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Dimethyl fumarate attenuates LPS induced septic acute kidney injury by suppression of NF-kB p65 phosphorylation through macrophage activation

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Objectives: Septic acute kidney injury (AKI) always accounts for high mortality of septic patients in ICU. Due to its not well understood mechanism for infection and immune-regulation in kidney dysfunction, there is a lack of effective therapy without side effects. Dimethyl fumarate (DMF) as an immunomodulatory molecule has been approved for treatment to multiple sclerosis. However, the therapeutic effect and immunomodulatory role underlying DMF action in septic AKI is unclear. This study aimed to elucidate the role of DMF in lipopolysaccharide (LPS)-induced septic AKI involving macrophage regulation.

Methods: We administered DMF by oral gavage to mice with LPS-induced AKI, then harvested serum and kidney at three different time points. We further isolated Bone marrow-derived macrophages (BMDMs) from mice and stimulated them with LPS followed by DMF treatment. To explore immunomodulatory role of DMF in macrophages, we depleted macrophages in mice using liposomal clodronate after DMF treatment upon LPS-induced sepetic AKI.

Results: we observed that DMF attenuated renal dysfunction and murine pathological kidney injury after LPS injection. DMF could inhibit translocation of phosphorylated NF-kB p65 and suppress macrophage activation in LPS-induced AKI. DMF also increased the secretion of Arg-1 and inhibited NF-kB p65 phosphorylation in BMDMs after LPS stimulation. Importantly, the effect of DMF against LPS-induced AKI, macrophage activation, and translocation of phosphorylated NF-kB p65 was impaired upon macrophage depletion. Thus, DMF could attenuate LPS-induced septic AKI by suppression of NF-kB p65 phosphorylation through macrophage activation.

Conclusions: This work suggested the potential therapeutic role of DMF for patients in ICU threatened by septic AKI.