The Innate Immune Response to Noninfectious Stressors

Human and Animal Models

Edited by

Massimo Amadori
Laboratory of Cellular Immunology,
Istituto Zooprofilattico Sperimentale della
Lombardia e dell'Emilia-Romagna,
Brescia, Italy

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125 London Wall, London EC2Y 5AS, UK
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, USA
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

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British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-801968-9

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Publisher: Sara Tenney
Acquisition Editor: Linda Versteeg-Buschman
Editorial Project Manager: Halima Williams
Production Project Manager: Chris Wortley
Designer: Mark Rogers

Typeset by Thomson Digital
Printed and bound in the United States of America

This book is dedicated to school teachers, colleagues, and friends who prompted me to doubt and question established dogmas, and deterred me from accepting easy and accessible truths for the sake of short-term community recognition.

Contributors

Massimo Amadori Laboratory of Cellular Immunology, Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna, Brescia, Italy

Ryutaro Fukui Division of Infectious Genetics, Institute of Medical Science, Tokyo, Japan

Stefania Gallucci Department of Microbiology and Immunology, Laboratory of Dendritic Cell Biology, Temple University, School of Medicine, Philadelphia, PA, USA

Segundo González Departamento de Inmunología, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain

Nicola Lacetera Department of Agriculture, Forests, Nature and Energy, University of Tuscia, Viterbo, Italy

Carlos López-Larrea Departamento de Biología Funcional, Inmunología, Universidad de Oviedo, Instituto Universitario de Oncología del Principado de Asturias, Asturias, Spain

Alejandro López-Soto Departamento de Inmunología, Hospital Universitario Central de Asturias, Oviedo; Departamento de Biología Funcional, Inmunología, Universidad de Oviedo, Instituto Universitario de Oncología del Principado de Asturias, Asturias, Spain

Outi Mantere Department of Health, Mental Health Unit, National Institute for Health and Welfare, Helsinki, Finland

Yoshiro Maru Department of Pharmacology, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan

Kensuke Miyake Division of Infectious Genetics, Institute of Medical Science, Tokyo, Japan

Livia Moscati Laboratory of Clinical Sciences, Istituto Zooprofilattico Sperimentale Umbria e Marche, Perugia, Italy

Elisabetta Razzuoli Laboratory of Diagnostics, S.S. Genova, Istituto Zooprofilattico Sperimentale del Piemonte, Liguria e Valle d'Aosta, Piazza Borgo Pila, Genova, Italy

Elena Riboldi Department of Pharmaceutical Sciences, Università del Piemonte Orientale "Amedeo Avogadro," Novara, Italy

Antonio Sica Department of Pharmaceutical Sciences, Università del Piemonte Orientale "Amedeo Avogadro," Novara; Department of Inflammation and Immunology, Humanitas Clinical and Research Center, Rozzano, Italy

Jaana Suvisaari Department of Health, Mental Health Unit, National Institute for Health and Welfare, Helsinki, Finland

Erminio Trevisi Faculty of Agriculture, Food and Environmental Sciences, Istituto di Zootecnica, Università Cattolica del Sacro Cuore, Piacenza, Italy

Cinzia Zanotti Laboratory of Cellular Immunology, Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna, Brescia, Italy

Preface

The concept of innate immune response to noninfectious stressors needs a definition of its foundation and of relevant underlying tenets. This way, the reader can be confronted with a coherent, unitary conceptual framework, in which diverse biological features of such a response can be adequately grasped and traced back to common cause/effect mechanisms.

Individuals are prompted to adapt in order to improve and optimize the interaction with their environment. In this respect, animals usually adopt a "feed forward" strategy – animals mount a corrective action to potentially noxious stimuli before whichever problem becomes substantial.[1] This process is affected by animal needs, which may refer to vital resources or to particular actions underlying the access to vital resources. Adaptation implies a stepwise corrective action, whereby activity and energy expense are proportional to the perceived threat. In this scenario, inflammation should be interpreted as a protective attempt to restore a homeostatic state of the host. Threats are caused by stressors, meant as whatever biological, or physico-chemical entities, real or unreal (psychotic) conditions affecting or potentially affecting the established levels of homeostasis, according to the host's perception. Adaptation to environmental stressors can be measured by different procedures, including the evaluation of physiological parameters. These indicate the onset of a biological defense action,[2] characterized by:

1. An early, biological response (neuro-endocrine and behavioral);
2. A later change of biological functions in different organs and apparata.

As for phase 2, immune functions represent a crucial reporter system of the adaptation process because of the strict functional and anatomical connections between brain and lymphoid organs; the brain itself is the main regulatory organ of the immune system. As highlighted in a previous review paper,[3] the two main circuits, "psycho-sensitive stimuli/behavioral response" and "antigenic stimuli/immune response," are indeed subsystems of a unitary integrated complex aimed at providing optimal conditions for the host's survival and adaptation (see Fig. P.1). In this conceptual framework, immune responses, stress, and inflammation should be considered an ancestral, overlapping set of responses aimed at the neutralization of stimuli perturbing body homeostasis.[4]

Within the immune system, innate immunity is the first line of defense against a plethora of *noxae* perturbing the host's homeostatic balance. It is based

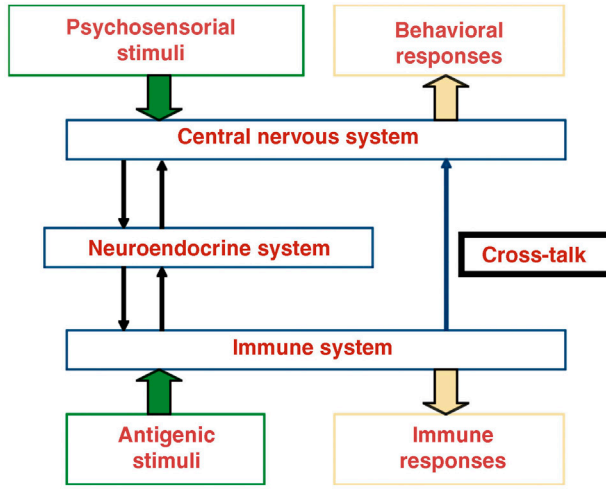

FIGURE P.1 The central nervous and immune systems are part of a unitary integrated complex.

on complex pathways of recognition and signaling for pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), as well as on diverse humoral and cell-mediated effector functions. Microbial components are recognized by means of pattern-recognition receptors (PRRs) including Toll-like and NOD-like receptors (TLRs and NLRs).[5] The activation of PRRs results in the expression of proinflammatory cytokines, chemokines, and antimicrobial peptides, initiating and regulating the immune response. The possible recognition of PAMPs and DAMPs implies that the innate immune system can detect (1) infectious microbial pathogens and (2) cellular stress caused by a plethora of noninfectious physico-chemical agents, or by the very response to microbial agents.[5] Both infectious and noninfectious agents can deliver in fact "danger" signals,[6] which are processed for subsequent humoral and cell-mediated responses. Danger signals may be soluble (DAMPs) or cell-associated (stress antigens) for a recognition by natural killer and some γδ T cell populations, in the framework of the "lymphoid stress surveillance system."[7]

The innate immune system may also have a profound impact on concomitant behavioral adaptation responses, as exemplified by the role of proinflammatory cytokines in the induction of sickness behavior (lethargy, anorexia, and curtailing of social and reproductive activities) that is a clearly defined motivational status.[8] Thus, the innate immune system reshuffles behavioral priorities toward a well-organized, integrated response to microbial infections; interestingly, behavioral depression was shown to provide an important adaptive advantage to sick animals, anorexia being thus associated to a better chance for survival under such conditions.[9]

The relationship between stress, inflammation, and immune functions deserves a few comments. Usually, transient acute stresses are not noxious for

healthy individuals, and they may be associated with better immune responses. These events are even thought of as nature's adjuvant under field conditions.[10] On the whole, the consequences of stress on immune functions are generally adaptive in the short term, whereas they can be damaging when stress is chronic, including predisposition to disease occurrence.

If innate immune functions represent a crucial reporter system of effective versus noneffective adaptation to infectious and noninfectious stressors, it goes without saying that a sound panel of clinical immunology tests may reveal subjects at risk for disease occurrence, as a result of poor environmental adaptation. Predisposition to disease occurrence after exposure to chronic stress may have two faces in the same coin:

1. Reduced clearance of common environmental pathogens.
2. Poor homeostatic control of the inflammatory response.

In general, a defective innate immune response forces the host to a wider use of the adaptive immune response (antibody and cytotoxic T lymphocytes), which is demanding in terms of energy expense.[11]

The innate immune response must be regulated to enable efficient pathogen killing but also to limit detrimental tissue pathology.[12] This is the reason why a complex of sensing receptors and signaling pathways developed along the phylogenetic evolution to allow the coordinated expression of proinflammatory and anti-inflammatory cytokines in response to environmental stress. In particular, the signaling pathway consisting of phosphoinositide 3 (Pi3)-kinase, Akt, and mechanistic target of rapamycin (mTor) is a key regulator of innate immune responses to environmental stress.[13] Among mitogen-activated protein kinases, p38 plays a crucial role in the regulation of mTor activity. p38 can be activated by TLR ligands, cytokines, and most importantly, by diverse physicochemical, noninfectious stress signals.[14] p38- and Pi3-driven signals coordinately act on mTor to regulate the expression of IL-12 and IL-10 in myeloid immune cells.[12]

Therefore, the innate immune system can finely tune pro- and anti-inflammatory responses in tissues after exposure to both infectious and noninfectious stressors.

Innate immune responses to both infectious and noninfectious stressors are finely modulated by the host's microbiota, meant as the ensemble of microorganisms that resides in an established environment. There are clusters of bacteria in different parts of the body, such as the gut, skin, mouth, vagina, and so on. Gut microbiota corresponds to the huge microbial population living in the intestine, containing trillions of microorganisms with some 1000 different species, most of them specific to each subject. The recognition of commensal microorganisms is essential for the development and function of the immune system in the mucosal and peripheral districts.[15] The activities of the innate immune system are finely tuned by commensal bacteria. These can, for example, inhibit NF-κB activation by disrupting the host cell control over ubiquitination and degradation,[16] thus exerting an anti-inflammatory control action. Also,

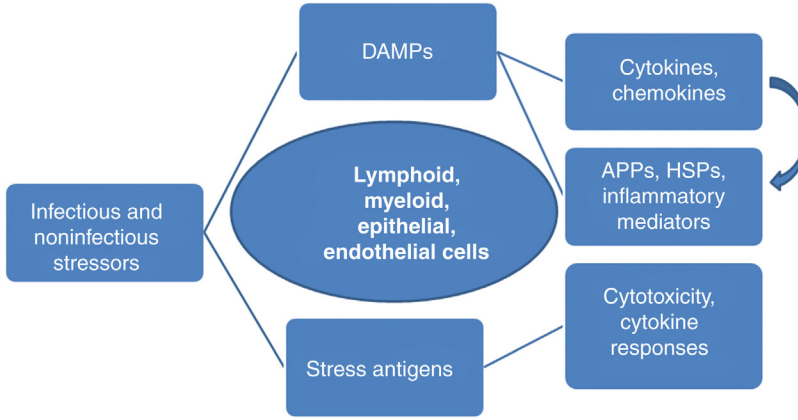

FIGURE P.2 Common features of infectious and noninfectious stressors. APPs, acute-phase proteins; HSPs, heat-shock proteins.

commensal bacteria can release metabolites of complex digested polysaccharides, which may induce the expression of anti-inflammatory cytokines such as IL-10.[17] Several aspects of innate immunity are stimulated by specific bacterial strains, whereas the whole microbiota exerts a substantial inflammatory control of the gut ecosystem and of pathogen susceptibility, in the framework of a continuous "cross-talk" with the mucosal immune system.[18] This interaction is critical; the microbiota is required for proper development and function of innate immune cells. In turn, these provide effector functions that maintain a stable microbiota, in the framework of interdependency and feedback mechanisms aimed at mutual homeostasis.[19]

The effective recognition of PAMPs and DAMPs and the related signaling pathways imply that *sensing, signaling, and effector mechanisms of the innate immune system are remarkably similar for both infectious and noninfectious stimuli, albeit differently modulated (Fig. P.2). This is the central tenet and subject of this book*, which deals with different kinds of noninfectious stressors in preclinical and clinical studies in both human and veterinary medicine.

Innate immune responses to noninfectious stressors can be best grasped by a few examples, in the light of consolidated research models:

- As illustrated in a previous review article,[3] a proinflammatory cytokine of the innate immune system like IL-1 induces activation of the hypothalamo-pituitary-adrenocortical axis as well as stimulation of cerebral noradrenaline; the effects of IL-1 are remarkably similar to those observed following either LPS administration (reminiscent of infectious stress) or acute, noninfectious stressing events in laboratory animals, such as electric shock or restraint.[20] Likewise, the brain produces interferon (IFN)-α in response to noninflammatory as well as inflammatory stress; the intracerebral injection

of this cytokine may alter the brain activity to exert a feedback effect on the immune system.[21]

- Pigs mount an IFN-α response to early weaning, which also affect the usual pattern of constitutive expression of type I IFN genes.[22] Early weaning is associated with the expression of inflammatory cytokine genes in the proximal and distal parts of the small intestine.[23] Calves also mount IFN-α responses to long-distance road journeys in trucks (M. Amadori, unpublished results). In the mentioned studies, both pigs and cattle did not show evidence of concomitant viral infections.
- Abnormal inflammatory responses and activation of the innate immune system (cytokines, acute phase responses) can be detected in high-yielding dairy cows submitted to the metabolic stress of lactation onset.[24]
- Heat stress can induce innate immune responses in cattle, as shown by Peli et al. in a field survey in one beef and one veal farm located in Northern Italy.[25] The survey was carried out during a meteoalarm issued in July 2009 by the Italian environmental control authorities. Blood samples were collected from 10 head/farm 1–2 days before the announced heat wave and 3–4 days after, a heat wave being defined as average daily temperature humidity index (THI) $\geq$73. In both farms, this threshold value was overstepped as a result of sudden THI increase (+6.5 points). A significant increase of white blood cell (WBC) counts took place in cattle, showing no correlation with hematocrit values. Cattle showed increases of serum IL-4 ($P < 0.01$), IL-6, and TNF-α, as well as a significant decrease of serum IFN-γ levels ($P < 0.01$) over the heat stress period. In general, the impact of the heat stress was more serious in steers than in calves. These data are fully in agreement with previous findings in humans after traumatic and burn injuries, which confirm a major downregulation of the TH1 response and an upregulation of the TH2 response.[26] These findings should be offset against the current figures of high mortality rates of farm animals in hot summer periods,[27] which are of concern in terms of both animal health and welfare.
- The innate immune response to endocrine disruptors is a fascinating issue, largely investigated in fish models. Thus, there is evidence that the fish immune system is a potential target for environmental endocrine disruptors.[28] Oxidative stress (an imbalance between production and depletion of reactive oxygen species, ROS) is the first response to environmental stressors,[29] as shown, for example, in a zebrafish model of exposure to atrazine.[30] ROS are associated with cell injury or death, lipid peroxidation, and membrane damage. Therefore, they cause the release of DAMPs and relevant innate immune responses. Thus, in another zebrafish model, the exposure to phthalate esters caused a significant increase of mRNA levels of interferon (IFN)-gamma, interleukin (IL)-1 beta, Mx protein, lysozyme and complement factor C3B genes.[31]
- Widespread toxic compounds in forages and milk like mycotoxins also induce responses of the innate immune system. Mycotoxins are secondary

metabolites of fungi, which may contaminate food and feeds. The same mold can produce different mycotoxins, but the presence of a particular mold does not always indicate that a certain mycotoxin is released; moreover, different fungi can contaminate the feed in different production phases (plant growth, harvest, and storage). In particular, mycotoxins can cause oxidative stress[32] and modulate the immune response, resulting in different forms of immunosuppression (depressed T- or B-lymphocyte activity, suppressed antibody production, and impaired macrophage/neutrophil-effector functions), and a release of proinflammatory cytokines (IL-1β, IL-6, and TNF-α), and acute phase proteins like haptoglobin and serum amyloid A.[33,34] Therefore, mycotoxins exert a two-sided interaction with the host, underlying (1) classical immunotoxic activities giving rise to different forms of immunosuppression[34] and (2) cellular stress causing innate immune responses. These two features may obviously overlap and act synergically in the host. Thus, increased susceptibility to human and animal infectious diseases can be observed after exposure to mycotoxins.[35] Because of their worldwide distribution and toxic effects mycotoxins are considered an important risk for human health.[36] Many studies demonstrated the immunotoxic and/or immunomodulatory effects of single mycotoxins, even though there are no clear data about the effects of a combined exposure to different mycotoxins.

- The systemic inflammatory response syndrome is an extremely serious innate immune response to tissue damages. This may be observed, for example, in some human patients with fractures, who develop high fever and shock after a couple of days. The traditional hypothesis of a reduced post-traumatic blood flow in the gut underlying increased intestinal permeability and bacteremia was discounted, since portal blood of these patients is sterile.[37] Instead, the plasma has a high concentration of mitochondrial DNA (a noninfectious stressor) as a result of cellular disruption by trauma. These mitochondrial DAMPs with evolutionarily conserved similarities to bacterial PAMPs can then signal through identical innate immune pathways to create a sepsis-like state.[37]
- As previously stated, one of the likely associations between noninfectious stress and innate immunity can be traced back to the lymphoid stress-surveillance system, that is, to the network of lymphocyte populations (mainly γδ T cells), which recognize neo-antigens like MIC on stressed cells,[7] that is, cells exposed to events as diverse as heat shock, infections, DNA damage, and so on. MIC and other proteins are ligands for the activating NK cell receptor NKG2D, expressed on NK cells, CD8+ αβ T cells and γδ T cells, also sustaining an IFN-γ response.[38] The response to stress antigens aims to control the negative consequences for the host in terms of tissue damage and biological fitness. This tenet is probably relevant to the impact of psychotic stressors, too. Thus, in murine models, the ability to control the consequences of mental stress is dependent on peripheral immunity. T cells specific to abundantly expressed CNS antigens are responsible for

brain tissue homeostasis and help the individual to cope with stressful life episodes, their activity being checked by regulatory CD4+ CD25+ T cells.[39] Animals with immune deficiency show a reduced ability to check the consequences of stress in terms of anxiety and startle response.[40] Interestingly, a short exposure to a psychotic stressor can enhance T-cell infiltration to the brain, associated with increased ICAM-1 expression by choroid plexus cells. The mental stress response can be reduced by immunization with a CNS-related myelin peptide.[40] This is an interesting example of "protective autoimmunity," in which a primary stress response gives rise to a protective adaptive immune response to self-tissue antigens.

- Psychologically stressful states may underlie inflammation in the visceral fat and vasculature of patients with cardiovascular disease.[41] Also, a psychological stress condition induces a shift in the type-1/type-2 cytokine balance toward a type-2 response, which may play a role in the course of hepatitis B virus infection.[42]
- Nutrient overload (obesity model of metabolic stress) promotes inflammation, sustained by inflammatory cytokines.[43] Obesity is characterized by chronic low-grade inflammation with permanently increased oxidative stress, which damages cellular structures, and leads to the development of obesity-related complications.[44]

Regardless of the triggering cause, the findings mentioned indicate that the innate immune and inflammatory response is triggered in the host to achieve a better ability to deal with both infectious and noninfectious stress.[5] At the same time, this response needs to be accurately controlled to avoid tissue damage and waste of metabolic energy.

In this conceptual framework, the book aims to illustrate the aforementioned concepts in established models of response to noninfectious, physical, chemical, metabolic, and psychotic stressors in both animals and humans. The reader will be presented with updated contributions on these subjects and given ideas and perspectives of leading edge research activities in these and other related fields of investigation.

The book is opened by an overview of the innate immune response by Stefania Gallucci. This overview is mainly focused on a detailed description of the sensors implied in the recognition of noninfectious stressors, their main categories, and signaling pathways. This way the reader can be aware of the strategies adopted by the host to check these stressors and prevent unwanted consequences in terms of homeostatic balance.

The above chapter is strictly correlated with the contribution by Kensuke Miyake on "homeostatic inflammation." DAMPs are produced not only by damaged cells in disease, but also by undamaged cells. This leads in turn to the new fascinating concept of autoimmune disease as an outcome of an excessive response of innate immune sensors to their endogenous ligands. This implies that the host steadily exerts a fine tuning of low-grade, physiological inflammatory

responses, aimed at optimizing homeostatic balance and major physiological functions. Homeostatic inflammation is therefore a foundation of successful environmental adaptation. Failure of either induction or control of these crucial circuits can give rise to serious clinical repercussions.

Lopèz-Soto et al. deals with the molecular basis of the immune response to stressed cells. The reader is confronted with the mechanisms controlling the expression of molecules (stress antigens) with key roles in immunity. The subsequent activation of dendritic cells and T-cell-mediated responses outlines an interesting model, whereby a primary signal of the innate immune system (stress antigens) gives rise to an effector innate response (NK cells), or to adaptive T cell responses. This is actually reminiscent of "protective autoimmunity" by the host's T cells, following exposure to the aforementioned psychotic stress. Since the response to stress antigens frequently takes place in the host, the prevalence of reactive NK and T cells may be high, which may have important consequences on diagnostic assays of cell-mediated immunity. These can be biased whenever responder lymphocytes are confronted *in vitro* with both Ag-specific and stress antigens, expressed, for example, in established cell lines.[45] Also, it would be worth investigating in the future the possible evolution of NK cell responses to self-stress antigens, in line with recent evidence of a "maturation" of NK responses to viral infections – NK cells can acquire in fact some form of immunological memory, and enhanced NK functions can be displayed during secondary, compared to primary exposure to virus infections.[46]

One of the major stressors involved in the generation of DAMPs is hypoxia, as illustrated in the contribution by Elena Riboldi and Antonio Sica. Hypoxia is linked to the production of reactive oxygen species (ROS), which underlies the generation of inflammasomes and the release of inflammatory cytokines like IL-1 and IL-18.[47] On the whole, hypoxia and inflammatory signals share selected transcriptional events, including the activation of members of both the hypoxia-inducible factor (HIF) and nuclear factor κB (NF-κB) families. These concepts are of paramount importance in the pathophysiology of human diseases ranging from cancer, to infections, to chronic inflammation. This is also relevant to an important large animal model, the pig. The percentage weight of the heart muscle has decreased from 0.38% in wild boars to 0.21% in modern Landrace pigs.[48] Such pigs show an accentuated mean capillary-to-fiber distance in larger (type II) muscle fibers, which hampers an effective removal of toxic metabolites and favors lactic acid accumulation.[49] The resulting tissue hypoxia induces conditions of persistent oxidative stress response, which paves the way to serious clinical conditions such as Mulberry Heart Disease, Porcine Stress Syndrome, and Osteochondrosis. Disease predisposition as a result of genetic selection of pigs is also highlighted in the chapter by Erminio Trevisi, Livia Moscati, and Massimo Amadori. In agreement with the preceding statements, lean muscle pigs show in fact abnormally high serum concentrations of reactive oxygen metabolites (ROMs), as opposed to rural swine.[48]

The concept of metabolic stress and its recognition by the innate immune system is highlighted in the chapter by Nicola Lacetera in another large animal model – the high-yielding dairy cow. In this chapter, fundamental features of a major metabolic stress (energy deficit and oxidative stress after lactation onset) are analyzed with respect to heat-shock protein (HSP) responses. HSPs can act as signaling intermediates and regulate innate and adaptive immune responses. The outcome of these regulatory actions may dictate the inflammatory profile of the immune response during infections and diseases. *De facto*, the prevalence of diverse disease cases and culling rates are high in the early lactation phase of high-yielding dairy cows.[50,51] These findings are also commented in the chapter by Erminio Trevisi, Livia Moscati, and Massimo Amadori.

The chapter by Yoshiro Maru deals with the role of innate immune responses in cancer metastasis. These are substantially different from those observed in primary tumor tissues, in that they can alter microenvironments, whether physically and functionally, in the organs that are distant from the primary site. This remote control cultivates the so-called "soil" before the actual arrival of tumor cells as "seed" from the primary site. It can be argued that fundamental components of the innate immune system, mainly Toll-like receptors and inflammasomes, play a fundamental role in effective metastatization of primary tumor cells. In this model, the innate immune response to a noninfectious, tumor stressor may turn detrimental to the host and give rise to serious clinical repercussions.

The correlation between innate immune responses and generation of psychotic disorders in humans is the topic of the chapter by Jaana Suvisaari and Outi Mantere. The authors outline fundamentals of psychoneuroimmunology (PNEI), as a comprehensive conceptual framework in which complex laboratory and clinical findings can be correctly grasped and evaluated. In practice, the canonical boundaries between immune and neuroendocrine control systems can be no longer recognized in a continuum of homeostatic circuits, in which a single recognized effector function is part of a wider strategy for better survival and adaptation. Such a strategy is based upon networks of multidirectional signaling and feedback regulations effected by neuroendocrine- and immunocyte-derived mediators.[52] In this scenario, the reader can understand why proinflammatory activation of the innate immune system and T-cells of the adaptive immune system underlie first-episode psychosis and chronic psychotic disorders. Whereas such alterations are most pronounced in the acute clinical phase, chronic psychotic disorders and chronic inflammation proceed together, and they are often accompanied by metabolic comorbidities such as obesity, type 2 diabetes, and dyslipidemias. In the framework of PNEI, Suvisaari and Mantere outline psychotic disorders as neurodevelopmental diseases. In this scenario, they review scientific data about alterations in innate immune response during neonatal period and data on childhood exposures that could be linked to psychotic disorders via inflammatory mechanisms. Also, they discuss animal and

genetic studies on schizophrenia supporting the role of immunological factors for disease occurrence.

The modulation of the IFN system by environmental, noninfectious stressors is illustrated in the chapter by Elisabetta Razzuoli, Cinzia Zanotti, and Massimo Amadori. Most data reviewed by the authors refer to Type I interferons, that is, a heterogeneous group including several distinct families (IFN-α, IFN-β, IFN-ε, IFN-ω, IFN-κ, IFN-δ, and IFN-τ), with some of them (like IFN-α) consisting of different subtypes.[53] Although type I IFNs were discovered as a potent antiviral substance accumulated in chick chorioallantoic membranes more than 50 years ago,[54] these cytokines were subsequently shown to exert a plethora of regulatory functions under both health and disease conditions: activation of immune effector cells, induction of Th1 responses, modulation of MHC expression, adrenocortical-stimulating, opioid-like and pyrectic properties, and induction of behavioral (psychotic) responses, to cite a few.[55] On the whole, type I IFNs have been highlighted as physiological modulators, with only one of their functions being the ability to hinder viral replication intracellularly. In this scenario, the authors review the accumulated evidence of an important role of Type I IFNs as homeostatic agents in the inflammatory response. As such, these cytokines can be detected following exposure to diverse environmental, noninfectious stressors inducing an inflammatory response in the host. IFN responses can be thus detected in large animal models of commingling, truck transportation, early weaning, as well as in human and animal models of psychotic stress and autoimmune diseases. The authors also discuss the constitutive expression of IFNs in tissues of healthy individuals, in view of its possible role and functions in the response to infectious and noninfectious stressors. Constitutive expression and a prevalent posttranscriptional control of expression outline a peculiar response system, dealt with by the authors on the basis of accumulated evidence in clinical and preclinical studies.

Clinical repercussions of altered innate immune responses to environmental stressors are illustrated in the final chapter by Erminio Trevisi, Livia Moscati, and Massimo Amadori. Cattle and pig models are illustrated in terms of time-course of a few clinical immunology and chemistry parameters, depicting the process of environmental adaptation in critical phases of the farming activities, in agreement with the contents of Lacetera's chapter. In particular, the authors illustrate the disease-predicting and prognostic potential of some laboratory parameters of innate immune responses to noninfectious stressors. The chapter is mainly focused on large animal models, that is, dairy cows and pigs, for which strong evidence has been accumulated of a timely prediction of disease risks on the basis of laboratory parameters of innate immunity. These large animal models are compared with human models of innate immune responses and their predictive and prognostic value for disease occurrence. The authors also discuss the diagnostic and prognostic potential of common parameters of immunosuppression in man and animals like the plasma concentrations of widespread opportunistic viruses (Anelloviridae and the like).