Glucocorticoid receptor intestinal epithelial knockout mice show attenuated colonic inflammatory response but unaffected permeability in early experimental sepsis

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Resumen

Introduction: Sepsis is defined as an organic dysfunction that threatens the life of patients due to an abnormally regulated response to infection [1]. The initial phase of sepsis is dominated by an increased production of proinflammatory cytokines, which leads to augmented capillary permeability, extravasation, hypercoagulability and myelopoiesis. One of the main sources of infection in sepsis is believed to be the intestinal microbiota via traslocation through the mucosa to the bloodstream. Systemic inflammation weakens intestinal barrier function (IBF) in animal models, resulting in increased bacterial traslocation [2]. Even if the management of sepsis has advanced in the last decades, mortality is still high and there are blanks in terms of pathological systems and long-term consequences. Thus, the search for effective treatments is clearly justified. Glucocorticoids (GC) are part of the drugs used in sepsis, but they have only shown a moderate therapeutic effect. This fact may be caused by harmful effects of GCs on IBF, whose compromise may limit GC clinical benefit by facilitating luminal translocation of microorganisms. Besides, GC treatment impairs epithelial healing in experimental colitis in mice [3]. Previous results of our research group have shown that mice with induced deletion of the GC receptor (GR) in intestinal epithelial cells (i.e. NR3C1$^{\Delta IEC}$ mice) are protected against dextran sulphate sodium (DSS)-induced colitis [4]. In turn, gene deletion results in a short lived inflammatory response in the colon [5].

Objective: Understanding the role of the intestinal epithelial GR and its involvement in IBF regulation in experimental sepsis, with the ultimate goal of improving the management of sepsis with GCs.

Matherial and methods: The cecal ligation and puncture (CLP) model of sepsis was applied to WT C57BL/6J and NR3C1$^{\Delta IEC}$ mice. Ceacum-exposed mice were used as control (Sham). Mice were sacrificed 24

hours after surgery. Four hours before sacrifice, mice were administered

4 kD FITC-dextran, a fluorescent marker of permeability. Colon, jejunum, adrenes, kidney and liver RT-qPCRs were performed as well as determination of plasma FITC-dextran and corticosterone plasma levels.

Results: After 24 h, CLP mice exhibited elevated corticosterone plasma levels with hypoglycemia and splenomegaly. Intestinal barrier function was weakened, as indicated by increased FITC-dextran plasma levels. A modest increase in inflammatory markers (*S100a8*, *Cxcl1*) was noted in the colon and jejunum. The expression of *Tjp1*, involved in barrier function, was downregulated in CLP mice. Similarly, the colonic expression of *Cyp11a1* and *Lrh1*, involved in local steroidogenesis, was lower in CLP mice, regardless of genotype. Markers of inflammation were also augmented in the lung and kidney. CLP mice exhibited hypercorticosteronemia, which was associated to increased *Cyp11a1* in the adrenes. Of note, both parameters were less pronounced in KO mice. The latter also exhibited dampened inflammatory response in the colon but not the jejunum. FITC-dextran plasma levels were similarly increased in WT and KO mice.

Conclusions: In the early stages of the CLP model of sepsis the colon and jejunum are inflamed, and epithelial deletion of the glucocorticoid receptor appears to modulate inflammation in the former, with no change in barrier function. Further studies will characterize the microbiota composition and phenotype in later stages and in the response to glucocorticoid treatment.

Palabras clave: sepsis; glucocorticoids; colitis; inflammatory markers; microbiota.

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