3rd International Conference on
Virology, Infectious Diseases and COVID-19
October 24-25, 2022/ Holiday Inn Express Dubai - Safa Park, an IHG Hotel
UNITED RESEARCH FORUM (CONNECT WITH RESEARCH WORLD)

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Effects of PDZ domain of ZO-1 on Pseudomonas aeruginosa LPS-activatedinflammation in the airway.

Pseudomonas aeruginosahas been known as an important pathogen in many human diseases. Therefore, examining the negative control mechanisms of tight junction protein ZO-1 on the exotoxin LPS of P. aeruginosa-induced diseases could be critical in the development of novel therapeutics. We found that ZO-1 expression dramatically decreased in inflammatory human lung tissues. Interestingly, PDZ1 deletion of the PDZ domain in the ZO-1 protein dramatically decreased LPS-induced F-actin formation and increased the expression of genes for pro-inflammatory cytokines, but not PDZ2 and PDZ3 of the ZO-1 protein. We also found that the consensus PDZ peptide (based on PDZ1) of ZO-1 down-regulates the expression of pro-inflammatory cytokine genes and F-actin formation; in contrast, the GG24,25AA mutant PDZ peptide cannot control these genes. LPS activates IL-8 secretion extracellularly in a time-dependent manner, while the secretion is inhibited by PDZ peptide. Whereas increased IL-8 secretion by LPS activates the CXCR2 receptor, overexpressed RGS12 negatively regulates LPS-induced CXCR2/IL-8 signaling. The PDZ peptide also decreases LPS-induced inflammatory cell populations, pro-inflammatory cytokine gene expression, and TEER in bronchoalveolar lavage fluid and cultured alveolar macrophages. Collectively, we suggest that the PDZ peptide may be a potential therapeutic for bacteria-induced respiratory diseases.

Keywords: LPS, ZO-1, proinflammatory cytokine, PDZ, IL-8, airway inflammation

http://doi.org/10.51219/URForum.2022.Kyoung-Seob-Song

ISBN: 978-1-8382915-5-6