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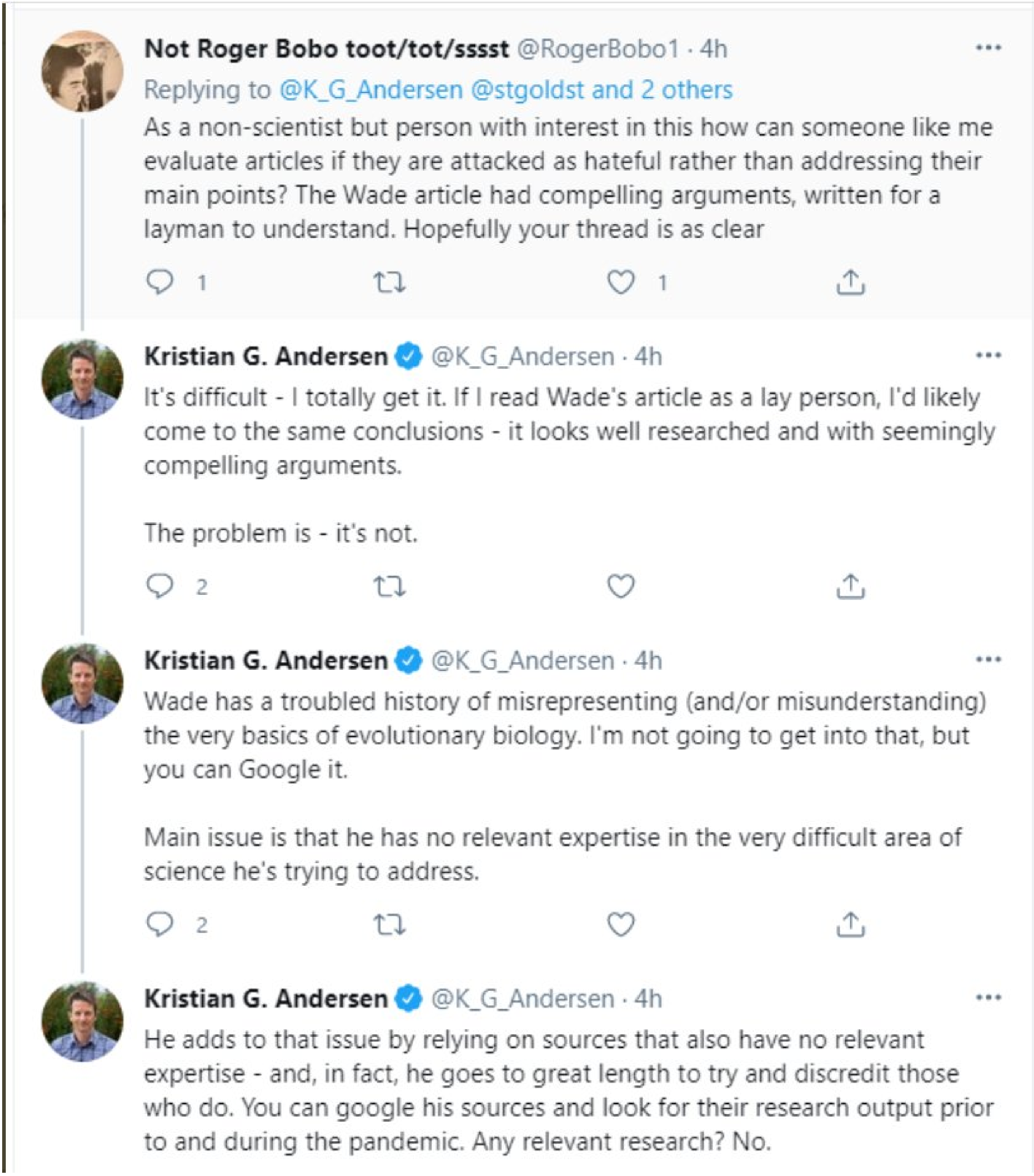
Twitter Thread by Rossana Segreto

Rossana Segreto
@Rossana38510044

I must say it, @K_G_Andersen never ends to surprise me with his compelling arguments... If you want to figure out why Wade is wrong you can Google it ■■■



Not Roger Bobo toot/tot/sssst @RogerBobo1 · 4h

Replying to @K_G_Andersen @stgoldst and 2 others

As a non-scientist but person with interest in this how can someone like me evaluate articles if they are attacked as hateful rather than addressing their main points? The Wade article had compelling arguments, written for a layman to understand. Hopefully your thread is as clear

Kristian G. Andersen @K_G_Andersen · 4h

It's difficult - I totally get it. If I read Wade's article as a lay person, I'd likely come to the same conclusions - it looks well researched and with seemingly compelling arguments.

The problem is - it's not.

Kristian G. Andersen @K_G_Andersen · 4h

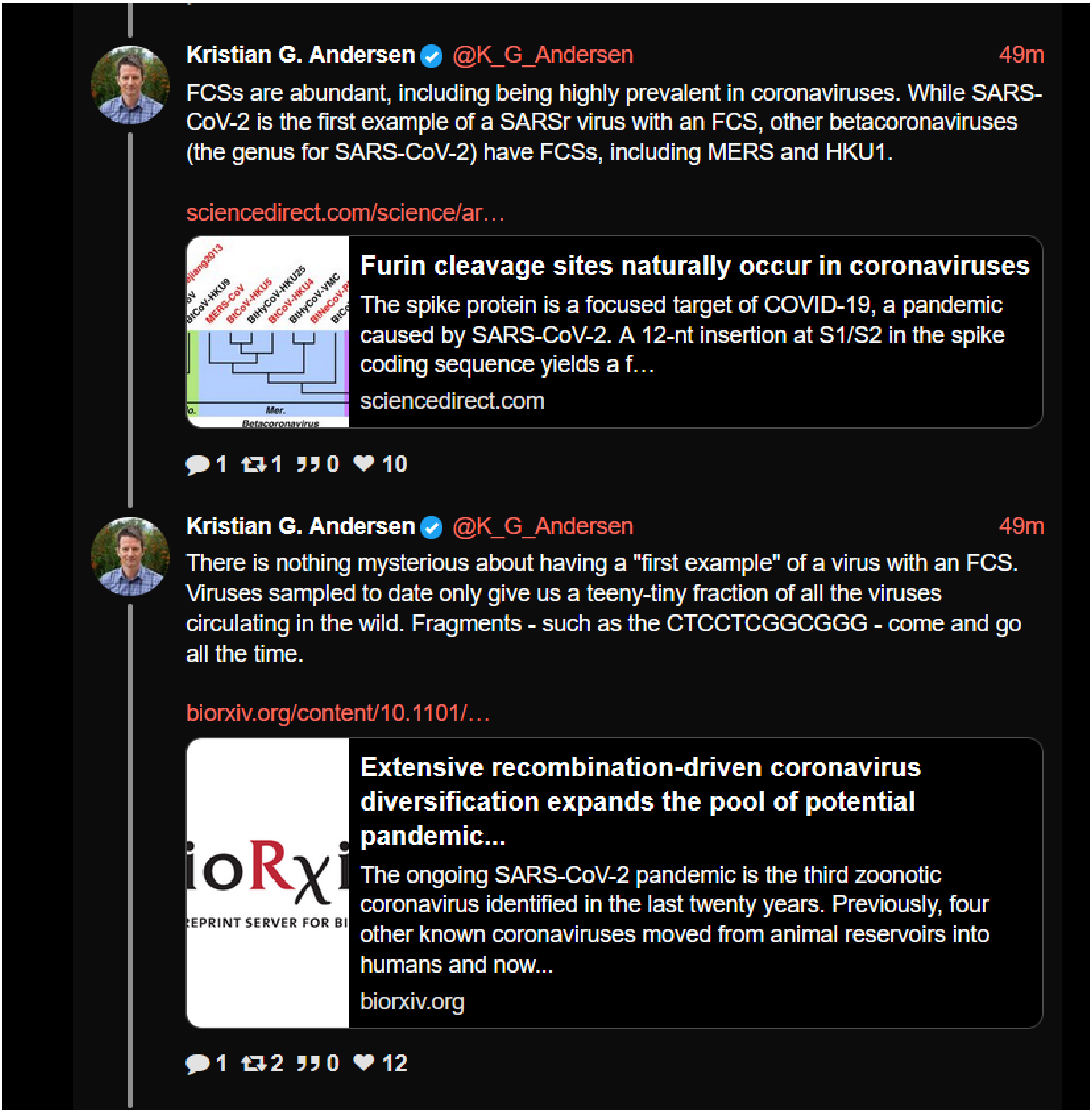
Wade has a troubled history of misrepresenting (and/or misunderstanding) the very basics of evolutionary biology. I'm not going to get into that, but you can Google it.

Main issue is that he has no relevant expertise in the very difficult area of science he's trying to address.

Kristian G. Andersen @K_G_Andersen · 4h

He adds to that issue by relying on sources that also have no relevant expertise - and, in fact, he goes to great length to try and discredit those who do. You can google his sources and look for their research output prior to and during the pandemic. Any relevant research? No.

Here he downplays the FCS of SARS2. These fragments do not really come and go all the time. I am not aware of experiments on CoV where the FCS arose by cell or animal passage. More on the FCS here:
https://t.co/oyPKBVVG4f



Kristian G. Andersen @K_G_Andersen 49m

FCSs are abundant, including being highly prevalent in coronaviruses. While SARS-CoV-2 is the first example of a SARSr virus with an FCS, other betacoronaviruses (the genus for SARS-CoV-2) have FCSs, including MERS and HKU1.

sciencedirect.com/science/ar…

Furin cleavage sites naturally occur in coronaviruses

The spike protein is a focused target of COVID-19, a pandemic caused by SARS-CoV-2. A 12-nt insertion at S1/S2 in the spike coding sequence yields a f…

sciencedirect.com

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Kristian G. Andersen @K_G_Andersen 49m

There is nothing mysterious about having a "first example" of a virus with an FCS. Viruses sampled to date only give us a teeny-tiny fraction of all the viruses circulating in the wild. Fragments - such as the CTCCTCGGCGGG - come and go all the time.

biorxiv.org/content/10.1101/…

Extensive recombination-driven coronavirus diversification expands the pool of potential pandemic...

The ongoing SARS-CoV-2 pandemic is the third zoonotic coronavirus identified in the last twenty years. Previously, four other known coronaviruses moved from animal reservoirs into humans and now...

biorxiv.org

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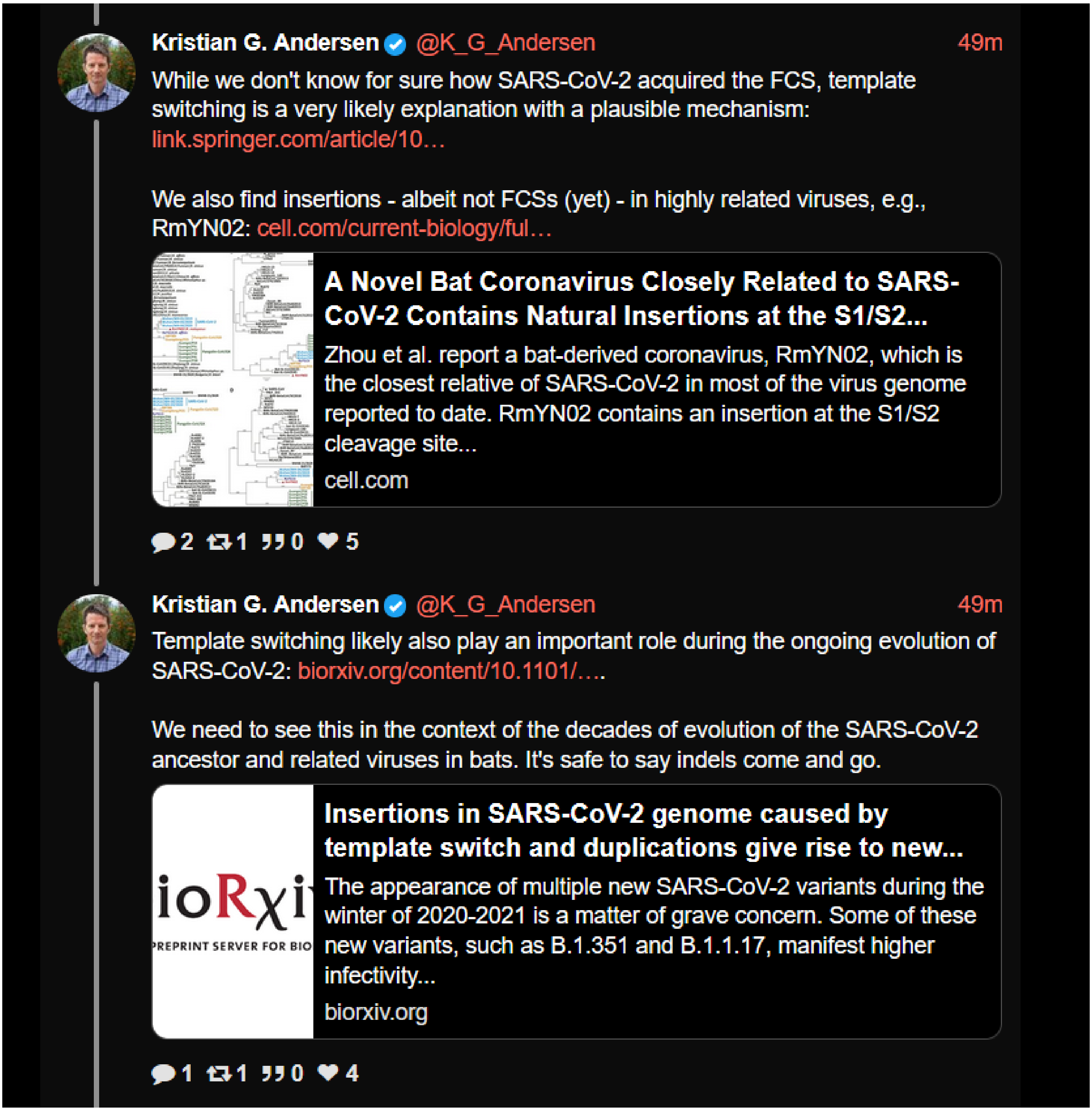
> The FCS is unique in the whole Sarbecovirus group to which SARS2 belongs. Here other reasons why it should be taken seriously. The codon used for arginine is very rare in CoVs but it translates very well in humans.https://t.co/s7q6Ynh7NYhttps://t.co/lHcshQp2Uq pic.twitter.com/kXKKb8FIk7
>
> — Rossana Segreto (@Rossana38510044) May 9, 2021

Here he refers to RmYN02, which has no insertion at the S1/S2 cleavage site
https://t.co/0Goapx6cXj
https://t.co/zEALrUUj8F
And to Gallaher's paper, with the fanciful theory of recombination on a train to Wuhan
Recombination is rare outside its group +
https://t.co/DBs7RMeq4X



Kristian G. Andersen @K_G_Andersen 49m

While we don't know for sure how SARS-CoV-2 acquired the FCS, template switching is a very likely explanation with a plausible mechanism: link.springer.com/article/10…

We also find insertions - albeit not FCSs (yet) - in highly related viruses, e.g., RmYN02: cell.com/current-biology/ful…

A Novel Bat Coronavirus Closely Related to SARS-CoV-2 Contains Natural Insertions at the S1/S2...

Zhou et al. report a bat-derived coronavirus, RmYN02, which is the closest relative of SARS-CoV-2 in most of the virus genome reported to date. RmYN02 contains an insertion at the S1/S2 cleavage site...

cell.com

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Kristian G. Andersen @K_G_Andersen 49m

Template switching likely also play an important role during the ongoing evolution of SARS-CoV-2: biorxiv.org/content/10.1101/….

We need to see this in the context of the decades of evolution of the SARS-CoV-2 ancestor and related viruses in bats. It's safe to say indels come and go.

Insertions in SARS-CoV-2 genome caused by template switch and duplications give rise to new...

The appearance of multiple new SARS-CoV-2 variants during the winter of 2020-2021 is a matter of grave concern. Some of these new variants, such as B.1.351 and B.1.1.17, manifest higher infectivity...

biorxiv.org

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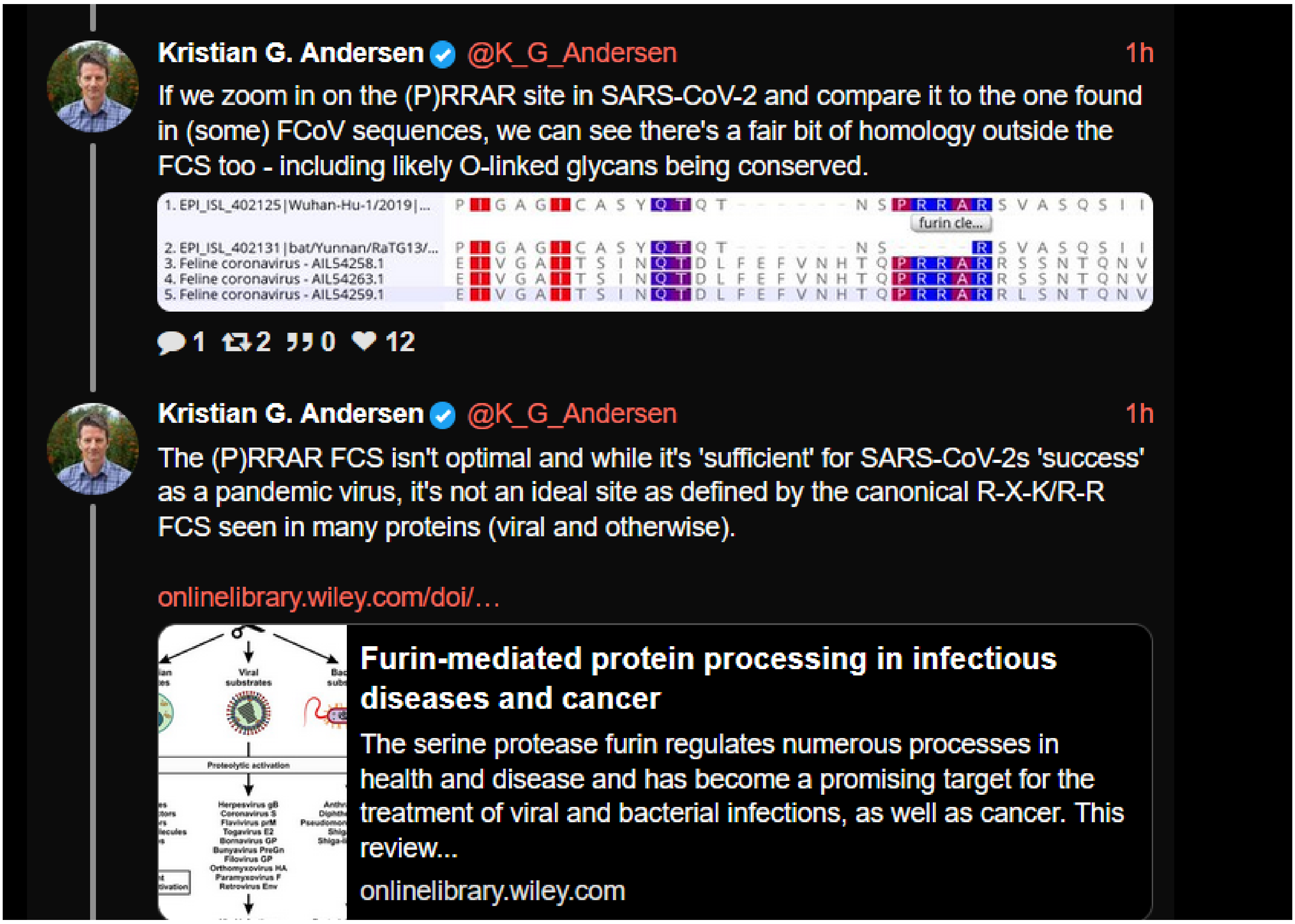
As also my co-author @ydeigin says
https://t.co/qrOG0nllzR
the FCS could be not optimal because part of a vaccine attenuation strategy
https://t.co/tHWG1Igf7Q
Andersen admitted to be wrong with his prediction of the O-linked glycans

> Could the uncharacteristic furin cleavage site in SARS2 have been a part of a vaccine attenuation strategy? You know, the pan-coronavirus vaccine that Fauci, Daszak and other have dreamed about? https://t.co/EpSXwzfBD6
>
> — Yuri Deigin (@ydeigin) May 9, 2021

The FCS might be similar at the aa level to some FCoV sequences, but less at the nt level.
https://t.co/Hvi3azygu6
Andersen does not mention that the FCS binds extremely well to heparan sulphate as possible result of cell passage
https://t.co/s7q6Ynh7NY



Kristian G. Andersen @K_G_Andersen 1h

If we zoom in on the (P)RRAR site in SARS-CoV-2 and compare it to the one found in (some) FCoV sequences, we can see there's a fair bit of homology outside the FCS too - including likely O-linked glycans being conserved.

```
1. EPI_ISL_402125|Wuhan-Hu-1/2019|...    P [illegible] G A G [illegible] C A S Y Q T Q T - - - - - - - N S P R R A R S V A S Q S I I
                                                                                                  furin cle...
2. EPI_ISL_402131|bat/Yunnan/RaTG13/...  P [illegible] G A G [illegible] C A S Y Q T Q T - - - - - - - N S - - - - R S V A S Q S I I
3. Feline coronavirus - AIL54258.1       E [illegible] V G A [illegible] T S I N Q T D L F E F V N H T Q P R R A R R S S N T Q N V
4. Feline coronavirus - AIL54263.1       E [illegible] V G A [illegible] T S I N Q T D L F E F V N H T Q P R R A R R S S N T Q N V
5. Feline coronavirus - AIL54259.1       E [illegible] V G A [illegible] T S I N Q T D L F E F V N H T Q P R R A R R L S N T Q N V
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Kristian G. Andersen @K_G_Andersen 1h

The (P)RRAR FCS isn't optimal and while it's 'sufficient' for SARS-CoV-2s 'success' as a pandemic virus, it's not an ideal site as defined by the canonical R-X-K/R-R FCS seen in many proteins (viral and otherwise).

onlinelibrary.wiley.com/doi/…

Furin-mediated protein processing in infectious diseases and cancer

The serine protease furin regulates numerous processes in health and disease and has become a promising target for the treatment of viral and bacterial infections, as well as cancer. This review...

onlinelibrary.wiley.com

> indeed. at the nucleotide level the FCS differ in the wobble bases. I initially thought of cold-adapted live-attenuated feline vaccines, which can be administered intranasally (e.g. Felocell FIP IN). pic.twitter.com/bcwdAEphlA
>
> — Chris de Z (@CZilcho) April 30, 2021

That the "P" is mutating towards residues creating more optimal furin sites could be reversion, which is not rare in live attenuated viruses, mostly if not completely attenuated because accidentally leaked.

"the exact (P)RRAR can be found in other coronaviruses." is true only at the amino acid level, not as nucleotides.

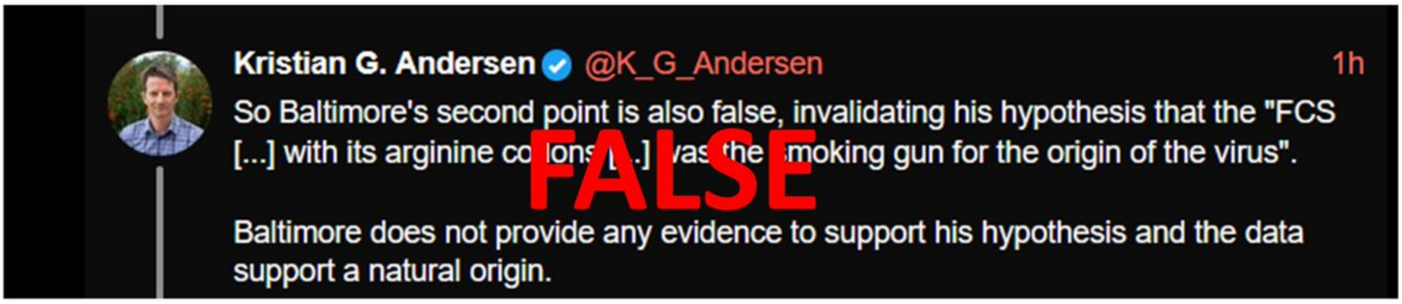
Andersen admits that the codon CGG is rare in CoV because it stimulates an immune reaction. It is only found in 3 % of arginine in SARS2. But he forgets to mention that CGG is double in the FCS, making it very special.
https://t.co/dgrP8nwPRz
Nothing unusual here.

> 22/ The FCS in SARS2 has highly CpG-rich insertion (CGG-CGG) which is extremely rare as double instance in CoVs and deoptimizes the codon for replication https://t.co/D4Z2AdS1AX pic.twitter.com/E0Ffr4vKXk
>
> — Rossana Segreto (@Rossana38510044) October 3, 2020

He forgets also to mention that by chance CGG is the best codon for arginine in humans, and CGA, used as second codon in FCoV is not that good (0.11 CGA vs 0.21 CGG)
https://t.co/KQpNwt6QLq

And the fact that the FCS is remarkably stable and necessary for human-to-human transmission in a virus which had only few months to adapt to a new host might hint to previous cell passage in human airways cells, where it is stable or humanized mice.

So all the points from Andersen to disprove Baltimore's observation on the FCS are false/misleading.



Kristian G. Andersen @K_G_Andersen 1h

So Baltimore's second point is also false, invalidating his hypothesis that the "FCS [...] with its arginine codons [...] was the smoking gun for the origin of the virus".

Baltimore does not provide any evidence to support his hypothesis and the data support a natural origin.

https://t.co/otPnkrF7KS
Actually our @Daoyu15 commented on this, but his replies have been hidden by @Merz. This is the way virologists welcome dissenting opinions.
https://t.co/X8DgaKljk0
https://t.co/THbWA1HhUz

> Re. the furin site present in SARS-CoV-2. A stem loop immediately follows it, immediately suggesting a mechanism for replicase stalling followed by strand slippage or template switching.
>
> I've not seen anyone else comment on this. https://t.co/27vhhvbrAQ
>
> — Alex Merz (@Merz) May 9, 2021

Andersen does not take into account also the other special feature of SARS2, which is its special RBD adapted from the first isolate for very efficient human infection. He tried to justify it with its presence in the pangolin CoV MP789, which we can't trust.

https://t.co/U2qvG3tXBG
And beside the special FCS and RBD we have a mountain of circumstantial evidence for a lab leak, well explained by Wade, which comprises deception of data and blocking a fair investigation.