Charlotte Esser *Editor*

Environmental Influences on the Immune System

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To my mother and father

Preface

The poetry of earth is never dead.
John Keats (1795–1821)

Environment (\in-ˈvī-rə(n)-mənt) is a noun that refers to the sum of physical, chemical, and biological factors that act upon an organism or an ecological community, but can also refer to all social and cultural conditions that influence the life of an individual or community. Thus, the environment comprises factors as diverging as climate, microbes, lifestyle, stress, diet, sun exposure, chemical pollution, and much more. Ultimately, the environment determines how we can live.

The term "immune system" appeared first in the early twentieth century and describes the many interacting and specialized body functions that protect from disease and infections. The immune system has evolved as the response of animals against bacteria, viruses, and fungi and it is most highly developed in vertebrate animals. It also serves to detect and eliminate cancer cells and contributes to epithelial integrity, thus protecting our barriers to the environment. Without our immune system, we cannot survive. Manipulating the immune status by vaccination and drugs and dietary compounds and supporting immune competence by hygiene measurements have saved countless human lives.

Looking at the interaction and communication of the immune system with the environment, especially the chemical environment in the broadest sense, is an interdisciplinary exercise. In the last decades, research was limited often to niches such as immunotoxicology and immunopharmacology. This is currently changing. There is a growing awareness in mainstream immunology that environmental conditions and environmental factors far beyond infections can influence the immune system. The influence can strengthen or weaken the immune system, including vaccination success, or give relevant cues for the adaptive direction an effective immune response should take.

There is a great need to understand how this communication between the environment and the immune system works. In a modern world we must understand how chemicals and the environment affect health: people suffering from allergies or autoimmunity, cancer, or immune-related morbidity want answers. Better knowledge will open new avenues for preventive or therapeutic strategies, informed policy decisions, or changes towards a healthier personal lifestyle.

This book wants to address this need and thus close an important gap. The book is divided into three parts, which cover human factors such as age, stress and diet, environmental factors, and important natural and man-made factors (UV light and chemicals). As a final section, a chapter looks at the gaps and challenges, and at the human rights perspective and the obligations coming with it. I have invited leading experts in the field for their contributions, and I am honored and grateful that so many have taken up the challenge. Thereby the book will serve as an excellent and up-to-date source of information for scholars from immunology, toxicology, allergy, and other fields. It will serve both scientists and those who make decisions in the field of public health to better understand the breadth and importance of understanding the influence of our environment on the immune system and thereby our health.

I am indebted to my current and former colleagues in immunology and toxicology for enthusiastic discussion and great science. Finally, I am grateful for the generous financial support by the Deutsche Forschungsgemeinschaft towards my lab over the years.

Düsseldorf, Germany Charlotte Esser
July 2015

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Abbreviations

4-n NP	4-n-nonylphenol
ACD	Allergic contact dermatitis
ACh	Acetylcholine
ACTH	Adrenocorticotropic hormone
AD	Atopic dermatitis
AfCHPR	African Charter on Human and Peoples' Rights
AHR/AhR	Aryl hydrocarbon receptor
ANA	Antinuclear autoantibodies
ANoA	Anti-nucleolar autoantibodies
ANS	Autonomic nervous system
APC	Antigen-presenting cells
ATSDR	Agency for Toxic Substances and Disease Registry (of the USA)
AU	African Union
AVP	Arginine vasopressin
BALF	bronchoalveolar lavage fluid
BPA	Bisphenol A
BSA	Bovine serum albumin
C57BL/6	An inbred mouse strain used in immunology
CD	Crohn's disease
CDC	Centers for Disease Control and Prevention (of the USA)
CHS	Contact hypersensitivity
CLR	C-type lectin receptors
CMV	Cytomegalovirus
CNS	Central nervous system
CNT	Carbon nanotubes
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CRS	Cytokine release syndrome, also called "cytokine storm"
CVB	Coxsackievirus B3
CVD	Cardiovascular disease
dACC	Dorsal anterior cingulate cortex

DAMP	Damage-associated molecular patterns
DC	Dendritic cells
DES	Diethylstilbestrol
DIT	Developmental immunotoxicity
DNMT	DNA methyltransferase
DOTC	di-*n*-octyltin dichloride
DPRA	Direct Peptide Reactivity Assay
dsRNA	Double-stranded ribonucleic acid
DTH	Delayed-type hypersensitivity
EAC	Emotional approach coping
EBV	Epstein-Barr virus
ECHR	European Convention for the Protection of Human Rights and Fundamental Freedoms
EDCs	Endocrine disrupting chemicals
ELISA	Enzyme-linked immunosorbent assay
EOGRTS	Extended one-generation reproductive toxicity study
EPA	United States Environmental Protection Agency
ERK	Extracellular signal-regulated kinase
EWAS	Environment-wide association
FICZ	6-Formylindolo[3,2-b]carbazole
FOXP3	Forkhead box P3
GABA-BDZ	γ-aminobutyric acid-benzodiazepines
GD	Graves' disease
GerES	German Environmental Survey
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage colony-stimulating factor
GSE	Gluten-sensitive enteropathy or celiac disease
GSH	Glutathione
HBV	Hepatitis B virus
HCB	Hexachlorobenzene
HCV	Hepatitis C virus
Hg	Mercury
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPA	Hypothalamic-pituitary-adrenal
HSC	Hematopoietic stem cells
HT	Hashimoto's thyroiditis
IACHR	Inter-American Commission on Human Rights
ICCPR	International Covenant on Civil and Political Rights
ICESCR	International Covenant on Economic, Social and Cultural Rights
IDF	International Diabetes Federation
IFN	Interferon
Ig	Immunoglobulin (can be of M, D, G, E, A type)
IL	Interleukin
ILC	Innate lymphoid cells

IVDK	Information Network of Departments of Dermatology for recording and scientific analysis of contact allergies
I-κB	Inhibitor of κB
JAK-STAT	Janus kinase/signal transducers and activators of transcription
JP-8	Jet propulsion 8
kDa	Kilodalton
LAL	Limulus amoebocyte lysate
LEDS	Life Events and Difficulties Schedule
LLNA	Local lymph node assay
LN	Lymph node
LPS	Lipopolysaccharide
MeHg	Methylmercury
MHC	Major histocompatibility complex
miRNA	MicroRNA
MPS	Mononuclear phagocyte system
MRL	Minimal risk levels
MS	Multiple sclerosis
MWCNT	Multi-walled carbon nanotubes
NAG	N-acetyl-β-d-glucosaminidase
NET	Neutrophil extracellular traps
NFκB	Nuclear factor kappa B
NHANES	National Health and Nutrition Examination Survey (of the USA)
NHP	Nonhuman primates
NIEHS	National Institute of Environmental Health Sciences (of the USA)
NIOHS	National Institute for Occupational Safety and Health (of the USA)
NK	Natural killer cell
NKT	Natural killer T cell
NLR	NOD-like receptors
NLRP3	NLR-related protein 3
NO_x	Nitrogen oxides
NP	Engineered nanoparticles
NPY	Neuropeptide Y
NSAID	Nonsteroidal anti-inflammatory drugs
OAS	Organization of American States
OAU	Organization of African Unity
OECD	Organisation for Economic Co-operation and Development
OVA	Ovalbumin
PAF	Platelet-activating factor (1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine)
PAMP	Pathogen-associated molecular patterns
PATHOS-D	Pathogen Host Defense
PBC	Primary biliary cirrhosis
PBMC	Peripheral blood mononuclear cells
PCBs	Polychlorinated biphenyls
PCR	Polymerase chain reaction

PEG	Polyethylene glycol
PFAS	Polyfluorinated alkylate substances
PFCA	Plaque forming cell assay
PFCs	Perfluorinated compounds
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PGE_2	Prostaglandin E2
PHENX	Phenotypes and exposures
PM	Particulate matter
PMN	Polymorphonuclear leukocytes
PNS	Parasympathetic nervous system
PPARs	Peroxisome proliferator-activated receptors
PPV23	Pneumococcal vaccine
PRR	Pattern-recognition receptors
PSS	Perceived Stress Scale
PUVA	Psoralen plus UVA
PVN	Paraventricular nucleus
RA	Rheumatoid arthritis
RANK	Receptor activator of NF-κB
RANKL	Receptor activator of NF-κB ligand
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (a European regulation)
RF	Rheumatoid factor
RfD	Reference dose
ROS	Reactive oxygen species
SCF	Stem cell factor
SCFA	Short-chain fatty acids
sICAM-1	Soluble intercellular adhesion molecule-1
SIgA	Secretory immunoglobulin A
SLE	Systemic lupus erythematosus
SMOL	Small molecules
SNS	Sympathetic nervous system
SOD	Superoxide dismutase
SO_x	Sulfur oxides
SRBC	Sheep red blood cells
sTNF-RII	Tumor necrosis factor receptor type-II
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TAS-20	Toronto Alexithymia Scale
TBTO	Tributyltin oxide
Tc	Cytotoxic T cells
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TCR	T cell receptor
Tdap	Tetanus, diphtheria, and pertussis vaccine
TGF	Transforming growth factor

Th/T_H	T helper
TLR	Toll-like receptors
TNF-α	Tumor necrosis factor-α
TREC	T cell receptor excision circles
Treg	Regulatory T cell(s)
TSP	Total suspended particles
TSST	Trier Social Stress Test
UC	Ulcerative colitis
UFP	Ultrafine particles
UN	United Nations
URTI	Upper respiratory tract infections
UV	Ultraviolet
UVA	Ultraviolet light, wavelength 320–400 nm
UVB	Ultraviolet light, wavelength 290–320 nm
UVC	Ultraviolet light, wavelength 100–290 nm
VIP	Vasoactive intestinal polypeptide
VZV	Varicella zoster virus
WHO	World Health Organization
WoE	Weight of evidence

Principles of the Immune System: Players and Organization

1

Charlotte Esser

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1.1 Introduction

The immune system of vertebrate organisms is an organ of enormous complexity (Abbas et al. 2015; Paul 2013). The immune system is necessary for survival, yet its dysfunction can lead to great morbidity or even mortality. The immune system enables the organism to cope with pathogenic microorganisms and their toxins, detect and kill cancer cells, and contribute to epithelial integrity at the barriers with the environment. These broad functions are reflected in a staggering variety of functionally diverse cell subsets and effector molecules. Indeed, new immune cell subsets and signaling molecules continue to be discovered, and for nonimmunologists the terminology is often daunting.[1]

[1] Cell surface proteins are often used to name or characterize immune cells. Cell surface proteins were first distinguished serologically in various laboratories by raising antibodies against immune cells, and if the same molecule was discovered in parallel, several names existed. Eventually, to bring order into chaos, the highly useful nomenclature of "clusters of differentiation," or CD molecules, was developed. CD molecules are assigned a number in chronological order (Zola et al. 2007). Currently, there are more than 350 CD known. For many CD molecules, the underlying proteins and their function(s) have been characterized by now.

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The immune system has a number of special characteristics not shared by other organs. First, the immune system functions via spatial interactions. Thus, immune cells and lymphoid tissues and organs are found across the entire body (Fig. 1.1). Many immune cells are migratory and capable to shuttle between tissues, interstitial tissue fluids, the bloodstream, lymph nodes, and the lymphatics; indeed, many immune cells circulate continuously. Migration can be either random or guided by chemokines, which attract cells to a site of inflammation. Meeting points, such as the lymph nodes, enable different immune cell subsets with different functions to communicate and interact closely in a coordinate fashion. Second, the immune system is characterized by comprehensive adaptability of responses against the insult. This concerns the participating cell subsets and thus the direction a response may take (e.g., tailored specifically to the type of pathogen), its intensity, its duration, or its spread. Usually the immune cells are classified into two big groups, namely, as belonging to the "innate" or "adaptive" immune system. The latter term is used for immunity based on the reaction of T and B cells. These cells undergo during their development a genetic process which results in each cell having a gene coding for a unique antigen-binding molecule (the antibodies in B cells, the T-cell receptor in T cells). Soluble antibodies or the surface-bound T-cell receptor recognize molecular structures (antigens) in the serum or on other cells and mount a humoral (=antibody based) or cellular immune response accordingly. T cells only recognize peptide antigens, whereas B cells can generate antibodies against proteins, lipids, carbohydrates, or any other molecule with minimal size requirements. The "gene rearrangement" to generate high affinity and high specificity antigen receptors has developed in vertebrates only (Hirano et al. 2011). T or B cells are not present in invertebrates. Cells of the innate immune system can detect antigen via their pathogenic molecular pattern (PAMP) receptors (Janeway and Medzhitov 2002). Such receptors (Toll-like receptors [TLR], the mannose receptor, to name important ones) detect only a limited number of molecular structures such as double-stranded RNA, lipopolysaccharides (LPS), unmethylated CpG, or flagellin; all such molecules are typical for evolutionary old molecular patterns of bacteria or viruses and are not made by higher organisms. Innate immune cells are highly diverse; they include granulocytes (which are the majority of white blood cells), dendritic cells, natural killer cells, macrophages, or mucosal-specific innate lymphoid cells. Upon recognition of such structures, innate immune cells immediately fight the infection by, e.g., phagocytizing the bacteria and oxidative burst or by inflammatory cytokine secretion. Moreover, some innate immune cells have the additional capacity to digest pathogen proteins and display it as small peptide pieces on their surface. This instructs and directs antigen-specific T cells that danger is at hand and thus starts the adaptive immune response. Specialists for this "antigen presentation" are the dendritic cells. T cells need the interaction with antigen-presenting cells to mature into effector cells. In turn, B cells need help from T cells to function. Only a subset of B produces antibodies without T-cell help. Finally, the immune system is continuously renewing itself from hematopoietic stem cells. All lineages are derived from common hematopoietic stem cells, which are found in the fetal liver before birth and in the

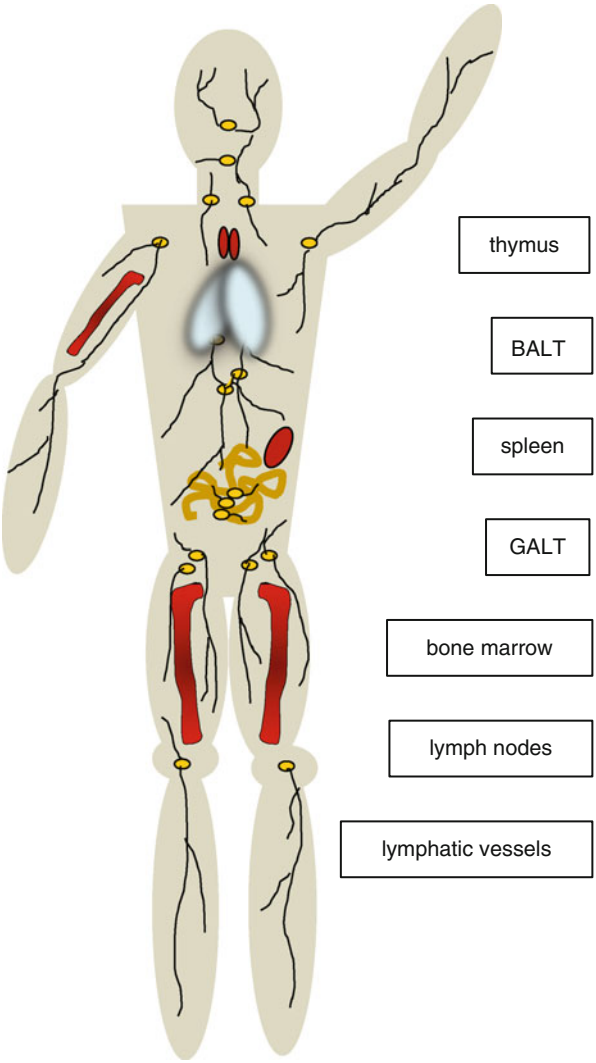

Fig. 1.1 The immune system as an organ across the body. Schematic presentation of major immune structures in the body. Primary lymphoid organs are the (1) sites of hematopoiesis, i.e., bone marrow of all hollow bones, and (2) the thymus which selects T cells that are neither autoreactive nor nonresponsive to foreign antigen presented to them. Secondary lymphoid organs are the spleen and the lymph nodes (LNs); LNs contain T cells, B cells, and dendritic cells; tissue fluid and cells drain via lymph vessels to the nodes; cells can also enter from the blood stream via high endothelial venule cells. LNs are coordination sites for T-cell differentiation upon antigen presentation; note that lymphatic vessels and lymph nodes are much more numerous than presented in this scheme. Lymph vessels empty into the bloodstream from the thoracic duct lymph vessel at the clavicular vein (not shown here). *BALT* (bronchoalveolar-associated lymphoid tissue). *GALT* (gut-associated lymphoid tissue: intraepithelial lymphocytes, Peyer's patches)

bone marrow after birth. The stem cells divide, and their descendants differentiate further, using intrinsic and extrinsic clues. The differentiation is irreversible. Many immune cells are short-lived and replaced by newly differentiated ones. However, some immune cells, in particular the memory cells and long-living plasma cells of the adaptive immune system, can stay around in niches of the bone marrow for years or decades. This allows the immune system to fight a new response faster and more vigorously than at the first encounter. Memory can last lifelong; thus, one gets some infectious diseases only once. The measles are well known for this. On the flip side, also autoimmune disorders and allergies can last as long as the specific memory T cells and long-lived plasma cells survive; allergies will flare up again and again upon renewed contact with antigen. This poses the major challenge for any therapy beyond treating symptoms. Last but not least, it is also a feature of the immune system that it can switch off immune responses (while preserving memory). This is vital of course as an ongoing inflammation or tissue destruction can lead to devastating health consequences. It requires again a complicated signaling network and involves cytokines, immunosuppressive enzymes, and surface molecules to give negative feedback signals to immune cells and stop their activity.

The basic principles of the immune system are *recognition* followed by *response*. What is "recognized" by the immune system, in other words: what are antigens? The answer appears trivial: pathogens, infective organisms, cancer cells, and toxins. However, the T- and B-cell receptors do not bind and react to (in immunology language: recognize) complete organisms, but they bind to organic molecules: lipids, carbohydrates, and proteins/peptides. Small molecular weight chemicals such as some toxins can be recognized by T cells only when bound to a protein. Not all of these molecules are specific for harmful pathogens; they also exist in harmless bacteria, in plants, in pollen, in food, or in one's own body. It is vital that the immune system does not use its destructive potential when there is no infectious risk or possible harm to the body or when the antigen is indeed a molecule of one's own body. Immunologists have coined the term "self" for this. Recognition thus must be able to distinguish between harmless and harmful organisms and molecules and between self and non-self. One way to ensure correct recognition are the pathogenic molecular pattern recognition receptors mentioned above. Another one is the requirement of several signals at the same time. One signal is the antigen recognition itself; the other is a costimulatory signal on the cell surface, usually provided by antigen-presenting cells. In addition, soluble cytokines contribute to the start and direction of an immune response.

Once started, an immune response leads to a response on a cellular level, where cells begin to migrate, produce, and secrete effector molecules such as cytokines and chemokines or differentiate to become effector cells themselves, e.g., able to kill infected cells via direct cell contact. The arsenal of responses possibilities is huge: phagocytosis and intracellular killing by oxidative burst; cytokine and mediator secretion to change the tissue micro-milieu and permeability, rendering immune cells more sensitive; direct killing of infected cells by T cells or natural killer (NK) cells; antibody production by B cells; complement activation; cell proliferation; and more.

As always, there is a prize to pay for such high sophistication, and thus, the immune system can go awry and become dangerous. When *recognition* goes wrong, the immune system can attack its own body cells and tissues (resulting in autoimmunity) or mount responses against harmless proteins or drugs such as food proteins, inhaled pollen, penicillin, etc. (resulting in allergies, asthma, eczema, etc.). In both cases, what the immune system recognizes as "danger" cannot be resolved and eliminated by the immune response. Thus, the immune response results in chronic, sterile inflammation and tissue damage. Figure 1.2 illustrates this. In general, therapy of the alerted immune system cannot revert it to a naive state. Rather, therapeutic options aim at treating the symptoms, dampening the immune response, or simply avoiding the antigen or inducing chemical (if that is possible).

On the other hand, when the *response* goes wrong, by whatever causes, the immune system can create an equally crippling outcome. A wrong response could be either a heightened inflammation by secretion of the wrong cytokines or a state of immunosuppression, where, for instance, B cells do not secrete enough antibodies or T cells remain unresponsive despite receiving proper signals. As a result, an infection might be resolved too slowly or not at all and eventually overwhelm the body. Chemicals such as environmental pollutants or drugs can cause or contribute to a response going wrong. Examples for immunosuppressive chemicals are diethylstilbestrol or 2,3,7,8-tetrachloro-dibenzo-p-dioxin. Other immunosuppressive drugs are cyclophosphamide or cortisol, which indeed are important therapeutics for autoimmune or allergic immune responses or in cases of transplantation.

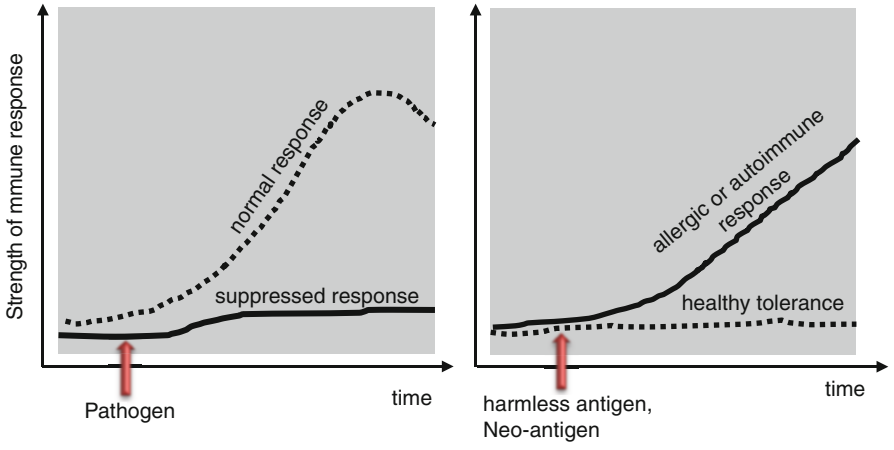

Fig. 1.2 Adverse immune reactions. Schematic representations of immune responses in an immuno-suppressive situation or an autoimmune/allergic situation. *Arrow*: exposure event; *dotted line*: normal/healthy response kinetics; *straight line*: adverse immune response; (**a**) immunosuppressive scenario, (**b**) allergic or autoimmune situation

1.2 Innate and Adaptive Immunity

The immune system is made up of various cell types (see Table 1.1), which have highly diverse functions and interact with each other at short or long distance. Communication is via cell–cell contact using receptor–ligand surface structures or over considerable distances via cytokines and chemokines. Lymph nodes situated throughout the body along the lymph vessels provide relevant spatial structures as meeting points for direct communication of immune cells.

There are two main arms of the immune system, the so-called innate immunity (which is evolutionary older) and the adaptive immune system (which evolved only in vertebrates). Macrophages, granulocytes, and dendritic cells (and many cell types; see below) belong to the former and T cells and B cells to the latter. Cells of the innate immune system mainly protect by phagocytosis (followed by intracellular destruction) of pathogens and by secreting cytokines, which generate and orchestrate an inflammatory tissue milieu unfavorable for pathogens. To detect pathogens, cells of the innate immune system have so-called pathogen recognition receptors for structures produced or found exclusively in bacteria, fungi, or viruses, such as lipopolysaccharides, flagellins, unmethylated CpG, or dsRNA. Upon recognition of such structures, innate immune cells immediately fight the infection by, e.g., phagocytosing the bacteria and oxidative burst. Secretion of various cytokines generates either a tolerogenic or inflammatory micro-milieu, adapted to the type of pathogen and the immunological situation. Moreover, some innate immune cells have the additional capacity to digest pathogen proteins and display it as small peptide pieces on special surface molecules (the major histocompatibility complex class I or class II, MHC-I or MHC-II). Specialists for this "antigen presentation" are the dendritic cells, but also macrophages and other innate immune cells, or even B cells can present antigen. Antigen presentation starts and directs the adaptive immune response by activating or suppressing T cells. T cells can recognize peptides on the MHC with their T-cell receptor. Naive T cells differentiate upon recognition of their cognate antigen and costimulatory signals provided by antigen-presenting cells (APC). APC activities range from ensuring immune tolerance against dietary antigens to the initiation of a potent immune response upon entering bacteria into skin wounds. Cytotoxic CD8+ T cells are capable of killing infected cells or cancer cells. T helper (Th) cells, on the other hand, orchestrate adaptive and innate immune responses by secretion of cytokines; for instance, they help B cells to differentiate and undergo immunoglobulin class switching and provide proinflammatory or immunosuppressive cytokines for other immune cells. Differentiation from naive CD4+ T cells into T helper (Th) 1, Th2, or Th17 cells is driven by combinations of cytokines in the micro-milieu, which are also provided by APC. Only a subset of B cells, the so-called CD5 B cells, produces antibodies without T-cell help.

The generation of the T-cell receptor (always cell surface bound) and the B-cell receptor (which can be surface bound or soluble and is then called antibody or immunoglobulin) requires a fascinating genetic process called gene rearrangement. Millions of different antigens exist, and the repertoire of B cells and T cells matches this high number. It is beyond the scope of this article to go into details, but the

Table 1.1 Cells of the immune system (excluding precursor and progenitor cells)

Cell name	Subsets	Function	Remark
Innate immune cells			
Macrophages	M1	Produce proinflammatory cytokines (e.g., TNF-α), promote Th1 response; strongly microbicidal	Monocytes in the circulation develop into macrophages in tissues under the influence of macrophage-stimulating factor
	M2	Produce immunosuppressive cytokines (e.g., IL-10) Promote tissue remodeling	
Granulocytes	Neutrophils Basophils Eosinophils Mast cells (see below)	Phagocytosis	Neutrophils constitute 40–70% of total white blood cells; first line of defense against infection. Granulocytes are also called polymorphonuclear cells (PMN) because of the lobed shape of their nuclei
Mast cells		Secretion of allergic mediators	Located at boundary of tissue with environment, cooperation with T cells due to their selective expression of cytokines upon stimulation
Dendritic cells	Lymphoid DC Myeloid DCs Langerhans cell Plasmacytoid DC CD103+ gut DC CD103– gut DC	Antigen recognition, transport into lymph nodes and presentation to T cells	Dendritic cells can be named and categorized in parallel for function (e.g., "tolerogenic" or "inflammatory," depending on how they act on T cells), for differentiation stage (as immature/mature), by motile behavior (migratory DC), or by lineage (lymphoid/myeloid). These subtypes overlap and can be very confusing at times. DCs are usually identified by various combinations of surface markers such as CD8, CD11b, CD11c, CD103, or DEC-205. It should be noted that the function of many CD molecules is not precisely known

(continued)

Table 1.1 (continued)

Cell name		Subsets	Function	Remark
Innate lymphoid cells (Spits et al. 2013) Derived from a common precursor Have a lymphoid morphology Classification is done on phenotype and function		Natural killer cells	Killing of virus-infected cells or cancer cells	Belong to group 1 ILC
		ILC1	IFN-γ secretion	Tissue development and remodeling, early immune response against microorganisms
		ILC2 (including nuocytes and natural helper cells)	IL-4, IL-5 secretion, amphiregulin	Resistance against nematodes, repair of lung tissue after viral infection, tissue development and remodeling, early immune response against microorganisms
		CCR6^{low}ILC3 (also called NK22 cells)	IL-17, IL-22 secretion immune response	Tissue development and remodeling, early immune response against microorganisms
		CCR6^{+} ILC3, /lymphoid tissue inducer cells (LTi)		Formation of secondary lymphoid organs during embryogenesis
Adaptive immune cells				
αβ T cell receptor (TCR) T cells	CD4 helper T cells	Th1 Th2 Th17	Cytokine production IFN-γ (and others) IL-4 (and others) IL-17, IL-22 Differentiate after antigen contact	All T cells undergo processes of selection in the thymus, which only a few percent of incoming precursor cell survive Naive T cells refer to T cells which have not recognized antigen
	Regulatory T cells (Treg)	CD4+CD24+FoxP3+ natural regulatory T cells (nTreg)	Down-modulation of immune response	Leave thymus as Treg
		Inducible CD4+ regulatory T cells (iTreg): CD4+Foxp3+ Treg CD4+Tr1 Treg CD4+ Th3 cells CD8+ inducible Treg	Suppression and limitation of immune responses, by cell–cell contact or secretion of cytokines, in particular IL-10	Are induced from naive T cells in the periphery
	Killer cells	CD8+ killer T cells NK T cells	Cytotoxicity Cytotoxicity	

Table 1.1 (continued)

Cell name	Subsets	Function	Remark
γδ TCR	Invariant TCR (skin) Invariant TCR (gut) Invariant TCR (vaginal) Variant TCR	Epithelial integrity, other functions unclear	γδ T cells are considered an intermediate between adaptive and innate immune responses Invariant γδ T cells are formed exclusively in the fetal thymus
B cells	Conventional B cells	Humoral immune response	The terminal differentiation stage of B cells is plasma cells, which secrete as many as 10,000 antibody molecules per second (Hibi and Dosch 1986)
	CD5 B cells	T-independent antibody production against certain bacterial antigens	

process uses stochastic assembly of gene segments from the T cell or immunoglobulin locus to generate individually in each cell a new full gene, which codes either for the T-cell receptor or the B-cell receptor. As a result, every T cell and every B cell has its own unique receptor, which is specific for a single antigen. The process generates also T or B cells with specificity for self-proteins, but these autoimmune cells are deleted in a complex series of selection processes. In addition, regulatory T cells are made both in the thymus and during immune responses to keep in check possible autoreactive responses.

A third group of immune cells, termed "innate lymphoid cells" (ILCs), has been discovered recently. They do not have specific, rearranged receptors like T or B cells, but are derived from the same precursor cells in hematopoiesis (the common lymphoid progenitor cells). ILCs are either cytotoxic (NK cells) or helper cells; the latter ILC can be subdivided according to the transcription factors needed to generate them and, similar to T helper cells, according to their typical patterns of secreted cytokines. For instance, ILC1 produce large amounts of IFN-γ and are needed for fast response against intracellular parasites. ILC2 secrete IL-4 and IL-13 and have special roles in fighting worm infections and contribute to allergies. ILC3 produce IL-17 and IL-22, are needed to fight certain bacterial infections, and subsets have lymphoid tissue inducer functions.

All cells of the immune system are generated throughout life from the common hematopoietic stem cell. They have individual life spans ranging from a few days to many years. Immune cells follow their intrinsic programs and/or adapt to external cues, relayed into the cells by surface receptors coupled to signal transduction pathways. Thus, transcription factors are pivotal in shaping the immune response, as all immune cells pass at some point through the executive steps of up- or downregulation of genes. Major pathways in immune cells are G protein-coupled receptors, the MAP kinases, NF-κB, or the Janus kinase (JAK)–STAT pathways. Another is direct activation by ligand of latent transcription factors (such as glucocorticoid receptors). As pointed out below, these signaling pathways can become targets of immune interfering molecules, which may result in toxicity or exploited pharmacologically.

1.3 Cytokines as Players

As discussed above, immune cells produce and react to soluble mediators, which are essential in any immune response. These mediators include cytokines, chemokines, and mediators such as histamine or antibacterial peptides. They act over long ranges or locally and are fundamental in communication between immune cells and information exchange of tissues. Whereas chemokines attract and direct immune cells spatially, cytokines take center stage in orchestrating immune responses. Cytokines are small glycoproteins secreted by many cells, not exclusively immune cells (the old name lymphokines or interleukins (IL) suggested wrongly that they are specific for lymphocyte communication), and act via binding to cognate receptors, which leads to changes in the receiving cells. Cytokines are pleiotropic and redundant and act synergistically and anergistically. Expression of cytokine

receptors allows the integration of a variety of cytokine signals. Their role in immune responses cannot be overstated. Changes in cytokine efficacy, regulation, or production – by environmental factors or by medical interventions – affect the immune response and thus can have unwanted adverse or desired beneficial effect. Originally cytokines were identified and named for function; by now most of them are simply numbered (currently IL-1 to IL-38). Cytokines operate at every stage in inflammation, drive lymphocyte proliferation and differentiation, regulate growth and repair of epithelial cells, maintain memory, trigger immunoglobulin class switching, start the acute phase response, cause fever, cause migratory behavior, act as pro- or antiapoptotic, signal lipogenesis, are proangiogenic, and more.

1.4 Signaling

Cells communicate with the "outer world" via receptors, either cell surface bound or intracytoplasmic. Once a ligand (which can be growth factors, cytokines, hormones, or small molecular weight chemicals) has bound to its receptor, a series of intracellular events is triggered, which eventually lead to changes in gene expression and an activity of the cell adapted to the changed environment: production of enzymes (or growth factors, chemokines, cytokines, etc.), proliferation, differentiation, apoptosis, and more. There are several major signaling pathways, some specific for immune cells. The activity of signaling molecules can be restricted to cell–cell contacts (where one cell has the ligand on its surface, the other the receptor) and be limited to nearby cells (called paracrine signaling) or across the body (endocrine signaling). Characteristic for cell signaling are response thresholds, the amplification of the signal within the cell, and the possibility to integrate signals derived from different pathways synergistically or antagonistically in a tightly controlled network. Finally, the outcome of signaling is cell specific and may vary according to, e.g., the target gene(s) accessibility at a distinct cellular stage. Immune cells evolved to sense changes in the environment, especially with respect to the living environment; from the complexity of response and communication described in the paragraphs above, it is clear that immune signaling must be very sophisticated to do its job. Again, cellular signaling can be a target of immune interference. Table 1.2 lists major signaling pathways in immune cells.

1.5 Immunotoxicology and Environmental Immunology

The term adverse or unwanted immune response concerns immune responses which go wrong. These are (1) autoimmunity, where the antigens are own body proteins; (2) allergies, where the antigens are noninfectious (harmless) proteins of the environment such as pollen or food antigens; and (3) immunosuppression, leading to weak or absent immune response against infections (Fig. 1.2).

Adverse immune responses are mostly studied in pharmacology or immunotoxicology, both of which disciplines look at the role of chemicals (Table 1.3).

Table 1.2 Major signaling pathways in immune cells

Receptor	Receptor kinase	G protein-coupled receptors (>1000 members in this family)	Latent cytoplasmic	Immunoglobulin superfamily
Typical ligand (immune system relevant)	Cytokines	Chemokines	Small molecular weight chemicals (e.g., glucocorticoids, dioxins)	Peptide on MHC molecule (T cell) Any other molecule (B cell)
Effects	Phosphorylation of tyrosines on key signaling molecules, e.g., STATs	G protein activation, generation of second messengers (cAMP; di-acyl-glycerat (DAG); inositol-3 phosphate; cyclic GMP; nitric oxide)	Transformation of receptor, which becomes transcription factor; gene induction	Antigen sensing
Example	EGF, TGF, erythropoietin, cytokine; IL-2, IL-4, IL-6, IL-7, IL-7, IL-10; interferons	CCR5, CXC3R	Arylhydrocarbon (Ah) receptor, glucocorticoid receptor, estrogen receptor	T-cell receptor, B-cell receptor

Immunotoxicology became a field of interest and hard science along with growing concerns about environmental pollution, in the search for causes of cancer and allergies and the advent of better tools and basic concepts in immunology (Kerkvliet 2012). The chapters in this book look at the environment in a broad sense: not only man-made factors such as (toxic) chemicals but also endogenous factors and lifestyle facts: foods, stress, exercise, and how being young or old affects our immune competence (Fig. 1.3).

1.5.1 Immunosuppression

Chemicals and drugs can interfere with cellular physiological functions of all cells, including cells of the immune system. Immunosuppression by chemicals can be caused by (a) killing of cells of the immune system, (b) changes in cell differentiation leading to fewer or incapacitated immune cells, and (c) changes in typical cell

Table 1.3 Some known immunotoxic chemicals causing…

Immunosuppression	Allergy	Autoimmunity (disease)
2,3,7,8-tetrachlorodibenzo-*p*-dioxin and other polycyclic aromatic hydrocarbons	Urushiol (from poison ivy)	Gold salts (rheumatoid arthritis)
Mercury salts	Penicillin	D-Penicillamine (Pemphigus vulgaris)
Organotin compounds (antifungal ship paint)	Formaldehyde	Procainamide (systemic lupus)
Arsenic (salts and organic arsenic)	Nickel (jewelry, dental braces, implants)	Vinyl chloride (sclerodermia)
Asbestos	Mercury salts	D-Methyldopa (hemolytic anemia)
Various insecticides	Volatile organic compounds	
Benzene	p-Phenylenediamine (compound in many hair dyes)	
Cyclophosphamide (drug)		
FK506 (drug)		
Glucocorticoids (stress)		
UV irradiation[b]		

[a]It is estimated that there are more than 100,000 chemicals on the market (Fischetti M. Sci. Am. 303:92 (2019); Foth and Hayes, Hum. Exp. Toxicol. 27:5 (2008). Only for a minority, immunotoxic properties have been systematically tested. Novel legislation in the European Union, known as the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), which entered into force on 1 June 2007, applies to all chemical substances produced at more than 1 ton/year and requires the provision of information for chemicals from companies

[b]UV irradiation is not a chemical, of course. However, the energy of UV radiation is high and can modify DNA bases. Moreover, UV radiation generates metabolites from intracellular compounds such as tryptophan, which can serve as signaling molecules and modulate Treg differentiation (Navid et al. 2013)

function such as cytokine secretion or expression of costimulatory molecules. Unfortunately, the exact mechanisms of interference by a given chemical are often unclear, and such lack of knowledge cripples treatment, prevention or optimizing drug usage in medicine. Immune interference may be caused by blockade or activation of intracellular enzymes, cell signaling molecules, transcription factors, or other proteins. The actions of dioxins, furans, or glucocorticoids are very good examples of this.

Immunosuppression is an operational term, which refers to an immune system operating with less efficiency than normal. Immune responses may start later, or they might be weaker. Immunosuppression might be general or restricted to certain pathogens. Whether caused intentionally by pharmacotherapy, unintentionally by environmental chemicals, or caused by aging processes, immunosuppressed individuals are more susceptible to infections and the development of spontaneous cancers. Immunosuppression can also cause inefficient vaccination. Epidemiologically, immunosuppression can be measured by comparing the average healthy population

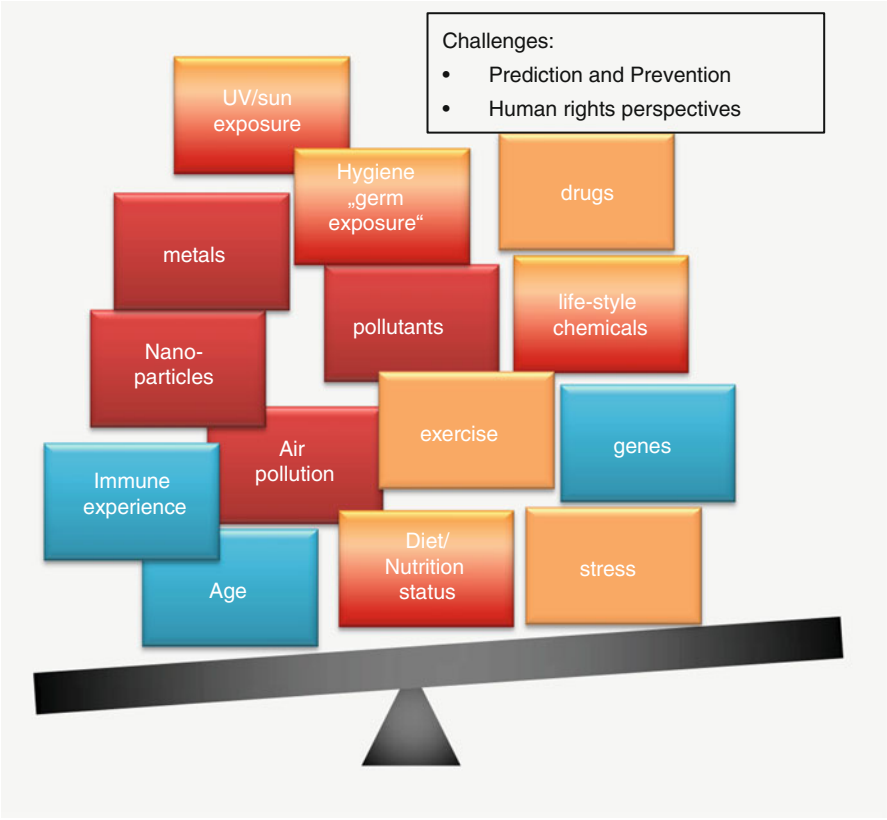

Fig. 1.3 Environmental influences. Factors influencing immune competence. Many factors contribute to the immune competence or induce adverse immune responses. Some set overall thresholds or capacities, such as the genetic predisposition, and cannot be influenced (*turquoise boxes*). Some factors can be influenced by oneself (*orange*), such as use of lifestyle chemicals, exercise, or a healthy diet. Other factors can be subject to changes in global health perspectives and political intervention (*red boxes*) such as extent of pollution or chemical exposure in consumer products, including food

with a particular subgroup, e.g., workers exposed to a toxic substance. However, no easily accessible and universally accepted markers for immunosuppression have been identified in vivo, and the considerable functional reserve of the immune system must be exceeded before immunosuppression becomes clinically relevant (Descotes 2005; Putman et al. 2003). Loss of immune cells (unless very high, like in AIDS) or a shift in proportion of cells in the blood or in lymphoid organs is of limited diagnostic value in humans. Standard immunotoxicity tests to detect immunosuppression or potentiation have been developed and validated (Luster et al. 1988, 1993). It is worth to keep in mind, though, that both acute clinical illness and small shifts in the susceptibility to normal infections can be of economic relevance on the population scale.

1.5.2 Autoimmunity and Allergy: Immunotoxicity Caused by Responses against Autoantigens or Harmless Antigens

Tolerance is the immunological term for the fact that the immune system does not react to its own body proteins, lipids, DNA, or other molecules, although they are potential antigens. One type of adverse immune reaction, often found with drugs, is a loss of tolerance, i.e., failure of the immune system to keep up the distinction between self and non-self. Tolerance can be lost in several ways. One way could be an unspecific impairment or loss of the cells important for tolerance, such as regulatory T cells. Another way is the drug-induced generation of self-peptides which are normally not made by standard protein degradation in the body or are not exposed to the immune system. To such self-antigens, the immune system has never acquired tolerance. T cells respond to peptide antigens presented to their T-cell receptors by MHC molecules on other cells. Importantly, also the body's own cellular proteins are continuously presented on MHC by all body cells. This is a way of tissue cells to signal "I am healthy" to the immune system. During protein catabolism in the cells, a typical range of peptides are generated and become presented on the surface. T cells do not react toward such normal peptides derived from its own body proteins, either because T cells with the respective specificity were eliminated in the thymus (termed "central tolerance"), or because they were silenced by regulatory T cells, or because they became unresponsive (termed "anergic") after antigen contact in the periphery (termed "peripheral tolerance"). During infection or in the case of cancer, the normal pattern of presented peptides changes, and different or additional peptides appear on the cell surface, tagging the cell as dangerous and in trouble. Notably, also chemicals can change the normal range of presented peptides of a cell, which appear as neoantigens. In other words, chemicals can render healthy cells recognizable by T cells. Chemicals might do this in several ways. First, they can covalently bind to self-peptides on MHC molecules (as "haptens") and be presented along with this peptide piggyback-like. In this case, a cell looks "foreign" or "infected," and there will be T cells in the body which consequently might attack it. In another scenario, some chemicals might interfere with the normal antigen processing and presentation of body proteins, leading to the presentation of normally cryptic self-antigens, against which no central T-cell tolerance exists. Examples for this mechanism are drugs containing gold salts (Griem et al. 1996). A T-cell reaction ensues, which, however, can calm down once the chemical or drug is removed (although memory cells persist). It is not always easy to predict whether a chemical will bind to cellular proteins and cause the formation of haptenated neoantigens or expose cryptic antigens. One indicator or risk factor is the presence of reactive groups in the chemical which can lead to the formation of protein adducts by chemicals. What type of an adverse immune reaction results from chemical exposure, and whether a reaction develops at all, depends on the chemical itself but also on auxiliary circumstances, the genetic predisposition, and exposure regimen and site. The outcome of chemical-induced antigen distortion can be autoimmunity or allergies. Predicting the immunotoxic potential of a given chemical is therefore still a great

challenge. Allergies are overacting immune responses against harmless antigens such as pollen or food proteins or chemicals. In the latter case, the binding to self-proteins as described above can be relevant. Penicillin allergy is a famous example for this. Allergic responses can be based on IgE secretion and mast cell degranulation or involve dominantly T cells which secrete proinflammatory cytokines leading to tissue destruction. Whether or not an allergy will develop is hard to predict; genetic disposition plays an important role and other auxiliary circumstances as well. Clinical manifestation often occurs only after several contacts with the antigen ("sensitization" phase).

1.6 Summary and Conclusion

The immune system is vital for well-being, health, and survival. Increasingly it is understood that environmental factors can become a risk or a benefit for the immune system, impairing or boosting its function. It is important to understand these environmental influences on a public health scale on the one hand and their underlying molecular mechanisms on the other hand. Together the knowledge will enable individuals, the science and medical community, and governments to take the necessary steps to discover, develop, and implement therapeutic and preventive opportunities and ensure a healthier environment for all.

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Part I

Age and Lifestyle

Influence of Early-Life Environmental Exposures on Immune Function Across the Life Span

2

Lisbeth A. Boule and B. Paige Lawrence

Contents

2.1 Receptor Binding Chemicals

Cell surface and intracellular receptors provide targets by which exogenous chemicals alter the function of the immune system. Indeed, this principle underlies the mechanism of action of numerous pharmaceutical agents and is exploited to design new drugs. However, these receptors also bind pollutants to which we are regularly exposed. Yet, how these exposures, particularly when they occur during

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development, lead to changes in the function of the immune system later in life is, for the most part, unknown. Nevertheless, evidence derived from human cohorts and animal models provides a compelling database that supports the idea that early-life exposures to several common environmental agents that bind specific cellular receptors have an impact on the development and function of the immune system (Table 2.1). In the following sections, we draw from this database and provide several examples. Relevant literature for receptor-binding chemicals that are not discussed below can be found in Table 2.1.

2.1.1 Aryl Hydrocarbon Receptor

One receptor that has been implicated in causing persistent changes in the function of the immune system after developmental activation is the aryl hydrocarbon receptor (AHR). Numerous environmentally derived chemicals bind this receptor, including dioxins, some polychlorinated biphenyls (PCBs), and polycyclic aromatic hydrocarbons. In addition, naturally derived molecules such as certain tryptophan metabolites, indoles and bioflavonoids, bind to the AHR (Nguyen and Bradfield 2008). Many studies have examined the consequences of activating the AHR on the immune system of adult animals. AHR activation alters multiple aspects of the immune system and subsequent disease outcome, with a range of outcomes observed depending upon the AHR ligand used (Lawrence and Vorderstrasse 2013).

While the metabolism, distribution, and excretion of all the ligands for the AHR have not been comprehensively studied, humans are regularly exposed to environmental contaminants that bind the AHR, primarily via our diet (Institute of Medicine 2003). Dioxins and PCBs cross the placenta and are excreted in breast milk (Gasiewicz et al. 1983). In fact, it is estimated that infants are exposed to considerably higher levels of these AHR ligands than adults due to bioaccumulation (Domingo and Bocio 2007). This information raises the question of whether activating the AHR inappropriately during development leads to persistent changes in the immune system. Summarized below are several studies that indicate that the answer to this question is yes: developmental exposure to anthropogenic AHR ligands elicits long-term changes in the function of the immune system.

The first studies that examined this were published several decades ago and showed that AHR activation during development altered function of the offspring's immune system (Faith and Moore 1977; Vos and Moore 1974; Thomas and Hinsdill 1979; Luster et al. 1980). Specifically, these studies showed that offspring of dams treated with the prototypical ligand 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exhibited impairment in hallmark immune responses later in life, including the antibody response to sheep red blood cells (SRBC) and delayed-type hypersensitivity (DTH) responses (Vos and Moore 1974; Faith and Moore 1977; Thomas and Hinsdill 1979; Walker et al. 2004; Gehrs et al. 1997; Gehrs and Smialowicz 1997, 1999). Other groups have studied this phenomenon, showing that AHR activation during development fundamentally changes disease processes later in life, including increased susceptibility to bacterial and tumor challenge and decreased antiviral