

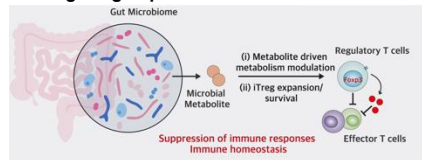
Metabolite induced Treg expansion restores immune homeostasis in multiple autoimmune murine models

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Introduction

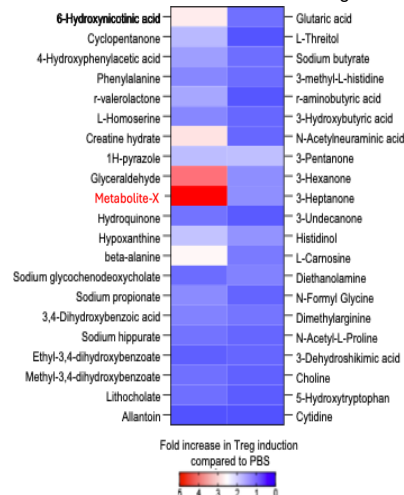
Background

- Autoimmune diseases currently affect 3-5% of the world's population [1]
- Microbial metabolites have gained traction for their impact on immune responses and have been implicated in numerous autoimmune diseases [2]
- The role of many microbial metabolites in regulating T cell immunity and differentiation is largely unknown
- NanoDiscs have been shown to effectively drain to the lymphatic system, and interact with immune cells [3]
- Further investigation of microbial metabolites for treatment of autoimmune diseases is a promising and novel approach
- We hypothesize that **delivery of microbial metabolites to the lymph nodes** allow for direct cross-talk with host immune cells and modulation of their metabolism, **inducing Treg expansion and survival**



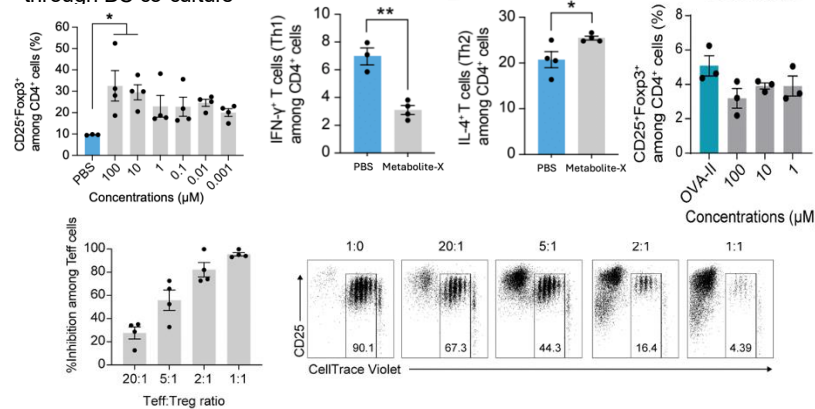
Approach

- Screening different microbial metabolites that can induce Treg differentiation and proliferation
- Metabolite library was curated from previous data, where inulin gel was administered to mice, and changed their metabolic profile [4]
- Metabolite-X is selected for further formulation with nanodiscs as it induced a 5-fold increase in Treg
- Development of Metabolite-X loaded Nanodiscs was evaluated for efficacy in multiple autoimmune murine models, and mechanism of action was further investigated



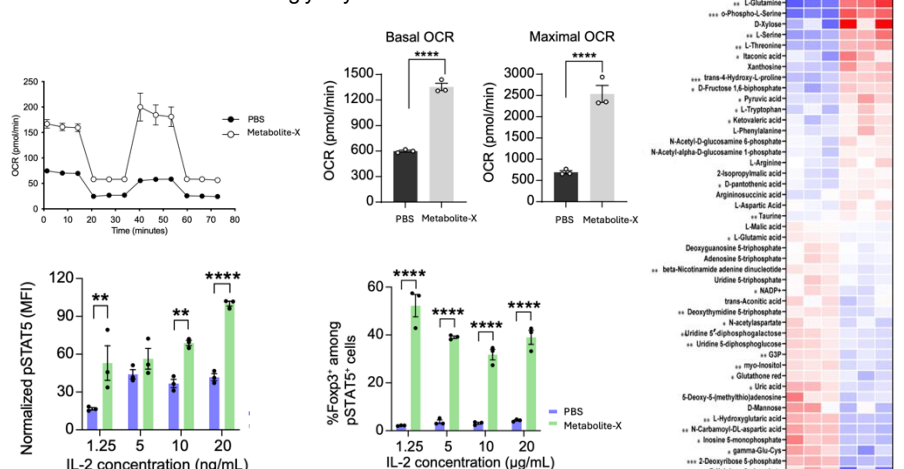
Metabolite-X induces Treg differentiation

- Induces Treg differentiation in vitro
- Decreases IFN- γ expressing Th1 cells and increases IL-4 expressing Th2 cells
- Metabolite-X does not induce Tregs through DC mediated mechanisms, as shown through DC co-culture



Metabolite-X increases oxygen consumption rate, likely by promoting OXPHOS, and induced pSTAT5 in CD4 T cells

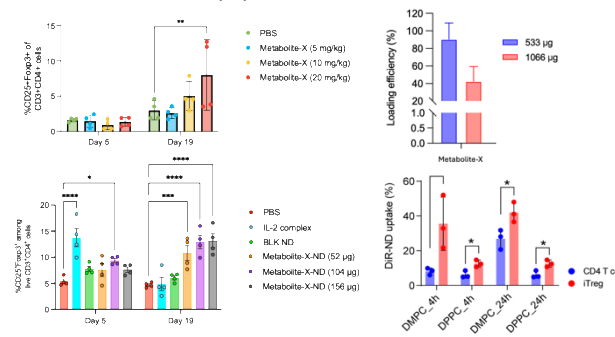
- Increases pSTAT5 expression, mainly in regulatory T-cells
- Decreases IFN- γ expressing Th1 cells and increases IL-4 expression
- Targeted metabolomics shows an increase in OXPHOS/mitochondrial metabolism and decreased glycolysis in CD4 T-cells



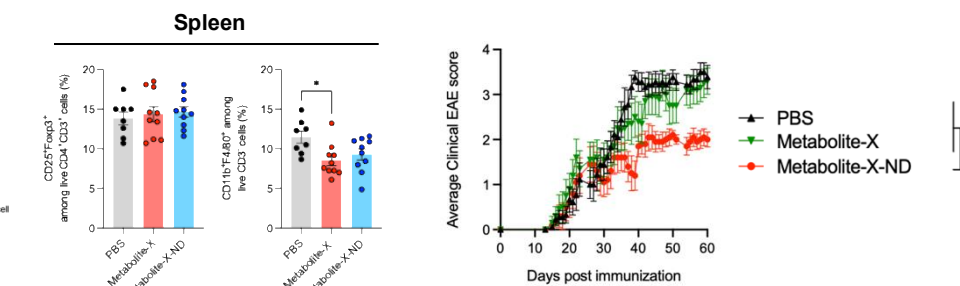
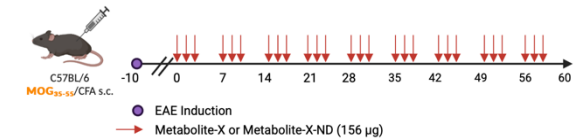
Result

Nanodiscs can be loaded with Metabolite-X and induce Treg expansion

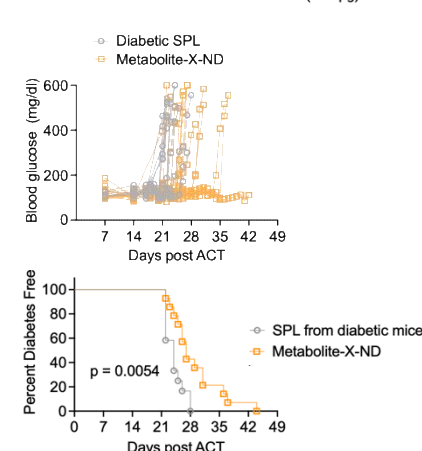
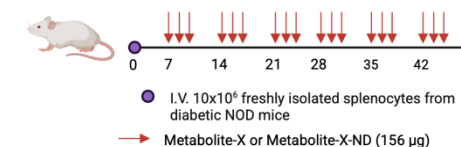
- Analysis of PBMCs from mice dosed with Metabolite-X and Metabolite-X-ND significantly increases Tregs
- High loading efficiency into nanodiscs, >80%
- Metabolite-X-ND are up taken significantly more by iTregs than CD4 T cell populations



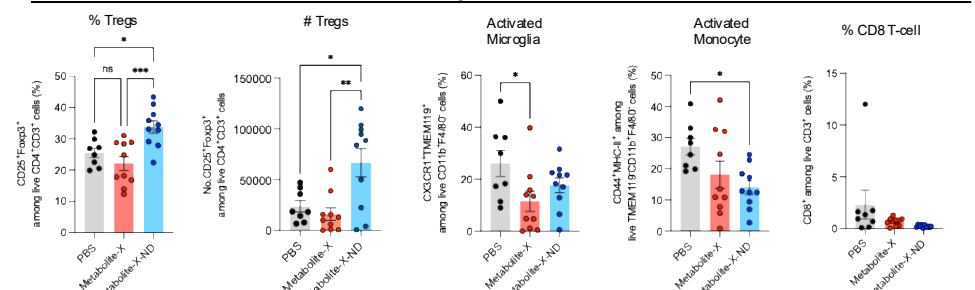
Metabolite-X-ND increases Tregs in the spinal cord, decreases activated microglia/monocytes, and ameliorates experimental autoimmune encephalomyelitis



Nanodiscs loaded with Metabolite-X exhibits efficacy in murine type-1 diabetes model



Spinal Cord



Summary

Conclusion:

- Metabolite-X induces Treg through pSTAT5 pathway, and metabolic remodeling
- Metabolite-X-ND can induce Tregs and exhibit robust efficacy in multiple autoimmune murine models
- This highlights a potential strategy for returning the immune system to homeostasis in the context of autoimmune diseases

Acknowledgement:

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Reference:

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- Zhang et al, Journal of Autoimmunity, 2020 (111) ;
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- Han K et al, Nat Biomed Eng. 2021