教學部讀書會

The proximal origin of SARS-CoV-2

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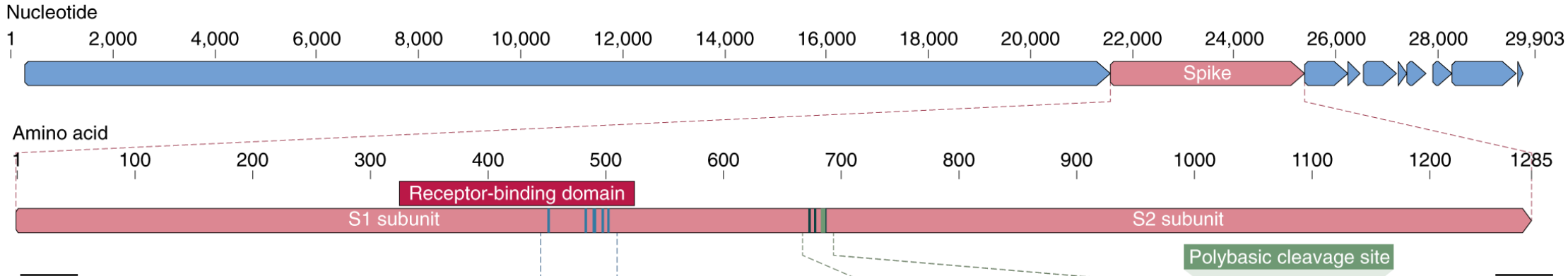
An evidence-based view to stop the rumors that SARS-CoV-2 is originated from laboratory

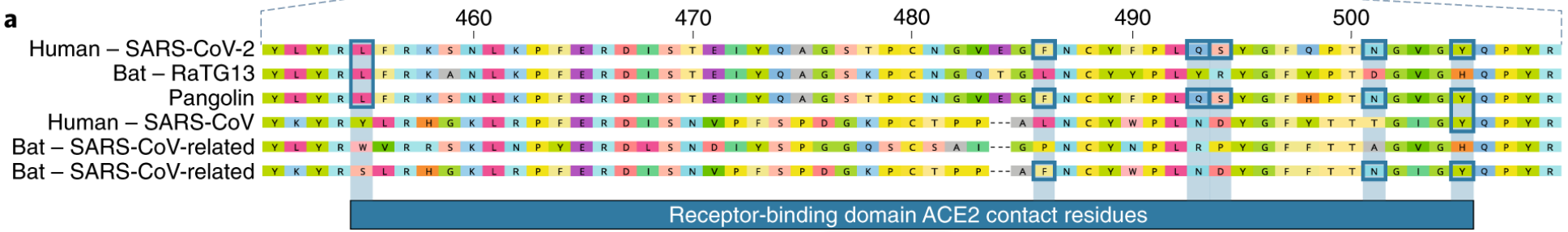
SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus.

- Deduced about the origin of SARS-CoV-2 from comparative analysis of genomic data
- A perspective on the notable features of the SARS-CoV-2 genome
- To discuss scenarios by which SARS-CoV-2 could have arisen

Fig. 1 Features of the spike protein in human SARS-CoV-2 and related coronaviruses. (From: The proximal origin of SARS-CoV-2)



1. 結構研究和生化實驗顯示： SARS-CoV-2優化了與人類受體ACE2的結合
2. 受體結合域(RBD)與人類、雪貂、貓和其他有高受體同源性的物種有高度親和力
3. 計算分析的結果顯示SARS-CoV-2與人類受體ACE2的結合比SARS-CoV差。推論是因對人類或類似人ACE2受體的自然選擇，演化出最佳的結合方式



RBD

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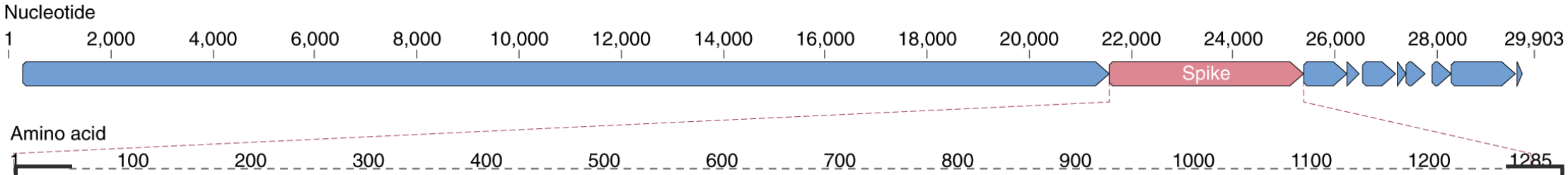
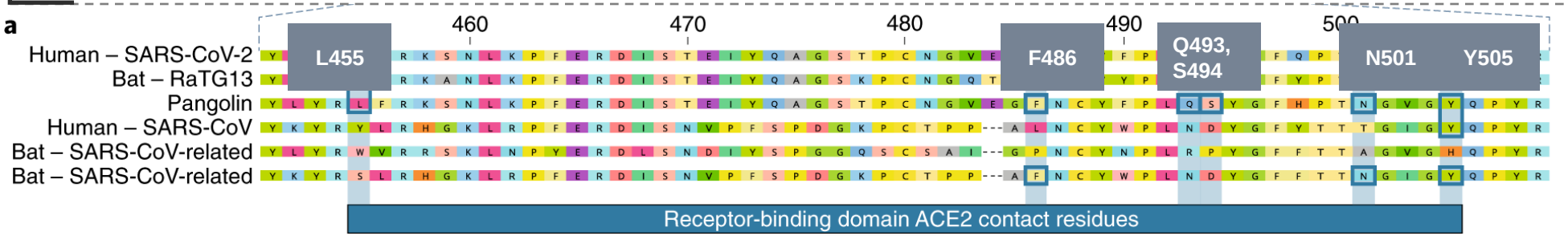


- The SARS-CoV-2 backbone varied significantly from those of definitely known coronaviruses.
- For the most part, looked like related viruses found in bats and pangolins.
- Six RBD amino acids (L455, F486, Q493, S494, N501 and Y505) shown critical for binding to ACE2 receptors and for determining the host range of SARS-CoV-like viruses



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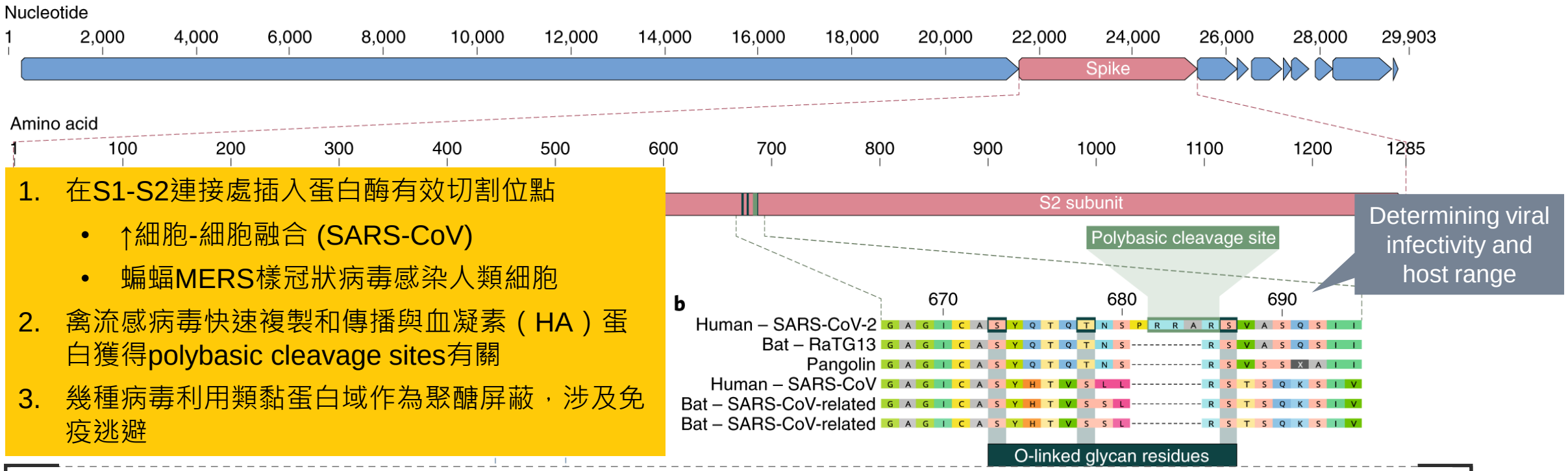


1. 在S1-S2連接處插入蛋白酶有效切割位點
   - ↑細胞-細胞融合 (SARS-CoV)
   - 蝙蝠MERS樣冠狀病毒感染人類細胞
2. 禽流感病毒快速複製和傳播與血凝素（HA）蛋白獲得polybasic cleavage sites有關
3. 幾種病毒利用類黏蛋白域作為聚醣屏蔽，涉及免疫逃避

- The polybasic cleavage site allows effective cleavage by **furin** and other proteases.
- An inserted leading proline predicted to result in the addition of O-linked glycans and flanking the cleavage site is unique to SARS-CoV-2.
- The function of both the polybasic cleavage site and O-linked glycans is unclear.
  - ➢polybasic cleavage site→ transmissibility
  - ➢O-linked glycans → mucin-like domain → shielding epitopes → immunoevasion

It is improbable that SARS-CoV-2 emerged through laboratory manipulation

01

The genetic data

SARS CoV-2 not derived from any previously used virus backbone

02

The optimized RBD for binding to human ACE2

with an efficient solution different from those previously predicted

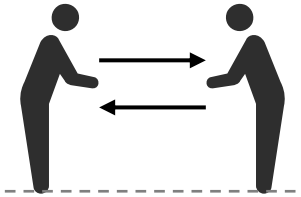
Two scenarios plausibly explaining the origin

- natural selection in an animal host before zoonotic transfer
- natural selection in humans following zoonotic transfer

Natural selection in an animal host before zoonotic transfer

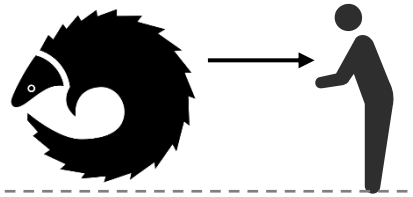
- Bat-RaTG13 is ~96% identical overall to SARS-CoV-2
- Some pangolin coronaviruses with strong similarity to SARS-CoV-2 in the RBD, including all six key RBD residues
- Mutations occurring near the S1–S2 junction of coronaviruses
- For a precursor virus to acquire both the polybasic cleavage site and mutations in the spike protein suitable for binding to human ACE2
  - a high population density of an animal host (to allow natural selection to proceed efficiently)
  - an ACE2-encoding gene similar to the human ortholog

Natural selection in humans following zoonotic transfer



A progenitor of SARS-CoV-2 jumped into humans

- adaptation during undetected human-to-human transmission
- acquiring the genomic features of SARS-CoV-2



The presence in pangolins of an RBD very similar to that of SARS-CoV-2

- probably the virus that jumped to humans
- the insertion of polybasic cleavage site occurring during human-to-human transmission

A period of unrecognized transmission in humans between the initial zoonotic event and the acquisition of the polybasic cleavage site

Selection during passage?

01

The finding of SARS-CoV-like coronaviruses from pangolins with nearly identical RBDs

a much stronger and more parsimonious explanation

02

The acquisition of the polybasic cleavage site

- only after prolonged passage of low-pathogenicity avian influenza virus
- repeated passage in cell culture or animals with ACE2 receptors similar to those of humans

03

The acquisition of predicted O-linked glycans

such features suggesting the involvement of an immune system

Conclusions

- 若能在動物身上觀察到中間型或完全一致蛋白酶有效切割位點 (polybasic cleavage sites) 會進一步支持自然選擇假設
- 目前證據指向SARS CoV-2不是人為操縱的病毒，因為觀察到優化的RBDs和polybasic cleavage sites
- 詳細了解動物病毒如何躍入物種邊界，有效地感染人類，對於預防人畜共患疾病是有幫助的

謝謝聆聽
敬請指教