UNIVERSITÁ DEGLI STUDI DI TERAMO

NUTRITIONAL AND APPLIED BIOCHEMISTRY

Enrico Dainese

Unit 1. Metabolic bioavailability of nutrients Food and nutrients. Structural and energy functions of nutrients. Macro- and micro-nutrients. Non-nutrients. Bioavailability of nutrients. Technological treatments of food, chemical and physical changes and bioavailability of nutrients. Nutrient carbohydrates: monosaccharides and disaccharides, polysaccharides. Biochemical processes in the digestion of carbohydrates. Molecular systems of absorption and transport of the carbohydrates. Carbohydrate reserves in humans: accumulation and mobilization. Mechanisms of regulation of blood glucose. Unavailable carbohydrate and fibers. Glycemic index. Technological processes and nutritional properties of carbohydrates. The example of cereals. Interactions between macro- and micro-nutrients (e.g., vitamins, polyphenols, oligonutrients, aromas, etc.) in various foods. The example of the grain, wine, olive oil. Changes of the main antioxidant compounds in food processing and during digestive metabolism. Biochemical and molecular bases of eating disorders. Molecular and enzymatic alterations in obesity. Obesity as a disease of endogenous biochemical systems that modulate inflammation but also behavioral aspects. Bioactive compounds in foods can prevent diseases spread wide and high social impact in industrialized countries. Nutrigenomics, epigenetic modulation and their role on major human diseases. Functional foods and nutraceuticals. Functional foods, food supplements, novel foods: biochemical and nutritional insights. Foods containing genetically modified organisms (GMOs) and biological nutritional quality, legislation and safety. Metabolic pathways of natural compounds (e.g., nutraceuticals, bioactive lipids, etc.) in foods of plant and animal origin. Bioactive food and nutraceutics. Study of bioactive compounds and metabolic enzymes involved in the quality and safety of food (e.g., wine, olive oil and fish).

Unit 2. Biochemical-nutritional role of proteins

Protein nutrients: proteins and their constituents. Plastic function and energy of proteins. Bioavailability and nutritional value of food protein sources. Digestion of food proteins. Absorption and transport of amino acids. Main mechanisms of regulation of protein turnover in tissues and systems of the human organism. Control of the metabolism of proteins in humans. Technological processes and nutritional properties of proteins. The example of cereals, legumes and fish. Unit 4. Biochemical-nutritional role of the lipids Lipid nutrients: fats, oils and their constituents. Biochemical processes in the digestion of lipids. Absorption and transport of lipids. Training and mobilization of lipid reserves in humans. Regulation of triglyceride and cholesterol. Technological processes and nutritional properties of lipids. Bioactive lipids in nutrition: eicosanoids, endocannabinoids. Leptin and recent advances in the control of appetite. Bioactive lipids in nutrition: the eicosanoids. Changes that occur during food processing on the physicochemical properties of lipids able to alter their metabolic bioavailability. The example of vegetable and fish oils.

Unit 3. Biochemical-nutritional role of the oligonutrients

Activation and biochemical role of water-soluble vitamins: B1, B2, B6, B12, C, H, PP, folic acid, pantothenic acid. Absorption and transport of vitamin B12. The fat soluble vitamins: A, D, E, K. Absorption, activation and biological role. Inorganic nutrients. Na, K, Ca, Mg and P: main biochemical roles of macro minerals. Fe, Zn, Cu, Mn, Mo, I, F, Cr, Se, Co: biochemical role of trace elements. Food suppliers.

Unit 4. Laboratory

Applied Biochemistry for food analysis Preparation and storage of solutions. Biochemical buffers. Use of the spectrophotometer. Main biochemical methodologies involved in the analysis of the quality, composition, purity and safety of food: protein assay methods (Bradford assay and spectrophotometric assay), SDS-PAGE, Western blotting, ELISA, ELISAsandwitch, fluorescence spectrophotometry and "Antibody arrays". Quality and safety methodologies, procedures in a biochemistry laboratory. Qualitative and quantitative analysis of food proteins by SDS-PAGE and ELISA. Measurement of protein solutions via UV spectrophotometry, Bradford assay and densitometric analysis of protein bands on polyacrylamide gel. Description and use of computer programs for the analysis and processing of data (Excel and Image J).

Procedures relating to the exam regulations

Laboratory and class exercises. Reading, discussing and comprehension of case studies.

Final exam on all units of the official program.

RECEPTION HOURS

At the end of class lessons and Friday 11-12 a.m.. Other days by appointment. Head of the Department of Biosciences and Agri-food and Environmental Technologies, Via Renato Balzarini 1, 64100 Teramo. Tel. 0861.266876. e-mail: edainese@unite.it

RECOMMENDED TEXTS

1. **COZZANI, I., DAINESE, E., Biochimica degli alimenti e della nutrizione, Piccin-Nuova Libraria, 2006**
2. **WILSON, K., WALKER, J., Biochimica e biologia molecolare, Raffaello Cortina Editore, 2006**
3. **Papers and case studies discussed during the course.**

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NUTRACEUTICS

The term "nutraceutics" was coined in 1979 by Stephen De Felice, the founder and President of the Foundation for Innovation in Medicine (FIM) located in Cranford, NJ. It resulted from the fusion of "nutrients" and "pharmaceutics."

A "nutraceutical" is defined as “any food or part of food (nutrient) considered to provide health benefits, including the prevention and treatment of disease.”

Though conceptually different, other related definitions were applied to dietary supplements and functional food (food engineered or supplemented to provide improved nutritional value).

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The Mediterranean-type diet

Daily physical activity!

Meat
Sweets

Monthly

Eggs
Poultry
Fish

Maximum four times a week

Fruits, vegetables, legumes and seeds

Extra Virgin Olive Oil
Pasta, bread and other cereals, potatoes.
Wine in moderation.

Daily

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Common foods are indeed nutraceuticals

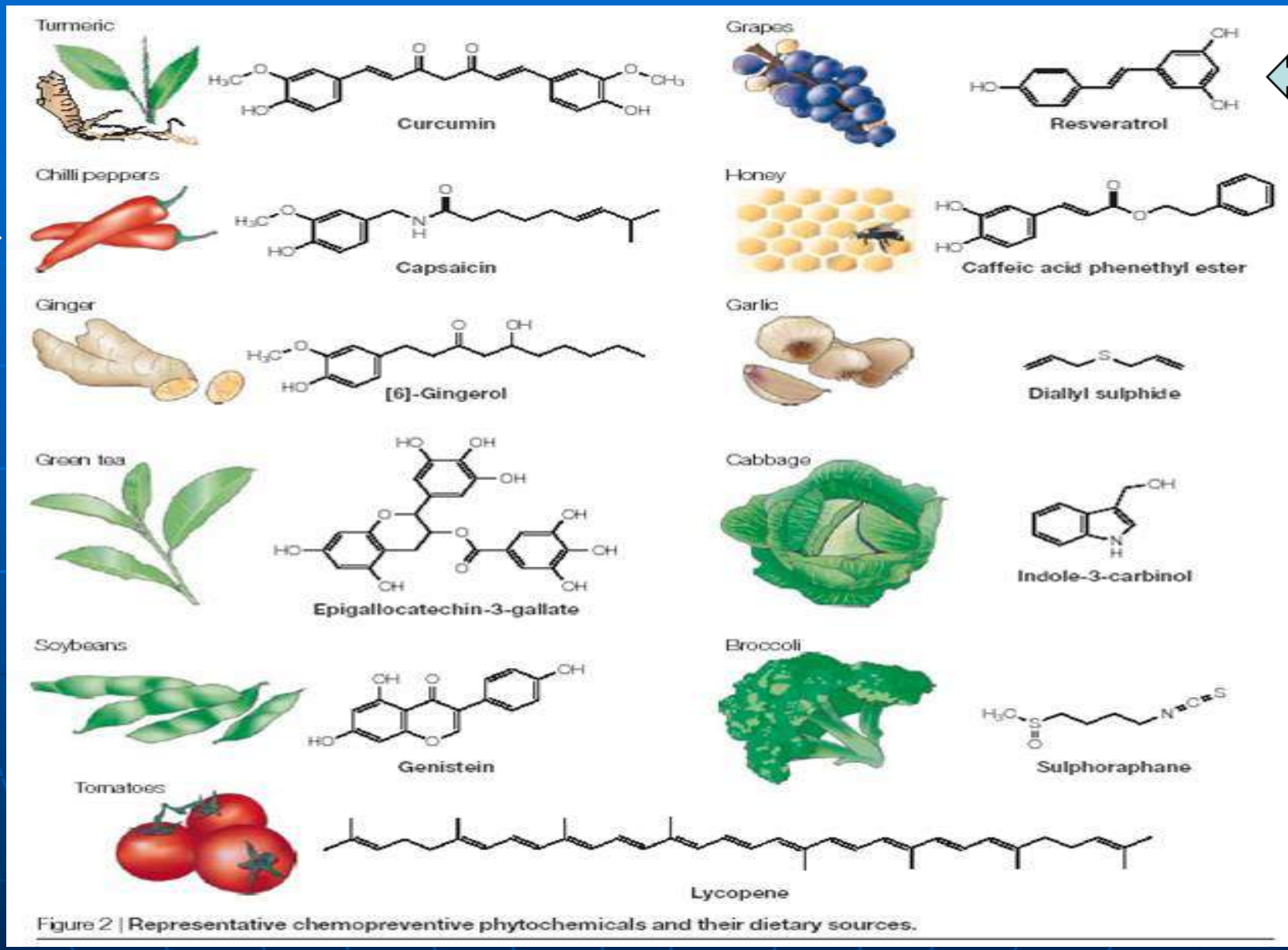

Figure 2 | Representative chemopreventive phytochemicals and their dietary sources.

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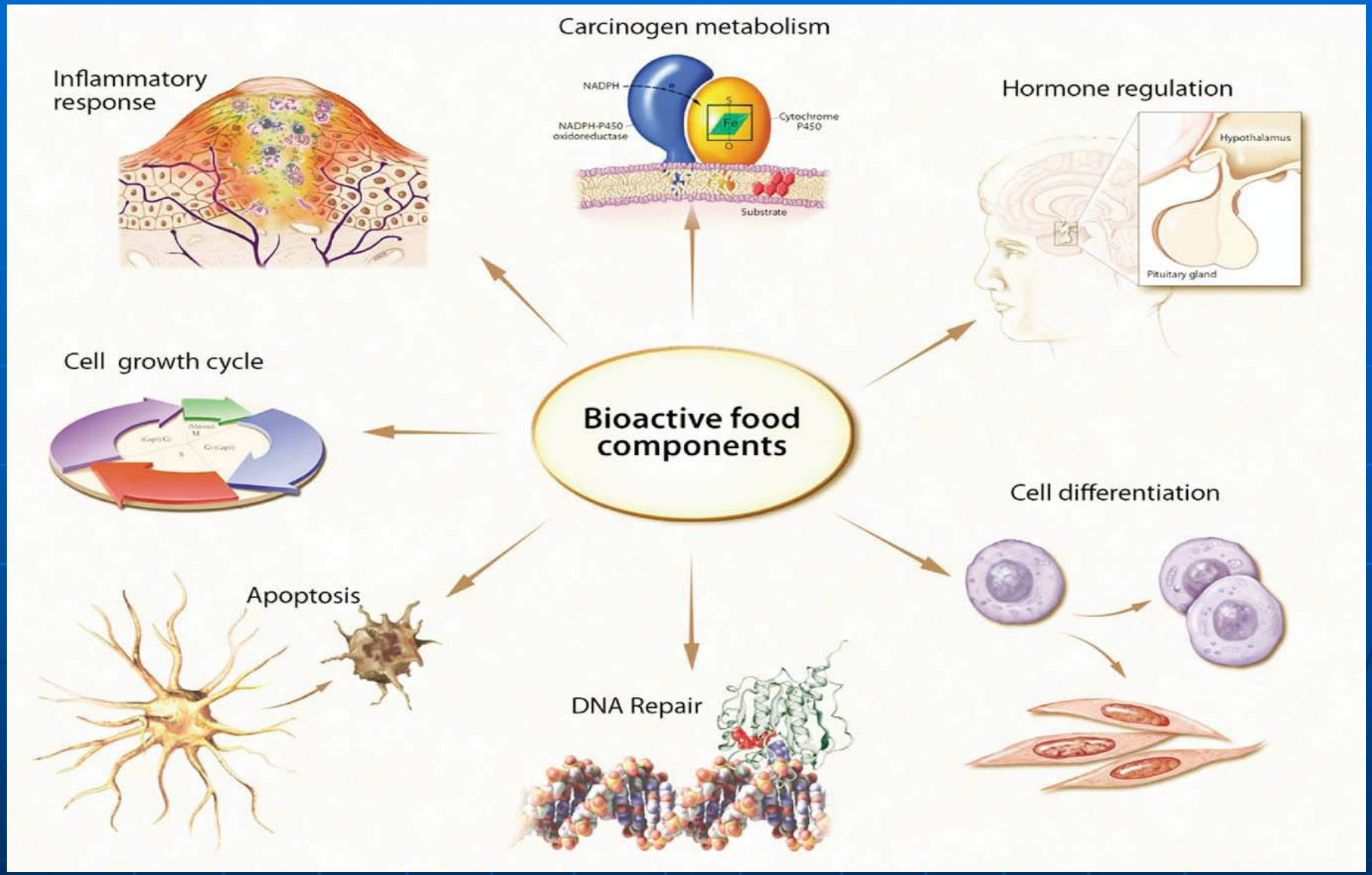
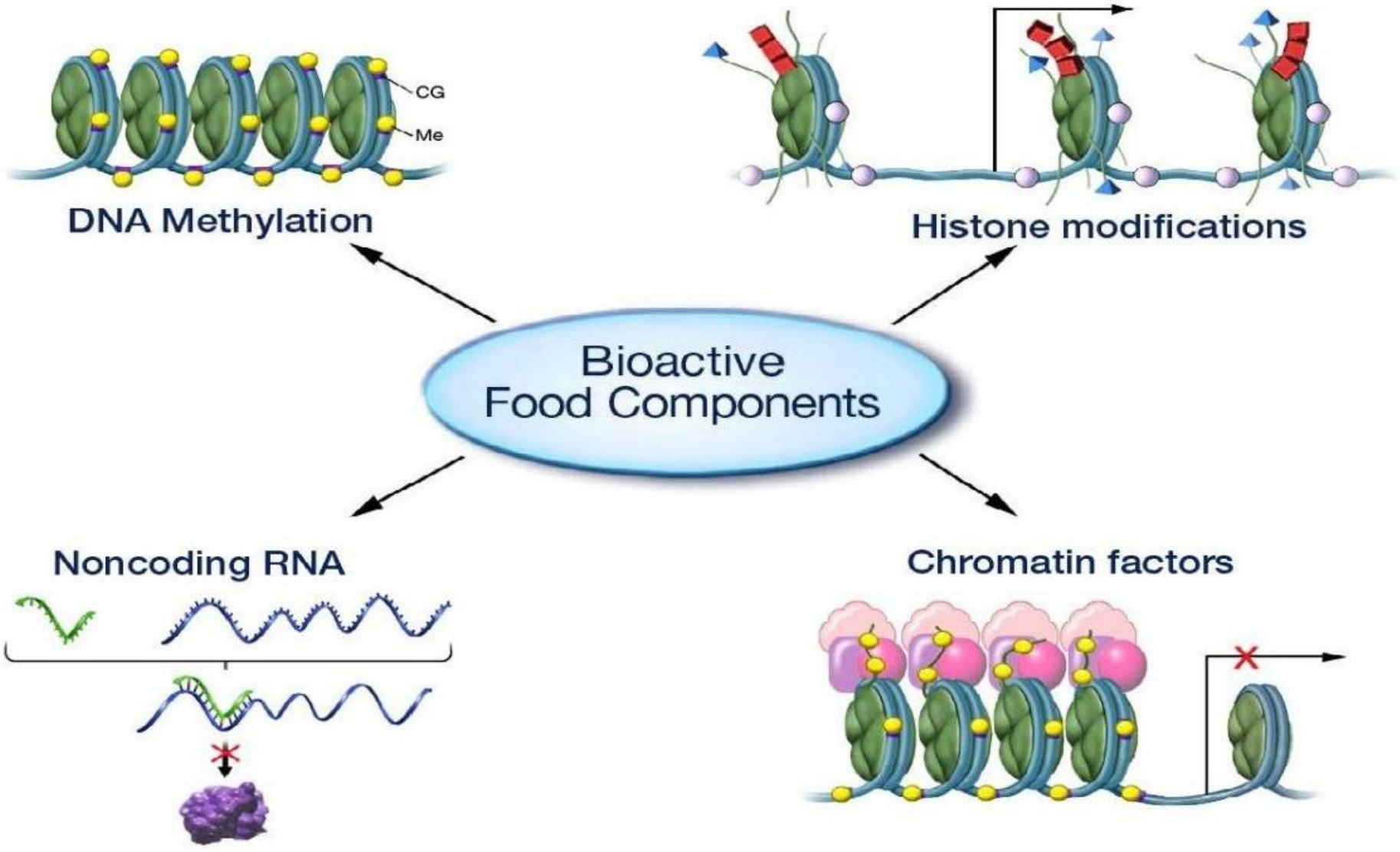
Nutrigenomics investigates the interactions of nutrients with genes



Epigenetics and diet



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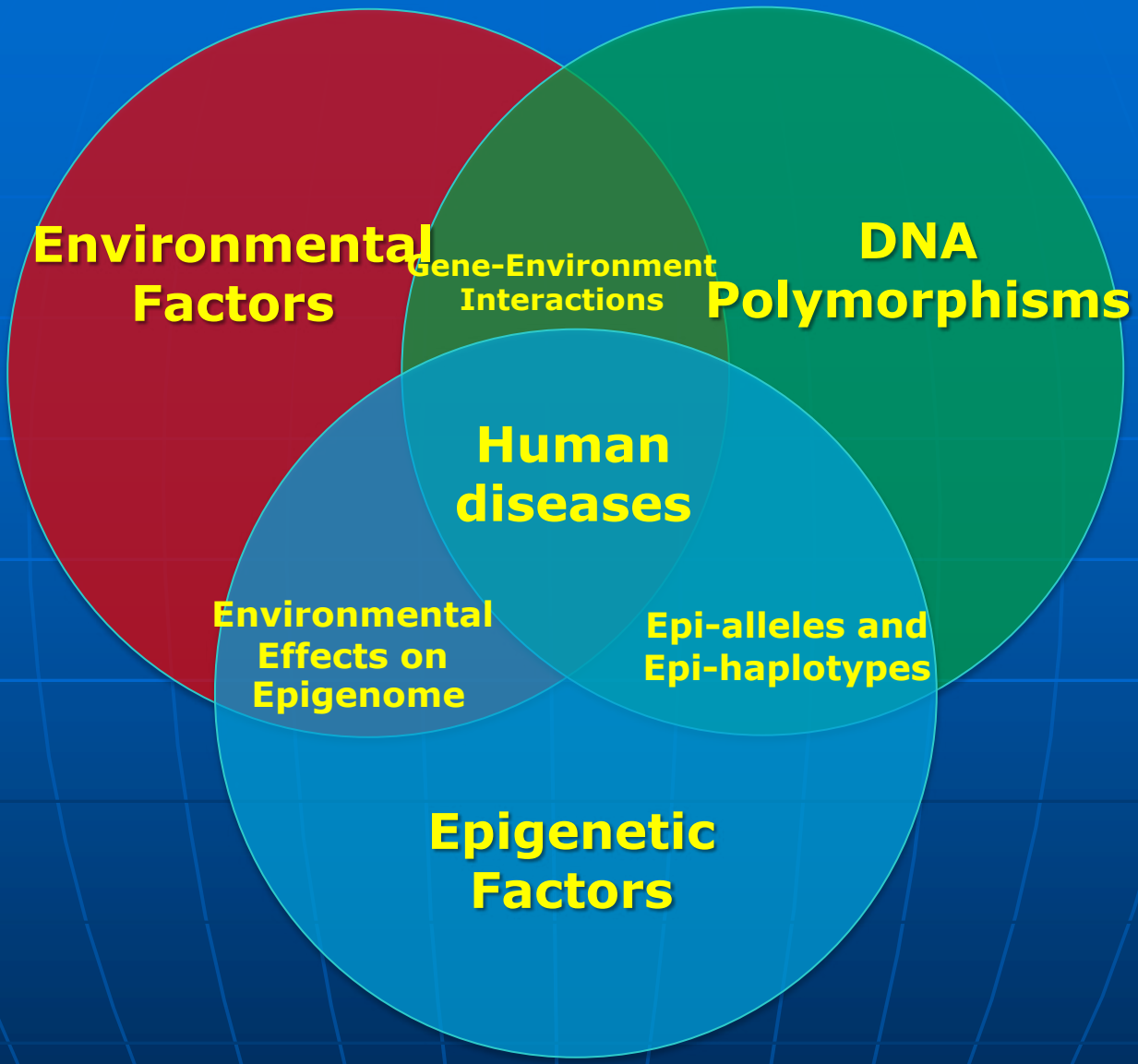
Epigenetics and human health



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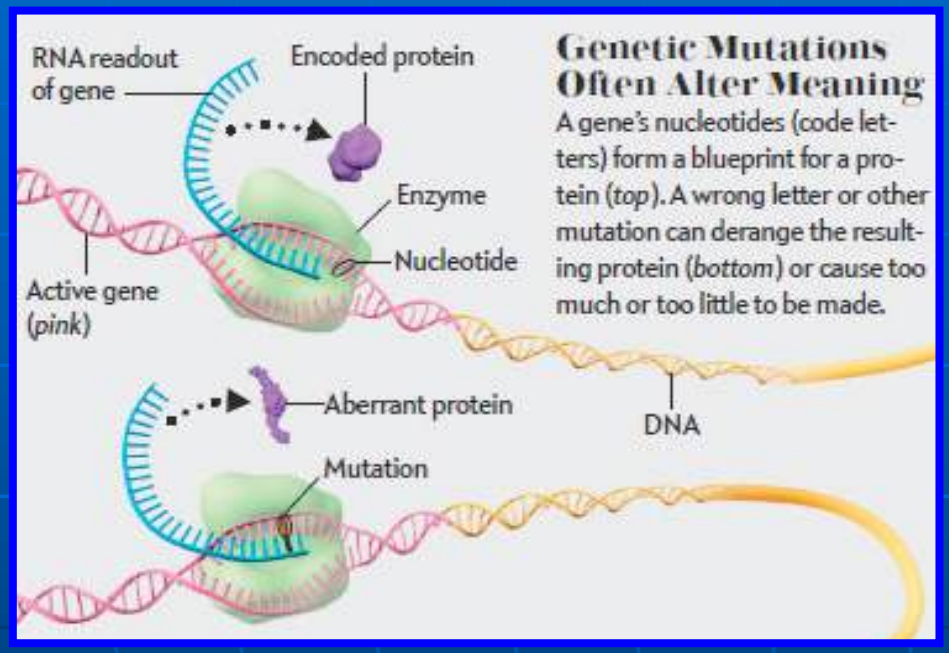
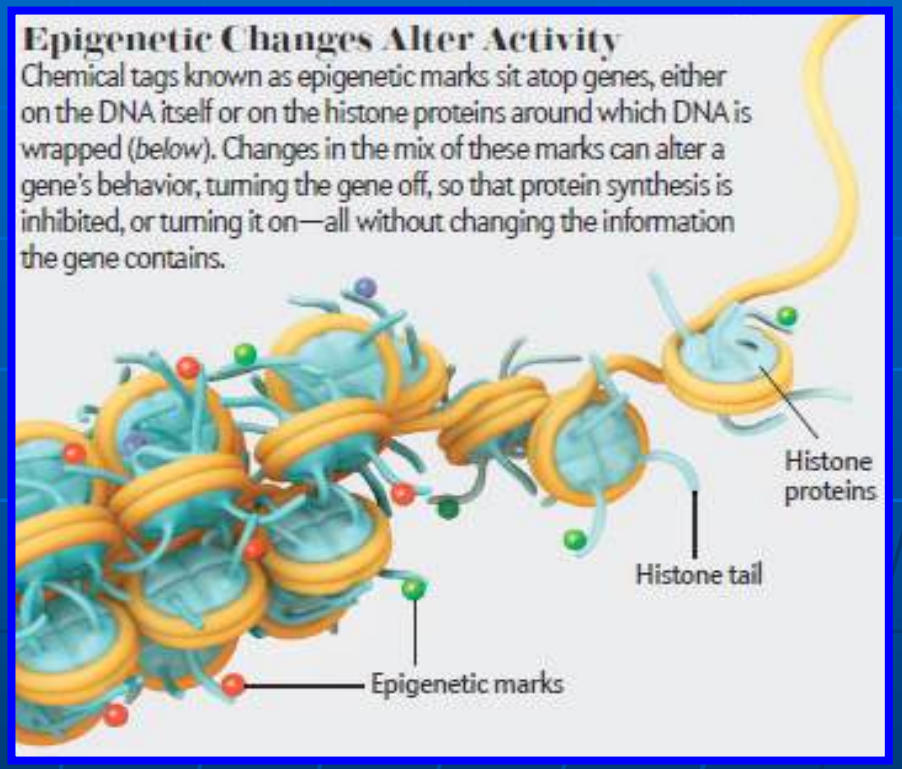
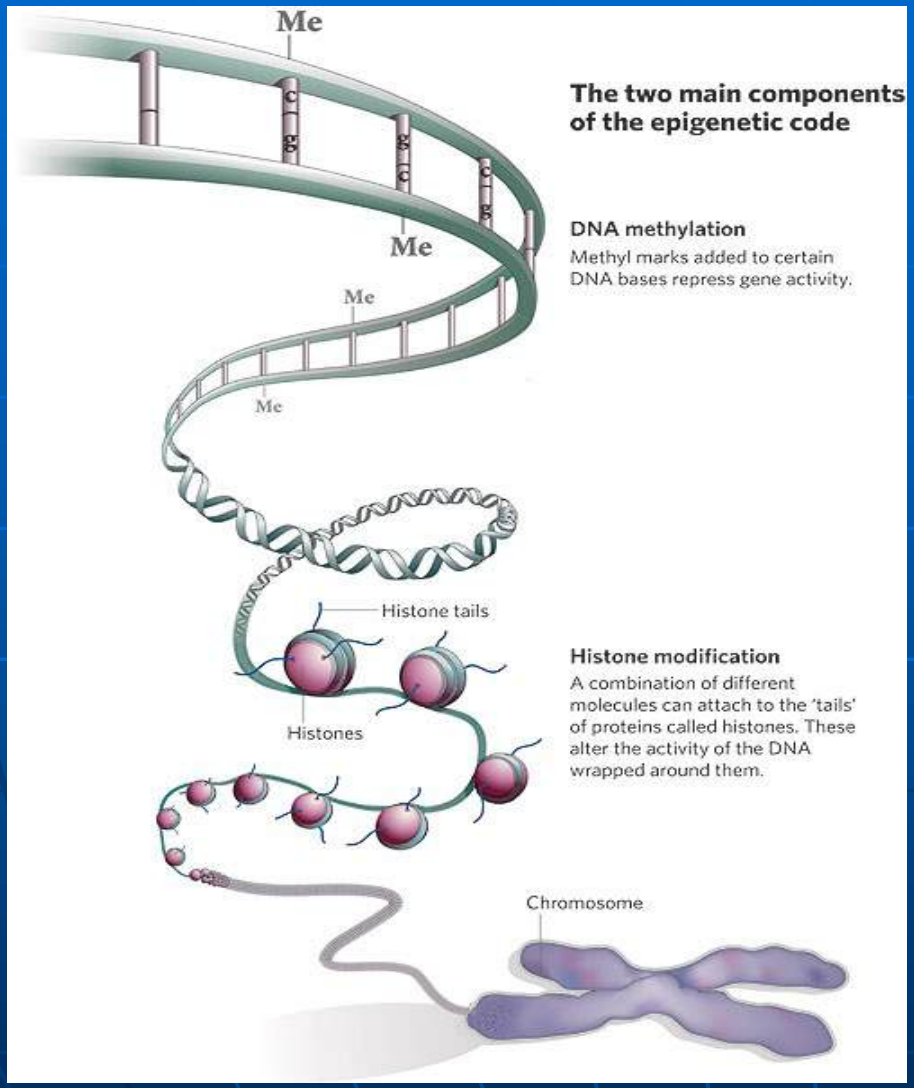
Epigenetics literally means “on top of genetics”

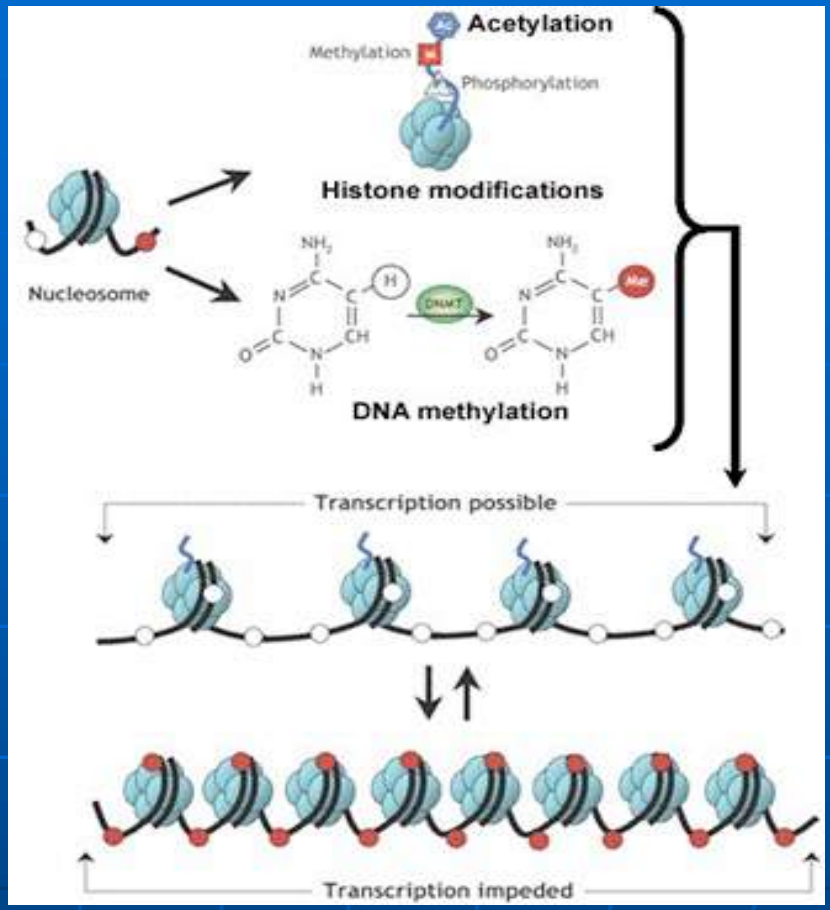
Genetics *vs* Epigenetics





Epigenetic mechanisms





Gene "switched on"
- active (open) chromatin
- unmethylated cytosins (white circles)
- acetylated histones

Gene "switched off"
- silent (condensed) chromatin
- methylated cytosines (red circles)
- deacetylated histones

Diet and intestine tumors

90% of gastrointestinal tract tumors appear to be attributable to the Western Diet.

Study of Dietary Habits among African-Americans (AA) and Native Africans (A)"

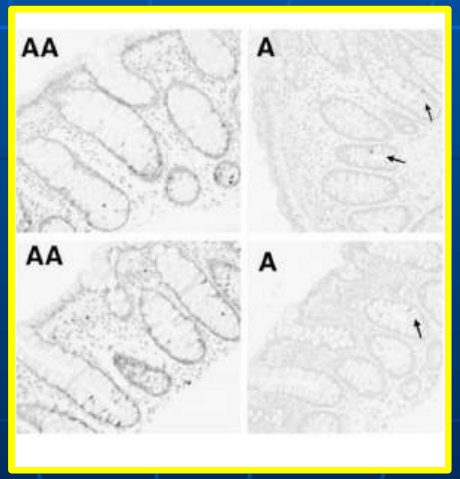
TABLE 1 Demographics and dietary measurements

	Native Africans	African Americans	Caucasian Americans
Age, *y*	55.2 (0.7)	53.2 (0.7)	55.9 (2.0)
BMI, *kg/m²*	28.0 (1.2)	30.5 (3.0)	28.9 (1.3)
Pulse, *b/min*	73 (3.0)	69 (3)	75 (4)
BP systolic, *mm Hg*	141 (6)	134 (4)	125 (6)
diastolic	82 (3)	82 (3)	75 (2)
Diet energy, *kcal/d*	1669 (160)**	2650 (230)	2695 (227)
Diet carbohydrate, *g/d*	282 (28)	312 (27)	301 (27)
Total diet protein, *g/d*	58 (4)*	94 (9)	108 (9)
Diet animal protein, *g/d*	26 (3)**	51 (5)	59 (13)
Total diet fat, *g/d*	38 (3)***	114 (11)	114 (13)
Diet sat fat, *g/d*	9 (0.7)***	35 (4)	33 (4)
Diet cholesterol, *mg/d*	165 (18)*	300 (36)	324 (43)
Diet fiber, *g/d*	17 (2)	20 (1.5)	23 (2.5)
Diet folate, *μg/d*	201 (22)**	480 (47)	526 (50)
Diet calcium, *mg/d*	228 (27)**	833 (99)	1049 (112)
Diet iron, *mg/d*	7.1 (0.5)**	18.3 (2)	18.9 (1.8)
Diet vitamin C, *mg/d*	48 (15)**	198 (22)	159 (20)
Diet vitamin A, *μg/d*	630 (162)*	1466 (194)	1642 (253)
Diet zinc, *mg/d*	6.7 (0.5)**	14 (1.5)	15 (1.5)
Blood hemoglobin, *g/L*	131 (10)	138 (3)	141 (3)
Fasting breath hydrogen, *ppm*	10.8 (1.8)	17.4 (2.4)	13.9 (3.3)
Fasting breath methane, *ppm*	33.9 (8.9)**	5.0 (2.0)	10.9 (3.9)

* $P < 0.05$, ** $P < 0.005$, *** $P < 0.0001$ vs. African Americans, ANOVA with post hoc Bonferroni-Dunn correction.

Colonoscopy
+++ Inflammatory mucosal alterations in AA (African-Americans)"

	Native Africans ($n = 18$)	African Americans ($n = 17$)
Polyps		
Hyperplastic	1	3
Adenomatous	1	4
Diverticulae	0	3
Hemorrhoids	2	11
Melanosis	0	0



"Higher immune reactivity - specific Ki-67 in AA (African-Americans)"

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Diet and Gastrointestinal Tumors

NATURE COMMUNICATIONS | ARTICLE

Fat, fibre and cancer risk in African Americans and rural Africans

Stephen J. D. O'Keefe, Jia V. Li, Leo Lahti, Junhai Ou, Franck Carbonero, Khaled Mohammed, Joram M. Posma, James Kinross, Elaine Wahl, Elizabeth Ruder, Kishore Vipperla, Vasudevan Naidoo, Lungile Mtshali, Sebastian Tims, Philippe G. B. Puylaert, James DeLany, Alyssa Krasinskas, Ann C. Benefiel, Hatem O. Kaseb, Keith Newton *et al.*

Nature Communications **6**, Article number: 6342 doi:10.1038/ncomms7342
Received 23 May 2014 Accepted 20 January 2015 Published 28 April 2015

Exchange of Dietary Habits for Two Weeks

20 African-Americans (AA) vs. 20 Rural South Africans (NA)"

Supplementary Table 1: Summary of Macronutrient and Fibre Compositions Before and After Diet Switch

Group	Period	Fat %	Carbohydrate %	Protein %	Fiber g/d
African American	Usual	35	47	15	14
Rural Africans	Usual	16	72	11	66
African American	Intervention	16	70	14	55
Rural Africans	Intervention	52	21	27	12

The macronutrient composition as % total energy for the usual and intervention diets in Africans and Americans before and after dietary change.

Diet and Gastrointestinal Tumors

Within just two weeks of the switch, there was a reduction in mucosal inflammation alterations of the colon (polyps and leukocytic infiltration) in the AA group, and the appearance of the same lesions in the NA group, which were previously absent.

b) Illustration of the higher densities of inflammatory cells within the lamina propria in Africans at baseline

Baseline Differences		African Americans		Africans		
		N	%	N	%	p-value
Lamina Propria (LP) inflammation	Normal	21	36.8%	0	0.0%	0.0001
	Mild	33	57.9%	18	50.0%	
	Moderate	3	5.3%	18	50.0%	
Total		57	100.0%	36	100.0%	

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Proanthocyanidins from grape seeds reduce the atherogenic risk associated with obesity, by repressing genes involved in the secretion of very low density lipoprotein.

International Journal of Obesity **33, 1007-1012 (2009).**

Josepa Salvadó and colleagues have shown that grape seed proanthocyanidin extracts (GSPE) can prevent the dyslipidemia caused by a high fat diet in rats. Their report in the *International Journal of Obesity* suggests that eating more proanthocyanidin-rich foods might counteract the increased risk of heart attack that is associated with a high-fat diet (HFD), obesity and metabolic syndrome.

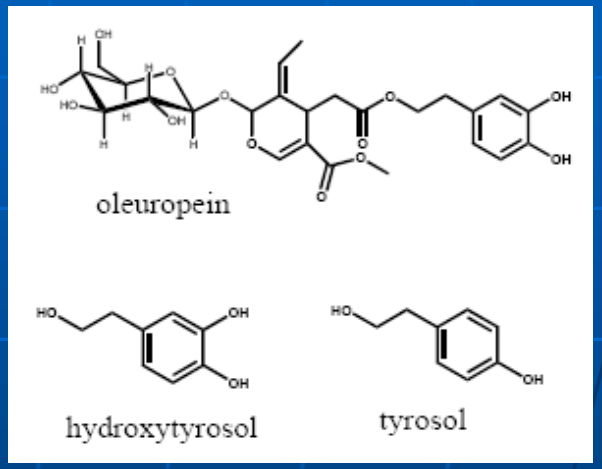
The levels of circulating lipids and lipoproteins are controlled by the liver, so the authors examined in rats the effect of the HFD and GSPE treatment on hepatic gene expression.

Thus, increasing the intake of foods rich in proanthocyanidins might be a strategy to reduce the risk of cardiovascular disease associated with obesity.

The benefits of extra-virgin olive oil minor components

Extra-virgin olive oil (EVOO) has always been considered a middle road between food and medicine, and there is growing evidence that its health benefits include reduction of coronary heart disease risk factor, prevention of several kind of tumors, and is involved in the modulation of immune and inflammatory responses.

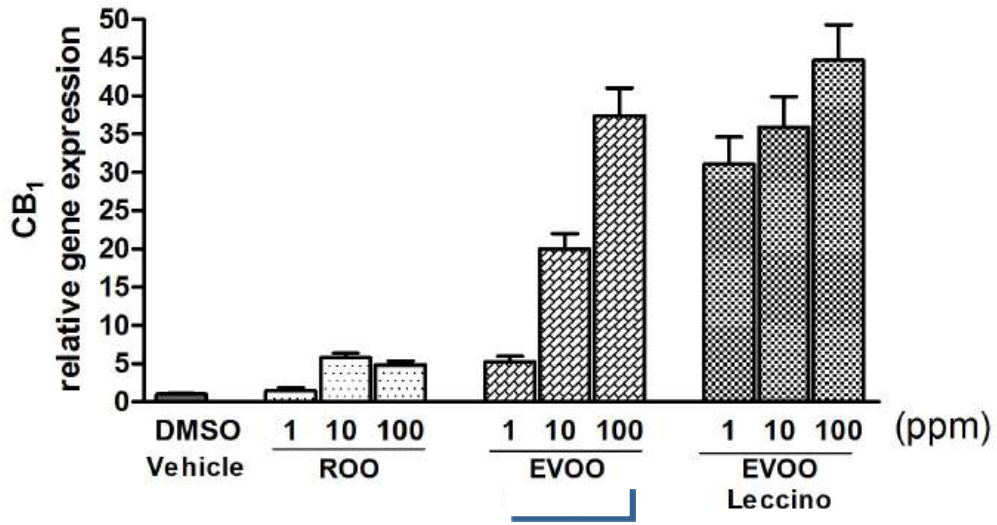
An example of nutraceutical properties, extra-virgin olive oil is a good source polyphenolic compounds (in particular hydroxytyrosol, or 4-(2-hydroxyethyl)-1,2-benzenediol), that may contribute to its overall therapeutic characteristics.



The hypothesis that polyphenols greatly contribute to the nutritional value of extra-virgin olive oil is supported by literature data, describing the biological properties of purified phenolic compounds. *However, the molecular and cellular mechanisms underlying these effects are only partly understood.*

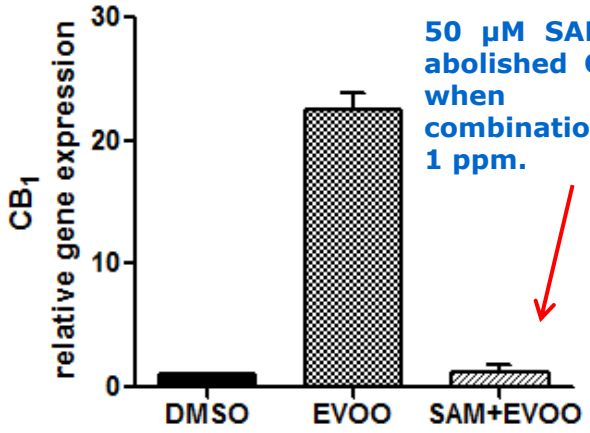
Extra-virgin olive oil (EVOO) induces antitumoral Cnr1 gene expression

Induction of CB_1 gene expression in human neuroblastoma, and Caco-2 cells exposed for 24 hr to increasing doses of EVOO.



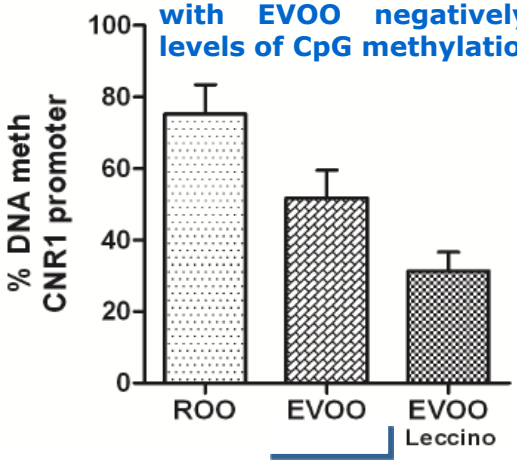
Rectified olive oil (ROO), obtained from EVOO by phenolic fraction removal, caused only a modest increase in CB_1 expression levels.

The methyl donor *S*-adenosyl-methionine (SAM) was able to inhibit the effects of EVOO on CB_1 gene expression.



50 μM SAM completely abolished CB_1 induction when given in combination with EVOO 1 ppm.

Expression levels of Cnr1 after incubation with EVOO negatively correlated with levels of CpG methylation at its promoter.



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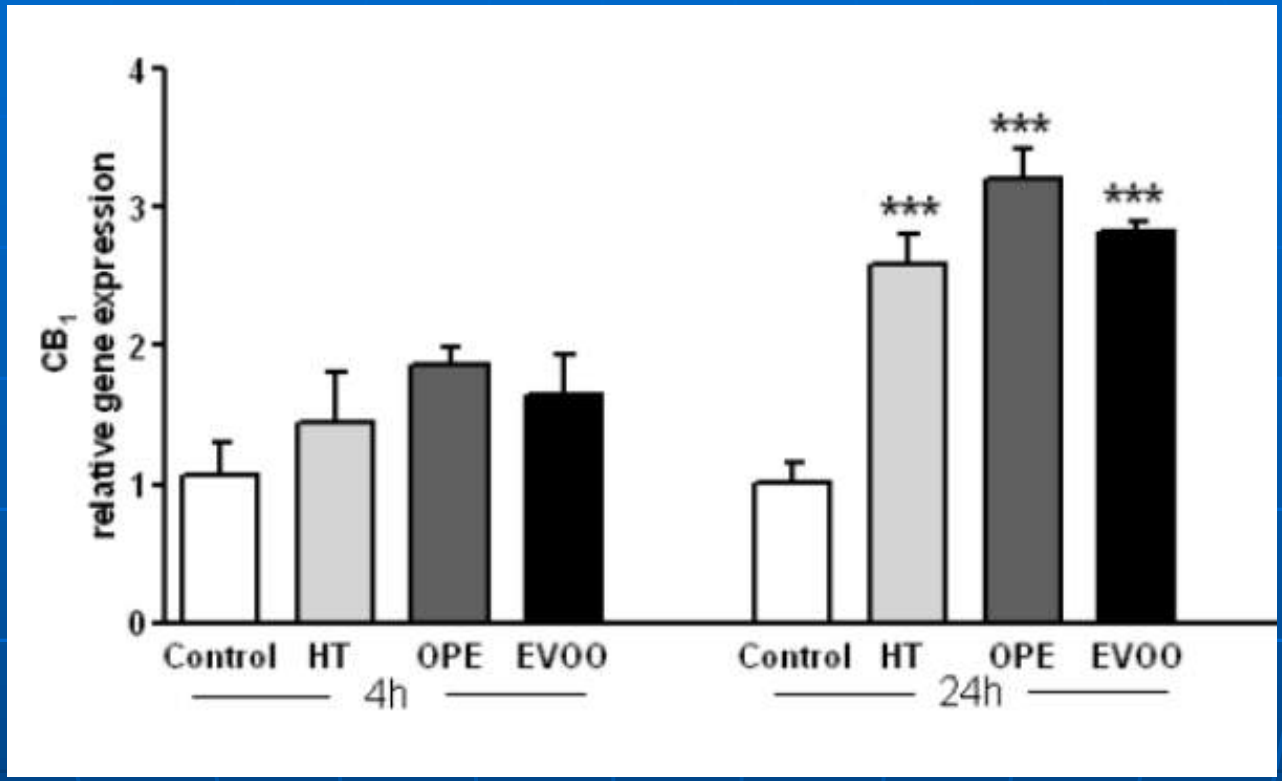
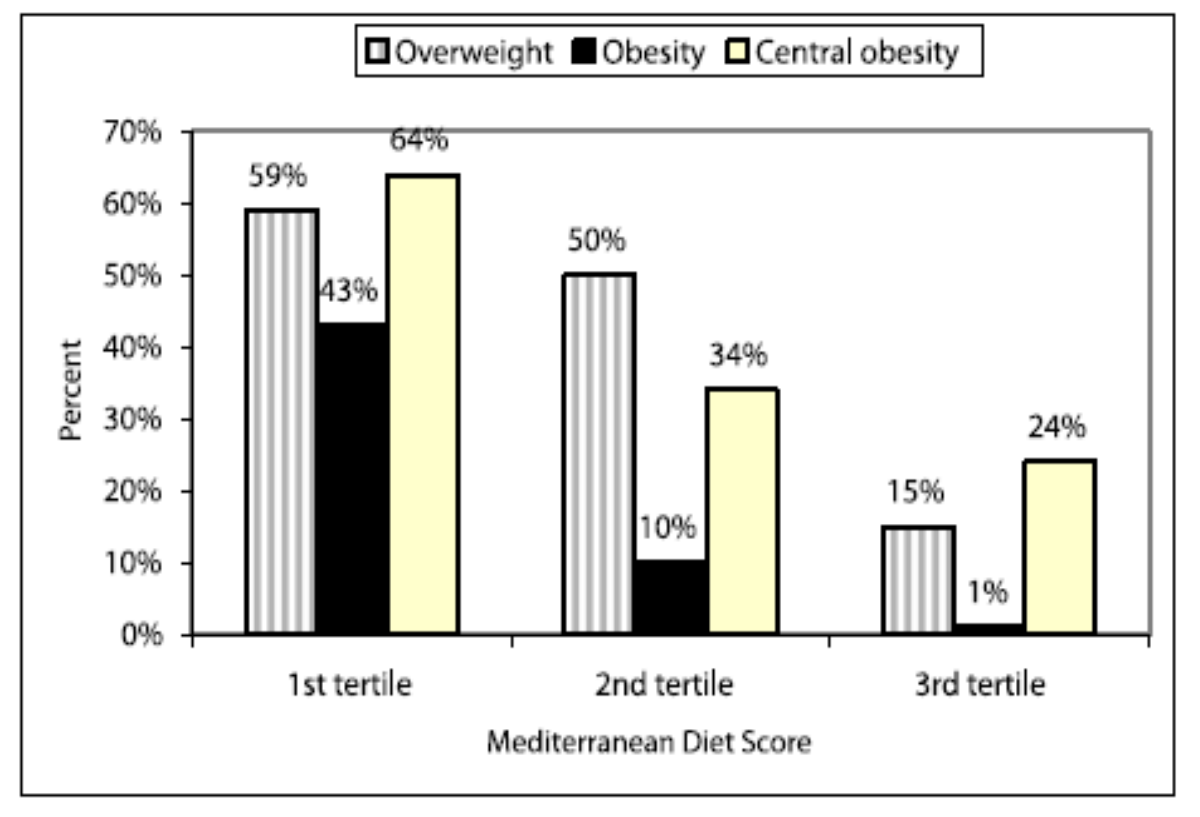
Effet of phenolic exctract and HT on Cnr1 gene expression





Prevalence of overweight (striped bars), obesity (black bars), and central obesity (white bars) by tertile of the Mediterranean diet score (highest tertile indicates greater adherence to the Mediterranean diet).

(modified from ATTICA study)

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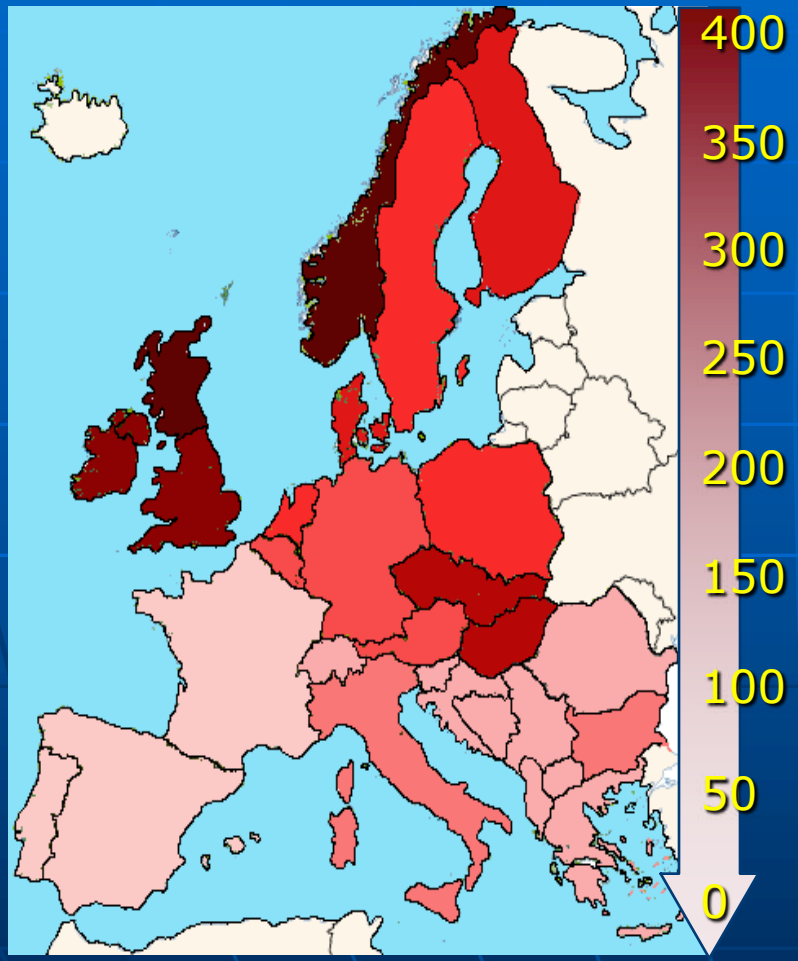
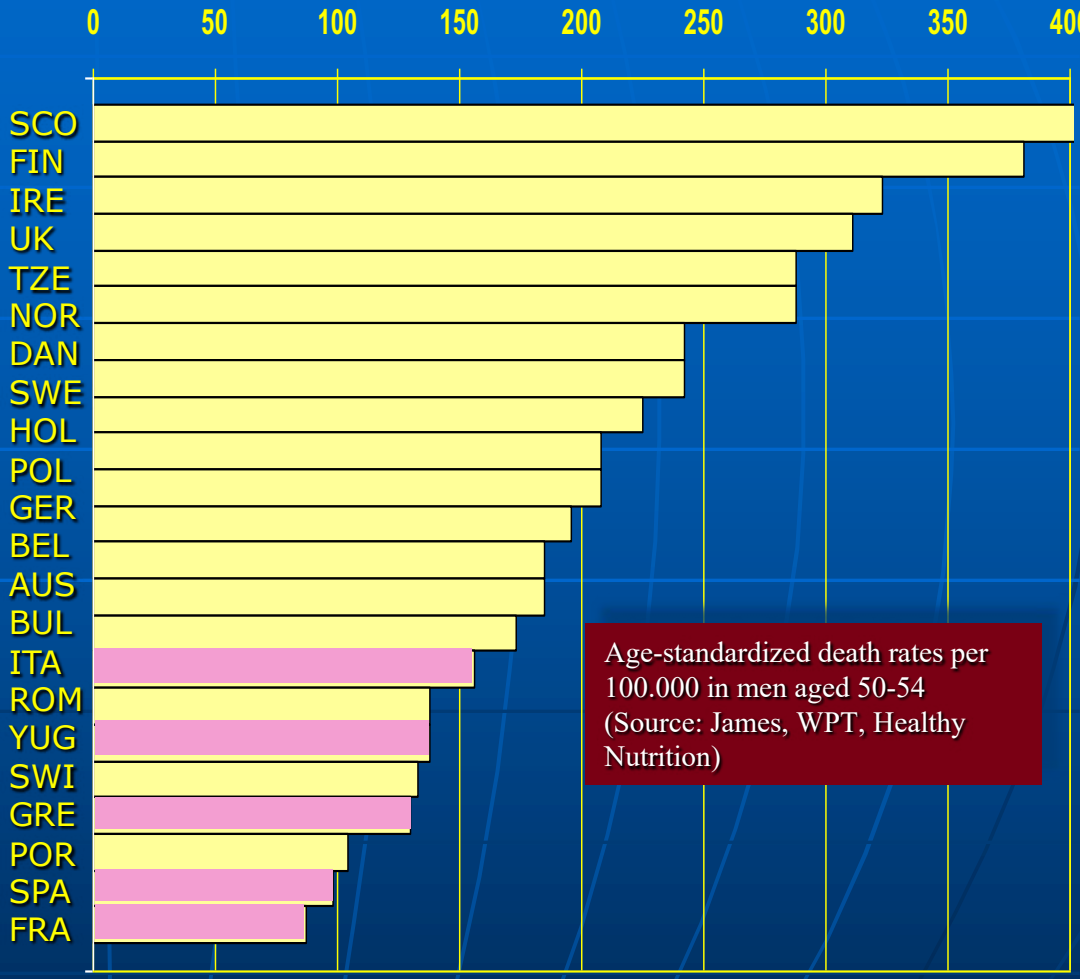
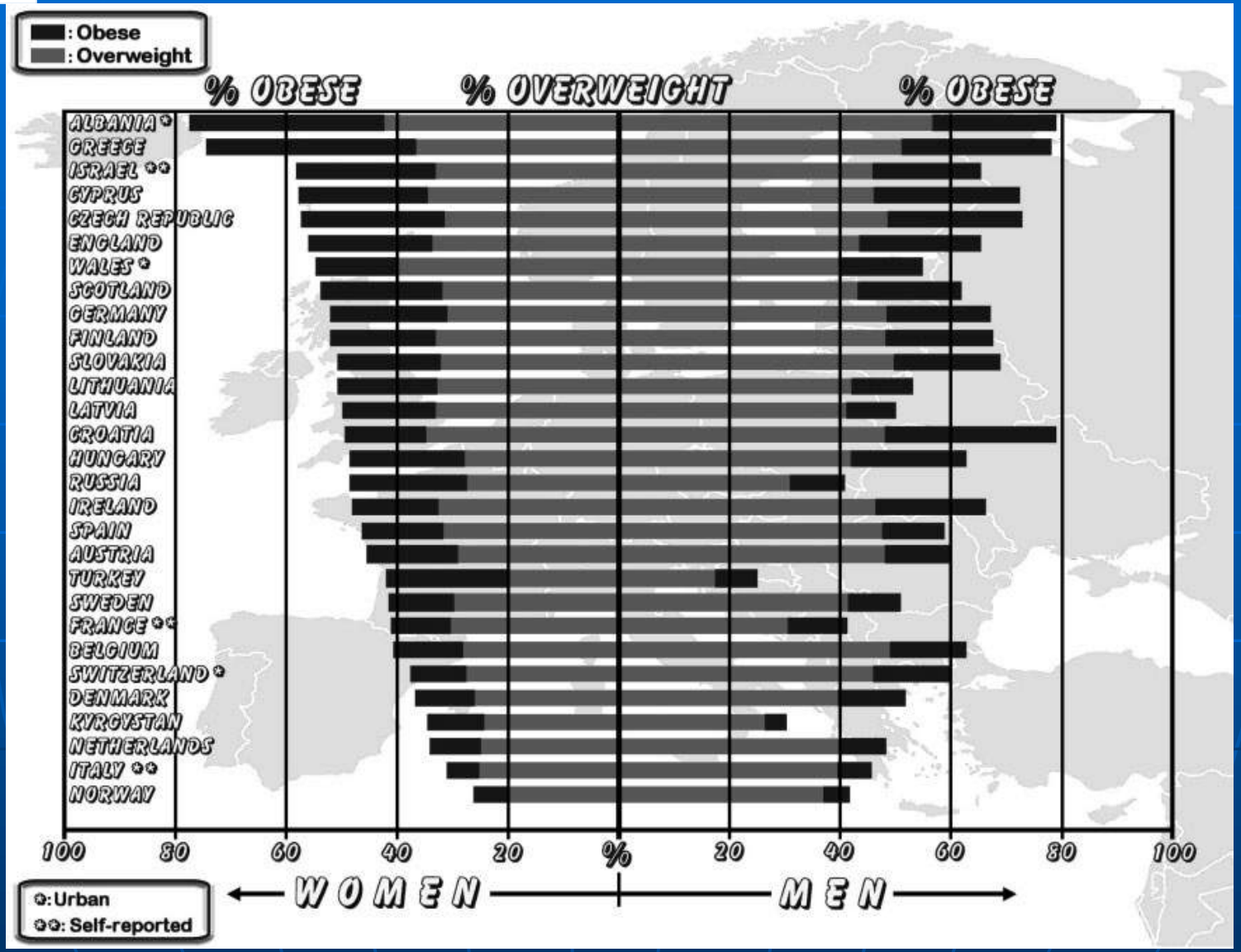
Age-standardized death rates for CVD in Europe

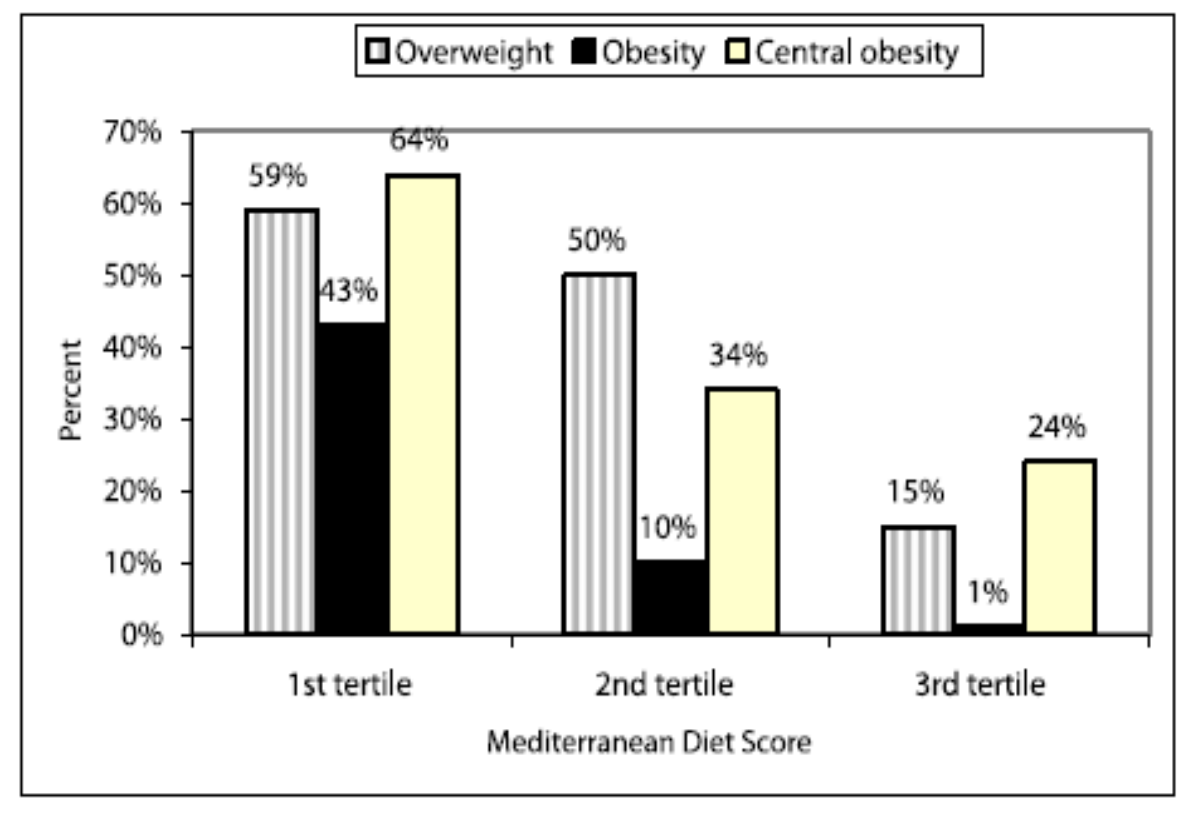




Age-standardized death rates per 100.000 in men aged 50-54 (Source: James, WPT, Healthy Nutrition)



Prevalence of obesity and overweight in Europe (Source: International Obesity Task Force, IOTF)



Prevalence of overweight (striped bars), obesity (black bars), and central obesity (white bars) by tertile of the Mediterranean diet score (highest tertile indicates greater adherence to the Mediterranean diet).

(modified from ATTICA study)

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Dietary lipids

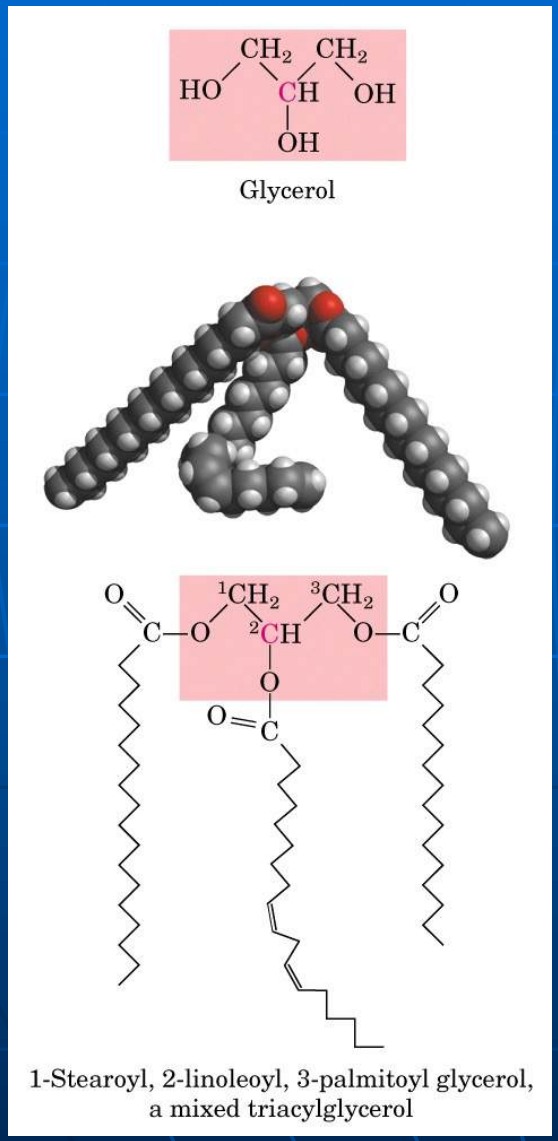
- Dietary lipids serve several crucial functions in the body. They act as an energy source, form structural components in cell membranes (such as cholesterol and phospholipids), and are involved in the structure of a small fraction of cellular proteins. Additionally, cholesterol is utilized in the synthesis of detergents that aid in the digestion and absorption of dietary lipids.

- Unlike many other nutrients, lipids are notable for their role as energy storage deposits, primarily in the form of fat stored in adipocytes. These reserves are gradually utilized throughout the day and can sustain survival for extended periods, sometimes even weeks, without the intake of food.

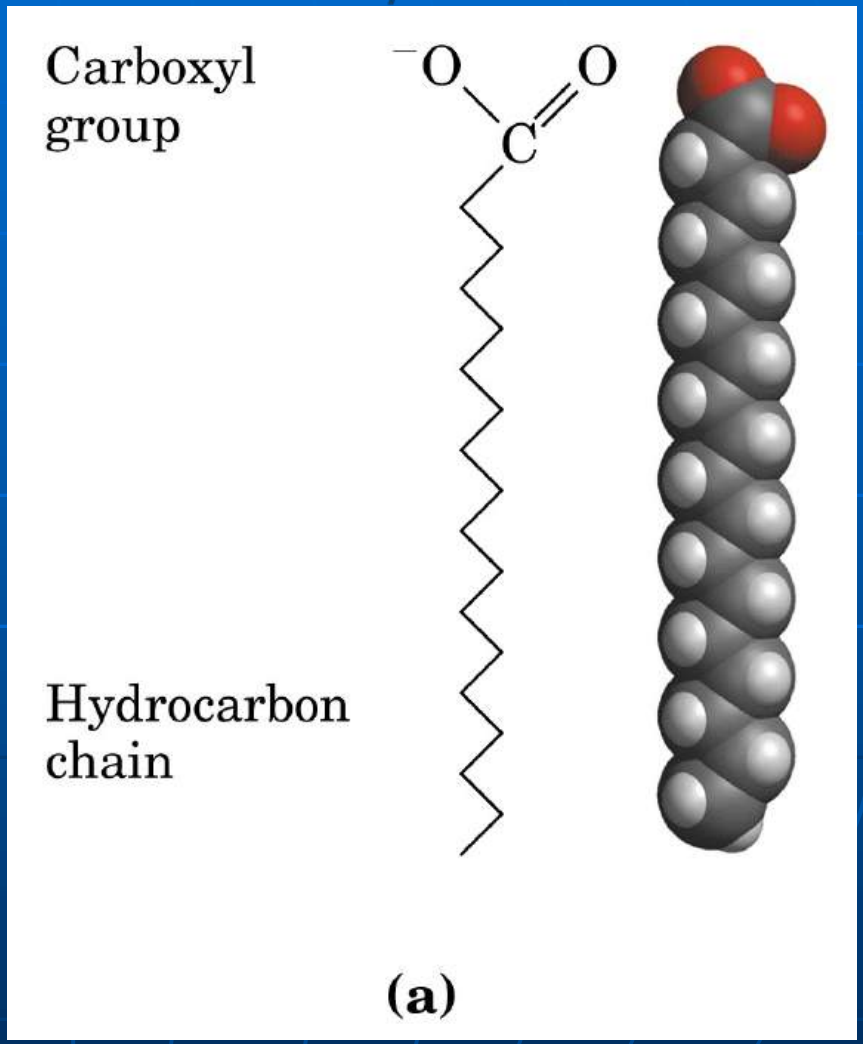
- Furthermore, lipids contribute significantly to the palatability of the diet. A diet consisting solely of protein and carbohydrates would generally not be as readily accepted by most individuals!

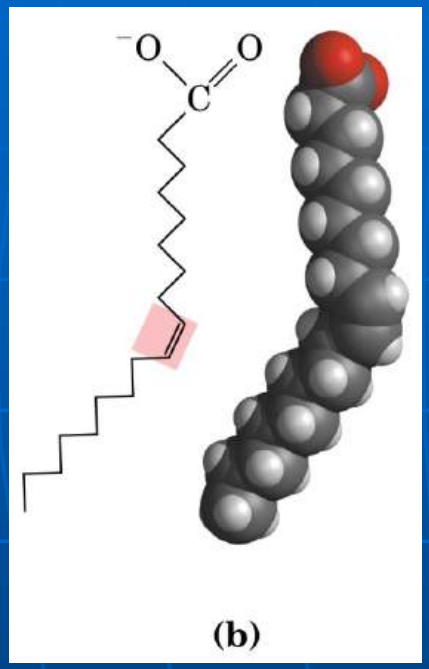
The lipids in food

Triglyceride

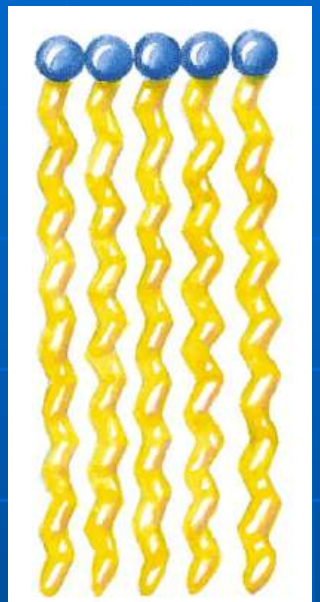


Fatty acid



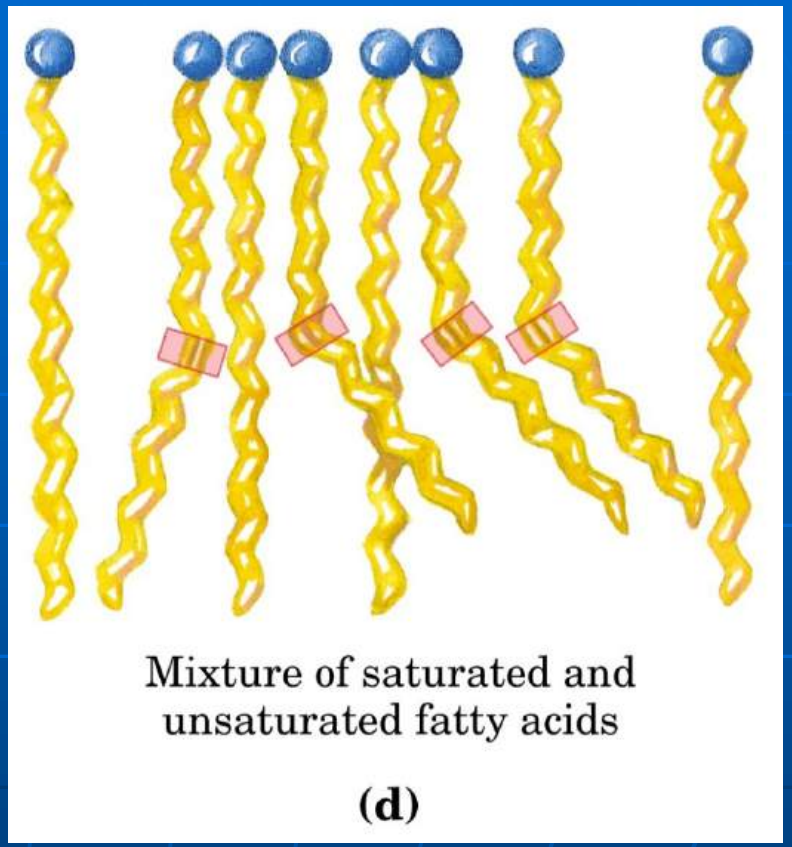


(b)



Saturated fatty acids

(c)



Mixture of saturated and unsaturated fatty acids

(d)

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saturated fatty acids

Laurate 12:0
Dodecanoic acid

Myristate 14:0
Tetradecanoic acid

Palmitate 16:0
Hexadecanoic acid

Stearate 18:0
Octadecanoic acid

Arachidate 20:0
Eicosanoic acid

Behenate 22:0
Docosanoic acid

Lignocerate 24:0
Tetracosanoic acid

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monounsaturated fatty acids

Palmitoleate 16:1 Δ9
9-Hexadecenoic acid

Petroselinate 18:1 Δ6
6-Octadecenoic acid

Vaccenate 18:1 Δ11
11-Octadecenoic acid

Oleate 18:1 Δ9
9-Octadecenoic acid

Gadoleate 20:1 Δ9
9-Eicosenoic acid

Cetoleate 22:1 Δ11
11-Docosenoic acid

Erucate 22:1 Δ113
13-Docosenoic acid

Elaidate 24:1 Δ9 trans
9-trans-Octadecenoic acid

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polyunsaturated fatty acids

Linoleate 18:2 Δ 9,12
(9,12-Octadecadienoic acid)

α–Linolenate 18:3 Δ 9,12,15
(9,12,15-Octadecatrienoic acid)

γ–Linolenate 18:2 Δ 6,9,12
(6,9,12-Octadecatrienoic acid)

Meadate 20:3 Δ 5,8,11
(5,8,11-Eicosatrienoic acid)

Parinarate 18:4 Δ 9,11,13,15
(9,11,13,15-Octadecatetraenoic acid)

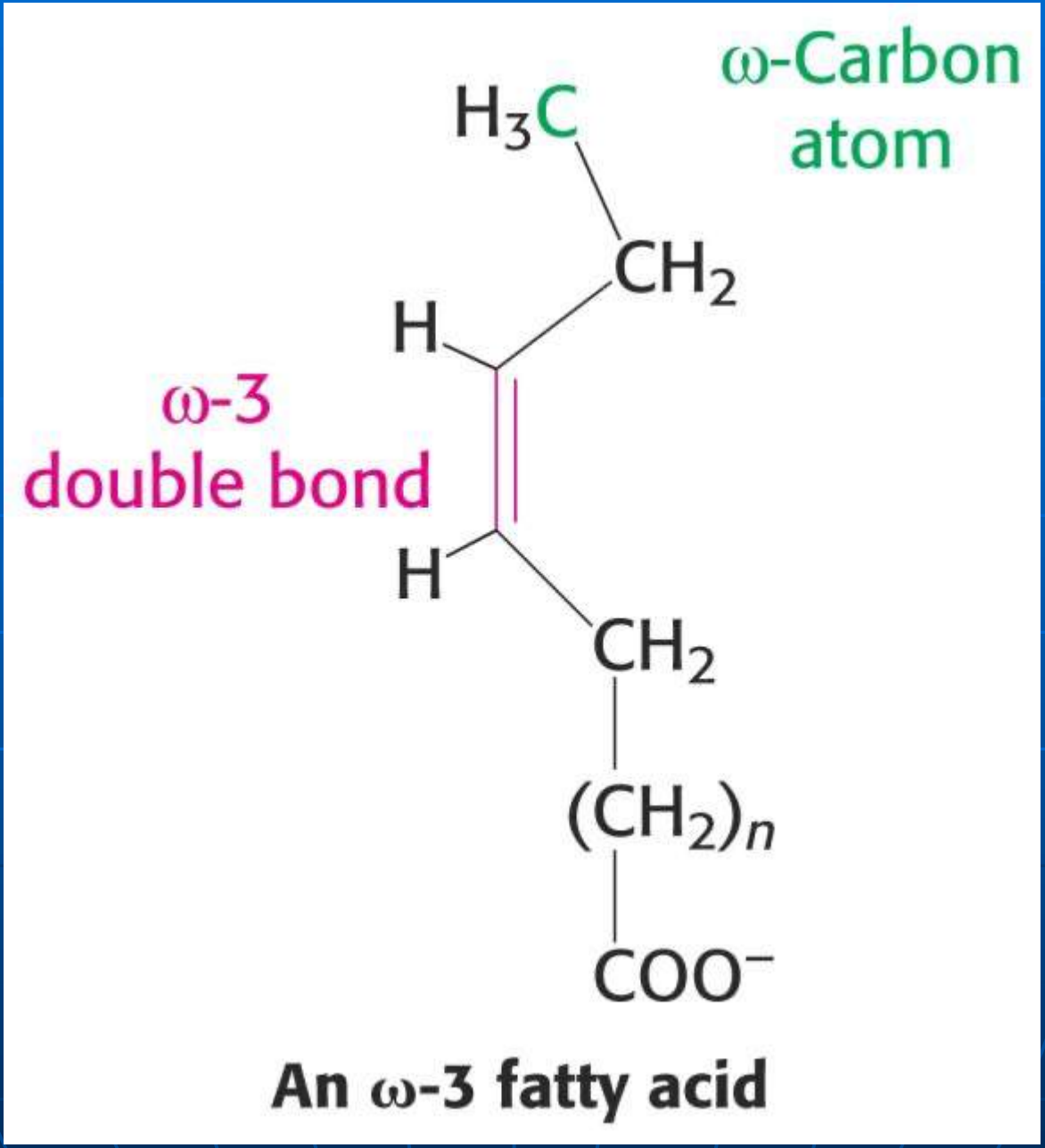
Arachidonate 20:4 Δ 5,8,11,14
(5,8,11,14-Eicosatetraenoic acid)

Timnodonate 20:5 Δ 5,8,11,14,17
(5,8,11,14,17-Eicosapentaenoic acid)

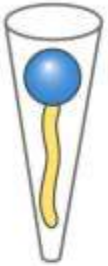
Adrenate 22:3 Δ 7,10,13,16
(7,10,13,16-Docosatetraenoic acid)

Clupanodonate 22:5 Δ 7,10,13,16,19
(7,10,13,16,19-Docosapentaenoic acid)

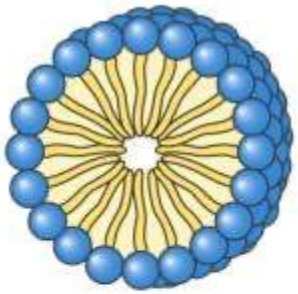
Cervonate 22:6 Δ 4,7,10,13,16,19
(4,7,10,13,16,19-Docosahexaenoic acid)



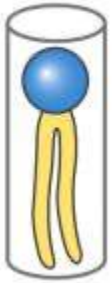
An ω-3 fatty acid



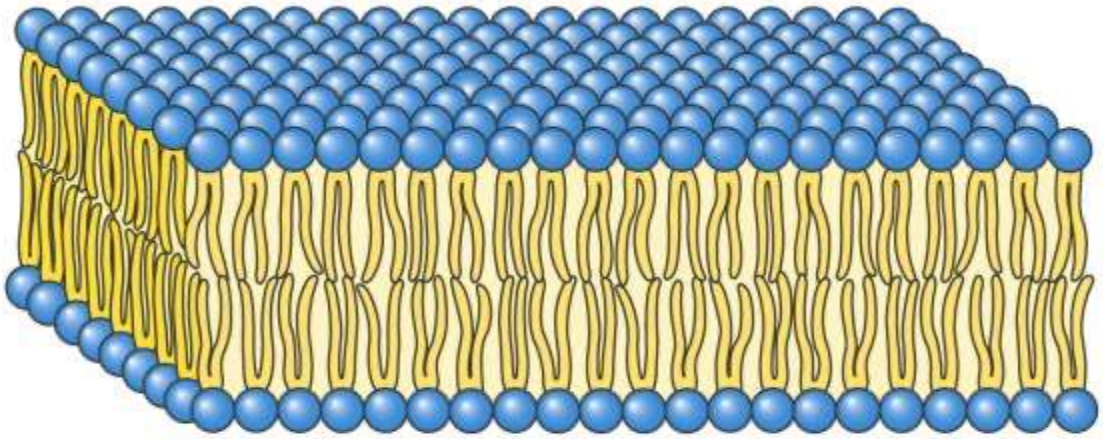
Individual units are wedge-shaped (cross-section of head greater than that of side chain)



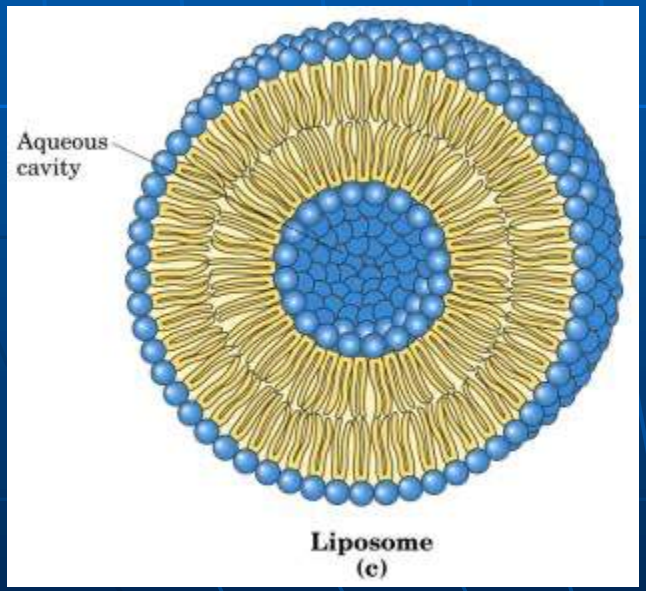
Micelle
(a)



Individual units are cylindrical (cross-section of head equals that of side chain)



Bilayer
(b)

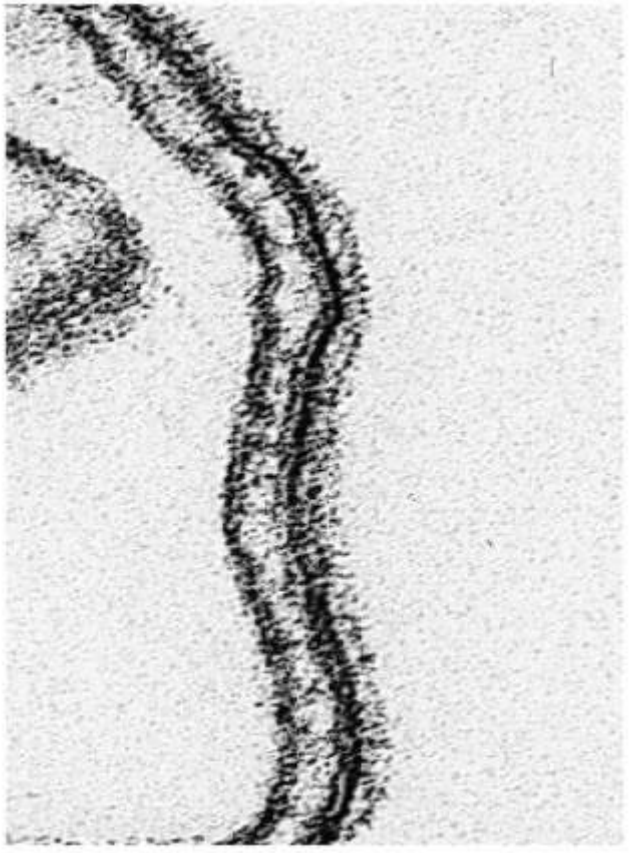


Liposome
(c)

Aggregates of amphipathic lipids that are formed in water

The cell membranes

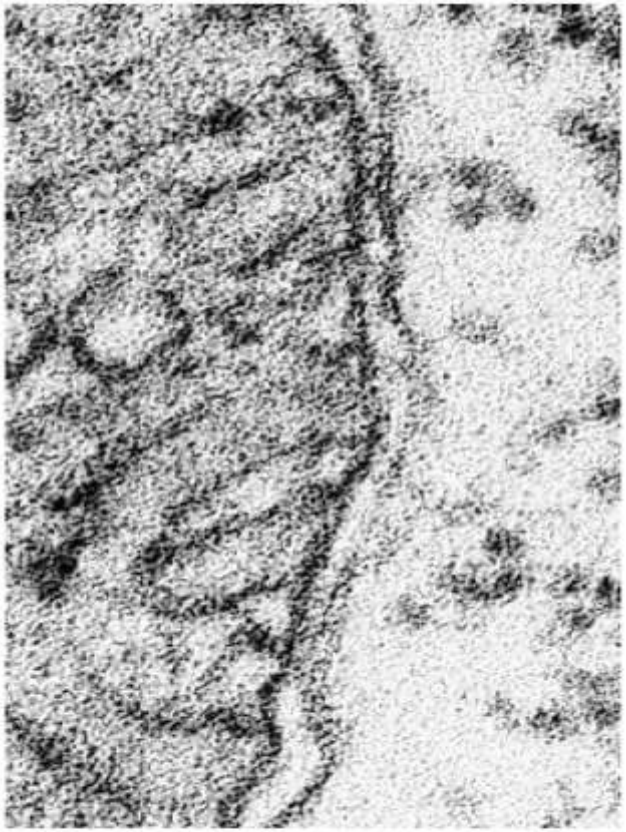
They define the outer boundaries of cells and regulate the traffic of molecules across these borders. In eukaryotic cells divide the interior space into discrete compartments, segregating their specific internal components and processes.



(a)

Plasma Membrane

- resistant
- flexible
- self-sealing
- selectively permeable
- Support for cellular processes



(c)

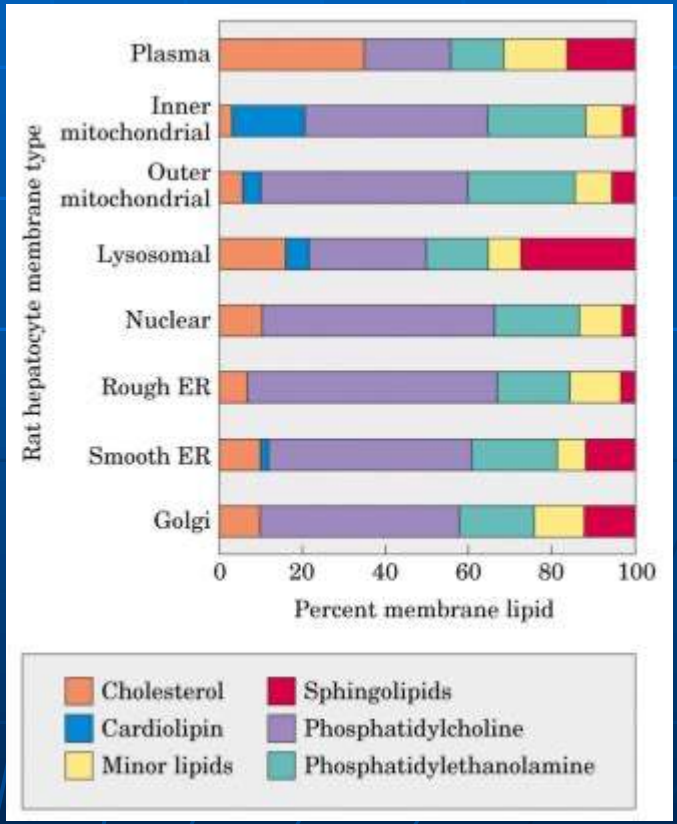
Mitochondrial membrane

table 12–1

Major Components of Plasma Membranes in Various Organisms

	Components (% by weight)				
	Protein	Phospholipid	Sterol	Sterol type	Other lipids
Human myelin sheath	30	30	19	Cholesterol	Galactolipids, plasmalogens
Mouse liver	45	27	25	Cholesterol	—
Maize leaf	47	26	7	Sitosterol	Galactolipids
Yeast	52	7	4	Ergosterol	Triacylglycerols, steryl esters
Paramecium (ciliated protist)	56	40	4	Stigmasterol	—
E. coli	75	25	0	—	—

The relative amounts of lipids and proteins vary depending on the membrane type and reflect the differences of their biological functions



Dietary lipids influence the composition of cell membranes

Dietary lipids serve various functions: they act as an energy source, serve as structural components in cell membranes (including cholesterol and phospholipids), and are structural components of a small fraction of cellular proteins.

Cholesterol is crucial for synthesizing detergents, such as bile salts, which aid in the digestion and absorption of dietary lipids, as well as for the synthesis of steroid hormones.

Dietary lipids affect cell membrane composition

TABLE 12.1 Some naturally occurring fatty acids in animals

Number of carbons	Number of double bonds	Common name	Systematic name	Formula
12	0	Laurate	*n*-Dodecanoate	$CH_3(CH_2)_{10}COO^-$
14	0	Myristate	*n*-Tetradecanoate	$CH_3(CH_2)_{12}COO^-$
16	0	Palmitate	*n*-Hexadecanoate	$CH_3(CH_2)_{14}COO^-$
18	0	Stearate	*n*-Octadecanoate	$CH_3(CH_2)_{16}COO^-$
20	0	Arachidate	*n*-Eicosanoate	$CH_3(CH_2)_{18}COO^-$
22	0	Behenate	*n*-Docosanoate	$CH_3(CH_2)_{20}COO^-$
24	0	Lignocerate	*n*-Tetracosanoate	$CH_3(CH_2)_{22}COO^-$
16	1	Palmitoleate	*cis*-Δ^9-Hexadecenoate	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COO^-$
18	1	Oleate	*cis*-Δ^9-Octadecenoate	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COO^-$
18	2	Linoleate	*cis,cis*-Δ^9,Δ^{12}-Octadecadienoate	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COO^-$
18	3	Linolenate	all-*cis*-$\Delta^9,\Delta^{12},\Delta^{15}$-Octadecatrienoate	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COO^-$
20	4	Arachidonate	all-*cis*-$\Delta^5,\Delta^8,\Delta^{11},\Delta^{14}$-Eicosatetraenoate	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COO^-$

The essential fatty acids: eicosanoid precursors

Linoleate 18:2 Δ 9,12
(9,12-Octadecadienoic acid)

α–Linolenate 18:3 Δ 9,12,15
(9,12,15-Octadecatrienoic acid)

Linoleic acid 18:2 ω-6	**Linolenic acid 18:3 ω-3**
↓ Unsaturation, elongation ↓	
Arachidonic acid 20:4 ω-6	**Eicosapentaenoic acid 20:5 ω-3 (EPA)**
↓ Elongation, Unsaturation ↓	
Docosapentaenoic acid 22:5 ω-6	**Docosahexaenoic acid (DHA) 22:6 ω-3**

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Medium content in fatty acids and vitamin E in different oils and fats

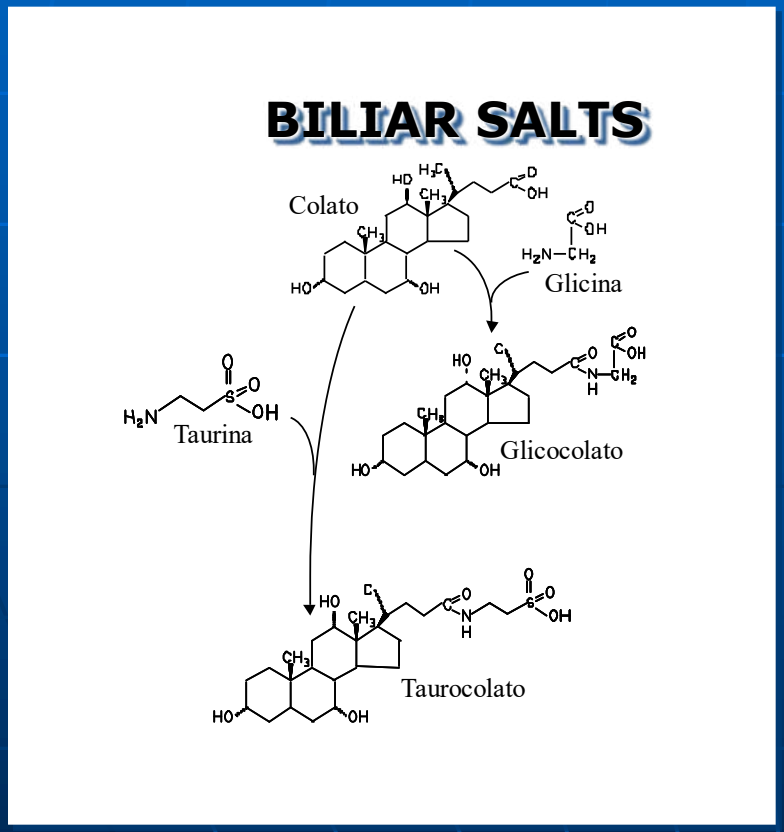
Oil/ fat	Fatty acids (%) saturated	mono-unsaturated	poly-unsaturated	Tocopherols mg/100 g
Olive oil	16	72	9	18
Corn oil	15	31	50	35
Soybean oil	14	23	59	18
Butter	49	24	3	2
Lard	43	43	12	N.D.

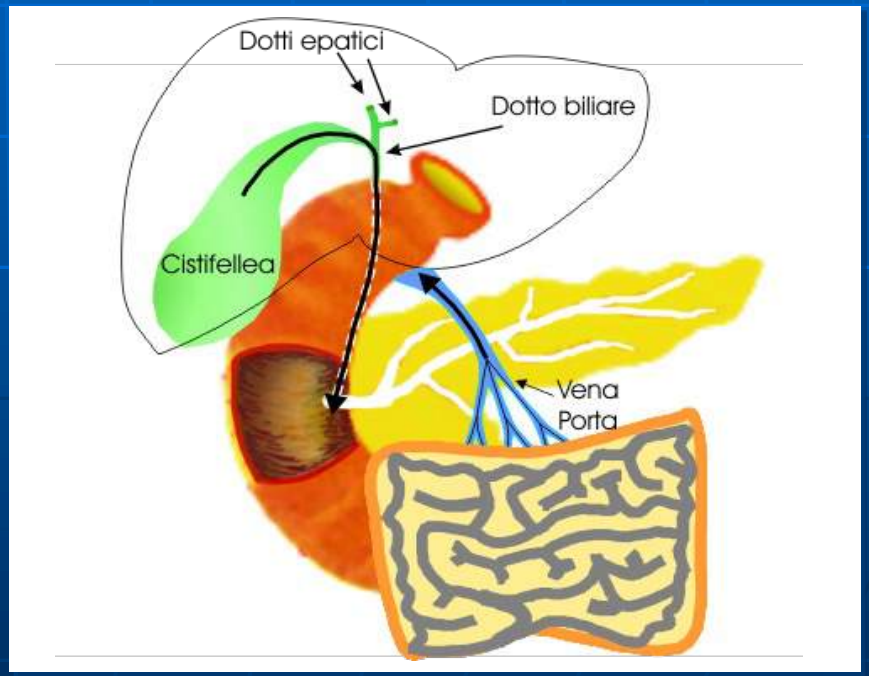
The main mono-unsatured fatty acid in olive oil is oleic acid.

Oleate 18:1 Δ9
9-Octadecenoic acid

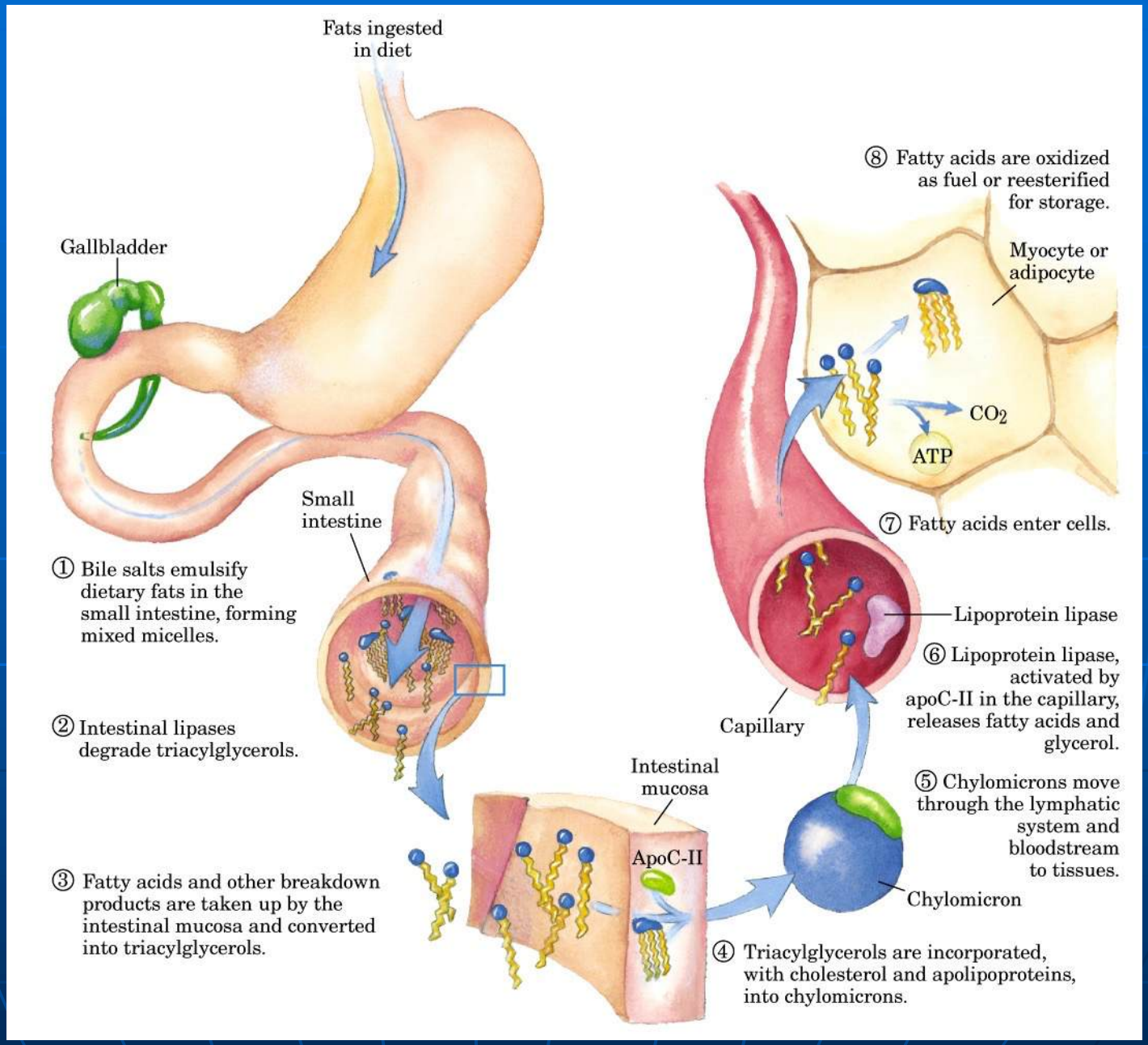
Digestion and absorption of lipids: the role of cholesterol

Cholesterol is the precursor of bile salts necessary for lipid digestion. This represents the only available biochemical pathway for cholesterol elimination (400 mg/day of bile salts).





Digestion and absorption of lipids



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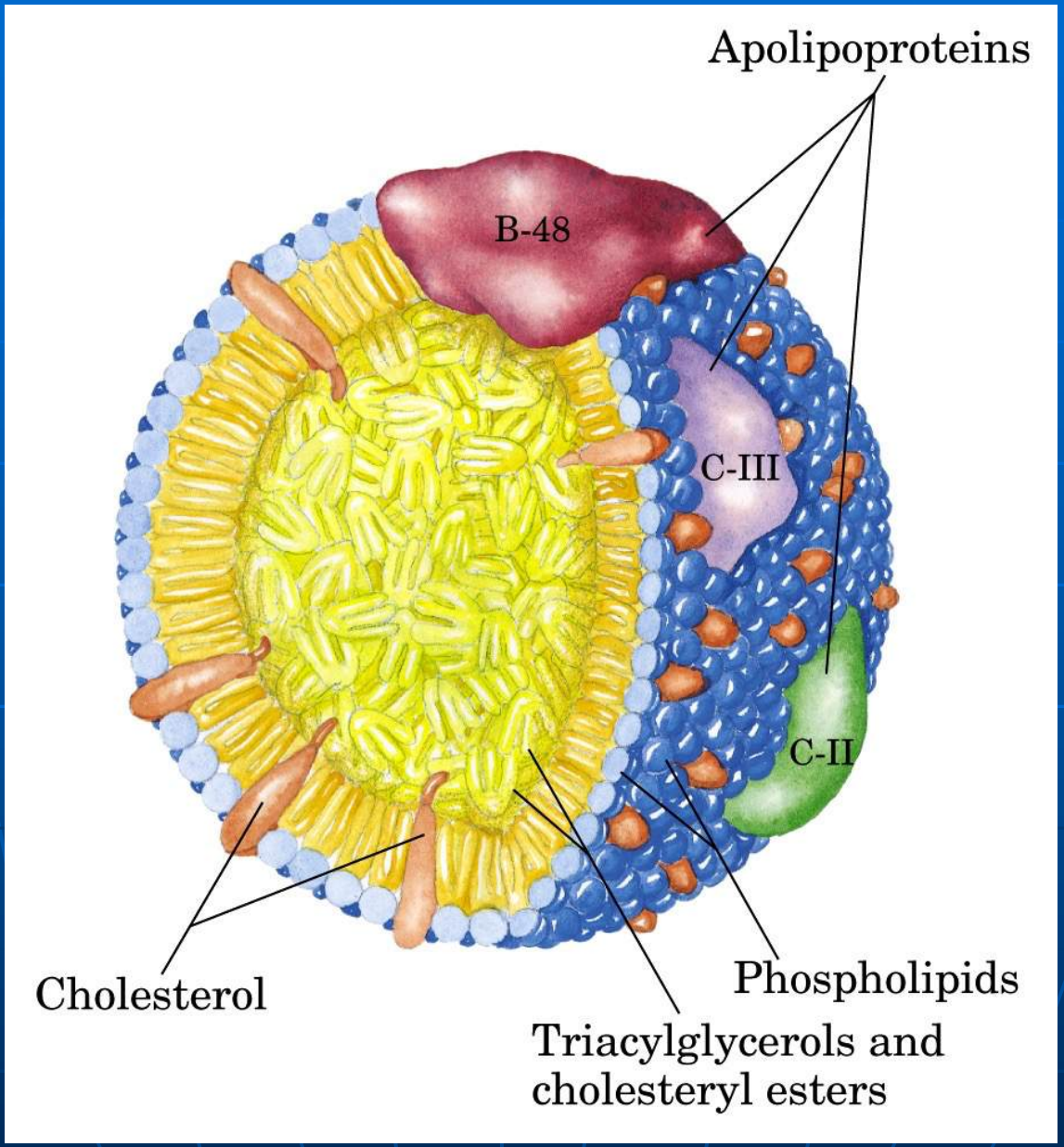
Special proteins, called apolipoproteins, are required for handling and transport of lipid droplets.



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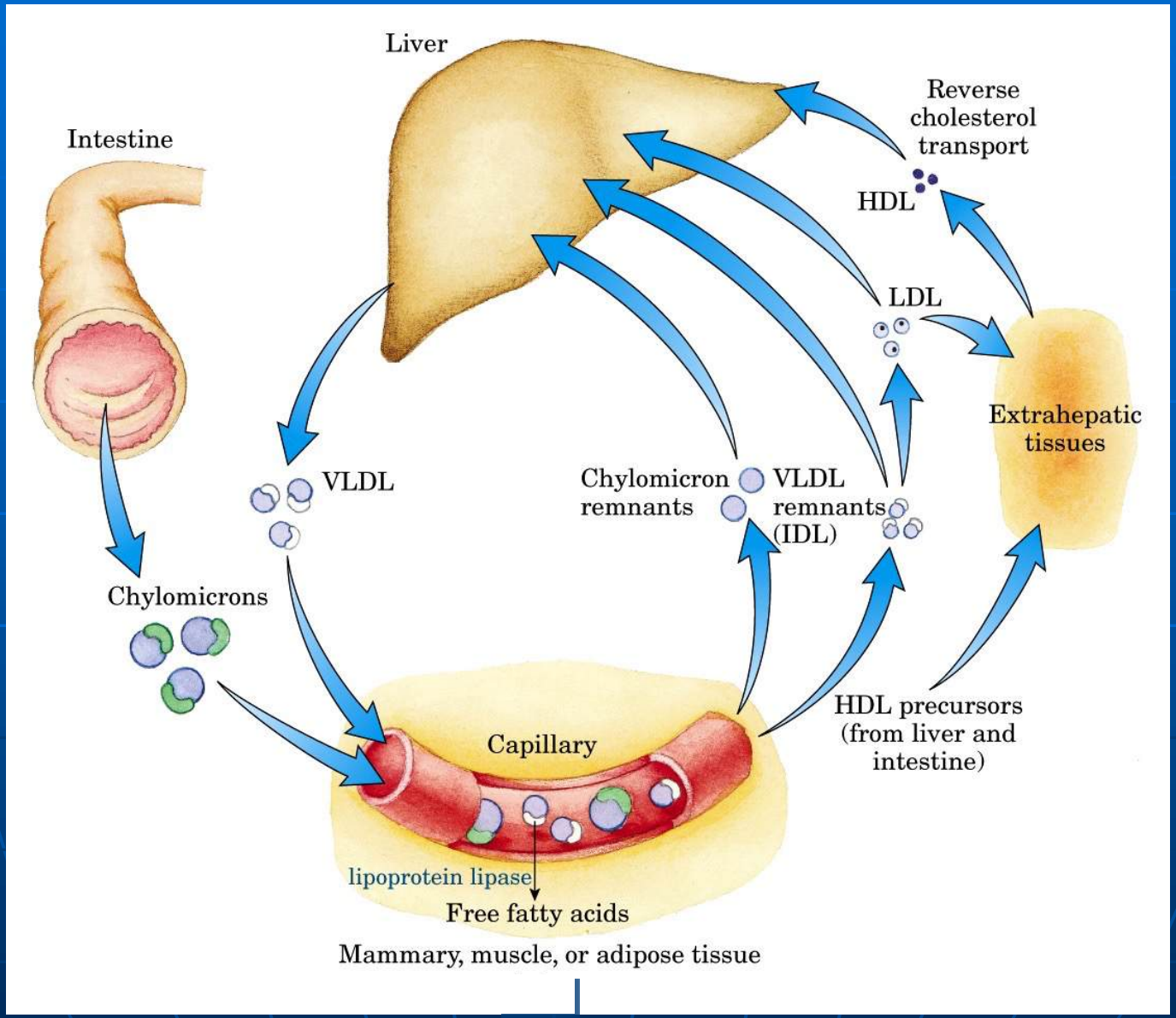
Lipoproteins and lipid's transport



“Bad” and “good” cholesterol

These terms are oversimplified, as cholesterol found in both LDLs and HDLs is essential for life.

LDLs, often labeled as "bad" cholesterol, serve as carriers, transporting cholesterol from the liver to different tissues. Elevated LDL levels can lead to the pathological accumulation of cholesterol in the arteries.

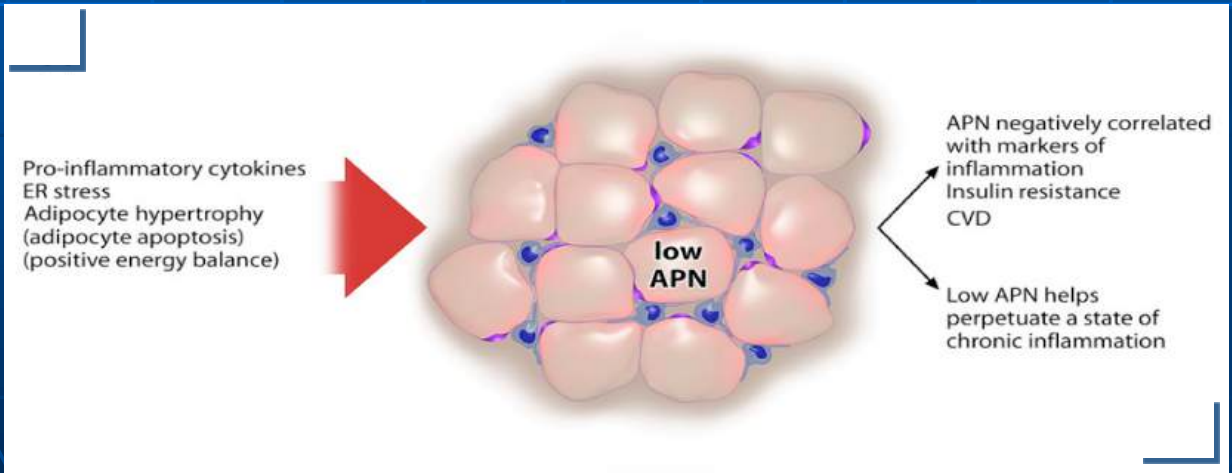
Conversely, high levels of HDL-cholesterol, known as "good" cholesterol, are linked to a reduced risk of cardiovascular disease. HDLs function as cleaners, removing cholesterol from various organs.

Evidence suggests that increased concentrations of HDLs in the bloodstream can counteract the pathological buildup of cholesterol in arterial walls, particularly in the heart.

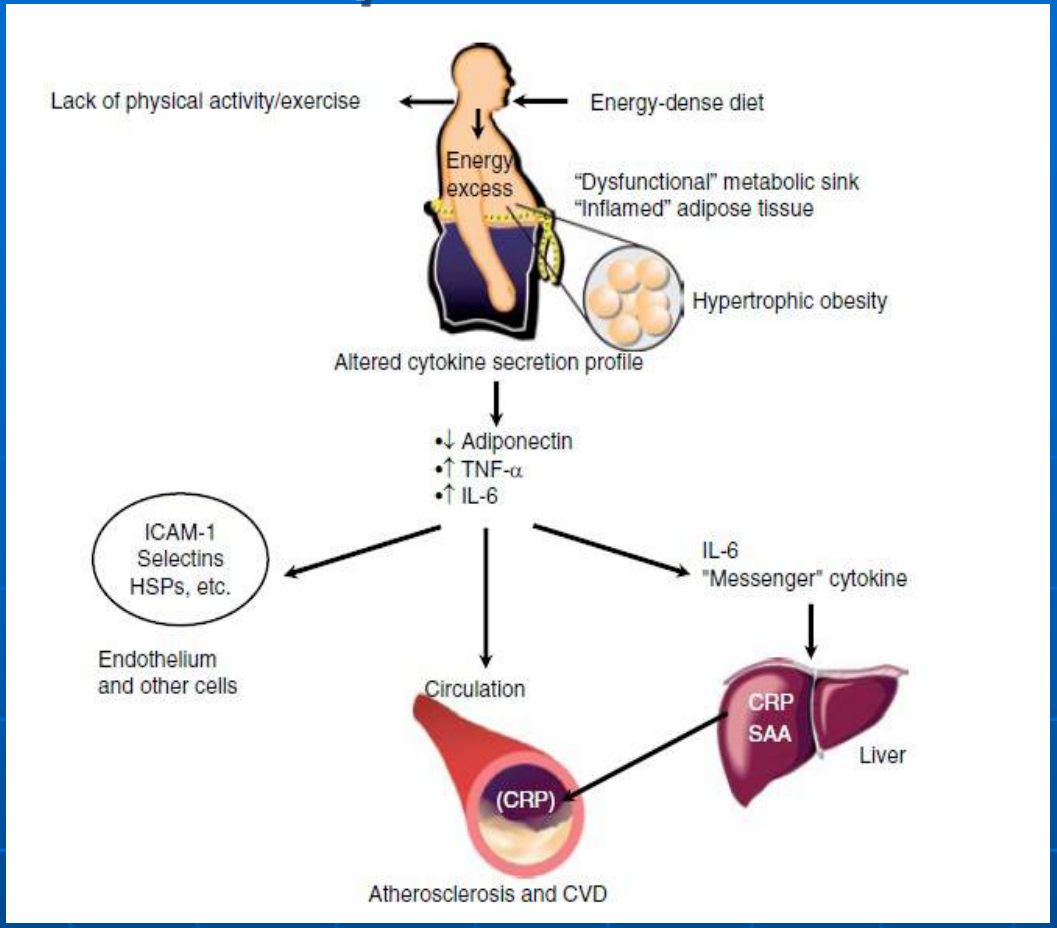
A modern view of the adipose tissue

In the past, the adipose tissue was mainly considered an energy store that is filled when an excess of metabolic energy is available but is depleted when energy is needed.

In contrast, the current view of the adipose tissue is that of an active endocrine organ sending out and responding to signals, which modulate food intake, energy consumption, insulin sensitivity, hormone homeostasis, bone metabolism as well as inflammation and immunity.



The "inflamed" adipose tissue of visceral obesity



Numerous studies conducted over the past three decades have provided solid evidence that the regional distribution of adipose tissue is the key factor explaining the relationship between adiposity and cardiometabolic risk. The biology of subcutaneous fat cells differs from that of visceral fat cells in many respects. Experimental studies have demonstrated that, as compared with their subcutaneous counterparts, visceral adipocytes are hyperlipolytic and have a distinct secretion profile of cytokines (often referred to as adipokines).

Obesity, Inflammation, and Cardiovascular Risk

Many metabolic investigations have shown that excess visceral adiposity is a key feature of a phenomenon referred to as ectopic fat deposition, which has been shown to be associated with a plethora of metabolic dysfunctions.

- insulin resistance;
- atherogenic dyslipidemia;
- hypertension;
- impaired fibrinolysis/increased risk of thrombosis;
- inflammation.

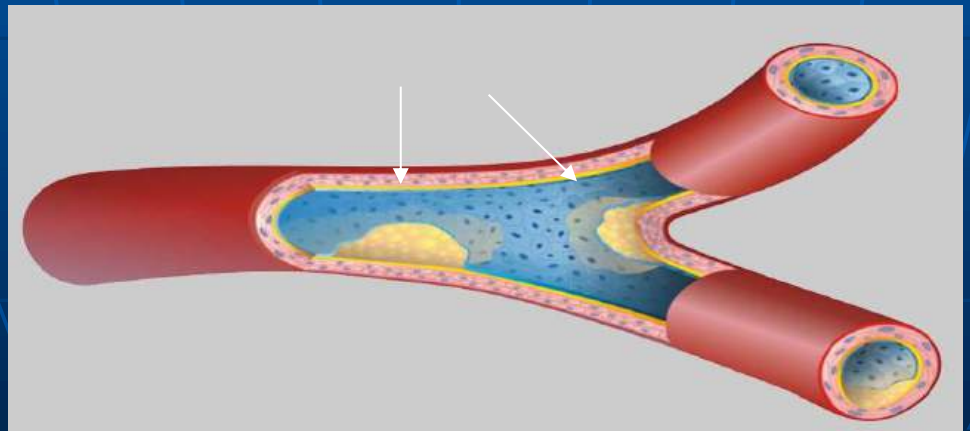
The biochemical processes in atherosclerosis

Atherosclerosis is a multifaceted disease characterized by intricate biochemical processes within arterial walls. Here's a more detailed yet simplified explanation:

Atherosclerosis begins with endothelial dysfunction, where the endothelial lining of arteries becomes inflamed or damaged due to various factors such as high blood pressure, smoking, or high levels of LDL cholesterol. In response to endothelial injury, LDL cholesterol particles penetrate the arterial wall and become oxidized, forming oxidized LDL (oxLDL).

OxLDL is recognized by scavenger receptors on macrophages within the arterial wall. When macrophages engulf oxLDL, they become foam cells, laden with lipid droplets. These foam cells, along with smooth muscle cells, contribute to the formation of fatty streaks, the earliest visible lesions of atherosclerosis.

As the disease progresses, inflammatory processes intensify within the arterial wall. In advanced lesions, foam cells undergo apoptosis (programmed cell death) and necrosis, leading to the release of lipid contents into the extracellular space. This lipid-rich necrotic core contributes to the formation of atherosclerotic plaques.



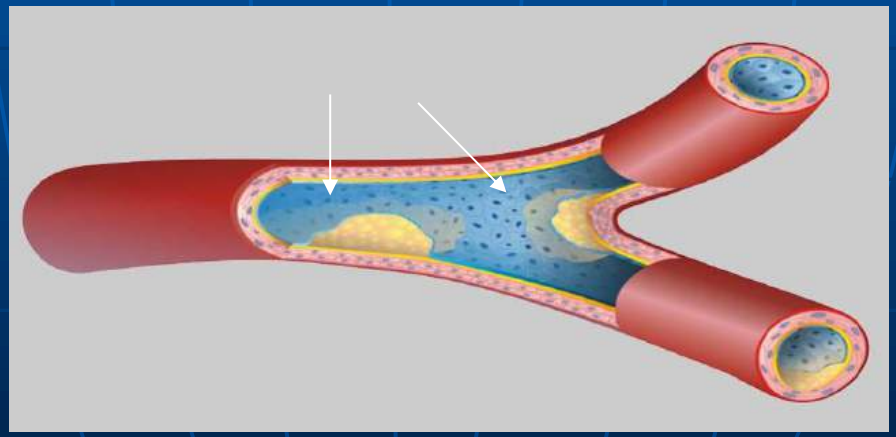
The inflammatory component of atherosclerosis

Polyunsaturated fatty acids (PUFAs), abundant components of LDL, are particularly susceptible to oxidation due to their multiple double bonds. Peroxidation of PUFAs generates reactive oxygen species (ROS) and lipid peroxides, exacerbating oxidative stress within the arterial wall.

Furthermore, PUFAs serve as substrates for enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX). These enzymes catalyze the formation of pro-inflammatory lipid mediators known as eicosanoids, which contribute to the progression of inflammation and atherosclerosis.

In atherosclerotic lesions, the expression of COX-2 (inducible form of COX) and 15-lipoxygenase (15-LOX) is upregulated, particularly in macrophages. COX-2-derived prostaglandins and 15-LOX-derived leukotrienes promote inflammation, oxidative stress, and plaque destabilization, contributing to the pathogenesis of atherosclerosis.

In summary, atherosclerosis involves a cascade of biochemical events, including LDL oxidation, foam cell formation, inflammation, and lipid peroxidation. Understanding these intricate molecular mechanisms is crucial for developing effective therapeutic strategies to combat atherosclerotic cardiovascular disease.



The arachidonic acid cascade

Phosphatidylcholine

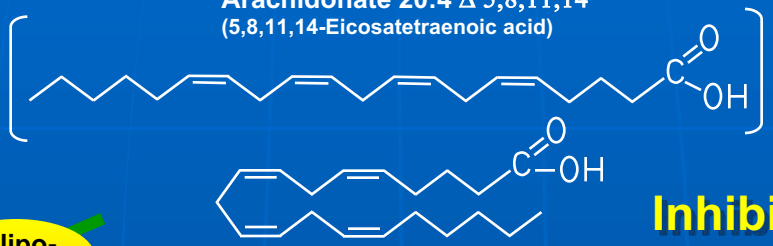
Phosphatidylinositol

$cPLA_2$

PLC

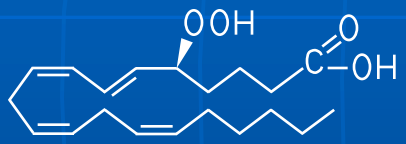
Diacylglycerol lipase

Arachidonate 20:4 Δ 5,8,11,14
(5,8,11,14-Eicosatetraenoic acid)



Leukotrienes

5-lipo-oxygenase

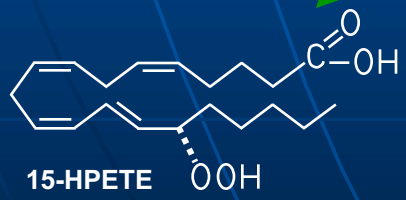


5-HPETE

12-lipo-oxygenase

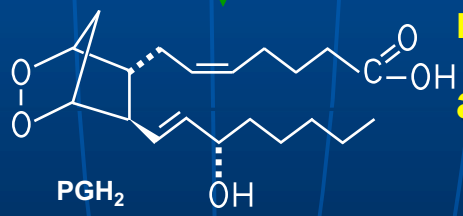
12-HPETE

15-lipo-oxygenase



15-HPETE

Cyclo-oxygenase



PGH_2

Inhibition of COX and LOX metabolism of AA, or the deactivation of AA hydroperoxides to form HETEs might help diminish death of macrophage foam cells in atherosclerotic lesions.

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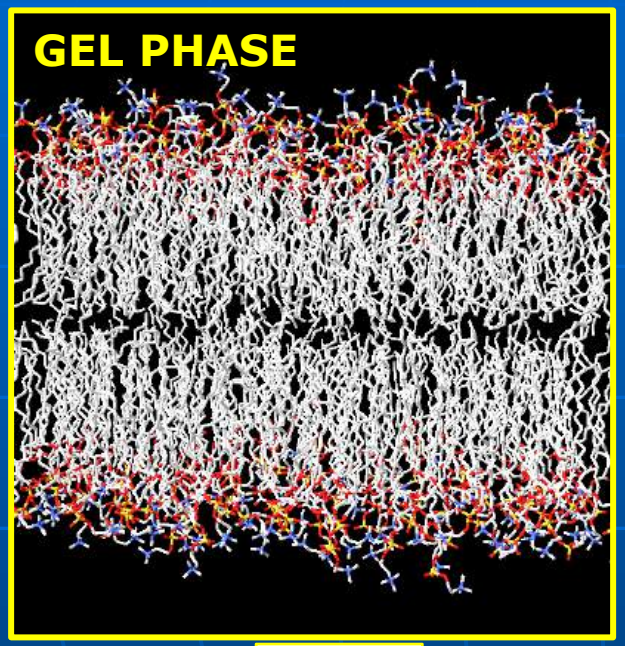
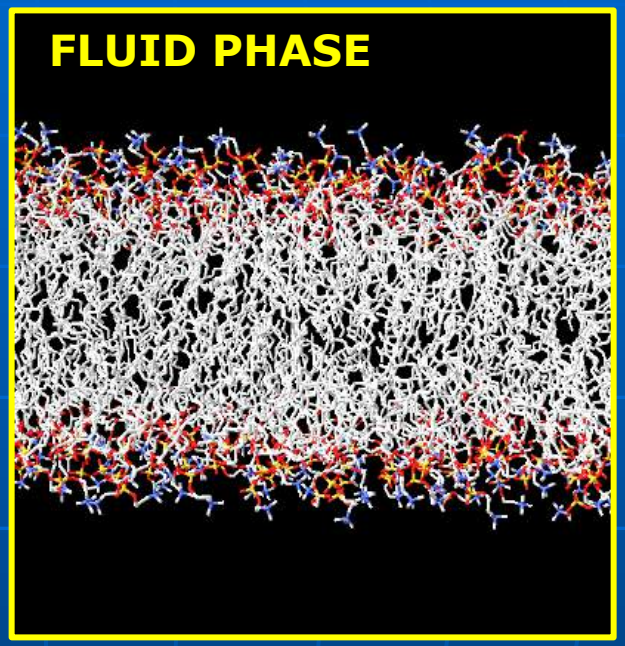
LIPID BILAYER PHASE STATES

The bilayer can adopt a solid gel phase state at lower temperatures …

… but it undergoes phase transition to a fluid state at higher temperatures





~52Å

~43Å

GEL

Liquid Disordered- L_d

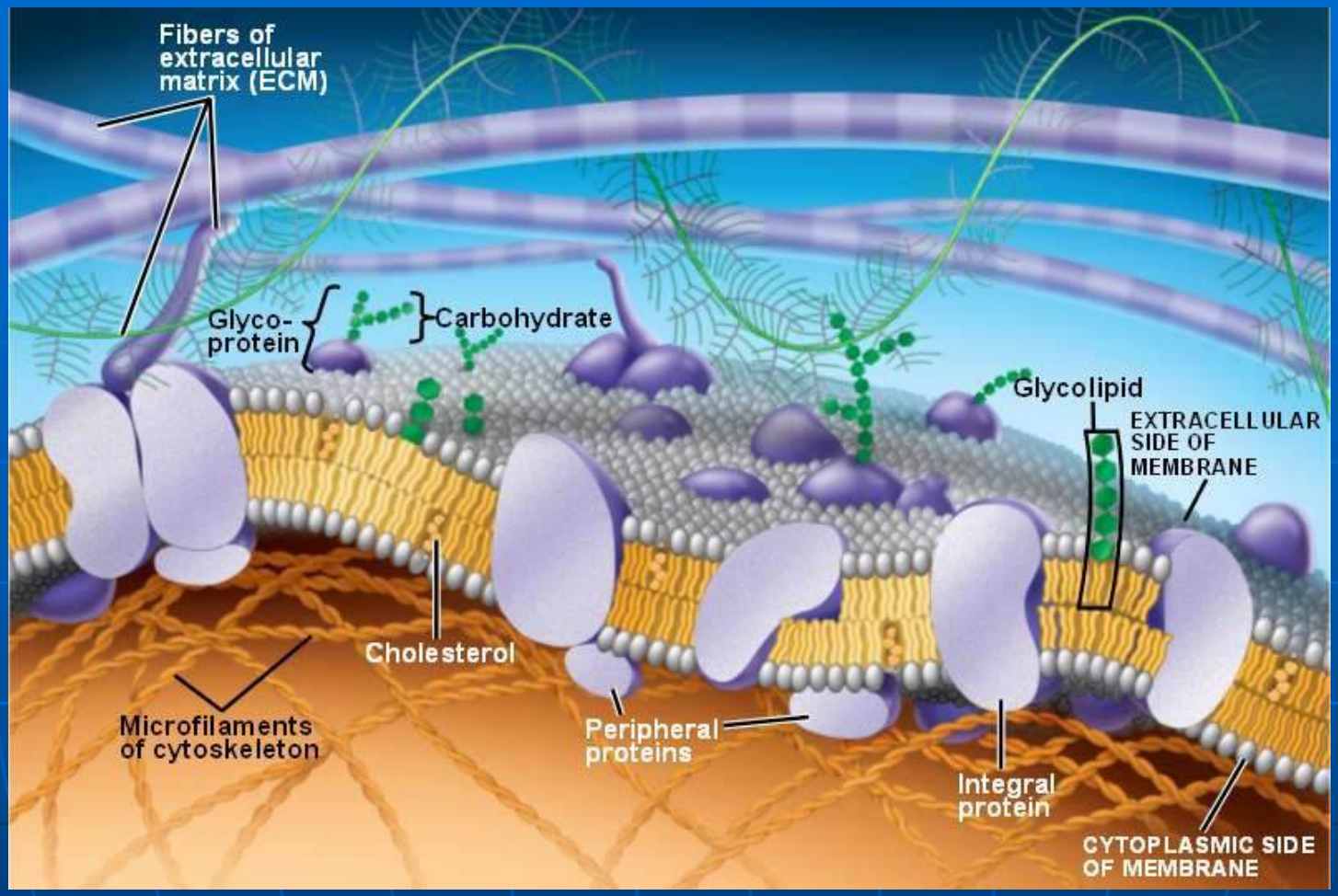
Lipid chain conformational and translational order

Lipid chain conformational and translational disorder

TEMPERATURE

Tm (melting temperature)

BIOLOGICAL MEMBRANES: The fluid mosaic model



According to the fluid mosaic model of S. J. Singer and G. Nicolson (1972) the **plasma membrane** is a **fluid** structure with a "**mosaic**"
of proteins embedded in or attached to a bilayer of **lipids**.

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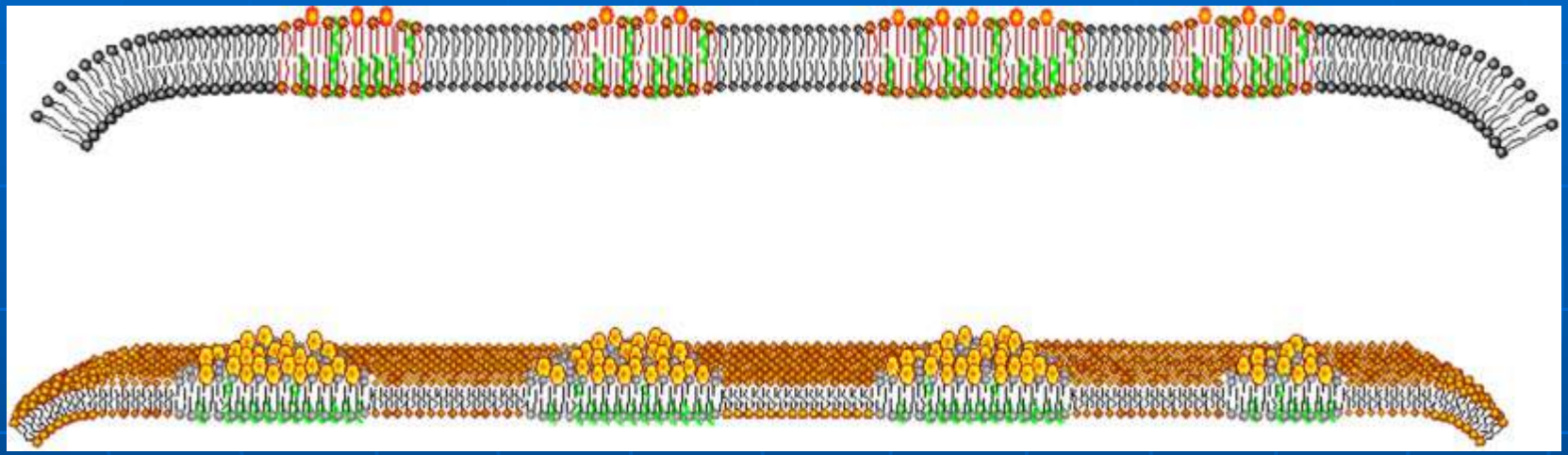
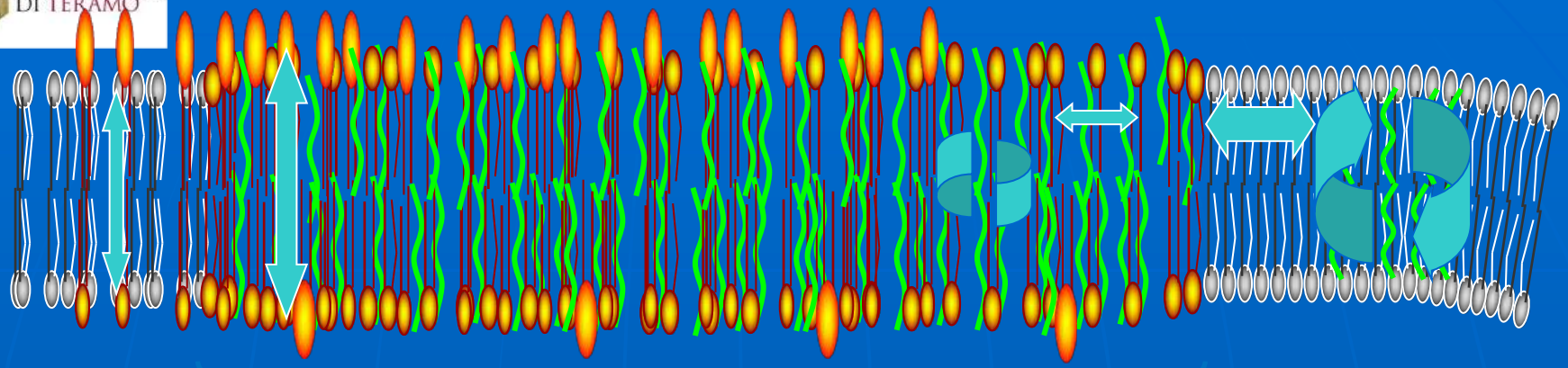
“lipid rafts” modulate lipid metabolism and signaling





Lipid rafts (LRs)
Liquid ordered phase (Lo)

= Sphingolipids

= Phospholipids

= Cholesterol

= Lateral diffusion

= Rate of flip-flop

= Membrane thickness