findings suggest that one could think of the body of a starfish (at least in terms of the anterior–posterior identity of its surface tissues) as a disembodied head walking about the sea floor on its lips — the lips having sprouted a fringe of tube feet, co-opted from their original function of sorting food particles, to do the walking. A more accurate characterization would be that a neurogenic domain — a region that gives rise to the nervous system, a bit of ancestral forehead in this case — has grown to encircle the mouth to produce nerves. Meanwhile, tissue that is fated to form the region below the mouth has expanded forward around the margin of the neurogenic domain to produce the tube feet. This is truly a radical transformation of the ancestral bilaterian body plan. Knowing how it was done means that we now have a much firmer foundation for interpreting early echinoderm fossils, and a better understanding of how the regions of our own brain compare with their echinoderm counterparts.

In a broader context, the *P. miniata* data provide a striking example of a trend in echinoderms, in which the tissue layers become decoupled during development and are patterned separately[8,9]. In principle, such decoupling should allow the layers greater freedom to evolve independently in innovative ways. Yet, the more common strategy across phyla, in insects and other arthropods for example, is to have a point-by-point correspondence between developmental events occurring in tissues on the body surface and those deeper within. The advantage of one strategy over another is still a puzzle, as is the role of chance and circumstance — evolutionary contingency — in producing such different outcomes[10].

There is also then the question of why, with this loss of correspondence between tissues, echinoderms have lost the trunk as an identifiable structure. One answer is that the trunk of ancestral deuterostomes (the larger phyletic grouping to which echinoderms, hemichordates and chordates belong) might not have been especially useful as a locomotory device in the face of the increasing levels of predation characterizing the explosion in animal diversity that happened during the Cambrian period some 530 million years ago[11]. In contrast to echinoderms, the chordate ancestors of humans responded to that challenge by vastly improving their swimming efficiency, through the addition of a new set of muscles derived from blocks of embryonic tissue known as somites — structures that have no obvious counterpart in other deuterostomes. We lack sufficient knowledge of the shared common ancestor to understand what predisposed chordates to take this step, but it clearly opened up new habitats and adaptive possibilities.

Although the common ancestor from which the three deuterostome phyla evolved is elusive, there are Cambrian fossils that might be phylogenetically close, for example small tentacle-bearing animals such as *Herpetogaster*[12]. However, if the initial split in the main deuterostome lineages happened before the Cambrian explosion (as is probably the case), the paucity of convincing bilaterian body fossils from that period leaves us relying on what can be learned from living taxa. Any insight is then useful so long as it tells us something about the prevailing conditions at the time of the divergence, the developmental constraints that the organisms might have faced and the molecular and developmental mechanisms that were available to help them to overcome those constraints. This is what makes the work by Formery *et al.* so informative, beyond even what it says of echinoderms themselves.

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Virology

Anti-COVID drug accelerates viral evolution

Sergei L. Kosakovsky Pond & Darren Martin

Molnupiravir, an antiviral drug used to treat COVID-19, induces numerous mutations in the SARS-CoV-2 genome that can increase the rate at which the virus evolves — yielding viral variants that might survive and be passed on. **See p.594**

Drugs are potent weapons against viral pathogens. During the early stages of the COVID-19 pandemic, there were intensive efforts to discover and implement antiviral drugs that could treat SARS-CoV-2 infections, either by reducing the intensity of symptoms or by shortening the duration of infection. One of the drugs identified as part of that work was molnupiravir. On page 594, Sanderson *et al.*[1]

"The rate of viral evolution could considerably exceed what is seen for standard antiviral drugs."

provide the most convincing evidence yet that molnupiravir-induced mutations in the SARS-CoV-2 genome can lead to new transmissible viral variants. Although there is no reason to think that any SARS-CoV-2 variant arose as a result of treatment with molnupiravir, public-health authorities should exercise caution when considering the therapeutic use of this drug and others that work in a similar way.

Most successful antiviral drugs, including those used to treat infections with HIV-1, hepatitis C and influenza A, work by selectively binding to a viral protein and thereby interfering with some key step in the viral replication cycle. Molnupiravir and other drugs that operate through a mechanism known as mutational error catastrophe are unusual because their intended function is simply to reduce the accuracy with which viruses copy their genomes. In theory, the drug-induced accumulation of numerous copying errors should yield viruses that are no longer viable — that is, they are unable to infect new cells, sustain replication or transmit to other hosts. But there is a danger that, instead of helping to control infection, drugs such as molnupiravir could occasionally yield heavily mutated yet viable viral variants. This is precisely what Sanderson *et al.* have found.

Knowing that molnupiravir almost always causes mutations of two particular types, Sanderson and colleagues developed a genomic 'fingerprinting' technique to scan millions of SARS-CoV-2 genome sequences for telltale signs of molnupiravir-induced mutations. Their analysis showed that thousands of viruses with many mutations — sometimes

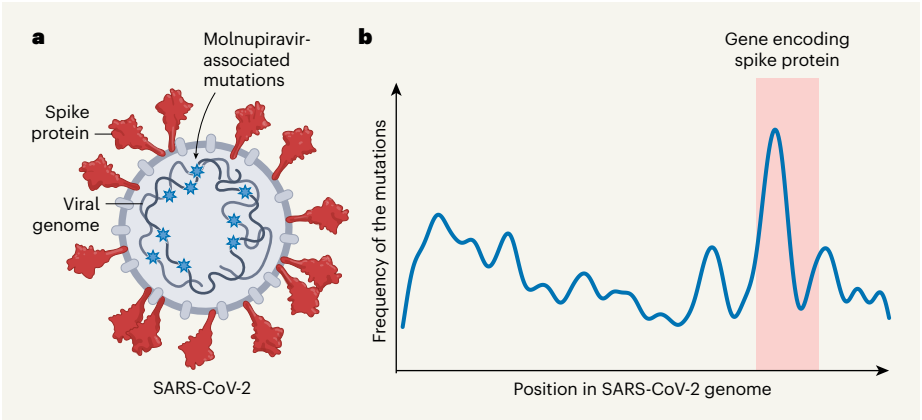

Figure 1 | Molnupiravir-associated mutations in the SARS-CoV-2 genome. **a**, Molnupiravir is an anti-COVID drug that is intended to prevent SARS-CoV-2 from replicating by inducing large numbers of mutations in the viral genome — including in regions that encode important proteins such as the spike protein, which mediates viral entry into the host's cells. **b**, Sanderson *et al.*[1] analysed SARS-CoV-2 genome-sequencing databases and found patterns of molnupiravir-associated mutations in viruses that had apparently survived treatment and had been transmitted to other people. Mutations that cause changes in amino-acid sequences were frequently found in the gene encoding the spike protein. Although there is no evidence that currently circulating SARS-CoV-2 variants are attributable to molnupiravir, its continued use could lead to heavily mutated and transmissible viral variants. (Graph adapted from Fig. 5 of ref. 1).

more than 100 — had apparently survived molnupiravir treatment. The mutated viruses had also been transmitted between individuals and had continued to accumulate mutations that would normally be expected to arise during the course of infection. This is a startling finding, because previous studies of such drugs have assumed that highly mutated viruses would not be viable, and that viruses would have to acquire a large number of mutations to become resistant to the drugs[2]. A study using mathematical modelling even rated molnupiravir as 'evolutionarily safe'[3].

Sanderson and colleagues found that the prevalence of viral genomes with signatures of molnupiravir-induced mutations was strongly correlated with when, where and how extensively the drug was used. These mutational signatures were also more common in viruses from older individuals, who tended to be treated with molnupiravir more often than younger people were. Although such associations are compelling, there are gaps in the available data — including biased sampling, unknown medical histories and the fact that who infected whom cannot be deduced from genome-sequencing data alone. It is not therefore possible at present to formally establish a causal relationship between molnupiravir treatment and the mutational effects observed.

SARS-CoV-2 evolved in a predictable manner for most of the pandemic: the virus gradually accumulated mutations, resulting in incrementally fitter variants that displaced their closely related predecessors. However, the evolution of several key variants — including Alpha, Omicron and, more recently, BA.2.86 — completely defied those expectations. All of these variants seem to have emerged after prolonged periods of 'cryptic evolution', during which large numbers of mutations rapidly accumulated without any trace of evolutionary intermediates linking them to previously dominant variants. Various lines of evidence suggest that accelerated evolution in individuals with chronic infections could explain how these variants arise[4].

Sanderson *et al.* show that drugs that increase viral mutation rates can have a similar effect to chronic infection, in that they push the viruses off a predictable evolutionary course. Although the authors do not find evidence that any commonly circulating SARS-CoV-2 variants are derived from molnupiravir treatment, we should not assume that widespread therapeutic use of such mutation-driving agents will never lead to potentially dangerous new viral variants.

It is especially concerning that exactly the same genomic positions are mutated in multiple lineages originating from viral sequences that seem to have been affected by molnupiravir. This pattern suggests that some of the mutations might be favoured by natural selection. Although it remains unclear what evolutionary advantages these recurring mutations might provide, some of them occur in the gene that encodes the spike protein — the protein that enables SARS-CoV-2 to enter host cells (Fig. 1). Mutations in this gene are therefore likely to influence the ability of the virus either to infect the host or to evade their immune system.

Most antiviral drugs are expected to transiently promote a slight acceleration in viral evolution. This usually results in the accumulation of a few mutations that confer drug resistance, both by altering the sites on viral proteins to which drugs bind and by compensating for the loss of fitness that these alterations cause. If drugs such as molnupiravir occasionally yield viable hypermutated viruses upon which natural selection can act, then the rate of viral evolution could considerably exceed what is seen for standard antiviral drugs.

The identification of transmissible viruses with clusters of mutations that resemble those expected to be induced by molnupiravir is a clear warning that some of the mutations caused by this drug are not as lethal to the virus as intended. The situation might be distinctly unsafe if natural selection can foster the continued evolution of the heavily mutated genomes. When considered together with the low efficacy of molnupiravir in reducing COVID-19 associated deaths or hospitalizations[5], and with data suggesting that such drugs can interact with (and therefore potentially mutate) host DNA[6,7], continued widespread administration of molnupiravir seems inadvisable. The discovery that a marginally effective antiviral drug can rapidly accelerate the evolution of SARS-CoV-2 speaks to an urgent need for more rigorous risk assessment, prudence in judging whether the use of certain drugs might have unintended consequences and respect for the multitude of ways in which viral pathogens can evolve and survive.

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