Nutritional Genomics

Impact on Health and Disease

Edited by Regina Brigelius-Flohé and Hans-Georg Joost

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Foreword

The idea of creating a book on nutritional genomics was born at the 55th Mosbach Colloquium in 2004, which covered the topic ''How nutrients influence gene activity.'' Regina Brigelius-Flohé and myself had organized this symposium together with the ''Gesellschaft für Biochemie und Molekularbiologie'' (GBM) in Germany with the clear intention of reanimating nutritional sciences and bringing them back onto the German research and funding agenda.

This discipline, like Sleeping Beauty, appeared to have fallen into a kind of dormancy after a flourishing period in the first half of the last century, when the basic metabolic pathways had been worked out and most vitamins and trace elements had been identified as precursors of coenzymes, cofactors, or pro-hormones. With the rapid advance of molecular biology during the last decade, however, new aspects of nutrition appeared on the horizon and the Prince was ready to kiss awake his Sleeping Beauty. Of primary importance was the discovery that dietary components interacted with various transcription factors of the nuclear receptor family that had previously been known to be affected only by hormones or drugs. Moreover, several ''orphan'' receptors now have been adopted by their natural ligands, which constitute nutritive components or are derived therefrom by intermediary metabolism in the organism. Dietary agents were also found to interfere with intracellular central signaling cascades and to induce gene expression, and the variability in such food-responsive systems appeared to provide a key to understanding the differential susceptibility of genetically diverse individuals to food-related diseases.

The Editors, Regina Brigelius-Flohé and Hans-Georg Joost, have succeeded in bringing together many renowned international experts to present their work in this new frontier of nutrition research and have managed to cover all the currently emerging trends in nutritional genomics, ranging from nutrigenomics to nutrigenetics and to basic receptor research, physiology, and pathophysiology. The book thus provides a topical state-of-the-art compilation of recent developments in this exponentially developing field. It certainly deserves a broad readership in the disciplines of nutrition, biology, medicine, and life sciences.

The newcomer to the field will enjoy the stimulatory introductory reviews and may dig deeper into specialized chapters, and the specialists can update and enlarge their horizons while reading the latest news from their expert colleagues.

Josef Köhrle
November 2005 Charité University Medicine Berlin

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Part III
Nutrigenetics (Nutrient–Genotype Interactions)

Preface

Nutrition is a key factor in the development of chronic diseases. Nutritional research has therefore evolved from a discipline that determines the required daily intake of calories and essential macro- and micronutrients into a biomedical science with a high potential for disease prevention. The food industry has responded to this awareness by designing foods that not only attempt to satisfy the hedonic preferences of the consumer but also promise additional health benefits. The chemical complexity of diets and the equally complex responses of individuals to a defined diet imply scientific challenges that are easily met neither by the stringent methodology of analytical biochemistry nor by descriptive epidemiology. Instead, the concerted approaches of functional genomics promise to provide reliable and more useful answers within a reasonable time frame.

Within nutritional science, functional genomics comprises two interrelated areas: the influence of nutrients on the transcriptional activity of genes and the heterogeneous response of gene variants to nutrients. The former is usually referred to as ''nutrigenomics'' and is generally studied with technologies of systems biology such as transcriptomics, proteomics, and metabolomics. The latter area is sometimes referred to as ''nutrigenetics''; its findings are to establish a scientific basis for the concept of a genotype-based, personalized nutrition. The title ''Nutritional Genomics'' is used to indicate that this book intends to cover progress made in both areas.

The first part of this book is devoted to the impact of particular food components on the machinery of gene expression. One of the introductory chapters elaborates on the potential blessings and limitations of current technologies in nutritional science. Another summarizes the state of the art in nuclear receptor research, which has for long remained a domain of endocrinology and pharmacology but is gaining increasing interest in nutritional science. In fact, many of these receptors, in particular the so-called orphan ones, turn out to respond specifically to dietary components with transcriptional activation or repression. In the following chapters particular aspects of food-responsive gene activities are presented by renowned experts, each chapter addressing, as far as possible, the molecular mechanisms, micro- or macronutrients involved, and the potential or established relevance to human health.

In Part III the problems of predispositions to food-related diseases are addressed. Clearly, the etiology and course of several complex diseases are associated with nutritional habits. For example, hypertension may depend on sodium intake and other dietary parameters, diabetes is a consequence of abdominal obesity, and obesity is to a large part due to a hypercaloric, energy-dense nutrition (the so-called cafeteria diet). There are also clear associations between dietary parameters in certain types of cancer as well as in inflammatory diseases. Yet individuals by no means respond identically to diets that are generally considered unhealthy nor is a "healthy diet" equally tolerated by everybody. This is because the genetic basis of related diseases is heterogeneous and, accordingly, the functional response to nutrients differs between individuals. Current research, therefore, aims to identify the variability of food-responsive genes that modulate the quality of the response and thus determine disease risks or other nutrition-dependent outcomes. The current knowledge on the genetics of some nutrition-associated diseases that is compiled here will reveal that the concept of a personalized nutrition, although being tested for particular conditions, still remains over the horizon.

The Editors wish to thank all the authors who have put considerable effort into their contributions, thereby providing a detailed overview on this exciting and rapidly advancing area of research. They also hope that this compilation of research frontiers will help readers to discriminate between fact and fiction and to plan their future with more certainty, whether in terms of nutritional research or personal lifestyle.

Nuthetal, November 2005

Regina Brigelius-Flohé
Hans-Georg Joost

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List of Abbreviations

AARE	amino acid response element
ABCA1	ATP-binding cassette transporter A1
ACBP	Acyl-CoA binding protein
ACE	angiotensin converting enzyme
ACL	ATP citrate lyase
ACS	acyl-CoA synthetase
ADH	alcohol dehydrogenase
ADRP	adipose differentiation-related protein
AF-1	activation function -1
AF-2	activation function -2
AgRP	agouti-related protein
AGT	angiotensinogen
ALDH	aldehyde dehydrogenase
AML	acute myeloid leukemia
aP2	adipocyte fatty acid-binding protein
Apaf-1	apoptosis protease-activating factor-1
APL	akute promyelocytic leukemia
ApoA1	apolipoprotein A1
ApoE	apolipoprotein E
AR	Androgen receptor
ARE	antioxidant responsive element
ASNS	asparagine synthetase
ASP	acylation-stimulating protein
AT1R	angiotensin II receptor type 1
AT2R	angiotensin II receptor type 2
ATF	activating transcription factor
ATRA	all trans retinoic acid
AZiP	mouse strain
BAF	BRG-1-associated factor
BaP	benzo[a]pyrene
Bcl-2	B-cell leukemia/lymphoma 2
BDNF	brain-derived neurotrophic factor
bHLH	basic helix-loop-helix

bHLH-LZ	basic helix-loop-helix leucine zipper
BMI	body mass index
BP	blood pressure
BRG-1	ATP-hydrolysing subunit of the chromatin remodeling SWI/SNF complex
C/EBP	CCAAT/enhancer binding protein
CAPN10	calpain 10
CAR	constitutive androstane receptor
CARM	cofactor-associated arginine methyltransferase
CAT	cationic amino acid transporter
CBP/P300	CREB-binding protein/p300(=adenovirus E1A-associated 300 kDa protein)
CD36	oxLDL scavenger receptor CD36
ChIP	chromatin immunoprecipitation
CHOP	C/EBP homologous protein
ChoRE (ChRE)	carbohydrate-responsive element
ChREBP	carbohydrate-responsive element-binding protein
CoRNR box	co-repressor nuclear receptor interaction box
COUP-TF	Chicken ovalbumin upstream promoter transcription factor
COX	cyclooxygenase
CPT-I	carnitin-palmitoyl transferase-I
CRE	cAMP responsive element
CREB	cAMP responsive element binding (protein)
CRP	C-reactive protein
CVD	cardiovascular disease
CYP11B1	11-β-hydroxylase
CYP11B2	aldosterone synthase
CYP7A	Cytochrome P450 7A
DAX-1	dosage-sensitive sex reversal adrenal hypoplasia congenita, critical region on the X chromosome, gene 1
db/db mice	mice lacking a functional leptin receptor
DBD	DNA binding domain
DGAT	diacylglycerol acyltransferase
DHA	docosahexaenoic acid
DNMT	DNA methyltransferase
DR	direct repeat
DRIP	vitamin D receptor-interacting protein
EFSec	selenocysteine-specific elongation factor
EGCG	epigallocatechin gallate
EH	essential hypertension
EH	epoxide hydrolase
eIF	eukaryotic translational initiation factor
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	estrogen receptor
ERR	estrogen related receptor

ERSR	endoplasmic reticulum stress response
FABP	fatty acid-binding protein
FADD	Fas-associated death domain
FAT	fatty acid translocase
FIAF	fasting-induced adipose factor
FIAF/ANGPTL4	fasting-induced adipose factor/angiopoietin-like protein 4
FOXO	forkhead transcription factor
FXR	farnesoid X receptor
GAP	GTPase-activating protein
GCN2	general control non-repressible 2 (an eIF-2a kinase)
GCNF	germ cell nuclear factor
GEF	guanine nucleotide exchange factor
GH	growth hormone
GPAT	glycerol-3-phosphate acyltransferase
GPx	glutathione peroxidase
GR	glucocorticoid receptor
GSK3β	glycogen synthase kinase 3β
GST	glutathione-S-transferase
HAA	heterocyclic aromatic amines
HAT	histone acetyltransferase 37
HBP	high blood pressure
HCA	heterocyclic amine
HCN	hyperpolarization activated cyclic nucleotide-gated potassium channel
HDAC	histone deacetylase
HGP	human genome project
HIF-1	hypoxia-inducible factor-1
HMT	histone methyltransferase
HNF	hepatocyte nuclear factor
HPFS	Health Professional Follow-up-Study
HRE	hormone responsive element
HUGO	human genome organization
IEF	isoelectric focusing
IFNγ	interferon γ
Ihh	indian hedgehog
IKKα	IkB kinase α
ILK	integrin-linked kinase
IMT	intima-media thickness
iNOS	inducible nitric oxide synthase
iNOS	inducible NO-synthase
InR	insulin receptor
INSIG	insulin-induced gene
IOI	iodothyronine deiodinase
IRES	internal ribosome entry site
IRS-1	insulin receptor substrate-1

JDP2	jun dimerization protein-2
KAR	3-keto acyl-CoA reductase
LBD	ligand binding domain
LCE	long chain fatty acid elongase
LD	linkage disequilibrium
LDL-R	LDL receptor
LOD	logarithm of odds
LRH1	liver receptor homologous protein 1
LXR	liver X receptor
MALDI-TOF	matrix-assisted laser desorption/ionization time-of flight mass spectrometry
MAPK	mitogen-activated protein kinase
MC4R	melanocortin-4, receptor
MCP-1	monocyte chemoattractant protein 1
ME	malic enzyme
MeIQ	2-amino-3,4-dimethylimidazo [4,5-f]quinoline
MeIQx	2-amino-3,8-dimethylimidazo [4,5-f]quinoxaline
MODY	maturity-onset diabetes of the young
MR	mineralocorticoid receptor;
MRE	metal responsive element
mRNP	messenger ribonucleotide particles
α-MSH	α-melanocyte-stimulating hormone
MTHFR	methylenetetrahydrofolate reductase
NAT	*N*-acetyltransferase
NCoR	nuclear co-repressor
NEFA	non-esterified fatty acids
NFκB	nuclear factor κB
NGFI-B	NGF-induced clone B
NIDDM1	non insulin dependent diabetes mellitus gene1
NPY	neuropeptide Y
NR	nuclear receptor
NRAMP1	natural restance-associated macrophage protein 1
Nrf2	nuclear factor-erythroid 2 p45-related factor 2
NRRE	nuclear receptor responsive element
NSRE	nutrient sensing response element
NSRU	nutrient sensing regulatory unit
ob/ob mice	mice lacking leptin
ORE	oxygen-responsive element
p160	family of nuclear coactivators 37
P3K	a homolog of the p110α submit of PI3K
PABP	poly(A)-tail-binding protein
PAS	period aryl hydrocarbon receptor/single minded homology
PBMC	peripheral blood mononuclear cells
PCAF	p300/CBP-associating factor
PDK1	phosphoinositide-dependent protein kinase-1

PGC-1	PPAR gamma co-activator 1
PhIP	2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine
PI3K	phosphoinositol-3-kinase
PLZF	promyeloic leukemia zinc finger
PML	promyelocytic leukemia
PNR	photoreceptor-specific nuclear receptor
POMC	pro-opiomelanocortin
PP2A	protein phosphatase 2A
PPAR	peroxisome proliferator-activated receptor
PR	progesterone receptor
PRMT	protein arginine methyltransferase
PTC	phenylthiocarbamide
PTEN	phosphatase and tensin homolog deleted on chromosome 10
PUFA	polyunsaturated fatty acid
PXR	pregnane X receptor
PYY	peptide $YY_{3\text{-}36}$
QTL	quantitative trait loci
QTN	quantitative trait nucleotide
RAAS	renin-angiotensin aldosterone system
RAR	retinoic acid receptor
RevErbA	reverse ErbA
Rheb	ras homolog enriched in brain
RID	nuclear receptor interacting domain
RNA	RNA interference technique
RXR	retinoid X receptor
RZR/ROR	retinoid Z receptor/retinoic acid-related orphan receptor
S6K	p70 S6 kinase
SBP	systolic blood pressure
SBP2	SECIS-binding protein-2
SCAP	SREBP cleavage-activating protein
SCD-1	stearoyl-CoA desaturase-1
SECiS	selenocysteine insertion sequence
SelB	selenocysteine-specific translation elongation factor
SelP	selenoprotein P
SelW	selenoprotein W
SERM	selective estrogen receptor modulator
SF-1/FTZ-F1	steroidogenic factor 1 Fushi Tarazu Factor 1
SHP	small heterodimeric partner
SHR	spontaneously hypertensive rat
Sin3	yeast transcriptional repressor
SLC 6A 14	solute carrier family 6 (neurotransmitter transporter) member 14
SMCC	Srb and mediator protein-containing complex
SMRT	silencing mediator for retinoic and thyroid hormone receptors
SNP	single-nucleotide polymorphism

SPPARM	selective PPAR modulators
SPS complex	an amino acid sensor complex consisting of three proteins: SSY1p, Pt-3p, SSy5p
SPS2	selenophosphate synthetase-2
SRB	suppressor of RNA polymerase B
SRC	steroid receptor co-activator
SREBP	sterol regulatory element-binding protein
ST2	streptozotocin
SULT	sulfotransferase
SUMO	small ubiquitin-related modifier
SWI/SNF	a chromatin remodeling complex
TCE	translation control element
TDT	transmission distortion/disequilibrium test
TER	trans-2,3-enoyl-CoA reductase
TGF	transforming growth factor
TLR	Toll-like receptors
TLX	Tailles-related receptor
TOR	target of rapamycin
TR	thyroid hormone receptor
TR1	thioredoxin reductase-1
TR2	testis receptor
TRAIL	tumor necrosis factor-related apoptosis inducing ligand
TRAP	thyroid hormone receptor (TR)
TRPM5	transient receptor potential cation channel, subfamily M, member 5
trsp	Selenocysteine $tRNA^{(ser)sec}$ gene
TSC	tuberous sclerosis complex
TSC-22	TGFβ-stimulated clone 22
TZD	thiazolidinedione
USF	upstream stimulating factor
3′UTR	3′ untranslated region
VCAM-1	vascular cell adhesion molecule 1
VDR	Vitamin D receptor
WAF1/Cip1(p21)	a general inhibitor of cyclin-dependent kinases
WINAC	WSTF including nucleosome assembly complex
WNK	with no K (lysine) kinase
WSTF	Williams syndrome transcription factor