50 Years Ago

By and large the effect of automization is to reduce severely the demand for unskilled and semi-skilled workers and to increase sharply the need for skilled workers … This trend is surely to be welcomed. Repetition work is an insult to the people who have to do it. It treats them as less than human. It is not surprising if it often turns them into something less than human. If you make a man spend eight hours a day in which he has nothing to … exercise his mental powers on, is it surprising that he is incapable of exercising those powers in his leisure time and must spend it watching television or wrecking a dance hall? Automation offers the prospect of giving every man and woman a job that is interesting and worth doing in itself, a job requiring initiative or creative thought. Surely that is as desirable an object as providing a higher standard of material living.
From *Nature* 22 June 1963

100 Years Ago

After expressing his admiration for the character of Wilbur Wright … the lecturer considered the resemblance and differences of the manufactured aëroplane and the living bird. The resemblance may be simply the result of copying the bird, or it may be that similar designs have been arrived at independently by birds and men … These resemblances are remarkable, but there are great differences … No flying animal uses a continuously rotating propeller to drive him forward on soaring wings, and it is perhaps scarcely too much to say that if birds only knew how, they would now copy the Wright brothers. Muscular action and the circulation of the blood, however, put supreme difficulties in the way of the development of the continuous rotation of a part of an animal.
From *Nature* 19 June 1913

from a balance of competing effects. As revealed by an ensemble representation of proteins, effector binding stabilizes both the active and inactive forms of the functional domain, which means that the effector is potentially an activator and an inhibitor. So what determines whether the effector will activate or inhibit?

The answer is the relative stability of each state in the ensemble. Under one set of conditions (Fig. 2a), the ensemble could be poised such that effector binding causes activation. But under another set (Fig. 2b), effector binding can cause inhibition. Crucially, a switch in cooperativity can arise as a result of any type of perturbation (such as the binding of another molecule, post-translational modification or protein truncation) that can redistribute the ensemble of conformations[11], even to the extent of transforming effector binding from activating to inhibiting, or vice versa.

Although Ferreon and colleagues' work does not reveal how the observed cooperativity switch occurs, it does help to clarify the following key questions that underlie a quantitative understanding of signalling in IDPs, and perhaps also in structured proteins. What states comprise the protein ensemble, and what are their probabilities? And are there ground rules that dictate whether signalling, or even activation–inhibition switching, can occur in an ensemble[10,11]? The take-home message of Ferreon and colleagues' work, and the reason that a switch is possible, is that proteins should not be thought of as multiple copies of identical structures that respond uniformly to a signal. Instead, proteins — especially IDPs — exist as ensembles of sometimes radically different structural states. This structural heterogeneity can produce ensembles that are functionally 'pluripotent', a property that endows IDPs with a unique repertoire of regulatory strategies. ■

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VIROLOGY

The virus whose family expanded

The discovery of many new species of hepaciviruses and pegiviruses, which exhibit enormous genetic diversity, in wild rodent and bat populations might help us to understand the origins of the hepatitis C virus.

OLIVER G. PYBUS & REBECCA R. GRAY

The hepatitis C virus does not give up its secrets lightly. Despite infecting about 3 out of every 100 people worldwide, a small proportion of whom consequently develop severe liver disease, the virus eluded discovery for decades. It was eventually identified in 1989 as the cause of 'non-A, non-B hepatitis'. Researchers who have since sought the origins of hepatitis C virus (HCV), as it is now known, have been frustrated in equal measure. The virus infects chimpanzees in the laboratory, but studies of wild and captive primates uncovered no evidence of an animal population that might have transmitted HCV to humans[1], contrasting with the success of other surveys that exposed close relatives of HIV-1 and human malaria in great apes[2]. Now, however, Kapoor *et al.*[3] and Quan *et al.*[4], writing in *mBio* and *Proceedings of the National Academy of Sciences*, respectively, report a diverse and widespread array of HCV-like viruses in wild populations of rodents[3] and bats[4]. Although none of these viruses can yet be claimed as the source of HCV, their discovery may represent the beginning of the end of the search for HCV's origins.

HCV belongs to the *Hepacivirus* genus of viruses, whose closest taxonomic neighbour is the *Pegivirus* genus[5]; the newly discovered bat and rodent viruses include members of both groups. Kapoor *et al.* found five provisional virus species among more than 400 blood samples from four North American rodent species. Quan and colleagues describe 11 virus lineages

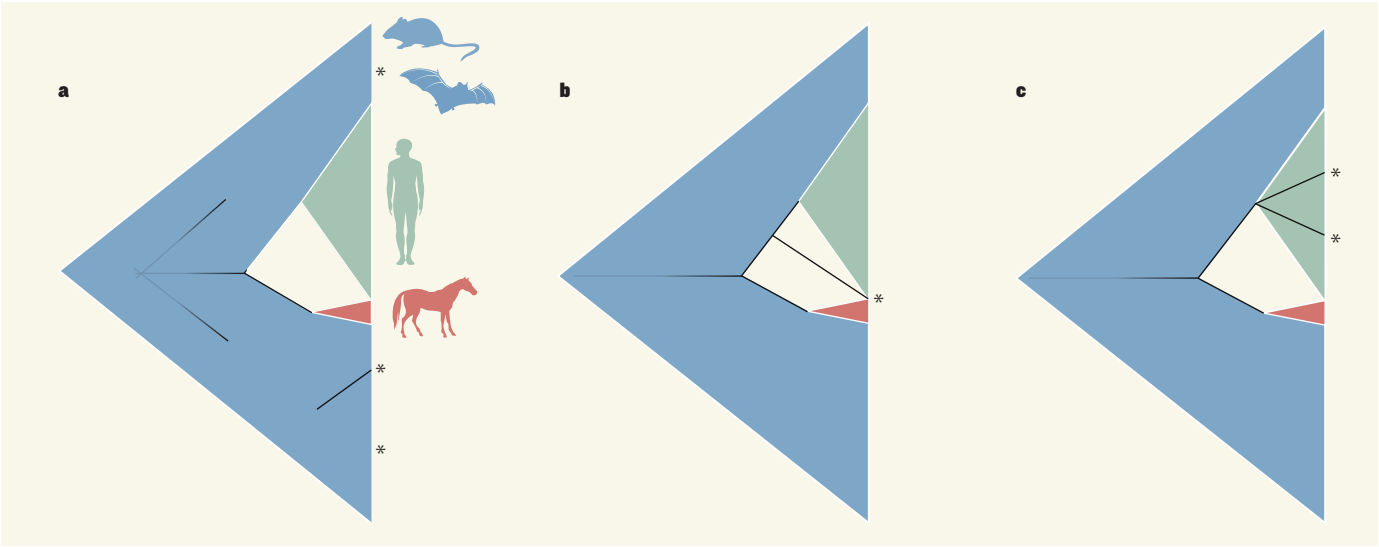

Figure 1 | Possible evolutionary trees of the hepaciviruses. Triangles represent the large genetic diversity of the hepaciviruses discovered by Kapoor *et al.*[3] and Quan *et al.*[4] in bats and rodents (blue), and the more limited diversity of human hepatitis C viruses (HCV; green) and the hepaciviruses found in horses (red). Future surveys in bats, rodents or other animals may discover more hepaciviruses (asterisks), the evolutionary position of which would define three possible scenarios for the origins of HCV. **a**, None of the new viruses is closely related to HCV and its origin remains unresolved. **b**, Viruses more similar to HCV than to equine hepacivirus, HCV's closest known relative, are found. This would suggest that all HCV strains arose from a single ancestral transfer to humans. **c**, The new viruses group within the known genetic diversity of HCV, indicating that it arose from two or more independent cross-species transmissions.

from around 1,700 samples taken from 58 bat species collected in Mexico, Bangladesh and sub-Saharan Africa. The most notable property of the new viruses is their exceptional genetic heterogeneity, which dwarfs the diversity of all previously known hepaciviruses and pegiviruses, including HCV, which is itself highly variable.

This diversity strongly implicates bats and rodents as natural and ancestral hosts for viruses of both genera, an idea supported by the comparatively high frequency of infection in wild animals (around 5%) and by Quan and colleagues' observations that some bats were co-infected with multiple viruses. Furthermore, all the infected bats seemed healthy when collected, which is consistent with a long evolutionary association between virus and host. But despite their already remarkable diversity, the viruses were isolated from approximately 5% of bat and less than 1% of rodent species known, and thus probably represent only a fraction of hepaciviruses and pegiviruses present in nature.

Before these reports, the hepaciviruses and pegiviruses were known as sparsely populated genera that between them contained fewer than ten species, isolated from a motley collection of hosts: humans, chimpanzees, horses, dogs, wild and captive New World primates, plus one bat pegivirus found[6] in 2010. The discovery of enormous viral genetic diversity in bats and rodents presents the possibility that each of the formerly identified species arose through successful cross-species transmission of a bat or rodent virus. Indeed, it is estimated that a quarter of recently emerged human pathogens originated from rodents or bats[7], and both animal groups are abundant, widely distributed and live in large numbers near human settlements or domesticated animals. This postulated cross-species transmission need not have been direct, but may have occurred through an intermediate host in even closer contact with humans — civet cats had such a role in the transfer of the SARS coronavirus to humans[8], and pigs in the transfer of the Nipah virus[9], both of which originate in bats.

Although none of the new hepaciviruses and pegiviruses are sufficiently genetically similar to those found in humans or other animals to be declared their immediate source, bats and rodents are now prime suspects in the hunt for the ultimate origins of HCV. Further sampling of small-mammal populations worldwide should reveal the true diversity and host range of these viruses, and may uncover viruses more similar to HCV. Three possible outcomes of such sampling can be imagined: new viruses are found but none are closely related to HCV and its origin remains unresolved (Fig. 1a); viruses more similar to HCV than to equine hepacivirus, HCV's closest known relative, are found, suggesting that all HCV strains arose from a single successful ancestral transfer to humans (Fig. 1b); or viruses are found that group within the current genetic diversity of HCV, indicating that it arose from two or more independent cross-species transmissions (Fig. 1c).

The third hypothesis is particularly intriguing as it potentially solves the enigma of 'endemic' HCV transmission: how some rural populations in central Africa and southeast Asia come to bear a range of divergent HCV strains, indicative of centuries of stable human-to-human transmission, in the absence of any consistently effective and widespread route of transmission. This riddle would be answered if the virus diversity originates not in humans but from an animal reservoir.

Although the immediate consequences of the current findings for human health seem minimal, only detailed investigation of the transmission and ecology of the new viruses in their natural hosts can elucidate their true potential for cross-species transmission. The ongoing emergence in humans of coronaviruses of probable bat origin[10], ten years after the successful eradication of SARS, is a timely reminder of the potential benefits to epidemiology and public health of understanding the dynamics of infectious disease in wild animal populations. ■

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