

Meteorin-like (METRNL) is associated with hypertrophic adipose tissue accumulation and related hyperinsulinemia and adipose tissue inflammation in humans.

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Background

- Meteorin-like (METRNL) = circulating factor from adipocytes (muscle, macrophages)
 - upregulated by exercise, cold, calorie restriction
 - potentially related to obesity (HFD mice)
 - effects: ⊕ energy expenditure, ⊕ glucose tolerance/insulin sensitivity, ⊕ neurite outgrowth, neuroprotection, antiinflammatory (almost all studies in mouse models)
- controversial results on relation to obesity, adipocyte differentiation, browning?

Objectives

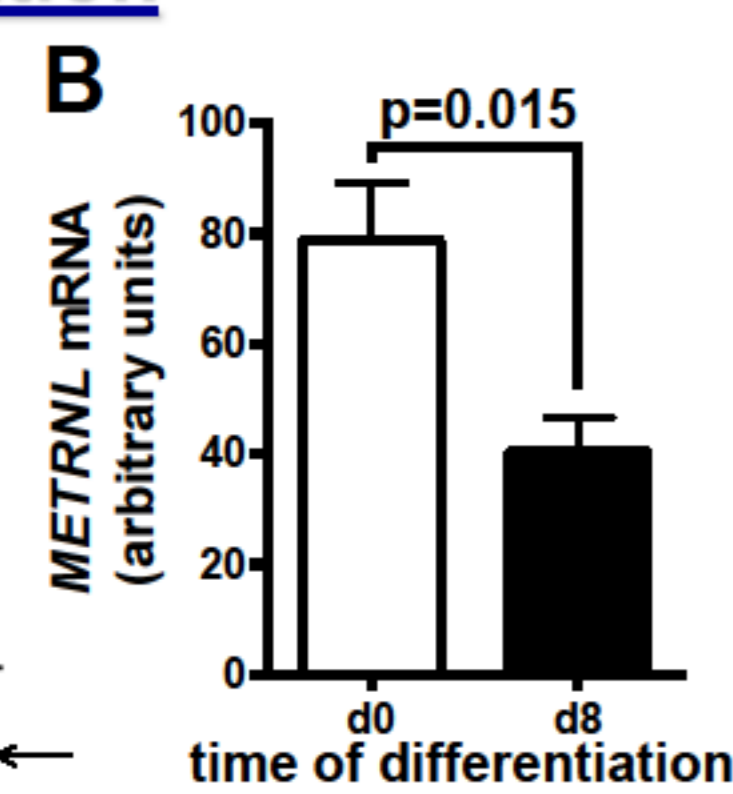
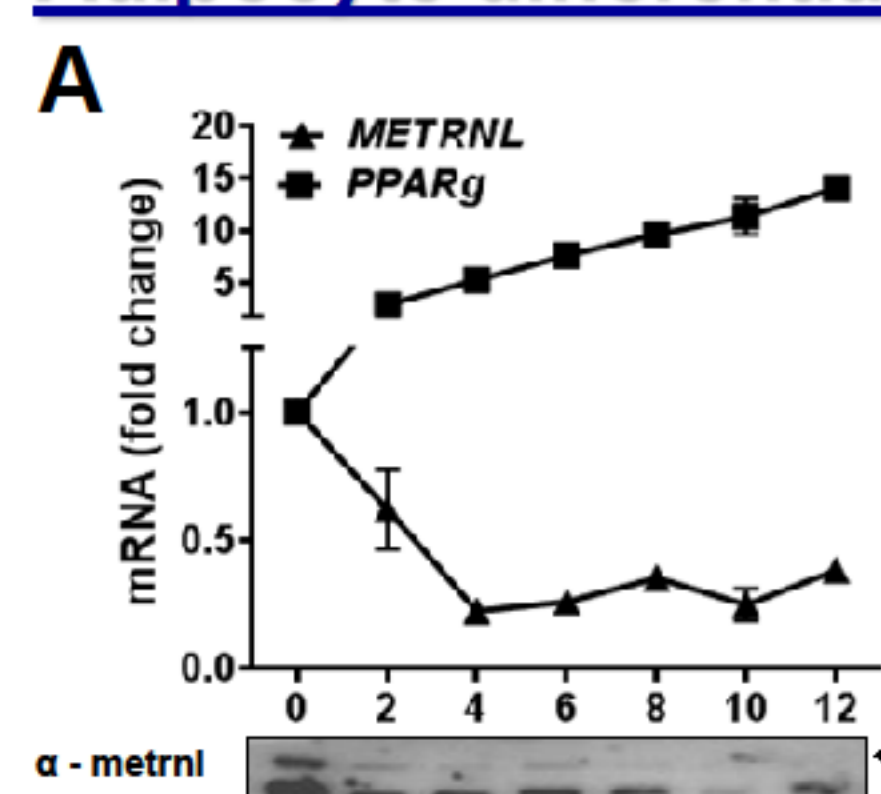
We evaluated the regulation and functional role of METRNL in human adipose tissue.

- How is *METRNL* expression regulated during human adipogenesis?
- What is the relationship to obesity and metabolic parameters in humans?
- What is the functional relevance of METRNL for human adipogenesis?

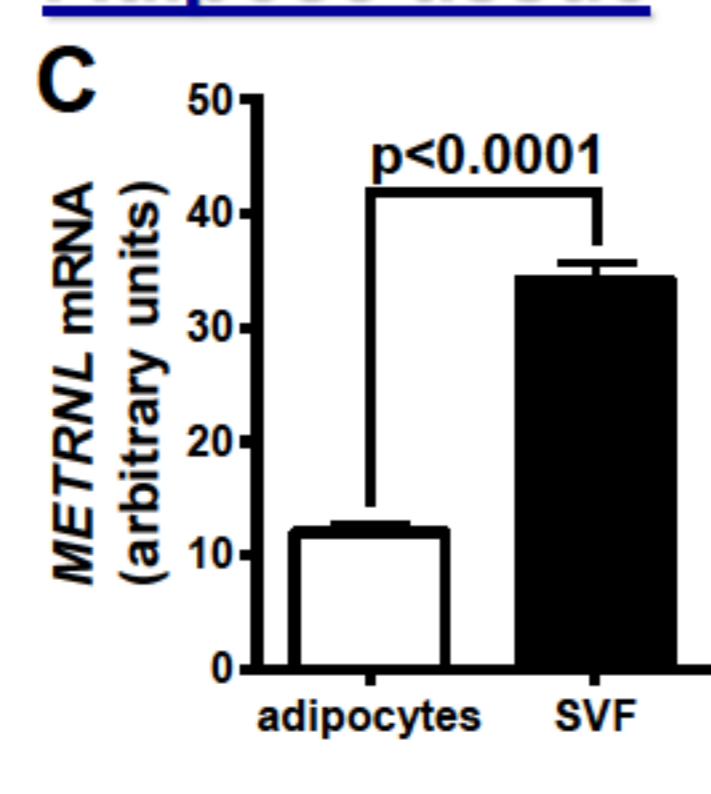
Results

1. METRNL decreases during human adipogenesis

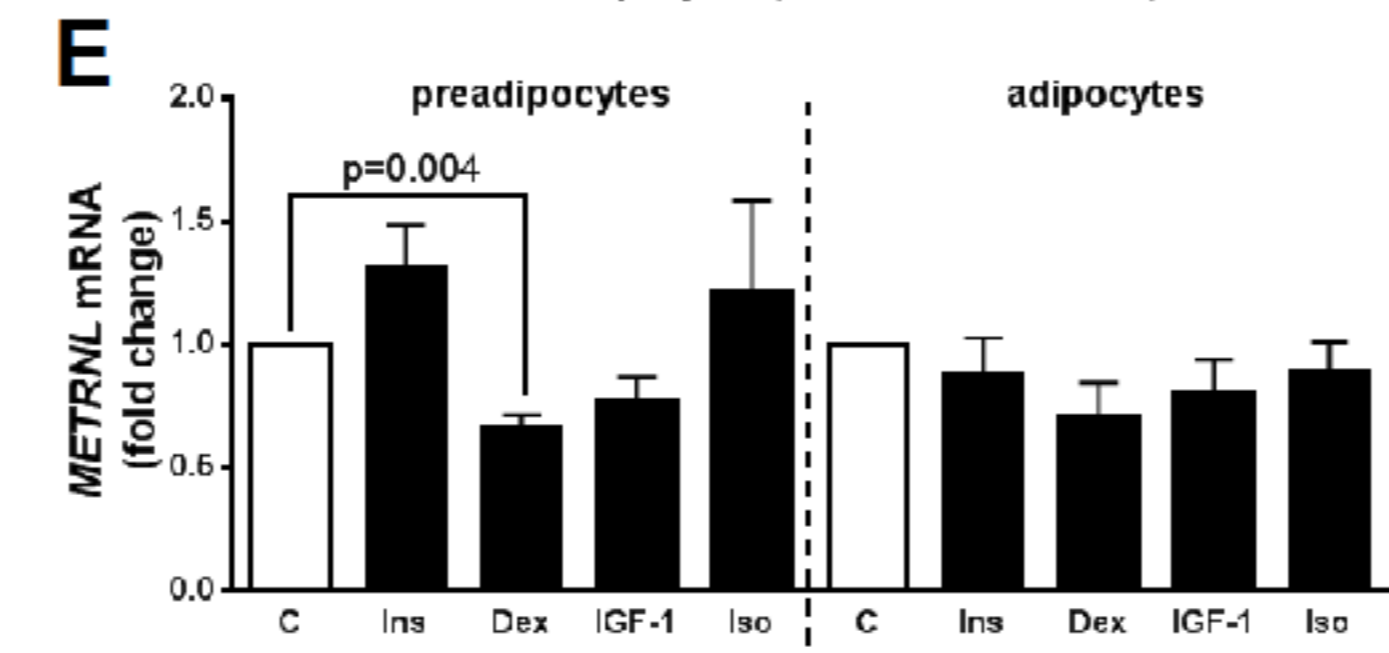
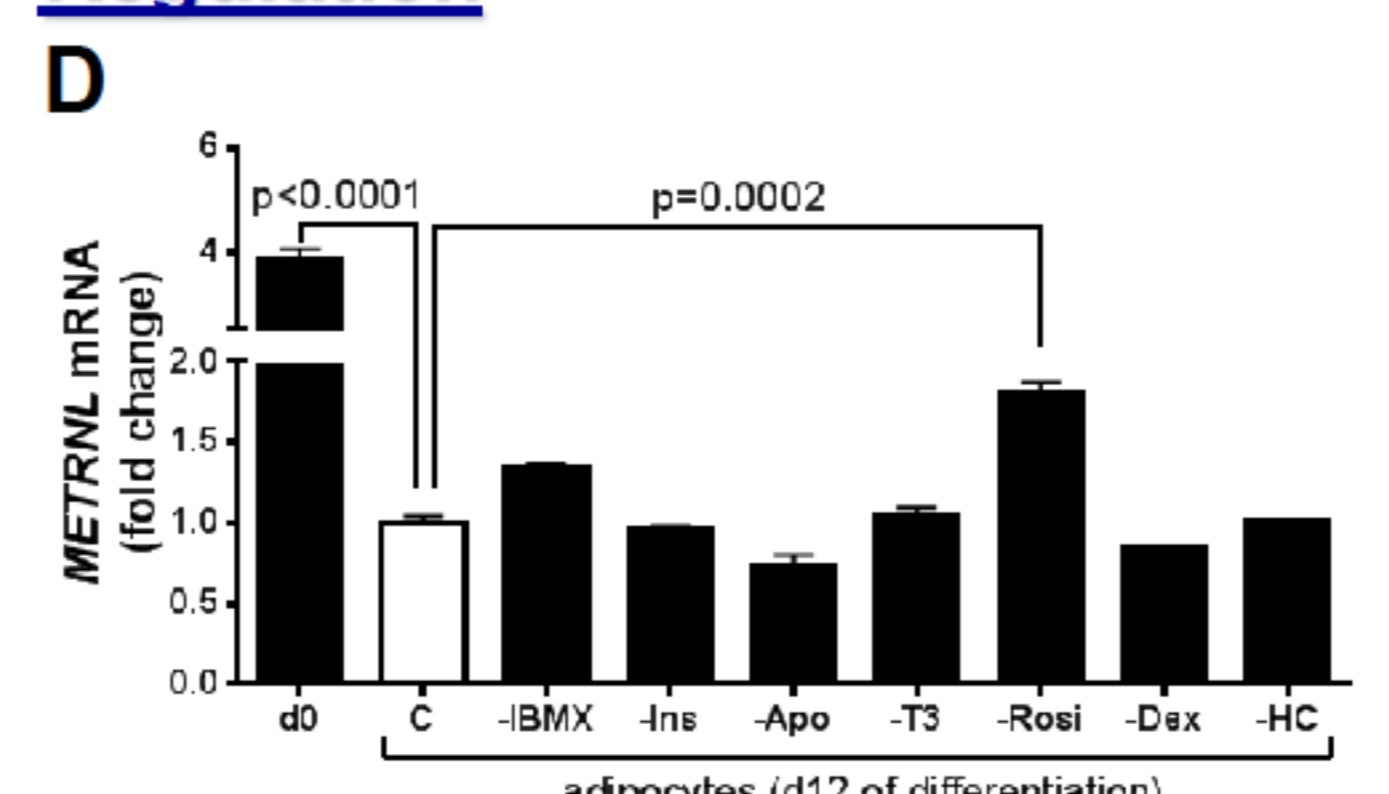
Adipocyte differentiation



Adipose tissue



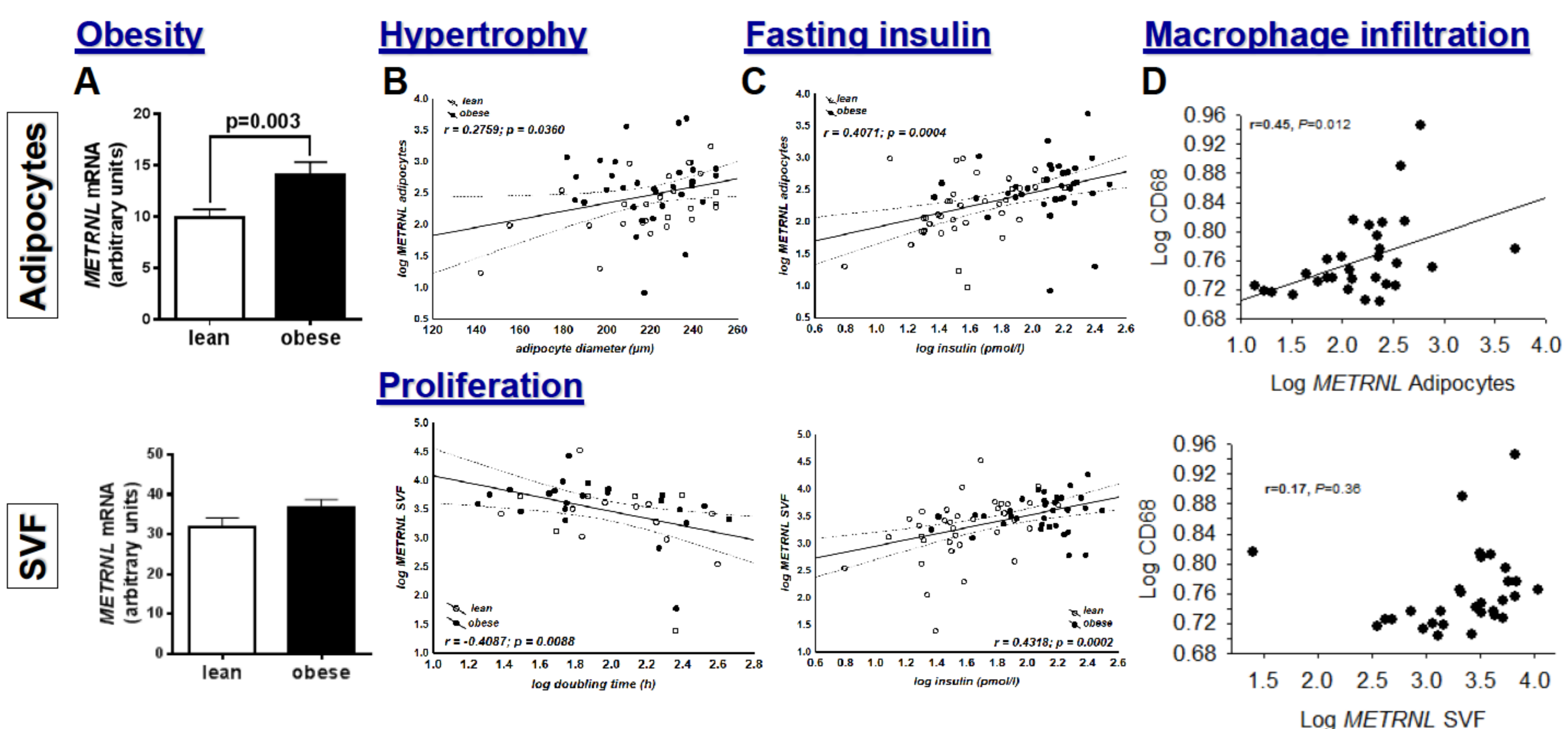
Regulation



METRNL mRNA and protein expression decreased during differentiation of human SGBS (A) and primary (B) preadipocytes into adipocytes. Concordantly, *METRNL* expression in primary adipocytes is lower than in SVF cells (C). Omission of PPAR γ agonist rosiglitazone preserved (D), while exposure of preadipocytes to dexamethasone inhibited *METRNL* expression (E).

SVF=stroma-vascular fraction; Ins=insulin; Apo=apolotransferin; T3=Triiodothyronin; Rosi=rosiglitazone; Dex=dexamethasone; HC=hydrocortisone; Iso=isoproterenol; C=control

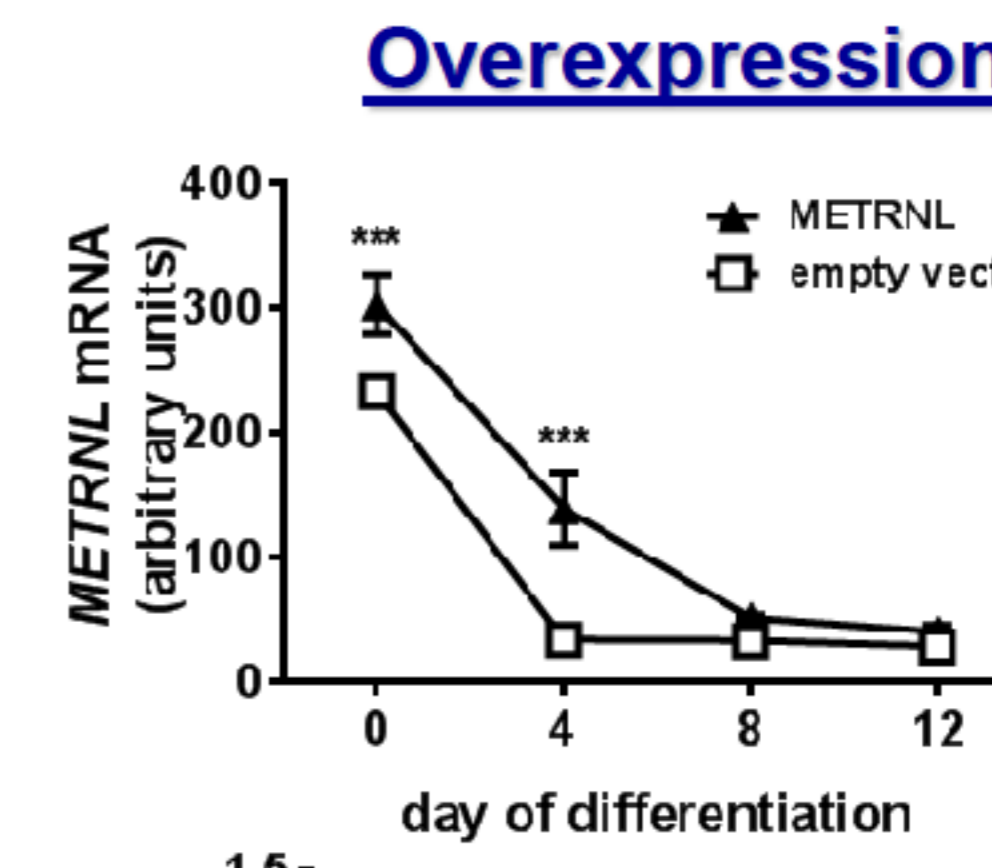
2. METRNL clinically correlates with insulin and inflammation



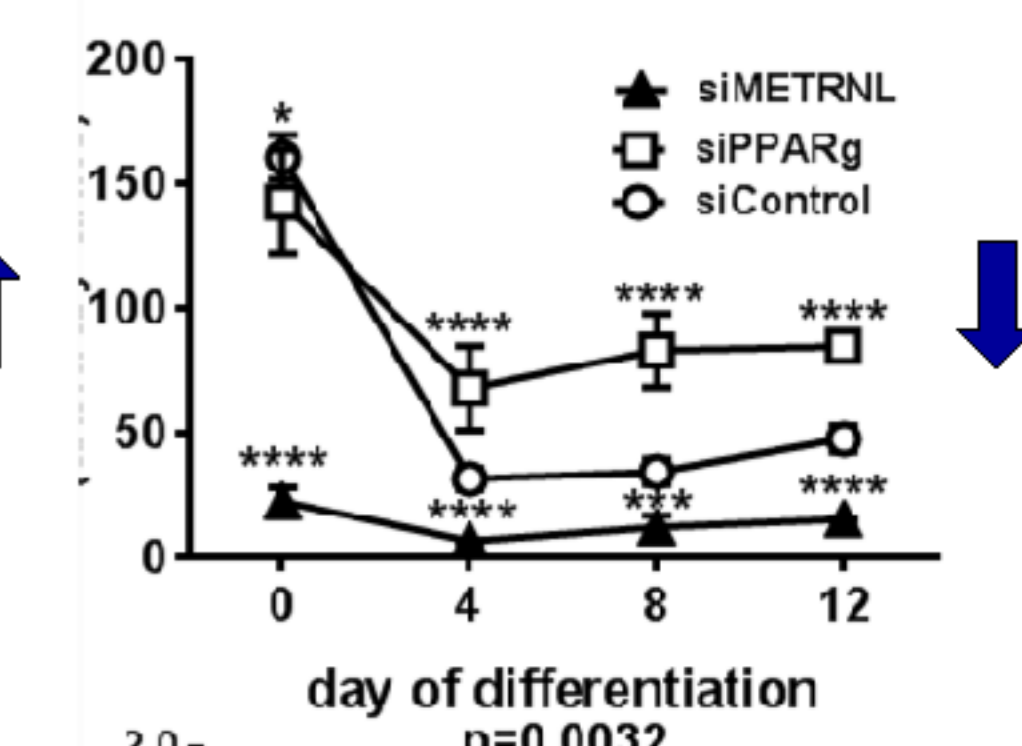
Obese children showed higher *METRNL* expression in isolated adipocytes, but not in SVF (A). In adipocytes, *METRNL* correlated with adipocyte size, whereas in SVF *METRNL* was positively related to proliferation (B). Both, adipocytes and SVF *METRNL* expression increased with circulating insulin levels (C), and in adipocytes *METRNL* was furthermore related to adipose tissue *CD68* mRNA expression as a marker of macrophage infiltration (D).

3. METRNL inhibits human adipogenesis

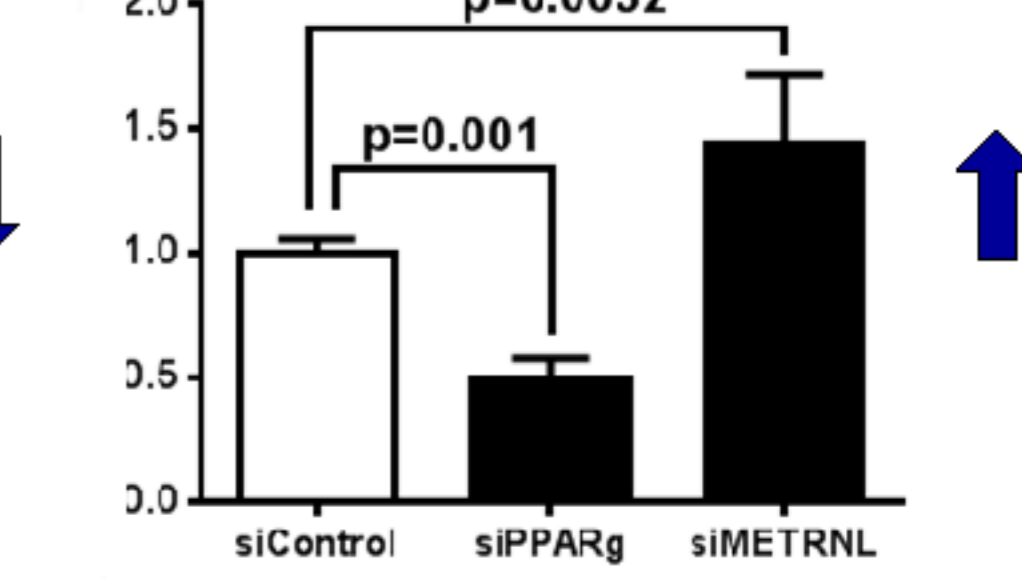
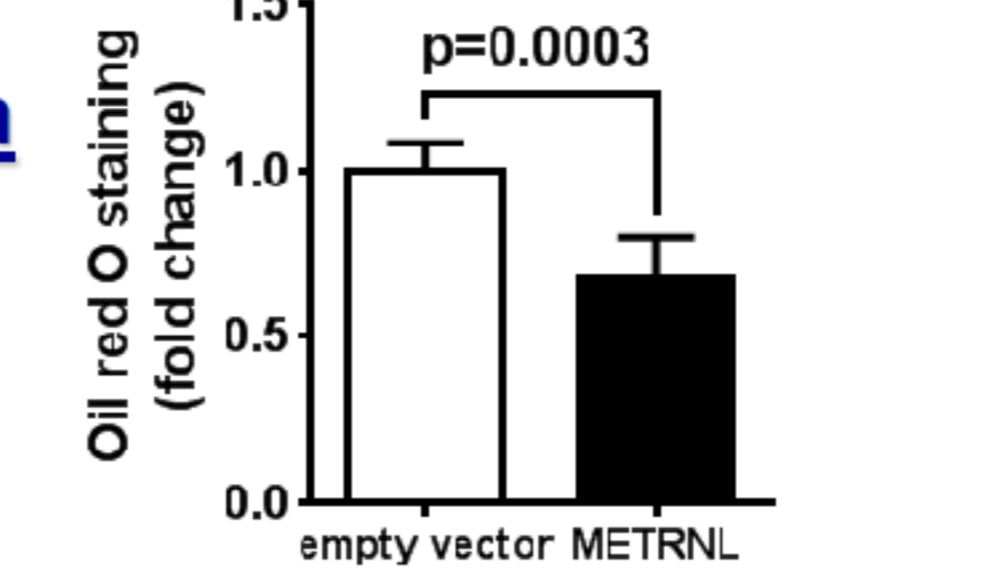
A METRNL expression



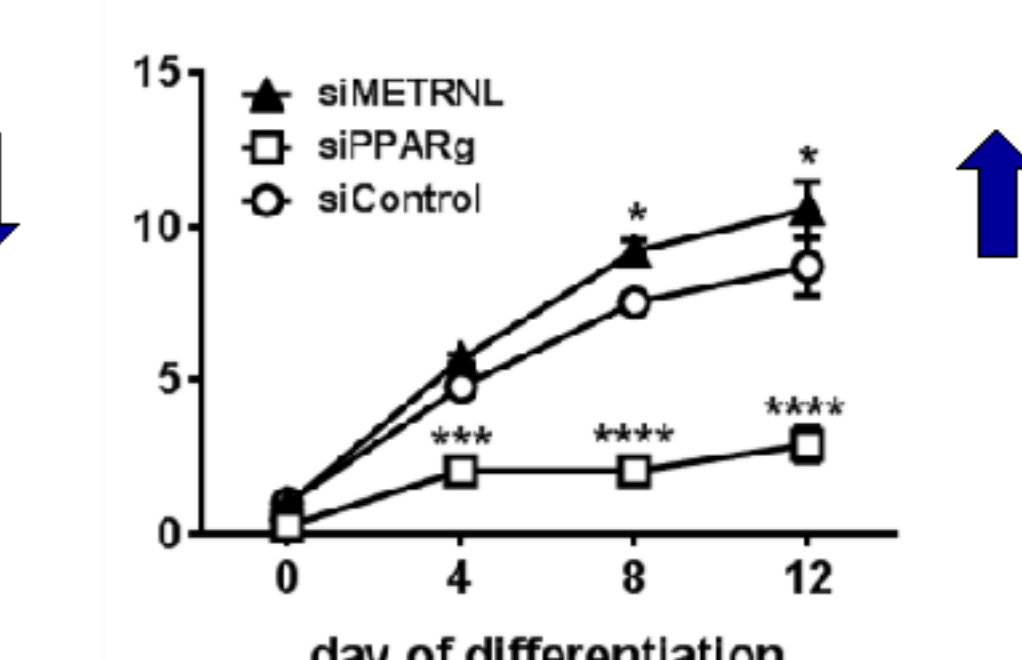
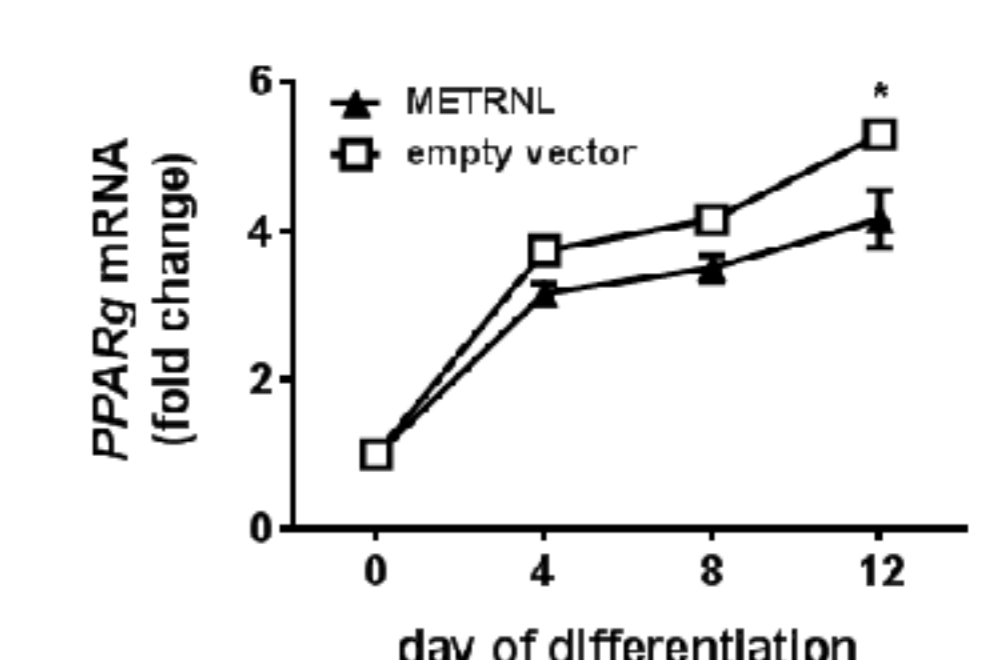
Knockdown (siRNA)



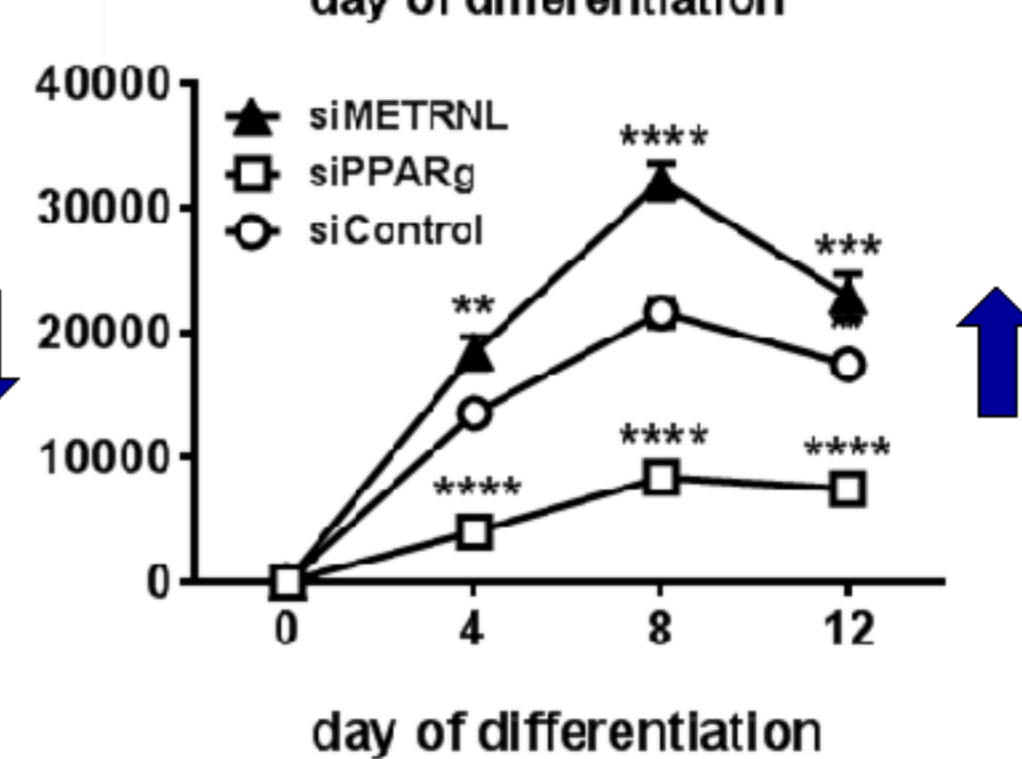
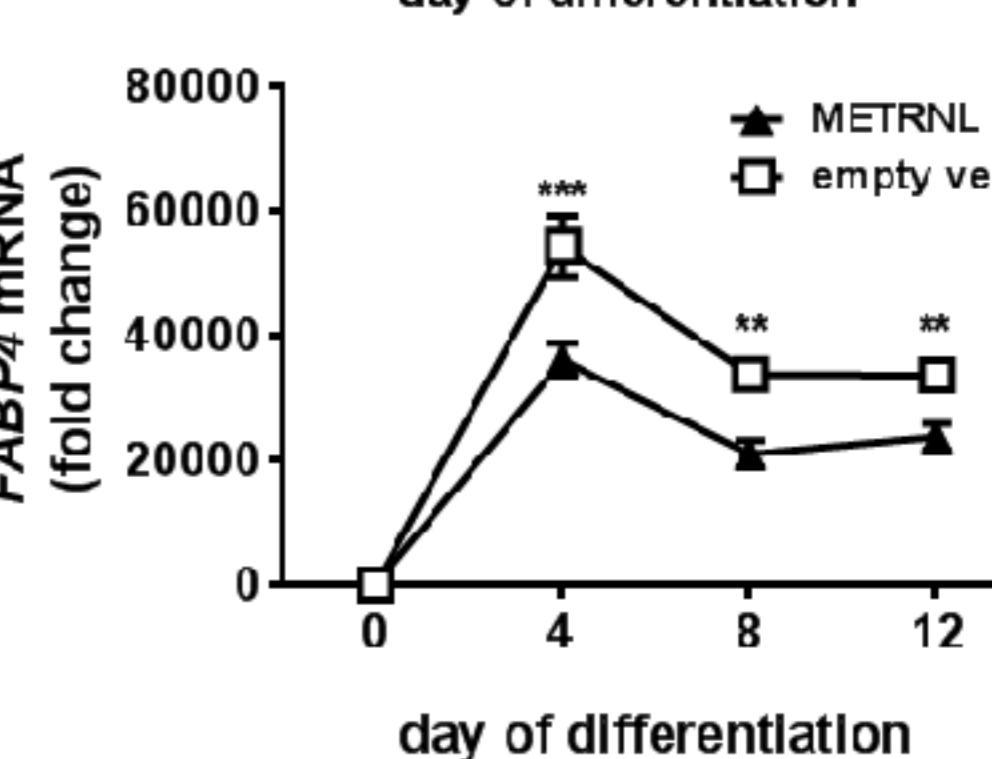
B Lipid accumulation



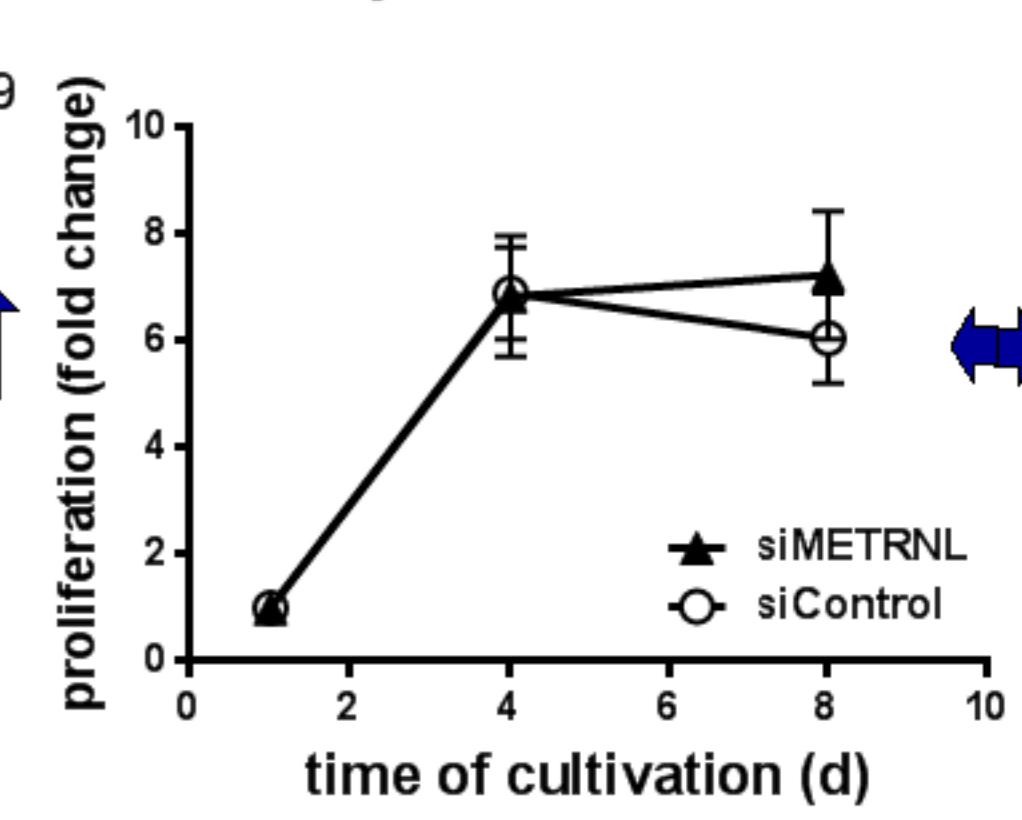
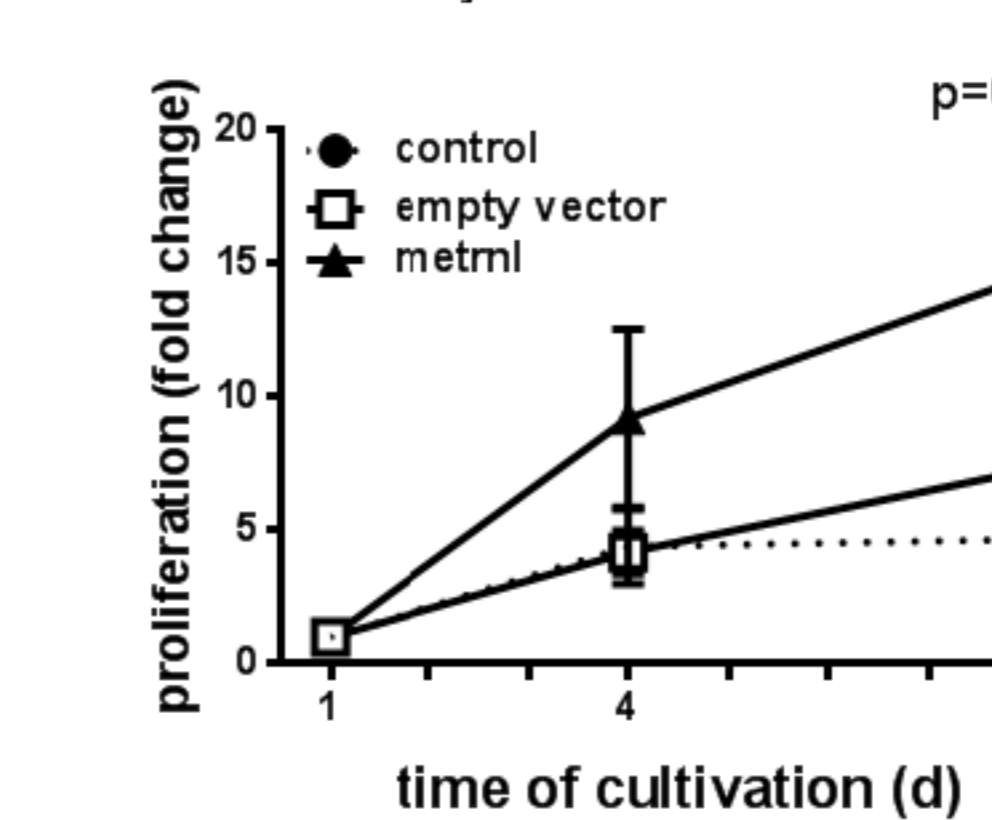
C PPARγ expression



D FABP4 expression



E Proliferation



Overexpression of METRNL inhibited human adipocyte differentiation, while downregulation of METRNL promoted adipogenesis (A-D). Proliferation of preadipocytes, in contrast, was advanced by METRNL overexpression (E).

Conclusions

Our results showing

- downregulation of METRNL (potentially PPAR γ dependent) during human adipogenesis and in mature adipocytes
 - METRNL association with adipocyte hypertrophy and SVF proliferation
 - METRNL inhibition of human adipogenesis
- indicate that METRNL is associated with hypertrophic adipose tissue accumulation in humans. Hypertrophy related hyperinsulinemia and adipose tissue inflammation are related to increasing METRNL expression level in human adipocytes.

