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A potential model for hepatic regulation of peripheral adipose tissue expansion

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A potential model for hepatic regulation of peripheral adipose tissue expansion

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- Background -

- Mesoderm specific transcript (*Mest*):
  - Maternally imprinted/Paternally expressed gene
  - Interfaces with lipid droplets at the ER membrane[1]
- *Mest* expression varies significantly between individual genetically identical mice fed high-fat diet.[2]
  - Variation occurs in controlled environmental conditions.
  - Variation is consistently and positively associated with fat mass expansion.[2]
  - Subtle differences in adipose *Mest* expression can predict obesogenic potential before mice are fed a high fat diet.
  - Coordinated expression across tissues implies existence of a universal driver involved in *Mest* regulation.
  - Universal driver likely originates from another organ.

Problem:

Identifying an epigenetic source of *Mest* regulation has proven to be difficult for several reasons.

Question:

Could the epigenetic regulation be centered on the suspected universal driver? And what is that driver?

Approach:

- Organ crosstalk facilitates complex whole-body responses to single challenges, such as a high fat diet.
- Liver is known to have a relationship with WAT and secretes circulating signaling factors called hepatokines.
- Microarrays run by our lab group in the past tested the relationship between hepatic and WAT gene expression.
- Most interested in *Enho* (*Energy homeostasis associated).*

- *Enho* Project: Next Steps -

Rationale:

- *Enho* codes for the hepatokine adropin.
- Adropin can suppress lipid accumulation in WAT.[3]
- Adropin knockout mice show increased adiposity while transgenic overexpression decreased adiposity.[4]
- Most significantly, levels of circulating adropin could serve as an early predictive marker of predisposition to obesity.

Our Initial Findings:

- Tested the relationship between hepatic *Enho* and WAT *Mest* expression in the context of different diets.
- Found that the correlation holds→
  - High-fat diet fed animals had low *Enho* and high *Mest*
  - Chow fed animals had high *Enho* and low *Mest*
- But does high *Enho* translate to high levels of circulating adropin?
- Necessary to test levels of circulating adropin to discover:
  - How hepatic *Enho* expression correlates with adropin
  - How circulating adropin correlates with WAT *Mest*
  - If adropin will predict (similar to *Mest*) disposition for obesity prior to feeding a high-fat diet
- Recently awarded BioME Seed grant allows us to gather this data to test adropin as the universal endocrine driver.
- Alternatively, can also begin to test other factors which could control both adropin and *Mest.*

Given the established relationship between liver and white adipose tissue, we hypothesize that hepatokines—particularly adropin—are the source of coordinated gene expression in peripheral adipose tissue driving fat mass expansion.

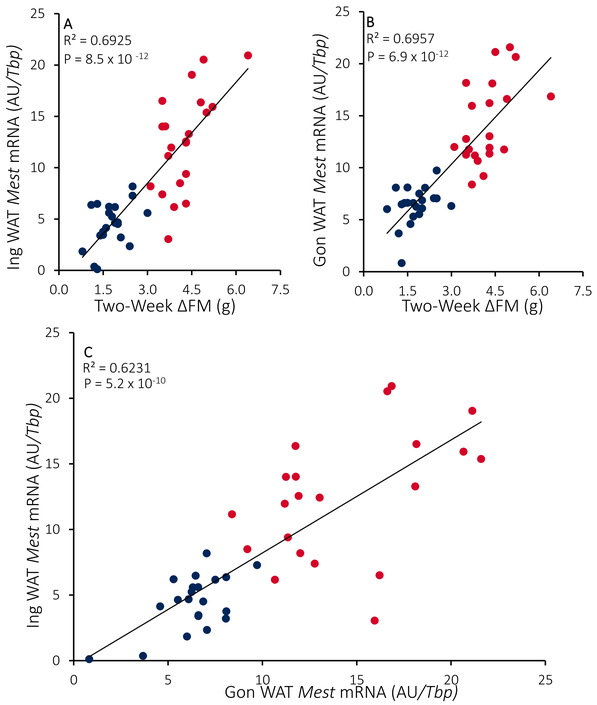

Fig 1. *Mest* expression and fat mass expansion. Fat mass was measured before and after mice were fed HFD for two weeks. RNA was then isolated from tissue collected following that period. RT-qPCR shows a significant difference in *Mest* mRNA between high (red) and low (blue) cohorts in both inguinal (A) and gonadal (B) WAT. *Mest* expression also significantly correlates with the change in fat mass across two weeks of HFD. Most significantly, however, subcutaneous inguinal and visceral gonadal WAT show a strong correlation in *Mest* expression across tissues (C).

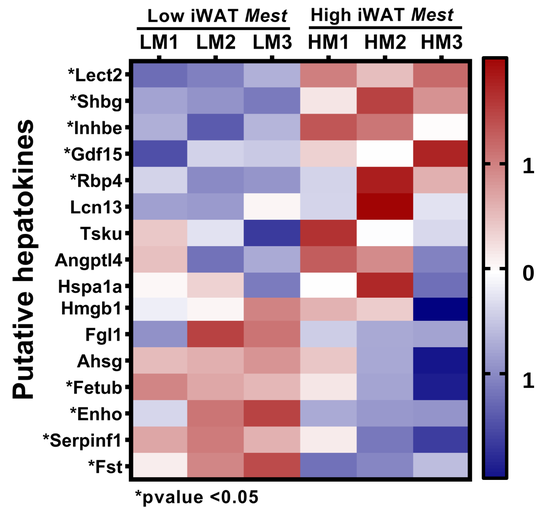

Fig 2. Microarray data identifies relationships between liver and WAT genes. Microarray analyses using liver samples from animals with low and high inguinal WAT *Mest* expression demonstrate that many hepatokines have a positive or negative correlative relationship with WAT *Mest* expression. * denotes statistically significant difference.

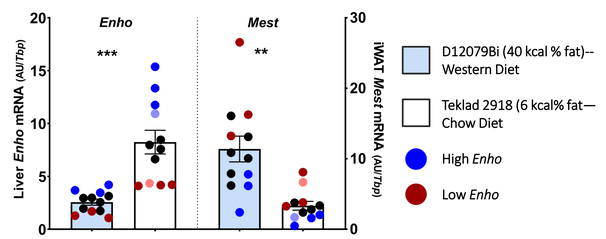

Fig 3. The *Mest/Enho* relationship is preserved across contexts. mRNA was collected from the livers of mice fed either a chow or 40% Kcal high fat diet (HFD) and compared with *Mest* expression levels via RT-qPCR. The negative correlative relationship first described by the microarray holds. Chow-fed animals, which had lower expression of *Mest,* showed higher expression of *Enho*, and HFD animals with high *Mest* have low *Enho* expression.

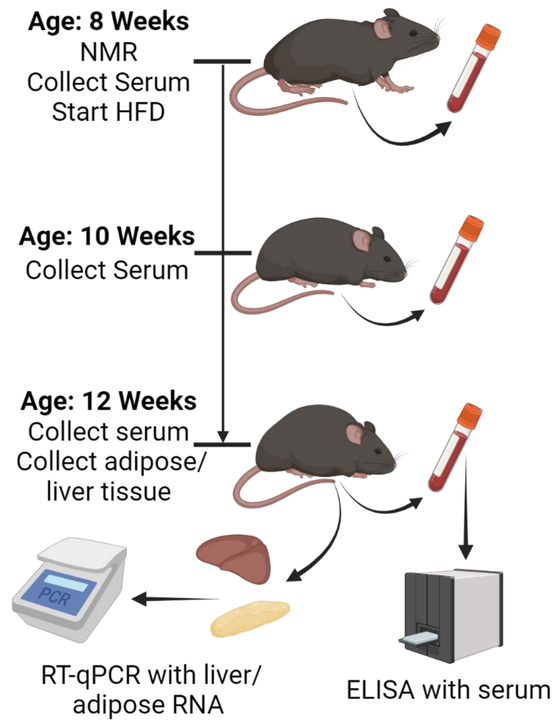

Fig 4. Experimental Schematic. The project described above will be funded by the BioME seed grant with the goal of identifying if levels of circulating adropin—like *Mest*—can act as a predictive marker for disposition to diet-induced obesity. The project will be completed this summer using 40 B6 mice. Serum will be collected at 8, 10, and 12 weeks of age over the course of a 4 week HFD. Liver and WAT will be collected at endpoint for mRNA analysis via RT-qPCR. Schematic generated using BioRender.

- Supported By and Thanks -

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- References -

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