Article

Literature mining based profiling of angiotensin-converting enzyme 2

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Abstract
COVID-19, caused by zoonotic coronavirus SARS-CoV-2, is not a first coronavirus infection, prior to this, two severe coronavirus infections were already faced by the humans at different parts of the world. COVID-19 is found to be more severe than its previous counterparts and cause respiratory syndrome along with some other pathophysiology effects. The main human protein which used by SARS causing coronavirus (SARS-CoV and SARS-CoV-2) is angiotensin-converting enzyme 2 (ACE2), a key member and regulator of RAS. Coronavirus shows a significant affinity with the ACE2, spike protein of the virus participate in this crucial interaction and initiate the infection cycle of the SARS. This ACE2 plays a very significant role in RAS, which directly affect the pathophysiology of humans, mainly of respiratory and cardiovascular diseases. Blockage or down-regulation of ACE2 can easily block the virus entry in the cells, but due to the other important role of the ACE2, the human system cannot afford its suppression or blockage. Due to its importance, it is required to understand the physiology and pathophysiological role of the ACE2, which can help to develop therapy against the SARS. This report provides a detailed account of ACE2, and help to understand about it, which will help to plan a possible way to fight against SARS-CoV-2 and other coronaviruses.

Keywords angiotensin-converting enzyme-2; coronavirus; COVID-19; RAS; SARS.

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1 Introduction

This 20th century is a witness of three severe coronavirus infections, i.e., SARS (2003; SARS CoV, Peiris et al., 2003), MERS (2012; MERS-CoV, Zaki et al., 2012) and COVID-19 (2019; SARS-CoV-19). All these three were caused by animal originated coronavirus that transmitted to humans. In all three infections, it has been observed that coronavirus first entered animals to humans and then spread through infected-human-to-human transmission process with close contact. The recent coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It found more severe than SARS

and MERS, in fact after recognizing its global severity, WHO declared it pandemic (Yi et al., 2020). The symptoms of COVID-19 may appear 7-14 days after exposure; and are similar to SARS that includes fever, cough, and shortness of the breath. Symptoms like muscle pain, diarrhea, sore throat, loss of smell, sputum production, and abdominal pain were observed as secondary symptoms. While the majority of cases result in mild symptoms, progress to pneumonia and multi-organ failure (Yi et al., 2020; Davis et al., 2023). SARS-CoV-2 mainly invades alveolar epithelial cells, resulting in respiratory symptoms (Li et al., 2020). These symptoms are more severe in patients with cardiovascular disease (CVD), which might be associated with increased secretion of ACE2 (angiotensin-converting enzyme 2) in these patients compared with healthy individuals (Guo et al., 2020; Zheng, et al., 2020). It has been reported that, like in case of the previous coronavirus, ACE2 is the main protein which is utilized as a gateway by COVID-19 to invade the host cells (Zhang et al., 2020; Oudit et al., 2023). COVID-19 origin and evolutionary related studies also suggest that COVID-19 is a naturally emerged virus from an animal, i.e., bat. Earlier research concluded that wildlife contains many coronaviruses with the capacity to jump species boundaries and adapt to new hosts. It is presumed that due to consumption of the animal's meat, in near future human may have to face more coronavirus attacks (Lam et al., 2020; Zhang et al., 2020). On the basis of the known coronavirus spike protein structure it can be hypothesized that ACE2 will be used as a potential gateway by not all but most of the coronavirus to enter in human cells (Hoffmann et al., 2020). As we knew that ACE2 is one of the very important proteins which are involved in various human pathophysiology, alteration in ACE2 expression will have a diverse set of situations, few of them will be lethal for the humans. In such circumstances, it is very imperative to understand the ACE2 and related process, which can help us to look at the possible solution or alternative therapy to face SARS-CoV-2 and its relatives in the near future (Pringle and Philp, 2023). This article provides literature and database mining based compressive insights of the ACE2 and related biological process, its role in SARS-CoV-2 and after infection consequences on human physiology.

2 ACE-2 (Angiotensin Converting Enzyme 2)

ACE2, homolog of ACE, is a type 1 transmembrane protein (N-terminus outside, C-terminus intracellular) which is made up of 805 amino acids (NP_001358344). It is mono-carboxypeptidase in nature, removing single amino acid from C-terminus of the substrate and known to metabolize several peptides (Donoghue et al., 2000). ACE2 predominantly localized on endothelial cells with ectoenzyme features, where its catalytic site (enzymatically active domain) is exposed on the surface of the cell to circulating vasoactive peptides (Warner et al., 2005). At this extracellular side of the cell, this catalytic transmembrane domain cleaved and released into the blood by another membrane bound protease (sheddase) ADAM17 (Mukerjee et al., 2019). The activity of ACE2, whenever required, can be modulated by reducing its expression level as well as by shedding/cleavage of catalytically active ectodomain (Clarke and Turner, 2012). ACE2 is well studied for its wide distribution and organ-specific gene expression; it shows presence on the outer surface of the cells in the lungs, arteries, heart, brain, kidney, liver and intestines (Oudit et al., 2009; Clarke and Turner, 2012).

ACE2 is a member of RAS, its comparative modelling studies revealed that despite homology with ACE, ACE2 active sites vary from ACE, and thus their catalytic activities differ, i.e., ACE is a carboxypeptidase (Towler et al., 2004). After SARS-CoV disease in 2003, the sequence and structure of ACE2 has been analyzed and further explored for various purposes. Structured based molecular interaction studies between ACE2 and SARS-S (spike protein of SARS-CoV) provided various crucial positions of ACE2 which plays an essential role for the interaction with the spike protein (Li et al., 2005), and cleavage by ADAM17, TMPRSS11D and TMPRSS2 during the infection process (Table 1).

Table 1 Positions of interest (ACE2), with their description.

S. No.	Position(s)	Description	Length (Residue)
1	30 – 41	Interaction with SARS-CoV spike glycoprotein	12
2	82 – 84	Interaction with SARS-CoV spike glycoprotein	3
3	353 – 357	Interaction with SARS-CoV spike glycoprotein	5
4	652 – 659	Essential for cleavage of ACE2 by ADAM17	8
5	697 – 716	Essential for cleavage of ACE2 by TMPRSS11D and TMPRSS2	20

Source: https://www.uniprot.org/uniprot/Q9BYF1.

3 Infection Process and Role of ACE2 As Entry Point

On the basis of the previous studies and knowledge regarding coronavirus (i.e., HCoV-NL63 and SARS-CoV) infection process (Li et al., 2003), supported by SARS-CoV-2 related experiments and comparative bioinformatics analysis, it is hypothesized that the primary receptor for SARS-CoV-2 in human is angiotensin-converting enzyme 2 (ACE2) (Hoffmann et al., 2020; Zhang et al., 2020). Protein modelling experiments on the spike protein of the virus suggested that like other known SARS virus, SARS-CoV-2 has sufficient affinity to interact and bind with ACE2 receptors of human cells to use them as a mechanism of cell entry (Rabi et al., 2020; Zhang et al., 2020; Gusev et al., 2022). Spike protein sequence comparison revealed ~76% amino acid identity between SARS-S und SARS-2-S protein, and comparison of the receptor-binding motif (RBM, a portion of RBD that make contact with ACE2) of both spike revealed that most amino acid residues essential for ACE2 binding by SARS-S are conserved in SARS-2-S (Lin et al., 2008; Hoffmann et al., 2020; Lan et al., 2020). Recently, through experiments, it has been reported that SARS-CoV-2 has a higher affinity to human ACE2 than the original SARS-CoV strain (Zhang et al., 2020). It has also been reported that, after binding with ACE2, like in case of SARS-CoV, entry of SARS-CoV-2 also get enhanced through priming/proteolysis of spike protein (Shulla et al., 2011). This priming is carried out by transmembrane protease/serine subfamily member 2 (TMPRSS2), a known human protease that co-localized with ACE2 on the cell membrane (Rabi et al., 2020; Hoffmann et al., 2020). Though, very less is reported about it but it is suggested that along with ACE2 and TMPRSS2 SARS-CoV-2 may also use basigin (BSG, CD147), an immunoglobulin superfamily protein, as an inducer to gain entry in the host cell (Jackson et al., 2022).

Now, after exhaustive scientific efforts, infection cycle of SARS-CoV-19 is quite explained and found similar with SARS-CoV. It begins with the interaction between SARS-CoV-2 and target cells ACE2 receptor that is followed by priming of spike protein by transmembrane serine protease 2 (TMPRSS2), which is reported to be essential for entry of SARS-CoV-2. The cell's protease TMPRSS2 cuts open the spike protein of the virus and exposed fusion peptide which help virus to fuse with the host cell. The virion then releases RNA into the host cell, forcing the cell to produce multiple copies of the virus that are disseminated to infect more cells. SARS-CoV-2 produces at least three virulence factors that promote shedding of new virions from host cells and inhibit the immune response. In parallel, binding of the spike protein to ACE2 induces ADAM17, which is responsible for the proteolytic release of several cell-surface proteins (Rabi et al., 2020), thereby activity of ADAM17 reducing the amount of ACE2 expressed on the cell surface.

4 Effect of Natural Variants and Isoform's on The Binding Affinity between ACE2 and Spike Protein

Nonsynonymous SNPs and isoforms (produced through alternative splicing) play a very important role in function or activity of the protein. On the basis of their position, they can enhance, reduce or block the activity of proteins (Katara, 2014; Bakhshandeh et al., 2021). With the aim to observe the effects of these natural variants, we survey the available information resources. Annotation available at uniprot suggested two natural variants for ACE2 that are located at 26 (K → R, dbSNP: rs4646116) and 638 (N → S, dbSNP: rs183135788) position of the protein. Uniprot also reported two isoforms for ACE2 that are i) Q9BYF1-1 (Length: 805; Mass: 92,463 Dalton) and ii) Q9BYF1-2 (556-805: Missing; Length: 555; Mass: 63,912 Dalton (Clark et al., 2003). The reported positions of variants (SNPs and isoforms) indicate that their presence does not affect the binding of spike protein. Cao et al. (2020) also performed the comparative study using, East-Asian (EAS) population-specific (database: ChinaMAP, 1KGP) 62 SNPs found in the coding region of the ACE2 and observed that none of these variants is fall in the interaction site. Thus, it is clear that all individuals with these reported variants are also at the same risk of COVID-19. Here, second isoform, i.e., Q9BYF1-2 will be of quite interest because it misses the portion (556 to 805) where cleavage site of ADAM17, TMPRSS11D and TMPRSS2 are lying.

5 Biological Role of ACE2

Since its discovery, ACE2 was observed for its different functions in human physiology. Its wide presence, location and activities make it a protein of importance. Now it is known for its role from vasopeptidase to coronavirus receptor (Kuba et al., 2010; Turner et al., 2004). Few of such key roles are mentioning here.

5.1 Renin-angiotensin system (RAS)

The renin-angiotensin system (RAS) is a central regulator of cardiovascular and renal functions and plays a key role in the pathophysiology of various diseases. The classical RAS consists of a series of enzymatic reactions begins from angiotensinogen (AGT; 485 amino acids) and concluding in the generation of ACE mediated vasoconstrictor peptide angiotensin II (Ang-II; 'Asp-Arg-Val-Tyr-Ile-His-Pro-Phe') in plasma as well as in various tissues including the heart, kidneys, lungs, brain (Fyhrquist and Saijonmaa, 2008; Ren et al., 2019). This angiotensin II is reported to play a very crucial role in various RAS related human pathophysiology mainly belongs to cardiovascular and renal diseases, i.e., hypertension, heart failure, blood pressure, peripheral vascular disease (Ferrario et al., 1989; Kurdi et al., 2005).

ACE2 is reported as crucial component that provides new dimensions to classical RAS, where it act as key carboxypeptidase enzyme and catalyzes the cleavage of angiotensin I (Ang-I; 'Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu') into different angiotensin peptides, i.e., angiotensin 1–9 ('Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His') and angiotensin 1–7 ('Asp-Arg-Val-Tyr-Ile-His-Pro'; a vasodilator), that are further recognized by MAS1 receptor (Santos et al., 2003). MAS1 is a G-protein coupled receptor, after binding with Ang 1-7 it activates the 'phospholipase C signaling pathway' and leads to a number of effects that are opposite to activation of the Ang-II type 1 receptor (AT1R) by Ang-II. It has been well observed that ACE2 counteracts the effect of ACE by cleaving Ang-II and affect the ACE mediated RAS-dependent pathophysiology (Fig. 1), due to its counteract role ACE2 is also considered as RAS regulator. Connection of ACE2 with coronavirus pathogenesis made RAS as a pathway of pathophysiology importance that triggered scientific community to explore the connection of RAS with human physiology and coronavirus pathogenesis at deep (Wevers and van der Hoek, 2010).

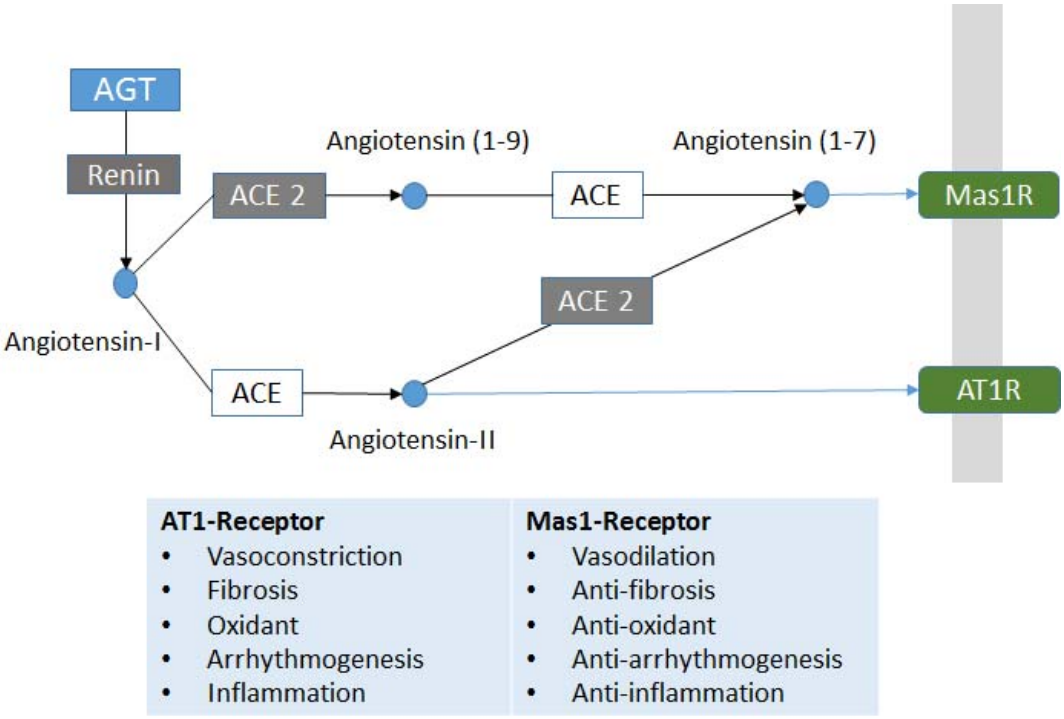

Fig. 1 Role of ACE2 in RAS pathway; angiotensin (1-7) activates MAS1 receptor and Angiotensin-II activate AT1 and AT2-receptor.

5.2 ACE2 as amino acid transporter

Along with above-mentioned pathophysiological functions, ACE2 also reported to play other important roles. One of them is its regulatory role in SLC mediated amino acid transportation; hartnup transporter (Kuba et al., 2010). SLC6A19, member of Solute carrier (SLC) transporters family, act as the major luminal sodium-dependent neutral amino acid transporter (Hartnup transporter) of the small intestine and proximal tubule (Yahyaoui and Pérez-Frías, 2019). It is reported that expression of SLC6A19 is depends on its association with ACE2, in fact interaction between these two is necessary for function of hartnup transporter. In case of failure of hartnup transporter, intestine/kidney cannot able to absorb/reabsorb the neutral amino acids thus cause their deficiency. Deficiency of these neutral amino acids, mainly of tryptophan results in hartnup disease (Camargo et al., 2009; Imai et al., 2010).

5.3 ACE2 as potential drug target/therapeutic modulator

Realizing the role of ACE2 in various pathophysiology, and it's counteract against ACE in RAS has added a new dimension to the classical RAS and related process. As a result there has been huge interest in ACE2 over the past decade as a potential modulator for various pathophysiology, i.e. heart (Haga et al., 2010), kidney (Koitka et al., 2008), lung (Imai et al., 2005; Imai et al., 2008), liver (Tikellis et al., 2011). Available ACE2 related literature is dominated by cardiovascular pathophysiology where it mainly elucidated as therapeutic modulator for lowering blood pressure and hypertension (Clarke and Turner, 2012), as well as essential regulator of cardiovascular function that make it a promising drug target for treating cardiovascular diseases (Chamsi-Pasha et al., 2014).

5.4 Associated risk of using ACE2/ACE targeted drug in SARS infection

As ACE2 serves as the main entry point into cells for some coronaviruses, including HCoV-NL63, SARS-CoV, and SARS-CoV-2, this might lead to believe that decreasing the expression of ACE2, will help in fighting the

infection (Hoffmann et al., 2020). In this regards various studies have been performed earlier, which suggested that expression of ACE and ACE2 are correlated, studies belong to ACE Inhibitors (ACEIs) shown that most of the inhibitors, along with their main pharmacological effects, display ability to upregulate ACE2 expression to inhibit ACE or AT1 receptor (Ferrario et al., 2005). Considering the correlation between the enhanced levels of ACE2 and susceptibility to SARS-CoV-2, some cardiologists suggest discontinuation of ACEIs in cardiac patients to avoid any potential increased risk of SARS-CoV-2 infection (Lia et al., 2020; Davis et al., 2023). In contrary, some studies reported a significant increase in serum level of Ang-II in COVID- 19 patients and exhibits a linear positive correlation between the viral load and lung injury (Liu et al., 2019), such high level of Ang-II can cause endothelial dysfunction and multiple organ (heart, kidney, and lung) injuries. In such circumstances, the intake of ACEIs might be therapeutically beneficial. In such wide possibilities, it is not an easy task for the cardiologists to assess the associated risk and take a straightforward recommendation regarding the use of ACE2/ACE targeted drug especially in CVD patients (Sommerstein et al., 2020).

6 Effect of CORONA (SARS-CoV/SARS-CoV-2) Infection on ACE2 and After Circumstances

Coronavirus infection down-regulates cellular expression of ACE2 through the different process (Oudit et al., 2009). Binding of the spike protein, induced ADAM17-dependent shedding of ACE2 N-terminal domain. This shedding has been reported to be essential for viral replication (Haga et al., 2010), and also stimulates uptake of virus into the cells (Haga et al., 2010; Rabi et al., 2020). Reduction in the ACE2 number on infected cells indirectly also helps virus to differentiate between infected and uninfected cells. Overall, down-regulation of ACE2 expression after coronavirus infection resulted in various pathological processes mainly belongs to severe lung injury and cardiac damage and dysfunction (Kuba et al., 2005; Wevers and van der Hoek, 2010).

7 ACE2 Enrichment Observation/Analysis

Bioinformatics can consider one of the potential tools particularly to get more about the functional genomics and proteomics systemically (Katara, 2014). To check the additional information about the involvement and importance of ACE2, protein-protein interaction network (PPIN) was observed. As presented in PPIN (9606.ENSP00000389326, Fig. 2), explored through STRING database (Szklarczyk et al., 2019), ACE2 shows strong interaction with various proteins, mainly includes DPP4, MME, AGT along with MEP1A, MEP1B, PRCP and XPNPEP2.

Detail analysis of PPIN centrality indicates ACE2 as a central node of this network which shows the connection with all 10 proteins. The network also indicates the presence of five-member clique which involves ACE2, MME (important in the destruction of opioid peptides that bind to opioid receptors in the brain, Wisner et al., 2006); able to cleave Ang-I, Ang-II and angiotensin 1-9, Rice et al., 2004), MEP1B (membrane metallopeptidase that sheds many membrane-bound proteins), XPNPEP2 (membrane-bound metalloprotease), MEP1A (hydrolysis of protein and peptide substrates), and DPPA (transmembrane transporter) with at least 3 edge (STRING-evidence) with each other. ACE2 also involved in another, three-member, clique which includes AGT (essential component of RAS, a potent regulator of blood pressure, body fluid and electrolyte homeostasis) and MME. Here it is very interesting that receptor of MERS, i.e., DPP4 (Seys et al., 2018), is very close to ACE2 and shows significant correlation that supported by three STRING-evidence, i.e., curated database, text mining and co-expression studies (Szklarczyk et al., 2019).

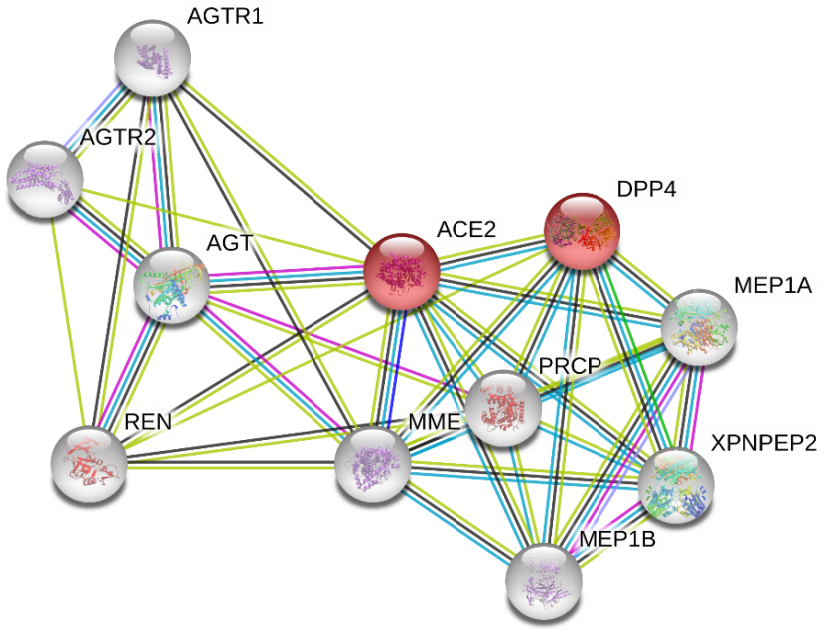

Fig. 2 PPIN network shows protein interaction of ACE2 with other proteins [Network features- Number of Nodes: 11; Number of edges: 37; Average node degree: 6.73; average local clustering coefficient: 0.844; expected number of edges: 11; PPI enrichment p-value: 1.29e-09].

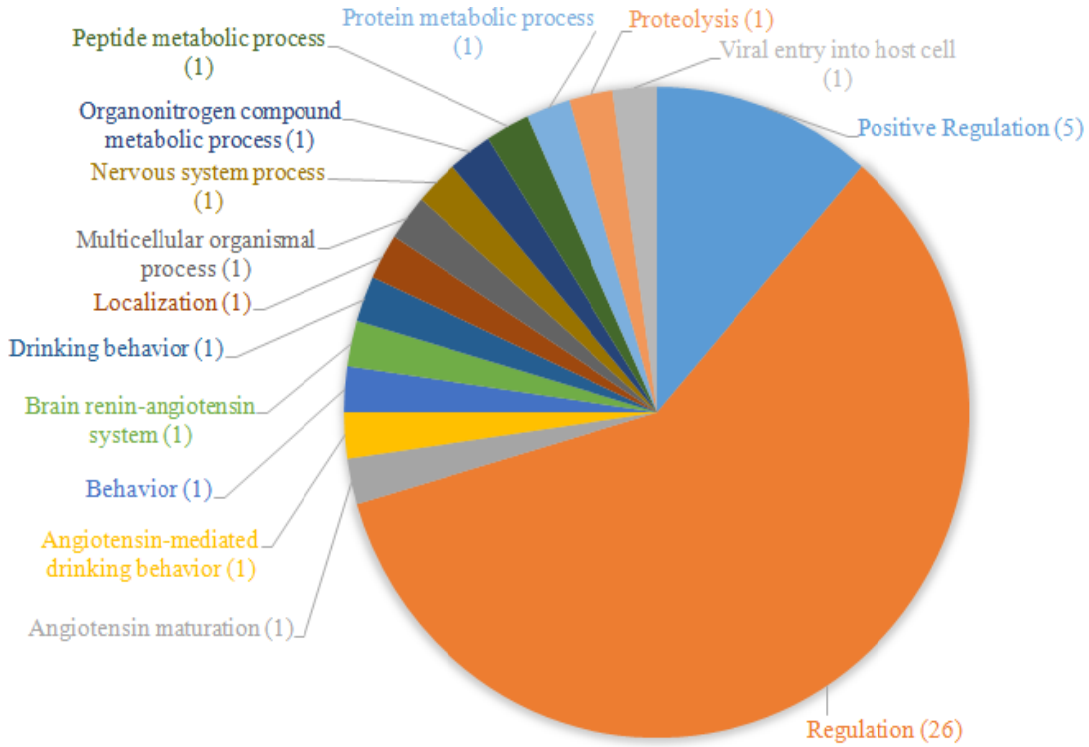

Fig. 3 Pie-chart showing the different biological process that includes the involvement of ACE2, here big share of the regulation process includes all kind of regulatory process in which ACE2 involves, and Positive regulation shows all kind of positive regulation process that involves ACE2.

Further protein enrichment for a biological process indicates that ACE2 involve in range of biological processes (Fig. 3). As shown in pie-chart most of these processes are regulatory in nature and as reported in the literature, mainly belongs to the lung and heart-related process, which are very sensitive in nature (Imai et al., 2008; Yang et al., 2023), e.g., regulation of systemic arterial blood pressure by circulatory renin-angiotensin, regulation of blood volume by renin-angiotensin, regulation of vasoconstriction, etc. As shown, ACE2 mainly involve in regulatory process, which make it enzyme of importance for human physiology. Apart from sensitive biological process, protein enrichment also shown its involvement in some secondary process as well, e.g., drinking behavior, localization.

8 Conclusion

Angiotensin-converting enzyme-2 is acted as a key player in RAS, where it converts angiotensin II into angiotensin 9/7, thus capable of modulating pathophysiology of various organs. Currently, it is in focus for its role as a receptor for SARS-CoV-2 which caused COVID-19 and responsible for millions of death globally. As discussed, ACE2 is a common receptor for both, SARS-CoV and SARS-CoV-2, and expected to be used as a receptor by more coronavirus. The review suggests that despite its central role in SARS it cannot be target against the coronavirus, the main reason behind that is its counter activity against ACE. Along with this, available literature and bioinformatics annotation believe that it also involves in various other biological processes as well. A lot of research has been done on ACE2 in last 20 years; still we are far from its systemic understanding. Its centric role in various biological processes of importance, including virus infection, force us to keep doing more research on it so that we can get some clues to control corona infections, as well as, its harmful patho-physiological effects in the near future.

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