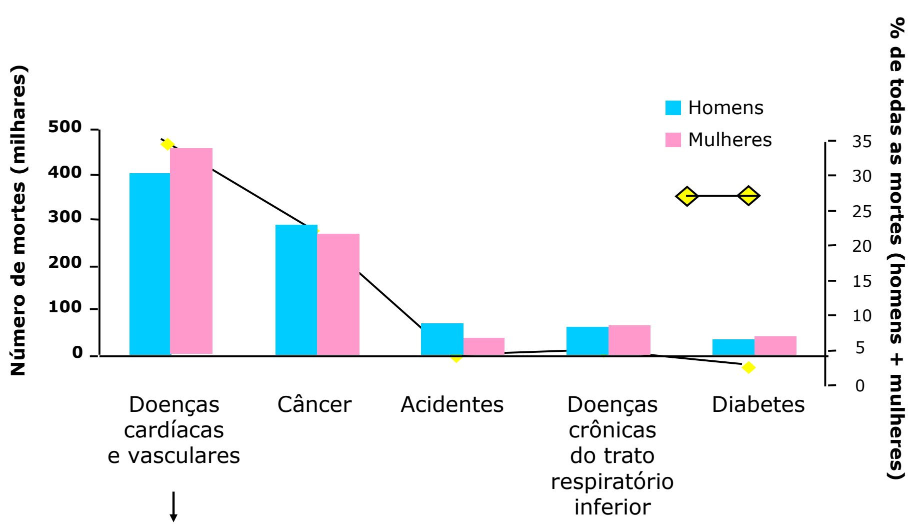
Obesidade e Sistema Cardiovascular

Prof. Dr. Rafael Menezes da Costa

Mortes e doenças cardiovasculares



Obesidade

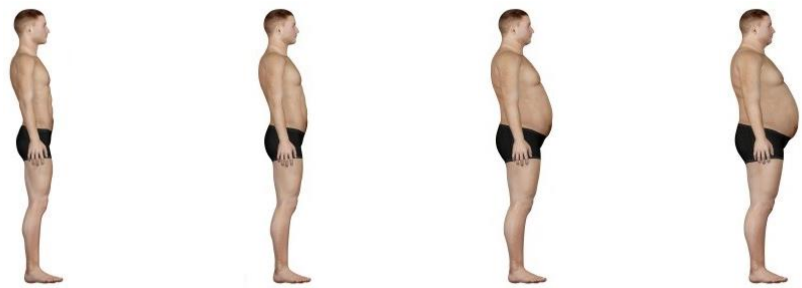
National Center for Health Statistics, 2018

Obesidade

Excesso de tecido adiposo

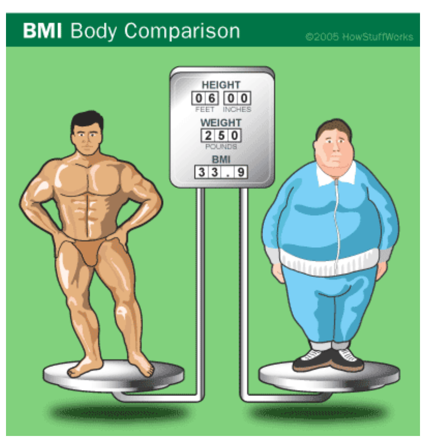
Kopelman, 2010

Classificação da obesidade



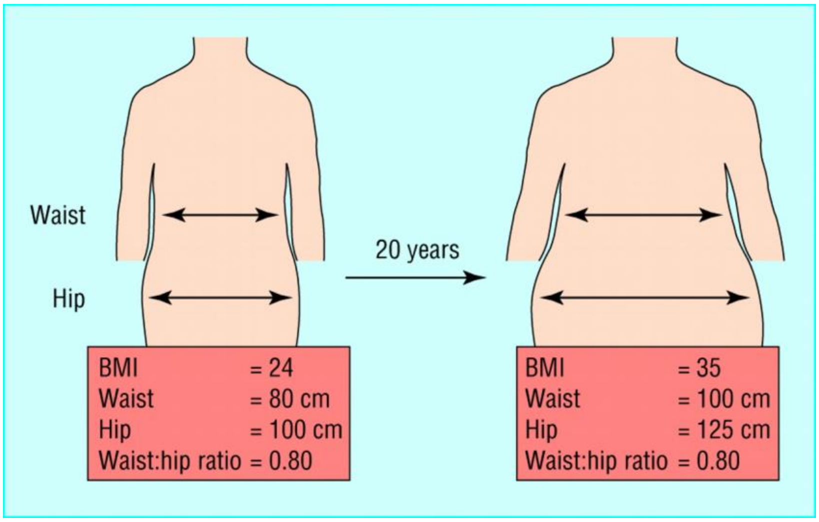
< 18,5 kg/m²	18,5 – 25 kg/m²	25 – 30 kg/m²	> 30 kg/m²
↓	↓	↓	↓
Abaixo do Peso	Peso Normal	Sobrepeso	Obeso

Classificação da obesidade

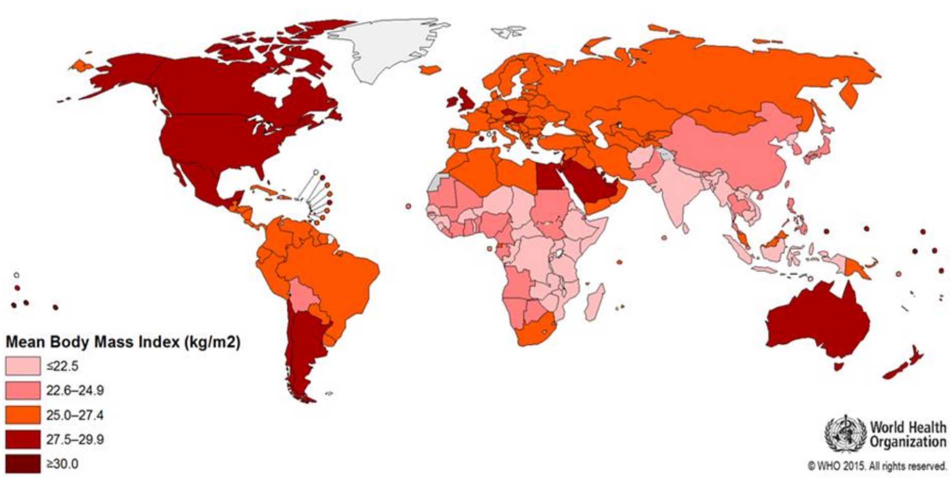


Alto Risco: circunferência da cintura	
Homem	> 102 cm
Mulher	> 88 cm

Classificação da obesidade



Obesidade no mundo



Obesidade no mundo

WHO, 2015

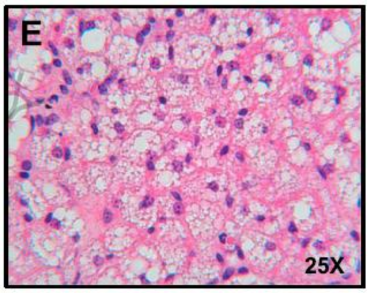
Obesidade infantil

- ✓ A obesidade infantil persiste em grande parte dos casos na fase adulta.
- ✓ Uma criança de 6 anos de idade obesa possui 50% de risco de se tornar um adulto obeso.
- ✓ 70-80% dos adolescentes obesos permanecem obesos na fase adulta.

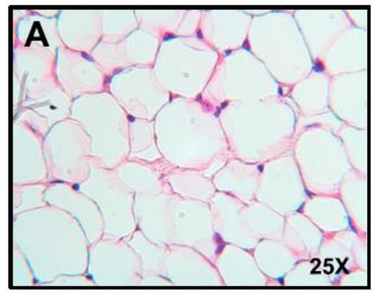
Kumar & Kaufman, 2018

Tecido adiposo

TAM

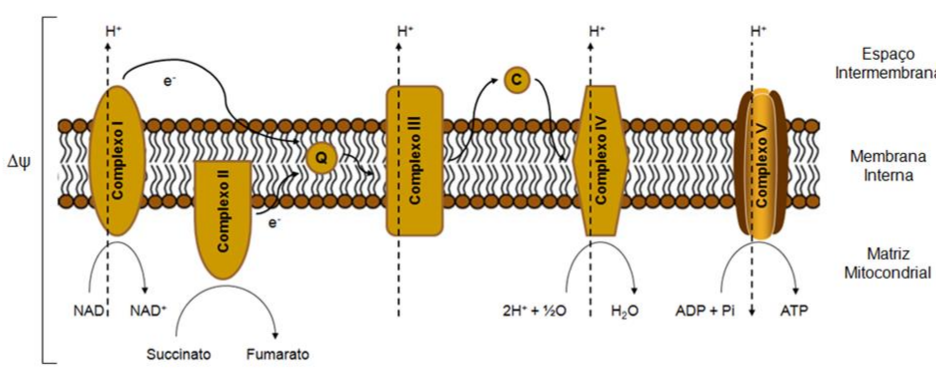


TAB



Fitzgibbons et al., 2011

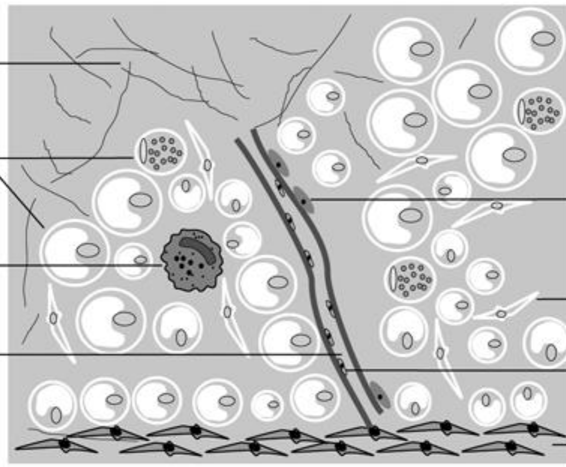
Tecido marrom



UCP-1

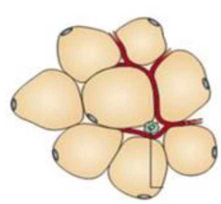
JunqueNelson & Cox, 2006

Tecido adiposo branco



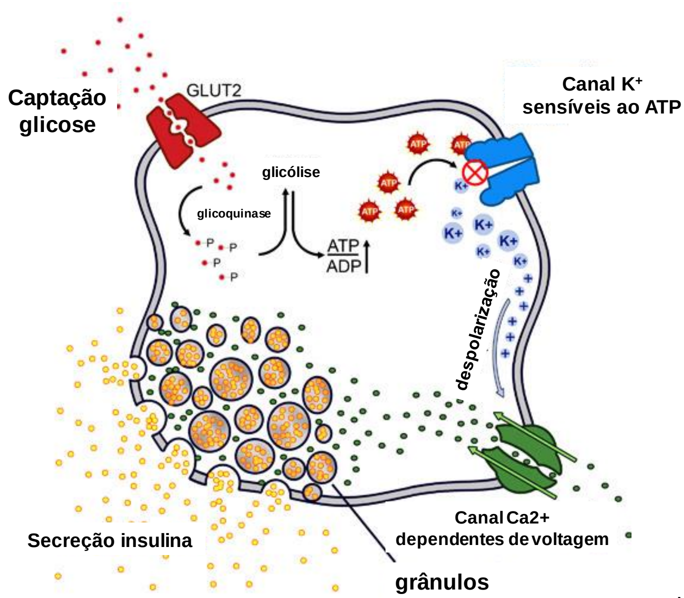
Ahima & Flier, 2000; Wajchenberg, 2010; Fonseca-Alaniz et al., 2016

Tecido adiposo



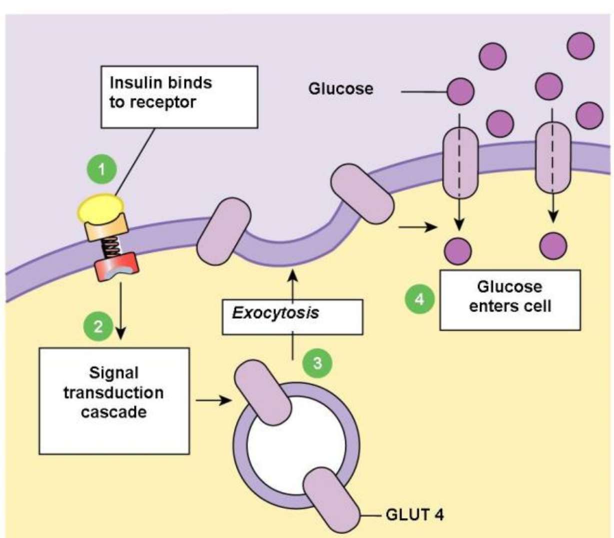
Fonseca-Alaniz et al., 2006; Lafontan et al., 2009

História



Mueller et al., 1925

História



Mueller et al., 1925

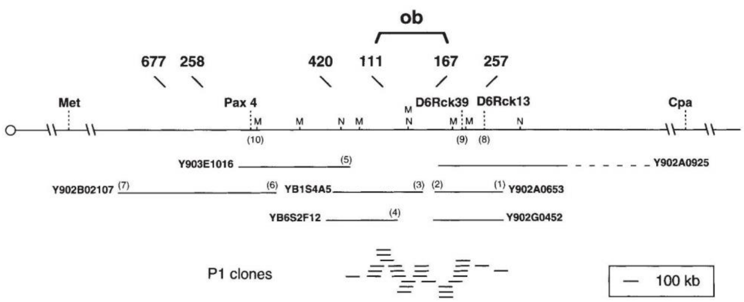
História

Positional cloning of the mouse *obese* gene and its human homologue

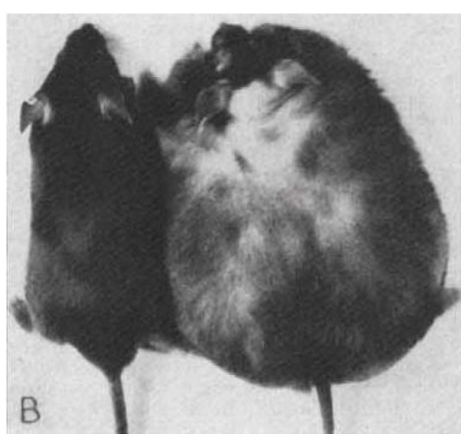
Yiying Zhang[*†], **Ricardo Proenca**[*†], **Margherita Maffei**[†], **Marisa Barone**[*†], **Lori Leopold**[*†] **& Jeffrey M. Friedman**[*†‡]

[*] Howard Hughes Medical Institute, † The Rockefeller University, 1230 York Avenue, New York, New York 10021, USA

The mechanisms that balance food intake and energy expenditure determine who will be obese and who will be lean. One of the molecules that regulates energy balance in the mouse is the *obese* (*ob*) gene. Mutation of *ob* results in profound obesity and type II diabetes as part of a syndrome that resembles morbid obesity in humans. The *ob* gene product may function as part of a signalling pathway from adipose tissue that acts to regulate the size of the body fat depot.



História



Zhang et al., 1994

História

ARTICLES

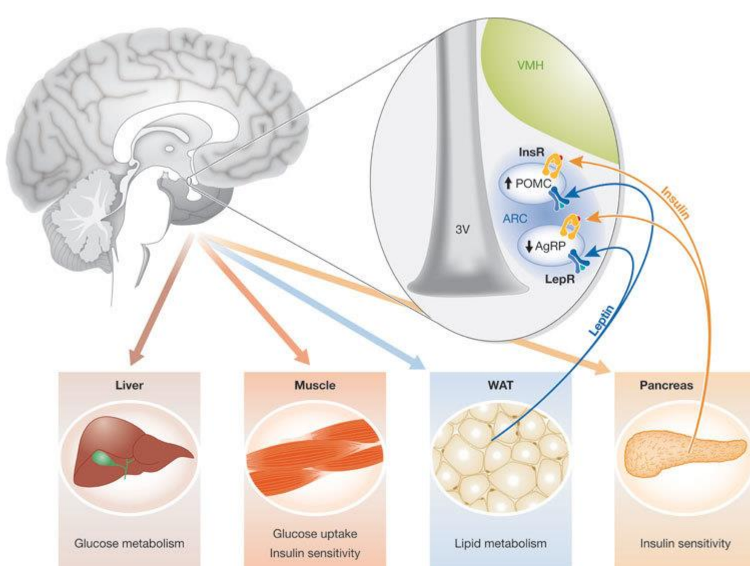
Leptin levels in human and rodent: Measurement of plasma leptin and *ob* RNA in obese and weight-reduced subjects

M. Maffei[1], J. Halaas[1], E. Ravussin[2], R.E. Pratley[2], G.H. Lee[1,5], Y. Zhang[1,5], H. Fei[1], S. Kim[1], R. Lallone[3], S. Ranganathan[4], P.A. Kern[4] & J.M. Friedman[1,5]

[1]Laboratory of Molecular Genetics, the Rockefeller University, 1230 York Avenue, New York, New York 10021, USA
[2]Clinical Diabetes and Nutrition Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 4212 North 16th Street, Room 541-A, Phoenix, Arizona 85016, USA
[3]Brookwood Biomedical ACC ste. 515, 2022 Brookwood Medical Center Drive, Birmingham, Alabama 35209, USA
[4]Cedars-Sinai Medical Center, Los Angeles, California 90048, USA
[5]Howard Hughes Medical Institute, the Rockefeller University, 1230 York Avenue, New York, New York 10021, USA
P.A.K. present address: Associate Chief of Staff, Research, Veterans Affairs Medical Center, Little Rock, Arkansas 72205, USA
Correspondence should be addressed to J.M.F.

Leptin, the gene product of the *obese* gene, may play an important role in regulating body weight by signalling the size of the adipose tissue mass. Plasma leptin was found to be highly correlated with body mass index (BMI) in rodents and in 87 lean and obese humans. In humans, there was variability in plasma leptin at each BMI suggesting that there are differences in its secretion rate from fat. Weight loss due to food restriction was associated with a decrease in plasma leptin in samples from mice and obese humans.

História



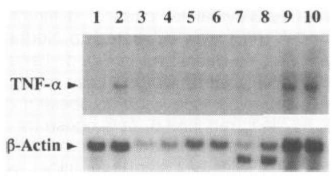
Varela & Horvath, 2012

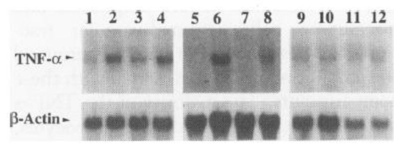
História

Adipose Expression of Tumor Necrosis Factor–α: Direct Role in Obesity-Linked Insulin Resistance

Gökhan S. Hotamisligil, Narinder S. Shargill,
Bruce M. Spiegelman*

Tumor necrosis factor–α (TNF-α) has been shown to have certain catabolic effects on fat cells and whole animals. An induction of TNF-α messenger RNA expression was observed in adipose tissue from four different rodent models of obesity and diabetes. TNF-α protein was also elevated locally and systemically. Neutralization of TNF-α in obese *fa/fa* rats caused a significant increase in the peripheral uptake of glucose in response to insulin. These results indicate a role for TNF-α in obesity and particularly in the insulin resistance and diabetes that often accompany obesity.





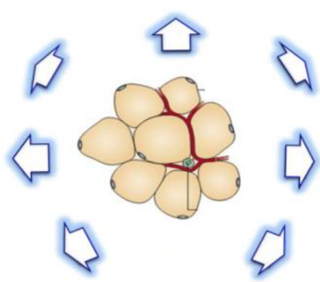
Tecido adiposo como órgão endócrino

"Proteína sintetizada e secretada pelo tecido adiposo"

↑ Leptina

↓ Adiponectina

Chemerim ↑



↑ TNF-α

PAI-1↑

↑ Aldosterona

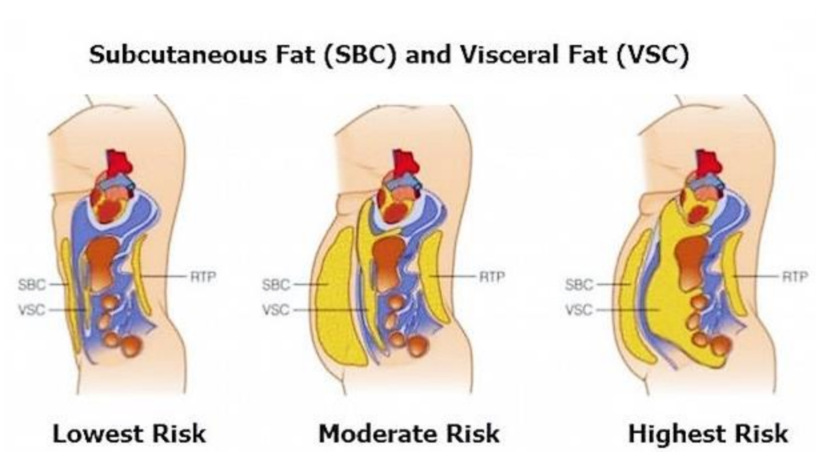
Resistina ↑

Disfunção cardiovascular?

Funahashi et al., 1999; Trayhurn & Wood, 2004; Dulloo & Montani, 2010

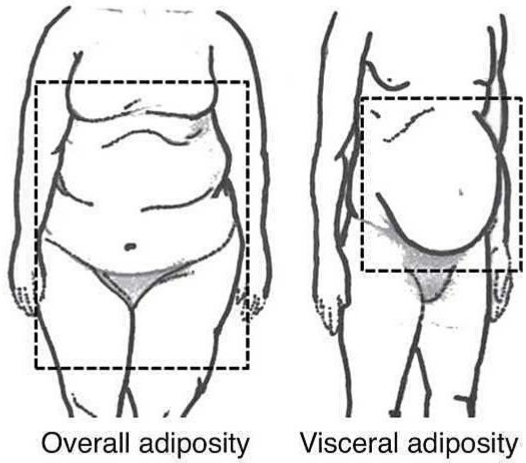
Quais os impactos da obesidade sobre o Sistema Cardiovascular?

Eventos associados à obesidade



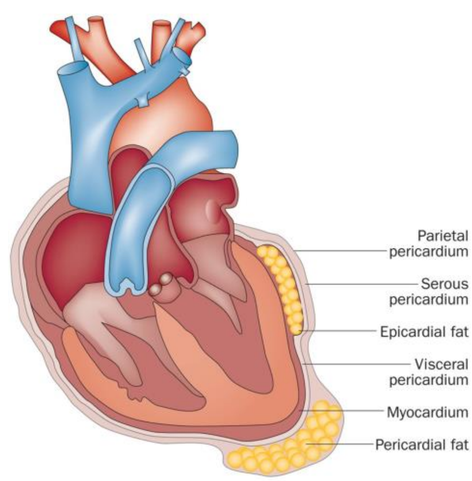
Nakamura et al., 2000

Eventos associados à obesidade



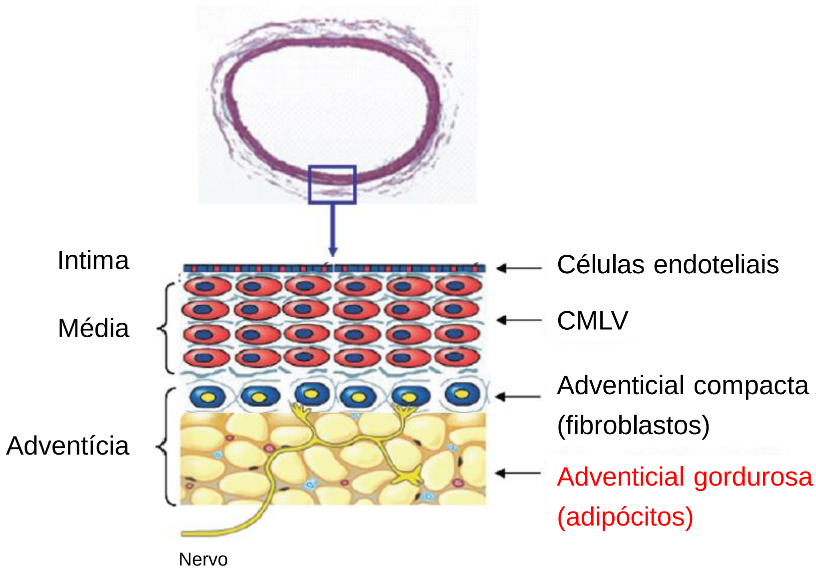
Nakamura et al., 2000

Tecido adiposo pericárdico



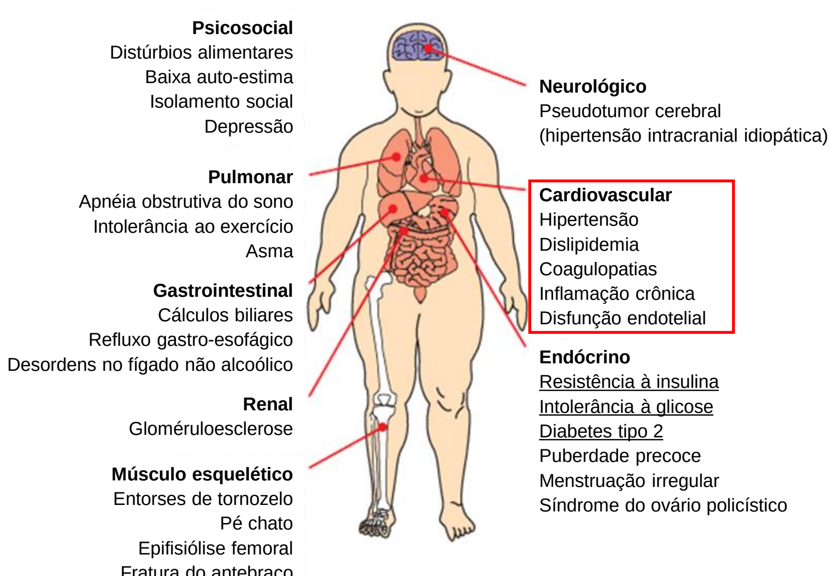
Iacobellis, 2015

Tecido adiposo perivascular (PVAT)



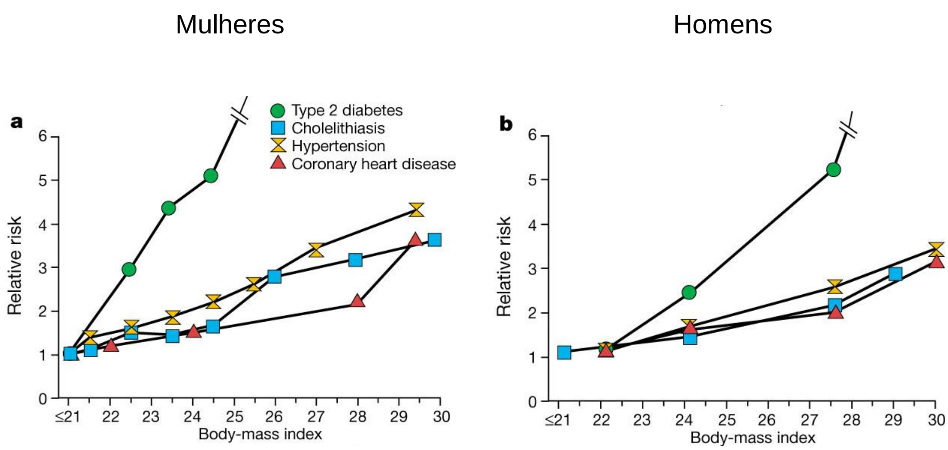
Soltis & Cassis, 1991

Eventos associados à obesidade

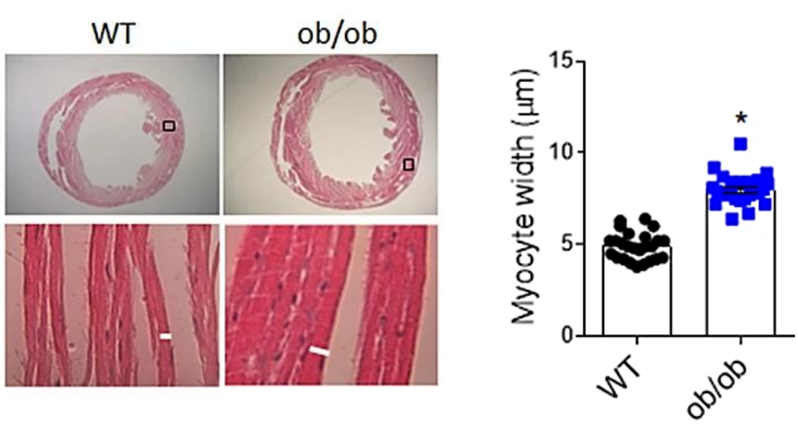


Afonso & Sichieri, 2002; Lopes, 2007

Eventos associados à obesidade

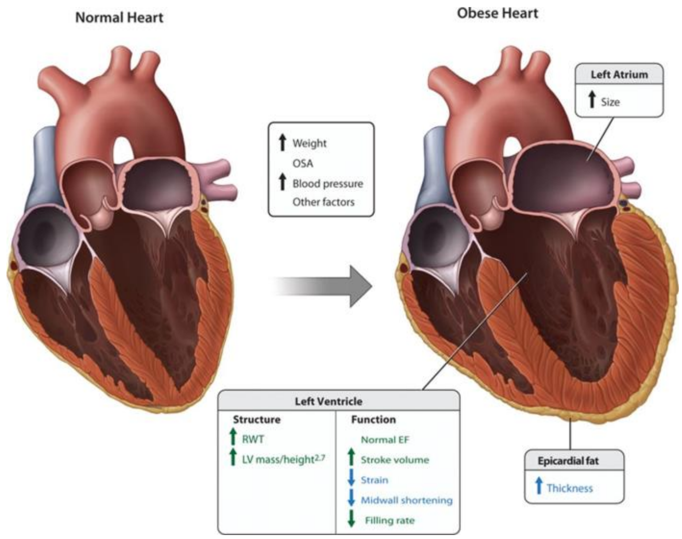


Disfunção cardíaca na obesidade



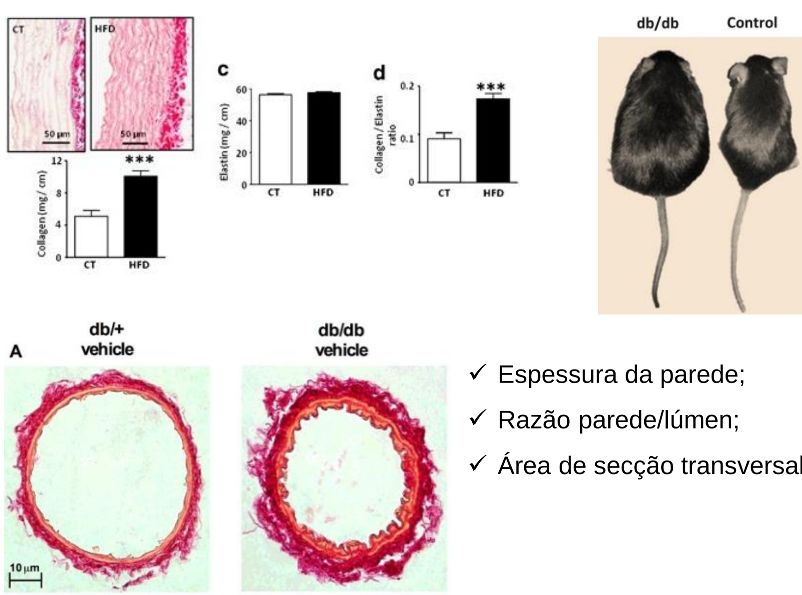
An et al., 2020

Disfunção cardíaca na obesidade



Aurigemma et al., 2013

Disfunção vascular na obesidade

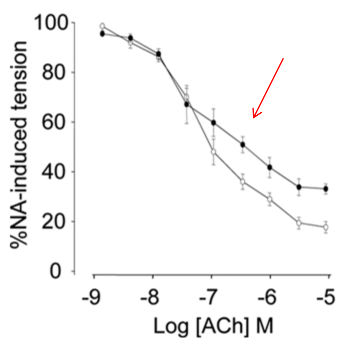


- ✓ Espessura da parede;
- ✓ Razão parede/lúmen;
- ✓ Área de secção transversal.

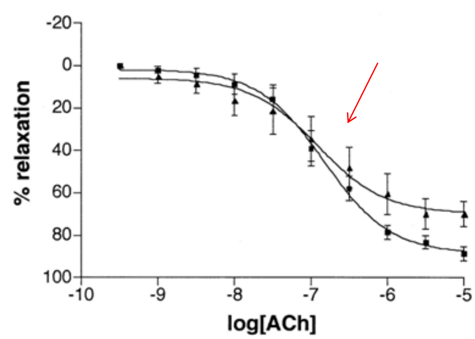
Martínez et al., 2014; Silva et al., 2015

Disfunção vascular na obesidade

Dieta hiperlipídica



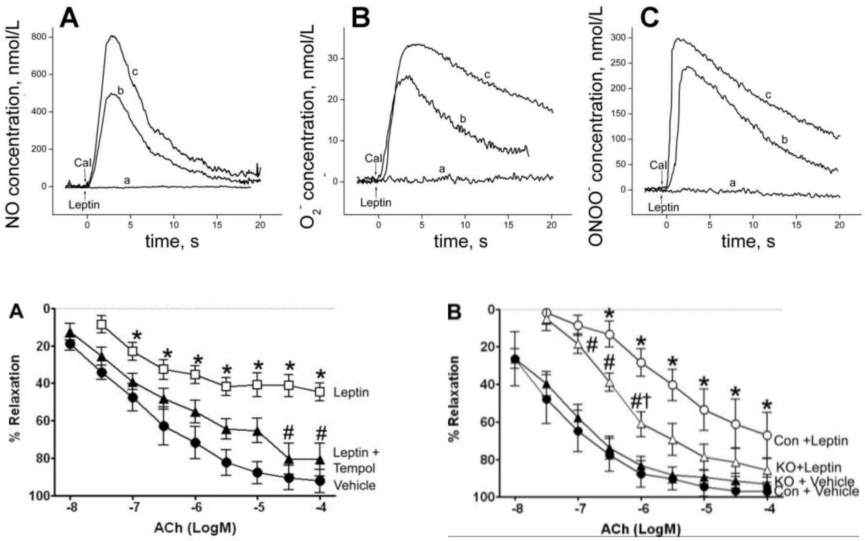
Ob/Ob



Winters et al., 2000; Samuelsson et al., 2008

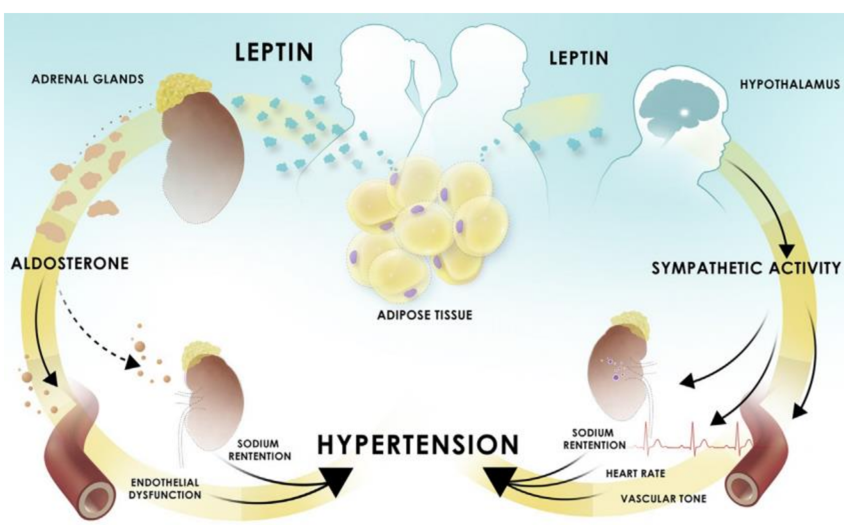
Mecanismos envolvidos?

Leptina induz disfunção vascular



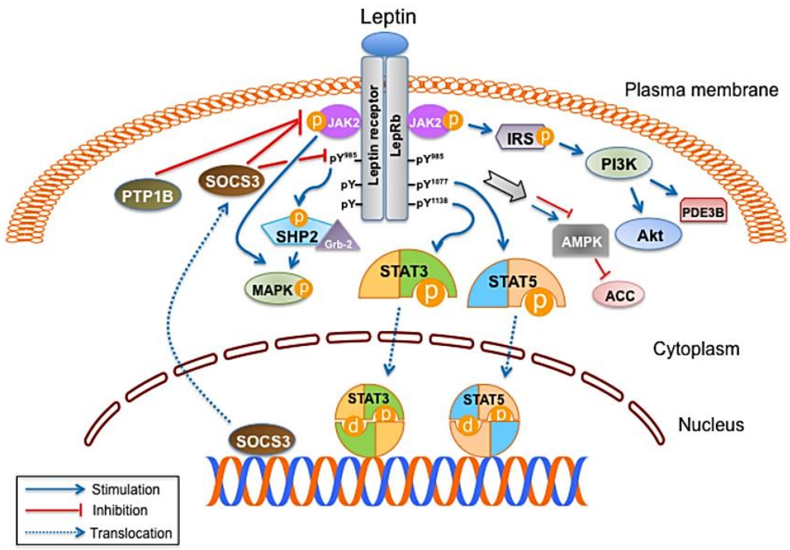
Korda et al., 2008; Ryan et al., 2016

Leptina induz disfunção vascular



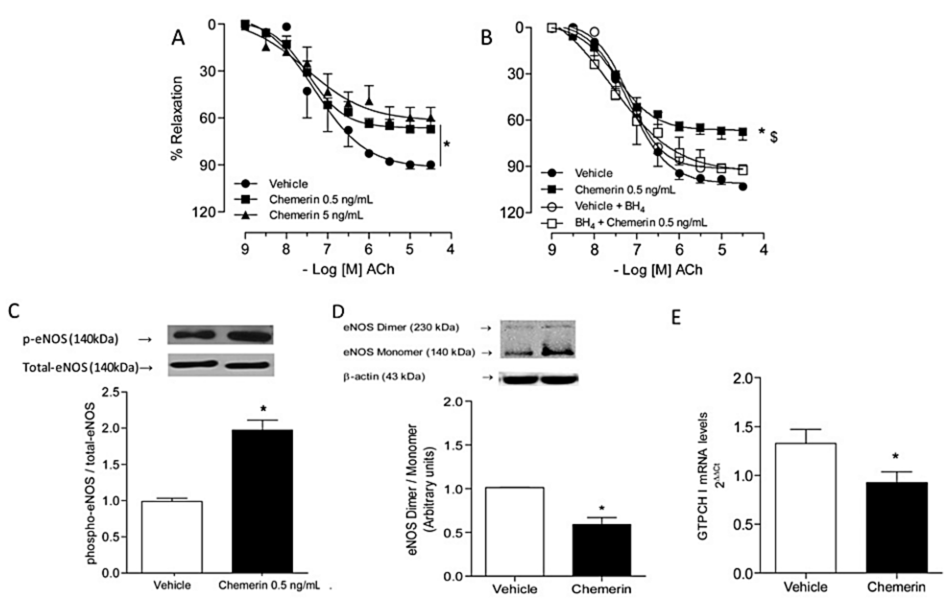
Faulkner & Belin de Chantemele, 2019

Leptina induz disfunção vascular



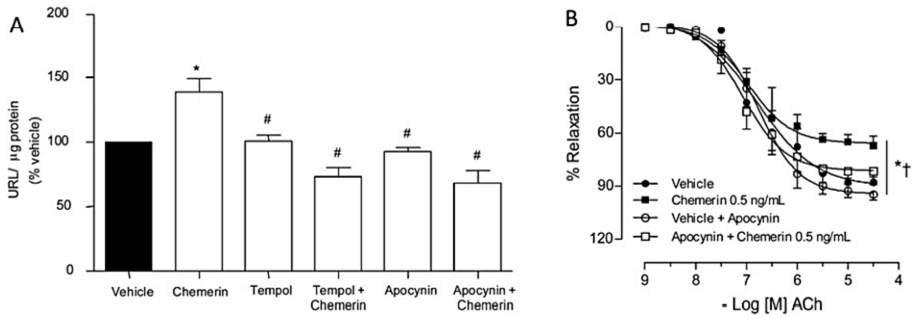
Park & Ahima, 2017

Chemerin induz disfunção vascular



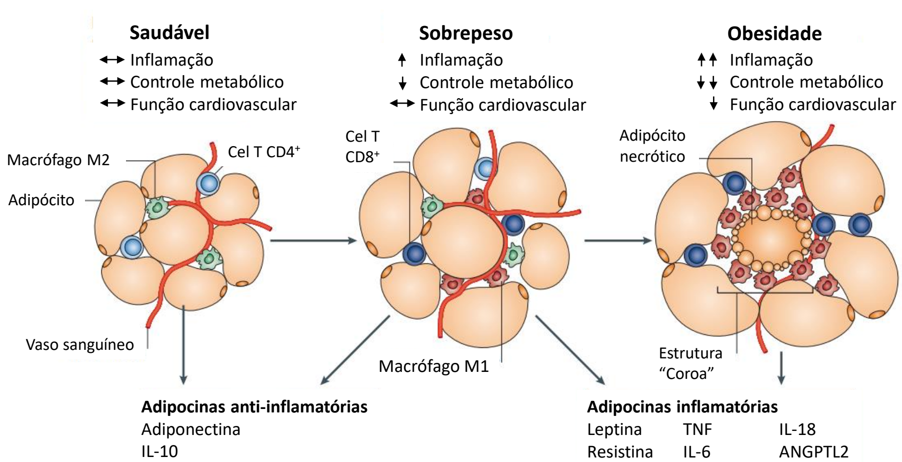
Neves et al., 2014

Chemerin induz disfunção vascular



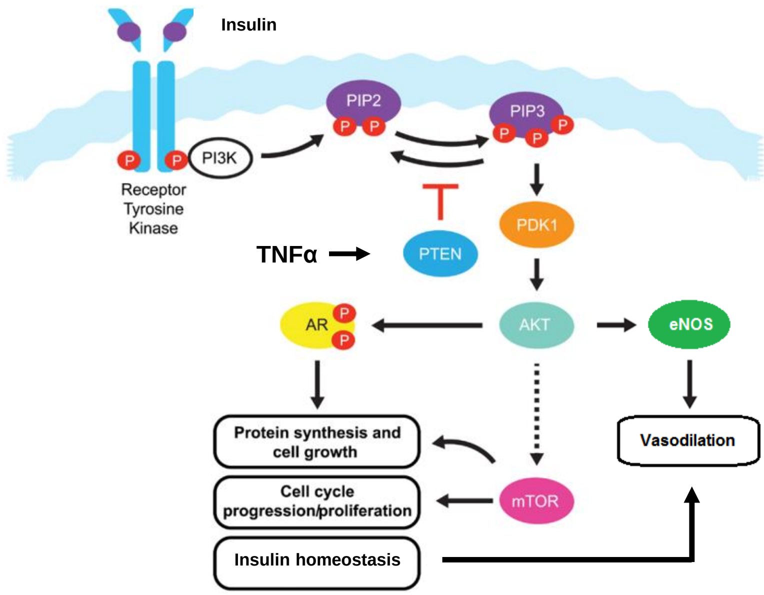
Neves et al., 2014

Inflamação do tecido adiposo na obesidade



Adaptado de Ouchi et al., 2012

Insulina



Adapted from Phin et al., 2013

Four week-old male

C57Bl/6J and **TNF-α receptor knockout mice**

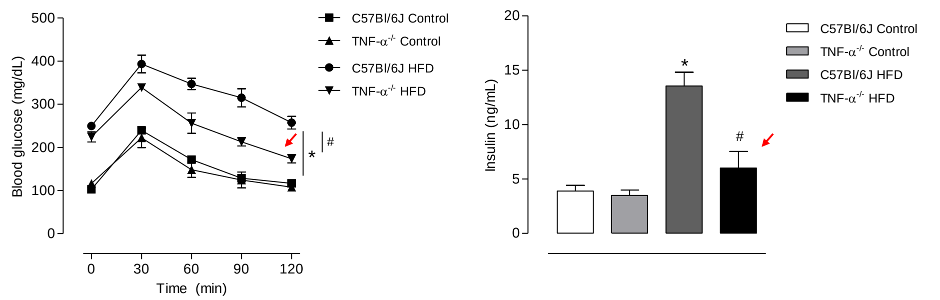
↓

18 weeks

Control diet 22% protein 70% carbohydrate 8% energy	→ 3,4 kcal/g	**High-fat diet** 10% protein 25% carbohydrate 65% energy	→ 9,6 kcal/g

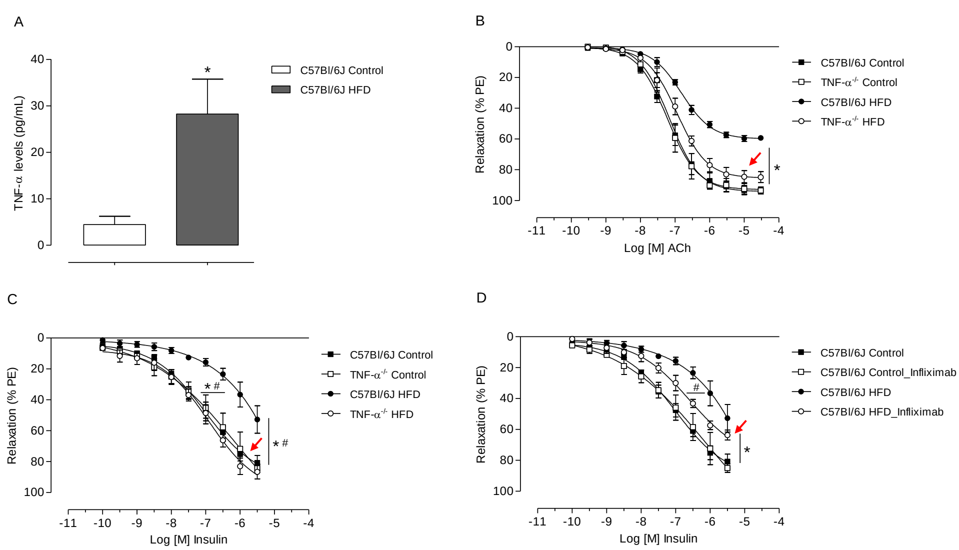
- Vascular reactivity: concentration-effect curves to Insulin in mesenteric arteries

TNF-α contributes to glucose intolerance and increased insulin levels in HFD-fed mice



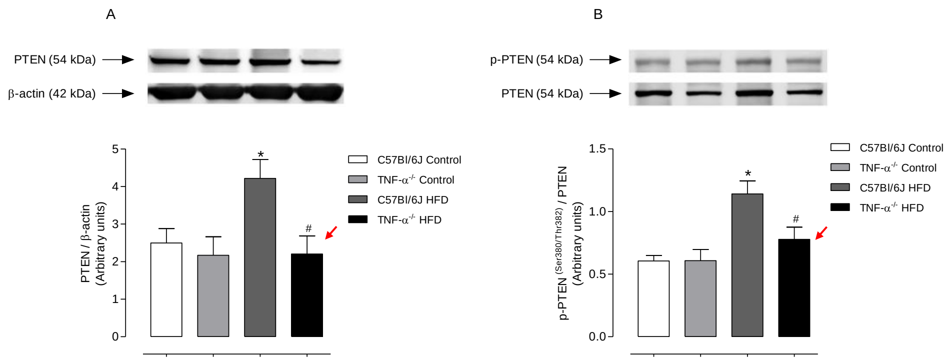
Data are expressed as mean ± SEM (n=8-10). *p<0.05 *vs*. C57Bl/6J Control; #p<0.05 *vs*. C57Bl/6J HFD

TNF-α decreases vascular relaxation in HFD-fed mice



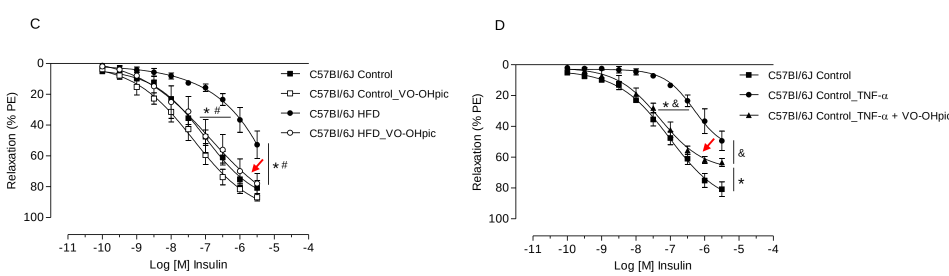
Data are expressed as mean ± SEM (n=8-10). *p<0.05 *vs*. C57Bl/6J Control; #p<0.05 *vs*. C57Bl/6J HFD

Vascular PTEN protein phosphorylation modulates insulin-induced relaxation in HFD-fed mice



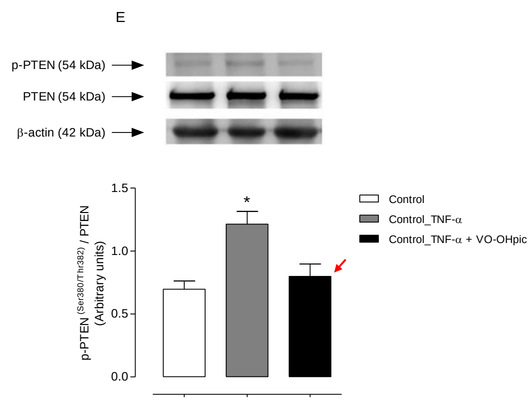
Data are expressed as mean ± SEM (n=8-10). *p<0.05 *vs*. C57Bl/6J Control; #p<0.05 *vs*. C57Bl/6J HFD

Vascular PTEN protein phosphorylation modulates insulin-induced relaxation in HFD-fed mice



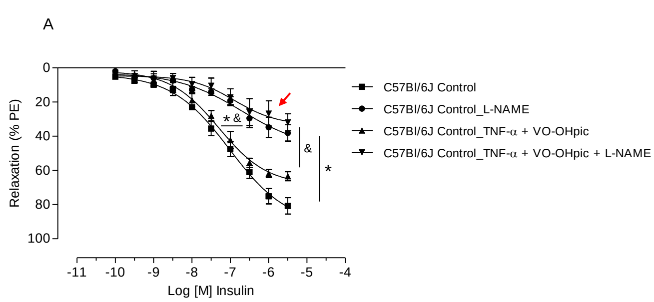
Data are expressed as mean ± SEM (n=8-10). *p<0.05 *vs*. C57Bl/6J Control; #p<0.05 *vs*. C57Bl/6J HFD

Vascular PTEN protein phosphorylation modulates insulin-induced relaxation in HFD-fed mice



Data are expressed as mean ± SEM (n=8-10). *p<0.05 *vs*. C57Bl/6J Control; #p<0.05 *vs*. C57Bl/6J HFD

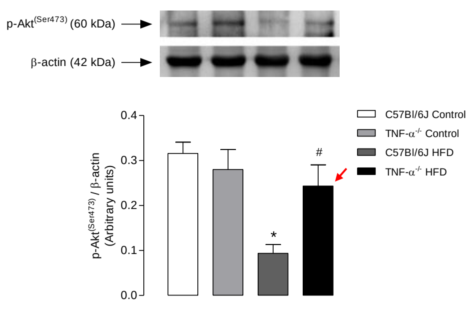
TNF-α contributes to decreased Akt/NO signaling in HFD-fed mice



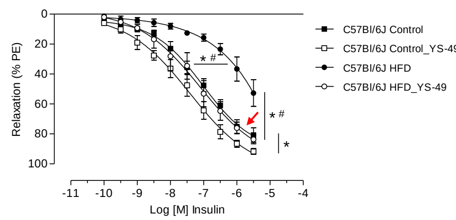
Data are expressed as mean ± SEM (n=8-10). *p<0.05 *vs*. C57Bl/6J Control; #p<0.05 *vs*. C57Bl/6J HFD

TNF-α contributes to decreased Akt/NO signaling in HFD-fed mice

B

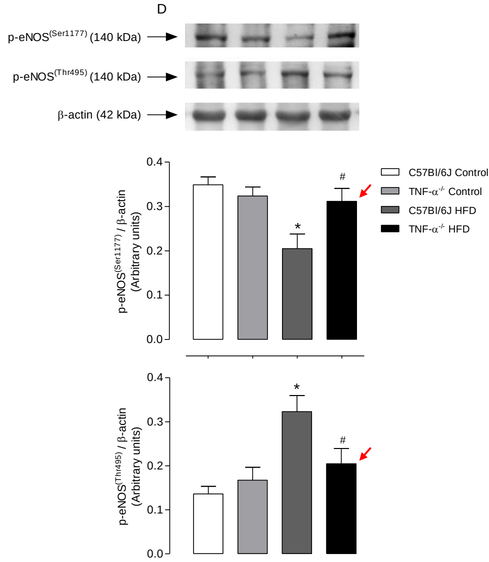


C

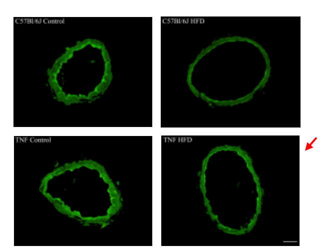


Data are expressed as mean ± SEM (n=8-10). *$p<0.05$ *vs*. C57Bl/6J Control; #$p<0.05$ *vs*. C57Bl/6J HFD

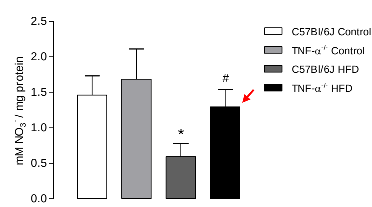
D



E



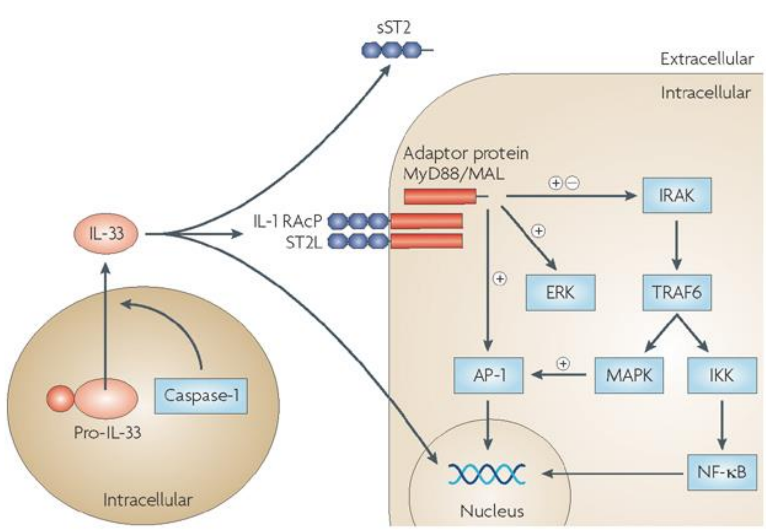
F



Data are expressed as mean ± SEM (n=8-10). *$p<0.05$ *vs*. C57Bl/6J Control; #$p<0.05$ *vs*. C57Bl/6J HFD

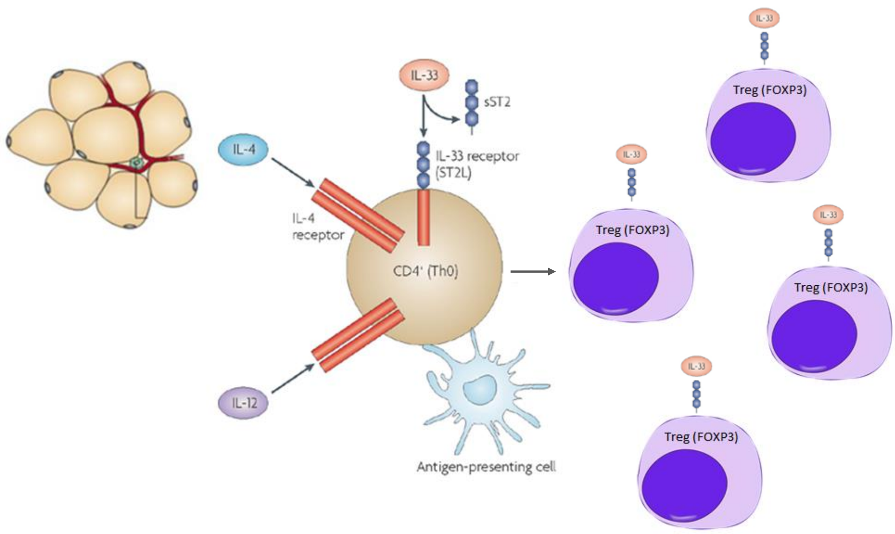
TNF-α induces vascular insulin resistance by increasing PTEN activity that negatively modulates Akt/eNOS/NO signaling and insulin vasodilation.

Interleucina 33



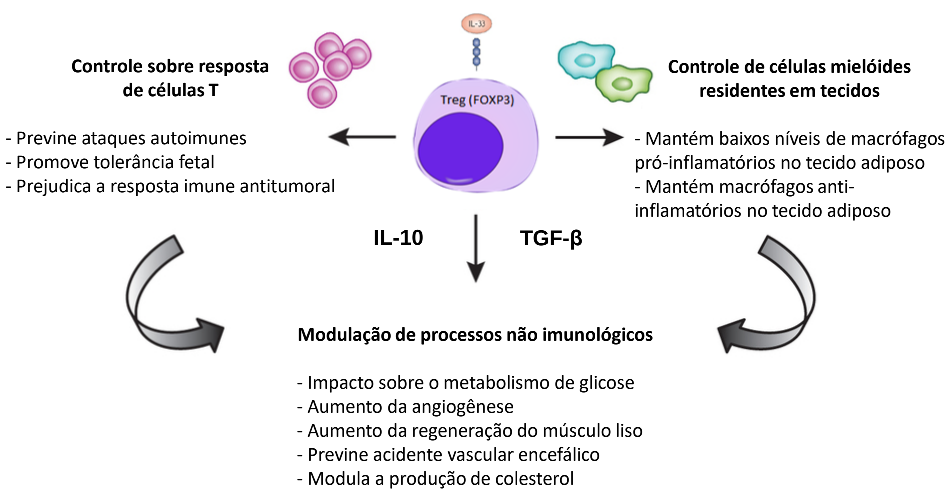
Kakkar et al., 2008

Interleucina 33 e Célula T reguladora



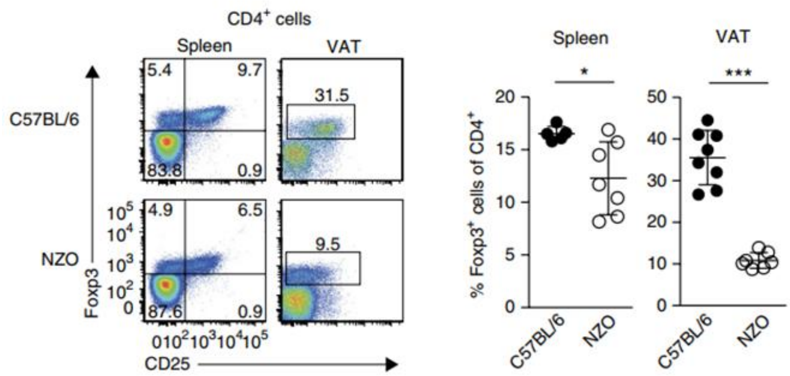
Adaptado de Kakkar et al., 2008

Célula T reguladora



Adaptado de Burzyn et al. 2013

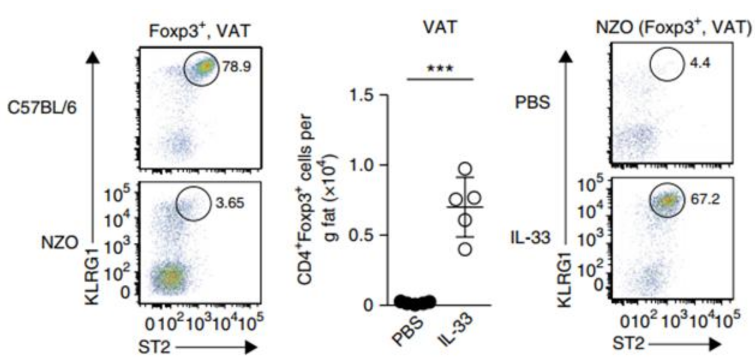
Célula T reguladora e obesidade



A obesidade reduz a população de Tregs no tecido adiposo

Vasanthakumar et al. 2015

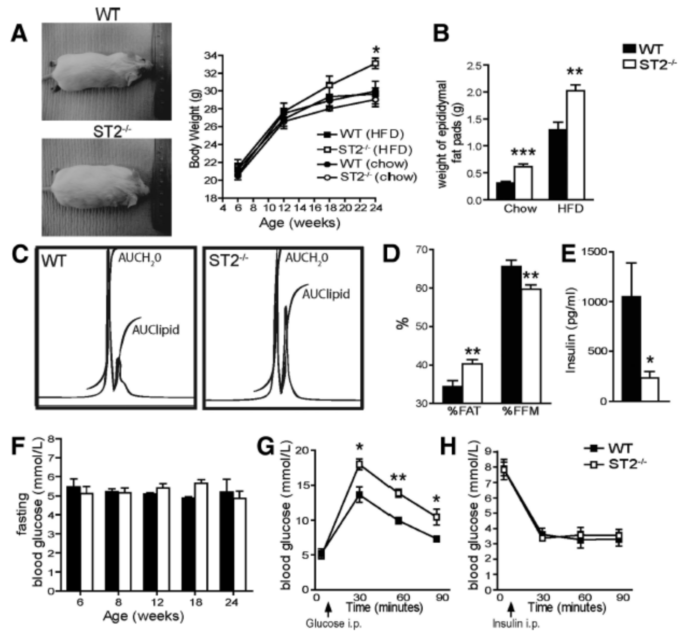
Célula T reguladora e obesidade



A diminuição de Tregs no tecido adiposo é mediada pela IL-33

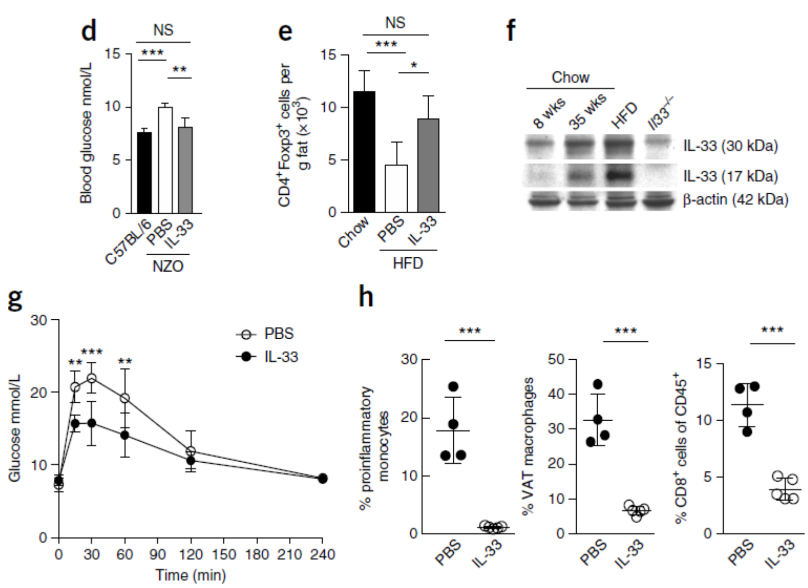
Vasanthakumar et al. 2015

IL-33/ST2 e obesidade

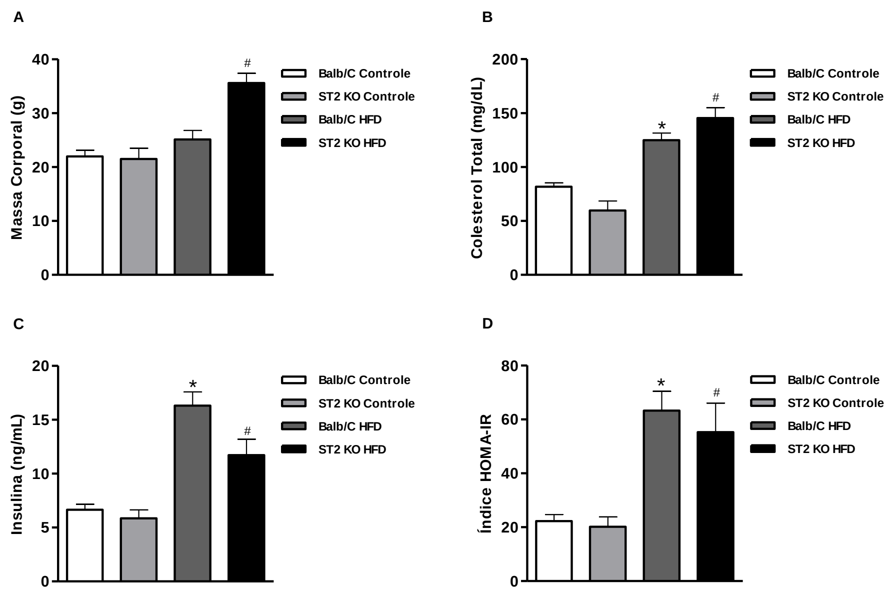


Miller et al. 2011

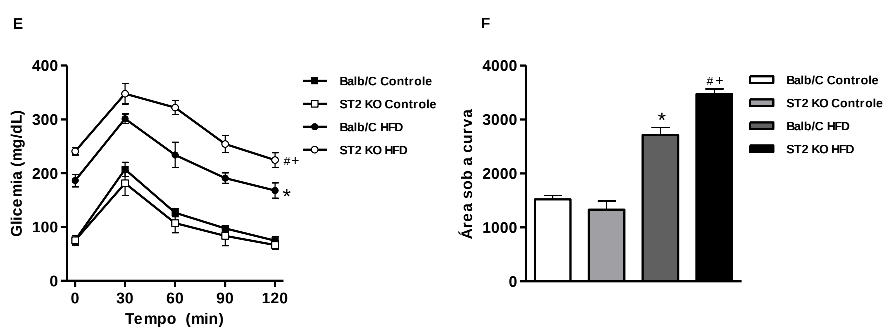
IL-33/ST2 e obesidade



Vasanthakumar et al. 2015



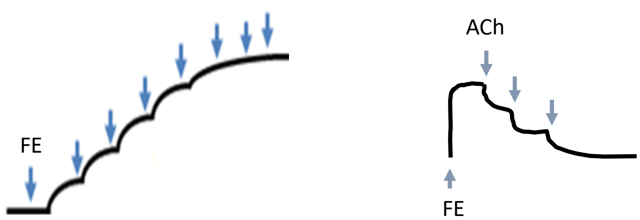
n=7-8/grupo. *, p<0,05 vs. Balb/C Controle; #, p<0,05 vs. ST2 KO Controle; +, p<0,05 vs. Balb/C HFD

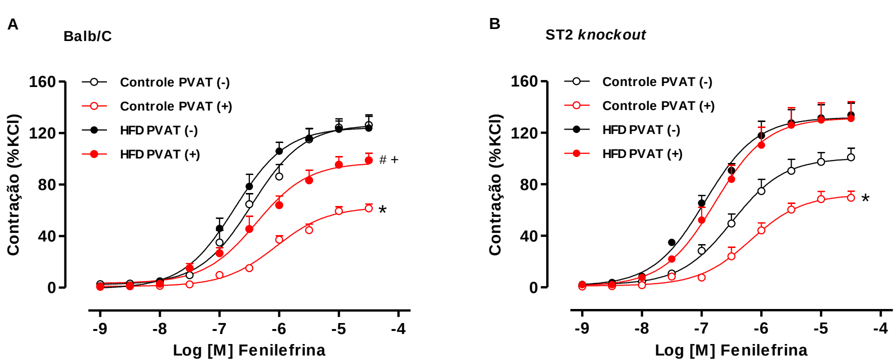


A dieta hiperlipídica compromete parâmetros metabólicos em camundongos Balb/C e *knockouts* para o receptor ST2

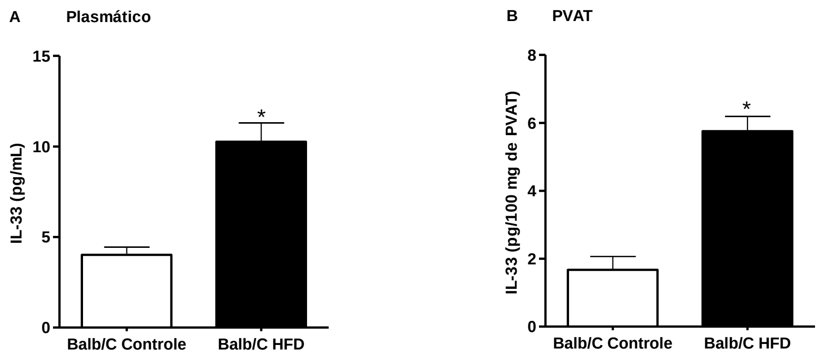
n=7-8/grupo. *, p<0,05 vs. Balb/C Controle; #, p<0,05 vs. ST2 KO Controle; +, p<0,05 vs. Balb/C HFD

Reatividade vascular – Balb/C e ST2 *knockouts*



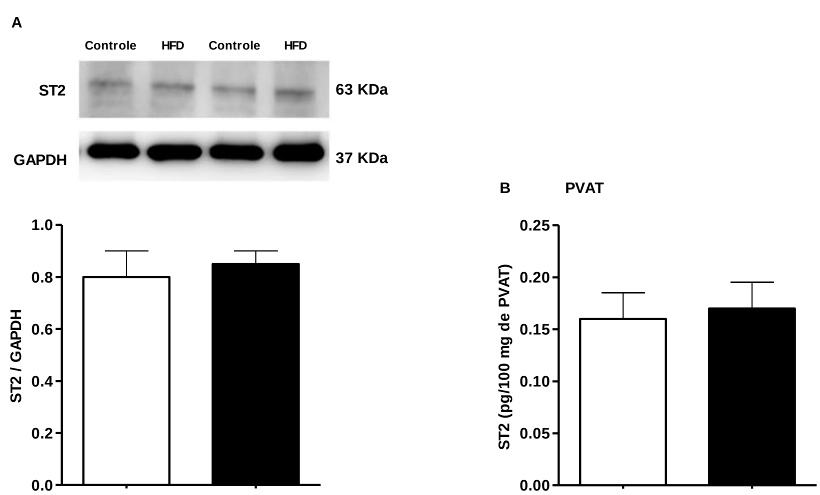


n=6-7/grupo. *, $p<0{,}05$ vs. Controle PVAT (-); #, $p<0{,}05$ vs. HFD PVAT (-); +, $p<0{,}05$ vs. Controle PVAT (+); π, $p<0{,}05$ vs. Balb/C HFD PVAT (+)

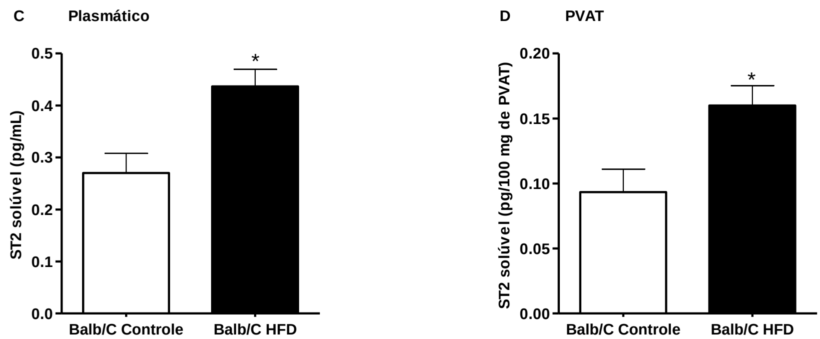


A dieta hiperlipídica aumenta os níveis de IL-33 no plasma e no PVAT que circunda artérias mesentéricas de resistência de camundongos Balb/C

n=5/grupo. *, p<0,05 vs. Balb/C Controle



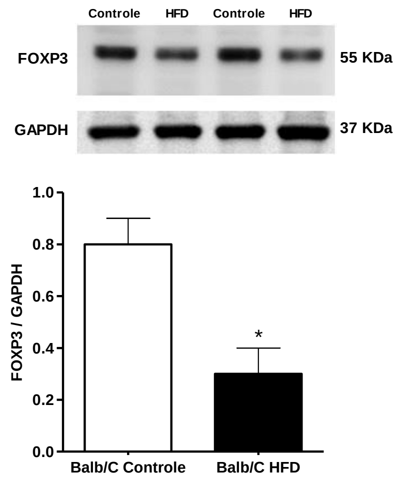
n=5/grupo. *, p<0,05 vs. Balb/C Controle



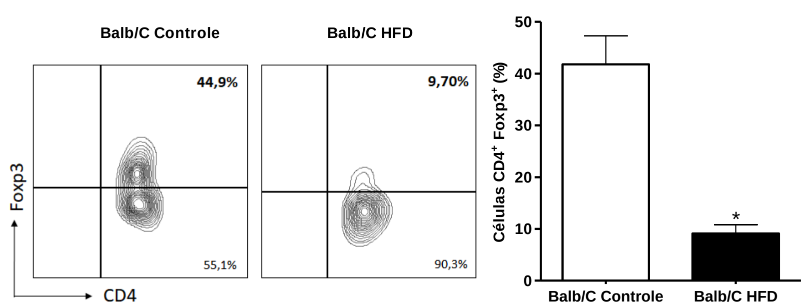
A dieta hiperlipídica aumenta os níveis de ST2 solúvel no plasma e no PVAT que circunda artérias mesentéricas de resistência de camundongos Balb/C

n=5/grupo. *, p<0,05 vs. Balb/C Controle

População de Tregs



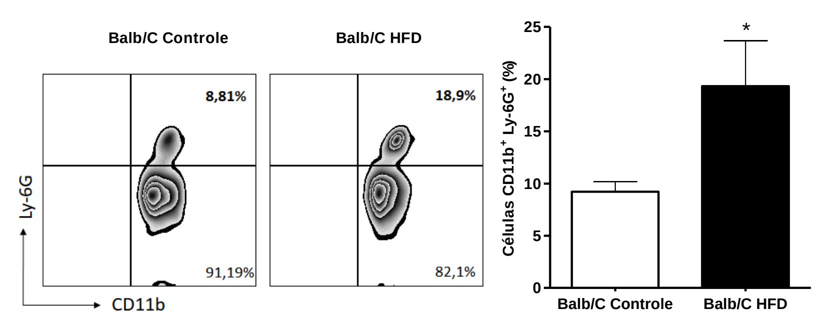
n=5/grupo. *, p<0,05 vs. Balb/C Controle



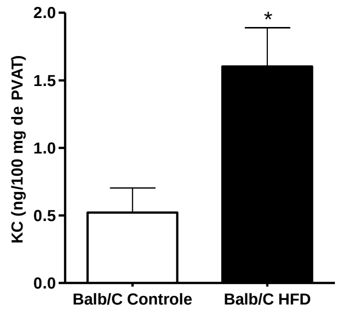
Dieta hiperlipídica promove diminuição de Tregs no PVAT

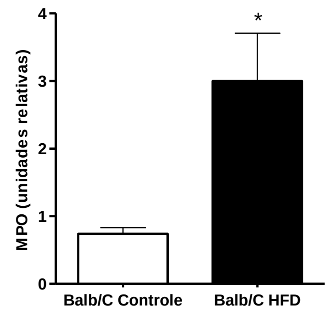
n=5-6/grupo. *, p<0,05 vs. Balb/C Controle

Inflamação



n=5-6/grupo. *, p<0,05 vs. Balb/C Controle

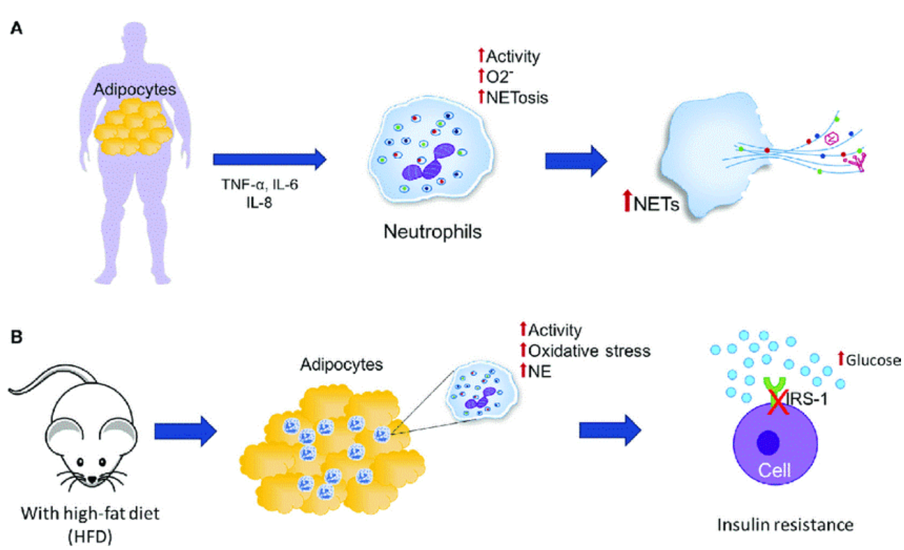




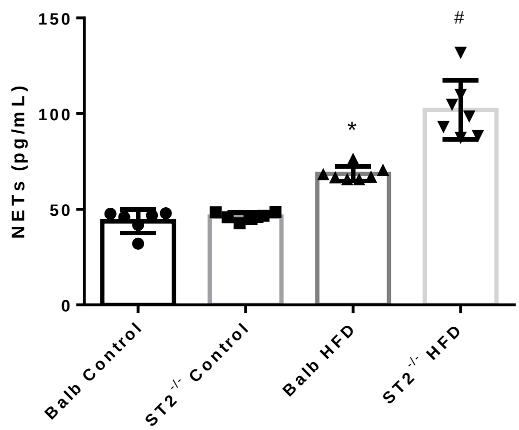
Dieta hiperlipídica promove aumento de neutrófilos no PVAT

n=5-6/grupo. *, p<0,05 vs. Balb/C Controle

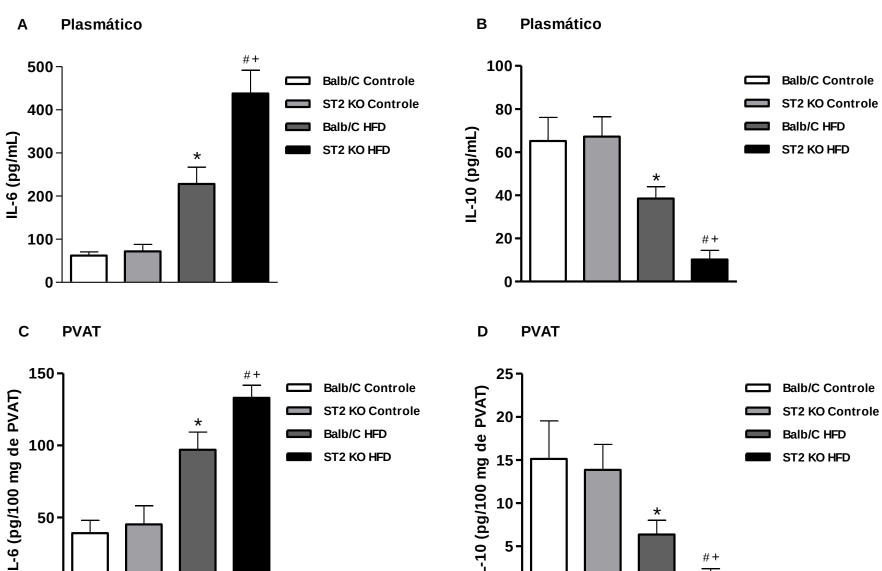
NETs



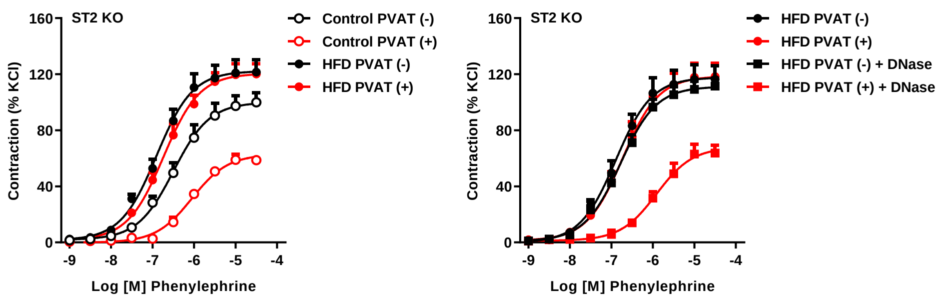
Rizo et al., 2017



n=7-8/grupo. *, p<0,05 vs. Balb/C Controle; #, p<0,05 vs. ST2 KO Controle; +, p<0,05 vs. Balb/C HFD



n=5/grupo. *, p<0,05 vs. Balb/C Controle; #, p<0,05 vs. ST2 KO Controle; +, p<0,05 vs. Balb/C HFD



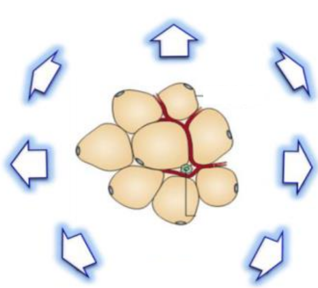
Destruir NETs restaura a função do PVAT e consequente função vascular

Conclusão

↑ Leptina

↓ Adiponectina

Chemerim ↑



↑ TNF-α

PAI-1 ↑

↑ Aldosterona

Resistina ↑

Disfunção cardiovascular!

Obrigado!