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SARS-CoV-2 infection: NLRP3 inflammasome as plausible target to prevent cardiopulmonary complications?

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Abstract. – NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome has recently become an intriguing target of several chronic and viral diseases. Here, we argue that targeting NLRP3 inflammasome could be a strategy to prevent cardiovascular outcomes [fulminant myocarditis, heart failure, venous thoromboembolism (VTE)] and acute respiratory distress syndrome (ARDS) in patients with SARS-CoV-2 infection. We discuss the rational for NLRP3 targeting in clinical trials as an effective therapeutic strategy aimed to improve prognosis of COVID-19, analyzing the potential of two therapeutic options (tranilast and OLT1177) currently available in clinical practice.

Key Words:
NLRP3, COVID-19, SARS-CoV-2, Myocarditis, Cytokines, Venous thoromboembolism.

Introduction

Incidence and mortality of pandemic Coronavirus disease 2019 (COVID-19) is constantly growing globally. To date of writing, over 13,6 million total cases are ascertained, with over 593,000 deaths[1]. Pending the vaccine, many drugs are being used in clinical trials to reduce COVID-19 mortality, including cytokine-blocking agents (monoclonal antibodies against Interleukin-1 or Interleukin-6), remdesivir, hydroxychloroquine, azithromycin. Here, we highlight on NLRP3 inflammasome as a considerable therapeutic target, being upstream of cytokine storm causing multi-organ failure in COVID-19, including myocarditis, venous thromboembolism (VTE), hypertension and acute respiratory distress syndrome (ARDS). SARS-CoV-2, an enveloped and non-segmented RNA based virus, is the etiological agent of Coronavirus disease 2019 (COVID-19)[2]. The main causes of death are cardiovascular diseases (mainly VTE, fulminant myocarditis, myocardial infarction) and ARDS[3]. Clinical characteristics of patients with COVID-19 clearly identified a cytokine storm, secondary to the interaction of SARS-CoV-2 with human cells expressing angiotensin converting enzyme-2 (ACE2), an integral (type I) membrane zinc metallopeptidase widely expressed in heart, lungs, esophagus, kidneys, bladder and small intestine[4].

NLRP3 as Potential Target in COVID-19

NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) is a macromolecular complex having a key role in the genesis of acute and chronic inflammatory processes, like cancer, diabetes, virus infection, and cardiovascular diseases[5]. Its role is based on the triggering of defense mechanisms against external agents and involves several pro-inflammatory cytokines modulating cell metabolism and cell mediated immunity. NLRP3 form a multi-molecular complex, termed an "inflammasome", that results in NOD-like receptor oligomerization, caspase-1 activation and

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enzymatic release of IL-1β and IL-18, which contribute to T cell activity[6]. For several virus-related diseases and SARS-CoV-2, NLRP3, in concert with MyD88 and NF-kB, drastically increased the production of pro-inflammatory and atherogenic cytokines inducing multi-organ failure, such as IL1-β, IL-6, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α, and VEGF[7].

SARS-CoV-2 infection, as other viral-related diseases, leads to secondary haemophagocytic lymphohistiocytosis (sHLH), a multi organ hyperinflammatory condition driven by cytokines[8]. sHLH induces hyperactivation of cytotoxic T lymphocytes, macrophages and natural killer cells, leading to multiorgan failure (including myocarditis and coronary artery aneurysm) and consequently to death. Although pathogenesis of sHLH is not well understood, in patients with sHLH monoallelic mutations or polymorphisms they have been detected in genes involved in cytokine production and signaling, such as NLRP3, other inflammasome proteins and toll like receptors[9]. Since sHLH is common in rheumatoid arthritis and viral infections, target therapy with anti-cytokine agents and NLRP3 could be considerable therapeutic strategies against SARS-CoV-2-induced sHLH.

NLRP3 Inhibitors: Therapeutic Options Currently Available in Clinical Practice

Inhibition of NLRP3 has been successfully studied in chronic inflammatory diseases, including rheumatoid arthritis, severe gout, cardiovascular diseases and ARDS[10]. Activation of the NLRP3 inflammasome exacerbates immunity response and mediates further cellular apoptosis, necrosis and fibrosis, as well as events of VTE[11]. Two therapeutic options are currently available in clinical seeing: tranilast (N-[3′,4′-dimethoxycinnamoyl]-anthranilic acid) and dapansutrile (OLT1177) both acting as direct NLRP3 inhibitors. Tranilast, a tryptophan metabolite, has demonstrated significant therapeutic and preventive outcomes in mice models of gout, Cryopyrin-Associated Periodic Syndrome, and Type-2 diabetes[12]. In another preclinical study[13] in pigs tranilast reduced ARDS and acute lung injury preventing pulmonary and airway vascular permeability and hypoxemia. In clinical settings, it is already approved as an anti-allergic drug and Matsumura et al[14] indicate that tranilast reduces cardiomyopathy in patients with muscular dystrophy after administration of 300 mg/day for three months. Dapansutrile, an orally available β-sulfonyl nitrile compound, reduced neutrophil infiltration and joint swelling in preclinical models of arthritis[15]; it is recently studied in phase 1 and 2 clinical trials for treatment of degenerative arthritis, acute gout and myocardial infarction[16]. Healthy humans receiving up to 1000 mg daily for 8 days of dapansutrile did not show any organ or hematological toxicity, indicating a good safety and tolerance[16].

Anti-cytokine treatments are currently under investigation worldwide in patients with COVID-19 in pre-ICU and in ICU stages; effective targets involve IL-1 (canakimumab)[17], IL-1receptor (anakinra)[18], IL-6 (siltuximab)[19], IL-6 receptor (tocilizumab)[20]. By targeting NLRP3, which activates upstream of many transcriptional factors (NF-kB, AP-1, p38-MAPK, JAK1/2-STAT3) and cytokines, most key players of direct myocardial damages[21], myocarditis[22], VTE and ARDS could be significantly disabled leading to improvements in prognosis of COVID-19[23,24].

Conclusions

As insight is gained into the clinical phenotypes associated with COVID-19, we propose NLRP3 as therapeutic target warranting rapid investigation in clinical trials highlighting cardiovascular, immunological and pulmonary outcomes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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