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Intranasal immunization with a live vaccine protects against Pseudomonas aeruginosa-associated pneumonia in mice

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Background: *Pseudomonas aeruginosa* is the nosocomial bacterial pathogen most commonly isolated from the human respiratory tract whereas chronic lung infection with this bacterium accounts for most of the morbidity and mortality associated with cystic fibrosis (CF). It also causes severe infections in patients with bronchiectasis. Despite intense efforts, an effective vaccine has not yet evolved. We previously characterized an experimental live vaccine against sepsis, composed of a D-glutamate (D-Glu) auxotrophic strain with inactivated Glutamate racemase (MurI), a key enzyme that provides the D-Glu required for peptidoglycan biosynthesis. Now, this study aims at identifying whether this D-Glu auxotroph holds the potential to be immunogenic and effective against *P. aeruginosa*-associated pneumonia in mice, when administered intranasally.

Material/methods: *P. aeruginosa* PAO1 was previously genetically manipulated to obtain a D-Glu auxotrophic strain, PAO1 Δ*murI*, by eliminating the MurI coding gene, *murI*. BALB/c mice were inoculated intranasally with PAO1 Δ*murI* (2×10^8 CFU) on days 0 and 14. An extra immunization was performed on day 7, when using a three-dose schedule. Control mice were inoculated saline. Serum levels of IgM, IgG, IgG1, IgG2a, IgG2b and IgG3 against PAO1 were determined using ELISA, from sera obtained at different time points during the immunization schedules. Cross-reactivity of the IgG's was determined against a panel of 11 heterologous *P. aeruginosa* strains. Four weeks after the last immunization, mice were anesthetized and intranasally challenged with *P. aeruginosa* PAO1 ExoU$^+$ (7×10^5 CFU; expressing the ExoU cytotoxin), PA14 (1×10^6 CFU; hypervirulent, ExoU$^+$) and ST235 (3×10^5 CFU; XDR epidemic clone), to further evaluate the protective effect generated by the vaccine against pneumonia. Then, mice were monitored for survival.

Results: The intranasal administration of PAO1 Δ*murI* using both a two- and three-dose vaccination schedule resulted in significant IgM, IgG, IgG1, IgG2a, IgG2b and IgG3 levels. IgG's obtained were cross-reactive against *P. aeruginosa* PA14, ST235, 21_ST175 (XDR high-risk clone), LES400 and 12142 (Liverpool epidemic strains from CF patients), 51442390 (Mem^R mucoid isolate from a CF patient), 29606 and 28757 (mucoid isolates from CF patients), LES431 (Liverpool epidemic strain from a non-CF patient), 51441321 and 28562 (MDR/mucoid isolates from bronchiectasis patients). Survival rates of vaccinated mice using a two-dose vaccination schedule were 86, 88 and 29% after challenge with PAO1 $ExoU^+$, PA14 and ST235, respectively; whereas control mice presented 0, 13 and 0% survival. Using the three-dose immunization schedule, survival rates of vaccinated mice were 83%, after challenge with PA14, whereas all control mice died.

Conclusions: Intranasal immunization of mice with a D-Glu auxotroph of *P. aeruginosa* - PAO1 Δ*murI* – induced antibody production and conferred protection against acute pneumonia caused by high-virulent and high-risk *P. aeruginosa* strains. Thus, PAO1 Δ*murI* is an attractive vaccine candidate to protect against respiratory infections in patients susceptible to this pathogen.