Preface

This book provides leading edge research on a cell cycle, which is an ordered and highly controlled set of events that leads to cell growth and proliferation. Cell cycle progression is driven by changes in the substrate specificity and subcellular localization of cyclin-dependent kinases (Cdks), which in turn are modulated by a collection of cyclins, Cdk-activating and Cdk-inhibiting kinases, and Cdk inhibitors (CDKIs). Regulation of the cell cycle is critical for the normal development of multicellular organisms and dysregulation of cell cycle could lead to cancer, a disease where normal cell growth and behavior are lost. Cell cycle regulation is tightly controlled by both synthesis and degradation of short-lived proteins, such as cyclins and CDKIs, and degradation of these proteins is mainly mediated by the ubiquitin-dependent proteasome pathway.

Short Communication - Microenvironmental stimuli cause multiple signal transduction pathways which determine cellular response. Mitogen-activated protein kinases (MAPKs) are pivotal signal cascades to transduce signals into dynamic gene expression waves in the nucleus. Gene expression patterns in given cells are totally dependent on the combined signals and integrity of activated transcription factors. The activating protein-1 (AP-1) is a classical transcription factor that can transduce MAPK signals into the gene expression pattern changes and this cellular system has a large impact on pathophysiological aspects of cells. Indeed, AP-1 is involved in a wide range of cellular events including cell proliferation, transformation, apoptosis, and stress response. Jun joins in with the AP-1 transcription complex as a homodimer or heterodimer, and has been identified as a mammalian cellular homologue of retroviral onco-proteins. Jun is known as an immediate early gene and its activity is largely regulated by MAPK signals. Expression of Jun can be induced by oncogenic stress. Taken together, these facts indicate that Jun is responsible for certain part of the AP-1 capability to modulate cellular response. It is also defined by the abundance of distinct members of AP-1 components within a given cell type and their surrounding stimuli. In this review, the authors focus on AP-1 function during cell fate determination. In particular, they review how Jun senses cellular stimuli and functions in a wide range of pivotal cellular processes.

Chapter I - This chapter discusses the role of the insulin-like growth factor (IGF) family in the proliferative regulation of vertebrate cells *in vitro* and *in vivo*. The initial part of this chapter peruses the fundamental knowledge in the regulation of cell cycle regulation, its

gatekeeper checkpoints, and markers commonly utilized for assessing and quantifying its progression. Recent findings in genomics and post-genomics position characteristics of the architecture and assembly mechanism of chromatin at a critical and pivotal point in the commitment of the cell to continue to pursue its proliferation schedule through the cell cycle, or to engage in apoptotic programmed cell death. The complex family of insulin-like growth factors (e.g., IGF-1 & 2), their receptors (i.e., IGF-1R, IGF-2R), and binding proteins (i.e., IGFBP's) together form a complex interactomic system, whose role in regulating traversal of the cell cycle is increasingly characterized, particularly in terms of its synergy with other cell proliferative factors. The chapter concludes with a discussion of the translational implications of this fundamental *in vitro* knowledge in the context of patients with diabetes, with cancer, and aging-neuro-degenerative diseases.

Chapter II - Cell cycle control is a fundamental process for maintenance of the genome stability. An aberrant cell cycle eventually transforms the cell into a malignant phenotype. Among cell cycle controllers, p53, c-Myc, and E2F1 are pivotal transcription factors, as they determine the cell fate during cell damage. MicroRNAs (miRNAs) are emergent members of small and non protein-coding RNA molecules of about 22 nucleotides in length that repress translation and promote mRNA degradation by sequence-specific interaction with mRNA. More than four hundred miRNAs have been identified so far in humans (http://microrna.sanger.ac.uk). Deregulation of miRNAs expression has been shown in human pathogenesis especially for many cancers; however, the overall picture as to what mechanisms deregulate miRNAs during tumor formation remains unclear. To better understand the molecular etiology of cancer, we need to take a count of miRNAs. In this review, the authors focus on recent advances concerning the functional link between miRNAs and transcriptional factors relevant to the cell cycle control and carcinogenesis.

Chapter III - All living entities, from cells to the human body, experience periodic functional and morphologic abnormalities, intermingled with the state of health. If and how the various states are related, and what factors assume greater or lesser significance in this process, however, is subject to discussion. This chapter considers that all the various states, experienced by biologic entities during their life cycles, are reflections of their compliance with systems principles. This view is based on the concept of cycles and systems inter-relatedness.

Systems science, complexity, and chaos theories were employed to construct a conceptual model applicable to living entities. For each state, representative systems' characteristics were matched to examples of approximate biologic equivalents. This model conceptualizes *a zone of order* and a *zone of chaos* with an overlapping but fragile *health territory*, the heart of this schema. The *health territory* is proposed to be a dynamic amalgamation of the proximate *outer core* of the *zone of order* and the *inner edge* of the *zone of chaos*. In addition, two extremes states are postulated as well: the *outer edge* of the *zone of chaos* and the *zone of entropy* which predominates within the *inner core* of the *zone of order*.

Examples of plausible correlations were found between cancer and the *outer edge* of the *zone of chaos*. A similar association was found between degenerative/inflammatory diseases, including aging, and the *zone of entropy*. Based on this model, biologic entities which stray into the postulated extreme states of *chaos* or *entropy* may still reverse back to the *health territory* by restoring their *organized complexity*. The exponential cellular growth within the

zone of chaos, characteristic of cancer, could be changed through a process of cyto-education which reverses *disorganized complexity* to an organized one by creating an environment which highly favors cellular differentiation instead of blind multiplication. The path back to the *health territory* from the second extreme, the system-engulfing *entropy*, would involve a process of increasing system's *complexity*.

Applying systems science principles to biologic entities, as attempted in this model, not only allows for the appreciation of disease states in a different light but also suggests what steps could be taken to return the entire system into the state of health.

Chapter IV - Signaling from Transforming Growth Factor-β (TGFβ) through its transmembrane receptor serine-threonine kinases plays an essential role in cell proliferation, differentiation, apoptosis, and the pathogenesis of many human diseases in various tissues including hematopoietic cells. One of the major functions of TGFβ in hematopoiesis is its inhibitory effect on cell proliferation. Downregulation of multiple cell cycle-regulatory molecules appears to be a dominant event in TGFβ-mediated growth inhibition of several human myeloid leukemia cell lines. At least, the inhibition of some of the molecules is regulated at mRNA level. Both G1-and G2-check point protein kinases participate in the regulation of TGFβ-mediated growth inhibition, whereas Cdk inhibitor p27-induced by TGFβ may have both a positive and negative role. TGFβ also rapidly inhibits phosphorylation of pRb at several serine and threonine residues and regulates the association of a repressor E2F transcription factor, E2F-4, with pRb family proteins (pRb, p107, and p130). Major p107-E2F complexes are found in proliferating cells whereas the under-phosphorylated pRb and p130 are associated with E2F-4 in G1 phase. Since TGFβ inhibits synthesis of p107 and has no effect on the expression of E2F-4, it suggests that E2F-4 is released from p107 and switched to pRb and p130 in response to TGFβ stimulation. Western blot and DNA binding experiments suggest that p130 and p107, but not pRb, play a critical role in regulating E2F response genes in TGFβ-mediated cell cycle control in human hematopoietic cells. Although the activation of SMAD-independent p44/42 MAPK signal by TGFβ has been recently reported in various cell types, which is linked to TGFβ-induced proliferation, apoptosis, and growth inhibition, TGFβ does not activate p44/42 MAP kinase pathways in human myeloid leukemia cells whose growth is inhibited by TGFβ, but turns off GM-CSF-induced p44/42 MAPK signal via inhibition of PI3-K-Akt pathway.

Chapter V - Cell cycle is dependent on correct cycling and activation of Cyclin Dependent Kinases (CDKs)/Cyclin pairs. Their protein levels and regulation mechanisms are altered in transformed cells and CDKs are considered attractive targets for cancer therapy. Data from knockout and siRNA experiments have shown a redundancy in CDKs functions. Recent clinical trials and preclinical studies have identified the possibility to use inhibitors specific for subclasses of cell-cycle CDKs (CDK1/2 or CDK4/6) as single agents for a few specific cancer types that show a more pronounced dependency on CDKs functions. Pan-CDK inhibitors are giving, instead, more promising results. They inhibit both cell-cycle CDKs and transcriptional CDKs by combining cytostatic and apoptotic effects in cancer cells. Apoptosis is induced through depletion of anti-apoptotic proteins, sensitive to inhibition of transcription because encoded by mRNAs with short half-lifes and rapid turnover. Recently, new crystal structures of transcriptional CDKs (CDK7 and CDK9) have provided molecular basis for targeting this subclass. Combinations of pan-CDK inhibitors

with traditional chemotherapic agents have shown a synergistic cytotoxic effect in a variety of cancers and the restoration of susceptibility in cancers that developed resistance to traditional therapies. Flavopiridol, a pan-CDK inhibitor, is also being used in clinical trials in combination with Histone deacetylase (HDAC) inhibitors, which are also being developed as anti-neoplastic drugs. Evidence has been reported of cross-talk between CDKs and HDACs that indicates the existence of a complex cross-regulation mechanism. This cross-talk between CDKs and HDACs mediated by Retinoblastoma (pRb) and/or CDK inhibitors (CKI) is of particular pharmacological relevance. It engenders the expectation that the combined pharmacological inhibition of CDKs and HDACs might have a higher therapeutic profile than the single treatment.

Chapter VI - Down syndrome or Trisomy 21 is the most frequent genetic cause (1/700 new birth) of the mental retardation. It is characterized by the triplication of human chromosome 21 in all cells and by overdosage of genes on this chromosome in all cells. Thus, trisomy 21 could provide a genetic model for the role of aneuploidy in leukemogenesis, tumorigenesis, cancerigenesis and neurogenesis abnormalities, and to decipher the molecular and cellular mechanisms involved in these different abnormalities. Genetic overdosage determines transcriptional alteration of most of the chromosome 21 genes. Thus, trisomic cells suffer of dosage imbalance of a lot of proteins that can potentially impair all molecular pathways, including cell cycle control. Trisomy 21 is a unique example of the parallel amplification of multiple genes, which may act cooperatively in the same leukemogenic, tumorigenic, cancerigenic or neurogenic pathway. A better knowledge of the function of genes mapping to chromosome 21 may contribute to the understanding of the several mechanisms of diseases, acting in patients with DS, such as leukaemia, tumors, cancer, and neurogenesis alterations related to cell cycle control alterations. Studies of the three oncogenes AML1, ERG and ETS2, higly related to the genesis of leukemias, are of the most interest to contribute to the general understanding of the oncogenic mechanisms of chromosomal aneuploidies, the most common abnormalities in cancer. In addition, the direct involvement of the human chromosome 21 Single minded 2 gene (SIM2) in the inhibition of gene expression, growth inhibition, inhibition of tumor growth as well as induction of apoptosis that could involve a block of cell cycle, establish SIM2 gene as a molecular target for cancer therapeutics and have additional important implications for the future diagnosis and treatment of specific solid tumors as well as for further understanding the cancer risk in Down syndrome patients. In addition, some members of the phosphorylation pathways that control the cell cycle are encoded by specific chromosome 21 genes, particularly the minibrain gene Dyrk1A, suggesting some alteration in cell cycle control in Down syndrome individuals. The involvement of Dyrk1A gene in the regulation of neural proliferation on the basis of alterations in the proliferation centres of brain of Drosophila minibrain (MNB) mutants and the altered levels of cell cycle regulators in transgenic mice overexpressing Dyrk1A as well as the phosphorylation of cell cycle regulators by DYRK1A support the evolutionary conservation of DYRK1A role as regulator of proliferation in neural progenitor and its role in cell cycle regulation. All these genes localized in the human chromosome 21 play important roles in cell cycle and cell growth and, with the recent developments in genomics and proteomics, could promise significant advancements in Down syndrome knowledge and considerable progresses to decode the molecular and cellular mechanisms

involved in the DS associated diseases related to cell cycle alterations in view of new development of drugs and treatments.

Chapter VII - Progression through each phase of the cell cycle (G1, S, G2 and M) is precisely controlled by the activity of distinct cyclin-dependent kinases (CDKs) and their associated regulatory subunits known as cyclins. The composition and regulation of CDKs vary according to cell type and environment. The transition from the first growth G1 phase to the DNA synthesis S phase is regulated by the phosphorylation of retinoblastoma protein (pRb). The cyclin D1/CDK4/6 complex phosphorylates pRb, while $p16^{INK4a}$, a CDK inhibitor that interacts with CDK4, inhibits this process. Further CDK inhibitors $p15^{INK4b}$, $p21^{CIP1/WAF1}$, and $p27^{KIP1}$ affect pRb. The tumor suppressor activity of TGFβ depends on its ability to regulate the expression of a number of proteins that play key roles in the control of cell cycle progression from the G1 phase to the S phase. TGFβ is able to induce growth arrest in a variety of cell types including epithelial, endothelial, hematopoietic, neural, and certain types of mesenchymal cells. TGFβ induces the transcription of genes for $p15^{INK4b}$ and $p21^{CIP1/WAF1}$. The $p15^{INK4b}$ specifically blocks the activation of CDK4 and CDK6, whereas $p21^{CIP1/WAF1}$ and $p27^{KIP1}$ inhibit the activity of CDK2. Induction of $p15^{INK4b}$ and $p21^{CIP1/WAF1}$ is important for TGFβ mediated growth arrest in epithelial cells, but not in hematopoietic cells where upregulation of $p57^{KIP2}$ is essential for TGFβ-induced growth arrest. In epithelial cells in addition to regulating the activity of CDK complexes, TGFβ also inhibits the transcription of the protooncogene c-myc that plays a role in controlling cell cycle entry into S phase in higher eukaryotes. Downregulation of c-myc by TGFβ is frequently impaired in cancer cells. The identification and characterization of TGFβ signaling pathway increased our understanding of the dual role of TGFβ as a tumor suppressor and prooncogenic factor. In late stages of epithelial tumorigenesis tumor cells become resistant to growth inhibition by TGFβ due to inactivation of TGFβ signaling pathway or aberrant regulation of the cell cycle. Solid tumors frequently harbor mutations in members of the TGFβ signaling pathway, including in Smad4 and TβRII. On the other hand, hematologic cancers generally become TGFβ resistant through decreased expression of TGFβ signaling by oncoproteins including Evi1, Tax and fusion proteins Runx1-Evi1, Runx1-ETO and PML-RARα. Tumor cells often show increased expression or production of TGFβ. TGFβ can regulate extracellular matrix composition and degradation that play complex roles in tumor invasion and metastasis.

Chapter VIII - The CCAAT/enhancer binding protein alpha (C/EBPα) is the founding member of a family of related leucine zipper transcription factors that play important roles in differentiation of liver, lung, adipocyte and myeloid cells. C/EBPα controls differentiation-dependent gene expression and inhibits proliferation in these types of cells. The capacity of C/EBPα to promote growth arrest has been studied *in vitro*, by analysis of knockout mice and by examination of leukemic cells. Several models of C/EBPα-induced growth arrest have been described. These include C/EBPα-mediated (1) stabilization of the cyclin-dependent kinase 2 (CDK2) inhibitor, $p21^{WAF1/CIP1}$, (2) regulation of growth-inhibiting Rb-E2F complexes, (3) interaction with free E2F, inhibition of E2F activity and down-regulation of the E2F target gene c-Myc, (4) interaction with Max, a member of the basic region –helix-loop-helix-leucine zipper proteins, that belongs to a network of transcription factors, which includes the Myc and Mad families of protein, (5) inhibition of CDK2 and CDK4 activity, and (6) interaction with the SWI/SNF chromatin remodelling complexes. C/EBPα may

promote growth arrest by cell specific mechanisms. This means that different models of C/EBPα-mediated cell cycle arrest operate in different cell types. Different regions of C/EBPα are involved in growth inhibition. According to the third model, C/EBPα interacts with free transcription factor E2F through the non-DNA binding surface of its basic region and N-terminal region of the C/EBPα also plays role in growth inhibition. The basic DNA-binding region of the C/EBPα is also involved in the C/EBPα and Max interaction. In the CDK2/CDK4 inhibition model, C/EBPα interacts with and inhibits the activity of CDK2/CDK4 through proline- and histidine-rich region located in the central part of C/EBPα. According to the SWI/SNF recruitment model, C/EBPα interacts with SWI/SNF components through a centrally located 75-amino acid region overlapping with the CDK2/CDK4 binding region. Acute myeloid leukemias (AMLs) are clonal disorders that are characterized by a block in differentiation along one or more haematopoietic lineage. Molecular abnormalities are frequently detected in AML. The genetic alterations in AML often affect transcription factors that also have an important role in normal hematopoiesis. C/EBPα mutations have been observed in AML patients with the frequency approximately 5-14% and are often associated with the induction of proliferation.

Chapter IX - Renal fibrosis is a common pathway of progressive renal disease and parallels the reduction in organ function that necessitates dialysis or transplantation. In the last decades, accumulating experimental and clinical evidence convincingly suggests that the renin-angiotensin system (RAS) is a key player in the progression of chronic kidney disease. Angiotensin II (ANG II), the main peptide of the RAS, was classically viewed as a vasoactive factor participating in the local and systemic hemodynamic regulation. With the progression of researches, it has emerged as a multifunctional cytokine exhibiting many non-hemodynamic effects such as growth, profibrotic, matrix metabolism and even proinflammation. These new understandings of ANG II have important clinical implications. It predicted and explained why blockade of the RAS would significantly slow the progression of fibrotic disease. However, it further suggested that higher doses and/or a combination of ANG II blockade with another agent or agents might truly halt the progressive fibrosis.

This review will focus on the non-hemodynamic aspect of ANG II and its contribution in renal fibrogenesis.

Chapter X - Aging is a complex set of phenotypes characterized by reduced repair and/or regeneration of lost or damaged cells. Mammalian ageing is associated with reduced regenerative capacity in tissues that contain stem cells. It has been proposed that this is at least partially caused by the senescence of progenitors with age. Mitogen-dependent progression through the first gap phase (G_1) and initiation of DNA synthesis (S phase) during the mammalian cell division cycle are cooperatively regulated by several classes of cyclin-dependent kinases (CDKs) whose activities are in turn constrained by CDK inhibitors (CKIs). CKIs are important negative regulators of the cell cycle. The Ink4a/Arf locus encodes 2 tumor suppressor molecules, p16INK4a and Arf, which are principal mediators of cellular senescence. Expression of the INK4a/ARF locus, is not only a major suppressor of cancer, but also an effector of mammalian aging. Ink4a/Arf expression is a biomarker of aging. The cell cycle inhibitor p16 (INK4A) is expressed in vivo in many tissues with age. The exposure of certain chronic stresses can trigger p16 (INK4A) expression and a senescence-like phenotype. Recent data suggest that expression of p16 (INK4a) induces an age-dependent

decrease in the proliferative capacity of certain tissue-specific stem cells and unipotent progenitors. Telomere shortening limits the proliferative lifespan of human cells by activation of DNA damage pathways, including upregulation of the cell cycle inhibitor p21. Cellular senescence induced by different stresses and telomere shortening appears to play an important role in the aging process.

Chapter XI - Maintenance of genomic integrity is critical for prevention of a wide variety of adverse cellular effects including apoptosis, cellular senescence, and malignant cell transformation. Under stress conditions and even during an unperturbed cell cycle, checkpoint proteins play the key role in genome maintenance by and mediating cellular response to DNA damage, and represent an essential part of the "cellular stress response proteome". Intact checkpoint signal transduction cascades check the presence of genome damage, trigger cell cycle arrest, and forward the information to the protein core of cell cycle machinery, replication apparatus, repair, and/or apoptotic protein cores. Genetic checkpoint defects lead to syndromes that demonstrate chromosomal instability, increased sensitivity to genotoxic stress, tissue degeneration, developmental retardation, premature aging, and cancer predisposition that is most extensively studied for the ATM-checkpoint mutated in *Ataxia telangiectasia*. Tissue specific epigenetic control over the function of cell cycle checkpoints can be, further, deregulated by aberrant DNA methylation status. The consequent checkpoint deregulation may result in tissue specific degenerative processes such as degeneration and calcification of heart aortic valves, diabetic cardiomyopathy, hyperhomocysteinemic cerebrovascular, peripheral vascular and coronary heart diseases, neurodegenerative disorders (Alzheimer and Parkinson diseases, amyotrophic lateral sclerosis, glaucoma), and premature aging frequently accompanied with cancer. This chapter focuses on the checkpoints shown to be crucial for unperturbed cell cycle regulation, deregulation of which might be considered as a potential molecular marker for early diagnosis of and therapy efficiency in neurodegenerative, cardiovascular and cancer diseases. An application of the most potent detection technologies such as "Clinical Proteomics" and "Disease-specific Transcriptomics" also considered here, allows a most specific selection of diagnostic markers.

Chapter XII - Dysregulation of cell cycle control is of major importance in cancer pathogenesis. Consequently, the identification of genetic and epigenetic changes in genes encoding cell cycle control proteins is instrumental to understand how dysregulation of the cell cycle machinery contributes to the proliferation of tumour cells. Coiled-coil domain containing 94 (CCDC94) was recently characterized as a novel human nuclear protein that plays a role in cell cycle control. Ectopic expression of CCDC94 protein *in vitro* results in cell cycle arrest whereas suppression of *CCDC94* mRNA induces a dramatic increase in cell proliferation. *CCDC94* was originally identified as a target gene of an acquired chromosome translocation in a patient with acute myeloid leukemia (AML) that resulted in its haplo-insufficiency in leukemic cells. *CCDC94* adds to a number of other genes involved in the cell cycle machinery whose expression is frequently altered in hematological malignancies. Chromosome rearrangements and deletions involving D-type cyclins, cyclin-dependent kinases (CDKs) or cyclin-dependent kinase inhibitors (CDKIs) are frequent in lymphoid tumours. In particular, chromosome translocations cause overexpression of D-type cyclins in mature B-cell neoplasms such as mantle cell lymphoma and multiple myeloma whereas different types of rearrangements lead to overexpression of CDK6 in mature T-cell

malignancies. In addition, deletion or promoter hypermethylation of *CDKN2A* and/or *CDKN2B* genes, which encode 2 members of the INK4A family of CDKIs, $p16^{INK4A}$ and $p15^{INK4B}$ respectively, are recurrent events in acute lymphoblastic leukemias. In contrast, patients with myelodysplastic syndrome and AML frequently present with hypermethylation of *CDKN2B* alone. This review summarizes the current knowledge on the molecular changes involving D-type cyclins, CDKs and CDKIs in several hematological neoplasms and addresses the most relevant effects of these alterations in the control of cell cycle.

Chapter XIII - Cell cycle is an ordered set of processes by which one cell grows and divides into two daughter cells. Drosophila is an attractive organism that has been used as a model for the study of the mitotic cell cycle. The fruit fly has not only been extensively used for genetics studies but also its developmental biology is highly suitable for studies of the mitotic cycle. The mitotic division in the early embryos consists of rapid successions of Mitosis (M) and DNA synthesis (S) phases with no discernible G1 or G2 (Gap) phases as found at later stages of development. In the subsequent development of the organism, two different types of tissue arise, having either proliferating diploid cells or cells that do not divide but become highly polyploid. This review presents the various modes of cell cycling that occur during Drosophila development and discusses their regulation in light of the latest findings.

Chapter XIV - This chapter introduces the concept of cell cycle control and the many enzymes involved. The authors provide a brief history on the first research and continue with their most recent research on this subject.

Chapter XV - Community pharmacists are integral members of the health care team who are ideally placed to offer and provide health education to patients in a timely and regular manner. Community pharmacists are highly skilled and knowledgeable health care professionals and, as with other members of the health care team, are assumed to have the skills to transfer their knowledge through effective education to the patient. However, knowledge associated with health and disease management is ever changing, and the need for pharmacists to effectively uptake knowledge and then transfer it to patients is one of the keys to effective disease management in the community setting.

This article reports on an innovative approach to pharmacist education, utilizing the "Train the Trainer" educational model, targeting appropriate inhaler use by people with asthma in the community. The authors highlight the way in which an educational module based on theory can be effectively delivered to community pharmacists and feasibly implemented into practice. Following the implementation process, the innovative educational module resulted in improved clinical and humanistic health outcomes for people with asthma in the community.

Chapter XVI - In recent years, several dietary compounds or nutritional agents, i.e. isoflavone genistein, indole-3-carbinol (I3C), 3,3'-diindolylmethane (DIM), curcumin, (-)-epigallocatechin-3-gallate (EGCG), resveratrol, lycopene, etc, have been recognized as cancer chemopreventive agents because of their anti-carcinogenic activity. Moreover, these compounds also exert their anti-tumor activities through the regulation of different cell signaling pathways, resulting in the cell cycle arrest and subsequent cell growth inhibition. The cell cycle is known to be tightly regulated by different cyclins and cyclin dependent kinases (CDKs), which form key regulatory complex, in different phases of the cell cycle.

The activity of cyclins/CDKs complex is negatively regulated by several CDK inhibitors (CDKIs) including $p21^{WAF1}$, $p27^{KIP1}$, $p16^{INK4a}$, etc. In addition, the molecules which interact with the key regulatory complex and CDKIs also influence the progression of cell cycle. The data from the authors' laboratory and others have demonstrated that dietary chemopreventive agents inhibit the kinase activity of CDKs and regulate the expression of cyclins, CDKs, and CDKIs, leading to the cell cycle arrest at different phases of cell cycle. A number of molecules, which are critical for the cell cycle control, have been found to be altered by chemopreventive agents in the cell cycle synchronization assay. Moreover, the authors and other investigators have utilized gene expression profiling showing alteration in the expression of genes that are related to cell cycle progression by chemopreventive agents. In summary, emerging studies using genomics and proteomics is likely to advance our knowledge regarding the molecular mechanism of cell cycle regulation as a target for the prevention and/or treatment of human cancers by nutritional agents.

Chapter XVII - Chromatin is the intricate complex of proteins and DNA that is involved in the control of the cell cycle and the modulation of gene expression in higher organisms. Methods in biochemistry and molecular biology have made it possible to identify and isolate many of the chromatin-related molecules vital to these processes. A wealth of information on the structure and function of these molecules and larger complexes is increasingly being elucidated by biophysical techniques, such as: mass spectrometry for highly accurate protein identification; electron microscopy (EM), nuclear magnetic resonance (NMR), small-angle X-ray and neutron scattering (SAXS & SANS) and in particular X-ray crystallography at third generation synchrotron radiation sources for solving complete three-dimensional static structures of macromolecules to atomic resolution.

In this review a non-exhaustive overview of the current status and recent developments in these and other biophysical techniques in relation to the structure and function of chromatin-related molecules is given. Some of the possibilities for this crucial area of research with single-molecule methods and future fourth-generation light sources are also discussed.