Identification of a common transcriptional signature for regulatory B cells in Humans and Mice

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Background

Regulatory B cells (Bregs) have been described in mice and humans for their ability to regulate inflammation through a variety of mechanisms in different pathological situations. Up to date, no consensual and common Breg phenotype has been described, and whether there is a Breg lineage commitment or if they acquire their function under certain environmental conditions remains unknown. To address these points, we performed a sample size weighted meta-analysis of publicly available transcriptomic data from 4 different Bregs studies in humans and 6 Bregs studies in mice.

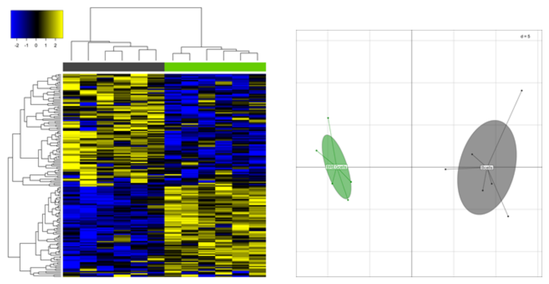
Materials and Methods

In human we retrieved four datasets comparing Bregs and non-Bregs: Van de Ven et al., JACI 2013, Lin et al., Immunol 2014, Bigot et al., AJT 2016 and Chesneau et al., submited. And 6 in mice: Shen et al., Nature 2014, Khan et al., Eur. J. Immunol 2015, Braza et al., Allergy 2015, Lino et al., Immunity 2018 and Ray et al., Nat com 2018. For each dataset, raw data were processed following a homogenous method and differentially expressed genes between Bregs and non-Bregs were identified using the limma R package with adjusted p-value <5% and fold change (FC) > 2 were considered as significantly differentially expressed. Finally, the sample size weighted meta-analysis (Stouffer's Z-score method) was performed using the METAL software (Willer et al., 2010).

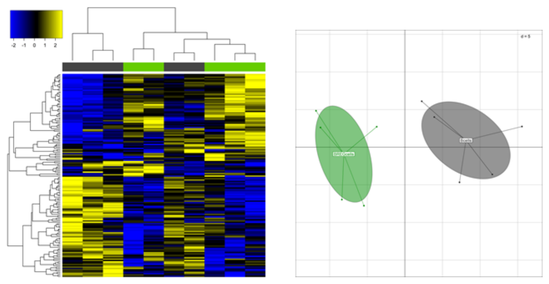
Results

Core gene signature discriminating Bregs from non-Bregs in human

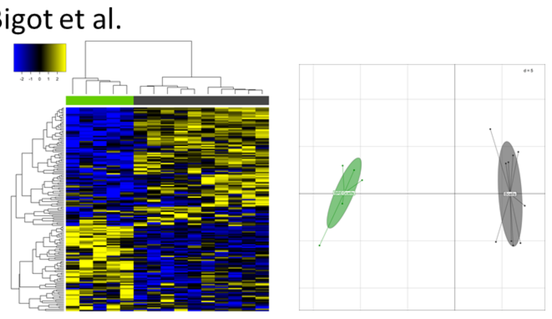
Veen et al.



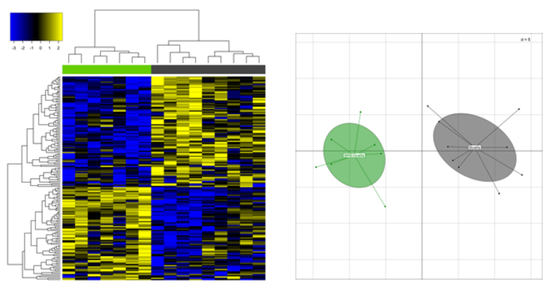
Lin et al.



Bigot et al.



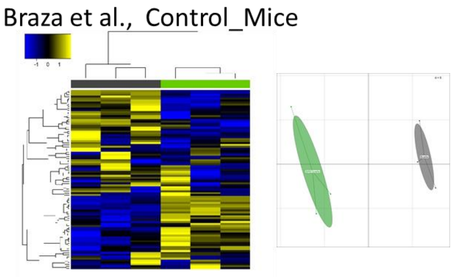
Chesneau et al.



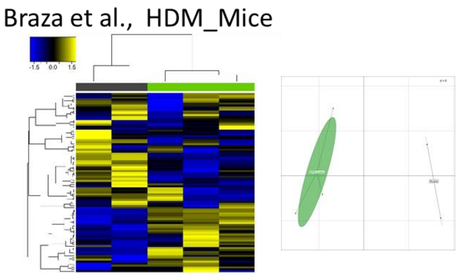
→ 165 common genes were identified to be differentially expressed between Bregs and non-Bregs in the meta-analysis of the four studies.
→ This human gene signature well discriminates Bregs and non-Bregs.

Core gene signature discriminating Bregs from non-Bregs in mice

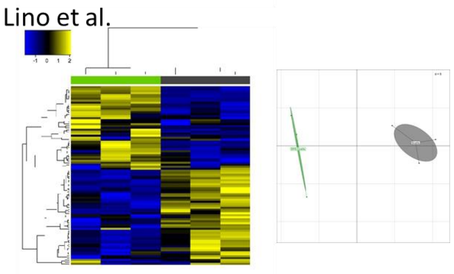
Braza et al., Control_Mice



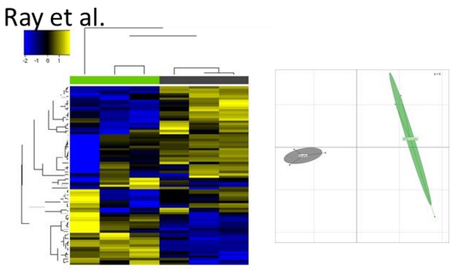
Braza et al., HDM_Mice



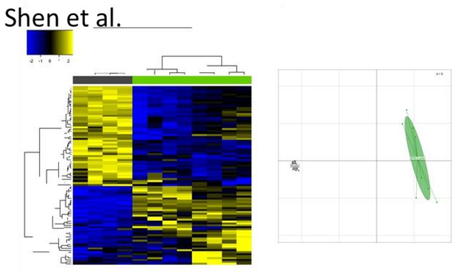
Lino et al.



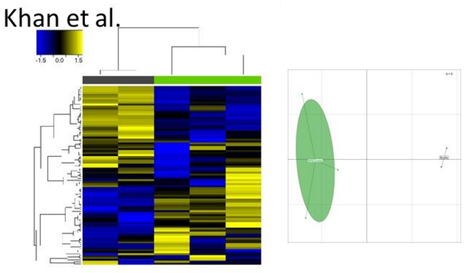
Ray et al.



Shen et al.



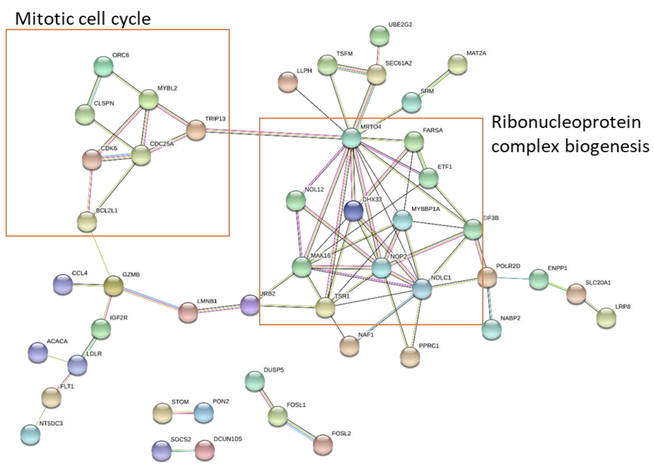
Khan et al.



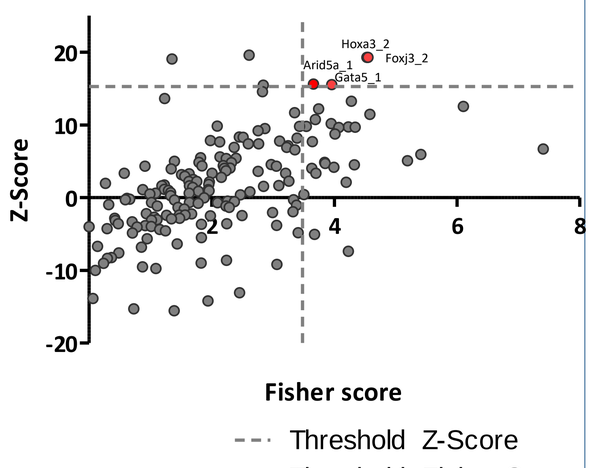
→ 93 common genes were identified with a great discrimination between Bregs and non-Bregs in mice datasets.

Predicted protein-protein interactions and potential enrichment of transcription factor targets in human Breg signature

String interaction among the Up-regulated differentially expressed genes



Enrichment of Transcription factors binding site



→ The human Breg signature is composed of genes known as involved in immune regulation and cell cycle and related to 4 transcription factors regulating genes implicated in B cell biology.

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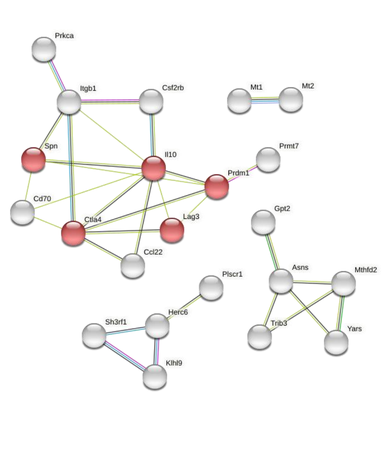
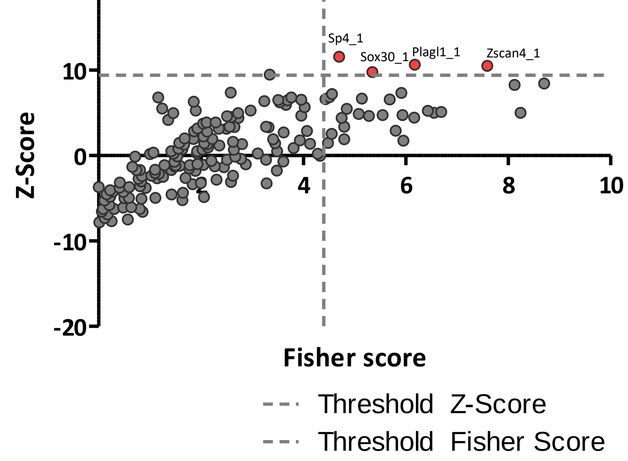
String interaction among the Up-regulated differentially expressed genes



Enrichment of Transcription factors binding site



→ Clear gene signature of mice Bregs with mostly up-regulated genes involved in regulation of immune response and an enrichment of transcription factor binding site in genes with an apoptotic function.

Conclusion

Our results highlight human Bregs with a proliferating state and provide new insights on possible mechanisms by which Bregs tightly regulate their homeostasis. In mice, Bregs exhibit a gene expression with function associated in the regulation of immune response. Moreover the absence of common signature between human and mice Bregs and the lack of a common transcription factor support the hypothesis of B cell acquiring their regulatory function under certain environmental conditions. Understanding what are the signal for B cells to become a Breg will help their study and understand their role in cancer, autoimmunity and in tolerance mechanisms.

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