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BRIEF COMMUNICATION

NF-κB signalling as a pharmacological target in COVID-19: potential roles for IKKβ inhibitors

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Abstract

Coronavirus disease 2019 (COVID-19) has been characterized by lymphopenia as well as a proinflammatory cytokine storm, which are responsible for the poor prognosis and multiorgan defects. The transcription factor nuclear factor-κB (NF-κB) modulates the functions of the immune cells and alters the gene expression profile of different cytokines in response to various pathogenic stimuli, while many proinflammatory factors have been known to induce NF-κB signalling cascade. Besides, NF-κB has been known to potentiate the production of reactive oxygen species (ROS) leading to apoptosis in various tissues in many diseases and viral infections. Though the reports on the involvement of the NF-κB signalling pathway in COVID-19 are limited, the therapeutic benefits of NF-κB inhibitors including dexamethasone, a synthetic form of glucocorticoid, have increasingly been realized. Considering the fact, the abnormal activation of the NF-κB resulting from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection might be associated with the pathogenic profile of immune cells, cytokine storm and multiorgan defects. Thus, the pharmacological inactivation of the NF-κB signalling pathway can strongly represent a potential therapeutic target to treat the symptomatology of COVID-19. This article signifies pharmacological blockade of the phosphorylation of inhibitor of nuclear factor kappa B kinase subunit beta (IKKβ), a key downstream effector of NF-κB signalling, for a therapeutic consideration to attenuate COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Inflammation · NF-kB · IKKβ inhibitors

At present, the persistent occurrence of obvious clinical symptoms like fever, dry cough, headache, fatigue, anosmia and hypogeusia along with abnormal inflammatory profile and prominent pulmonary dysfunction resulting from the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has been designated as coronavirus disease 2019 (COVID-19) (Li et al. 2020b; Huang et al. 2020; Kandasamy 2020). The clinical manifestation of COVID-19 appears to be highly comorbid and differs from person to person depending on the viral load, ethnicity, immunity, health status and lifestyle (Goldstein 2010; Guan et al. 2020; Vishnevetsky and Levy 2020). Though the scientific knowledge on the pathological consequences of COVID-19 has gradually been improving at biochemical, physiological, immunological, neurological and genetic aspects, its overall burden of comorbidity and pathogenicity leading to multiorgan defects and mortality is yet to be fully revealed (Zhou et al. 2020; Li et al. 2020a; c; Kandasamy 2020). Recently, elevated levels of proinflammatory molecules in the circulation have been reported as the key pathogenic hallmark of COVID-19 (Mehta et al. 2020; Coperchini et al. 2020; Nile et al. 2020). In general, inflammation refers to an intricate biological response of the human body towards any sort of pathogenic stimuli in which the cellular components of the immune system are highly activated (Chen et al. 2017). Notably, the replication and functions of the immune cells are pathogenically triggered to secrete proinflammatory factors to counteract the harmful substances or pathogens including viruses (Chaplin 2010). However, such an immune response of the body needs to shortly be neutralized, and if not, the chronic inflammatory process will lead to unexpected adverse effects (Lawrence and Gilroy 2007). While vaccination can be an ultimate way to prevent the known viral diseases, an insight

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into the pathogenic molecular pathways elicited as a consequence of SARS-CoV-2 infection, and identification of the potent pharmacological targets are also highly important.

COVID-19 has been characterized by lymphopenia, a haematological condition with reduced lymphocyte count, and cytokine storm in the circulation, especially in severe cases and elderly population (Del Valle et al. 2020; Coperchini et al. 2020; Kandasamy 2020; Zhao et al. 2020). The degree of lymphopenia has been proposed to influence the severity of the disease and recovery rate (Huang and Pranata 2020). Recently, immune cell profiling studies in the blood samples of COVID-19 patients revealed the depletion of the $CD4^+$, $CD8^+$ T cells and natural killer cells, thereby accounting for the occurrence of lymphopenia (Chen and John Wherry 2020; Zheng et al. 2020). However, some studies have indicated the evidence for the activation of the circulating $CD4^+$ and $CD8^+$ T cells in COVID-19 patients (Chen and John Wherry 2020; Mathew et al. 2020). Abnormal activation of T cells followed by their depletion have been identified as the key course of immunological response in many viral infections, while the circulating surplus number of viral pathogens can provoke other types of leukocytes (Del Valle et al. 2020; Mathew et al. 2020; Yang et al. 2020). As a result, abnormal activation and increased number of monocytes, neutrophils, macrophages, plasma cells, T helper (Th) cells 1 and 17 in the circulation as well as in many organs including the lungs have been increasingly evident in COVID-19 (Cascella et al. 2020; Mathew et al. 2020; Huang et al. 2020). The activated myelogenous cells in the circulation represent the potential basis of the hyperinflammatory feature in COVID-19 (Park 2020). Also, abruptly elevated levels of a large number of proinflammatory factors such as tumour necrosis factor (TNF)-α, interferon (IFN)-γ and vascular endothelial growth factor (VEGF) have been known to elicit detrimental effects in COVID-19 (Li et al. 2020c; Zhang et al. 2020). Additional studies suggest that elevated levels of interleukins like IL-1β, IL-6, IL-12 and IL-18 also play a major role in the pathogenicity of COVID-19 (Del Valle et al. 2020; Li et al. 2020c). Moreover, the outcome of the assessment of biochemical parameters in blood from individuals with COVID-19 revealed increased levels of many innate immune cytokines including interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP1) and macrophage inflammatory protein-(MIP)1α (Li et al. 2020c; Chi et al. 2020). Besides, elevated levels of transforming growth factor (TGF)-β, a prominent initiator and mediator of the inflammation, have been reported to be associated with the pathogenesis of COVID-19 (Chen 2020). Taken together, the unregulated downstream signalling pathways resulting from various proinflammatory molecules have been proposed as the underlying basis of multiorgan dysfunctions in COVID-19. Thus, constitutively active inflammatory signalling pathways have been considered as the potential molecular targets to address the mulitiorgan dysfunctions and damages in COVID-19. However, a collective blockade of the aforementioned cytokines may be highly challenging to mitigate pathogenic inflammation in COVID-19. Thus, the expedition of a centralized molecular axis that conjointly regulates the expression and function of the overlapping inflammatory factors has become a scientific quest.

Initial experimental evidence for the presence and immunogenic roles of nuclear factor kappa B (NF-κB) in plasma cells has been established by Ranjan Sen, David Baltimore and colleagues in 1986 (Singh et al. 1986; Sen and Baltimore 1986a, b). NF-κB is a family of highly conserved dimeric transcription factors that include Rel-like domain-containing proteins p65/RelA, RelB, c-Rel, NF-κB1 and NF-κB2 (Oeckinghaus and Ghosh 2009). Among them, NF-κB1 and NF-κB2 are produced as latent forms, namely p105 and p100 (Oeckinghaus and Ghosh 2009). The p105 and p100 are proteolytically cleaved to generate their active forms p50 and p52 respectively (Oeckinghaus and Ghosh 2009; Nagel et al. 2014). The activation and functions of NF-κB have been known to be modulated by a family of proteins known as IκBs which include IκBα, IκBβ, IκBγ, IκBε and Bcl-3 (Oeckinghaus and Ghosh 2009; Wan and Lenardo 2009). In general, the NF-κB signalling involves the phosphorylation and degradation of the IκB kinase beta (IKKβ), thereby leading to the liberation of the p50 and p65 dimers (Karin 1999; Lawrence 2009; Liu et al. 2017) (Fig. 1). Subsequently, these subunits translocate into the nucleus where they act as potential transcriptional factors to regulate an array of genes responsible for various functions including inflammation (Karin 1999; Lawrence 2009). While the basal expression of NF-κB has been recognized in various cell types, abnormal activation of its downstream signalling components upon various pathogenic stimuli such as stress hormones, radiation, free radicals and microbial pathogens has been clearly evident (Oeckinghaus and Ghosh 2009; Lawrence 2009). Ample experimental evidence demonstrated that many essential genes have the binding site for NF-κB in their upstream regions (Oeckinghaus and Ghosh 2009; Wan and Lenardo 2009; Brignall et al. 2019). Hence, NF-κB has widely been recognized as a master regulator of various signalling cascades that are involved in the development, cellular physiology, neuroplasticity, cell survival mechanisms and immunological functions (Mattson and Camandola 2001; Oeckinghaus and Ghosh 2009; Lawrence 2009). The NF-κB signalling is important for the development of secondary lymphoid organs and it further aids in the production and activation of immune cells upon inflammation and infection of microbial pathogens (Alcamo et al. 2002; Oeckinghaus and Ghosh 2009; Lawrence 2009). Dysregulation of NF-κB signalling has been identified as a distinguished pathogenic molecular signature of immunological disorders, inflammations, metabolic diseases and progression of

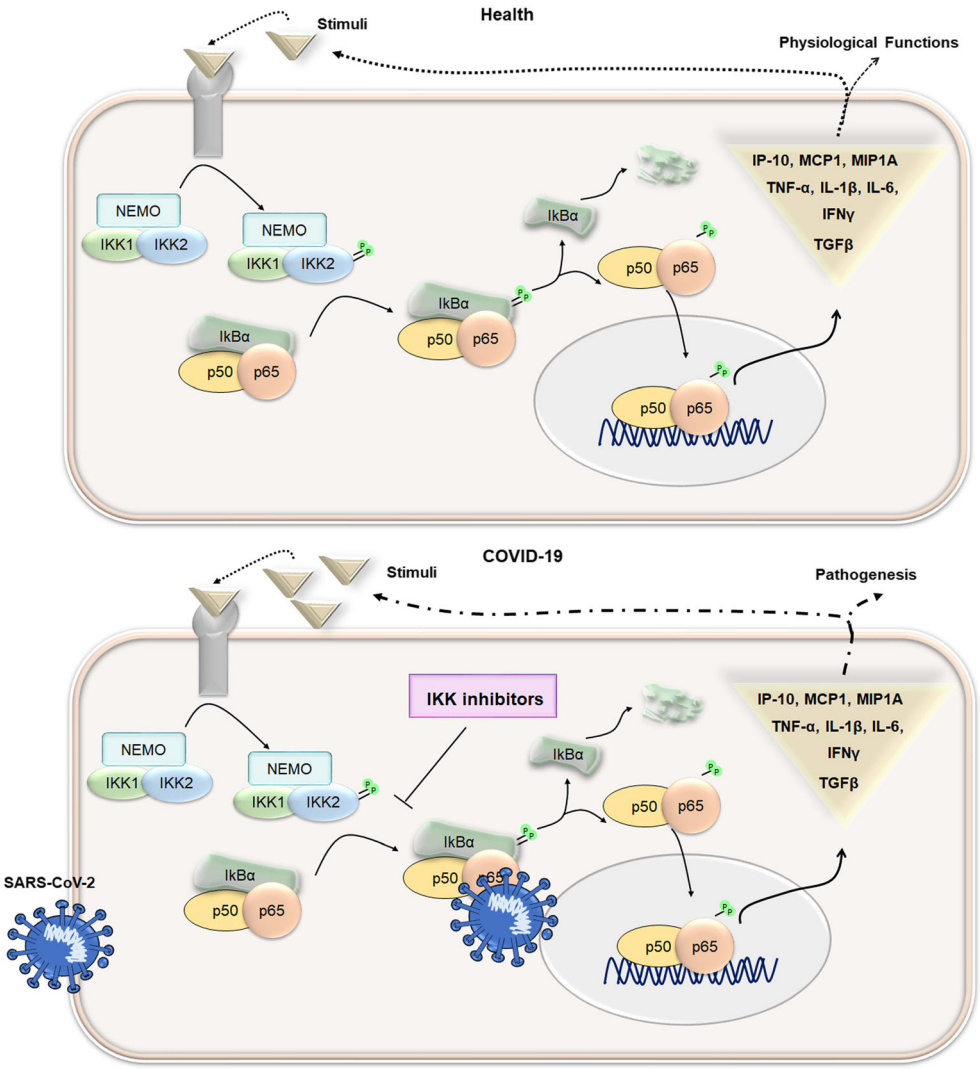

Fig. 1 Digital illustration of the NF-κB signalling pathway in healthy and COVID-19 condition in association with proinflammatory factors

neurodegenerative disorders (Mattson and Camandola 2001; Kumar et al. 2004; Lawrence 2009). With reference to the inflammatory processes noticed in different pathological situations, NF-κB appears to be activated by various cytokines, interleukins and microbial toxins including TNFα, IL1β and lipopolysaccharides (LPS) respectively (Liu et al. 2017; Andreakos et al. 2004). Besides, NF-κB has also been known to be induced by and synchronized with IFNγ-mediated signal transducers and activators of transcription (STAT) and TGFβ (Sizemore et al. 2004; Freudlsperger et al. 2013). Notably, the NF-κB signalling cascade has also been known to be abruptly triggered by viral infections (Santoro et al. 2003). Especially, the invasion of the RNA viruses has been known to be associated with prominent elevation of NF-κB mediated inflammasomes through the TNF receptor–associated factor 2 (TRAF2) cascade (Schmitz et al. 2014). However, potential pathogenic stimulants of NF-κB signalling and overlapping molecular networks with its downstream effectors are highly multifactorial and complex. Thus, understanding the definitive roles and functions of the NF-κB signalling along the inflammatory process in human diseases has been an important field of research focus.

The activated NF-κB signalling cascade has been known to induce the abnormal expression of proinflammatory factors that include its activators such as TNFα, IL1β, IFNγ and TGFβ (Lawrence 2009; Freudlsperger et al. 2013; Liu et al. 2017) (Fig. 1). Furthermore, NF-κB has been reported to mediate the generation of reactive oxygen species (ROS), thereby accounting for the induction of cellular oxidative stress and cell death pathways in different types of tissues (Morgan and Liu 2011). Notably, the involvement of abnormal NF-κB signalling in lung fibrosis and neurodegeneration has been highly recognized (Mattson and Camandola 2001; Tian et al. 2017). With reference to the treatment options of COVID-19, many drugs have been implemented to manage the clinical symptoms and reduce the mortality rate (McKee et al. 2020; Md Insiat Islam Rabby 2020; Zhou et al. 2020; Kandasamy 2020). Among them, the therapeutic use of dexamethasone has been

known to provide an impressive recovery rate in patients with COVID-19 (Kaddoura et al. 2020; Tomazini et al. 2020). Dexamethasone is a therapeutic form of corticosteroid that has widely been used to reduce fever and block the release of proinflammatory molecules in various clinical conditions (Bunim et al. 1958; Barnes 2006; Ramamoorthy and Cidlowski 2016). Many clinical trials have revealed that the treatment regime of dexamethasone provides potential cure even for COVID-19 patients in critical condition and drastically decreases mortality rate (Tomazini et al. 2020; RECOVERY Collaborative Group et al. 2020; Budhathoki et al. 2020). Dexamethasone has been reported to have the ability to repress the expression of many proinflammatory factors including TNF-α, IL-1β, IFN-γ and TGF-β that are known to be elevated in COVID-19 (Shepherd et al. 1994; Bessler et al. 1999; Jang et al. 2013; Russell et al. 2020). Moreover, dexamethasone has been known to upregulate IκBα, a potent blockade of the NF-kB signalling (Auphan et al. 1995; Scheinman et al. 1995; Oeckinghaus and Ghosh 2009). Besides, dexamethasone has been reported to obstruct the nuclear translocation of p65 (Scheinman et al. 1995; Yamamoto and Gaynor 2001). Considering the aforementioned facts, the dexamethasone-mediated therapeutic benefits seen in COVID-19 conditions might be largely due to the inhibition of NF-κB signalling. While the aberrant NF-κB signalling has been reported during the previous outbreak of SARS-CoV, its activation can also be associated with the ongoing SARS-CoV-2 mediated cytokine storm and tissue damage (Liao et al. 2005; DeDiego et al. 2014; Hirano and Murakami 2020). Thus, NF-κB can unequivocally be considered as a potential druggable target to combat COVID-19. Therefore, identification and proper implementation of potential NF-κB inhibitors might be of great therapeutic aid for the effective management of COVID-19 regardless of the proposed vaccinations against SARS-CoV-2.

The primary downstream effectors of the NF-κB are the complex of three subunits namely, IKKβ, IKKα and NF kappa B essential modulator (NEMO) (Solt and May 2008; Oeckinghaus and Ghosh 2009). Among them, the phosphorylation of IKKβ followed by its degradation plays a significant role in the activation of NF-κB signalling pathways (Santoro et al. 2003; Gilmore and Herscovitch 2006; Oeckinghaus and Ghosh 2009; Lawrence 2009; Liu et al. 2017) (Fig. 1). Thus, the prevention of phosphorylation of IKK-β has been regarded as a key step to inactivate NF-κB in providing therapeutic benefit against many diseases that cause inflammation. A large number of pharmacological inhibitors have been identified to block the phosphorylation of IKK-β including PS-1145, SAR113945, IKK-16, TPCA-1, BAY11-7082, BAY11-7085, SC-514, TBK-1, ML-120B, BMS-345541,vinpocetine and resveratrol (Gilmore and Herscovitch 2006; Jeon et al. 2010; Bhatti et al. 2019; Ren et al. 2013). PS-1145 has been reported to prevent TNFα-induced phosphorylation of IKK-β and minimize the abnormal proliferation and migration of carcinoma cell lines through the suppression of activation of IL-6 (Yemelyanov et al. 2006). Inhibition of the NF-κB signalling by SAR-113945 has been reported to be highly beneficial in the treatment for arthritis as it suppresses the expression of TNFα and prostaglandins (Grothe et al. 2017). Importantly, IKK-16 has been recognized to be a highly efficient antagonist of NF-κB and rescue multiple organ dysfunction in the preclinical models of sepsis through the activation of the endothelial nitric oxide synthase (eNOS) pathway (Coldewey et al. 2013). TPCA-1 appears to impede both the NF-κB and STAT signalling pathway and is beneficial to attenuate the TNF-α mediated inflammation (Bhatti et al. 2019). BAY11-7082 and BAY11-7085 have been identified as potent NF-κB inhibitors. While BAY11-7082 displays a wide range of anti-inflammatory action, BAY11-7085 has been known to block peroxisome proliferator–activated receptor gamma (PPAR-γ)–induced pathogenesis (Lee et al. 2012; Relic et al. 2016). Likewise, SC-514, TBK-1, ML1-20B and BMS-345541 are recognized to be efficient inhibitors of NF-κB as they act against LPS mediated inflammatory responses and are involved in the knockdown of abnormal IL-1β expression (Tan et al. 2016). Vinpocetine has been ascertained as a potent anti-inflammatory drug, while it has also been identified to inactivate the NF-κB signalling (Jeon et al. 2010). Resveratrol has been shown to exert beneficial effects against various pathological conditions. Resveratrol in combination with curcumin has been known to suppress the abnormal NF-κB signalling leading to a decrease in the expression of TNF-α, IL-1β, IL-6 and COX-2 (Ren et al. 2013). Recently, therapeutic botulinum neurotoxin (BoNT) has been proposed as a treatment option for COVID-19 (Kandasamy 2020). Clinical significance of a low dose of BoNT has been recognized against many human diseases with inflammation (Yoo et al. 2014; Kandasamy 2020). While there exists ample evidence that BoNT reduces the expression of TNF-α, IL-1β and other proinflammatory cytokines (Kim et al. 2015; Zychowska et al. 2016; Kandasamy 2020), inhibition of NF-κB signalling pathway by BoNT has increasingly been evident (Piotrowska et al. 2017). Taken together, this article supports the idea that the therapeutic form of BoNT might directly or indirectly involve in the suppression of IKKβ phosphorylation in order to yield its beneficial effects against many diseases. In conclusion, the pharmacological knockdown of NF-κB signalling might represent as a disease-modifying strategy to combat the severity of COVID-19 (Fig. 1).

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Author contribution M.K. developed the concept, made literature search, wrote the manuscript and prepared the digital illustrations.

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Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

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The author declares that all data were generated in-house and that no paper mill was used.