PATHOPHYSIOLOGY of NAFLD

"Multiple Hits/Multiple epiphenomena model"

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Why We Have to Know the Pathophysiology of NAFLD?

- WHAT THE PATHOPHYSIOLOGY SAY?

  HOW IT START

  HOW IT AFFECT

  HOW IT CONTINUE

- TO DETECT:

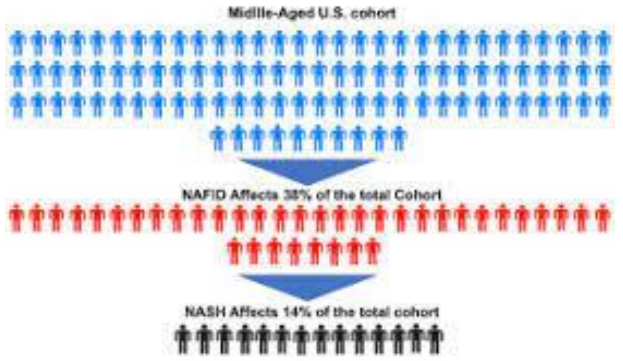
  “at-risk” Population

  Stage of Disease (Diagnostic Tests)

  Treatment Plan (Therapeutics)

CVD and Heart Failure **Renal Disease**

HTN DM2 Atherosclerosis



NAFLD spectrum

Healthy liver → **NAFL** → **NASH** → **Compensated cirrhosis** → **Decompensated cirrhosis** → **HCC**

Fat in < 5% of hepatocytes

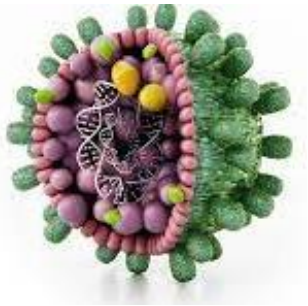
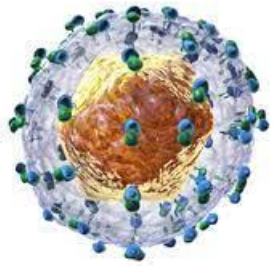
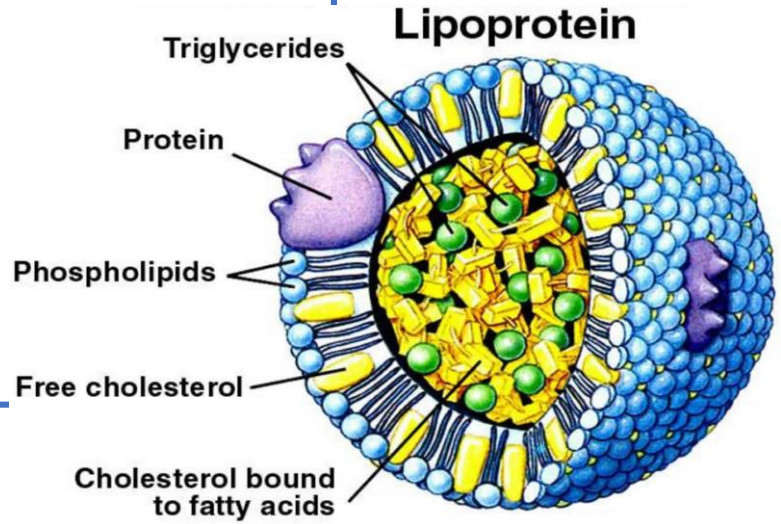
Steatosis (Fat in ≥5% of hepatocytes)

Steatosis with inflammation and fibrosis

Dead cells and severe fibrosis

20 Yrs. 30 Yrs. **Time** 40 Yrs. 50 Yrs.

Why We Have to Know the Pathophysiology of NAFLD?

CHB	CHC
	 Hepatis C Virus (HCV)
HBV	HCV
DILI	NAFL
	
Drug	FAT

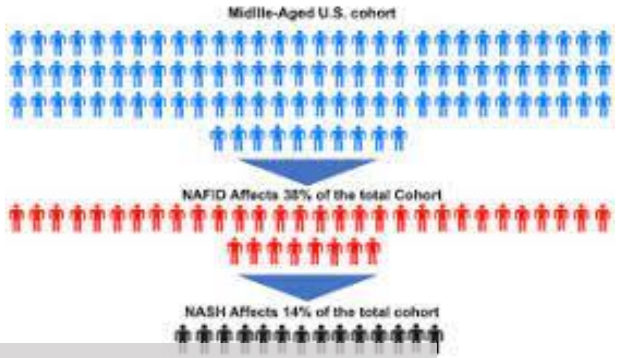
NAFLD Lipid

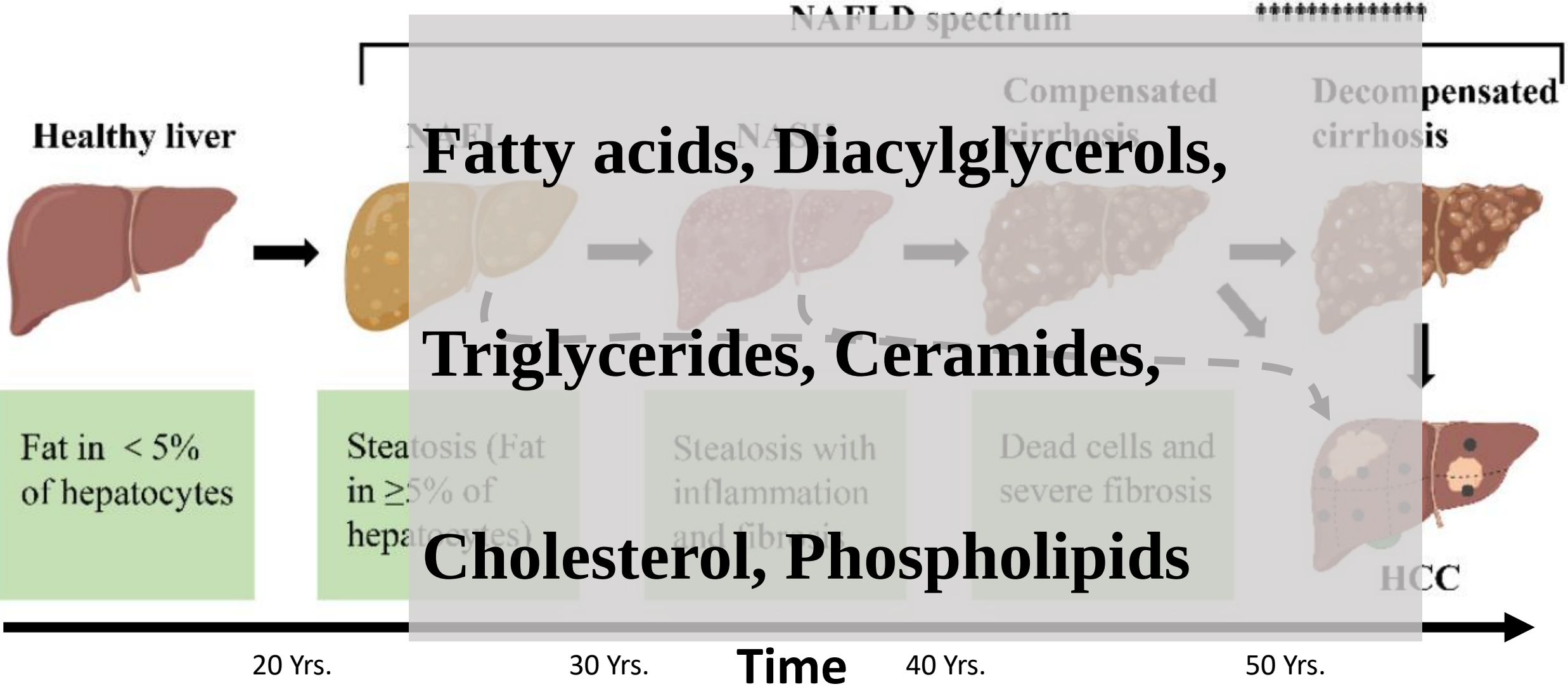
NAFLD Lipotoxicity

NAFLD Lipid-induce Liver injury (LILI)

CVD and Heart Failure **Renal Disease**

HTN DM2 Atherosclerosis





Fatty acids, Diacylglycerols,

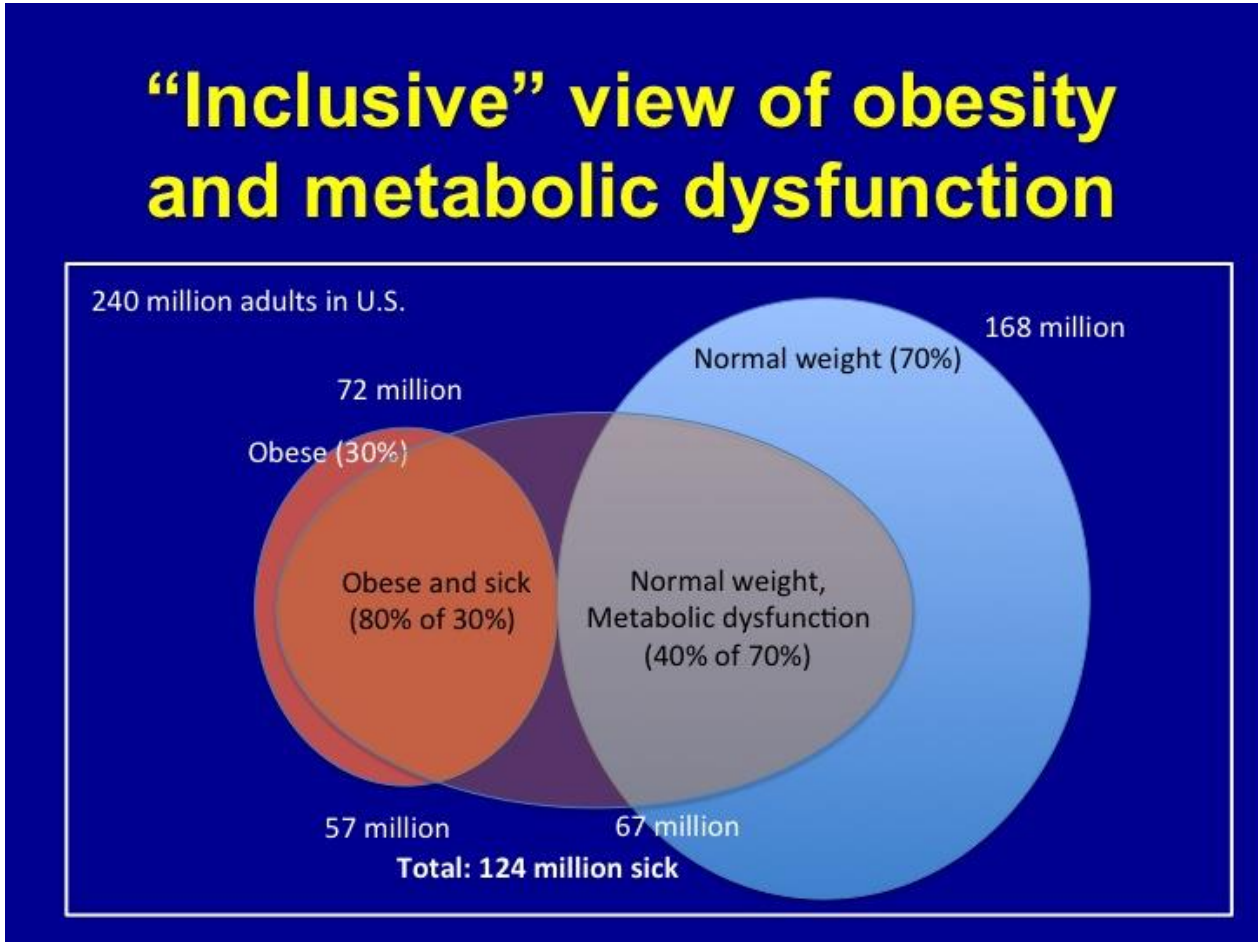
Triglycerides, Ceramides,

Cholesterol, Phospholipids

NAFLD has Two Clinical Variants :

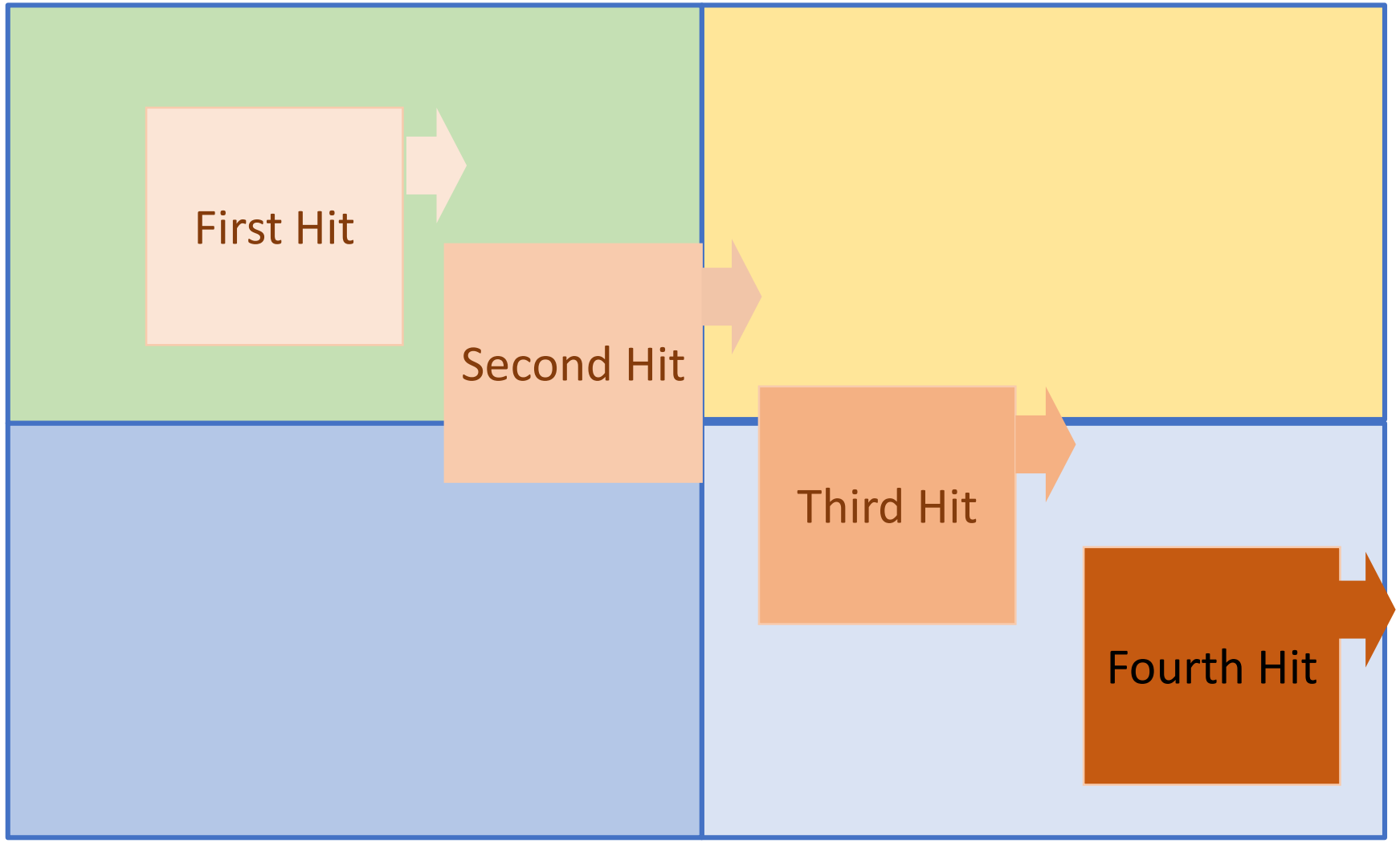
- **With Significant Lipid (fat) Excess**
  Overweight/Obese/Non-Lean NAFLD

- **Without Significant Lipid (fat) Excess**
  Lean NAFLD



MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"



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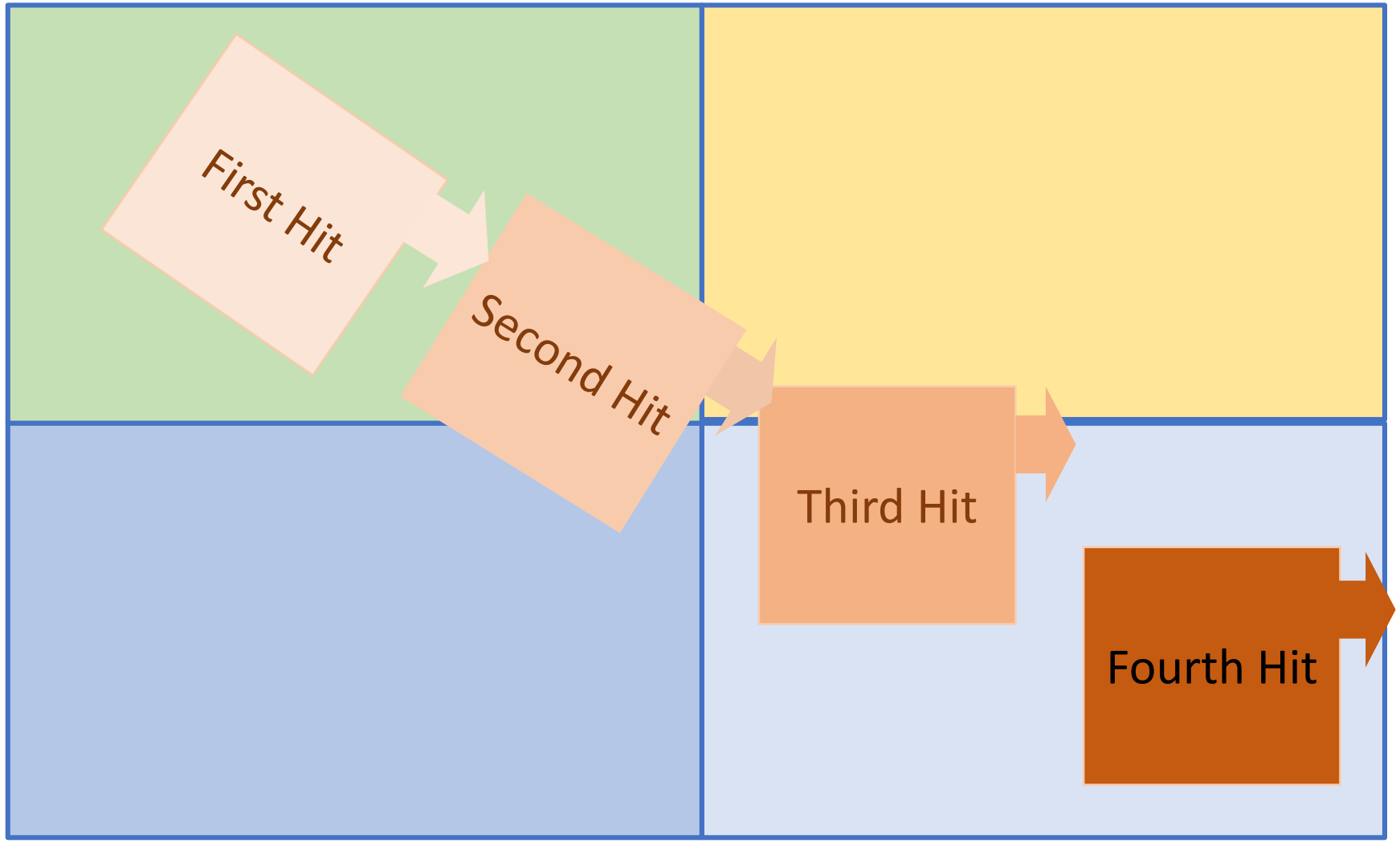
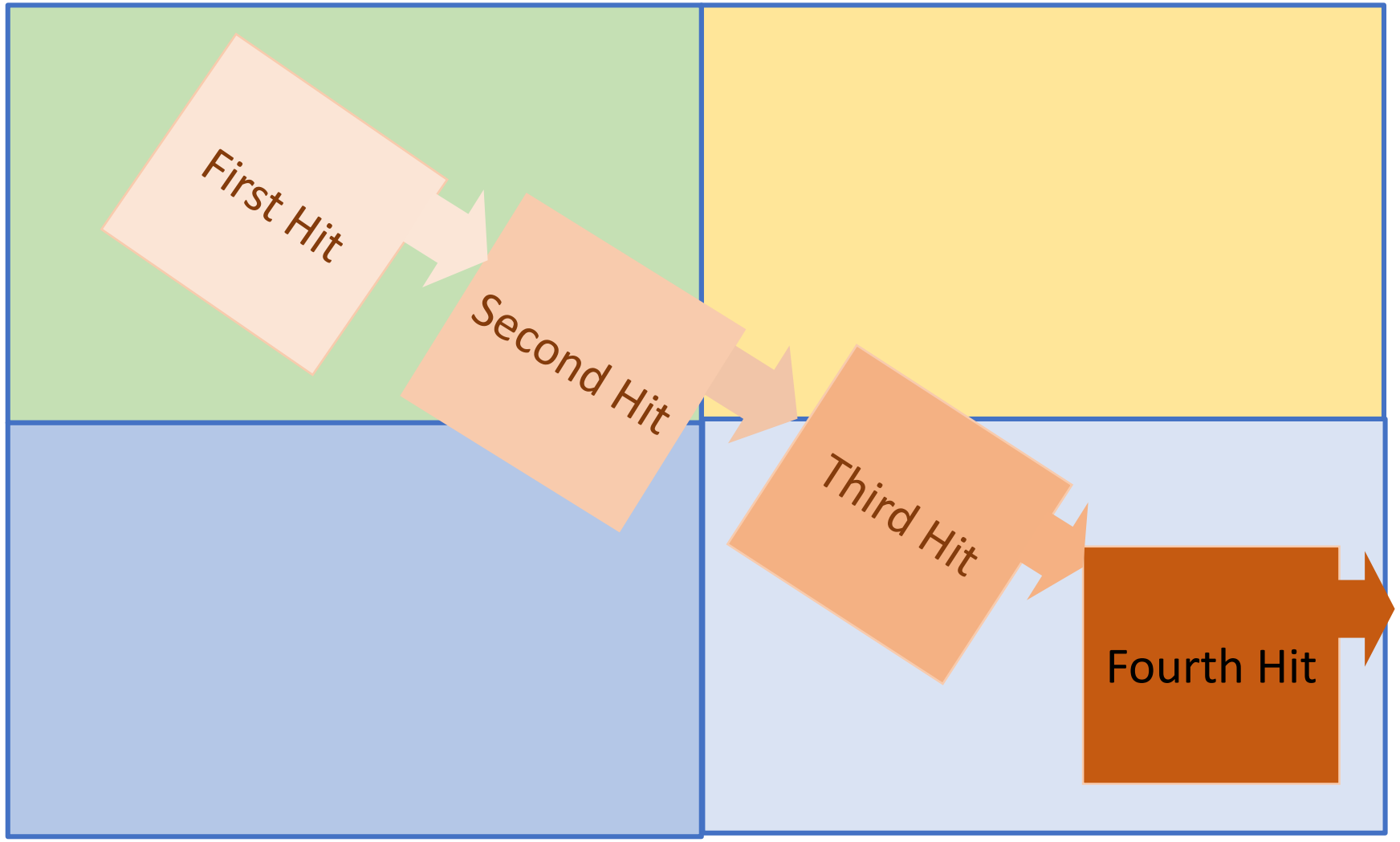

First Hit
Second Hit
Third Hit
Fourth Hit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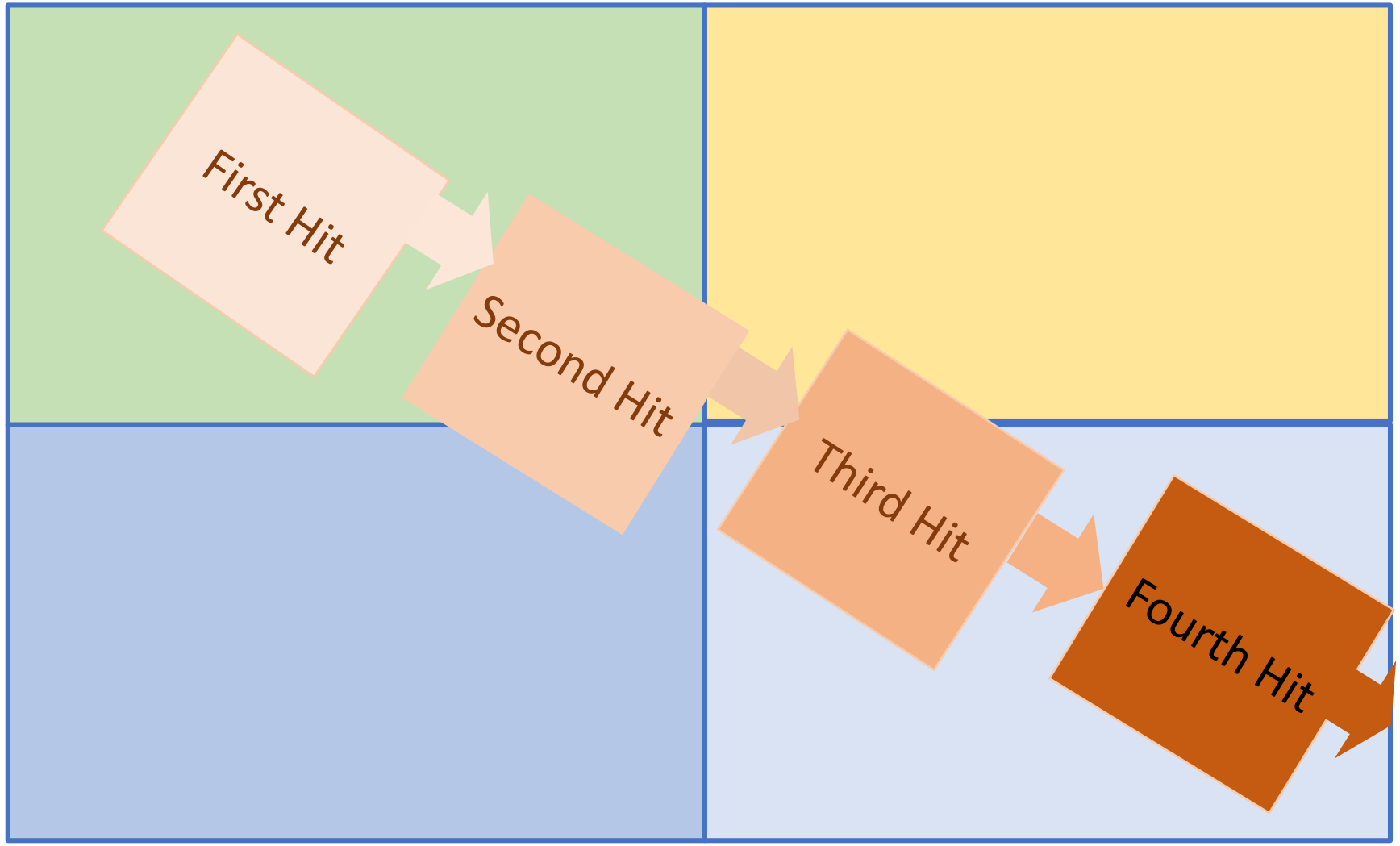
First Hit
Second Hit
Third Hit
Fourth Hit

Nutrition epiphenomen
Gut Microbiota epiphenomen
Genetic epiphenomen
Epigenetic
henomen
First Hit
Second Hit
Third Hit
Fourth Hit

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

“Multiple Hits/Multiple epiphenomena model”

First Hit

Fat Excess

Overweight/Obese/ Non-Lean NAFLD start with Fat excess

Imbalance Between Calories Intake & Energy Disposal

Energy intake exceeds metabolic needs and disposal capacity,

lead to adipose tissue expansion

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

First Hit

First Hit

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Fat Excess

Diet, Food intake & nutrient delivery to the body

Satiety mechanism (hormonal, psychology)
Food availability and food desirability

Metabolic Need and Energy disposal capacity of the body

Exercise ability and Exercise and Extrahepatic energy disposal

Fructose, sucrose, carbohydrates and cholesterol change to Triglyceride and **store without inducing cell stress in Adipose Tissue**

Depend on personal, community, corporate, societal, and legislative status

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

“Multiple Hits/Multiple epiphenomena model”

First Hit

Fat Excess

Calories Intake > **Energy Disposal**

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

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First Hit

First Hit

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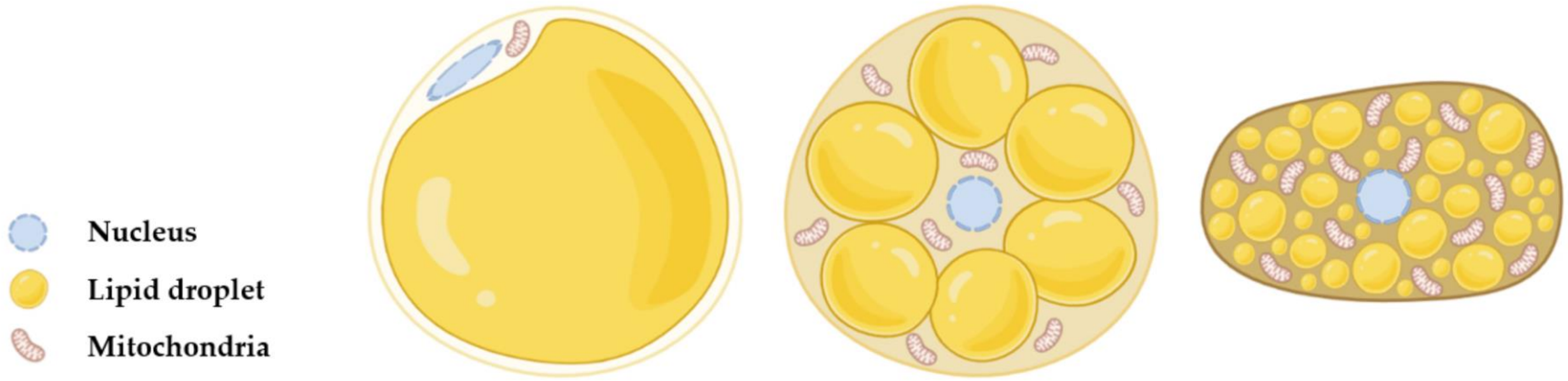
Fat Excess



	White adipocyte	Beige/brite adipocyte	Brown adipocyte
UCP1 expression	Negative	Positive	Positive
Mitochondria density	Low	Medium	High
LD morphology	One large lipid droplet	Small multiple droplet	Small multiple droplet
Function	Store excess energy as fat	Heat generation	Heat generation

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

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First Hit

First Hit

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Fat Excess

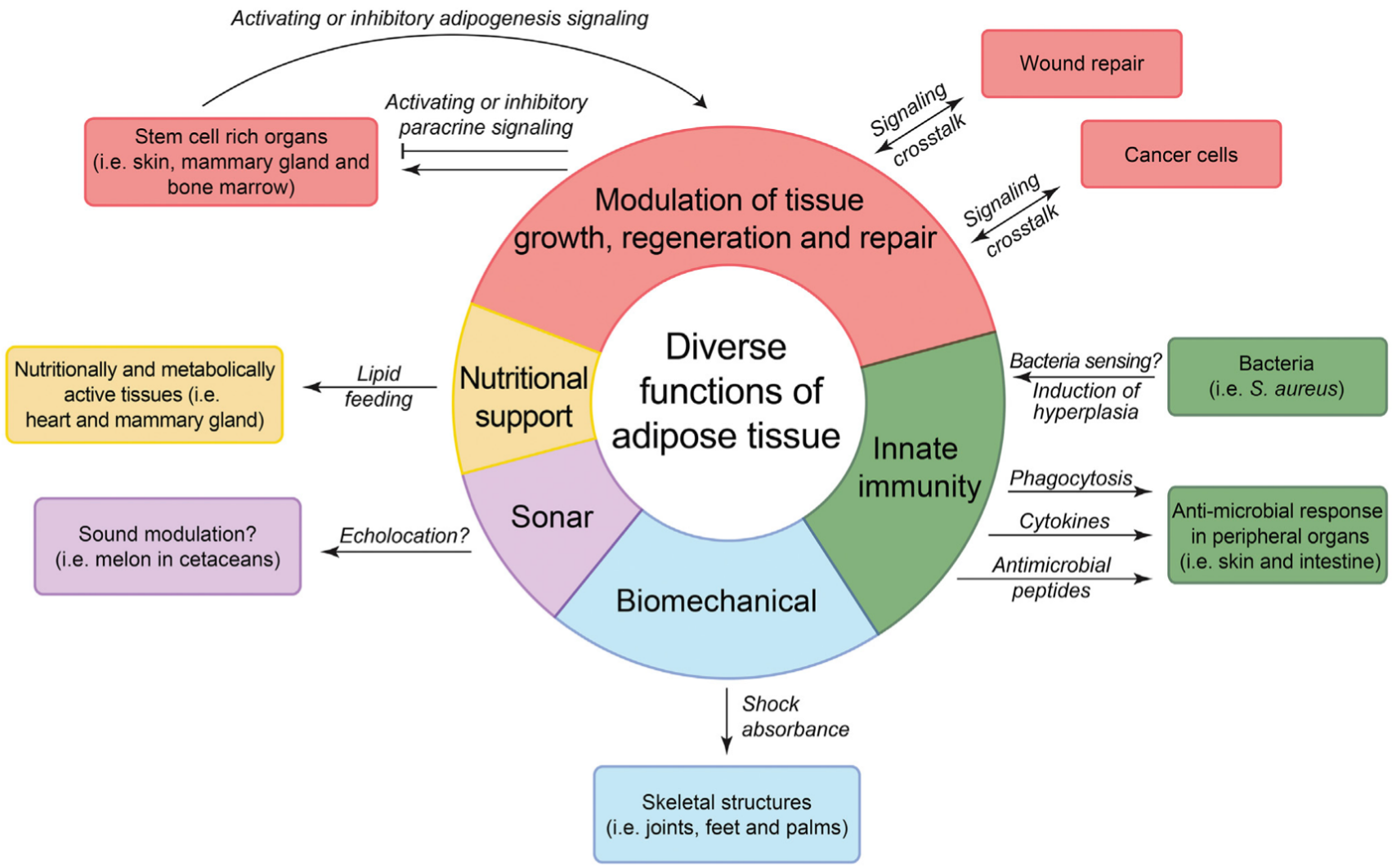

Figure 4. Diverse Functions of Tissue-Associated Adipose Depots

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

“Multiple Hits/Multiple epiphenomena model”

First Hit

First Hit

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Fat Excess

Adipose tissue excess can happen in ;

Specialized Adipose tissue

Specialized in handling of lipid-induce metabolic stress

Non-specialized Adipose tissue

non-specialized in handling of lipid-induce metabolic stress

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

“Multiple Hits/Multiple epiphenomena model”

First Hit

First Hit

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Fat Excess

Specialized Adipose tissue

specialized in handling of lipid-induce metabolic stress

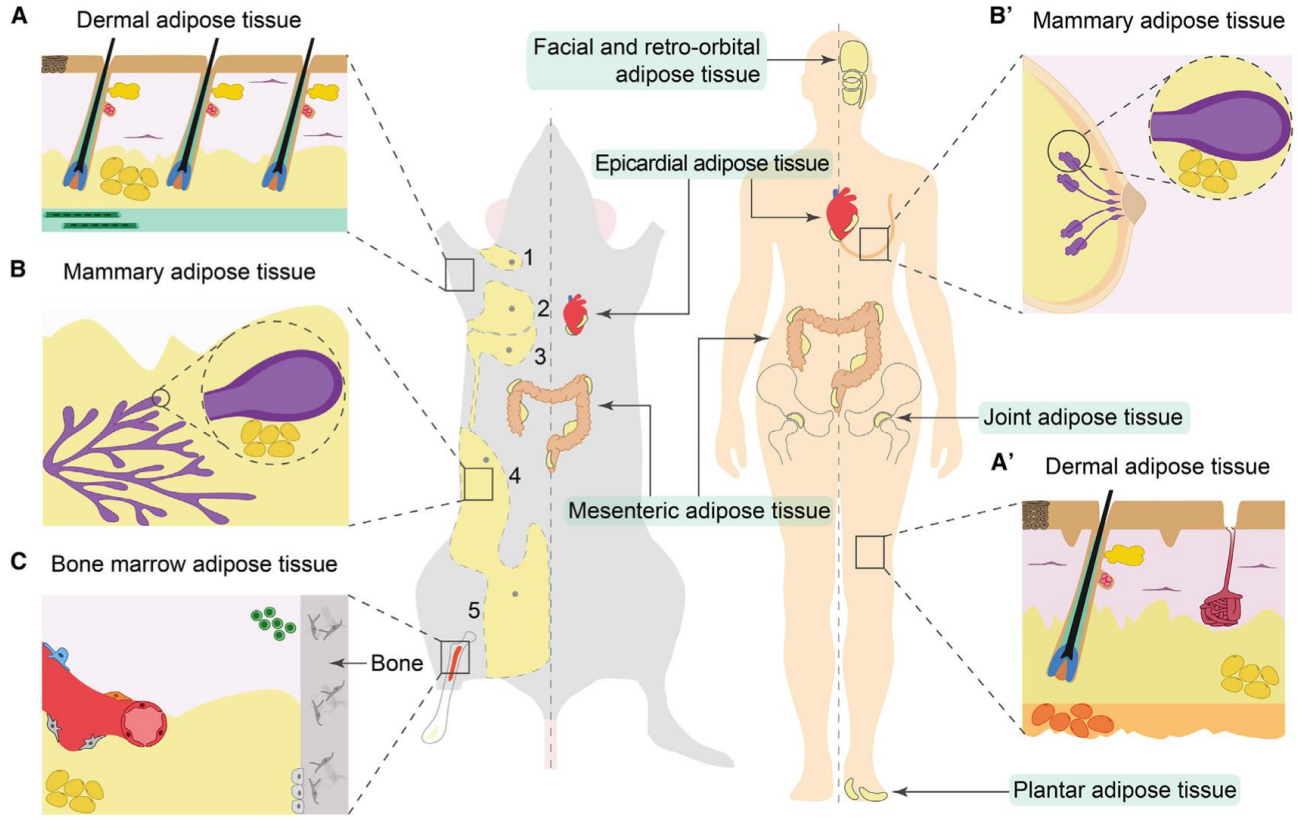

Figure 1. Anatomy of Adipose Depots

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

“Multiple Hits/Multiple epiphenomena model”

First Hit

First Hit

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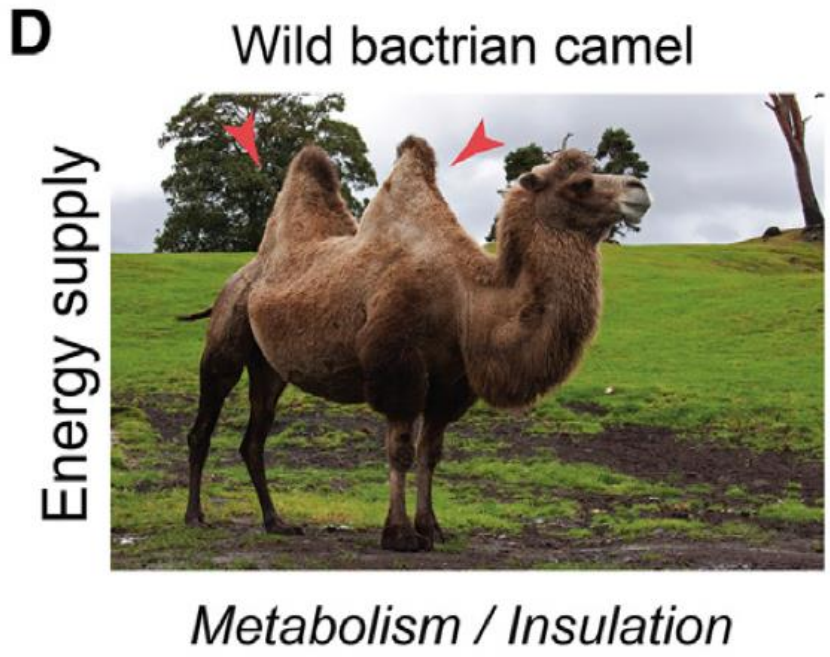
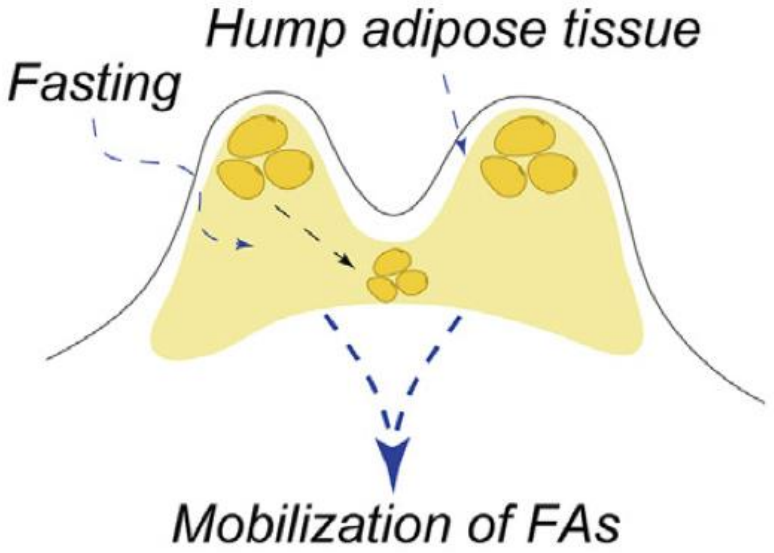
Fat Excess

Specialized Adipose tissue

specialized in handling of lipid-induce metabolic stress





MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

First Hit

First Hit

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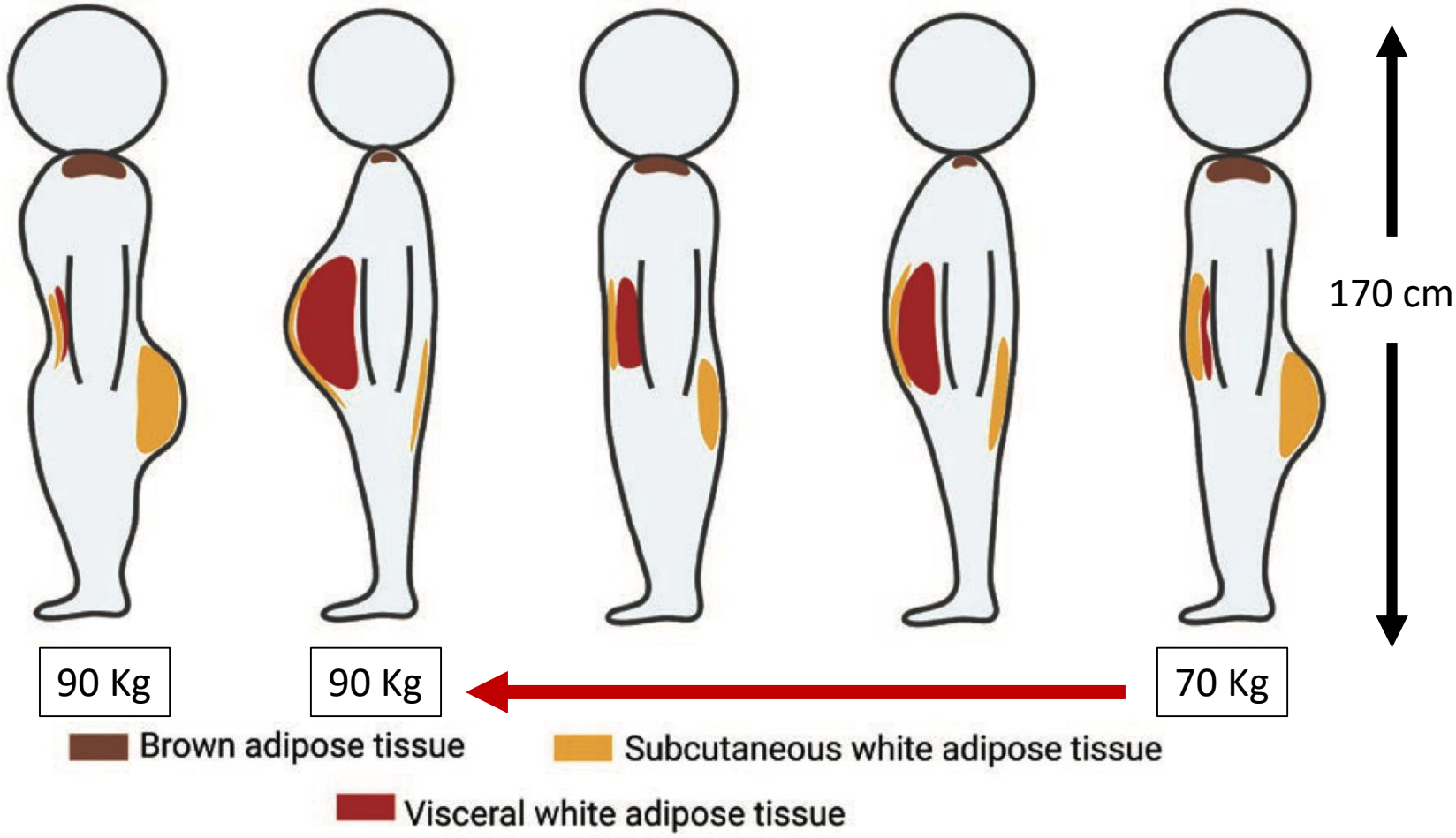
Fat Excess

Adipose tissue excess can happen in

Non-specialized Adipose tissue



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First Hit

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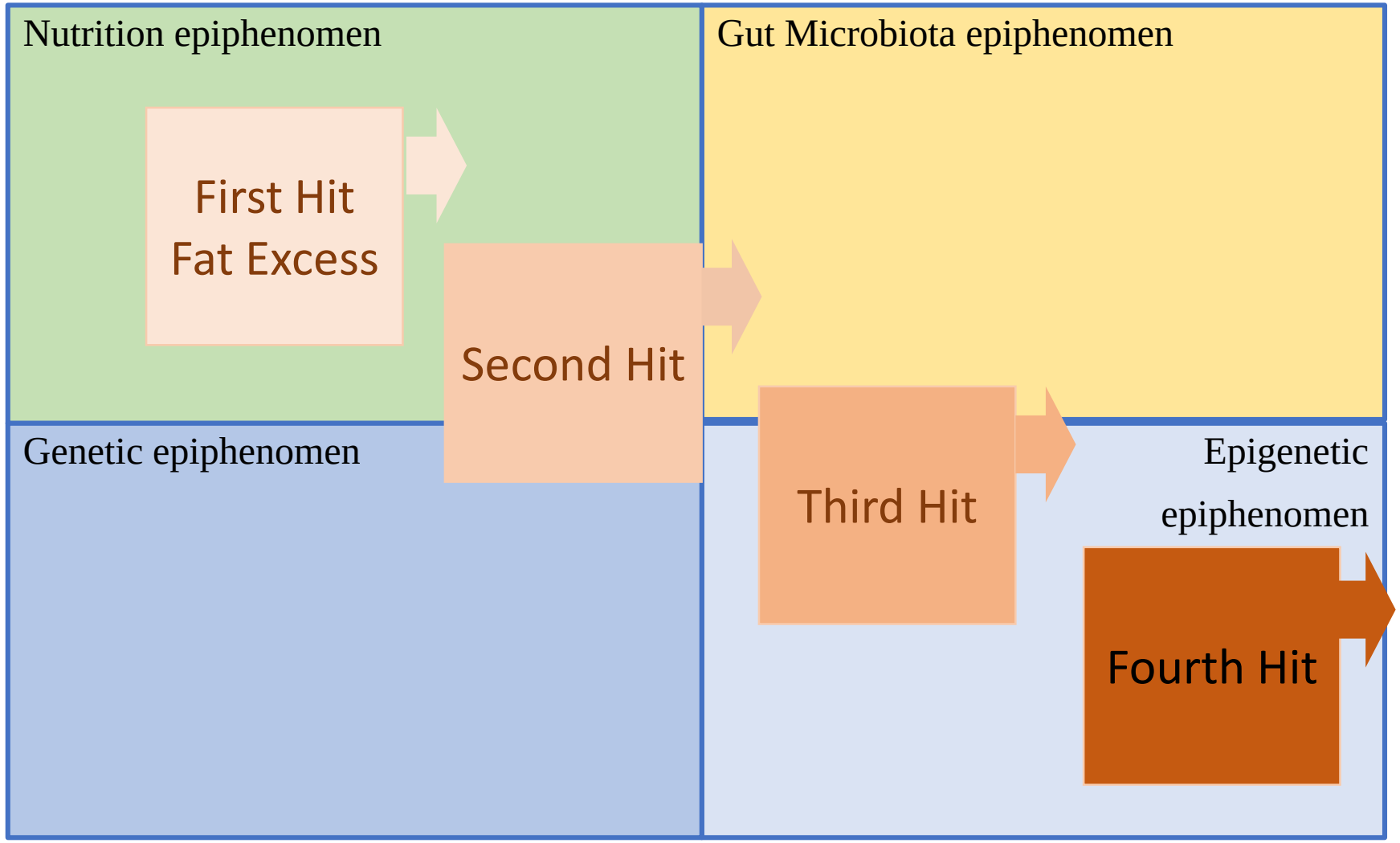
MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"



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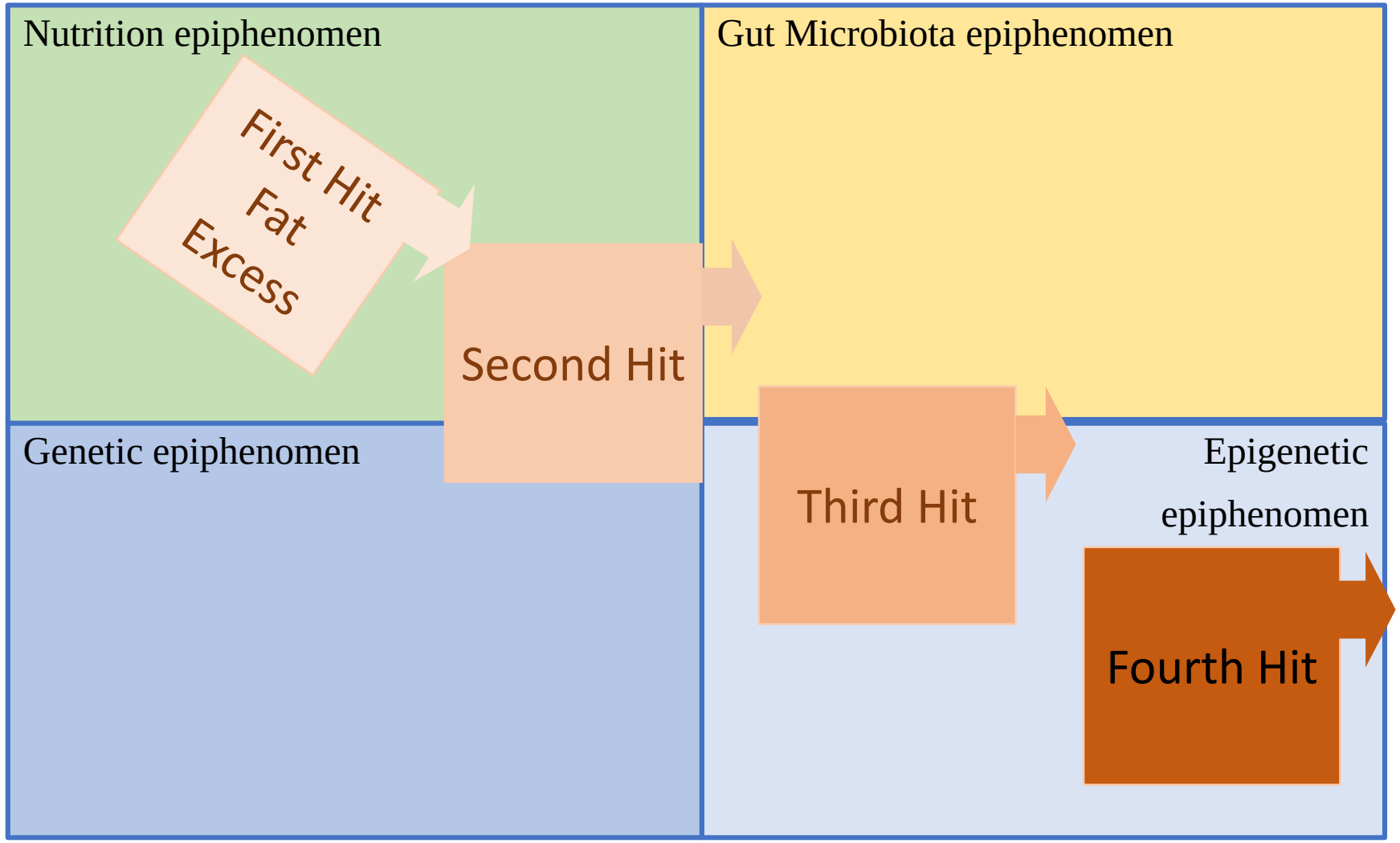

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

“Multiple Hits/Multiple epiphenomena model”

Second Hit

Adipose tissue Expansion in Non-specialized Fat Tissue

Adipose tissue stress

Fat tissue expansion Lead to Angiogenesis

Ischemia

Adipocyte Necrosis

Inflammation in lipocells of the body

Macrophage recruitment in the body

Insulin resistance in the body

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Second Hit

Second Hit

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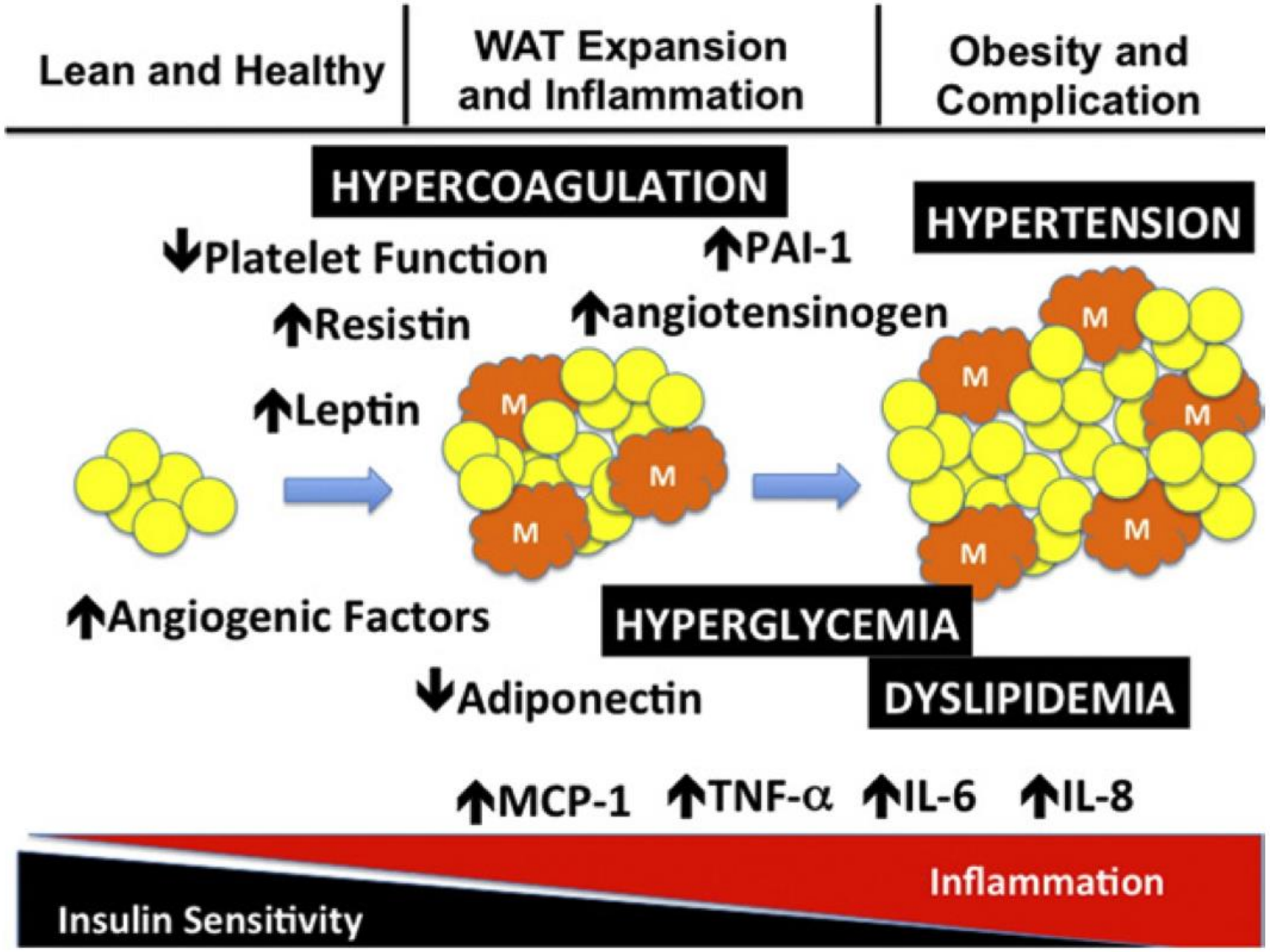
Inflammation/IR



MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

“Multiple Hits/Multiple epiphenomena model”

Second Hit

Second Hit

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Inflammation/IR

Insulin Resistance Vicious Cycle of Metabolic Dysfunction

Local fat tissue IR ----→ Systemic peripheral IR

Store more triglyceride (TG) with inducing cell stress in non-specialized tissues

Activates inflammatory pathways first in adipose tissue and second outside of adipose tissue

Lead to:

- More Lipid turnover and Lipid disorder
- More DM
- More HTN
- More Fat in the liver

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Second Hit

Second Hit

=

Inflammation/IR

Obesity-induced chronic inflammation

More lipid oxidation in fat tissue

More lipid oxidative injury in fat tissue

More oxidative Stress Radicals in fat tissue

More Systemic Inflammation

More TNF, IL, Cytokines (Fatigue, body aches, increased CRP)

Increased circulating Free Fatty Acid -→ Fatty Liver

Increasing IR + Increasing VLDL --→ Atherosclerosis and CVD

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

HOMA index

$$\frac{\text{Fasting Glucose X Fasting Insulin}}{405}$$

FBS = 95

Ins = 8

HOMA = 1.8

FBS = 95

Ins = 12

HOMA = 2.8

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Second Hit

Second Hit

=

Inflammation/IR

Fat Excess (overweight)

Lead to

Obesity-induced Insulin Resistance and chronic inflammation

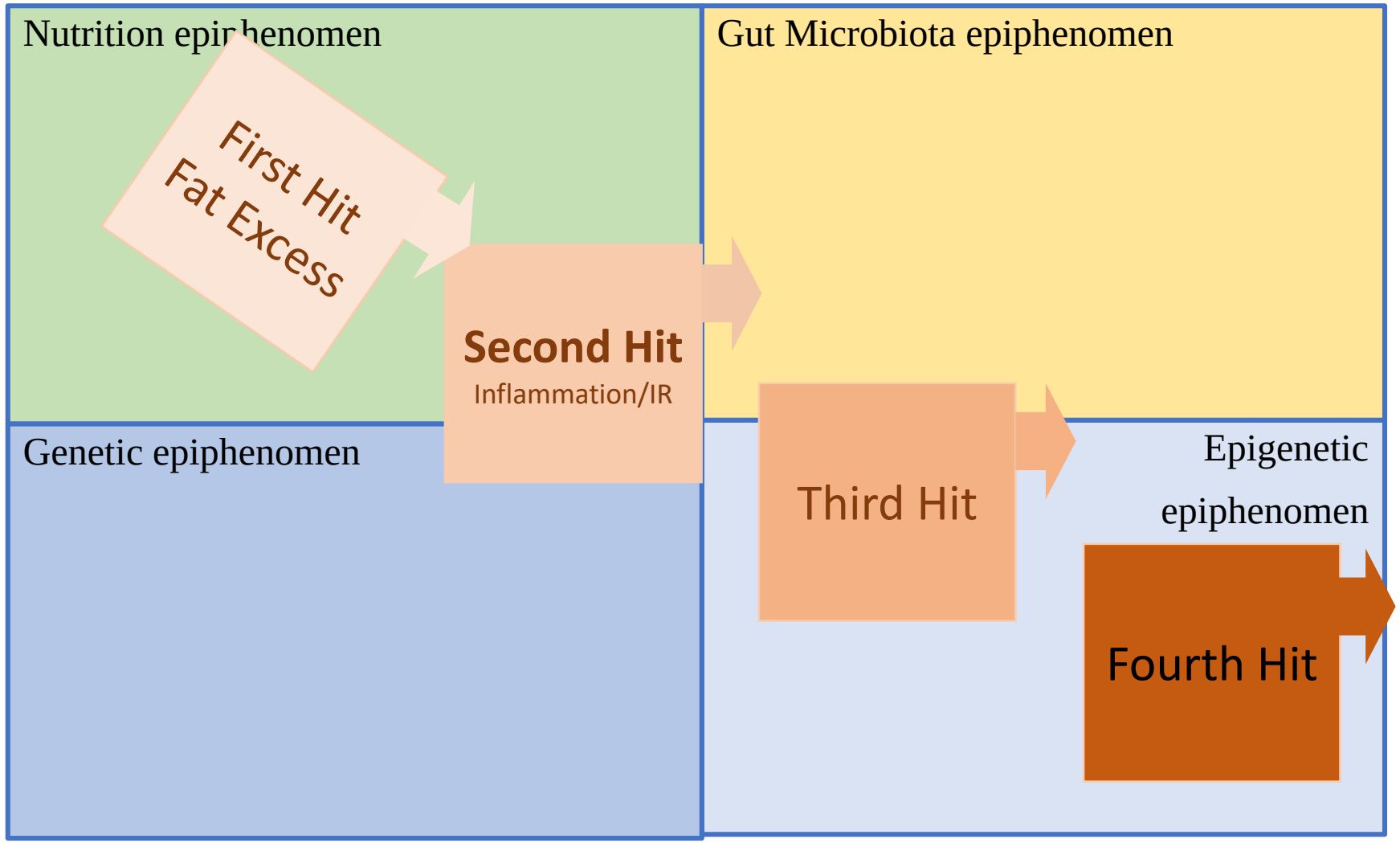
Lead to

Fatigue, body aches, increased CRP

Start of atherosclerosis and CVD

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"



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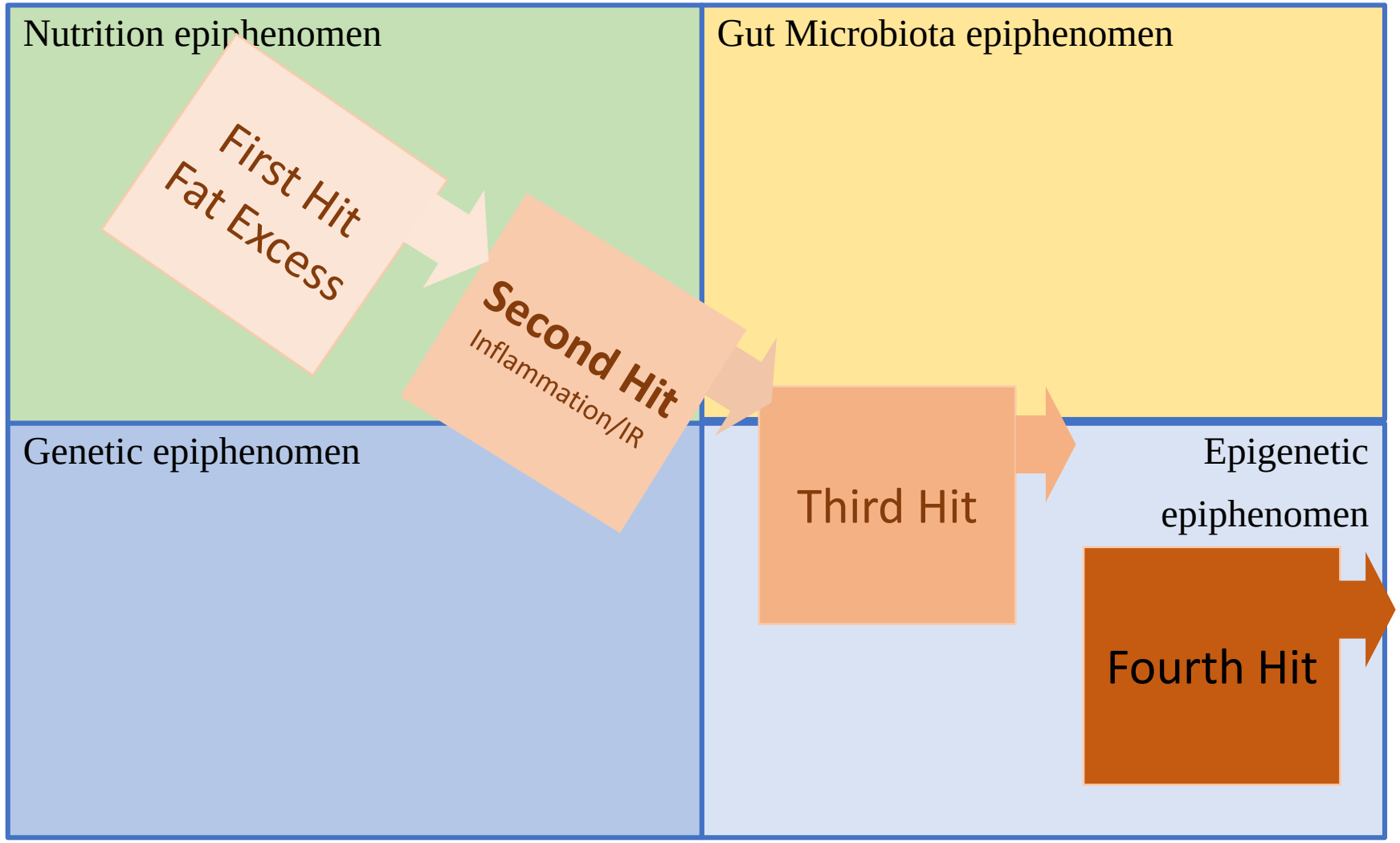

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Third Hit

Response of the Liver to Insulin resistance

Insulin resistance is nearly universal in patients with NAFLD and is present in the liver and muscle, which worsens with the progression of NAFLD to NASH.

increased circulating Free Fatty Acid

Increasing Intrahepatic Free Fatty Acid and TG (intrahepatic droplets)

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Third Hit

Third Hit

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Intrahepatic Fat Excess

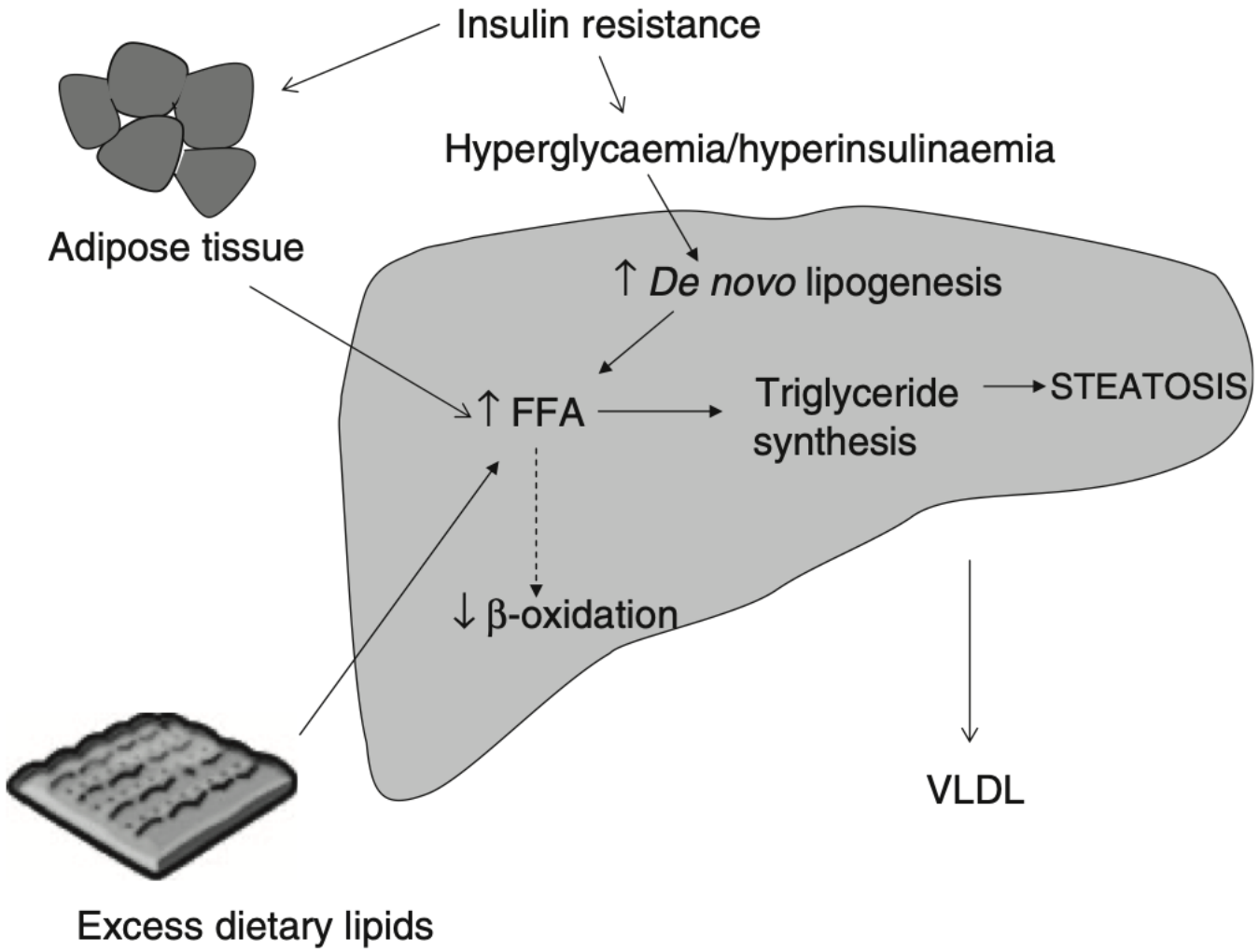

Figure 2. Mechanisms of hepatic fat accumulation.

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Third Hit

Third Hit

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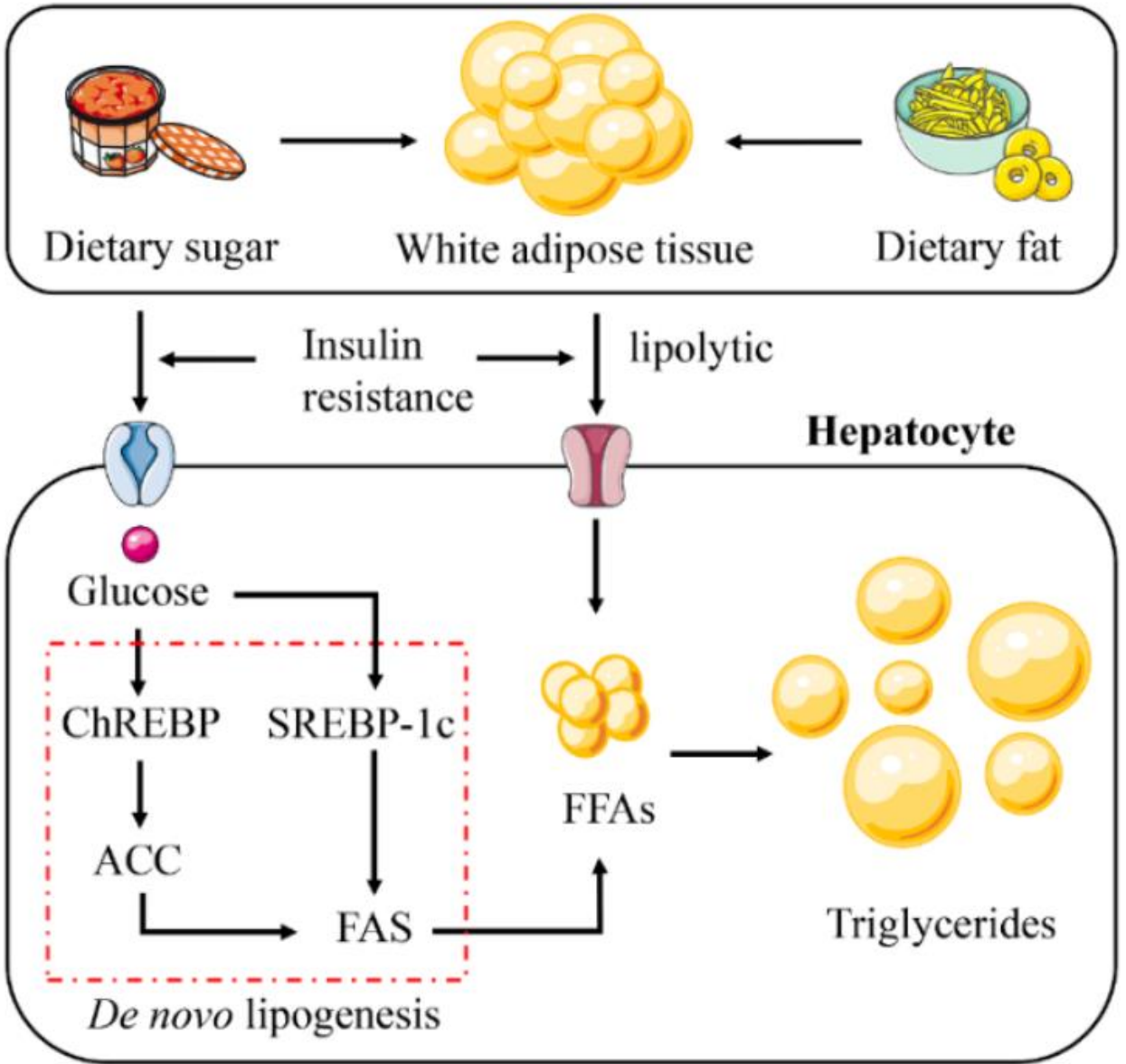
Intrahepatic Fat Excess



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Third Hit

Fat Excess (overweight)

Lead to

Obesity-induced Insulin Resistance and chronic inflammation (atherosclerosis and CVD, increased CRP)

Lead to

Fatty Liver in Ultrasound with Normal LFT

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

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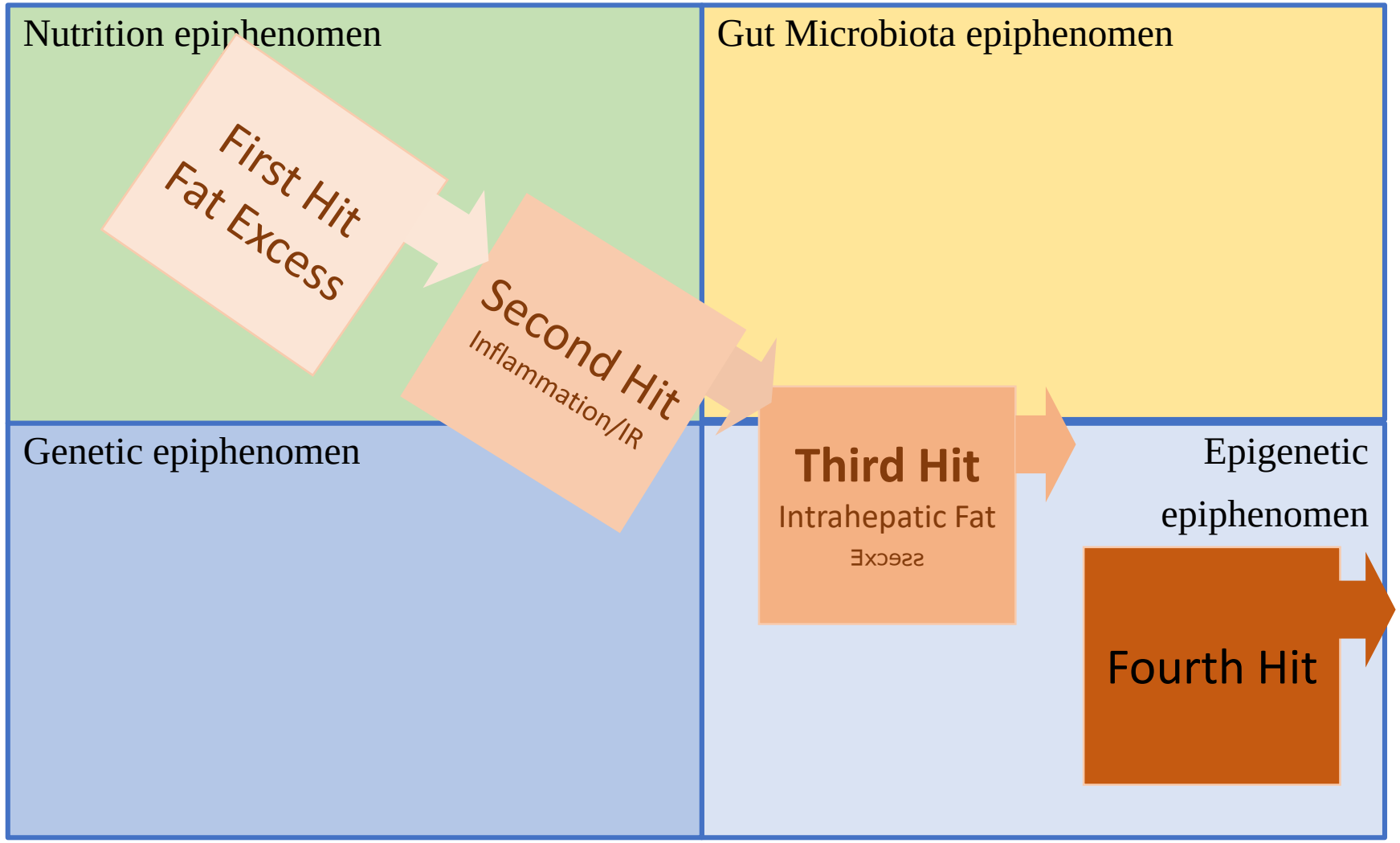

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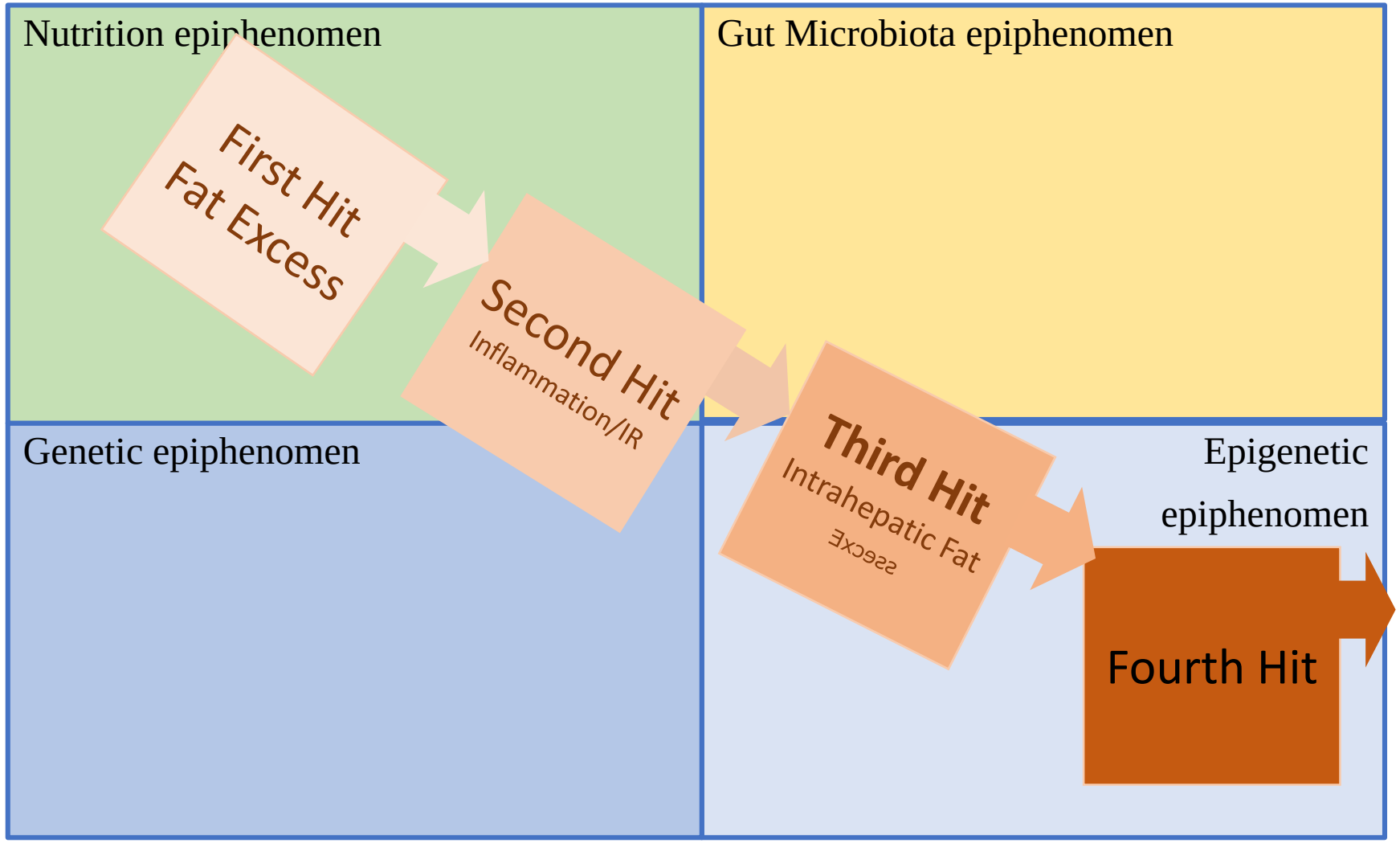

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Fourth Hit

Hepatocyte Lipid Handling

Lipotoxic Liver Injury with Inflammation and Cell necrosis.

Activation and Recruitment of resident macrophages, which further contributes to hepatocellular injury and stellate cell activation as part of a complex interplay among hepatic cell types.

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Fourth Hit

Fourth Hit

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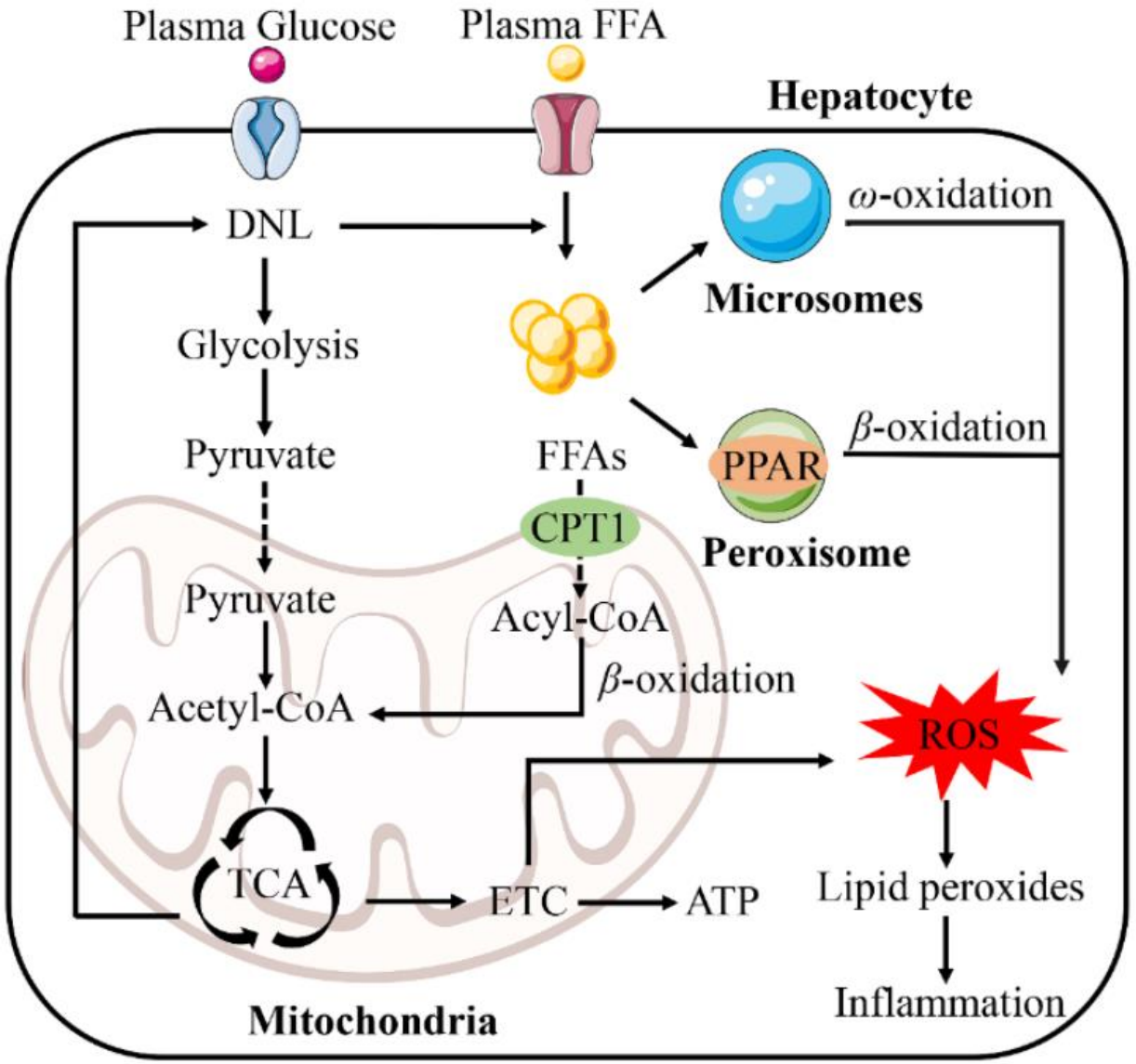
Hepatic Inflammation/cell necrosis



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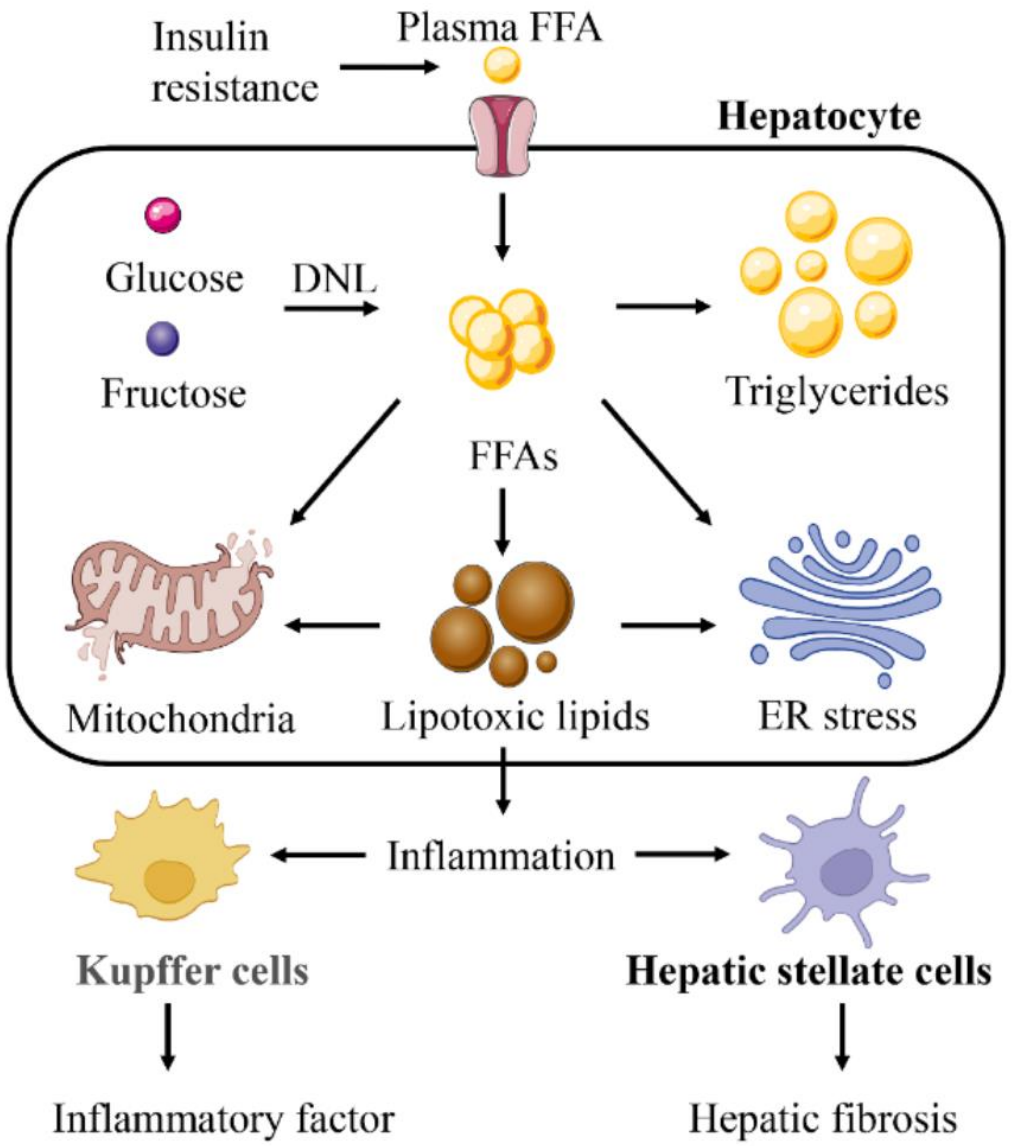
Hepatic Inflammation/cell necrosis



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Fourth Hit

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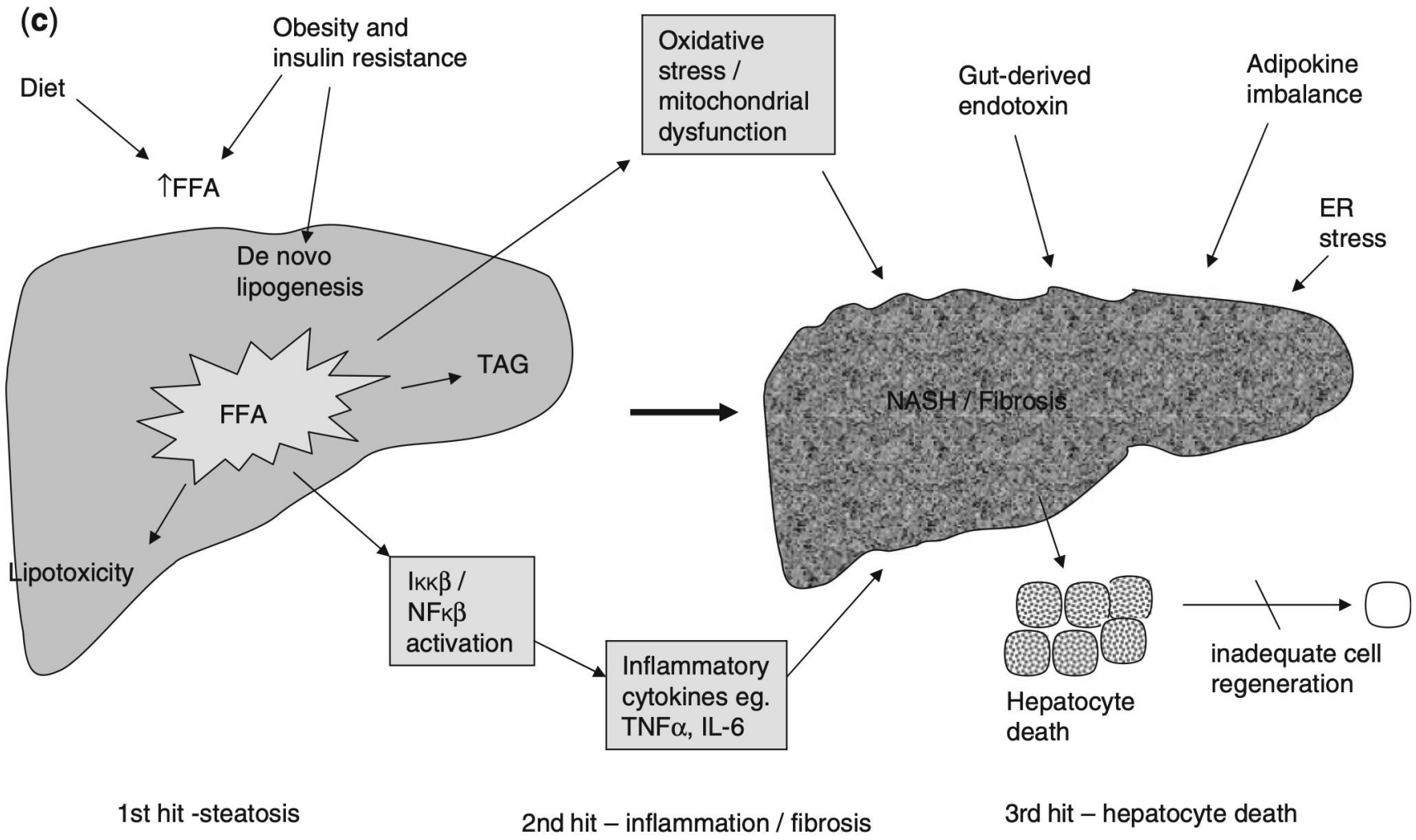
Hepatic Inflammation/cell necrosis



MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Fourth Hit

Fat Excess (overweight)

Lead to

Obesity-induced Insulin Resistance and chronic inflammation (atherosclerosis and CVD, increased CRP)

Lead to

Fatty Liver in Ultrasound with Normal LFT

Lead to

Liver inflammation and cell necrosis

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

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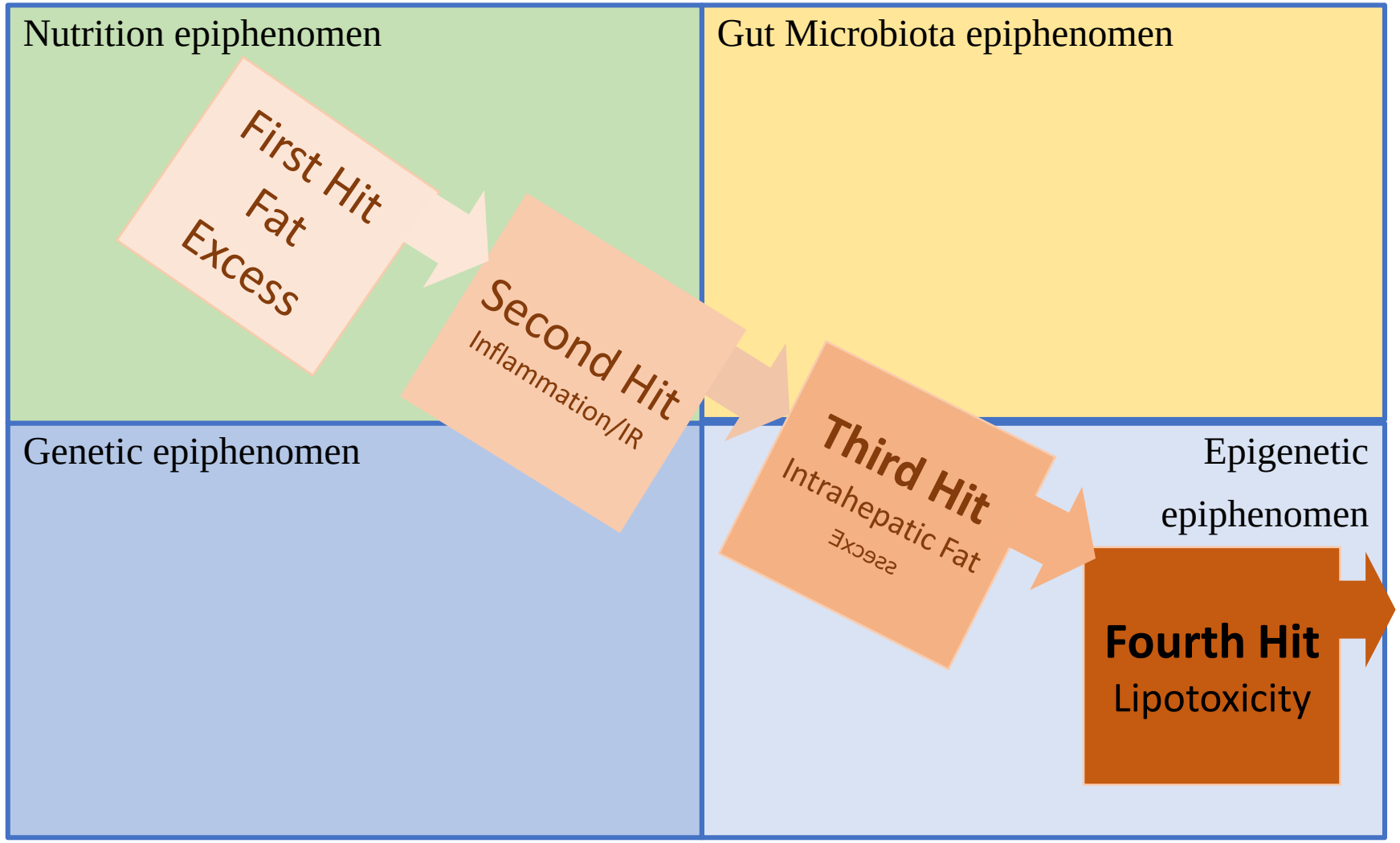

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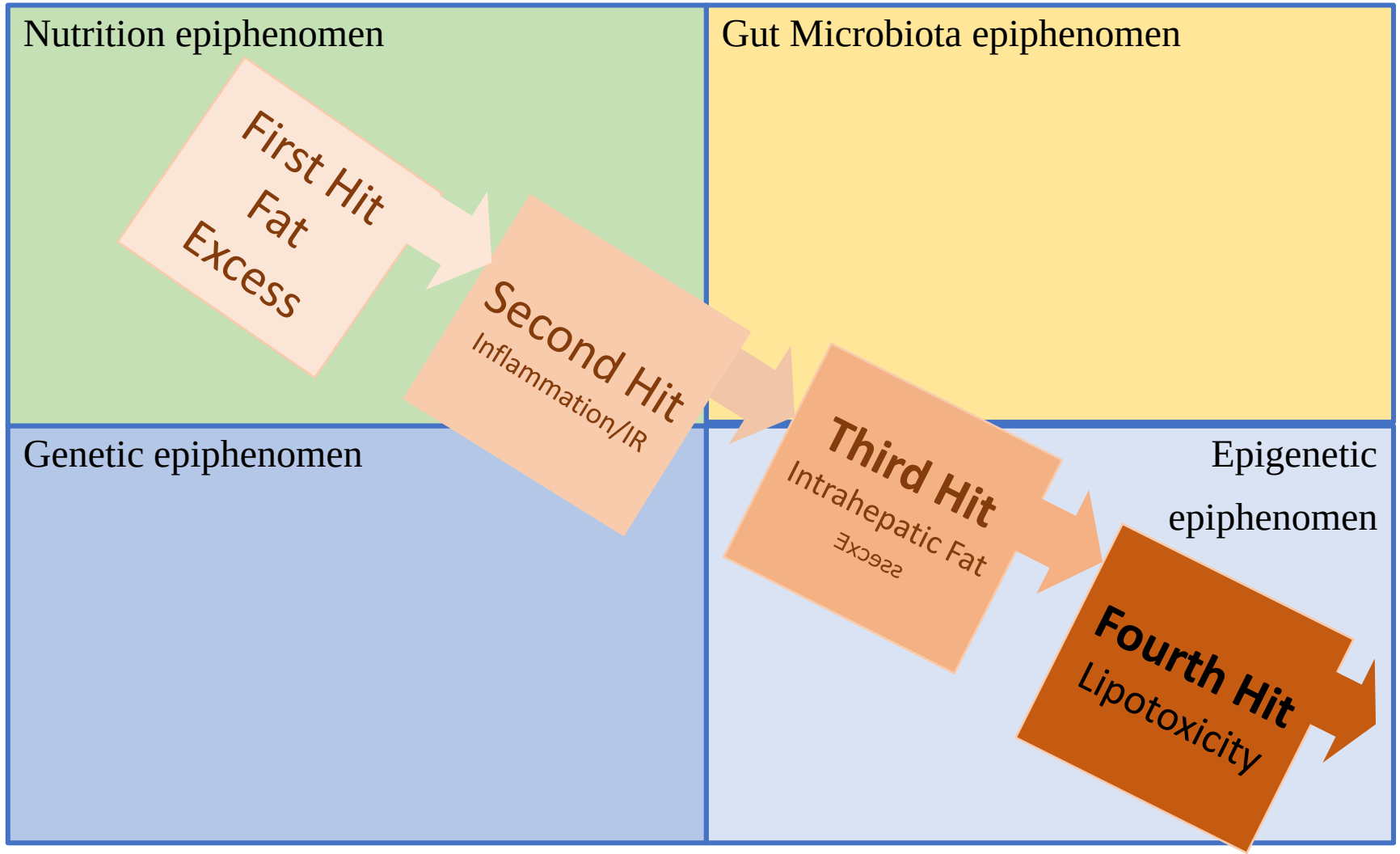

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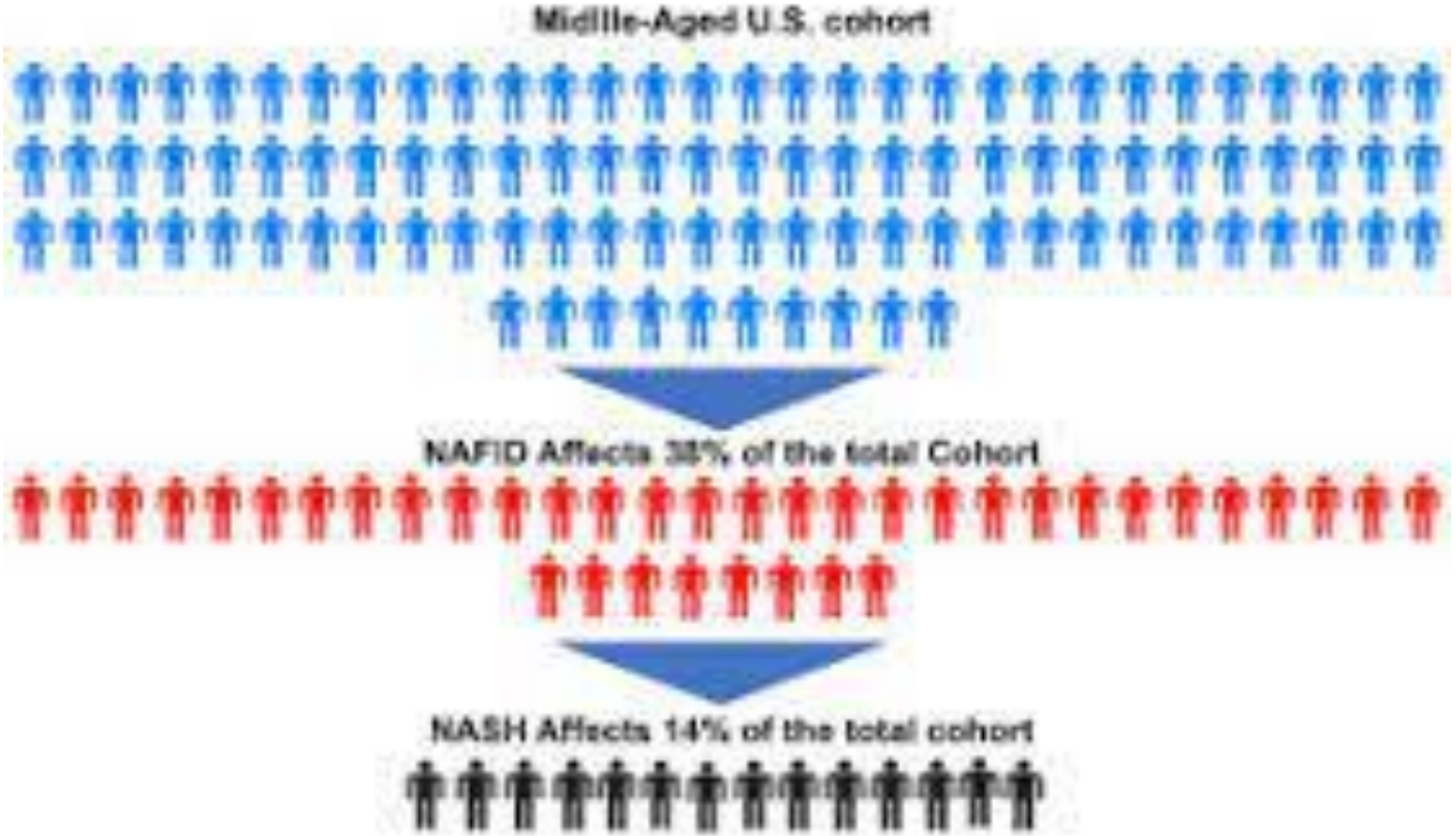

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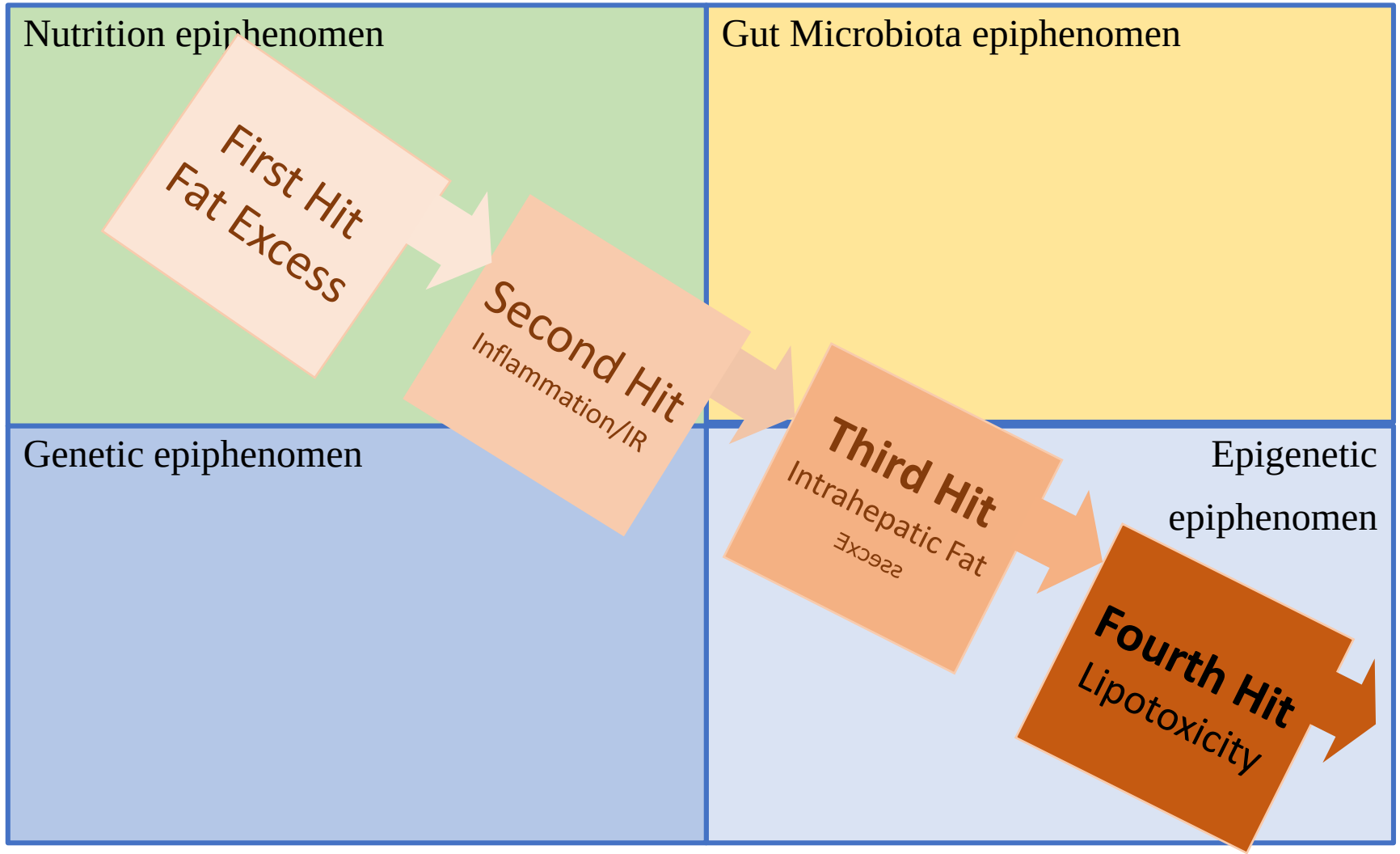

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

“Multiple Hits/Multiple epiphenomena model”

Nutrition epiphenomen

- Saturated and trans fats
- High glycemic index foods

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Gut Microbiota epiphenomen

- Altered gut flora leads to :

  further production of fatty acids in the bowel

  increased small bowel permeability

  increased fatty acid absorption and raised circulating levels of molecules

  Activation of inflammatory pathways and release of proinflammatory cytokines such as IL- 6 and TNF-α

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

"Multiple Hits/Multiple epiphenomena model"

Genetic epiphenomen

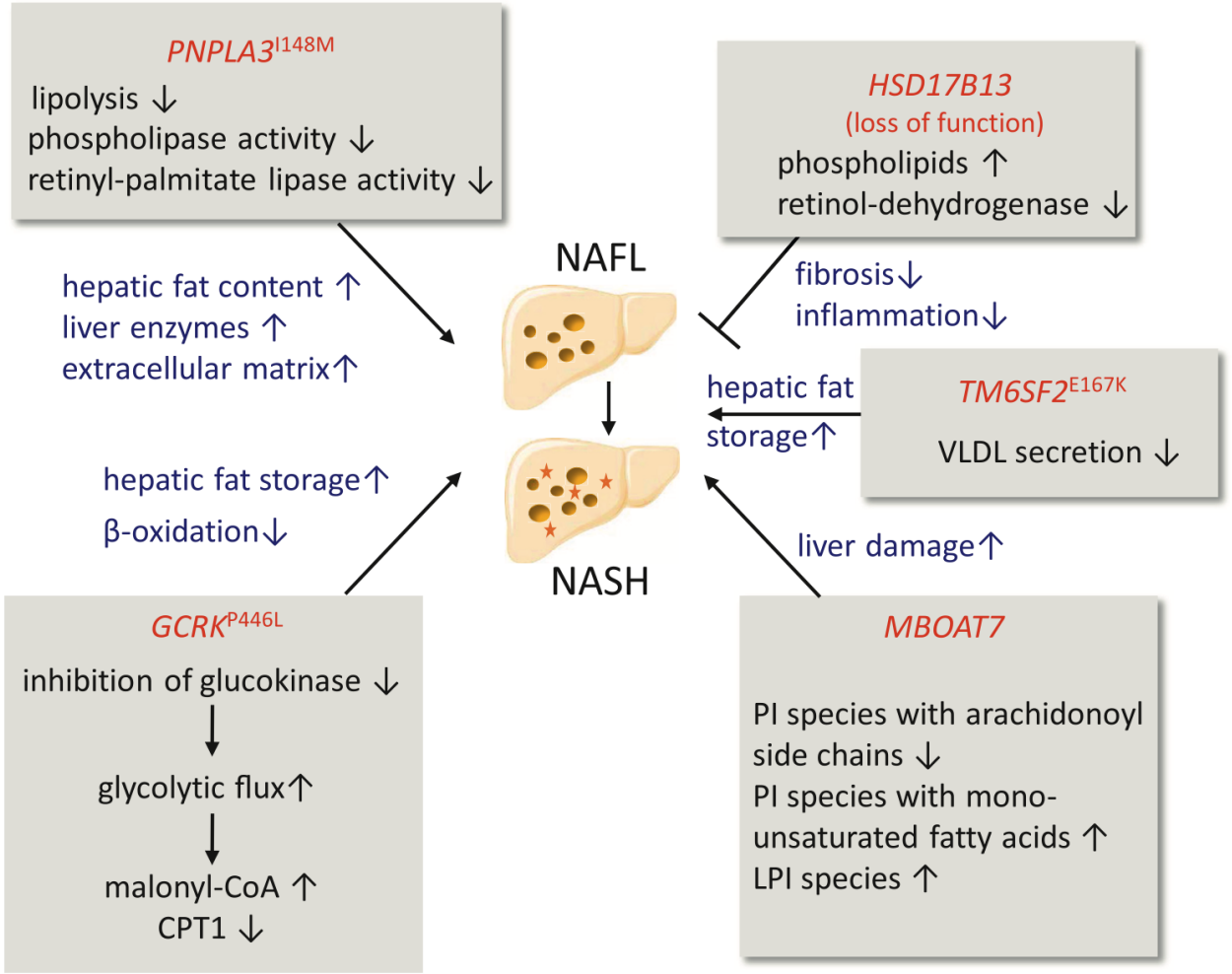

Figure 1: Frequent gene variants associated with NAFL and/or NASH and their major effects. CPT1, carnitine palmitoyl transferase-1; LPI, lysophosphatidylinositol; PI, phosphatidylinositol.

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

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Epigenetic

Epiphenomen

could trigger disease development and are reversible.

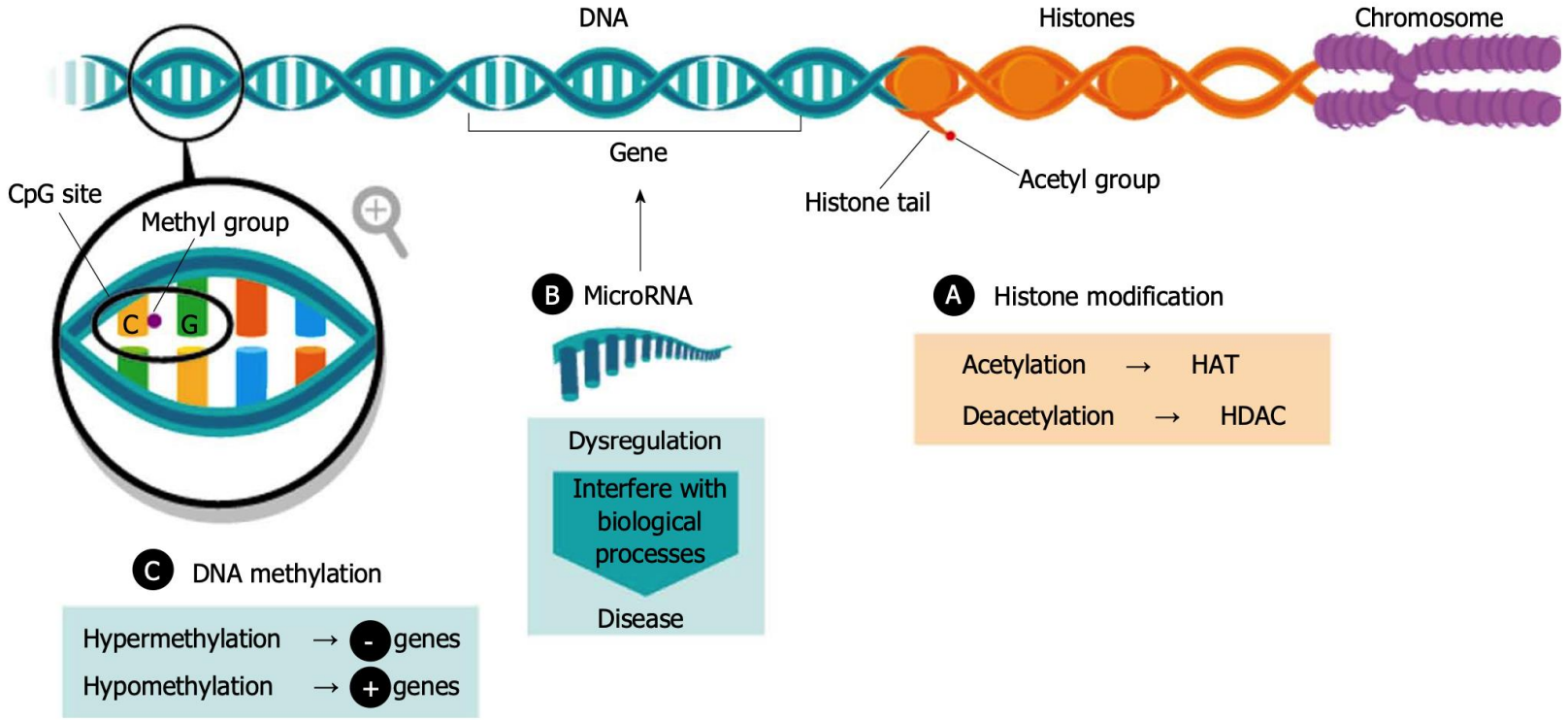

Figure 1 Epigenetic phenomena. HAT: Histone acetyltransferase; HDAC: Histone deacetylase.

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Epigenetic

Epiphenomen

could trigger disease development and are reversible.

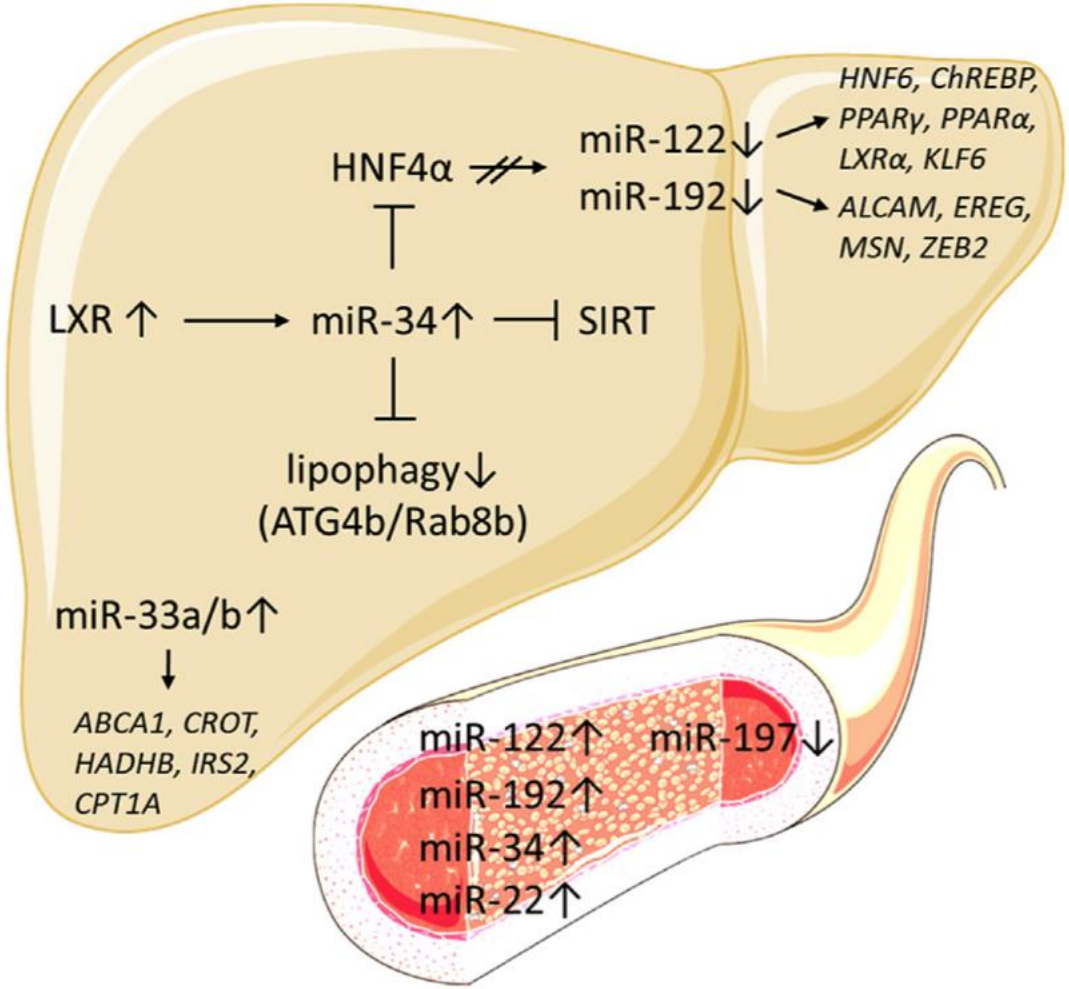

Figure 2: Summary of the most relevant miRNAs and their targets in the liver and those detected in the plasma of NAFL and NASH patients.

MOLECULAR and CELLULAR PATHOGENESIS of NAFLD

“Multiple Hits/Multiple epiphenomena model”

Epigenetic

Epiphenomen

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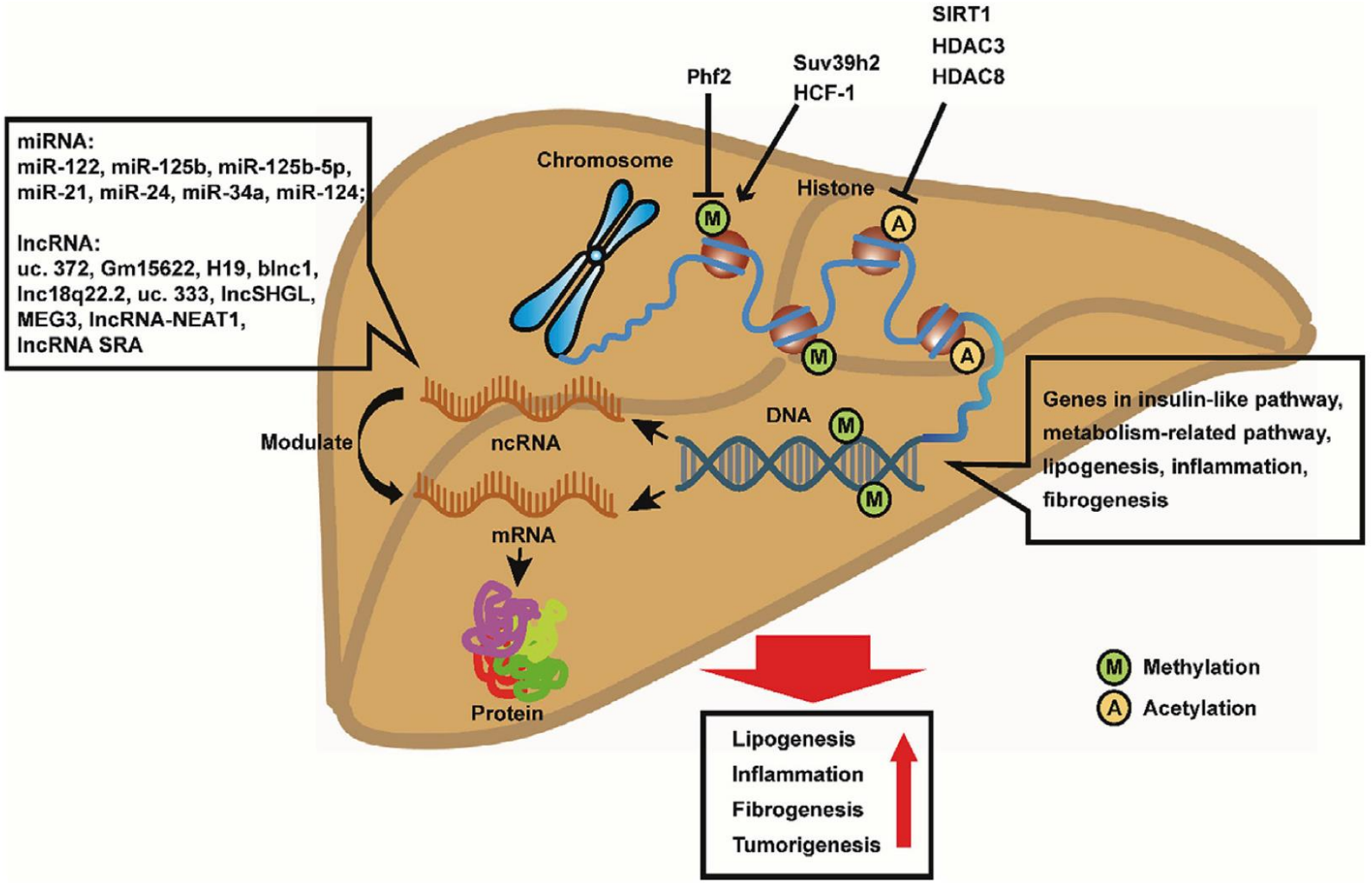
F. Xu, W. Guo / Liver Research 4 (2020) 118–123



Thank you For Your Attention

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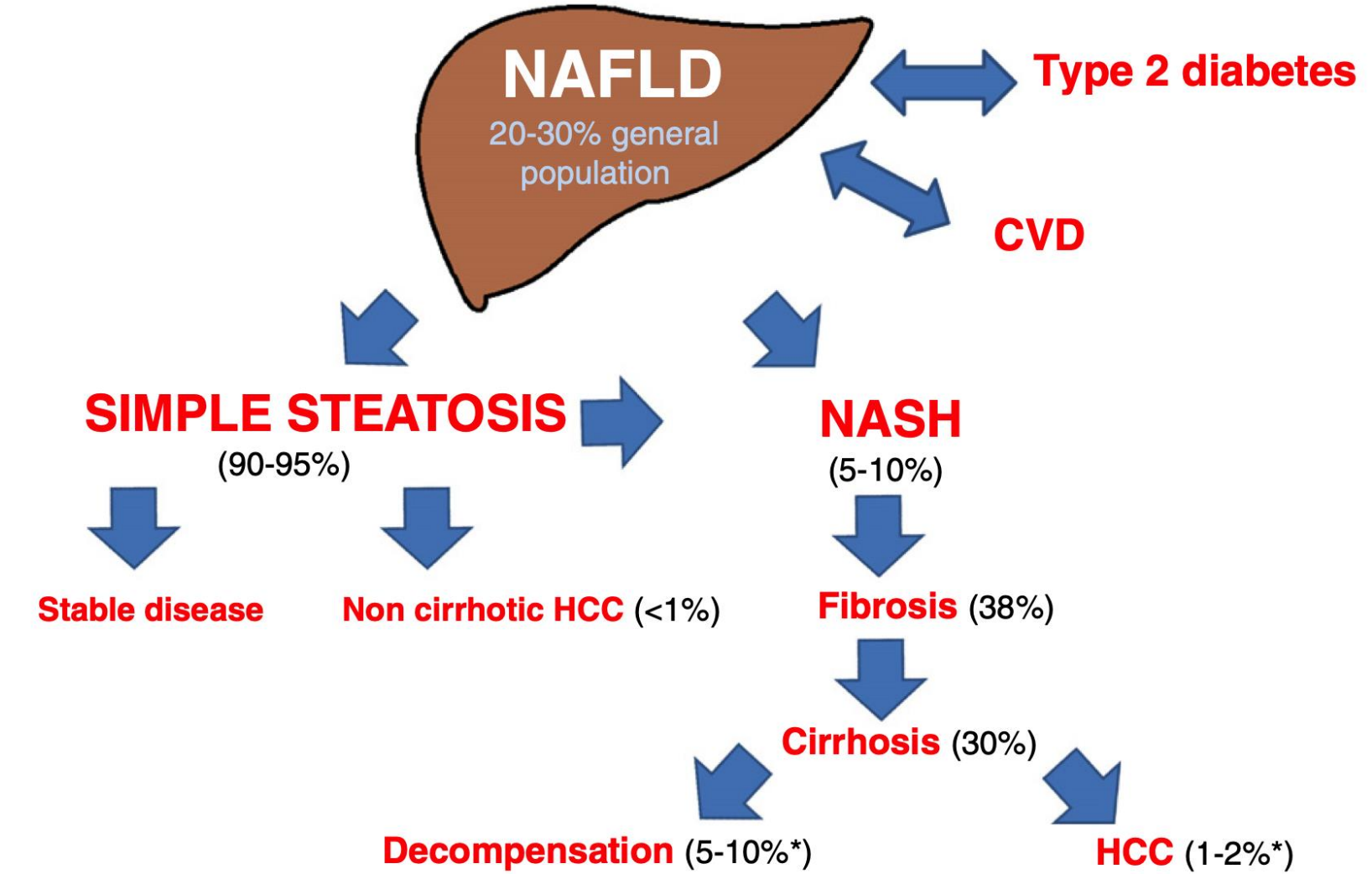
METABOLISM CLINICAL AND EXPERIMENTAL 65 (2016) 1038–1048

Fourth Hit

Fourth Hit

=

Hepatic Inflammation/cell necrosis



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