GPR110-Dependent Macrophage Polarization Mediates the Therapeutic Effect of V-N_3P Single-Atom Catalyst in Septic Intestinal Injurys

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Abstract

Background: Sepsis-induced intestinal injury involves complex pathological processes, including dysregulated macrophage polarization, gut microbiota dysbiosis, and metabolic disturbances. Vanadium-based single-atom catalysts (SACs) with defined coordination structures show promise for inflammatory diseases, but their role and mechanisms in septic intestinal injury remain unclear. *Methods*: Two coordination-defined SACs, V-N_4 and V-N_3P, were synthesized and evaluated. Density functional theory calculations analyzed their electronic structure and catalytic activity. Sepsis models were established using cecal ligation and puncture in mice and pigs, with in vitro validation using LPS-stimulated RAW264.7 macrophages. Techniques including immunofluorescence, Western blot, RNA sequencing, 16S rRNA gene sequencing, and metabolomics were employed to investigate the effects on intestinal barrier, macrophage polarization, gut microbiota, host metabolism, and underlying mechanisms. *Results*: V-N_3P exhibited superior reactive oxygen species scavenging ability over V-N_4, attributed to phosphorus-induced charge delocalization. In septic mice, V-N_3P significantly improved survival, restored intestinal mucosal integrity, upregulated tight junction proteins (ZO-1, occludin) and MUC2, and reduced pro-inflammatory cytokine levels. V-N_3P promoted a shift from M1 to M2 macrophage polarization, which was reversible by a GPR110 agonist, identifying GPR110 as a key target. Mechanistically, V-N_3P downregulated GPR110, suppressed the JNK/NF-κB/ERK pro-inflammatory axis, and activated the A20/STAT3 anti-inflammatory pathway. Furthermore, V-N_3P restored gut microbiota α-diversity, enriched beneficial bacteria, and remodeled host metabolic profiles. *Conclusion*: The V-N_3P single-atom catalyst alleviates septic intestinal injury by targeting GPR110 to rebalance macrophage polarization and regulate the microbiota-metabolism network. This study provides a novel therapeutic strategy and theoretical basis for SAC-based "catalytic medicine" in treating inflammatory diseases.

Keywords

Vanadium-based Single-atom Catalysts, Sepsis, Intestinal Injury, GPR110, Macrophage Polarization