Review Article

Chemotherapeutic Prevention and Treatment of COVID-19 Myocardial Injury with Thalidomide and Celecoxib

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Abstract

Older people and patients with an underlying disorder are more susceptible to COVID-19 infection, which can be exacerbated by a cytokine storm or hypercytokinemia. Myocardial injury is the most serious and life-threatening complication may be a major cause of death as a result of infection with Covid 19. Studies have shown that patients who do not suffer from acute myocardial infarction (AMI) injury recover by a large percentage compared to those infected.Galectin-3 acting a significant

pathophysiological role in inflammatory responses, atherosclerosis, and diabetes. The transcription factor NF-κB regulates inflammatory responses and expresses more than 400 genes associated with a variety of processes, including all biochemical and biophysical process. Thalidomide act as an immunomodulatory agent that, in combination with the COX-2 inhibitor celecoxib, strongly suppresses activated NF-κB. The combination improves the prognosis of COVID-19 patients with myocardial injury.

Key words

Thalidomide, Celecoxib, COVID-19, Proinflammatory Cytokines, Acute Myocardial Infarction.

Introduction

Myocardial injury is one the principal cause of serious and life-threatening complication accompanying with a lethal effect of COVID-19 [1]. Concomitant development for acute myocardial infarction (AMI) and pulmonary embolism is rarely extreme [2]. Inflammation causing thrombosis production a vital role in heart disease and myocardial infarction, including valve blockages, brain strokes, and coronary artery blockages [3]. The relationship between systemic inflammatory processes and infection is complex [4, 5]. However, these processes produce a variety and large number of proinflammatory cytokines (a 'cytokine storm') that cause systemic and ischemic organ injuries through the nuclear factor kappa B (NF-κB). The NF-κB signaling pathways are attractive targets of strategies for the treatment of ischemic disorders. Platelets have vital starring role in heart injury through thromboembolism by orchestrating the function of prostanoids and proinflammatory cytokines.

Toll-like receptors (TLRs) and angiotensin-converting enzyme 2(ACE2)

Toll-like receptors (TLRs) is one of the receptors used to recognize microorganisms through pattern recognition receptors [6, 7]. Where these receptors work to differentiate between parts of the body and foreign organisms, which are useful in identifying microorganisms as soon as they enter the body, and they also have the ability to recognize and feel the substances that are produced to stimulate the immune system in the event of infection of one of the organs [8].

Scientific studies have shown that TLRs are responsible for many diseases that affect humans, including cancerous diseases, respiratory diseases, asthma, immune diseases, as well as heart diseases [9-11]. Research has shown that changing TLR pathways is effective in preventing heart muscle disease. Both SARS-CoV and 2019-nCoV are distinguished from other viruses in that they contain spike (S) proteins that have the ability to penetrate the body and reach the desired cells through angiotensin-converting enzyme 2 (ACE2) [12]. Therefore, controlling ACE2 is a major cause of resistance to corona viruses, as it prevents these viruses from reaching target cells, so it has an effective role in infection [13].

ACE2 has been shown to be the major host cell receptor in COVID-19 [14, 15]. The ACE2 receptor is localized in several human organs, including alveolar epithelial cells of the lungs and enterocytes of the small intestine [16]. Usually, TLR and myeloid differentiation factor (MyD88) pathways are associated with viral RNA and DNA in the endosome. The complex downstream pathways of the ACE2 receptor are believed to be the same as those of TLRs [14].

Downstream signaling pathways of TLRs activate NF-κB [17] principally via MyD88 [18-21]. The signals cannot travel from TRLs to activate NF-κB without endosomal acidification [22] and maturation. TLR signaling pathways produce inflammatory signals as cytokines and interferons. TLRs have been identified to be expressed immune cells and non-immune cells,

including fibroblasts, epithelial cells, and endothelial cells in humans [23, 24]. TLR3 might detect RNA viruses and modify the progress of lung diseases. Injuries to lung cells occur in human epithelial cells, and macrophage [25]. TRL4 expression increases upon inflammation in response to a viral infection such as coronavirus in epithelial of the lower respiratory tract [20, 26]. In nucleated cells, pathogens drive platelet activation through the TLR2/4–NF-κB pathway in a non-genomic way. This pathway produces proinflammatory cytokines and the eicosanoid thromboxane A2 (TXA2) [27, 28].

Symbiosis and COVID-19 infection

More than 100 trillion microbes reside in human gut contributing human health through the immune system of the host [29]. Probiotics sustains the homeostasis of gut microbiota and havea significant effect in disease alleviation, maintenance human health [30]. Microbes that constitute the gut microbiota are able to survive to the distal gut enduring through adverse microenvironment such as strong PH, high oxygen concentration and immune response system in the gut [31, 32]. Dysbiosis, imbalance of healthy gut microbiota, is associated with gastrointestinal diseases and also systemic unhealthy condition and diseases [33]. More than 50 phyla have been reported to colonize in human gut, however Bacteroidetes and Firmicutes constitute more than 90% in the human gut [33, 34]. Actinobacteria and Proteobacteria are not abundant; however play a diverse role in the adult gastrointestinal tract. Other phyla are Fusobacteria and Verrucomicrobia [35]. A standard adult fecal microbiota is comprised of 4principal groups:*C. coccoides, C. leptum,, Bifidobacterium, and Bacteroides*. Next dominants are *Desulfovibrio, Lactobacilli Enterobacteriaceae, Atopobium, and Sporomusa* [36].

Bacteroides cross from mother to child during vaginal birth and the early days of life, from breast milk with other Gram-positive cocci such as *Bifidobacteria, Lactobacilli and Coliforms* [37]. Gut Bacteroidetes are anaerobic and can be beneficial or harmful role to human host. They degrade dietary fiber and starch and release energy via the production of propionate. Bacteroidetes are ubiquitous found mostly in soil and freshwater, however resides especially in the G I [32]. Members of the phylum Bacteroidetes (Prevotella, Bacteroides, Porphyromonas) are most commonly colonized Western gut microbiome [38]. Some members however play a significant role in suppressing inflammation. However, some have the ability to stimulate inflammation as a pathogen [31]. Although *Bacteroides fragilis* is less in number (0.5%) in the colon flora, it has been shown to be principle anaerobic pathogen with vehement virulence factors [39]. Oxygen is toxic to anaerobic bacteria because they lack detoxification enzymes such as catalase, superoxide dismutase and peroxidase enzymes [40]. Anaerobe infections are characteristically polymicrobial with aerobic and anaerobic infections, synergistically exacerbating the infection [41, 42]. The major microbes of strictly anaerobic gut bacteria include many genera of bacteria, including Fusobacterium, Bifidobacterium, Bacteroides, and Atopobium, while facultative anaerobic bacteria include *Lactobacilli, Enterococci, Streptococci and Enterobacteriaceae* are comprised of a minority [43, 44]. Anaerobic infections are caused in injured areas of the whole body with low oxygen concentration.

Fusobacteriumnucleatum is a Gram-negative anaerobe and primally a periodontal pathogen associated with a wide spectrum of human systemic diseases [45]. Emerging data have revealed that periodontal disease is progressed by smoking. The effects of smoking containing nicotine and cotinine on subgingival microflora that causes the infectious disease are not clearly demonstrated [46]. It is imperative to understand that this microbe is anaerobic; therefore it grows under hypo oxidative circumstance induced by

smoking. In human gingival fibroblast (GFs) study, *F. nucleatum* inhibit GF proliferation, promote cell apoptosis, and yield ROS, and inflammatory cytokine such as IL-1β and TNFα through AKT signaling passageways [47]. It is reported that oral presence of ureolytic bacteria such as *H. pylori* and *C. ureolyticus* is associated with stomach pain and pH [48]. *H. pylori* produce gastric urease and make alkalized circumstances which allow to oral organism to colonize or easily pass via the stomach [49]. The relationship between members such as *F. nucleatum* and *B. fragilis* and colorectal adenoma and carcinoma is most extensively studied [50].

In the tumor microenvironment inflammation and host immune response induced by *F. nucleatum* promote colorectal adenoma, cancer initiation and development. *F. nucleatum* stimulates adhesion to the cell surface of intestinal epithelium through FadA, Fap2 and RadD [51]. This adhesion produces proinflammatory cytokines [52], and cyclooxygenase-2 (COX-2) which favors tumor growth. The function of immune cells is repressed by *F. nucleatum* [52]. The cell surface proteins, *Fusobacterium*adhesin A (FadA), fibroblast activation protein 2 (Fap2) are vital virulence factors from *F. nucleatum* which regulates adhesion and invasion of the microbe.

FadA proteins and host E-cadherin signaling pathways with radiation genes (RadD and induce the activation of AP-1 and NF-kB [52]. Fap2 binds with lectin which is high expressed in colorectal adenocarcinoma, and promote the development of colorectal cancer [53, 54].

Toll-like receptors (TLRs) sense pathogens, such as TLR3 accepting viral nucleic acids and TLR2/4-bacterial lipopolysaccharide (LPS) [55], ACE2 senses COVID-19. TLRs are required for peakmotivation of NF-κB and ACE2 might pass through the same pathway. Stimulation of these pathways results in cytokines, nitric oxide (NO), or type I interferon (IFN) [52, 55]. Lung microbiota colonize in the host to maintain symbiotic homeostasis in the lung via immune response [56]. Lung microbiota four phyla (Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria) and rate of microbial population (Bacteroidetes and Firmicutes predominate) are identical with gut microbiota [56].

There are more than 200 different species of Firmicutes phylum constitute including *Lactobacillus, Bacillus, Clostridium, Enterococcus,* and *Ruminicoccus*. 95% of the Firmicutes phyla is Clostridium genera [57]. Gut dysbiosis is associated with various pathologic conditions, and emerging data have demonstrated that the Firmicutes/ Bacteroidetes ratio correlates with numerous pathological conditions such as obesity [58].

Probiotics are predominantly anaerobic microbes' resistant to acidity such as gastric and bile. They prevent pathogenic microbes from adhesion to mucus or epithelial cells resulting in antimicrobial activity [59]. Among the majority of gut microbiota, *Bifidobacterium* and *Lactobacillus* are considered to be probiotics, and others are a nonpathogenic strain of *E. coli*, *Clostridium butyricum, Streptococcus salivarius*and *Saccharomyces boulardii* (a non-pathogenic strain of yeast) [60]. *Lactobacillus* and *Bifidobacterium* genera play a beneficial role for human health via immunomodulatory responses that prevent and treat a variety of diseases [61]. This immunomodulation is dependent on prevention of cytotoxic effect of non-probiotic microbes and production of antimicrobial molecules [62]. Probiotics are defined as viable microorganisms (*Lactobacillus, Bifidobacteria, casei*or the *L. acidophilus*-group, *Saccharomyces boulardii*) which can enter the intestine in positive health effects [63]. The role of probiotics of epithelial tight junctions is the most extensively studied that probiotics maintain barrier function against injury and stress through different signaling [57, 64]. The role of intestinal epithelium, having two major functions, has

barrier function against harmful intraluminal substances and filter function of absorbing nutrients [65, 66]. Some strain of probiotics increases tight-junction barrier function through MAPKs signaling pathways and some strain induces barrier integrity inhibiting NF-κB signaling. This inhibition prevents cytokine-induced barrier dysfunction [67, 68]. Berberine improves intestinal barrier function and reduces inflammation and oxidative stress [69]. The most abundant bacterial fermentation products (≥95%) from undigested dietary fibers are short-chain fatty acids (SCFAs). The acids play a significant role in host pathophysiology linking between the microbiota and the different components of immune system [70, 71].

SCFAs, mainly acetate, propionate, and butyrate, are produced by anaerobic fermentation of dietary fibers of Bacteroidetes and Firmicutes [71], Although colonic butyrate is mainly produced by Firmicutes and acetate and propionate are mostly produced by Bacteroidetes, the producers are phylogenetically diverse[72]. SCFAs regulate lipid, glucose, and cholesterol metabolism in various tissues [73]. Acetate absorbed by gut epithelium is transported to liver through portal vein and then to peripheral tissues where it is metabolized mainly muscle [74]. There exist enteroendocrine cells among colonic epithelium, which express the high density of glucagon like peptide-1 (GLP-1)- and peptide-YY (PYY).

Acetate and butyrate significantly drive colonic GLP-1 secretion, and to a lesser extent also PYY secretion [75]. These proteins trigger an anorectic signal (satiety) through hypothalamic neuronal activation and result in antidiabetic and antiobesity effects [75, 76]. Acetate is the primary substrate for cholesterol synthesis, however high amount of acetate promote lipogenesis at the liver [74, 77]. The secreted acetate and other fermentation acids during growth inhibits growth of microbes [78]. Butyrate has the effects of energy source (provide 60–70% of colonic mucosa energy) for colonocytes that promote proliferation and differentiation. In association with these functions, butyrate possesses immunomodulatory effects that suppress colonic inflammation leading to prevention of colitis and cancer [74]. Butyrate enhances immunomodulatory effects through transcriptional factors such as NF-κ Band peroxisome proliferator-activated receptor-γ (PPARγ), and through inhibition of the interferon-γ production and/or signaling [79]. Butyrate suppresses activated NF-κB controlling a variety of factors including proinflammatory cytokines, inducible NO synthase and COX-2, adhesion molecules and growth factors [79]. Older people and patients with an underlying disorder such as hypertension, obesity and Diabetes Mellitus (DM) are more susceptible to COVID-19 infection.

TLR4 Signaling

By contacting CD14 with the receptors and in the presence of bacterial LPS, people predict the occurrence of a global phenomenon that works to initiate vital processes. And it begins with the steps to attack and secrete the anti-inflammatory that it developed in the old period [80].

Hypertension

Hypertension is an intricate condition that is comprised of endogenous and environmental factors. There is increasing evidence demonstrating the important role of gut microbiota, immunity and inflammation [81, 82]. Effector like T cells infiltrate into kidney and vascular systems by stimuli like angiotensin II, excessive catecholamines. The effector T cells and infiltrated macrophages in the regions express proinflammatory cytokine including IL-17, IFN-γ, TNFα and IL-6. These cytokines induce renal and vascular dysfunction and damage resulting in hypertension [82]. The crosstalk via G protein-coupled receptors (GPCRs) between SCFAs and blood pressure is believed to prevent hypertension. There is a major unmet medical explanation for

hypertension that it is not a disease but symptom of metabolic syndromes [83, 84]. However, further studies delving into the complex network of signaling cascades that drive hypertension are clearly required [85].

Obesity

Obesity is induced by various factors including increased adiposity, low-grade inflammation, dysbiosis and hormonal imbalances [86]. The microbiota in overweight subjects shows raised proportion of Firmicutes and a reduced population of Bacteroides. Firmicutes/ Bacteroidetes (F/B) ratio is supposed to be meaningful to estimate how much dysbiosis correlates with obesity [87]. The microbiota in obese subjects show a higher F/B ratio, conversely a low ratio is associated with weight loss [88, 89]. Elevated F/B ratio is also observed in the gut microbiota of hypertensive individuals [81]. Probiotics exert positive health effects for obesity [88].

Adipose tissue is a major immunoendocrine system which secrete adipokines, that is, secreted proteins from adipocyte. Insulin resistance is a function failure of glucose uptake in the insulin dependent tissues. Obesity and aging are major factors that are associated with inflammation, hyperinsulinemia, lipotoxicity and oxidative stress for insulin resistance [90]. Proinflammatory cytokines increase in obesity, therefore, obesity is the and insulin resistance [91-93].

Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus is metabolic disorders, in which the level of glucose and disturbance in pancrease function [94]. One of major metabolic diseases, T2DM, is characterized with hyperglycemia, insulin resistance and pancreatic β-cell dysfunction. Dysbiosis alters repertoire of metabolites and drives significant diverse immune responses of the host. Metabolic diseases could be defined as chronic subclinical inflammation of metabolic tissues such as liver, adipose, muscles, and pancreatic islets [94; 95]. The role of gut microbiota is the most complicated, however *Bacteroides* and *Bifidobacterium* represent beneficial genera for T2DM and *Ruminococcus, Fusobacterium,* and *Blautia*have been reported to exacerbate T2DM [95]. T2D exacerbates with activated NF-κB and elevated pro-inflammatory cytokines as IL-1β, IL-6, IL-8 and TNF-α Beneficial microbes prevent inflammation by suppressing proinflammatory cytokines [96].

Aging

Composition of gut microbiota and secondary bile acids may have a connection with aging [97]. The gut microbiota in hypertension is characterized by decreased F/B ratio and loss of bacterial diversity [98]. Aging is develop chronic low-grade inflammation [99]. Therefore, aging may be well-defined as the degree of inflammation. The elevated age-related inflammation suppresses immune systems. These irregulated immune responses may cause several age-related diseases such as coronary heart disease [100].

Thromboembolism

Due to the significant relationship between AMI and COVID-19 infection, the majority of patients with ischemic heart disease require cardiovascular care [101]. Pathologically, thrombosis is the major underlying cause of cardiovascular injuries [102-104]. Thrombosis is likely to occur in the soleal vein with incomplete valves and turbulent flow. Peripheral venous thrombosis invades into central venous system [3]. It is very important to prevent the formation of soleal vein thrombi in bedridden patients [105]. Although thrombosis occurs from hemostatic reaction in injured veins, cytokine storm cause myocardial injury with an excessive amount of thrombi. Venous thrombosis is initiated by complicated crosstalk between innate immune cells, platelets, and the venous endothelial cells [3]. Platelets play a significant role in promoting the interaction between the

endothelium and innate immune cells those results in inflammation and thrombosis [106]. Endothelial cells regulate the inflammatory response through various mechanisms. In particular, they release cytokines that initiate and regulate inflammation [107, 108], and the life-threatening complication associated with a fatal outcome of COVID-19 infection [1].

Platelets and Cytokines

Ischemic injury has been shown to be a complex process of inflammation mediated by resident cells [109]. inflammatory cells, and proinflammatory cytokines [110]. Platelets, when activated, participate in the process of inflammation through a variety of membrane receptors and soluble mediators [111]. Platelets activated in the periphery trigger hypertension and promote the inflammatory response [112]. When platelets are activated by thrombin, more than 300 proteins [113, 114]. During this process, selectin, which has anbiovital role in platelet–leukocyte interactions, is expressed on the platelet membrane [115]. selectin and TXA2 play a fundamental role in the crosstalk between platelets, leukocytes, and endothelial cells [43]. Acute lung injury induces the production of proinflammatory cytokines such as IL-1β, TNFα, IL-6, and IL-8, which are expressed by alveolar macrophages, epithelial cells, fibroblasts, and endothelial cells [115, 116].

Galectins are a family of carbohydrate-binding proteins (lectins) that bind the carbohydrate portions of glycolipids and glycoproteins [117]. Galectins show high affinity for β-galactosides [118]. A positive inter-relation between galectins and proinflammatory cytokines [119]. Galectin-3 secretion is linked with stress responses, such as hypoxia, via activation of NF-κB but the mechanism is still uncertain [120]. Galectin-3 could be prognostic biomarker of AMI [121]. It may be possible to suppress the development of AMI by suppressing the secretion of Galectin-3.

Thromboxane A2 and COX-2

Considerable evidence shows that prostanoids - consisting of prostaglandins and thromboxanes (TXs) - are metabolites of arachidonic acid and synthesized by cyclooxygenases (COX-1 and COX-2) in macrophages [122, 123]. Therefore, COX-2 induces inflammatory responses, particularly the response associated with vascular inflammation [124, 125]. Prostanoids can have different - even opposing - effects on the promotion and resolution of inflammatory and immune responses [126]. Although cardiotoxicity associated with COX-2 inhibition had been shown by epidemiological studies, celecoxib and aspirin has been proved to be cardioprotective [127]. However, the COX-2 inhibitor celecoxib preserves COX-1's effects at therapeutic doses, and exerts insignificant effects on platelet aggregation and hemostasis [124]. It is now broadly accepted that celecoxib has suppress activities of COX-2 inhibitor [128, 129]. This disparity demonstrates that celecoxib reduces NF-κB expression in a COX-2-independent manner [130].

NF-κB, Thalidomide, and Celecoxib

Cardiovascular injury is closely related to dysregulated immune responses, including cytokine storm. Activated or dysregulated NF-κB plays a pivotal role in a cytokine storm [131]. Immunomodulatory drugs may improve the outcome of a cardiovascular injury, even without a combination of antiviral agents [132]. Thalidomide has been established to exert both an anti-inflammatory and an anti-oncogenic effect through the suppression of activated NF-κB [133-135]. Thalidomide exerts an immunomodulatory effect with the COX-2 inhibitor celecoxib and suppresses the production of proinflammatory cytokines through the inhibition of NF-κB by inhibiting the activity of the IκB kinase [136]. Thalidomide may be a powerful life-saving drug in severe cases of COVID-19 pneumonia. Proinflammatory cytokines enhance hypoxia and release HIF-1, which induces angiogenesis. Hypoxia itself leads to the production of inflammation cytokinase

[137]. Therefore, a combination of thalidomide and celecoxib may suppress the production of VEGF, bFGF, and COX-2, which are three vital mediators of angiogenesis [138].

Treatment of COVID 19

However, it is important to differentiate between an antiviral treatment and the prevention of cytokine storms that cause moderate-to-severe pneumonia and AMI in order to reduce the fatality rate [139]. The first option for the treatment of AMI by COVID-1 infection is thrombolysis. If thrombolysis fails, then a percutaneous coronary intervention should be considered [140]. The ultimate goal of pneumonia and AMI prevention and treatment strategies is to target the mediating pathogens that bind to TLRs and/or ACE2 and to select those agents that act on NF-κB.

Thalidomide and Celecoxib

A combination of thalidomide and celecoxib with a molecular weight of less than 350 mg can enter into cells and work directly on NF-κB and various downstream signaling pathways.

Conclusion

Cytokine storms are associated with inflammatory cytokines, resident cells, and inflammatory cells. NF-κB plays a vital role in cytokine storms. Thalidomide has been established to exert both an anti-inflammatory and an anti-oncogenic effect through the suppression of activated NF-κB. Therefore, large molecular agents more than 350 cannot enter the cell and could not suppress activated NF-κB.

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