

NutriGenomics

Ecole Polytechnique de Lausanne

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NutriGenomics: A Definition

- **Nutrigenomics**

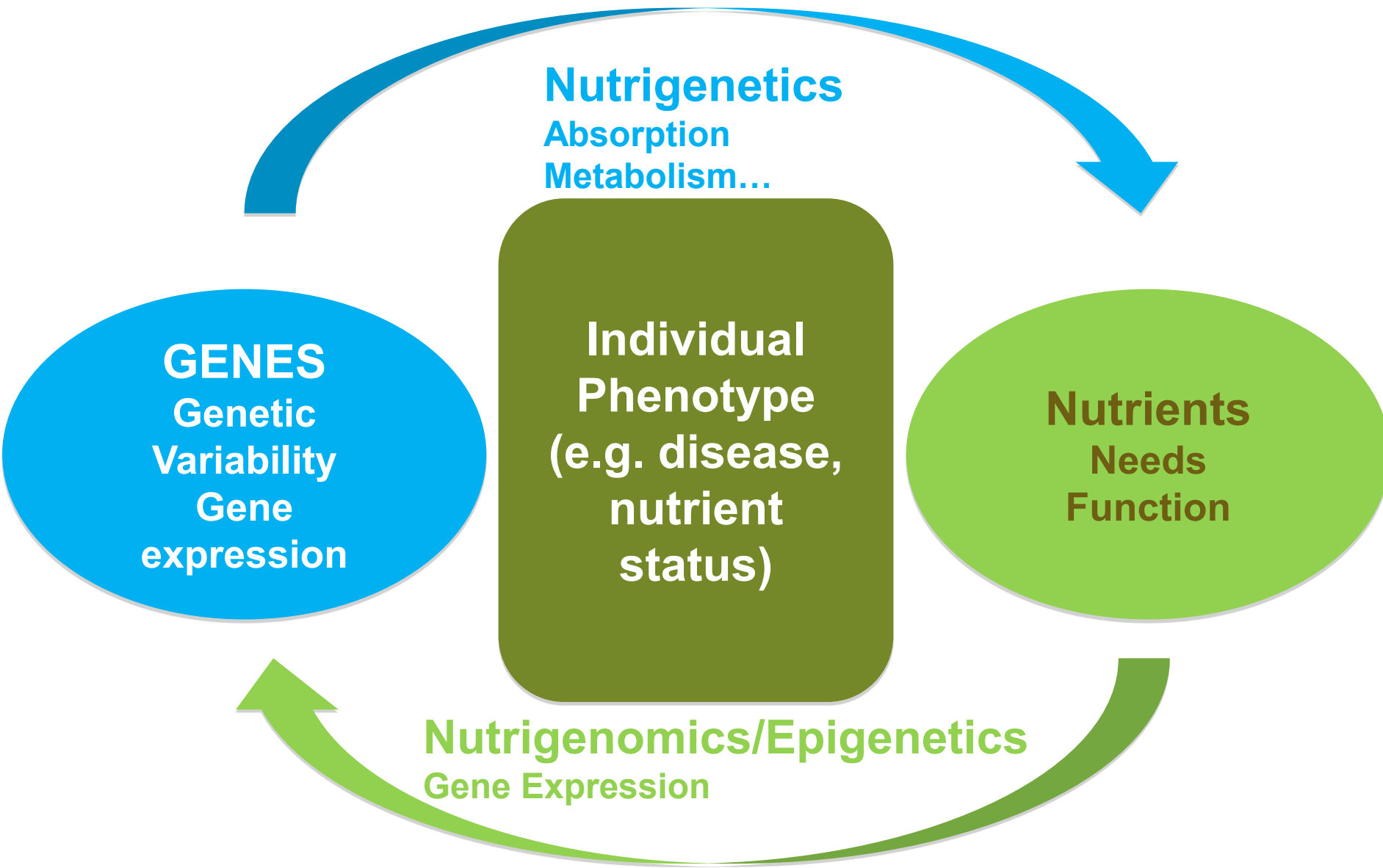
- The study that investigates
 - How your nutrition affects the expression of your genes and vice versa
 - How subsequently your genes control your health

- **Nutrigenomics** is needed to find out

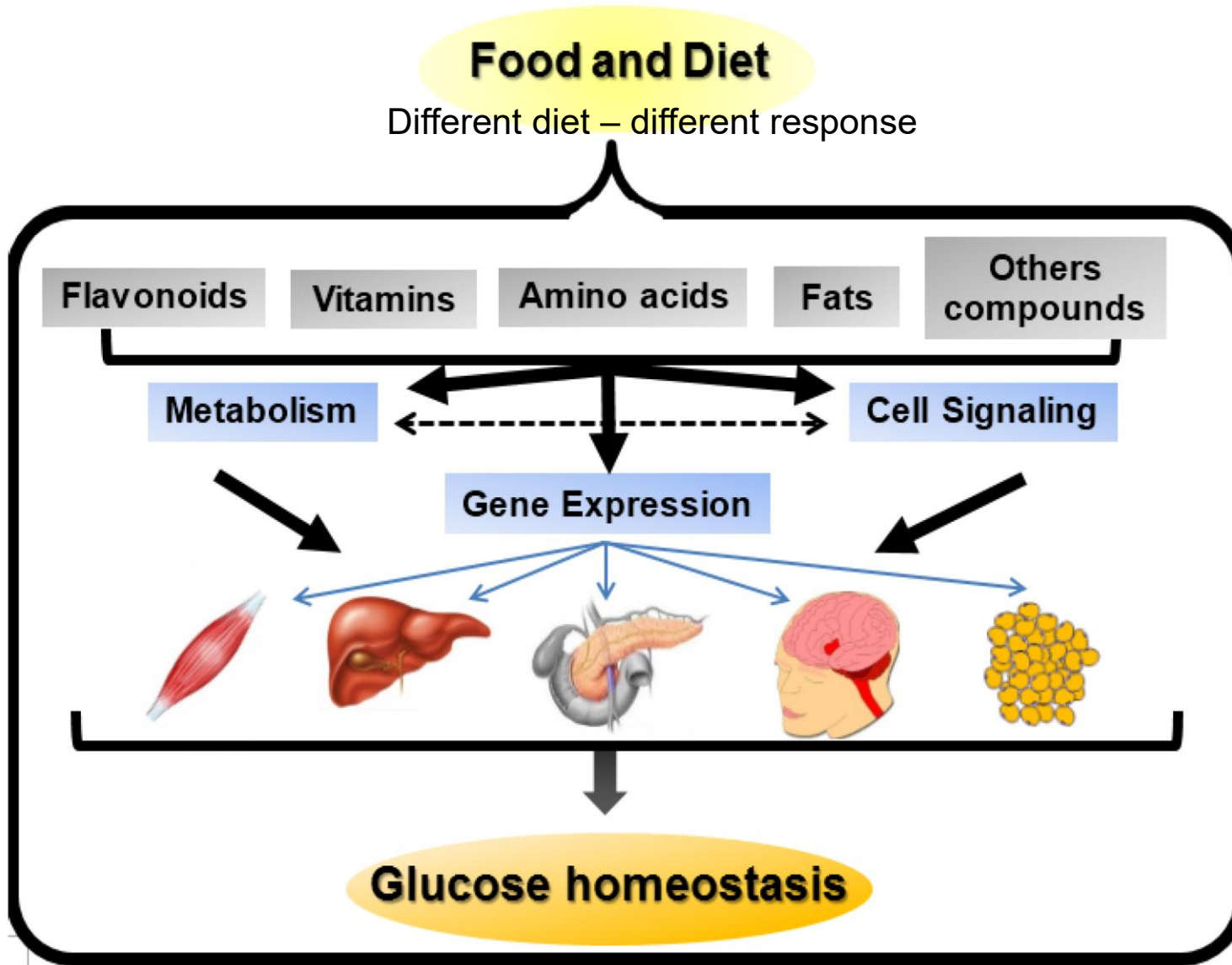
- How different food components can interact with particular genes influencing risks of diseases

- **Nutrigenomics** is the application

- High throughput genomics tools in nutrition research



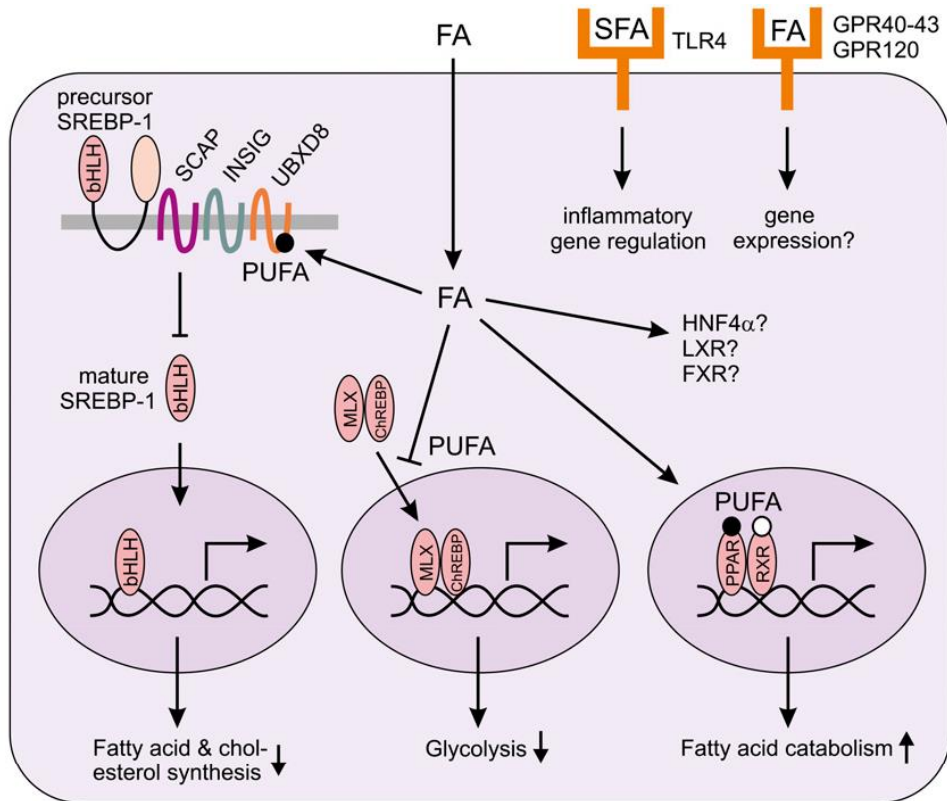
Why are we interested in Nutrigenomics?



Nutrients that can affect gene expression

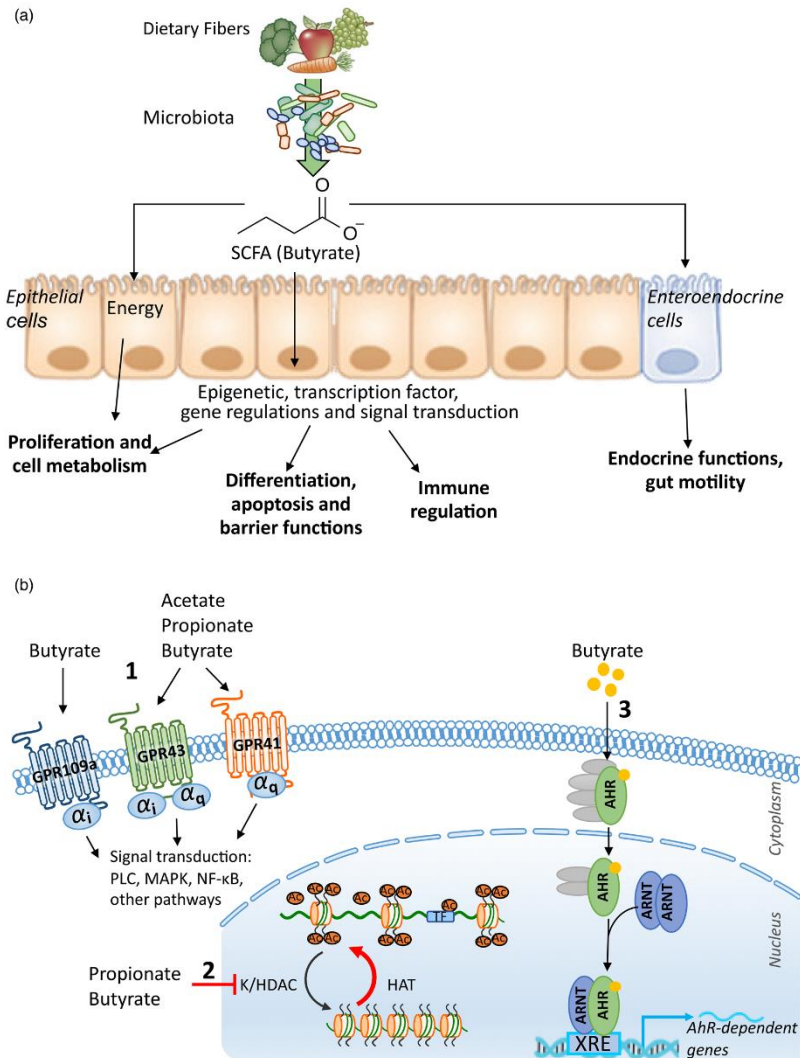
- **Metabolites (examples)**
 - glucose (other sugars),
 - Amino-acids ;
 - Fatty-acids;
 - Vitamins (e.g. Folate)
 -
- **Xenobiotics (phytochemicals, examples)**
 - Polyphenols;
 - Terpenoids;
 - Thiols;
 -

Nutrigenomics: Effects of Fatty acids on gene expression and energy metabolism



- profound effects on gene expression, leading to changes in metabolism, growth, and cell differentiation.
- The effects of dietary fat on gene expression reflect an adaptive response to changes in the quantity and type of fat ingested.

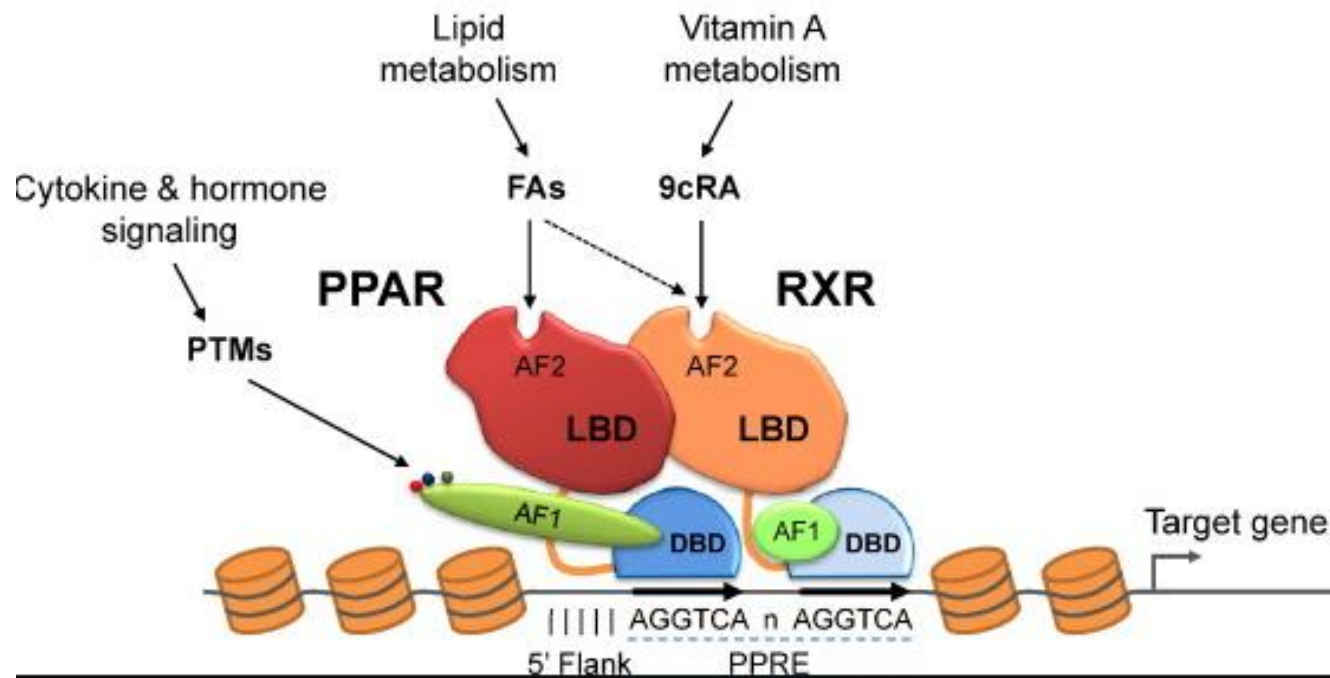
Nutrigenomics: Effects of Fatty acids on gene expression



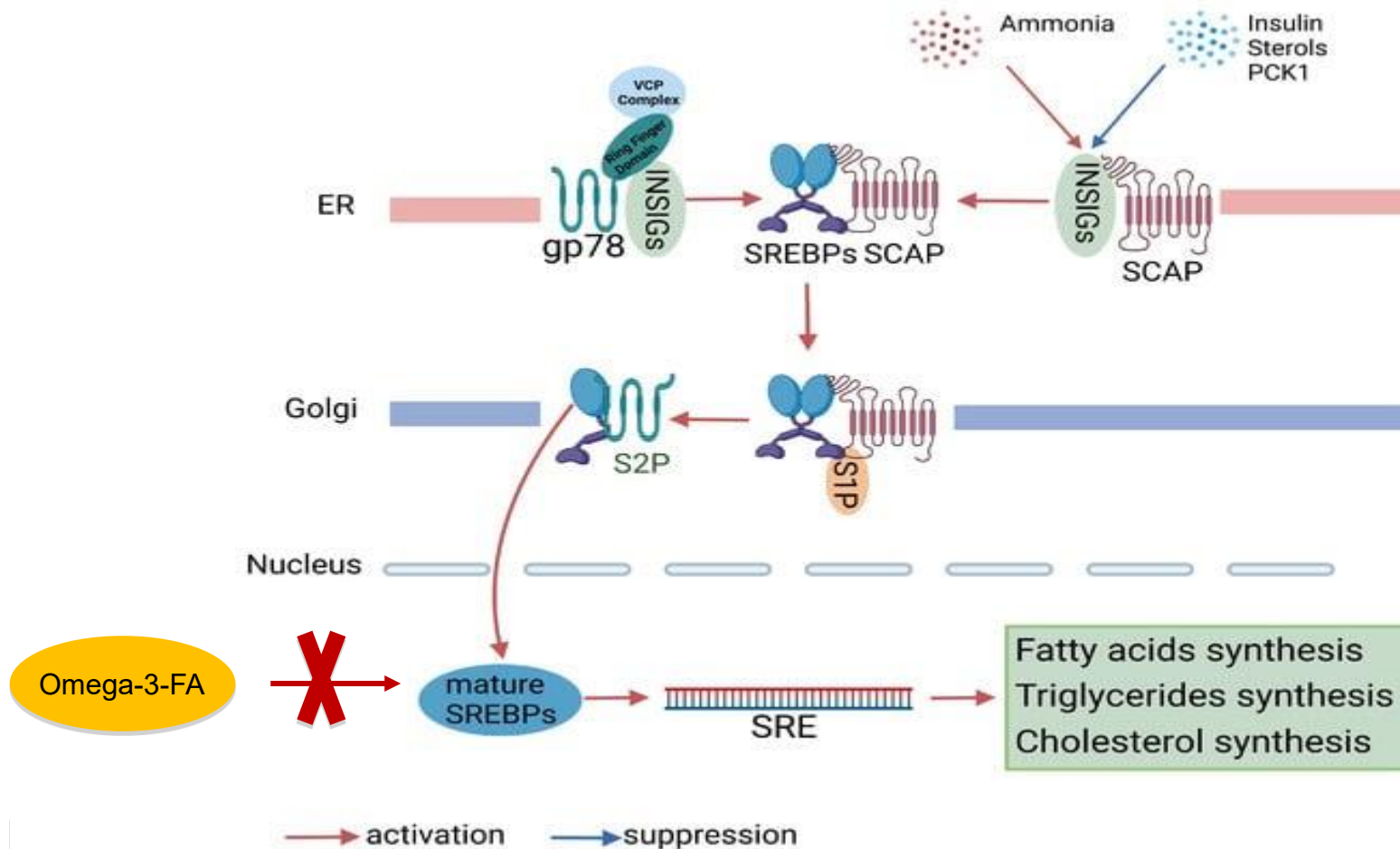
- Unspecific activation of gene expression through acetylation of histones
- Specific activation of gene expression through binding to specific transcription factors

Camille Martin-Gallusiaux et al. SCFA: mechanisms and functional importance in the gut. Proceedings of the Nutrition Society, 2020

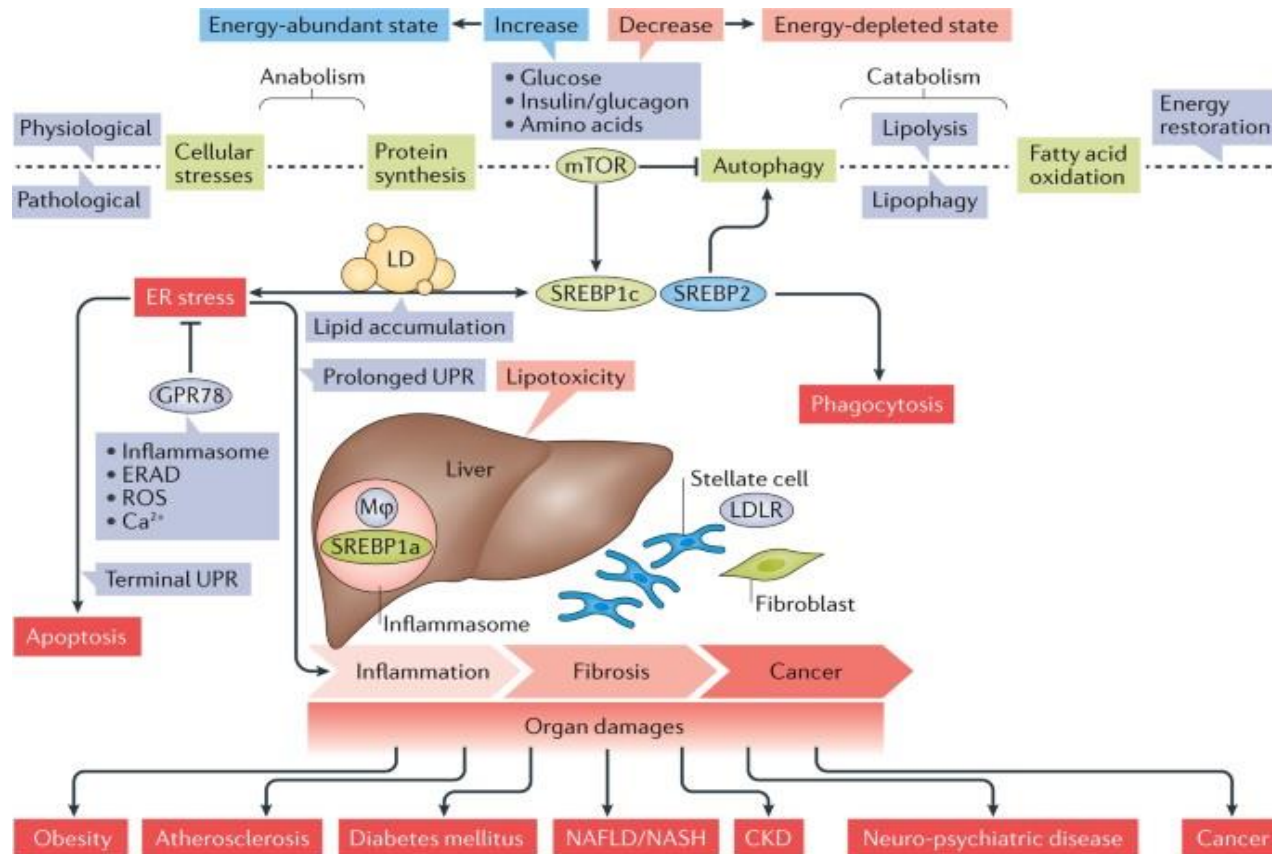
Nutrigenomics: Fatty acids are ligands of transcription factors & drive gene expression



Nutrigenomics: Omega-3 FA effects on sterol-metabolism are mediated through inhibition of SREBP TF.



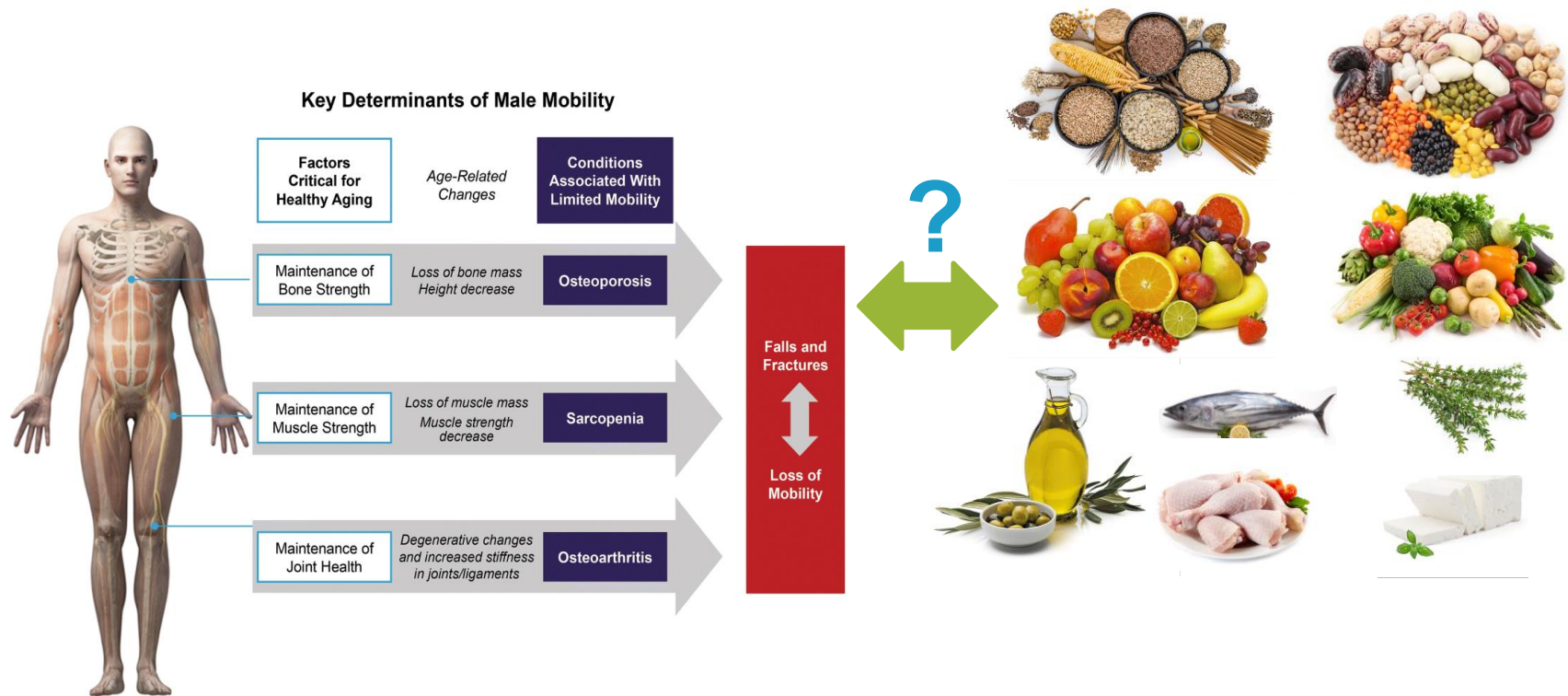
Nutrigenomics: SREBP overexpression is involved in multiple disease processes like heart disease.



Nature Reviews | Endocrinology

Identification of bio-active compounds in food that improve health related symptoms

Example: Mobility during ageing



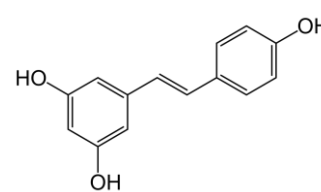
Food contains a wealth of secondary plant metabolites

The Mediterranean diet is an example for a rich, varied dietary regime with health benefits...

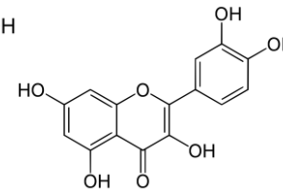


... making it a good source for the search for secondary metabolites.

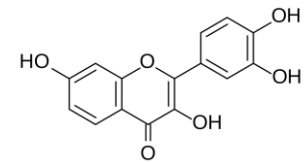
Examples of secondary plant metabolites



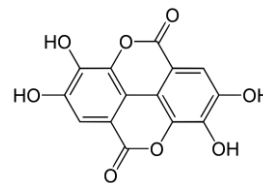
resveratrol



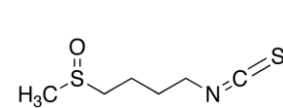
quercetin



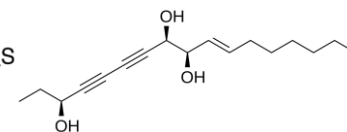
fisetin



ellagic acid
(Urolithin A precursor)

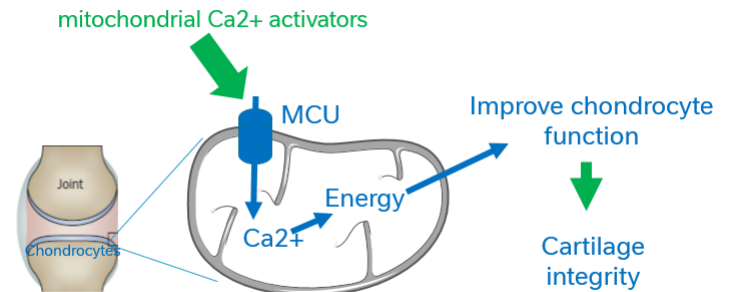
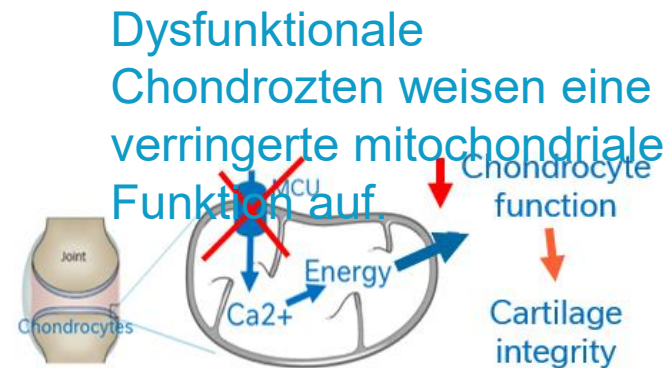
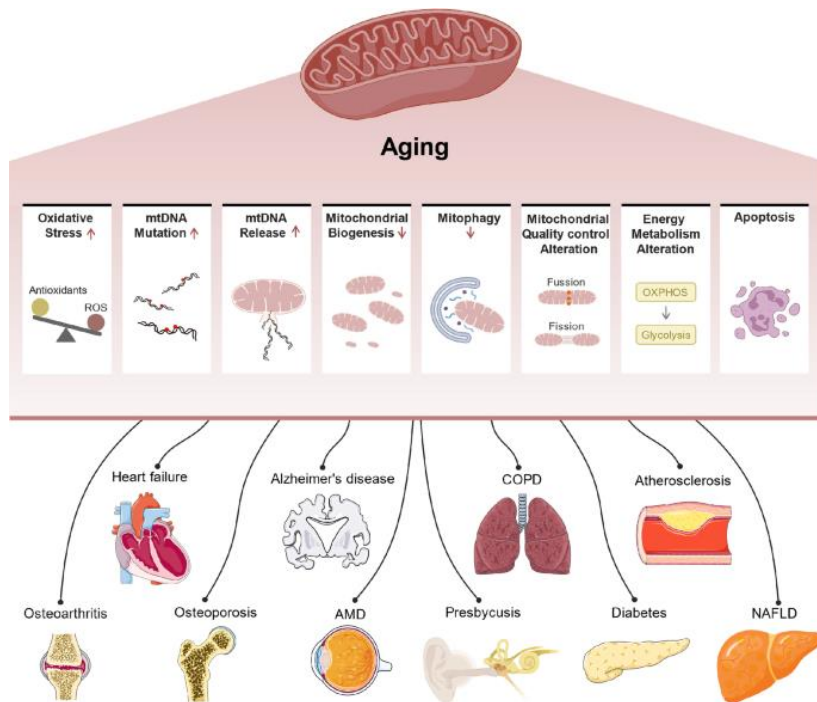


sulforaphane



Isofalcarintriol

Identifying bio-active secondary metabolites – understanding the disease mechanisms.

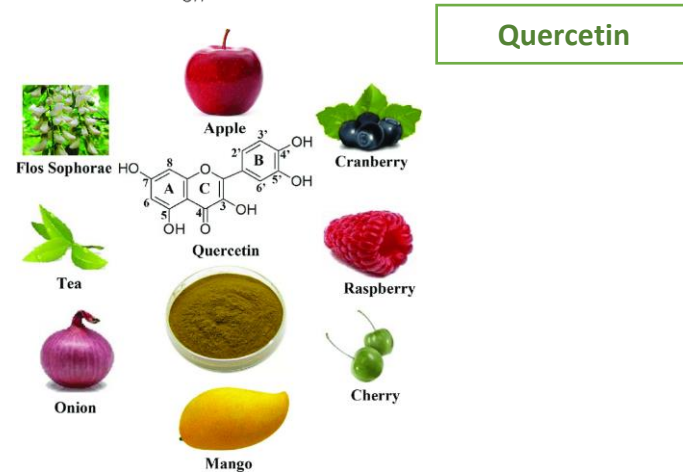
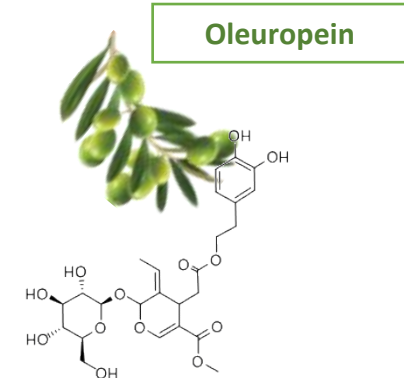
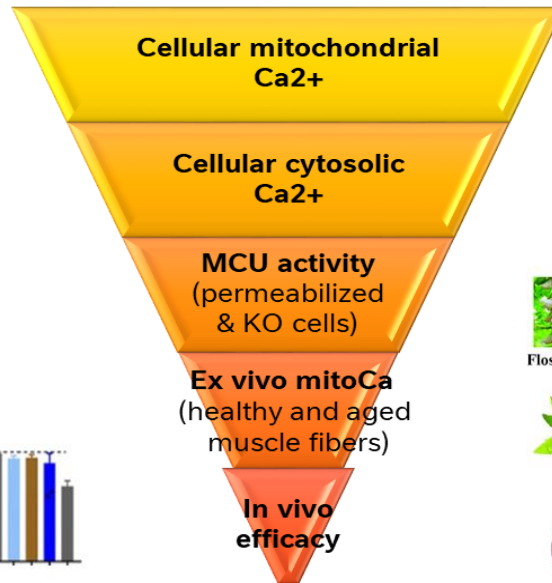
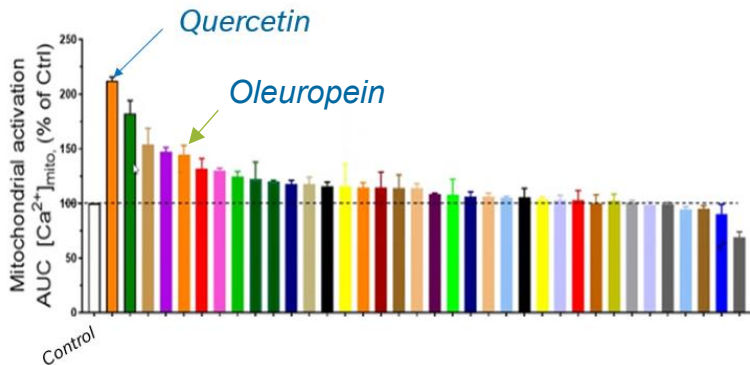
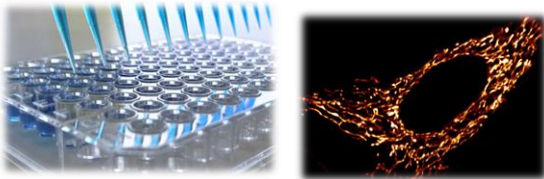


Guo et al. Signal Transduction and Targeted Therapy, 2022

Molecular screening to identify secondary metabolites that influence disease relevant molecular processes.

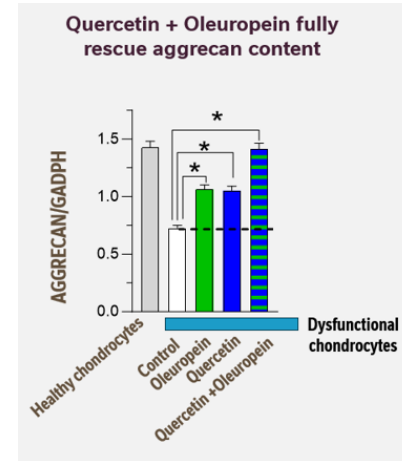
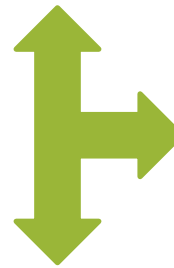
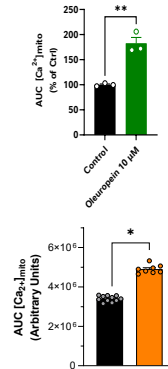
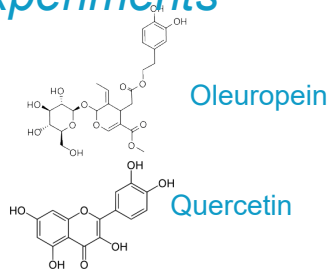
Mitochondrial Ca²⁺ Activator Screening

Library: **5000** natural molecules from edible plants

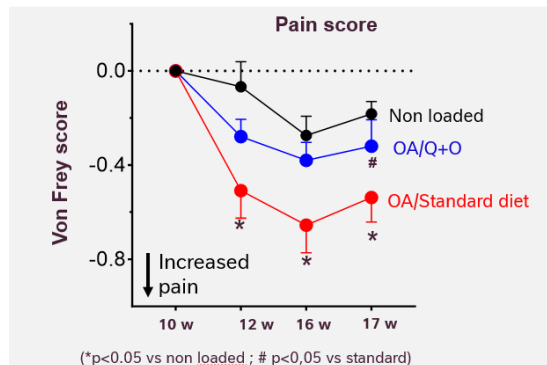


Oleuropein and Quercetin have synergistic effects to restore normal chondrocyte function.

In vitro Experiments

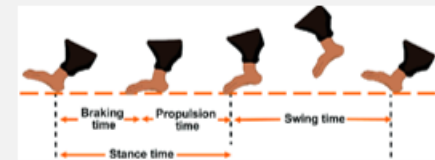


Clinical Studies



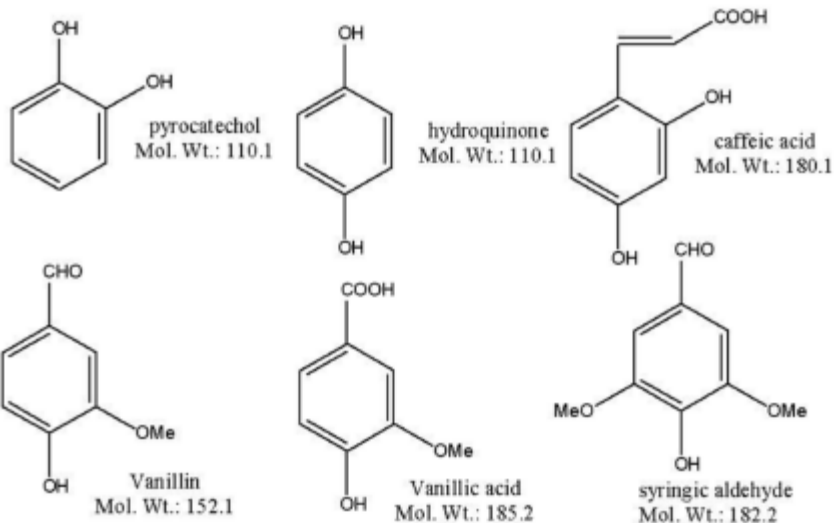
Gait

Stance time increased 7 times in Q+O vs standard group (p=0.013)



Nutrigenomics: Polyphenols

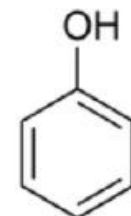
- Po
- Th
- Pc
- ad



es



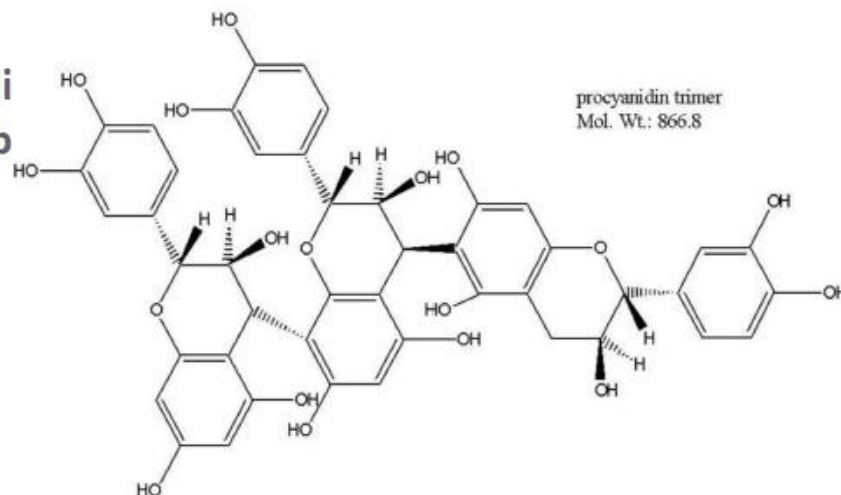
the presence of phenol units



Phenol

olism which help plants

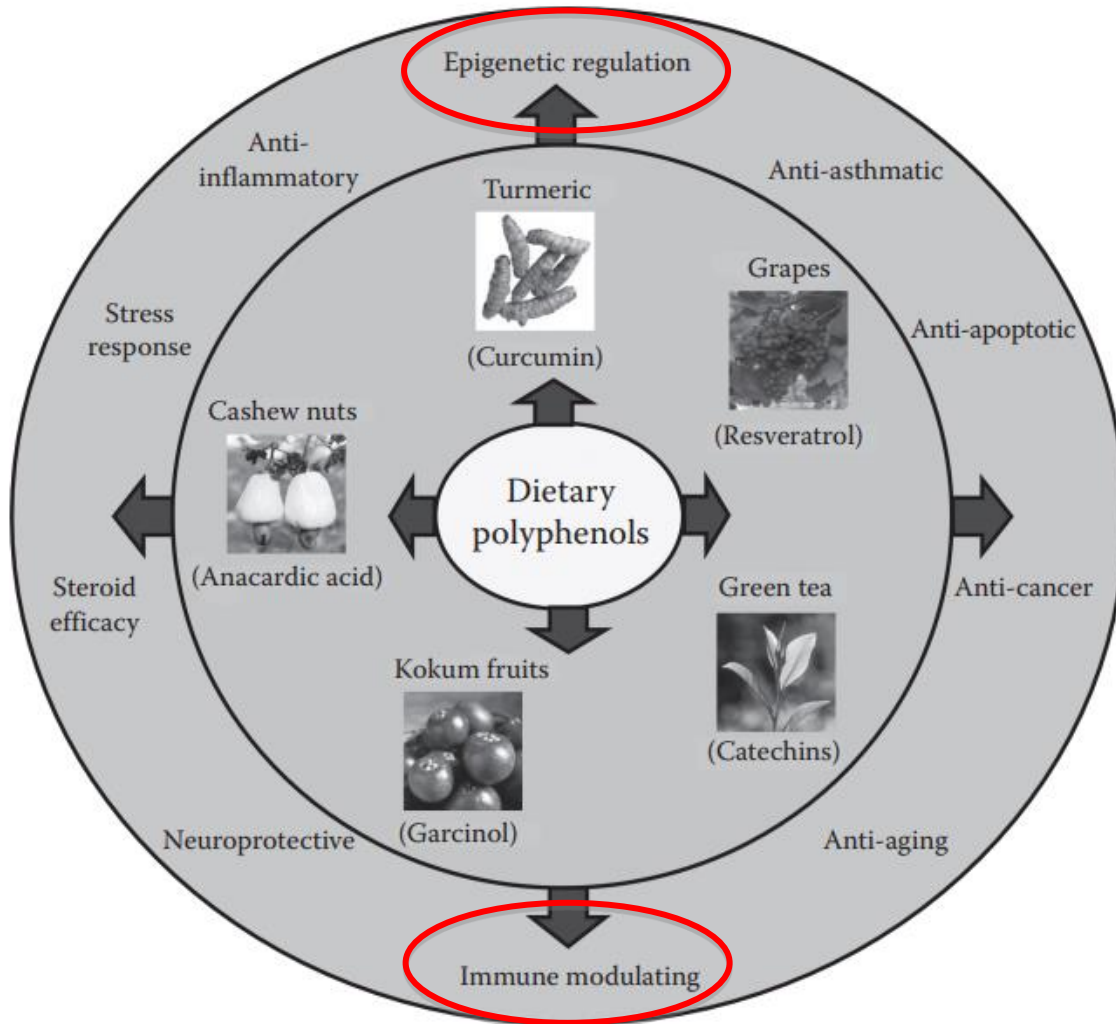
- Examples: pigments to attract insects for pollination e.g. Flavanoids like anthocyanidins are responsible for dark colors like red and blue
- Protect against UV damage
- Deterrent against herbivores & pathogens



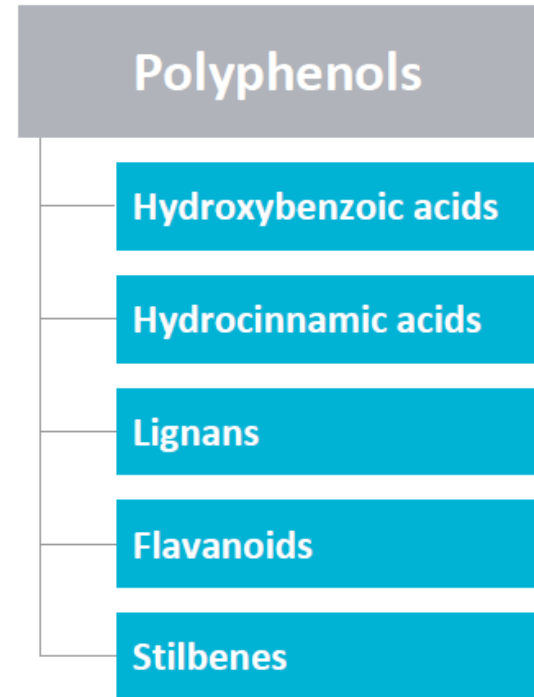
cyanin content
ticulturalae.

Tzima, Brunton & Rai. Plants, 2018

Nutrigenomics: Effects of polyphenols on biological processes



- Several hundred polyphenols identified in edible plants
- Classified according to their chemical structure

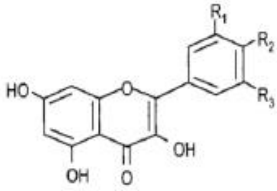


Nutrigenomics: Flavanoids- examples of dietary sources

The majority of bio-active polyphenols studied to date belong to the group of Flavanoids

Flavanoids

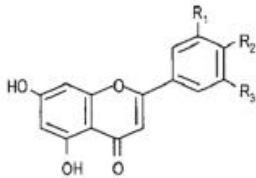
Flavanols



Kaempferol
Quercetin
Myricetin



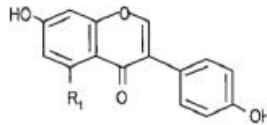
Flavones



Apigenin
Luteolin



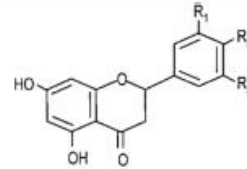
Isoflavones



Daidzein
Genistein



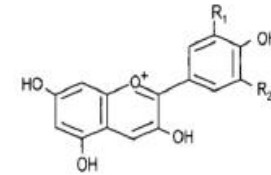
Flavanones



Naringenin
Hesperetin



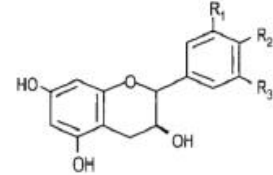
Anthocyanidins



Pelargonidin
Cyanidin
Malvidin



Flavonols

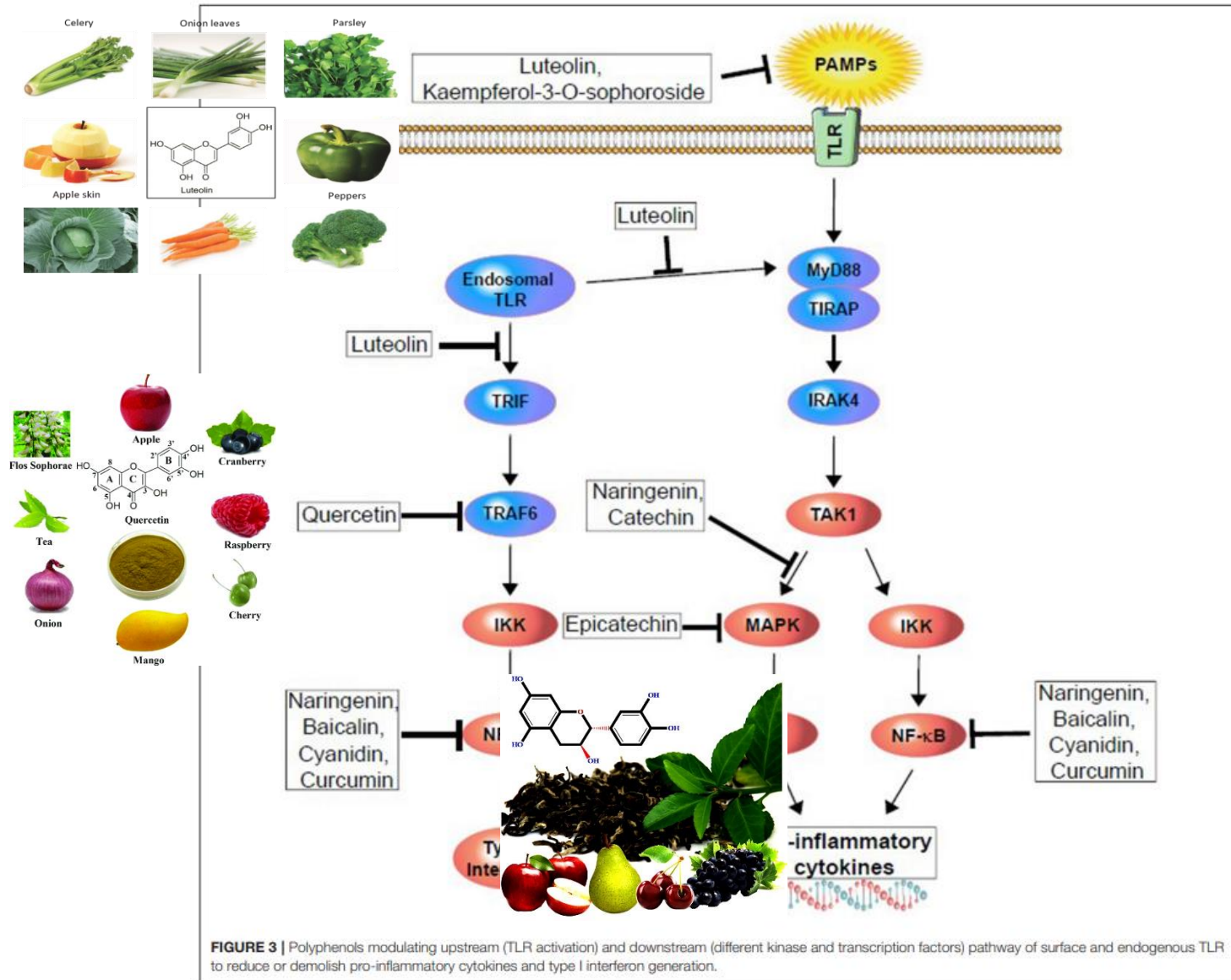


Catechins



Structure image from Manach et al. (2005). Polyphenols: food sources and bioavailability. American Journal of Clinical Nutrition.

Nutrigenomics: Effects of polyphenols on toll like receptor (TLR) mediated inflammation signaling



Diet effects on epigenetic regulation- a special case of nutrigenomic diet-gene expression interaction

- C.H. Waddington coined the term epigenetics to mean above or in addition to genetics.
- **Epigenetics** is the study of heritable phenotype changes that do not involve alterations in the DNA sequence.
- Epigenetic effects can be transmitted across generations (of cells or organisms).

Mechanisms of epigenetic regulation

■ DNA methylation

- on cytosine nucleotides
- In CpG islands (gene promoter)
- Reduce/shut down gene expression

■ Histone methylation/ acetylation

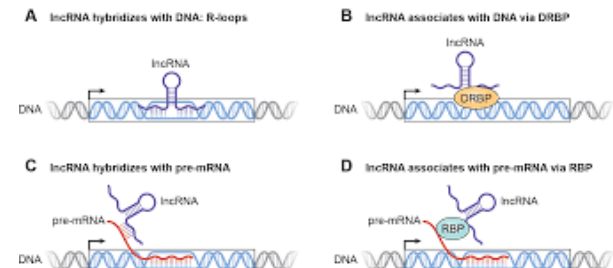
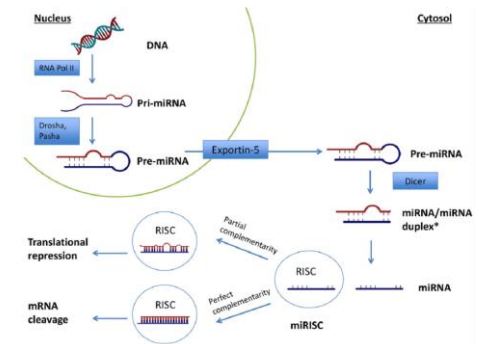
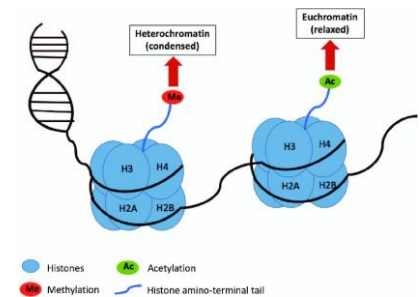
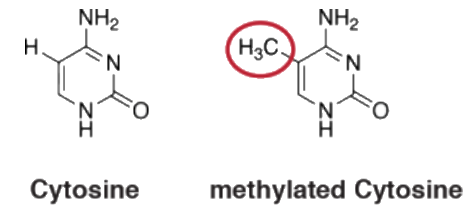
- Enhances or reduces DNA accesibility
- Methylation (generally) reduces acces
- Acetylation enhances access

■ μRNAs

- Small nuclear RNAs that show homology to sequences in target genes
- Influence gene expression and/or mRNA translation

■ lncRNAs

- Long
- Complex regulatory functions
- Often target multiple genes at the same time



Nutrigenomics: Epigenetic effects of polyphenols- example resveratrol

Polyphenols

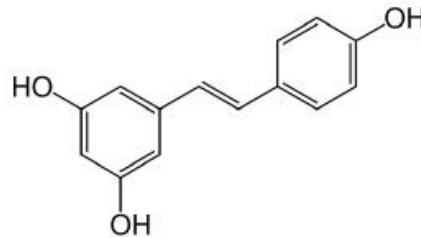
Hydrobenzoic acids

Hydrocinnamic acids

Lignans

Flavanoids

Stilbenes



The French Paradox



Berries are rich in resveratrol
Resveratrol is found in knotweed

Nutrigenomics: Epigenetic effects of polyphenols- example resveratrol

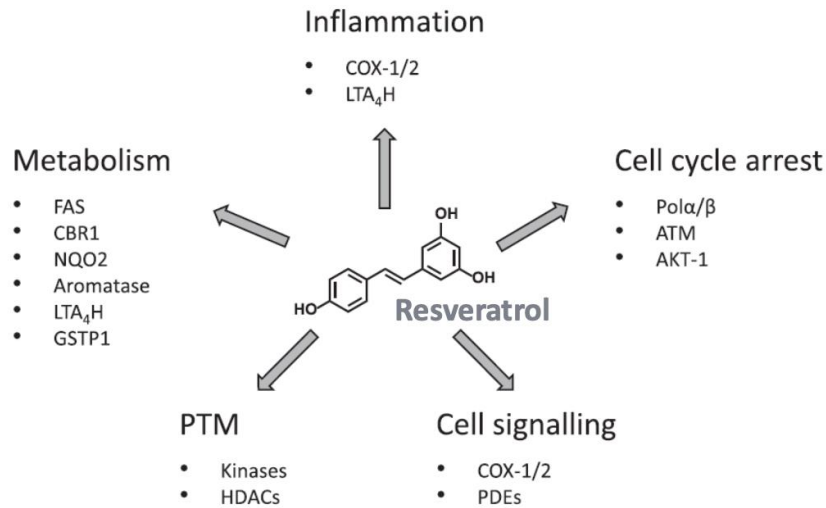


Image from Britton et al. (2015). Direct molecular targets of resveratrol: identify interactions to unlock complex mechanisms.

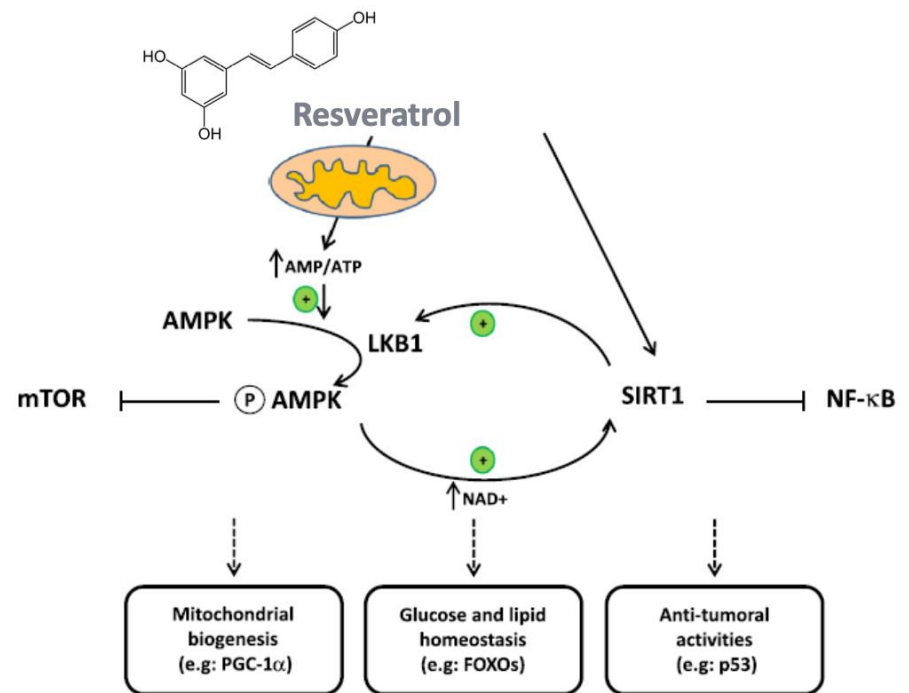
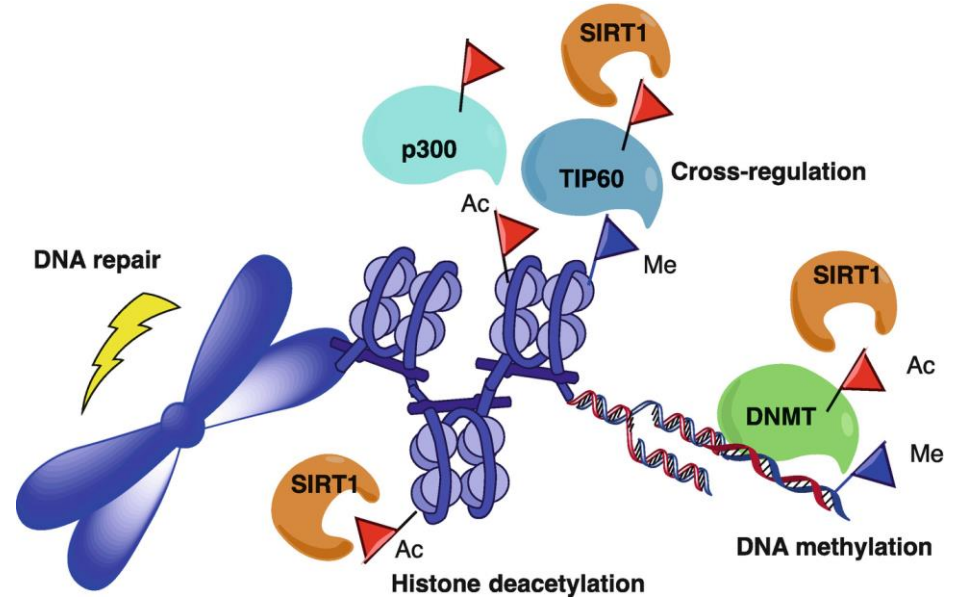
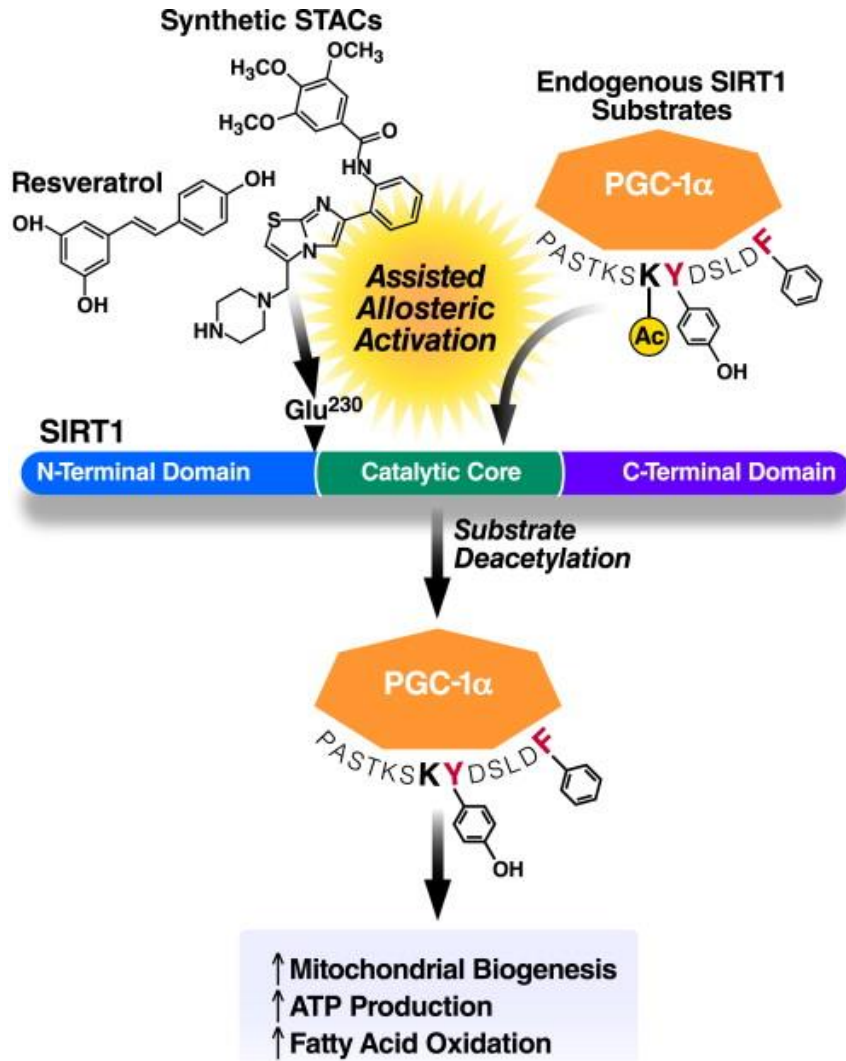


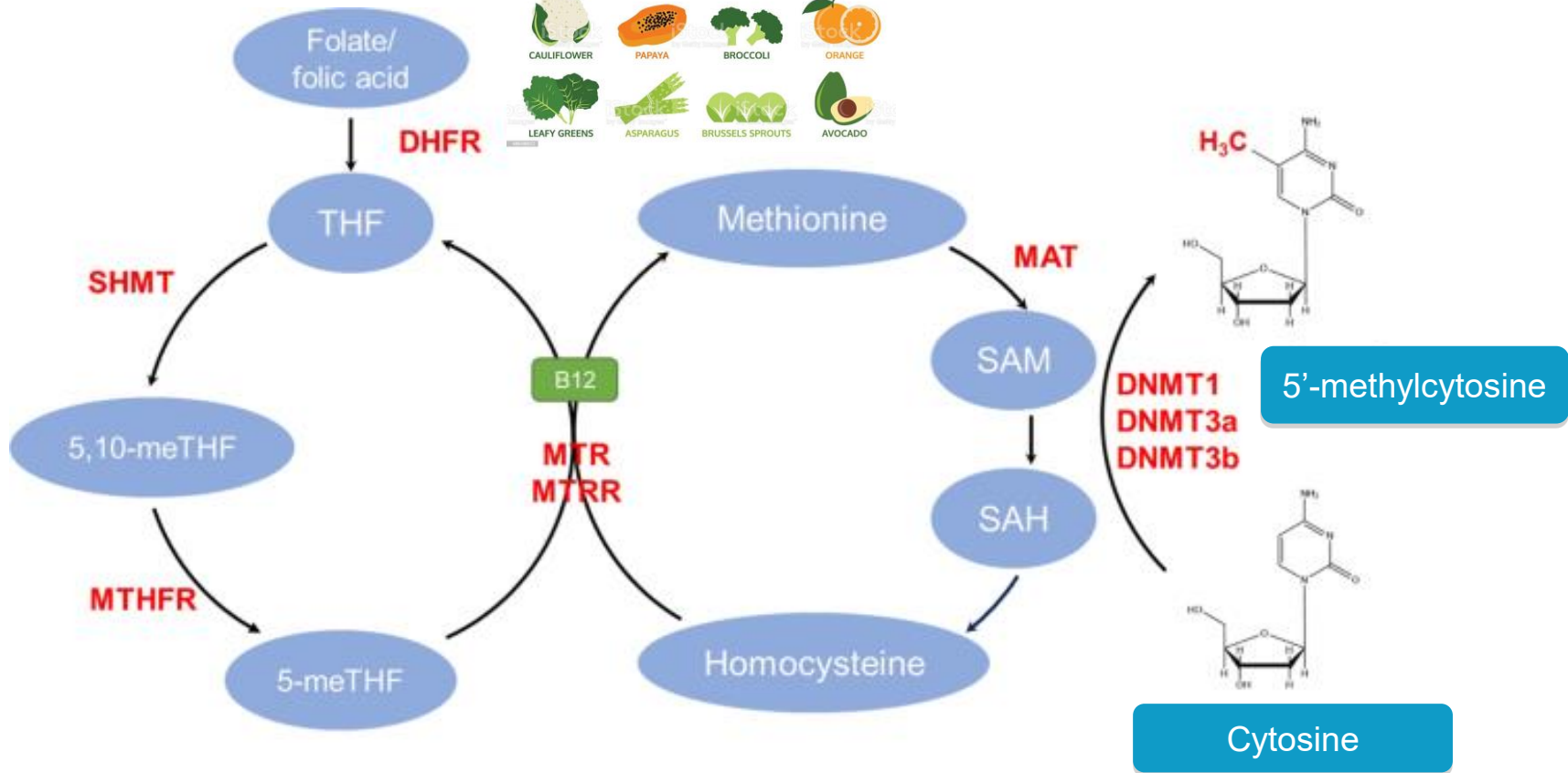
Image from Kulkarni and Canto (2015). The molecular targets of resveratrol

Nutrigenomics: Epigenetic effects of polyphenols- example resveratrol



Wang, Hsu and Liu: Role of SIRT1 in epigenetics. Handbook of Nutrition, Diet and Epigenetics. 2019: pp 311-29

Nutrigenomics: Folate (B9), 1-carbon cycle and DNA methylation



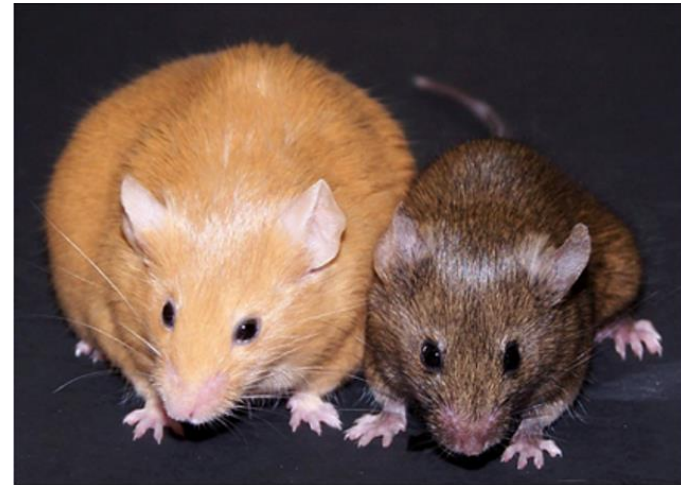
SAH- S-Adenosyl-L-homocysteine
 SAM- S-Adenosylmethionine

Epigenetic effects and Nutrition

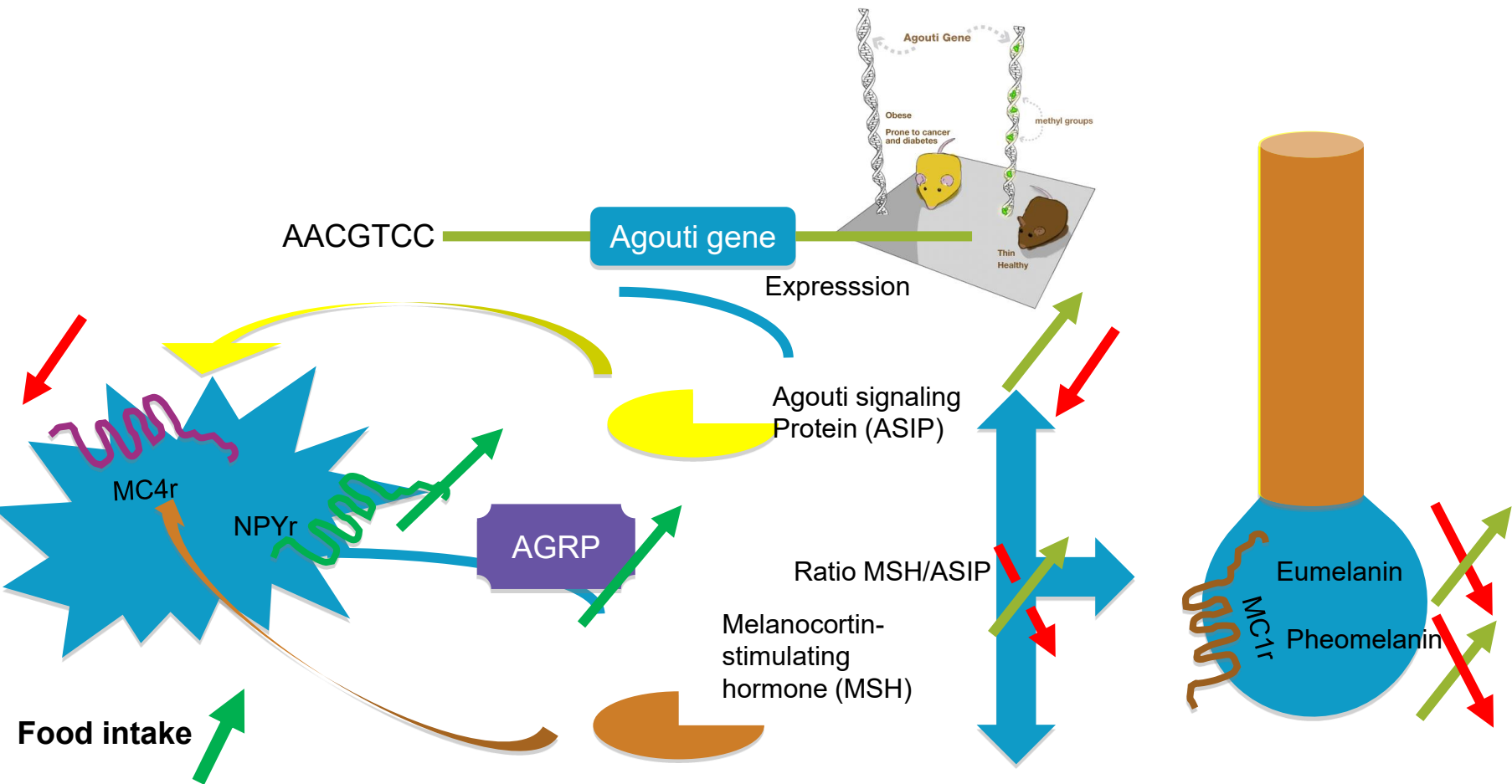
Genetically identical “agouti” mice



High fat diet leads to massive obesity in “yellow” mice

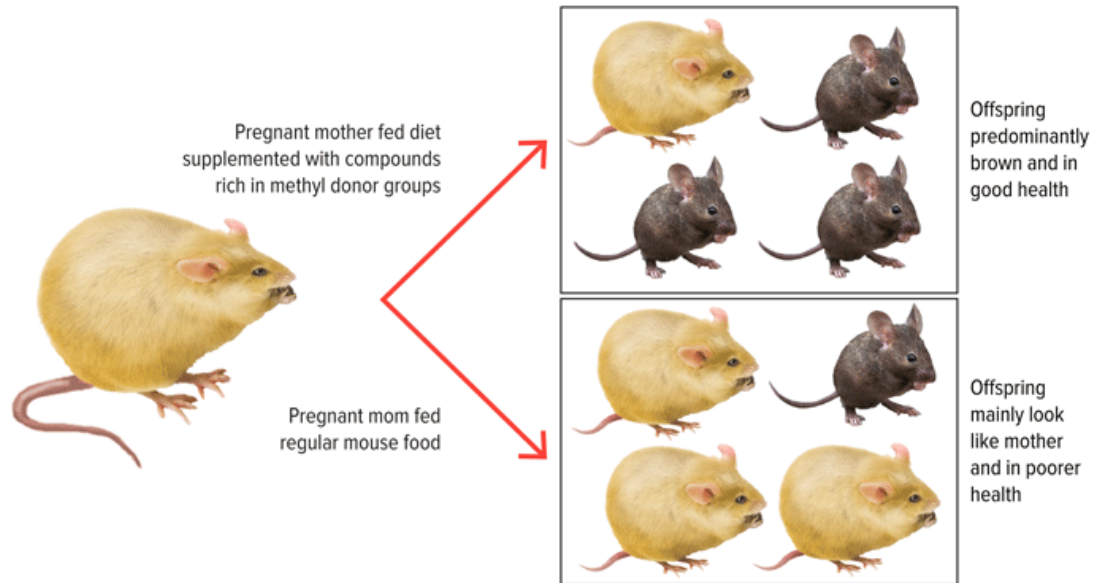
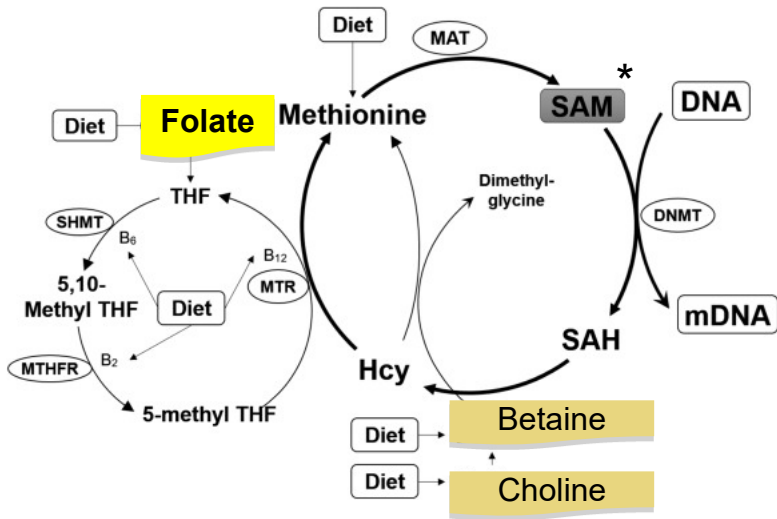


Nutrigenomics: Methylation status of the agouti gene determines coat color AND metabolic flexibility



Nutrigenomics: Correction of the agouti effect through diet

1-carbon cycle



*S-adenosylmethionine

Using nutrients and bio-actives in food and supplements: Considerations

- Regulatory framework:
 - What can I claim?
 - Can I use my bio-active in a product
- How much can I put in my product?
- Interactions with other food components & shelf life.

Using nutrients and bio-actives in food and supplements: Regulatory Considerations

- What can I claim

In the United States (U.S) different types of claims can be made for dietary supplement ingredients (depending on the ingredient and degree of support for the claim). These include **Health, Qualified Health, Structure Function, Nutrient Content, or Amount or Percentage of Dietary Ingredient.**

In Europe, he.), several health claims are defined as claims that state, suggest or imply that a relationship exists between a food category, a food or one of its components and health. This definition includes:

- 1. Health claims related to (a) the role of a nutrient** or other substance in growth, development or function of the body; (b) psychological and behavioral functions, or (c) slimming, weight-control, satiety or reduction of available energy (defined in article 13 of Regulation (EC) No 1924/2006 (1) AND
- 2. Health claims referring to the reduction of a risk factor** in the development of a disease and related to children's development (defined in article 14 of Regulation (EC) No 1924/2006) (1)

Using nutrients and bio-actives in food and supplements: Regulatory Considerations Example

Region	Claim Type	System/ Endpoint	Permitted Language	Reference
US	Amount or Percentage Claim	Heart	Contains x grams of omega-3 fatty acids per serving	Link
Europe	Nutrition	Amount	X is a source of (or good source) of omega-3 fatty acids ^a	Link
US	Qualified Health	Heart	Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of [Name of the food] provides [] gram of EPA and DHA omega-3 fatty acids. [See nutrition information for total fat, saturated fat, and cholesterol content.]	Link
US	SF	Heart	Omega-3 fatty acids support heart health ^b	
Europe	Health (generic)	Heart	EPA and DHA contribute to the normal function of the heart ^c	Link
Europe	Health (generic)	Blood pressure	DHA and EPA contribute to the maintenance of normal blood pressure ^c	Link
Europe	Health (generic)	Triglycerides	DHA and EPA contribute to the maintenance of normal concentrations of triglycerides ^c	Link 1 Link 2
US	SF	Brain	Omega-3 fatty acids support healthy cognitive function ^b	
Europe	Health (generic)	Brain	DHA contributes to the maintenance of normal brain function ^c	Link
US	SF	Eyes	Omega-3 fatty acids support eye health ^b	
Europe	Health (generic)	Eyes	DHA contributes to the maintenance of normal vision ^c	Link
Europe	Health (children development)	Eyes	DHA contributes to the visual development of infants ^c	Link 1 Link 2
generic = article 13.1; children's development = article 14.1; SF = structure function; ^a see text for levels required; ^b Example employing required elements; ^c Consult reference for concentrations required for claims				

Regulatory bodies:

Europe- EFSA (European Food Safety Administration)

USA- FDA (Food and Drug Administration)

Using nutrients and bio-actives in food and supplements: can I use it?

1. Has it been used in human consumption in significant amounts?
 - a. Yes- EU- case by case evaluation based on scientific/clinical evidence. US- GRAS (generally regarded as safe) status can be used in food and supplements.
 - b. No – Novel food filing with efficacy, toxicology and adverse effects data.

2. What is the dose?
 - a. Within normal range found in food – food fortification and/or supplement.
 - b. Pharmacological – drug regulation.

Using nutrients and bio-actives in food and supplements: How much can I use?

1. Food fortification – generally for micronutrients with established RDAs
 - a. Up to 15% of the RDA.

2. Food supplement –
 - a. Minimum - 15% of RDA
 - b. Maximum – i) upper limit (UL) defined in nutrition recommendations for micronutrients with known adverse effects at high doses (e.g. vitamin D), ii) none for micronutrients considered without risk (e.g. vitamin B12).

Using nutrients and bio-actives in food and supplements: Interactions

Some foods/extracts with bio-active compounds also contain botanicals that interact with nutrients and can cause problems (e.g. decreased uptake of minerals).

Example: Phytic acid (e.g. beans & nuts) and green tea catechins like epicatechin and theoflavin are strong chelators of metal minerals (iron, zinc..)

TABLE 2 Summary of herb-micronutrient interactions and their mechanisms¹

Phytochemical	Micronutrient affected	Effect and interaction mechanism
Plant polyphenols (tea catechins, phloretin, quercetin)	Iron	Reduced absorption via complexation
	Folate, ascorbate	Reduced absorption via uptake transporter inhibition
Silymarins	Iron	Reduced absorption via complexation
Phytic acid	Calcium, iron, zinc	Reduced absorption via complexation
St. John's wort (hyperforin)	Vitamin D ₃	Enhanced plasma clearance via induction of CYP3A4 metabolism

¹CYP, cytochrome P450.

Q & A

Time to take a break....