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ACE2: At the crossroad of COVID-19 and lung cancer

Gunnar Gottschalk [a], Konstance Knox [b], Avik Roy [a,*]

[a] Technology Innovation Center, 10437 W Innovation Drive, Suite # 325, Wauwatosa, WI 53226, United States of America
[b] Coppe Laboratories, W229N1870 Westwood Dr, Waukesha, WI 53186, United States of America

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ABSTRACT

Upregulation of Angiotensin Converting Enzyme-2 (ACE2) was frequently observed in patients with lung cancer. Interestingly, our recent study revealed that the same ACE2 receptor was also strongly upregulated in lungs during SARS-CoV2 infection. Therefore, it is possible that the upregulated expression of ACE2 in lung tumors might increase the susceptibility to COVID-19 infection in lung cancer patients. However, the molecular mechanism for the regulation of ACE2 is known neither in lung tumors nor in COVID-19. Under this review, we attempt to identify transcription factors (TFs) in the promoter of ACE2 that promote the expression of ACE2 both in COVID-19 infection and lung cancer. This review would decipher the molecular role of ACE2 in the upscaled fatality of lung cancer patients suffering from COVID-19.

1. Physiological role of ACE2 in fluid balance, salt re-absorption, blood pressure maintenance and vasodilation

ACE2 is an important enzyme in renin-angiotensin system (RAS) of angiotensin metabolism (Burrell et al., 2004a). RAS is widely known endocrine pathway that regulates electrolyte balance, body fluid volume and cardiovascular control in peripheral circulation (Fountain and Lappin, 2020). RAS initiates with the reduction of renal blood flow and drop in fluid volume that directly stimulates the release of renin from kidney cortex (Handa and Johns, 1985) that in turn converts angiotensin precursor protein angiotensinogen to angiotensin-I (Reid and Moffat, 1978). Angiotensin converting enzyme (ACE), located at lungs, then enzymically transforms angiotensin-I to angiotensin-II (Erdos, 1976), which binds to the angiotensin1 subtype b (AT1b) receptor (Dabouras et al., 1973; Peach, 1977), triggers inward calcium current (Zhu et al., 1998), activates calcium-dependent CAM Kinase (CAMK) (Thomas et al., 1999), and phosphorylates Myosin light chain (MLC)(Anderson et al., 1981). Phosphorylation of MLC causes contraction of muscle that finally leads to the vasoconstriction (Zelis, 1983) resulting elevated blood pressure. In an indirect mechanism, angiotensin-1 also controls the reabsorption of minerals and water in kidney via synthesis of mineralocorticoid hormone in adrenal cortex (Brewster et al., 2003). Therefore, persistent activation of RAS pathway, upregulation of ACE, and elevated circulating levels of angiotensin- II directly lead to the development of hypertension and increased reabsorption in kidney. However, this physiological mechanism of water and salt balance by RAS has gained much importance after the discovery of angiotensin converting enzyme-2 in 2000 (Donoghue et al., 2000). Since then, ACE2 has been characterized as a ubiquitously-expressed, membrane-bound receptor that counterbalances the physiological action of ACE via enzymic conversion of angiotensin-II to Ang (1–7)(Allred et al., 2000). As a result, ACE2 facilitates the vasodilative response to lower blood pressure and maintain the fluid balance.

2. Pathological evidences support the beneficial role of ACE2 in preventing metabolic disorders

Besides its physiological roles, upregulation of ACE2 is also associated with the amelioration of pathogenesis of many metabolic disorders including liver fibrosis(Warner et al., 2007; Schrom et al., 2017), chronic kidney disease(Soler et al., 2013), heart failure (Crackower et al., 2002; Patel et al., 2017), and diabetes (Tikellis et al., 2003). Lipidoid nanoparticle-mediated delivery (Schrom et al., 2017), adeno-associated viral delivery (Mak et al., 2015) and pharmacological stimulation of ACE2 in hepatic stellate cells (Huang et al., 2010) was observed to attenuate the inflammation, reduce oxidative stress, and improve the morphological impairments in fibrotic livers. Similarly, adenoviral upregulation of ACE2 was found to improve glomerular

Abbreviations: ACE2, Angiotensin Converting Enzyme 2; RAS, Renin Angiotensin System; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HSV, Herpes Simplex Virus; STAT, signal transducer and activator of transcription.

* Corresponding author at: Technology Innovation Center, 10437 W Innovation Drive, Suite # 325, Wauwatosa, WI 53226, United States of America.
E-mail address: aroy@sotira-scientific.com (A. Roy).

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filtration rate, lower systemic hypertension, and attenuate the expression of inflammatory genes (Lo et al., 2015) in mouse model of type-1 diabetes. Downregulation of ACE2 expression was also found to be correlated with kidney injury (Gupta et al., 2007; da Silveira et al., 2010; Velkoska et al., 2010) and inflammation in chronic kidney diseases such as glomerulopathy, diabetic nephropathy and hypertensive renal disease (Ye et al., 2006; Mizuiri et al., 2011; Burrell et al., 2012; Soler et al., 2013). Consequently, adenoviral overexpression of ACE2 gene through intravenous route was observed to completely reverse the glomerular injury in rat model of chronic kidney disease (Liu et al., 2011). Exogenous overexpression of recombinant ACE2 was found to be beneficial in preclinical model of heart failure in terms of improvement in endothelial dysfunction, suppression of tissue inflammation and myocardial fibrosis, correction of metabolic dysfunction, and reversal of pathological hypertrophy (Mori et al., 2014; Basu et al., 2017; Patel et al., 2017). These evidences collectively demonstrate how the activation of ACE2 directly improves the adverse pathological events in many metabolic disorders.

3. Upregulated expression of ACE2 is correlated with lung cancer

However, apart from all these beneficial roles, the expression of ACE2 was also found to be strongly upregulated in lung cancer tissue (Zhang et al., 2020). Upregulation of different epigenetic factors such as

Table 1
Promoter analysis of ACE-2. Human Promoter sequence of ACE2 was derived from NCBI reference sequence ID: NG_068141. Promoter analysis was performed in MatInspector application of Genomatix gene analysis tool. Promoter length is 1947 base pairs (bp). Start and end numbers were calculated considering the start bp of open reading frame as 0. Core bases of the sequence were shown in block letters and possible biological functions were listed in the last column.

Transcription factor	Start	End	Match factor	ResponseElement	Function
BCL6	−1946	−1930	0.969	ggtTTCCtggaatgtgg	Tumorigenic
STAT3	−1947	−1930	0.968	aggtTTCCtggaatgtggg	Tumorigenic
WT-1	−1938	−1919	0.967	gaatgtgGGAGgagctttt	Tumorigenic
SMARCA-3	−1852	−1842	0.986	tattACTTata	Lung cancer and tumorigenesis
GKLF	−1824	−1806	0.965	ttttttaAAAGgagagtat	Tumor suppressor (colorectal cancer)
MEIS-1	−1752	−1736	0.969	actaaatcTGTCatctt	Myeloid Leukemia, viral integration
MIZ-1	−1724	−1710	1	aaggcCCTCtg	Esophageal cancer
CDPCR3HD	−1634	−1612	0.957	aatacataGATCcatgttctgat	Cancer (?)
YY1	−1627	−1607	0.973	atagatCCATgttctgattccat	Lung oncogene and tumorigenesis
AARE	−1613	−1605	0.975	aTTCCatca	Pulmonary obstruction and Lung cancer
CPHX	−1617	−1605	0.977	tcTGATtccatcatttgttagct	Development of Ovary
NKX2.5	−1600	−1582	0.984	ttagcTGAGtgagatatag	Thyroid organogenesis and cancer
NKX2.5	−1563	−1546	0.951	tttcaTAATtcataaaatg	Thyroid organogenesis and cancer
SOX6	−1494	−1472	0.986	ataacACAAagcactttgaatag	Neurodevelopment and chondrogenesis
SMARCA-3	−1473	−1462	0.986	agttACTTata	Chromatin remodeling and anti-depression
DLX-3	−1473	−1455	0,959	agttacttaTAATtgtttt	Folliculogenesis
NOBOX	−1471	−1452	0.978	ttacttaTAATtgtttttt	Folliculogenesis
S8	−1469	−1450	0.995	acttaTAATtgttttttcct	Folliculogenesis
NFAT	−1422	−1404	0.954	gaataaGGAAaagcagtgg	T cell proliferatio and inflammation
GKLF	−1400	−1382	0.97	ttttttAAAGgcttgatt	Apoptotic
LHX6	−1395	−1373	0.975	ttaaaggctTGATtattgcaatg	Neuro and lymphoid development
AREB6	−1375	−1363	0.978	atgtCACCtgaac	Lung cancer and tumorigenesis
ZNF35	−1382	−1352	0.97	tattgcaatgtcacctgaacctggAAGActt	Tumor suppressor
CEBPB	−1344	−1329	0.952	tgggtgaaGAAAtat	Macrophage function and inflammation
SMARCA3	−1279	−1269	0.985	tgCCATttaaa	Chromatin remodeling and anti-depression
NKX3.1	−1276	−1258	0.955	catttaaAGTGctcctctc	Prostate development and tumor suppressor
EVI1	−1195	−1179	1	ttgacaAGATaaccact	Viral integration and myeloid leukemia
GATA1	−1192	−1180	0.957	acaaGATAaccac	Erythroid development
CHR	−1173	−1161	0.967	ctctTTGAattct	RNA polymerase activation
RFX4	−1126	−1108	0.958	gagttgacataGATActct	Spermatogenesis
SMARCA3	−1097	−1087	0.975	taCCATgtgga	Chromatin remodeling and anti-depression
ARNT	−1078	−1062	0.95	tacttccaCGTGacctt	Toxin metabolism and hepatocellular carcinoma
MNT	−1077	−1061	0.992	acttcCACGtgaccttg	Transcriptional repressor of cell growth
DEC2	−1076	−1062	0.978	cttccaCGTGacctt	Regulation of sleep and circadian rhythm
CARF	−1033	−1022	0.97	agaagGAGGca	Neuroprotection
ERG	−983	−962	0.96	gagaaataGGAAatgagcttt	Prostate tumor (fused with TMPRSS)
CRX	−853	−837	0.963	gcctgtaATCCtagcac	Photoreception and melatonin secretion
ESRRB	−821	−799	0.978	tgggcagatcacaAGGTcaggag	Neuroprotection, Stem cell pluripotency
SF1	−814	−799	0.996	atcaCAAGgtcagga	Reproductive organ development
GATA1	−803	−791	0.961	aggaGATAgagac	Blood cell maturation
GKLF	−739	−721	0.988	agctgggcGTGGtggtggg	Tumor Suppressor and cell reprogramming
AREB6	−724	−712	0.968	tgggCACCtgtag	Lung cancer and tumorigenesis
ZNF750	−500	−486	1	cgggaGGCTgaggca	Squamous epithelial cell development
IKZF3	−521	−509	0.995	ggaagGGAAaatg	Lymphocyte development and differentiation
STAT3	−495	−477	0.98	gagtttctgGGAAtatgat	Viral infection and tumor development
IK2	−491	−479	0.986	ttctGGGAatatg	Embryonic development
SALL-1	−472	−460	0.977	aaATAAaaataaa	Embryonic development of kidney and heart
GATA-4	−458	−446	0.965	gtgaGATAaccta	Cardiac development
LMX1A	−453	−431	0.969	ataacctaTTAAtgaaattgtct	Insulin secretion
RU49	−310	−304	1	aAGTAcc	Cerebellar development
GRHL	−309	−297	0.973	agtaccGGTTttg	Embryonic development
STAT3	−335	−316		agctTTCTaggaaaatatt	Tumor formation and viral infection
PDEF	−188	−168	0.958	cctctccaGGATgaactttat	Prostate-derived tumor suppressor
NRL	−169	−145	1	atattggctcAGCAgattgtttact	Rod photoreceptor development
TCF7L2	−95	−79	0.973	ccaagttcAAAGgctga	HIV or HIV/HCV-coinfection and diabetes
GKLF or KLF4	−94	−76	0.98	caagttcAAAGgctgataa	Tumor Suppressor and cell reprogramming
GATA	−84	−72	0.995	ggctGATAagaga	Growth, development and tumorigenesis

HAT-1, HDAC-2 and KDM5B are reported to trigger the transcription of ACE2 in patients with lung disease (Pinto et al., 2020). Although the signaling pathway behind the upregulated expression of ACE2 is not known yet, literatures (Burrell et al., 2004b; Uhal et al., 2012) suggest that the upregulation of ACE2 might contribute to an anti-tumorigenic response that catalyzes the synthesis of growth suppressive Ang1–7 peptide, which in turn slows down the tumor growth via *mas* receptor activation (Murphy et al., 2019) and subsequent inhibition of tumor-promoting MAP kinases (Lee et al., 2005). Therefore, the induced expression of ACE2 might be a compensatory mechanism to suppress the growth and progression of lung tumor. In lung cancer tissue, ACE2 expression was also tightly regulated with the strong attenuation of RAS pathway as supported by the significant reduction of ACE activity (Danilov et al., 2019). Combining all these evidences, upregulation of ACE2 is critical in the development of lung cancer pathogenesis, however, the mechanism involved in the expression of ACE2 is still unknown.

The most reliable strategy to understand the genetic regulation of ACE2 is to search its promoter for the transcription factor (TF) binding sites. Accordingly, MatInspector, a Genomatix software tool and a popular web-based program for predicting potential TF binding sites, was used to identify TFs in the ACE2 promoter. ACE2 promoter is located at chromosome X with 1947 nucleotide long sequence, which was extracted from PubMed (NCBI reference sequence ID: NG_068141), formatted in a FASTA format, loaded in the search box of MatInspector, and finally run through the search program. The possible TFs were summarized in a table (Table 1) with start and end position, core matching factors, and reported biological functions. TFs with core-match factor less than 0.95 were excluded from our study and those with more than 0.95 were selected as most suitable TFs. Since TFs were identified based on a predictive algorithms, to increase the confidence high cut-off value (0.95) was applied. Our analysis was further validated with TFs binding only to positive strand of ACE2 promoter. Total 51 TFs were identified on the promoter region of ACE2 (Table 1). Interestingly, many TFs with high-confidence binding sites (Match factor $>$ 0.95) at ACE2 promoter are tumor-promoting transcription factors such as B-cell lymphoma 6 (BCL6), Wilms' tumor protein (WT1), Signal transducer and activator of transcription 3 (STAT3), Yin Yang-1 (YY1), AREB6, ERG, GKLF (or KLF4) and GATA TFs (Kumar et al., 2012; Hashiguchi et al., 2017). All these transcription factors are well-established contributing factors in the pathogenesis of lung and other tumors. Upregulation of BCL6 (Cardenas et al., 2017) and STAT3 (Tong et al., 2017) in bronchiolar epithelia are frequently observed in Non-small cell lung carcinoma tissue (NSCLC) (Deb et al., 2017). Transcriptional activation of Zinc finger containing transcription factor AREB6 also promoted migration and invasion of NSCLC (Guo et al., 2017). Upregulation

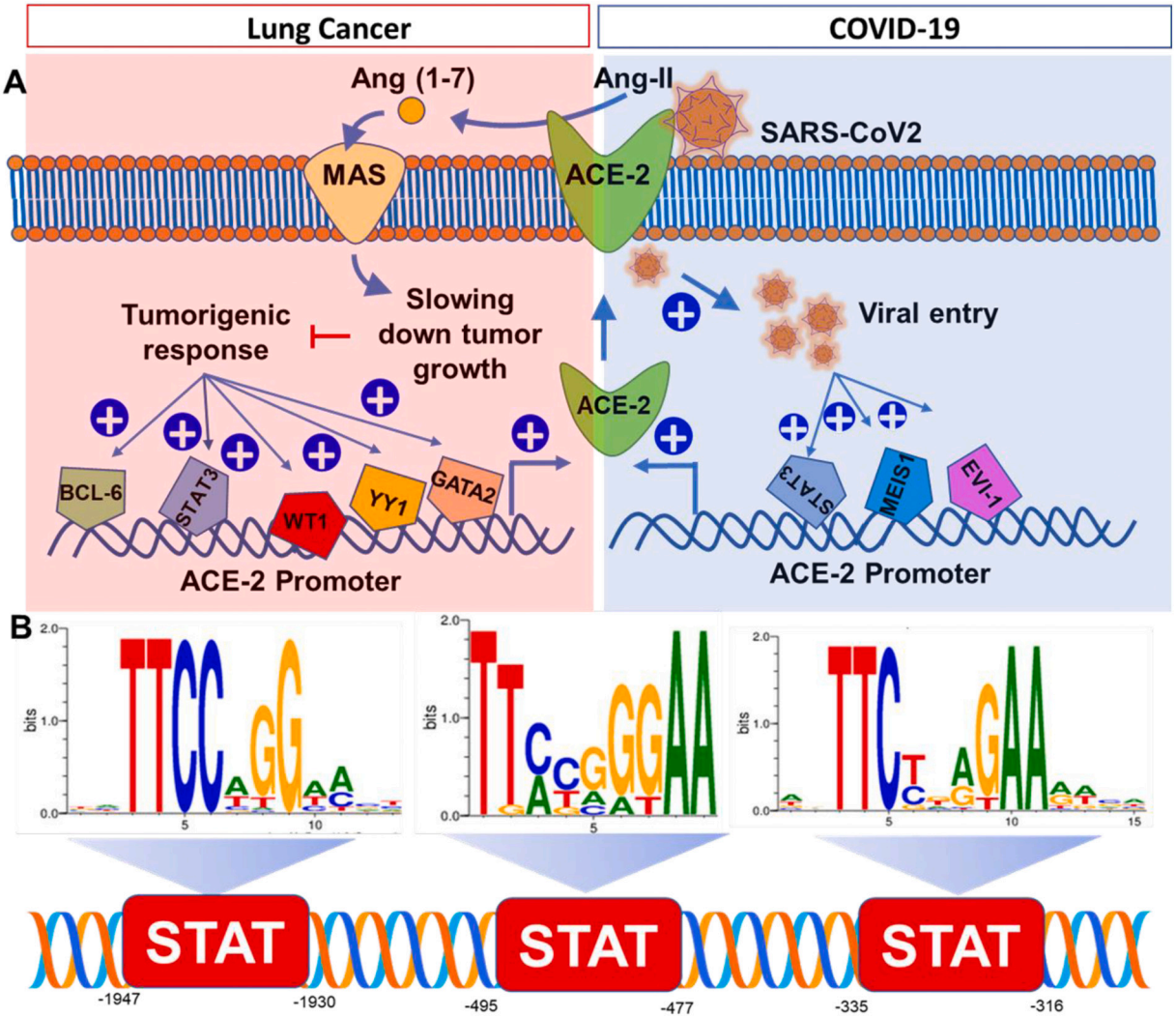

Fig. 1. ACE2 at the crossroad of lung cancer and COVID-19 infection. (A) Pathobiological roles of ACE2 during lung tumor progression (enclosed in red square) and COVID-19 (enclosed in blue square). (B) Promoter analysis of ACE2 for STAT3 binding. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of WT-1 was frequently detected in solid tumor tissue harvested from one of every 12 lung cancer patients (Menssen et al., 2000). Lung cancer patients with higher expression of YY1 had larger tumor size, poor differentiation, and higher rate of metastasis (Huang et al., 2017). Although, activation of ERG, an ETS gene family TF, contributes to the growth and spreading of prostate cancer (Sreenath et al., 2011), its activation was also noted in lung tumors (Scheble et al., 2010). Activation of GKLF or KLF-4 is frequently observed in stage III and IV lung tumors and considered as a potential prognostic biomarker in advanced lung cancer patients (Fadous-Khalife et al., 2016). GATA3 and GATA2 were reported to be a potential prognostic marker for lung adenocarcinoma (Hashiguchi et al., 2017) and NSCLC (Kumar et al., 2012) respectively. All these cancer-promoting transcription factors are highly expressed in lung tumors and could directly stimulate the transcription of ACE2 (Fig. 1A) during different stages of lung tumor progression.

4. SARS-COV2 stimulated the expression of ACE2 in lung and kidney tissue

Recently, our study highlighted (Gottschalk et al., 2020) that the intranasal inoculation of Wuhan-standard SARS-CoV2 strongly upregulated the expression of ACE2 in both lungs and kidneys of K18-hACE2 mice. K18-hACE2 mice express human ACE2 receptor in lungs, kidney, and other tissue. Hence, these mice display human-like clinical manifestations of COVID-19 pathologies in lungs and kidney upon intranasal administration of SARS-CoV2 virus. Twenty-four hours after the viral inoculation, we observed that these mice experienced severe loss of oxygen saturation, drop in heart rate, hypothermia, and acute death response close to 30%. While investigating the mechanism, we observed strong upregulation of ACE2 in bronchiolar epithelium of lungs, glomerular epithelium, and renal tubular cells in kidney tissue of these animals. Moreover, that upregulation of ACE2 was positively correlated with the numbers of SARS-CoV2 virus particles entered within lung and kidney parenchyma suggesting that the stimulated expression of ACE2 was indeed involved in the entry of virus. Therefore, the cellular entry of SARS-CoV2 might operate through a feed-forward loop that stimulates the expression of ACE2 in order to facilitate the entry of more virus particles in pulmonary and renal epithelial cells. However, how the SARS-CoV2 infection triggers the expression of ACE2 is not known yet. While analyzing the promoter of ACE2, we detected multiple TFs that are known to be activated during viral infection. These include Myeloid ecotropic viral integration site 1 protein (MEIS1), ectopic viral integration transcription factor EVI1, cell cycle genes homology region protein CHR, STAT3, and Transcription factor 7-like 2 TCF7L2. All these nuclear factors are activated during the infection of positive-sense single-stranded RNA viruses. MEIS1 was originally discovered as a nuclear protein that was activated by the retroviral integration in the chromosome of myeloid leukemia tumor cells (Moskow et al., 1995). EVI1 is another TF that serves as common retroviral integration site in AKXD murine myeloid tumors (Metais and Dunbar, 2008). Constitutive activation of STAT3 exhibits a proviral function in several viral infections, including those of HBV, HCV, HSV-1, varicella zoster virus, human CMV and measles virus (Chang et al., 2018). Chronic hepatitis C, HIV, and HIV-HCV *co*-infection stimulates the polymorphism of TCF7L2 gene (Pineda-Tenor et al., 2015). Interestingly, promoter of ACE2 gene harbors high-confidence (>0.95) binding sites for all of these TFs indicating their potential involvement in the transcription of ACE2 gene upon infection of SARS-CoV2 (Fig. 1B).

5. Elevated expression of ACE2 was reported in lung cancer patients suffering from COVID-19

Patients with cancer are typically at higher risk of COVID-19 infection because of compromised host defenses and suppressed immunological responses due to strong side-effects of chemotherapeutic treatment (Ganatra et al., 2020). However, the molecular mechanism of upscaled COVID-19 infection in these patients was not known. One possible explanation might be the induced expression of ACE2 in these cancer patients promotes the viral infection. In fact, the expression of ACE2 was indeed found to be elevated in COVID-19 patients who has been suffering from chronic lung disease. Apart from cancer, Patients with pre-existing conditions such as diabetes, hypertensions and chronic obstructive lung disease also exhibited upregulated expression of ACE2 in lungs upon infection with SAR-CoV2 (Pinto et al., 2020).

Therefore, it is important to identify TFs, which might regulate the expression of ACE2 in COVID-19 patients with pre-existing condition of lung cancer. TFs that are possibly activated during retroviral infections such as STAT3, MEIS1, and EV-1 are also known to be involved in the pathogenesis of lung cancer. MEIS1 promotes the proliferation and migration of lung arterial cells suggesting its possible involvement in the chronic lung disease (Yao et al., 2020). STAT3 stimulates viral infection and infection-associated proliferation and migration of lung tumor cells (Lu et al., 2017). Transcriptional activation of EVI1 was reported to stimulate chromosomal rearrangements in solid lung tumor (Liang and Wang, 2020). Tumor microenvironment in lungs possibly induces the expressions of all these TFs that might promote the upregulation of ACE2 and subsequent infection of SARS-CoV2 virions through ACE2 receptors (Fig. 1).

6. Conclusion

In summary, we identified 7 TFs named as WT1, STAT3, YY1, AREB6, ERG, GKLF, and GATA2 as possible inducers of ACE2 transcription in Lung tumors, whereas 5 TFs including MEIS1, EVI1, CHR, STAT3, and TCF7L2 as potential stimulators of ACE2 during SARS-CoV2 infection. Combining all these predictions, MEIS1, EVI1, STAT3 are predicted TFs that serve as common TFs in stimulating the expression of ACE2 both in SARS-CoV2 infection and lung tumor pathogenesis. Among all these TFs, STAT-binding site was frequently observed in ACE2 promoter. Distal binding site is 1930 bp upstream (score = 0.968), proximal binding site is 495 bp upstream (score = 0.98) and the intermediate binding site is 335 bp upstream of start site (Fig. 1B). Therefore, based on our comprehensive promoter analysis of ACE-2, we conclude that STAT3-mediated upregulation of ACE2 might play critical roles both in lung tumor progression and COVID-19 infection. SARS-CoV2 infection might stimulate the binding of STAT3 in the promoter of ACE2 resulting the enhanced expression of ACE-2. That mechanism might turn on a feed-forward loop with upscaled entry of virus through ACE2 receptor. On the other hand, cancer pathologies in lung tissue also switches on the transcription of STAT3 leading to the upregulated expression of ACE2 in cancer cells.

Declaration of competing interest

Authors declare no conflict of interest.

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