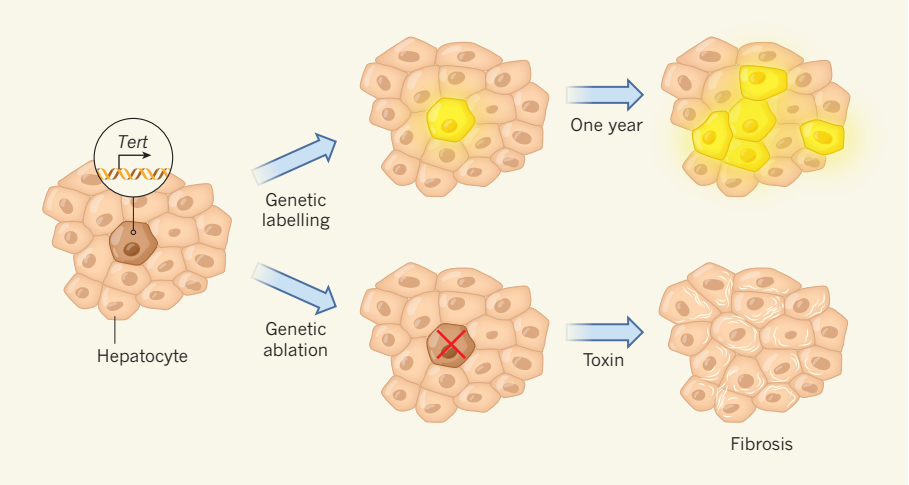

Figure 1 | Lineage tracing in the liver. Lin *et al.*[6] characterize the hepatocyte cells in the mouse liver that express high levels of the gene *Tert*, which encodes a subunit of the enzyme telomerase. The authors generated mice that carry a genetically engineered version of *Tert*: when the mice are treated with a drug, any cells expressing *Tert* are indelibly labelled with a fluorescent protein. Those cells and all their descendants fluoresce, and so can be tracked. Only 3–5% of cells fluoresced immediately after drug treatment. One year later, about 30% of cells fluoresced, but most of these did not express *Tert*, indicating that the rare *Tert*-expressing cells give rise to new hepatocytes to help regenerate the liver. If the *Tert*-expressing cells are genetically ablated, the liver is susceptible to scarring (fibrosis) after toxin damage.

to determine the processes by which cells transition from Tert^{High} to Tert^{Low}, and how this change relates to homeostatic control of liver mass.

Importantly, stem cells typically reside in a special tissue compartment, or niche, that supports their regenerative capacity. Yet the Tert^{High} cells are dispersed throughout the liver. This dispersal of Tert^{High} cells is interesting because hepatocytes reside in different zones in each lobe of the liver, and earlier studies[7] implicated one zone or another as being more relevant to liver regeneration. By contrast, Lin *et al.* provide evidence for a 'distributed model' for hepatocyte renewal. The research indicates that, although the Tert^{High} hepatocytes possess features of stem cells, those features are not of a conventional type.

In the past three years, one regenerative hepatocyte population near the central vein has attracted particular attention. The population responds to venous signals to self-renew during homeostasis, producing progeny that migrate outwards from the central zone[8]. Lin *et al.* found a few Tert^{High} hepatocytes in the central zone in healthy livers, but these cells did not reside close enough to the central vein to respond to its signals. However, when the authors damaged the central-vein zone, Tert^{High} descendants appeared there and responded to venous signals. Moreover, after damage to the liver tissue in another region, around the portal vein, hepatocytes descended from Tert^{High} cells appeared abundantly in the periportal and mid-lobular zones, and the researchers found that ablation of Tert^{High} hepatocytes impaired this regenerative response, leading to liver fibrosis. Taking the above findings together with those of other studies of liver injury, it seems that various types of hepatocyte (as well as cells from the bile duct)[9–12] can regenerate the mouse liver under a range of damage conditions.

In the future, it will be crucial to assess how relevant these findings in mice are to human liver regeneration. The fact that ablation of Tert^{High} hepatocytes results in fibrosis in the injured mouse liver seems to support relevance for humans, because people who harbour mutations in *TERT* and genes that encode other telomere-related factors can also exhibit fibrosis and cirrhosis (the latter being a predictor of liver cancer)[5]. However, Tert^{High} hepatocytes have not been seen in human livers — although the possibility has not yet been assessed with the sensitivity of the genetic-labelling approach used in mice by Lin and colleagues. An alternative explanation for diseases in humans who have telomerase-related mutations is that excessive telomere shortening in early development might affect many organ progenitors in a nonspecific way.

More-detailed studies in humans will be needed to confirm how telomerase-based regeneration forestalls liver disease, and possibly liver cancer. Nevertheless, Lin and colleagues' study provides insight into a previously unidentified, dispersed-cell mode of liver regeneration. ■

Kenneth S. Zaret *is in the Department of Cell and Developmental Biology, Institute for Regenerative Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.*
e-mail: zaret@pennmedicine.upenn.edu

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EVOLUTION

Backbone of RNA viruses uncovered

The evolutionary history of viruses is largely unknown. Large-scale discovery of vertebrate RNA viruses shows that, although viruses often jump between hosts, most have co-evolved with their hosts over millions of years. SEE ARTICLE P.197

MARK ZELLER & KRISTIAN G. ANDERSEN

Many human diseases, from the common cold to deadly haemorrhagic fevers, are caused by RNA viruses. Most of these viruses are thought to have originated from close relatives that infected mammals[1,2], and so the majority of virus-discovery studies have focused on mammals and birds[3]. RNA viruses, however, are probably older than the last common ancestor of life on Earth[4,5]. Detailed genetic information for RNA viruses from other classes of vertebrate is sorely needed if we are to fully understand long-term virus evolution. On page 197, Shi *et al.*[6] report the discovery of previously unidentified vertebrate RNA viruses from across evolutionary timescales.

The authors analysed the viruses in 186 vertebrate species using an approach called metatranscriptomic sequencing, in which all of the RNA present in a sample is sequenced. The samples were taken from

species of fish, amphibian and reptile — every vertebrate class except mammals and birds. In these samples, Shi and colleagues discovered a total of 214 viruses, dramatically increasing the number of known RNA viruses in each vertebrate class. For example, they identified more than 20 RNA viruses that infect amphibians, whereas just a few had previously been identified[7–9].

The analysis also revealed an astonishing level of biodiversity — the researchers identified previously unknown viruses in almost every RNA-virus family known to infect mammals. These include viruses highly pathogenic to humans, such as influenza virus, arenaviruses and filoviruses, that have not previously been reported in fish or amphibians.

Shi *et al.* used this information to construct phylogenetic trees that describe the evolutionary relationships between viruses. They found that the phylogenies of RNA viruses were broadly comparable to those of the viruses' vertebrate hosts. This shows that RNA viruses followed a similar evolutionary trajectory to vertebrates, and have co-evolved with their hosts over millions of years (Fig. 1). The evolution of vertebrates began more than 500 million years ago — vertebrate life then divided into several classes of fish, followed by the evolution of amphibians that moved on to land (http://www.onezoom.org). The authors' findings indicate that mammalian RNA viruses probably originated from viruses that infected fish, and then followed vertebrates on to land.

However, the researchers also show that some viruses can infect multiple hosts, indicating that, in addition to co-evolution, viruses have made jumps between species. In fact, many virus outbreaks in humans are the result of animal-to-human transmission, as exemplified by the recent Ebola epidemic in West Africa[10]. Most cross-species transmission events result in limited or no onwards transmission (the virus typically continues to circulate only temporarily in the new host species), and the ability of a virus to establish itself depends on a range of factors, including host divergence[11]. Thus, transmission between animals belonging to the same vertebrate class (bats to humans, for example) is more likely than that between animals belonging to different vertebrate classes (such as reptiles to mammals). But Shi and colleagues' phylogenies reveal that viruses regularly jump between vertebrate classes, with successful onwards transmission that can continue for millions of years.

The current study greatly expands our knowledge of vertebrate virus evolution. However, it is not without limitations. First, excluding birds and mammals, there are more than 50,000 vertebrate species. And although the current study is one of the largest of its kind, Shi *et al.* sampled less than 0.5% of these species. Moreover, the authors focused their sampling towards common taxa such as ray-finned fishes, and included relatively few amphibians. This means that the group's findings represent only a minuscule fraction of the total diversity of RNA viruses. We are just scratching the surface of these viruses' evolutionary history. Our understanding of viral evolution will continue to expand as we sample RNA viruses from across deeper evolutionary timescales.

Another limitation of the current study is that — as is typical for this type of work — new viruses are identified on the basis of genetic similarity to those that have been sequenced previously. This strategy has the potential to introduce biases. It is therefore possible that there are entire groups of viruses yet to be discovered, because they cannot be detected using similarity-based approaches.

Finally, it is becoming increasingly clear that only a tiny fraction of RNA viruses will ever infect humans, and the factors that contribute to virus emergence in humans are not fully understood. As Shi *et al.* show, phylogenetic analyses are a powerful tool for identifying cross-species transmissions that happened in the past. But they cannot be used to predict host jumps and virus emergence of the future — the complexity of successful cross-species transmission renders efforts to predict disease emergence by mapping non-human virus diversity ineffective[12]. Studies that give us a more fundamental understanding of RNA-virus evolution and diversity, as Shi and colleagues work does, will be crucial to inform future surveillance efforts in humans.

It took us many decades to understand the basics of the evolutionary history of vertebrates. It will probably take even longer before we can confidently say that we are beginning to understand the enormous diversity of RNA viruses and their complex relationships with humans and other vertebrates. Shi *et al.* have provided an exciting starting point from which to strike out towards this goal. ■

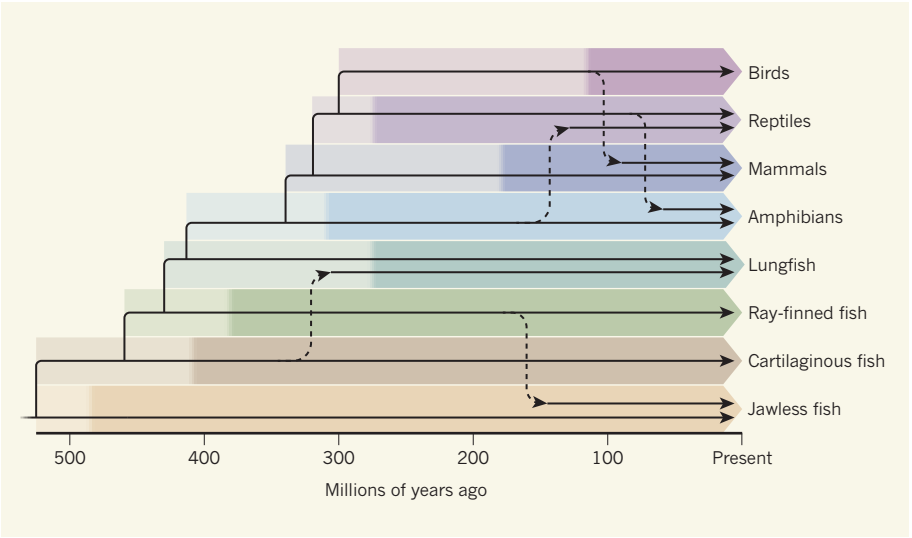

Figure 1 | Tracking the evolution of RNA viruses. Shi *et al.*[6] sequenced RNA viruses present in various classes of vertebrate, and constructed trees of virus evolution. Over a period of 525 million years, vertebrates branched off into several classes. The beginning of each coloured blocked arrow indicates the divergence between a vertebrate group and that below it in the figure; the beginning of the darker shading indicates the time that the most recent common ancestor of currently extant members of a class arose. The authors found that RNA viruses co-diverged with their vertebrate hosts (black lines indicate virus evolution). Each vertebrate class is dominated by its own set of RNA viruses; however, occasional cross-species transmissions occur (dashed arrows), introducing new viruses into a particular class. This phylogenetic tree is a simplified schematic to exemplify RNA-virus evolution as a whole, and does not reflect precise dates or cross-species transmission events found by the authors.

Mark Zeller *and* **Kristian G. Andersen** *are in the Department of Immunology and Microbiology, The Scripps Research Institute, La Jolla, California 92037, USA.* **K.G.A.** *is also in the Department of Integrative Structural and Computational Biology, The Scripps Research Institute, and at the Scripps Translational Science Institute.*
e-mails: zellerm@scripps.edu; andersen@scripps.edu

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