Review Article

Implication effect of Probiotics and chemotherapy drugs in prohibition and remediation of lung carcinoma induced by COVID-19

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International Archives of Integrated Medicine, Vol. 10, Issue 12, December, 2023.
Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 21-11-2023 **Accepted on:** 30-11-2023
Source of support: Nil **Conflict of interest:** None declared.

How to cite this article: Masato Hada, El HadjiSeydou Mbaye, Muhammad Akram, Umme Laila, Momina Iftikhar, Sundus Saleem, Rida Zainab, FethiAhmet Ozdemir, WalaaFikry Elbossaty, Pragnesh Parmar. Implication effect of Probiotics and chemotherapy drugs in prohibition and remediation of lung carcinoma induced by COVID-19. IAIM, 2023; 10(12): 45-55.

Abstract

Patients with severe Covid-19 infection exacerbate their symptoms with IPF, more severe in various disorders as hypertension, obesity, diabetes mellitus, smoking intoxication, heart diseases finally resulting in respiratory failure and death. Underlying disorders are linked to gut microbiota especially to dysbiosis. An innate immune response is caused by environmental stimuli such as viral infection and smoking, and inflammation is triggered by pro-inflammatory cytokines. Inflammation drives angiogenesis in the process of development of inflammation with overproduction of cytokines and

growth factors. Pathogens, proinflammatory cytokines, and growth factors plays a central role in carcinogenesis between epithelial cells, myofibroblasts through NF-κB. Probiotics are live bacteria and yeasts such as the genus Lactobacillus and Bifidobacterium and lead beneficial effects against harmful microbes such as F. nucleatum in the gut that induce underlying diseases. Among the factors that have an effective role in the process of carcinogenesis is NF-κB, as it works on the rapid response to pathogenic stress, inflammation, angiogenesis and carcinogenesis. The suppression of unregulated or activated NF-κB is able to be the chemotherapeutic target with NF-κB inhibitors such as thalidomide and celecoxib. Especially patients with underlying diseases who experience COVID-19 infection-induced pulmonary fibrosis after several years or more might be predicted to have a higher probability of developing NSCLC, if not with proper follow-up and treatment with symbiosis and small molecular NF-κB inhibitors.

Key words

Covid-19 Infection, Idiopathic Pulmonary Fibrosis (IPF), Thalidomide, Celecoxib, Valproic Acid, Lung Carcinoma.

Introduction

The mechanism of lung damage by action of covid-19 infection remains unclear and incomprehensible. However, long term impairment of lung after COVID-19 pneumonia could be estimated from the prognosis of idiopathic pulmonary fibrosis (IPF) [1]. The repair process from organ injury is complex and dysregulation of this process contributes fibrosis [2]. It is possible to eradicate SARS-CoV-2, however removal of the cause of fibrotic irreversible interstitial lung disease is difficult [3]. IPF is defined to be the disorders of unknown origin [4]. However, it is comprised in inflammatory and fibrotic interstitial lung disease (ILD) [5]. Pathophysiologically, IPF is caused and exacerbate by acute and chronic inflammation promoted by pro-inflammatory cytokines.

Intriguingly, IPF is a risk factor for lung cancers and characterized by a bad prognosis and the armamentarium of drugs for their treatment is very poor. The major underlying cause of both diseases is made up of smoking and viral infections [4]. Fusobacteriumnucleatum (F. nucleatum) causes oral disorders such as gingivitis and periodontitis mutually cooperating with about 600 other oral microbes (species-level) [6]. Moreover, F.nucleatum has been shown to drive not only diseases of digestive tracts but also systemic disorders together with about 1000 microbes（species-level）in the gut [7, 8].

Symbiotic

There are several metabolites called short-chain fatty acids result from a complex interaction between gut microbiota, and dietary fibers and/or resistant starch [9].

Short chain fatty acids activate protein receptors, especially G protein-coupled receptors, in duodenal cells in a dose-dependent manner [10, 11]. SCFAs promote beneficial function of intestinal epithelial cells and immune cells intracellularly and /or extracellularly. Various inflammatory cytokines are produced in immune inflammatory cells that damage intestinal epithelial cells and cause intestinal and extra-intestinal symptoms [12].

Inabilities of the receptors induce irregulated inflammatory responses resulting in intestinal inflammation and epithelial barrier dysfunction [10, 13]. Short chain fatty acids are able to prevent the proliferation and migration of cancer cells in lung and colon cancer through the mechanism of programmed cell death [14]. Macrophagic cells play an important role in responding to the effects of microorganisms, as

there are two types pro-inflammatory (M1) and anti-inflammatory (M2) [15]. M2cells may perhaps be a beneficialgoal in treatment of inflammatory bowel disease and lung and colorectal cancer [12]. SCFAs, especially butylate, decrease pro-inflammatory cytokine expression through activated NFκB and IκBα degradation. Butyrate could also be also a therapeutic target [11, 16].

F. nucleatumis Gram-negative anaerobic bacillus and resides in the human mouth, gastrointestinal tract and elsewhere [17]. The etiologic role of F.nucleatum is associated with gastrointestinal diseases and extra-intestinal diseases [18]. Scientific research has confirmed that F. nucleatum has the ability to cause colon and rectal cancer by triggering the production of pro-inflammatory cytokines, which have the ability to angiogenesis and then the spread and division of cancer cells. Inflammatory responses promote chronic inflammation, angiogenesis and facilitate tumor formation and progression [19, 20]. Activated TLR4 /ACE2 by LPS or virus stimulates MyD88/ MAPK/ JNK pathway and leads to augmented migration , metastasis of lung carcinoma [21].

Underlying disorders (UDs) and Dysbiosis

Currently there has been considerable interest in hypertension, obesity, diabetes, heart diseases, and aging as UDs caused by dysbiosis. Endothelial dysfunction, vascular inflammation [22], arterial remodelling, atherosclerosis [23], and dyslipidemia [24] have been implicated in pathophysiological conditions of UDs [25]. UDs are linked to dysbiosis of gut microbiota that up-regulate pro-inflammatory cytokines. These cytokines cause chronic low-grade cytokine storm in cooperation with cytokines produced by COVID-19 pneumonia and exacerbate pulmonary fibrosis. Firmicutes/ Bacteroidetes ratio (F/B) ratio is used as a biomarker for dysbiosis and pathophysiological conditions [26].

Hypertension

Hypertension play a multifactorial clinical role in cardiovascular risk factors through chronic inflammation [27]. Significant decrease in microbial richness, diversity and an increased F/B ratio predict the possibility of hypertension [26].

There is considerable evidence that inflammatory cytokines are important mediators in formation of atherogenesis and promote endothelial dysfunction caused by deficiencies in NO level and prostacyclin and increased manufacture of ROS [27, 28]. ROS contribute in the initiation and progression the cardiovascular dysfunction, that is observed as symptoms of T2DM, hypertension and chronic heart failure [29]. ROS activate transcription factor NF-κB that promote to produce a majority of pro-inflammatory cytokines.

RAS expressed variety tissues and associated with atherosclerosis, cardiovascular diseases, T2DM and renal fibrosis [30, 31, 32]. Inhibitors of angiotensin converting enzyme (ACE) have protecting special effects against cardiac diseases. This effect has been described to be associated with T cell dependent IL-6 playing a pivotal role as a mediator of Angiotensin II (Angio II) induced thrombo-inflammation [32]. Angio II is most potent hypertensive octapeptidehormone that respond to AT1 receptor and AT2 receptor.

The major pathophysiological roles of AT1receptor are regulation of cardiovascular responses. AT1 receptor signaling triggers to increase the levels of cytokines in microenvironment. Fibroblasts play a pivotal role in immune response as stromal cells. There are different types from cytokines result from microenvironment. These cytokines are produced via NF-κB [33]. AT1 receptor pathway also promotes tumor relevant macrophage infiltration and induces tissue VEGF expression [34]. Chronic stimulation of the AT1 receptor leads to hypertension, cardiac arrhythmia, angiogenesis and cancer [35]. AT1 receptor blockers (ARBs)

are clinically used for the treatment of hypertension [36]. The role of RAS is to develop both physiologic and pathologic blood vessel growth [37]. AT1receptor is associate with tumor growth, angiogenesis and metastasis and an ACE inhibitor and AT1R blocker, clinically used as antihypertensive drugs, could be potent therapeutic options [38].

Obesity andT2DM

One of major metabolic diseases, T2DM, is characterized with high glucose level, disturbance in pancreatic functions. Dysbiosis alter repertoire of metabolites and exert significant diverse immune responses of the host. Metabolic diseases are accompanied with moderate rate of inflammation in tissues such as liver, adipose, muscles, and pancreatic islets [39]. Dysbiosis are characterized by beneficial genera such as Bacteroides, bifidobacterium, and Akkermansia, while genera of Ruminococcus, Fusobacterium and Blautia are classified as harmful microbes for T2DM [40]. Dysbiosis is regulated by a variety of environmental factors such as diet and pathogens. Pathogens play a major role in immune response of T2DM destructing pancreatic β-cells [41].

Obesity and T2DM could be defined as the disorders with chronic low-grade inflammation and insulin resistance [42]. Insulin/insulin-like growth factor (IGF), hyperglycemia and inflammatory cytokines are associated with cancer proliferation and apoptosis for all types of cancers except sexual organs cancers [43]. T2DM subjects have pro-inflammatory cytokines such as TNF-α and IL-6 much higher than healthy controls. Such cytokines promote cancer initiation through proinflammatory pathway in epithelial cells [44].

Aging

Aging is characterized to be chronic low-grade inflammatory state lead by pro-inflammatory cytokines [45, 46]. Tissue macrophage plays positive and negative roles in the inflammatory and immune response and in the stress response [46, 47]. Age-related macrophage function is closely related with the health of elderly. There is increasing evidence demonstrating the important roles of macrophages that are implicated in Toll-Like Receptor signalling, polarisation and phagocytosis [48].

LPS stimulates macrophages in binding to TLR4 and produce pro-inflammatory cytokines and cytotoxic nitric oxide through NF-κB [49]. Alveolar macrophages clear environmental dusts, pathogen and regulate alveolar surfactant by secretion of GM-CSF. White blood cells known as monocytes turn into macrophagesin response to inflammation [50].

Patients with COVID-9 exacerbate their condition resulting in cytokine storm both by pro-inflammatory cytokines produced by SARS-CoV-2 and by cytokines expressed by underlying disorders caused by dysbiosis. The chronic low-grade unnoticeable cytokine storm leads to chronic inflammation, angiogenesis and cancer initiation.

Idiopathic Pulmonary Fibrosis and Tumorigenesis

Acute inflammation usually plays a pivotal role in normal wound healing. When acute inflammation does not ameliorate, it turns into a chronic inflammation. This process induces non physiological wound repair, resulting in permanent fibrotic change that occur in any organ including the lung, skin, heart, kidney and liver [51]. One of the diseases that the elderly suffer from is pulmonary fibrosis of unknown cause, and this is accompanied by fibrosis of the pulmonary cells. Treatment depends on the use of radiation therapy for pneumonia [52].

The fibrosis is a sophisticated process by lung parenchymal cells, epithelial cells, endothelial cells and macrophages mediated by pro-inflammatory cytokines [51]. Pathogens and/or epithelial injuries leads to up-regulate a variety of cytokines that lead to epithelial dysfunction [53].

Fibroblasts play a central role in inflammation resulting in fibrosis and remodeling after lung injury triggered by COVID-19 infection [54]. The knowledge of cellular mechanisms in progressive lung injury has grown exponentially and IPF is a risk factor for lung cancer initiation [4]. Fibroblasts turn into cancer associated fibroblasts (CAFs) through pro-inflammatory cytokines secreted by inflammatory cells in the tumor microenvironment (TME) [55]. Cancer-associated fibroblasts (CAFs) exploit parenchymal cells and macrophage to facilitate promoting tumor cell growth, extracellular matrix remodeling, and angiogenesis, through pro-inflammatory cytokines [56, 57].

Disturbed epithelial–mesenchymal transition (EMT) induces fibrogenic factors such as VEGF, FGF and PDGF that promote the function of pulmonary fibroblasts resulting in trigger of cancer initiation [58, 59]. In many cancers, stromal cells including CAFs promote cancer progression in inflammatory TME with inflammation-stroma interactions through TNF-α and IL-1β [60, 61]. Crosstalk between pathogens, pro-inflammatory cytokines, and growth factors via NF-κB plays a central role in carcinogenesis of epithelial cells with myofibroblasts and macrophages [62, 63].

Activated NF-κBby COVID-19 pneumonia have effective role in proliferation cells through ACE2/MyD88 pathway, and in proinflammatory cytokines [64]. NF-κB could be the potential targets for therapy in cancer. Pulmonary carcinoma results in death within a few years after diagnosis despite chemotherapy targeting a variety of signal pathways [65].

The major underlying cause of ineffective chemotherapy is that the selection of drugs is not appropriate. Currently, drugs with low weight that performance in a straight line on activated NF-kB have not been used, however we have been using the small molecular drugs, thalidomide and celecoxib, for cancer treatment since 2000 [66].

The probability of IPF developing NSCLC is from 2.7% to 48%. Although there are large variations, it tends to be higher than general [58]. An innate immune response is caused by environmental stimuli such as viral infection and smoking, and inflammation is triggered by pro-inflammatory cytokines. Inflammation drives angiogenesis in the process of development of inflammation with overproduction of cytokines. Crosstalk between pathogens, pro-inflammatory cytokines, and growth factors via NF-κB plays a central role in carcinogenesis of epithelial cells with myofibroblasts and macrophages [62, 63].

Epigenesis

Epigenetic alterations have been implicated in pulmonary fibrosis through histone acetylation or deacetylaion, that is well-ordered by HATs and HDACs. HATs and HDACs cause structural modification of chromatin, and HDACs promote chromatin condensation and suppress gene transcription [2, 64]. The HDACs super family is play an important role in inflammation, especially HDAC 3 has a pro-inflammatory role [65, 66, 67]. HDCAs performance a major role in the balance of inflammatory response by regulation of histone acetylation of NF-κB and AP-1. Smoking inhibits HDAC function, and thereafter inducing pro-inflammatory gernes through NF-κB resulting in production of ROS that exacerbate pulmonary diseases [68].

Valproic acid is a potent HDAC inhibitor [69] belonging to the short-chain fatty acids showing the antitumor effects by acting on class I and IIa HDACs [70].

Prevention and Treatment of IPF

The poor outcomes in the COVID-19 patients are closely related to ACE2 receptors and dysbiotic gut microbiota that induce to express a great amount of pro-inflammatory cytokines resulting in severe pulmonary fibrosis. Suppression of activated NF-κB of both lung epithelial cells and gut microbiota is important. The loss of lung epithelial cell function leads the patients to lethal outcomes without oxygen permeability [71].

Although lung cancer cells in IPF can be eliminated by NF-κB inhibitors, it is impossible to recover lung epithelial function. Therefore, it is important use NF-κB inhibitors as soon as the onset of lung fibrosis is confirmed because lung epithelial cells cannot be regenerated [66].

Brain Metastases from Lung Cancer

Thalidomide, celecoxiband cytotoxic agents are able to destroy or control active cells such as cancer cells. However, once damaged pulmonary epithelial cells cannot survive. They are images for confirmation.

Drugs for Prevention as well as Treatment of IPF and NSCLC

Scientific research has proven the ability of the gut microbiota to control the resistance of malignant cells to toxic agents. However, this condition requires a balance of prebiotics, microbiota, and berberine [72].

Probiotics

Probiotics are microorganisms beneficial to human health. They include Lactobacillus and Bifid bacterium. Studies have shown that probiotics have a strong anti-inflammatory and anti-cancer effect [29, 73, 74, 75].

Prebiotics

Leaving fatty acids for a long time leads to its fermentation, and thus leaves it producing many secondary metabolite compounds, as these substances act as HDAC inhibitors, thus modifying induction and immune stimulation [74]. Synbiotics (probiotica and prebiotics) play preventive and therapeutic role in various diseases such as tissue fibrosis, cancer and allergy [73, 76].

Berberine

Berberine is one of the Japanese herbs used to treat diarrhea. It has an effective effect in terms of. This is through the activation of AMP-activated protein kinase, and the inhibition of NF-κ [77-80].

Thalidomide

Thalidomide is a powerful immunomodulatory agent. It works to stop the growth of cells, inhibiting [81, 82].

Celecoxib

The rate of COX-2 increases in lung cancer cells caused by the street. The rate also increases in some amazing pathological conditions. As the COX-2 oil has been placed in order to reduce the levels of antioxidants, or the thickness of the resin, I have a job [83].

Valproic acid

Short mental acid, works to protect tissues. It works to inhibit the activity of, HDAC

Alone, or with other medicines that are used in the field of birds [84].

Conclusion

The ultimate goal is to avoid viral binding to the ACE2 receptor, prevent the growth of COVID-19 in lung epithelial cells, and prevent IPF. Then select and use drugs that act on transcription factors such as tissue fibrosis, cytokine storms, and carcinogenesis-promoting NF-kB as soon as possible.

1. Thalidomide induced in low does

Thalidomide (200 mg/day); celecoxib (400 mg/day)

2. Epigenetic agents: Valproic acid (600 mg/day)
3. Suppress the production of pro-inflammatory cytokines in the intestine, especially, with berberine. Berberine 100-300 mg/day p.o

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