

DIETARY COMPONENTS AND IMMUNE FUNCTION

NUTRITION \diamond AND \diamond HEALTH

Adrienne Bendich, PhD, FACN, Series Editor

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DIETARY COMPONENTS AND IMMUNE FUNCTION

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Series Editor Introduction

The Nutrition and Health series of books has, as an overriding mission, to provide health professionals with texts that are considered essential because each includes: (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, interchapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patients/health professionals and questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor(s) has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapters. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book; define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed *de novo*, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

“Dietary Components and Immune Function”, edited by Ronald R. Watson, Ph.D., Sherma Zibadi, M.D., and Victor Preedy, Ph.D. exemplifies the goals of the Nutrition and Health Series. Unlike many other books in the area of nutritional immunology, this text provides a critical assessment of the field based upon recent *in vitro*, laboratory animal studies as well as epidemiological and clinical intervention studies. Each of the editors has extensive experience in clinical immunology and the combined experiences in academia, and clinical practice provides a broad perspective on the role of food and food components, diet and diet modifications, nutrients and the multitude of nonessential components of the diet on critical aspects of human immune responses.

The editors have chosen 85 internationally recognized experts who are active investigators of the impact of overall diet on the risks of infection, cancer, autoimmune disease and environmental stressors in different age groups, in different countries throughout the world, and in both sexes. This important text provides practical, data-driven resources, including over 4,000 up-to-date references and more than 40 well-organized tables and figures that assist the reader in evaluating the nutritive value of the immunomodulatory vitamins and minerals and other dietary constituents, such as probiotics, long chain fatty acids, conjugated linoleic acid, traditional Chinese medicines, plant polyphenols, tannins, and many other components of foods. Moreover, the critical

value of nutrition for at-risk populations, including those living with cancer, allergies and/or asthma, autoimmune diseases, the very young and the very old are extensively reviewed in several unique chapters.

Each chapter begins with comprehensive bulleted Key Points followed by the list of key words, and includes an overview and historic review, examination of the literature with critical focus on comparisons between studies, discussion of the chemical composition of actives, where appropriate and conclusions and perspectives on future research areas. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of many dietary components that are routinely consumed by patients and clients with the hope that immune responses will be enhanced. This important volume provides health professionals with balanced, data-driven answers to numerous questions about the validity of the science to date and also provides researchers with opportunities to clarify areas where many questions still exist about the effects of specific nutrients/dietary factors on human immune responses.

The editors have organized the volume into six sections that reflect the breadth and depth of current knowledge in the area of dietary factors that affect immune responses. In the first section entitled Development of Human Immune Responses, the editors have wisely included an introductory chapter that clearly outlines the embryonic development of the human immune system, and this chapter as well as subsequent chapters review in depth the value of breast milk for the development of neonatal as well as lifetime immunity. Unique areas of focus include an analysis of the effects of maternal undernutrition on immune responses in neonates, and of relevance is the chapter on the effects of undernutrition on parasitic invasion. The second section on Nutrients and Immunomodulation contains complementary chapters on the role of fatty acids, especially long chain fatty acids on the immune system in general, and these chapters are followed by reviews of the specific effects with regard to the brain, fat tissue, and obesity, and effects on cancer cells and immune responses to tumors. There is a separate chapter on vitamins and minerals and another on trace minerals and the third examines the effects of vitamin supplements in women with HIV infections. The third section provides in-depth, separate chapters devoted to the Role of the Immune System in Cancer Prevention and Treatment and the effects of some of the thousands of dietary bioactive compounds including, but not limited to the vitamins, carotenoids, and minerals. Certain immune cells can directly kill tumor cells, and this potential can be enhanced by certain components of the diet. Fruit and vegetable intake above the average has been associated with decreased risk of several cancers, and the components of fruits and vegetables are reviewed with regard to enhanced tumor cell killing by cytotoxic immune cells. Lactoferrin, one of the whey proteins in milk, also has anticancer and immunoenhancing effects in vitro and in animal models that are outlined in a separate chapter. Other unique chapters review in detail the plant-derived drugs and semi-synthetic derivatives that are used to treat cancer and compare these with bioactive plant compounds used in Traditional Chinese Medicine (TCM). Some of these compounds are directly cytotoxic to cancer cells, whereas many stimulate immune cells to kill tumor cells. The differences between the emphasis of TCM on restoring balance and prolonging life compared to treating the tumor in Western medicine is clearly described in the two complementary chapters.

The fourth section on Dietary Components in Allergy and Asthma includes chapters that examine controversial areas such as genetic factors and interactions between fetal and early neonatal exposure to allergens from the maternal sources versus diet and the increased risk of asthma in childhood. The importance of the neonatal colonization by gut microflora and the development of immune function resulting in tolerance of environmental antigens are also reviewed. The value of breast feeding is emphasized as is the delay of complementary feeding until 4–6 months of age. Dietary factors considered to be associated with the reduction in the risk of allergy/asthma development include long chain omega-3 polyunsaturated fatty acids, antioxidants, and certain probiotics. Preliminary evidence of the potential for an extract from a specific mushroom to affect the development of IgE responses is also included in a separate chapter. Authors of these chapters have been particularly inclusive and objective; extensive references to the published literature are provided. The fifth section looks mainly at the preliminary data from *in vitro* and small animal studies on the effects of Botanical Extracts and Bioactive Foods and includes separate chapters on resveratrol and on other bioactive flavonoids; immunoactive components of cocoa; extracts used in TCM; microalgae; extracts from edible mushrooms, including their immunoenhancing polysaccharides; soy sauce and its bioactive polysaccharides, and anti-inflammatory actions of cinnamon extracts. These chapters contain extensive, detailed tables that bring the reader up-to-date on the state of the science linking the compounds to immune function, specific immune cell interaction effects on allergy, antiviral activity, and disease resistance. The important emphasis on ethnopharmacology and the potential role of plants and their constituents as direct antivirals, anticancer, and immunostimulatory agents is of great value, especially as the data presented are balanced and objectively tabulated for the reader. Bioactive foods can also be considered as those that contain factors that can be immunotoxic such as aflatoxin, alcohol, methyl mercury, nitrosamines, polychlorinated compounds, as examples. This section ends with a critically important and unique chapter on immunotoxicology of foods. The last section includes four chapters that review the data on pre- and probiotics. The chapters examine the important role of the gastric mucosal immune system and the significance of gut bacteria in health as well their potential beneficial effects for those suffering from pancreatitis or irritable bowel diseases in separate chapters.

Understanding the complexities of the human immune system and the effects of food/environment/age/sex/concomitant disease/drugs/stressors certainly is not simple and the interactions can often seem daunting. However, the editors and authors have focused on assisting those who are unfamiliar with this field in understanding the critical issues and important new research findings that can impact their fields of interest. Drs. Watson, Zibadi, and Preedy have carefully chosen the very best researchers from around the world who can communicate the relevance of dietary components in both the maintenance of a healthy immune system and the potential for bioactive food components to affect the course of infections and chronic diseases. The authors have worked hard to make their information accessible to health professionals interested in public health, those practicing in medical specialties from pediatrics to geriatrics, those in general medical practice, nursing, pharmacy, educators, students as well as nutrition-related allied health professionals. The editors have taken special care to use the same terms and abbreviations between chapters, and provide a clearly written glossary of terms as well as a list of abbreviations used throughout the volume.

In conclusion, “Dietary Components and Immune Function”, edited by Ronald Ross Watson, Sherma Zibadi, and Victor Preedy provides health professionals in many areas of research and practice with the most up-to-date, well-referenced volume on the importance of dietary factors for optimal immune function. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Parsippany, NJ

Adrienne Bendich, PhD, FACN

Preface

The Strategic Plan of the United States' National Institute of Health stresses the pursuit of mechanistic studies as an overarching priority. Among the basic mechanisms identified as needing exploration are immune-focused studies. Many dietary components are believed to exert their activities by modulating immune function. These are highly sought by patients in the absence of an effective standard pharmaceutical therapy. Numerous botanical extracts as well as high dose vitamin supplements are used by the public with the expectation that they will boost and/or modulate immune responses. As the number of seniors grows interest in their loss of immune defenses (immunosenescence) increases and is linked to longevity or lack thereof. The desire to maintain wellness by preventing and treating infectious diseases are among the key reasons for responses. Normal functioning of the immune system is critical to health. One new tumor cell appears about every day and is eliminated by the immune system. Aging, stress, diseases like AIDS, autoimmune reactions, chemical treatments to suppress immune responses in arthritis, and transplants can facilitate the survival of a cancer, leading to clinical disease. Can dietary modulation thereafter help treat cancer? Putative immune-modulating agents and practices are also being used with the belief that they will maintain wellness by reversing the immune decline-associated aging and the immunosuppression associated with cancer, its treatment, and with HIV/AIDS. Thus, an increased focus on understanding the efficacy of botanicals and other dietary supplements on immune function is warranted.

This book focuses on dietary modalities that modulate immune function. The first section discusses various nutrients that alter innate and/or adaptive immunity humoral and cellular responses affecting both immune mechanisms and disease endpoints. The second section investigates the role of nutraceuticals in immune-mediated cancer resistance. The third one investigates their role in asthma and allergy. The fourth segment reviews the role of botanical extracts and supplements in enhancing responses to pathogens, which should have significant public health value. Indeed, the usage of foods and their extracts as therapeutic tools appear in ancient and modern cultures. Thus, the first set of reviews investigates bioactive foods in immunodeficiency diseases. The next section looks at the role of nonpathogenic bacteria, prebiotics, and probiotics in immune modulation. Finally, the authors review dietary supplements in viral diseases. Historically, famine preceded disease and likely was treated by dietary therapy of the immunodeficiency due to dietary insufficiency.

Clearly, information is vital for the researcher, physician, and particularly the lay public as they are exposed to increased availability and media evidence that they may have efficacy. Importantly, in the USA the use of botanicals and their extracts are widely available, part of a 20 billion dollar business. The majority of seniors use dietary supplements and nutrients to promote health. How effective are these agents in doing so via

immune restoration or regulation? Therefore, information from scientific research is critical to help people make decisions on their benefits, risks, or value in the prevention and treatment of immune dysfunction with loss of resistance.

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Abbreviations

AA	Arachidonic acid
AGI	Astragalus injection
AKT	Protein kinase b
ALA	Alpha linolenic acid
AP-1	Activator protein-1
APC	Antigen-presenting cells
ARE	Adenylate and uridylate-rich element
ASP	<i>Astragalus</i> polysaccharide
BMDCs	Bone marrow-derived DCs
BZYQT	Bu Zhong Yi Qi Tang
CD14	CD14 surface receptor
CE	Cinnamon extract
CLA	Conjugated linoleic acid
Con A	Concanavalin A
COX	Cyclooxygenase
CP	Cinnamon polyphenol
CRP	C-reactive protein
CTL	Cytotoxic T lymphocyte
DCs	Dendritic cells
DGLA	Dihomo-g-linoleic acid
DHA	Docosahexaenoic acid
EGF	Epidermal growth factor
EPA	Eicosapentaenoic acid
ErbB2	Leukemia viral oncogene homolog 2 ErbB2
ERK	Extracellular signal regulated protein-kinase
ES-PL	Extract of the seeds of <i>Plantago asiatica</i> L.
FA	Fatty acids
FAO	Food and Agricultural Organization
FGF	Fibroblast growth factor
GALT	Gut-associated lymphoid tissue
GL	<i>Ganoderma lucidum</i>
GLA	Gamma linolenic acid
GL-M	GL mycelium extract
GL-P	GL mycelium polysaccharides
GL-S	GL spore extracts
GLUT	Glucose transporter
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GPCR	G protein-coupled receptor

HETE	Hydroxyeicosatetraenoic acid
HPEP	Hydroperoxyeicosapentaenoic acid
HPETE	Hydroperoxyeicosatetraenoic acid
HSV-1	Herpes simplex virus type-1
i.p.	Intraperitoneal
i.r.	Intrarectal
i.v.	Intravenous
IBD	Inflammatory bowel disease
ICAM-1	Intercellular adhesion molecule
IFN-g	Interferon-g
IGF	Insulin growth factor
IKK	I κ B-kinase
IL	Interleukin
IL-2R	IL-2 receptor
iNOS	Inducible nitric oxide synthase
I κ B	Inhibitory subunit of nuclear factor κ B
JNK	c-jun N-amino terminal kinase
LA	Linoleic acid
LBP	<i>L. barbarum</i> polysaccharide–protein complex
LBP3p	The third fraction of LBP
LC	Liquid chromatography
LCPUFA	Long chain polyunsaturated fatty acids
LDH	Lactate dehydrogenase
LN _s	Lymph nodes
5-LOX	Lipoxygenase
LPS	Lipopolysaccharide
LT	Leukotriene
LTB ₄	Leukotriene B ₄
MAMP	Microbe-associated molecular pattern
MAPK	Mitogen-activated protein kinases
MAPKK1	MAPK-kinase-1
MCP	Monocyte chemoattractant protein
MEK	Mitogen activated kinase-kinase
MHC	Major histocompatibility complex
MIP	Macrophage inflammatory proteins
MLN	Mesenteric lymph nodes
MLR	Mixed leukocyte reaction
MMP	Matrix metalloproteinases
MoDCs	Monocyte-derived DCs
mRNA	Messenger RNA
MS	Mass spectrometry
NF- κ B	Nuclear factor- κ B
NK cells	Natural killer cells
NMR	Nuclear magnetic resonance
NO	Nitric oxide
NOD	Nucleotide-binding oligomerization domain receptors

NOD2	Nucleotide-binding oligomerization domain 2
OVA	Ovalbumin
p.o.	Per os (oral route)
PAMP	Pathogen-associated molecular patterns
PBMC	Peripheral blood mononuclear cell
PDGF	Platelet-derived growth factor
PG	Prostaglandin
PGE ₂	Prostaglandin E ₂
PGN	Peptidoglycan
PHA	Phytohemagglutinin
PMA	Phorbol 12-myristate 13-acetate
PP	Peyer's patches
PPAR	Peroxisome proliferator-activated receptor
PRR	Pattern recognition receptors
PS-G	Polysaccharide from GL
PUFA	Polyunsaturated fatty acids
RAR	Retinoic acid receptors
RIG-like helicases	Retinoic acid-inducible gene-like helicases
ROS	Reactive oxygen species
RT-PCR	Real-time polymerase chain reaction
RXR	Retinoid X receptors
SOD	Superoxide dismutase
STAT	Activator of transcription
TCM	Traditional Chinese medicines
TCR	T cell receptor
TF	Transcription factor
TGF	Transforming growth factor
Th	T helper
Th1/Th2	T lymphocytes helper 1/2
TKR	Tyrosine kinase receptors
TLRs	Toll-like receptors
TNBS	Trinitrobenzene sulfonate
TNF	Tumor necrosis factor
TTP	Tristetraprolin
TX	Thromboxane
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
ZFP36	Zinc finger protein 36

Section A
Development of Human
Immune Responses

1

Nutrition, The Infant and the Immune System

Ger T. Rijkers, Laetitia Niers, Marianne Stasse-Wolthuis, and Frans M. Rombouts

Key Points

- The human newborn possesses a functional but immature immune system in order to provide defense against a world teeming with microorganisms.
- Breast milk contains a number of biological active compounds which support the infant's immune system.
- These include secretory IgAs, which confer specific protection against enteric pathogens, as well as many other immunological active ingredients.
- A number of these ingredients can and are being used as supplements for infant nutrition formulas.
- The strength of the evidence for immunostimulating effects of selected minerals, vitamins, fatty acids, pre- and probiotics and nucleotides is reviewed.

Key Words: Infant immune system, cordblood, breast milk, pre- and probiotics, nutrition.

1.1 THE INFANT IMMUNE SYSTEM

1.1.1 Development of the Immune System

The development of the immune system starts during embryogenesis when the first hematopoietic cells develop outside the embryo, in the yolk sac. Then, in the 6th week of gestation, the first committed hematopoietic stem cells can be detected in the mesoderm of the fetus, the so-called aorta-gonad-mesonephros (1). Next, these hematopoietic stem cells migrate to the fetal liver and there they initiate erythropoiesis (2). During the 7th week of gestation, progenitor cells seed the developing thymus. Seeding into the bone marrow occurs much later (by week 20) (3, 4). The T lymphocytes develop in the thymus,

Dietary Components and Immune Function

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