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Complement peptide C4a mitigates LPS-induced endothelium disruption, cytokine production, ERK activation, and [Ca^{2+}] influx from human moncytes- A new therapeutic intervention for endotoxin shock

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Activation of the complement cascade is a major effector of the inflammatory response. Cleavage of complement components in the course of activation produces low-molecular-weight peptides, including C3a, C4a, and C5a. Both C3a and C5a have potent anaphylatoxin properties. Our recent study idnetified that C4a mediates effector functions through binding to protease-activated receptors (PAR) 1 and PAR4. Early study demonstrated that animals with complement C4 deficiency were reported to be more susceptable to endotoxic shock, suggesting that C4 protects animals from endotoxic effects. However, the molecular mechanism for C4 protective effect on endotoxin shock in animals is poorly understood. We propose that C4 activation peptide, C4a, possiblly through binding to PAR1/4 on platelets, monocytes, and endothelial cells, inhibits LPS-induced platelet aggregation, IL-1β and TNFα cytokine production from monocytes, and endothelium permeability to achieve C4 protective effects in endotoxin shock animal models. In the present study, we found that pretreatment with C4a to human primary monocytes can significantly inhibit LPS-induced IL-1β and TNFα production. Moreover, LPS-induced ERK phosphorylation and [Ca^{2+}] influx were significantly inhibited by the pretreatment of C4a. Our experiments also revealed that C4a significantly decreased endothelium permeability when human endothelial cells were cultured in the presence of LPS, indicating under endotoxemia condition, C4a prevents endothelium disruption. Our data provide deeper insight into the mechanism of C4's protective effect on endotoxic shock and would provide a valuable resource for the wider scientific community to generate future therapeutic interventions for the treatment of clinical endotoxemia.

Biography

Hongbin Wang received his PhD in 2010 from the University of Pennsylvania and Post-doctoral training from University of Pennsylvania Perelman School of Medicine. Now, he is an Assistant Professor of Pharmacology in the Department of Pharmaceutical and Biomedical Sciences at the California Nothstate University College of Pharmacy. He has published more than 40 papers in peer reviewed journals.

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