Cytokine and Growth Factor Reviews 53 (2020) 63–65

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Acute inflammation and pathogenesis of SARS-CoV-2 infection: Cannabidiol as a potential anti-inflammatory treatment?

1. Acute inflammation and pathogenesis of SARS-CoV-2 infection

SARS-CoV-2 is a new beta coronavirus first reported in China with a 14-day incubation period [1]. Infected persons may be either asymptomatic carriers, during which time they can transmit the virus to others [2], or develop mild disease involving cough and rhinitis, with or without mild pneumonia. In severe disease, persons develop dyspnea and hypoxia, accompanied by patchy infiltrates on chest x-ray within a few days. Individuals with severe infection by SARS-CoV-2 can also develop acute respiratory distress syndrome (ARDS). Other symptoms include fatigue, anorexia, myalgias and diarrhea [3]. In a proportion of individuals, critical illness develops and is characterized by respiratory failure, shock and multi-organ dysfunction [4]. Mortality estimates vary based on the study population examined, with mortality among persons requiring mechanical ventilation as high as 88% [4]. Severe illness has been seen in otherwise healthy persons of any age, but is most frequent in persons of advanced age with comorbidities such as cardiovascular and respiratory diseases and diabetes [4].

SARS-CoV-2 infects types I and II pneumocytes via its receptor angiotensin converting enzyme (ACE)2 which is also the main receptor for SARS-CoV [1,5,6]. Under healthy circumstances, bronchoalveolar lavage fluid is made up of predominantly alveolar macrophages (< 80%) and lymphocytes (~10–20%) [7]. Alveolar macrophages police the lungs for pathogens, eliminate senescent cells, engage in reparation of damaged tissue and enhance T-cell specific responses [8]. In addition, macrophages also facilitate neutrophil recruitment which contributes to pathogen clearance and further attraction of inflammatory cells [9,10]. Some coronaviruses including MERS-CoV [11], SARS-CoV [12], HCoV-229E [13] and HCoV–OC43 [14] can infect human macrophages and induce pro-inflammatory cytokine secretion. Although ACE2 in pulmonary tissues is expressed mainly by type I and II pneumocytes [15], not only alveolar macrophages, but also tissue-resident $CD169^+$ macrophages in spleens and lymph nodes, can be infected by SARS-CoV-2 [16–18]. Importantly, SARS-CoV-2 results in hyper-activation of lung macrophages as well as massive infiltration of pro-inflammatory monocyte-derived macrophages (MDMs) into small airways [19,20]. In lethal SARS-CoV infection of mice, disease progression depends on infiltration to the lungs of monocytes which produce interleukin (IL)-6, IL-1β and Tumor necrosis factor (TNF)-α [21]. Acute macrophage activation initiates a massive pro-inflammatory response including IL-6 and IL-1β which mediate the recruitment of neutrophils and cytotoxic CD8 T-cells into the lungs mucosal tissues [9]. Transcriptomic analysis, in addition to cytokine quantification in plasma and bronchoalveolar lavage fluid from SARS-CoV-2 patients demonstrate tremendous amounts of various cytokines, chemokines and soluble inflammatory mediators including tumor TNF-α, IL-6, IL-1β, IL-2R, IL-8, inducible protein (IP)-10, C-reactive protein and D-dimer [22,23], which culminates in a cytokine storm. In contrast to SARS-CoV, which is believed to elicit suboptimal interferon (IFN) responses, SARS-CoV-2 activates expression of many IFN-inducible genes having increased capacity for pathogenesis. Moreover, genes implicated in inflammation are over-represented [24]. Furthermore, increased expression of chemokines critical for recruiting neutrophils (CXCL17) and monocytes (CCL2, CCL7) into the lungs is observed [24].

T-cells also play an important role in lung mucosal immunity. During SARS-CoV and MERS-CoV infections, airway memory CD4 T-cells induce protection via the production of IFN-γ [25]. In SARS-CoV and MERS-CoV a rapid, specific memory CD8 T-cell response is needed to guard against infection [25,26]. In addition, SARS-CoV infection induces a potent and long-lived T-cell response in humans [27]. However, severe SARS-CoV-2 infection results in CD4 and CD8 T-cell lymphopenia and decreased INF-γ-producing T-cells [22,28]. Meanwhile, hyper-activation of both CD4 and CD8 T-cells ($HLA\text{-}DR^+CD38^+$ co-expression), an increase in CD8 T-cell cytotoxic granules, and increased frequencies of pro-inflammatory $CCR6^+$ Th17 cells have been recently reported in SARS-CoV-2 patients [29].

2. Cannabidiol to decrease SARS-CoV-2 associated inflammation

Cannabidiol (CBD) is a phytocannabinoid with various clinical applications and has proven efficacy for certain medical conditions, along with a favorable safety and tolerability profile [30,31]. Furthermore, unlike Δ9-tetrahydrocannabinol (THC), CBD does not induce any psychotropic effects, also making it desirable for therapeutic applications [32]. Cannabinoids can suppress immune activation and inflammatory cytokine production [32], suggesting their potential for tempering excessive inflammation. Endocannabinoid receptors include CB1 and CB2. CB1 has higher expression in the central nervous system and a lesser expression on peripheral tissues, including the lungs [33]. Airway epithelial cells respond to both CB2 receptor-dependent and independent effects of cannabinoids [34]. CB2 is expressed by varieties of immune cells including circulating lymphocytes, monocytes and tissue mast cells and in lymphoid tissues [33,35]. Activation of CB2 receptor can suppress release of inflammatory IL-1, IL-6, IL-12 and TNF-α [36]. Constitutive production of endocannabinoids occurs by human lung resident macrophages, which is protective in acute and chronic inflammation, mostly via CB2 receptors [37]. Importantly, human lung resident macrophages also express both CB1 and CB2 receptors [38]. Agonists of CB2 have been shown to inhibit TNF-α from $CD14^+$ monocytes and M1 macrophages, and increase expression of anti-inflammatory cytokine IL-10 [37]. CB2 agonists also induce anti-inflammatory $FoxP3^+$ regulatory T-cells (Tregs) which produce TGF-β and IL-10 [39]. In addition, CBD has been shown to induce the differentiation of functional immunosupressive Tregs [40].

In murine models of lung injury, CBD reduced lipopolysaccharide (LPS)-induced acute pulmonary inflammation [41,42]. In rat models of

https://doi.org/10.1016/j.cytogfr.2020.05.008
Received 14 May 2020
Available online 20 May 2020

experimental asthma, CBD treatment reduced airway inflammation, as well as levels of serum IL-4, IL-5, IL-13, IL-6 and TNF-α, which are implicated in airway inflammation and fibrosis in asthma [43,44]. Moreover, CBD was able to directly suppress T-cell secretion of IL-1 and IFNγ [45]. In piglets with hypoxic-ischemic lung damage, CBD reduced histologic damage, decreased leukocyte infiltration and modulated IL-1 concentration in bronchoalveolar lavage fluid [46], while in a rat model of sepsis, CBD reversed oxidative stress and reduced mortality [47]. In humans, cannabinoid use prevented induction of pro-inflammatory $CD16^+$ monocytes and production of IP-10, suggesting anti-inflammatory effects in humans [48]. In another human study, in addition to reduction of pro-inflammatory monocytes, heavy cannabis use was also associated with decreased frequencies of $HLA\text{-}DR^+CD38^+$ activated CD4 and CD8 T-cells and frequencies of IL-10, IL-12 and TNF-α -producing antigen presenting cells compared to non-cannabis users [49]. The anti-inflammatory effects of cannabinoids are now under investigation in clinical trials, as such, our team in now conducting a clinical trial in the context of HIV infection [50].

Therefore, as SARS-CoV2 induces significant damage through pro-inflammatory cytokine storm mediated by macrophages and other immune cells and based on the fact that CBD has broad anti-inflammatory properties, CBD might represent as a potential anti-inflammatory therapeutic approach against SARS-CoV2-induced inflammation. In this regard, first a deeper understanding of the specific effects of SARS-CoV2 on human macrophages and T-cell physiology and immunological functions is needed. As CBD is already a therapeutic agent used in clinical medicine and has a favorable safety profile, the results of *in vitro* and animal model proof-of-concept studies would provide the necessary supporting evidence required before embarking on costly and labor-intensive clinical trials.

Declaration of Competing Interest

Tilray Inc. will provide study medication for use in a clinical trial the authors will be conducting on safety, tolerability and efficacy of cannabinoids in people living with HIV (CIHR Canadian HIV Trials Pilot Study 028). There are no conflict of interests to declare regarding the publication of this specific paper and no funding was received for its preparation.

Acknowledgement

CTC holds a *Fonds de recherche du Québec-Santé* (FRQ-S) Junior 1 research salary award. MAJ holds the CIHR Canada Research Chair tier 2 in Immuno-virology.

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