Chromatin organizers SATB1 and BACH1 regulate (auto)immunity

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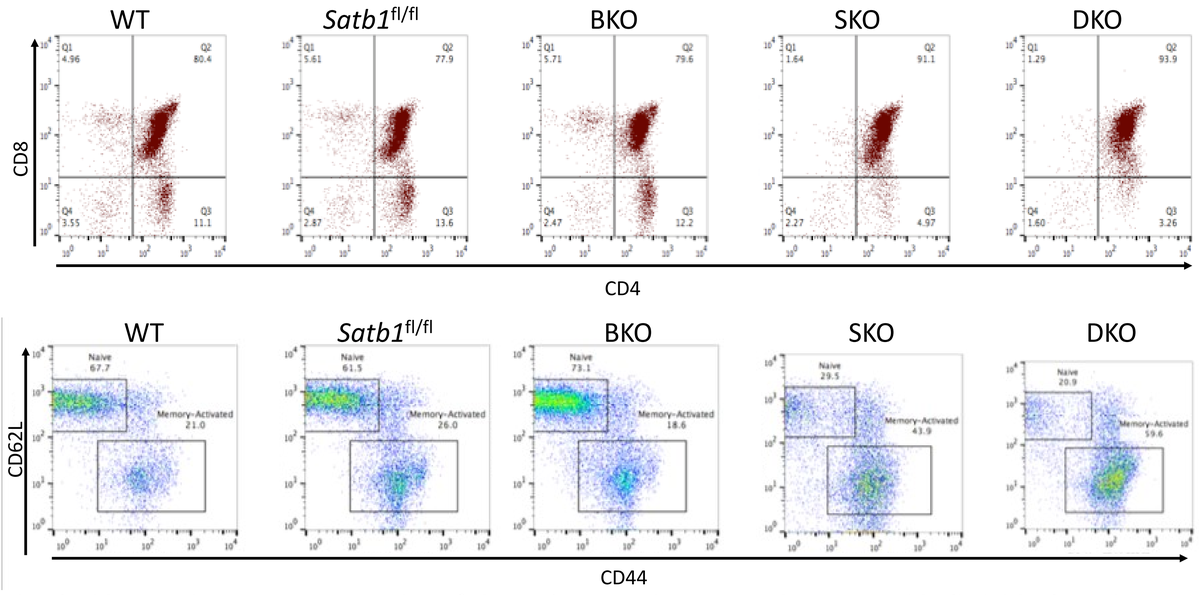
INTRODUCTION

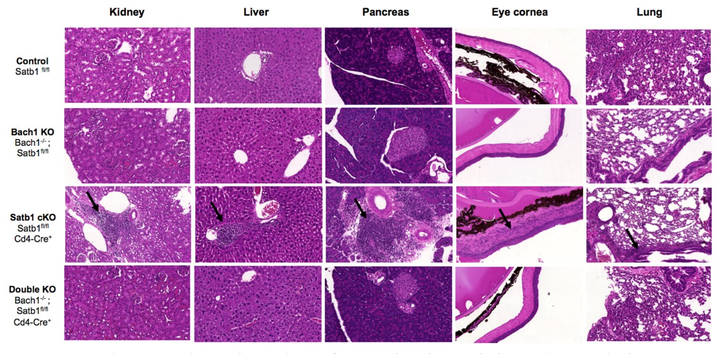
The heart of the adaptive immune system lies in the proper spatiotemporal T cell development. These processes are governed by the cellular communication in the thymus and the expression and function of several cytokines and pioneer transcription factors[1,2]. SATB1 and BACH1 are two protein factors that were identified as strong interactors of the Th2 locus, that contains the genes that express the main pro-inflammatory cytokines that regulate the Th2 cell fate, indicating a potential role of these factors in T cell development. Here we show the functional interplay of these two protein factors in T cell development and autoimmune disease-like pathophysiology of murine T cells.

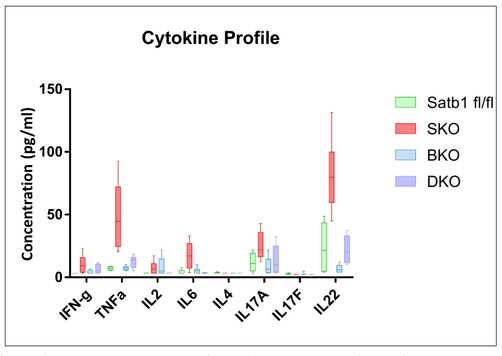
RESULTS

In the host lab there are three different mouse models, *Satb1*$^{fl/fl}$*Cd4*-Cre^{+} (*Satb1* cKO, **SKO**), BACH1$^{-/-}$ (BACH1 KO, **BKO**) and *Cd4*-Cre^{+}BACH1$^{-/-}$*Satb1*$^{fl/fl}$ (Double KO, **DKO**) mice. Phenotypical and cellular studies have demonstrated that *Satb1* cKO mice suffer from extensive autoimmune disease-related symptoms such as joint inflammation, low reproduction rate, decreased thymus size and increased peripheral lymph organ size. In a cellular level there is a blockage of the T cell development in the double positive (DP) cell stage accompanied by ectopic release of T cells in the peripheral lymph organs and T cell infiltration in several organs[3]. The BACH1 KO mice are phenotypically stable, without any obvious changes in thymus or lymph organ size but still demonstrate problematic development through the DP T cell stage.



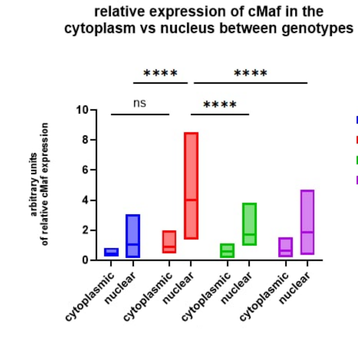
The double KO mice present a reversion of the *Satb1* cKO mice severe phenotype with diminished autoimmune disease-related features such as normal thymus and peripheral lymph organs, normal cytokine levels and no T cells infiltration of several organs. These observations point out to a possible role of BACH1 in mediating some of these features when SATB1 cannot safeguard the proper T cell development.

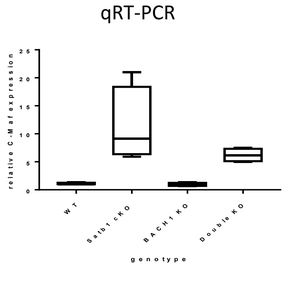


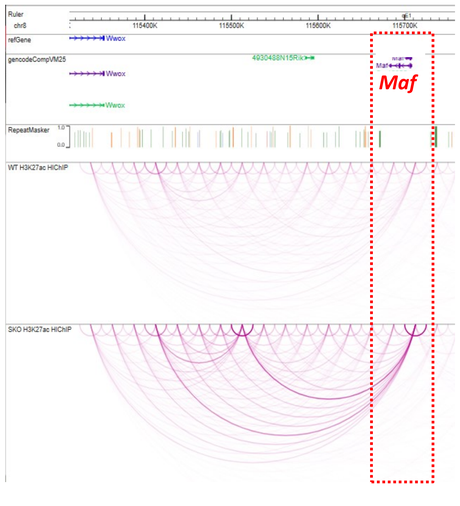


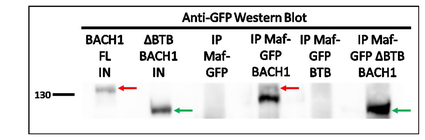
RNAseq data and HIChIP data from the host lab indicated that cMaf is the most upregulated gene in the absence of SATB1 and 21 overinteracting loops are newly created in the Maf gene locus of Satb1 KO thymocytes. cMaf is upregulated, uptakes a nuclear localization and interacts physically with BACH1 in the absence of SATB1.

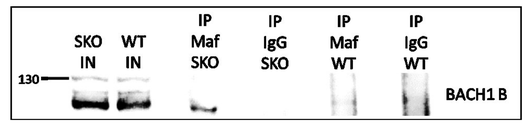
Gene	Locus	WT FPKM	SATB1KO FPKM	Log2 Fold change	q_value
Maf	8:115682941-115707794	0.34	64.77	7.58	0.00111048
Sdc1	12:8771322-8793715	0.64	61.24	6.59	0.00111048
Actn2	13:12269159-12340760	0.24	17.12	6.13	0.00111048
Ankrd35	3:96670130-96691033	0.06	4.22	6.07	0.00111048
Hlf	11:90336535-90390895	0.11	7.26	6.06	0.00111048

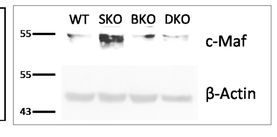




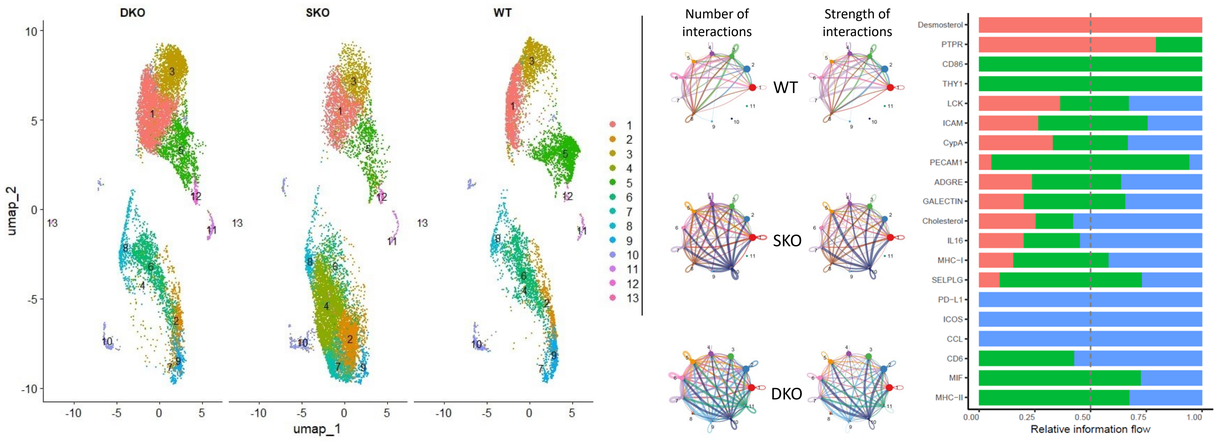




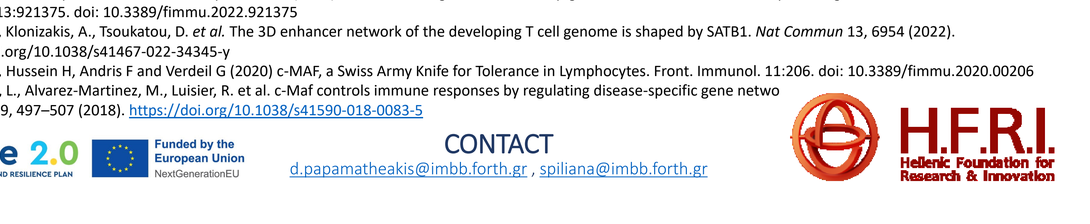




scRNA-seq analysis in whole thymi from WT, SKO and DKO mice indicated the existence of 5 newly formed clusters in the SKO and DKO mice in contract to WT. Cell chat analysis indicated that the differential clusters in the SKO mice express proinflammatory cell surface molecules which highlight an activated phenotype in the absence of SATB1.

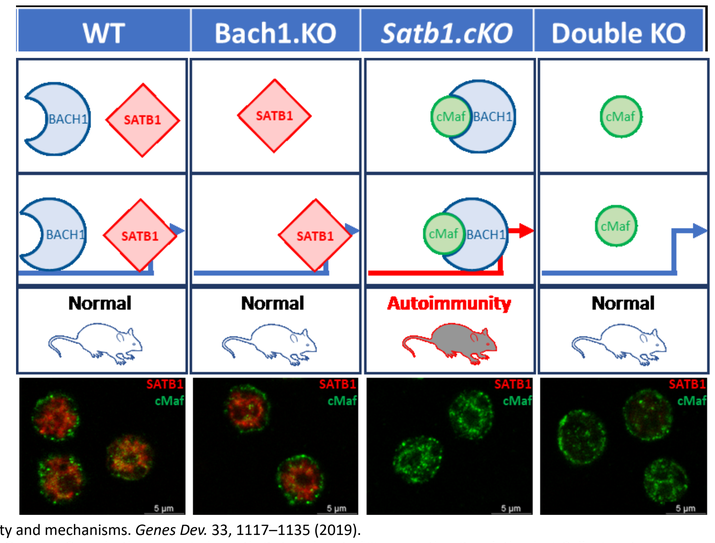


One of the most upregulated gene in the newly formed clusters of the SKO is the transcription factor cMaf[4,5]. These two clusters present a set of several pro inflammatory genes which give these cells an activated-like signature.



CONCLUSIONS

- *Satb1* cKO mice present extensive autoimmune disease-like features due to deregulation of the 3D enhancer landscape of the developing T cells.
- Loss of both SATB1 and BACH1 reversed this pathological phenotype.
- Maf is a strong candidate that in cooperation with BACH1 mediated some of the pathological features observed in the absence of SATB1.



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