

## **Dexamethasone as Repurposing Drug and the Possibility of Its Mitigating Role on NRF2-Dependent Anti-SARS-Cov2 Effect**

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### **Abstract**

SARS-CoV2 infection is a fatal case of pandemic disease, which is the burning issue all over the world. Scientists are trying to prevent the disease pathology and in this case scientists are focusing on drug repurposing concept as still now there is no selective drug for the treatment of SARS-CoV2 infection. Recent studies have proved that activation of nuclear erythroid factor 2 related factor 2 (NRF2), a master gene regulator of detoxification system, redox homeostasis and so on, showed effective treatment measure of SARS-CoV2 infection. Dexamethasone treatment as a repurposing drug for the COVID-19 treatment although shows a transient benefit but the severe health concern is it would have lots of side effect and based on previous reports, in this mini-review I explained the possible side effect relating to mitigating NRF2-dependent pathway.

**Keywords:** *Dexamethasone, Drug repurposing, SARS-CoV2, NRF2*

### **SARS-CoV2 infection**

The current world is going through an adverse situation and that is due to novel Corona virus infection. The novel corona virus, also known as SARS-CoV2 or COVID-19, is a single-stranded RNA virus and its outbreak is too devastating that leads the interruption of social and global life. The spreading rate of SARS-CoV2 has already exceeded the previous terms and the major concern is its controlling measure [1]. Scientists are still working hard to know its pathogenesis and searching an effective measure of therapy. Since there are no available drugs for selective therapy of SARS-CoV2 infection, medical scientists are now focusing on alternative drugs, drugs repurposing, that have been used for the treatment of some diseases, which have similar disease symptoms and signs.

Patients having SARS-CoV2 infection suffers with persistent high fever, sore throat, and severe respiratory distress. The pathogenesis of this disease involves massive cytokine storm and the fatality is much more severe if the patient is already immunocompromised [2]. Scientists investigated the pathological mechanisms of SARS-CoV2 infection to host and most of them confirmed that the virus infects human by binding with the angiotensin converting enzyme 2 (AEC2) receptor that is predominantly expressed in the alveolar epithelial cells in lung [3] though recent study also proved the involvement of neuropilin-1 (NRP1) [4] as another entry route for its pathology. After its entry into host cells, the virus multiplies as like other viruses and causes severe damage to host cells by releasing a cytokine storm that is mediated by NLRP3 inflammasome [5]. Beside this, the virus also releases lots of reactive oxygen species (ROS) to make more vulnerable of the adjacent cells as its next target of inflammatory surge [6, 7].

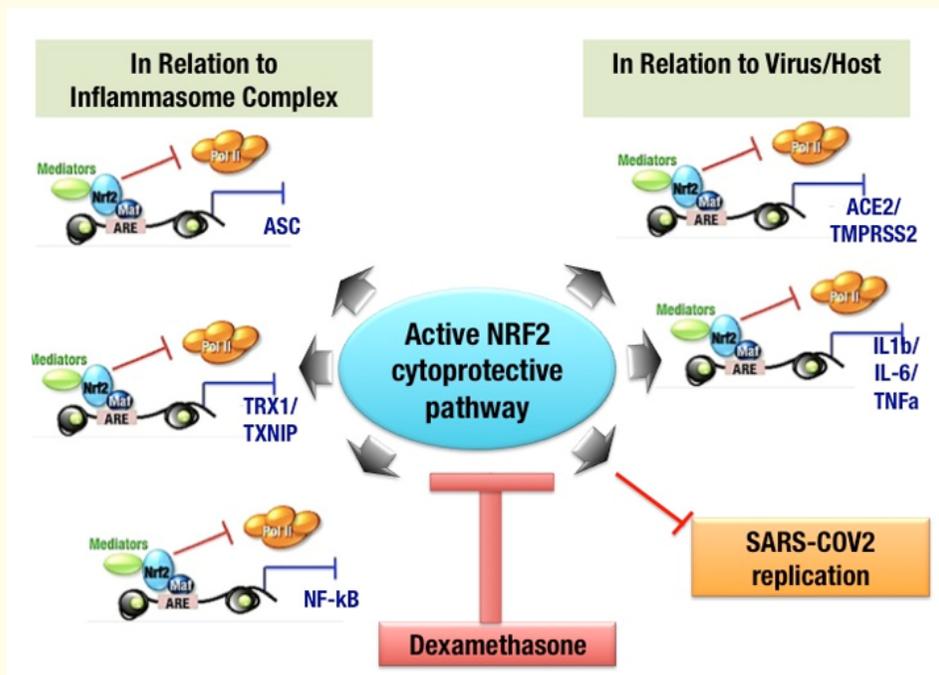
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**NRF2 activation mitigates SARS-CoV2 infection**

Nuclear erythroid factor 2 related factor 2 (NRF2) is a transcription activator that mediates activation of antioxidant responsive genes, detoxification genes, and so on. On the other hand, KEAP1 negatively regulates the NRF2 protein stability through ubiquitin-proteasomal degradation pathway under normal homeostatic condition [8]. KEAP1 is inactivated under oxidative stress that leads to the stabilization of NRF2 and finally NRF2 translocates into nucleus to bind to the antioxidant response element (ARE) followed by the activation of its downstream target genes that are involved in the synthesis of GSH, NADPH, elimination of ROS, and inactivation of pro-inflammatory cytokine genes [8, 9].

NRF2-dependent SARS-CoV2 infection can be explained in two broad senses: first, in relation to inflammasome inactivation, and second, in relation to support host immunity (Figure 1). Concerning the former relation, various research investigations support that activated NRF2 suppresses NLRP3 inflammasome. Sulforaphane-induced NRF2 activation predominantly inhibits ASC formation [10], a core unit of NLRP3 inflammasome, as well as some other inflammsomes like AIM2, NLRP1 and NLRP4 [11]. Activated NRF2 also inhibits the thioredoxin 1 (TXN1)/TXNIP complex formation, which is important inflammasome activation [12] as well as interfere NF-kB signaling [13]. In relation to host immunity, bunch of reports suggest that NRF2 activation alleviate host immunity. A recent report suggested that NRF2 activation suppresses angiotensin converting enzymes 2 (ACE2) receptor and TMPRSS2 activation, which are key to SARS-CoV2 binding in the host cell [14, 15]. Beside this, activated NRF2 also inhibits RNA polymerase II binding to the promoter region of IL-1b, IL-6 and also interfere TNFα activation [16]. A very exciting recent report suggested that NRF2 activation inhibit SARS-CoV2 replication [14]. It is very well known that NRF2 activation plays a key role in redox balance inside living system [17, 18]. This property of NRF2 also mitigates the ROS levels that are generated by SARS-CoV2 infection. Depending on all these findings suggests that activated NRF2 would be a priming tool to combat SARS-CoV2 infection.



**Figure 1:** NRF2-dependent prevention of SARS-CoV2 infection and Dexamethasone-mediated suppression of NRF2 activity.

### Dexamethasone-mediated mitigation of NRF2-dependent anti-SARS-CoV2 effect

Dexamethasone is a steroid hormone. It is also known as glucocorticoid that exerts its functional activities through glucocorticoid receptor (GR) signaling pathway. Dexamethasone/GC (glucocorticoid) regulates a variety of physiological functions and also maintain stress-related homeostasis [19]. Dexamethasone-dependent GR signaling itself is beneficial to human as it contributes to metabolic homeostasis, for example, it has some beneficial aspects like anti-inflammatory, anti-angiogenesis, glucose metabolism, rheumatoid arthritis, asthma and COPD, organ transplant, psoriasis, eczema and so on [20]. Though it possesses strong anti-inflammatory activity but excessive dexamethasone/GC also exerts fatty liver development, which is conducted by GC-GR-induced increased insulin resistance and impaired glucose tolerance [21], GC-mediated activation of miR-17-5p [22] as well as accumulation of granulocytic (G)-myeloid-derived suppressor cell (MDSC) in liver [23]. In addition to its adverse effects, excessive use of dexamethasone/GC has some other deleterious aspects like obesity, hyperglycemia, cardiovascular disease, osteoporosis, psychiatric disorders, glaucoma, gonadal virilization and so on [24].

At present, as there are no available selective drugs for the treatment of SARS-CoV2 infection, scientists are now trying to mitigate the effect of this virus by using drug repurposing concept. In this line, along with other drugs, dexamethasone is considered as one of the suitable repurposing drug for the elimination of the adverse effect of this virus concerning its anti-inflammatory effect, but still now it is in debate. As *NRF2* activation is considered as a key to suppress the SARS-CoV2 mediated disease pathology [7], Alam., *et al.* showed both *in vitro* and *in vivo* that dexamethasone treatment transrepresses *NRF2*-dependent transcriptional activation of its downstream target genes and their group also proved that dexamethasone treatment deacetylates *NRF2* target genes leading to chromatin compaction. Thus, dexamethasone interferes *NRF2*-dependent activation of various genes involved in detoxification system, ROS elimination and inhibition of various anti-inflammatory genes by GR-mediated tethering mechanism [25]. Thus, using dexamethasone as a repurposing drug for the COVID-19 treatment would have severe side effects concerning to the suppressive role on *NRF2*-dependent pathway.

### Conclusion

Treatment of COVID-19 is a burning issue all over the world. Various strategies have been taken for the remedy of such devastating viral infection and among them, vaccine development, selective drug development are the first two health measures. As selective drugs are not available, drug repurposing is the alternative way and in this regard, dexamethasone treatment would not be a suitable drug to use as a repurposing drug for the treatment of novel corona virus infection. So, it is obvious that scientists should clarify the selectivity and adverse effects while selecting a repurposing drug.

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