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Frontiers in Drug Design and Discovery

Co-Editors:
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M. Iqbal Choudhary

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(Volume 7)

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PREFACE

Modern drug design, discovery, and development are inherently interdisciplinary in nature where researchers of various disciplines work together, equipped with the most sophisticated technologies and recent understanding of the diseases at the molecular level. Despite overwhelming activities in this area in the past three decades, a large number of diseases have either remained untreated or their currently available treatments are not sufficiently effective. Emerging drug resistance, and drug associated adverse affects are further complicating this situation. Among the 21, 000 registered drugs, only 1,357 are unique in their structures. This clearly highlights the growing need of innovative and creative health care solutions which can reduce the human suffering.

The 7th volume of *Frontiers in Drug Design and Discovery* comprises seven excellent reviews, contributed by leading experts in these fields. Mahbuba Rahman has contributed a review on metabolic pathways in cancer cells and their relationship with emerging resistance. Metabolic pathways play an important role in promoting cancer cell survival and growth. Metabolic reprogramming is a hallmark of cancer cell proliferation, supporting enhanced nutrient uptake to supply energetic and biosynthetic pathways. Rahman has highlighted the importance of understanding these pathways and their association with chemotherapeutic resistance. Such in-depth understanding of metabolic reprogramming in cancer cells and its various implications can be used for identifying new targets for anti-cancer drug discovery.

Cancer chemotherapy is known to have a number of adverse effects on patients, including cardiotoxicity. Bras-Silva *et al.* have contributed a detailed review on a whole range of cardiovascular problems associated with the long term use of anti-cancer drugs, including heart failure, ventricular systolic dysfunction, hypertension, thromboembolic disease, cardiomyopathy, arrhythmias, and myocardial ischemia. The need of cardiac monitoring, and careful risk assessment is also discussed. The review ends with a summary of various new approaches and therapies which can reduce the risk of cardiovascular events during cancer chemotherapy.

Crispi *et al.* focus their review on innovative therapies and new approaches for cancer treatment. The need for better drugs and improved drug delivery systems against cancers is greatly felt. The review highlights the most recent advances in the field, particularly the use of novel combination therapies and development of nanocarriers for improved drug bioavailability and site specific drug release. These key developments have helped in achieving greater efficacy and lower toxicity in cancer treatment. These approaches also have the capacity to circumvent the emerging drug resistance in cancer chemotherapy.

Yoshino *et al.* have contributed a comprehensive review on various combination of anticancer drugs clinically tried for the treatment of a rare type of uterine sarcomas. This rare cancer has three histological variants, *i.e.* carcinosarcoma, leiomyosarcoma, and endometrial stromal sarcoma. Because of the rarity of this cancer, the search for specific treatments and well-designed clinical trials on various combination therapies is not vigorously pursued. This review provides a commentary of innovative combinations of anti-cancer agents that are now being tested for the treatment of all three variants of uterine sarcomas.

Angiogenesis is a normal process for healing and reproduction. This involves the growth of new capillary blood vessels. However, in pathological conditions, angiogenesis leads to abnormal blood vessel growth. This then becomes the underlying process for many deadly diseases, including cancers. Roslida Abd Hamid *et al.* have reviewed various strategies targeting biochemical and cellular events involved in the tumor angiogenesis. Most of the anti-cancer drugs are non-specific in nature, and thus associated with numerous side effects. Moreover, substances which inhibit angiogenesis specifically act on new cells. The authors have reviewed the various classes of natural substances, including marine natural products, with anti-angiogenic activities. Methods for validating the anti-angiogenic inhibitory activities of test substances have also been mentioned.

Biaoru Li has focused the next chapter on recent developments on the emerging field of personalized medicine. The entire concept is presented in an easy to understand manner by systematically describing personalized chemotherapy. This starts with the genomic analysis from tumor tissue sampling and ends at the identification of the most sensitive substances from the available drugs. Through this case study, the concept of personalized medicine *i.e.* "*the right treatment for the right person at the right time*", is skillfully described. With the introduction of next generation sequencing, and system modeling related to drug discovery, the concept of personalized medicine would be widely applied.

The last review in this volume is related to the application of nanotherapeutics in the treatment of infectious diseases. Nanotherapy is the newest mode of treatment that can be applied for the treatment for various diseases. Sheikh *et al.* describe the hypothesis and idea of a nanotherapeutic system, and the various aspects related to it such as change of properties of substances at the nano-levels, testing of the new drugs, and the safety assessment of the new nano-substances. The key challenges in the treatment of infectious diseases include drug resistance, less bioavilability, and non-specificity of potent antibiotics. This review highlights the advances in drug delivery through nanocarriers which can solve most of these problems associated with conventional antiobiotics therapeutics.

In the end, we are extremely grateful to all the contributors for the timely submission of their reviews. The 7th volume of the eBook series is the results of the efficient coordination and

excellent management of the entire team of Bentham Science Publishers. We would like the recognize the efforts of Mr. Omer Shafi (Assistant Manager Publications), Shehzad Naqvi (Senior Manager Publications) and team leader Mr. Mahmood Alam (Director Publications) for putting together an excellent treatise of well written articles in a time efficient manner. We are confident that this volume of eBook series will receive a wide appreciation from students, young researchers, and established scientists.

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CHAPTER 1

Metabolic Pathways and Chemotherapy Drugs

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Abstract: Chemotherapy drugs are long being used to treat cancer either as single drug or in combination with other treatment strategies. However, the current problem with treatment is the development of chemo-resistance properties of cancer cells that causes relapses at the later stages of the treatment. It is therefore necessary to design and develop new drugs or modify existing treatment strategies. Cancer cells show abnormal cell growth and adopt metabolic pathways that are different from normal cells. There are also links between metabolic pathways and chemo-resistance development in cancer cells. This indicates the importance of integration of knowledge on the metabolic pathways of cancer cells prior to new drug design and development for cancer treatment. In this review, we discuss the metabolic pathways associated with chemo-resistance development and focus on existing or new drugs targeting these pathways.

Keywords: Antimetabolites, Autophagy, Chemotherapy drugs, Chemoresistance, Drug design and Development, Metabolic pathways, Regulatory proteins, Signalling molecules, Systems biology.

INTRODUCTION

Cancer is a multifactorial genetic disease. As such different treatments such as surgery, radiotherapy and chemotherapy are used to treat cancer. Chemotherapy is used either as single treatment modality or as 'adjuvant therapy' or 'neoadjuvant therapy'. 'Adjuvant therapy' refers to the use of chemotherapy drugs after surgery

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to destroy or kill cancer cells, whereas 'neoadjuvent therapy' is used to shrink cancer cells before surgery or radiation therapy. Chemotherapy is also used in combination where multiple drugs are used in a certain order or in certain combinations. The ultimate goal of using chemotherapy is to cure or resist the spread of cancer [1, 2].

The term 'chemotherapy' was coined by the German chemist Paul Ehrlich in early 1900s and defined it to use chemicals to treat disease. He developed arsenical drugs to treat bacterial disease (*e.g.*, syphilis), which was later used to treat acute promyelocytic leukemia (APL). In 1940, mustard gas was injected in the veins of several cancer patients who were suffering from advanced lymphomas. At that time several chemicals were synthesized to treat cancer. However, the lack of appropriate models and clinical trials limited the application of chemotherapies during that era. In 1960, surgery and radiotherapy was used as main treatment for cancer, but the cure rate was only 33%. Besides, these are used as local treatments and effective only in one area of the body such as breast, lungs or prostate. Chemotherapies differ from these treatments as they are used as 'systemic treatment', where the drugs travel throughout the body to reach cancer cells. The combination of chemotherapy with the local treatments had a better cure rate of patients with advanced cancers. Since then, combined modality treatment became the standard clinical practice for cancer [2 - 4].

At present, there are more than 100 different chemotherapy drugs available for different types of cancer. These drugs are divided into several groups. The grouping is based on their chemical structure and mechanism of action (Table **1**) [5 - 7]. The anticancer effect of chemotherapy drugs reside in interrupting cell cycle resulting in either irreversible damage to the cell or induction of the apoptotic pathways. Many of the chemotherapy drugs target nucleic acid (DNA/RNA) biosynthesis directly or indirectly.

There are 5 phases in the cell cycle: G_O phase (resting phase), G_1 phase, S phase, G_2 phase and M phase. Normally the G_O phase is considered as the starting or resting point for the cell cycle. In G_1 phase, the cells grow and prepare to synthesize DNA, at G_2 phase, the cells prepare to divide and at the M or mitosis phase, cell division occurs [6, 7].

Table 1. List of major chemotherapy drugs available for the treatment of cancer [5 - 7].

Chemotherapy groups	Mechanism of action	Examples	Type of cancers treated	Side effects
Alkylating agents	Damage DNA directly at every phases of the cell cycle.	*Nitrogen mustards*: mechlorethamine, chlorambucil, cyclophosphamide (Cytoxan®) etc. *Nitrosoureas*: streptozocin, carmustine (BCNU) etc. *Alkyl sulfonates*: busulfan *Triazines*: dacarbazine (DTIC), temozolomide (Temodar ®) etc. Ethyleneimines: thiotepa, altretamine (hexamethylmelamine) etc.	Leukemia, lymphoma, Hodgkin' disease, multiple myeloma, sarcoma, lung cancer, breast cancer and ovarian cancer.	(i) Long-term damage to the bone marrow may sometimes lead to acute leukemia. (ii) Cytotoxicity may lead to hair loss, breathlessness, fatigue, memory and eating challenges, nausea, pain sterility. (iii) Recurrence. (iv) Drug resistance.
Antimetabolites	These drugs interfere with DNA and RNA formation by substituting the normal building blocks of RNA and DNA.	5-fluorouracil (5-FU) 6-mercaptopurine (6-MP) Capecitabine (Xeloda®) Cladribine Cloafarabine Cytarabine (Ara-C®) Floxuridine Fludarabine Gemicitabine (Gemzar®) Hydroxyurea Methotrexate Pemetrexed (Alimata®) Pentostatin Thioguanine	Leukemia, breast cancer, ovarian cancer, intestinal tracts and other types of cancer.	
Antitumor antibiotics	These drugs interfere with enzymes involved in DNA replication and works in all phases of the cell cycle.	Anthracyclines: Daunorubin, Doxorubixin (Adriamycin®), Epirubicin etc. Actinomycin-D Bleomycin Mitomycin-C	Used for a variety of cancers.	High doses cause permanent damage to the heart.

CHAPTER 2

Cardiotoxicity of Cancer Chemotherapy–Recent Developments

Rui Adão[1], Carolina Maia-Rocha[1], Diana Santos-Ribeiro[2], Pedro Mendes-Ferreira[1], Adelino F. Leite-Moreira[1], Carmen Brás-Silva[1,3,*]

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Abstract: The extensive use of chemotherapy in clinical practice has led to considerable controversy due to their potential adverse cardiovascular effects in surviving cancer patients. Among the effects of chemotherapeutic agents on the cardiovascular system, the most frequent and serious is heart failure with ventricular systolic dysfunction. Other harmful effects include hypertension, thromboembolic disease, pericardial disease, arrhythmias and myocardial ischemia. Cancer therapy-induced cardiomyopathy was almost exclusively associated with the use of cumulative doses of anthracyclines. However, new therapeutic agents, such as the monoclonal antibody trastuzumab, induce transient reversible myocyte dysfunction. Recent research to limit cardiotoxicity has focused on early monitoring and risk stratification to identify patients that are 'at risk' for cardiotoxicity, using biochemical markers and the prophylactic use of novel cardioprotective agents. This chapter reviews the clinical course, pathogenesis, cardiac monitoring and new concepts in diagnosing and preventing chemotherapy cardiotoxicity.

Keywords: Anthracyclines, Cancer, Cardiomyopathy, Cardio-oncology, Cardiotoxicity, Chemotherapy, Monitoring, Prevention, Radiotherapy, Trastuzumab.

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INTRODUCTION

Cancer is the second leading cause of death after cardiovascular diseases in the US [1]. By 2020, The incidence of cancer will increase among men by 24.1% to > 1 million cases, and by 20.6% among women to >900,000 cases [2]. In recent years, the rapid development of intensive antineoplastic therapies effectively tailored to the individual has significantly improved prognosis for cancer patients. Unfortunately, due to an increase in the use of cardiotoxic agents, success in treating cancer might be followed by defeat from life-threatening conditions caused by cytotoxicity [3]. For several decades, the problem was almost entirely related with anthracyclines, for which cumulative dose-related cardiac damage was the use-limiting step. However, a new dimension of the problem has emerged when drugs targeting the activity of certain tyrosine kinases or tumor receptors were recognized to carry an unwanted effect on the cardiovascular system [4, 5]. The term cardiotoxicity includes a number of heterogeneous side effects including cardiomyopathy, arrhythmias, changes in blood pressure, myocardial ischemia or thrombosis (Fig. **1**) [6].

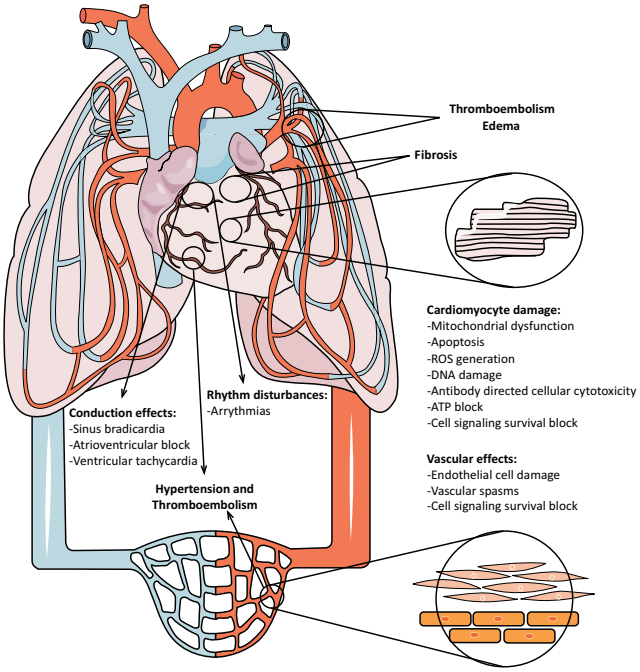

Fig. (1). Examples of major mechanisms causing cardiotoxicity of anticancer treatments.

The extensive use of anticancer drugs in the clinical setting has raised concern on the long-term cardiovascular side effects among cancer survivors. However, there are no evidence-based guidelines for monitoring myocardial function in these patients and no predictive models have been developed to estimate this risk [7]. Currently, oncologists must be fully conscious of cardiovascular risks to avoid or prevent adverse cardiac effects, and cardiologists must now be ready to support oncologists by performing evaluations relevant to the choice of treatment. There is a need for cooperation between these two areas and this integrative approach has been termed cardio-oncology [8]. This chapter summarizes the potential cardiovascular toxicities for a range of cancer chemotherapeutic agents and their mechanistic pathways. We also review the clinical course, cardiac monitoring and new concepts in diagnosing and preventing chemotherapy cardiotoxicity.

DEFINITION OF CARDIOTOXICITY

Cardiotoxicity is defined by the National Cancer Institute in general terms as the 'toxicity that affects the heart' (www.cancer.gov/dictionary/). A growing body of researches is now studying long-term side effects of anticancer therapy, however a clear understanding of what cardiotoxicity is and the certain mechanisms involved are lacking [9]. One of the most precise definitions was proposed by the Cardiac Review and Evaluation Committee supervising clinical trials of the monoclonal antibody trastuzumab (Table **1**) [10]. This definition does not include subclinical cardiovascular damage which can occur as an initial reaction to some chemotherapeutic agents [11].

Table 1. Criteria to confirm or revise a preliminary diagnosis of cardiac dysfunction. [Adapted from Seidman *et al*. [10]].

I) Cardiomyopathy characterized by a decrease in LVEF that was either global or more severe in the septum
II) Symptoms of CHF
III) Associated signs of CHF, including S3 gallop, tachycardia, or both
IV) Decline in LVEF of at least 5% to less than 55% with signs or symptoms of CHF, or a decline in LVEF of at least 10% to below 55% without signs or symptoms

CHF: congestive heart failure; LVEF: left ventricular ejection fraction. [Adapted from Seidman *et al.*[10]].

CHAPTER 3

Advances in Cancer Therapy: Novel Approaches in Combined Drug Treatments

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Abstract: Drug resistance and poor efficacy of anticancer therapies prompt to investigate innovative therapeutic strategies aimed to improving efficacy and lowering toxicity. Recent advances in chemotherapeutics have been achieved using specific pharmaceutical combinations or ameliorating drug delivery by drug encapsulation.

Novel combined treatments are based on the use of drugs, typically natural active or intended for other uses combined with the classical anti-cancer drug. These compounds promote synergistic effects even more enhanced when drug delivery is achieved by nanocarriers. Nanotechnologies provide a site-specific delivery at the tumor site, resulting from receptor-mediated endocytosis and prolonged circulation time. Nanocarriers also increase drug bioavailability and biocompatibility contributing to a drug increase inside the tumor and determining a minor toxicity and a better efficacy.

This chapter reports recent findings about novel anticancer combined treatments and about the latest drug delivery systems based on the use of nanocarriers.

Keywords: Cannabinoids, Combined treatment, Curcumin, Epigallocatechingallate, Liposomes, Nanoparticles oncolytic viruses, Phytochemicals, Resveratrol, Small interfering RNA, γ-tocotrienol.

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INTRODUCTION

The major limitations in conventional cancer treatments that compromise therapeutic efficacy are the serious side effects and the frequent development of resistance to therapies. Recent advances in cancer therapy include the introduction of new chemotherapeutic agents that target specific molecular abnormalities in the tumor cells, with fewer side effects. In addition, novel therapeutic strategies based on anticancer drug combinations have been developed [1]. It has been shown that DNA random mutations can be selected following monotherapy, and that they often are responsible for drug resistance. In combined treatments multiples mutations should be actively selected in order to determine drug resistance. Thus, combined treatments have been shown to improve treatment efficacy in comparison to single drug administration due to synergistic effects, which allows for a drug doses reduction [2].

More recently, in order to reduce the use of cytotoxic drugs, several phytochemicals, natural compounds already utilized in different fields of medicine, have been considered and deeply investigated for cancer treatment as complementary therapy. Different *in vitro* and *in vivo* studies have reported that phytochemicals can regulate the expression of factors involved in carcinogenesis, and also display synergism when combined with anticancer drugs that result in increased apoptosis [3]. Nevertheless, the use of combined treatments is limited by drug toxicity or by short drug half-life or bioavailability. Investigators are working to overcome these limitations by developing specific drug delivery systems (DDS) with specific size, shape, material and coating [4, 5].

Recent technological improvements have allowed the scientific community to produce nanocarriers specifically functionalized to recognize cellular key structures and to target tumor cells exclusively. These systems allow for a passive nano-drugs concentration through the enhanced permeability and retention (EPR) effect [6, 7]. The employment of different biomaterials and functionalization led to produce different nanoparticles (NP) formulations such as lipid-based NP, polymer conjugates NP, inorganic NP, nanocrystals and cyclodextrins NP [8].

Currently, the scientific community has focused its attention on the application of

dual-drug delivery systems (DDDS) in cancer therapy. DDDS allow the simultaneous loading of NP with two different drugs, which play a dual therapeutic role exploiting the advantages of drug delivery [9]. Promising results have been reached since several DDDS–based clinical trials have been developed. In addition, *in vivo* analyses are being performed to test the efficacy of different DDDS formulations [10, 11].

In this chapter, we are going to describe the latest applications used in cancer therapy to improve treatment efficacy. In particular, we are going to describe the use of phytochemicals in chemotherapy in combination with conventional cytotoxic drugs, and also the employment of nucleic acids - such as viral genome or small interfering RNA (siRNA) - as new promising tools in cancer therapy. Finally, the chapter reports the very recent progresses reached in DDDS, describing the main formulations employed in the drug delivery system and the results obtained.

NATURAL AGENTS FOR NOVEL CANCER THERAPIES

1. Phytochemicals

Phytochemicals are natural bioactive compounds extracted from fruits, vegetables, grain and oils known to preserve health and reduce the risk of developing several chronic diseases [12]. Their natural properties enable the protection of the cells from free radicals and the oxidative stress.

Moreover, their use is not associated with the onset of side effects that occur with the use of conventional drugs. Among phytochemicals, different Phase II or III clinical trials are ongoing for epigallocatechingallate, curcumin, and resveratrol for the treatment of different cancer [13]. γ-tocotrienol has been recently evidenced to reduce the risk of prostate cancer development [14]. Other interesting natural compounds are the phytocannabinoids derived from *Cannabis Sativa.* Natural and synthetic cannabinoids are able to deregulate tumor growth and to improve survival [15].

Many *in vitro* and *in vivo* studies have explored the use of phytochemicals in association with conventional chemotherapeutics in order to enhance cytotoxicity

CHAPTER 4

Chemotherapy for Uterine Sarcomas: A Review

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Abstract: Uterine sarcomas are relatively rare tumors, constituting only 8%-10% of all uterine malignancies. Its three most common histologic variants are carcinosarcoma (CS), leiomyosarcoma (LMS), and endometrial stromal sarcoma (ESS). Because of its frequent resistance to existing chemotherapeutic drugs (caused by several mechanisms), standard chemotherapeutic regimens have not yet been established. Presently, CSs are treated in the same way as high-grade endometrioid endometrial carcinomas. A combination of carboplatin and paclitaxel is the most commonly used adjuvant therapy regimen in advanced or recurrent CS. For LMS, the key drugs are doxorubicin, ifosfamide, gemcitabine, and docetaxel. These drugs are used as single agents or in combination for the treatment of patients with advanced or recurrent LMS. For ESS treatment, hormonal agents have been used because ESS expresses estrogen and progesterone receptors. Because of its rarity, well-designed random controlled trials are required for future investigations of the efficacy of chemotherapy for patients with uterine sarcoma.

Keywords: Carcinosarcoma, Chemotherapy, Endometrial stromal sarcoma, Leiomyosarcoma, Uterine sarcoma.

INTRODUCTION

Uterine sarcomas, arising from the smooth muscle or connective tissue, are relatively rare tumors, constituting only 8%–10% of all uterine malignancies. The

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three most common histologic variants of uterine sarcoma are carcinosarcoma (CS), leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS).

The first-line of treatment should be surgical management; however, uterine sarcomas frequently recur and carry a poor prognosis, despite complete surgical resection. Compared with the more common endometrial carcinomas, uterine sarcomas behave more aggressively and typically have worse prognoses [1].

There are few effective chemotherapeutic agents for sarcoma patients. Because of their poor response rates (RRs) to chemotherapeutic agents, no standard chemotherapeutic regimens for advanced and recurrent forms of uterine sarcomas have been established. This is in contrast to other gynecologic malignancies, such as ovarian cancers, where platinum drugs are important for chemotherapy, and they have shown high RRs (60%–80%) [2]. However, cisplatin has played a limited role in uterine sarcoma patients. Previous reports found that, of 63 uterine CS cases treated with cisplatin, only five had complete responses (CR; 8%) and seven had partial responses (PR; 11%). For the 33 patients with LMS, only one PR (3%) was observed [3]. Various drugs, such as cisplatin, etoposide, topotecan, and paclitaxel, have failed to show efficacy, particularly in LMS patients [3 - 6]. These reports, which set uterine sarcoma apart from other gynecologic cancers, show that this sarcoma needs a distinctive therapeutic treatment.

In this study, we describe the molecular mechanisms behind the chemoresistance of uterine sarcomas. We follow this with a review of the therapeutic agents presently in use.

The Mechanisms of Chemoresistance in Uterine Sarcomas

It is usually the multidrug resistance of uterine sarcomas that leads to their poor clinical courses [7]. Currently, several mechanisms of chemoresistance have been proposed, including pre-target, on-target, and post-target mechanisms. The speed of tumor cell proliferation also plays a role [8]. A pre-target mechanism of drug resistance is one where cancer cells somehow elude the cytotoxic potential of the drugs binding to their cytoplasmic targets. On-target mechanisms involve the repair of adducts at an increased pace and/or the ability of tumor cells to tolerate unrepaired DNA lesions while undergoing cell replication, reflecting the activity

of a particular class of DNA polymerases. Post-target resistance to chemotherapeutic agents may follow several alterations, including defects in apoptotic signal transduction pathways and issues with cell death machinery. Although studies concerning the molecular mechanisms of uterine sarcoma drug resistance are limited, the pre-target mechanism has been relatively better investigated compared with other mechanisms.

Permeability glycoprotein-1 (PGP1) and multidrug resistance 1 (MDR1)-related protein (MRP) are associated with multidrug resistance *via* pre-target resistance mechanisms [9 - 11]. PGP is also known as MDR1, adenosine triphosphate (ATP)-binding cassette sub-family B member 1 (ABCB1), or cluster of differentiation 243 (CD243). PGP1 is a 170-KDa cell membrane protein with 12 transmembrane regions and two ATP-binding sites [12, 13]. PGP and MRP proteins are members of the ATP-binding cassette (ABC) family, which are membrane transporters; they are found in the cell's outer membrane and act as ATP-dependent drug-efflux pumps with broad substrate specificity [14]. These pumps induce the efflux of many foreign substances, including cytotoxic drugs and decrease their intracellular accumulation, resulting in the reduced efficacy of cytotoxic drugs in uterine sarcomas.

A common feature of drug resistance is the reduced accumulation of several different classes of chemotherapeutic drugs, including the vinca alkaloids, anthracycline, epipodophyllotoxin, and taxanes. In uterine sarcomas, PGP is associated with the resistance of vinblastine, paclitaxel, and doxorubicin [15]. According to one model of doxorubicin drug resistance in uterine sarcoma, the mechanism involves both drug efflux and anti-apoptosis processes. When doxorubicin concentrations within cells rise because of diffusion into the cytoplasm, induced levels of PGP pump the doxorubicin back out, relying on hydrolysis of ATP for energy, and the cells become increasingly resistant to chemotherapy [16].

Hua *et al*. showed that PGP/MDR-1 gene silencing reverses the resistance to doxorubicin in the constitutively doxorubicin-resistant human uterine sarcoma cell line MES-SA/DX5 [13]. These reports suggest that PGP plays an important role in the drug resistance of uterine sarcoma.

CHAPTER 5

Angiogenesis Inhibitors from Natural Sources

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Abstract: A multi-target strategies targeting on various biochemical and physiological pathways implicated in tumour pathogenesis should be developed with the ultimate aim to manage patients with cancer and reduce the normal-tissue toxicity. Tumor angiogenesis has been recently discovered as an important strategy in treating cancer as most tumors rely on angiogenesis to survive, develop, invade and metastasize. Targeting angiogenesis to inhibit the progression of tumorigenesis has recently been a focus in developing novel anti-cancer development. This is mainly due to the specificity that anti-angiogenic possesses: it targets on newly-formed blood vessels and spares the existing ones. With that being said, inhibiting angiogenesis is now considered a promising strategy in the development and selection of new anti-cancer drug candidates. To date, there are cytotoxic drugs which also exhibit antiangiogenic activity but not angiogenesis inhibitors in whole. In this chapter, we will be discussing selected natural sources including marine products which have been investigated for their antiangiogenic activities. Various methods in validating the effects as well as their possible multiple pathways will also be contended in this chapter.

Keywords: Angiogenesis, Antiangiogenic, Cancer development, Marine products, Phytochemicals.

INTRODUCTION

Angiogenesis, also known as neovascularization is defined as the new capillaries

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formation from existing blood vessels. It is likely a fundamental process involved in several pathophysiological processes [1, 2]. Recently, angiogenesis has been widely studied as it has been known as an important series of events that contributes significantly to the pathogenesis and development of cancer. Recent development of anti-cancer studies is directed on developing therapies and strategies to interfere with the angiogenesis process, which is prominently augmented in a wide variety of cancer therapies. As tumor growth, invasion and metastasis are angiogenesis-dependent, therefore, the ability to activate angiogenesis is of paramount importance in controlling tumor progression [3]. It has been estimated that 90% of the overall morbidity and mortality of cancer is due to metastases [4]. Except in a much underserved populations, it is unusual for patients with cancer to die from the complications produced by the primary cancer, signifying the importance of the thorough understanding of the regulation of angiogenesis in pathological conditions, in the effort to strategize ways to manage it. Having said the utmost importance of controlling angiogenesis in our tireless effort to develop effective cancer therapy, ever since angiogenesis is first hypothesized by the late Nobel Prize Winner, Judah Folkman more than four decades ago, it has become the most studied subject for thousands of cancer researchers, therefore providing a wide array of unique therapeutic interventions in cancer treatment [5].

Antiangiogenic drugs are currently used to inhibit tumor growth in both preclinical and clinical trials, and a variety of antiangiogenic agents have been reported to exhibit promising antitumor responses [6]. Nevertheless, it is interesting to note that current antiangiogenic treatments have been shown to provide a modest survival rate, despite their promising activity in various types of cancer in patients. To address this scenario, attempts have been made to combine existing therapeutic modalities with antiangiogenic drugs. This type of combination, which involves conventional cytotoxic chemotherapies may lead to optimal therapeutic activity, as anti-angiogenics are generally known as cytostatic, rather than cytoreductive. In addition, antiangiogenic agents are considered a much safer option to be administered over an extended period of time, compared to standard maximum tolerated dose (MTD) chemotherapies, which are reported to exhibit severe adverse effects [7].

One of the well- established strategies to treat cancer is by targeting angiogenesis. Although theoretically, the attempt to attenuate angiogenesis will lead to a better management of cancer, the problem lies in the difficulty to develop suitable *in vitro* and *in vivo* methods for the assessment and quantification of the angiogenic response, at both basic and applied levels. Current *in vitro* and *ex vivo*/*in vivo* assays are used due to the advantages that they possess, although there are restrictions and limitations of several individual assays which should be taken into consideration. Identifying the advantages and disadvantages of each individual assays and executing them in combination to test various aspects of angiogenesis are of utmost important, to ensure the consistent resemblance of angiogenic mimicry in these models to the actual human body scenario.

The discovery of new drugs derived from phytochemicals has a long history and diverse natural sources, such as plant, animal and marine sources provide an excellent platform for the development of natural angiogenesis inhibitors. The search for antiangiogenic agents from natural compounds, especially plant secondary metabolites has long been initiated, ever since the emergence of evidences reporting the suppression and prevention of malignant tumors by cutting off their blood supply; their main means of nutrient and oxygen supply. Cytotoxic agents are also demonstrated to exert antiangiogenic activities at a lower dose, hence, by applying optimal dosage, the plant phytochemicals that are priorly shown to exhibit chemotherapeutic activities, may also show anti-angiogenic activities. By employing reliable *in vitro* and *in vivo* assays, further elucidation of anti-angiogenic effect of these compounds can be carried out.

Although not yet completely understood, the complex process of tumor angiogenesis involves a highly regulated orchestration of multiple signalling pathways. Apart from the proangiogenic factors secreted by the tumor and host cells when ‘angiogenic switch’ is initiated, there are other factors which contributed to the regulation of equilibrium between angiogenic activators and inhibitors. Direct and indirect influence of angiogenic switch have been evidently shown by vascular endothelial growth factor receptor (VEGFR) tyrosine kinase, methionine aminopeptidase-2 (MetAP-2), p53, tubulin, cyclooxygenase-2 (COX-2), and matrix metalloproteinases (MMPs) [8]. Whilst, the proangiogenic signalling molecule vascular endothelial growth factor (VEGF) and its cognate

CHAPTER 6

Personalized Chemotherapy of Tumor Disease Based on System Modeling

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Abstract: Clinically, personalized medicine also referred to as precision medicine is a new medical model to be directly tailored for the care of individual patients. It is often called "the right treatment for the right person at the right time." Most successful examples of personalized treatments require a rational clinical genomic analysis. Following Research and Development (R&D) of techniques and analysis of clinical genomic expression, genomic expression profile along with system modeling has been increasingly applied for personalized therapy. Now personalized chemotherapy, one of personalized therapy, has been brought forward to the field of cancer. According to protocol of personalized chemotherapy from tumor tissue sampling to clinical application in queue, I will introduce the entire process including clinical sampling, analyzing mRNA genomic expression level with its diagnosis, discovering gene expression signature by system modeling and uncovering sensitive drugs from drug-bank for clinical application. At present, after next-generation sequencing is brought into the new field, system modeling related with drugs discovery will make great contribution for future personalized chemotherapy of tumor diseases.

Keywords: Cancer stem cells (CSCs), Circulating tumor cells (CTCs), Clinical genomics analysis, Clinical genomic diagnosis, Drug targeting, Encyclopedia of DNA Elements (ENCODE), Flow-cytometric cell sorting (FACS), Gene expression signature (GES), Genome-wide association studies (GWAS), Laser-captured micro-dissection (LCM), Magnetic cell separation (MACS), Networks, Personalized chemotherapy, Personalized medicine, Proteomics, Single nucleotide polymorphisms (SNP), System biology and system modeling, Transcriptome.

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INTRODUCTION

Cancer is a broad group of various diseases with the challenges of effective treatment and cure [1]. This is the reason why physicians and scientists are beginning to utilize all new-generation tools available. Now important breakthroughs in improving the effectiveness of cancer chemotherapy have emerged in clinical fields such as "personalized medicine" [2]. Personalized medicine (now called as precision medicine) is new medical module based on individual characteristics of each patient rather than "rigid uniformity" administration by traditional medicine. Detecting patient's genomics profile is prerequisite of personalized medicine. These genomic profiles can be used to predict susceptiblity of individuals to certain diseases or to predict the efficacy of treatment modalities [3]. Recent research and development of cancer has enabled physicians and scientists to understand how certain type of cancers to respond to chemotherapy by using genome-wide association studies (GWAS) for single nucleotide polymorphisms (SNP) [4]. Because most of FDA drugs are directed at phenotype alteration (or function change of tumor cell related with mRNAs and proteins expression level) rather than on DNA informative archives, mRNA and protein products of DNA genotype change should have a great impact on a new-generation medicine [5]. Moreover, other genomic profiles such as epigenetics profiles, microRNA profiles and non-coding DNA sequencing profiles are also uncovered to relate to mRNAs or proteins expression level onto phenotype alteration of tumor cell (Fig. **1**) [6].

Scientists and physicians are going to focus on genomic expression profiles of tumor cell or integration of genomic expression among them (transcriptome-GWAS, transcriptome-epigenetics, transcriptome-microRNA, all genomics profiles or Encyclopedia of DNA Elements, ENCODE) to study therapeutic targeting [7]. Furthermost, optimal dosage with best therapeutic effect and minimal toxicities is relied on dynamic change of gene expression level in an individual patient [8] because many factors individually impact drug absorption and clearance [9]. Among genomic expression level profiles including transcriptome and proteomics, theoretically, proteomics should be the best method to apply for system modeling of biomarkers discovery and therapeutics targeting

[10]. Unfortunately, proteomics has proven difficult application for clinical targeting discovery according to current evidence such as purity of clinical sample and detection sensitivity [11]. In order to set up rational network for personalized therapy, at present, system biology based on transcriptome such as microarray and RNA-Seq have been progressively reported [12].

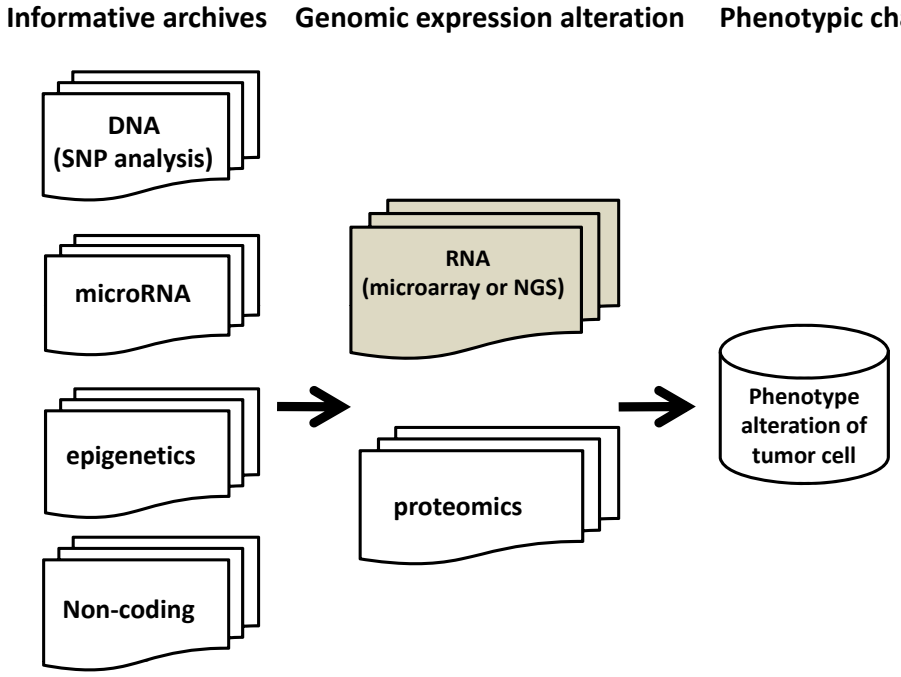

Fig. (1). Three levels of analyses include genomic archives (GWAS, epigenetics and microRNA and non-coding genomics analysis); genomics expression analysis including transcriptomes and proteomics; clinical phenotype changes of tumor cells. Grey color is main part in the manual.

According to workflow of personalized chemotherapy based on system-modeling (Fig. **2**), In the chapter, I will first introduce (A) clinical genomic expression techniques and then present (B) clinical genomics diagnosis because of purity requirement of genomic profiles and gene expression level for further system modeling; discuss in detail (C) system model including concept and development of system model for personalized chemotherapy; finally, I will briefly present (D) drug targeting related with system modeling and different validation methods for personalized chemotherapy. In conclusion section, I will discuss challenges and future development of personalized chemotherapy based on the system modeling.

CHAPTER 7

Nanotherapeutics: Future Medicine For Infectious Diseases

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Abstract: Infectious diseases are increasingly becoming a major health concern annually afflicting millions of humans worldwide. Presently, the greatest challenge to any successful effective treatment of a particular pathogen is the emergence of drug-resistance, less bioavailability and non-specificity of potent antibiotics at the target sites, requiring large doses of medicine over a longer period of time, resulting in maximum toxicity to patients. However, drug delivery is a powerful concept in nanomedicine which is constantly growing at a burgeoning pace, could provide an efficient alternative to target any pathogens at any site in the body using advanced combined nanoparticle platforms or nanocarriers with fewer side effects. Significantly, nanotherapeutics could be administered through various specific routes such as oral, parenteral, and topical for effective treatment.

In summary, this chapter would highlight the role of targeted antibiotics as an advancement of future nanomedicine over conventional therapeutics against virulent infectious diseases.

Keywords: Antimicrobial, Bioavailability, Biofilm, Infection, Metallic, Nano-particles, Photodynamic therapy, Photothermal therapy, Resistance, Targeted.

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1. INTRODUCTION

Infectious diseases caused by pathogenic microbes such as bacteria, viruses, protozoa, and fungi are the leading cause of death in the world. Although vaccination has undoubtedly contributed to reduced prevalence of certain infections and improved human health considerably over the last century, there are quite a few infections which are currently responsible for increased morbidity and mortality. The advent of antibiotics coupled with better sanitation and hygiene has significantly reduced the burden of infectious diseases. However, surfacing of new pathogenic microbes and growing resistance of old microbes to conventional therapies is a peril in the treatment of infections [1]. The incessant efforts and mammoth investments in research have not translated into the discovery of new antimicrobials at a rate commensurate with that of growing antibiotic resistance [2]. Intracellular delivery of antimicrobials is another daunting challenge in the treatment of infections [3]. Both these facts necessitate the design of smart nanotherapeutics to overcome the drawbacks of conventional antimicrobial therapies and achieve superior therapeutic outcomes to combat the growing menace of infections. The chapter introduces the types of infections, highlights the challenges associated with conventional therapy of different types of infections, and focuses on the immense potential of nanotherapeutics to revolutionize infectious disease therapy in manifold ways.

2. TYPES OF INFECTIONS

Infections may be classified depending on the causative agent as bacterial, viral, fungal or parasitic as shown in Table **1**. They may also be classified as topical

Table 1. Types of infections.

Origin	Infection	Causative microbes
Bacterial	Tuberculosis	*Mycobacterium tuberculosis*
	Impetigo	*Staphylococcus aureus* and *Streptococcus pyogenes*
	Typhoid	*Salmonella typhi*
	Peptic ulcer	*Helicobacter pylori*
	Periodontitis	*Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans*
	Conjunctivitis	*Staphylococcus aureus*

(Table 1) contd.....

Origin	Infection	Causative microbes
Viral	AIDS	Human Immunodeficiency Virus
	Chicken pox	Varicella zoster virus
	Herpes	Herpes zoster virus
Fungal	Candidiasis	*Candida albicans*
	Onychomycosis	*Trichophyton rubrum, Trichophyton mentagrophytes,* and *Candida albicans*
Parasitic	Malaria	*Plasmodium falciparum, Plasmodium vivax*, *Plasmodium ovale, Plasmodium malariae*, and *Plasmodium knowlesi*
	Leishmaniasis	*Leishmania donovani, Leishmania infantum, Leishmania major,* and *Leishmania tropica*
	Amoebiasis	*Entamoeba histolytica*

(ocular infections, buccal cavity infections, skin infections, vaginal, and rectal infections) and systemic (malaria, Human Immunodeficiency Virus (HIV)) depending on the affected body areas.

3. PROBLEMS ASSOCIATED WITH CONVENTIONAL THERAPY OF INFECTIONS

3.1. Increased Antimicrobial Resistance

Microbes have developed resistance to most of the conventional antimicrobials which once comprised first line therapy for infectious diseases. Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococcus* are very difficult to treat owing to their resistance to commonly used antimicrobials [2]. Increased doses of antimicrobials need to be administered in order to overcome resistance which leads to increased side effects and toxicity [3].

3.2. Limited Oral Bioavailability of Antimicrobials

Most of the antimicrobials suffer from poor oral bioavailability due to poor solubility (efavirenz, amphotericin B, nevirapine) [4 - 6], decreased permeability through intestinal membranes (amphotericin B) [5], first pass metabolism (saquinavir) [7], and P-gp induced efflux (saquinavir, tobramycin) [7, 8].

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