CiBARI
il cibo della salute
Bari, 1-2-3 Dicembre 2023
Teatro Petruzzelli
Camera di Commercio di Bari

LA NUTRIGENOMICA DELL'OLIO: COME TI ACCENDO I GENI

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Università degli Studi di Bari Aldo Moro
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Wellcome Trust | MRC IMS Institute of Metabolic Science
University of Cambridge
LITMUS

Nutrition – History and Trends

1900 **Detection/ prevention of deficiencies** (e.g. vitamin A, Iron)

1970 **Balanced diet**
- **Nutritional recommendations** (the concept of calories)
- **Supply of sufficient nutrients** (carbohydrates , fats, proteins, minerals, vitamins)

1990 **Benefits of specific functional foods** ("beyond the balanced diet"– role of non nutrients)

2000-2010 **Nutritional Genomics**

Functional Foods & Rainbow Diet

Colors	Foods	Colorful Protective Substances and Possible Actions
Red	Tomato and tomato products, watermelon, guava	Lycopene: antioxidant, cuts prostate cancer risk
Orange	Carrot, yam, sweet potato, mango, pumpkin	Beta-carotene: supports immune system; powerful antioxidant
Yellow-orange	Citrus fruits—orange, lemon, grapefruit, papaya, peach	Vitamin C, flavonoids: inhibit tumor cell growth, detoxify harmful substances
Green	Spinach, kale, collard, and other greens	Folate: builds healthy cells and genetic material
Green-white	Broccoli, brussels sprouts, cabbage, cauliflower	Indoles, lutein: eliminate excess estrogen and carcinogens
White-green	Garlic, onion, chive, asparagus	Allyl sulfides: destroy cancer cells, reduce cell division, support immune system
Blue	Blueberries, purple grapes, plums	Anthocyanins: destroy free radicals
Red-purple	Grapes, berries, plums	Reservatrol: may decrease estrogen production
Brown	Whole grains, legumes	Fiber: carcinogen removal

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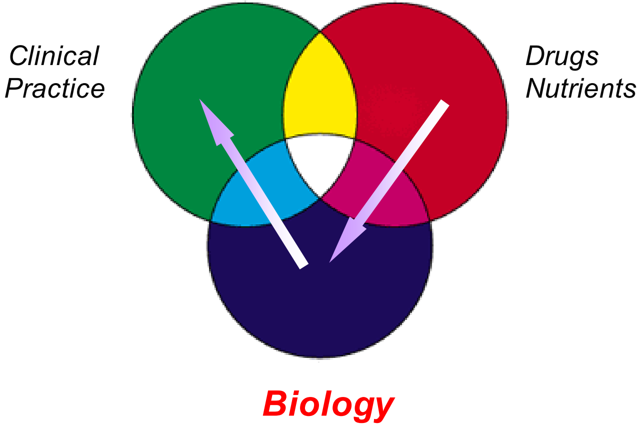
2000-2010 **Nutritional Genomics**

Nutritional Genomics - Definition

"The study of how different foods can interact with particular genes to increase/decrease the risk of diseases"

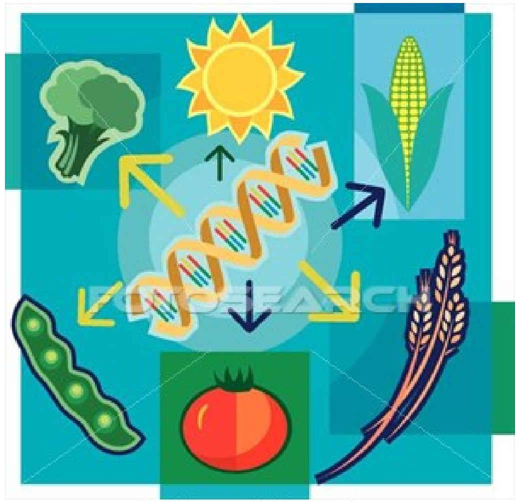


Goal

Use of personalized diets to:

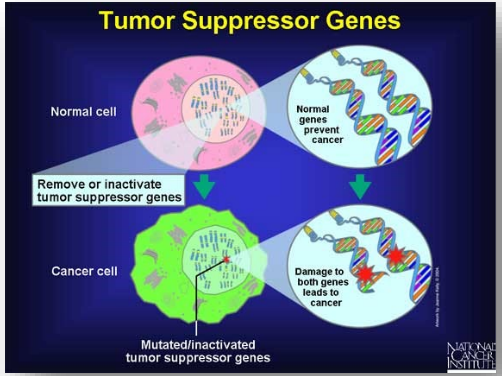
–prevent or delay the onset of disease

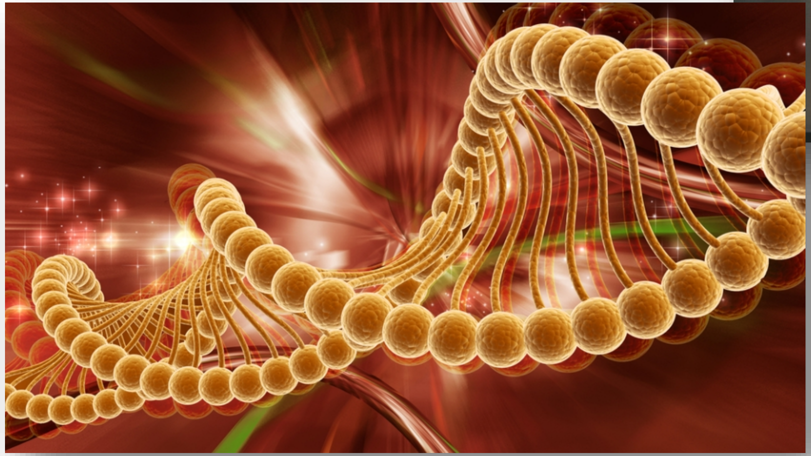
–optimize and maintain human health



vmo0960 www.fotosearch.com

The first step of Nutrigenomics: Decoding the Genetic Code of Life





Nutritional Genomics – Main assumptions

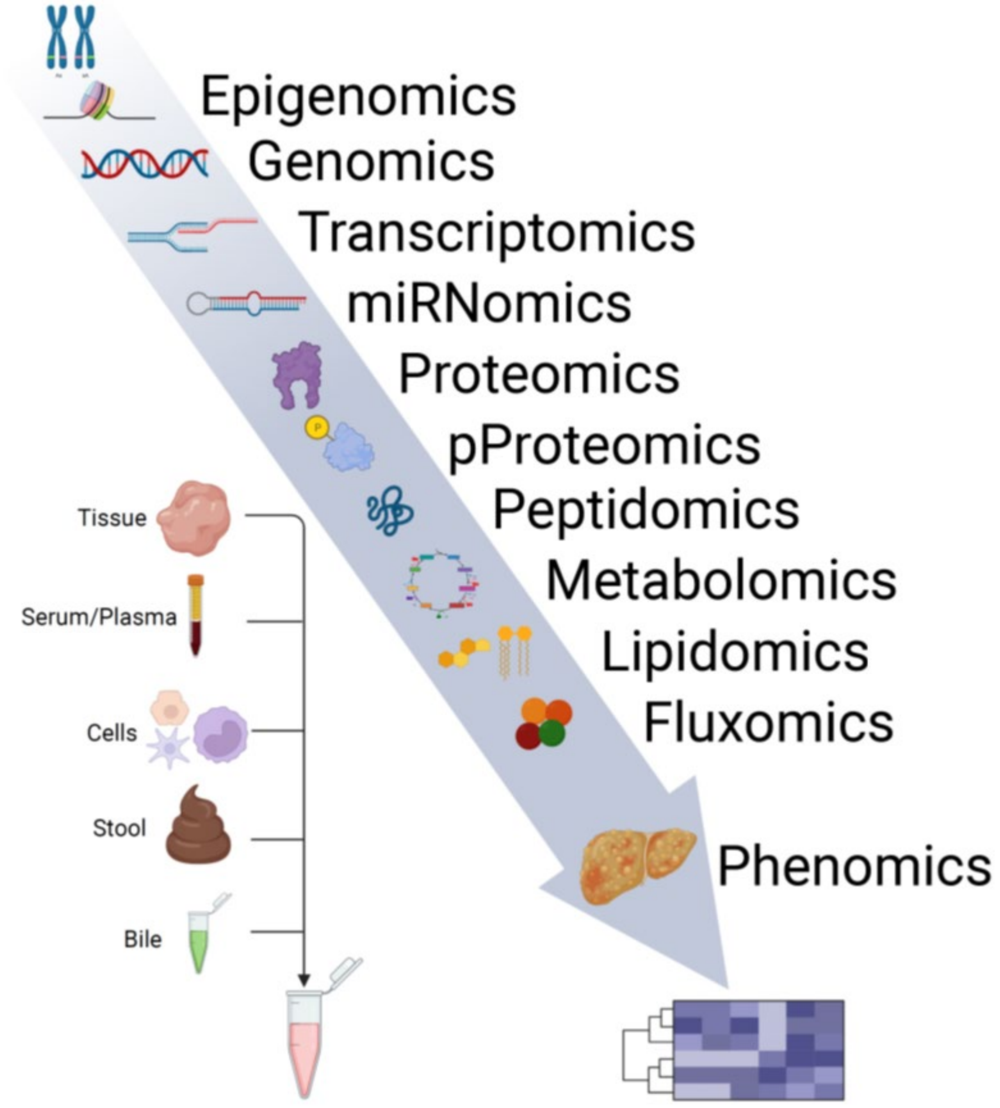
- The DNA sequence brings only the "**Genetic Code**"
- The **Phenotype** is the resultant of the interaction of this genetic code with the environment
- **Genes can be turned "*on*" or "*off*" by:**
  - Intracellular processes (e.g. signaling cascades)
  - Hormones (e.g. steroids)
  - Environmental influences (e.g. cold)
  - Drugs (Pharmacogenomics)
  - **Diet (Nutrigenomics)**

  inducing a rewiring in the activation status of different pathways and a modification of cell behavior

- The composition of food goes **beyond "caloric" content** as it can influence the biology of our body;

From Nutritional Genomics to System Biology

"The beginning of a revolution"



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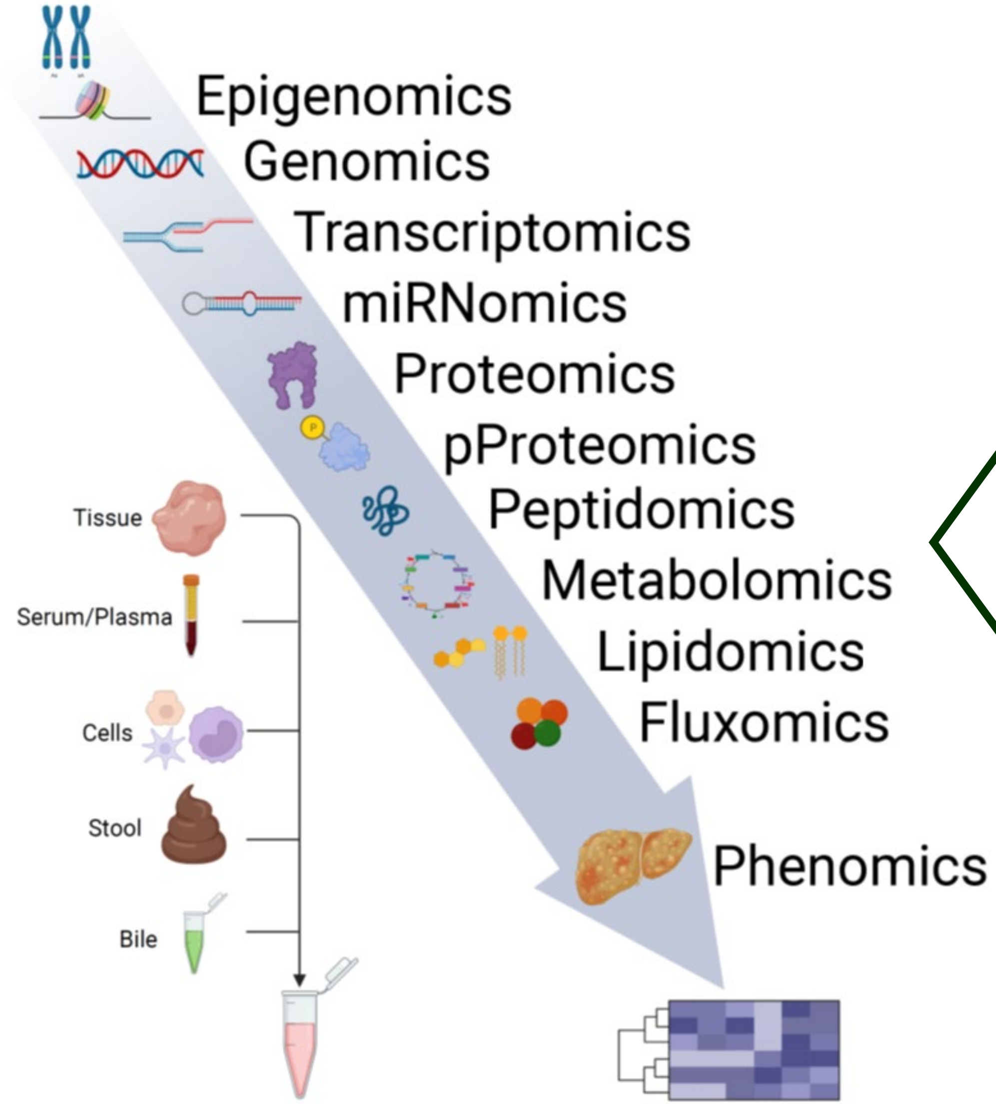

Nutrients

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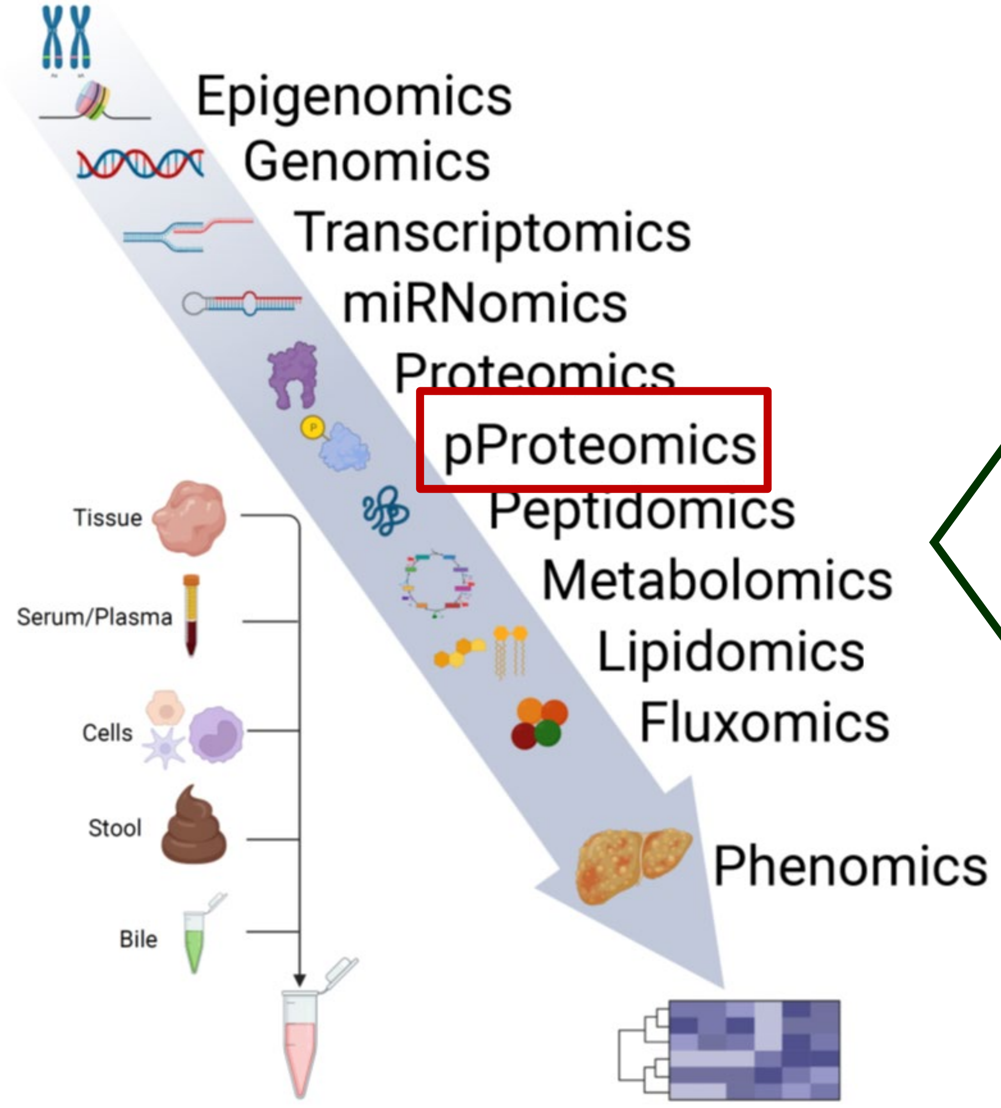

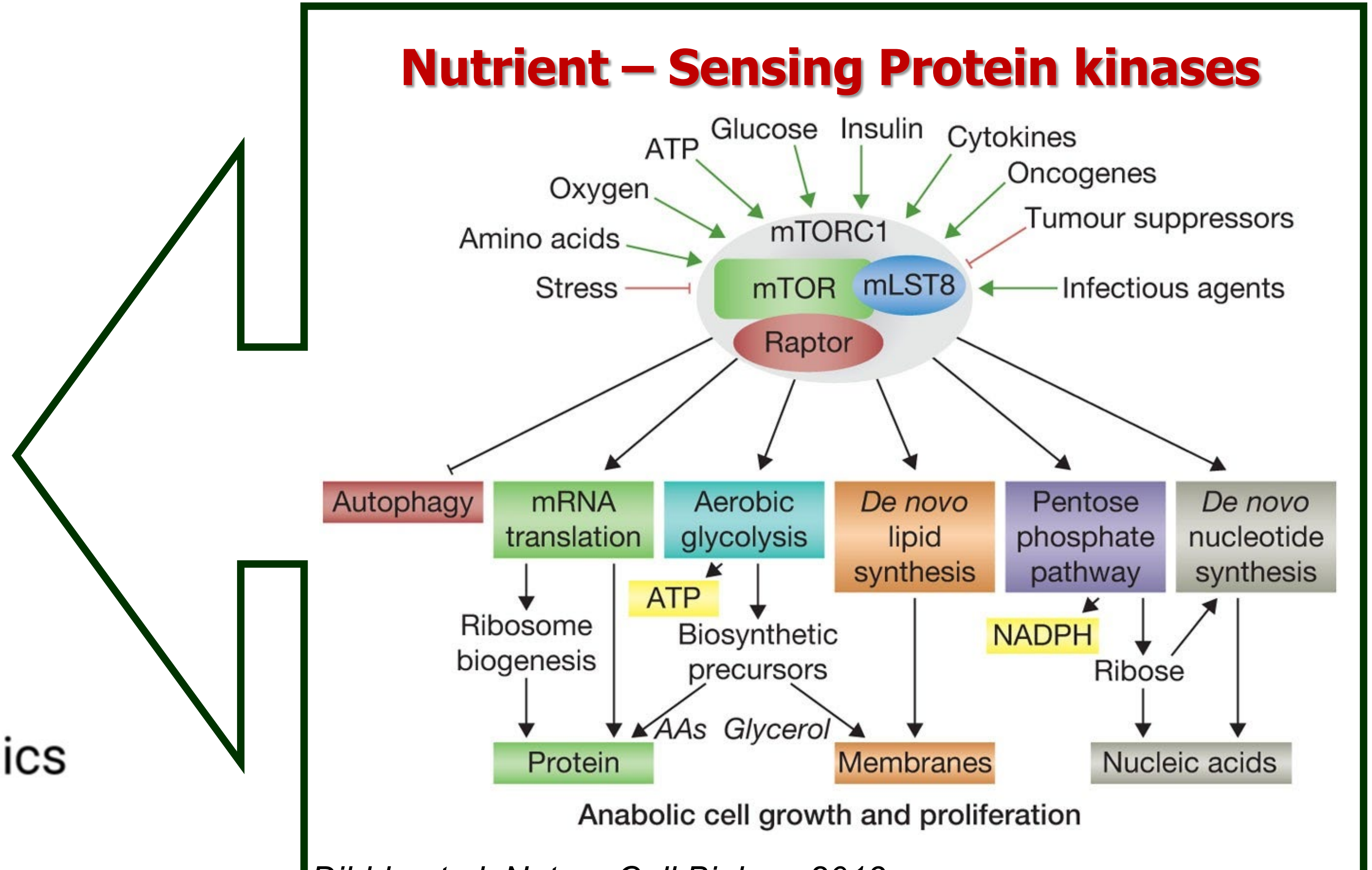

Dibble et al, Nature Cell Biology 2013

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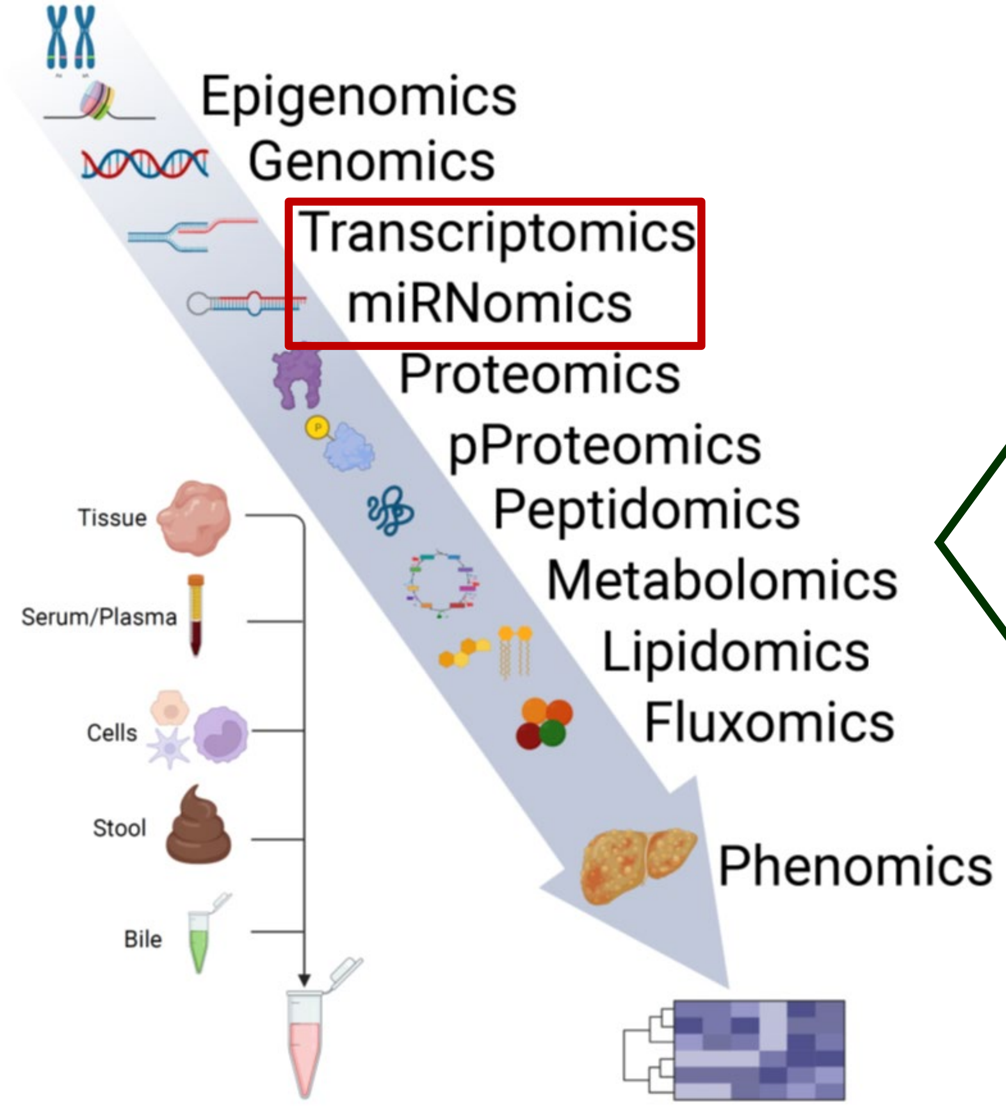
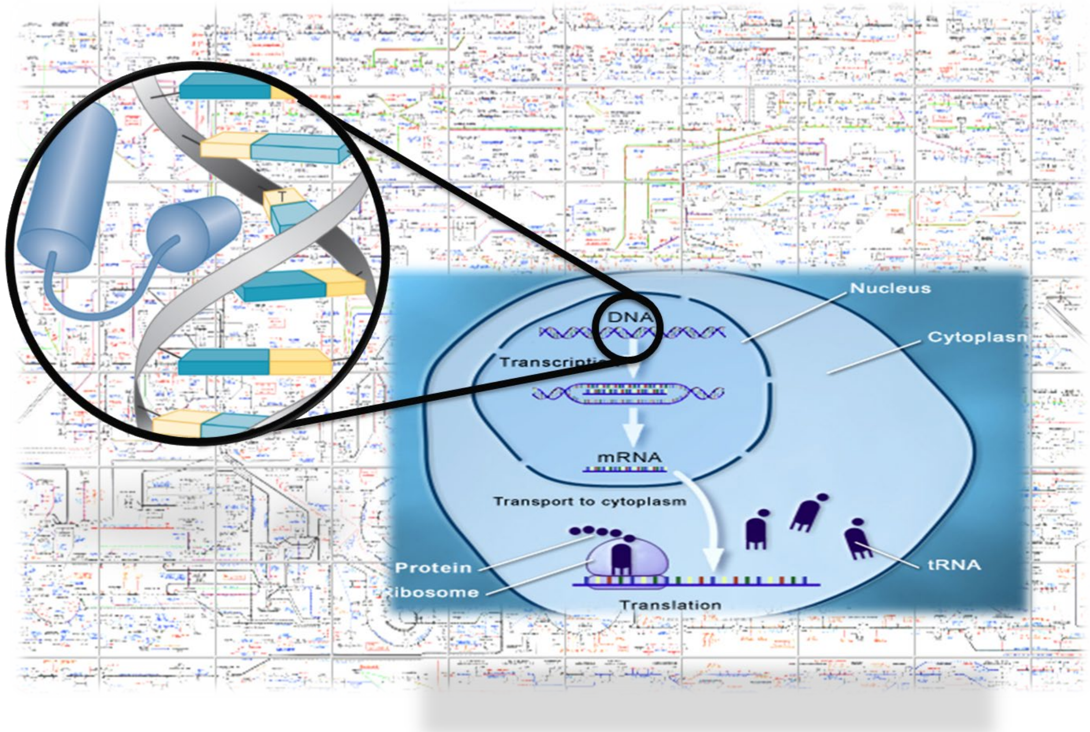
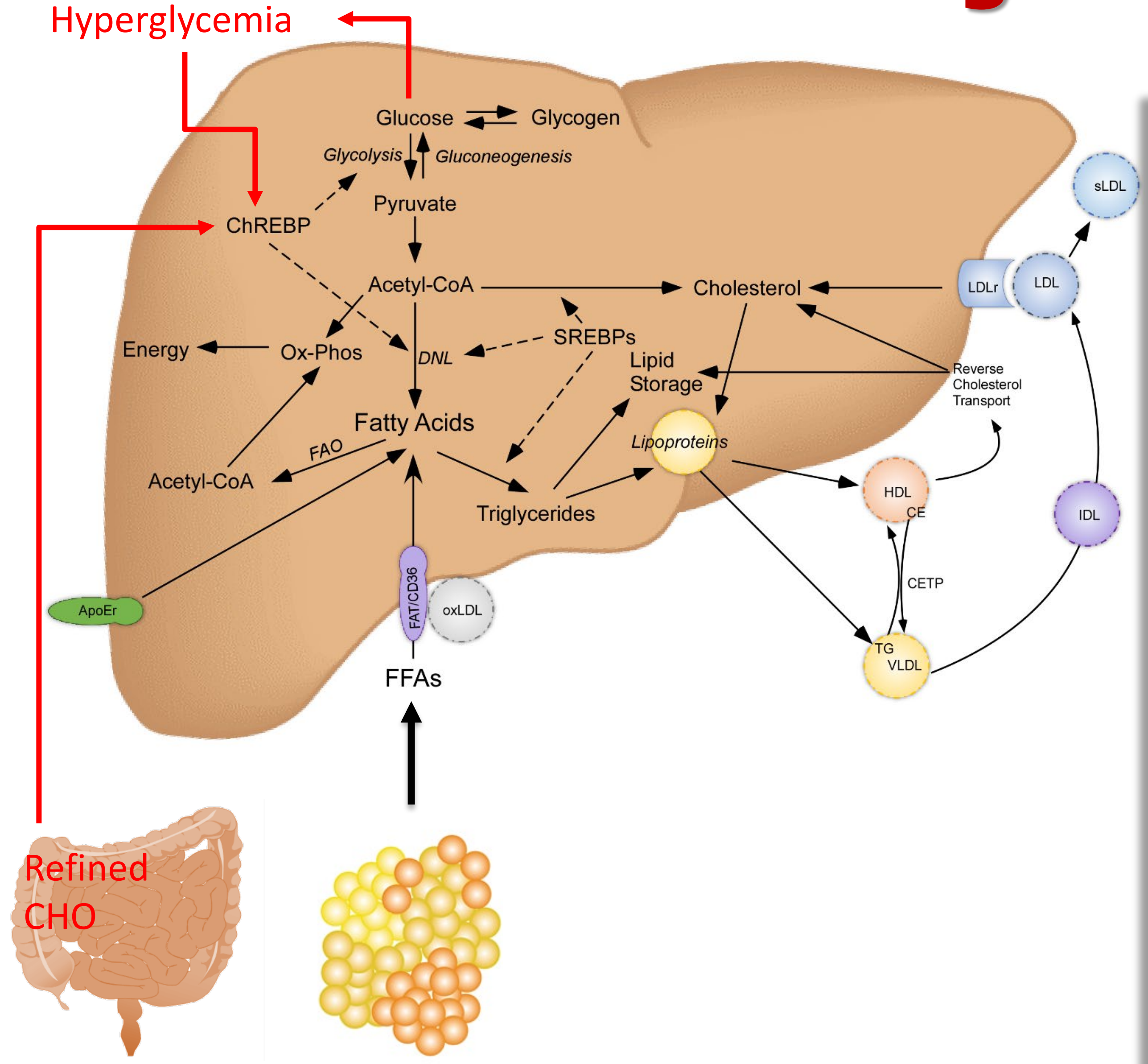


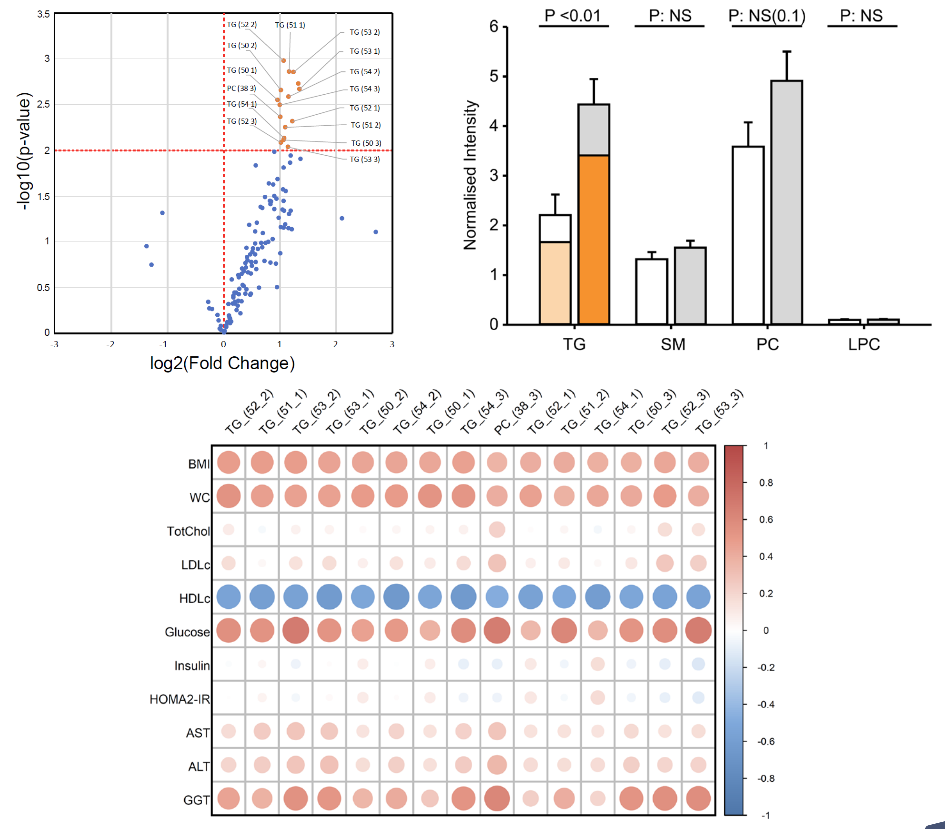
Nutrients can modify gene transcription



Nutrient – Sensing Transcription Factors

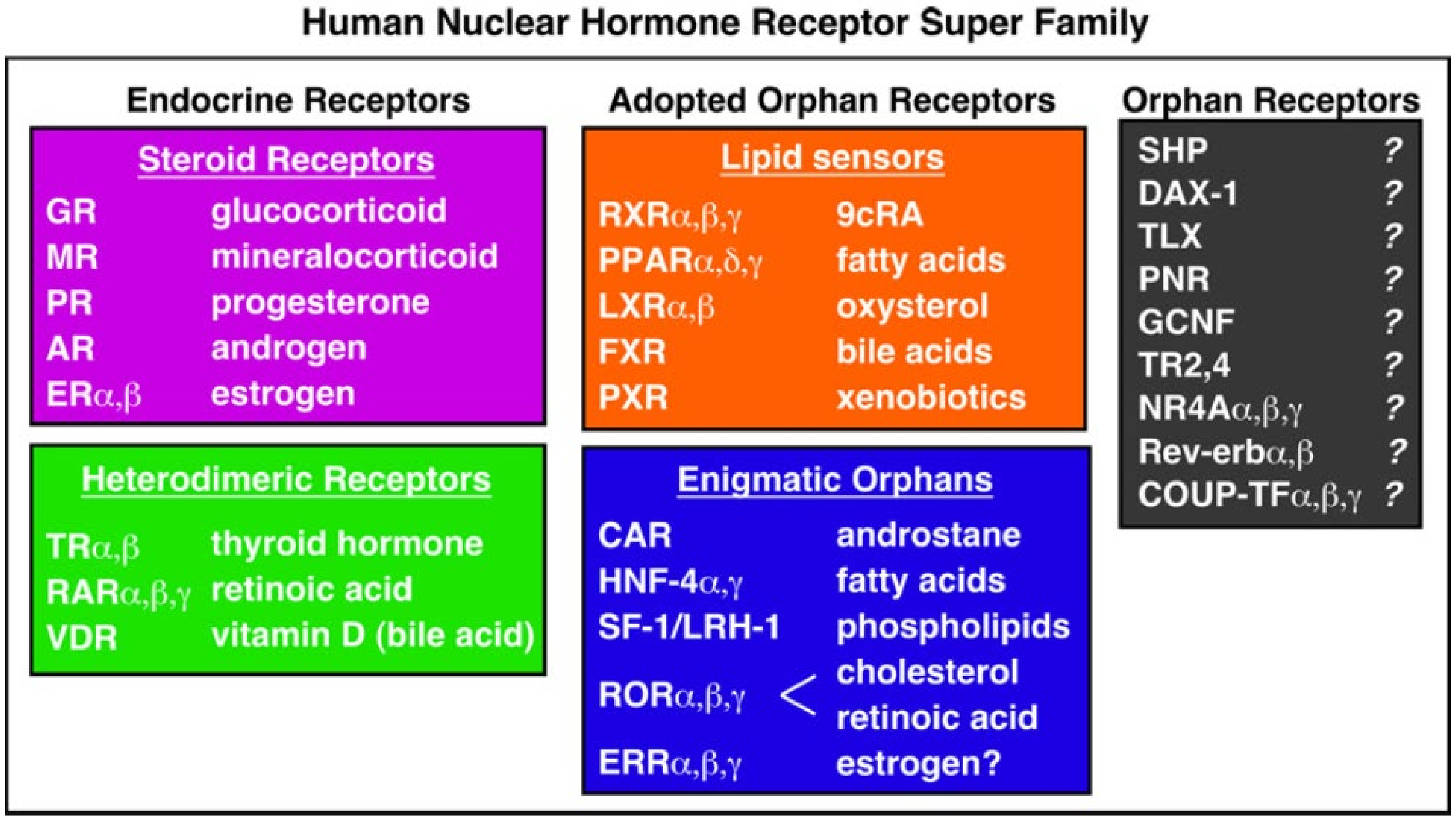


TG enriched in DNL products are increased in the VLDL of patients with MetS/NAFLD



Mocciaro G. & Vacca, unpublished results – Collaboration with Simona D'Amore & Antonio Moschetta

Nutrient – Sensing Transcription Factors

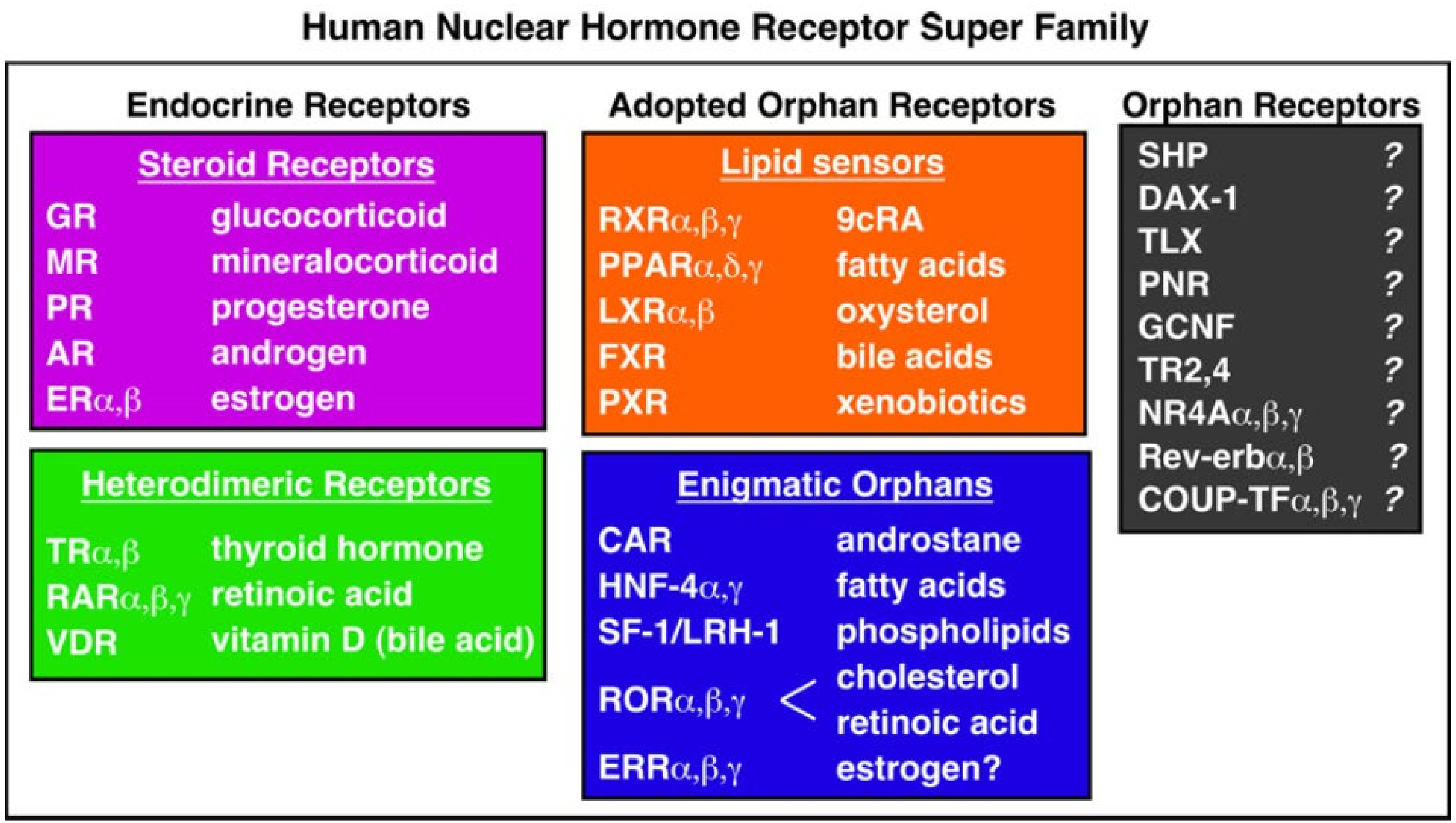


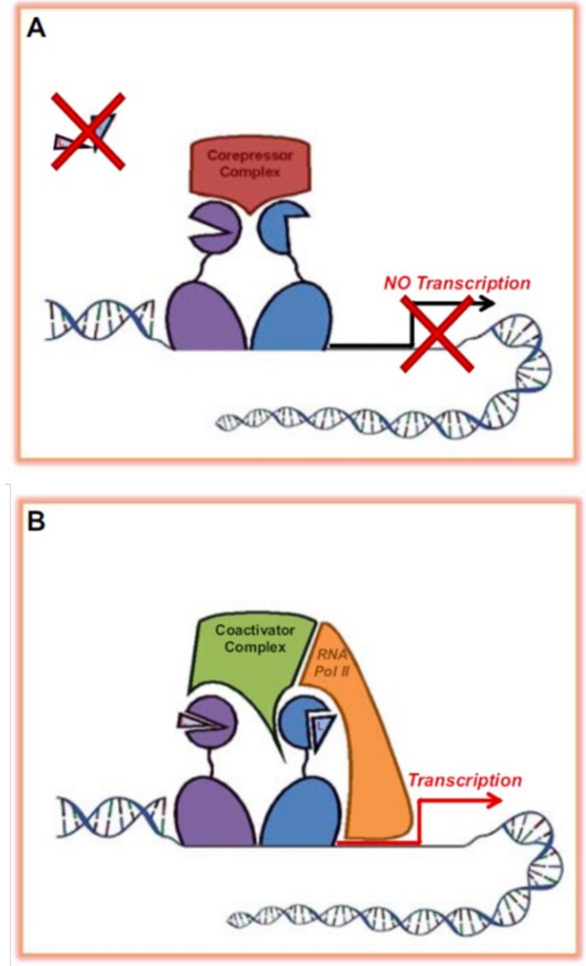
There are sensors for:

- Retinoids (Vitamin A)
- Fatty acids
- Cholesterol
- Bile acids

Sonoda et al, FEBS Lett. 2008

Nutrient – Sensing Transcription Factors





Sonoda et al, FEBS Lett. 2008

Nutrient – Sensing Transcription Factors

Human Nuclear Hormone Receptor Super Family

Endocrine Receptors

Steroid Receptors	
GR	glucocorticoid
MR	mineralocorticoid
PR	progesterone
AR	androgen
ERα,β	estrogen

Heterodimeric Receptors	
TRα,β	thyroid hormone
RARα,β,γ	retinoic acid
VDR	vitamin D (bile acid)

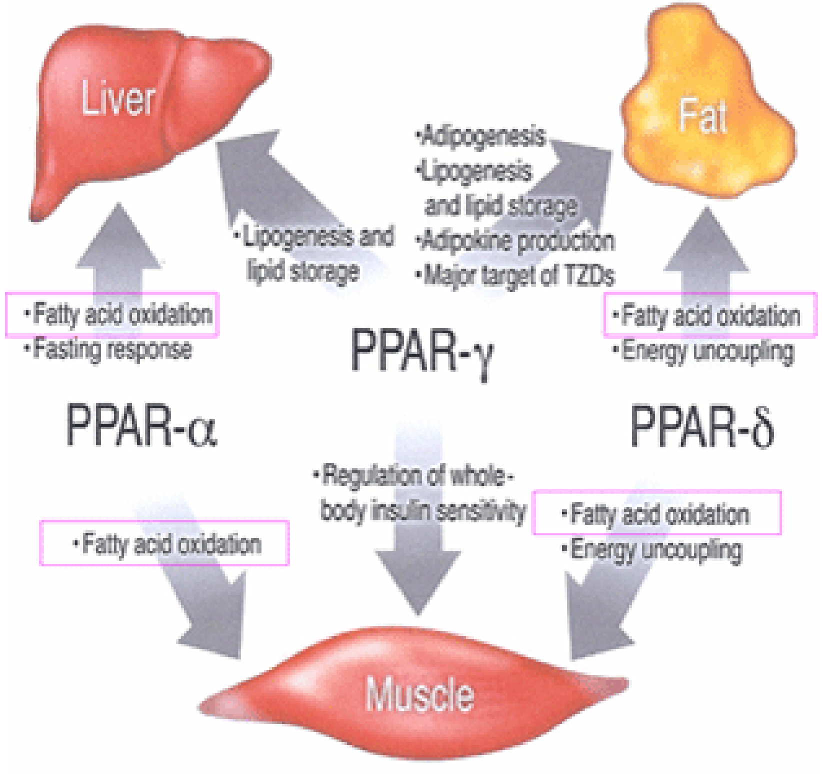
Adopted Orphan Receptors

Lipid sensors	
RXRα,β,γ	9cRA
PPARα,δ,γ	fatty acids
LXRα,β	oxysterol
FXR	bile acids
PXR	xenobiotics

Enigmatic Orphans	
CAR	androstane
HNF-4α,γ	fatty acids
SF-1/LRH-1	phospholipids
RORα,β,γ <	cholesterol; retinoic acid
ERRα,β,γ	estrogen?

Orphan Receptors

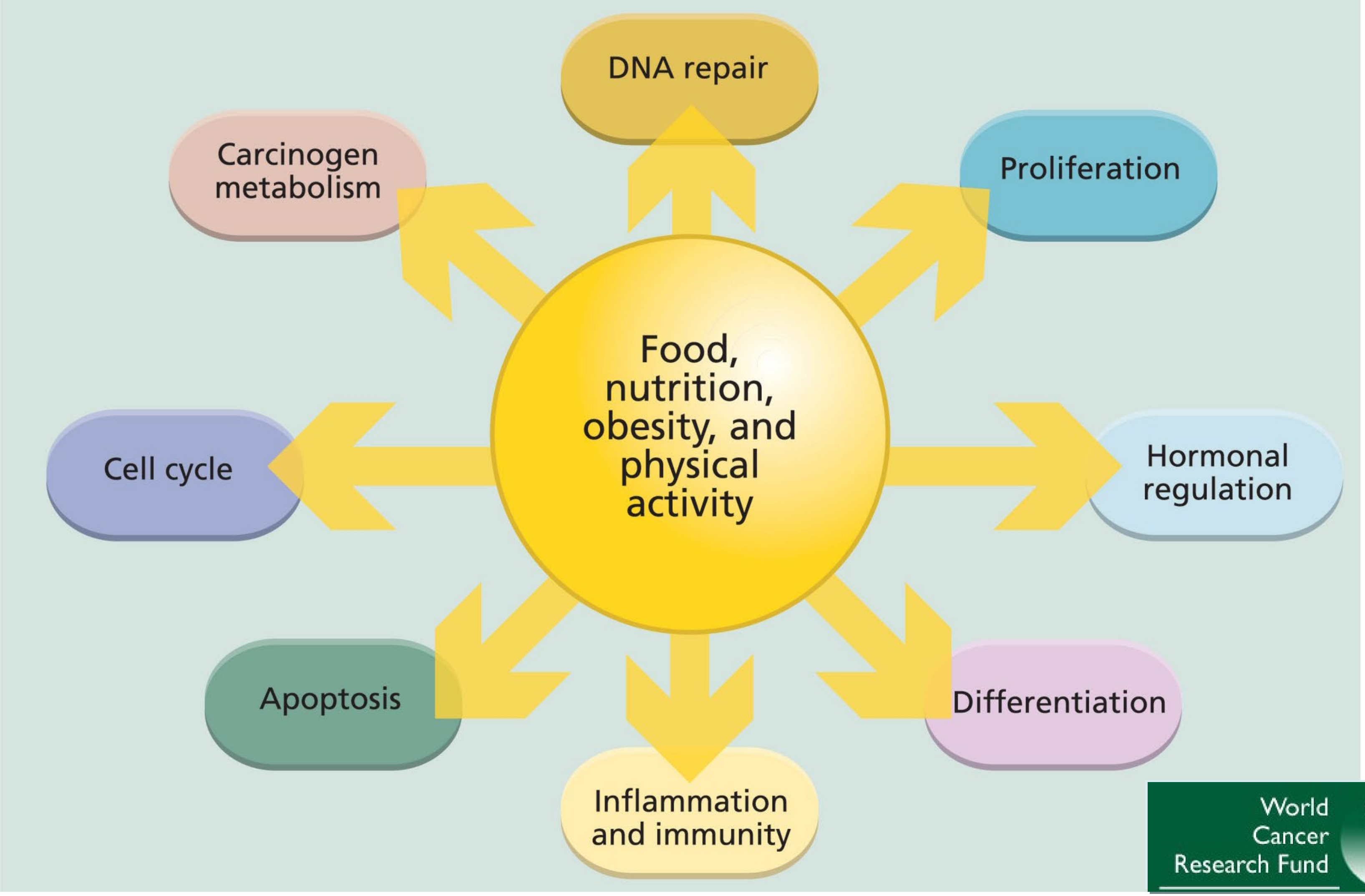
SHP	?
DAX-1	?
TLX	?
PNR	?
GCNF	?
TR2,4	?
NR4Aα,β,γ	?
Rev-erbα,β	?
COUP-TFα,β,γ	?



Sonoda et al, FEBS Lett. 2008

From Nutritional Genomics to System Biology

"The beginning of a revolution"



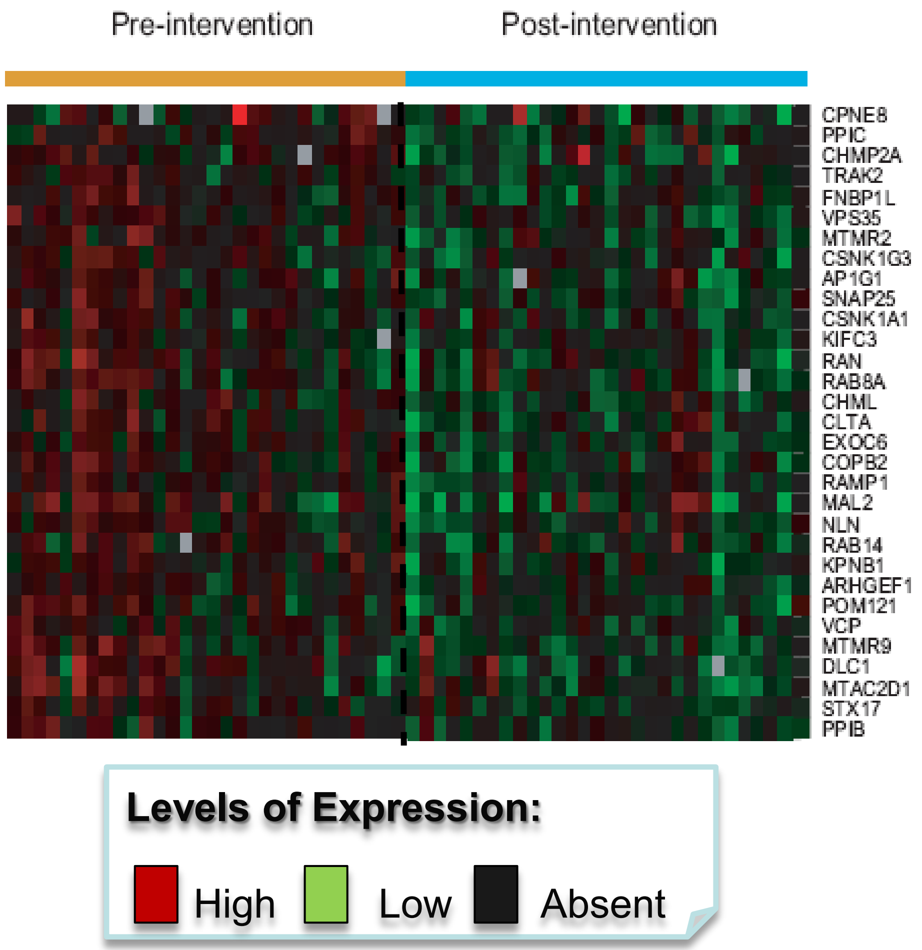
World Cancer Research Fund
American Institute for Cancer Research

From Nutritional Genomics to System Biology

"The beginning of a revolution"

Effects of Lifestyle Changes, Diet & Physical Exercise on gene expression of patients with Prostate Cancer

Metabolic Changes	Delta
Body mass index (BMI)	-2.6 kg/m^2
Systolic BP	-9.2 mmHg
Diastolic BP	-5.4 mmHg
Total cholesterol	**-45.2 mg/dL**
LDL cholesterol	**-34.2 mg/dL**
HDL cholesterol	-8.3 mg/dL
LDL/HDL ratio	-0.4



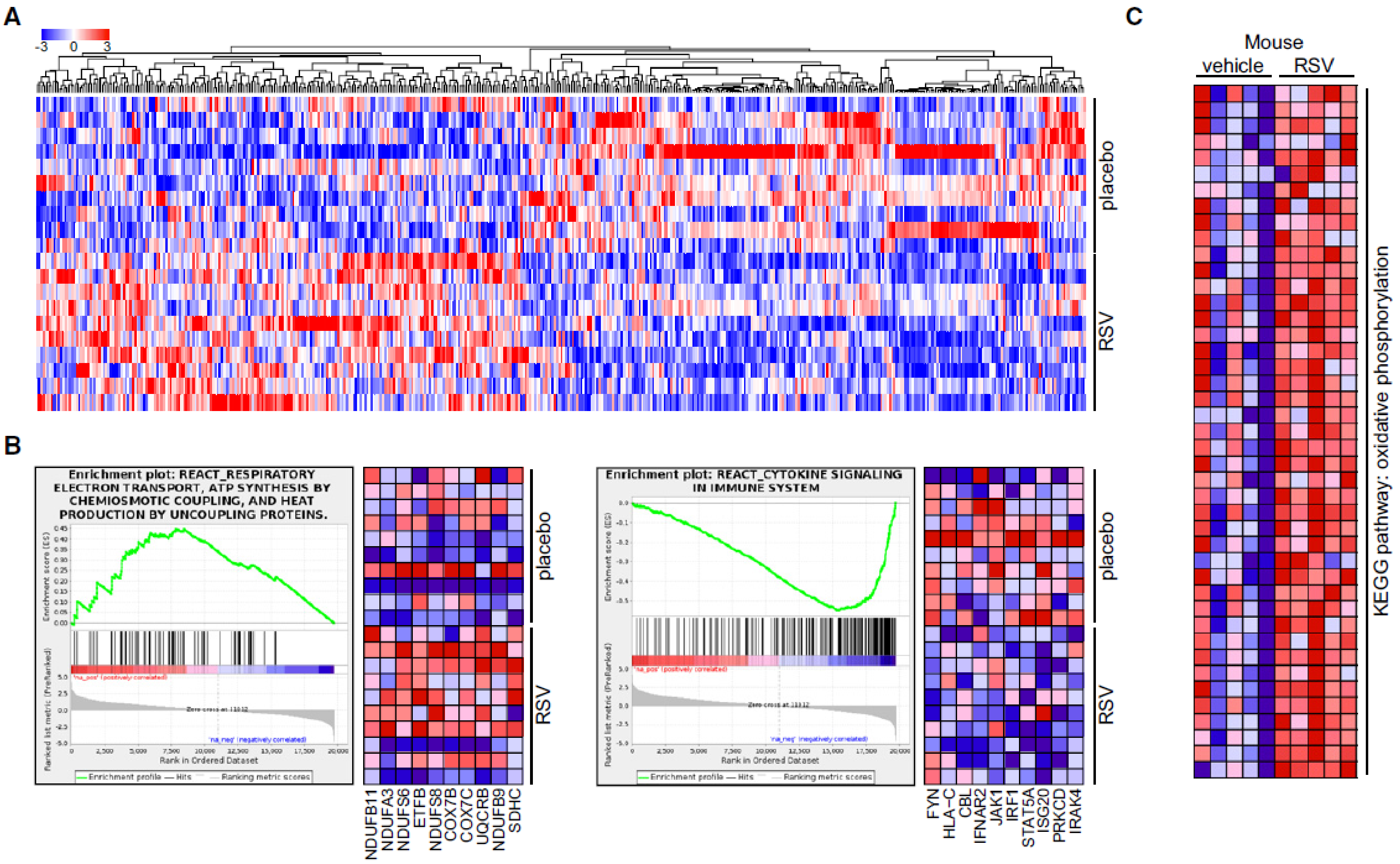
Ornish, et al. PNAS 2008

From Nutritional Genomics to System Biology

"The beginning of a revolution"

Cell Metabolism
Article

Calorie Restriction-like Effects of 30 Days of Resveratrol Supplementation on Energy Metabolism and Metabolic Profile in Obese Humans



Cell PRESS

From Nutritional Genomics to System Biology

"The beginning of a revolution"

Cell Metabolism
Article

Calorie Restriction-like Effects of 30 Days of Resveratrol Supplementation on Energy Metabolism and Metabolic Profile in Obese Humans

Table 2. Plasma Biochemistry

	Placebo	Resveratrol	P value
Resveratrol (ng/ml)	Not detectable	182.59 ± 30.33	-
Dihydroresveratrol (ng/ml)	Not detectable	289.14 ± 93.57	-
Glucose (mmol/l)	5.28 ± 0.15	5.06 ± 0.13	0.05
Insulin (mU/l)	11.94 ± 1.11	10.31 ± 1.25	0.04
HOMA index	2.80 ± 0.20	2.43 ± 0.24	0.03
Triglycerides (mmol/l)	2.29 ± 0.23	2.16 ± 0.21	0.03
Nonesterified fatty acids (μmol/l)	572 ± 77	621 ± 38	0.59
Leptin (ng/ml)	14.28 ± 1.98	12.91 ± 1.84	0.04
Adiponectin (μg/ml)	6.47 ± 0.55	6.45 ± 0.56	0.95
CRP (ng/ml)	1.52 ± 0.35	1.33 ± 0.31	0.11
IL-1β (pg/ml)	1.33 ± 0.27	0.94 ± 0.15	0.20
IL-6 (pg/ml)	3.13 ± 0.67	2.42 ± 0.38	0.09
IL-8 (pg/ml)	4.94 ± 0.59	4.28 ± 0.25	0.19
TNF-α (pg/ml)	16.15 ± 2.27	15.14 ± 2.03	0.04
Leukocytes (10^9/l)	7.03 ± 0.44	6.48 ± 0.39	0.03
ALAT (U/l)	31.91 ± 2.21	28.09 ± 1.54	0.02

Plasma values after 30 days of resveratrol or placebo supplementation. Values are given as means ± SEM (n = 11). See also Table S1.

Table 3. Clinical Improvement after Resveratrol

	Placebo	Resveratrol	P value
24 hr respiratory quotient	0.89 ± 0.007	0.91 ± 0.006	0.09
Respiratory quotient daytime	0.89 ± 0.004	0.91 ± 0.003	0.001
Respiratory quotient nighttime	0.87 ± 0.007	0.88 ± 0.009	0.18
24 hr energy expenditure (MJ/day)	11.86 ± 0.29	11.91 ± 0.29	0.64
Sleeping metabolic rate first night (MJ/day)	8.09 ± 0.24	7.75 ± 0.23	0.007
Sleeping metabolic rate second night (MJ/day)	8.06 ± 0.22	7.90 ± 0.18	0.06
Diet-induced thermogenesis (MJ/day)	1.02 ± 0.13	1.14 ± 0.17	0.33
Physical activity index	1.49 ± 0.02	1.50 ± 0.01	0.37
Systolic blood pressure (mmHg)	130.5 ± 2.7	124.7 ± 3.1	0.006
Diastolic blood pressure (mmHg)	81.6 ± 2.8	80.0 ± 2.9	0.18
Mean arterial pressure (mmHg)	97.9 ± 2.7	94.9 ± 2.9	0.02

Energy metabolism (n = 10), and blood pressure (n = 11) after 30 days of resveratrol or placebo supplementation. Values are given as means ± SEM. See also Table S2.

Where Olive Oil Stands from a «Nutrigenomics» standpoint?

Olive Oil

98-99% Major components

- **Unsaturated fatty acids (85%):**
  - Monounsaturated fatty acids
    - Oleic acid: (70-80%)
  - Polyunsaturated fatty acids (omega-6)
    - Linoleic acid (4-12%)
- **Saturated fatty acids (small amounts):**
  - Palmitic acid (7-15%)
  - Stearic acid (2-6%)

0.5-2% Minor components:

- Alcohols
- Plant Sterols
- Polyphenols
- Hydrocarbons

Nutr Metab Cardiovasc Dis. 2010, Olive oil and health: summary of the II international conference on olive oil and health consensus report, Jaén and Córdoba (Spain) 2008
Mauro Finicelli et al, Polyphenols, the Healthy Brand of Olive Oil: Insights and Perspectives MDPI 2021

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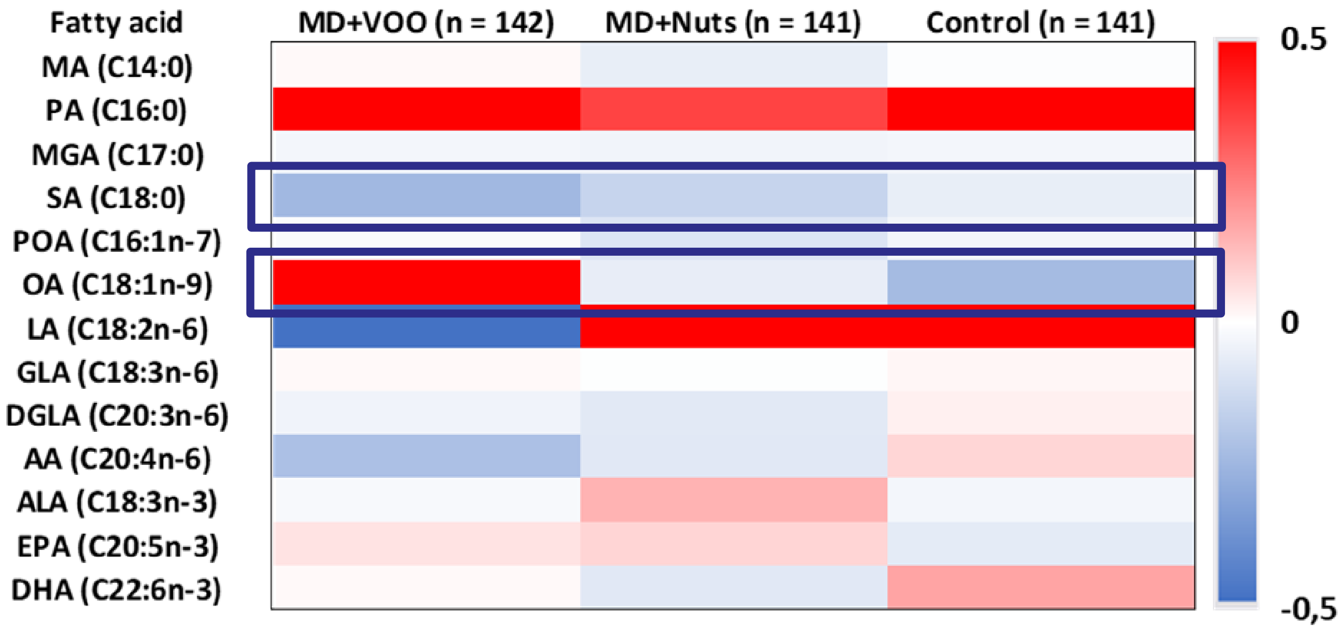
Total plasma fatty acid % changes after 1 year interventional study (PREDIMED)



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Plant Sterols

- Anti-inflammatory effect
- Competition with cholesterol absorbtion
- Activation of pathways involved in: signal transduction, cellular response to stress, cell proliferation and differentiation
- Reduction of:
  - LDL cholesterol (6-15% - The combined intake of phytosterols and statins results in an additional reduction of 4.5-6.4% in LDL cholesterol)
  - Triglycerides (8%)

Adapted from Mayneris-Perxachs J et al., PlosOne 2014

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Olive Oil

Polyphenols

decrease of

- oxidative damage induced by lipid
- endothelial dysfunction
- pro-thrombotic state
- pro-inflammatory state

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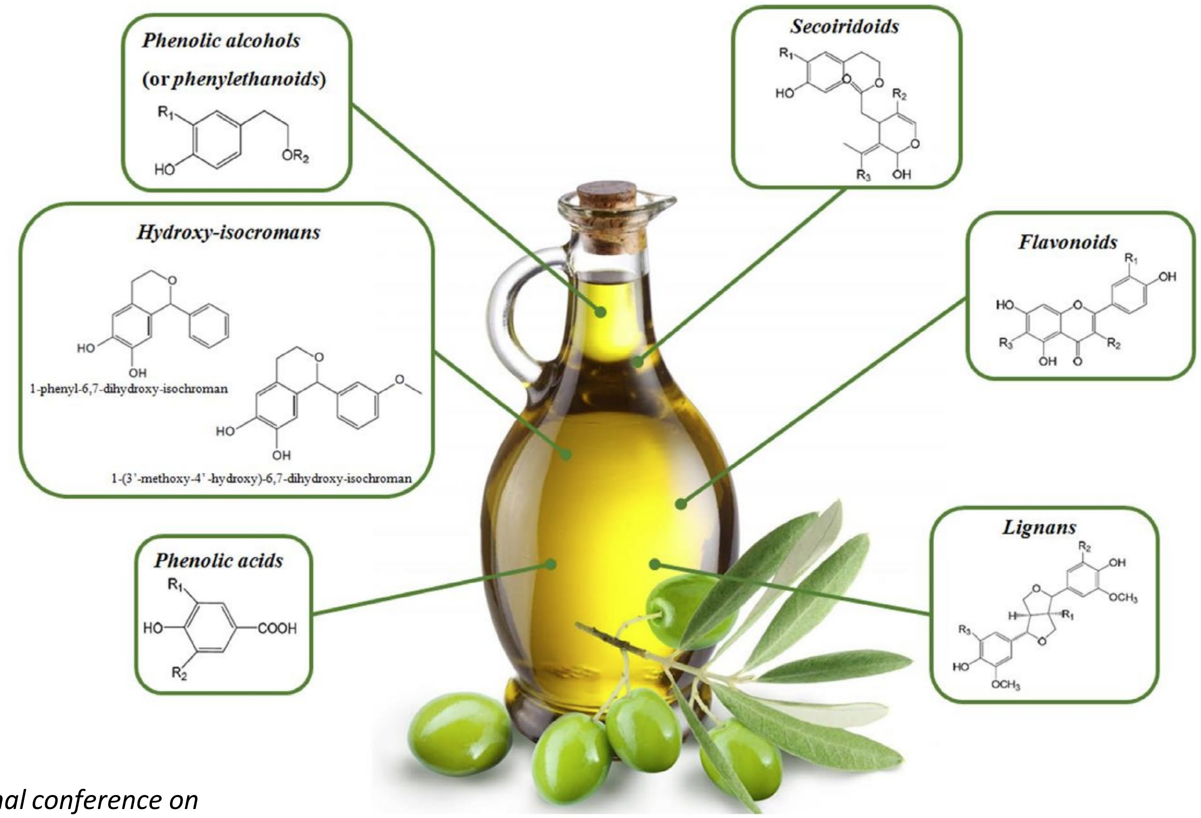

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Table 1. Classification of the main hydrophilic phenolic compounds found in virgin olive oils and their average concentration in different types of olive oil.

Chemical Structure	Components	ROO mg/kg * (Mean ± SD)	Virgin (Fine) mg/kg * (Mean ± SD)	EVOO mg/kg * (Mean ± SD)
Phenolic acids	benzoic	-	-	-
	gallic	-	-	-
	p-hydroxybenzoic	-	0.37 ± 0.37	-
	protocatechuic	-	1.47 ± 0.56	-
	syringic	-	0.81 ± 1.17	0.25 ± 0.25
	vanillic	-	1.22 ± 2.04	0.64 ± 0.50
	caffeic	-	0.21 ± 0.63	0.19 ± 0.45
	cinnamic	-	-	0.17 ± 0.14
	o-coumaric	-	-	-
	p-coumaric	-	0.24 ± 0.81	0.92 ± 1.03
	ferulic	-	0.19 ± 0.50	0.19 ± 0.19
	sinapic	-	-	-
Phenolic alcohols	hydroxytyrosol (3,4-DHPEA)	6.77 ± 8.26	3.53 ± 10.19	7.7 2 ± 8.81
	tyrosol (*p*-HPEA)	4.11 ± 2.24	5.34 ± 6.98	11.32 ± 8.53
Secoiridoids	oleuropein	-	-	1.65 ± 1.85
	oleuropein aglycone	125.40 ± 41.80	120.57 ± 125.53	36.63 ± 24.34
	ligstroside aglycone	59.93 ± 18.58	82.01 ± 67.78	17.44 ± 18.13
	monoaldehydic form of oleuropein aglycone (3,4-DHPEA-EA)	10.90 ± 0.00	95.00 ± 116.01	72.20 ± 64.00
	monoaldehydic form of ligstroside aglycone (*p*-HPEA-EA)	15.20 ± 0.00	69.05 ± 69.00	38.04 ± 17.23
	dialdehydic form of decarboxymethyl elenolic acid linked to hydroxytyrosol (oleacein: 3,4-DHPEA-EDA)	57.37 ± 27.04	77.83 ± 256.09	251.60 ± 263.24
	dialdehydic form of decarboxymethyl elenolic acid linked to tyrosol (oleocanthal: *p*-HPEA-EDA)	38.95 ± 9.29	71.47 ± 61.85	142.77 ± 73.17
Flavonoids	flavones			
	luteolin	1.17 ± 0.72	1.29 ± 1.93	3.60 ± 2.32
	apigenin	0.30 ± 0.17	0.97 ± 0.71	11.68 ± 12.78
	flavanonol			
	taxifolin	-	-	-
Lignans	(+)-1-acetoxypinoresinol	7.52 ± 9.10	4.43 ± 21.28	6.63 ± 10.78
	(+)-pinoresinol	24.05 ± 10.02	23.71 ± 17.03	4.19 ± 2.78
Hydroxy-isocromans	1-phenyl-6,7-dihydroxy-isochroman	-	-	-
	1-(3′-methoxy-4′hydroxy)-6,7-dihydroxy-isochroman	-	-	-
Polyphenols, total		198.0 ± 14.85	206.73 ± 150.08	551.42 ± 235.02

Source: Adapted from Cicerale et al., [81] and Rothwell et al., [93,94]. * Fresh weight. ROO: refined olive oil; EVOO: extra virgin olive oil.

Lopes de Souza A. P. et al., Nutrients 2017

Nutr Metab Cardiovasc Dis. 2010, Olive oil and health: summary of the II international conference on olive oil and health consensus report, Jaén and Córdoba (Spain) 2008
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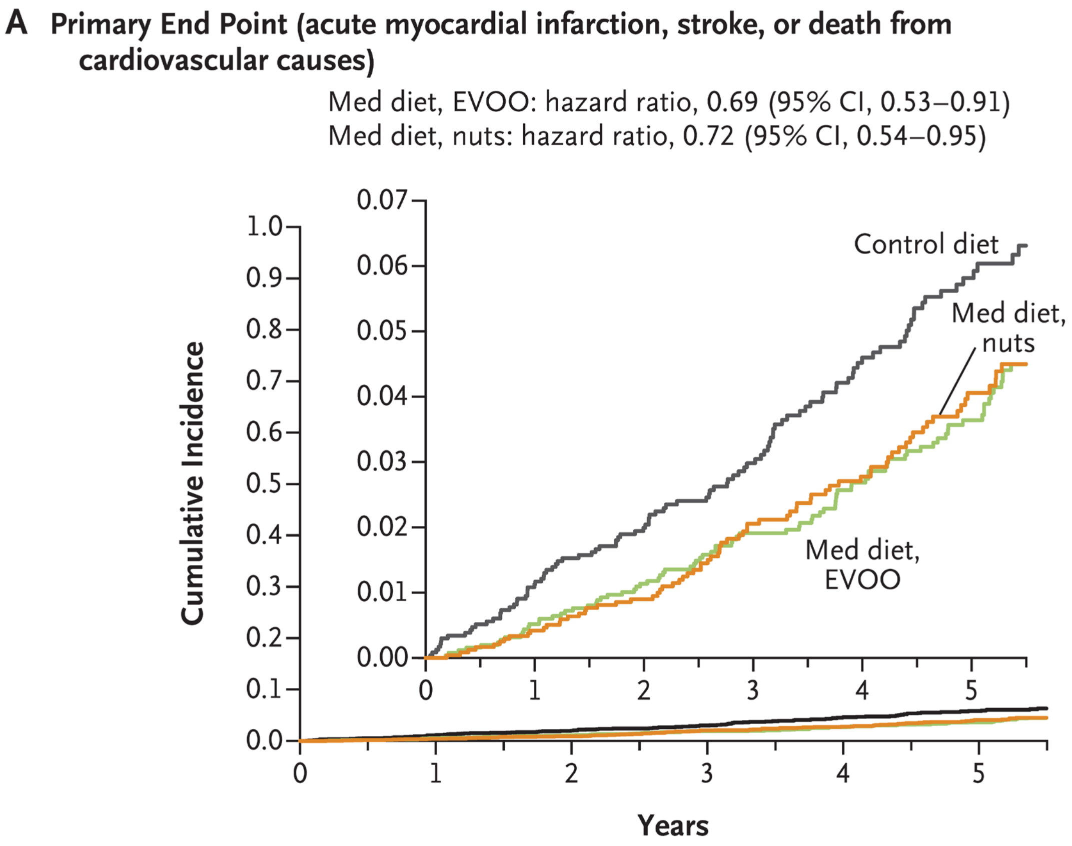
Olive Oil

- Major component of the Mediterranean Diet
- Functional food:
  - anti-inflammatory
  - anti-oxidant
  - anti-thrombotic
  - anti-atherosclerotic
- Potential therapeutic efficacy:
  - Cardiovascular system;
  - Metabolism;
  - Hepatobiliary and intestinal tracts;
  - Immune system;



30% reduction in major CVD events in 7447 high CVD risk subjects followed for 5 years.

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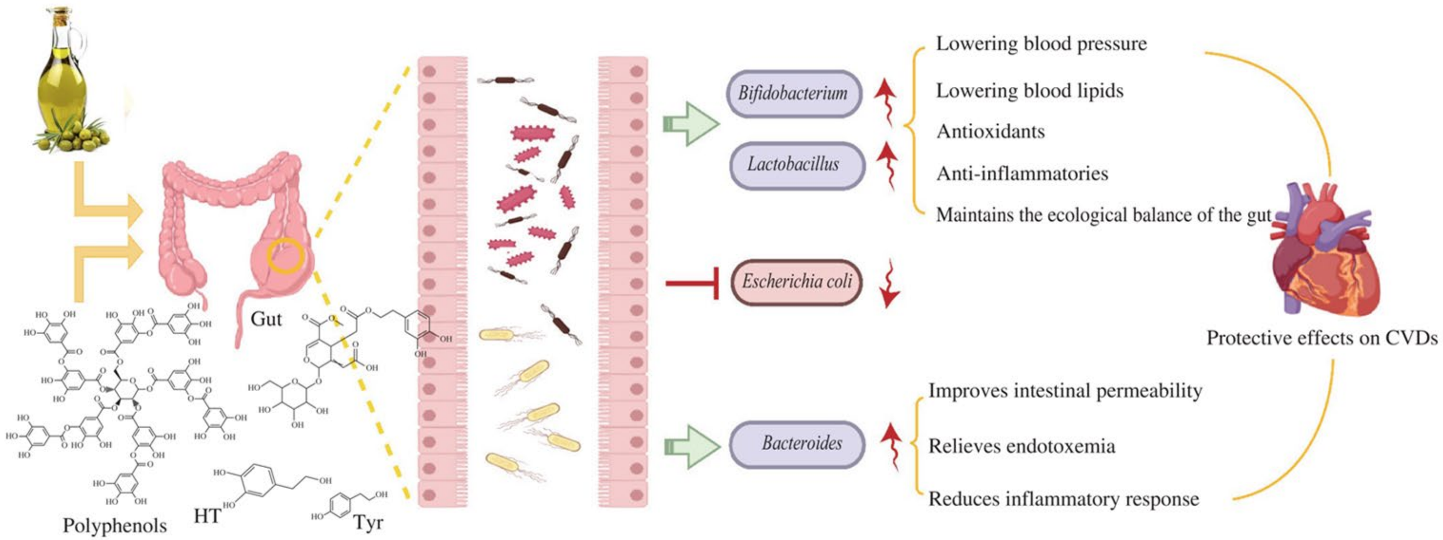

Fig. 3 Contribution of OO on CVDs by intestinal microbiota regulating. Ole: oleuropein. Tyr: tyrosol. Green arrows: promoting effect. Red arrows: inhibitory action.

Lu Y et al., Food Science and Human Wellness 2023
Ducheix S et al., Gastroenterology 2018

Nutr Metab Cardiovasc Dis. 2010, Olive oil and health: summary of the II international conference on olive oil and health consensus report, Jaén and Córdoba (Spain) 2008
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Nutrigenomics Effects of High Polyphenol EVOO
Study Design

Population Study
24 subjects

12 healthy subjects
(6F+6M)

12 patients with MS
(6F+6M)

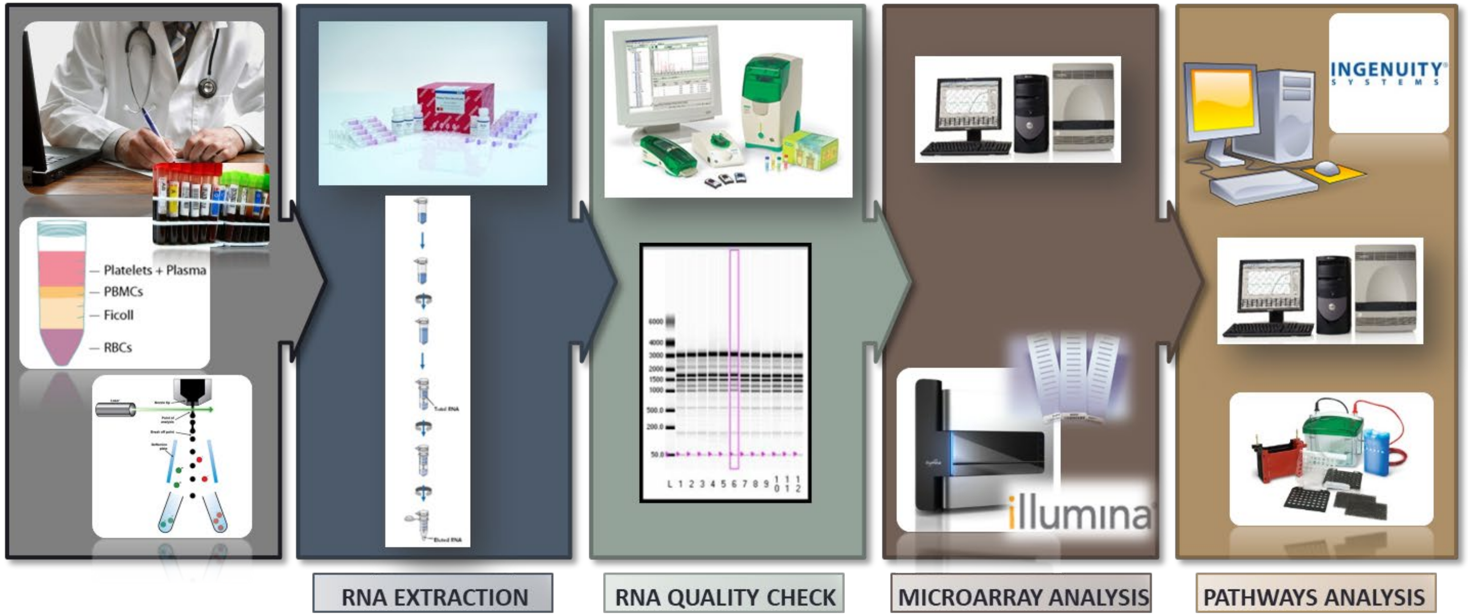
T0

Physical examination
Biochemical measurements
Instrumental exams
PBMCs Isolation

4 hours after intake of high phenols content VOO (50 ml)

T1

Biochemical measurements
PBMCs Isolation



D'Amore, et al BBA 2016

Changes in PBMC transcriptomics after acute EVOO intake

CTRL

2056 GENES

Anti-inflammatory

Anti-cancer

Metabolism

- β-oxidation of fatty acids
- Energy expenditure
- Insulin sensitivity

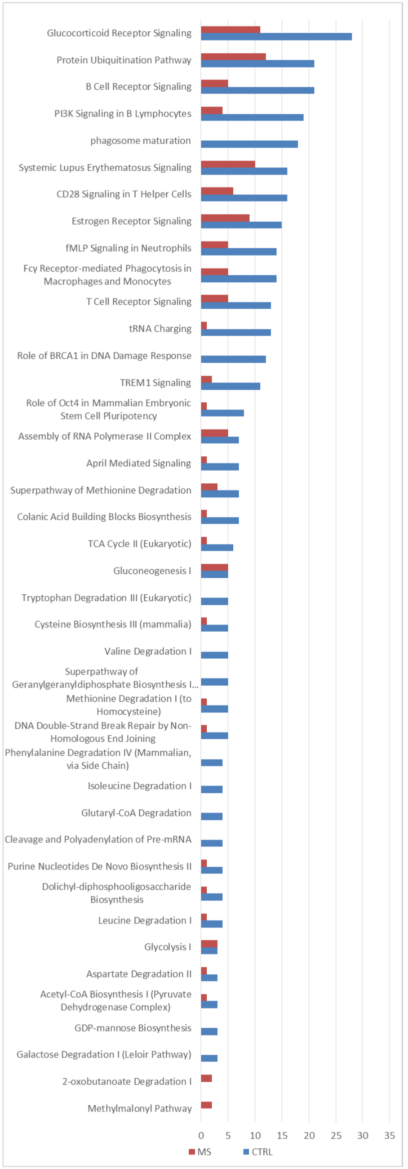
Pro-inflammatory

Pro-cancer

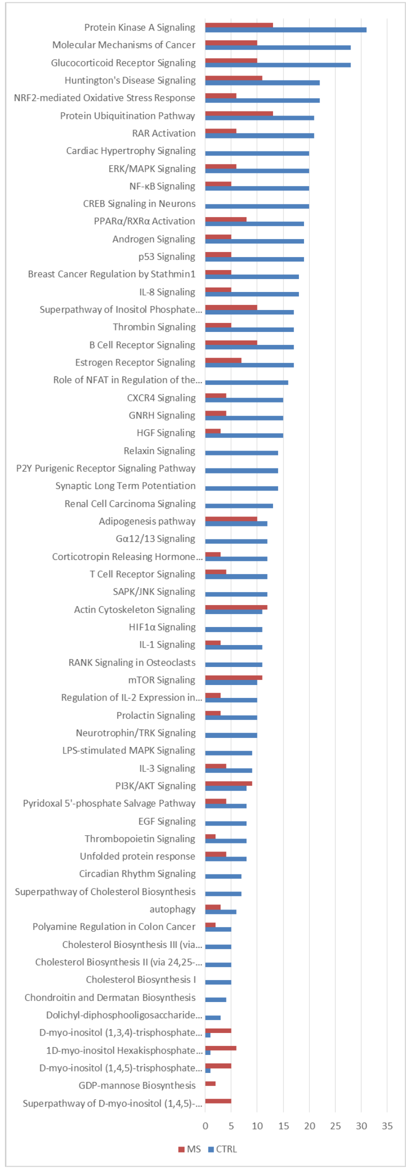
- Hypoxia factor pathway
- Wnt/β-catenin Signaling

circadian rhythms

Pathways Upregulated



Pathways Downregulated



D'Amore, et al BBA 2016

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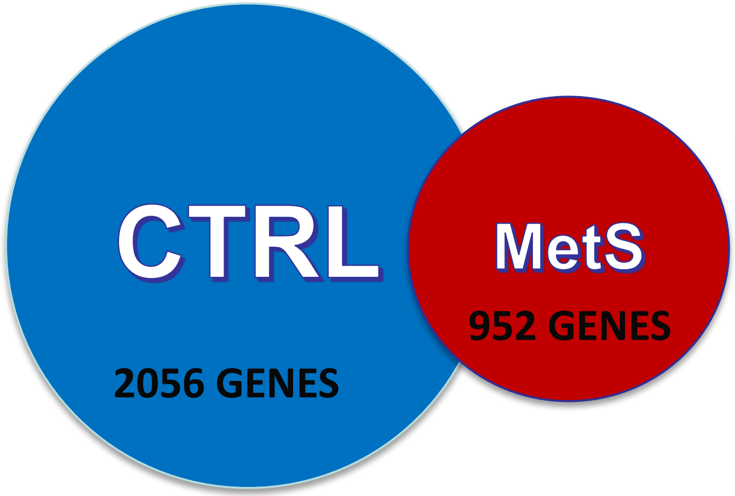
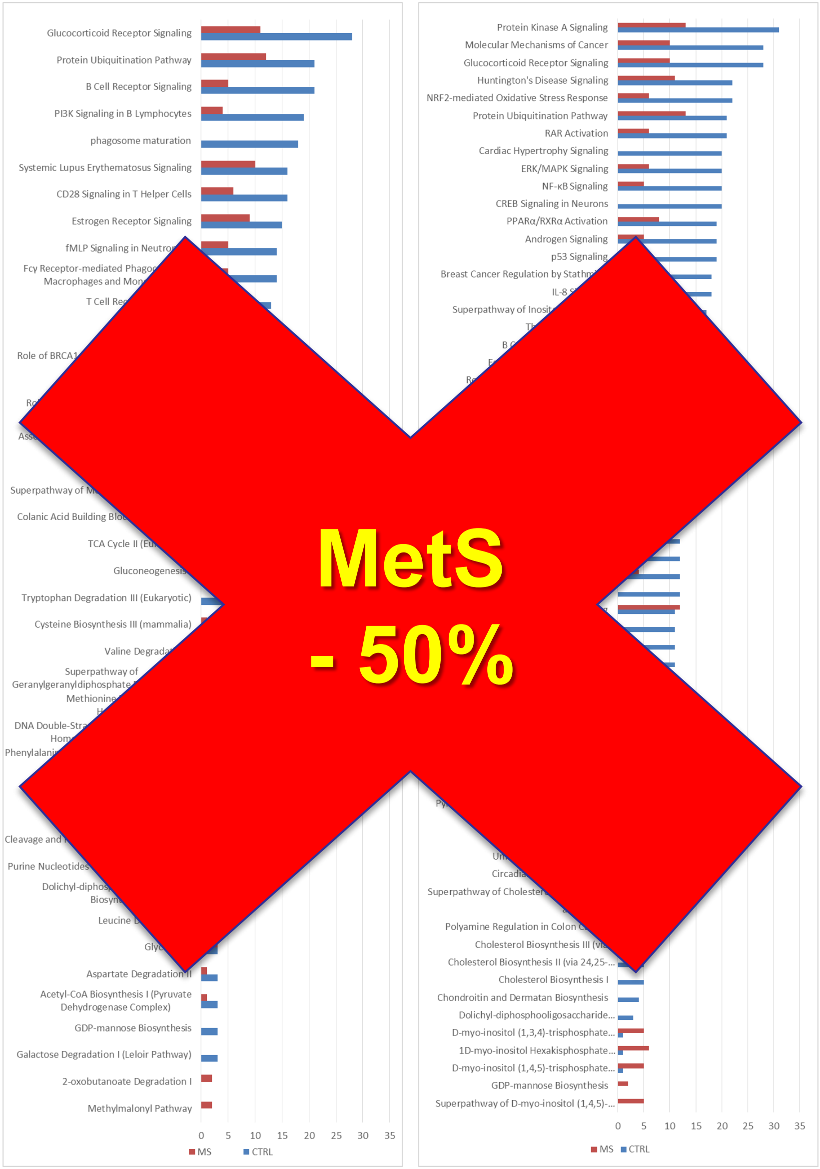
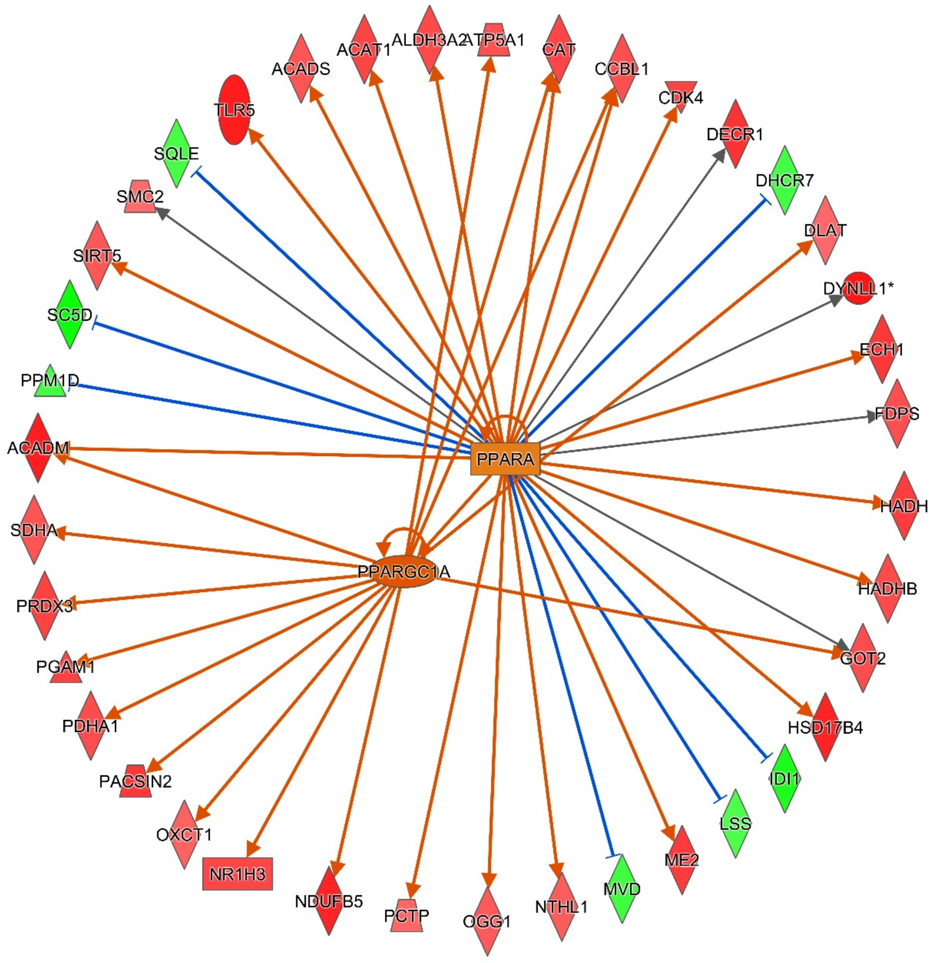


Pathways Upregulated **Pathways Downregulated**

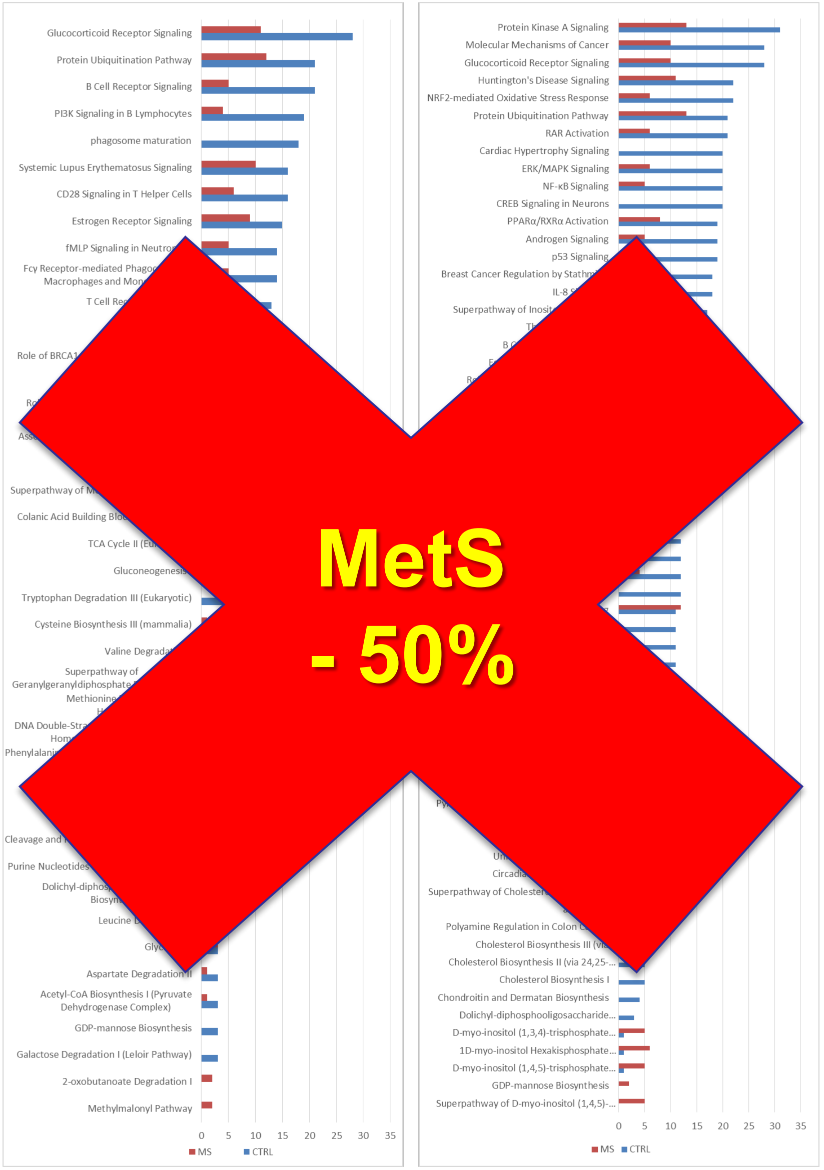


D'Amore, et al BBA 2016

Changes in PBMC transcriptomics after acute EVOO intake

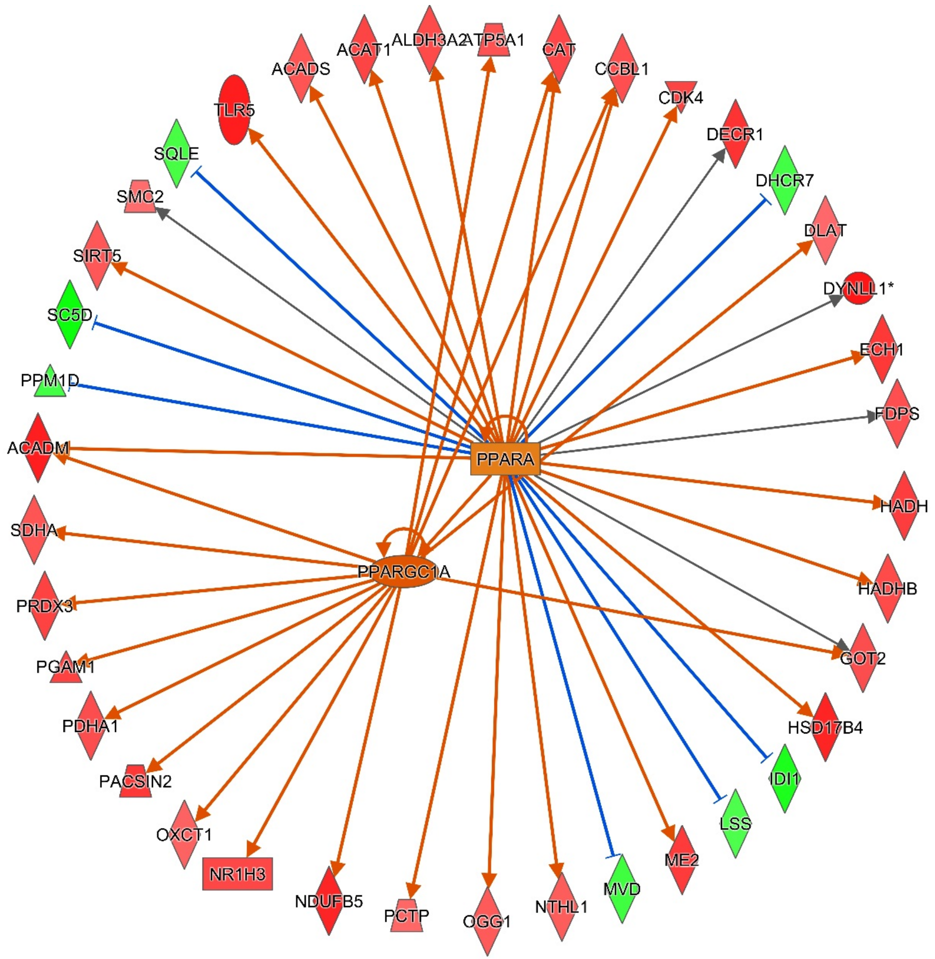


Pathways Upregulated **Pathways Downregulated**

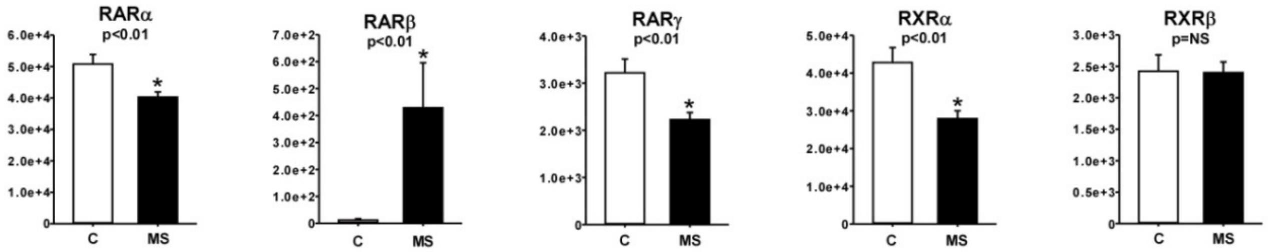


D'Amore, et al BBA 2016

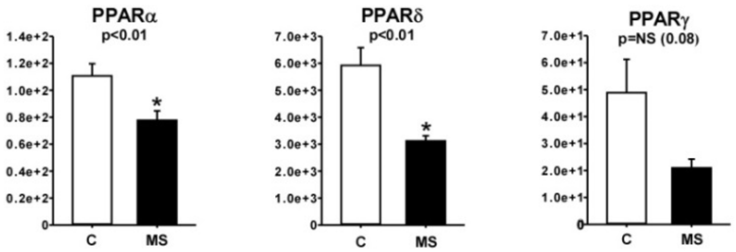
Changes in PBMC transcriptomics after acute EVOO intake



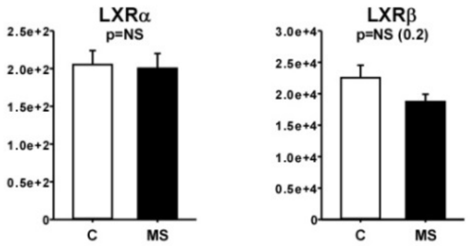
RETINOIC ACID SENSORS



FATTY ACIDS SENSORS



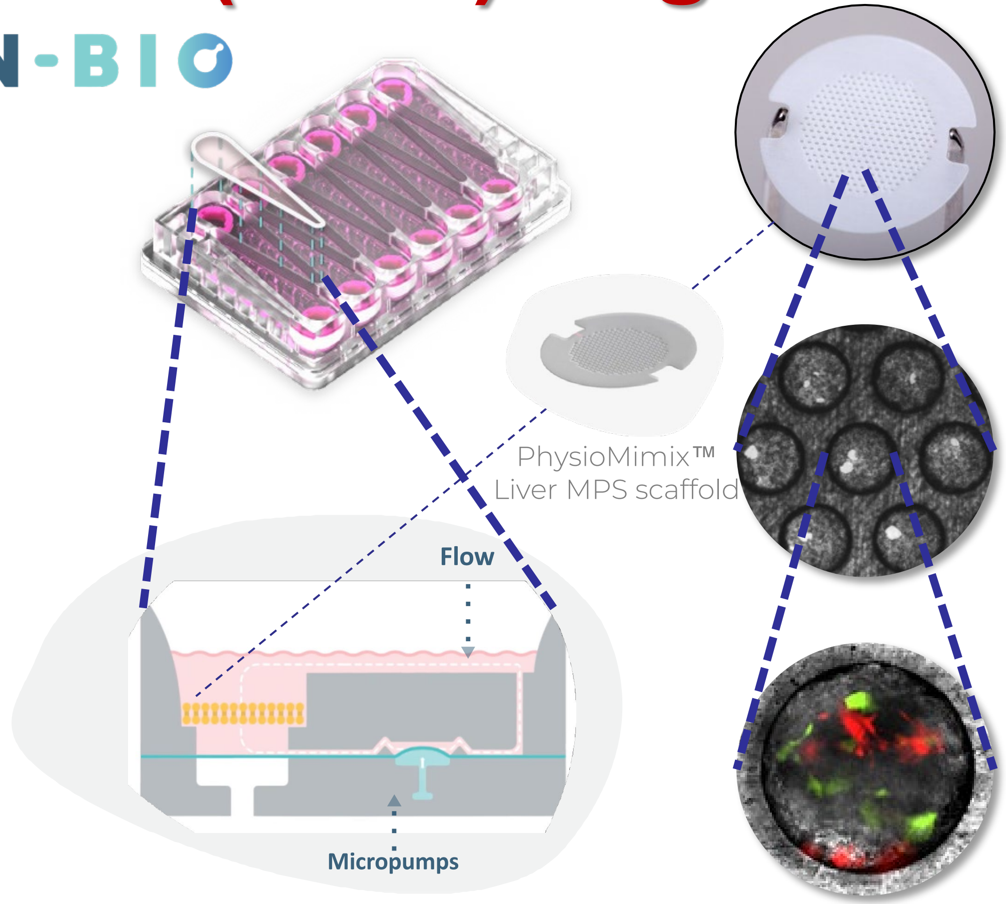
OXYSTEROLS SENSORS



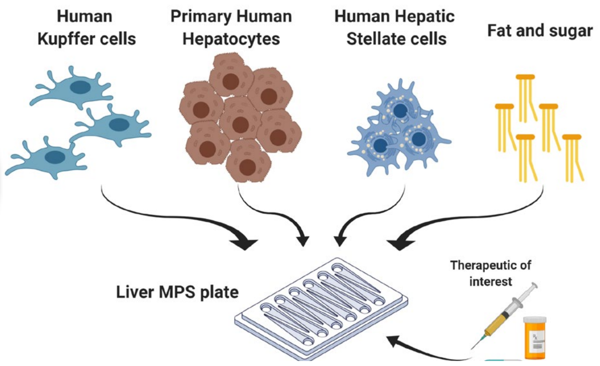
D'Amore, et al, BBA 2013

Future Perspective (Multi) Organ On Chip (OOC)

Courtesy of CN-BIO



Cells are cultured on a scaffold within the LC12 MPS plates



- 3D Human *in vitro* microfluidic NASH model
- Uses the PhysioMimix^{TM} LiverChip
- This OOC model allows long term culture of cells that are continuously perfused

Hepatocytes are seeded with **Kupffer** and **stellate** cells at 10:1:1 ratio

D1: 'Fat' Media

D8: Treatment

D0 Seed cells

Media change every 2 days

D10: Exp End

Polyphenols

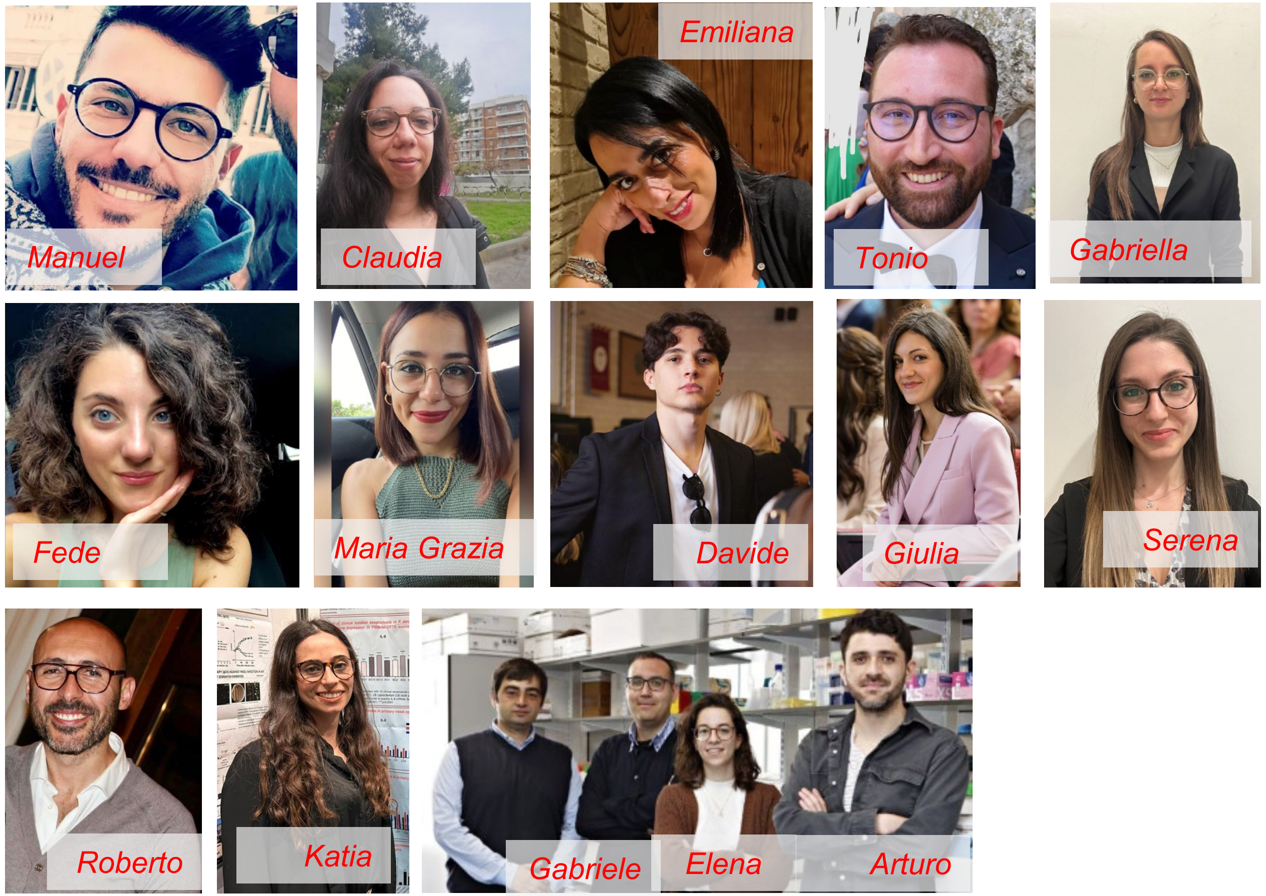
Fatty Acids

Conclusions

- Nutrigenomics approaches can help to understand at molecular level the beneficial effects of a specific nutrient;

- EVOO intake exerts different beneficial effects (anti-inflammatory, metabolic, anti-cancer) for the body thus being useful in promoting health
  - Part of this effect is mediated by direct effects on gene transcription
  - Caution should be made in specific disease;

Acknowledgements



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onfoods

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