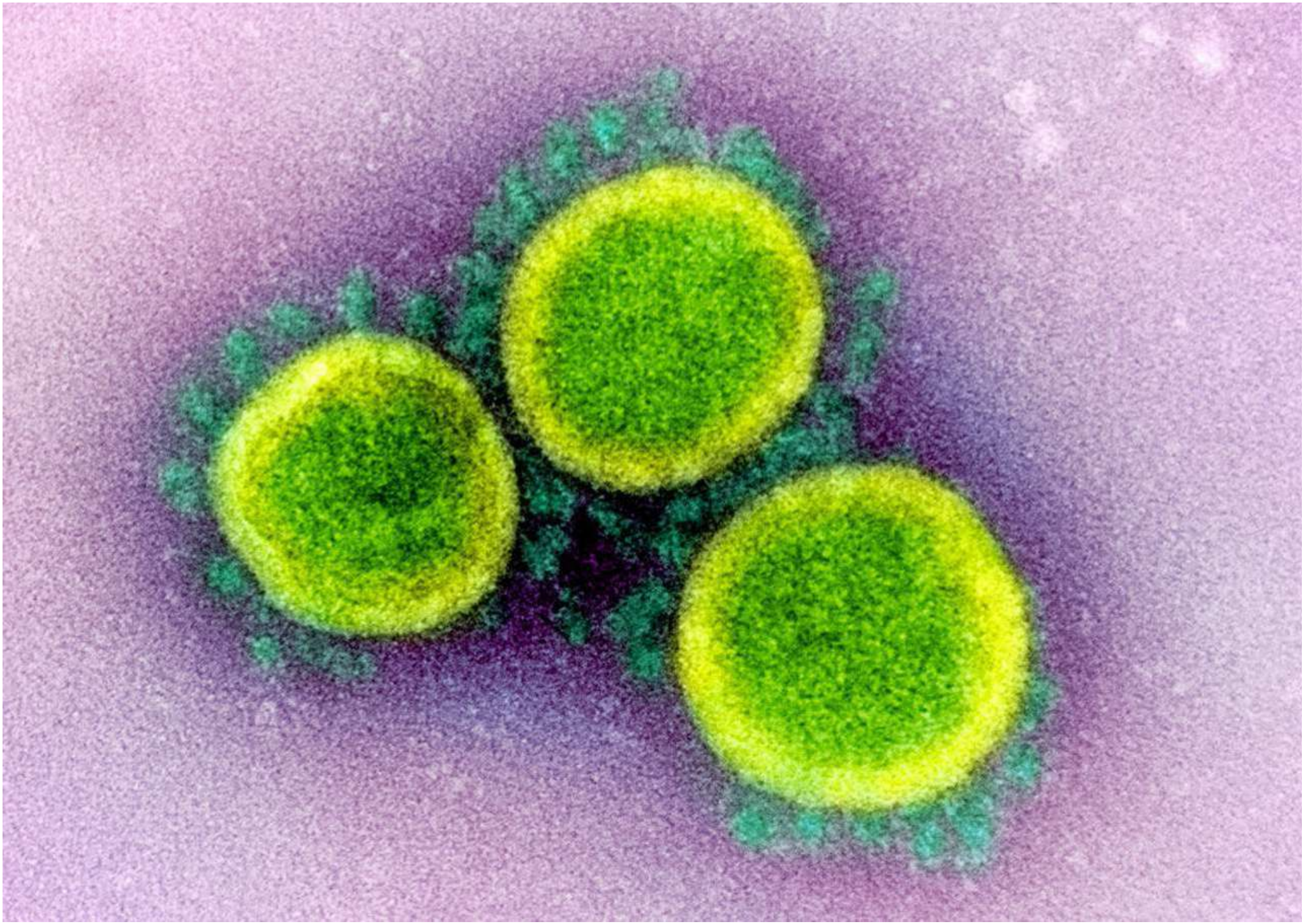
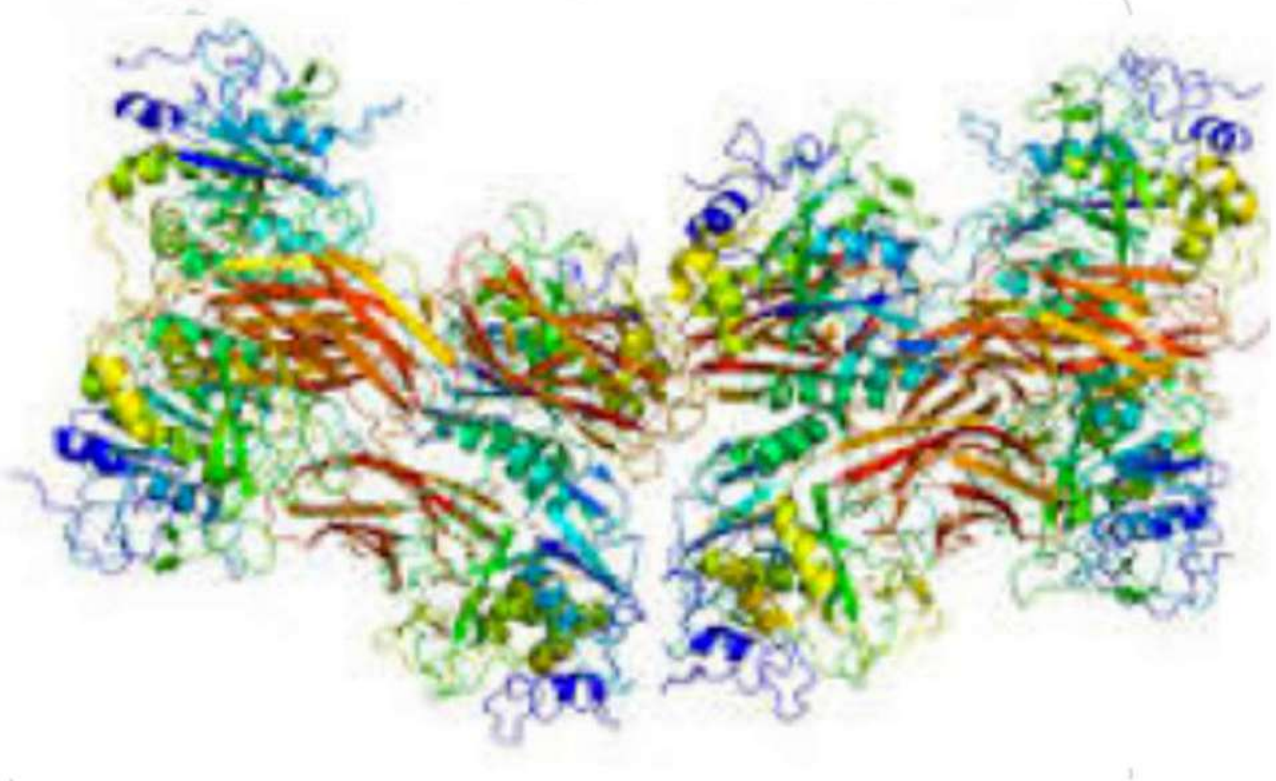


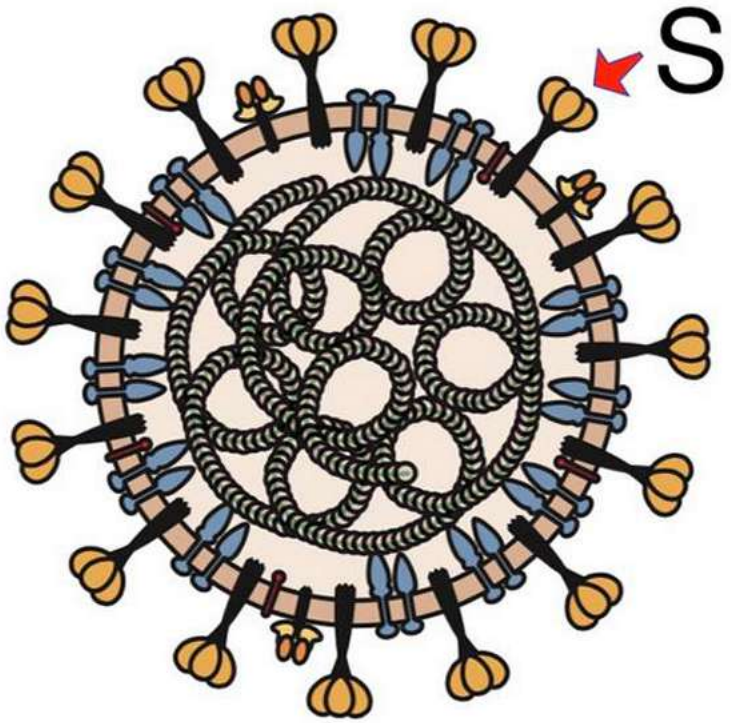
The nature of the cell protease that cleaves the S glycoprotein varies according to the coronavirus. The MERS-CoV S glycoprotein contains a furin cleavage site and is probably processed by these intracellular proteases during exit from the cell. The virus particles are therefore ready for entry into the next cell. In contrast, the SARS-CoV S glycoprotein is uncleaved upon virus release from cells; it is likely cleaved during virus entry into a cell.

La **furine** est une protéase à sérine qui catalyse le clivage d'un polypeptide au niveau typiquement d'une séquence basique de la forme –Arg–Xaa–(Arg/Lys)–Arg-|- où Xaa représente un résidu d'acide α-aminé protéinogène quelconque.



fr.wikipedia.org › wiki › Furine ▾

13 FEBRUARY 2020



The spike glycoprotein of the newly emerged SARS-CoV-2 contains a potential cleavage site for furin proteases. This observation has implications for the zoonotic origin of the virus and its epidemic spread in China.

The membrane of coronaviruses harbors a trimeric transmembrane spike (S) glycoprotein (pictured) which is essential for entry of virus particles into the cell.

The Spike glycoprotein must be cleaved by cell proteases to enable exposure of the fusion sequences and hence is needed for cell entry. Comparison of the S1/S2 cleavage site sequence from Pangolin CoV and bat-SARS-CoV-2 shows an insertion of the furin recognition motif. This indicates a distinct mechanism for entry of the viral genome into the host cytoplasm for replication as shown in Figure 3.

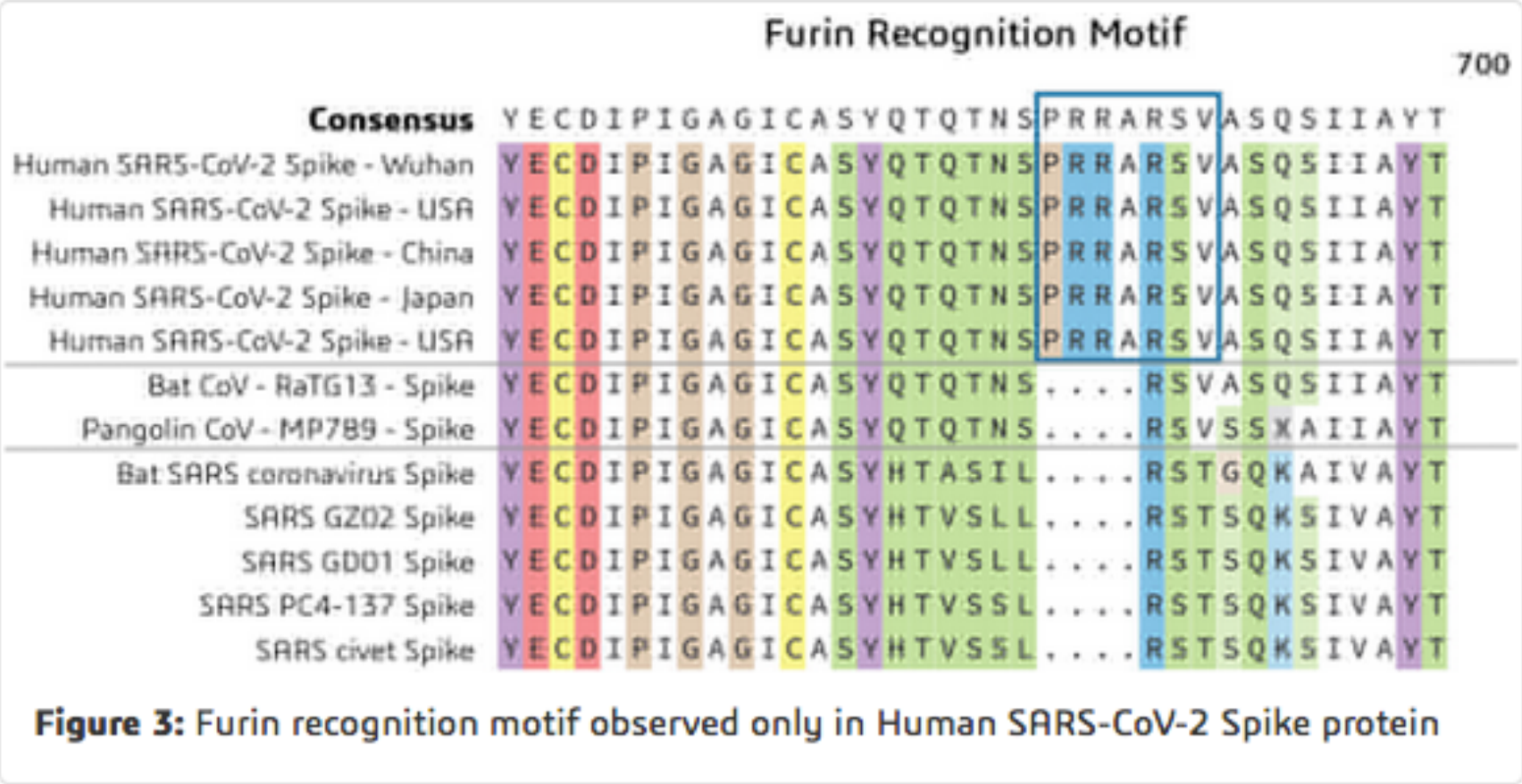
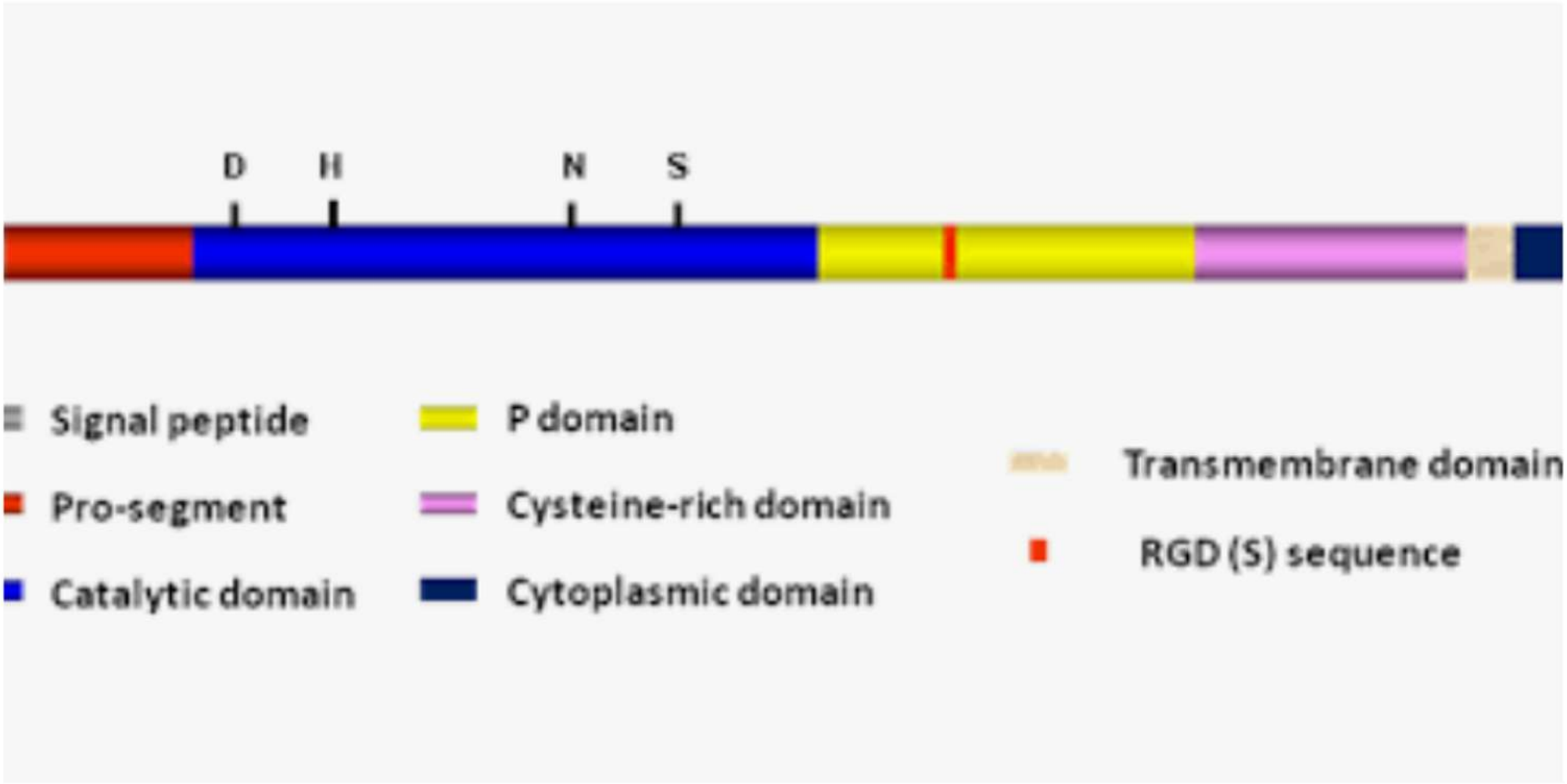


Figure 3: Furin recognition motif observed only in Human SARS-CoV-2 Spike protein

What is the role of the furin recognition motif? In humans, the furin recognition motif (PRRARSV) is recognized by the FURIN protein, a member of the S8 family of subtilisin-like peptidases that helps to remove sections of the protein to change their conformation from an inactive to an active state.

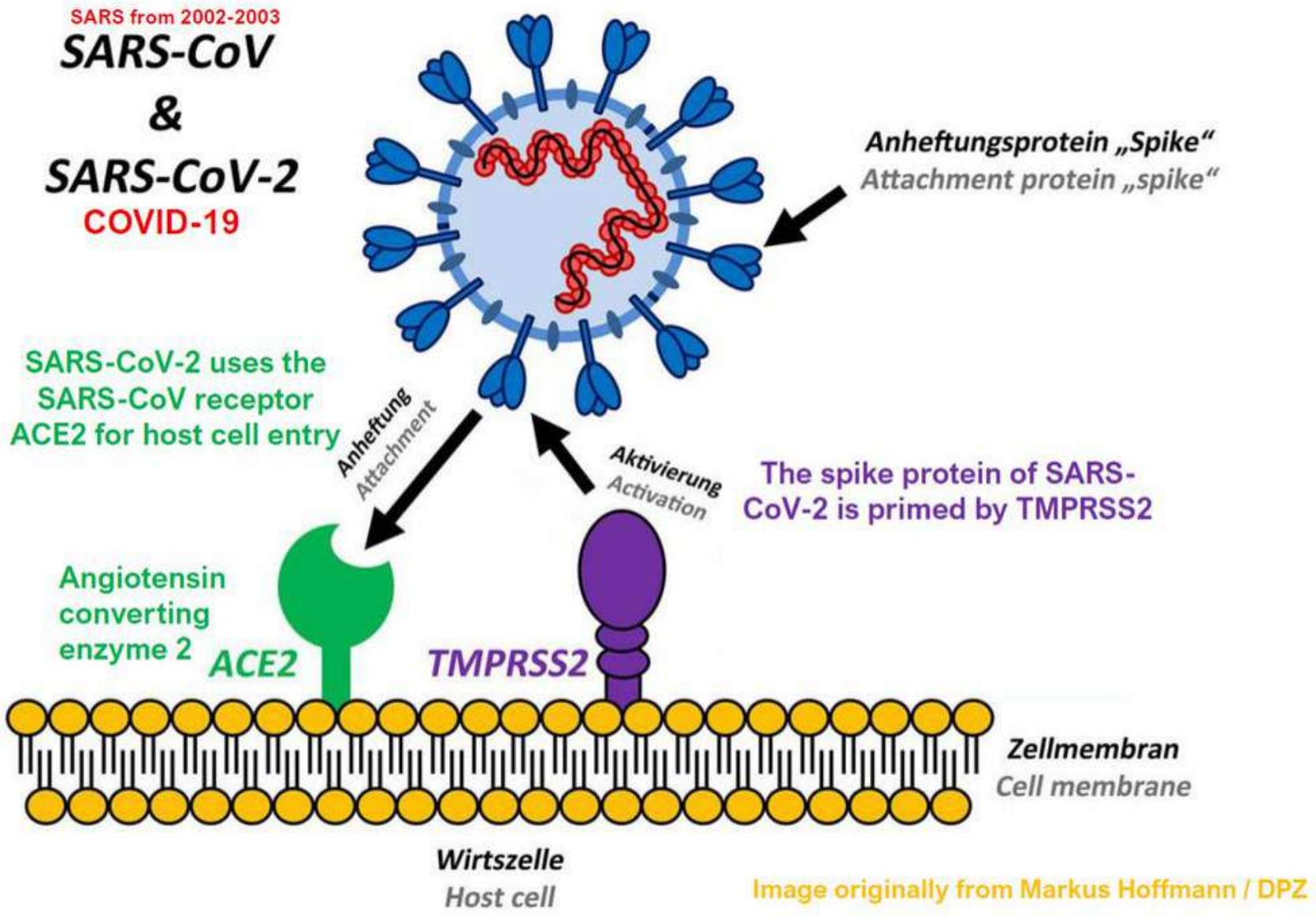
Proteolytic cleavage of the S glycoprotein can determine whether the virus can cross species, e.g. from bats to humans. For example, the S glycoprotein from a MERS-like CoV from Ugandan bats can bind to human cells but cannot mediate virus entry. However, if the protease trypsin is included during infection, the S glycoprotein is cleaved and virus entry takes place. This observation demonstrates that cleavage of the S glycoprotein is a barrier to zoonotic coronavirus transmission.

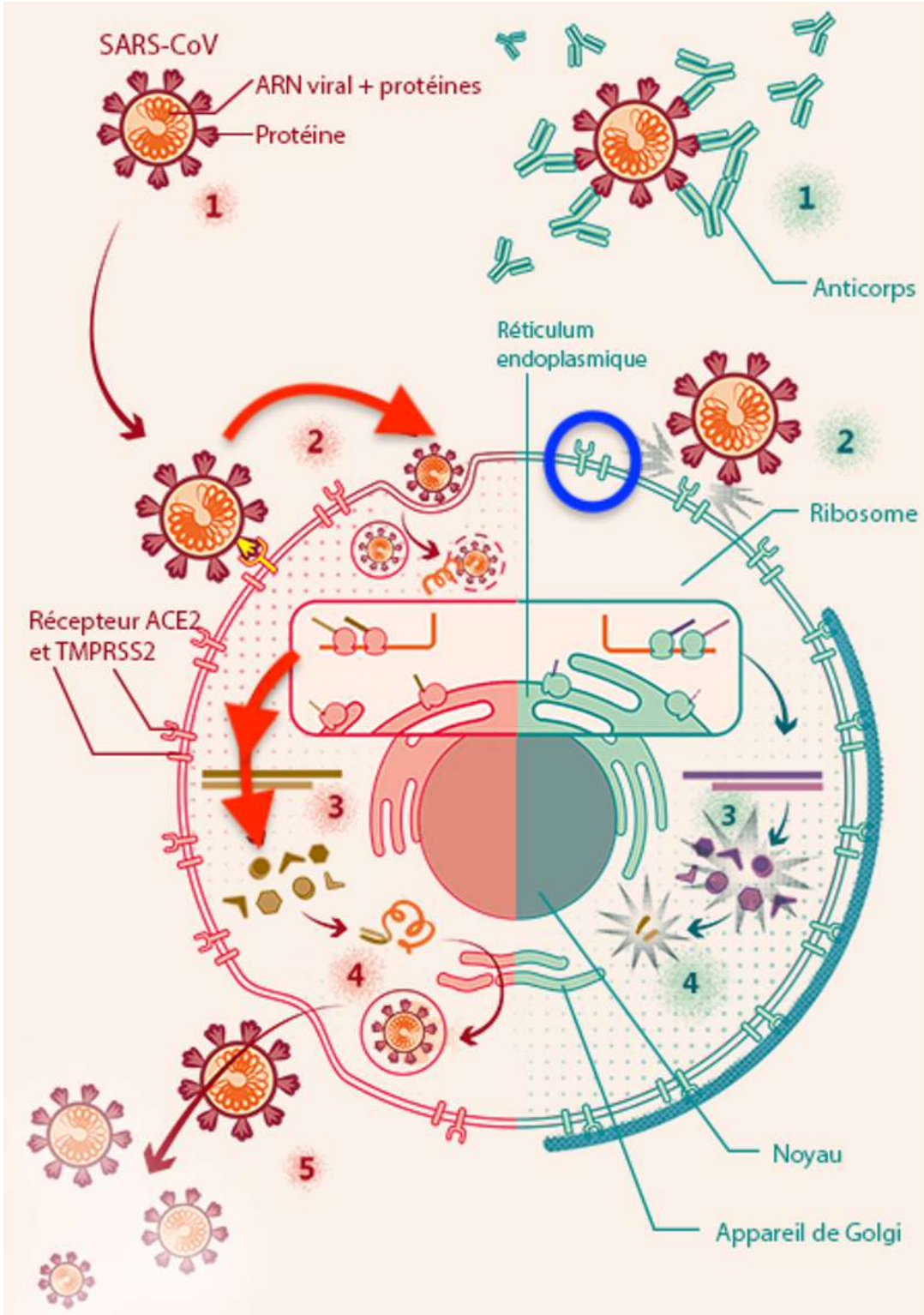
The membrane of coronaviruses harbors a trimeric transmembrane spike (S) glycoprotein (pictured) which is essential for entry of virus particles into the cell. The S protein contains two functional domains: a receptor binding domain, and a second domain which contains sequences that mediate fusion of the viral and cell membranes. The S glycoprotein must be cleaved by cell proteases to enable exposure of the fusion sequences and hence is needed for cell entry.



FURIN (furin (paired basic amino acid cleaving enzyme))

atlasgeneticsoncology.org


SARS from 2002-2003
SARS-CoV
&
SARS-CoV-2
COVID-19
Anheftungsprotein „Spike“
Attachment protein „spike“
SARS-CoV-2 uses the
SARS-CoV receptor
ACE2 for host cell entry
Anheftung
Attachment
Aktivierung
Activation
The spike protein of SARS-
CoV-2 is primed by TMPRSS2
Angiotensin
converting
enzyme 2
ACE2
TMPRSS2
Zellmembran
Cell membrane
Wirtszelle
Host cell
Image originally from Markus Hoffmann / DPZ



Cycle viral du SARS-CoV-2

1 Grâce aux protéines Spike présentes à sa surface, le SARS-CoV-2 s'accroche à une cellule au niveau d'un récepteur nommé ACE2 et du corécepteur TMPRSS2.

2 Le virus est alors internalisé par cette cellule et y libère son contenu, en particulier son matériel génétique.

3 L'ARN viral est immédiatement traduit par la machinerie cellulaire en une longue chaîne protéique, qui est ensuite découpée par protéolyse pour former des protéines virales nécessaires à la suite des opérations.

4 Elles vont en particulier permettre la synthèse de nouvelles copies du génome du virus et d'ARN messager permettant eux-même la synthèse des protéines de structure du virus.

5 Une fois tous ces composants synthétisés, ils s'auto-assemblent pour former des nouveaux virions, qui s'échapperont de la cellule pour aller infecter les voisines.

Pistes pour la mise au point de traitements antiviraux

1 **Bloquer le virus avant qu'il infecte les cellules**
Des anticorps pourraient conduire à la destruction du virus avant même qu'il ne pénètre dans une cellule pour s'y multiplier, ou bloquer son entrée.

2 **Bloquer le récepteur ACE2 ou le corécepteur TMPRSS2**
Des inhibiteurs du récepteur et/ou du corécepteur du virus pourraient stopper le virus à l'entrée dans nos cellules.

3 **Bloquer l'expression des protéines virales**
En empêchant la synthèse des protéines nécessaires à sa réplication, on bloquerait le cycle du virus. L'inhibition de différents acteurs de cette étape peut être envisagée.

4 **Bloquer la réplication du génome viral**
Inhiber la synthèse de nouvelles copies de son génome est une autre option. Là encore, les cibles thérapeutiques possibles sont multiples.

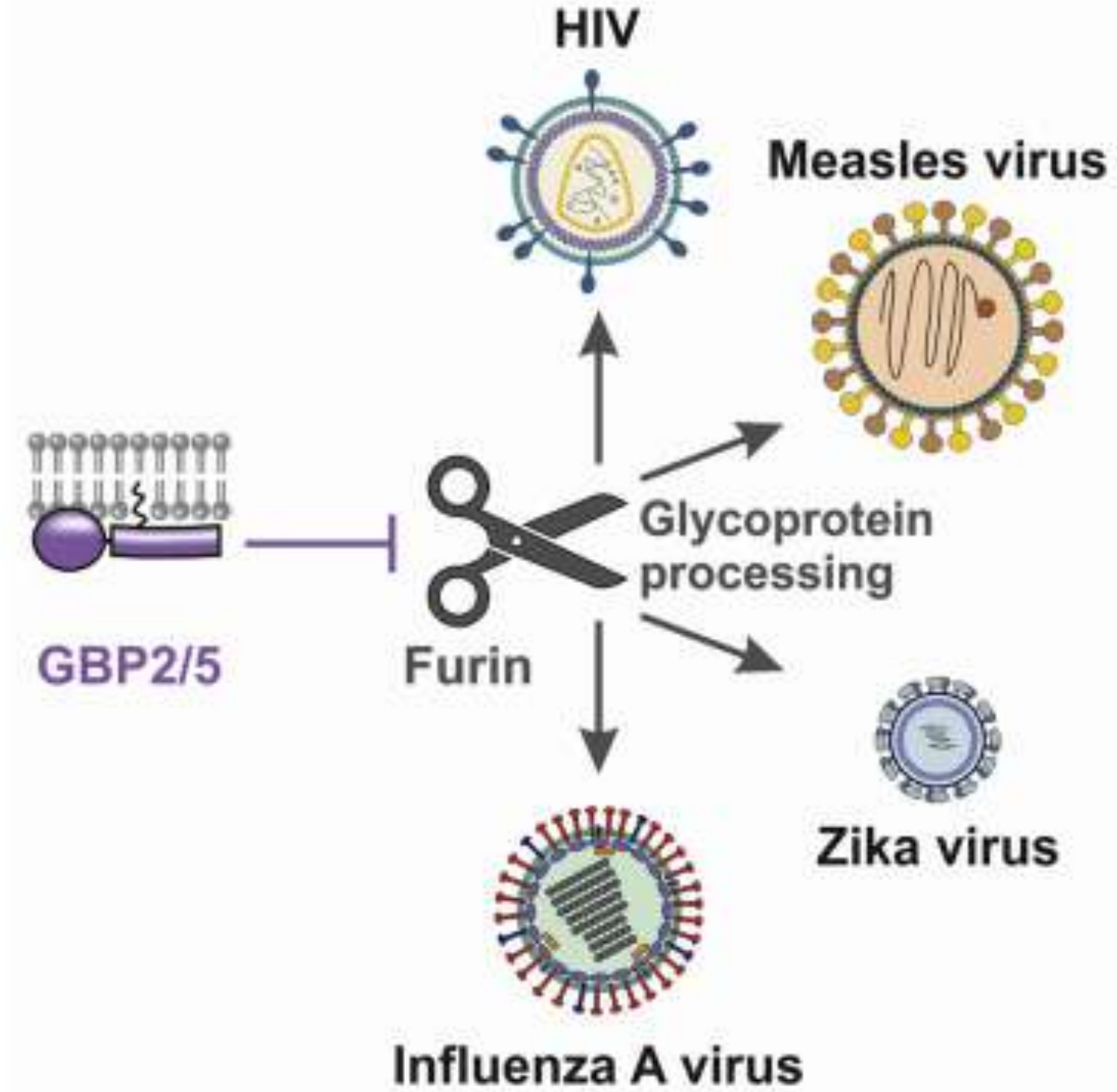
Examination of the protein sequence of the S glycoprotein of SARS-CoV-2 reveals the presence of a furin cleavage sequence (PRRARS|V). The CoV with the highest nucleotide sequence homology, isolated from a bat in Yunnan in 2013 (RaTG-13), does not have the furin cleavage sequence.

Because furin proteases are abundant in the respiratory tract, it is possible that SARS-CoV-2 S glycoprotein is cleaved upon exit from epithelial cells and consequently can efficiently infect other cells. In contrast, the highly related bat CoV RaTG-13 does not have the furin cleavage site.

(1) If MERS-CoV also had this “site 1” furin-like cleavage site, why did it have a similarly low infectivity to SARS?

(2) The “site 1” aa sequence in SARS-CoV-2019 is different than those of the other CoV possessing a furin-like cleavage “site 1”. Is it possible to find this specific sequence in another viruses, which could implicate them as a co-infection partner that led to this mutation?

Furins are also known to control infection by avian influenza A viruses, in which cleavage of the HA glycoprotein is needed for entry into the cell. Low-pathogenic avian influenza viruses contain a single basic amino acid at the cleavage site in the HA protein which is cleaved by proteases that are restricted to the respiratory tract. Insertion of a furin cleavage site in the HA of highly pathogenic avian H5N1 influenza viruses leads to replication in multiple tissues and higher pathogenicity, due to the distribution of furins in multiple tissues.


HIV
Measles virus
Glycoprotein
processing
GBP2/5
Furin
Zika virus
Influenza A virus