# The beneficial effect of lomitapide on the cardiovascular system in LDLr$^{-/-}$ mice with obesity

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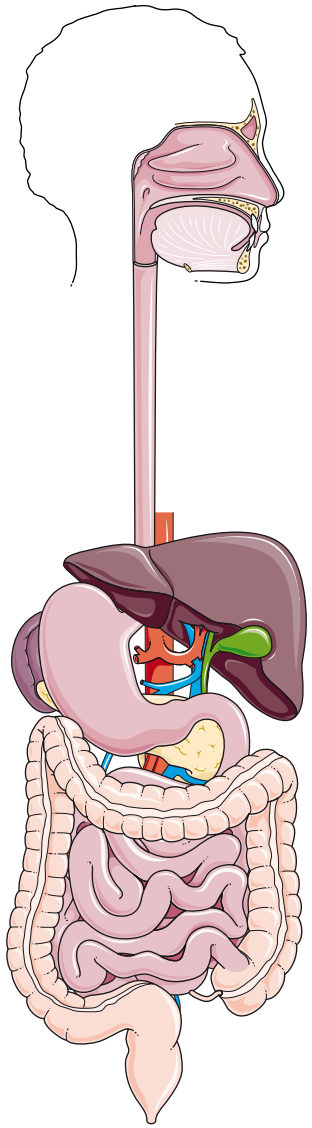
# *Background*



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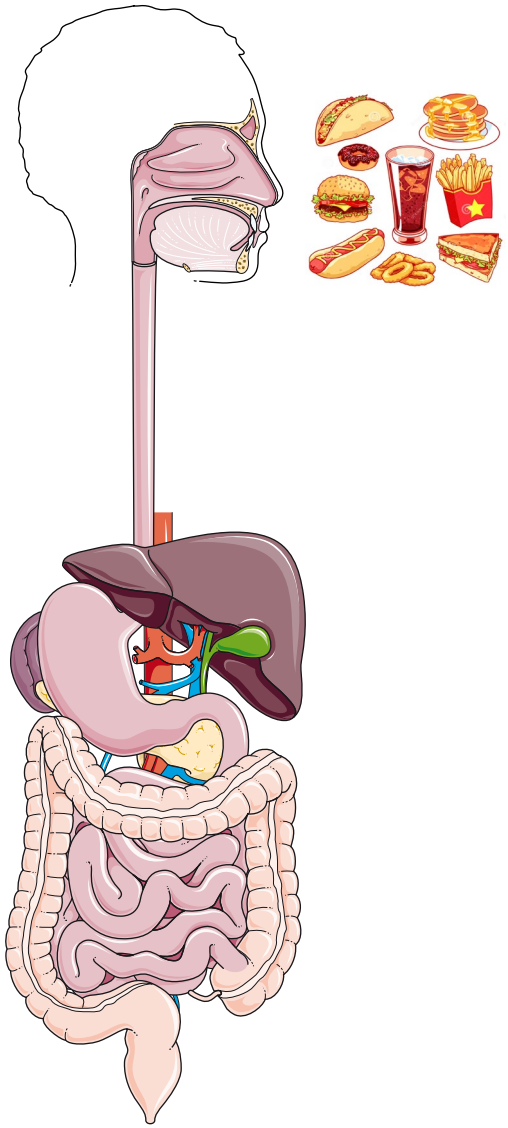

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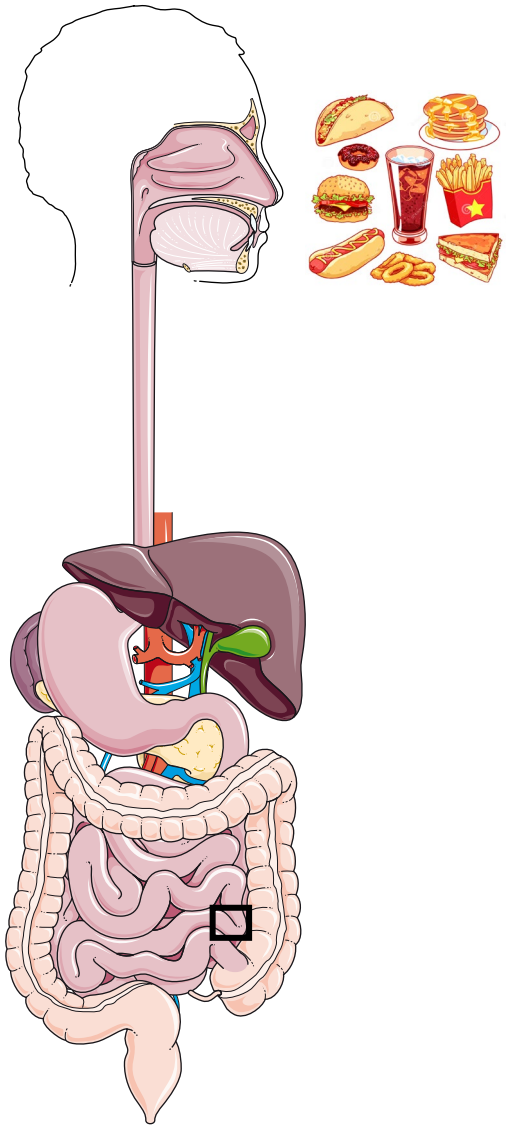

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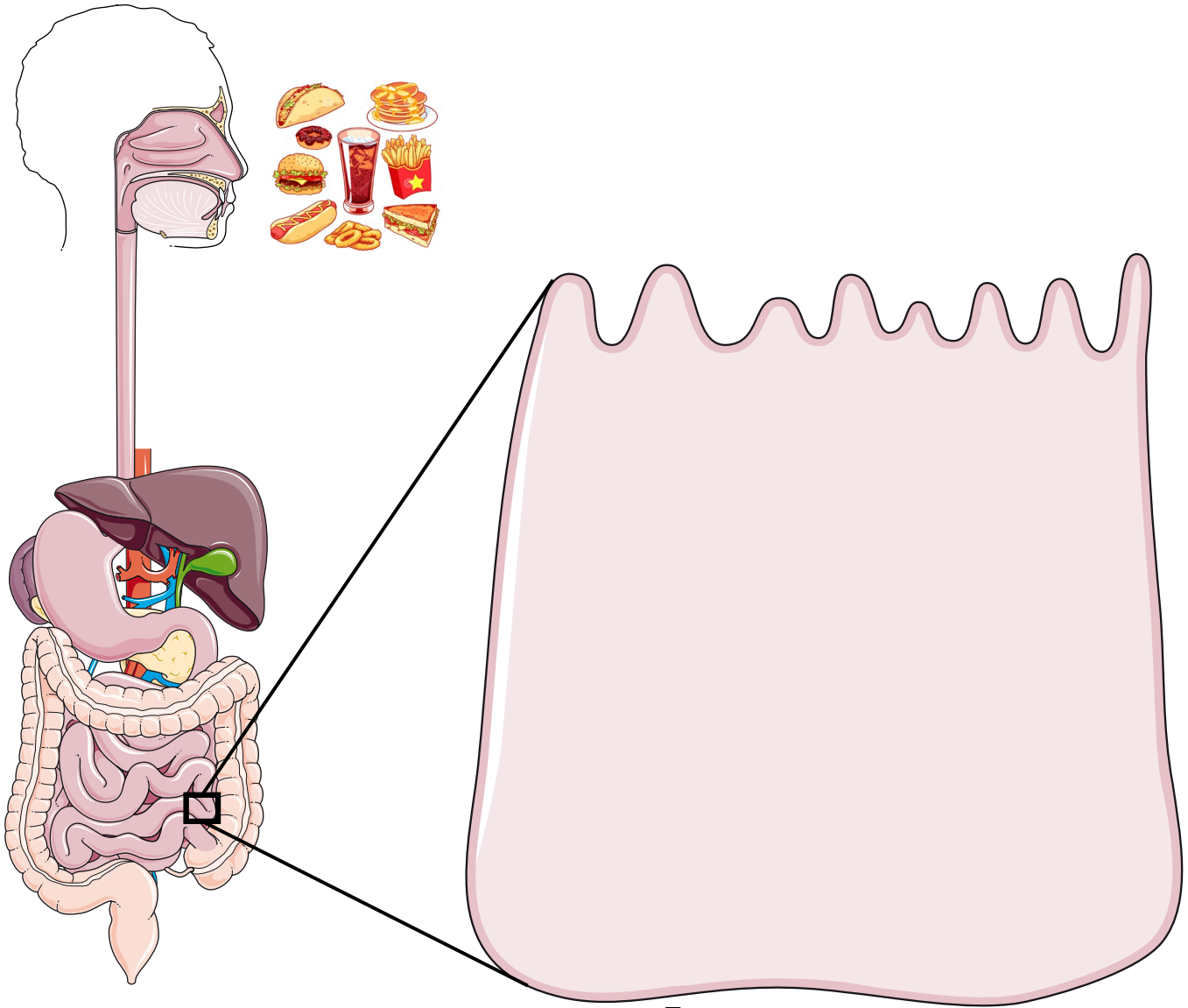
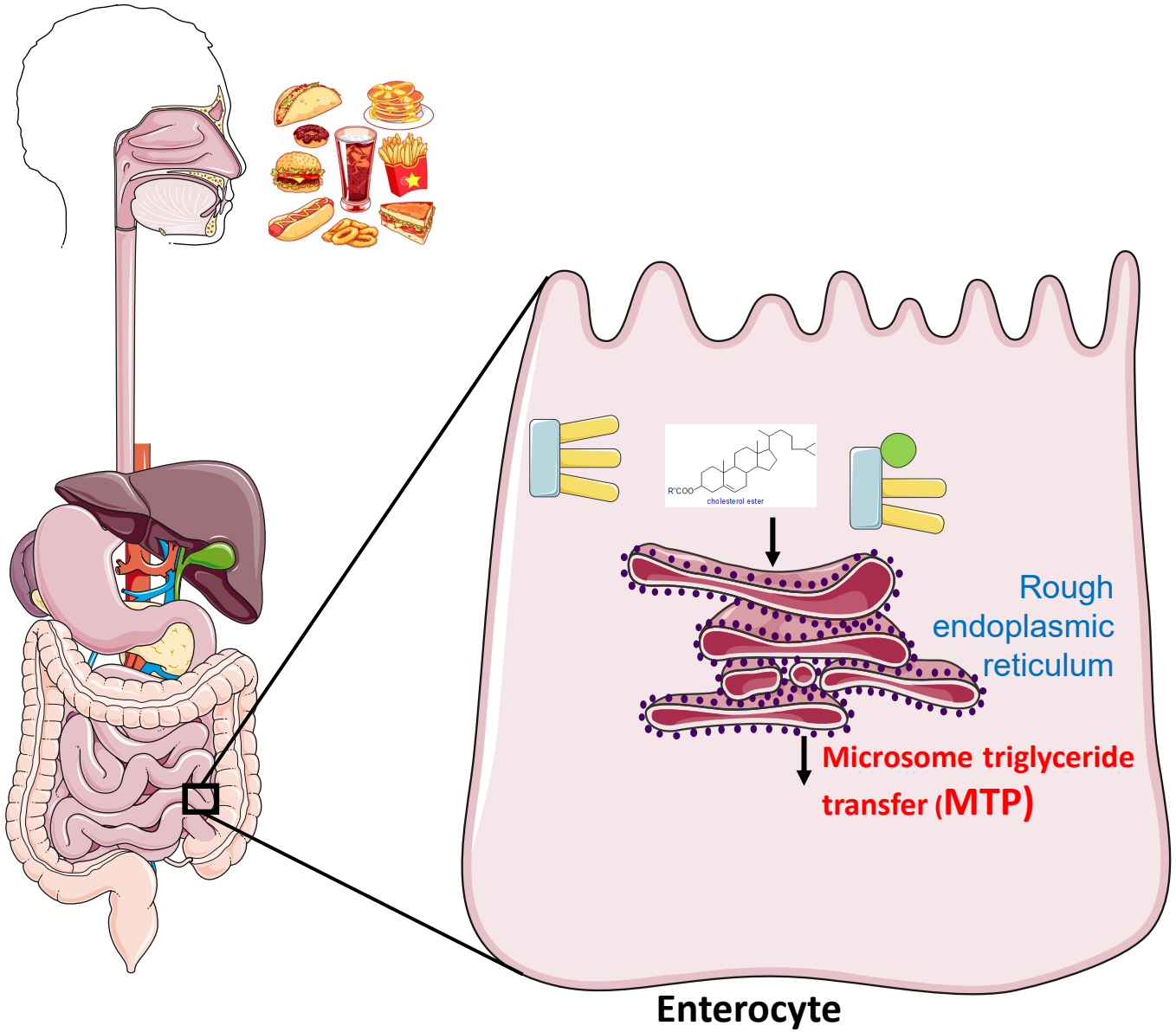
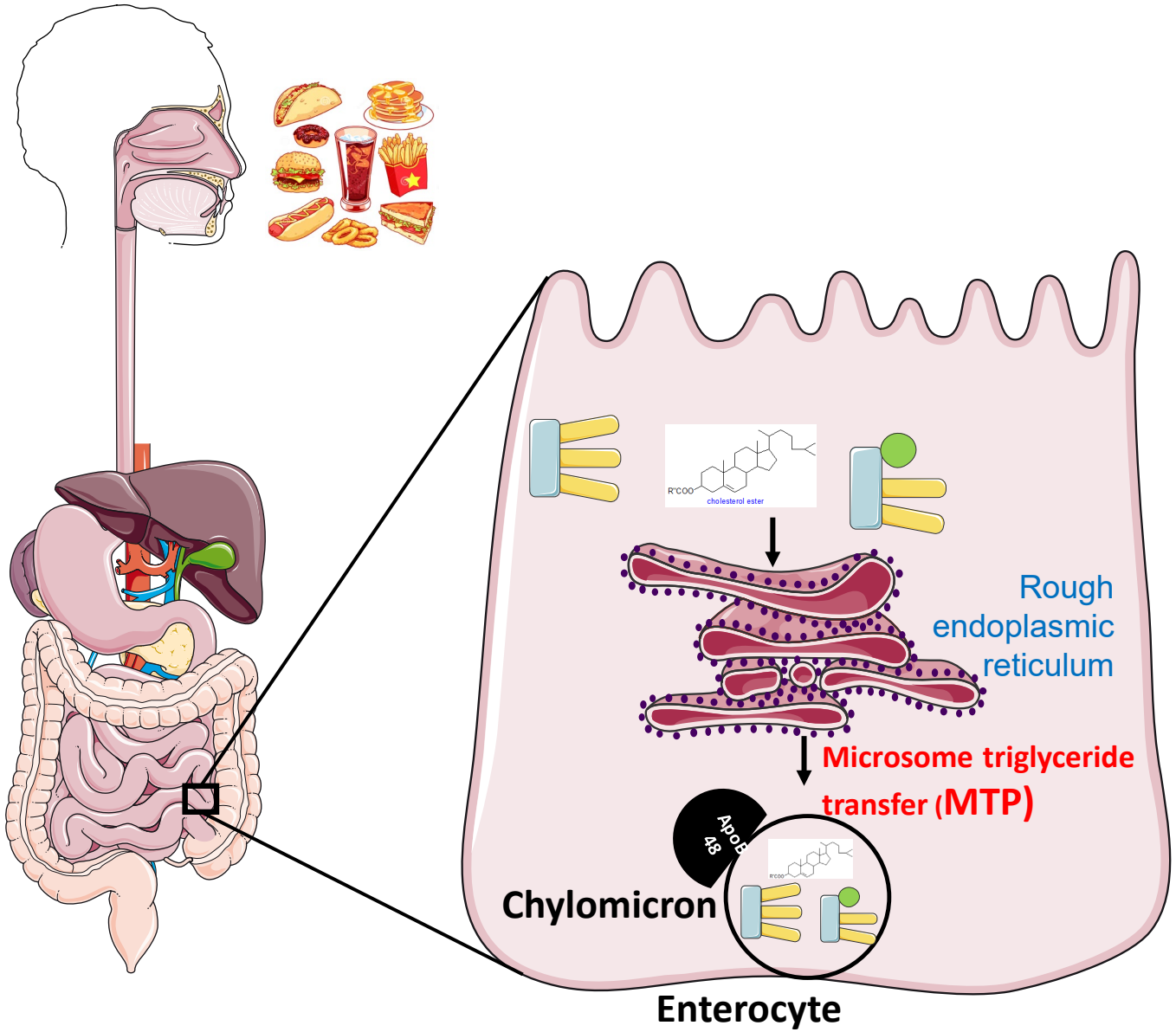


Enterocyte

# Background

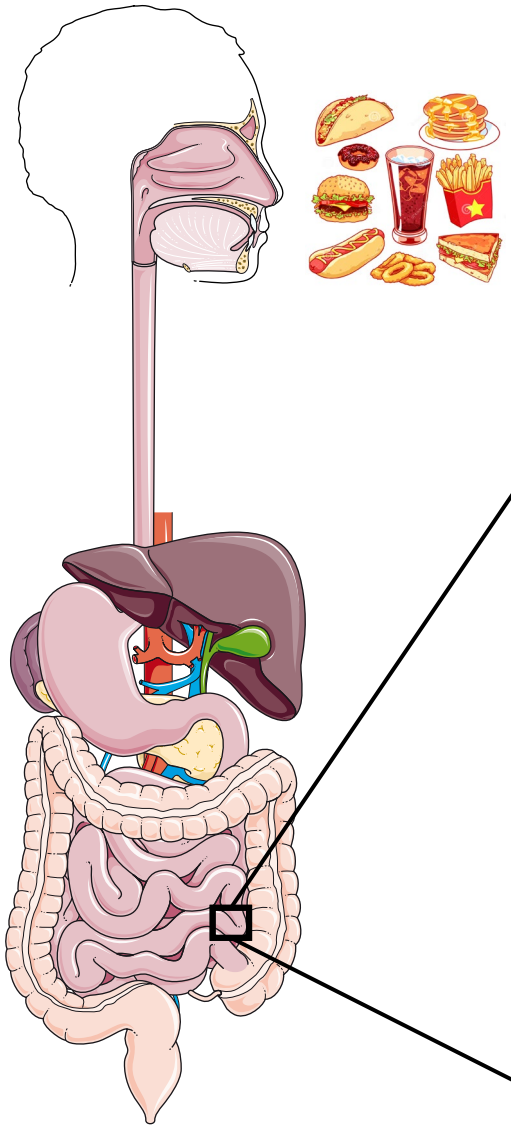

R'COO
cholesterol ester
Rough endoplasmic reticulum
Microsome triglyceride transfer (MTP)
Enterocyte

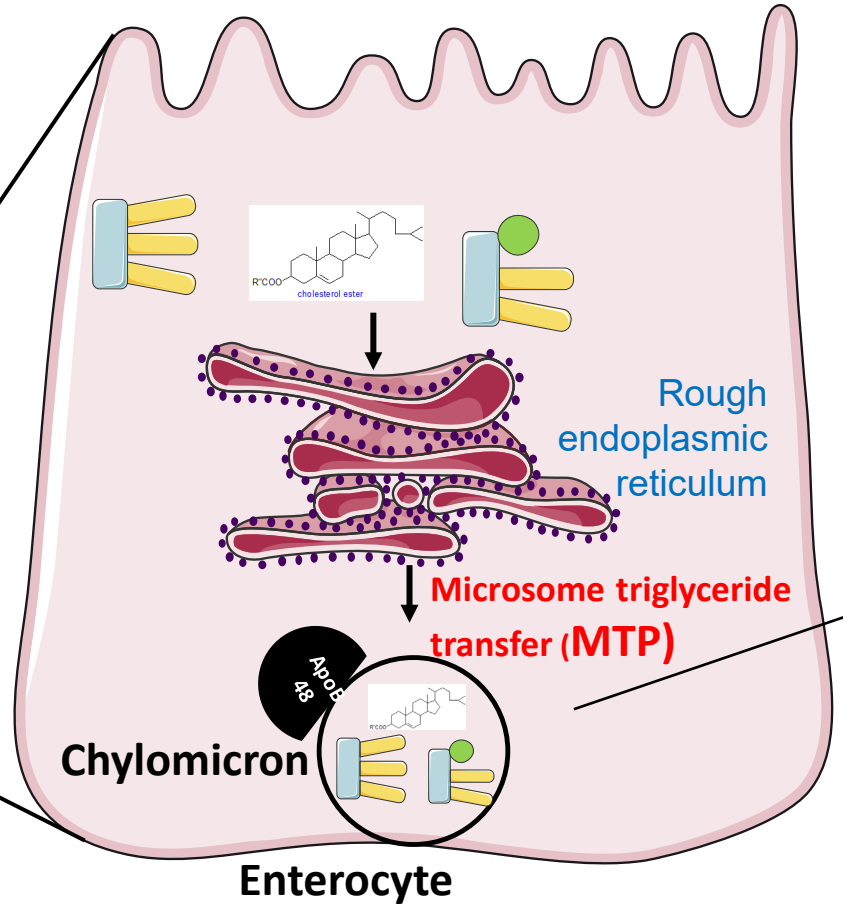
# Background


R'COO
cholesterol ester
Rough endoplasmic reticulum
Microsome triglyceride transfer (MTP)
ApoB 48
Chylomicron
Enterocyte

# Background

LDL



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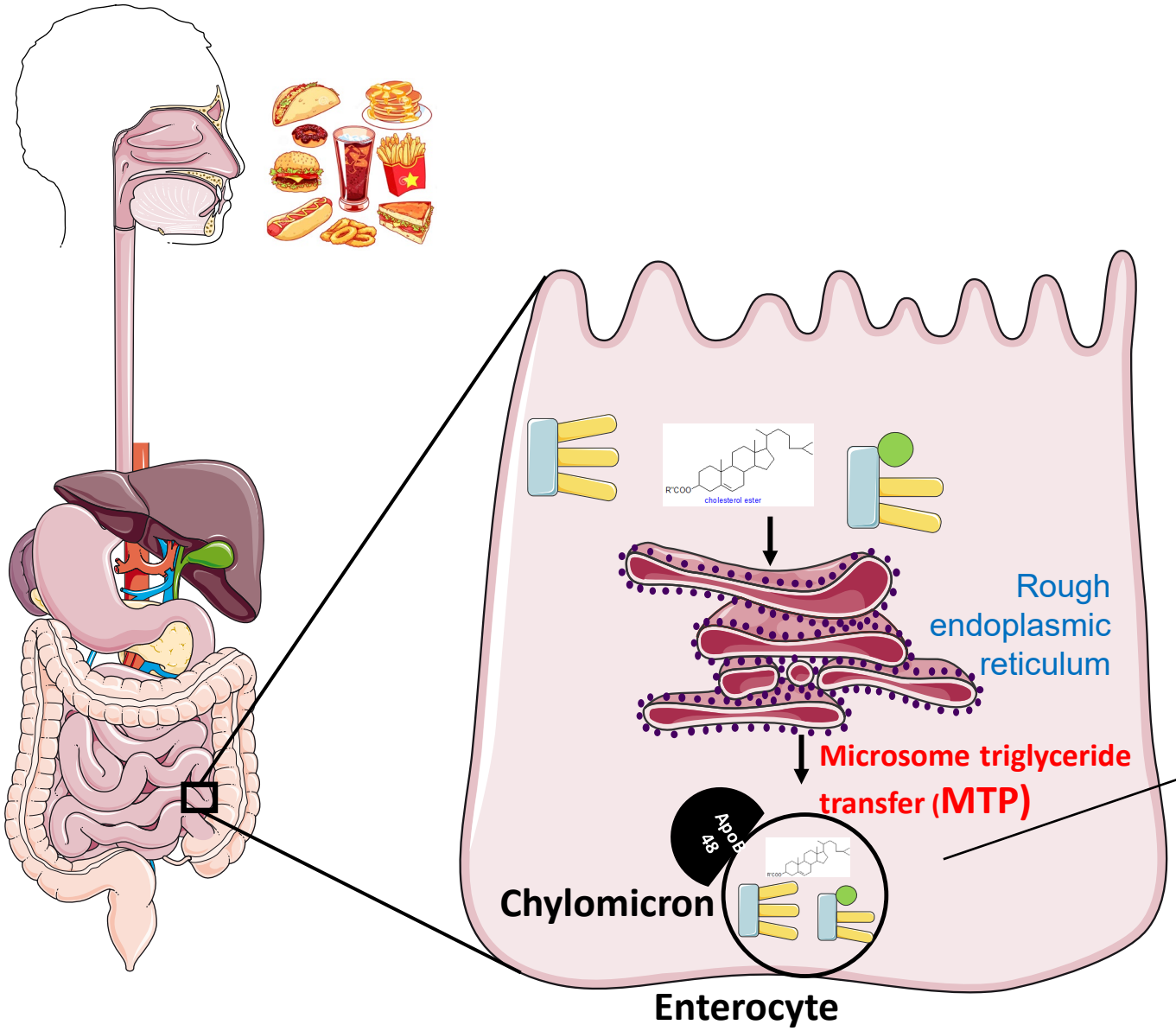
LDL

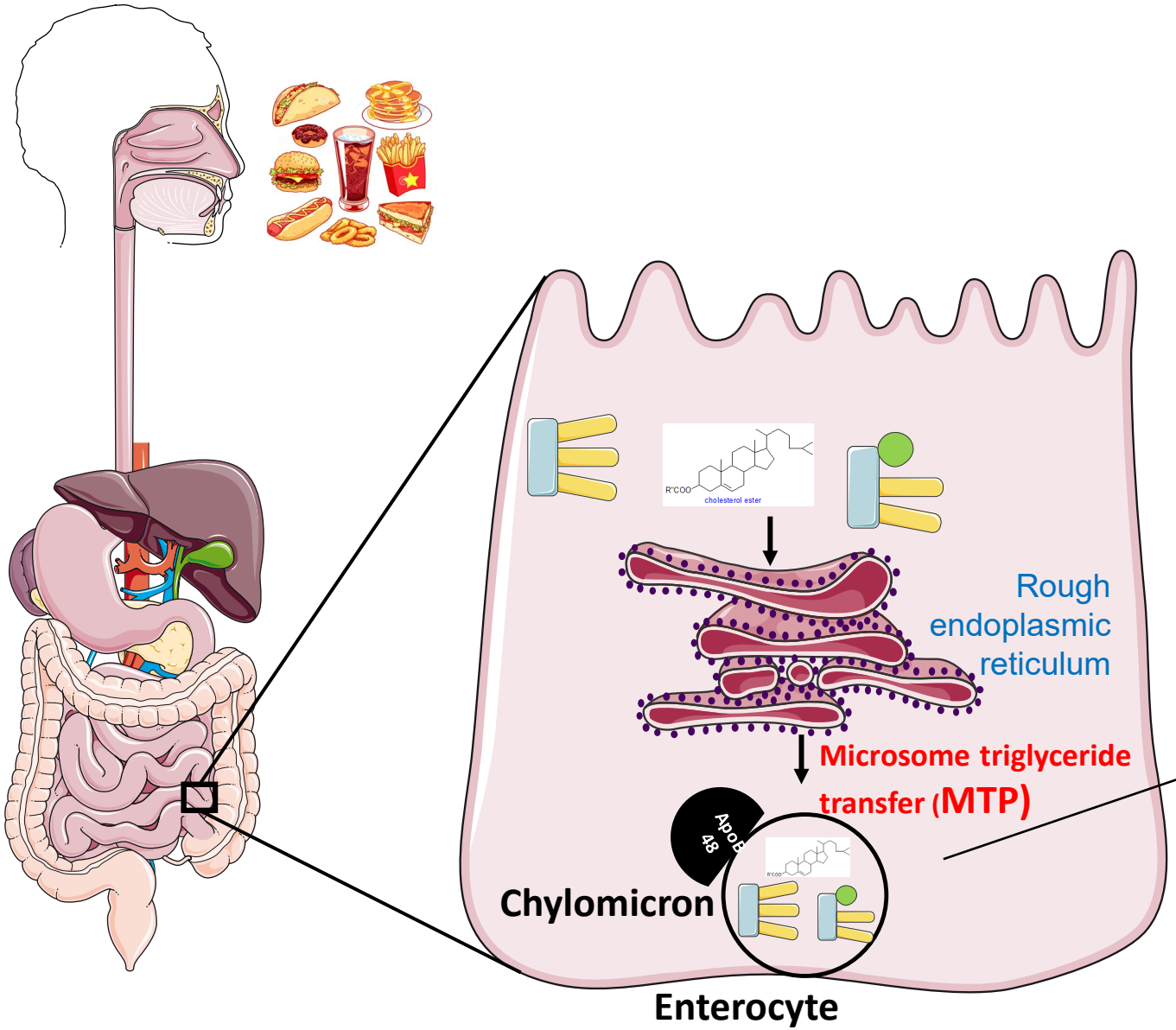




- build muscle during resistance training
- Cholesterol to form bile Acids, storage or for membrane
- Cholesterol is a building block for steroid hormones

# Background

LDL





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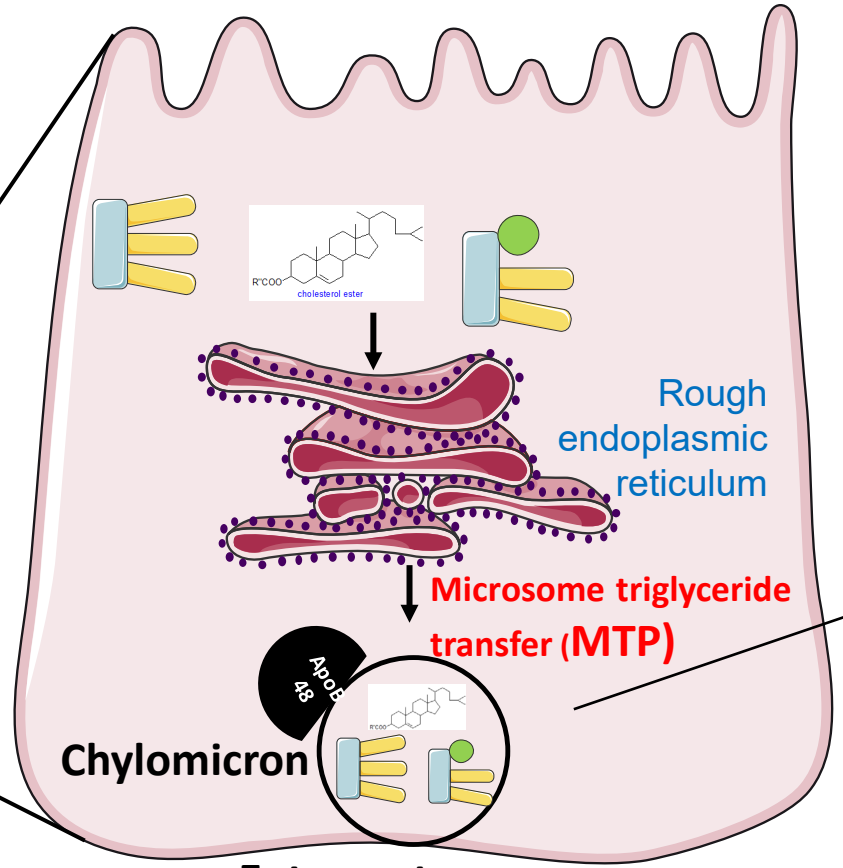
LDL

LDLr





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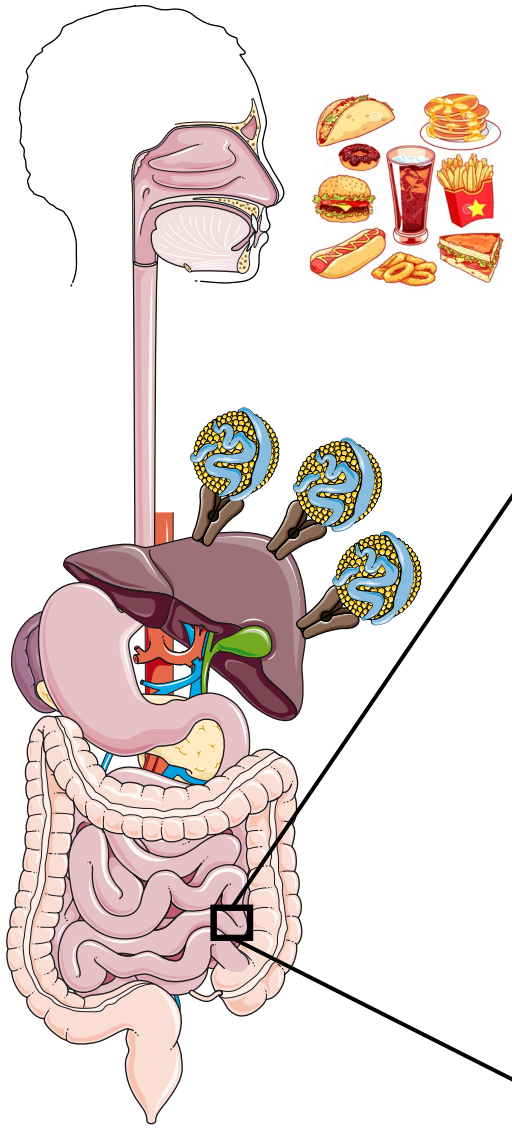
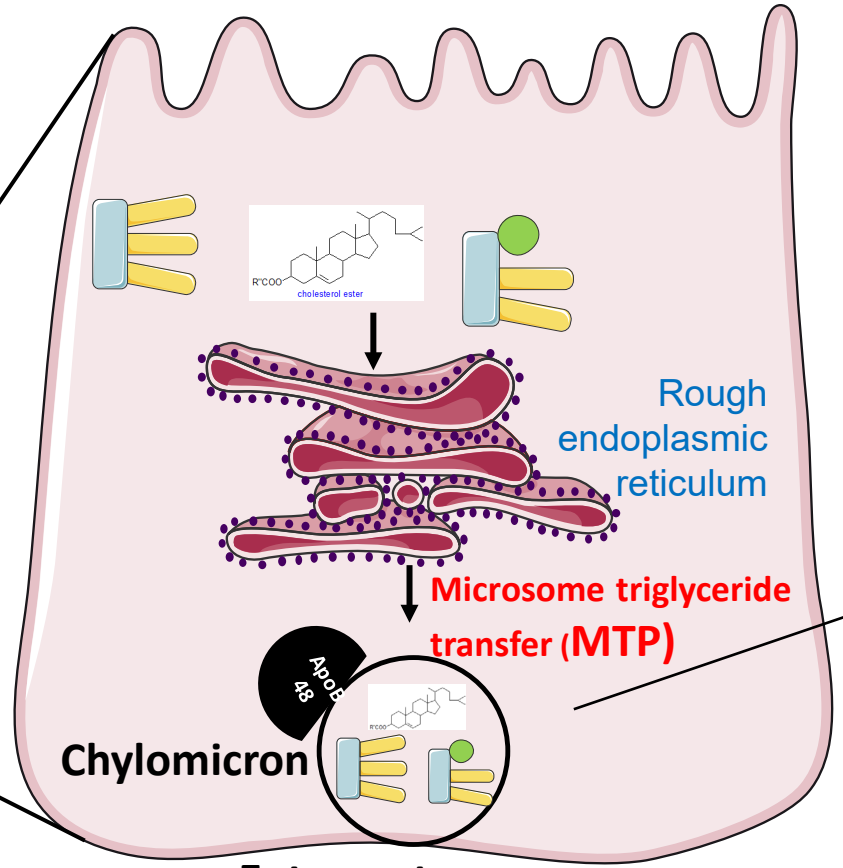
LDL

LDLr







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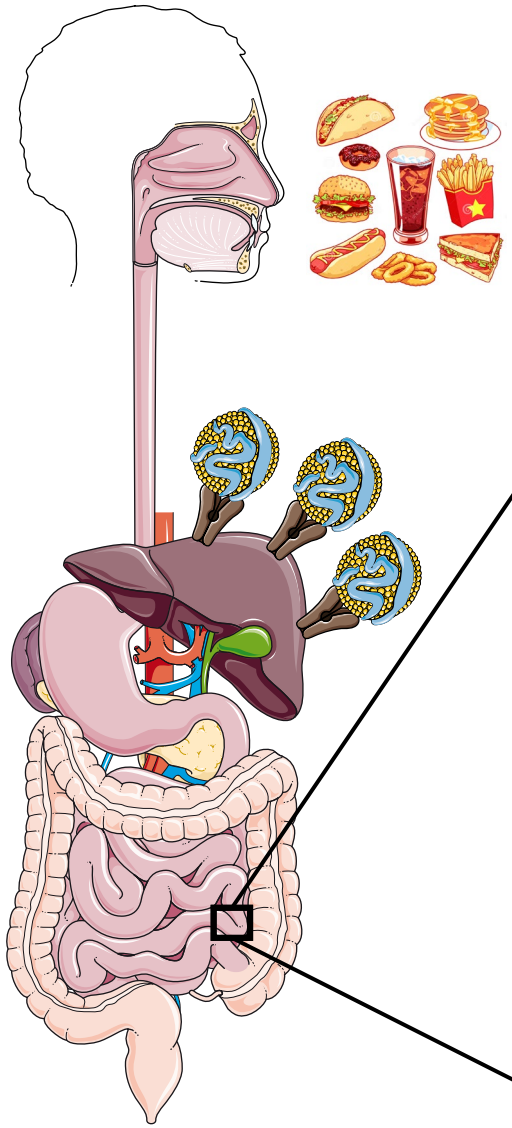
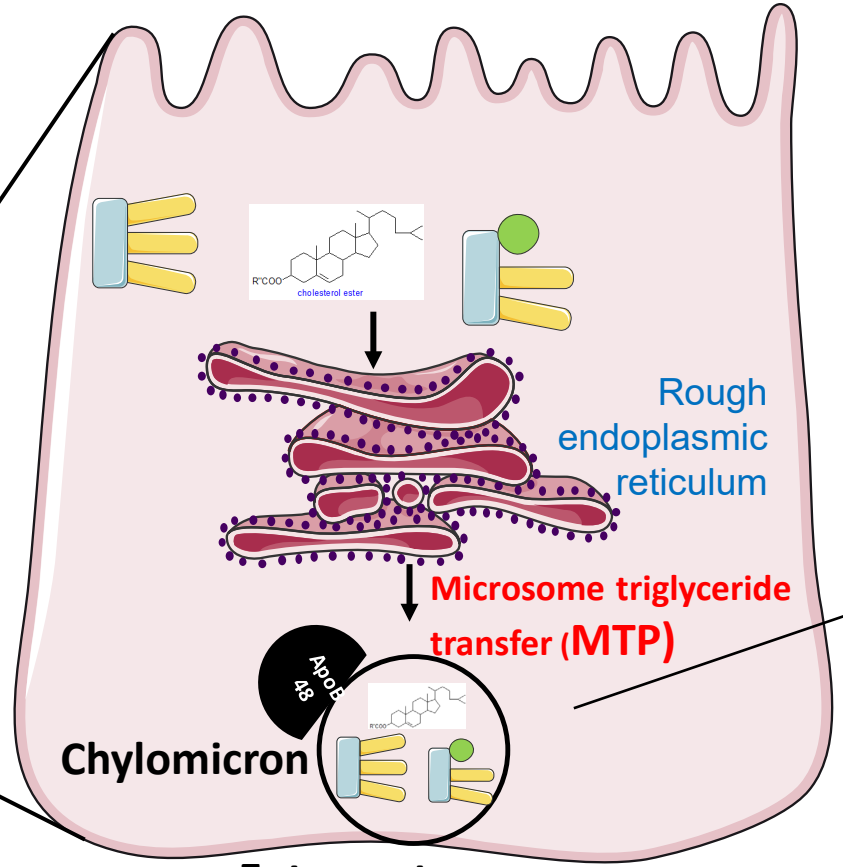
LDL

LDLr







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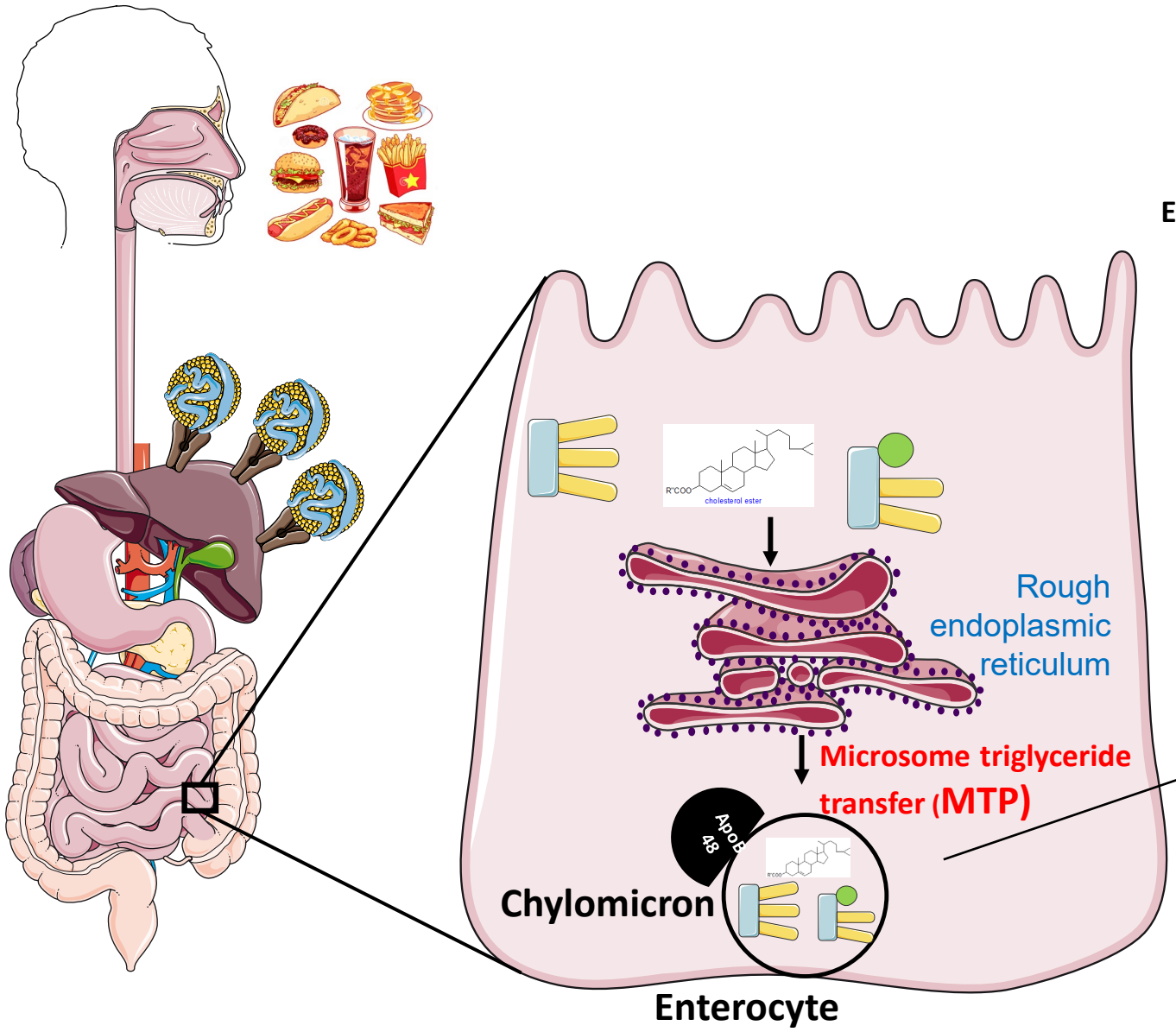


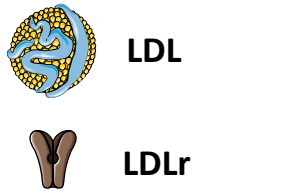


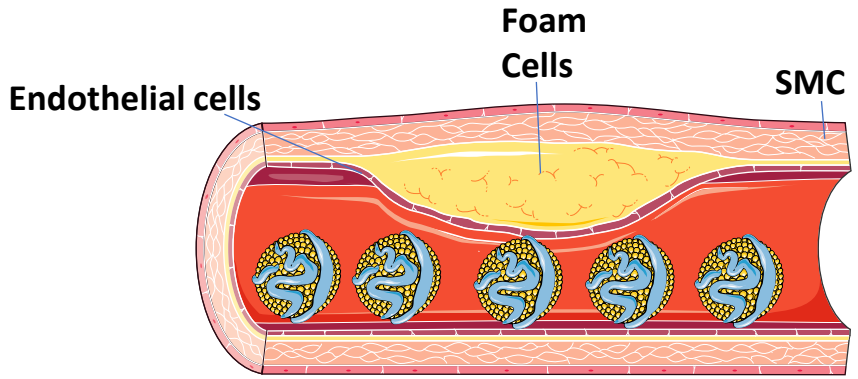



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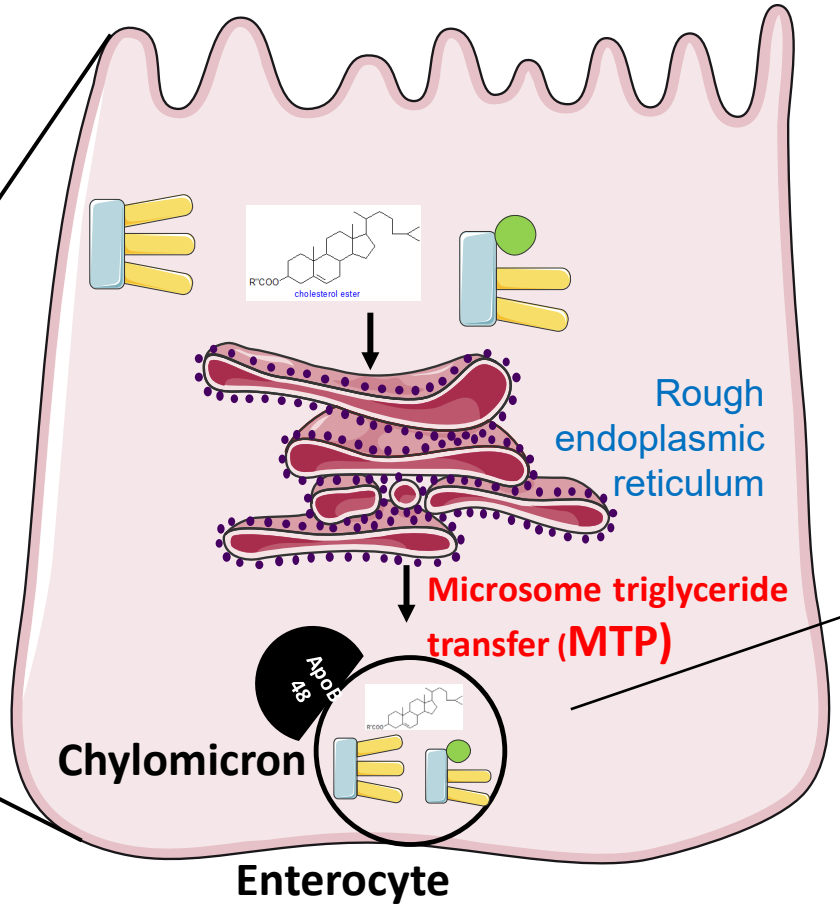
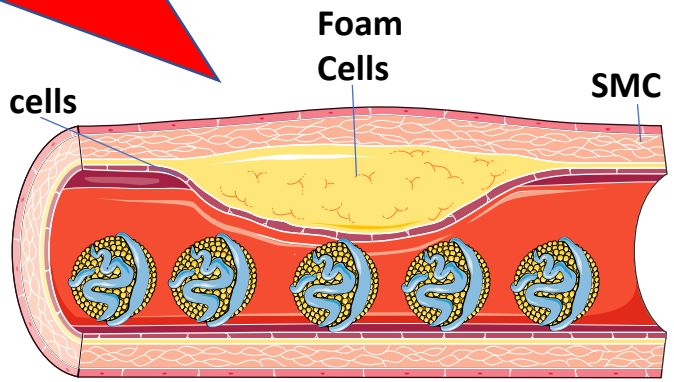
# Background

Cardiovascular diseases

LDL

LDLr





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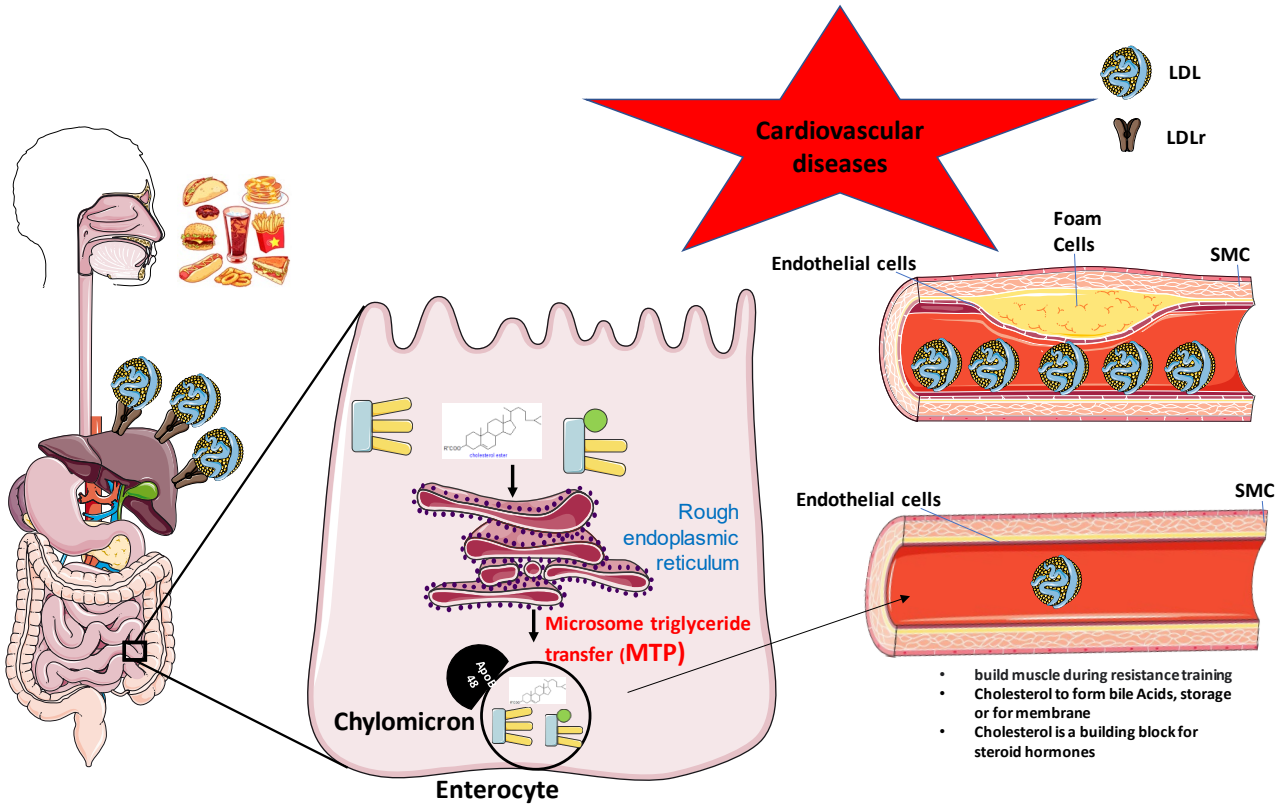
# *Homozygous familial hypercholesteremia (HoFH)*

- (HoFH) is a rare autosomal dominant metabolic disorder mainly caused by mutation of LDLr.
- HoFH patients exhibit higher levels of LDL from birth onward which lead to a rapid formation of atherosclerotic plaque, endothelial dysfunction and cardiovascular diseases.
- HoFH patients are minimally responsive to available drug therapies due to limited treatment options.
- Lomitapide is an oral inhibitor of microsome triglyceride transfer (MTP) protein approved by the Food and Drug Administration (FDA) for use in adults with HoFH
- Clinical trials showed that lomitapide markedly reduced plasma LDL, total cholesterol, and triglyceride (TG) levels and had anti-inflammatory effect.

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# *Objective*

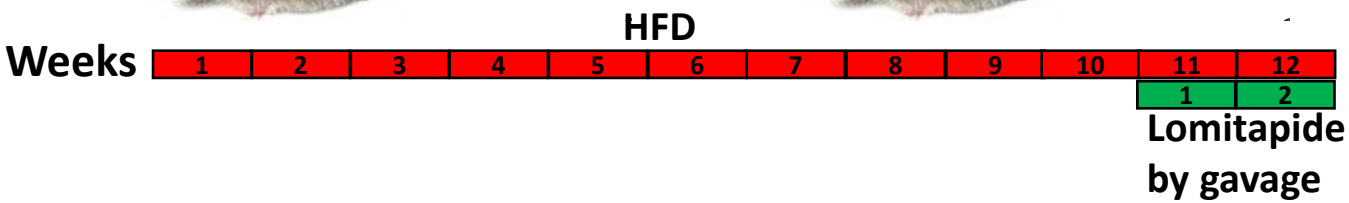
**This research aims to assess the effect of lomitapide on HFD-induced hyperlipidemia and cardiovascular diseases (CVD) using LDLr-/- mice on a high-fat diet (HFD).**

# *Methodology*

LDLr$^{-/-}$

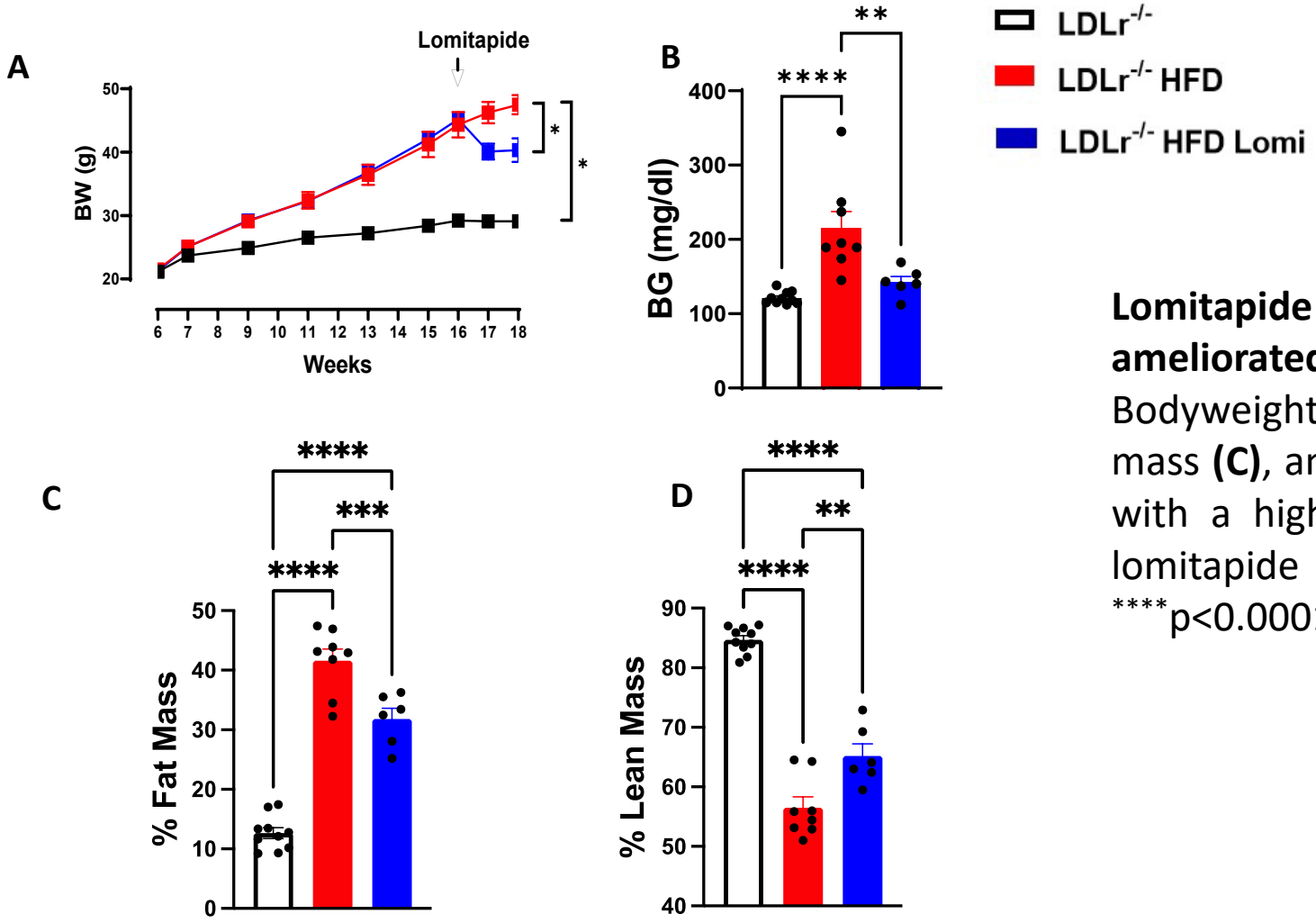
LDLr$^{-/-}$ on HFD

LDLr$^{-/-}$ on HFD Treated with lomitapide (1mg/kg/day)



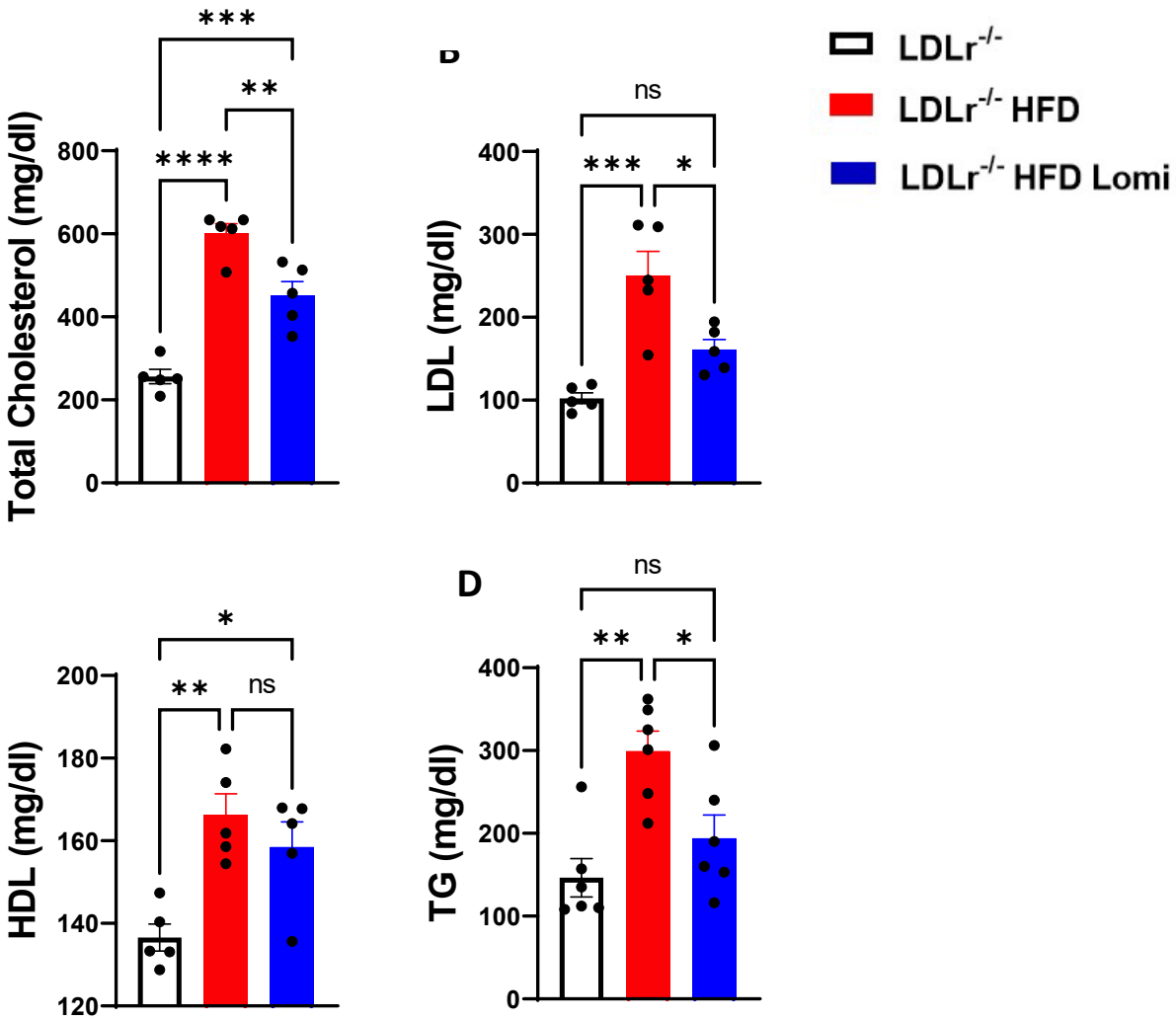

- Body Weight and composition
- Serum to measure lipid profile, glucose and inflammatory markers
- Aorta to determine vascular function

# Results



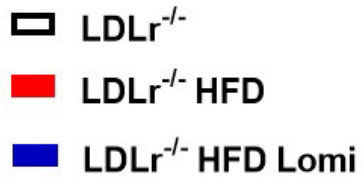

**Lomitapide reduced body weight, blood glucose and ameliorated body composition profile in LDLr$^{-/-}$ mice on HFD.** Bodyweight (BW) **(A)**, blood glucose (BG) **(B)**, percentage of fat mass **(C)**, and lean mass **(D)** in LDL$^{-/-}$ control mice and mice fed with a high-fat diet (HFD) in the presence and absence of lomitapide treatment (n=6-10). $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; $^{****}p<0.0001$

# Results



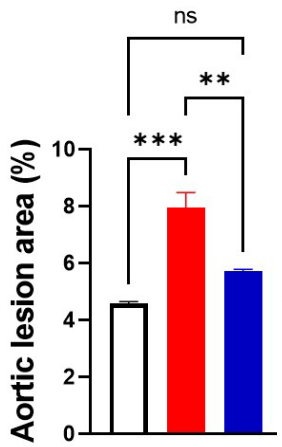

**Lomitapide enhanced the lipid profile in LDLr$^{-/-}$ mice on HFD.** Total cholesterol **(A)**, LDL **(B),** HDL **(C),** and TG **(D)** in plasma from LDL$^{-/-}$ control mice and mice fed with a high-fat diet (HFD) treated with vehicle or lomitapide (n=5-6). LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglyceride. ns>0.05; $^{*}$p<0.05; $^{**}$p<0.01; $^{***}$p<0.001; $^{****}$p<0.0001

# Results



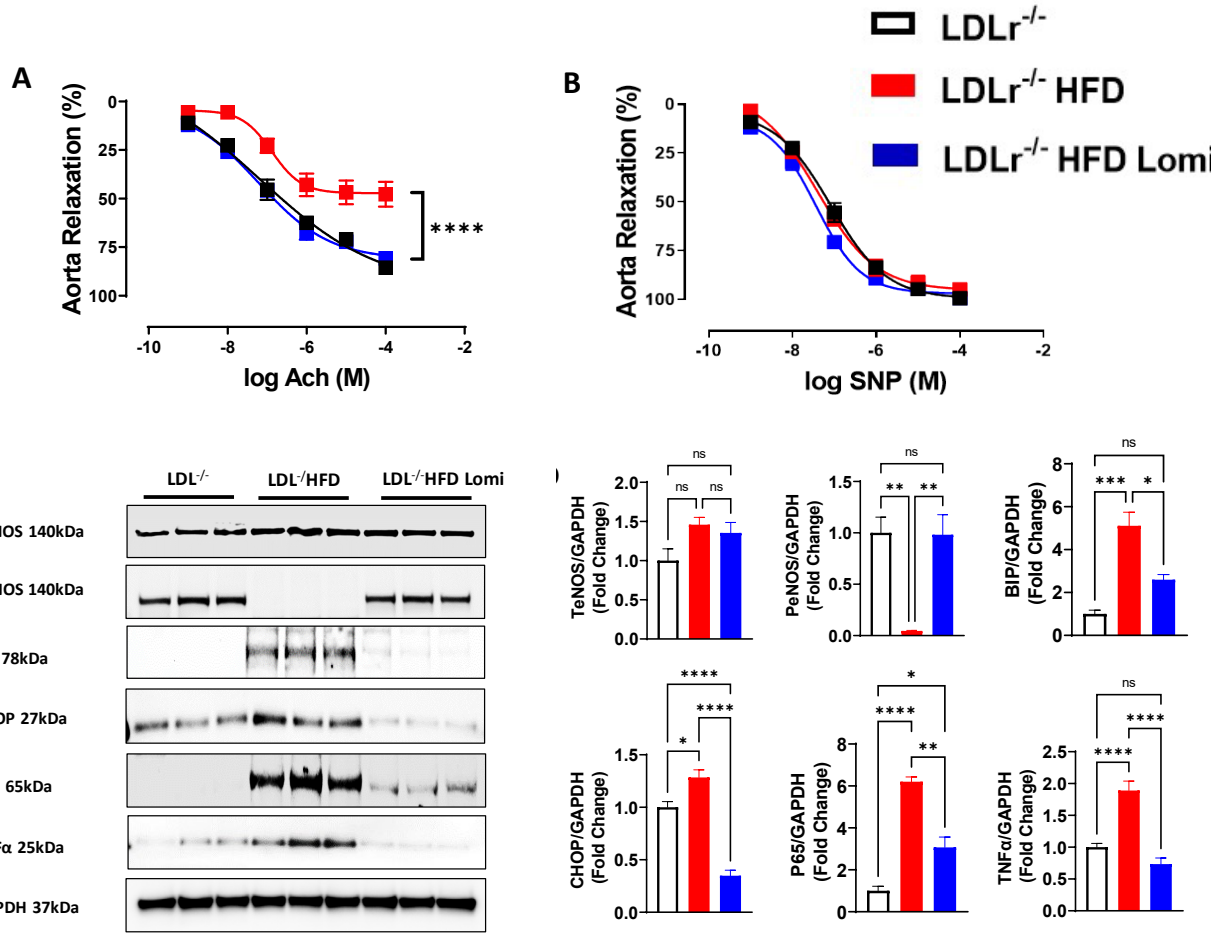

A


B



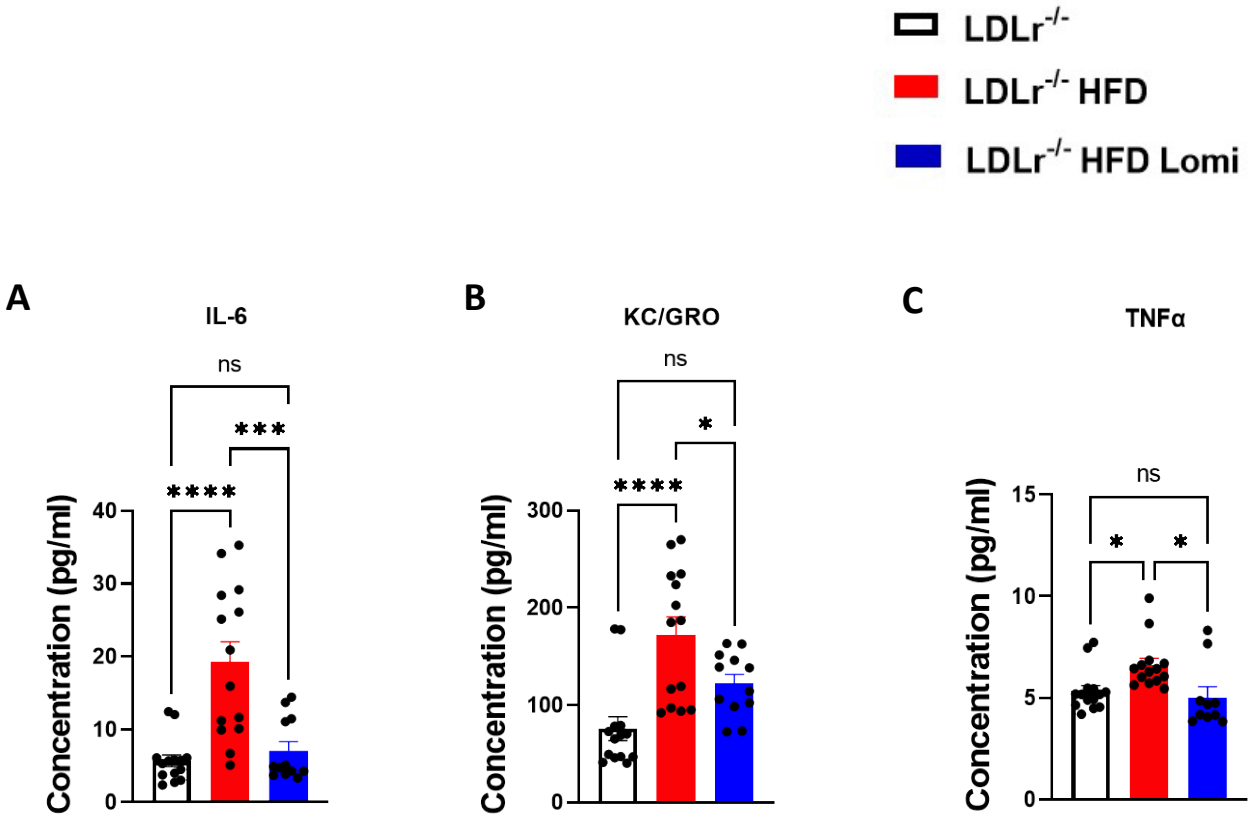

**Oil O Red staining and quantification of plaque lesion area.** Lomitapide decreased plaque surface area in the thoracic aorta from LDL$^{-/-}$ mice with obesity (n=3). Representative images of en face staining by Oil O red of the entire aorta are shown **(A)**, and the quantification of the lesion area **(B)**. ns>0.05; $^{**}p<0.01$; $^{***}p<0.001$ assessed by ANOVA followed by the Tukey test for multiple comparisons.

# Results



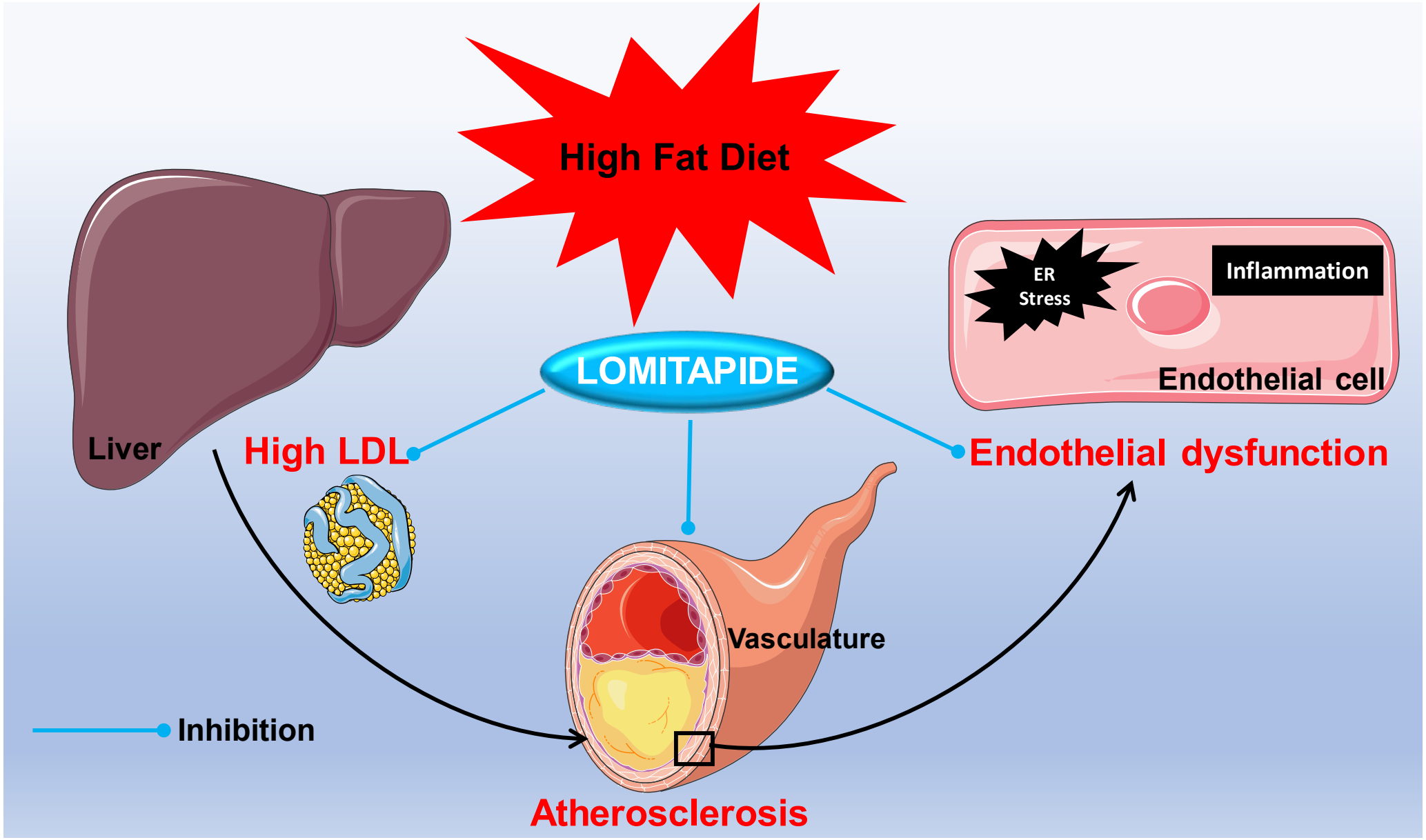

**Lomitapide prevented endothelial dysfunction in the thoracic aorta from LDLr$^{-/-}$ mice on HFD.** Endothelium-dependent dilation to Ach **(A)**, endothelium-independent dilation to SNP **(B)** (n=11-14), immunoblots showing (T-eNOS, p-eNOS, BIP, CHOP, P65, TNFα, and GAPDH) **(C),** and quantification **(D)** in thoracic aorta from LDL$^{-/-}$ lean mice and LDL$^{-/-}$ obese mice treated with vehicle or lomitapide (n=3-6). Ach: acetylcholine; SNP: Sodium nitroprusside; T-eNOS: total endothelial nitric oxide synthase; p-eNOS: phosphorylated endothelial nitric oxide synthase; BIP: GRP78; CHOP: The C/EBP Homologous Protein; P65: NF-kappa-B; TNFα: Tumor Necrosis Factor-alpha. ns>0.05; $^{*}$p<0.05; $^{**}$p<0.01; $^{***}$p<0.001; $^{****}$p<0.0001.

# *Results*




**Lomitapide treatment showed an anti-inflammatory effect in LDLr$^{-/-}$ mice with obesity.** lomitapide treatment significantly decreased inflammatory cytokines IL-6 **(A)**, KC/GRO **(B)**, and TNFα **(C)** in LDL$^{-/-}$ obese mice (n=12-14). IL-6: Interleukin 6; KC/GRO: Neutrophil activating protein 3; TNFα: Tumor Necrosis Factor-alpha. ns>0.05; $^{*}$p<0.05; $^{**}$p<0.01; $^{***}$p<0.001; $^{****}$p<0.0001.

# Conclusion


High Fat Diet
LOMITAPIDE
Liver
High LDL
ER Stress
Inflammation
Endothelial cell
Endothelial dysfunction
Vasculature
Inhibition
Atherosclerosis

# *Acknowledgment*


Undral Munkhsaikhan, PhD
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