Histone deacetylase inhibition reverses sepsis-induced susceptibility to *Pseudomonas aeruginosa* pneumonia

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Introduction

- Sepsis induces long lasting alterations of transcriptional programs, subsequent protracted inflammation, sepsis-induced immune suppression (SIIS), secondary infections, and death (1-3)
- A shift toward repressive histone modifications with an overexpression of histone desacetylases (HDACs) is observed in patients with SIIS (4-5)
- We hypothesized that HDACs inhibitors could prevent sepsis-induced overexpression of HDACs, repressive gene expression and thus prevent SIIS.
- **To test this hypothesis, we studied the effects of histone deacetylases (HDAC) inhibition with Trichostatin A (TSA) in a murine model of SIIS and secondary pneumonia**

Material and methods

- C57BL/6 mice were treated with TSA (2 mg/kg intraperitoneal) or saline serum (CTL) 30 min before induction of sepsis by cecal ligation puncture (CLP). Sham mice did not undergo CLP.
- Surviving mice underwent intratracheal instillation of *P. aeruginosa* (2 – 2.5 x10^6 CFU) 8 days after CLP
- We evaluated the effect of TSA on histone 3 acetylation in T-cells by Luminex Histone PTM Multiplex
- Effect of TSA on SIIS was evaluated by :
  - Pneumonia survival, through Kaplan-Meier curves and compared by the log rank test
  - Bacterial clearance in BAL (CFU) at 4h of infection
  - Lymphocytes sepsis-induced abnormalities 1 and 8 days after initial CLP by flow cytometry (apoptosis, PD-1 and PDL-1expression)
- Continuous variables were represented as means ± SD and compared using Student T-test $P<0.05$, represented as * and ** indicated statistically significant differences

Results

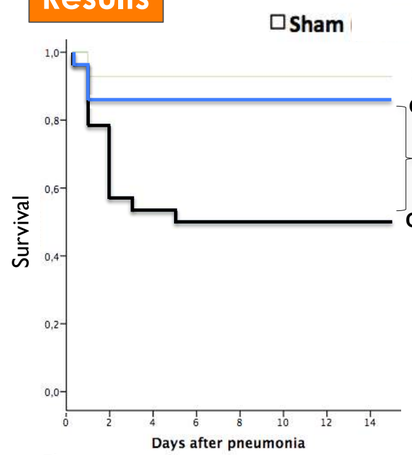

Figure 1. TSA improves survival after secondary *P. aeruginosa* pneumonia

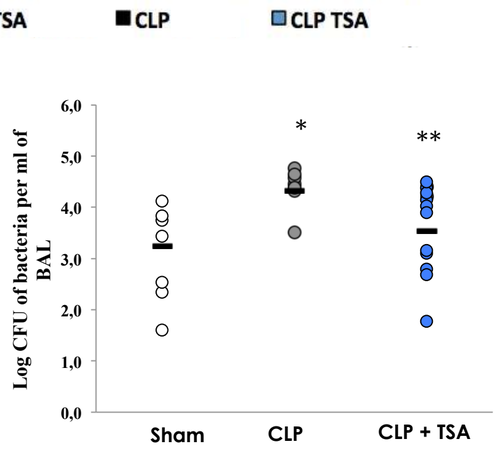

Figure 2. TSA improves bacterial clearance in broncho-alveolar lavage (BAL) at H4 of secondary *P. aeruginosa* pneumonia

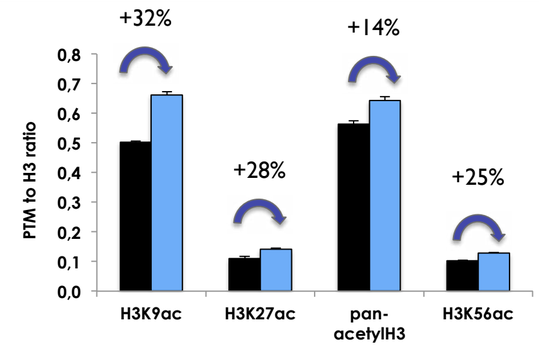

Figure 3. TSA increases H3 acetylation in T-cells

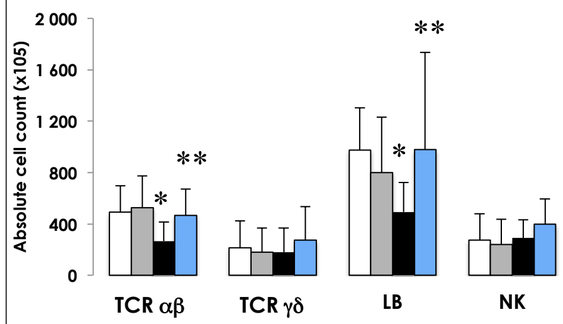

Figure 4. TSA prevents sepsis-induced T and B-cells depletion 8 days after sepsis

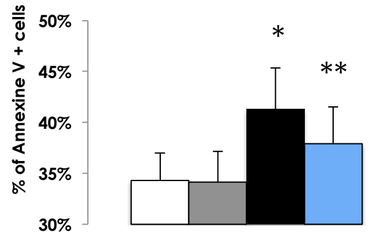

Figure 5. TSA prevents sepsis-induced T-lymphocyte apoptosis one day after sepsis

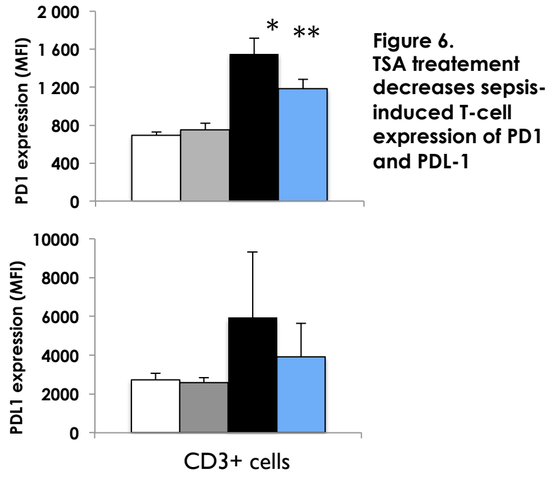

Figure 6. TSA treatement decreases sepsis-induced T-cell expression of PD1 and PDL-1

Conclusion

- HDAC inhibition by TSA improves survival and bacterial clearance in our murine model of secondary *P.aeruginosa* pneumonia
- TSA has an impact on H3 acetylation and T-cell phenotype and prevents from sepsis-induced T-cell apoptosis and PD-1/PDL-1 overexpression
- These results confirm that sepsis-induced epigenetic changes contribute to the advent of SIIS.

Références

1. Singer M et al. Jama 2016 ; 2. Yende S et al. Trends Mol Med. 2014; 3. Hotchkiss RS et al. Nat Rev Immunol. 2013; 4. Carson WF et al. European Journal of Immunology 2010; 5. Carson WF et al. Adv in Prot Chem and Struct Biology 2017