Open Peer Review on Qeios

Role of Nicotine in RAS and Fibrosis Linked to Severe COVID-19 Manifestations

Ma Xiaoli[1], Jia Yanfei[1]

1 Shandong First Medical University (SDFMU)

Funding: This research was supported by grants from the Natural Science Foundation of Shandong Province (ZR2021MH322); National Natural Science Foundation of China (31970728).

Potential competing interests: The author(s) declared that no potential competing interests exist.

Abstract

Smoking is one of the most important risk factors for cardiovascular and pulmonary disease (CVPD). Novel coronavirus (SARS-CoV-2) has caused epidemic pneumonia, corona virus disease 2019 (COVID-19), in various parts of the world. Severe patients occurred severe clinical inflammatory storm, pulmonary fibrosis or even multiple organ failure. SARS-CoV-2 combined with angiotesin-converting enzyme 2 (ACE-2) can cause severe pneumonia, however the cause of multiple organ injury caused by SARS-CoV-2 is unknown. The potential cardiopulmonary risk of nicotine and its related products has been concerned. Nicotine alters the homeostasis of the rennin angiotensin system (RAS) by upregulating ACE/angiotensin (ANG)-II/ANG II type 1 receptor axis and downregulating the compensatory ACE2/ANG-(1–7)/Mas receptor axis, contributing to the development of CVPD. Moreover, nicotine involves in the process of cell fibrosis, such as the damage of epithelial/endothelial barrier, the recruitment of inflammatory cells, the production of reactive oxygen species (ROS), and so on. Therefore, nicotine may be one of the reasons for the multiple organ damage of COVID-19. To understand the role of nicotine in RAS and fibrosis is of great significance for the prevention and treatment of multiple organ injury caused by SARS-CoV-2.

Xiaoli Ma*[1], Ph.D., and Yanfei Jia[1], Ph.D.

[1]Research Center of Basic Medicine, Central Hospital Affiliated to Shandong First Medical University, Jinan, China 250013

**Corresponding author*

Email address: mxl7125@126.com

ORCID ID: 0000-0003-0279-8354

Keywords: Nicotine; SARS-CoV-2; RAS; Fibroblast; COVID-19

Background

Novel coronavirus (SARS-CoV-2) is a positive-sense single-strand RNA virus with membrane[1]. Its S protein binds with converting enzyme II (ACE2) and then enters epithelial cells in mucosa angiotens of human airway. The binding power of SARS-CoV-2 is 10-20 times higher than that of SARS CoV, so it is more infectious[2]. At present, most patients with SARS-CoV-2-induced epidemic pneumonia (Corona Virus Disease 2019, COVID-19) are characterized by fever, fatigue and dry cough. A few patients have symptoms such as nasal congestion, runny nose, sore throat and diarrhea. Severe patients often have dyspnea and/or hypoxemia after one or two weeks of onset. More severe patients will quickly progress to acute respiratory distress syndrome, septic shock, respiratory distress syndrome, respiratory distress syndrome and so on. Critically ill patients also appear kidney, heart and other multiple organ damage, and even functional failure[3][4]. In the study of pathological anatomy of the patient's remains, it is found that the development of severe patients can lead to pulmonary interstitial fibrosis with the progress of the disease[5]. By far, the cause of multiple organ failure caused by SARS-CoV-2 is not clear.

Smoking is one of the most important risk factors for cardiovascular and pulmonary disease (CVPD), and smokers are 2-4 times more likely to develop CVPD than nonsmokers[6][7]. Nicotine, an addictive component of tobacco, interacts with nicotinic acetylcholine receptor (nAChR) in endothelial cells, vascular epithelial cells and epithelial cells of various organs. Studies have shown that nicotine interacts with renin angiotensin system (RAS) through its receptor nAChR, and RAS is one of the most important autonomic, cardiovascular and pulmonary regulatory systems in health and disease[8]. Moreover, in many organs, nicotine regulates the function of fibroblasts and affects fibrosis[9][10][11]. Nicotine may be an inducement of multiple organ failure in critically ill patients with COVID-19.

1. Interaction between nicotine and RAS in multiple organs

1.1 Nicotine and the RAS in cardiovascular dysfunction

Inhalation of nicotine can lead to acute increase of systolic and diastolic blood pressure, accompanied by the increase of plasma angiotensin converting enzyme (ACE) activity, indicating that there is a correlation between nicotine and RAS[12]. Smoking and/or nicotine use increased the activity of plasma ACE, the conversion of angiotensin I (ANG I) to blood ANG II, and promoted vasorelaxation injury. Irbesartan, an angiotensin II type-1 receptor (AT1R) antagonist (also known as ANG receptor blocker), can reduce arterial stiffness in patients with hypertension. Compared with non-smokers, the response of smokers to bradykinin was impaired. After injection of ACE inhibitor enalapril, the response of smokers to bradykinin returned to the level of non-smokers[13].

In the heart, ANG Ⅱ activates AT1R, leading to myocardial fibrosis, cardiomyocyte hypertrophy and inflammation. AT2R, as the balance of AT1R, plays a role on anti-fibrosis, hypertrophy and anti-inflammatory[14][15]. The heart consists of different cell types, including cardiomyocytes, fibroblasts, endothelial cells and smooth muscle cells. Each cell has a different RAS expression profile. ACE was expressed in vascular endothelial cells, fibroblasts and cardiomyocytes, and ACE2 was mainly expressed in vascular endothelial cells. All cardiomyocytes express AT1R and AT2R, but AT2R is low expressed in healthy hearts. The primary effects of ANG II are mediated through interactions with AT1R under normal conditions[16][17].

Nicotinic acetylcholine receptor (nAChR) is widely expressed in the heart. Chronic smoking or nicotine exposure will aggravate heart induced hypertension[18][19]. At the molecular level, smoking decreased the expression of cardiac compensatory collagen, promoted the expression of matrix metalloproteinase (MMP)-9 and tissue inhibitor of matrix metalloproteinase-1, and blocked HIF-1α, VEGF and TGF-β compensatory increase via nAChR signaling[20]. Cigarette smoke extract or nicotine promotes fibroblast proliferation and collagen synthesis through α7-nAChR/MAPK pathway. Nicotine can aggravate ANG II induced cardiovascular remodeling, including increased heart rate, increased myocardial MMP-2 expression and aortic wall thickening[21]. Possible cardiotoxic interaction between nicotine and the RAS was also demonstrated in a mouse model of systemic hypertension[21][22]. Nicotine and ANGII were delivered through subcutaneous osmotic minipumps either individually or incombination. Nicotine was shown to exacerbate cardiovascular remodeling induced by ANGII, which included increased heart rate, increased myocardial MMP-2 expression, and increased thickening of the aortic wall.

1.2 Nicotine and the RAS in nervous system

nAChR is widely expressed in the central nervous system. Endogenous acetylcholine and exogenous nicotine act on the receptor to regulate brain activity and physiological function. Long term nicotine exposure increases blood-brain barrier permeability[23][24]. In the brain, nicotine promotes behavior dependence by regulating the release of glutamate and other neurotransmitters through nAChR. Nicotine also affects the activity of autonomic nervous region and promotes sympathetic stress response through hypothalamus pituitary adrenal axis[25].

Nicotine can affect the autonomic nucleus through the interaction with RAS in the brain[26][27]. Chronic smoking related adverse addiction and cardiovascular sequelae are partly regulated by nAChR-activated striatal dopaminergic and hypothalamic noradrenergic systems. AT1R is involved in nicotine induced release of dopamine and norepinephrine, and the activation of AT1R in striatum is counteracted by AT2R. In addition, the interaction between nicotine and brain RAS may be related to the sympathetic effect of nicotine and neurogenic hypertension mediated by AT1R. In hypothalamus and subfornical organ, nicotine interacts with brain RAS[28]. Intracerebroventricular injection of Ang Ⅱ and nicotine could increase the expression of c-fos in subfornical organs and significantly promote drinking behavior. Perinatal nicotine exposure changes brain RAS, resulting in increased sympathetic activity in adult offspring[29].

1.3 Nicotine and the RAS in the lung

A variety of lung cells express nAChR, including bronchial epithelial cells, type II alveolar epithelial cells, alveolar macrophages, pulmonary endothelial cells and interstitial fibroblasts[30][31]. These cells also express RAS components. Pulmonary microvascular endothelial cells express high level of ACE, which is helpful for the system to regulate blood pressure and body fluid balance. In lung, AT1R and AT2R are widely expressed. AT1R is located in vascular smooth muscle cells, macrophages and stromal fibroblasts under airway epithelium, while AT2R is expressed in bronchial epithelium. AT2R is also expressed in fibroblasts, macrophages and pulmonary endothelial cell subsets[32]. ACE2 and MAS receptor (MASR) are mainly expressed in bronchial epithelial cells[33]. In addition to pulmonary hypertension, pulmonary RAS is also involved in many pulmonary diseases unrelated to blood pressure and fluid balance, including pulmonary infection/inflammation, acute lung injury/acute respiratory distress syndrome and pulmonary fibrosis[34].

Nicotine can activate the expression and activity of ACE in lung tissue[35]. In patients with pulmonary hypertension (PAH), the expression of ACE in pulmonary artery/arteriole endothelium was significantly increased. In chronic cigarette smoke induced PAH, ang Ⅱ level increased with the increase of ACE expression and the decrease of ACE2 expression[36]. Losartan can reduce Ang II, restore ACE2 expression, improve pulmonary vascular remodeling and smoke induced right ventricular systolic blood pressure. Chronic cigarette smoke exposure down regulates the expression of ACE2 through ang Ⅱ and AT1R dependent extracellular signal regulated kinase (ERK)/p38 MAPK signaling pathway[37]. The relationship between smoking and RAS has been widely accepted.

2. Nicotine participates in the process of cell fibrogenesis

Fibrogenesis is a gradual process, including epithelial/endothelial barrier damage, release of transforming growth factor-β1 (TGF-β1), the recruitment of inflammatory cells, production of ROS, activation of collagen-producing cells, extracellular matrix-dependent activation of myofibroblast cells[38]. Numerous studies over the past decade have provided compelling evidence for the involvement of nicotine in the modulation of fibroblast activation and function[39][40]. Understanding the role and mechanism of nicotine in stimulating fibrosis will provide a basis for the clinical significance of nicotine replacement therapy.

2.1 Nicotine promotes damage to epithelial/endothelial barriers

Damage to epithelial cell and vascular endothelial cell barrier plays an important role in the activation of fibrosis. Chronic epithelial damage and/or apoptosis followed by tissue healing can lead to the release of inflammatory factors that trigger immune-cell infiltration and activation of local fibroblasts[41]. In vivo studies have shown that nicotine can directly affect the ion homeostasis of epithelial cells, and the change of Na^+ and Cl^+ balance can lead to epithelial cell damage and inflammatory reaction of cell damage[42]. In trachea and gastrointestinal tract, chronic exposure to nicotine stimulates the edema of lamina propria cells, increases the number of eosinophils, increases the expression of epithelial mesenchymal transition (EMT) molecules, and aggravates the damage to basal cells[43]. Nicotine also regulates the expression of nitric oxide synthase (NOS), ACE, tissue plasminogen activator (t-PA) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, and promotes plaque growth and angiogenesis in mice[44]. Nicotine regulated endothelial cell gene expression, which promoted plaque growth and angiogenesis in mice[45].Consistent with these findings, in vitro treatment of primary human coronary endothelial cells with nicotine for 24h increased expression of nitric oxidesynthase, ANG-I-converting enzyme, t-PA, and VCAM-1, which are factors known to promote the development of atherosclerotic plaques[46].

2.2 Nicotine mediates the production and release of TGF-β1

TGF-β1 is an important cytokine involved in wound healing and repair in many types of cells and tissues. TGF-β1 stimulates the production of ECM proteins and plays a key role in the regulation of fibrosis[47][48]. Various model of fibrosis, nicotine significantly up-regulated TGF-β1 and stimulates fibroblast functions in an autocrine fashion[49][50]. In the

model of atrial fibrosis, nicotine upregulated TGF-β1 and stimulated the proliferation and collagen deposition of atrial fibroblasts[51]. Moreover, nicotine induced expressions of connective tissue growth factor (CTGF) and TGF-β in fibroblasts through α7-nAChR-dependent activation in breast cancer[52].

2.3 Nicoitne recruits inflammatory cells

Recruitment of infiltrating inflammatory cells is a key event to fibrosis, and a pathogenic result of acute and chronic tissue injury[53]. Changes of inflammatory cells play an important role in a number of diseases associated with smoking. Therefore, it is relevant to discern the effects of nicotine on both the recruitment and activation of inflammatory cells and to identify inflammatory mediators/cytokines involved. In several systems, the effects of nicotine are controversial and appear concentrationdependent. A number of in vitro and in vivo studies have described nicotine's profound effects on neutrophils during emphysem[54]. Nicotine activated F-actin formation and intracellular Ca^{2+} release in neutrophils and was postulated to play a role in neutrophil migration and/or degranulation during pulmonary disease. In addition to neutrophils, other inflammatory cells types, such as macrophages, dendritic cells (DCs), and lymphocytes, respond to nicotine[55][56][57]. Further studies are needed to understand the role of nicotine in inflammatory cell-mediated fibrosis.

2.4 Nicotine causes accumulation of ROS

ROS are strong modulators of inflammatory processes in the central nervous system (CNS), development of atherosclerosis in vessels, stroke injury, renal epithelial damage, pulmonary cell damage, and critical factors in fibrogenesis[58][59]. Nicotine induces oxidative stress in a number of cell types, including epithelial cells, macrophages, fatty liver cells, and mesangial cells[60]. Nicotine is closely related to the increase of lipid peroxidation and the decrease of antioxidant activity of macrophages. Studies have shown that nicotine reduces the activity of scavenging enzymes, and induces ROS production in the liver[61]. The ability of nicotine to reduce antioxidant levels indicates its effect on lipid peroxidation. Nicotine alone or combined with ethanol decreased glutathione (GSH) activity in liver and lung, and nicotine and ethanol increased lipid peroxidation. Nicotine induced the increase of superoxide anion and hydrogen peroxide content, resulting in the decrease of antioxidant[62].

2.5 Nicotine activates collagen-producing cells

In the process of fibrosis, collagen synthesized by fibroblasts is an important component of extracellular matrix (ECM)[63]. In general, fibroblasts need stimulating factors such as TGF-β1 activating the secretion of collagen. Meantime, α-smooth muscle actin (α-SMA), vimentin and extracellular matrix proteins increased. Studies have shown that smoking increases collagen deposition and promotes myocardial fibrosis[64]. Nicotine induced collagen deposition through fibroblasts. The deposition of collagen in atrial myocardium was correlated with the concentration of nicotine and the history of excessive smoking.

3. Understanding the importance of nicotine in COVID-19

As a new type of pneumonia, the pathogenesis of COVID-19 is still unclear, and there is no clear and effective treatment.

Systematic understanding of the interaction between nicotine and RAS in multiple organs and the role of nicotine in the process of cell fibrosis has important guiding significance for the prevention and treatment of multiple organ failure caused by COVID-19. If the patient's multiple organ failure is closely related to nicotine, then banning smoking is one of the most effective measures for multiple organ failure. At the same time, we may also explain why some patients are prone to multiple organ failure, while others are not.

Conclusions

Nicotine can change RAS homeostasis by regulating ACE/ANG-II/ANG-II type 1 and ACE2/Ang-(1-7)/MAS receptor axis. Meantime, nicotine participates in the process of cell fibrosis, affects multiple organ fibrosis. To understand the role of nicotine in RAS and fibrosis may be of great significance for the prevention and treatment of multiple organ injury caused by SARS-CoV-2. For patients with a history of smoking, we may consider early intervention with nAChR inhibitors to avoid the development of multiple organ failure and reduce the mortality.

Abbreviations

SARS-CoV-2: Novel Coronavirus

COVID-19: Corona Virus Disease 2019 COVID-19

ACE-2: Angiotesin-converting Enzyme 2

CVPD: Cardiovascular and Pulmonary Disease

RAS: Rennin Angiotensin System

ANG: Angiotensin

ROS: Reactive Oxygen Species

nAChR: Nicotinic Acetylcholine Receptor

AT1R: Angiotensin II Type-1 Receptor

MMP: Matrix Metalloproteinase

PAH: Pulmonary Hypertension

TGF-β1: Transforming Growth Factor-β1

EMT: Epithelial Mesenchymal Transition

NOS: Nitric Oxide Synthase

t-PA: Tissue Plasminogen Activator

VCAM-1: Vascular Cell Adhesion Molecule-1

CTGF: Connective Tissue Growth Factor

DCs: Dendritic Cells

CNS: Central Nervous System

GSH: Ethanol Decreased Glutathione

ECM: Extracellular Matrix

α-SMA: α-smooth Muscle Actin

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This research was supported by grants from the Natural Science Foundation of Shandong Province (ZR2021MH322); National Natural Science Foundation of China (31970728).

Author Contributions

XM wrote and revised the paper. YJ contributed to the interpretation of data. All authors made the final editing of the review and approved the final manuscript.

Acknowledgments

The authors thank the funding agencies for support.

Authors' information

Central Hospital Affiliated to Shandong First Medical University, Jinan, China 250013

References

1. ^*C. Huang, Y. Wang, X. Li. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 395(10223):497–506. doi:10.1016/s0140-6736(20)30183-5*
2. ^*R. Li, S. Qiao, G. Zhang. (2020). Analysis of angiotensin-converting enzyme 2 (ACE2) from different species sheds some light on cross-species receptor usage of a novel coronavirus 2019-nCoV. J Infect. doi:10.1016/j.jinf.2020.02.013*
3. ^*D. Wang, B. Hu, C. Hu. (2020). Clin Charact 138 Hosp Patients 2019 Nov Coronavirus-Infected Pneumonia Wuhan.*
4. ^*H. Crook, S. Raza, J. Nowell, M. Young, P. Edison. (2021). Long covid-mechanisms, risk factors, and management*

[J. BMJ. 374:n1648.

5. ^*Roquetaillade C, Bredin S, Lascarrou JB. (2021). Timing and causes of death in severe COVID-19 patients. Crit Care. 25(1). doi:10.1186/s13054-021-03639-w*
6. ^*A. Jamal, E. Phillips, A. S. Gentzke. (2018). Current Cigarette Smoking Among Adults - United States, 2016 [J. MMWR Morb Mortal Wkly Rep. 67(2):53–59.*
7. ^*J. C. Smith, E. L. Sausville, V. Girish. (2020). Cigarette Smoke Exposure and Inflammatory Signaling Increase the Expression of the SARS-CoV-2 Receptor ACE2 in the Respiratory Tract [J. Dev Cell. 53(5):514–529.*
8. ^*Lopes Scholz JR, Saraiva M, Colombo JFK, F.C. (2020). COVID-19, Renin-Angiotensin System, Angiotensin-Converting Enzyme 2, and Nicotine: What is the Interrelation? J Arq Bras Cardiol. 115(4):708–711.*
9. ^*K. Jensen, D. Nizamutdinov, M. Guerrier, S. Afroze, D. Dostal, et al. (2012). General mechanisms of nicotine-induced fibrogenesis [J. FASEB J. 26(12):4778–4787.*
10. ^*B. T. Kopp, R. Thompson, J. Kim. (2019). Secondhand smoke alters arachidonic acid metabolism and inflammation in infants and children with cystic fibrosis [J. Thorax. 74(3):237–246.*
11. ^*Fels Elliott DR, Shah R, Hess CA. Giant cell interstitial pneumonia secondary to cobalt exposure from e-cigarette use. European Respiratory Journal.: European Respiratory Society (ERS) 2019. doi:10.1183/13993003.01922-2019*
12. ^*M. Caruso, A. Distefano, R. Emma. (2021). Role of Cigarette Smoke on Angiotensin-Converting Enzyme-2 Protein Membrane Expression in Bronchial Epithelial Cells Using an Air-Liquid Interface Model [J. Front Pharmacol. 12(652102).*
13. ^*A. Ramalingam, S. B. Budin, N. Mohd Fauzi, R. H. Ritchie, S. Zainalabidin. (2019). Angiotensin II Type I Receptor Antagonism Attenuates Nicotine-Induced Cardiac Remodeling, Dysfunction, and Aggravation of Myocardial Ischemia-Reperfusion Injury in Rats [J. Front Pharmacol. 10(1493).*
14. ^*B. S. Chow, T. J. Allen. (2016). Angiotensin II type 2 receptor (AT2R) in renal and cardiovascular disease [J. Clin Sci. 130(15):1307–1326.*
15. ^*N. Suffee, T. Moore-Morris, B. Jagla. (2020). Reactivation of the Epicardium at the Origin of Myocardial Fibro-Fatty Infiltration During the Atrial Cardiomyopathy [J. Circ Res. 126(10):1330–1342.*
16. ^*A. Sas-Strozik, P. Donizy, K. Koscielska-Kasprzak. (2020). Angiotensin II Type 1 Receptor Expression in Renal Transplant Biopsies and Anti-AT1R Antibodies in Serum Indicates the Risk of Transplant Loss [J. Transpl Proc. 52(8):2299–2304.*
17. ^*J. D. Vadhan, R. C. Speth. (2021). The role of the brain renin-angiotensin system (RAS) in mild traumatic brain injury (TBI. Pharmacol Amp Ther. 218(107684):107684. doi:10.1016/j.pharmthera.2020.107684*
18. ^*A. Kiss, Y. Tratsiakovich, A. Mahdi. (2017). Vagal nerve stimulation reduces infarct size via a mechanism involving the alpha-7 nicotinic acetylcholine receptor and downregulation of cardiac and vascular arginase [J. Acta Physiol. 221(3):174–181.*
19. ^*F. Rader, M. Rashid, T. T. Nguyen. (2020). E-Cigarette Use and Subclinical Cardiac Effects [J. Circ Res. 127(12):1566–1567.*
20. ^*J. M. Bradley, J. B. Nguyen, A. C. Fournett, J. D. Gardner. (2012). Cigarette smoke exacerbates ventricular remodeling and dysfunction in the volume overloaded heart [J. Microsc Microanal. 18(1):91–98.*

21. [a, b]E. S. Colombo, J. Davis, M. Makvandi. (2013). Effects of nicotine on cardiovascular remodeling in a mouse model of systemic hypertension [J. Cardiovasc Toxicol. 13(4):364–369.
22. ^J. M. Oakes, J. Xu, T. M. Morris. (2020). Effects of Chronic Nicotine Inhalation on Systemic and Pulmonary Blood Pressure and Right Ventricular Remodeling in Mice [J. Hypertension. 75(5):1305–1314.
23. ^B. Han, W. Xie, Y. Zhang. (2020). The influx/efflux mechanisms of d-peptide ligand of nAChRs across the blood-brain barrier and its therapeutic value in treating glioma [J. J Control Release. 327:384–396.
24. ^L. Colas, M. Domercq, P. Ramos-Cabrer. (2018). In vivo imaging of Alpha7 nicotinic receptors as a novel method to monitor neuroinflammation after cerebral ischemia [J. Glia. 66(8):1611–1624.
25. ^M. ArunSundar, T. S. Shanmugarajan, V. Ravichandiran. (2018). 3,4-Dihydroxyphenylethanol Assuages Cognitive Impulsivity in Alzheimer's Disease by Attuning HPA-Axis via Differential Crosstalk of alpha7 nAChR with MicroRNA-124 and HDAC6 [J. ACS Chem Neurosci. 9(12):2904–2916.
26. ^T. Jiang, J. T. Yu, X. C. Zhu. (2014). Angiotensin-(1-7) induces cerebral ischaemic tolerance by promoting brain angiogenesis in a Mas/eNOS-dependent pathway [J. Br J Pharmacol. 171(18):4222–4232.
27. ^E. Bartova, S. Legartova, J. Krejci, O. A. Arcidiacono. Cell differentiation and aging accompanied by depletion of the ACE2.
28. ^N. J. Hunt, B. Russell, M. K. Du, K. A. Waters, R. Machaalani. (2016). Changes in orexinergic immunoreactivity of the piglet hypothalamus and pons after exposure to chronic postnatal nicotine and intermittent hypercapnic hypoxia [J. Eur J Neurosci. 43(12):1612–1622.
29. ^F. Yu, Y. Li, J. Yang, J. Qian, X. Li, et al. (2017). Prenatal Nicotine Exposure Results in the Inhibition of Baroreflex Sensitivity Induced by Intravenous Injection Angiotensin II in the Adult Male Offspring Rats [J. Cardiovasc Toxicol. 17(2):200–207.
30. ^W. L. Cheng, K. Y. Chen, K. Y. Lee, P. H. Feng, S. M. Wu. (2020). Nicotinic-nAChR signaling mediates drug resistance in lung cancer [J. J Cancer. 11(5):1125–1140.
31. ^X. Chen, Y. Jia, Y. Zhang, D. Zhou, H. Sun, et al. (2020). alpha5-nAChR contributes to epithelial-mesenchymal transition and metastasis by regulating Jab1/Csn5 signalling in lung cancer [J. J Cell Mol Med. 24(4):2497–2506.
32. ^K. Asakawa, K. Yoshizawa, A. Aoki. (2020). Comparison of cytokine profiles between anti-ARS antibody-positive interstitial lung diseases and those with anti-MDA-5 antibodies [J. Clin Rheumatol.
33. ^Y. Zhang, Y. Li, C. Shi, X. Fu, L. Zhao, et al. (2018). Angiotensin-(1-7)-mediated Mas1 receptor/NF-kappaB-p65 signaling is involved in a cigarette smoke-induced chronic obstructive pulmonary disease mouse model [J. Env Toxicol. 33(1):5–15.
34. ^K. S. Schweitzer, T. Crue, J. M. Nall. (2021). Influenza virus infection increases ACE2 expression and shedding in human small airway epithelial cells [J. Eur Respir J. 58(1).
35. ^N. D. Fried, T. M. Morris, A. Whitehead, E. Lazartigues, X. Yue, et al. (2021). Angiotensin II type 1 receptor mediates pulmonary hypertension and right ventricular remodeling induced by inhaled nicotine [J. Am J Physiol Heart Circ Physiol. 320(4).
36. ^J. M. Leung, C. X. Yang, D. D. Sin. COVID-19 and nicotine as a mediator of ACE-2. European Respiratory Journal.: European Respiratory Society (ERS) 2020. doi:10.1183/13993003.01261-2020

37. ^*Y. H. Hung, W. Y. Hsieh, J. S. Hsieh. (2016). Alternative Roles of STAT3 and MAPK Signaling Pathways in the MMPs Activation and Progression of Lung Injury Induced by Cigarette Smoke Exposure in ACE2 Knockout Mice [J. Int J Biol Sci. 12(4):454–465.*
38. ^*A. T. J. Maria, C. Bourgier, C. Martinaud. (2020). From fibrogenesis towards fibrosis: Pathophysiological mechanisms and clinical presentations. J Rev Med Interne.*
39. ^*Y. Zhou, X. Zuo, Y. Li, Y. Wang, H. Zhao, et al. (2012). Nicotine inhibits tumor necrosis factor-alpha induced IL-6 and IL-8 secretion in fibroblast-like synoviocytes from patients with rheumatoid arthritis [J. Rheumatol Int. 32(1):97–104.*
40. ^*H. Han, G. Peng, M. Meister. (2021). Electronic Cigarette Exposure Enhances Lung Inflammatory and Fibrotic Responses in COPD Mice [J. Front Pharmacol. 12(726586).*
41. ^*C. Mihai, R. Dobrota, S. Assassi, M. D. Mayes, O. Distler. (2020). Enrichment Strategy for Systemic Sclerosis Clinical Trials Targeting Skin Fibrosis: A Prospective, Multiethnic Cohort Study [J. ACR Open Rheumatol. 2(8):496–502.*
42. ^*P. Kumar, P. Scholze, M. Fronius, G. Krasteva-Christ, M. I. Hollenhorst. (2020). Nicotine stimulates ion transport via metabotropic beta4 subunit containing nicotinic ACh receptors [J. Br J Pharmacol. 177(24):5595–5608.*
43. ^*M. F. Grondahl, J. I. Bagger, A. Lund. (2018). Effects of Smoking Versus Nonsmoking on Postprandial Glucose Metabolism in Heavy Smokers Compared With Nonsmokers [J. Diabetes Care. 41(6):1260–1267.*
44. ^*J. Zhu, K. Nelson, J. Toth, J. E. Muscat. (2019). Nicotine dependence as an independent risk factor for atherosclerosis in the National Lung Screening Trial [J. BMC Public Health. 19(1).*
45. ^*M. Koga, Y. Kanaoka, M. Okamoto. (2020). Varenicline aggravates atherosclerotic plaque formation in nicotine-pretreated ApoE knockout mice due to enhanced oxLDL uptake by macrophages through downregulation of ABCA1 and ABCG1 expression [J. J Pharmacol Sci. 142(1):9–15.*
46. ^*P. Petsophonsakul, M. Burgmaier, B. Willems, J.]. Cardiovasc Res. Nicotine promotes vascular calcification via intracellular Ca2+-mediated, Nox5-induced oxidative stress and extracellular vesicle release in vascular smooth muscle cells. Cardiovascular Research.: Oxford University Press (OUP) 2021. doi:10.1093/cvr/cvab244*
47. ^*Y. T. Chen, P. Y. Jhao, C. T. Hung. (2021). Endoplasmic reticulum protein TXNDC5 promotes renal fibrosis by enforcing TGF-beta signaling in kidney fibroblasts [J. J Clin Invest. 131(5).*
48. ^*R. A. Louzada, R. Corre, R. Ameziane El Hassani. (2021). NADPH oxidase DUOX1 sustains TGF-beta1 signalling and promotes lung fibrosis [J. Eur Respir J. 57(1).*
49. ^*J. Soeda, M. Morgan, C. McKee. (2012). Nicotine induces fibrogenic changes in human liver via nicotinic acetylcholine receptors expressed on hepatic stellate cells [J. Biochem Biophys Res Commun. 417(1):17–22.*
50. ^*L. L. Zhou, M. Wang, F. Liu. (2019). Cigarette smoking aggravates bleomycin-induced experimental pulmonary fibrosis [J. Toxicol Lett. 303:1–8.*
51. ^*X. Han, C. Cai, J. Huang. The intervention effect of nicotine on cervical fibroblast-myofibroblast differentiation in lipopolysaccharide-induced preterm birth model through activating.*
52. ^*P. C. Chen, W. Y. Lee, H. H. Ling, C. H. Cheng, K. C. Chen, et al. (2018). Activation of fibroblasts by nicotine promotes the epithelial-mesenchymal transition and motility of breast cancer cells [J. J Cell Physiol. 233(6):4972–4980.*
53. ^*R. Schuster, J. S. Rockel, M. Kapoor, B. Hinz. (2021). The inflammatory speech of fibroblasts [J. Immunol Rev.*
54. ^*M. Manevski, T. Muthumalage, D. Devadoss. (2020). Cellular stress responses and dysfunctional Mitochondrial-*

cellular senescence, and therapeutics in chronic respiratory diseases [J. Redox Biol. 33(101443).

55. ^*G. L. Serpa, N. D. Renton, N. Lee, M. J. Crane, A. M. Jamieson. (2020). Electronic Nicotine Delivery System Aerosol-induced Cell Death and Dysfunction in Macrophages and Lung Epithelial Cells [J. Am J Respir Cell Mol Biol. 63(3):306–316.*
56. ^*N. Alkhattabi, I. Todd, O. Negm, P. J. Tighe, L. C. Fairclough. (2018). Tobacco smoke and nicotine suppress expression of activating signaling molecules in human dendritic cells [J. Toxicol Lett. 299:40–46.*
57. ^*Z. Liu, B. Han, P. Li, Z. Wang, Q. Fan. (2014). Activation of alpha7nAChR by nicotine reduced the Th17 response in CD4(+)T lymphocytes [J. Immunol Invest. 43(7):667–674.*
58. ^*S. Chatterjee, A. Balram, W. Li. (2021). Convergence: Lactosylceramide-Centric Signaling Pathways Induce Inflammation, Oxidative Stress, and Other Phenotypic Outcomes [J. Int J Mol Sci. 22(4).*
59. ^*C. Guo, S. Lv, Y. Liu, Y. Li. (2021). Biomarkers for the adverse effects on respiratory system health associated with atmospheric particulate matter exposure [J. J Hazard Mater. 421(126760).*
60. ^*R. S. Moheimani, M. Bhetraratana, F. Yin. (2017). Increased Cardiac Sympathetic Activity and Oxidative Stress in Habitual Electronic Cigarette Users: Implications for Cardiovascular Risk [J. JAMA Cardiol. 2(3):278–284.*
61. ^*X. Chen, E. Owoseni, J. Salamat, A. I. Cederbaum, Y. Lu. (2018). Nicotine enhances alcoholic fatty liver in mice: Role of CYP2A5 [J. Arch Biochem Biophys. 657:65–73.*
62. ^*X. Wu, H. Zhang, W. Qi. (2018). Nicotine promotes atherosclerosis via ROS-NLRP3-mediated endothelial cell pyroptosis [J. Cell Death Dis. 9(2).*
63. ^*R. Schuster, J. S. Rockel, M. Kapoor, B. Hinz. (2021). The inflammatory speech of fibroblasts [J. Immunol Rev. 302(1):126–146.*
64. ^*S. Ray, H. Adelnia, H. T. Ta. (2021). Collagen and the effect of poly-l-lactic acid based materials on its synthesis [J. Biomater Sci. 9(17):5714–5731.*