks. This will aid our understanding of metastable states of hyperon pairs or of the compressibility of nuclear matter at high densities. The latter is relevant not only for the stability of neutron stars, but also for neutron-star mergers and heavy-ion collisions.

In a lucky coincidence, recent developments in theoretical physics[9,10] allow nuclear forces to be calculated from first principles so that the results can be compared with experimental findings. The precision with which nucleon–nucleon interactions can be determined from experimental data is still superior to that obtained from these calculations, but the ALICE Collaboration's measurements of the proton–hyperon interactions almost exactly match those obtained from theory.

A wealth of high-precision measurements of proton–hyperon interactions is expected from the LHC in the next decade, following on from its recent upgrade. Moreover, various other facilities that will study particle collisions at lower energies than those produced at the LHC are expected to go into full operation in the coming years, including NICA in Russia, J-PARC in Japan and FAIR in Germany. Although fewer proton–hyperon pairs are generated per collision in lower-energy collisions, a greater proportion of those pairs will be emitted at low momenta – which might turn out to be advantageous, because more data are needed to reduce the statistical errors in measurements of low-momentum systems. Increases in computing power should also substantially reduce the uncertainties of first-principles calculations of nuclear forces. Taken together, these developments bode well for future research into the final frontier of the standard model of particle physics.

Manuel Lorenz is at the Institute for Nuclear Physics, Goethe University, Frankfurt 60438, Germany.
e-mail: m.lorenz@gsi.de

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Virology

Cracking the cell access code for a deadly virus

James Zengel & Jan E. Carette

The discovery that the receptor protein LDLRAD3 is essential for infection of human cells by Venezuelan equine encephalitis virus could inform strategies to combat this potentially lethal infection. **See p.308**

When viruses jump from animals to humans, disease outbreaks can follow. A striking example is Venezuelan equine encephalitis virus (VEEV). This virus causes sporadic disease outbreaks in horses in Latin America that frequently spill over into humans, resulting in often-deadly neurological disease[1]. Because of its pathogenicity in livestock and humans, VEEV has been studied as a biological weapon by several countries, including the United States[2]. Treatments for the disease are therefore highly desirable. It has been unknown how VEEV co-opts cellular pathways to establish infection in people – in particular, which host receptor protein allows VEEV to cross the cell membrane and initiate its replication cycle. On page 308, Ma *et al.*[3] describe the long-sought receptor for VEEV, and show that it is essential for viral replication in both human cells and mouse models.

Interactions between a virus and its host receptor protein can control which tissue types in the body support viral growth, thus influencing the type of disease that results. Furthermore, these interactions can determine how well the virus spreads through a host population. During the continuing SARS-CoV-2 pandemic, for instance, viral strains that had a specific mutation in the virus's spike protein became predominant soon after the virus

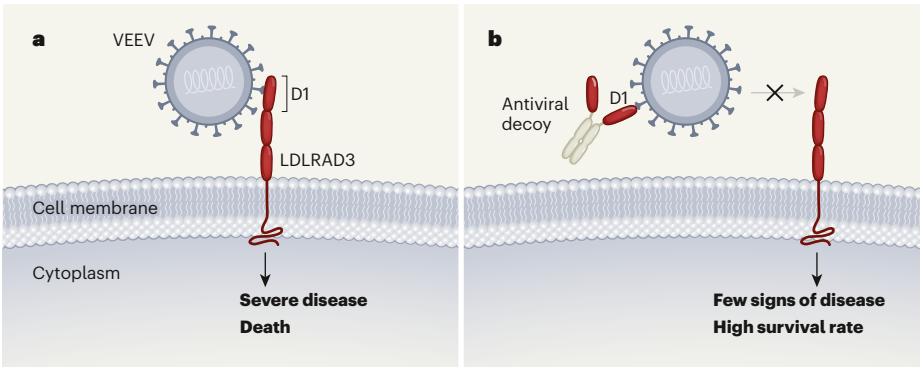

Figure 1 | Preventing infection by Venezuelan equine encephalitis virus (VEEV) in mice. a, Ma *et al.*[3] report that LDLRAD3 is the mammalian receptor protein for VEEV. Entry of VEEV into cells is mediated by binding to LDLRAD3's domain 1 (D1). VEEV infection in mice causes severe disease and death in all cases. **b**, The authors fused D1 to part of an antibody. This construct acts as an antiviral decoy, binding to VEEV and so preventing it from interacting with LDLRAD3. The decoy treatment protected mice from VEEV infection – the animals showed few signs of disease and had a much higher survival rate than did untreated animals.

jumped to humans – this mutation enhances binding between the spike protein and its receptor on human cells, ACE2 (ref. 4).

Despite the importance of host receptors for understanding infection, their identities for VEEV and other alphaviruses (a category of mainly mosquito-borne RNA viruses) have mostly been elusive . Alphaviruses that infect humans can cause either severe arthritis or – as VEEV does – inflammation of the brain (encephalitis). In 2018, previous work[5] from some of the authors of the current study uncovered Mxra8 as a mammalian receptor protein for multiple arthritogenic alphaviruses, but not for encephalitis-causing alphaviruses.

Ma *et al.* therefore went in search of the mammalian receptor for VEEV. The authors made use of a gene-editing tool called CRISPR–Cas9 to introduce mutations into more than 20,000 genes in mouse neuronal cells. They then screened the cells to determine which mutations prevented infection by a modified form of VEEV (the version used was less pathogenic than normal, to enable safe experimentation in the laboratory). The screen revealed that *Ldlrad3* was the gene most commonly mutated in infection-resistant cells. Subsequent experiments in a broad range of human and mouse cell types demonstrated that the LDLRAD3 protein is essential for VEEV entry into host cells.

LDLRAD3 is a poorly characterized member of a large group of membrane-bound receptors called the LDL scavenger receptor family. This family is mainly known for its role in bringing lipoprotein particles into the cell in vesicles (a process called endocytosis). Other members of the family have been shown to be co-opted by viruses unrelated to alphaviruses to gain entry into the cell[6].

Ma and colleagues identified a specific region called domain 1 (D1) in the extracellular portion of LDLRAD3 through which VEEV-like particles directly bind to the receptor (Fig. 1a). But, intriguingly, deletion of the intracellular domain of LDLRAD3 – which typically mediates endocytosis in this receptor family – did not prevent VEEV entry. This could mean that binding of VEEV to LDLRAD3 triggers fusion of the viral and cell membranes, resulting in direct release of viral RNA into the cell. Alternatively, LDLRAD3 might mainly mediate virus binding, with another, unknown factor controlling endocytosis. Future studies are needed to distinguish between these possibilities.

Finally, the authors investigated whether modulating LDLRAD3 could protect mice from VEEV infection. Strikingly, deletion of *Ldlrad3* completely protected the animals from otherwise-lethal infection with highly pathogenic VEEV strains (Fig. 1b). The authors gave wild-type mice a soluble form of LDLRAD3 in which D1 of the receptor was fused to part of an antibody. The construct binds to VEEV, preventing interactions with LDLRAD3 on cells. Administration of the soluble construct before or after infection with VEEV led to near-complete protection in wild-type mice.

A key question is whether LDLRAD3 mainly mediates infection in the brain, where it causes encephalitis, or whether it also takes part in VEEV infection in the different cell types involved in spreading the virus through the body after an initial mosquito bite. The broad expression pattern of LDLRAD3 in many tissues suggests that the protein has roles in viral spread throughout the body. Indeed, the authors show that soluble LDLRAD3 almost totally blocked virus replication in several tissues that are involved in such spread, including the blood serum, spleen and brain.

In the future, deletion of *Ldlrad3* in specific mouse tissues could help to reveal more about how VEEV spreads and causes disease. By abolishing infection in chosen tissues in this way, one could rigorously test various unknown aspects of disease progression. Are blood cells (specifically, a type called myeloid cells) key in initiating viral spread and fuelling viral infection in the blood after a mosquito bite? Does VEEV reach the central nervous system through the peripheral nervous system, or more directly by crossing the blood–brain barrier[7]? And do these steps require LDLRAD3?

LDLRAD3 mediates cell entry of VEEV, but Ma and colleagues found that it does not control entry of related encephalitic alphaviruses such as Western and Eastern equine encephalitis viruses. This is somewhat unexpected, given the strong similarities in structure[8] and pathogenesis between the three. An intriguing possibility is that other members of the LDL scavenger receptor family act as receptors for distinct encephalitic alphaviruses. Further structural studies defining the LDLRAD3–VEEV interface will provide clues to why this interaction is seemingly so specific.

What are the therapeutic implications of Ma and colleagues' work? Precise characterization of the LDLRAD3-binding site on VEEV could aid the development of highly neutralizing antibodies that block the VEEV–LDLRAD3 interaction. A similar antibody therapy that prevents interactions between the Ebola virus and its human receptor protein NPC1 has shown success, reducing the mortality from Ebola[9,10]. Another strategy is to use soluble LDLRAD3 as an antiviral decoy. The authors have provided strong proof of principle in mice that this might work, although further optimization to enhance the binding affinity and half-life of soluble LDLRAD3 *in vivo* might be required, equivalent to developing engineered ACE2 that has a greatly enhanced potency in blocking SARS-CoV-2 infection[11]. The discovery of LDLRAD3 has therefore revealed a range of ways in which we might, in the future, combat severe VEEV disease.

James Zengel and **Jan E. Carette** are in the Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, California 94305, USA.
e-mail: carette@stanford.edu

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