

Adipose Tissue Function, Dysfunction, and Fat Fibrosis. What Does This All Mean?

*NIH Workshop:
Obesity and Fat Metabolism in HIV Infected Individuals
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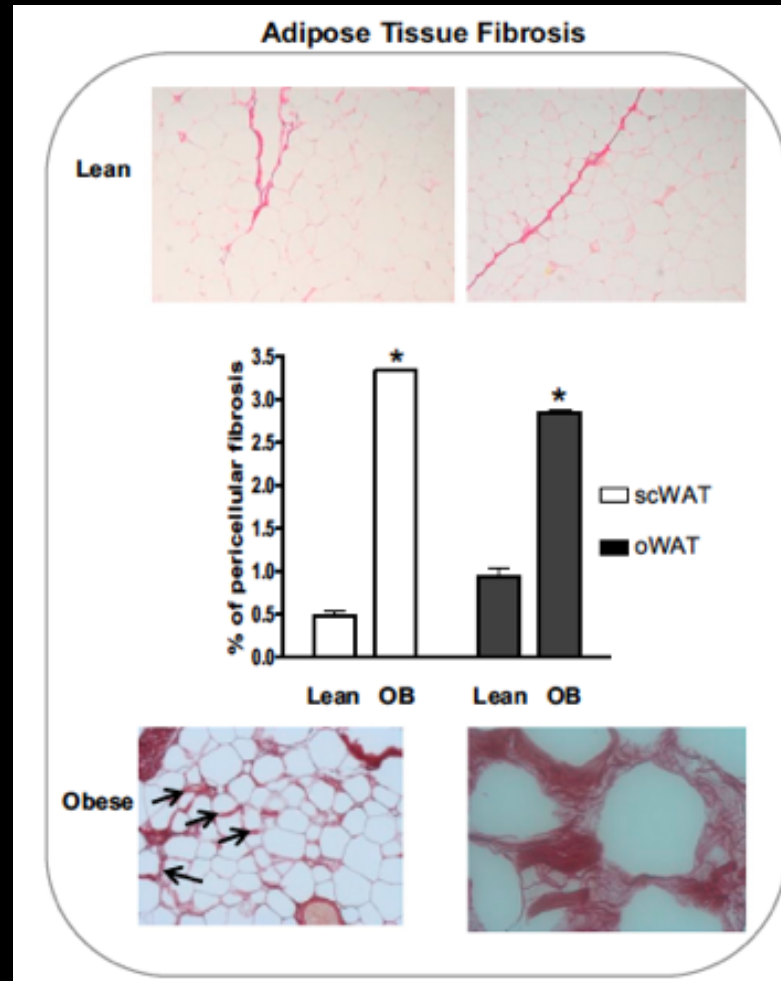


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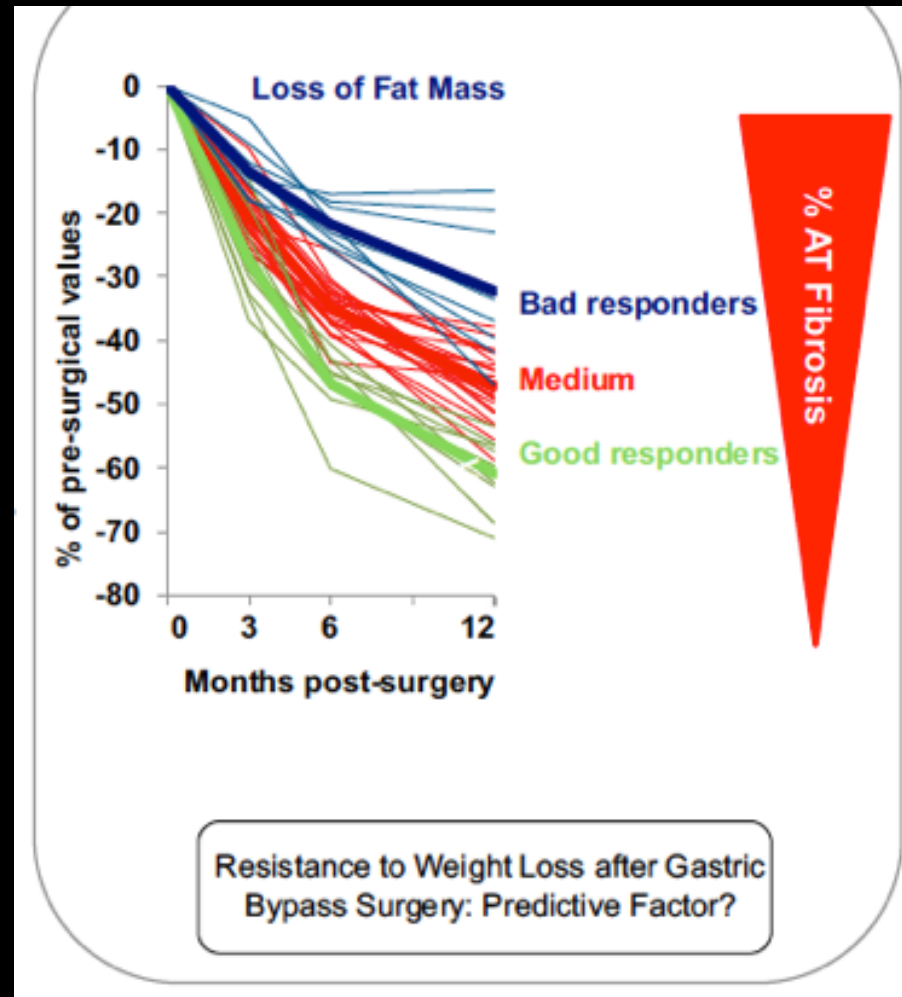
Subcutaneous Adipose Tissue (SCAT) Fibrosis and the Paradox of Ectopic Lipid Deposition

In fact, another possibility is that expansion of the intrabdominal depot may be an adaptation to a primary defect of the subcutaneous fat pad, resulting in preferential visceral deposition analogous to other ectopic deposition (Ali et al. 2011 ; Britton and Fox 2011). This perspective is supported by data showing metabolic dysfunction related to defective storage capacity in subcutaneous adipose tissue (Alligier et al. 2013) as well as a beneficial metabolic response associated with expansion of the SAT depot (Jensen 2008 ; Kim et al. 2007).

Obesity-Associated WAT Fibrosis Occurs in the SCAT and the VAT



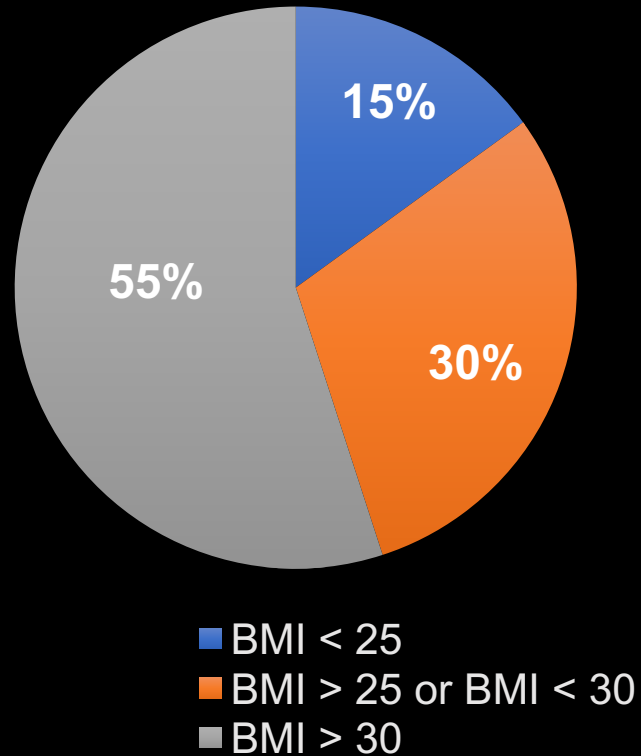
SCAT Fibrosis Has Clinical Consequences: Bariatric Surgery



Koliwad Lab: Unexpected Pathways Regulating Fat Distribution in People

Drivers of Insulin Resistance

Obesity and T2DM In the United States



Among people diagnosed with Type 2 diabetes, 55% are BMI ≥ 30 (obese), 30% are BMI ≥ 25 or ≤ 30 (overweight)

15 percent have a BMI ≤ 25 (classified as normal weight).

~70% of Overweight and Obese People do not develop T2DM

Ethnicity Impacts T2DM Risk

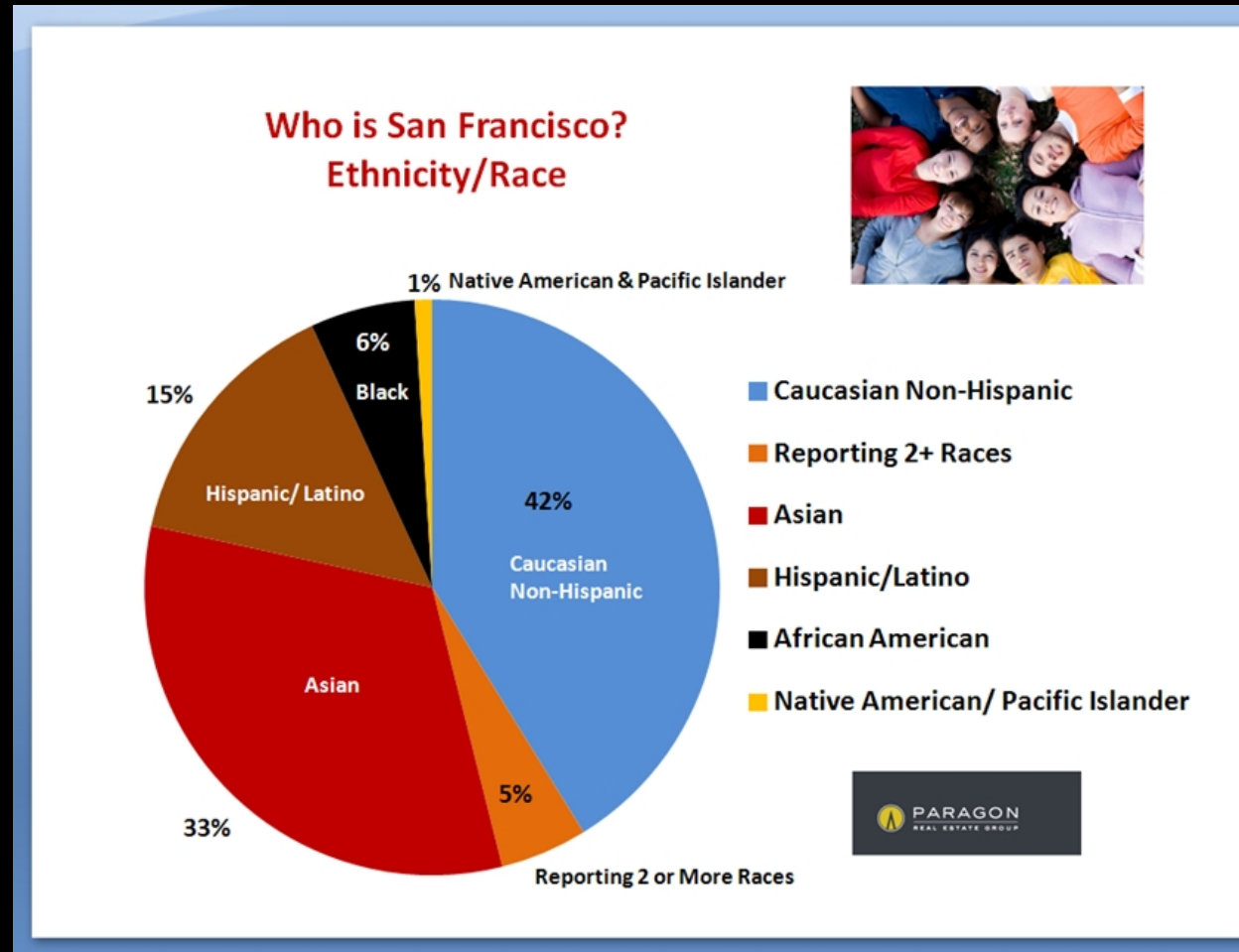
Nurse's Health Study

Table 2—RR (95% CI) of type 2 diabetes associated with ethnicity during 20 years of follow-up among 78,419 women

	Ethnic group			
	White	Asian	Hispanic	Black
n	75,584	801	613	1,421
Person-years of follow-up	1,254,454	11,671	9,248	19,427
Incident cases of diabetes	3,624	49	48	123
Age adjusted	1.0 (ref.)	1.43 (1.08–1.90)	1.76 (1.32–2.34)	2.18 (1.82–2.61)
Age and BMI adjusted	1.0 (ref.)	2.26 (1.70–2.99)	1.86 (1.40–2.47)	1.34 (1.11–1.61)
Multivariate*	1.0 (ref.)	1.94 (1.46–2.58)	1.70 (1.28–2.26)	1.36 (1.14–1.63)
Additional adjustment for dietary score† and energy intake	1.0 (ref.)	1.99 (1.50–2.64)	1.73 (1.30–2.31)	1.38 (1.15–1.66)

*Adjusted for age (5-year categories), BMI (continuous), family history of diabetes, alcohol intake (none, 0.1–4.9, 5–14.9, and 15+ g/day), smoking status (never, past smoker, current 1–14, current 15–24, and current 25+ cigarettes/day), and moderate/vigorous exercise (0–0.9, 1–1.9, 2–3.9, 4–6.9, and 7+ h/week) (updated variables). †The dietary score is the sum of quintile values for cereal fiber, ratio of polyunsaturated fat to saturated fat (ascending order), glycemic load, and trans fat (descending order). A higher score indicates a healthier diet (updated variables).

The San Francisco Bay Area: A Unique Research Opportunity for Obesity



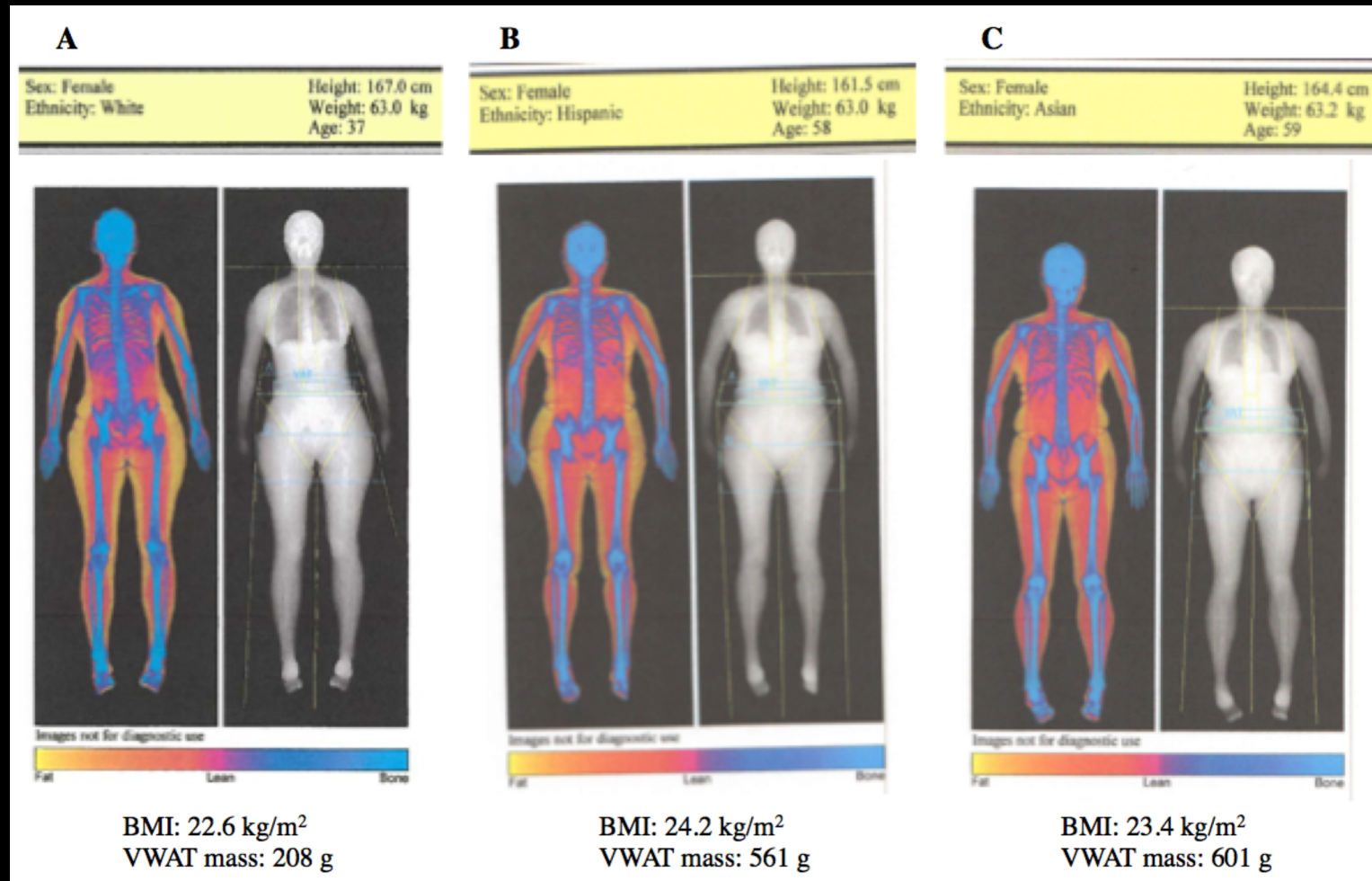
Inflammation, Diabetes, Ethnicity and Obesity (*IDEO*) Cohort: Study Participants

- Men and Women – ages 25-65
- Diabetic and Non-Diabetic
- Hispanic, Chinese (Cantonese), and Caucasian patients enrolled from UCSF and ZSFG clinics.
- Efforts underway to expand ethnicity.
- Nonsurgical obese, bariatric surgery, lean controls, other abdominal surgical controls.
- Exclusion criteria

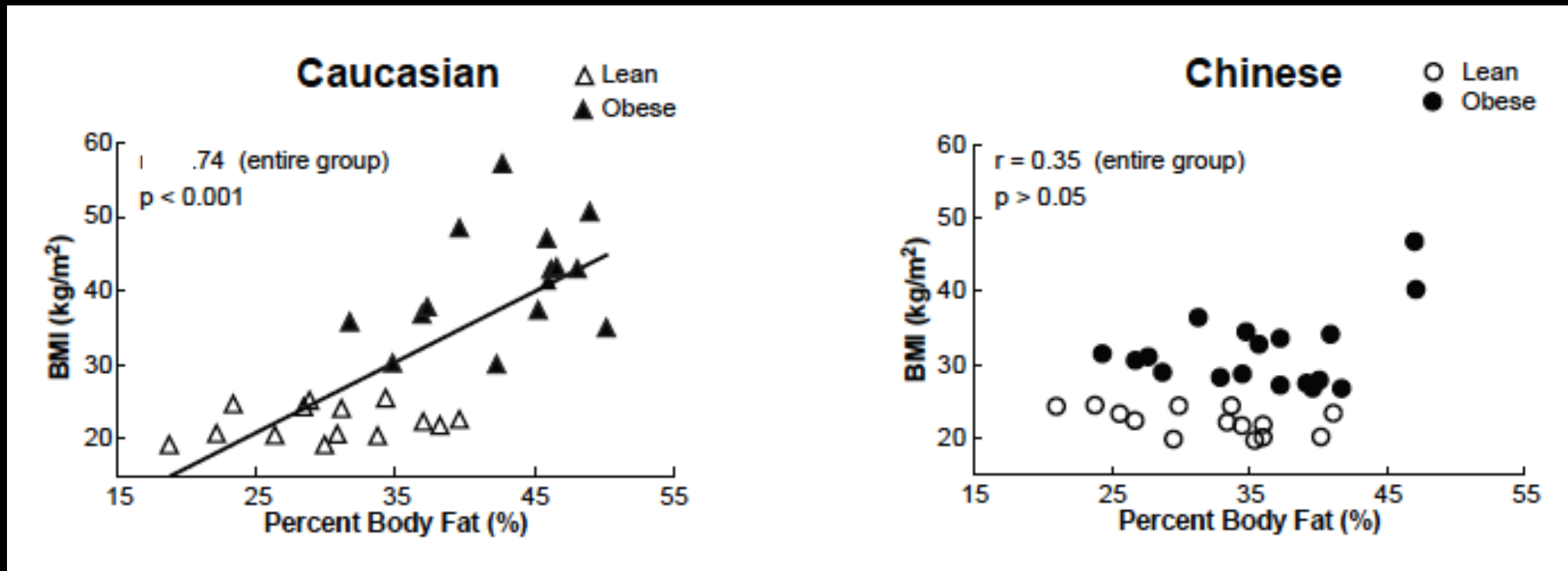
Recruited: **Over 120 Subjects; New project focused on HIV**

Blood, Fat, Cells, Stool, Imaging, Behavioral Data: **Over 100 Subjects**

Ethnicity-Specific Body Composition Differences: *IDEO* Participant DXA

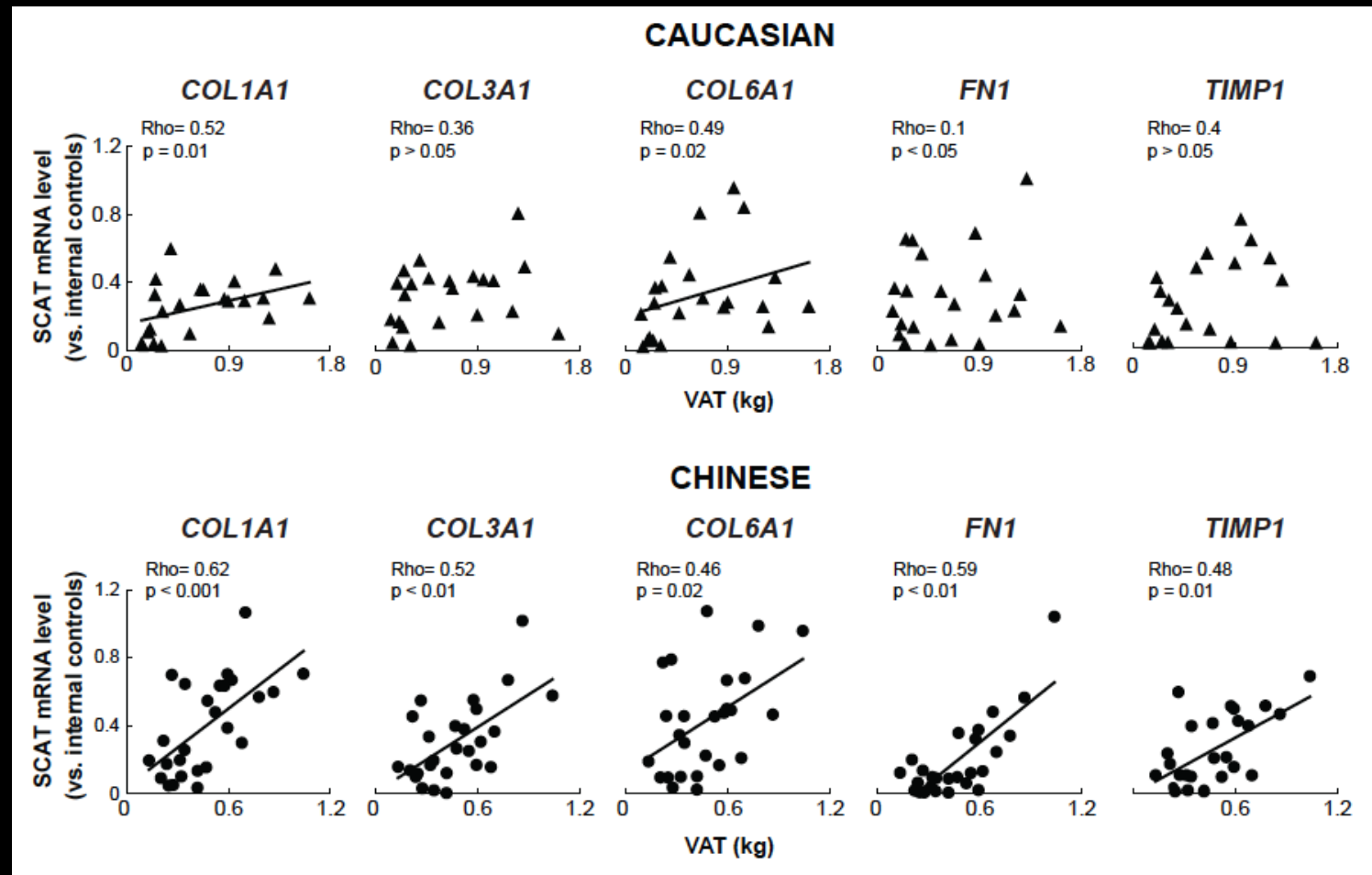


BMI and Total Adiposity are Differentially Related in Caucasian and Chinese Individuals.

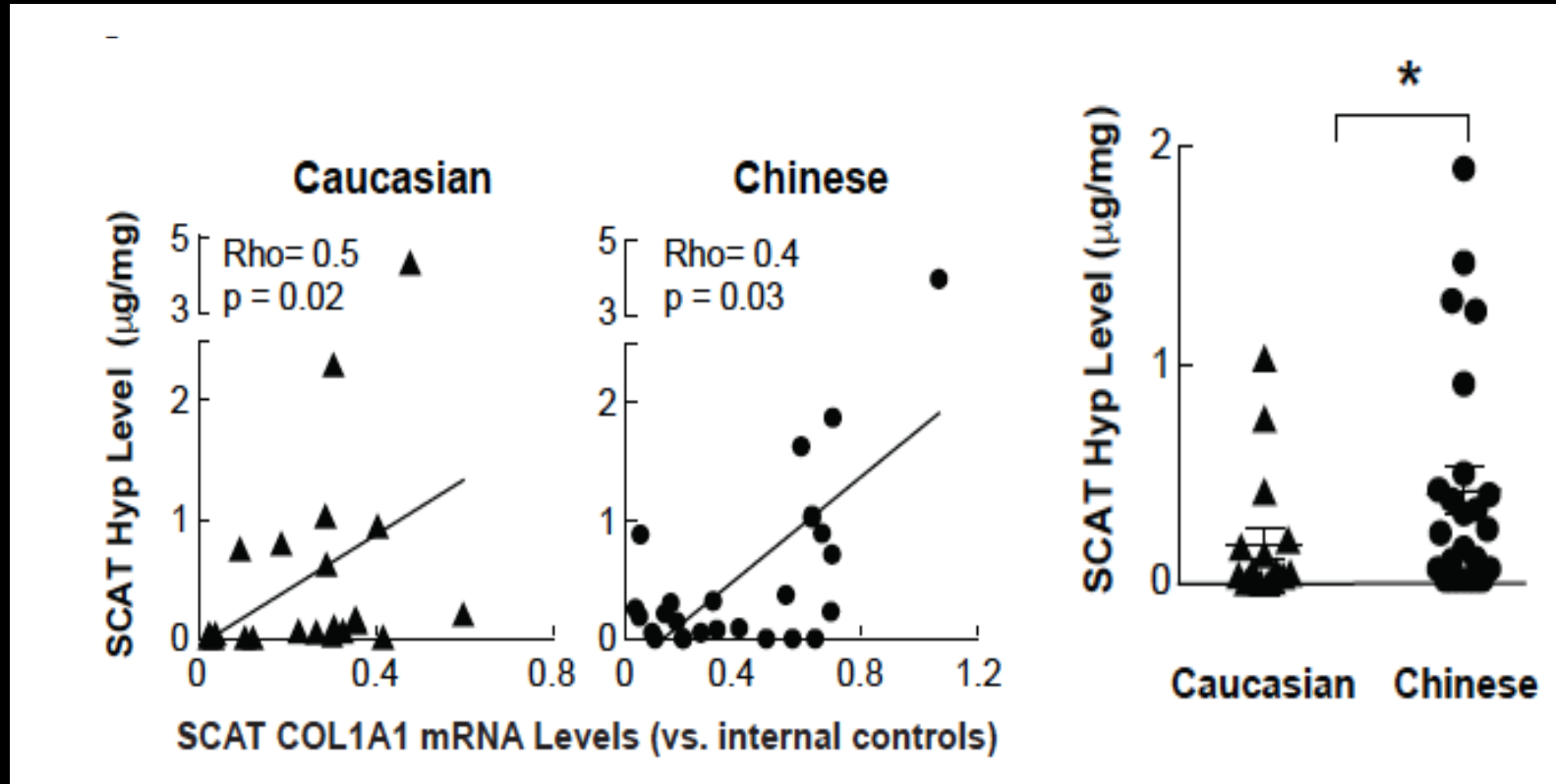


Lean defined < BMI 25, Obese defined as BMI above 30 for Caucasian and above 27.5 for Chinese using WHO cutoffs

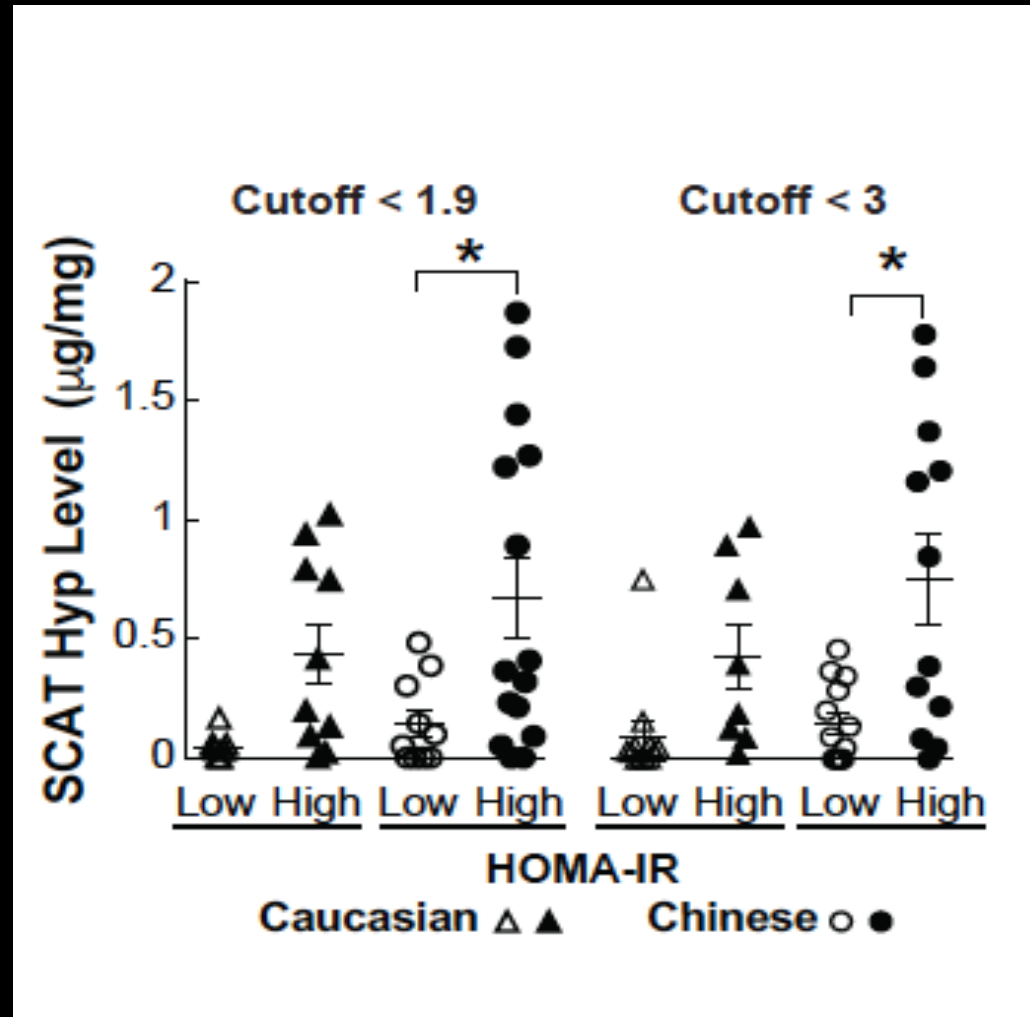
Visceral Adiposity is More Associated with SCAT Fibrosis in Chinese than in Caucasian Members of IDEO



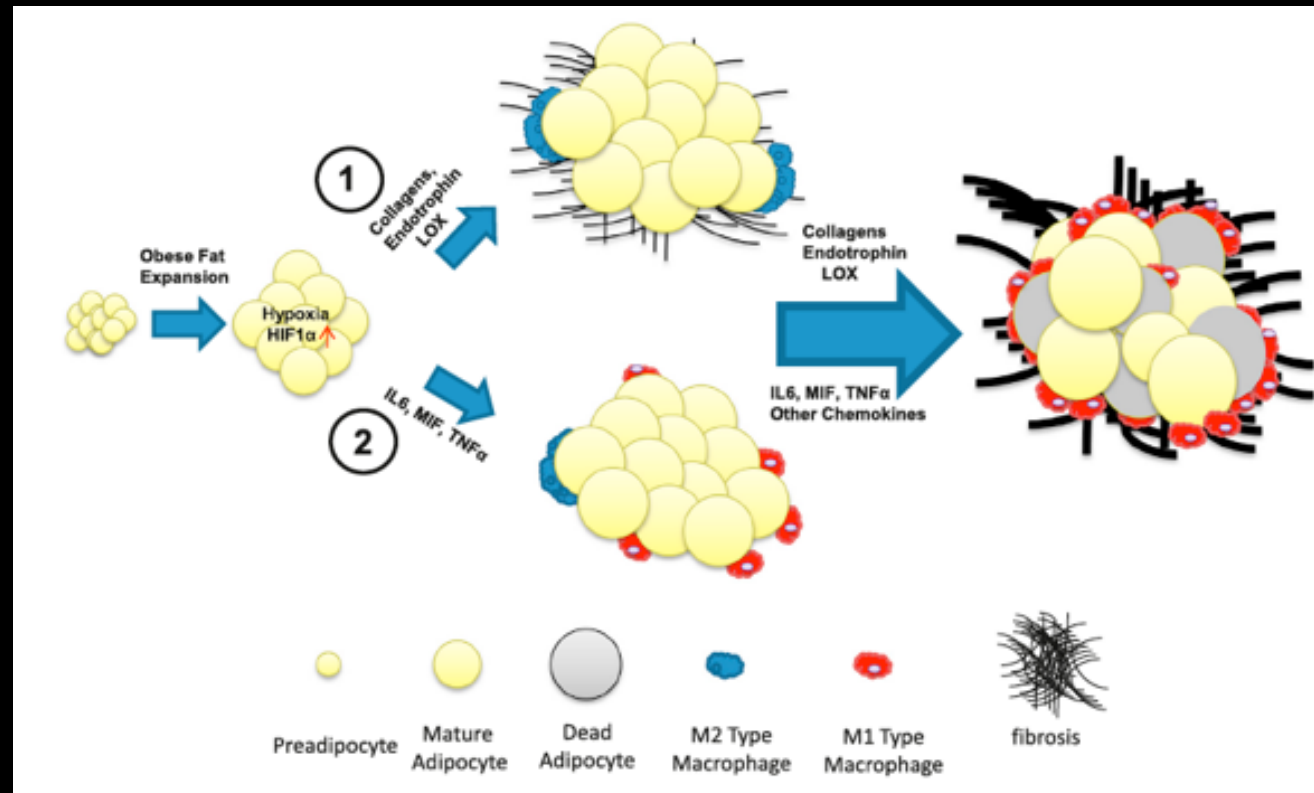
Chinese Individuals Develop More SCAT Fibrosis than do Caucasians



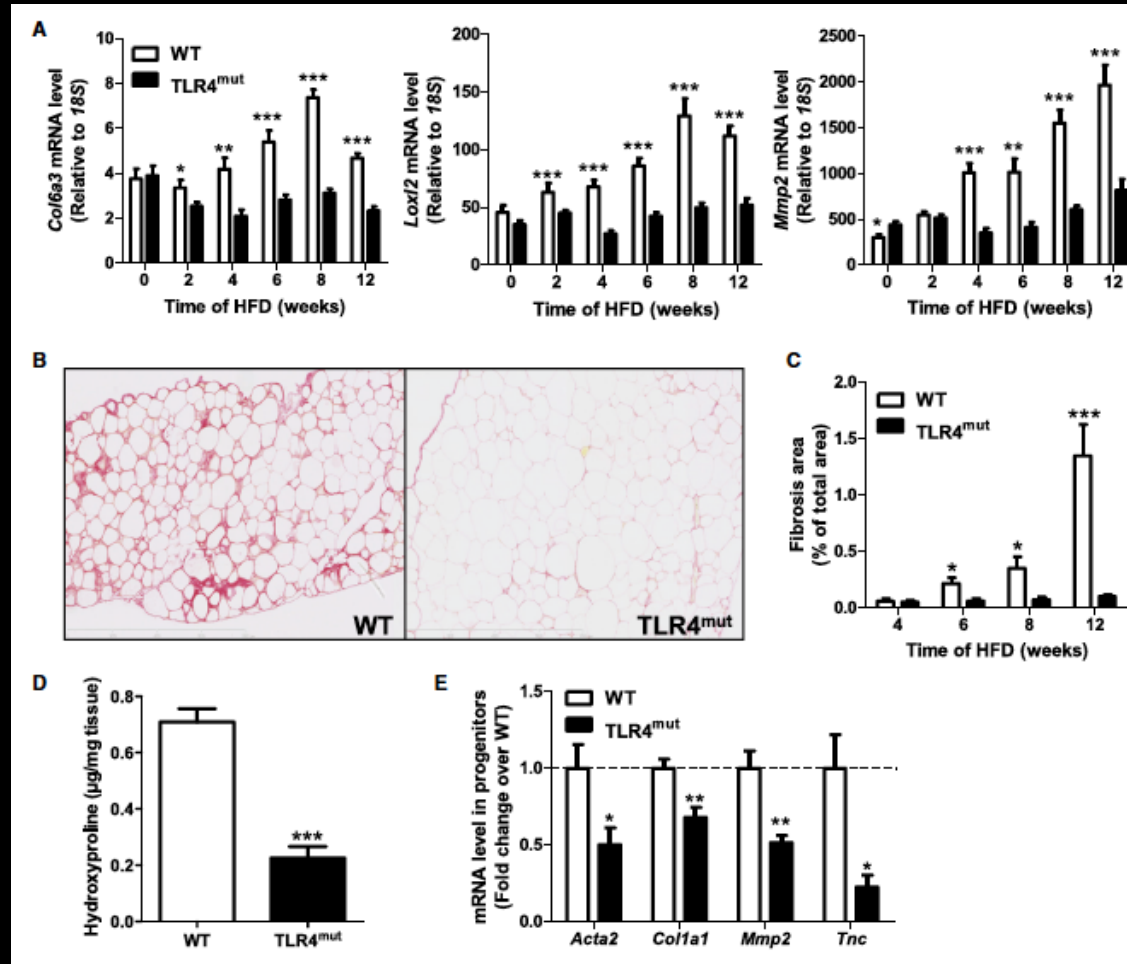
SCAT Fibrosis is More Closely Linked to Insulin Resistance in Chinese than Caucasian Subjects



Initial Mechanistic View: WAT Fibrosis is a Response to Inflammation



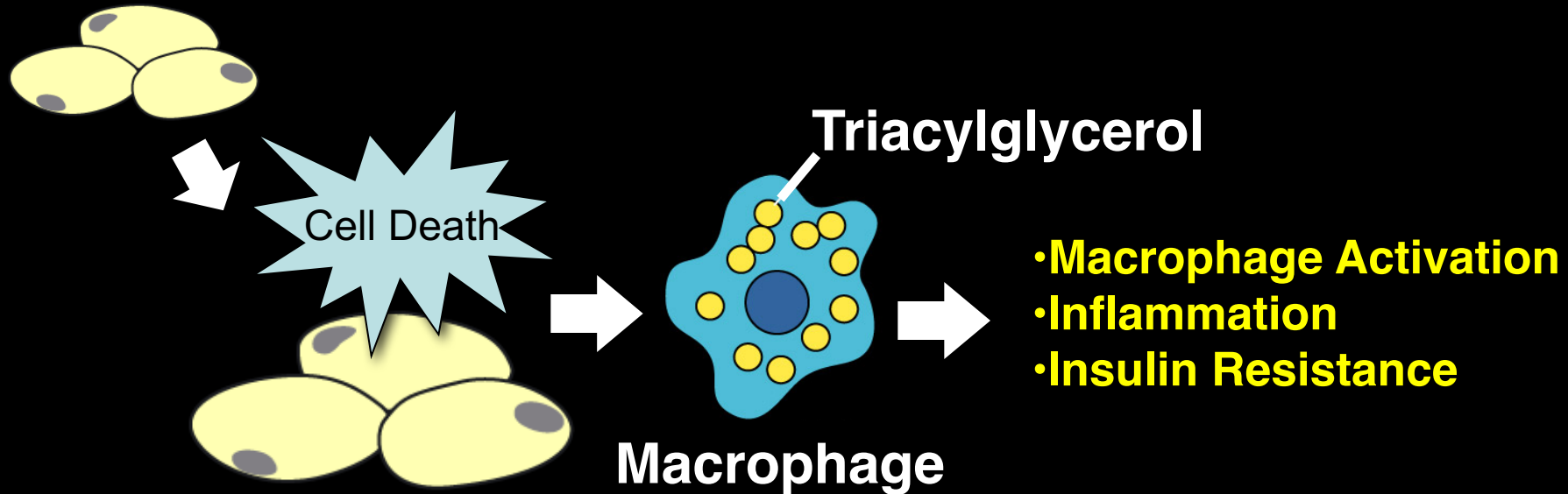
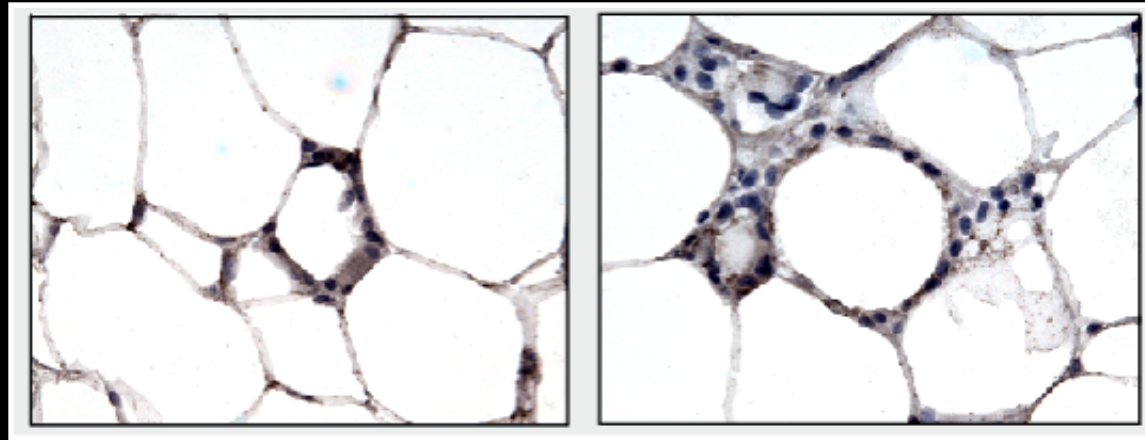
WAT Fibrosis is a Response to Inflammation: TLR4



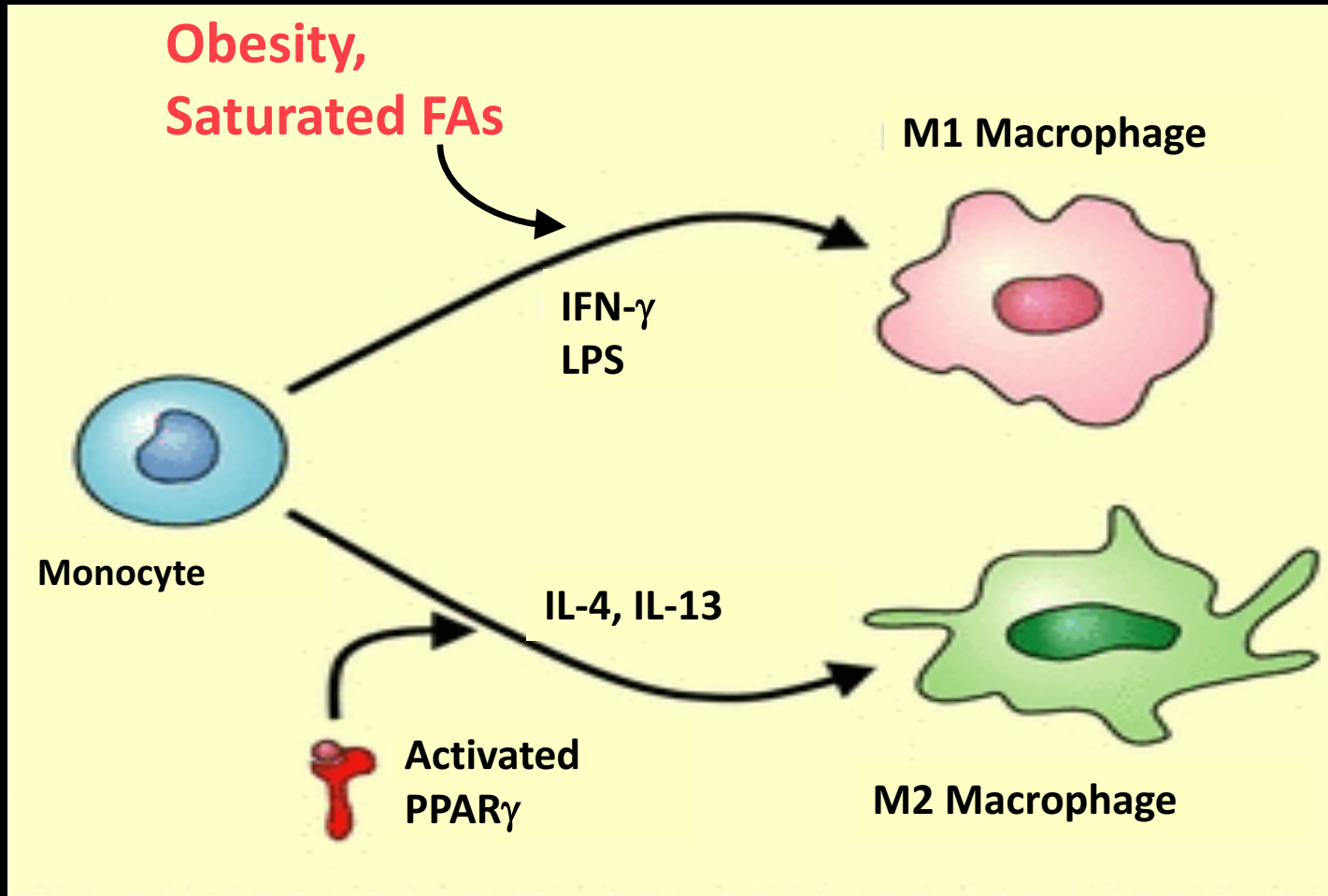
Obesity: A Chronic Inflammatory Disease

Chow

High-Fat



Inflammation: A Tale of Two Macrophages?



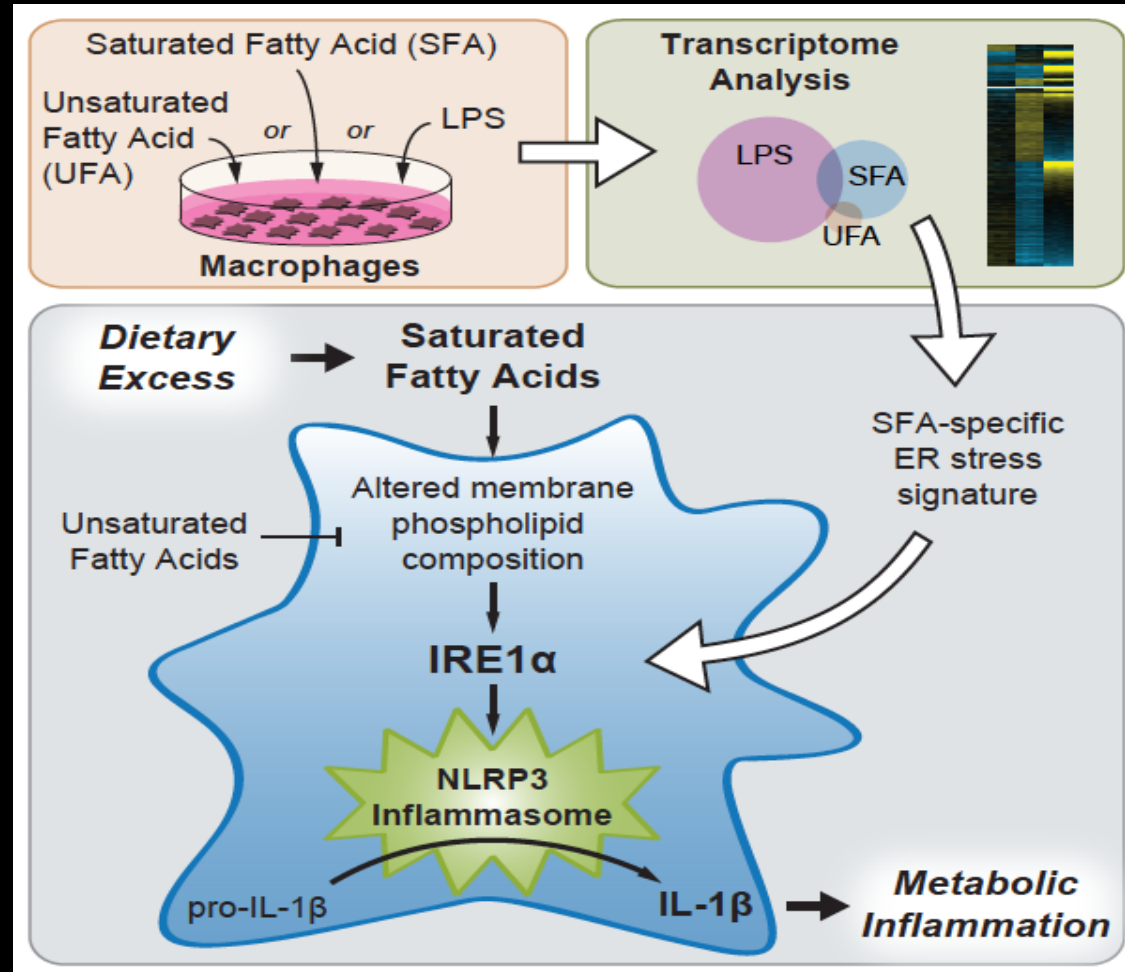
Classically Activated Macrophage (M1)

- Antigen presentation
- Microbicidal activity
- Express MHC class II molecules

Alternatively Activated Macrophage (M2)

- Anti-inflammatory
- Cell growth and tissue repair
- Endocytic activity

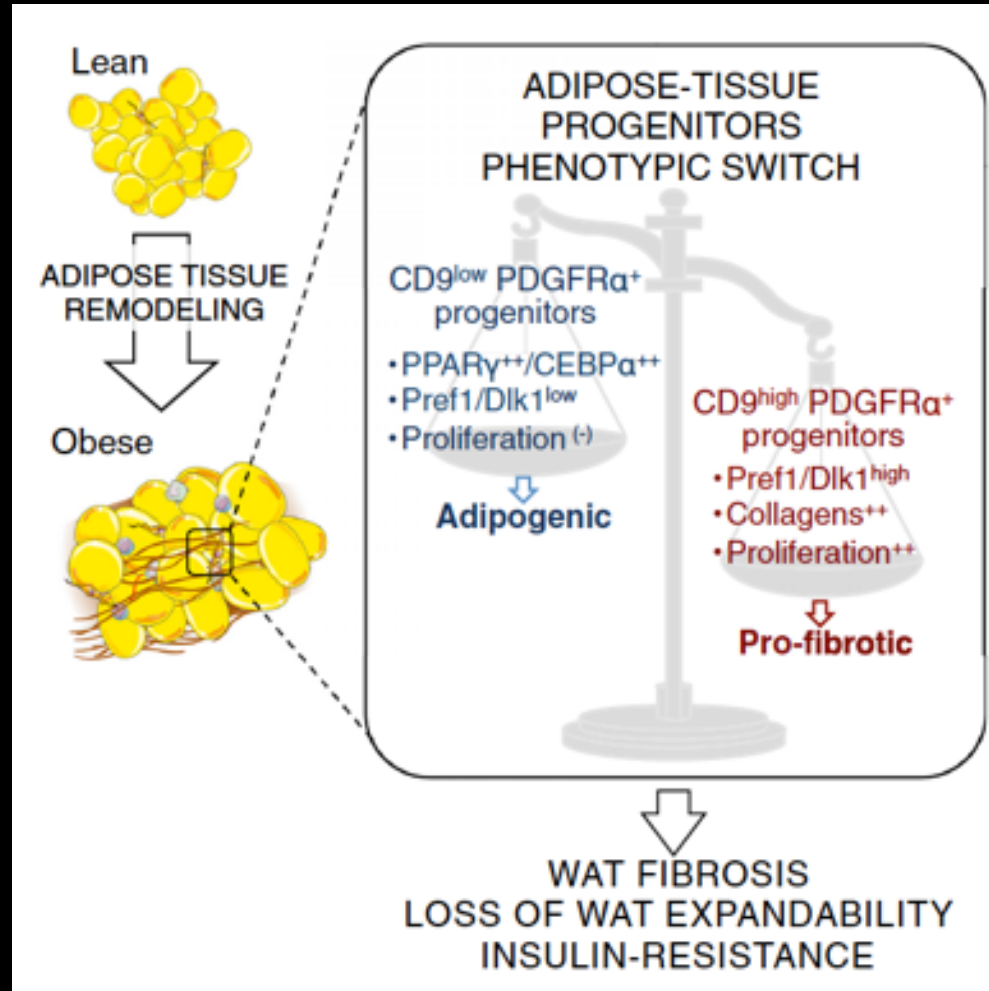
Metabolically-activated macrophages (M_{me}): IRE1 α as an intracellular lipid sensor and regulator of inflammatory function in myeloid cells



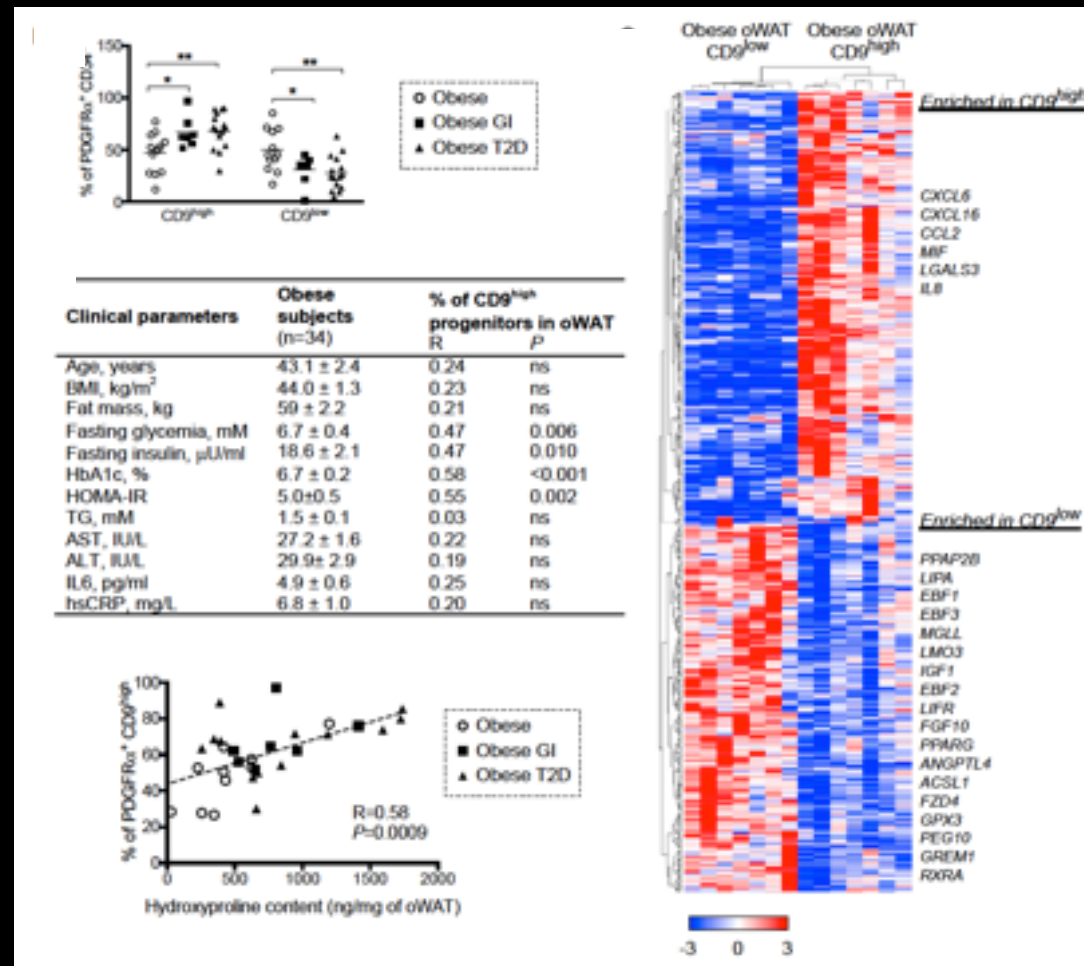
Robblee, M. et al. Cell Reports, 2016

Volmer, et al. PNAS, 2013; Halbeib, K., et al. Mol. Cell. 2017; Tufanli, O. et al. PNAS, 2017; Sjan, et al. Nat. Immunol. 2017; Lancaster, et al. Cell Metab, 2018, Lark, et al. F1000 Research, 2017.

Alternate Mechanistic View: WAT Fibrosis is Triggered by Pro-Fibrotic WAT Precursor Cells



CD9 distinguishes a population PDGFRa+; CD29+; CD34+; GP38+ cells predisposed to the fibroblast lineage

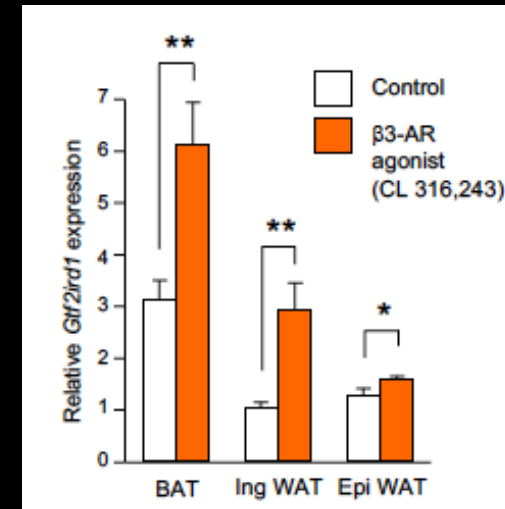
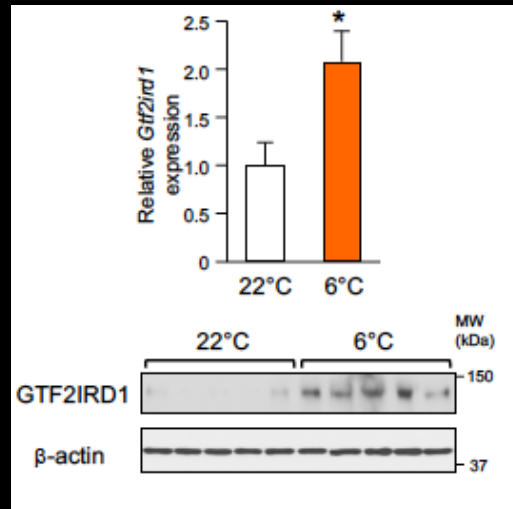
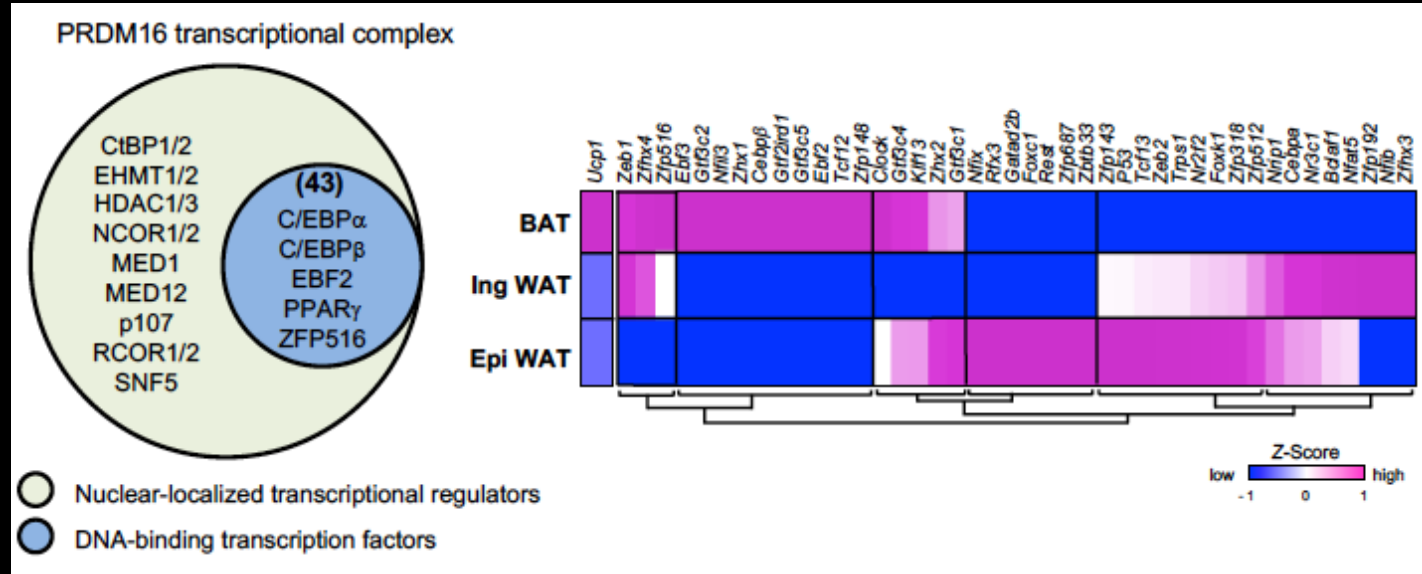


Are these cells akin to fibro-adipogenic precursors (also Pdgfr+) in muscle (FAPs) that have fibrotic potential and poor adipogenic potential in the context of injury?

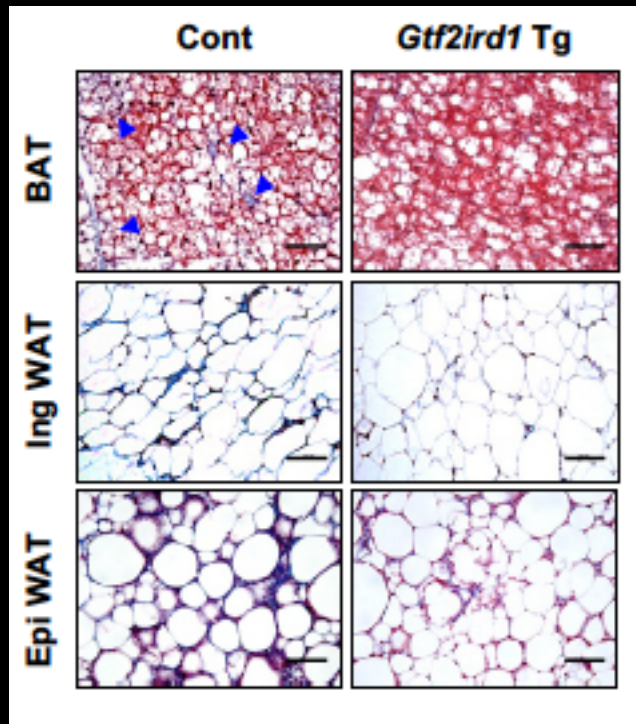
Koliwad Lab: Probing The Cell-Autonomous Regulation of White Adipose Fibrosis

Work of Yutaka Hasegawa (Kajimura Lab at UCSF) and Diana Alba (Koliwad Lab)

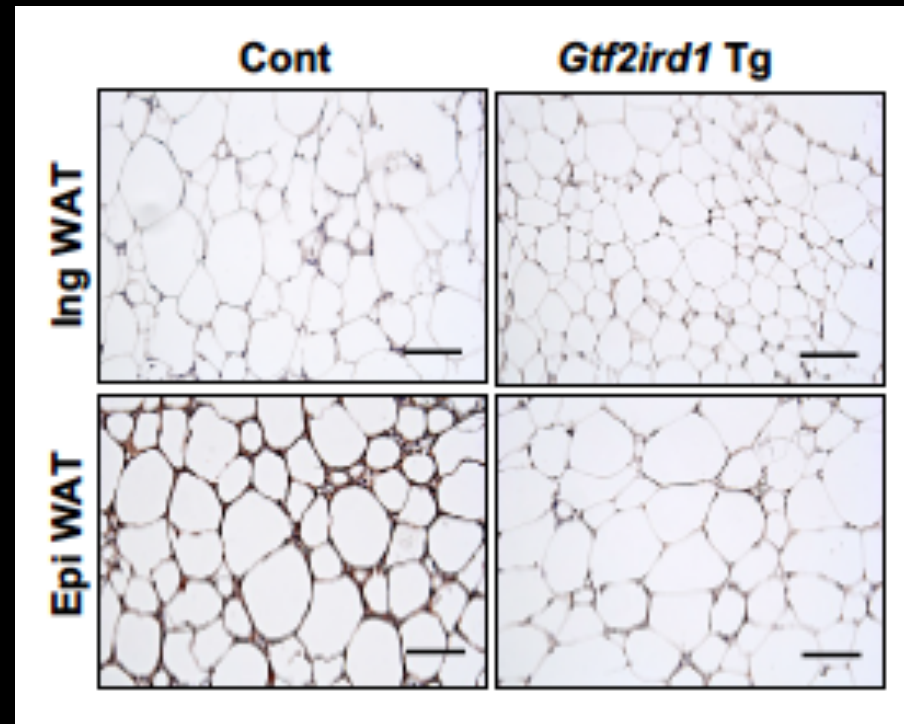
GTF2IRD1 is an Inducible Component of The PRDM16-EHMT1 Transcriptional Complex



aP2-*Gtf2ird1* Transgenic Mice Have Reduced BAT and iWAT Fibrosis

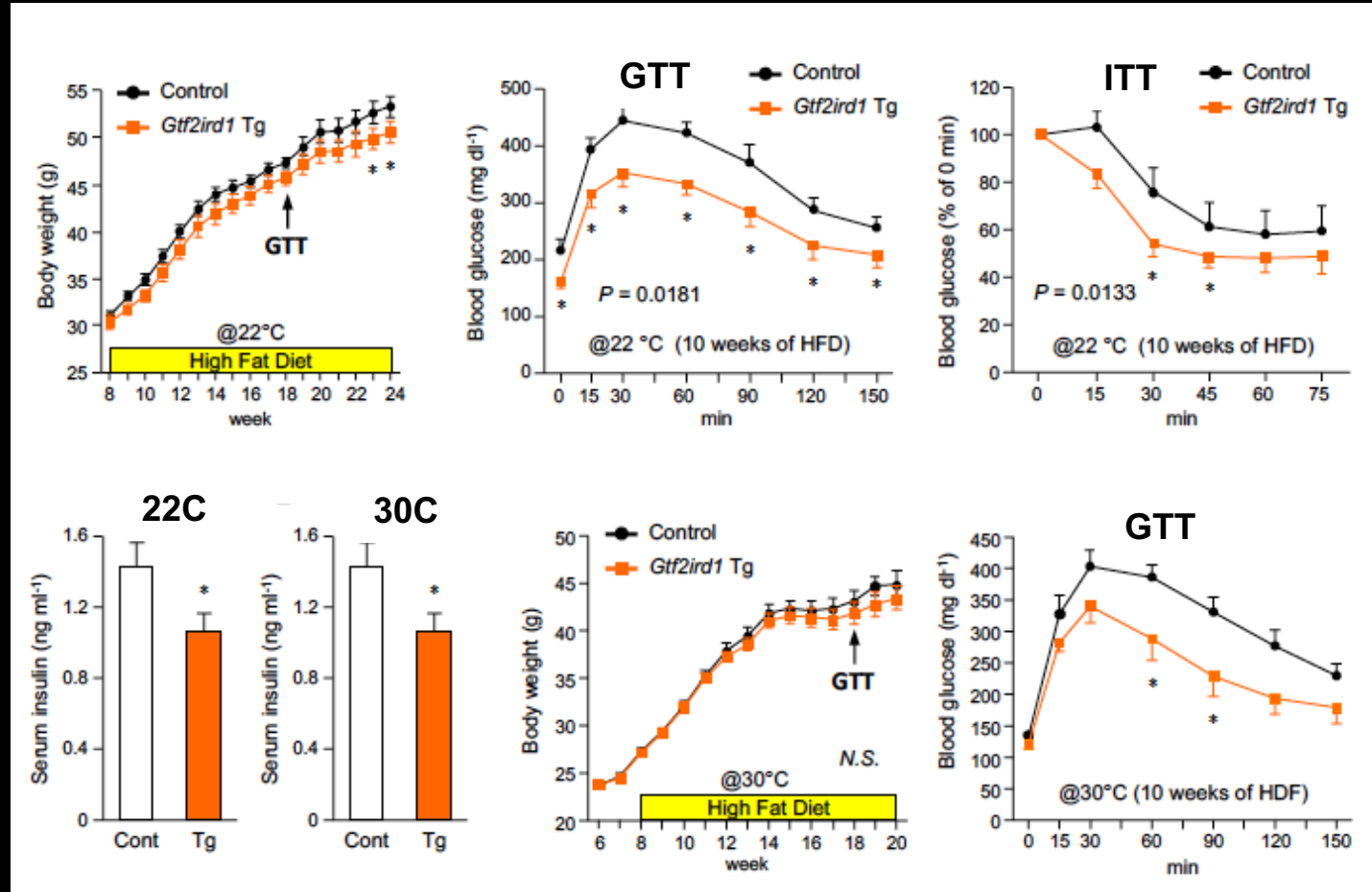


Masson's Trichrome

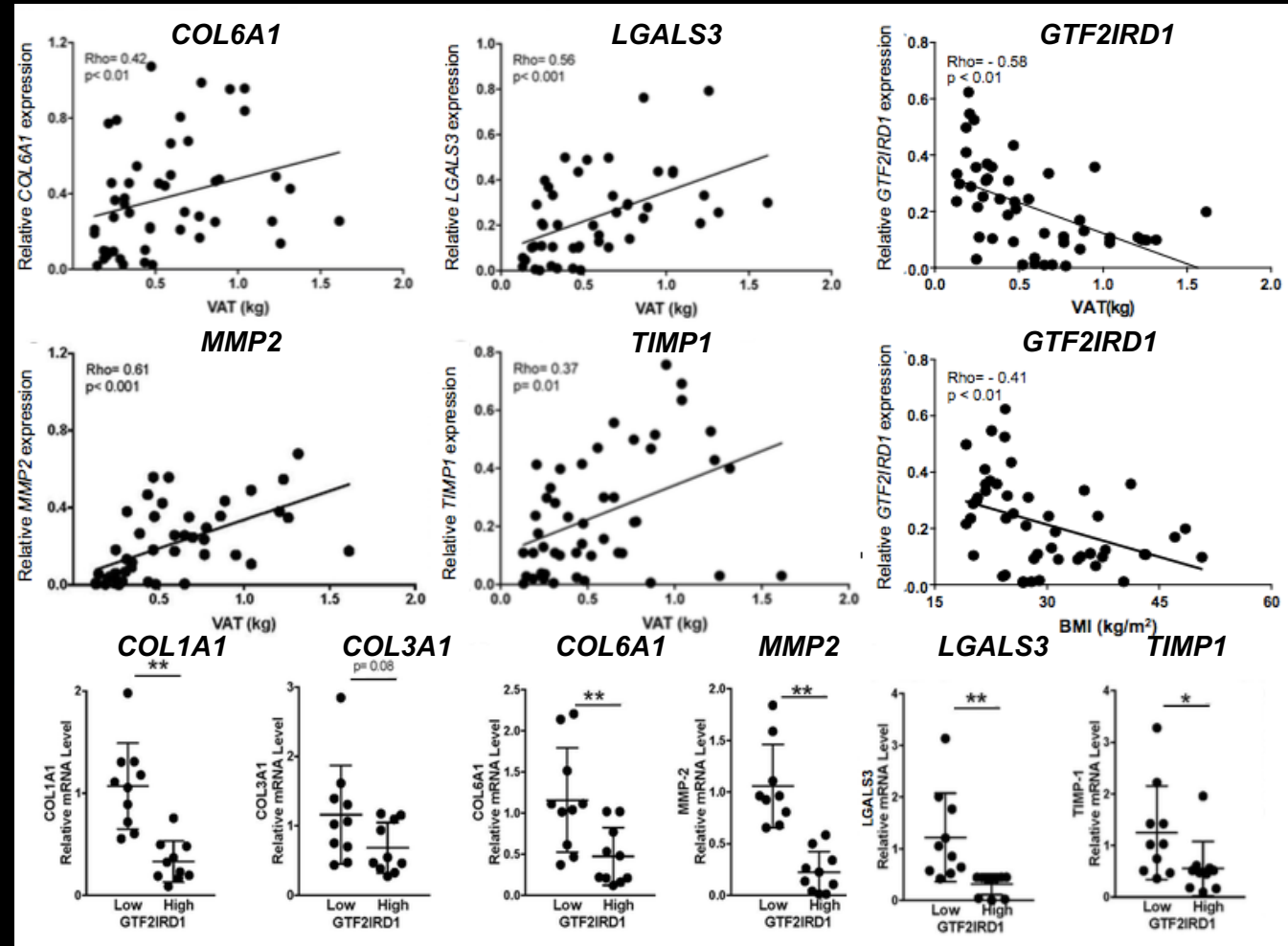


Collagen Breakdown: Endotrophin

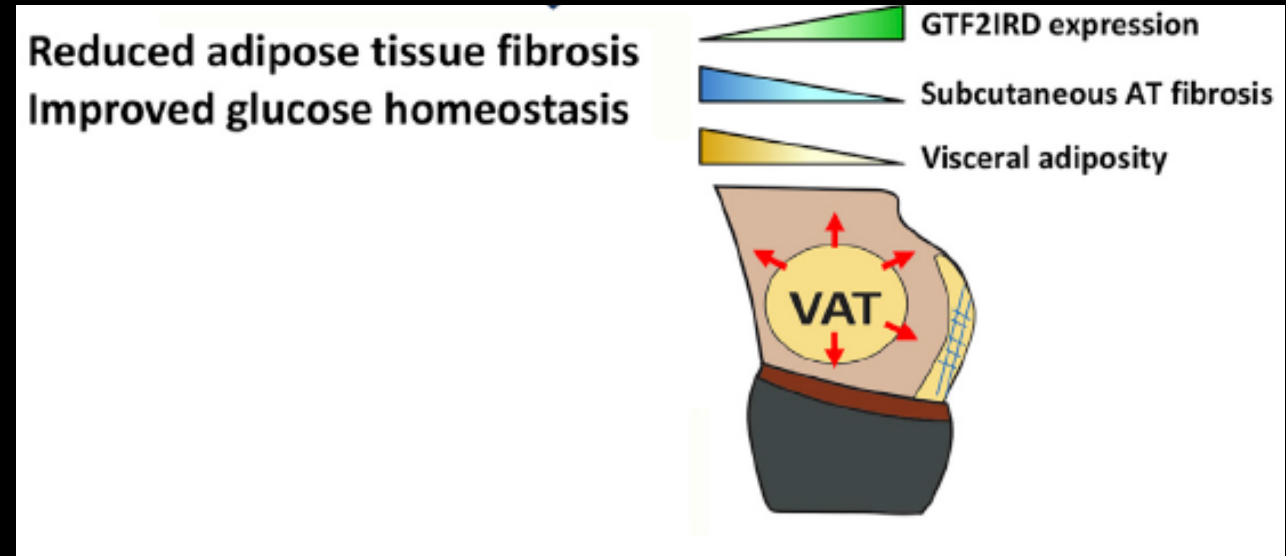
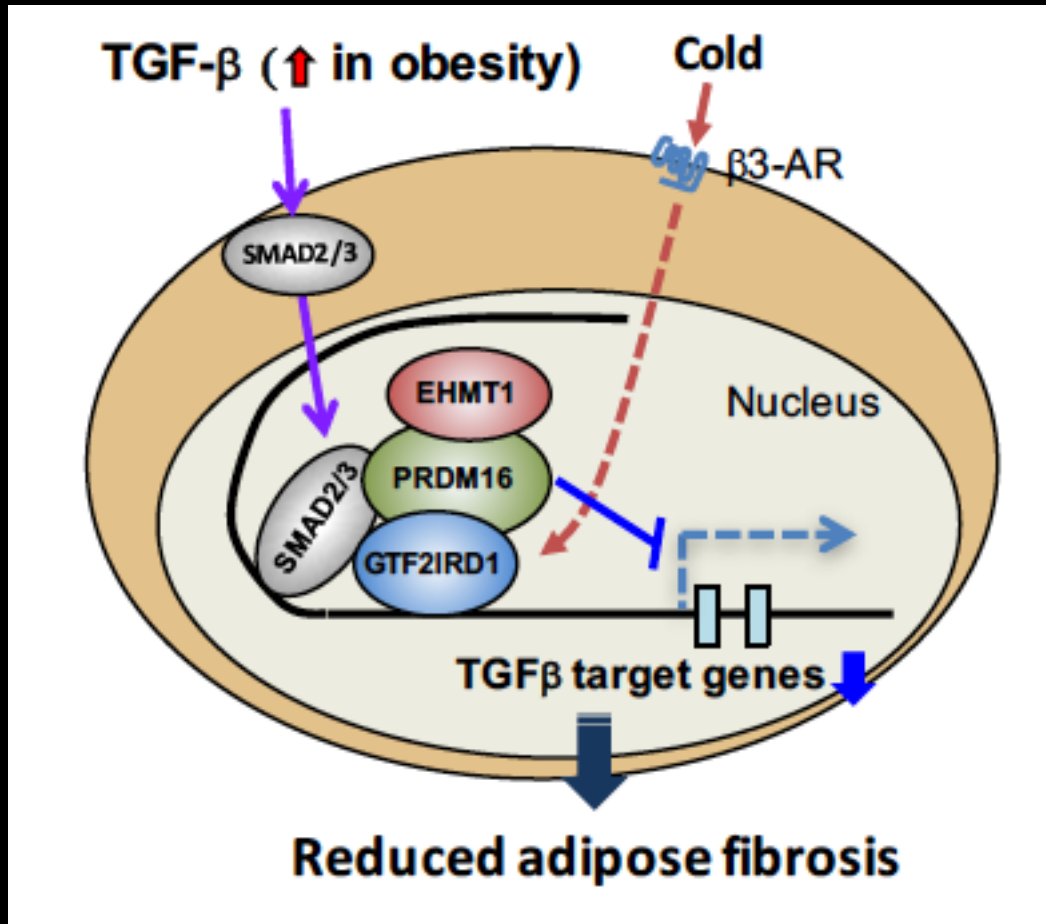
aP2-Gtf2ird1 Mice Have Improved Glucose Homeostasis



IDEO Cohort: SCAT *GTF2IRD1* Levels Correlate Inversely with Visceral Adiposity and Fibrosis

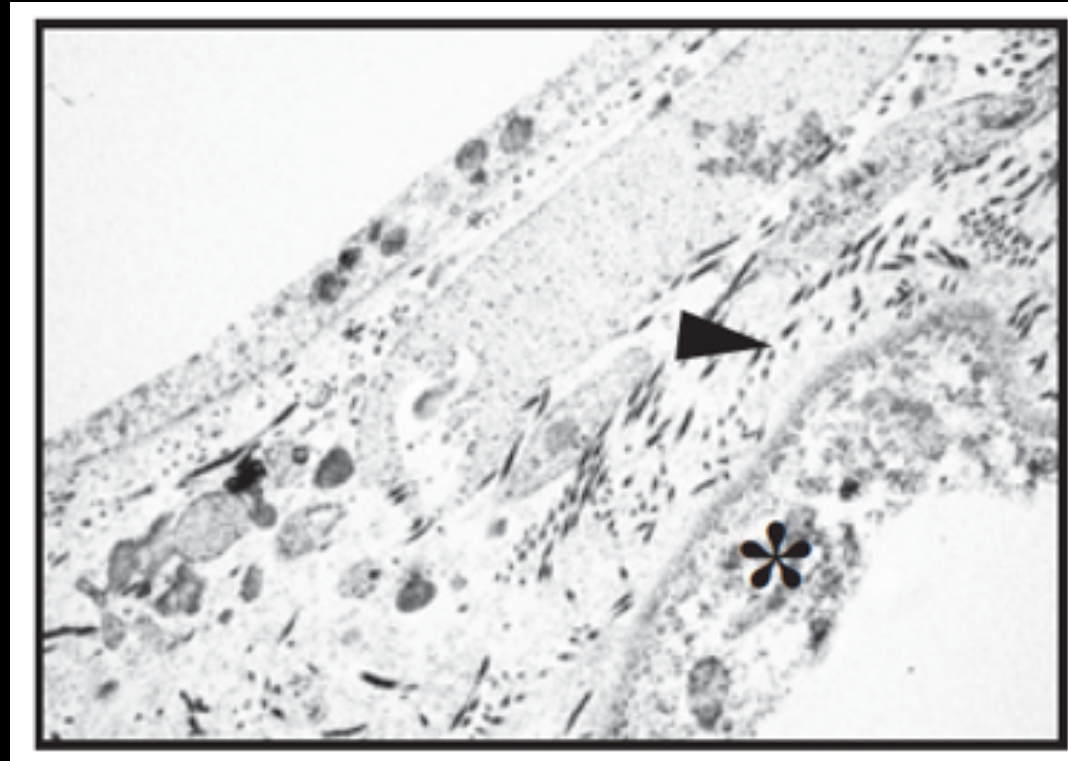


Summary: GTF2IRD1 as a PRDM16-Associated Transcriptional Regulator of Fat Fibrosis and Visceral Adiposity



Adipose Fibrosis in HIV

ART-Treated HIV is Associated with WAT Fibrosis: Description in Dorsocervical Fat



*Bereziat, et al.
Am. J. Pathol, 2011*

No prospective studies have been done focusing on this issue. Several of the early descriptions were made in the era of common PI use. This description occurs in conjunction with those mentioning alterations in adipocyte size, morphology, and inflammation. No direct links have been drawn between HIV-associated WAT fibrosis and metabolic alterations, glucose intolerance, or T2DM.

Commonalities between WAT Fibrosis in Obesity and HIV Infection.

- Both are associated with visceral adiposity (reviewed in Sun, Tordjman, Clement, Scherer, Cell Metabolism 2013).
- Increased VAT mass in both states is associated with insulin resistance and T2DM.
- Both conditions are associated with evidence of WAT inflammation, myeloid cell infiltration, and alterations in adipocytokine levels within the tissue and potentially systemically (Reviewed by Koethe, J., Compr Physiol 7:1339-1357, 2017).
- Emerging evidence to indicate that HIV-associated WAT fibrosis is not simply an indicator of lipoatrophy/distrophy induced by PI therapy.

Samaras K, et al. Diabetes Care. 2007; Ledergerber, B. et al. Clin Infect Dis. 2007; Brar I, et al. J Acquir Immune Defic Syndr. 2007; Carr A, et al. Lancet. 1999; De Wit S, et al. Diabetes Care. 2008; Hunt PW. Curr Opin HIV AIDS. 2014; Butt AA, et al. Hepatology. 2004.

Thank You

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