# EFFECT OF SURFACTANT PROTEIN-D ABLATION ON CHEMOTHERAPY INDUCED GASTROINTESTINAL TOXICITY IN MICE

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## INTRODUCTION

- Surfactant protein D (SP-D) is an innate host defense molecule produced by epithelial cells.
- SP-D has recently been shown to be differentially regulated in the gastrointestinal mucosa of chemotherapy-treated piglets.
- SP-D may be involved in the homeostasis and protection of mucosal surfaces after chemotherapy.

## OBJECTIVES

To investigate the effect of SP-D ablation on chemotherapy induced gastrointestinal toxicity and inflammation in a murine model.

## METHODS

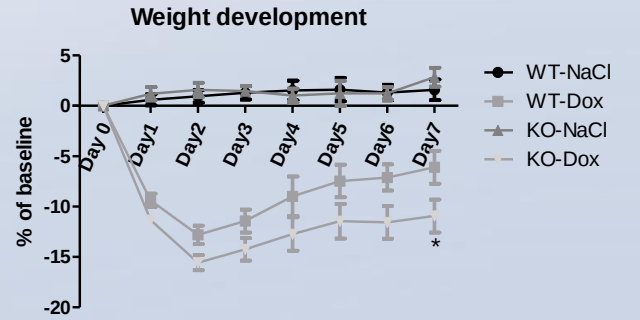
- SP-D knockout (KO) mice and wildtype (WT) littermates were treated with doxorubicin (20 mg/kg) or saline by i.p. injection and sacrificed at day 3 or at day 7 post-administration.
- Gastrointestinal toxicity and inflammation was evaluated by weight change, bone marrow cellularity, citrulline levels, intestinal length, histopathological evaluation and quantitative real-time PCR (RT-qPCR) of key genes related to chemotherapy induced mucositis, inflammation, apoptosis and repair of damaged epithelium including *Tnf, IL-1β, Casp-1, Casp-3, Bax, Mmp-2, Mmp-12, Serpina3n, Akr1b8, Gsdmc2, Gsdmc3, Gsdmc4*.

C57/B6 (n=66)
WT (n=31) vs. KO (*Sftpd*$^{-/-}$) (n=35)
10-12 weeks old

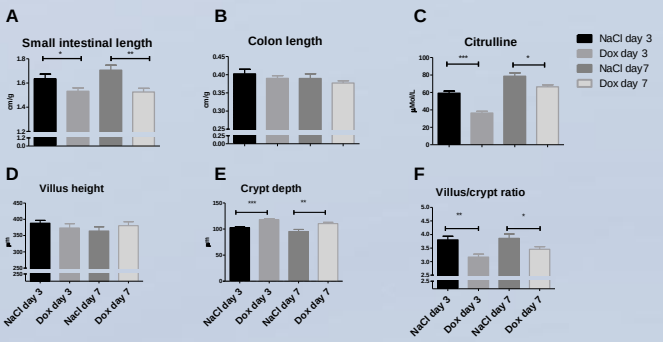

## CONCLUSIONS

- SP-D had limited effect on gastrointestinal toxicity after induction of mucositis
- *Increased Tnf* and *Mmp2* expression in the intestine indicates that SP-D may modulate the inflammatory response after chemotherapy with possible implications for the ensuing tissue injury.

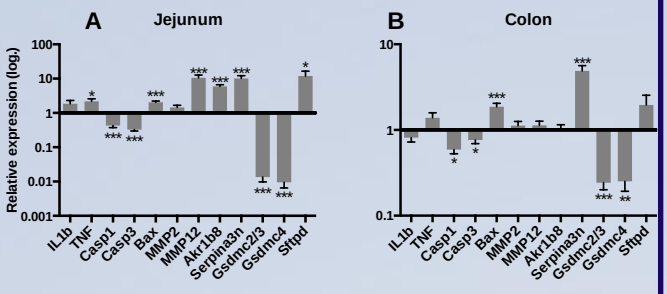
## RESULTS



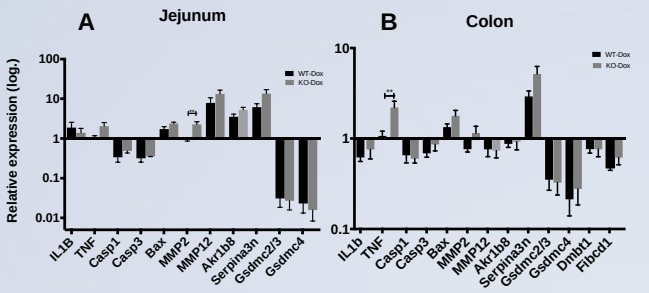

Body weight changes throughout the experiment after doxorubicin chemotherapy
Values are shown as means and SEM. * p<0.05, (Two-way ANOVA of grouped data.)




**(A)** Small intestinal and **(B)** colon length, **(C)** citrulline levels, **(D)** villus heights, **(E)** crypt depth and **(F)** and villus/crypt ratios in doxorubicin treated mice across genotypes compared with saline controls and sacrificed at day 3 or day 7. All values are means and SEM. *P<0.05, ** P<0.01, ***P<0.001 as analyzed by the unpaired, two-tailed t test. No genotype related differences detected.




Relative expression across genotypes of genes related to GI inflammation and toxicity in **(A)** jejunum and **(B)** colon of Doxorubicin-treated mice sacrificed at day 3, normalized to saline-treated controls. Relative expression determined by RT-qPCR analysis, and normalized to *GAPDH* and *TBP*. Data are presented as mean ± SEM. *P<0.05, **P<0.01, ***P<0.001 (Mann-Whitney test).




Genotype specific relative expression of genes related to GI inflammation and toxicity in **(A)** jejunum and **(B)** colon of Doxorubicin-treated wildtype (WT-Dox) and SP-D knockout (KO-Dox) mice sacrificed at day 3, normalized to saline-treated WT controls. Relative expression determined by RT-qPCR analysis, and normalized to *GAPDH* and *TBP*. Data are presented as mean ± SEM. *P<0.05, **P<0.01, ***P<0.001 (Mann-Whitney test).

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