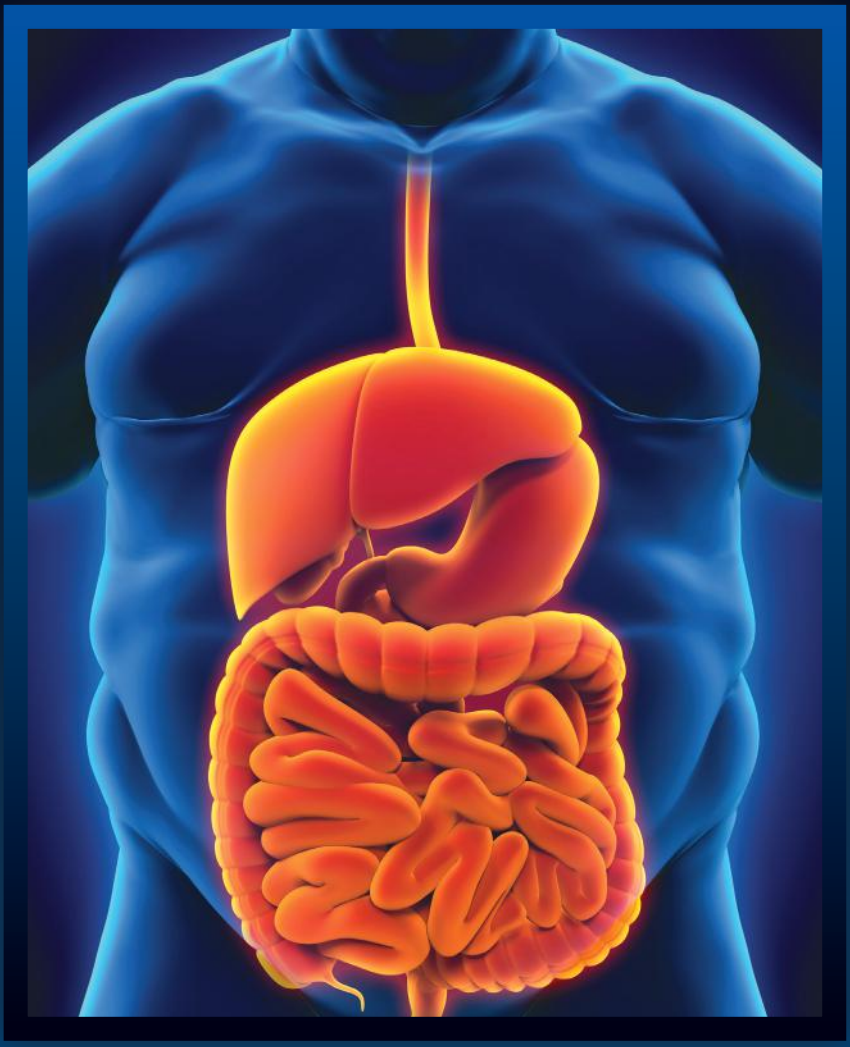
Immunonutrition

Interactions of Diet, Genetics, and Inflammation



Edited by

Bharat B. Aggarwal • David Heber

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Preface

Immune function and nutrition are closely intertwined in human health. The immune system is composed of an innate immune system and an adaptive immune system. The latter is only found in vertebrates while the former is an ancient system that goes back in evolution to insects and plants.

It is the innate immune system that is overactivated in response to the Western diet and obesity-associated diseases due to chronic low-grade inflammation. These diseases range from type 2 diabetes to heart disease, which are closely aligned with the accumulation of visceral and liver fat resulting in insulin resistance. Individuals who are about 30 lb overweight or have a body mass index (BMI) of 30 or more have a 30-fold increased risk of type 2 diabetes mellitus. This 3000% increased risk is not simply another risk factor but an intrinsic part of the pathogenesis of diabetes bringing us to call this condition *diabesity*. However, the etiology of diabetes is not simply linked to weight but to visceral fat. Individuals in India and China can accumulate visceral fat at normal or even low BMI. Some 70 million Americans have high blood sugar or prediabetes, and the syndrome, called metabolic syndrome, affects 50% of individuals between the ages of 50 and 65 in the United States and many other countries.

The interaction of immune function and nutrition underlies the low-grade chronic inflammation involved in the etiology of many of the common age-related chronic disease conditions covered in this textbook. The largest portion of the immune system is located adjacent to the gastrointestinal tract. Plants, which also have an innate immune system, live in soil that is made up of both friendly and potentially toxic bacteria. Plant roots attract helpful bacteria and repel those bacteria that could attack them. Humans carry their soil with them in the form of trillions of gut bacteria, which interact with the immune system. Both dietary intake and obesity influence the gut microflora, called the microbiome. Plants affect the local bacteria in the soil; it is thus not surprising that dietary phytochemicals and prebiotics in the human diet also affect gut microflora.

Diet and exercise are necessary strategies in efforts to reduce visceral fat and modulate systemic immune function through increased intakes of fruits, vegetables, plant protein, fish oils, prebiotic fibers, and spices. Nutrition in the broadest sense determines the health of the immune system. When malnutrition results in death, it is most commonly caused by infections due to loss of immune function. Therefore, both in obesity and malnutrition, nutritional factors influence immune function. This close interaction is the genesis of the term *immunonutrition*, which represents a new interdisciplinary field of nutritional and medical research.

It is our hope that this textbook will stimulate increased interest in this new interdisciplinary field among students and junior investigators who will carry this field into the future. There is a need for more human studies to complement the exciting

basic research already developed in cell culture and animal models demonstrating the mechanisms underlying the interaction of nutrition and immune function. We hope that this book will achieve these objectives.

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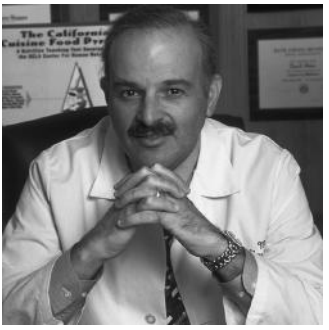

David Heber, MD, PhD, FACP, FACN, is the director of the UCLA Center for Human Nutrition at the University of California, Los Angeles. He has been on the faculty of the UCLA School of Medicine since 1978 and is currently professor of medicine and public health. Dr. Heber is board certified in internal medicine and endocrinology and metabolism by the American Board of Internal Medicine and is certified as a physician nutrition specialist. He is a former chair of the Medical Nutrition Council of the American Society of Nutrition. He directed both the NCI-funded Clinical Nutrition Research Unit and the NIH Nutrition and Obesity Training Grants at UCLA. He has written over 230 peer-reviewed scientific articles and 60 book chapters, as well as three professional texts. He has written four books for the public, including *What Color Is Your Diet?* (Harper Collins/Regan Books, 2001) and the *L.A. Shape Diet* (Harper Collins/Regan Books, 2004). His main research interests are obesity prevention and treatment and phytonutrients in cancer prevention and treatment.

Dr. Bharat B. Aggarwal is a Ransom Horne, Jr. Distinguished Professor of Cancer Research, Professor of Cancer Medicine, Professor of Immunology, Professor of Biochemistry, and Professor of Experimental Therapeutics, as well as Chief, Cytokine Research Section, in the Department of Experimental Therapeutics at the University of Texas MD Anderson Cancer Center (MDACC), Houston, Texas. He also serves as a member of the University of Texas Graduate School of Biomedical Sciences, Houston; as an adjunct professor at Albert B. Alkek Institute of Biosciences and Technology, Texas A&M University, Houston, Texas; and as a member in various institutional committees of MDACC.

Dr. Aggarwal earned his PhD in biochemistry from the University of California, Berkeley, and received his postdoctoral training from the Hormone Research Laboratory at the University of California Medical Center, San Francisco. He then started his career with Genentech Inc., where he worked for almost 10 years. His work led to the discovery of TNF-α and TNF-β, essential components of the immune system, and to the identification of their receptors.

In 1989, Dr. Aggarwal accepted the position of professor and chief of the Cytokine Research Section at M. D. Anderson Cancer Center, where he currently

holds the Ransom Horne, Jr., Endowed Professorship in Cancer Research. Since then, he has been investigating the role of inflammatory pathways mediated through TNF, NF-kappaB, and STAT3 for the prevention and therapy of cancer and other chronic diseases. While searching for novel and safe anti-inflammatory agents, his group has identified more than 50 novel compounds from dietary sources and from traditional medicine that interrupt these cell-signaling pathways. These agents have been tested in various animal models, and some of them are now in clinical trials. Dr. Aggarwal has published more than 600 papers in peer-reviewed international journals (including *Science*, *Nature*, *Cancer Cell*, *PNAS*, *Journal of Experimental Medicine*, *Blood*, *JBC*, *Cancer Research*, and *Journal of Immunology*), invited reviews, and book chapters.

Dr. Aggarwal is an inventor/coinventor of over 33 patents. He has been included in ISI Highly Cited among the most popular authors in the immunology category since 2001. He has also been listed as one of the top 25 researchers worldwide in the area of apoptosis. His papers exhibit very high citation index (some exceed 1000). His overall citation is now at 75,900 with an H-index of 106.

Dr. Aggarwal currently serves as a member of the editorial boards of 24 international journals. He has previously served as a reviewer for more than 160 journals, various grant proposals, and of several PhD theses. Dr. Aggarwal has edited 12 books and has served as guest editor for special issues of *Biotherapy*, *Cancer Letters*, and *Current Opinion in Pharmacology*. He has trained over 80 postdoctoral fellows and visiting professors from around the world. He has co-organized and served as a member in many national and international conferences and symposia, started the International Society of Translational Cancer Research, and has delivered over 350 lectures/seminars/keynote talks in more than 50 countries.

He has recently authored a book entitled *Healing Spices* (released in January 2011 by Sterling), which is already a bestseller.

Dr. Aggarwal has received numerous awards, including the following:

- ARTOI Award, Association for Research Integrated Oncology Therapies, Rome, Italy, 2012
- 2011 James A. Duke Award Excellence in Botanical Literature Award, American Botanical Council, Anaheim, California, 2012
- World Congress Science Prize from Oxygen Club of California, 2010
- Excellence in Research Award of McCormick Research Institute from the American Association of Nutrition, 2008
- Outstanding Scientist Award from the American Association of Indian Scientists in Cancer Research, 2006
- Ranbaxy Award for Outstanding Scientist of the Year, 2004

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1 Evolution of Innate and Adaptive Immunity

David Heber and Bharat B. Aggarwal

CONTENTS

INTRODUCTION

The human immune system can be divided into two functional entities: the innate and the adaptive immune systems. The innate immune system appeared early in evolution prior to the time that plants and animals took separate paths, but the basic mechanisms of pathogen recognition and activation of the innate immune response are conserved throughout the evolution of plants and animals including humans [1]. Innate immunity is the first line of defense against infectious microorganisms in humans and relies on germ line–encoded pattern recognition receptors (PRRs) to recognize pathogen-derived substances [1]. Activation of the innate immune system through these receptors leads to the expression of a vast array of antimicrobial effector molecules that attack microorganisms at many different levels.

The innate immune system has been studied extensively in fruit flies (*Drosophila melanogaster*) [2] and even in worms such as *Caenorhabditis elegans*. These animals have the same genes as vertebrates, including mice and humans, that encode intracellular signaling pathways leading to the activation of the transcription factor nuclear factor-kappa B (NFκB). These gene cassettes encode various proteins

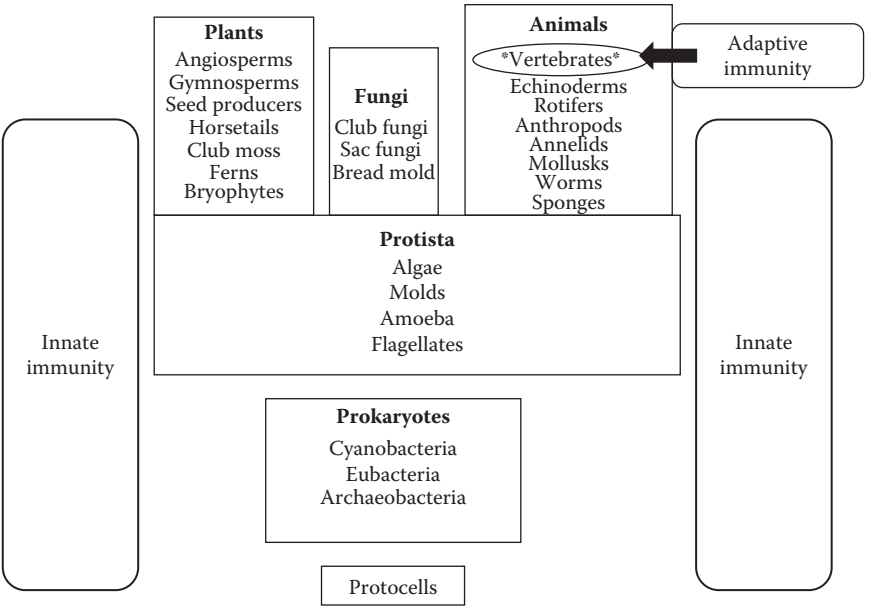

FIGURE 1.1 Adaptive immune function is a late evolutionary development in vertebrates while innate immune function can be traced back to the earliest cell types including bacteria.

of signaling pathways modulating NFκB activation and inflammation discussed elsewhere in this textbook. This evolutionary history combined with other evidence supports the notion that the activation of NFκB is the central signaling pathway of activation in innate immunity, leading in turn to the transcription of a set of genes dependent on NFκB [3]. Moreover, this pathway is a universal pathway that leads to activation in all host defense systems.

The adaptive immune system evolved much later in higher species (see Figure 1.1).

In contrast to innate immunity, the adaptive immune system generates antigen-specific receptors, antibodies, and T-cell receptors by somatic cell DNA rearrangement [4]. These receptors, found only in higher eukaryotes, recognize specific pathogen-encoded proteins. Mammals have a complex immune response, which relies on communication between the innate and adaptive arms of the immune system.

In the human gut, trillions of bacteria live in symbiosis with the host and affect both host nutrition and immune function. Studies confirm that gut microbiota carry on a dynamic interaction with the intestinal innate and adaptive immune systems, affecting different aspects of its development and function. Communication between the mucosal immune system and endogenous microflora favors mutual growth, survival, and inflammatory control of the intestinal microbiome [5].

Since humans evolved in equilibrium with plants, insects, and bacteria, the innate and adaptive immune systems were clearly influenced by the innate immune