

Class: ACE2 Receptor

Attributes:

Synonyms: Angiotensin-converting enzyme 2

Molecular weight:

Number of amino acids: 805

Structure:

1) Homology:

- homologous to two isoforms
- somatic ACE which has two homologous domains each containing a catalytic site
- testis-specific ACE corresponds to the C domain of somatic ACE and has only one active site
- 43% sequence homology

2) Domains:

- type I integral membrane protein
- contains one HEXXH and E zinc-binding consensus sequence (1)
- extracellular region is comprised of two domains (1)
 - zinc metalloproteinase domain (aa 19 to 611) (1)
 - ~42 % identical to corresponding domains of somatic and testicular ACE (1)
 - comprised of twenty alpha-helical segments and nine 3_{10} helical segments that together make up ~62% of the structure (1)
 - six short beta-structural segments make up ~3.5% of the structure
 - further divided into two subdomains (1)
 - form the sides of a cleft ~40 Å long X ~15 Å wide and ~25 Å deep connected at the floor of the active site cleft (1)
 - S1 subsite topology and chemical environment is dictated by Y510, R514, F504 and T347 which are expected to restrict size of substrate P1 side chains
 - S1' subsite side chain residues F274, P346, T371, M360 and disulfide link C334/C361 provide hydrophobic environment
 - zinc binding site is near bottom on one side of the subdomain I nearly midway along its length
 - zinc is coordinated by H374, H378, E402 and one water molecule
 - second domain is located at the C-term (aa 612 to 740) (1)
 - ~48 % identical to human collectrin
 - formation of the ES complex causes bending (~160°) movement of subdomain I toward subdomain II which brings important residues into position for catalysis (1)
 - a chloride ion is bound in native ACE2 coordinated by R169, W477 and K481 in subdomain II (1)
 - possibly is the site responsible for the anion activation effect (1)
 - Nε and NH1 of R169 are both 3.2 Å from Cl⁻ (1)
 - indole NH of W477 is 3.5 Å from Cl⁻ (1)
 - Nε of K481 is 5.0 Å from Cl⁻ (1)
 - proton transfer from H505 to the leaving nitrogen atom of the P1' residue (1)
 - a catalytic role is suggested (1)

3) Substrate specificity:

- proline and leucine were the preferred P1 residues, a partiality for hydrophobic residues in the P1' position but basic residues at P1' were also cleaved (1)

4) Regions of S1 and ACE2 Receptor Association

- electrostatic analysis revealed mostly positive charges on the surface particularly an electronegative loop containing residues K439, R441, R444, H445, K447 on the spike protein (2)
 - positive charges of the receptor binding domain compliment the negative charges of the ridges of the receptor (2)
- negatively charged ridges surrounding the channel may provide a possible binding site for the positively charged receptor-binding domain of the S-glycoprotein (2)
 - contains loops, helices and a portion of a beta sheet (2)
 - ridges contain residues D136, E150, N154, D157, D292, D295, and D299 (2)
 - D136, N154 and D157 have 109, 108 and 80 Å², respectively (2)
 - possible that some of these residues contribute to specific binding
 - binding site of S protein was localized between aa 303 and 537 (3)
- hydrophobic residues at the ACE2 surface were noted at close proximity to the charged ridges that contribute to binding (2)
 - at least three hydrophobic regions comprising different residues including Phe, Trp, and Tyr could contribute to binding in addition to the charged binding surface (2)
- mutation of the zinc coordinating residues, H374 and H378 has no effect on syncytia formation suggesting that interfering with the active sites as no effect on S-protein binding (4)

Processing:

- glycosylation is suggested by the presence of electron density at all six potential N-linked sites: N53, N90, N103, N322, N432, and N546 (1)
 - highest density at N90, N103 and N546 allowed building of three N-acetyl glucosamine groups (1)
 - only two (53 and 90) aligned with the tACE structure (2)

-shared the pattern NXTX (except 103) (2)

-three disulfide bonds of ACE2 , C133/C141, C344/C361 and C530/C542 are conserved in sACE and tACE (1)

Location:

somatic ACE
testis-specific ACE

Functions:

-thought to be an essential regulator of cardiac function (5)
-facilitates entry of SARS-CoV into the cell by serving as its primary receptor

Responsibilities:

Initiates viral infection

Collaborators:

Spike protein

- 1) Towler, P., et al., (2004) ACE2 X-ray structures reveal a large hinge-bending motion important for inhibitor binding and catalysis, *J Biol Chem*, **279(17)**, 17996-8007.
- 2) Prabakaran, P., Xiao, X., and Dimitrov, D.S., (2004) A model of the ACE2 structure and function as a SARS-CoV receptor, *Biochem Biophys Res Commun*, **314(1)**, 235-41.
- 3) Xiao, X., et al., (2003) The SARS-CoV S glycoprotein: expression and functional characterization, *Biochem Biophys Res Commun*, **312(4)**, 1159-64.
- 4) Li, W., et al., (2003) Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus., *Nature*, **426(6965)**, 450-4.
- 5) Crackower, M.A., et al., (2002) Angiotensin-converting enzyme 2 is an essential regulator of heart function, *Nature*, **417(6891)**, 822-8.