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REVIEW

Nutrigenomics: a case for the common soil between cardiovascular disease and cancer

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Abstract The border between health and disease is often set by a complex equilibrium between two elements, genetics on one hand, lifestyle on the other, To know it better, means to give new weapons, often crucial, in the hands of the doctors and their patients. It also means to adjust therapies, to find out which drug is good for a patient and which prevention strategy will work better for him/her. Nutrigenomics is an approach to individualize or personalize food and nutrition, and ultimately health, by tailoring the food to the individual genotype. In this review, we present the interaction between certain genetic polymorphisms and diet and increased cardiovascular or cancer risk. It is, indeed, now clear that a large number of bioactive food components may provide risk or protection at several stages of both atherosclerosis and cancer formation processes. We are giving here few examples of gene-food interactions relevant for both the risk of cardiovascular disease and cancer, since a common soil could exist in the genesis of cardiovascular disease and of some types of cancer (mainly gastrointestinal tract and hormone-dependent).

Keywords Nutrigenomics · Cardiovascular disease · Cancer · Polyunsaturated fatty acids

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Introduction

The border between health and disease is often set by a complex equilibrium between two elements, genetics on one hand, lifestyle on the other, To know it better means to place new weapons, often crucial, in the hands of medical doctors and of their patients. It also means to adjust therapies, to find out which drug is good for a patient and which prevention strategy will work better for him/her.

Nutrigenomics is an approach to nutrition and human health that studies the effect of genetic differences in human response to food and how food has an impact on gene expression, biochemistry, metabolism and promotion of health [6, 54]. It is based on two main observations: (1) the nutritional environment modifies the expression of genes, and (2) depending on the genotype of an individual, the metabolism of nutrients may vary and ultimately result in a different health status [3]. Thus, nutrigenomics treats food as a major environmental factor in the gene-environment interaction, with the final aim to individualize or personalize food and nutrition, and ultimately individual strategies to preserve health, by tailoring the food to the individual genotype, similarly to the way pharmacogenetics would personalise therapeutic approaches by tailoring drugs to the individuals' genetic background [12].

A common soil presumably exists in the genesis of cardiovascular disease and some cancers, in particular gastro-intestinal cancers and those hormone-dependent, such as breast, prostate or ovarian cancers [4].

It is now clear that a large number of bioactive food components may provide risk or protection at several stages of both atherosclerosis or cancer formation processes.

We are giving here few examples of gene-food interactions relevant for both the risk of cardiovascular disease and cancer.

Nutrigenomics and cardiovascular disease

Nutrition has been largely recognized as an important risk protection factor for cardiovascular disease. Among dietary factors total fat and specific fatty acids have been mostly studied. Fatty acids food composition has been strongly related to lipid metabolism and consequently to metabolic risk factors and the risk of cardiovascular disease. However, such relation could be modulated by variations in genes that play a function in FA metabolism [42].

Apolipoprotein A1

Apolipoprotein (apo) A-1 is primarily found in high density lipoprotein particles (HDL). HDLs are produced by the liver and intestine and are responsible for the transport of cholesterol from peripheral tissues back to the liver for metabolism through a series of complex interactions with other lipoproteins, enzymes, transfer proteins, and receptors [62]. Both Apo A-I and HDL-associated cholesterol have been identified as protective factors for CVD [26, 59].

The gene coding for apo A-1, APOA1, which is found on the long arm of chromosome 11, is highly polymorphic and a specific single-nucleotide polymorphism (SNP) in its promoter region, known as APOA1–75G>A, [21, 36] has been extensively studied in relation to apo A-1and HDL-cholesterol concentrations. A meta-analysis concluded that the rarer A allele may be associated with mildly increased apo A-1 concentrations [21].

One way in which diet may influence APOA1 gene expression is the intake of n-3 and n-6 polyunsaturated fatty acids (PUFAs). PUFAs can modulate the gene expression of several enzymes involved in lipid and carbohydrate metabolism [48, 50]. In a study involving 50 men and women fed diets rich in PUFA, reductions in LDL cholesterol associated with the PUFA diet compared with the saturated fat diet were more marked in women who were carriers of the rarer A allele than in women who were homozygous for the G allele, but no such effect was evident in men [35]. In another study, a significant interaction in terms of HDL-cholesterol concentration was observed between APOA1 genotype and PUFA intake [41]. In the latter study, subjects were divided into low (<4% of energy), medium (4–8% of energy) and high (>8% of energy) PUFA intake groups. In women who were carriers of the A allele, HDL-cholesterol concentrations increased significantly with increasing PUFA intake. The opposite effect was seen in women who were homozygous for the G allele (HDL-cholesterol decreased as PUFA intake increased). In men, PUFA intake had no significant effect on either HDL cholesterol or apo A-1 concentrations.

This meant that when PUFA intake provided <4% of energy, women who were homozygous for the G allele had ~14% higher-cholesterol concentrations than did carriers of the A allele, and when PUFA intake provided >8% of energy, HDL-cholesterol concentrations in carriers of the A allele were 13% higher than those of *G/G* subjects. This raises the possibility of providing individualized nutritional advice on the basis of genotype: women who are carriers of the A allele should increase their intake of PUFAs to increase HDL-cholesterol concentrations and reduce CVD risk.

Apolipoprotein A5

The apolipoprotein A5 gene is another good example of recently reported gene-diet interactions. APOA5 gene is an important regulator of triglyceride (TG)-rich lipoprotein (TRL) metabolism [46] with two roles, (1) by assembling VLDLs [51, 58]; (2) as activator of intravascular TG hydrolysis by lipoprotein lipase (LPL) [16, 37].

Several common APOA5 SNPs have been associated with increased plasma total TG, RLP, and VLDL concentrations [27, 28, 43]. However, the association between APOA5 gene and postprandial lipid levels was suggested to be modulated by the type of fat consumed with the diet [20, 34].

In particular, the hypothesis that FA intake may modulate the effect of APOA5 variants on lipid metabolism was assessed in the Framingham population by Lai et al. [27], who examined the interaction between the APOA5–1131T>C and 56C>G polymorphisms and FA intake in their relation to the body mass index (BMI) and obesity risk in men and women. They found a consistent and statistically significant interaction between the –1131T>C SNP (but not the 56C>G) and total fat intake for BMI. In subjects homozygous for the –1131T major allele, BMI increased as total fat intake increased. Conversely, this increase was not present in carriers of the –1131C minor allele. The same authors found also significant interactions in determining obesity and overweight risks. APOA5–1131C minor allele carriers had a lower obesity and overweight risk compared with TT subjects in the high fat intake groups, but not when fat intake was low. When specific fatty acid group were analyzed, monounsaturated fatty acids showed the highest statistical significance for these interactions [27].

Endothelial nitric oxide synthase

NO is synthesized from the amino acid L-arginine by a family of enzymes, referred to as NO synthase (NOS). Three distinct isoforms of NOS have been identified to date [38]. The inducible NOO is expressed in vessel walls and

macrophages by certain cytokines and endotoxin lipopolysaccharides in pathological conditions [39]. The constitutive neuronal NOS is expressed in the central and peripheral nervous system as well as in the macula densa of kidneys. It plays important roles in physiological [52] and pathophysiological [23] conditions. The constitutive endothelial NO synthase (eNOS) is expressed in the endothelium, where it produces NO from L-arginine. NO diffuses from the endothelium to vascular smooth muscle cells, where it increases the concentration of cGMP by stimulating soluble guanylate cyclase, leading to vascular relaxation.

Several studies suggest that the basal release of NO from the endothelium contributes to basal vascular tone [44, 57] and regulates blood flow and blood pressure. Recent reports have suggested a possible role of NO in the pathogenesis of coronary spasm [25]; moreover, it inhibits the proliferation of smooth muscle cells [11], protects against platelet aggregation in vitro [9] and in vivo [60] and inhibits platelet adhesion to endothelium [45]. All these processes are important events during atherogenesis. A Glu298Asp polymorphism in the eNOS gene has recently been associated with development of ischemic heart disease and myocardial infarction [18, 19]. Preliminary data also indicated that Glu-Asp298 polymorphism is associated with coronary spasm [18, 19, 31, 61].

Dietary supplementation with n-3 fatty acids has been shown to improve microvascular endothelial function, in vitro, in those at risk for cardiovascular disease [40], and this may be a mechanism for the inverse association between fish consumption, the major dietary source of n-3 fatty acids, and cardiovascular disease mortality [15]. However, the impact on endothelial function of n-3 FA depends on eNOS genotype, a greater influence being observed in Asp298 carriers of Glu298Asp eNOS. Flow-mediated arterial dilation (FMD), a nitric oxide-dependent endothelial response that can be measured non-invasively in vivo using high-resolution ultrasound is, indeed, influenced by such a SNP. Leeson et al. [31] found a positive association between plasma n-3 FA and FMD in Asp298 carriers, while in Glu298 homozygotes no association was found. The difference by genotype in the association between FMD and plasma n-3 FA levels was significant in an interaction model. Similar patterns were seen with red blood cell membrane n-FA.

Arachidonate 5-lipoxygenase (Alox 5 or 5-LO)

Another gene the activity of which can be modulated by PUFA is the arachidonate 5-lipoxigenase (5-LOX) gene. It is a key enzyme in the biosynthesis of leukotrienes, important mediators of inflammation [8]. In particular, the dihydroxy leukotriene B_4 is a potent leukocyte chemoattractant, whereas the cysteinyl leukotrienes increase vascular permeability and promote contraction of vascular smooth muscle [49]. The 5-lipoxygenase pathway has been linked to atherosclerosis, a chronic inflammatory process involving the recruitment and accumulation of monocytes, macrophages, and dendritic cells in arterial walls, through ecicosanoid activation. [32, 47].

PUFA, n-6 or n-3 derived, can differently affect eicosanoid syntheisis. Indeed, intake of omega 6 fatty acids increases while intake of omega 3 fatty acids decreases the production of leukotriens [7, 22].

Variation in the 5-lipoxygenase promoter have been demonstrated to alter eicosanoid-mediated inflammatory circuits in the arterial wall and promote atherogenesis. Carriers of the variant alleles of the tandem Sp1 binding motifs in the promoter of 5-LOX gene showed increased mean intima-media thickness (IMT) as compared with carriers of the wild-type allele.

Dwyer et al. [5] observed that dietary arachidonate and linoleic acid (n-6 FA) intake was associated with increased IMT in carriers of the variant 5-LOX genotypes, but not in wild type carriers. Conversely, dietary EPA and DHA (n-3 FA) intake was associated with a decrease in IMT in carriers of two variant alleles. Probably, dietary arachidonic acid and its metabolic precursor (linoleic acid) amplified the atherogenic effect of the variant genotypes by increasing the levels of eidcosanoids. In contrast, increased intake of eicosapentaenoic and docosahiexaenoic acids would reduce the production of inflammatory leukotrienes and inhibit their pro-atherosclerotic effect.

Nutrigenomics and cancer

Several pieces of evidence have repeatedly implicated dietary components and genetic susceptibilities as important determinants of cancer risk and tumor behaviour. Variation in cancer incidence among and within populations with similar dietary patterns suggests that an individual's response may reflect interactions with genetic factors, which may modify gene, protein and metabolite expression patterns. Diet composition in fatty acids has strong implications in the risk of cancer development and such effect may be mediated through gene-environment interactions as it has been described for cardiovascular disease risk.

Cyclooxygenase-2

Dietary intake of marine fatty acids from fish may protect against prostate cancer development. This association is

modified by genetic variations in cyclooxygenase-2 (COX-2), a key enzyme in fatty acid metabolism and inflammation [17].

Increasing evidence from animal and *in vitro* studies shows that omega-3 (ω-3) fatty acids, especially long chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), protect against prostate cancer [29, 53]. EPA and DHA are mainly found in fatty fish, and recent epidemiological studies showed that frequent consumption of fish is associated with reduced risk of prostate cancer [1, 55, 56].

Polyunsaturated fatty acids, both n-3 and n-6, are converted in the body to eicosanoids, such as prostaglandins and thromboxanes. These compounds have several biological effects, including modulation of inflammatory and immune responses, cell differentiation and cellular growth. One of the mechanisms by which n-3 fatty acids may affect carcinogenesis is through their suppressive effect on the byosinthesis of eicosanoids derived from arachidonic acid (AA). In general, AA-derived eicosanoids have proinflammatory effects and may promote carcinogenesis, whereas EPA-derived eicosanoids have anti-inflammatory effects and may inhibit prostate cancer growth. A diet with a high ratio of n-3 to n-6 fatty acids results in a shift toward production of EPA-derived eicosanoids rather than AA-derived eicosanoids and, as a result, may inhibit the development of prostate cancer.

Cyclooxygenase-2 (COX-2), a key enzyme in eicosanoid synthesis, is overexpressed in prostate cancer tissue when compared to benign tissue from the same patients [24, 30]. Also, use of nonsteroidal anti-inflammatory drugs (NSALDs), which inhibit the activity of COX enzymes, is associated with a decreased risk of prostate cancer [33].

In a case control study on 1,378 patients with prostate cancer and 782 controls in Sweeden, Hedelin and coworkers [17] observed a significant interaction between intake of salmon-type fish, rich in n-3 fatty acids and a genetic variant of COX-2 in determining the risk of prostate cancer. Among homozygotes or heterozygotes of the variant allele of +6365 T/C SNP of COX-2 gene, high intake of salmon-type fish was associated with a significant decrease in the risk of prostate cancer, while there was no association between fish intake and cancer risk in carriers of the wild-type allele.

Glutathione s-transferases

Marine n-3 fatty acids have been also associated with a protective effect against breast cancer in experimental studies and in post-menopausal women [10, 13, 14]. This inhibition is correlated with the extent of lipid peroxidation generated in tumor tissues or cells [2, 13]. The suppression of cancer growth by n-3 FA is enhanced by drugs that increase lipid peroxidation and it is eliminated by antioxidants through inhibition of lipid peroxidation. Since glutathione S-transferases (GSTs) are potential major catalysts in the elimination of these beneficial by-products, women possessing low activity GST genotypes might exhibit a stronger marine n-3 fatty acid-breast cancer inverse association than those possessing the high activity genotypes.

In the Singapore Chinese Health Study, there were no associations between GSTM1 and GSTP1 genotype and breast cancer risk. However, the GSTT1 null genotype was associated with a 30% reduced risk of breast cancer. Moreover, the association between marine n-3 fatty acid and breast cancer was analysed after stratification by GSTM1, GSTT1 and GSTP1 genotypes. They found that women with genetic polymorphisms encoding lower or no enzymatic activity of GSTT1 experienced more breast cancer protection from marine n-3 fatty acids than those with high activity genotypes, consistent with the hypothesis that the peroxidation products of n-3 fatty acids are directly involved in breast anticarcinogenesis.

Conclusion and perspectives

The Nutrigenomic approach may offer some clues to the proposed "common soil" between cardiovascular disease and cancer. Nutritional factors, indeed, are important mechanisms for development of both ischemic cardiovascular disease and highly prevalent types of cancer. However, the mechanisms linking diet to these diseases are still not completely understood. The area of nutrigenomics is expanding and gaining momentum. Although the evidence base is growing, consistent data are lacking, which hampers the ability to make specific recommendations. This can be addressed with population studies of appropriate experimental design, clinical trials of adequate size and quality, and product-specific trials in subjects selected for specific genetic variants.

As progress continues to be made in developing the scientific evidence base for nutrigenomics, attention must also be paid to addressing some of the other issues surrounding the field, such as acceptance by the public and establishing appropriate, credible sources to disseminate information.

References

1. Astorg P (2004) Dietary N-6 and N-3 polyunsaturated fatty acids and prostate cancer risk: a review of epidemiological and experimental evidence. Cancer Causes Control 15:367–386
2. Chajes V, Sattler W, Stranzl A, Kostner GM (1995) Influence of n-3 fatty acids of the growth of human breast cancer cells in vitro:

relationship to peroxides and vitamin-E. Breast Cancer Res Treat 34:199–212
3. Corthesy-Theulaz I, den Dunnen JT, Ferre P, Geurts JM, Muller M, van Belzen N et al (2005) Nutrigenomics: the impact of biomics technology on nutrition research. Ann Nutr Metab 296:1858–1866
4. Donati MB (2003) Cancer and cardiovascular disease: does a common soil exist? Pathophysiol Haemost Thromb 33(suppl 2):1
5. Dwyer JH, Allayee H, Dwyer KM et al (2004) Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. N Engl J Med 350:29–37
6. Elliott R, Ong TJ (2002) Nutritional genomics. BMJ 324:1438–1442
7. Ferretti A, Nelson GJ, Scmidt PC, Kelley DS, Bartolini G, Flanagan VP (1997) Increased dietary arachidonic acid enhances the synthesis of vasoactive eicosanoids in humans. Lipids 32:435–439
8. Funk CD (2001) Prostaglandins and leukotrienes: advances in eicosanoid biology. Science 294:1871–1875
9. Furlong B, Henderson AH, Lewis MJ, Smith JA (1987) Endothelium-derived relaxing factor inhibits in vitro platelet aggregation. Br J Pharmacol 90:687–692
10. Gago-Dominguez M, Castelao JE, Sun CL et al (2004) Marine n-3 fatty acid intake, gluthatione S-transferase polymorphisms and breast cancer risk in post-menopausal Chinese women in Singapore. Carcinogenesis 25:2143–2147
11. Garg UC, Hassid A (1989) Nitric oxide-generating vasodilators and 8-bromo-cycling guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. J Clin Invest 83:1774–1777
12. Ghosh D, Skinner MA, Laing WA (2007) Pharmacogenomics and nutrigenomics: synergies and differences. Eur J Clin Nutr 61:567–574
13. Gonzales MJ, Schemmel RA, Gray JI, Dugan L-Jr, Sheffield LG, Welsch CW (1991) Effect of dietary fat on growth of MCF-7 and MDA-MB231 human breast carcinomas in athymic nude mice: relationship between carcinoma growth and lipid peroxidation product levels. Carcinogenesis 12:1231–1235
14. Gonzalez MJ, Schemmel RA, Dugan L Jr, Gray JI, Welsch CW (1993) Dietary fish oil inhibits human breast carcinoma growth: a function of increased lipid peroxidation. Lipids 28:827–832
15. Goode GK, Garcia S, Heagerty AM (1997) Dietary supplementation with marine fish oil improves in vitro small artery endothelial function in hypercholesterolemic patients. Circulation 96:2802–2807
16. Grooskopf I, Barouk N, Lee SJ, Kamari Y, Harats D, Rubin EM, Pennacchio LA, Cooper AD (2005) APOA5 deficiency results in marked hypetriglyceridemia attributable to decreased lipolysis of triglyceride-rich lipoproteins and removal of their remnants. Arterioscler Thromb Vasc Biol 25:2573–2579
17. Hedelin M, Chang ET, Wilklund F, Bellocco R et al (2006) Association of frequent consumption of fatty fish with prostate cancer risk is modified by COX-2 polymorphism. Int J Cancer 120:398–405
18. Hibi K, Ishigami T, Tamura K, Mizushima S et al (1998) Endothelial nitric oxide synthase gene polimorphism and acute myocardial infarction. Hypertension 32:521–526
19. Hingorani AD, Liang CF, Fatibene J et al (1999) A common variant of the endothelial nitric oxide synthase ($Glu^{298} \rightarrow Asp$) is a major risk factor for coronary artery disease in the UK. Circulation 100:1515–1520
20. Jang Y, Kim JY, Kim OY, Lee JE, Cho H, Ordovas JM, Lee JH (2004) The -1131T>C polymorphism in the APOA5 gene is associated with post-prandial hypertricylglycerolemia; elevated small, dense LDL concentrations; and oxidative stress in non-obese Korean men. Am J Clin Nutr 80:832–840
21. Juo SH, Wyszynski DF, Beaty TH, Bailey-Wilson JE (1999) Mild association between the A/G polymorphism in the promoter of the apolipoprotein A-I gene and apolipoprotein A-I levels: a meta-analysis. Am J Med Genet 82:235–241
22. Kelley DS, Taylor PC, Nelson GJ, Mackey BE (1998) Arachidonic acid supplementation enhances synthesis of eicosanoids without suppressing immune functions in young healthy men. Lipids 33:125–130
23. Kihara M, Umemura S, Kadota T, Yabana M, Tamura K, Nyui N, Ogawa N, Murakami K, Fukamizu A, Ishii M (1997) The neuronal isoform of constitutive nitric oxide synthase is up-regulated in the macula densa of angiotensinogen gene-knockout mice. Lab Invest 76:285–294
24. Kirschenbaum A, Klausner AP, Lee R, Unger P, Yao S, Liu XH, Levine AC (2000) Expression of cyclooxygenase-1 and cyclooxygenase-2 in the human prostate. Urology 56:671–676
25. Kugiyama K, Yasue H, Okumura K, Ogawa H, Fujimoto K, Nakao K, Yoshimura M, Motoyama T, Inobe Y, Kawano H (1996) Nitric oxide activity is deficient in spasm arteries of patients with coronary spastic angina. Circulation 94:266–272
26. Kwiterovich PO Jr, Coresh J, Smith HH, Bachorik PS, Derby CA, Pearson TA (1992) Comparison of the plasma levels of apolipoproteins B and A-I, and other risk factors in men and women with premature coronary artery disease. Am J Cardiol 69:1015–1021
27. Lai C-Q, Corella D, Demissie S et al (2006) Dietary Intake of n-6 fatty acids modulates effect of apolipoprotein A5 gene on plasma fasting triglycerides, remnant lipoprotein concentrations, and lipoprotein particle size. Circulation 113:2062–2070
28. Lai CQ, Demissie S, Cupples LA, Zhu Y, Adiconis X, Parnell LD, Corella D, Ordovas JM (2004) Influnce of the APOA5 locus on plasma triglyceride, lipoprotein subclasses, and CVD risk in the Framingham heart study. J Lipid Res 45:2096–2105
29. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A (2004) Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr 79:935–945
30. Lee LM, Pan CC, Cheng CJ, Chi CW, Liu TY (2001) Expression of cyclooxygenase-2 in prostate adenocarcinoma and benign prostatic hyperplasia. Anticancer Res 21:1291–1294
31. Leeson CP et al (2002) Glu298Asp endothelial nitric oxide synthase gene polymorphism interacts with environmental and dietary factors to influence endothelial function. Cir Res 90:1153–1158
32. Lusis AJ (2000) Atherosclerosis. Nature 407:233–241
33. Mahmud S, Franco E, Aprikian A (2004) Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis. Br J Cancer 90:93–99
34. Martin S, Nicaud V, Humphries SE, Talmud PJ, on behalf of the EARS group (2003) Contribution of APOA5 gene variants to plasma triglyceride determination and to response to both fat and glucose tolerance challenges. Biochim Biophis Acta 1637:217–225
35. Mata P, Lopez-Miranda J, Pocovi M et al (1998) Human apolipoprotein A-I gene promoter mutation influences plasma low density lipoprotein cholesterol response to dietary fat saturation. Atherosclerosis 137:367–376
36. Matsunaga A, Sasaki J, Han H et al (1999) Compound heterozygosity for an apolipoprotein A1 gene promoter mutation and a structural nonsense mutation with apolipoprotein A1 deficiency. Arterioscler Thromb Vasc Biol 19:348–355
37. Merkel M, Loeffler B, Kluger M, Fabig N, Geppert G, Pennacchio LA, Laatsch A, Heeren J (2005) APOA5 accelerates plasma hydrolysis of triglyceride-rich lipoproteins by interaction with proteoglycan-bound lipoprotein lipase. J Biol Chem 280:21553–21560
38. Moncada S, Higgs A (1993) The L-arginine-nitric oxide pathway. New Engl J Med 329:2002–2012

39. Moncada S (1992) The L-arginine-nitric oxide pathway. Acta Physiol Scand 145:201–227
40. Nestel PJ (2000) Fish oil and cardiovascular disease: lipids and arterial function. Am J Clin Nutr 71:228–231
41. Ordovas JM, Corella D, Cupples LA et al (2002) Polyunsaturated fatty acids modulate the effects of the APOA1 G-A polymorphism on HDL-cholesterol concentrations in a sex-specific manner: the Framingham study. Am J Clin Nutr 75:38–46
42. Ordovas JM (2006) Genetic interactions with diet influence the risk of cardiovascular disease. Am J Clin Nutr 83(suppl 2):443S–446S
43. Pennacchio LA, Oliver M, Hubacek JA, Krauss RM, Rubin EM, Cohen JC (2002) Two independent APOA5 haplotypes influence human plasma triglyceride levels. Hum Mol Genet 11:3031–3038
44. Quyyumi AA, Dakak N, Andrews NP, Husain S, Arora S, Gilligan DM, Panza JA, Cannon RO III (1995) Nitric oxide activity in the human coronary circulation. J Clin Invest 95:1747–1755
45. Radomski MW, Palmer RMJ, Moncada S (1987) Endogenous nitric oxide inhibits human platelet adhesion to vascular endhotelium. Lancet 2:1057–1058
46. Rensen PC, van Dijk KW, Havekes LM (2005) APOA5: low concentration, high impact. Arterioscler Thromb Vasc Biol 25:2445–2447
47. Ross R (1999) Atherosclerosis–an inflammatory disease. N Engl J Med 340:115–126
48. Sampath H, Ntambi JM (2005) Polyunsaturated fatty acid regulation of genes of lipid metabolism. Annu Rev Nutr 25:317–340
49. Samuelsson B, Dahlen SE, Lindgren JA, Rouzer CA, Serhan CN (1987) Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. Science 237:1171–1176
50. Sessler AM, Ntambi JM (1998) Polyunsaturated fatty acid regulation of gene expression. J Nutr 128:923–6
51. Shaap FG, Rensen PC, Voshol PJ, Vrins C, van der Vliet HN, Chamuleau RA, Havekes LM, Groen AK, van Dijk Kw (2004) APOA5 reduces plasma triglycerides by inhibiting VLDL-TG production and stimulating lipoprotein lipase-mediated VLDL-TG hydrolysis. J Biol Chem 279:27941–27947
52. Shibuki K, Okada D (1991) Endogenous nitric oxide release required for long-term synaptic depression in the cerebellum. Nature 349:326–328
53. Simopoulos A, Cleland L (2003) Omega-6/omega-3 essential fatty acid ratio: the scientific evidence. Basel: Karger AG
54. Stover PL (2006) Influence of human genetic variations on nutritional requirements. Am J Clin Nutr 83:436S–442S
55. Terry PD, Rohan TE, Wolk A (2003) Intakes of fish and marine fatty acids and the risks of cancers of the breast and prostate and of other hormone-related cancers: a review of the epidemiologic evidence. Am J Clin Nutr 77:532–543
56. Terry PD, Terry JB, Rohan TE (2004) Long chain (n-3) fatty acid intake and risk of cancers of the breast and the prostate: recent epidemiological studies, biological mechanisms, and directions for future research. J Nutr 134:S3412–S3420
57. Vallance P, Collier J, Moncada S (1989) Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. Lancet 2:997–1000
58. Weinberg RB, Cook VR, Beckstead JA, Martin DD, Gallagher JW, Shelness GS, Ryan RO (2003) Structure and interfacial properties of human APOA5. J Biol Chem 278:34438–34444
59. Wilson PW, Abbott RD, Castelli WP (1988) High density lipoprotein cholesterol and mortality. The Framingham heart study. Ateriosclerosis 8:737–741
60. Yao S-K, Ober CJ, Krishnaswami A, Ferguson JJ, Anderson V, Golino P, Buja LM, Willerson JT (1992) Endogenous nitric oxide protects against platelet aggregation and cyclic flow variations in stenosed and endhotelium-injured arteries. Circulation 86:1302–1309
61. Yasue H, Yoshimura M, Sugiyama S, Sumida H, Okumura K, Ogawa H, Kugiyama K, Ogawa Y, Nakao K (1995) Association of a point mutation of the endothelial cell nitric oxide synthase (eNOS) gene with coronary spasm. Circulation 92:I–363. Abstract
62. Ye SQ, Kwiterovich PO Jr (2000) Influence of genetic polymorphisms on responsiveness to dietary fat and cholesterol. Am J Clin Nutr 72:1275S–1284S