Adiposity, Chronic Disease Risk and Aging: The potential role of adipocyte lineage

Kathleen Gavin, PhD

Postdoctoral Fellow
Division of Geriatric Medicine
University of Colorado School of Medicine
Anschutz Medical Campus

Geriatric Medicine Grand Rounds
October 29, 2015
Outline

• Adipose tissue – a role in chronic disease
• Age related alterations in adiposity
• Adipocyte development
• Basic evidence for a novel adipocyte lineage - bone marrow progenitor (BMP)-derived adipocytes
• Evidence for BMP-derived adipocytes in humans
• Conclusions
Adipose Tissue – A Fascinating Organ!
Extraordinary Capacity to Shrink or Expand

Both extremes have serious health consequences.

- Lipodystrophy
  - Hypertriglyceridemia
  - Insulin Resistance
  - Hepatic Steatosis
  - Hypertrophic Cardiomyopathy

- Obesity
  - Metabolic Syndrome
  - Type 2 Diabetes
  - Cardiovascular Disease
  - Pulmonary, Liver, and Kidney disorders
  - Cancer

Canadian Obesity Network
Body Fat Distribution and Disease Risk

Why Does Adipose Tissue Differ by Depot? Adipose Tissue Heterogeneity

• Local Tissue Microenvironment:
  – Local circulation
  – Local innervation
  – Non-adipocyte cell populations: preadipocytes, endothelial cells, pericytes, multipotent stem cells, and various immune cells (macrophages, T-cells, neutrophils, lymphocytes)

• Genetically (or epigenetically) programmed developmental differences in adipocytes and precursors.
  – Adipocytes can retain depot-specific characteristics even when differentiated in vitro (e.g., gene expression and insulin signaling).

• Distinct developmental pathways produce functionally distinct adipocytes in different body locations (and maybe within adipose depots).

Changes in Body Composition with Age

↑ Adiposity and ↓ Fat-free mass

### TABLE 1

<table>
<thead>
<tr>
<th>Sex and BMI</th>
<th>Age 20–39</th>
<th>Age 40–59</th>
<th>Age 60–79</th>
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<tbody>
<tr>
<td>Women</td>
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<tr>
<td>BMI &lt; 18.5</td>
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<td>Men</td>
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<tr>
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<tr>
<td>BMI ≥ 30</td>
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<td>28</td>
<td>30</td>
</tr>
</tbody>
</table>

*BMI values are in kilograms of weight per meter of height squared (kg/m²). Values shown are for African Americans and whites.


Chapman, IM. *Interdiscip Top Gerontol.* 37:20-36, 2010
Changes in Body Fat Distribution with Age

- Inability to store fat subcutaneously, particularly in the lower body.
- Lipid accumulation in non-subcutaneous depots or in lean tissue.
  - ↑ visceral, liver, inter- and intra-muscular, and other ‘ectopic’ fat depots.
- Due, in part, to age related dysregulation of lipid metabolism in SQ adipocytes?
- Or, to age related alterations in adipocyte developmental pathways?

Geriatric Obesity Paradox

• Obesity (BMI ≥ 30 kg/m²) does not carry the same mortality risk in older adults as younger adults.
• Association between BMI and mortality in older individuals is neutral or inverse.

Relative risk of all-cause mortality across BMI categories, stratified by age group, based on NHANES I, II and III data.

Identity of Adipocyte Progenitor Cells

• Mature adipocytes do not divide, so new adipocytes must arise from a precursor cell.


• Undifferentiated adipocyte precursor cells have long been assumed to reside and self-renew in stromal-vascular fraction of the adipose tissue.

• Only in the last decade has some convincing evidence been described for the presence of distinct adipocyte progenitor populations between adipose depots. (Majka, S. M., et al. *Stem Cells* 29(7): 1034-1040, 2011)

Adapted from Otto, TC & Lane, MD Crit Rev in Biochem & Mol Biol 40:229–242, 2005
Other Sources of Adipocyte Progenitors: What about bone marrow?

- Tissues throughout the body contain progenitor cells capable of adipogenic differentiation.
- Including bone marrow - a rich source for both mesenchymal and hematopoietic stem cells.
- Marrow mesenchymal cells do not enter the circulation
  - Hematopoietic cells do leave the marrow and traffic to other tissues.
- Why couldn’t they traffic to adipose tissue and become adipocytes?

A subpopulation of adipocytes arises from bone marrow (BM) progenitor cells – Basic Models

- 8 wk female wild type mice
- Transplant: BM from adiponectin-cre LSL Luciferase mice
- Whole body adipocyte production measured by \textit{in vivo} imaging (Ivis System) following injection with luciferin

Conclusions:
Accumulation of BMP-derived adipocytes:
- increases over time
- is present in major white adipose depots of mice.

Gavin, KM. \textit{et al.} \textit{FASEB J} In Review
BMP-derived adipocytes are a sizable component of the total adipocyte population.

Within 8-16 wks BMP-derived adipocytes comprise from 5-25% of total adipocyte pool depending on gender, depot, time post transplant/birth.

BMP-derived adipocytes are a distinct cell population.

Principal component analysis

BMP-derived adipocytes exhibit decreased expression of genes related to fuel oxidation and mitochondrial/peroxisomal activity.

Cluster of 46 genes had 2.6 to 21 fold lower in BMP-derived fat cells

BMP-derived adipocytes exhibit increased expression of certain inflammatory and chemotactic cytokine genes.

Hierarchical clustering
3.6 to 14 fold higher in BMP-derived fat cells

Ovarian hormones regulate the accumulation of BMP-derived adipocytes.

Whole body luciferase activity:
- is highest in the OVX and αERKO mice
- is decreased by both E2 and P add-back.

*Klemm, et al. Unpublished*
Some adipocytes do arise from bone marrow progenitors in mouse models.

BMP: bone marrow progenitor

Does this have clinical relevance?

- Do BMP-derived adipocyte accumulate in humans?
- Could their accumulation be a mechanistic link underlying adipose related chronic disease risk?
Donor-derived adipocytes are present in human adipose tissue from bone marrow transplant (BMT) patients

Donor chimerism in adipocytes
9.875 ± 10.9% (range 0-35%)

Age
49.25 ± 16.7 yrs (range 24-75 yrs)

Post-transplant duration
2.145 ± 1.2 yrs (range 1-3.6 yrs)

Mean ± standard deviation

Linear regression

Donor-derived adipocytes accumulate over time

Blue, red, and green data points represent values from participants with repeat biopsies (7-12 months apart).

Gavin, KM, et al. FASEB J In Review
Conclusions

• Alternative development pathways for adipocytes exist (e.g., mesenchymal versus myeloid origin progenitors)
  – Likely contribute to the functional diversity of distinct adipose depots.

• Accumulation of BMP-derived adipocytes may be a mechanism underlying adipose related chronic diseases in humans.
  – Explain some anomalies such as the obesity paradox in aging (lower accumulation in people that live to older age)?
  – Play a role in shifts in body fat distribution and elevated chronic disease risk with the menopausal transition in women?

• Determining interventions to minimize the accumulation of BMP-derived adipocytes may be important in future preventative strategies for aging and/or adipose related chronic disease.
Acknowledgements

Mentors:
- Wendy Kohrt, PhD
- Dwight Klemm, PhD
- Jonathan Gutman, MD
- Karen Shea, MD
- Klemm Laboratory
  - Heidi Miller, Tim Sullivan and Paul Erickson

Funding:
- K. Gavin: T32 AG000279, CCTSI CO-Pilot Mentored Faculty Award, CCTSI Novel Methods Pilot, F32 AG046957, UC Denver NORC Pilot Award, Center for Women’s Health Research
- D. Klemm: NIH R01 DK078966; GRECC Pilot
- W. Kohrt: NIH R21 DK092718, P50 HD073063
- NIH/NCATS Colorado CTSA Grant Number UL1 TR001082
- NIH/NCI CCDG P30 CA046934
References


Vision for Future Research

**Proof-of-Concept**
- Measure microchimerism of subcutaneous adipose tissue from bone marrow transplantation patients
- Delineate/define specific lineage development pathway

**Develop Measurement Tools**
- Identify and confirm biomarker for measurement in non-transplant humans
- Characterize gene expression fingerprint in human cells
- Determine metabolic phenotype (parallel gene expression fingerprint to murine models?)

**Utilize Tools in Healthy Humans**
- Determine region specific accumulation: subcutaneous vs. visceral, central vs. peripheral
- Are measurements of subcutaneous tissue an appropriate surrogate for visceral adipose?
- Determine triggers for accumulation: Aging, (loss of) sex hormones…

**Long Term Future Directions**
- Physiological consequences of accumulation, links to disease risk? Independent of obesity?
- Test interventions that may help prevent accumulation (exercise, weight loss).
  - *New approach to evaluate the therapeutic impact of an intervention on metabolic risk?*
Donor-derived Adipocytes Exist in Humans
Chimerism Results

<table>
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<th>Patient</th>
<th>Transplant Type</th>
<th>Biopsy #</th>
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<th>Post-transplant (months)</th>
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<td>41</td>
<td>43</td>
<td>9   91</td>
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PBSC = peripheral blood stem cells; BM = bone marrow.