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Poster presentation

T-cell-specific peroxisome proliferator-activated receptor gamma depletion inhibits T-cell apoptosis and improves survival of septic mice via an IL-2-dependent mechanism

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Introduction

Immune paralysis with massive T-cell apoptosis is a central pathogenic event during sepsis and correlates with septic patient mortality. Previous observations implied a crucial role of peroxisome proliferator-activated receptor gamma (PPARγ) during T-cell apoptosis.

Methods

To elucidate mechanisms of PPARγ-induced T-cell depletion, we used an endotoxin model as well as the caecal ligation and puncture sepsis model to imitate septic conditions in wild-type versus conditional PPARγ knockout (KO) mice.

Results

PPARγ KO mice showed a marked survival advantage compared with control mice. Their T cells were substantially protected against sepsis-induced death and showed a significantly higher expression of the pro-survival factor IL-2. Since PPARγ is described to repress nuclear factor of activated T cells (NFAT) transactivation and concomitant IL-2 expression, we propose inhibition of NFAT as the underlying mechanism allowing T-cell apoptosis. Corroborating our hypothesis, we observed up-regulation of the pro-apoptotic protein

BIM and downregulation of the anti-apoptotic protein Bcl-2 in control mice, which are downstream effector proteins of IL-2 receptor signaling. Application of a neutralizing anti-IL-2 antibody reversed the pro-survival effect of PPARγ-deficient T cells and confirmed IL-2-dependent apoptosis during sepsis.

Conclusion

Apparently antagonizing PPARγ in T cells might improve their survival during sepsis, which concomitantly enhances defence mechanisms and possibly provokes an increased survival of septic patients.

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