FAPESP Week 2017

09/21/2017

Texas Tech University

Dr Naima Moustaid-Moussa
Texas Tech University

Dr Latha Ramalingam
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University of Sao Paulo

Dr Sonia Jancar
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PhD candidate,
Immunology
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Dr Luciano Filgueiras
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Anti-Inflammatory Effects of Omega 3 Fatty Acids in Metabolic Disorders: Role of Lipid Mediators and MicroRNAs

Presenters

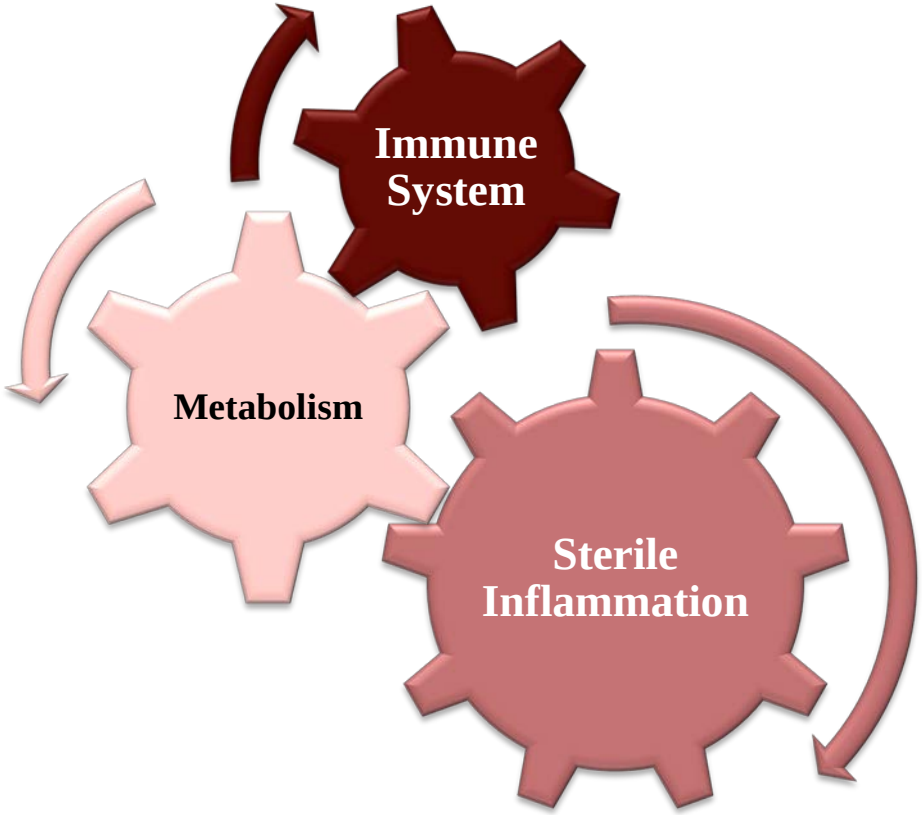
Texas Tech University

Dr Naima Moustaid-Moussa
Texas Tech University

University of Sao Paulo

Theresa Ramalho MS
PhD candidate,
Immunology
ICB-USP

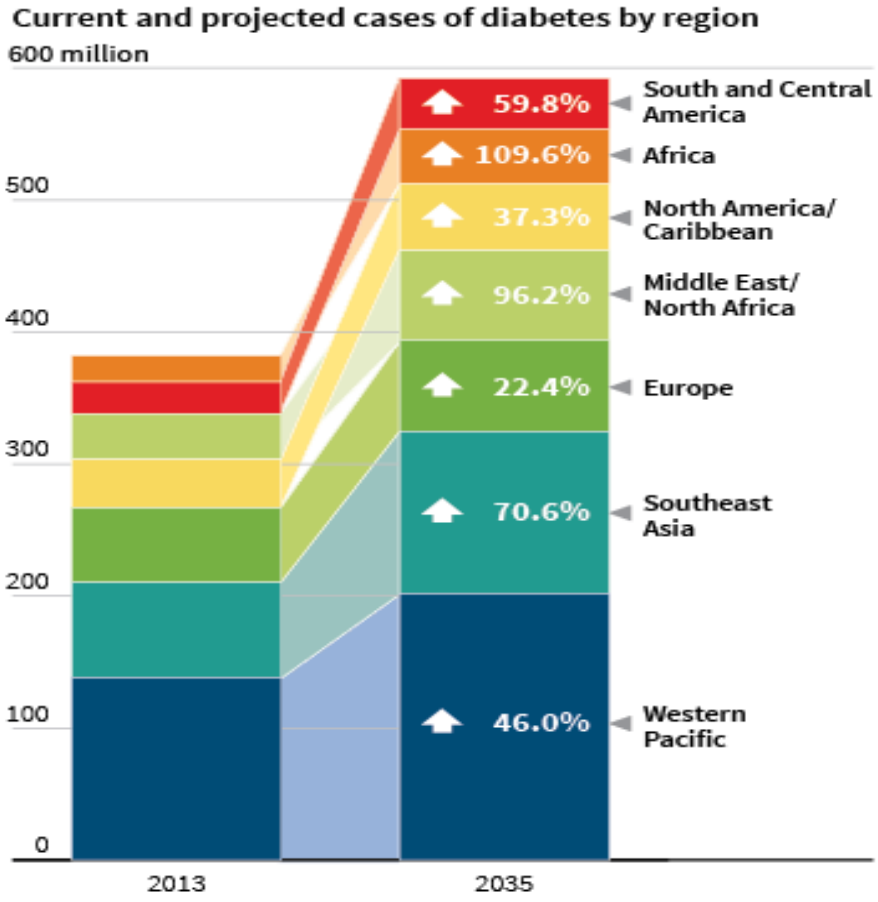
Metabolic Disorders

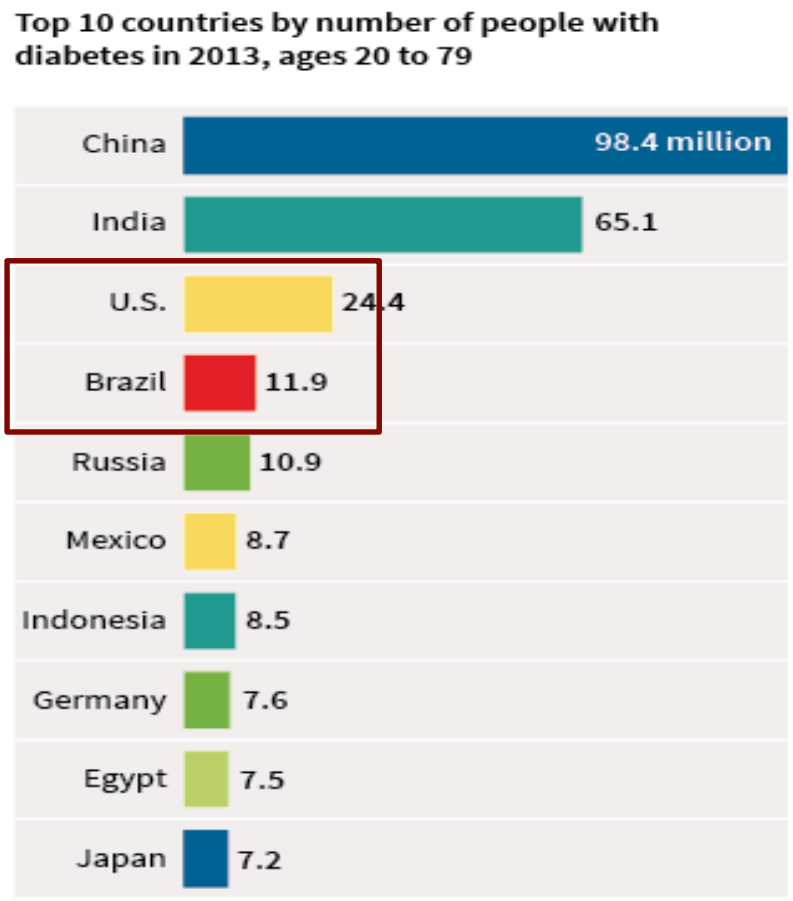


- Atherosclerosis
- Obesity
- Metabolic syndrome
- Diabetes

Diabetes Incidence

World diabetes cases expected to jump 55 percent by 2035





Source: International Diabetes Federation

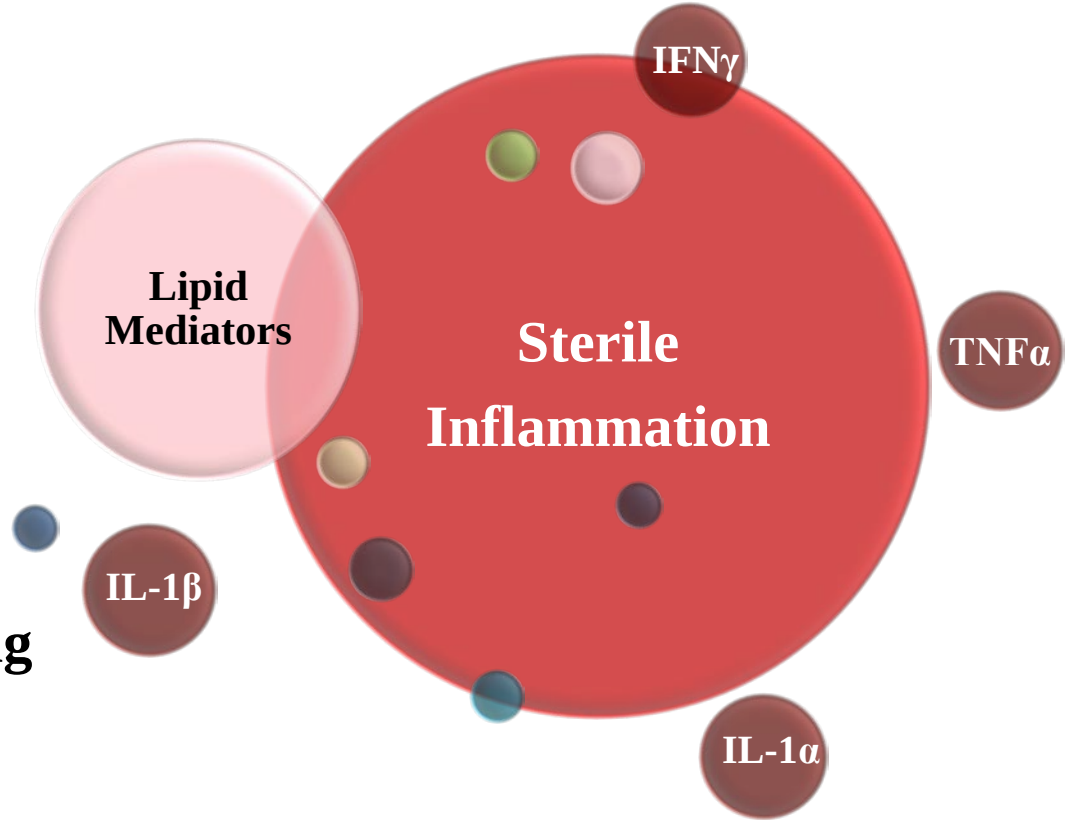
S. Culp, 12/11/2013

REUTERS

Diabetes Physiology

Hyperglycemia
- **Insulin resistance**
- **Steatosis**

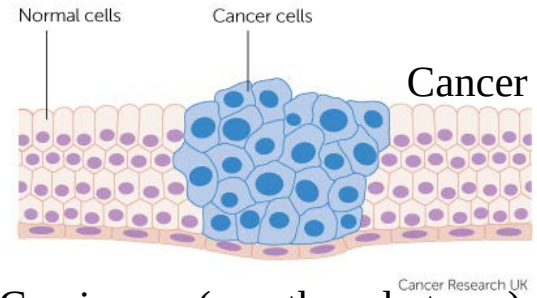
Co-morbidities
- **Retinopathy**
- **Neuropathy**
- **Defective wound healing**



IL = Interleukin; TNF: Tumor Necrosis Factor; IFN: Interferon

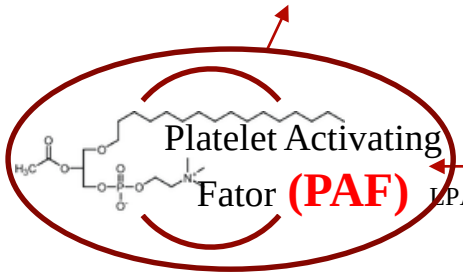
Lipid Mediators (PAF)

Metabolic Syndrome (PAFR KO)



Cancer

Carcinoma (mouth and uterus)
Melanoma

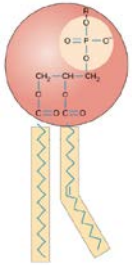


Platelet Activating Fator **(PAF)**

LPAT

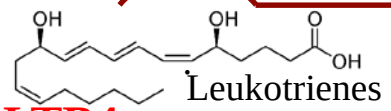
Arachdonic Acid

PLA2



Membrane Phospholipid

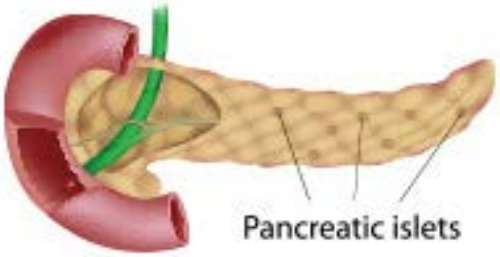
5-LO



Leukotrienes

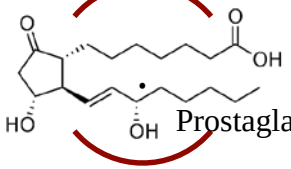
LTB4

Type 1 Diabetes
Streptozotocin model

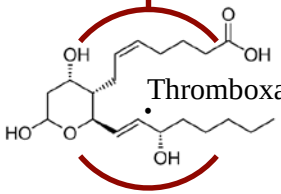


COX

TXAS



Prostaglandins

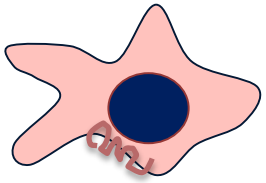


Thromboxanes

PAFR and Metabolic Homeostasis

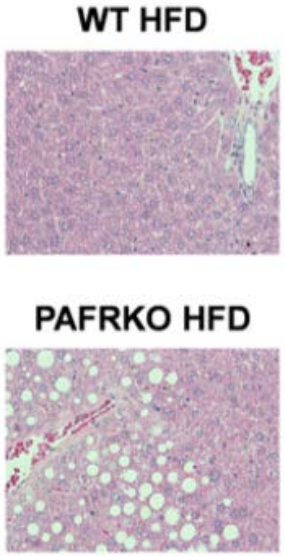
PAFR and Metabolic Homeostasis

Macrophage

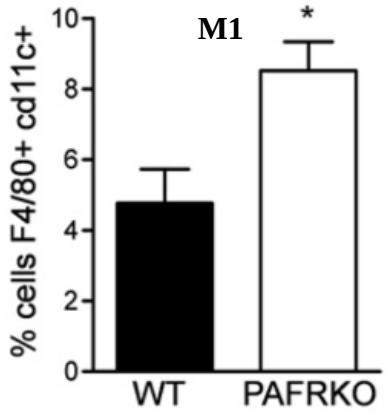


PAF receptor
Anti-inflammatory
phenotype

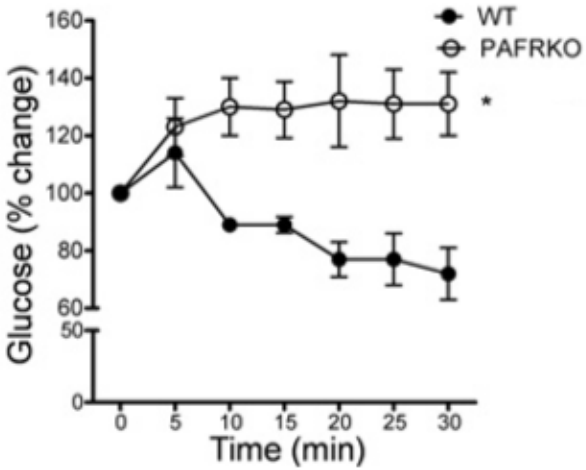
Steatosis in PAFR KO



Inflammatory macrophage infiltration in adipose tissue in PAFR KO mice

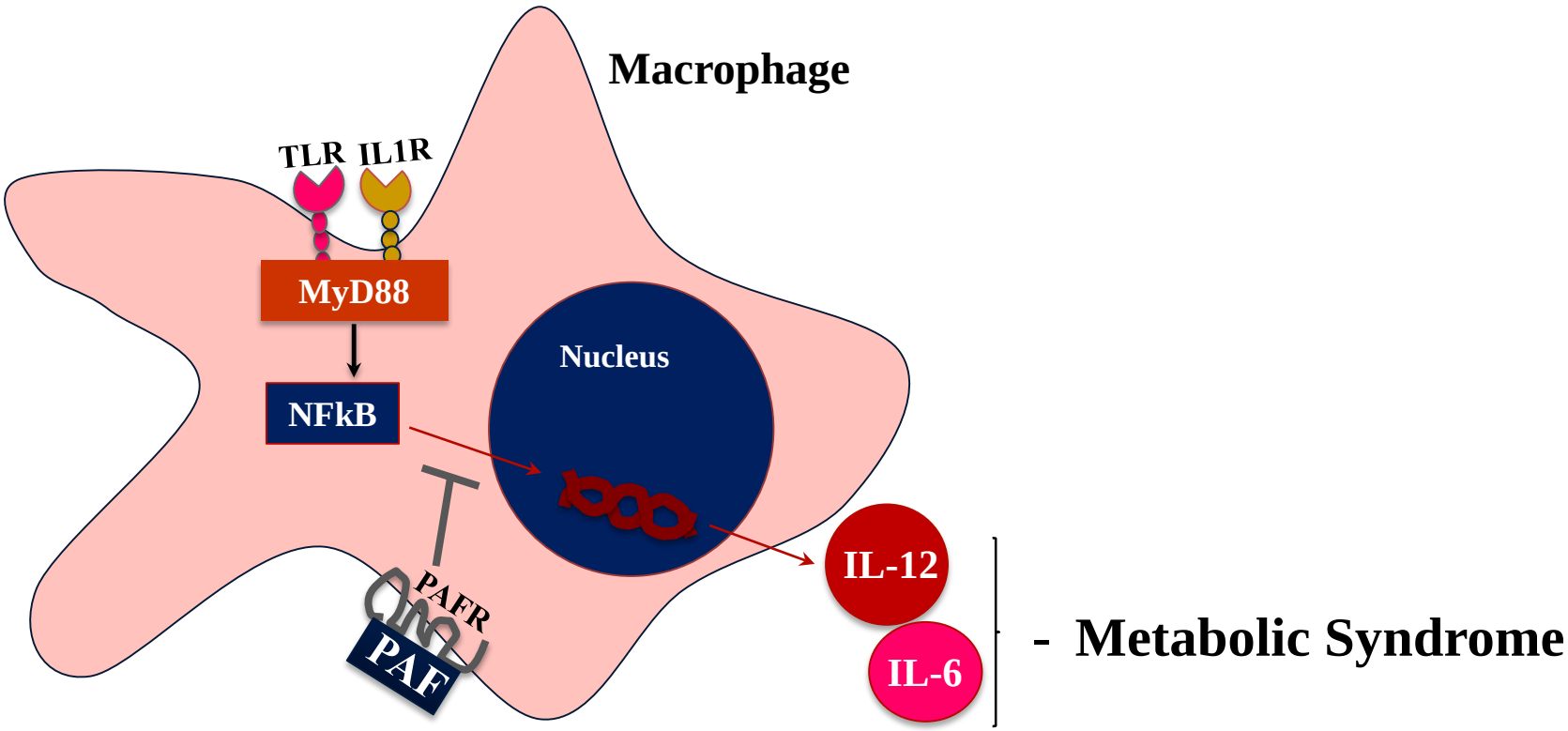


Insulin Resistance in PAFR KO mice



Filgueiras LR et al., **Clinical Science,** 2016
Ishizuka Eket al, Sci Rep, 2016

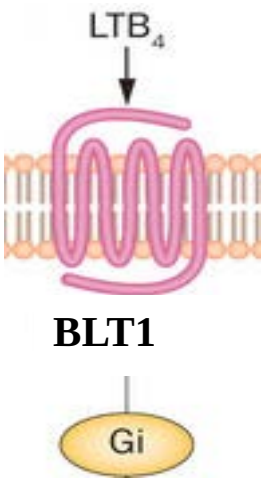
PAFR and Metabolic Homeostasis

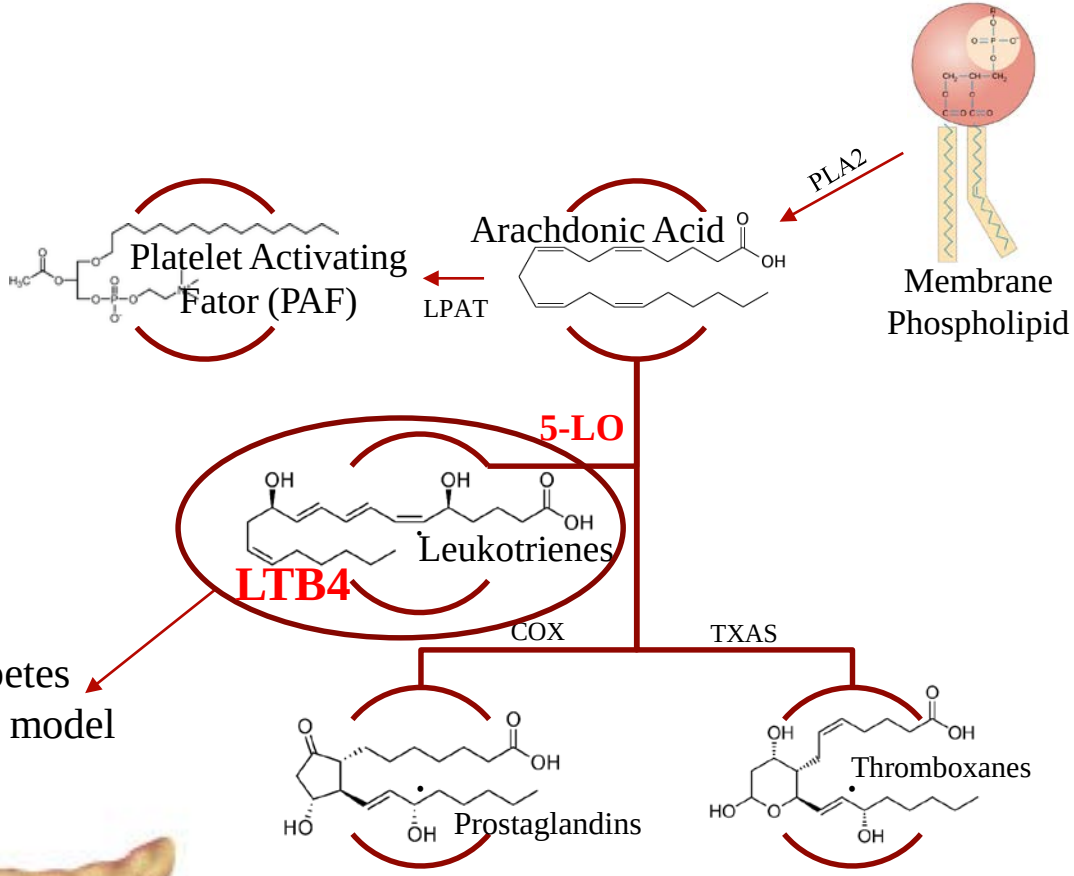


Filgueiras LR et al., **Clinical Science,** 2016
Ishizuka Eket al, Sci Rep, 2016

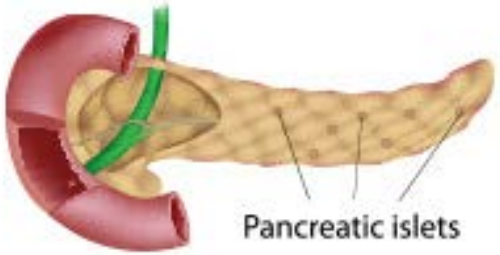
LTB4 in Type 1 Diabetes

Lipid Mediators (LTB4)



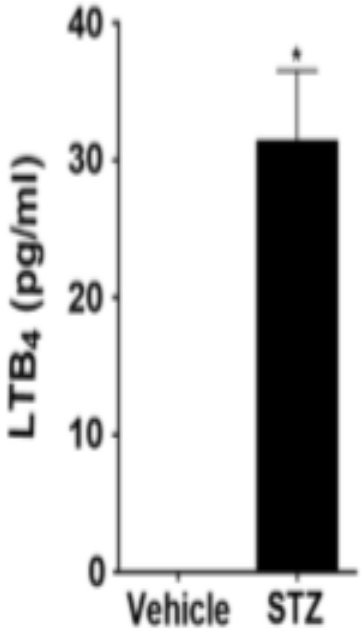


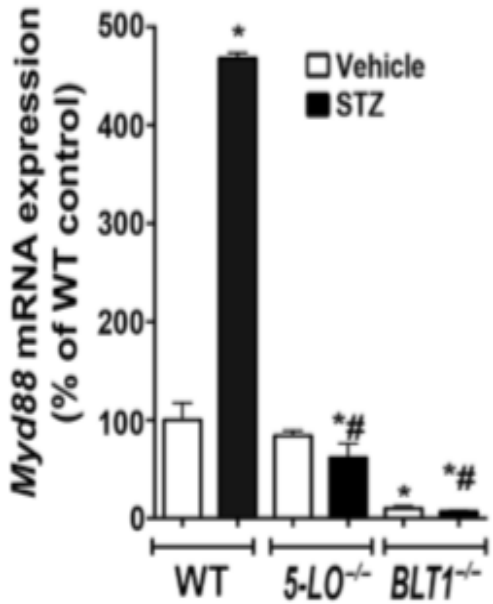
Type 1 Diabetes
Streptozotocin model

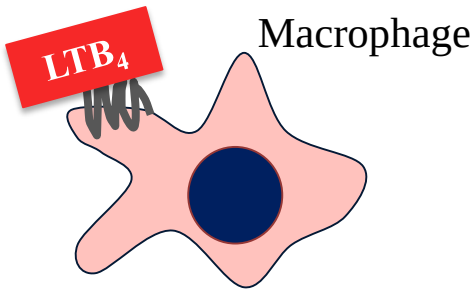


LTB4 in Type 1 Diabetes

LTB4 promotes sterile inflammation



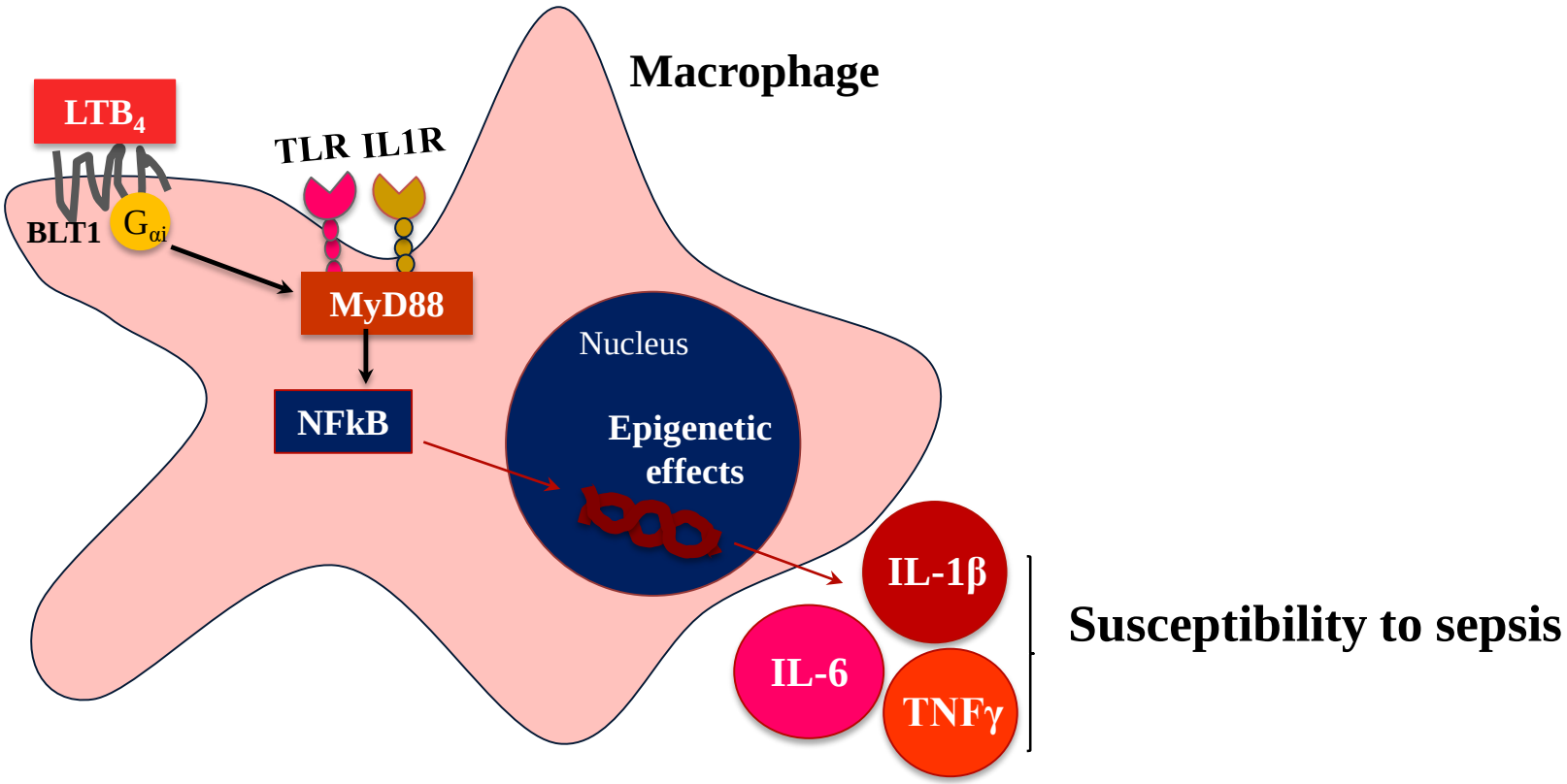




BLT1 receptor
Pro-inflammatory
phenotype

Filgueiras LR et al., **Sci Sign**, 2015
Ramalho TR et al, **Unpublished**, 2017

LTB4 in Type 1 Diabetes



Filgueiras LR et al., **Sci Sign**, 2015
Filgueiras LR et al., **J Diabetes Comp,** 2016
Ramalho TR et al, **Unpublished**, 2017

Progress & Accomplishments

1. TTU and USP team met in Summer 2016 at the International Immunology meeting in Australia

2. Jancar's Postdoc Luciano attended the 2016 FAPESP meeting at TTU, presented the SPRINT project and visited Moustaid-Moussa's lab

3. TTU Team visited USP in March 2017 and Moustaid-Moussa gave an invited lecture in the dept. of Immunology, USP

4. Visiting scholar (Theresa) at TTU for one year (funded by CAPES, Brazil)

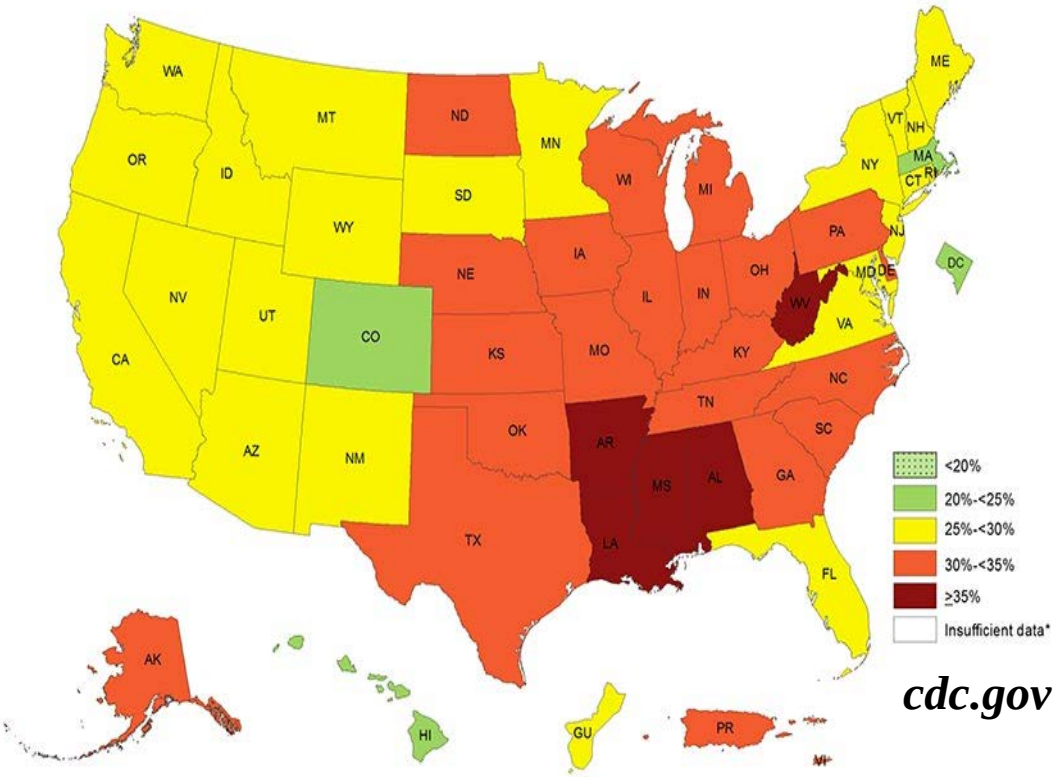
5. Invited presentation by AFMR, April 2017, and invited peer-reviewed manuscript in press

6. Poster presentations at the Immuno-metabolism and Chronic Disease conference, Fiji, Aug 2017

Obesity, a global & complex disease

Obesity

- Complex disease
  - 1/3 of American adults
  - Medical costs
    - *Per capita medical spending $2,741 higher*



cdc.gov

- Increases risk for metabolic diseases
  - Health Disparities

- Linked to changes in metabolism/inflammation (sterile inflammation)

17.9% Obesity

52.5% Overweight

Ministry of Health Brazil

POTENTIAL CONTRIBUTORS TO OBESITY

2015

Inside the Person

Disordered Eating (*night eating syndrome, binge eating, "food addiction"*)

Emotional Coping

Hyper-reactivity to Environmental Food Cues

Heightened Hunger Response

Delayed Satiety

Increased Intake

Age Related Changes (*i.e. menopause, mobility decline, hormones*)

Pathological Sources of Endocrine Dysregulation (*i.e. thyroid dysfunction, PCOS, Cushing's Syndrome*)

Central & Peripheral Regulators of Appetite & Adipose Tissue

Chronic Inflammation (*i.e. altered insulin signaling and glucose homeostasis*)

Genetic & Epigenetic Factors

Gestational Diabetes

Intake & Expenditure (Or Unknown)

Self-regulatory & Coping Deficits

Trauma History

Mood Disturbance (*i.e. depression, anxiety, bipolar etc.*)

Mental Disabilities

Thermogenesis

Gut Microbiota

Pain Sensitivity

Physical Disabilities (*i.e. functional impairments and regulatory dysfunction*)

Social Anxiety (*i.e. exercise avoidance*)

Decreased Expenditure

Outside the Person

Environmental/ Chemical Toxins

Increased Availability of Energy Dense, Nutrient Poor Foods & Beverages

Larger Portion Sizes

Eating as Recreation, Snacking, Special Occasions

Lack of Nutritional Education

Skipping Meals

Food Insecurity

Diet Patterns

Eating Away From Home

Lack of Family Meals

Market Economy

Food Surplus

Pervasive Food Advertising

Increased Intake

Maternal Employment

Breast Feeding and/ or Related Factors

Maternal Stress

Maternal Smoking

Maternal Obesity

Delayed Prenatal Care

Birth Order (*first-born in family*)

Having Children (*for women*)

Non-parental Childcare

Maternal Over-nutrition During Pregnancy

Birth by C-section

Infection (*i.e. human adenovirus 36*)

Weight Gain Inducing Drugs

Smoking Cessation

Sleep Deficits

Intake & Expenditure (Or Unknown)

Family Conflict

Social Networks

Weight Bias & Stigma (*i.e. avoidance of medical care, self esteem, teasing history*)

Entering Into a Romantic Relationship

Lack of Employer Preparedness to Assist with Obesity

Lack of Health Care Provider Support/Knowledge & Inadequate Access to Care

Stress

Child Maltreatment

Weight Cycling (*yo-yo dieting*)

Westernization & Economic Development

Low SES & Nutrition Support

Living in Crime-prone Areas

Decreased Expenditure

Consistent Temperature (*i.e. air conditioning/heating, thermoregulation*)

Increased Sedentary Time (*i.e. inactive leisure "screen" time, inactive job requirements*)

Built Environment (*i.e. stairwell design/access, building design, absence of or poor sidewalks*)

Decreased Opportunity for Non-exercised Based Physical Activity (*i.e. driving vs. walking to work and school, sedentary jobs*)

Labor Saving Devices

Pre-natal Air Pollution

Contributors to Energy Storage

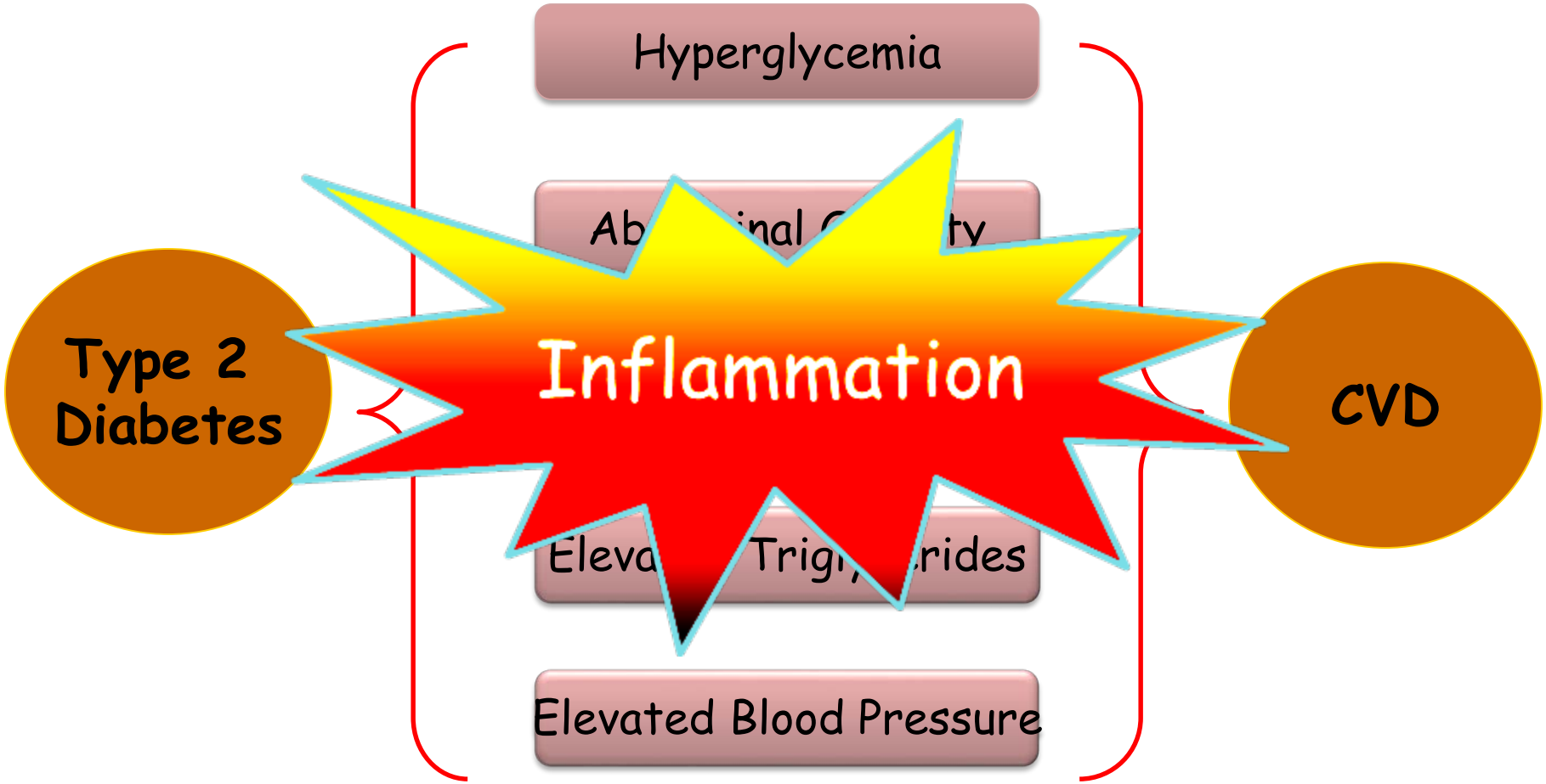
* Potential contributors indicate anything that has been put forth in the research literature as a question of investigation and is not intended to be a verification of whether or not, or the extent to which, each may or may not contribute.

Contributor/Influencer

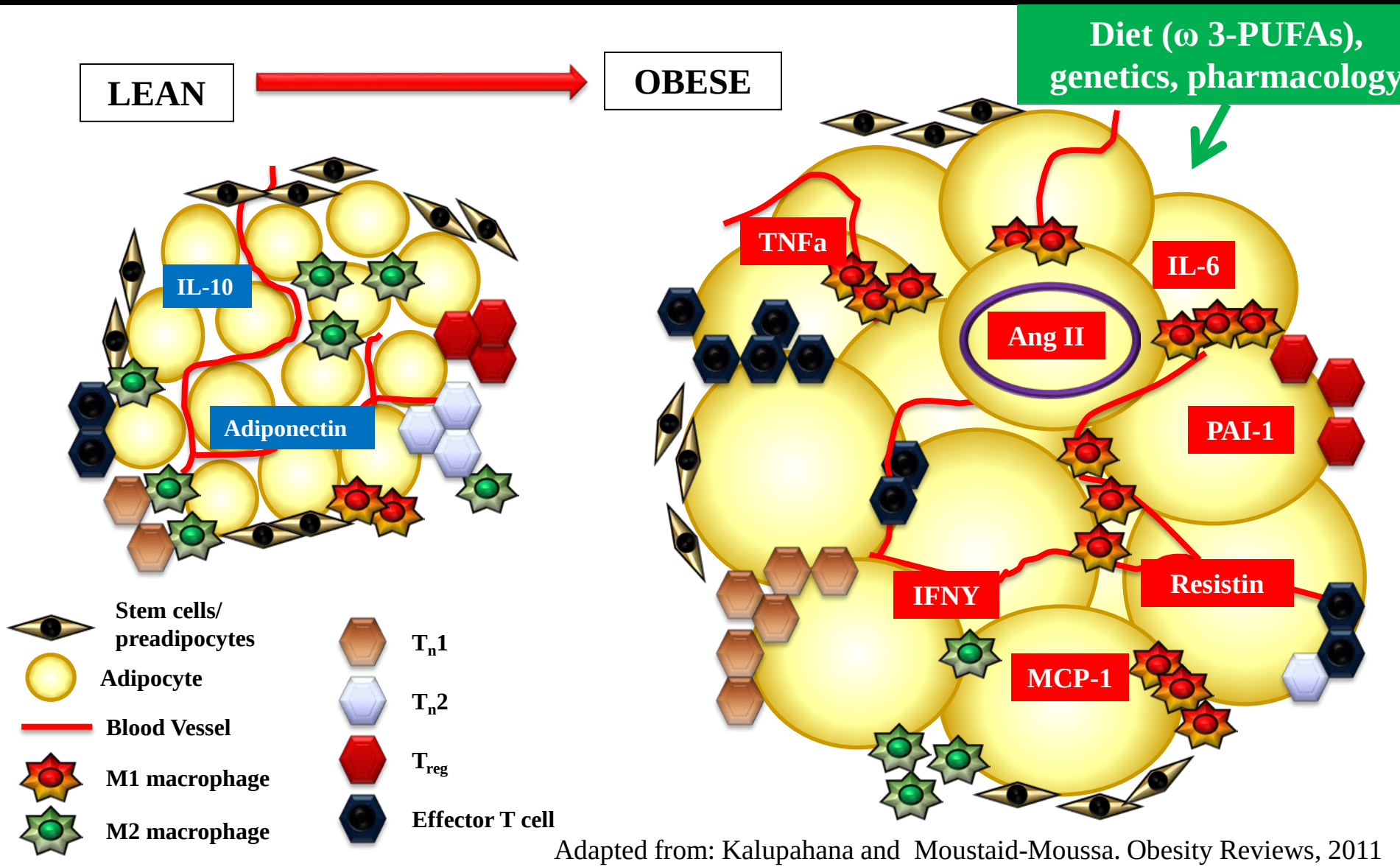
- Environmental Pressures on Physical Activity
- Biological/ Medical
- Maternal/ Developmental
- Economic
- Food and Beverage Behavior/Environment
- Psychological
- Social

OBESITY SOCIETY
Research. Education. Action.
www.obesity.org

Obesity and the Metabolic Syndrome

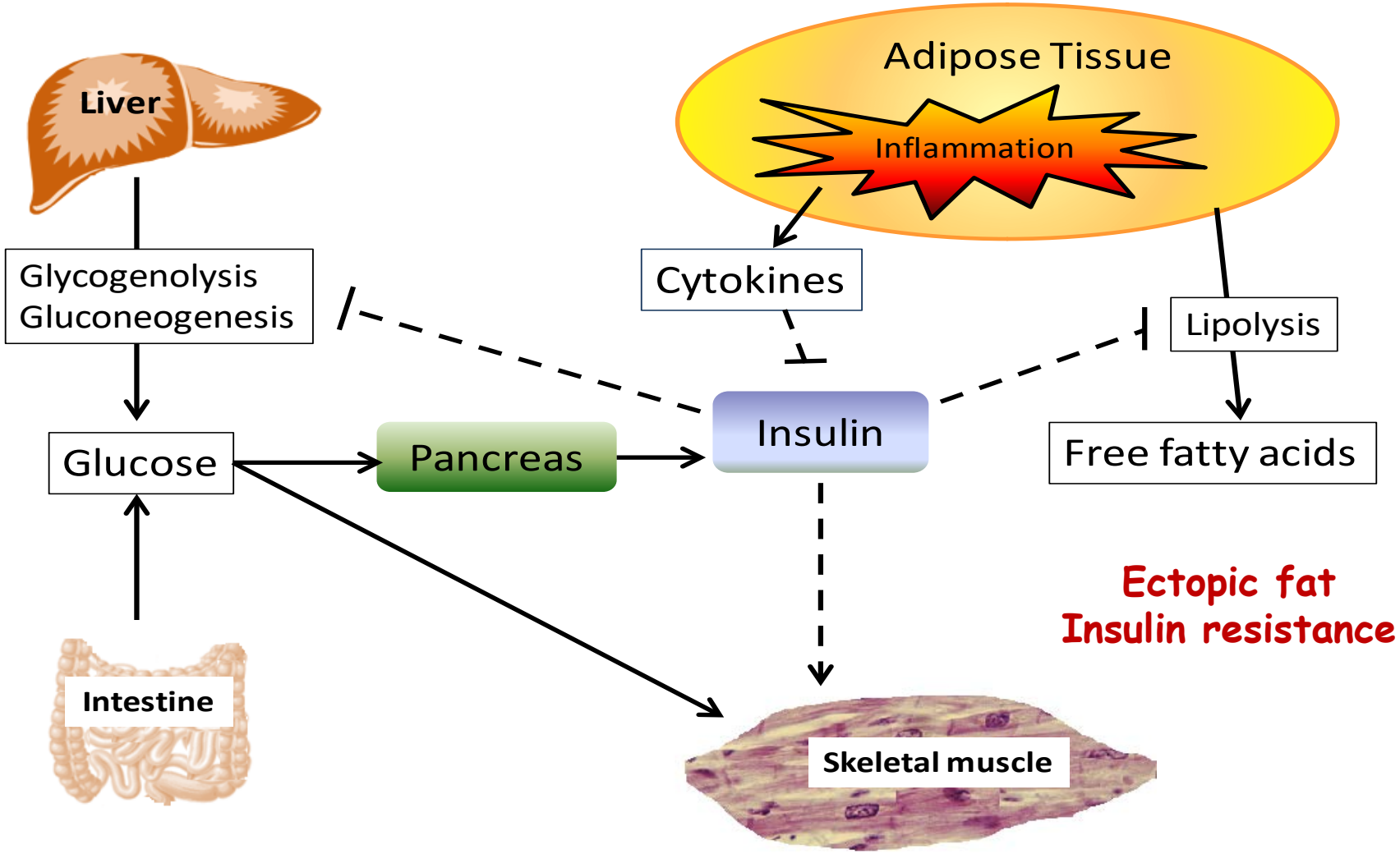


Obesity and inflammation



Adapted from: Kalupahana and Moustaid-Moussa. Obesity Reviews, 2011

Pathogenesis of obesity-associated insulin resistance



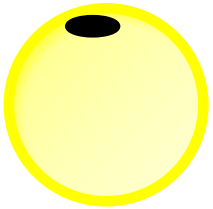
Kalupahana, Moustaid-Moussa and Claycombe. Molecular Aspects of Medicine 2012

Dietary/genetic regulation of adipose tissue inflammation

Food and Plant Bioactives

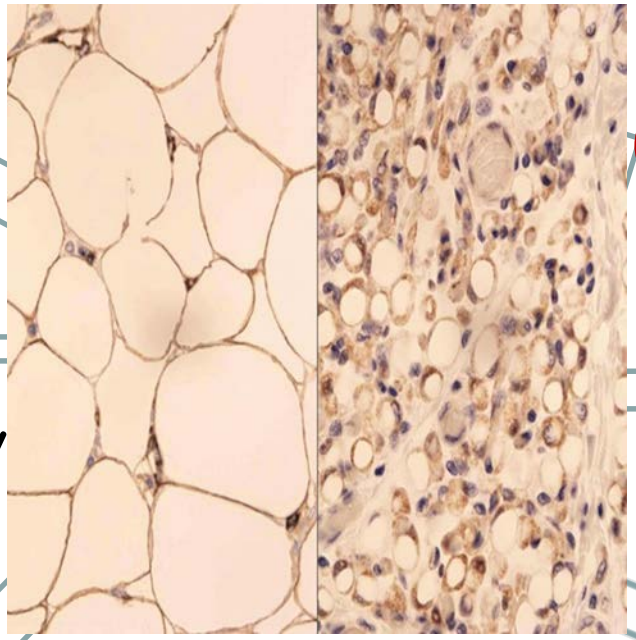
(**Omega 3's**, tart cherry anthocyanins, tocotrienols, Switchgrass extracts)

Cells, animals, model organisms, bariatric patients



Small Adipocytes

Obesity



Large inflamed Adipocytes

Endocrine systems
(Renin Angiotensin System)

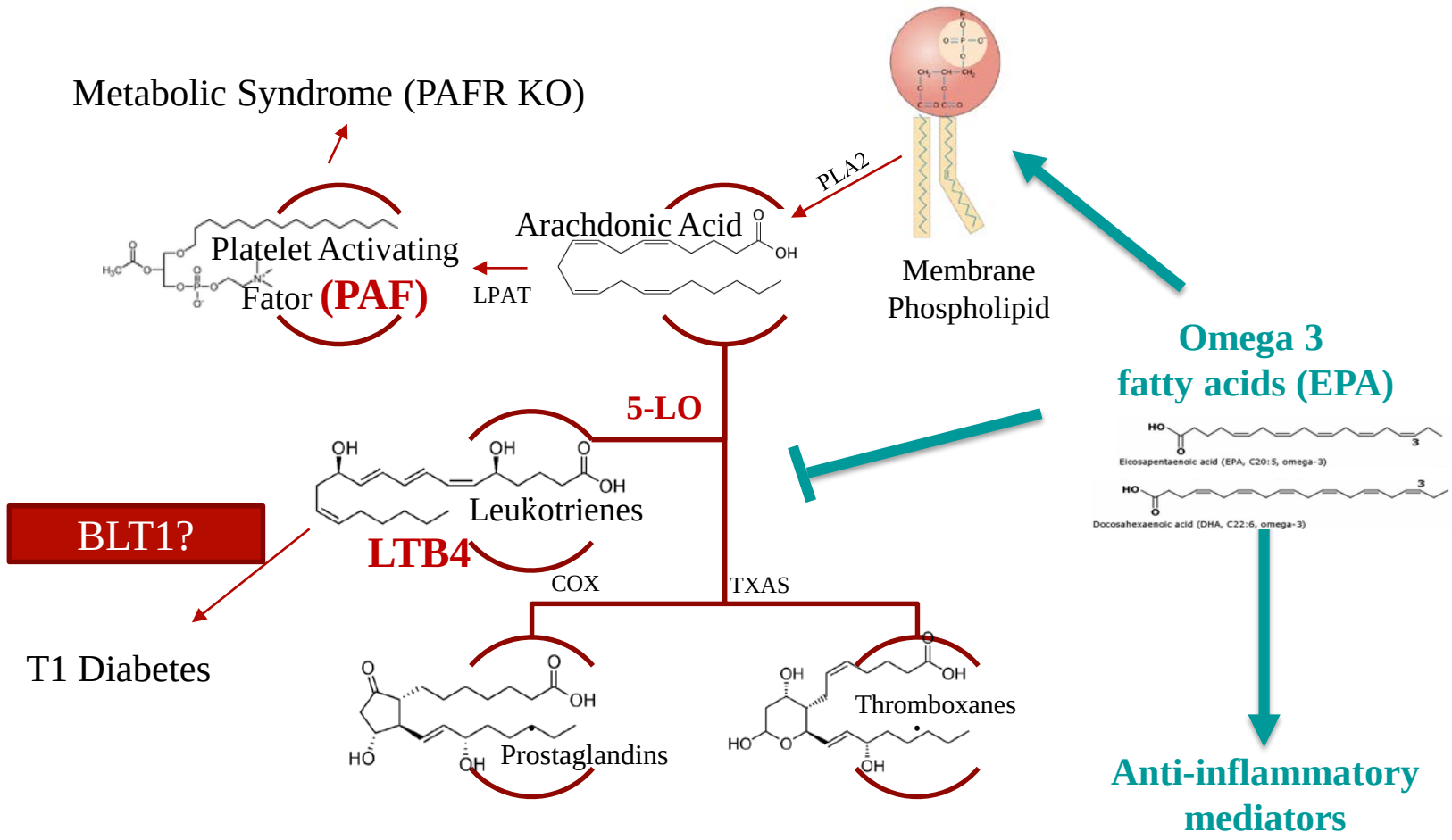
Metabolic Syndrome

Breast Cancer

Mechanisms linking adipocyte inflammation to metabolic disorders

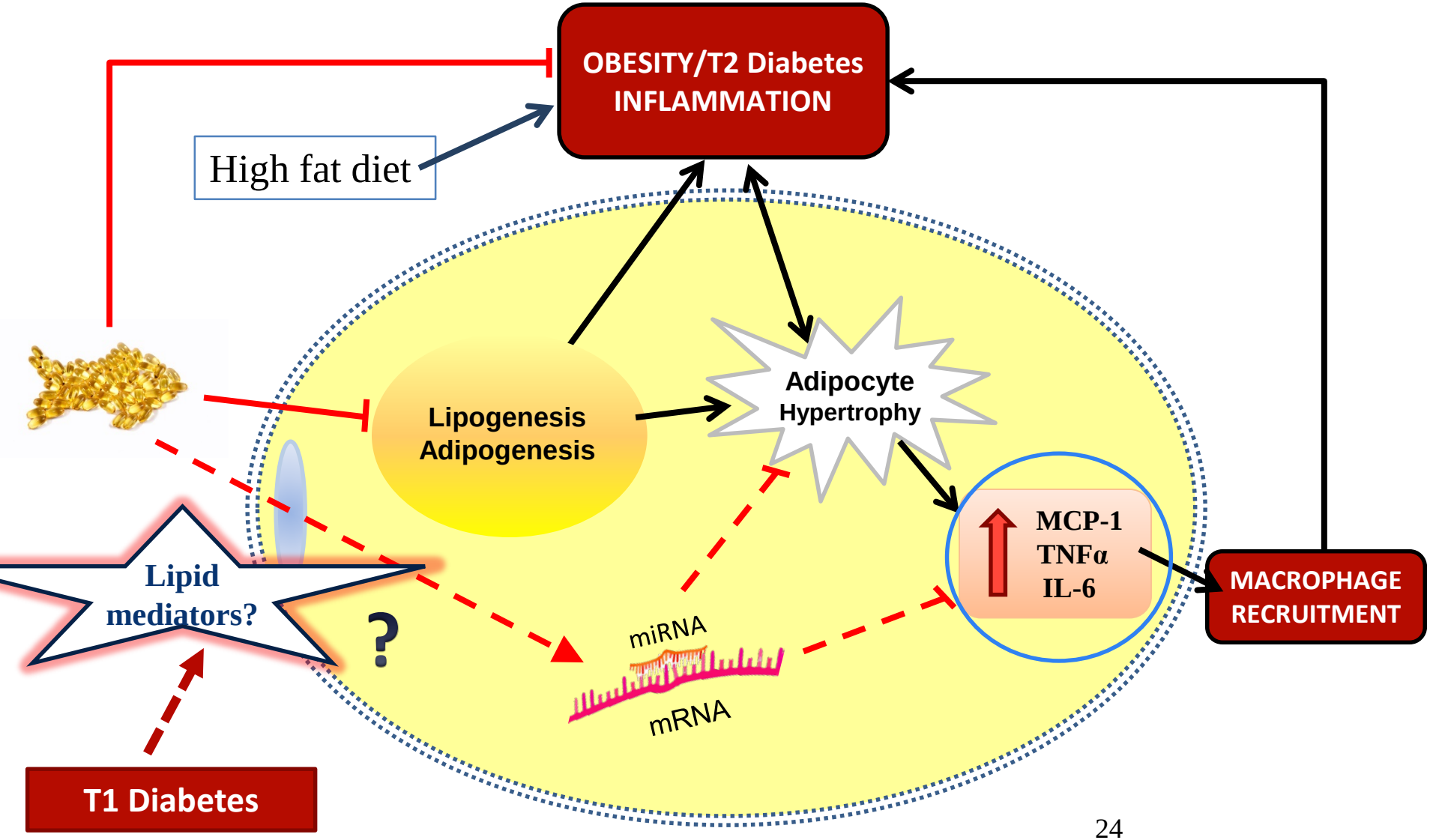
Omega 3 fatty acids prevent diet-induced obesity and inflammation

Lipid Mediators



Omega 3 fatty acids: hypotriglyceridemic, cardioprotective and anti-inflammatory

Research Hypothesis



Study design

Male C57BL/6J mice

LF

Low-fat diet (10% fat, 70% CHO, 20%proteins)

HF

High-fat diet (45% fat, 35% CHO, 20%proteins)

HF-EPA-P

EPA diet (HF with 36g/kg EPA)

HF-EPA-R

High-fat diet

6 weeks

EPA diet

5 weeks

11 Weeks

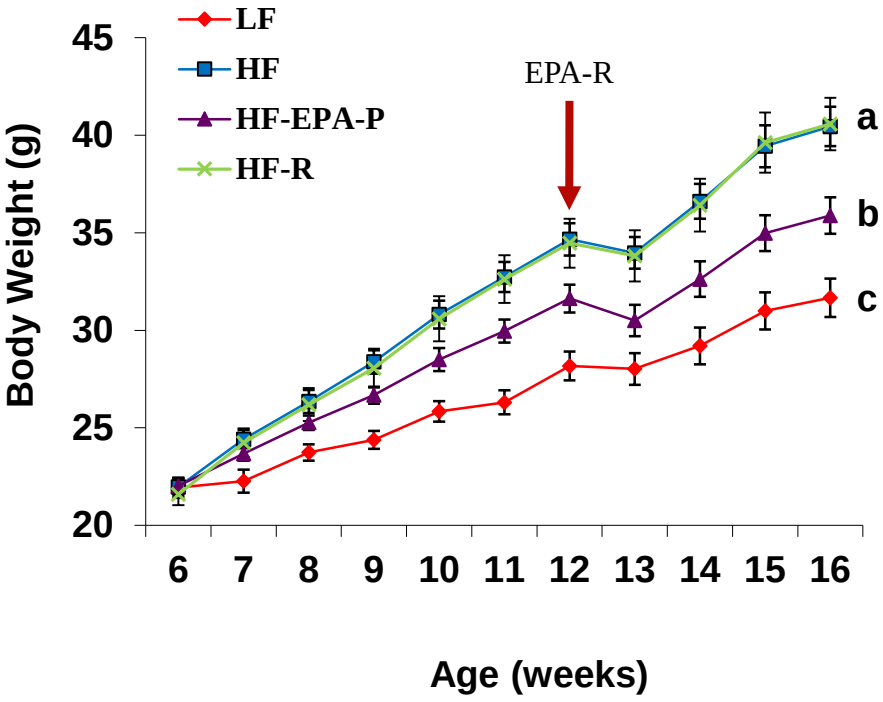
Tissue collection and analyses

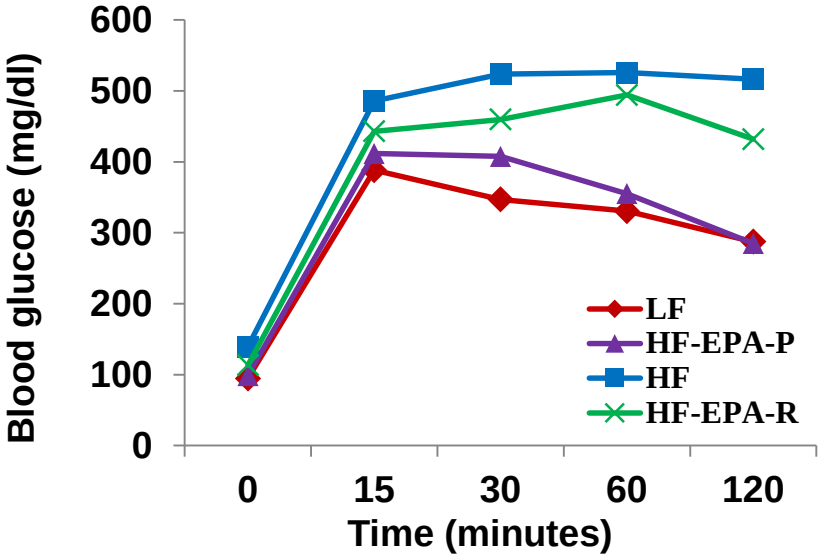
Metabolic Changes → Cell Culture Experiments

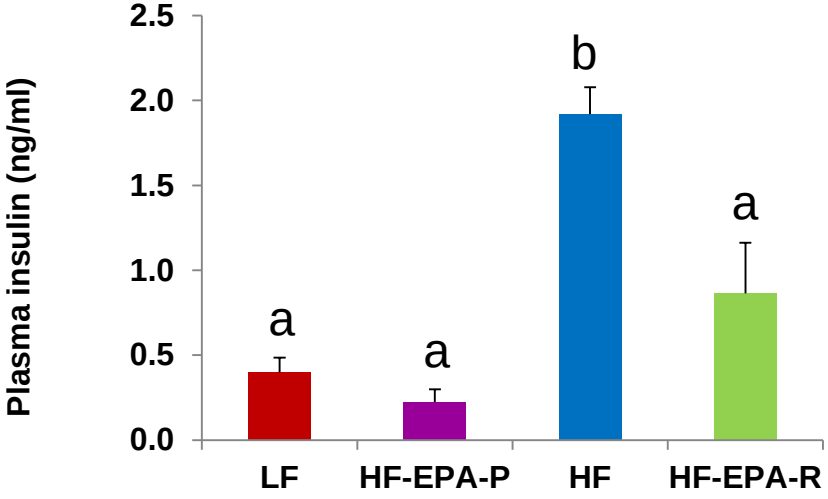
Gene Expression → Microarray qRT-PCR

Inflammation → Macrophage infiltration; Adipokines secretion

EPA reduces body weight and restores glucose tolerance

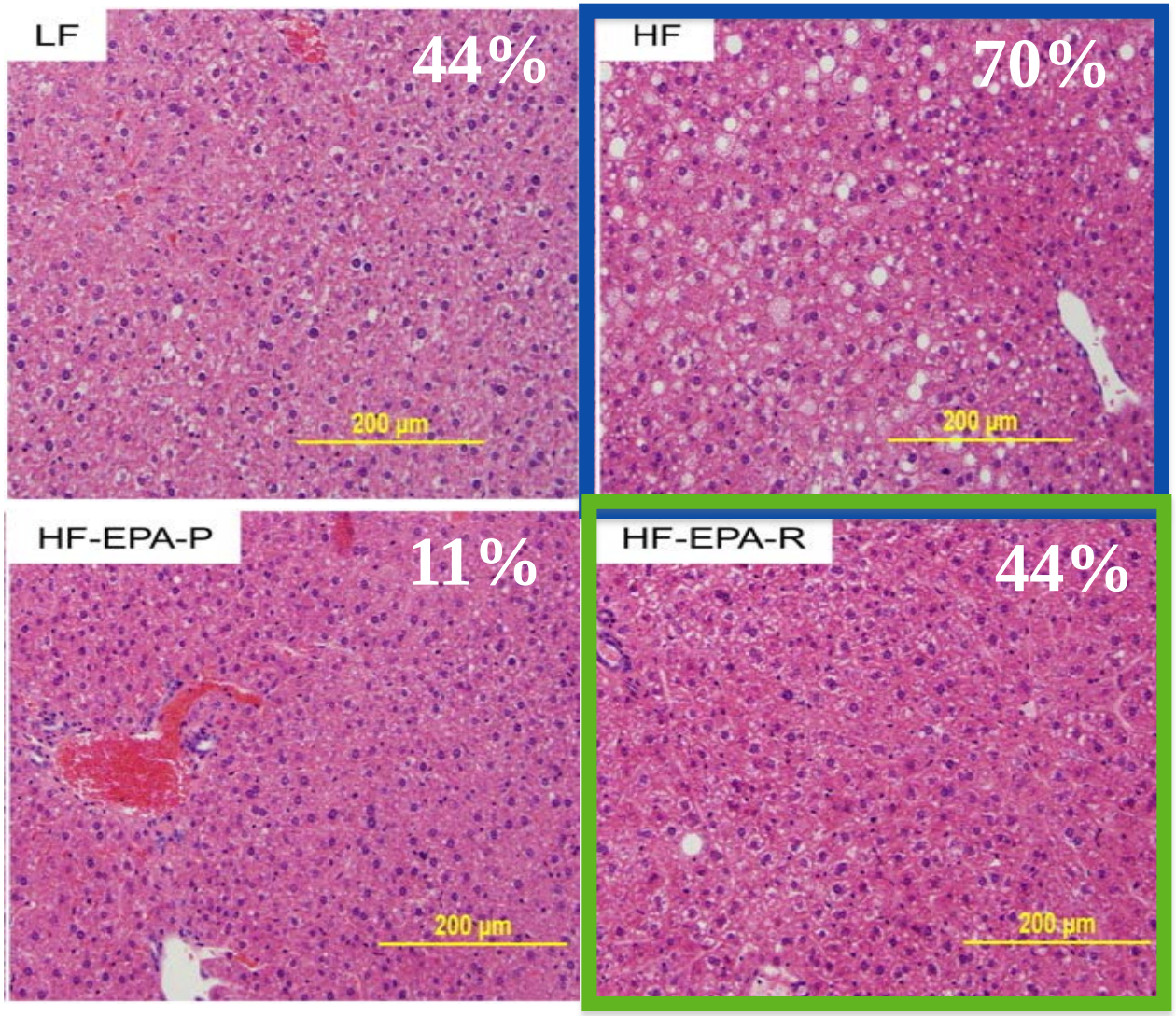






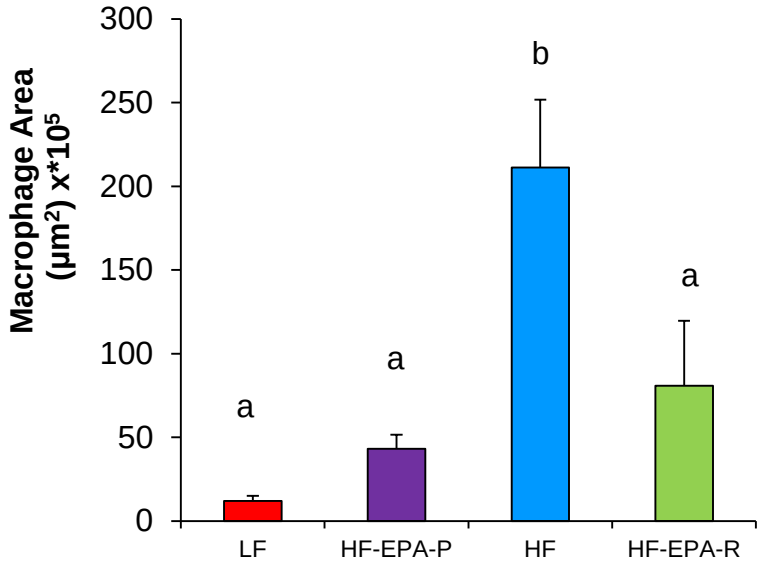
Kalupahana NS et al. *J Nutr* 2010, 140:1915-1922.

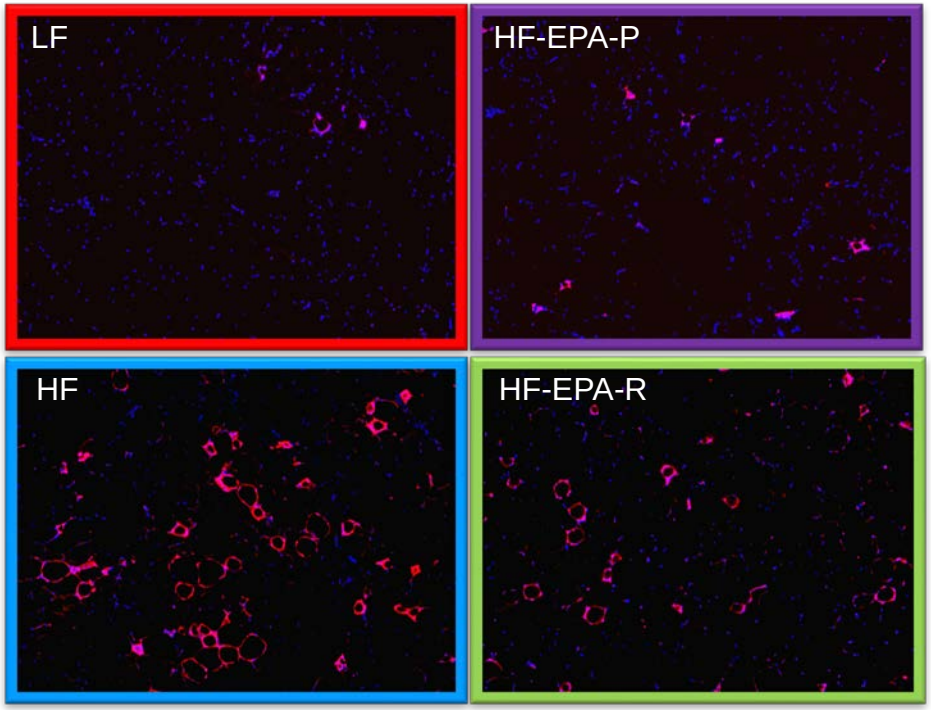
EPA Lowers TG Deposition in Liver



Kalupahana et al. J Nutr 2010

EPA reduces adipose macrophages independent of adiposity





Mechanisms mediating these anti-inflammatory effects?

LeMieux, M.J. *et* al. J Nutr. 2015

Labeled means without a common letter differ, $P < 0.05$

Summary of Results

Omega 3 fatty acids target specific miRNAs and genes related to inflammation and lipid mediators (unpublished)

We thank members of Prof. Jancar and Prof Moustaid-Moussa's lab for their contributions to this SPRINT project

Future studies

- Validation of gene and miRNA findings
- Effects of EPA on LTB4 in adipose tissue
- Inhibition of LTB4/BLT1 and PAFR in wild type, obese and diabetic animals to determine effects on:
  - *Inflammation*
  - *Target genes and miRNAs*
- Research Manuscript
- Funding after research publication: NIH-FAPESP and other funding agencies

Thank you!

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http://www.depts.ttu.edu/hs/nhr/research/nior/
https://www.depts.ttu.edu/hs/obesityresearch/

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