IL-2 mediated Treg expansion is associated with the dual outcomes of ductular reaction and liver fibrosis

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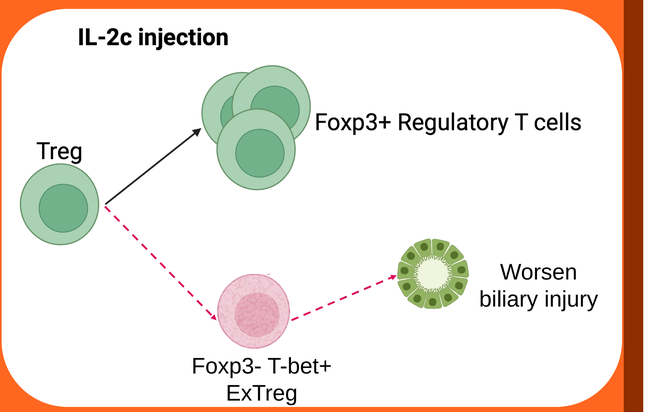
- IL-2c expands Foxp3+ Treg
- IL-2c also promotes Foxp3+Treg to acquire a T-bet+ proinflammatory phenotype.
- Treg is unstable during biliary injury
- T-bet+ exTreg is associated with increased severity of the biliary injury

Graphical abstract



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Introduction

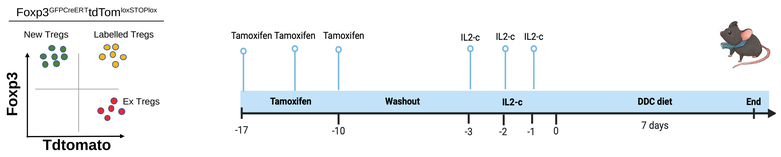
Regulatory T cells (Tregs) exert immune-modulatory functions through suppression of immune responses. Expanding Treg number has become an attractive option for controlling excessive inflammation during liver disease. Methods to manipulate Tregs as therapeutics have been performed in mouse models and clinically, including the use of IL-2 complexes (IL-2c) aiming to control the development and proliferation of CD4+ T cells. However, mixed results have been reported from these studies.

Aim

We aim to explore the possibility of using IL-2c to expand Tregs and investigate the underlying mechanisms of the discrepancy between studies that use Tregs as therapies.

Methods

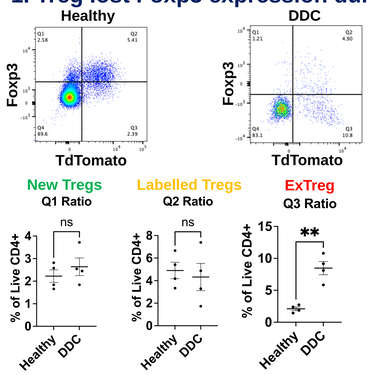
Tamoxifen was given to the *Foxp3*^{CreERT}*Ai14* Tregs fate-mapping mice, inducing the expression of red fluorescence (RFP) in Tregs. A low dose of IL-2 complexes (IL-2 protein and anti-IL2 antibody) or PBS control was injected into the mice. All mice were then given the 3,5-Diethoxycarbonyl-1,4-Dihydrocollidine (DDC) diet to induce biliary injury.



Using Foxp3 fate mapping mice, Treg was labelled in red after receiving tamoxifen.
Treg was subdivided into three subpopulations:
Foxp3+Tdtomato- New Treg; Foxp3+Tdtomato+ labelled Treg; Foxp3-Tdtomato+ ExTreg

Results

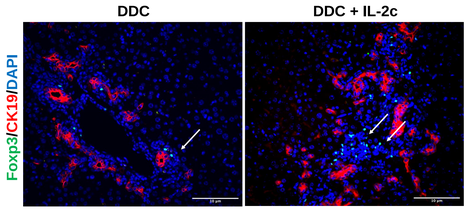
1. Treg lost Foxp3 expression during biliary injury



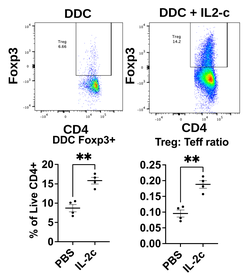
Tregs lose Foxp3 expression following biliary injury and become exTreg.

Intrahepatic exTreg population increased by 3-fold during DDC-induced biliary injury.

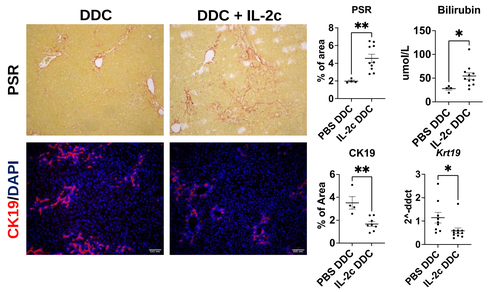
2. *In vivo* expansion of Tregs with IL-2c in a mouse model of biliary injury



IL-2c mediated Tregs expansion doubled the number of Treg during DDC-induced biliary injury.

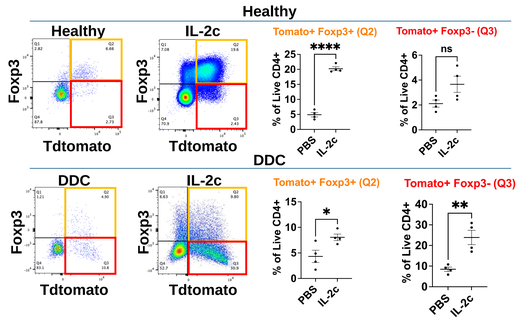


3. *In vivo* expansion of Treg with IL-2c worsens the biliary injury



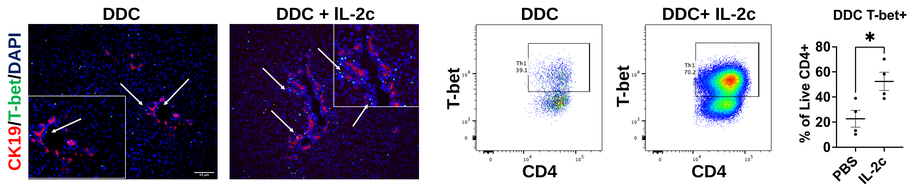
In vivo expansion by IL-2c injection resulted in increased fibrosis (PSR), reduced ductular reaction (CK19+ cells) and increased serum bilirubin.

4. Injection of IL-2c increases the number of exTreg

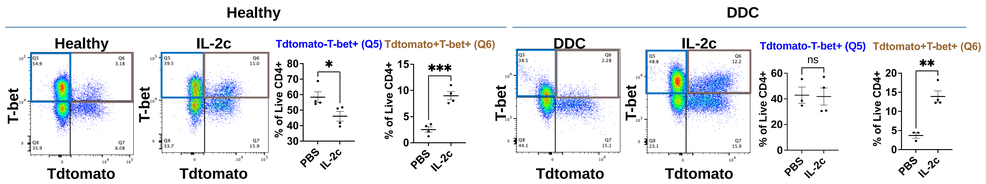


In vivo expansion of Tregs by IL-2c injection further expanded the exTreg population in the biliary injured mice, but not in the healthy mice.

5. IL-2c injection promotes Tregs to express T-bet transcription factor



IL-2c injection increases T-bet expressing cells by 2.5-fold.



IL-2c promotes Treg to express T-bet, which contributes to the increase in the T-bet+ population.

Conclusions

- IL-2c injection expanded intrahepatic Treg during biliary injury; however, it showed a dual effect on liver fibrosis and ductular reaction.
- IL-2c increased pro-inflammatory Foxp3- exTreg population, which may contribute to the worsened biliary injury.
- IL-2c increased the T-bet+ population during injury, and most of this population is contributed by Foxp3 Tregs

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