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기 초

O-009

Anti-Inflammasome Property of Poly-Gamma-Glutamic Acid in Macrophages

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Introduction: Poly-gamma-glutamic acid (γ-PGA) is a natural, edible, and non-toxic polymer synthesized by Bacillus subtilis and is suggested as a safe biomaterial for use in hydrogels and vaccine adjuvants. However, the effect of γ-PGA on inflammasome activation has not yet been studied in macrophages. Inflammasomes, which are intracellular multi-protein complexes, promote acute and chronic inflammation via interukin-1β or -18 maturation, and they are known targets for metabolic syndromes and cancer.

Materials and Methods: For bone marrow-derived macrophages (BMDMs), bone marrow cells were obtained by flushing tibia and femur bones from C57BL/6 mice and cultured in DMEM supplemented with 10% FBS in the presence of L929 cell conditioned medium containing granulocyte macrophage colony-stimulating factor. THP-1 cells were differentiated into macrophage-like cells using PMA. BMDMs or PMA-differentiated THP-1 cells were plated primed with LPS for 3h. After LPS priming, cells were replaced by RPMI 1640 containing the inflammasome activators in the present of γ-PGA.

Results: In this study, we observed that γ-PGA attenuated NLRP3, NLRC4, and AIM2 inflammasome activation, whereas it up-regulated expression of pro-inflammatory cytokines in human and murine macrophages. Although γ-PGA had conflicting effects on cytokine production and maturation, it clearly alleviated severity of LPS-induced endotoxin shock in an animal model.

Conclusions: These results show that γ-PGA attenuates the severity of inflammasome-mediating inflammatory diseases while up-regulating production of pro-inflammatory cytokines [1].

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O-010

Evaluation of Fluoroquinolone Activity against Emergence of Resistant *Salmonella enterica serovar* Typhimurium Using *In Vitro* Dynamic Models

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Introduction: The objectives of this study were to determine pharmacokinetic/pharmacodynamic(PK/PD) indices of fluoroquinolones that minimize the emergence of resistant *Salmonella enterica serovar* Typhimurium (*S.* Typhimurium) using *in vitro* dynamic models, and to establish mechanisms of resistance.

Materials and Methods: Three fluoroquinolones, difloxacin (DIF), enrofloxacin (ENR) and marbofloxacin (MAR), at five dose levels and 3 days of treatment were simulated. Bacterial killing-regrowth kinetics and emergence of resistant bacteria after antibacterial drug- exposure were quantified. PK/PD indices as sociated with different levels of antibacterial activity were computed. Mechanisms of fluoroquinolone resistance were determined by analyzing target mutations in the quinolone resistance determining regions (QRDRs) and by analyzing overexpression of efflux pumps.

Results: Maximum losses in susceptibility of fluoroquinolone-exposed *S.* Typhimurium occurred when drug concentrations fell in the mutant selection window (MSW) for significant proportion of the dosing interval of 24 h (T_{MSW} = 90% for DIF and ENR and 66% for MAR),which overlapped with simulated AUC_{24h}/MIC ratio of 47-71. Target mutations in *gyrA* (S83F) and overexpression of *acrAB-tolC* contributed to decreased susceptibility in fluoroquinolone-exposed *S.* Typhimurium.

Conclusions: The current data suggest AUC_{24h}/MIC(AUC_{24h}/MPC)-dependent selection of resistant mutants of *S.* Typhimurium with AUC_{24h}/MPC ratios of 69 (DIF), 62 (ENR) and 39 (MAR) being protective against selection of resistant mutants. These values could not be achieved in veterinary clinical area under the current recommended therapeutic doses of the fluoroquinolones, suggesting the need to reassess the current dosing regimen to include both clinical efficacy and minimization of emergence of resistant bacteria.

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