BEIGE AND BROWN FAT: BASIC BIOLOGY AND NOVEL THERAPEUTICS

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Definitions:

- **WAT (White Adipose Tissue)** or White Fat – lipid storage tissue found in mammals. Each cell contains a single large fat droplet (unilocular) which forces the nucleus into a thin rim at the periphery of the cell. WAT primary function is to store energy **however** WAT is also a signaling molecule. WAT has receptors for insulin, growth hormones, norepinephrine and glucocorticoids. Distributed amongst various depots throughout the body. Secretes leptin.

- **BAT (Brown Adipose Tissue)** or Brown Fat – is a heat generating tissue. BAT is multilocular. BAT is found abundantly in newborn and hibernating mammals. Its primary function is to generate heat through a non-shivering mechanism (so called NST – non-shivering thermogenesis). BAT is high in mitochondria which contain iron resulting in a brown color, hence the name brown fat. Brown fat is rich in capillaries to provide mitochondria with oxygen.

- **Beige Fat** – induced in white fat in response to various activators, i.e. cold stress, surgical denervation, norepinephrine, β-agonists. Beige fat metabolically resembles BAT. Increased activity of inducible beige fat could lead to promising therapies for metabolic diseases including diabetes, obesity and fatty liver disease.
18F-Deoxyglucose PET is used to indicate areas of brown/beige fat activity.
**Obesity:**

- We know what ultimately causes obesity – it results when energy intake exceeds energy expenditure – today, the only proven therapy for obesity is bariatric surgery.
- What if we could increase energy expenditure to combat excessive accumulation of white adipose tissue (WAT)?
- Rodents, humans and hibernators all have specialized tissue – brown adipose tissue (BAT) – with the unique capacity to regulate energy expenditure by non-shivering thermogenesis.
- How can pathways that affect BAT be manipulated to increase metabolism?
Definitions:

- **Myocytes** - Muscle cells and brown fat cells are of the same lineage being derived from the same embryonic stem cells. Both share the myogenic factor 5 (Myf5) cell surface marker. WAT does not. Also think of muscle tissue as a signaling molecule that interplays with WAT and BAT: myocytes secrete the peptide hormone *irisin* in response to exercise (of mice or men?)

- **CNS and SNS** – directional and bidirectional communication exists between the brain and WAT. CNS signaling results in the initiation of lipolysis through adrenal medullary secretion of catecholamine and the inhibition of lipolysis by pancreatic insulin. WAT signaling to the brain is exemplified by adipokines secretion such as leptin. Bidirectional signaling occurs via sympathetic nervous system (SNS) and sensory innervation of tissue. Possible negative feedback loop to regulate lipolysis?

- **UCP1** - uncoupling protein 1 in brown adipose tissue is the enzyme in brown fat mitochondria that UCP1 “uncouples” oxidation from phosphorylation in the OXPHOS pathway. The result of uncoupling is heat generation.

- **PPARα and PPARγ** - PPARα is a dietary lipid sensor. PPARγ is highly expressed in adipose tissue and is required for adipose tissue differentiation.
Beige Fat/Brown Fat: Basic Biology

(a) Brown adipocytes are derived from a Myf5-expressing progenitor population. Ebf2 cooperates with Ppar-γ to promote the expression of Prdm16, which drives a brown-fat cell fate. Thermogenesis in mature brown adipocytes is activated by norepinephrine (NE), a β3 agonist, released from sympathetic neurons. NE signals through β-adrenoreceptors to increase the expression and activity of Pgc-1α, a transcriptional coactivator that coordinates gene programming in response to activation.

(b) In inguinal fat, β-adrenergic stimulation triggers predominantly de novo differentiation of precursor cells (large arrow). We leave open the possibility that under some conditions, mature white fat cells can transdifferentiate into beige cells (small dashed arrow). In epididymal WAT, caloric excess causes bipotent progenitors to differentiate into white adipocytes, whereas β-adrenergic activators stimulate beige adipocyte development. TZD agonists of Ppar-γ promote beiging both by increasing the stability of Prdm16 and through the Sirt1-dependent deacetylation of Ppar-γ, which recruits Prdm16 to Ppar-γ target genes. β-adrenergic signaling drives the expression and activity of Pgc-1α in beige adipocytes. Pgc-1α is targeted by numerous repressors to block beige adipocyte development.

In rodents, a number of tissues and cell types have been found to secrete factors that regulate brown and beige adipose activity through systemic, autocrine and paracrine mechanisms. Neurons and alternatively activated macrophages secrete norepinephrine; cardiac tissue secretes natriuretic peptides; liver and BAT secrete Fgf21; muscle secretes irisin; and thyroid secretes the hormone T₄ (which is then converted to T₃). BAT also produces Bmp8b and Vegf, which increase thermogenic function in an autocrine manner. Additionally, orexin and Bmp7 promote brown fat development, but their cellular source is unknown. Oxr1, Oxidation resistance 1; Alk7 (also called Acvr1c), Activin A receptor type 1C.

Figure 1. UCP1 location and function in the mitochondrial respiratory chain (MRC). Numbers I-IV correspond to the MRC complexes. ATP-synthase is the fifth complex of the MRC. During respiration, protons are pumped through the MRC complexes, and a proton gradient is generated. The energy of the proton gradient drives the synthesis of ATP by the ATP-synthase complex. UCP1 catalyzes a regulated re-entry of protons into the matrix, uncoupling the MRC and, consequently, reducing ATP synthesis and generating heat.
UCP1 activity is affected by various factors including:
- Exposure to cold
- Drugs
  - Drugs that elevate blood pressure and cardiac function
  - Novel drugs that elevate NST but do not elevate BP or heart rate.
Exposure to cold – human and mouse models
Brown Adipose Tissue Activity
(PET-CT with $^{18}$F-FDG)

Lean, Thermoneutral

Lean, Cold Exposure

Overweight, Cold Exposure
Non-Shivering Thermogenesis (NST) human and mouse models

NST increases Total Energy Expenditure

Increase in NST could shift paradigm for metabolic diseases.
Drugs that elevate blood pressure and cardiac function

- Many have been known for decades but these are of little therapeutic value because of cardiac stress, i.e.- ephedrine.
- Some may be of dubious commercial value:
Novel therapeutic drugs that affect hBAT either through NST or other pathways.

- **Amlexanox** – inhibitor of TBK1/IKKε suggests link between inflammation and obesity and insulin resistance (in mice).

- **Roscovitine** – inhibits CDK5. In mice obesity activates CDK5. This results in phosphorylation of PPARγ at S273. Leads to metabolic dysregulation. Also S112 is of interest.

- **Rosiglitazone** – an insulin sensitizer, that binds to PPAR receptors in fat cells making the cells more responsive to insulin.


- **Mirabegron** – a β3-AR agonist for overactive bladder. Activates metabolism and brown fat BUT increases basal heart rate, metabolic rate and blood pressure.
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