Fat as an immunologically active tissue: Defining the scope and cell types

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Obesity and Fat Metabolism in HIV-Infected Individuals NIH Workshop

Why does obesity increase risk for so many diseases?

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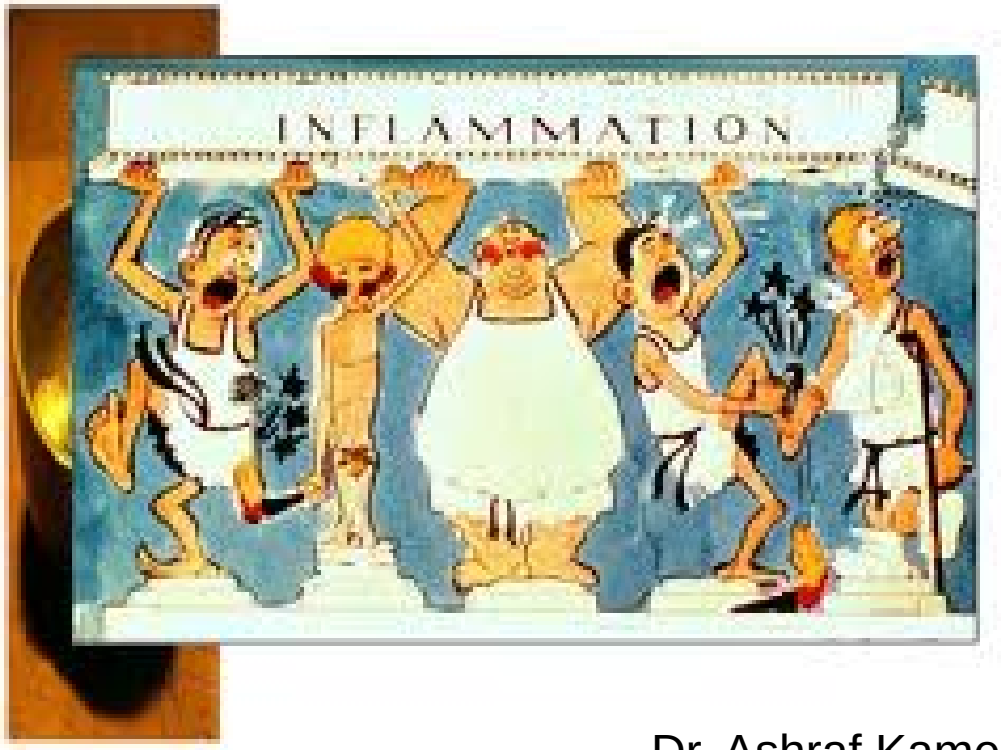
CHRONIC INFLAMMATION

Four Cardinal Signs of Acute Inflammation

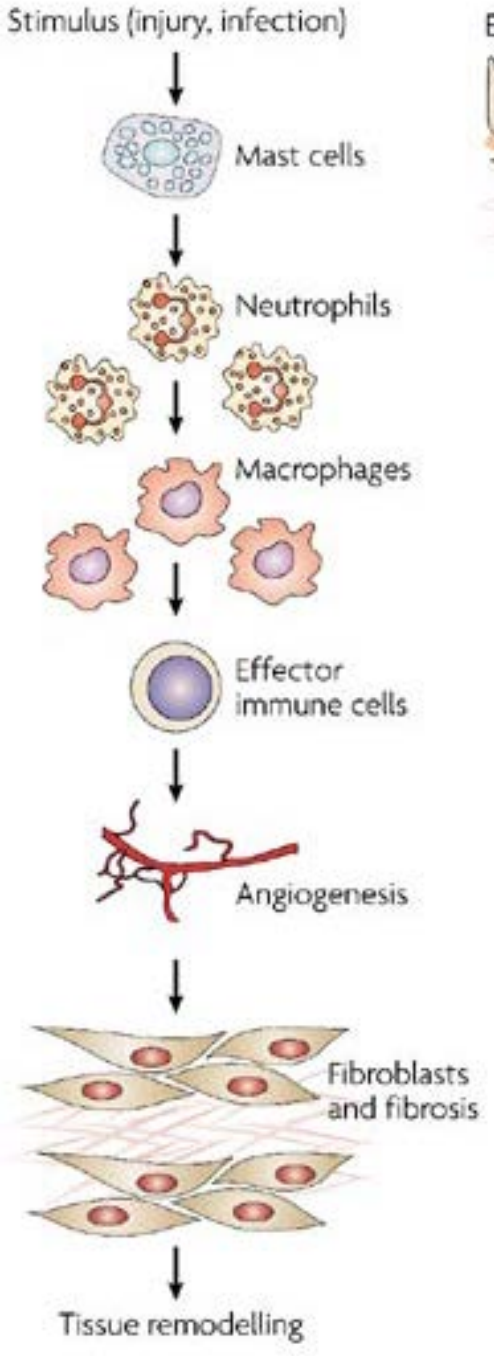
- Color (heat)
- Dolor (pain)
- Rubor (redness)
- Tumor (swelling)



Dr. Ashraf Kamel

Acute Inflammation

- Release of chemoattractants
- Neutrophils and mast cells are recruited to wounded site to release toxins and cytokines
- Macrophages recruited to phagocytose dead cells and debris
- Secondary immune response effector cells respond
- The wounded area is repaired and tissue homeostasis is restored



Acute versus chronic inflammatory responses

ACUTE	CHRONIC

• Stays localized
• Short duration
  • (minutes-days)
• Repair and resolution of the inflammation
	• **Many** different organ systems involved
	• **Long duration**
	  • (days-years)
	• **Resolution rarely occurs resulting in tissue damage**

Recent Discoveries in Adipose Tissue Biology

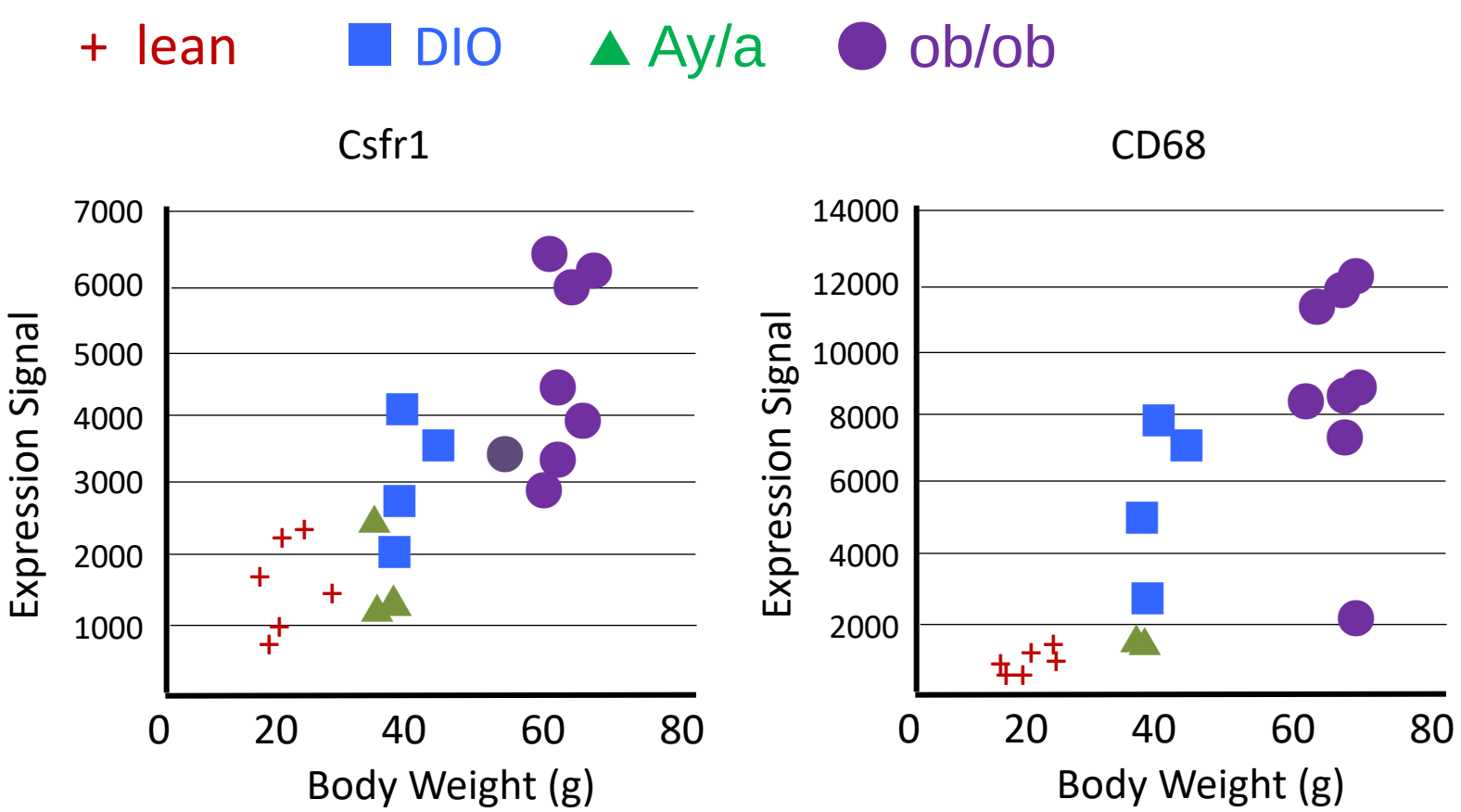
- Recognition that adipose tissue is a storage site for excess energy
- Identification of transcription factors involved in adipogenesis
- Identification of enzymes and proteins involved in control of fatty acid storage and lipolysis
- Discovery of an adipose tissue-CNS networks for energy homeostasis
- Recognition that adipose tissue secretes MANY different proteins, hormones, adipokines, and chemokines
- Adipose tissue displays signs of chronic inflammation in obesity

Many of the adipose tissue secreted products are inflammatory

- In the mid-1990's it was established that adipose tissue is a source of inflammation in obesity
- In 2003, seminal papers were published in the *JCI* describing the presence of increased numbers of macrophages in obese adipose tissue

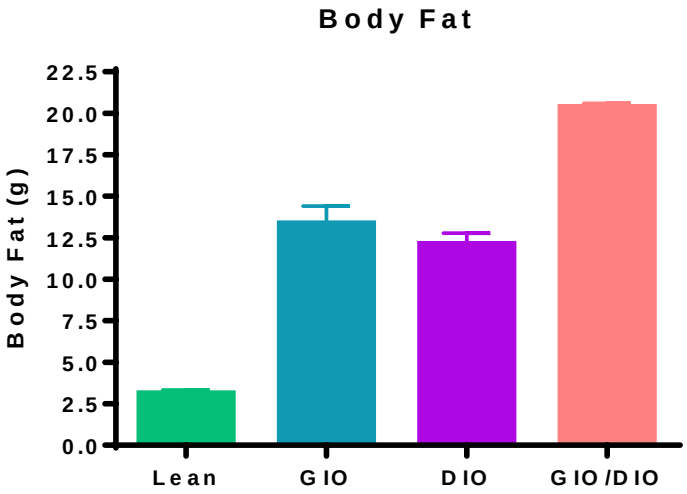
Xu et al. JCI 2003; Weisberg et al. JCI 2003

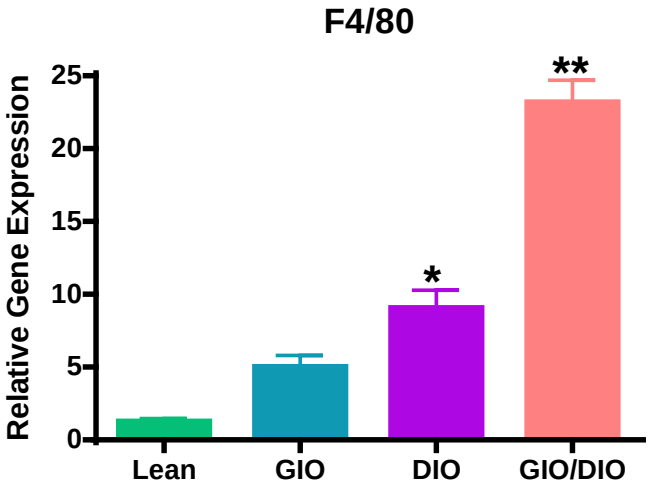
Macrophage Infiltration into Adipose Tissue is Increased in Obesity

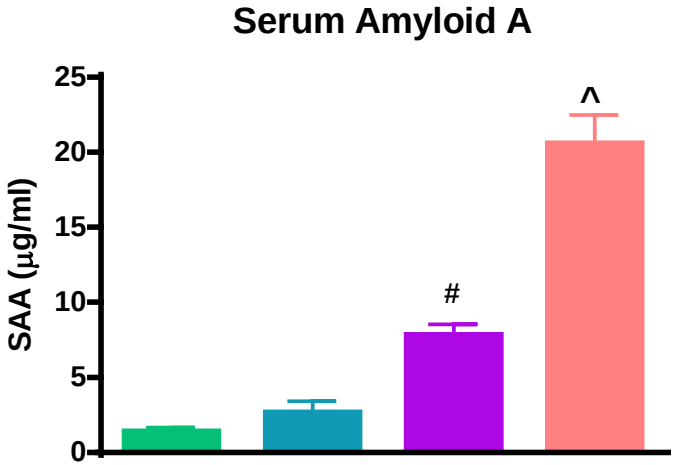


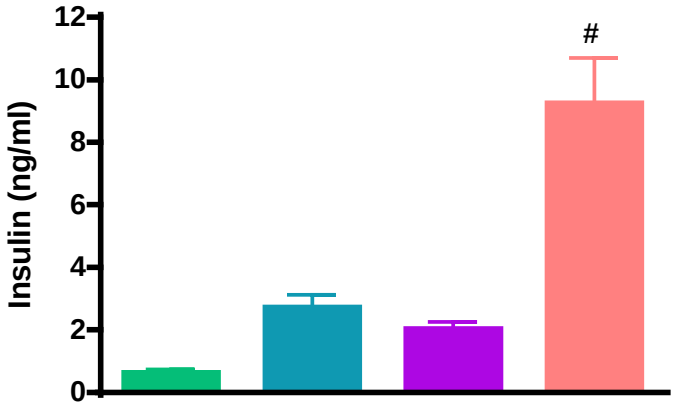
Recreated from Weisberg et al. *JCI* 2003

Systemic effects of adipose tissue inflammation









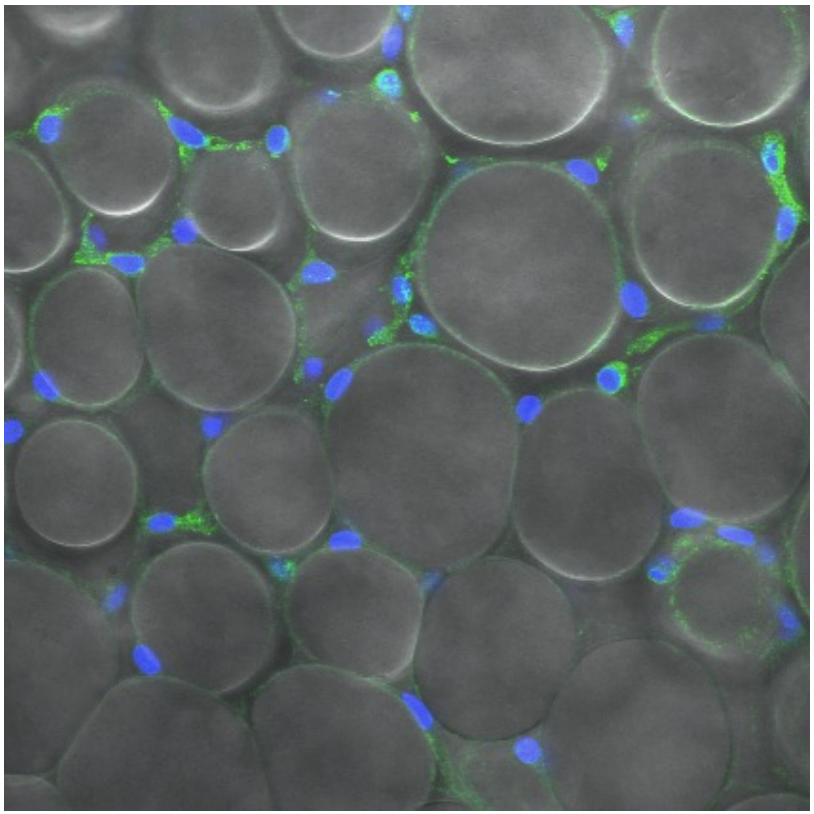
KR Coenen and AH Hasty. *AJP:E&M*. 2007

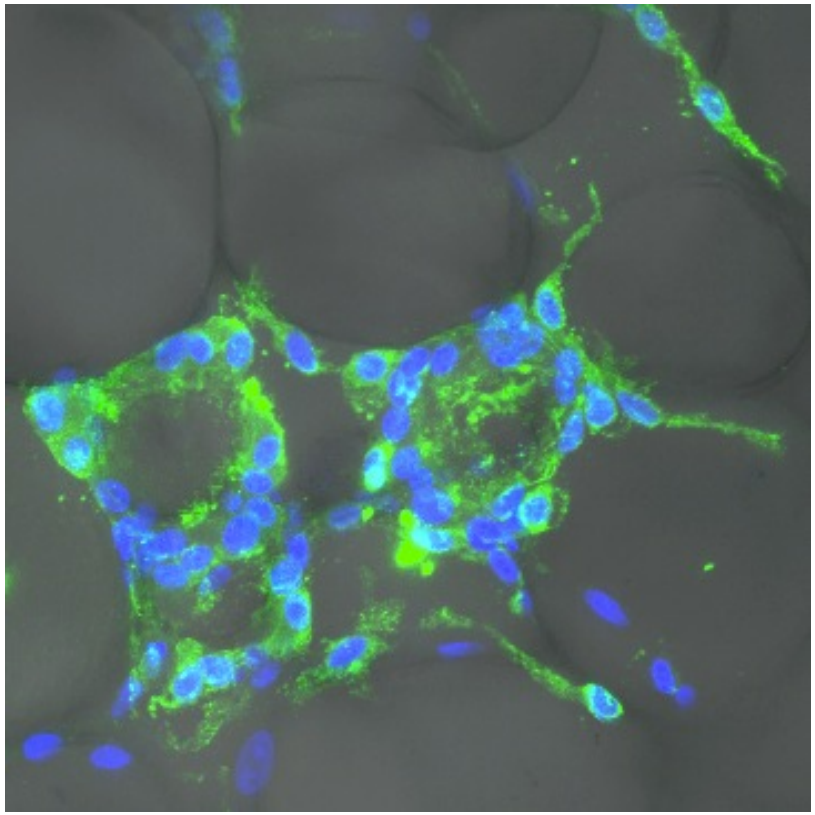
Macrophages in obese adipose tissue form in crown-like structures

Lean

Obese

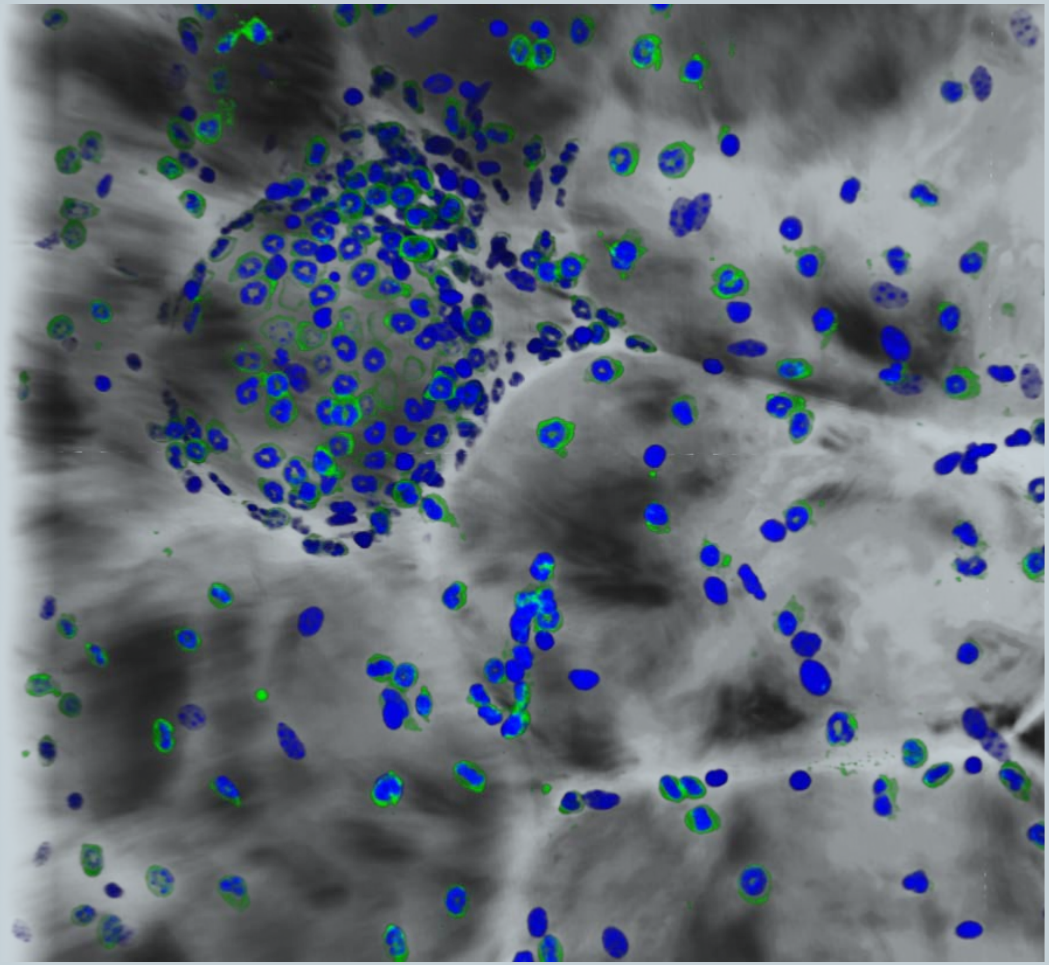
Dapi F4/80



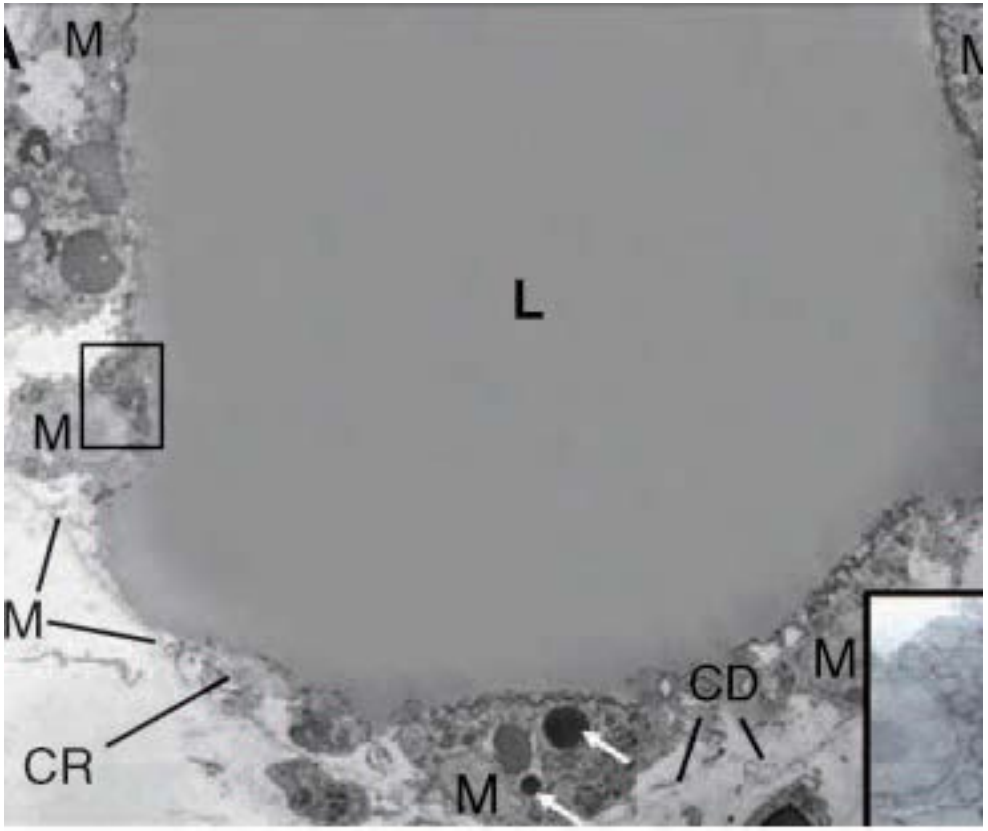


Emily Anderson

Macrophages in obese adipose tissue form in crown-like structures



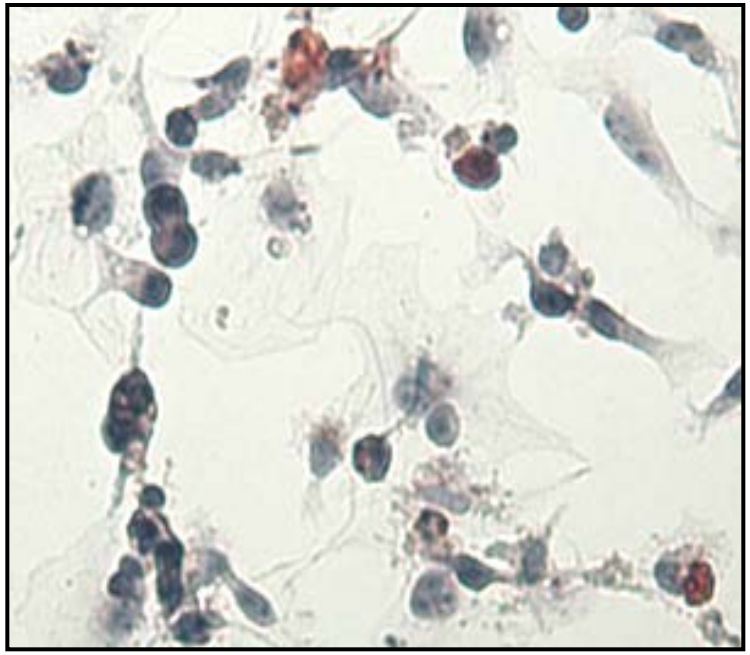
Adipocyte apoptosis initiates macrophage recruitment to adipose tissue



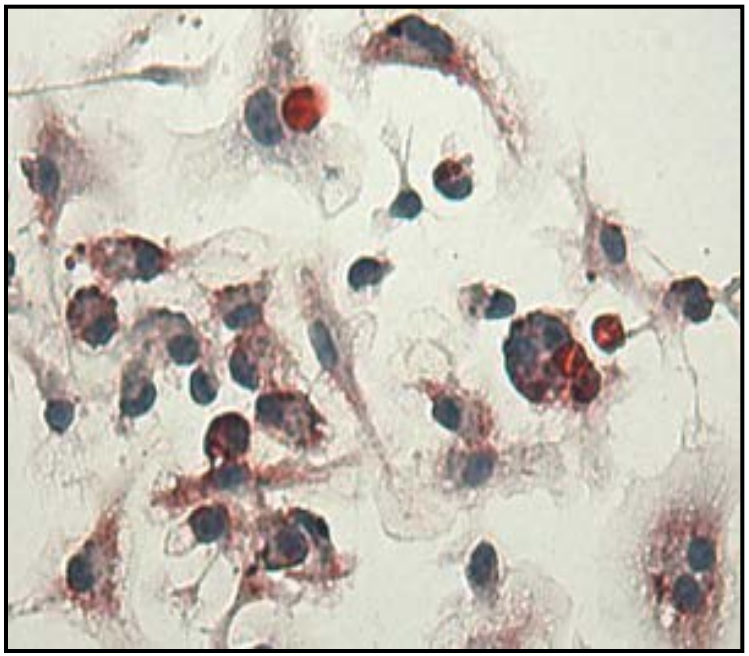
Cinti et al. *J. Lipid Res. 2005*

ATMs accumulate lipids

Low fat

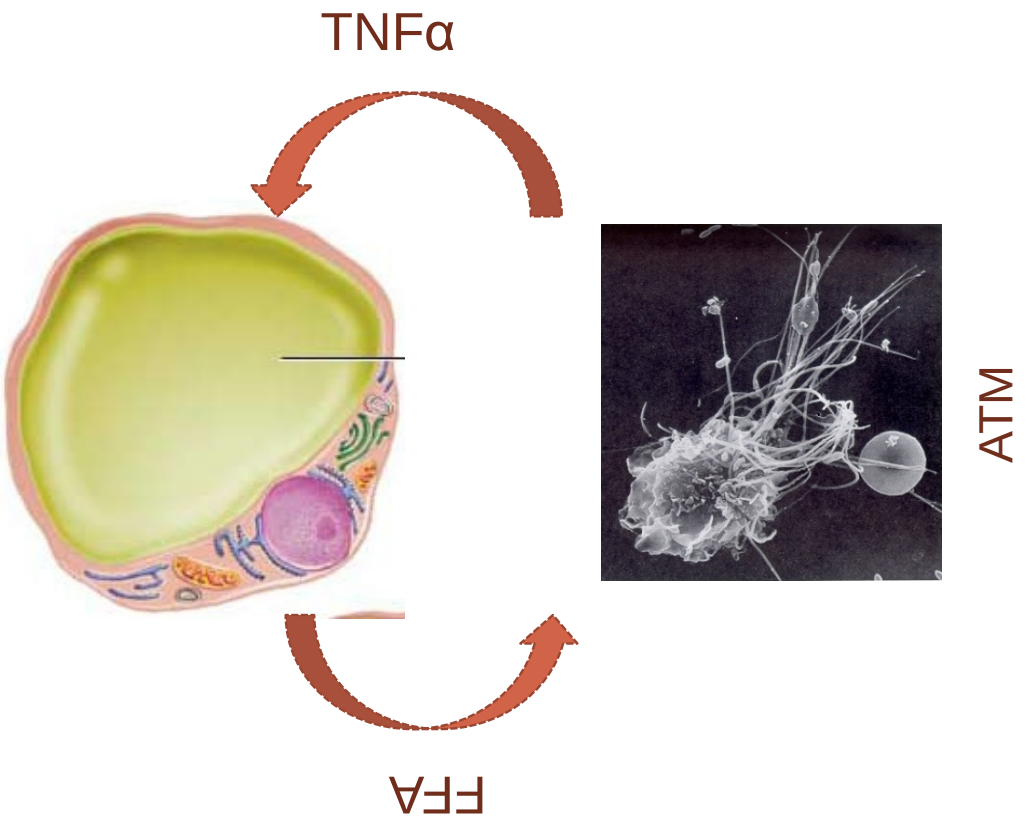


High fat



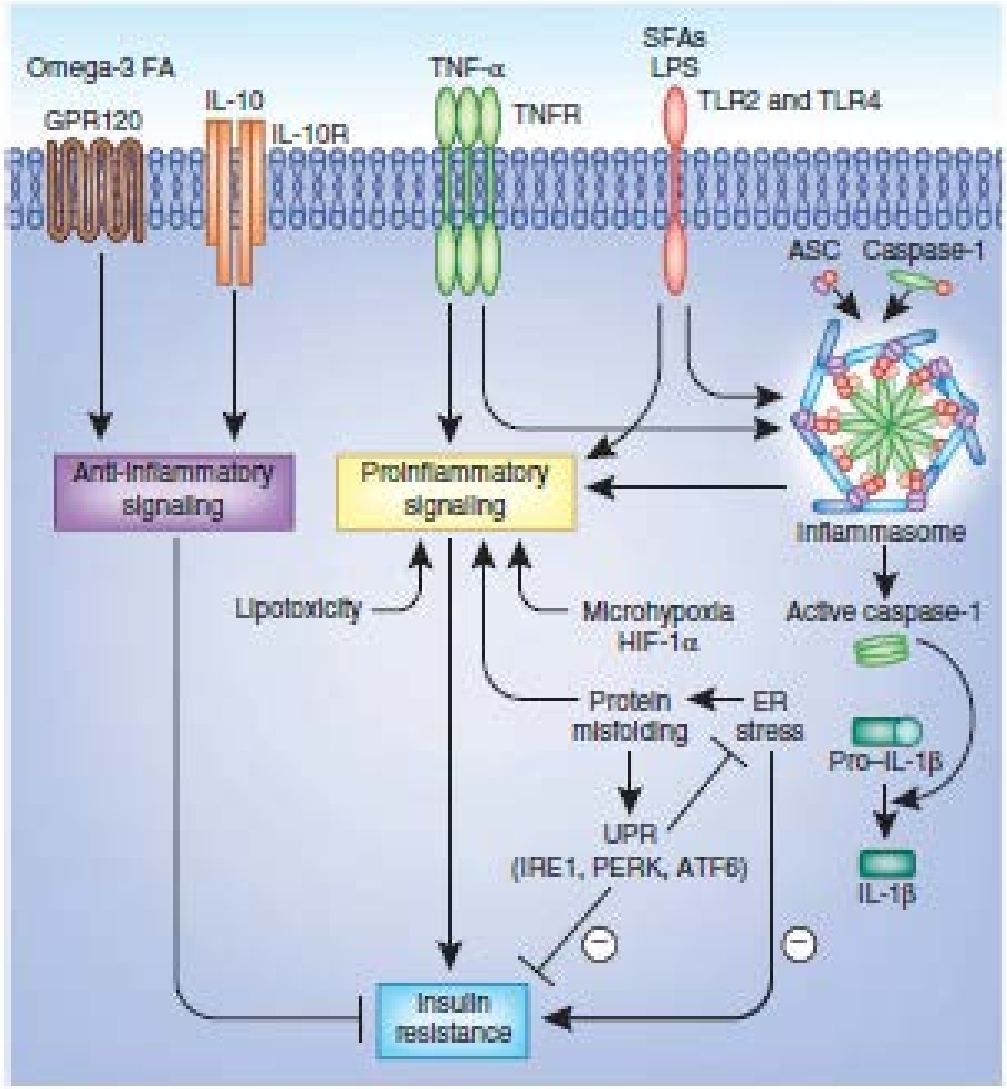
Saraswathi and Hasty, *ATVB* 2009

Adipocyte–ATM Crosstalk



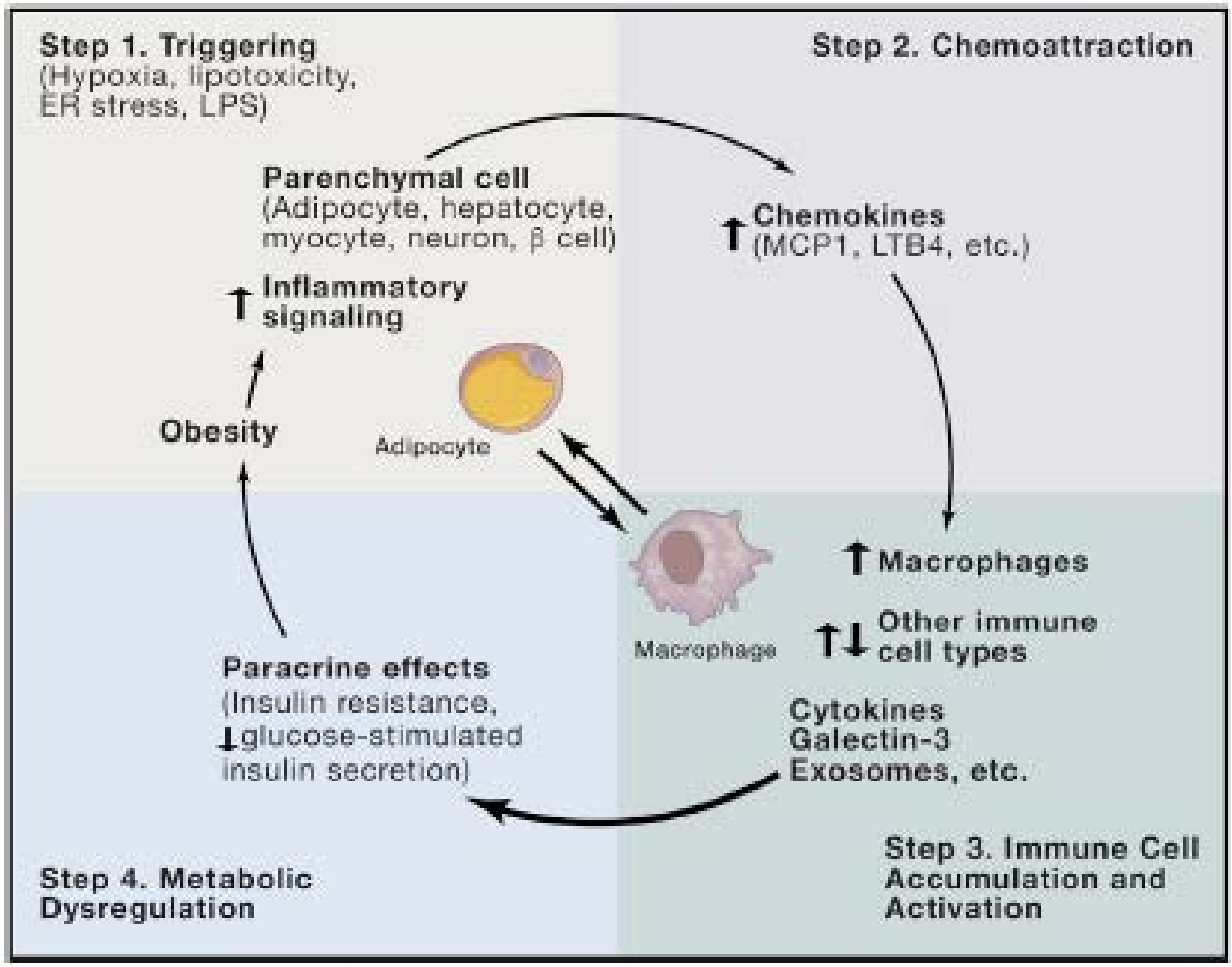
Suganami et al. *ATVB 27:84-91*

Intracellular Inflammatory Pathways



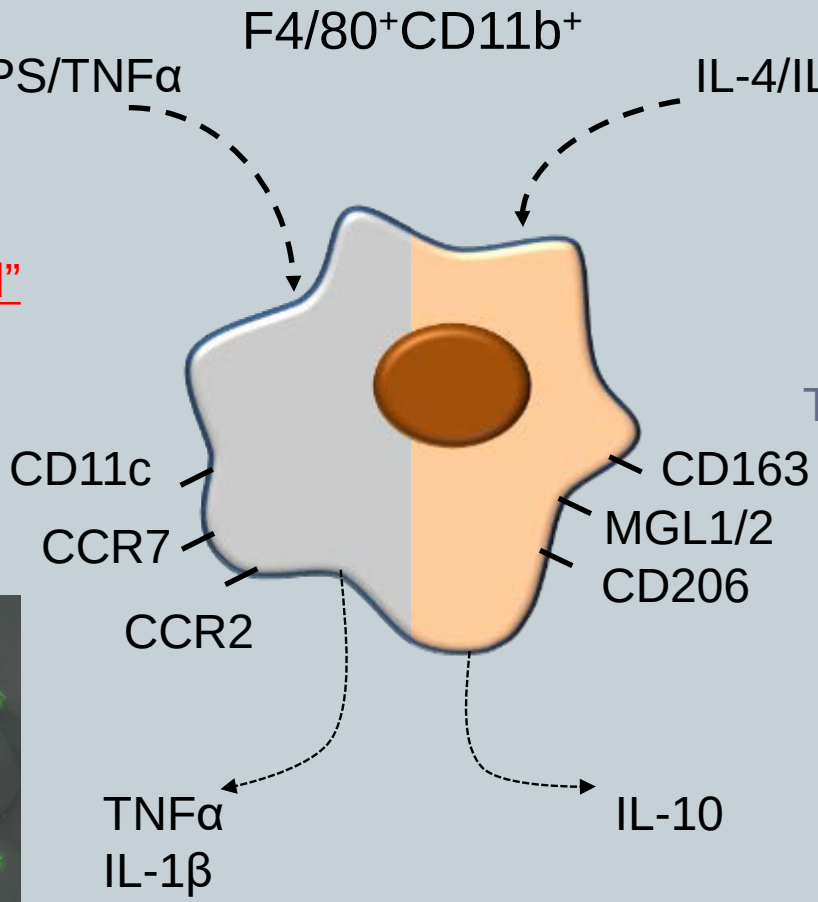
Olefsky. Nature Medicine. 2012

Pathways to Adipose Inflammation and Metabolic Dysregulation



Lee and Olefsky, Cell. 2018

Macrophage polarization

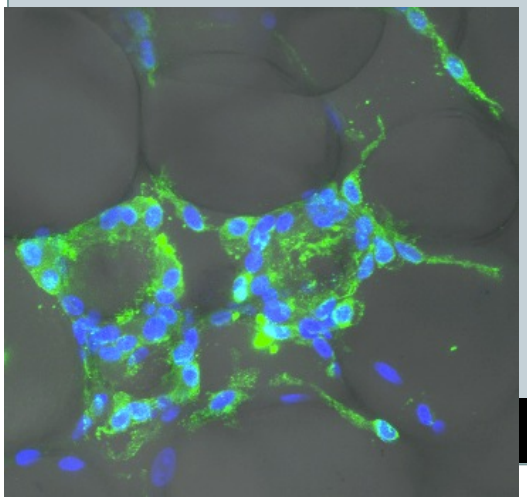


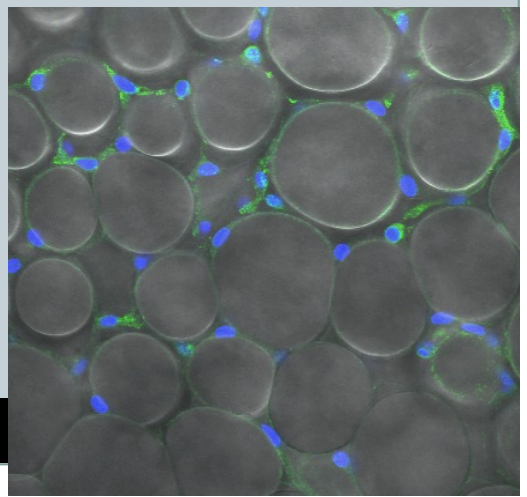
M1-like

"Classically Activated"
Inflammatory
Bactericidal

M2-like

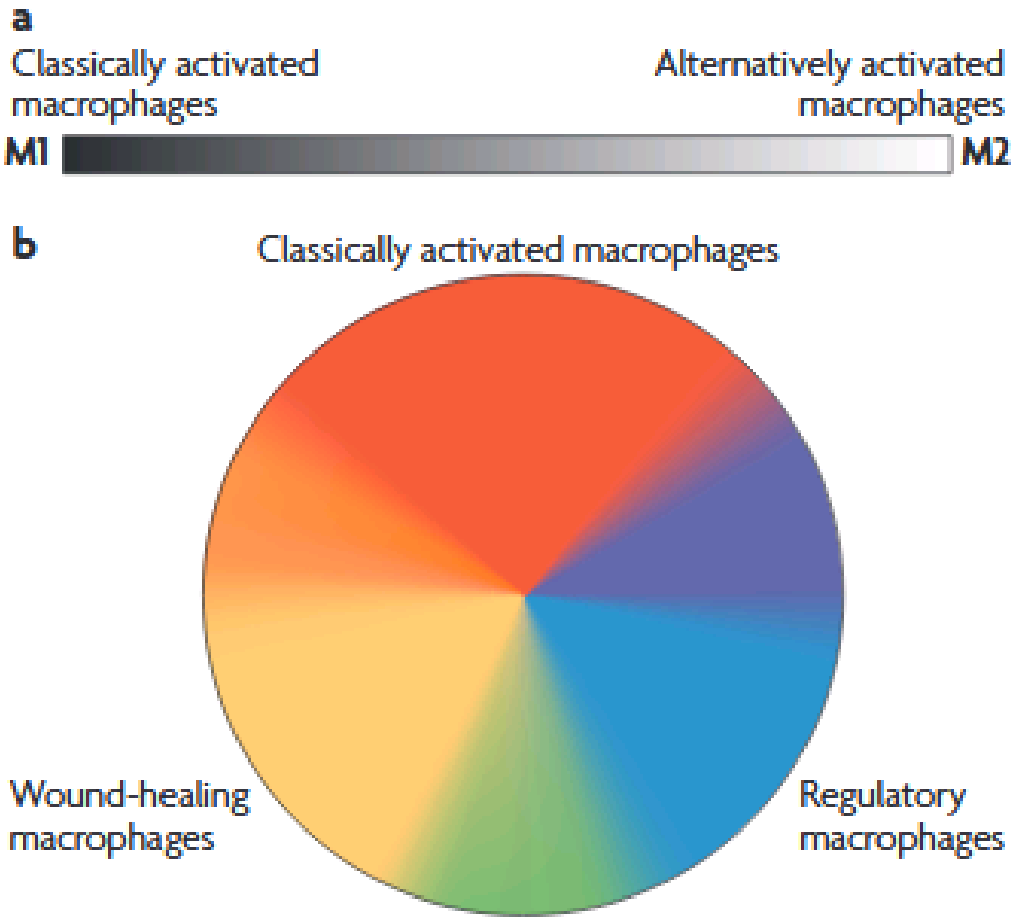
"Alternatively Activated"
Anti-inflammatory
Antiparasitic
Tissue repair/remodeling





Lumeng et al. *J. Clin. Invest. 2007*

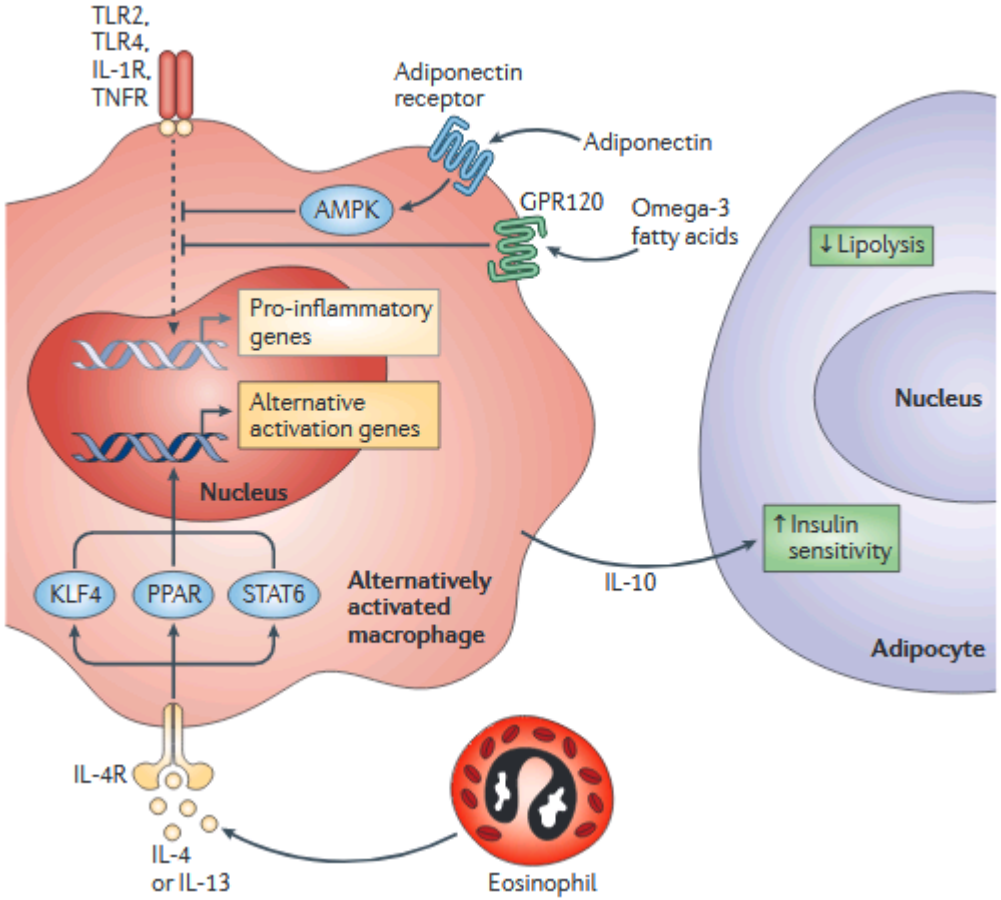
Macrophage are on a Spectrum of Polarization



In obese adipose tissue, macrophages have an “Mme” or “metabolically activated” phenotype

Edwards, Nature Reviews Immunology 2010

Generation and Maintenance of M2-like Alternatively Activated ATMs

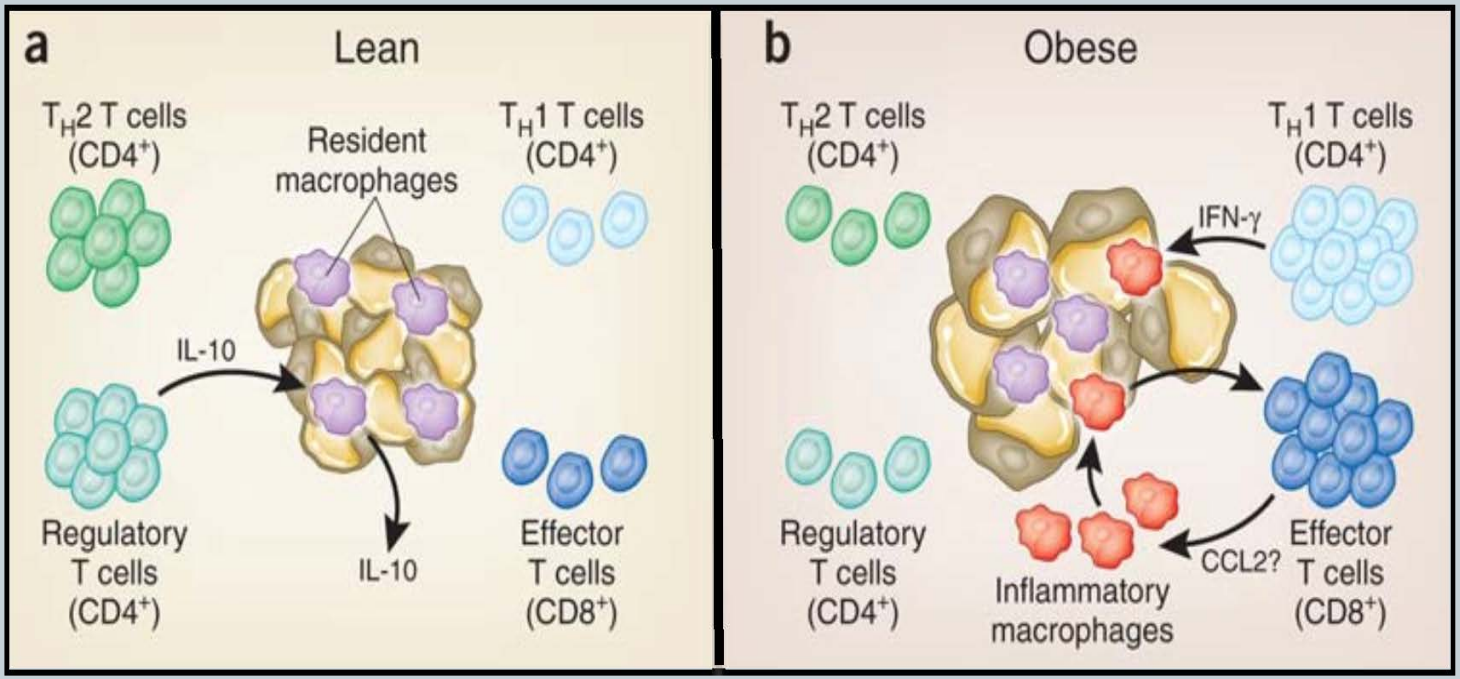


Chawla, Nature Reviews Immunology 2011

Roles of M2-like, Alternatively Activated Macrophages in AT Maintenance

- Anti-inflammatory cytokine production
- Iron handling
- Support adipogenesis
- Catecholamine synthesis and/or recycling
- Apoptotic cell clearance
- Angiogenesis
- Lipid trafficking
- Secretion of extracellular vesicles

Adaptive Immune System Involvement in Obesity



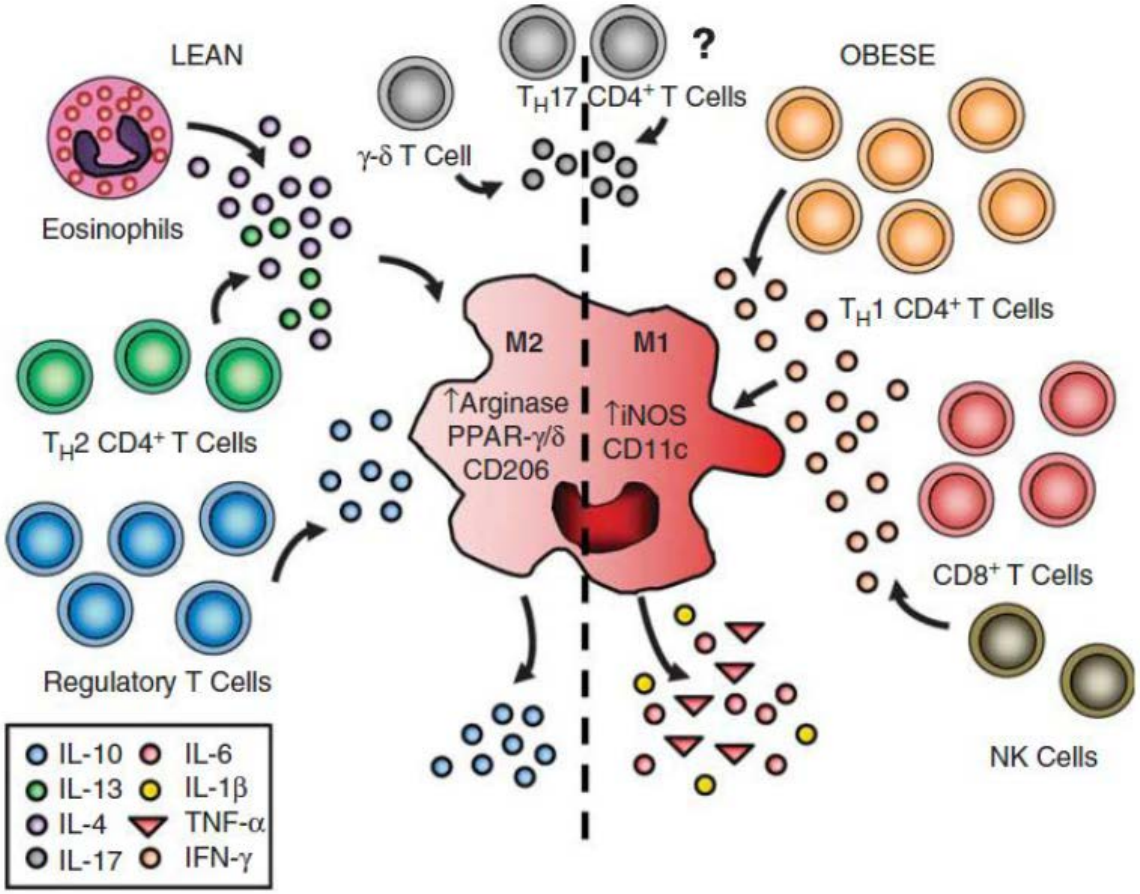
Nishimura, *et al*. (2009). Nat Med., Winer, *et al.* (2009). Nat Med.

Lumeng, *et al* (2009). Nat. Med.

Summary as of 2012

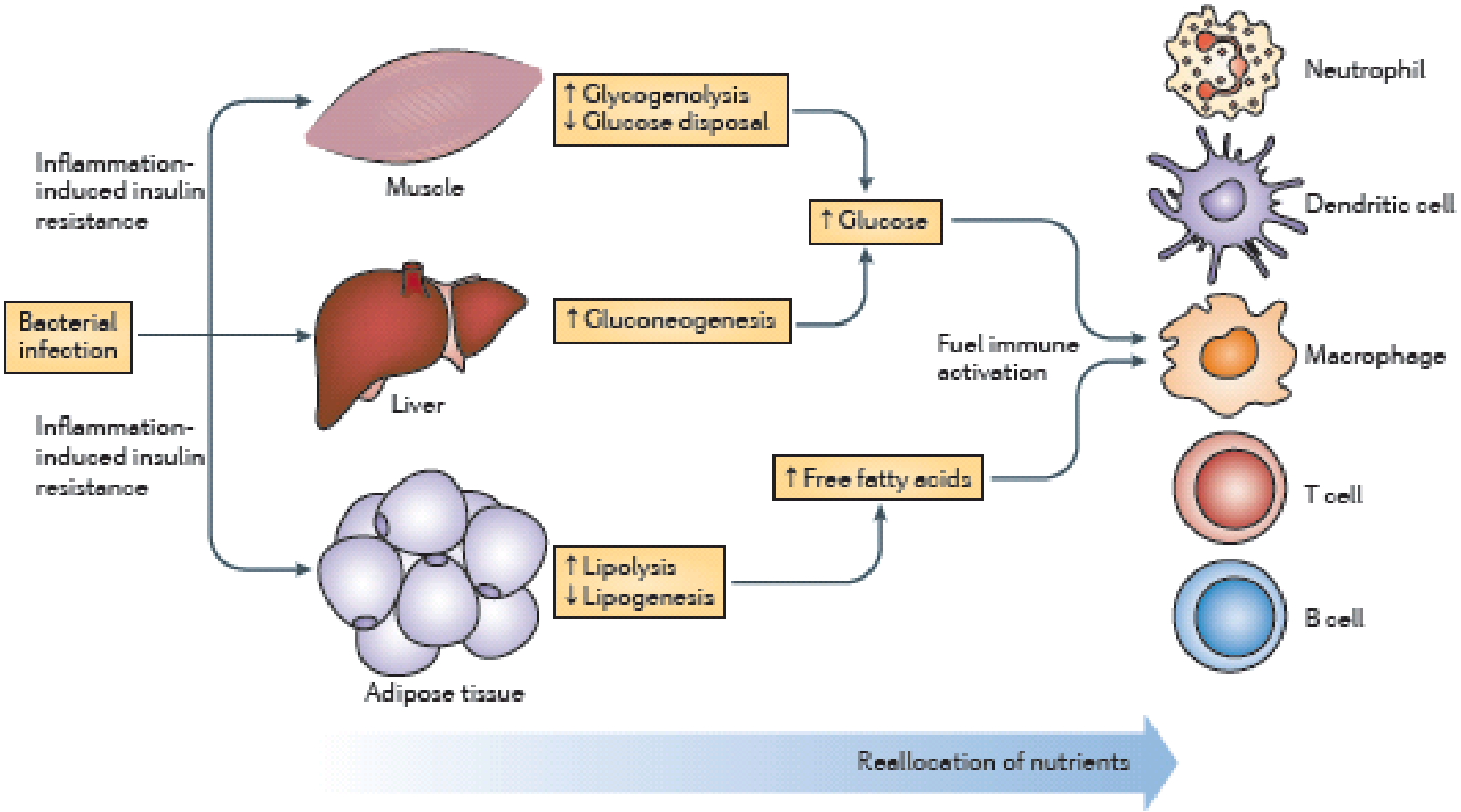
Lean

Obese



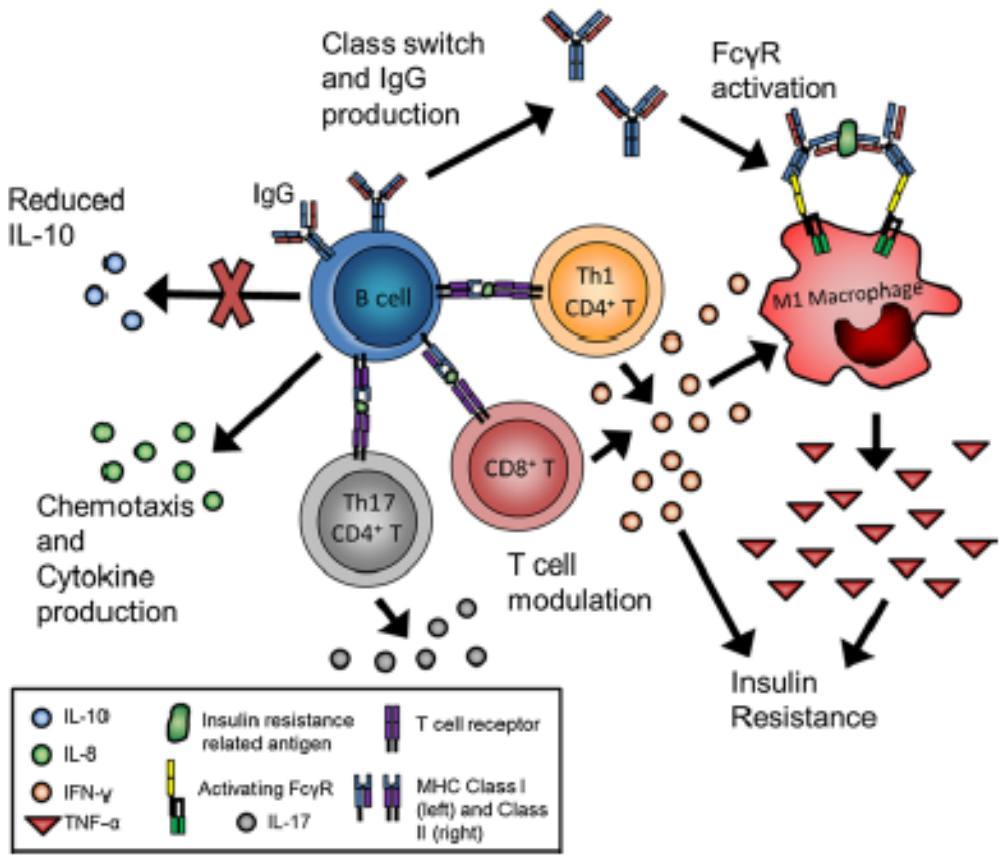
Winer and Winer, *Immunology and Cell Biology*, 2012

Integrated View as of 2011



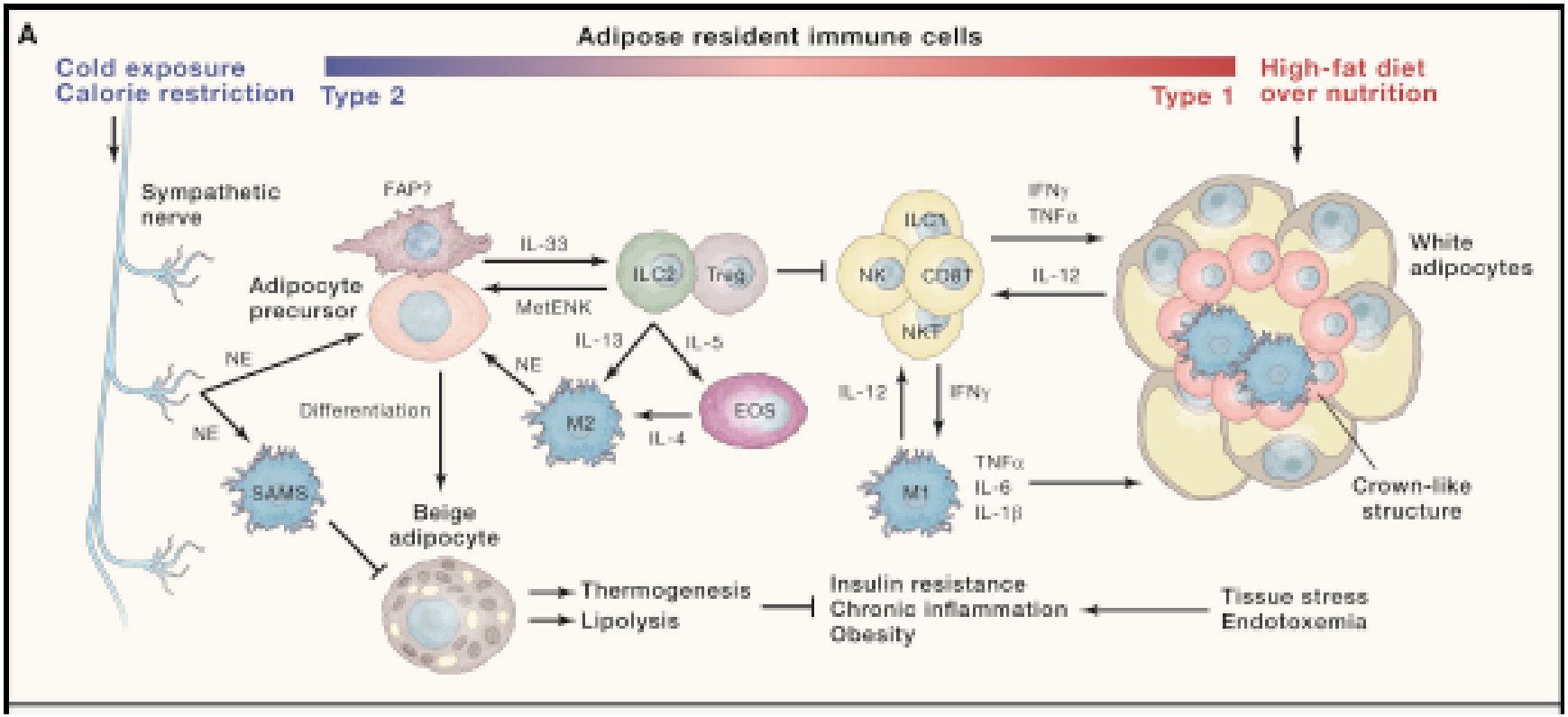
Chawla, Nature Reviews Immunology 2011

B Cells in Adipose Tissue



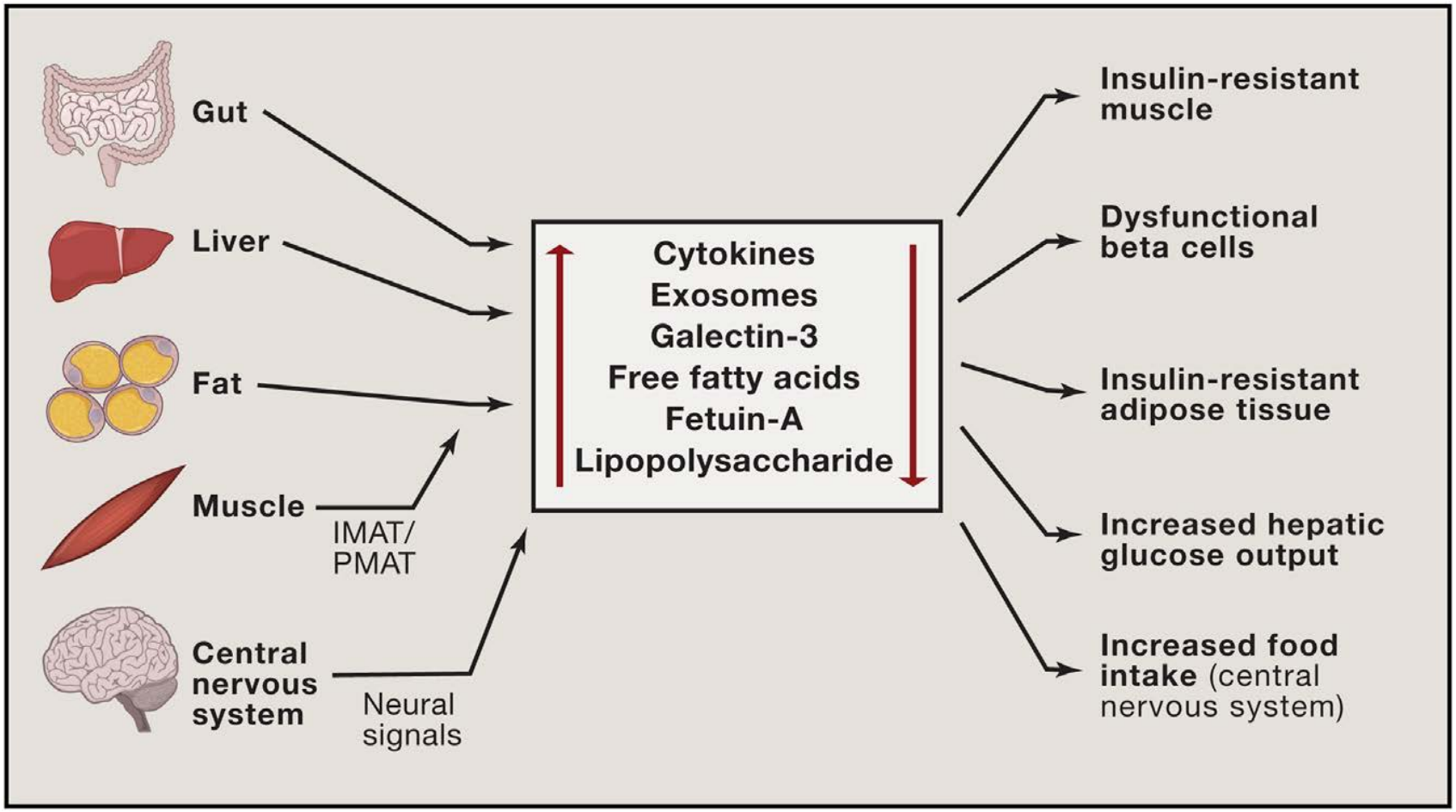
Winer and Engleman, Cell Mol. Life Sci.. 2014

Summary as of 2018



Artis. Cell. 2018

Integrated View as of 2018



Lee and Olefsky, Cell. 2018

Recent Advances to Consider

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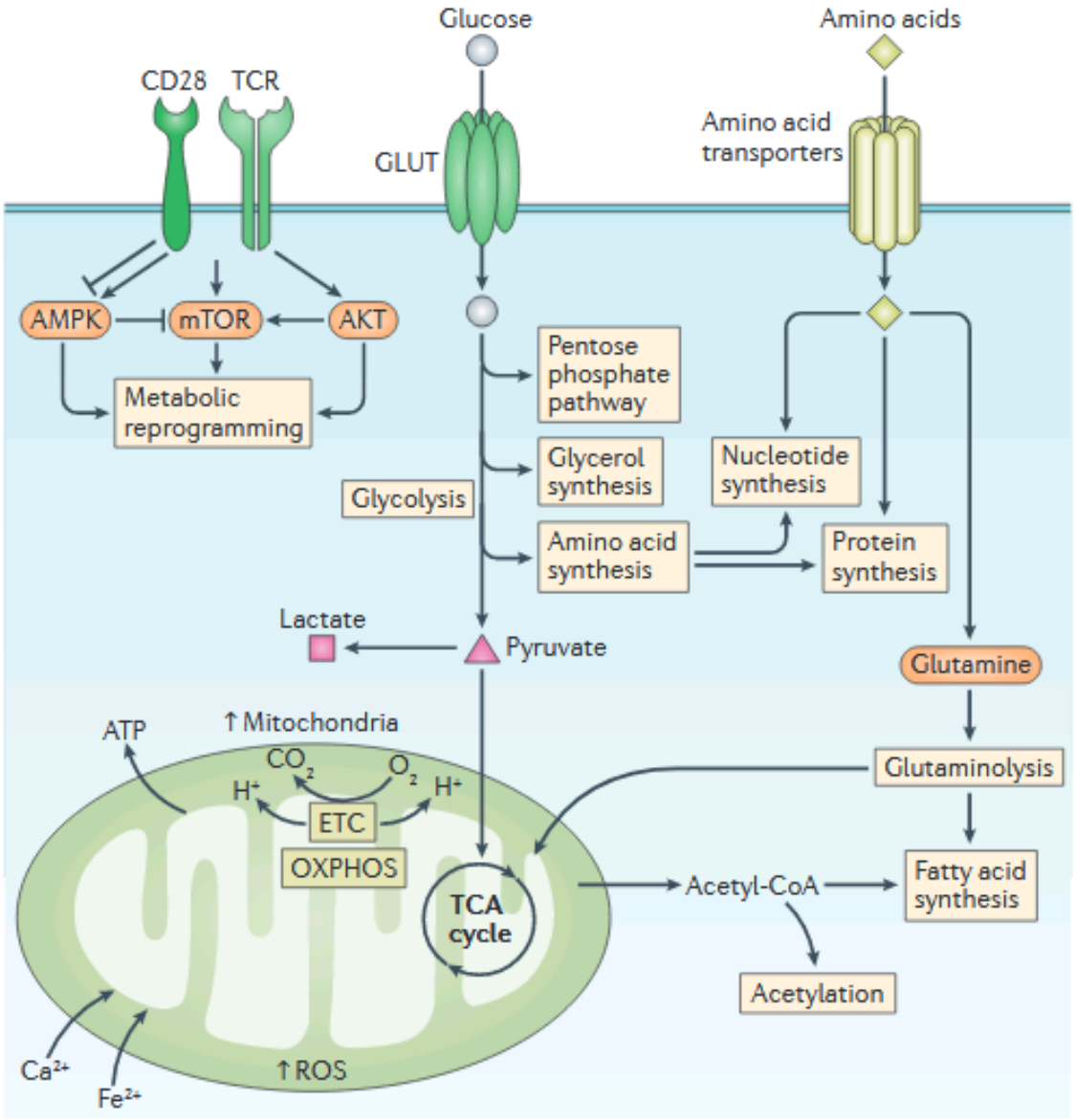
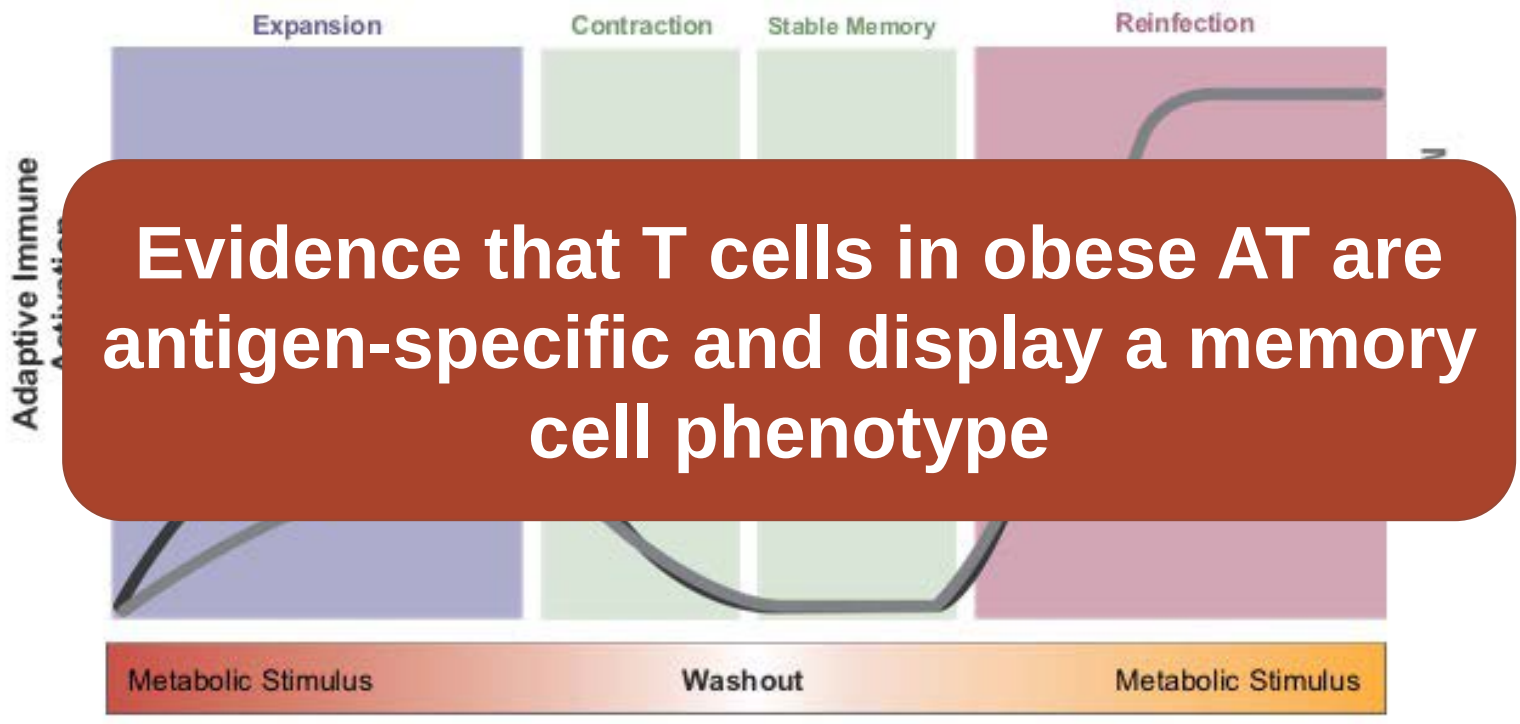
Intracellular Metabolism and Fuel Utilization



Hess, Nature Reviews Immunology 2018

Adaptive Immunity → Secondary Immune Response



Evidence that T cells in obese AT are antigen-specific and display a memory cell phenotype

Trained Innate Immunity

- Discovered in field of virology and bacteriology
- Innate immune cells, such as macrophages, have long-term memory to priming by certain stimuli
- These cells then have exaggerated responses to future stimuli
- The second stimulus doesn’t have to be the same as the first stimulus
- The reprogramming is completed via persistent epigenetic changes

Adipocyte and ATM exosome release

Immune Cells in BAT

- Very few macrophages or eosinophils
- Some T cells
- 20-30% B cells
- B cells and eosinophils increase with obesity, while macrophages decrease

Peterson and Hasty, Obesity. 2017

Remaining Questions

- How does HIV-infected adipose tissue immunometabolism change upon aging?
- Does HIV infection alter the intracellular metabolism of individual immune cells?
- Does HIV infection impact gut immune responses?
- How does the viral load impact adipocyte-immune cell cross-talk?
- Is adaptive innate immunity involved in obesity and/or HIV related AT immune cell dysfunction?
- Does cycling in and out of increased viral load impact secondary immune responses and metabolic processes?
- Is AT exosome release different in HIV-infected individuals?
- Obese adipose tissue vs. lipodystrophic adipose tissue