IL-7 pathway controls human T cell homing to the gut and culminates in inflammatory bowel disease mucosa

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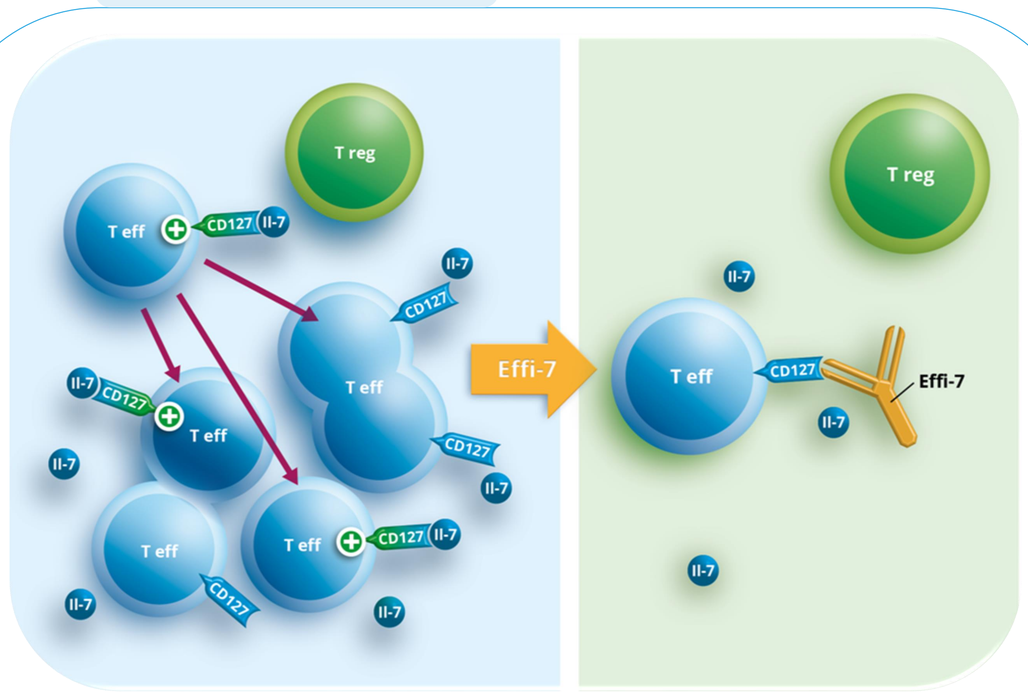
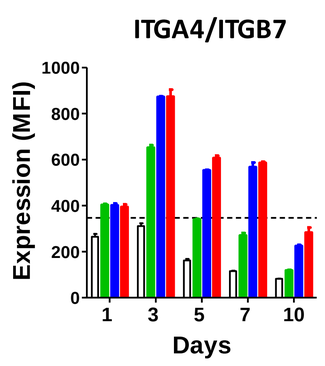
Introduction

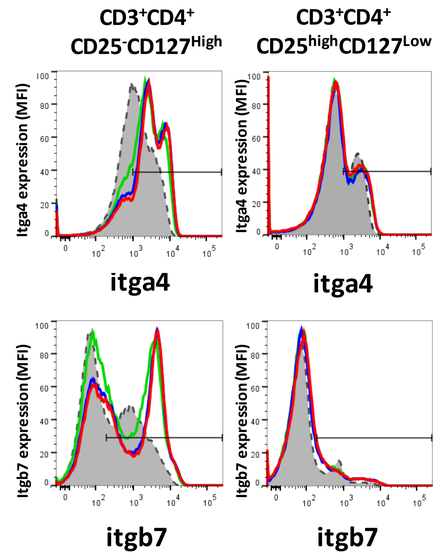


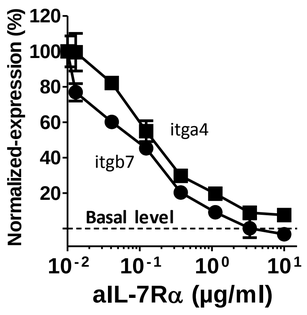
Interleukin-7 (IL-7) is a limiting and non-redundant non-classical cytokine produced essentially by epithelial and stromal cells which regulates T-lymphocytes homeostasis. Almost all conventional mature T lymphocytes express the IL-7 receptor (IL-7R), with a particular exception for naturally-occurring regulatory T-cells (Tregs), constituting a rare opportunity to selectively target pathogenic effectors while preserving natural regulators. The signaling networks perpetuating chronic inflammatory bowel disease in man remain unclear. While in mice IL-7 is known to play a role in systemic inflammation, here we found that IL-7 specifically in humans controls α4/β7 integrin expression and imprints gut-homing specificity on T cells.

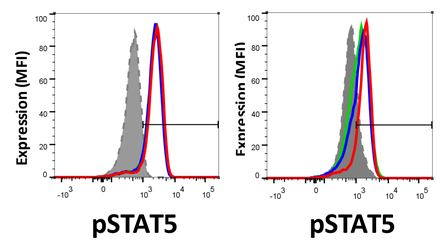
Results

I- IL-7 controls human effector, but not regulatory T lymphocyte α4/β7 integrin expression





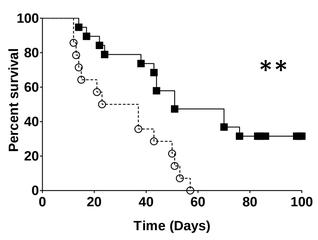


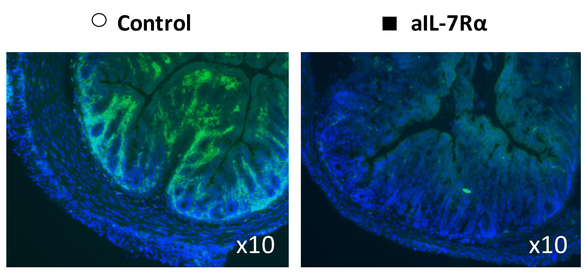


- ITGA4/ITGB7, two integrins implicated in the migration of T cells into the gut, are up-regulated by human recombinant IL-7 (rhIL-7) on effector ($CD4^+CD25^-CD127^{high}$) but not on regulatory T cells (Tregs: $CD4^+CD25^{high}CD127^{low}$) .
- Up regulation of ITGA4/ITGB7 on effector ($CD4^+CD25^-CD127^{high}$) T cells is blocked by anti-IL-7R antibodies.
- Induction of pSTA5 in response to IL-7 was observed in T cell and in Treg cells, demonstrating that in spite of low CD127 expression level, Tregs are able to respond to IL-7.

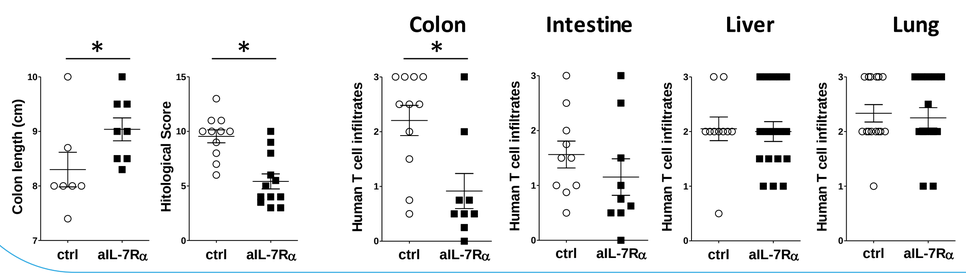
human IL-7: medium; 1 ng/ml; 5 ng/ml; 25 ng/ml

II- Anti-IL-7Ra delays colon inflammation in GVHD humanized mice model

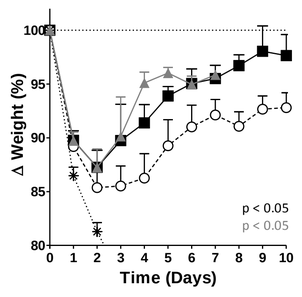


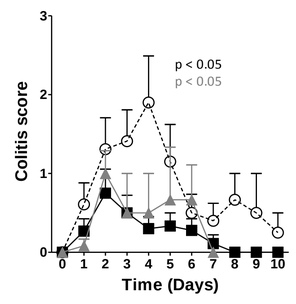


- GVHD was induced after infusion of 50.10^6 human PBMC in NSG mice. Anti-IL7Ra mAb significantly prolonged survival. Strikingly, colon inflammation and human T-cell infiltration in the colon were abolished, without impact on other target tissue of GVHD (intestine, liver and lung).

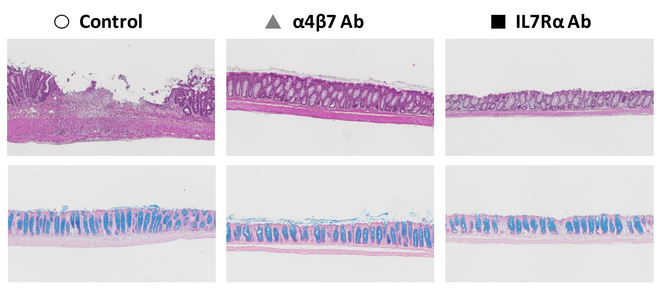


III- Anti-IL-7Ra prevents acute colitis in humanized mice model

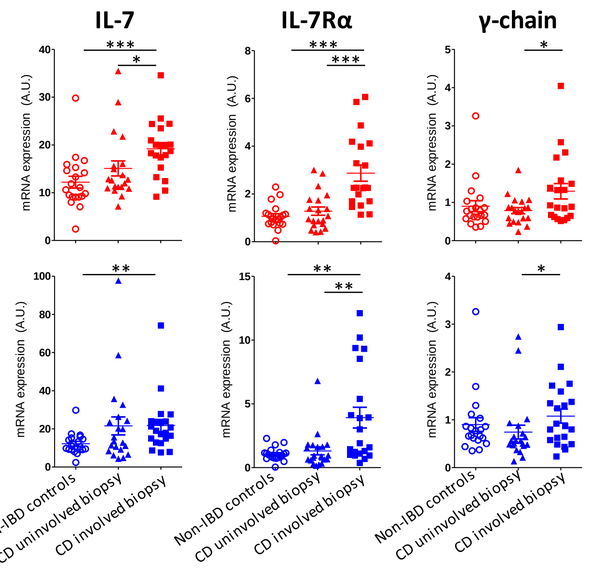


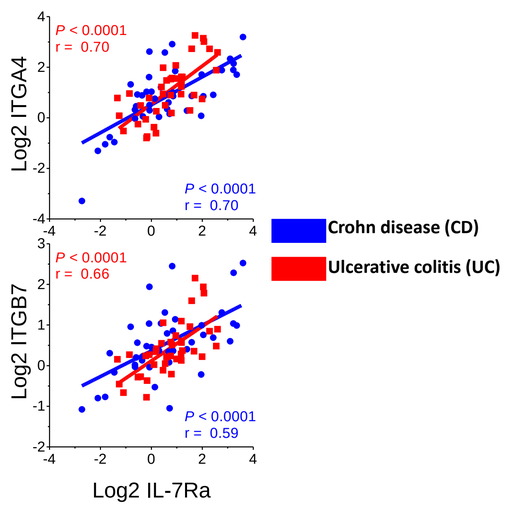


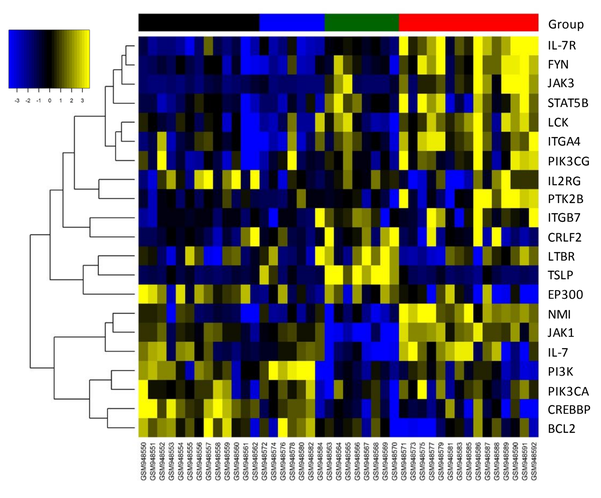
- Acute colitis was induced by intrarectal TNBS/Ethanol administration in humanized mice reconstituted with human $CD34^+$ cord blood hematopoietic stem cells. Anti-IL-7Ra mAb prevented colitis with an efficacy similar to Vedolizumab (anti- α4/β7 integrin mAb).

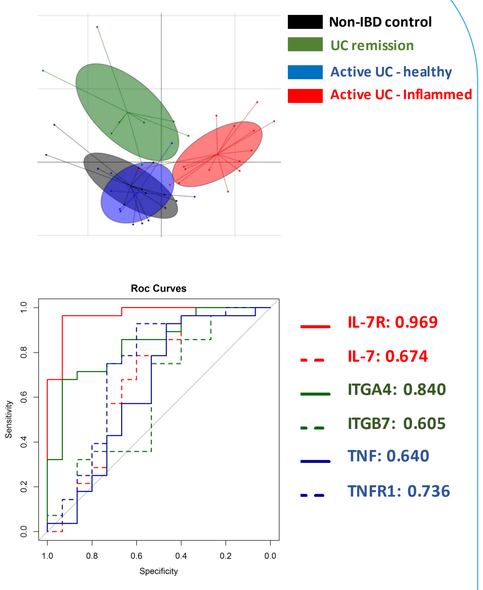


IV- IL-7/IL-7R mRNA pathway is accumulated in colon biopsies from UC and CD patients and correlates with treatment-refractory disease





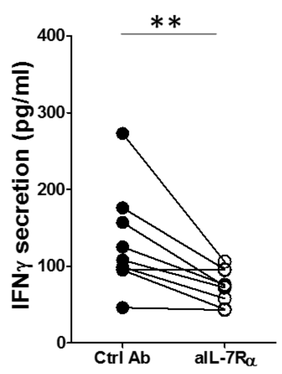




- IL-7/IL-7Ra pathway mRNA expression is significantly increased in the involved colon of CD and UC patients in comparaison with uninvolved biopsy from same patients or Non-IBD controls.
- IL-7Rα mRNA expression is correlated to ITGA4/ITGB7 mRNA expression in UC and CD patients : (ITGA4 : p< 0,0001 ; ITGA4 : p<0,0001 and ITGB7 : p<0,0001 ; ITGB7 : p<0,0001).
- 21 genes from the IL-7 signaling pathway were re-analyzed from a transcriptomic study of colon biopsies from UC patients. This IL-7 signature segregates into three distinct blocs according to the clinical status. Principal Component Analysis (PCA) of this IL-7 mucosal signature in UC patients displayed a clear and distinct separation between responders versus non-responder patients. IL-7Rα micro-array values discriminated UC patients with inflamed versus non-inflamed mucosa (ROC analysis: AUC = 96.9%).

V- Anti-IL7Ra mAb decreases ex-vivo IFNg production by UC colon biopsies

- Colon biopsies from inflamed area of UC patients (n=10) were cultured ex-vivo for 24 hours. These tissues spontaneously release proinflammatory cytokines such as IFNg (130± 19 pg/ml). Anti-IL7Rα mAb applied at 10 µg/ml in this organ culture assay significantly decreased inflammation as measured by IFNγ secretion level.



Conclusion

- IL-7 controls α4/β7 integrin expression in human effector T lymphocytes, but not in Tregs
- Anti-IL7Ra mAb decreases specifically colon inflammation in humanized mice models
- Anti-IL7Ra mAb decreases IFNg production in human organ culture assay
- Transcripts of the IL-7 pathway accumulate in UC biopsies and correlate with absence of response to treatments