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Immunomodulatory Nanoparticles as a Multimodal Approach to Attenuate Immune Dysregulation in Severe Inflammation and Sepsis

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Extended Abstract

Sepsis is a life-threatening multifactorial organ dysfunction caused by a dysregulated host response to an infection [1]. Despite being recognized as a global health priority and over 100 clinical trials, there is currently no FDA-approved treatment that improves patient survival. First line therapies for sepsis involve supportive care such as broad-spectrum antibiotics for infection control, fluid administration to reduce vascular leakage, and vasopressors for blood pressure regulation [2]. The host response during the initial pathogenic insult involves the activation of innate immune cells that secrete proinflammatory cytokines to elicit a multitude of responses, including the recruitment of immune cells. During the onset of sepsis, this acute inflammatory response is often uncontrolled and subsequently results in multiorgan damage [3]. Nanoparticles have emerged as a drug delivery platform that display physicochemical property-dependent immunomodulatory effects. Our group has developed inherently anti-inflammatory, cargo-less poly(lactic acid) (PLA)-based nanoparticles (iNPs) capable of blunting innate immune cell proinflammatory responses to the Toll-like receptor 4 (TLR4) agonist, lipopolysaccharide (LPS) [4], [5].

Here, we examined the therapeutic effects of iNP treatment using a lethal LPS-induced endotoxemia mouse model of sepsis and a clinically relevant cecal ligation and puncture (CLP) mouse model of polymicrobial sepsis. We have demonstrated that the local administration of iNPs significantly improve mice survival under LPS challenge. Additionally, iNPs effectively reduced plasma MIP-1α, GROα, and MIP-1β and no toxicity was observed in the spleen or liver via histology. Since iNPs reduced mortality and displayed beneficial anti-inflammatory properties, we further assessed iNPs using a clinically relevant lethal CLP mouse model. Concomitant local administration of iNPs with a broad-spectrum antibiotic regimen significantly improved survival, whereas animals treated with antibiotic alone did not survive. The administration of antibiotics was determined to be critical for therapeutic efficacy as iNP only treated mice did not show improved survival compared to CLP controls. Investigation of various immune cell populations provides insights to the role of iNP treatment in modulating splenic myeloid-derived suppressor cells (MDSCs), peritoneal resident monocytes, and peritoneal inflammatory monocytes and how these cell types correspond with a reduction in local proinflammatory cytokine production. The observed effects could potentially be attributed to the lactate delivery from the PLA-based iNPs, as lactate has shown to induce an immunosuppressive phenotype. The presented work highlights the potential of iNPs as a multimodal immunomodulatory therapeutic for local and systemic immunomodulation for future therapeutic development for severe inflammation and sepsis.

References

[1] K. Reinhart, R. Daniels, N. Kissoon, F. R. Machado, R. D. Schachter, and S. Finfer, "Recognizing Sepsis as a Global Health Priority — A WHO Resolution," *New England Journal of Medicine*, vol. 377, no. 5, pp. 414–417, 2017, doi: 10.1056/NEJMP1707170/SUPPL_FILE/NEJMP1707170_DISCLOSURES.PDF.

[2] M. P. Fink and H. Shaw Warren, "Strategies to improve drug development for sepsis," *Nat Rev Drug Discov*, vol. 13, no. 10, pp. 741–758, 2014, doi: 10.1038/nrd4368.

[3] B. G. Chousterman, F. K. Swirski, and G. F. Weber, "Cytokine storm and sepsis disease pathogenesis," *Semin Immunopathol*, vol. 39, pp. 517–528, 2017, doi: 10.1007/s00281-017-0639-8.

[4] L. M. Casey, S. Kakade, J. T. Decker, J. A. Rose, K. Deans, L. D. Shea, R. M. Pearson, "Cargo-less nanoparticles program innate immune cell responses to toll-like receptor activation," *Biomaterials*, vol. 218, Oct. 2019, doi: 10.1016/j.biomaterials.2019.119333.

[5] J. J. M. Lasola, A. L. Cottingham, B. L. Scotland, N. Truong, C. C. Hong, P. Shapiro, R. M. Pearson, "Immunomodulatory Nanoparticles Mitigate Macrophage Inflammation via Inhibition of PAMP Interactions and Lactate-Mediated Functional Reprogramming of NF-κB and p38 MAPK," *Pharmaceutics*, vol. 13, no. 11, p. 1841, Nov. 2021, doi: 10.3390/PHARMACEUTICS13111841.