

Defining the contribution of adipose resident tissue macrophages to adipogenesis

Jia Zhao & Adriana Payan-Medina

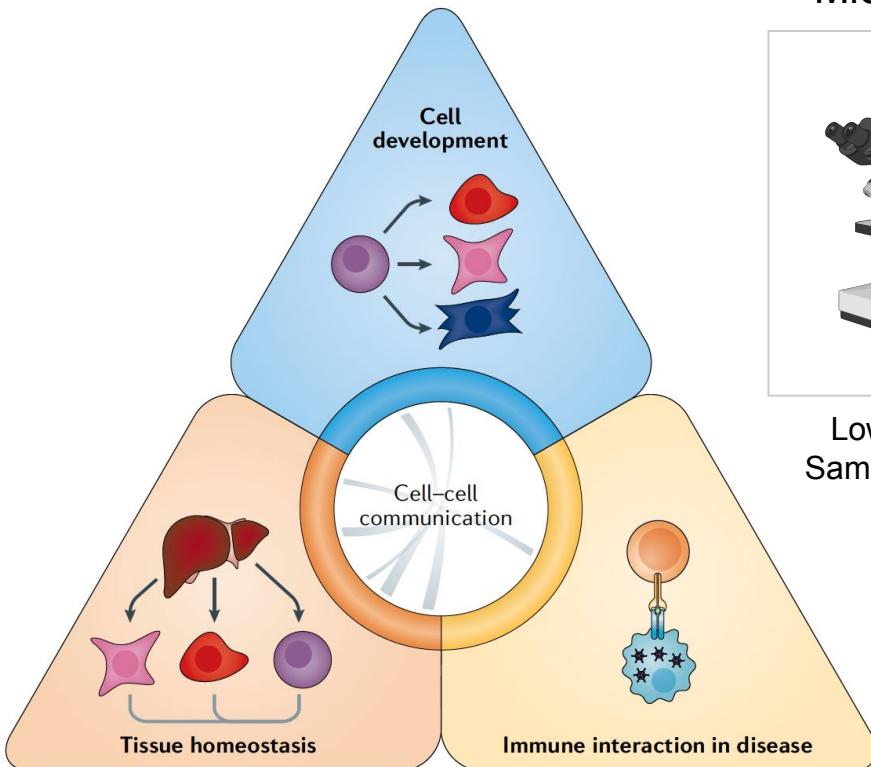
20.440 group project

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All codes and figures are available at

https://github.com/Jia-Zhao1998/20.440-Group_Project_JZ_APM

Intercellular communication is crucial but challenging to study

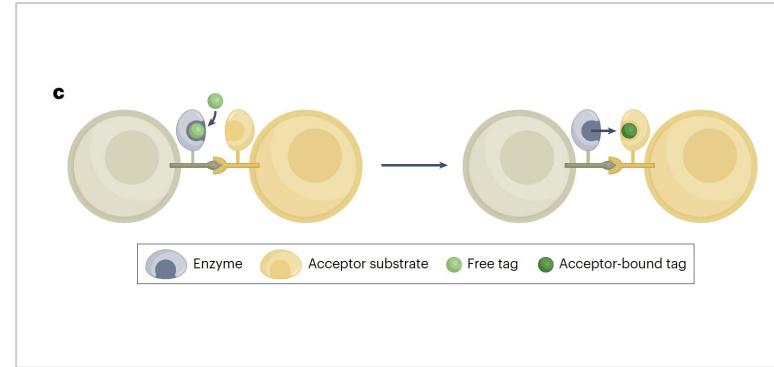


Microscopy



Low throughput
Sample processing

Proximity labeling



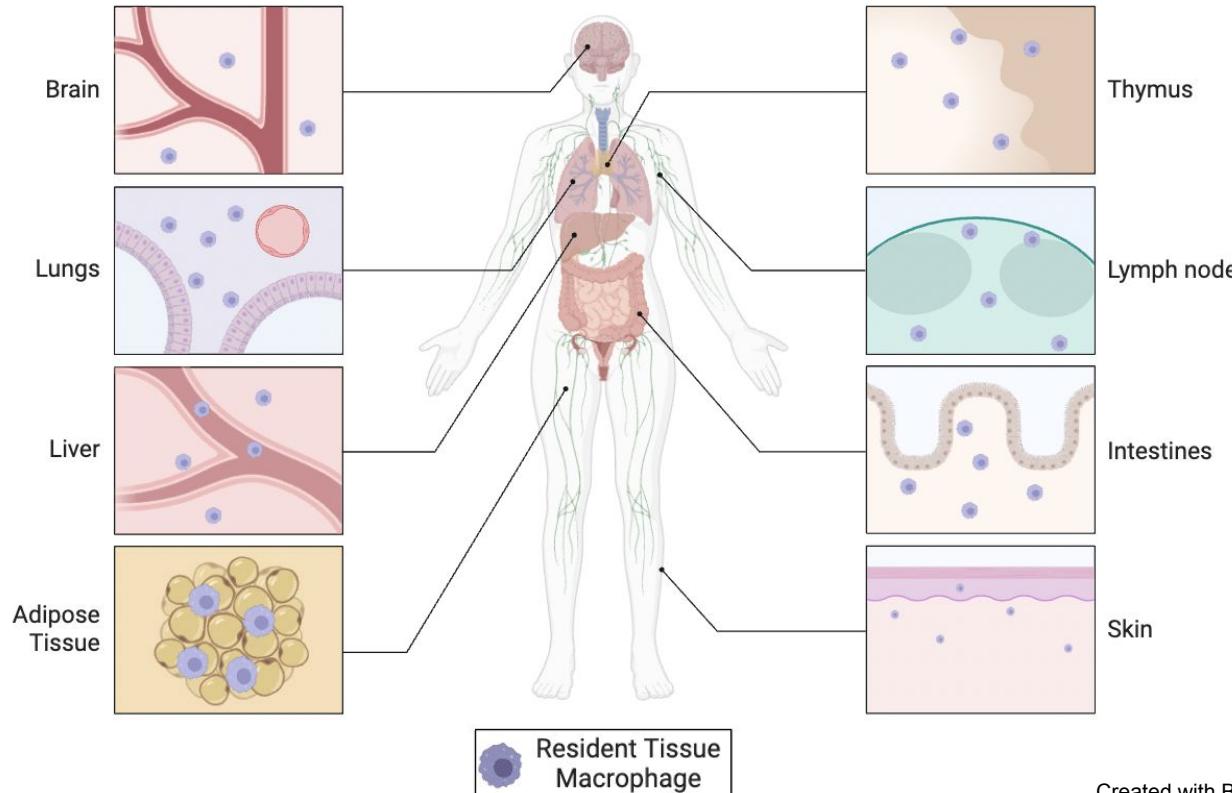
Require mouse models
Takes long

Computational tools

High throughput
Low cost
Fast

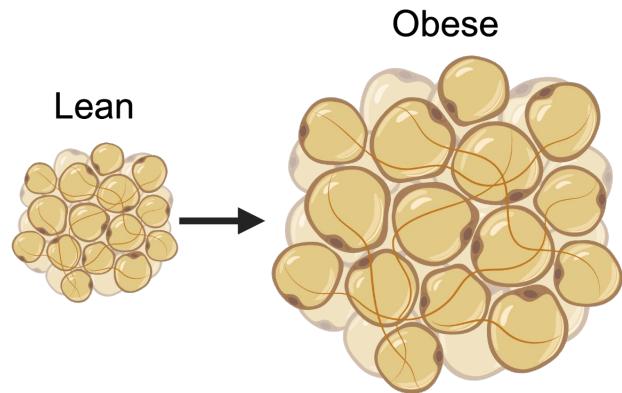
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Resident Tissue Macrophages (RTMs) are professional communicators to support tissue function

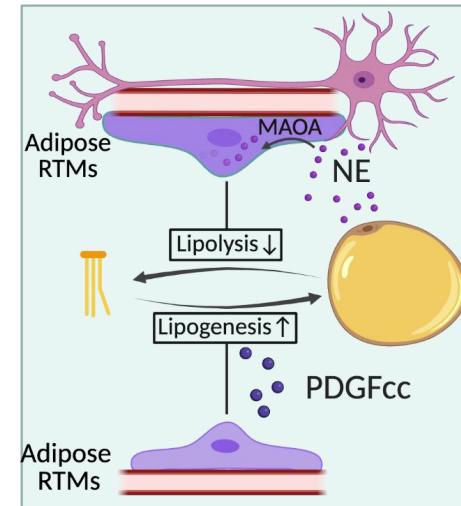


Adipose RTMs are important for fat function

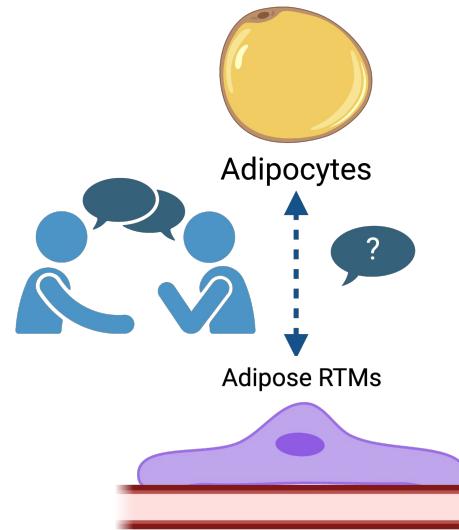
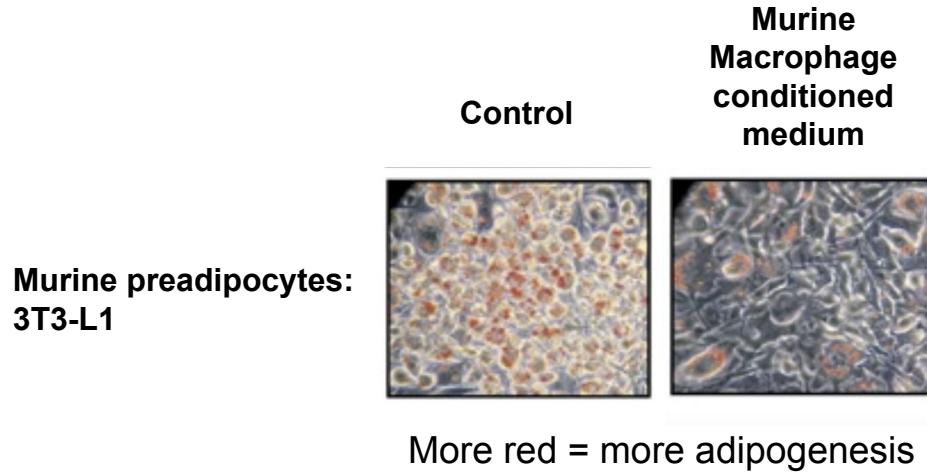
Fat is associated with obesity and type II diabetes



Do adipose RTMs regulate adipogenesis?



Do adipose RTMs regulate adipogenesis?



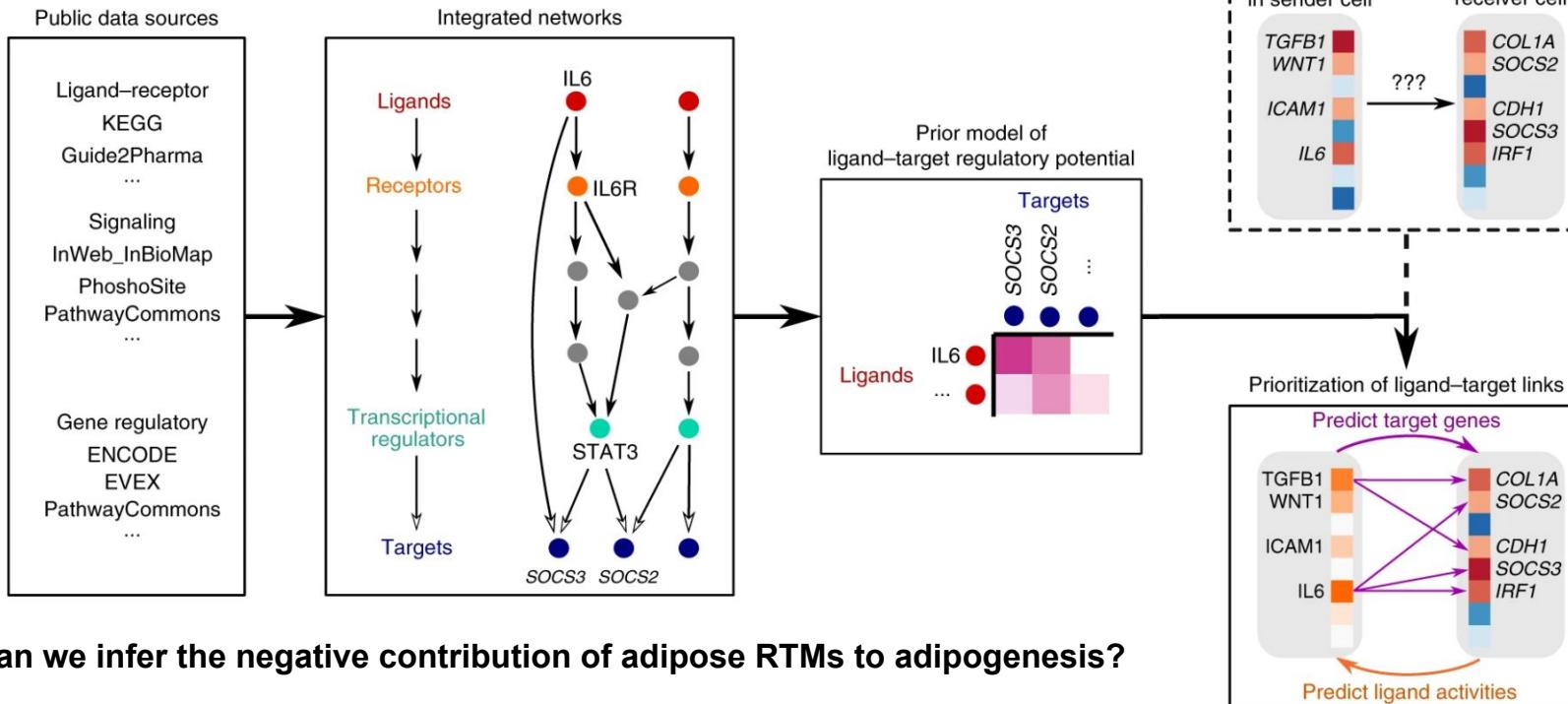
Hypothesis: adipose RTMs inhibit adipogenesis

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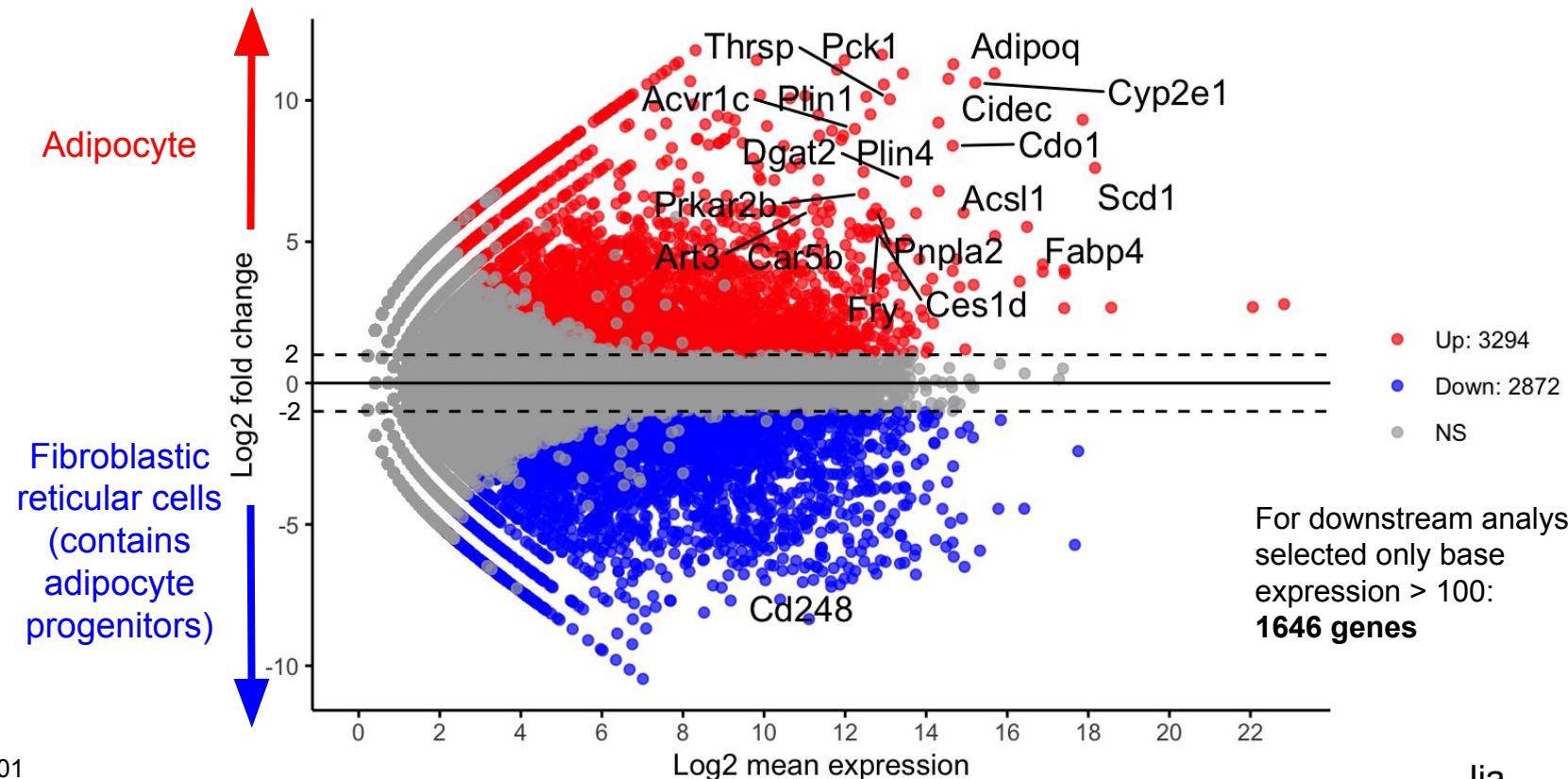
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NicheNet: modeling intercellular communication by linking ligands to target genes

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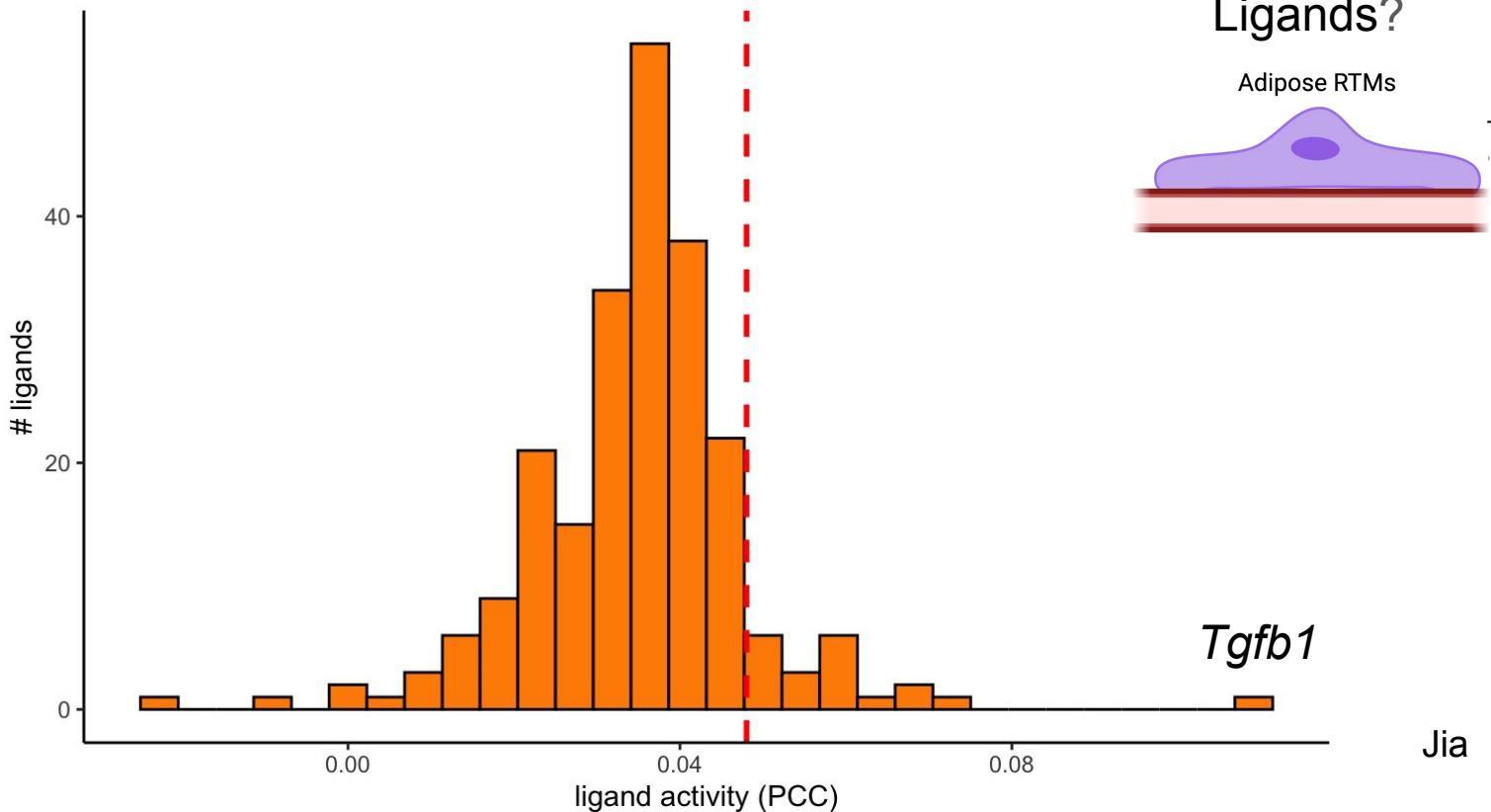


Identify a potential gene set important for adipogenesis

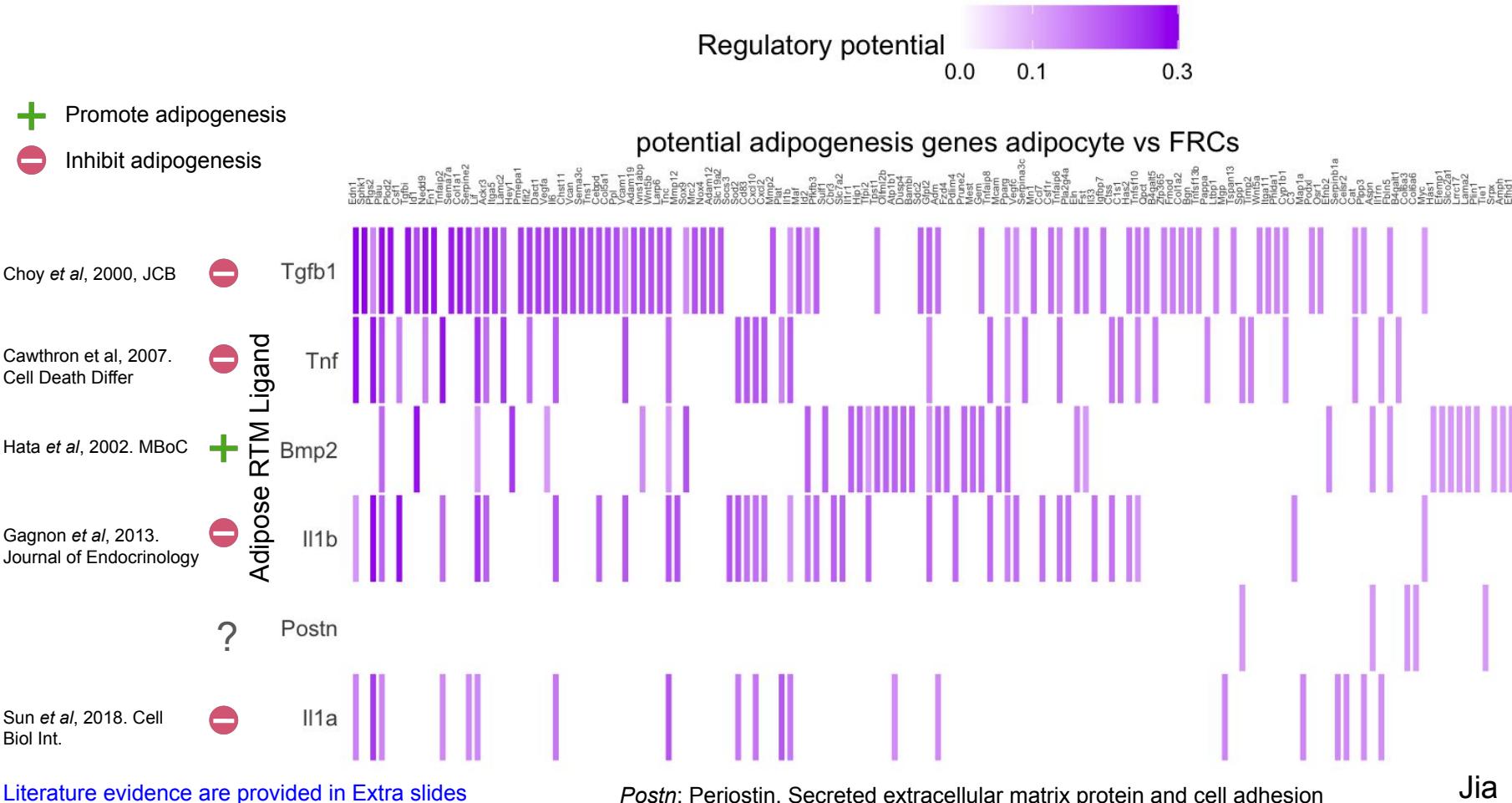


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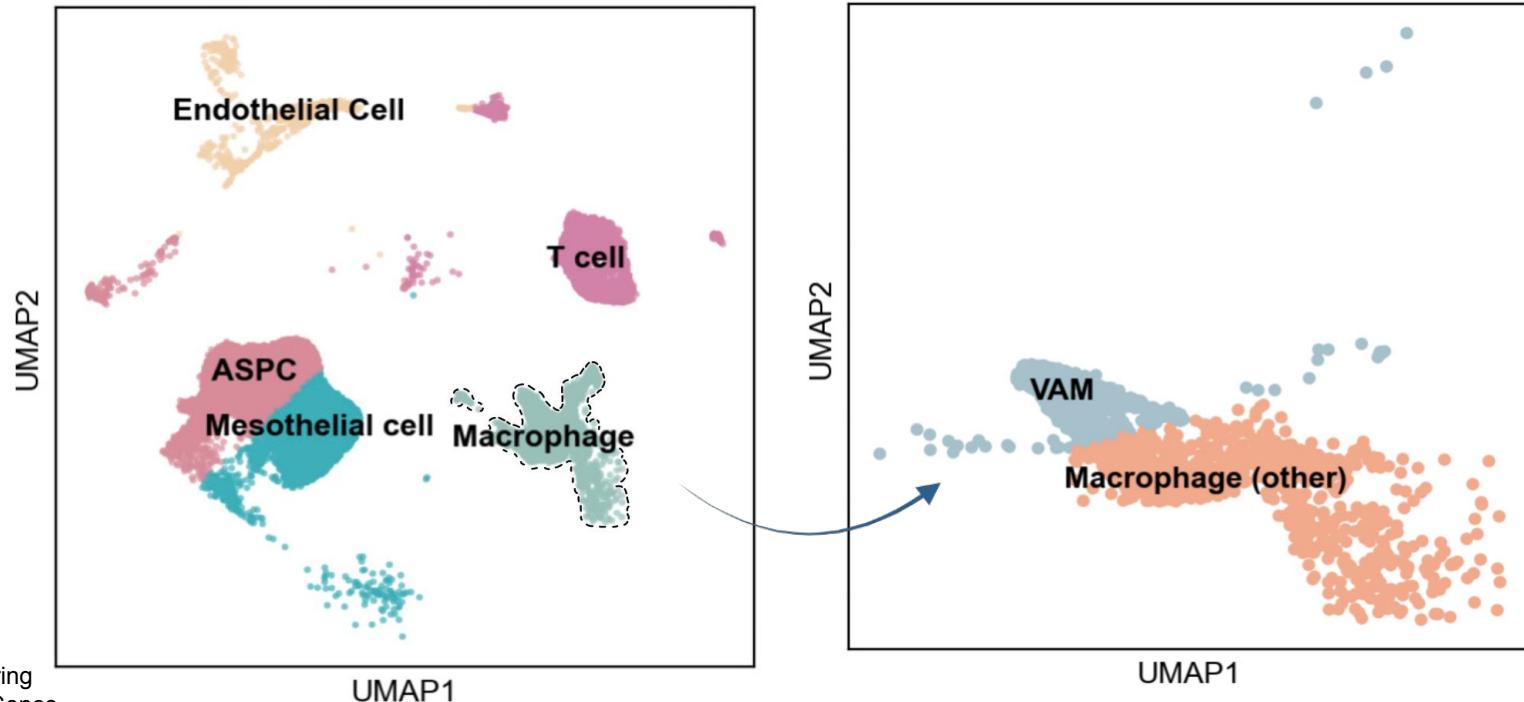
Predicted top 20 adipose RTM ligands to regulate adipogenesis



Adipose RTM ligands show links to adipogenic gene set supported by literature



Identified human adipose RTM subpopulation involved in adipogenesis



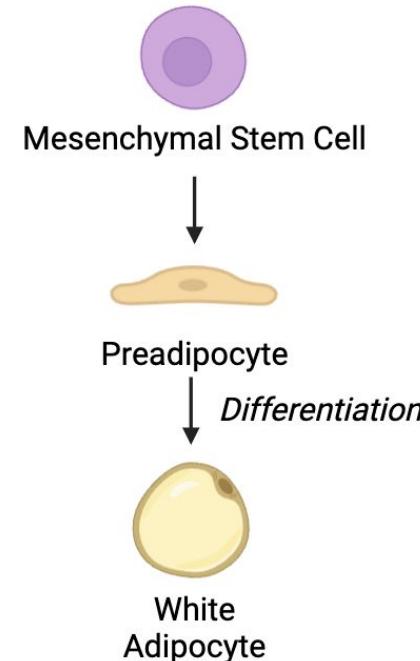
Adriana¹⁰

Identified human adipose RTM subpopulation involved in adipogenesis

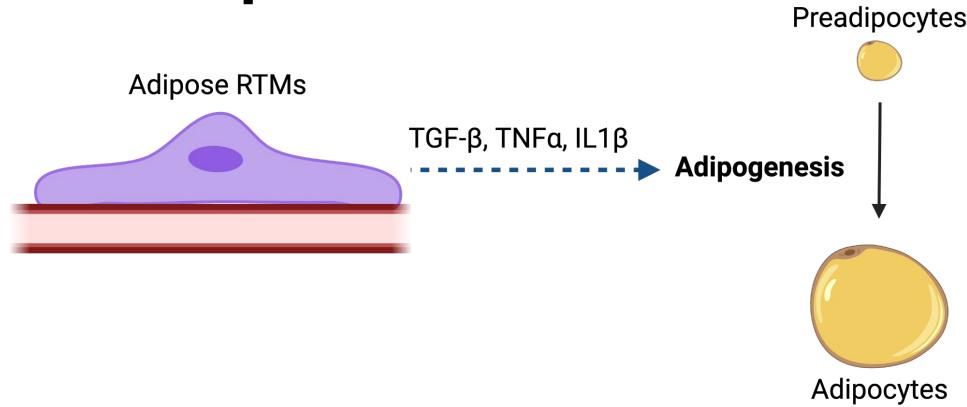
Pathway	FDR
Fat cell differentiation	4.39E-04
Regulation of fat cell differentiation	1.17E-03

Additional relevant pathways identified included:

- Cell cycle regulation & transition
- Apoptotic signaling
- Signaling pathway regulation



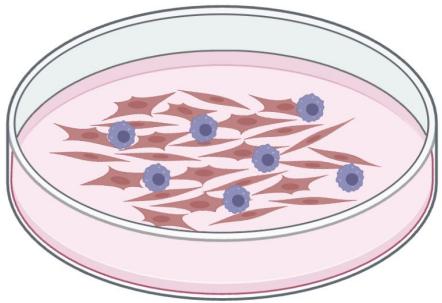
Conclusion and Impact



- Identified human adipose RTM subpopulation involved in adipogenesis
- Limitations:
 - Lack of a confident adipogenic gene set dataset
 - NicheNet can not effectively predict *in vivo* intracellular communication
 - Different computational algorithms?

Future work includes experimental validation and enhanced cell-cell communication analysis scope

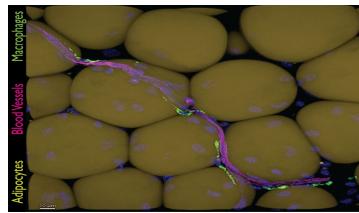
Adipogenic assay



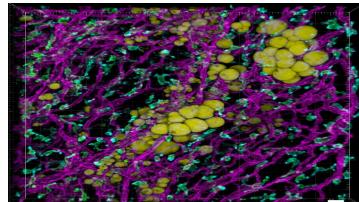
Resident Tissue Macrophage
Preadipocyte

Is adipose RTM function in adipogenesis age-dependent?

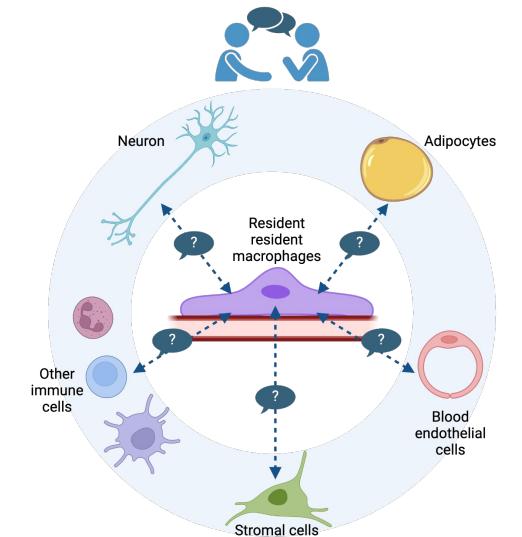
Adult



Neonate

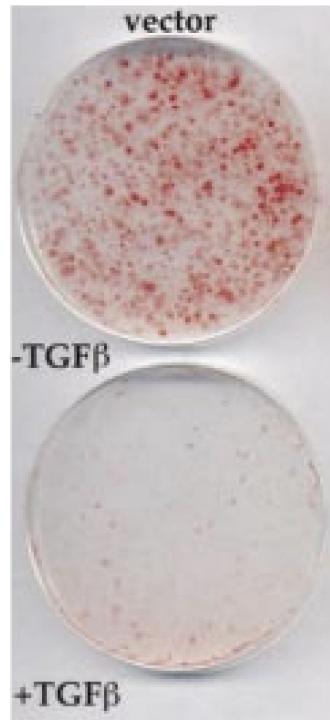


Exploration with additional cell types



Extra slides

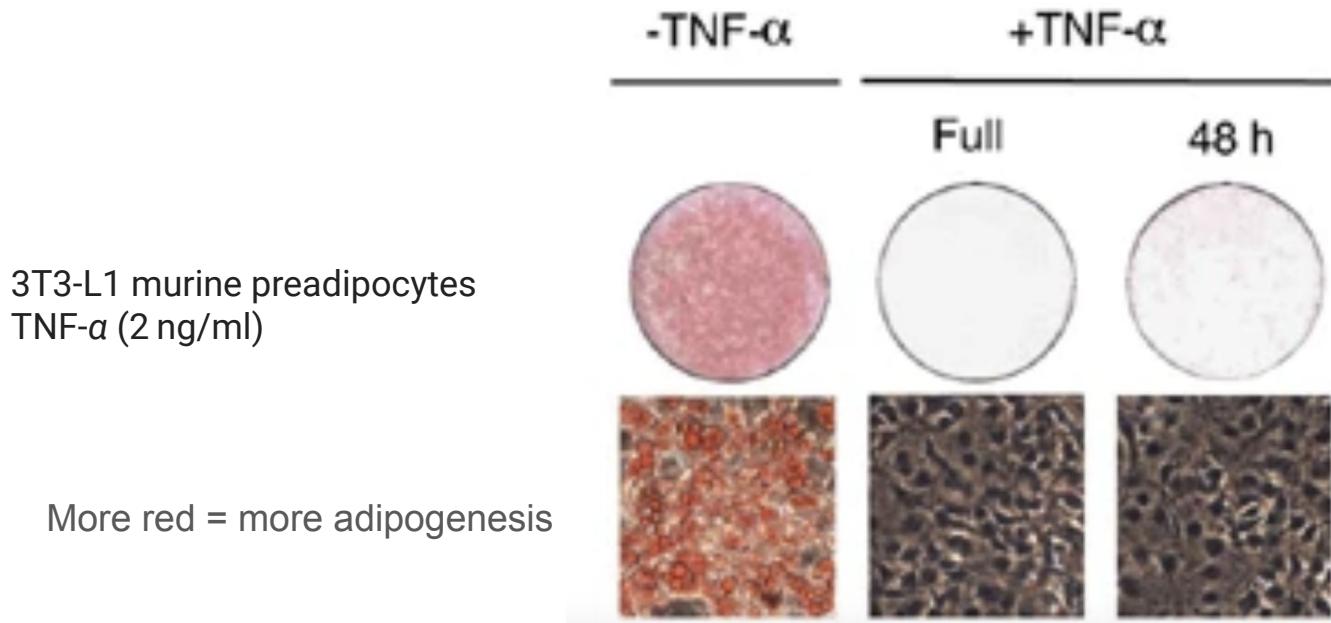
Literature evidence: TGF- β signaling inhibits adipogenesis in vitro



Murine preadipocyte cell line 3T3-F442A
Oil Red O staining after 8 d in
differentiation medium, either without or
with 1 ng/ml TGF- β

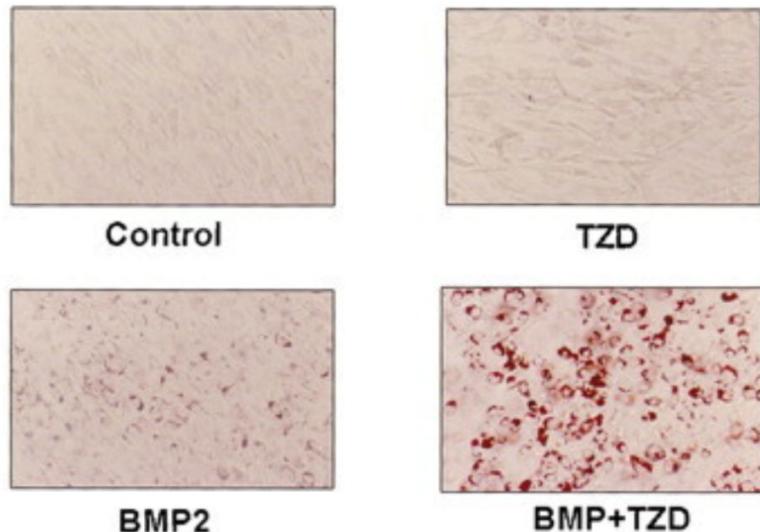
More red = more adipogenesis

Literature evidence: Tumour necrosis factor- α (TNF α) inhibits adipogenesis in vitro



Literature evidence: BMP (Bone morphogenetic protein 2) signaling promotes adipogenesis in vitro

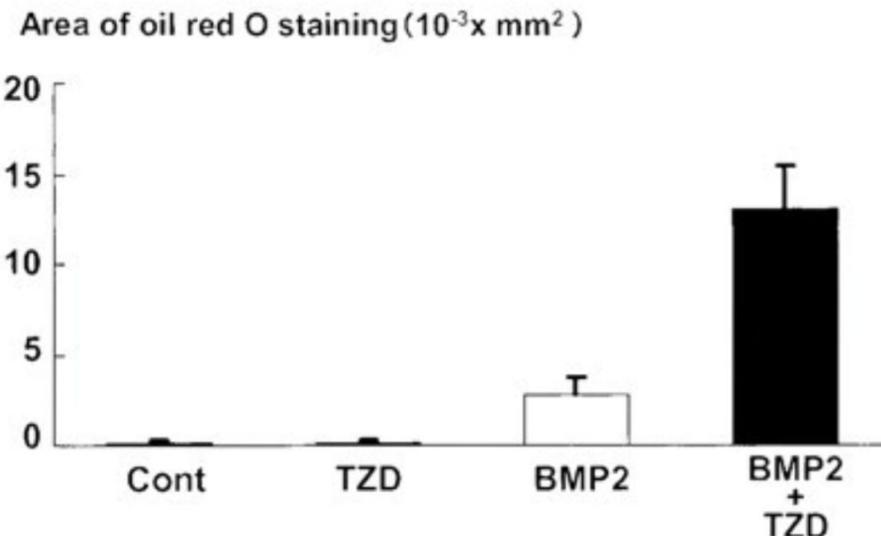
A Murine preadipocyte cell line
C3H10T1/2



More red = more adipogenesis

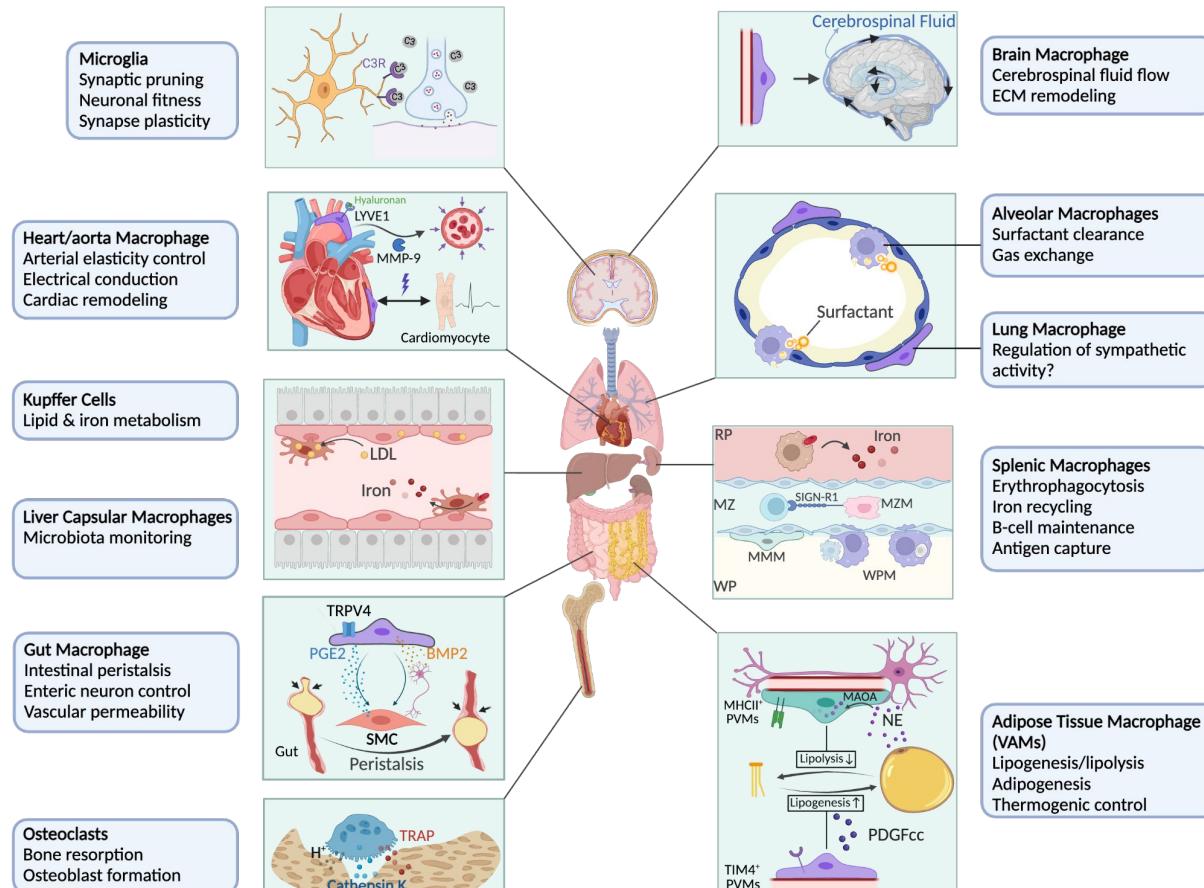
TZD = troglitazone = a ligand for PPAR γ : a key nuclear transcription factor that regulates adipogenesis

B



Jia

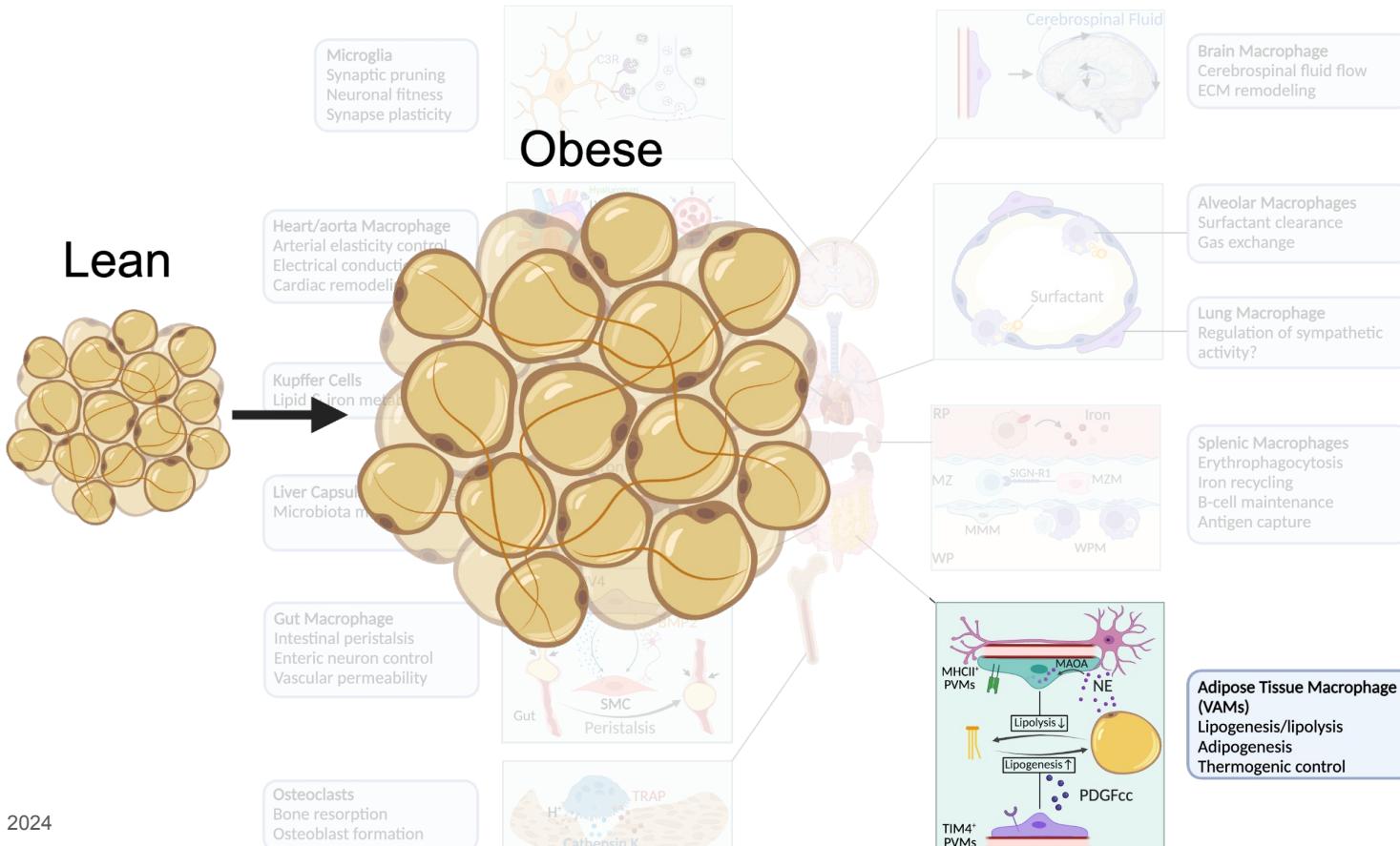
Tissue Resident Macrophages (TRMs) are professional communicator to support tissue function



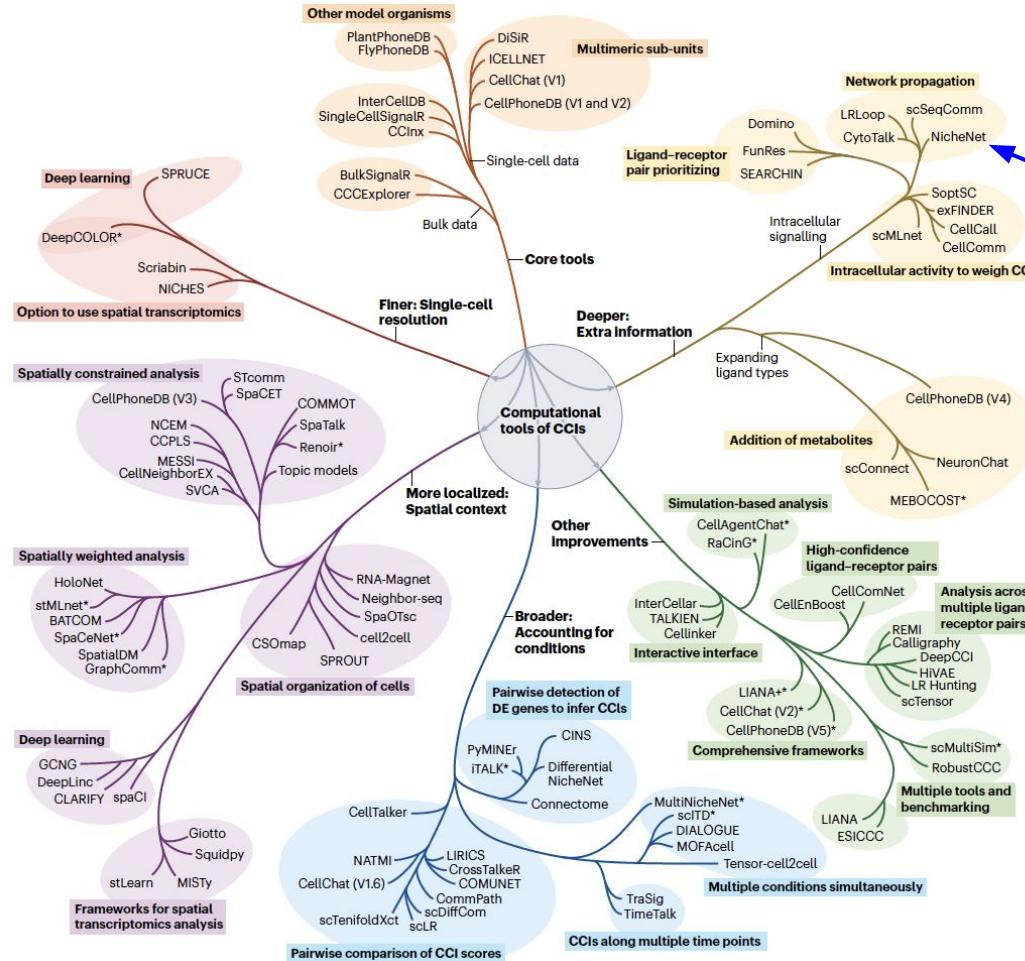
Jia

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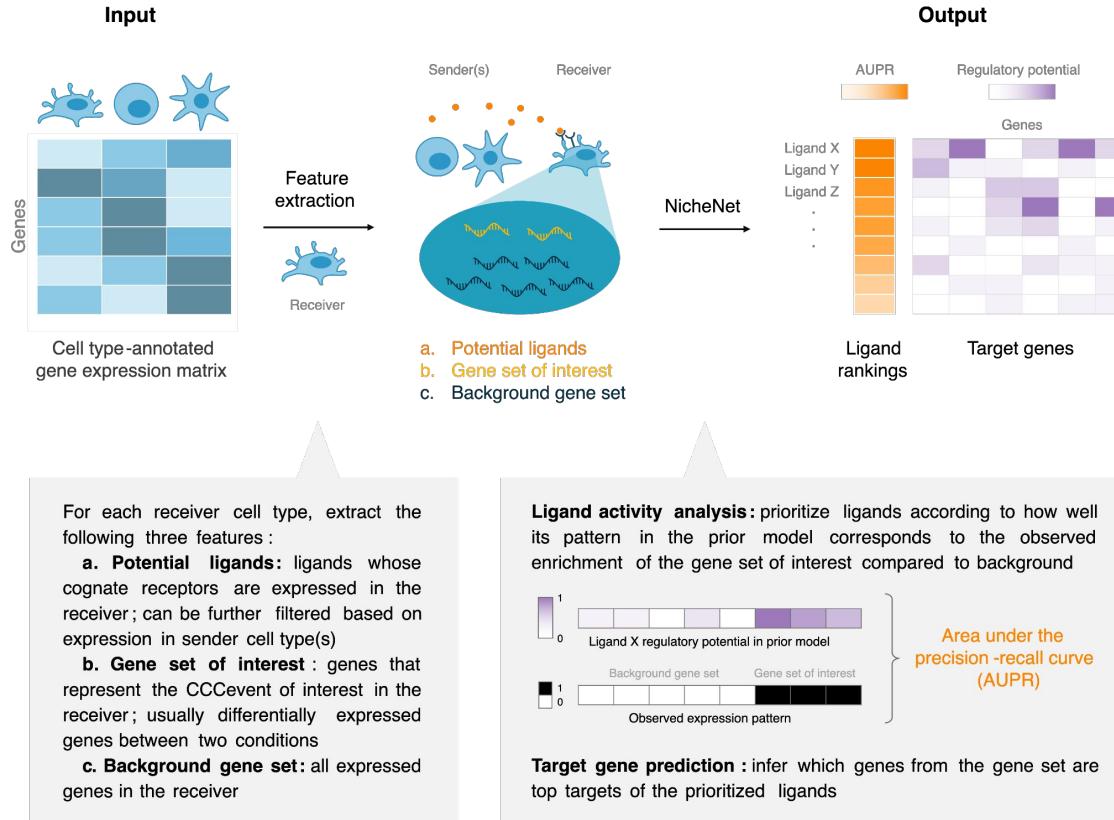
Resident Tissue Macrophages (RTMs) are professional communicator to support tissue function



Future directions: try different cell-cell interaction tools

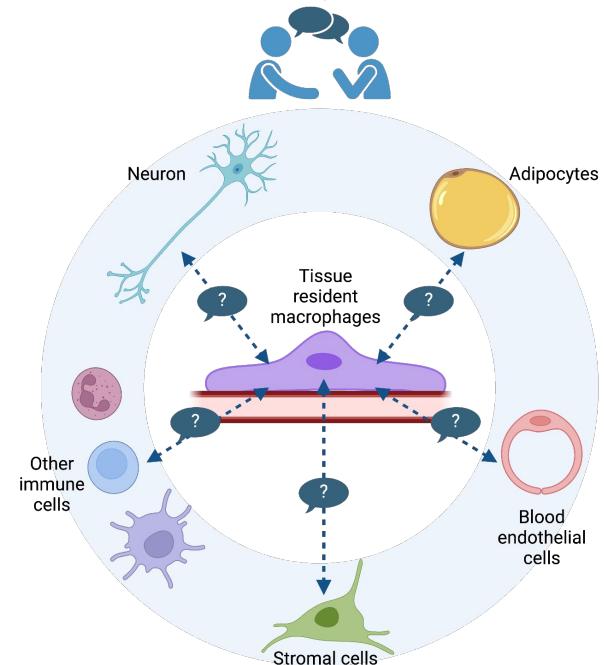


NicheNet: modeling intercellular communication by linking ligands to target genes



Future direction

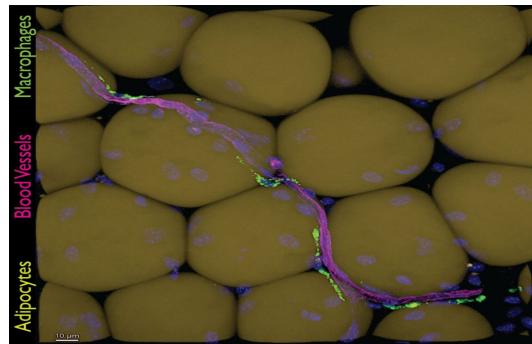
- Experimental validation:
 - Adipogenic assay: delete *Tgfb1* in VAMs (VAM Δ) and culture with preadipocytes to measure the adipogenesis
 -



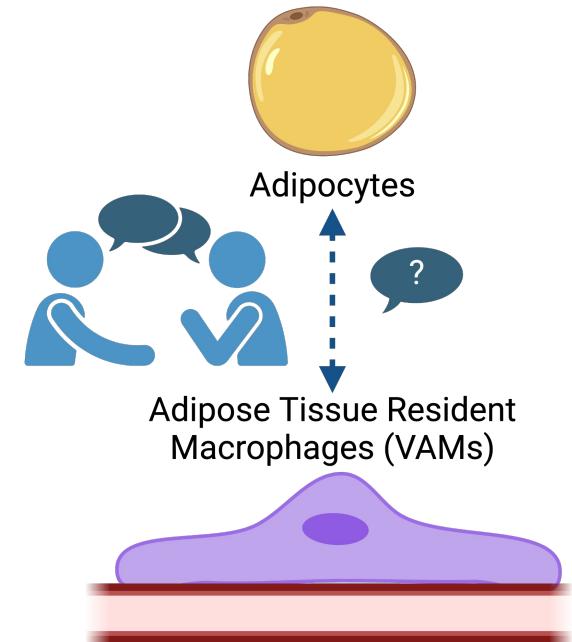
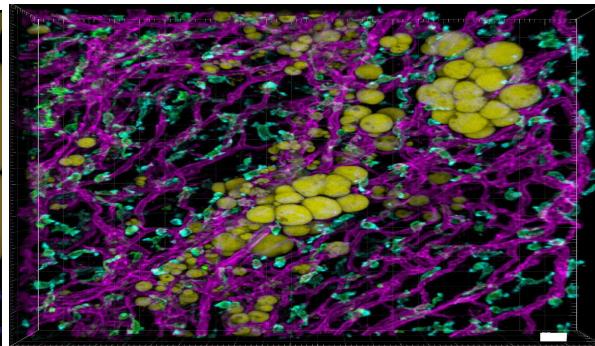
Do adipose RTMs contribute to adipogenesis?

Adipose RTMs seed the fat pad site in early embryo long before adipocytes fully mature

Fat (Adult mouse)



Fat (Newborn mouse)

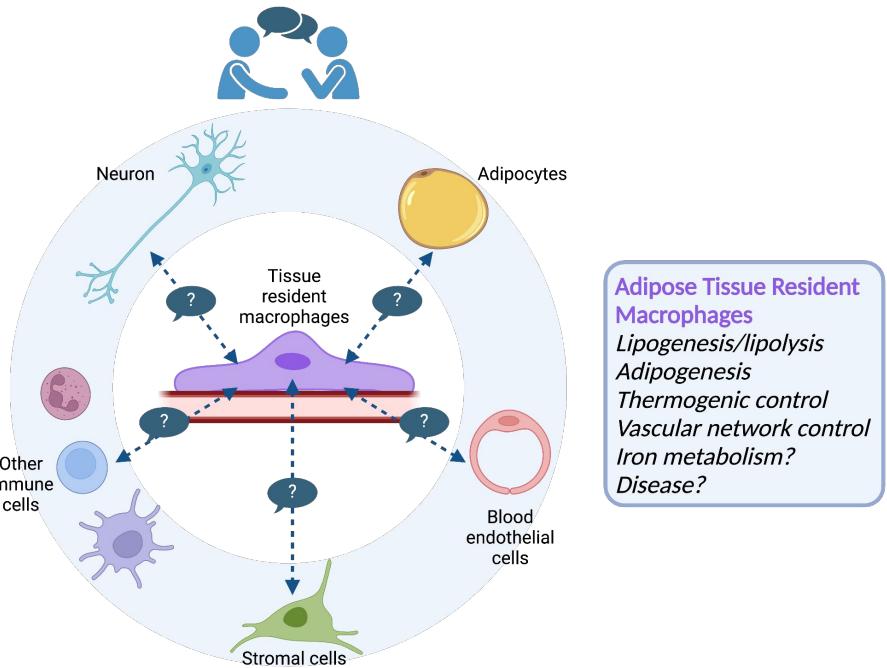


Defining the contribution of tissue resident macrophages to cellular circuit supporting tissue function in white adipose tissue

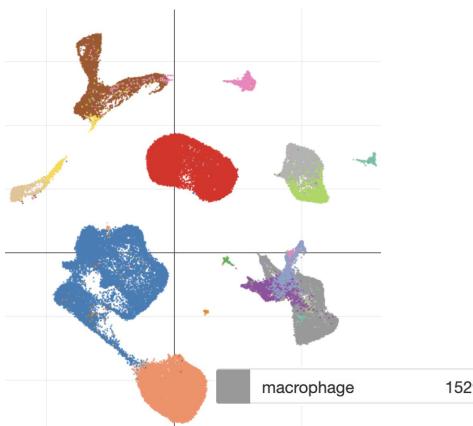
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¹Massachusetts Institute of Technology

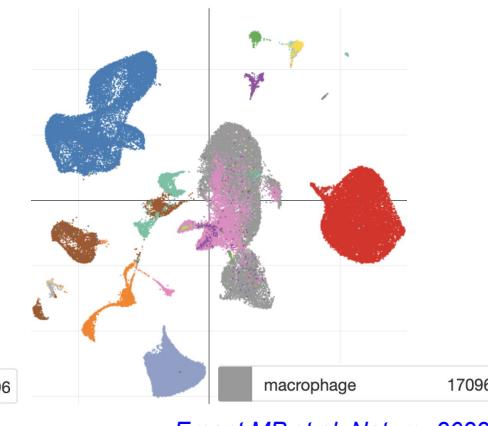
PROBLEM DEFINITION



Human WAT UMAP

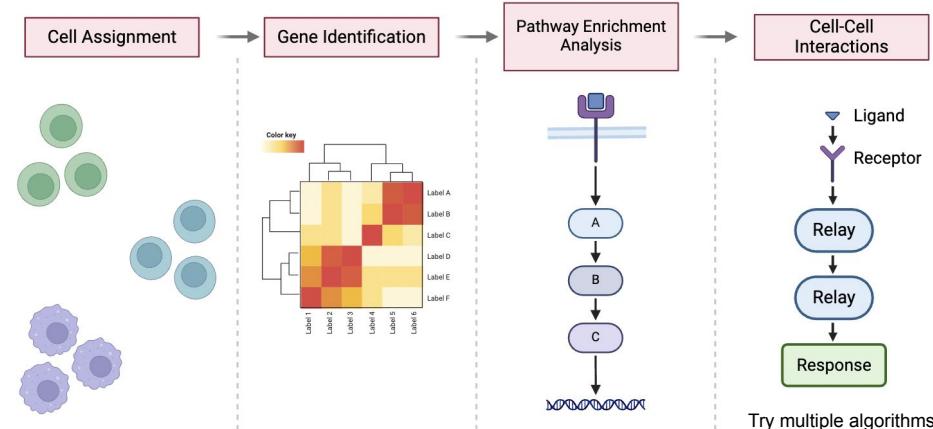


Mouse WAT UMAP

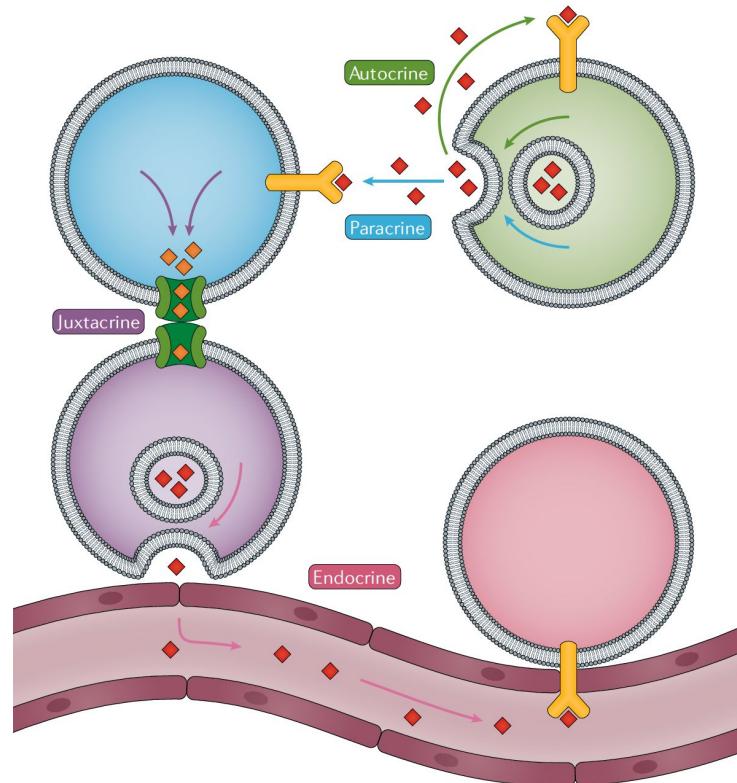


Emont MP et al, Nature, 2022

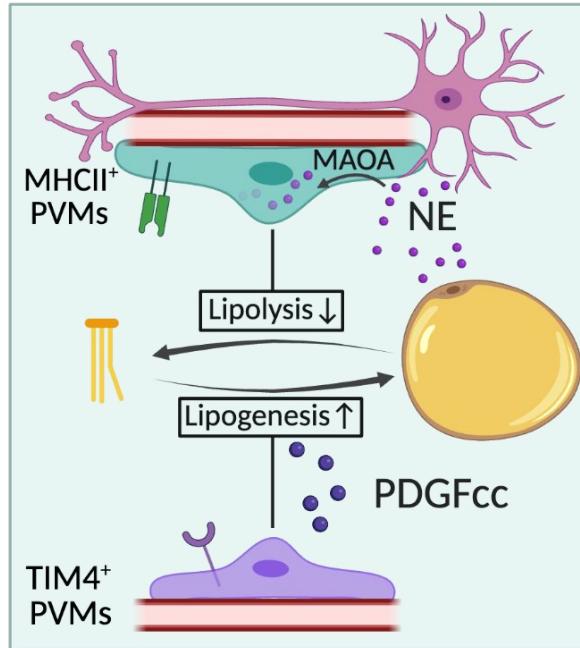
METHODS OVERVIEW



Types of cell-cell interactions and communications



Adipose RTMs support adipose tissue function by regulating lipolysis and lipogenesis



Adipose Tissue Macrophage (VAMs)
Lipogenesis/lipolysis
Adipogenesis
Thermogenic control