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# Inflammation, Aging and Cancer: Friend or Foe?

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## 1. Introduction

Rudolph Virchow, in the 19th century noted that "*the signs of inflammation are four; redness, and swelling, with heat & pain*". Since this historical observation, the role of inflammation in the genesis and progression of many acute diseases (e.g., sepsis, pneumonia, meningitis or major trauma), allergies (e.g., asthma, emphysema, skin and ocular inflammatory diseases), age-associated chronic, neurodegenerative, autoimmune and other inflammatory diseases (e.g., hypertension, colitis, gastritis, hepatitis, nephritis, prostatis, pancreatitis, appendicitis, opthalmitis, Bechet's, esophagitis, neuritis, diabetes and cardiovascular complications, stroke, rheumatoid arthritis, atherosclerosis, lupus, psoriasis, Alzheimer's, multiple sclerosis) and many cancers (e.g., lung, colon/rectal, breast, prostate, bladder, liver, gall bladder, appendix, ovarian, pancreas, brain, lymphoid tissue) has been reported in literature. However, the mechanisms of inflammatory responses in the induction of a wide range of inflammatory diseases or cancer that are manifested in tissues as site- specific conditions are not understood. For example, the ongoing debates and controversies in literature whether inflammation is protective in preventing carcinogenesis or it is a cause of cancer demonstrate lack of understanding in differentiating the role of acute and chronic inflammatory responses in preventing or inducing cancer. Consequently, despite heavy public investment for over four decades on cancer war, too many expensive and out-of-focus clinical trials that use potent drugs which are pro-inflammatory mediators or inhibitors of growth factors (poisons) have caused serious and life-threatening side-effects for cancer patients (reviewed in Khatami 2011 a, b).

This chapter will provide a brief overview of recent definitions for acute and chronic inflammation and the role that inflammation plays in the induction of acute and age-associated chronic diseases, with emphasis on cancer. Attempts were made to demonstrate that self-terminating natural property of immune system (immune surveillance) in acute inflammation is protective to the body ('Friend'). However, unresolved and persistent inflammation (oxidative stress) could change the dynamics of immune responses creating an immunological chaos or 'immune tsunami' that would cause loss of architectural integrity and function in susceptible tissues leading to initiation, progression and manifestation of a wide range of chronic conditions or cancer ('Foe') that are very likely interrelated and potentially preventable (Khatami, 2008, 2009, 2011 a, b). Evaluation of current approaches in 'targeted' therapies will be summarized. Outlines of a framework for future designs of clinical trials based on a concept that

inflammation is a common denominator in the genesis and manifestation of a wide range of age-associated chronic diseases and cancer will also be presented.

## 2. Acute inflammation: Protective, self-terminating property of immune system: Body's immune surveillance

During evolutionary process, inflammation became an inherent protective and self-limiting property of immune system to guard the body against harmful elements that the body recognizes as foreign elements (stimuli or irritants). Briefly, effective immunity is provided through natural pleiotropy or duality (polarity) of immune cells via acute inflammation to facilitate the organ systems the ability to return to normal physiological function after encountering internal or external foreign elements [e.g., microorganisms (e.g., viruses, bacteria, parasites), allergens, biological, chemical or environmental hazards, carcinogens, useless or non-functional proteins/enzymes, genetic and epigenetic defects (e.g., mutated DNA/RNA, hypo- hypermethylated genetic components), useless cells (e.g., polyclonal B cell complexes, senescent and cancerous cells), oxidized metabolites (e.g., crystalline uric acid)], so that the body can survive and thrive throughout life (Khatami, 2008, 2009, 2011 a, b).

Acute inflammatory process was recently defined as the balance between two highly regulated and biologically opposing arms termed 'Yin' (apoptosis, growth-arresting, pro-inflammatory or tumoricidal) and 'Yang' (wound healing, growth-promoting, anti-inflammatory, tumorigenic) responses of immune cells with intimate participation of vasculature (Khatami, 2008) (Figure 1).

Stimuli-induced local or systemic immune responses or cell mediated and humoral immunity (CMI, HI), are provided by a highly sophisticated and precise communications between activated innate immune cells [e.g., natural killer cells (NKs), macrophages (MΦs), dendritic cells (DCs), mast cells (MCs)] and their counterparts in the adaptive immune cells [e.g., T and B cells, and subpopulations (cytotoxic T cells, Th1, Th2, Treg)], vasculature and neuroendocrine system to initiate and transmit danger signals within cellular compartments for the purpose to destroy and eliminate the foreign elements as well as terminate and resolve inflammatory responses (Abraham and John 2010, Bonasio and von Andrian 2006, Bosch et al, 2002, Corthay 2006, Crotzer and Blum 2010, Davalos et al, 2010, Fischetti and Tedesco 2006, Gurish and Boyce 2006, Kabelitz and Medzhitov 2006, Khatami 2008, 2009, 2011, a, b, Lodoen and Lanier 2006, Serbina et al, 2008, Serhan and Savill 2005, Thompson et al, 2006, Wagner and Frenette 2008).

The principal mission of acute inflammation (immune surveillance) is two folds:

1. Encounter (sense), process/digest, destroy and eliminate intrinsic or extrinsic foreign elements and infected/injured host tissue,
2. Resolve and terminate inflammation and repair and construct or remodel the target/injured host tissue.

The major outcome of an acute inflammation is lymphocyte-derived clonal expansion, increased synthesis of allergen- or pathogen-specific antibodies and plasma and memory T and B cells (Khatami 2008, 2009, 2011 a, b).

Simply described, apoptosis ('Yin') is responsible for production of death signals and oxidants to destroy the enemy and injured host cells, while wound healing ('Yang') is required to counteract apoptosis and neutralize and remove the toxic 'debris' from the 'battle field' and to reconstruct and repair the host and resolve or terminate inflammation.

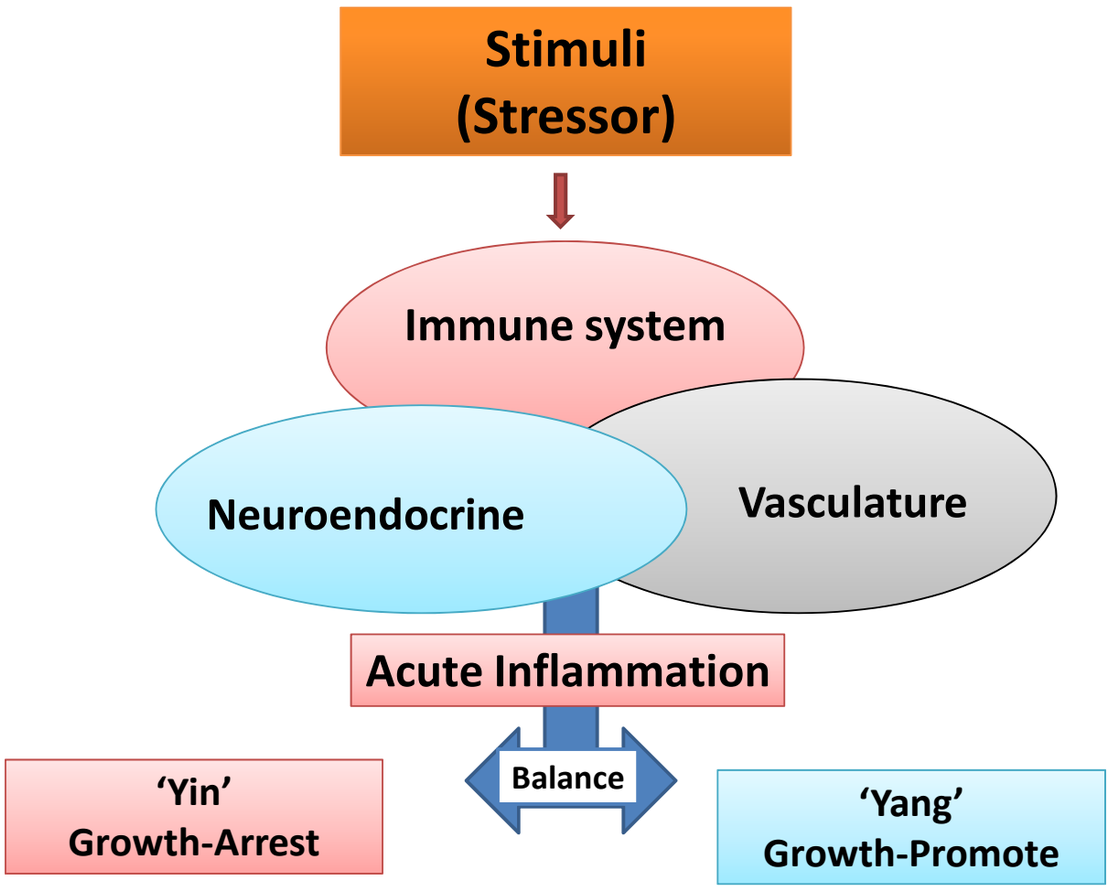



Fig. 1. Schematic representation of 'Yin' and 'Yang' in acute inflammation. Stimuli- (stressor-) induced a well balanced signals between 2 biologically opposing arms, 'Yin' (growth-arresting) and 'Yang' (growth-promoting) processes through elaborate cross-talks between immune and non-immune systems (e.g., vasculature and neuroendocrine) to combat and destroy foreign elements and injured host tissue and to neutralize, resolve and terminate inflammation and to repair and reconstruct the damaged target tissues.

## 3. Specialized and complementary features of cell mediated and humoral immunity (CMI, HI): Antigen presenting and effector cells

Crucial shared and special features of host defense mechanisms are recognition, uptake and clearance of a wide variety of external or internal foreign elements or hazardous materials (stimuli) by resident and/or infiltrated/recruited mononuclear phagocytes and their subpopulations within innate immune cells [e.g, MΦs, NKs, DCs, MCs, eosinophils (Eos)] and their counterparts in adaptive immune cells (T and B cells)]. The host defense system has also tolerance and remembrance capacities to develop memory and regulatory T or B cells when encountering specific foreign elements including cancerous cells (Khatami 2005 a, 2007, 2008, 2009, 2011 a).

In general, CMI that are mediated by MΦs (classical M1 or alternative M2) and DCs [classical/immature DC1, mature DC2, or their tissue lineage subset population (e.g., $CD11^{-}$ $CD4^{+}$ $CD45RA^{+}$, phenotypes plasmacytoid) or neuronal myeloid] play key roles in

combating viruses and bacteria. CMI that mediates through NKs and/or cytotoxic T cells (CTs) is essential for elimination of virus-infected cells and neoplastic cells (internal microorganisms). On the occasions that B cells become antigen presenting cells (APCs) [e.g., stimuli-induced activation of conjunctival-associated lymphoid tissues (CALTs), gut-associate lymphoid tissues (GALTs), lung airways, etc], B cells are responsible for sensing and processing microorganisms or allergens/antigens; activation and biosynthesis of specific antibodies that determine which innate immune cells are required for processing, digestion and destruction of hazardous elements and how pathogen-host interactions are directed to induce appropriate responses including induction of memory B and T cells. For example, CMI mediated by MCs and eosinophils (Eos) are involved in elimination of helminth (parasitic infections) and clearance of allergens/antigens. Under these conditions, B cells function as APCs and MCs are effector cells within innate immunity. Activation and differentiation of B cells and their transformation to plasma cells induce expression of antigen-specific IgE antibodies that sensitize MCs (e.g., induction of antigen-specific Fcε receptors, surface proteins adaptor molecules), followed by degranulation of MCs and release of potent preformed or newly synthesized mediators [e.g., histamine, heparin, oxidants, enzymes (e.g., chymase, tryptase), arachidonic acid (AA) metabolism, activation of cyclo-oxygenase (COX) and lipo-oxygenase (LO) pathways, biosynthesis and release of prostaglandins and cytokines/chemokines, etc], induction of vascular hyperpermeability, activation of blood complement cascades, activation of membrane metalloproteases (MMPs), cell adhesion molecules (CAMs), infiltrations of other inflammatory cells (e.g., Eos) to the site of injury. These events include simultaneous expression of anti-inflammatory mediators, hormones and growth factors (e.g., NFkB, interleukins, VEGF, FGF, cortisol, etc) enzymes and antioxidants [e.g., catalase, superoxide dismutases (SODs)]. The inflammatory responses induce pain and swelling (e.g., perhaps through binding of histamine-receptor-nerves within target tissue vasculatures) or tearing that would facilitate destruction and/or dilution of microorganisms and injured cells as well as termination of inflammation and tissue repair and reconstruction (Abraham and John 2010, Akhiani 2005, Bonetti et al, 2003, Boon et al, 2006, Diz et al, 2008, Drayton et al, 2006, Fischetti and Tedesco 2006, Helleboid et al, 1991, Khatami etal, 1984, 1985, Khatami 2005 a, b, 2008, 2009, Khazaie et al, 2011, Serhan and Savill 2005, Smith and Popmihajlov 2008, Soehnlein and Lindbom 2010, Spite and Serhan 2010, Vasto et al, 2007).

These interdependent and complex immunobiological cross talks are examples of numerous other sophisticated bilateral communications between immune and non-immune systems that are orchestrated during acute inflammatory responses to maintain and protect the psychophysiological and architectural integrity of organ systems throughout life.

Communications errors between CMI and HI due to oxidative stress-induced over-, or under expression of immune or non-immune responses, aberrations in chromosomal, genetic and epigenetic components, enzymes, antibodies, receptors/adaptors or surface molecules are implicated in a variety of chronic allergies, neurodegenerative and autoimmune diseases, non-Hodgkin lymphoma, Sjogren's disease, and/or tumorigenesis and cancer (Berosbaken et al, 2009, Booman et al, 2008, Culmsee and Landshamer 2006, D'Amato et al, 2007, Davis et al, 2011, Drayton et al, 2006, Dvorak 1986, Harvey et al, 2008, Kabelitz and Medzhitov 2006, Khatami 2005 a, b, 2008, 2009).

**Polarization of Immune Cells:** As shown in Table 1, inflammatory mediators with known dual (polarization) properties include toll-like receptors (TLRs 1-9), tumour necrosis factor-α and receptor (TNF-α/TNFR), MCP-1-CCL2, macrophage colony-stimulating factor (M-CSF), transforming growth factor-β(TGF-β), granulocyte M-CSF (GM-CSF), histamine, heparin,

membrane metaloproteases (MMPs), prostaglandins (e.g., PGF1α/PGI-2 to PGE2), cytokine suppressor molecules (e.g., S100 family of calcium-binding proteins), enzymes (e.g., tryptase/chymase, neutrophil-derived serine proteases, indolamine 2, 3-dioxygenase),

| **Factor/Mediator** | **Immune Cell** | **Major Effects/Function** |
|---|---|---|
| Toll-like receptors (TLRs 1-9) | DC1/DC2/TADC<br>M1/M2/TAMs<br>MCs (granulated)<br>LMCs (partially granulated), TAMCs (?) | AI: Signal transduction, 'Yin'-'Yang'<br>CI: decoy receptors in tumour microenvironment |
| TNF-a/TNFR | DCs/TADCs, MFs/TAM<br>MCs/LMCs/TAMCs | AI: induction of apoptosis,<br>CI: decoy receptor, intracellular, growth promotion, tumourigenic |
| TGF-β | MFs, DCs, MCs(?) | AI: immune regulation<br>CI: decoy receptor, tumorigenic |
| Histamine | MCs, LMCs, TAMCs | AI: vasoactive, IgE Fc-dependent receptor binding;<br>CI: independent of IgE-Fc receptor, tumorigenic |
| Macrophage colony stimulating factor-(MCSF) | M1, M2, TAMs | AI: apoptosis/wound healing;<br>CI: decoy receptor, immune suppressor |
| Indolamine 2, 3-dioxygenase (IDO) | DC1/DC2/TADC<br>MCs/MΦs (?) | AI : Wound healing<br>CI: Local immune-privileged, carcinogen |
| Prostaglandins (PGs) | DCs, MCs, MΦs, T and B cells | AI: PGF1α/PGI 2, tumoricidal<br>CI: PGE2, tumorigenic |
| Other factors<br>Interleukins (ILs)<br>Chemokines,<br>Cytokines,<br>Enzymes,<br><br>Genetic/epigenetic | MΦs (M1/M2) or TAMs<br>DCs, T and B cells (?)<br>MCs (?) | AI: TNF-α, IL-1, IL-12, INF-γ, iNOS (arginine), constitutive CXCL1/NFkB, apoptosis-wound healing; endogenous lymphotrophic hormones (ILs); negative control of immune response; etc<br>CI: IL-1RA (decoy), TNF-a/TNFR (decoy), IL-3, IL-4-Eotaxin-2/CCL24, CCL-18, arginase/ornithine-polyamine; CXCl inducible CCL2; Ser/ Thr Ks; PGs/PGE2; MAPKs, PI3K; etc |

Table 1. Inherent polarization of immune cells. Acute inflammation induces bilateral and balanced responses between apoptotic ('Yin') and wound healing ('Yang') pathways. Immune response dynamics alter under chronic inflammation. [AI, acute inflammation; CI, chronic inflammation. Modified from Khatami 2011 b, Cell Biochem Biophys with permission]

cytokines, chemokines, endogenous lymphotrophic hormone-like interleukins (ILs, e.g., IL-2, IL-3, IL-5, IL-10, IL-12, IL-13) and receptor molecules that are involved in feedback or negative control (switching off the positive driving force of immune response after antigen clearance or oxidative stress, or auto-antigens, tumour antigens, infections or allografts), interferons (IFNs, e.g., IFN-γ), eosinophils chemotactic factor of anaphylaxis (ECFA), SCF, c-kit, antibodies (e.g., IgE, IgG isotypes, IgA, IgM), platelet-derived growth factor (PDGF) and gene activation pathways, mutated DNA, hypo-hyper-methylation and expression of abnormal proteins that are identified in cancer research (e.g., p53, p27, p70, MAPKs, KRAS, BRAF, ALK, Myc, BCR, ABL, MGMT, TKIs, PI3ks, tyr/ser Ks, etc) or surface antigens, adaptor molecules or cell recognition molecules (CDs, e.g., CD2, CD11, CD18, CD22, CD25, CD26, CD40, CD 50, CD54, CD63, CD69, CD88, CD154, etc) (Al-Sarireh and Eremin 2000, D'Amato et al, 2007, Diz et al, 2008, Fischetti and Tedesco 2008, Gordon 2005, Gounaris etal, 2007, 2009, Gurish and Boyce 2006, Khatami 2008, 2009, 2011 a, b, Lee et al, 2002, Mackawa and Watanabe 2007, Nishioka et al, 2011, Peerschke et al, 2006, Ribatti et al, 2003, Smith and Popmihajlov 2008, Soehnlein and Lindbom 2010, Suzuki et al, 1998, Thompson et al, 2006, Quezada et al, 2004, Valencia et al, 2011, Wagner 2008). (Table 1, Figure 2).

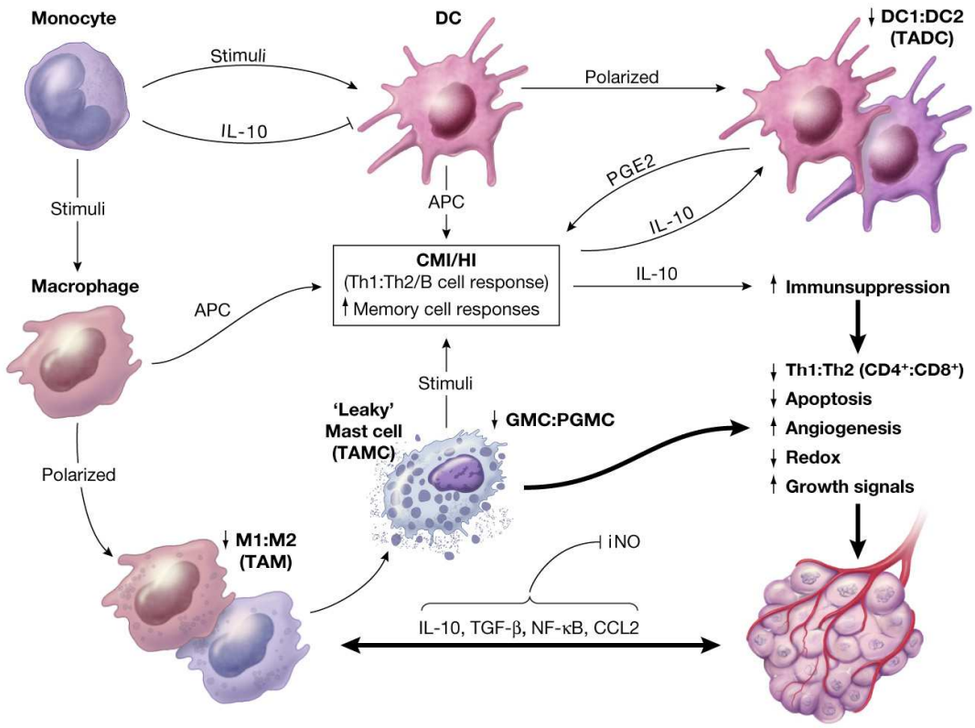



Fig. 2. Pleiotropic roles of immune responses and oxidative stress-induced immune suppression. Oxidative stress can decrease ratios of (DC1/DC2), M1/ M2 (tumour-associated MΦs-TAMs), and/or granulated mast cells (GMC) to partially granulated ('leaky' or TAMCs). These immune response changes could contribute to altered function of cell mediated and humoral immunity (CMI/HI), B- and T- or memory cell responses (e.g., decrease in Th1/Th2 (CD4/CD8 ratios), expression of PGE2, IL-10, NFkB, CCL2, in the direction of immune suppression, reduced apoptosis, redox potential, and increased growth signals for tumor growth and angiogenesis. [Reproduced from Khatami 2008, Exp Opin Biol Ther, 2008 with permission].

## 4. Unresolved inflammation: 'Immune tsunami' and loss of architectural integrity in immune-responsive and immune-privileged tissues

Unresolved inflammation was defined as the loss of balance between 'Yin' and 'Yang' of acute inflammation. Briefly, acute inflammation provides immunity (immune surveillance) and protection of target tissues via two major mechanisms (reviewed in Khatami 2009, 2011 a):

a. Immune-responsive tissues, the sites of initial contact and processing of internal or external stimuli include squamous and grandular epithelial tissues, epithelial-associated mucosal surfaces (e.g., goblet cells), endothelial, stroma, fibroblasts, lymphoid tissues and vasculatures.
b. Immune-tolerant (privileged) tissues including avascular cornea, neuroretina, retinal pigment epithelium (RPE), blood brain barrier (BBB), central nervous system (CNS), hair follicles, testis or uterus, prohibit the processing and spread of pathogen- or stimuli-induced inflammation because these episodes threaten the delicate integrity and function of these stress-sensitive tissues. Immune surveillance in the immune-privileged tissues (self tolerance or ignorance) is provided by presence of one or a combination of barriers [e.g., limited or absence of vasculature, few APCs or recognition molecules such as major histocompatibility class molecules (MHC) class I or II or HLA].

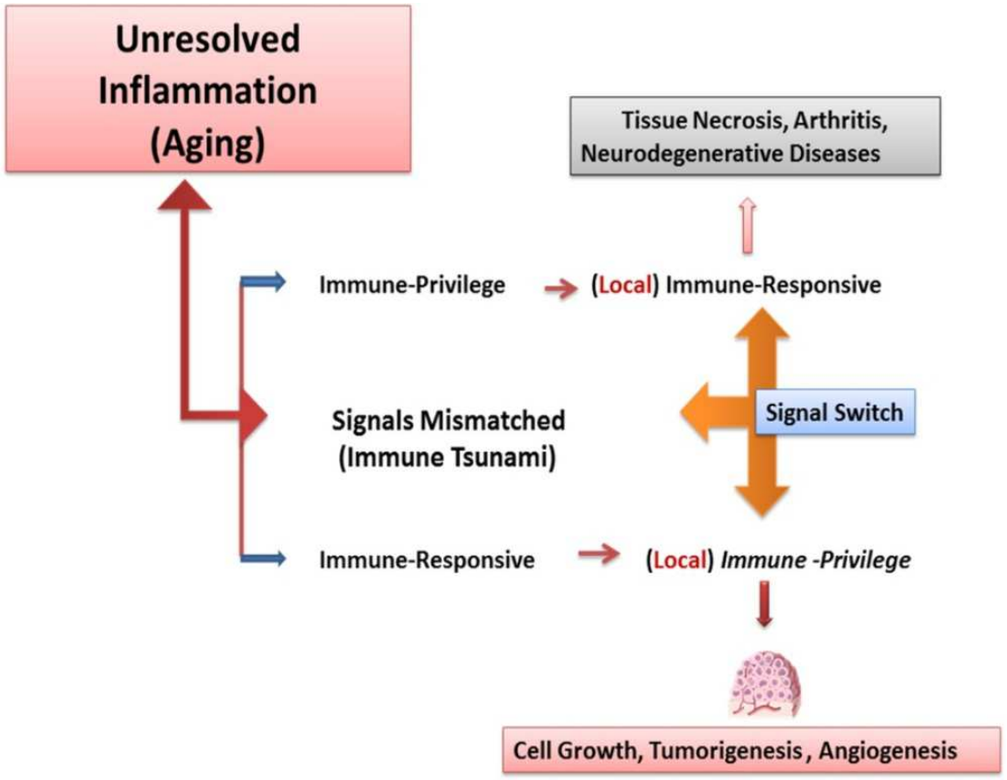



Fig. 3. Unresolved inflammation and altered immune signals in susceptible target tissues. Inflammation and aging could create immune dysfunction (immune tsunami) that cause signal switches by inducing local immune-responsiveness in tissues that are naturally immune-privileged causing tissue necrosis and neurodegenerative disorders. Chronic inflammation can also cause loss of integrity in immune-responsive tissues by induction of local immune-privilege to satisfy increased growth requirements of cancerous cells leading to cancer metastasis and angiogenesis.

Oxidative stress or continuous exposure to irritants could damage immune surveillance (protection) in either or both immune-responsive and immune-privileged tissues (Figure 3). Oxidative stress could induce exaggerated co-expression of apoptotic and/or wound healing factors in target tissues and create an 'immunological chaos' ('immune tsunami') that would erode the architectural integrity and function of naturally immune-responsive or immune-privileged tissues (Khatami 2011 a) leading to the induction of a wide range of allergies, chronic infections, autoimmune or neurodegenerative diseases as well as cell growth, neoplasia, cancer metastasis and angiogenesis (Abrahams et al, 2003, Culmsee and Landshamer 2006, Ferguson and Griffith 2007, Hamrah et al, 2003, Karman et al, 2004, Khatami 2009, 2011 a, Kwidzinski et al, 2003, Niederkorn 2006, O'Brien et al, 2008, Schneider et al, 2011, Siffrin et al, 2007, Streilein et al, 2002, Widera et al, 2008, Zamiri et al, 2007) (Figure 3).

## 5. Acute inflammatory diseases

Severe acute inflammatory diseases (e.g., sepsis, respiratory diseases, meningitis, major trauma, etc), and perhaps anti-cancer drug-induced cachexia, anorexia and sarcopenia, often lead to multiple organ failure (MOF) (Coss et al, 2011, Hall et al, 2011, Harrois et al, 2009, Hotamisisligil 2006, Khatami 2011 a, b, Lyman 2011, Okamoto 2002, Suzuki et al, 2011, Terrabui et al, 2007). In severe acute inflammatory conditions, potent pathogens and their products (e.g., endotoxins, pneumonia, meningitis, etc) can induce rapid destruction of vascular integrity allowing pathogens to gain direct access to host tissues at multiple sites and inducing expression of massive quantities of apoptotic factors and toxins ('cytokine storm' or 'immune tsunami') such as TNF-α, ILs, strong oxidants (e.g., peroxynitriles) that can rapidly shift the balance between apoptosis and wound healing pathways in favor of growth-arresting properties of immune cells and causing severe damage to important host cellular components (e.g., mitochondrial oxidative damage, interruption in electron transfer system, changes in oxido-redux ratios, accumulation of free radicals and severe toxicity to intracellular and/or cytoplasmic membrane components) leading to increased risk of organ failure in lung, kidney, brain, central nervous system and/or heart, in a matter of hours or days (Akamizu et al, 2010, Aubert and Lansdorp 2008, Braun and Marks 2010, Khatami 2011 a, b, Suzuki et al, 2011, Terrabui et al, 2007).

The end results of long-term inflammatory conditions (unresolved inflammation) during the aging process were suggested to be similar to those described for acute inflammatory diseases that lead to organ dysfunction and the genesis of chronic conditions such as neurodegenerative and autoimmune diseases and cancer (Khatami 2011 a, b). Therefore, while acute inflammation is considered a 'friend' that protects the body against harmful elements, chronic or persistent inflammation becomes a 'foe' that destroys the tissue integrity and function.

## 6. Inflammation and age-associated diseases

Biology of aging is a complex process involving declines, slow-down or alterations in expression or function of multiple important hormones (e.g., estrogen, testosterone, DHA, insulin, cortisol) and altered metabolism or transport of nutrients and metabolites (e.g., vitamin C, glucose, myo-inositol, etc) that would lead to biological rearrangements in organs/tissues (biological senescence). Aging process is also associated with minor or major changes in immune response profiles and co-expression and co-existence of mismatched or

misdirected inflammatory mediators (e.g., TNF-α, IL-6, IFN-α,β, IFNs, PGE2, etc) features that are characteristics of immunoscenescence involved in a wide range of chronic diseases (Davalos et al 2010, Ginaldi et al, 2005, Chung et al., 2008, Khatami 2008, 2009, 2011a, Nagai et al, 2010, Ren et al, 2009, Romanyukha and Yashin 2003, Sansoni et al, 2008, Sedivy et al, 2008, Serbina et al, 2008, Siffrin et al, 2007, Zhang 2010) (Figures 3 and 4).

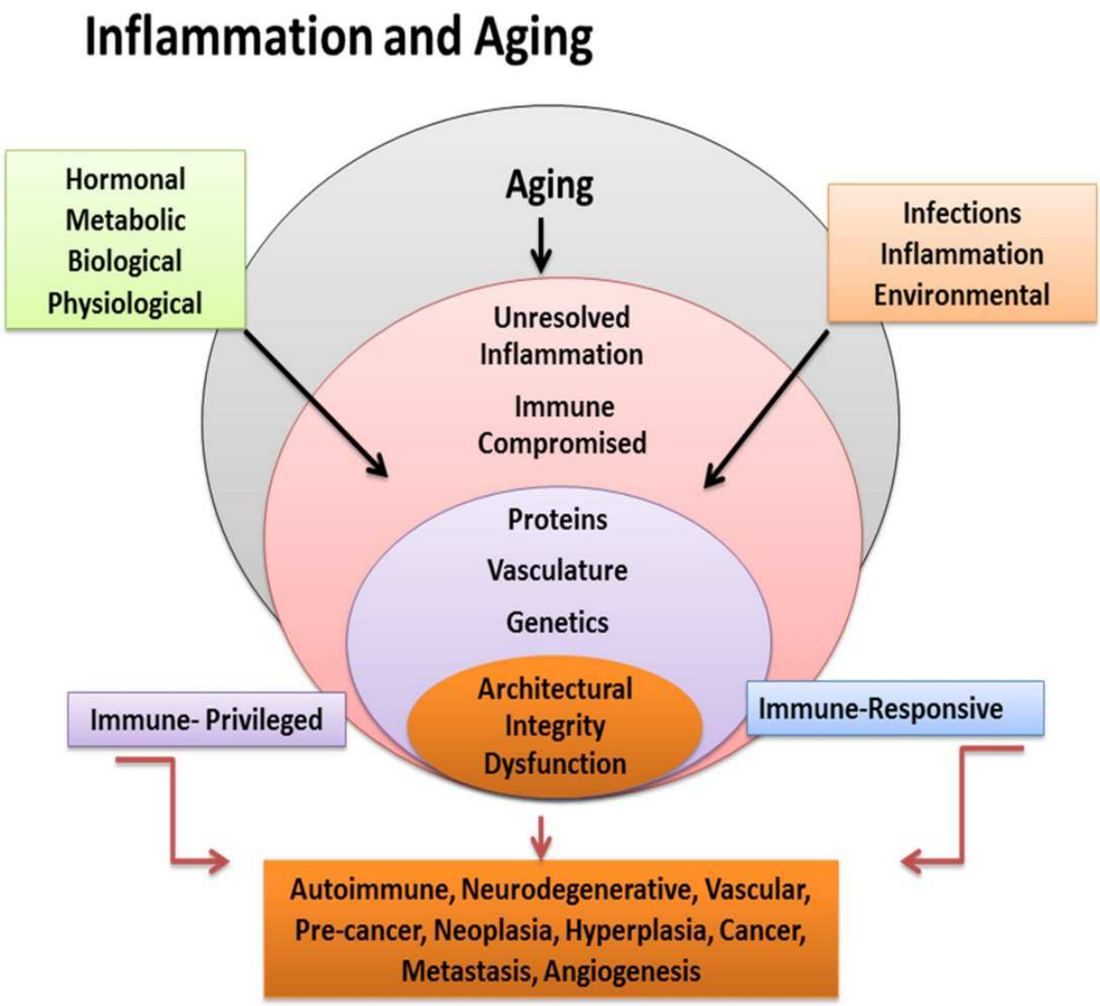



Fig. 4. Schematic representation of chronic (persistent) inflammation and aging as co-morbidity and co-mortality risk factors in the genesis and progression of chronic diseases. Unresolved inflammation could induce shifts in immune responses in naturally immune-privileged and/or immune-responsive tissues and initiating damage to the cellular components such as proteins, genes and vasculature that would lead to destruction of architectural integrity and function of susceptible tissues and induction of chronic diseases such as autoimmune or neurodegenerative conditions, cardiovascular conditions or tumour growth, cancer metastasis and angiogenesis.

Briefly, low grade (unresolved or subclinical) inflammation and longevity are known as co-morbidity and co-mortality risk factors in the genesis and progression of nearly all chronic

illnesses. Accumulation of confluent, complex and useless cells is considered additional sources of oxidative stress that would maintain activation of immune cells and unresolved inflammation. However, longevity and the rate of functional capacities of organ systems and susceptibility to chronic diseases vary in individuals, due to a combination of genetics, immunological or biological factors and the frequency of exposure to diverse environmental hazards. In an attempt to find a common forum on enormous amount of fragmentary information on the biology of chronic diseases that are linked to inflammation, highlights of major molecular theories of aging are outlined in the following (reviewed in Khatami 2009):

a. **Oxidative Stress:** Aging and stress-induced alterations in redox state of cells is likely a major cause of progressive damage to the biological systems. Oxidative stress is associated with activation of NADPH and NADH oxidases and peroxisome proliferators-activated receptors (PPARs) that could lead to the declines in host tissue reducing powers [e.g., superoxide dismutases (SODs), catalase, NADH/NAD+ reductases, GSH/GSSG and vitamin E regeneration pathways, etc]. The peroxidation-induced accumulation of free radicals [e.g., reactive oxygen species (ROS), reactive nitrogen species (RNS)] could damage extracellular and intracellular signaling pathways, inducing interruption of the electron transfer activities and detoxifying and reducing enzymes (e.g., cytochrome p450, SODs, etc), declines in energy out put (e.g., reduced ATP/ADP ratios), impairment of oxidative metabolism in mitochondria, as well as inducing abnormal protein bindings to chromosomal components (e.g., fos, c-jun, c-myc, b actin, etc) and altered activities of immune and non-immune cell response profiles. Oxidative stress-induced altered activity of immune cells would lead to co-expression of inflammatory mediators causing tissue necrosis and/or growth. These immunobiological changes in tissue function are implicated in a wide range of age-associated conditions such as hypertension, asthma, multiple sclerosis, arthritis, diabetes and cardiovascular complications, stroke, atheroma, emphysema, autoimmune and neurodegenerative diseases, Alzheimer's, and cancer (Deng et al, 2008, Ginaldi et al, 2005, Goronzy and Wevand 2005, Khatami 2009, 2011 a, Nagai et al, 2010, Siffrin et al, 2007, Vasto et al, 2008, Zhang 2010).

b. **Immunoscenescence:** Immunoscenescence is the results of readjustment (remodeling) of immune cell functions, a basis for hyper- or hypo-sensitivity (skewing) responses toward new or self-antigens and an overall defects in lymphohematopoetic progenitor competence. Aging and atrophy of thymus is associated with dysfunction of stem cells (manufacturers of hematopoietic cells) and the declines in total number of T lymphocytes subpopulation (CD3+, CD4+, CD8+), decreases in generation and/or exhaustion of naïve/virgin T cells (T0 or CD95-), Th1/Th2 ratios, increases in activities of cytotoxic T cells (CTs) and NKs, declines in B cells function, clonal expansion of CD28+ T and memory B cells. Defects in stem cells function are associated with increased severity of cardiovascular pathology, increased production of low density lipoproteins (LDL) and arteriosclerosis plaque formation, as well as up-regulation of pro- (e.g., IL-2, TNF-α, histamine, NO) (or anti- (e.g., IL-4, IL-5, IL-6, IL-8, IL-10, PGE2) inflammatory mediators in arthritis, atherosclerosis, multiple sclerosis, neurological disorder, dementia/Alzheimer's, osteoporosis, diabetes, lymphoid hypertrophy or cancer. Other contributing factors in changes of immune competency include alterations in bone marrow remodeling and regenerative processes. Age-induced declines in T cell repertoire and accumulation of memory effector cells and oligoclonal complexes (megaclones) result in tissue vulnerability toward infectious agents. Oxidative stress

also influences immune response modifications of MHC-binding regions (epitopes), alterations of antigen processing, accumulation of terminally differentiated effector T cells and skewed lymphocytes polyclonal complexes that could be a basis for inability of immune and non-immune systems to properly respond to new antigenic challenges (e.g., viral, bacterial, neoplastic cells or vaccines) and enhanced vulnerability toward chronic illnesses or cancer (Campisi 2011, Chidgev et al, 2007, Chung et al, 2008, Davalos et al, 2010, Deng et al, 2008, Gounaris et al, 2006, 2009, Khatami 2008, 2009, 2011 a, Klein et al, 2009, Montavani et al, 2004, 2008, O'Brien et al, 2008, Romanyukha and Yashin 2003) (Figures 3 and 4).

c. **Hormones, Metabolites and Lipids in Biology of Aging:** Aging process is associated with altered functions of important hormones (e.g., estrogen, progesterone, insulin, glucagon, androgen, andosterone, testosterone, thyroxine, glucocorticoids, epinephrine, cortisol, mineralcorticoids, dehydroepiandosterone-DHEA, etc) and hormone-like growth factors (e. g., IGF-1, FGF, EGF, VEGF, etc). The influence of these hormones and growth factors on multiple organs and sub-cellular systems (e.g., CNS and brain cognition, stem cells, mitochondrial function, neurogenesis and myelination, traumatic injury, wound healing responses) in reproductive and non-reproductive, immune and non-immune systems and their association in the development of chronic diseases or cancer have been the topic of extensive studies (Davis et al, 2011, Deng et al, 2008, Khatami 2009, Mikkola and Clakson 2002, Pisani 2008, Piatkliewicz and Czech 2011, Poulsen and Kruger 2006, Rauvala and Rouhianen 2001, Ren et al, 2009, Schwarts and Pashko 2004).

For example, steroids or insulin play important roles not only in the function of reproductive organs and regulation of fluid homeostasis and/or metabolic pathways and immune responses to stress, but they are also involved in physiology, function and remodeling of bone, neuronal function, myelination and neurogeneration of brain and CNS and/or membrane-associated fatty acid metabolism (Bosch et al, 2002, Brunello et al, 2011, Campisi 2011, Chung et al, 2011, Goronzy and Wavand 2005, Hotamisisligil 2006, Khatami 1990, 2009, Li et al, 1986, Mikkola and Clarkson 2002, Sansoni et al, 2008, Simon and Balkau 2010, van Kruijsdijk et al, 2009). Insulin deficiency, insulin-resistance or hyper- insulinimia, or glucose toxicity and hyperglycemia of diabetes-induced increased glycosylation of proteins (advanced glycation end-products-AGE and their receptors RAGE) are associated with disturbances in transport and metabolism of important nutrients (e.g., ascorbic acid, pyridoxal phosphate, myo-inositol, etc), increased oxidative stress, accumulation of ROS, and co-expression of pro- and anti- inflammatory mediators such as NF-kB, VEGF, TNF-α, IL-1a, IL-6, IL-8, IL-12, and Ikappa B kinase (IKK-β), platelets' CD40L, VCAM-1, in endothelial, hepatocytes or myeloid cells and/or tissues that are insulin-dependent (e.g., muscle, liver, adipocytes) or insulin-independent (e.g., vasculature, kidney, nerves, retina, RPE, lens) for glucose transport or metabolism (Khatami 1988, 1990, 2009, Li et al, 1986, Park et al, 2005, Pisan 2008, Piatkiewicz and Czech 2011, Simon and Balkau 2010, Stern et al, 2002).

The relationship between diabetes, inflammation and production of AGE/RAGE and the increased risk of certain cancers has been the topic of many recent studies (Piatkiewicz and Czech 2011, Simon and Balkau 2010, Simon et al, 2010, Zhang and Hu 2010). It should also be noted that chronic inflammation in patients with neurodegenerative diseases, asthma or diabetes are reported to increase the risks for certain site-specific cancers (e.g., lung cancer in asthmatic patients, or liver and pancreas in diabetics) and decreased risk for certain other cancers (e.g., prostate in diabetics) (Brunello and Kappor 2011, Khatami 2011 b, Piatkkiewicz and Czech 2011, Stern et al, 2002, Vena et al, 1985, Vesterinen et al, 1993, Vingeri et al. 2009,

Zhang and Hu 2010, manuscript in preparation). It is possible that expression and release of abnormal inflammatory factors into circulation would induce growth-arresting or growth-promoting impact at site-specific susceptible/accessible tissues.

**Lipids:** Long-chain polyunsaturated fatty acids or essential fatty acids (FAs) including membrane arachidonic acid (AA) metabolites, prostaglandins (e.g., PGI2/PGF-1α, PGD, PGE2) and leukotrienes (e.g., LT4, LTC), phosphatidylinositol (PI), phosphatidylserine (PS), and associated enzymes (e.g., COX, LO, phospholipases A, B and C) play critical roles in metabolism, integrity and function of tissues, including signal transduction, immune responses, vascular toning, bone remodeling and function (Al-Sarireh et al, 2000, Bosch et al, 2002, Baso 2008, Helleboid et al, 1991, Khatami 2005, 2007, 2009, Parks et al, 2005, Plourde et al, 2008, Poulsen and Kruger 2006, Spite and Serhan 2010, Wagner and Frenette 2008). Aging, oxidative stress and certain life styles (e.g., smoking or heavy alcohol consumption) are associated with decreases in capacity to metabolize and convert precursor of FAs into polyunsaturated FAs, decreases in bone mass, resorption and remodeling and impaired calcium balance, alterations in osteoblastogenesis, osteoclastogenesis, and functions of osteoblast and osteoclast during menopause, as well as rheumatoid arthritis. Bone remodeling and function is regulated by activation of a sophisticated signal transduction in cellular membrane-lipid complexes and intracellular soluble form of ligands and inflammatory mediators (e.g., nuclear-kappa B ligand binding, RANK to RANKL, decoy receptor proteins and bone-specific osteoprotegerin-OPG) that are essential for differentiation and activation of osteoclasts (Basu 2008, Khatami 2009, Plourde et al, 2008, Poulsen and Kruger 2006, Spite and Serhan 2010).

d. **Inflamm-Aging and Genetic and Epigenetic Damage:** Inflammation is considered a precancerous state of cells that initiates genetic mutations, epigenetic abnormalities, and accumulation of genetic errors, impaired regulation of gene expression. Epigenetics modification events (e.g., methylation, DNA binding proteins, histone proteins, repair and related enzyme modifications) or telomere-telomerase pathways are sensitive to oxidative stress. Aging and chronic inflammation can cause alterations of multiple genomic functions including mutations of suppressor genes (e.g., p25, p35, p38, or p53), instability in somatic maintenance and repair, proliferative control of gene expression, DNA damage response and hypo- or hypermethylation, alterations in polymorphism and contact inhibition regulation, cell cycle regulation and cyclin-dependent kinases (e.g., ser-thr kinases), or telomere shortening. Furthermore, mitogen-activated protein kinase (MAPK) pathways (p38 suppressor genes) are involved in regulation of extracellular-signal regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and inactivation or mutations in suppressor gene pathways that could cause enhancement of cellular transformation and disruption in the induction of senescence concurrent with tumor development. In addition, abnormalities in DNA methylation of CpG islands which are important checkpoints in gene expression events potentially influence healthy aging, carcinogenesis, inflammation and viral infection (Aubert and Lansdorp 2008, Bannar and Gerner 2011, Barber 2011, Khatami 2009, 2011 b, Mackawa and Watanabe 2007, Osborne et al, 2004, Shames et al, 2007, Song and Rudolph 2009, Vasto et al, 2008, Yung and Julius 2008, Zingg et al, 2008).

## 7. Cancer immunobiology

Cancer cell may be viewed as an evolutionary opportunistic defective cell, inherently possessing independent oncogenic properties like viruses, parasites or bacteria, which coexist

within multi-cellular layers of host tissues. As such, cancer cell, like viruses or bacteria is a foreign entity whose growth is routinely monitored and arrested by body's effective immune system (immune surveillance). Due to its inherent oncogenic and stem cell-like features, cancer cell has the potential to become independent (atavistic metamorphosis) and behave like single-celled viruses, parasites or bacteria to grow and multiply and feed itself at the cost of destroying the host organ (Arguella 2011, Khatami 2009, 2011 b).

Carcinogenesis is a multistep progressive erosion of interactions between activating and deactivating immune and non-immune biological activities of host tissue that result in progressive destruction of integrity of susceptible primary and/or secondary tissues (metastasis). The microenvironments of malignant and non-malignant cells (e.g., stroma or vasculature) are cluttered by chaotic, heterogeneous and misdirected communications between normal and mutant cell populations, expressing inappropriate growth arresting and growth promoting factors in the direction of cell growth and selective apoptosis to benefit cancer invasiveness. In the microenvironments of tumor cells, exaggerated or inappropriate expression of apoptotic and wound healing (growth) factors, derived from genetic errors, DNA mutations and epigenetic components (e.g., TNF-α, MMPs, proteases or ROSs, kinases, telomerase, VEGF, etc) are required for tumor growth and proliferation, as well as membrane degradation and invasion to the neighboring tissues and migration through vasculature and lymphatic channels during metastasis (Al-Sarireh and Ermin 2000, Arguello 2011, Booman et al, 2008, Davalos et al, 2010, Dryaton et al, 2006, Ferrantini et al, 2008, Dvorak 1986, Gounaris et al, 2007, Ibrahim et al, 2006, Innocenti et al, 2011, Khatami 2007, 2008, 2009, 2011a, b, Kimura et al, 2007, Meeker 2006, Montavani et al, 2004, 2008, Muller et al, 2008, Nardin and Abastado 2008, Nyakern et al, 2006, Osborne et al, 2004, Peggs et al, 2008, Risques et al, 2007, Rodriguez et al, 2005, Rook and Dalgleish 2011, Sethi et al, 2008, Shames et al, 2007, Vena et al, 1985, Vire et al, 2011, Zitvogel et al, 2008).

The following is a list of major interrelated immunobiological features in carcinogenesis:

a. Destruction of immune surveillance (loss of balance in 'Yin' and 'Yang' of acute inflammation) in the microenvironment of susceptible target tissues. In order to satisfy their enhanced growth requirements cancer cells induce decoy receptors [e.g., TNFR (d), IL-1R (d), M-CSF-R (d)] that cause misguided oxidative signals and abnormal growth activation pathways (e.g., MAPKs, IP3Ks, PKC, PGE2, ILs, etc), genetic and epigenetic modifications that would further impair immune responses (Figures 2 and 4). The weakened or loss of immune competency and altered tumoricidal vs tumorigenic ratios of immune system, particularly during aging process, is perhaps the first essential opportunistic events for cancer cell to impose its oncogenic features on host machinery for its enhanced growth requirements, like any other opportunistic pathogen;
b. Decline/loss of cell contact inhibition perhaps due to oxidative stress-induced damage to extracellular/intracellular communication signals causing under-, or over-expression of receptor molecules or enzymes or other factors (e.g., MMPs, ECM, CAMs, collagen type IV, fibronectin, cell surface proteins/enzymes and antigens, oxidases, antibodies, cytokines/chemokines, etc) that would further facilitate cancer growth and motility;
c. Capability of cancer cells to grow under hypoxic conditions perhaps due to increased ratios of neovascularization (angiogenesis) to vascular cell number and/or damage to mitochondria oxidative metabolism and declines in energy output (ATP/ADP) accompanied by increased anaerobic glycolysis. Having enhanced glucose utilization requirements, cancer cell could also interfere with active transport (ATP-dependent) or

facilitated diffusion of glucose or other important metabolites (e.g., ascorbate or myo-inositol) which share or compete with glucose transporters into epithelial or endothelial tissues (Khatami, 1988, manuscript in preparation);

d. Loss of vascular integrity that would lead cancer cell clumps to access to other tissues (secondary sites);
e. Invasion of cancer cells in lymphoid organs and circulation and access to bone structures;
f. Metastasis and multiple organ failure (MOF) (Khatami 2009, 2011 a, manuscript in preparation.

## 8. Association between inflammation and cancer

### 8.1 Circumstantial evidence

Observations by Ehrlich (1909) that tumor cells are recognized and eliminated by immune system were later evolved to the theory of immune surveillance or killing of cancer cells by immune system (Burnet 1957). However, while numerous reports on circumstantial evidence for an association between chronic inflammation and many cancers (e.g., lung, breast, colon, prostate, gastric, liver, bladder, pancreas, esophagus, ovarian) have accumulated for more than a century (reviewed in Khatami 2005 a, 2007, 2008, 2009, 2011 a, b), except for our 'accidental' discoveries in 1980's (Khatami et al, 1989), little/no evidence demonstrated a direct link between inflammation and tumorigenesis. In addition, except for our publication (Khatami 2005 a) no other data demonstrated time course kinetics of inflammation-induced identifiable developmental phases of immune dysfunction that would lead to tumorigenesis and angiogenesis.

### 8.2 Direct evidence: Models of acute and chronic inflammatory diseases

In 1980s/90's, our research team at the University of Pennsylvania, established experimental models of acute and chronic inflammatory diseases in conjunctival-associated lymphoid tissues (CALTs) in guinea pigs, by topical (unilateral and/or bilateral) application of fluoresceinyl-ovalbumin (FLOA, antigen), in the presence or absence of infective agents (e.g., A Suum and its extracts), adjuvant or tumour promoting agents (TPAs) for up to 30 months (Khatami et al, 1984, 1985, 1989, Haldar et al 1990, Helleboid et al 1991, Khatami 2005 a, 2008). At least three distinct developmental phases of inflammatory responses were identified:

1. **Acute phase:** Clinical and histopathological findings; initiated 9 days after topical immunization and challenges induced strong or weak acute (type 1) clinical reactions including tearing, conjunctival edema, milky secretions in tears, IgE-dependent mast cells (MCs) degranulation, release of histamine and prostaglandin (PGs) and vascular hyperpermeability. Time course kinetics of histamine and PGs (6-keto-PGF-1α; or PGI2) release in tears suggested that histamine was a primary mediator that activated arachidonic acid metabolism and cyclooxygenase pathways and the synthesis and release of prostanoids via constituent and/or infiltrating inflammatory cells. No correlation was found between circulating homocytotropic-IgE and the degree of clinical reactions. Preliminary observations suggested tight binding (high affinity) of IgE-MCs-Fc-ε receptor molecules in CALTs and other tissues (e.g., lung MCs, or maternal/paternal antibody transfer to new-born babies).
2. **Intermediate phase (down-regulation phenomenon)**: Occurring within 2 months of repeated sensitization and challenge, involved minimal tearing or tissue edema, loss

(exhaustion) of mast cell function, increased infiltration of eosinophils into subepithelium and mucus secreting GCs and neovascularization.

3. **Chronic response phase (tumorigenesis):** Occurring between 12 to 30 months of continuous challenges with antigen, involved induction of tumor-like lesions in conjunctival tissues, angiogenesis, massive lymphoid hyperplasia, follicular formation with germinal centers, activated macrophages, increased swollen GCs, degranulated-partially granulated ('leaky') MCs, involvement of lymphatic channels, extensive epithelial thickening (growth) and/or thinning (necrosis) that often observed in the same tissue sections. Cross-sectional areas of massive hyperplastic lymphoid nodules from animals that were continuously challenged with antigen were at least five times greater than lymphoid tissues in normal-untreated animals (Figures 5 and 6).

Animals treated with a mixture of FLOA and TPAs showed development of tumor-like lesions within 6 months after commencement of sensitization suggesting shifts in time course kinetics of immune response alterations through activation of protein kinase C (PKC) and/or other related tumor growth pathways.

From a total of 400 eyes that were examined, 12/40 (30%) of eyes from animals that were not sacrificed during earlier immunization periods developed tumor-like lesions or hyperplasia of CALTs. Tumor development in CALTs primarily occurred in animals that produced minimal early type 1 responses toward antigen challenge. Monitoring percentage of tumor-like lesions developed with strong or weak responses during the entire course of immunization is perhaps among the important knowledge gaps that awaits future investigations.




Fig. 5. Inflammation-induced tumour-like lesions in guinea pigs. Multiple round follicular lymphoid masses originating from upper and lower conjunctiva, 18 months after repeated topical (conjunctival) immunization and challenge with FLOA. [Reproduced from Khatami et al, 1989. Copyright American Medical Association @1989. All rights reserved.]

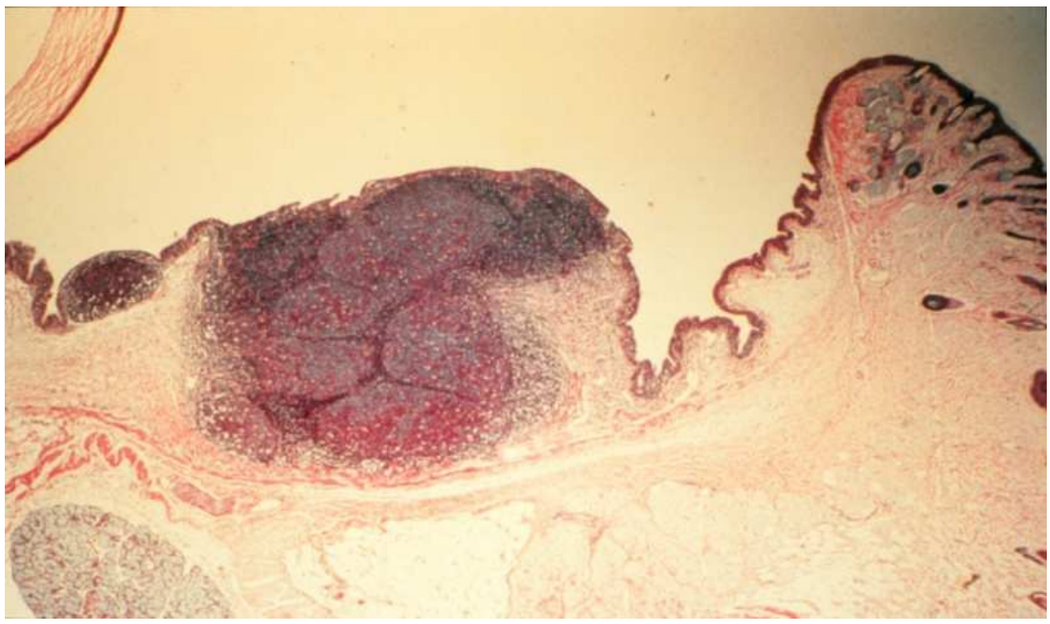


Fig. 6. Histopathological section of eyelid in an animal that was repeatedly immunized and challenged with FLOA, showing hyperplasia of CALTs. [Reproduced from Khatami et al 1989. Copyright American Medical Association @1989. All rights reserved.]

**Antibody Isotypes:** Comparison of antibody profiles (i.e., IgG1/IgG2 isotypes) in ocular and/or splenic tissues in highly sensitized animals during the course of immunization suggested that chronic inflammation-induced site-specific/local (CALTs) alterations in B-plasma cells (or memory cells) expression profiles of immunoglobulin subclass (e.g., IgG1/IgG2 ratios). Stimuli-induced B-plasma cell-derived expression of Ig isotype specificities and profiles and binding to respective receptors [e.g., FcεR ( IgE), FCγR1 (IgG1), FcγRII (IgG2), FcγRIII (IgG3), FcαR (IgA) or FcμR (IgM)] have been identified in a number of inflammatory and infectious disease processes, tumorigenesis and cancer including conjunctival associated lymphoid hyperplasia, gut-associated lymphomas, asthma, polyps, chronic lymphocytic leukemia, Sjogren's disease, squamous cell carcinoma in atopic eczema of conjunctiva (Akhiani 2005, D'Amato et al, 2007, Drayton et al, 2006, Diz et al, 2008, Gouranis et al, 2007, Gurish 2006, Haldar et al, 1988, Heinz et al, 2003, Khatami et al, 1989, Khatami 2005 a, Vire et al, 2011).

**Role of Mucus Secreting Goblet Cells.** Mucus secreting GCs seemed to play a role in developmental phases of immune dysfunction and genesis of tumor-like lesions in CALTs. Heavy eosinophil infiltration into GCs was identified during the intermediate stage of immune responses. The number of swollen GCs also increased in massive hyperplastic tissues (Khatami et al, 1985, 1989, Khatami 2005 a, 2008, 2009). Others reported a role for mucosal immunity and GCs in human inflammatory diseases such as appendicitis and neoplasia of endocrine system or carcinomas (Hanson et al, 2004, Henson and Alborez-Saavedra 2001, Leiper et al, 2001).

These studies are suggestive of the first evidence for a direct link between inflammation and tumor development and a first report on developmental phases of inflammation-induced immune dysfunction that would lead to tumorigenesis and angiogenesis. Confirmation and identification of inflammation-induced developmental phases of immune dysfunction in

different tissues/organs and expression of various mediators that are produced during acute, intermediate and chronic phases of inflammatory responses that would lead to tumor growth are perhaps among the first essential steps in understanding the mechanisms of inflammatory diseases or cancer.

Since 1998, at the National Cancer Institute (NCI), during author's involvement in review of major expensive clinical studies, such as prostate-lung-colorectal-ovarian (PLCO) Cancer Screening Trials, it was suggested that inflammatory mediators are ideal targets for diagnosis, prevention and therapy of several cancers. The design of a cohort clinical study was developed based on a framework that inflammation is a basis for induction of many chronic illnesses and cancer. Furthermore, cancer biomarkers criteria were standardized by creating data elements as a foundation of a database tracking system and M-CSF was used as a prototype to test the data elements (e.g., comparison of superior specificity and sensitivity with conventional biomarkers (Khatami 1999, 2005 a, b, 2007, NCI-Invention-Federal Register, 2005, NCI proposals 1999, 2004, 2006). Over the last decade, the number of funded projects that are focused on the role of various inflammatory mediators in cancer has significantly increased within and outside NCI/NIH. The Omics fields of proteomics, glycomics, metabolomics, lipidomics or genomics and related technologies/ nanotechnologies, symposia, networks and applications of a wide range of 'targeted' therapies and clinical trials have flourished in cancer research. However, these fragmented approaches have created more chaos in selection of 'personalized' or 'targeted' therapies for site-specific cancers (see the following section). Furthermore, cancer community has resisted to systematically study the role of oxidative stress or unresolved inflammation, in the loss of balance between tumoricidal vs tumorigenic ('Yin' and 'Yang') properties of immune system and the developmental phases of immune response dysfunction that participate in the many simultaneous events involved in carcinogenesis, particularly during aging process (Khatami 2011 b).

## 9. Evaluation of current 'targeted' therapies or 'personalized' medicine

Majority of current approaches in 'targeted' therapies or 'personalized' medicine focus on utilization of potent apoptosis-inducing factors (poisons) to inhibit specific events in numerous growth pathways that are involved in support of tumorigenesis (Alberts et al, 2011, Arguello 2011, Bannar and Gerner 2011, Boon et al, 2006, Cataldo et al, 2011, Chen et al, 2011, Coss et al, 2011, Del Fabbro et al, 2011, Florescu et al, 2011, Innocenti et al, 2011, Khatami 2011 a, b, Lesterhuis etal, 2011, Nishioka et al, 2011, Nyakern et al, 2006, Osborne et al, 2004, Ramsdale et al, 2011, Rove and Flaig 2010, Zitvogel et al, 2008). These drugs [e.g., apoptotic factors (TNF-α), monoclonal antibodies against growth factors or enzymes (e.g., VEGF, kinases), mutated genes, epigenetic modifications, etc] introduce additional oxidative stress ('immune tsunami') to an already immune-compromised body, causing additional damage not only to the primary target tissue, but also to other tissues, resulting in devastating side effects, such as cancer-associated cachexia, anorexia, sarcopenia, severe inflammation, venous thromoembolism, diarrhea, excessive loss of appetite and weight, drug-resistance and cancer relapse and multiple organ failure (MOF). Mechanisms of drug-induced cancer cachexia are very likely the results of significant systemic shifts in the balance between 'tumoricidal' and 'tumorigenic' properties of the immune system, features that are shared by potent pathogens-(e.g., endotoxins, meningitis or pneumonia viruses)

induced 'cytokine storm' or 'immune tsunami' in severe acute inflammatory diseases such as sepsis, pneumonia, or meningitis and MOF (Khatami 2011 a, b) (Figure 7). These drugs could induce simultaneous production of oxidants (e.g., superoxide-$O2^-$, nitric oxide-NO and peroxynitrite) that would disrupt and damage electron chain transport and detoxifying enzymes (e.g., cytochrome C electron carriers, glutathione-GSSG/GSH, $NAD^+$/NADH and/or vitamin E regeneration pathways) and impair mechanisms of removal of reactive oxygen species (ROS), reactive nitrogen species (RNS), peroxides and byproducts of the citric acid cycle. Furthermore, drug-induced oxidative damage to mitochondrial integrity and function could further impact catabolism of muscle proteins that would induce sarcopenia, and oxidation of adipose tissues, leading to excessive loss of appetite and weight and MOF (Akamizu and Kangawa 2010, Alberts et al, 2011, Blum et al, 2011, Chen et al, 2011, Del Fabbro et al, 2011, Hall et al, 2011, Khatami 2011 a, b, Okamoto 2002, Suzuki et al, 2011, Terrabui et al, 2007, manuscript in preparation).

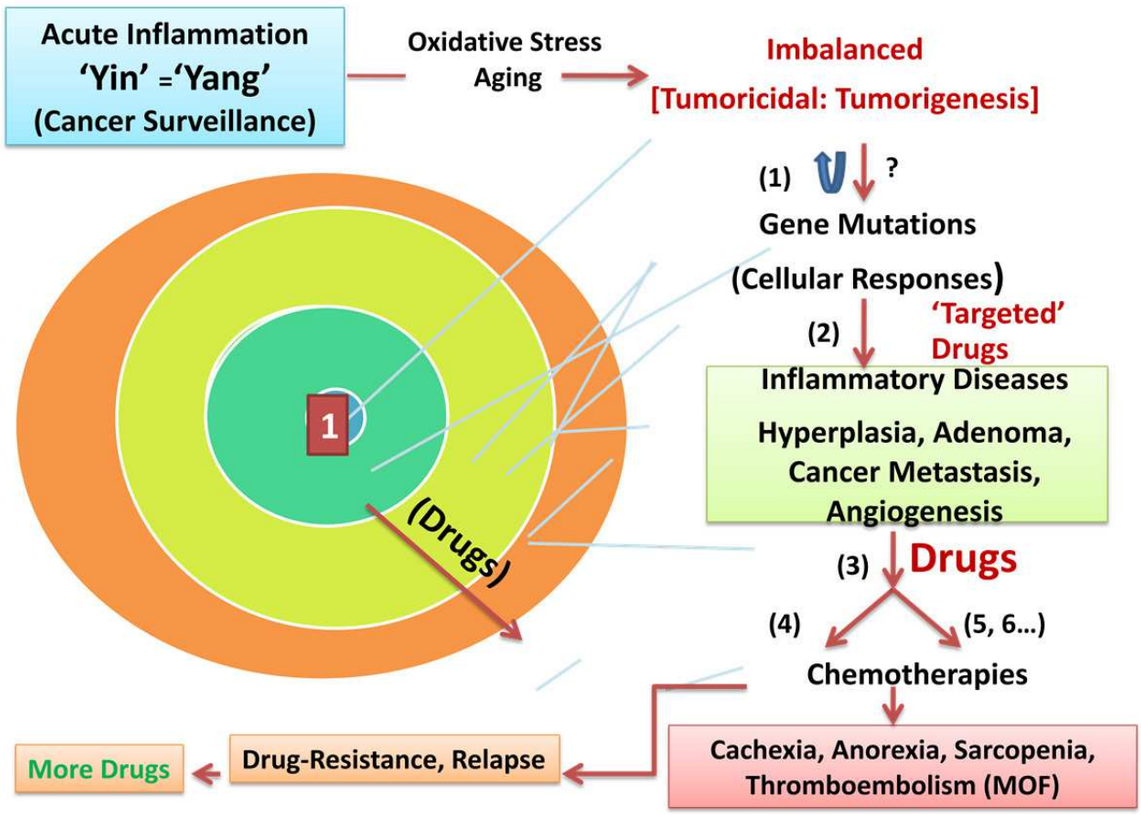



Fig. 7. Dartboard representation of current 'targeted' therapies. The figure schematically shows where we are and where we should be in 'targeting' cancer therapies. Correct/actual target is the loss of balance between tumoricidal and tumorigenic ability of immune system or loss of cancer surveillance (marked as [1]) shown at the center of dartboard. However, the claimed 'targeted' therapies for site-specific cancers are inhibitors of one or few specific genes or factors from hundreds or thousands of other molecular components that are routinely identified in pathways at multi-stages in tumorigenesis. [Modified from Khatami 2011 b, Cell Biochem. Biophys. All Right Reserved]

While the isolated molecular components, identified and/or used for 'targeted' therapies, are part (s) of the molecular pathways identified in cancer biology, they should not be considered as 'target' for therapy as they have little/no value on their own for translational purposes in treating or preventing cancer. Investigators using such approaches in 'targeted' or 'personalized' medicine fail to consider that pathways involved in cell growth-arrest ('Yin') or growth-promote ('Yang') are inherently capable of activating or deactivating alternative and interdependent pathways in immune and non-immune systems (e.g., vasculature and neuroendocrine). Several recent studies demonstrated increased risks of metastasis (cancer relapse) and additional immune suppression after radiotherapy and 'targeted' therapies in site-specific cancers (e.g., hepatic carcinoma, colon, lung, prostate, lymphoid tissues, etc). The life-threatening side effects of such 'targeted' therapies include development of cachexia, aneroxia, arterial hypertension, secondary interstitial pneumonia and diffuse alveolar damage and pulmonary edema, broncopneumonia, lung hemorrhage, pulmonary and venus thromboembolism, metastasis and cancer relapse, as well as depression and fatigue ('sickness behaviors') (Blum et al, 2011, Braun and Marks 2010, Del Fabbro et al, 2011, Elamin 2011, Hall et al, 2011, Khatami 2011 a, b, Lukaszewicz and Payen 2010, Lyman 2011, Ranmsdale et al, 2011, Suzuki et al, 2011, Terrabui et al, 2007). In addition, 'targeted' therapy-induced cancer cachexia and associated involuntary excessive loss of weight and appetite in patients are accompanied by significant declines in nutritional intake (e.g., zinc, vitamin B, anti-oxidants, etc) that contribute to the metabolic abnormalities and conditions such as hypothyroidism,, hypoadrenalism, and hypogonadism as well as induction of systemic inflammation and excessive expression of inflammatory mediators (e.g., IL-6, IL-1β, IL-8 and TNF-α, potent oxidants, etc). These drug-induced metabolic and inflammatory conditions are catabolic forces in driving the tissues toward hyper metabolism and destruction of adipocytes and muscle integrity and function that would lead to multiple organ failure or cancer relapse (manuscript in preparation).

In this section it is appropriate to remember the 1959 statement made by Peyton Rous (Nobel Laureate in Physiology or Medicine 1966) that "*A hypothesis is best known by its fruits. What have been those of the somatic mutation hypothesis? It has resulted in no good thing as concerns the cancer problem, but in much that is bad . . . . Most serious of all the results of the somatic mutation hypothesis has been its effect on research workers. It acts as a tranquilizer on those who believe in it.*" This statement was made over fifty years ago, well before the genetic study in cancer was put on steroids! (Khatami 2011 b).

## 10. Concluding remarks and future direction

Maintenance of immune or cancer surveillance, or the balance between 'Yin' and 'Yang' of acute inflammation is a key to healthy aging. Proposed future studies in the designs of effective diagnostic, preventive or therapeutic measures, based on the concept that unresolved inflammation is a common denominator in the genesis and progression of many age-associated diseases or cancer are summarized in the following.

1. Systematic studies on the role of unresolved inflammation in the loss of balance between inherent 'tumoricidal' vs 'tumorigenic' ('Yin' and 'Yang') protective properties of immune cells as primary focus in understanding the cancer biology and/or other chronic diseases.
2. Role of unresolved inflammation or oxidative stress in the induction of immune dysfunction in tissues that are naturally immune-privileged or immune-responsive and could cause neurodegenerative and autoimmune diseases or cancer.

3. Tissue susceptibility toward oxidative stress in immune-responsive and immune-privileged tissues, and in insulin-dependent or insulin-independent tissues for glucose transport.
4. Tissues susceptibility in immune-responsive, immune-privileged, insulin-dependent or insulin-independent tissues for glucose transport, toward oxidative stress-induced damage to genetic modifications of immune and non-immune systems.
5. Pathogen-host interaction profiles that include identification of principal response features on pathogen-, allergen-, oxidative stress-induced activation of resident or recruited immune cells in target tissues.
6. Potential reversibility of early stages of inflammation-induced immune dysfunction [e.g., pathways identified between a (acute) and b (intermediate) phases in our studies described above] that include identification of altered initial immune responses and cellular chromosomal/genetic material that would lead to cellular growth and induction of hyperplasia, neoplasia/precancer or cancer-malignancy deserve detailed studies. Outcomes of these studies are anticipated to lay a foundation for translational approaches in designs of effective prevention, diagnosis and/or therapy of cancer and many age-associated chronic diseases.
7. Potential health benefits of antioxidants, anti-inflammatory agents, or sulfhydryl-containing agents (e.g., Amifostine, isothiocyanate, mercaptoethanol, N-acethylcysteine or captopril) or precursors of glutathione on redox-sensitive transcription factors (e.g., NF-kB), leukocyte adherence to be examined at early stages of immune dysfunction for potential promotion and/or stabilization of innate and adaptive immune cells.

Promotion and/or stabilization of inherent ability of immune system toward healthy aging, that include identifying the features of pathogen-host interactions in susceptible organ systems bring their own intellectual and technical challenges but the outcomes are expected to hold serious promises in understanding how cancer cells become a threat to body and how effectively translate biology of cancer into effective clinical studies.

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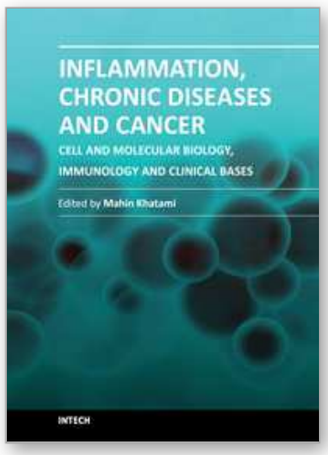
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This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

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