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Comparative effectiveness of immune-cell depletion and a targeted therapy against LTβR-signaling in the treatment of autoimmune pancreatitis

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Background: Long-term management of autoimmune pancreatitis (AIP) - a relapsing steroid-responsive disorder - is still elusive. To study AIP pathogenesis and develop novel, steroid sparing therapies, we used our recently published mouse model, Tg(Ela1-Lta,b), that develops autoimmunity reminiscent to human AIP including tertiary lymphoid organ (TLO) formation. In this model we have previously shown that in contrast to corticosteroids, which only diminished inflammation, inhibition of Lymphotoxin beta receptor signaling (LTβR-Ig) also abrogated autoimmunity.
Aim: To investigate the effectiveness of LTβR inhibition compared to depletion of specific immune cell subsets (B-cells, CD4+ T-cells), which are suggested to be involved in AIP development.
Materials & methods: Transgenic mice with established AIP were treated with anti-CD20, anti-CD4 mAb or LTβR-Ig fusion protein. Histology, autoantibodies, cytokine and chemokine expression, TLO integrity and extrapancreatic manifestations were tested. Macrophage and T helper cell polarization was evaluated upon different treatments.
Results: LTβR-Ig and anti-CD20 treatment led to significant improvement of AIP. The molecular mechanism of this beneficial effect possibly involves downregulation of Stat3 and non-canonical NF-κb activation. Additionally, in contrast to anti-CD20 and anti-CD4, blocking LTβR-signaling reverted acinar-to-ductal metaplasia formation and disrupted TLOs. Anti-CD4 treatment resulted in reduced Th1 and Th2 polarization; however did not ameliorate AIP.
Conclusion: In this unique genetic mouse model of AIP, we demonstrate that therapy with LTβR-Ig and anti-CD20 antibody is superior to CD4+ T-cell depletion. With these targeted therapies we reveal novel anti-inflammatory and anti-autoimmune mechanisms. Assessing parameters associated with AIP pathogenesis, LTβR-Ig achieved the greatest improvements. Therefore, inhibition of LTβR-signaling could become an alternative or supplementary approach for AIP treatment.