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

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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 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)(Alreed 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
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 promote angiogenesis, suppress senescence, and protect cell from apoptosis through Nrf2 pathway (Zhang et al., 2020).

Table 1

| Transcription factor | Start | End | Match factor | Response Element | Function |
|----------------------|-------|-----|--------------|------------------|----------|
| BCL6                 | -1946 | -1930 | 0.969 | ggtTTCGggaGatgg | Tumorogenic |
| STAT3                | -1947 | -1930 | 0.967 | aggtTCCGggaGatgg | Tumorogenic |
| WT-1                 | -1938 | -1919 | 0.969 | gaagGGAGGagatggT | Tumorogenic |
| SMARCA-3             | -1852 | -1842 | 0.968 | tattGTTTTG | Lung cancer and tumorigenesis |
| GKLFL                | -1824 | -1806 | 0.965 | trmtAAAAGGagatggT | Tumor suppressor (colorectal cancer) |
| MEIS-1               | -1752 | -1736 | 0.969 | actaatGCTGatctt | Myeloid Leukemia, viral integration |
| MIZ-1                | -1724 | -1710 | 1     | aagggCCTTtg | Esophageal cancer |
| CPDX                 | -1634 | -1612 | 0.957 | aatactatGCTGacttctgat | Cancer (7) |
| YY1                  | -1627 | -1607 | 0.973 | atgactGTGTgtctgattctc | Lung oncogene and tumorigenesis |
| AARE                 | -1613 | -1605 | 0.975 | aTTCatctc | Pulmonary obstruction and Lung cancer |
| CPHX                 | -1617 | -1605 | 0.977 | tGGAACatcacttgattctgat | Development of Ovary |
| NXX2.5               | -1600 | -1582 | 0.984 | ttagTGATGagtattag | Thyroid organogenesis and cancer |
| NXX2.5               | -1563 | -1546 | 0.951 | tttaAAATcactaatag | Thyroid organogenesis and cancer |
| SOM6                 | -1494 | -1472 | 0.976 | atacacaAAGacttattctgat | Neurodevelopment and chondrogenesis |
| SMARCA-3             | -1173 | -1462 | 0.986 | agttaTCTGatctt | Chromatin remodeling and anti-depression |
| DLX-3                | -1473 | -1455 | 0.959 | ttgaagaTGTAatcttctgat | Foliculogenesis |
| NOBOX                | -1471 | -1452 | 0.978 | taactataATGTTTTttt | Foliculogenesis |
| S8                   | -1469 | -1450 | 0.995 | actataATGTTTTTTTct | Foliculogenesis |
| NFAT                 | -1422 | -1404 | 0.954 | gatataAAAGagatggT | T cell proliferati and inflammation |
| GKLFL                | -1400 | -1382 | 0.978 | trmtAAAAGGagatggT | Neuroprotection |
| LHX6                 | -1395 | -1373 | 0.975 | ttaagggTCTGatcttctgat | Neuro and lymphoid development |
| AREB6                | -1375 | -1363 | 0.978 | agtagCRCCGagac | Lung cancer and tumorigenesis |
| ZNF35                | -1382 | -1352 | 0.977 | tattcgactctactgaatctggTAAGAcct | Tumor suppressor |
| CEBPB                | -1344 | -1329 | 0.982 | ttgggatcAAAGAtat | Macrophage function and inflammation |
| SMARCA3              | -1279 | -1269 | 0.985 | ttcaAAATcactaatag | Chromatin remodeling and anti-depression |
| NXX3.1               | -1276 | -1258 | 0.955 | cattaaAGTTCTTcttc | Prostate development and tumor suppressor |
| EVI1                 | -1195 | -1179 | 1     | ttagcAAATcactaatag | Viral integration and myeloid leukemia |
| GATA1                | -1192 | -1180 | 0.978 | acaaAGAAcactaatag | Erythroid development |
| GHR                 | -1173 | -1167 | 0.967 | cttCTGAtctt | RNA polymerase activation |
| BFX4                 | -1126 | -1108 | 0.958 | agtagctctactaatag | Spermatogenesis |
| SMARCA3              | -1097 | -1087 | 0.975 | tttCAAGTtgaa | Chromatin remodeling and anti-depression |
| ARNT                | -1078 | -1062 | 0.95 | tactctaatGTTGctt | Toxin metabolism and hepatocellular carcinoma |
| MNT                 | -1077 | -1061 | 0.992 | actctACACGagctc | Transcriptional repressor of cell growth |
| DEC2                | -1076 | -1062 | 0.978 | ctctctaatGTTGctt | Regulation of sleep and circadian rhythm |
| CARF                | -1033 | -1022 | 0.977 | agtaagAGGaa | Neuroprotection |
| ERG                 | -983 | -962 | 0.96 | gagataatGAAGagatcttt | Prostate tumor (fused with TMIPRRS) |
| CRX                 | -853 | -837 | 0.963 | gcttgtaATCCTaagtc | Photoreception and melatonin secretion |
| ESRRB                | -821 | -799 | 0.978 | ttggcactctacaGGCTCaggag | Neuroprotection, Stem cell pluripotency |
| SFI                 | -814 | -799 | 0.966 | agtagCATagagc | Reproductive organ development |
| GATA1                | -803 | -791 | 0.961 | atctCTGAtctt | Blood cell maturation |
| GKLFL                | -739 | -721 | 0.988 | ctagcactctactaatag | Tumor Suppressor and cell reprogramming |
| AREG6                | -724 | -712 | 0.968 | tggcCACCCTtag | Lung cancer and tumorigenesis |
| ZNF750               | -500 | -486 | 1     | cggactGCTGagagca | Squamous epithelial cell development |
| IKZF5               | -521 | -509 | 0.995 | gagagGGAAatag | Lymphocyte development and differentiation |
| STAT3                | -495 | -487 | 0.986 | gtagctctactaatag | Viral infection and tumor development |
| I2K                 | -491 | -479 | 0.986 | ttagcGAGatctt | Embryonic development |
| SALL-1               | -472 | -460 | 0.977 | aataatATATTagatcacttct | Embryonic development of kidney and heart |
| GATA-4               | -458 | -446 | 0.965 | aataatATATTagatcacttct | Cardiac development |
| LMX1A                | -453 | -431 | 0.969 | atataatATATTagatcacttct | Insulin secretion |
| REX5                | -419 | -404 | 1     | aATGAc | Cerebellar development |
| GRIL                | -308 | -297 | 0.973 | agataccGGTTTtgtt | Embryonic development |
| STAT3                | -335 | -316 | 0.988 | agctctTCTTtgagatcacttct | Tumor formation and viral infection |
| PDEF                | -388 | -387 | 0.986 | cctcTctcGATGAtatcctt | Prostate-derived tumor suppressor |
| NGL                | -186 | -185 | 0.954 | atcttgctcAGPapgtcccttct | Rod photoreceptor development |
| TCFL7L             | -95 | -97 | 0.973 | cagagtcATAGagctgctt | HIV or HPV/HCV-co-infection and diabetes |
| GKLFL or KLF4        | -94 | -76 | 0.98 | cagatctatAGGagctgctt | Tumor Suppressor and cell reprogramming |
| GATA              | -84 | -72 | 0.995 | ggtGTAagagga | Growth, development and tumorigenesis |

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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...
patients suffering from COVID-19

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 chemotherapy 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, hypertension 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 (Yang et al., 2020). STAT3 stimulates viral infection and infection-associated proliferation and migration of lung tumor cells (Lu et al., 2017). Transcriptional activation of EV11 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, AREG, ERG, GKL1, and GATA2 as possible inducers of ACE2 transcription in lung tumors, whereas 5 TFs including MEIS1, EV11, CHR, STAT3, and TCF7L2 as potential stimulators of ACE2 during SARS-CoV2 infection. Combining all these predictions, MEIS1, EV11, 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 pathways 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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