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Review Article

Nrf2-ACE2R Pathway to Halt the Entrance of SARS-CoV-2 in Human: A New Strategy in Targeted Therapy

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Abstract

The nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) regulates many important genes that encode of our body antioxidant systems and display diverse and important physiological functions. Loss of Nrf2 is associated with an upregulated expression of angiotensin converting enzyme 2 receptor (ACE2R) in experimental animals. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) use ACE2R for the entry in human lung epithelial and enteric cells through binding with its spike glycoprotein (S). ACE2 upregulation is associated with many diseases, including liver injury, inflammation and insulin resistance, myocardial dysfunction, acute decompensated heart failure, and type 2 diabetes. However, deletion or loss of its activity is associated with atherosclerotic renal injury and kidney diseases, heart failure, and pulmonary arterial hypertension. Therefore, targeting Nrf2 alone or Nrf2-ACE2 modulators might be helpful to manage these types of patients with SARS-CoV-2 infection. Adequate pre-clinical and clinical research is necessary to establish this concepts.

Keywords: ACE2; Nrf2; SARS-CoV-2; Covid-19; Targeted Therapy

Abbreviations

ACE2R: Angiotensin Converting Enzyme 2 Receptor; ALI: Acute Lung Injury; ARDS: Acute Respiratory Distress Syndrome; CTGF: Connective Tissue Growth Factor; eNOS: Endothelial NOS; ER: Endoplasmic Reticulum; GSH: Reduced Glutathione; IL: Interleukin; JNK: c-Jun N-terminal Kinase; MAPK: Mitogen-Activated Protein Kinases; NAAE: N-(2 aminoethyl)-1 Aziridine-Ethanamine; NADPH: Reduced Nicotinamide Adenine Dinucleotide Phosphate; nCoV-19: Novel Coronavirus 2019; NF-κB: Nuclear Factor-κB; Nrf2: Nuclear Factor-Erythroid 2 p45-related Factor 2; p-ERK: Extracellular Signal-Regulated Kinase; PPARγ: Peroxisome Proliferator-Activated Receptor-γ; p-STAT3: Phospho Signal Transducer and Activator of Transcription 3; ROS: Reactive Oxygen Species; SARS: Severe Acute Respiratory Syndrome; TGFβ: Tumor Growth Factor Beta; UPR: Unfolded Protein Response

Introduction

The nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) regulates genes encoding key components of our body antioxidant systems as well as multidrug-resistance-associated efflux pumps. It plays a key role in both intrinsic resistance and cellular adaptation to reactive oxygen species (ROS) and xenobiotics. Activation of Nrf2 leads chemical carcinogenesis by promoting futile redox cycling of polycyclic aromatic hydrocarbon metabolites or growing resistance to chemotherapeutic drugs. Nrf2 controls genes involved in reduced nicotinamide adenine dinucleotide phosphate (NADPH) generation, purine biosynthesis and β-oxidation of fatty acids [1].

Too little or downregulation of Nrf2 activity leads to loss of cytoprotection, reduce in antioxidant capacity and lowering of β-oxidation of fatty acids [2]. However, Nrf2 deficiency was seen to reduce aggregation of mutant proteins and preventing reductive

stress-induced hypertrophic cardiomyopathy in experimental animals [3]. In another study, Nrf2 deficiency was found to encounter urethane-induced lung tumorigenesis in mice [4]. In contrast, too much or an upregulated Nrf2 activity may disturb the homeostatic balance of the redox system due to overproduction of reduced glutathione (GSH) and NADPH) enzymes, blunts ROS-based signal transduction, causes epithelial cell hyperplasia, results inappropriate differentiation of certain cell types, promote resistance to anti-cancer drugs and malignancy [4]. The aberrant activation or accumulation of Nrf2 also provides advantages to cancer cells and poor prognosis, therefore, Nrf2 has emerged as a promising target in cancer treatment [2].

Type 2 diabetes mellitus has reached pandemic proportions. Nrf2 activation has been seen to ameliorate insulin resistance, β-cell dysfunction and diabetic complications [5]. Nrf2 dysfunction is linked to exert deleterious effects on obesity, impairing neurovascular coupling mechanisms, blood brain barrier (BBB) integrity, synaptic function and promoting neuroinflammation [6]. Rojo *et al*. (2017) and Zhang *et al*. (2018) demonstrated that normal Nrf2 activity declines with ageing [7,8].

Generally, coronaviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first replicate in lung epithelial cells and enteric cells [9]. The human receptor angiotensin-converting enzyme 2 receptor (ACE2R) has been detected as a binding receptor with the viral spike glycoprotein (S) of SARS-CoV-2 [10]. Some additional co-factors are thought to be essential for efficient cellular infection by the coronaviruses [11], including SARS-CoV-2. It has been depicted that using ACE2 inhibitors might be one of the potential targets to inhibit SARS-CoV-2 invasion in lung cells.

Generally, ACE2 catalyses the conversion of angiotensin II to angiotensin 1 - 7, results as a vasodilator and exerts protective effects in the cardiovascular system [12]. ACE2 deficiency impaired endothelial function in cerebral arteries in adult mice and augmented endothelial dysfunction during aging [13]. Therefore, the ACE2-angiotensin 1 - 7 pathway might provide a useful therapeutic target for the treatment of cardiovascular disease, especially in patients with overactive renin-angiotensin system [12,14]. Kuster., *et al*. (2020) recommended ACE1 and angiotensin II type 1 receptor blockers therapies for the patients having heart failure, hypertension, or myocardial infarction with coronavirus disease 2019 (Covid-19) [12].

However, in a study, it has been seen that the loss of Nrf2 upregulated ACE2R expression in renal proximal tubule cells in Akita mice [15]. Loss of ACE2 resulted muscle weakness and muscle senescence [16], increases systolic blood pressure and promoted obesity-hypertension in mice [17], while a resistance to growth hormone decreases systolic blood pressure, leading to hypotension in experimental animals [18]. Hypoxia may also increase ACE2 expression in human [19]. However, ageing endothelial cells, in hypoxia/reoxygenation condition was found to down-regulate ACE2 along with the ROS overproduction, higher rate of apoptosis, upregulation of the phagocyte NADPH oxidase (Nox2), miR-18a and endothelial NOS (eNOS), and compromised tube formation ability [8]. Hypotension and hypoxia are predictors of negative patient outcomes and increased in-hospital mortality in non-cardiac arrest patients, thus avoidance or mitigation of hypoxia and hypotension may be considered during critical cases [20]. Loss of growth hormone receptor upregulates ACE2 expression [18] and inflammatory process may develop growth hormone resistance in our cells [21].

Inhaled particulate matter 2.5 ($PM_{2.5}$) induced severe acute lung injury through pulmonary inflammation *via* phospho extracellular signal-regulated kinase (p-ERK1/2) and phospho signal transducer and activator of transcription 3 (p-STAT3) pathways. ACE2 knockdown has been evident to increase in pulmonary p-STAT3 and p-ERK1/2 levels in the $PM_{2.5}$-induced acute lung injury in ACE2 gene knockout (ACE2 KO) mice [22]. STAT3 becomes activated after phosphorylation of tyrosine 705 in response to some ligands, including interferons, interleukin (IL-)5, IL-6 as well as *via* phosphorylation of serine 727 by mitogen-activated protein kinases (MAPK) [23]. It plays essential roles in the process of atherosclerosis and loss-of-function or mutations in the *STAT3* gene results in the hyperimmunoglobulin E syndrome, associated with recurrent infections [24].

Coronavirus infection causes endoplasmic reticulum (ER) stress and induces unfolded protein response (UPR) in the infected cells, which is closely associated with a number of major signaling pathways, including autophagy, apoptosis, the MAPK pathways, innate immunity and pro-inflammatory response [25]. Generally, the MAPK/ERK pathway (also known as Ras-Raf-MEK-ERK pathway) communicates a signal from a receptor on the cell surface to the nuclear DNA of the cell through a signaling molecule, thus produces some changes in the cell, including cell division. ERK1/2

inhibition modulated STAT3 levels in oral squamous carcinoma cells [26]. Diminazene aceturate (an anti-infective medication for animals that acts against some protozoa such as Babesia, Trypanosoma, Cytauxzoon, etc.) has been seen to inhibit lipopolysaccharide-induced inflammatory response by activating ACE2/Ang-(1-7)/Mas axis in human retinal pigment epithelium cells through inhibiting p38MAPK, ERK1/2, c-Jun N-terminal kinase (JNK), and nuclear factor-κB (NF-κB) pathways [27].

The expression of Nrf2 levels varies depending on physiological and pathological context, therefore, properly timed and targeted manipulation of the Nrf2 pathway may be helpful to manage the ACE2R expression in coronavirus infection [28]. Till date, P4 and P5 peptides and *N*-(2aminoethyl)-1aziridine-ethanamine (NAAE) have been marketed that interact with ACE2 and the block SARS coronavirus S-mediated cell fusion [29,30]. However, these drugs have a narrow spectrum of activity and may affect important biological functions such as blood pressure regulation. In a study, emodin (an anthraquinone derived from genus *Rheum* and *Polygonum*), was seen to block the SARS coronavirus S protein and ACE2 interaction in a dose-dependent manner [31]. In this study, it was also seen to inhibit the infectivity of S protein to Vero E6 cells. Kesic., *et al*. (2011) found an inverse relationship between the levels of Nrf2 expression and influenza A viral entry/replication in human nasal epithelial cells [32]. Moreover, melatonin (an anti-inflammatory and anti-oxidative molecule) acts against acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) caused by viral and other pathogens, which might be beneficial in SARS-CoV-2 infection management [33]. Melatonin activates Nrf2 through the MT1/MT2 receptor pathway, stimulates endoplasmic reticulum-associated degradation, inhibits NF-κB and endoplasmic reticulum stress [34]. The cytoplasmic RNA viruses fine-tune NF-κB signaling at multiple levels and profoundly reprogram the host cellular chromatin landscape, leading to orchestrate the proper expression of genes involved in multiple signaling, immunoregulatory and metabolic processes [35]. Irbesartan prevented ACE2 deficiency-mediated pathological hypertrophy and myocardial fibrosis in ACE2 mutant mice *via* activation of the peroxisome proliferator-activated receptor-γ (PPARγ) signaling and suppression of the tumor growth factor beta (TGFβ)-connective tissue growth factor (CTGF)-ERK signaling, resulting in attenuation of myocardial injury [36].

ACE2 upregulation is associated with the chronic liver injury [37,38], inflammation and insulin resistance [39], myocardial dysfunction [40], acute decompensated heart failure [41], diabetes [42,43], while deletion or loss of its activity causes atherosclerotic renal injury and kidney diseases [44], heart failure [45] and pulmonary arterial hypertension [46].

A very recent study reports that Nrf2 activation might be an important option to reduce viral pathogenesis via inhibiting virus entry through upregulation of ACE2 along with the induction of gene expression of anti-viral mediators, including retinoic acid-inducible gene I (RIG-1) and integrative nuclear FGFR1 signaling (INFs) pathway, stimulating body anti-oxidant enzymes with a an important role in inhibiting NF-κB, apoptosis proteins and toll-like receptors (TLRs) expression [47]. For example, the Nrf2 activators sulforaphane and bardoxolone methyl are already in clinical trials. The safety and efficacy profiles in humans, along with their cytoprotective and anti-inflammatory effects in a number of pre-clinical studies, suggesting that these compounds might be armory for the deployment to fight against SARS-CoV-2 [48].

Conclusion

Therefore, targeting Nrf2 alone or Nrf2-ACE2 modulators might be helpful for these types of patients with Covid-19. However, before implementing this novel strategy in this current pandemic we must address a number of important issues, including clear concept on SARS-CoV-2-Nrf2 interactions, other impacts of downregulation of ACE2 in human lung, clear concepts on Nrf2 in metabolic reprogramming and adaptation of immune cells such as macrophages and T cells, pharmacological activation of NRF2 and its impact on the viral entrance into the host cell, and so on. Taken together, more research is necessary with adequate pre-clinical and clinical trials to establish this strategy.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing Interests

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Authors' Contributions

MTI design, data collection and analysis, drafting and reviewing this letter. Finally, reading and approving this manuscript.

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