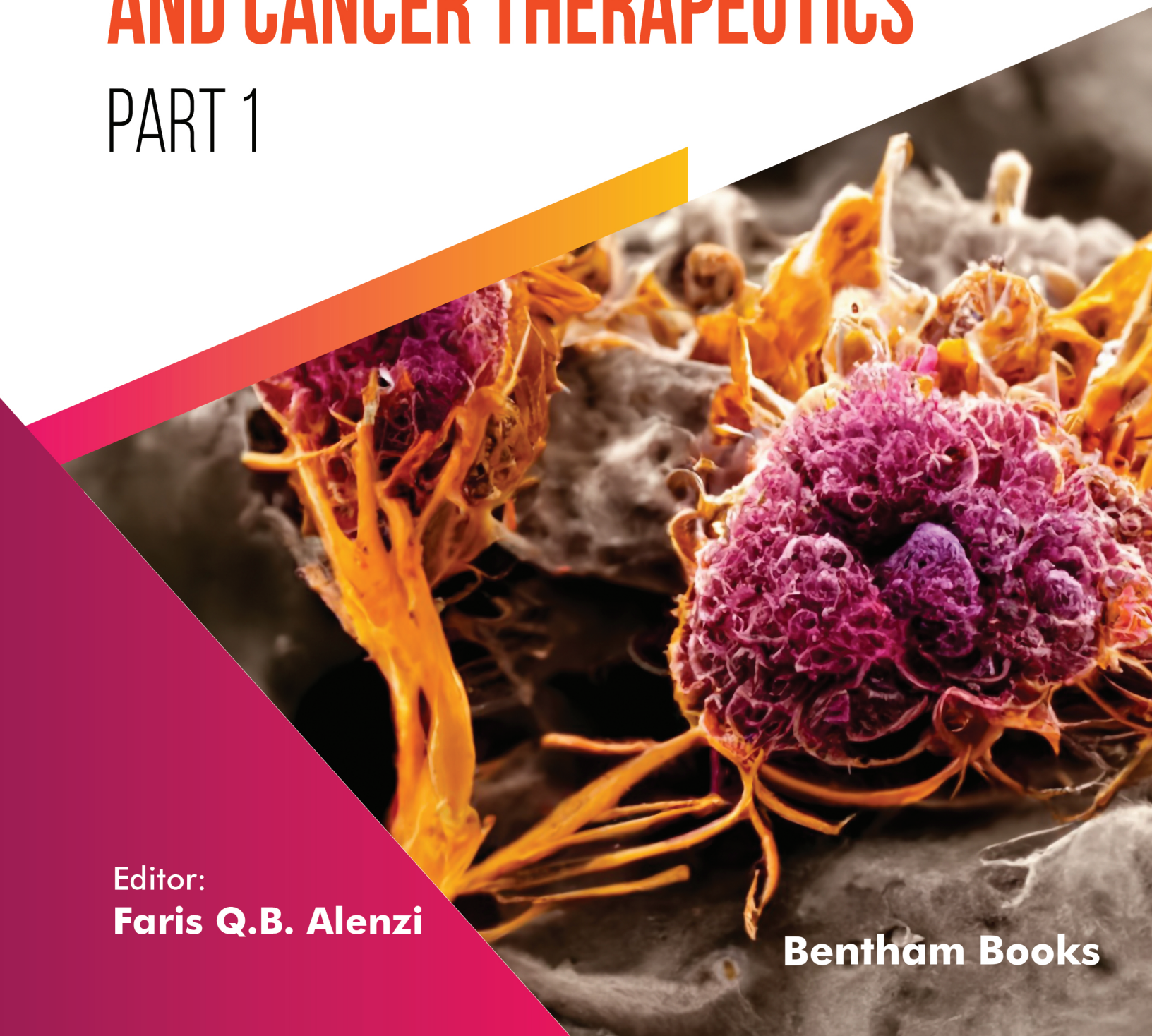
MOLECULAR TARGETS AND CANCER THERAPEUTICS

PART 1



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Molecular Targets and Cancer Therapeutics (Part 1)

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PREFACE

Oncology is a fast-evolving field. The last decade had witnessed enormous, complex discoveries in cancer biology, genetics, mutations, diagnostics and new targeted biological therapies. The team of expert contributors to this book tried to present these major aspects including, cancer traits, exogenous factors of cancer, the biology of cancer, growth factors of cancer, signaling pathways of cancer and epigenetic factors of cancer, in a simple but, at the same time, using up to date information. The book will be a great resource for medical students, scientists, physicians and other healthcare professionals involved in cancer care and cancer research.

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DEDICATION

I dedicate this book to those who lost their lives because of this disease. May Allah bless them all!

To,

Fatema S. Albady Alanazi

Talal H. Almosaieed Alanazi

Saeed A. Baqader

Abdulla S. Alsiary

Moqaeem A. Alanazi

Nadda F. Alhassainan

Shaikha A. Alhabrdi

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CHAPTER 1

Introduction

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Abstract: Cancer is a complex family of diseases that usually begins with carcinogenesis, in which abnormal cells divide or develop wildly by not following the regular path of cell division and likewise can invade nearby tissues. Cancer cells demonstrate transformations in metabolism, which is frequently more anaerobic than normal and probably can tolerate hypoxic surroundings. The remarkable variability of the disease, at all levels, is the major challenge for cancer medicine. Six biological abilities gained during the multi-stage advances of human tumors are the maintenance of proliferative signaling, the prevention of growth suppressors, cell death resistance, replicative immortality allowance, angiogenesis induction, invasion, and metastasis activation. In this chapter, we discuss the features of cancer cells and the epidemiology of cancer for better understanding.

Keywords: Cancer, Characteristics, Definition, Epidemiology, Features.

INTRODUCTION

The biological revolution of the 20th century completely redesigned all fields of biomedical knowledge, including cancer research. The revolution partially produced by Watson and Crick's finding of the DNA double helix, which began in the mid-century, and continues to this day [1]. Furthermore, understanding its true significance and its long-standing ramifications is still in process. The stream of molecular biology, derived from this finding, provided answers to the most insightful problem of 20th-century biology and described how the genetic structure of a cell or organism determines its outlook and function [2].

Like many other biological disciplines, modern cancer research would have remained a theoretical science if this molecular foundation did not exist. By exploiting the evolution in the sciences of molecular biology and genetics, many

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diverse biological phenomena, including cancer, currently have been partially explained. Surprisingly, it is also seen that most of the perceptions of the origins of malignant disease are out of the laboratory benches of cancer researchers. As a substitute, significant knowledge that drives the need to achieve rapid development in cancer research is delivered from the study of diverse organisms, ranging from yeast to worms to flies [3].

Definition

Cancer is a disease in which an assembly of abnormal cells divides or develops wildly by not following the regular path of cell division and likewise can invade nearby tissues. Persistent subjection of the normal cells to signals that control whether the cell should rest, divide into another cell or die. A degree of autonomy from these signals could result in uncontrolled growth and proliferation develops cancer cells. This could become lethal if this development continues and expands, leading to a major cause of cancer-related deaths owing to the spreading of tumors, and a procedure termed metastasis [4].

The concepts of modern cancer biology are based upon unpretentious principles. Fundamentally, all mammalian cells share analogous molecular networks that control cell proliferation, differentiation, and cell death. Ordinary cells are malformed into cancers as an effect of alterations in these networks at several levels, including the molecular, biochemical, and cellular ones. Such mechanisms for these changes are limited and can be determined.

In the past decade, phenomenal research developments in cancer have given us a perception of how cancer cells progress this autonomy. The present definition of cancer is that it is a disease that involves alterations or mutations in the cell genome. These alterations (DNA mutations) yield proteins that spoil the delicate cellular stability between cell division and quiescence, causing cells that keep multiplying to form cancers [5].

Characteristics of Cancer

Cancer is a complex family of diseases that usually begins with a process called carcinogenesis. Such a complex process involves converting an ordinary cell into a cancer cell in the body. The cancer cells display cellular and nuclear pleomorphic, then lose normal arrangement of cells, therefore developing alterations in the cell membranes and organelles, and hence exhibit abnormal mitoses and chromosomal abnormalities [6].

Intervallic cellular adhesiveness (for the solid surface) and contact inhibition (amid cells) may be the consequences of alterations in the cell surface

glycoproteins and the underdeveloped tight junctions and desmosomes in malignant cells. Fluctuations in motility, adhesiveness, and contact inhibition possibly will promote invasion and the consequent formation of secondary malignant development metastasis.

Compared to a normal cell, cancer cells demonstrate transformations in metabolism. This metabolism of malignant cells is frequently more anaerobic than compared to normal hastily separating cells and is immensely speeded. Malignant cells can probably tolerate hypoxic surroundings. Glucose and amino acid uptake might be greater than before. These cells have extraordinary levels of hexokinase accumulation in their glucose consumption. In this scenario, the cancer cells lose the ability to synthesize specialized proteins distinct from segregated cells. Tumor growth is based on enzymes and other proteins produced by cancer cells [6].

The Hallmarks of Cancer

The remarkable variability of the disease at all levels, is the major challenge for cancer medicine. In the fall of 1999, Robert A. Weinberg and Hanahan depicted there were no credible organizational rules for the biological characteristics of tumors. In January 2000, they published an article "The Hallmarks of Cancer" to summarize these rules. The hallmarks of cancer constitute a fundamental belief that may deliver a rational basis for refining this complexity to better understand the mechanisms of the disease in its various manifestations [7].

For rationalizing the dynamics of neoplastic disorder, the hallmarks represent an organizing concept. Six biological abilities gained during the multi-stage advances of human tumors are the hallmarks of cancer. They comprise the maintenance of proliferative signaling, the prevention of growth suppressors, cell death resistance, replicative immortality allowance, angiogenesis induction, invasion, and metastasis activation. Underlying these hallmarks is genome instability, which produces the genetic variation which fast-tracks their acquisition, and inflammation, which nurtures several hallmark roles. Former era, conceptual advancement has added two emerging hallmarks of future generality to this list: energy metabolism reprogramming and evading immune destruction [7]. Apart from cancer, cell tumors demonstrate another measurement of complexity: they include a repertoire of engaged, ostensibly normal cells that contribute to the acquisition of hallmark characteristics by creating the "tumor microenvironment". Increasingly, awareness of the extensive application of these ideas will inspire the creation of innovative ways of treating human cancer.

The conceptualization includes eight acquired abilities-cancer hallmarks, and two generic neoplastic disease characteristics that promote their acquisition during the multi-stage neoplastic growth and malignant progression phase. Numerous cell

CHAPTER 2

Cancer Traits; Present and Future

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Abstract: This chapter on "Cancer Traits; Present and Future" begins with a description of the process of carcinogenesis and, finally, the abnormal process leading to carcinogenesis.

Cancer is a multi-step mechanism in which cells undergo biochemical and behavioral changes, causing them to proliferate in an unnecessary and untimely manner. These changes occur from modifications in mechanisms that regulate cell proliferation and longevity, relationships with neighboring cells, and the ability to escape the immune system. Modifications that contribute to cancer require genetic modifications that alter the DNA sequence. Another way to alter the program of cells is to adjust the conformation of chromatin, the matrix that bundles up DNA and controls its access through DNA reading, copying and repair machinery. These modifications are called "epigenetic. The abnormal process that leads to carcinogenesis includes early mutational events in carcinogenesis, microRNAs in human cancer and cancer stem cell hypothesis, Contact inhibition of proliferation, autophagy, necroptosis, signaling pathways, telomere deregulation, microenvironment, growth suppressors evasion, resisting cell death and sustained cell survival, enabling replicative immortality through activation of telomeres, inducing angiogenesis, ability to oppose apoptosis, and activating invasion and metastasis. Intensive research efforts during the last several decades have increased our understanding of carcinogenesis and have identified a genetic basis for the multi-step process of cancer development. Recognition and understating of the prevalent applicability of cancer cell characterization will increasingly affect the development of new means to treat human cancer.

Keywords: Angiogenesis, Apoptosis, Metastasis, Proliferation, Telomerase.

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Faris Q.B. Alenzi (Ed.)

INTRODUCTION

Mechanisms of Contact Inhibition and its Evasion

The term ‘contact inhibition’ denotes two separate but carefully related processes in cell biology, proliferation contact inhibition and locomotive contact inhibition, established by fibroblasts while in connection with each other. Fibroblasts, until they come into contact with a neighboring cell, they move about the culture dish surface. It leads to the inhibition of further cell migration, and regular cells attach each other, making a collection of cells on the culture dish. Around the surface of the culture dish, standard fibroblasts travel until they meet a neighboring cell. Regular cells bind to each other, and further cell migration is inhibited [1].

The elementary property (Contact inhibition of Proliferation (CIP)), by which cells stop to multiply and differentiate as allotted space is filled at the confluence point. CIP is upturned under conditions including augmented cell growth and proliferation, such as healing wounds or tissue regeneration and development of the embryo. However, CIP is absent in cancer cells, and the absence of this factor leads to tumorigenesis [2].

CIP is a regulatory process that helps prevent cells from expanding into a single cell layer of thickness. If the usable substrate space in the cell is more, it duplicates easily and travels liberally. This process will last until the cells surmount the entire substratum. Regular cells would avoid replicating at this stage. When motile cells come across the confluent cultures, they display diminished mitotic activity and mobility over time. Further, though mitotic inhibition occurs later, the ascending growth occurs between colonies in contact for several days. This delay between cell interaction and the initiation of inhibition of proliferation decreases as the culture becomes more mingled. Therefore, cell-cell contact is a necessary prerequisite for preventing the spread of contact but for mitotic inhibition, it is inadequate. In addition to interaction with further cells, under the restrictions and mechanical tension exerted by neighboring cells, the cell area of the contact-inhibited cell, reduces. Mechanical stress has also been proposed to serve as an inhibitory indication for mitosis. Also, mitotic inhibition is a spatial phenomenon that happens among a small number of cells in a potentially diverse population [3].

Unchanged human cells display natural cell activity and mediate their development and spread through interactions between signaling of growth factor, cell density and environmental nutrients. As cell density rises and uniform culture is formed, cell cycle arrest is activated, and mitogen signaling pathways are regulated independently of cell metabolism or external factors. This effect is known as CIP and is important for the suitable development of the embryo as well

as for differentiation, morphogenesis and tissue recovery; CIP is one of the main deregulation mechanisms in transformed cells during tumorigenesis. Many cancer cells are unaffected by confluence-tempted proliferation. Several theories were suggested to clarify the beginning of contact-reliant development arrest, like the discharge of inhibitory composites, the part of cell form on nutritional fatigue or growth aspects or growth or in the culture medium. This results in the migration of adjacent tissues, their metastases to adjacent organs, and ultimately tumorigenesis [1].

Cell-cell interactions influence intracellular signaling trails, such as ERK and Akt, and cell cycle growth is inhibited. To receptors that ease cell bonds, such as E/VE-Cadherin, growth factor receptors, interact themselves. Also, by automatically bonding adjacent cells and disturbing the spreading of traction powers, cadherins avoid interaction in multicellular clusters. Family proteins of ERM, Atypical Cadherin, Fat and Merlin, are also a part of the Hippo pathway that has developed as unique key regulators for the determination of organ size in both mammalian systems and drosophila, and contact inhibition. The lack of immunity related to malignant cell contact suppression will be affected by a reduction in the bond between the disk surface and malignant cells. Also, it could be from a rise in adhesion amid the regular and malignant cells, representing the *vitro* substitute as contact inhibition to the method to keep normal tissue homeostasis *in vivo*. When faced with normal cells, the movement of malignant cells in a given direction is not inhibited. The passage of regular cells, on the other hand, is obstructed when it is met by cells of malignancy. The cells are more rounded and extended than the malignant ones, which are spindle-made. Rounding of the cell is perhaps the index of the cell absence of adhesion to the substrate. Gene activation is caused by Cell-cell contact [1].

Recently, the NF2 gene product has been recognized by Merlin that it is involved in the suppression of the binding of adhesion molecules to the tyrosine kinase transmembrane receptor. The adhesivity of Merlin improves Cadherin-linked cell-to-cell bonding, and by recapturing receptors of growth factors, its ability to produce mitogenic signals is condensed. The other way of inhibition includes the epithelial polarity protein (LKB1), which escapes the mitogenic properties of enhanced Myc oncogene in ordered epithelial structures; on the other side, when expression LKB1 is inhibited, epithelial reliability is weakened, leading to Myc-induced renovation.

Cell adhesion affects a variety of cell behaviors by providing a wide range of mechanical and biochemical signals for cells. The Hippo-YAP pathway, which is primarily responsible for hindering cell formation in mammals, is one such pathway. Mainly, this pathway consists of a phosphorylation cascade, which is

CHAPTER 3

Exogenous Factors and Cancer

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Abstract: The causation of cancer, whether exogenous or endogenous, is a cornerstone of cancer prevention and treatment. Many intrinsic factors are discussed in other chapters of this book; this chapter will shed light on exogenous factors influencing cancer with detailed specific examples of microbial, physical and chemical factors.

Microbial role in cancer has been debated over many centuries, whether as an antagonist or a cause, since Imhotep's time through the mid-17th century when cancer was considered contagious, and later cancer hospitals were forcefully moved out of the cities as isolation camps. There are now vivid evidences that specific microbial pathogens are causing up to 25% of cancer cases (lymphoma, solid or others), and in some cases, a single pathogen was found in association with many types of cancer, such as HPV and EBV, to a lesser extent.

Also, several non-biological factors are classified as carcinogens as humans are exposed to millions of chemicals whether in environment or smoke processed food.

Keywords: Bacterial carcinogen, Free Radicals, Microbial carcinogenesis, Parasitic carcinogen, Radioactive cancer, Smoke and cancer, Viral carcinogen.

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INTRODUCTION

Since cancer was first described as a human disease in 2600 BC., microbes were thought to play a role in cancer but rather as an antagonist than a cause. This was reflected by the practice of the Egyptian physician Imhotep who would incise the area of tumor to infect such location so that infection, would cause tumor regression [1].

Centuries later, Zacutus Lusitani and Nicholas Tulp promoted the contagion theory in 1649 and 1652, respectively, concluding that cancer was contagious based on their experiences with breast cancer in members of the same household in the Netherlands. They further proposed patient isolation, that has been officially adopted later in France in 1779 when cancer hospitals were moved by force out of the cities as the public belief was that cancer is contagious [2, 3].

In addition to many theories attributing cancer to intrinsic factors discussed in the other chapters of this book, the role of exogenous causes of cancer was still active. In 1921, after discovering the active cancer-causing agents (carcinogens) in cigarette smoke, the Institute of Cancer Research assigned Sir Ernest Kennaway to investigate the carcinogenic properties of tars and oils [4].

Only a few years after describing Burkitt lymphoma in 1958, it was the first time ever to associate a specific microbe with human cancer when Burkitt lymphoma was linked to Epstein-Barr virus (EBV) in 1964 [5]. In 1980s, human papillomavirus DNA of HPV types 16 and 18 were linked to cervical carcinogenesis after being identified in a high proportion of cervical cancer biopsies [6], and soon after, other types of cancer were identified in association with HPV [7].

On the other hand, a century after the first successful surgical treatment of gastric cancer in 1881, *C. pyloridis* (later named *H. pylori*) has been proved to be causing gastric ulcer in 1983 [8] and soon after a cause of gastric cancer [9].

As humans and other living beings have potential exposure to millions of environmental chemicals worldwide, controlling inflammation and its resolution will be a critical component of successful cancer prevention and treatment of cancer [10]. Epidemiological studies guided the resolution of the World Health Organization's International Agency for Research on Cancer to classify processed meat as a group I carcinogen of which the risk category is similar to that of alcohol and cigarettes [11]. Currently, around 25% of human cancers are associated with infectious diseases, of which some have been confirmed as the cause [12].

BACTERIA AND CANCER

Although microbial infections have been associated with cancer for centuries but not specifically among the leading causes of cancer. However, nominating *H. pylori* as the first bacteria to be identified as a cause of human cancer in humans, followed by the discovery of its inflammatory mechanism of carcinogenesis in the early 1990s, by which bacteria cause cancer made the proof of causation [13]. *Chlamydophila pneumoniae* is an intracellular Gram-negative bacillus that has been detected in a number of chronic lung diseases, most commonly in adults. However, there is more evidence that links *C. pneumoniae* infection and lung carcinomas, especially in heavy smokers [14]. In addition, studies on survivors of colorectal cancer (CRC) have concluded the causative role of *Streptococcus bovis* in colon malignancy where *S. bovis* bacteremia was the strongest signal [15].

Direct Bacterial Carcinogenesis

Microbial Carcinogenesis is a multistep process orchestrated by both host genetic and epigenetic changes in either the oncogenes, tumor suppressor genes or different molecules involved in cell adhesion in addition to microbial toxins or metabolites that also modulate host cell transformation [16].

This is reflected classically in *H. pylori* infection, where the bacteria release reactive nitrogen species (RNS) and reactive oxygen species (ROS), where both strongly trigger “stem cell” hyperplasia followed by increased telomerase activity and, therefore, telomere reduction in parallel with overexpression of hTRT. Consequently, DNA replication errors, DNA hypermethylation, and p53 mutations, along with CD44 abnormal transcripts composing the early steps of well-differentiated gastric cancer [17].

In addition, the risk is considerably driven by *H. pylori* strain virulence variation exacerbated by the host immunogenetics governing the resulting inflammatory response. Such interactions can directly cause specific tissue damage, leading to gastric cancer development [18]. Because of underreporting tumor-associated clinical symptoms prior to diagnosing the disease, nearly half of cases end up being advanced complicated type gastric cancer upon the first visit and therefore, the prognosis is poor [19].

Indirect Bacterial Carcinogenesis

The second bacterial oncogenesis mechanism is driven by the oncogenic metabolites of bacteria. The best example is the microbiota-associated colon

CHAPTER 4

Biology of Cancer

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Abstract: Loss of genomic stability in the cell due to defects in the checkpoint of DNA damage, mitotic checkpoint, and telomere maintenance led to increased incidences of base pair alterations. Therefore, that genomic instability plays a critical role in tumor initiation and progression. Tumor progression requires a dynamic tumor/normal exchange in their microenvironment to support tumor growth. The histological alteration seen in the tumor at early stages confirms that the surface between the epithelium and the stroma undergoes progressive disturbance. Tumor progression is also affected by the immune system in which chronic inflammations promote the growth of tumor. Tumor cells experience altered metabolic profiling to support their growth. Cancer cells are characterized by uncontrolled cell division. For that, they utilize glucose as a source of energy to help them grow faster than normal cells. Hence, Glycolysis is a key metabolomics pathway consumed at a high rate during carcinogenesis.

Keywords: Cancer Biology, Cancer Cell Metabolism, Cell Cycle, Pericytes, TME.

INTRODUCTION

Stem cells are distinguished by their ability to continue to grow and differentiate into various cell types. In this chapter, we'll glance at the most common types of cells in the human body. The body's cells go through a constant cycle of renewal,

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aging, and eventually death. Endothelial cells, for example, are renewed every 150 days in adults. Mutations disturb this cycle in some cases, causing an abnormal accumulation of defects in the tissues, which finally leads to the formation of cancer cells. The cancer spreads uncontrollably and is linked to cell mass, which is influenced by a variety of factors, including blood supply, extracellular matrix, and cell-cell interactions, as well as changes in oncogenes and tumor suppressor genes. Endothelial cells are important in the function of blood vessels, including angiogenesis. As a result, endothelial cell defects may contribute to tumor development. As endothelial cells line the inside of the vessel wall, pericytes cover the surface of the vascular tube and sustenance the tumor microenvironment and cross-talk with cancer cells.

CANCER CELLS AND CANCER STEM CELLS

INTRODUCTION

In the human body, stem cells can differentiate into different cell types. They are characterized by a continuation of development, differentiation and tissue repair. There is a relationship between stem cells and cancer cells; they share the self-renewal property, which is a highly essential characteristic. Indeed, stem cells are affected by mutations that cause the accumulation of cancer and produce cancer cells [1].

Several studies have reported that the cells in the body are in a continuous cycle of renewal, aging and then dying. In fact, this cycle is disrupted in some conditions by mutations to the deoxyribonucleic acid (DNA)and causes abnormal accumulation of tissues and different types of cancer cells, including cancer stem cells (CSCs), which are generated from stem cells. Therefore, both stem cells and cancer stem cells show a critical role in the initiation and progression of cancer (Fig. **4.1**) [2]. Furthermore, there are always changes in the mechanism of cancer due to cancer proliferation. In fact, cancer development is uncontrolled and has a relationship with cell mass, which depends on many factors such as blood supply, extracellular matrix, cell contacts, differentiation, immune attack and cell death. In addition, cancer development is dependent on any changes to the cancer regulatory systems, which are oncogenes and tumor suppressor genes [3].

Cancer and Tumor

There is a misunderstanding between the definition of cancer, tumor and neoplasm. The following explanation is to clarify the meaning and the difference between them. Cancer is an abnormal progression of cells, which divide uncontrollably anywhere in the body tissues and invade neighboring tissues [4, 5].

Indeed, the actions of cancer are changeable during cancer development. Thus, the process involved in the formation of cancer is the multi-pathway mechanism called carcinogenesis [6].

However, cancer is illustrated by oncogenic mutations in a target cell or appears after several years [1]. In fact, the breast, lung, bone marrow, gut and prostate tissues contain stem cells that play an important role in cancer development [1]. Moreover, there are different types of cancers, such as carcinoma, leukemia, lymphoma, melanoma and sarcoma. The main diagnosed type is carcinoma, which is a cancer of many organs and glands, such as the breast, lungs, pancreas and skin. Furthermore, the cancer of the blood is called leukemia. In addition, the cancer of lymphocytes is lymphomas, and the cancer of melanocytes is melanoma. However, the rarest type of cancer is sarcoma, which starts in the bones and in the soft connective tissues, such as tendons of the arms or legs [4].

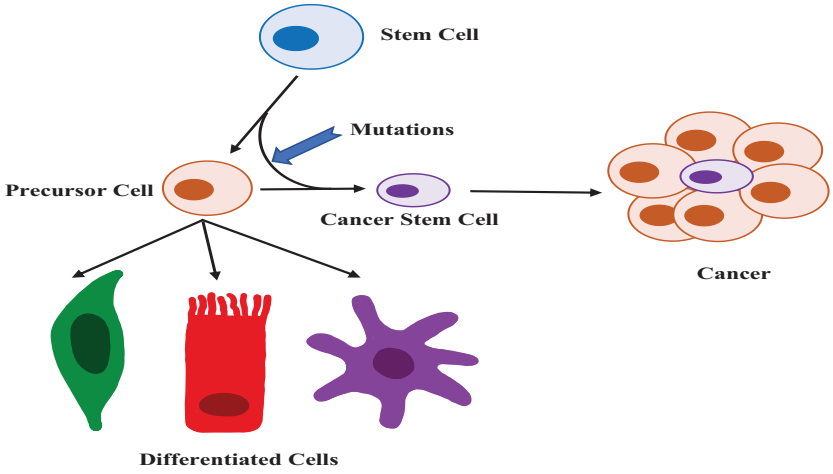

Fig. (4.1). Generation of cancer stem cells (CSCs) from stem cells and progenitor cells and formation of cancer [4].

A tumor is not certainly cancer. Moreover, a tumor is an uncontrolled development of cells without inflammation in the body tissues. In addition, the body does not need them, and they don't die [5]. However, the origination of the tumor is from the transformation of normal stem cells [7]. Furthermore, a tumor can be benign or malignant. Also, a collection of pus can be a tumor [5]. Indeed, tumors heterogeneity plays an important role in cancer cell types [8].

On the other hand, neoplasms are defined as the innovative growth independent from the nature of that growth [6].

CHAPTER 5

Growth Factors and Cancer

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Abstract: Cancer causes major patient morbidity and mortality and is a critical health concern worldwide. The recent GLOBOCAN 2019 factsheet recorded nearly 19.2 million new cancer cases, 9.9 million cancer deaths and 50.55 million people suffering from different kinds of cancer globally within 5 years after diagnosis. Growth factors (GF) are a group of proteins that can affect cellular processes, including differentiation, division, intravasation, extravasation and dissemination. The circulating tumor cells in the bloodstream can populate distant tissues and organs and believe to be the primary cause of metastasis. Extravasation is a crucial phase in the metastasis process, in which tumor cells leave the bloodstream and enter the host tissue. The progress of metastasis is triggered by the tendency of cancer cells to disseminate to target organs from the site of the primary tumor. Despite extensive basic scientific and clinical investigations, cancer is still a major clinical and public health problem. The development of cancer can be influenced by genetics, environmental factors, gene-environment interaction, lifestyle, age and a number of other factors. The harnessing and enhancement of the body's own cytotoxic cells to prevent basement membrane rupture and the intervening dissemination processes can provide useful insight into the development of cancer. The mutation in oncogenes and tumour suppressor genes, and chromosomal aberration is a cornerstones of the molecular basis of cancer. The basement Membrane (BM) acts as a cell invasion shield, thus identification of processes that underlie in breaching of BM can contribute to understanding the disease pathogenesis. TGF-β is known for its dual function; it requires inhibition in the advanced stage however, the growth inhibitory properties are displayed in the early stages of tumorigenesis. Therefore, inhibition of TGF-β signalling in the CD8+ T cell compartment may be necessary for tumor immunity to be restored. Quantitation of tumour cell dissemination is important and plays significant role in elucidating mechanisms of cancer and strategies for therapeutic intervention.

Keywords: Cancer, Growth Factors, Oncogenesis, Tyrosine Kinase Inhibitors.

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GROWTH FACTOR INDUCED BASEMENT MEMBRANE BREAKDOWN AND INVASION IN CANCER

Cancer, which causes major patient morbidity and mortality, is a critical health concern worldwide. Metastasis is a multistep process caused by tumor growth, angiogenesis, detachment of tumor cells, and invasion of the extracellular matrix that can lead to uncontrolled growth potential and metastasis into surrounding tissues [1]. Each of these steps is critical for the survival of tumor cells and the development of secondary lesions. Interactions between tumor cells and the host microenvironment influence tumor survival and development. Tumor invasion involves the disruption of the basement membrane and infiltration of the underlying stroma. Invasion necessitates significant changes in cell morphology and phenotype, especially in epithelial cells, which are the precursors of more than 90% of human cancers. It includes adhesion between cell-cell and cell-matrix could be responsible for the degradation of the matrix and cellular motility [2].

Tumor development is only permitted after the dissolution of the decorating secretory ducts of the basement membrane. Growth factors play a crucial role in the destruction of the basement membrane, the intrusion into adjacent tissues by cancer cells, the vascular or lymphatic networks (intravasation), as well as exit from the bloodstream (extravasation) and eventual invasion of distant organs [3]. In experimental data conducted on clinical specimens and ErbB-2/HER2-overexpression, spheroids resembling mammary ductal carcinoma *in situ* (DCIS) raised the likelihood that invasive growth was underpinned by TGF-β or 14-3-3-zeta adaptor overexpression [4, 5]. In *in vitro* models, TGF-β and other growth factors seem to have been involved in certain transformations. GFs have been shown to cause multiple adhesion molecular switches, such as a loss of epithelial E-cadherin and a gain of mesenchymal N-cadherin [6]. Tensin-3 is a connective protein that links the actin cytoskeleton and the extracellular matrix, which is replaced by tensin-4, resulting in the disruption of the bridge and facilitating cell migration [7]. In certain epithelial tumours, E-dual cadherin's growth arrest and adhesive functions are lost by mutational inactivation, transcriptional suppression, or extracellular cadherin domain proteolysis. A number of GFs, which include TGF-β, EGF, and Notch cleaved proteins, affect the expression of repressors of E-cadherin. Further, E-cadherin cleavage, ubiquitylation, and endocytosis may cause E-cadherin downregulation [8].

The degree and timing of invasion and metastasis may be affected by several factors, including genetic and epigenetic heterogeneity within the tumor, extrinsic factors and growth factors [9]. Growth factors and cytokines produced by the tumour microenvironment and tumour cells themselves, are the key extracellular triggers that control these migration programs and, thus, regulate strategies for

adaptive invasion. They can work in an autocrine, paracrine or endocrine manner to orchestrate central cell functions, including proliferation, differentiation, apoptosis and cell migration [10]. Metastases are a major reason for the failure of modern cancer therapies and associated mortality and are caused by the detachment of malignant cells from the primary tumor site and colonisation of close and remote organ sites. Precise knowledge of the molecular mechanisms regulating each step of metastasis is required to understand the pathophysiology of cancer. Cancer metastasis is a multi-step process that comprises local invasion, neoangiogenesis, circulatory system survival, extravasation to the target organ, and so on. Tumor cells must remodel, or lose their basement barrier, in order to reach vessels and get access to distant organs [11]. Research so far has strongly suggested that the basement membrane acts as a cell invasion shield, therefore investigations into basement membrane invasion can provide useful insight into the development of cancer.

Growth Factor-Induced Basement Membrane Breakdown and Invasive Growth

Growth factors are small polypeptides that bind to kinase-activating transmembrane receptors to activate a certain set of intracellular signaling pathways. Examples include mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), phospholipase C-γ, and transcription factors, such as STATs or SMAD proteins [12, 13]. Growth factors encourage cell growth and proliferation, and are considered the main growth regulatory molecules for cells *in vitro* culture and likely *in vivo*. In culture conditions, non-transformed cells display an absolute necessity of growth factors for proliferation. And in most cases, more than one factor is needed. Growth factors are exhausted more quickly than other media components under standard culture conditions and hence rate limiting for proliferation. in neoplastic transformed cells, there is commonly a lack or reduced requirement for specific growth factors, which is the hall mark of cancer cells [12, 14]. The accumulation of genetic changes and genomic instability leads to tumorigenesis. Genomic instability describes a genome containing variation in a genetic sequence that may affect gene expression, and protein expression, known as mutation. It also includes epigenetic and chromosomal alteration [14]. Genomic instability is considered the cornerstone of the molecular classification of cancer. The most prevalent form of genomic instability is chromosomal instability, and the presence of a high degree of chromosome structural modifications has been reported in tumour cells [15]. A driver mutation is an alteration that gives cancer cells a selective advantage compared to other cells, leading to cell proliferation and tumor growth [16]. Previous studies suggested the role of GFs in the step-wise progression of cancers.

CHAPTER 6

Cell Signaling Pathways in Cancer

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Abstract: Cancer is characterized by atypical cell proliferation that has the possibility of dissemination to different body parts. Tumor formation is influenced by genetic mutations and environmental pollutants. The formation and progression of malignancies have been linked to a diversity of molecular paths. The JAK/STAT, NOTCH, PI3K/AKT pathway, mitogen-activated protein kinase (MAPK), transforming growth factor-beta (TGF-beta) (TGF-), NF-B, and Wnt signaling pathways will be highlighted in this chapter. Cancer development has been linked to various changes to the signaling pathways' components. As a result, various initiatives to target signaling pathways in order to build distinct treatment lines have been approved. In this chapter, we discuss the role of signal transduction in cancer-associated processes and how their targets influence the behavior of the tumor cells.

Keywords: Cancer, JAK/STAT, Map Kinase/Erk, NFκB, Notch, PI3K/AKT/mTOR, TGF-β, Wnt/β catenin.

INTRODUCTION

Malignance is a widespread disease described by genetic modifications in signaling pathways, for instance, cell division, death, and proliferation. Mutations in proto-oncogenes can alter cell formation and homeostasis by regulating signaling pathways such as NFB, TGF-β, PI3K/AKT/mTOR, MAP Kinase/ERK,

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Notch, JAK/STAT, and Wnt/catenin. These pathways will give crucial information for the proper identification of cancer biomarkers in the future, which will aid in the treatment and prevention of cancer. During cancer formation, genetic and epigenetic changes cause cells to break free from homeostatic control, multiply, expand, and spread to other organs [1].

Liver, Lung, breast, skin, and pancreatic cancers arise in epithelial cells. Sarcomas in fibroblasts, myocytes, adipocytes, and osteoblasts are thought to originate in the mesenchymal tissues. Non-epithelial tumors, on the other hand, develop in nervous system cells such as glioma cells and hematopoietic tissues such as leukemia and lymphoma [2]. In solid tumors, such cellular changes drive the evolution of benign tumors into proliferative malignancies [1]. The tumor cell loses access to oxygen and other nutrients during tumor excursion, causing the development of angiogenesis, which restores cell's access to oxygen and nutrients [3]. Consequently, the tumor cells gain the potential to travel beyond their normal bounds to surrounding organs, enter circulation, and start metastasis, indicating that the tumor is malignant [4].

This design illustrates how complicated cancer-related events occur in a linear sequence in a varied manner in which cancers differ from one another and between tumour locations. This sequence also offers a useful foundation for various signaling pathways tangled during cancer onset and course [5]. The major reason for malignancy, as stated above, is epigenetics or genetic abnormalities in tumor cells. Tumor cells also have a variety of distinct characteristics. These factors include resistance to apoptosis and other kinds of cell death, metabolic changes, genetic instability, angiogenesis activation, and other factors with greater travelling potential, in addition to cell proliferation [6]. The majority of these features are caused by the dysregulation of various cellular signal transduction pathways [7, 8].

JAK/STAT Signaling Pathway

General Features of the JAK/STAT Pathway

JAK-STAT signaling pathways are based on traditional signaling models in which a ligand binds to the transmembrane receptor's extracellular side and initiates a cascade of phosphorylation events [9]. Phosphorylation of JAK kinases, the receptor cytoplasmic tail and STAT transcription factors are among these processes. STAT phosphorylation leads to nuclear localization, DNA binding, and gene regulation [10]. Combining a variety of ligands and receptors with four JAK proteins (JAK1, TYK2, JAK2 and JAK3), 7STAT members (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) are cytokine signaling

suppressors. Proteins (SOCS), and multiple STAT-dependent operons allow for fine control of expression (Fig. **6.1**) [11].

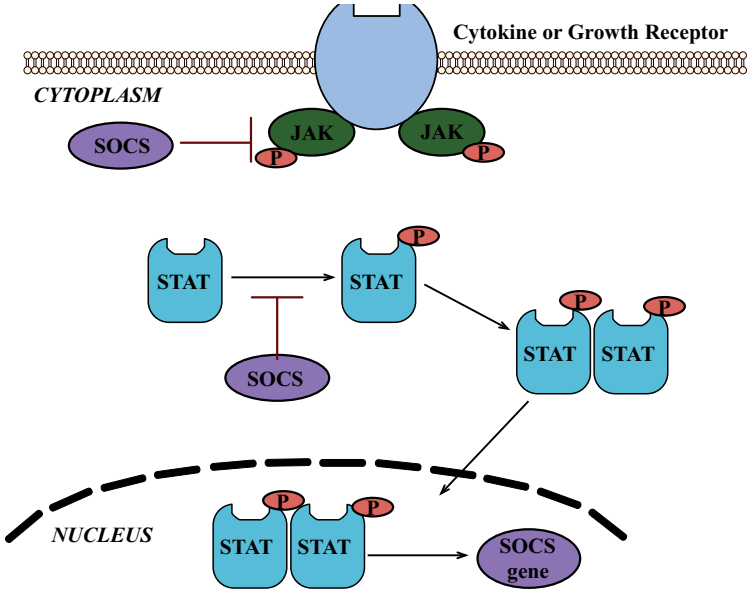

Fig. (6.1). JAK/STAT signaling pathway. The JAK/STAT signaling pathway is a signaling system that involves the proteins JAK and STAT proteins. JAK is phosphorylated by cytokines and growth receptors, and it recruits signal transducers and transcription activators (STAT). Dimer phosphorylated STAT enters the nucleus and stimulates gene transcription, where it attaches to DNA, regulates immunity, and promotes cell growth and survival.

JH1 encompasses the kinase domain, JH2 encompasses the inhibitory pseudo kinase domain, JH3-5 contains the SH2 receptor interaction domains, and JH6-7 contains the FERM domain [12]. In the most basic paradigm, ligand-receptor interaction modifies the shape of receptor-JAK complexes, permitting the phosphorylation of certain tyrosine residues in JH1. This causes additional conformational shifts in JAK proteins, resulting in receptor phosphorylation and the creation of STAT protein binding sites [13].

The JAK/STAT signaling system can be triggered by external stimuli, for instance, cytokines. JAK and STAT are intracellular proteins that work with the transmembrane receptor to deliver signals to the nucleus, allowing DNA transcription and gene expression to occur [14]. STAT acts as a JAK substrate, phosphorylating and transporting to the nucleus to stimulate gene transcription.

The JAK/STAT signaling system is involved in stem cell maintenance, hematopoiesis, and the immune response [15].

CHAPTER 7

Transcription Factors in Cancer

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Abstract: Different types of signalling pathways have been approved to be involved in cancer imitation and progression. These signalling pathways include the JAK-STAT signalling, NF-κB signalling, Wnt, Notch and Hedgehog. STAT (Signal Transducer and Activator of Transcription) transports signals between proteins from the cell membrane into the nucleus to contribute to cancer progression. NF-κB signalling is essential for the survival of the B cell tumor types. The Wnt, Notch, and Hedgehog signalling pathways play a significant role in carcinogenesis by upregulating the genes associated with these pathways. Hence, pharmacological inhibitors of WNT, NOTCH, and HH pathways are required in clinical studies. Such inhibitors have features that make them important during the clinical trial since they offer great potential as novel therapeutics for cancer. They also have an antitumor response which should be taken into consideration. The three signalling pathways are also known to shape cell fate determination and differentiation. In case of depletion of a single molecular component within the three pathways, embryonic lethality will form.

Keywords: HH signalling pathways, Hedgehog, NF-κB, NOTCH, Signaling, STAT, Transcription, Wnt (β)-Catenin.

TRANSCRIPTION FACTORS IN CANCER

A transcription factor is a sequence-based DNA-binding protein that regulates the transcription of genetic material from DNA to messenger RNA *via* binding to specific DNA sequences in molecular biology and genetics. There are three types of transcription factors that are believed to play a role in human cancer.

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1- Steroid receptors, such as oestrogen receptors and androgen receptors, in breast cancer and prostate cancer, respectively. Anti-oestrogen and anti-androgen agents have been in clinical use for several years, such as tamoxifen and bicalutamide. Activated glucocorticoids have also been extensively used due to their ability to promote apoptosis, at least in lymphoid cells [1].

2- Resident nuclear proteins, which are activated by serine kinase cascades, are also transcription factors linked to cancer [2]. For example, JUN was identified as an oncogene in 1987, first as the viral Jun (v-Jun), then as the cellular Jun (c-Jun), and then as a transcription factor shortly after.

3- Latent cytoplasmic factor is the third and most recently identified group of transcription factors with oncogenic potential, whose function is usually activated by receptor-ligand interaction at the cell surface [2]. These transcription factors are triggered by serine or tyrosine kinases at the cell surface, or by a variety of cytoplasmic biochemical events that include kinases (some of which are regulated by Ca^{2+} flux) or precisely controlled proteolysis.

After synthesis, several transcription factors reach the nucleus spontaneously [2]. The bZip proteins include JUNB, c-JUN, c-FOS, JUND, ATFs, FRA, and the CREB-CREM family, the ETS proteins, the cEBP family, and the MAD box family, are among the main classes of structurally related proteins. In mammals, these classes comprise at least several hundred different proteins, only a few of which have been widely considered [3]. A general picture of the activities that regulate the resident nuclear-transcription factors' maximal transcriptional activity has arisen. While no JUN mutations have been identified in human cancers, upstream activators of JUN3 have been identified in a large number of mutations.

There are a variety of resident nuclear transcription factors that are overexpressed or presented as hyperactive fusion proteins in cancers. MYC, which is widely enhanced in cancer, is the most common of all [4]. MYC does not govern transcription by itself; instead, it forms a dimer with another protein called MAX [5]. E2F proteins are usually free in the tumor due to the common lack of RB. E2F is required for cell-cycle development, according to studies in cultured cells, though depletion of E2F prevents S-phase entry the most [6]. E2F dysfunction has been documented in cancer, despite the fact that most cancers have normal levels of E2F protein production. E2F level was significantly higher in 90% of small-cell lung cancer patients, but not in adenocarcinoma or squamous-cell lung carcinoma [7].

Signal Transducer and Activator of Transcription (STAT)

Definition

"STAT (Signal Transducer and Activator of Transcription) factors are proteins that have the ability to transduce signals from the cell membrane into the nucleus, thus activating gene transcription" [8, 9].

Types of STATs

In the human genome, up till now, seven kinds of STAT genes have been discovered, and they are as follows; "STAT1 chromosomal location 2q32.2, STAT2 12q13.3, STAT3 17q21.2, STAT4 2q32.), STAT5a 17q21.), STAT5b 17q21.2, STAT612q13.3" [8, 9].

Their signal transduction is included in numerous usual physiological cell procedures, counting propagation, variation, angiogenesis apoptosis and immune ruling. Irregularities may occur in its pathways, leading to abnormal STAT rules, which in turn lead to various pathological events, such as malicious alteration and "metastasis" of cells [10].

Features of the STAT Group of Proteins

All of the "STAT proteins" are made up of a quantity of functionally and as well as structurally preserved areas [11].

1. The "Src-homology 2 SH2" field, along with the "N-terminal domain ND" intercedes homo- and "heterodimerization" of STAT monomers throughout stimulation.

2. The "coiled-coil domain CCD" works as a signal of the nuclear locale by incriminating interactions between protein-protein.

3. The C-terminal "transcriptional activation domain TAD", endures "serine phosphorylation" and thus employs extra activators that are transcriptional, improving the actions of STAT pertaining to transcriptions.

4. The "DNA-binding domain DBD" is responsible for the determination of DNA association [12, 13].

Some of the STAT proteins institute isoforms by alternate mRNA interweaving or processing of "post-translational proteolytic". The isoforms that are of complete length are labelled "α isoforms", while their corresponding items that are full-length are termed "β, γ or δ" [13].

CHAPTER 8

Epigenetic and Genetics Factors

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Abstract: Despite variations in the morphology and behaviors of human body cells, every single cell in our body is composed of identical DNA material. The variation in cell phenotypes is a result of a specific regulatory mechanism known as epigenetics, by which gene expression undergoes some modifications without the actual nucleotide sequence being affected [1]. This phenomenon is accomplished through several mechanisms, such as cytosine residue methylation, modifications of histone units, and RNA interference. Therefore, epigenetics performs a key function in embryonic growth and development, cellular RNA expression, gene imprinting, and silencing of females' X chromosomes [2]. Any impairment in these mechanisms may cause various human disorders, including cancer [3]. In carcinogenesis, defective epigenetic machinery at several distinct levels results in abnormal cellular functions [4].

This chapter highlights epigenetics' importance in cancer development and its potential applications for cancer treatment.

Keywords: Cancer, Epigenetics, Histone, Methylation, miRNA.

MOLECULAR MACHINERY FOR METHYLATING DNA

DNA methylation is a central epigenetic process occurring in DNA, as it regulates gene expression and cell differentiation without altering nucleotide sequences [5, 6]. DNA methylation changes dynamically as cells develop, but the process becomes static as they begin to differentiate. This distinctive regulatory modification is indispensable for proper development, managing the expression of particular genes in specific tissues, allowing a cell to terminate DNA transcription, silencing one of the X chromosomes, and facilitating genomic imprinting.

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Normally, methylation occurs primarily in regions where cytosine-guanine dinucleotide repeats are highly condensed, also known as CpG islands [7]. Throughout our genome, CpG sites are not randomly distributed, and most cytosine residues are methylated. Around 70% of promoters contain these clusters, which are unmethylated to keep euchromatic conformation and allow transcription factors to bind in order to initiate gene expression [5, 8]. The methylation machinery is propelled by the DNA methyltransferase (DNMT) family [2]. This enzyme family used SAM as a group donor to add the CH3 group to cytosine [9]. DNMTs are classified into three major types: DNMT1, DNMT2, and DNMT3. The latter has three sub-members: DNMT3A, DNMT3B, and DNMT3L [2]. DNMT1 is a maintenance enzyme that has a high affinity toward the hemimethylated region in the DNA helix. During cell division, the methylating activity of DNMT1 mimics the methylation process that takes place prior to DNA replication by binding to anew synthesized DNA. Further, The DNMT1 protein also helps to restore DNA methylation [10].

In contrast to other members, DNMT2 shows no enzyme activity, and its role in DNA methylation is still largely unknown; however, it appears to be involved in methylating the amino acid tRNA cytosine. A DNMT3 enzyme family is usually involved in *de novo* methylation. *De novo* methylation occurs during gametogenesis through both DNMT3A and DNMT3B. In the case of DNMT3L, it is involved in the *de novo* methylating regulatory factor in extraembryonic tissue [11].

These covalent modifications can be removed at distinct development levels from the DNA helix through a mechanism called DNA demethylation. TET enzymes catalyze the conversion of 5-methylcytosine to 5-hydroxymethylcytosine using oxygen atoms to demethylate DNA [12, 13]. There are two types of demethylations: active and passive. Active DNA demethylation is an enzyme-driven process that demethylates methylated cytosine residues by removing the methyl group from these residues. Passive DNA demethylation takes place during successive stages of replication, leading to the loss of 5-methylcytosine [12].

MOLECULAR MACHINERY FOR HISTONE MODIFICATION

Acetylation of Lysine

Histone lysine (K) undergoes acetylation\ deacetylation through the involvement of two antagonistic enzymes; acetyltransferases (HATs) and deacetylases (HDACs) [14]. HATs allocate acetyl groups to the side chains of lysine by using acetyl CoA as a cofactor. In turn, it promotes DNA liberation by diminishing positive charges on lysine residues, consequently enhancing its approachability to

transcription factors and RNA polymerase complexes [15, 16]. There are three main groups of HATs: p300/CBP, MYST (which includes MOZ, MOF, TIP60, HBO1), and GNAT (which includes GCN5, PCAF) [17]. There are many cytoplasmic acetyltransferases, including MCM3AP, ARD1 and TFIIB, which can also acetylate-free histones and newly synthesized histones [18]. Moreover, acetyltransferases are capable of acetylating many non-histone proteins, allowing them to regulate the DNA binding, protein stability, and enzymatic functions [19].

Conversely, HDACs stop the histone acetylation process by restoring the lysine residue's positive charge and creating a closed chromatin conformation, allowing stabilization of the chromatin structure and controlling the gene silencing [15]. Human HDACs have four major classes [16, 20]. Together, these classes promote the closure of chromatin and the repression of gene expression. Moreover, as part of epigenetic modifications, HDAC removes acetyl groups from many non-histone proteins [21]. As transcriptional corepressors, HDACs typically form various functional complexes with other class members. HDAC1 and HDAC2 are usually present together within three distinct complexes NURD, Sin3a, and Co-REST complexes. It has been shown that the purified forms of HDAC1 and HDAC2 exhibit weak deacetylation activity [22]. HDAC3 increases its activity by forming complexes with the SMRT and NCoR. Moreover, HDAC1, HDAC2, HDAC4, HDAC5, and HDAC7 deacetylases interact with NCoR without forming a complex [23 - 25]. Therefore, existing HDAC members made it difficult to distinguish which activity is responsible for a specific action. Thus, inhibitors targeting HDACs activity are now being developed as potential cancer therapy.

Methylation of Histone

During both the differentiation and development process, histone methylation occurs in a reversible and dynamic manner. As opposed to acetylation, methylation leaves the charge unchanged on lysine and arginine residues [15]. Gene activity can be induced or inhibited by methylating histones. For instance, a methyl group can inhibit gene expression at H4K20, H3K9, and H3K27, while methylating lysine at H3K79, H3K36, and H3K4 can activate gene expression [26].

Methylation of Lysine

Six major classes of histone lysine methyltransferase (HKMTs) can methylate the N-terminal lysine. Aside from KMT4, all HKMTs possess an equivalent SET motif that is necessary for enzymatic catalysis [15, 27, 28]. These enzymes catalyze methyl transfer to amino groups on the side chains of lysine using SAM

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Prof. Faris Alenzi received his MSc and PhD from Imperial College London in 2003. Prof. Faris is a passionate educator and researcher in allergy, immunology and cancer. Prof. Faris's interests go further than teaching as he is keen on serving his community through his community work. He is the founder of multiple charities including: The Saudi Society for Allergy, Asthma and Immunology, Saudi Society for Cell Death, Moafa Health Charity, Roya Fekrya Charity. He is also an editor and publisher for five Arabic books. Prof. Faris is a recipient of the British Journal of Hematology Award & the Leukemia Research Fund Award, London, UK. He obtained many research grants in total ~2M USD. In March 2019, he was among the Professional Achievement Award Finalists. In October 2022, he was selected among The Stanford University top 2% researchers in the world.