Nouvelles fonctions de CD36, une protéine avec trop de tâches

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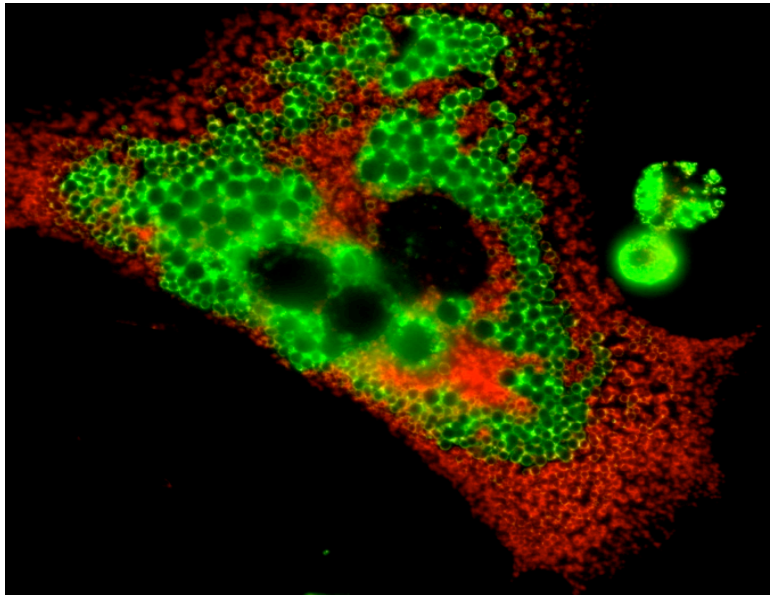
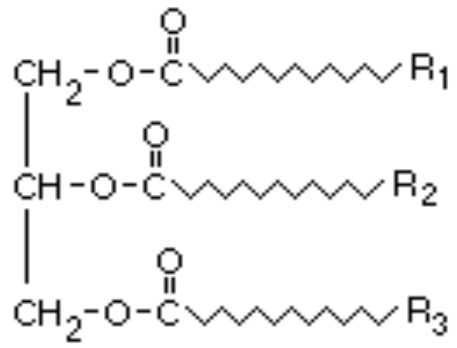
Je déclare l'absence de conflits d'intérêts financiers

FA STORED AS TG IN ADIPOSE TISSUE

- **Fatty acids from dietary sources are incorporated into tilgycerides and stored within lipid droplets in the cytoplasm.**



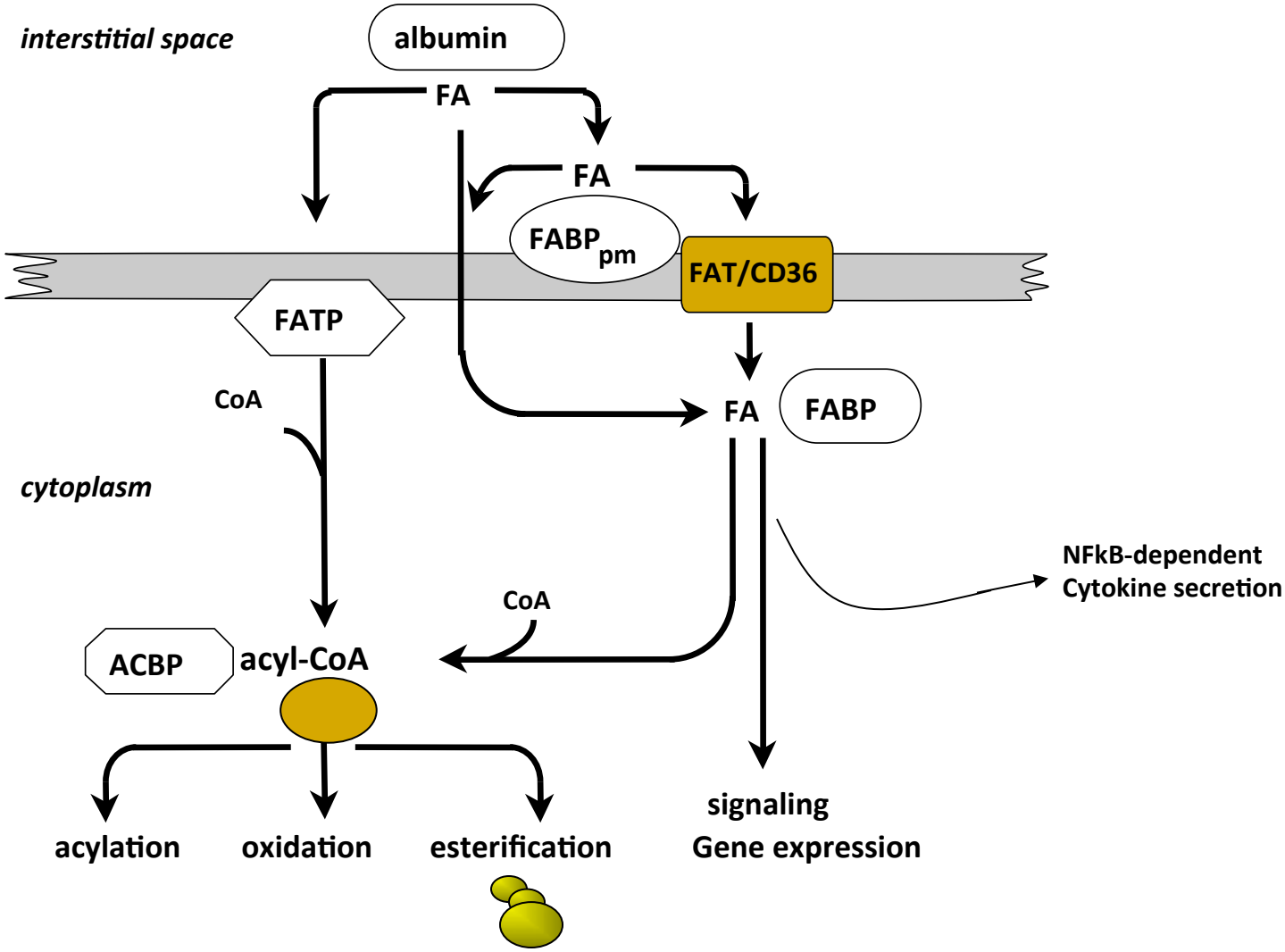
Adipose Cell (Wolins N)



A triacylglycerol

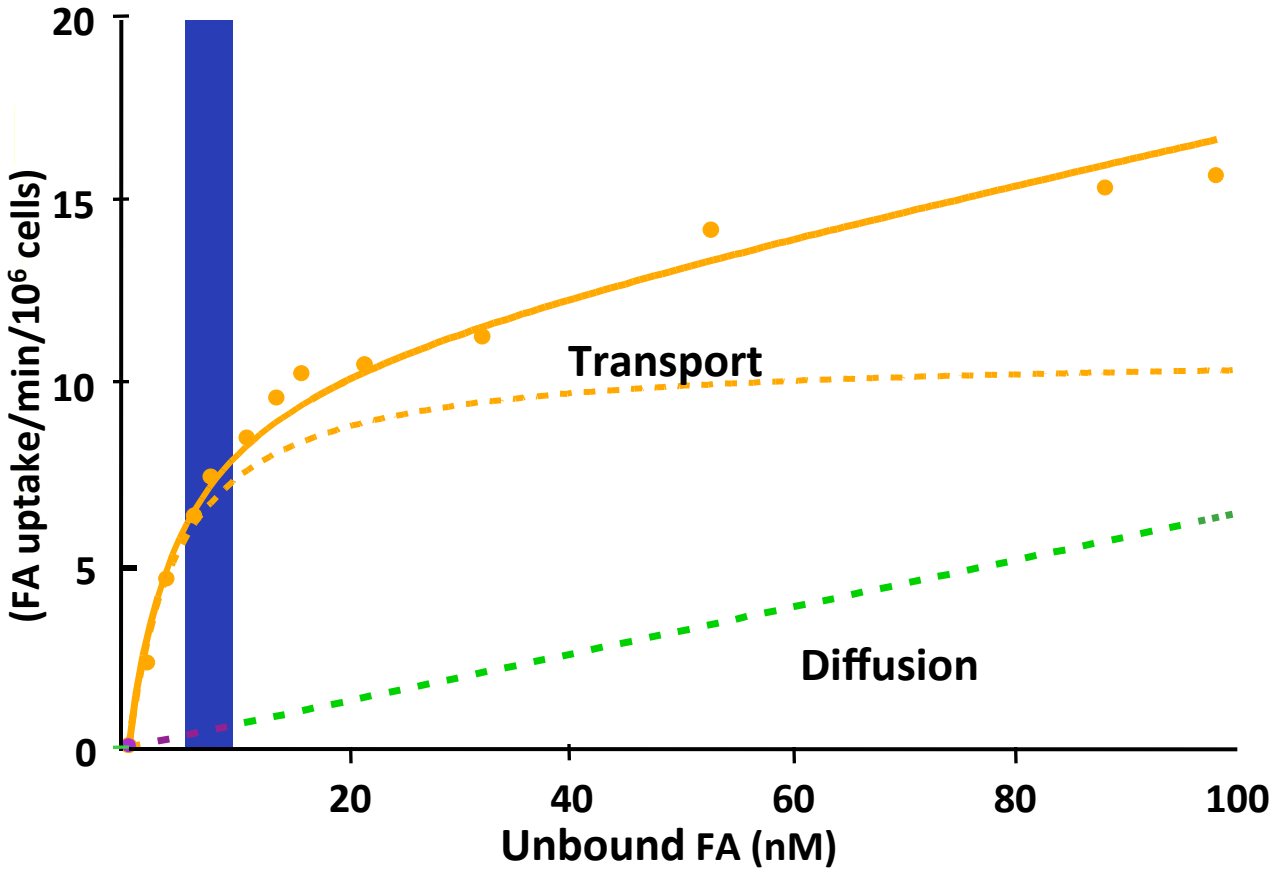
R_1 is often palmitate.
R_2 is often oleate.
R_3 is often oleate or a polyunsaturated fatty acyl group.

Fate of intracellular FA

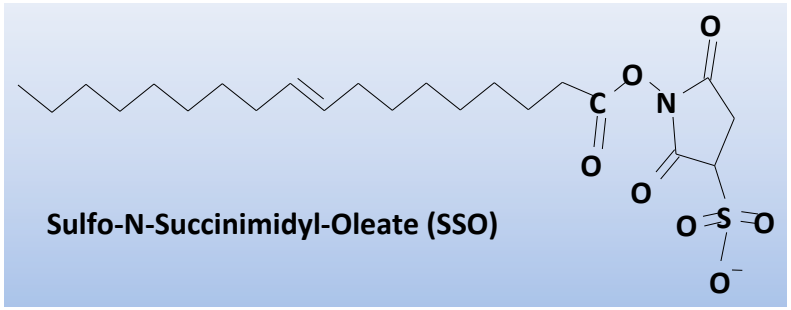


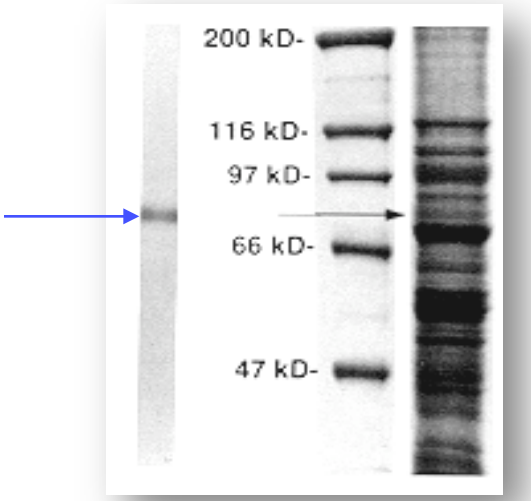
Koonen DPY et al (2005) *BBA* 1736, 163

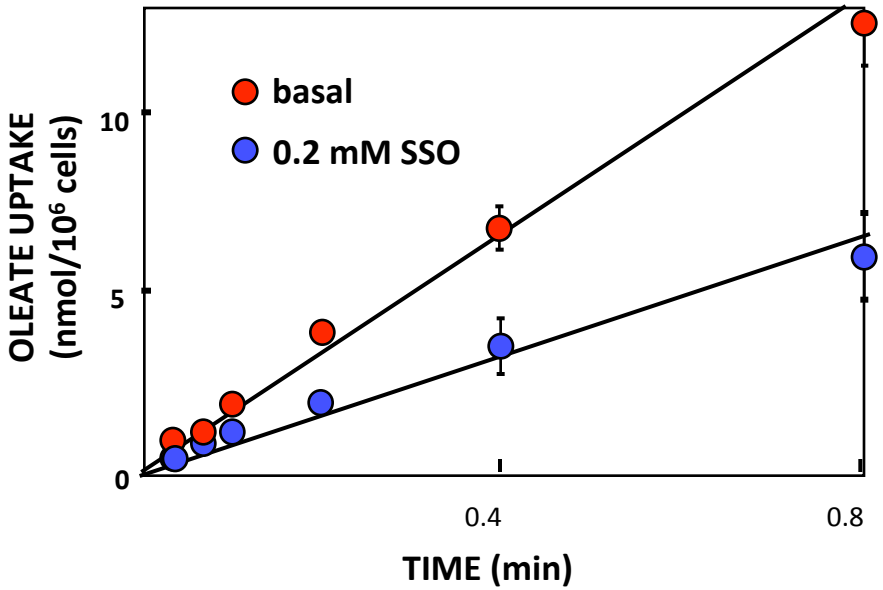
Two components of FA uptake in isolated fat cells



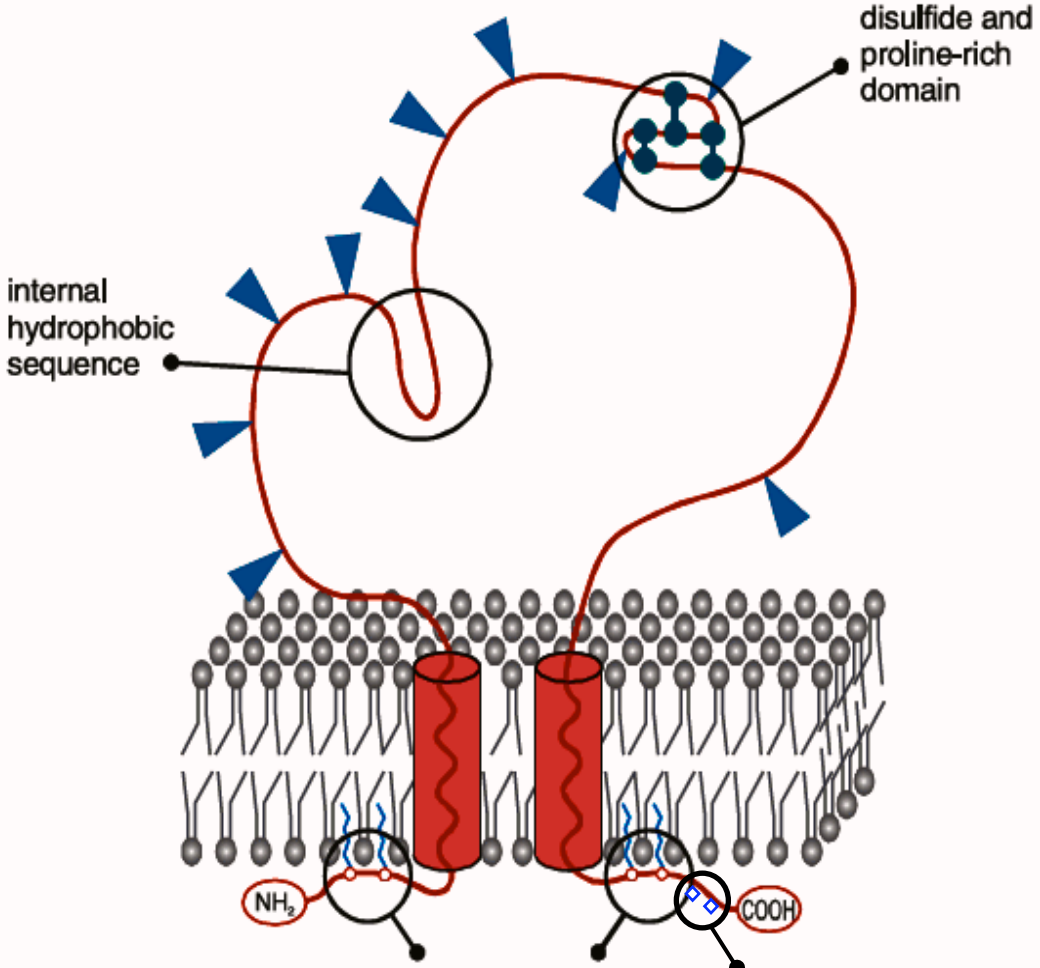
SSO inhibits FA transport & labels CD36







Harmon et al, J Memb Biol., 1993
Abumrad A et al., JBC, 1993


disulfide and
proline-rich
domain
internal
hydrophobic
sequence
NH2
COOH
N- & C-terminal
palmitoylations
K469 and K472 are sites of
ubiquitination

• **88-KD, 472 amino acid heavily glycosylated transmembrane protein**

•**Broad specificity. Ligands include lipids: LCFA, native or modified lipoproteins (HDL, VLDL, oxLDL) and non lipids: glycated proteins, thronbospondin-1 & 2, collagen, amyloid B, malaria infected-RBC.**

•**Abundant in heart, skeletal muscle, adipose tissue, intestine and the capillary endothelium, immune cells.**

•**CD36 binding to LCFA and other ligands is associated with signal transduction mostly through the Src kinases that interact with the carboxyl tail of the protein.**

•**CD36 deficiency is relatively common in populations of Asian or African ancestry (3-10%), uncommon in Caucasians <0.3%.**

•**Common polymorphisms in the CD36 gene in Caucasians and African Americans associate with blood lipids and with risk of the metabolic syndrome and stroke.**

(Reviewed in Silverstein R, 2009; Su and Abumrad, 2009, Love-Gregory and

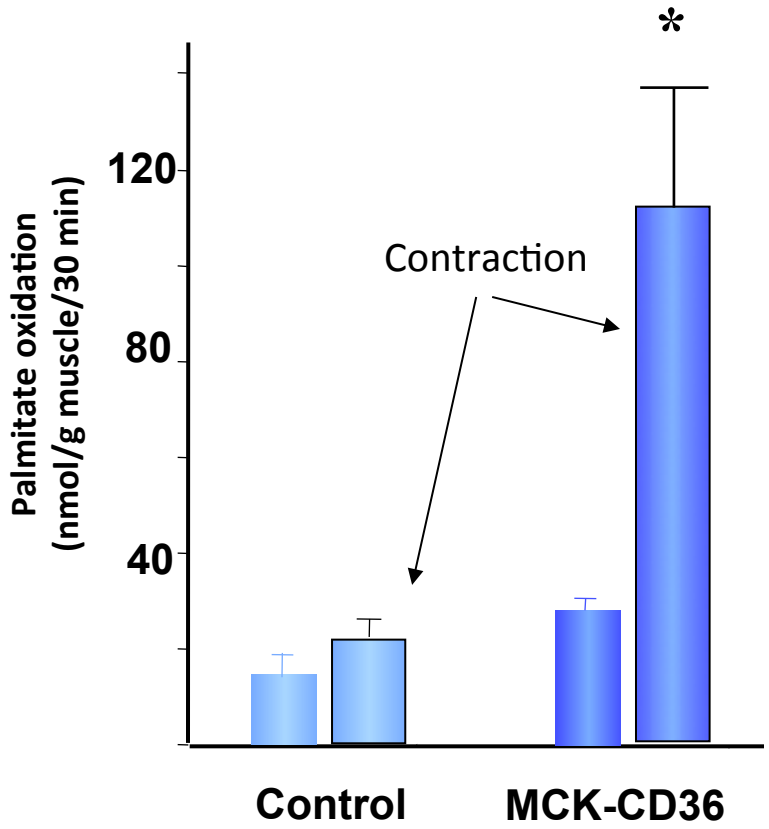
Evidence that CD36 Facilitates Membrane FA Transfer

- Over-expression/knockdown in cultured cells
- Mice with CD36 deficiency or over-expression
- Humans with CD36 deficiency or with polymorphisms in the CD36 gene

Metabolic Adaptation and Flexibility

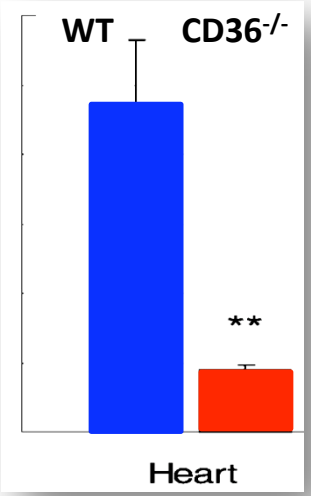
Mice with CD36 over-expression in muscle

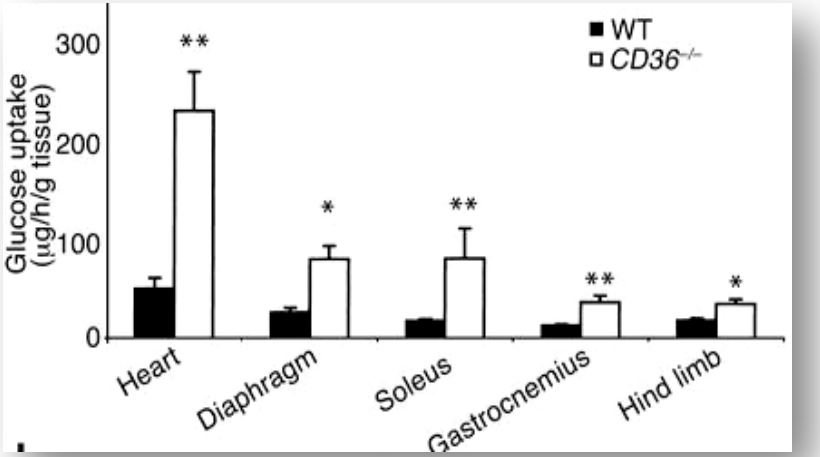
- Lower serum FA
- Lower serum TG (VLDL)
- Lower serum cholesterol
- High glucose and insulin
- Low muscle TG



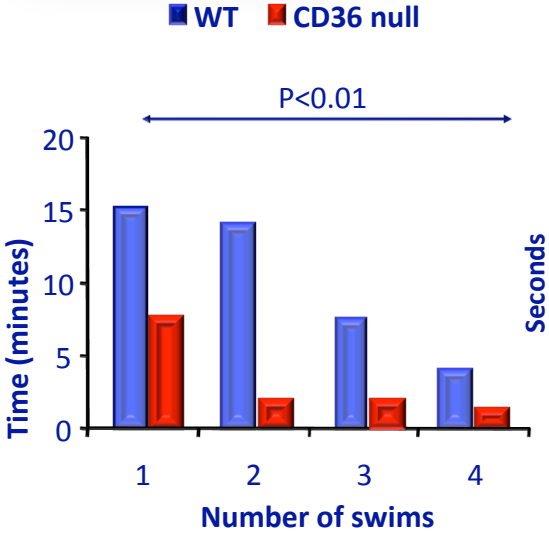
Ibrahimi et al., JBC, 1999

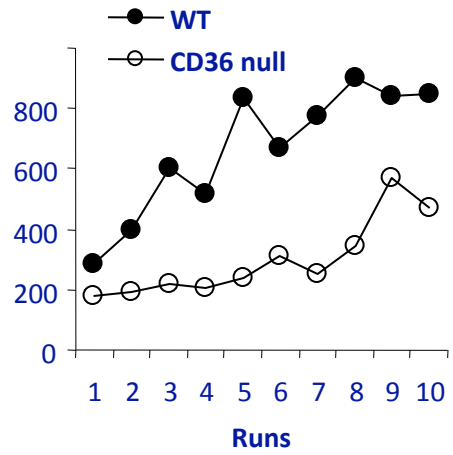
Mice with CD36 Deficiency



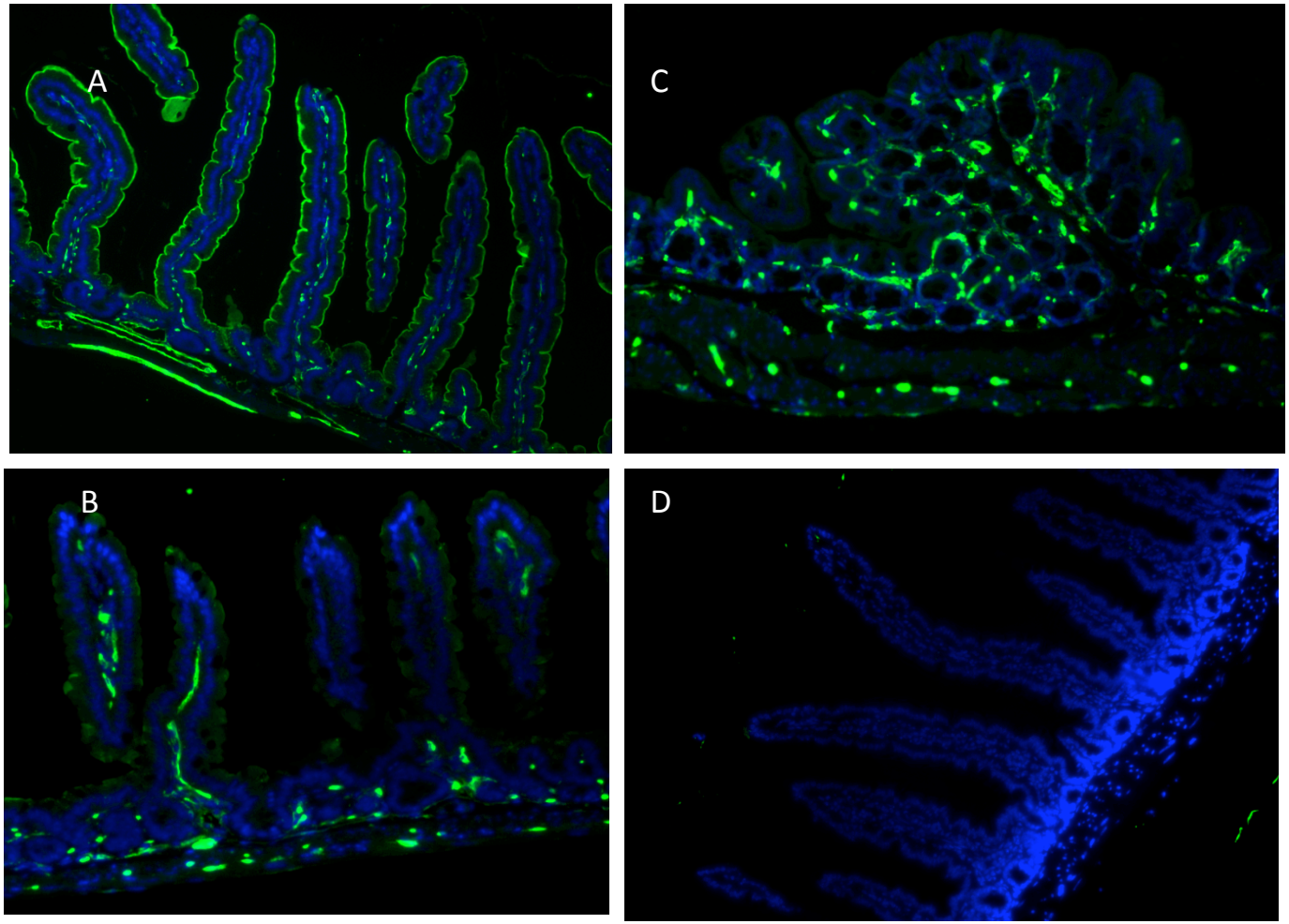


FA uptake by the CD36$^{-/-}$ heart is decreased Glucose utilization is increased





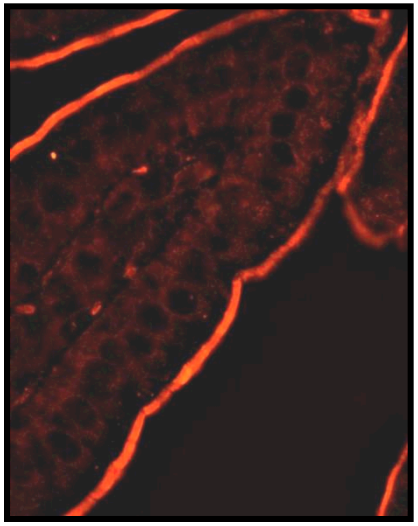
Intestine CD36



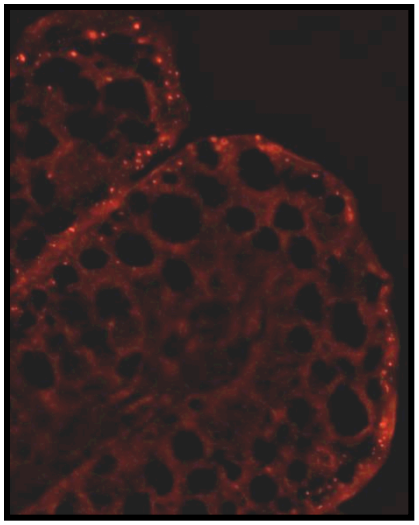
CD36 expression in the mouse intestine.
CD36 (green) in the duodenum/jejunum (A), ileum (B), and proximal colon (C) of a wild type mouse. The duodenum of a $CD36^{-/-}$ mouse (D).

Epithelial expression of CD36 is high proximally. It is decreased after food intake.

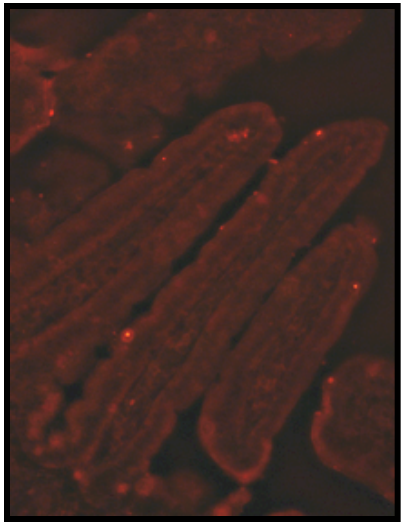
Postranslational Regulation of CD36



Fasted CD36 $^{+/+}$



Oral lipid load CD36 $^{+/+}$

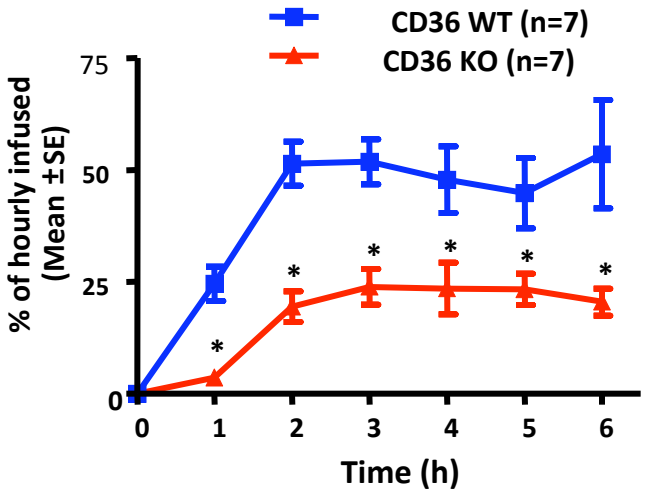


Fasted CD36 $^{-/-}$

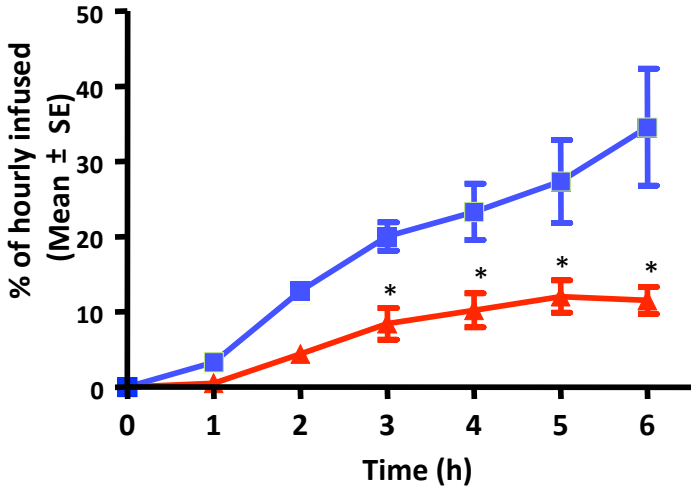
•CD36 immunostaining disappears from the villi starting an hour after administration of a meal containing even a small amount of fat.
(Tran T, and Isabelle Niot, JBC, 2011)

Net uptake of FA and cholesterol is not impaired in CD36KO mice
But secretion of lipid into the lymph is decreased. The particles secreted are smaller and their clearance from the blood is delayed .

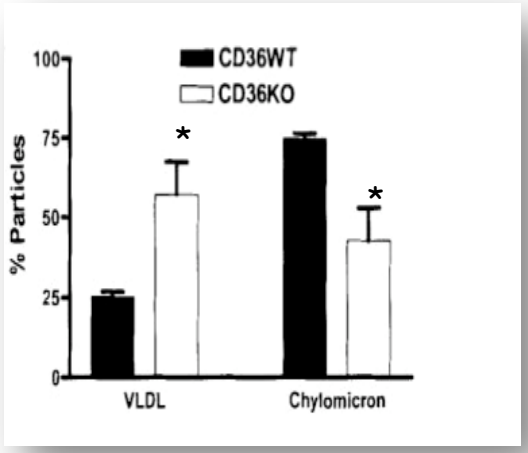
Lymph Triolein Recovery



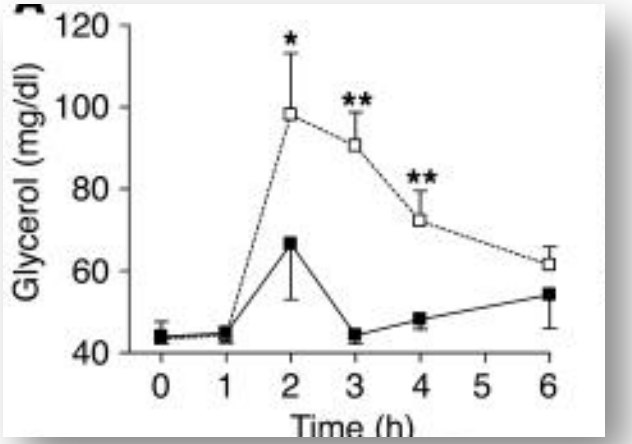
Lymph Cholesterol



Secreted Lipid Particles

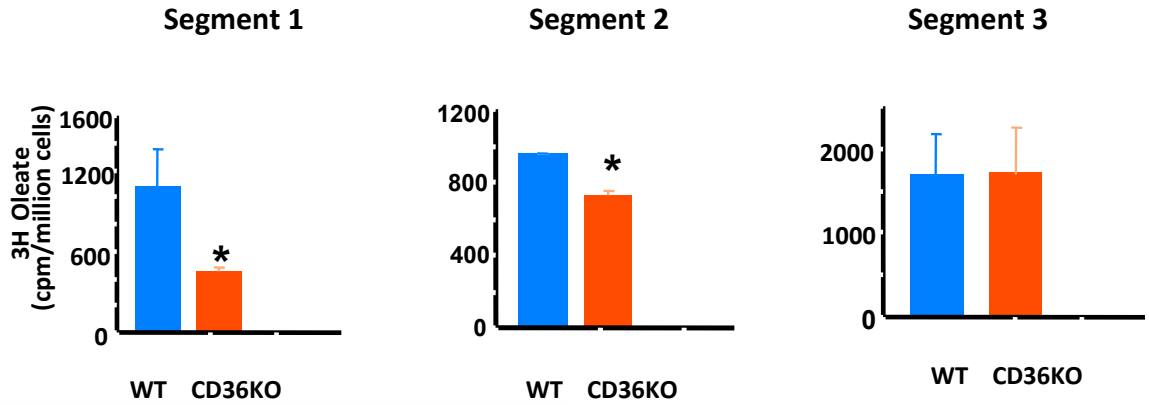


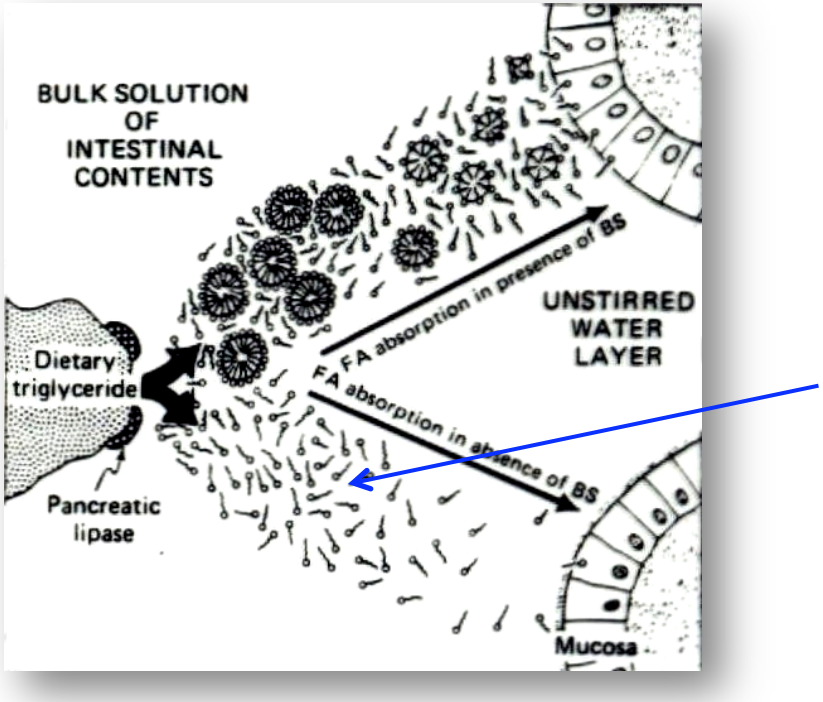
Postprandial TG



Drover et al., JCI 2005;
Nauli et al., Gastroent. 2006

Proximal to Distal Gradient in CD36-facilitated FA uptake by enterocytes .





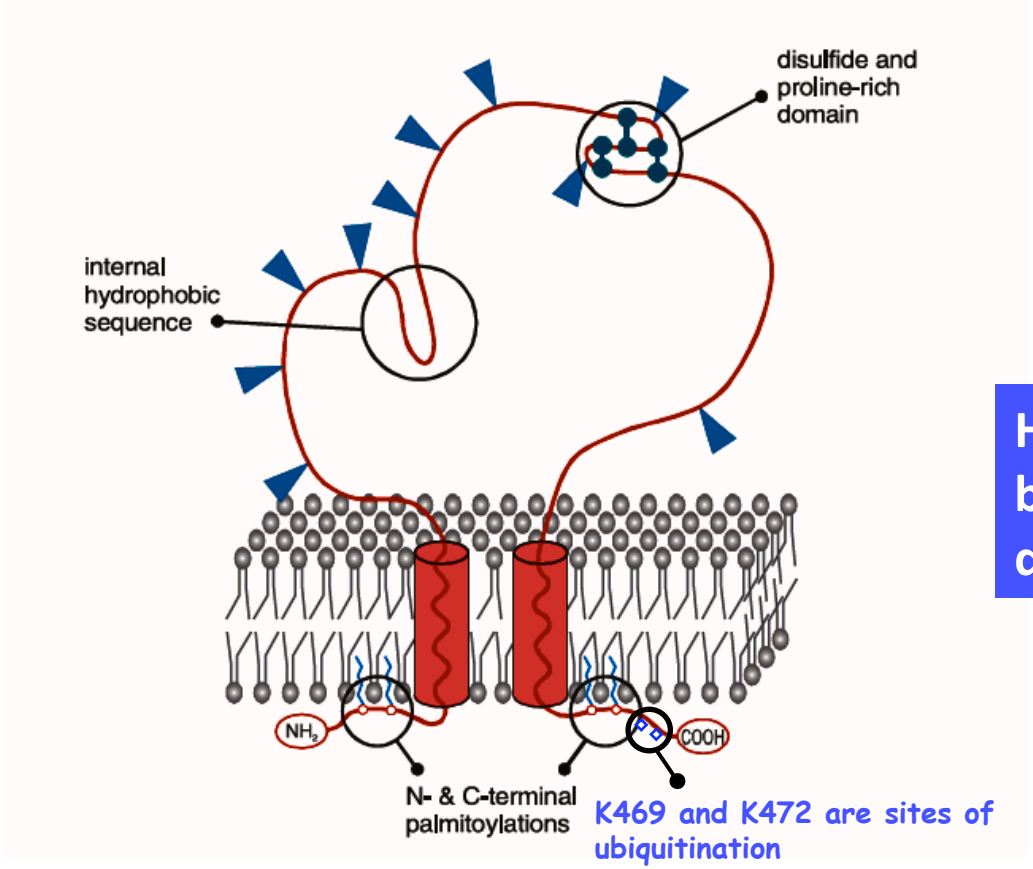
- Uptake Km is in the nM range similar to what was determined in muscle and adipose cells.
- Concentration of FA monomer in equilibrium with micelles is in the low uM (versus nM in the circulation). Intestinal CD36 would be saturated very early during digestion.
- CD36 may play a regulatory role in intestinal FA uptake

Nassir F et al. J. Biol. Chem. 2007;282:19493-19501

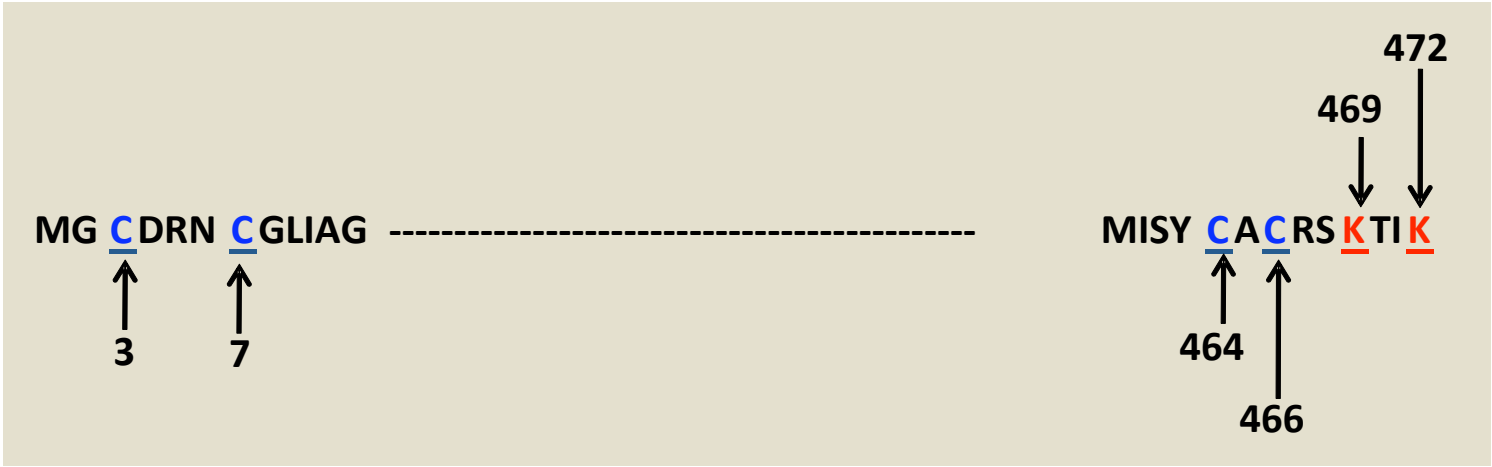
Conclusions: CD36$^{-/-}$ Intestine

- Reduced FA uptake in the proximal intestine
- Lipid absorption overall is delayed, not altered.
- Defect in chylomicron secretion. More VLDL size particles.
- CD36 is part of the multiprotein complex required to generate prechylomicron vesicles from ER to Golgi.
- Clearance of intestinal particles in the blood is delayed.
- <u>CD36 deficient Humans:</u>
- Defect in chylomicron production.
- Slow clearance of postprandial TG

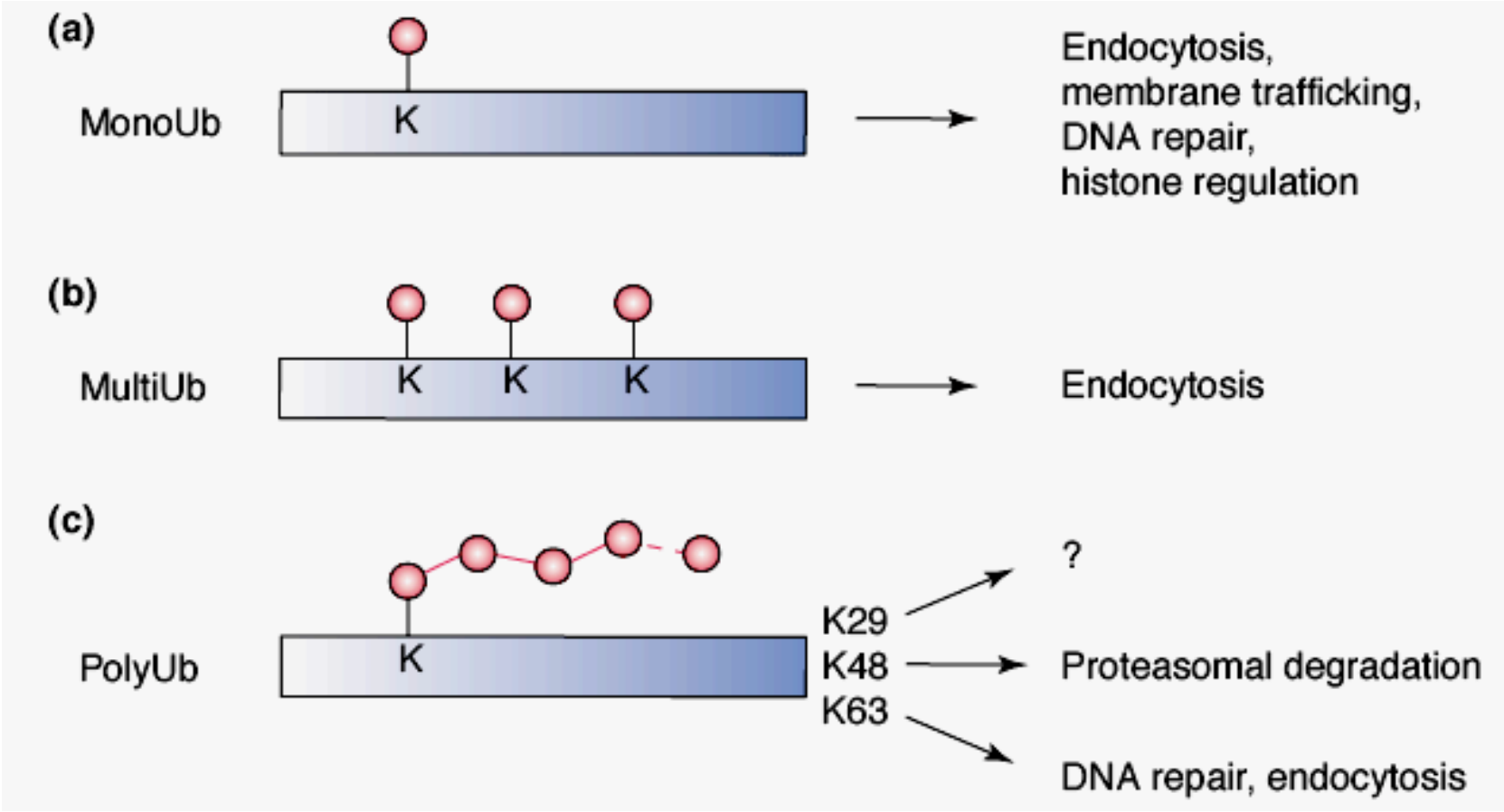
Would targeting intestinal CD36 be beneficial?



How can CD36 become dysfunctional?

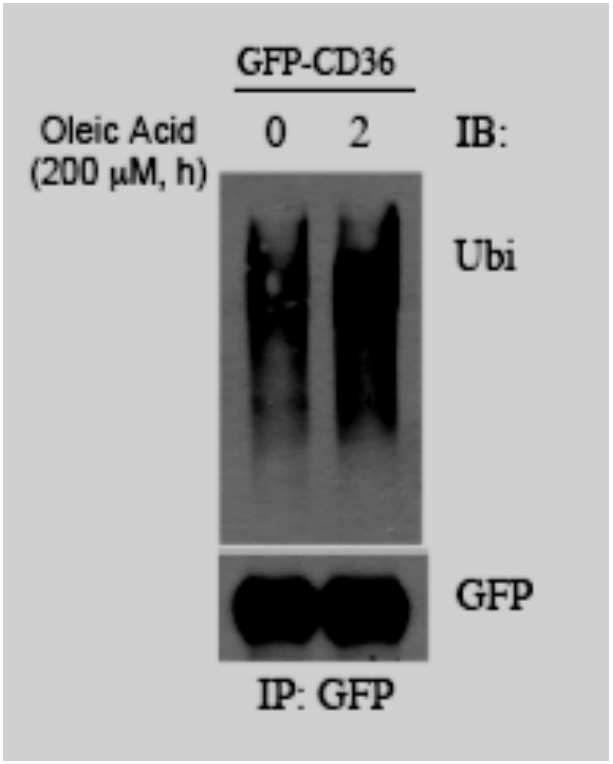


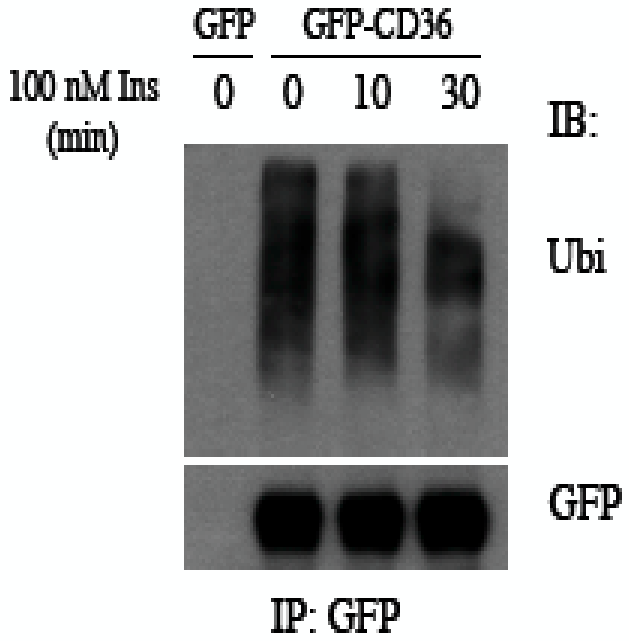
Different forms of ubiquitin modification



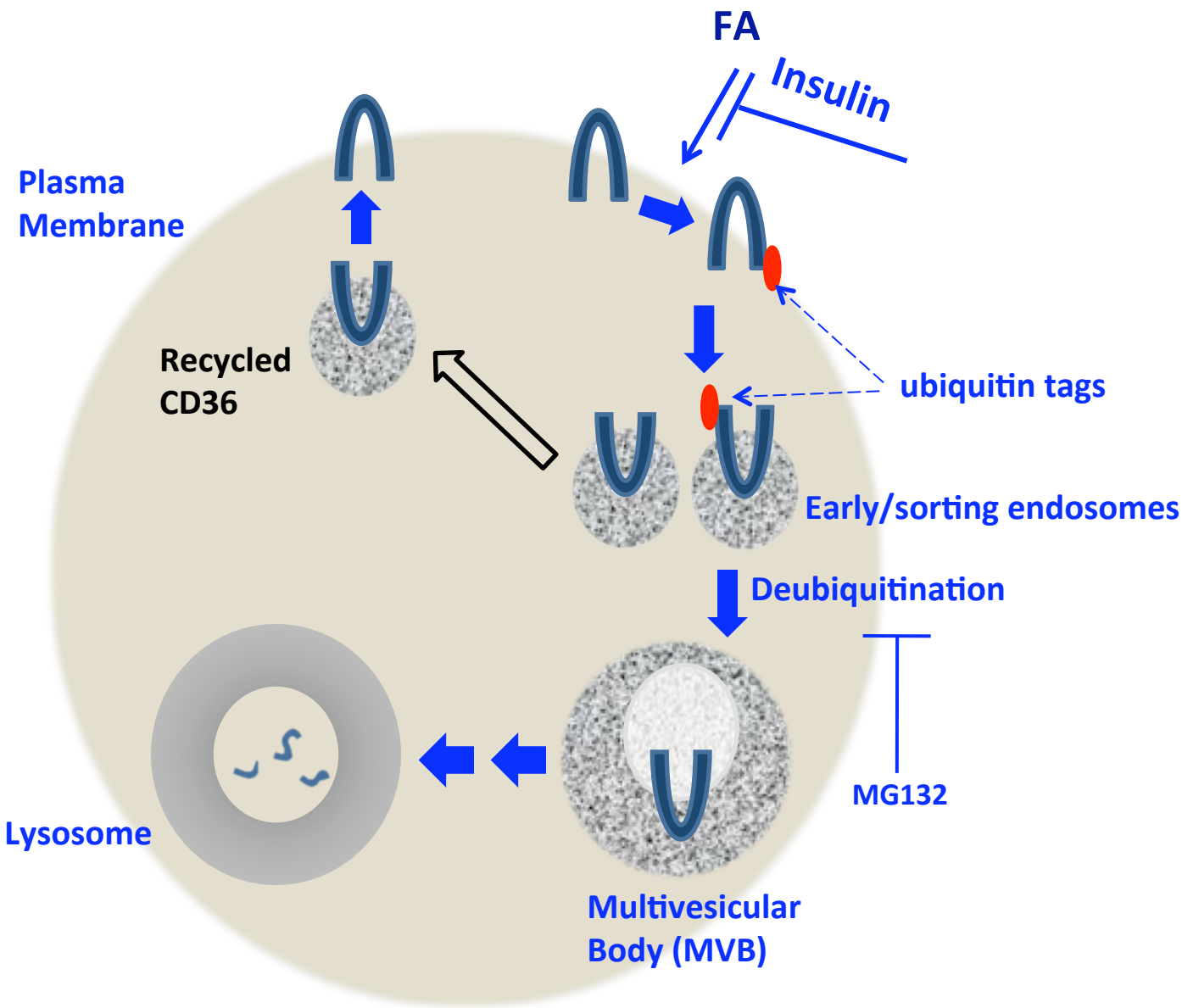
Isopeptide bond between glycine and lysine

CD36 Ubiquitination: enhanced by FA, inhibited by insulin



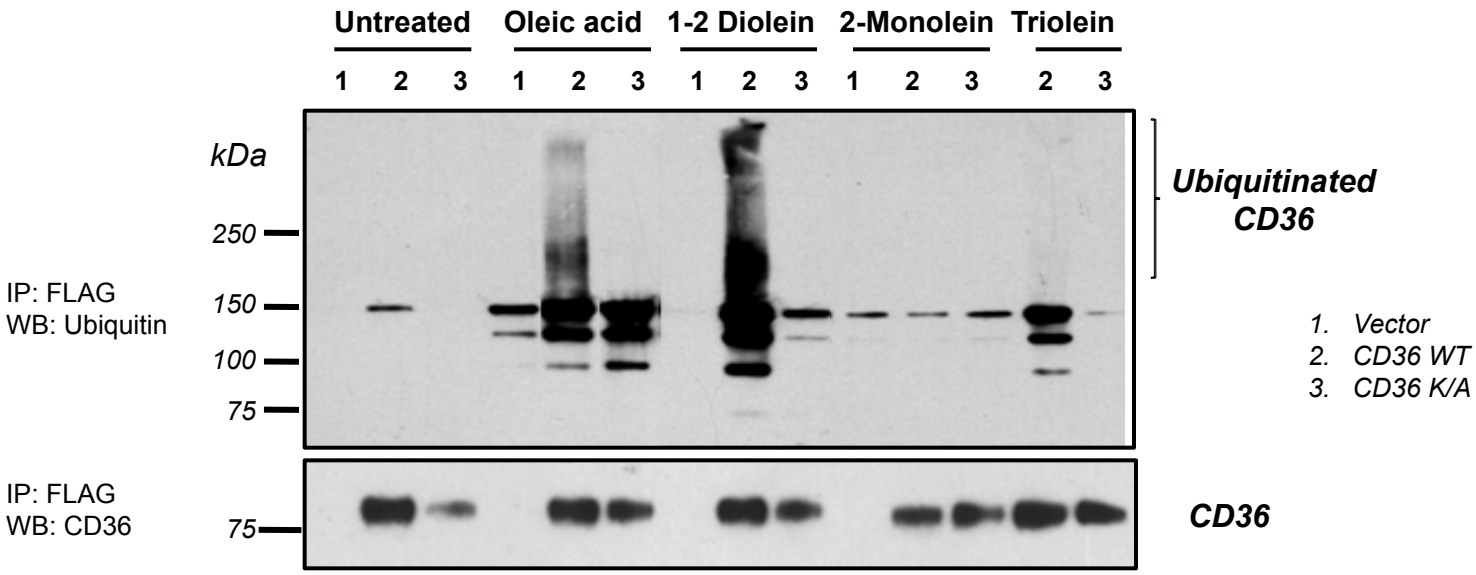


Smith, Su et al., JBC, 2008

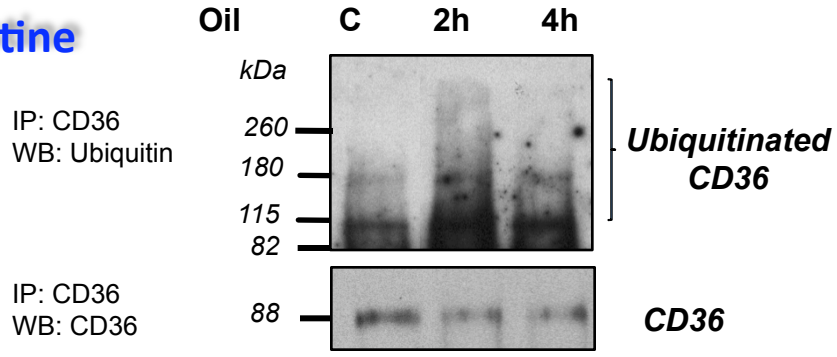


Su and Abumrad Trends in Endocr 2009

CHO cells



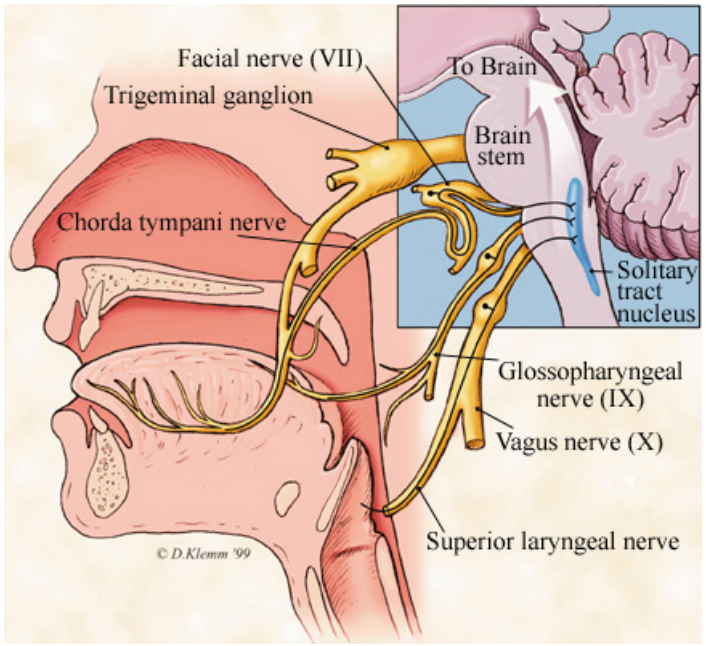
Mouse Intestine

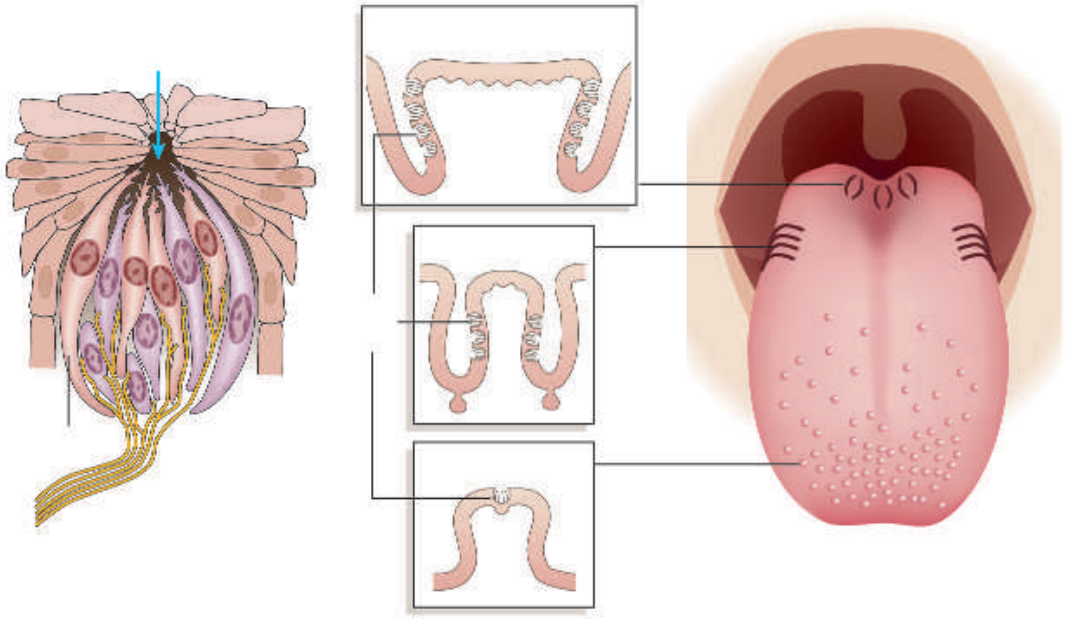


CD36 in the intestine is downregulated via ubiquitination by lipid digestion products. Negative feedback loop may serve to limit fat induced inflammation.

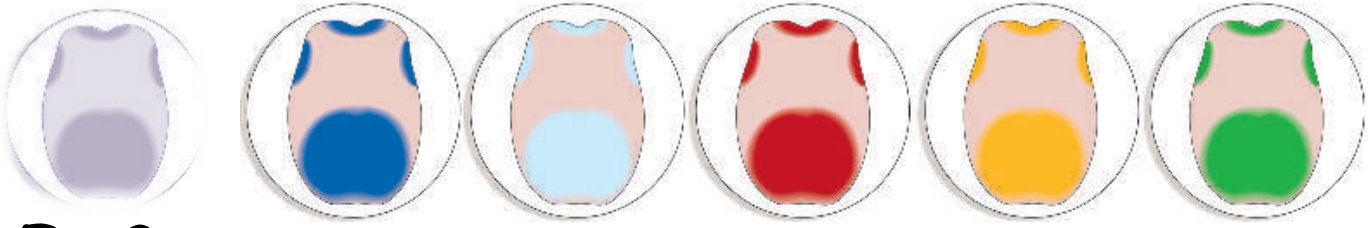
Tran T JBC 2011

Human taste perception

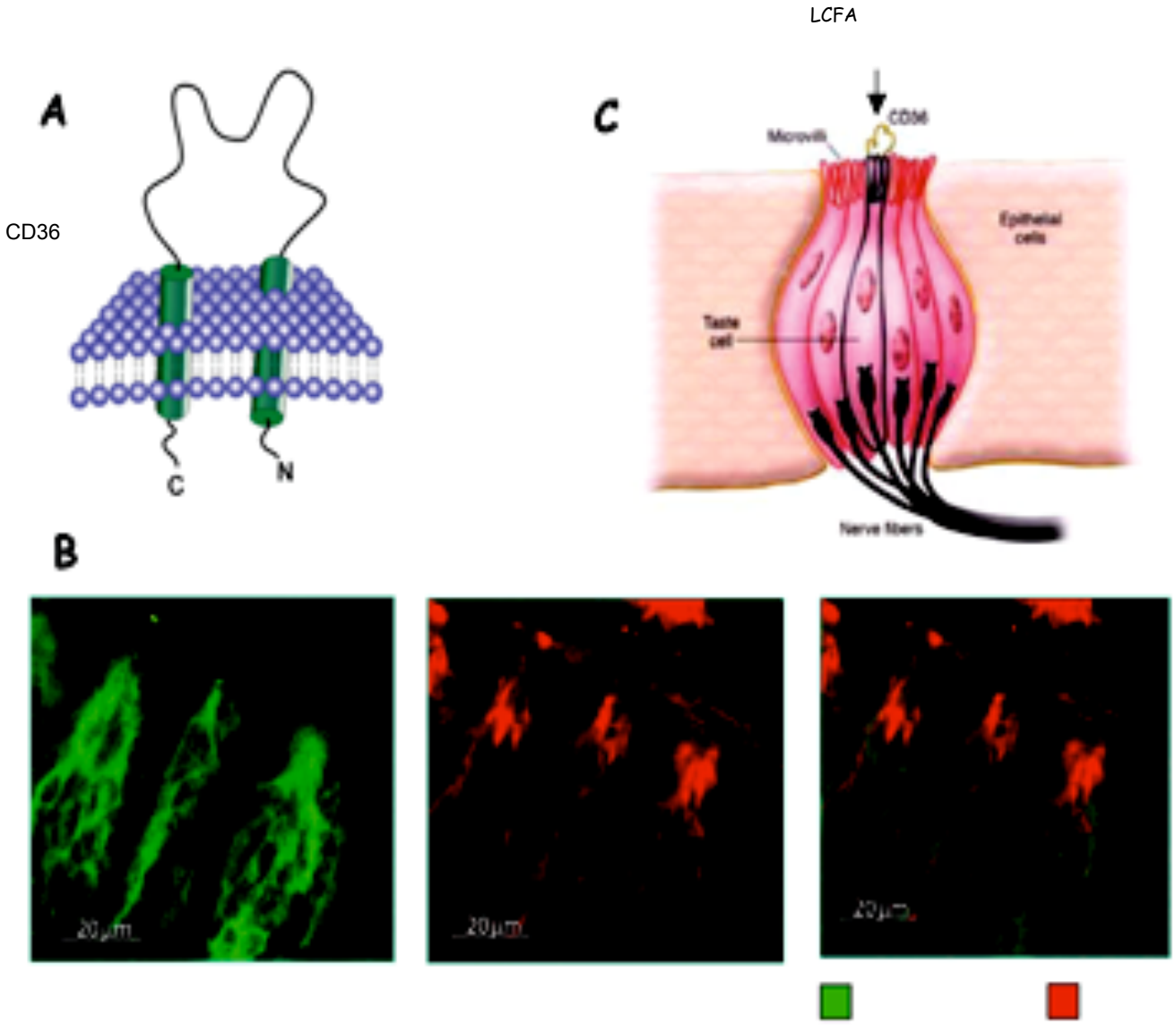




R. F. Margolskee, Sci. STKE (2005)



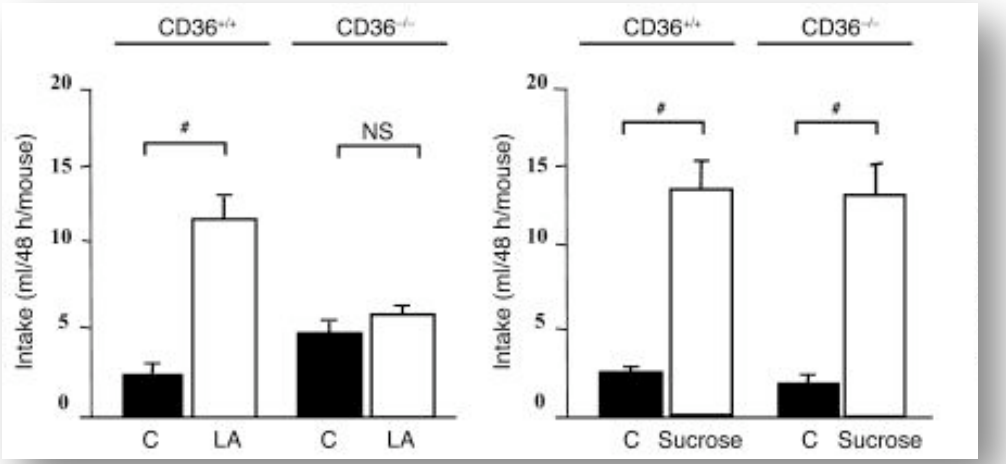
Chandrashekar, Hoon, Ryba & Zuker; Nature (2006)



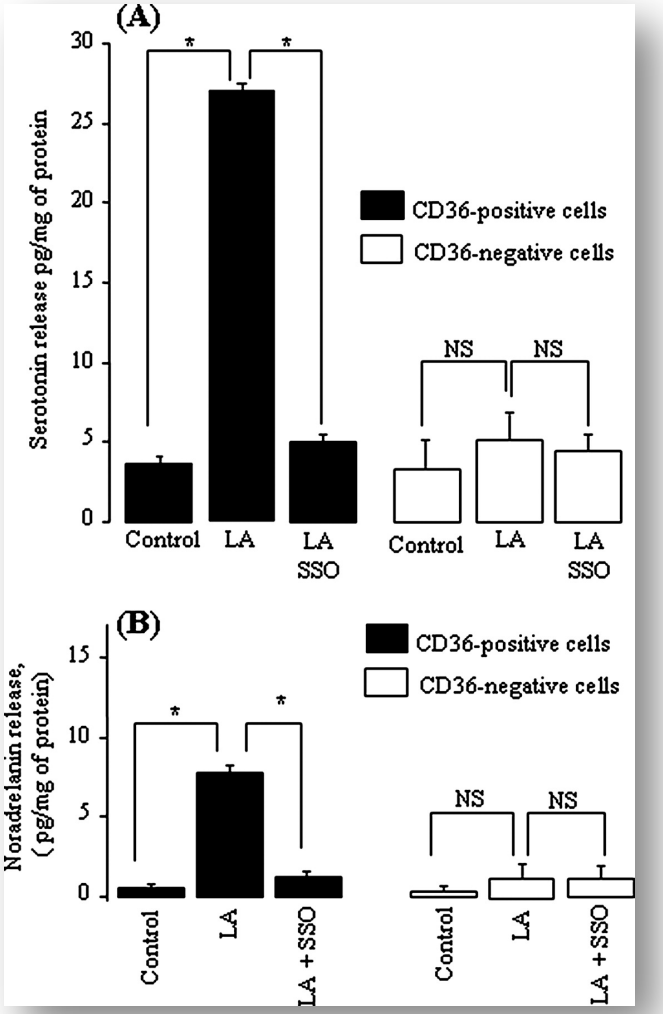
Fukuwatari, T., et al. 1997. FEBS Lett.
Lauguerette JCI 2005

CD36 null mice do not exhibit spontaneous preference for fatty acids.

Laugerette et al., JCI 2005.

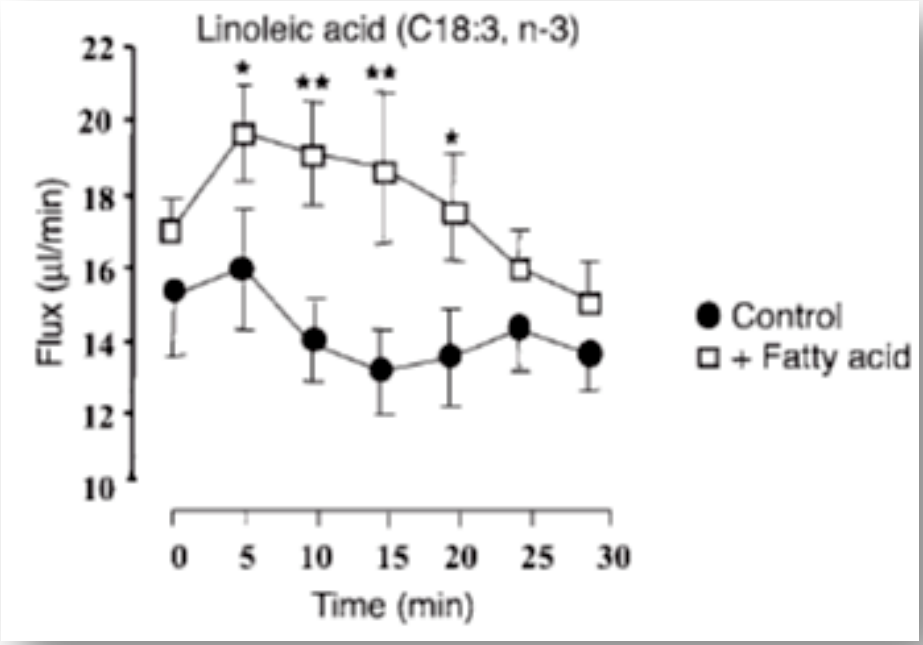


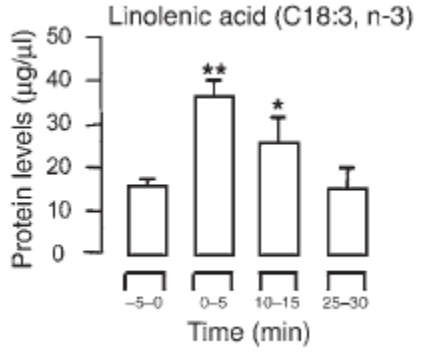
Gustatory cells lacking CD36 fail to release monoamine neurotransmitters in response to FA

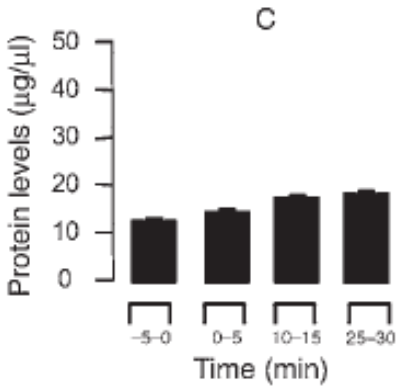


El-Yassimi A et al. J. Biol. Chem. 2008

Lingual application of fatty acids increases bile flux and protein content in pancreatic secretion in rats





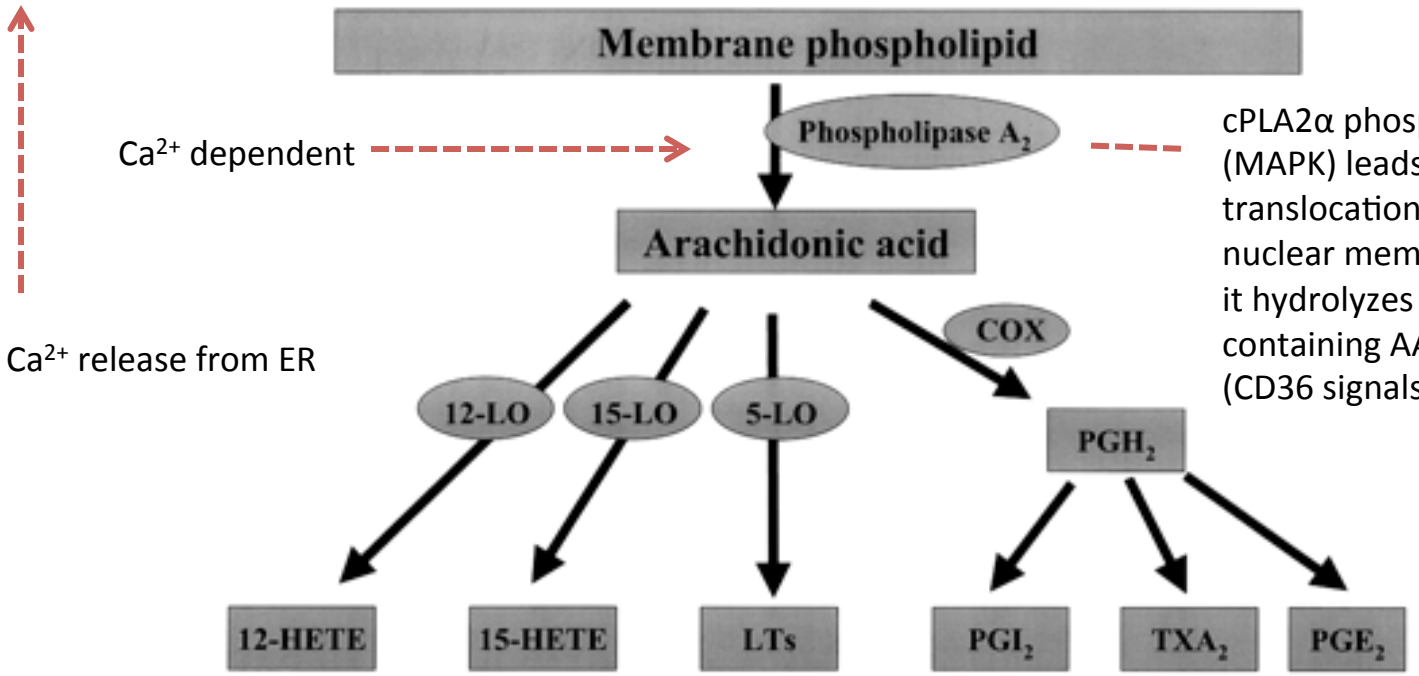


$CD36^{-/-}$ mice lack the cephalic phase of bile secretion (Bile release in response to taste without/before intake).

Laugerette et al., JCI 2005

Eicosanoid Production

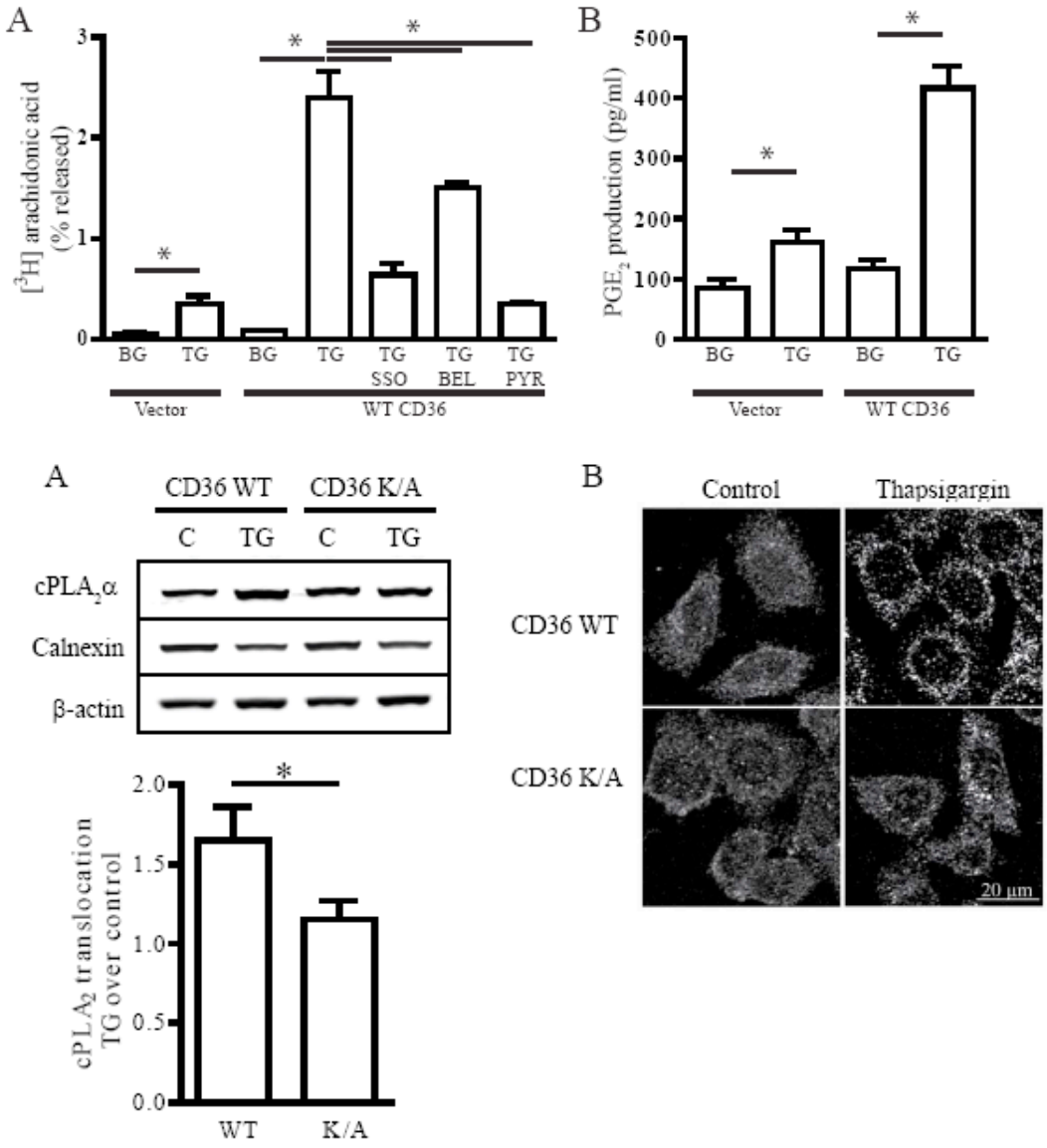
Ca^{2+} influx via store operated channels (regulated by Fyn, which interacts with CD36)



cPLA2α phosphorylation (MAPK) leads to its translocation to ER and nuclear membranes where it hydrolyzes phospholipids containing AA.
(CD36 signals to MAPK)

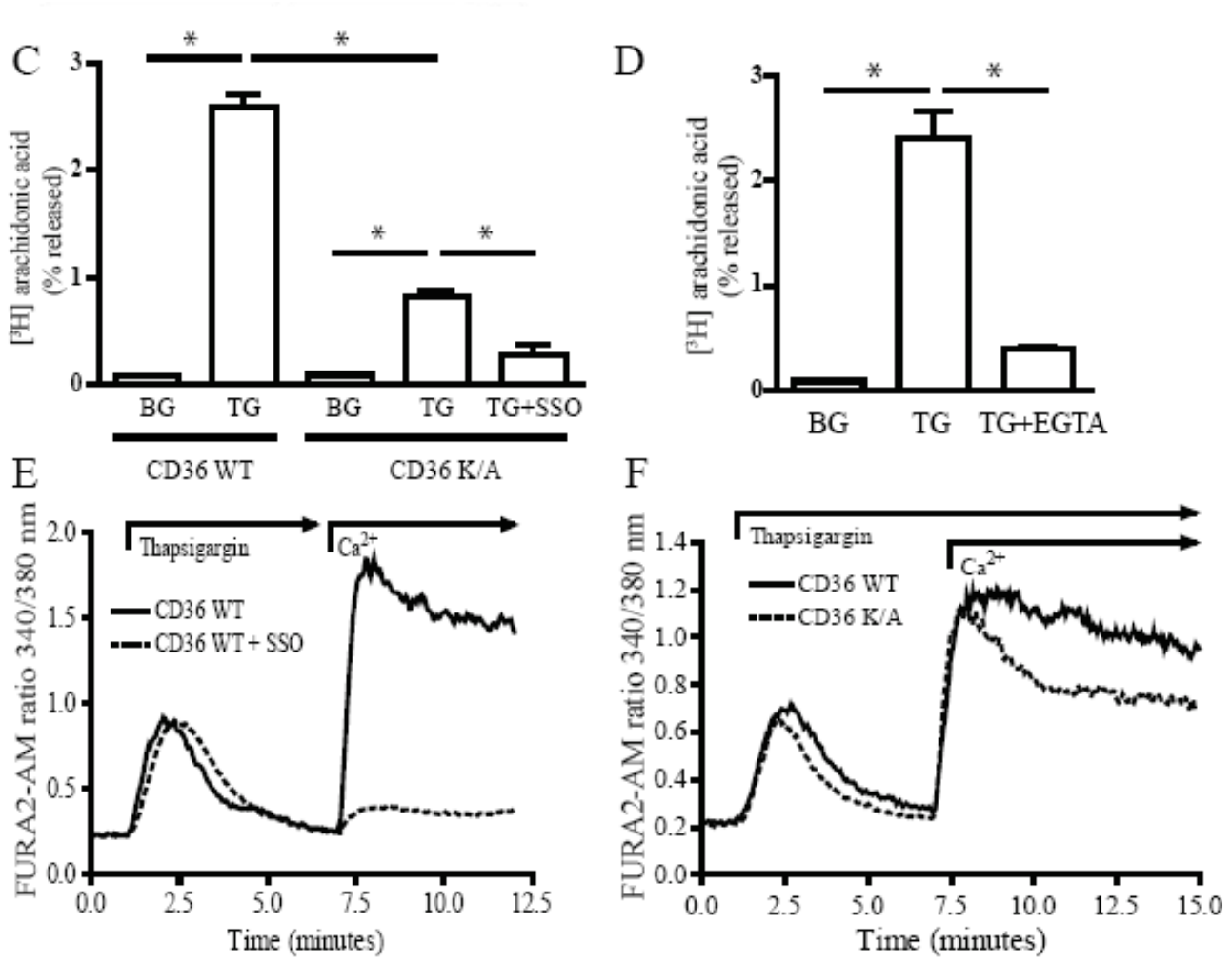
A variety of pro-inflammatory effects:
vasoconstriction or vasodilation, coagulation, pain, fever, allergies, Atherosclerosis, GI diseases, matrix deposition, fibrosis etc

CD36 regulates release of Arachidonic Acid from Phospholipids



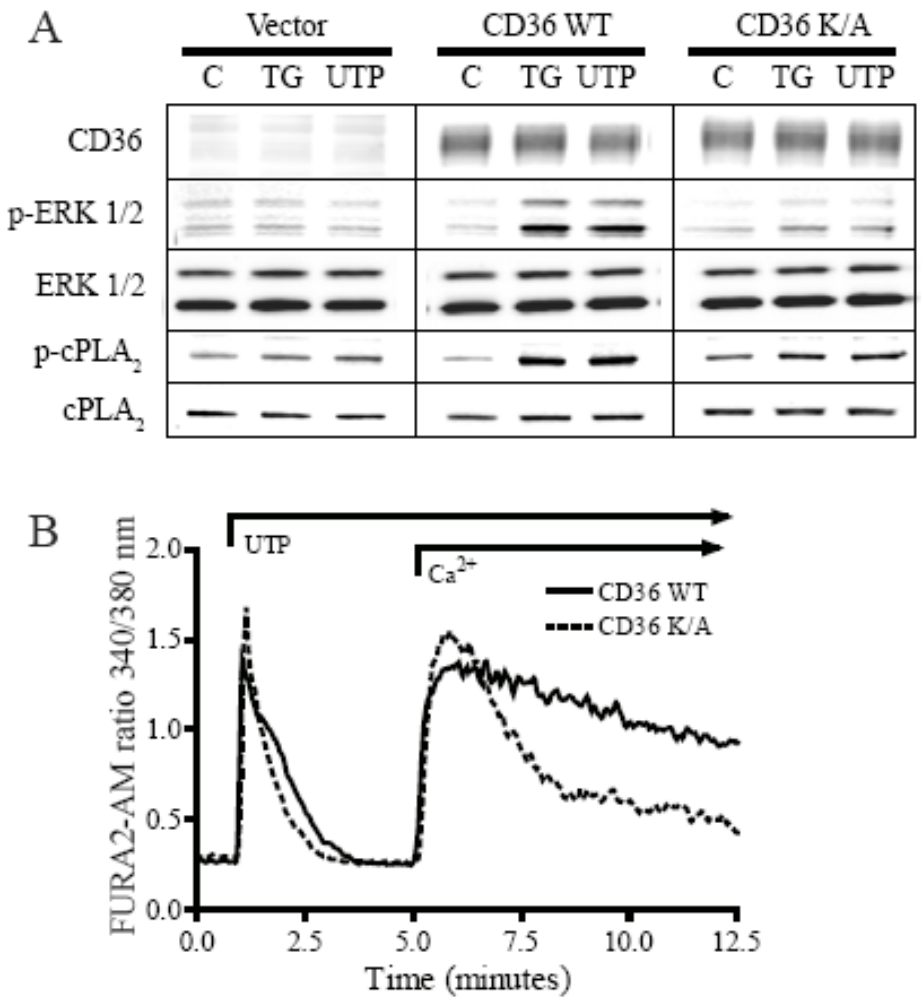
Kuda O, JBC 2011

CD36 regulates PGE2 production via influencing Ca^{++} homeostasis

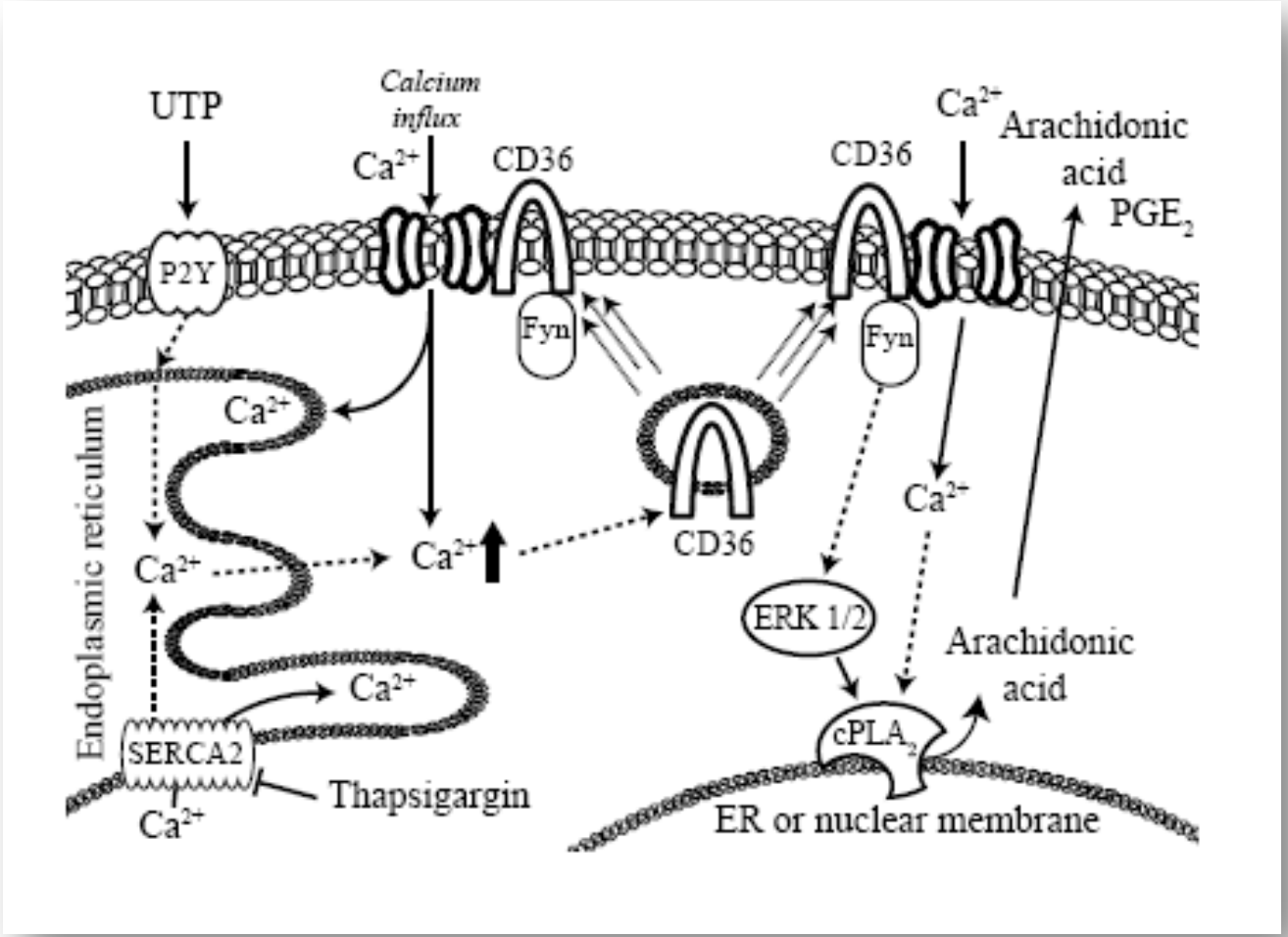


Kuda O et al., JBC 2011

Purinergic Receptors

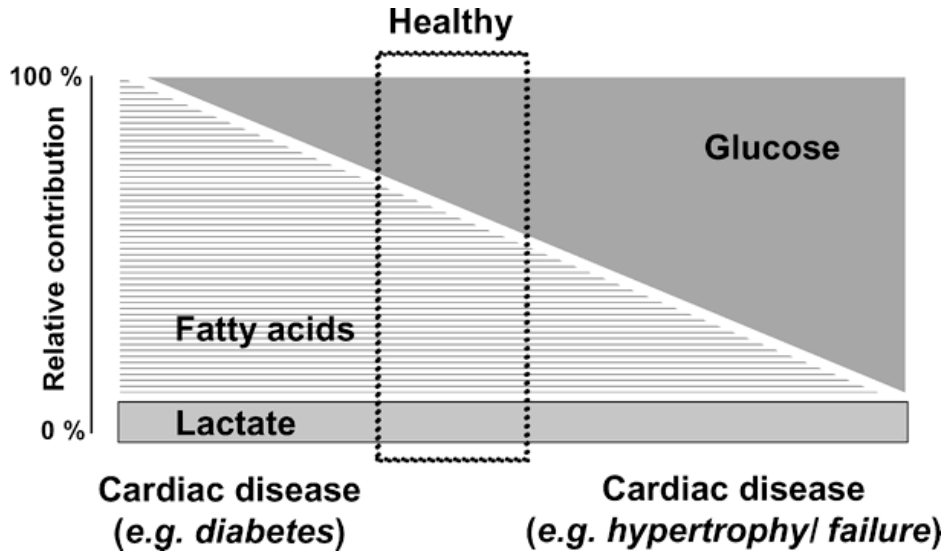


CD36 Regulation of Ca^{++} Homeostasis and Eicosanoid Production



The CD36 deficient Heart

Balance between glucose and FA utilization is essential

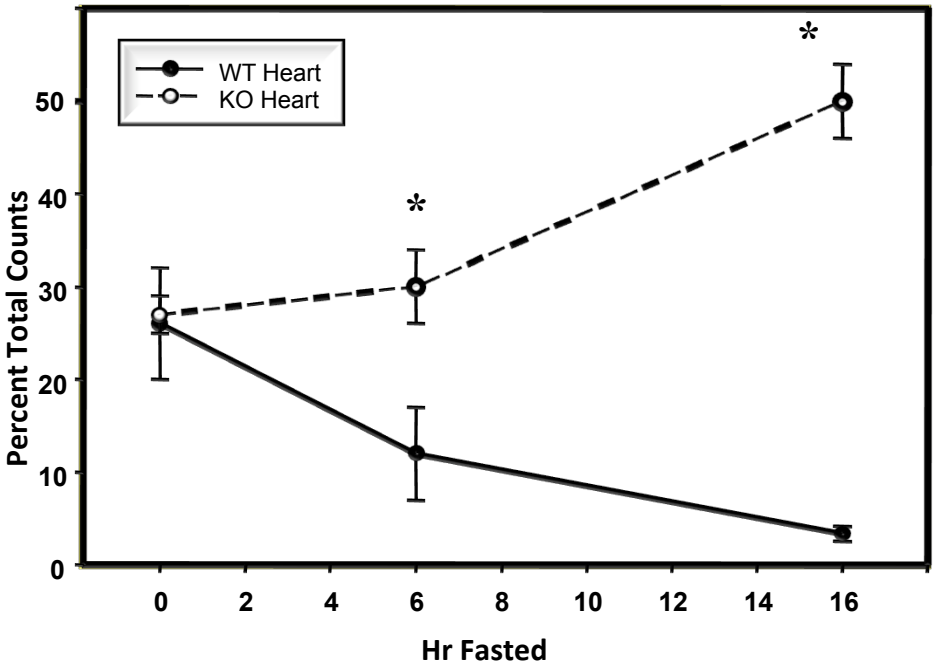


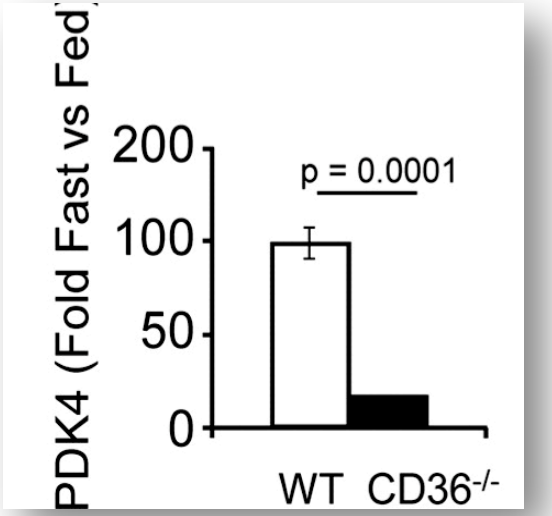
Does CD36 regulates Ca^{2+} homeostasis in cardiomyocytes

Glatz J. Cardiovasc Drugs Ther 2006

CD36$^{-/-}$ heart does not reduce its glucose utilization in fasting.

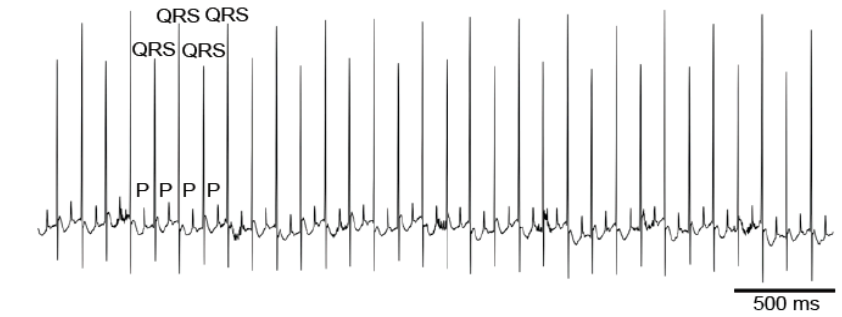
Blunted induction of PDK4, the enzyme that inhibits glucose oxidation.

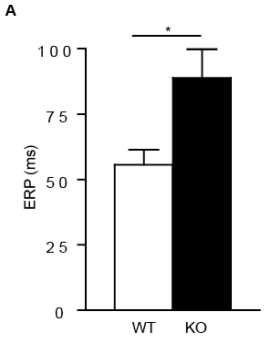


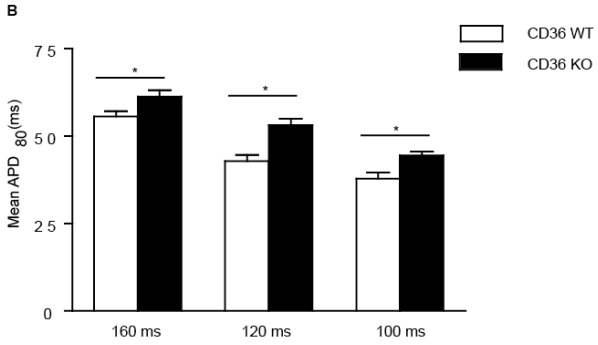


Coburn et al., JBC 2000
Hajri et al., JCI 2002
Nahle et al., JBC 2008

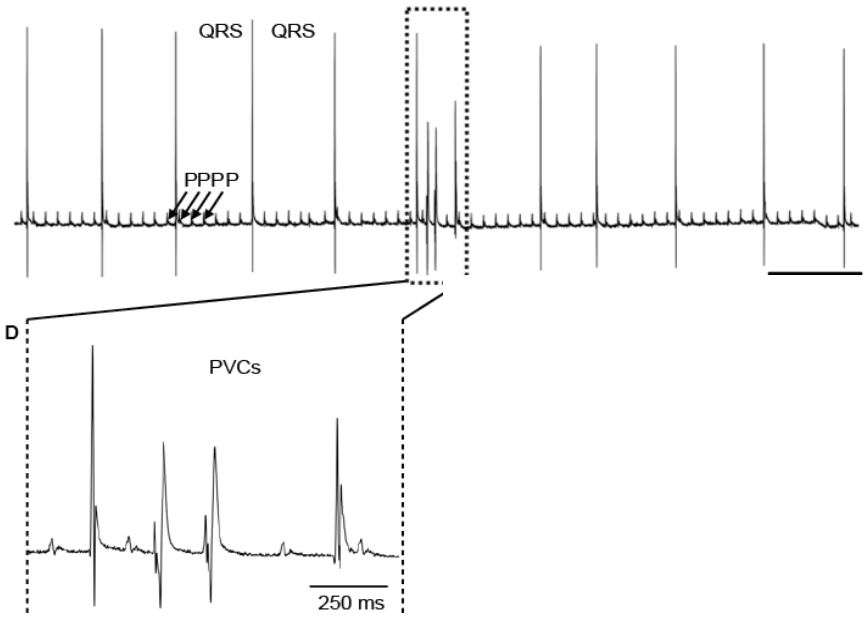
Functional response to fasting of CD36 deficient heart

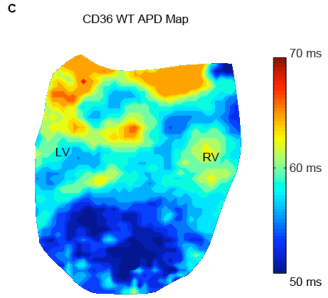


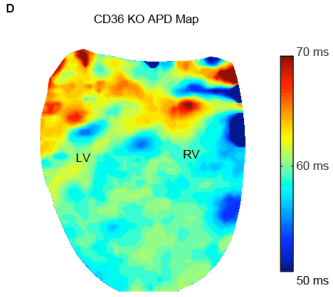




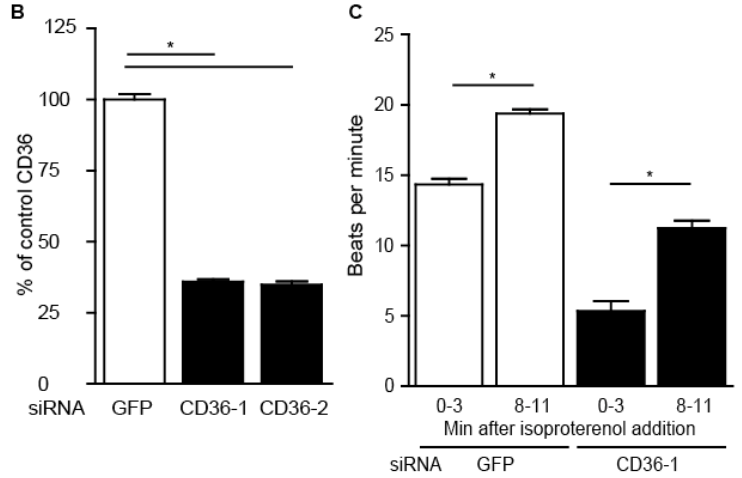
B Fasted CD36KO - AV Block and PVCs

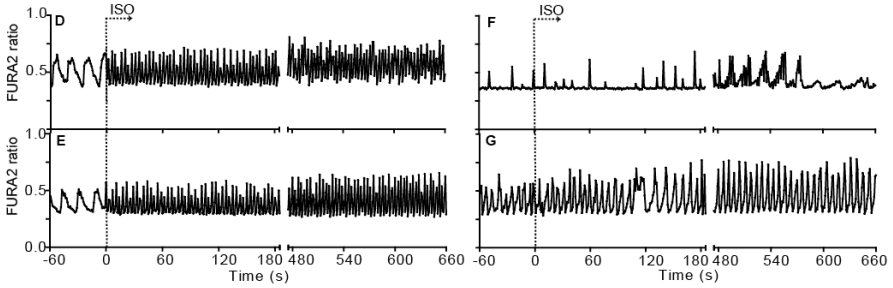


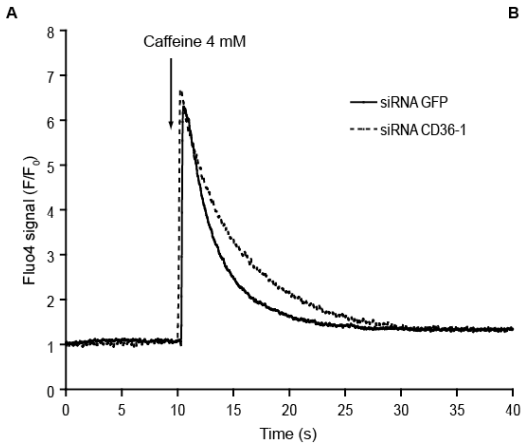


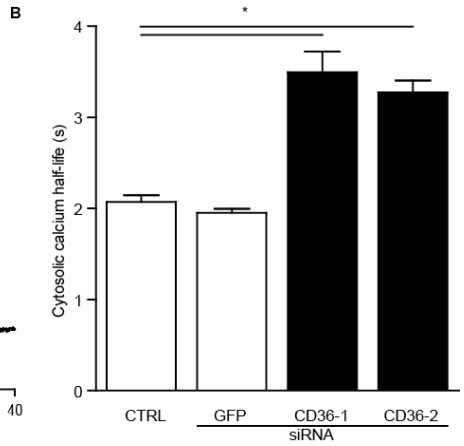


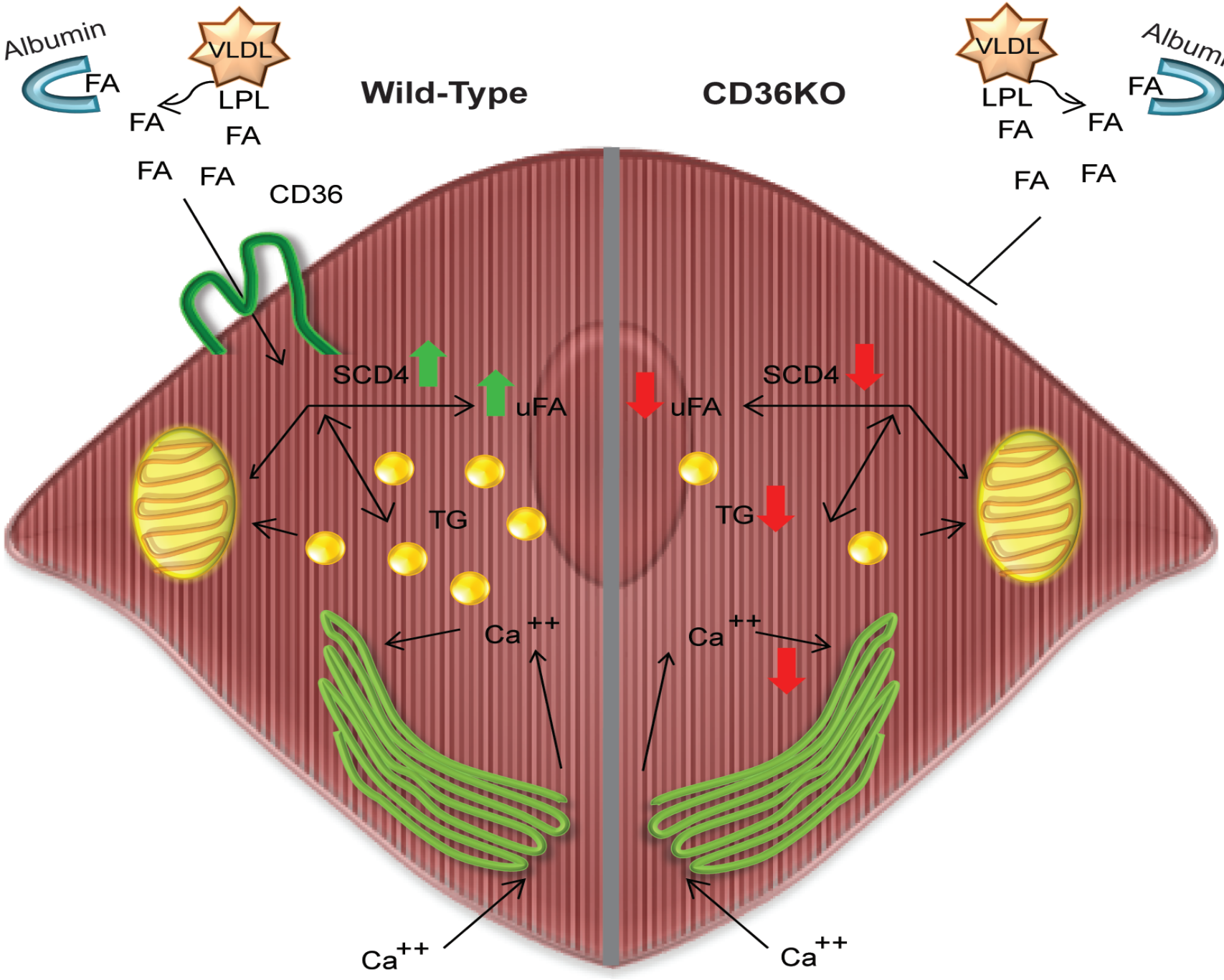
CD36 on Regulation of Ca^{2+} homeostasis in Cardiomyocytes









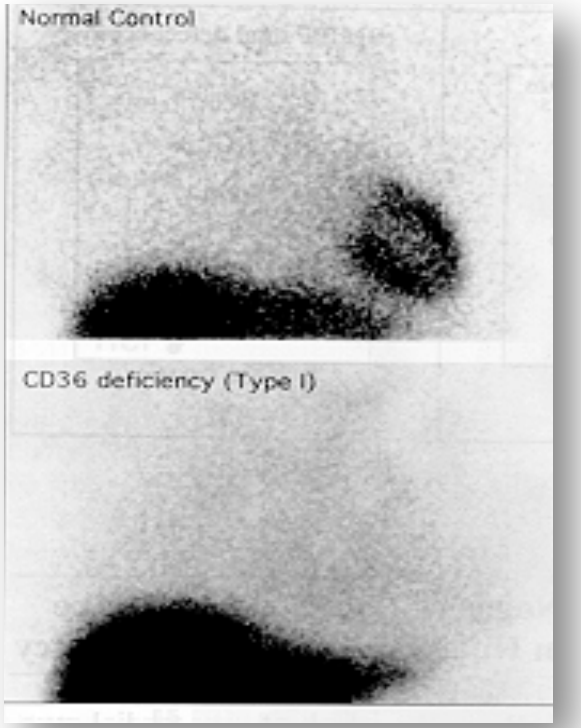

Albumin
FA
VLDL
LPL
FA
FA
FA
FA
CD36
Wild-Type
CD36KO
VLDL
LPL
FA
Albumin
FA
FA
FA
SCD4
uFA
TG
Ca ++
Ca++
SCD4
uFA
TG
Ca ++
Ca++

Summary

2 - CD36$^{-/-}$ deficient heart has impaired FA uptake, low FA oxidation, high glucose utilization.

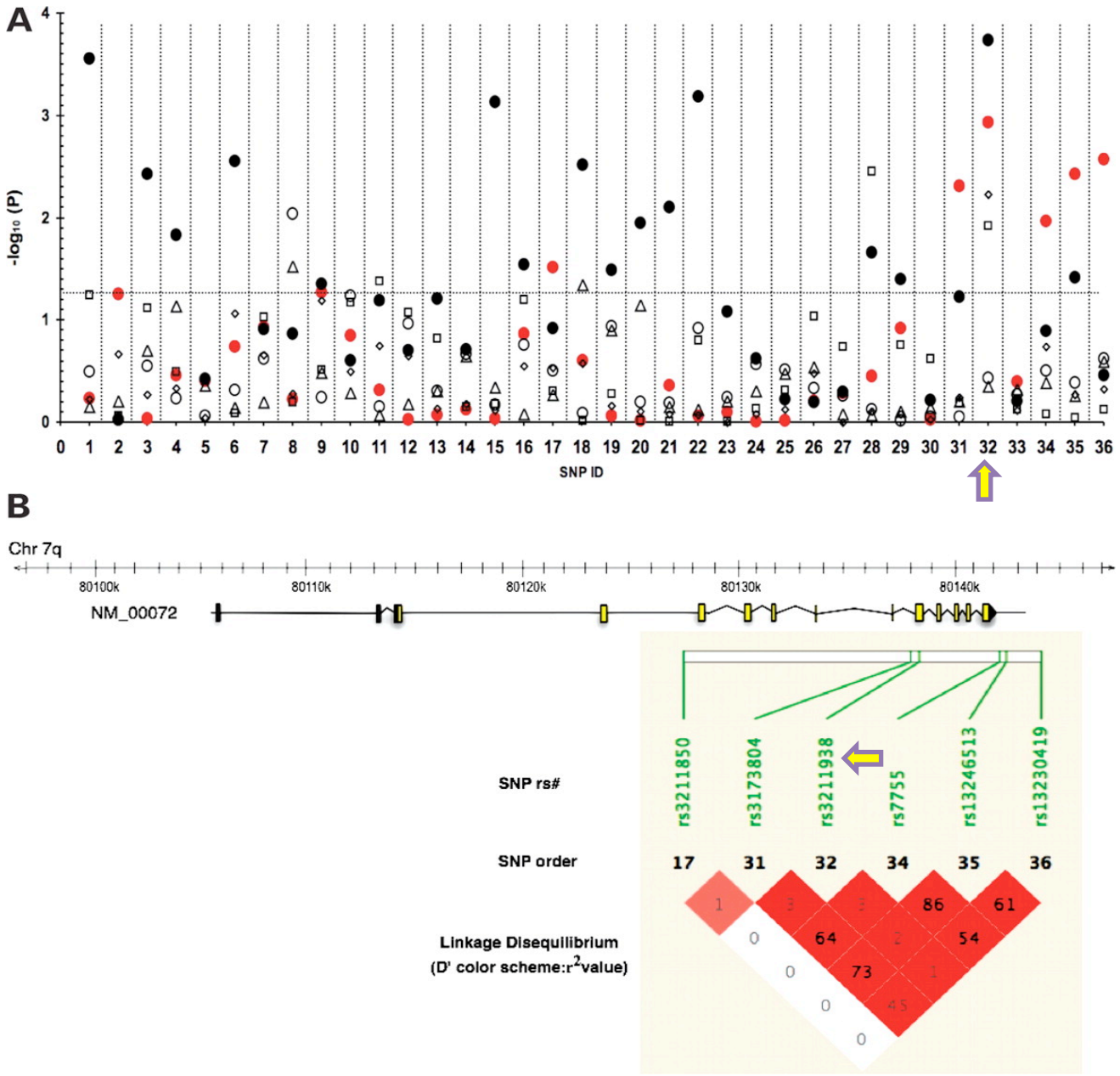
3- Blunted metabolic adaptation to fasting, which associates with AV block and occasional death.

4- Humans deficient in CD36 have defective myocardial FA uptake, enhanced glucose uptake.



Tanaka JLR 2001,

Plot of association analysis between 36 CD36 tag SNPs, the metabolic syndrome and its components.



HDL-C
Waist Circumference
Fasting Glucose
Hypertension
Triglycerides
MetS

Love-Gregory L et al. Hum. Mol. Genet. 2008;17:1695-1704

Conclusion I

- CD36 est impliquée dans les effets des acides gras et leur utilisation par les cellules

- La fonction de CD36 est influencée par le métabolisme qui modifie son expression et sa localisation

- L'absence ou la réduction de l'expression de CD36 réduit la capacité d'adaptation métabolique du coeur et de l'appareil digestif ainsi que de la gustation

Conclusion 2

Les travaux effectués chez les rongeurs commencent à être validés chez l'homme et montrent l'importance de CD36 dans:

- Le métabolisme cardiaque
- La libération des chylomicrons intestinaux
- Le métabolisme des lipides dans les tissus périphériques
- L'étiologie de l'insulino-résistance


I NOW PRONOUNCE YOU SPOUSE AND SPOUSE. YOU MAY KISS YOUR SPOUSE.
BUT WE ONLY CAME IN HERE FOR A FISHING LICENSE!!!
SAN FRANCISCO
CITY HALL
JONES
The Free Lance-Star

Acknowledgments

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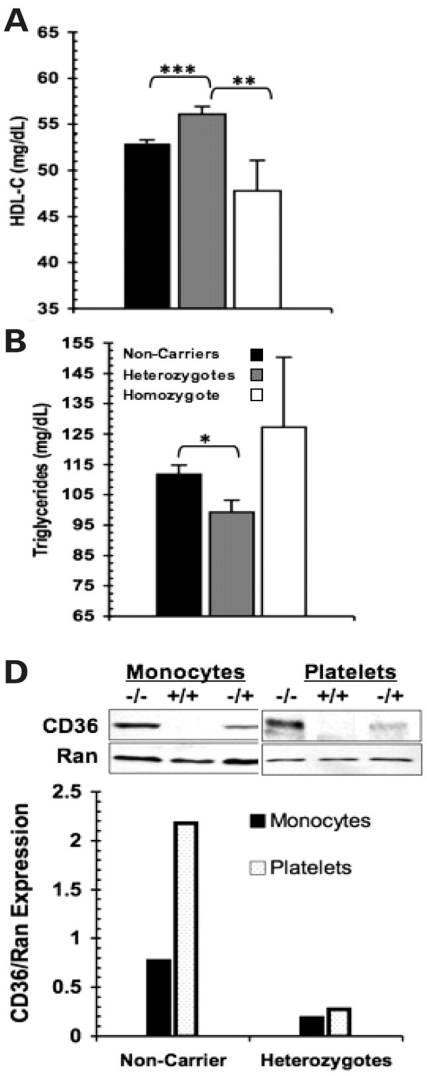
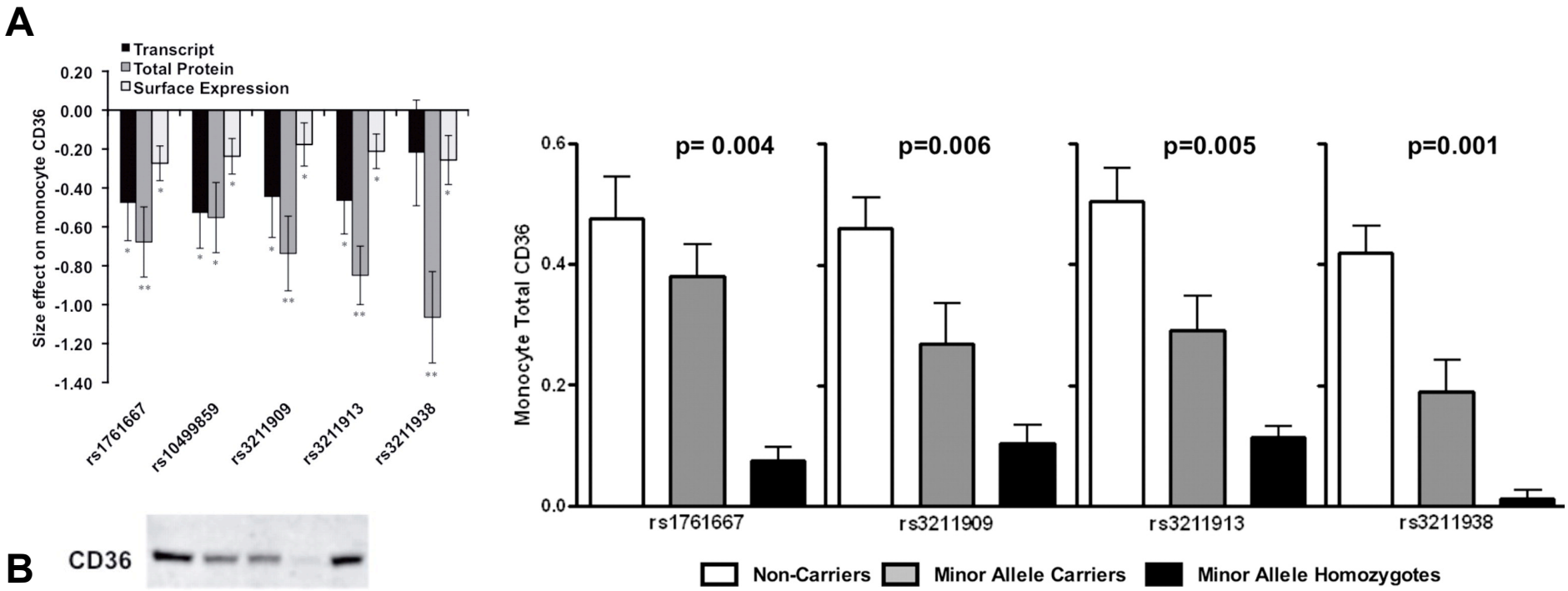
- Richard Gross
- Chris Jenkins
- Sung-Ho Moon
- Phil Stahl
- Xiong Su
- Jeanne Nerbonne
- Wei Wang (David)
- Alan Permutt
- Alessandro Doria
- Ira Goldberg
- Sam Klein
- Patrick Tso

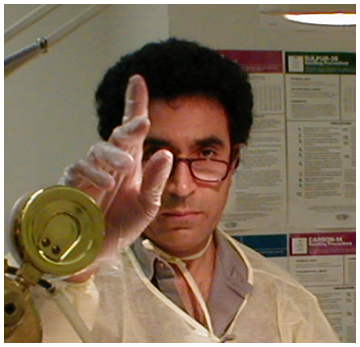

A
HDL-C (mg/dL)
65
60
55
50
45
40
35
***
**
B
Triglycerides (mg/dL)
155
145
135
125
115
105
95
85
75
65
Non-Carriers
Heterozygotes
Homozygote
*
D
Monocytes
Platelets
-/-
+/+
-/+
-/-
+/+
-/+
CD36
Ran
CD36/Ran Expression
2.5
2
1.5
1
0.5
0
Monocytes
Platelets
Non-Carrier
Heterozygotes

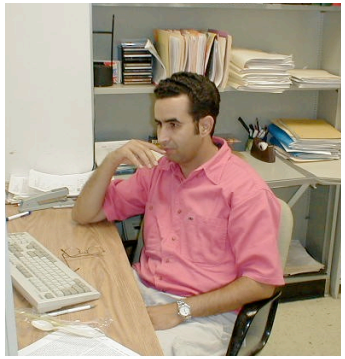
Inverse relationship between CD36 expression and HDL-associated SNPs.

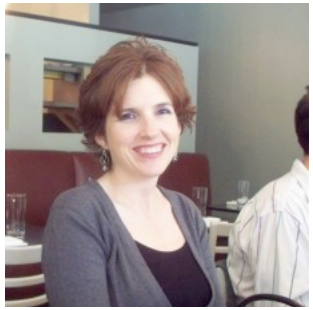


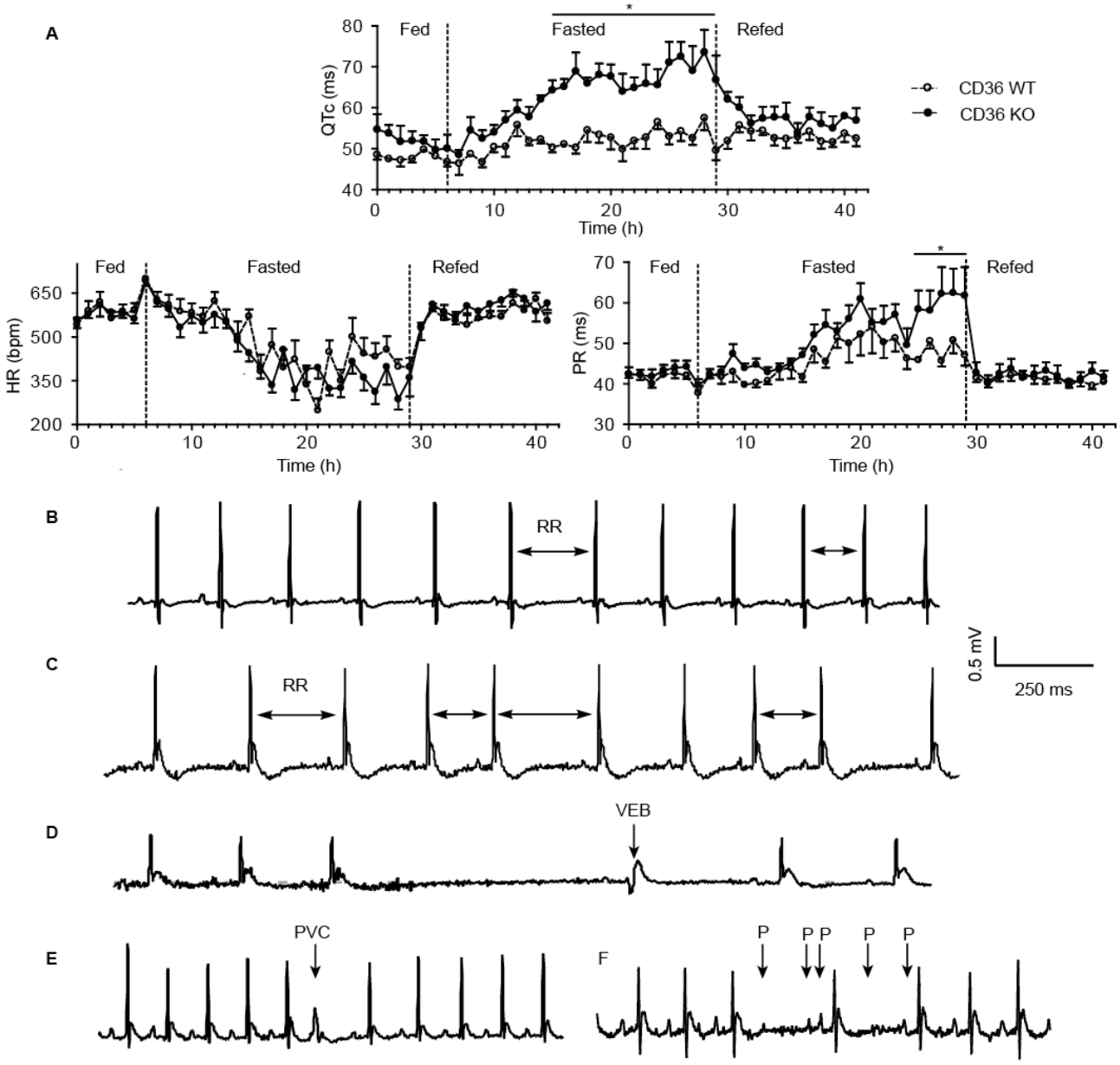
Polymorphisms that increase HDL reduce CD36 expression.

Love-Gregory L et al. Hum. Mol. Genet. 2011;20:193-201

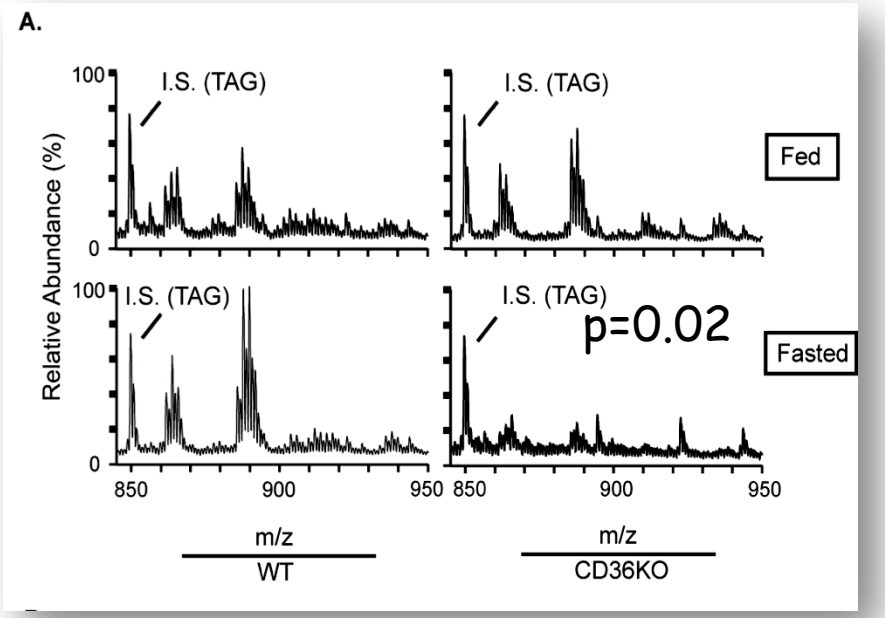


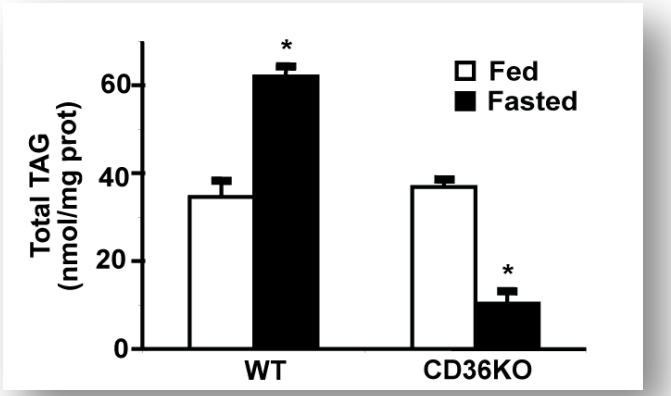




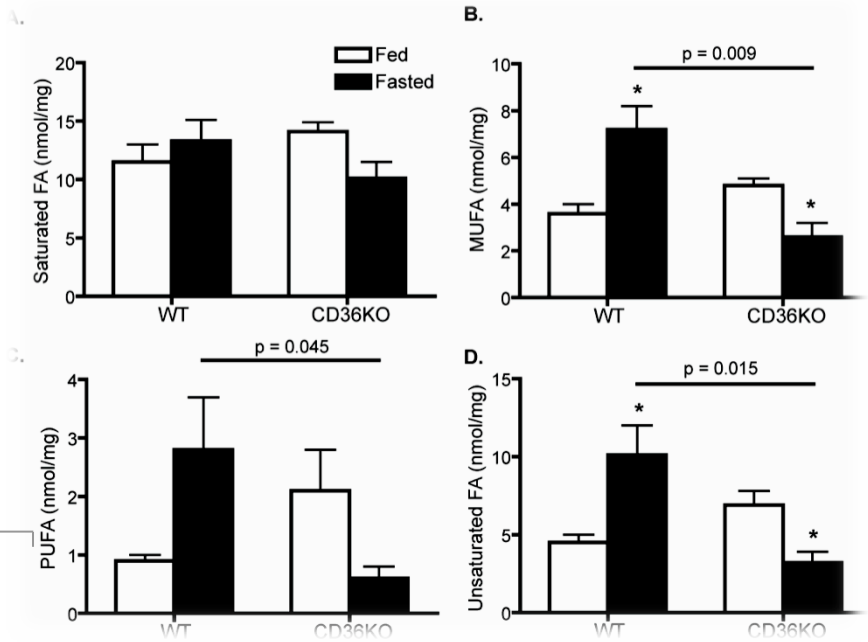

A
Fed
Fasted
Refed
*
QTc (ms)
Time (h)
CD36 WT
CD36 KO
HR (bpm)
PR (ms)
B
RR
C
RR
0.5 mV
250 ms
D
VEB
E
PVC
F
P
P P
P
P

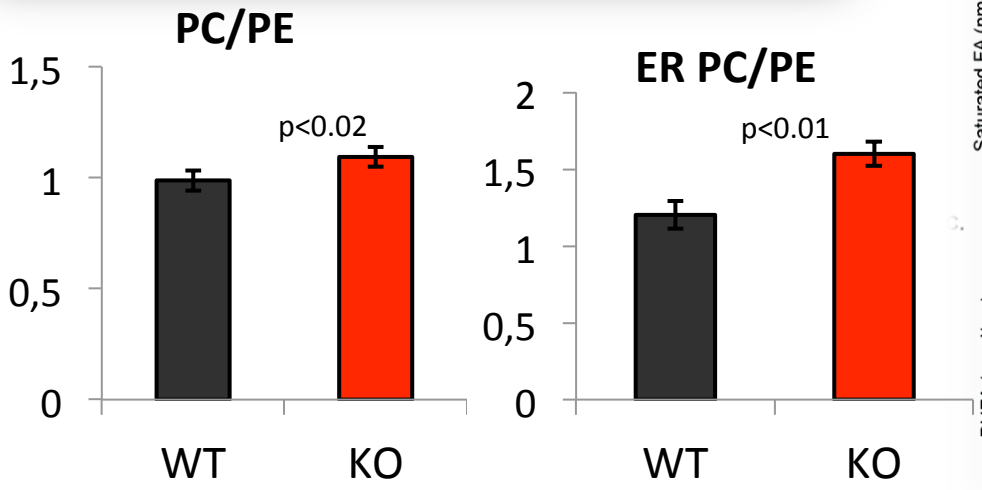
LOSS OF MYOCRADIAL TG DURING FASTING in CD36KO





Preferential Depletion of unsaturated FA





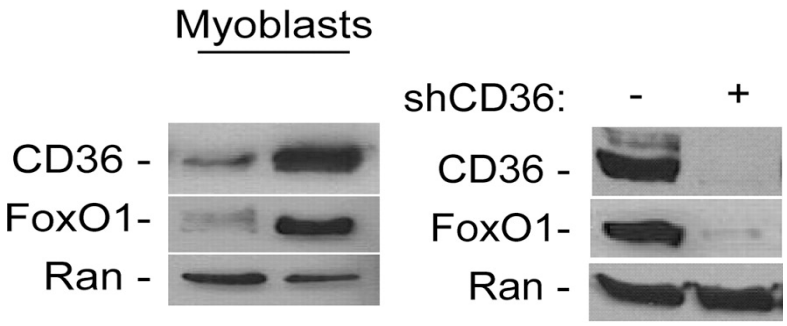
How does this impact heart function?

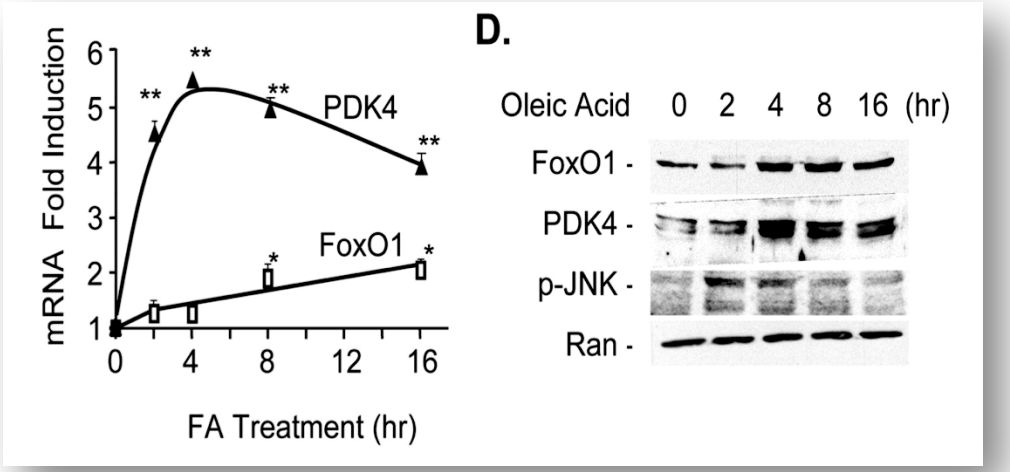
CD36 deficiency and insulin responsiveness (rodents)

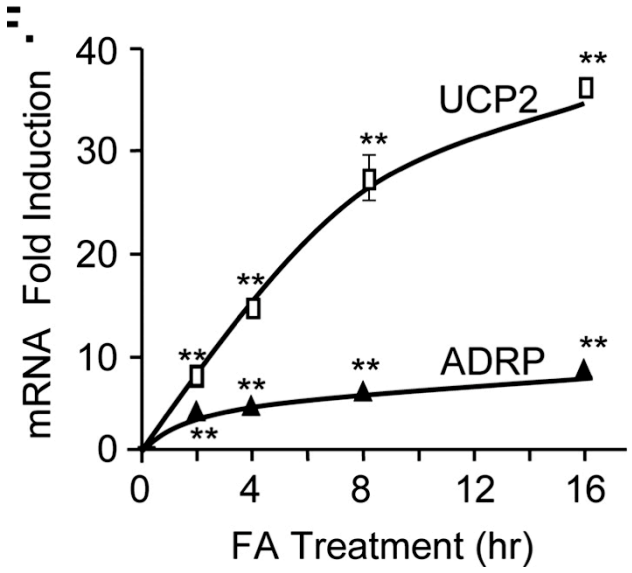
- CD36 deficiency enhances peripheral insulin sensitivity.
- Increases susceptibility to insulin resistance from high fructose/sucrose.
- Partially protects from insulin resistance caused by high fat.

Hajri et al., JCI 2002
Hajri et al., Diabetes 2007

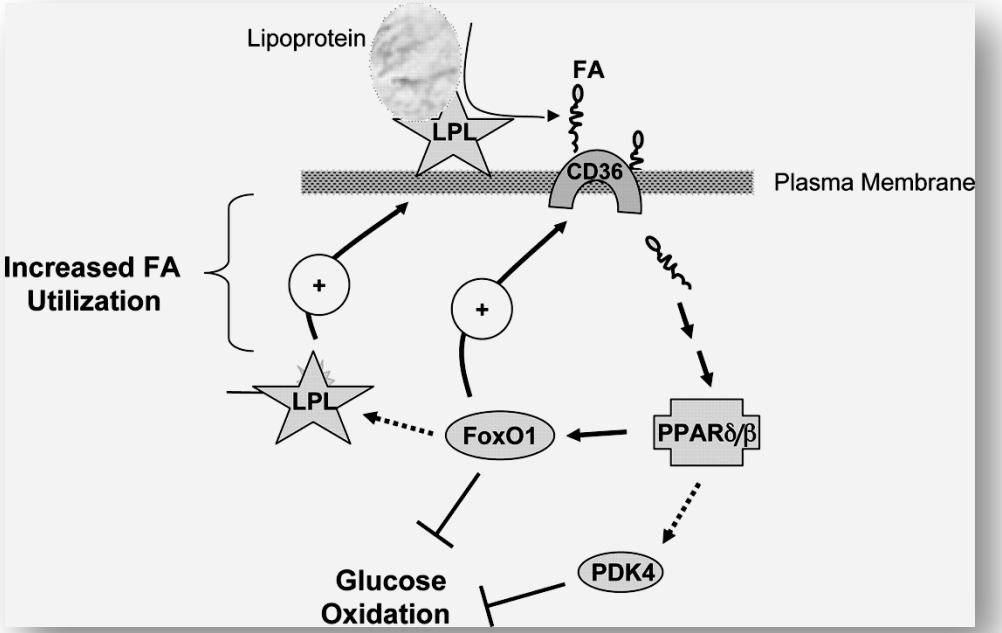
CD36 contributes to regulation of muscle FoxO1 and PDK4 via PPARd







Nahle et al., JBC 2008



CD36: The Good

Uptake of apoptotic cells that occur as a part of normal homeostasis and in the context of inflammatory resolution

Uptake of pathogens; triggering the immune response

Uptake of modified proteins / lipids / lipoproteins that occur non-pathologically

Uptake of fatty acids

Inhibition of angiogenesis in the context of wound resolution

Down modulation of the immune response in the context of inflammatory resolution

CD36: The Bad

Uptake of modified proteins / lipids / lipoproteins that occur in a pathological setting (e.g. hyperlipidemia, atherosclerosis, diabetes, alzheimer's disease)

Inhibition of angiogenesis in hyperlipidemic and diabetic settings

Triggering a pro-inflammatory response in the context of uptake of modified lipoprotein and protein ligands (e.g. fibrillar β-amyloid)

Dysregulation of insulin responsiveness as a result of fatty acid uptake in a diabetic setting

Febbraio and Silverstein, 2007