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Medical Research. Practical Action.

Overview of the underlying biology of immune activation linking it to obesity

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OVERVIEW

Metabolic reprogramming during immune cell activation & inflammatory responses (canonical pathways)

Consequences of CD4 T cell and monocyte metabolic reprogramming in HIV infection

Immunometabolism: Bidirectional relationship adipocyte–immune cell interaction

Immunometabolism: Auxiliary pathways in immune cell activation

Sources of immune activation and metabolic disorders in ART-treated PLWH

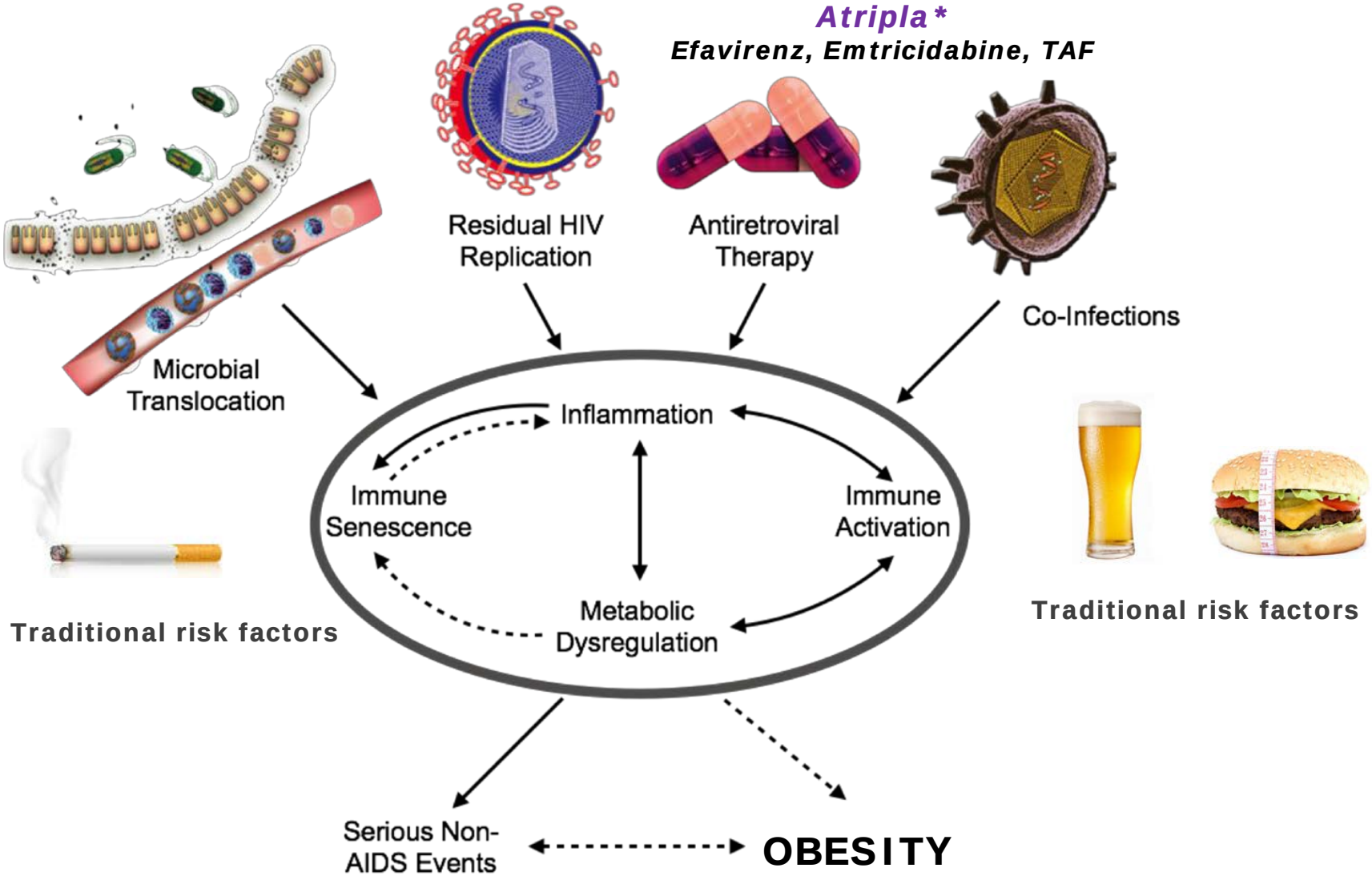
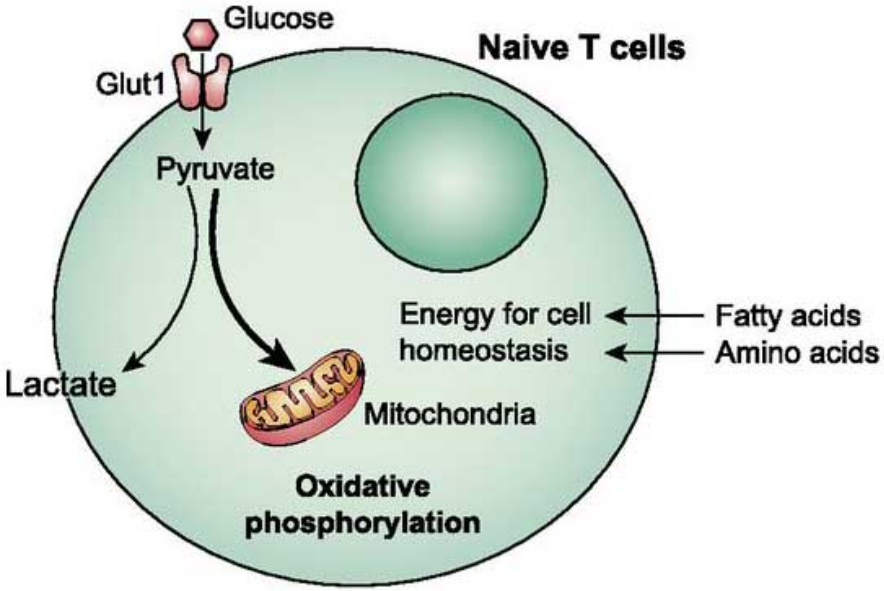
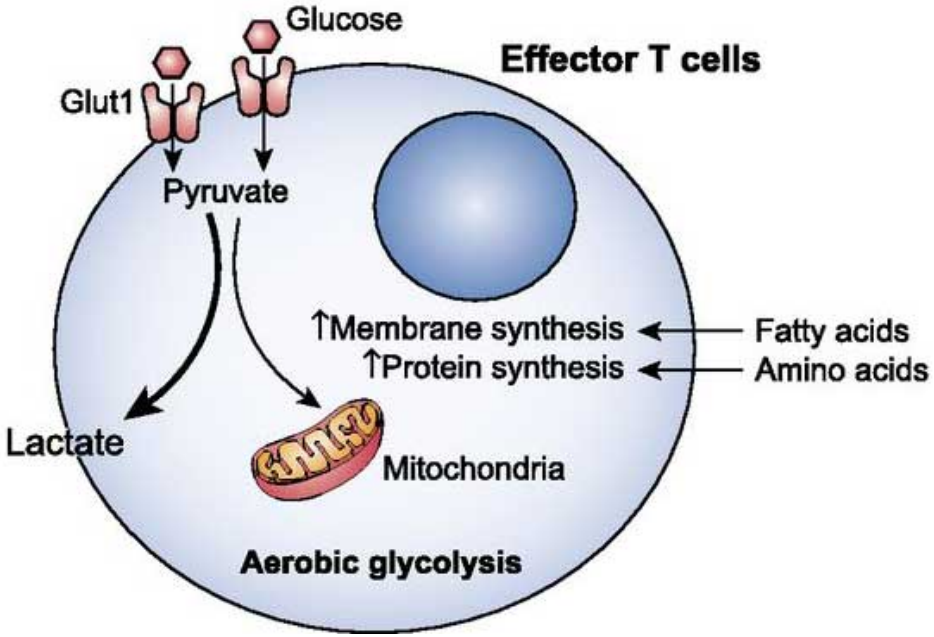


Image credit: Palmer HIV Immunometabolism Laboratory

Activated T cells reprogram glucose metabolism from oxidative phosphorylation to glycolysis





Michalek et al., Immunol Rev, 2010
Pearce et al., 2013, Science

Palmer et al., Journal of Immunology 2016
Palmer et al Ebiomedicine, 2016

Activated T cells reprogram glucose metabolism from oxidative phosphorylation to glycolysis

Naive T cells

Metabolically Quiescent

- Low Glut1
- Low PI3K-mTOR signaling
- Basal nutrient uptake
- Basal glycolytic rate
- Minimal biosynthesis
- No net growth

Effector T cells

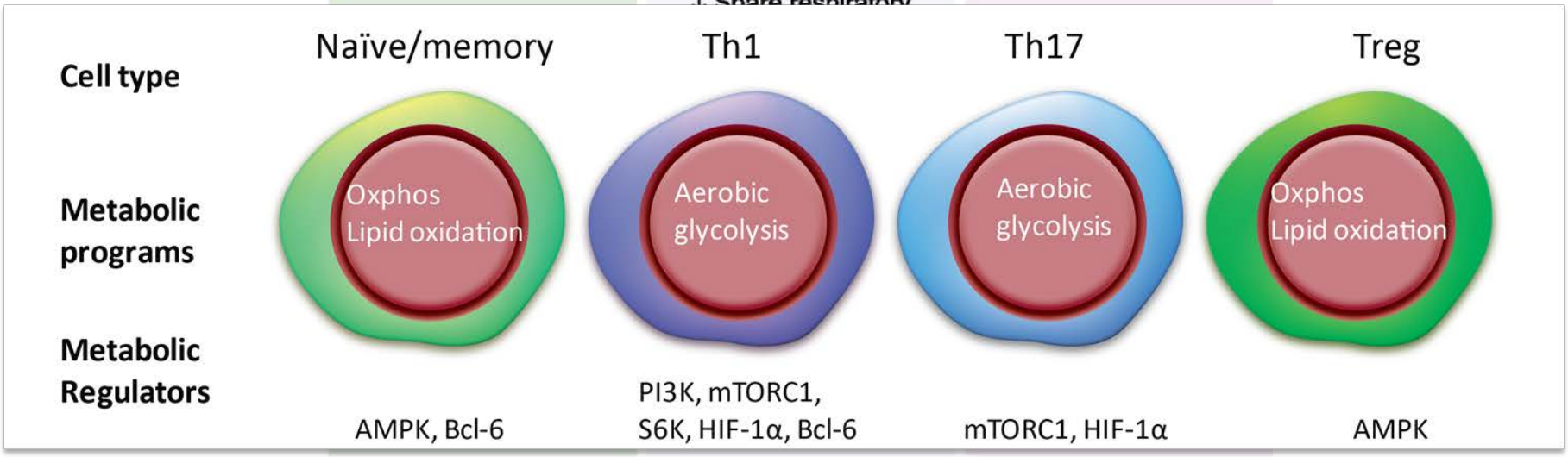
Metabolically Activated

- High Glut1
- High PI3K-mTOR signaling
- ↑ Nutrient uptake
- ↑ Glycolytic rate
- ↑ Protein, lipid and nucleic acid synthesis

Memory T cells

Metabolically Primed

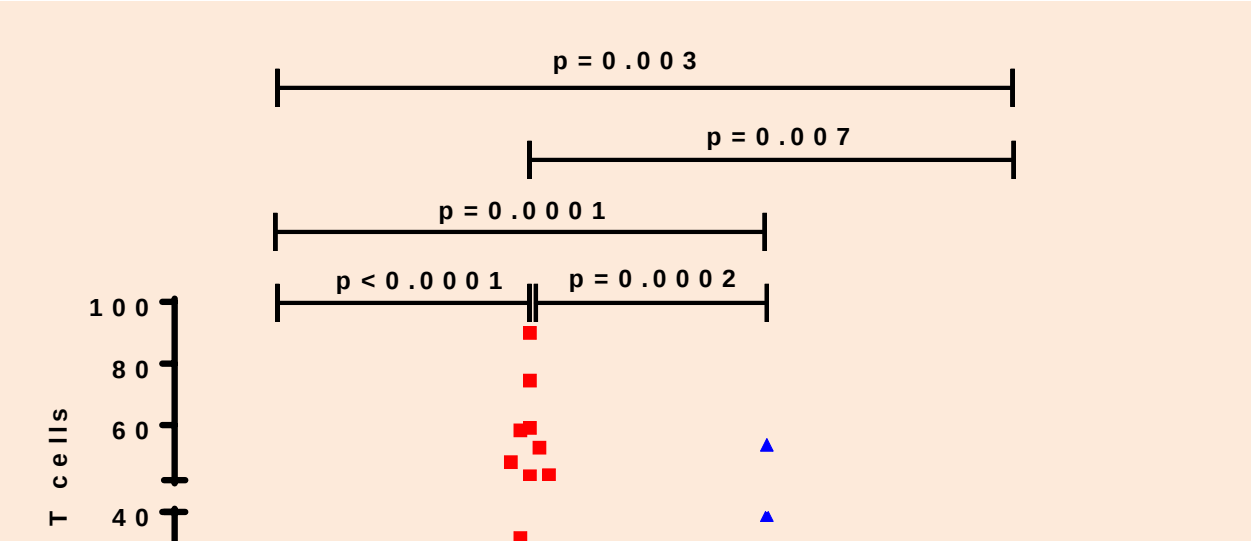
- Medium to high Glut1
- Moderate PI3K-mTOR signaling
- ↑ Mitochondrial mass
- ↑ Spare respiratory capability
- Basal nutrient uptake



MacIver et al. Annu Rev Immunol., 2013

Palmer et al. Front. Immunology 2015
Palmer et al. Journal of Immunology 2016

Glycolytic metabolism remains elevated in CD4+ T cells in virally suppressed patients receiving cART



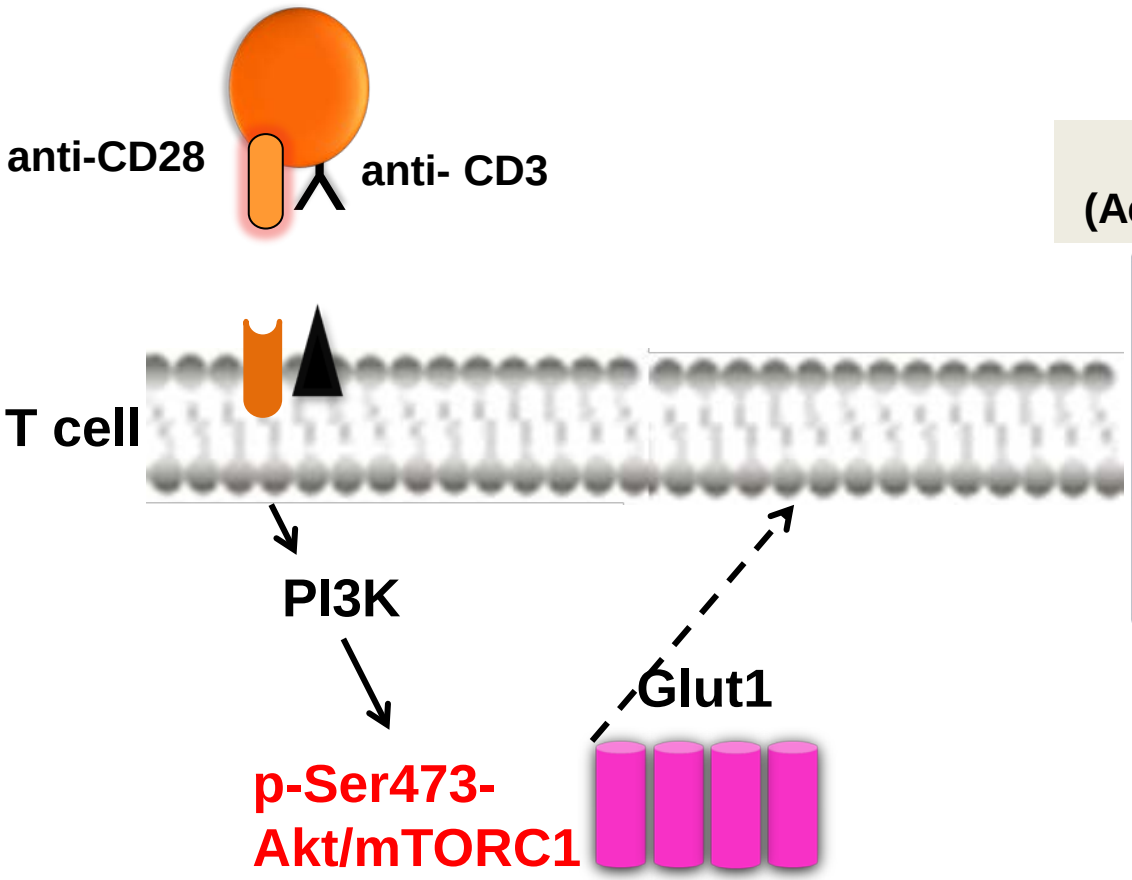
Cell Metab. 2014 July 1; 20(1): 61–72. doi:10.1016/j.cmet.2014.05.004.

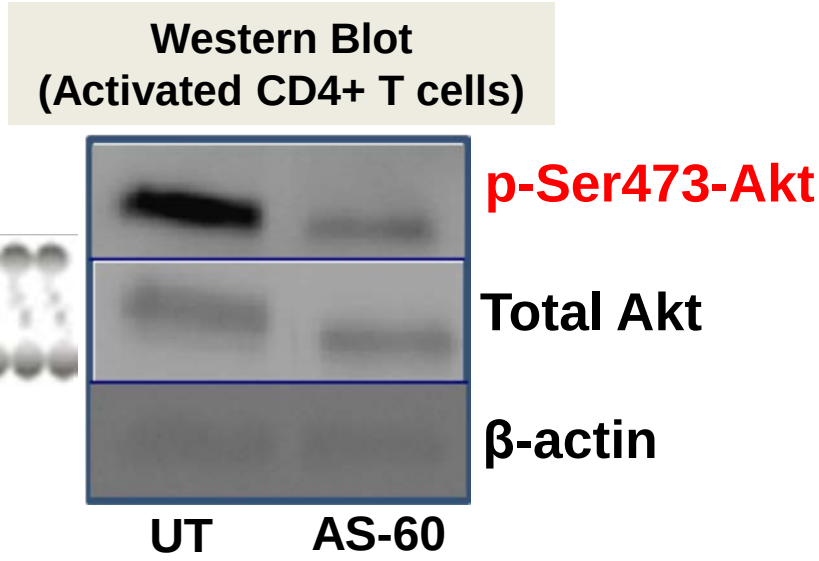
The Glucose Transporter Glut1 is Selectively Essential for CD4 T Cell Activation and Effector Function

Andrew N. Macintyre[#1], Valerie A. Gerriets[#1], Amanda G. Nichols[1], Ryan D. Michalek[1], Michael C. Rudolph[2], Divino Deoliveira[3], Steven M. Anderson[2], E. Dale Abel[4], Benny J. Chen[3], Laura P. Hale[5], and Jeffrey C. Rathmell[1,^]

Palmer et al., AIDS 2014

PI3K and mTOR regulate Glut1 expression on T cells



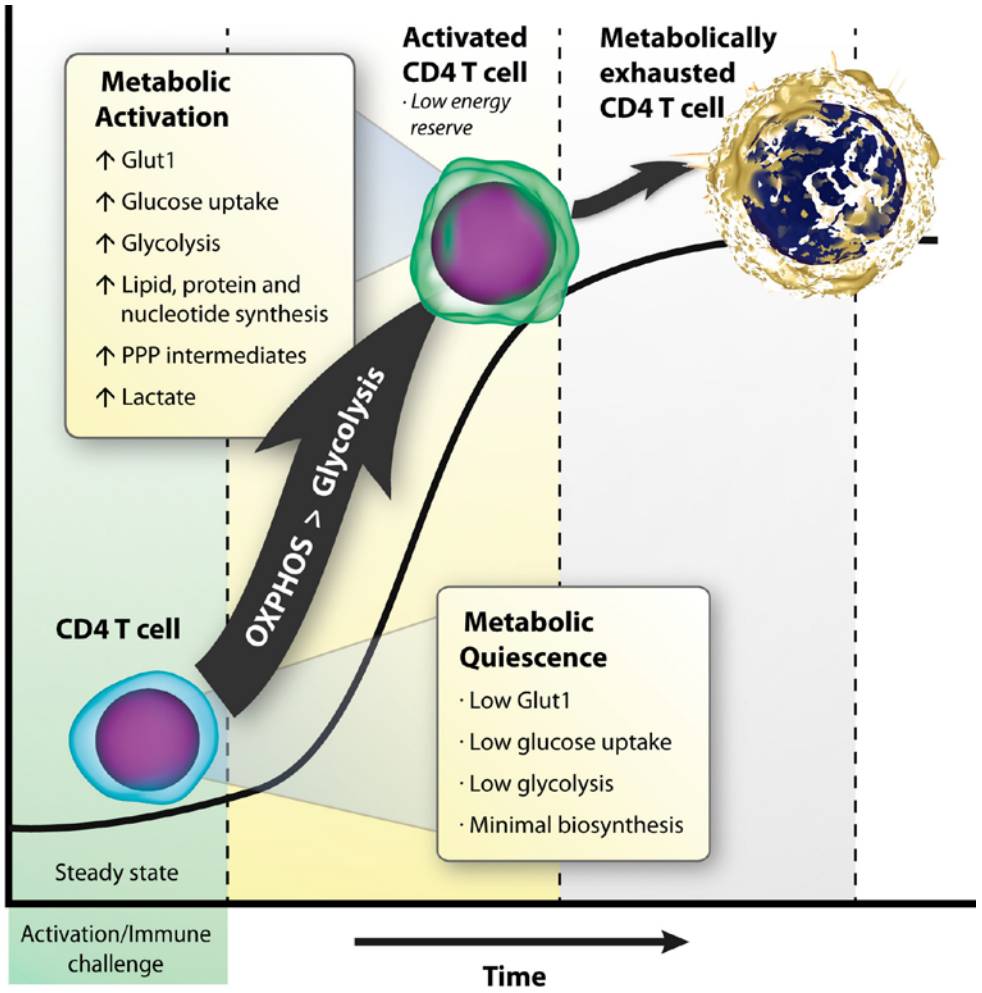


Macintyre et al., Cell Met. 2014
Palmer et al., FEBS Letters, 2017

CD4 metabolic activation in HIV

INCREASED:

- Glucose uptake
- Lactate production
- Hexokinase activity
- PI3K-mTOR activity
- HIV infectivity
- PD1 levels
- Exhaustion markers

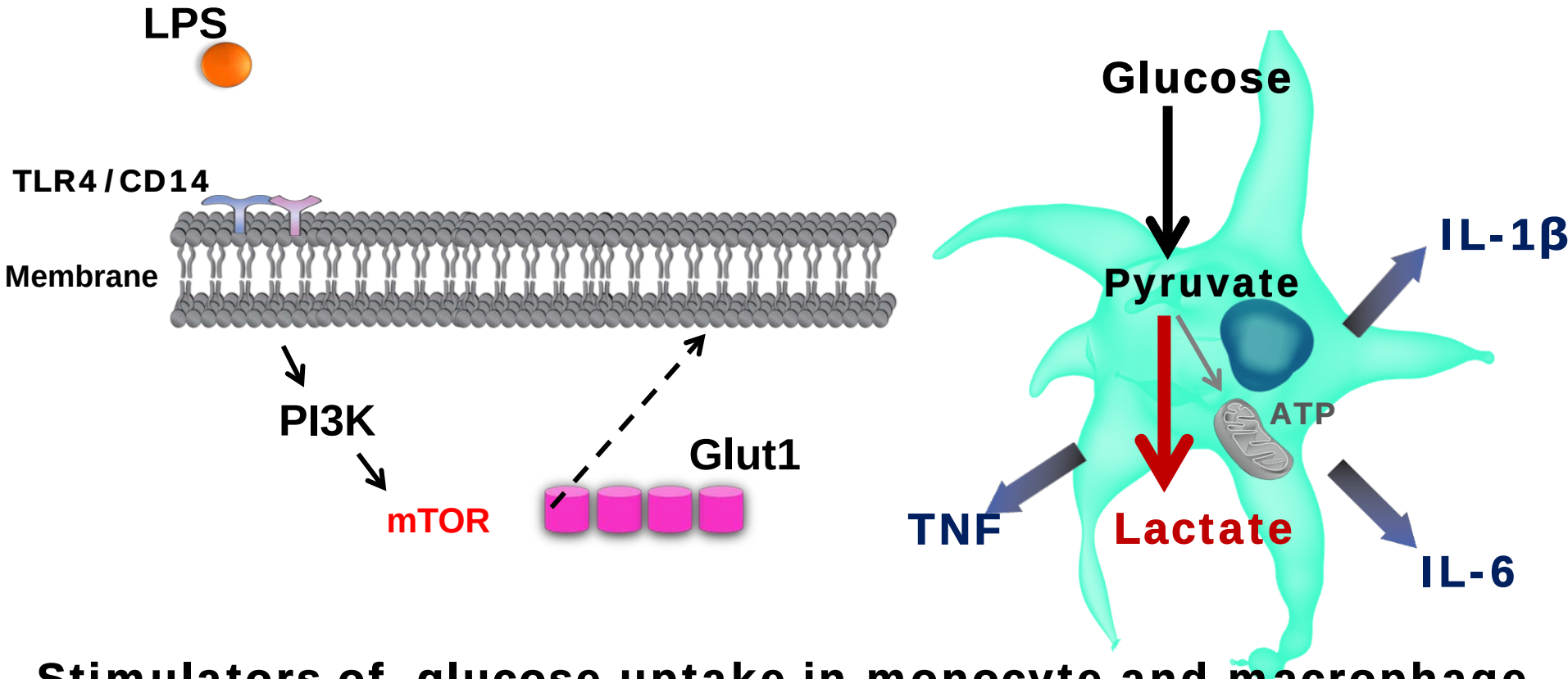


Palmer et al, AIDS 2014
Palmer et al, EBiomedicine 2016

Hegedus et al, Retrovirol. 2014
McKinney et al, Nat Immunol 2018

Palmer et al, FEBS Letters, 2017
Masson et al, Front. Immunol. 2018

PI3K/mTOR regulate glycolysis in activated monocytes and inflammatory (M1) macrophages



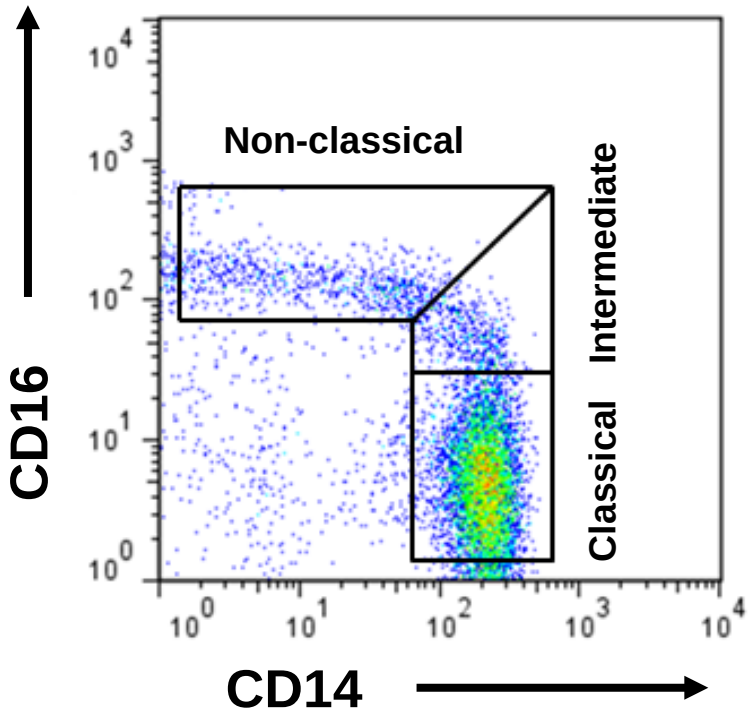
Stimulators of glucose uptake in monocyte and macrophage

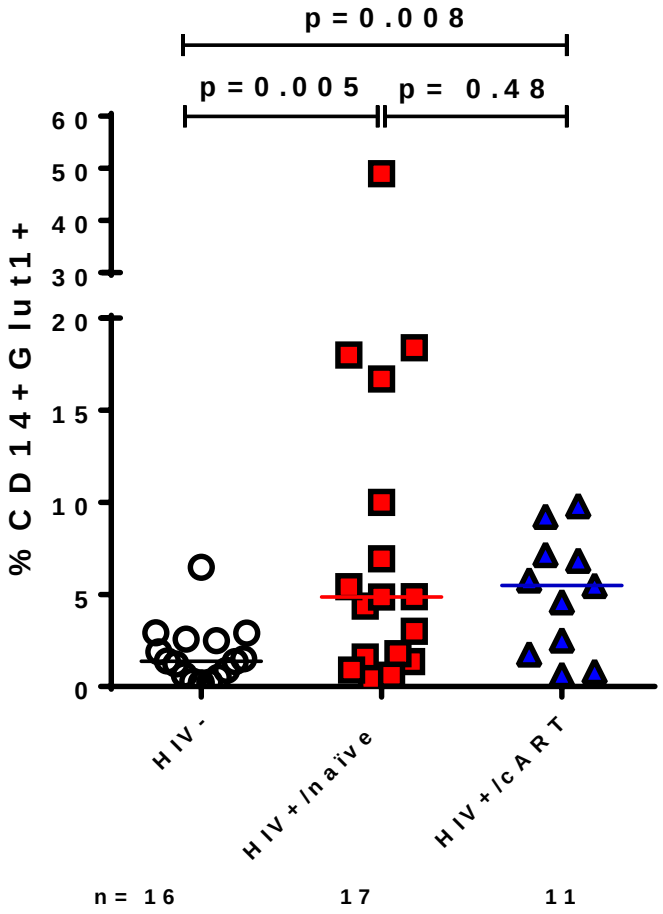
- LPS
- Pro-inflammatory cytokines/adipokines
- oxLDL

Lee et al., J Nucl Med, 2014

Palmer et al., EBiomedicine, 2016

Frailty in Aging PLWH (Melbourne Silver Aging Cross Sectional Study)

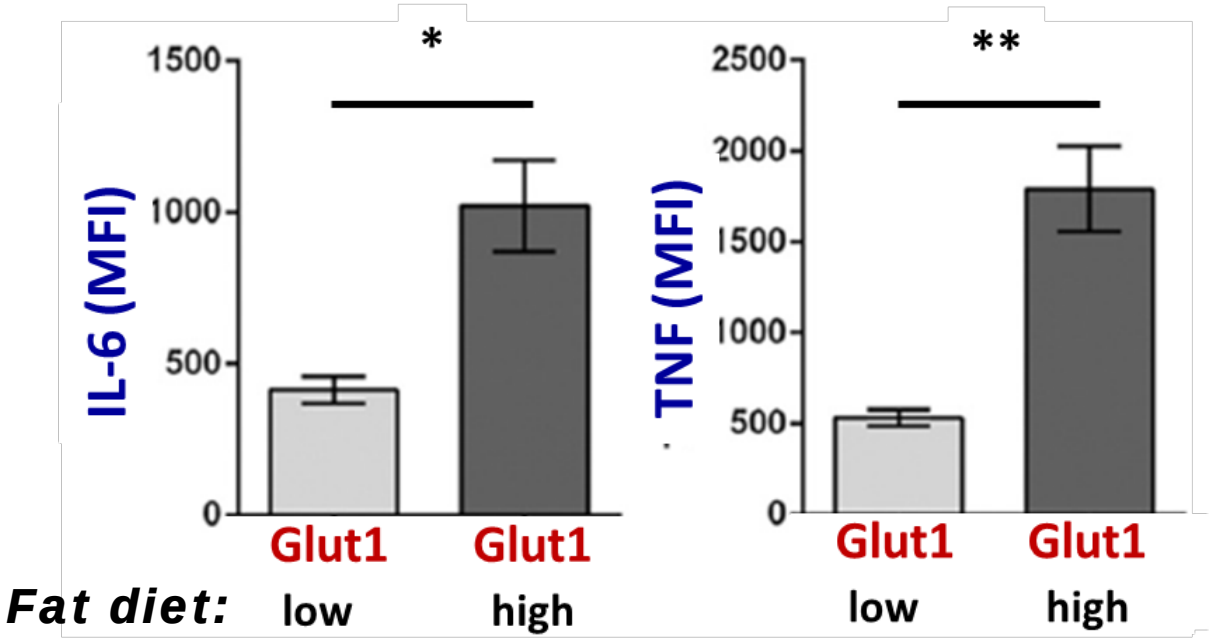




Palmer et al., Journal of Immunology, 2014

GLUT1-dependent glycolysis increases inflammatory cytokine production

Adipose tissue-derived macrophages



Freemerman et al., J Biol Chem, 2014

AIDS 2017

Increased glucose transporter-1 expression on intermediate monocytes from HIV-infected women with subclinical cardiovascular disease

Butterfield, Tiffany R.; Hanna, David B.; Kaplan, Robert C.; Kizer, Jorge R.; Durkin, Helen G.; Young, Mary A.; Nowicki, Marek J.; Tien, Phyllis C.; Golub, Elizabeth T.; Floris-Moore, Michelle A.; Titanji, Kehmia; Fischl, Margaret A.; Heath, Sonya L.; Martinson, Jefferey; Crowe, Suzanne M.; Palmer, Clovis S.; Landay, Alan L.; Anzinger, Joshua J.

Women's Interagency HIV Study

Participants with more than 75th percentile and less than 25th percentile

Age-adjusted intima-media thickness (IMT) at the right common carotid artery and bifurcation

Unique metabolic activation of adipose tissue macrophages in obesity promotes inflammatory responses

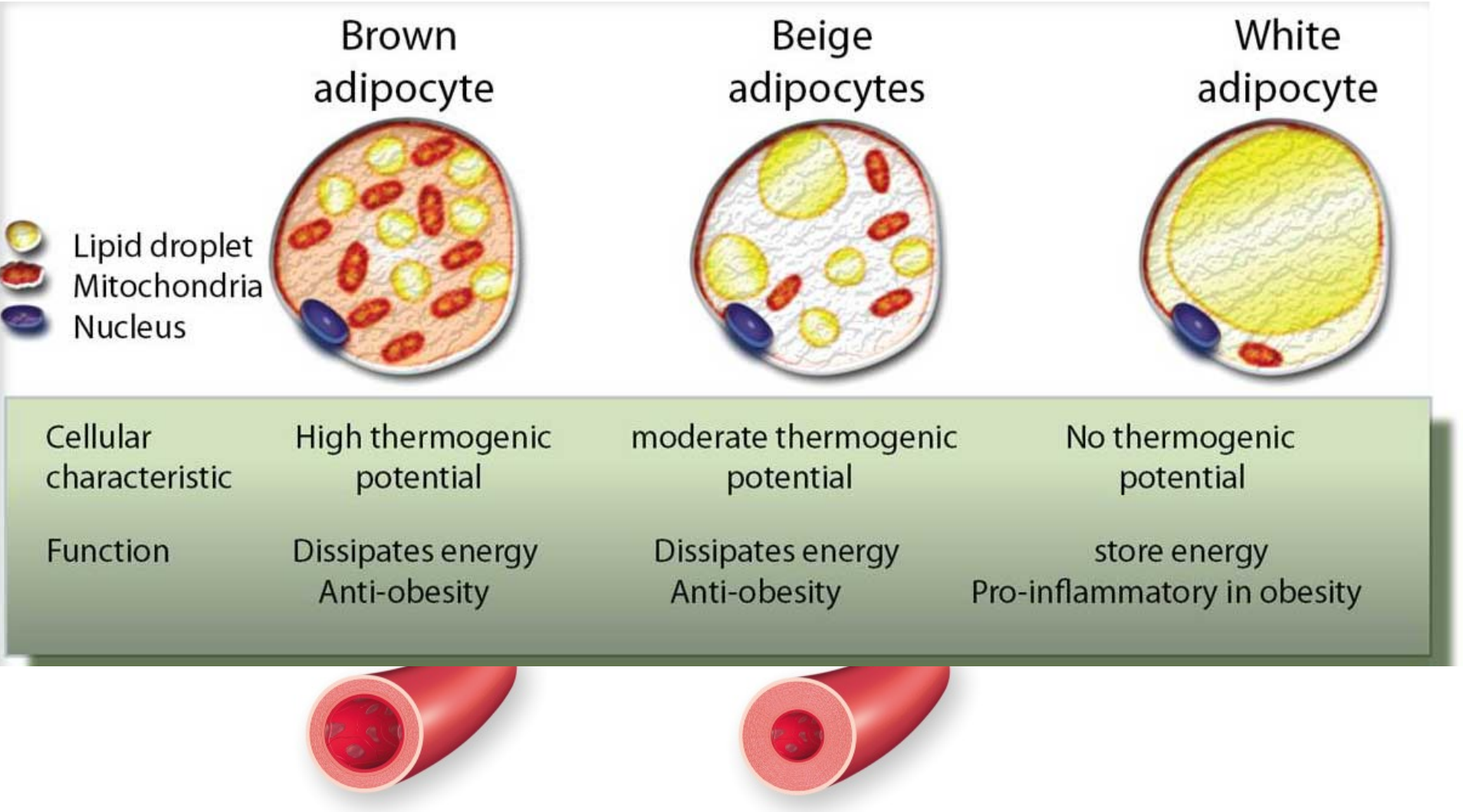
Diabetologia, 2018

Lily Boutens · Guido J. Hooiveld · Sourabh Dhingra Robert A. Cramer · Mihai G. Netea · Rinke Stienstra

KEY POINTS

- Mouse adipose tissue macrophages (ATM) have **BOTH** increased glycolysis and oxphos (Extracellular flux measurement)
- Metabolic routes for cytokine release from ATM in *lean adipose* tissue: **glycolysis, FAO and glutaminolysis**
- Pro-inflammatory ATM traits in obese adipose tissue: **glycolysis**
- **HIF-1α**, a key regulator of glycolysis played no role in pro-inflammatory activation of ATMs

Dysfunctional AT promotes development of metabolic and vascular disease



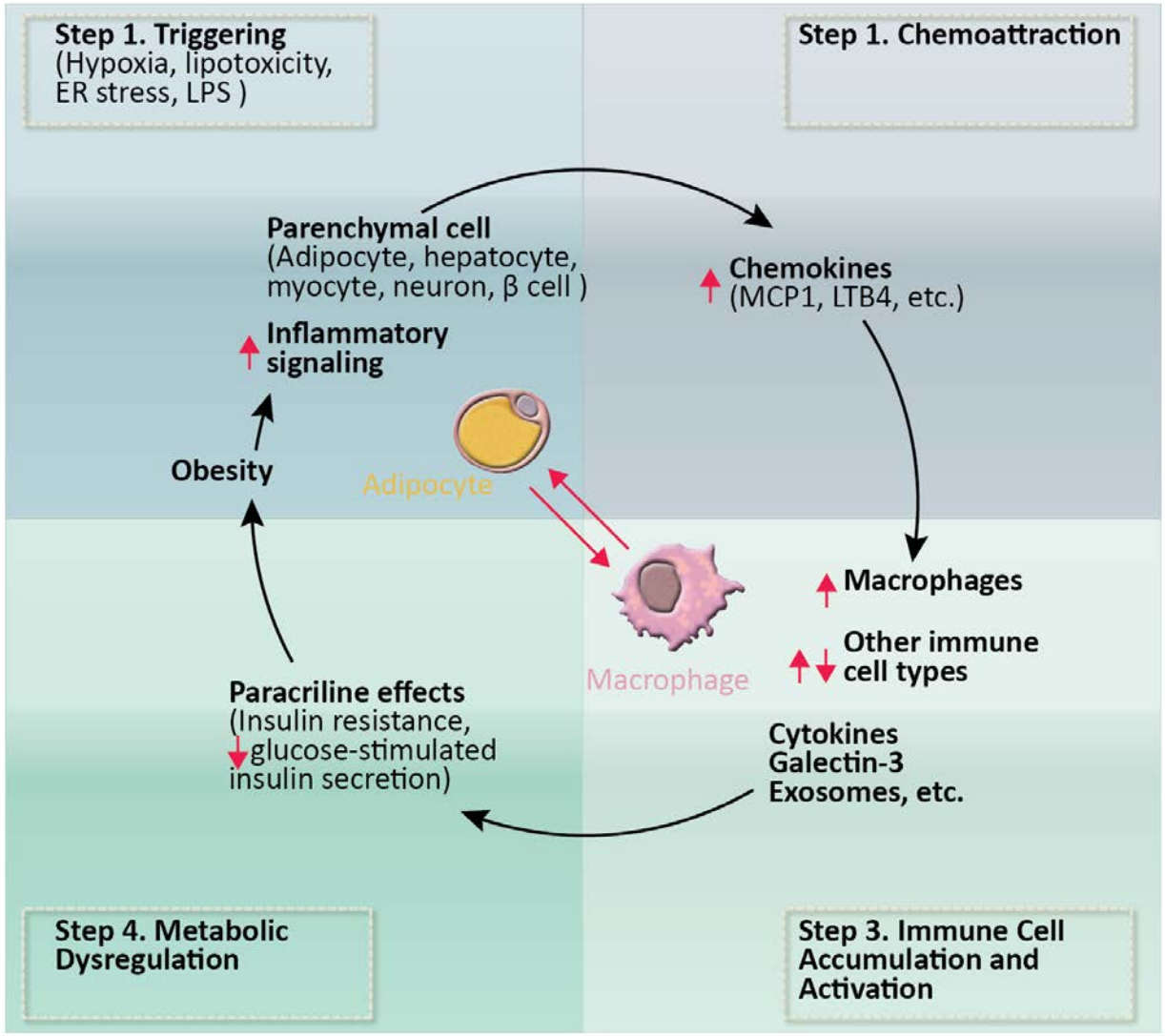
Mod: Guzik et al., Cardiovascular research, 20117

Leptin Promotes Glycolytic Metabolism in Activated T Cells

One well-established connection between systemic nutritional status and immune cell metabolism is through leptin. As mentioned above, leptin is secreted by adipocytes in proportion to adipocyte mass and leptin levels, thereby trending with nutritional status (106). In states of malnutrition or following fasting, circulating leptin levels are decreased, whereas in obesity, leptin levels are increased. Leptin acts directly on CD4+ T cells through the LepR to direct changes in T cell metabolism and function (26, 27, 107–110). Since T cell metabolism and function are intimately linked, any change in immune cell metabolism can lead to a change in the function of that cell, altering cellular proliferation, differentiation, and cytokine production. Leptin has been shown to promote both CD4+ T cell inflammatory cytokine production and glucose metabolism. Indeed, T cells unable to respond to leptin had impaired upregulation of glucose uptake and glycolysis following T cell activation (26). In the context of malnutrition, fasting-induced hypoleptinemia caused activated CD4+ T cells to produce less inflammatory cytokines IFN-γ and IL-2 (26, 27). That functional defect did not extend to naïve T cells or Treg cells, however, presumably because those cells do not depend on increased glycolytic metabolism to fuel immune surveillance or regulatory function. In subsequent stud-

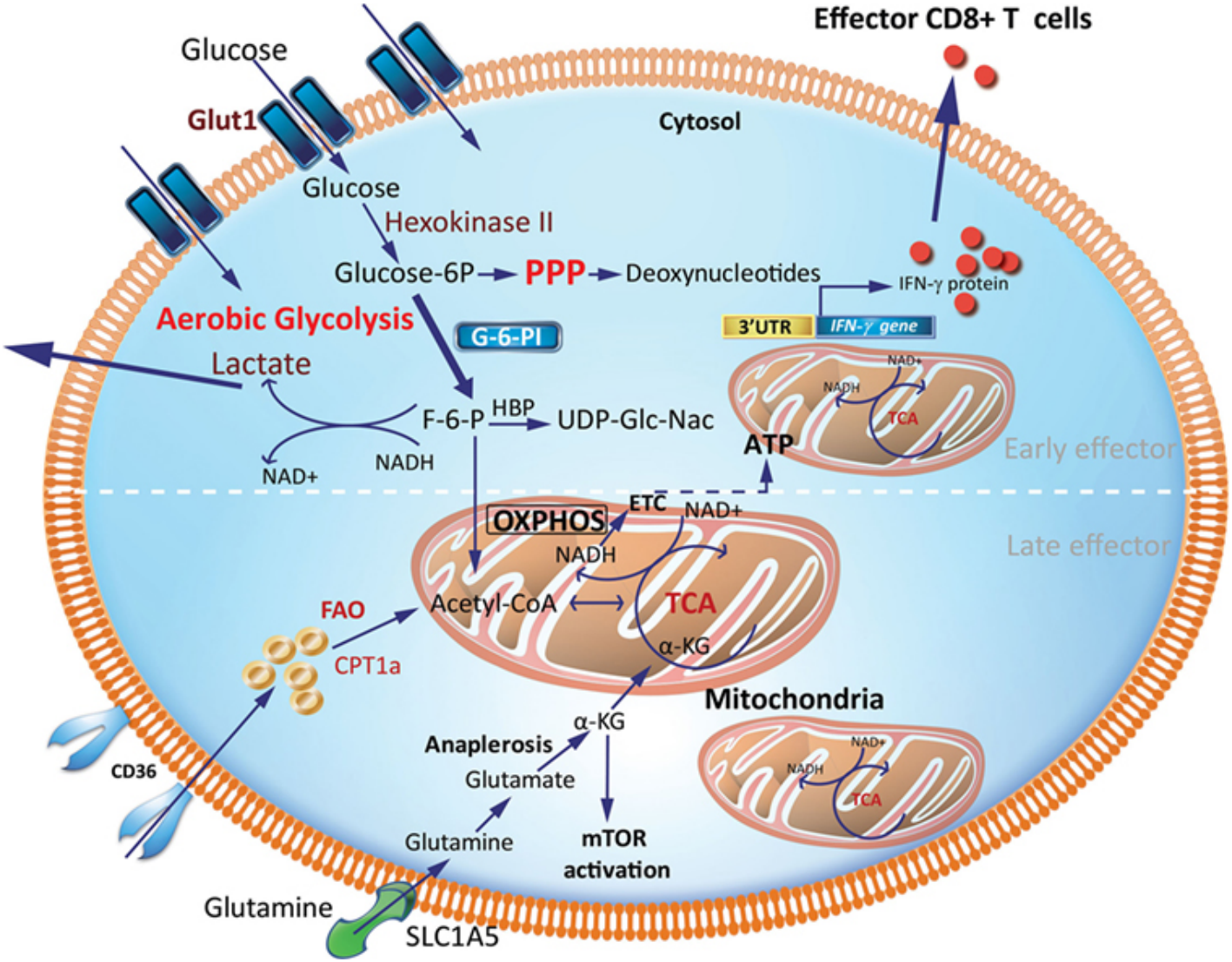
Alwarawrah et al., Front Immunol 2018

Bidirectional relationship: adipocyte-immune cell interaction



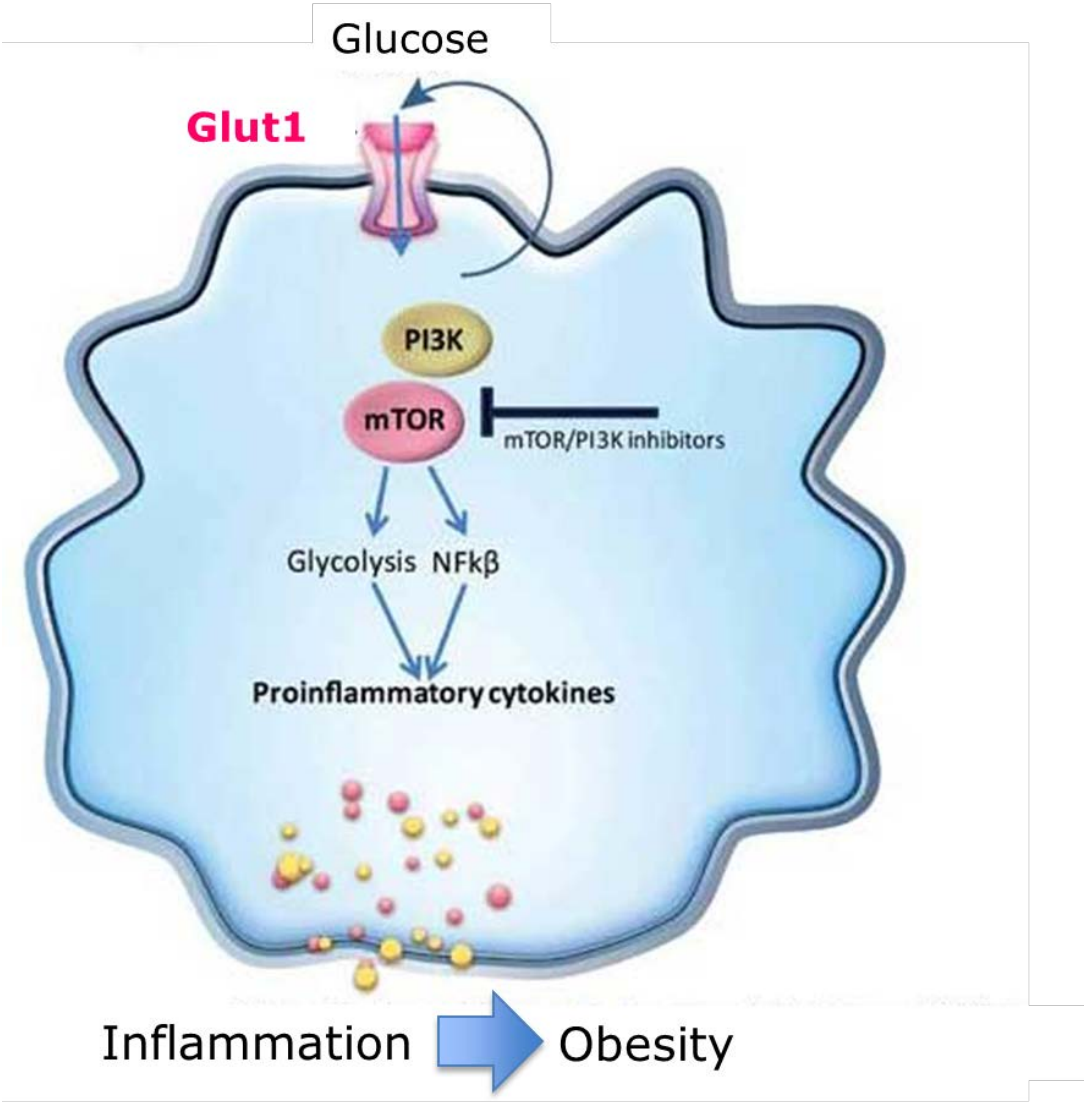
Mod: Lee et al., Cell 2017

Auxiliary pathways in immune cellular activation



Hesham et al., Front. Immunol., 2017

Immunometabolism provides new therapeutic opportunities for inflammation and obesity



Mod: Palmer et al., F1000 Reviews 2018

CONCLUDING POINTS

- Metabolic reprogramming of monocytes from oxidative phosphorlyation to glycolysis is associated with inflammatory responses
- Metabolic reprogramming of immune cells is influenced by adipose tissue-derived molecules receptor engagement (e.g AdipoR1, LepR
- Immunometabolic targetting offers new therapeutic opportunities for obesity

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