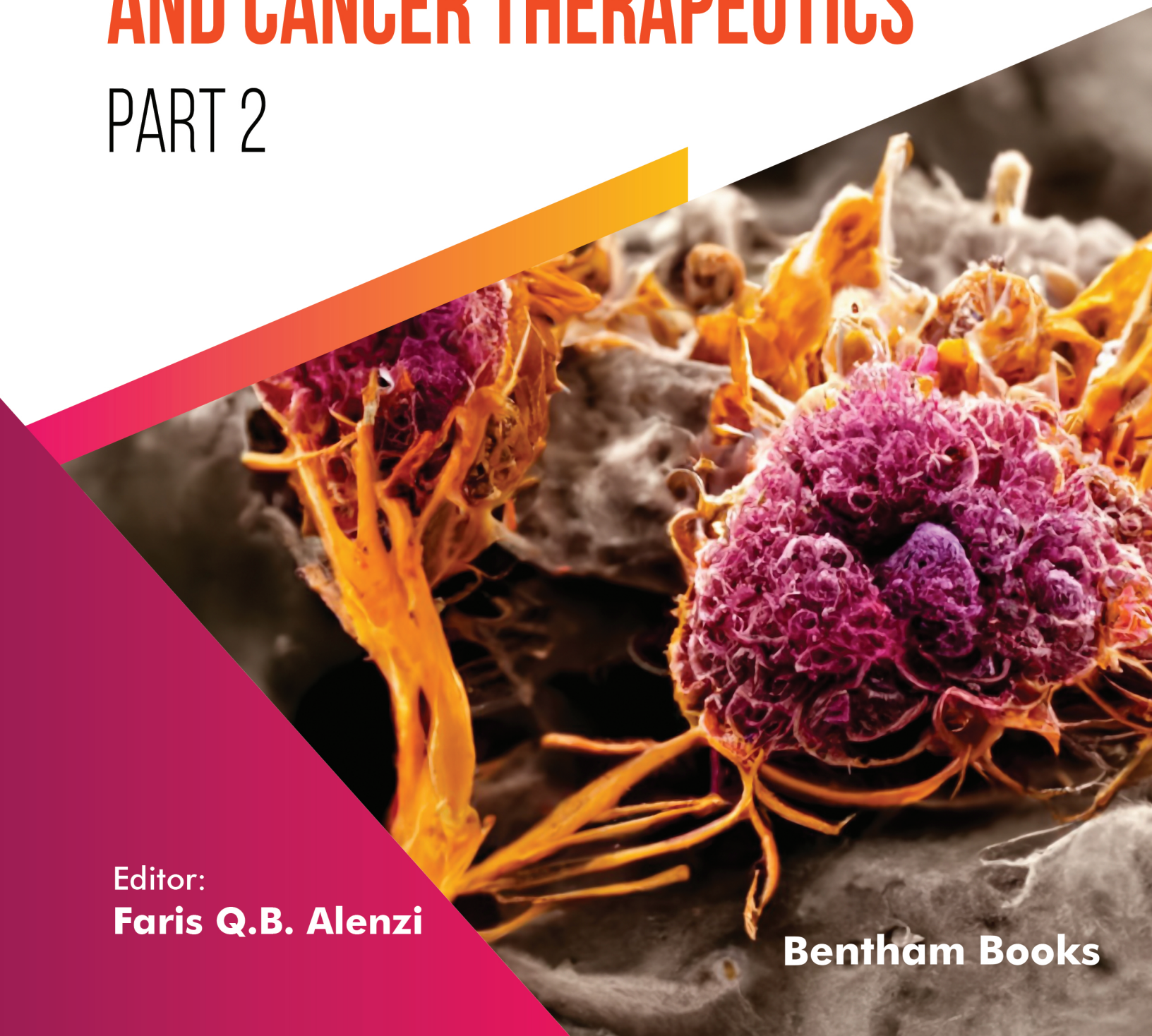
MOLECULAR TARGETS AND CANCER THERAPEUTICS

PART 2



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Molecular Targets and Cancer Therapeutics (Part 2)

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PREFACE

Cancer is a complex disease that affects all anatomical sites in the human body, causing a significant global health burden since it is considered the second leading cause of death worldwide. Recent advances in science and technology have improved the understanding of cancer evolution to discover new effective therapies. This book provides a state-of-art review of advances in cancer, including a broad overview of cancer classifications, surveillance, diagnosis and cancer treatment with a focus on innovative therapeutic approaches, such as immunotherapy, vaccines, nanomedicine, and precision medicine, in addition to cancer's surveillance.

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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

Hawazn W. Alnaam

Halah F. Alnaam

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CHAPTER 1

Cancer Types

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Abstract: Normally, to replace damaged cells or for the purpose of growth, healthy cells can divide according to the proliferation potency, in a systematic and controlled manner. When this mechanism is interfered with in such a way that the cell multiplies beyond the control system, a neoplasm may originate. The name (neoplasm) comes from the ancient Greek words *neo*, which means “new,” and *plasma*, which means “creation, formation.”. Even after the underlying trigger is removed, a neoplasm's growth is disorganized with that of the healthy surrounding tissue, and it continues to grow abnormally. When this abnormal neoplastic growth creates a mass, it is referred to as a ” tumor”. There are four primary types of neoplasms (tumor): benign (non-cancerous), *in situ*, malignant (cancerous), and neoplasms of unclear or unidentified behaviour, which follow the pattern of cell development. Oncology is concerned with malignant neoplasms, which are commonly known as malignancies or cancers. In Oncology, many cancer classifications emerged, however, the most notable of which is based on the nomenclature by the type of tissue from which it arises, or by the primary site in the body where it originally appeared. Herein, this chapter will go over the definition of cancer, classifications as well as the key differences between the types of cancers. This chapter will also cover the pathophysiology and epidemiology of the many types of cancers.

Keywords: Cancer, Carcinoma, Neoplasm, Pathophysiology, Sarcoma, Tumors.

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INTRODUCTION

Cancer is a prominent cause of death across the globe, as each year has caused millions of deaths on a global scale. The threatening nature of the diseases has a significant impact across the social, health, and economic burdens, amongst all other diseases. While it is not the main cause of mortality in all countries, it exerts a significant burden to be among the top five leading causes of death. Globally, WHO (2021) reports that cancer killed at least ten million people in 2020 and was the leading cause of death. Cancer is of many types, and many of them are yet to have a significantly established cause and cure. This chapter will examine the understanding of cancer so far and explore established classifications based on their origin.

Definition

Cancer is a general term used to refer to hundreds of diseases that occur anywhere in the body as a result of abnormal cell growth [1]. The abnormalities result from numerous factors and arise from different body parts; leading to a classification system to allow ease of identification. Cancer cells are also known as malignant cells, depending on the course of their progression. Cancer development has numerous risk factors that could lead to the abnormal growth of cells. Many factors have been put forward, including environmental or personal factors. These include certain viruses such as the Human Papilloma Virus, radiation, certain chemical compounds, genetics, dietary problems, age, stress, hormones such as estrogen, and many others [2].

The onset of cancer is marked with signs and symptoms like any other disease, which are reliant on the type of cancer. The location, for example, can be a determining factor in what symptoms would be felt first. For example, cancer located in the brain regions could have major symptoms of seizures, while for breast cancer, lumps on the breast could be felt. However, in some forms of cancer, the symptoms often do not appear until it is too late [3]. However, some general signs and symptoms are recommended to follow up on in case they occur, including but not limited to loss of appetite and weight for no reason, persistence in nausea and fatigue, increasing pain in parts that were not so before, and recurrent infections without reason.

Cancer development is not straightforward, and the presence of a carcinogen does not always imply it will develop. A series of complex processes and procedures are always inhibited at every stage through the body's defence mechanisms. However, upon failure of these mechanisms, cancer will develop through a series of changes that allow the carcinogens of agents in the body to produce factors that

promote tumor growth. These carcinogens often target the cells at the DNA level to destroy or reduce the function of these cells to carry out their expected roles and thus, over time, render the cell a good site to start developing uncontrollable growth. Sometimes these cells escape and move from their initial site to neighbouring cells and cause further damage to these news cells, thus causing significant spread.

Nomenclature

Cancers are classified into numerous categories, as mentioned depending on the site or origin or the cause. The classification into the correct types through naming is known as nomenclature. According to Singer *et al.*, the process is critical for various reasons, including ensuring a correct diagnosis [4]. Discovering the right type of cancer means that the response would be highly specific since different types of cancers have their own responses and therapeutics that would be best for the patient at that given time. For example, breast cancer might be treated differently from brain cancer due to the location of the tumors. Since cancers are not fully understood, researchers are still building profiles and uncovering new information about the different types of cancers that occur in people. Therefore, having the right naming system can help researchers further understand what they are dealing with. It has also been shown that correct naming and identification of cancer allows oncologists to inform the patient more clearly on the progression of the disease, the aetiology, and expectations. Most importantly, the different types of cancers are now being studied using far more advanced methods, such as biomarker studies that have identified specific genes and molecules within the body that could be targeted far more precisely compared to if randomised studies were used. A good example is the identification of the HER2+ gene; a growth factor that impacts women to cause aggressive breast cancer and has a high fatality rate. By correctly identifying whether women with breast cancer are positive for the gene, they can be treated with advanced medication specifically made for the gene, and their progress tracked using biomarker studies, thus increasing the chances of quickly identifying what works and what works does not. This is because, as mentioned, there are hundreds of cancers and not all are well understood. Therefore, nomenclature becomes essential.

As cancer is a collection of diseases rather than a single disease, arising from different parts, the nomenclature is based on the origin of the cell as well as the possible cause. This is so because the biological properties in the cells provide a common origin or shared characteristics. As the cancer cells develop, they involve numerous tissues, carcinogens, and mechanisms, thus, tracking it based on where it affects has been seen as not ideal to some degree. One of the most common

CHAPTER 2

Diagnosis of Cancer

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Abstract: Cancer has a higher chance of being cured when it is diagnosed, detected, and treated early. Diagnosis of cancer in its early stages also results in the highest chance of survival with the improvement of lifestyle of cancer patients. A comprehensive physical exam and a full family medical history are needed before a cancer diagnosis can be made. Self-examination or other screening procedures will normally detect visible forms of cancers, such as melanoma and breast cancer, before the condition progresses. However, several forms of other types of cancer are discovered and diagnosed after disease development and severe signs have already occurred. This chapter discusses the diagnostic approaches that are often utilized to aid in the diagnosis of cancer.

Keywords: Biopsy, Cancer, Diagnosis, Endoscopy, Imaging, Sample, Tumors Markers, Tumor.

INTRODUCTION

Cancer is suspected depending on a person's symptoms, physical examination results, and, in some cases, screening test results. Screening procedures are used to predict the presence of a disease before symptoms appear. Until performing screening tests, the physicians will evaluate whether the patient has any risk factors for cancer due to age, gender, family background, previous history, or lifestyle. Further examination confirms or disproves the results. When a physician suspects a patient has cancer, diagnostic tests are performed. As cancer is discove-

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red, staging testing can help assess how advanced the cancer is in terms of its spread. When cancer is diagnosed, staging tests help assess the extent of the disease in terms of its position, size, and metastasis to proximal or distal organ systems. Staging tests help physicians to assess the best course of treatment as well as the prognosis. The primary goal of this chapter is to improve our comprehension of widely used cancer diagnosis strategies: Biopsy, Endoscopy, Diagnostic Imaging and Blood tests.

BIOPSY

Tumor biopsy is the cornerstone of the diagnostic approaches for most of the tumors in the human body. It provides a significant amount of information for oncologists and radiotherapists regarding a histopathological diagnosis, staging of the disease and genetic profile for the tumors, to guide diagnostic and therapeutic approaches [1]. With the rapid growth of imaging and image guidance technologies, the utilization of the biopsies technique has advanced significantly. It is, usually, performed by either surgeons or/and interventional radiologists [2].

Nowadays, image-guided percutaneous biopsies are widely adopted as an abridgment of molecular and biomarker methodology. This approach has several benefits, including detecting prognosis, planning a therapeutic response, assessing treatment resistance, and detecting disease progression. Therefore, biopsies are essential in clinical trials where we aim to evaluate the effects of drugs, identify the most related biomarkers and detect genetic mutations of the tumors [3].

We can associate biopsies adoption expansion with the increased integration of biomarker studies into clinical trials [4 - 6]. In the past, obtaining samples from metastatic tumors is known to be challenging due to logistical reasons since most of those metastatic lesions are inoperable. Accordingly, the demand increased to create a new biospecimen methodology for an easier, safer, and more efficient method for metastatic lesion analysis.

Clinical biopsy-type specimens, such as liquid biopsies, are considered next-generation biospecimens. Usually, it is collected from tissues at predetermined time points according to a prespecified treatment plan. Thereafter, the collected samples are ready for further analysis using multidimensional high-throughput technologies. The aforementioned analysis can use either a targeted approach or a global (comprehensive) approach. The former is utilized to evaluate cases such as cancer-related alterations, while the latter is used for sequencing of whole genome and epigenetic profiling, for instance [7, 8]. In contrast to this approach, the conventional hospital-based biobanks generally consist of specimen sections collected from surgical resection, which are mostly the residue of primary tumors

used for diagnostic purposes [9 - 12]. Table **2.1** illustrates the differences between traditional tumor biobanks and next-generation biobanks.

Table 2.1. The table illustrates the differences in variables between the traditional tumor techniques *vs.* next-generation tumor sampling.

Variables	Traditional Tumor Biobank	Next-Generation Tumor Biobank
Sample collector	Pathologists and surgeons	Interventional radiologists, surgeons, pulmonologists, dermatologists, and other physicians
Biopsy location	Primary site (usually surgical excisions)	Either primary recurrence or mets to other organ systems
Quantity of the biopsy	Abundant	Minimal
Time of collection	Initial diagnosis	Various time points
Sample preservation method	FFPE or Flsh-frozen	FFPE, Flash-Frozen, collected in tissue preserver, or OCT-embedded
Sample sharing	Common	Uncommon
Clinical data	Limited	Detailed

Abbreviations: Mets, Metastasis; FFPE, formalin-fixed paraffin-embedded tissue; OCT, optimal cutting temperature compound.

Different types of cancers respond to the same targeted therapy, although they harbor the exact same mutations. Hence, conventional histopathology derives its BRAF V600E mutations are frequent in skin cancer and central nervous system astrocytoma patients with excellent response rates to BRAF inhibitors. Contrary to colorectal cancer cases with the same mutation, the latter demonstrates an inadequate response rate [13]. In the field of surgery, several studies have confirmed that micropapillary and solid histologic subtypes are predictors of inadequate prognosis and high local recurrence, even in entirely surgical excision early-stage lung adenocarcinomas. This demonstrates the significance of the histological classification of invasive lung adenocarcinoma tumors with respect to recurrence patterns and post-recurrence survival rate [14, 15]. The limited knowledge we possess regarding the molecular correlates of the aforementioned subtypes generates a poor understating of this issue, indicating the importance of histological classification and genetic profiles of each tumor.

Regardless of the significant progress in molecular tumor characterization, some issues have remained unresolved thus far. These issues jeopardize our ability to move forward in molecular medicine. For instance, a large phase II precision trial was discontinued due to a temporary analysis indicating that only 87% of submitted cases were good enough to be used for tumor testing [16]. In addition,

CHAPTER 3

Treatment of Cancer

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Abstract: Surgery, the oldest cancer treatment, is a mainstay in the cure and control of most cancers. Indeed, for many patients, surgery, usually in combination with chemotherapy, is the only hope for long-term survival or cure. But surgery can do more than treat cancer; it can also diagnose cancer (diagnostic surgery), investigate cancer further (staging surgery), debulk tumors (debulking surgery), relieve pain (palliative surgery), prevent cancer from occurring in the first place (preventative surgery), restore the appearance or function of the body after cancer surgery (reconstructive surgery) and help medical staff to administer chemotherapy (access surgery). This chapter looks at each of these purposes of cancer surgery in detail.

Keyword: Biopsy, Cancer, Endoscopy, Resection, Surgery.

INTRODUCTION

Cancer is one of the leading causes of death worldwide [1]. More than a quarter of people will be affected by cancer at some point in their lives [2]. There are many types of cancer treatments, of which surgery is the oldest. Surgery, where a surgeon cuts the tumor from the patient's body, is also one of the most common cancer treatments. Still to this day, surgery remains a mainstay in the cure and control of most cancers. This chapter will discuss cancer surgery in detail.

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Types of Cancer Surgery

When people hear the term 'cancer surgery', they usually think of the removal of cancer from a patient's body. However, it is important to understand that there are many other reasons why cancer patients have surgery. The most common reasons cancer patients have surgery are:

- **Diagnostic surgery** to determine whether a patient has cancer or not.
- **Staging surgery** to determine where the cancer is located, whether the cancer has spread and whether the cancer affects other organs in the body.
- **Curative surgery** to try to remove the cancer from the body and cure the patient.
- **Debulking surgery** to remove some, but not all, of a cancer tumor. This is not the ideal option, but it can be the only option in cases where removing an entire tumor (curative surgery) might damage an organ or the body.
- **Palliative surgery** to ease cancer symptoms in late-stage cancer patients.
- **Preventative surgery** to prevent cancer from occurring in the first place.
- **Reconstructive surgery** to restore function and normal appearance after curative surgery.
- **Access surgery** to make it easier for doctors and nurses to administer chemotherapy medications.

This chapter will now discuss each of these types of cancer surgery in turn.

DIAGNOSTIC SURGERY

Before cancer is treated, the medical team must get an accurate diagnosis. Sometimes cancer can be diagnosed based on the patient's history, physical tests, lab tests, and imaging studies alone. However, these methods can be unreliable. To get the most accurate diagnosis, by far, the most reliable and common way is surgery.

When doctors perform surgery for diagnosis reasons, it is called 'diagnostic surgery' or a tissue diagnosis. This is where a surgeon makes an incision into the skin and removes some or all of the suspicious tissue. A pathologist then examines the tissue under a microscope and writes a report based on the finding.

Diagnostic cancer surgery comes with risks because cutting into any patient is invasive. Complications of surgery include hematoma, wound problems and can even spread the tumor. The goal of any biopsy is to obtain an adequate amount of tissue for a pathologist to make an accurate diagnosis, in the least invasive

manner, while avoiding risks and avoiding jeopardizing future surgical management.

Because every patient is different, many different techniques have evolved to diagnose cancer. These techniques vary depending on the type of cancer, its location, and the patient. The main techniques are open biopsy, needle biopsy, endoscopy and laparotomy, which will now be discussed in detail.

Open Biopsy

Open biopsy is known by several other names, including surgical biopsy, wide local excision, wide local surgical biopsy, incisional biopsy and lumpectomy. It is the gold standard for soft tissue mass diagnosis due to its high accuracy [3]. The procedure is very simple and involves making a one- to two-inch cut in the skin to remove all or part of the abnormal lump.

Open biopsy has several advantages and disadvantages compared to other cancer diagnostic methods.

Advantages of Open Biopsy

- Very high accuracy of 94% to 99% [4].
- More reliable at establishing the exact diagnosis than needle biopsy [3].
- The surgeon works with direct sight, thereby minimizing sampling error.

Disadvantages of Open Biopsy

- Expensive (between $4321 and $7234) [3].
- Invasive.
- Has a complication rate of up to 16%, including hematoma, tumor spread, and wound problems that may interfere with adjuvant treatments [4, 5].

As with all types of surgery, open biopsy carries risk of complications, although usually, these complications are not serious. Potential complications of open surgery include:

- Bleeding at the surgical site.
- Hematoma formation.
- Infection.
- Nerve damage.

The risk of bleeding and hematoma can be lowered by applying pressure dressings and ice to the site after the operation, while the risk of infection can be

CHAPTER 4

Immunotherapy and Cancer Stem Cells

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Abstract: Immunotherapy is one of the important modalities in the treatment of cancer since it can directly target the tumor and its microenvironment with lesser side effects and cytotoxicity. The main goal of immunotherapy in the treatment of cancer is the reactivation of the immune system against cancer cells. In this way, the body fights against cancer using its immune system rather than relying on external agents which might be harmful to other healthy parts of the body. The development of monoclonal antibodies (Mabs) has delivered a significant therapeutic effect. Mab therapy is one of the most evolving techniques in cancer immunotherapy and has shown efficacy in controlling several types of malignancies. There are several other methods by which the activation of the immune system can be achieved, such as by using small molecules or by targeting ligands. Interestingly, studies have demonstrated that cancer stem cells have also been found as a target for effective immunotherapy. Additionally, the complete elimination of the cancer cells requires longer sustainability of tumor-specific T cells. Primitive results suggest that these T cells can be localized to tumor cells, mediating highly effective immunotherapy. However, despite these huge successes, several problems still persist and must be overcome. This chapter discusses the current and cutting-edge immunotherapeutic approaches to fight against cancer cells.

Keywords: Cancer, Immunotherapy, Monoclonal therapy, Stem cells, Tumour microenvironment, Vaccines.

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INTRODUCTION

The recent advances in understanding the molecular landscape and pathogenesis of cancer have led to the successful introduction of targeted therapies for several types of human malignancies that involve a wide range of direct and indirect approaches. Monoclonal antibodies (Mabs) target signalling molecules and small molecules that interfere with the target proteins are regarded as direct approaches. Tumor antigens that are expressed on the cell surface serve as target devices for ligands containing different kinds of effector molecules when targeted is termed to be an indirect approach. Thus, in these approaches, using tumor-specific Mabs or peptide ligands binding to receptors on tumor cells can be effectively used to target tumors. These types of cancer therapeutic approaches seem to be more effective than currently available treatments as they are less harmful to normal cells. Two types of monoclonal antibodies are utilized:

1- Naked monoclonal antibodies – These form most of the antibodies used currently. They are plain antibodies that are used without alteration.

2- Conjugated monoclonal antibodies – As the name indicates, these are joined to another element, which is either cytotoxic or radioactive. Chemotherapeutic drugs are routinely used toxic chemicals, but other toxic chemicals can also be employed. When used, the antibody binds to the specific antigens on the surface of tumor cells and regulates the drug or the amount of radiation delivered to the tumor. Once the antibodies are linked to these radioactive compounds, they are alluded to as radiolabelled. When these antibodies are coupled with chemotherapeutic drugs or toxins, they are reputed as chemolabelled or immunotoxins, respectively [1, 2].

MONOCLONAL ANTIBODIES (MABS)

Immunotherapy, in recent years, has evolved in the treatment of cancer, moving from non-specific treatment such as chemotherapy surgery and radiotherapy to specific treatment immunotherapy. Immunotherapy is one of the important modalities in the treatment of cancer since it can directly target the tumor and its microenvironment with lesser side effects and cytotoxicity [3, 4]. The main goal of immunotherapy in the treatment of cancer is the reactivation of the immune system against cancer cells. One of the main cancer immunotherapy methods is monoclonal antibodies. Antibodies are a very important component of the immune system. The multifunction of the antibodies includes facilitating cellular and humoral reactions to different antigen's self or non-self-substance.

Antibodies are either polyclonal molecules produced from a single B cell clone or produced by several B lymphocytes or monoclonal molecules, where they have a different specificity for the target antigen. Antibodies can recognize the epitope regions on the antigen. When an antibody is produced against a single epitope instead of an entire epitope, this antibody is called a monoclonal antibody (Mab) [5].

The hybridoma technology was discovered in 1975, and Mab was initially produced by this technology. The first Mabs developed as potential human therapeutic agents were mouse antibodies. Clinical trials showed that with repeatedly administering mouse Mab because of their short half-life, their immunogenicity in humans decreased with poor ability to induce human immune effector responses. This is caused by the high immunity of mouse antibodies in the human body and the development of a human anti-mouse antibody (HAMA) response [6 - 8].

Chimeric, humanized and fully human monoclonal antibodies have been developed to overcome these problems. Chimeric antibodies are encoded by genes from more than one species, with antigen-binding regions from mouse genes and constant regions from human genes. On the other hand, humanized antibodies are genetically engineered mouse antibodies in which the protein sequence has been modified to mimic that of human antibodies [9, 10].

Antibodies are sectioned into two antigen-binding fragments (Fab), as well as the crystallisable fragment (Fc) forming the Y shape. The Fab is composed of the variable region, which forms the antigen-binding site of the antibody and confers antigen specificity. The Fc can bind to immune effector cells and complement that can both mediate antibodies directed the immune killing. The revolution in anticancer therapy in the last century with using of monoclonal and then the development of chemotherapy monoclonal antibodies (CmMabs), which have become the standard therapeutic agent for many human malignancies [10].

Classification of Chemotherapeutic Monoclonal (CmMab) Antibodies

Advanced genetic engineering produces 4 types of CmAbs: murine, chimeric, humanized and human Cm-Mabs.

1. Murine source Mabs is a rodent Mabs with excellent affinities and specificity generated using conventional hybridoma technology. It’s derived from mice. The patient treated with murine Mab developed a human anti-mouse antibody (HAMA) response. The disadvantages of this type are: rapid clearance of the Mab, poor tumor penetration and hypersensitivity reactions.

CHAPTER 5

Nanotechnology and Precision Medicine

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Abstract: Nanoscience and Nanotechnology are now almost in every field of Science. The field has been growing since it was started in 1959 when the Nobel Prize American physicist, Richard Feynman introduced the concept of nanotechnology; since then, it has involved in almost every field of Science, including chemistry, biology, computer science, physics, and engineering. Nanoscience and nanotechnology are now at the frontline of modernistic research. The term 'nano' referred to a Greek prefix meaning "dwarf" with a scale of one thousand millionths of a meter (10^{-9} m). Nanoscience is the study of particles and structures on the scale of nanometers.

Early detection of cancer plays an important role in successful treatment. The detection of cancer in the early stage has been delayed by the limits of conventional cancer detection methods. Recently, the uprising in the use of Nanomedicine and nanotechnology in health care offers hope for the detection, prevention, and treatment of cancer. Nanomedicine drugs have been observed to be involved in the treatment of solid tumors. Also, it is based on enhanced Permeability and Retention (EPR). The main characteristics of EPR are related to tumor vessel permeability which allows enhanced permeability (EP) of large particles (macro molecules proteins, micelles & liposomes). Nanomedicine transport can be hindered from Tumor-associated microphage (TAM) by poor blood perfusion, high Extracellular Matrix (ECM) dense and high tumor stromal cells. Electrochemotherapy is commonly used in palliative settings for the treatment of patients with unresectable tumors to relieve pain and improve the quality of life. It is also frequently used in the treatment of neoplasia at a late stage and when comprehensive surgical treatment is not possible due to the size, location, and the number of the lesion. As the treatment does not involve tissue heating, so Electrochemotherapy is used for the treatment of tumors near or close to important structures like vessels and nerves. Electrochemotherapy has a favorable side effect in the form of local and transient, moderate local pain, edema, erythema, and muscle contractions during electroporation.

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INTRODUCTION

Unique Roles of Nanotechnology in Cancer

Nanoscience and Nanotechnology are now almost in every field of Science. The field has been growing since it was started in 1959 when the Nobel Prize American physicist Richard Feynman introduced the concept of nanotechnology; since then, it has become involved in almost every field of Science, including chemistry, biology, computer science, physics, and engineering. Nanoscience and nanotechnology are now at the frontline of modernistic research. The term 'nano' referred to a Greek prefix meaning “dwarf” with a scale of one thousand millionths of a meter (10^{-9}m). Nanoscience means studying particles and structures on the nanoscale. Nanotechnology is the application of nanoscience in useful products [1].

In 2008, Nanomachines were successfully able to walk along DNA paths and manipulate structures. The application of nanotechnology in medicine is currently used to deliver drugs more efficiently, as in vaccines filled with nanoparticles of iron and gold to ensure sterility and help uptake into the human bloodstream. It is used to coat surgical equipment to keep them sterile. Nanotechnology also showed a promise in the treatment for different types of cancer.

In cancer therapy, the oncologist is looking for a tumor-specific anticancer agent to reduce the side effects and increase the efficacy of chemotherapeutic drugs in the patients. To overcome these barriers and increase the survival rate of patients with Cancer, Nanotechnology displays the unique and safe delivery of cancer therapy agents [2].

A lot of research was conducted to develop a novel therapeutic formulation to target cancer cells and avoid the cytotoxic effect on healthy cells [3].

A wide range of Nanostructures such as liposomes, Nano-diamonds, quantum dots, peptides, cyclodextrin, carbon nanotubes (CNTs), graphene, and metal-based nanoparticles, are used for diagnostic or therapeutic purposes [4].

The small size and large surface area of nanoparticles allow them to cross the cellular membranes and avoid detection by the reticular endothelial system, so they will not be debased, making them ideal for medical uses [5].

Nano drugs are unique and complex, so we must understand their structure, chemical, and physical characteristics. The targeting with nano drugs based on

delivery systems could be selectively targeted to the tumors *via* (selective targeting) using a peptide or an antibody that can specifically bind to a molecule that is selectively expressed on targeted cancer cells. Another mechanism is passive targeting where drugs should "passively target" cell-specific functions or local environments to facilitate the uptake and accumulation in tumor tissues and inflammatory sites with significant clinical success [6].

The Role of Nanotechnology in Cancer

Early detection of cancer plays an important role in successful treatment. The detection of cancer in the early stage has been delayed by the limits of conventional cancer detection methods. Recently the uprising in the use of Nanomedicine and nanotechnology in health care offers hope for the detection, prevention, and treatment of cancer. With the increase in the number of cancer cases which was estimated by GLOBOCAN 2018, 18.1 million with 9.6 million cancer-related death, with a prediction of 30 million death each year by 2030 [7, 8].

The present biomedical imaging, such as X-ray and computer-assisted diagnosis (CAD), and histopathology techniques are carried out to help clinicians in cancer diagnosis and treatment [9]. Nonetheless, most of these methods cannot effectively and independently be used to detect cancer at the early stage [10]. Therefore, the detection of cancer at an early stage before metastasis is a major challenge. To overcome the obstacles in the existing methodology and to improve outcomes, nanotechnology is used as a diagnostic method in the clinical setting, so the conjunction of nanotechnology with the current screening technologies will lead to an increase in the percentage of cancers that are diagnosed in the early stage and improved outcomes for cancer patients [10].

Nanoparticles (NPs) are used to capture cancer biomarkers, such as cancer-associated proteins, circulating tumor DNA, circulating tumor cells, and exosomes [11]. The main advantage of applying nanoparticles for cancer detection is based on their large surface area to volume ratio relative to bulk material [12]. So the nanoparticle surface can be covered with antibodies, peptides, and other moieties that can bind and identify specific cancer molecules [10].

Nanotechnology and Cancer

Nanoscale devices are one hundred to ten thousand times smaller than human cells. They are similar in size to biomolecules such as enzymes and receptors.

CHAPTER 6

Cancer Surveillance

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Abstract: Surveillance against tumors is governed by both intrinsic (non-immune) and extrinsic (immune) surveillance. While research on non-immune surveillance started as early as the 1960s when it was demonstrated that cell environment within and around can induce tumor-suppressing mechanisms, a major part of the progress is missing compared to immune surveillance. Part of the reason could be due to the fact that immune surveillance is seen to have more potential in therapeutic application in curing cancerous tumors compared to non-immune surveillance mechanisms. Many of the non-immune mechanisms are still under investigation as theories, although a few studies have shown their possibility. Contrary to this, there is a plethora of studies on immune surveillance. The immune system has been proven to have a role in the surveillance against tumors, thus conferring a certain degree of protection. However, not all tumor cells are successfully detected by innate immunity, and many of them have developed strategic ways of escaping adaptive immunity. The immunosurveillance in both animal models and humans shows overwhelmingly that cells with immunodeficiencies are more susceptible to tumor development. However, it is confounding that even immune-competent individuals develop tumors, and thus a significant process is responsible. Thus, immunoediting was proposed as a theory to explain why tumors can escape immunosurveillance. This chapter provides detailed evidence from animal and human tumors and analyses the mechanisms, pathways, and components implicated in tumor immune surveillance. The findings suggest that while immune surveillance could be the key to promoting immune function against the development of tumors, there is more research and understanding needed in the various mechanisms and cells implicated. This is because most, if not all, of the therapeutic studies using immune effectors have proved to be poor in preventing, treating, or regulating the development of tumors.

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INTRODUCTION TO CANCER SURVEILLANCE

In multicellular organisms, the protection from irregulated and abnormal growth of cells is necessary and constant as much as the protection against external threats. The surveillance system is designed to keep checks on the cell processes and provide an appropriate trigger mechanism to initiate the right response. These surveillance mechanisms for the prevention of both benign and malignant cells, are divided into the most common and well-known forms, like immune surveillance. However, other mechanisms exist that do not utilize the immune surveillance direct response. The non-immune surveillance mechanisms are independent and rely on certain cellular structures. This section will introduce what some of them are. The non-immune surveillance system is known as intrinsic surveillance, while the immune surveillance is extrinsic. While most malignant cancers arise from virus-induced tumors, the surveillance system always works to suppress both viral and carcinogenic tumors. Those tumors that escape such surveillance, mutate, and adapt are those capable of causing further growth and eventual cancer to an individual. Both intrinsic and extrinsic immune surveillance mechanisms are always working together in a continuous manner rather than being independent.

Immune surveillance as the main type of protection against cancer was, at first, a theory that was proposed by Thomas and MacFarlane [1]. With time, the theory has been proven through experiments in a lab that have shown that immune surveillance is present and always works to keep tumors at bay. While it has been proposed to be successful in many instances, immune surveillance has also failed in many because cancer incidents are increasing. This has been attributed to certain mechanisms in the cancer cells to possess the ability to either evade surveillance or suppress and escape it altogether. Tumor genesis does not bode well for most of the immune surveillance because mechanisms are deployed that lead to loss of function. Besides immune surveillance, other types of protection are implemented and include genetic surveillance, which is mainly involved in the repair of DNA to allow proper functions within the cell. Intracellular activities form a type of surveillance that utilize apoptosis. Epigenetics and intercellular activities have also been implicated. The subsequent sections will discuss these in detail.

NON-IMMUNE SURVEILLANCE

Genetic Surveillance

Genetic surveillance is a defense mechanism that occurs within the DNA itself. When tumors start to develop, there are chances that mutations in the DNA have an effect. This means that by carefully ensuring control of the processes like mitosis, the tumors will be kept at bay. The genes initiate control at the chromosomal level to prevent aspects like loss of heterozygosis or microsatellite instability [2]. The most known mechanism of genetic surveillance is that of the p53 pathway that tends to be present to repair the damage done to the DNA. This protein often appears when there has been damage to the DNA, and increases in number significantly until complete healing occurs. The gene binds itself to DNA in order to stop any growth or mutation process from occurring. This protein thus initiates healing and repair within the DNA itself through growth arrest and self-repair. After the DNA has managed to repair itself, the p53 levels decrease within the cell, and the process of cell division, growth and other cell functions resume [3]. In cells that are unable to complete the healing and repair process, another mechanism known as apoptosis is initiated, as will be discussed later.

Based on studies done on the role of p53 in tumor cells, it has been found that cells with tumors have up to 50% mutations in the p53 gene. This is significant and shows that p53 does play a role not just through the focus on healing, but by the fact that cancer cells seek to alter or eliminate its functions [4]. The impairments mostly relate to the ability of the gene to bind itself to DNA and thus serve its ability to regulate the DNA repairs. These aberrant cells thus contain DNA mutated at the basic level, no control or healing mechanism, and mitotic capacity to continue dividing. Therefore, cells arising from this are mutated at a micro level and hence the possibility of malignant cancer.

The genes controlling the mutation process have significant roles to play in ensuring the efficiency of DNA chromosomal separation, DNA repair and proper replication procedures are followed. One of the earliest cases of failure of genetic surveillance is a skin cancer condition known as Xeroderma pigmentosa. As the name suggests, the skin condition is characterized by pigments of the dermis that are caused by an inability of the DNA to repair itself. The main pathway implicated in this failure is a recessive mutation in the nucleotide repair system. This system is responsible for proception against ultraviolet (UV) rays from the sun, and upon their mutation, they become useless. Therefore, any form of light affects the skin of these patients because of the inability of thymidine dimmers to protect them. These patients have to remain away from any form of UV light at all times. However, it is never enough, as these patients develop several carcinomas

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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.