

Chapter 2

Immune Surveillance in Health and Diseases of Aging: Definitions of Acute and Chronic Inflammation [Yin and Yang]

Abstract Acute inflammation is a secretive success of self-terminating and inherent property of the immune system that protects the host tissue against internal (intrinsic) or external (extrinsic) foreign elements so that the body survive and thrive throughout life. For over a century, a role for inflammation in many acute and chronic diseases such as sepsis, allergies, neurodegenerative and autoimmune diseases, diabetes and cardiovascular complication, Alzheimer's, lupus as well as site-specific cancer has been documented. However, ongoing controversies, debates, misinformation and misunderstanding on the role of inflammation in chronic diseases, particularly cancer research and therapy, continue to be very costly for the society, as ageing population around the world increases. In recent years, Khatami defined acute inflammation as the balance between two tightly regulated and biologically opposing arms, termed 'Yin' (apoptosis, pro-inflammatory, initiation or tumoricidal) and 'Yang' (wound healing, post-inflammatory, termination or tumorigenic) properties of effective immunity (immune surveillance). The self-termination ability of acute inflammation is governed by a complex and precise series of signal transductions and cross communications between immune cells, genetic/epigenetic- neuronal-hormonal-metabolic and physiological responses of tissues toward internal or external hazardous agents (e.g., defective cells or proteins, allergens, pathogens or low level carcinogens) that threaten body's health. The two principal arms (positive and negative control switches) in acute inflammation, 'Yin', is responsible for production of death signals and oxidants to destroy both the enemy and injured host cells, requiring efficient energy from mitochondrial oxidative phosphorylation; while the 'Yang' arm is responsible for simultaneous removal of toxicity and debris and repair or remodeling of host, requiring low energy from glycolysis. Chronic or unresolved inflammation was hypothesized as loss of balance between 'Yin' and 'Yang' of immune responses or exaggerated expression and co-expression of mismatched factors in target host. Oxidative stress and longevity could cause defects in dynamics of innate and adaptive immune cell responses along with molecular, mechanical and physical changes in vascular, neuronal and metabolic integrities and functions leading to dysregulation of response profiles. Oxidative stress-induced altered local or systemic activities of cellular and humoral responses that create antigen burden could result an 'immunological chaos' or 'immune tsunami' and differentially influence architectural integrity and function of immune-

responsive or immune-privileged tissues and initiation of chronic diseases. Future research directions and designs of clinical studies are proposed on promotion of homeostasis of immune surveillance, or inherent properties of Yin and Yang of acute inflammation.

Keywords Acute inflammation • Allergen • Antibody • Angiogenesis • Antigen-load • Antigen presenting cells • Apoptosis • ATP hydrolysis • Autophagy • Bacteria • B cells • Bioenergetics • Cancer risk factors • Cell-mediated immunity • Chronic/unresolved inflammation • Dendritic cells • Early immune dysfunction • Effector cells • Effective immunity • Epigenetic modifications • Genetically modified organisms • Growth arrest • Growth promote • Humoral immunity • Immediate hypersensitivity • Immune dysfunction • Immune-privileged • Immune surveillance • Macrophages • Mast cells • Metabolism • Mitochondria • Mitophagy • Multipotent stem cells • Natural killer cells • Neuronal • Oncosis • Oxidative phosphorylation • Parasites • Pathogen • Phagocytes • Polarization • Programmed cell death • Pro-inflammatory • Post-inflammatory • Pyroptosis • Reactive oxygen species • Redox potential • T cells • Tissue susceptibility • Toll-like receptors • Tumoricidal • Tumorigenic • Vasculature • Viruses • Wound healing • Yin and Yang

1 Introduction

Rudolph Virchow, in the nineteenth century noted that the signs of inflammation were four; “*redness and swelling, with heat & pain*“. In 1909, Ehrlich recorded important observations that tumor cells are recognized and eliminated by immune/inflammatory cells. In 1957, Sir McFarland Burnet developed the important theory of immune surveillance or the body’s defense mechanism for controlling cancer growth [1–4]. Since these historical observations, a role for defective inflammatory processes reported in the genesis of many immune disorders, including the severe immediate anaphylactic hypersensitivity or delayed type hypersensitivity (DTH) and variations of defective immune responses (e.g., type I, II, III and IV reactions) [4–17]. The induction of mild or severe hypersensitivity syndromes often involve molecular defects in the dynamics of immune and non-immune cells, including mast cells (MCs), eosinophils (Eos), basophils, B and T lymphocytes, vascular activation, complement cascades and platelets in susceptible tissue. Altered activities of cell-mediated or humoral immunity (CMI, HI) have been reported in a number of potent pathogen-induced acute inflammatory diseases (e.g., sepsis, pneumonia, meningitis) or major trauma; chronic allergies (e.g., asthma, emphysema, skin and ocular inflammatory diseases), immunodeficiency syndromes, bacterial, parasitic or viral infectious diseases (AIDS, tuberculosis, rubella, rabies, measles) [3–5, 11–20]. The role of inflammation in age-associated chronic illnesses such as neurodegenerative and autoimmune diseases, or in hypertension, colitis, gastritis, hepatitis, nephritis, prostatitis, pancreatitis, appendicitis, ophthalmitis, Bechet’s, esophagitis,

neuritis, diabetes and other metabolic disorders, cardiovascular complications, stroke, rheumatoid arthritis, atherosclerosis, lupus, psoriasis, Alzheimer's, multiple sclerosis and other immune or metabolic disorders also have been widely reported in the literature [3–5, 21–47]. Regarding the role of inflammation in cancer research and therapy, although for many decades circumstantial evidence reported a role for inflammation in cancer, the decision makers in the cancer community ignored and downplayed these reports including the historically important observations of Ehrlich and Burnet in early twentieth century [1–6, 48–68]. In 1998, Khatami presented compelling evidence, based on extension of her earlier 'accidental' discoveries that were established in 1980s and demonstrated a direct association between inflammation and tumorigenesis to the NCI upper management. The originally submitted concepts including proposal that 'inflammatory mediators are ideal targets for molecular diagnosis, prevention and therapy of many cancers' and related designs of clinical trials, and introduction of several anti-inflammatory agents (i.e., aspirin, Captopril and Sulindac) met with serious opposition, downplay, denials and rejections by the NCI upper management [3–5, 50, 55, 63–68], NCI/NIH documents, since 1998]. However, in the last decade, increasing number of funded projects, networks, symposia and technologies focused on the roles of numerous inflammatory mediators and their influence in cancer research without a vision to conduct such funded programs on systematic bases to understand what inflammation does with regard to cancer and how to prevent or treat it. The many funded projects include molecular markers identification, design of clinical trials, 'targeted' therapies and immunotherapies for soft or solid site-specific cancers such as lung, colon/rectal, breast, prostate, bladder, liver, ovarian, pancreas, brain, lymphoid tissues or leukemia, in experimental models of tumors or cancer clinical trials [3, 4, 37, 60–108].

However, the ongoing debates, controversies, misunderstanding or misinformation on the role of inflammation, whether it is protective in preventing cancer or it causes cancer are among the major reasons for the extremely costly and wrong approaches in cancer immunotherapy with proven failed outcomes [3, 4, 50, 63, 64]. Current modalities and therapies, using anti-inflammatory mediators, hormone replacement therapy and steroids to manage chronic inflammatory diseases, particularly claimed cancer 'targeted' therapies or 'personalized' or 'precision' medicine, often have serious and life-threatening side effects [3, 4, 50, 63–65, 69, 80, 85, 101–109].

Since 1960s, several worthy investigations reported the definitions and classifications on mechanisms of cell death, primarily based on morphological features of tissues and types of cell death or tissue necrosis. The categories of cell death included 'type I', involved in heterophagy; 'type II', associated with autophagy and 'type III', which was not included in morphological categories of any type of digestion and corresponding to apoptosis, as autophagic cell death and necrosis. Cell necrosis defined as a regulated event that played significant role in numerous physiological and pathological activities, including DNA damage, excitotoxins having specific death receptors for binding to death factors such as caspases and other oxidants under special conditions [109–118]. Many investigators also reported the mechanisms of actions of numerous mediators of inflammatory processes and

identification of cancer markers; receiving federal and private funding to separately develop networks and technologies in the fields of proteomics, genomics, lipidomics, metabolomics, glycomics searching for hundreds and thousands of molecules and many such molecules were suggested or claimed as molecular targets for cancer research and therapy [3, 4, 37, 55, 63–68, 71, 72, 74–107, 109, 118–128].

However, despite the availability of enormous data on the roles that inflammation play in health and diseases, a clear definition of what acute and chronic inflammation do in maintaining health or initiating diseases, particularly during aging and the development of multistep carcinogenesis has been missing in the literature. With regard to cancer, numerous circumstantial evidence document a role for inflammation in site-specific cancers [3, 4, 37, 60–68, 70–80, 83–109, 125]. However, as noted above, except for the ‘accidental’ discoveries that we established in 1980s and extended in recent years [3–5, 16, 17, 63, 66–68, 81, 82, 109], direct evidence that oxidative stress (chronic, persistent or recurrent inflammation) is linked to the genesis of benign or malignant tumors/cancers in mammals has yet to be established. Consequently, little or no information is available on the developmental stages of inflammation-induced altered immune response dynamics that would lead to tumorigenesis or angiogenesis. The author suggests that a major serious obstacle in advancing our efforts to understand the cancer biology and effectively design clinical trials and drug development is intentional lack of interest to systematic understanding of the roles that immune disruptors (intrinsic or extrinsic stimuli) play in the induction of early/initial changes in response dynamics in susceptible tissues (see Chaps. 4 and 6) [3, 4, 63–68, 81, 82, 109].

A major focus of this chapter is to describe the recent definitions of acute and chronic inflammation in health and diseases, with emphasis on multistep carcinogenesis. The original concept that acute inflammation possesses two biologically opposing arms, termed Yin and Yang was introduced in the literature in 2008 (Ref. [66]).¹ The fundamental idea was proposed after detailed analyses of data from a series of our earlier experiments on experimental models of acute and chronic inflammatory diseases that were established in 1980s and resulted in tumorigenesis and angiogenesis, and later became ‘accidental’ discoveries. Definition of Yin-Yang included review of a large amount of scattered data that intellectually and logically would fit the Yin and Yang arms of self-terminating properties of acute inflammation (immune-surveillance) for maintenance of health (see below). Furthermore, a preliminary roadmap on the role of inflammation in the genesis and progression of age-associated chronic diseases was developed and led to hypotheses that chronic inflammation is a common denominator in the genesis and progression of nearly all

¹The article that was published in 2008 was originally prepared for and submitted to Nat. Rev. Cancer in 2006 (NPG Manuscript Tracking System NY-610A-NPG&MTS); the editor rejected it, claiming their journal was not interested in mast cells. In 2007, the manuscript was submitted to Nat. Rev. Immunol the editor stated that while the manuscript would potentially be of interest to the readership of their journal, a similar topic has been commissioned to someone else!! The topic is now the focus of numerous projects and published articles.

age-associated chronic diseases or site-specific cancers [3–5, 15–17, 50, 55, 63–69, 81, 82, 109].

Currently, numerous important biological knowledge gaps exist in basic understanding of how the protective properties of immunity turn against the body in the direction of multi-phases immune destruction that threaten its survival. A goal for preparing this and other chapters in this book was to address such biological gaps in the context of influence of inflammatory processes in specific target tissues (e.g., immune-responsive or immune-privileged) and the induction and progression of age-associated chronic diseases or site-specific cancers.

The present chapter was an attempt to continue analyses and integration of information on the overall roles that inflammation play in tissue metabolism, neuronal, hormonal, vasculature and immune cells in maintaining health or initiating age-associated chronic diseases or site-specific cancers. Potential interdependence between immune-mediated programmed cell death and other mechanisms of cell death, such as necrosis, pyroptosis, oncosis, and the energy requirements and biological recycling pathways (e.g., autophagy, mitochondria/mitophagy or ribosome/ribophagy) that contribute to the homeostasis of immunity or initiation of diseases will be outlined (details in Chap. 6).

Future proposed studies are directed on systematic understanding of the role of sustained oxidative stress (stimuli, immune disrupters) in alterations of Yin-Yang balance and differential energy requirements of mitochondria in maintenance of health or initiation of disease processes, with emphasis on cancer [109]. The results are anticipated to guide scientists to find logical approaches for developing cost-effective strategies for accurate formulation of risk assessment of diseases, as well as effective prevention, and control of chronic diseases and/or multistep carcinogenesis.

2 Acute Inflammation: Division of Labor in Programmed Cell Death. Protective, Self-Terminating Property of Immune Surveillance. Balancing Growth-Arrest (Yin) and Growth-Promote (Yang) Arms of Immunity

Acute inflammation is part of a biologically amazing complex and secretive success of the body's effective immunity (immune surveillance) that protects the body against unwanted (foreign) elements or immune disruptors that could threaten the body's survival throughout life. Stimulation of the host/target tissue by any intrinsic or extrinsic immune disruptors (stimuli), evokes an inflammatory response; an elaborate and precise signal transduction and crosstalk, between innate and adaptive immune cells and closely facilitated and orchestrated by non-immune pathways, such as the vasculature, metabolic, hormonal and neuronal systems (the entire network is referred to as effective immunity). Stimuli-induced local/host tissue responses are initiated by expression of alarming signals, death factors and receptor

molecules from activated immune cells. The processes engage a tightly regulated and sophisticated generation of often thousands or millions of other required chemicals from recruiting and attracting (activating) other inflammatory or non-inflammatory cells via the activation of vasculature, metabolic and neuronal pathways.

Recently, acute inflammation was defined as the inherent immune responses of two biologically and functionally opposing and reversible arms, termed; Yin (pro-inflammatory, initiation, growth-arrest or tumoricidal) and Yang (post-, anti-inflammatory, wound healing, resolution, growth-promote or tumorigenic) responses [66].

To better understand the roles that each arm plays in acute inflammation, the Yin and Yang events are separately described below (Fig. 2.1).

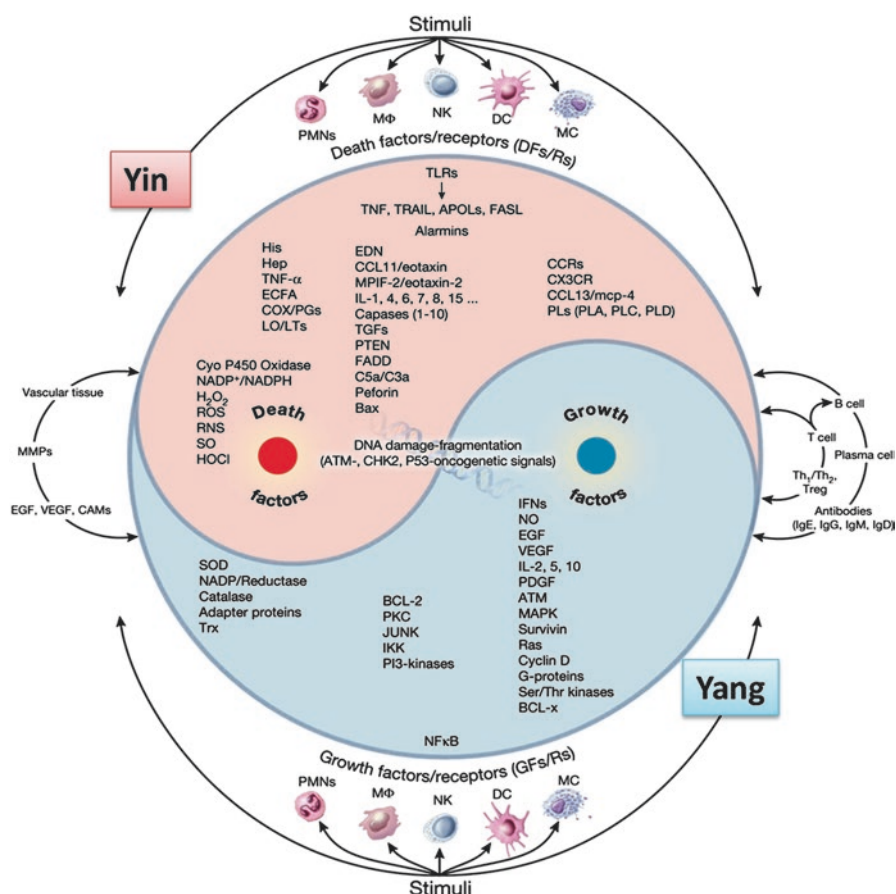


Fig. 2.1 Schematic representation of original definitions of Yin and Yang processes in acute inflammation (Modified with permission from Ref. [66], Exp. Opin. Biol. Ther. 2008. Informa Healthcare, all rights reserved)

2.1 Yin Phenomenon: Pro-inflammatory or Initiation Stage: Apoptosis, Program Cell Death, Growth-Arresting or Tumoricidal [DRESSED TO KILL!]

As schematically represented in Fig. 2.1, the overall role in Yin processes is generation of death factors, toxins and oxidants for the purpose of destruction and elimination of foreign components and also destruction of the injured/infected host tissue. Depending on the type of tissue and inflammatory condition, the major responses include a combination of the following interdependent biological events that occur to destroy the unwanted elements and injured tissue (Fig. 2.1) [3, 4, 63–68, 81, 82, 109]:

- (i) Stimuli-induced activation of appropriate antigen presenting cells (APCs) within innate and/or adaptive immune system;
- (ii) Encounter and recognize the nature of stimuli (e.g., pathogens, allergen, antigens);
- (iii) Process of destruction of pathogens/antigens by induction of expression of danger signal molecules and receptors, generation of a wide range of death factors, oxidants and toxins from host activated immune cells and/or recruited cells from vasculature, neuronal or metabolic pathways;
- (iv) Induction of stimuli-specific antibodies, surface and receptor molecules and activation of immune cells, aggregation of specific receptors and effector (pharmacological) function;
- (v) Changes in oxidative status of tissue, burst of energy in activated immune cells (e.g., MΦs) resulting in ATP hydrolysis from mitochondrial oxidative phosphorylation and generation of ROS and other oxidants and enzymes; changes/increases in intracellular ionic (Na⁺ and/or Ca⁺⁺) levels needed to destroy/kill cells (lysis of pathogen structure and infected host), disruption of membrane integrity and efflux of required intracellular components;
- (vi) Vasculature-derived activation of complement cascade enzymes (e.g., C1–C5) facilitating cell fixation and perforation/lysis of infective agents and injured host cells;
- (vii) Induction of cell/tissue edema, often accompanied by coagulation of plasma proteins/lipids in injured tissue, perhaps as part of ‘temporary’/immediate healing (filling) process of the damaged cell/tissue and/or to dilute toxicity;
- (viii) Simultaneous initiation of termination processes from polarized cells for healing the tissue and terminating inflammation (Yang events, below).

External and internal hazardous elements (immune disruptors) include a wide range of antigens or allergens (e.g., pollen, ragweed, foodstuff), infective agents/microbiomes, pathogens, carcinogens/mutagens, chemical, biological and environmental hazards. The stimuli include intrinsic or extrinsic changes in the levels of hormones and their functions occurring naturally in aging process or treated individuals with hormones or steroids. Among intrinsic immune disruptors are accumulation of defective, senescent or useless (non-functional) cellular and molecular

components [e.g., immune or non-immune cells, B lymphocyte complexes or cancerous cells, damaged chromosomal, genetic and epigenetic materials (mutated DNA/RNA and epigenetic hypo-, hyper methylated molecules, related repair enzymes or repressor molecules), oxidized metabolites (e.g., crystallized uric acid) or accumulation of pathogen-specific particles, use of fetal tissue and adjuvant (e.g., mercury, L-histidine) in vaccines] [3–5, 15–17, 63–68, 81, 82, 109–125].

As depicted in Fig. 2.1, depending on the nature of stimuli, specialized host inflammatory cells, such as innate immune cells (e.g., NKs, MΦs, DCs or MCs), are sensitized or activated and prepared for appropriate responses. Activated host cells also provide signals to activate, mature, differentiate and recruit (infiltrate) other immune cells and blood components through activation of vasculature and expression of precise quantities of required pro-inflammatory mediators, vasoactive agents, oxidants, enzymes or cytokines/chemokines to destroy the unwanted components (Fig. 2.1, Yin processes identified as Death Factors) [3–5, 63–68, 81, 82, 109].

The pro-inflammatory mediators that are expressed during Yin processes (death factors) include toll-like receptors (TLRs), vasoactive components (e.g., histamine), acidic glycoproteins (e.g., heparin), eosinophil chemotactic factor of anaphylaxis (ECFA), CCL11/eotaxin-1, MPIF-2/eotaxin-2, tumor necrosis factor- α (TNF- α), transforming growth factors (TGFs), PTEN, FADD, interleukins (e.g., IL-1 β , IL-4, IL-6, IL-8), caspases family of enzymes (caspases 1–10), blood-born complement cascades (e.g., C1-C5), perforin molecules, Bax, prostaglandins (PGs), leukotrienes (LTs), a variety of cytokines and chemokines receptor molecules (e.g., TNFR/TNFSF5, IgE-Fc ϵ R, TGF α s, CCL13/mcp-4, CCR family of chemokine receptors, CX3CR1, ILBrA, XCR1/CCXCR1), membrane phospholipases, antibodies (e.g., IgE, IgA, IgG, IgM), NO and genesis of free radicals and oxidants [e.g., reactive oxygen species (ROS), reactive nitrogen species (RNS), superoxide radicals, hydrogen peroxide,...] (Fig. 2.1, Yin) [3–11, 15–17, 63–65, 109].

The Yin activities often require receptor aggregation and synthesis of immunoglobulins (e.g., IgG to activate myeloid cells or IgE to activate and degranulate MCs). These events also involve activation of membrane enzymes phospholipases (PLs, e.g., PLA, PLC or PLD), sphingosine kinase and metabolism of arachidonic acid [e.g., activation of cyclooxygenase (COX) and lipoxygenase (LO)] pathways and biosynthesis of prostaglandins [(PGs), PGF1 α , PGI2, PGE2 and leukotrienes (LTs, LTA, LTC) and thromboxanes (TXs)] to produce the required pharmacological effects [3–5, 15–17, 63, 66–68, 81, 82, 109, 125–128].

In the list of immune disruptors or antigens that potentially increase the risk of chronic diseases, the genetically engineered or modified food products, genetically modified organisms (GMOs) should be included. These and other components of preserved foods or environmental hazards, as well as pathogen-specific vaccines, are likely important contributors of the reported increasing risks of allergies (or perhaps cancers) among both older and younger individuals in America in the last couple of decades [63–65, 125]. GMOs (e.g., corn, soybean products, cotton, fruits) are bacteria-crops, and considered 'transgenic', herbicide and insecticide resistant foods. They have long shelf lives and are marketed for animal and/or human consumption. Recent articles discuss controversies regarding the health benefits, ethics,

biotechnologies and environmental challenges of such products for human or animal use [129–134]. The digested modified proteins of the GMO foods are likely antigen burden for the immune system. Like the pathogen-specific vaccines, the genomic components or amino acids of bacteria-derived GMO products may interfere with body's ecosystem of microbiomes in the gastrointestinal tract and potentially lead to a wide range of health conditions (details Chaps. 5 and 6). Currently, the health concerns of consumption of GMO foods are expressed primarily for the American population compared with other developed nations. That is because the United States is the major producer and consumer of genetically engineered foods. These products are heavily endorsed and publicized by a powerful lobbying group who minimizes and ignores the potential adverse influence of these health hazards for human.

2.2 Yang Phenomenon: Post-inflammatory or Termination/Resolution of Acute Inflammation (Wound Healing, Growth-Promoting, Tissue Repair, Tumorigenic). Host Revival!

The Yang (termination, post-inflammatory, wound healing, growth promote or tumorigenic) arm of acute inflammation is responsible for neutralizing the toxicity of death factors and oxidants that are generated in Yin events and to resolve and terminate the inflammation. The overall activities involved in Yang processes include the following steps [3, 4, 50, 63–68, 81, 82, 109]:

- (i) Simultaneous polarization of immune cells that signal for immune suppression. The polarization of immune cells include generation of mature DCs (DC2, TADC), induction of M2 (TAM) phenotypes, induction of regulatory T (Treg) or memory cells for expression of appropriate growth factors and antioxidants from activated immune cells, and/or recruited cells from vasculature. Yang events are often facilitated by hormonal, neuronal and metabolic pathways that signal for immune suppression.
- (ii) Removal/expel and/or dilution of the unwanted components and oxidants by production of tears, mucus secretion from goblet cells, or influx of plasma proteins to the site of injury;
- (iii) Induction of signals for generation of reducing power to offset the oxidative status of injured tissues. In this process expression of several inhibitors of apoptosis, decoy receptor molecules (e.g., TNFRdr), immune suppressor interleukins (e.g., IL-1dR or IRAK-M), interferons and growth factors, antioxidants and enzymes are involved to reduce/inhibit energy consumption within mitochondria via inhibition of ATPase activities creating 'temporary' hypoxic condition for expression of growth factors (e.g., HIF1-VEGF), induction of kinases (mTOR/PI3K/AKT) for growth promotion and repair of the injured host tissue (anabolic events);

- (iv) Resolution and termination of inflammation for repairing and/or remodeling of the injured host tissue also involve neovascularization or angiogenesis under hypoxic conditions to resolve injury and return tissue to normal function;

Therefore, the Yang phase involves simultaneous activation of appropriate anti-inflammatory pathways to precisely neutralize and remove the toxicity generated during the pro-inflammatory (Yin) response processes and to heal and repair or remodel the injured host tissue and terminate the inflammation (Figs. 2.1 and 2.2). As depicted in Fig. 2.1 (Yang), a wide range of signals from activated immune and non-immune cells induce expression of growth factors and inhibitors of oxidative materials and generation of reducing powers to terminate the inflammation [3, 4, 63–68, 81, 82, 109].

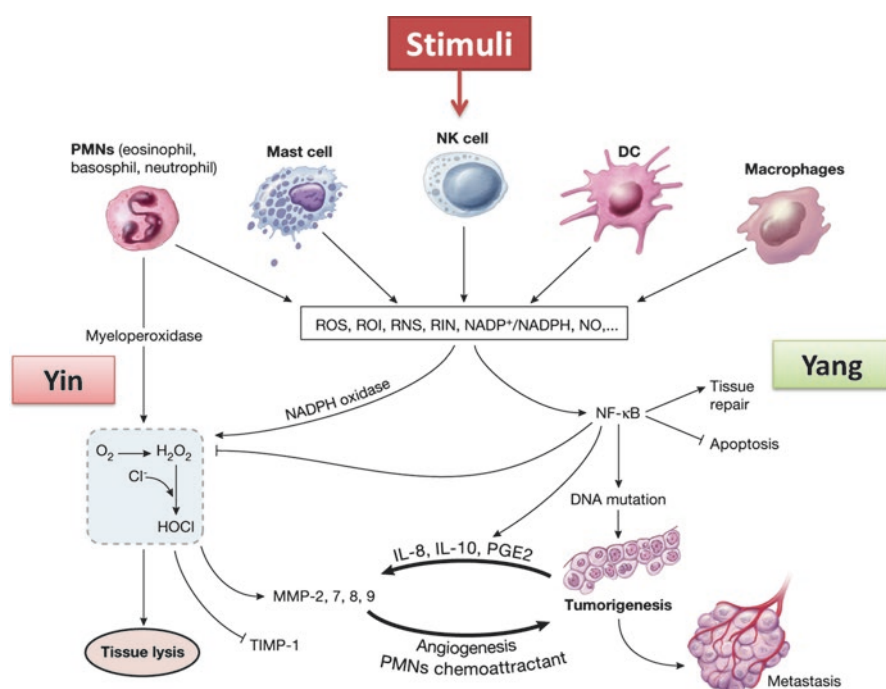


Fig. 2.2 Schematic representation of acute inflammatory responses during Yin (apoptosis) and Yang (wound healing). Stimuli-induced activation of immune cells such as polymorphonuclear, mast cells, natural killer cells, dendritic cells or macrophages lead to generation of oxidants such as reactive oxygen species and intermediates (ROS, ROI), reactive nitrogen species and intermediate (RNS or RIN), increased ratio of NADP⁺/NADPH, nitric oxide (NO) by activation of enzymes such as NADPH oxidase to produce precise quantity of toxic material that lead to lysis of pathogen and host tissue as well as induction of vascular hyperpermeability. The Yin events simultaneously signal for production of anti-oxidants and growth factors to neutralize the toxicity generated in Yin. The figure depicts that continued stimulation of tissue would change the balance between Yin and Yang of acute inflammation in favor of cell growth and induction of cancer, angiogenesis and metastasis (Modified from Khatami (Ref. [67]) all rights reserved)

Again, depending on the nature, potency and type of stimulation, extent of tissue injury and/or the composition of host immune and non-immune cells, the wound healing pathways involve appropriate expression of growth promoting factors such as lymphocyte-derive nuclear factor (NF- κ B) and receptor molecules, BCL-2, protein kinases (e.g., PKC, PI3 kinase-related kinases and mutated-ATM, MAPK family, JUNK, IKK, Ataxia Telangiectasia), synthesis of related receptor molecules, inhibitors of pro-inflammatory mediators (decoy receptors), immune suppressor factors, or inhibition of oxidative components [e.g., histaminases, iNOS, cytosolic or mitochondrial super-oxide dismutases (SODs), catalase, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), metalloproteases (MMPs), chemokines or cytokines [e.g., interferons (IFNs), interleukins (ILs)...] (Figs. 2.1 and 2.2) [3–5, 15–25, 37, 63, 66–68, 72, 80–128, 135–175].

Therefore, the principal function of post-inflammatory responses in Yang is to:

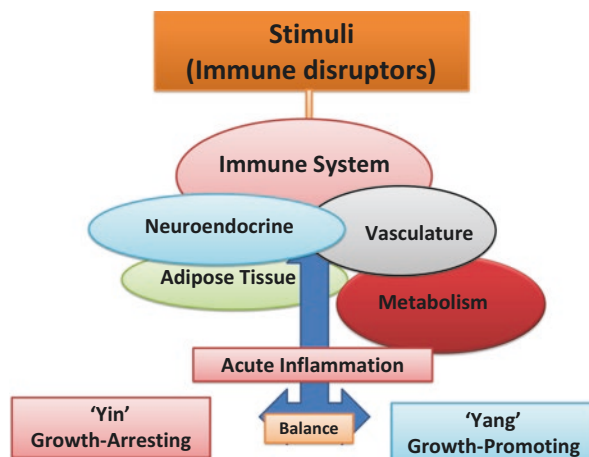
- (i) Neutralize and/or remove death factors and toxins from the injured target tissue;
- (ii) Provide the required growth factors and reducing powers that would repair any damage or scar (tissue necrosis) caused by expression of pro-inflammatory responses in Yin processes;
- (iii) Switch from high energy to low energy consumption, shutting down mitochondrial oxidative phosphorylation, ATP utilization from glycolysis (Warburg effect);
- (iv) Repair and remodel the cellular DNA damage, tumor suppressor genes (e.g., p53) and genomic integrity in the target tissue;
- (v) Resolution and termination of inflammation;

2.3 Contribution of Non-immune Systems in Acute Inflammation in Balancing Yin-Yang

To accomplish its protective and self-terminating role, acute inflammation through Yin and Yang processes, induces a complex, well-orchestrated, elaborate and precise chemical signal communications between mediators of innate and adaptive immune cells that are intimately facilitated by vasculature, metabolic, hormonal and neuronal responses. The following sections briefly incorporate the contributions of intracellular components such as mitochondria, ER and ribosomal activities during completion and/or clearance of byproducts of inflammatory responses. Analyses and integration of large amount of scattered data from basic and clinical research on complex biological rules are helpful for initiating a roadmap on the importance of maintenance of effective immunity for protecting health [3–6, 15–17, 47, 58, 63–66, 71, 79–82, 84, 103, 109, 113–122, 126, 136–151, 157–195]. The integration of such data also provides opportunities to identify major biological gaps as well as insights into correcting and delaying the age-, and oxidative stress-induced alterations of effective immunity toward preventing or delaying initiation of multistep diseases (details in Chap. 6). The overall analyses and integration of data will also reveal important knowledge gaps that are suggested to be major obstacles in advancing the goals of effective disease prevention and/or therapeutic approaches.

Examples of major interrelated biological activities that are likely to contribute to self-terminating properties of Yin-Yang of acute inflammation (immune surveillance) are outlined below (detailed in Chap. 6) [3–6, 15–17, 47, 58, 63–66, 71, 79–82, 84, 103, 109, 113–122, 126, 136–151, 157–195] (Figs. 2.1, 2.2 and 2.3).

Fig. 2.3 Role of immune and non-immune systems in acute inflammation. Maintaining balance between Yin (growth-arresting) and Yang (growth-promoting) arms of immunity is through activation of immune cells assisted by vasculature, metabolic and neuronal pathways including contribution from adipose tissue (Modified from Khatami [4] InTech Publishing)



2.3.1 Bioenergetics of Yin ['Dressed to Kill'] -Role of Mitochondria

During Yin responses (the 'dressed to kill' phase of acute inflammation), burst of oxygen and production of high energy released from mitochondria of activated immune cells (e.g., MΦs, NKs, MCs, DCs, T or B cells) are required. It is not clear to what extent activated non-immune cells (e.g., epithelium, mucus-secreting cells or vascular endothelium) contribute to the host production of high energy at this phase of inflammation. The rapid generation of free energy requirements comes from oxidative phosphorylation of mitochondria via activation of ATPase that hydrolyze ATP.

Hydrolysis of ATP rapidly lowers cellular ATP/ADP/AMP ratios and changes (increases) influx of $[Ca^{++}]$ and mobilization and intracellular $[Na^+]$, resulting in increased host oxido-redux potential. The high energy production temporarily decreases the tissue reducing powers (e.g., NADH/NAD⁺ or NADPH/NADP⁺, glutathione recycling pathways) and allows generation of reactive oxygen species (ROS), reactive nitrogen species (RNS), NO, superoxide radicals and activate oxidizing enzymes (e.g., caspases, NADPH oxidase, myeloperoxidase, membrane metalloproteases). The increased levels of oxidants in tissue are perhaps signals that would further facilitate increased vasculature hyperpermeability and activation and infiltration of other immune cells and/or blood complement cascades contribution during lysing pathogens and injured host tissue. As noted above, the biological events in Yin are often initiated by induction of pathogen (stimuli)-specific danger molecules or TLRs (TRL 1–11). The events in Yin are further accompanied by expression of hun-

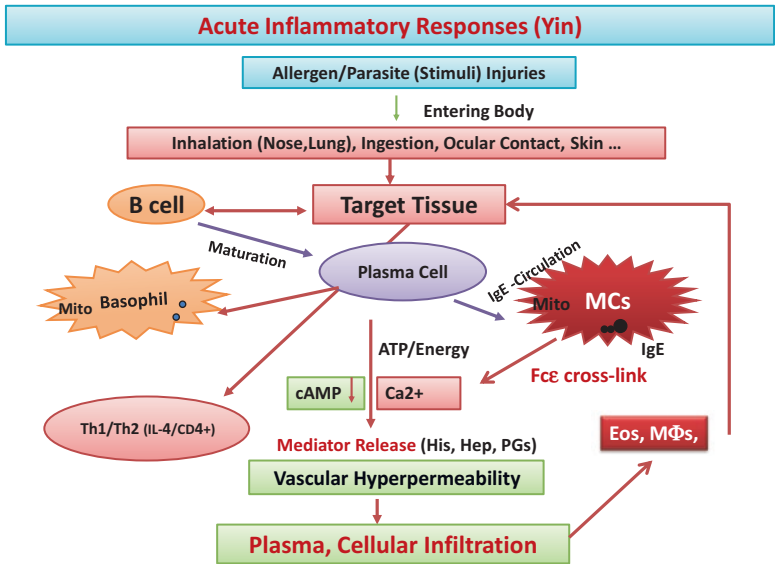


Fig. 2.4 Schematic representation of steps involved in acute (immediate) hypersensitivity responses, primarily Yin (pro-inflammatory) events. It depicts the three major stages of sensitization, activation and effector (pharmacological) function of tissues, involving primarily mast cells (MCs). See text

dreds of respective adaptor and surface molecules or expression of oxidative enzymes or release of vasoactive components (e.g., histamine) and interleukins (e.g., IL-1) or prostaglandins (PGF1 α) that activates other tissue components (e.g., nuclear membrane, DNA/RNA, cytoplasmic, membrane lipid, ion transport). These steps are suggested to be simultaneous and well orchestrated for the purpose of destroying pathogens and the injured tissues in Yin responses (Figs. 2.1, 2.2 and 2.4). See text.

2.3.2 Shift/Reversal of Energy Consumption and Metabolism in Yang ('Revival' of Host from Death')

Following killing of the foreign elements, the injured host tissue needs to simultaneously recover and repair by biological activities that possess opposite properties (growth-promote) from the growth-arrest actions of Yin pathways. As schematically represented in Figs. 2.1 and 2.2, the Yang responses ('recovery from death') involve simultaneous shift in oxidative metabolism by polarization of immune and non-immune systems for wound healing of injured tissue. The Yang events require switching away from high energy production of oxidative phosphorylation (shutting down mitochondrial function) to aerobic glycolysis (Warburg effect), a condition that also occurs in tumor microenvironment during tumor growth. Polarized immune cells (e.g., MΦs in M2 or TAMs phenotypes, degranulated or 'leaky' MCs, DC2 or TADCs) signal for induction of hypoxic conditions (impaired mitochondria) and

expression of hypoxia induced factor 1 (HIF1), also known as vascular endothelial growth factor (VEGF) and induction of neovascularization. The high energy ATP level that is spent during Yin causes mitochondria to conserve/reduce oxidative metabolism for its TCA cycle intermediates and anabolic/catabolic homeostasis. Events in Yang also accompany simultaneous generation of reducing powers, antioxidants and growth factors from activation of adrenal (production of cortisol) and/or thyroid (immune suppression by thyroxine, thyrotropin or TSH) glands. Among numerous important metabolites that are likely involved in Yang, are the activation of adenosine deaminase and generation of adenosine monophosphate (AMP) and related surface molecule CD 73, a key event in energy reversal for facilitating termination of inflammation and recovery of tissue. The AMP signaling is perhaps needed for ATP synthesis from aerobic glycolysis and expression of growth factors and enzymes such as PI3 kinase, PKC, reducing enzymes (e.g., SODs, catalase) or FGF, VEGF and membrane proteases to promote growth under hypoxic conditions (Figs. 2.1 and 2.2).

2.3.3 Shared Features of Yang Processes and Tumor Growth

As noted above, there are shared features between metabolism of activated immune cells, under oxidative stress, and growth of tumor cells. For example, both Yang processes and tumor growth utilize aerobic glycolysis (Warburg effect) for wound healing (termination of cell death or growth). Similarly, several growth promoting factors (e.g., mTOR/PI3 Kinase, MAPKinase, PKC, VEGF, FGF, IFNs, NFkB...) or other immune suppressors and growth promoting angiogenic factors are involved in Yang events as well as during tumor cell growth (Figs. 2.1 and 2.2, Yang arm of acute inflammation). In 1986, Dvorak suggested that tumors are wound that do not heal [51]. This cogent observation stood the test time in cancer research. However, even recent review of the literature does not seem to differentiate the metabolic and bioenergetic requirements of Yin vs. Yang processes in acute inflammation or the Warburg phenomena in tumor growth [63, 109, 179]. Recently, the author hypothesized that the oxidative phosphorylation in mitochondria (during Yin) and the aerobic glycolysis (Warburg effect) in cytosol (during Yang) use differential energy requirements for the ‘duality’ that effective immunity has for self-terminating function of acute inflammation [63, 109]. In other words, upon tissue stimulation, the activated immune cells first engage in rapid generation of free energy (ATP) by utilizing the oxidative phosphorylation from mitochondria, that otherwise is needed for tricarboxylic acid (TCA) cycle intermediates and biosynthesis of lipids, related enzymes and homeostasis of mitochondrial energy power for cells. Providing rapid energy (ATP hydrolysis) from oxidative metabolism, enables immune cells (e.g., M1, tumoricidal phenotype of MΦs) to produce pro-inflammatory mediators and generate needed toxicity for killing/destroying pathogens or foreign elements (Fig. 2.1 Yin arm). However, Yang responses that are involved in resolution of inflammation simultaneously use activated/polarized immune cells (e.g., M2 or TAMs phenotype) with growth promoting features. The

Yang responses shift to low energy requirements from aerobic glycolysis (Warburg effect) and under hypoxic condition, which signals for expression of HIF1 (VEGF), in the neighborhood of hypoxic neovasculature, for the purpose of resolving and terminating inflammation, repairing or remodeling and returning target tissue to resting status. The energy shifts away from mitochondrial ATP hydrolysis during Yang also enable the tissue to correct Yin-induced rise in tricarboxylic acid (TCA) cycle intermediates (e.g., succinate, fumarate) and reduced production of ROS in mitochondria.

However, it is suggested that sustained oxidative stress or persistent unresolved inflammation increases utilization of aerobic glycolysis (Warburg effect) for energy consumption due to overwhelming/exhaustion of oxidative phosphorylation pathways and the need for production of wound healing factors to terminate inflammation. The validity of this hypothesis seems supported by findings that angiogenesis and hypoxic conditions are primary features in tumor microenvironment and inflammatory diseases. One should also keep in mind that oxidative stress and aging retard the effectiveness of immunity to fight new antigens, perhaps as the result of loss of tightly regulated Yin and Yang processes toward necrosis and/or tissue growth promotion and ineffectiveness in energy homeostasis (Fig. 2.2) (details in Chaps. 3, 4 and 6).

2.3.4 Activation of Vasculature

Being the gatekeeper of the immune cell trafficking, vasculature has the most crucial function in facilitating both, the Yin (tumoricidal) and Yang (tumorigenic) processes by expression of precise quantities of death and growth factors. Activation of vascular tissue often involves activation of complement cascades (e.g., C3, C5 enzymes) to assist perforation and lysis of infective agents and/or damaged host (Yin); release of granules from platelets and expression of required amounts of growth factors (e.g., PDGF, EGF, VEGF, MMPs, CAMs) (Yang) for completion of Yin and Yang processes (Figs. 2.1, 2.2, 2.3 and 2.4). In addition, vascular endothelial cells provide receptor molecules for vasoactive components (e.g., histamine, heparin) that contribute to vascular hyperpermeability, cell adhesion, infiltration of immune cells, influx of plasma proteins, induction of edema and coagulation of plasma proteins to potentially facilitate ‘temporary’ wound healing [3–5, 11, 24, 56–60, 63, 72, 74, 87, 95, 96, 99, 100, 109, 155], (Figs. 2.1 and 2.4).

2.3.5 Activation of Neuronal and Endocrine Systems

Expression of several other factors and receptors for inflammatory mediators such as histamine receptors and hormones, metabolites or neuropeptides such as serotonin, adrenalin/ norepinephrine or cortisol contributes to the induction of pain and wound healing processes, respectively, during inflammatory reactions (details in Chap. 6) [3, 4, 63, 109, 177, 178, 180–187, 190, 191].

2.3.6 Role of Adipose Tissue in Inflammation

Immunologically, adipose tissue is a large and active tissue composed of innate and adaptive immune cells, such as B and T cells, MΦs and neutrophils. The polarized or subtype forms of such cells play important roles in immune surveillance, or induction of metabolic diseases such as insulin-resistant, hyperglycemia of diabetes or obesity. Adipose tissue perhaps contributes directly or indirectly in the induction of other diseases such as atherosclerosis, cardiovascular complications or cancer. Inflammatory mediators such as IL-6 and receptor molecule activation are linked to insulin-insufficiency and deterioration of glucose homeostasis in adipose tissue and a shift in MΦs polarization that results in expression of IL-4 and increased susceptibility to lipopolysaccharide (LPS)-induced endotoxemia [63, 171, 173, 192–194].

2.4 *Mission and Outcomes of Acute Inflammation (Yin-Yang) or Effective Immunity (Immune Surveillance)*

The principal mission of an inflammatory process (Yin and Yang) is twofold:

- (a) To encounter, recognize, process, destroy and eliminate the external or internal foreign elements that may harm the target/host tissue; and
- (b) To neutralize the death factors and oxidants and remove toxins that is present in the host cell and to repair the damaged cells and terminates inflammation.

The time course kinetics for induction and termination (resolution) of an inflammatory condition often depend on the quality and/or severity of an inflammatory condition. With the exception of non-specific or minimal tissue stimulation (e.g., acid burn or minor injuries), the major outcomes of an inflammatory reaction include:

- (a) Synthesis of allergen/pathogen-specific antibodies and receptor molecules;
- (b) Increased synthesis of memory B and T cells (T reg);
- (c) Upon tissue exposure to the same types of stimuli, the ‘initiated’ immune system can unleash appropriate responses (e.g., expression of antigen-specific antibodies) to destroy unwanted foreign elements and terminate inflammation.

In summary, effective immunity that protects the body against all potential harms plays a crucially important, exact and justifying role in health. Acute inflammation possesses two opposing biological properties characterized as (Yin) that is responsible for production of death signals to destroy both the enemy and the injured host cells; and (Yang) that is responsible for removal of toxicity and debris generated in target tissue and to repair and remodel the host and resolve inflammation (Figs. 2.1, 2.2, 2.3, and 2.4).

3 Sequence of Events in Immediate Hypersensitivity Reactions

The exact time course kinetics and mechanisms of actions of responses involved in inflammatory processes are not fully understood. Overall analyses of relevant data on sequences of events occurring during immediate type 1 (acute) hypersensitivity reactions in host tissues whose prominent immune cells are MCs and lymphoid tissues [e.g., conjunctival-associated lymphoid tissues (CALTs), lung airways, gut-associated lymphoid tissues (GALTs), perivascular or perhaps the skin], include three major phases of sensitization, activation and effector function (pharmacological effects or outcomes).

It is noteworthy that mast cells (MCs) that are categorized within the innate immune cells often function as effector cells for producing an effect, while B cells that are categorized as effector cells for humoral immunity within the adaptive immune cells often function as antigen presenting cells (APCs) to sensitize and activate MCs [3–10, 15–17, 38, 63–68, 72, 81, 82, 87, 89, 109, 120–124, 137, 144, 145, 159, 196].

Briefly, the three stages of sensitization, activation and effector function of immediate (type 1) hypersensitivity reactions include the following sequence of events (Figs. 2.1 and 2.4):

- (a) **Tissue exposure:** Antigen, parasites or allergen inhaled, ingested or administered via lung, skin, gut or ocular tissues;
- (b) **Circulating blood:** Antigen is engulfed by circulating blood phagocytes and delivered to B lymphocytes (B cells);
- (c) **B cells activation and response:** B cell differentiation into plasma cells and biosynthesis of antigen-specific IgE antibodies;
- (d) **Mast cells sensitization:** At low levels, IgE antibodies (Abs) circulate throughout the body without causing any reaction or harm, perhaps as part of tolerance. Upon exposure to higher levels of antigen, or repeated tissue encounter with the same antigen the circulating IgE Abs attach to the surface of mast cells (or basophils) through specific receptor binding (MCs-IgE-fcε receptors), which sensitizes MCs. Sensitization of MCs may last for weeks or years, without any severe responses. However, depending on the type of allergen or antigen, further contact of target tissue with the same antigen initiates an allergic response from the sensitized tissue (effector or pharmacological phase).
- (e) **Effector phase: Mast cells activation or degranulation and pharmacological effects:** Activation of MCs occurs when IgE bound to high affinity Fc receptor (FcεR1) on the surface of sensitized MCs are cross-linked (aggregated) by allergen to trigger degranulation and release of preformed granule-derived mediators and proteases or express newly synthesized mediators. Release and expression of mediators from activated MCs include vasoactive histamine, acidic glycoproteins such as heparin, enzymes (e.g., tryptase and chymase), expression of chemotactic mediators that are released in the circulating blood to

attract and recruit other inflammatory cells (e.g., eosinophils) for additional production of toxicity at the site of injury that may cause further injury to the tissue. In occasions where IgE Abs produced against parasitic infection, helminths (e.g., *Ascaris Suum* or its extracts), the responses from MCs are stronger and the damage to the tissues are severe. Furthermore, while circulating IgE antibodies preferentially sensitize MCs of the susceptible host (target exposed tissue), often the circulating (homocytotropic) IgE Abs sensitize other MCs that are distant from the target. In addition, as we reported for inflammatory responses in ocular tissues (details in Chap. 4), the severity of type 1 reactions may not necessarily correlate with the circulating levels of IgE [3, 5, 81, 82, 109]. For example, repeated topical and unilateral sensitization and challenge of ocular tissues with antigen caused not only strong responses from contralateral eye (untreated eye), they occasionally produced asthma-like wheezing symptoms in immunized animals suggesting sensitization and activation of MCs in lung airways. In addition, newborn babies from repeatedly sensitized animals (guinea pigs) demonstrated severe ocular allergies upon the first or second challenge with the antigen suggesting antibody transfer maternally or paternally (genetic predisposition?) [3–5, 66–68, 81, 82, 109].

4 Molecular Mechanisms of Acute Inflammation

As noted above, the exact molecular mechanisms of activation of multiple interdependent and complex pathways that are involved in the two phases of self-terminating acute inflammation are not understood. The signals initiated/generated from the activated innate and/or adaptive immunity for the purpose of destruction of foreign elements and injured tissue during Yin (growth-arrest) responses, would simultaneously signal for induction of Yang (growth-promote) pathways to resolve, neutralize and terminate the pro-inflammatory phase-induced tissue damage and resolve inflammation [3–5, 63, 66–68, 82, 109]. Therefore, resolution of acute inflammation means returning to normal activities of all immune cells, the vasculature and the metabolic and neuronal pathways (resting status of immunity) with little or no harm to the host. The dual inherent properties of immunity during termination and resolution of acute inflammation and generation of decoy receptor molecules, in all likelihood, are inclusive of the shift in energy consumption, away from oxidative phosphorylation (in Yin) toward aerobic glycolysis (Warburg effect). Yang processes are accompanied by the scavenger roles of metabolites and antioxidants or reducing enzymes (e.g., vitamin E, ascorbate, NADPH reductase, GSH, catalase, SODs) for reducing/neutralizing the toxicities of ROS/RNS and other oxidants that are generated in host. Therefore, stimuli-induced burst of energy in immune cells and rapid production of ATP from oxidative phosphorylation causes rapid ATP hydrolysis, followed by a change (rise) in the tricarboxylic acid (TCA) cycle intermediates (e.g., succinate or citrate) that are required for lipid biosynthesis and maintenance of mitochondria energy homeostasis.

Because multiple factors are involved in inflammatory processes, the outcomes of inflammation present infinite possibilities. In general, factors influencing the outcomes of inflammation, include the nature, quantity and potency of foreign elements, frequency of inflammatory conditions, competency of immune and non immune components (individual's genetic makeup) of target tissue, route of exposure, types of target tissue (e.g., immune-privileged, immune-responsive, insulin-dependent or insulin-independent for glucose transport and/or utilization), as well as the age of individual.

5 Interrelated Cell Death Categories

The nomenclature of cell death (necrosis, accidental cell death, oncosis, pyroptosis) or apoptosis, also known as Type I, Type II or Type III, cell death are confusing and ambiguous when mechanisms of immune-independent or immune-regulated cell death are defined [3, 4, 20, 80, 63, 66–68, 109–119, 138, 197–219]. These terminologies for cell death are often used when cell death occurs principally independent of programmed cell death, without extensive involvement of immune pathways that was described for Yin and Yang of acute inflammation. Highlights of known mechanisms of cell death with limited shared features with programmed cell death include the following: (Fig. 2.5):

1. **Accidental necrosis, oncosis and pyroptosis:** Accidental tissue necrosis happens as the results of significant or sudden increases in tissue oxidative stress causing extensive depletion of adenosine triphosphate (ATP) accompanied by the loss of cytosolic components and membrane integrity. The special feature of accidental necrosis is the absence of death signaling, which is different from Yin pathways in programmed cell death. Analyses of related data suggest that accidental necrosis and programmed cell death present limited shared physiological features. Both processes occur as the result of decreased host ATP levels (or increased ATPase activity for ATP hydrolysis) followed by an increased level of intracellular sodium ions $[Na^+]$. These events cause opening of the ion channels that lead to membrane and cytoskeleton rupture (membrane 'leakiness'), loss of cellular membrane integrity, osmotic swelling of intracellular organelles along with disruption of nuclear components and condensation of chromatin structure, a phenomenon also called oncosis (Fig. 2.5) [20, 109–117, 197–203]. It is not clear however, what conditions (nature of stimuli or tissue type) would induce sudden drop in ATP hydrolysis and how the intrinsic inappropriate synthesis of cells (e.g., cancerous cell or viruses) or drugs contribute to the accidental cell death. Another question is whether cytotoxic T cells are able to induce accidental cell death without involvement of the programmed cell death (Fig. 2.5).

The outcomes of accidental cell necrosis are different from apoptosis in programmed cell death since in the absence of wound healing processes (Yang), necrotic bodies that accumulate in tissues need to be neutralized and/or recycled by other mechanisms. It is possible that necrotic bodies are simply digested by circulat-

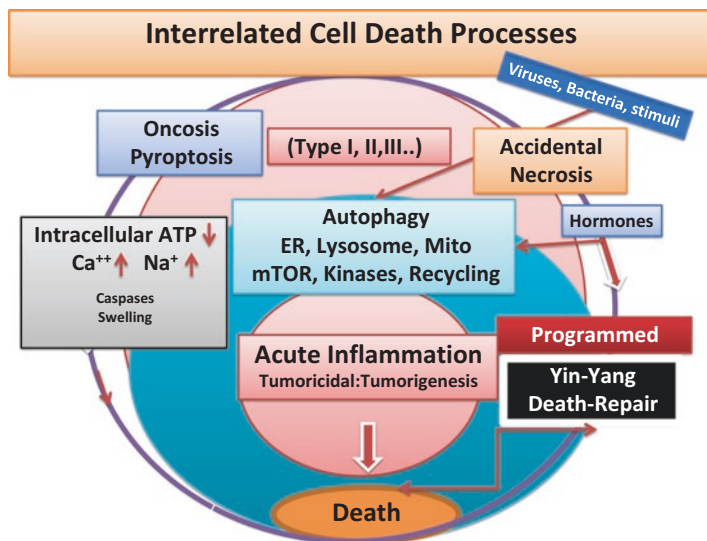


Fig. 2.5 Schematic representation of interrelated cell death. Major categories of cell death are oncosis/pyroptosis, accidental tissue necrosis and programmed cell death (Yin-Yang) of acute inflammation involving ATP hydrolysis and autophagy. See text

ing phagocytes as part of acute inflammation and/or autophagy. Accumulation of necrotic bodies from accidental necrosis may be considered as the biological byproducts in tissue; they form useless or toxic materials (antigen loads, internal stimuli) and could activate immune responses and/or autophagy. The accidental necrosis perhaps is a ‘one way’ cellular killing, compared with programmed cell death in ‘Yin-Yang’ pathways that requires complex participation of immune and non-immune pathways. However, the role of low-level activation of caspases and interleukins (e.g., IL1 β), to trigger pyroptosis in non-inflammatory elimination of pathogens and maturation of dendritic cells have been demonstrated. Furthermore, activation of caspase 1 does not seem to lead to cell death (pyroptosis) in all cells such as the epithelial cells [20, 23, 26, 63, 66–68, 109–120]. These interesting observations suggest that a reason for caspase activation not leading to cell death in epithelium is that epithelium is an immune-responsive tissue and could trigger many other signals for induction of wound healing processes of acute inflammation that lead to repair and survival of the tissue.

2. **Autophagy or macroautophagy:** The term ‘autophagy’ derived from Latin meaning ‘self’ and ‘eating’. Autophagy is an essential and dynamic process of tissue homeostasis, involving continuous degradation and recycling of cytosolic components, membrane formation and fusion. Autophagy has intracellular anti-viral and anti-bacterial functions and plays a role in the initiation of response processes from innate and adaptive immune system against viral and bacterial infections. In general, there are three types of autophagy, macroautophagy, microautophagy and chaperone-mediated autophagy (CMA). Briefly, the overall

processes in autophagy involve six major steps of membrane and protein assembly and degradation processes often initiated by mTOR (mammalian target of rapamycin)/PI3K/AKT signaling pathway in the induction of autophagy as the following (details in Chap. 6) [63, 109, 138, 201–219]:

- (a) **Initiation of membrane isolation.** The process also called phagophore, or preautophagosome. mTOR kinase signaling initiate complex association of cell membrane and cytosolic materials [e.g., endoplasmic reticulum (ER) and related vesicles]. The process requires autophagy-related protein–enzymes complexes (e.g., DFCP1, Atgs).
- (b) **Omeasome formation.** The process involves autophagy-related gene protein (Atgs) expression products, phospholipid phosphatases, ATPases, kinases complexes (e.g., Atg12-Atg5-Atg16, ULK1-Atg13-FIP200-Atg101) and components of ER and Golgi complexes, which are formed inside the ring of the omeasome.
- (c) **Elongation of the isolated membranes.** This process further engulfs cytoplasmic components including mitochondria and ER. The elongation of membranes involves many negative (inhibitors) and positive (inducers) proteins and enzymes that control the extent of membrane isolation and elongation.
- (d) **Autophagosome formation.** The next steps in autophagy are associated with a number of other autophagic-related proteins, enzymes and ligands (e.g., Atg5-Atg12-Atg16L), followed by membrane fusion and dissociation factors (e.g., LC3-II, LC3-PE) to form autophagosome (maturation step) that prepare the complex for degradation.
- (e) **Autophagosome-lysosome fusion.** Following maturation of the autophagosome, cytoplasmic lysosome fuse with the autophagosome (autophagosome-lysosome fusion).
- (f) **Degradation and recycling.** In this process, a number of lysosomal hydrolases are involved in degradation of autophagosomal contents. As the result of this process, protolysosome is elongated from autolysosome.

In brief, the essential factor or the ‘core’ for the above six major events involves energy-driven autophagy-related (Atg) protein kinase complexes and conjugate systems (e.g., ULK1 protein kinase, Atg9-WIPI-1, Vps34-becl in1 class III PI3-kinase, and the Atg12 and LC3), as well as PI3 binding proteins and phosphatases and Rab proteins pathways initiated through mTOR-dependent signaling. Elegant studies demonstrate that while some viruses encode virulence factors for blocking the autophagy, others utilize autophagy components for their intracellular growth or cellular budding [138, 206–220].

(g) **Selective Functions of Autophagy: Mitophagy, Reticulophagy, Ribophagy and Xenophagy**

In addition to the non-selective function of autophagy, the selective autophagy that includes mitophagy, a type of autophagy specific for degradation of mitochondria; reticulophagy for the recycling of endoplasmic reticulum; ribophagy for

degradation/recycling of ribosomes; or piecemeal autophagy for the nucleus/chromosomal components; and xenophagy for pathogens have been identified and reported in the literature. Defects in multistep complex processes of autophagy are associated with a wide range of chronic diseases such as neurodegenerative diseases, diabetes complications, cardiomyopathy, fatty liver pathology and tumorigenesis. For example, changes in mTOR/PI3K/AKT pathways implicated in longevity, malignant transformation and growth or endocrine/hormonal control of metabolism and adipose tissue biology. Details of biological processes that are involved in non-selective or selective autophagy and degradation- assembly of cellular components for maintenance of health or induction of diseases are available in a number of recent publications (Fig. 2.5) [138, 203–229].

In summary, autophagy is a bulk process of degradation of cytoplasmic components and membrane organelles or vesicles. Autophagosomes and autolysosomes are transient structures during protein/lipid degradation and recycling in autophagy. It seems that both killing of pathogens through programmed cell death (Yin-Yang) or accidental cell death, often requires simultaneous involvement of metabolic signals that are dependent on cellular burst of energy (changes in oxido-redox potential), accompanied by increased ratios of NADP⁺/NADPH and hydrolysis of ATP involving ATPase and alterations in ADP/AMP levels. As noted above, accomplishing Yin-Yang events in programmed cell death of self-terminating acute inflammation, the complex apoptotic response pathways involve burst of energy from the mitochondria of activated APCs (e.g., MCs) to release mediators (e.g., Histamine) and enzymes such as tryptase or chymase, phosphatases, caspases, adenosine deaminase (ADA) and cell surface molecules (e.g., CD 73), also involving aggregation of receptor molecule (e.g., antigen-induced IgE-fcεR and MCs degranulation). These events are energy requiring and produce the required pharmacological effects. The Yin events are followed by shifting away from high energy consumption to utilization of low energy produced in glycolysis and induction of growth pathways to repair the tissue and terminate inflammation (Figs. 2.4 and 2.5).

6 Chronic Inflammation: ‘Immunological Chaos’ in Host Tissue and Initiation of Disease Process. Not All Immune Disruptors Created Equal!

Unresolved inflammation (oxidative stress, chronic, subclinical) was defined as the loss of balance between the two tightly regulated and biologically opposing arms of acute inflammation, Yin (growth-arrest, apoptosis or tumoricidal) and Yang (growth promote or tumorigenic) of immunity. We proposed that sustained oxidative stress could lead to exaggerated expression and co-expression of death and growth factors in susceptible host tissues. Depending on the nature of stimuli (immune disruptor) and/or the extent of expression of growth or death factors, and type and composition of host tissue (e.g., immune-responsive or immune-privileged) loss of balance in

Yin and Yang processes could determine the outcomes of tissue damage. Those immune disruptors (e.g., potent pathogens, strong carcinogens, major trauma), that manage to cause serious imbalance in the homeostasis of immunity, would take advantage of inherent dualities of dynamics of biological responses (feedback control mechanisms) to initiate serious damages in the susceptible tissues and organ systems and induction of chronic diseases [3, 4, 63, 66–68, 81, 82, 92, 109].

In 2009, Khatami proposed that unresolved inflammation was a common denominator in the genesis and progression of nearly all age-associated chronic health problems including site-specific cancers [67]. The extensive alterations or defects in the pathways of immune and non-immune networks, seem to be the principal contributors to increased risks of allergies, asthma, autoimmune and neurodegenerative diseases, hypertension, diabetes and cardiovascular complications, stroke, multiple sclerosis, Hodgkin's, lupus, Alzheimer's, and induction of soft or solid tumors, the illnesses that primarily develop in older adults [3, 4, 63, 66–68, 82]. As detailed in Chaps. 3 and 6, aging process itself induces minor or major alterations in the function of immune and non-immune systems altering the inflammatory response profiles toward new stimuli or accumulated senescent cells [3–5, 21–28, 31–34, 40, 41, 63, 66–68, 82, 92, 196, 217–237].

In brief, shifting from oxidative phosphorylation during Yin, to aerobic glycolysis and the induction of VEGF or HIF1 around neovascular tissue during Yang, are examples of inherent duality of the immune cells, assisted by non-immune systems during initiation and termination of inflammation. Oxidative stress and/or aging process could adversely influence the inherently dual capacity of immunity to generate exact amount of decoy receptors required for termination of inflammation (Yang). Retardation of immunity and expression of mismatched apoptotic or wound healing mediators accompanied by altered oxido-redox potential in tissues are perhaps essential components for immune suppression and initiation of chronic inflammatory diseases or tumorigenesis. In general, alterations in activation-induced cell death (AICD) or damage-induced cell death (DICD) of apoptosis (programmed cell death) are suggested as contributing factors in the dysfunction of immune responses during the aging process [63–68, 109, 221–232].

7 Stem Cells; Shared or Special Features in Innate and Adaptive Immune Cell Responses in Health and Age-Associated Chronic Diseases or Cancer

Antigen presenting cells (APCs), to varying degrees, possess distinct functions for regulation and control of death and survival signals that influence the effector cell function for pharmacological response. The outcomes of specific inflammatory conditions in host tissues are the results of interdependent immune responses. As schematically shown in Fig. 2.6, each immune cell that is generated by stem cells, the giant manufacturer of immune cells, has the capacity to directly or indirectly

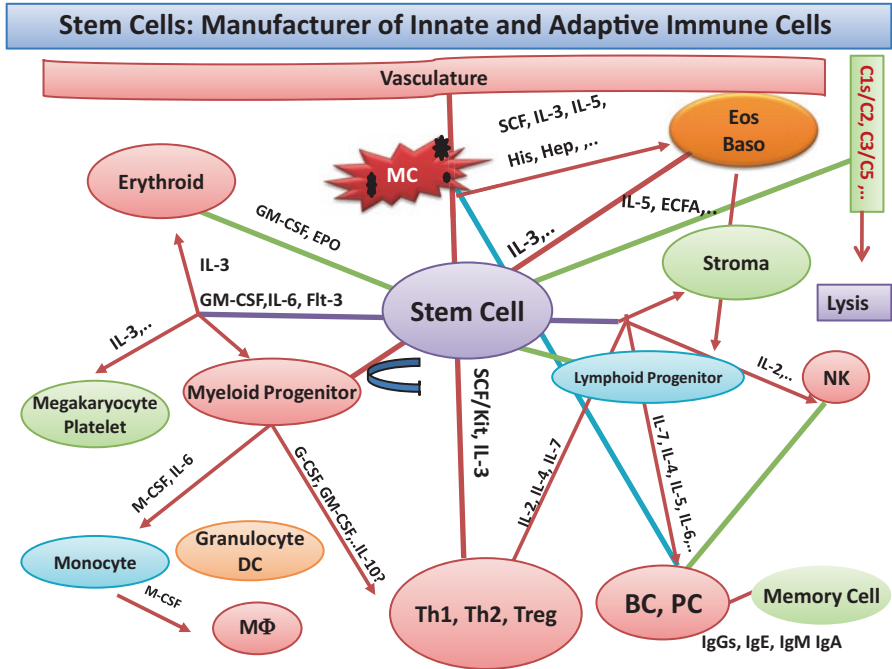


Fig. 2.6 Schematic representation of complex interdependent influence of innate and adaptive immune cells in growth and function of hematopoietic cells. Stem cells considered as the giant manufacturer of all hematopoietic cells whose growth and differentiation to specific immune cells are potentially directed by the signal transductions guided by specific tissues with special immune and non-immune compositions and/or under certain inflammatory conditions and tissue requirements. See text

influence activation, proliferation, differentiation, growth and maturation (polarization) of other immune cells. (Table 2.1) [3, 4, 63, 66, 81, 82, 109].

Depending on requirements of the target tissue and function, innate and adaptive immune cells, and their counter parts in non-immune systems are capable of diverse dual functions to change the dynamics of Yin-Yang balance (tumoricidal: tumorigenic ratio) in acute inflammation. For example, DCs, MΦs or MCs, as well as T or B lymphocytes can be induced to function as polarized cells during, development, maturation, wound healing and in response to tumorigenesis (Fig. 2.6) [3, 4, 63–65, 81, 82, 109]. Growth and maturation of immune cells include maturation and survival of self, or those of T cells subpopulation Th1, Th2 (Treg), transformation of macrophages into M1/M2 (or tumor associated TAMs) phenotypes, mast cells maturation (granulation, IgE Fcε-dependent phenotypes) and degranulation, or they can become IgEfcε-independent ‘leaky’ MCs or TAMCs form, transformation of dendritic cells from immature/tumoricidal (DC1) to mature/tumorigenic (DC2 or TADCs) phenotypes (Fig. 2.6, Table 2.1).

Therefore, pro- and anti-inflammatory signals regulate the levels and efficiency of inflammatory cytokine receptor coupling and amplification of effector function.

Table 2.1 Example of dual (pleiotropy) properties of immune cells and mediators in acute (AI) and chronic inflammation (CI) [3, 4, 63, 67, 109]

Mediator/Factor	Cell polarization	Major biological effects
Toll like receptors (TLRs 1–9)	DC1/DC2 (TADC); M1/M2 (TAM); MC/‘leaky’ (TAMC)	AI: Signal for death factor-Yin CI: Decoy receptor, growth promotion-Yang
Tumor necrosis factor α (TNF- α) and TNFR	DC1/DC2 (TADC); M1/M2 (TAM); MC/‘leaky’ (TAMC)	AI: Induction of apoptosis CI: Decoy receptor, growth promotion
Histamine	MC/‘leaky’ (TAMC)	AI: Vasoactive, apoptosis, IgE-fc ϵ -rec-dependent, vascular hyperpermeability CI: Release independent of IgE- fce-rec, growth promotion
Macrophage colony stimulating factor (M-CSF)	M1/M2/TAM	AI: Induction of apoptosis CI: Decoy receptor, immune suppressor, tumorigenic
Interleukins (ILs) (IL-1- α , IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13,...)	Innate and adoptive immune cells	AI: Apoptosis CI: Decoy receptor, growth

Pro-inflammatory cytokines such as IL-1, IL-6, IL-8, TNF- α , M-CSF, GM-CSF, eotaxin, as wells as, histamine, prostaglandins (e.g., PGF1 α or PGI2), leukotrienes, heparin or enzymes (e.g., chymase, tryptase) other proteases released by activated resident (local) and/or recruited inflammatory cells are capable of contributing to the progression of responses. In all likelihood, increased local concentrations of special mediators produced by resident inflammatory cells signal for expression, interactions and synergies between recruited and infiltrated cells (e.g., eosinophils, MΦs, vasculatures) are requirements of an effective immunity to accomplish a task, such as removal of an infectious agent and repair of damaged host. Details on the roles of immune cells under inflammatory conditions and carcinogenesis are provided in Chap. 6.

8 Differential Influence of Acute and Chronic Inflammation in Immune-Privileged and Immune-Responsive Tissues and Chronic Diseases

Molecular mechanisms that govern the tightly regulated processes of acute inflammation somewhat differ in immune-privileged and immune-responsive host tissues. In general, acute inflammation provides immune protection in target tissues via two mechanisms:

1. Immune surveillance in the immune-responsive tissues for killing of cancer cells, destruction of infective agents/pathogens (stimuli) and resolution of inflammation, remodeling or regeneration of host cells; and
2. Immune ignorance, immune evasiveness and tolerance in the oxidative-sensitive immune-privileged tissues.

8.1 Immune Surveillance (Protection) in Immune-Responsive Tissues

Immune-responsive tissues are generally the sites of initial contact and processing of internal or external stimuli. These tissues include squamous and glandular epithelial tissues, epithelial-associated mucosal surfaces (e.g., goblet cells), endothelial and stromal cells, fibroblasts, lymphoid tissues and vasculature.

The disease outcomes of chronic inflammation-induced immune dysfunction in immune-responsive tissues are a wide range of allergies (e.g., asthma, emphysema, food, ocular or skin allergies), chronic diseases such as hypertension, vasculitis, diabetes and cardiovascular complications, colitis, gastritis, pancreatitis, thyroiditis, esophagitis, psoriasis, lupus, prostatitis and/or cellular growth, hyperplasia, dysplasia, neoplasia/pre-cancer or cancer (e.g., prostate, lung, colorectal, uterine, breast, ovarian, stomach, pancreas, esophagus, bladder, cervix), metastasis and angiogenesis (details in Chap. 6) [3, 4, 63, 66–68, 82].

In certain chronic diseases such as diabetes complications, the hyperglycemia of diabetes is associated with glycosylation of proteins, and accumulation of advanced glycation end-products (AGE) and maillard reactions, complexes that are known to induce inflammatory reactions and interference with antigen-antibody binding [3, 4, 63, 82, 109, 238–240]. AGE, is viewed by tissues as non-self and additional risk factors for induction of not only adult on-set diabetes mellitus (DM) complications (e.g., retinopathy, cardiovascular diseases, hypertension, neuropathy, nephropathy, stroke) but they also increase the risk of several cancers (e.g., liver, pancreas, endometrium, colon, rectum, bladder, breast). The author suggested that the damaging impact of inflammatory responses toward hyperglycemia of diabetes may be different in insulin-dependent (e.g., muscle, adipocytes or liver) or insulin-independent (e.g., vasculature, retina, kidney or neuronal) tissues for glucose transport and utilization, and/or immune-privileged or immune-responsive tissues [3, 63, 109].

8.2 Immune Protection (Tolerance) in Immune-Privileged Tissues

Immunobiology of protection against pathogens, chemical or biological insults in immune-privileged tissues and neighboring cells are complex and not well understood.

Immune-privileged sites, in general, prohibit the processing and spread of pathogen-induced inflammation because these episodes can threaten delicate integrity and function of these stress-sensitive tissues. The most prominent examples of immune-privileged tissues are central nervous system (CNS), blood brain barrier (BBB), ocular tissues [e.g., cornea, neurosensory retina and retinal pigment epithelium (RPE)], hair follicles and reproductive organs (e.g., testis and uterus). Due to low capacities for self-renewal, the immune-privileged tissues are particularly vulnerable toward infections, chemical insults or injuries as even minor persistent inflammation could have long-term effects on survival of these tissues. Immune responses in these tissues either do not proceed, or proceed in a limited fashion that differs from those described for immune-responsive tissues. Induction of inflammatory processes in immune-privileged tissues is restricted by one or a combination of immunological barriers including the absence or limited presence of vasculature (e.g., avascular cornea), lymphatic channels; antigen presenting cells (APCs, Langerhans, microglial or dendritic cells/DCs) and/or immune recognition and adapter molecules (e.g., MHC class I or II, or HLA). These immunological barriers provide 'immune unresponsiveness', 'immune ignorance' or 'immune tolerance' for the immune-privileged tissues. Exposure to foreign elements often results in sequestration of antigen and avoidance of encounter with stimuli which also limits activation of lymphoid tissues for humoral and/or cell-mediated delayed hypersensitivity responses by other antigen presenting cells (Fig. 2.7, Table 2.2) [3, 4, 63, 67, 68, 109, 190, 236, 237, 241–245].

The immunological unresponsiveness in the immune-privileged tissues is termed 'immunological ignorance' or the term sometimes used for immune tolerance [3, 4, 67, 68, 109, 241–244]. In immune-privileged sites, immune protection appears to involve site-specific processes that deal with the invaders before they spread to stress-sensitive tissues. Localized immunity provided in these tissues by immune deviation or immunomodulation that includes active or passive suppression of responses from immune cells (e.g., NKs, DCs or MΦs). Preliminary studies to compare the viability of rabies virus in cultures of bovine retinal pigment epithelial (RPE) with human neuroblastoma cells suggested phagocytic/protection role for RPE cells that prevented virus's survival and propagation (Khatami, unpublished observations). Others reported the immune protection of neuroretina and cornea against pathogens [63, 67, 68, 241, 242].

Table 2.2, shows examples of immunomodulation in immune-privileged tissues, by site-specific expression of growth inhibitors, immunosuppressive cytokines, neuropeptides, limited expression of MHC I, II complex and complement regulatory proteins, as well as increased expression of selective apoptotic or death-inducing factors such as TNF-related ligands (e.g., FasL and TNF-related apoptosis-inducing ligand (TRAIL), heat shock proteins (e.g., α - β -crystalline) or

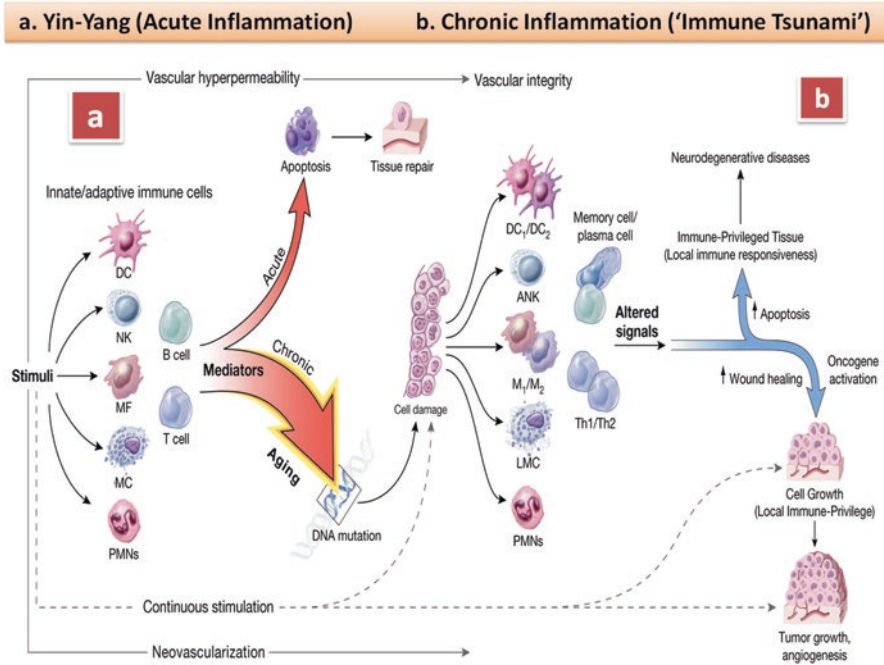


Fig. 2.7 Schematic representation of impact of acute and chronic inflammation in tissue. *Left panel (a)* represents self-terminating property of acute inflammation (Yin-Yang). Stimuli-induced activation of immune cell responses, facilitated by vascular hyperpermeability to defend tissues against stimuli. *Right panel (b)* represents oxidative stress could cause continuous activation of immune cells (e.g., DC1/DC2, M1/M2) that would lead to DNA damage and mismatched or co-expression of wound healing and apoptotic factors to differentially impact immune-privileged and immune-responsive tissues in the direction of altered architectural integrity of tissues and initiation of neurodegenerative diseases or tumorigenesis (Modified from Khatami (EXP Opin Biol Ther. Ref. [68]) with permission. All rights reserved)

proteolytic enzymes to effectively destroy inflammatory cells and limit the spread of inflammation and cell growth and minimize vascular hyperpermeability and neovascularization during exposure to stimuli or pathogenic infections (e.g., bacterial *Staphylococcus aureus*) [63, 67, 68]. Increased expression of selective death-inducing molecules or growth inhibitors are poised to destroy inflammatory cells that would otherwise initiates manifestation of neurodegenerative diseases and oxidative-induced damage to the brain, CNS, induction of endophthalmitis, neovascularization and infiltration of inflammatory cells within the confines of these vulnerable tissues [68].

However, the immune-privileged status of these oxidative stress-sensitive tissues does not provide complete barriers. Immune ignorance in these tissues can be breached when tissues are overwhelmed by infections or sustained oxidative stress, particularly during the aging process (Fig. 2.7). Unresolved inflammation could seriously threaten these stress-sensitive tissues, causing enhanced cell death and increased risk of neurodegenerative and autoimmune disorders such as multiple

Table 2.2 Immune tolerance and structural barriers for inflammatory mediator responses in immune-privileged tissues during acute and chronic inflammatory conditions [63, 68, 236, 237, 241–244]

Structural and response barriers	Acute inflammation	Chronic inflammation (Diseased stage)
Blood brain barrier (BBB)	Brain integrity	Loss of BBB, hemorrhage, stroke (?)
Avascular (cornea)	Limited immune response	Induction of vascular activity
Lymphatic channels NK, Langerhans, astrocytes, microglia, DCs, MΦs	Absence or limited presence- immune deviated	Induction of activity, increased presence/immune responsive
Retinal pigment epithelium/RPE	Immune deviation, informal phagocytes	Loss of phagocytic activity (?) Immune-responsive
Inflammatory mediators		
MHC class I,II or HLA	Limited presence	Activated
Immune suppressive cytokines	Increased activity	Reduced function (?)
FasL, (CD95L) TRAIL, complement proteins	Increased activity	Loss of activity
TGF-β	Expression of T reg (CD4-CD8)	PE (IPE, CBPE, RPE)
M-CSF	Limited expression	Increased activity
NF-kB	Limited expression	Increased activity
Thrombospondin1 (TSP-1)	Provides autoimmunity	Reduced activity (?)
CD86 (B7–2)	Expression (ocular PEs)	Reduced activity (?)
Pigment epithelial-derived factor (PEDF)	Expression (ocular PEs)	Reduced activity (?)
Cytotoxic T lymphocyte antigen-2α (CTLA-2α)	Expression (ocular PEs)	?
Heat-shock proteins (α,β crystalline)	Increased activity	Reduced function (?)
S100A (neutrophils-derived)	Increased activity (clearance)	Loss of activity (?)

sclerosis and demyelination of CNS, encephalomyelitis, stroke or Alzheimer's, ocular inflammatory complications as well as, induction of cell growth and tumorigenesis [3, 63, 67, 68, 109]. Chronic inflammation-induced expression of mediators such as GM-CSF, neuron-, or antigen-reactive lymphocytes have been demonstrated to break the immunological barriers via activation and cross-presentation of MHC class I/II to T cells (CD8 subtypes) in immune-privileged tissue causing collateral and serious damage to tissues (e.g., demyelination and axonal or cellular degeneration). Studies on pathobiology of Alzheimer's disease suggest that inflammatory cells, such as microglia, and deposition of complement proteins (e.g., C3, C4) and expression of wound healing or growth factors such as NF-kB or GM-CSF are involved in the genesis of amyloid precursor proteins (APP) plaque formation and

changes of astrocyte subpopulations [26, 42, 63, 68, 197, 198, 244]. Similarly, reports on neurodegenerative diseases demonstrated that neuron- or antigen-reactive lymphocytes can escape immune tolerance and break the immunological barriers via cross-presentation of MHC class I/II to T cells (CD8 subtypes) and invade the tissues (e.g., ocular anterior chamber, retinal and neuronal tissues, CNS or brain) resulting in collateral tissue damage. The anti-inflammatory property of the intra-ocular environment is critical to the survival of immune-privileged ocular tissues. Induction of oxidative stress and alterations in the immune protection and clearance properties of ocular tissues are important factors in several blinding disorders, including age-associated macular degeneration, uveitis, ophthalmitis, corneal inflammatory and diabetic ocular complications (e.g., retinopathy, neuroretinopathy or retinopathy of prematurity) [63, 68, 241–243].

In certain neurodegenerative diseases such as multiple sclerosis or acute encephalomyelitis, or uveitis, it has been shown that neuron- or antigen-reactive lymphocytes can escape immune tolerance and invade the tissue (e.g., CNS) and induce significant tissue damage (e.g., demyelination and axonal degeneration) [42, 45, 63, 68, 241–244].

In summary, significant dysfunction of immune responses and progressive erosions of natural integrity in both immune-privileged and immune-responsive host tissues could be a foundation for genesis of the majority of age-associated chronic illnesses. Inflammation-induced increased expression of apoptotic factors could cause major shifts in local immune responsiveness and integrity of immune-privileged tissues that lead to neurodegenerative or autoimmune diseases. On the other hand, exaggerated co-expression of wound healing and selected apoptotic factors could induce local immune-privilege (immune tolerance, immune evasion) and loss of immune surveillance in the immune-responsive tissue, in the direction of growth promotion, neoplasia, cancer, metastasis and angiogenesis (Fig. 2.7).

We hypothesized that there are comparable mechanisms of actions in potent pathogens-induced severe acute inflammatory diseases (e.g., sepsis, or shock, meningitis or respiratory distress syndromes) with life-threatening side effects of cancer claimed ‘targeted’ drugs that cause cachexia, anorexia, sarcopenia and/or relapse [3, 63, 68]. Both conditions induce ‘cytokine storm’ or ‘immune tsunami’ that increase the risk of multiple organ failure (MOF) or death, due to rapid induction of immune dysfunction that otherwise occur over a longer periods of time. In acute inflammatory diseases, the prominent presence of mediators in host tissues is due to severe pathogen-driven expression of excessive amounts of apoptotic factors and toxic materials (tumoricidal) that could occur at any age. Under these conditions, it was suggested that strong pathogens would bypass orderly immunological processes by first destroying the integrity of the vasculature and gaining direct access to tissues causing induction of large amount of pro-inflammatory mediators that are toxic to host tissues [3, 55, 63, 68].

9 Clinical and Immunological Features of Immune Deficiencies

Recent studies have advanced the notion that chronic inflammation is a major risk factor underlying aging and age-related diseases. We suggested that low-grade unresolved inflammation is a common denominator in nearly all age-related pathological processes [3, 4, 63, 67, 68, 109]. Continuous (chronic) upregulation of pro-inflammatory mediators (e.g., TNF- α , IL1 β , COX2, iNOS) induced during the aging process due to redox imbalance may activates many anti-inflammatory signaling pathways, including NF- κ B and kinases that could inappropriately induce expression of factors in the direction of chronic illnesses such as increased allergies, atherosclerosis, arthritis, or benign or aggressive tumor growth.

The following sections describe bird's eye view on interrelated examples of inflammatory mediators, during acute and chronic inflammation in health or aging process in the direction of multistep tumorigenesis and angiogenesis. The roles that APCs play in immunity are at the center of critical decision of the immune system dynamics. That is because APCs are responsible for capturing antigens or pathogens in the periphery and migrating to the lymphoid organs and presenting the processed peptides and viral/bacterial particles to T cells for priming for either tolerance or induction of a response. The extent of expression of mediators from activated immune and non-immune cells is likely to influence the outcomes of inflammation as summarized in the following (details in Chap. 6) [3, 4, 63, 66–68, 81–100, 109]:

- (a) **Angiogenesis and expression of VEGF (HIF-1):** Formation of new capillaries is a normal process occurring in wound healing (Yang or resolution of acute inflammation), embryonic and placental development, ovulation, chronic inflammation, as well as induction of chronic diseases, tumor growth and metastasis. Angiogenesis is a key event in tumor growth and progression. The most important signal that links these different angiogenic-dependent processes is perhaps the degree of cell hypoxia. Nearly all of the components of the wound healing (Yang responses in acute inflammation, tumorigenic arm) or chronic inflammation-induced angiogenic processes have shared characteristics with the angiogenesis occurring during tumor growth and metastasis. Under oxidative stress, polarized immune cells such as macrophages produce proangiogenic, as well as antiangiogenic molecules that could cause damage to the integrity of blood vessels. For example, M-CSF-induced TAM-derived metalloelastase generates angiostatin. Irregular vascularization (neovascularization) and hypoxia are characteristics of hyperplastic and neoplastic tissues which also affect macrophage infiltration/migration, distribution and function in affected tissues [3, 4, 56, 60, 63, 66–68, 92–109, 195]. TAMs accumulate preferentially in poorly vascularized regions of tumors characterized by low oxygen tension. TAMs or skewed M2 population have altered antitumor properties; they are less mobilized or immobilized in poorly vascularized and avascular or necrotic and hypoxic areas of tumors or perhaps hyperplastic tissues. Compelling

elegant studies show that hypoxic cells, particularly tumor cells, initially respond to stress by expression of vascular endothelial cytokine, originally known as hypoxia-inducible factor 1 (HIF1), or vascular endothelial growth factor (VEGF) to increase the genesis of vessel growth in an attempt to compensate for the lack of sufficient oxygen. The functional changes associated with expression of transcription factors HIF-1 HIF-2a or VEGF, bFGF and CXCL18 result in amplification of tumor angiogenesis [3, 4, 56–60, 62, 63, 66–68, 100, 109, 169, 195]. In human glioblastomas, highly expressed VEGF are identified near focal necrosis and hypoxic area where the new capillaries alongside VEGF-producing cells are localized. The extent of tumor hypoxia and angiogenesis in immune-responsive tissues likely determine the extent of tumor growth. In immune-privileged tissue, oxidative stress and induction of hypoxia could cause changes to the avascular tissues (e.g., cornea) causing local tissue immune responsiveness and vascularization, bypassing immune tolerance in these stress-sensitive tissues (Fig. 2.7, Table 2.2).

- (b) **Oxidative damage: generation of ROS and RNS and physiological consequences:** The free radical theory has been primarily related to the damaging effects of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and their intermediate superoxide components that are produced during inflammatory responses to destroy various toxins (Figs. 2.1 and 2.2). However, generation of ROS and reactive RNS is part of normal metabolism of tissues and byproducts of oxidative metabolism. Under normal metabolism, the generation of these molecules is routinely and effectively neutralized by a wide range of cellular reducing powers and scavengers of oxidants [e.g., superoxide dismutases (SODs), NADH/NAD⁺, NADPH/NADP⁺ reductases, ascorbate-semidehydroascorbate reductase, vitamin E and glutathione recycling pathways], as well as, the presence of reducing metal ions (e.g., Zn²⁺, Fe²⁺, Mg²⁺) within cellular components (e.g., Hb, albumin, mitochondria, Golgi apparatus, plasma membrane). The advanced damaging effects of enhanced state of oxidation (e.g., accumulation of free radicals and decrease in ratio of redox potentials) on biological systems toward initiation and promotion of chronic diseases such as cancer have been extensively documented [3, 4, 36, 63, 66–68, 71, 81, 82, 90, 118–124, 210, 245, 246]. Routine quantification of a panel of inflammatory mediators or the status of oxidative stress (e.g., histamine, TNF, PGs, neurotransmitters, CRP, NAD⁺/NADH) to determine the status of individual health over the years, and to target for early detection of cancer, perhaps would be effective diagnostic methods of personal health. An example of dual roles that inflammatory cytokines play in carcinogenesis is tumor necrosis factor-alpha (TNF- α), a cysteine-rich family of cytokines and receptors. TNF- α is involved in maintenance of tissue homeostasis and elimination of cells with damaged DNA, pathways in apoptosis (Yin) or programmed cell death. Environmental, chemical or biological stimuli (exogenous or endogenous) can trigger the synthesis and production of TNF- α in a variety of cell types such as macrophages, T cells (Th1, Th2), MCs, or keratinocytes. The

TNF-receptors (e.g., TNFR-1, TNF-Rp55, TNF-Rp75) act as transducers of TNF by receiving and transmitting signals that trigger inflammatory responses. The TNFRs signaling is involved in mediation of a wide range of biological functions including cytotoxicity/cell death; antiviral activity; fibroblast or thymocyte proliferation, as well as induction of superoxide dismutase and NFkB activation. Accumulation of free radicals or oxidative stress will cause damage to cell components leading to inappropriate expression of decoy receptor proteins for TNF (TNF α R) or chemokines and create unresolved inflammation. Unresolved inflammation leads to damages, to varying degrees, of microstructure of tissue chromosomes or mitochondrial DNA (mutations), as well as cellular proteins or lipids and alterations in the immune system response dynamics and the function and integrity of host. An important damaging effect of oxidative stress is progressive alterations and decreases in energy output by mitochondria below the requirements of tissues that lead to hypoxia-induced growth promotion in immune-responsive tissues [63, 67, 90, 118–124, 210, 245–248] (Figs. 2.2 and 2.7, Table 2.1). In stress-sensitive immune-privileged tissues, accumulation of ROS could lead to destruction of immunity, induction of local immune-responsiveness, tissue necrosis and initiation of neurodegenerative diseases (Fig. 2.7). In brief, chronic inflammation (oxidative stress) and accumulation of ROS, RNS and superoxide radicals would increase, to varying degrees, the rate of damage to plasma and intracellular membranes and nuclear components, leading to DNA/RNA mutations and altered oxidative metabolism and bioenergetics of tissues toward the induction of hypoxia that further damage the integrity of vascular endothelial membrane structure and tissue function.

- (c) **Natural Killer Cells (NKs):** NKs have critical roles in tumor immune surveillance, infections, autoimmunity and hematopoietic stem cell transplants. NKs exhibit cytotoxicity against a number of inflammatory conditions in oxidative stressed tissues by secreting a number of mediators that facilitate adaptive immune responses (Fig. 2.6). NKs share many similarities with cytotoxic T cells (CTCs) including expression of cell surface receptor molecules for perforin-dependent killing activities or NK cell-mediated lysis. However, NKs are distinct from CTCs since their inherent cytotoxicity is independent from adaptive role of MHC-related sensitization of T lymphocytes [4, 32, 49, 63, 66–68, 109, 128, 163]. While NKs cytotoxicity features have been recently considered for cancer immunotherapy, the effective use of these cells is yet to be demonstrated. As with other innate or adaptive immune cells, phenotype presence of NKs (tumor-associate NKs, TANKs) in tumor microenvironment assists immune evasion and facilitates enhanced growth requirements of tumor cells perhaps due to expression of decoy receptors or surface molecule that retards their cytotoxicity.
- (d) **Macrophages (M1/M2 or TAMs):** As noted above, under oxidative stress, activated MΦs (increased M2/M1 or TAMs) could induce over-expression of monocyte-(MΦs)-colony stimulating factor-1 (MCSF-1) and/or its receptor c-fms in tissues and contribute to the tissue hyperplasia and tumorigenesis in conjunctival-associated lymphoid tissues (CALTs), vascular dysfunction,

mammary glands of transgenic mice, human ovarian adenocarcinoma and other gynecological cancers and metastasis [3, 4, 37, 52, 58, 60–63, 66–68, 73–76, 87, 88, 93, 94, 109, 175, 194, 195]. Clinical features of phagocytic disorders are often found in individuals suffering from lymphadenitis, skin and visceral abscesses, cellulites, and gingivitis. Activated MΦs (TAMs or M2) and eosinophils that are recruited by tissues (e.g., conjunctiva or perhaps lung airways or gut-associated lymphoid tissues) whose principal resident immune cells are MCs and lymphocytes were suggested to play crucial synergistic roles in enhancing the growth promoting capacities of host toward tumorigenesis [3, 4, 63, 109]. Increased proliferation of neoplastic tissue is associated with increased requirements for nutrients and growth factors and induction of hypoxia. High efficiency of pro-neoplastic M2 (TAM) activity relates to their ability to accumulate and function under the oxygen-deficient regions of the tissue. In addition to over expression of MCSF, TAMs express and release an array of growth and pro-angiogenic factors that are concurrently chemotactic factors (decoy receptors) for monocytes and macrophages and act as tumorigenic or scavengers of oxidants during growth promotion and signals for abnormal growth promotion (skewed wound healing). Therefore, growth promoting factors that are normally expressed during Yang event to terminate inflammation can be excessively expressed in the hypoxic environment of accumulated TAM for expression of VEGF, bFGF, CXCL8, PDGF, EGF, and TGF- β . Factors such as PDGF promote the proliferation of neoplastic tissue and acts as a pro-angiogenic mediator for recruiting pericytes and stabilizing the newly formed vessels. Epidermal growth factor (EGF) stimulates neoplastic cells to synthesize and release M-CSF. Aside from the chemotaxis of macrophages (M2 or TAM phenotype), M-CSF1 induces differentiation and migration of peripheral monocytes that result in the enhanced infiltration of macrophages into the tumor microenvironment and enhanced expression of EGF, further influence induction of MCSF and expression of decoy receptors that would additionally facilitate macrophage-dependent intensive proliferation of neoplastic cells. MCSF-1 binding to its receptor molecule c-fms, a cell surface family of tyrosine kinase receptors, results in dimerization and phosphorylation of c-fms, the signaling requirements for macrophage proliferation to M2 phenotype to facilitate growth. We suggested that over expression of M-CSF from M2 phenotypes produces signals that are cumulative and synergistic with host mediators (e.g., low levels of histamine released into the media from ‘leaky’ MCs, independent of IgE-fc ϵ R binding) causing tumor-directed expression of decoy receptors and immune suppressive factors (e.g., TNF α , IL-5, IL-10, TGF- β , PGE2) [3, 4, 63]. Furthermore, in their role as pro-inflammatory cells, MΦs are involved in stroma remodeling releasing a slate of pro-inflammatory factors that constitute a signal of danger for immune cells. The outcomes of MΦs activities and polarization in tissue contribute to; (a), activation of cytotoxic T lymphocytes and NK cells; (b), infiltration of dendritic cells; (c), migration and differentiation of monocytes in a pro-inflammatory state (Figs. 2.2 and 2.4). M-CSF was suggested a suitable biomarker for cancer diagnosis and technology development

because of its superior sensitivity and specificity, compared with conventional cancer biomarkers (e.g., CA-125, CA-19-9) (details in Chap. 6) [3, 4, 63, 109, 141].

- (e) **Mast cells activation:** As discussed above, MCs activation usually occurs when IgE bound to high affinity Fcε receptor (FcεR1) on the surface of MCs cross-linked by allergen to trigger degranulation and release of preformed granule-derived mediators and proteases (effector function). Degranulation of mast cells also includes synthesis and release of newly formed lipid products (e.g., phospholipids, arachidonic acid metabolism and synthesis of prostaglandins and leukotrienes), activation of membrane enzymes (e.g., phospholipases-PLA, PLC, phosphatidylserine) and transcription of a number of cytokines that produce pharmacological effects in target tissue [3–12, 17, 38, 63, 66–68, 87, 89, 120–124, 137, 144, 159, 196, 232–234, 249, 250]. Oxidative stress-induced changes in MCs function and integrity have been associated with induction of a number of chronic allergies (e.g., asthma, emphysema, dermatitis, conjunctivitis) and cellular growth promotion and tumorigenesis, angiogenesis or cancer metastasis [3, 63, 66–68, 87, 89, 120–124, 137, 196, 249, 250].
- (f) **Dendritic cells maturation:** As professional APCs, DCs are crucial for the initiation of primary immune responses. They form a network of innate or sentinel cells in the periphery to recognize, capture and transport/ferry pathogenic antigens to secondary lymphoid tissues for further processes. Immature DCs (DC0 s) in the blood can undergo polarization into immature type 1 dendritic cells, also known as DC1 (Yin response), and mature type 2 dendritic cells, known as DC2 or tumorigenic phenotype TADCs (Yang response), during migration under the influence of a variety of growth factors, cytokines/chemokines such as IL-1β, IL-10, and receptor molecules to terminate inflammation and cause immune suppression [3, 4, 42, 63, 109, 158, 166, 174, 244]. The inflammatory signals that are involved in DCs maturation and migration to lymphoid organs, simultaneously induce a chemokine receptor switch, which normally cause down-regulation of inflammatory receptors (e.g., CCR1, CCR2, CCR5) and induction of CCR7 to terminate and resolve inflammation. Concomitant exposure to lipopolysaccharide (LPS) and IL-10 blocks the chemokine receptor switch associated with DC maturation [3, 4, 29, 42, 43, 79, 158, 166, 174, 175, 244]. LPS + IL-10-treated DCs showed low expression of CCR7 and high expression of CCR1, CCR2 and CCR5 and become growth-promoting mediators. Furthermore, uncoupled receptors expressed on LPS+ IL-10-treated cells sequester and scavenge inflammatory chemokines and potentially signal for expression of imbalanced growth factors, to create unresolved inflammatory environment that scavenge the apoptotic factors and oxidants. Thus, in an inflammatory environment, it seems the mature phenotype of DCs (DC2) generates IL-10 functional decoy receptors on DCs and/or perhaps other monocytes in an attempt to terminate and resolve inflammation. Sustained oxidative stress suggested to cause a decrease in the ratios of DC1:DC2 (TADCs) leading to exaggerated expression of wound healing mediators in the direction of immune suppression and cell growth promotion. Since small numbers of DCs

are sufficient to induce an immune response, DCs can act as the most potent stimulators of T cells. Furthermore, DCs are the only APCs able to present novel antigens to resting naïve T cells (T0) and initiate the primary immune response. For this reason, DCs are prime targets for immunotherapy. Owing to the highly specific and important roles of DCs in body's defense, any minor modulation in DCs function could result in significant alterations in immune responses [14, 29, 63, 78, 152, 166, 174, 175].

- (g) **B cell memory function:** Analyses of data from several studies on the induction of activities and transformation of B cells into plasma cells and genesis of B memory cells, induction of tolerance and humoral immunity (HI), suggest that oxidative stress and/or aging lead to repertoire maturation of these cells to proceed at lower pace. In some instances memory B cells exhibit autoreactivity and population shifts that influence CMI such as T cell effector responses, proliferation and cyclin D2 expression and altered antibody response profiles [3–5, 7, 13, 16, 25, 30, 48, 63, 79, 82, 109, 142, 147, 149, 184, 249, 251, 252]. The minor or major changes in the ratios of Th1/Th2 (CD4+/CD8+) potentially contribute to the altered immune response dynamics of lymphoid tissues and vascularization of lymphatic channels in affected tissues. Categories in clinical features of B cell-derived immunodeficiencies relate to primary deficiencies in IgA antibodies, IgG subclass (e.g., IgG1/IgG2 or IgG3), common variable immunodeficiency (CVID), complement deficiency, and specific antibody deficiency of normal immunoglobulins. Clinical features of disorders in the function of B lymphocytes and antibody production include recurrent sinopulmonary infection, sepsis, aseptic meningitis, autoimmune diseases, dermatitis, and increased incidence of malignancies [63, 109, 235, 249, 252, 253]. Deficiencies in complement cascades are often associated with pyogenic bacterial infections, neisserial meningitis, and autoimmune diseases. However, some immunodeficiencies (e.g., IgA antibodies) are clinically asymptomatic. In such cases, the inherent pleiotropic ability of immune cells, is likely to compensate and overcome the genetically defects in biological functions of such abnormalities, particularly in younger individuals. The role of dysregulated autophagy and hyperglycemia-induced glycosylation of immunoglobulins in regulation of B cells and biosynthesis of antibodies have been identified as contributing factors in B cell-related immunodeficiencies, malignancies and metabolic disorders [63, 79, 109, 239–241, 245, 248, 249].
- (h) **T effector lymphocytes.** In human, T cell antigen receptors (TCRs) couple in millions of combinations that enable them complex and unique repertoires for each individual processed antigenic molecules. TCRs recognize processed foreign peptides bound to major histocompatibility complex classes (MHC I, II) proteins and lipid antigens, such as *Mycobacterium tuberculosis* during infections. Detailed analyses of data indicate that the antimicrobial activities of MHC class I and II and expression of inflammatory cytokines (e.g., TNF α , INF- γ) induced by T helper subclasses (e.g., Th1, Th2, Treg, Th17), and/or involvement of regulatory phenotypes (e.g., CD4(+)CD25(+)CD127(lo)CD45RA(+) and CD4(+)CD25(+)CD127(lo)CD45RA(-)...), present highly

complex polymorphic organizations in a wide range of inflammatory conditions, aging and therapies including Crohns' disease, graft vs host disease, diabetes complications, dermatitis or cancers [61, 63, 67, 109, 127, 163, 176–178, 181–184]. That is to say any given foreign protein sequence encoded by HLA-A, HLA-B, HLA-C, HLA-DP and HLA-DQ loci can bind many peptides for a response. Aging or repetitive stimulation of host cells with antigens or mitogens could retard the competency of T cells, which influence B cell production of antibodies against specific antigens that are T cell dependent (TD) and require appropriate help from CD4+ T cells in the form of cytokines and cell-cell contact. Age-induced thymic involution leads directly to a decreased production of both naïve T cells and ultimately, a decrease in repertoire diversity of T cells in the periphery [3, 4, 31, 61, 63, 67, 78, 92, 102, 109, 127, 153, 176, 177, 178, 180, 182–184, 188, 204, 222–224, 231]. However, as in the case of B-lymphocytes, the total number of circulating T cells does not appear to decrease with age, despite the decline in thymic production. These observations are suggestive of subtle changes in subpopulation distribution of T cells that result in significant accumulation of long-lived memory T cells production. Furthermore, the homeostasis of circulating T cells in older adults seems to be due to the development of extra-thymic T cell. It is reasonable to predict that age-induced increase in the presence of memory T or B cells are viewed by immune system as 'antigen overload' or oxidative stress and contributors of tardiness of immune response (immune suppression) toward new or old immune disruptors. In general, the clinical features of T cell immunodeficiency disorders often include failure to thrive, increased viral opportunistic infections (e.g., pneumonia, HIV), frequent and prolonged or severe infections, disseminated infections with unusual organisms or organisms of low virulence, chronic diarrhea, hematologic disorders, dermatitis and increased incidence of cancer malignancies (details in Chap. 6) [109, 184, 217–222, 245–246].

- (i) **Cell surface markers of APCs:** Analyses of data from multiple experimental studies demonstrate that in general, long-standing chronic inflammation and aging process produce minor or major defects in the co-stimulatory activity of APCs, through surface marker regulation that contribute to the altered immune dynamics and retardation of the recognition phase of immunity. For example, specialized dendritic cells (DCs) or the follicular DCs (FDCs), have distinct function in antigen presentation to T cells through binding of immune complexes. Oxidative stress and aging cause FDCs to express considerable amount of cell surface molecules and complement receptors; but the serum levels of complement proteins seem not reflective of DCs surface molecules. This is perhaps due to the induction of immune complexes with surface molecule ligands such as CD21 (CD21L) to retard responses for B cell activation during aging or perhaps under long-standing chronic inflammatory conditions [3, 4, 46, 60, 63, 67, 102]. Oxidative stress-induced continued DCs polarization from DC1(tumoricidal) to DC2 (or TADCs, tumorigenic phenotypes) could retard the capacity of DCs to capture antigen, and present the processed antigen to T cells. This is potentially due to increased expression of surface molecule

involved in chemotaxis and T cell activation of major histocompatibility complexes I and II, and costimulatory surface molecule CD-40 [3, 4, 63, 66–68, 82–87, 109, 229]. Mature DC2 also produce T cell stimulatory cytokines IL-12 and IFN- γ during wound healing processes. Under normal conditions (acute inflammatory responses), soon after antigen specific interaction with T cells occurs, mature DCs undergo apoptosis via CD40 and FAS ligation, a mechanism suggested to control unnecessary and excessive activation and expansion of T cells [63, 109, 184, 227–229, 234]. Partial activation of CD4 T cells suggests contribution to tolerance by resting B lymphocytes [184].

- (j) **Antigen-induced altered prostaglandin synthesis:** Metabolism of membrane arachidonic acid and induction of activities of cyclooxygenase and lipooxygenase pathways that results in synthesis of prostaglandins (e.g., PGI₂/PGF1 α , PGE₂) during acute and chronic inflammatory conditions have been extensively studied [3, 4, 17, 63, 66–68, 82, 109]. Increased expression of cyclooxygenase observed in LPS-stimulated macrophages, or perhaps aged DCs or during chronic inflammation would lead to enhanced production of growth promoting PGE₂ and decreasing the ratios of PGI₂ (PGF1 α). The enhanced production of PGE₂ contributes to the age-, or inflammation-induced immune suppression and inhibition of T cell function, changes in CD4⁺:CD8⁺ ratios, or perhaps induction of such enzymes as urokinase receptor (CD87) in tumor growth and angiogenesis [3–5, 15–17, 60, 63, 66–68, 81, 82, 109]. Analyses of data also suggest that aging and/or chronic inflammation failed the expression of phosphatidylserine in macrophages or fibroblasts that is required for recognition and ingestion of antigens and proper apoptosis. In contrast, reports on aging and oxidative stress seem to activate phosphatidylinositol-3 kinase PI3K, in MCs or other APCs leading to the induction of PGE₂ and immune suppression and cell growth [63, 246, 247, 252–256].

Although it is not clear how inflammation influences the disease outcomes, one can intellectually argue that the combination of minor or major cellular/biological, genetic or immunological defects, at multi-level crosstalk of immune and non-immune systems could retard the balance between Yin (tumoricidal) and Yang (tumorigenic) of acute inflammation, particularly during the aging process. Defects in immune response pathways include one or combination of changes in the dynamics of cellular or humoral immunity (CMI, HI) and/or loss of exact biological signaling among immune and non-immune (e.g., vasculature, metabolism or neuronal) pathways that contribute to altered tissue bioenergetics and initiation of diseases. Therefore, longevity and frequent stimulation of tissues (antigen burden, oxidative stress) could induce exaggerations of the expression and co-expression of cellular and humoral response profiles to create an ‘immunological chaos’ and loss of balance between Yin (tumoricidal) and Yang (tumorigenic) properties of acute inflammation.

10 Challenges in Understanding Dynamics of Immune Responses and Inflammation

Maintenance of the balance between ‘Yin’ (tumorcidal) and ‘Yang’ (tumorigenic) properties of acute inflammation, is most likely a key to host defense mechanisms in preventing or delaying the onset of chronic illnesses such as neurodegenerative and autoimmune diseases, or induction of hyperplasia, neoplasia, tumor growth, cancer metastasis and angiogenesis. Strategies for promotion of the inherent ability of innate immune cells, can potentially influence proper polarization of other cells within innate and adaptive immune system including Th1 and Treg and improve the natural ‘tumorcidal’ versus ‘tumorigenic’ properties of defense mechanism [3, 4, 63, 66–68, 82, 109]. Recent approaches in immunotherapy that consider promotion of innate and adoptive immunity, through active and/or passive methods of stimulation of tumor-associated antigen or induction of monoclonal antibodies and/or enhancement of innate and adaptive immune cell defense capacity (e.g., T cells MHC complex I and II or death factors ability of DCs) are encouraging. However, there are important scientific considerations and biological gaps in conducting such studies to be effective as outlined below (details in Chaps. 5 and 6) [3, 63, 109].

Major challenges in better understanding the complexity of dynamics of immune/inflammatory responses in maintenance of health or initiation of chronic diseases or site-specific cancers include:

1. Lack of systematic studies in identification of early immune response profiles toward a wide range of immune disrupters (stimuli) that could potentially be controlled or reversed or prevented from advancing to ‘mild’, ‘moderate’ or ‘severe’ immune disorders.
2. Lack of understanding of the heterogeneities in immune and non-immune cell compositions of site-specific tissues, and variations of interactions and synergies between host/tissue resident immune cells and those recruited cells/factors activated and infiltrated to the host tissue. Detailed understanding of the composition and heterogeneities of immune and non-immune cell responses in site-specific tissue with host-pathogen should be the primary focus of future studies. In our studies on experimental models of acute and chronic ocular inflammatory diseases, we discovered that repeated challenges with antigen caused partially granulated mast cells (exhausted or ‘leaky’ MCs) to sequentially signal for recruiting other activated inflammatory cells (e.g., eosinophils and macrophages) at the site of injury contributing to the developmental phases of immune dysfunction toward tumorigenesis and angiogenesis. In the immune-responsive tissues, such as lung airways, gut-associated lymphoid tissues (GALTs) or conjunctival associated lymphoid tissues (CALTs) whose primary immune cell compositions are mast cells and lymphoid tissues, the response profiles are perhaps somewhat different from those whose primary immune cell

composition are MΦs or dendritic cells [3–5, 63, 66–68, 81, 82, 109] (details in Chaps. 4 and 6).

3. Heterogeneities in antigen clearing effects and immune response profiles (strong or weak acute inflammatory reactions) are among important challenges because the extent of antigen permeability and access to inter-epithelial and sub-epithelial cells in tissues that are immune responsive may produce significantly different outcomes. We suggested that a strong type 1 reaction could restrict the penetration/exposure of antigen to trans-epithelial surface by an outward flow of fluids (e.g., mucus secretion, tearing or copious leakage of vascular plasma from hyperpermeable vasculature) in protecting host during acute inflammation. However, whether increased or repeated exposures to stimuli and cumulative permeability of low levels antigens or low level release of histamine from exhausted MCs would predispose the epithelial tissue toward antigen penetration and tissue damage are among biological gaps that deserve further investigations. Furthermore, a weak initial type 1 response due to defects in structure or function of MCs, B/plasma cells or GCs, may result greater net promotion of antigen penetration and/or increased epithelial exposure to higher doses of antigen or environmental toxins for inducing damages to tissues [3–5, 16, 17, 63, 66–68, 81, 82, 109].
4. Poor understanding of host-pathogen interactions and extent of immune response alterations in multistep disease processes.
5. Lack of understanding in minor or major heterogeneities of immune-biological response profiles in individuals, toward potential carcinogens (external and internal stimuli) that body recognizes hazardous to its survival, particularly during aging process.
6. Major biological gaps in the role of immune protection in immune-responsive and immune-privileged tissues, as well as difference in response profiles in insulin-dependent or insulin-independent tissues, for glucose transport or metabolism, toward oxidative stress.
7. Lack of knowledge in potential differential characteristics of mitochondrial development and function for energy requirements in tissues during stages of life; fetus growth and development, after birth and adulthood and aging and disease processes. It was recently suggested that the bioenergetics of mitochondrial development and function parallel the features of high energy requirements (oxidative phosphorylation from mitochondria) for tumoricidal (Yin) and low energy requirements (from glycolysis) of tumorigenic (Yang) pathways at different stages of life (details in Chap. 6) [109].

11 Concluding Remarks

Acute inflammation is a molecular village of complex signaling and energy requiring biological events between and among immunological, neuronal, hormonal vascular, genetic and physiological responses toward intrinsic (internal) and extrinsic

(external) stimuli to guard and maintain the body's health throughout life. In an effective immunity, immediate (acute) hypersensitivity reactions are initiated by a highly regulated and exquisitely precise pro- and post-inflammatory crosstalk between local and systemic immune and non-immune systems for the purpose of neutralizing and eliminating the hazardous components while repairing the damaged host tissue.

Dysfunction of immunity and development of abnormal cell growth promotion and/or tissue necrosis that often are manifested as age-associated chronic diseases, such as neurodegenerative and autoimmune diseases or benign and malignant tumors and angiogenesis are perhaps the results of slow and progressive alterations in the dynamics of biological response profiles of persistent and unresolved inflammation. The nature and extent of exposures to intrinsic and extrinsic biological hazards together with age-induced altered hormonal, metabolic and immunological changes are likely the determining factors in homeostasis of immune surveillance and the risks of chronic diseases. Identification and understanding of developmental stages of immune response dysfunction in initiation of 'mild', 'moderate' or 'severe' immune disorders that are manifested as different diseases in immune-responsive or immune-privileged tissues deserve systematic and careful studies.

With regard to cancer, a single most pointing question that needs to be addressed for future research directions is how the growth-arresting properties of acute inflammation that is the body's defense mechanism, switch to growth-promoting function under persistent inflammatory conditions in the genesis of benign or malignant tumors. Similarly, how altered immunity could lead to tissue necrosis in immune-privileged tissues and genesis of neurodegenerative or autoimmune diseases or metabolic disorders. To answer such questions systematic studies of the dynamics of inherent properties of tumoricidal vs. tumorigenic (Yin-Yang) of acute inflammation are the first steps toward understanding the complex biology of immune surveillance and the mechanisms that are involved in controlling the growth of tissue, or induction of necrosis. Focusing on the promotion of the balance between tumoricidal (Yin or apoptosis) and tumorigenic (Yang or wound healing) of acute inflammation including the differential energy requirements of the two arms of immunity could provide unique opportunities and challenges toward effective approaches to combating illnesses, developing universal vaccines for preventing diseases or treating a wide range of immune disorders including cancer for a healthier growing population around the world.

Detailed integrated studies of molecular complexes of chemical and bioenergetic signaling that fall into the biological roadmaps of factors that contribute to the maintenance of body's anabolic and catabolic molecular resources deserves careful and detailed studies. The search for answers into biology of health starts with systematically understanding of how a well orchestrated biological system can be disturbed by aging process or sustained oxidative stress.

The author's original definitions of Yin (tumoricidal) and Yang (tumorigenic) properties of effective immunity may serve larger applications for understanding the biphasic (dual) activities of system biology in sustenance of health or initiation of diseases.

Throughout this book attempts were directed to demonstrate that:

- (a) Cancer is an induced disease of Twentieth century, facilitated by medical/cancer establishment for huge corporate profit;
- (b) Cancer is a symptom of violations of time-controlled biological circadian rhythms with differential bioenergetics.

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Inflammation, Aging and Cancer
Biological Injustices to Molecular Village of Immunity
that Guard Health

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