Dampening of Inflammatory Markers and Understanding COVID-19 Viral Disease Development: A Combinatorial Approach

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Abstract

One of the hallmarks of the global pandemic of coronavirus disease 2019 (COVID-19) is that it targets the immune system by producing inflammatory cytokines. COVID-19 has expedited investigations on numerous therapeutics to fight the disease-causing virus SARS-CoV-2, some without well-established safety or efficacy data. The severity of the disease depends on a number of factors, including genetic background and preexisting conditions. The difference in the genetic makeup makes everyone unique and the understanding of the COVID-19 cure arduous. To dampen these inflammatory markers and to understand the viral disease dynamics, accounting for genetic variability, a combinational three-way approach involving bioinformatics, nutrigenomics, and pharmacogenomics will give answers to many unanswered questions involving patient care. A futuristic approach to prevention and cure calls for continuous research with practice and training provision to the right group, accompanied with the awareness enhancing its utility.

Keywords

Inflammation · COVID-19 · SARS-CoV-2 · Bioinformatics · Nutrigenomics · Pharmacogenomics

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16.1 Introduction

The global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) underscores the need to deepen our understanding of the impact of viral infections on the immune system. Lymphocytes, consisting of B cells, T cells, and natural killer cells, are the first responders to the virus, triggering the immune response. T cells are the most crucial in responding to viruses and they are comprised of cytotoxic T cells (T_C cells) and helper T cells (T_H cells). T_C cells clear the infection by killing virus-infected cells, and T_H cells control the immune response by preventing its overreaction. In some viral attacks, the inability of T_H cells to effectively regulate the immune system can lead to the overproduction of inflammatory cytokines. Heightened levels of inflammation-associated molecules are frequently observed in COVID-19 patients (Mehta et al. 2020).

SARS-CoV-2 has many similarities to other disease-causing viruses, but is more adept at causing an inflammatory response. In addition to attracting lymphocytes, rapid viral replication signals the recruitment of macrophages and monocytes which induce the release of cytokines and chemokines, commonly referred to as the cytokine storm (Tay et al. 2020). The cytokine storm attracts T_H cells and activates other aspects of the immune response (Xu et al. 2020; Wu et al. 2020). A meta-analysis showed the association of inflammatory markers with the severity of SARS-CoV-2 infection, further substantiating this relationship (Zeng et al. 2020). Within the cell, the NF-κB pathway is critical for attracting an immune response (Deng et al. 2018). However, this pathway is suppressed when the cell is attacked by SARS-CoV-2, which allows for viral replication and disease progression (Okamoto and Ichikawa 2021). Henceforth, dampening these inflammatory markers (cytokines, chemokines, NF-κB pathway) to prevent progression and tissue damage is crucial. A study published recently stated how these pro-inflammatory cytokines causing severe lung damage are reversed with early dose of short-course corticosteroid (Kolilekas et al. 2020). As we cannot rely on steroids for longer duration because of deleterious side effects, we need to understand the genes involved and identify the bioactive compounds impacting this cytokine storm. Studies targeting inflammation-inducing pathways with nutrition are imperative and demand in-depth understanding of the markers. To understand the various markers involved, studies involving nutrition and bioinformatics will allow us to study the genes involved in the immune system responsiveness to viral attack.

16.2 Everyone Is Unique

Individuals who are immunocompromised do not have the same innate or adaptive immunity to fight viral infections as compared to their healthy counterparts and display disease symptoms ranging from mild to severe (Shah 2020). This current situation of vaguely known pathogenic mechanisms of SARS-CoV-2 makes it critical to find ways to identify prime molecular predictors of heightened inflammatory markers which can further be explored to understand the molecular

pathogenesis impacting humans (Lingeswaran et al. 2020). One possible predictor of the severity of COVID-19 symptoms is nutritional deficits.

Suppressed immune responses can result from nutritional deficits. Certain essential polyunsaturated fatty acid (PUFA) precursors (arachidonic acid [AA], eicosapentaenoic acid [EPA], and docosahexaenoic acid [DHA]) assist in activating receptors. Some combination of nutrients used in a timely manner demonstrates strong inhibitory effect on experimental inflammation targeting several mediators of inflammation and its related mechanisms (Ivanov et al. 2008). Terpenoid-based drugs and dietary compounds (zinc, vitamin D, vitamin C) have been shown to suppress certain molecular targets such as NF-kB pathway, which regulate inflammation (Ivanov et al. 2008). As demonstrated by Ivanov et al., including certain nutrient compounds as a component of nutrient mixture consisting of ascorbic acid, quercetin, naringenin, hesperetin, tea catechins, lysine, proline, arginine, and N-acetyl cysteine has a strong impact on controlling experimental *in vivo* and in vitro inflammation. We postulate that nutrition adjustments can dampen the inflammation response to viral infection, leading to better clinical outcomes. Integrating bioinformatics (study of biology and computer science to help analyze and interpret biological data), nutrigenomics (study of the intersection of human genome, nutrition, and health), and pharmacogenomics (study of the role of genome in drug response) should provide a novel approach towards combating tissue damage due to viral infection (Fig. 16.1).

Comparing and integrating data have been always essential to science, but the current global pandemic has made this practice more important. Accumulating evidence has suggested the association of several inflammatory markers associated with COVID-19 disease progression (Gao et al. 2020, Qin et al. 2020). Some of these markers include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), serum ferritin, interleukin-6 (IL-6), serum amyloid A

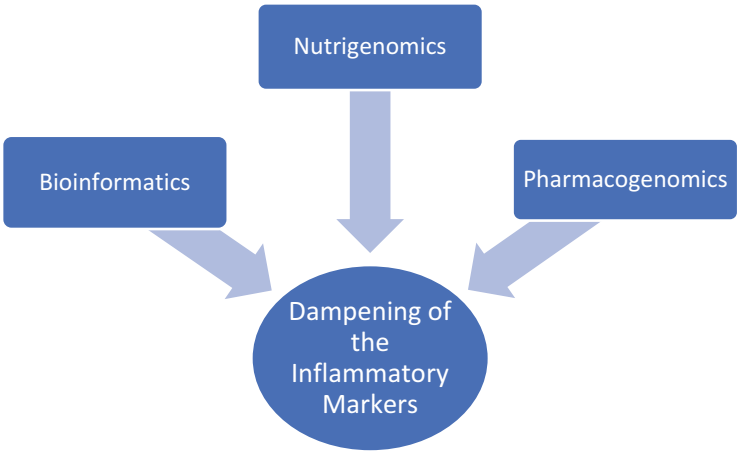

Fig. 16.1 The three-way approach to tackle futuristic care through dampening of the inflammatory markers

(SAA) lactate dehydrogenase (LDH), alanine transaminase (ALT), and TNF-α (Cheng et al. 2020, Xiang et al. 2020). Other possible targets involved in COVID-19 progression are the NFkB pathway, lack of type 1 IFNs, presence of specific autoantibodies, and an undefined marker on the X chromosome (Zhang et al. 2020; Guisado-Vasco et al. 2020; Tay et al. 2020).

16.3 Bioinformatics

A broad sampling of global bioinformatics data can be employed to gain insight into how COVID-19 causes life-threatening pneumonia. For example, relatively early in the pandemic it was observed that the percentage of men who die from COVID-19 is higher than women (Bakelmun 2020). For example, in India the ratio of men to women deaths is 1.8 and in Denmark the ratio is 1.3. There are several possible explanations for this outcome, including a higher frequency of preexisting conditions in men such as diabetes and heart disease (Sharma et al. 2020).

Another factor for the high death rate amongst men is the immune system. Interferons (IFNs) are protein cytokines that interfere with viral infection. Type I IFNs bind to the cell IFN-α/β receptors and block viral replication. In the case of SARS-CoV-2, type I IFNs block viral infection in vitro (Bastard et al. 2020). Bastard et al. (2020) decided to characterize the autoantibodies in COVID-19 patients. It was observed that 10.2% of patients with life-threatening COVID-19 pneumonia ($n = 987$) had neutralizing IgG autoantibodies against certain type I IFN family members (IFN-α, IFN-ω). These autoantibodies were not found in 663 individuals with mild or asymptomatic SARS-CoV-2 infection and were only found in 0.3% of healthy volunteers ($n = 1227$). Other data showed that the autoantibodies were present prior to infection, indicating that they select for disease progression. Thus, the severe disease is due to autoantibodies that inhibit IFN-α and IFN-ω, which allows the SARS-CoV-2 to replicate and cause COVID-19 pneumonia.

Interestingly, 97 out of 101 COVID-19 pneumonia patients with autoantibodies were men. This suggests that the production of autoantibodies against type I IFNs is linked to the X-chromosome. Future experiments that focus on the specific gene (s) on this chromosome will hopefully sort this out. It should be noted that SARS-CoV-2 is a poor inducer of type I IFN response and these IFNs are not part of the cytokine storm response. Yet, this low level of type I IFNs is protective against the virus.

Clinical applications of this finding are the following: (1) Prophylactic treatment of highly susceptible (i.e., immunocompromised) individuals with type I IFNs that do not have autoantibodies (such as IFN β) may be protective against SARS-CoV-2. (2) Patients shown to produce type I IFN autoantibodies should be treated with a class of IFNs which are not reactive to the autoantibodies to combat further viral infection. (3) Patients shown to produce type I IFN autoantibodies should be treated with drugs that inhibit the maturation of B cells that produce the autoantibodies. (4) Such patients should not be considered for donations of convalescent plasma, lest their autoantibodies aggravate COVID-19 in the recipients. From this interesting

study, one may consider altering the diet to lower the level of autoantibodies. This is certainly feasible given that we know that a gluten-free diet effectively lowers the level of several autoantibodies (the major one targeting transglutaminase 2) that appear to be causative for the majority of cases in celiac disease (Dieterich et al. 1997, Lebwohl et al. 2018).

16.4 Genomics

The success in mapping/sequencing of the human genome and development of sophisticated genomic analysis tools have further sparked the new era in personalized nutrition and medicine. Personalization, which is the need of the hour, has been brought more effectively into practice with in-depth genetic analysis making nutrigenomics and pharmacogenomics the imperative tool. How an individual is unique based on their genetic makeup and metabolic profile can be explored through research, practice, training, and awareness (Fig. 16.2). **Research:** Persistent research is needed so that we generate more and more evidence of the said science. This will help in enriching our understanding of the subject. **Practice:** Physicians and dieticians should implement the science in the clinic by understanding its scope and limitations. **Training:** Training about the science should be given to healthcare experts. **Awareness:** Awareness drives amongst common man are the key to enhancing the utility of nutrigenomics and pharmacogenomics.

The objective of both disciplines (nutrigenomics and pharmacogenomics) is to personalize medicine, diet, and nutrition as a prime component of patient care by aligning the drug or the nutrition to the individual genotype (Ghosh et al. 2007).

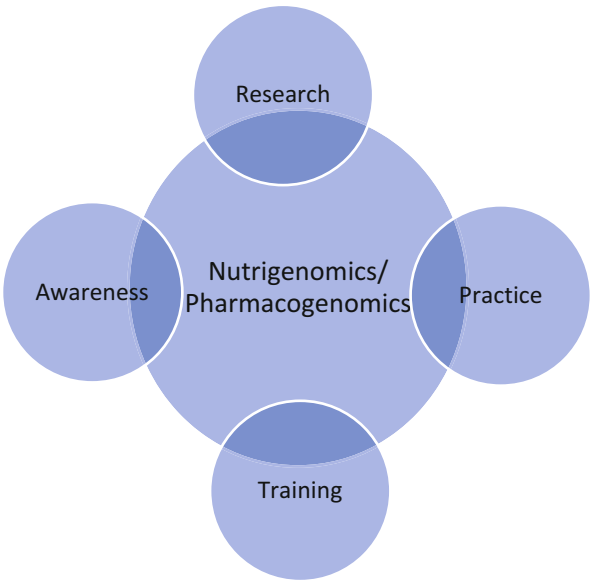

Fig. 16.2 Four key components to nutrigenomics/pharmacogenomics—futuristic approach to prevention and cure. Research, practice, training, and awareness

16.4.1 Genomics and Viral Susceptibility

The abundance of a specific type of protein receptor which is the direct target of virus in respiratory epithelial cells may make some people genetically more susceptible than others (Swanson 2020). Furthermore, the genetic basis of ACE2 receptor expression and function is still not fully understood in different populations. The differential allele frequency of ACE2 receptor in some individuals makes them more susceptible to the risk of infection and severity (Cao et al. 2020). Recent research shows that variation in the expression of these protein receptors amongst races is associated with differential responses to COVID-19 amongst different populations under similar conditions. The genetic analysis of expression quantitative trait loci (eQTLs) and potential functional coding variants in ACE2 amongst populations suggests fast spreading rate in East Asian (EAS) and other populations as compared to German people. This requires epidemiological investigations to further substantiate this abovementioned finding (Cao et al. 2020).

Nutrigenomics can be useful in understanding how immunity can be further enhanced in an individual by providing the right support to modulate metabolic activities such as oxidative stress, inflammation, and detoxification. Hence it can help in providing further personalization in improving the ability to resist and fight against infections. Nutrients such as resveratrol, vitamin B3, vitamin C, and vitamin D increase the expression of the ACE2 receptor (McLachlan 2020). There are many nutrient interventions which can directly or indirectly influence the cellular activity of ACE 2 receptor. About 25 selenoprotein genes (GPX family) have been identified in human genome known to protect from oxidative stress and free radical production during viral attack (Guillin et al. 2019). A knockout GPX model of mice, mice with selenium deficiency (Beck et al. 1998), and mice with vitamin E deficiency exhibited higher pathogenic effects of coxsackievirus infection (B3 (CVB3/0)) as compared to the control mice (Beck et al. 2003). The best small animal for testing the efficacy of diet and nutrition on COVID-19 disease is the ferret (Muñoz-Fontela et al. 2020). It would be worthwhile to determine if diets supplemented with vitamin E lower the level of inflammation in the alveoli and decrease ferret-to-ferret transmission rates.

16.4.2 Pharmacogenomics and Combating Virus

Varied responses to drug, from no effect to high toxicity in COVID-19 patients, suggest that human genome variabilities play a role in the drug effectiveness. Pharmacogenomics will undoubtedly increase our understanding of efficacy and safety of drugs being used for COVID-19 treatment. In one study, researchers showed several drug-gene variant pairs that alter the pharmacokinetics of the drugs being used and the adverse effects with their usage (Takahashi et al. 2020). For example, individuals who are G6PD (glucose-6-phosphate dehydrogenase) deficient are relatively at higher risk of hemolytic anemia (Rosenberg et al. 2020) and/or retinopathy (Allikmets et al. 1997) upon treatment with hydroxychloroquine or chloroquine. In regard to the family of IFNs, IFN-ß1b is currently being

investigated for the treatment of COVID-19 alone or in combinational therapy like lopinavir/ritonavir which had previously demonstrated some efficacy against SARS and MERS coronaviruses (Bhimraj et al. 2020). Furthermore, antibiotic treatment showed different responses based on pharmacokinetics. Azithromycin, an antibacterial drug with anti-inflammatory properties, showed up to twofold lower peak concentrations in 20 healthy volunteers with genetic variation in ABCB1, after a single dose (He et al. 2009). As azithromycin exhibits lower number of interactions with proteins, another study demonstrated lesser drug-drug interactions with the usage of azithromycin as opposed to other macrolide antibacterial agents like erythromycin or clarithromycin (Fohner et al. 2017). The in vitro studies suggest that remdesivir (a RNA polymerase inhibitor) is a substrate for drug-metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for OATP1B1 and P-glycoprotein transporters (Fact sheet 2020, Seithel et al. 2007). To date, there is no pharmacogenomic data in patients to decide whether these metabolizing enzymes alter the effectiveness of remdesivir. Although remdesivir became available for severe COVID-19 in the USA via FDA Emergency Use Authorization on May 1, 2020 (FDA Letter 2020), the known variants of the abovementioned genes (CYP2C8 PharmVar Consortium 2020; CYP2D6 PharmVar Consortium 2020; CYP3A4 PharmVar Consortium 2020) could theoretically affect the pharmacokinetics for its continued use and better outcomes.

16.5 Conclusion

Hyperactivated T cells can cause severe immune injury due to activation of the cytokine storm and generation of heightened inflammatory markers. Suppressing or inhibiting these markers may be a step towards improving the response to the virus. We discussed a few examples where COVID-19 disease severity can be traced to the genetic background of the patients.

1. Men exhibit a higher frequency of COVID-19 pneumonia than women because they produce autoantibodies to type I virus-fighting interferons. This is likely linked to the X-chromosome.
2. ACE2 gene variants and allelic frequency are associated with increased virus spread in East Asian populations and low virus spread in German populations.

Given that diet and nutrition alter metabolism and gene expression, it is imperative that we use this knowledge in combination with genomic data to provide personalized treatment of COVID-19 patients.

The unique genetic makeup of individuals substantiates the use of a three-way approach to dampen the inflammation for better cure and recovery. This approach involving bioinformatics, nutrigenomics, and pharmacogenomics will provide insight to our understanding of the COVID-19 disease variability. Although no substantial pharmacogenomics data is available for COVID-19 patients at this time, the genetic determinants may play a role in combating and understanding the

right cure. Combining bioinformatics data with genomics is more important than ever to improve the efficacy of the treatment ensuring safety. This further calls for continual research, practice, training, and awareness around the globe. In-depth research into this will enhance our ability to accelerate answers as a global community.

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