Contents lists available at ScienceDirect

Biochemical Pharmacology

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

Mn-TAT PTD-Ngb ameliorates inflammation through the elimination of damaged mitochondria and the activation of Nrf2-antioxidant signaling pathway

Cui Zhang, Ruirui Yang, Xuehui Hao, Zhirong Geng*, Zhilin Wang*

State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Collaborative Innovation Center of Advanced Microstructures, Nanjing University, Nanjing 210023, PR China

ARTICLE INFO

Keywords:
Mn-TAT PTD-Ngb
ROS
Inflammatory response
Nrf2
NLRP3

ABSTRACT

Inflammation, mitochondrial dysfunction and oxidative stress are closely associated with neurological diseases. In this study, Mn-TAT PTD-Ngb, a novel artificial recombinant protein, exerted inhibitory effects on the inflammatory response and inflammasome activation. During the lipopolysaccharide (LPS)-induced inflammatory response, Mn-TAT PTD-Ngb suppressed the nuclear translocation of nuclear factor kappa B (NF-κB) and the release of proinflammatory cytokines and attenuated the phosphorylation of mitogen-activated protein kinase (MAPK). Furthermore, the recombinant protein blocked reactive oxygen species (ROS) production, abated mitochondrial dysfunction and significantly suppressed the assembly of the inflammasome, which led to the overproduction of proinflammatory cytokines IL-1β and IL-18. Mn-TAT PTD-Ngb increased the level of nuclear factor-erythroid 2 -related factor 2 (Nrf2), which protected against oxidative stress and improved pyroptosis. Mn-TAT PTD-Ngb might be a promising drug for curing neurological diseases.

1. Introduction

Neurological diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and traumatic brain injury often lead to adult death and disability and impose great burdens on family and society [1–5]. Accumulating evidence has indicated that inflammation, mitochondrial dysfunction and oxidative stress are closely associated with neurological diseases [6–9]. The NF-κB and MAPK signaling pathways are critical for regulating the release of inflammatory factors such as IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) [10–15]. The NLRP3 inflammasome is an intracellular signaling platform formed through the recruitment of NLRP3, the adaptor protein ASC, and procaspase-1 [16]. The assembly of NLRP3 promotes the activation of inflammatory caspases and release of proinflammatory cytokines, such as IL-1β and IL-18, which aggravate the inflammatory response and eventually lead to programmed necrosis/pyroptosis [17–21]. Mitochondrial dysfunction, including the release of mtROS and mitochondrial membrane potential collapse, is closely involved in promoting the inflammatory response and the activation of NLRP3 inflammasome [22]. Consequently, developing drugs that prevent the inflammatory response and inflammasome activation may provide effective therapeutic avenues for curing neurological diseases [23].

Great efforts have been made to exploit drugs that block the inflammatory response in the central nervous system (CNS). Selfotel is an N-methyl-D-aspartic acid receptor (NMDA) receptor antagonist that significantly prevents the inflammatory process; however, it exhibits side effects and a high risk of death [24]. Minocycline [25] and the immunosuppressant cyclosporine, are clinically ineffective or still under clinical investigations [24–26]. The extracts of natural plants [27] and marine algae showed potential anti-inflammatory effect [27,28]. Moreover, researchers have exploited small molecule NLRP3 inhibitors such as MCC950 to block NLRP3-mediated inflammatory responses [29,30]. Recently, a number of proteins with neuroprotective properties, such as zinc finger protein A20 (A20) [31–34], erythropoietin (EPO) [35,36], progesterone [37,38] and neuroglobin (Ngb) [39], have been reported to be implicated in the inhibition of neuroinflammation. Ngb, a newly identified member of the globin family, is present in both reactive and astrogliotic scar-forming astrocytes and has anti-inflammatory and antioxidant activity [40–44]. Ngb was presumed to serve as a scavenger of ROS [45]. It was reported that Ngb acted as key regulator of Nrf-2 antioxidant pathway activity [46]. Nrf2 activation upregulated downstream enzymes such as heme oxygenase 1 (HO-1), superoxide dismutase (SOD), which fight against the production of ROS [47,48]. Mitochondria play crucial roles in energy

* Corresponding authors.
E-mail addresses: gengzr@nju.edu.cn (Z. Geng), wangzl@nju.edu.cn (Z. Wang).

https://doi.org/10.1016/j.bcp.2020.114055
Received 29 March 2020; Accepted 22 May 2020