Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2


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Outline

I. SARS-CoV-2 is a novel virus
II. SARS-CoV-2 infects the host by interacting with ACE2
III. The purpose of the Yang et al. (2020) study is to provide a full-length sequence of human ACE2 to better understand the structure-function relationship between the enzyme and virus
IV. The main results of the study are:
   A. PD influences conformational change and dimerization in ACE2
   B. RBD-SARS-CoV-2 interacts with ACE-PD
   C. Variation in residues changes strength of interaction
V. The study provides a base for exploring structure-function relationship but is limited by its ignorance of cofactors
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus

- SARS-CoV-2 is a positive RNA virus (Yan et. al., 2020)
- Causes coronavirus disease 2019 (COVID-19), which has become a global pandemic
  - As of April 15, 2020: 2,064,815 confirmed cases (Dong et. al., 2020)
- Shares 80% of its sequence with SARS-CoV, another coronavirus (Yan et. al., 2020)

SARS-CoV-2 particles isolated from a patient
Source: NIAID IRF (2020)
S protein of SARS-CoV interacts with human ACE2 during viral infection

- S protein is cleaved into two subunits
  - RBD of S1 binds to ACE2-PD and S1-ACE2 complex dissociates
  - S2 begins membrane fusion after S1-ACE2 complex dissociates

Song et al. (2018)
Two conformations for ACE2-B0AT1 complex that differ in rotation of PD

- CLD in blue
- PD in cyan
- B^0AT1 promoters shown in grey and pink
Dimerization of ACE2 is mediated by the neck region and PD
Addition of RBD from SARS-CoV-2 produced only closed conformation
Contact between RBD and ACE2 can be seen in three clusters of polar interactions.
RBD in SARS-CoV-2 and SARS-CoV show variation in residues interacting with ACE2
Discussion

● Overall, study shows neck and PD domains in ACE2 structure allow for homodimer formation
● Study also shows that SARS-CoV-2 binds to ACE2 in a similar to SARS-CoV
  ○ Residues variation may determine if SARS-CoV-2 binds more strongly to ACE2
● A previous study showed the S protein in SARS-CoV-2 had a trimeric structure
  ○ This study confirms that the RDB of the virus can only bind to ACE2 in the up conformation
● One limitation of the study is that effect of cofactors on binding is not examined
● In the future, researchers can use the structure of ACE2 and SARS-CoV-2 to determine what ligands may be able to block the interaction
Summary

- SARS-CoV-2 is a novel coronavirus that causes COVID-19
- Cryo-EM structures of ACE2-B0AT1 complex show full-length structure of ACE2 homodimer
- Polar interactions stabilize binding between the RBD in SARS-CoV-2 and PD in ACE2
- Sequence variation in SARS-CoV and SARS-CoV-2 affects binding affinity between the RBD in each virus and ACE2
- Structural information can be used to help design molecules that inhibit binding between SARS-CoV-2 and ACE2
Acknowledgements

Kam D. Dahlquist, PhD
Yang et al.
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References