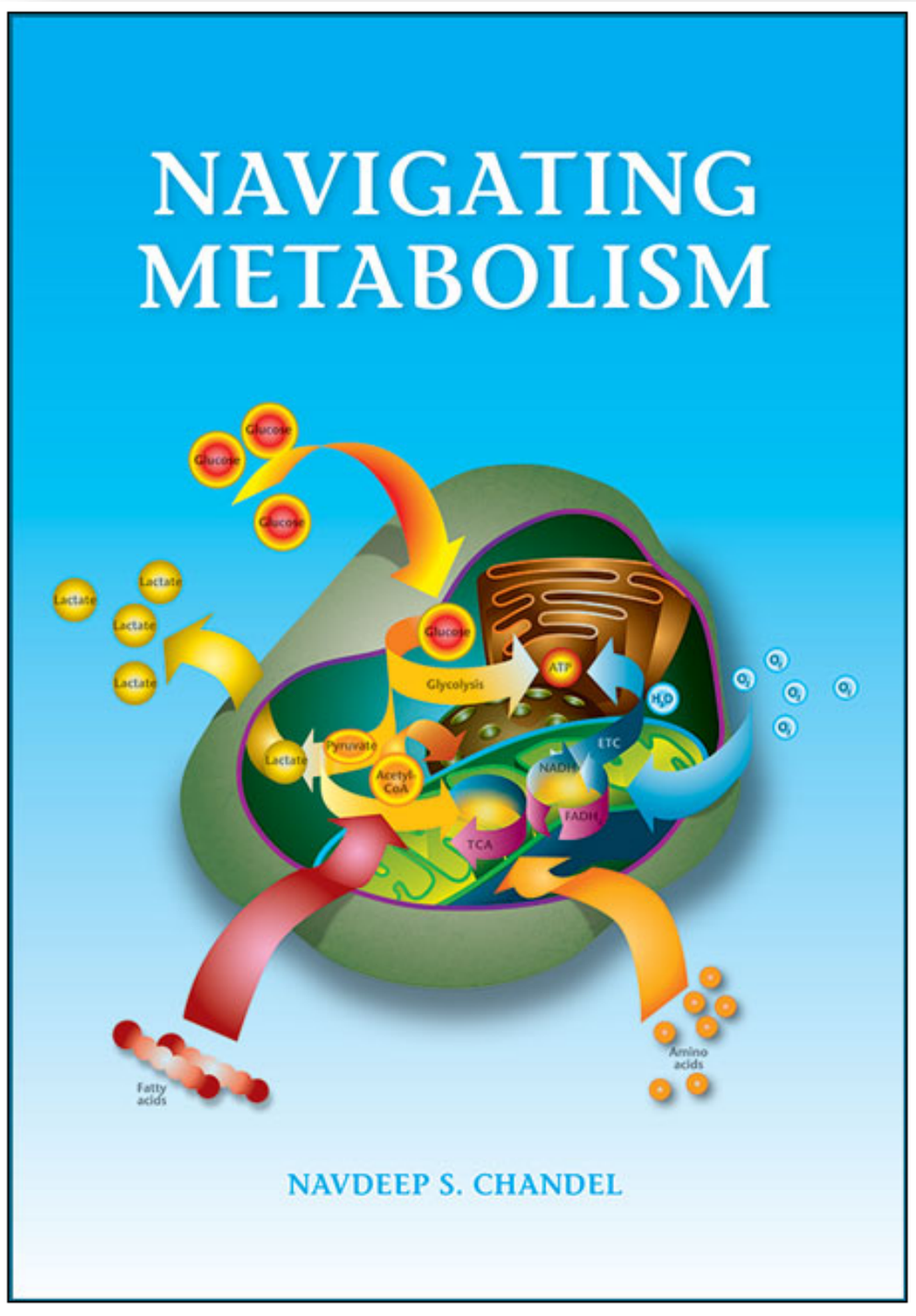
Metabolism & Metabolomics

How and why cells reprogram their machinery for energy and biomass production

Additional Reading on Metabolism



Cell Metabolism
Perspective

The Emerging Hallmarks of Cancer Metabolism

Natalya N. Pavlova[1] and Craig B. Thompson[1,*]
[1]Cancer Biology and Genetics Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
*Correspondence: thompsonc@mskcc.org
http://dx.doi.org/10.1016/j.cmet.2015.12.006

nature reviews molecular cell biology
https://doi.org/10.1038/s41580-022-00572-w

Review article
Check for updates

Metabolites as signalling molecules

Steven Andrew Baker[1] & Jared Rutter[2,3,4]

Nutrient–sensing mechanisms and pathways

Alejo Efeyan[1,2,3,4], William C. Comb[1,2,3,4] & David M. Sabatini[1,2,3,4,5]

Cancer metabolism: looking forward

Inmaculada Martínez-Reyes and Navdeep S. Chandel

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Why study metabolism?

Old view: Metabolism is a servant for cell biosynthetic demands

New view: Metabolism is a driver of biology

Normal processes
- Proliferation
- Cell death
- Differentiation
- Gene expression
- Response to stress
- Aging

Pathology
- Cancer
- Inflammation
- Obesity
- Diabetes
- Neurodegeneration

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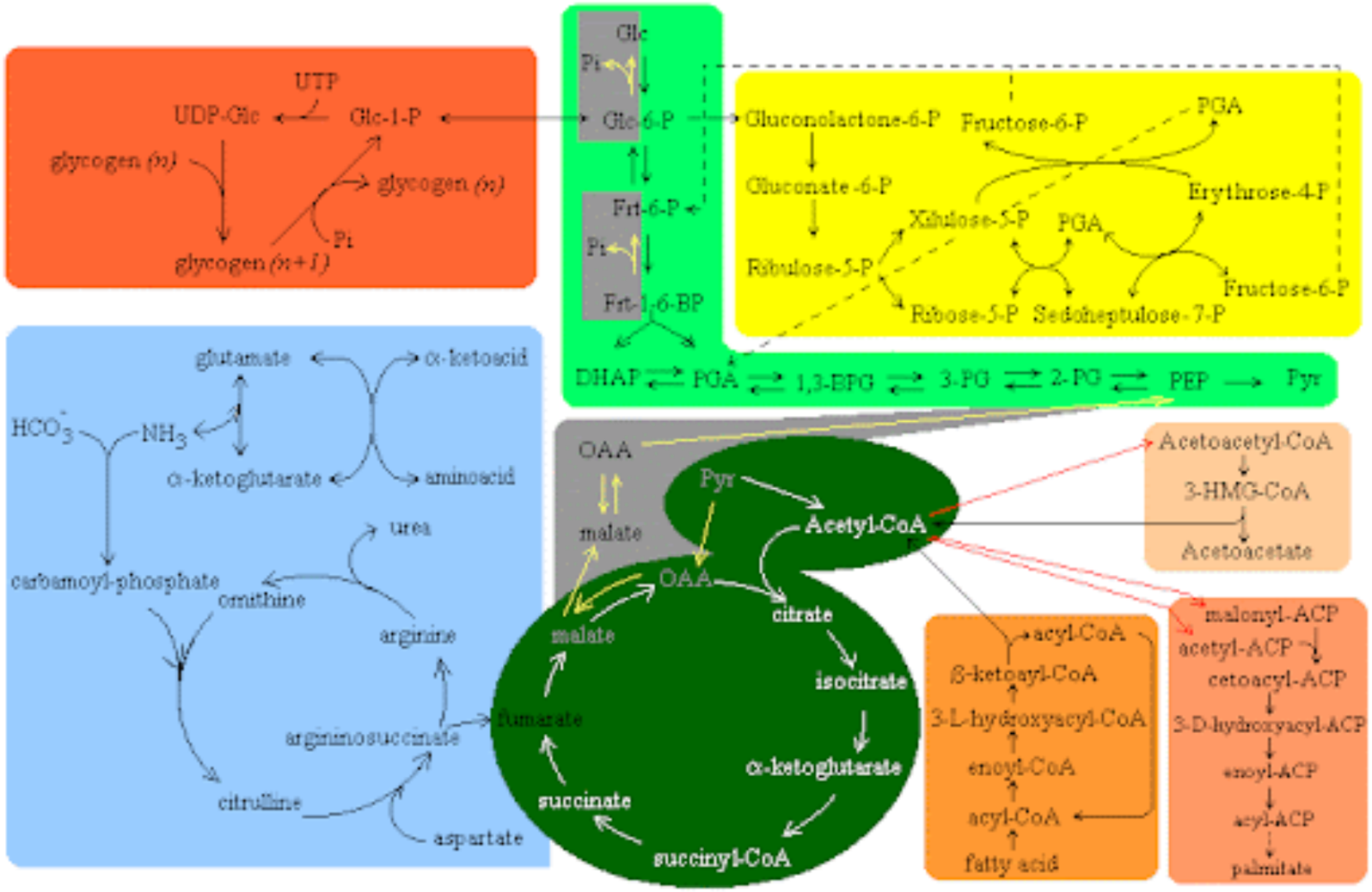
What are the mechanisms?

What is the difference with Biochemistry I, II, III, ….?



What is the difference with Biochemistry I, II, III, ….?

Metabolic Metro Map

Carbohydrate Metabolism

Ascorbate (Vitamin C)
Sugar Acids
Double/Multiple Sugars & Glycans
Glyco-genolysis
Simple Sugars
Inositol-P
Amino Sugars & Sialic Acids
Glyco-genesis
Nucleotide Sugars
Hexose-P
Gluconeo-genesis
Glycolysis
Triose-P
Glycerol
Pentose Phosphate Pathway
Pentose-P
Tetrose-P
Glyoxylate
Carbon Fixation
← CO_2
Photo-respiration
O_2 → H_2O_2
P-glycerate
Direct / C4 / CAM Carbon Intake
CO_2
O_2
H_2O → O_2
Light
NADPH, ATP
Light Reactions
Photosystems
Chloroplast
Peroxisome
Cytosol

Photosynthesis

Cellular Respiration

Homoserine Group & Lysine
Aspartate Group
P-glycerates
Serine Group
Malate
Oxalo-acetate
Citrate Shuttle
Pyruvate
Alanine
Lactate
Fermentation
Polyketides
Pyruvate Decarb-oxylation
Acetyl-CoA
Branched Amino Acids
Citrate
Citric Acid Cycle
CO_2 ←
Succinyl-CoA
α-Keto-glutarate
Ketogenic & Glucogenic Amino Acids
Ketolysis
Ketogenesis
Propionyl-CoA
NADH, $FADH_2$
Ketone Bodies
Mitochondrion
O_2
O_2 → H_2O
ATP & Heat
NADH, $FADH_2$
Oxidative Phosphorylation
Respiratory Chain
CO_2
Mitochondrion
Urea Cycle
Amino Acid Deamination
NH_3 → Urea
Creatine & Polyamines
Arginine
Urea
feeders to Gluconeogenesis
Glutamate Group & Proline
δ-ALA
Succinate
Bile Pigments
Hemes
Chlorophylls
Cobalamins (Vitamin B_{12})
Chloroplast
Glyoxylate Cycle
Acetyl-CoA
Peroxisomal Beta Oxidation
Peroxisome

Amino Acid Metabolism

Vitamin & Cofactor Metabolism

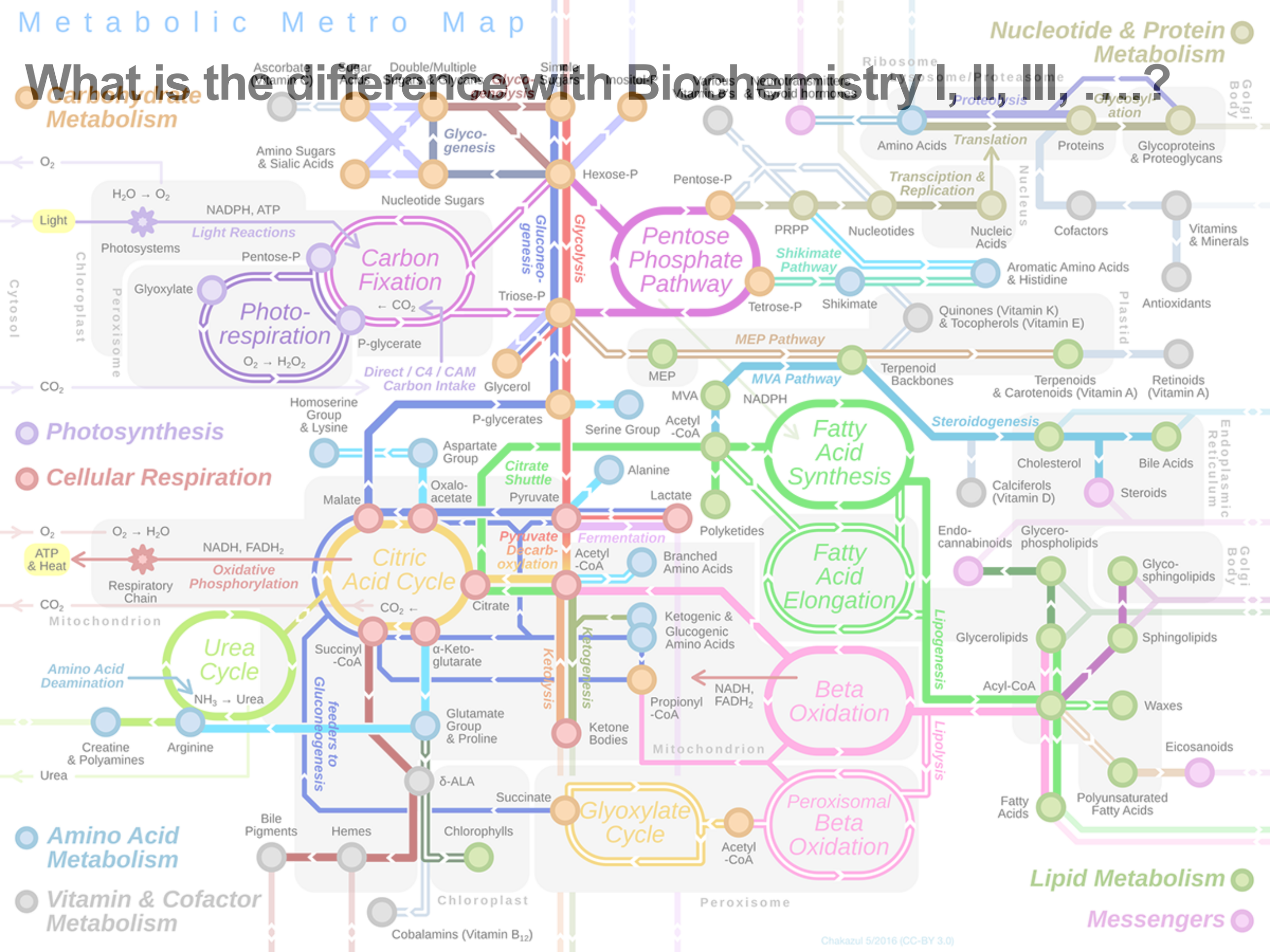
Nucleotide & Protein Metabolism

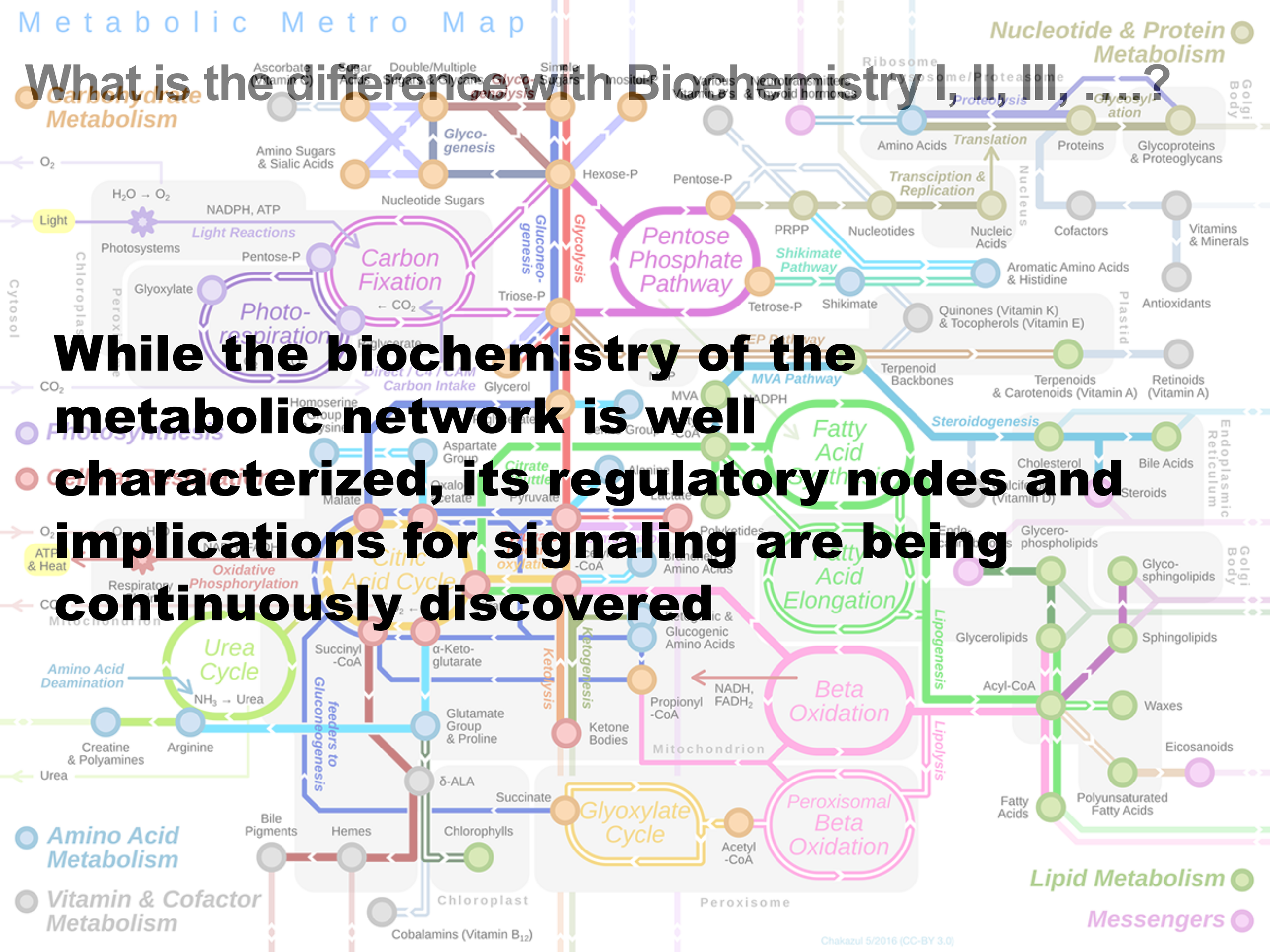
Ribosome
Lysosome/Proteasome
Various Vitamin B's
Neurotransmitters & Thyroid hormones
Proteolysis
Glycosyl-ation
Golgi Body
Amino Acids
Translation
Proteins
Glycoproteins & Proteoglycans
Transciption & Replication
Nucleus
Pentose-P
PRPP
Nucleotides
Nucleic Acids
Cofactors
Vitamins & Minerals
Shikimate Pathway
Aromatic Amino Acids & Histidine
Shikimate
Antioxidants
Quinones (Vitamin K) & Tocopherols (Vitamin E)
Plastid
MEP Pathway
MEP
MVA Pathway
MVA
NADPH
Terpenoid Backbones
Terpenoids & Carotenoids (Vitamin A)
Retinoids (Vitamin A)
Steroidogenesis
Cholesterol
Bile Acids
Calciferols (Vitamin D)
Steroids
Endoplasmic Reticulum
Fatty Acid Synthesis
Fatty Acid Elongation
Endo-cannabinoids
Glycero-phospholipids
Glyco-sphingolipids
Golgi Body
Glycerolipids
Sphingolipids
Lipogenesis
Acyl-CoA
Waxes
Beta Oxidation
Lipolysis
Eicosanoids
Fatty Acids
Polyunsaturated Fatty Acids

Lipid Metabolism

Messengers

What is the difference with Biochemistry I, II, III, ...?




What is the difference with Biochemistry I, II, III, ...?
While the biochemistry of the metabolic network is well characterized, its regulatory nodes and implications for signaling are being continuously discovered
Metabolic Metro Map
Carbohydrate Metabolism
Nucleotide & Protein Metabolism
Amino Acid Metabolism
Vitamin & Cofactor Metabolism
Lipid Metabolism
Messengers
Photosynthesis
Cellular respiration
Carbon Fixation
Photo-respiration
Light Reactions
Photosystems
Pentose Phosphate Pathway
Glycolysis
Gluconeo-genesis
Glycogen-olysis
Glycogen-esis
Citric Acid Cycle
Urea Cycle
Oxidative Phosphorylation
Fatty Acid Synthesis
Fatty Acid Elongation
Beta Oxidation
Peroxisomal Beta Oxidation
Glyoxylate Cycle
MVA Pathway
Steroidogenesis
Lipogenesis
Lipolysis
Ketogenesis
Ketolysis
Transcription & Replication
Translation
Proteolysis
Glycosyl-ation
Shikimate Pathway
Amino Acid Deamination
Direct / C4 / CAM Carbon Intake
feeders to Gluconeogenesis
Nucleus
Golgi Body
Endoplasmic Reticulum
Plastid
Peroxisome
Chloroplast
Mitochondrion
Cytosol
Chakazul 5/2016 (CC-BY 3.0)

Metabolism is DYNAMIC.

Cells need to reprogram their metabolism in order to:

- **Produce more biomass (cell division; cell growth)**
- **Produce more nucleotides (cell division; meiosis)**
- **Preserve energy (storage; response to nutrient scarcity)**
- **Cope with (oxidative) stress (replication and nutrient stress)**
- **Compartmentalize toxic metabolites (iron overload)**
- **Adapt to different environments (mobility, 3D growth)**
- **Secrete immunomodulatory molecules (immune response)**
- **Adjust availability of "signaling metabolites" (support signals)**
- **Support epigenetic rewiring (differentiation)**

…NOT to "produce" more energy

Class layout:

Part 1: Basics of integrated metabolism (AC)

Part 2: Impact of metabolism on biological processes (MS)

Part 3: Contribution of metabolism to pathophysiology (AC/MS)

Part 4: Metabolism across scales (AC)

Part 5: Journal clubs (AC/MS)

Part 6: Methods in metabolic research (hybrid)

What is metabolism?

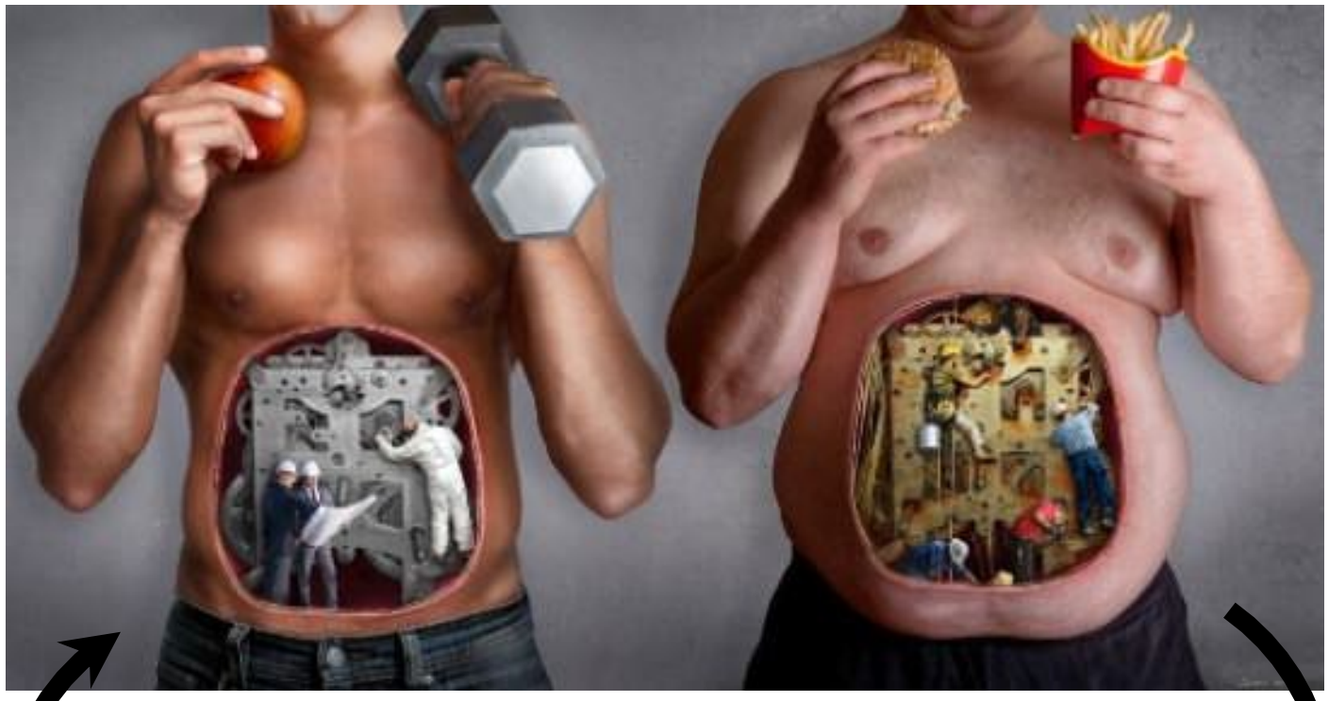
What is metabolism?

Humans ingest, metabolize or encounter more than 200,000 metabolites#. Metabolite classes include peptides, lipids, amino acids, nucleic acids, carbohydrates and minerals found in the diet, as well as food additives, drugs, cosmetics, contaminants and pollutants incorporated from our modern life.

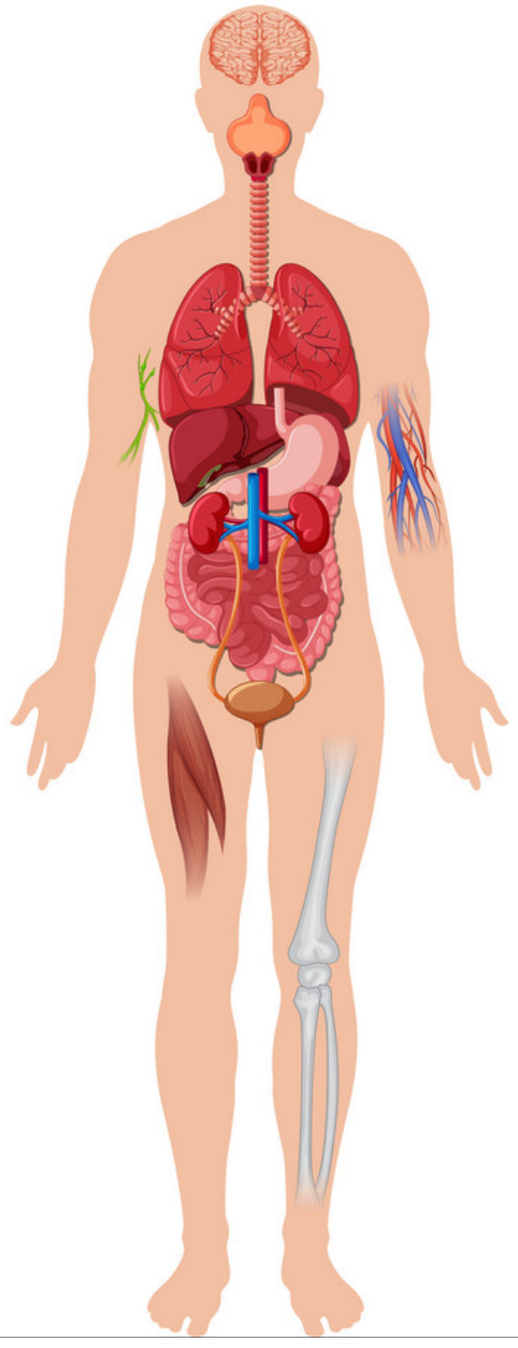
METABOLISM removes unwanted or toxic substances and ensures adequate levels of energy and building blocks in a dynamic environment.

Ref: Wishart DS et al. HMDB 5.0: the Human Metabolome Database for 2022. Nucleic Acids Res. 50, D622–D631 (2022). [PubMed: 34986597]

Metabolism is linked to body health and performance



Systemic Metabolism



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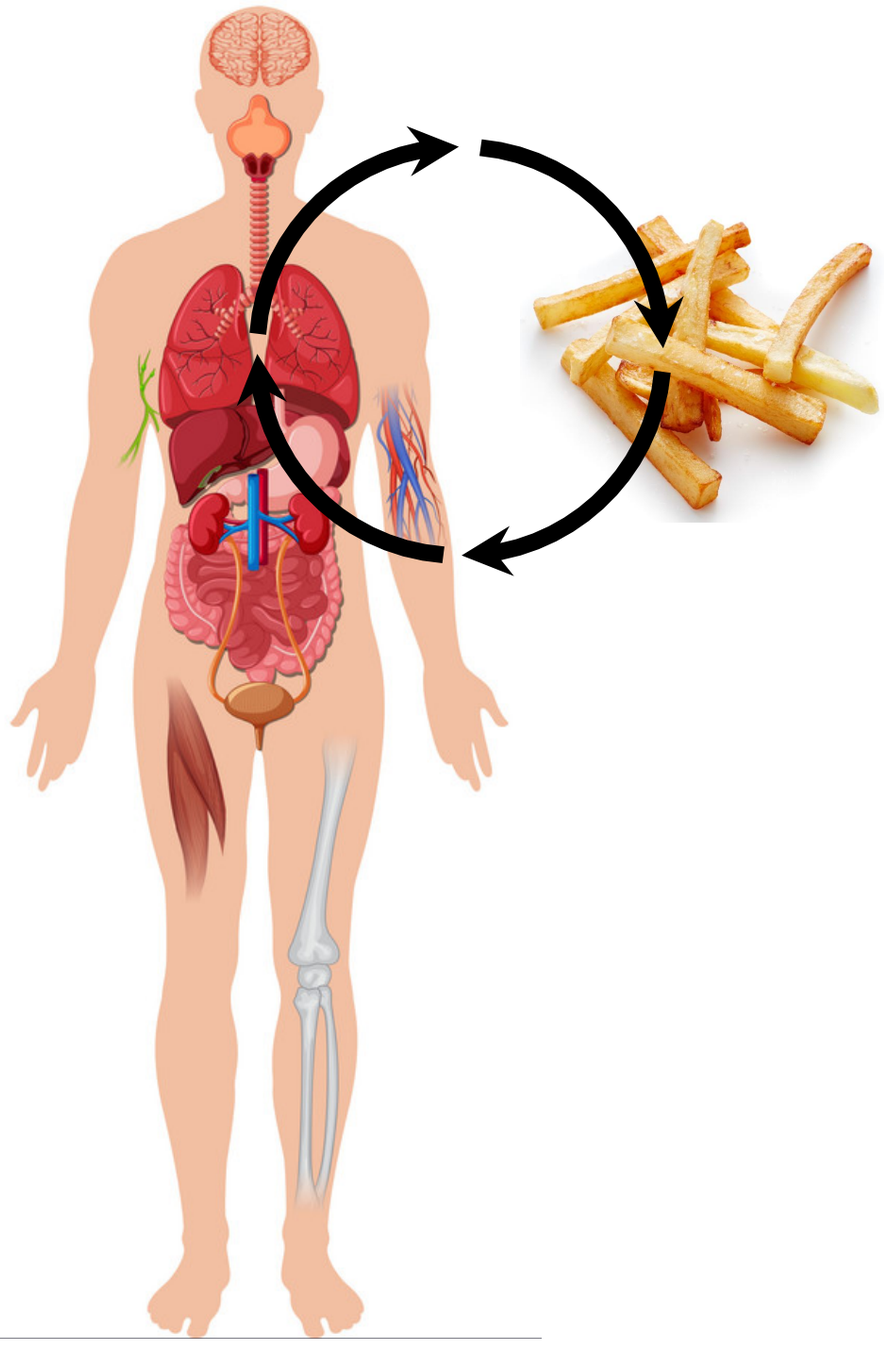
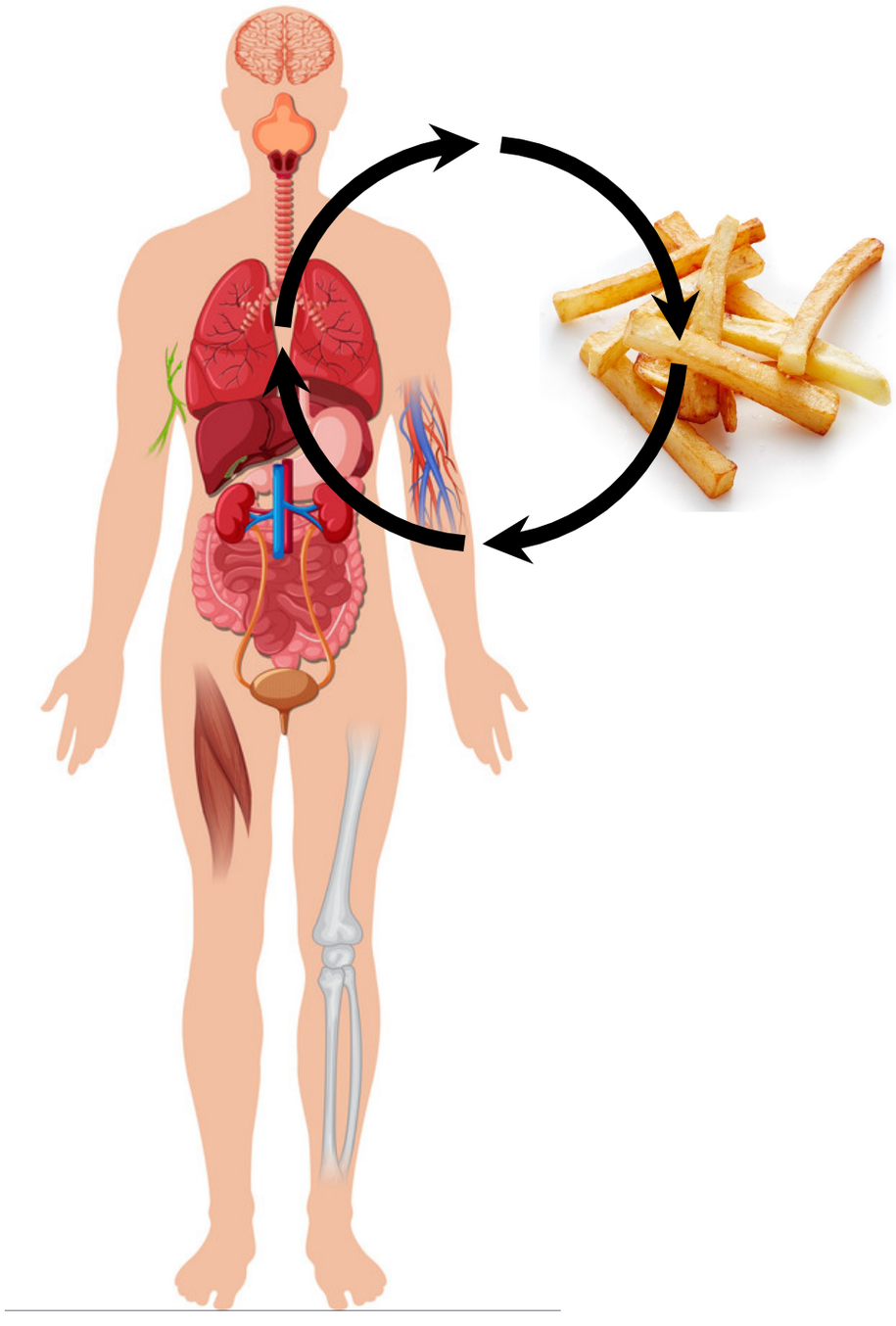
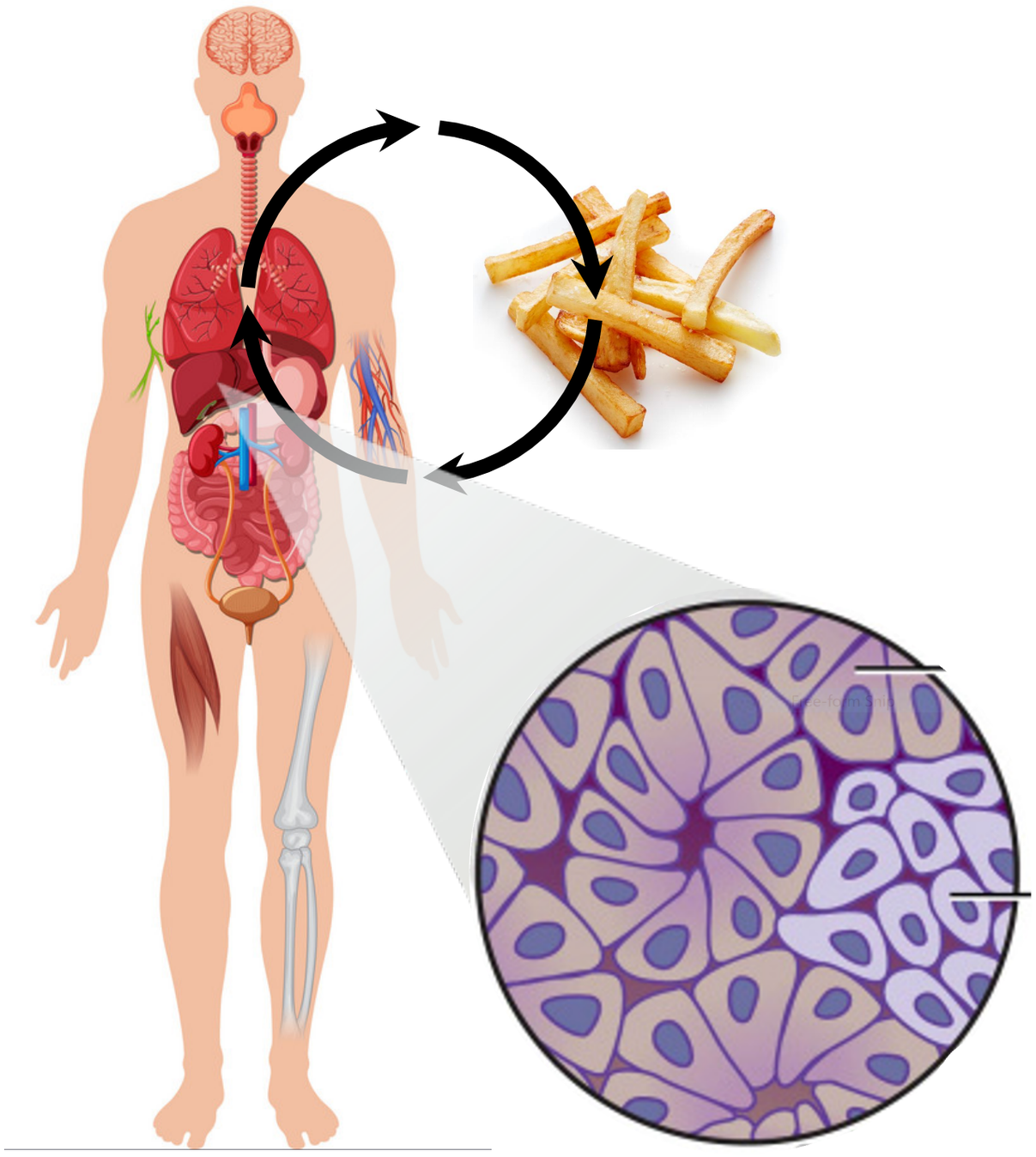
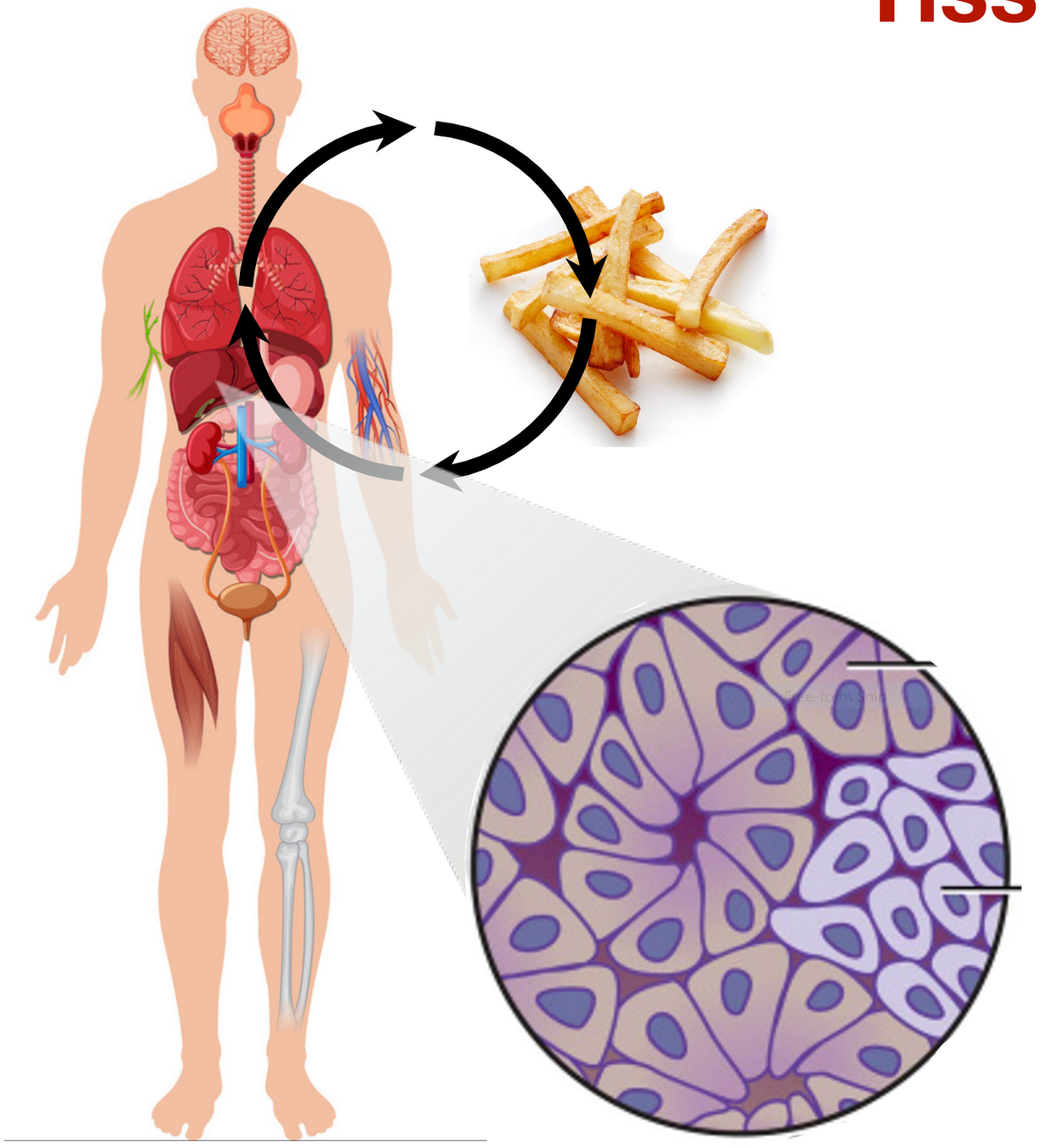
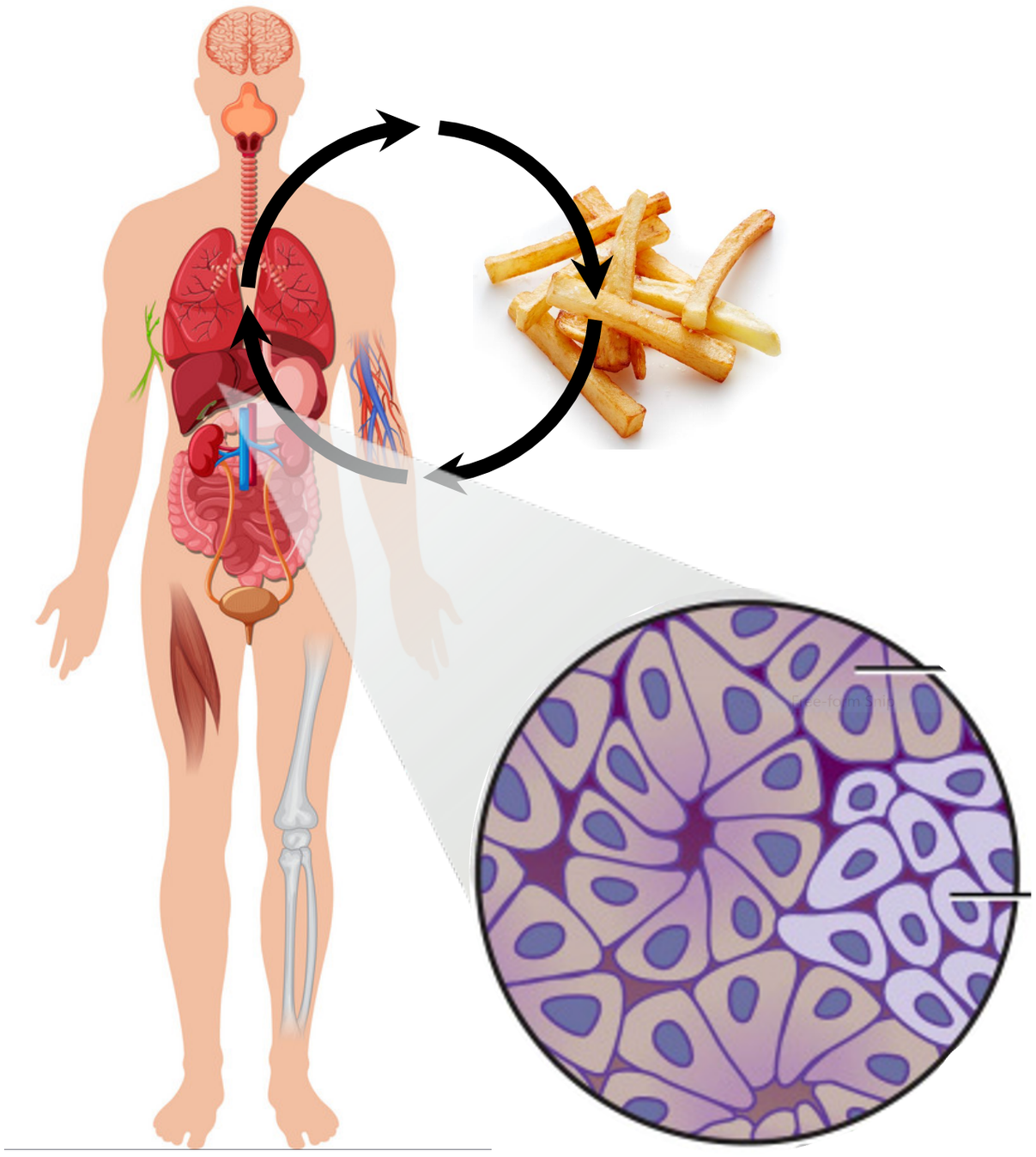


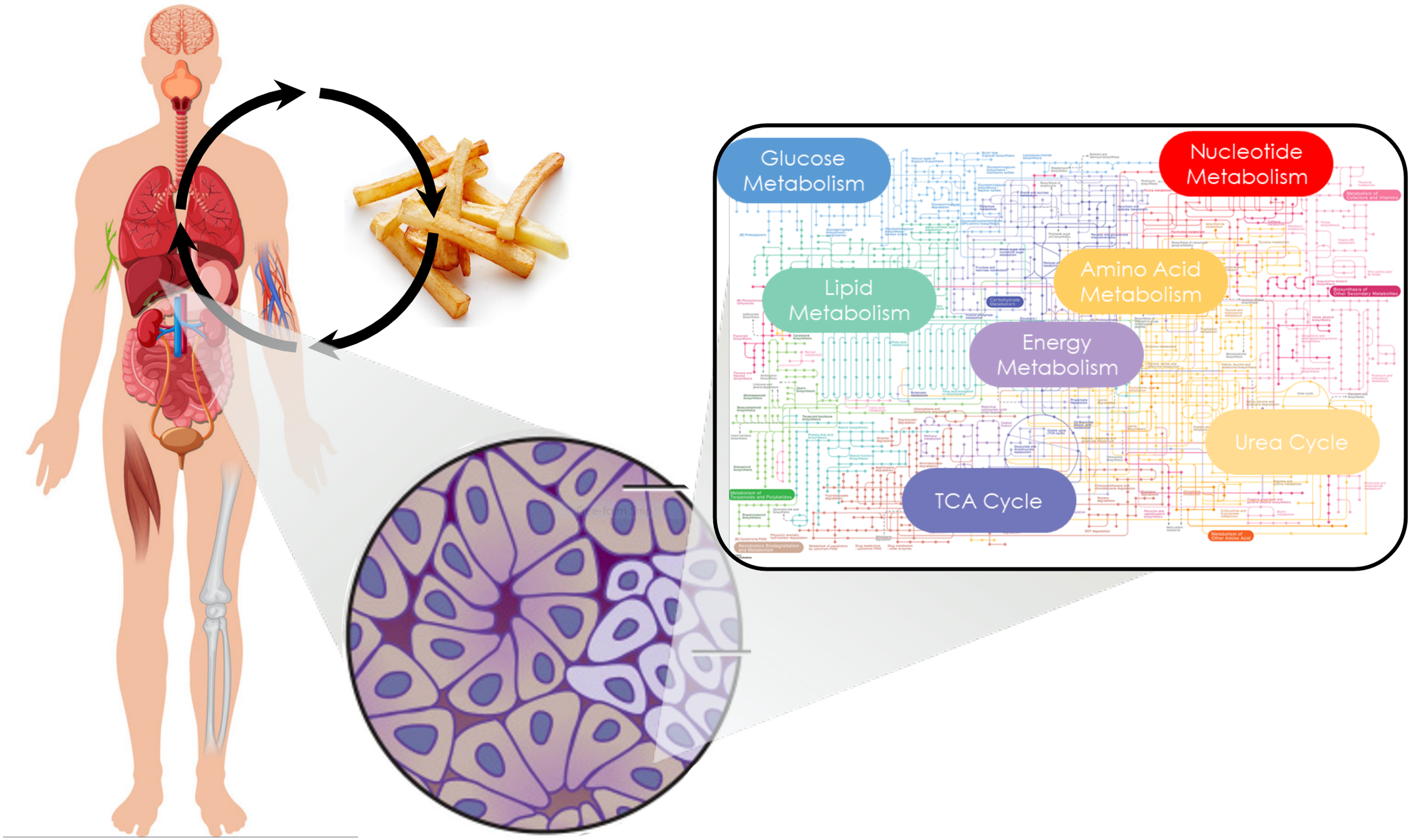




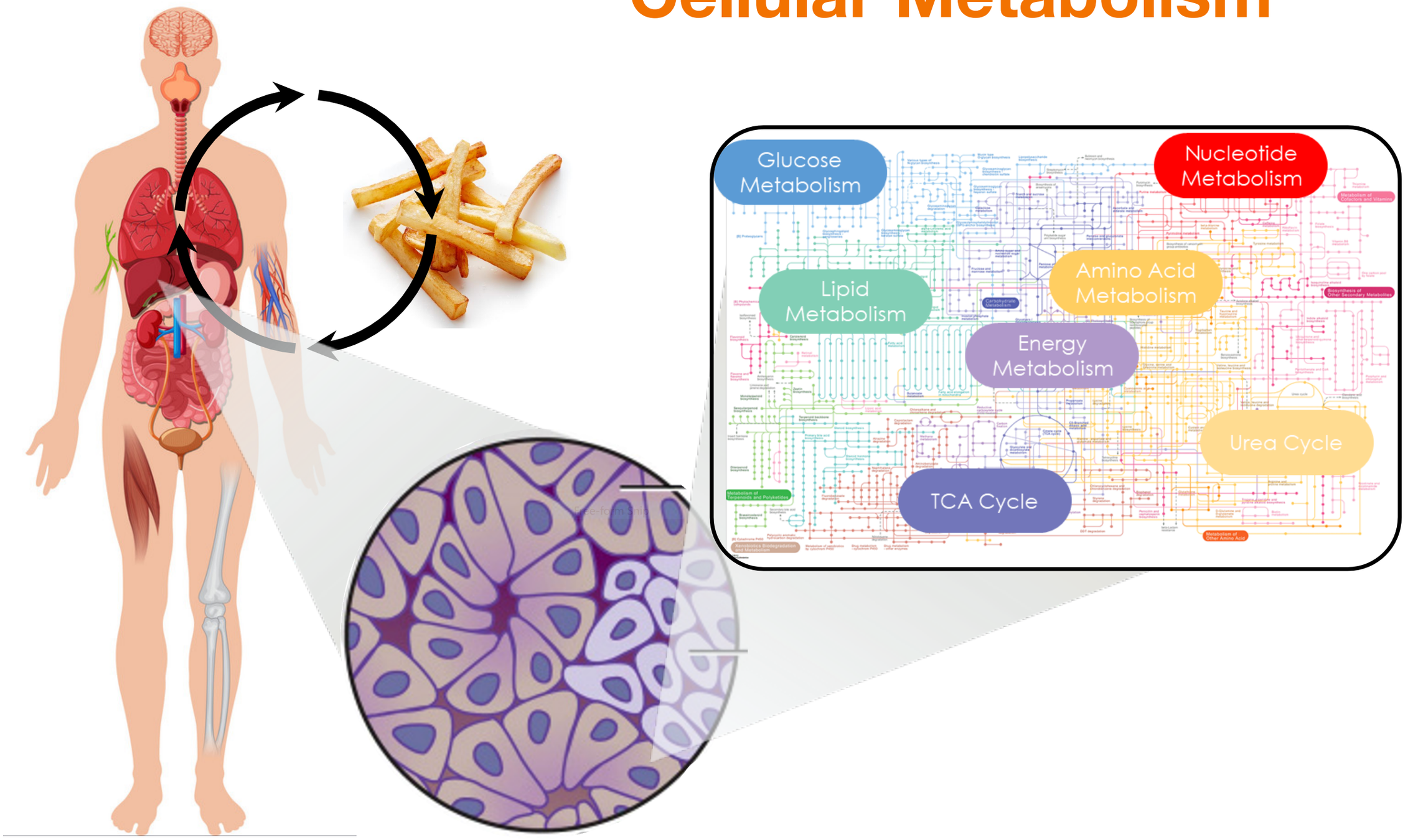
Tissue Metabolism



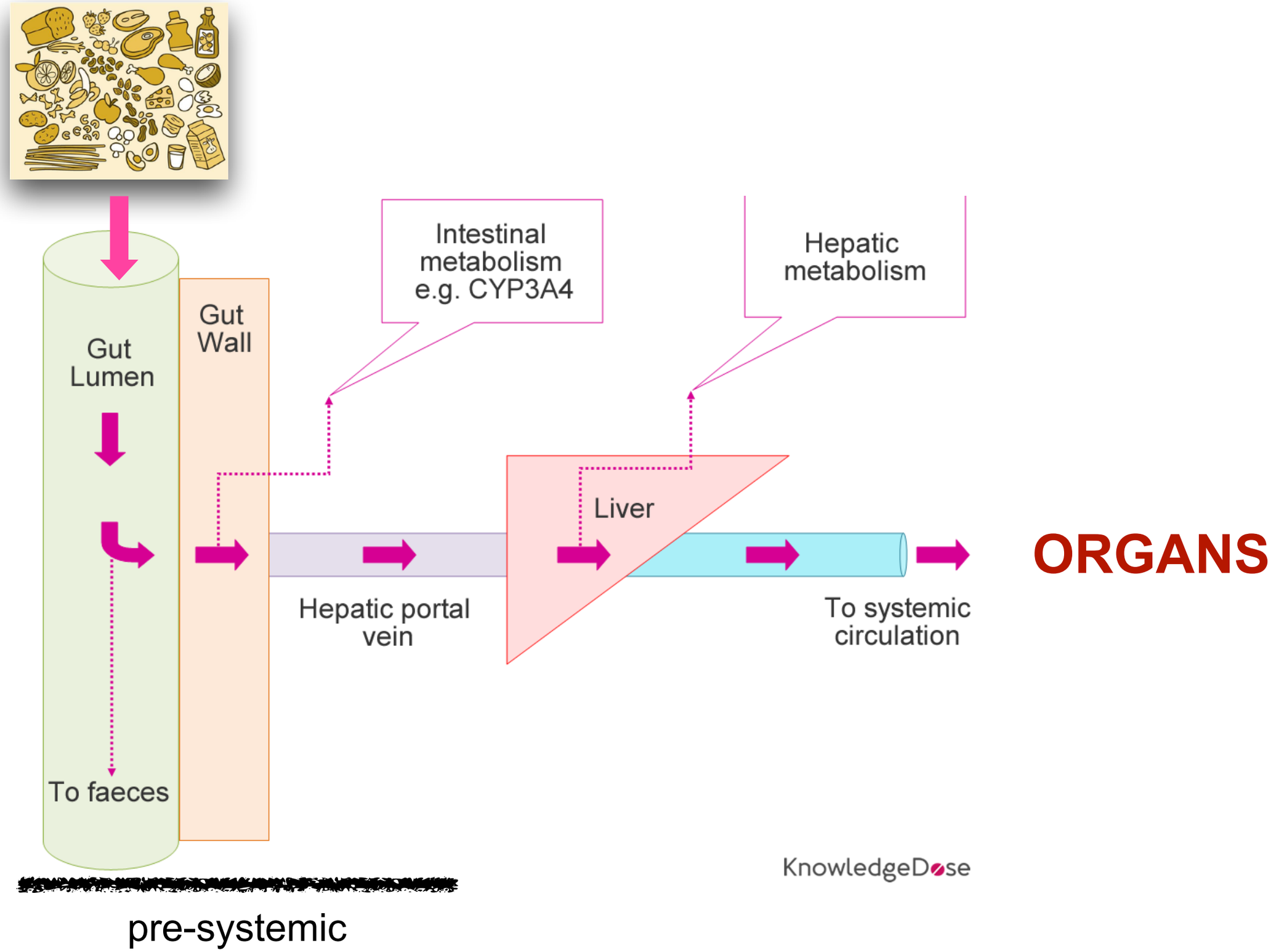



Glucose Metabolism
Nucleotide Metabolism
Lipid Metabolism
Amino Acid Metabolism
Energy Metabolism
Urea Cycle
TCA Cycle

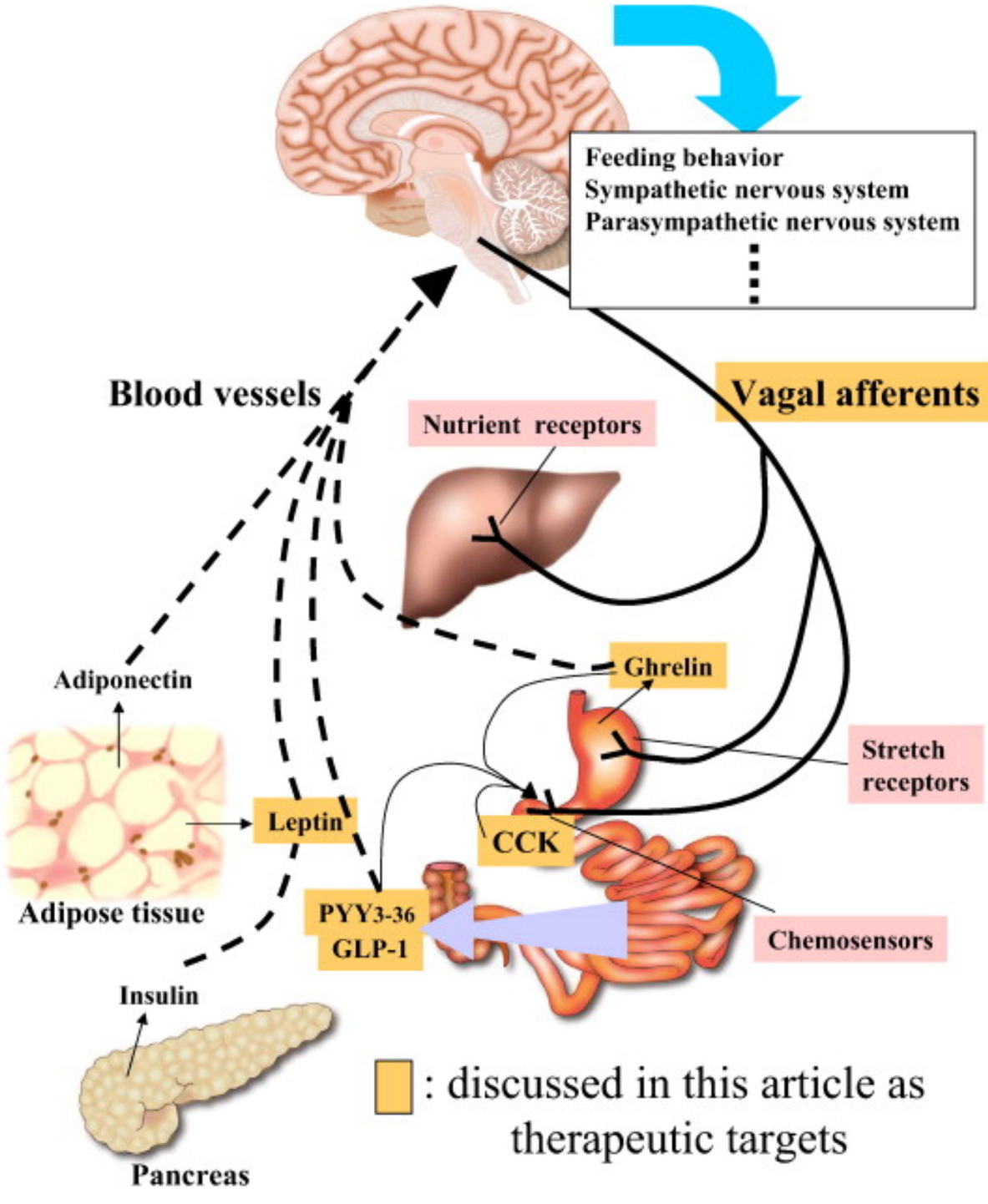
Cellular Metabolism



What is Systemic Metabolism?

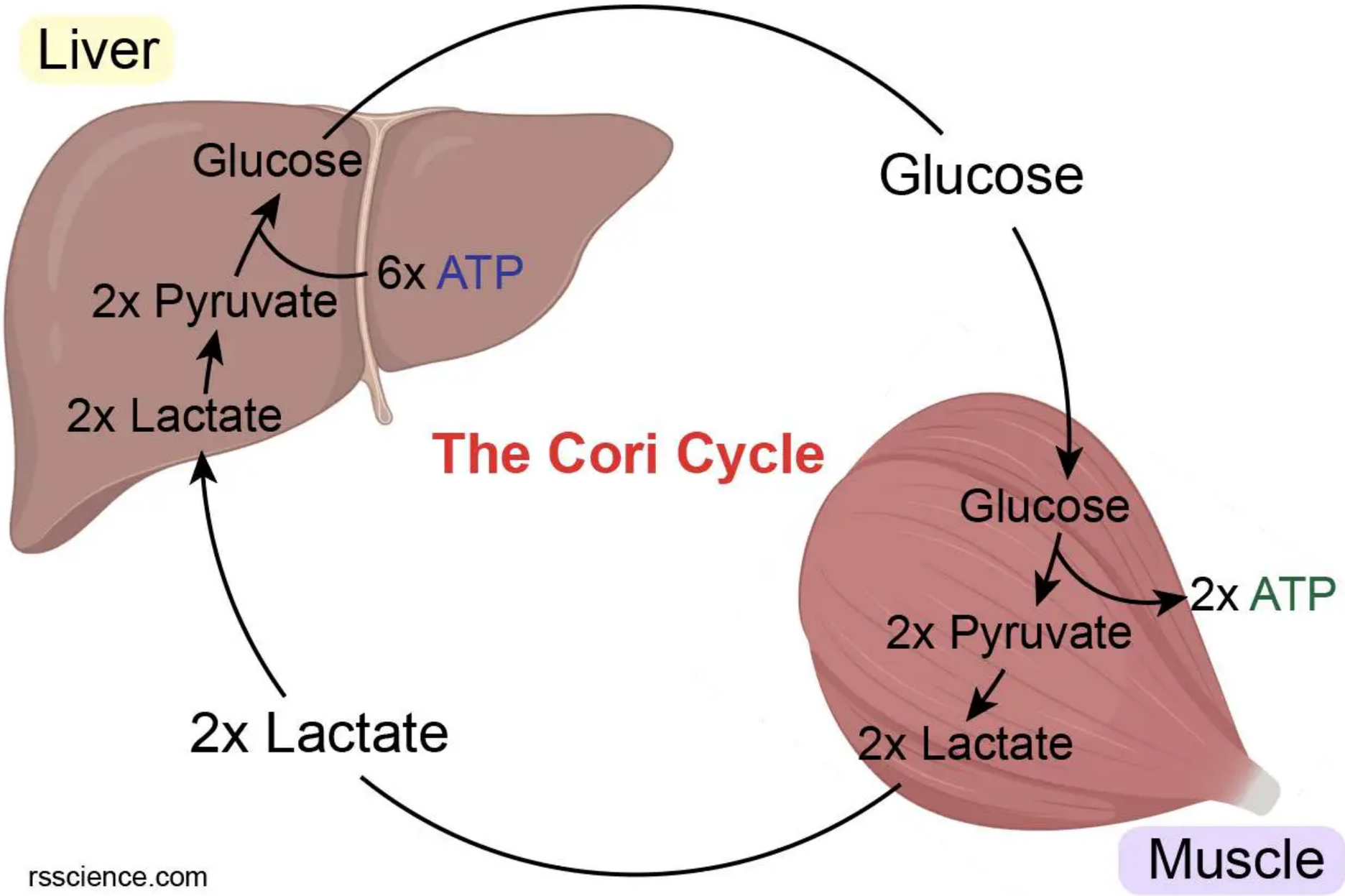


Systemic metabolism is a multi-organ affair

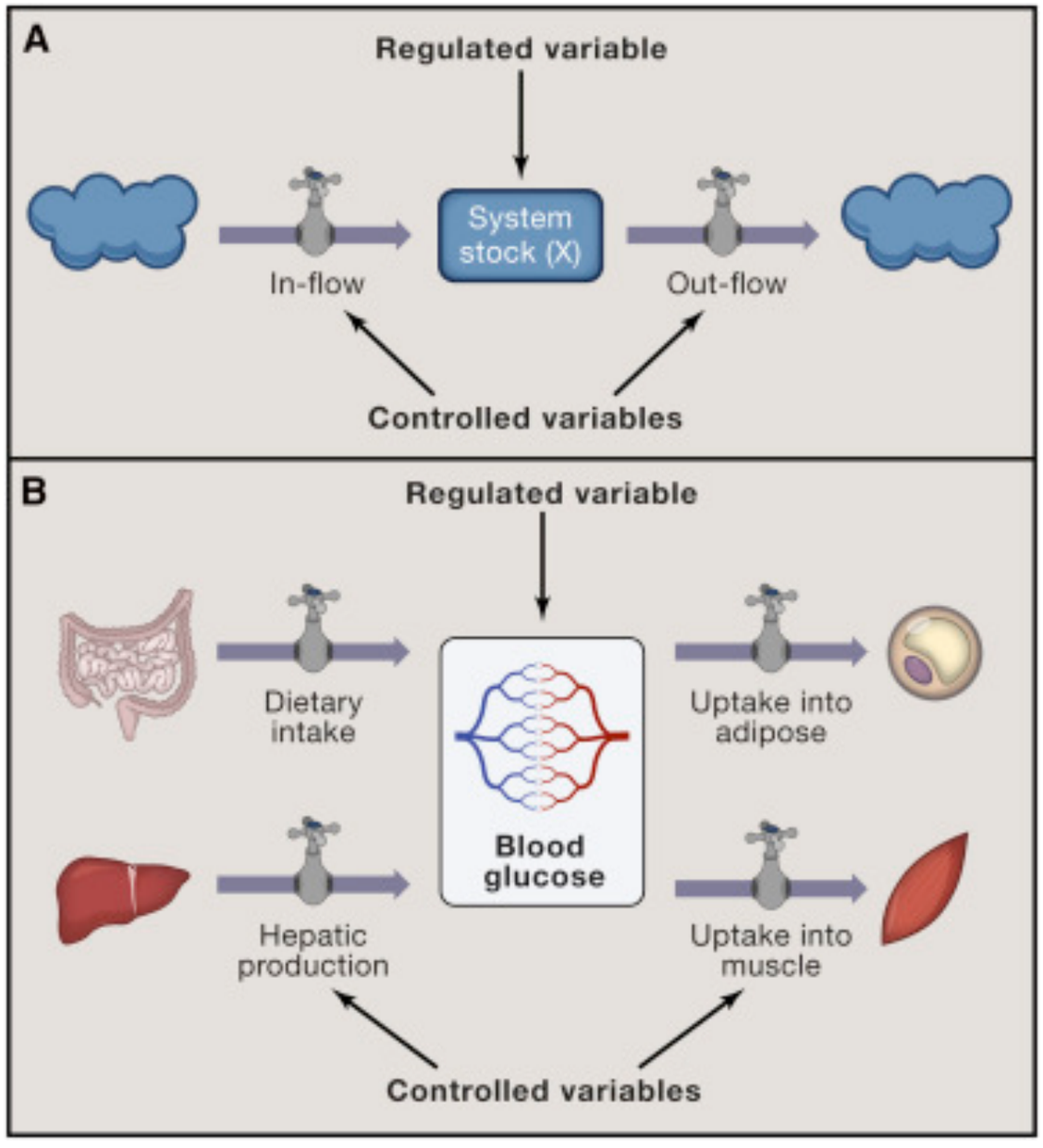


Inter-organ communication contributes significantly to nutrient uptake and metabolite availability.

Inter-organ metabolism provides nutrient supply to satisfy tissue-specific demands



Systemic metabolism tends to homeostasis



In the 19th century, Claude Bernard articulated the need to maintain a stable internal environment that would allow biological processes to proceed despite variations in the external environment. Bernard's concept was further explored, developed, and popularized by Walter Cannon, who coined the term "**homeostasis**" in describing how key physiological variables are maintained within a predefined range by feedback mechanisms.

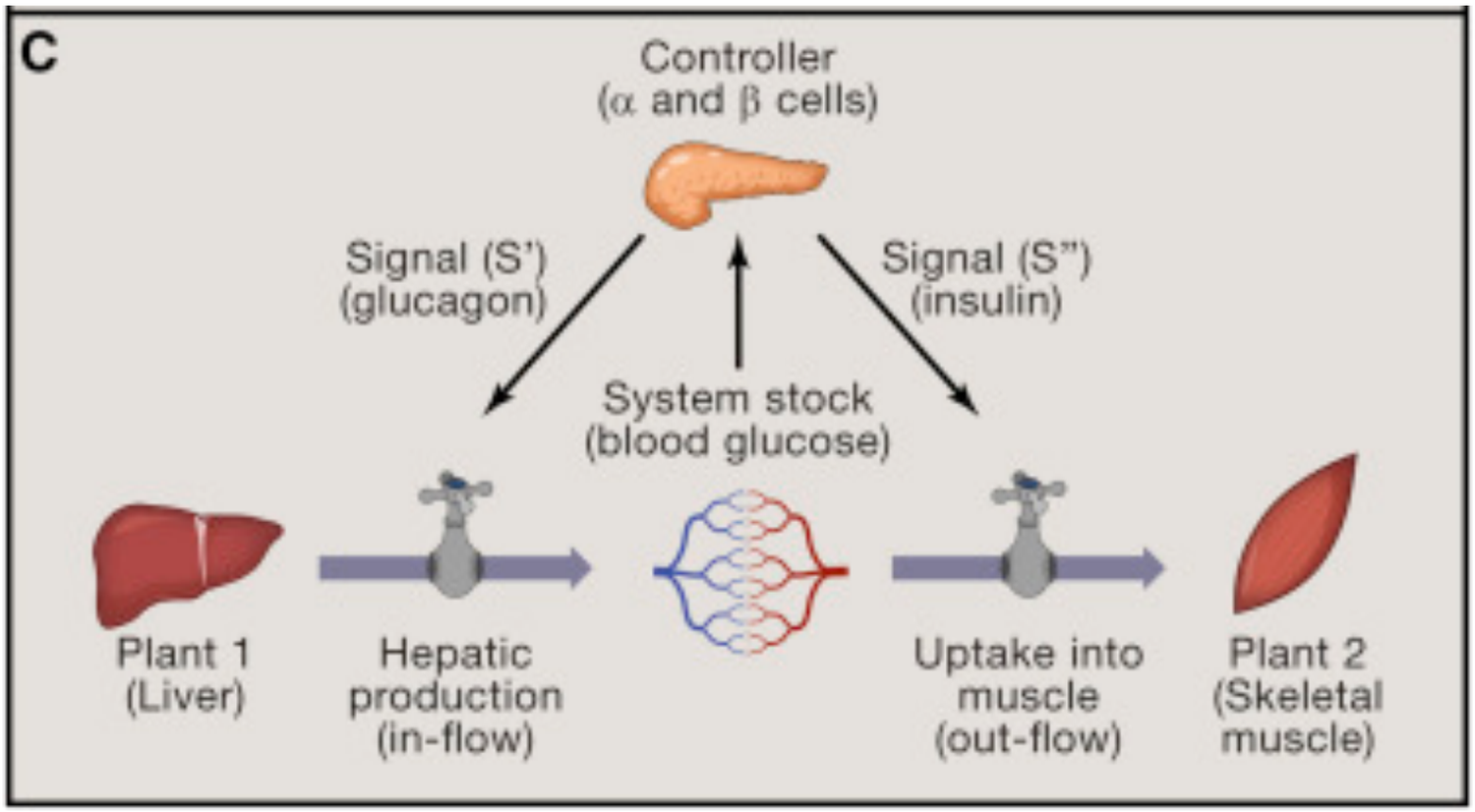
In 1954, James Hardy proposed a model in which homeostatic mechanisms maintain physiological variables within an acceptable range.

Regulated variables: physiological parameters that are maintained at stable levels

Controlled variables: activities (or rates) of the processes that contribute to the stability of the RV

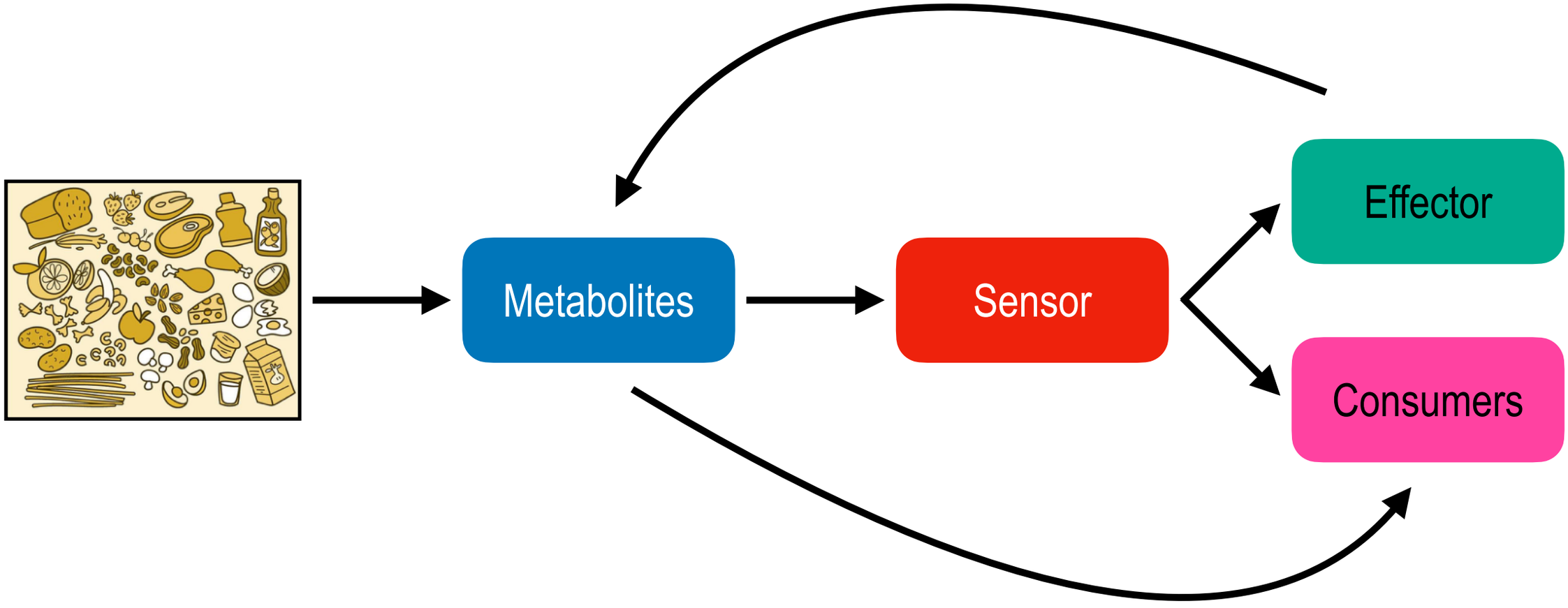
*Kotas & Medzhitov, **Cell**, 2015*

Systemic metabolism tends to homeostasis



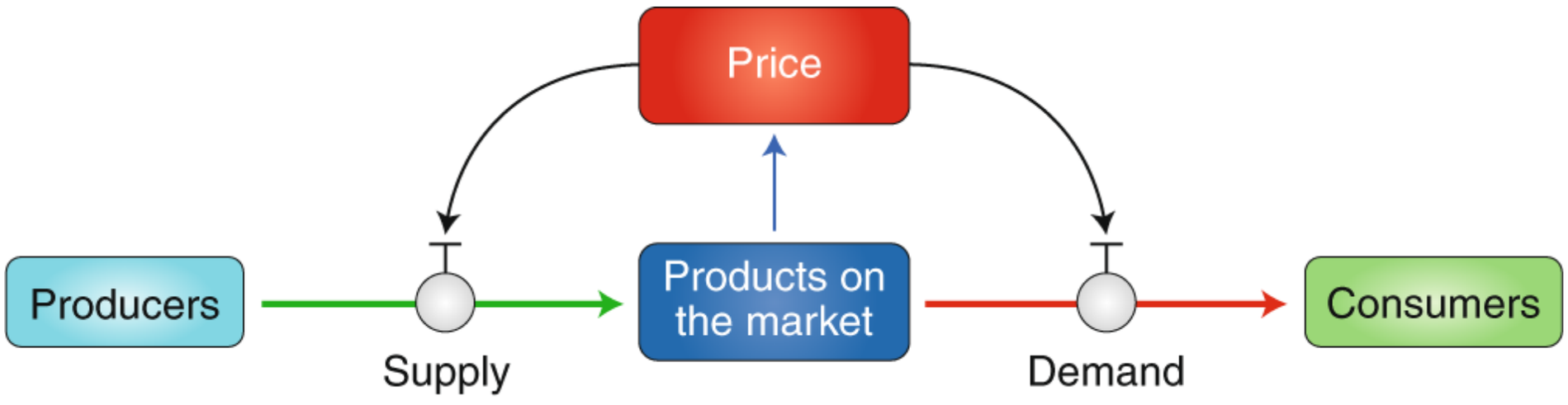
Kotas & Medzhitov, ***Cell****, 2015*

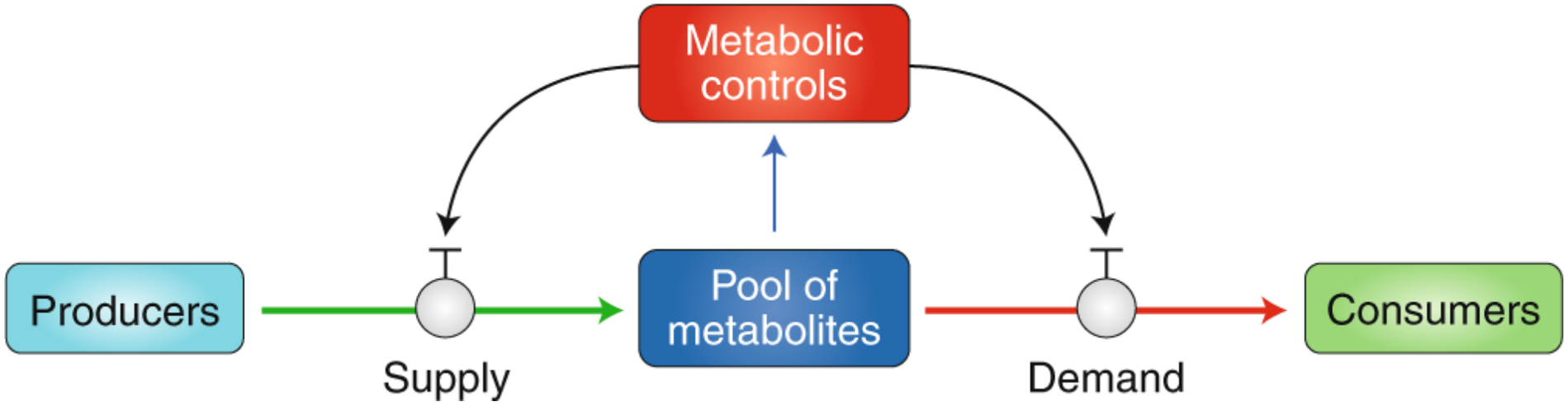
Metabolites mediate homeostatic mechanisms



Adapted from: Ye & Medzhitov, ***Nat Metab****, 2019*

Homeostatic mechanisms are subject to regulation

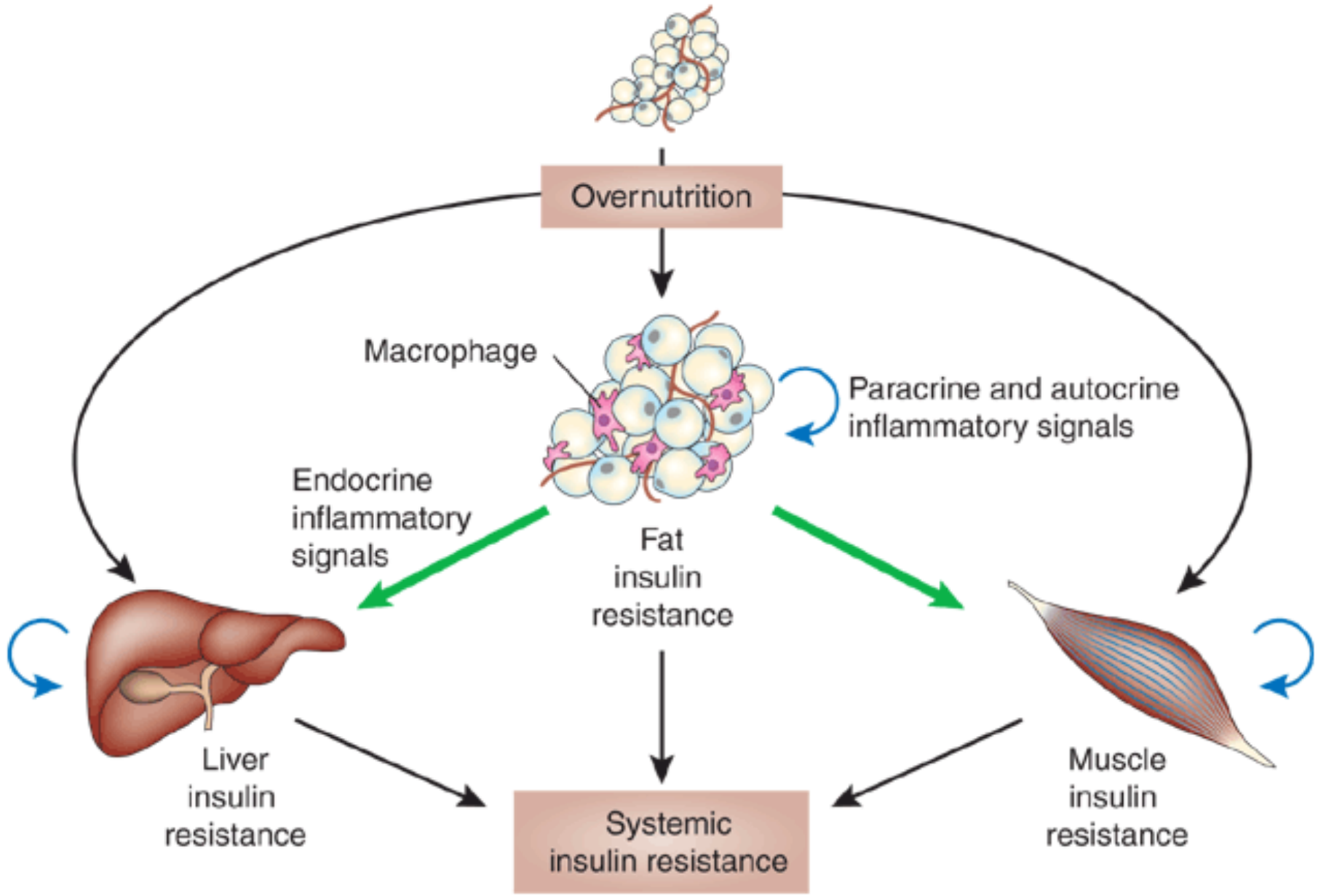




In addition to being subject to well-appreciated homeostatic control, metabolism is subject to supply-driven and demand-driven controls, each operated by a dedicated set of signals throughout various physiological states

Ye & Medzhitov, ***Nat Metab****, 2019*

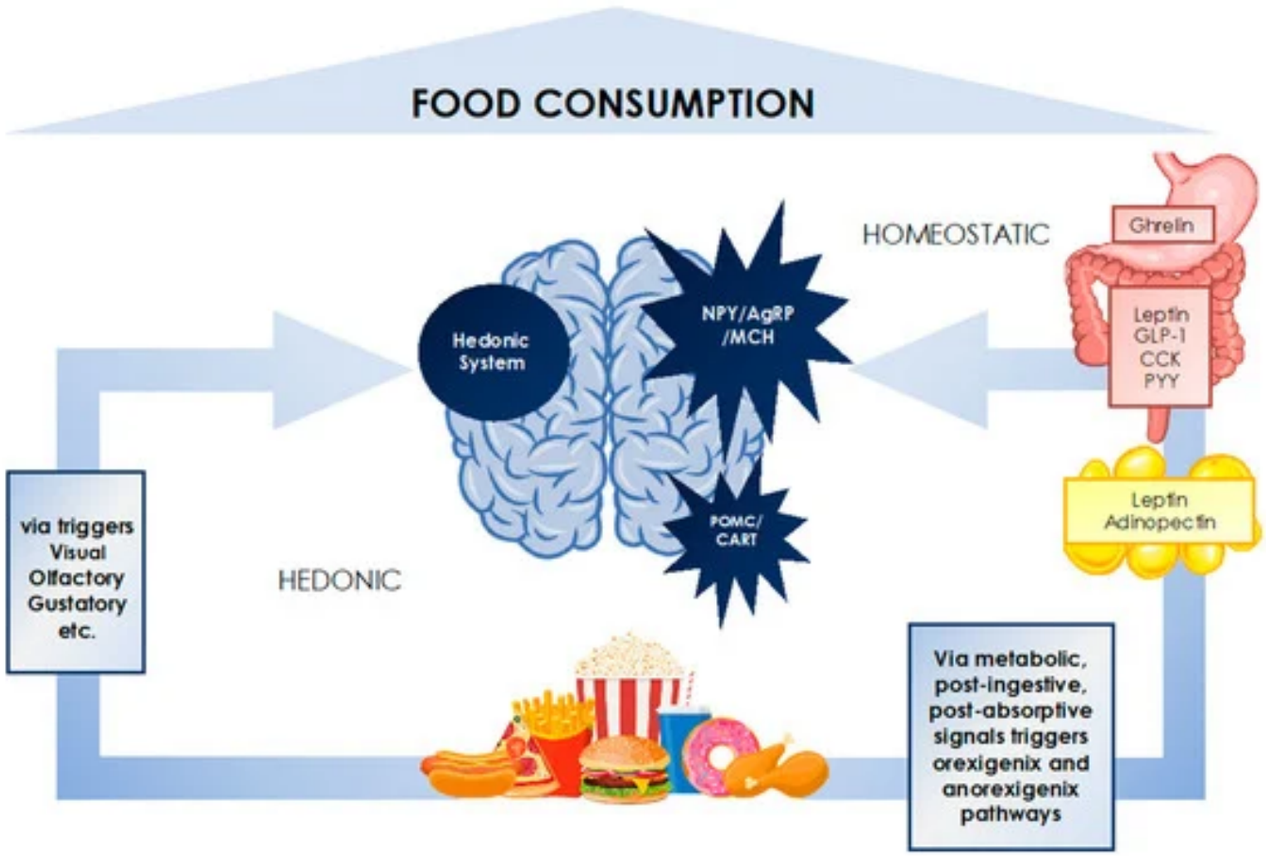
Food intake impacts systemic homeostasis

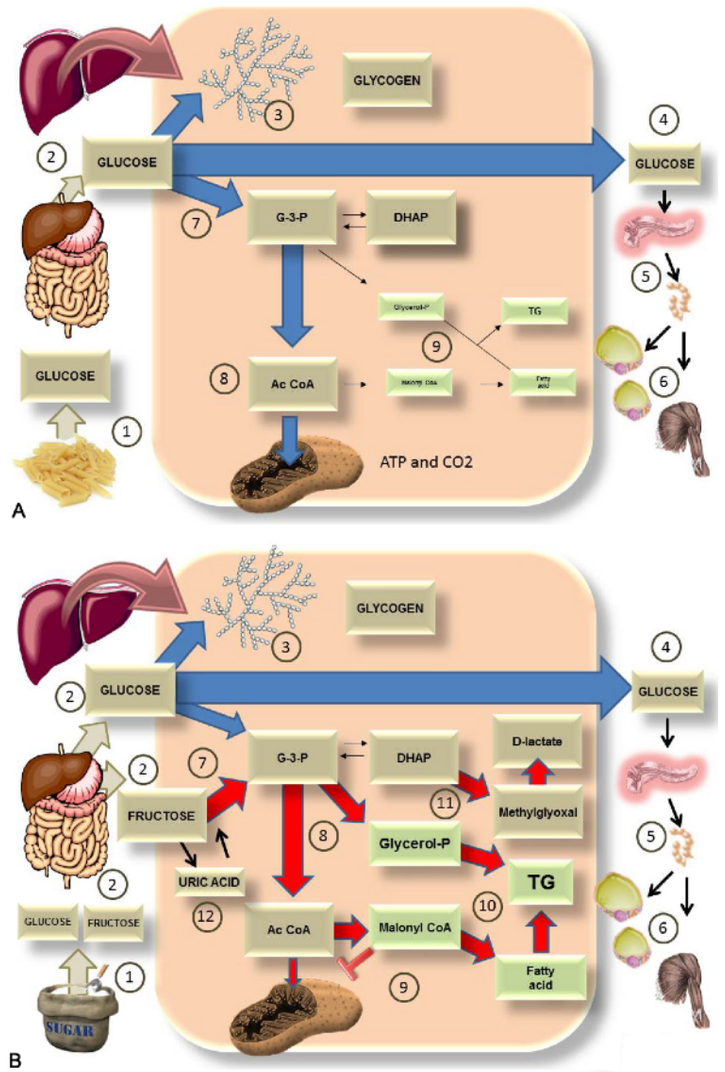


Overnutrition (or excessive fat intake) initiates a series of event that leads to systemic dyshomeostasis

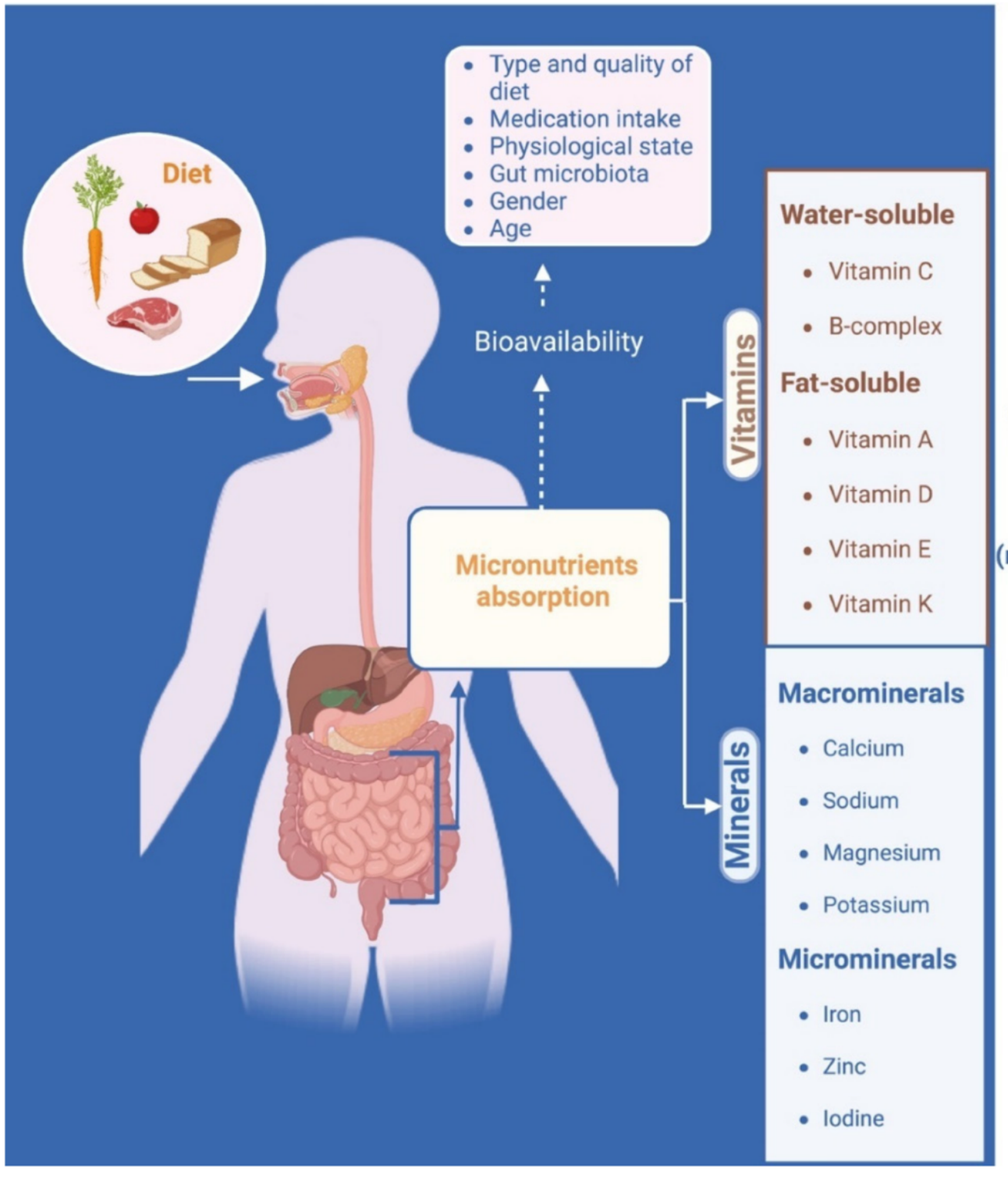
Some nutrients bypass homeostatic regulation

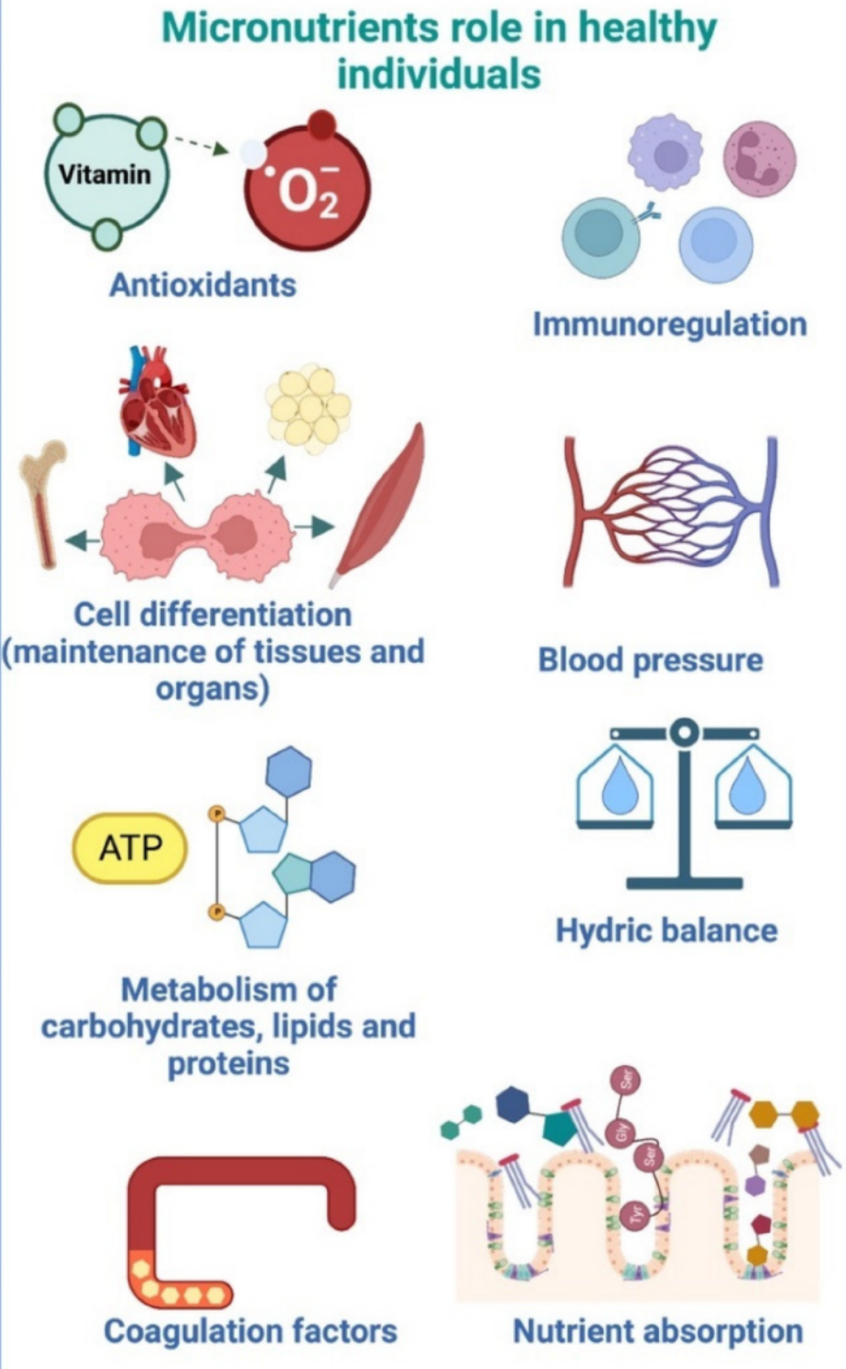
Hedonic or reward-based regulation can override the homeostatic pathway during periods of relative energy abundance by increasing the desire to consume foods that are highly palatable



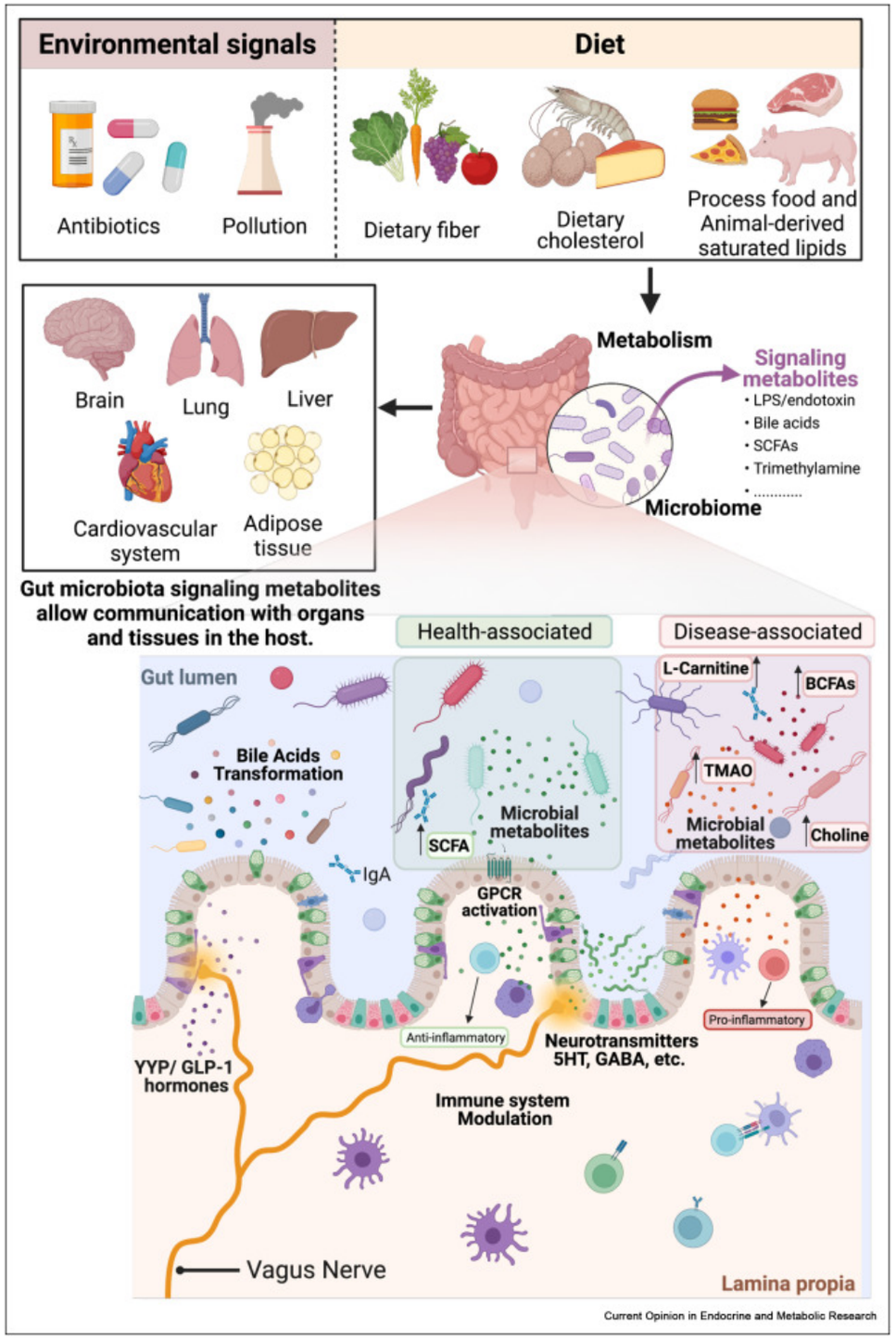


Some micronutrients bypass homeostatic regulation

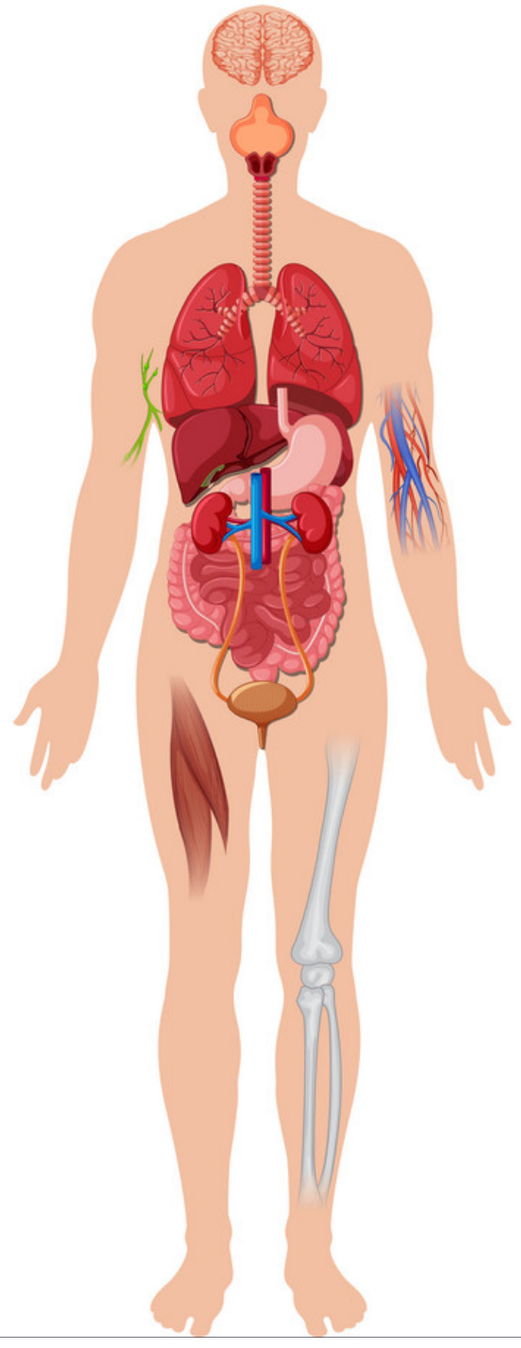




Nutrient uptake (and bioavailability) is regulated by the microbiome

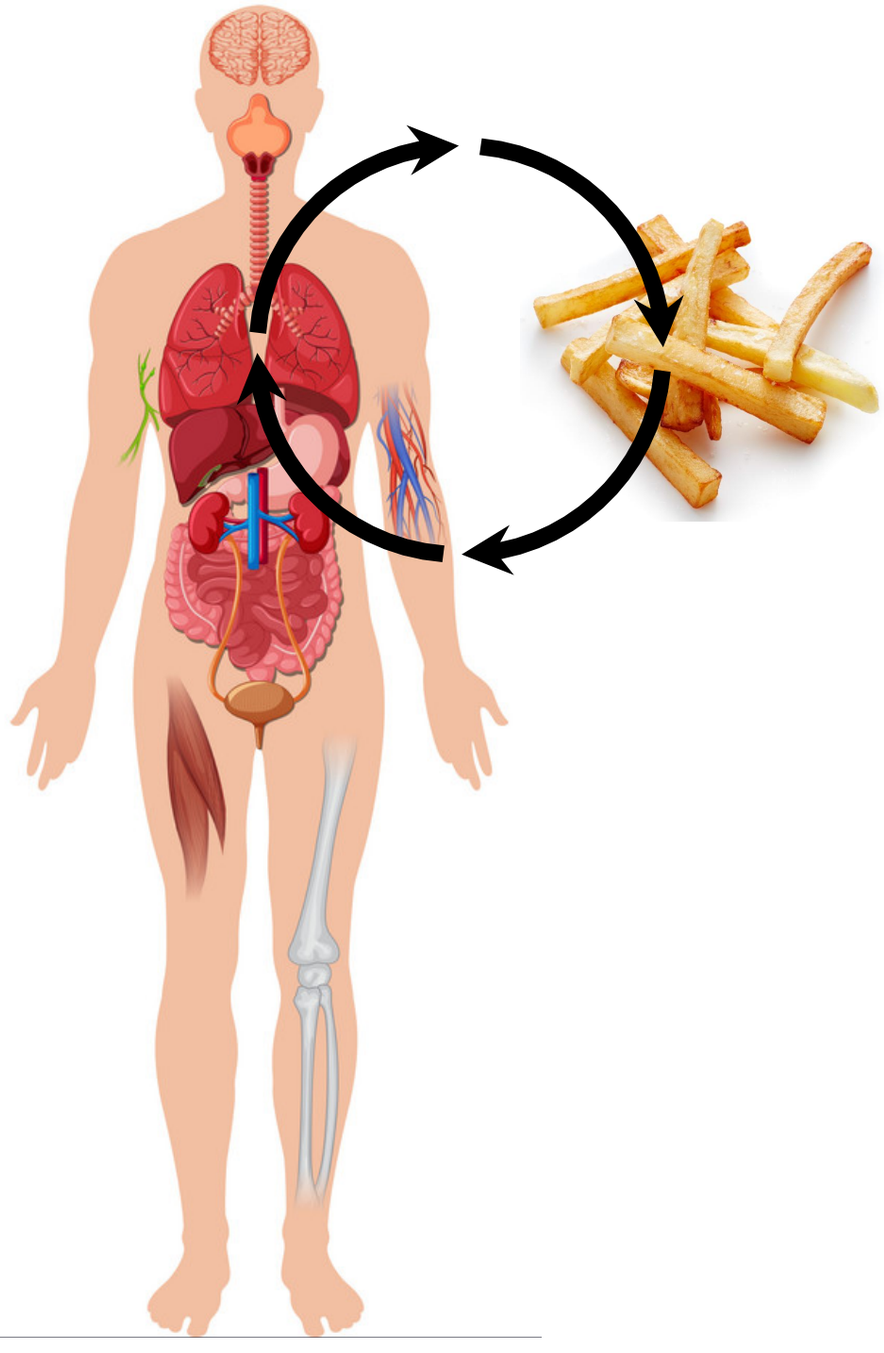


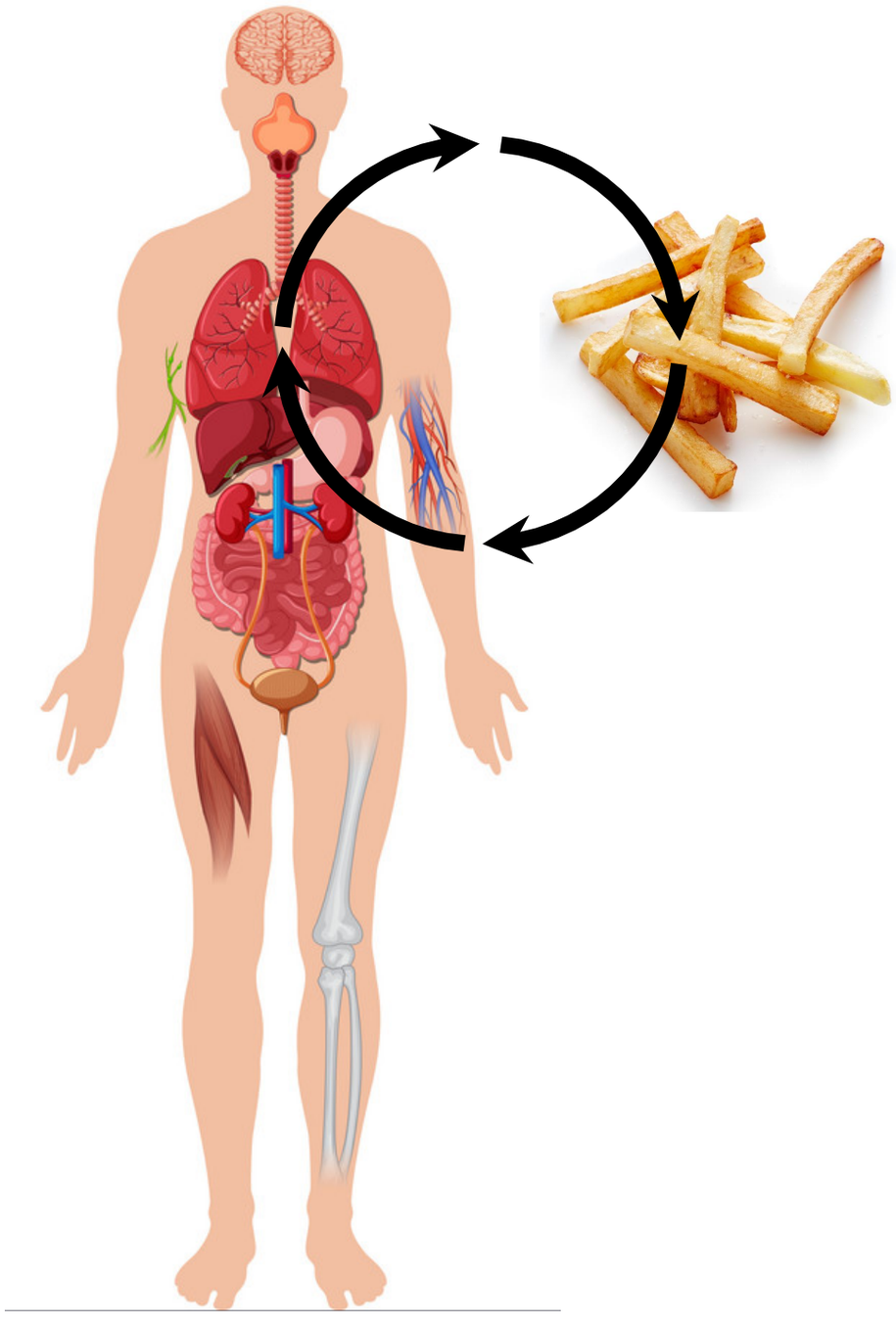
Mavros & Ronda, ***Curr Opin Endocr Metab****, 2022*

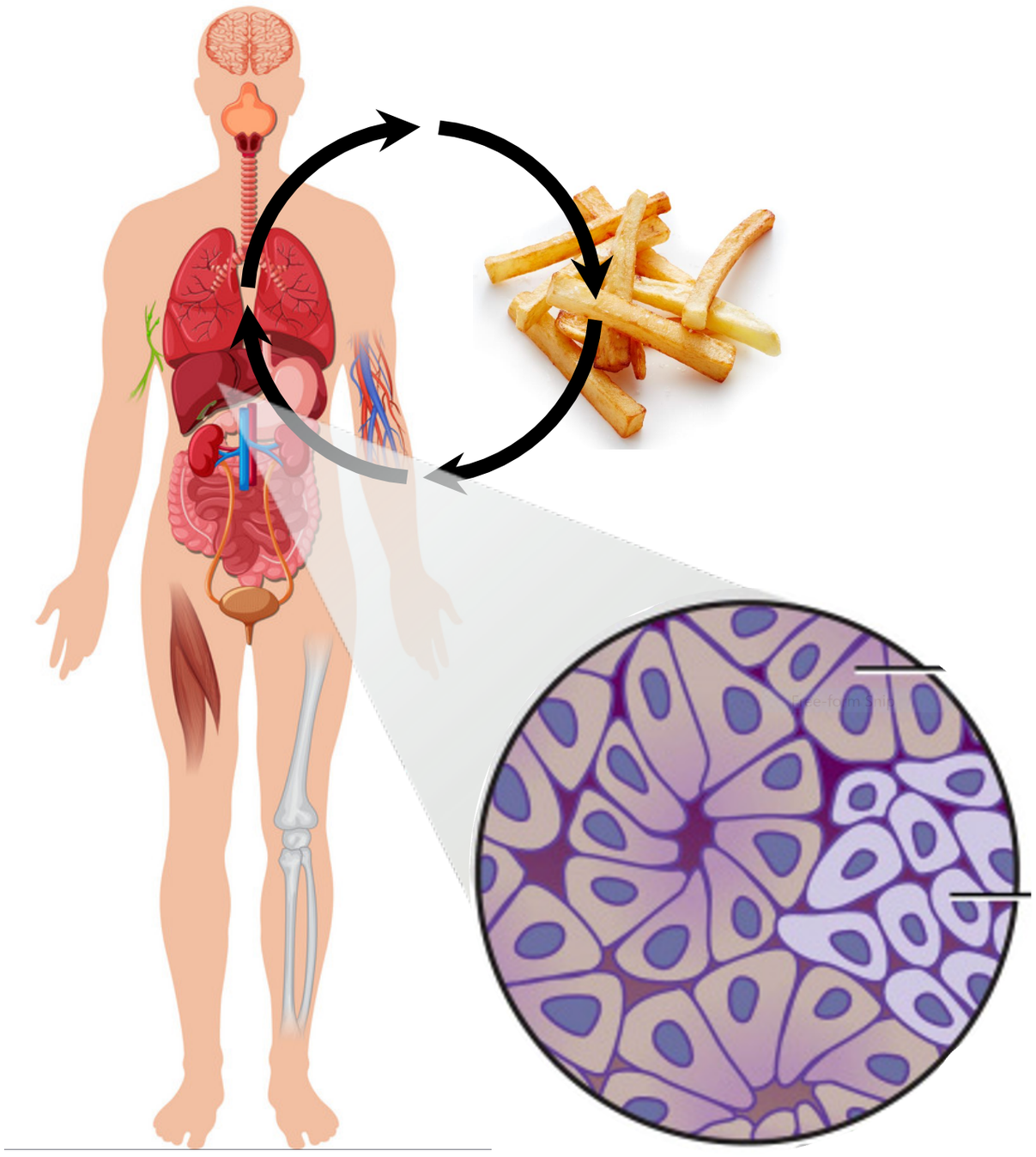


Systemic Metabolism

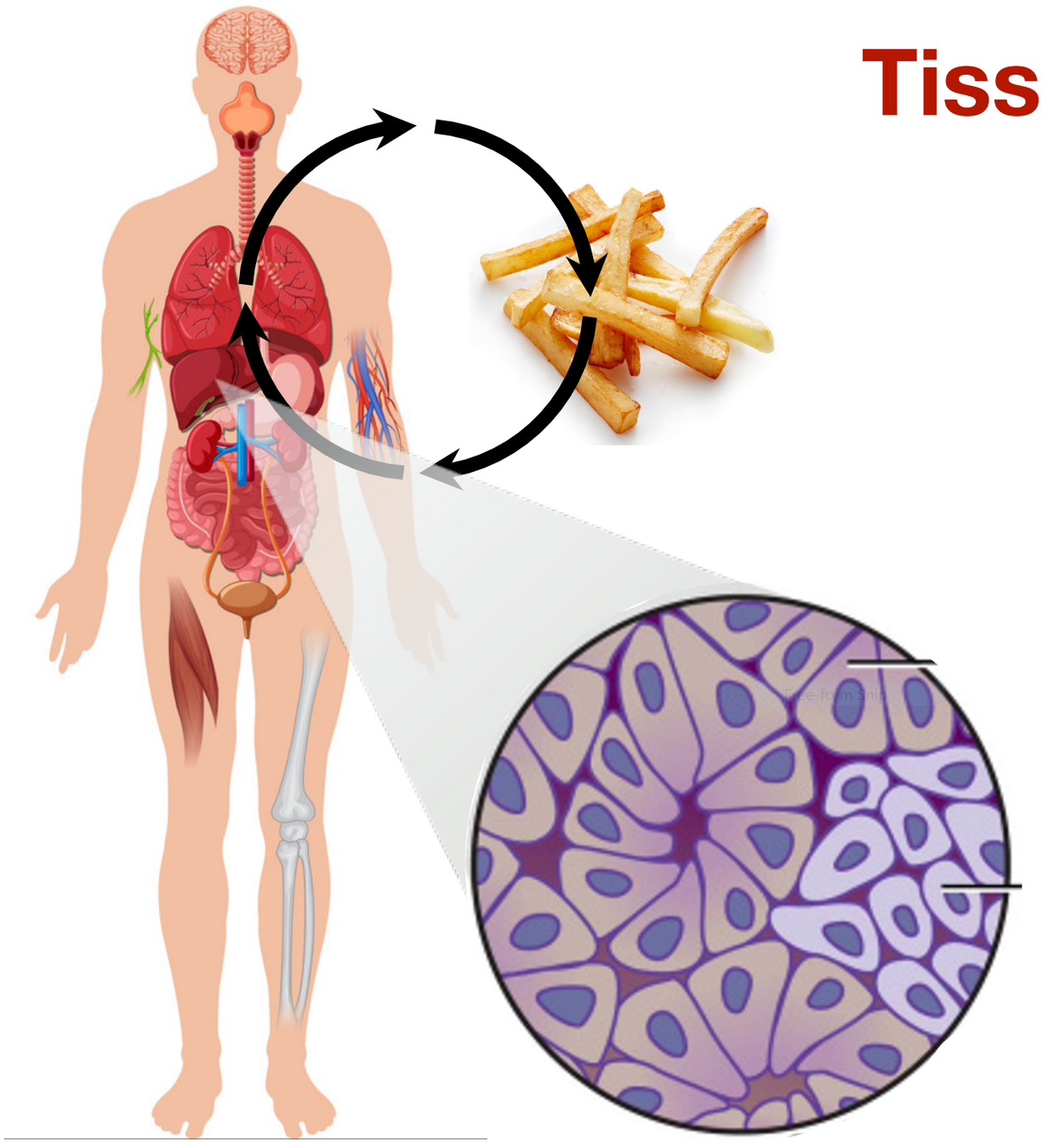
Systemic Metabolism

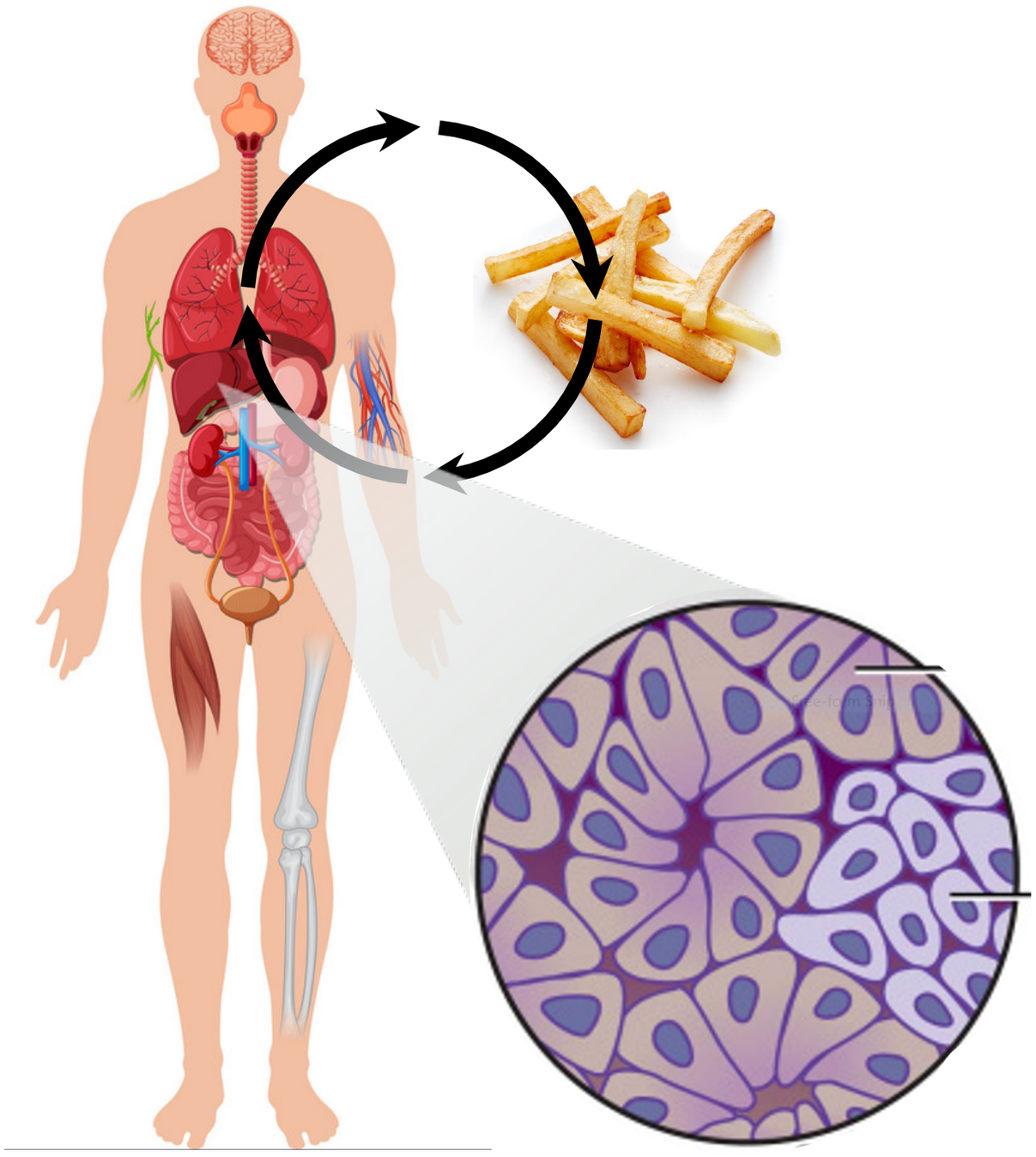




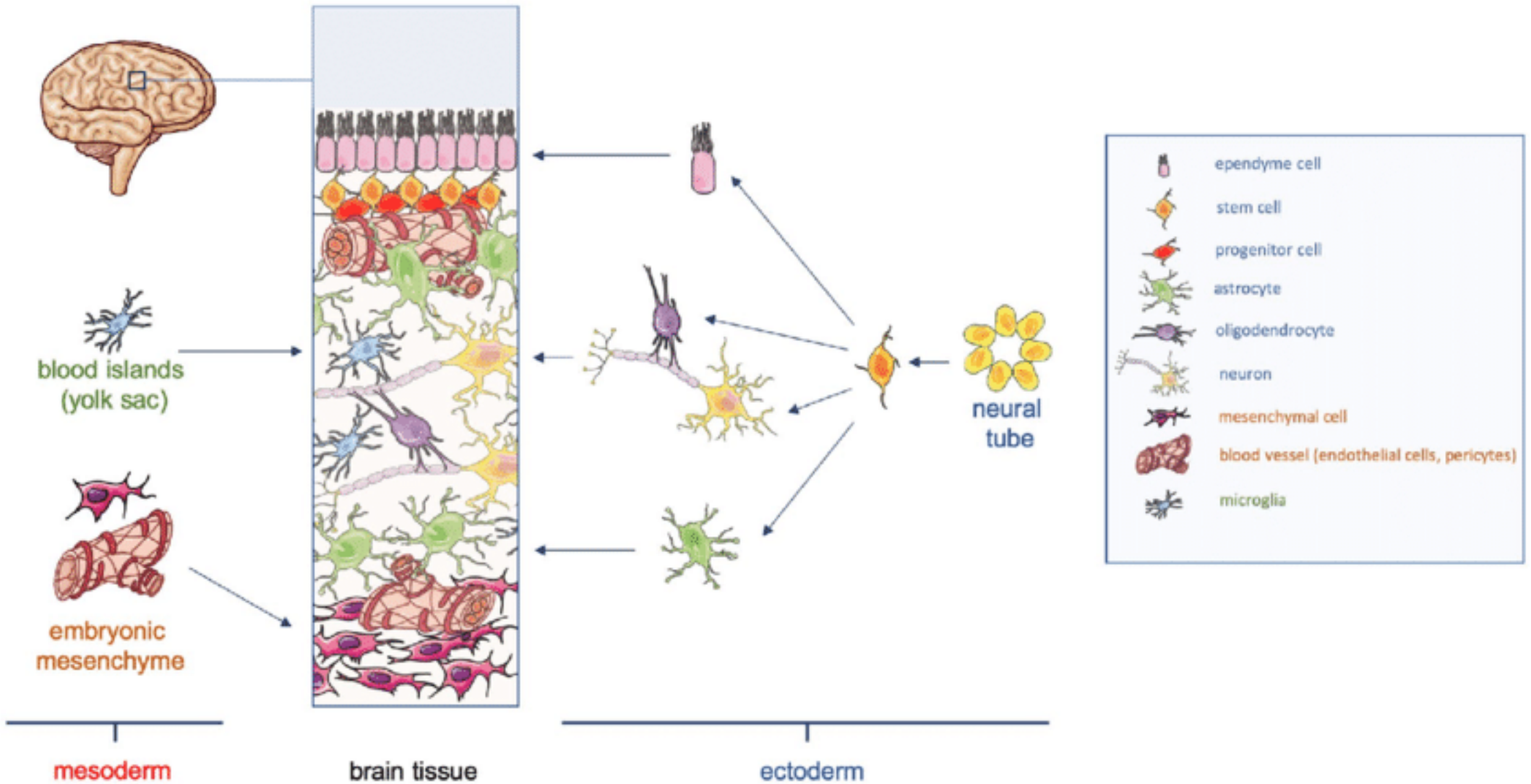


TissueMetabolism





What is Tissue Metabolism?



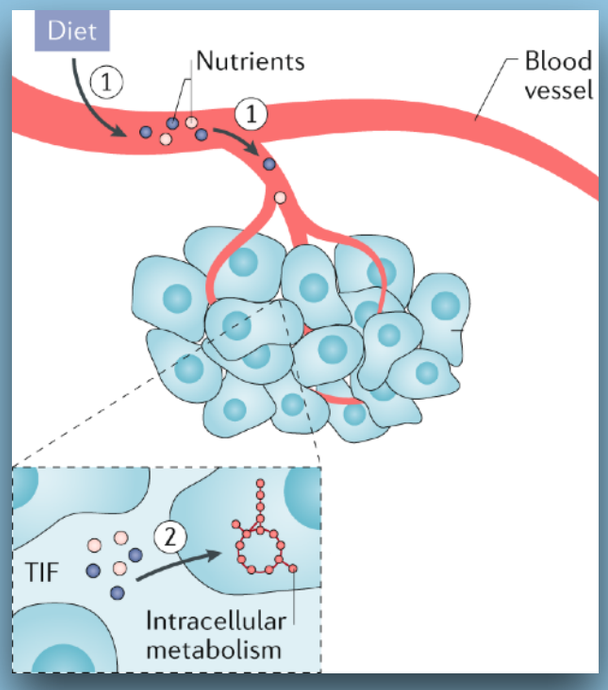
Every tissue is composed by a mixture of different cell types (and states), each having specific metabolic demands/activities

Balance dictates LOCAL nutrient availability

Tissue metabolism is multifactorial

1

Dietary intake dictates local abundance of metabolites in peripheral tissues

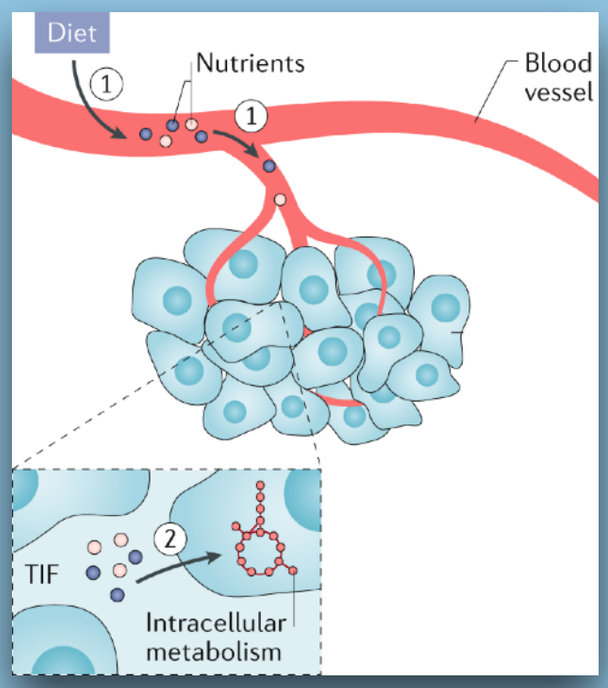


SYSTEMIC/TISSUE RELATIONSHIP

Tissue metabolism is multifactorial

1

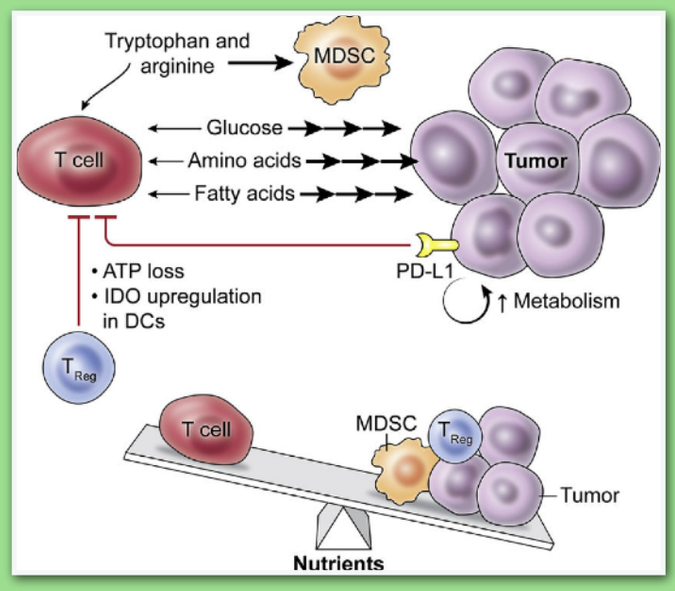
Dietary intake dictates local abundance of metabolites in peripheral tissues



SYSTEMIC/TISSUE RELATIONSHIP

2

Different cell types often compete for the same nutrients.

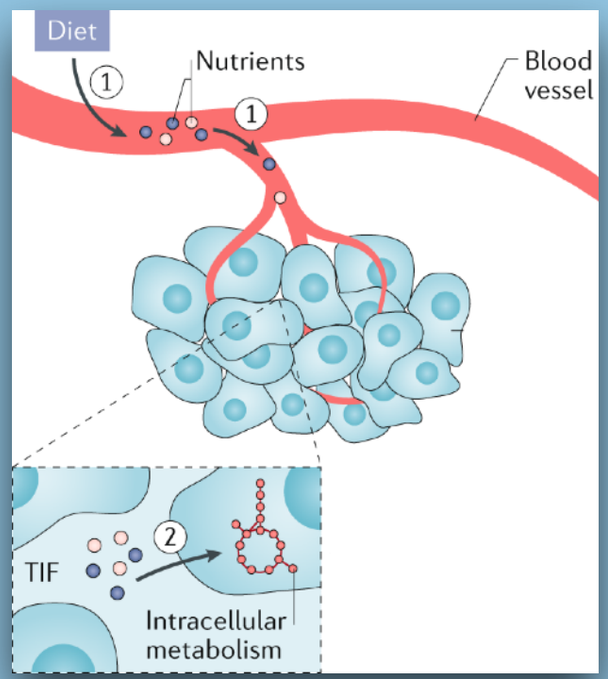


METABOLIC COMPETITION

Tissue metabolism is multifactorial

1

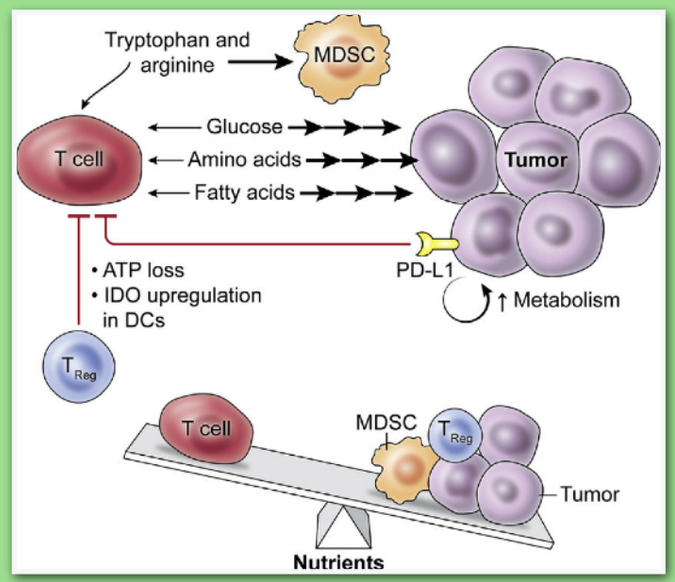
Dietary intake dictates local abundance of metabolites in peripheral tissues



SYSTEMIC/TISSUE RELATIONSHIP

2

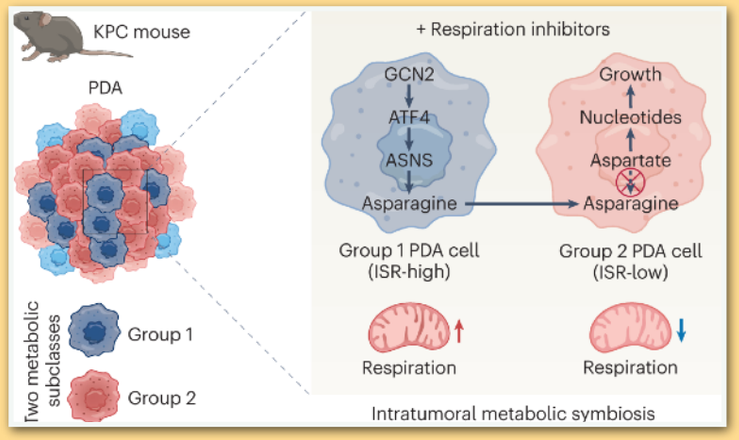
Different cell types often compete for the same nutrients.



METABOLIC COMPETITION

3

Nutrients can be provided by a different cell type in the tissue



METABOLIC COOPERATION/ SYMBIOSIS

nature chemical biology

Article

https://doi.org/10.1038/s41589-022-01154-9

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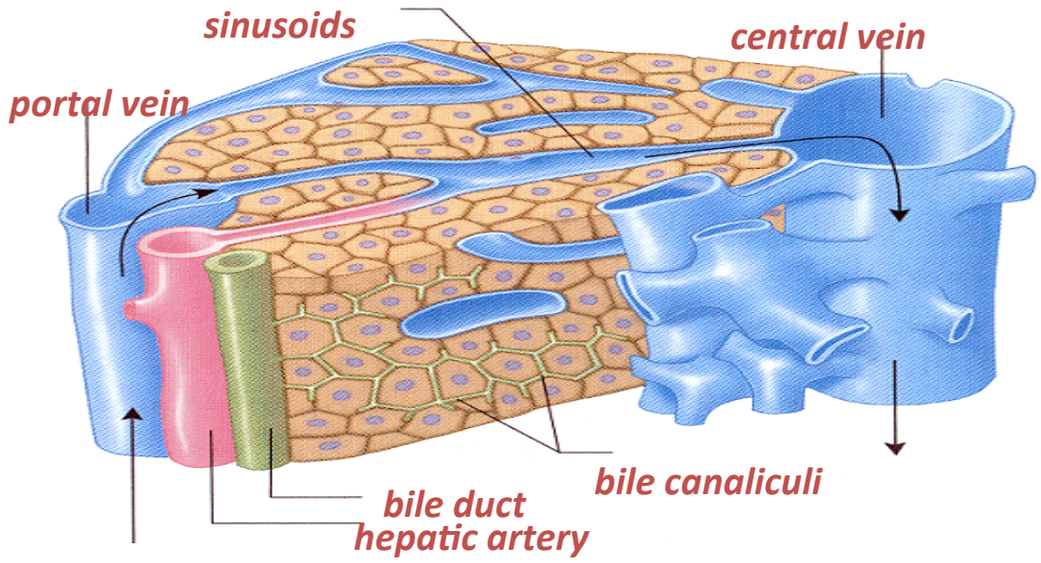

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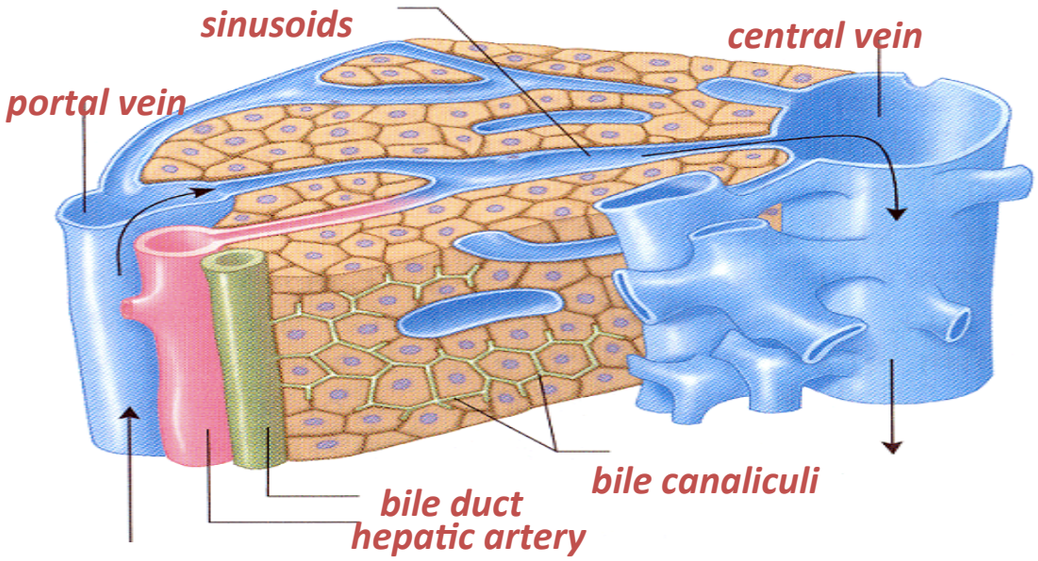

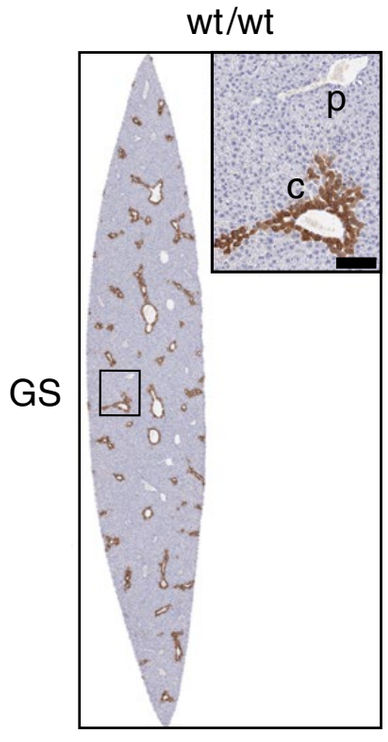

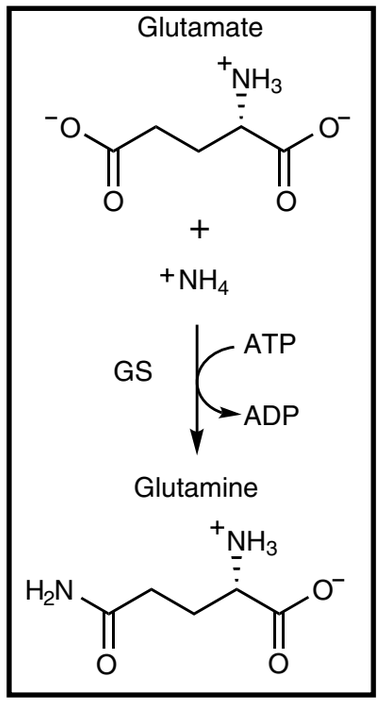

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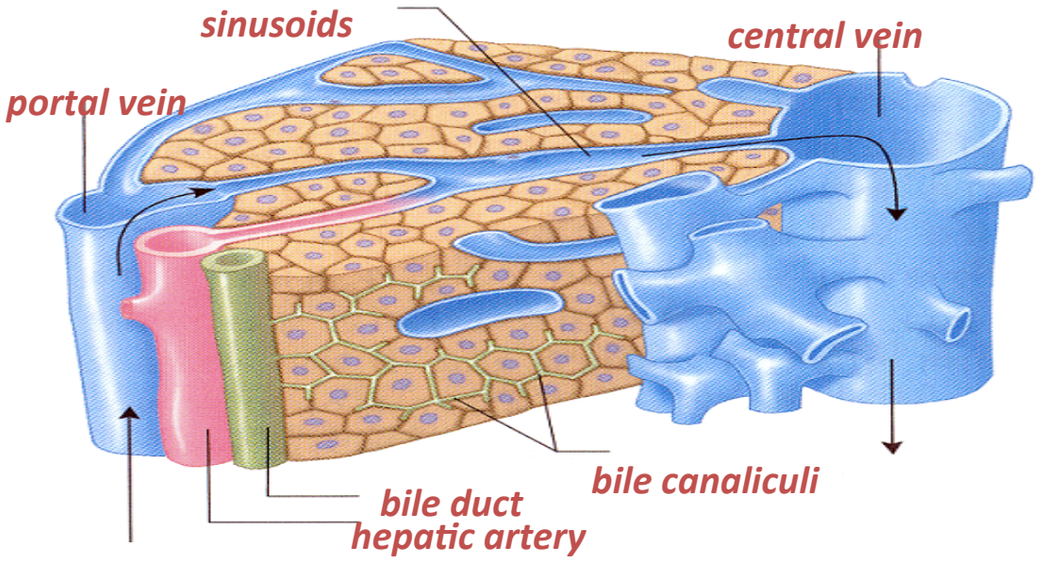

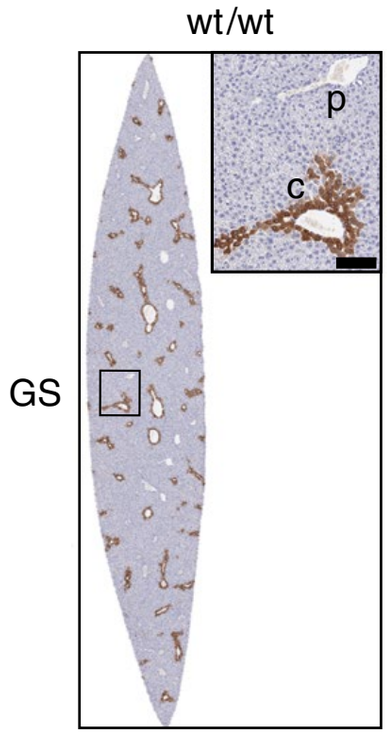

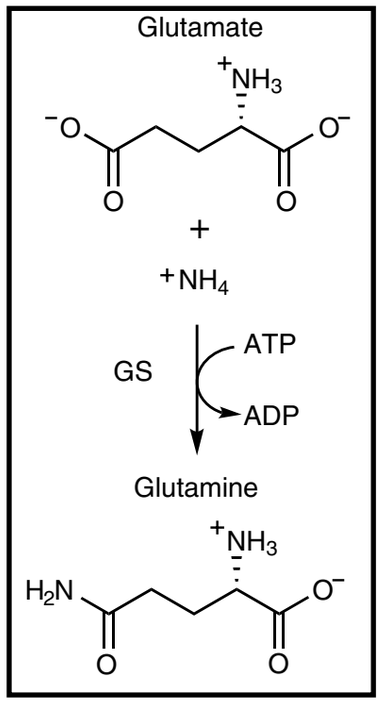

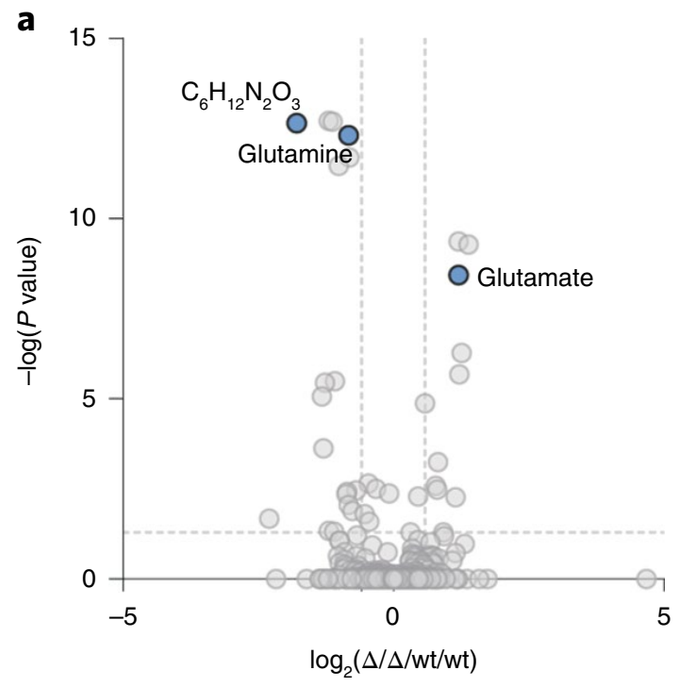

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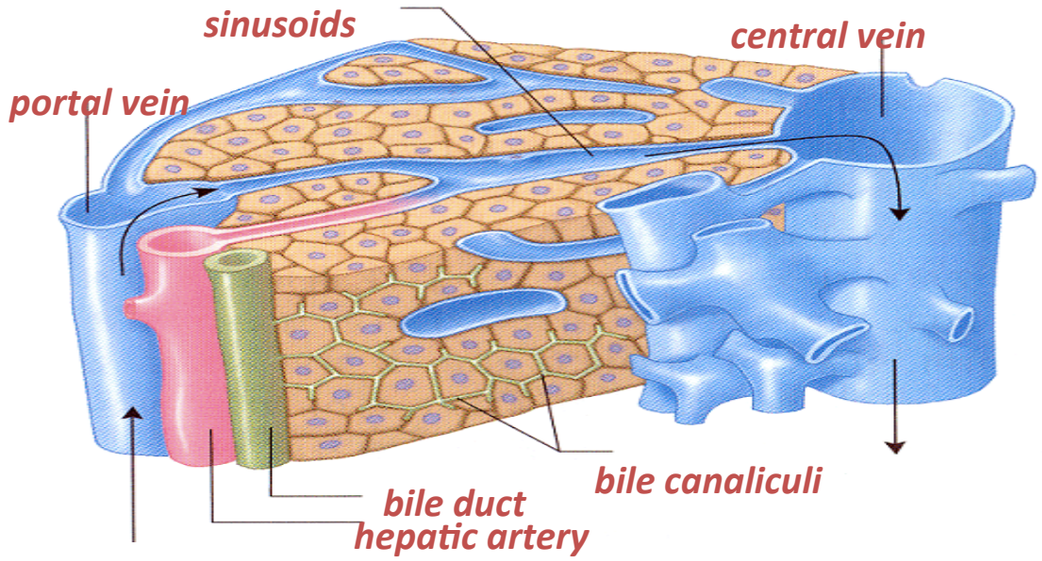
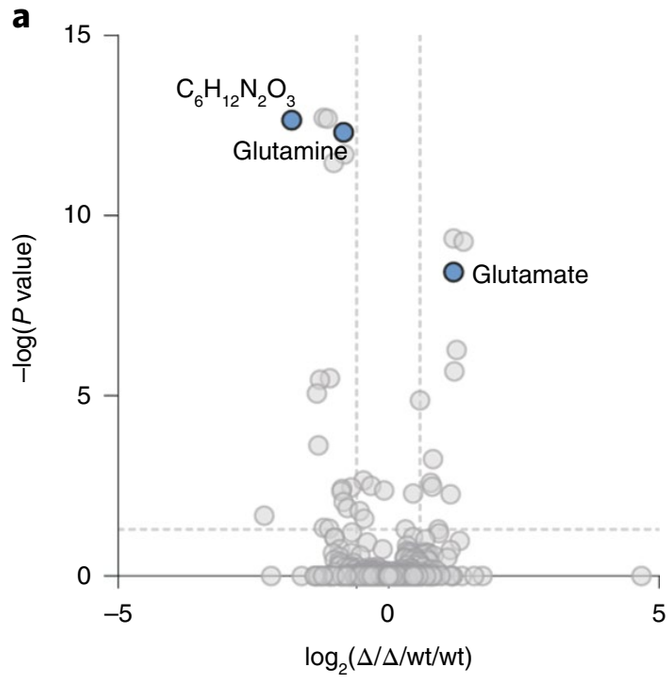
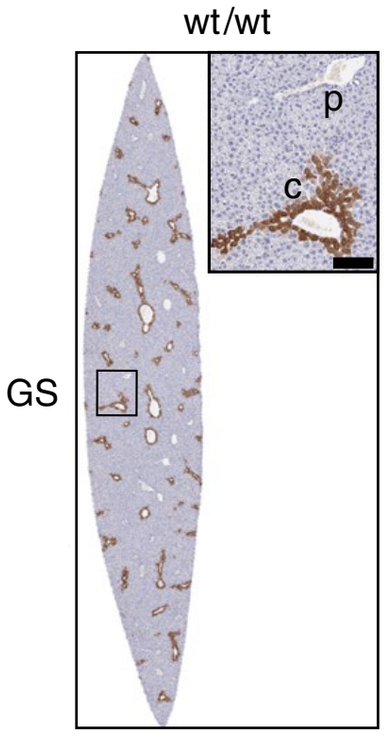
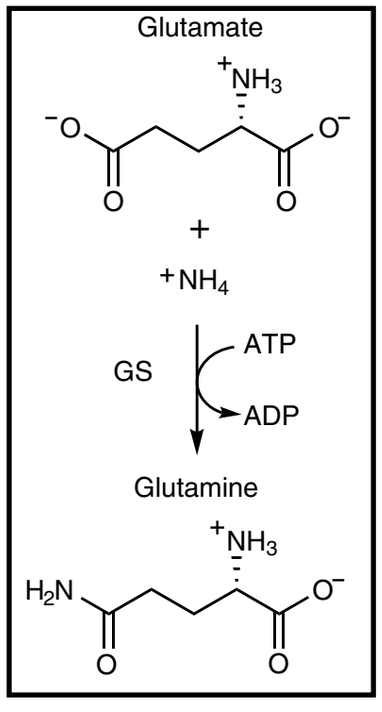
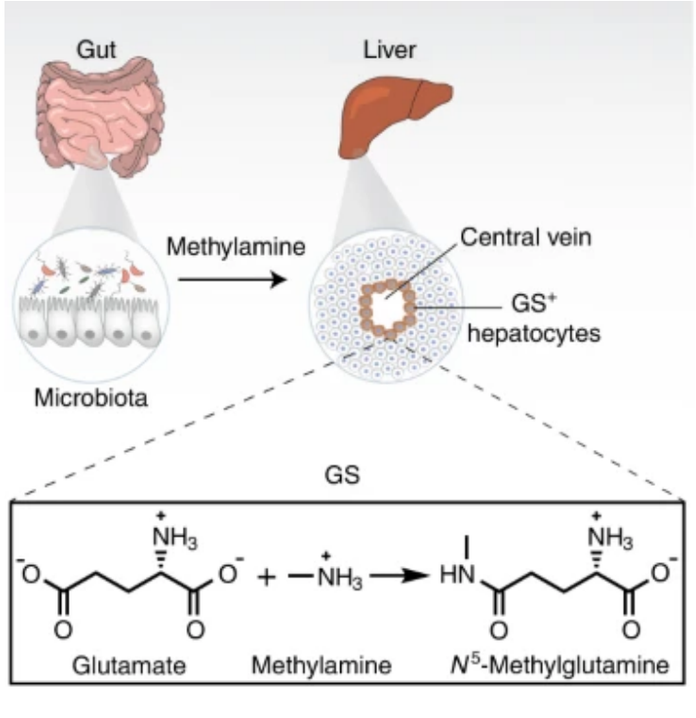
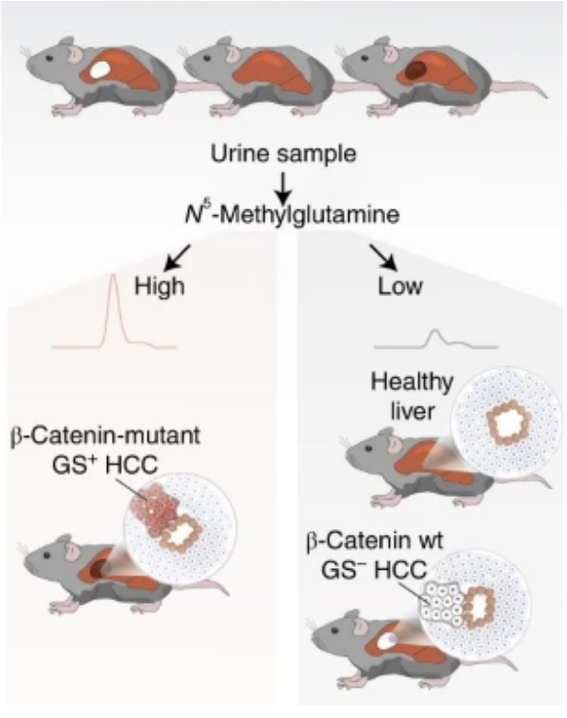




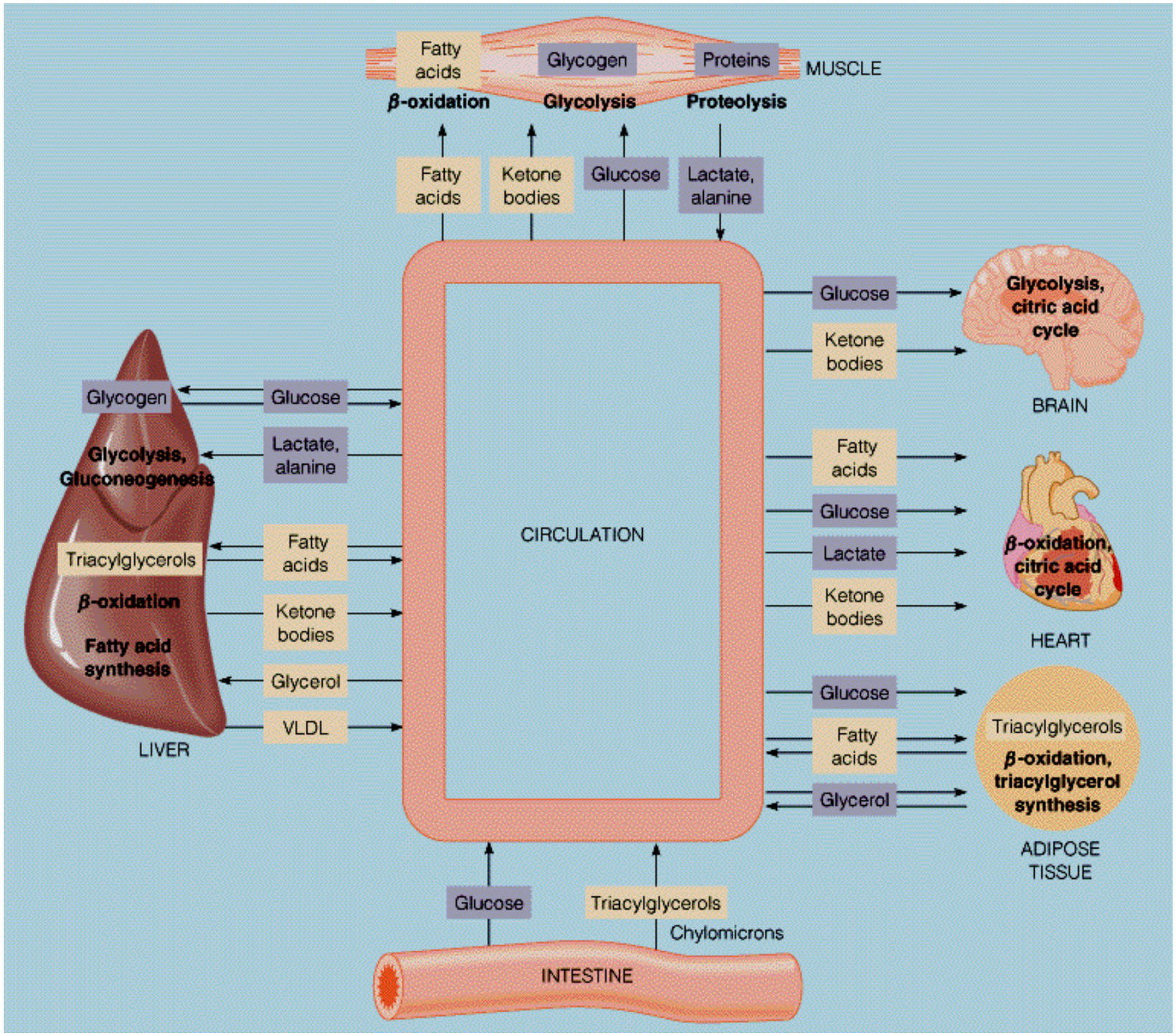








Tissue metabolism is heterogeneous



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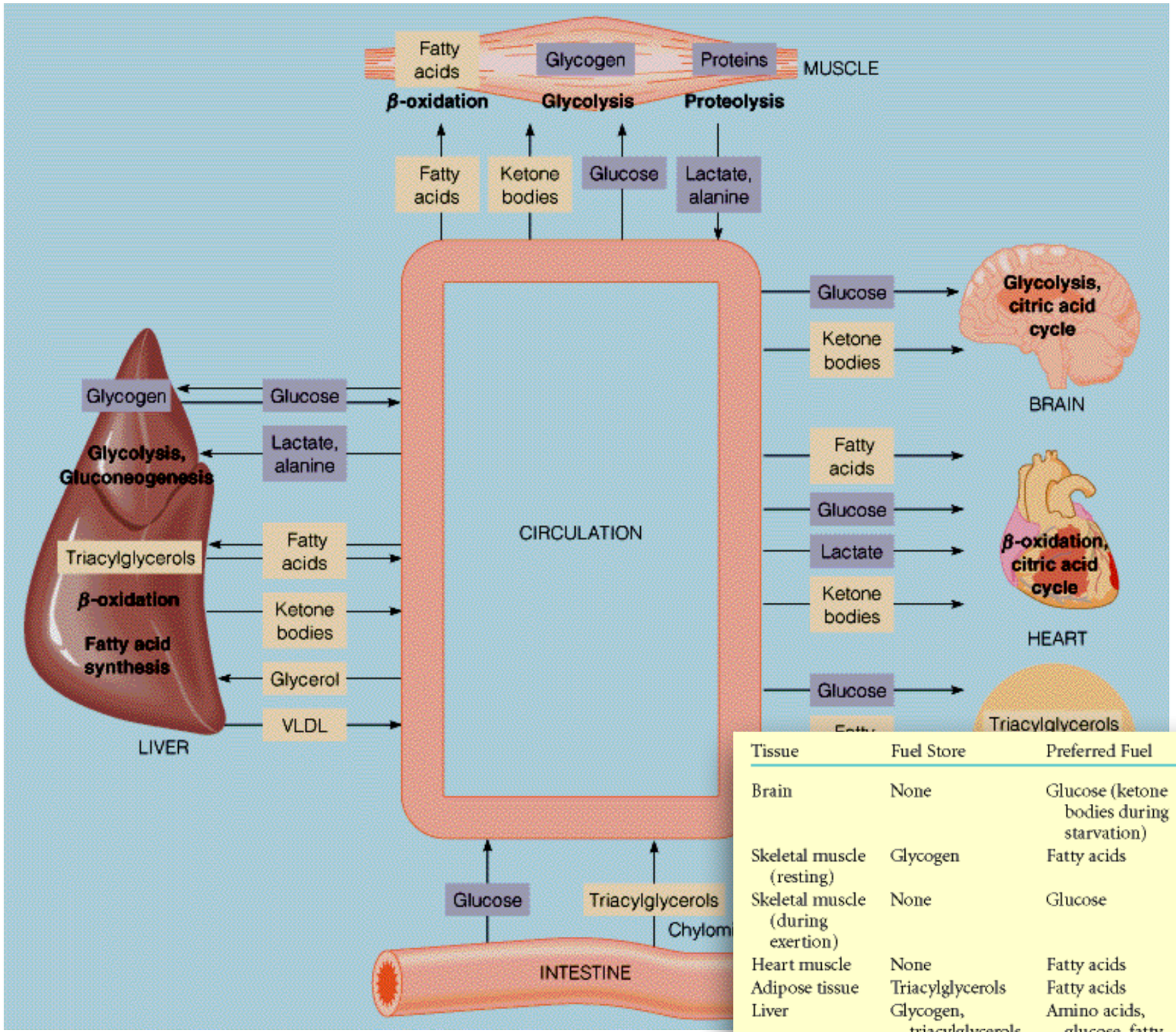
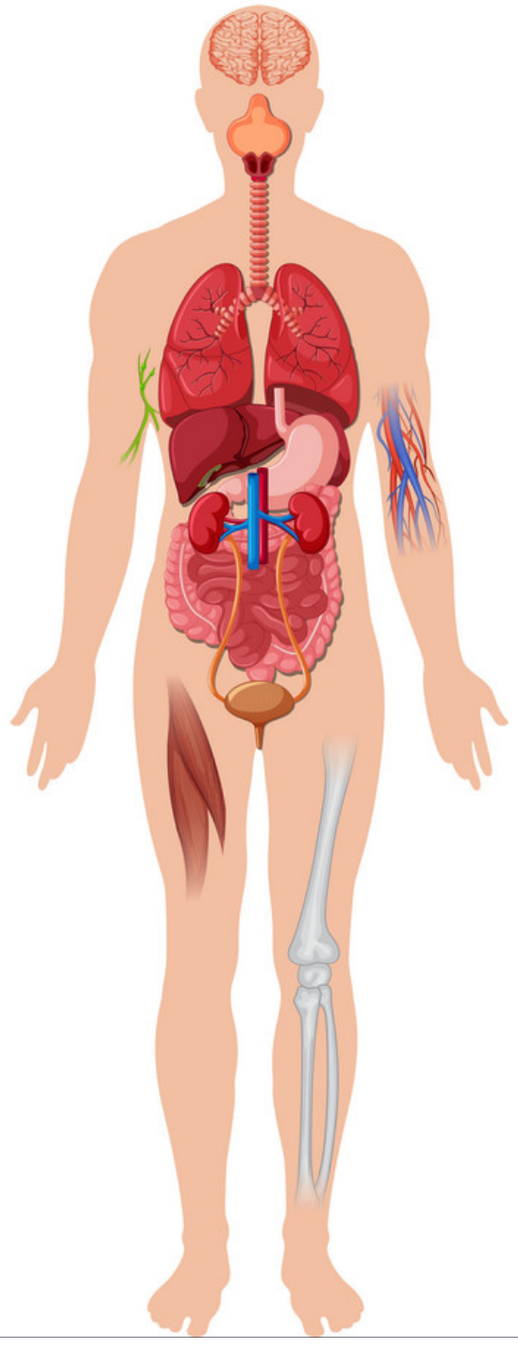


Tissue	Fuel Store	Preferred Fuel	Fuel Sources Exported
Brain	None	Glucose (ketone bodies during starvation)	None
Skeletal muscle (resting)	Glycogen	Fatty acids	None
Skeletal muscle (during exertion)	None	Glucose	Lactate, alanine
Heart muscle	None	Fatty acids	None
Adipose tissue	Triacylglycerols	Fatty acids	Fatty acids, glycerol
Liver	Glycogen, triacylglycerols	Amino acids, glucose, fatty acids	Fatty acids, glucose, ketone bodies

Systemic Metabolism



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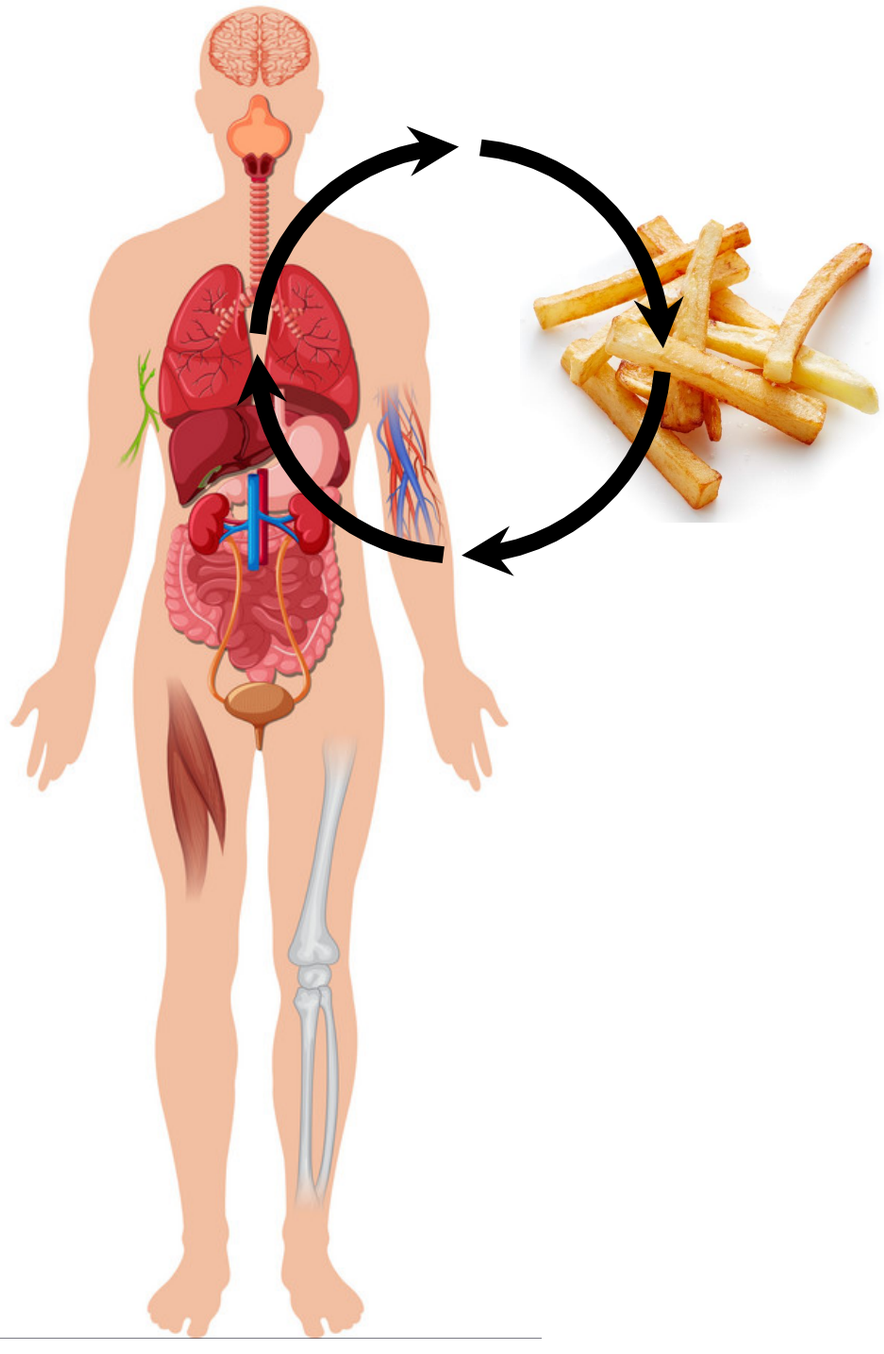

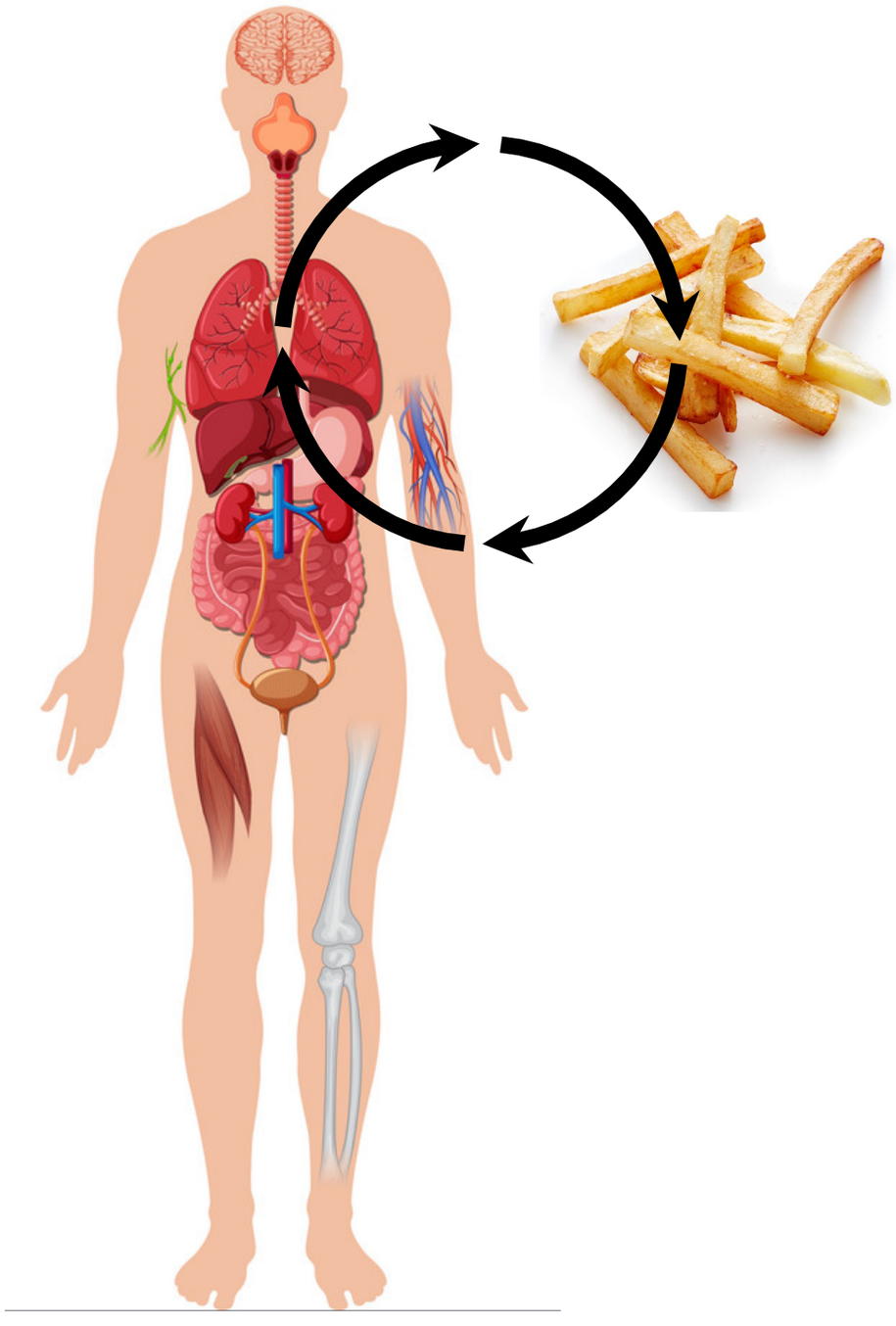

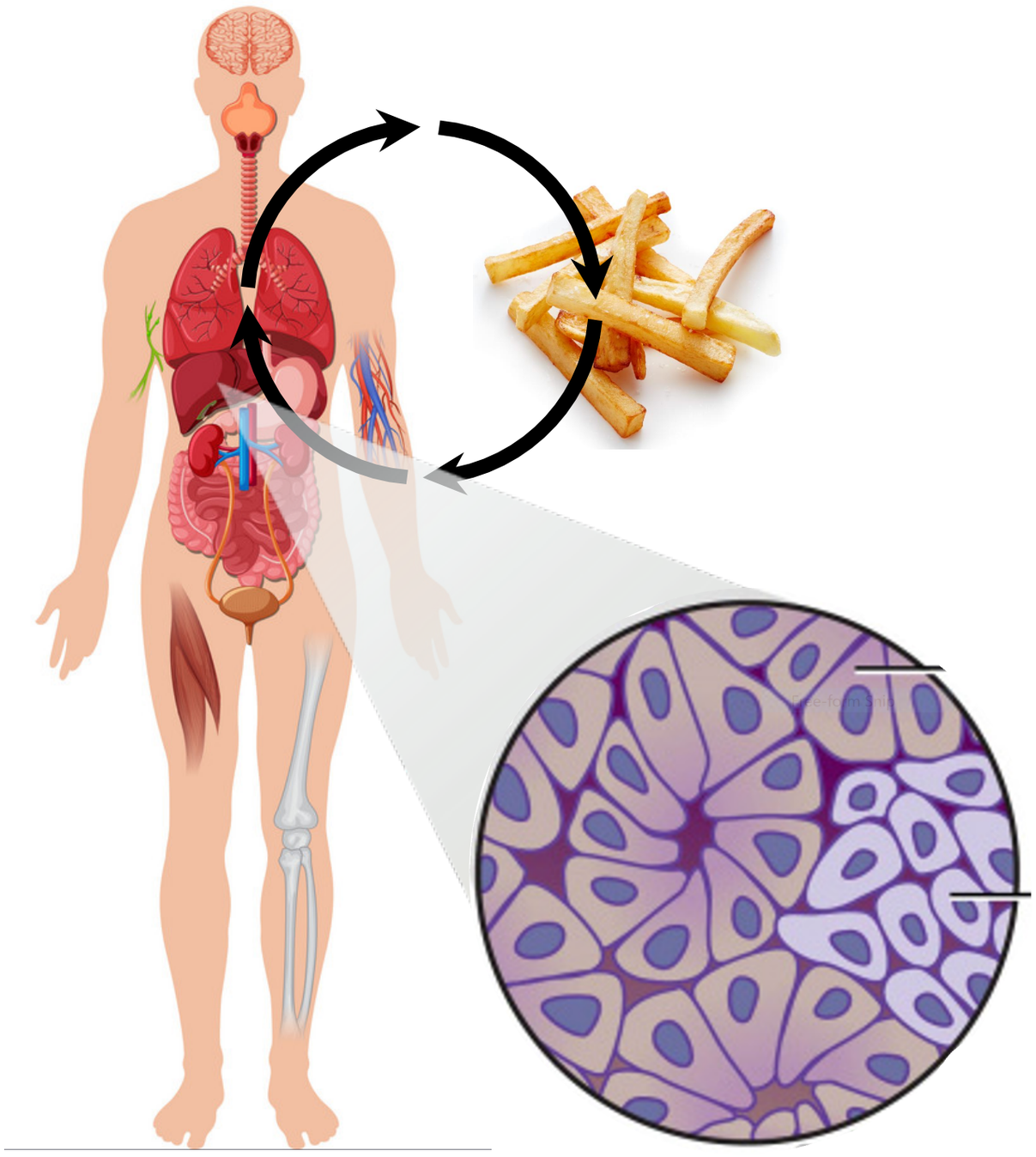

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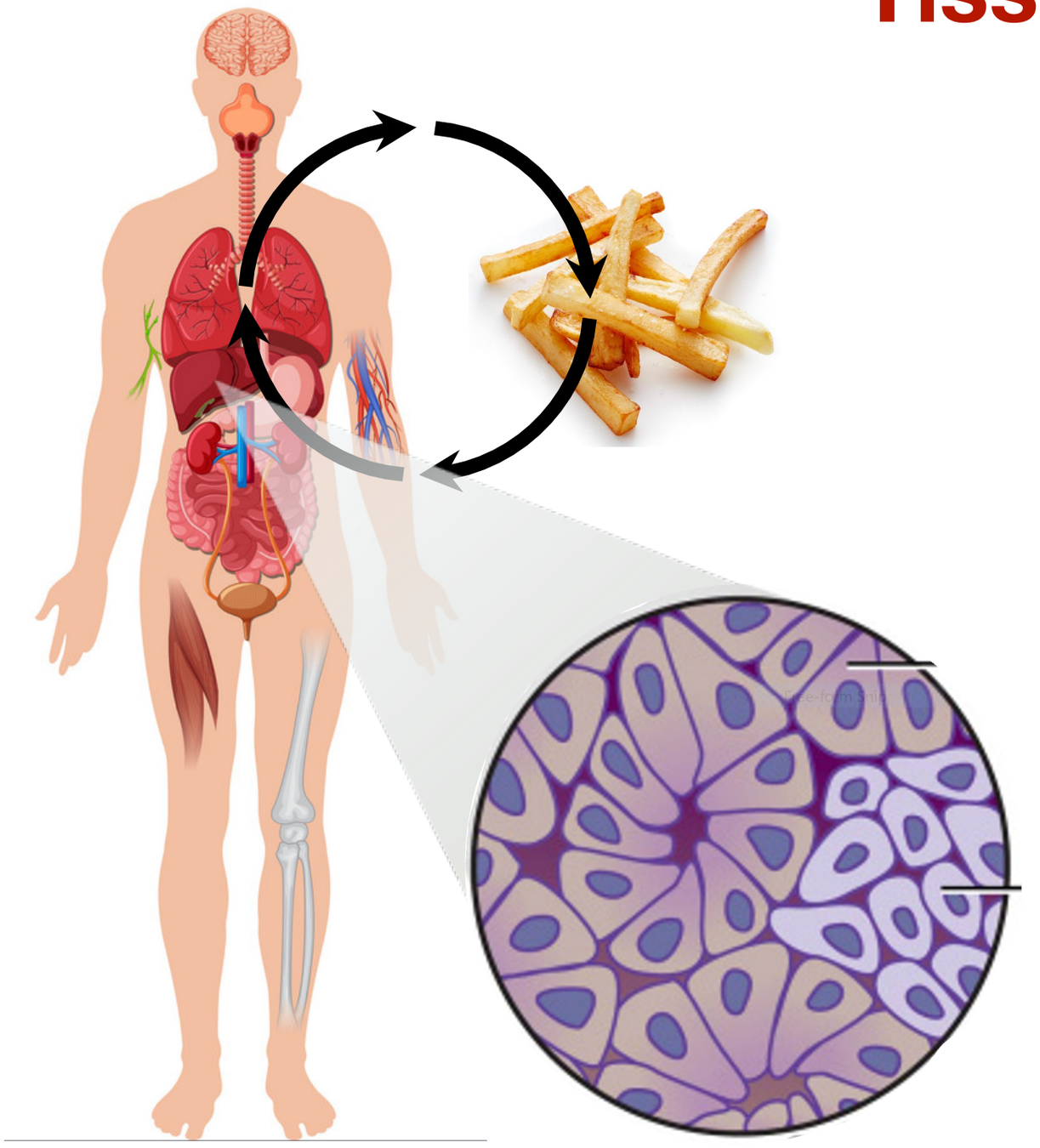
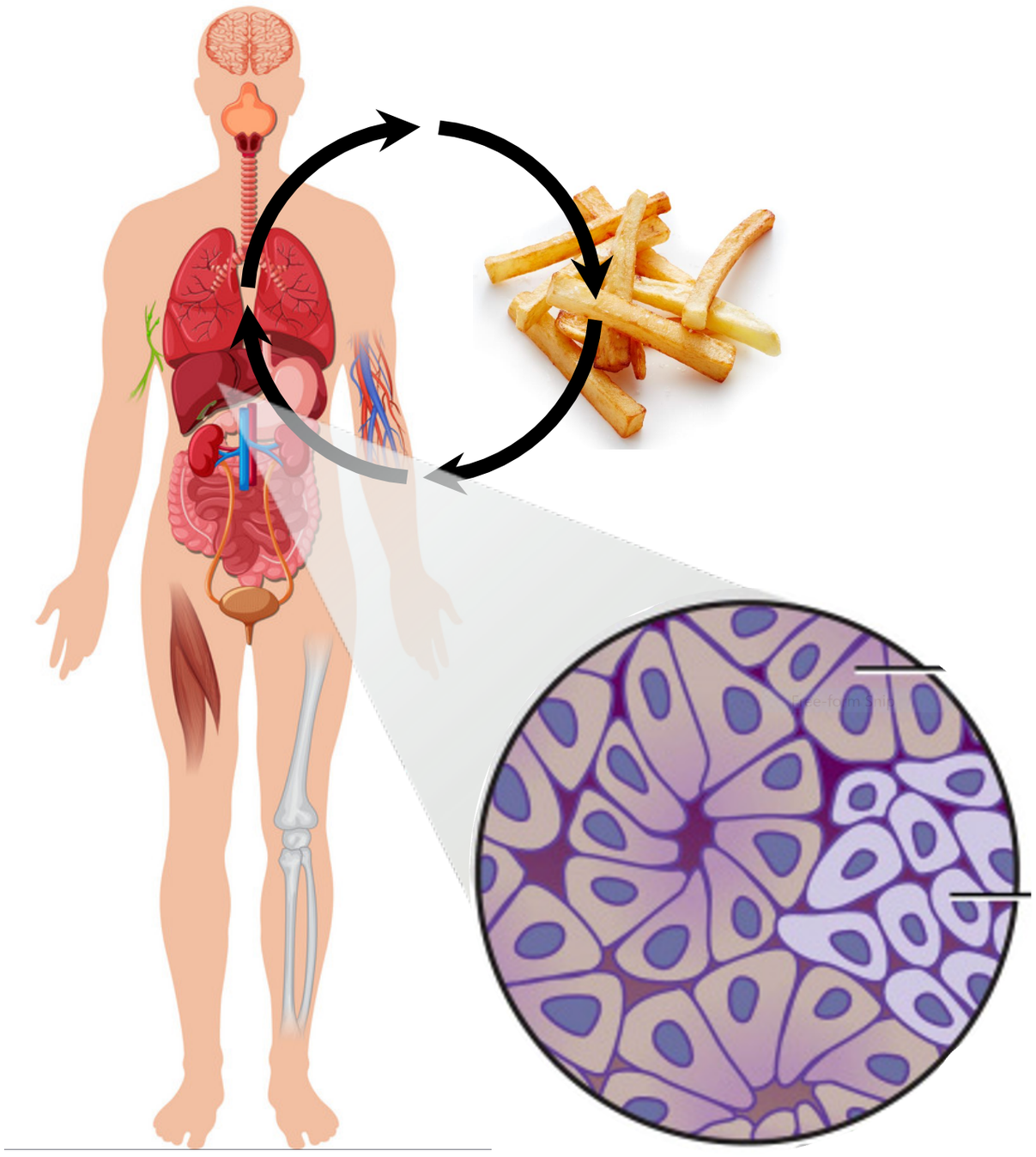
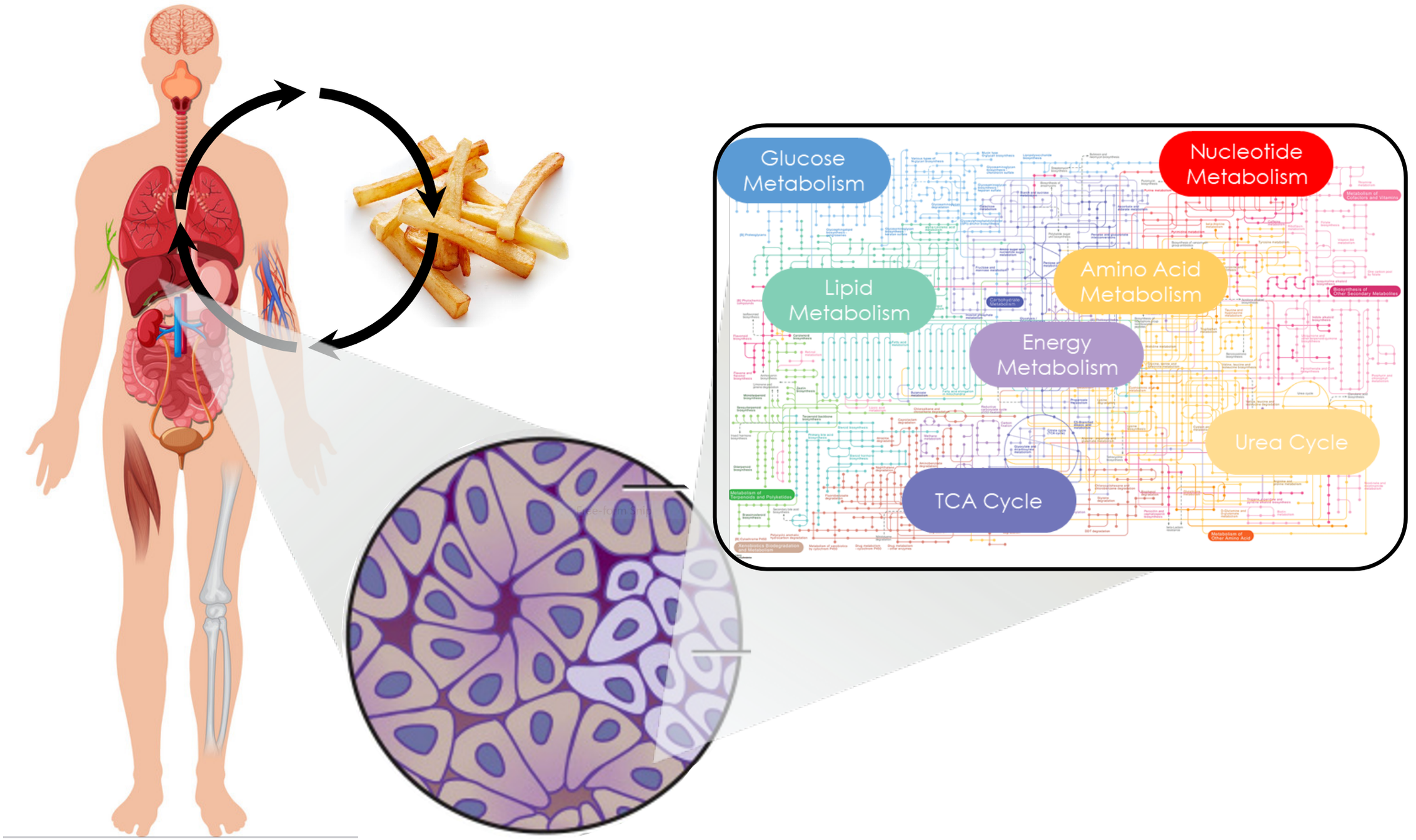
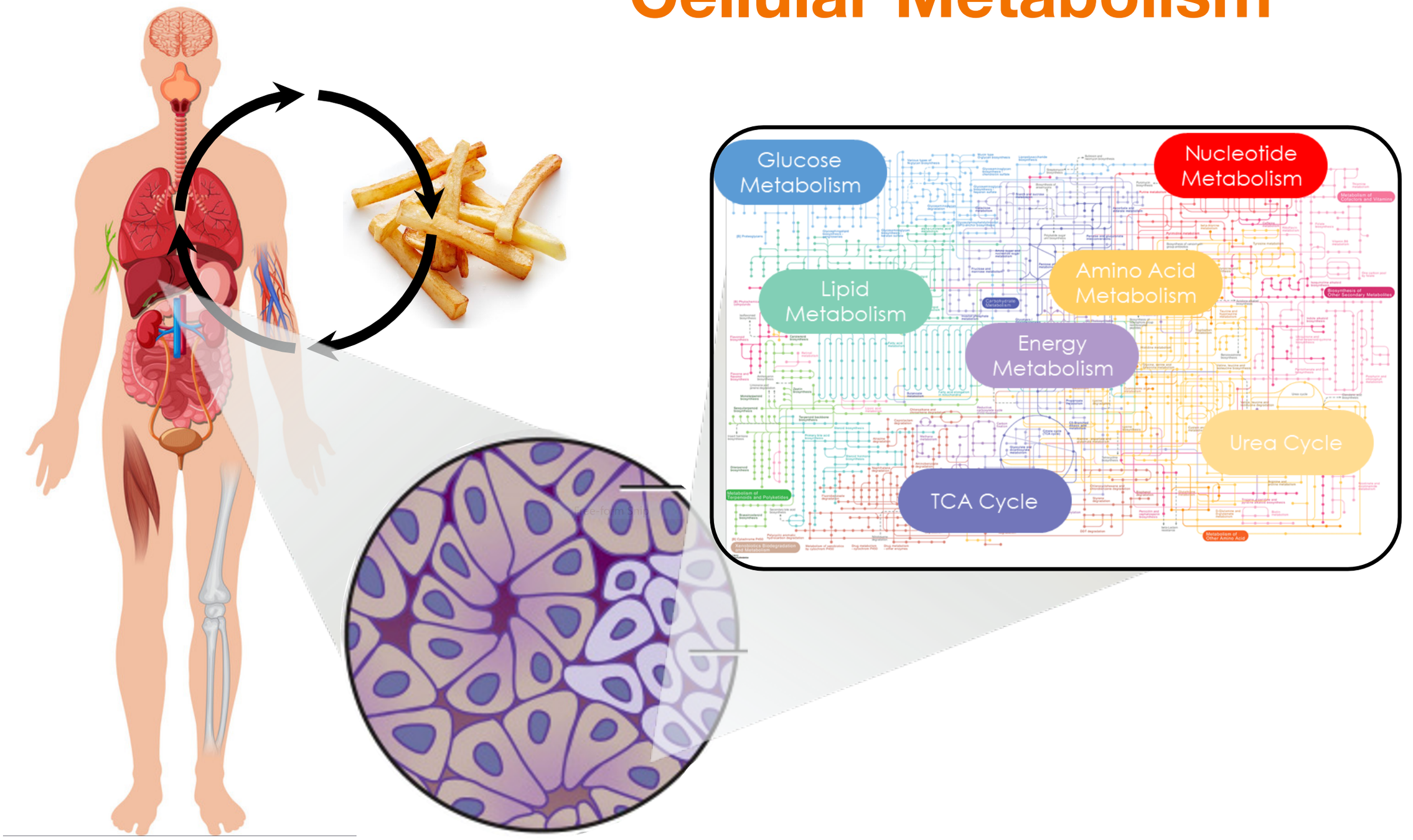





Glucose Metabolism
Nucleotide Metabolism
Lipid Metabolism
Amino Acid Metabolism
Energy Metabolism
Urea Cycle
TCA Cycle

Cellular Metabolism



What is Cellular Metabolism?

Cellular metabolism is a collective term that denotes a wide set of biochemical processes whereby small molecules (called “metabolites”) change in abundance over time and in the steady states that characterize various physiologic conditions.

Metabolites are small molecules that supply the cell with energy, structural constituents and the materials to enable the synthesis of other macromolecules such as DNA or proteins.

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Underscoring the importance of metabolic reactions in cellular and organismal fidelity, it is estimated that more than 30% of human genes are involved in metabolism (Human Metabolome Database 5.0), accounting for ~3,000 possible chemical reactions. Defects in these pathways or their regulation can result in human disease, with inborn errors of metabolism thought to underlie over 1,300 disorders. The vast complexity of human metabolism necessitates a high degree of organization.

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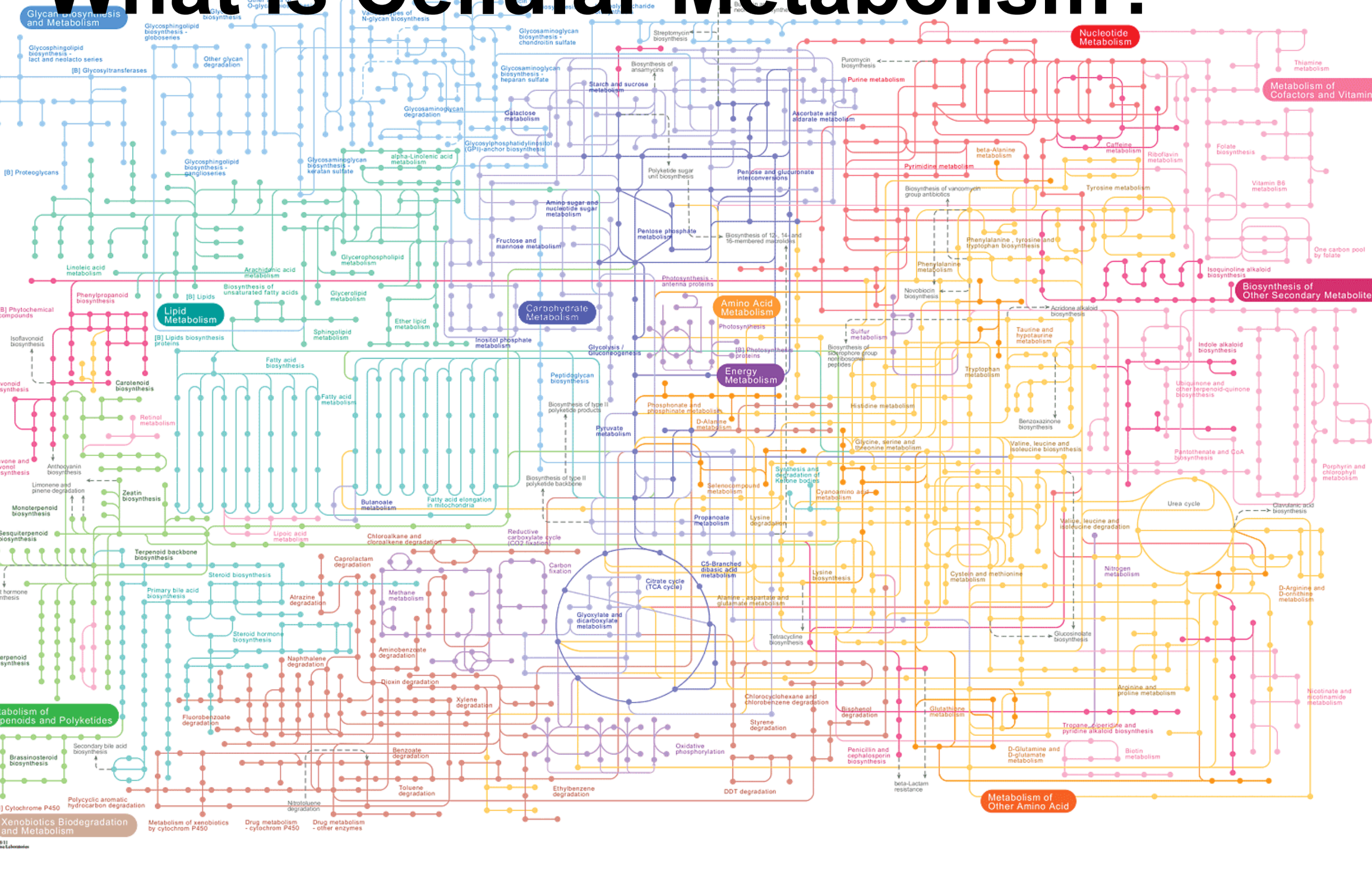

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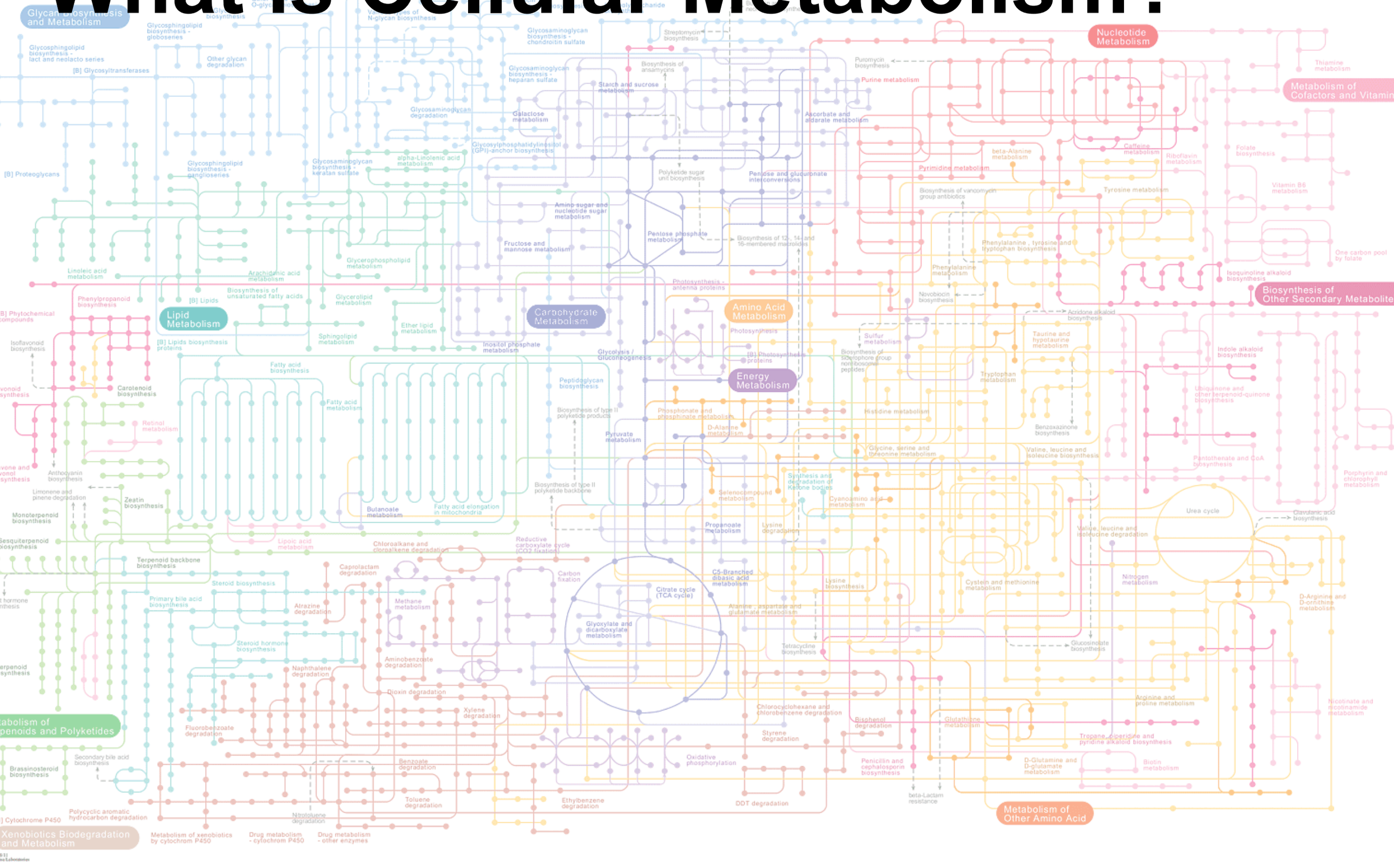

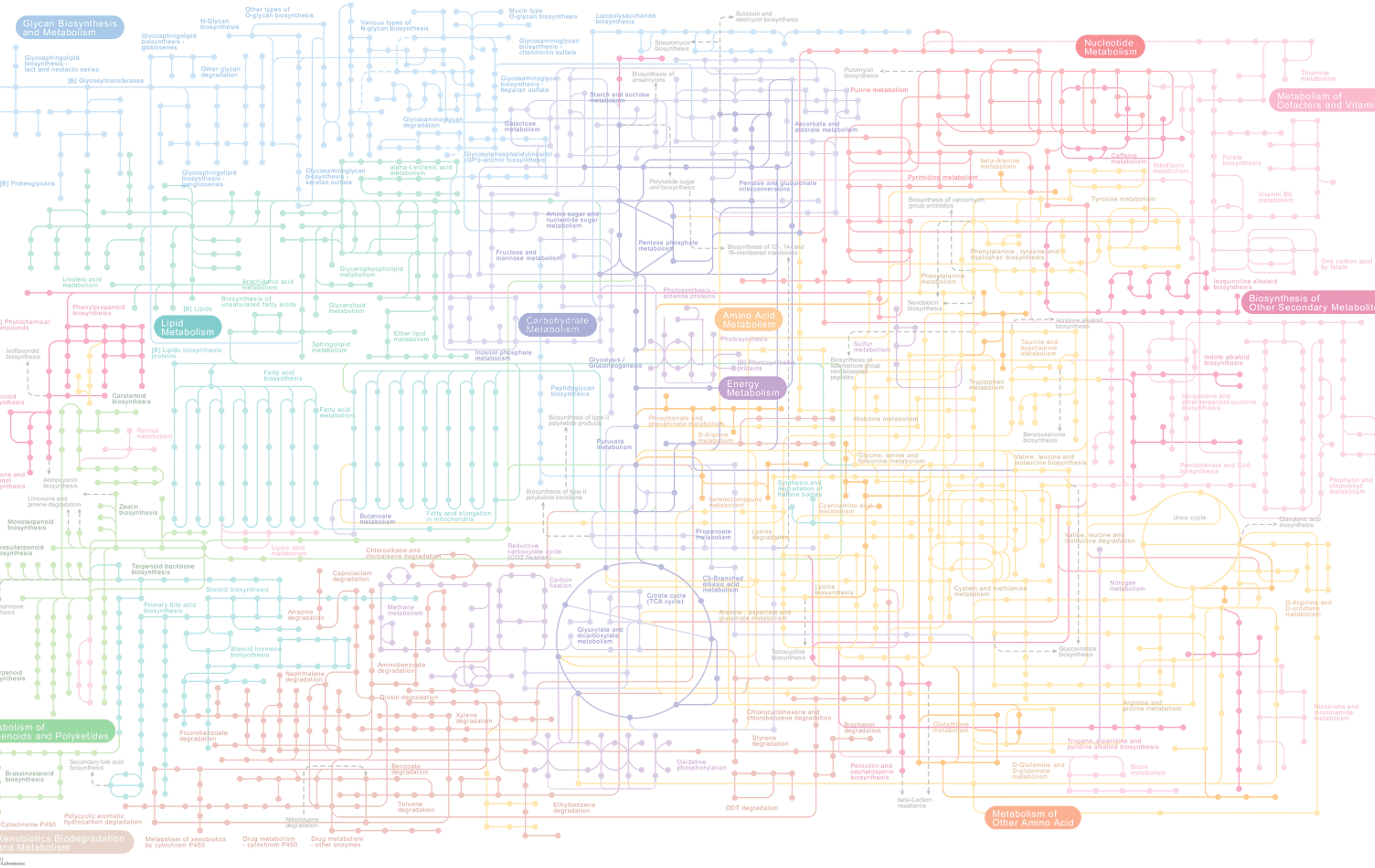
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Cysteine and methionine metabolism
Glycine, serine and threonine metabolism
Histidine metabolism
Sulfur metabolism
Biosynthesis of siderophore group nonribosomal peptides
Taurine and hypotaurine metabolism
Tryptophan metabolism
Phenylalanine metabolism
Phenylalanine , tyrosine and tryptophan biosynthesis
Tyrosine metabolism
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Nitrotoluene degradation
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Dioxin degradation
Naphthalene degradation
Aminobenzoate degradation
Atrazine degradation
Caprolactam degradation
Steroid biosynthesis
Steroid hormone biosynthesis
Primary bile acid biosynthesis
Secondary bile acid biosynthesis
Terpenoid backbone biosynthesis
Limonene and pinene degradation
Monoterpenoid biosynthesis
Zeatin biosynthesis
Anthocyanin biosynthesis
Carotenoid biosynthesis
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Retinol metabolism
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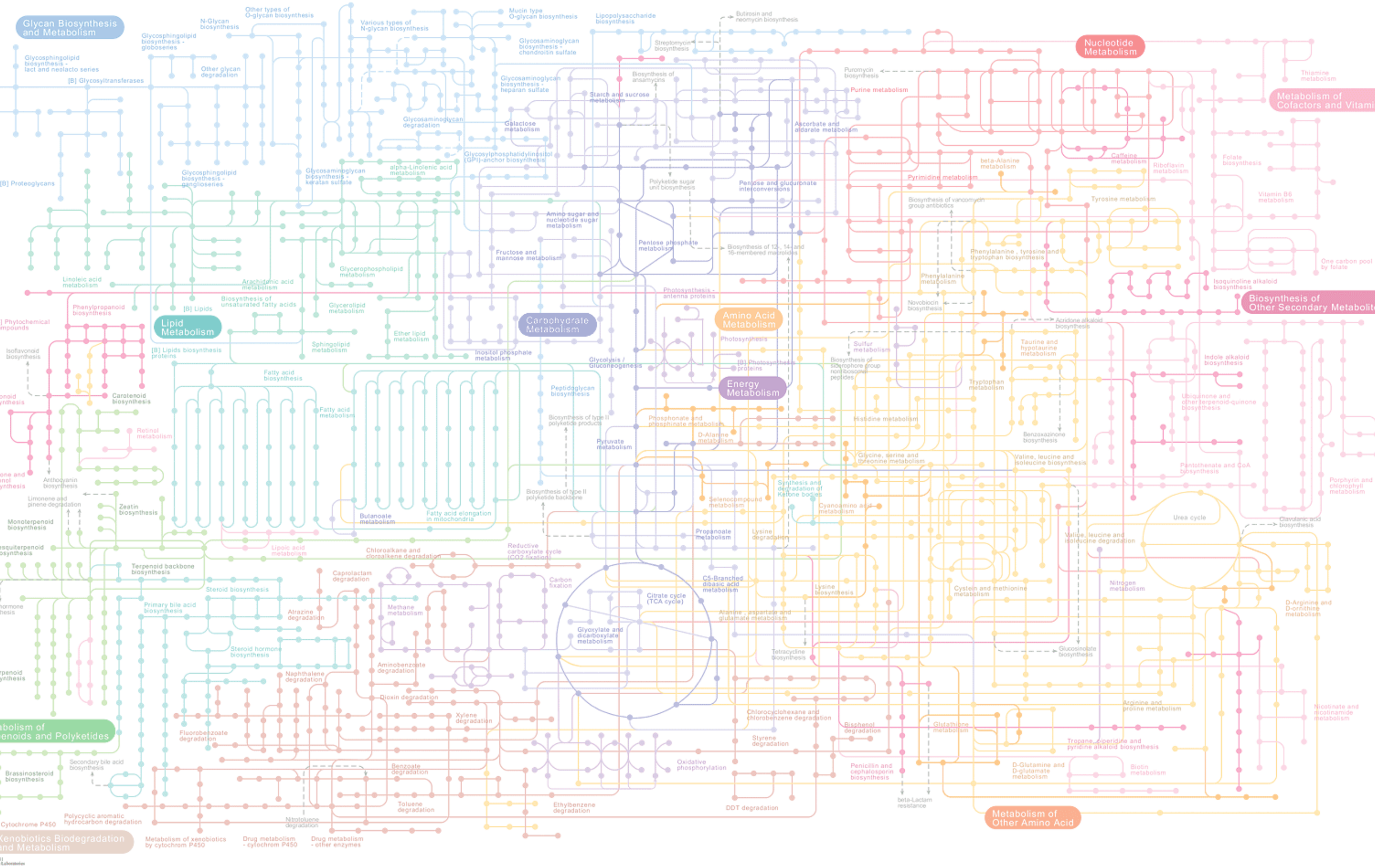
Metabolism of xenobiotics by cytochrom P450
Drug metabolism - cytochrom P450
Drug metabolism - other enzymes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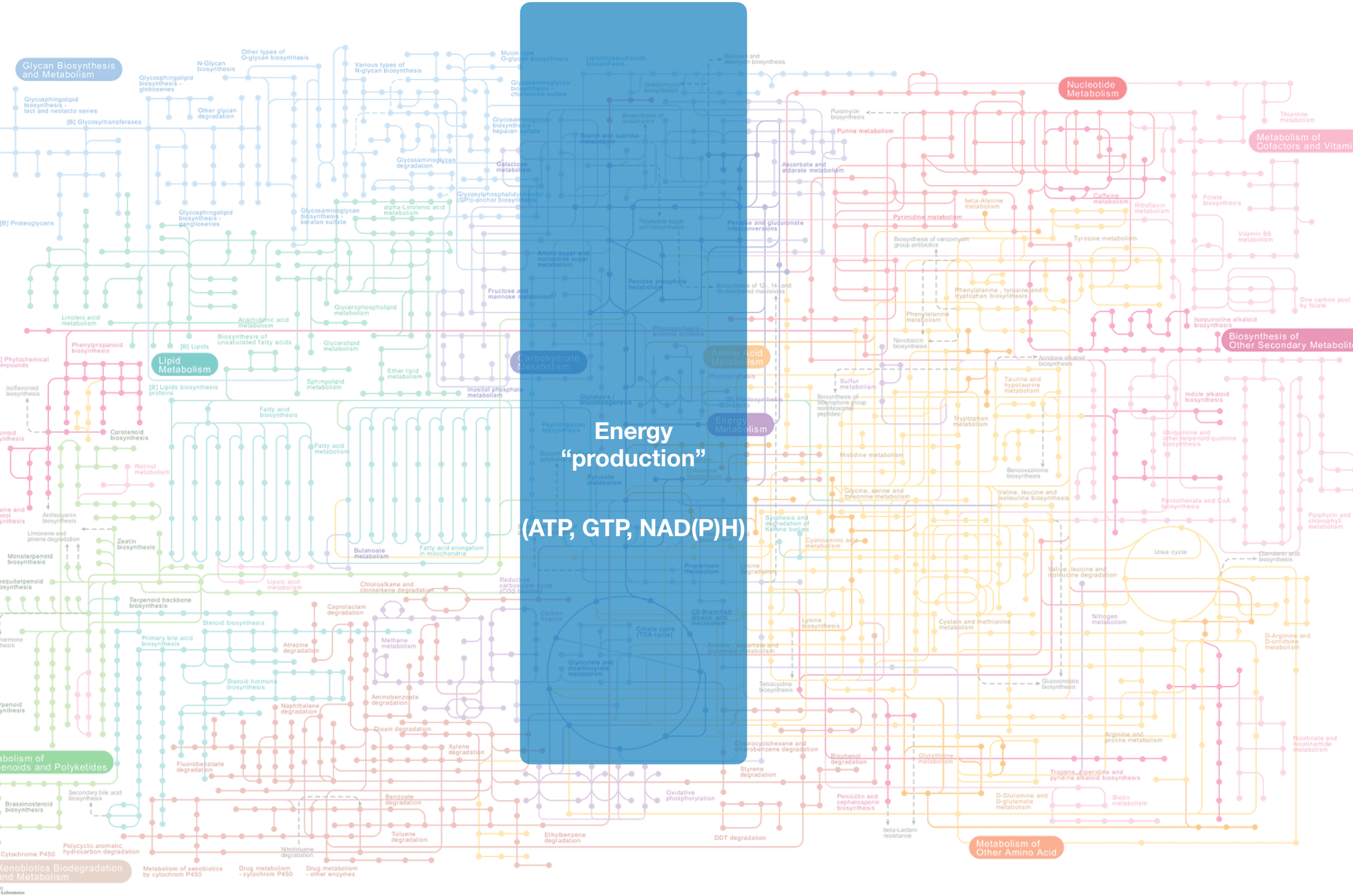
Energy
“production”
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Brassinosteroid biosynthesis
Caprolactam degradation
Atrazine degradation
Methane metabolism
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Naphthalene degradation
Dioxin degradation
Fluorobenzoate degradation
Xylene degradation
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Thiamine metabolism
Folate biosynthesis
Vitamin B6 metabolism
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Phenylalanine metabolism
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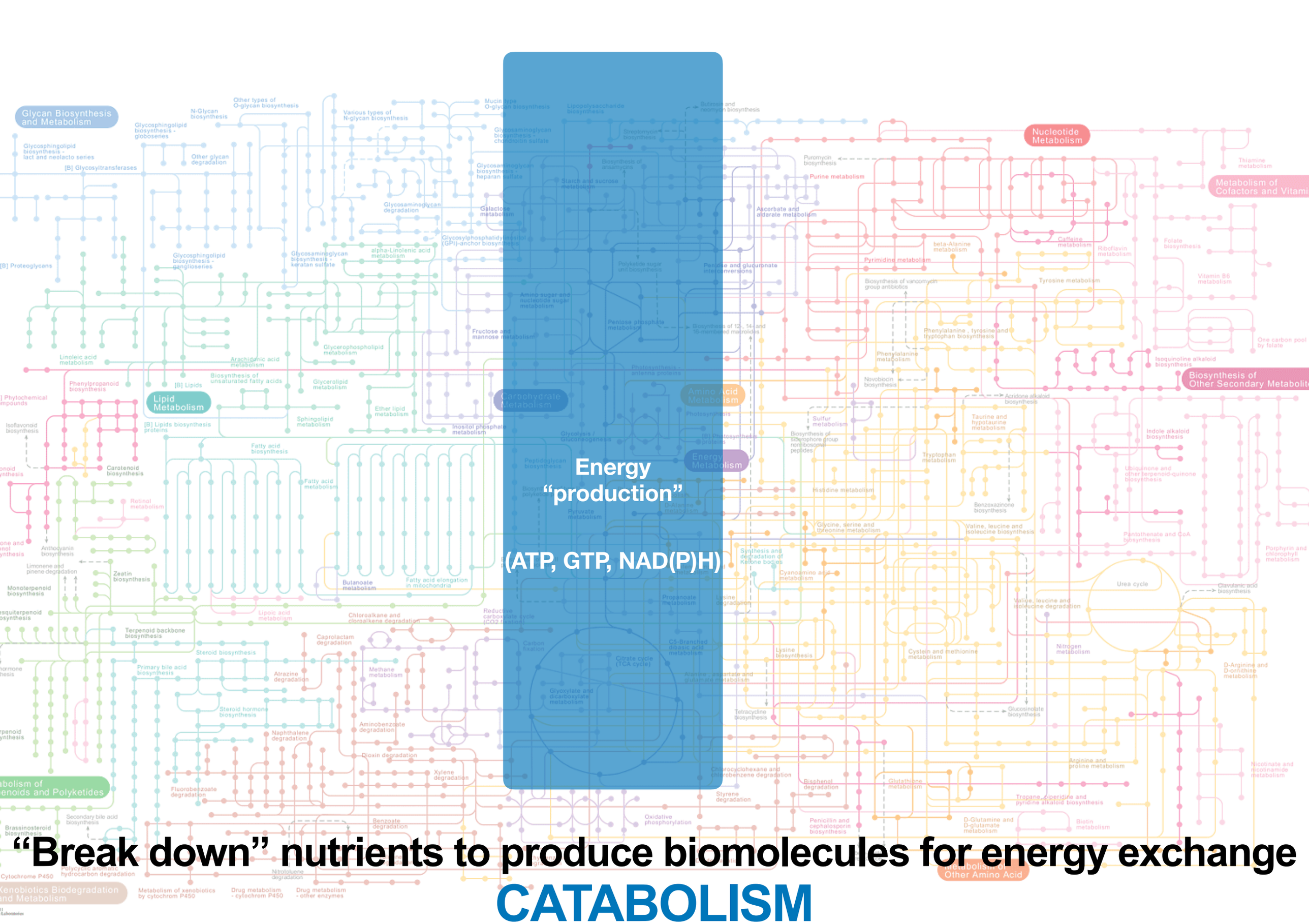
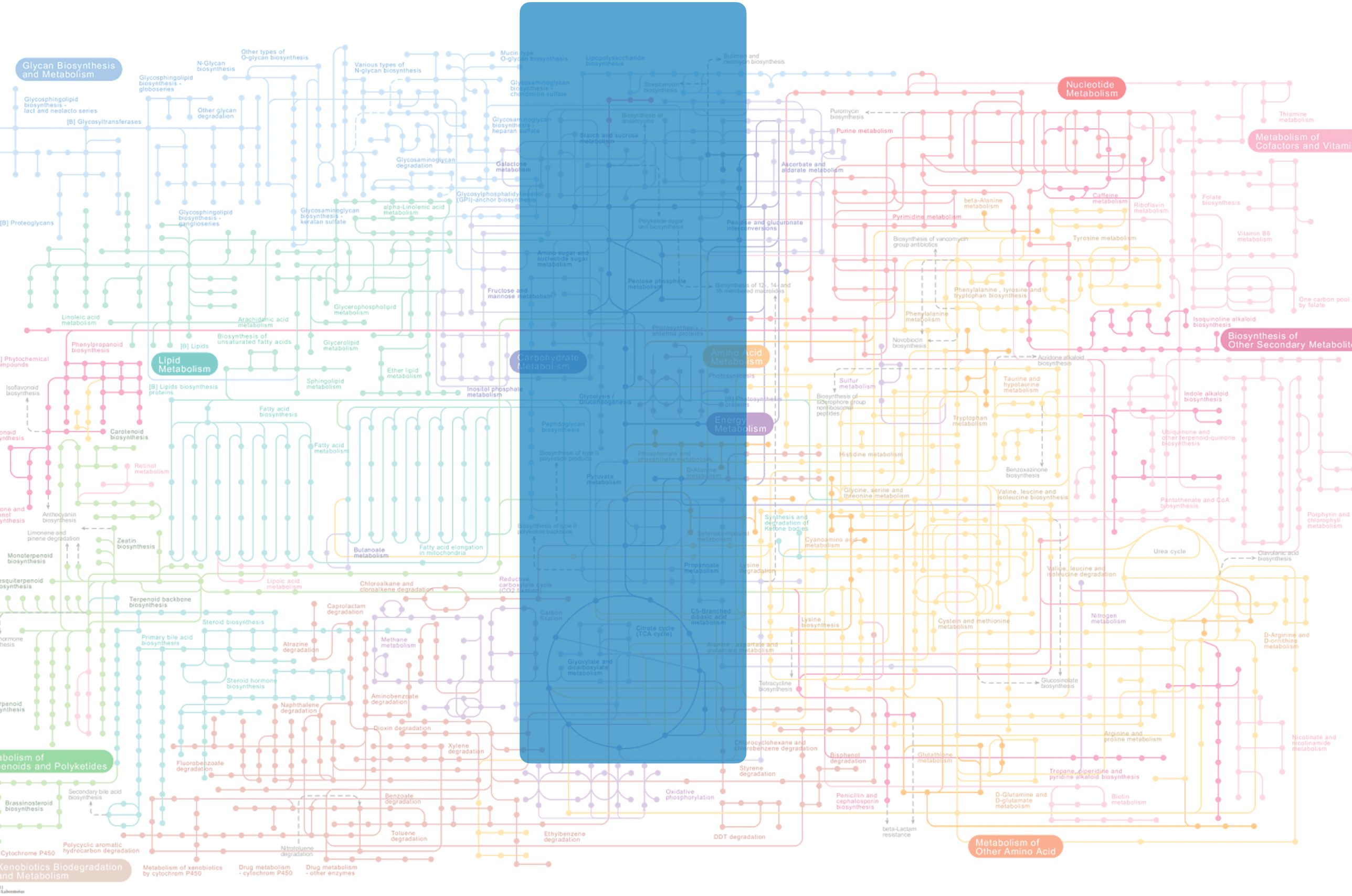


“Break down” nutrients to produce biomolecules for energy exchange

CATABOLISM


Glycan Biosynthesis and Metabolism
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Linoleic acid metabolism
Arachidonic acid metabolism
Glycerophospholipid metabolism
Biosynthesis of unsaturated fatty acids
Glycerolipid metabolism
Phenylpropanoid biosynthesis
[B] Lipids
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Sphingolipid metabolism
Ether lipid metabolism
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Fatty acid metabolism
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Retinol metabolism
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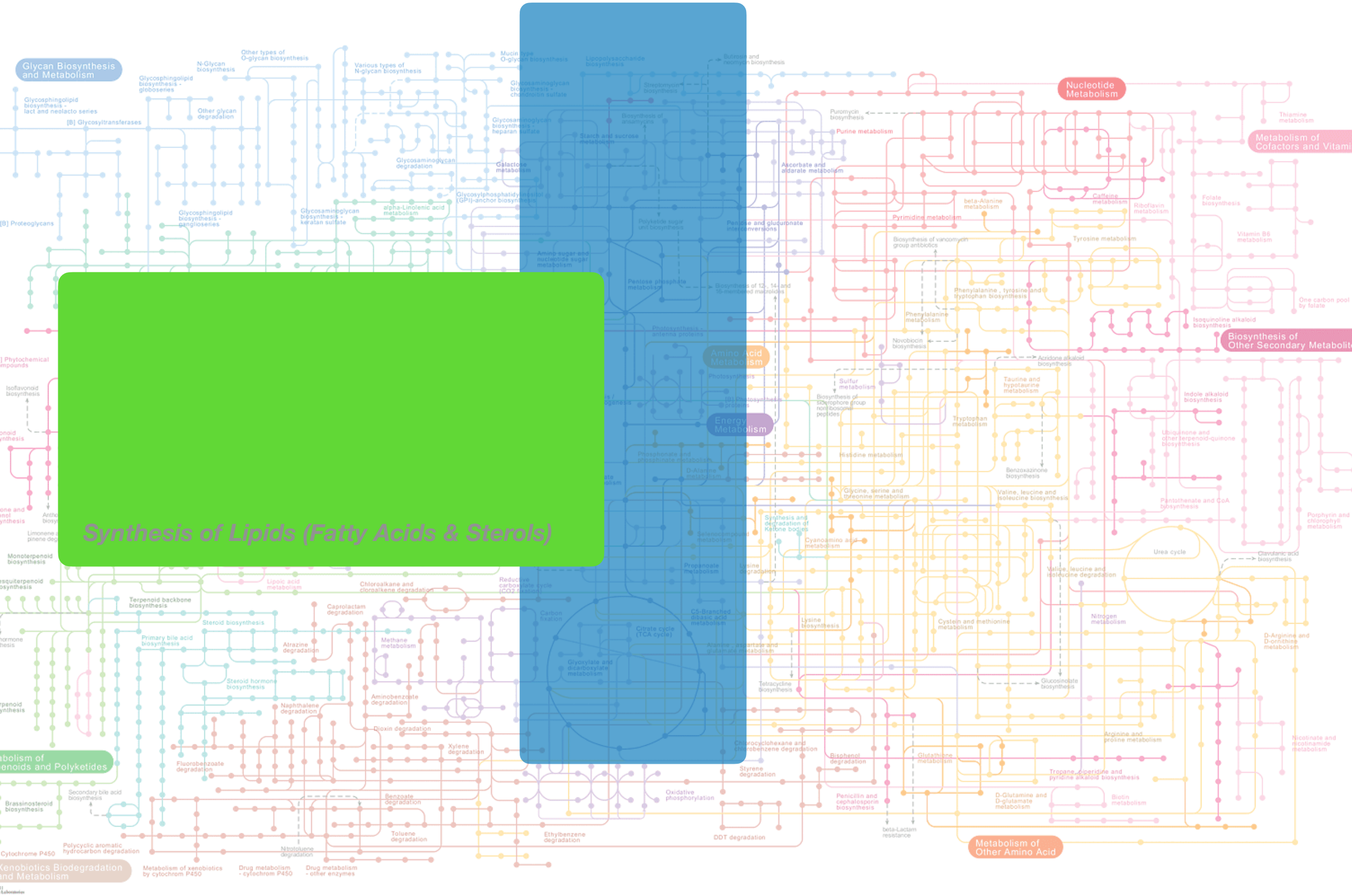
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Synthesis of Nucleotides

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Synthesis of Non-Essential Amino Acids (NEAA)

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Waste

Waste

Redox Balance

Waste

Metabolism of Amino Acids

Synthesis of Glycans

Synthesis of Nucleotides

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Synthesis of Lipids (Fatty Acids & Sterols)

Redox Balance

Waste

Waste

Waste

Metabolism of Amino Acids

“Build up” components of cell dry mass

ANABOLISM

Synthesis of Glycans

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Synthesis of Lipids (Fatty Acids & Sterols)

Redox Balance

Waste

Waste

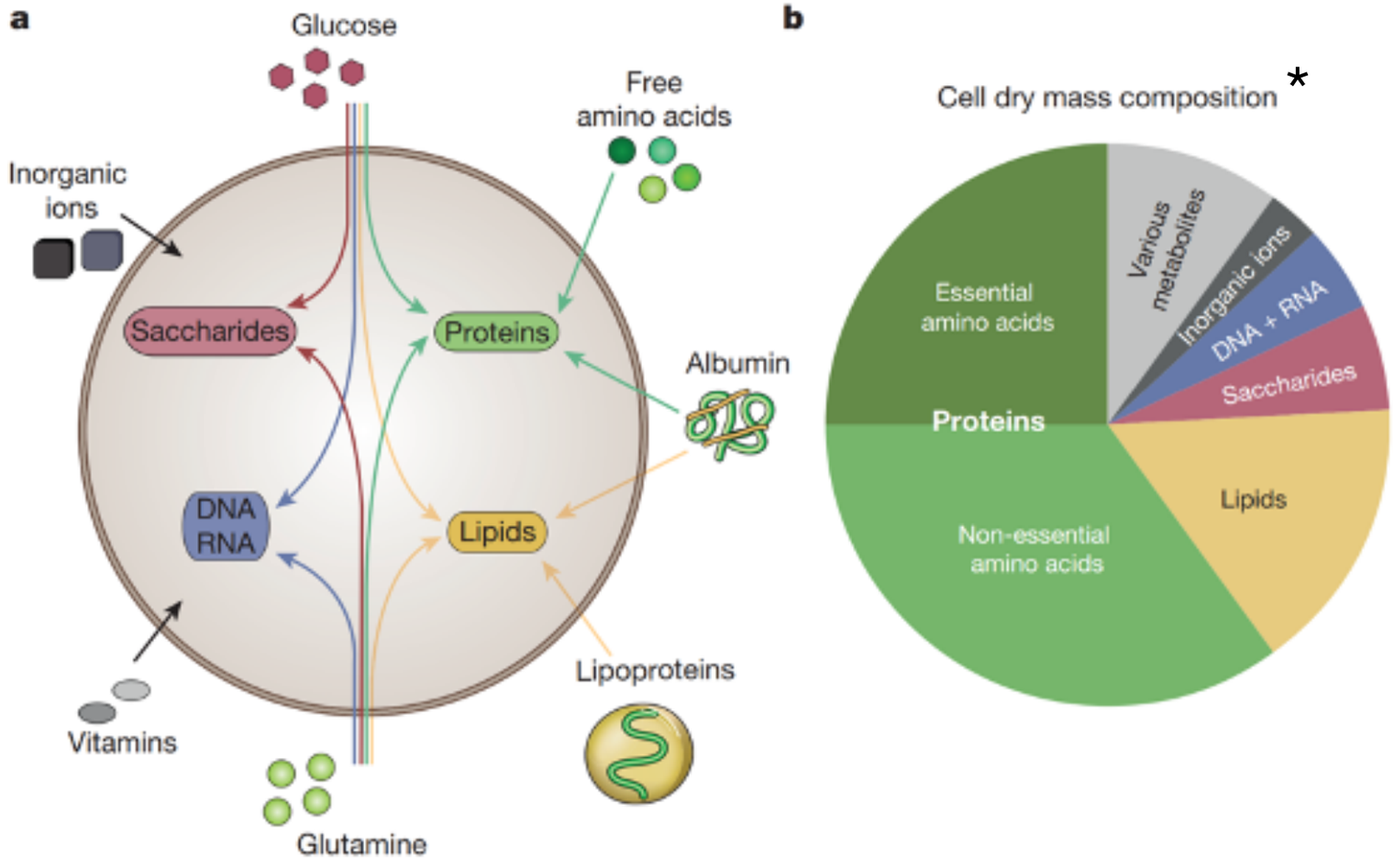
Waste

Metabolism of Amino Acids

“Build up” components of cell dry mass

ANABOLISM

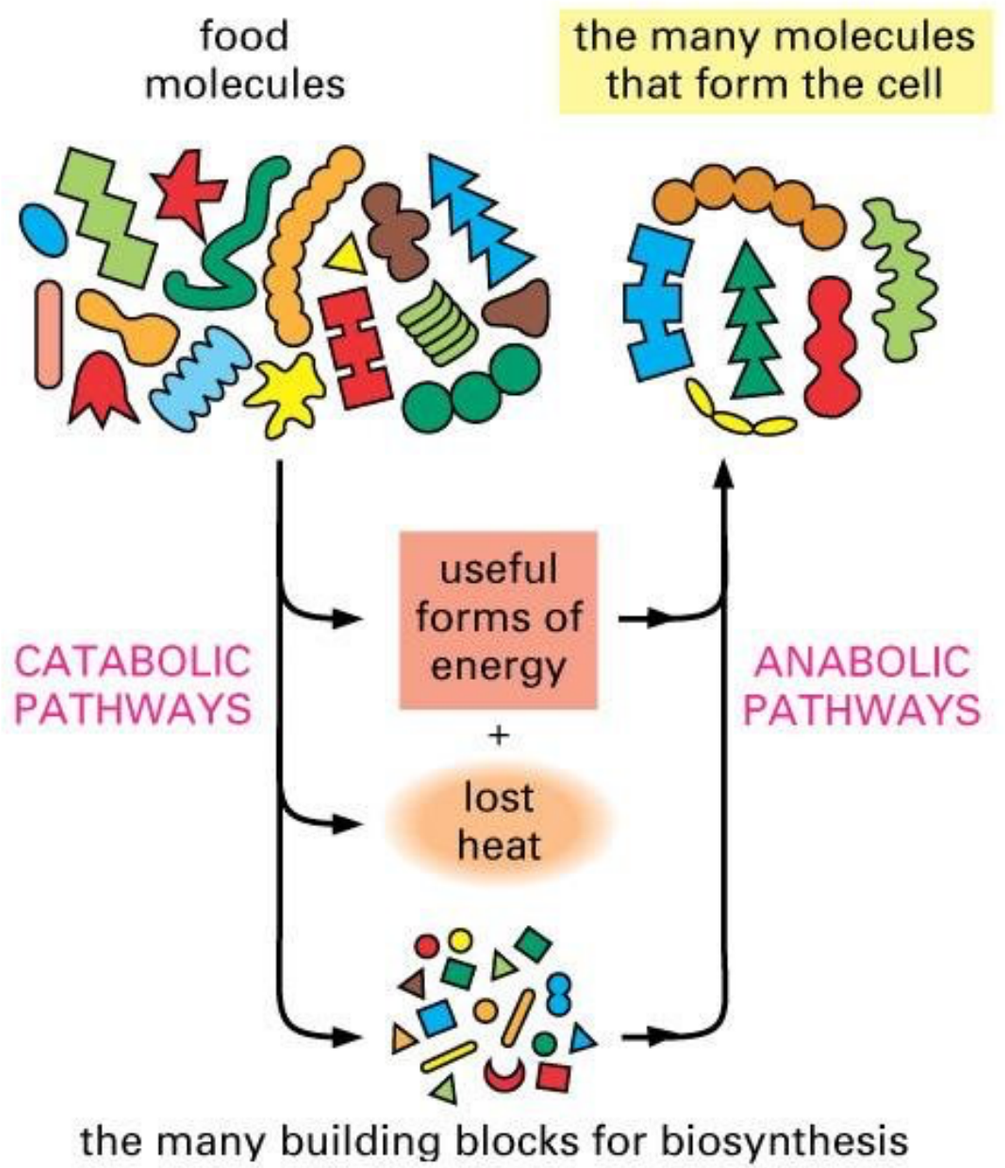
Macromolecules compose 70/80%* of the cell mass



* different in quiescent/proliferating

Palm & Thompson, ***Nature****, 2017*

Catabolism and Anabolism determine energy balance



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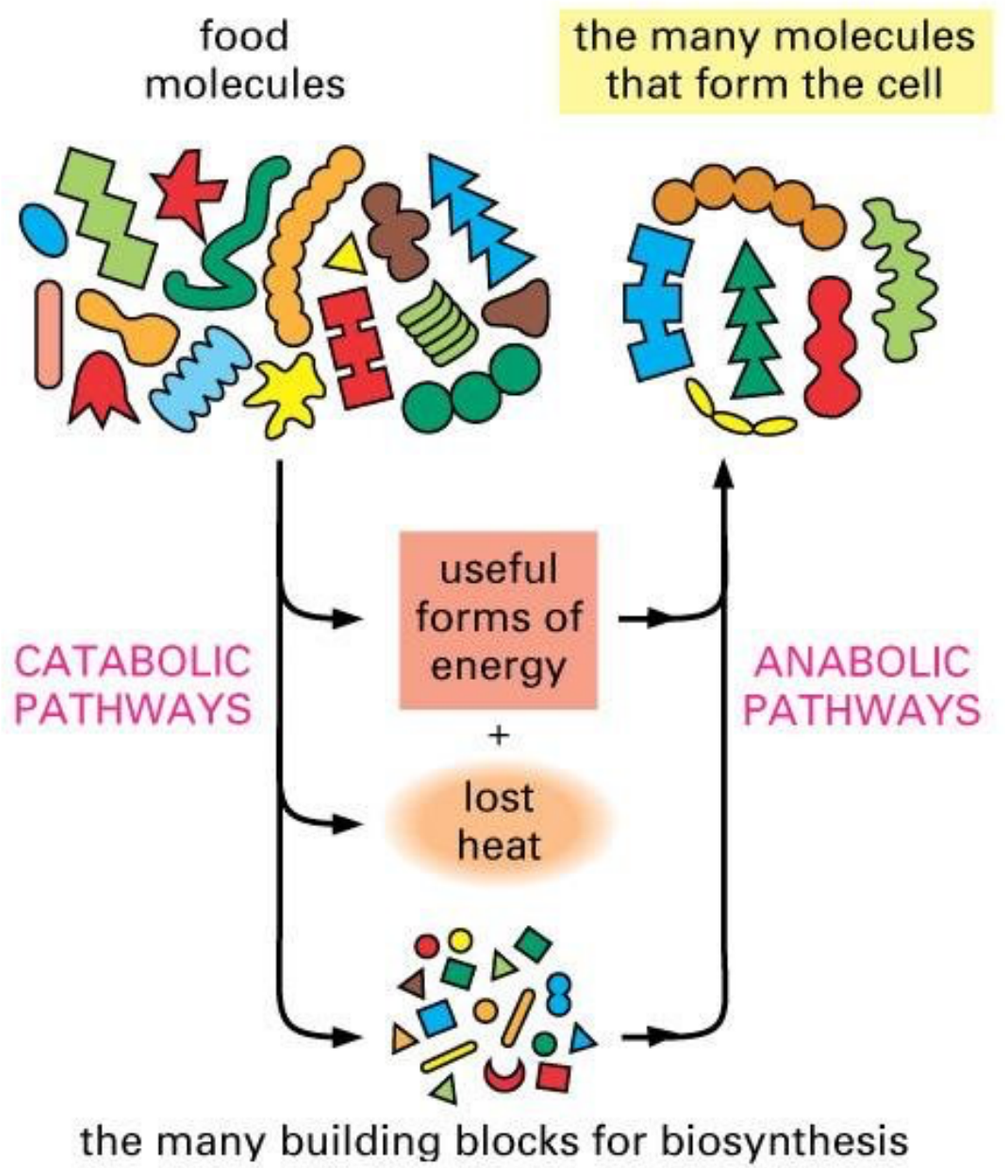

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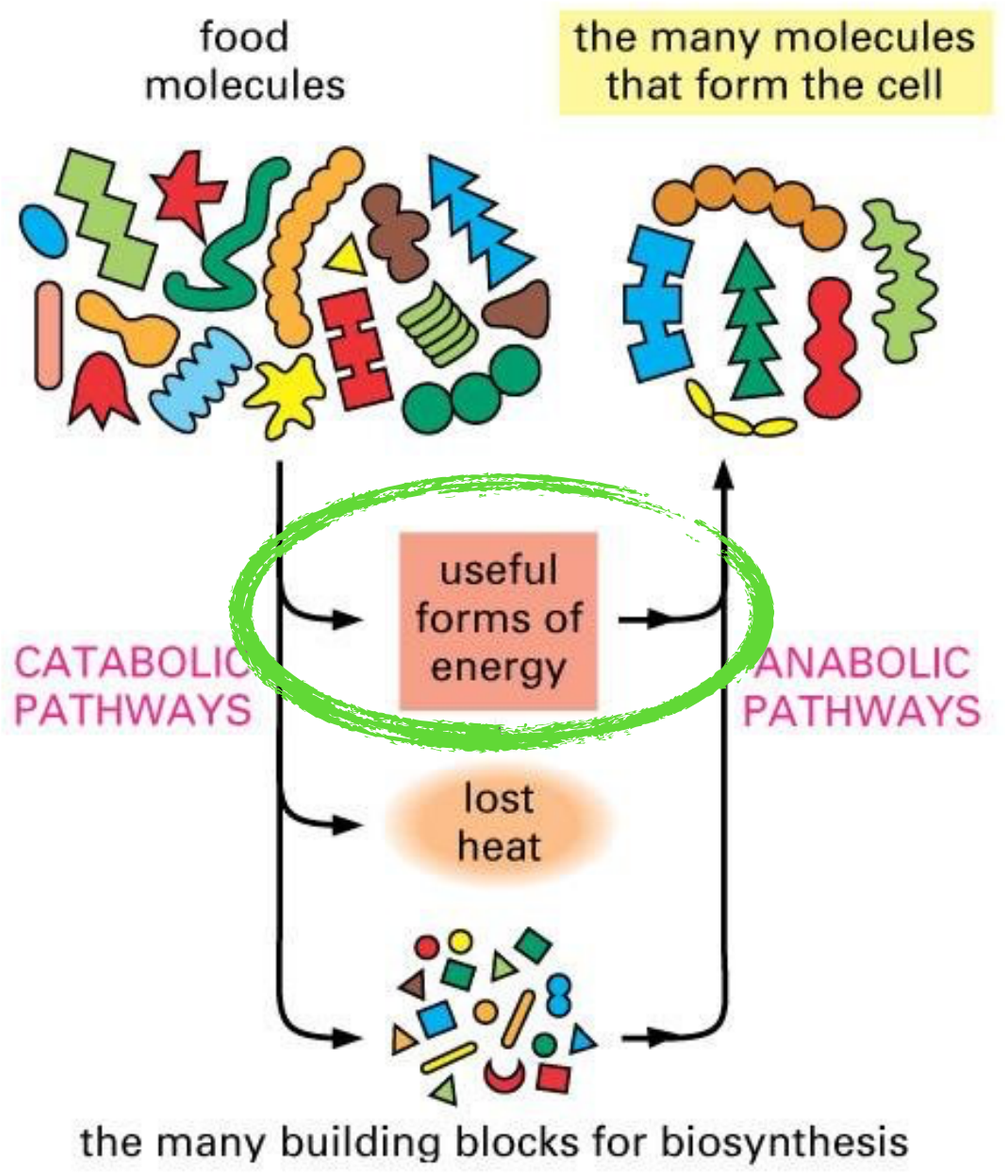
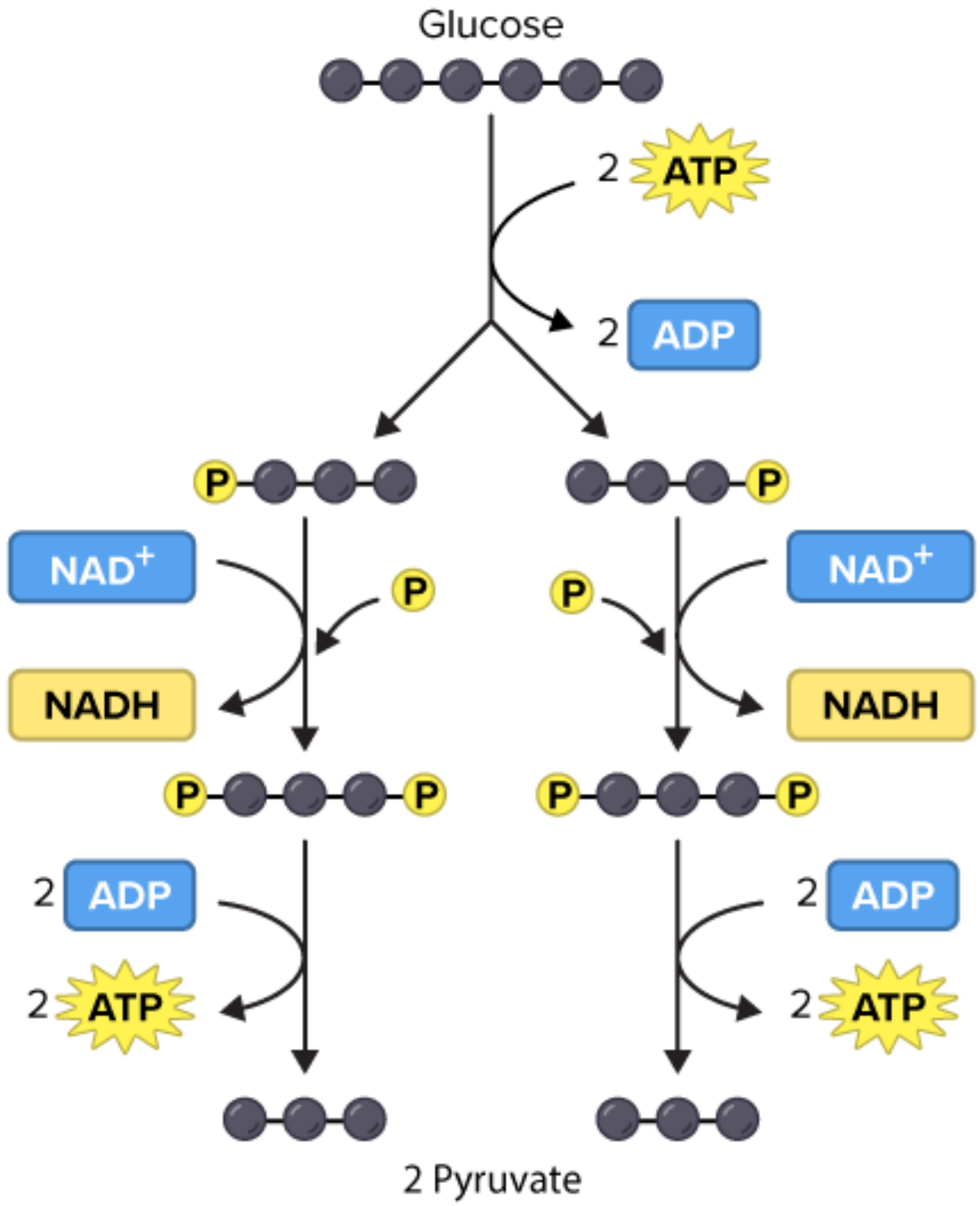


which can be stored in high-energy molecules.

Catabolism transfers energy to ATP and electron donors



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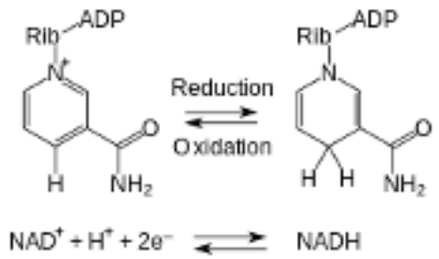
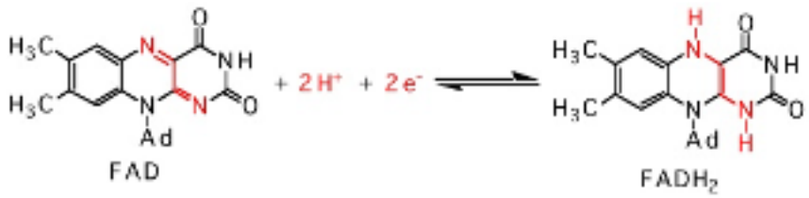
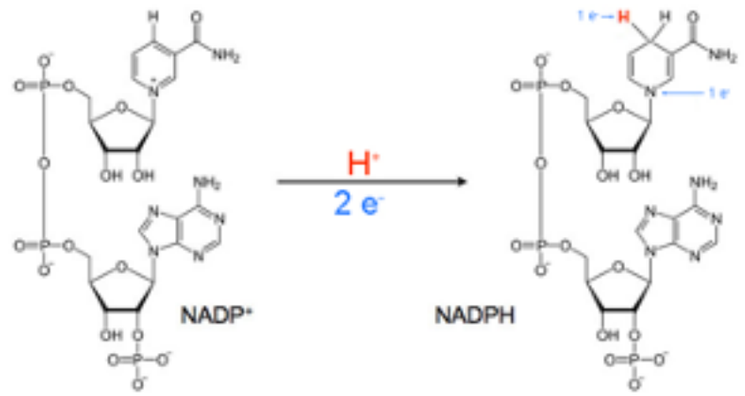






NADH and $FADH_2$ donate electrons to ETC to generate ATP (*mitochondria*)

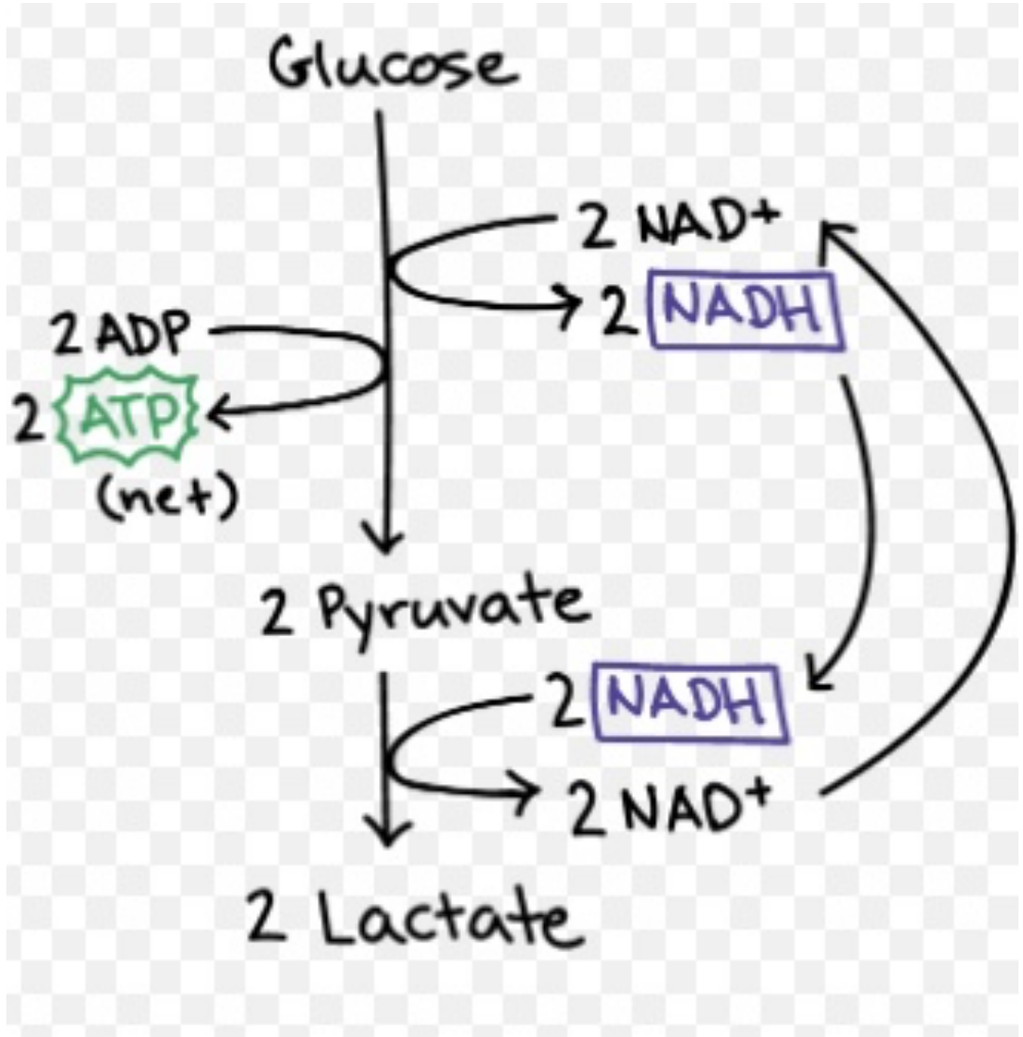
NADPH donates electrons for reductive biosynthesis (*e.g.: lipid synthesis*)

Catabolism and Anabolism determine energy balance

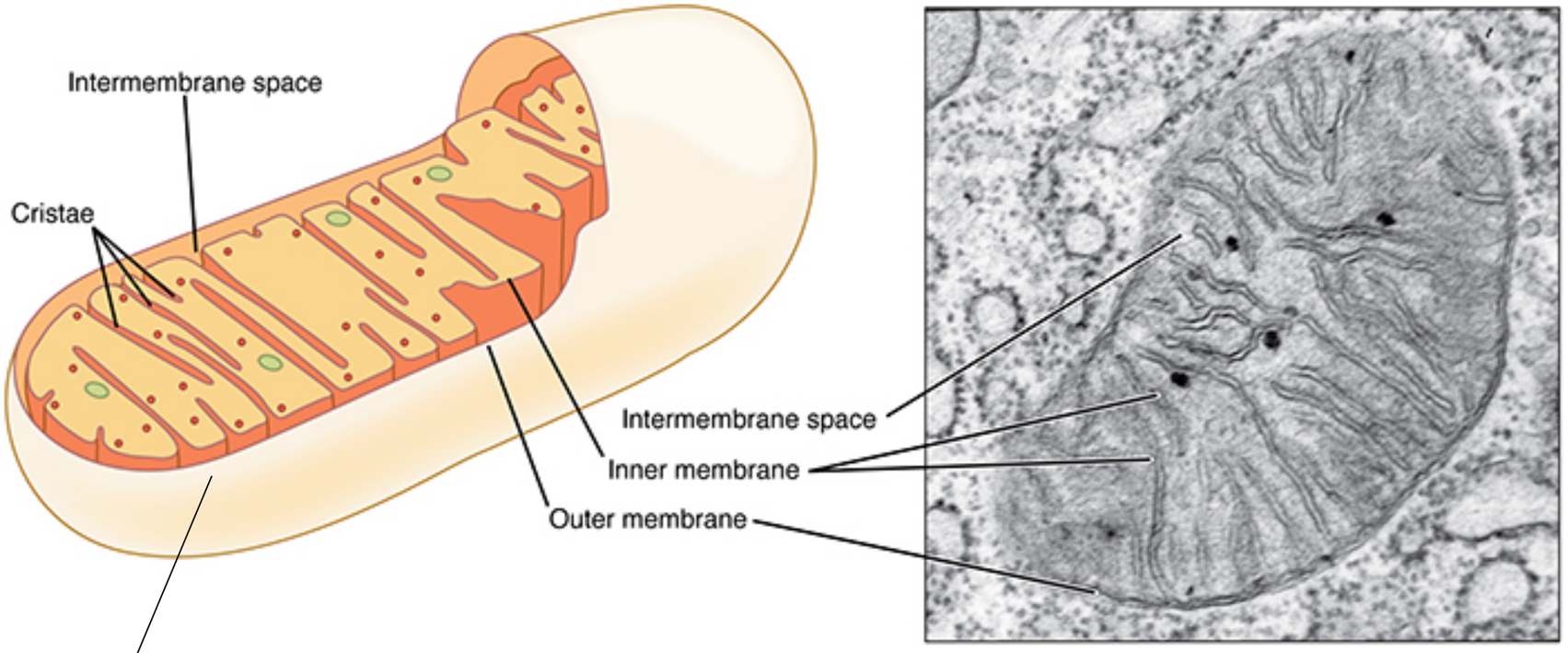
NADH and NAD cannot cross the mitochondrial membrane

In cells with functioning mitochondria and oxygen available, NADH is shuttled into the mitochondria via the malate-aspartate shuttle with electrons transferred to the electron transport chain (this is relatively slow)

Rates of NADH usage and compartmentalization are dictated by multiple conditions (i.e.: hypoxia, differentiation stage, etc)

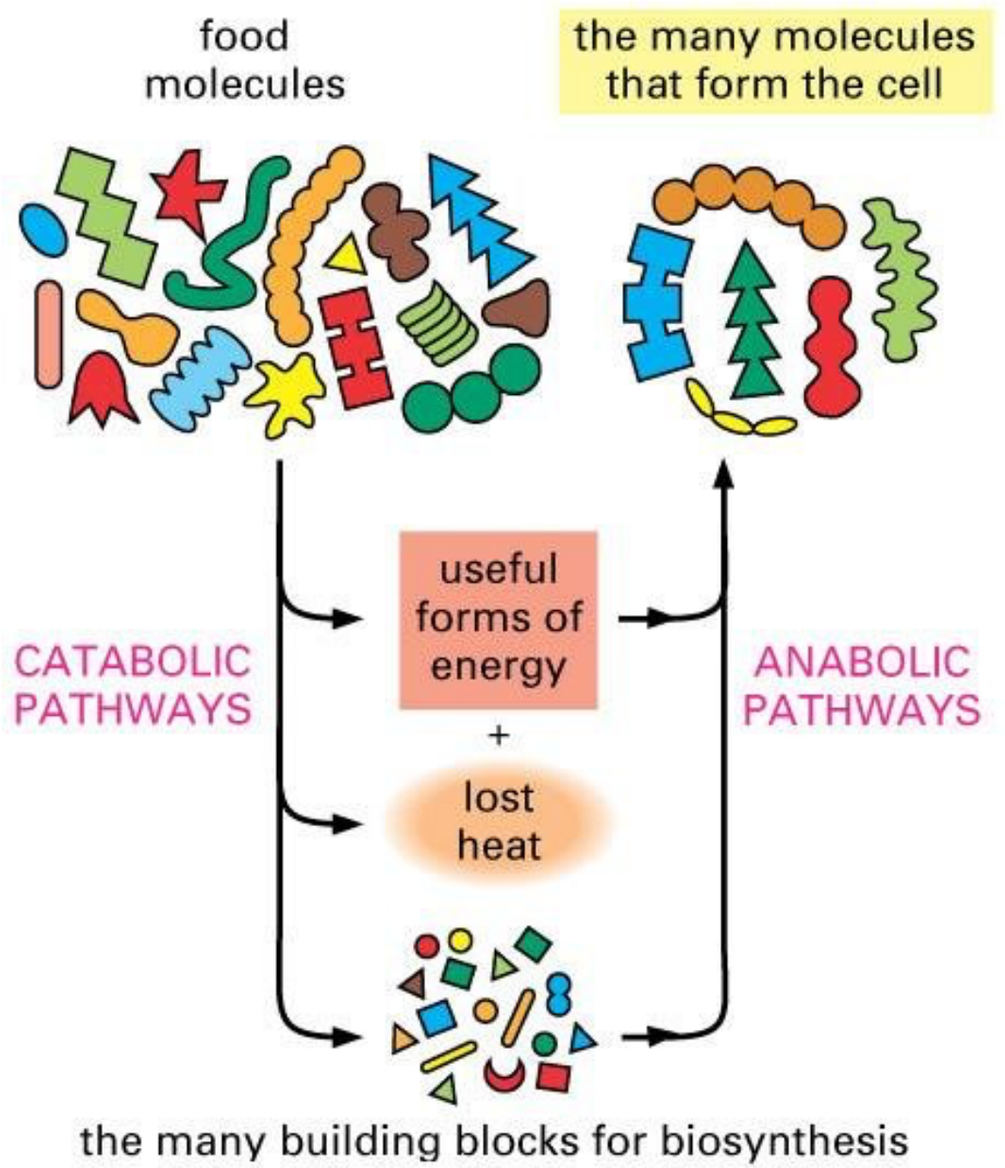


Mitochondria



Mitochondrial DNA
(many copies, maternally inherited, 37 genes, 13 in OXPHOS)

Catabolism and Anabolism determine energy balance



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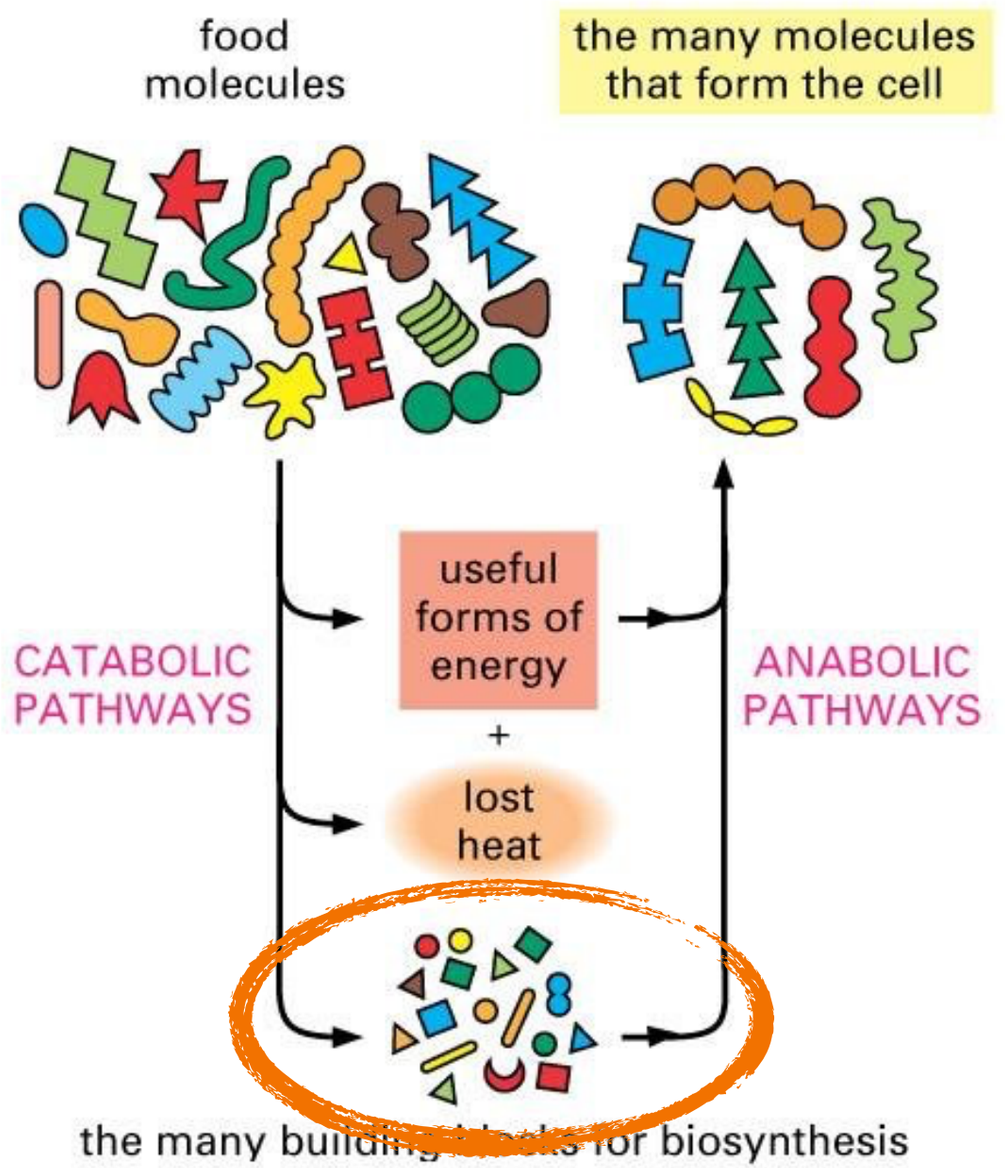
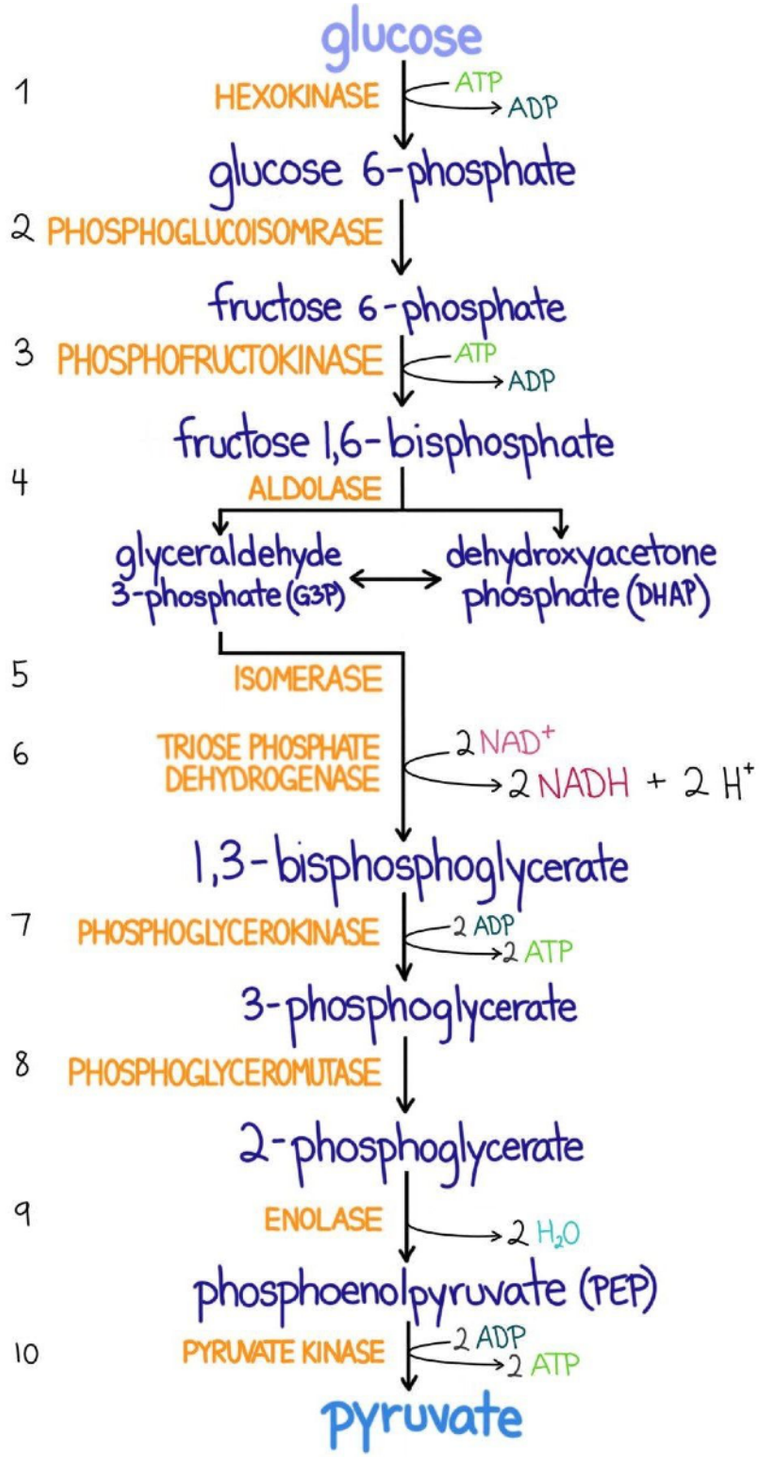


…and levels of intracellular metabolic intermediates!!

Glycolytic flux provides substrates for biosynthetic pathways



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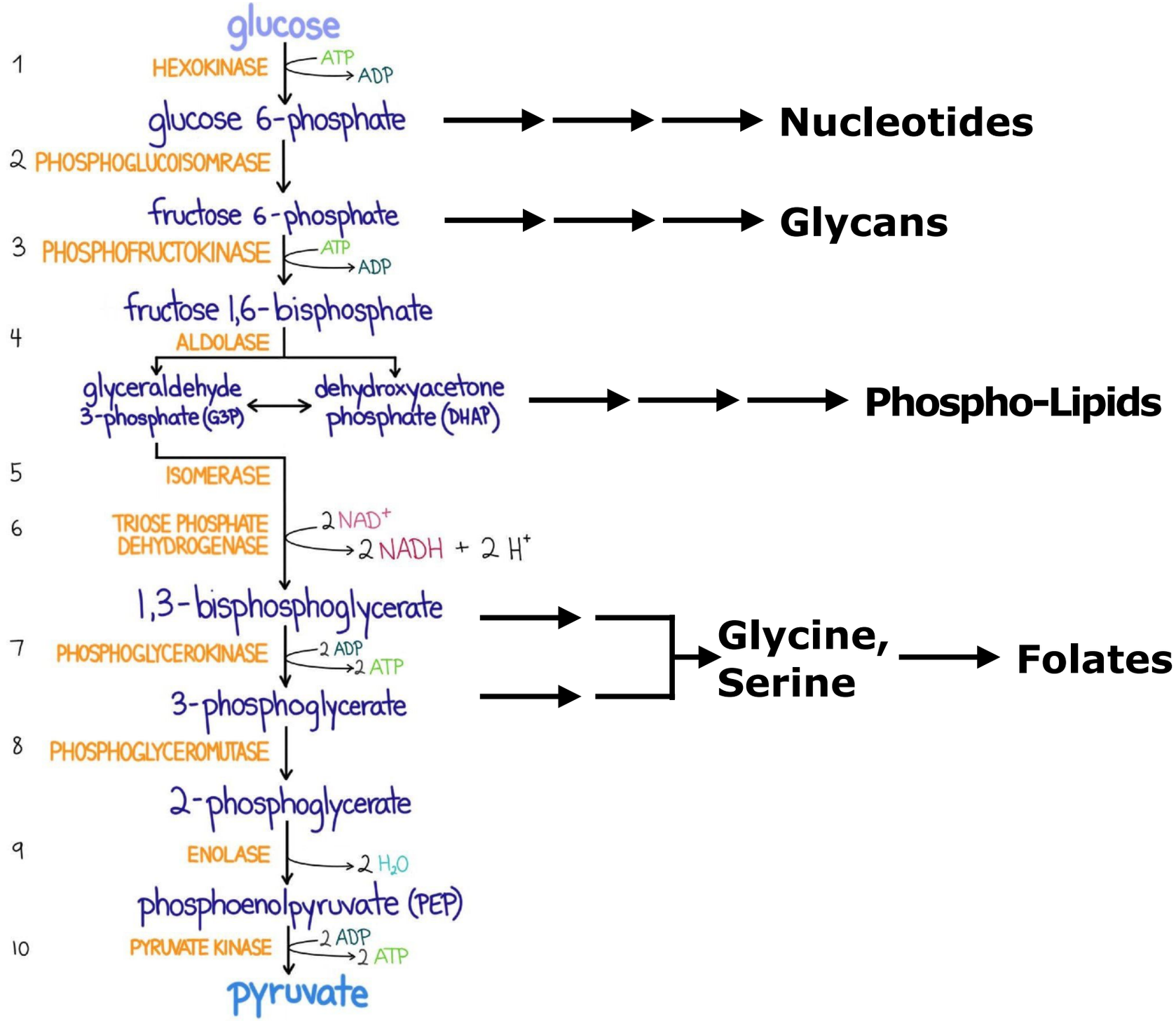

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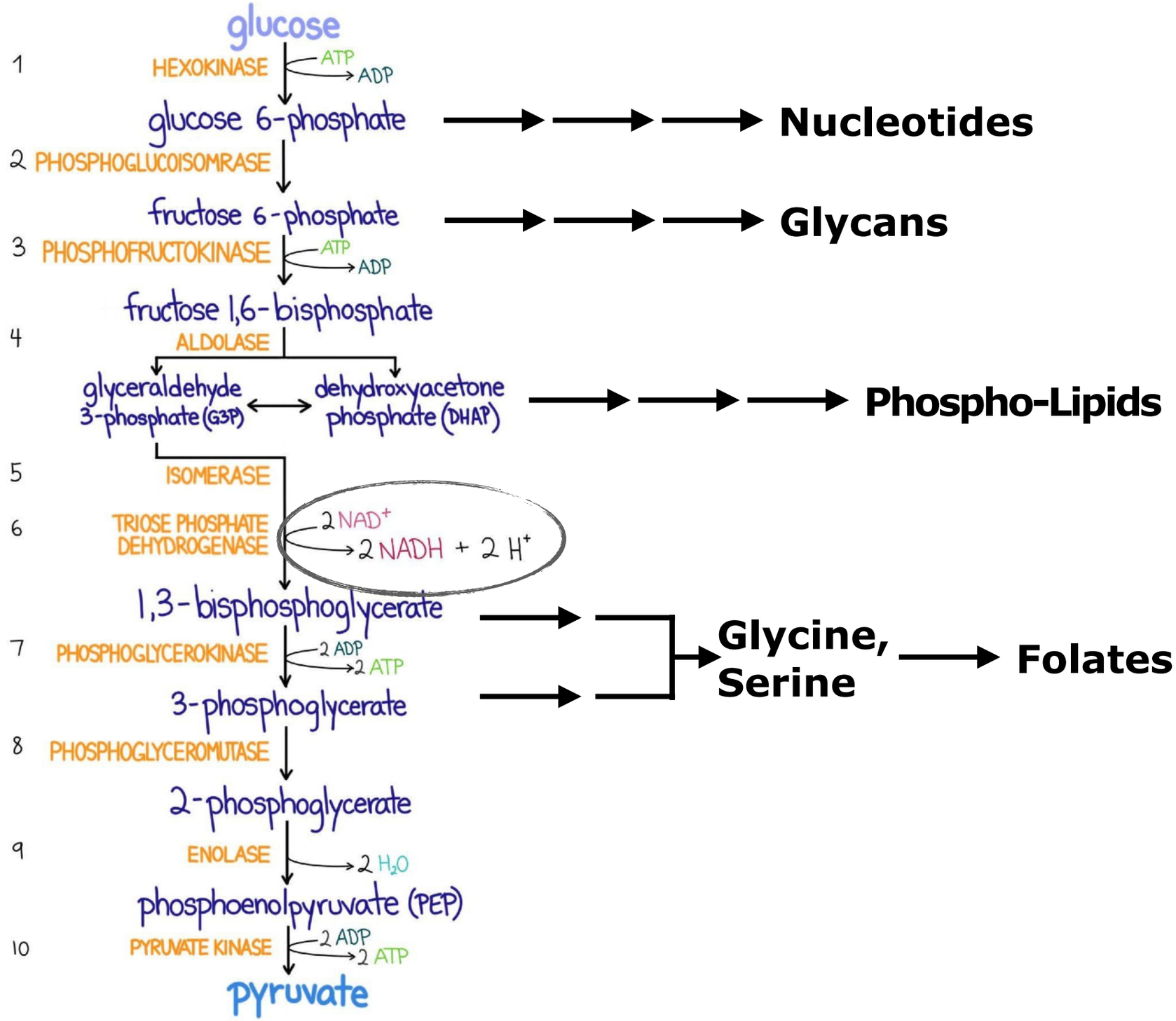
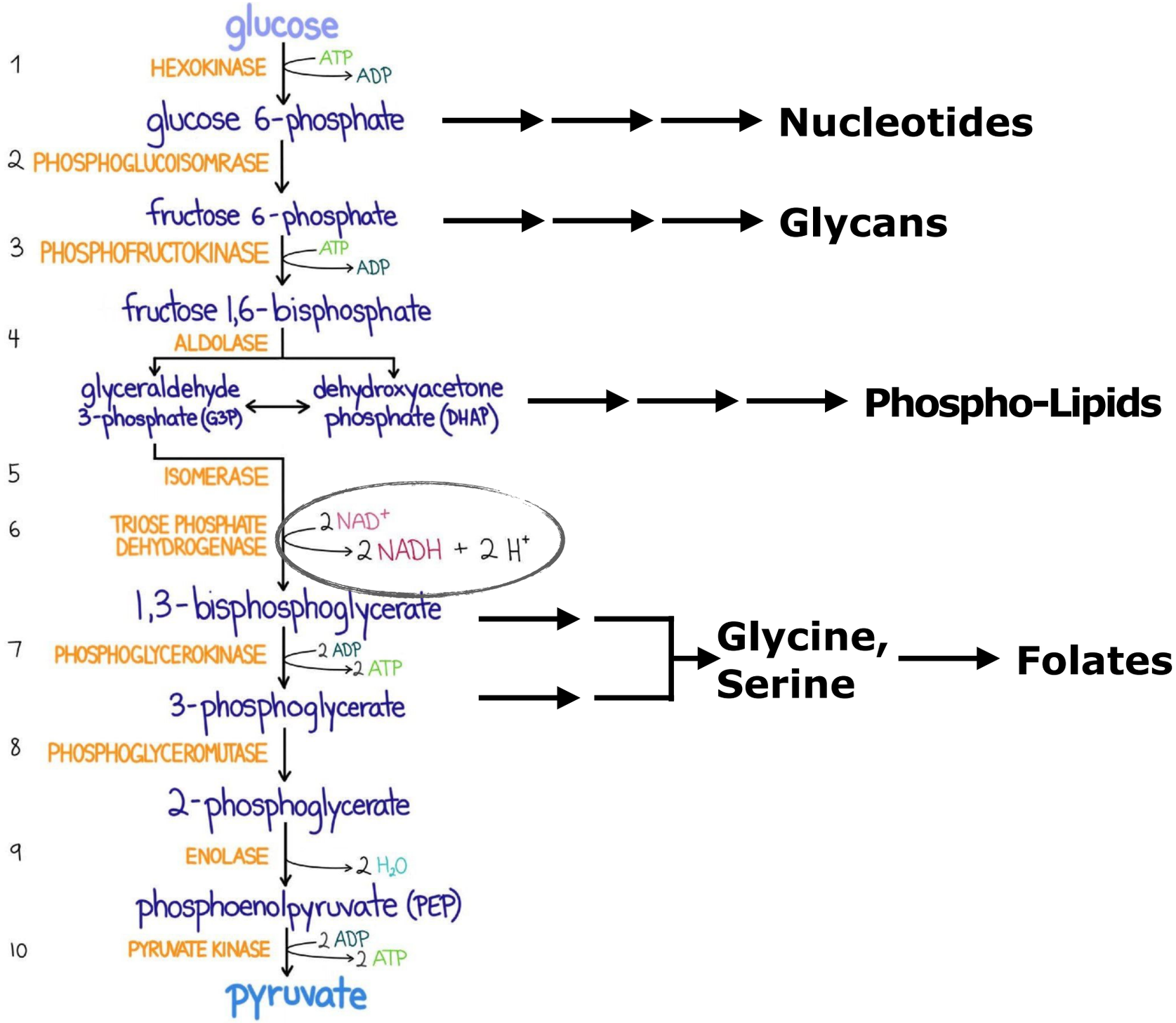


Glycolytic flux provides substrates for biosynthetic pathways

ATP,
TCA cycle intermediates



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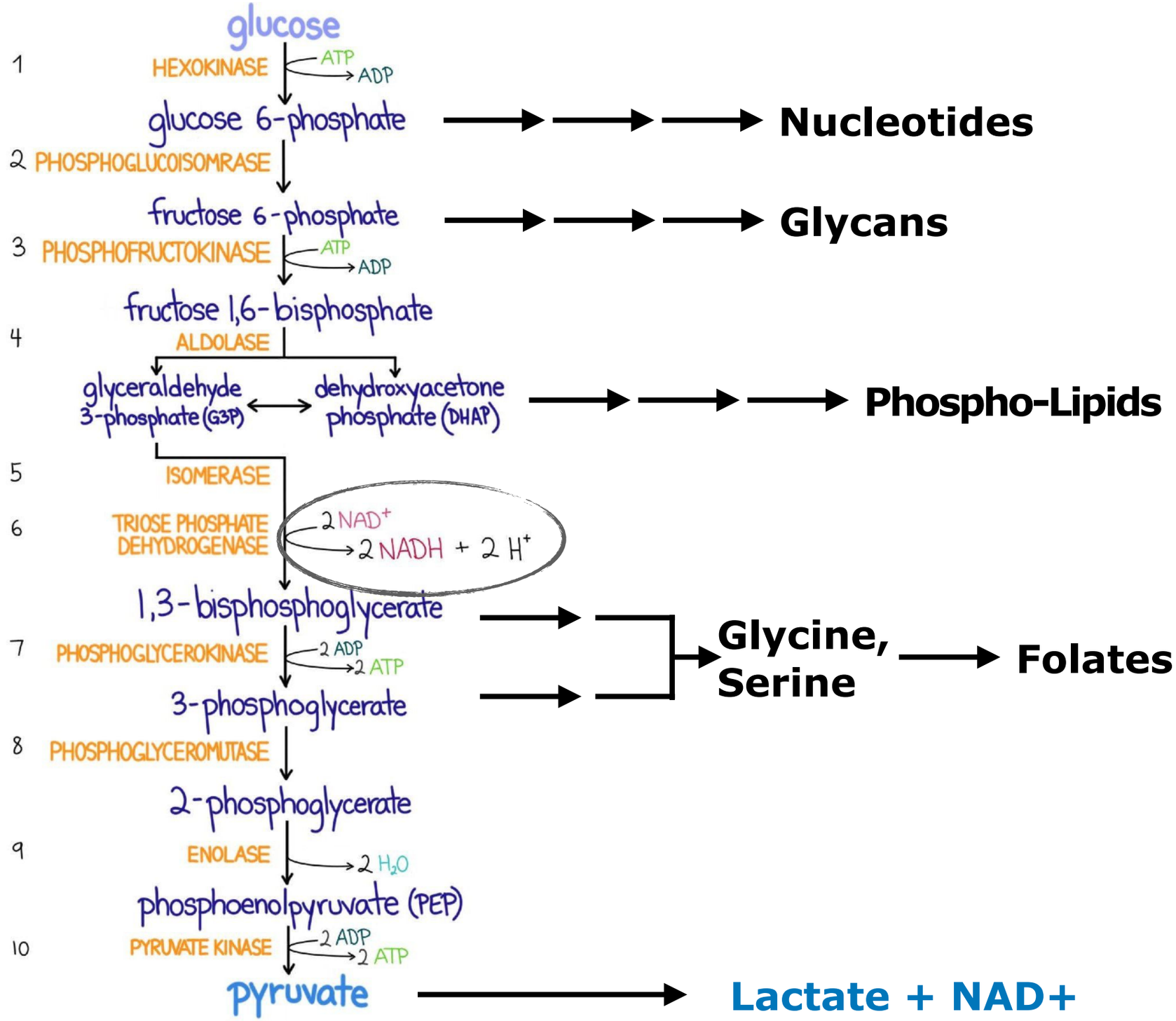
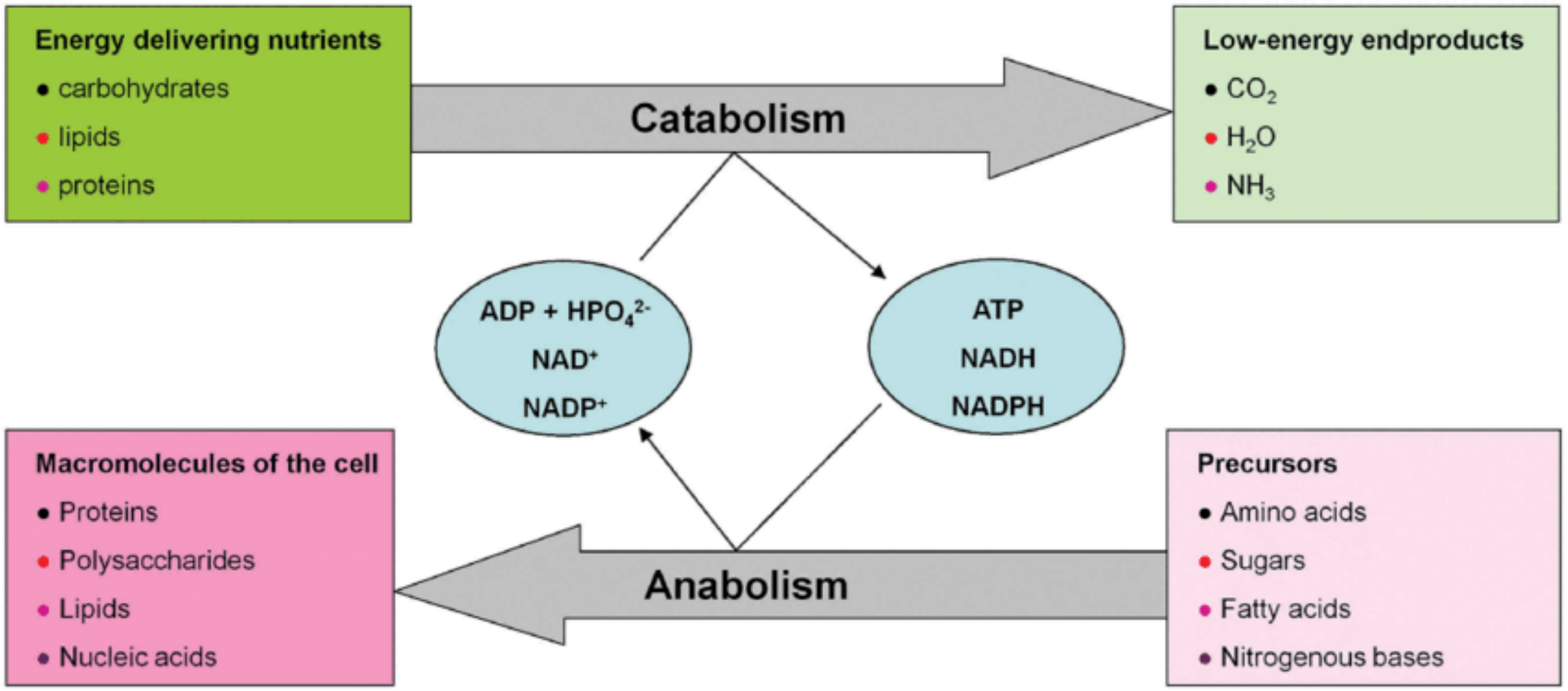


Catabolism and Anabolism coexist in each cell



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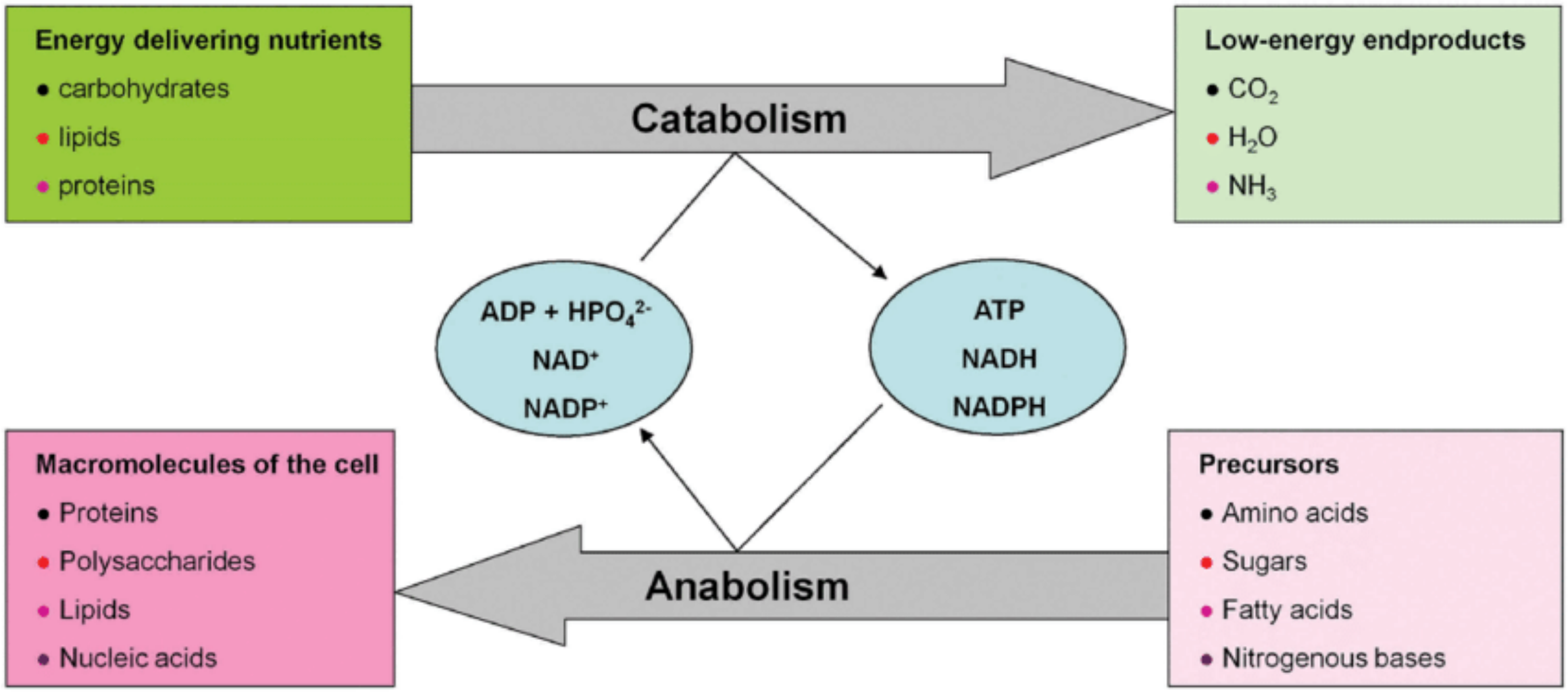
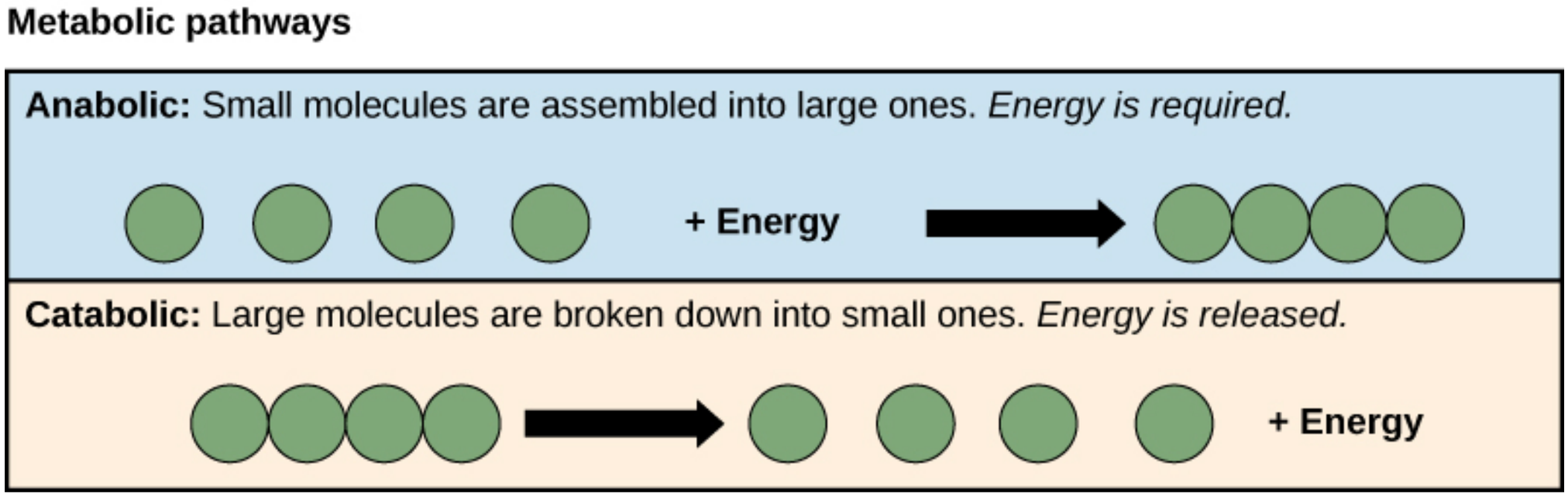
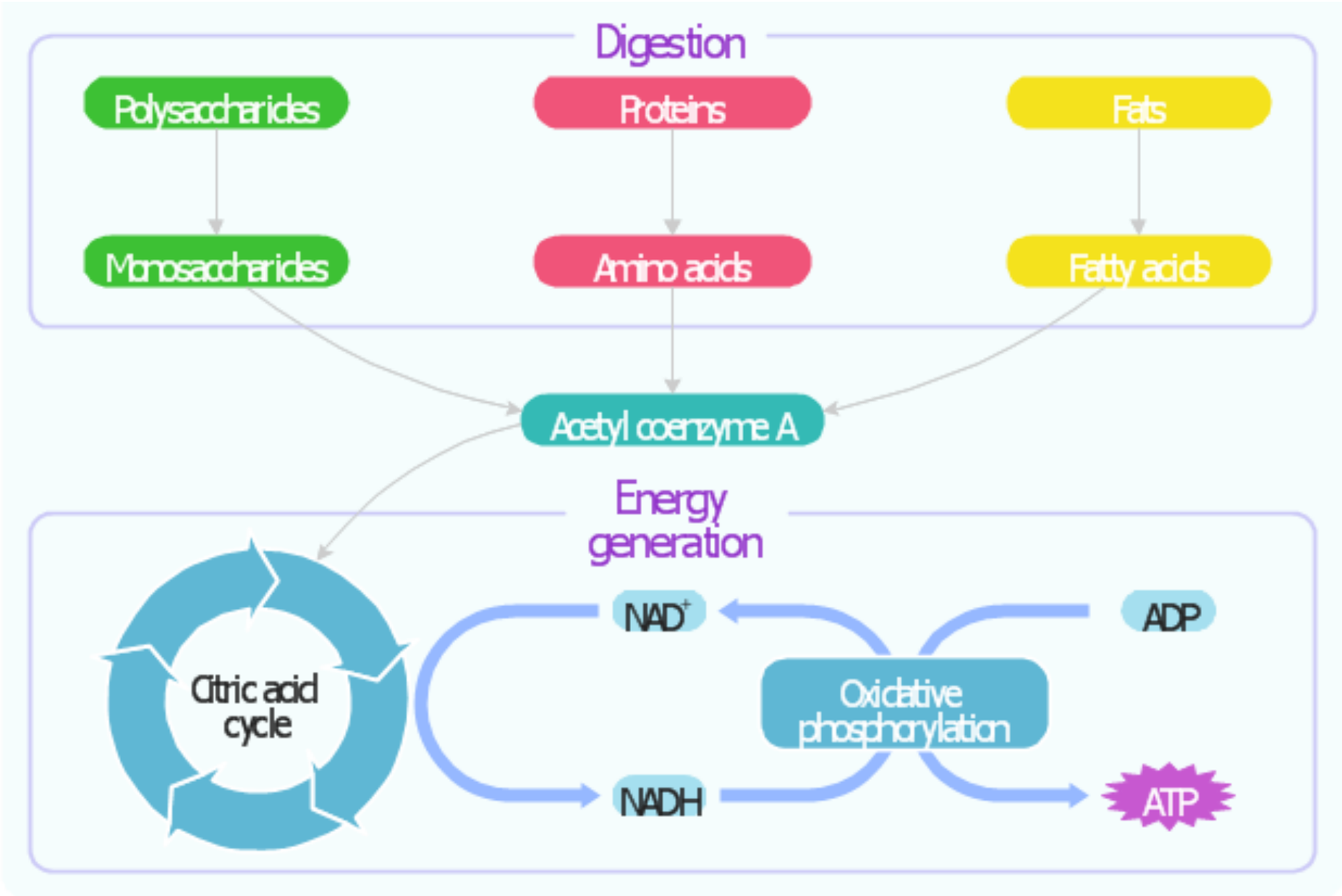


…and their equilibrium is tightly regulated by sensing mechanisms!!

What is Cellular Metabolism?

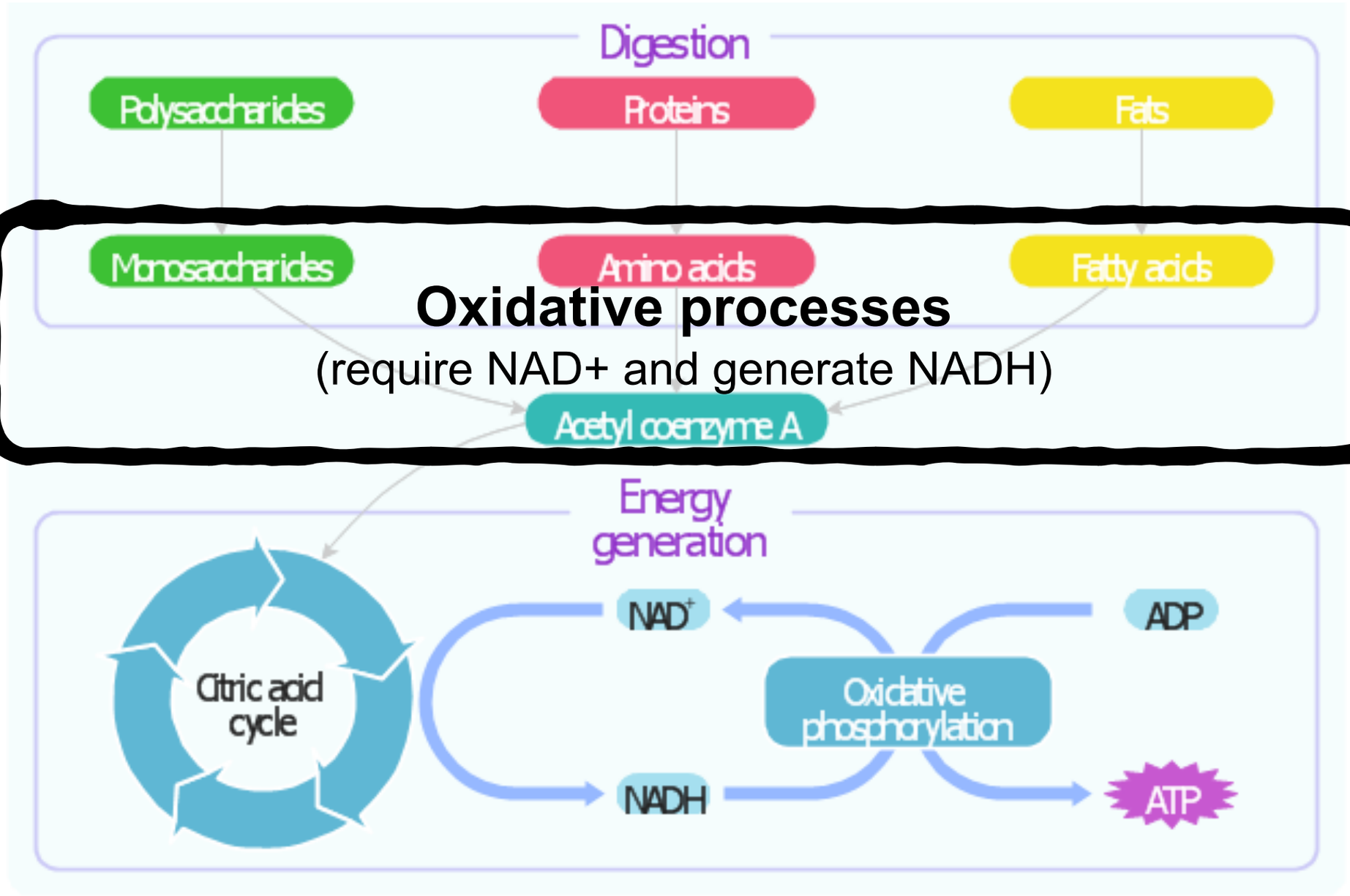


Main catabolic pathways



In eukaryotes, catabolic pathways converge to generate acetyl-CoA - a pivotal metabolite

Main catabolic pathways



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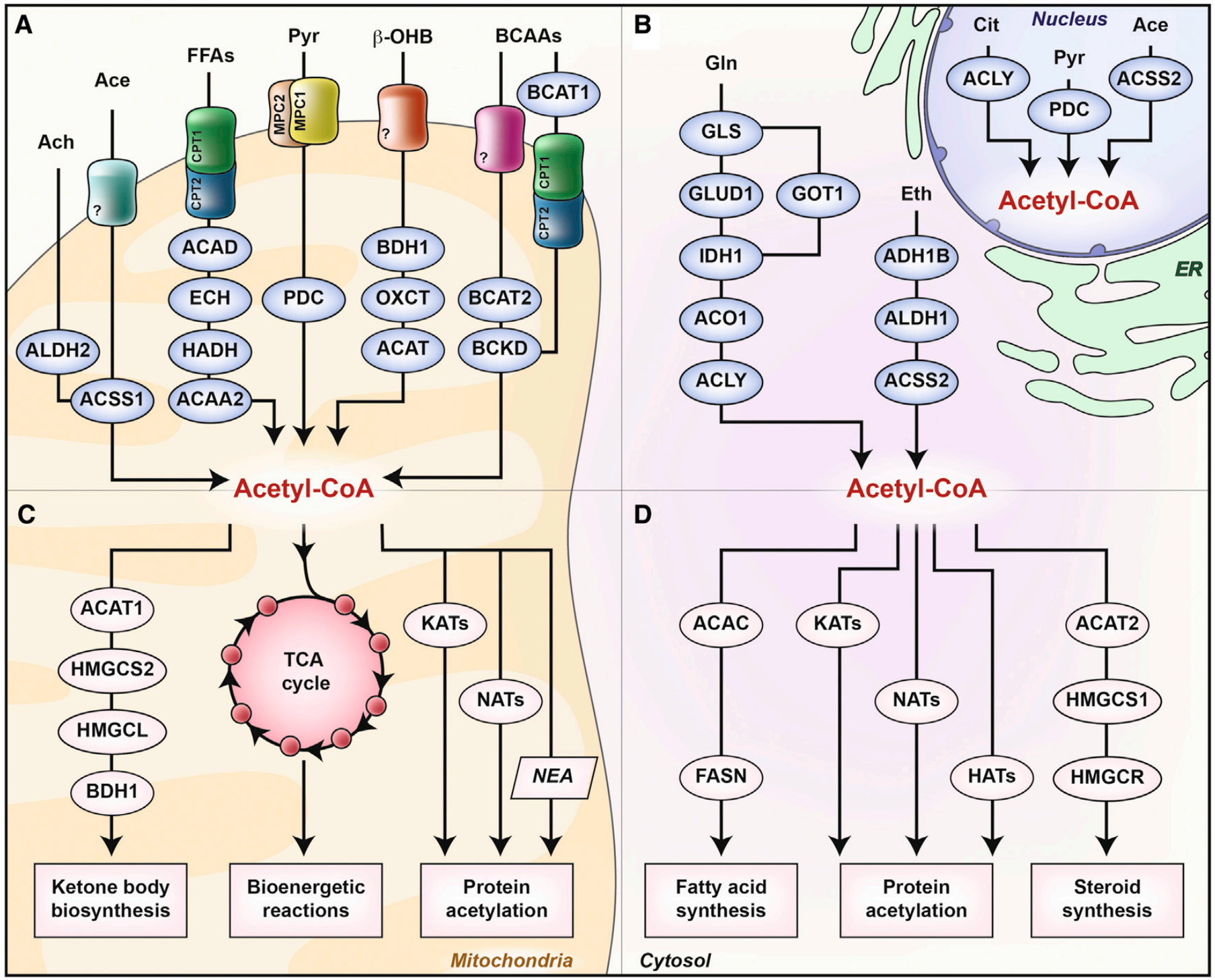
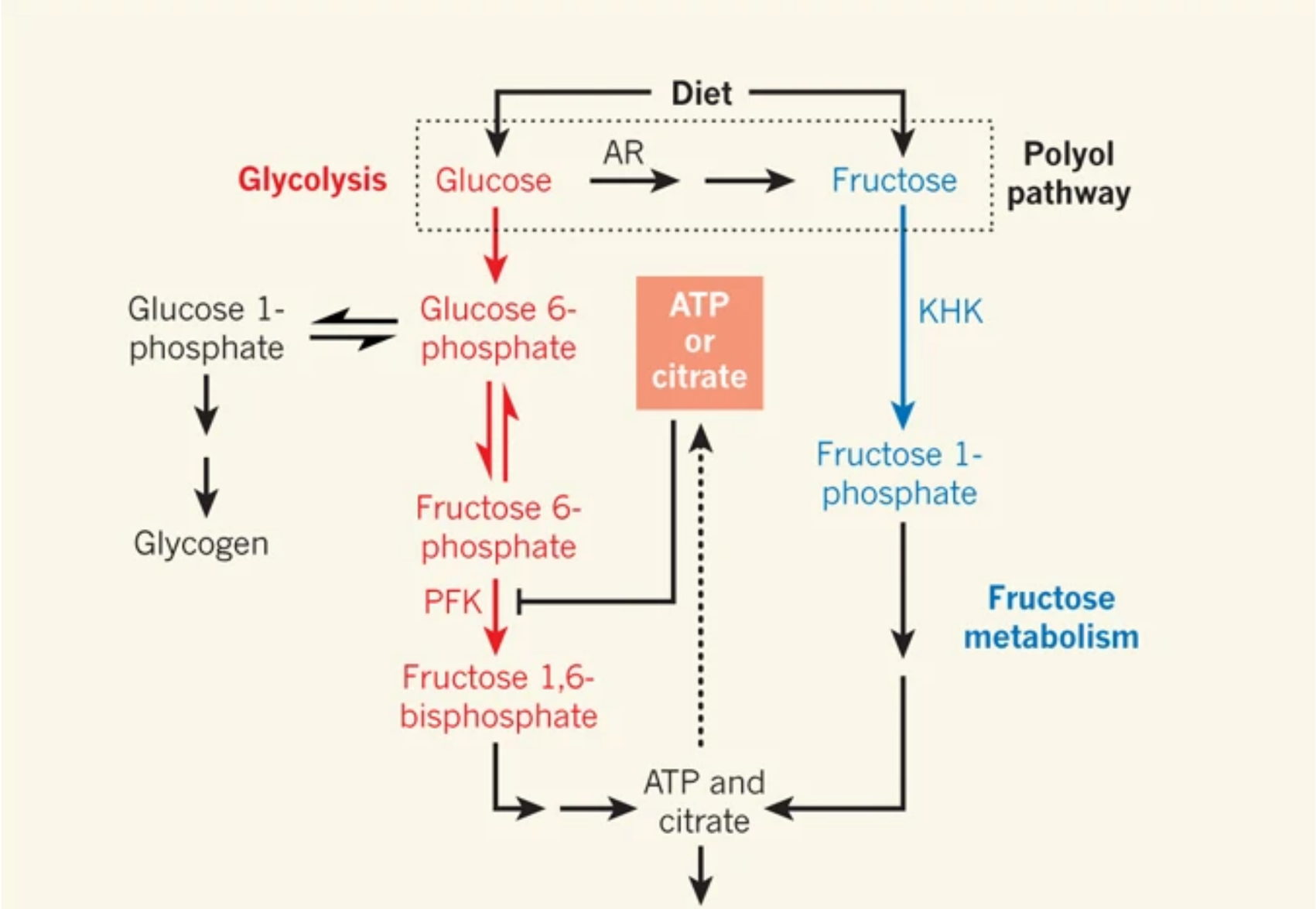


Pietrocola et al, ***Cell Metab****, 2015*

Acetyl-CoA is a central metabolite because:

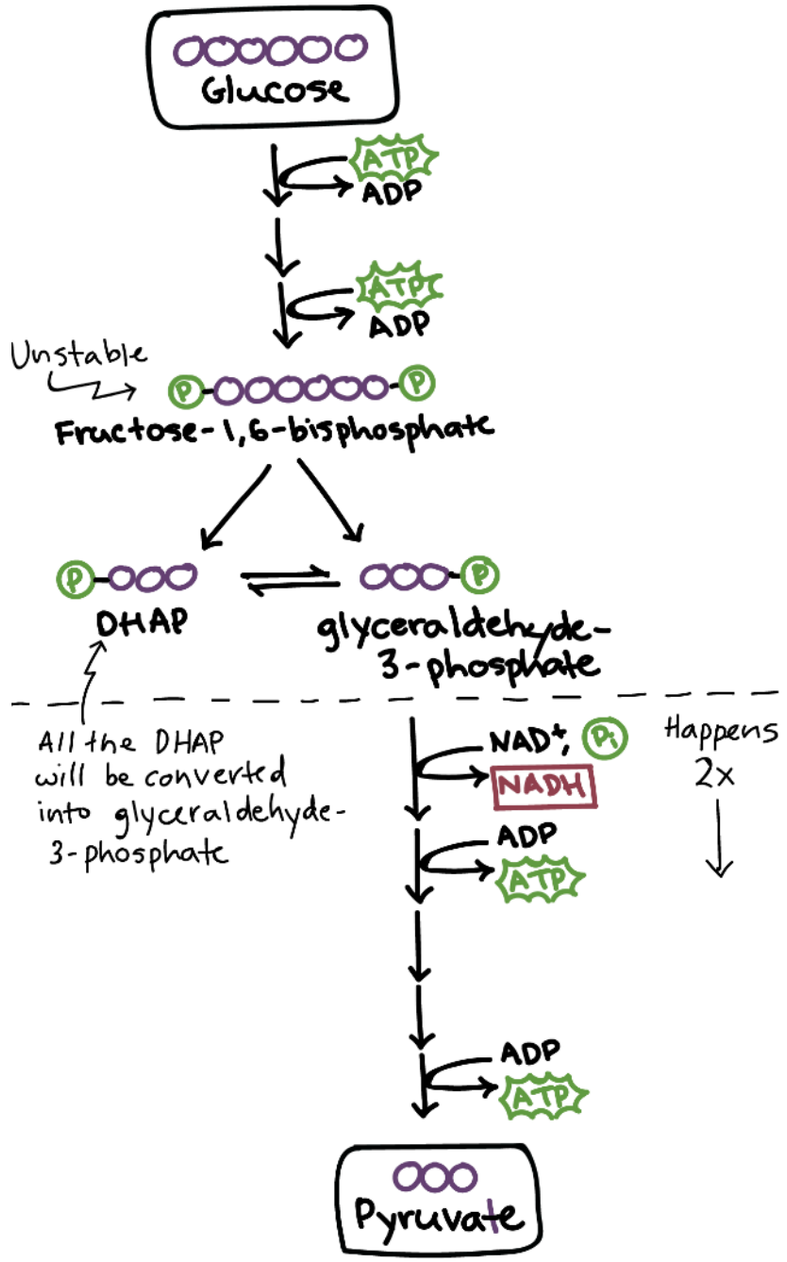
- It is at the cross-road of all catabolic pathways
- It is the building block for the synthesis of several macromolecules (fatty acids, sterols, glycans)
- It regulates protein acetylation
- It is compartmentalized
- Its levels fluctuate constantly
- Highly regulated / controlled / monitored

Main catabolic pathways: carbohydrates



acetyl-CoA

Central carbon metabolism: glycolysis



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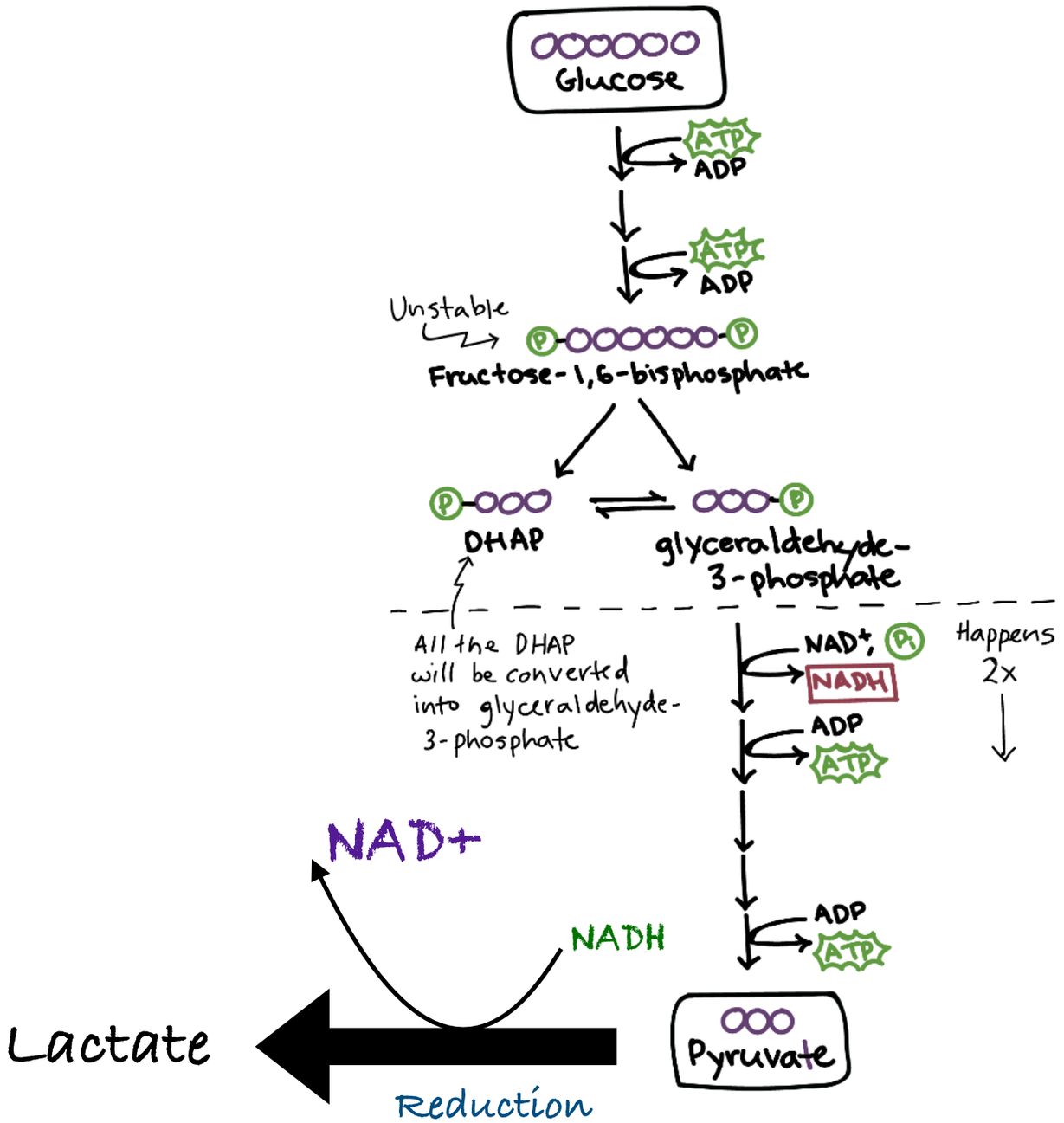

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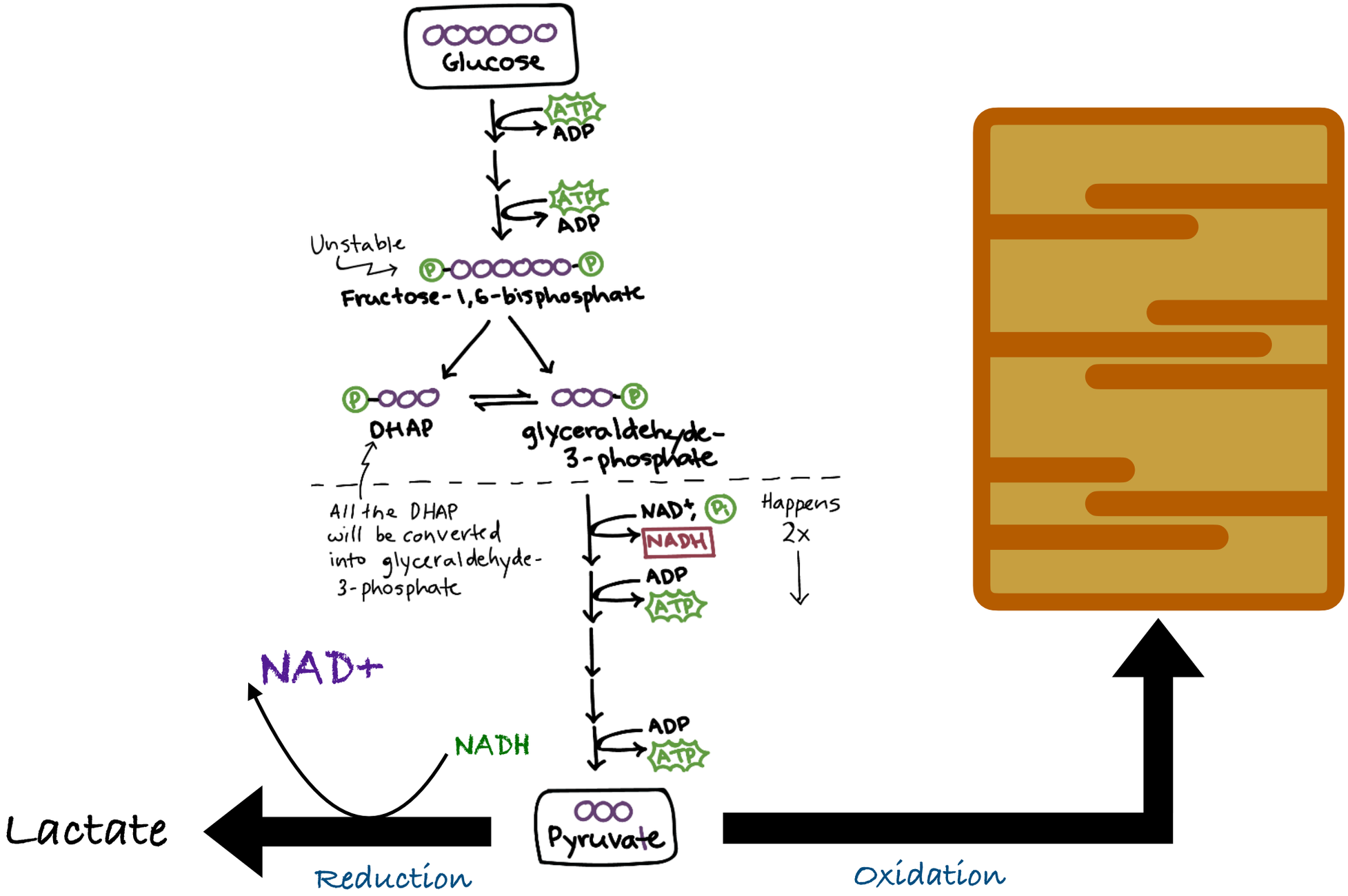
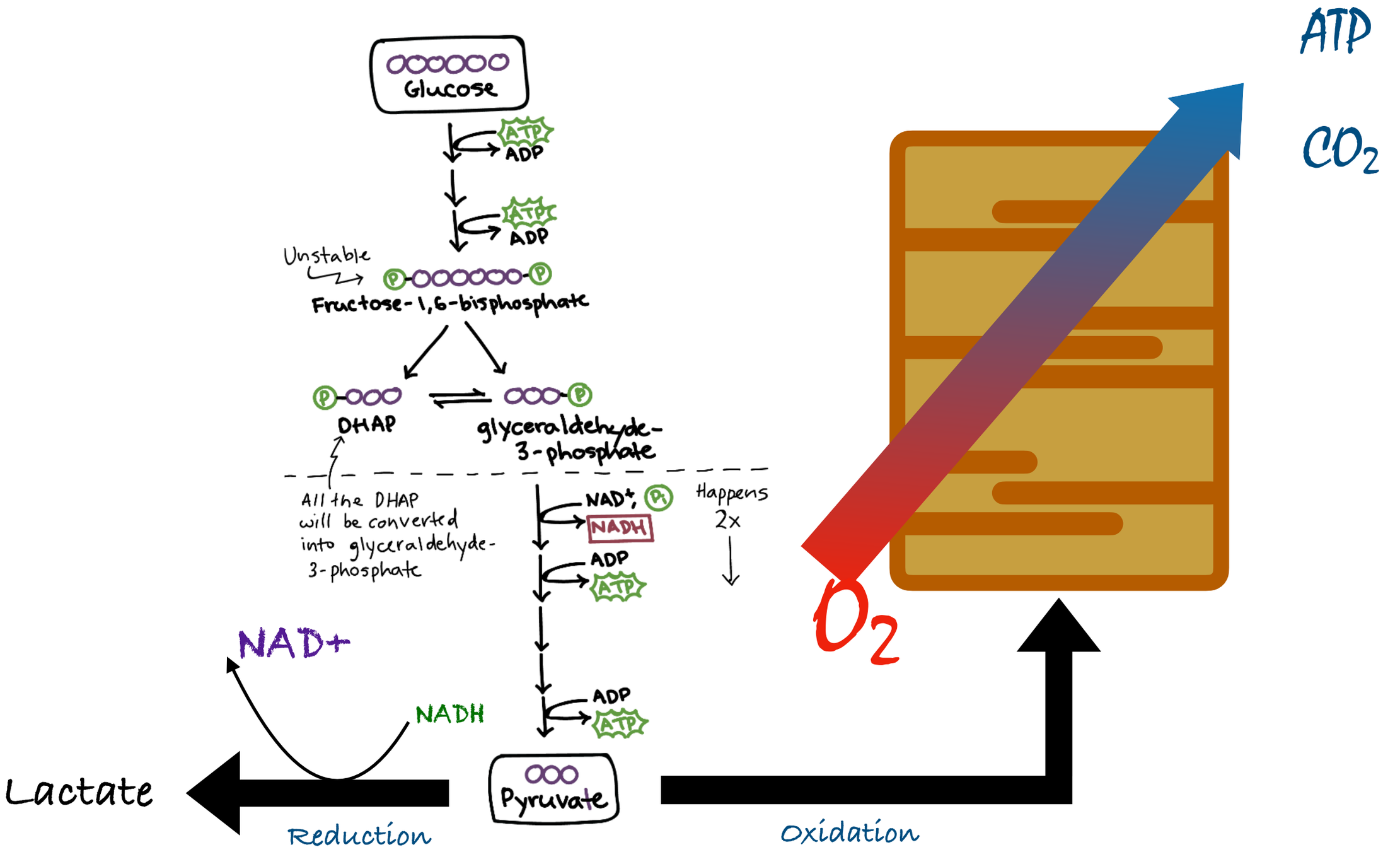
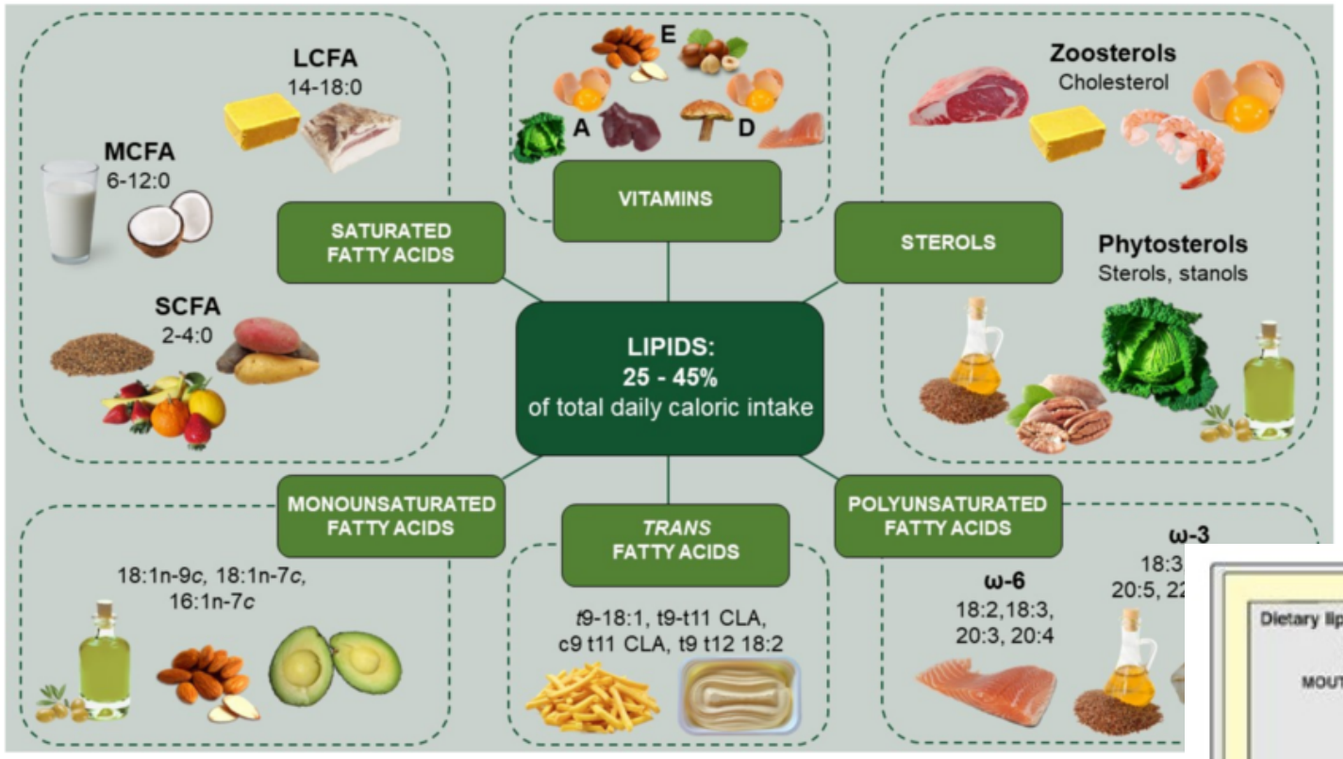


Central carbon metabolism: glycolysis

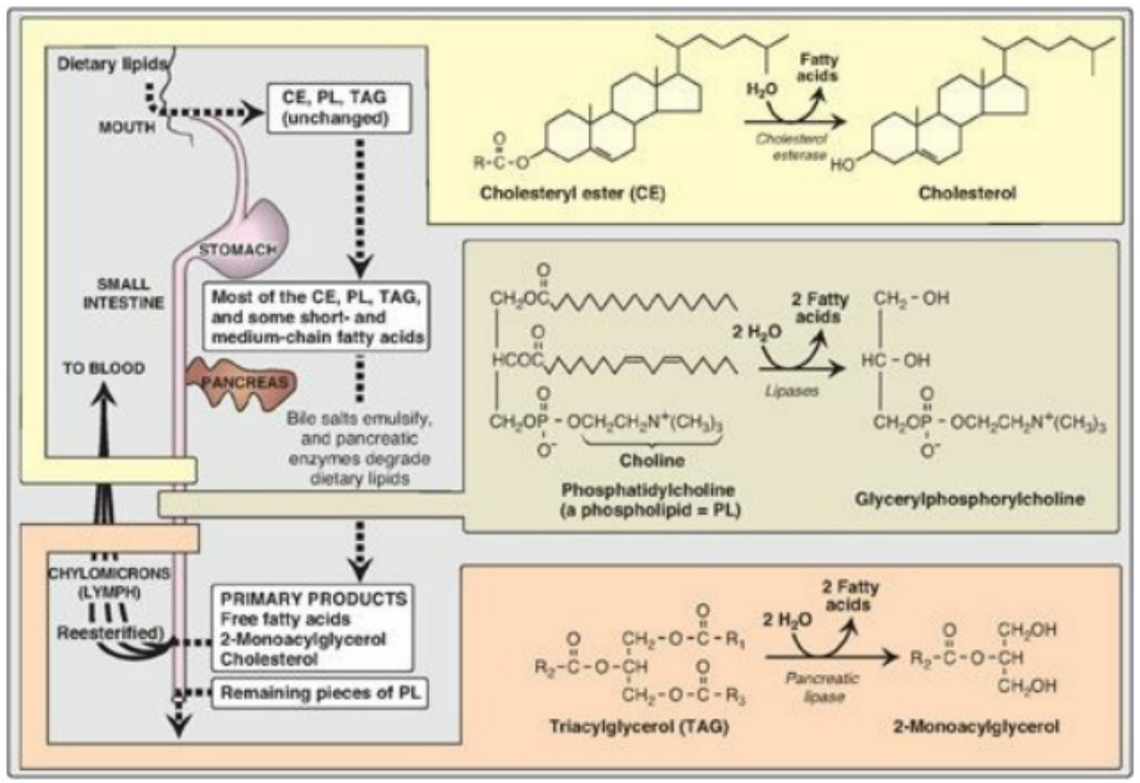


Main catabolic pathways: lipids

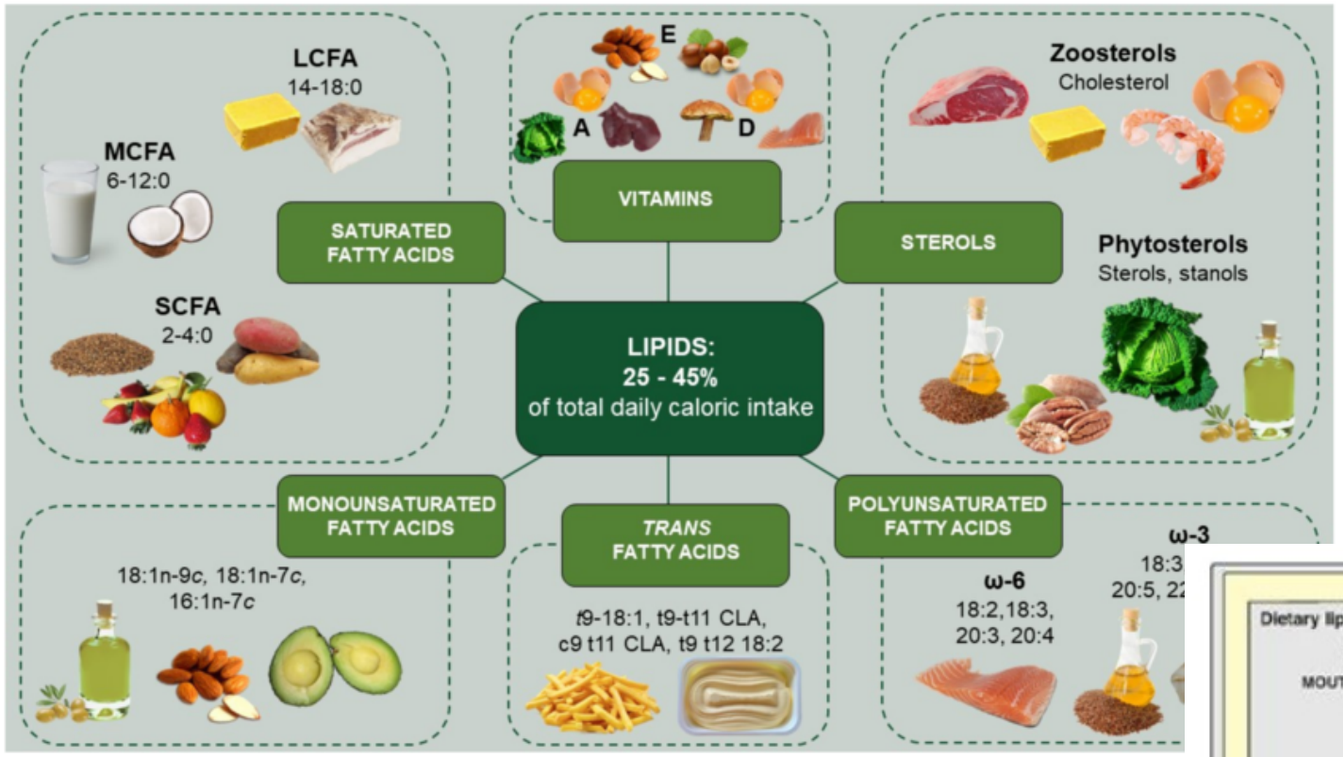


Diet comprises a large set of lipid species, but two primarily enter the circulation:

- Fatty acids (as TAGs)
- Cholesterol (as LDL/HDL particles)



Main catabolic pathways: lipids



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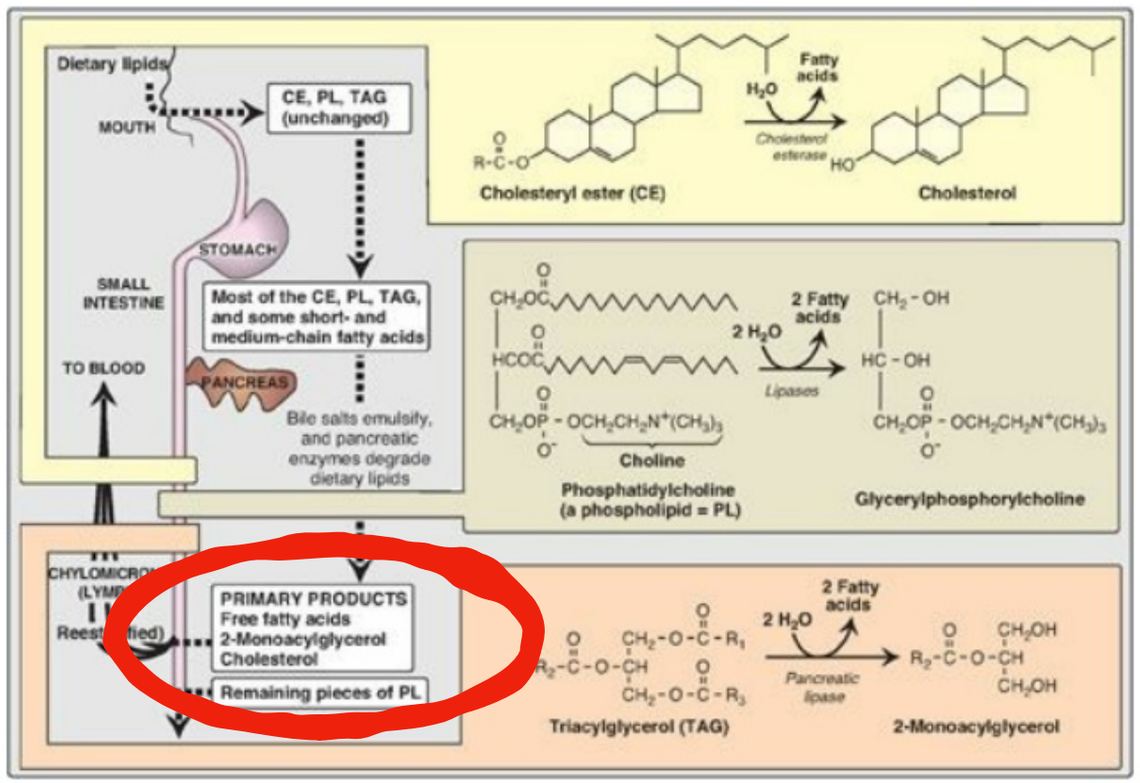
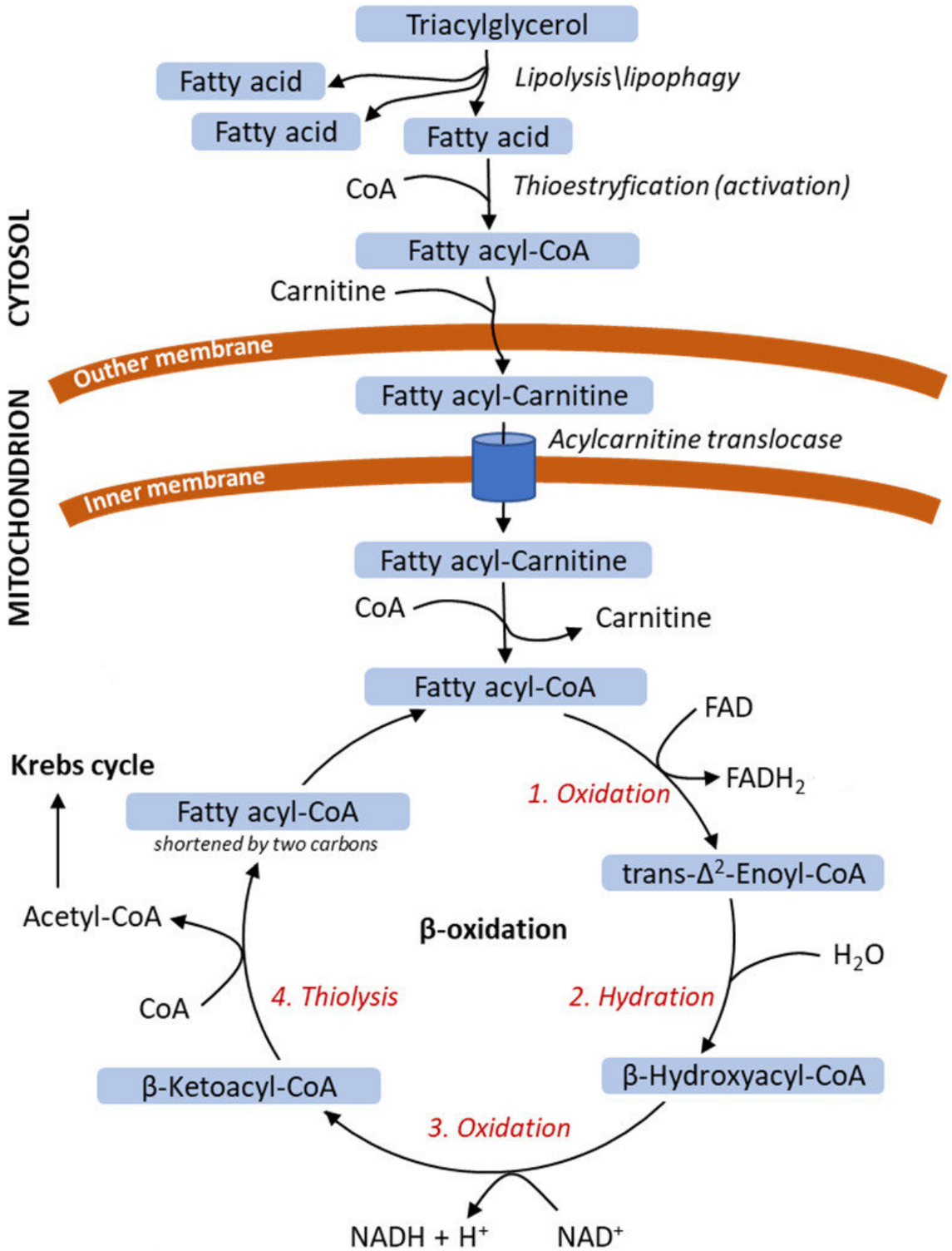
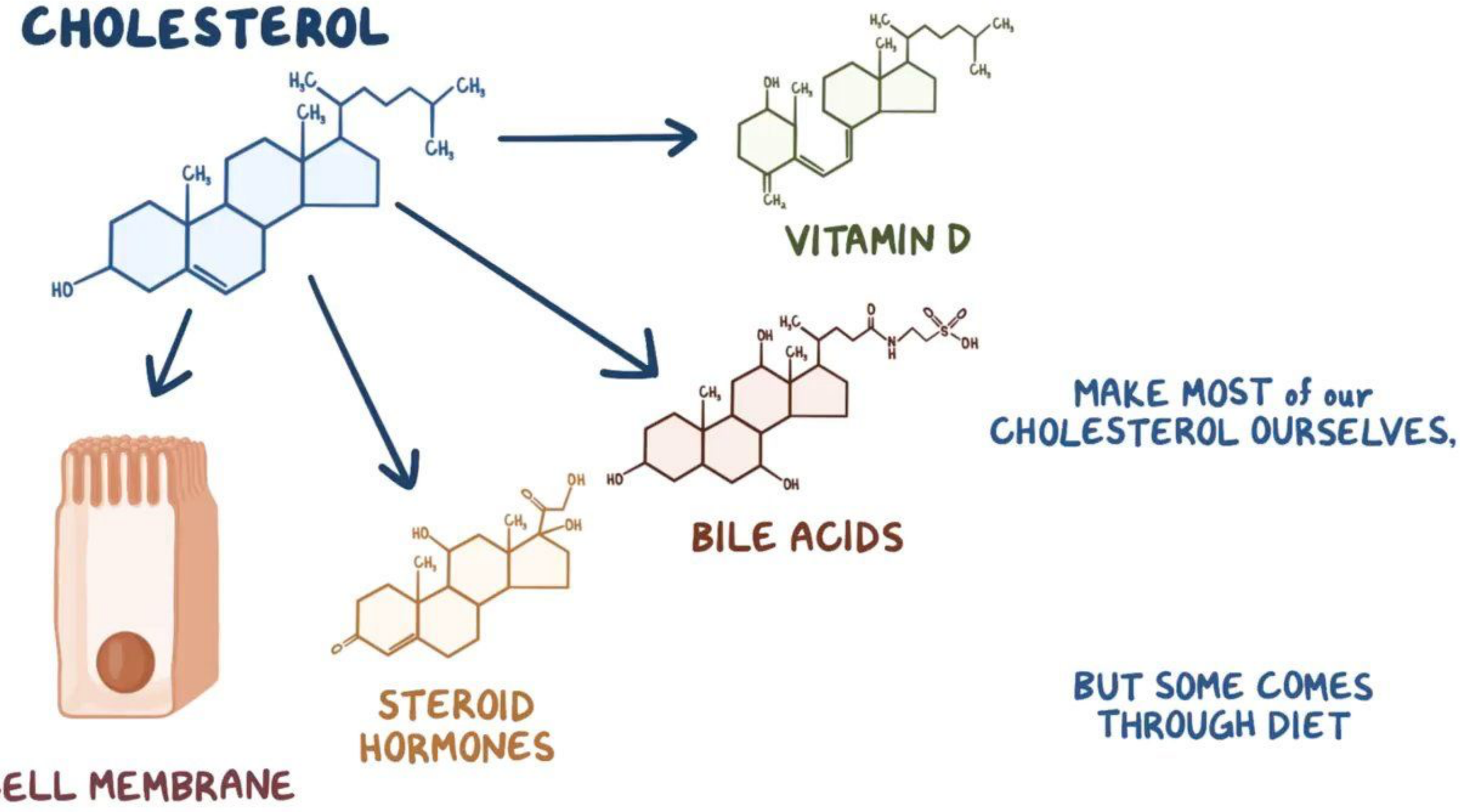


Main catabolic pathways: fatty acids oxidation (FAO)

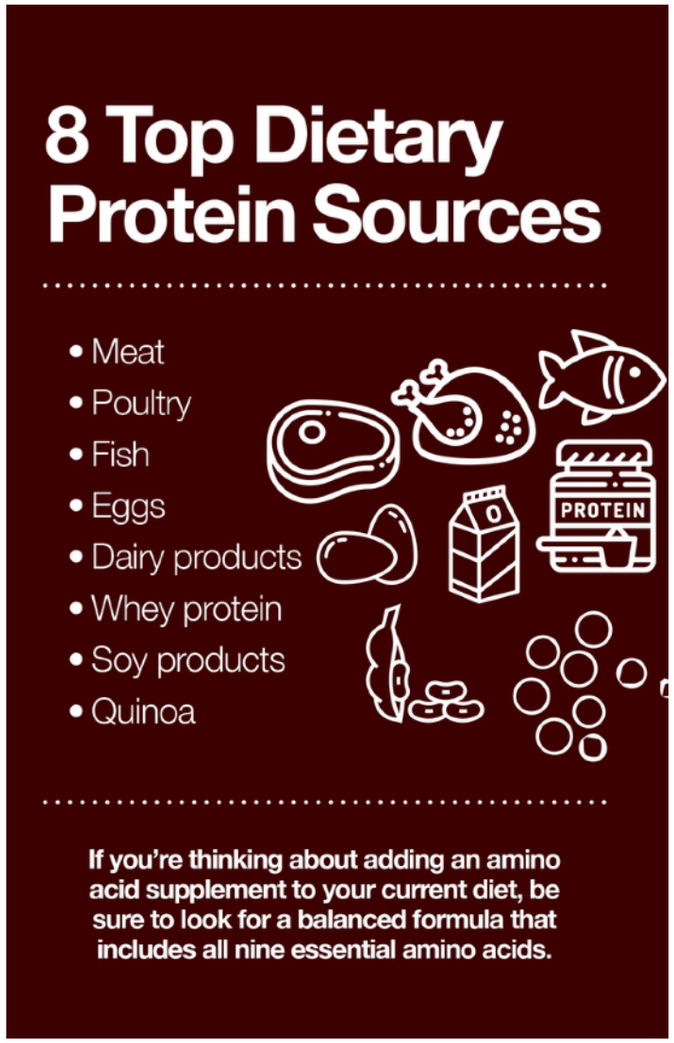


- Fatty acids are incorporated into the cell by dedicated transporters (e.g.: CD36)
- Fatty acids are activated by CoA ligation
- An acyl-carnitine shuttle brings them into the mitochondria
- Beta-ox of FA occurs in the mitochondrial matrix
- Beta-ox is a cyclic reaction that breaks FAs into multiple acetyl-CoA molecules (ANAPLEROSIS)
- Palmitoyl-CoA + 7CoA + 7NAD^+ + 7FAD + 7H_2O $\rightarrow\rightarrow$ 8Acetyl-CoA + 7NADH + 7$FADH_2$ + 7H^+
- Ton of ATP

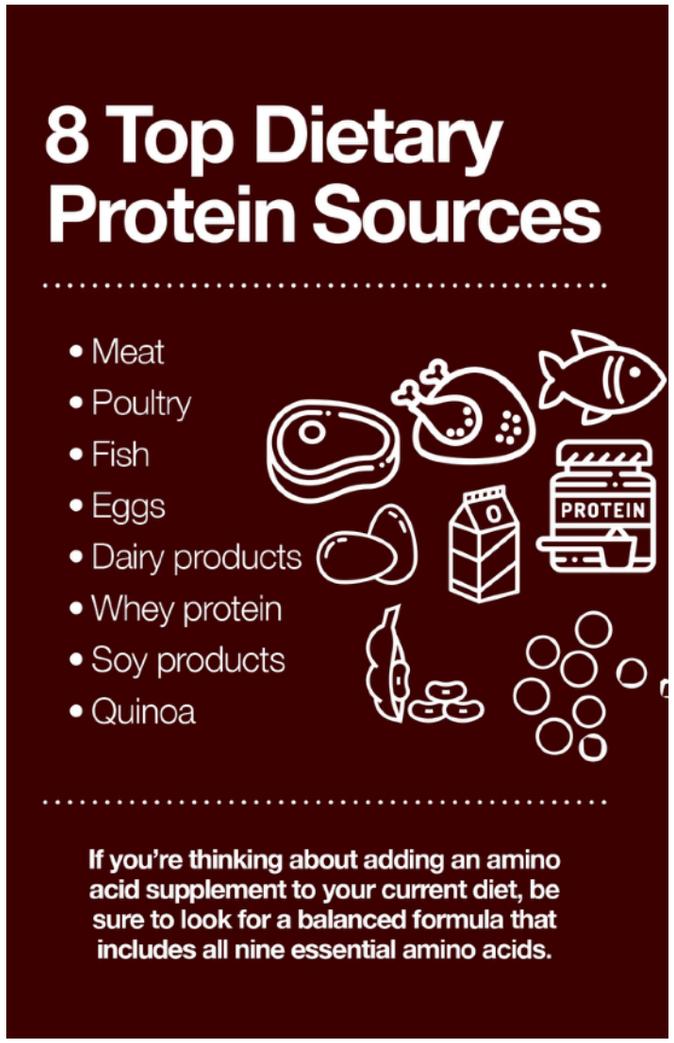
Main catabolic pathways: cholesterol is metabolically inert

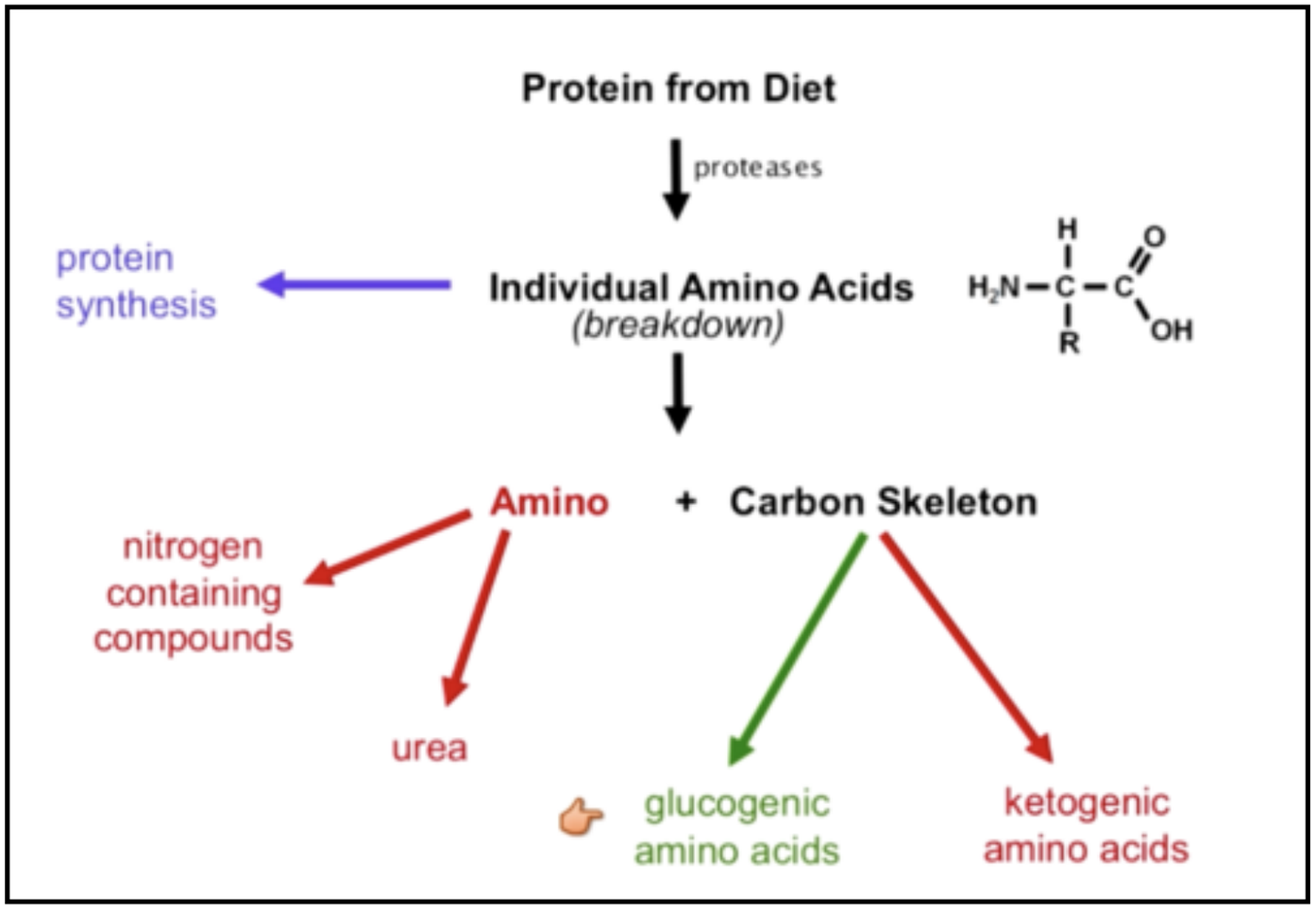


Main catabolic pathways: proteins and amino acids



Main catabolic pathways: proteins and amino acids

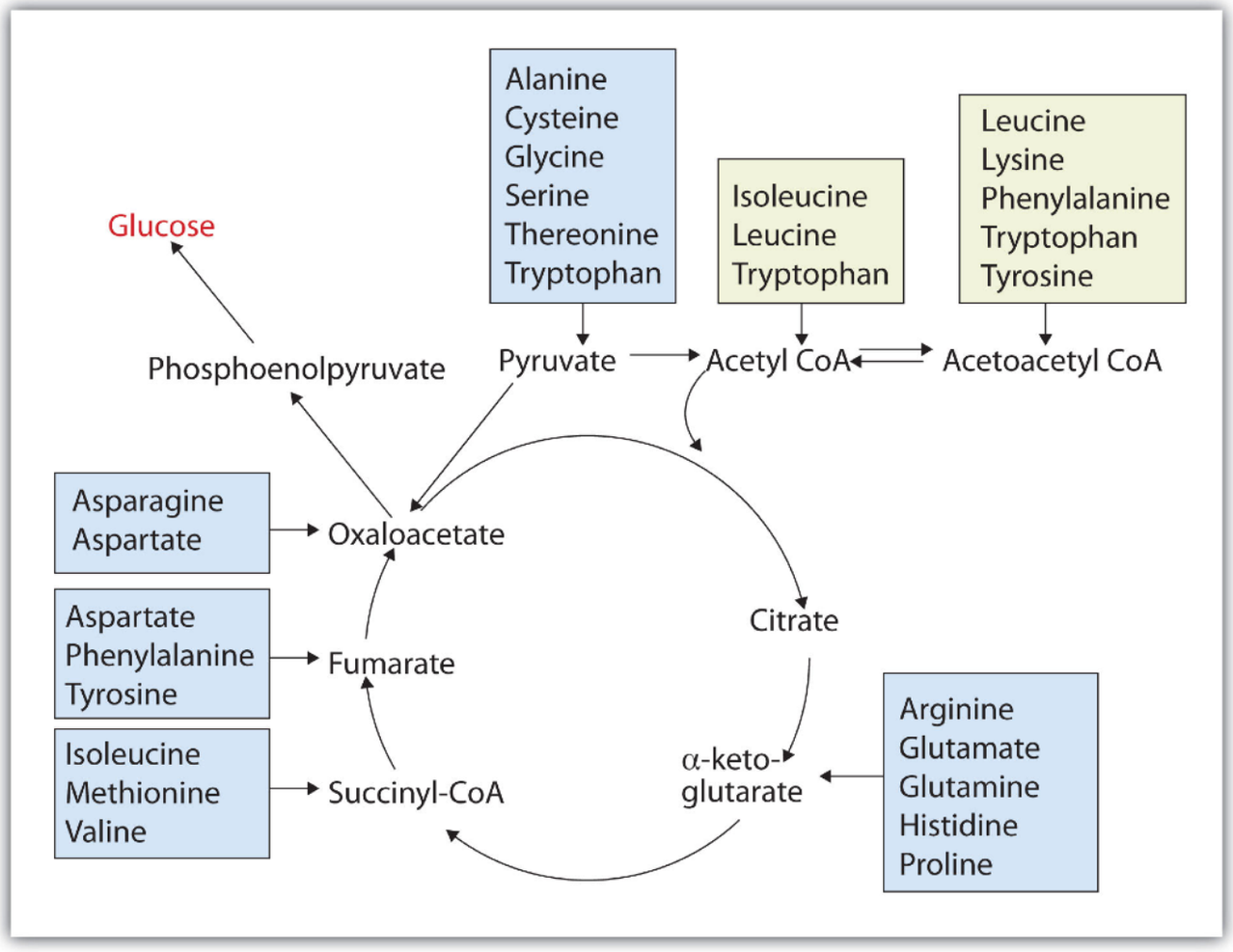




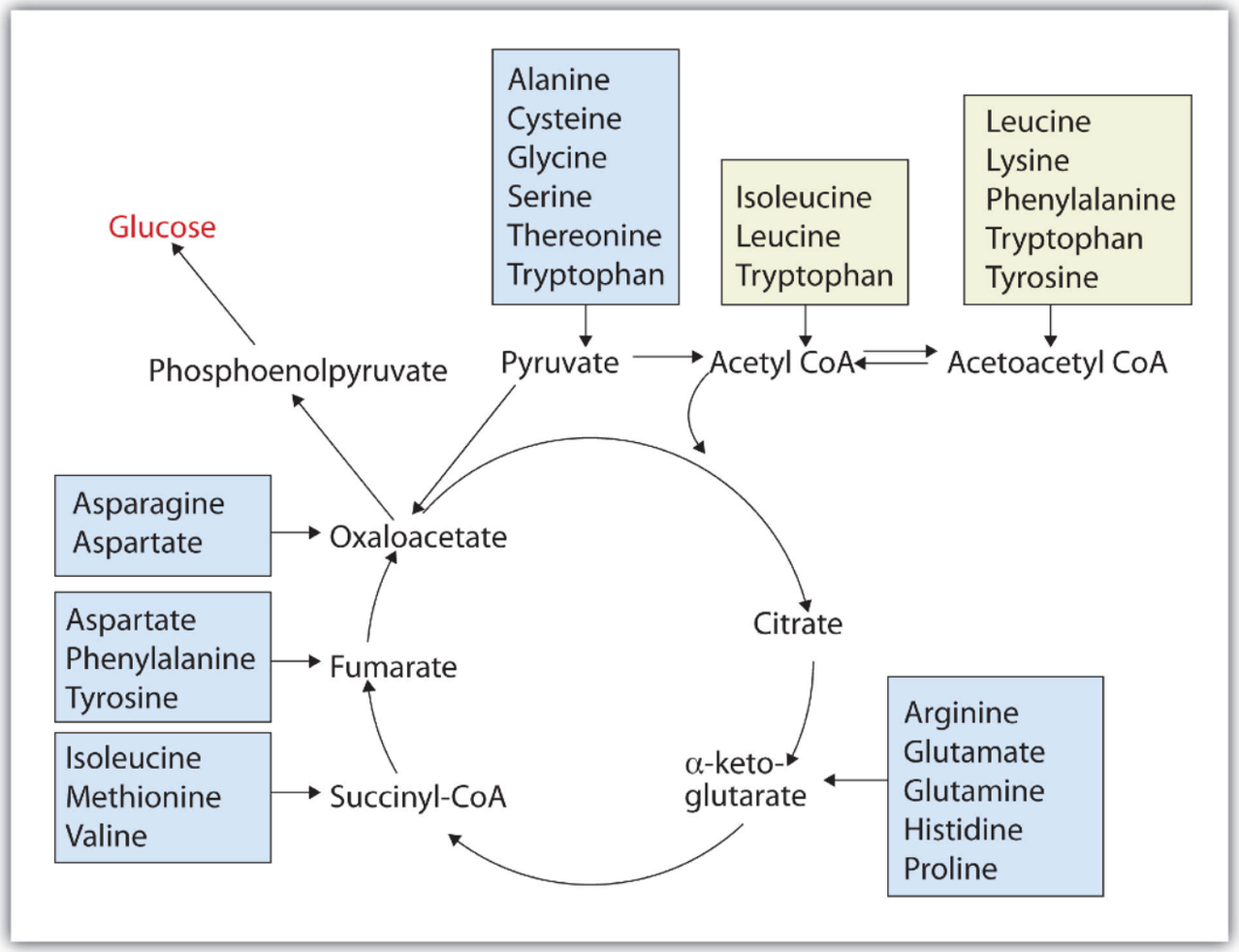
Transaminases swap nitrogen to and from different amino acid carbon backbones

Nitrogen groups can be funneled into nucleotide biosynthesis, synthesis of other amino acids, synthesis of bioactive amines, or the urea cycle

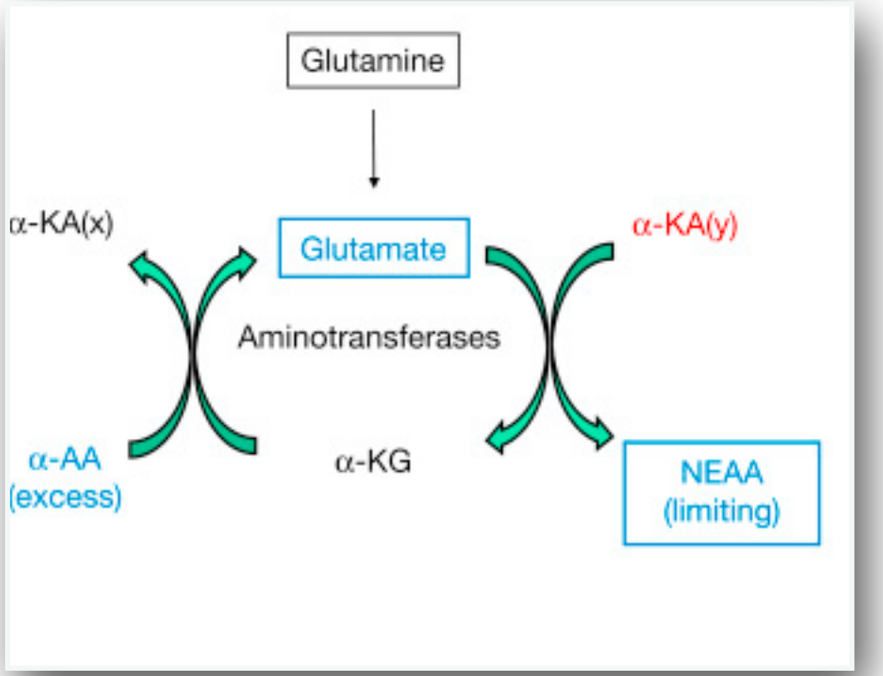
Main catabolic pathways: amino acids



Main catabolic pathways: amino acids

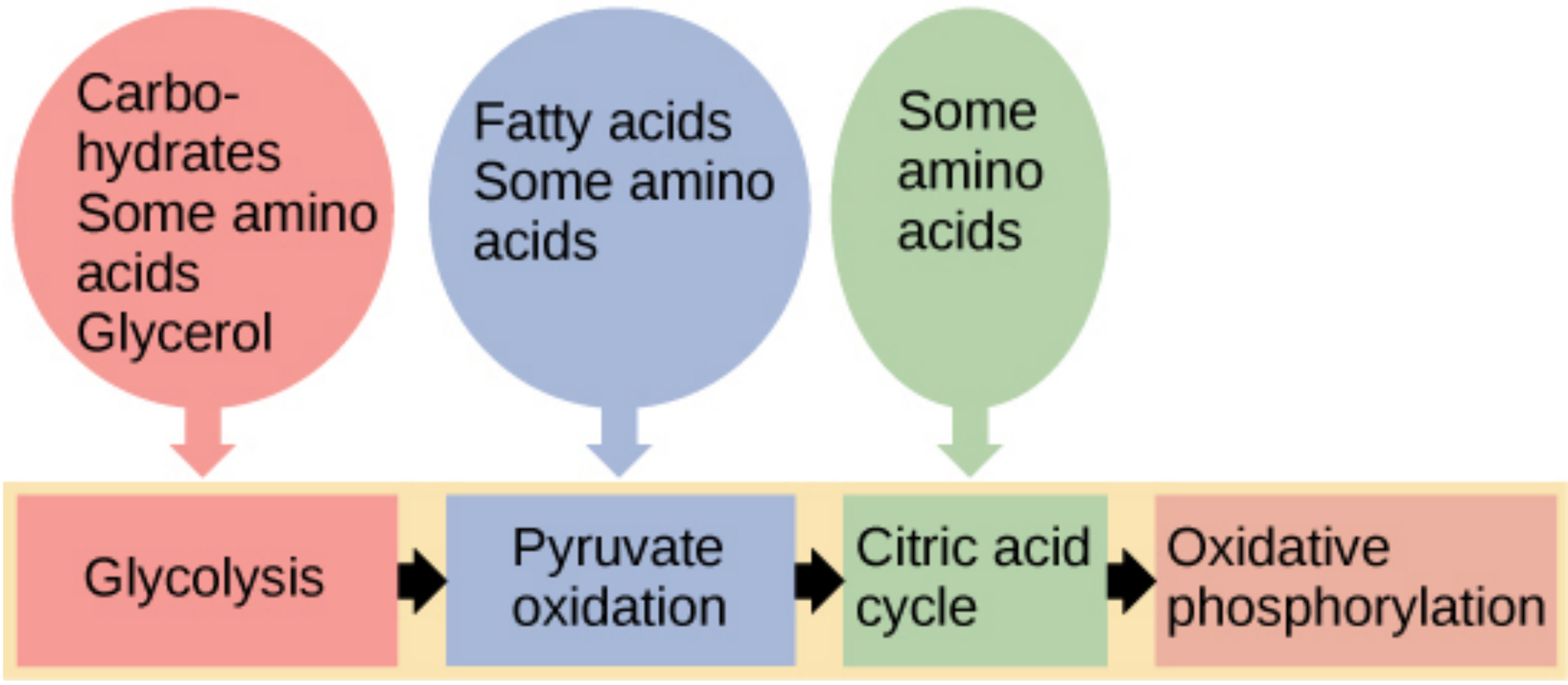


Glutaminolysis

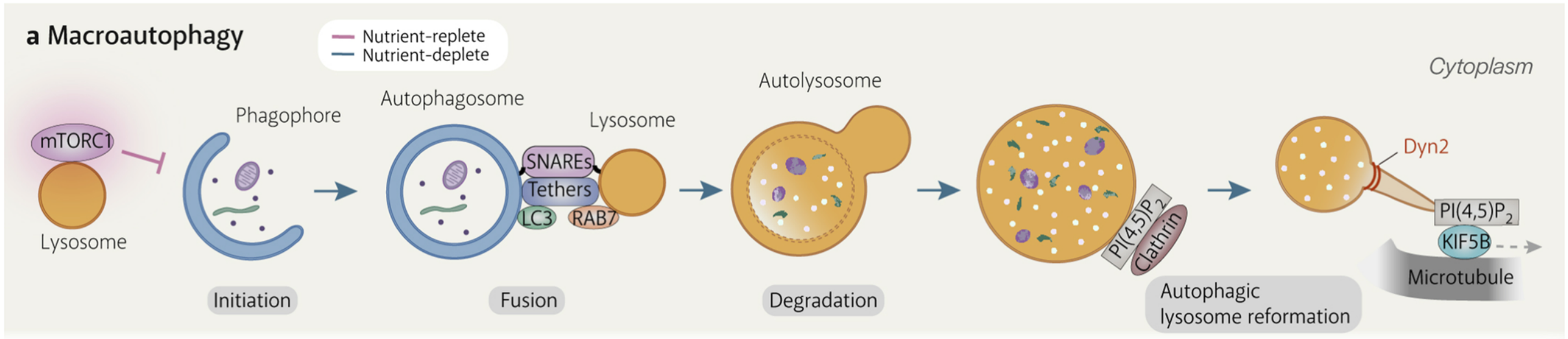


Glutamine is the most abundant EAA in the circulation

Multi-layer view of cell catabolism

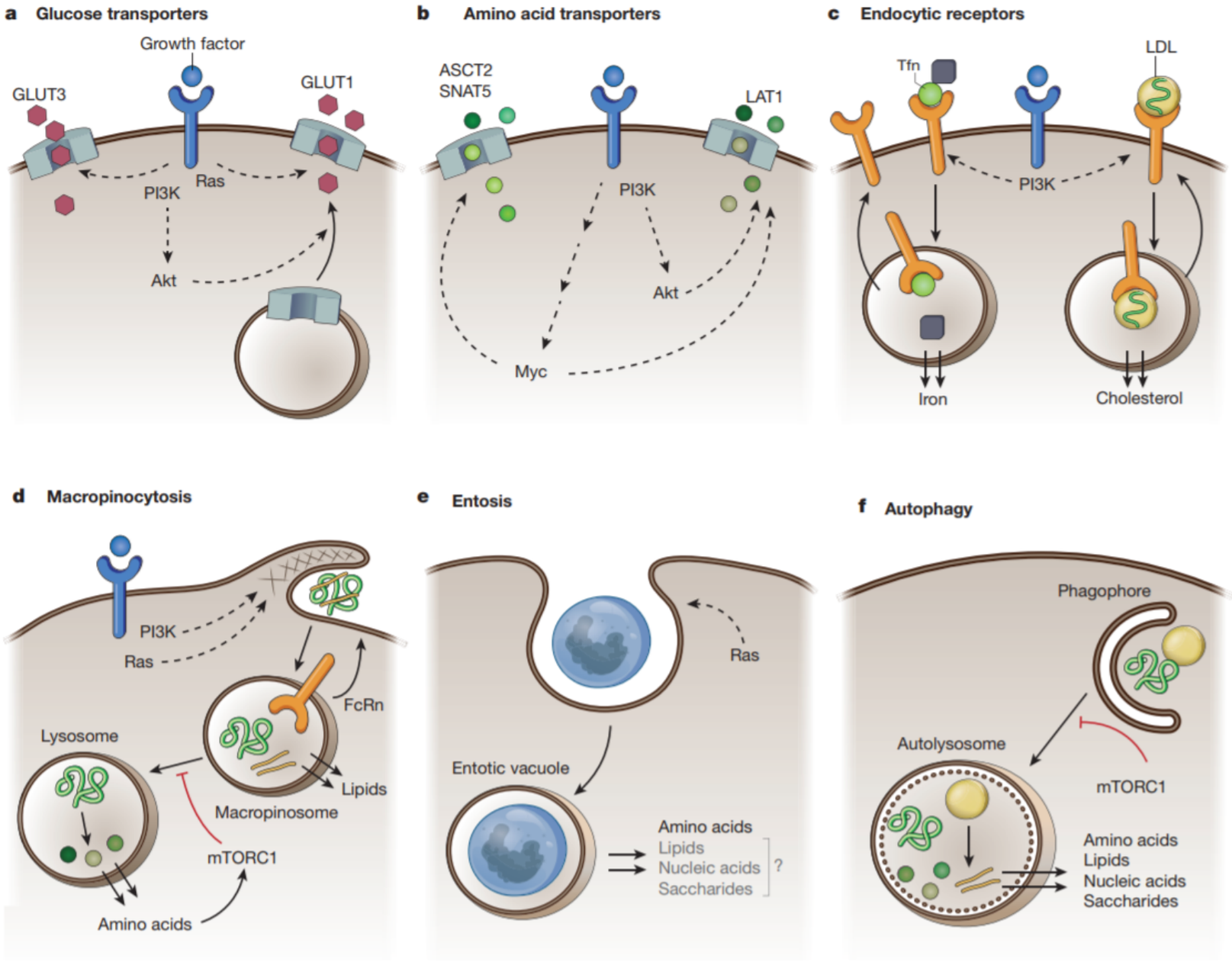


Unconventional catabolic pathway: AUTOPHAGY



- Self degradation of cellular proteins/structures within dedicated acidic compartments (lysosomes)
- Specific (targets exhausted proteins/organelles, or specific proteins)
- Inhibited in nutrient-replete conditions
- Triggered by nutrient sensors through the recruitment of ULK1 initiation complex
- Requires autophagy-related genes/proteins (ATGs)
- Marker: lipoylation of LC3

Catabolism can be opportunistic



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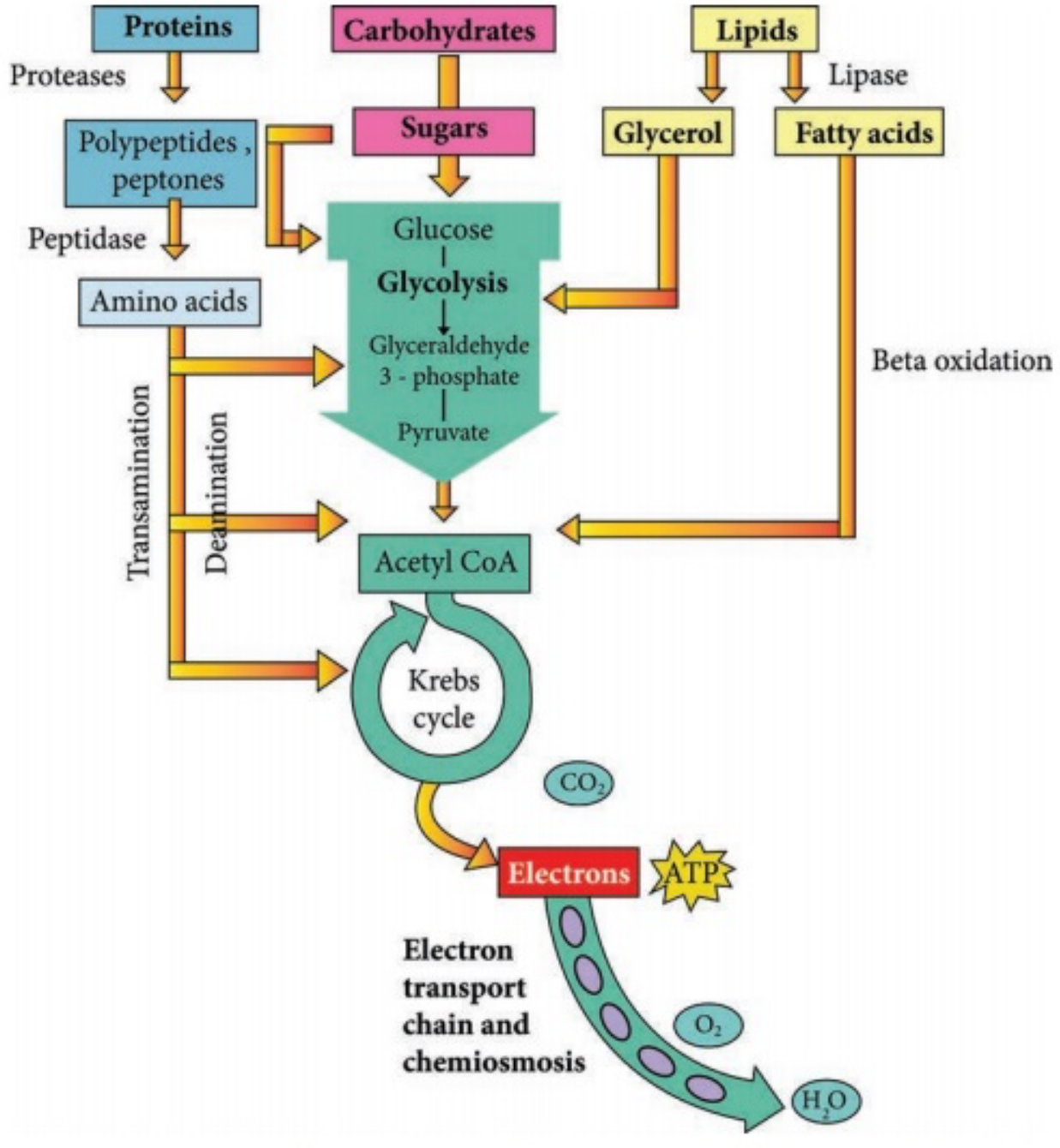
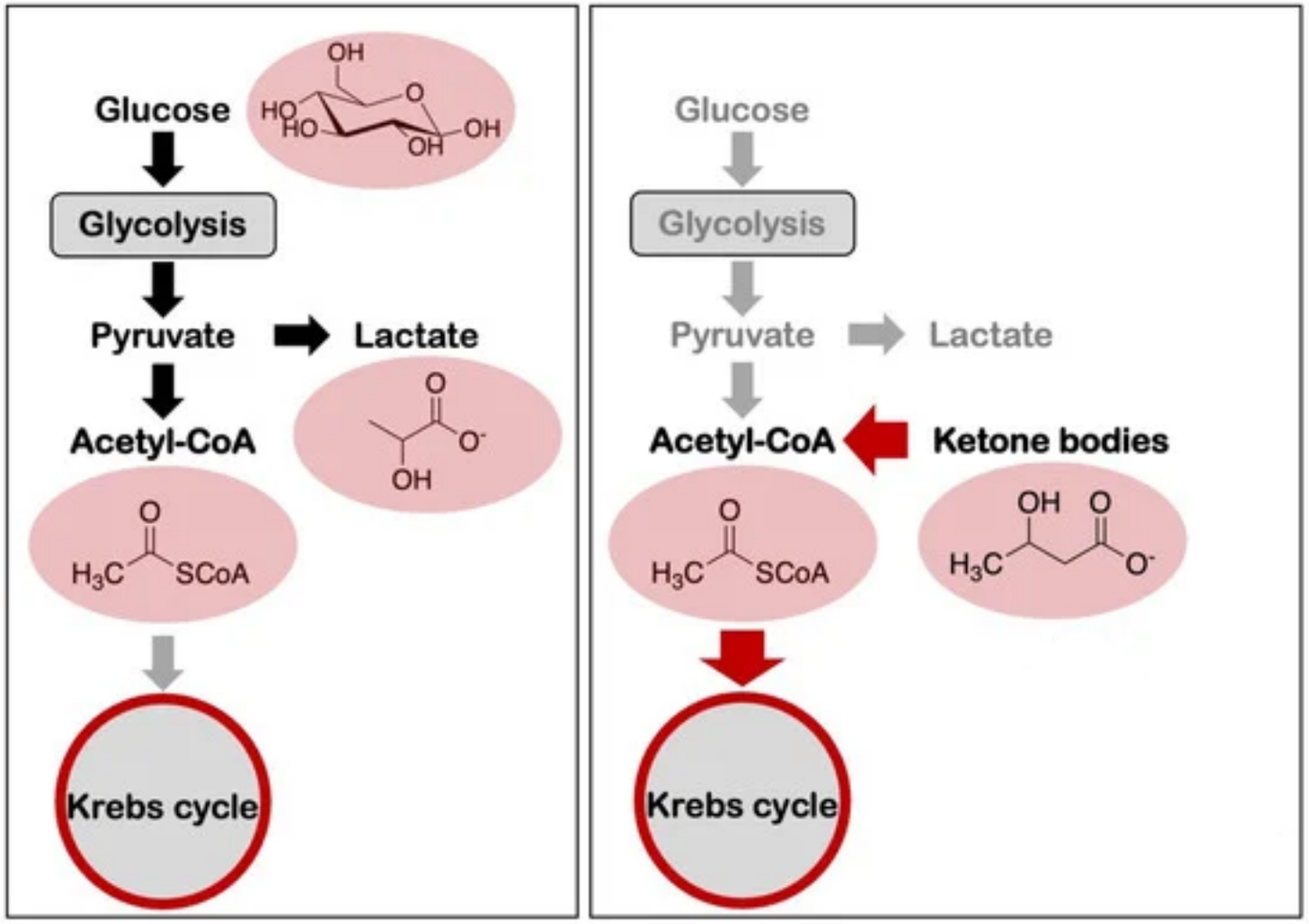


Figure 4.8: Overall Metabolism of Protein , Carbohydrates and Lipids

Cells can utilize non-canonical nutrients

Ketone bodies are small, water-soluble lipids (containing ketone group) that are produced in excess during fed state and can be mobilized as alternative energy source.



Also: lactate, uridine, inosine, SCFA, formate, vitamins, still growing……

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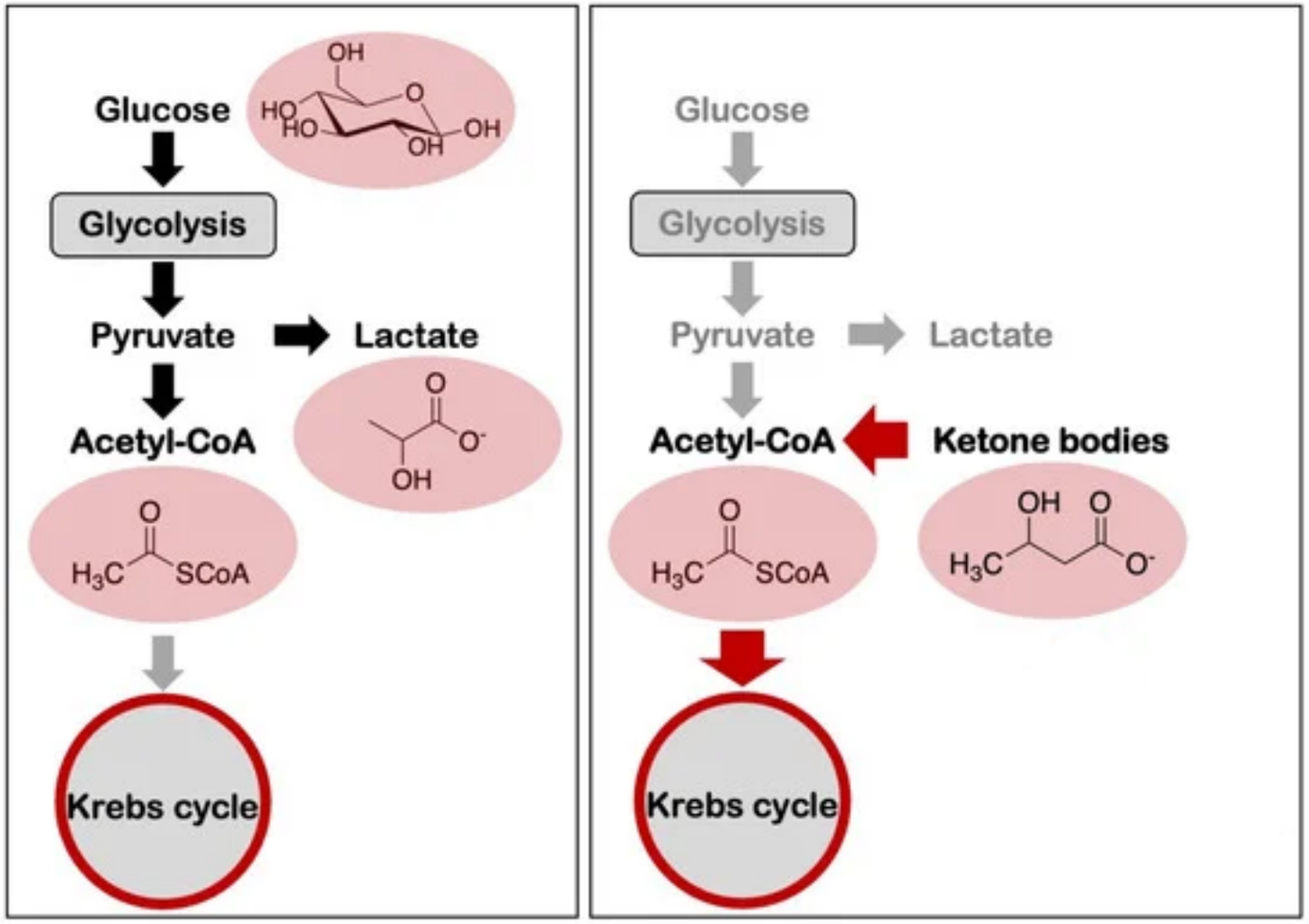
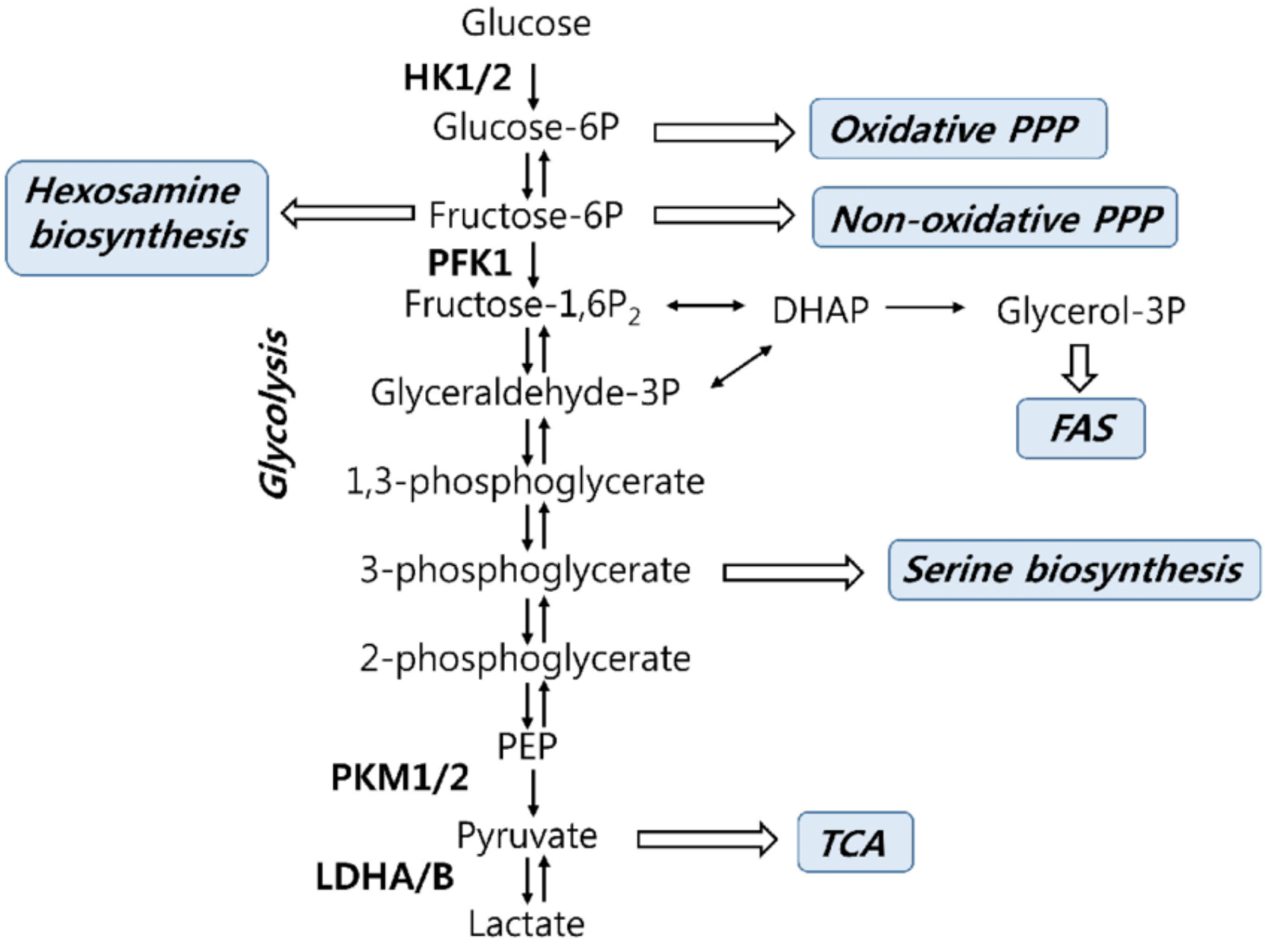


Also: lactate, uridine, inosine, SCFA, formate, vitamins, still growing……

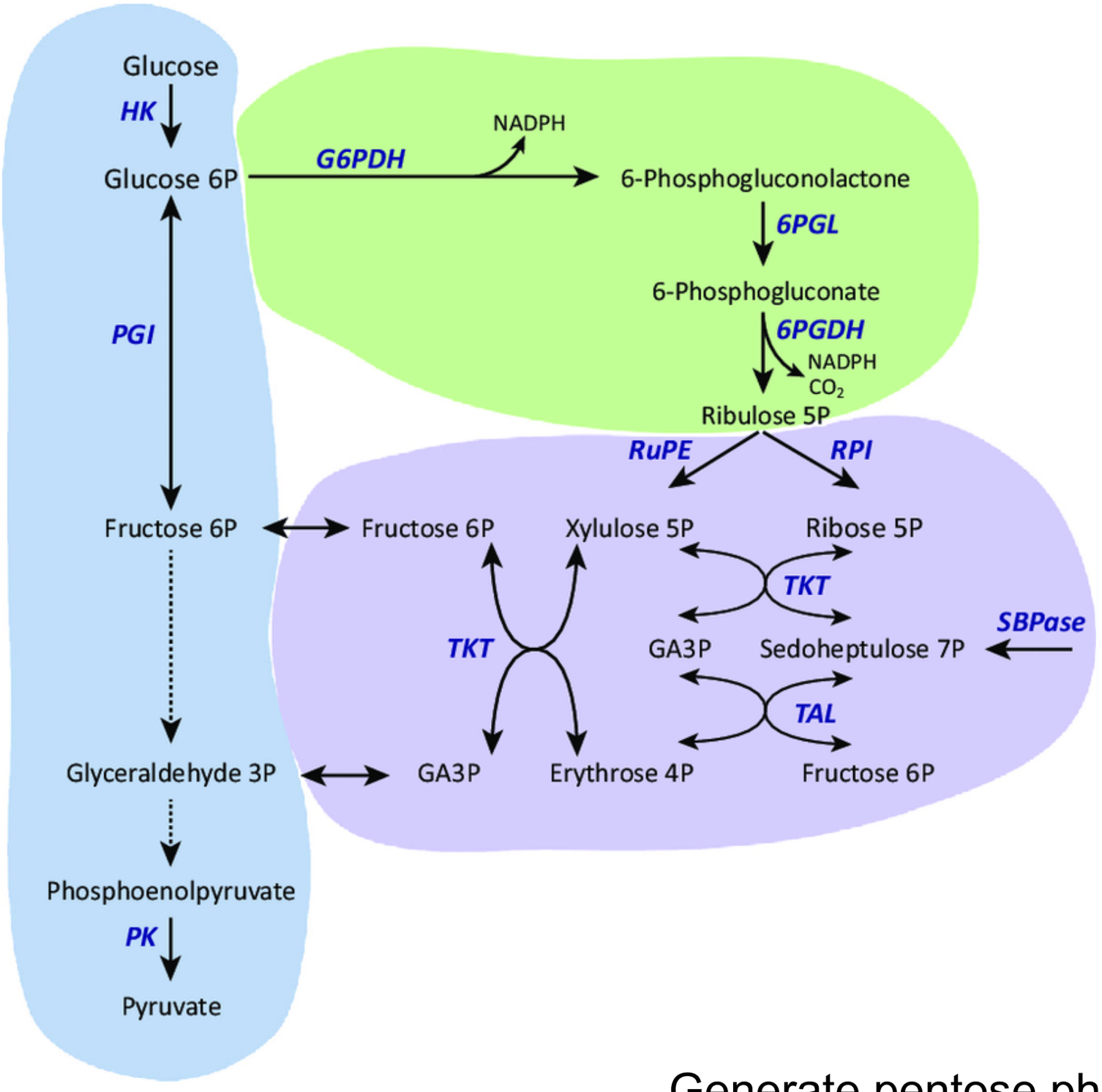
CARBON SOURCE: molecule that can provide carbon units to living cells for biosynthetic purposes

Main anabolic pathways

Typically linked to catabolic pathways (*ex: glycolysis branching pathways*)



Pentose Phosphate Pathway (PPP)



oxidative

non-oxidative

Generate pentose phosphates

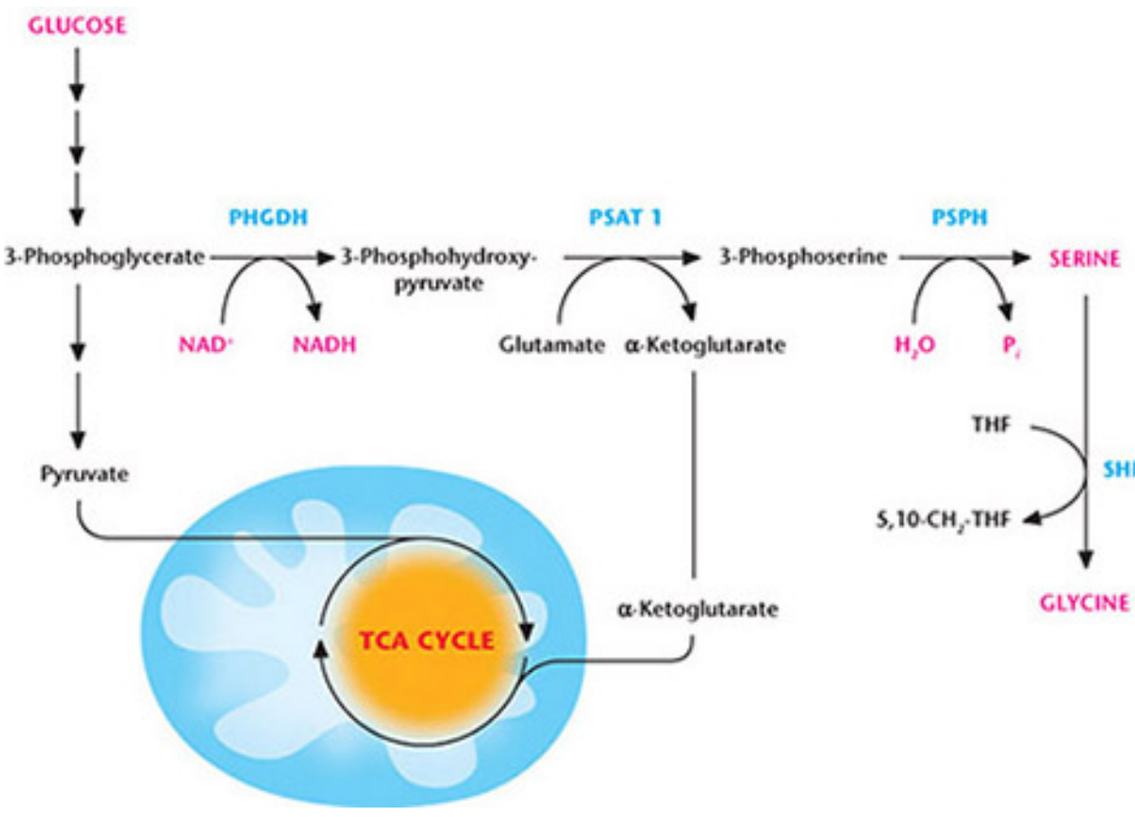
Serine/glycine pathway is a branch of glycolysis

Serine/glycine pathway is branch off glycolysis at 3-phosphoglycerate

3-phosphoglycerate dehydrogenase (PHGDH) requires NAD^+ (must have functional ETC)

Conversion of serine to glycine generate one-carbon folate units for methylation (DNA/RNA/protein) and nucleotide biosynthesis

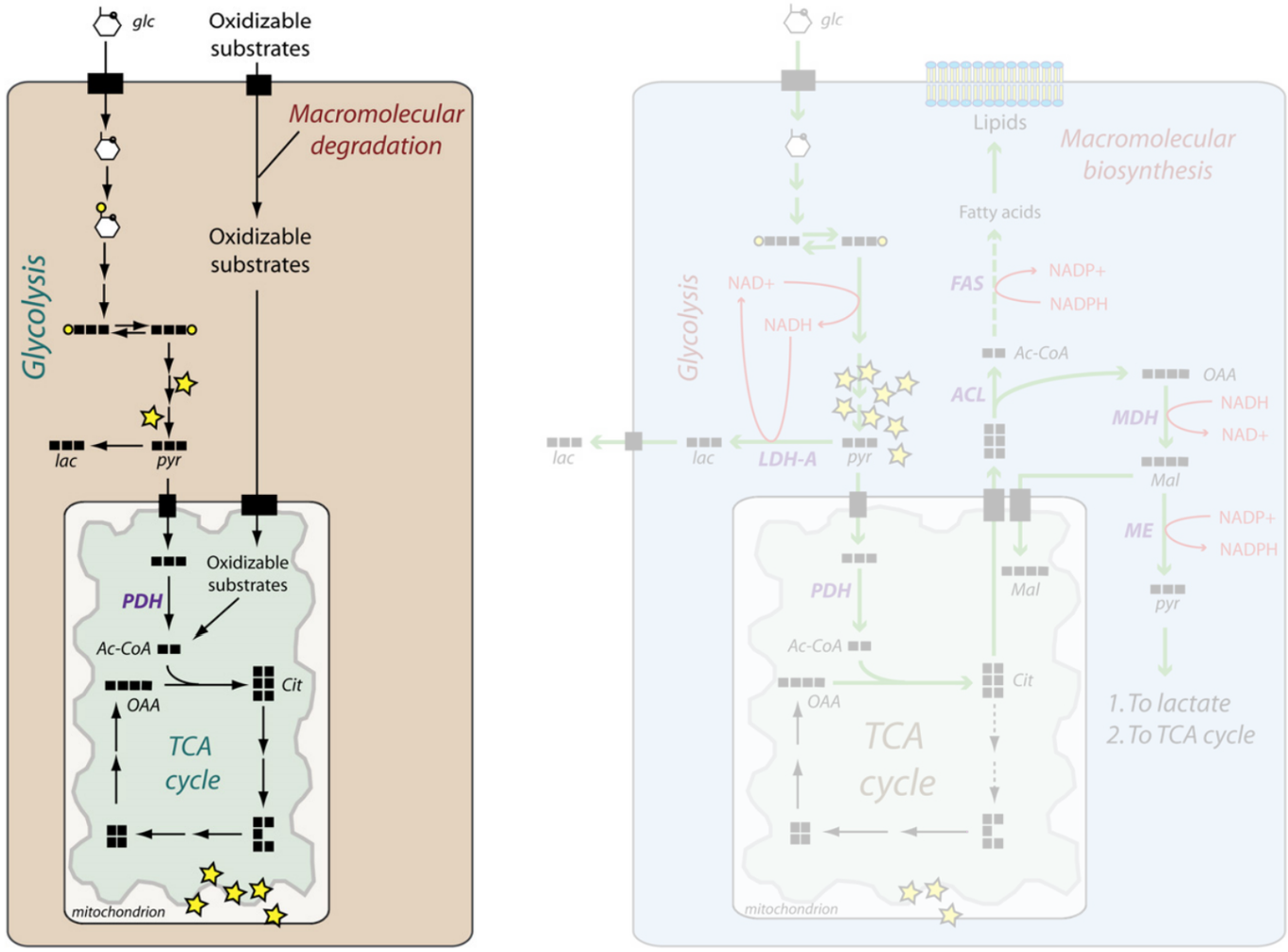
PHGDH is amplified in several cancers



Chandel “Navigating Metabolism”

Main anabolic pathways

Mitochondria are major metabolic hubs



DeBerardinis RJ, Thompson CB, ***Cell Metab****, 2008*

Main anabolic pathways

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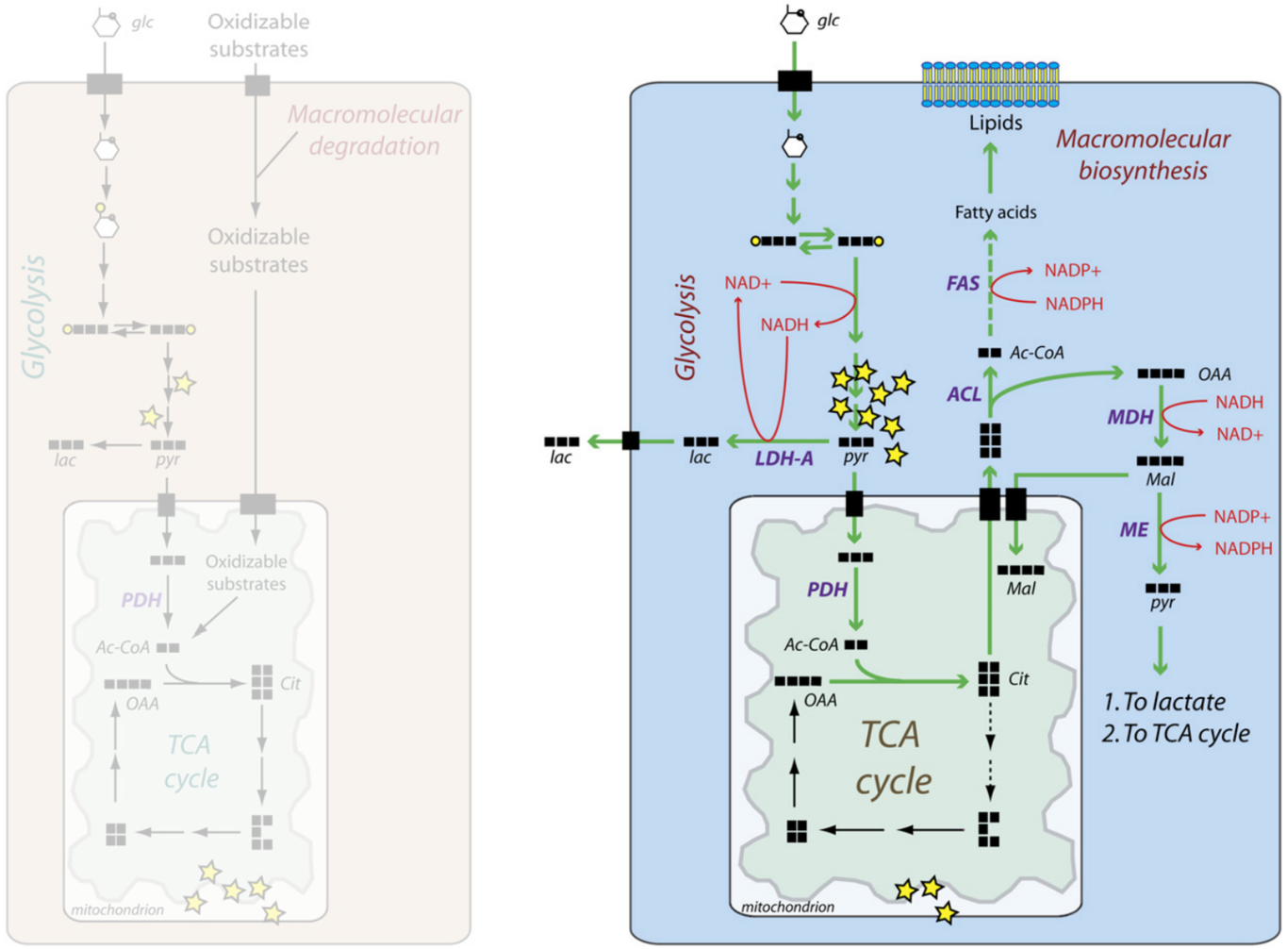

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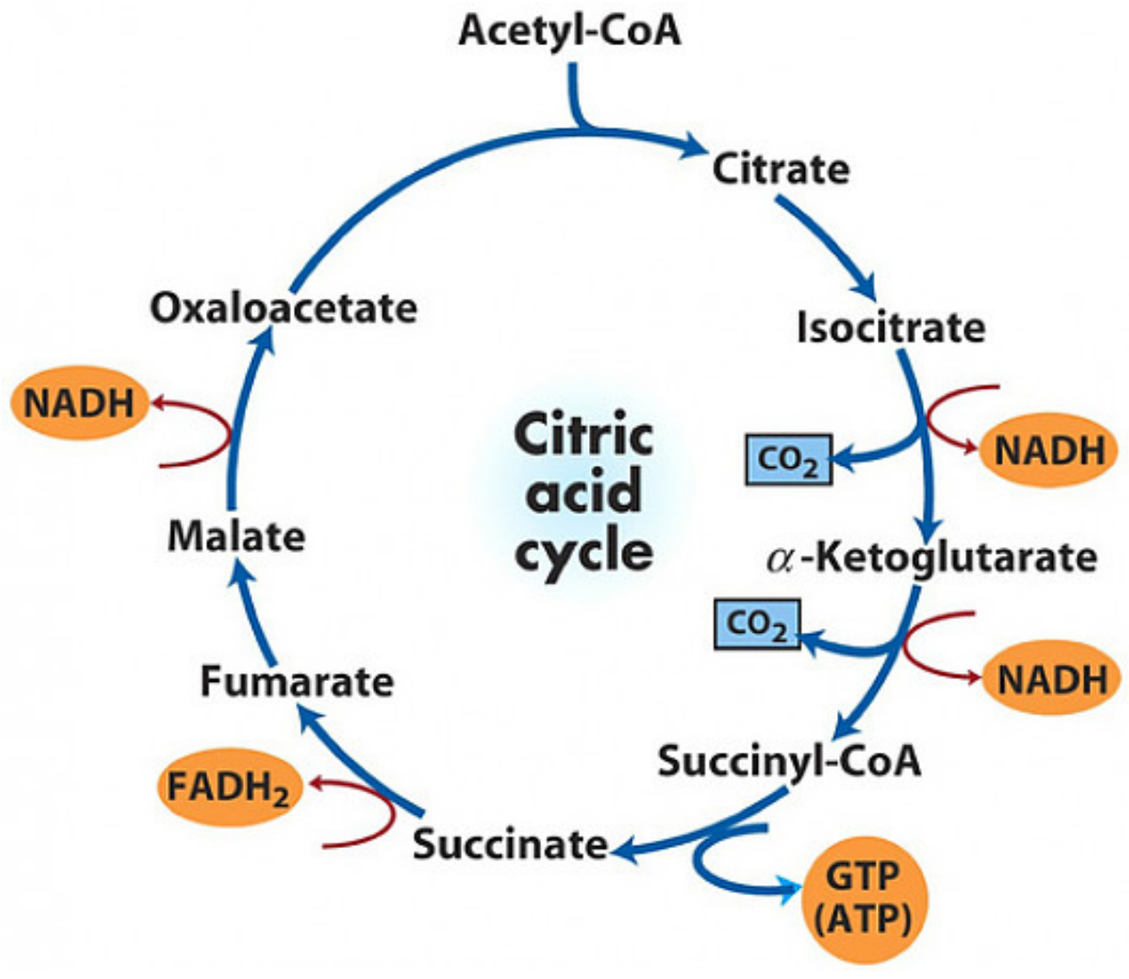
The TCA cycle at the crossroad of catabolism and anabolism



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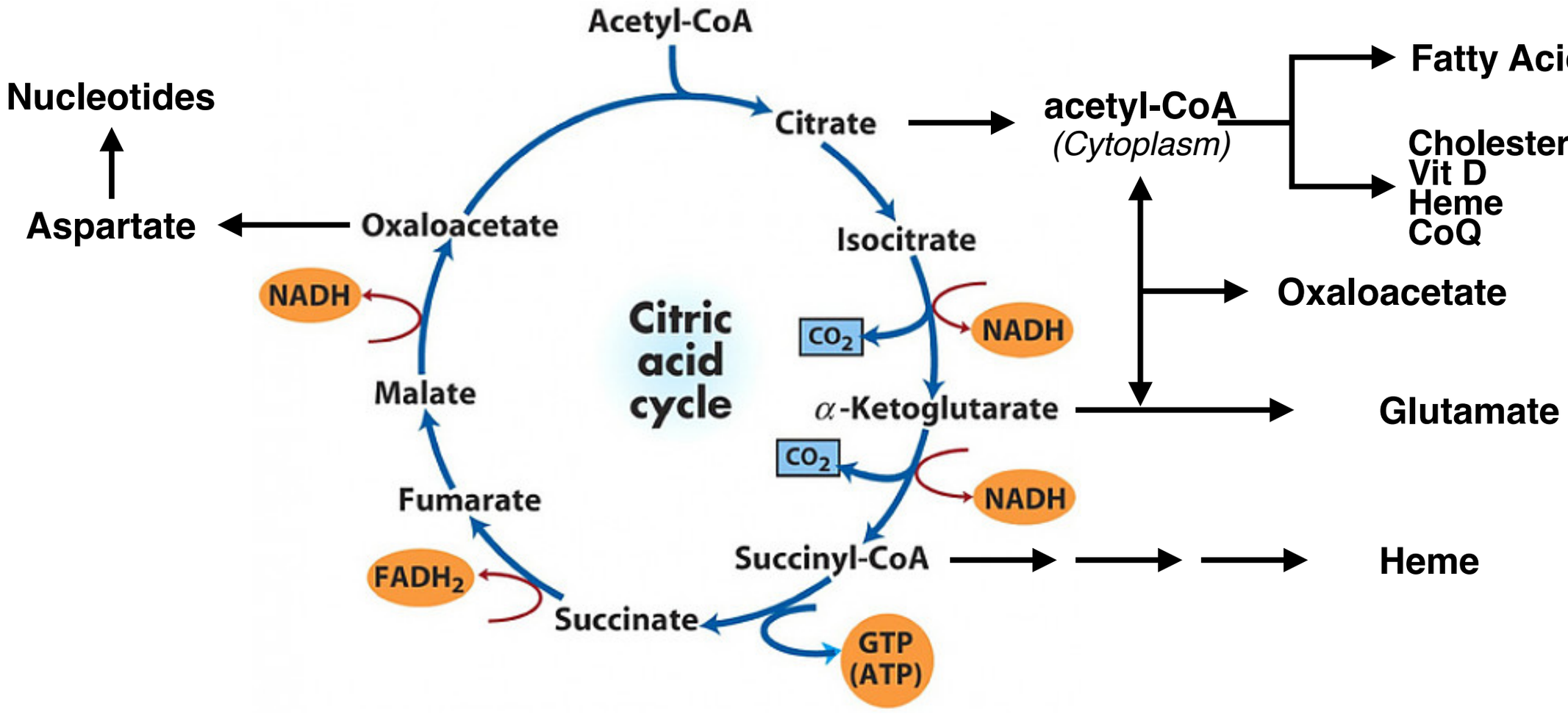


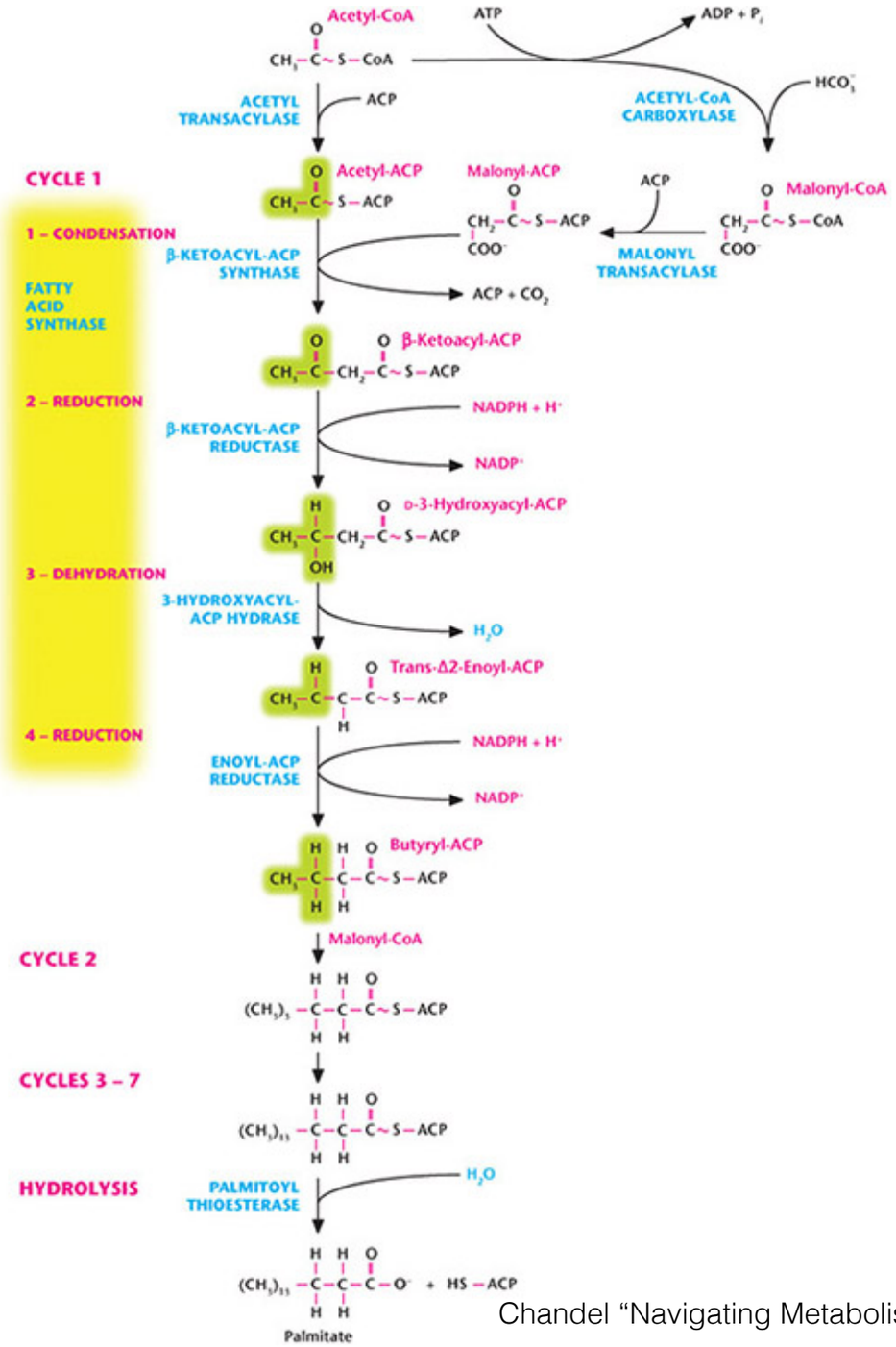
Fatty acid synthesis

Fatty acid synthesis is an iterative elongation by 2-carbon acetyl-CoA units and reduction by NADPH

Acetyl-CoA carboxylase is key enzyme regulating fatty acid synthesis

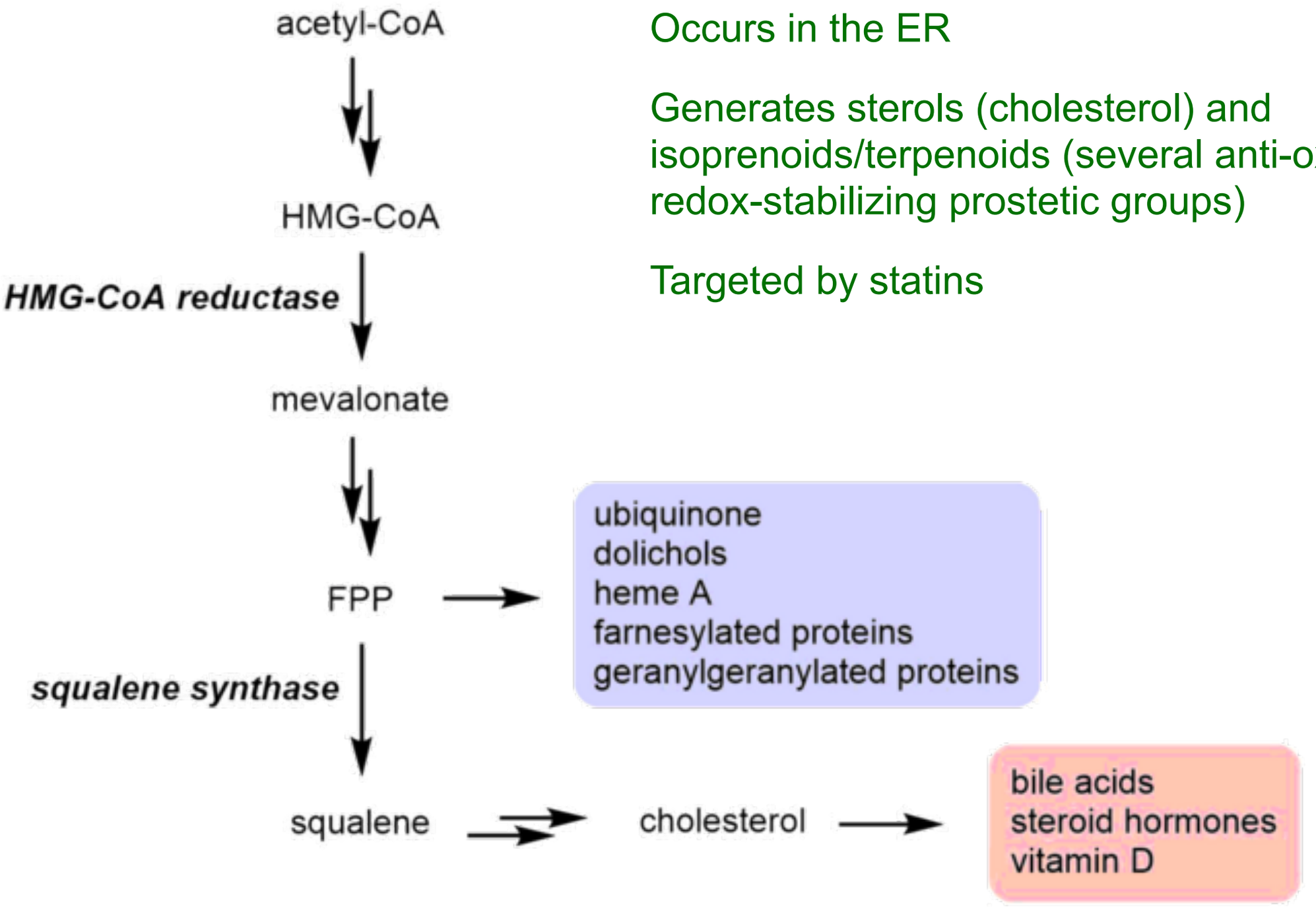
- ACC uses ATP to carboxylate acetyl-CoA and make 3-carbon malonyl-CoA
- Malonyl-CoA condenses with first with acetyl-CoA, then repeatedly with elongating fatty acid chain, each time undergoing decarboxylation, in effect adding acetyl-CoA units (coupling elongation to decarboxylation of malonyl-CoA is energetically favorable)

2 NADPH are used to reduce each acetyl-CoA unit



Chandel "Navigating Metabolism"

Mevalonate Pathway

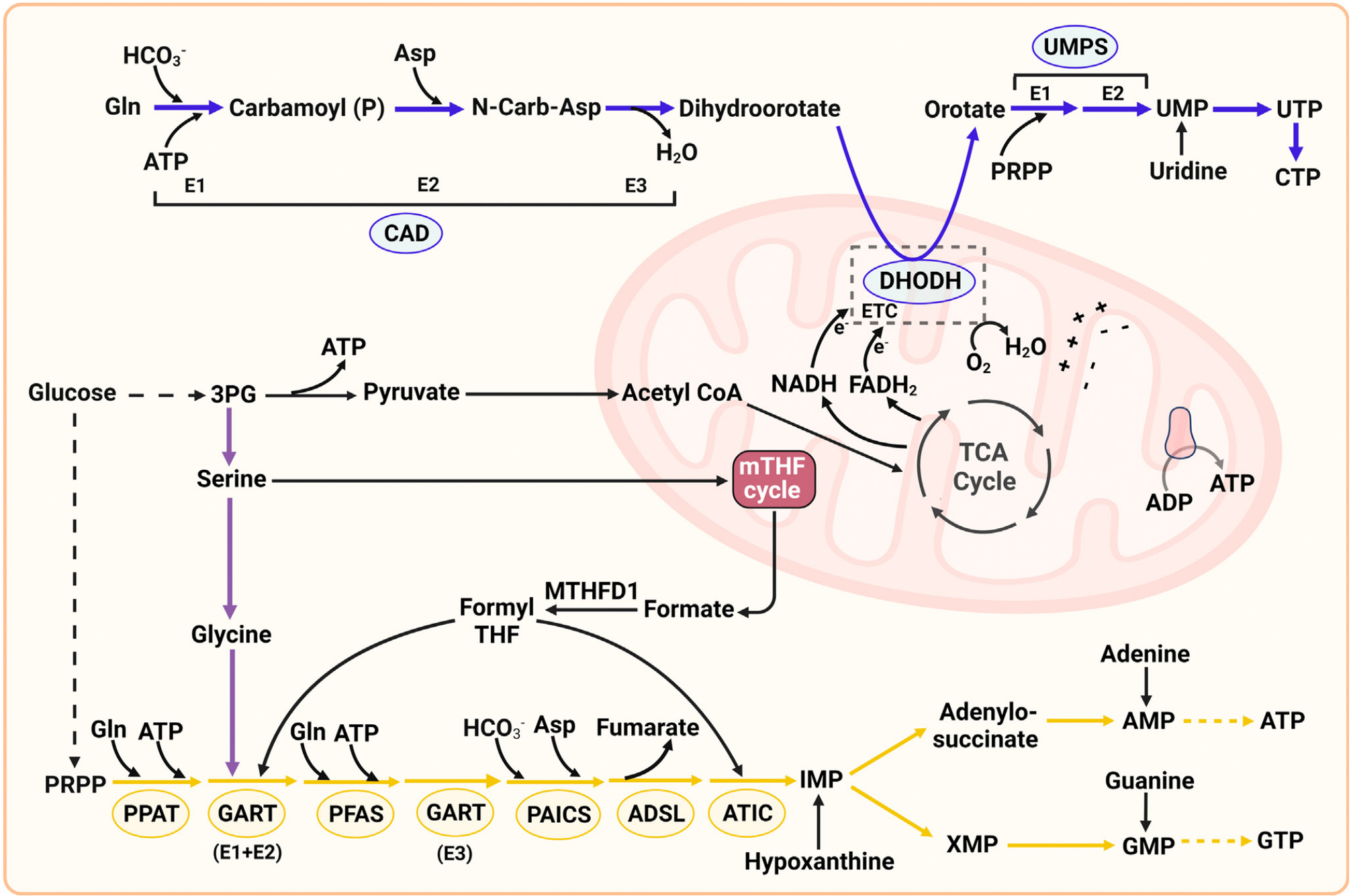


Occurs in the ER

Generates sterols (cholesterol) and isoprenoids/terpenoids (several anti-oxidants or redox-stabilizing prostetic groups)

Targeted by statins

Nucleotide synthesis



Critically different for purines (double ring: 6C+5C) and pyrimidines (one ring: 5C)

Nucleotide synthesis

Different for purines and pyrimidines

Purines nucleotide synthesis begins with 5-phosphoribosyl-1-pyrophosphate (PRPP) which ultimately is converted to inosine-5'-monophosphate (IMP)

Requires glutamine, glycine, aspartate (NAD^+), one carbon folate units, and lots of ATP

IMP can be converted to AMP->ADP or GMP->GDP (IMP->GMP directly requires NAD^+, while IMP->AMP requires aspartate)

Humans cannot catabolize purine rings; partial catabolism produces uric acid

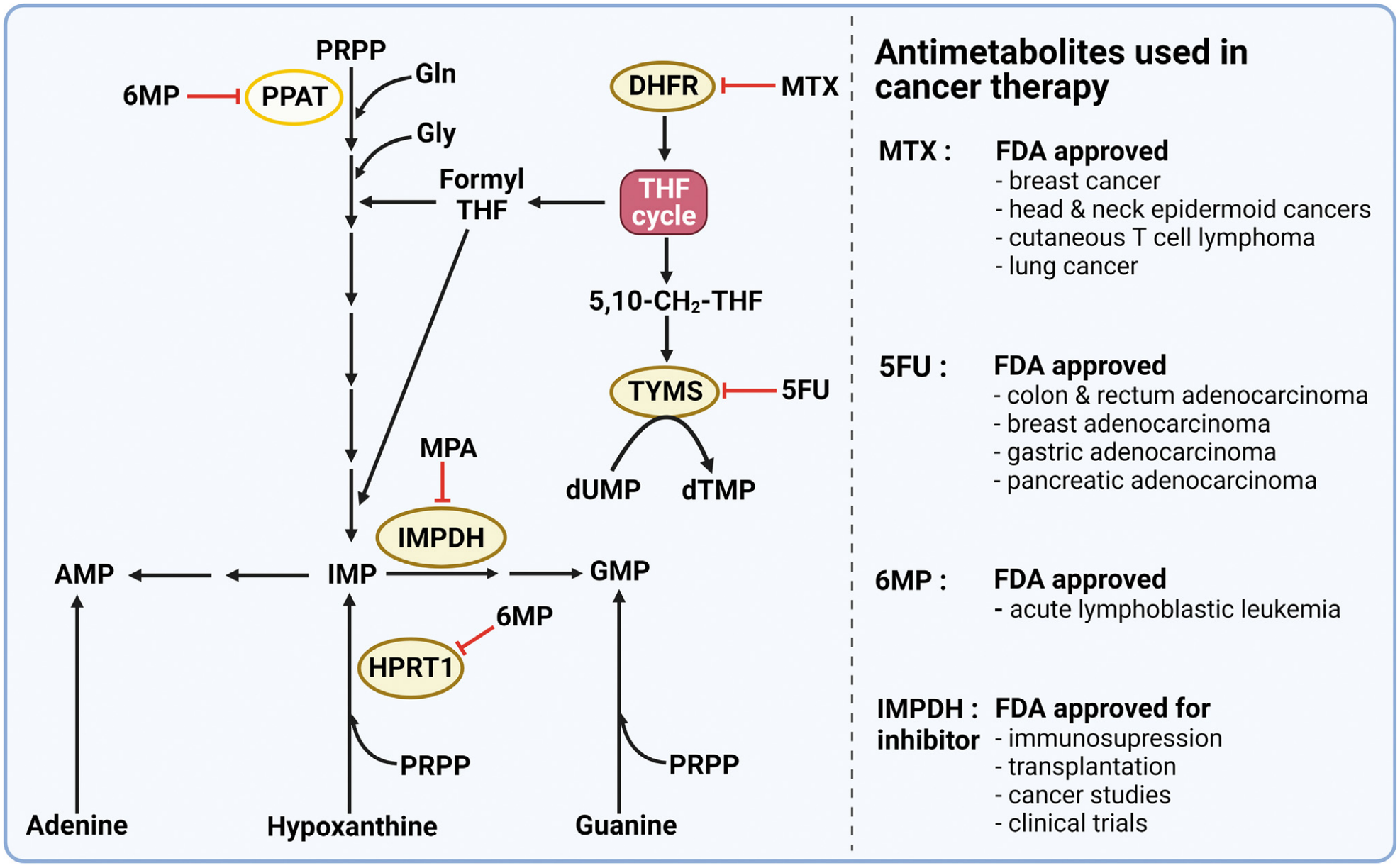
Pyrimidine synthesis begins with carbamoyl-phosphate and aspartate generating the pyrimidine base orotate

Requires glutamine, aspartate (NAD^+) and ATP

Dihydroorotate dehydrogenase (DHODH) is located in the mitochondria (interesting);

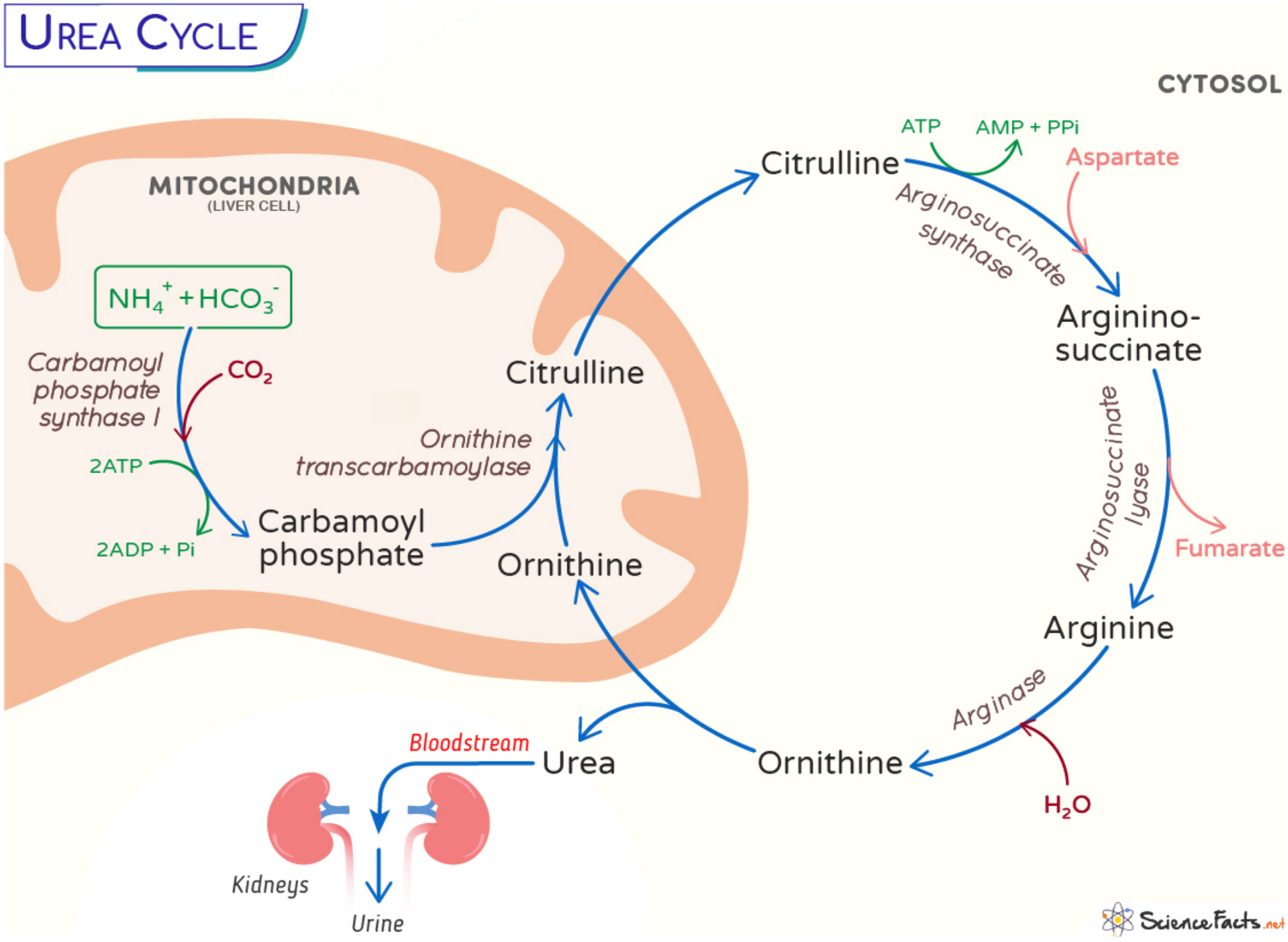
Pyrimidine rings can be completely catabolized

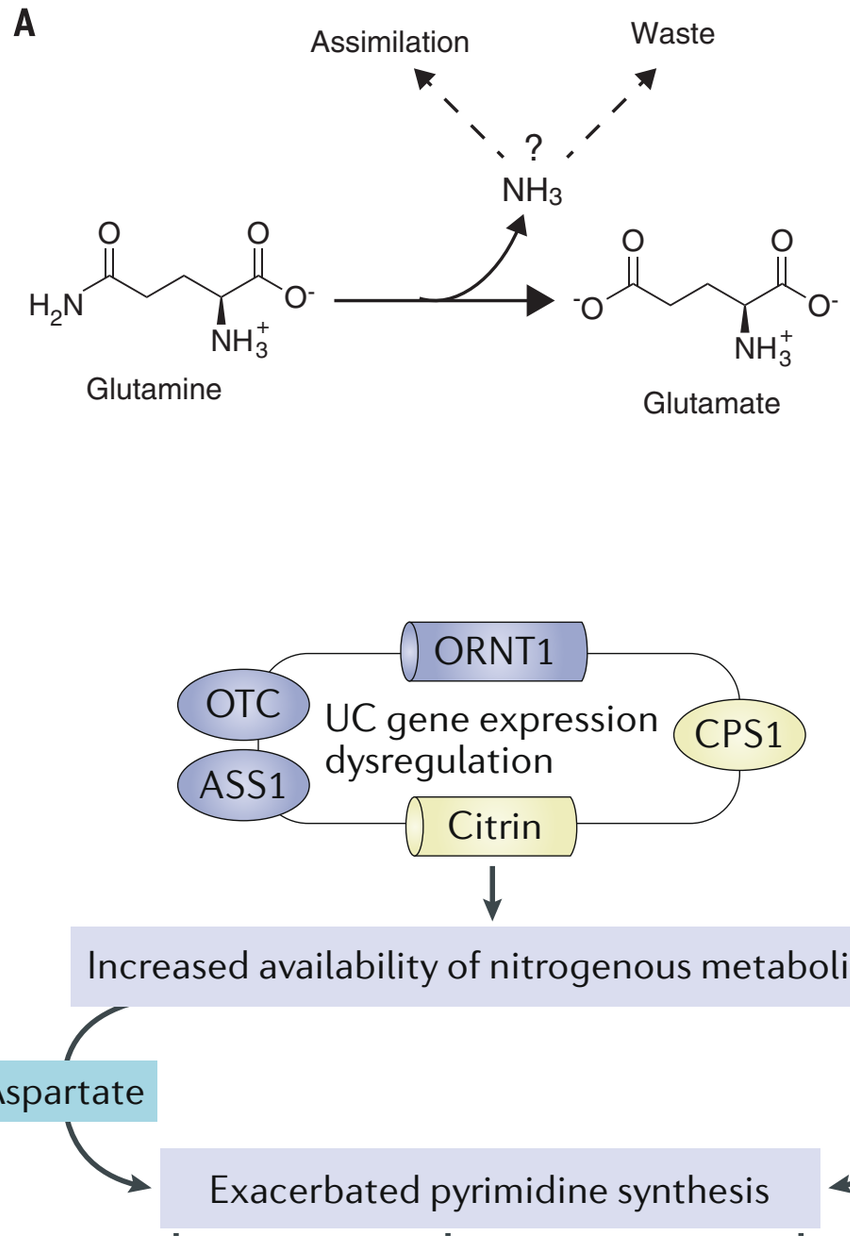
Nucleotide synthesis is targeted in cancer therapy



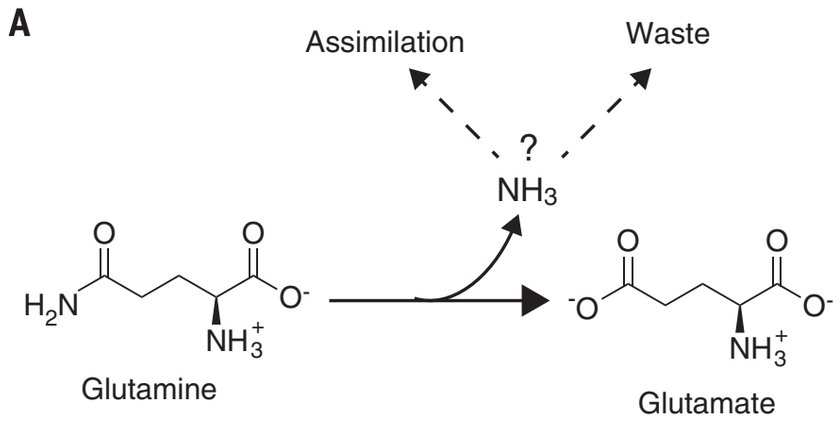
MTX was the first drug used (approved) to treat cancer (chemotherapy)

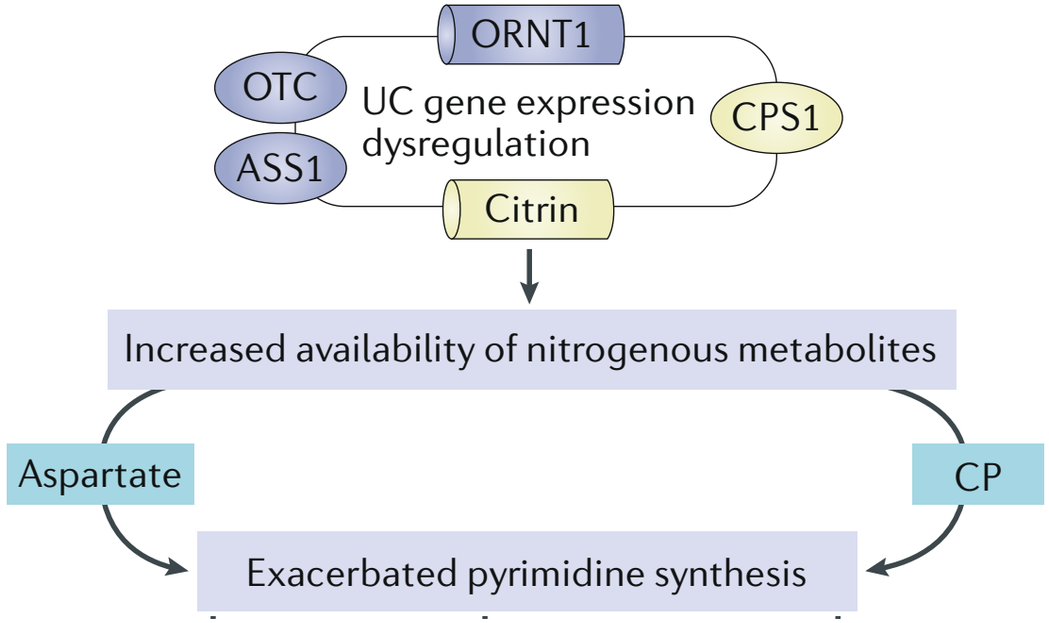
Metabolic waste (or sinking) pathways





Keshet et al, ***Nat Rev Cancer****, 2020*

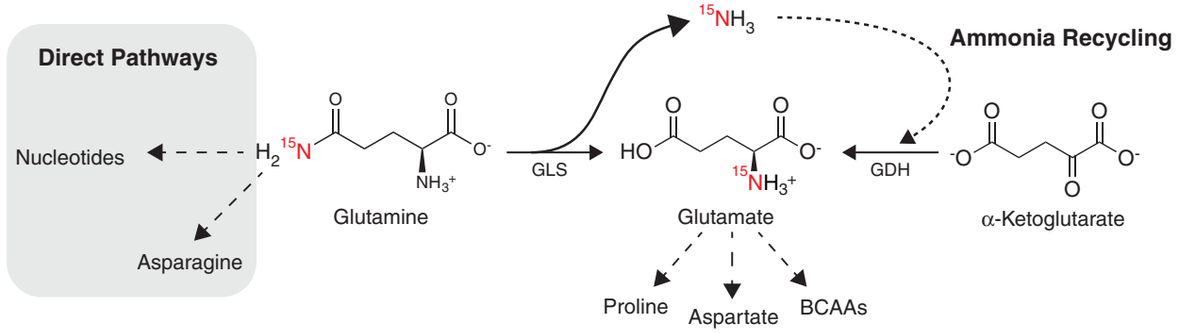


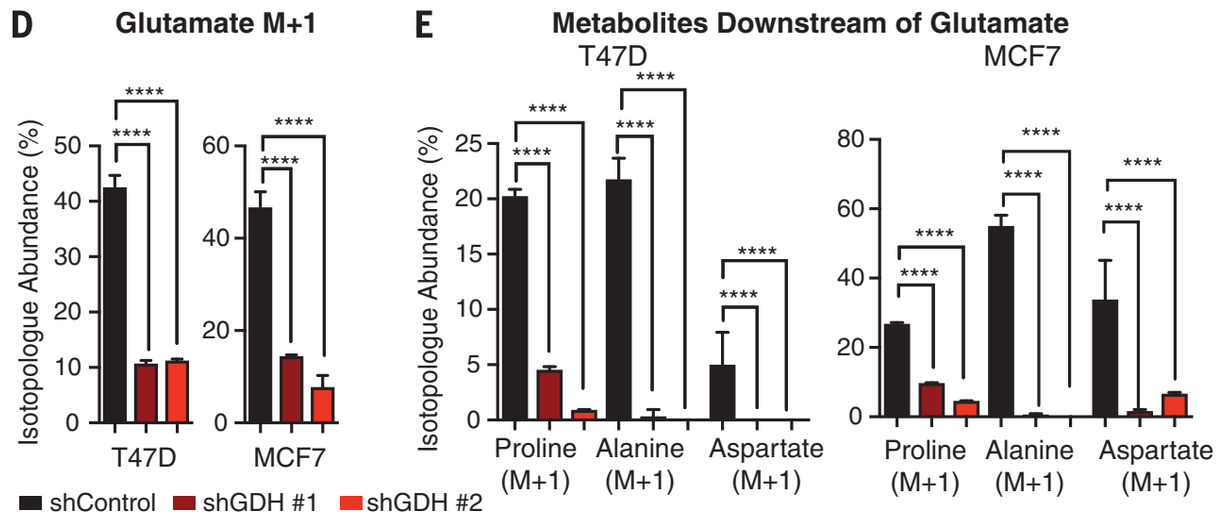


Keshet et al, ***Nat Rev Cancer****, 2020*

Metabolic recycling of ammonia via glutamate dehydrogenase supports breast cancer biomass

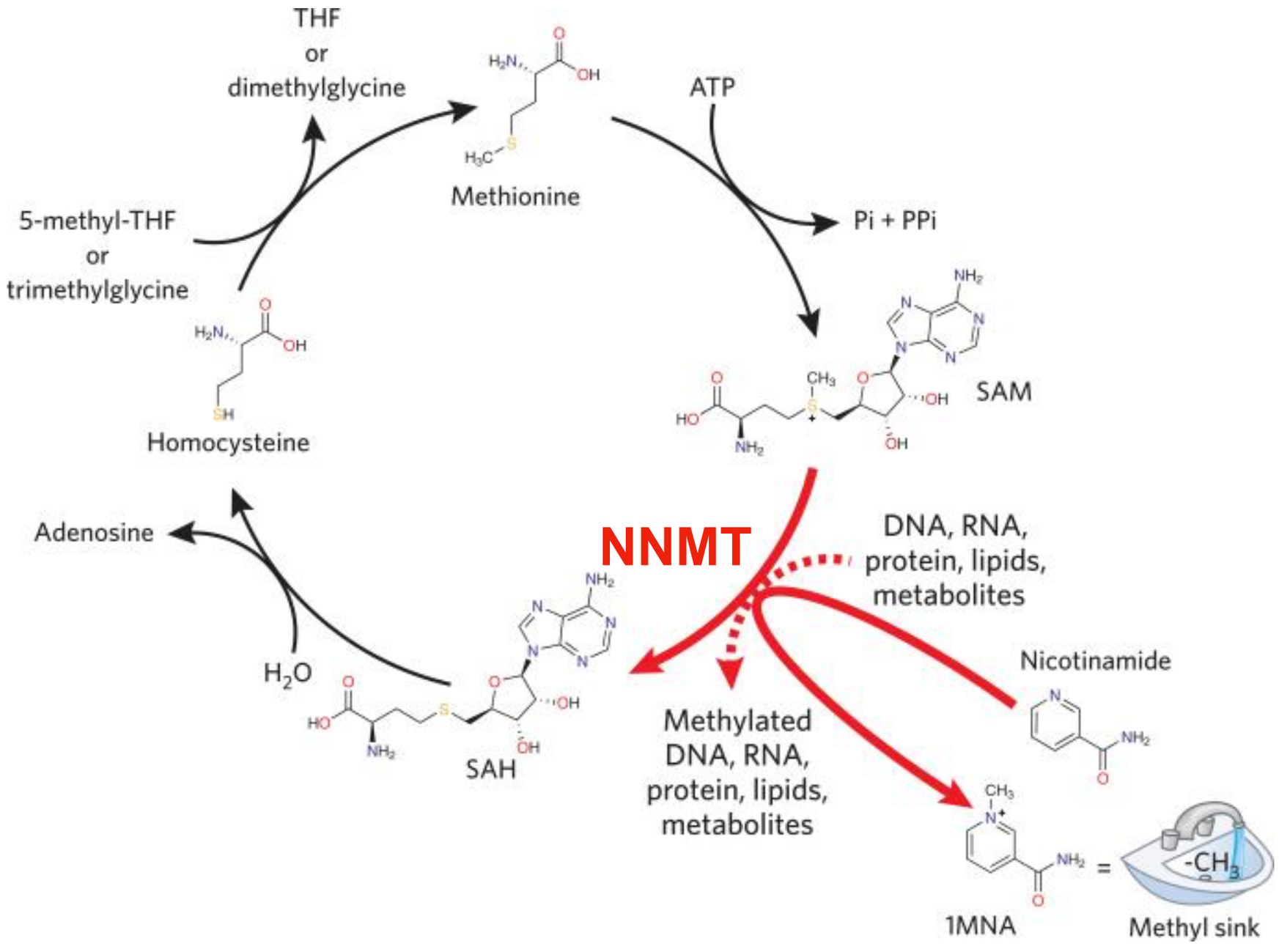
Jessica B. Spinelli,[1,2] Haejin Yoon,[1] Alison E. Ringel,[1] Sarah Jeanfavre,[2] Clary B. Clish,[2] Marcia C. Haigis[1]*





Spinelli et al, ***Science****, 2017*

Metabolic waste (or sinking) pathways



*Shlomi & Rabinowitz, , **Nat Chem Biol**, 2013*

*Ulanovskaya et al, **Nat Chem Biol**, 2013*