Preface

Cells of the immune system communicate with each other, and respond to abnormal conditions by releasing soluble proteins, named cytokines. Abnormal or dangerous conditions include infection, trauma and injury, neurological disorders, and cancer. The balance between pro- and anti-inflammatory cytokines can comfort or exacerbate the symptoms in these diseases. This book focuses on counter-regulatory and the role of cytokines in different diseases. The goal is to understand contribution of cytokines in the progression of the disease as well as therapeutic potential of cytokines in the treatment of the disease by understanding cytokine counter-regulation.

Chapter I - Interleukin-12 (IL-12), a potent pro-inflammatory cytokine that links innate and adaptive immunity, has been evaluated extensively as a potential vaccine adjuvant and anti-tumor therapeutic. Incorporation of IL-12 into different immunization protocols enhances long-term protection of mice from pathogenic challenge. Similarly, systemic administration of IL-12 can promote cytotoxicity of NK and CD8+ T cells and result in tumor regression in murine tumor models. However, the antitumor activity of IL-12 has been found to be transient in mice with advanced disease and more importantly, in cancer patients. Whereas the biology of this cytokine and the effector pathways it promotes are well-defined, the molecular mechanisms underlying its transient activity in the cancer setting have received limited attention. Three major mechanisms of counter-regulation, which limit the duration of IL-12-mediated T-effector cell responses, have been identified. These include secretion of IL-10 by activated T-cells, production of nitric oxide (NO) by Macrophages and the induction of indoleamine 2,3 dioxygenase-expressing tolerogenic dendritic cells. The distinct molecular pathways that drive these feedback inhibitory mechanisms are highlighted.

Chapter II - The central nervous system (CNS) and the immune system share multiple chemical messengers ranging from small molecules, such as corticotropin-releasing factor (CRF) to large proteins, such as cytokines and growth factors. The immune system is capable of sending signals to the brain through an elaborate system of bi-directional communication. These signals induce responses to the damage caused by viruses, bacteria, parasites and molecules, such as the damage associated molecular pattern molecules (DAMP). The blood-brain barrier prevents the entry of antibodies, complement factors, immune cells and cytokines into the interior of brain parenchyma. Notably, cells of the CNS lack CCR5, B cells, dendritic cells and activated macrophages in a homeostatic state. This organization diminishes immune responses in the brain. It has now been demonstrated that CNS is

permanently under the control and surveillance of activated macrophages and dendritic cells, as well as Th cells that are located in the meninges and choroid plexus. These strategic areas can safeguard ventricular and subarachnoid compartments. There are multiple anatomo-physiological connections between the CNS, immune system and autonomous nervous system (ANS) via the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary axis (SAM). Cytokines are mediators of intra- and extracellular communications which serve as powerful regulators of neuropeptidergic systems. They maintain neuroendocrine homeostasis, and are involved in responses to stress and depression. Chemokines and prostaglandins (PGs) are essential to generate a powerful response from the immune system. Some of the cytokines involved include TNF-α, IL-1ß, IL-4, IL-6, IL-10, IL-12, IL-15, IL-19, IL-18, IL-33 and interferon type I (IFN-β and IFN-α) and type-II (IFN-γ). These molecules act as potent modulators of responses in the neuroendocrine system. In this chapter the authors review interactions between the immune system and nervous system.

Chapter III - Hypoxic-ischemic insults during the perinatal/ neonatal period cause damage to the brain particularly the periventricular white matter (PWM) region. Perinatal hypoxia can occur in response to a variety of risk factors such as maternal diabetes, multiple gestation pregnancy or pulmonary and/or cardiac dysfunction in the neonate. Injuries that occur to the developing PWM in response to hypoxia often manifest as severe cognitive and/or motor disturbances over time, and are characterized by death of oligodendrocytes and damage to axons. Such neuropathies are augmented via the production of neuroinflammatory mediators by activated glia as an aftermath of injury. Dysregulated expression of cytokines has been shown to have an important role in mediating hypoxic PWM damage (PWMD). In this chapter, the authors emphasize on the expression and role of cytokines, especially those which are implicated in hypoxic PWMD, such as interleukin-1β, tumor necrosis factor-α, macrophage colony stimulating factor, interferon-γ, as well as chemokines including monocyte cheomoattractant protein-1. The primary focus of this chapter is on glial cells and the factors that mediate synthesis of cytokines, thereby contributing to neuroinflammatory responses and resulting in death of oligodendrocytes following hypoxic insult.

Chapter IV - Neurodegenerative diseases are defined as hereditary and sporadic conditions, which are characterized by progressive nervous system dysfunction. These disorders are often associated with atrophy of the affected central or peripheral structures of the nervous system. Neurodegenerative diseases such as Alzheimer disease (AD), Parkinson disease (PD), Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS) are among the most important health problems in developed countries. In recent years, progress has been made in developing new therapies that target the immune system and cytokines as therapeutic agents.

Generation and deposition of amyloid beta peptides and neurofibrillary tangle formation are key mechanisms involved in AD pathogenesis. Several lines of evidence suggest that cytokines may promote Aβ formation, aggregation and deposition at multiple levels. For example, IL-1 has been implicated in the transformation of diffuse β-amyloid aggregates into β- amyloid plaques.

MS is characterized by the breaking down of immunological self tolerance, with damage to the myelin sheath that may be mediated by Th1 cells via secretion of pro-inflammatory cytokines. The balance between Th1 and Th2 is etiologically important such that Th2 type cytokines may have a beneficial effect. Novel treatment strategies should promote a deviation

to a predominant Th2 response, which has the potential of immune modulation as well as neuroprotection.

Stimulation of immunocompetent cells and hyperproduction of cytokines are considered to play a role in the development and progression of PD. Cytokines from activated microglia in the SN and putamen may be initially neuroprotective, but may later become neurotoxic during the progress of PD.

The role of pro-inflammatory cytokines in pathophysiology of ASL and during the progression of brain injury is not clear. Despite intense interest, only a few studies have evaluated the release of cytokines. However, there is no sufficient evidence to suggest either a cause-effect relationship or validity of these cytokines in predicting clinical outcomes.

Specific inhibition or activation of the biological activities of cytokines could result in therapeutic benefits for the neurodegenerative disorders. The aim of this review is to outline recent progress on the development of cytokines modulators as potential therapeutic approaches for neurodegenerative diseases.

Chapter V - Dysregulation in cytokines produced by T helper cells of the immune system may play a critical role in stress-related illnesses. Post-traumatic stress disorder (PTSD) is a severe anxiety disorder induced following exposure to extremely stressful life events such as war, rape and abuse. PTSD is often a chronic disorder in veterans. It has been documented that PTSD is associated with modulation in the hypothalamus-pituitary-adrenal (HPA) axis, resulting in changes in hormones, such as cortisol and catecholamines, that affect cellular and humoral immunity. Furthermore, there is evidence for altered glucocorticoid receptor (GR) expression and functions in peripheral blood mononuclear cells (PBMC) in PTSD patients, leading to immunomodulatory changes. Dysregulation in both HPA axis and GR may induce a cytokine storm that plays a pivotal role in the pathogenesis of PTSD. Increased levels of pro-inflammatory cytokines, such as IL-1β, IL-6, IFN-γ and TNF-α, have been detected in such patients. Thus, induction of the anti-inflammatory cytokine response may offer a novel strategy for the prevention or treatment of PTSD. Multiple signaling pathways involved in immune cell regulation may play a crucial role in the development of PTSD. It is likely that the traumatic events experienced by PTSD patients may trigger epigenetic modulation of the immune system leading to an altered profile of the immune responses. Thus, identifying such epigenetic pathways may offer novel biomarkers as well as new approaches in understanding the molecular basis of immune dysfunction in PTSD patients. The possible functions and mechanisms involved in individual dysregulated cytokines in PTSD have also been discussed in this chapter.

Chapter VI - Cytokine is a generic name used for a diverse group of soluble low molecular mass, biochemically distinct glycoproteins, found in most cells and tissue types. They are similar to peptide hormones since they have the ability to facilitate communication, trigger specific receptor signaling and modulate the function of various cells and tissues at a very low concentration (nano to picomolar). Being pleiotropic and functionally redundant, cytokines can be classified into six distinct groups namely, Interleukins (ILs); Colony Stimulating Factors (CSFs); Tumour Necrosis Factors (TNFs); Interferons (IFNs); Transforming Growth Factors (TGFs) and Chemokines. Cytokines undergo physiological changes during infection or tissue damage in order to play a role in defense or repair processes. Therefore, their function is to trigger cellular responses. However, there are some cytokines which can potently facilitate harmful cellular responses; but there are also compounds, i.e. antagonists, that can prevent or limit such harmful effects. Controlled release

of these glycoproteins into the micro-environment is essential for their mode of action, functioning and stability.

Although most cytokine receptors are multi-subunit structures that bind to ligands, they also have the ability to function as signal transducers due to intrinsic Tyrosine Kinase (TK) activity. Signal transduction components can be shared by different receptors which explains functional redundancy. Various cytokines have been associated with carcinogenesis or an ability to promote cancer as well as other abnormalities. Therefore, perturbations in the production and activity of cytokines may lead to unfavorable effects on cellular homeostasis.

Multiple cytokines and growth factors including Interleukin (IL)-1, IL-6 and TNF alpha (TNF-α) are involved in wound healing. In abnormal or diseased state(s) such as diabetes mellitus (DM) or psoriasis, production of these growth factors or cytokines is altered such that inflammatory cytokines are usually elevated. Phototherapy has been reported to accelerate wound healing, attenuate pain and cease inflammation. However, the effect of phototherapy on cytokine modulation has not been explored extensively, especially under various stress mechanisms. Furthermore, the pathway that Photomodulation induces pro-inflammatory cytokines has not been clearly elucidated. This chapter explores the basic classification and function of cytokines focusing on their role during diseased states such as wound healing, and finally identifies the possible contribution of Photomodulation in up-regulation of specific cytokines involved in wound healing process.

Chapter VII - Cardiomyoplasty consists of implanting stem cells into ischemic tissue to reduce cellular death or induce cellular regeneration. In vivo studies demonstrated that tissue damage inflicted by ischemia was lessened in the presence of stem cells. Three mechanisms have been proposed to explain this effect. These include cellular differentiation, cell fusion, or secretion of paracrine factors. Recent studies suggest that secretion of cytokines may explain the regenerative process observed in stem cells. It appears that a delicate interplay between pro-inflammatory and anti-inflammatory cytokines regulates the expression of enzymes linked to cellular degradation. These findings will help redefine the direction of cardiomyoplasty research in new directions.

Chapter VIII - Osteoarthritis (OA) is the most common form of joint disease. It is the most common cause of chronic disability in older adults. OA has enormous socioeconomic consequences for healthcare systems in North America, Europe and throughout the rest of the developed world. OA is associated with articular cartilage destruction, subchondral bone remodeling and synovial thickening. Although OA was traditionally viewed as a "wear and tear" degenerative condition of synovial joints, recent studies have demonstrated a significant inflammatory component to the disease, which includes increased expression and activity of several secreted proinflammatory cytokines in the joint tissues that drive production of matrix-degrading enzymes. Interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-α) are key cytokines involved in degeneration of articular cartilage matrix, which makes them and their downstream signaling pathways prime targets for novel therapeutic strategies. Apart from IL-1β and TNF-α, several other cytokines and chemokines including IL-6, IL-8 and IL-17 are implicated in OA. These proinflammatory cytokines bind to their respective cell surface receptors and activate inflammatory signaling pathways culminating with the activation of nuclear factor κB (NF-κB) a transcription factor that can be triggered by stress-related stimuli, including excessive mechanical stress and extracellular matrix (ECM) degradation products. Once activated, NF-κB regulates the expression of many cytokines, chemokines, adhesion molecules, inflammatory mediators, and several matrix-degrading

enzymes. Therefore, proinflammatory cytokines and their cell surface receptors, as well as NF-κB and associated signaling pathways can be targeted in OA. This chapter reviews the current state of play regarding the role of proinflammatory cytokines in the pathophysiology of OA, and addresses the potential of anti-cytokine and anti-NF-κB therapy in the treatment of this disease. The authors also discuss the potential for complementary therapies using natural products such as curcumin and resveratrol.

Chapter IX - Scavenger receptor A (SRA), also called CD204, is a phagocytic pattern recognition receptor primarily expressed on myeloid cells, such as macrophages and dendritic cells. Over the past 20 years, tremendous advances have been made in elucidating the diverse functions of SRA/CD204 in different cellular processes, including lipid metabolism, recognition and clearance of pathogens or modified self molecules, as well as immune homeostasis. In this chapter, the authors examine the current understanding of the important roles of SRA/CD204 in inflammatory responses, cytokine production, host defense and pathogenesis of diseases. The authors highlight a previously unrecognized feature of SRA/CD204 action in the attenuation of adaptive immune responses and tumor immunity. The molecular details of functional interference of toll-like receptor-elicited inflammatory signaling cascades by SRA/CD204 are also discussed. It is believed that a better understanding of the physiological functions of SRA/CD204 will lead to new opportunities for therapeutic intervention in cancer, cardiovascular disease and other diseases characterized by chronic inflammation.

Chapter X - Cancer is a complex process in which cytokines are thought to play an important role. Cytokines are low-molecular weight soluble proteins that transmit signals between cells and are involved in several disorders. It has been well established that interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α), named pro-inflammatory cytokines, play a key role in inflammatory processes by triggering activation of nuclear factor-kappa B (NF-kB).

TNF-α can induce apoptosis through the intracellular signal transduction pathway involving the protein kinases TRAF-2 (integration point of apoptotic and survival signals), ASK1 (pro-apoptotic protein), MEK-4 (p38 activator and metastasis suppressor gene), JNK (stress mitogen activated protein kinase) and the transcription factor AP-1. TNF-α also induces cell proliferation either by p38 activation or when TRAF-2 simultaneously induces NIK-mediated activation of NF-kB. NIK and p38 may also be activated by IL-1. In fact, p38 activates several transcription factors, such as Elk-1, ATF-2 and NF-kB. The antitumor effects of TNF-α are mediated by inducing the expression of pro-apoptotic proteins, such as members of bcl-2 family as well as cell cycle inhibitors including p53 and p21. TNF-α also participates in oncogenesis and metastasis of different tissues.

IL-1 is another physiological regulator of p38 and NIK which activates PAK-1by binding to two GTPases, called Cdc42 and Rac. These two molecules activate PAK-1, which in turn induces activation of MEK-6 and p38. IL-1 also activates NIK and stimulates IKK-β, which induces IkB-α degradation. IKK complex phosphorylates IkB, following its ubiquitination and rapid degradation, resulting in the nuclear translocation of NF-kB. This in turn, activates target genes involved in carcinogenesis: tumor initiation, malignant transformation and metastasis

IL-6 exerts its effects through the membrane receptor complex composed of IL-6 receptor α (IL-6Rα) and glycoprotein 130 (gp130). The binding of IL-6 to IL-6Rα induces

dimerization of gp130 and, subsequently, the activation of constitutively-associated gp130 Jak proteins. Jak proteins can simultaneously trigger functionally distinct and even opposing signaling pathways. One of the pathways leads to the activation of Ras by stimulating the exchange of Ras-bound GDP and GTP. Then, Ras initiates a MAPK cascade by sequential phosphorylation of Raf-1, MEK1/2 and ERK1/2 in a process that culminates in modulation of gene transcription through activation of several transcription factors, such as c-Myc, ATF-2, Elk-1 or NF-kB.

The aim of this review is to elucidate the possible involvement of TNF-α/IL-1/IL-6 signal transduction pathways in the progression of prostate cancer and their role in altering the balance between apoptosis and cell proliferation. The authors will also discuss the importance of some components of the signaling pathways as potential therapeutic targets for prostate cancer.

Chapter XI - Angiogenesis, the formation of new blood vessels from pre-existing ones, takes place in various physiological and pathological conditions and is fundamental for tumor progression in the form of growth, invasion, and metastasis.

Vascular endothelial growth factor (VEGF) is a major regulator of tumor-associated angiogenesis, which promotes tumor growth, invasion, and metastasis. The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor. VEGF gene encodes for VEGF-A isoforms (VEGF-A121–206) by alternative splicing. The heparin-binding domains help VEGF-A to anchor to the extracellular matrix (ECM), and are involved in binding to heparan sulfate and presentation to VEGF receptors (VEGFR).

All the VEGF isoforms share common tyrosine kinase receptors, including VEGFR-1 or Flt-1, VEGFR-2 or KDR/Flk-1, and VEGFR-3 or Flt-4. VEGF isoforms bind with high-affinity to VEGFRs and play an essential role in angiogenesis, vasculogenesis, and lymphangiogenesis. A non-kinase receptor, neuropilin-1, initially shown to mediate guidance of neurite growth, acts as a high-affinity co-receptor that enhances the binding of VEGF-A to VEGFR-2, and is expressed on the surface of endothelial as well as tumor cells. VEGFRs relay signals via phospho-tyrosine residues, located in the carboxy-terminal region of a tyrosine kinase cascade that involvs various intracellular proteins. MAP kinases (MAPK) are the final effectors of the signal transduction to nucleus, where they modulate the expression of genes involved in several biological activities of endothelial cells.

VEGF exerts autocrine and paracrine effects in multiple myeloma (MM) by stimulating motility and survival of tumor cells that express VEGFR as well as in endothelial cells and other stromal cells of the bone marrow milieu. Many antiangiogenic drugs targeting VEGF/VEGFR pathway (i.e., Bevacizumab, Thalidomide and its immunomodulatory derivatives, proteasome inhibitors, arsenic trioxide, tyrosine kinase inhibitors) are actually employed in the treatment of MM patients, and other molecules are under preclinical development.

Chapter XII - Periodontal disease is a multifactorial infectious disease initiated by bacteria colonized the tooth surface and gingival sulcus, and characterized by inflammatory responses leading to the destruction of the tooth-supporting gingival connective tissue and bone. It has been considered that the networks of pro-inflammatory cytokines, such as interleukin (IL)-1, tumor necrosis factor (TNF)-α and interferon (IFN)- γ,, produced by a number of cell types, including T cells, B cells, keratinocytes, fibroblasts, dendritic cells, and endothelial cells, play important roles in the process of periodontal disease. Peri-implantitis, an inflammatory condition that affects alveolar bone and soft tissues around dental implants,

is also associated with increased levels of pro-inflammatory cytokines in the peri-implant crevicular fluid. As endogenous risk factors, gene polymorphisms on cytokine expression also involve in these chronic-destructive inflammatory diseases. In addition to local chronic inflammation, the association between periodontal disease and systemic diseases, such as diabetes mellitus, preterm birth, stroke and atherosclerotic cardiovascular disease, has been proposed. Especially, because of the increase in pro-inflammatory cytokines and an ongoing cytokine-induced acute-phase response, type 2 diabetes and obesity can contribute to periodontal disease. Recently, it has been suggested that epigenetic alterations, such as hyper- and hypo-methylation of cytokine genes, influence the pathogenesis of periodontal disease by inducing a change in cytokine profile. Further investigations on the role of cytokines in periodontal disease may provide insight into the processes underlying the onset and progression of this chronic-destructive inflammatory disease.